Med Chem Res (2012) 21:3119–3132
DOI 10.1007/s00044-011-9842-7

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of novel 3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one condensed *s*-triazinyl piperazines and piperidines as antimicrobial agents

Rahul V. Patel · Amit B. Patel · Premlata Kumari · Kishor H. Chikhalia

Received: 19 August 2011 / Accepted: 21 October 2011 / Published online: 11 November 2011
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Abstract Synthesis and antimicrobial activity of a new series of 3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-ones based on various substituted piperazines and piperidines incorporating a 1,3,5-triazine moiety are reported in this article. 3-{5-[(4,6-dichloro-1,3,5-triazin-2-yl)sulfanyl]-1,3,4-oxadiazol-2-yl}-2H-chromen-2-one **3** was obtained by the reaction of 2,4,6-trichloro-1,3,5-triazine **1** with 3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one **2** which was obtained by following the method reported in the literature. Intermediate **3** was then condensed with 8-hydroxyquinoline **4** to form 3-(5-{[4-chloro-6-(quinolin-4-yloxy)-1,3,5-triazin-2-yl]sulfanyl}-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one **5**. This was further treated with various substituted piperazines and piperidines to obtain the title compounds **7a**–**u**, which were then subjected to determine their in vitro biological efficacy against bacterial and fungal strains as two Gram-positive bacteria (*S. aureus*, *B. cereus*), six Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhi*, P. vulgaris, and *S. flexneria*) and two fungal species (*A. niger*, and *C. albicans*) with an intent to develop novel class of antimicrobial agents. The results indicate that some of the novel *s*-triazines have noteworthy activity in MIC (μg/ml) and zone of inhibition (mm) indicating potential leads for further drug discovery study. All the final compounds were structurally elucidated on the basis of IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectroscopy, and elemental analysis.

Keywords 3-(5-Sulfanyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one · 2,4,6-Trichloro-1,3,5-triazine · Antimicrobial activity

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Introduction

During the past few decades, the human population is affected with significant increase in the frequency of life-treating infectious diseases because of the increasing number of multi-drug-resistant microbial pathogens. These organisms possessed the ability to withstand attack by antimicrobial drugs currently available, and the uncontrolled rise in resistant pathogens, which threatens lives (Nathan, 2004). Significant impact of the affliction of infectious disease in developing countries highlights the need for more antimicrobial therapeutic alternatives with increased potency to maintain a pool of new bioactive candidates. Its success crucially relies on the search for new chemical entities, which are distinct from those of the well-known classes of antimicrobial agents.

1,3,5-Triazines, electron-rich nitrogen heterocycles, occupies an extremely important role in the field of medicinal chemistry since they display a fascinating array of pharmacological properties such as antimicrobial (Udaya *et al*., 2010; Zhou *et al*., 2008; Srinivas *et al*., 2006), antimycobacterial (Jignesh *et al*., 2010), anticancer (Bakharev *et al*., 2008; Rita *et al*., 2004), and antiviral (Yuan-Zhen *et al*., 2008). Besides, 1,3,4-oxadiazoles

nucleus has drawn great attention because of its pharmacological importance as antibacterial (Desai and Amit, 2011; Mohammed *et al*., 2010; Jha *et al*., 2010; Chawla *et al*., 2010; Vivek *et al*., 2008; Cacic *et al*., 2006; Sahin *et al*., 2002) and antifungal (Liu *et al*., 2008; Chen *et al*., 2007). Due to appealing diverse biological properties among all the hydroxyquinoline derivatives, the adorable chemistry of 8-hydroxyquinoline has gained much importance such as antimicrobial (Ritu *et al*., 2010; Okide *et al*., 2000) and antituberculosis (Crystal and Carl, 2010; Urbanski *et al*., 1951). In addition, piperazine and piperidine derivatives have proved to elicit wide range of inhibitory activities (Kerns *et al*., 2003; Upadhayaya *et al*., 2004). Encouraged by the afore-mentioned findings, it was rationalized to synthesize novel biologically active *s*-triazinyl compounds supported with a variety of pharmacophoric groups which would impart potential bioactivities. Recently, we reported the synthesis and antimicrobial activity of some new *s*-triazine analogues (Patel *et al*., 2011) bearing 4-hydroxycoumarin as well as 7-hydroxy-4-methyl coumarin moieties, and the compounds showed good in vitro antimicrobial activity. Locking at the above findings and to extend the structure–activity relationships (SARs) of such *s*-triazine-based analogues, we have decided to introduce coumarin moiety in the form of oxadiazole nucleus to the *s*-triazine core. The purpose of this investigation was to elucidate the influence of the presence of various cyclic amines to the *s*-triazine core and the effect of the oxadiazole nucleus based on coumarin moiety to the biological profiles of the resultant molecules.

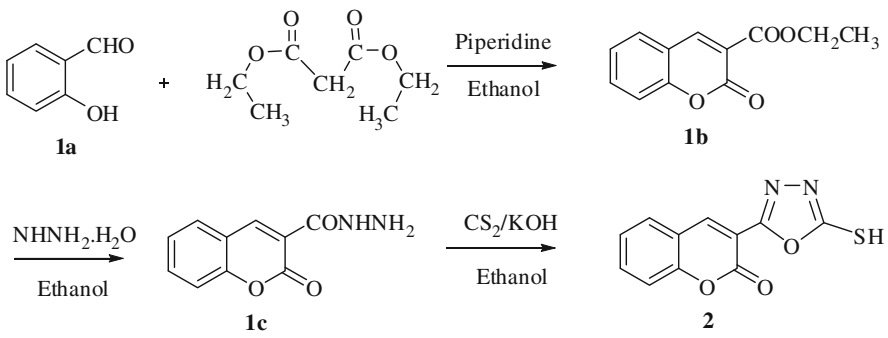
Results and discussion

Chemistry

Synthesis of intermediates and target compounds was accomplished according to the steps illustrated in Scheme 1. Salicylaldehyde and diethylmalonate were reacted in the presence of piperidine in ethanol to form ethyl-2-oxo-2H-chromene-3-carboxylate **1b** which on treatment with 99% hydrazine hydrate yielded 2-oxo-2H-chromonene-3-carbohydrazide **1c**. The resulting carbohydrazide moiety was cyclized using sodium hydroxide in the presence of carbon disulfide to form the corresponding cyclized oxadiazole nucleus, 3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one **2**. The resulting oxadiazole intermediate was further treated with 2,4,6-trichloro-1,3,5-triazine in the presence of triethyl amine at 0–5°C to obtain compound **3** in good yield. The intermediate **3** was reacted with 8-hydroxyquinoline at 45–50°C to afford the final intermediate **5** which was then treated with various piperazine and piperidine bases to obtain the aimed compounds **7a**–**u** at reflux temperature. The correct synthesis of **7a**–**u** was confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectral analyses (Dandia *et al*., 2004), and the purity was ascertained by elemental analysis (Scheme 2).

