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SHORT COMMUNICATION

Synthesis, Characterization and biological activity of various substituted (E)-5-benzylidene-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl) amino)thiazol-4(5H)-one derivatives

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ABSTRACT

2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole was synthesized via reaction of chloroacetic acid with 4-nitrobenzohydrazide in phosphonyl chloride(4). Compound 4 was treated with 4-aminophenol to form 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)aniline(5) having free -NH_2 group,which is reacted with chloroacetyl chloride to give 2-chloro-N-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide(6). Compound 6 was cyclized by ammonium thiocyanate to form 2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)amino)thiazol-4(5H)-one(7) with thiazolone ring. Compound was reacted different aldehydes to form (E)-5-benzylidene -2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl) amino)thiazol-4(5H)-one derivatives(8a-j). In vitro antibacterial activity of the target compounds were investigated using two types of bacteria, Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative). The results indicated that the newly synthesized (E)-5-benzylidene-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)

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phenyl)amino)thiazol-4(5H)-one derivatives (compounds 8d and 8f) showed enhanced activity against Gram-negative bacteria when compared with that of the control drug (gentamycin).

***Keywords*:** oxadiazole, thiazolone, antibacterial, antifungal, In vitro antibacterial

1. INTRODUCTION

The thiazolone is five-membered heterocycles containing one nitrogen atom and one sulphur [1]. Thiazolone heterocycle is an important intermediate and building block in the construction of a variety of biologically active compounds [2]. Thiazolone compounds showed a variety of biological activities such as antibacterial, antitubercular, antifungal, anti-HIV, antileishmanial, antinociceptive, anti-inflammatory and analgesic activities [3,4]. They are also used for the treatment of schistosomiasis infections [5], anticonvulsant activity and reduced toxicity [6], antidiabetic [7,8]. thiazolone have antitumor, antiarrhytmic and antiandrogenic activity. The activity of thiazolone depends on the nature of substitution of thiazolone ring. Among thiazolone phenytoin is known as antiepileptic drug and antihypertensive substance.

Oxadiazoles are cyclic compounds containing one oxygen and two nitrogen atoms in a five- membered ring. The sequence of these atoms may be different as 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole or 1,3,4-oxadiazole [9]. Oxadiazole moiety is derived from furan by replacing two -CH= group with two pyridine typed nitrogen (-N=) [10]. Five-membered N-containing heterocyclic aromatic compounds found in natural products [11]. Oxadiazoles have often been described as bioisosteres for amides and esters [12].

