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A Study of Antibacterial Activity of Some Novel 8-Methoxy-4-methyl-quinoline Derivatives

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In the present study, some quinoline derivatives have been synthesized like 8-methoxy-4-methyl-2-amino-(3'-chloro-2'-oxo-4'-substituted aryl-1'-azetidinyl)quinolines **8-12** and 8-methoxy-4-methyl-2-amino-(2'-substituted aryl-4'-oxo-1',3'-thiazolidin-3'-yl) quinolines **13-17** from 8-methoxy-4-methyl-2-(substituted arylidenyliminoamino)-quinolines **3-7**. The structural assignments of these compounds were based on spectral (IR, ^{1}H-NMR, Mass) and elemental (C, H, N) analysis. Further, these compounds were evaluated for antibacterial activity against various bacterial strains. Three compounds **10, 11** and **16** were found to exhibit potent antibacterial activity as compared to the standard drug amphicillin.

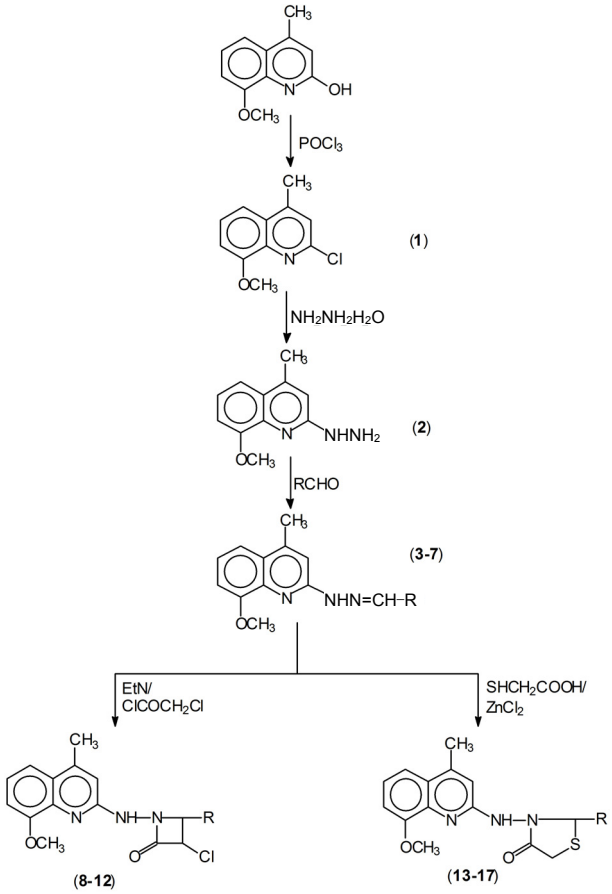
Key Words: Quinoline, Schiff base, Azetidinone, Thiazolidinone, Antibacterial activity

Introduction

To treat the infectious diseases caused by various bacteria is still remain challenging due to the increasing number of drug resistant microbial pathogens, this in turn unable the drugs to control the growth of harmful microorganisms. By considering this fact, it was suggested to employ structurally novel therapeutic agents with enhanced broad spectrum of potency against increasingly resistant pathogens.[1] Therefore, there is a need to explore some novel antibacterial agents. The recent decades have seen that medicinal chemists have devoted significant efforts to develop various derivatives of quinoline as antibacterial agents. Literature survey has indicated that quinoline derivatives possess diverse pharmacological activities like antimicrobial,[2] anti-malarial,[3] antiviral,[4] anti-tumor,[5] immunomodulatory,[6] antileishmanial,[7] anti-inflammatory activity,[8] and many more. The congeners of schiff base,[9-10] azetidinone[11-12] and thiazolidinone[13-14] have also been proved to exhibit promising antibacterial activity. These finding prompted us to synthesize the substituted quinoline derivatives by the combination of azetidinone or thiazolidinone moieties in one frame, this may lead to the compounds with interesting antibacterial profile.

Chemistry

The starting material 8-methoxy-4-methyl-2-chloroquinoline **1** was prepared by 8-methoxy-4-methyl-quinolin-2-ol on reaction with phosphorous oxychloride. This compound was reacted with hydrazine hydrate to furnish hydrazide congener: 8-methoxy-4-methyl-2-hyrazinoquinoline **2**, which on reaction with numerous aromatic aldehydes in presence of glacial acetic acid to yield schiff bases: 8-methoxy-4-methyl-2-(substituted arylidenyliminoamino)-quinolines **3-7**. Compounds **3-7** were treated with chloroacetyl chloride and triethylamine to produce azetidinones: 8-methoxy-4-methyl-2-amino-(3'-chloro-2'-oxo-4'-substituted aryl-1'-azetidinyl)quinolines **8-12**. On the other hand, substituted thiazolidinones: 8-methoxy-4-methyl-2-amino-(2'-substituted aryl-4'-oxo-1',3'-thiazolidin-3'-yl)quino-



Scheme 1

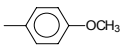
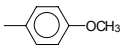
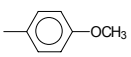
lines **13-17** have been procured from compounds **3-7** on reaction with thioglycolic acid and zinc chloride. The synthetic route of above said compounds is shown in Scheme 1.

