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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Quinoline-based azetidinone and thiazolidinone analogues as antimicrobial and antituberculosis agents

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Abstract New azetidinone and thiazolidinone class of bioactive agents based on quinoline nucleus have been synthesized. 2-Chloroquinoline-3-carbaldehyde reacted with various substituted amine to form the corresponding Schiff base intermediates. We have derived final azetidinone and thiazolidinone analogues from Schiff bases using chloroacetyl chloride and 2-mercaptoacetic acid, respectively. The newly synthesized analogues were then examined for their antimicrobial activity against some bacterial and fungal strains as two gram −ve bacteria (*Escherichia coli* MTCC 739 and *Pseudomonas aeruginosa* MTCC 741), two gram +ve bacteria (*Staphylococcus aureus* MTCC 96 and *Bacillus subtilis* MTCC 430), two fungal species (*Aspergillus niger* MTCC 282 and *Candida albicans* MTCC 183) as well as against *Mycobacterium tuberculosis* strain H37Rv to develop a novel class of bioactive agents. The results of bioassay showed that some of the newly synthesized azetidinones and thiazolidinones emerged as lead molecules with excellent MIC (mg/mL) values against mentioned microorganisms compared to standard drugs. The structure of the final analogues has been confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

Keywords 2-Chloroquinoline-3-carbaldehyde · Substituted anilines · Azetidinone · Thiazolidinone · Antimicrobial activity

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Introduction

Quinoline is a heterocyclic scaffold of paramount importance to human race. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Indeed quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases. The bark of Cinchona plant containing quinine was utilized to treat palpitations (Samuel levy and Salomon Azoulay, 1994), fevers, and tertians since more than 200 years ago. Quinidine, a diastereoisomer of quinine was in the early twentieth century, acknowledged as the most potent of the ant arrhythmic compounds isolated from the Cinchona plant (Wenckebach, 1923). The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties such as antimicrobial agents (Donnell *et al*., 2010), antituberculosis (Mungra *et al*., 2010), antibacterial (Makawana *et al*., 2011). There are many methods available for fused quinolines, the Vilsmeier approach has been recently, explored by Katritzky and others. More recently, synthesis of functionalized quinoline and their benzo/hetero-fused analogues has been reported from the reaction of α-oxoketen-N, S-acetals with Vilsmeier reagent. It will suffice to mention here that currently available antimicrobial drugs such as norfloxacin, ciprofloxacin, ketoconazole contain quinoline ring in their structures. In fact, 2-chloroquinoline-3-carbaldehyde, the primary intermediate, is a good starting material for the preparation of different quinoline derivatives. In addition, literature survey revealed that quinoline-based azetidinones (Ross *et al*., 2004; Halve *et al*., 2007; Wang *et al*., 2009; Rajasekaran *et al*., 2010; Dua *et al*., 2010; Rokade and Dongare, 2010; Bhat *et al*., 2011) and thiazolidinones (Kumar *et al*., 2007; Bhati and Kumar, 2008;

Shingade *et al*., 2011; Desai *et al*., 2011; Pawar and Mulwad, 2004; Patel and Patel, 2010; Pareek *et al*., 2011) are proved promising antimicrobial agents.

Results and discussion

Chemistry

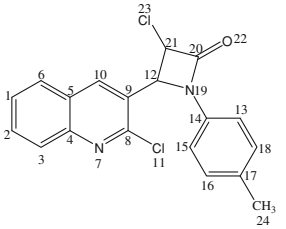
Various routes have been developed for the synthesis of functionalized quinolines, the Vilsmeier (Meth-Cohn and Bramha, 1978) approach is found to be most efficient. Thus, in this communication the synthesis of 2-chloro-quinoline 3-carbaldehyde **2** from *N*-aryl acetamides followed by reaction with Vilsmeier reagent and transformation into different functionalities. The required acetanilide **1** was readily prepared from the reaction of corresponding anilines with acetic anhydride in aqueous medium. The Vilsmeier cyclization of acetanilide **1** was carried out by adding phosphorus oxychloride to the *N*-aryl acetamides in DMF at 0–5°C followed by heating at 90°C to afford 2-chloro 3-carbaldehyde **2** in good yield. The IR spectra of compound **2** showed a strong absorption in the range of 1,680–1,696 cm^{-1} for the aldehydic group. The carbaldehyde group in quinolines **2** was also transformed into other functionalities to afford new quinolines which are equally important synthons for the synthesis of fused quinoline systems. Thus, carbaldehyde group in quinolines **2** was converted into substituted quinoline Schiff base derivatives **4a**–**l** in ethanol at refluxed temperature. Schiff base compounds **4a**–**l** showed most prominent peak of imine function group (–C=N–) at 1,658 cm^{-1}.The substituted Schiff base derivatives **4a**–**l** also reacted with chloroacetylchloride in the presence of triethylamine which act as a catalyst in 1,4 dioxane to undergo cyclization to obtain quinoline azetidin-2-one derivatives **5a**–**l**. The IR spectrum of compounds **5a**–**l** showed sharp peak near 1,731 cm^{-1} indicates the presence of ketone (–C=O) functional group of azetidinone ring. A corresponding peak of C–N–CO was observed at 1,530 cm^{-1}. Chlorine functional group exhibited a peak at 760 cm^{-1}. The ^{1}H NMR spectra of compounds **5a**–**l** showed the signal at 5.70 ppm due to –CH–Cl on azetidinone ring. Doublets was observed at 6.90 ppm due to CH–N proton on azetidinone ring, 2.24 ppm due to the presence of $–CH_3$ group at phenyl ring and aromatic protons resonated in the range of 6.90–8.08 ppm. In the ^{1}H NMR spectra of the final compounds, a peak obtained as doublet of doublet in the range 7.88–7.95 ppm was assigned due to the C-3 proton of the quinoline ring, as well as a doublet of triplate was observed at 7.60–7.69 ppm attributed to the C-6 quinoline proton. In addition, C-1, C-2, and C-10 proton atoms of the quinoline ring were appeared to resonate at around 7.49–7.55 and 7.72–7.86 ppm, respectively. ^{13}C NMR spectral assigned signals in the range between 162.71 and 166.58 due to presence of ketone (–C=O) functional group of azetidinone ring, 60.20–62.65 range showed the presence of (–C–Cl) group of azetidinone ring, 147.56–149.51 ppm range indicates the presence of (–C–Cl) group of quinoline ring, 67.37–69.98 range showed the linkage of azetidinone ring, while remaining all aromatic carbons resonated in the range of 112–150.62. The same Schiff base derivatives **4a**–**l** were heated with 2-mercaptoacetic acid in the presence of anhydrous zinc chloride which acts as a catalyst and solvent DMF undergo cyclization to give quinoline thiazolidin-4-one derivatives **6a**–**l**. The IR spectrum of compounds **6a**–**l** showed sharp peak near 1,734 cm^{-1} indicates the presence of ketone (–C=O) functional group of azetidinone ring. It also showed corresponding peak of C–N–CO at 1,536 cm^{-1} and showed peak of C–S–C at 621 cm^{-1}. Chlorine functional group showed a peak at 761 cm^{-1}. The ^{1}H NMR spectra of compounds **6a**–**l** showed the signal at 6.49 ppm due to –CH–N on thiazolidinone ring. Doublets of doublet were observed at 3.93 ppm due to CH–S proton on thiazolidinone ring, 2.24 ppm due to the presence of $–CH_3$ group at phenyl ring, and aromatic protons resonated in the range of 6.90–8.20 ppm. Moreover, proton positional assignment for the final compounds **6a**–**l** was found to be in agreement as per the interpretation of compounds **5a**–**l**. ^{13}C NMR spectral assigned signals in the range between 172.35 and 178.37 due to presence of ketone (–C=O) functional group of thiazolidinone ring, 56.93–59.66 range showed the linkage of thiazolidinone ring, 149.68–151.65 ppm range indicates the presence of (–C–Cl) group of quinoline ring, 35.23–37.58 ppm indicates the presence of $–CH_2$ group in thiazolidinone ring, while remaining all aromatic carbons resonated in the range of 115.57–149.81.

