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Original article

Discovery of new 1,3,5-triazine scaffolds with potent activity against *Mycobacterium tuberculosis* H37Rv

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ABSTRACT

A series of eighty one 2,4,6-trisubstituted-1,3,5-triazines were synthesized and evaluated *in vitro* for the growth inhibition of *Mycobacterium tuberculosis* H37Rv. Fifteen compounds from this series exhibited good to moderate activity with an MIC in the range 1.56–3.12 μg/mL and most of them were found to be nontoxic against VERO cells and MBMDMQs (mouse bone marrow derived macrophages). This is for the first time that 2,4,6-trisubstituted-1,3,5-triazines were identified as a potent inhibitors of *M. tuberculosis* H37Rv.

1. Introduction

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*, which is responsible for the deaths of about 1 billion people during the last two centuries [1]. According to the World Health Organization (WHO), 2 million people die every year and at least 9 million are getting infected with this infection [2]. In addition, the evolution of its new virulent forms like multidrug resistant (MDR-TB) and extensively drug resistant (XDR-TB) has become a major threat to the humankind [1]. The present chemotherapy DOTS (directly observed treatment short-course) has a cure rate of up to 95% if patient gives compliance. Despite the fact that it is treatable and preventable, the disease has been spreading at a steady rate due to the length of the therapy, that makes patient compliance difficult and noncompliance is a frequent source for multidrug resistant strains (MDR-TB). Especially, the resurgence in TB is alarming due to the development of pathogenic synergy with HIV [3,4]. In developing countries, the prevalence of MDR-TB was reported to be as high as 50% due to inadequate supply of the drugs as a consequence of poor financial resources [5]. Thus the above mentioned factors reveal the necessity to develop effective and affordable anti-tubercular agents.

Dihydrofolate reductase (DHFR) is a key enzyme of folate biocycle [6] and also a prime target for infectious diseases [7]. DHFR catalyzes the dihydrofolate to tetrahydrofolate, the folate cofactor involved in the DNA replication as well as for the synthesis and/or catabolism of several amino acids (Met, Gly, Ser, Glu, His). Therefore, the inhibition of DHFR enzyme hampers the biosynthesis of DNA which leads to the inhibition of cells proliferation [8,9]. In addition, this enzyme has high binding affinities and selectivity towards the substrate analogues that are not readily displaced by the natural substrates [10]. This made the DHFR as an ideal target for rational and efficient drug design for anti-infective agents. Moreover, the enzyme is thoroughly explored for the development of antibacterial agents after the discovery of trimethoprim (TMP). TMP is used as a synergiser [11] due to its good DHFR binding selectivity [12–14]. Therefore, antifolates targeting the DHFR represent a validating approach for the development of anti-mycobacterial agents due to their well established mode of actions [15] and a higher degree of selectivity for the microbial enzymes than the human enzymes [14,16,17].

In search of such folate antagonists, Gangjee et al. synthesized tricyclic tetrahydropyrido furo[2,3-*d*]pyrimidines and found benzoyl-L-glutamic acid derivative potent against *Mycobacterium avium* DHFR [18]. Similarly, Rosowsky et al. synthesized 2,4-diaminopteridine analogues with a bridged diarylamine side chain and found that the compound having seven-membered ring in the dibenz[*b,f*]azepine moiety was more selective and most active

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against *M. avium* DHFR [19]. With the same motivation, Shoen et al. synthesized 2,4-diamino-5-methyl-5-deazapteridines (DMDP) having structures similar to the trimetrexate/piritrexim and identified their antimycobacterial activity against *M. avium* complex (MAC) [20], in the continuation Suling et al. established the DMDPs activity and selectivity towards the DHFR of MAC/Human [21]. Additionally, Meyer et al. [22] and Gerum et al. [23] also identified WR99210 (1,3,5-triazine derivative) and its analogues as potent inhibitors of MAC and *M. tuberculosis* DHFR, respectively. While El-Hamamsy et al. [24] verified the activity and selectivity of substituted 2,4-diaminopyrimidines against DHFR of *M. tuberculosis*. Moreover DHFR is also a target for anti-tubercular drug isoniazid [25]. Therefore, folate antagonists represent a premier class for the development of antimycobacterial agents.

In this context, we would like to mention our continuous efforts devoted to the synthesis of novel heterocycles as anti-infective agents. We earlier reported the antiparasitic activity of substituted pyrimidines and triazines [26–36]. Here, we report the excellent anti-tubercular activity of easily synthesizable 2,4,6-trisubstituted-1,3,5-triazine derivatives, using the hits obtained from the pyrimidino-triazine derivatives (**1**–**22**) which were previously reported for their anti-leishmanial activity, along with some substituted pyrimidines (**23**–**29**) by our group [37] (Fig. 1). These pyrimidino-triazine compounds were found to have moderate anti-tubercular activity, while substituted pyrimidines showed deprived activity. This confirms that hybrids may be active due to the presence of 1,3,5-triazine moiety and thus we initiated the exploration of 2,4,6-trisubstituted-1,3,5-triazines for their anti-tubercular activity. For this purpose, we initially synthesized a series of triazines monosubstituted with 1,2,3,4-tetrahydroquinoline (**48**–**55**), piperidine (**56**–**63**) and disubstituted with 1,2,3,4-tetrahydroquinoline/tetrahydroisoquinoline (**36**–**47**), which have shown moderate anti-tubercular activity. So, in an effort to increase the activity, we have developed a novel series by incorporating isoniazid with 1,3,5-triazine moiety (**64**–**87**) and found them with a promising anti-tubercular activity. In this manuscript, synthesis of 2,4,6-trisubstituted-1,3,5-triazines and their anti-tubercular activity against *M. tuberculosis* H37Rv have been reported and also it is for the first time that they have been identified as an anti-mycobacterial agents (Fig. 2).

2. Chemistry

Our synthetic approach towards the targeted compounds is concerned with inexpensive chemicals and easily accessible conversions in good yield. 2,4,6-trisubstituted triazines were synthesized from the precursor cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and the addition of amines (Table 1 and 2) was carried out based on the strength and structure of nucleophile (Scheme 1). The intermediates 2-chloro-4,6-substituted-[1,3,5] triazine (**30**, **31**) were obtained by reacting cyanuric chloride with 1,2,3,4-tetrahydroquinoline (THQ)/isoquinoline (THIQ) respectively in the presence of K_2CO_3 in dry THF. These compounds were further subjected to nucleophilic substitution with different amines to obtain trisubstituted triazines having THQ (**36**–**41**) and THIQ (**42**–**47**) at 2,4-positions. While the derivatives having mono-substitution of tetrahydroquinoline (**48**–**54**), piperidine (**57**–**63**) at 2-position and different amines at 4,6-positions, were obtained from their respective intermediates **32** and **34**. Whereas compounds **55**, **56** were obtained by reacting **32** and **34** respectively with 50% ethylamine solution in acetone. These intermediates, including **33** (THIQ) and **35** (aniline) were prepared by reacting cyanuric chloride with respective amines in the presence of K_2CO_3 in dry THF.

To synthesize the compounds with different substitutions at 2,4,6-positions of 1,3,5-triazine (**64**–**87**), the intermediates **32**, **33**, **34** and **35** were subjected to nucleophilic substitution with various amines (Table 1, 2), followed by the isonicotinohydrazide in the presence of K_2CO_3 in THF to furnish their respective compounds. All the synthesized compounds were well characterized by IR, Mass, NMR and the purity was established with elemental analysis.

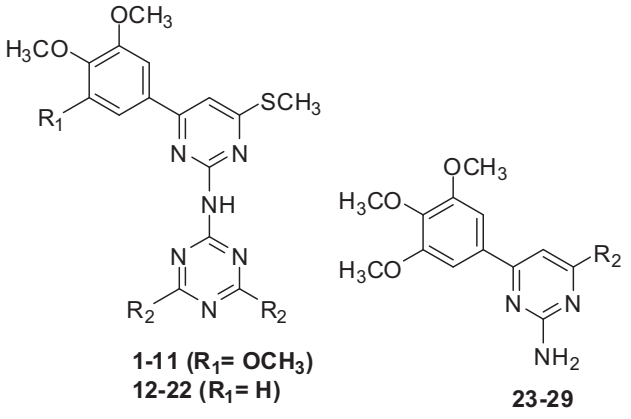


Fig. 1. Pyrimidino-triazines and pyrimidines with anti-leishmanial and anti-tubercular activity.

3. Biological activities

3.1. In vitro anti-tubercular assay

Evaluation of anti-tubercular activity against *M. tuberculosis* H37Rv was carried out with a recommended protocol [38] using Middlebrook (MB) 7H10 agar medium. A 100 μL of serial two fold dilutions of the stock (1.0 mg/mL in DMSO, Dimethyl Sulphoxide) of test compounds and standard anti-tubercular drug {isoniazid (INH)} were incorporated in the medium (final volume, 2 mL/tube) supplemented with OADC (oleic acid, albumin fraction IV, dextrose and catalase). Compounds/drug containing tubes were kept in slanting position till the medium solidified. Culture of *M. tuberculosis* H37Rv grown on Lowenstein–Jensen (L–J) was harvested in N-saline containing 0.05% Tween-80. The culture was vigorously agitated with glass beads to make a single cell suspension. A working inoculum (2×10^7 cfu/mL; 10 μL/tube) of mycobacterium was spread on the surface of the medium and the tubes were kept at 37 °C for 4 weeks for the appearance of colonies. Tubes containing no drug served as control. The minimum concentration of the drug (INH)/compounds that completely inhibited the growth of mycobacterium was recorded as Minimum Inhibitory Concentration (MIC) with respect to the used inoculum.

3.2. Cytotoxicity evaluation

3.2.1. Evaluation against VERO cells

Cell line was procured from laboratory animal division of CDRI. The cell suspension was plated in 96-well tissue culture plates at a density of 20,000 cells per well (in 100 μL) in minimal essential medium (MEM) with antibiotics + 10% fetal bovine serum (FBS). The monolayers were then incubated overnight at 37 °C and 5% CO_2 for allowing adherence of cells. Compounds of different concentrations were added in MEM + 10% FBS. As a positive control, a known toxic compound was used. DMSO was used as negative control. After 24 h incubation, 20 μL of MTS solution (tetrazolium compound, Owen's reagent) was added to each well and incubated for 2 h at 37 °C, 5% CO_2. Reading was taken at 490 nm using a plate

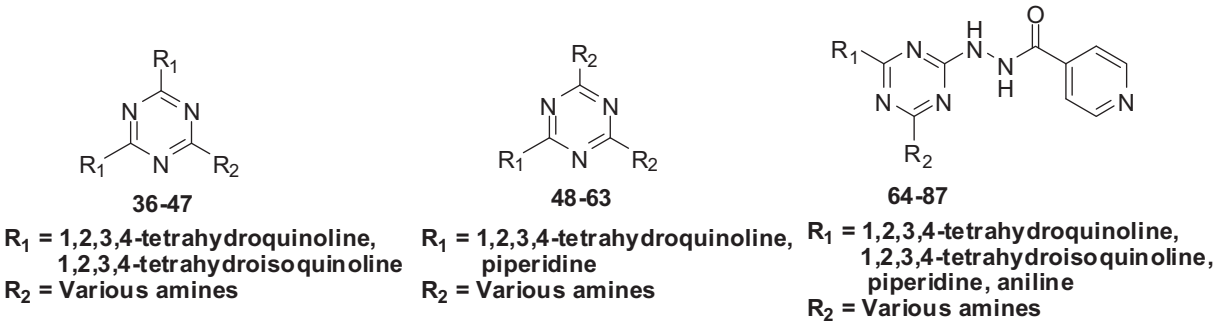


Fig. 2. Novel 2,4,6-trisubstituted-1,3,5-triazines with anti-tubercular activity.

reader. Absorbance shown by DMSO containing wells is taken as 100% survivors [39]. A compound is considered toxic if it causes 50% inhibition at concentration 10 fold higher than its MIC.