Results and Discussion

With the aim to develop new antibacterial agents, we have reported the synthesis of 8-methoxy-4-methyl-2-(substitutedarylidenyliminoamino)-quinolines **3-7**, 8-methoxy-4-methyl-2-amino-(3'-chloro-2'-oxo-4'-substituted aryl-1'-azetidinyl)quinolines **8-12** and 8-methoxy-4-methyl-2-amino-(2'-substitutedaryl-4'-oxo-1',3'-thiazolidin-3'-yl) quinolines **13-17**. Then, these compounds were screened *in vitro* for antibacterial activity against gram positive bacteria: Staphylococcus aureus ATCC 25923 (*S. aureus*), Bacillus subtilis ATCC 6051 (*B. subtilis*) and Staphylococcus epidermis ATCC 14940 (*S. epidermis*) and gram negative bacteria Escherichia coli ATCC 25922 (*E. coli*), Klebsiella pneumoniae ATCC 10031 (*K. pneumoniae*) and Pseudomonas aeruginosa ATCC 27853 (*P. aeruginosa*) at a concentration of 250 μg/mL. Amphicillin was served as standard. Results of inhibition zone and minimal inhibitory concentration (MIC) were noted and illustrated in Table 1.

It has been found from the results of antibacterial screening that out of all the tested compounds, three compounds **10**, **11**

Table 1. Antibacterial activity[a] of the compounds **3-17** against tested bacterial strains

Compound No.	R	*S. aureus* ATCC 25923	*B. subtilis* ATCC 1633	*S. epidermis* ATCC 14940	*E. coli* ATCC 25922	*K. pneumoniae* ATCC 10031	*P. aeruginosa* ATCC 27853
3		10 (> 100)	11 (> 100)	07 (> 100)	09 (> 100)	-	06 (> 100)
4		12 (> 100)	15 (> 100)	-	08 (> 100)	13 (> 100)	17 (50)
5		16 (50)	18 (> 100)	14 (50)	12 (> 100)	10 (> 100)	21 (25)
6		19 (25)	22 (50)	20 (12.5)	15 (> 100)	18 (3.125)	23 (25)
7		09 (> 100)	06 (125)	10 (> 100)	-	07 (> 100)	08 (> 100)
8		22 (25)	25 (50)	18 (25)	17 (50)	14 (25)	25 (25)
9		26 (12.5)	29 (25)	24 (6.25)	27 (12.5)	19 (3.125)	31 (6.25)
10		-	34 (6.25)	27 (6.25)	24 (25)	27 (0.781)	30 (6.25)
11		35 (1.562)	38 (3.125)	30 (3.125)	32 (6.25)	21 (3.125)	39 (1.562)
12		21 (25)	27 (25)	23 (12.5)	20 (50)	-	28 (12.5)
13		18 (25)	21 (50)	-	-	16 (6.25)	22 (25)
14		24 (12.5)	23 (50)	21 (12.5)	22 (25)	-	27 (12.5)
15		30 (6.25)	31 (12.5)	25 (6.25)	24 (25)	20 (3.125)	30 (6.25)
16		32 (3.125)	34 (6.25)	23 (12.5)	30 (6.25)	21 (3.125)	31 (6.25)
17		17 (25)	27 (25)	21 (12.5)	19 (50)	17 (6.25)	23 (25)
DMSO[b]		0	0	0	0	0	0
Amphicillin		29 (6.25)	32 (12.5)	26 (6.25)	28 (12.5)	24 (1.562)	35 (3.125)

[a]Concentration was 250 μg/mL. [b]Served as control, denotes no inhibition zone was observed. Values in brackets are MIC.

and **16** exhibited prominent antibacterial activity against different bacterial strains (Table 1). Among these three compounds, compound **10** has shown substantial activity than standard drug against the bacterial strains: *B. subtilis* and *K. pneumoniae* with MIC 6.25 μg/mL and 0.781 μg/mL, respectively. Compound **11** (azetidinone moiety bearing *p*-methoxyphenyl substituent) reflected excellent antibacterial activity against all the bacterial strains except *K. pneumoniae* with MIC 1.562 - 6.25 μg/mL (Table 1). Moreover, compound **16** (thiazolidinone moiety having *p*-methoxyphenyl group) showed better efficacy as compared to standard drug against *S. aureus* (MIC 3.125 μg/mL), *B. subtilis* (MIC 6.25 μg/mL) and *E. coli* (MIC 6.25 μg/mL). Results has also indicated that compounds **9** and **15** displayed equipotent antibacterial activity as compared to the reference drug against all the bacterial strains tested (Table 1). The rest compounds of this series were found to be less active as compared to the standard drug.

