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NOVEL COUMARINYL-OXADIAZOLYL-AZETIDINONE & THIAZOLIDINONE DERIVATIVES: DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY

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ABSTRACT: In the present article, a series of novel 3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl) -1,3,4-oxadiazol-2-yl) thio)-2H-chromen-3-yl) -1-Substituted phenylazetidin-2-one (10a-j) and 2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-3-Substituted phenyl thiazolidin-4-one (11a-j) have been efficiently synthesized in four steps by the use of $POCl_3$, Carbon disulphide, Chloro acetyl chloride and Thioglycolic acid. The structures of all the newly synthesized analogues were characterized by ^{1}H-NMR, ^{13}C-NMR spectroscopy and mass analysis. All the final synthesized analogues were examined for their preliminary *in vitro* antibacterial activity against Gram-positive (*Staphylococcus aureus and Streptococcus pyogenes*) Gram-negative (*Escherichia coli and Pseudomonas aeruginosa*) bacteria and antifungal activity against (*Candida albicans, Aspergillus niger and Aspergillus clavatus*) strains by using broth dilution technique. The results of antimicrobial study revealed that some of the newly synthesized compounds exhibit potent activity against the present specific microbial strains.

KEYWORDS: Azetidinone, Thiazolidinone, Coumarin, 1,3,4-Oxadiazole, Antimicrobial activity.

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1.INTRODUCTION

From last centuries, many reports and patents have been published in which some of the research articles deals with pharmacological studies of several heterocylces systems.[1] Microbial disease has become a growing medical problem in the treatment of infectious diseases caused by fungi and bacteria so, it is needed to designed some more efficient antimicrobial agents.[2,3] In the field of medicinal chemistry, many natural products are well known due to their activity and ability to react

against the other targeted molecules, it give us inspiration to synthesized new analogues with improved pharmacological profile. [4] In this century, a major challenge in the area of drug discovery is the design of highly efficient chemical reaction sequences by minimum numbers of steps to get best activity. [5] Azetidinones are commonly known as β-lactam, they show broad range of biological activities. Azetidinones and thiazolidinone have played an exclusive role in biological as well as medicinal chemistry. Azetidin-2-one scaffold is a well-known saturated form of azetidin. It is nitrogen based cyclobutane containing β-lactam ring organic compound. It is the carbonyl derivatives of azetidines containing carbonyl group at position-2. A large number of 3-chloro monocyclic β-lactam exhibits potent antibacterial [6,7], antitubercular [8-10], antifungal [11,12], anticancer [13], antioxidant [14], anti-HIV [15], anti-inflammatory [16] etc. furthermore, thiazolidinone are also an effective analogues in the medicinal field, its derivatives also gives broad range of biological activities like anticonvulsant [17], hypnotic [18], anti-inflammatory [19], anticancer [20], antioxidant [21], antiproteolytic [22], antitubercular [23], anthelmintic [24], cardiovascular effects [25], antibacterial [26,27], antiviral [28], antifungal [29], insecticidal, herbicidal activities and an effective on the central nervous system and also function as enzyme inhibitors. The activity of some famous antibiotics such as Cephalosporin, Penicillin are attributed to the presence of 2-azetidinone moiety in their structure (Figure-1).

