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Synthesis and Antimicrobial Study of Novel Heterocycles Containing Azetidinone, Benzotriazole and 1,3,4-Oxadiazole Moieties

Keyur M. Pandya[a]*, Piyush S. Desai[b], Navin B. Patel[c] and Bhavesh P. Dave[d]

[ab]*Department of Chemistry, Arts, Science and Commerce College, Veer Narmad South Gujrat University, Surat, Gujrat, India.*
[c]*Department of Chemistry, Veer Narmad South Gujarat University, Surat, Gujarat, India.*
[d]*Department of Chemistry, M.B.Patel Science College, Sardar Patel University, Anand, Gujarat, India.*
*E-mail: pandya.keyurkumar@gmail.com**
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Abstract: To design, synthesize and characterize a novel series of N-(2-Substituted-3-chloro-4-oxoazetidine-1-yl)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3] triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamide and evaluate for antimicrobial activity. All compounds were structurally elucidated on the basis of spectroscopic and elemental analysis. The microbial screening was carried out by employing a broth dilution method. The zone of inhibition (µg/mL) of each compound was determined and compared with that of standard drugs Penicillin and Streptomycin. Some of the derivatives found to be potent against the bacterial strain.

Keywords: Benzotriazole; Oxadiazole; Azetidinone; Antimicrobial.

Introduction

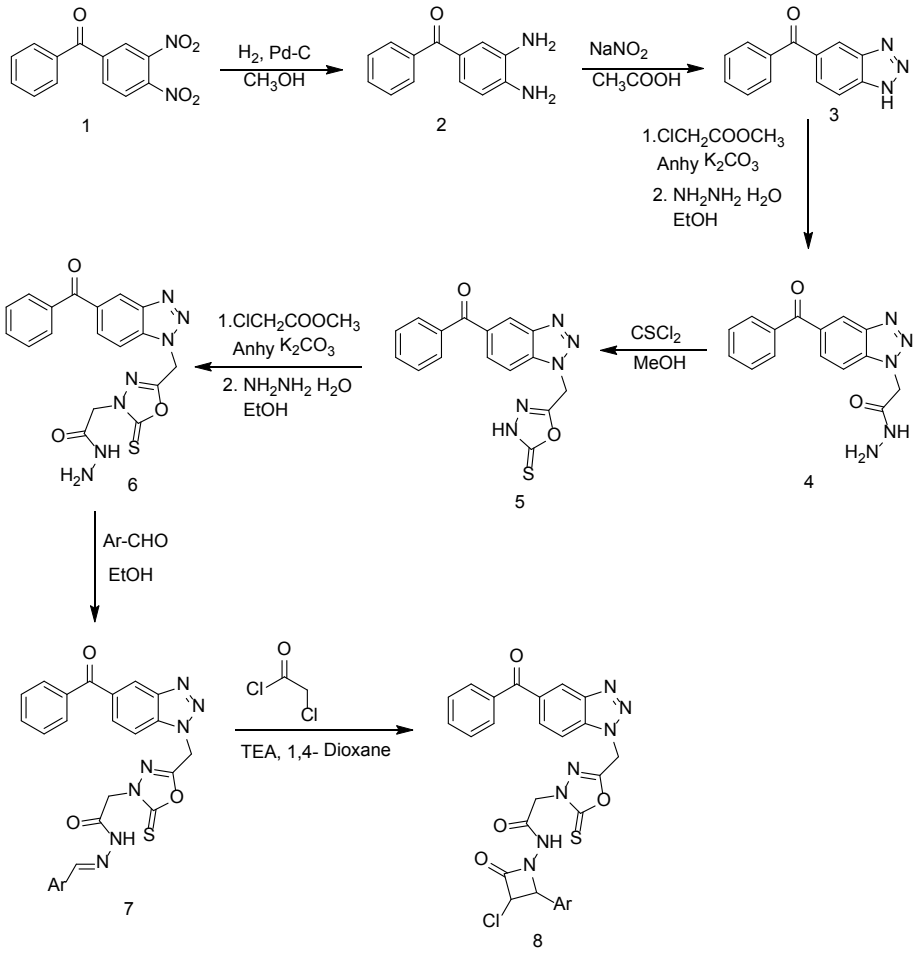
Research on new drugs possessing antibacterial activity has drawn attention owing to the continuing increase in bacterial resistance. Further, infection caused by various microorganisms pose a serious challenge to the medical community, and the need for an effective therapy has led to the search for novel antimicrobial agents.