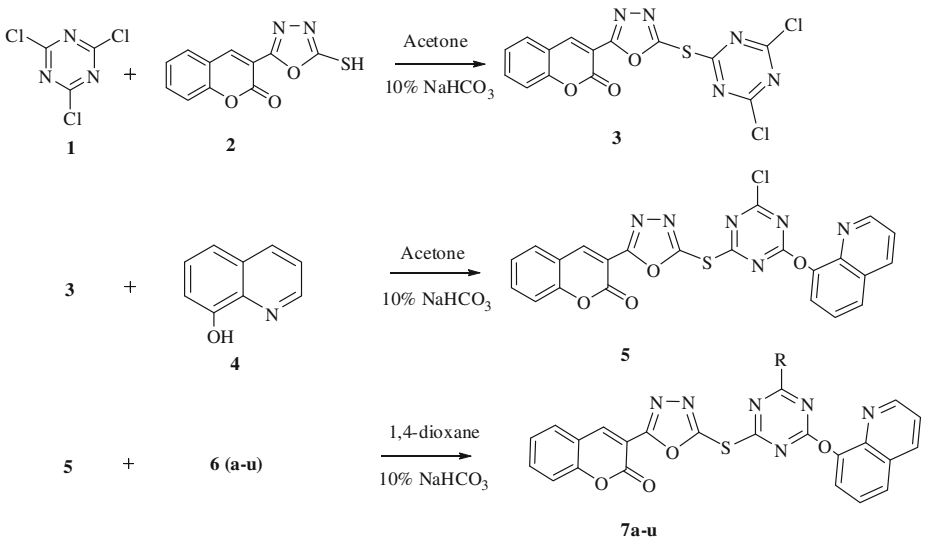
Antimicrobial activity

The antibacterial investigation carried out for the title compounds presented in Table 1 revealed that all the final analogues succeeded to indicate excellent to moderate activity against the examined representative microorganisms. Compounds **7s**, **7t**, and **7u** with strong electronegative trifluoromethyl functional group and electron-donating methoxy functionalization at the phenyl ring of piperazine base condensed to the nucleus contributed considerable activity (MIC, 12.5 μg/ml) against both the mentioned Gram-positive bacteria. In addition, same methoxy group-substituted analogues (**7t** and **7u**) along with compounds **7h**, **7n**, and **7i** bearing electron-donating acetyl linkage to the *N*-atom of piperazine ring and two methyl functional groups at the third and fifth positions of piperidine moiety and in the form of isopropyl linkage, respectively, endowed with excellent activity (MIC, 12.5 μg/ml) against Gram-negative strains, *P. aeruginosa*, *S. typhi, and S. flexneria*. Final analogues with electron-withdrawing halogen substituent(s) like chlorine (**7c**, **7d**, and **7p**) and fluorine (**7q**, **7r**, and **7s**) exhibited strong inhibitory action toward Gram-negative strains *E. coli* and *P. vulgaris* at the MIC level of 25 μg/ml. Moreover, condensation of unsubstituted heterocyclic moieties in the form of piperidine **7e** and morpholine **7f** as well as in the form of pyridine or pyrimidine



Scheme 1 Synthetic pathway for oxadiazole intermediate **2**

Scheme 2 Synthetic pathway for final analogues **7a–u** where, [**6a–u** (**R**)] bases coupled to compound **5**



Where, [**6a-u** (**R**)] bases coupled to compound **5**

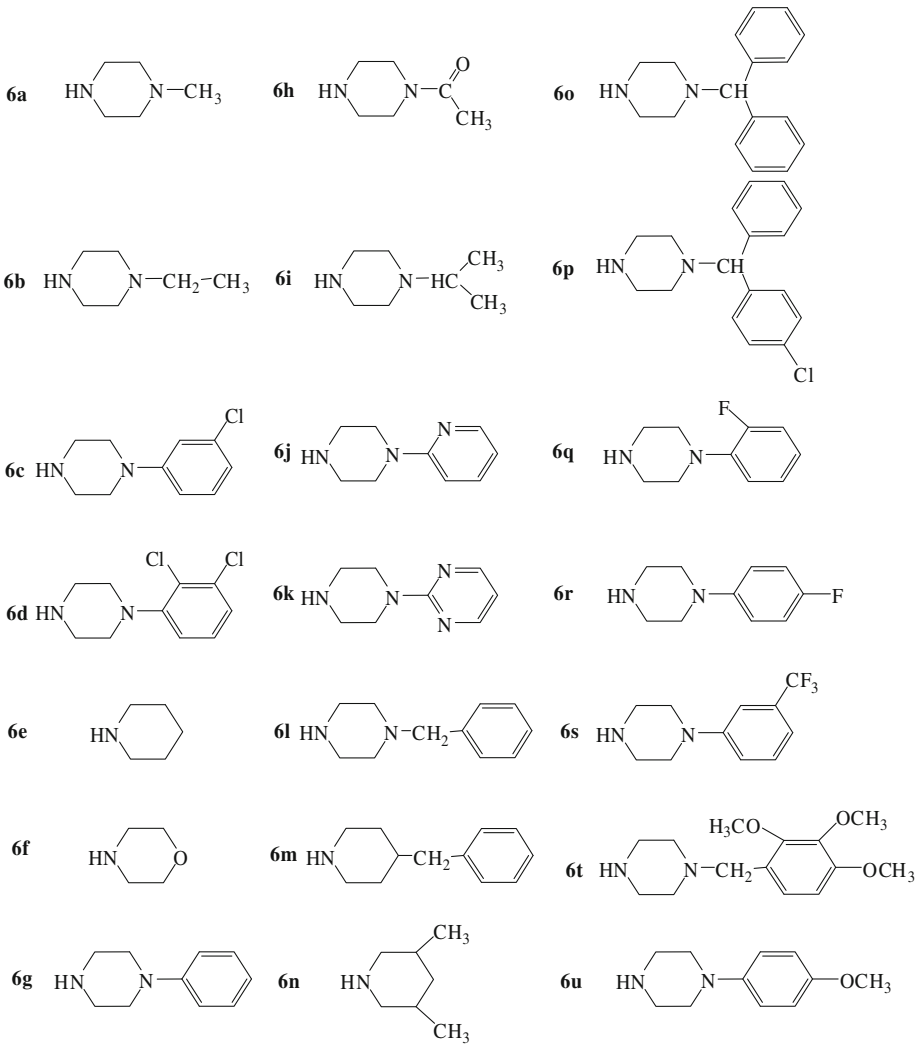
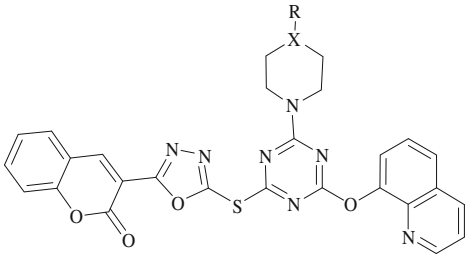


Table 1 In-vitro antimicrobial activity



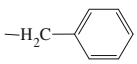
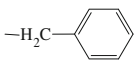
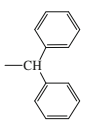
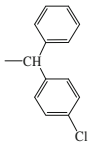
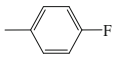
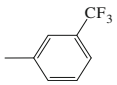
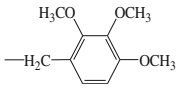
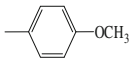
Entry	R	X	Zone of inhibition [mm (MIC in μg/ml)]							
			S.a	*B.c*	*E.c*	*P.a*	*K.p*	*S.t*	*P.v*	*S.f*
7a	CH_3	N	13 (100)	<10 (100)	12 (100)	19 (100)	12 (100)	16 (100)	11 (100)	18 (100)
7b	C_2H_5	N	15 (100)	13 (100)	16 (100)	18 (100)	14 (100)	16 (100)	12 (100)	20 (100)
7c		N	17 (100)	17 (100)	25 (25)	14 (100)	15 (100)	17 (100)	19 (100)	19 (100)
7d		N	21 (50)	22 (25)	24 (25)	20 (50)	21 (25)	19 (100)	17 (100)	21 (100)
7e		$-CH_2$	11 (100)	<10 (100)	<10 (100)	15 (100)	20 (50)	14 (100)	<10 (100)	<10 (100)
7f		O	14 (100)	15 (100)	<10 (100)	16 (100)	22 (25)	16 (100)	<10 (100)	11 (100)
7g		N	<10 (100)	12 (100)	<10 (100)	13 (100)	11 (100)	<10 (100)	15 (100)	<10 (100)
7h	$COCH_3$	N	20 (50)	22 (25)	15 (100)	23 (12.5)	13 (100)	22 (12.5)	18 (100)	23 (25)
7i		N	19 (100)	16 (100)	16 (100)	21 (25)	14 (100)	20 (50)	15 (100)	24 (25)
7j		N	21 (50)	21 (50)	15 (100)	18 (100)	22 (25)	14 (100)	14 (100)	22 (50)
7k		N	21 (50)	22 (25)	19 (100)	18 (100)	22 (25)	18 (100)	16 (100)	22 (50)
7l		N	13 (100)	17 (100)	16 (100)	19 (100)	<10 (100)	<10 (100)	<10 (100)	13 (100)
7m		$-CH_2$	16 (100)	13 (100)	12 (100)	<10 (100)	<10 (100)	14 (100)	<10 (100)	11 (100)
7n	3,5-CH_3	$-CH_2$	22 (25)	21 (50)	20 (50)	22 (12.5)	16 (100)	23 (12.5)	19 (100)	24 (25)
7o		N	18 (100)	14 (100)	13 (100)	<10 (100)	14 (100)	12 (100)	<10 (100)	14 (100)