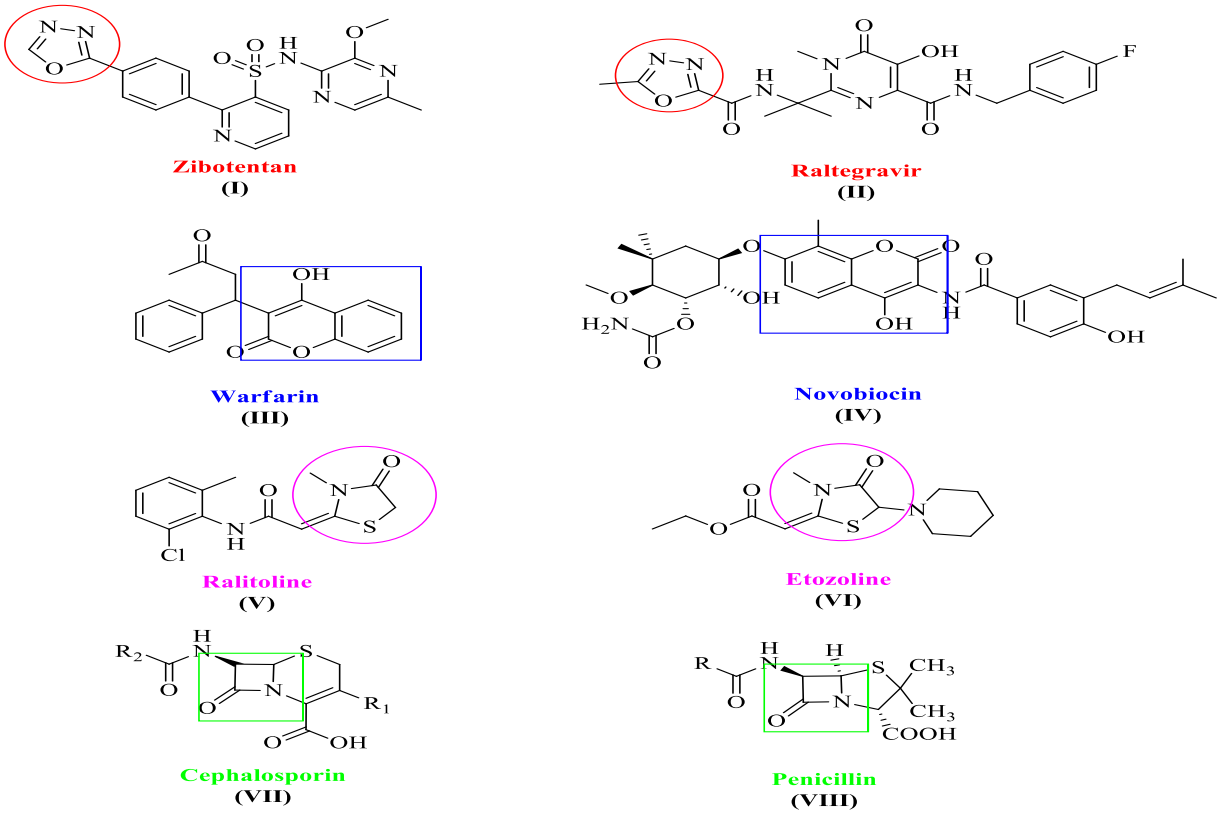
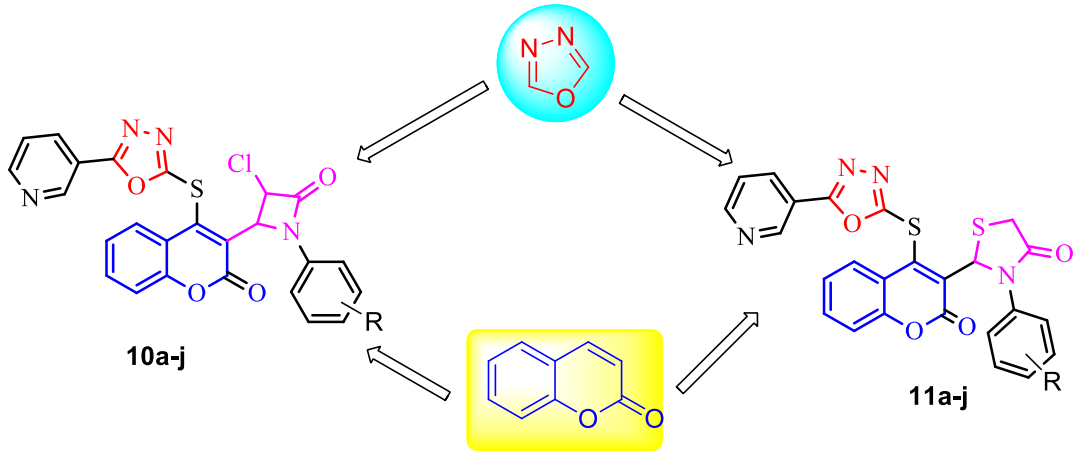


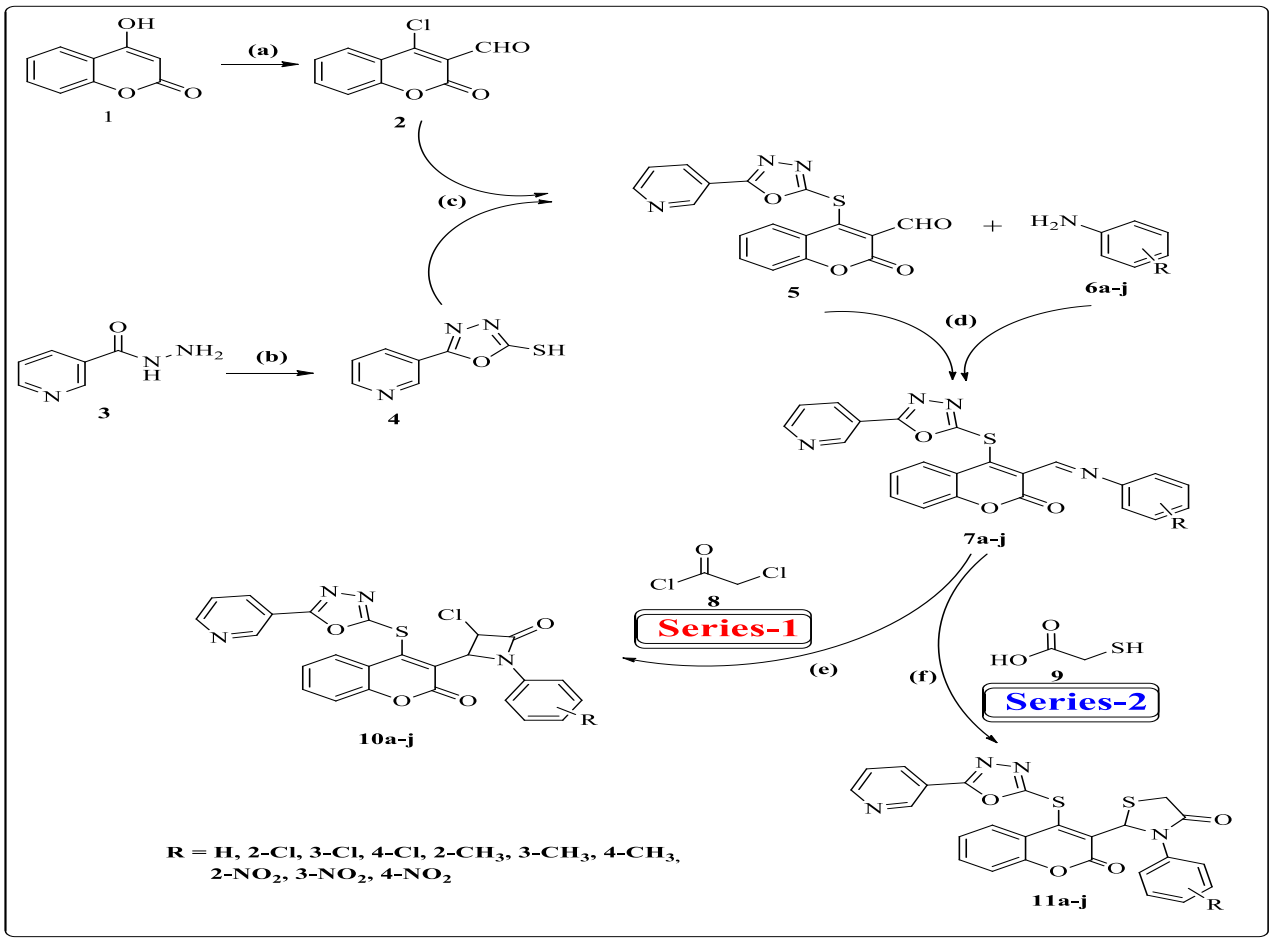
Figure 1: Drugs containing Oxadiazole (I, II), Coumarin (III, IV), Thiazolidinone (V, VI) and Azetidinone (VII,VIII) moieties

