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SYNTHESIS AND EVALUTION OF THIAZOLIDINONE FOR ANTIBACTERIAL ACTIVITY AND ANTIFUNGAL ACTIVITIES

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ABSTRACT
2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (2a-e) in good yields. Cyclocondensation of compounds (2a-e) with thioglycolic acid yields N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamide (3a-e). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.
Keywords: acetohydrazide, thiazolidine, antibacterial activity and antifungal activities.

INTRODUCTION

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties[1-15]. These heterocyclic systems find wide use in medicine, agriculture and industry. 4-Thiazolidinones and its arylidene compounds give good pharmacological properties[16-20]. 4-thiazolidinones are also known to exhibit antitubercular[21], antibacterial[22], antifungal[23] and anticonvulsant activities. Hence, it was thought of interest to merge both of thiazolidinone and hydrazide moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of phenoxyl oxadiazole hydrazide containing thiazolidinone moiety. Hence the present communication comprises the synthesis of N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamide (3a-e). The synthetic approach is shown in Scheme-1.

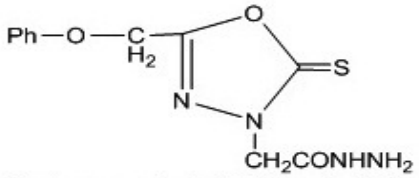
EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL 01046.

Preparation N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) aceto hydrazide (2a-e)
An equimolecular mixture of 2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (1), (0.01mole) and the aromatic aldehydes (a-e) in ethanol (15ML) was refluxed on a water bath for 1-2 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1.

Preparation of N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide (3a-e)
A mixture N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) aceto hydrazide (2a-e) (0.01 mole) in THF (30ML) and mercapto acetic acid (thioglycolic acid) (0.01 mole) with a pinch of anhydrous

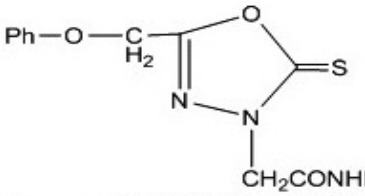
$ZnCl_2$ was refluxed for 12 hrs. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using benzene: chloroform (8:2; v/v) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 4-thiazolidinones (2a-e), which were obtained in 50-65% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.



2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetohydrazide

(1)

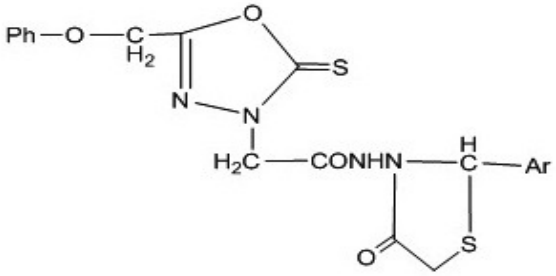
(i) EtOH
(ii) ArCHO



N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetohydrazide

(2a-e)

$SHCH_2COOH$
Anhy. $ZnCl_2$/DMF



N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetamide

(3a-e)

Where, Ar = (a) C_6H_5 (b) 4-CH_3-C_6H_4

(c) 4-OCH_3-C_6H_4 (d) 4-OH-C6H4

(e) 2-OH-C_6H_4

Scheme-1: Synthesis of Thioxadiazole

Biological screening

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ML by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in cm. Compounds 2c, 2d, 3c and 3d were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -3 and 4.

Table-1: Analytical Data and Elemental Analysis of Compounds (2a-e)

Compd.	Molecular formula (Mol. Wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		% H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{18}H_{16}N_4O_3S$ (368)	375	85	228-230	58.6	58.68	4.3	4.38	15.1	15.21
2b	$C_{19}H_{18}N_4O_3S$ (382)	396	80	229-232	59.6	59.67	4.7	4.74	14.6	14.65
2c	$C_{19}H_{18}N_4O_4S$ (398)	409	75	222-223	57.2	57.27	4.5	4.55	14.0	14.06
2d	$C_{19}H_{16}N_4O_4S$ (384)	393	72	220-221	56.2	56.24	4.1	4.20	14.5	14.57
2e	$C_{19}H_{16}N_4O_4S$ (384)	397	78	225-227	56.2	56.24	4.1	4.20	14.5	14.57