It is significant note form the antibacterial results that the conversion of compounds **3**-**7** into azetidinone congeners **8**-**12** and thiazolidinone congeners **13**-**17** increased the inhibition action against the growth of various pathogens. However, compounds **8**-**12** consisting β-lactam ring displayed improved antibacterial activity as compared to thiazolidinone derivatives **13**-**17**.

Furthermore, the effect of different substituents on antibacterial activity was examined and after reviewing the antibacterial results of compounds **3**-**17** few observations could be drawn like:

It has been observed that compounds **6**, **11** and **16** bearing *p*-methoxyphenyl group furnished most potent antibacterial activity in their respective class of compounds **3**-**7**, **8**-**12** and **13**-**17**, respectively.

It is interesting to point out that compounds having *o*-hydroxyphenyl group as seen in compounds **5**, **10** and **15** has elicited remarkable inhibitory action.

Compounds having furfuryl (**7**, **12**, **17**) and *o*-chlorophenyl (**4**, **9**, **14**) groups has yielded less but still adequate antibacterial activity.

Experimental

Chemistry. All the reagents and solvents were generally received form commercial supplier. Reactions were done in dried glassware. Melting points were taken in open capillaries by thermonic melting point apparatus, (Campbell Electronic Mumbai, India) and are uncorrected. The purity of the newly synthesized compounds was checked by thin layer chromatography (TLC) on silica gel-G coated plates by using different solvent systems. Infrared (IR) spectra were determined on Bruker IFS-66 FTIR (Bruker Bioscience, USA) using KBr pallets and wave number (ν) was reported in cm^{-1}. The ^{1}H-NMR spectra were taken on Jeol GSX -300 FT NMR (Jeol, Tokyo, Japan) in $CDCl_3$ or DMSO-d_6, and chemical shifts (δ) are given in ppm. Tetramethylsilane (TMS) was used as internal reference standard. Mass spectra were recorded on Spec Finnigan Mat 8230 MS. The carbon, hydrogen and nitrogen analysis were performed on Carlo Erba-1108 (Carlo Erba, Milan, Italy), and the results were found with in ±0.4% of the theoretical values.

General procedure for the synthesis of 8-methoxy-4-methyl-2-chloroquinoline 1. A mixture of 8-methoxy-4-methyl-quinolin-2-ol (38.0 g; 0.75 mol) and freshly distilled phosphorous oxychloride (21.55 mL; 0.9 mol) was maintained at 80 - 85 °C on water bath for 15 minutes until most of the solids have dissolved. This reaction mixture was heated for another 15 minutes. Then, this hot mixture was poured onto crushed ice containing 1 L of water. Further, the obtained product was extracted by using 700 mL ether and 200 mL water and then dried over 50 g of potassium carbonate. After the removal of the ether, the residual oil is distilled off. Then, colorless distillate boils at 132 - 135 °C. The distillate is melted, if necessary, and poured into 250 mL of petroleum ether (40 - 45 °C). The solution is then chilled in a freezing mixture; the crystals are filtered by suction and dried in a vacuum desiccator over paraffin. Compound **1**: mp 65 °C; yield: 32.30 g (85.0%); IR (KBr) ν in cm^{-1}: 3070 (C-H aromatic ring), 2950 (C-H aliphatic), 1560 (C-----C of aromatic ring), 1160 (C-N), 1075 (C-O-C), 735 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ 7.92 (s, 1H, H_3 of quinoline), 7.81 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.78 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.65 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 3.49 (s, 3H, OCH_3), 2.84 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 207.5 and [M+2] at *m*/*z* 209.5. Anal. calcd for $C_{11}H_{10}NOCl$: C, 63.61; H, 4.82; N, 6.75; Found: C, 63.79; H, 4.65; N, 6.92.

General procedure for the synthesis of 8-methoxy-4-methyl-2-hyrazinoquinoline 2. An aqueous solution of hydrazine hydrate (99 - 100%; 14.52 mL; 0.02 mol) has added to a suspension of compound **1** (31.0 g; 0.01 mol) in ethanol (95 mL). The reaction mixture was refluxed for 6 h and then cooled at room temperature. The separated crystalline product was filtered, washed with little ethanol, dried and recrystallized form absolute ethanol to give compound **2**: mp 262 °C; yield: 24.8 g (80 - 0%); IR (KBr) ν in cm^{-1}: 3245 (NH), 3065 (C-H aromatic ring), 2965 (C-H aliphatic), 1564 (C-----C of aromatic ring), 1174 (C-N), 1091 (C-O-C), 1039 (N-N). ^{1}H-NMR ($CDCl_3$) δ 9.65 (bs, 1H, N*H*NH_2, exchangeable with D_2O), 7.93 (s, 1H, H_3 of quinoline), 7.80 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.79 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.63 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 3.51 (s, 3H, OCH_3), 2.86 (s, 3H, CH_3), 4.58 (s, 2H, NHNH_2, exchangeable with D_2O). MS: $[M]^+$ at *m*/*z* 203. Anal. calcd for $C_{11}H_{13}N_3O$: C, 65.02; H, 6.40; N, 20.69; Found: C, 64.88; H, 6.32; N, 20.51.