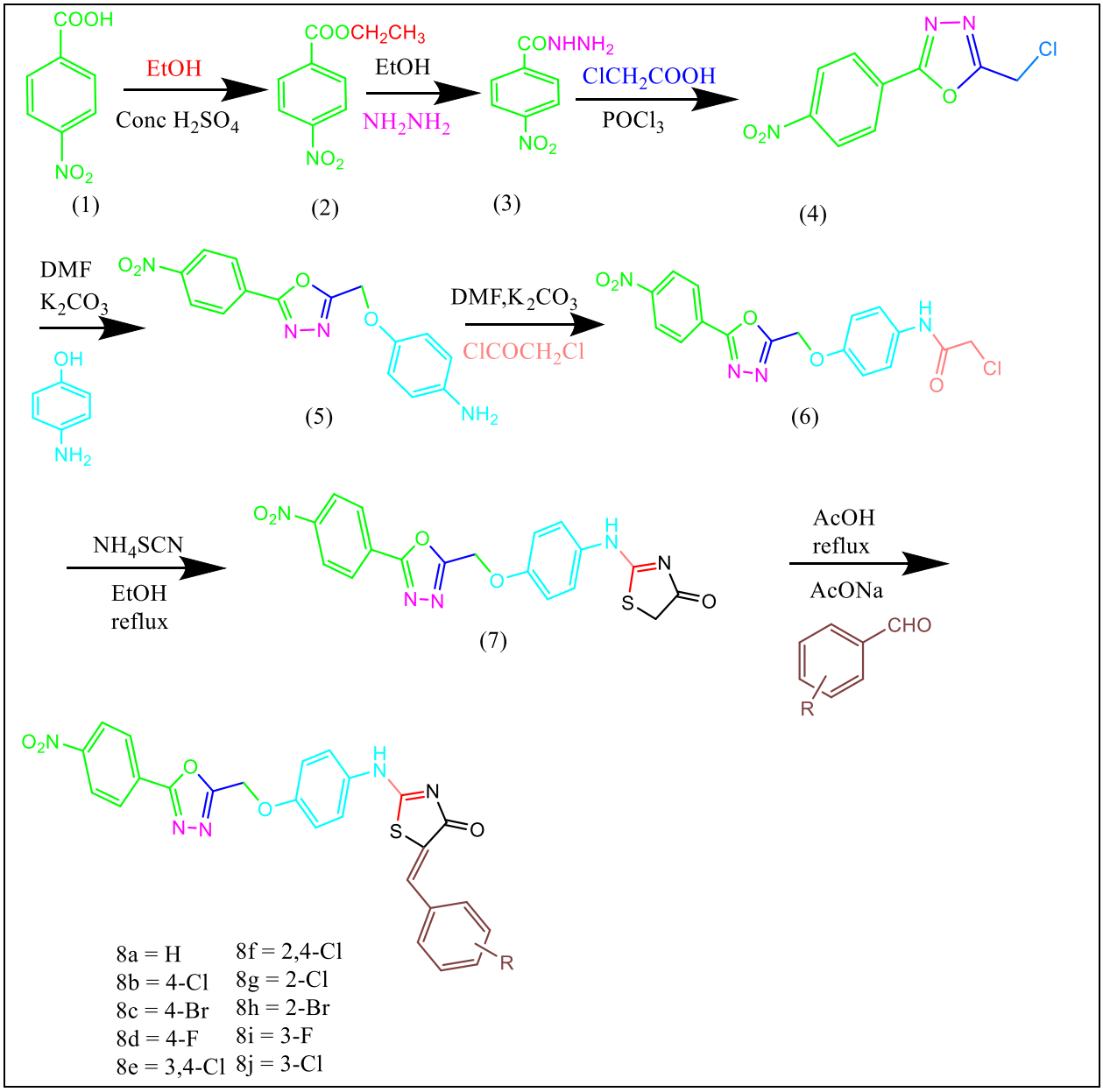
Furthermore the 1,3,4 oxadiazole derivatives have some industrial applications in the fields of dyes, photosensitivity electrical materials and liquid crystals [13]. 1,3,4-Oxadiazoles and their derivatives represent an important scaffold that has been found in many natural and synthesized molecules because of their remarkable biological activities [14] as anticancer [15], antifungal [16], antitumor [17], antibacterial, antiparasitic, anti-HIV, anti-infective, muscle relaxants, antiseptics and cathepsin K inhibitors.

2. EXPERIMENTAL

4-Nitrobenzohydrazide was converted to 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole(4) by treating it with monochloroacetic acid in $POCl_3$. Alkylation between compound 4 and p-aminophenol gives compound 5 and it reacted with chloroacetyl chloride to give an amide(6).

Compound 6 was cyclized by ammonium thiocyanate to give thiazolone(7), which is reacted with different aldehydes and form derivatives of (E)-5-benzylidene -2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)amino)thiazol-4(5H)-one(8a-j) Scheme 1.

The chemical structures of the target compounds synthesized were confirmed from IR, ^{1}H NMR, ^{13}C NMR and MS spectra analysis and were in good agreement with the proposed structures.



Scheme 1

2. 1. Biological evaluation

Antifungal activity: all synthesize compound of (E)-5-benzylidene -2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl) amino)thiazol-4(5H)-one derivatives (8a-j) were evaluation for their antifungal activity by measuring minimum inhibitory concentration (µg/mL).the results of antifungal activities (Table 1) indicated that most of the target compounds 8a, 8b, 8c, 8d, 8f, 8h, 8i and 8j display very potent antifungal activity against C. albicans and A. niger, while Compound 8a,8i and 8j show more potent activity better than Nystatin, Greseofulvin, Ciprofloxacin, Chloramphenicol.

Antibacterial activity: Based on the antimicrobial results for all the synthesized (E)-5-benzylidene-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)amino)thiazol-4(5H)-one derivatives 8a-j only compound 8a, 8b, 8h and 8i exhibited good antibacterial activity (Table 1) againstthe various gram positive (S. aureus, S. pyogenes) and gram negative (E. coli, P. aeruginosa) bacterial strains and MIC values were comparable to those observed against the standard drugs Nystatin, Greseofulvin, Ciprofloxacin, Chloramphenicol.

