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NOVEL 4-THIAZOLIDINONE DERIVATIVES AS ANTI-MICROBIAL AND ANTIFUNGAL ACTIVITY

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ABSTRACT

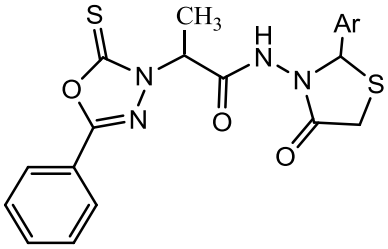
The Fused Novel heterocyclic compounds (3a-h) namely N-(3,5diphenyl-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl propanamide were prepared and characterized. The compound N-(4-oxo-2-phenylthiazolidin-3-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide (1a-h) reacted with benzaldehyde gives Benzilidine derivatives (2a-h). Such compounds 2a-h on Condensation with hydroxyl amine gives title compounds i.e. 3a-h. All the compounds were screened for their antimicrobial activity.

KEYWORDS: Oxadiazolo-thiazolidinones, Benzilidine 1,3,4-oxadiazol, antibacterial and antifungal activities.

INTRODUCTION

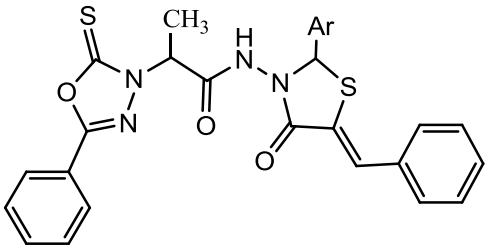
The heterocyclic compounds containing thiazolidinones have important role in pharmaceutical industry[1-3]. Thiazolidinones are also know as exhibit antibacterial, antifungal, anticancer, antitubercular, anti-inflammatory, analgesic and anticonvulsant activities[4-8]. There are so many One of the 1,3,4-oxadiazol derivatives were extensively studied in recent years for their biological and medicinal applications. 1,3,4-oxadiazol derivatives displayed on broad range of biological activity such as antimicrobial agents, antimicrobial, antitubercular, anti-HIV, anticancer, anti-inflammatory activity and anthelmintic activities[9-13]. These also Wide use in shows biochemical and physiochemical effects[14,15]. Hence, it was thought of interest to develop new 1,3,4-oxidiazol derivatives containing thiazolidinone nucleus which may enhance the biological activity of compounds. Hence the present communication comprises the synthesis of N-(3,5-diphenyl-3,3a-

dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide **(3a-h)**. The synthetic approach is shown in **scheme**.



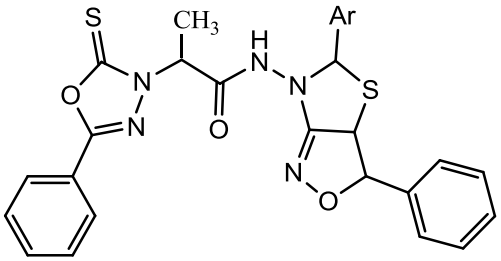
1a-h

Ph-CHO



2a-h

NH_2OH



3a-h

Where Ar = (a) C_6H_5 -
(b) 2-OH-C_6H_4 -
(c) 4-OH-C_6H_4 -
(d) 4-OCH_3-C_6H_4 -
(e) 4-Cl-C_6H_4 -
(f) 2-CH_3-C_6H_4 -
(g) 4-CH_3-C_6H_4 -
(h) 4-Br-C_6H_4 -

Scheme: Synthetic approach of targeted derivatives

EXPERIMENTAL

Materials and Methods

All the chemicals used were of laboratory grade. N-(4-oxo-2-phenylthiazolidin-3-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide **(1a-h)** was prepared by the reported method[16].

Melting points were determined by open capillary method and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO solvent with TMS as internal standard on a Bruker spectrometer at 400 MHz.

Preparation of Benzilidine derivatives (2a-h):

A mixture of 0.01 mole N-(4-oxo-2-phenylthiazolidin-3-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide(1), and 15ml benzaldehyde in ethanol was refluxed on a water bath for 3-4 hrs. The solid yield was separated by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds (2a-h) are given in **Table-1**.

Synthesis of N-(3,5diphenyl-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl propanamide (3a-h):

A mixture of 0.01 mole Benzilidine derivatives **(2a-h)** in 50ml ethanol with a NH_2OH was refluxed for 5-6 hrs. The resultant mixture was filtered and further crystallized from alcohol to give N-(3,5-diphenyl-3,3a-dihydrothiazolo[4,5-c] isoxazol-6(5H)-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide**(3a-h)** which were obtained in good yield. The yields, melting points and other characterization data of these compounds are given in **Table-2**.

BIOLOGICAL SCREENING

Antibacterial activities

Synthesized samples were screened for their 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 mm. Compounds 3a and 3e were found more toxic for microbes. Other compounds found to be less or moderate active then tetracycline **Table-3**.