General procedure for the synthesis of 8-methoxy-4-methyl-2-(substituted arylidenyliminoamino)quinolines 3-7. To a solution of compound **2** (0.01 mol) in methanol (80 mL), aromatic aldehyde (0.01 mol) along with few drops of glacial acetic acid was added. This resulting mixture was refluxed for 10 - 12 h, while TLC monitored progress and completion of the reaction. The volatiles were evaporated, and the remaining mixture was filtered. The solid separated out was recrystallized from appropriate solvent to get compounds **3**-**7**.

8-Methoxy-4-methyl-2-(arylidenyl-iminoamino)quinoline 3: Reagents: compound **2** (4.5 g, 0.01 mol), benzaldehyde (2.25 mL, 0.01 mol), methanol (80 mL), mp 168 °C; yield: 3.69 g (82.0%); Recrytallization solvent : Acetone; IR (KBr) ν in cm^{-1}: 3285 (NH), 3075 (C-H aromatic ring), 2964 (C-H aliphatic), 1579 (C-----C of aromatic ring), 1188 (C-N), 1045 (N-N). ^{1}H-NMR ($CDCl_3$) δ 8.11 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.91(s, 1H, H_3 of quinoline), 7.79 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.74

(d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.61 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.25(m, 5H, Ar-*H*), 6.65 (s, 1H, N*H*, exchangeable with D_2O), 3.52 (s, 3H, OCH_3), 2.82 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 291. Anal. calcd for $C_{18}H_{17}N_3O$: C, 74.23; H, 5.84; N, 14.43; Found: C, 74.37; H, 5.62; N, 14.63.

8-Methoxy-4-methyl-2-(o-chloroarylidenyl-iminoamino)quinoline 4: Reagents: compound **2** (4.5 g, 0.01 mol), *o*-chlorobenzaldehyde (2.49 mL, 0.01 mol), methanol (80 mL), mp 180 °C; yield: 3.83 g (85.0%); Recrytallization solvent: Ethanol; IR (KBr) ν in cm^{-1}: 3256 (NH), 3064 (C-H aromatic ring), 2962 (C-H aliphatic), 1594 (C-----C of aromatic ring), 1187 (C-N), 1074 (N-N), 765 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ 8.13 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.89 (s, 1H, H_3 of quinoline), 7.81 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.72 (d, 1H, H_7 of quinoline, J = *9.0* Hz), 7.63 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.22-7.45 (m, 4H, Ar-*H*), 6.65 (s, 1H, N*H*, exchangeable with D_2O), 3.51 (s, 3H, OCH_3), 2.81 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 325.5 and [M + 2] at *m*/*z* 327.5. Anal. calcd for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4.92; N, 12.90; Found: C, 66.50; H, 4.76; N, 13.12.

8-Methoxy-4-methyl-2-(o-hydroxyarylidenyl-iminoamino) quinoline 5: Reagents: compound **2** (4.5 g, 0.01 mol), *o*-hydroxybenzaldehyde (2.36 mL, 0.01 mol), methanol (80 mL), mp 225 °C; yield: 3.38 g (75.0%); Recrytallization solvent: Ethyl acetate; IR (KBr) ν in cm^{-1}: 3565 (OH), 3274 (NH), 3075 (C-H aromatic ring), 2961 (C-H aliphatic), 1582 (C-----C of aromatic ring), 1191 (C-N), 1065 (N-N). ^{1}H-NMR ($CDCl_3$) δ 10.11 (s, 1H, O*H*, exchangeable with D_2O), 8.14 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.92 (s, 1H, H_3 of quinoline), 7.81 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.78 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.64 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.2-7.46 (m, 4H, Ar-*H*), 6.63 (s, 1H, N*H*, exchangeable with D_2O), 3.52 (s, 3H, OCH_3), 2.83 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 307. Anal. calcd for $C_{18}H_{17}N_3O_2$: C, 70.36; H, 5.54; N, 13.68; Found: C, 70.46; H, 5.30; N, 13.79.

8-Methoxy-4-methyl-2-(o-methoxyarylidenyl-iminoamino) quinoline 6: Reagents: compound **2** (4.5 g, 0.01 mol), 2-methoxybenzaldehyde (2.70 mL, 0.01 mol), methanol (80 mL), mp 210 °C; yield: 3.87 g (86.0%); Recrytallization solvent : Methanol; IR (KBr) ν in cm^{-1}: 3265 (NH), 3055 (C-H aromatic ring), 2974 (C-H aliphatic), 1572 (C-----C of aromatic ring), 1177 (C-N), 1071 (C-O-C), 1045 (N-N). ^{1}H-NMR (DMSO-d_6) δ 8.12 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.90 (s, 1H, H_3 of quinoline), 7.80 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.79 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.63 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.22-7.45 (m, 4H, Ar-*H*), 6.65 (s, 1H, N*H*, exchangeable with D_2O), 3.51 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.81 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 321. Anal. calcd for $C_{19}H_{19}N_3O_2$: C, 71.03; H, 5.92; N, 13.04; Found: C, 70.95; H, 5.84; N, 13.15.

