Different Heterocycles Functionalized *s*-Triazine Analogues: Design, Synthesis and *In Vitro* Antimicrobial, Antituberculosis, and Anti-HIV Assessment

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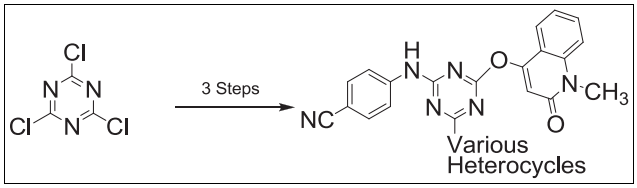


Some new quinolone condensed *s*-triazine derivatives endowed with different heterocycles and 4-aminobenzonitrile moiety has been synthesized and examined for their bioactivities against eight bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Proteus vulgaris*, and *Shigella flexneri*), two fungi (*Aspergillus niger*, *Candida albicans*) by using agar streak dilution method, and *Mycobacterium tuberculosis* H37Rv by using Lowenstein and Jensen MIC method. Upon preliminary biological screening, it was observed that the majority of the compounds were found to possess a significant broad spectrum antimicrobial (MICs: 6.25–25 μg/mL) and antitubercular (MIC: 12.5 μg/mL) potential. Hence, anti-HIV activity against two types of HIV viral strains [HIV-1 (III_B) and HIV-2 (ROD)] has been carried out using the MTT assay. From this bioassay, we have identified some potent inhibitors acting as anti-HIV-1 agents (IC_{50}: 4.45 μg/mL) with promising therapeutic index of 16 for analogue 7 h. The structural assignments of the new products were carried out on the basis of IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis.

INTRODUCTION

Throughout history, there has been a continual battle between humans and the multitude of microorganisms that cause infection and disease. [1]. The contemporary treatment of such opportunistic microbial infectious diseases involves administration of a multidrug regimen over a long period, which has led to the rapid emergence of multidrug-resistant strains and a high level of patient noncompliance [2]. Several reports have shown that antibacterial resistance is increasing at a rapid pace in both community and hospital settings [3]. The therapeutic problem has achieved increasing importance in hospitalized patients, in immune-suppressed patients with AIDS, or undergoing anticancer therapy or organ transplantation. Furthermore, tuberculosis is retrieving its place among theses infectious diseases, and today, nearly one-third of the world's population is infected with *Mycobacterium tuberculosis* with approximately three million patients decreasing every year. The mortality and spread of this disease have been further aggravated by its synergy with HIV. By destroying the two most important cells to the containment of tubercle bacilli (macrophages and CD4-receptor-bearing lymphocytes), HIV vigorously promotes the progression of recent or remotely acquired TB infection to active disease. The deadly synergy between TB and HIV has led to a quadrupling of TB cases in several African and Asian countries [4]. Thus, both the current HIV pandemic and multidrug-resistant *M. tuberculosis* have emerged as major obstacles for public health control. The reverse transcriptase of the HIV type-1 (HIV-1) that causes acquired immune deficiency syndrome (AIDS) in humans is an essential enzyme for the life cycle of the virus [5]. Non-nucleoside RT inhibitors (NNRTIs) are a variety of hydrophobic compounds that are potent noncompetitive inhibitors of the DNA polymerase activity of HIV-1 RT. Unfortunately, HIV-1 RT is a flexible protein with an outstanding ability to tolerate mutations (that develop quite rapidly in virions in AIDS patients treated with anti-HIV-1 drugs), while still remaining functionally active. As a result, many of these RT mutants are resistant to the commonly used anti-RT drugs. Consequently, new inhibitors are constantly required to increase the available arsenal against HIV-1 and to fight AIDS. Hence, an effort has been made to synthesize and screen novel *s*-triazinyl derivatives towards the envisaged biological targets.

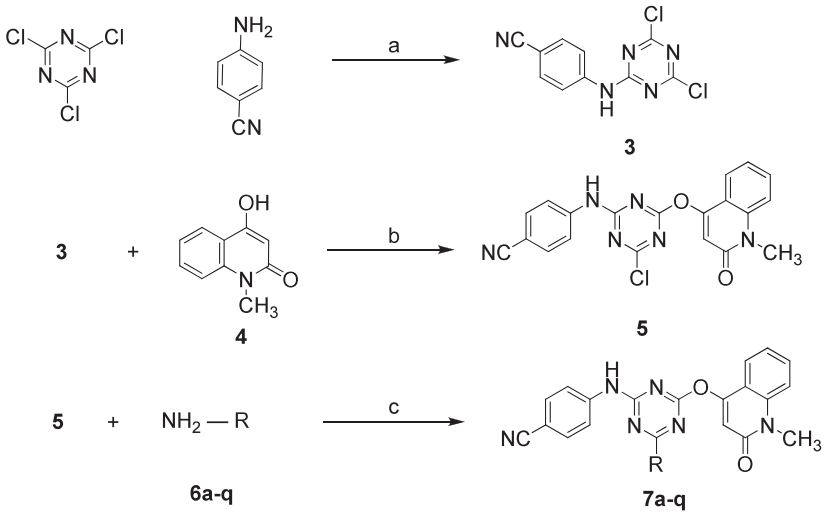
Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. One possible explanation is that

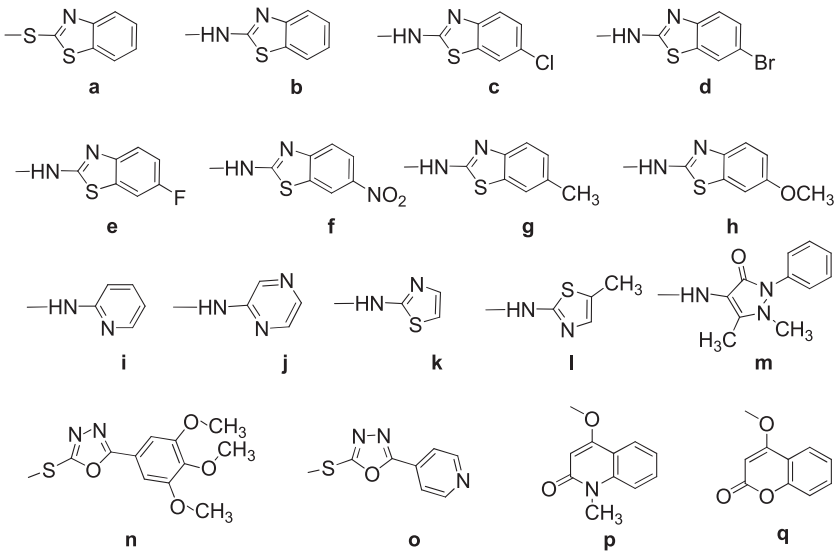
heterocyclic rings have hydrogen bond donors and acceptors in a semirigid framework and they can therefore present a diverse array of pharmacophores [6]. Hence in a view of aforementioned facts, we were directed to substitute various heterocycles to the C-6 position of the *s*-triazine ring in the form of thiazole, benzothioazole, coumarin, quinoline, pyridine, pyrimidine, and oxadiazoles. A vast number of nitrogen-containing heterocyclic building blocks have applications in pharmaceuticals and agrochemical research and drug discovery. Therefore, an attempt has been made to use the well known medicinally important [7–9] 1,3,5-triazine ring as a nucleus of the resultant analogues. Benzothiazole derivatives hold a broad potential for various bioactivities as inhibitors of HIV-1 [10] and antimicrobial agents [11,12]. Furthermore, we have recently reported the antimicrobial efficacies of the combination of quinoline/coumarin–triazine ring systems [13]. In addition, we have also reported the importance of incorporation of oxadiazole nucleus to the *s*-triazine ring as antimicrobial agents [14]. In a view of the aforementioned findings, we have synthesized some novel *s*-triazine bases derivatives involving substitution of biolabile pharmacophores.

RESULTS AND DISCUSSION

Chemistry. The synthesis of compounds **7a–q** was undertaken as in Scheme 1. The first step expressed the formation of intermediate **3** in very good yield 90% by

Scheme 1. Reagents and conditions: (a) 4-aminobenzonitrile, acetone, K_2CO_3, 0–5°C, 4–5 h; (b) 4-hydroxy-*N*-methylquinolin-2(1*H*)-one acetone, K_2CO_3, 40–45°C, 6–7 h; (c) substituted heterocycles, THF, K_2CO_3, reflux, 6–24 h.





the nucleophilic displacement of one chlorine atom of *s*-triazine ring by 4-aminobenzonitrile in the presence of anhydrous potassium carbonate in acetone solvent at 0–5°C. Compound **3** displayed an absorption band at 2228 cm^{-1} confirming the presence of a C≡N group, and a strong band near 3277 cm^{-1} further confirmed the presence of an –NH group. The synthesis of disubstituted *s*-triazine intermediate 4-(4-chloro-6-(1-methyl-2-oxo-1,2-dihydroquinilin-4-yloxy)-1,3,5-triazin-2-ylamino)-benzonitrile **5** was achieved in 88% of yield by the reaction between 4-(4,6-dichloro-1,3,5-triazin-2-ylammino)benzonitrile **3** and 4-hydroxy-*N*-methylquinolin-2(1*H*)-one in the presence of anhydrous potassium carbonate in acetone solvent at 45–50°C. A characteristic band appearing at 1256 cm^{-1} corresponded to the C– O– C linkage in the IR spectra of compound **5**. Subsequent coupling of the so-formed compound **5** with the desired substituted heterocycles in the presence of anhydrous potassium carbonate in tetrahydrofuran solvent at reflux temperature provided the target compounds **7a–q**. This reaction proceeded in good yield and is general for different substituted heterocycles. The correct synthesis of **7a–q** was confirmed on the basis of IR, ^{1}H NMR, and ^{13}C NMR spectral analyses, and the purity was ascertained by elemental analysis.