1,3,4-Oxadiazole is a heterocycle, an interesting bioactive scaffolds in the synthetic as well as natural compounds. It possess potent antibacterial properties. One of the most important diazole compound is 1,3,4-oxadiazole that contains five membered ring with two neighboring nitrogen and oxygen containing moiety. It's skeleton has considered as versatile occurring products. Among these, 1,3,4-oxadiazole used as an antifungal and antibacterial properties. The compounds of substituted oxadiazole play vital role in nature and they possess a broad range of biological properties such as antibacterial [30], antimycobacterial [31], antifungal [32], anti-inflammatory [33], analgesic [34], anticonvulsant [35] and anticancer [36] properties. One of the most important diazole compound is 1,3,4-oxadiazole that contains five membered ring with two neighboring nitrogens and one oxygen containing moiety. It's skeleton has considered as versatile building block of the naturally occurring products. Among these 1,3,4-oxadiazole used as an antifungal and antibacterial properties. Over the years, *2H*-chromen-2-ones are naturally occurring oxygen heterocyclic compounds. They are well-known forms of lactones ring containing benzopyrone skeletal which are found extensively in nature. The coumarin core is also present in various antibiotics such as coumermycin A_1, Chlorobiocin and Novobiocin [37]. Derivatives of coumarin possess versatile biological activities such as antifungal, anti-tubercular, antioxidant, antibacterial, anticancer, anti-inflammatory, antiviral, anticoagulant and anti-malarial properties [38]. As is well known antimicrobial agents Cephalosporin, Penicillin, Zibotentan, Raltegravir, Ralitoline, Etozoline, Warfarin and Novobiocin are all based on the keywords. (Figure-1). In the present articles, we have described the design and synthesis of a new series of azetidin-2-one and thiazolidin-4-one heterocycles derivatives by the combination of Oxadiazole and Coumarin (Figure-2). In the structure of 10a-j and 11a-j both different pharmacophores such as thiazole and coumarin merged by thio (-S-) linkage. These both pharmacophores rises antimicrobial activity. As a result, oxadiazole and coumarin comprising azetidin-2-one and thiazolidin-4-one moieties are expected much more enhanced activities. Thus, these observation encouraged us to synthesized new title derivatives.



CHEMISTRY

To accomplish the synthesis of desired compounds (10a-j) & (11a-j), the tracks outlined in Scheme-1 and 2 were implemented. It can be observed from the topography of 4-hydroxy coumarin that it has both nucleophilic and electrophilic properties. The most reactive site of 4-hydroxy coumarin at 3rd position of coumarin nucleus, it is required that motif 4-chloro-2-oxo-*2H*-chromen-3-carbaldehyde (2) was generated through Vilsmeier-Haack reaction from commercially available 4-hydroxy-chromen-2-one (1) [33,34] then compoundnicotinohydrazide (3) was treated with carbon disulphide in the presence of potassium hydroxide to yield 5-(pyridine-3-yl)-1,3,4-oxadiazol-2-thiol (4). Then compound (2) & (4) get combined in the presence of dimethyl formamide and potassium carbonate refluxed it to get compound (5) 2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromene-3-carbaldehyde. Then compound 5 is further treated with various amines (6a-j) in the presence of ethanol and glacial acetic acid to get compound (7a-j) 3-((substituted phenylimino)methyl)-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-2-one. Here the pathways to get title compounds are distributed. In Scheme-1 compounds (7a-j) were treated with chloroacetyl chloride (8) in triethyl amine using 1,4-dioxane as a solvent to get the title compounds (10a-j) and in Scheme-2 compounds (7a-j) were treated with thioglycolic acid (9) in presence of toluene as a solvent and get desired products (11a-j). The entire compounds were further confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral studies and elemental analysis.



2. MATERIALS AND METHODS

All the chemicals and solvents used for the synthesis work acquired from commercial sources were of analytical grade and used without further purification. Melting points were determined by using open capillary tubes and are uncorrect. TLC was check on E-merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light or iodine. NMR spectra were recorded on 400 MHz Briker Avance instrument using TMS as internal standard and measured chemical shift in δ ppm amd DMSO- d_6 as a solvent. Spectra were taken with a resonant frequency of 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The splitting patterns are designated as follows: s-singlet,: d-doublet: dd-double doublet: t-triplet and m-multiplet. Elemental analysis was done on "Haraeus Rapid Analyzer". The mass spectra were recorded on JOEL SX-102 (EI) model with 60 eV ionizing energy.