* Uncorrected

Table-2: Analytical Data and Elemental Analysis of Compounds (3a-e)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		%H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{20}H_{18}N_4O_4S_2$ (442)	462	67	209-210	54.2	54.28	4.0	4.10	12.6	12.66	14.4	14.49
3b	$C_{21}H_{20}N_4O_4S_2$ (456)	478	64	206-208	55.2	55.25	4.4	4.42	12.2	12.27	14.0	14.05
3c	$C_{21}H_{20}N_4O_5S_2$ (472)	496	62	196-198	53.3	53.38	4.2	4.27	11.8	11.86	13.5	13.57
3d	$C_{20}H_{18}N_4O_5S_2$ (458)	477	72	192-194	52.3	52.39	3.9	3.96	12.2	12.22	13.9	13.99
3e	$C_{20}H_{18}N_4O_5S_2$ (458)	471	67	197-198	52.3	52.39	3.9	3.96	12.2	12.22	13.9	13.99

* Uncorrecte

Table-3: Antibacterial Activity of Compounds (2a-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
2a	52	53	62	47
2b	56	58	54	58
2c	62	59	59	64
2d	70	66	76	48
2e	55	57	67	62
Tetracycline	55	79	74	84

Table-4: Antibacterial Activity of Compounds (3a-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
3a	58	56	66	51
3b	57	62	57	63
3c	71	69	78	71
3d	61	64	62	69
3e	56	52	69	66
Tetracycline	55	79	72	84

Table-5: Antifungal Activity of Compounds (2a-e)

Zone of Inhibition at 1000 ppm (%)					
Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum	Fusarium oxyporium
2a	67	66	64	56	71
2b	58	51	61	63	67
2c	70	70	71	60	75
2d	68	68	69	71	68
2e	64	62	61	76	74

Table-6: Antifungal Activity of Compounds (3a-e)

Zone of Inhibition at 1000 ppm (%)					
Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum	Fusarium oxyporium
3a	70	68	59	49	66
3b	60	59	64	67	66
3c	77	69	68	69	77
3d	73	69	64	71	69
3e	68	64	63	73	69

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum***,** *Fusarium oxyporium*. The antifungal activity of all the compounds (2a-e) & (3a-e) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^{o} C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\textbf{Percentage of inhibition} = 100(X-Y) / X$$

Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (2a-e) and (3a-e) is shown in Tables-5 and 6.

RESULTS AND DISCUSSION

It was observed that 2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (1), on condensation with aromatic aldehydes, yields N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-

3(2H)-yl)acetohydrazide (2a-e). The structures of (2a-e) were confirmed by elemental analysis and IR spectra showing an absorption band at 1620-1640 (C=N), 3030-3080 cm^{-1} (C-H, of Ar.), 2815-2850 cm^{-1} (-OCH_2). ^{1}H NMR : 6.95 – 7.91 (5H, m) (Ar - H), 11.80-11.81 (1H, s) (-CONH), 8.43-8.80 (1H, s) (-N=CH), 2b; 2.41 (3H, s) (-CH_3), 2c; 3.90 (3H, s) (-OCH_3), 2d,2e; 4.09 (2H,s) (OH).^{13}C NMR:117.9-118.1, 121.8-122.0, 128.9-129.1, 129.5-130.0, 131.2-131.5, 133.9-134.3, 159.6-160.0 (Ar-8C), 163.5-163.8(-CONH), 146.9-150.4 (-CH); 2c: 55.5-56.7 (-OCH_3); 2b: 22.5 (CH_3). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(phenoxy methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamide (3a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1690cm^{-1} (C=O of thiazolidinone ring), 718cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095cm^{-1} (CH_2 of thiazolidinone ring), 3030-3080cm^{-1}(C-H, of Ar.), 3450-3550 cm^{-1} (-OH), 1660-1670 cm^{-1} (-CONH) for (3a) compound.

^{1}H NMR: 3.85-3.95 (2H, s) (-CH_2 of the ring), 5.950-5.959 (1H, s) (-CH), 6.90-7.95 (8H, m) (Ar-H), 8.20-8.22 (1H, s) (-CONH), 3b; 2.43 (3H, s) (-CH_3), 3c; 3.91 (3H, s) (-OCH_3), 2d,2e; 4.09 (2H,s) (OH). ^{13}C NMR:115.9-116.2, 121.3-121.5, 126.9-127.6, 128.3-128.5, 128.9-129.2, 156.9-157.5, 168.9-169.3 (Ar-10C), 38.9-39.5 (–CH_2 of the ring), 67.8-68.3 (–CH), 164.8-165.9(-CONH), 168.9-169.9 (-CO of the ring), 3c: 56.0-56.4 (-OCH_3); 3b: 22.9 (CH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of all compounds are presented in Tables-1, 2.

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