Pharmacology.

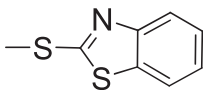
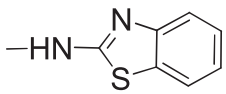
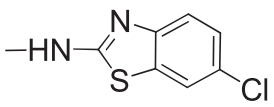
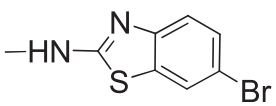
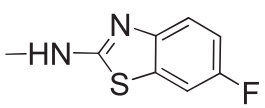
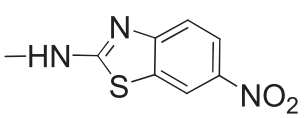
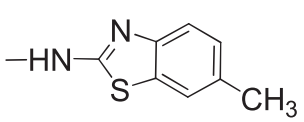
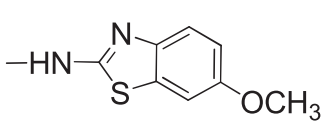
***In vitro* antimicrobial activity.** The newer analogues were investigated for their antimicrobial activities, and the results are summarized in Tables 1 and 2. Furthermore, we have studied the effects of various functional groups attached to the *s*-triazine-condensed heterocycles towards the different bacteria, fungi, and viral strains, and from these results, it can be stated that bioactivities can vary by varying the functional groups to a large extent. The presence of electron-withdrawing or electron-donating substituent significantly affects the relative bioactivities. In case of antibacterial activity of the final scaffolds, those with halogen substituents **7c**, **7d**, and **7e** showed significant growth inhibitory potential against both the Gram-positive bacteria at an MIC of 6.25–12.5 μg/mL and against Gram-negative strain *Pseudomonas aeruginosa* at an MIC of 25 μg/mL. However, it can be said that analogues with the highly electronegative fluoro substituent **7e** were more active when compared with other derivatives with remaining halogens. The order of increased activity against the mentioned panel of microorganisms was F > Br > Cl. Additionally in case of antifungal activity, both the final analogues with bromo **7d** or fluoro **7e** substituent showed potential inhibition towards the growth of *Candida albicans* fungi at 25 μg/mL of MIC, whereas an analogue with strong electron-withdrawing nitro functional group **7f** displayed potential bioactivity against *Aspergillus niger* fungi at an MIC of 12.5 μg/mL. Final derivatives contained heterocycles bearing electron-donating alkyl or alkoxy substituents, and it can be seen that their presence significantly affected the bioprofiles of the resultant analogues. Final derivative with alkyl methyl functional group either in the form of thiazole **7l**, benzothiazole **7g**, or nitro-heterocycle **7m** moiety showed diminished antibacterial efficacies against *Klebsiella pneumoniae* at an MIC level of 50 μg/mL, whereas the presence of an alkoxy group in the benzothiazole **7h** and oxadiazole **7n** moieties condensed to the *s*-triazine ring indicated improved activity against both the Gram-positive strain and Gram-negative *Escherichia coli* (MIC range: 6.25–25 μg/mL). In the present research work, the condensation of nitrogen rich pyridine and pyrazine moieties was also attempted, and the said analogues **7i** and **7j** were found potentially active against Gram-negative *Shigella flexneri* at an MIC of 25 μg/mL. The analogues **7p** and **7q** can be viewed as a combination of two similar quinolone moiety in the *s*-triazine ring: they gave excellent activity against *Salmonella typhi* (MIC: 12.5 μg/mL); however, replacement of the quinolone moiety by a coumarin made the molecule strongly active against *P. aeruginosa* and *Proteus vulgaris* (MIC: 25 and 50 μg/mL, respectively), along with anti *P. vulgaris* activity of **7a** at an MIC of 50 μg/mL. The large number of remaining analogues displayed good to moderate antimicrobial activities against the mentioned panel of microorganisms at an MIC range of 50–100 μg/mL.

***In vitro* antituberculosis activity.** *In vitro* antituberculosis activity of the newer analogues was examined using Lowenstein and Jensen (LJ) MIC method, and the results are presented in μg/mL of MIC and percentage inhibition of *M. tuberculosis* H37Rv at the respective concentration in Table 3. The majority of the analogues were active against H37Rv. An analogue with three electron-donating methoxy groups in addition to oxadiazole ring system **7n** showed the highest inhibition of mycobacteria with 99% inhibition efficacy at 12.5 μg/mL of MIC. This compound was considered as the most potent antituberculosis agents among the 17 studied. The analogue with the electron-withdrawing fluoro substituent **7e** was the second most active analogue in this bioassay with a similar percentage inhibition potency at an MIC of 25 μg/mL. Furthermore, two of the analogues namely **7d** with a bromo-benzothiazole substituent and **7p** with a quinolone substituent provided 97% and 96%, respectively, inhibition of H37Rv at 50 μg/mL. Additionally, three of the molecules, such as **7h** with a methoxy substituent, **7m** with two methyl groups, and **7o** with pyridyl oxadiazole moieties, showed 96–97% of mycobacterial inhibition at 62.5 μg/mL of MIC. All the remaining analogues exhibited moderate to poor activity against the mycobacterial strain used.

***In vitro* anti-HIV activity.** In the present research work, the *in vitro* anti-HIV activity of the analogue was determined by MTT bioassay method against HIV-1 (III_B) and type-2 (ROD), and the results are summarized in Table 4. The data are given as EC_{50} values (compound

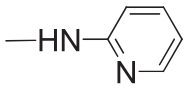
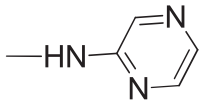
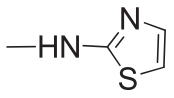
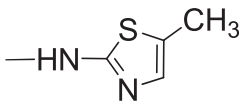
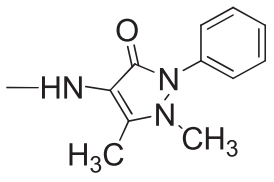
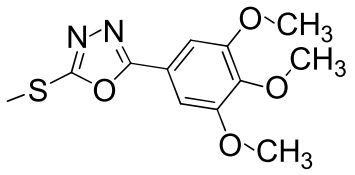
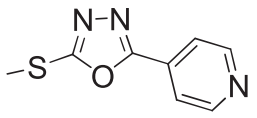
Table 1

In vitro antibacterial activity.

		MIC in μg/mL							
		Gram-positive		Gram-negative					
Compounds	*R*	*S.a*	*B.c*	*E.c*	*P.a*	*K.p*	*S.t*	*P.v*	*S.f*
7a		200	100	50	100	100	500	**50**	50
7b		250	100	200	500	200	500	100	100
7c		25	50	100	100	250	100	200	100
7d		12.5	25	50	**25**	100	200	100	50
7e		**6.25**	**12.5**	100	**25**	100	100	100	50
7f		50	25	100	50	200	250	100	50
7g		100	250	250	500	**50**	200	250	250
7h		50	100	**25**	100	100	100	200	100

(*Continued*)

Table 1
(Continued)

Compounds	*R*	MIC in μg/mL							
		Gram-positive		Gram-negative					
		S.a	*B.c*	*E.c*	*P.a*	*K.p*	*S.t*	*P.v*	*S.f*
7i		250	500	500	100	500	500	500	**25**
7j		200	500	500	200	250	500	500	**25**
7k		100	250	250	100	500	500	250	100
7l		100	250	200	500	**50**	200	500	500
7m		50	100	100	100	**50**	100	200	250
7n		**6.25**	**6.25**	**25**	50	100	100	250	50
7o		12.5	**6.25**	50	200	250	250	200	100

(*Continued*)

Table 1
(Continued)