Table 1 continued

Entry	R	X	Zone of inhibition [mm (MIC in μg/ml)]							
			S.a	*B.c*	*E.c*	*P.a*	*K.p*	*S.t*	*P.v*	*S.f*
7p		N	20 (50)	21 (50)	25 (25)	16 (100)	19 (100)	19 (100)	20 (100)	16 (100)
7q		N	19 (100)	20 (50)	23 (25)	19 (100)	20 (50)	20 (50)	22 (25)	19 (100)
7r		N	22 (25)	21 (50)	23 (25)	21 (50)	16 (100)	19 (100)	21 (50)	17 (100)
7s		N	24 (12.5)	24 (12.5)	22 (50)	21 (25)	21 (25)	21 (50)	23 (25)	21 (100)
7t		N	23 (12.5)	23 (12.5)	19 (100)	22 (12.5)	18 (100)	24 (12.5)	20 (100)	23 (25)
7u		N	22 (25)	23 (12.5)	17 (100)	23 (12.5)	19 (100)	24 (12.5)	18 (100)	22 (50)
Cip.			30 (1.56)	31 (0.39)	32 (1.56)	33 (0.78)	33 (0.78)	30 (0.39)	31 (0.39)	32 (1.56)
DMSO			–	–	–	–	–	–	–	–

Cip.—ciprofloxacin, *S.a—Staphylococcus aureus*, *B.c—Bacillus cereus*, *E.c—Escherichia coli*, *P.a—Pseudomonas aeruginosa*, *K.p—Klebsiella pneumoniae*, *S.t—Salmonella typhi*, *P.v—Proteus vulgaris*– *S.f—Shigella flexneria*

moieties attached to the piperazine coupling agent were found essential to contribute to potential efficacy (MIC, 25 μg/ml) to inhibit the growth of Gram-negative strain *K. pneumoniae*. The bioassay results obtained for the efficacy of the newly synthesized analogues against fungal strains is summarized in Table 2 revealed that the final analogues with fluorine, chlorine, and methoxy substitution at the phenyl ring of piperazine base (**7c**, **7d**, **7n**, **7p**, **7r**, **7s**, **7t**, and **7u**) contributed the best antifungal activity against both the mentioned fungal strains at the MIC level ranging from 25 to 50 μg/ml.

Conclusion

From the bioassay it is clear that the introduction of appropriate substituent on the *s*-triazine ring would lead to the more active antimicrobial derivatives. It can be stated that the variation of antimicrobial activity may be associated with the nature of the tested microorganisms and is due to the chemical structure of the tested compounds. In general, the compounds showed improved antibacterial activity when compared to their antifungal activity. Among these compounds a clear trend of improved activity has been shown to be because of the chloro or fluoro, methyl linker in the form of acetyl group, isopropyl linker, and two methyl group-substituted piperidine moieties as well as in the form of methoxy functional group substitution to the phenyl ring of piperazine bases. The oxadiazole nucleus played an important role to contribute to the enhanced activity. Therefore, it was concluded that there exists ample scope for further study in this class of compounds with appropriate structural modification. In order to gain more bioactivity profile, the compounds are subjected to determine anticancer and anti-HIV activities, and the results will be published in due course.

Experimental section

Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and used as uncorrected. IR spectra (4,000–400 cm^{-1}) of synthesized compounds were

recorded on a Shimadzu 8400-S FT-IR spectrophotometer (Shimadzu India PVT. LTD., Mumbai, India) using KBr pellets at S. V. National Institute of Technology, Surat, India. Thin layer chromatography was performed on object glass slides (2 × 7.5 cm) coated with silica gel-G and spots were visualized under UV irradiation. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz model spectrometer (Varian India PVT. LTD., Mumbai, India) using DMSO as a solvent and TMS as internal standard with ^{1}H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. ^{19}F NMR spectra were obtained on the same spectrometer using $CDCl_3$ as a solvent and $CFCl_3$ as an external standard, positive for downfield shift with ^{19}F resonant frequency of 400 MHz. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si) and $CFCl_3$ and were performed at Centre for Excellence, Vapi, India. The splitting patterns are designated as follows: s, singlet; d, doublet; m, multiplet. Elemental analyses were performed on a Heraeus Carlo Erba 1180 CHN analyzer. All the spectral data were consistent with the proposed structure and micro-analysis within ±0.2% of theoretical values which are summarized in Table 3 along with physical data.

Synthetic part

Synthesis of ethyl 2-oxo-2H-chromene-3-carboxylate ***1b***

Salicylaldehyde **1a** (10 g, 0.045 mol) and diethylmalonate (7.34 g, 0.045 mol) were dissolved in ethanol (150 ml) to give clear solution. Piperidine (18 ml) was added, and the mixture was refluxed for 5 h. After the completion of the reaction (monitored by thin layer chromatography in toluene–ethyl acetate solvent system), the content was concentrated to small volume. Then, the reaction mixture was poured onto crushed ice, and the resulting solid was filtered, dried, and recrystallized from ethanol to afford **1b** as a white solid. Yield: 86%, mp: 124–125°C, IR (KBr) cm^{-1}: 1745 (C=O, ester), 1725 (CO, coumarin), 1677 (C=O), 1231 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (1H, s, H-4, coumarin), 7.52–7.29 (4H, m, Ar–H), 3.56 (q, $J = 5.9$ Hz, 2H, –$COOCH_2$–), 1.29 (t, $J = 6.6$ Hz, 3H, –$COOCH_2CH_3$).

Synthesis of 2-oxo-2H-chromene-3-carbohydrazide ***1c***

2-Oxo-2H-chromene-3-carboxylate, **1b** (5.0 g, 0.023 mol) and hydrazine hydrate 99% (1.15 g, 0.023 mol) were dissolved in ethanol (100 ml) to give clear solution and refluxed for 10 h. The content was concentrated to half of the volume and allowed to cool. The solid mass thus obtained (reaction was monitored by thin layer chromatography in toluene–acetone solvent system) on cooling was retained by filtering and washed with small amount of ice-cooled ethanol to afford **1c** as white solid, Yield: 88%, mp: 137–140°C, IR (KBr) cm^{-1}: 3385, 3290 (NHs), 1721 (CO, coumarin), 1687 (C=O, amide); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (1H, s, H-4, coumarin), 8.12 (m, 1H, CONHNH$_2$), 7.62–7.39 (4H, m, Ar–H), 4.78 (s, 2H, NH_2, D_2O exchangeable).

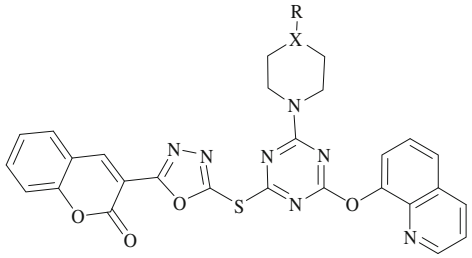
Synthesis of 3-(5-mercapto-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one ***2***

To a solution of the 2-oxo-2H-chromene-3-carbohydrazide, **1c** (2.5 g, 0.01 mol) in ethanol (50 ml) at 0°C, carbon disulfide (0.01 mol), and potassium hydroxide (0.01 mol) were added, and the reaction mixture was refluxed until the evolution of H_2S gas ceased. Excess solvents were evaporated under reduced pressure, and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%) to pH 6. The precipitate was filtered off, dried, and crystallized from ethanol to give **2** (Bhat *et al*., 2008). The completion of reaction was monitored by thin layer chromatography in *n*-hexane: ethyl acetate (8:2) solvent system. Yield 72%, mp: 166–168°C, IR (KBr) cm^{-1}: 2591 (SH), 1726 (CO, coumarin), 1629, 1531 (2C=N, oxadiazole), 1043 (C–O–C, oxadiazole); ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.51 (br s, 1H, SH), 8.21 (1H, s, H-4, coumarin), 7.58–7.37 (m, 4H, Ar–H).

3-{5-[(4,6-Dichloro-1,3,5-triazin-2-yl)sulfanyl]-1,3,4-oxadiazol-2-yl}-2H-chromen-2-one ***3***

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine (18.4 g, 0.1 mol) in acetone (80 ml), the solution of 3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (24.6 g, 0.1 mol) in acetone (100 ml) was added at 0–5°C, and the pH was maintained neutral by the addition of potassium bicarbonate solution. Stirring was continued at 0–5°C for 4 h. After the completion of the reaction, the stirring was stopped, and the solution was treated with crushed ice. The solid product obtained was filtered and dried. The progress of the reaction was monitored by TLC using ethyl acetate–hexane (6:4) as an eluent. The crude product was purified by crystallization from absolute alcohol to get the title compound **3** (Patel *et al*., 2010); Yield 85%, mp: 178–180°C; IR (KBr) cm^{-1}: 1729 (C=O, coumarin), 1624, 1527 (2C=N, oxadiazole), 1040 (C–O–C, oxadiazole), 696 (C–S–C), 833 (*s*-triazine C_3N_3 str.), 752 (–Cl str.).