Antimicrobial activity

The antimicrobial bioassay results summarized in Tables 1 and 2 revealed that some of the newly synthesized azetidinone or thiazolidinone analogues indicated excellent growth inhibitory profiles. It is worth to mention that thiazolidinone analogues were displayed better activity against the mentioned microorganisms that of azetidinone analogues. The minimum inhibitory concentration (MIC) profiles of thiazolidinone analogues were also strong than that of the azetidinone class. It was observed that both the class of newly synthesized analogues with electro-withdrawing nitro and electro-withdrawing halo (–Cl, –F) substituent demonstrated potential antimicrobial properties.

From the bioassay it can be stated that all the final analogues with electro-donating alkyl ($–CH_3$) substituent were inactive against all the mentioned bacterial and fungal strains. However, compounds with unsubstituted amino

Table 1 In vitro antimicrobial study (MIC μg/mL) of azetidinone analogues (**5a–l**) MIC



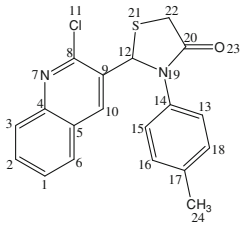
Comp. (100 μg/disc)	R	Zone of inhibition [mm (MIC in μg/mL)]					
		Gram −ve		Gram +ve		Fungal species	
		S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
5a	Aniline	<10 (100)	<10 (100)	<10 (100)	<10 (100)	<10 (100)	<10 (100)
5b	2-Methyl aniline	16 (100)	<10 (100)	<10 (100)	<10 (100)	<10 (100)	<10 (100)
5c	3-Methyl aniline	<10 (100)	18 (100)	14 (100)	16 (100)	20 (100)	<10 (100)
5d	4-Methyl aniline	17 (100)	16 (100)	15 (100)	13 (100)	<10 (100)	19 (100)
5e	2-Nitro aniline	20 (100)	21 (62.5)	22 (100)	21 (62.5)	22 (50)	20 (100)
5f	3-Nitro aniline	25 (25)	21 (50)	22 (62.5)	22 (50)	26 (50)	19 (100)
5g	4-Nitro aniline	**25 (12.5)**	23 (50)	20 (100)	**23 (12.5)**	24 (50)	19 (100)
5h	2-Chloro aniline	24 (62.5)	**24 (12.5)**	21 (62.5)	20 (50)	19 (100)	18 (100)
5i	3-Chloro aniline	25 (25)	23 (12.5)	21 (62.5)	22 (25)	25 (62.5)	20 (62.5)
5j	4-Chloro aniline	21 (50)	**24 (12.5)**	22 (50)	23 (25)	22 (100)	21 (62.5)
5k	4-Fluoro aniline	23 (25)	23 (25)	23 (25)	22 (50)	**26 (25)**	**24 (50)**
5l	2-Amino 5-methyl thaizole	23 (50)	21 (50)	**24 (25)**	21 (50)	23 (62.5)	23 (100)
Ciprofloxacin (100 μg/disc)		30 (≤1)	31 (≤1)	32 (≤1)	33 (≤1)	–	–
Ketoconazole (100 μg/disc)		–	–	–	–	30 (≤3)	33 (≤1)
DMSO		–	–	–	–	–	–

The MIC values were evaluated at concentration range of 3.12–100 μg/mL

Data values in bold letter represents the highest activity

functionality were also to be inactive in all the bioassay studied. Final azetidinone-based analogues with electron *ortho*-nitro (**5e**) and *meta*-nitro (**5f**) aniline substituent indicated poor activity, but the presence of similar constituents (**6e**, **6f**) in thiazolidinone nucleus demonstrated excellent activity against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* at 12.5 μg/mL of MIC, respectively. In addition, the insertion of electro-withdrawing *para*-nitro aniline substituent to both of the nucleus as azetidinone (**5g**) and thiazolidinone (**6g**) systems proved beneficial to display strong activity against *S. aureus* and *P. aeruginosa* (12.5 μg/mL). However, compound (**6g**) was also appeared with good inhibitory efficacy against *C. albicans* fungi at 25 μg/mL of MIC. Presence of electron-withdrawing *ortho*-chloro (**5h**) and *para*-chloro (**5j**) substituents to the azetidinone ring system display potential antigrowth activity against gram +ve strain *B. subtilis* at 12.5 μg/mL of MIC, whereas, similar *meta*-halo-substituted aniline with thiazolidinone nucleus demonstrated potential activity against the same strain at similar concentration level. Compound (**6j**) with electron-withdrawing *para*-chloro aniline-substituted was also efficacious to inhibit *B. subtilis* at 12.5 μg/mL of MIC along with similar efficacy against *Aspergillus niger* fungi. Hence, it can be stated that all the newer analogues with chloro functionality were active against gram +ve strains as well as fungal strains. Final analogues with strong electro-negative fluoro substituents either in the form of azetidinone (**5k**) or thiazolidinone (**6k**) class showed diminished activity against both the type of fungal strains at the MIC range 12.5–50 μg/mL. However, the MIC profile exhibited by thiazolidinone class of fluro-based analogues (**6k**) was excelled as compared to that of azetidinone class. Final analogues with amino-heterocycles with sulfur atom functionality showed good efficacy against gram −ve *E. coli* strain at 25 μg/mL of MIC. All the final potent analogues exhibited excellent inhibitory zones against all the mentioned microorganisms with good range as compared to that of standard drugs. Again, it will suffice to mention that inhibitory zones displayed by

Table 2 In vitro antimicrobial study (MIC μg/mL) of thiazolidinone analogues (**6a–l**) MIC



Comp. (100 μg/disc)	R	Zone of inhibition [mm (MIC in μg/mL)]					
		Gram −ve		Gram +ve		Fungal species	
		S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
6a	Aniline	17 (100)	<10 (100)	<10 (100)	13 (100)	14 (100)	<10 (100)
6b	2-Methyl aniline	<10 (100)	<10 (100)	<10 (100)	<10 (100)	<10 (100)	<10 (100)
6c	3-Methyl aniline	18 (100)	17 (100)	<10 (100)	16 (100)	19 (100)	13 (100)
6d	4-Methyl aniline	19 (100)	19 (100)	17 (100)	20 (62.5)	<10 (100)	17 (100)
6e	2-Nitro aniline	25 (25)	21 (62.5)	**24 (12.5)**	**25 (12.5)**	22 (50)	20 (100)
6f	3-Nitro aniline	**26 (12.5)**	22 (50)	22 (62.5)	24 (12.5)	24 (25)	23 (25)
6g	4-Nitro aniline	**26 (12.5)**	23 (50)	21 (62.5)	**25 (12.5)**	24 (12.5)	**24 (25)**
6h	2-Chloro aniline	21 (50)	23 (12.5)	21 (62.5)	21 (25)	20 (62.5)	21 (62.5)
6i	3-Chloro aniline	26 (25)	**24 (12.5)**	22 (62.5)	23 (25)	24 (50)	20 (100)
6j	4-Chloro aniline	23 (50)	**24 (12.5)**	23 (50)	24 (25)	**25 (12.5)**	22 (50)
6k	4-Fluoro aniline	24 (25)	23 (12.5)	23 (25)	24 (25)	**25 (12.5)**	**24 (25)**
6l	2-Amino 5-methyl thaizole	24 (50)	23 (50)	24 (25)	22 (50)	24 (62.5)	23 (100)
Ciprofloxacin (100 μg/disc)		30 (≤1)	31 (≤1)	32 (≤1)	33 (≤1)	–	–
Ketoconazole (100 μg/disc)		–	–	–	–	30 (≤3)	33 (≤1)
DMSO		–	–	–	–	–	–

The MIC values were evaluated at concentration range of 3.12–100 μg/mL

Data values in bold letter represents the highest activity

thiazolidinone analogues (24–26 mm) were better as compared to that of azetidinone class (23–26 mm) with respect to standard drugs (31–33 mm). All the remaining analogues were displayed good-to-moderate activity with the MIC range of 50–100 μg/mL (see Figs. 1, 2).