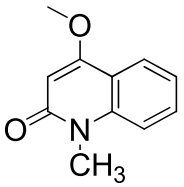
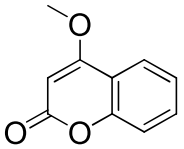
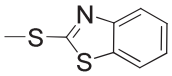
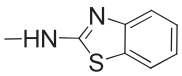
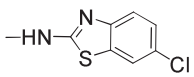
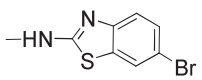
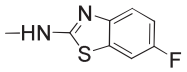
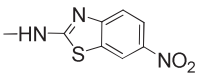
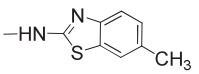
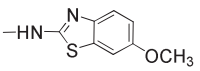
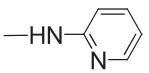
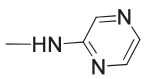
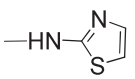
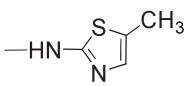
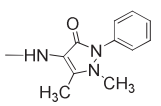
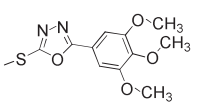
Compounds	*R*	MIC in μg/mL							
		Gram-positive		Gram-negative					
		S.a	*B.c*	*E.c*	*P.a*	*K.p*	*S.t*	*P.v*	*S.f*
7p		100	200	100	50	200	**12.5**	100	250
7q		250	100	250	**25**	500	500	**50**	500
	DMSO	—	—	—	—	—	—	—	—
	Ampicillin	12.5	12.5	6.25	25	25	25	12.5	50
	Gentamicin	6.25	6.25	12.5	12.5	25	12.5	6.25	25
	Ciprofloxacin	1.0	1.0	1.0	1.0	1.0	1.0	1.0	≤3

Table 2
In vitro antifungal activity.

Compounds	*R*	MIC in μg/mL	
		A. niger	*C. albicans*
7a		50	500
7b		200	500
7c		100	50
7d		50	**25**

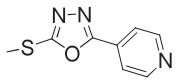
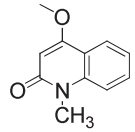
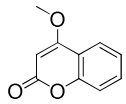
(*Continued*)

Table 2
(Continued)

Compounds	*R*	MIC in μg/mL	
		A. niger	*C. albicans*
7e		25	**25**
7f		**12.5**	50
7g		500	500
7h		100	100
7i		500	>500
7j		250	>500
7k		500	500
7l		500	500
7m		200	500
7n		25	50

(*Continued*)

Table 2
(Continued)

Compounds	*R*	MIC in μg/mL	
		A. niger	*C. albicans*
7o		50	200
7p		100	250
7q		200	250
	DMSO	—	—
	Fluconazole	6.25	12.5
	Ketoconazole	≤3	1.0

concentration required to protect MT-4 cells against viral cytopathogenicity by 50%), CC_{50} value (compound concentration that decreases the uninfected MT-4 cell viability by 50%), and selectivity index (ratio of CC_{50}/EC_{50}). The analogue with the 6-methoxy benzothiazole substituent **7h** linked through an amino linkage to the basic *s*-triazine core displayed activity at an EC_{50} level of 4.45 μg/mL against HIV-1 (III_B), whereas being minimal cytotoxic at 72.13 μg/mL, thus achieving a selectivity index of 16. This compound was the most potent and (and only) selective anti-HIV analogue. Some of the derivatives studied such as **7c**, **7d**, and **7e** with halo-substituents (–Cl, –Br, and –F) showed EC_{50} values of >2.19, >14.50, and >2.26 μg/mL but were cytotoxic at these concentrations. In addition, a single analogue from those bearing an alkyl functional group (**7g**) displayed an EC_{50} of >3.88 μg/mL against HIV-1 (III_B) but again, was cytotoxic at this concentration. All the remaining analogues were inactive against HIV and cytotoxic at concentrations of >65 to >125 μg/mL.

EXPERIMENTAL

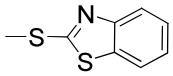
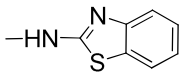
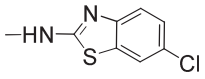
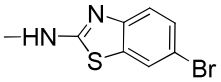
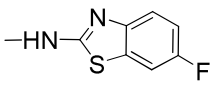
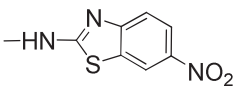
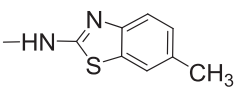
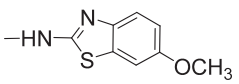
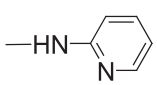
2,4,6-Trichloro-1,3,5-triazine, 4-hydroxy-*N*-methylquinolin-2(1*H*)-one, and 4-aminobenzonitrile were purchased from Sigma-Aldrich, Germany. Acetone and tetrahydrofuran were AR grade and purchased from Merck, India and were used without further purification. Coupled heterocycles as **6a, 6b**, and **6m** were purchased from Spectrochem Pvt. Ltd, Vadodara, India and **6i, 6j**, and **6k** were purchased from ACS chemicals Pvt. Ltd, Ahmedabad, India. Heterocycle **6l** and **6q** were gifts from Nivika Chemo Pharma Pvt. Ltd, Ankleshwar, India and Ami Organics Pvt. Ltd, Sachin, India, respectively.

Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. IR spectra (4000–400 cm^{-1}) of synthesized compounds were recorded on a Shimadzu 8400–S FTIR spectrophotometer (Shimadzu India Pvt. Ltd., Mumbai, India) using KBr pellets. TLC was performed on object glass slides (2 × 7.5 cm) coated with silica gel G, and spots were visualized under UV irradiation. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz model spectrometer (Varian India Pvt. Ltd., Mumbai, India) by using DMSO as a solvent and TMS as internal standard with ^1H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. The ^1H NMR and ^{13}C NMR chemical shifts (δ) were reported as parts per million (ppm) downfield from TMS (Me_4Si) and were performed at Center for Excellence, Vapi, India. The splitting patterns are designated as follows; s, singlet; br s, broad singlet; d, doublet; m, multiplet. Elemental analyses (C, H, N) were performed using a Heraeus Carlo Erba 1180 CHN analyzer (Hanau, Germany).

General synthetic procedure for 2-amino-6-substituted benzothiazoles (6c–h). A mixture of (0.1 mol) of 4-substituted aniline and 19.43 g (0.2 mol) of potassium thiocyanate (KCNS) in 100 mL glacial acetic acid (AcOH) was cooled in an ice bath and stirred for 10–20 min, and then,

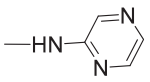
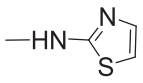
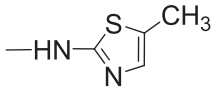
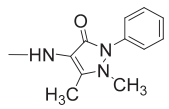
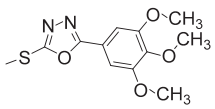
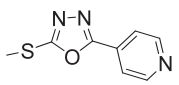
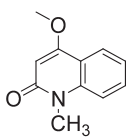
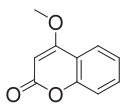
Table 3

In vitro antituberculosis activity.

		LJ MIC method[a]	
Compounds	*R*	MIC (μg/mL)	Inhibition (%)
7a		100	96
7b		200	95
7c		100	95
7d		50	97
7e		25	99
7f		100	95
7g		250	94
7h		62.5	97
7i		500	94

(*Continued*)

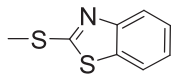
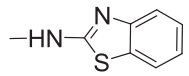
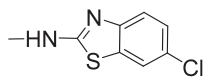
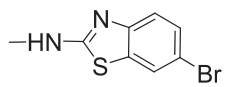
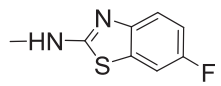
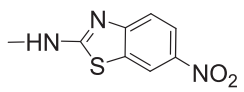
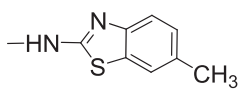
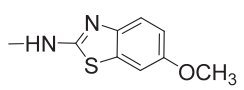
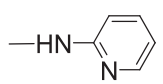
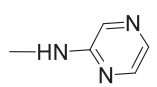
Table 3
(Continued)

Compounds	*R*	LJ MIC method[a] MIC (μg/mL)	Inhibition (%)
7j		250	96
7k		200	94
7l		100	96
7m		62.5	96
7n		**12.5**	**99**
7o		62.5	97
7p		50	96
7q		100	96
	Isoniazid	0.20	99
	Rifampicin	0.25	99
	Ethambutol	3.12	99
	Pyrazinamide	6.25	99

[a]Each value is the mean of three independent experiments.

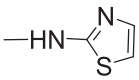
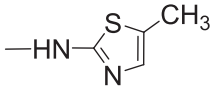
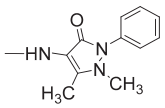
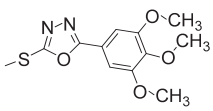
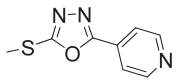
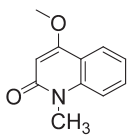
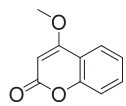
Table 4

In vitro anti-HIV activity.