3.2.2. Evaluation against mouse bone marrow derived macrophages (MBMDMQs)

Mouse was euthenized by exposure to CO_2 and the femur bones were dissected out. The bones were trimmed at each end, and the marrow was flushed out (using 26-gauge needle) with 5 ml of Dulbecco's minimal essential medium (DMEM) supplemented with 10% FBS, 15% L-929 fibroblast conditioned supernatant (prepared as described below), and non essential amino acids. Cells were washed twice and plated in 96-well tissue culture plates at a concentration of 10^5 cells per well (100 μL) in supplemented DMEM. The monolayers were then incubated at 37 °C in 5% CO_2 with the medium change every 3rd day. Macrophages were used 5 days later. Different concentrations of compounds were added in antibiotic free, FBS supplemented, DMEM and incubated at 37 °C in 5% CO_2. After 48 h, 20 μL of MTS solution was added to each well and incubated for 2 h at 37 °C in 5% CO_2. Reading was taken at 490 nm using a plate reader. Absorbance shown by DMSO containing wells is taken as 100% survivors [40]. A compound is considered toxic if it causes 50% inhibition at concentration 10 fold higher than its MIC.

Table 1
In vitro anti-tubercular and cytotoxic activities of targeted compounds[a].

Compounds	R_1	R_2	MIC (μg/mL)	Cytotoxicity	
			MTB-H37Rv	VERO	MBMDMQ
1	methoxy	2-aminoethylmorpholine	12.5	ND	ND
2	methoxy	3-aminopropylmorpholine	12.5	ND	ND
5	methoxy	*t*-butylamine	3.12	NT	T
6	methoxy	piperidine	6.25	ND	ND
7	methoxy	*N*-methylpiperazine	12.5	ND	ND
10	methoxy	isopropylamine	3.12	T	T
11	methoxy	*N*-ethylpiperazine	12.5	ND	ND
14	hydrogen	*N*,*N*-diethylethylenediamine	6.25	ND	ND
15	hydrogen	*N*,*N*-dimethylethylenediamine	6.25	ND	ND
16	hydrogen	*t*-butylamine	6.25	ND	ND
21	hydrogen	isopropylamine	12.5	ND	ND
22	hydrogen	*N*-ethylpiperazine	12.5	ND	ND
42	tetrahydroisoquinoline	2-aminoethylmorpholine	3.12	NT	T
45	tetrahydroisoquinoline	*N*-methylpiperazine	6.25	ND	ND
57	piperidine	*n*-propylamine	12.5	ND	ND
58	piperidine	isopropylamine	12.5	ND	ND
64	tetrahydroquinoline	*n*-butylamine	6.25	ND	ND
65	tetrahydroquinoline	*t*-butylamine	3.12	NT	NT
66	tetrahydroquinoline	isopropylamine	3.12	NT	NT
67	tetrahydroquinoline	morpholine	3.12	NT	NT
69	tetrahydroisoquinoline	piperidine	3.12	NT	T
70	tetrahydroisoquinoline	*n*-butylamine	3.12	NT	NT
71	tetrahydroisoquinoline	*t*-butylamine	3.12	NT	T
72	tetrahydroisoquinoline	isopropylamine	3.12	NT	NT
73	tetrahydroisoquinoline	tetrahydroisoquinoline	3.12	NT	T
74	piperidine	2-aminopyrimidine	3.12	NT	NT
75	piperidine	*n*-butylamine	3.12	NT	NT
76	piperidine	*t*-butylamine	6.25	ND	ND
77	piperidine	isopropylamine	3.12	NT	NT
78	piperidine	piperidine	6.25	ND	ND
79	aniline	morpholine	1.56	NT	NT
81	aniline	cyclohexylamine	6.25	ND	ND
84	aniline	*n*-butylamine	6.25	ND	ND
86	aniline	isopropylamine	6.25	ND	ND
Isoniazid (INH)			0.025	NT	NT

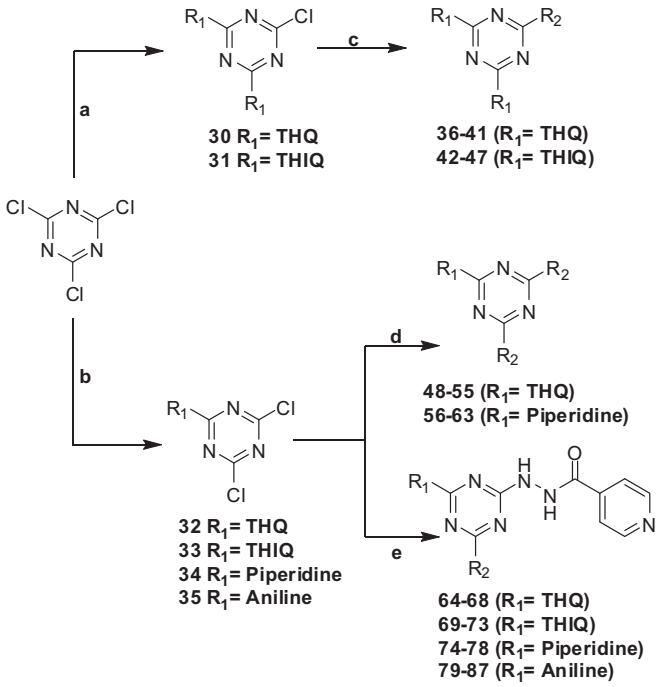
[a] MTB: *Mycobacterium tuberculosis*; MBMDMQ: mouse bone marrow derived macrophages; NT: nontoxic; T: Toxic (A compound is considered toxic if it causes 50% inhibition at concentration 10 fold higher than its MIC); ND: not done.

Table 2
In vitro anti-tubercular activity of rest of the synthesized compounds against *M. tuberculosis* H37Rv.

Compounds	R_1	R_2	MIC (μg/mL)
3	methoxy	*N*,*N*-diethylethylenediamine	>12.5
4	methoxy	*n*-butylamine	>12.5
8	methoxy	*n*-propylamine	>12.5
9	methoxy	morpholine	>12.5
12	hydrogen	2-aminoethylmorpholine	>12.5
13	hydrogen	3-aminopropylmorpholine	>12.5
17	hydrogen	piperidine	>12.5
18	hydrogen	*N*-methylpiperazine	>12.5
19	hydrogen	*n*-propylamine	>12.5
20	hydrogen	morpholine	>12.5
23	methoxy	2-aminoethylmorpholine	>12.5
24	methoxy	3-aminopropylmorpholine	>12.5
25	methoxy	*N*,*N*-diethylethylenediamine	>12.5
26	methoxy	*n*-butylamine	>12.5
27	methoxy	piperidine	>12.5
28	methoxy	*N*-methylpiperazine	>12.5
29	methoxy	morpholine	>12.5
36	tetrahydroquinoline	2-aminoethylmorpholine	>12.5
37	tetrahydroquinoline	3-aminopropylmorpholine	>12.5
38	tetrahydroquinoline	*t*-butylamine	>12.5
39	tetrahydroquinoline	*N*-methylpiperazine	>12.5
40	tetrahydroquinoline	*N*,*N*-diethylethylenediamine	>12.5
41	tetrahydroquinoline	morpholine	>12.5
43	tetrahydroisoquinoline	3-aminopropylmorpholine	>12.5
44	tetrahydroisoquinoline	*t*-butylamine	>12.5
46	tetrahydroisoquinoline	*N*,*N*-diethylethylenediamine	>12.5
47	tetrahydroisoquinoline	morpholine	>12.5
48	tetrahydroquinoline	*n*-propylamine	>12.5
49	tetrahydroquinoline	isopropylamine	>12.5
50	tetrahydroquinoline	3-aminopropylmorpholine	>12.5
51	tetrahydroquinoline	*t*-butylamine	>12.5
52	tetrahydroquinoline	*N*,*N*-diethylethylenediamine	>12.5
53	tetrahydroquinoline	*N*,*N*-dimethylethylenediamine	>12.5
54	tetrahydroquinoline	2-aminoethylmorpholine	>12.5
55	tetrahydroquinoline	ethylamine	>12.5
56	piperidine	ethylamine	>12.5
59	piperidine	*t*-butylamine	>12.5
60	piperidine	2-aminoethylmorpholine	>12.5
61	piperidine	3-aminopropylmorpholine	>12.5
62	piperidine	*N*,*N*-dimethylethylenediamine	>12.5
63	piperidine	*N*,*N*-diethylethylenediamine	>12.5
68	tetrahydroquinoline	3-aminopropylmorpholine	>12.5
80	aniline	piperidine	>12.5
82	aniline	3-aminopropylmorpholine	>12.5
83	aniline	aniline	>12.5
85	aniline	*t*-butylamine	>12.5
87	aniline	isonicotinohydrazide	>12.5

4. Results and discussion

Out of eighty one compounds screened for their *in vitro* anti-tubercular activity against *M. tuberculosis* H37Rv, thirty four compounds were found active with MIC in the range of 12.5–1.56 μg/mL (Table 1) and the rest were with MIC >12.5 μg/mL (Table 2). The compounds with potent MIC of 3.12, 1.56 μg/mL were also tested for their cytotoxicity against VERO cells and MBMDMQs (mouse bone marrow derived macrophages) and most of them were found to be nontoxic. In pyrimidino-triazine derivatives, compounds **5** and **10** having methoxy group as R_1 (similar to that of trimethoprim) and *t*-butylamine, isopropylamine respectively as R_2, showed MIC of 3.12 μg/mL, while their dimethoxyphenyl analogues **16** and **21** have shown decreased activity with an MIC of 6.25, 12.5 μg/mL respectively. Similarly, trimethoxyphenyl derivatives **1**, **2**, **6** and **7** have shown more potency in comparison to their dimethoxyphenyl derivatives. Moreover, compound **5** was found to be nontoxic against VERO cells, which lead to the synthesis of trimethoxyphenyl substituted pyrimidines derivatives (**23**–**29**). These compounds showed MIC more than 12.5 μg/mL. This observation confirmed that the antimycobacterial activity of pyrimidino-triazine derivatives is majorly due to the presence of 1,3,5-triazine moiety. Therefore, in order to explore the structure–activity relationship of 2,4,6-trisubstituted-1,3,5-triazines, triazines monosubstituted with 1,2,3,4-tetrahydroquinoline (**48**–**55**), piperidine (**56**–**63**), isoniazid (**64**–**87**) and disubstituted with tetrahydroquinoline (**36**–**41**), tetrahydroisoquinoline (**42**–**47**) were synthesized.



