

Antimicrobial Activity Evaluation Of New 1,3,4-oxadiazole Derivatives

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ABSTRACT

In this study, we have synthesized seven novel 2-[(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-substituted benzothiazol-2-yl)acetamide derivatives (**4a-g**) starting from ethyl 4-chlorophenyl acetate. The antimicrobial activity of the compounds was screened against seven Gram positive and Gram negative bacteria and four fungi species; *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 35218, *Enterococcus faecalis* ATCC 51299, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Candida albicans*, *Candida krusei*, *Candida glabrata*, *Candida parapsilosis*. Minimum inhibitor concentration (MIC) was calculated and compared with standard drugs, chloramphenicol and ketoconazole. Regarding the results of MIC, all compounds exhibited potency either at the higher concentrations or at the same concentrations compared with positive controls.

Keywords: 1,3,4-oxadiazole, benzothiazole, antibacterial, antifungal

INTRODUCTION

Infectious diseases are one of the most deadly diseases in the world¹. Recently, the number of bacterial and fungal infections has risen dangerously². Antibiotics and antifungals are the most important drug groups used in the treatment of bacterial and fungal infections. With the discovery of antibiotics, these drugs have begun to be used as main drugs in the treatment of infections. But over time, bacteria have begun to develop resistance because of frequent use and misuse. An uncontrolled increase in resistance of pathogenic microorganisms has wasted health resources³⁻⁵. This resistance to antimicrobial agents has shown

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By using acid hydrazides, phosphorus oxychloride, sulfuric acid, and thionyl chloride, the oxadiazole ring was obtained in several steps^{14,15,19}. However, the method of synthesis of 1,3,4-oxadiazoles by reaction of carboxylic acid and acid hydrazides is not a highly preferred method because it is expensive and requires a long time²⁰.

In this study, we have synthesized seven novel compounds combining 5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-thiol and 2-chloro-*N*-(2-benzothiazolyl)acetamide derivatives. The antimicrobial activity of the synthesized compounds was investigated against different microorganisms compared with standard drugs chloramphenicol and ketoconazole.

METHODOLOGY

Chemistry

All chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck Chemicals (Merck KGaA, Darmstadt, Germany). All melting points (m.p.) were determined by MP90 digital melting point apparatus (Mettler Toledo, Ohio, USA) and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: IR, Shimadzu Affinity 1S spectrophotometer (Shimadzu, Tokyo, Japan); NMR, Agilent 300 MHz NMR spectrometer (Agilent technologies, California, USA), in DMSO-*d*₆, using TMS as internal standard; M+1 peaks were determined by Shimadzu 8040 LC/MS/MS system (Shimadzu, Tokyo, Japan). Elemental analyses were performed on a Leco 932 CHNS analyzer (Leco, Michigan, USA).

Synthesis of ethyl 4-chlorophenyl acetate (1)

4-Chlorophenyl acetic acid (0.40 mol) was refluxed with excess ethanol for 12h catalyzed with H₂SO₄. After TLC check, the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with salty water and dried with sodium sulfate. Ethyl acetate was evaporated under reduced pressure to gain ester compound (**1**).

Synthesis of 2-(4-chlorophenyl)acetohydrazide (2)

Ethyl 4-chlorophenyl acetate (0.25 mol) was dissolved in ethanol (150 ml). Hydrazine hydrate (0.50 mol) added and the mixture stirred in room temperature for 2h. After completion of reaction, the solvent was separated by filtration to acquire hydrazide compound **2**.

Synthesis of 5-(4-chlorobenzyl)-1,3,4-oxadiazole-2-thiol (3)

2-(4-Chlorophenyl)acetohydrazide (0.20 mol) was dissolved in ethanol (250 ml). 0.24 mol of potassium hydroxide was dissolved in ethanol (100 mL) and added to the mixture. Secondly, carbon disulfide (0.60 mol) was added to the mixture, and it was refluxed for 5 hours. After this period, cold water and dilute HCl were added to the reaction mixture to gain product **3**.

Synthesis of 2-[(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-substituted benzothiazol-2-yl)acetamide derivatives (4a-g)

5-(4-Chlorobenzyl)-1,3,4-oxadiazole-2-thiol (10 mmol) was dissolved in acetone (50 mL), potassium carbonate (12 mmol) and appropriate 2-chloro-N-(2-benzothiazolyl)acetamide derivatives were added to this solution and stirred for 12h in room temperature. After TLC screening, the solvent was evaporated under reduced pressure then water was added to wash the resulting solid and the mixture was filtered, dried and recrystallized from ethanol to give final compounds **4a-g**.