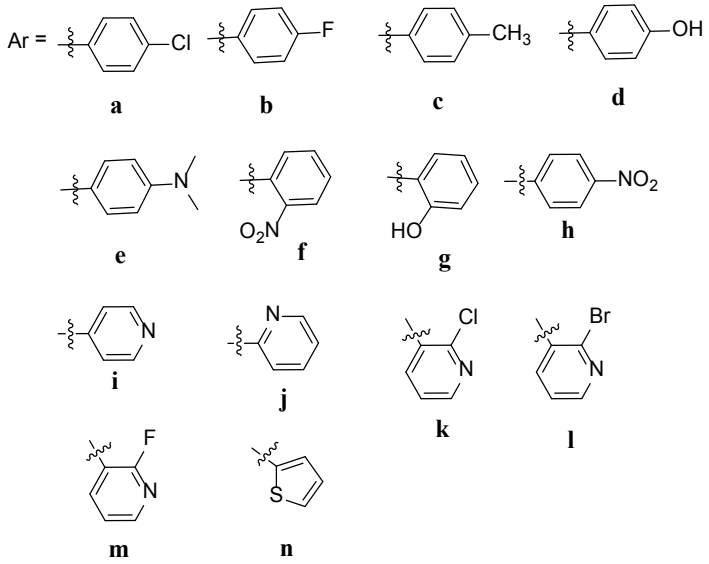
In the present study we report the synthesis and antimicrobial activity of novel heterocycles containing benzotriazole, azetidinone and 1,3,4 oxadiazoles moieties Substituted benzotriazoles[1,2] have biological and chemical assets that are flexible in the pharmaceutical industry. Benzotriazole derivatives operate as an agonist for several proteins. As vorozole and alizapride have valuable inhibitory properties in contrast to distinct proteins and benzotriazole esters have been stated to perform as mechanism-

based fascinator for many acute respiratory syndrome 3CL proteases. [3] Benzo condensed azoles are a class of heterocyclic molecules of that area attractive to medicinal chemistry field owing to their properties and applications. Benzimidazole and its derivatives have been evaluated for years [4] and drugs containing this heterocycle scaffold as central element have been broadly used for their pharmaceutical properties, for example, as anthelmintic in humans. [5] Benzo-fused azole consists of three heteroatoms, which are benzoxazole, benzothiazole and benzotriazole [6,7] and have been widely investigated for their thorough length biological activity. Benzotriazole is enduring expeditious growth in the synthesis of heterocycles since it can be used a template to construct novel biologically active molecules. It is also served as a synthetic supplement [8-13] as well as leaving group after reaction with different carbonyl groups [14-16].

The recent literature demonstrated that the oxadiazoles and azetidinones were becoming of immense practical implication, which interests mainly drug synthesis, polymers [17], dyes etc. Specifically, substituted oxadiazoles and azetidinones have gained the prime consideration for decades as active biomolecules [18]. These investigations and curiosity in the research work based on a synthesis of novel benzotriazole clubbed with oxadiazole upon addition of lactam ring led us to evaluate their potency against pathogenic bacteria since benzotriazole coupled with oxadiazoles exhibit activity like antibacterial [19], antifungal, anticancer [20] and anti-inflammatory [21] activities.

Results and Discussion





Scheme 1. The synthesis of compounds **8a-n**.

Biological Evaluation

Antibacterial Activity

All the synthesized compounds were screened for their minimum inhibitory Concentration (MIC, µg/mL) against two gram-positive (Staphylococcus aureus and Bacillus subtilis) and two gram-negative (Escherichia coli and Pseudomonas aeruginosa) bacteria by the broth dilution method as recommended by the National Committee for Clinical Laboratory Standards. Penicillin and Streptomycin were used as standard antibacterial agents. Solutions of the tested compounds and reference drugs were dissolved in dimethylsulfoxide at preparative concentrations of 100, 50, 25, 12.5, and 6.25 µg/mL. The chemical compound broth medium in serial test tube dilution inoculated with each bacterium was incubated on a rotary shaker at 37º C for 24h at 150 rpm. The incubation chamber was kept humid at the end of the incubation period, MIC values were recorded as the lowest concentration of the substance that give no visible turbidity, i.e. no growth of inoculated bacteria. Table 1, suggest that compounds 8a, 8k and 8l are highly active against S. aureus and B. Subtilis respectively. Compounds 8b and 8e are also highly active against P. aeruginosa and E. coli. The rest of the compounds were found to be either moderately active, slightly active or inactive against the examined microorganisms.

