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Short communication

Synthesis and biological evaluation of some thiazolidinones as antimicrobial agents

Divyesh Patel [a], Premlata Kumari [a,*], Navin Patel [b]

[a] Applied Chemistry Department, S.V. National Institute of Technology, Surat 395007, India
[b] Department of Chemistry, V.N. South Gujarat University, Surat 395007, India

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ABSTRACT

A novel series of thiazolidinone derivatives namely 4-(4-dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-4-oxo-2-phenylthiazolidin-3-yl]-phenylamino}-[1,3,5]triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one have been synthesized from the key intermediate 4-[4-(4-aminophenylamino)-6-dimethylamino-[1,3,5]triazin-2-yloxy]-1-methyl-1*H*-quinolin-2-one (**7**). Condensation reaction of compound **7** with different aldehyde derivatives were performed to obtain Schiff base derivatives, which after cyclization gave thiazolidinones and finally they were reacted with *N*-ethylpiperazine to get target compounds. The newly synthesized compounds were evaluated for their antimicrobial activity against eight bacterial strains (*Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris, Shigella flexneri*) and four fungal strains (*Aspergillus niger, Candida albicans, Aspergillus fumigatus, Aspergillus clavatus*).

1. Introduction

The increasing incidence of infection caused by the rapid development of microbial resistance to most of the known antibiotics is a serious health problem. There are number of factors responsible for mutations in the microbial genomes. As multidrug resistant microbial strains proliferate, the necessity for effective therapy has stimulated research on the synthesis of novel antimicrobial molecules [1].

The advent of 1,3,5-triazines, associated with diverse biological activities such as antimicrobial [2,3], antiprotozoal [4], anticancer [5], antimalarial [6] and antiviral [7] activity accelerated the rate of progress of 1,3,5-triazine derivatives. Thiazolidinones are an important class of heterocyclic compounds known for their potential pharmaceutical applications [8]. In the development of an efficient procedure for the synthesis of some new thiazolidinone derivatives, we reported herein synthesis of key intermediate 4-[4-(4-aminophenylamino)-6-dimethylamino-[1,3,5]triazin-2-yloxy]-1-methyl-1*H*-quinolin-2-one (**7**) which contain quinolone derivative. Quinolone derivatives are used as anticancer [9], anti-HIV [10], antitumor [11], antioxidant, anti-inflammatory [12] and antithyroid agents [13]. On account of the prominent biological applications of 1,3,5-triazines and quinolones, the intermediate compound **7** seems to be a good candidate to fulfill our objective via its condensation with different aldehydes to afford Schiff base and further cyclization to get thiazolidinones. Piperazines and substituted piperazines are important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry [14–16]. Literature survey ascribes that Mannich reaction for thiazolidinone derivatives are important and these types of derivatives possess significant biological activities [17]. In view of these conceptions, we reported the synthesis of thiazolidinone derivatives attached with *N*-ethylpiperazine. All the novel derivatives were screened for their antimicrobial activity and their results are discussed.

2. Chemistry

The synthetic strategy adopted to obtain the target compounds is depicted in Scheme 1. 2,4,6-Trichloro-[1,3,5]triazine (**1**) on reaction with dimethylamine (**2**) at 0–5 °C yielded (4,6-dichloro-[1,3,5]triazin-2-yl)-dimethylamine (**3**). Further on reaction with 4-hydroxy-*N*-methylquinolone (**4**) yielded 4-(4-chloro-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one (**5**). The key intermediate 4-[4-(4-aminophenylamino)-6-dimethylamino-[1,3,5]triazin-2-yloxy]-1-methyl-1*H*-quinolin-2-one (**7**) was prepared in an excellent yield by condensation of compound **5** with *p*-phenylenediamine (**6**). Compound **7** when

* Corresponding author. Tel.: +91 9904003863.
E-mail address: premlatakumari1@gmail.com (P. Kumari).

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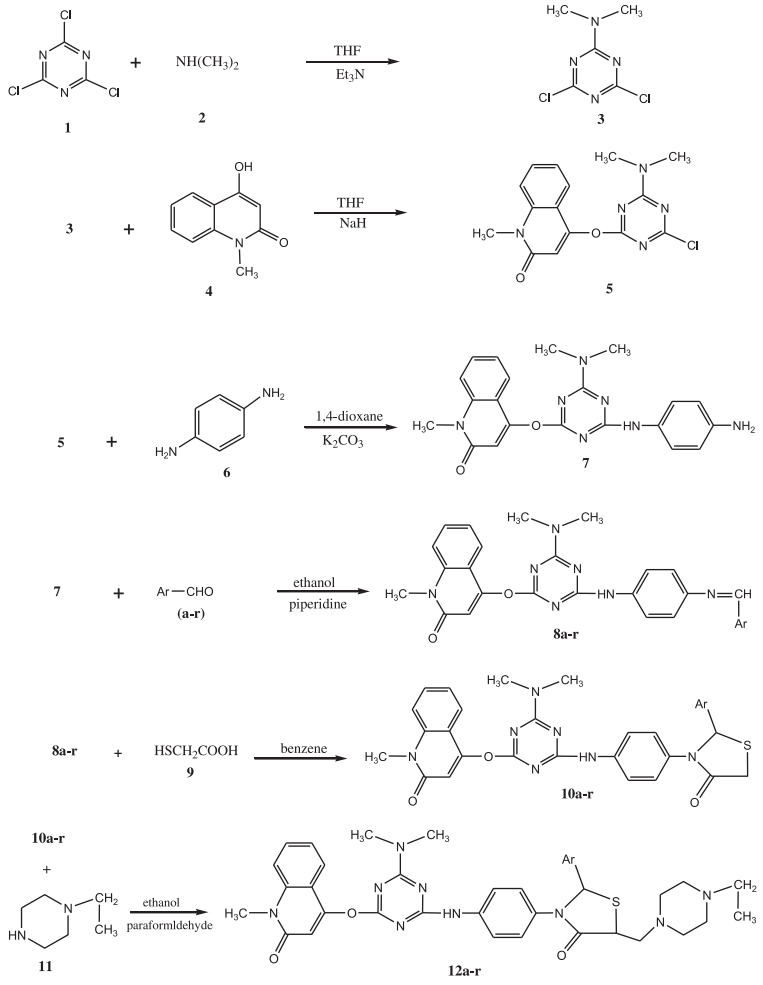
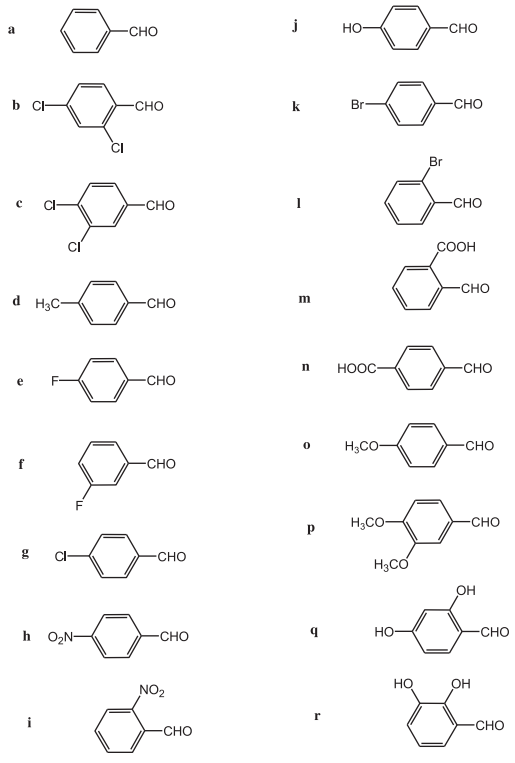


Where Ar-CHO **(a-r)** = Aromatic aldehydes



Scheme 1. Synthesis approach.

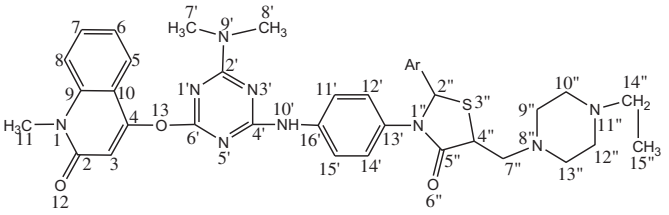


Fig. 1. General structure and numeration of thiazolidinone derivatives **12a**–**r**.

treated with aromatic aldehydes (**a**–**r**) gave the corresponding hydrazones **8a**–**r**. Cyclization of hydrazones with mercaptoacetic acid (**9**) led to the formation of thiazolidinones **10a**–**r**. Finally the target compounds **12a**–**r** were prepared by the reaction of **10a**–**r** with a mixture of paraformaldehyde and *N*-ethylpiperazine (**11**) in absolute ethanol (Fig. 1).