8-Methoxy-4-methyl-2-(furfurylidenyl-iminoamino)quinoline 7: Reagents: compound **2** (4.5 g, 0.01 mol), furfuraldehyde (1.84 mL, 0.01 mol), methanol (80 mL); mp 191 °C; yield: 3.33 g (74.0%); Recrytallization solvent: Acetic acid; IR (KBr) ν in cm^{-1}: 3288 (NH), 3045 (C-H aromatic ring), 2964 (C-H aliphatic), 1552 (C-----C of aromatic ring), 1187 (C-N), 1081 (C-O-C), 1064 (N-N). ^{1}H-NMR (DMSO-d_6) δ 8.13 (d, 1H, C*H*-A*r*, J = 11.0 Hz), 7.91 (s, 1H, H_3 of quinoline), 7.82 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.78 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.65 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.13-7.32 (m, 3H, Ar-*H*), 6.67 (s, 1H, N*H*, exchangeable with D_2O), 3.51 (s, 3H, OCH_3), 2.81 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 281. Anal. calcd for $C_{16}H_{15}N_3O_2$: C, 68.32; H, 5.33; N, 14.94; Found: C, 68.41; H, 5.26; N, 14.87.

General procedure for the synthesis of 8-methoxy-4-methyl-2-amino-(3'-chloro-2'-oxo-4'-substituted aryl-1'-azetidinyl)quinolines 8-12: To a solution of compound (**3-7**, 0.01 mol) in DMF (60 mL), chloroacetyl chloride (0.02 mol) and triethyl amine (0.02 mol) were added at 0 - 5 °C temperature with constant stirring. This reaction mixture was refluxed on water bath for 6 - 8 h; then excess of solvent was distilled off. The precipitated product was cooled, poured in ice-water then filtered, further recrystallized from appropriate solvent to procure compounds **8-12**.

8-Methoxy-4-methyl-2-amino-[3'-chloro-2'-oxo-4'-(phenyl)-1'-azetidinyl]quinoline 8: Reagents: compound **3** (1.6 g, 0.01 mol), chloroacetyl chloride (0.87 mL, 0.02 mol), triethyl amine (1.53 mL, 0.02 mol), DMF (60 mL); mp 112 °C; yield: 0.96 g (60.0%); Recrytallization solvent: Ethanol; IR (KBr) ν in cm^{-1}: 3261 (NH), 3055 (C-H aromatic ring), 2981 (C-H aliphatic), 1765 (C=O), 1575 (C-----C of aromatic ring), 1155 (C-N), 1064 (N-N), 761 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ 8.12 (d, 1H, C*H*-A*r*, J = 11.0 Hz), 7.90 (s, 1H, H_3 of quinoline), 7.81 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.79 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.62 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.27(m, 5H, Ar-*H*), 6.63 (s, 1H, N*H*, exchangeable with D_2O), 6.52 (d, 1H, C*H*-Cl J = 6.0 Hz), 3.54 (s, 3H, OCH_3), 2.81 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 367.5 and [M + 2] at *m*/*z* 369.5. Anal. calcd for $C_{20}H_{18}N_3O_2Cl$: C, 65.31; H, 4.90; N, 11.43; Found: C, 65.50; H, 4.72; N, 11.55.

8-Methoxy-4-methyl-2-amino-[3'-chloro-2'-oxo-4'-(o-chlrophenyl)-1'-azetidinyl]quinoline 9: eagents: compound **4** (1.7 g, 0.01 mol), chloroacetyl chloride (0.83 mL, 0.02 mol), triethyl amine (1.46 mL, 0.02 mol), DMF (60 mL); mp 171 °C; yield: 1.11 g (65.0%); Recrytallization solvent: Acetic acid; IR (KBr) ν in cm^{-1}: 3254 (NH), 3044 (C-H aromatic ring), 2947 (C-H aliphatic), 1776 (C=O), 1585 (C-----C of aromatic ring), 1154 (C-N), 1068 (N-N), 785 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ 8.13 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.89 (s, 1H, H_3 of quinoline), 7.80 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.77 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.61 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.22-7.41 (m, 4H, Ar-*H*),6.61 (s, 1H, N*H*, exchangeable with D_2O), 6.53 (d, 1H, C*H*-Cl J = 6.0 Hz), 3.54 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 402 and [M + 2] at *m*/*z* 404. Anal. calcd for $C_{20}H_{17}N_3O_2Cl_2$: C, 59.70; H, 4.23; N, 10.45; Found: C, 59.50; H, 4.33; N, 10.60.

