ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

SYNTHESIS AND BIOLOGICAL SIGNIFICANCE OF AZETIDINONE CLUBBED QUINOLINE DERIVATIVES

Kunj M. Trivedi, Jayesh J. Maru*

Department of Chemistry, School of Sciences, Gujarat University, Gujarat, India

**Corresponding author: jaymaru@gujaratuniversity.ac.in*

ABSTRACT

Novel series of quinoline clubbed oxadiazolyl-pyridinyl-azetidin-2-one derivatives have been synthesized via the formation of Schiff base. The desired motif had been generated through annulation of Schiff base by condensation with chloroacetyl chloride. The synthesized molecules were characterized by ^{1}H NMR, ^{13}C NMR, mass spectral analysis and CHN analysis. The entire series of the synthesized compounds was evaluated for their biological activity against two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. Compound 8b and 8h exhibited good activity against bacterial strain whereas compound 8a and 8h shown very good activity against fungal strain.

Keywords: Antimicrobial activity, Azetidinone, Quinoline, 1,3,4-Oxadiazole

1. INTRODUCTION

Infectious diseases have raised dramatically due to various microorganisms especially bacteria and fungi resistant in last two decades, resulting in several threats to health of human body. In spite of ample availability of various types of antibiotic drugs, multidrug resistance (MDR) has been observed continuously for used drugs in many of the pathogenic bacterial isolates [1, 2]. To overcome this issue, we were tempted to design and synthesize some novel heterocycle based quinoline and 2-azetidinone, which might have better antimicrobial potency compared to existing standard drugs. Quinoline, a bicyclic nitrogen containing heterocycle, naturally as well as synthetically occurring compound, constitutes large number of heterocyclic moieties. Its various derivatives have acquired great importance in the field of organic and medicinal chemistry due to its excellent pharmacological properties such as antimicrobial [3-7], antioxidant [8], anti-inflammatory [9], anticancer [10,11] and anti-HIV [12,13]. Its extraordinary broad range biological profile and immense therapeutic agents encouraged us to design novel molecules containing quinoline with other heterocycles such as oxadiazole and pyridine as core units with the aim of exploring and modifying its antimicrobial profile. The literature survey reveals that quinoline containing azomethine linkage at C-3 position shows better pharmacological activities with potential clinical importance [14-16]. Likewise, oxygen and nitrogen containing heterocyclic analogs such as oxadiazole clubbed pyridine compounds are very vital building blocks in pharmaceutical chemistry. Oxadiazole is associated with other heterocyclic or aromatic ring; it stimulates research activity in the field of the medicinal chemistry [17, 18]. Derivatives of 1,3,4-oxadiazole possess versatile biological activities such as antifungal, antitubercular, antioxidant, antibacterial, anticancer, anti-inflammatory, antiviral and antimalarial properties [19-22].

Furthermore, the significance of azetidin-2-ones derivatives is well-known for their biological properties and when they are conjugated with other heterocyclic compound, exhibits various types of biological activities such as antitubercular [23], antimicrobial [24,25], anti-inflammatory [26], antidepressant [27], antimalarial [28], antioxidant [29] and anti-HIV [30]. The significance of heterocyclic analogs like quinoline, oxadiazole, pyridine and azetidin-2-one in the field of medicinal chemistry is remarkable. Thus to explore the scope of these motifs we were prompted to develop the novel heterocyclic derivatives comprising all these scaffolds in a single molecular framework. So, we have developed novel hybrid quinoline clubbed Oxadiazolyl-pyridine derivatives *via* exploration of 2nd and 3rd position of quinoline with sulfur linkage and azomethine, respectively. Furthermore, synthesized molecules were examined for their antimicrobial activity against various Gram-positive, Gram-negative

bacterial strains and fungal strains. As the well-known drugs, which contains aforesaid heterocycles are readily available and used in practices are Zibotentan, Raltegravir, and Cephalosporin (Fig. 1).