2. 2. Experimental section

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. 1H (400 MHz), 13C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl3 and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

Table 1. Antibacterial/fungal activity table [microgramme/ml]

Compounds and standard drugs	Antibacterial activity				Antifungal acitivity	
	Minimum inhibitory concentration µg/ml				Minimum inhibitory concentration µg/ml	
	Gram +Ve Bacteria		Gram -Ve Bacteria			
	S. aureus	***S.p yogenes***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. niger***
(8a)	15.62	62.5	**15.625**	**15.625**	**15.625**	**31.25**
(8b)	31.25	15.625	**15.625**	**7.82**	62.5	**31.25**
(8c)	62.5	31.25	31.25	31.25	**15.625**	62.5
(8d)	15.62	62.5	31.25	62.5	**15.625**	62.5
(8e)	31.25	**7.82**	15.625	62.5	62.5	62.5
(8f)	7.81	31.25	**7.82**	62.5	**31.25**	62.5
(8g)	15.625	15.625	**15.625**	62.5	**15.625**	62.5
(8h)	**7.82**	62.5	31.25	31.25	**31.25**	62.5
(8i)	31.25	31.25	**15.625**	**15.625**	**15.625**	**15.625**
(8j)	15.62	31.25	31.25	**15.625**	**15.625**	**15.625**

Nystatin	-	-	-	-	31.25	31.25
Greseofulvin					15.625	15.625
Ciprofloxacin	7.8	7.8	15.625	15.625	-	-
Chloramphenicol	7.8	7.8	7.8	7.8	-	-

Synthetic procedure of ethyl 4-aminobenzoate (2)
A mixture of p-amino benzoic acid (1 mmol) and ethanol (3 mmol) were refluxed in 60 ml for 4 hours.the resultant mixture was concentrated, cool and poured into ice cold water. The solid mass thus separated out was dried.

Synthetic procedure of 4-nitro benzohydrazide (3)
A mixture of ethyl 4-aminobenzoate (1 mmol) and hydrazine hydrate (2 mmol) were refluxed in ethanol for 7 hours. The resultant mixture was concentrated, cooled and poured into crushed ice. The solid mass thus seperated out was dried and recrystallized from ethanol.

Synthetic procedure of 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (4)
Add 4-nitrobenzohydrazide(1 mmol) in the mixture of phosphonyl chloride (1.5 mmol) and monochloroacetic acid (1 mmol) in cooling condition. Reflux the reaction for 2-3 hrs. product is isolated by pouring the reaction mass in ice cold water.

Synthetic procedure of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)aniline (5)
Mix 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (1 mmol), p-aminophenol(1 mmol) and K_2CO_3 (2 mmol) in DMF solvent and reflux for 7-8 hrs. Pour the reaction mass in cold water to isolate product.

Synthetic procedure of 2-chloro-N-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)acetamide (6)
Mix 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)aniline (1 mmol), chloroacetyl chloride (1 mmol) and K_2CO_3 (2 mmol) in DMF solvent and stir for 3-4 hrs at room temperature. Pour the reaction mass in cold water to isolate product.

Synthetic procedure of 2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl) amino)thiazol-4(5H)-one (7)
Reflux the mixture of 2-chloro-N-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)acetamide and ammonium thiocyanate in ethanol for 2 hrs. Product fall out after 2 hrs.

Synthetic procedure of (E)-5-benzylidene-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)amino)thiazol-4(5H)-one derivatives (8a-j)
2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)amino)thiazol-4(5H)-one and various aldehydes was refluxed in acetic acid in presence of sodium acetate overnight. Reaction mixture is poured in ice cold water to separate the product.

(E)-5-benzylidene-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)amino) thiazol-4(5H)-one (8a)
White coloured, Yield: 79% compound, m.p: 173-175 ºC, ^{1}H NMR (400 MHz, Chloroform) δ 8.39 – 8.25 (m, 2H), 7.9 – 7.7(m, 2H), 7.6 – 7.4 (m, 2H), 7.4 (t, *J* = 7.0 Hz, 3H), 7.3 (s, 1H), 6.8 – 6.6 (m, 2H), 6.6 – 6.5 (m, 2H), 5.1 – 5.0 (m, 2H), 4.5 (s, 1H). ^{13}C NMR (100 MHz) δ 176 (s), 168 (s), 162(s), 162(s), 154(s), 147 (s), 135 (s), 134 (s), 132 (s), 132 (s), 13 (s), 129 (m), 128 (m), 127 (m), 124(m), 123.34 (m), 118(m), 112 (s), 57 (s).Mol. Formula: $C_{25}H_{17}N_5O_5S$**,** m/z: 499

