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Synthesis and characterization of some quinoline based azetidinones and thiazolidinones as antimicrobial agents

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ABSTRACT

A series of potentially active quinoline based azetidinones and thiazolidinones analogues has been synthesized by simple and efficient synthetic protocol. The tetrazole nucleus formed from 2-chloroquinoline-3-carbaldehyde using p-toluenesulphonic acid and sodium azide followed by reaction with various substituted amine to form the corrosponding schiff base intermediates. Attempt made to derive final azitidinone and thiazolidinone analogues from Schiff base intermediates by using chloroacetyl chloride and 2-marcapto acetic acid respectively. The newly synthsiszed analogues were then examined for antimicrobial activity against some human pathogenic bacterial and fungal strains as 2 gram –Ve bacteria (E. coli, P. aeruginosa), 2 gram +Ve bacteria (S. aerues, B. subtilis) and 2 fungal species (C. albicans, A. niger) to develop novel class of anti microbial agents with varied mode of action. The results of bioassay showed that some of the newly synthesized azetidinones and thiazolidinones analogues emerged as lead molecules with excellent MIC (mg/ml) values against mentioned organisms. 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, azetidinones, thiazolidinones, antimicrobial activity.

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 [1], fevers and tertians since more than 200 years ago. Quinidine, a diastereoisomer of quinine was in the early 20th century acknowledged as the most potent of the ant arrhythmic compounds isolated from the Cinchona plant [2]. The quinoline skeleton is often used for the design of many synthetic compounds with

diverse pharmacological properties such as, anti-inflammatory [3], antimicrobial agents [4], cytotoxic activity [5], antidotal and antibacterial [6], antitumor activity [7], antimalarial [8]. Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents [9]. They are also used as polymers, catalysts, corrosion inhibitors, preservatives, and as solvent for resins and terpenes. Furthermore, these compounds find applications in chemistry of transition metal catalyst for uniform polymerization and luminescence chemistry [10]. Quinoline derivatives also act as antifoaming agent in refineries [11]. Owing to the mentioned significance, the synthesis of substituted quinolines has been a subject of great interest in organic chemistry. In addition, various fused system of quinolines were studied for their intercalative DNA binding properties. A literature survey reveals the antitumor activity is due to the intercalation between the base pairs of DNA and interferences with the normal functioning of enzyme topoisomerase II, which is involved in the breaking and releasing of DNA strands [12]. The antitumor drugs that intercalate DNA are of growing interest in the field of anticancer derivatives. Generally, they are characterized by planar chromophore, which is often constituted by three or four condensed rings, which can intercalate into base pairs. Results of these various binding studies have been useful in designing new and promising anticancer agent for clinical use [13]. 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 have been reported from the reaction of α-oxoketen-N, S-acetals with Vilsmeier reagent. It will suffice to mention here that currently available potent antimicrobial drugs such as ciprofloxacin, norfloxacin, ofloxacin contains quinoline constitutents 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, we have obtained quinoline based azitidinones [14-17] and thiazolidinones [18-24] analogues, the final analogues which are proved to be much more efficious antimicrobial agents.

MATERIALS AND METHODS

Experimental: 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 (4000-400 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 (2x7.5 cm) coated with silica gel-G, using appropriate mobile phase system and spots were visualized under UV radiation. Nuclear magnetic resonance spectra were recorded on Varian 400 MHz model spectrometer using DMSO as a solvent and TMS as internal standard (Chemical shifts in δ ppm). All new compounds were subjected to elemental analysis and the results were in acceptable range.

General procedure for the synthesis of 2-chloro-quinoline 3-carbaldehyde (2).
To a solution of 1a (5 mole) in dry DMF (15 mole) at 0-5 ^{0}C with stirring $POCl_3$ (60 mole) was added dropwise and the mixture stirred at 80-90 ^{0}C for time ranging between 4-15hr. 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 recrystallisation from either ethyl acetate or acetonitrile.

Synthesis of tetrazolo[1,5-1]quinoline-4-carbaldehyde (3).
To a solution of **2** (0.01 mole) taken in absolute ethanol, p-toluenesulphonic acid (0.01 mole) and sodium azide (0.015 mole) were added and the reaction mixture was heated under reflux for time

ranging between 5-10hr. After completion of the reaction (monitored by 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 **3**. The compounds were purified by recrystallisation from acetone.

General procedure for the Synthesis of N-[(Z)tetrazolo[1,5-a]quinoline-4-yl methyllidene]substituted amine 5a-l.

Tetrazolo[1,5-1]quinoline-4-carbaldehyde (0.01 mole) **3**, substituted aromatic amine **4a-l** (0.01 mole) were taken in ethanol with catalytic amount of conc. H_2SO_4 (2 ml) and heated to refluxed for 6-7 hrs. 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 **5a-l**. The compounds were purified by recrystallisation from ethanol.

General procedure for preparation of compounds 6a-l.

A mixture of N-[(Z)tetrazolo[1,5-a]quinoline-4-yl methyllidene]substituted amine **5a-l** (0.01 mole) and triethylamine (0.02 mole) was dissolved in 1, 4-dioxane (50 ml). to this well stirred cooled solution chloroacetylchloride (0.02 mole) was added drop wise during 30 min. the reaction-mixture was then stirred for further 1 hr and refluxing for 10 hr. 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 ethanol.