Table 1: Results of in vitro antibacterial activity.

MIC (µg/ML)				
Compound	**Gram positive bacteria**		**Gram negative bacteria**	
	S. aureus	B. subtilis	P. aeruginosa	E.coli
Penicillin	1.562	1.562	6.25	12.5
Streptomycin	6.25	6.25	3.125	3.125
8a	6.25	6.25	-	50
8b	50	50	8.25	12.5
8c	25	50	-	50
8d	25	12.5	-	25
8e	50	25	-	13.5
8f	25	12.5	-	50
8g	12.5	50	25	50
8h	25	25	-	25
8i	50	25	-	25
8j	12.5	12.5	-	25
8k	6.25	6.25	-	50
8l	6.25	6.25	25	25
8m	12.5	12.5	-	50
8n	25	50	-	25

Experimental

Materials

All the reactants were of reagent grade, and purchased from Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from local suppliers. TLC plates (Silica Gel) were purchased from Sigma-Aldrich.

Instrumentation

Melting points were determined in open capillary tubes on a Stuart SMP 10 melting point apparatus and are uncorrected. Nuclear Magnetic Spectroscopy (NMR) NMR spectra were produced using the Varian 300 MHz spectrophotometer. The instrument was maintained at 25° C operating at 300 MHz for ^{1}H NMR, and 75 MHz for ^{13}C NMR. The deuterated solvent (DMSO-d_6) used for each respective spectrum is referenced to the appropriate literature peak shift. C, H, N elemental analysis was carried out on a PerkinElmer 2400.

*General Procedure for the Synthesis of Compound **2**.*

Compound **1** (1 eq.) was dissolved in methanol (15 ml), and 10% Pd–C (10 eq.) was added into the solution. The reaction mixture was stirred at room temperature under an H_2 atmosphere. After 22 h, the mixture was passed through a membrane filter to remove the catalyst and then evaporated under vacuum to afford compound **2** (yield ~90.3%).

*General Procedure for the Synthesis of Compound **3**.*

In a solution of (3,4-diaminophenyl) (phenyl) methanone **2** (2 mmol), in acetic acid (15 mL) was added at 5°C the sodium nitrite (0.30 g, 4.34 mmol) and irradiated in a water bath of the ultrasonic cleaner at 5-10° C for 15-20min. After 15-20 Min, the solvent was removed, the organic phase extracted with methylene dichloride (50 mL), washed with water (5 X 10 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the products were isolated with a satisfactory purity. [23]

*General Procedure for the Synthesis of Compound **4**.*

To the solution of reactant **3** (1eq.) in absolute Methanol (65ml), methyl chloroacetate (1eq.), hydrazine monohydrate and anhydrous K_2CO_3 (1eq.) were added and the reaction mixture was heated under reflux for 16hrs. The potassium salt was filtered off and the excess of ethanol was removed. The residue solidified on cooling to give the desired product. [24,25]

*General Procedure for the Synthesis of Compound **5**.*

A Mixture of compound **4** (1eq.) was added in MeOH (150ml), potassium hydroxide (0.5eq) and heated with $CSCl_2$ (1eq.) and refluxed for about 12hrs at 65º C. The separated solid was filtered, dried in vacuum and purified over a column of silica gel, eluted with C_6H_6: $CHCl_3$ (2:8 v/v) mixture to give a final product which was crystallized with $CHCl_3$[26]

*General Procedure for the Synthesis of Compound **6**.*

To the solution of reactant **5** (1eq.) in absolute Methanol (70ml), methyl chloroacetate (1eq.), hydrazine monohydrate and anhydrous K_2CO_3 (0.01mol) were added and the reaction mixture was heated under reflux for 19hrs. The potassium salt was filtered off and the excess of ethanol was removed. The residue solidified on cooling to give the product. [27]