Scheme 1. Reagents and conditions: (a) 1,2,3,4-Tetrahydroquinoline (for **30**) and 1,2,3,4-Tetrahydroisoquinoline (for **31**), K_2CO_3, THF, 0–60 °C, 4 h; (b) Respective amines, K_2CO_3, THF, 0 °C–rt, 3 h; (c) Different amines, K_2CO_3, THF, reflux, 8 h; (d) Different amines, K_2CO_3, THF, reflux, 7–8 h; 50% ethylamine sol., Acetone, reflux, 8 h (for **55**, **56**); (e) i. Different amines, K_2CO_3, THF, rt, 2 h; ii. Isonicotinohydrazide, reflux, 8 h.

Among all the above synthesized compounds, those having substitution of isonicotinohydrazide (INH) at 6-position of 1,3,5-triazine (**64**–**87**) were found to be more promising anti-tubercular candidates when compared to others. Compound **64** having 1,2,3,4-tetrahydroquinoline as R_1 and *n*-butylamine as R_2 showed MIC of 6.25 μg/mL, while compounds with same R_1 and *t*-butylamine (**65**), isopropylamine (**66**) and morpholine (**67**) as R_2 have shown equal potency of 3.12 μg/mL and nontoxic against both the VERO and the MBMDMQs. Surprisingly, irrespective of substitution of R_2 and having 1,2,3,4-tetrahydroisoquinoline as R_1, compounds (**69**–**73**) have shown equal potency of 3.12 μg/mL, but compounds **69**, **71** and **73** were found to be toxic against MBMDMQs. Compounds **74**, **75** and **77** having piperidine as R_1 and 2-aminopyrimidine, *n*-butylamine, and isopropylamine as R_2 respectively, showed MIC of 3.12 μg/mL and were nontoxic. Compound **79**, having aniline as R_1 and morpholine as R_2 was found to be the most active amongst these analogues with nontoxic profile. The activity profile of these compounds clearly suggests that the isonicotinohydrazide has promoted the anti-tubercular activity of 1,3,5-triazines.

5. Conclusions

Development of antimycobacterial agents based on identified targets and their mechanisms of action is a productive approach for the lead generation. In this perception, we have chosen to explore 1,3,5-triazine moiety known to be targeting DHFR enzyme, which

was also identified as a prime target for anti-tubercular drug Isoniazid. With this aim, we designed and synthesized easily accessible 2,4,6-trisubstituted-1,3,5-triazines and a systematic SAR study was carried out. Activity results suggest that the incorporation of anti-tubercular drug INH increased the potency of 1,3,5-triazines. Thus our studies reveal that these 1,3,5-triazines are novel anti-tubercular agents and can be proved as potential drug candidates. This calls for the further exploration of SAR of these compounds to understand the mechanistic aspects and to develop them as drugs in our fight against tuberculosis.

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. The samples (dissolved in suitable solvents such as methanol/acetonitrile/water) were introduced into the ESI source through a syringe pump at the rate of 5 μl per min. The ESI capillary was set at 3.5 kV and the cone voltage was 40 V. The spectra were collected in 6s scans and the print outs are averaged spectra of 6–8 scans. In case of multiplets the signals are reported as intervals. Signals were abbreviated as s, singlet; d, doublet; t, triplet; m, multiplet. The electron spray mass spectra were recorded on triple quadrupole mass spectrometer. EI mass spectra were recorded on JEOL JMS-D-300 spectrometer with the ionization potential of 70 eV and ES mass on Quantro-II, micro mass. Purity of all tested compounds was ascertained on the basis of their elemental analysis and 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 **30** and **31**

The solution of 1,2,3,4-tetrahydroquinoline/1,2,3,4-tetrahydroisoquinoline (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 during 30 min. The reaction mixture was stirred at room temperature for 1 h and then stirred mechanically at 60 °C for 3 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 and dried over anhydrous Na_2SO_4, concentrated and purified with flash column chromatography using hexane to ethyl acetate gradient elution to afford compounds **30** and **31** respectively.

6.1.1. 1,1′-(6-Chloro-1,3,5-triazine-2,4-diyl)bis(1,2,3,4-tetrahydroquinoline) (**30**)

Yield: 78%; mp 138–140 °C; FAB-MS: 378 (M + 1); IR (KBr) 3025, 1608, 1555, 1479, 1339, 1318, 1233, 1175, 1036, 837 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.72 (d, 2H, $J = 7.87$ Hz), 7.28–7.11 (m, 6H), 4.06 (t, 4H, $J = 6.29$ Hz), 2.82 (t, 4H, $J = 6.68$ Hz), 2.11–1.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.39, 163.97, 136.68, 131.65, 128.52, 125.91, 125.25, 124.23, 45.35, 26.80, 23.52; Anal. Calcd for $C_{21}H_{20}ClN_5$: C, 66.75; H, 5.33; N, 18.53; Found: C, 66.53; H, 5.19; N, 18.51.

6.1.2. 2,2′-(6-Chloro-1,3,5-triazine-2,4-diyl)bis(1,2,3,4-tetrahydroisoquinoline) (**31**)

Yield: 83%; mp 130–132 °C; FAB-MS: 378 (M + 1); IR (KBr) 3010, 1557, 1474, 1373, 1349, 1232, 1154, 1043, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.25–7.20 (m, 8H), 4.95 (s, 4H), 4.09 (t, 4H, $J = 5.62$ Hz), 2.99 (t, 4H, $J = 5.58$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 170.16, 163.98, 134.07, 131.86, 128.55, 127.19, 126.83, 126.46, 46.26, 42.31, 28.49. Anal. Calcd for $C_{21}H_{20}ClN_5$: C, 66.75; H, 5.33; N, 18.53; Found: C, 66.59; H, 5.30; N, 18.46.

6.2. General procedure for the synthesis of compounds **32**–**35**

To the solution of cyanuric chloride (2,4,6-trichloro-1,3,5-triazene) (1.2 equiv) and K_2CO_3 (1 equiv) in dry THF, 1,2,3,4-tetrahydroquinoline (1 equiv) in dry THF was added dropwise at 0 °C during 1 h and continued to stir for 2 more hours at room temperature. After the completion of reaction, the mixture was evaporated to dryness and purified with flash column chromatography using chloroform to methanol gradient elution to afford compound **32**. Same method was applied to obtain intermediates **33**, **34** and **35** using tetrahydroisoquinoline, piperidine and aniline respectively.

6.2.1. 1-(4,6-Dichloro-1,3,5-triazin-2-yl)-1,2,3,4-tetrahydroquinoline (**32**)

Yield: 76%; mp 126–129 °C; FAB-MS: 280 (M + 1); IR (KBr) 3039, 1608, 1561, 1473, 1330, 1316, 1233, 1172, 1027, 833 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.74 (d, 1H, $J = 7.63$ Hz), 7.30–7.12 (m, 3H), 4.05 (t, 2H, $J = 6.44$ Hz), 2.82 (t, 2H, $J = 6.47$ Hz), 2.13–1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.37, 163.97, 136.58, 131.61, 128.48, 125.91, 125.22, 124.23, 45.33, 26.78, 23.46; Anal. Calcd for $C_{12}H_{10}Cl_2N_4$: C, 51.27; H, 3.59; N, 19.93; Found: C, 51.19; H, 3.54; N, 19.82.

6.2.2. 2-(4,6-Dichloro-1,3,5-triazin-2-yl)-1,2,3,4-tetrahydroisoquinoline (**33**)

Yield: 80%; mp 73–75 °C; ESMS: 281 (M + 1); IR (KBr): 2854, 1561, 1464, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.29–7.18 (m, 4H), 4.82 (s, 2H), 3.89 (m, 2H), 2.85 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): 167.84, 165.37, 135.62, 131.75, 129.58, 128.82, 124.74, 48.78, 44.14, 31.69; Anal. Calcd for $C_{12}H_{10}Cl_2N_4$: C, 51.27; H, 3.59; N, 19.93; Found: C, 51.12; H, 3.45; N, 19.98.

6.2.3. 2,4-Dichloro-6-(piperidin-1-yl)-1,3,5-triazine (**34**)

Yield: 84%; mp 142–143 °C; ESMS: 233 (M + 1); IR (KBr) 2945, 1574, 1472, 1217, 765 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.81 (t, 4H, $J = 5.18$ Hz), 1.68–1.59 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 170.54, 164.43, 45.74, 26.06, 24.63; Anal. Calcd for $C_8H_{10}Cl_2N_4$: C, 41.22; H, 4.32; N, 24.04; Found: C, 41.26; H, 4.29; N, 24.11.

6.2.4. 4,6-Dichloro-N-phenyl-1,3,5-triazin-2-amine (**35**)

Yield: 85%; mp 219–221 °C; ESMS: 241 (M + 1); IR (KBr): 3426, 1554, 1465, 750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.12 (bs, 1H), 7.67 (m, 2H), 7.22 (m, 1H), 6.89 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): 168.92, 166.76, 138.63, 128.18, 122.34, 119.81; Anal. Calcd for $C_9H_6Cl_2N_4$: Calculated C: 44.84; H: 2.51; N: 23.24; Found: C: 44.76; H: 2.52; N: 23.18.

6.3. General procedure for the synthesis of compounds **36**–**41**

The mixture of compound **30** (1 equiv), different amines (1.2 equiv) and K_2CO_3 (1.2 equiv) in dry THF was refluxed for 8 h. The reaction mixture was filtered and the filtrate was evaporated under vacuum. The obtained solid residue was purified with flash column chromatography using chloroform to methanol gradient elution to afford the targeted compounds **36**–**41**.