3. Result and discussion

The structures of the synthesized compounds were confirmed by spectral data and elemental analysis and they were in full agreement with the proposed structures. A C_3N_3 stretching in the *s*-triazine ring was observed at 825–840 cm^{-1} in IR spectrum. The formation of compound **3** was confirmed by the appearance of a singlet signal at δ 3.10 ppm due to $-C\underline{H}_3$ in ^1H NMR spectra. The formation of compound **5** bearing quinolone moiety was confirmed by ^1H NMR spectra which indicate signal at δ 3.55 ppm for $-C\underline{H}_3$ of quinolone. Protons corresponding to the quinolone moiety resonated at 6.05–8.31 ppm, in which doublet of doublet signal was observed at 8.31 ppm due to C-5 proton of quinoline ring of compound **5**. Furthermore, in the IR spectra, the band at 1666 cm^{-1} (C=O of quinolone) also confirmed the formation of compound **5**. Moreover, a characteristic band appeared at 1256 cm^{-1} corresponded to the C–O–C linkage, while disappearance of the –OH peak at 3600–3650 cm^{-1}, belonging to the 4-hydroxy-*N*-methylquinolone, gave correction to the formation of intermediate compound **5**.

The formation of key intermediate compound **7** was supported by the appearance of singlet signals at δ 11.48 ppm for $-N\underline{H}_2$ and δ 9.73 ppm for $-N\underline{H}$ in ^1H NMR spectrum and IR spectrum for NH and NH_2 at 3370 and 3480 cm^{-1} respectively also confirmed the formation of compound 7. Absence of a C–Cl stretching band at 700–760 cm^{-1} in the IR spectra confirmed the formation of compound **7** by condensation of *p*-phenylenediamine with *s*-triazine ring. Compound **7** when treated with aromatic aldehydes gave the corresponding hydrazones **8a**–**r**. For example when compound **7** treated with benzaldehyde (**a**) gave compound **8a** which did not show signals for NH_2 but showed the presence of a signal at δ 7.58 ppm for one proton of N=C$\underline{H}$–Ph. The signal observed at 9.77 ppm in the ^1H NMR spectra of compound **8a** was attributed to –NH group. The ^1H NMR spectra of compound **10a** showed the presence of doublet signals at δ 3.66, 3.76 ppm for two protons of S–C$\underline{H}_2$ and singlet at δ 5.12 ppm for S–C$\underline{H}$–N, which confirm the formation of the thiazolidinone ring. Compound **10a** showed a characteristic absorption for the cyclic carbonyl group at 1722 cm^{-1} in the IR spectra. The ^1H NMR spectra of compounds **12a**–**r** showed the absence of doublet signal for $-CH_2$ of thiazolidinone ring and showed the signal for methylene (4C$\underline{H}_2$) of *N*-ethylpiperazine. The newly obtained derivatives were evaluated for their *in vitro* antimicrobial activity against different types of bacterial strains and fungal strains and the results are summarized in Tables 1–3.

The antibacterial potency of the synthesized compounds was compared with broad spectrum antibiotic namely ciprofloxacin and

Table 1
In vitro (gram-positive) antibacterial activity of newly synthesized compounds.

Compound (100 μg/disc)	Zone of inhibition in mm (MIC in μg/mL)[a]	
	Gram-positive	
	S. aureus	*B. cereus*
12a	14 (100)	16 (100)
12b	25 (6.25)	19 (12.5)
12c	15 (25)	17 (12.5)
12d	26 (50)	24 (50)
12e	27 (6.25)	28 (6.25)
12f	20 (12.5)	23 (6.25)
12g	26 (6.25)	28 (6.25)
12h	22 (50)	22 (50)
12i	13 (100)	17 (50)
12j	23 (25)	20 (50)
12k	15 (100)	18 (100)
12l	<10 (100)	13 (100)
12m	21 (100)	21 (50)
12n	26 (25)	23 (12.5)
12o	28 (6.25)	27 (6.25)
12p	23 (25)	24 (12.5)
12q	15 (100)	17 (100)
12r	<10 (100)	12 (100)
Ciprofloxacin (100 μg/disc)	30 (1.0)	31 (1.0)
DMSO	–	–

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

their minimum inhibitory concentration (MIC) values were summarized in Tables 1 and 2. A close investigation of the MIC values indicates that all the compounds exhibited a varied range (6.25–100 μg/mL) of antibacterial activity against all the tested bacterial strains. Compound **12a** without any substituent at *ortho*, *meta* and *para* position of the phenyl group on thiazolidinone ring showed MIC = 100 μg/mL against studied gram-positive bacterial strains, also depicted MIC = 25 μg/mL against *Escherichia coli* and MIC = 100 μg/mL against all other gram-negative bacterial strains. In case of compounds **12b** and **12c**, which were having electron withdrawing chloro substituent, respectively at the *ortho*–*para* for compound **12b** and *meta*–*para* for compound **12c** position of phenyl ring attached at thiazolidinone ring shows effective inhibitory effect against all bacterial strains. Compound **12b** exhibited equipotent in terms of MIC = 6.25 μg/mL against *Staphylococcus aureus along with* compounds **12e**, **12g** and **12o**. Same compound **12b** found equipotent in terms of MIC = 6.25 μg/mL with **12n** with slight reduced inhibition zone (26 mm) against *Shigella flexneri*. Compound **12d** which has electron donating methyl group on *para* position of phenyl ring showed good ability (MIC = 50 μg/mL) to inhibit *S. aureus* and *Bacillus cereus*. The best activity for compound **12d** (MIC = 6.25 μg/mL) was observed against *Pseudomonas aeruginosa* and *Proteus vulgaris* among all the synthesized compounds. Compounds **12e**, **12f** and **12g**, which were having electron withdrawing fluoro and chloro substituents on phenyl ring attached to thiazolidinone moiety exerted significant activity with MIC value in the range of 6.25–50 μg/mL against all the tested bacterial strains. Compounds **12e** and **12g** showed the highest zone of inhibition 28 mm with excellent MIC = 6.25 μg/mL against *B. cereus* along with compound **12f** with reduced inhibition zone (23 mm). Compound **12e** exhibited the greatest activity against *E. coli* and *Salmonella typhi* at MIC = 6.25 μg/mL. Besides, compound **12f** was found to have inhibitory effect with the same MIC value against *E. coli* and *S. typhi* with slight reduced in inhibitory zones (23 mm and 24 mm respectively). Compound **12g** found to be superior in inhibiting the growth (26 mm of zone of inhibition) of *Klebsiella pneumoniae* (MIC = 6.25 μg/mL). Thiazolidinones **12h** and **12i**, with $-NO_2$ group substituted at phenyl ring on *para* and *ortho* position respectively exhibit similar MIC = 50 μg/mL against *B. cereus* and MIC = 100 μg/mL against *E. coli*, *P. aeruginosa*

Table 2
In vitro (gram-negative) antibacterial activity of newly synthesized compounds.

Compound (100 μg/disc)	Zone of inhibition in mm (MIC in μg/mL)[a]					
	Gram-negative					
	E. coli	*P. aeruginosa*	*K. pneumoniae*	*S. typhi*	*P. vulgaris*	*S. flexneri*
12a	22 (25)	13 (100)	<10 (100)	16 (50)	15 (100)	12 (100)
12b	24 (12.5)	21 (25)	23 (25)	15 (50)	20 (12.5)	26 (6.25)
12c	17 (25)	23 (25)	19 (12.5)	12 (50)	19 (25)	22 (12.5)
12d	24 (25)	26 (6.25)	24 (50)	23 (50)	27 (6.25)	24 (50)
12e	28 (6.25)	25 (12.5)	25 (25)	27 (6.25)	22 (25)	19 (25)
12f	23 (6.25)	20 (50)	22 (25)	24 (6.25)	19 (50)	25 (12.5)
12g	27 (12.5)	23 (50)	26 (6.25)	20 (50)	25 (25)	26 (12.5)
12h	24 (100)	18 (100)	23 (50)	22 (100)	25 (50)	22 (50)
12i	14 (100)	16 (100)	15 (100)	15 (100)	17 (100)	14 (100)
12j	16 (50)	14 (100)	19 (50)	17 (50)	16 (100)	13 (100)
12k	19 (100)	16 (100)	19 (100)	17 (100)	17 (100)	15 (100)
12l	<10 (100)	14 (100)	12 (100)	12 (100)	15 (100)	11 (100)
12m	18 (50)	13 (100)	16 (50)	13 (100)	12 (100)	15 (100)
12n	27 (6.25)	22 (25)	26 (12.5)	22 (50)	25 (12.5)	27 (6.25)
12o	27 (6.25)	25 (12.5)	25 (25)	26 (6.25)	21 (50)	26 (6.25)
12p	24 (25)	24 (12.5)	23 (50)	25 (25)	23 (50)	22 (50)
12q	15 (100)	17 (100)	16 (100)	14 (100)	14 (100)	16 (100)
12r	<10 (100)	11 (100)	16 (100)	14 (100)	13 (100)	<10 (100)
Ciprofloxacin (100 μg/disc)	32 (1.0)	33 (1.0)	33 (1.0)	30 (1.0)	31 (1.0)	32 (≤3)
DMSO	–	–	–	–	–	–