*General Procedure for the Synthesis of Compound **7a-n**.*

Take the compound **6** and Aromatic aldehyde

(listed in scheme 1) in a molar ratio (1:1 or 1:2) and make soluble in the EtOH (160ml) and reflux in for about 7-8hrs at 79º C with a catalytic amount of glacial acetic acid (1-2 drops) on a water bath. The product will be separated, recrystallized it from EtOH. [28]

*General Procedure for the Synthesis of Compound **8a-n**.*

A mixture compound **7** (1eq.) and triethylamine (TEA) (0.5 eq.) were dissolved in 1,4-dioxane (70mL), cooled and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.5 eq.) was added dropwise within a period of 30Min. The reaction mixture was stirred for an additional 6 hours and left at room temperature for 3days. After completion of the reaction (TLC). The resultant mixture was concentrated, poured into ice-cold water and then air dried the crude product was purified column chromatography (100:200 silica gel, 25:75 ethyl DCM: MeOH) to give **8a-n** as colourless solid. [29]

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)acetamide (8a) Yield: 62.2 %; colorless solid, mp 152 – 153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, *J* = 2.2, 0.5 Hz, 1H), 8.09 (dd, *J* = 10.2, 0.5 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.87 (d, *J* = 2.2 Hz, 0H), 7.84 – 7.78 (m, 2H), 7.64 – 7.56 (m, 1H), 7.54 – 7.49 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.35 (m, 2H), 5.51 (d, *J* = 5.3 Hz, 1H), 5.18 (dt, *J* = 5.3, 0.6 Hz, 1H), 4.66 (s, 1H), 4.51 – 4.41 (m, 2H), 4.25 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.9, 181.4, 171.0, 168.8, 143.3, 142.6, 137.6, 137.1, 133.6, 133.3, 132.3, 131.9, 129.7, 129.1, 128.9, 128.5, 127.6, 118.0, 110.1, 69.0, 64.6, 48.0, 44.8. ESIMS: m/z calculated for $C_{27}H_{19}Cl_2N_7O_4S$ $(M+H)^+$ 608.06 found 608.05, Anal. Calc. for $C_{27}H_{19}Cl_2N_7O_4S$: C, 53.30; H, 3.15; N, 16.11%; found: C, 53.29; H, 3.14; N, 16.11%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)acetamide (8b) Yield: 66 %; colorless solid, mp 144 – 145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, *J* = 2.2, 0.5 Hz, 1H), 8.09 (dd, *J* = 10.2, 0.5 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.87 (d, *J* = 2.2 Hz, 0H), 7.85 – 7.78 (m, 2H), 7.64 – 7.55 (m, 1H), 7.52 (t, *J* = 0.8 Hz, 1H), 7.51 – 7.42 (m, 3H), 7.16 – 7.08 (m, 2H), 5.51 (d, *J* = 5.3 Hz, 1H), 5.18 (dd, *J* = 5.3, 0.7 Hz, 1H), 4.66 (s, 1H), 4.51 – 4.40 (m, 2H), 4.25 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.9, 181.4, 171.0, 168.8, 164.5, 161.1, 143.3, 142.6, 137.6, 135.7, 135.7, 133.6, 133.3, 131.9, 129.7, 128.9, 128.5, 127.7, 127.6, 118.0, 116.08, 115.8, 110.1, 69.0, 64.6, 48.0, 44.7. ESIMS: m/z calculated for $C_{27}H_{19}ClFN_7O_4S$ $(M+H)^+$ 520.09 found 520.07, Anal. Calc. for $C_{27}H_{19}ClFN_7O_4S$: C, 54.78; H, 3.24; N, 16.56%; found: C, 54.77; H, 3.22; N, 16.55%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-oxo-4-(p-tolyl)azetidin-1-yl)acetamide (8c) Yield: 59.7 %; colorless solid, mp 152 – 154 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, *J* = 2.2, 0.5 Hz, 1H), 8.08 – 8.06 (m, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.64 – 7.56 (m, 1H), 7.54 – 7.46 (m, 2H), 6.96 (dq, *J* = 8.1, 0.7 Hz, 2H), 6.91 – 6.86 (m, 2H), 5.51 (d, *J* = 5.3 Hz, 1H), 5.18 (dt, *J* = 5.3, 0.7 Hz, 1H), 4.66 (s, 1H), 4.51 – 4.40 (m, 2H), 4.25 (s, 1H), 4.21 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.9, 181.4, 171.0, 168.7, 143.2, 142.6, 137.6, 136.7, 136.5, 133.6, 133.2, 131.9, 129.7, 129.5, 128.9, 128.4, 126.8, 118.0, 110.1, 69.0, 64.6, 48.0, 44.7, 18.9. ESIMS: m/z calculated for $C_{28}H_{22}ClN_7O_4S$ $(M+H)^+$ 588.11 found 588.1, Anal. Calc. for $C_{28}H_{22}ClN_7O_4S$: C, 57.19; H, 3.77; N, 16.67%; found: C, 57.19; H, 3.76; N, 16.66%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-