6.3.1. 4,6-bis(3,4-dihydroquinolin-1(2H)-yl)-N-(2-morpholinoethyl)-1,3,5-triazin-2-amine (**36**)

Yield: 68%; mp 96–98 °C; FAB-MS: 472 (M + 1); IR (KBr) 3425, 2943, 2815, 1593, 1428, 1352, 1118, 862, 759 cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$): δ (ppm) 7.84 (d, 2H, $J = 8.12$ Hz), 7.15–6.97 (m, 6H), 5.34 (bs, 1H), 4.00 (t, 4H, $J = 5.59$ Hz), 3.68 (t, 4H, $J = 4.49$ Hz), 3.45 (t, 4H, $J = 5.93$ Hz), 2.77 (t, 4H, $J = 6.59$ Hz), 2.53–2.42 (m, 4H), 2.00–1.88 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.34, 165.36, 139.87, 131.12, 128.90, 126.33, 125.17, 123.45, 67.31, 58.01, 53.84, 44.45, 37.41, 27.79, 24.22; Anal. Calcd for $C_{27}H_{33}N_7O$: C, 68.76; H, 7.05; N, 20.79; Found: C, 68.59; H, 6.98; N, 20.84.

*6.3.2. 4,6-bis(3,4-dihydroquinolin-1(2H)-yl)-N-(3-morpholinopropyl)-1,3,5-triazin-2-amine (**37**)*

Yield: 62%; mp 115–118 °C; FAB-MS: 486 (M + 1); IR (KBr) 3259, 2956, 2813, 1578, 1444, 1309, 1117, 882, 752 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.81 (d, 2H, $J = 8.12$ Hz), 7.19–7.05 (m, 6H), 5.49 (bs, 1H), 4.00 (t, 4H, $J = 5.63$ Hz), 3.71 (t, 4H, $J = 4.45$ Hz), 3.45 (t, 4H, $J = 5.90$ Hz), 2.79 (t, 4H, $J = 5.84$ Hz), 2.49–2.41 (m, 4H), 2.02–1.99 (m, 4H), 1.80–1.67 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 169.20, 165.93, 138.57, 131.96, 128.98, 126.07, 125.52, 124.80, 67.35, 57.24, 54.13, 45.08, 40.23, 27.50, 26.18, 24.08; Anal. Calcd for $C_{28}H_{35}N_7O$: C, 69.25; H, 7.26; N, 20.19; Found: C, 69.38; H, 7.22; N, 20.07.

*6.3.3. N-tert-Butyl-4,6-bis(3,4-dihydroquinolin-1(2H)-yl)-1,3,5-triazin-2-amine (**38**)*

Yield: 73%; mp 99–102 °C; FAB-MS: 415 (M + 1); IR (KBr) 3350, 2957, 2833, 1572, 1436, 1399, 1112, 871, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.73 (d, 2H, $J = 7.80$ Hz), 7.17–7.05 (m, 6H), 5.31 (bs, 1H), 4.01 (t, 4H, $J = 6.01$ Hz), 2.78 (t, 4H, $J = 6.52$ Hz), 2.00 (t, 4H, $J = 6.19$ Hz), 1.37 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): 169.04, 165.08, 138.54, 132.15, 128.76, 126.46, 125.68, 124.90, 45.39, 29.16, 27.45, 24.18; Anal. Calcd for $C_{25}H_{30}N_6$: C, 72.43; H, 7.29; N, 20.27; Found: C, 72.36; H, 7.26; N, 20.22.

*6.3.4. 1,1′-(6-(4-Methylpiperazin-1-yl)-1,3,5-triazine-2,4-diyl)bis(1,2,3,4-tetrahydroquinoline) (**39**)*

Yield: 72%; semisolid; FAB-MS: 442 (M + 1); IR (Neat) 2935, 2849, 2792, 1543, 1487, 1366, 1174, 1004, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.84 (d, 2H, $J = 7.99$ Hz), 7.10–6.95 (m, 6H), 4.01 (t, 4H, $J = 6.03$ Hz), 3.78 (t, 4H, $J = 4.74$ Hz), 2.78 (t, 4H, $J = 6.59$ Hz), 2.41 (t, 4H, $J = 4.88$ Hz), 2.31 (s, 3H), 2.08–1.92 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.34, 165.61, 140.14, 130.94, 128.82, 126.14, 125.05, 123.05, 55.40, 46.67, 44.50, 43.44, 27.96, 24.19; Anal. Calcd for $C_{26}H_{31}N_7$: C, 70.72; H, 7.08; N, 22.20; Found: C, 70.58; H, 7.19; N, 22.13.

*6.3.5. N^1-(4,6-bis(3,4-Dihydroquinolin-1(2H)-yl)-1,3,5-triazin-2-yl)-N^2,N^2-diethylethane-1,2-diamine (**40**)*

Yield: 63%; mp 105–108 °C; FAB-MS: 458 (M + 1); IR (KBr) 3266, 3165, 2962, 2832, 1613, 1576, 1444, 1312, 1100, 886, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.75 (d, 2H, $J = 7.99$ Hz), 7.31–6.98 (m, 6H), 5.56 (bs, 1H), 3.99 (t, 4H, $J = 5.87$ Hz), 3.53 (m, 2H), 2.78 (t, 4H, $J = 6.48$ Hz), 2.45 (m, 6H), 2.03–1.94 (m, 4H), 1.25 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 169.24, 166.10, 138.57, 131.97, 128.99, 126.05, 125.58, 124.80, 51.65, 47.04, 45.08, 38.72, 27.49, 24.09, 12.02; Anal. Calcd for $C_{27}H_{35}N_7$: C, 70.87; H, 7.71; N, 21.43; Found: C, 70.76; H, 7.64; N, 21.45.

*6.3.6. 4-(4,6-bis(3,4-Dihydroquinolin-1(2H)-yl)-1,3,5-triazin-2-yl) morpholine (**41**)*

Yield: 73%; mp 134–136 °C; FAB-MS: 429 (M + 1); IR (KBr) 3074, 2954, 2851, 1537, 1484, 1362, 1111, 855, 761 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.81 (d, 2H, $J = 8.16$ Hz), 7.10–6.96 (m, 6H), 4.00 (t, 4H, $J = 5.98$ Hz), 3.72–3.71 (m, 8H), 2.78 (t, 4H, $J = 6.54$ Hz), 1.94 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): 165.79, 165.34, 140.04, 131.12, 128.90, 126.21, 125.12, 123.31, 67.29, 44.55, 44.13, 27.95, 24.23; Anal. Calcd for $C_{25}H_{28}N_6O$: C, 70.07; H, 6.59; N, 19.61. Found: C, 70.11; H, 6.52; N, 19.43.

*6.4. General procedure for the synthesis of compounds **42**–**47***

The mixture of compound **31** (1 equiv), different amines (1.2 equiv) and K_2CO_3 (1.2 equiv) in dry THF was refluxed for 8 h. The reaction mixture was filtered and the filtrate was evaporated under vacuum. The solid residue was purified with flash column chromatography using chloroform to methanol gradient elution to obtain the targeted compounds **42**–**47**.

*6.4.1. 4,6-bis(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2-morpholinoethyl)-1,3,5-triazin-2-amine (**42**)*

Yield: 67%; mp 104–105 °C; FAB-MS: 472 (M + 1); IR (KBr) 3429, 2928, 2854, 1540, 1444, 1360, 1113, 806, 746 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.14–7.05 (m, 8H), 5.32 (bs, 1H), 4.81 (s, 4H), 3.92 (t, 4H, $J = 5.09$ Hz), 3.62 (t, 4H, $J = 4.53$ Hz), 3.45–3.42 (m, 2H), 2.80 (t, 4H, $J = 5.13$ Hz), 2.48–2.38 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): 166.46, 165.42, 136.30, 134.88, 129.16, 126.91, 126.64, 126.53, 67.35, 58.22, 53.98, 45.99, 41.23, 37.60, 29.47. Anal. Calcd for $C_{27}H_{33}N_7O$: C, 68.76; H, 7.05; N, 20.79. Found: C, 68.61; H, 7.12; N, 20.84.

*6.4.2. 4,6-bis(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(3-morpholinopropyl)-1,3,5-triazin-2-amine (**43**)*

Yield: 65%; mp 102–105 °C; FAB-MS: 486 (M + 1); IR (KBr) 3358, 2929, 2852, 1585, 1492, 1446, 1359, 1115, 931, 750 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.16–7.05 (m, 8H), 5.47 (bs, 1H), 4.81 (s, 4H), 3.93 (t, 4H, $J = 5.51$ Hz), 3.64 (t, 4H, $J = 4.45$ Hz), 3.44–3.35 (m, 2H), 2.79 (t, 4H, $J = 5.48$ Hz), 2.36–2.33 (m, 6H), 1.74–1.60 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.04, 165.01, 135.20, 133.39, 129.13, 126.88, 126.88, 126.59, 126.48, 67.43, 57.57, 54.15, 45.95, 41.17, 40.04, 29.43, 26.81; Anal. Calcd for $C_{28}H_{35}N_7O$: C, 69.25; H, 7.26; N, 20.19; Found: C, 69.17; H, 7.13; N, 20.11.

*6.4.3. N-tert-Butyl-4,6-bis(3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-amine (**44**)*

Yield: 69%; mp 108–110 °C; FAB-MS: 415 (M + 1); IR (KBr) 3425, 2967, 2927, 1577, 1450, 1365, 1226, 927, 745 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.19–7.17 (m, 8H), 5.33 (bs, 1H), 4.90 (s, 4H), 4.02 (t, 4H, $J = 5.80$ Hz), 2.91 (t, 4H, $J = 5.69$ Hz), 1.47 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): 168.99, 164.93, 164.62, 135.72, 133.50, 129.07, 126.88, 126.60, 126.47, 46.04, 41.32, 29.71, 29.40, 29.19; Anal. Calcd for $C_{25}H_{30}N_6$: C, 72.43; H, 7.29; N, 20.27. Found: C, 72.29; H, 7.24; N, 20.32.

*6.4.4. 2,2′-(6-(4-Methylpiperazin-1-yl)-1,3,5-triazine-2,4-diyl)bis(1,2,3,4-tetrahydroisoquinoline) (**45**)*

Yield: 73%; mp 100–102 °C; FAB-MS: 442 (M + 1); IR (KBr) 3017, 2929, 2844, 2763, 1543, 1440, 1364, 1170, 1002, 805, 743 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.19–7.12 (m, 8H), 4.90 (s, 4H), 4.02 (t, 4H, $J = 5.83$ Hz), 3.87 (t, 4H, $J = 4.90$ Hz), 2.88 (t, 4H, $J = 5.72$ Hz), 2.48 (t, 4H, $J = 4.99$ Hz), 2.36 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 166.79, 165.66, 135.80, 135.01, 129.12, 126.90, 126.53, 126.44, 55.49, 46.74, 46.00, 43.50, 41.18, 29.49. Anal. Calcd for $C_{26}H_{31}N_7$: C, 70.72; H, 7.08; N, 22.20. Found: C, 70.79; H, 7.14; N, 22.04.