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

and *S. typhi*. Compound **12h** having *para* substituted $-NO_2$ group on phenyl ring depicted higher zone of inhibition against all the bacterial strains as compared to **12i**. Compound **12j**, with −OH group on phenyl ring at *para* position displayed better activity in terms of MIC and zone of inhibition as well against both gram-positive bacteria compared to compounds **12q** and **12r**, possessing dihydroxy substituent at phenyl ring. Compounds **12q** and **12r** showed weak inhibitory activity at 100 μg/mL of MIC against all bacterial strains. In addition, a close survey of inhibition zones of compound **12q** against *E. coli*, *P. aeruginosa* and *S. flexneri* were found higher than compound **12r**. Antibacterial activity of electron withdrawing bromo substituted compounds **12k** and **12i** showed lesser activity in terms of MIC = 100 μg/mL compared to fluoro and chloro substituted compounds **12e**, **12f** and **12g**. Strong inhibitory effect was shown by final derivatives **12n** and **12o** with MIC = 6.25 μg/mL (27 mm zone of inhibition) against *E. coli* along with similar efficacy of compounds **12e** and **12f** in terms of MIC = 6.25 μg/mL against the same bacterial strains. Same compounds, **12n** and **12o** showed similar MIC = 6.25 μg/mL with 27 mm and 26 mm zone of inhibition respectively, which were found most potent among all the synthesized compounds against *S. flexneri*. Compound **12o** was also found equipotent as **12e** and **12f** in terms of MIC with 26 mm diameter of inhibition zone against *S. typhi*. Compound **12o** exhibited the greatest activity against *S. aureus* at 6.25 μg/mL of MIC. Besides, two compounds **12e** and **12g** were found to have inhibitory effect with the same MIC value against *S. aureus* with slight reduced inhibitory zones (27 mm and 26 mm respectively). Compound **12p** also showed effective action against all bacterial strains in terms of MIC in the range of 12.5–50 μg/mL.

Table 3
In vitro antifungal activity of newly synthesized compounds.

Compound(100 μg/disc)	Zone of inhibition in mm (MIC in μg/mL)[a]			
	A. niger	*A. fumigatus*	*A. clavatus*	*C. albicans*
12a	12 (100)	<10 (100)	<10 (100)	14 (100)
12b	28 (6.25)	17 (25)	25 (12.5)	28 (12.5)
12c	21 (25)	16 (50)	19 (50)	23 (25)
12d	21 (100)	24 (50)	26 (25)	23 (50)
12e	26 (12.5)	28 (12.5)	25 (25)	25 (25)
12f	25 (12.5)	24 (50)	24 (50)	25 (25)
12g	26 (25)	26 (12.5)	23 (12.5)	27 (12.5)
12h	23 (50)	20 (100)	21 (100)	17 (100)
12i	<10 (100)	13 (100)	15 (100)	19 (100)
12j	18 (100)	21 (50)	21 (100)	19 (100)
12k	14 (100)	14 (100)	16 (100)	12 (100)
12l	<10 (100)	<10 (100)	13 (100)	<10 (100)
12m	15 (100)	11 (100)	17 (100)	17 (100)
12n	27 (25)	20 (50)	23 (50)	25 (100)
12o	25 (12.5)	27 (12.5)	24 (12.5)	26 (12.5)
12p	21 (100)	26 (25)	24 (50)	23 (50)
12q	11 (100)	15 (100)	17 (100)	<10 (100)
12r	<10 (100)	13 (100)	12 (100)	<10 (100)
Ketoconazole (100 μg/disc)	30 (≤3)	29 (1.0)	31 (1.0)	33 (1.0)
DMSO	–	–	–	–

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

The *in vitro* antifungal activities of compounds **12a**–**r** were studied against the fungal strains viz., *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus clavatus* and *Candida albicans*. Ketoconazole was used as a standard drug. The data of antifungal tests are depicted in Table 3. A close survey of the MIC in μg/mL values indicates that all the compounds **12a**–**r** exhibited a varied range (MIC = 6.25–100 μg/mL) of antifungal activity against all the tested fungal strains. Compound **12a** which has no substituent at *ortho*, *meta* and *para* position of the phenyl ring to thiazolidinone ring showed MIC = 100 μg/mL against all fungal strains. Compound **12b** which has electron withdrawing chloro substituent at the *ortho* and *para* position of phenyl ring exerted excellent activity against *A. niger* at MIC = 6.25 μg/mL with 28 mm of zone of inhibition. A significant inhibition was also observed toward *A. clavatus* and *C. albicans* at 12.5 μg/mL of MIC with 25 mm and 28 mm inhibitory zones respectively. Similar minimum inhibitory concentration level (MIC = 12.5 μg/mL) observed against the same fungi for compounds **12g** and **12o** with slightly reduced inhibition zone. Compound **12e** having electron withdrawing fluoro substituent at *para* position of phenyl ring exerted activity in the range of MIC = 12.5–25 μg/mL against all fungi. Compound **12e** exhibited the greatest activity against *A. fumigatus* at 12.5 μg/mL of MIC. Besides, two compounds **12g** and **12o** were found to have same MIC value against *A. fumigatus* with marginally reduced inhibitory

zones (26 mm and 27 mm respectively). Compound **12e** and **12f** showed MIC = 12.5 μg/mL against *A. niger*. Compound **12o**, which were having electron donating methyl substituent at *para* position of phenyl ring attached to thiazolidinone moiety shows admirable antifungal activity against all the tested fungal strains at MIC = 12.5 μg/mL with significant inhibitory zone in the range of 24––27 mm against all the fungal strains. All the remaining final thiazolidinone derivatives exerted good to moderate activity.

4. Conclusion

From the antimicrobial study we ascertained that some of the newly synthesized compound containing electron withdrawing group like chloro, fluoro as substituent on phenyl ring at thiazolidinone moiety **12b**, **12e**, **12f**, and **12g** showed significant activity against both the gram-positive as well as gram-negative bacteria. On the other hand, compound **12o** having electron donating group methoxy as substituent on phenyl ring also showed good activity against both bacterial strains (gram-positive and gram-negative). Antifungal screening was carried out on *A. niger*, *A. fumigatus*, *A. clavatus* and *C. albicans*. Among the tested compounds **12b** showed the highest inhibition against *A. niger* at 6.25 μg/mL, *A. clavatus* and *C. albicans* at 12.5 μg/mL respectively. Compounds **12e** and **12o** depicted significant activity against *A. fumigatus* among all synthesized derivatives. The antimicrobial study of the synthesized compounds permitted us to state that the variation of antimicrobial activity may be associated with the nature of tested bacterial and fungal strains and the substituent on phenyl ring at thiazolidinone moiety. The results unfold the way for investigation of new potential lead compounds for investigating antimicrobial activity.

5. Experimental

Chemicals and solvents were obtained from commercial sources and used as received throughout the investigation. 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 FT-IR spectrophotometer (Shimadzu India Pvt. Ltd., Mumbai, India) using KBr pellets. 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. ^1H 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 ^1H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. The ^1H NMR and ^{13}C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si) and were performed at Centre for Excellence, Vapi, India. The splitting patterns are designated as follows; s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All new compounds were subjected to elemental analysis using a Heraeus Carlo Erba 1180 CHN analyzer (Hanau, Germany).