(E)-5-(4-chlorobenzylidene)-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)amino) thiazol-4(5H)-one (8b)
White coloured, Yield: 77% compound, m.p: 193-195 ºC, ^{1}H NMR (400 MHz, Chloroform) δ 8.4 – 8.2 (m, 2H), 7.9 – 7.7 (m, 2H), 7.5 – 7.4 (m, 4H), 7.3 (s, 1H), 6.8 – 6.6 (m, 2H), 6.6 – 6.5 (m, 2H), 5.1 – 5.0 (m, 2H), 4.4 (s, 1H). ^{13}C NMR (100 MHz) δ 176 (s), 168 (s), 162 (s), 162 (s), 154 (s), 147 (s), 135 (s), 135 (s), 134 (s), 132 (s), 132 (s), 130 (m), 129 (m), 127(m), 124.(m), 123 (m), 118 (m), 112.(s), 57 (s). Mol. Formula: $C_{25}H_{16}ClN_5O_5S$, m/z: 534

(E)-5-(4-bromobenzylidene)-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)amino) thiazol-4(5H)-one (8c)
White coloured, Yield: 82% compound, m.p: 187-189 ºC,, ^{1}H NMR (400 MHz, Chloroform) δ 8.38 – 8.23 (m, 2H), 7.89 – 7.74 (m, 2H), 7.65 – 7.51 (m, 2H), 7.47 – 7.33 (m, 2H), 7.29 (s, 1H), 6.80 – 6.65 (m, 2H), 6.60 – 6.46 (m, 2H), 5.10 – 5.06 (m, 2H), 4.44 (s, 1H). ^{13}C NMR (100 MHz) δ 176.95 (s), 168.55 (s), 162.29 (s), 162.07 (s), 154.97 (s), 147.39 (s), 135.79 (s), 134.39 (s), 132.10 (dd, *J* = 22.2, 8.2 Hz), 130.50 – 130.29 (m), 127.56 – 127.34 (m), 124.90 (s), 124.79 – 124.57 (m), 123.55 – 123.34 (m), 118.02 – 117.62 (m), 112.88 (s), 57.05 (s). Mol. Formula: $C_{25}H_{16}BrN_5O_5S$, m/z: 578

(E)-5-(4-fluorobenzylidene)-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)amino) thiazol-4(5H)-one (8d)
White coloured, Yield: 82% compound, m.p: 182-184 ºC, ^{1}H NMR (400 MHz, Chloroform) δ 8.39 – 8.25 (m, 2H), 7.90 – 7.76 (m, 2H), 7.51 – 7.47 (m, 2H), 7.27 (s, 1H), 7.17 – 7.11 (m, 2H), 6.80 – 6.65 (m, 2H), 6.59 – 6.45 (m, 2H), 5.12 – 5.08 (m, 2H), 4.44 (s, 1H). ^{13}C NMR (125 MHz, Common NMR Solvents) δ 176.95 (s), 168.55 (s), 162.95 (t, *J* = 150.4 Hz), 162.07 (s), 162.07 (s), 154.97 (s), 147.39 (s), 135.79 (s), 134.39 (s), 132.08 (s), 131.90 – 131.23 (m), 130.75 (s), 127.56 – 127.34 (m), 124.79 – 124.57 (m), 123.55 – 123.34 (m), 118.02 – 117.62 (m), 116.17 – 113.87 (m), 112.88 (s), 57.05 (s). Mol. Formula: $C_{25}H_{16}FN_5O_5S$, m/z: 518

(E)-5-(3,4-dichlorobenzylidene)-2-((4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl) amino)thiazol-4(5H)-one (8e)
White coloured, Yield: 70% compound, m.p: 183-185 ºC, ^{1}H NMR (400 MHz, Chloroform) δ 8.4 – 8.3 (m, 2H), 7.9 – 7.7 (m, 2H), 7.5 (s, 1H), 7.5 – 7.3 (m, 3H), 6.9 – 6.6 (m, 2H), 6.59 – 6.45 (m, 2H), 5.13 – 5.09 (m, 2H), 4.45 (s, 1H). ^{13}C NMR (100 MHz) δ 176 (s), 168 (s), 162 (s), 162 (s), 154 (s), 147.39 (s), 135.79 (s), 134.77 (s), 133.41 (d, *J* = 10.9 Hz), 132.33 (s), 132.08 (s), 129 (s), 129 (s), 127 (s), 127– 127 (m), 124 – 124 (m), 123 – 123 (m), 118.02 – 117.62 (m), 112.00 (s), 57 (s). Mol. Formula: $C_{25}H_{15}Cl_2N_5O_5S$, m/z: 568

3. CONCLUSIONS

All the final compounds 5a-j successfully synthesized. Purified by Column chromatography and characterized by different spectroscopical techniques like ^{1}H NMR, ^{13}C NMR and MS analysis, all the compounds were carried out for their antibacterial and anti-fungal activity using 2 gram positive and 2 gram negative bacterias as well as two fungal stain. From this study we came to know that all the compounds emerged out as potent antibacterial and anti-fungal agents expect 5a, 5b, 5i and 5j.

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