Antituberculosis activity

The antimycobacterial biological screening was performed using Lowenstein–Jensen (L–J) MIC method and it is worthwhile to note that two derivatives, **5l** with 2-amino 5-methyl thaizole moiety to the azetidinone class as well as **6k** with electron-withdrawing and strong electro-negative fluoro substituent within the thiazolidinone class exhibited good inhibitory potential at 12.5 μg/mL of MIC against H37Rv strain. The inhibitory potential of the said derivatives was half-fold as compared to standard drugs (Table 3). In addition, similar fluoro-derivative within the azetidinone class (**5k**) as well as derivative **6l** with 2-amino 5-methyl thaizole within the thiazolidinone class appeared with good inhibitory effect against H37Rv strain at 25 μg/mL of MIC. Four of the final derivatives (**5i**, **5g**, **6i**, and **6g)** with either *para*-nitro or *meta*-chloro aniline substituent demonstrated moderate inhibitory activity at 50 μg/mL of MIC, while remaining derivatives were found inactive at the MIC range ranging from 62.5 to 1,000 μg/mL.

Experimental

Materials and methods

All the chemicals used in the synthesis were of analytical grade. The melting points were determined in open capillary on Veego (Model: VMP-D) electronic apparatus and are uncorrected. The IR spectra (4,000–400 cm^{-1}) of synthesized compounds were recorded on Shimadzu 8400-S FT-IR spectrophotometer with KBr pellets. Thin layer chromatography was performed on microscopic glass slides (2 × 7.5 cm) coated with silica gel-G, using appropriate

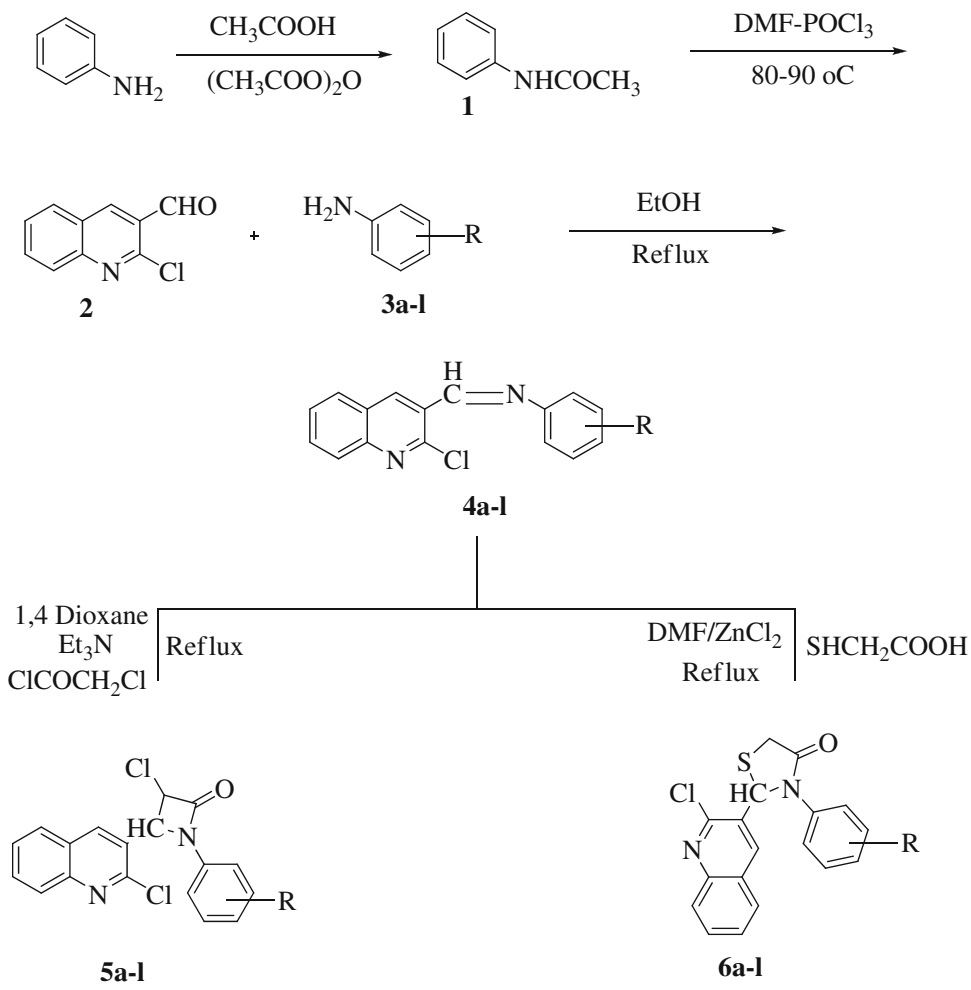


Fig. 1 Schematic diagram for the synthesis of azetidinone and thiazolidinone derivatives

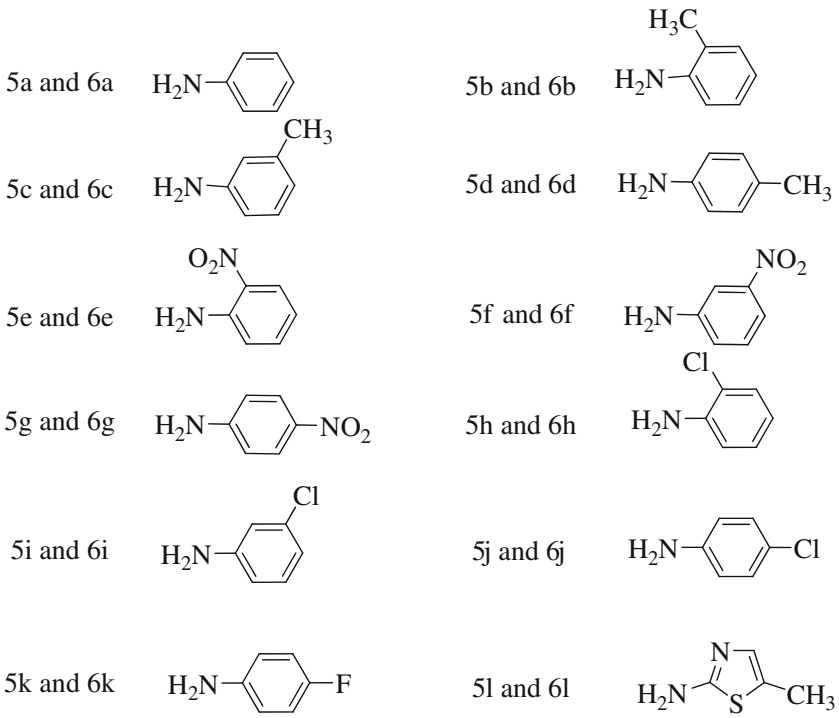


Fig. 2 [(**4a–l**), R] Bases coupled to compound **5a–l** and **6a–l**

Table 3 In vitro antituberculosis activity

Entry	R	L–J MIC method	
		MIC (μg/mL)	% Inhibition
5a	Aniline	500	90
5b	2-Methyl aniline	1,000	91
5c	3-Methyl aniline	500	90
5d	4-Methyl aniline	200	94
5e	2-Nitro aniline	250	92
5f	3-Nitro aniline	100	93
5g	4-Nitro aniline	50	96
5h	2-Chloro aniline	62.5	97
5i	3-Chloro aniline	50	98
5j	4-Chloro aniline	100	95
5k	4-Fluoro aniline	25	98
5l	2-Amino 5-methyl thaizole	12.5	99
6a	Aniline	250	92
6b	2-Methyl aniline	500	90
6c	3-Methyl aniline	500	90
6d	4-Methyl aniline	250	94
6e	2-Nitro aniline	200	93
6f	3-Nitro aniline	100	94
6g	4-Nitro aniline	50	97
6h	2-Chloro aniline	100	95
6i	3-Chloro aniline	50	97
6j	4-Chloro aniline	62.5	96
6k	4-Fluoro aniline	12.5	99
6l	2-Amino 5-methyl thaizole	25	98
Ethambutol		3.12	99
Pyrazinamide		6.25	99

mobile phase system and spots were visualized under UV radiation. Nuclear magnetic resonance spectra were recorded on Varian 400 MHz model spectrometer using dimethylsulfoxide (DMSO) as a solvent and TMS as internal standard (Chemical shifts in δ ppm). The mass spectra were recorded on JOEL SX-102 model and were performed at CDRI, Lucknow. Elemental analyses (C, H, N) were performed using a Heraeus Carlo Erba 1180 CHN analyzer (Hanau, Germany). All the novel compounds gave C, H, and N analyses within 0.2 % points from the theoretical values.