3-chloro-1-phenyl-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6a)

Yield: 77%; m.p. 240^{0}C (dec.); IR (KBr,cm^{-1}) : 1730 (C=O of β-lactum), 1550 (C=C), 1530 (C-N), 780 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.84 (1H, d, C<u>H</u>-Cl at azitidinone ring), 6.92 (1H, d, C<u>H</u>-N at azitidinone ring), 7.20-7.35 (5H, m, Ar-H), 7.43-8.09 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ; 170.78 (C-23, -<u>C</u>=O), 66.38 (C-22, -<u>C</u>-Cl), 139.66-118.11 (15C, -Ar-C), 61.22 (C-14, -Ar.-Azitidinone ring linkage); Anal. Calcd. for $C_{18}H_{12}ClN_5O$: C, 65.81; H, 3.46; N, 20.02%; Found: C, 65.79; H, 3.44; N, 20.03%.

3-chloro-1-(2-methylphenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6b)

Yield: 75%; m.p. 261^{0}C (dec.); IR (KBr,cm^{-1}) : 1735 (C=O of β-lactum), 1556 (C=C), 1532 (C-N), 785 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.15 (3<u>H</u>, s, Ar-CH_3), 5.94 (1H, d, C<u>H</u>-Cl at azitidinone ring), 6.95 (1H, d, C<u>H</u>-N at azitidinone ring), 7.05-7.31 (4<u>H</u>, m, Ar-H), 7.45-8.10 (5<u>H</u>, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 167.24 (C-23, -<u>C</u>=O), 65.33 (C-22, -<u>C</u>-Cl), 140.36-117.15 (15C, -Ar-C), 60.35 (C-14, -Ar.-Azitidinone ring linkage), 19.60 (C-26, <u>C</u>-CH_3); Anal. Calcd. for $C_{19}H_{14}ClN_5O$: C, 62.73; H, 3.88; N, 19.25%; Found: C, 62.70; H, 3.90; N, 19.23%.

3-chloro-1-(3-methylphenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6c)

Yield: 70%; m.p. 255^{0}C (dec.); IR (KBr,cm^{-1}) : 1737 (C=O of β-lactum), 1553 (C=C), 1528 (C-N), 783 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.29 (3<u>H</u>, s, Ar-CH_3), 5.87 (1H, d, C<u>H</u>-Cl at azitidinone ring), 6.99 (1H, d, C<u>H</u>-N at azitidinone ring), 7.03-7.35 (4<u>H</u>, m, Ar-H), 7.44-8.10 (5<u>H</u>, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 159.33 (C-23, -<u>C</u>=O), 64.27 (C-22, -<u>C</u>-Cl), 137.57-116.15 (15C, -Ar-C), 61.63 (C-14, -Ar.-Azitidinone ring linkage), 22.53 (C-26, -<u>C</u>-CH_3); Anal. Calcd. for $C_{19}H_{14}ClN_5O$: C, 62.73; H, 3.88; N, 19.25%; Found: C, 62.70; H, 3.90; N, 19.23%.

3-chloro-1-(4-methylphenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6d)
Yield: 73%; m.p. 265^{0}C (dec.); IR (KBr,cm^{-1}) : 1727 (C=O of β-lactum), 1558 (C=C), 1525 (C-N), 779 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.34 (3H, s, Ar-CH_3), 5.84 (1H, d, CH-Cl at azitidinone ring), 6.96 (1H, d, CH-N at azitidinone ring), 6.92-7.15 (4H, m, Ar-H), 7.45-8.06 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 165.21 (C-23, -C=O), 67.66 (C-22, -C-Cl), 135.68-119.23 (15C, -Ar-C), 63.23 (C-14, -Ar.-Azitidinone ring linkage), 21.15 (C-26, -C-CH_3); Anal. Calcd. for $C_{19}H_{14}ClN_5O$: C, 62.73; H, 3.88; N, 19.25%; Found: C, 62.71; H, 3.89; N, 19.24%.

3-chloro-1-(2-nitrophenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6e)
Yield: 68%; m.p. 270^{0}C (dec.); IR (KBr,cm^{-1}) : 1737 (C=O of β-lactum), 1560 (C=C), 1537 (C-N), 781 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.80 (1H, d, CH-Cl at azitidinone ring), 7.84 (1H, d, CH-N at azitidinone ring), 7.45-8.31 (4H, m, Ar-H), 7.47-8.09 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 173.23 (C-23, -C=O), 62.63 (C-22, -C-Cl), 137.91-117.09 (14C, -Ar-C), 61.56 (C-14, -Ar.-Azitidinone ring linkage), 145.27 (C-19, -C-NO_2); Anal. Calcd. for $C_{18}H_{11}ClN_6O_3$: C, 54.76 H, 2.81; N, 21.29%; Found: C, 54.74; H, 2.83; N, 21.27%.