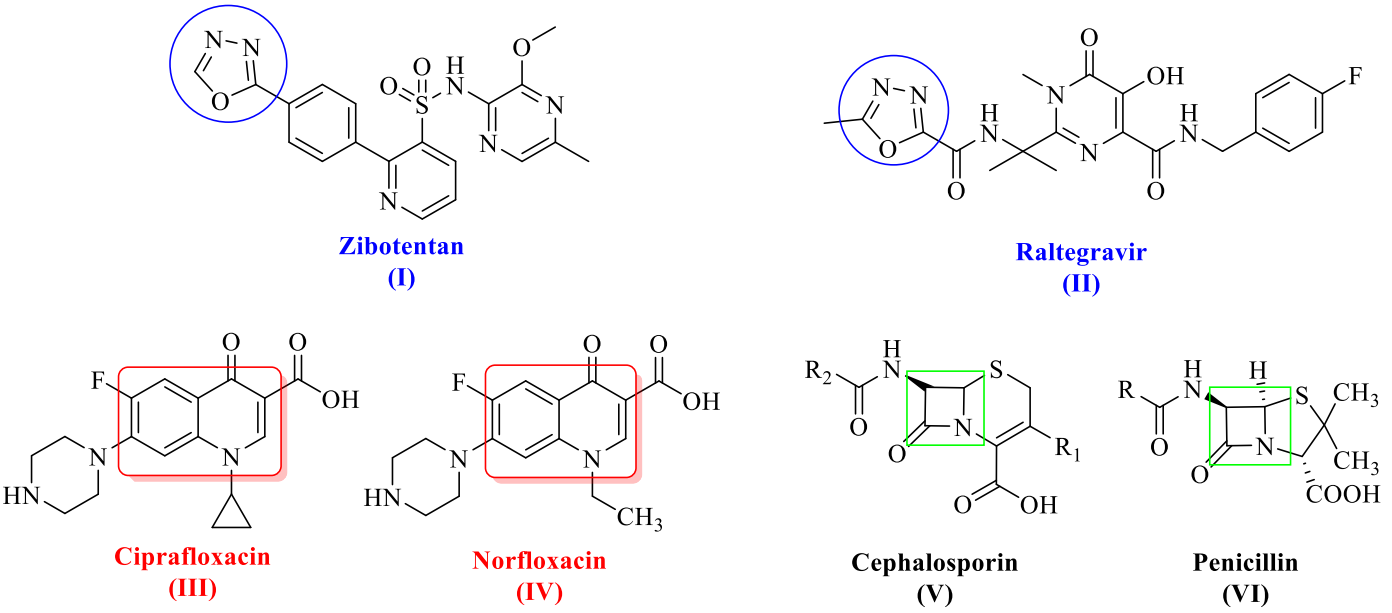
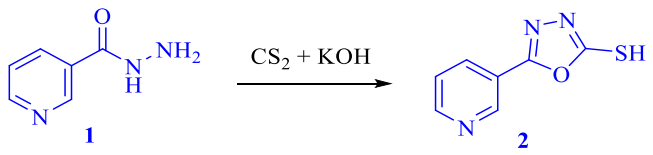


Fig. 1: Drugs containing Oxadiazole (I,II), Quinoline (III,IV) and Azetidinone (V,VI) moieties

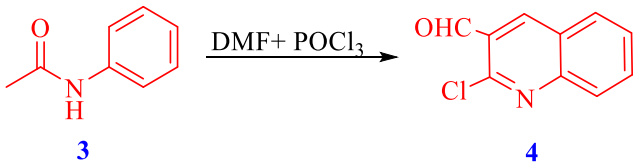
2. EXPERIMENTAL SECTION

2.1. Material and methods

All the chemicals used were analytical grade, originated from Sigma-Aldrich or Spectrochem and used without further purification. The melting points of newly synthesized compounds were determined by the open capillary tube method on Veego electronic apparatus VMP-D. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz on Bruker AM 400 Spectrometer with TMS as an internal standard. The ^{1}H NMR and ^{13}C NMR chemical shifts were reported in parts per million (ppm). Molecular mass of the synthesized compounds was recorded on LC/MS Shimadzu mass spectrometer. The purity of synthesized compounds was checked using thin layer chromatography (TLC) on silica-gel coated aluminium sheet (Merck Kiesel 60 GF-254, 0.2 mm thickness). The antimicrobial activity was carried out using broth dilution method [31] to determine minimum inhibitory concentration (MIC).