Methods for in vitro antimicrobial evaluations of the newer analogues

The synthesized azetidinone and thiazolidinone derivatives (**5a–l** and **6a–l**) were examined for antimicrobial activity against several bacteria (*S. aureus* MTCC 96, *B. subtilis* MTCC 430, *E. coli* MTCC 739, *P. aeruginosa* MTCC 741) and fungi (*A. niger* MTCC 282, *Candida albicans* MTCC 183) species using the paper disc diffusion technique (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 spread 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 activities, respectively.

To determine the MIC (Hawkey and Lewis, 1994), agar streak dilution method was used in which 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.

Methods for in vitro antituberculosis evaluations of the newer analogues

In vitro antituberculosis activity assay was carried out using L–J MIC method against *Mycobacterium tuberculosis* H37Rv and the results are expressed in terms of MIC (Isenberg, 1992). Stock solutions of primary 1,000, 500, 250 μg/mL, and secondary 200, 100, 62.5, 50, 25, 12.5, 6.25, 3.25 μg/mL dilutions of each test compound in DMSO were added in the liquid L–J medium and then media were sterilized by inspissation method. A culture of *M. tuberculosis* H37Rv growing on L–J medium was harvested in 0.85 % saline in bijou bottles. These tubes were then incubated at (37 ± 1)°C for 24 h followed by streaking of *M. tuberculosis* H37Rv (5×10^4 bacilli per tube). These tubes were then incubated at (37 ± 1)°C.

Growth of bacilli was seen after 12, 22, and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* H37Rv. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC concentration of test compound. The standard strain *M. tuberculosis* H37Rv was tested with known drugs ethambutol and pyrazinamide.

General procedure for the synthesis of 2-chloroquinoline 3-carbaldehyde (**2**)

To a solution of **1** (15 g, 0.05 mol) in dry DMF (24.5 mL, 0.15 mol) at 0–5°C with stirring $POCl_3$ (204.1 mL, 0.6 mol) was added dropwise and the mixture stirred at 80–90°C for time ranging between 4 and 15 h. The mixture was poured into crushed ice, stirred for 5 min and the resulting solid filtered, washed well with water, and dried. The compounds were purified by recrystallization from either ethyl acetate or acetonitrile. Yield: 85 %, m.p. 146–149°C (dec.). IR (KBr) cm^{-1}: 1,680–1,696 cm^{-1} (–CHO).

General procedure for the synthesis of (2-chloroquinoline-3-yl-methylene)-phenyl-substituted amine (**4a–l**)

2-Chloro-quinoline 3-carbaldehyde (0.01 mol) **2**, substituted aromatic amine **3a–l** (0.01 mol) were taken in ethanol with catalytic amount of conc. H_2SO_4 (2 mL) and heated to refluxed for 6–7 h. After conclusion of the reaction (TLC), the reaction mixture was poured onto crushed ice; the solid mass thus separated out was filtered, washed with water, and dried to give desired compounds **4a–l**. The compounds were purified by recrystallization from ethanol.

General procedure for preparation of compounds (**5a–l**)

A mixture of (2-chloro-quinoline-3-yl-methylene)-phenyl-substituted amine **4a–l** (0.01 mol) and triethylamine (0.02 mol) was dissolved in 1,4-dioxane (50 mL). To this well-stirred cooled solution, chloroacetylchloride (0.02 mol) was added dropwise during 30 min. The reaction mixture was then stirred for further 1 h and refluxing for 10 h. the triethylamine hydrochloride salt formed was filtered to separate the salt. The filtrate was concentrated to half of its initial volume and then poured onto crushed ice. The product obtained was filtered, washed with water, and recrystallized from DMF.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-phenyl-azetidin-2-one (**5a**)*

Yield: 77 %. m.p. 240–243°C (DMF). IR (KBr) cm^{-1}: 1,731 (C=O of β-lactam ring), 1,589 (C=C), 1,531 (C–N), 760 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.70 (d, $J = 6.5$ Hz, 1H, C<u>H</u>–Cl at azetidinone ring), 6.90 (d, $J = 6.6$ Hz, 1H, C<u>H</u>–N at azetidinone ring), 7.20–7.35 (m, 5H, Ar–<u>H</u>), 7.52 (m, $J = 1.6$ Hz, 1H, C-1 proton of quinoline), 7.64 (dt, $J = 7.5, 1.7$ Hz, 1H, C-6 proton of quinoline), 7.77–7.80 (m, 2H, C-2, and C-10 proton of quinoline), 7.94 (dd, $J = 8.0, 1.5$ Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 61.78 (1C, C-21, C–Cl of β-lactam ring), 67.37 (1C, C-12, –Ar–azetidinone ring linkage), 146.78–119.22 (14C, Ar–C), 149.51 (1C, C-8, C–Cl of quinoline ring), 165.57 (1C, C-20, C=O). EMI–MS (*m/z*): 344.74 (M^+). Anal. Calcd. for $C_{18}H_{12}Cl_2N_2O$: C, 62.99; H, 3.52; N, 8.16. Found: C, 62.90; H, 3.61; N, 8.21.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-o-tolyl-azetidin-2-one (**5b**)*

Yield: 75 %. m.p. 261–263°C (DMF). IR (KBr) cm^{-1}: 1,734 (C=O of β-lactam ring), 1,580 (C=C), 1,533 (C–N), 770 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 3H, Ar–C<u>H</u>$_3$), 5.75 (d, $J = 6.7$ Hz, 1H, C<u>H</u>–Cl at azetidinone ring), 6.91 (d, $J = 6.4$ Hz, 1H, C<u>H</u>–N at azetidinone ring), 7.01–7.35 (m, 4H, Ar–<u>H</u>), 7.53 (m, $J = 1.4$ Hz, 1H, C-1 proton of quinoline), 7.64 (dt, $J = 7.7, 1.5$ Hz, 1H, C-6 proton of quinoline), 7.76–7.83 (m, 2H, C-2, and C-10 proton of quinoline), 7.93 (dd, $J = 8.1, 1.7$ Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 22.59 (1C, C-26, C–CH_3), 62.43 (1C, C-21, C–Cl of β-lactam ring), 67.93 (1C, C-12, –Ar.–azetidinone ring linkage), 145.81–120.45 (14C, Ar–C), 147.56 (1C, C-8, C–Cl of quinoline ring), 166.17 (1C, C-20, C=O). EMI–MS (*m/z*): 358.86 (M^+). Anal. Calcd. for $C_{19}H_{14}Cl_2N_2O$: C, 63.88; H, 3.95; N, 7.84. Found: C, 63.94; H, 3.90; N, 7.93.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-m-tolyl-azetidin-2-one (**5c**)*

Yield: 70 %. m.p. 255–257°C (DMF). IR (KBr) cm^{-1}: 1,736 (C=O of β-lactam ring), 1,585 (C=C), 1,529 (C–N), 773 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H, Ar–C<u>H</u>$_3$), 5.71 (d, $J = 6.6$ Hz, 1H, C<u>H</u>–Cl at azetidinone ring), 6.89 (d, $J = 6.5$ Hz, 1H, C<u>H</u>–N at azetidinone ring), 7.05–7.39 (m, 4H, Ar–<u>H</u>), 7.50 (m, $J = 1.7$ Hz, 1H, C-1 proton of quinoline), 7.61 (dt, $J = 7.6, 1.7$ Hz, 1H, C-6 proton of quinoline), 7.73–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.91 (dd, $J = 7.9, 1.6$ Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 24.87 (1C, C-26, C–CH_3), 61.37 (1C, C-21, C–Cl of β-lactam ring), 69.70 (1C, C-12, –Ar.–azetidinone ring linkage), 146.91–114.56 (14C, –Ar–C), 149.29 (1C, C-8, C–Cl of quinoline ring), 164.95 (1C, C-20, C=O). EMI–MS (*m/z*): 358.73 (M^+). Anal. Calcd. for $C_{19}H_{14}Cl_2N_2O$: C, 63.88; H, 3.95; N, 7.84. Found: C, 63.80; H, 3.87; N, 7.91.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-p-tolyl-azetidin-2-one (**5d**)*