2-[(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(benzothiazol-2-yl)acetamide (4a)

Yield: 69 %. M.p. 231°C.

¹H-NMR (300 MHz, DMSO-d₆, ppm) δ: 4.27 (2H, s, -CH₂), 4.40 (2H, s, -COCH₂), 7.30-7.37 (5H, m, Ar-H), 7.46 (1H, t, J= 7.44 Hz, Ar-H), 7.78 (1H, d, J= 7.95 Hz, aromatic-H), 7.99 (1H, d, J= 7.41 Hz, aromatic-H), 12.74 (1H, s, -NH).

¹³C-NMR (75 MHz, DMSO-d₆, ppm) δ: 30.46 (CH₂), 36.01 (CH₂), 121.19 (CH), 122.26 (CH), 124.23 (CH), 126.70 (CH), 129.10 (CH), 131.93 (CH), 132.48 (C), 133.59 (C), 148.98 (C), 158.06 (C), 163.43 (C), 166.75 (C), 166.97 (C).

For C₁₈H₁₃ClN₄O₂S₂ calculated: 51.86 % C, 3.14 % H, 13.44 % N, found: 51.82 % C, 3.15 % H, 13.47 % N.

HRMS (m/z): [M+H]⁺ calcd for C₁₈H₁₃ClN₄O₂S₂: 417.0241; found 417.0232.

2-[(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-methylbenzothiazol-2-yl)acetamide (4b)

Yield: 72 %. M.p. 244°C.

¹H-NMR (300 MHz, DMSO-d₆, ppm) δ: 2.41 (3H, s, -CH₃), 4.27 (2H, s, -CH₂), 4.39 (2H, s, -COCH₂), 7.25-7.38 (5H, m, Ar-H), 7.66 (1H, d, J= 8.22 Hz, Ar-H), 7.78 (1H, s, aromatic-H), 12.67 (1H, s, -NH).

¹³C-NMR (75 MHz, DMSO-d₆, ppm) δ: 21.46 (CH₃), 30.46 (CH₂), 35.99 (CH₂), 121.83 (CH), 122.41 (CH), 123.35 (CH), 128.62 (CH), 129.10 (CH), 131.26 (C),

132.06 (C), 132.48 (C), 133.72 (C), 146.91 (C), 157.19 (C), 163.44 (C), 166.59 (C), 166.96 (C).

For $C_{19}H_{15}ClN_4O_2S_2$ calculated: 52.96 % C, 3.51 % H, 13.00 % N, found: 52.91 % C, 3.52 % H, 13.04 % N.

HRMS (m/z): $[M+H]^+$ calcd for $C_{19}H_{15}ClN_4O_2S_2$: 431.0394; found 431.0394.

2-[(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-methoxybenzothiazol-2-yl)acetamide (4c)

Yield: 75 %. M.p. 241°C.

1H -NMR (300 MHz, DMSO- d_6 , ppm) δ : 3.80 (3H, s, $-OCH_3$), 4.26 (2H, s, $-CH_2$), 4.38 (2H, s, $-COCH_2$), 7.04 (1H, dd, $J= 8.42$ Hz, $J= 2.58$ Hz, Ar-H), 7.29-7.37 (4H, m, Ar-H), 7.57 (1H, s, aromatic-H), 7.65 (1H, d, $J= 8.85$ Hz, 12.61 (1H, s, -NH).

^{13}C -NMR (75 MHz, DMSO- d_6 , ppm) δ : 30.46 (CH_2), 35.96 (CH_2), 56.10 (OCH_3), 121.79 (CH), 124.45 (CH), 128.62 (CH), 129.09 (CH), 131.26 (CH), 132.48 (C), 133.25 (C), 133.59 (C), 143.00 (C), 156.00 (C), 156.74 (C), 163.45 (C), 166.44 (C), 166.95 (C).

For $C_{19}H_{15}ClN_4O_3S_2$ calculated: 51.06 % C, 3.38 % H, 12.54 % N, found: 51.11 % C, 3.39 % H, 12.58 % N.

HRMS (m/z): $[M+H]^+$ calcd for $C_{19}H_{15}ClN_4O_3S_2$: 447.0347; found 447.0328.

2-[(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-ethoxybenzothiazol-2-yl)acetamide (4d)

Yield: 68 %. M.p. 233°C.