*6.4.5. N^1-(4,6-bis(3,4-Dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-yl)-N^2,N^2-diethylethane-1,2-diamine (**46**)*

Yield: 61%; mp 94–96 °C; FAB-MS: 458 (M + 1); IR (KBr) 3441, 2967, 2874, 1578, 1441, 1368, 1236, 1040, 803, 744 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.14–7.06 (m, 8H), 5.26 (bs, 1H), 4.80 (s, 4H), 3.92 (t, 4H, $J = 5.47$ Hz), 3.47–3.38 (m, 2H), 2.77 (t, 4H, $J = 5.51$ Hz), 2.61–2.40 (m, 6H), 0.97 (t, 6H, $J = 7.14$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.66, 165.76, 135.70, 134.92, 129.10, 126.86, 126.55, 126.45, 54.46, 47.43, 45.95, 41.16, 38.79, 29.45, 12.24; Anal. Calcd for $C_{27}H_{35}N_7$: C, 70.87; H, 7.71; N, 21.43; Found: C, 70.76; H, 7.74; N, 21.40.

*6.4.6. 4-(4,6-bis(3,4-Dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-yl)morpholine (**47**)*

Yield: 69%; mp 149–152 °C; FAB-MS: 429 (M + 1); IR (KBr) 3073, 2959, 2845, 1546, 1445, 1363, 1114, 804, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.19–7.13 (m, 8H), 4.90 (s, 4H), 4.02 (t, 4H, J = 5.81 Hz), 3.81–3.72 (m, 8H), 2.88 (t, 4H, J = 5.74 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.84, 165.59, 135.76, 134.92, 129.11, 126.88, 126.55, 126.45, 67.40, 45.98, 44.17, 41.19, 29.44; Anal. Calcd for $C_{25}H_{28}N_6O$: C, 70.07; H, 6.59; N, 19.61; Found: C, 70.12; H, 6.51; N, 19.47.

6.5. General procedure for compound synthesis

*(a) General procedure for the synthesis of compounds **48**–**54** and **57**–**63***

The mixture of compound **32** (1 equiv), different amines (2.2 equiv) and K_2CO_3 (2.2 equiv) in dry THF was refluxed for 7–8 h. The reaction mixture was filtered and the solvent was evaporated to dryness under vacuum. The residue was purified with flash column chromatography using chloroform to methanol gradient elution to afford respective compounds **48**–**54**. The same procedure was carried out to synthesize compounds **57**–**63** from **34**.

*(b) General procedure for the synthesis of compounds **55** and **56***

The mixture of compound **32** (1 equiv), 50% ethylamine aqueous solution (10 equiv) in acetone was refluxed for 8 h. The reaction mixture was evaporated to dryness under vacuum. The residue was purified with flash column chromatography using chloroform to methanol gradient elution to afford the targeted compound **55**. The same procedure was carried out to synthesize final compound **56** from the intermediate **34**.

*6.5.1. 6-(3,4-Dihydroquinolin-1(2H)-yl)-N^2,N^4-dipropyl-1,3,5-triazine-2,4-diamine (**48**)*

Yield: 68%; Semisolid; ESMS: 327 (M + 1); IR (KBr) 3382, 3264, 2987, 1571, 1462, 1171, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.83 (m, 1H), 7.11–6.98 (m, 3H), 5.03 (bs, 2H), 4.01 (m, 2H), 3.31 (m, 4H), 2.79 (t, 2H, J = 6.27 Hz), 1.99–1.93 (m, 2H), 1.63–1.49 (m, 4H), 0.95 (t, 6H, J = 7.24 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.17, 139.38, 131.19, 128.88, 126.42, 125.19, 123.53, 44.55, 42.97, 27.83, 24.22, 23.51, 11.91; Anal. Calcd for $C_{18}H_{26}N_6$: C, 66.23; H, 8.03; N, 25.74; Found: C, 66.17; H, 8.01; N, 25.66.

*6.5.2. 6-(3,4-Dihydroquinolin-1(2H)-yl)-N^2,N^4-diisopropyl-1,3,5-triazine-2,4-diamine (**49**)*

Yield: 71%; Semisolid; ESMS: 327 (M + 1); IR (Neat) 3276, 3143, 2928, 2852, 1573, 1436, 1325, 1316, 1224, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.81 (m, 1H), 7.14–6.98 (m, 3H), 4.77 (bs, 2H), 4.14–4.02 (m, 2H), 3.99 (m, 2H), 2.78 (t, 2H, J = 6.14 Hz), 1.99–1.92 (m, 2H), 1.19 (d, 12H, J = 6.34 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 166.11, 165.72, 139.47, 132.17, 129.20, 126.06, 125.90, 124.86, 43.28, 27.37, 26.87, 24.13; Anal. Calcd for $C_{18}H_{26}N_6$: C, 66.23; H, 8.03; N, 25.74; Found: C, 66.21; H, 7.96; N, 25.63.

*6.5.3. 6-(3,4-Dihydroquinolin-1(2H)-yl)-N^2,N^4-bis(3-morpholinopropyl)-1,3,5-triazine-2,4-diamine (**50**)*

Yield: 61%; Semisolid; ESMS: 497 (M + 1); IR (Neat) 3328, 3162, 2967, 1586, 1432, 1357, 1218, 1122, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.82 (m, 1H), 7.10–6.97 (m, 3H), 5.75 (bs, 2H), 3.99 (m, 2H), 3.73 (m, 8H), 3.44 (m, 4H), 2.78 (t, 2H, J = 6.58 Hz), 2.63–2.45 (m, 12H), 1.98–1.92 (m, 2H), 1.77–1.71 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.35, 165.18, 139.83, 131.18, 128.89, 126.43, 125.13, 123.52, 67.35, 57.54, 54.11, 44.46, 40.09, 27.80, 26.51, 24.20; Anal. Calcd for $C_{26}H_{40}N_8O_2$: C, 62.88; H, 8.12; N, 22.56; Found: C, 60.72; H, 8.07; N, 22.50.

*6.5.4. N^2,N^4-Di-tert-butyl-6-(3,4-dihydroquinolin-1(2H)-yl)-1,3,5-triazine-2,4-diamine (**51**)*

Yield: 65%; mp 142–144 °C; ESMS: 355 (M + 1); IR (KBr) 3261, 3144, 2964, 1595, 1502, 1413, 1211, 1066, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.74 (d, 1H, J = 7.84 Hz), 7.16–6.98 (m, 3H), 5.03 (bs, 2H), 3.97 (m, 2H), 2.77 (t, 2H, J = 6.65 Hz), 1.99–1.93 (m, 2H), 1.41 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): 164.87, 139.93, 131.36, 128.70, 126.47, 125.31, 123.45, 51.11, 44.69, 29.78, 27.76, 24.35; Anal. Calcd for $C_{20}H_{30}N_6$: C, 67.76; H, 8.53; N, 23.71; Found: C, 67.72; H, 8.45; N, 23.66.

*6.5.5. N^1,$N^{1'}$-(6-(3,4-Dihydroquinolin-1(2H)-yl)-1,3,5-triazine-2,4-diyl)bis(N^2,N^2-diethylethane-1,2-diamine) (**52**)*

Yield: 63%; mp 97–99 °C; ESMS: 441 (M + 1); IR (KBr) 3263, 3161, 2961, 1614, 1575, 1482, 1309, 1203, 1100, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.81 (d, 1H, J = 7.81 Hz), 7.16–7.01 (m, 3H), 6.14 (bs, 2H), 4.03 (t, 2H, J = 5.76 Hz), 3.56–3.42 (m, 4H), 2.79–2.51 (m, 14H), 2.02–1.97 (m, 2H), 1.01 (t, 12H, J = 7.07 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 169.36, 165.76, 138.62, 132.01, 129.06, 126.06, 125.59, 124.82, 51.84, 47.04, 45.10, 38.71, 27.51, 24.10, 11.97; Anal. Calcd for $C_{24}H_{40}N_8$: C, 65.42; H, 9.15; N, 25.43; Found: C, 65.38; H, 9.02; N, 25.37.

*6.5.6. N^1,$N^{1'}$-(6-(3,4-Dihydroquinolin-1(2H)-yl)-1,3,5-triazine-2,4-diyl)bis(N^2,N^2-dimethylethane-1,2-diamine) (**53**)*

Yield: 63%; Semisolid; ESMS: 385 (M + 1); IR (Neat) 3271, 3152, 2953, 1583, 1471, 1277, 1123, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.82 (d, 1H, J = 7.64 Hz), 7.14–6.97 (m, 3H), 6.09 (bs, 2H), 4.01 (t, 2H, J = 5.81 Hz), 3.56–3.44 (m, 4H), 2.81–2.49 (m, 6H), 2.29 (s, 12H), 2.01 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 165.01, 139.31, 132.25, 128.87, 126.19, 125.35, 124.21, 58.33, 44.61, 43.82, 36.45, 27.29, 24.16; Anal. Calcd for $C_{20}H_{32}N_8$: C, 62.47; H, 8.39; N, 29.14; Found: C, 62.43; H, 8.32; N, 29.06.

*6.5.7. 6-(3,4-Dihydroquinolin-1(2H)-yl)-N^2,N^4-bis(2-morpholinoethyl)-1,3,5-triazine-2,4-diamine (**54**)*

Yield: 62%; Semisolid; ESMS: 469 (M + 1); IR (Neat) 3330, 2945, 2859, 1547, 1437, 1340, 1118, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.81 (m, 1H), 7.11–6.94 (m, 3H), 5.56 (bs, 2H), 4.01 (m, 2H), 3.71 (m, 8H), 3.49–2.41 (m, 4H), 2.79 (t, 2H, J = 6.67 Hz), 2.56–2.47 (m, 12H), 1.99–1.93 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.01, 165.25, 139.80, 131.29, 128.93, 126.37, 125.21, 123.60, 67.27, 58.01, 53.84, 44.52, 37.43, 27.76, 24.24; Anal. Calcd for $C_{24}H_{36}N_8O_2$: C, 61.52; H, 7.74; N, 23.91; Found: C, 61.51; H, 7.66; N, 23.82.

*6.5.8. 6-(3,4-Dihydroquinolin-1(2H)-yl)-N^2,N^4-diethyl-1,3,5-triazine-2,4-diamine (**55**)*

Yield: 62%; Semisolid; ESMS: 299 (M + 1); IR (Neat) 3412, 3278, 2970, 1563, 1478, 1339, 1172, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.86 (m, 1H), 7.15–6.93 (m, 3H), 4.99 (bs, 2H), 4.01 (m, 2H), 3.42–3.34 (m, 4H), 2.79 (t, 2H, J = 6.51 Hz), 1.99–1.93 (m, 2H), 1.18 (t, 6H, J = 7.28 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.25, 139.85, 131.16, 128.90, 126.39, 125.22, 123.49, 44.51, 35.98, 27.83, 24.24, 15.52; Anal. Calcd for $C_{18}H_{26}N_6$: C, 64.40; H, 7.43; N, 28.16; Found: C, 64.36; H, 7.36; N, 28.04.