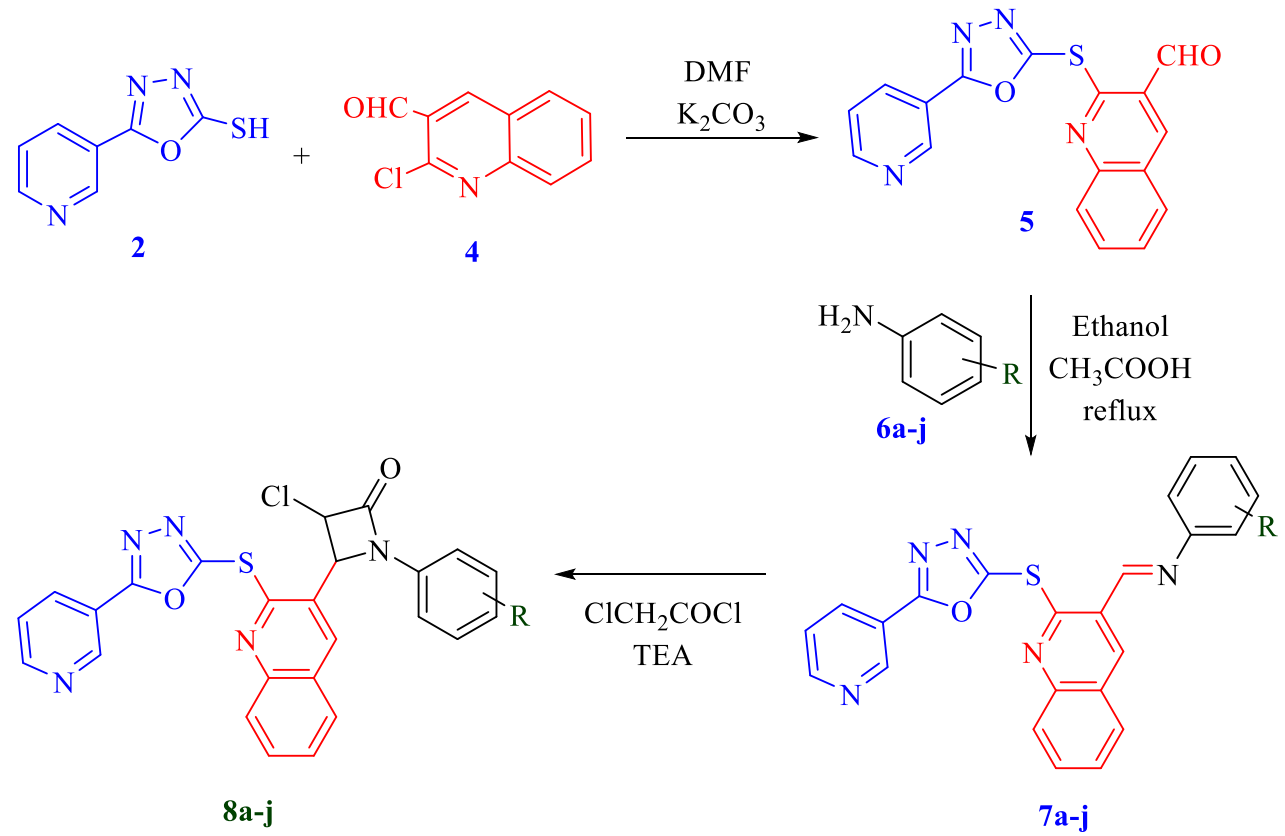
Scheme 1: Synthesis of 5-(pyridin-3-yl)-1,3,4-oxadiazole-2-thiol



Scheme 2: Synthesis of 2-chloroquinoline-3-carbaldehyde

2.1.1. Synthesis of 5-(pyridine-3-yl)-1,3,4-oxadiazole-2-thiol (2)

A combination of nicotinohydrazide (0.05 mol), carbon disulphide (0.05 mol) and aqueous potassium hydroxide (50%, 0.05 mol) in methanol (20 ml) was stirred for 30 minutes at room temperature in 100 ml two-neck RBF. Then the temperature was raised gradually up to 60-70 °C, and heated for 7-8 hours. Progress of the reaction was continuously monitored by TLC using ethyl acetate: hexane (7:3) as eluent. After completion of the reaction, reaction mixture was allowed to cool at room temperature and then poured into cold water. The product thus obtained was subjected to filtrations followed by washing with water. Recrystallized product obtained by using ethanol to get the desired compound (2).



Scheme 3: Reaction route for the synthesis of compounds (8a-j)

2.1.2. Synthesis of 2-chloroquinoline-3-carbaldehyde (4)

The Vilsmeier-Haack reagent prepared by using phosphoryl chloride (0.15 mol) and N,N'-dimethyl formamide (0.6 mol) at 0-5 °C, was added to acetanilide (0.05 mol) slowly. After addition, the mixture was heated at 80 °C for 14 hours. Progress of reaction was monitored by TLC using ethyl acetate: hexane (7:3) as eluent. After the completion of reaction, it was poured into crushed ice. Filtered the precipitates and washed with water and recrystallized from ethanol to get the title compound (4).