3-chloro-1-(3-nitrophenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6f)
Yield: 65%; m.p. 275^{0}C (dec.); IR (KBr,cm^{-1}) : 1740 (C=O of β-lactum), 1551 (C=C), 1540 (C-N), 777 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.85 (1H, d, CH-Cl at azitidinone ring), 7.65 (1H, d, CH-N at azitidinone ring), 7.55-8.20 (4H, m, Ar-H), 7.43-8.08 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 178.57 (C-23, -C=O), 65.21 (C-22, -C-Cl), 135.92-119.17 (14C, -Ar-C), 60.08 (C-14, -Ar.-Azitidinone ring linkage), 150.53 (C-17, -C-NO_2); Anal. Calcd. for $C_{18}H_{11}ClN_6O_3$: C, 54.76 H, 2.81; N, 21.29%; Found: C, 54.77; H, 2.80; N, 21.30%.

3-chloro-1-(4-nitrophenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6g)
Yield: 67%; m.p. 262^{0}C (dec.); IR (KBr,cm^{-1}) : 1731 (C=O of β-lactum), 1557 (C=C), 1536 (C-N), 788 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.80 (1H, d, CH-Cl at azitidinone ring), 7.57 (1H, d, CH-N at azitidinone ring), 6.97-8.09 (4H, m, Ar-H), 7.44-8.04 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 175.36 (C-23, -C=O), 63.81 (C-22, -C-Cl), 137.91-117.71 (14C, -Ar-C), 62.43 (C-14, -Ar.-Azitidinone ring linkage), 144.47 (C-15, -C-NO_2); Anal. Calcd. for $C_{18}H_{11}ClN_6O_3$: C, 54.76 H, 2.81; N, 21.29%; Found: C, 54.75; H, 2.82; N, 21.28%.

3-chloro-1-(2-chlorophenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6h)
Yield: 73%; m.p. 280^{0}C (dec.); IR (KBr,cm^{-1}) 1739 (C=O of β-lactum), 1558 (C=C), 1533 (C-N), 792 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.63 (1H, d, CH-Cl at azitidinone ring), 7.40 (1H, d, CH-N at azitidinone ring), 7.10-7.67 (4H, m, Ar-H), 7.47-8.12 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 171.56 (C-23, -C=O), 62.57 (C-22, -C-Cl), 135.71-119.89 (15C, -Ar-C), 67.56 (C-14, -Ar.-Azitidinone ring linkage); Anal. Calcd. for $C_{18}H_{11}Cl_2N_5O$: C, 56.27 H, 2.89; N, 18.23%; Found: C, 56.29; H, 2.91; N, 18.24%.

3-chloro-1-(3-chlorophenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6i)
Yield: 68%; m.p. 269^{0}C (dec.); IR (KBr,cm^{-1}) : 1733 (C=O of β-lactum), 1560 (C=C), 1531 (C-N), 785 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.84 (1H, d, CH-Cl at azitidinone ring), 6.98 (1H, d, CH-N at azitidinone ring), 7.09-7.59 (4H, m, Ar-H), 7.46-8.15 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 173.78 (C-23, -C=O), 63.87 (C-22, -C-Cl), 137.33-115.63 (15C, -Ar-C), 65.89 (C-14, -Ar.-Azitidinone ring linkage); Anal. Calcd. for $C_{18}H_{11}Cl_2N_5O$: C, 56.27 H, 2.89; N, 18.23%; Found: C, 56.26; H, 2.87; N, 18.21%.

3-chloro-1-(4-chlorophenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6j)
Yield: 73%; m.p. 253^{0}C (dec.); IR (KBr,cm^{-1}) : 1738 (C=O of β-lactum), 1553 (C=C), 1538 (C-N), 792 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.87 (1H, d, CH-Cl at azitidinone ring), 7.03 (1H, d, CH-N at azitidinone ring), 7.36 (4H, m, Ar-H), 7.43-8.02 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 170.89 (C-23, -C=O), 62.76 (C-22, -C-Cl), 136.77-116.98 (15C, -Ar-C), 64.56 (C-14, -Ar.-Azitidinone ring linkage); Anal. Calcd. for $C_{18}H_{11}Cl_2N_5O$: C, 56.27 H, 2.89; N, 18.23%; Found: C, 56.28; H, 2.90; N, 18.22%.

3-chloro-1-(4-fluorophenyl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6k)
Yield: 66%; m.p. 290^{0}C (dec.); IR (KBr,cm^{-1}) : 1737 (C=O of β-lactum), 1561 (C=C), 1541 (C-N), 784 (C-Cl); ^{1}H NMR (400 MHz, DMSO- d_6) δ 5.81 (1H, d, CH-Cl at azitidinone ring), 6.97 (1H, d, CH-N at azitidinone ring), 7.15-7.27 (4H, m, Ar-H), 7.44-8.07 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 168.89 (C-23, -C=O), 163.68 (C-15, -C-F), 64.78 (C-22, -C-Cl), 131.99-115.78 (14C, -Ar-C), 64.56 (C-14, -Ar.-Azitidinone ring linkage); Anal. Calcd. for $C_{18}H_{11}ClFN_5O$: C, 58.79 H, 3.01; N, 19.04%; Found: C, 58.81; H, 3.02; N, 19.02%.