5.1. Synthesis of (4,6-dichloro-[1,3,5]triazin-2-yl)-dimethylamine (**3**)

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine **1** (20.0 g, 0.10 mol) in anhydrous THF (150 mL), dimethylamine **2** (4.89 g, 0.10 mol) was added very slowly drop wise at 0–5 °C. The resulting reaction mixture was stirred at this temperature for 2 h, then triethyl amine (10.97 g, 0.10 mol) was added subsequently into the reaction mixture and stirring was continued for another 4 h. The resulted reaction mixture was then treated with crushed ice, followed by neutralization by dilute HCl and then filtered, dried. In above process a very minor di-substituted compound was also formed, thus compound **3** was purified by column chromatography over silica gel using n-hexane:ethyl acetate as eluent system. Yield: 14.86 g, 77%. M.p. 126–128 °C; IR (KBr, cm^{-1}): 806 (*s*-triazine, C–N str.); ^1H NMR (DMSO-d_6): δ 3.10 (s, 6H, $2CH_3$); ^{13}C NMR (DMSO-d_6): δ 166.97, 163.41 (2C, Ar–C), 37.44 (C-7′, C-8′). Anal. Calcd for $C_5H_6Cl_2N_4$: C, 31.11; H, 3.13; N, 29.02%. Found: C, 31.17; H, 3.06; N, 29.06%.

5.2. Synthesis of 4-(4-chloro-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**5**)

To a stirred solution of 4-hydroxy-*N*-methylquinolone **4** (13.0 g, 0.074 mol) and 60% NaH (1.78 g, 0.074 mol) in anhydrous THF (150 mL), compound **3** (14.28 g, 0.074 mol) was added into the reaction mixture and first it was stirred for 1 h at room temperature and then it was continued for another 14 h at 45–50 °C. After completion of the reaction, it was treated with crushed ice, filtered, dried and recrystallized from acetone to afford compound **5**. Yield: 20.59 g, 84%. M.p. 210–215 °C; IR (KBr, cm^{-1}): 1666 (C=O of quinolone), 1256 (C–O–C), 806 (*s*-triazine, C–N str.); ^1H NMR (DMSO-d_6): δ 8.31 (dd, $J = 7.4$, 1.6 Hz, H-5), 8.05–7.61 (m, 3H, Ar–H of quinolone), 6.05 (s, 1H, H-3), 3.55 (s, 3H, H-11), 3.10 (s, 6H, $2CH_3$); ^{13}C NMR (DMSO-d_6): δ 170.96 (C–Cl), 170.15 (C-6′), 165.51 (C-2′), 161.12 (C-2), 151.69 (C-4), 141.20, 131.97, 123.14, 122.52, 116.77, 115.84, 96.10 (7C, Ar–C), 37.15 (C-7′, C-8′), 32.66 (C-11). Anal. Calcd for $C_{15}H_{14}ClN_5O_2$: C, 54.30; H, 4.25; N, 21.11%. Found: C, 54.22; H, 4.29; N, 21.05%.

5.3. Synthesis of 4-[4-(4-aminophenylamino)-6-dimethylamino-[1,3,5]triazin-2-yloxy]-1-methyl-1H-quinolin-2-one (**7**)

To a solution of compound **5** (15.0 g, 0.045 mol) in 1,4-dioxane (150 mL), *p*-phenylenediamine (4.88 g, 0.045 mol) was added and the reaction mixture was refluxed for 10–15 h as per TLC monitoring. Potassium carbonate was used for the neutralization of the reaction mixture. After completion of the reaction, it was treated with crushed ice, neutralized by dilute HCl. The precipitate thus obtained was filtered and dried. During the reaction dimer compound was formed along with compound **7**, so it was treated by column chromatography using n-hexane:ethyl acetate as eluent system to obtained pure compound **7**. Yield: 14.52 g, 80%. M.p. 198–203 °C; IR (KBr, cm^{-1}): 3370 (–NH), 3480 ($-NH_2$), 1666 (C=O of quinolone), 806 (*s*-triazine, C–N str.); ^1H NMR (DMSO-d_6): δ 11.48 (s, 2H, $-NH_2$), 9.73 (s, 1H, –NH), 8.35 (dd, 1H, $J = 7.6$, 1.5 Hz, H-5), 8.02–7.52 (m, 3H, Ar–H of quinolone), 7.27–6.80 (m, 4H, Ar–H), 6.02 (s, 1H, H-3), 3.47 (s, 3H, H-11), 3.13 (s, 6H, $2CH_3$); ^{13}C NMR (DMSO-d_6): 167.10 (C-6′), 163.98 (C-4′), 164.15 (C-2′), 161.42 (C-2), 152.69 (C-4), 139.90, 138.49, 138.41, 132.77, 127.56, 127.44, 123.67, 123.53, 122.96, 122.69, 116.75, 115.68, 97.14 (13C, Ar–C), 37.19 (C-7′, C-8′), 32.71 (C-11). Anal. Calcd for $C_{21}H_{21}N_7O_2$: C, 62.52; H, 5.25; N, 24.30%. Found: C, 62.46; H, 5.29; N, 24.36%.

5.4. General procedure for the synthesis of Schiff bases ***8a–r***

To a solution of compound **7** (2.0 g; 0.0049 mol) in absolute ethanol (50 mL), containing a catalytic amount of piperidine, equimolecular amount of the appropriate aldehydes (for e.g. benzaldehyde (**a**) – 0.52 g; 0.0049 mol) was added. The reaction mixture was refluxed for 5–6 h. It was then cooled at room temperature, poured into crushed ice, filtered, washed, dried and recrystallized from DMF to yield 4-{4-[4-(benzylidene-amino)-phenylamino]-6-dimethylamino-[1,3,5]triazin-2-yloxy}-1-methyl-1*H*-quinolin-2-one (**8a**). Yield: 1.75 g, 73%. M.p. 219–223 °C; IR (KBr, cm^{-1}): 3366 (–NH), 1666 (C=O of quinolone), 806 (*s*-triazine,

C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.77 (s, 1H, –NH), 8.29 (dd, 1H, J = 7.1, 1.6 Hz, H-5), 7.58 (s, 1H, N=CH–Ph), 8.10–7.65 (m, 3H, Ar–H of quinolone), 6.79–7.41 (m, 9H, Ar–H), 6.07 (s, 1H, H-3), 3.44 (s, 3H, H-11), 3.09 (s, 6H, 2CH$_3$); ^{13}C NMR (DMSO-d_6): 169.17 (C-6′), 165.62 (C-4′), 164.75 (C-2′), 161.47 (C-2), 152.73 (C-4), 141.12 (C=N of Schiff base), 139.45, 138.63, 138.57, 131.77, 128.90, 128.87, 128.25, 128.31, 127.79, 127.62, 127.33, 127.39, 123.90, 123.39, 123.20, 122.72, 115.90, 115.33, 96.87 (19C, Ar–C), 37.16 (C-7′, C-8′), 32.65 (C-11). Anal. Calcd for $C_{28}H_{25}N_7O_2$: C, 68.42; H, 5.13; N, 19.95%. Found: C, 68.37; H, 5.16; N, 19.86%. Other Schiff bases **8b**–**r** were obtained in similar manner.

5.5. General procedure for the synthesis of thiazolidinones **10a**–**r**

A mixture of compound **8a** (1.0 g; 0.002 mol) and thioglycolic acid (0.36 g; 0.004 mol) in dry benzene (40 mL) was refluxed for 6 h. Water formed during the reaction was removed azeotropically by Dean–Stark apparatus. Progress of the reaction the reaction was checked by TLC using benzene/ether as eluent. After the completion of reaction benzene was removed by distillation to give solid, which was dissolved in methanol (20 mL). This solution was warmed and treated with sodium bicarbonate solution to remove unreacted acid. The solid obtained was filtered, washed with ether and purified by crystallization from methanol to get 4-{4-dimethylamino-6-[4-(4-oxo-2-phenylthiazolidin-3-yl)-phenylamino]-[1,3,5]triazin-2-yloxy}-1-methyl-1*H*-quinolin-2-one (**10a**). Yield: 69%. M.p. 256–261 °C; IR (KBr, cm^{-1}): 3366 (–NH), 1722 (C=O of thiazolidinone), 1667 (C=O of quinolone), 807 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.69 (s, 1H, –NH), 8.32 (dd, 1H, J = 7.6, 1.5 Hz, H-5), 8.06–7.77 (m, 3H, Ar–H of quinolone), 6.83–7.37 (m, 9H, Ar–H), 6.10 (s, 1H, H-3), 5.12 (s, 1H, H-2″), 3.76 (d, J = 12.1 Hz, 1H), 3.66 (d, J = 12.1 Hz, 1H), 3.41 (s, 3H, H-11), 3.04 (s, 6H, 2CH$_3$); ^{13}C NMR (DMSO-d_6): 170.95 (C-5″), 169.23 (C-6′), 166.10 (C-4′), 164.71 (C-2′), 161.59 (C-2), 151.97 (C-4), 140.12, 138.72, 138.62, 131.62, 128.83, 128.90, 128.11, 128.05, 127.56, 127.45, 126.98, 126.77, 123.86, 123.48, 123.35, 121.90, 115.79, 115.15, 98.29 (19C, Ar–C), 68.19 (C-2″), 37.10 (C-7′, C-8′), 33.94 (–CH$_2$ of thiazolidinone), 32.57 (C-11). Anal. Calcd for $C_{30}H_{27}N_7O_3S$: C, 63.70; H, 4.81; N, 17.33%. Found: C, 63.65; H, 4.86; N, 17.37%. Similarly, other compounds **10b**–**r** have been synthesized.