Compounds	*R*	EC_{50} (μg/mL)[a] HIV-1 (III_B)	EC_{50} (μg/mL)[a] HIV-2 (ROD)	CC_{50} (μg/mL)[b]	SI[c] (HIV-1 III_B)
7a		>72.78	>72.78	72.78	<1
7b		>82.93	>82.93	82.93	<1
7c		>2.19	>2.19	2.19	<1
7d		>14.50	>14.50	14.50	<1
7e		>2.26	>2.26	2.26	<1
7f		>69.28	>69.28	69.28	<1
7g		>3.88	>3.88	3.88	<1
7h		**4.45**	>72.13	**72.13**	**16**
7i		>74.10	>74.10	≥74.10	≤1
7j		>83.58	>83.58	83.58	<1

(Continued)

Table 4
(Continued)

Compounds	*R*	EC_{50} (μg/mL)[a] HIV-1 (III_B)	EC_{50} (μg/mL)[a] HIV-2 (ROD)	CC_{50} (μg/mL)[b]	SI[c] (HIV-1 III_B)
7k		>107.88	>107.88	107.88	<1
7l		>125.00	>125.00	>125.00	1
7m		>125.00	>125.00	>125.00	1
7n		>65.13	>65.13	65.13	<1
7o		>68.75	>68.75	68.75	<1
7p		>79.48	>79.48	79.48	<1
7q		>69.20	>69.20	69.20	<1
	Nevirapine	0.040		>4.00	>101
	Zidovudine	0.0032	0.0036	>25.00	>7899
	Dideoxycytidine	0.37	0.49	>20.00	>55
	Efavirenz	0.0018		>2.00	>1133
	Delaviridine	0.025		>2.00	>81

[a]Compound concentration required to protect MT-4 cells against viral cytopathogenicity by 50%.
[b]Compound concentration that decreases the uninfected MT-4 cell viability by 50%.
[c]Selectivity index: CC_{50}/EC_{50} ratio (WT).

5.1 mL (0.1 mol) bromine in 25 mL glacial acetic acid was added dropwise at such a rate to keep the temperature below 10°C throughout the addition. The reaction mixture was stirred at room temperature for 2–4 h, the hydrobromide (HBr) salt thus separated out was filtered, washed with acetic acid, dried, dissolved in hot water, and brought up to pH 11.0 with ammonia solution (NH_4OH), and the resulting precipitate was filtered, washed with water, and dried to obtain the desired product **6c–h** [15,16]. The progress of the reaction was monitored by TLC using toluene:acetone (8:2) solvent system.

Compounds *2-(methylthio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole* (***6n***) and *5-Pyridin-4-yl-1,3,4-oxadiazole-2-thiol* (***6o***) were synthesized by following the procedure described earlier [17,18].

Compounds *4-(4,6-dichloro-1,3,5-triazin-2-ylamino)benzonitrile* (**3**) and *4-(4-chloro-6-(1-methyl-2-oxo-1,2-dihydroquinilin-4-yloxy)-1,3,5-triazin-2-ylamino)-benzonitrile* (**5**) were synthesized according to the procedure described in the literature [19].

General procedure for the synthesis of 4-(substituted phenylamine)-6-(4-cyanophenylamino)-1,3,5,-triazine-2-yloxy)-1-methylquinolin-2(1*H*)-one (7a–q). Mixture of compound **5** (1.01 g, 2.5 mmol), anhydrous potassium carbonate (0.35 g, 2.5 mmol), and substituted heterocycles **6a–q** (2.5 mmol) in 50 mL tetrahydrofuran. The reaction mixture was refluxed for 5–24 h in a water bath; progress of the reaction was monitored by TLC using toluene/acetone (7:3, v/v) solvent system as an eluent. After the completion of the reaction, the resultant mixture was poured in crushed ice. The solid product was obtained, filtered, washed with distilled water, and dried and purified by column chromatography using toluene:acetone system as an eluent.

4-(4-(Benzo[d]thiazol-2-ylthio)-6-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7a). This compound was obtained as off-white solid, yield 1.29 g (96%), mp 230°C; IR (KBr): 3275 (N–H), 2223 (C≡N), 1648 (C═O), 1570 (C═N in BT), 1348 (C–N), 1259 (C–O–C), 835 (C_3N_3, *s*-triazine), 648 (C–S) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.76 (s, 1H, –NH proton of *s*-triazine to aminobenzonitrile linkage), 8.16 (d, $J = 7.5$ Hz, 1H, C-8 proton of quinoline), 7.75 (t, $J = 7.6$ Hz, 1H, C-7 proton of quinoline), 7.66 (d, $J = 8.3$ Hz, 1H, C-5 proton of quinoline), 7.58 (t, $J = 8.1$ Hz, 1H, C-6 proton of quinoline), 7.46–7.20 (m, 8H, Ar–H proton of aromatic), 6.78 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.71 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 172.42 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 166.12, 165.08 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and C–S of *s*-triazine to mercaptobobenzothiazole linkage), 162.98 (1C, –C═O of hydroxy quinoline moiety), 157.13 (1C, C–S, of mercaptobenzothiazole), 151.28, 149.83, 148.09, 146.8, 144.39, 142.98, 141.01, 138.78, 136.43, 134.69, 130.28, 128.47, 126.01, 124.89, 121.63, 120.09, 119.01, 116.20 (18C, Ar–C of aromatic), 105.1 (1C, –C≡N of aminobenzonitrile), 103.00 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 96.5 (1C, –C–C≡N of aminobenzonitrile), 30.67 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal*. Calcd for $C_{27}H_{17}N_7O_2S_2$: C, 60.55; H, 3.20; N, 18.31. Found: C, 60.48; H, 3.12; N, 18.36.

4-(4-(Benzo[d]thiazol-2-ylamino)-6-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7b). This compound was obtained as brown solid, yield 0.82 g (63%), mp 224–226°C; IR (KBr): 3278 (N–H), 2221 (C≡N), 1656 (C═O), 1565 (C═N in BT), 1329 (C–N), 1262 (C–O–C), 843 (C_3N_3, *s*-triazine), 654 (C–S) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.66 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage and benzothiazole linkage), 10.08 (s, 1H, –NH proton of *s*-triazine to benzothiazole linkage), 8.20 (d, $J = 7.2$ Hz, 1H, C-8 proton of quinoline), 7.71 (t, $J = 7.6$ Hz, 1H, C-7 proton of quinoline), 7.64 (d, $J = 8.2$ Hz, 1H, C-5 proton of quinoline), 7.56 (t, $J = 7.9$ Hz, 1H, C-6 proton of quinoline), 7.47–7.19 (m, 8H, Ar–H proton of aromatic), 6.83 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.66 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 173.10 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 165.98, 164.28 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and benzothiazole linkage), 161.88 (1C, –C═O of hydroxy quinoline moiety), 158.33 (1C, C–S, of benzothiazole), 152.34, 150.98, 149.08, 147.68, 145.86, 141.88, 140.01, 138.98, 137.05, 135.69, 133.68, 131.47, 128.88, 127.01, 125.63, 123.58, 122.01, 121.39 (18C, Ar–C of aromatic), 105.49 (1C, –C≡N of aminobenzonitrile moiety), 103.98 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 96.58 (1C, –C–C≡N of aminobenzonitrile moiety), 31.67 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal*. Calcd for $C_{27}H_{18}N_8O_2S$: C, 62.54; H, 3.50; N, 21.61. Found: C, 62.63; H, 3.44; N, 21.57.

4-(4-(6-Chlorobenzo[d]thiazol-2-ylamino)-6-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7c). This compound was obtained as off-white solid, yield 0.91 g (71%), mp195°C; IR (KBr): 3272 (N–H), 2228 (C≡N), 1649 (C═O), 1579 (C═N in BT), 1338 (C–N), 1267 (C–O–C), 834 (C_3N_3, *s*-triazine), 738 (C–Cl), 651 (C–S) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.59, (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage and benzothiazole linkage), 9.91 (s, 1H, –NH proton of *s*-triazine to aminobenzothiazole linkage) 8.16 (d, $J = 7.4$ Hz, 1H, C-8 proton of quinoline), 7.81 (t, $J = 7.3$ Hz, 1H, C-7 proton of quinoline), 7.67 (d, $J = 8.2$ Hz, 1H, C-5 proton of quinoline), 7.55 (t, $J = 7.8$ Hz, 1H, C-6 proton of quinoline), 7.50 (d, $J = 1.7$ Hz, 1H, C-5 proton of benzothiazole), 7.44–7.19 (m, 6H, Ar–H proton of aromatic), 6.82 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.68 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 171.98 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 167.12, 164.28 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and benzothiazole linkage), 160.99 (1C, –C═O of hydroxy quinoline moiety), 156.88 (1C, C–S, of benzothiazole), 150.58, 149.03, 147.95, 145.62, 144.09, 141.88, 140.01, 139.07, 137.83, 136.09, 133.28, 131.67, 130.01, 128.12, 125.06, 122.19, 120.44, 117.39 (18C, Ar–C of aromatic), 104.98 (1C, –C≡N of aminobenzonitrile moiety), 102.09 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 96.88 (1C, –C–C≡N of aminobenzonitrile moiety), 30.69 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal*. Calcd for $C_{27}H_{17}ClN_8O_2S$: C, 58.64; H, 3.10; N, 20.26. Found: C, 58.57; H, 3.16; N, 20.34.