3-chloro-1-(5-methyl-1,3-thiazol-2-yl)-4-(tetrazolo[1,5-*a*]quinolin-4-yl)azetidin-2-one (6l)
Yield: 59%; m.p. 295^{0}C (dec.); IR (KBr,cm^{-1}) : 1740 (C=O of β-lactum), 1537 (C-N), 787 (C-Cl), 757 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.35 (3H, s, Ar-CH_3 at thaizole ring), 5.71 (1H, d, CH-Cl at azitidinone ring), 7.17 (1H, d, CH-N at azitidinone ring), 7.15(1H, d, Ar-H at thaizole ring), 7.46-8.11 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 169.60 (C-17, -C=O), 158.03 (C-22, -N-C at azitidinone-heterocyclic coupling ring), 131.99-115.78 (11C, -Ar-C), 65.01 (C-16, -C-Cl), 64.56 (C-14, -Ar.-Azitidinone ring linkage), 15.56 (-C-CH_3 in sulfur heterocycle) Anal. Calcd. for $C_{16}H_{11}ClN_6OS$: C, 51.82 H, 2.99; N, 22.66%; Found: C, 51.84; H, 2.97; N, 22.64%.

General procedure for preparation of compounds 7a-l.
A mixture of N-[(Z)tetrazolo[1,5-a]quinoline-4-yl methyllidene]substituted amine **5a-l** (0.01 mole) and catalytic amount of zinc chloride (0.05 gm) in DMF was taken in Dean stark apparatus and to it thioglycolic acid (0.02 mole) in DMF was added slowly. The reaction mass was refluxed for 12hr. 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 ethanol.

3-phenyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7a)
Yield: 63%; m.p. 245^{0}C (dec.); IR (KBr,cm^{-1}) : 1734 (C=O of β-lactum), 1561 (C=C), 1541 (C-N), 784 (C-Cl), 751 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.85 (2H, d, CH-S at thiazolidinone ring), 6.51 (1H, s, CH-N at thiazolidinone ring), 7.21-7.37 (5H, m, Ar-H), 7.42-8.01 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ; 171.35 (C-16, -C=O), 138.27-117.23 (15C, -Ar-C), 63.54 (C-14, -Ar.- thiazolidinone ring linkage), 33.37 (C-19, -S-C); Anal. Calcd. for $C_{18}H_{13}N_5OS$: C, 62.23 H, 3.77; N, 20.16%; Found: C, 62.25; H, 3.76; N, 20.18%.

3-(2-methylphenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7b)
Yield: 67%; m.p. 265^{0}C (dec.); IR (KBr,cm^{-1}) : 1732 (C=O of β-lactum), 1559 (C=C), 1536 (C-N), 781 (C-Cl), 754 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.07 (3H, s, Ar-CH_3), 3.92 (2H, d, CH-S at thiazolidinone ring), 6.43 (1H, s, CH-N at thiazolidinone ring), 7.02-7.31 (4H, m, Ar-H), 7.43-8.08 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 168.96 (C-16, -C=O), 141.87-116.59 (15C, -Ar-C), 61.35 (C-14, -Ar.- thiazolidinone ring linkage), 18.36

(C-26, C-CH_3), 35.69 (C-19, -S-C); Anal. Calcd. for $C_{19}H_{15}N_5OS$: C, 63.14 H, 4.18; N, 19.38%; Found: C, 63.11; H, 4.17; N, 19.40%.

3-(3-methylphenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7c)
Yield: 63%; m.p. 259^{0}C (dec.); IR (KBr,cm^{-1}) : 1739 (C=O of β-lactum), 1557 (C=C), 1536 (C-N), 786 (C-Cl), 757 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.29 (3H, s, Ar-CH_3), 3.95 (2H, d, CH-S at thiazolidinone ring), 6.48 (1H, s, CH-N at thiazolidinone ring), 7.07-7.35 (4H, m, Ar-H), 7.44-8.07 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 175.75 (C-16, -C=O), 138.27-115.23 (15C, -Ar-C), 58.78 (C-14, -Ar.- thiazolidinone ring linkage), 23.46 (C-26, C-CH_3), 37.57 (C-19, -S-C); Anal. Calcd. for $C_{19}H_{15}N_5OS$: C, 63.14 H, 4.18; N, 19.38%; Found: C, 63.15; H, 4.20; N, 19.41%.

3-(4-methylphenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7d)
Yield: 67%; m.p. 269^{0}C (dec.); IR (KBr,cm^{-1}) : 1736 (C=O of β-lactum), 1557 (C=C), 1537 (C-N), 780 (C-Cl), 748 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.26 (3H, s, Ar-CH_3), 3.93 (2H, d, CH-S at thiazolidinone ring), 6.42 (1H, s, CH-N at thiazolidinone ring), 7.05-7.37 (4H, m, Ar-H), 7.47-8.11 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 173.56 (C-16, -C=O), 137.89-112.23 (15C, -Ar-C), 60.79 (C-14, -Ar.- thiazolidinone ring linkage), 22.27 (C-26, C-CH_3), 34.59 (C-19, -S-C); Anal. Calcd. for $C_{19}H_{15}N_5OS$: C, 63.14 H, 4.18; N, 19.38%; Found: C, 63.16; H, 4.19; N, 19.37%.