1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)acetamide (8d) Yield: 63.4 %; colorless solid, mp 142 – 144 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 9.21 (s, 1H), 8.42 (dd, *J* = 2.2, 0.6 Hz, 1H), 8.07 (d, *J* = 0.4 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.64 – 7.55 (m, 1H), 7.54 – 7.45 (m, 2H), 7.06 – 6.99 (m, 2H), 6.72 – 6.66 (m, 2H), 5.51 (d, *J* = 5.3 Hz, 1H), 5.18 (dt, *J* = 5.3, 0.7 Hz, 1H), 4.66 (s, 1H), 4.51 – 4.40 (m, 2H), 4.25 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 168.7, 157.6, 143.2, 142.6, 137.6, 133.6, 133.3, 132.7, 131.9, 129.7, 128.9, 128.5, 127.3, 118.0, 115.6, 110.1, 69.0, 64.7, 48.0, 44.8. ESIMS: m/z calculated for $C_{27}H_{20}ClN_7O_5S$ $(M+H)^+$ 590.09 found 590.09, Anal. Calc. for $C_{27}H_{20}ClN_7O_5S$: C, 54.96; H, 3.42; N, 16.62%; found: C, 54.96; H, 3.40; N, 16.61%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)acetamide (8e) Yield: 57.1 %; colorless solid, mp 169 – 170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, *J* = 2.2, 0.5 Hz, 1H), 8.09 (dd, *J* = 10.2, 0.4 Hz, 1H), 7.89 (dd, *J* = 10.2, 2.2 Hz, 1H), 7.82 (t, *J* = 1.3 Hz, 1H), 7.80 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.52 (t, *J* = 0.8 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.13 (d, *J* = 0.7 Hz, 1H), 7.11 (d, *J* = 0.7 Hz, 1H), 6.72 (d, *J* = 1.3 Hz, 1H), 6.70 (d, *J* = 1.3 Hz, 1H), 5.51 (d, *J* = 5.3 Hz, 1H), 5.18 (dt, *J* = 5.2, 0.6 Hz, 1H), 4.72 (s, 0H), 4.66 (s, 1H), 4.51 – 4.40 (m, 2H), 4.25 (s, 1H), 3.00 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 197.8, 181.3, 171.0, 168.7, 151.2, 143.2, 142.6, 137.6, 133.6, 133.2, 131.9, 130.8, 129.7, 128.9, 128.4, 126.7, 118.09, 116.2, 110.1, 69.0, 64.6, 48.0, 44.7, 39.9. ESIMS: m/z calculated for $C_{29}H_{25}ClN_8O_4S$ $(M+H)^+$ 617.14 found 617.13, Anal. Calc. for $C_{29}H_{25}ClN_8O_4S$: C, 56.45; H, 4.08; N, 18.16%; found: C, 56.44; H, 4.06; N, 18.16%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl)acetamide (8f) Yield: 52.4 %; colorless solid, mp 166 – 167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, *J* = 2.2, 0.5 Hz, 1H), 8.12 – 8.06 (m, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.89 (dd, *J* = 10.2, 2.2 Hz, 1H), 7.82 (t, *J* = 1.3 Hz, 1H), 7.80 (dd, *J* = 2.1, 1.3 Hz, 1H), 7.72 (td, *J* = 7.5, 1.6 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.54 – 7.46 (m, 2H), 5.51 (d, *J* = 5.0 Hz, 1H), 5.18 (dd, *J* = 5.0, 0.6 Hz, 1H), 4.66 (s, 1H), 4.51 – 4.41 (m, 2H), 4.21 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 168.7, 155.5, 143.2, 142.6, 137.6, 133.6, 133.2, 131.9, 130.5, 130.3, 129.7, 128.9, 128.4, 127.7, 126.8, 126.4, 118.0, 110.1, 67.7, 65.2, 48.0, 44.7. ESIMS: m/z calculated for $C_{27}H_{19}ClN_8O_6S$ $(M+H)^+$ 618.08 found 618.07, Anal. Calc. for $C_{27}H_{19}ClN_8O_6S$: C, 52.39; H, 3.09; N, 18.10%; found: C, 52.38; H, 3.07; N, 18.10%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)acetamide (8g) Yield: 49.9 %; colorless solid, mp 143 – 145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 9.68 (s, 1H), 8.42 (dd, *J* = 2.2, 0.6 Hz, 1H), 8.09 (dd, *J* = 10.2, 0.5 Hz, 1H), 7.89 (dd, *J* = 10.2, 2.2 Hz, 1H), 7.82 (t, *J* = 1.3 Hz, 1H), 7.80 (dd, *J* = 2.1, 1.3 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.52 (t, *J* = 0.8 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.14 (ddd, *J* = 8.7, 7.9, 1.4 Hz, 1H), 6.92 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H), 6.85 (dd, *J* = 8.8, 1.5 Hz, 1H), 6.78 (td, *J* = 8.0, 1.5 Hz, 1H), 5.51 (d, *J* = 5.5 Hz, 1H), 5.18 (dd, *J* = 5.4, 0.7 Hz, 1H), 4.66 (s, 1H), 4.49 (d, *J* = 5.7 Hz, 1H), 4.43 (d, *J* = 9.7 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 168.7, 160.6, 143.2, 142.6, 137.6, 133.6, 133.2, 131.9, 129.8, 129.7, 128.9, 128.4, 126.0, 123.0, 120.1, 118.0, 117.2, 110.1, 65.2, 63.0, 48.0, 44.7. ESIMS: m/z calculated for $C_{27}H_{20}ClN_7O_5S$ $(M+H)^+$ 590.09