*6.5.9. N^2,N^4-Diethyl-6-(piperidin-1-yl)-1,3,5-triazine-2,4-diamine (**56**)*

Yield: 64%; Semisolid; ESMS: 251 (M + 1); IR (Neat) 3442, 3282, 2972, 2850, 1592, 1452, 1341, 1281, 1132 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.91 (bs, 2H), 3.71 (m, 4H), 3.41–3.31 (m, 4H), 1.58 (m, 6H), 1.16 (t, 6H, J = 7.23 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.82,

164.95, 44.47, 35.90, 26.23, 25.35, 15.47; Anal. Calcd for $C_{12}H_{22}N_6$: C, 57.57; H, 8.87; N, 33.57; Found: C, 57.52; H, 8.81; N, 33.48.

*6.5.10. 6-(Piperidin-1-yl)-N^2,N^4-dipropyl-1,3,5-triazine-2,4-diamine (**57**)*

Yield: 66%; mp 56–58 °C; ESMS: 279 (M + 1); IR (KBr) 3273, 2959, 2867, 1561, 1469, 1356, 1290, 1175 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.07 (bs, 2H), 3.86–3.72 (m, 4H), 3.32 (m, 4H), 1.59–1.53 (m, 10H), 0.93 (d, 6H, J = 7.06 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.99, 164.95, 44.48, 42.88, 26.22, 25.34, 23.44, 11.90; Anal. Calcd for $C_{14}H_{26}N_6$: C, 60.40; H, 9.41; N, 30.19; Found: C, 60.33; H, 9.37; N, 30.11.

*6.5.11. N^2,N^4-Diisopropyl-6-(piperidin-1-yl)-1,3,5-triazine-2,4-diamine (**58**)*

Yield: 64%; mp 147–149 °C; ESMS: 279 (M + 1); IR (KBr) 3266, 2964, 2852, 1604, 1501, 1440, 1370, 1304, 1195 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.66 (bs, 2H), 4.17–4.07 (m, 2H), 3.69 (m, 4H), 1.58 (m, 6H), 1.17 (d, 12H, J = 6.47 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.74, 165.24, 44.42, 42.51, 26.24, 25.39, 23.42; Anal. Calcd for $C_{14}H_{26}N_6$: C, 60.40; H, 9.41; N, 30.19; Found: C, 60.35; H, 9.38; N, 30.17.

*6.5.12. N^2,N^4-Di-tert-butyl-6-(piperidin-1-yl)-1,3,5-triazine-2,4-diamine (**59**)*

Yield: 63%; Semisolid; ESMS: 307 (M + 1); IR (Neat) 3430, 2968, 2854, 1583, 1506, 1462, 1386, 1215, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.17 (bs, 2H), 3.86 (m, 4H), 1.58 (m, 6H), 1.43 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.70, 54.04, 51.31, 29.63, 29.35, 26.67, 24.02; Anal. Calcd for $C_{16}H_{30}N_6$: C, 62.71; H, 9.87; N, 27.42; Found: C, 62.66; H, 9.79; N, 27.38.

*6.5.13. N^2,N^4-bis(2-Morpholinoethyl)-6-(piperidin-1-yl)-1,3,5-triazine-2,4-diamine (**60**)*

Yield: 65%; Semisolid; ESMS: 421 (M + 1); IR (Neat) 3420, 2935, 2857, 1582, 1469, 1358, 1281, 1116 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.56 (bs, 2H), 3.88 (m, 4H), 3.72 (m, 8H), 3.48 (m, 4H), 2.55–2.43 (m, 12H), 1.62 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 167.46, 67.28, 57.76, 54.27, 53.76, 44.75, 26.22, 25.12; Anal. Calcd for $C_{20}H_{36}N_8O_2$: C, 57.12; H, 8.63; N, 26.64; Found: C, 57.04; H, 8.49; N, 26.56.

*6.5.14. N^2,N^4-bis(3-Morpholinopropyl)-6-(piperidin-1-yl)-1,3,5-triazine-2,4-diamine (**61**)*

Yield: 61%; Semisolid; ESMS: 449 (M + 1); IR (Neat) 3336, 3161, 2934, 2872, 1586, 1437, 1357, 1217, 1118 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.71 (bs, 2H), 3.92 (m, 4H), 3.77 (m, 8H), 3.46 (m, 4H), 2.58–2.45 (m, 12H), 1.77–1.69 (m, 4H), 1.59 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.27, 165.21, 67.26, 57.61, 53.82, 53.26, 44.86, 30.09, 26.27, 25.13; Anal. Calcd for $C_{22}H_{40}N_8O_2$: C, 58.90; H, 8.99; N, 24.98; Found: C, 58.79; H, 8.92; N, 24.86.

*6.5.15. N^1,$N^{1\prime}$-(6-(Piperidin-1-yl)-1,3,5-triazine-2,4-diyl)bis(N^2,N^2-dimethylethane-1,2-diamine) (**62**)*

Yield: 64%; Semisolid; ESMS: 337 (M + 1); IR (Neat) 3276, 2956, 2853, 1583, 1458, 1328, 1243, 1128 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.98 (bs, 2H), 3.94 (m, 4H), 3.55 (m, 4H), 2.70–2.64 (m, 4H), 2.29 (s, 12H), 1.59 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 165.18, 164.76, 59.07, 54.17, 47.18, 45.83, 26.37, 25.26; Anal. Calcd for $C_{16}H_{32}N_8$: C, 57.11; H, 9.59; N, 33.30; Found: C, 57.03; H, 9.52; N, 33.24.

*6.5.16. N^1,$N^{1\prime}$-(6-(Piperidin-1-yl)-1,3,5-triazine-2,4-diyl)bis(N^2,N^2-diethylethane-1,2-diamine) (**63**)*

Yield: 62%; Semisolid; ESMS: 393 (M + 1); IR (Neat) 3402, 2969, 2933, 2854, 1536, 1470, 1361, 1216, 1128 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.94 (bs, 2H), 3.86 (m, 4H), 3.59 (m, 4H), 2.87–2.78 (m, 12H), 1.54 (s, 6H), 1.11 (t, 12H, J = 6.98 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 164.97, 54.30, 52.17, 47.58, 44.50, 26.21, 25.29, 11.36; Anal. Calcd for $C_{20}H_{40}N_8$: C, 61.19; H, 10.27; N, 28.54; Found: C, 61.11; H, 10.13; N, 28.51.

*6.6. General procedure for the synthesis of compounds **64**–**86***

To a mixture of intermediate **32** (1 equiv) and K_2CO_3 (1.5 equiv) in dry THF, respective amines (1 equiv) were added and the reaction mixture was stirred at room temperature for 2 h. After the completion of reaction, isonicotinohydrazide (1.2 equiv) was added to the above reaction mixture and refluxed for 8 h. When the reaction is completed, solvent was evaporated to dryness under vacuum. The solid residue obtained was purified with flash column chromatography using chloroform to methanol gradient elution to obtain the final compounds **64**–**68**. The same procedure was carried out to synthesize targeted compounds **69**–**73**, **74**–**78** and **79**–**86** from the intermediates **33**, **34** and **35** respectively.

*6.6.1. N′-(4-(Butylamino)-6-(3,4-dihydroquinolin-1(2H)-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**64**)*

Yield: 68%; mp 162–164 °C; ESMS: 419 (M + 1); IR (KBr): 3412, 2978, 2925, 2846, 1647, 1553, 1495, 1438, 1251, 1105 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.56 (bs, 1H), 8.69 (bs, 1H), 8.62 (d, 1H, J = 6.45 Hz), 7.81 (m, 2H), 7.05 (m, 2H), 6.72 (m, 1H), 6.56 (m, 1H), 6.88 (bs, 1H), 3.84 (s, 2H), 3.42 (m, 2H), 2.71–2.66 (m, 2H), 1.96 (m, 2H), 1.48 (m, 2H), 1.37 (m, 2H), 0.93 (t, 3H, J = 7.12 Hz); ^{13}C (50 MHz, $CDCl_3$,): 168.35, 167.58, 166.72, 165.24, 151.27, 150.81, 140.62, 128.83, 126.55, 122.24, 120.74, 46.29, 44.35, 32.26, 26.33, 25.26, 20.47, 14.63; Anal. Calcd for $C_{22}H_{26}N_8O$: C, 63.14; H, 6.26; N, 26.78; Found: C, 63.06; H, 6.18; N, 26.73.

*6.6.2. N′-(4-(tert-Butylamino)-6-(3,4-dihydroquinolin-1(2H)-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**65**)*

Yield: 71%; mp 196–198 °C; ESMS: 419 (M + 1); IR (KBr): 3425, 3017, 2937, 2854, 1638, 1526, 1496, 1437, 1249, 1112 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.49 (bs, 1H), 8.77 (bs, 1H), 8.63 (d, 2H, J = 7.92 Hz), 7.78 (m, 2H), 7.09 (m, 2H), 6.74 (m, 1H), 6.57 (m, 1H), 4.13 (bs, 1H), 3.88 (m, 2H), 2.72–2.69 (m, 2H), 1.96 (m, 2H), 1.29 (s, 9H); ^{13}C (50 MHz, $CDCl_3$): 168.56, 167.71, 166.49, 165.13, 151.22, 150.95, 140.38, 128.94, 126.58, 122.30, 120.76, 51.11, 44.64, 29.93, 27.66, 24.23; Anal. Calcd for $C_{22}H_{26}N_8O$: C, 63.14; H, 6.26; N, 26.78; Found: C, 63.17; H, 6.24; N, 26.69.

*6.6.3. N′-(4-(3,4-Dihydroquinolin-1(2H)-yl)-6-(isopropylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**66**)*

Yield: 67%; mp 168–170 °C; ESMS: 405 (M + 1); IR (KBr): 3424, 3019, 2967, 2853, 1609, 1560, 1486, 1437, 1215, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.46 (bs, 1H), 8.90 (bs, 1H), 8.76 (d, 2H, J = 4.76 Hz), 7.68 (m, 2H), 7.09–6.74 (m, 4H), 4.13 (bs, 1H), 3.88 (m, 3H), 2.73–2.68 (m, 2H), 1.81 (m, 2H), 1.12 (d, 6H, J = 7.02 Hz); ^{13}C (50 MHz, $CDCl_3$): 168.71, 166.57, 165.34, 164.75, 151.29, 150.73, 141.34, 128.82, 126.59, 121.61, 120.75, 51.14, 42.49, 27.53, 24.26, 23.57; Anal. Calcd for $C_{21}H_{24}N_8O$: C, 62.36; H, 5.98; N, 27.70; Found: C, 62.31; H, 5.95; N, 27.62.