4-(4-(6-Bromobenzo[d]thiazol-2-ylamino)-6-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7d). This compound was obtained as off-white solid, yield 0.99 g (66%); mp 227°C; IR (KBr): 3277 (N–H), 2222 (C≡N), 1658 (C═O), 1566 (C═N in BT), 1332 (C–N), 1268 (C–O–C), 832 (C_3N_3, *s*-triazine), 643 (C–S); 568 (C–Br) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.69 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 9.72 (s, 1H, –NH proton of *s*-triazine to benzothiazole linkage), 8.20 (d, $J = 7.5$ Hz, 1H, C-8 proton of quinoline), 7.79 (t, $J = 7.6$ Hz, 1H, C-7 proton of quinoline), 7.71 (d, $J = 1.4$ Hz, 1H, C-5 proton of benzothiazole), 7.63 (d, $J = 8.2$ Hz, 1H, C-5 proton of quinoline), 7.59 (t, $J = 7.8$ Hz, 1H, C-6 proton of quinoline), 7.45–7.21 (m, 6H, Ar–H proton of aromatic), 6.83 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.66 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C

NMR (DMSO-d_6): δ 171.69 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 166.46, 165.25 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and benzothiazole linkage), 162.01 (1C, –C═O of hydroxy quinoline moiety), 156.46 (1C, C–S, of benzothiazole), 151.78, 150.01, 148.89, 147.11, 145.63, 143.98, 142.21, 140.26, 138.49, 136.09, 135.02, 133.14, 130.01, 128.89, 126.47, 124.09, 121.69, 118.87 (18C, Ar–C of aromatic), 105.68 (1C, –C≡N of aminobenzonitrile moiety), 103.20 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 97.51 (1C, –C–C≡N of aminobenzonitrile moiety), 30.56 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal*. Calcd for $C_{27}H_{17}BrN_8O_2S$: C, 54.28; H, 2.87; N, 18.76. Found: C, 54.21; H, 2.83; N, 18.82.

4-(4-(6-Fluorobenzo[d]thiazol-2-ylamino)-6-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7e). This compound was obtained as brown solid, yield 1.01 g 75%, mp 225°C; IR (KBr): 3275 (N–H), 2225 (C≡N), 1643 (C═O), 1579 (C═N in BT), 1359 (C–N), 1259 (C–O–C), 1043 (C–F), 839 (C_3N_3, *s*-triazine), 648 (C–S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.84 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 10.16 (s, 1H, –NH proton of *s*-triazine to benzothiazole linkage), 8.14 (d, J = 7.3 Hz, 1H, C-8 proton of quinoline), 7.75 (t, J = 7.4 Hz, 1H, C-7 proton of quinoline), 7.65 (d, J = 7.9 Hz, 1H, C-5 proton of quinoline), 7.57 (t, J = 8.2 Hz, 1H, C-6 proton of quinoline), 7.54 (dd, J = 8.4, 2.4 Hz, 1H, C-7 proton of benzothiazole), 7.46–7.21 (m, 5H, Ar–H proton of aromatic), 7.12 (dt, J = 8.1, 2.2 Hz, 1H, C-5 proton of benzothiazole), 6.70 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.63 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 173.40 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 166.12, 165.08 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and benzothiazole linkage), 162.96 (1C, –C═O of hydroxy quinoline moiety), 157.83 (1C, C–S, of benzothiazole), 150.69, 149.13, 147.91, 145.78, 144.03, 142.87, 141.15, 139.95, 137.43, 134.99, 133.12, 130.84, 127.46, 125.89, 124.03, 122.44, 120.01, 118.98 (18C, Ar–C of aromatic), 105.25 (1C, –C≡N of aminobenzonitrile moiety), 102.66 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 97.35 (1C, –C–C≡N of aminobenzonitrile moiety), 29.99 (1C, ——N–CH_3 of hydroxy quinoline moiety). *Anal*. Calcd for $C_{27}H_{17}FN_8O_2S$: C, 60.44; H, 3.19; N, 20.88. Found: C, 60.38; H, 3.24; N, 20.79.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(6-nitrobenzo[d]thiazol-2-ylamino)-1,3,5-triazin-2-ylamino)benzonitrile (7f). This compound was obtained as light yellow solid, yield 1.03 g (73%), mp 200°C; IR (KBr): 3279 (N–H), 2228 (C≡N), 1652 (C═O), 1569 (C═N in BT), 1536 and 1349 (N═O), 1330 (C–N), 1263 (C–O–C), 833 (C_3N_3, *s*-triazine), 654 (C–S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.56 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 10.09 (s, 1H, –NH proton of *s*-triazine to benzothiazole linkage), 8.21 (d, J = 7.5 Hz, 1H, C-8 proton of quinoline), 7.79 (t, J = 7.6 Hz, 1H, C-7 proton of quinoline), 7.67 (d, J = 8.3 Hz, 1H, C-5 proton of quinoline), 7.60 (d, J = 2.2 Hz, 1H, C-5 proton of benzothiazole), 7.54 (t, J = 7.9 Hz, 1H, C-6 proton of quinoline), 7.43–7.19 (m, 6H, Ar–H proton of aromatic), 6.86 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.66 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 172.23 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 165.92, 164.68 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and benzothiazole linkage), 163.08 (1C, –C═O of hydroxy quinoline moiety), 158.09 (1C, C–S, of benzothiazole), 152.34, 150.46, 148.89, 146.99, 145.09, 143.18, 140.97, 138.78, 135.81, 134.02, 132.68, 129.86, 125.01, 124.11, 122.63, 120.76, 118.55, 116.98 (18C, Ar–C of aromatic), 106.03 (1C, –C≡N of aminobenzonitrile moiety), 102.29 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 96.88 (1C, –C–C≡N of aminobenzonitrile moiety), 33.04 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal*. Calcd for $C_{27}H_{17}N_9O_4S$: C, 57.54; H, 3.04; N, 22.37. Found: C, 57.61; H, 2.99; N, 22.43.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(6-methylbenzo[d]thiazol-2-ylamino)-1,3,5-triazin-2-ylamino)benzonitrile (7g). This compound was obtained as light brown solid, yield 1.01 g (76%), mp 225–227°C; IR (KBr): 3282 (N–H), 2955 (C–H), 2224 (C≡N), 1654 (C═O), 1561 (C═N in BT), 1328 (C–N), 1261 (C–O–C), 838 (C_3N_3, *s*-triazine), 647 (C–S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.78 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 9.98 (s, 1H, –NH proton of *s*-triazine to benzothiazole linkage), 8.12 (d, J = 7.5 Hz, 1H, C-8 proton of quinoline), 7.77 (t, J = 7.4 Hz, 1H, C-7 proton of quinoline), 7.65 (d, J = 8.2 Hz, 1H, C-5 proton of quinoline), 7.52 (t, J = 8.1 Hz, 1H, C-6 proton of quinoline), 7.49–7.23 (m, 7H, Ar–H proton of aromatic), 6.85 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.70 (s, 3H, –N–CH_3 proton of quinoline moiety), 1.99 (s, 3H, –CH_3 proton of benzothiazole); ^{13}C NMR (DMSO-d_6): δ 170.87 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 167.31, 165.08 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and benzothiazole linkage), 162.01 (1C, –C═O of hydroxy quinoline moiety), 158.21(1C, C–S, of benzothiazole), 150.88, 148.79, 147.25, 146.38, 144.59, 142.78, 141.01, 139.69, 137.04, 135.79, 133.02, 130.59, 127.91, 125.06, 122.89, 120.59, 118.76, 116.89 (18C, Ar–C of aromatic), 105.43 (1C, –C≡N of aminobenzonitrile moiety), 101.86 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 97.07 (1C, –C–C≡N of aminobenzonitrile moiety), 32.61 (1C, –N–CH_3 of hydroxy quinoline moiety), 22.87 (1C, –CH_3 of benzothiazole). *Anal*. Calcd for $C_{28}H_{20}N_8O_2S$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.09; H, 3.75; N, 20.98.