1H -NMR (300 MHz, DMSO- d_6 , ppm) δ : 1.35 (3H, t, $J= 6.93$ Hz, $-CH_3$), 4.07 (2H, q, $J= 6.90$ Hz, $-OCH_2$), 4.27 (2H, s, $-CH_2$), 4.37 (2H, s, $-COCH_2$), 7.03 (1H, dd, $J= 8.70$ Hz, $J= 2.49$ Hz, Ar-H), 7.30-7.37 (4H, m, Ar-H), 7.56 (1H, s, aromatic-H), 7.65 (1H, d, $J= 8.82$ Hz, 12.59 (1H, s, -NH).

^{13}C -NMR (75 MHz, DMSO- d_6 , ppm) δ : 15.15 (CH_3), 30.46 (CH_2), 35.95 (CH_2), 64.08 (OCH_2), 121.80 (CH), 124.80 (CH), 129.10 (CH), 131.26 (CH), 132.47 (C), 133.25 (C), 133.60 (C), 135.12 (C), 142.96 (C), 155.96 (C), 163.45 (C), 166.39 (C), 166.96 (C).

For $C_{20}H_{17}ClN_4O_3S_2$ calculated: 52.11 % C, 3.72 % H, 12.15 % N, found: 52.15 % C, 3.73 % H, 12.18 % N.

HRMS (m/z): $[M+H]^+$ calcd for $C_{20}H_{17}ClN_4O_3S_2$: 461.0503; found 461.0494.

2-[(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-chlorobenzothiazol-2-yl)acetamide (4e)

Yield: 71 %. M.p. 247°C.

¹H-NMR (300 MHz, DMSO-d₆, ppm) δ: 4.28 (2H, s, CH₂), 4.41 (2H, s, -CH₂CO), 7.31-7.37 (4H, m, Ar-H), 7.47 (1H, dd, *J* = 8.70 Hz, *J* = 2.22 Hz, Ar-H), 7.77 (1H, d, *J* = 8.64 Hz, aromatic-H), 8.14 (1H, d, *J* = 2.13 Hz, Ar-H), 12.85 (1H, s, -NH).

¹³C-NMR (75 MHz, DMSO-d₆, ppm) δ: 30.46 (CH₂), 35.97 (CH₂), 121.98 (CH), 122.39 (CH), 127.05 (CH), 128.29 (C), 128.63 (C), 129.08 (CH), 131.24 (CH), 132.48 (C), 133.57 (C), 147.84 (C), 158.95 (C), 163.40 (C), 166.97 (C).

For C₁₈H₁₂Cl₂N₄O₂S₂ calculated: 47.90 % C, 2.68 % H, 12.41 % N, found: 47.81 % C, 2.69 % H, 12.45 % N.

HRMS (m/z): [M+H]⁺ calcd for C₁₈H₁₂Cl₂N₄O₂S₂: 450.9851; found 450.9832.

2-[(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-florobenzothiazol-2-yl)acetamide (4f)

Yield: 69 %. M.p. 241°C.

¹H-NMR (300 MHz, DMSO-d₆, ppm) δ: 4.26 (2H, s, CH₂), 4.39 (2H, s, -CH₂CO), 7.27-7.36 (5H, m, Ar-H), 7.76-7.81 (1H, m, Ar-H), 7.91 (1H, dd, *J* = 8.70 Hz, *J* = 2.64 Hz, aromatic-H), 12.76 (1H, s, -NH).

¹³C-NMR (75 MHz, DMSO-d₆, ppm) δ: 30.46 (CH₂), 35.94 (CH₂), 108.55 (C), 108.90 (C), 114.68 (C), 115.00 (CH), 122.27 (CH), 122.40 (CH), 129.09 (CH), 131.26 (CH), 132.47 (C), 133.59 (C), 157.62 (C), 160.80 (C), 163.41 (C), 166.85 (C), 166.97 (C).

For C₁₈H₁₂ClFN₄O₂S₂ calculated: 49.71 % C, 2.78 % H, 12.88 % N, found: 49.81 % C, 2.77 % H, 12.84 % N.

HRMS (m/z): [M+H]⁺ calcd for C₁₈H₁₂ClFN₄O₂S₂: 435.0147; found 435.0137.

2-[(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-N-(6-nitrobenzothiazol-2-yl)acetamide (4g)

Yield: 73 %. M.p. 245°C.