*6.6.4. N′-(4-(3,4-dihydroquinolin-1(2H)-yl)-6-morpholino-1,3,5-triazin-2-yl)isonicotinohydrazide (**67**)*

Yield: 69%; mp 183–185 °C; ESMS: 433 (M + 1); IR (KBr): 3398, 3012, 2925, 2854, 1608, 1525, 1496, 1437, 1272, 1094 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.55 (bs, 1H), 9.00 (s, 1H), 8.76 (d, 2H, J = 3.58 Hz), 7.77 (m, 2H), 7.57 (d, 1H, J = 8.32 Hz), 7.10 (m, 2H), 6.97 (m, 1H), 3.63–3.53 (m, 8H), 3.16 (m, 2H), 2.66 (m, 2H), 1.79 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): 168.58, 167.42, 166.65, 165.28, 151.33, 150.81, 140.34, 128.86, 126.59, 122.43, 120.62, 67.51, 51.95, 44.63, 27.54, 24.29; Anal. Calcd for $C_{22}H_{24}N_8O_2$: C, 61.10; H, 5.59; N, 25.91; Found: C, 61.13; H, 5.26; N, 25.44.

*6.6.5. N′-(4-(3,4-dihydroquinolin-1(2H)-yl)-6-(3-morpholinopropylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**68**)*

Yield: 58%; mp 167–169 °C; ESMS: 490 (M + 1); IR (KBr): 3409, 2985, 2923, 2856, 1621, 1558, 1499, 1438, 1257, 1105 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.48 (bs, 1H), 9.15 (s, 1H), 8.76 (m, 2H), 7.77 (m, 2H), 7.58 (bs, 1H), 7.09–6.98 (m, 3H), 6.75 (m, 1H), 3.90–3.76 (m, 4H), 3.54 (m, 4H), 2.68 (m, 4H), 2.35 (m, 6H), 1.82 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): 168.72, 167.46, 166.68, 165.13, 151.32, 150.91, 140.33, 128.86, 126.57, 122.38, 120.72, 67.39, 57.37, 53.45, 44.72, 41.31, 27.69, 24.33; Anal. Calcd for $C_{25}H_{31}N_9O_2$: C, 61.33; H, 6.38; N, 25.75; Found: C, 61.32; H, 6.10; N, 25.54.

*6.6.6. N′-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**69**)*

Yield: 67%; mp 87–89 °C; ESMS: 431 (M + 1); IR (KBr): 3359, 3016, 2925, 2857, 1681, 1525, 1445, 1254, 1112 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.61 (bs, 1H), 8.93 (s, 1H), 8.83 (d, 2H, $J = 3.80$ Hz), 7.71 (d, 2H, $J = 3.80$ Hz), 7.19–7.17 (m, 4H), 4.85 (s, 2H), 3.78–3.72 (m, 6H), 2.88 (m, 2H), 1.45–1.32 (m, 6H); ^{13}C ($CDCl_3$, 50 MHz): 168.94, 167.68, 166.35, 165.92, 153.17, 135.43, 135.27, 131.79, 129.56, 128.84, 124.76, 120.91, 48.66, 44.35, 44.16, 31.72, 25.49, 24.93; Anal. Calcd for $C_{23}H_{26}N_8O$: C, 64.17; H, 6.09; N, 26.03; Found: C, 64.08; H, 6.06; N, 26.04.

*6.6.7. N′-(4-(Butylamino)-6-(3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**70**)*

Yield: 70%; mp 116–118 °C; ESMS: 419 (M + 1); IR (KBr): 3346, 3019, 2964, 1599, 1538, 1508, 1455, 1216, 1045 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.48 (bs, 1H), 8.77 (m, 2H), 8.62 (bs, 1H), 7.68 (m, 2H), 7.14 (m, 4H), 6.92 (bs, 1H), 4.79 (s, 2H), 3.80–3.78 (m, 4H), 2.79–2.73 (m, 2H), 1.26–1.21 (m, 4H), 1.02 (t, 3H, $J = 7.21$ Hz); ^{13}C (50 MHz, $CDCl_3$): 168.86, 166.11, 165.95, 164.43, 151.28, 135.76, 135.04, 129.57, 127.19, 122.21, 78.17, 45.82, 42.37, 32.25, 28.86, 20.43, 14.62; Anal. Calcd for $C_{22}H_{26}N_8O$: C, 63.14; H, 6.26; N, 26.78; Found: C, 63.07; H, 6.24; N, 26.70.

*6.6.8. N′-(4-(tert-Butylamino)-6-(3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**71**)*

Yield: 68%; mp 125–127 °C; ESMS: 419 (M + 1); IR (KBr): 3347, 2967, 2929, 1591, 1542, 1501, 1452, 1231, 1106 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.46 (bs, 1H), 8.76 (m, 2H), 8.62 (bs, 1H), 7.78 (m, 2H), 7.14 (m, 4H), 6.35 (s, 1H), 4.67 (s, 2H), 3.90 (m, 2H), 2.81 (m, 2H), 1.22 (s, 9H); ^{13}C (50 MHz, $CDCl_3$): 168.95, 167.38, 165.24, 164.76, 153.15, 135.13, 131.71, 129.63, 129.68, 124.94, 120.75, 51.29, 48.71, 44.13, 31.81, 29.72; Anal. Calcd for $C_{22}H_{26}N_8O$: C, 63.14; H, 6.26; N, 26.78; Found: C, 63.02; H, 6.23; N, 26.80.

*6.6.9. N′-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)-6-(isopropylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**72**)*

Yield: 63%; mp 99–101 °C; ESMS: 405 (M + 1); IR (KBr): 3406, 3025, 2962, 2854, 1647, 1565, 1496, 1448, 1253, 1114 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.42 (bs, 1H), 8.77 (s, 2H), 8.65 (bs, 1H), 7.78 (m, 2H), 7.14 (m, 4H), 4.78 (s, 2H), 4.41 (m, 1H), 3.89–3.80 (m, 4H), 1.11 (d, 6H, $J = 4.84$ Hz); ^{13}C (50 MHz, $CDCl_3$): 167.86, 166.14, 165.95, 164.47, 151.33, 135.72, 134.96, 129.68, 127.14, 122.32, 78.45, 45.71, 42.37, 28.83, 23.41; Anal. Calcd for $C_{21}H_{24}N_8O$: C, 62.36; H, 5.98; N, 27.70; Found: C, 62.32; H, 5.91; N, 27.73.

*6.6.10. N′-(4,6-bis(3,4-Dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**73**)*

Yield: 67%; mp 161–163 °C; ESMS: 479 (M + 1); IR (KBr): 3407, 3024, 2925, 2851, 1683, 1524, 1490, 1448, 1240, 1101 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.52 (bs, 1H), 8.90 (s, 1H), 8.77 (m, 2H), 7.78 (d, 2H, $J = 4.86$ Hz), 7.14 (m, 8H), 4.84 (s, 4H), 3.93 (m, 4H), 3.08 (m, 4H); ^{13}C (50 MHz, $CDCl_3$): 168.75, 166.13, 165.78, 153.35, 135.81, 135.44, 131.67, 129.32, 128.97, 124.85, 120.83, 48.67, 44.18, 31.84; Anal. Calcd for $C_{27}H_{26}N_8O$: C, 67.77; H, 5.48; N, 23.42; Found: C, 67.70; H, 5.36; N, 23.34.

*6.6.11. N′-(4-(Piperidin-1-yl)-6-(pyrimidin-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**74**)*

Yield: 66%; mp 112–114 °C; ESMS: 393 (M + 1); IR (KBr): 3408, 3020, 2929, 2858, 1720, 1567, 1512, 1448, 1216, 1073 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 11.15 (bs, 1H), 8.74 (s, 1H), 8.19 (d, 2H, $J = 4.56$ Hz), 7.68 (m, 2H), 7.19 (d, 2H, $J = 5.28$ Hz), 6.52 (m, 1H), 4.12 (bs, 1H), 3.58–3.49 (m, 4H), 1.54–1.46 (m, 6H); ^{13}C (50 MHz, $CDCl_3$): 168.76, 167.81, 166.43, 165.49, 164.54, 158.87, 150.85, 132.53, 129.58, 110.92, 68.76, 29.24, 24.22; Anal. Calcd for $C_{18}H_{20}N_{10}O$: C, 55.09; H, 5.14; N, 35.69; Found: C, 54.93; H, 5.04; N, 35.66.

*6.6.12. N′-(4-(Butylamino)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl) isonicotinohydrazide (**75**)*

Yield: 72%; mp 143–145 °C; ESMS: 371 (M + 1); IR (KBr): 3386, 2971, 2913, 2856, 1638, 1531, 1498, 1448, 1252, 1068 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.07 (bs, 1H), 9.24 (s, 1H), 8.67 (d, 2H, $J = 3.84$ Hz), 7.71 (d, 2H, $J = 2.12$ Hz), 6.86 (bs, 1H), 3.67 (m, 4H), 3.34–3.16 (m, 2H), 1.54–1.44 (m, 8H), 1.29 (m, 2H), 0.94 (t, 3H, $J = 5.68$ Hz); ^{13}C (50 MHz, $CDCl_3$): 168.24, 166.67, 165.35, 164.27, 151.19, 140.83, 122.35, 44.48, 32.36, 27.64, 24.16, 20.53, 14.62; Anal. Calcd for $C_{18}H_{26}N_8O$: C, 58.36; H, 7.07; N, 30.25; Found: C, 58.28; H, 7.12; N, 30.14.

*6.6.13. N′-(4-(tert-butylamino)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**76**)*

Yield: 68%; mp 110–112 °C; ESMS: 371 (M + 1); IR (KBr): 3412, 2961, 2924, 2856, 1654, 1527, 1495, 1437, 1242, 1093 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.46 (bs, 1H), 9.14 (bs, 1H), 8.74 (d, 2H, $J = 4.48$ Hz), 7.77 (m, 2H), 6.28 (bs, 1H), 3.64 (m, 4H), 1.56–1.42 (m, 6H), 1.21 (s, 9H); ^{13}C (50 MHz, $CDCl_3$): 167.84, 166.75, 165.51, 164.83, 151.27, 141.19, 122.25, 50.82, 44.36, 29.89, 26.24, 25.35; Anal. Calcd for $C_{18}H_{26}N_8O$: C, 58.36; H, 7.07; N, 30.25; Found: C, 58.32; H, 7.12; N, 30.27.

*6.6.14. N′-(4-(Isopropylamino)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)isonicotinohydrazide (**77**)*

Yield: 67%; mp 102–104 °C; ESMS: 357 (M + 1); IR (KBr): 3412, 2965, 2917, 2845, 1610, 1527, 1499, 1447, 1274, 1114 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.12 (bs, 1H), 9.34 (s, 1H), 8.65 (d, 2H, $J = 4.64$ Hz), 7.69 (m, 2H), 4.16 (bs, 1H), 4.02–3.97 (m, 1H), 3.67 (m, 4H), 1.52–1.47 (m, 6H), 1.15 (d, 6H, $J = 4.82$ Hz); ^{13}C (50 MHz, $CDCl_3$): 168.25, 166.63, 165.27, 164.83, 151.28, 140.85, 122.54, 51.47, 47.29, 26.34, 24.31, 23.18; Anal. Calcd for $C_{17}H_{24}N_8O$: C, 57.29; H, 6.79; N, 31.44; Found: C, 57.31; H, 6.70; N, 31.36.