2.1.3. Synthesis of 2-((5-(pyridine-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinoline-3-carbaldehyde (5)

5-(Pyridine-3-yl)-1,3,4-oxadiazole-2-thiol (0.05 mol) was dissolved in DMF (15 ml) in round bottom flask and charged with potassium carbonate (0.15 mol) then stirred for 15 minutes. Then, 2-chloroquinoline-3-carbaldehyde (0.05 mol) was added slowly to the reaction mixture with continuous stirring. Reaction mixture was stirred at 100 °C for 4-5 hours. Progress of the reaction was observed on TLC using ethyl acetate: hexane (7:3) as eluent. After completion of the reaction, mixture was allowed to stand at room temperature for 30 minutes and then poured into cold water. The organic phase was extracted from the reaction mixture by using ethyl acetate, and gave washes of brine solution and cold water, respectively. Moisture was removed by using sodium sulphate, and the solvent removed under reduced pressure. The product was thus obtained as yellow solid, which was further purified by crystallization using ethanol to afford the desired compound (5).

2.1.4. General procedure for the Synthesis of N-substitutedphenyl-1-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinolin-3-yl) methanimine (7a-j)

Equimolar mixture of 2-((5-pyridin-3-yl)-1,3,4-oxadiazole-2-yl)thio)quinoline-3-carbaldehyde (5) (0.001 mol, 0.33gm) and various substituted anilines (6a-j) (0.001 mol) in ethanol (5 ml) and glacial acetic acid (0.2 ml) were refluxed for 4-5 hours. Progress of the reaction was monitored by TLC using ethyl acetate:

hexane (3:7) as eluent. After the completion of reaction, it was further stirred at room temperature for 30 minutes and poured into crushed ice. The precipitate obtained was filtered, washed with water and crystallized using ethanol to get the title compounds 7a-j.

2.1.5. General procedure for the synthesis of 3-chloro-1-substituted phenyl-4-(2-((5-(pyridine-3-yl)-1,3,4-oxadiazol-2-yl)thio) quinoline-3-yl)-azetidin-2-one (8a-j)

Compound 7a-j (0.001 mol) was added to constantly stirred solution of 1,4-dioxane (5 ml), triethyl amine (1-2 ml), and chloro acetyl chloride (0.0012 mol) at 0-5 °C. The reaction mixture was stirred at 50-60 °C. This mixture was then kept at room temperature for 30 minutes. The precipitate was obtained by cooling the mixture, which was filtered and thoroughly washed with water. Recrystallized it with ethanol to get the title and final compounds 8a-j.

3. RESULTS AND DISCUSSION

It can be observed from the topography of quinoline that it has both nucleophilic and electrophilic properties. The most reactive site of quinoline is 4th position due to the higher nucleophilicity. Here, we explored 2nd and 3rd positions of quinoline by substitution reactions; explored great importance in the field of medicinal chemistry. Hence, in the present study, the first step comprises cyclization of nicotinohydrazide with carbon disulfide in the presence of potassium hydroxide to produce 5-(pyridin-3-yl)-1,3,4-oxadiazole-2-thiol (2) in good yield. Subsequently, *N*-phenylacetamide (3) was treated with dimethylformamide (DMF) and phosphoryl chloride to get 2-chloroquinoline-3-carbaldehyde (4). Furthermore, compound-2 and compound-4 were condensed in the presence of dimethylformamide and potassium carbonate to yield 2-((5-(pyridine-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinoline-3-carbaldehyde (5). Condensation of compound-5 with various anilines (6a-j) in the presence of glacial acetic acid in ethanol yielded corresponding *N*-substitutedphenyl-1-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinolin-3-yl)methanemine (7a-j). Synthesized compound (7a-j) was further treated with chloro acetyl chloride in the presence of triethyl amine to yield the desired compounds 3-chloro-1-substituted phenyl-4-(2-((5-(pyridine-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinoline-3-yl)-azetidin-2-one (8a-j). All the synthesized compounds were further confirmed by ^{1}H NMR, ^{13}C NMR and elemental analysis.