Table 2 In-vitro antifungal activity



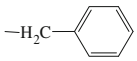
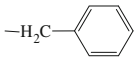
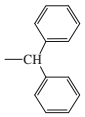
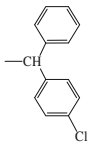
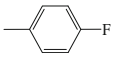
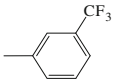
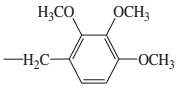
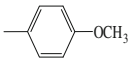
Entry	R	X	Zone of inhibition [mm (MIC in μg/ml)]	
			A.n	*C.a*
7a	CH_3	N	<10 (100)	11 (100)
7b	C_2H_5	N	<10 (100)	13 (100)
7c		N	20 (100)	20 (50)
7d		N	23 (25)	21 (50)
7e		$-CH_2$	<10 (100)	<10 (100)
7f		O	12 (100)	<10 (100)
7g		N	<10 (100)	<10 (100)
7h	$COCH_3$	N	16 (100)	13 (100)
7i		N	12 (100)	11 (100)
7j		N	14 (100)	17 (100)
7k		N	16 (100)	17 (100)
7l		N	<10 (100)	<10 (100)
7m		$-CH_2$	<10 (100)	13 (100)
7n	3,5-CH_3	$-CH_2$	23 (25)	16 (100)
7o		N	11 (100)	<10 (100)
7p		N	22 (50)	22 (50)

Table 2 continued

Entry	R	X	Zone of inhibition [mm (MIC in μg/ml)]	
			A.n	*C.a*
7q		N	21 (100)	19 (100)
7r		N	21 (100)	22 (50)
7s		N	24 (25)	21 (50)
7t		N	24 (25)	22 (50)
7u		N	24 (25)	22 (50)
Kit.			30 (1.56)	33 (1.56)
DMSO			–	–

Kit.—ketoconazole, *A.n—Aspergillus niger*, *A.f—Aspergillus fumigates*, *A.c—Aspergillus clavatus*, *C.a—Candida albicans*

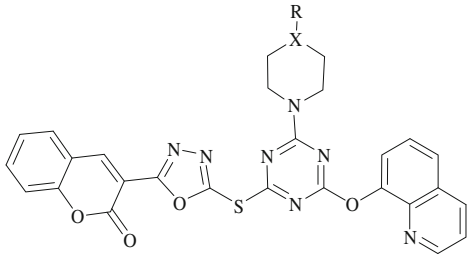
3-{5-[4-Chloro-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-2H-chromen-2-one ***5***

To a stirred solution of 3-{5-[(4,6-dichloro-1,3,5-triazin-2-yl) sulfanyl]-1,3,4-oxadiazol-2-yl}-2H-chromen-2-one (19.70 g, 0.05 mol) which was dissolved in acetone and potassium bicarbonate solution was added to maintain the pH. Then, the solution of 8-hydroxyquinoline (7.26 g, 0.05 mol) in acetone was added dropwise, and the reaction was monitored by TLC by using toluene–acetone (9:1) as an eluent. After the completition of the reaction, it was poured into crushed ice, filtered, and dried to get **5**. Yield: 82%, mp: 242–245°C. IR (KBr) cm^{-1}: 1741 (C=O, coumarin), 1619, 1540 (2C=N of oxadiazole), 1256 (C–O–C), 1041 (C–O–C, oxadiazole), 829 (*s*-triazine C_3N_3 str.), 749 (–Cl str.), 701 (C–S–C).

General procedure for preparation of compounds (**7a–u**)

To a solution of **5** (0.005 mol) in 1,4-dioxane (30 ml), the respective substituted piperazine and piperidines derivatives (0.005 mol) were added and potassium bicarbonate solution was added to maintain the pH. The reaction mixture was refluxed for 8–10 h. Progress of the reaction was monitored by TLC using toluene–acetone (8:2) as eluent. The mixture was then treated with crushed ice and neutralized by dilute HCl. The precipitate thus obtained was filtered off, dried, and recrystallized from THF to afford the desired compounds **7a–u.**

Table 3 Physical and analytic data of the synthesized compounds



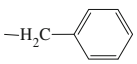
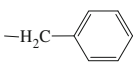
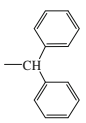
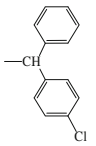
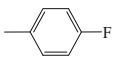
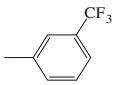
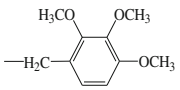
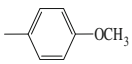
Entry	R	X	Yield (%)	M.P (°C)	Molecular formula	Elemental analysis					
						Found (%)			Calc. (%)		
						C	H	N	C	H	N
7a	CH_3	N	78	240–243	$C_{28}H_{22}N_8O_4S$	59.35	3.91	19.78	59.26	3.83	19.82
7b	C_2H_5	N	74	234–235	$C_{29}H_{24}N_8O_4S$	59.99	4.17	19.30	59.87	4.09	19.14
7c		N	69	245–247	$C_{33}H_{23}ClN_8O_4S$	59.77	3.50	16.90	59.78	3.46	16.94
7d		N	80	252–254	$C_{33}H_{22}Cl_2N_8O_4S$	56.82	3.18	16.06	56.73	3.25	15.94
7e		$-CH_2$	66	189–192	$C_{28}H_{21}N_7O_4S$	60.97	3.84	17.78	60.82	3.81	17.73
7f		O	62	177–179	$C_{27}H_{19}N_7O_5S$	58.58	3.46	17.71	58.48	3.32	17.63
7g		N	70	278–279	$C_{33}H_{24}N_8O_4S$	63.05	3.85	17.82	63.09	3.76	17.80
7h	$COCH_3$	N	79	240–241	$C_{29}H_{22}N_8O_5S$	58.58	3.73	18.85	58.41	3.66	18.80
7i		N	73	222–224	$C_{30}H_{26}N_8O_4S$	60.59	4.41	18.84	60.51	4.40	18.78
7j		N	65	255–256	$C_{32}H_{23}N_9O_4S$	61.04	3.68	20.02	61.07	3.61	19.92
7k		N	77	270–271	$C_{31}H_{22}N_{10}O_4S$	59.04	3.52	22.21	59.00	3.43	22.26
7l		N	71	219–222	$C_{34}H_{26}N_8O_4S$	63.54	4.08	17.44	63.39	3.98	17.59
7m		$-CH_2$	69	265–266	$C_{35}H_{27}N_7O_4S$	65.51	4.24	15.28	65.52	4.15	15.31
7n	3,5-CH_3	$-CH_2$	61	261–262	$C_{30}H_{25}N_7O_4S$	62.16	4.35	16.92	61.99	4.21	16.81
7o		N	59	289–290	$C_{40}H_{30}N_8O_4S$	66.84	4.21	15.59	66.86	4.17	15.62

Table 3 continued

Entry	R	X	Yield (%)	M.P (°C)	Molecular formula	Elemental analysis					
						Found (%)			Calc. (%)		
						C	H	N	C	H	N
7p		N	61	280–282	$C_{40}H_{29}ClN_8O_4S$	63.78	3.88	14.88	63.68	3.74	14.77
7q		N	73	255–257	$C_{33}H_{23}FN_8O_4S$	61.29	3.59	17.33	61.15	3.56	17.37
7r		N	71	251–253	$C_{33}H_{23}FN_8O_4S$	61.29	3.59	17.33	61.18	3.53	17.28
7s		N	65	282–283	$C_{34}H_{23}F_3N_8O_4S$	58.62	3.33	16.08	58.51	3.39	16.12
7t		N	62	292–293	$C_{37}H_{32}N_8O_7S$	60.65	4.40	15.29	60.59	4.31	15.30
7u		N	83	219–220	$C_{34}H_{26}N_8O_5S$	62.00	3.98	17.01	62.04	3.91	16.98

3-{5-[4-(4-Methyl-piperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7a**. IR (KBr) cm^{-1}: 1734 (C=O, coumarin), 1623, 1536 (2C=N of oxadiazole), 1258 (C–O–C), 1140 (N–N, oxadiazole), 1050 (C–O–C–, oxadiazole), 830 (*s*-triazine C_3N_3 str.), 699 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (dd, $J = 7.5$, 1.6 Hz, 1H, C_2 proton of quinoline), 8.61 (dt, $J = 7.5$, 1.6 Hz, 1H, C_4 proton of quinoline), 8.02 (s, 1H, C_4 proton of coumarin), 7.74 (dd, $J = 7.2$, 1.8 Hz, 1H, C_5 proton of coumarin), 7.61 (dt, $J = 7.1$, 1.3 Hz, 1H, C_5 proton of quinoline), 7.52–7.28 (m, Ar–H), 3.45 (br s, 4H, piperazine), 3.85 (br s, 4H, piperazine), 1.92 (s, 1H, N–C<u>H</u>$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.82$ (1C, C-2, <u>C</u>–S–C, *s*-triazine to oxadiazole ring), 172.54 (1C, C-4, <u>C</u>–O–C, *s*-triazine to quinoline ring), 169.69, 168.23 (2C, C=O, coumarin and *s*-triazine to piperazine <u>C</u>–N), 163.27 (C-2, oxadiazole), 159.20 (C-5, oxadiazole), 149.45-117.93 (17C, Ar–C), 49.94, 46.37 (4C, piperazine), 23 (1C, N–<u>C</u>H$_3$).