Yield: 73 %. m.p. 263–264°C (DMF). IR (KBr) cm^{-1}: 1,738 (C=O of β-lactam ring), 1,571 (C=C), 1,527 (C–N), 767 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H, Ar–C$\underline{H}_3$), 5.77 (d, $J = 6.8$ Hz, 1H, C$\underline{H}$–Cl at azetidinone ring), 6.90 (d, $J = 6.4$ Hz, 1H, C$\underline{H}$–N at azetidinone ring), 6.85–7.15 (m, 4H, Ar–$\underline{H}$), 7.52 (m, $J = 1.6$ Hz, 1H, C-1 proton of quinoline), 7.63 (dt, $J = 7.8$, 1.6 Hz, 1H, C-6 proton of quinoline), 7.75–7.83 (m, 2H, C-2, and C-10 proton of quinoline), 7.94 (dd, $J = 8.2$, 1.4 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 25.41 (1C, C-26, C–CH_3), 62.65 (1C, C-21, C–Cl of β-lactam ring), 69.98 (1C, C-12, –Ar.–azetidinone ring linkage), 147.75–127.32 (14C, Ar–C), 149.29 (1C, C-8, C–Cl of quinoline ring), 165.33 (1C, C-20, C=O). EMI–MS (*m/z*): 358.79 (M^+).Anal. Calcd. for $C_{19}H_{14}Cl_2N_2O$: C, 63.88; H, 3.95; N, 7.84. Found: C, 63.84; H, 3.91; N, 7.86.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(2-nitro-phenyl)-azetidin-2-one (**5e**)*

Yield: 68 %. m.p. 270–271°C (DMF). IR (KBr) cm^{-1}: 1,737 (C=O of β-lactam ring), 1,577 (C=C), 1,538 (C–N), 769 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.67 (d, $J = 6.6$ Hz, 1H, C$\underline{H}$–Cl at azetidinone ring), 7.09 (d, $J = 6.7$ Hz, 1H, C$\underline{H}$–N at azetidinone ring), 7.37–8.31 (m, 4H, Ar–$\underline{H}$), 7.54 (m, $J = 1.8$ Hz, 1H, C-1 proton of quinoline), 7.66 (dt, $J = 7.5$, 1.4 Hz, 1H, C-6 proton of quinoline), 7.73–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.94 (dd, $J = 8.0$, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 60.59 (1C, C-21, C–Cl of β-lactam ring), 69.56 (1C, C-12, –Ar.–azetidinone ring linkage), 147.09–121.31 (13C, Ar–C), 145.01 (1C, C-8, C–Cl of quinoline ring), 148.27 (1C, C-13, C–NO_2), 166.58 (1C, C-20, C=O). EMI–MS (*m/z*): 389.56 (M^+). Anal. Calcd. for $C_{18}H_{11}Cl_2N_3O_3$: C, 55.69; H, 2.86; N, 10.82. Found: C, 55.73; H, 2.84; N, 10.85.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(3-nitro-phenyl)-azetidin-2-one (**5f**)*

Yield: 65 %. m.p. 275–277°C (DMF). IR (KBr) cm^{-1}: 1,733 (C=O of β-lactam ring), 1,580 (C=C), 1,533 (C–N), 773 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.63 (d, $J = 6.3$ Hz, 1H, C$\underline{H}$–Cl at azetidinone ring), 7.03 (d, $J = 6.5$ Hz, 1H, C$\underline{H}$–N at azetidinone ring), 7.53–8.20 (m, 4H, Ar–$\underline{H}$), 7.51 (m, $J = 1.6$ Hz, 1H, C-1 proton of quinoline), 7.62 (dt, $J = 7.2$, 1.2 Hz, 1H, C-6 proton of quinoline), 7.73–7.79 (m, 2H, C-2, and C-10 proton of quinoline), 7.90 (dd, $J = 7.8$, 1.6 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 61.12 (1C, C-21, C–Cl of β-lactam ring), 68.90 (1C, C-12, –Ar.–azetidinone ring linkage), 150.62–112.09 (13C, Ar–C), 147.21 (1C, C-8, C–Cl of quinoline ring), 149.93 (1C, C-13, C–NO_2), 163.78 (1C, C-20, C=O). EMI–MS (*m/z*): 389.63 (M^+). Anal. Calcd. for $C_{18}H_{11}Cl_2N_3O_3$: C, 55.69; H, 2.86; N, 10.82. Found: C, 55.65; H, 2.81; N, 10.85.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(4-nitro-phenyl)-azetidin-2-one (**5g**)*

Yield: 67 %. m.p. 262–264°C (DMF). IR (KBr) cm^{-1}: 1,738 (C=O of β-lactam ring), 1,591 (C=C), 1,536 (C–N), 762 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.70 (d, $J = 6.5$ Hz, 1H, C$\underline{H}$–Cl at azetidinone ring), 7.09 (d, $J = 6.7$ Hz, 1H, C$\underline{H}$–N at azetidinone ring), 6.95–8.09 (m, 4H, Ar–$\underline{H}$), 7.54 (m, $J = 1.7$ Hz, 1H, C-1 proton of quinoline), 7.65 (dt, $J = 7.5$, 1.5 Hz, 1H, C-6 proton of quinoline), 7.75–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.93 (dd, $J = 8.1$, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 60.29 (1C, C-21, C–Cl of β-lactam ring), 68.37 (1C, C-12, –Ar.–azetidinone ring linkage), 149.41–122.62 (13C, Ar–C), 145.95 (1C, C-13, C–NO_2), 148.29 (1C, C-8, C–Cl of quinoline ring), 162.98 (1C, C-20, C=O). EMI–MS (*m/z*): 389.79 (M^+). Anal. Calcd. for $C_{18}H_{11}Cl_2N_3O_3$: C, 55.69; H, 2.86; N, 10.82. Found: C, 55.73; H, 2.94; N, 10.73.

*3-Chloro-1-(2-chloro-phenyl)-4-(2-chloro-quinoline-3-yl)-azetidin-2-one (**5h**)*

Yield: 73 %. m.p. 280–281°C (DMF). IR (KBr) cm^{-1}: 1,738 (C=O of β-lactam ring), 1,592 (C=C), 1,533 (C–N), 777 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.73 (d, $J = 6.4$ Hz, 1H, C$\underline{H}$–Cl at azetidinone ring), 6.80 (d, $J = 6.5$ Hz, 1H, C$\underline{H}$–N at azetidinone ring), 7.10–7.87 (m, 4H, Ar–$\underline{H}$), 7.52 (m, $J = 1.4$ Hz, 1H, C-1 proton of quinoline), 7.68 (dt, $J = 7.2$, 1.7 Hz, 1H, C-6 proton of quinoline), 7.73–7.82 (m, 2H, C-2, and C-10 proton of quinoline), 7.91 (dd, $J = 8.0$, 1.6 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 60.29 (1C, C-21, C–Cl of β-lactam ring), 68.37 (1C, C-12, –Ar.–azetidinone ring linkage), 149.41–122.62 (14C, Ar–C), 148.29 (1C, C-8, C–Cl of quinoline ring), 165.98 (1C, C-20, C=O). EMI–MS (*m/z*): 378.89 (M^+). Anal. Calcd. for $C_{18}H_{11}Cl_3N_2O$: C, 57.25; H, 2.94; N, 7.42. Found: C, 57.33; H, 2.89; N, 7.49.

*3-Chloro-1-(3-chloro-phenyl)-4-(2-chloro-quinoline-3-yl)-azetidin-2-one (**5i**)*

Yield: 68 %. m.p. 269–270°C (DMF). IR (KBr) cm^{-1}: 1,733 (C=O of β-lactam ring), 1,595 (C=C), 1,540 (C–N), 766 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.68 (d,

$J = 6.1$ Hz, 1H, C<u>H</u>–Cl at azetidinone ring), 6.94 (d, $J = 6.3$ Hz, 1H, C<u>H</u>–N at azetidinone ring), 7.04–7.69 (m, 4H, Ar–<u>H</u>), 7.55 (m, $J = 1.3$ Hz, 1H, C-1 proton of quinoline), 7.64 (dt, $J = 7.4$, 1.5 Hz, 1H, C-6 proton of quinoline), 7.74–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.89 (dd, $J = 7.8$, 1.4 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 60.98 (1C, C-21, C–Cl of β-lactam ring), 68.01 (1C, C-12, –Ar.–azetidinone ring linkage), 146.23–117.95 (14C, Ar–C), 148.56 (1C, C-8, C–Cl of quinoline ring), 162.71 (1C, C-20, C=O of β-lactam ring). EMI–MS (*m/z*): 378.80 (M^+).Anal. Calcd. for $C_{18}H_{11}Cl_3N_2O$: C, 57.25; H, 2.94; N, 7.42. Found: C, 57.20; H, 2.92; N, 7.48.