3.1. Spectral data of synthesized compounds

3.1.1. 3-Chloro-1-phenyl-4-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinolin-3-yl) azetidin-2-one (8a)

White solid, Yield: 72%; ***M.P.:*** 194°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***5.169 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.443 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 7.158-7.249 (m, 5H, aromatic amine ring), 7.315-7.603 (m, 4H, quinoline ring), 7.984 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.061 (s, 1H, quinoline ring), 8.672 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.752 (s, 1H, pyridine ring); ***^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm:*** 61.45, 66.97, 120.27, 122.41, 123.62, 126.24, 126.77, 127.38, 128.34, 128.38, 128.87, 129.04, 129.16, 129.31, 134.10, 135.74, 137.67, 144.96, 148.34, 149.17, 154.91, 158.73, 159.55, 160.49. ***Anal. calcd.*** for $C_{25}H_{16}ClN_5O_2S$: C, 61.79; H, 3.32; N, 14.41. ***Found:*** C, 61.74; H, 3.30; N, 14.38. ***ESI-MS (m/z):*** 485.07 (M^+).

3.1.2. 3-Chloro-1-(2-chlorophenyl)-4-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio) quinolin-3-yl)azetidin-2-one (8b)

Off-white solid, Yield: 68%; ***M.P.:*** 199°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:*** 5.169 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 5.441 (d, *J*=6.0 Hz, 1H, azetidinon-2-one ring), 6.968-7.274 (m, 4H, aromatic amine ring), 7.318-7.604 (m, 4H, quinoline ring). 7.995 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.042 (s, 1H, quinoline ring), 8.673 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.801 (s, 1H, pyridine ring); ***^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm:*** 61.45, 66.97, 120.27, 123.62, 126.24, 126.77, 127.38, 128.34, 128.38, 128.87, 129.04, 129.16, 129.31, 134.10, 135.74, 137.67, 144.96, 148.34, 149.17, 154.91, 158.73, 159.55, 160.49. ***Anal. calcd.*** for $C_{25}H_{15}Cl_2N_5O_2S$: C, 57.70; H, 2.91; N, 13.46. ***Found:*** C, 57.73; H, 2.93; N, 13.47. ***ESI-MS (m/z):*** 519.03 (M^+).

3.1.3. 3-Chloro-1-(3-chlorophenyl)-4-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio) quinolin-3-yl)azetidin-2-one (8c)

Off-white solid, Yield: 64%; ***M.P.:*** 203°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***5.168 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.443 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 6.917-7.310 (m, 4H, aromatic amine ring), 7.386-7.601 (m, 4H, quinoline ring), 7.982 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.063 (s, 1H, quinoline ring), 8.672 (d, *J*=6.2 Hz, 1H pyridine ring),

8.761 (s, 1H, pyridine ring); ***Anal. calcd.*** for $C_{25}H_{15}Cl_2N_5O_2S$: C, 57.70; H, 2.91; N, 13.46. ***Found:*** C, 57.71; H, 2.89; N, 13.45. ***ESI-MS (m/z):*** 519.13 (M^+).

3.1.4. 3-Chloro-1-(4-chlorophenyl)-4-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio) quinolin-3-yl)azetidin-2-one (8d)

Off-white solid, Yield: 60%; ***M.P.:*** 224°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***5.162 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.445 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 7.108-7.271 (m, 4H, aromatic amine ring), 7.312-7.603 (m, 4H, quinoline ring), 7.987 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.061 (s, 1H, quinoline ring), 8.680 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.832 (s, 1H, pyridine ring); ***^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm:*** 61.45, 66.97, 120.27, 123.62, 126.24, 126.77, 127.38, 128.34, 128.38, 128.87, 129.04, 129.16, 129.31, 134.10, 135.74, 137.67, 144.96, 148.34, 149.17, 154.91, 158.73, 159.55, 160.49. ***Anal. calcd.*** for $C_{25}H_{15}Cl_2N_5O_2S$: C, 57.70; H, 2.91; N, 13.46. ***Found:*** C, 57.68; H, 2.95; N, 13.49. ***ESI-MS (m/z):*** 519.03 (M^+).

3.1.5. 3-Chloro-4-((2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinolin-3-yl)-1-(o-tolyl)azetidin-2-one (8e)

White solid, Yield: 75%; ***M.P.:*** 232°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***2.301 (s, 3H, methyl group), 5.163 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.442 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 6.963-7.176 (m, 4H, aromatic amine ring), 7.310-7.605 (m, 4H, quinoline ring), 7.972 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.065 (s, 1H, quinoline ring), 8.672 (d, *J*=6.2 Hz,1H pyridine ring), 8.803 (s, 1H, pyridine ring); ***Anal. calcd.*** for $C_{26}H_{18}ClN_5O_2S$: C, 62.46; H, 3.63; N, 14.01. ***Found:*** C, 62.40; H, 3.60; N, 14.03. ***ESI-MS (m/z):*** 499.09 (M^+).