5.6. General procedure for the synthesis of target compounds **12a**–**r**

A mixture of paraformaldehyde (0.21 g; 0.002 mol) and *N*-ethylpiperazine (0.5 g; 0.0043 mol) was taken in 25 mL of absolute ethanol and it was refluxed for 30 min. So, the solubility of paraformaldehyde achieved. Then warmed solution of compound **10a** (4.86 g, 0.0086 mol) in 30 mL of ethanol was subsequently added to the reaction mixture. The whole reaction mixture was refluxed for 10–12 h and left at room temperature under stirring for three days and after that the volatile material was evaporated. The dry residue was extracted with DMF to form 4-(4-dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-4-oxo-2-phenylthiazolidin-3-yl]-phenylamino}-[1,3,5]triazin-2-yloxy)-1-methyl-1*H*-quinolin-2-one (**12a**). Similarly, other final compounds have been synthesized.

5.7. Characterization data of synthesized compounds **12a**–**r**

5.7.1. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-4-oxo-2-phenylthiazolidin-3-yl]-phenylamino}-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12a**)

Recrystallization from THF. Yield: 68%. M.p. 254–258 °C; IR (KBr, cm^{-1}): 3363 (–NH), 1724 (C=O of thiazolidinone), 1664 (C=O of quinolone), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.72 (s, 1H, –NH), 8.46 (dd, 1H, J = 7.5, 1.4 Hz, H-5), 8.10–7.64 (m, 3H, quinolone), 7.36–6.83 (m, 9H, Ar–H), 6.11 (s, 1H, H-3), 5.17 (s, 1H, H-2″), 3.56 (br s, 8H, piperazine), 3.38 (s, 3H, H-11), 3.35 (t, J = 7.3 Hz, H-4″), 3.21–3.14 (m, 2H, H-7″), 3.07 (s, 6H, 2CH$_3$), 2.39 (q, J = 6.3 Hz, 2H, H-14″), 1.22 (t, J = 6.6 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 173.33 (C-5″), 168.42 (C-6′), 166.29 (C-4′), 164.85 (C-2′), 161.79 (C-2), 152.15 (C-4), 141.22–96.56 (19C, Ar–C), 67.15 (C-2″), 62.78, 59.21 (4C, piperazine), 57.74 (C-7″), 54.33 (C-4″), 51.40 (C-14″), 36.69 (C-7′, C-8′), 32.50 (C-11), 13.55 (C-15″). Anal. Calcd for $C_{37}H_{41}N_9O_3S$: C, 64.23; H, 5.97; N, 18.22%. Found: C, 64.27; H, 5.91; N, 18.16%.

5.7.2. 4-(4-{4-[2-(2,4-Dichlorophenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12b**)

Recrystallization from DMF. Yield: 71%. M.p. 235–239 °C; IR (KBr, cm^{-1}): 3361 (–NH), 1719 (C=O of thiazolidinone), 1664 (C=O of quinolone), 807 (*s*-triazine, C–N str.), 784 (–Cl); ^{1}H NMR (DMSO-d_6): δ 9.76 (s, 1H, –NH), 8.42 (dd, 1H, J = 7.4, 1.5 Hz, H-5), 8.12–7.56 (m, 3H, quinolone), 7.41–6.83 (m, 7H, Ar–H), 6.15 (s, 1H, H-3), 5.14 (s, 1H, H-2″), 3.58 (br s, 8H, piperazine), 3.41 (s, 3H, H-11), 3.32 (t, J = 7.5 Hz, H-4″), 3.24–3.11 (m, 2H, H-7″), 3.04 (s, 6H, 2CH$_3$), 2.33 (q, J = 6.4 Hz, 2H, H-14″), 1.08 (t, J = 6.2 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.20 (C-5″), 168.33 (C-6′), 166.14 (C-4′), 164.75 (C-2′), 162.14 (C-2), 151.83 (C-4), 134.60 (C–Cl), 133.42 (C–Cl), 141.16–96.41 (17C, Ar–C), 66.22 (C-2″), 64.19, 60.55 (4C, piperazine), 57.69 (C-7″), 54.41 (C-4″), 51.33 (C-14″), 36.89 (C-7′, C-8′), 32.60 (C-11), 13.67 (C-15″). Anal. Calcd for $C_{37}H_{39}Cl_2N_9O_3S$: C, 58.42; H, 5.17; N, 16.57%. Found: C, 58.36; H, 5.21; N, 16.51%.

5.7.3. 4-(4-{4-[2-(3,4-Dichlorophenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12c**)

Recrystallization from DMF. Yield: 65%. M.p. 256–259 °C; IR (KBr, cm^{-1}): 3363 (–NH), 1714 (C=O of thiazolidinone), 1667 (C=O of quinolone), 807 (*s*-triazine, C–N str.), 791 (–Cl); ^{1}H NMR (DMSO-d_6): δ 9.80 (s, 1H, –NH), 8.45 (dd, 1H, J = 7.6, 1.3 Hz, H-5), 8.07–7.66 (m, 3H, quinolone), 7.31–6.87 (m, 7H, Ar–H), 6.19 (s, 1H, H-3), 5.10 (s, 1H, H-2″), 3.56 (br s, 8H, piperazine), 3.36 (s, 3H, H-11), 3.19 (t, J = 7.3 Hz, H-4″), 3.17–3.03 (m, 2H, H-7″), 3.08 (s, 6H, 2CH$_3$), 2.40 (q, J = 6.3 Hz, 2H, H-14″), 1.11 (t, J = 6.5 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 171.69 (C-5″), 167.47 (C-6′), 165.35 (C-4′), 164.56 (C-2′), 161.92 (C-2), 152.14 (C-4), 135.06 (C–Cl), 133.19 (C–Cl), 142.22–97.10 (17C, Ar–C), 67.31 (C-2″), 62.73, 58.61 (4C, piperazine), 57.49 (C-7″), 55.62 (C-4″), 51.39 (C-14″), 36.77 (C-7′, C-8′), 32.30 (C-11), 12.89 (C-15″). Anal. Calcd for $C_{37}H_{39}Cl_2N_9O_3S$: C, 58.42; H, 5.17; N, 16.57%. Found: C, 58.38; H, 5.23; N, 16.49%.

5.7.4. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-4-oxo-2-p-tolylthiazolidin-3-yl]-phenylamino}-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12d**)

Recrystallization from THF. Yield: 62%. M.p. 223–228 °C; IR (KBr, cm^{-1}): 3359 (–NH), 1722 (C=O of thiazolidinone), 1666 (C=O of quinolone), 1446 (–CH$_3$), 807 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.77 (s, 1H, –NH), 8.31 (dd, 1H, J = 7.1, 1.6 Hz, H-5), 8.16–7.67 (m, 3H, quinolone), 7.39–6.78 (m, 8H, Ar–H), 6.11 (s, 1H, H-3), 5.09 (s, 1H, H-2″), 3.56 (br s, 8H, piperazine), 3.37 (s, 3H, H-11), 3.35 (t, J = 7.2 Hz, H-4″), 3.19–3.13 (m, 2H, H-7″), 3.07 (s, 6H, 2CH$_3$), 2.38 (q, J = 6.6 Hz, 2H, H-14″), 2.21 (s, 3H, CH$_3$ at phenyl), 1.34 (t, J = 6.3 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 171.32 (C-5″), 169.03 (C-6′), 165.20 (C-4′), 164.66 (C-2′), 161.19 (C-2), 152.45 (C-4), 138.89 (C–CH$_3$), 141.40–101.24 (18C, Ar–C), 67.38 (C-2″), 62.75, 59.67 (4C, piperazine), 56.60 (C-7″), 55.20 (C-4″), 51.23 (C-14″), 36.78 (C-7′, C-8′), 32.71 (C-11), 14.36 (CH$_3$ at phenyl), 12.17 (C-15″). Anal. Calcd for: $C_{38}H_{43}N_9O_3S$: C, 64.66; H, 6.14; N, 17.86%. Found: C, 64.61; H, 6.17; N, 17.92%.