*3-Chloro-1-(4-chloro-phenyl)-4-(2-chloro-quinoline-3-yl)-azetidin-2-one (**5j**)*

Yield: 73 %. m.p. 253–254°C (DMF). IR (KBr) cm^{-1}: 1,733 (C=O of β-lactam ring), 1,576 (C=C), 1,539 (C–N), 770 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.71 (d, $J = 6.3$ Hz, 1H, C<u>H</u>–Cl at azetidinone ring), 6.91 (d, $J = 6.5$ Hz, 1H, C<u>H</u>–N at azetidinone ring), 7.32 (m, 4H, Ar–<u>H</u>), 7.53 (m, $J = 1.6$ Hz, 1H, C-1 proton of quinoline), 7.61 (dt, $J = 7.7$, 1.6 Hz, 1H, C-6 proton of quinoline), 7.71–7.79 (m, 2H, C-2, and C-10 proton of quinoline), 7.87 (dd, $J = 8.1$, 1.7 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 60.59 (1C, C-21, C–Cl of β-lactam ring), 68.35 (1C, C-12, –Ar.–azetidinone ring linkage), 145.31–119.91 (14C, Ar–C), 148.78 (1C, C-8, C–Cl of quinoline ring), 163.11 (1C, C-20, C=O). EMI–MS (*m/z*): 378.92 (M^+).Anal. Calcd. for $C_{18}H_{11}Cl_3N_2O$: C, 57.25; H, 2.94; N, 7.42. Found: C, 57.21; H, 2.86; N, 7.38.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(4-fluoro-phenyl)-azetidin-2-one (**5k**)*

Yield: 66 %. m.p. 290–292°C (DMF). IR (KBr) cm^{-1}: 1,738 (C=O of β-lactam ring), 1,593 (C=C), 1,541 (C–N), 773 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.75 (d, $J = 6.5$ Hz, 1H, C<u>H</u>–Cl at azetidinone ring), 6.93 (d, $J = 6.6$ Hz, 1H, C<u>H</u>–N at azetidinone ring), 7.11–7.29 (m, 4H, Ar–<u>H</u>), 7.54 (m, $J = 1.5$ Hz, 1H, C-1 proton of quinoline), 7.63 (dt, $J = 7.9$, 1.7 Hz, 1H, C-6 proton of quinoline), 7.73–7.80 (m, 2H, C-2, and C-10 proton of quinoline), 7.90 (dd, $J = 8.3$, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 60.59 (1C, C-21, C–Cl of β-lactam ring), 68.35 (1C, C-12, –Ar.–azetidinone ring linkage), 145.31–119.91 (14C, Ar–C), 148.78 (1C, C-8, C–Cl of quinoline ring), 163.11 (1C, C-20, C=O). EMI–MS (*m/z*): 362.71 (M^+). Anal. Calcd. for $C_{18}H_{11}Cl_2FN_2O$: C, 59.85; H, 3.07; N, 7.76. Found: C, 59.81; H, 3.12; N, 7.80.

*3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(5-methyl-thiazol-2-yl)-azetidin-2-one (**5l**)*

Yield: 59 %. m.p. 295–296°C (DMF). IR (KBr) cm^{-1}: 1,731 (C=O of β-lactam ring), 1,539 (C–N), 762 (C–Cl), 650 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H, Ar–C<u>H</u>$_3$ at thaizole ring), 5.73 (d, $J = 6.7$ Hz, 1H, C<u>H</u>–Cl at azetidinone ring), 6.96 (d, $J = 6.5$ Hz, 1H, C<u>H</u>–N at azetidinone ring), 7.21 (d, 1H, Ar–<u>H</u> at thaizole ring), 7.52 (m, $J = 1.7$ Hz, 1H, C-1 proton of quinoline), 7.69 (dt, $J = 7.7$, 1.5 Hz, 1H, C-6 proton of quinoline), 7.75–7.83 (m, 2H, C-2, and C-10 proton of quinoline), 7.93 (dd, $J = 8.0$, 1.6 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 14.77 (1C, C–CH$_3$ in sulfur heterocycle), 60.21 (1C, C-15, C–Cl of β-lactam ring), 64.56 (1C, C-12, –Ar.–azetidinone ring linkage), 122.81–145.96 (10C, Ar–C), 147.88 (1C, C-8, C–Cl of quinoline ring), 158.07 (1C, C-20, -N–C at azetidinone-heterocyclic coupling ring), 159.26 (1C, C-14, C=O). EMI–MS (*m/z*): 365.59 (M^+). Anal. Calcd. for $C_{16}H_{11}Cl_2N_3OS$: C, 52.76; H, 3.04; N, 11.54. Found: C, 52.82; H, 3.10; N, 11.49.

General procedure for preparation of compounds (**6a–l**)

A mixture of (2-chloro-quinoline-3-yl-methylene)-phenyl-substituted amine **4a–l** (0.01 mol) and catalytic amount of zinc chloride (0.05 g) in DMF was taken in Dean stark apparatus and to it thioglycolic acid (0.02 mol) in DMF was added slowly. The reaction mass was refluxed for 12 h the DMF was distilled off to get the solid mixture. This was then treated with an excess of 10 % sodium bicarbonate solution to remove excess of thioglycolic acid. The product obtained was filtered, washed several times with water, and recrystallized from DMF.

*2-(2-Chloro-quinoline-3-yl)-3-phenyl-thiazolidin-4-one (**6a**)*

Yield: 63 %. m.p. 245–247°C (DMF). IR (KBr) cm^{-1}: 1,734 (C=O of β-lactam), 1,588 (C=C), 1,536 (C–N), 761 (C–Cl), 621 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.93 (dd, $J = 12.3$ Hz, 2H, C<u>H</u>–S at thiazolidinone ring), 6.49 (s, $J = 6.5$ Hz, 1H, C<u>H</u>–N at thiazolidinone ring), 7.17–7.39 (m, 5H, Ar–<u>H</u>), 7.48 (m, $J = 1.6$ Hz, 1H, C-1 proton of quinoline), 7.63 (dt, $J = 7.6$, 1.5 Hz, 1H, C-6 proton of quinoline), 7.73–7.79 (m, 2H, C-2, and C-10 proton of quinoline), 7.89 (dd, $J = 7.8$, 1.6 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 36.92 (1C, C-22, S–C at thiazolidinone ring), 57.87 (1C, C-12, –Ar.–thiazolidinone ring linkage), 148.23–125.34 (14C, Ar–C), 150.88 (1C, C-8, C–Cl at quinoline ring), 172.35 (1C, C-20, C=O). EMI–MS (*m/z*): 342.15 (M^+).

Anal. Calcd. for $C_{18}H_{13}ClN_2OS$: C, 63.43; H, 3.84; N, 8.22. Found: C, 63.40; H, 3.89; N, 8.28.

*2-(2-Chloro-quinoline-3-yl)-3-o-tolyl-thiazolidin-4-one (**6b**)*

Yield: 67 %. m.p. 265–266°C (DMF). IR (KBr) cm^{-1}: 1,738 (C=O of β-lactam), 1,596 (C=C), 1,536 (C–N), 767 (C–Cl), 625 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (s, 3H, Ar–C$\underline{H}_3$), 3.95 (dd, J = 12.5 Hz, 2H, C$\underline{H}$–S at thiazolidinone ring), 6.47 (s, J = 6.6 Hz, 1H, C$\underline{H}$–N at thiazolidinone ring), 7.01–7.31 (m, 4H, Ar–$\underline{H}$), 7.45 (m, J = 1.7 Hz, 1H, C-1 proton of quinoline), 7.65 (dt, J = 7.8, 1.6 Hz, 1H, C-6 proton of quinoline), 7.73–7.79 (m, 2H, C-2, and C-10 proton of quinoline), 7.94 (dd, J = 8.0, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 18.21 (1C, C-24, C–CH_3), 36.11 (1C, C-22, S–C at thiazolidinone ring), 58.67 (1C, C-12, –Ar.–thiazolidinone ring linkage), 147.61–124.88 (14C, Ar–C), 151.65 (1C, C-8, C–Cl at quinoline ring), 173.53 (1C, C-20, C=O). EMI–MS (m/z): 356.23 (M^+). Anal. Calcd. for $C_{19}H_{15}ClN_2OS$: C, 64.31; H, 4.26; N, 7.89. Found: C, 64.36; H, 4.31; N, 7.85.