3-(2-nitrophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7e)
Yield: 78%; m.p. 257^{0}C (dec.); IR (KBr,cm^{-1}) : 1741 (C=O of β-lactum), 1553 (C=C), 1532 (C-N), 790 (C-Cl), 750 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.88 (2H, d, CH-S at thiazolidinone ring), 6.47 (1H, s, CH-N at thiazolidinone ring), 7.47-8.31 (4H, m, Ar-H), 7.44-8.07 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 175.68 (C-16, -C=O), 137.91-117.09 (14C, -Ar-C), 62.39 (C-14, -Ar.- thiazolidinone ring linkage), 145.53 (C-24, -C-NO_2), 35.98 (C-19, -S-C); Anal. Calcd. for $C_{18}H_{12}N_6O_3S$: C, 55.10 H, 3.08; N, 21.42%; Found: C, 55.08; H, 3.10; N, 21.41%.

3-(3-nitrophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7f)
Yield: 57%; m.p. 283^{0}C (dec.); IR (KBr,cm^{-1}) : 1739 (C=O of β-lactum), 1557 (C=C), 1535 (C-N), 792 (C-Cl), 752 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.91 (2H, d, CH-S at thiazolidinone ring), 6.41 (1H, s, CH-N at thiazolidinone ring), 7.60-8.20 (4H, m, Ar-H), 7.45-8.06 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 176.27 (C-16, -C=O), 139.48-116.57 (14C, -Ar-C), 61.63 (C-14, -Ar.- thiazolidinone ring linkage), 149.47 (C-23, -C-NO_2), 33.17 (C-19, -S-C); Anal. Calcd. for $C_{18}H_{12}N_6O_3S$: C, 55.10 H, 3.08; N, 21.42%; Found: C, 55.11; H, 3.09; N, 21.43%.

3-(4-nitrophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7g)
Yield: 59%; m.p. 249^{0}C (dec.); IR (KBr,cm^{-1}) : 1743 (C=O of β-lactum), 1558 (C=C), 1535 (C-N), 795 (C-Cl), 757 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.89 (2H, d, CH-S at thiazolidinone ring), 6.46 (1H, s, CH-N at thiazolidinone ring), 6.97-8.11 (4H, m, Ar-H), 7.42-8.07 (5H, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 175.38 (C-16, -C=O), 137.89-117.49 (14C, -Ar-C), 62.62 (C-14, -Ar.- thiazolidinone ring linkage), 145.42 (C-22, -C-NO_2), 34.57 (C-19, -S-C); Anal. Calcd. for $C_{18}H_{12}N_6O_3S$: C, 55.10 H, 3.08; N, 21.42%; Found: C, 55.09; H, 3.06; N, 21.40%.

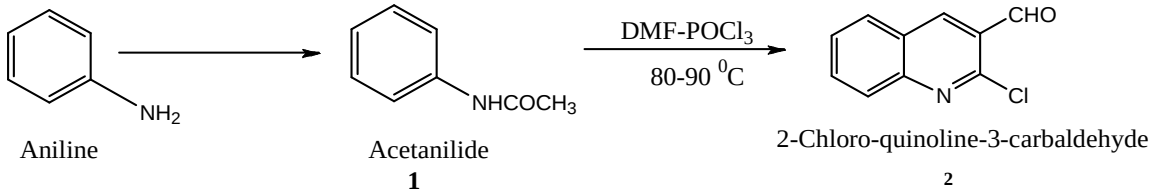
3-(2-chlorophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7h)
Yield: 60%; m.p. 287^{0}C (dec.); IR (KBr,cm^{-1}) : 1730 (C=O of β-lactum), 1556 (C=C), 1536 (C-N), 788 (C-Cl), 760 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.93 (2H, d, C<u>H</u>-S at thiazolidinone ring), 6.47 (1H, s, C<u>H</u>-N at thiazolidinone ring), 7.16-7.67 (4<u>H</u>, m, Ar-H), 7.43-8.06 (5<u>H</u>, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 177.41 (C-16, -<u>C</u>=O), 135.26-115.78 (14C, -Ar-C), 61.77 (C-14, -Ar.- thiazolidinone ring linkage), 130.35 (C-24, -<u>C</u>-Cl), 37.37 (C-19, -S-<u>C</u>); Anal. Calcd. for $C_{18}H_{12}ClN_5OS$: C, 56.62H, 3.17; N, 18.34%; Found: C, 56.61; H, 3.19; N, 18.35%.

3-(3-chlorophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7i)
Yield: 62%; m.p. 286^{0}C (dec.); IR (KBr,cm^{-1}) : 1733 (C=O of β-lactum), 1558 (C=C), 1531 (C-N), 785 (C-Cl), 751 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.95 (2H, d, C<u>H</u>-S at thiazolidinone ring), 6.41 (1H, s, C<u>H</u>-N at thiazolidinone ring), 7.05-7.51 (4<u>H</u>, m, Ar-H), 7.44-8.11 (5<u>H</u>, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 172.42 (C-16, -<u>C</u>=O), 136.23-119.27 (14C, -Ar-C), 62.67 (C-14, -Ar.- thiazolidinone ring linkage), 135.48 (C-24, -<u>C</u>-Cl), 34.45 (C-19, -S-<u>C</u>); Anal. Calcd. for $C_{18}H_{12}ClN_5OS$: C, 56.62H, 3.17; N, 18.34%; Found: C, 56.63; H, 3.16; N, 18.36%.