*5.7.5. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl]-phenylamino}-[1,3,5] triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12e**)*

Recrystallization from DMF. Yield: 60%. M.p. 239–243 °C; IR (KBr, cm^{-1}): 3354 (–NH), 1724 (C=O of thiazolidinone), 1666 (C=O of quinolone), 1160 (C–F), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.68 (s, 1H, –NH), 8.35 (dd, 1H, J = 7.4, 1.4 Hz, H-5), 8.13–7.60 (m, 3H, quinolone), 7.43–6.85 (m, 8H, Ar–H), 6.17 (s, 1H, H-3), 5.12 (s, 1H, H-2″), 3.57 (br s, 8H, piperazine), 3.39 (s, 3H, H-11), 3.37 (t, J = 7.6 Hz, H-4″), 3.21–3.17 (m, 2H, H-7″), 3.03 (s, 6H, $2CH_3$), 2.29 (q, J = 6.5 Hz, 2H, H-14″), 1.01 (t, J = 6.3 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.11 (C-5″), 168.45 (C-6′), 167.70 (C–F), 164.88 (C-4′), 164.53 (C-2′), 160.76 (C-2), 151.43 (C-4), 140.95–101.54 (18C, Ar–C), 66.15 (C-2″), 63.19, 58.75 (4C, piperazine), 55.89 (C-7″), 55.11 (C-4″), 50.41 (C-14″), 37.02 (C-7′, C-8′), 31.86 (C-11), 13.30 (C-15″). Anal. Calcd for: $C_{37}H_{40}FN_9O_3S$: C, 62.61; H, 5.68; N, 17.76%. Found: C, 62.65; H, 5.62; N, 17.81%.

*5.7.6. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-2-(3-fluorophenyl)-4-oxothiazolidin-3-yl]-phenylamino}-[1,3,5] triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12f**)*

Recrystallization from DMF. Yield: 54%. M.p. 264–269 °C; IR (KBr, cm^{-1}): 3359 (–NH), 1718 (C=O of thiazolidinone), 1667 (C=O of quinolone), 1164 (C–F), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.75 (s, 1H, –NH), 8.29 (dd, 1H, J = 7.3, 1.1 Hz, H-5), 8.17–7.64 (m, 3H, quinolone), 7.35–6.88 (m, 8H, Ar–H), 6.23 (s, 1H, H-3), 5.19 (s, 1H, H-2″), 3.61 (br s, 8H, piperazine), 3.44 (s, 3H, H-11), 3.25 (t, J = 7.6 Hz, H-4″), 3.17–3.11 (m, 2H, H-7″), 3.10 (s, 6H, $2CH_3$), 2.45 (q, J = 6.4 Hz, 2H, H-14″), 1.03 (t, J = 6.6 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 174.24 (C-5″), 168.09 (C–F), 167.41 (C-6′), 165.34 (C-4′), 164.51 (C-2′), 161.49 (C-2), 152.45 (C-4), 142.29–98.44 (18C, Ar–C), 66.24 (C-2″), 64.83, 60.72 (4C, piperazine), 58.25 (C-7″), 56.40 (C-4″), 52.43 (C-14″), 36.86 (C-7′, C-8′), 32.47 (C-11), 12.27 (C-15″). Anal. Calcd for: $C_{37}H_{40}FN_9O_3S$: C, 62.61; H, 5.68; N, 17.76%. Found: C, 62.67; H, 5.64; N, 17.80%.

*5.7.7. 4-(4-{4-[2-(4-Chlorophenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12g**)*

Recrystallization from THF. Yield: 67%. M.p. 244–248 °C; IR (KBr, cm^{-1}): 3357 (–NH), 1725 (C=O of thiazolidinone), 1664 (C=O of quinolone), 808 (*s*-triazine, C–N str.), 784 (Cl); ^{1}H NMR (DMSO-d_6): δ 9.66 (s, 1H, –NH), 8.45 (dd, 1H, J = 7.5, 1.6 Hz, H-5), 8.10–7.54 (m, 3H, quinolone), 7.49–6.90 (m, 8H, Ar–H), 6.10 (s, 1H, H-3), 5.18 (s, 1H, H-2″), 3.53 (br s, 8H, piperazine), 3.42 (s, 3H, H-11), 3.40 (t, J = 7.3 Hz, H-4″), 3.25–3.18 (m, 2H, H-7″), 3.07 (s, 6H, $2CH_3$), 2.37 (q, J = 6.3 Hz, 2H, H-14″), 1.41 (t, J = 6.3 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 174.60 (C-5″), 168.12 (C-6′), 165.24 (C-4′), 163.81 (C-2′), 161.19 (C-2), 152.33 (C-4), 133.19 (C–Cl), 143.27–97.54 (18C, Ar–C), 67.24 (C-2″), 62.74, 57.70 (4C, piperazine), 55.80 (C-7″), 54.92 (C-4″), 52.13 (C-14″), 36.88 (C-7′, C-8′), 32.86 (C-11), 12.70 (C-15″). Anal. Calcd for: $C_{37}H_{40}ClN_9O_3S$: C, 61.19; H, 5.55; N, 17.36%. Found: C, 61.23; H, 5.47; N, 17.40%.

*5.7.8. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-2-(4-nitrophenyl)-4-oxothiazolidin-3-yl]-phenylamino}-[1,3,5] triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12h**)*

Recrystallization from DMF. Yield: 59%. M.p. 260–262 °C; IR (KBr, cm^{-1}): 3361 (–NH), 1719 (C=O of thiazolidinone), 1665 (C=O of quinolone), 1540 (N=O str.), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.69 (s, 1H, –NH), 8.31 (dd, 1H, J = 7.4, 1.2 Hz, H-5), 8.06–7.67 (m, 3H, quinolone), 7.42–6.86 (m, 8H, Ar–H), 6.13 (s, 1H, H-3), 5.11 (s, 1H, H-2″), 3.59 (br s, 8H, piperazine), 3.45 (s, 3H, H-11), 3.41 (t, J = 7.1 Hz, H-4″), 3.31–3.23 (m, 2H, H-7″), 3.10 (s, 6H, $2CH_3$), 2.34 (q, J = 6.4 Hz, 2H, H-14″), 1.05 (t, J = 6.6 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 171.24 (C-5″), 169.33 (C-6′), 165.89 (C-4′), 165.19 (C-2′), 162.28 (C-2), 151.47 (C-4), 148.52 (C–NO_2), 145.02–101.67 (18C, Ar–C), 66.58 (C-2″), 63.80, 59.21 (4C, piperazine), 58.70 (C-7″), 55.24 (C-4″), 50.17 (C-14″), 36.79 (C-7′, C-8′), 32.45 (C-11), 12.77 (C-15″). Anal. Calcd for: $C_{37}H_{40}N_{10}O_5S$: C, 60.31; H, 5.47; N, 19.01%. Found: C, 60.36; H, 5.53; N, 19.04%.

*5.7.9. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-2-(2-nitrophenyl)-4-oxothiazolidin-3-yl]-phenylamino}-[1,3,5] triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12i**)*

Recrystallization from DMF. Yield: 55%. M.p. 272–276 °C; IR (KBr, cm^{-1}): 3363 (–NH), 1722 (C=O of thiazolidinone), 1667 (C=O of quinolone), 1543 (N=O str.), 807 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.78 (s, 1H, –NH), 8.50 (dd, 1H, J = 7.2, 1.1 Hz, H-5), 8.13–7.53 (m, 3H, quinolone), 7.38–6.79 (m, 8H, Ar–H), 6.21 (s, 1H, H-3), 5.15 (s, 1H, H-2″), 3.52 (br s, 8H, piperazine), 3.49 (s, 3H, H-11), 3.34 (t, J = 7.1 Hz, H-4″), 3.29–3.08 (m, 2H, H-7″), 3.04 (s, 6H, $2CH_3$), 2.27 (q, J = 6.3 Hz, 2H, H-14″), 1.18 (t, J = 6.5 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.33 (C-5″), 168.51 (C-6′), 165.83 (C-4′), 165.12 (C-2′), 162.43 (C-2), 151.65 (C-4), 149.17 (C–NO_2), 143.10–101.75 (18C, Ar–C), 67.19 (C-2″), 63.92, 60.41 (4C, piperazine), 57.94 (C-7″), 54.21 (C-4″), 51.65 (C-14″), 36.69 (C-7′, C-8′), 32.51 (C-11), 12.89 (C-15″). Anal. Calcd for: $C_{37}H_{40}N_{10}O_5S$: C, 60.31; H, 5.47; N, 19.01%. Found: C, 60.34; H, 5.51; N, 19.05%.