4-(4-(6-Methoxybenzo[d]thiazol-2-ylamino)-6-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7h). This compound was obtained as light yellow solid, yield 1.03 g (75%), mp 217°C; IR (KBr): 3277 (N–H), 2824 (O–CH_3), 2221 (C≡N), 1648 (C═O), 1566 (C═N in BT), 1338 (C–N), 1269 (C–O–C), 831 (C_3N_3, *s*-triazine), 644 (C–S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.34 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 10.07 (s, 1H, –NH proton of *s*-triazine to benzothiazole linkage), 8.19 (d, J = 7.6 Hz, 1H, C-8 proton of quinoline), 7.78 (t, J = 7.5 Hz, 1H, C-7 proton of quinoline), 7.68 (d, J = 8.0 Hz, 1H, C-5 proton of quinoline), 7.55 (t, J = 7.8 Hz, 1H, C-6 proton of quinoline), 7.47–7.19 (m, 7H, Ar–H proton of aromatic), 6.81 (s, 1H, –CH–(C═O)–N proton of quinoline moiety), 3.81 (s, 3H, –O–CH_3 proton of benzothiazole), 3.59 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 171.83 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 166.43, 165.20 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and benzothiazole linkage), 161.91 (1C, –C═O of hydroxy quinoline moiety), 157.49 (1C, C–S, of benzothiazole), 149.91, 148.15, 147.68, 145.78, 144.11, 142.83, 141.12, 139.59, 137.93, 135.09, 132.90, 131.17, 129.01, 126.89, 125.13, 122.88, 120.18, 118.71 (18C, Ar–C of aromatic), 105.81 (1C, –C≡N of aminobenzonitrile moiety), 103.12 (1C, –C–(C═O)–N of hydroxy quinoline moiety), 96.25 (1C, –C–C≡N of aminobenzonitrile moiety), 64.98 (1C, –O–CH_3 of benzothiazole), 30.61 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal*. Calcd for $C_{28}H_{20}N_8O_3S$: C, 61.30; H, 3.67; N, 20.43. Found: C, 61.40; H, 3.70; N, 20.39.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(pyridin-2-ylamino)-1,3,5-triazin-2-ylamino)benzonitrile (7i). This compound was obtained as light yellow solid, yield 0.90 g (78%), mp 215°C; IR (KBr): 3279 (N–H), 2229 (C≡N), 1645 (C═O),

1561 and 1413 (C=C and C=N in pyridine), 1331 (C–N), 1259 (C–O–C), 837 (C_3N_3, *s*-triazine) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.68 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 9.97 (s, 1H, –NH proton of *s*-triazine to pyridyl linkage), 8.13 (d, $J = 7.6$ Hz, 1H, C-8 proton of quinoline), 7.78 (t, $J = 7.2$ Hz, 1H, C-7 proton of quinoline), 7.68 (d, $J = 8.3$ Hz, 1H, C-5 proton of quinoline), 7.53 (t, $J = 7.7$ Hz, 1H, C-6 proton of quinoline), 7.46–7.21 (m, 7H, Ar–H proton of aromatic), 7.08 (dd, $J = 7.9$, 2.0 Hz, 1H, pyridyl), 6.83 (s, 1H, –CH–(C=O)–N proton of quinoline moiety), 3.67 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 173.09 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 165.96, 164.68 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and pyridyl linkage), 161.78 (1C, –C=O of hydroxy quinoline moiety), 151.01, 149.09, 146.81, 144.95, 143.01, 141.61, 139.25, 138.07, 135.87, 133.45, 131.21, 128.67, 126.46, 123.77, 120.69, 118.07, 116.88 (17C, Ar–C of aromatic), 105.26 (1C, –C≡N of aminobenzonitrile moiety), 102.59 (1C, –C–(C=O)–N of hydroxy quinoline moiety), 97.19 (1C, –C–C≡N of aminobenzonitrile moiety), 32.61 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal.* Calcd for $C_{25}H_{18}N_8O_2$: C, 64.93; H, 3.92; N, 24.23. Found: C, 64.98; H, 3.88; N, 24.19.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(pyrazin-2-ylamino)-1,3,5-triazin-2-ylamino)benzonitrile (7j). This compound was obtained as light yellow solid, yield 0.93 g (80%), mp 224–226°C; IR (KBr): 3282 (N–H), 2224 (C≡N), 1654 (C=O), 1568 and 1433 (C=C and C=N), 1336 (C–N), 1261 (C–O–C), 839 (C_3N_3, *s*-triazine) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.84, (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 10.13 (s, 1H, –NH proton of *s*-triazine to pyrazine linkage), 8.21 (d, $J = 7.1$ Hz, 1H, C-8 proton of quinoline), 7.76 (t, $J = 7.7$ Hz, 1H, C-7 proton of quinoline), 7.63 (d, $J = 7.9$ Hz, 1H, C-5 proton of quinoline), 7.60 (t, $J = 8.1$ Hz, 1H, C-6 proton of quinoline), 7.49–7.14 (m, 7H, Ar–H proton of aromatic), 6.86 (s, 1H, −CH–(C=O)–N proton of quinoline moiety), 3.64 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 173.27 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 164.10, 165.25 (2C, C–NH of *s*-triazine to aminobenzonitrile linkage and pyrazine linkage), 161.78 (1C, –C=O of hydroxy quinoline moiety), 150.55, 147.61, 145.36, 143.09, 140.81, 140.01, 138.78, 135.98, 133.58, 130.66, 128.01, 125.81, 122.77, 119.01, 118.25, 116.87 (16C, Ar–C of aromatic), 106.01 (1C, –C≡N of aminobenzonitrile moiety), 101.69 (1C, –C–(C=O)–N of hydroxy quinoline moiety), 97.09 (1C, –C–C≡N of aminobenzonitrile moiety), 31.86 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal.* Calcd for $C_{24}H_{17}N_9O_2$: C, 62.20; H, 3.70; N, 27.20. Found: C, 62.13; H, 3.74; N, 27.25.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-ylamino)benzonitrile (7k). This compound was obtained as brown solid, yield 0.79 g (67%), mp 226°C; IR (KBr): 3274 (N–H), 2229 (C≡N), 1649 (C=O), 1335 (C–N), 1259 (C–O–C), 835 (C_3N_3, *s*-triazine), 647(C–S) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.76 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 9.88 (s, 1H, –NH proton of *s*-triazine to thiazole linkage), 8.23 (d, $J = 7.5$ Hz, 1H, C-8 proton of quinoline), 7.80 (t, $J = 7.2$ Hz, 1H, C-7 proton of quinoline), 7.68 (d, $J = 8.2$ Hz, 1H, C-5 proton of quinoline), 7.52 (t, $J = 7.8$ Hz, 1H, C-6 proton of quinoline), 7.44–7.17 (m, 5H, Ar–H proton of aromatic), 6.83 (d, $J = 7.8$ Hz, 1H, C-5 proton of thiazole), 6.76 (s, 1H, –CH–(C=O)–N proton of quinoline moiety), 3.61 (s, 3H, –N–CH_3 proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 172.01 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 165.70, 166.18 (2C, –C–NH of *s*-triazine to aminobenzonitrile linkage and thiazole linkage), 160.99 (1C, –C=O of hydroxy quinoline moiety), 158.13 (1C, –NH–C, of thiazole moiety), 149.13, 146.08, 144.19, 142.18, 139.25, 137.71, 135.69, 132.45, 129.99, 127.01, 124.89, 121.03, 119.01, 117.25 (14C, Ar–C of aromatic), 105.11 (1C, –C≡N of aminobenzonitrile moiety), 102.78 (1C, –C–(C=O)–N of hydroxy quinoline moiety), 95.91 (1C, –C–C≡N of aminobenzonitrile moiety), 33.02 (1C, –N–CH_3 of hydroxy quinoline moiety). *Anal.* Calcd for $C_{23}H_{16}N_8O_2S$: C, 58.97; H, 3.44; N, 23.92. Found: C, 59.07; H, 3.41; N, 23.87.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(5-methylthiazol-2-ylamino)-1,3,5-triazin-2-ylamino)benzonitrile (7l). This compound was obtained as brown solid, yield 0.73 g (60%), mp 211–214°C; IR (KBr): 3282 (N–H), 2948 (C–H), 2221 (C≡N), 1654 (C=O), 1332 (C–N), 1264 (C–O–C), 833 (C_3N_3, *s*-triazine), 651(C–S) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.68 (s, 1H, –NH proton of *s*-triazine to aminobenzonitriles linkage), 10.02 (s, 1H, –NH proton of *s*-triazine to thiazole linkage), 8.12 (d, $J = 7.6$ Hz, 1H, C-8 proton of quinoline), 7.75 (t, $J = 7.7$ Hz, 1H, C-7 proton of quinoline), 7.66 (d, $J = 8.3$ Hz, 1H, C-5 proton of quinoline), 7.58 (t, $J = 8.2$ Hz, 1H, C-6 proton of quinoline), 7.45–7.21 (m, 5H, Ar–H proton of aromatic), 6.78 (s, 1H, –CH–(C=O)–N proton of quinoline moiety), 3.79 (s, 3H, –N–CH_3 proton of quinoline moiety), 2.23 (s, 3H, –CH_3, proton of thiazole); ^{13}C NMR (DMSO-d_6): δ 172.05 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 165.79, 166.08 (2C, –C–NH of *s*-triazine to aminobenzonitrile linkage and thiazole linkage), 162.08 (1C, –C=O of hydroxy quinoline moiety), 157.13 (1C, –NH–C of thiazole moiety), 150.88, 148.25, 146.69, 143.15, 139.98, 137.13, 135.69, 132.98, 129.04, 127.46, 124.09, 121.63, 119.01, 117.19 (14C, Ar–C of aromatic), 104.19 (1C, –C≡N of aminobenzonitrile moiety), 103.36 (1C, –C–(C=O)–N of hydroxy quinoline moiety), 95.69 (1C, –C–C≡N of aminobenzonitrile moiety), 33.02 (1C, –N–CH_3 of hydroxy quinoline moiety), 19.92 (1C, –CH_3, thiazole). *Anal.* Calcd for $C_{24}H_{18}N_8O_2S$: C, 59.74; H, 3.76; N, 23.22. Found: C, 59.81; H, 3.79; N, 23.26.