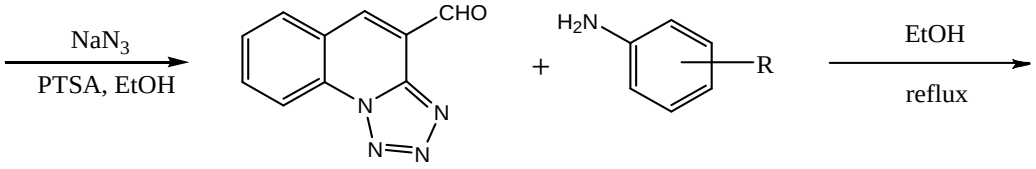
3-(4-chlorophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7j)
Yield: 65%; m.p. 260^{0}C (dec.); IR (KBr,cm^{-1}) : 1735 (C=O of β-lactum), 1560 (C=C), 1537 (C-N), 789 (C-Cl), 754 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.92 (2H, d, C<u>H</u>-S at thiazolidinone ring), 6.44 (1H, s, C<u>H</u>-N at thiazolidinone ring), 7.37 (4<u>H</u>, m, Ar-H), 7.42-8.09 (5<u>H</u>, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) 176.66 (C-16, -<u>C</u>=O), 138.38-115.23 (14C, -Ar-C), 59.89 (C-14, -Ar.- thiazolidinone ring linkage), 130.11 (C-22, -<u>C</u>-Cl), 37.78 (C-19, -S-<u>C</u>); Anal. Calcd. for $C_{18}H_{12}ClN_5OS$: C, 56.62H, 3.17; N, 18.34%; Found: C, 56.63; H, 3.16; N, 18.36%.

3-(4-fluorophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7k)
Yield: 59%; m.p. 295^{0}C (dec.); IR (KBr,cm^{-1}) : 1738 (C=O of β-lactum), 1553 (C=C), 1536 (C-N), 787 (C-Cl), 749 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.91 (2H, d, C<u>H</u>-S at thiazolidinone ring), 6.47 (1H, s, C<u>H</u>-N at thiazolidinone ring), 7.35 (4<u>H</u>, m, Ar-H), 7.45-8.12 (5<u>H</u>, m, Ar-H at quinoline ring); ^{13}C NMR (400 MHz, DMSO- d_6) 172.72 (C-16, -<u>C</u>=O), 139.98-119.23 (14C, -Ar-C), 63.14 (C-14, -Ar.- thiazolidinone ring linkage), 162.65 (C-22, -<u>C</u>-F), 36.58 (C-19, -S-<u>C</u>); Anal. Calcd. for $C_{18}H_{12}FN_5OS$: C, 59.17H, 3.31; N, 19.17%; Found: C, 59.15; H, 3.33; N, 19.15%.

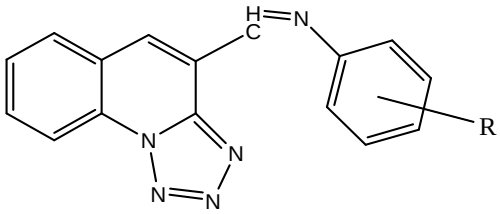
3-(5-methyl-1,3-thiazol-2-yl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3-thiazolidin-4-one (7l)
Yield: 55%; m.p. 298^{0}C (dec.); IR (KBr,cm^{-1}) : 1738 (C=O of β-lactum), 1557 (C=C), 1535 (C-N), 783 (C-Cl), 749 (C-S-C); ^{1}H NMR (400 MHz, DMSO- d_6) δ 3.85 (2H, d, C<u>H</u>-S at thiazolidinone ring), 6.51 (1H, s, C<u>H</u>-N at thiazolidinone ring), 7.21-7.37 (5<u>H</u>, m, Ar-H), 2.35 (3<u>H</u>, s, Ar-CH_3 at thaizole ring), 7.51 (1H, s, C<u>H</u>-C at thaizole ring); ^{13}C NMR (400 MHz, DMSO- d_6) δ 180.88 (C-16, -<u>C</u>=O), 53.66 (C-14, -Ar at thiazolidinone-heterocyclic coupling ring), 151.66-115.78 (12C, -Ar-C), 16.66 (C-23, -C-<u>C</u>H_3 in heterocycles ring), 35.02 (C-25, -S-<u>C</u>); ; Anal. Calcd. for $C_{16}H_{12}N_6OS_2$: C, 52.16 H, 3.28; N, 22.81%; Found: C, 52.18; H, 3.29; N, 22.82%.