¹H-NMR (300 MHz, DMSO-d₆, ppm) δ: 4.26 (2H, s, CH₂), 4.43 (2H, s, -CH₂CO), 7.29-7.37 (4H, m, Ar-H), 7.92 (1H, d, *J* = 8.97 Hz, Ar-H), 8.28 (1H, dd, *J* = 8.70 Hz, *J* = 2.43 Hz, aromatic-H), 13.15 (1H, s, -NH).

¹³C-NMR (75 MHz, DMSO-d₆, ppm) δ: 30.46 (CH₂), 36.03 (CH₂), 119.61 (CH), 121.30 (CH), 122.30 (CH), 129.08 (CH), 131.24 (CH), 132.47 (C), 132.68 (C), 133.57 (C), 143.60 (C), 153.83 (C), 163.35 (C), 163.60 (C), 167.00 (C), 167.56 (C).

For $C_{18}H_{12}ClN_4O_4S_2$ calculated: 46.81 % C, 2.62 % H, 15.16 % N, found: 46.89 % C, 2.63 % H, 15.21 % N.

HRMS (m/z): $[M+H]^+$ calcd for $C_{18}H_{12}ClN_4O_4S_2$: 462.0092; found 462.0084.

Antimicrobial activity

Antimicrobial activity against *Escherichia coli* (ATCC 25922), *Escherichia coli* (ATCC 35218), *Enterococcus faecalis* (ATCC 51299), *Enterococcus faecalis* (ATCC 29212), *Staphylococcus aureus* (ATCC 22019), *Klebsiella pneumoniae* (ATCC 700603), *Pseudomonas aeruginosa* (ATCC 27853), *Candida albicans* (ATCC 24433), *Candida krusei* (ATCC 6258), *Candida glabrata* (ATCC 90030), *Candida parapsilosis* (ATCC 90030) was determined by the microbroth dilutions technique using the Clinical Laboratory Standards Institute (CLSI) recommendations²¹.

The lowest concentration that completely inhibited growth of the microorganism was defined as the minimum inhibitor concentration (MIC). MIC was screened and the results were compared to chloramphenicol and ketoconazole as positive controls. Each experiment was replicated twice.

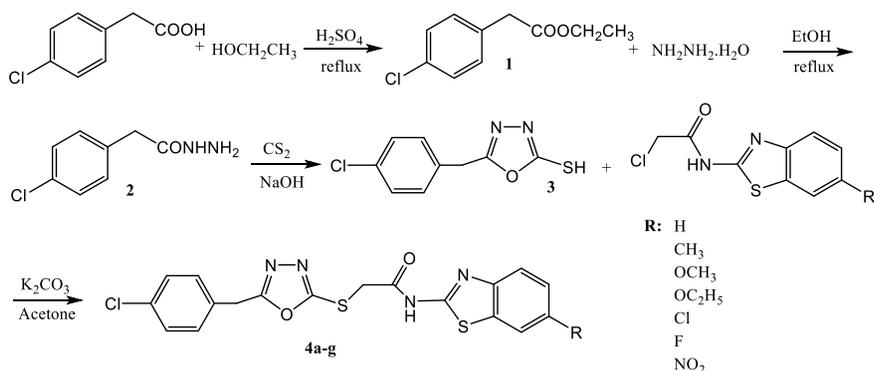
RESULTS AND DISCUSSION

Chemistry

In this study, we have synthesized 2-[(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl)thio]-*N*-(6-substituted benzothiazol-2-yl)acetamide derivatives (**4a-g**) with four step synthetic procedure as shown **Scheme 1**. In the first step, compound **1** was synthesized by reacting 4-chlorophenyl acetic acid with H_2SO_4 in ethanol at reflux conditions. In the second step, compound **2** was synthesized by reacting 4-chlorophenyl acetate with hydrazine hydrate in ethanol at the room temperature. In the third step, compound **3** was synthesized by reacting 2-(4-chlorophenyl)acetohydrazide with potassium hydroxide and carbon disulfide in ethanol at the reflux conditions. In the last step, compounds **4a-g** were synthesized by reacting 5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-thiol with 2-chloro-*N*-(2-benzothiazolyl)acetamide derivatives in acetone at room temperature. The gained raw products were crystallized from ethanol.