3-{5-[4-(4-Ethyl-piperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7b**. IR (KBr) cm^{-1}: 1739 (C=O, coumarin), 1630, 1542 (2C=N of oxadiazole), 1254 (C–O–C), 1148 (N–N, oxadiazole), 1045 (C–O–C–, oxadiazole), 832 (*s*-triazine C_3N_3 str.), 697 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (dd, $J = 7.2$, 1.3 Hz, 1H, C_2 proton of quinoline), 8.66 (dt, $J = 7.8$, 1.7 Hz, 1H, C_4 proton of quinoline), 7.99 (s, 1H, C_4 proton of coumarin), 7.79 (dd, $J = 7.7$, 1.6 Hz, 1H, C_5 proton of coumarin), 7.64 (dt, $J = 7.3$, 1.4 Hz, 1H, C_5 proton of quinoline), 7.49–7.31 (m, Ar–H), 3.42 (br s, 4H, piperazine), 3.84 (br s, 4H, piperazine), 2.46 (q, $J = 8.2$ Hz, 2H, N–C<u>H</u>$_2$), 1.76 (t, $J = 6.6$ Hz 3H, N–CH$_2$–C<u>H</u>$_3$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 176.95$ (1C, C-2, <u>C</u>–S–C, *s*-triazine to oxadiazole ring), 171.84 (1C, C-4, <u>C</u>–O–C, *s*-triazine to quinoline ring), 169.93, 168.04 (2C, *s*-triazine to piperazine <u>C</u>–N and C=O, coumarin), 163.55 (C-2, oxadiazole), 159.8 (C-5, oxadiazole), 151.63–119.07 (17C, Ar–C), 49.13, 45.61, 44.95 (**7c**, piperazine ring carbon atoms and N–<u>C</u>H$_2$), 23.98 (1C, –<u>C</u>H$_3$).

3-{5-[4-[4-(3-Chloro-phenyl)-piperazin-1-yl]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7c**. IR (KBr) cm^{-1}: 1733 (C=O, coumarin), 1624, 1530 (2C=N of oxadiazole), 1256 (C–O–C), 1162 (N–N, oxadiazole), 1028 (C–O–C–, oxadiazole), 827 (*s*-triazine C_3N_3 str.), 700 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (dd, $J = 7.8$, 1.4 Hz, 1H, C_2 proton of quinoline), 8.65 (dt, $J = 7.7$, 1.3 Hz, 1H, C_4 proton of quinoline), 8.05 (s, 1H, C_4 proton of coumarin), 7.78 (dd, $J = 7.6$, 1.7 Hz, 1H, C_5 proton of coumarin), 7.66 (dt, $J = 7.8$, 1.5 Hz, 1H, C_5 proton of quinoline), 7.55–7.34 (m, Ar–H), 7.02 (t, $J = 7.2$ Hz, 1H), 6.89 (dt, $J = 6.8$,

1.1 Hz, 1H), 3.47 (br s, 4H, piperazine), 3.81 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.46$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.91 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 169.83, 168.12 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 164.24 (C-2, oxadiazole), 159.99 (C-5, oxadiazole), 150.93–118.28 (23C, Ar–C), 48.31, 46.85 (4C, piperazine).

3-{5-[4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7d**. IR (KBr) cm^{-1}: 1729 (C=O, coumarin), 1625, 1533 (2C=N of oxadiazole), 1255 (C–O–C), 1167 (N–N, oxadiazole), 1052 (C–O–C–, oxadiazole), 835 (*s*-triazine C_3N_3 str.), 699 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (dd, $J = 7.2$, 1.1 Hz, 1H, C_2 proton of quinoline), 8.67 (dt, $J = 7.6$, 1.6 Hz, 1H, C_4 proton of quinoline), 8.01 (s, 1H, C_4 proton of coumarin), 7.80 (dd, $J = 7.5$, 1.9 Hz, 1H, C_5 proton of coumarin), 7.59 (dt, $J = 7.2$, 1.3 Hz, 1H, C_5 proton of quinoline), 7.50–7.28 (m, Ar–H), 7.18 (dd, $J = 6.6$, 1.2 Hz, 1H), 6.92 (dd, $J = 7.1$, 1.4 Hz, 1H), 6.79 (t, $J = 8.1$ Hz, 1H), 3.49 (br s, 4H, piperazine), 3.85 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 178.15$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.69 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 170.38, 168.62 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 163.17 (C-2, oxadiazole), 160.23 (C-5, oxadiazole), 151.44-123.85 (23C, Ar–C), 49.02, 48.28 (4C, piperazine).

3-{5-[4-Piperidin-1-yl-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7e**. IR (KBr) cm^{-1}: 1724 (C=O, coumarin), 1631, 1551 (2C=N of oxadiazole), 1254 (C–O–C), 1146 (N–N, oxadiazole), 1051 (C–O–C–, oxadiazole), 829 (*s*-triazine C_3N_3 str.), 701 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (dd, $J = 7.2$, 1.6 Hz, 1H, C_2 proton of quinoline), 8.62 (dt, $J = 7.3$, 1.5 Hz, 1H, C_4 proton of quinoline), 7.98 (s, 1H, C_4 proton of coumarin), 7.73 (dd, $J = 7.2$, 1.4 Hz, 1H, C_5 proton of coumarin), 7.63 (dt, $J = 7.7$, 1.2 Hz, 1H, C_5 proton of quinoline), 7.48–7.35 (m, Ar–H), 3.87 (t, $J = 5.5$ Hz, 4H, piperidine), 3.71 (t, $J = 5.3$ Hz, 4H, piperidine), 1.72–1.68 (m, 2H, piperidine). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.49$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 171.58 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 170.31, 168.72 (2C, *s*-triazine to piperidine C–N and C=O, coumarin), 163.74 (C-2, oxadiazole), 159.06 (C-5, oxadiazole), 152.07–118.28 (17C, Ar–C), 46.68, 29.11, 22.90 (**7c**, piperidine).

3-{5-[4-Morpholin-4-yl-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7f**. IR (KBr) cm^{-1}: 1730 (C=O, coumarin), 1619, 1547 (2C=N of oxadiazole), 1375 (Morpholine C–O–C str.), 1256 (C–O–C), 1139 (N–N, oxadiazole), 1043 (C–O–C–, oxadiazole), 834 (*s*-triazine C_3N_3 str.), 698 (C–S–C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 8.98 (dd, $J = 7.9$, 1.7 Hz, 1H, C_2 proton of quinoline), 8.56 (dt, $J = 6.9$, 1.8 Hz, 1H, C_4 proton of quinoline), 8.06 (s, 1H, C_4 proton of coumarin), 7.81 (dd, $J = 7.6$, 1.9 Hz, 1H, C_5 proton of coumarin), 7.66 (dt, $J = 7.8$, 1.6 Hz, 1H, C_5 proton of quinoline), 7.54–7.37 (m, Ar–H), 3.94 (t, $J = 4.7$ Hz, 4H, morpholine), 3.66 (t, $J = 5.6$ Hz, 4H, morpholine). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.92$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 173.64 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 169.44, 168.22 (2C, *s*-triazine to morpholine C–N and C=O, coumarin), 163.68 (C-2, oxadiazole), 159.77 (C-5, oxadiazole), 150.54-119.62 (19C, Ar–C), 66.47 (morpholine C-3 and C-5), 53.67 (morpholine C-2 and C-6).