4-(4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylamino)-6-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7m). This compound was obtained as off-white solid, yield 1.24 g (87%), mp 178–180°C; IR (KBr): 3508 and 3348 (N–CH_3 in 4-aminoantipyrine), 3277 (N–H), 2940 (C–H), 2223 (C≡N), 1652 (C=O), 1436 and 1401 (C–CH_3 in 4-aminoantipyrine), 1339 (C–N), 1270 (C–O–C), 836 (C_3N_3, *s*-triazine) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.81 (s, 1H, −NH proton of *s*-triazine to aminobenzonitriles linkage), 10.12 (s, 1H, –NH proton of *s*-triazine to pyrazole linkage), 8.12 (d, $J = 7.3$ Hz, 1H, C-8 proton of quinoline), 7.78 (t, $J = 7.5$ Hz, 1–H, C-7 proton of quinoline), 7.68 (d, $J = 8.1$ Hz, 1H, C-5 proton of quinoline), 7.59 (t, $J = 7.9$ Hz, 1H, C-6 proton of quinoline), 7.45–7.28 (m, 9H, Ar–H proton of aromatic), 6.86 (s, 1H, –CH–(C=O)–N proton of quinoline moiety), 3.63 (s, 3H, –N–CH_3 proton of quinoline moiety), 2.43 (s, 3H, –N–CH_3 proton of pyrazole), 2.31 (s, 3H, –C–CH_3 proton of pyrazole); ^{13}C NMR (DMSO-d_6): δ 171.49 (1C, C–O–C, *s*-triazine to 4-HMQ linkage), 167.19, 166.21 (2C, –C–NH of *s*-triazine to aminobenzonitrile linkage and pyrazole linkage), 163.10 (1C, –C=O of hydroxy quinoline moiety), 158.33 (1C, –NH–C of pyrazole moiety), 152.34, 150.89, 149.10, 148.01, 146.88, 144.45, 142.12, 140.66, 139.18, 137.43, 135.16, 133.88, 130.87, 129.01, 127.89, 124.99, 123.29, 121.01, 119.11, 117.20 (20C, Ar–C of aromatic), 105.16 (1C, –C≡N of aminobenzonitrile moiety), 103.08 (1C, –C–(C=O)–N of hydroxy quinoline moiety), 97.77 (1C, –C–C≡N of

aminobenzonitrile moiety), 29.99 (1C, –N–$\underline{C}H_3$ of hydroxy quinoline moiety), 21.67, 19.82 (2C, –N–$\underline{C}H_3$ and –C–$\underline{C}H_3$ of pyrazole moiety). *Anal*. Calcd for $C_{31}H_{25}N_9O_3$: C, 65.14; H, 4.41; N, 22.05. Found: C, 65.08; H, 4.46; N, 22.09.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)-1,3,5-triazin-2-ylamino) benzonitrile (7n). This compound was obtained as off-white solid, yield 1.32 g (83%), mp 152–154°C; IR (KBr): 3284 (N–H), 2837 (O–CH_3), 2225 (C≡N), 1655 (C═O), 1633, 1542 (2C═N, oxadiazole), 1348 (C–N), 1261 (C–O–C), 1070 (C–O–C, oxadiazole), 831 (C_3N_3, *s*-triazine), 743 (C–S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.71 (s, 1H, –N$\underline{H}$ proton of *s*-triazine to aminobenzonitriles linkage), 8.11 (d, J = 7.1 Hz, 1H, C-8 proton of quinoline), 7.76 (t, J = 7.7 Hz, 1H, C-7 proton of quinoline), 7.65 (d, J = 8.3 Hz, 1H, C-5 proton of quinoline), 7.61 (t, J = 7.7 Hz, 1H, C-6 proton of quinoline), 7.44–7.12 (m, 6H, Ar–$\underline{H}$ proton of aromatic), 6.73 (s, 1H, –C$\underline{H}$–(C═O)–N proton of quinoline moiety), 3.66 (s, 3H, –N–$\underline{C}H_3$ proton of quinoline moiety), 1.84 (s, 9H, –O–$\underline{C}H_3$ oxadiazole); ^{13}C NMR (DMSO-d_6): δ 170.81 (1C, $\underline{C}$–O–C, *s*-triazine to 4-HMQ linkage), 168.54 (1C, C–5 (C–$\underline{C}$) of oxadiazole), 166.08 (1C, C–2 ($\underline{C}$–S) of oxadiazole), 165.36, 163.98 (2C, –$\underline{C}$–NH of *s*-triazine to aminobenzonitrile linkage and –$\underline{C}$–S of *s*-triazine to oxadiazole linkage), 162.08 (1C, –$\underline{C}$═O of hydroxy quinoline moiety), 150.89, 149.21, 147.18, 145.36, 143.66, 141.48, 139.78, 137.55, 136.16, 133.99, 130.47, 128.81, 126.80, 124.77, 121.61, 120.01, 118.41, 117.11 (18C, Ar–$\underline{C}$ of aromatic), 105.64 (1C, –$\underline{C}$≡N of aminobenzonitrile moiety), 102.05 (1C, –$\underline{C}$–(C═O)–N of hydroxy quinoline moiety), 96.61 (1C, –$\underline{C}$–C≡N of aminobenzonitrile moiety), 66.54 (3C, –O–$\underline{C}H_3$ of oxadiazole moiety), 30.79 (1C, –N–$\underline{C}H_3$ of hydroxy quinoline moiety). *Anal*. Calcd for $C_{31}H_{24}N_8O_6S$: C, 58.48; H, 3.80; N, 17.60. Found: C, 58.55; H, 3.76; N, 17.66.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-ylthio)-1,3,5-triazin-2-ylamino)benzonitrile (7o). This compound was obtained as brown solid, yield 1.07 g (78%), mp 218–220°C; IR (KBr): 3274 (N–H), 2222 (C≡N), 1648 (C═O), 1621, 1532 (2C═N, oxadiazole), 1548 and 1438 (C═C and C═N in pyridine), 1343 (C–N), 1272 (C–O–C), 1082 (C–O–C, oxadiazole), 839 (C_3N_3, *s*-triazine), 756 (C–S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.66 (s, 1H, –N$\underline{H}$ proton of *s*-triazine to aminobenzonitriles linkage), 8.21 (d, J = 7.5 Hz, 1H, C-8 proton of quinoline), 7.80 (t, J = 7.2 Hz, 1H, C-7 proton of quinoline), 7.64 (d, J = 8.2 Hz, 1H, C-5 proton of quinoline), 7.59 (t, J = 8.2 Hz, 1H, C-6 proton of quinoline), 7.43–7.17 (m, 8H, Ar–$\underline{H}$ proton of aromatic), 6.80 (s, 1H, –C$\underline{H}$–(C═O)–N proton of quinoline moiety), 3.70 (s, 3H, –N–$\underline{C}H_3$ proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ): 173.04 (1C, $\underline{C}$–O–C, *s*-triazine to 4-HMQ linkage), 167.36 (1C, C–5 (C–$\underline{C}$) of oxadiazole), 166.34 (1C, C–2 ($\underline{C}$–S) of oxadiazole), 165.08, 164.83 (2C, –$\underline{C}$–NH of *s*-triazine to aminobenzonitrile linkage and –$\underline{C}$–S of *s*-triazine to oxadiazole linkage), 162.68 (1C, –$\underline{C}$═O of hydroxy quinoline moiety), 151.75, 150.01, 148.99, 146.18, 144.87, 142.18, 140.95, 139.17, 137.48, 135.90, 134.12, 130.87, 129.01, 127.85, 125.60, 122.45, 119.97 (17C, Ar–$\underline{C}$ of aromatic), 106.11 (1C, –$\underline{C}$≡N of aminobenzonitrile moiety), 101.29 (1C, –$\underline{C}$–(C═O)–N of hydroxy quinoline moiety), 97.26 (1C, –$\underline{C}$–C≡N of aminobenzonitrile moiety), 31.98 (1C, –N–$\underline{C}H_3$ of hydroxy quinoline moiety). *Anal*. Calcd for $C_{27}H_{17}N_9O_3S$: C, 59.23; H, 3.13; N, 23.02. Found: C, 59.17; H, 3.17; N, 23.07.