Synthesis of 4-chloro2-oxo-2H-chromen-3-carbaldehyde (Compound 2):

The formylating reagent prepared from phosphorus oxytrichloride (2.9 ml, 0.0189 mole) and *N,N'*-dimethyl formamide (2.4 ml, 0.0324 mole) at 0-5°C was added to 4-hydroxy-2H-chromen-2-one **1** (5.0 g, 0.0308 mole). The mixture was heated at 80-90°C for 10 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 cold water, filtered the precipitates and washed with water and recrystallized form methanol to get the title compound 2.

Synthesis of 5-(pyrin-3yl)-1,3,4-oxadiazol-2-thiol (Compound 4):

A combination of nicotine hydrazide (5.0 g, 0.0364 mole), carbon disulphide (2.19 ml, 0.0287 mole) and aqueous potassium hydroxide (50 %) (5.0 ml, 0.0171 mole) in methanol (20 ml) was stirred for 30 minutes at room temperature in a 150 ml conical flask. 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 an eluent. After the completion of reaction, reaction mixture was allowed to cool at room temperature and then poured in to cold water. The product thus obtained was subjected to filtrations followed by washing with water and was recrystallized from ethanol to get the desired compound 4.

Synthesis of 2-oxo-4-((5-pyridin-3-yl)- 1,3,4-oxadiazol-2-yl) thiol-2H- chromen-3-carbaldehyde (Compound 5):

The mixture of compound 2 (5.0 g, 0.0239 mole) and compound 4 (5.0 g, 0.0279 mole) were dissolved in 4.0 ml of dimethyl formamide and 8 ml of potassium carbonate solution in round bottom flask and stirred for 15 minutes. Keep on stirring for 15 minutes. Keep on stirring the reaction mixture at 0-5°C for 6 hours in ice-bath. Progress of the reaction was observed on TLC using ethyl acetate: hexane (5:5) solvent system. After completion of the reaction, reaction mixture was allowed to cool at room temperature and then pour it in the cold water. The product thus obtained which further purified by crystallization from ethanol to give compound 5.

General procedure for the synthesis of 3-(phenylimino) methyl)-4-((5-pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thiol)-2H-chromen-2-one (Compound 7a-j)

An equimolar mixture of compound 5 (5.0 g, 0.0142 mole) and various substituted anilines 6a-j (0.0143 mole) in ethanol (20 ml) and glacial acetic acid (0.5 ml) was 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 precipitates obtained were filtered washed with water and crystalline form methanol to get the title compounds 7a-j.

General procedure for the synthesis of 3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-1-Substituted phenylazetidin-2-one (Compounds 10a-j)

Compounds 7a-j was added to a constantly (3.0 g, 0.00703 mole) stirred solution of 1,4-dioxane (15 ml), triethyl amine (0.98 ml, 0.00976 mole) and chloro acetyl chloride compound 8 (0.56 ml, 0.00486 mole). The reaction mixture was stirred at 50°C. The reaction vessel was then kept at room temperature for 30 minutes and refluxed for 8 hours. On cooling the precipitates were obtained, which was filtered and thoroughly washed with water. The progress of reaction was monitored by TLC using ethyl acetate: hexane (5:5) solvent system. Purified the precipitates by charcoal method to get the title compounds 10a-j. All the series compounds were further synthesized by the same method which is given above.

General procedure for the synthesis of 2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-3-Substituted phenyl thiazolidin-4-one (Compounds 11a-j)

A mixture of thioglycolic acid (0.5 ml, 0.00532 mole) and compounds 7a-j (0.00703 mole) in toluene (10 ml) was refluxed for 10-12 hours. The water formed during the reaction was removed azeotropically by Dean-strack apparatus. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (3:7) as eluent. After the completion of the reaction the resultant mixture was poured in ice. Filtered and washed with 10 % NaHCO3 to remove unreacted acid. The solid left was separated by filtration and crystallized from methanol to get the title compounds 11a-j. All the series compounds were synthesized by the same method which is described above.

Table 1: Physical constant of newly synthesized compounds 10a-j and 11a-j

Comp. No.	-R	Molecular Formula	M.P. °C	Yield %	Elemental analysis			
						% C	% H	% N
10a	H	$C_{25}H_{15}ClN_4O_4S$	190	76	R F	59.70 59.68	3.01 3.04	11.14 11.17
10b	2-Cl	$C_{25}H_{14}Cl_2N_4O_4S$	199	72	R F	55.88 55.87	2.63 2.64	10.43 10.40
10c	3-Cl	$C_{25}H_{14}Cl_2N_4O_4S$	203	70	R F	55.88 55.82	2.63 2.68	10.43 10.44