3-{5-[4-(4-Phenyl-piperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7g**. IR (KBr) cm^{-1}: 1733 (C=O, coumarin), 1626, 1532 (2C=N of oxadiazole), 1256 (C–O–C), 1170 (N–N, oxadiazole), 1041 (C–O–C–, oxadiazole), 829 (*s*-triazine C_3N_3 str.), 701 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (dd, $J = 7.6$, 1.1 Hz, 1H, C_2 proton of quinoline), 8.59 (dt, $J = 7.0$, 1.4 Hz, 1H, C_4 proton of quinoline), 8.03 (s, 1H, C_4 proton of coumarin), 7.77 (dd, $J = 7.8$, 1.6 Hz, 1H, C_5 proton of coumarin), 7.61 (dt, $J = 7.7$, 1.5 Hz, 1H, C_5 proton of quinoline), 7.50–7.29 (m, Ar–H), 3.49 (br s, 4H, piperazine), 3.86 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.01$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 171.92 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 169.77, 167.07 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 164.05 (C-2, oxadiazole), 158.82 (C-5, oxadiazole), 151.65–117.36 (23C, Ar–C), 49.42, 46.64 (4C, piperazine).

3-{5-[4-(4-Acetyl-piperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7h**. IR (KBr) cm^{-1}: 1732 (C=O, coumarin), 1622, 1540 (2C=N of oxadiazole), 1256 (C–O–C), 1149 (N–N, oxadiazole), 1054 (C–O–C–, oxadiazole), 831 (*s*-triazine C_3N_3 str.), 700 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (dd, $J = 7.7$, 1.2 Hz, 1H, C_2 proton of quinoline), 8.65 (dt, $J = 7.3$, 1.6 Hz, 1H, C_4 proton of quinoline), 8.05 (s, 1H, C_4 proton of coumarin), 7.79 (dd, $J = 7.6$, 1.4 Hz, 1H, C_5 proton of coumarin), 7.66 (dt, $J = 7.8$, 1.6 Hz, 1H, C_5 proton of quinoline), 7.52–7.36 (m, Ar–H), 3.46 (br s, 4H, piperazine), 3.85 (br s, 4H, piperazine), 2.21 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 178.10$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.18 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 170.09, 169.91, 167.63 (3C, *s*-triazine to piperazine C–N, C=O, coumarin and C=O of acetyl linkage), 163.94 (C-2, oxadiazole), 159.86 (C-5, oxadiazole), 152.18–120.42 (17C, Ar–C), 49.35, 46.90 (4C, piperazine), 23.37 (1C, –CH_3).

3-{5-[4-(4-Isopropyl-piperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7i**. IR (KBr) cm^{-1}: 1733 (C=O, coumarin), 1640, 1551

(2C=N of oxadiazole), 1255 (C–O–C), 1154 (N–N, oxadiazole), 1062 (C–O–C–, oxadiazole), 837 (*s*-triazine C_3N_3 str.), 697 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (dd, $J = 7.6$, 1.8 Hz, 1H, C_2 proton of quinoline), 8.55 (dt, $J = 7.6$, 1.4 Hz, 1H, C_4 proton of quinoline), 8.00 (s, 1H, C_4 proton of coumarin), 7.80 (dd, $J = 7.3$, 1.3 Hz, 1H, C_5 proton of coumarin), 7.64 (dt, $J = 7.3$, 1.9 Hz, 1H, C_5 proton of quinoline), 7.55–7.31 (m, Ar–H), 3.45 (br s, 4H, piperazine), 3.80 (br s, 4H, piperazine), 2.21 (d, $J = 6.2$ Hz, 6H, –2C$\underline{H}_3$), 1.90 (m, 1H, –C$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.40$ (1C, C-2, $\underline{C}$–S–C, *s*-triazine to oxadiazole ring), 172.68 (1C, C-4, $\underline{C}$–O–C, *s*-triazine to quinoline ring), 170.34, 168.25 (2C, *s*-triazine to piperazine $\underline{C}$–N and C=O, coumarin), 162.82 (C-2, oxadiazole), 157.70 (C-5, oxadiazole), 150.74–121.48 (17C, Ar–C), 53.80, 50.34, 48.13 (**7c**, piperazine ring and N–$\underline{C}$H at isopropyl linkage), 30.48 (2C, 2$\underline{C}$H$_3$).

3-{5-[4-(4-Pyridin-2-yl-piperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7j**. IR (KBr) cm^{-1}: 1740 (C=O, coumarin), 1620, 1533 (2C=N of oxadiazole), 1254 (C–O–C), 1165 (N–N, oxadiazole), 1061 (C–O–C–, oxadiazole), 833 (*s*-triazine C_3N_3 str.), 696 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (dd, $J = 7.6$, 1.8 Hz, 1H, C_2 proton of quinoline), 8.60 (dt, $J = 7.2$, 1.7 Hz, 1H, C_4 proton of quinoline), 8.06 (s, 1H, C_4 proton of coumarin), 7.81 (dd, $J = 7.6$, 1.5 Hz, 1H, C_5 proton of coumarin), 7.59 (dt, $J = 6.8$, 1.2 Hz, 1H, C_5 proton of quinoline), 7.49–7.25 (m, Ar–H), 7.09 (dd, $J = 8.0$, 1.2 Hz, 1H, pyridyl), 6.78–6.81 (m, 2H), 3.52 (br s, 4H, piperazine), 3.88 (br s, 4H, piperazine), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 176.36$ (1C, C-2, $\underline{C}$–S–C, *s*-triazine to oxadiazole ring), 172.90 (1C, C-4, $\underline{C}$–O–C, *s*-triazine to quinoline ring), 169.21, 168.04 (2C, *s*-triazine to piperazine $\underline{C}$–N and C=O, coumarin), 163.32 (C-2, oxadiazole), 159.30 (C-5, oxadiazole), 151.57-118.15 (21C, Ar–C), 48.52, 44.98 (4C, piperazine).

3-{5-[4-(4-Pyrimidin-2-yl-piperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7k**. IR (KBr) cm^{-1}: 1729 (C=O, coumarin), 1636, 1546 (2C=N of oxadiazole), 1255 (C–O–C), 1164 (N–N, oxadiazole), 1055 (C–O–C–, oxadiazole), 829 (*s*-triazine C_3N_3 str.), 700 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (dd, $J = 6.8$, 2.2 Hz, 1H, C_2 proton of quinoline), 8.64 (dt, $J = 7.8$, 1.9 Hz, 1H, C_4 proton of quinoline), 8.47–8.49 (m, 2H, pyrimidyl), 8.07 (s, 1H, C_4 proton of coumarin), 7.72 (dd, $J = 7.1$, 1.0 Hz, 1H, C_5 proton of coumarin), 7.60 (dt, $J = 7.5$, 1.4 Hz, 1H, C_5 proton of quinoline), 7.55–7.31 (m, Ar–H), 6.71 (t, $J = 6.6$ Hz, 1H, pyrimidyl), 3.39 (br s, 4H, piperazine), 3.89 (br s, 4H, piperazine), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 176.94$ (1C, C-2, $\underline{C}$–S–C, *s*-triazine to oxadiazole ring), 172.34 (1C, C-4, $\underline{C}$–O–C, *s*-triazine to quinoline ring), 169.57, 167.22 (2C, *s*-triazine to piperazine $\underline{C}$–N and C=O, coumarin), 164.70 (C-2, oxadiazole), 159.38 (C-5, oxadiazole), 148.16–119.03 (21C, Ar–C), 49.58, 47.34 (4C, piperazine).

3-{5-[4-(4-Benzyl-piperazin-1-yl)-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7l**. IR (KBr) cm^{-1}: 1741 (C=O, coumarin), 1622, 1531 (2C=N of oxadiazole), 1256 (C–O–C), 1160 (N–N, oxadiazole), 1041 (C–O–C–, oxadiazole), 833 (*s*-triazine C_3N_3 str.), 699 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (dd, $J = 7.7$, 1.5 Hz, 1H, C_2 proton of quinoline), 8.66 (dt, $J = 7.8$, 1.1 Hz, 1H, C_4 proton of quinoline), 8.03 (s, 1H, C_4 proton of coumarin), 7.76 (dd, $J = 7.1$, 1.1 Hz, 1H, C_5 proton of coumarin), 7.59 (dt, $J = 7.0$, 1.5 Hz, 1H, C_5 proton of quinoline), 7.47–7.27 (m, Ar–H), 3.50 (br s, 4H, piperazine), 3.81 (br s, 4H, piperazine), 2.19 (s, 2H, N–C$\underline{H}_2$); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.67$ (1C, C-2, $\underline{C}$–S–C, *s*-triazine to oxadiazole ring), 172.55 (1C, C-4, $\underline{C}$–O–C, *s*-triazine to quinoline ring), 169.85, 168.35 (2C, *s*-triazine to piperazine $\underline{C}$–N and C=O, coumarin), 164.32 (C-2, oxadiazole), 160.67 (C-5, oxadiazole), 152.43–116.76 (23C, Ar–C), 66.90 (N–$\underline{C}$H$_2$, piperazine nitrogen atom to phenyl ring), 51.28, 46.34 (4C, piperazine).