found 590.1, Anal. Calc. for $C_{27}H_{20}ClN_7O_5S$: C, 54.96; H, 3.42; N, 16.62%; found: C, 54.96; H, 3.41; N, 16.61%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)acetamide (8h) Yield: 57.3 %; colorless solid, mp 155 – 156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, J = 2.2, 0.5 Hz, 1H), 8.19 (d, J = 1.4 Hz, 1H), 8.17 (d, J = 1.3 Hz, 1H), 8.09 (dd, J = 10.2, 0.4 Hz, 1H), 7.89 (dd, J = 10.2, 2.2 Hz, 1H), 7.82 (t, J = 1.3 Hz, 1H), 7.80 (dd, J = 1.7, 0.8 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.58 – 7.55 (m, 1H), 7.52 (t, J = 0.8 Hz, 1H), 7.51 – 7.46 (m, 1H), 5.51 (d, J = 5.3 Hz, 1H), 5.18 (dd, J = 5.3, 0.7 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.52 – 4.40 (m, 2H), 4.23 (d, J = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 168.7, 146.7, 143.2, 142.6, 140.5, 137.6, 133.6, 133.2, 131.9, 129.7, 128.9, 128.4, 126.8, 124.8, 118.0, 110.1, 69.0, 64.6, 48.0, 44.7. ESIMS: m/z calculated for $C_{27}H_{19}ClN_8O_6S$ $(M+H)^+$ 619.08 found 619.08, Anal. Calc. for $C_{27}H_{19}ClN_8O_6S$: C, 52.39; H, 3.09; N, 18.10%; found: C, 52.38; H, 3.08; N, 18.10%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-oxo-4-(pyridin-4-yl)azetidin-1-yl)acetamide (8i) Yield: 68.7 %; colorless solid, mp 172 – 173 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.46 – 8.40 (m, 1H), 8.09 (dd, J = 10.2, 0.5 Hz, 1H), 7.89 (dd, J = 10.2, 2.2 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.64 – 7.55 (m, 1H), 7.53 – 7.46 (m, 1H), 7.42 (dt, J = 4.4, 0.8 Hz, 1H), 5.51 (d, J = 5.3 Hz, 1H), 5.18 (dd, J = 5.3, 0.7 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.51 – 4.40 (m, 1H), 4.23 (d, J = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 197.8, 181.3, 171.0, 168.7, 149.4, 143.2, 142.6, 139.3, 137.6, 133.6, 133.3, 131.9, 129.7, 128.9, 128.5, 123.6, 118.0, 110.1, 69.0, 64.8, 48.0, 44.8. ESIMS: m/z calculated for $C_{26}H_{19}ClN_8O_4S$ $(M+H)^+$ 575.09 found 575.07, Anal. Calc. for $C_{26}H_{19}ClN_8O_4S$: C, 54.31; H, 3.33; N, 19.49%; found: C, 54.30; H, 3.32; N, 19.48%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-oxo-4-(pyridin-2-yl)azetidin-1-yl)acetamide (8j) Yield: 63.0 %; colorless solid, mp 162 – 164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.59 (dd, J = 4.7, 1.8 Hz, 1H), 8.42 (dd, J = 2.2, 0.5 Hz, 1H), 8.09 (dd, J = 10.3, 0.5 Hz, 1H), 7.89 (dd, J = 10.2, 2.2 Hz, 1H), 7.82 (t, J = 1.3 Hz, 1H), 7.80 (dd, J = 1.7, 0.8 Hz, 1H), 7.63 (dd, J = 7.8, 1.7 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.54 – 7.45 (m, 2H), 7.21 – 7.11 (m, 2H), 5.46 (d, J = 5.3 Hz, 1H), 5.00 (dd, J = 5.3, 0.7 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.51 – 4.40 (m, 2H), 4.23 (d, J = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.4, 171.0, 168.8, 153.4, 148.6, 143.3, 142.6, 137.6, 137.4, 133.6, 133.2, 131.9, 129.7, 128.9, 128.5, 128.4, 122.1, 118.0, 110.1, 67.1, 67.1, 48.0, 44.7. ESIMS: m/z calculated for $C_{26}H_{19}ClN_8O_4S$ $(M+H)^+$ 575.09 found 575.09, Anal. Calc. for $C_{26}H_{19}ClN_8O_4S$: C, 54.31; H, 3.33; N, 19.49%; found: C, 54.30; H, 3.31; N, 19.49%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(2-chloropyridin-4-yl)-4-oxoazetidin-1-yl)acetamide(8k) Yield: 59.7 %; colorless solid, mp 165 – 167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.65 (d, J = 4.7 Hz, 1H), 8.42 (dd, J = 2.2, 0.5 Hz, 1H), 8.20 (ddd, J = 4.7, 2.2, 0.7 Hz, 1H), 8.09 (dd, J = 10.2, 0.4 Hz, 1H), 7.89 (dd, J = 10.2, 2.2 Hz, 1H), 7.82 (t, J = 1.3 Hz, 1H), 7.80 (dd, J = 2.1, 1.3 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.52 (t, J = 0.8 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.35 (dd, J = 2.3, 0.7 Hz, 1H), 5.51 (d, J = 5.3 Hz, 1H), 5.18 (dt, J = 5.3, 0.6 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.51 – 4.40 (m, 2H), 4.23 (d, J = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 168.7, 149.0, 145.8, 143.2,