*5.7.10. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl]-phenylamino}-[1,3,5] triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12j**)*

Recrystallization from DMF. Yield: 73%. M.p. 247–255 °C; IR (KBr, cm^{-1}): 3362 (–NH), 3223 (–OH), 1723 (C=O of thiazolidinone), 1666 (C=O of quinolone), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.82 (s, 1H, –NH), 8.36 (dd, 1H, J = 7.4, 1.5 Hz, H-5), 8.17–7.64 (m, 3H, quinolone), 7.40–6.88 (m, 8H, Ar–H), 6.09 (s, 1H, H-3), 5.17 (s, 1H, H-2″), 4.63 (s, 1H, –OH), 3.62 (br s, 8H, piperazine), 3.48 (s, 3H, H-11), 3.45 (t, J = 7.4 Hz, H-4″), 3.43–3.29 (m, 2H, H-7″), 3.13 (s, 6H, $2CH_3$), 2.38 (q, J = 6.1 Hz, 2H, H-14″), 1.04 (t, J = 6.5 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.13 (C-5″), 168.29 (C-6′), 164.77 (C-4′), 163.12 (C-2′), 161.44 (C-2), 158.61 (C–OH), 152.71 (C-4), 141.24–97.54 (18C, Ar–C), 67.12 (C-2″), 62.73, 58.19 (4C, piperazine), 56.34 (C-7″), 55.51 (C-4″), 52.25 (C-14″), 36.85 (C-7′, C-8′), 32.37 (C-11), 12.63 (C-15″). Anal. Calcd for: $C_{37}H_{41}N_9O_4S$: C, 62.78; H, 5.84; N, 17.81%. Found: C, 62.72; H, 5.89; N, 17.76%.

*5.7.11. 4-(4-{4-[2-(4-Bromophenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12k**)*

Recrystallization from DMF. Yield: 64%. M.p. 271–274 °C; IR (KBr, cm^{-1}): 3360 (–NH), 1716 (C=O of thiazolidinone), 1667 (C=O of quinolone), 808 (*s*-triazine, C–N str.), 729 (–Br); ^{1}H NMR (DMSO-d_6): δ 9.64 (s, 1H, –NH), 8.42 (dd, 1H, J = 7.3, 1.4 Hz, H-5), 8.11–7.59 (m, 3H, quinolone), 7.48–6.86 (m, 8H, Ar–H), 6.14 (s, 1H, H-3), 5.11 (s, 1H, H-2″), 3.55 (br s, 8H, piperazine), 3.39 (s, 3H, H-11), 3.25 (t, J = 7.4 Hz, H-4″), 3.23–3.10 (m, 2H, H-7″), 3.06 (s, 6H, $2CH_3$), 2.33 (q, J = 6.6 Hz, 2H, H-14″), 1.15 (t, J = 6.3 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.24 (C-5″), 167.31 (C-6′), 164.83 (C-4′), 163.08 (C-2′), 161.37 (C-2), 151.89 (C-4), 121.70 (C–Br), 140.33–96.51 (18C, Ar–C), 66.58 (C-2″), 63.83, 59.47 (4C, piperazine), 57.51 (C-7″), 55.49 (C-4″), 51.39 (C-14″), 37.08 (C-7′, C-8′), 32.40 (C-11), 12.58 (C-15″). Anal. Calcd for: $C_{37}H_{40}BrN_9O_3S$: C, 57.66; H, 5.23; N, 16.36%. Found: C, 57.74; H, 5.16; N, 16.43%.

*5.7.12. 4-(4-{4-[2-(2-Bromophenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12l**)*

Recrystallization from DMF. Yield: 57%. M.p. 283–287 °C; IR (KBr, cm^{-1}): 3363 (–NH), 1721 (C=O of thiazolidinone), 1666 (C=O of quinolone), 807 (*s*-triazine, C–N str.), 733 (–Br); ^{1}H NMR (DMSO-d_6): δ 9.77 (s, 1H, –NH), 8.31 (dd, 1H, J = 7.4, 1.2 Hz, H-5), 8.23–7.71 (m, 3H, quinolone), 7.54–6.91 (m, 8H, Ar–H), 6.25 (s, 1H, H-3), 5.15 (s, 1H, H-2″), 3.59 (br s, 8H, piperazine), 3.43 (s, 3H, H-11), 3.37 (t, J = 7.6 Hz, H-4″), 3.29–3.14 (m, 2H, H-7″), 3.11 (s, 6H, $2CH_3$), 2.27 (q, J = 6.6 Hz, 2H, H-14″), 1.26 (t, J = 6.5 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 171.30 (C-5″), 168.12 (C-6′), 165.79 (C-4′), 163.64 (C-2′), 161.43 (C-2), 152.26 (C-4), 121.60 (C–Br), 144.38–98.16 (18C, Ar–C), 66.31 (C-2″), 62.54, 60.47 (4C, piperazine), 58.47 (C-7″), 56.12 (C-4″), 50.34 (C-14″), 36.15 (C-7′, C-8′), 31.89 (C-11), 12.67 (C-15″). Anal. Calcd for: $C_{37}H_{40}BrN_9O_3S$: C, 57.66; H, 5.23; N, 16.36%. Found: C, 57.72; H, 5.19; N, 16.45%.

*5.7.13. 2-[3-{4-[4-Dimethylamino-6-(1-methyl-2-oxo-1,2-dihydro-quinolin-4-yloxy)-[1,3,5]triazin-2-ylamino]-phenyl}-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-2-yl]-benzoic acid (**12m**)*

Recrystallization from THF. Yield: 79%. M.p. >300 °C; IR (KBr, cm^{-1}): 3363 (–NH), 1722 (C=O of thiazolidinone), 1720 (–COOH), 1668 (C=O of quinolone), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.84 (s, 1H, –NH), 8.45 (dd, 1H, J = 7.3, 1.5 Hz, H-5), 8.12–7.55 (m, 3H, quinolone), 7.43–6.78 (m, 8H, Ar–H), 6.07 (s, 1H, H-3), 5.17 (s, 1H, H-2″), 3.60 (br s, 8H, piperazine), 3.43 (s, 3H, H-11), 3.31 (t, J = 7.3 Hz, H-4″), 3.29–3.24 (m, 2H, H-7″), 3.09 (s, 6H, $2CH_3$), 2.32 (q, J = 6.6 Hz, 2H, H-14″), 1.34 (t, J = 6.4 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.32 (C-5″), 170.40 (C=O of COOH), 168.19 (C-6′), 163.13 (C-4′), 162.89 (C-2′), 161.31 (C-2), 152.35 (C-4), 131.29 (C–COOH), 138.30–95.42 (18C, Ar–C), 67.15 (C-2″), 63.14, 61.69 (4C, piperazine), 57.74 (C-7″), 55.61 (C-4″), 50.23 (C-14″), 36.94 (C-7′, C-8′), 32.37 (C-11), 12.52 (C-15″). Anal. Calcd for: $C_{38}H_{41}N_9O_5S$: C, 62.02; H, 5.62; N, 17.13%. Found: C, 62.05; H, 5.57; N, 17.17%.

*5.7.14. 4-[3-{4-[4-Dimethylamino-6-(1-methyl-2-oxo-1,2-dihydro-quinolin-4-yloxy)-[1,3,5]triazin-2-ylamino]-phenyl}-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-2-yl]-benzoic acid (**12n**)*

Recrystallization from THF. Yield: 84%. M.p. >300 °C; IR (KBr, cm^{-1}): 3361 (–NH), 1725 (C=O of thiazolidinone), 1722 (–COOH), 1666 (C=O of quinolone), 807 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.65 (s, 1H, –NH), 8.38 (dd, 1H, J = 7.4, 1.6 Hz, H-5), 8.09–7.55 (m, 3H, quinolone), 7.36–6.89 (m, 8H, Ar–H), 6.24 (s, 1H, H-3), 5.10 (s, 1H, H-2″), 3.63 (br s, 8H, piperazine), 3.49 (s, 3H, H-11), 3.44 (t, J = 7.1 Hz, H-4″), 3.31–3.12 (m, 2H, H-7″), 3.04 (s, 6H, $2CH_3$), 2.40 (q, J = 6.4 Hz, 2H, H-14″), 1.20 (t, J = 6.5 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.40 (C-5″), 170.13 (C=O of COOH), 167.23 (C-6′), 164.56 (C-4′), 162.77 (C-2′), 161.46 (C-2), 152.39 (C-4), 131.34 (C–COOH), 142.25–96.29 (18C, Ar–C), 66.08 (C-2″), 62.17, 60.76 (4C, piperazine), 58.71 (C-7″), 56.24 (C-4″), 51.27 (C-14″), 37.16 (C-7′, C-8′), 31.84 (C-11), 13.30 (C-15″). Anal. Calcd for: $C_{38}H_{41}N_9O_5S$: C, 62.02; H, 5.62; N, 17.13%. Found: C, 62.07; H, 5.59; N, 17.19%.