8-Methoxy-4-methyl-2-amino-[3'-chloro-2'-oxo-4'-(o-hydroxyphenyl)-1'-azetidinyl]quinoline 10: eagents: compound **5** (1.5 g, 0.01 mol), chloroacetyl chloride (0.78 mL, 0.02 mol), triethyl amine (1.36 mL, 0.02 mol), DMF (60 mL); mp 216 °C; yield: 1.05 g (70.0%); Recrytallization solvent: Methanol; IR (KBr) ν in cm^{-1}: 3565 (OH), 3271 (NH), 3065 (C-H aromatic ring), 2941 (C-H aliphatic), 1755 (C=O), 1575 (C-----C of aromatic ring), 1167 (C-N), 1055 (C-O-C), 1031 (N-N), 743 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ 10.13 (s,1H, O*H* , exchangeable with D_2O), 8.12 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.89 (s, 1H, H_3 of quinoline), 7.83 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.76 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.66 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.20-7.39 (m, 4H, Ar-*H*), 6.61 (s, 1H, N*H*, exchange-

able with D_2O), 6.55 (d, 1H, C*H*-Cl J = 6.0 Hz), 3.51 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 383.5 and [M + 2] at *m*/*z* 385.5. Anal. calcd for $C_{20}H_{18}N_3O_3Cl$: C, 62.58; H, 4.69; N, 10.95; Found: C, 62.74; H, 4.48; N, 10.70.

8-Methoxy-4-methyl-2-amino-[3'-chloro-2'-oxo-4'-(p-methoxyphenyl)-1'-azetidinyl]quinoline 11: Reagents: compound **6** (1.7 g, 0.01 mol), chloroacetyl chloride (0.84 mL, 0.02 mol), triethyl amine (1.48 mL, 0.02 mol), DMF (60 mL); mp 193 °C; yield: 1.22 g (66.0%); Recrytallization solvent : Acetone; IR (KBr) ν in cm^{-1}: 3271 (NH), 3075 (C-H aromatic ring), 2971 (C-H aliphatic), 1745 (C=O), 1585 (C-----C of aromatic ring), 1157 (C-N), 1085 (C-O-C), 1064 (N-N), 761 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ 8.11 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.91 (s, 1H, H_3 of quinoline), 7.82 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.78 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.64 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.19-7.41 (m, 4H, Ar-*H*), 6.63 (s, 1H, N*H*, exchangeable with D_2O), 6.54 (d, 1H, C*H*-Cl J = 6.0 Hz), 3.53 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3),2.79 (s, 3H, CH_3).MS: $[M]^+$ at *m*/*z* 397.5 and [M + 2] at *m*/*z* 399.5. Anal. calcd for $C_{21}H_{20}N_3O_3Cl$: C, 63.40; H, 5.03; N, 10.57; Found: C, 63.64; H, 4.85; N, 10.70.

8-Methoxy-4-methyl-2-amino-[3'-chloro-2'-oxo-4'-(furfuryl)-1'-azetidinyl]quinoline 12: Reagents: compound **7** (1.5 g, 0.01 mol), chloroacetyl chloride (0.85 mL, 0.02 mol), triethyl amine (1.49 mL, 0.02 mol), DMF (60 mL); mp 179 °C; yield: 0.92 g (61.0%); Recrytallization solvent: Methanol; IR (KBr) ν in cm^{-1}: 3284 (NH), 3043 (C-H aromatic ring), 2961 (C-H aliphatic), 1785 (C=O), 1575 (C-----C of aromatic ring), 1163 (C-N), 1075 (C-O-C), 1043 (N-N), 758 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ 8.13 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.93 (s, 1H, H_3 of quinoline), 7.81 (d, 1H, H_5 of quinoline, J = 9.0 Hz), 7.75 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.66 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.14-7.33 (m, 3H, Ar-*H*), 6.64 (s, 1H, N*H*, exchangeable with D_2O), 6.52 (d, 1H, C*H*-Cl J = 6.0 Hz), 3.54 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 357.5 and [M + 2] at *m*/*z* 359.5. Anal. calcd for $C_{18}H_{16}N_3O_3Cl$: C, 60.42; H, 4.48; N, 11.75; Found: C, 60.53; H, 4.53; N, 11.81.

General procedure for the synthesis of 8-methoxy-4-methyl-2-amino-(2'-substituted aryl-4'-oxo-1',3'-thiazolidin-3'-yl)quinolines 13-17: A solution of compound (**3-7**, 0.01 mol) and thioglycolic acid (0.01 mol) in dry dioxane (60 mL) in presence of anhydrous $ZnCl_2$ (2-0 g) was refluxed for 9 - 11 h. Reaction was routinely followed by TLC. After completion of the reaction, excess of solvent was removed through distillation, and solid thus obtained was poured onto crushed ice, then filtered, dried and recrystallized from appropriate solvent to yield the compounds **13-17**.