10d	4-Cl	$C_{25}H_{14}Cl_2N_4O_4S$	208	73	R F	55.88 55.86	2.63 2.66	10.43 10.46
10e	2-CH_3	$C_{26}H_{17}ClN_4O_4S$	214	74	R F	60.41 60.48	3.31 3.35	10.84 10.87
10f	3-CH_3	$C_{26}H_{17}ClN_4O_4S$	218	75	R F	60.41 60.45	3.31 3.35	10.84 10.85
10g	4-CH_3	$C_{26}H_{17}ClN_4O_4S$	230	60	R F	60.41 60.39	3.31 3.29	10.84 10.78
10h	2-NO_2	$C_{25}H_{14}ClN_5O_6S$	234	64	R F	54.80 54.76	2.58 2.50	12.78 12.72
10i	3-NO_2	$C_{25}H_{14}ClN_5O_6S$	238	68	R F	54.80 54.84	2.58 2.62	12.78 12.82
10j	4-NO_2	$C_{25}H_{14}ClN_5O_6S$	188	72	R F	54.80 54.85	2.58 2.60	12.78 12.80
11a	H	$C_{25}H_{16}N_4O_4S_2$	194	62	R F	59.99 59.94	3.22 3.20	11.19 11.14
11b	2-Cl	$C_{25}H_{15}ClN_4O_4S_2$	199	50	R F	56.13 56.10	2.83 2.85	10.47 10.49
11c	3-Cl	$C_{25}H_{15}ClN_4O_4S_2$	203	54	R F	56.13 56.15	2.83 2.85	10.47 10.50
11d	4-Cl	$C_{25}H_{15}ClN_4O_4S_2$	224	56	R F	56.13 56.10	2.83 2.80	10.47 10.42
11e	2-CH_3	$C_{26}H_{18}N_4O_4S_2$	232	64	R F	60.69 60.62	3.53 3.50	10.89 10.82
11f	3-CH_3	$C_{26}H_{18}N_4O_4S_2$	236	58	R F	60.69 60.63	3.53 3.64	10.89 10.94
11g	4-CH_3	$C_{26}H_{18}N_4O_4S_2$	240	64	R F	60.69 60.71	3.53 3.61	10.89 10.91
11h	2-NO_2	$C_{25}H_{15}N_5O_6S_2$	248	68	R F	55.04 55.08	2.77 2.79	12.84 12.86
11i	3-NO_2	$C_{25}H_{15}N_5O_6S_2$	254	70	R F	55.04 55.09	2.77 2.80	12.84 12.91
11j	4-NO_2	$C_{25}H_{15}N_5O_6S_2$	232	72	R F	55.04 55.11	2.77 2.79	12.84 12.89

CHARACTERIZATION OF COMPOUNDS

Compound 10a:

3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)-1-phenylazetidin-2-one

White solid, Yield 76%; m.p. 190℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 7.003-7.677 (m, 9H, aromatic ring & coumarin), 7.731-8.655 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 59.94, 61.58, 113.20, 117.13, 120.27, 121.72, 123.62, 125.89, 126.24, 128.38, 128.87, 128.90, 133.14, 135.74, 137.67, 148.34, 148.89, 149.17, 150.65, 154.91, 159.43, 161.31, 164.60. Anal. calcd. For $C_{25}H_{15}ClN_4O_4S$: C, 59.70; H, 3.01; N, 11.14. Found: C, 59.68; H, 3.04; N, 11.17. ESIMS (m/z): 503.25 (M+).

Compound 10b:

3-chloro-1-(2-chlorophenyl)-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)azetidin-2-one

White solid, Yield 72%; m.p. 199℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 6.949-7.669 (m, 8H, aromatic ring & coumarin), 7.993-8.750 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 59.62, 61.58, 113.20, 117.13, 121.72, 123.62, 125.70, 125.89, 127.53, 127.90, 128.38, 128.90, 129.39, 132.95, 133.14, 135.74, 136.17, 148.34, 148.89, 149.17, 150.65, 154.91, 160.06, 161.31, 164.60. Anal. calcd. For $C_{25}H_{14}Cl_2N_4O_4S$: C, 55.88; H, 2.63; N, 10.43. Found: C, 55.87; H, 2.64; N, 10.40. ESIMS (m/z): 537.01 (M+).

Compound 10c:

3-chloro-1-(3-chlorophenyl)-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)azetidin-2-one

Off-white solid, Yield 70%; m.p. 203℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 6.926-7.410 (m, 8H, aromatic ring & coumarin), 7.549-8.817 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 59.94, 61.58, 113.20, 117.13, 117.49, 120.46, 121.72, 123.62, 125.42, 125.89, 128.38, 128.79, 128.90, 133.14, 134.45, 135.74, 140.42, 148.34, 148.89, 149.17, 150.65, 154.91, 159.43, 161.31, 164.60. Anal. calcd. For $C_{25}H_{14}Cl_2N_4O_4S$: C, 55.88; H, 2.63; N, 10.43. Found: C, 55.82; H, 2.68; N, 10.44. ESIMS (m/z): 537.01 (M+).

Compound 10d:

3-chloro-1-(4-chlorophenyl)-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)azetidin-2-one

White solid, Yield 73%; m.p. 208℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 7.116-7.687 (m, 8H, aromatic ring &

coumarin), 7.969-6.817 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ ppm: 59.94, 61.58, 113.20, 117.13, 120.56, 121.72, 123.62, 125.89, 128.38, 128.78, 128.90, 131.08, 133.14, 135.74, 137.33, 148.34, 148.89, 149.17, 150.65, 154.91, 159.43, 161.31, 164.60. Anal. calcd. For $C_{25}H_{14}Cl_2N_4O_4S$: C, 55.88; H, 2.63; N, 10.43. Found: C, 55.86; H, 2.66; N, 10.46. ESIMS (m/z): 537.01 (M+).