4-(4,6-bis(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7p). This compound was obtained as light brown solid, yield 1.14 g (84%), mp 209–210°C; IR (KBr): 3279 (N–H), 2222 (C≡N), 1658 (C═O), 1313 (C–N), 1268 (C–O–C), 837 (C_3N_3, *s*-triazine) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.83 (s, 1H, –N$\underline{H}$ proton of *s*-triazine to aminobenzonitriles linkage), 8.20 (d, J = 7.6 Hz, 2H, C-8 proton of quinoline), 7.79 (t, J = 7.1 Hz, 2H, C-7 proton of quinoline), 7.67 (d, J = 7.8 Hz, 2H, C-5 proton of quinoline), 7.53 (t, J = 8.2 Hz, 2H, C-6 proton of quinoline), 7.48–7.19 (m, 4H, Ar–$\underline{H}$ proton of aromatic), 6.79 (s, 2H, –C$\underline{H}$–(C═O)–N proton of quinoline moiety), 3.73 (s, 6H, –N–$\underline{C}H_3$ proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 170.88 (2C, $\underline{C}$–O–C, *s*-triazine to 4-HMQ linkage), 167.12 (1C, –$\underline{C}$–NH of *s*-triazine to aminobenzonitrile linkage), 161.90 (2C, –$\underline{C}$═O of hydroxy quinoline moiety), 152.30, 150.26, 148.89, 146.39, 143.88, 142.10, 140.86, 139.52, 137.33, 135.79, 134.02, 131.77, 130.01, 128.25, 125.63, 123.79, 120.25, 118.54, 116.88 (19C, Ar–$\underline{C}$ of aromatic), 106.11 (1C, –$\underline{C}$≡N of aminobenzonitrile moiety), 102.09 (2C, –$\underline{C}$–(C═O)–N of hydroxy quinoline moiety), 97.05 (1C, –$\underline{C}$–C≡N of aminobenzonitrile moiety), 31.62 (2C, –N–$\underline{C}H_3$ of hydroxy quinoline moiety). *Anal*. Calcd for $C_{30}H_{21}N_7O_4$: C, 66.29; H, 3.89; N, 18.04. Found: C, 66.23; H, 3.94; N, 17.98.

4-(4-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yloxy)-6-(2-oxo-2H-chromen-4-yloxy)-1,3,5-triazin-2-ylamino)benzonitrile (7q). This compound was obtained as light brown solid, yield 1.13 g (85%), mp 248°C; IR (KBr): 3272 (N–H), 2227 (C≡N), 1727 (C═O of cumarin), 1649 (C═O of quinoline), 1335 (C–N), 1272 (C–O–C), 833 (C_3N_3, *s*-triazine) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.72 (s, 1H, –N$\underline{H}$ proton of *s*-triazine to aminobenzonitriles linkage), 8.25 (s, 1H, –C$\underline{H}$–(C═O)–C proton of coumarin), 8.13 (d, J = 7.5 Hz, 1H, C-8 proton of quinoline), 7.75 (t, J = 7.3 Hz, 1H, C-7 proton of quinoline), 7.68 (d, J = 8.2 Hz, 1H, C-5 proton of quinoline), 7.56 (t, J = 7.9 Hz, 1H, C-6 proton of quinoline), 7.47–7.21 (m, 8H, Ar–$\underline{H}$ proton of aromatic), 6.85 (s, 1H, –C$\underline{H}$–(C═O)–N proton of quinoline moiety), 3.67 (s, 3H, –N–$\underline{C}H_3$ proton of quinoline moiety); ^{13}C NMR (DMSO-d_6): δ 172.39 (1C, $\underline{C}$–O–C, *s*-triazine to 4-HMQ linkage), 166.45 (C, –$\underline{C}$–NH of *s*-triazine to aminobenzonitrile linkage linkage), 163.51 (1C, –$\underline{C}$═O of coumarin moiety), 163.06 (1C, –$\underline{C}$═O of hydroxy quinoline moiety), 151.85, 150.13, 148.69, 146.78, 145.15, 143.26, 141.91, 139.88, 138.09, 136.86, 135.16, 133.28, 130.67, 128.97, 125.98, 124.23, 121.76, 120.56, 119.11, 117.25 (20C, Ar–$\underline{C}$ of aromatic), 104.89 (1C, –$\underline{C}$≡N of aminobenzonitrile moiety), 103.33 (1C, –$\underline{C}$–(C═O)–N of hydroxy quinoline moiety), 96.59 (1C, –$\underline{C}$–C≡N of aminobenzonitrile moiety), 94.56 (1C, –$\underline{C}$–(C═O)–C of coumarin moiety), 33.19 (1C, –N–$\underline{C}H_3$ of hydroxy quinoline moiety). *Anal*. Calcd for $C_{29}H_{18}N_6O_5$: C, 66.29; H, 3.89; N, 18.04. Found: C, 66.35; H, 3.86; N, 18.10.

BIOLOGICAL ASSAY

***In vitro* evaluation of antimicrobial activity.** The synthesized derivatives **(7a–q)** were examined for antimicrobial activity against several bacteria, two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Bacillus cereus* MTCC 430), six Gram-negative bacteria (*E. coli* MTCC 739, *P. aeruginosa* MTCC 741, *S. typhi* MTCC 733, *P. vulgaris* MTCC 1771, *K. pneumoniae* MTCC 109, and *S. flexneri* MTCC 1457), and two fungal species (*A. niger* MTCC 282, *C. albicans* MTCC 183) species. All MTCC cultures were collected from the Institute of Microbial Technology, Chandigarh. MIC of the compound was determined by agar streak dilution method [20]. *In vitro*

evaluation of antituberculosis activity was carried out using LJ MIC method [21] for the measurement of MIC as reported earlier [22].

***In vitro* evaluation of anti-HIV assay.** Evaluation of the antiviral activity of the test compounds against HIV-1 strain (III_B) and HIV-2 strain (ROD) in MT-4 cells were performed using the MTT assay method as previously described [23,24]. Briefly, stock solutions (10× final concentration) of test compounds were added in 25 μL volumes to two series of triplicate wells so as to allow simultaneous evaluation of their effects on mock-infected and HIV-infected cells at the beginning of each experiment. Serial fivefold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays by using a Biomek 3000 robot (Beckman instruments). Untreated control HIV-infected and mock-infected cell samples were included for each sample. HIV-1 (III_B) [25] or HIV-2 (ROD) [26] stock (50 μL) at 100 –300 $CCID_{50}$ (50% cell culture infectious dose) or culture medium was added to either the HIV-infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compound. Exponentially growing MT-4 cells [27] were centrifuged for 5 min at 1000 rpm (220 g), and the supernatant was discarded. The MT-4 cells were resuspended at 6×10^5 cells/mL, and 50 μL volumes were transferred to the microtiter tray wells. Five days after infection, the viability of mock-infected and HIV-infected cells was examined spectrophotometrically by the MTT assay.

The MTT assay is based on the reduction of yellow-colored 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Acros Organics) by mitochondrial dehydrogenase of metabolically active cells to a blue-purple formazan that can be measured spectrophotometrically. The absorbances were read in an eight-channel computer-controlled photometer (Safire, Tecan), at two wavelengths (540 and 690 nm). All data were calculated using the median optical density (OD) value of tree wells. The 50% cytotoxic concentration (CC_{50}) was defined as the concentration of the test compound that reduced the absorbance (OD540) of the mock-infected control sample by 50%. The concentration achieving 50% protection from the cytopathic effect of the virus in infected cells was defined as the 50% effective concentration (EC_{50}).

CONCLUSION

The work was focused on the development of some novel *s*-triazine-based analogues having different structural characteristics and their bioevaluations against multiple targets. From the results, it is worth to note here that majority of the final analogues revealed good antimicrobial and antituberculosis activities with appreciable MIC values as compared with the control drugs. Attempt has been made to determine the efficacy of various pharmacophores involving different electron-withdrawing/donating functional groups towards particular bacteria, fungi, mycobacteria, or viral strains. In the anti-HIV bioassay, only one compound (**7h**) showed selective anti-HIV-1 activity with minimum cytotoxicity and promising therapeutic index compared with the control drugs. Thus, such scaffolds provide an important starting point for the development of novel lead molecules with increased potency by suitable structural optimization. Such studies are underway in our laboratory, and the results will be published in due course.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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