8-Methoxy-4-methyl-2-amino-[2'-(phenyl)-4'-oxo-1',3'-thiazolidin-3'-yl]quinoline 13: Reagents: compound **3** (1.6 g, 0.01 mol), thioglycolic acid (0.38 mL, 0.01 mol), zinc chloride (2.0 g), dioxane (60 mL); mp 127 °C; yield: 1.09 g (68.0%); Recrytallization solvent: DMF; IR (KBr) ν in cm^{-1}: 3265 (NH), 3081 (C-H aromatic ring), 2954 (C-H aliphatic), 1734 (C=O), 1554 (C-----C of aromatic ring), 1158 (C-N), 1075 (N-N), 695 (C-S-C). ^{1}H-NMR ($CDCl_3$) δ 8.13 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.91 (s, 1H, H_3 of quinoline), 7.80 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.73 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.61 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.28 (m, 5H, Ar-*H*), 6.61 (s, 1H, N*H*, exchangeable with D_2O), 3.73 (s, 2H, CH_2 of thiazolidinone), 3.55 (s, 3H, OCH_3), 2.76 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 365. Anal. calcd for $C_{20}H_{19}N_3O_2S$: C, 65.75; H, 5.21; N, 11.51; Found: C, 65.88; H, 5.10; N, 11.62.

8-Methoxy-4-methyl-2-amino-[2'-(o-chlrophenyl)-4'-oxo-1',3'-thiazolidin-3'-yl]quinoline 14: Reagents: compound **4** (1.7 g, 0.01 mol), thioglycolic acid (0.36 mL, 0.01 mol), zinc chloride (2.0 g), dioxane (60 mL); mp 198 °C; yield: 1.07 g (63.0%); Recrytallization solvent: Methanol; IR (KBr) ν in cm^{-1}: 3275 (NH), 3085 (C-H aromatic ring), 2982 (C-H aliphatic), 1752 (C=O), 1534 (C-----C of aromatic ring), 1157 (C-N), 1065 (N-N), 765 (C-Cl), 635 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ 8.12 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.89 (s, 1H, H_3 of quinoline), 7.83 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.78 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.63 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.20-7.38 (m, 4H, Ar-*H*), 6.62 (s, 1H, N*H*, exchangeable with D_2O), 3.72 (s, 2H, CH_2 of thiazolidinone), 3.53 (s, 3H, OCH_3), 2.73 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 399.5 and [M + 2] at *m*/*z* 401.5. Anal. calcd for $C_{20}H_{18}N_3O_2SCl$: C, 60.08; H, 4.51; N, 10.51; Found: C, 60.12; H, 4.68; N, 10.40.

8-Methoxy-4-methyl-2-amino-[2'-(o-hydroxyphenyl)-4'-oxo-1',3'-thiazolidin-3'-yl]quinoline 15: Reagents: compound **5** (1.5 g, 0.01 mol), thioglycolic acid (0.34 mL, 0.01 mol), zinc chloride (2.0 g), dioxane (60 mL); mp 247 °C; yield: 0.98 g (65.0%); Recrytallization solvent: Ethanol; IR (KBr) ν in cm^{-1}: 3355 (OH), 3261 (NH), 3043 (C-H aromatic ring), 2949 (C-H aliphatic), 1735 (C=O), 1569 (C-----C of aromatic ring), 1179 (C-N), 1082 (C-O-C), 1045 (N-N), 671 (C-S-C). ^{1}H-NMR ($CDCl_3$) δ 10.11 (s,1H, O*H* , exchangeable with D_2O), 8.13 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.92 (s, 1H, H_3 of quinoline), 7.83 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.74 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.63 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.22-7.41 (m, 4H, Ar-*H*), 6.64 (s, 1H, N*H*, exchangeable with D_2O), 3.73 (s, 2H, CH_2 of thiazolidinone), 3.52 (s, 3H, OCH_3), 2.74 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 381. Anal. calcd for $C_{20}H_{19}N_3O_3S$: C, 62.99; H, 4.99; N, 11.02; Found: C, 62.85; H, 5.10; N, 11.15.