Compound 10e:

3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)-1-(o-tolyl) azetidin-2-one

Yellowish-white solid, Yield 74%; m.p. 214℃; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ ppm: 2.141 (s, 3H, methyl group), 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 6.926-7.665 (m, 8H, aromatic ring & coumarin), 7.951-8.775 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ ppm: 17.22, 59.62, 161.58, 113.20, 117.13, 121.22, 121.72, 12362, 125.89, 126.62, 128.16, 128.38, 128.90, 129.96, 133.14, 135.74, 136.37, 136.95, 148.34, 148.89, 14917, 150.65, 154.65, 154.91, 160.06, 161.31, 164.60. Anal. calcd. For $C_{26}H_{17}ClN_4O_4S$: C, 60.41; H, 3.31; N, 10.84. Found: C, 60.48; H, 3.35; N, 10.87. ESIMS (m/z): 517.07 (M+).

Compound 10f:

3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)-1-(m-tolyl)azetidin-2-one

Off-white solid, Yield 75%; m.p. 218℃; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ ppm: 2.328 (s, 3H, methyl group), 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 6.915-7.686 (m, 8H, aromatic ring & coumarin), 7.966-8.818 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ ppm: 21.20, 59.94, 61.56, 113.20, 117.13, 118.28, 121.72, 123.62, 125.52, 125.89, 128.38, 128.42, 128.90, 130.18, 133.14, 135.74, 139.24, 141.82, 148.34, 148.89, 150.65, 154.91, 159.43, 161.31, 164.60. Anal. calcd. For $C_{26}H_{17}ClN_4O_4S$: C, 60.41; H, 3.31; N, 10.84. Found: C, 60.45; H, 3.35; N, 10.85; ESIMS (m/z): 517.07 (M+).

Compound 10g:

3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-1-(p-tolyl)azetidin-2-one

White solid, Yield 60%; m.p. 230℃; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ ppm: 2.298 (s, 3H, methyl group), 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 7.119-7.687 (m, 8H, aromatic ring & coumarin), 7.965-8.813 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ ppm: 21.12, 59.94, 61.58, 113.20, 117.13, 121.72, 123.62, 125.59, 125.89, 128.38, 128.90, 130.97, 133.14, 133.60, 135.74, 136.77, 148.34, 148.89, 149.17, 150.65, 154.91, 159.43, 161.31, 164.60 . Anal. calcd. For $C_{26}H_{17}ClN_4O_4S$: C, 60.41; H, 3.31; N, 10.84. Found: C, 60.39; H, 3.29; N, 10.78. ESIMS (m/z): 517.07 (M+).

Compound 10h:

3-chloro-1-(2-nitrophenyl)-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)azetidin-2-one

Yellowish-white solid, Yield 64%; m.p. 234°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 7.196-7.678 (m, 8H, aromatic ring & coumarin), 7.966-8.829 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 59.62, 61.58, 113.20, 117.13, 121.72, 122.69, 123.62, 125.89, 126.19, 126.56, 128.38, 128.90, 133.09, 133.14, 135.21, 135.74, 141.99, 148.34, 14889, 149.71, 150.95, 154.91, 160.06, 161.31, 164.60. Anal. calcd. For $C_{25}H_{14}ClN_5O_6S$: C, 54.80; H, 2.58; N, 12.78. Found: C, 54.76; H, 2.50; N, 12.72. ESIMS (m/z): 548.04 (M+).

Compound 10i:

3-chloro-1-(3-nitrophenyl)-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)azetidin-2-one

Dark yellow solid, Yield 68%; m.p. 238°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 7.202-8.126 (m, 8H, aromatic ring & coumarin), 8.316-8.824 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 59.94, 61.58, 113.20, 115.45, 117.13, 121.72, 121.75, 123.33, 123.62, 125.89, 128.38, 128.90, 130.88, 133.14, 135.74, 139.03, 148.34, 148.89, 149.17, 150.33, 150.65, 154.91, 159.43, 161.31, 164.60. Anal. calcd. For $C_{25}H_{14}ClN_5O_6S$: C, 54.80; H, 2.58; N, 12.78. Found: C, 54.84; H, 2.62; N, 12.82. ESIMS (m/z): 548.04 (M+).

Compound 10j:

3-chloro-1-(4-nitrophenyl)-4-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)azetidin-2-one

Light Yellow solid, Yield 72%; m.p. 188°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 4.560 (d, *J*=6.2 Hz, 1H, azetidinone), 5.090 (d, *J*=5.8 Hz, 1H, azetidinone), 7.208-7.996 (m, 8H, aromatic ring & coumarin), 8.188-8.649 (m, 4H, pyrimidine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 59.94, 61.58, 113.20, 117.13, 121.72, 123.62, 125.35, 125.49, 125.89, 128.38, 128.90, 133.14, 135.74, 141.62, 147.29, 148.34, 148.89, 149.17, 150.65, 154.91, 159.43, 161.31, 164.60. Anal. calcd. For $C_{25}H_{14}ClN_5O_6S$: C, 54.80; H, 2.58; N, 12.78. Found: C, 54.85; H, 2.60; N, 12.80. ESIMS (m/z): 548.04 (M+).

Compound 11a:

2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)-3-phenylthiazolidin-4-one

White solid, Yield 62%; m.p. 194°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.483 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 7.163-7.543 (m, 9H, aromatic ring and coumarin) and 7.604-8.797 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 34.57, 55.38, 104.84,

117.13, 123.62, 125.83, 125.89, 127.44, 128.90, 129.61, 133.14, 135.74, 148.34, 149.17, 150.41, 150.65, 152.95, 154.91, 164.60, 175.01; Anal. calcd. For $C_{25}H_{16}N_4O_4S_2$: C, 59.99; H, 3.22; N, 11.19. Found: C, 59.94; H, 3.20; N, 11.14. ESIMS (m/z): 500.06 (M+).