*2-(2-Chloro-quinoline-3-yl)-3-m-tolyl-thiazolidin-4-one (**6c**)*

Yield: 63 %. m.p. 259–260°C (DMF). IR (KBr) cm^{-1}: 1,739 (C=O of β-lactam), 1,581 (C=C), 1,538 (C–N), 769 (C–Cl), 631 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 3H, Ar–C$\underline{H}_3$), 3.95 (dd, J = 12.4 Hz, 2H, C$\underline{H}$–S at thiazolidinone ring), 6.41 (s, J = 6.4 Hz, 1H, C$\underline{H}$–N at thiazolidinone ring), 7.05–7.37 (m, 4H, Ar–$\underline{H}$), 7.47 (m, J = 1.5 Hz, 1H, C-1 proton of quinoline), 7.69 (dt, J = 7.6, 1.7 Hz, 1H, C-6 proton of quinoline), 7.77–7.86 (m, 2H, C-2, and C-10 proton of quinoline), 7.95 (dd, J = 8.1, 1.7 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 22.25 (1C, C-24, C–CH_3), 36.55 (1C, C-22, S–C at thiazolidinone ring), 58.86 (1C, C-12, –Ar.–thiazolidinone ring linkage), 148.23–121.56 (14C, Ar–C), 150.77 (1C, C-8, C–Cl at quinoline ring), 172.83 (1C, C-20, C=O). EMI–MS (m/z): 356.34 (M^+). Anal. Calcd. for $C_{19}H_{15}ClN_2OS$: C, 64.31; H, 4.26; N, 7.89. Found: C, 64.37; H, 4.21; N, 7.92.

*2-(2-Chloro-quinoline-3-yl)-3-p-tolyl-thiazolidin-4-one (**6d**)*

Yield: 67 %. m.p. 269–271°C (DMF). IR (KBr) cm^{-1}: 1,736 (C=O of β-lactam), 1,579 (C=C), 1,532 (C–N), 773 (C–Cl), 629 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H, Ar–C$\underline{H}_3$), 3.93 (dd, J = 12.6 Hz, 2H, C$\underline{H}$–S at thiazolidinone ring), 6.47 (s, J = 6.7 Hz, 1H, C$\underline{H}$–N at thiazolidinone ring), 7.01–7.37 (m, 4H, Ar–$\underline{H}$), 7.44 (m, J = 1.8 Hz, 1H, C-1 proton of quinoline), 7.64 (dt, J = 7.5, 1.5 Hz, 1H, C-6 proton of quinoline), 7.74–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.91 (dd, J = 8.0, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 21.89 (1C, C-24, C–CH_3), 36.77 (1C, C-22, S–C at thiazolidinone ring), 58.05 (1C, C-12, –Ar.–thiazolidinone ring linkage), 148.89–123.31 (14C, Ar–C), 151.21 (1C, C-8, C–Cl at quinoline ring), 173.09 (1C, C-20, C=O). EMI–MS (m/z): 356.19 (M^+). Anal. Calcd. for $C_{19}H_{15}ClN_2OS$: C, 64.31; H, 4.26; N, 7.89. Found: C, 64.25; H, 4.21; N, 7.95.

*2-(2-Chloro-quinoline-3-yl)-3-(2-nitro-phenyl)-thiazolidin-4-one (**6e**)*

Yield: 78 %. m.p. 257–258°C (DMF). IR (KBr) cm^{-1}: 1,741 (C=O of β-lactam), 1,576 (C=C), 1,539 (C–N), 774 (C–Cl), 621 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (dd, J = 11.9 Hz, 2H, C$\underline{H}$–S at thiazolidinone ring), 6.47 (s, J = 6.8 Hz, 1H, C$\underline{H}$–N at thiazolidinone ring), 7.43–8.35 (m, 4H, Ar–$\underline{H}$), 7.49 (m, J = 1.4 Hz, 1H, C-1 proton of quinoline), 7.68 (dt, J = 7.7, 1.3 Hz, 1H, C-6 proton of quinoline), 7.78–7.86 (m, 2H, C-2, and C-10 proton of quinoline), 7.88 (dd, J = 7.9, 1.4 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 35.23 (1C, C-22, S–C at thiazolidinone ring), 58.26 (1C, C-12, –Ar.–thiazolidinone ring linkage), 148.26–124.85 (13C, Ar–C), 145.03 (1C, C-13, C–NO_2), 150.96 (1C, C-8, C–Cl at quinoline ring), 174.02 (1C, C-20, C=O). EMI–MS (m/z): 387.09 (M^+). Anal. Calcd. for $C_{18}H_{12}ClN_3O_3S$: C, 56.03; H, 3.13; N, 10.89. Found: C, 56.07; H, 3.10; N, 10.93.

*2-(2-Chloro-quinoline-3-yl)-3-(3-nitro-phenyl)-thiazolidin-4-one (**6f**)*

Yield: 57 %. m.p. 283–285°C (DMF). IR (KBr) cm^{-1}: 1,739 (C=O of β-lactam), 1,579 (C=C), 1,537 (C–N), 776 (C–Cl), 619 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (dd, J = 12.2 Hz, 2H, C$\underline{H}$–S at thiazolidinone ring), 6.43 (s, J = 6.6 Hz, 1H, C$\underline{H}$–N at thiazolidinone ring), 7.51–8.20 (m, 4H, Ar–$\underline{H}$), 7.46 (m, J = 1.7 Hz, 1H, C-1 proton of quinoline), 7.66 (dt, J = 7.5, 1.6 Hz, 1H, C-6 proton of quinoline), 7.73–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.86 (dd, J = 8.1, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 35.89 (1C, C-22, S–C at thiazolidinone ring), 56.93 (1C, C-12, –Ar.–thiazolidinone ring linkage), 149.81–119.57 (13C, Ar–C), 148.03 (1C, C-18, C–NO_2), 151.08 (1C, C-8, C–Cl at quinoline ring), 173.63 (1C, C-20, C=O). EMI–MS (m/z): 387.13 (M^+). Anal. Calcd. for $C_{18}H_{12}ClN_3O_3S$: C, 56.03; H, 3.13; N, 10.89. Found: C, 56.01; H, 3.19; N, 10.83.

*2-(2-Chloro-quinoline-3-yl)-3-(4-nitro-phenyl)-thiazolidin-4-one (**6g**)*

Yield: 59 %; m.p. 249–250°C (DMF). IR (KBr) cm^{-1}: 1,740 (C=O of β-lactam), 1,575 (C=C), 1,538 (C–N), 780 (C–Cl), 627 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.91 (dd, $J = 12.0$ Hz, 2H, C<u>H</u>–S at thiazolidinone ring), 6.46 (s, $J = 6.7$ Hz, 1H, C<u>H</u>–N at thiazolidinone ring), 6.91–8.11 (m, 4H, Ar–<u>H</u>), 7.48 (m, $J = 1.5$ Hz, 1H, C-1 proton of quinoline), 7.68 (dt, $J = 7.4$, 1.8 Hz, 1H, C-6 proton of quinoline), 7.75–7.82 (m, 2H, C-2, and C-10 proton of quinoline), 7.90 (dd, $J = 7.9$, 1.7 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 35.49 (1C, C-22, S–C at thiazolidinone ring), 58.15 (1C, C-12, –Ar.–thiazolidinone ring linkage), 148.75–121.07 (13C, Ar–C), 144.86 (1C, C-17, –C–NO_2), 151.23 (1C, C-8, C–Cl at quinoline ring), 174.11 (1C, C-20, C=O). EMI–MS (*m*/*z*): 387.18 (M^+).Anal. Calcd. for $C_{18}H_{12}ClN_3O_3S$: C, 56.03; H, 3.13; N, 10.89. Found: C, 56.09; H, 3.15; N, 10.85.