3-{5-[4-(4-Benzyl-piperidin-1-yl)-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7m**. IR (KBr) cm^{-1}: 1733 (C=O, coumarin), 1627, 1548 (2C=N of oxadiazole), 1256 (C–O–C), 1157 (N–N, oxadiazole), 1050 (C–O–C–, oxadiazole), 835 (*s*-triazine C_3N_3 str.), 696 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (dd, $J = 7.3$, 1.6 Hz, 1H, C_2 proton of quinoline), 8.62 (dt, $J = 7.5$, 1.2 Hz, 1H, C_4 proton of quinoline), 8.08 (s, 1H, C_4 proton of coumarin), 7.73 (dd, $J = 7.1$, 1.5 Hz, 1H, C_5 proton of coumarin), 7.64 (dt, $J = 7.3$, 1.2 Hz, 1H, C_5 proton of quinoline), 7.51–7.30 (m, Ar–H), 3.77 (4H, t, $J = 7.8$ Hz, piperidine), 3.59 (4H, t, $J = 8.3$ Hz, piperidine), 2.48 (2H, s, N–C$\underline{H}_2$), 1.94 (1H, t, $J = 6.8$ Hz, -C$\underline{H}$, piperidine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.90$ (1C, C-2, $\underline{C}$–S–C, *s*-triazine to oxadiazole ring), 173.24 (1C, C-4, $\underline{C}$–O–C, *s*-triazine to quinoline ring), 169.57, 168.65 (2C, *s*-triazine to piperidine $\underline{C}$–N and C=O, coumarin), 162.91 (C-2, oxadiazole), 160.05 (C-5, oxadiazole), 148.95–122.51 (23C, Ar–C), 48.07, 43.61, 36.46, 30.77 (6C, piperazine ring carbon atoms and N–$\underline{C}$H$_2$).

3-{5-[4-(3,5-Dimethyl-piperidin-1-yl)-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7n**. IR (KBr) cm^{-1}: 1740 (C=O, coumarin), 1625, 1540 (2C=N of oxadiazole), 1258 (C–O–C), 1159 (N–N, oxadiazole), 1048 (C–O–C–, oxadiazole), 836 (*s*-triazine C_3N_3 str.), 699 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (dd, $J = 7.7$, 1.8 Hz, 1H, C_2 proton of quinoline), 8.57 (dt, $J = 7.1$, 1.0 Hz, 1H, C_4 proton of quinoline), 8.01 (s, 1H, C_4 proton of coumarin), 7.76 (dd, $J = 7.4$, 1.4 Hz, 1H, C_5 proton of coumarin), 7.67 (dt, $J = 7.6$, 1.5 Hz, 1H,

C_5 proton of quinoline), 7.54–7.26 (m, Ar–H), 3.73 (dd, $J = 12.5$, 7.2 Hz, 2H, piperidine), 2.91 (dd, $J = 12.9$, 7.3 Hz, 2H, piperidine), 1.79–1.73 (m, 3H, piperidne), 1.63 (d, $J = 6.7$ Hz, 6H, $2C\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.23$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.07 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 170.24, 167.44 (2C, *s*-triazine to piperidine C–N and C=O, coumarin), 163.44 (C-2, oxadiazole), 159.15 (C-5, oxadiazole), 149.08–118.20 (17C, Ar–C), 48.17, 46.71, 29.16 (**7c**, piperidine), 19.18 (2C, $2\underline{C}H_3$).

3-{5-[4-(4-Benzhydryl-piperazin-1-yl)-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7o**. IR (KBr) cm^{-1}: 1744 (C=O, coumarin), 1630, 1550 (2C=N of oxadiazole), 1251 (C–O–C), 1144 (N–N, oxadiazole), 1047 (C–O–C–, oxadiazole), 830 (*s*-triazine C_3N_3 str.), 701 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (dd, $J = 7.5$, 1.6 Hz, 1H, C_2 proton of quinoline), 8.65 (dt, $J = 7.7$, 1.6 Hz, 1H, C_4 proton of quinoline), 8.04 (s, 1H, C_4 proton of coumarin), 7.72 (dd, $J = 7.0$, 1.6 Hz, 1H, C_5 proton of coumarin), 7.60 (dt, $J = 7.2$, 1.3 Hz, 1H, C_5 proton of quinoline), 7.51–7.25 (m, Ar–H), 4.09 (s, 1H, N–C$\underline{H}$), 3.51 (br s, 4H, piperazine), 3.89 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 178.35$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.54 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 169.14, 167.17 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 162.70 (C-2, oxadiazole), 158.44 (C-5, oxadiazole), 150.54–117.14 (30C, Ar–C), 49.77, 47.79 (4C, piperazine).

3-{5-[4-{4-[(4-Chloro-phenyl)-phenyl-methyl]-piperazin-1-yl}-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7p**. IR (KBr) cm^{-1}: 1732 (C=O, coumarin), 1616, 1521 (2C=N of oxadiazole), 1255 (C–O–C), 1153 (N–N, oxadiazole), 1042 (C–O–C–, oxadiazole), 829 (*s*-triazine C_3N_3 str.), 696 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (dd, $J = 7.1$, 1.2 Hz, 1H, C_2 proton of quinoline), 8.57 (dt, $J = 7.3$, 1.1 Hz, 1H, C_4 proton of quinoline), 7.99 (s, 1H, C_4 proton of coumarin), 7.79 (dd, $J = 7.3$, 1.4 Hz, 1H, C_5 proton of coumarin), 7.61 (dt, $J = 7.5$, 1.0 Hz, 1H, C_5 proton of quinoline), 7.49–7.27 (m, Ar–H), 3.99 (s, 1H, N–C$\underline{H}$), 3.42 (br s, 4H, piperazine), 3.79 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.94$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.11 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 168.97, 167.75 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 163.96 (C-2, oxadiazole), 161.34 (C-5, oxadiazole), 151.40–116.84 (30C, Ar–C), 47.4, 46.0 (4C, piperazine).

3-{5-[4-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7q**. IR (KBr) cm^{-1}: 1738 (C=O, coumarin), 1630, 1531 (2C=N of oxadiazole), 1256 (C–O–C), 1166 (N–N, oxadiazole), 1041 (C–O–C–, oxadiazole), 829 (*s*-triazine C_3N_3 str.), 700 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (dd, $J = 7.6$, 1.3 Hz, 1H, C_2 proton of quinoline), 8.66 (dt, $J = 7.7$, 1.2 Hz, 1H, C_4 proton of quinoline), 8.04 (s, 1H, C_4 proton of coumarin), 7.80 (dd, $J = 7.5$, 1.8 Hz, 1H, C_5 proton of coumarin), 7.69 (dt, $J = 7.8$, 1.5 Hz, 1H, C_5 proton of quinoline), 7.56–7.35 (m, Ar–H), 6.82 (dd, $J = 12.6$, 6.5 Hz, 2H), 6.70–6.74 (m, 1H), 6.57 (dd, $J = 12.8$, 6.3 Hz, 1H), 3.47 (br s, 4H, piperazine), 3.83 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 176.84$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.82 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 169.61, 168.37 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 164.78 (C-2, oxadiazole), 158.71 (C-5, oxadiazole), 152.26 (1C, C–F), 151.31-118.17 (22C, Ar–C), 51.62, 48.33 (4C, piperazine); ^{19}F NMR (400 MHz, $CDCl_3$): δ −119.93 (1F, s, C–F).