*5.7.15. 4-(4-Dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl]-phenylamino}-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12o**)*

Recrystallization from DMF. Yield: 69%. M.p. >300 °C; IR (KBr, cm^{-1}): 3365 (–NH), 1718 (C=O of thiazolidinone), 1666 (C=O of quinolone), 1290 (–OCH_3), 807 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.79 (s, 1H, –NH), 8.30 (dd, 1H, J = 7.2, 1.1 Hz, H-5), 8.11–7.66 (m, 3H, quinolone), 7.47–6.90 (m, 8H, Ar–H), 6.16 (s, 1H, H-3), 5.12 (s, 1H, H-2″), 3.87 (s, 3H, –OCH_3), 3.56 (br s, 8H, piperazine), 3.41 (s, 3H, H-11), 3.32 (t, J = 7.5 Hz, H-4″), 3.29–3.18 (m, 2H, H-7″), 3.12 (s, 6H, $2CH_3$), 2.34 (q, J = 6.2 Hz, 2H, H-14″), 1.08 (t, J = 6.2 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 171.45 (C-5″), 167.12 (C-6′), 164.29 (C-4′), 162.83 (C-2′), 162.05 (C-2), 160.10 (C–OCH_3), 151.20 (C-4), 145.46–101.73 (18C, Ar–C), 68.11 (C-2″), 64.18, 61.79 (4C, piperazine), 56.08 (–OCH_3), 57.86 (C-7″), 55.66 (C-4″), 49.17 (C-14″), 37.03 (C-7′, C-8′), 32.48 (C-11), 12.55 (C-15″). Anal. Calcd for: $C_{38}H_{43}N_9O_4S$: C, 63.23; H, 6.00; N, 17.46%. Found: C, 63.18; H, 6.07; N, 17.55%.

*5.7.16. 4-(4-{4-[2-(3,4-Dimethoxyphenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12p**)*

Recrystallization from DMF. Yield: 73%. M.p. 291–297 °C; IR (KBr, cm^{-1}): 3361 (–NH), 1714 (C=O of thiazolidinone), 1668 (C=O of quinolone), 1288 (–OCH_3), 807 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.87 (s, 1H, –NH), 8.48 (dd, 1H, J = 7.3, 1.3 Hz, H-5), 8.04–7.51 (m, 3H, quinolone), 7.33–6.83 (m, 7H, Ar–H), 6.11 (s, 1H, H-3), 5.09 (s, 1H, H-2″), 3.84 (s, 3H, –OCH_3), 3.71 (s, 3H, –OCH_3), 3.63 (br s, 8H, piperazine), 3.43 (s, 3H, H-11), 3.40 (t, J = 7.3 Hz, H-4″), 3.21–2.97 (m, 2H, H-7″), 2.91 (s, 6H, $2CH_3$), 2.29 (q, J = 6.6 Hz, 2H, H-14″), 1.12 (t, J = 6.1 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.69 (C-5″), 168.15 (C-6′), 164.43 (C-4′), 163.87 (C-2′), 161.90 (C-2), 152.34 (C-4), 150.23 (C–OCH_3), 148.18 (C–OCH_3), 142.28–98.64 (17C, Ar–C), 67.15 (C-2″), 63.81, 58.75 (4C, piperazine), 57.89 (C-7″), 56.10 (–OCH3), 54.89 (C-4″), 51.25 (C-14″), 36.12 (C-7′, C-8′), 32.61 (C-11), 12.47 (C-15″). Anal. Calcd for: $C_{39}H_{45}N_9O_5S$: C, 62.30; H, 6.03; N, 16.77%. Found: C, 62.25; H, 6.08; N, 16.84%.

*5.7.17. 4-(4-{4-[2-(2,4-Dihydroxyphenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12q**)*

Recrystallization from DMF. Yield: 80%. M.p. >300 °C; IR (KBr, cm^{-1}): 3364 (–NH), 3229 (–OH), 1722 (C=O of thiazolidinone), 1666 (C=O of quinolone), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.71 (s, 1H, –NH), 8.73 (s, 1H, –OH), 8.39 (dd, 1H, J = 7.2, 1.5 Hz, H-5), 8.10–7.65 (m, 3H, quinolone), 7.46–6.85 (m, 7H, Ar–H), 6.16 (s, 1H, H-3), 5.12 (s, 1H, H-2″), 4.63 (s, 1H, –OH), 3.59 (br s, 8H, piperazine), 3.46 (s, 3H, H-11), 3.35 (t, J = 7.2 Hz, H-4″), 3.29–3.10 (m, 2H, H-7″), 3.07 (s, 6H, $2CH_3$), 2.34 (q, J = 6.3 Hz, 2H, H-14″), 1.05 (t, J = 6.4 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.54 (C-5″), 167.32 (C-6′), 163.44 (C-4′), 162.92 (C-2′), 161.78 (C-2), 158.13 (C–OH), 155.43 (C–OH), 151.45 (C-4), 139.39–97.23 (17C, Ar–C), 68.21 (C-2″), 64.15, 61.70 (4C, piperazine), 58.31 (C-7″), 54.57 (C-4″), 51.63 (C-14″), 37.15 (C-7′, C-8′), 32.43 (C-11), 12.67 (C-15″). Anal. Calcd for: $C_{37}H_{41}N_9O_5S$: C, 61.39; H, 5.71; N, 17.42%. Found: C, 61.36; H, 5.64; N, 17.47%.

*5.7.18. 4-(4-{4-[2-(2,3-Dihydroxyphenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenylamino}-6-dimethylamino-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin-2-one (**12r**)*

Recrystallization from DMF. Yield: 86%. M.p. 295–299 °C; IR (KBr, cm^{-1}): 3360 (–NH), 3231 (–OH), 1725 (C=O of thiazolidinone), 1667 (C=O of quinolone), 806 (*s*-triazine, C–N str.); ^{1}H NMR (DMSO-d_6): δ 9.70 (s, 1H, –NH), 8.69 (s, 1H, –OH), 8.27 (dd, 1H, J = 7.4, 1.2 Hz, H-5), 8.14–7.55 (m, 3H, quinolone), 7.40–6.83 (m, 7H, Ar–H), 6.25 (s, 1H, H-3), 5.17 (s, 1H, H-2″), 4.66 (s, 1H, –OH), 3.53 (br s, 8H, piperazine), 3.40 (s, 3H, H-11), 3.32 (t, J = 7.5 Hz, H-4″), 3.30–3.18 (m, 2H, H-7″), 3.11 (s, 6H, $2CH_3$), 2.37 (q, J = 6.5 Hz, 2H, H-14″), 1.23 (t, J = 6.3 Hz, 3H, H-15″); ^{13}C NMR (DMSO-d_6): 172.69 (C-5″), 168.46 (C-6′), 164.41 (C-4′), 162.97 (C-2′), 161.84 (C-2), 158.17 (C–OH), 155.40 (C–OH), 152.10 (C-4), 142.61–96.81 (17C, Ar–C), 67.30 (C-2″), 62.67, 58.24 (4C, piperazine), 57.15 (C-7″), 55.63 (C-4″), 51.33 (C-14″), 36.19 (C-7′, C-8′), 31.97 (C-11), 12.79 (C-15″). Anal.

Calcd for: $C_{37}H_{41}N_9O_5S$: C, 61.39; H, 5.71; N, 17.42%. Found: C, 61.33; H, 5.65; N, 17.49%.

5.8. Antimicrobial assay

The synthesized thiazolidinone derivatives **12a**–**r** were examined for antimicrobial activity against several bacteria (*S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhi*, *P. vulgaris*, *S. flexneri*) and fungi (*A. niger*, *A. fumigatus*, *A. clavatus*, *C. albicans*) species using paper disc diffusion technique [18]. 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 discs 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 disc 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/disc) were used as control drugs for antibacterial and antifungal activity, respectively.

MIC of the compound was determined by agar streak dilution method [19]. 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 and Sabouraud dextrose agar for antifungal activity, respectively. 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 approximately 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.

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