Compound 11b:

3-(2-chlorophenyl)-2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl) thiazolidin-4-one

Off-white solid, Yield 50%; m.p. 199℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.647 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 6.490-7.649 (m, 8H, aromatic ring and coumarin) and 7.965-8.649 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 34.57, 55.61, 104.84, 117.13, 123.62, 125.89, 127.90, 128.52, 128.90, 130.23, 130.25, 132.87, 133.14, 135.74, 148.34, 149.17, 150.41, 150.65, 152.95, 154.91, 164.60, 173.14; Anal. calcd. For $C_{25}H_{15}ClN_4O_4S_2$: C, 56.13; H, 2.83; N, 10.47. Found: C, 56.10; H, 2.85; N, 10.49. ESIMS (m/z): 534.02 (M+).

Compound 11c:

3-(3-chlorophenyl)-2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl) thiazolidin-4-one

White solid, Yield 54%; m.p. 203℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.607 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 7.017-7.649 (m, 8H, aromatic ring and coumarin) and 7.972-8.825 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 34.57, 55.38, 104.84, 117.13, 121.72, 122.70, 123.62, 125.00, 125.47, 125.89, 128.90, 129.12, 133.14, 133.74, 135.74, 148.34, 149.17, 150.41, 150.65, 152.95, 154.91, 164.60, 175.01; Anal. calcd. For $C_{25}H_{15}ClN_4O_4S_2$: C, 56.13; H, 2.83; N, 10.47. Found: C, 56.15; H, 2.85; N, 10.50. ESIMS (m/z): 534.02 (M+).

Compound 11d:

3-(4-chlorophenyl)-2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl) thiazolidin-4-one

Brown solid, Yield 56%; m.p. 224℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.450 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 7.139-7.550 (m, 8H, aromatic ring and coumarin) and 7.602-8.759 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 34.57, 55.38, 104.84, 117.13, 123.62, 125.83, 125.89, 128.90, 129.61, 133.14, 135.74, 135.74, 135.77, 148.34, 149.17, 150.41, 150.65, 152.95, 154.91, 164.60, 175.01; Anal. calcd. For $C_{25}H_{15}ClN_4O_4S_2$: C, 56.13; H, 2.83; N, 10.47. Found: C, 56.10; H, 2.80; N, 10.42. ESIMS (m/z): 534.02 (M+).

Compound 11e:

2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)-3-(o-tolyl) thiazolidin-4-one

White solid, Yield 64%; m.p. 232℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.259 (s, 3H, methyl group), 3.652 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 6.908-7.550 (m, 8H, aromatic

ring and coumarin) and 7.638-8.649 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 17.22, 34.57, 55.61, 104.84, 117.13, 123.62, 125.89, 126.78, 127.30, 128.38, 128.39, 128.90, 13116, 133.14, 135.74, 148.34, 149.17, 150.41, 150.65, 152.95, 154.91, 164.60, 173.14; Anal. calcd. For $C_{26}H_{18}N_4O_4S_2$: C, 60.69; H, 3.53; N, 10.89. Found: C, 60.62; H, 3.50; N, 10.82. ESIMS (m/z): 514.08 (M+).

Compound 11f:

2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)-3-(m-tolyl) thiazolidin-4-one

White solid, Yield 58%; m.p. 236℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.314 (s, 3H, methyl group),3.476 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 6.957-7.545 (m, 8H, aromatic ring and coumarin) and 7.691-8.797 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 21.20, 34.57, 55.38, 104.84, 117.13, 121.72, 121.95, 123.57, 123.62, 125.89, 128.90, 129.84, 130.09, 133.14, 135.74, 137.83, 148.34, 149.17, 150.41, 150.65, 152.95, 154.91, 164.60, 175.01; Anal. calcd. For $C_{26}H_{18}N_4O_4S_2$: C, 60.69; H, 3.53; N, 10.89. Found: C, 60.63; H, 3.64; N, 10.94. ESIMS (m/z): 514.08 (M+).

Compound 11g:

2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)-3-(p-tolyl) thiazolidin-4-one

Off-white solid, Yield 64%; m.p. 240℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.281 (s, 3H, methyl group), 3.474 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 7.126-7.545 (m, 8H, aromatic ring and coumarin) and 7.691-8.797 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 21.12, 34.57, 55.38, 104.84, 117.13, 121.72, 122.28, 123.62, 125.89, 128.90, 130.83, 133.14, 134.73, 15.74, 148.34, 149.17, 150.41, 150.65, 152.95, 154.91, 164.60, 175.01; Anal. calcd. For $C_{26}H_{18}N_4O_4S_2$: C, 60.69; H, 3.53; N, 10.89. Found: C, 60.71; H, 3.61; N, 10.91. ESIMS (m/z): 514.08 (M+).

Compound 11h:

3-(2-nitrophenyl)-2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl) thiazolidin-4-one

Dark Yellow solid, Yield 68%; m.p. 248℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.539 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 7.162-7.545 (m, 8H, aromatic ring and coumarin) and 7.669-8.632 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 34.57, 55.61, 104.84, 117.13, 123.62, 125.72, 125.89, 127.24, 128.33, 128.90, 133.14, 135.51, 135.74, 142.57, 148.34, 149.71, 150.41, 150.65, 152.95, 154.91, 164.60, 173.14; Anal. calcd. For $C_{25}H_{15}N_5O_6S_2$: C, 55.04; H, 2.77; N, 12.84. Found: C, 55.08; H, 2.79; N, 12.86. ESIMS (m/z): 545.05 (M+).