8-Methoxy-4-methyl-2-amino-[2'-(p-methoxyphenyl)-4'-oxo-1',3'-thiazolidin-3'-yl]quinoline 16: Reagents: compound **6** (1.7 g, 0.01 mol), thioglycolic acid (0.37 mL, 0.01 mol), zinc chloride (2.0 g), dioxane (60 mL); mp 207 °C; yield: 1.14 g (67.0%); Recrytallization solvent : Ethanol; IR (KBr) ν in cm^{-1}: 3285 (NH), 3065 (C-H aromatic ring), 2949 (C-H aliphatic), 1725 (C=O), 1564 (C-----C of aromatic ring), 1167 (C-N), 1075 (C-O-C), 1055 (N-N), 675 (C-S-C). ^{1}H-NMR (DMSO-d_6) δ 8.14 (d, 1H, C*H*- A*r*, J = 11.0 Hz), 7.90 (s, 1H, H_3 of quinoline), 7.81 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.78 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.62 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.21-7.38 (m, 4H, Ar-*H*), 6.63 (s, 1H, N*H*, exchangeable with D_2O), 3.71 (s, 2H, CH_2 of thiazolidinone), 3.54 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3), 2.75 (s, 3H, CH_3).MS: $[M]^+$ at *m*/*z* 395. Anal. calcd for $C_{21}H_{21}N_3O_3S$: C, 63.80; H, 5.32; N, 10.63; Found: C, 63.93; H, 5.40; N, 10.51.

8-Methoxy-4-methyl-2-amino-[2'-(furfuryl)-4'-oxo-1',3'-thiazolidin-3'-yl]quinoline 17: Reagents: compound **7** (1.5 g, 0.01 mol), thioglycolic acid (0.37 mL, 0.01 mol), zinc chloride (2.0 g), dioxane (60 mL); mp 183 °C; yield: 0.89 g (59.0%); Recrytallization solvent : Acetone; IR (KBr) ν in cm^{-1}: 3275 (NH), 3075 (C-H aromatic ring), 2951 (C-H aliphatic), 1742 (C=O), 1562 (C-----C of aromatic ring), 1171 (C-N), 1055

(C-O-C), 1035 (N-N), 641 (C-S-C). ^{1}H-NMR ($CDCl_3$) δ 8.12 (d, 1H, C*H*- Ar, J = 11.0 Hz), 7.91 (s, 1H, H_3 of quinoline), 7.83 (d, 1H, H_5 of quinoline, J = 6.0 Hz), 7.73 (d, 1H, H_7 of quinoline, J = 9.0 Hz), 7.63 (t, 1H, H_6 of quinoline, J = 7.5 Hz), 7.13-7.32 (m, 3H, Ar-*H*), 6.65 (s, 1H, N*H*, exchangeable with D_2O), 3.73 (s, 2H, CH_2 of thiazolidinone), 3.55 (s, 3H, OCH_3), 2.76 (s, 3H, CH_3). MS: $[M]^+$ at *m*/*z* 355. Anal. calcd for $C_{18}H_{17}N_3O_3S$: C, 60.85; H, 4.79; N, 11.83; Found: C, 60.91; H, 4.69; N, 11.91.

Biological Evaluation

Antibacterial activity. The newly synthesized compounds **3-17** and reference drug, amphicillin, were screened for antibacterial activity against different bacterial strains (gram positive bacteria: *S. aureus, B. subtilis, and S. epidermis* and gram negative bacteria*: E. coli, K. pneumoniae* and *P. aeruginosa*) at a concentration of 250 μg/mL by filter paper disc method.[15] DMSO served as control and due this there was no visible change in bacterial growth. The discs of Whatmann filter paper were prepared with standard size (7.0 mm) and kept into 1.0 Oz screw capped wide mouthed containers for sterilization. These bottles are kept in to hot air oven at a temperature of 150 °C. Then, the prepared solutions of test compounds and standard drug (dissolved in DMSO) of desired concentration were poured into their respective bottles. Further, the discs are transferred to the inoculated plates with a pair of fine pointed tweezers. To prevent contamination tweezers may be kept with their tips in 70% alcohol and flamed off before used. Before using the test organisms, which were grown on nutrient agar, they were sub-cultured in nutrient broth at a temperature of 37 °C for 18 - 20 h. Each disc was applied carefully to the surface of agar without lateral movement once the surface had been touched. Now, the plates were incubated for 24 h at a temperature of 37 °C. Care was taken not to stockpile the plates. Clear zones of inhibition in millimeters have indicated the relative susceptibility of the bacteria to the compounds **3-17** and amphicillin, standard.

Minimal inhibitory concentration (MIC). The antimicrobial activity was assayed *in vitro* by the two fold broth dilution[16] against different bacterial strains (gram positive bacteria: *S. aureus*, *B. subtilis*, *and S. epidermis* and gram negative bacteria*: E. coli*, *K. pneumoniae* and *P. aeruginosa*). The minimal inhibitory concentrations (MIC, μg/mL) were defined as the lowest concentrations of compound that completely inhibited the growth of the bacterial strain. All compounds dissolved in dimethylsulfoxide (DMSO) were added to culture the media. Mueller hinton broth for bacteria to obtain final concentrations ranging from 100 μg/mL to 0.781 μg/mL. The amount of DMSO was never exceeded from 1% v/v. Inocula was consisted of 5.0 × 10^4 bacteria/mL. The MICs were noted after incubation at a temperature of 37 °C for 24 h. Media and media with 1% v/v DMSO were employed as growth controls, and amphicillin was used as a standard drug.

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