*6.6.15. N′-(4,6-Di(piperidin-1-yl)-1,3,5-triazin-2-yl) isonicotinohydrazide (**78**)*

Yield: 71%; mp 153–155 °C; ESMS: 383 (M + 1); IR (KBr): 3387, 3014, 2924, 2852, 1645, 1530, 1487, 1438, 1254, 1108 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 11.16 (bs, 1H), 10.46 (s, 1H), 8.74 (d, 2H, $J = 3.72$ Hz), 7.73 (d, 2H, $J = 4.34$ Hz), 3.88 (m, 8H), 1.53–1.42 (m, 12H); ^{13}C (50 MHz, $CDCl_3$): 168.44, 165.86, 165.43, 151.21, 141.37, 122.25, 44.36, 26.21, 25.49; Anal. Calcd for $C_{19}H_{26}N_8O$: C, 59.67; H, 6.85; N, 29.30; Found: C, 59.60; H, 6.81; N, 29.18.

*6.6.16. N′-(4-Morpholino-6-(phenylamino)-1,3,5-triazin-2-yl) isonicotinohydrazide (**79**)*

Yield: 66%; mp 180–182 °C; ESMS: 393 (M + 1); IR (KBr): 3414, 2926, 2923, 2854, 1648, 1561, 1502, 1436, 1272, 1113 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.65 (bs, 1H), 9.17 (s, 1H), 9.04 (s, 1H),

8.78 (m, 2H), 7.83 (m, 2H), 7.63 (m, 2H), 7.23 (m, 1H), 6.93 (m, 2H), 3.68–3.64 (m, 8H); ^{13}C (50 MHz, $CDCl_3$): 168.92, 166.75, 164.83, 164.27, 151.61, 140.54, 138.96, 128.16, 122.34, 121.69, 119.82, 66.43, 43.47; Anal. Calcd for $C_{19}H_{20}N_8O_2$: C, 58.15; H, 5.14; N, 28.55; Found: C, 58.02; H, 5.10; N, 28.39.

*6.6.17. N′-(4-(Phenylamino)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl) isonicotinohydrazide (**80**)*

Yield: 62%; mp 193–195 °C; ESMS: 391 (M + 1); IR (KBr): 3409, 2923, 2914, 2855, 1647, 1560, 1501, 1438, 1273, 1112 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.62 (bs, 1H), 9.08 (s, 1H), 8.95 (s, 1H), 8.78 (d, 2H, J = 5.08 Hz), 7.82 (m, 2H), 7.63 (m, 2H), 7.25 (m, 1H), 6.91 (m, 2H), 3.71 (m, 4H), 1.59–1.49 (m, 6H); ^{13}C (50 MHz, $CDCl_3$): 168.47, 166.34, 165.26, 164.43,. 151.39, 141.22, 140.16, 128.97, 122.25, 122.23, 120.48, 44.54, 26.36, 25.29; Anal. Calcd for $C_{20}H_{22}N_8O$: C, 61.52; H, 5.68; N, 28.70; Found: C, 61.44; H, 5.58; N, 28.78.

*6.6.18. N′-(4-(Cyclohexylamino)-6-(phenylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**81**)*

Yield: 75%; mp 157–159 °C; ESMS: 405 (M + 1); IR (KBr): 3421, 2930, 2927, 1679, 1565, 1507, 1438, 1274, 1014 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.60 (bs, 1H), 9.09 (s, 1H), 8.93–8.77 (m, 3H), 7.82–7.67 (m, 4H), 7.21 (m, 1H), 6.90 (m, 2H), 3.85 (bs, 1H), 2.52 (m, 1H), 1.84–1.48 (m, 6H), 1.22 (m, 4H); ^{13}C (50 MHz, $CDCl_3$): 168.51, 166.38, 165.75, 165.13, 151.26, 141.34, 140.78, 128.94, 122.36, 122.15, 52.83, 33.56, 26.22, 25.96; Anal. Calcd for $C_{21}H_{24}N_8O$: C, 62.36; H, 5.98; N, 27.70; Found: C, 62.30; H, 5.86; N, 27.59.

*6.6.19. N′-(4-(3-Morpholinopropylamino)-6-(phenylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**82**)*

Yield: 62%; mp 136–138 °C; ESMS: 450 (M + 1); IR (KBr): 3443, 2928, 3015, 2855, 1682, 1572, 1500, 1436, 1277, 1022 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.62 (bs, 1H), 9.23 (s, 1H), 9.11 (bs, 1H), 8.78 (m, 2H), 7.65 (d, 2H, J = 3.94 Hz), 7.66 (m, 2H), 7.21 (m, 1H), 6.90 (m, 2H), 6.82 (bs, 1H), 3.59 (m, 6H), 2.36 (m, 6H), 1.73–1.70 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): 167.84, 166.61, 165.35, 164.39, 151.25, 141.37, 140.72, 128.98, 122.34, 122.46, 122.13, 66.86, 56.62, 53.77, 38.34, 26.47; Anal. Calcd for $C_{22}H_{27}N_9O_2$: C, 58.78; H, 6.05; N, 28.04; Found: C: 58.64; H: 6.12; N: 27.86.

*6.6.20. N′-(4,6-bis(Phenylamino)-1,3,5-triazin-2-yl) isonicotinohydrazide (**83**)*

Yield: 68%, mp 247–249 °C; ESMS: 399 (M + 1); IR (KBr): 3416, 3012, 2928, 1647, 1534, 1500, 1443, 1261, 1107 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.67 (bs, 1H), 9.26 (s, 1H), 9.19 (bs, 2H), 8.81 (d, 2H, J = 5.76 Hz), 7.87 (d, 2H, J = 1.54 Hz), 7.84–7.55 (m, 4H), 7.28 (m, 2H), 7.12–6.96 (m, 4H); ^{13}C (50 MHz, $CDCl_3$): 168.25, 165.43, 165.18, 164.74, 151.36, 140.81, 140.69, 129.53, 122.54, 122.19, 120.96; Anal. Calcd for $C_{21}H_{18}N_8O$: C, 63.31; H, 4.55; N, 28.12; Found: C, 63.45, H, 4.64; N, 28.04.

*6.6.21. N′-(4-(Butylamino)-6-(phenylamino)-1,3,5-triazin-2-yl) isonicotinohydrazide (**84**)*

Yield: 72%; mp 113–115 °C; ESMS: 379 (M + 1); IR (KBr): 3378, 3026, 2935, 2854, 1659, 1520, 1492, 1437, 1241, 1115 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.43 (bs, 1H), 9.14 (bs, 1H), 8.91–8.76 (m, 3H), 7.78 (m, 4H), 7.47–7.36 (m, 1H), 7.14–7.11 (m, 2H), 6.89 (bs, 1H), 3.44 (m, 2H), 1.49 (m, 2H), 1.35 (m, 2H), 0.91 (t, 3H, J = 7.08 Hz); ^{13}C (50 MHz, $CDCl_3$): 167.85, 166.37, 165.51, 164.84, 151.27, 141.43, 140.76, 128.72, 122.37, 122.19, 122.24, 40.36, 31.45, 19.81, 13.78; Anal. Calcd for $C_{19}H_{22}N_8O$: C, 60.30; H, 5.86; N, 29.61; Found: C, 60.17; H, 5.80; N, 29.59.

*6.6.22. N′-(4-(tert-Butylamino)-6-(phenylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**85**)*

Yield: 58%; mp 147–149 °C; ESMS: 379 (M + 1); IR (KBr): 3428, 3019, 2925, 1610, 1548, 1497, 1443, 1251, 1109 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.57 (bs, 1H), 8.93 (s, 1H), 8.77 (m, 3H), 7.82 (m, 4H), 7.21 (m, 1H), 6.89 (m, 2H), 6.49 (bs, 1H), 1.21 (s, 9H); ^{13}C (50 MHz, $CDCl_3$): 167.84, 166.36, 165.57, 164.71, 151.28, 141.24, 140.78, 128.93, 122.35, 122.15, 122.56, 51.22, 29.86; Anal. Calcd for $C_{19}H_{22}N_8O$: C, 60.30; H, 5.86; N, 29.61; Found: C, 60.16; H, 5.64; N, 29.65.

*6.6.23. N′-(4-(Isopropylamino)-6-(phenylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide (**86**)*

Yield: 64%; mp 215–217 °C; ESMS: 365 (M + 1); IR (KBr): 3430, 3017, 2916, 1692, 1505, 1468, 1439, 1245, 1115 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.59 (bs, 1H), 9.08 (s, 1H), 8.90 (bs, 1H), 8.78 (d, 2H, J = 3.04 Hz), 7.82–7.69 (m, 4H), 7.20 (m, 1H), 6.89 (m, 2H), 4.12 (m, 1H), 1.12 (d, 6H, J = 4.17 Hz); ^{13}C (50 MHz, $CDCl_3$): 168.33, 166.78, 165.85, 165.13, 151.36, 141.34, 140.87, 128.94, 122.35, 122.18, 120.42, 42.34, 23.48; Anal. Calcd for $C_{18}H_{20}N_8O$: C, 59.33; H, 5.53; N, 30.75; Found: C, 59.14; H, 5.49; N, 30.70.

*6.7. Procedure for the synthesis of compound **87***

To a mixture of intermediate **35** (1 equiv) and K_2CO_3 (2 equiv) in dry THF, isonicotinohydrazide (2.1 equiv) was added and the reaction mixture was refluxed at 80 °C for 8 h. After the completion of reaction, the solvent was evaporated to dryness and the solid residue obtained was purified with flash column chromatography using chloroform to methanol gradient elution to afford the compound **87**.

*6.7.1. N′,N″-(6-(Phenylamino)-1,3,5-triazine-2,4-diyl) diisonicotinohydrazide (**87**)*

Yield: 55%; mp 142–144 °C; ESMS: 443 (M + 1); IR (KBr): 3436, 2927, 3015, 1608, 1558, 1496, 1442, 1252, 1103 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 10.58 (bs, 2H), 9.11 (s, 2H), 8.91–8.78 (m, 5H), 7.82–7.65 (m, 6H), 7.20 (m, 1H), 6.89 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): 168.52, 166.36, 165.74, 151.28, 141.93, 140.75, 128.96, 122.43, 122.16, 120.59; Anal. Calcd for $C_{21}H_{18}N_{10}O_2$: C, 57.01; H, 4.10; N, 31.66; Found: C, 57.14; H, 4.02; N, 31.53.

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