Compound 11i:

3-(3-nitrophenyl)-2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl)

thiazolidin-4-one

Light Yellow solid, Yield 70%; m.p. 254℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.626 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 7.177-7.647 (m, 8H, aromatic ring and coumarin) and 7.977-8.776 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 34.57, 55.38, 104.84, 117.13, 121.56, 121.72, 121.75, 123.62, 125.89, 128.90, 129.220, 131.46, 133.14, 135.74, 143.90, 144.83, 148.34, 149.17, 150.41, 150.65, 152.95, 164.60, 175.01; Anal. calcd. For $C_{25}H_{15}N_5O_6S_2$: C, 55.04; H, 2.77; N, 12.84. Found: C, 55.09; H, 2.80; N, 12.91. ESIMS (m/z): 545.05 (M+).

Compound 11j:

3-(4-nitrophenyl)-2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*2H*-chromen-3-yl) thiazolidin-4-one

Yellow solid, Yield 72%; m.p. 232℃; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.439 (s, 2H, thiazolidinone), 6.069 (s, 1H, thiazolidinone), 7.201-7.972 (m, 8H, aromatic ring and coumarin) and 8.184-8.596 (m, 4H, pyridine ring); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 34.57, 55.38, 104.84, 117.13, 121.72, 121.79, 123.62, 125.89, 126.27, 128.90, 133.14, 135.74, 143.909, 144.863, 148.34, 149.17, 150.41, 150.65, 152.95, 164.60, 175.01; Anal. calcd. For $C_{25}H_{15}N_5O_6S_2$: C, 55.04; H, 2.77; N, 12.84. Found: C, 55.11; H, 2.79; N, 12.89. ESIMS (m/z): 545.05 (M+).

3. RESULTS AND DISCUSSION

In Vitro Antibacterial Activity

In this series, we have synthesized a series of compounds containing azetidinyl-oxadiazole and thiazolidinyl-oxadiazole fused motif with coumarin through sulphur bridge. Functionalization has been done on phenyl nucleus of azetidinone ring to develop different compounds. It has been twigged that the test compounds (10a-j & 11a-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 i.e. 10b, 10d, 11b and 11d showed very good potency against specific bacterial strain. The final derivatives containing electron withdrawing nitro group i.e. 10h, 10j, 11h and 11j 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 and thiazolidinone compounds i.e. 10a and 11a 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 2: *In vitro* antibacterial activity of newly synthesized compounds 10a-j & 11a-j

Compounds	Minimal inhibitory concentration (µG/ml)				
	-R	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococcus Pyogenes*
		MTCC 442	MTCC 441	MTCC 96	MTCC 443
10a	H	50	100	100	100
10b	2-Cl	25	50	100	62.5
10c	3-Cl	50	50	100	50
10d	4-Cl	50	62.5	125	50
10e	2-CH_3	200	250	500	500
10f	3-CH_3	100	62.5	500	500
10g	4-CH_3	125	200	250	100
10h	2-NO_2	100	25	100	50
10i	3-NO_2	62.5	50	100	50
10j	4-NO_2	100	62.5	62.5	50
11a	H	25	100	100	125
11b	2-Cl	25	100	100	62.5
11c	3-Cl	50	50	100	100
11d	4-Cl	50	62.5	100	100
11e	2-CH_3	200	250	500	250
11f	3-CH_3	100	62.5	500	250
11g	4-CH_3	100	200	250	100
11h	2-NO_2	100	25	100	50
11i	3-NO_2	62.5	100	62.5	50
11j	4-NO_2	100	50	100	50
Ciprofloxacin	-	25	25	50	50
Chloramphenicol	-	50	50	50	50

***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 compounds 10a and 11a exhibited virtuous inhibition against the fungal strain *A. clavatus*. Furthermore, compounds 10b, 10c, 10i, 10j, 11b, 11c, 11i and 11j 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

Table 3. *In vitro* antifungal activity of newly synthesized compounds 10a-j & 11a-j

Compounds	Minimal fungicidal concentration (µg/ml)			
	-R	*Candida albicans*	*Aspergillus niger*	*Aspergillus clavatus*
		MTCC 227	MTCC 282	MTCC 1323
10a	H	100	500	250
10b	2-Cl	250	250	500
10c	3-Cl	100	500	100
10d	4-Cl	500	100	250
10e	2-CH_3	1000	>10000	>1000
10f	3-CH_3	500	1000	1000
10g	4-CH_3	500	1000	1000
10h	2-NO_2	250	100	250
10i	3-NO_2	500	250	250
10j	4-NO_2	250	500	500
11a	H	1000	>1000	>1000
11b	2-Cl	200	250	200
11c	3-Cl	100	500	500
11d	4-Cl	200	>1000	>1000
11e	2-CH_3	250	500	500
11f	3-CH_3	1000	500	500
11g	4-CH_3	>1000	>1000	>1000
11h	2-NO_2	>1000	>1000	>1000
11i	3-NO_2	500	500	500
11j	4-NO_2	100	1000	1000
Nystatin	-	100	100	100
Griseofulvin	-	500	100	100

4. CONCLUSION

The goal of our research work was the synthesis of new scaffolds without existing prior art. In conclusions we 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 phenylazetidin-2-one (10a-j) and 2-(2-oxo-4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-3-Substituted phenyl thiazolidin-4-one (11a-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 7a-j were evaluated and it was revealed that compounds are 10a, 10b, 10c, 10d, 11a, 11b, 11c, 11d, 10h, 11h, 10i, 11i, 10j and 11j 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 of 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.

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CONFLICT OF INTEREST

Authors don't have any conflict of interest.

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