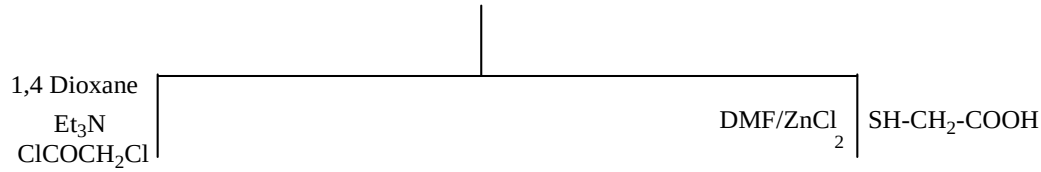
Aniline — Acetanilide **1** — 2-Chloro-quinoline-3-carbaldehyde **2**

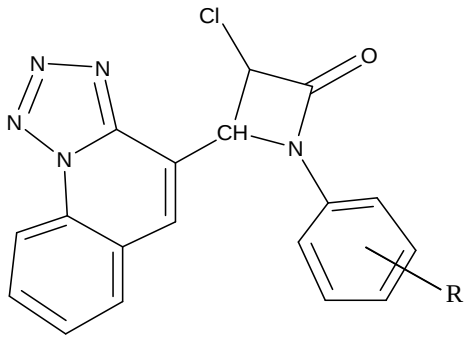


tetrazolo[1,5-a]quinoline-4-carbaldehyde **3** + Substituted aromatic amine **4a-l**

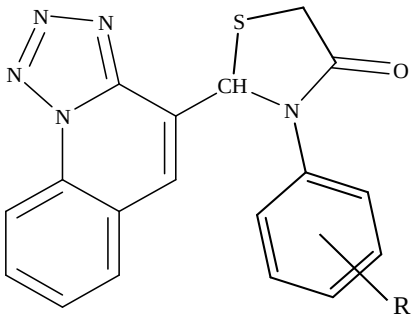


N-[(Z)tetrazolo[1,5-a]quinoline-4-yl methyllidene]substituted amine **5a-l**





6a-l



7a-l

R (Substituted –Ar. amines)

a	Aniline
b	2-Methyl aniline
c	3-Methyl aniline
d	4-Methyl aniline
e	2-Nitro aniline
f	3-Nitro aniline
g	4-Nitro aniline
h	2-Chloro aniline
i	3-Chloro aniline
j	4-Chloro aniline
k	4-Floro aniline
l	2-Amino 5-methyl aniline

Antimicrobial activity

All the newly synthesized compounds were examined for their in vitro antibacterial and antifungal activity (MIC-minimum inhibition concentration) by broth dilution method [25] with two gram positive bacteria *S. aureus* and *B. subtilis*, two gram negative bacteria *E. coli*, *P. aeruginosa* and fungi species like *C. albicans*, *A. niger* organisms. Ciprofloxacin, Ampicillin, Chloramphenicol, Norfloxacin, Flucanazole, Griseofulvin, and Nystatin were used in assay as a standard control drug. Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for test. DMSO was used as a diluent which is ineffective to the growth of microbes.

RESULTS AND DISCUSSION

Although many routes have been developed for functionalized quinolines, the Vilsmeier approach is found to be among the most efficient for achieving useful transformations and heteroannulations. Thus, in this communication is reported the synthesis of tetrazolo[1,5-1]quinoline-4-carbaldehyde **3** from the reaction 2-chloro-quinoline 3-carbaldehyde **2** and the synthesis of compounds **2** from the reaction N-aryl acetamides with Vilsmeier reagent and transformation of the 2-chloro and 3-carbaldehyde groups into different functionalities. The required acetanilide **1** was readily prepared from the reaction of corresponding anilines with acetic anhydride in aqueous medium. The Vilsmeier cyclisation of acetanilides **1** was carried out by adding $POCl_3$ to the substrate in DMF at 0-5 ^{0}C followed by heating to 90 ^{0}C to afford 2-chloro and 3-carbaldehyde **2** in good moderate yield. The chlorine atom in quinolines **2** could not be displaced by N-nucleophiles (such as amines) under various conditions. However, the reaction of sodium azide with quinolines **2** in the presence of p-toluenesulphonic acid easily displaced the chlorine atom to afford tetrazolo[1,5-1]quinoline-4-carbaldehyde **3** in good yield. The carbaldehyde group in quinolines **3** 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 **3** was converted into substituted quinoline Schiff base derivatives **5a-l** in ethanol at refluxed temperature. The substituted Schiff base derivatives **5a-l** were also reaction with chloroacetylchloride in presence of triethylamine which act as a catalyst and 1, 4 Dioxane undergo cyclisation give quinoline azetidin-2-one derivatives **6a-l.** The same Schiff base derivatives **5a-l** were heating with 2-marcapto acetic acid in presence of anhydrous zinc chloride which act as a catalyst and solvent DMF undergo cyclisation to give quinoline thiazolidin-4-one derivatives **7a-l**.