3.1.6. 3-Chloro-4-((2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinolin-3-yl)-1-(m-tolyl)azetidin-2-one (8f)

Off-white solid, Yield: 74%; ***M.P.:*** 236°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***2.301 (s, 3H, methyl group), 5.163 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.442 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 6.902-7.232 (m, 4H, aromatic amine ring), 7.311-7.606 (m, 4H, quinoline ring), 7.989 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.073 (s, 1H, quinoline ring), 8.679 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.742 (s, 1H, pyridine ring); ***Anal. calcd.*** for $C_{26}H_{18}ClN_5O_2S$: C, 62.46; H, 3.63; N, 14.01. ***Found:*** C, 62.43; H, 3.65; N, 14.00. ***ESI-MS (m/z):*** 499.09 (M^+).

3.1.7. 3-Chloro-4-((2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)quinolin-3-yl)-1-(p-tolyl)azetidin-2-one (8g)

Off-white solid, Yield: 73%; ***M.P.:*** 240°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:*** 2.283 (s, 3H, methyl group), 5.163 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.442 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 7.105-7.115 (m, 4H, aromatic amine ring), 7.310-7.606 (m, 4H, quinoline ring), 7.987 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.062 (s, 1H, quinoline ring), 8.679 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.763 (s, 1H, pyridine ring); ***Found:*** C, 62.44; H, 3.61; N, 14.05.

3.1.8. 3-Chloro-1-(2-nitrophenyl)-4-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio) quinolin-3-yl)azetidin-2-one (8h)

Yellow solid, Yield: 70%; ***M.P.:*** 248°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***5.160 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.442 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 7.209-7.482 (m, 4H, aromatic amine ring), 7.501-7.614 (m, 3H, quinoline ring), 8.021 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.094 (s, 1H, quinoline ring), 8.661 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.752 (s, 1H, pyridine ring); ***Anal. calcd.*** for $C_{25}H_{15}ClN_6O_4S$: C, 56.55; H, 2.85; N, 15.83. ***Found:*** C, 56.51; H, 2.88; N, 15.82.

3.1.9. 3-Chloro-1-(3-nitrophenyl)-4-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio) quinolin-3-yl)azetidin-2-one (8i)

Dark yellow solid, Yield: 72%; ***M.P.:*** 254°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***5.160 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.442 (d, *J*=5.8 Hz, 1H, azetidinon-2-one ring), 7.310-7.493 (m, 4H, quinoline ring), 7.453-8.353 (m, 4H, aromatic amine ring), 8.059 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.118 (s, 1H, quinoline ring), 8.687 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.787 (s, 1H, pyridine ring).

3.1.10. 3-Chloro-1-(4-nitrophenyl)-4-(2-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio) quinolin-3-yl)azetidin-2-one (8j)

Light Yellow solid, Yield: 76%; ***M.P.:*** 232°C; ***^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:***5.160 (d, *J*=6.2 Hz, 1H, azetidinon-2-one ring), 5.440 (d, *J*=5.8 Hz, 1H,

azetidinon-2-one ring), 7.352-8.014 (m, 4H, quinoline ring), 7.484-8.207 (m, 4H, aromatic amine ring), 8.016 (d, *J*=5.6 Hz, 2H, pyridine ring), 8.121 (s, 1H, quinoline ring), 8.697 (d, *J*=6.2 Hz, 1H, pyridine ring), 8.875 (s, 1H, pyridine ring).

3.2. *In vitro* antibacterial activity

We have synthesized a series of compounds containing azetidinyl-oxadiazole fused motif with Quinoline through sulfur bridge. Functionalization has been done on phenyl nucleus of azetidinone ring to develop analogous. It has been twigged that the test compounds (8a-j) exhibited interesting antibacterial activity against bacterial strains such as *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Streptococcus pyogenes* (Table 2), however with a degree of variation. The chloro group containing final compounds (8b and 8d) showed very good potency against specific bacterial strain. The final derivatives containing electron withdrawing nitro group (8h and8j) exhibited superior inhibition profile for the selected bacterial strains. On the other hand, significant deviation of activity has been observed against Gram-negative strains where the unsubstituted phenyl ring containing azetidinone compound (8a) exhibited higher inhibition against the bacterial strain *P. aeruginosa*. Rest of the other compounds exhibited moderate to poor activity. Ciprofloxacin (MIC 5 μG/ml) and chloramphenicol (MIC 5 μG/ml) were used as standard control drugs for antibacterial activity.