In 1H -NMR spectra of the synthesized compounds (**4a-g**), peaks of acetamide ($-CH_2CONH-$) moiety belongs to methylene and amide protons were identified at about 4.37-4.43 ppm and 12.59-13.15 ppm, respectively. If we look at the characteristic 1H -NMR properties of the molecule, we detected peaks of methyl group ($-CH_3$) at 2.41 ppm for **4b**, peaks of methoxy group ($-OCH_3$) at 3.80 ppm for **4c**. For compound **4d**, peaks of methyl ($-CH_3$) and methylene group ($-OCH_2$) were

seen at 1.35 ppm and 4.07 ppm as broad singlet peaks. In the ^{13}C -NMR spectra, all carbons were determined between 15.15-167.56 ppm range. The peaks resonated at about 30.46 ppm and 35.94-36.03 ppm were assigned to $-\text{SCH}_2-$ and $-\text{CCH}_2-$ carbons, respectively. In the ^{13}C -NMR spectra of the compounds **4b**, **4c** and **4d**, signals at 21.46, 56.10 and 15.15, 64.08 ppm were assigned to the carbon atoms of methyl, methoxy and ethoxy groups on benzothiazole ring. In aromatic region, signals with higher values were determined for the carbon atoms of the heterocyclic rings. In the MS spectra of the compounds, M^+ peaks were observed in agreement with molecular weights of the compounds. Elemental analysis for C, H, O atoms were within $\pm 0.4\%$ of the theoretical values.



Scheme 1. The synthesis of the compounds (**4a-g**).

Biology

All synthesized compounds were tested for determining their antimicrobial activity against seven Gram positive and Gram negative bacterial and four fungal microorganisms; *E.coli* ATCC 25922, *E. coli* ATCC 35218, *E. faecalis* ATCC 51299, *E. faecalis* ATCC 29212, *S. aureus*, *K.pneumoniae*, *P. aeruginosa*, *C. albicans*, *C.krusei*, *C.glabrata*, *C. parapsilosis*. MIC values were determined against standard drugs, ketoconazole and chloramphenicol and represented in **Table 1**. MIC values of the compounds were found between 50-100 $\mu\text{g}/\text{ml}$ and they were identified between 12.5-50 $\mu\text{g}/\text{ml}$ for reference drugs. Compound **4a** showed antimicrobial activity against all microorganisms at 50 $\mu\text{g}/\text{ml}$ concentration. Compounds **4b**, **4c**, **4e** and **4g** exhibited activity against *E. coli* ATCC 35218 and *P. aeruginosa* at 100 $\mu\text{g}/\text{ml}$ and against other bacteria at 50 $\mu\text{g}/\text{ml}$. MIC values were calculated against *P. aeruginosa* as 100 $\mu\text{g}/\text{ml}$ for compound **4d** and against *E. coli* ATCC 35218 as 100 $\mu\text{g}/\text{ml}$ for **4f**. Additionally, all compounds showed potency at the higher concentration against six bacteria *E.coli* ATCC 25922, *E. coli* ATCC 35218, *E. faecalis* ATCC 51299, *E. faecalis* ATCC 29212, *S. aureus*, *K.pneumoniae*. **4a** and **4f** exhibited same potency against *P.*

aeruginosa compared with chloramphenicol. All compounds showed lower activity against *C. albicans* than ketoconazole and they exhibited same potency against three fungal microorganisms *C. krusei*, *C. glabrata*, *C. parapsilosis* compared reference.

Table 1. Antimicrobial activities of the compounds ($\mu\text{g/mL}$)

Comp.	A	B	C	D	E	F	G	H	I	J	K
4a	50	50	50	50	50	50	50	50	50	50	50
4b	50	100	50	50	50	50	100	50	50	50	50
4c	50	100	50	50	50	50	100	50	50	50	50
4d	50	50	50	50	50	50	100	50	50	50	50
4e	50	100	50	50	50	50	100	50	50	50	50
4f	50	100	50	50	50	50	50	50	50	50	50
4g	50	100	50	50	50	50	100	50	50	50	50
Ref. 1	12.5	12.5	25	25	25	12.5	50	-	-	-	-
Ref. 2	-	-	-	-	-	-	-	25	50	50	50

Reference 1: Chloramphenicol, Reference 2: Ketoconazole

A: *E. coli* ATCC 25922, **B:** *E. coli* ATCC 35218, **C:** *E. faecalis* ATCC51299, **D:** *E. faecalis* ATCC 29212, **E:** *S. aureus*, **F:** *K. pneumonia*, **G:** *P. aeruginosa*, **H:** *C. albicans*, **I:** *C. krusei*, **J:** *C. glabrata*, **K:** *C. parapsilosis*.

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