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

Compd.	Molecular formula (Mol.wt.)	% of Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2a	$C_{27}H_{22}N_4O_3S_2$ (514)	80	228-229	63.03	63.3	4.28	4.0	10.89	10.8	12.45	12.4
2b	$C_{27}H_{22}N_4O_4S_2$ (530)	78	218-219	61.13	61.1	4.15	4.1	10.56	10.6	12.07	12.0
2c	$C_{27}H_{22}N_4O_4S_2$ (530)	75	219-220	61.13	61.1	4.15	4.1	10.56	10.6	12.07	12.0
2d	$C_{28}H_{24}N_4O_4S_2$ (544)	78	224-225	61.76	61.7	4.41	4.4	10.29	10.9	11.76	11.7
2e	$C_{27}H_{21}ClN_4O_3S_2$ (549)	75	231-233	59.01	58.2	3.82	3.8	10.20	10.2	11.65	11.6
2f	$C_{28}H_{24}N_4O_3S_2$ (528)	70	220-222	63.06	63.6	4.54	4.5	10.60	10.6	12.12	12.2
2g	$C_{28}H_{24}N_4O_3S_2$ (528)	72	221-222	63.06	63.6	4.54	4.5	10.60	10.6	12.12	12.2
2h	$C_{27}H_{21}BrN_4O_3S_2$ (593)	67	236-238	55.9	53.9	3.54	3.5	9.44	9.4	10.79	10.9

***** Uncorrected

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

Compd.	Molecular formula (Mol.wt.)	%of Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{27}H_{23}N_5O_3S_2$ (529)	74	237-238	61.24	61.2	4.34	3.9	13.23	13.2	12.09	11.2
3b	$C_{27}H_{23}N_5O_4S_2$ (545)	72	223-225	59.44	58.4	4.22	3.2	12.84	12.8	11.74	11.1

3c	$C_{27}H_{23}N_5O_4S_2$ (529)	70	227-228	61.24	61.4	4.34	3.9	13.23	13.2	12.09	11.2
3d	$C_{28}H_{25}N_5O_4S_2$ (559)	70	230-231	60.10	59.2	4.47	4.1	12.52	12.5	11.44	10.2
3e	$C_{27}H_{22}ClN_5O_3S_2$ (563)	68	240-242	57.50	56.4	3.90	3.5	12.43	12.7	11.36	10.2
3f	$C_{28}H_{25}N_5O_3S_2$ (543)	65	225-226	61.80	60.1	4.60	4.2	12.89	12.6	11.78	11.1
3g	$C_{28}H_{23}N_5O_3S_2$ (543)	67	224-225	61.80	60.1	4.60	4.2	12.89	12.6	11.78	11.1
3h	$C_{27}H_{22}BrN_5O_3S_2$ (608)	62	243-244	55.20	54.6	3.61	3.2	11.51	11.2	10.52	10.5

***** Uncorrected

Table:-3 Antibacterial Activity of Compounds (3a-h)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	Escherichia coli	Klebsiella promioe
3a	58	71	70	79
3b	52	72	62	72
3c	50	62	60	71
3d	54	74	64	78
3e	57	78	67	80
3f	48	64	68	70
3g	49	68	60	72
3h	49	65	64	71
Tetracycline	59	82	76	87

Antifungal Activities

Synthesized samples were screened for their 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. The antifungal activities of all the compounds **(3a-h)** 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 1ml. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120°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:

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 **(3a-h)** is shown in **Table-4**.

Table-4 Antifungal Activity of Compounds (3a-h)

Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum
3a	68	50	60	52
3b	58	54	56	54
3c	56	55	54	56
3d	62	59	58	58
3e	64	59	59	54
3f	54	50	55	49
3g	57	52	57	50
3h	60	52	58	54

RESULTS AND DISCUSSION

The N-(4-oxo-2-phenylthiazolidin-3-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) propanamide (1a-h) undergoes on condensation with benzaldehyde to prepare the corresponding Benzilidine derivatives (z)-N-(5-benzylidene-4-oxo-2-phenyl thiazolidin-3-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide **(2a-h)**. The structure of resultant compounds **(2a-h)** were determined by elemental analysis. **IR:** The IR spectra showing an absorption bands at around, 1630-1650 cm^{-1} (C=N), 3380 (NH), 2950 (CH_2), 1720-1740(CO), 1690 cm^{-1} (C=O of thiazolidinone ring), 718 cm^{-1} (C-S-C of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar), 3430(OH),2824 cm^{-1} (-OCH_3), 1550-1570(C=C) **^{1}H NMR:** 7.15-7.90 (15H, m) (Ar - H), 4.5 (2H, d, CH_2), 7.05 (1H, s) (oxadiazole ring N=CH), 8.10 (1H, s) (CH), 10.52 (1H, s) (NH), 2.b;5.30 (1H, s) (-OH). 2c; 5.35(1H,s)(-OH),2d; 3.80 (1H,s) (-OCH_3), 2f; 2.30 (3H,s) (-CH_3) ,2g; 2.34 (3H,s) (-CH_3) The C,H, analysis data of all compounds are presented in **Table-1**.

The structure determination of **N-(3,5-diphenyl-3,3a-dihydrothiazolo[4,5-c] isoxazol-6(5H)-yl)-2-(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide (3a-h)** were supported by the elemental analysis. **IR:** The IR spectra showing an absorption bands at 1630-1650 cm^{-1}(C=N), 3380 cm^{-1} (N-H), 2950 cm^{-1} (CH_2), 1720 cm^{-1} (CH_2), 1720-1740 cm^{-1} (CO), 718 cm^{-1} (C-S-C thiazolidinone ring) 3030-3080 cm^{-1} (C-H of Ar.), 3430(OH), 2824 cm^{-1} (-OCH_3). Only difference found that missing of thiazolidinone ring containing CO group in these derivatives. **1H^{1}HNMR:** 7.30-7.92 (15H, m) (Ar-H), 4.5 (2H, d, CH_2), 5.7 (1H, s) (oxadiazole ring N=CH), 10.52 (1H, s) (NH), 3b; 5.29 (1H, s) (-OH). 3c; 5.32(1H,s)(-OH), 3d; 3.82(1H,s) (-OCH_3), 3f; 2.32 (3H, s) (-CH_3). 3g; 2.34 (3H,s) (-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 element contents are consistence with the predicted structure shown in **Scheme**. The IR data, also equivalent for assignment of the predicted structure.

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