*3-(2-Chloro-phenyl)-2-(2-chloro-quinoline-3-yl)-thiazolidin-4-one (**6h**)*

Yield: 60 %. m.p. 287–289°C (DMF). IR (KBr) cm^{-1}: 1,741 (C=O of β-lactam), 1,591 (C=C), 1,536 (C–N), 770 (C–Cl), 630 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.91 (dd, $J = 12.1$ Hz, 2H, C<u>H</u>–S at thiazolidinone ring), 6.43 (s, $J = 6.5$ Hz, 1H, C<u>H</u>–N at thiazolidinone ring), 7.15–7.69 (m, 4H, Ar–<u>H</u>), 7.51 (m, $J = 1.8$ Hz, 1H, C-1 proton of quinoline), 7.63 (dt, $J = 7.6$, 1.6 Hz, 1H, C-6 proton of quinoline), 7.76–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.89 (dd, $J = 8.0$, 1.6 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 36.51 (1C, C-22, S–C at thiazolidinone ring), 59.66 (1C, C-12, –Ar.–thiazolidinone ring linkage), 149.43–125.57 (14C, Ar–C), 150.88 (1C, C-8, C–Cl at quinoline ring), 175.66 (1C, C-20, C=O). EMI–MS (*m*/*z*): 376.73 (M^+). Anal. Calcd. for $C_{18}H_{12}Cl_2N_2OS$: C, 57.61; H, 3.22; N, 7.46. Found: C, 57.56; H, 3.20; N, 7.41.

*3-(3-Chloro-phenyl)-2-(2-chloro-quinoline-3-yl)-thiazolidin-4-one (**6i**)*

Yield: 62 %. m.p. 286–288°C (DMF). IR (KBr) cm^{-1}: 1,743 (C=O of β-lactam), 1,587 (C=C), 1,538(C–N), 777 (C–Cl), 632 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.90 (dd, $J = 11.9$ Hz, 2H, C<u>H</u>–S at thiazolidinone ring), 6.43 (s, $J = 6.4$ Hz, 1H, C<u>H</u>–N at thiazolidinone ring), 7.05–7.51 (m, 4H, Ar–<u>H</u>), 7.49 (m, $J = 1.6$ Hz, 1H, C-1 proton of quinoline), 7.61 (dt, $J = 7.4$, 1.4 Hz, 1H, C-6 proton of quinoline), 7.74–7.79 (m, 2H, C-2, and C-10 proton of quinoline), 7.87 (dd, $J = 7.8$, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 37.55 (1C, C-22, S–C at thiazolidinone ring), 57.97 (1C, C-12, –Ar.–thiazolidinone ring linkage), 148.11–124.63 (1C, 14C, Ar–C), 149.68 (1C, C-8, C–Cl at quinoline ring), 174.03 (1C, C-20, C=O). EMI–MS (*m*/*z*): 376.59 (M^+). Anal. Calcd. for $C_{18}H_{12}Cl_2N_2OS$: C,57.61; H, 3.22; N, 7.46. Found: C, 57.69; H, 3.25; N, 7.50.

*3-(4-Chloro-phenyl)-2-(2-chloro-quinoline-3-yl)-thiazolidin-4-one (**6j**)*

Yield: 65 %. m.p. 260–261°C (DMF). IR (KBr) cm^{-1}: 1,739 (C=O of β-lactam), 1,593 (C=C), 1,535 (C–N), 773 (C–Cl), 628 (C–S–C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.92 (dd, $J = 12.3$ Hz, 2H, C<u>H</u>–S at thiazolidinone ring), 6.44 (s, $J = 6.5$ Hz, 1H, C<u>H</u>–N at thiazolidinone ring), 7.38 (m, 4H, Ar–<u>H</u>), 7.52 (m, $J = 1.5$ Hz, 1H, C-1 proton of quinoline), 7.63 (dt, $J = 7.7$, 1.6 Hz, 1H, C-6 proton of quinoline), 7.75–7.83 (m, 2H, C-2, and C-10 proton of quinoline), 7.90 (dd, $J = 8.1$, 1.7 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 37.09 (1C, C-22, S–C at thiazolidinone ring), 57.35 (1C, C-12, –Ar.–thiazolidinone ring linkage), 149.37–125.88 (14C, Ar–C), 150.07 (1C, C-8, C–Cl at quinoline ring), 174.58 (1C, C-20, C=O). EMI–MS (*m*/*z*): 376.57 (M^+). Anal. Calcd. for $C_{18}H_{12}Cl_2N_2OS$: C, 57.61; H, 3.22; N, 7.46. Found: C, 57.65; H, 3.26; N, 7.48.

*2-(2-Chloro-quinoline-3-yl)-3-(4-fluoro-phenyl)-thiazolidin-4-one (**6k**)*

Yield: 59 %. m.p. 295–297°C (DMF). IR (KBr) cm^{-1}: 1,738 (C=O of β-lactam), 1,589 (C=C), 1,536 (C–N), 765 (C–Cl), 617 (C–S-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.93 (dd, $J = 12.4$ Hz, 2H, C<u>H</u>–S at thiazolidinone ring), 6.45 (s, $J = 6.8$ Hz, 1H, C<u>H</u>–N at thiazolidinone ring), 7.10–7.31 (m, 4H, Ar–<u>H</u>), 7.55 (m, $J = 1.7$ Hz, 1H, C-1 proton of quinoline), 7.67 (dt, $J = 7.8$, 1.7 Hz, 1H, C-6 proton of quinoline), 7.73–7.82 (m, 2H, C-2, and C-10 proton of quinoline), 7.93 (dd, $J = 8.3$, 1.5 Hz, 1H, C-3 proton of quinoline). ^{13}C NMR (400 MHz, DMSO-d_6) δ 36.67 (1C, C-22, S–C at thiazolidinone ring), 57.06 (1C, C-12, –Ar.–thiazolidinone ring linkage), 148.07–115.57 (14C, Ar–C), 150.67 (1C, C-8, C–Cl at quinoline ring), 173.79 (1C, C-20, C=O). EMI–MS (*m*/*z*): 360.08 (M^+). Anal. Calcd. for $C_{18}H_{12}Cl_2FN_2OS$: C, 60.25; H, 3.37; N, 7.81; Found: C, 60.20; H, 3.39; N, 7.84.

2′-(2-Chloro-quinoline-3-yl)-5-methyl-[2, 3′]bithiazolyl-4′-one (**6l**)

Yield: 55 %. m.p. 296–298°C (DMF). IR (KBr) cm^{-1}: 1,737 (C=O of β-lactam), 1,583 (C=C), 1,535 (C–N), 770

(C–Cl), 629 (C–S-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 3H, Ar–C$\underline{H}_3$ at thaizole ring), 3.89 (dd, $J = 12.2$ Hz, 2H, C$\underline{H}$–S at thiazolidinone ring), 6.48 (s, $J = 6.5$ Hz, 1H, C$\underline{H}$–N at thiazolidinone ring), 7.49 (m, $J = 1.8$ Hz, 1H, C-1 proton of quinoline), 7.63 (dt, $J = 7.7$, 1.5 Hz, 1H, C-6 proton of quinoline), 7.75–7.81 (m, 2H, C-2, and C-10 proton of quinoline), 7.86 (dd, $J = 8.0$, 1.7 Hz, 1H, C-3 proton of quinoline). 7.21 (s, 1H, C$\underline{H}$-C at thaizole ring). ^{13}C NMR (400 MHz, DMSO-d_6) δ 15.23 (1C, C-23, C–CH_3 in heterocycles ring), 35.02 (1C, C-21, S–C at thiazolidinone ring), 57.08 (1C, C-12, -Ar at thiazolidinone-heterocyclic coupling ring), 148.69–124.33 (10C, Ar–C), 151.38 (1C, C-8, C–Cl at quinoline ring), 156.65 (1C, C-20, C–N) 178.37 (1C, C-14, C=O). EMI–MS (*m*/*z*): 363.11 (M^+). Anal. Calcd. for $C_{16}H_{12}ClN_3OS_2$: C, 53.11; H, 3.34; N, 11.61. Found: C, 53.16; H, 3.37; N, 11.59.

Conclusion

In this study various quinoline-based azetidinone and thiazolidinone analogues were synthesized and screened in vitro against various microorganisms as well as against mycobacteria. Briefly, high potency has been observed with the final scaffolds in the form of azetidinones and thiazolidinones bearing various amines containing halogen(s) such as chloro or fluoro and nitro functional groups. The final results indicated that quinoline-based thiazolidinones are more efficacious antimicrobial agents compared to quinoline-based azetidinones analogues. Hence, there is enough scope for further study in developing such compounds as a good lead activity.

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