The antimicrobial activity results presented in Table 1 and Table 2 revealed that the final quinoline based azitidinone analogues **6a-l** showed moderate to good activity towards all the mentioned panel of bacterial and fungal strains. The bioassay showed that unsubstituted anilines as well as ortho, meta and pera substituted aniline azitidinones analogues, that are 6a to 6d, showed moderate activity against all the strains. Whereas, the final azitidinone analogues 6e and 6g containing ortho nitro aniline and pera-nitro aniline substituents respectively showed promising activity against wide range of mentioned gram +Ve and gram –Ve bacterial strains. The final azitidinones bearing chloroamines proved to exhibit moderate activity but the activity increased in the order of ortho, meta and pera substitutions. In addition, the fluoro aniline azitidinone analogue showed excellent activity against all the bacterial and fungal strains with good minimum inhibitory concentration as compared to standard drugs. Finally, the azitidinone analogues bearing 2-amino-5-methyl aniline 6l showed moderate activity towards the mentioned organisms.

Table 1 Antimicrobial study (MIC µg/mL) of azitidinone analogues 6a-l

Comp.	R	Gram negative		Gram positive		Fungal species	
	Azitidinone Derivatives	*E.coli*	*P.aeruginosa*	*S.aureus*	*B.subtilis*	*C.albicans*	*A. niger*
6a	Aniline	1000	500	250	500	500	>1000
6b	2-Methyl aniline	250	200	250	500	800	>1000
6c	3-Methyl aniline	250	200	200	250	1000	>1000
6d	4-Methyl aniline	200	250	200	250	800	>1000
6e	2-Nitro aniline	**50**	**150**	100	**150**	500	500
6f	3-Nitro aniline	100	200	150	100	250	500
6g	4-Nitro aniline	**50**	200	**50**	100	250	400
6h	2-Chloro aniline	250	250	250	200	400	500
6i	3-Chloro aniline	250	400	250	250	400	500
6j	4-Chloro aniline	150	200	200	**150**	800	400
6k	4-Floro aniline	**50**	**150**	100	200	**200**	**250**
6l	2-Amino5-methyl aniline	250	250	200	250	500	500
Ampicillin		100	100	250	100	-	-
ciprofloxacin		25	25	50	50	-	-
chloramphenicol		50	50	50	50	-	-
Norfloxacin		10	10	10	10	-	-
Griseofulvin						500	100
Nystatin						100	100
Flucanazole						10	10

Table 2 Antimicrobial study (MIC µg/mL) of thiazolidinone analogues 7a-l

Comp.	R	Gram negative		Gram positive		Fungal species	
	Thiazolidinone Derivatives	*E.coli*	*P.aeruginosa*	*S.aureus*	*B.subtilis*	*C.albicans*	*A.niger*
7a	Aniline	500	250	150	400	400	500
7b	2-Methyl aniline	200	200	150	500	500	500
7c	3-Methyl aniline	250	200	200	200	500	500
7d	4-Methyl aniline	200	**150**	150	250	500	500
7e	2-Nitro aniline	**50**	**150**	100	**150**	**200**	400
7f	3-Nitro aniline	50	**150**	150	100	400	500
7g	4-Nitro aniline	100	**150**	**50**	100	250	400
7h	2-Chloro aniline	200	250	150	150	250	**250**
7i	3-Chloro aniline	200	200	100	250	400	500
7j	4-Chloro aniline	150	200	150	200	500	400
7k	4-Floro aniline	**50**	**150**	100	**150**	**200**	**250**
7l	2-Amino 5-methyl aniline	150	200	150	250	250	400
Standard Drugs							
Ampicillin		100	100	250	100	-	-
ciprofloxacin		25	25	50	50	-	-
chloramphenicol		50	50	50	50	-	-
Norfloxacin		10	10	10	10	-	-
Griseofulvin						500	100
Nystatin						100	100
Flucanazole						10	10

The microbial investigation was further continued for the quinoline based thiazolidinon analogues, presented in Table 2 revealed that the activity of unsubstituted amine and its ortho, meta and pera analogues was proved to be moderate against all the strains but the slight increase in the minimum inhibitory concentration has been observed compare to its azitidinone analogues. In fact, pera-methyl aniline thiazolidinones showed strong inhibitory action against gram –Ve P. aeruginosa. Similar to azitidinone analogues, the ortho, meta and pera nitro

substituted thiazolidinone analogues showed greater inhibitory efficacy against all the mentioned microbial organisms with the excellent minimum inhibitory concentration. Whereas, thiazolidinone analogue 7h bearing ortho-chloro aniline exhibited strong activity result against C. albicans fungi. Finally, 4-fluoro aniline thiazolidinones proved to be more beneficial agents with promising anti bacterial as well as antifungal activity against all the strains.

CONCLUSION

In summary, we have developed a novel, efficient and potent quinoline based azitidinone and thiazolidinone analogues. quinoline nucleus is one of the active constituents present in many standard drugs, and is known to increase in pharmacological activity of the molecules. The presence of substituted amines is also an instrumental in contributing the net biological activity. Briefly, high potency has been observed with the final scaffolds in the form of azitidinones and thiazolidinones bearing various amines containg halogen(s) such as chloro or fluoro and nitro functional groups. The final results indicated that quinoline based thiazolidinones are more efficious antimicrobial agents compared to quinoline based azitidinone analogues. Hence, there is enough scope for further study in developing such compounds as a good lead activity. Overall conclusion placed for synthesized compounds is that most of the compounds shown moderate to promising activity as compared to standard drug against all representative panel of bacterial and fungal strains.

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