142.6, 142.4, 137.6, 133.6, 133.2, 131.9, 129.7, 128.9, 128.4, 124.29, 123.9, 118.0, 110.1, 69.1, 64.6, 48.0, 44.7. ESIMS: m/z calculated for $C_{26}H_{18}Cl_2N_8O_4S$ $(M+H)^+$ 609.05 found 609.05, Anal. Calc. for $C_{26}H_{18}Cl_2N_8O_4S$: C, 51.24; H, 2.98; N, 18.39%; found: C, 51.24; H, 2.97; N, 18.37%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(2-(2-bromopyridin-4-yl)-3-chloro-4-oxoazetidin-1-yl)acetamide (8l) Yield: 64.2 %; colorless solid, mp 171 – 172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.47 (d, J = 4.5 Hz, 1H), 8.42 (dd, J = 2.2, 0.5 Hz, 1H), 8.13 – 8.06 (m, 2H), 7.89 (dd, J = 10.2, 2.2 Hz, 1H), 7.84 – 7.78 (m, 3H), 7.64 – 7.56 (m, 1H), 7.52 (t, J = 0.8 Hz, 1H), 7.51 – 7.45 (m, 1H), 5.51 (d, J = 5.3 Hz, 1H), 5.18 (dt, J = 5.3, 0.6 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.52 – 4.40 (m, 2H), 4.23 (d, J = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 168.7, 145.9, 145.1, 143.2, 142.6, 142.1, 137.6, 133.6, 133.2, 131.9, 129.7, 128.9, 128.4, 126.9, 123.8, 118.0, 110.1, 69.1, 64.6, 48.0, 44.7. ESIMS: m/z calculated for $C_{26}H_{18}BrClN_8O_4S$ $(M+H)^+$ 653.0 found 653.01, Anal. Calc. for $C_{26}H_{18}BrClN_8O_4S$: C, 47.76; H, 2.77; N, 17.14%; found: C, 47.74; H, 2.77; N, 17.14%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-(2-fluoropyridin-4-yl)-4-oxoazetidin-1-yl)acetamide (8m) Yield: 68.5 %; colorless solid, mp 163 – 164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, J = 2.2, 0.5 Hz, 1H), 8.32 (d, J = 5.5 Hz, 1H), 8.13 – 8.06 (m, 1H), 8.03 (ddd, J = 5.5, 2.2, 0.6 Hz, 1H), 7.89 (dd, J = 10.2, 2.2 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.64 – 7.56 (m, 1H), 7.52 (t, J = 0.8 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.34 – 7.28 (m, 1H), 5.51 (d, J = 5.3 Hz, 1H), 5.18 (dt, J = 5.3, 0.6 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.51 – 4.40 (m, 2H), 4.23 (d, J = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 168.7, 162.4, 159.0, 145.7, 145.5, 143.2, 142.6, 137.6, 137.6, 137.5, 133.6, 133.2, 131.9, 129.7, 128.9, 128.4, 119.4, 119.4, 118.0, 110.1, 106.1, 105.8, 69.2, 69.1, 64.6, 48.0, 44.7. ESIMS: m/z calculated for $C_{26}H_{18}ClFN_8O_4S$ $(M+H)^+$ 693.08 found 693.06, Anal. Calc. for $C_{26}H_{18}ClFN_8O_4S$: C, 52.66; H, 3.06; N, 18.90%; found: C, 52.65; H, 3.04; N, 18.89%