3-{5-[4-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7r**. IR (KBr) cm^{-1}: 1741 (C=O, coumarin), 1622, 1533 (2C=N of oxadiazole), 1256 (C–O–C), 1150 (N–N, oxadiazole), 1043 (C–O–C–, oxadiazole), 834 (*s*-triazine C_3N_3 str.), 700 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (dd, $J = 8.1$, 1.6 Hz, 1H, C_2 proton of quinoline), 8.60 (dt, $J = 7.1$, 1.6 Hz, 1H, C_4 proton of quinoline), 8.00 (s, 1H, C_4 proton of coumarin), 7.74 (dd, $J = 7.4$, 1.7 Hz, 1H, C_5 proton of coumarin), 7.66 (dt, $J = 7.6$, 1.4 Hz, 1H, C_5 proton of quinoline), 7.52–7.31 (m, Ar–H), 7.11 (dd, $J = 13.5$, 7.4 Hz, 2H), 6.66–6.63 (m, 1H), 6.49 (dd, $J = 12.8$, 6.8 Hz, 1H), 3.45 (br s, 4H, piperazine), 3.85 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.04$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 173.07 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 170.25, 168.01 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 163.51 (C-2, oxadiazole), 158.54 (C-5, oxadiazole), 152.88 (1C, C–F), 152.08–118.59 (22C, Ar–C), 50.90, 46.93 (4C, piperazine); ^{19}F NMR (400 MHz, $CDCl_3$): δ −116.38 (1F, s, C–F).

3-(5-{4-(Quinolin-4-yloxy)-6-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-1,3,5-triazin-2-ylsulfanyl}-[1,3,4]oxadiazol-2-yl)-chromen-2-one **7s**. IR (KBr) cm^{-1}: 1730 (C=O, coumarin), 1638, 1531 (2C=N of oxadiazole), 1256 (C–O–C), 1166 (N–N, oxadiazole), 1046 (C–O–C–, oxadiazole), 838 (*s*-triazine C_3N_3 str.), 698 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (dd, $J = 7.7$, 1.5 Hz, 1H, C_2 proton of quinoline), 8.64 (dt, $J = 7.3$, 1.4 Hz, 1H, C_4 proton of quinoline), 8.07 (s, 1H, C_4 proton of coumarin), 7.75 (dd, $J = 7.8$, 1.6 Hz, 1H, C_5 proton of coumarin), 7.61 (dt, $J = 7.4$, 1.7 Hz, 1H, C_5 proton of quinoline), 7.53–7.28 (m, Ar–H), 7.05 (dt, $J = 7.5$, 1.6 Hz, 1H), 3.48 (br s, 4H, piperazine), 3.84 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 176.96$ (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.16 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 170.46, 167.35 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 162.98 (C-2,

oxadiazole), 158.66 (C-5, oxadiazole), 149.38-119.92 (24C, Ar–C including C–CF_3 at 130.12 and CF_3 at 125.02), 51.55, 49.57 (4C, piperazine); ^{19}F NMR (400 MHz, $CDCl_3$): δ −64.6 (6F, s, 2-CF_3).

3-(5-{4-(Quinolin-4-yloxy)-6-[4-(2,3,4-trimethoxy-benzyl)-piperazin-1-yl]-1,3,5-triazin-2-ylsulfanyl}-[1,3,4]oxadiazol-2-yl)-chromen-2-one **7t**. IR (KBr) cm^{-1}: 1736 (C=O, coumarin), 1631, 1540 (2C=N of oxadiazole), 1252 (C–O–C), 1150 (N–N, oxadiazole), 1039 (C–O–C–, oxadiazole), 833 (*s*-triazine C_3N_3 str.), 701 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (dd, J = 7.2, 1.2 Hz, 1H, C_2 proton of quinoline), 8.55 (dt, J = 7.0, 1.3 Hz, 1H, C_4 proton of quinoline), 8.05 (s, 1H, C_4 proton of coumarin), 7.80 (dd, J = 7.7, 1.3 Hz, 1H, C_5 proton of coumarin), 7.67 (dt, J = 7.8, 1.7 Hz, 1H, C_5 proton of quinoline), 7.55–7.24 (m, Ar–H), 7.06 (d, J = 7.4 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 3.89 (br s, 4H, piperazine), 3.78 (s, 1H, *N*-CH_2), 3.68 (s, 9H, 3OCH_3), 3.49 (br s, 4H, piperazine); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.17 (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.90 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 169.07, 168.15 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 164.05 (C-2, oxadiazole), 160.61 (C-5, oxadiazole), 153.71–121.62 (23C, Ar–C), 60.78, 60.34 (3C, 3OCH_3), 48.31, 44.83 (4C, piperazine), 39.22 (1C, –CH_2).

3-{5-[4-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-6-(quinolin-4-yloxy)-1,3,5-triazin-2-ylsulfanyl]-[1,3,4]oxadiazol-2-yl}-chromen-2-one **7u**. IR (KBr) cm^{-1}: 1740 (C=O, coumarin), 1620, 1543 (2C=N of oxadiazole), 1257 (C–O–C), 1158 (N–N, oxadiazole), 1041 (C–O–C–, oxadiazole), 834 (*s*-triazine C_3N_3 str.), 697 (C–S–C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (dd, J = 7.9, 1.7 Hz, 1H, C_2 proton of quinoline), 8.58 (dt, J = 7.2, 1.2 Hz, 1H, C_4 proton of quinoline), 8.01 (s, 1H, C_4 proton of coumarin), 7.81 (dd, J = 7.7, 1.5 Hz, 1H, C_5 proton of coumarin), 7.63 (dt, J = 7.4, 1.7 Hz, 1H, C_5 proton of quinoline), 7.52–7.34 (m, Ar–H), 7.13 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 4.07 (s, 3H, OCH_3), 3.82 (br s, 4H, piperazine), 3.50 (br s, 4H, piperazine). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.77 (1C, C-2, C–S–C, *s*-triazine to oxadiazole ring), 172.44 (1C, C-4, C–O–C, *s*-triazine to quinoline ring), 169.55, 168.44 (2C, *s*-triazine to piperazine C–N and C=O, coumarin), 163.04 (C-2, oxadiazole), 160.32 (C-5, oxadiazole), 151.97–118.38 (23C, Ar–C), 56.07 (1C, –OCH_3), 50.0, 48.1 (4C, piperazine).

Antimicrobial activity

The synthesized *s*-triazinyl derivatives (**7a**–**u**) were examined for antimicrobial activity against several bacteria (*Staphyloccoccus aureus* MTCC 96, *Bacillus cereus* MTCC 619, *Escherichia coli* MTCC 739, *Pseudomonas aeruginosa* MTCC 741, *Klebsiella pneumoniae* MTCC 109, *Salmonella typhi* MTCC 733, and *Proteus vulgaris* MTCC 1771) and fungi (*Aspergillus niger* MTCC 282, *Aspergillus fumigatus* MTCC 343, *Aspergillus clavatus* MTCC 1323, and *Candida albicans* MTCC 183) species using the agar diffusion test (Gillespie, 1994). The Mueller–Hinton agar media were sterilized (autoclaved at 120°C for 30 min), poured at uniform depth of 5 mm and allowed to solidify. The microbial suspension (10^5 CFU/ml) (0.5 McFarland Nephelometery Standards) was streaked over the surface of media using a sterile cotton swab to ensure even growth of the organisms. The tested compounds were dissolved in dimethyl sulfoxide to give solutions of 3.12–100 μg/ml. Sterile filter paper disks measuring 6.25 mm in diameter (Whatman no. 1 filter paper), previously soaked in a known concentration of the respective test compound in dimethyl sulfoxide, were placed on the solidified nutrient agar medium that had been inoculated with the respective microorganism, and the plates were incubated for 24 h at (37 ± 1) °C. A control disk impregnated with an equivalent amount of dimethyl sulfoxide without any sample was also used and did not produce any inhibition. Ciprofloxacin and ketoconazole (100 μg/disk) were used as control drugs for antibacterial and antifungal activities, respectively, and assayed for MICs at the concentration levels 1.56, 0.39, 1.56, 1.56, 0.78 and 0.39 μg/ml in the present study.

To determine the minimum inhibitory concentration (Hawkey and Lewis, 1994), a stock solution of the synthesized compound (100 μg/ml) in dimethyl sulfoxide was prepared, and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar, i.e., nutrient agar for evaluation of antibacterial activity and sabouraud dextrose agar for antifungal activity. The medium containing the test compound was poured into a Petri dish at a depth of 4–5 mm and allowed to solidify under aseptic conditions. A suspension of the respective microorganism of ~10^5 CFU/ml was prepared and applied to plates with serially diluted compounds with concentrations in the range of 3.12–100 μg/ml in dimethyl sulfoxide and incubated at (37 ± 1) °C for 24 h (bacteria) or 48 h (fungi). The lowest concentration of the substance that prevents the development of visible growth is considered to be the MIC value.

Acknowledgments The authors are thankful to the faculty of the Department of Applied Chemistry, S. V. National Institute of Technology, Surat for providing the scholarship, encouragement, and facilities.

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