Table 1: *In vitro* antibacterial activity of newly synthesized compounds 8a-j

Compound ID	-R	Minimal inhibitory concentration (μG/ml)			
		Escherichia coli MTCC 442	*Pseudomonas aeruginosa* MTCC 441	*Staphylococcus aureus* MTCC 96	*Streptococcus Pyogenes* MTCC 443
8a	H	50	100	100	100
8b	2-Cl	25	50	100	62.5
8c	3-Cl	50	50	100	50
8d	4-Cl	50	62.5	125	50
8e	2-CH_3	200	250	500	500
8f	3-CH_3	100	62.5	500	500
8g	4-CH_3	125	200	250	100
8h	2-NO_2	100	25	100	50
8i	3-NO_2	62.5	50	100	50
8j	4-NO_2	100	62.5	62.5	50
Ciprofloxacin	-	25	25	50	50
Chloramphenicol	-	50	50	50	50

Table 2: *In vitro* antifungal activity of newly synthesized compounds 8a-j

Compounds ID	-R	Minimal inhibitory concentration (μG/ml)		
		Candida albicans MTCC 227	*Aspergillus niger* MTCC 282	*Aspergillus clavatus* MTCC 1323
8a	H	100	500	250
8b	2-Cl	250	250	500
8c	3-Cl	100	500	100
8d	4-Cl	500	100	250
8e	2-CH_3	1000	>1000	>1000
8f	3-CH_3	500	1000	1000
8g	4-CH_3	500	1000	1000
8h	2-NO_2	250	100	250
8i	3-NO_2	500	250	250
8j	4-NO_2	250	500	500
Nystatin	-	100	100	100
Griseofulvin	-	500	100	100

3.3. *In vitro* antifungal activity

All the newly synthesized compounds have been screened *in vitro* for their antimicrobial activity against fungal strains such as *Aspergillus niger, Aspergillus clavatus* and *Candida albicans*. Antifungal activity data (Table 3) revealed that the final compound (8a) exhibited virtuous inhibition against the fungal strain *A. clavatus*. Furthermore, compounds 8b, 8c, 8i and 8j showed good inhibition against *C. albicans*, *A. niger* and *A. clavatus*. Rest of the other compounds appeared with moderate to poor activity profile. Nystatin (MIC 5 μG/ml) and griseofulvin (MIC 5 μG/ml) were used as standard control drugs for antifungal activity.

4. CONCLUSION

The goal of our research work was to synthesize new scaffolds without existing prior art. In conclusions, we have established an efficient synthesis of a series of some novel 3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-1-substituted phenyl azetidin-2-one (8a-j). The structures of newly synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and mass spectral analysis and also were tested for their antibacterial activity against various bacterial strains such as *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* and their antifungal activity against various fungal strains such as *C. albicans*, *A. niger* and *A. clavatus*. The antimicrobial activities of the newly synthesized compounds 8a-j were evaluated, and it was revealed that compounds are 8a, 8b, 8c, 8d, 8h, 8i and 8j potent antimicrobial agents against the tested microorganisms. Other analogues had moderate activity against different strains. It was possible to note that an aromatic ring lacking chloro group on *o, m* & *p* positions are important for the antibacterial activity of these compounds. So, it can be considered potential lead molecules for further design and development of antimicrobial agents.

5. ACKNOWLEDGEMENTS

Authors are very thankful to Department of Chemistry, School of Sciences, Gujarat University, India for providing research facility. The authors wish to offer their deep gratitude to Hitech Healthcare Laboratory and Research Centre, Ahmedabad, India for carrying out spectral analysis.