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(3-chloro-2-oxo-4-(thiophen-2-yl)azetidin-1-yl)acetamide (8n) Yield: 66.0 %; colorless solid, mp 178 – 179°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.42 (dd, J = 2.2, 0.6 Hz, 1H), 8.09 (dd, J = 10.2, 0.5 Hz, 1H), 7.89 (dd, J = 10.2, 2.2 Hz, 1H), 7.82 (t, J = 1.3 Hz, 1H), 7.81 – 7.78 (m, 1H), 7.64 – 7.56 (m, 1H), 7.52 (t, J = 0.8 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.29 (dd, J = 5.4, 1.7 Hz, 1H), 6.96 (dd, J = 6.5, 5.4 Hz, 1H), 6.86 (ddd, J = 6.5, 1.8, 0.7 Hz, 1H), 5.46 (d, J = 4.9 Hz, 1H), 5.00 (dd, J = 4.9, 0.6 Hz, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.51 – 4.40 (m, 2H), 4.23 (d, J = 13.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 197.8, 181.3, 171.0, 164.5, 143.2, 142.6, 141.0, 137.6, 133.6, 133.2, 131.9, 129.7, 128.9, 128.4, 125.7, 124.8, 118.0, 116.9, 110.1, 63.3, 63.3, 48.0, 44.7. ESIMS: m/z calculated for $C_{25}H_{18}ClN_7O_4S_2$ $(M+H)^+$ 580.06 found 580.05, Anal. Calc. for $C_{25}H_{18}ClN_7O_4S_2$: C, 51.77; H, 3.13; N, 16.90%; found: C, 51.77; H, 3.12; N, 16.89%

Conclusion

In summary, we have developed 14 novel azetidinone derivatives containing different substitutions and examined their biological activities. The antimicrobial activities were affected by substitutions on the azetidinone ring. Compounds 8a, 8b, 8e, 8k, 8l exhibited potent antibacterial activity against gram positive and gram-negative bacteria. Compound 8a, 8k and 8l showed the best activity. It has been shown that the activity and selectivity of these molecules

make them valid leads for synthesizing novel compounds that exhibits better potency.

Conflicts of interest

The author declares no conflicts of interest

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