6. REFERENCES

1. Tanwar J, Das S, Fatima Z, Hameed S. *Interdisciplinary perspectives on infectious diseases.* 2014.
2. World Health Organization. Antimicrobial resistance: global report on surveillance. World Health Organization; 2014.
3. Makawana JA, Sangani CB, Teraiya SB, Zhu HL. *Medicinal Chemistry Research*, 2014; **23(1)**:471-479.
4. Khan T, Yadav R, Gound SS. *Journal of heterocyclic chemistry, 2018;* **55(4)**:1042-1047.
5. Eswaran S, Adhikari AV, Shetty NS. *European journal of medicinal chemistry,* 2009; **44(11)**:4637-4647.
6. Praveen C, DheenKumar P, Muralidharan D, Perumal PT. *Bioorganic & medicinal chemistry letters*, 2010; **20(24)**:7292-7296.
7. Frapwell CJ, Skipp PJ, Howlin RP, Angus EM, Hu Y, Coates AR, Allan RN, Webb JS. *Antimicrobial Agents and Chemotherapy*, 2020; 21; **64(5)**.
8. Naik HR, Naik HS, Naik TR, Naika HR, Gouthamchandra K, Mahmood R, Ahamed BK. *European Journal of Medicinal Chemistry*, 2009; **44(3)**:981-989.
9. Wen X, Wang SB, Liu DC, Gong GH, Quan ZS. *Medicinal Chemistry Research*, 2015; **24(6)**:2591-2603.
10. R Solomon V, Lee H. *Current medicinal chemistry*, 2011; **18(10)**:1488-1508.
11. Patel RV, Kumari P, Rajani DP, Chikhalia KH. *European Journal of Medicinal Chemistry*, 2011; **46(9)**:4354-4365.
12. Bedoya LM, Abad MJ, Calonge E, Saavedra LA, Gutierrez M, Kouznetsov VV, Alcami J, Bermejo P. *Antiviral research*, 2010; **87(3)**:338-344.
13. V Kouznetsov VA, Rojas Ruiz FY, Vargas Mendez LP, Gupta M. *Letters in Drug Design & Discovery*, 2012; **9(7)**:680-686.
14. Mahmud H, Lovely CJ, Dias HR. *Tetrahedron*, 2001; **57(19)**:4095-4105.
15. Adsule S, Barve V, Chen D, Ahmed F, Dou QP, Padhye S, Sarkar FH. *Journal of medicinal chemistry*, 2006; **49(24)**:7242-7246.
16. Mistry BM, Jauhari S. *Medicinal Chemistry Research*, 2013; **22(2)**:647-658.
17. Nazarbahjat N, Ariffin A, Abdullah Z, Abdulla MA, Shia JK, Leong KH. *Medicinal Chemistry Research*, 2016; **25(9)**:2015-2029.
18. Rapolu S, Alla M, Bommena VR, Murthy R, Jain N, Bommareddy VR, Bommineni MR. *European journal of medicinal chemistry*, 2013; **66**:91-100.
19. Salahuddin, Mazumder A, Yar MS, Mazumder R, Chakraborthy GS, Ahsan MJ, Rahman MU. *Synthetic Communications,* 2017; **47(20)**:1805-1847.

20. Chandrakantha B, Shetty P, Nambiyar V, Isloor N, Isloor AM. *European Journal of Medicinal Chemistry*, 2010; **45(3)**:1206-1210.
21. Ahmed MN, Sadiq B, Al-Masoudi NA, Yasin KA, Hameed S, Mahmood T, et al. *Journal of Molecular Structure,* 2018; **11(55)**:403-413.
22. Othman AA, Kihel M, Amara S. *Arabian Journal of Chemistry*, 2019; **12(7)**:1660-1675.
23. Mehta PD, Sengar NP, Pathak AK. *European journal of medicinal chemistry*, 2010; **45(12)**:5541-60.
24. Deep A, Kumar P, Narasimhan B, Meng LS, Ramasamy K, Mishra RK, Mani V. *Pharmaceutical Chemistry Journal*, 2016; **50(1)**:24-28.
25. Patel, NB, Patel, MD. *Medicinal Chemistry Research*, 2017, **26(8):**1772-1783.
26. Srivastava SK, Srivastava S, Srivastava SD. *Indian Journal of Chemistry-B*, 1999; **38(2)**:183-187.
27. Thomas AB, Nanda RK, Kothapalli LP, Hamane SC. *Arabian Journal of Chemistry*, 2016; **9**:79-90.
28. Raj R, Biot C, Carrère Kremer S, Kremer L, Guérardel Y, Gut J, et al. *Chemical Biology & Drug Design*, 2014; **83(2)**:191-197.
29. Saundane AR, Yarlakatti M, Walmik P, Katkar V. *Journal of Chemical Sciences*, 2012; **124(2)**:469-481.
30. Patel RN, Patel PV, Desai KR, Purohit PY, Nimavat KS, Vyas KB. *Heterocyclic Letters*, 2012; **2(1)**:99-105.
31. Wiegand I, Hilpert K, Hancock RE. *Nature Protocols*, 2008, **3(2)**:163.