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SYNTHESIS AND BIOLOGICAL STUDY OF SOME NEW THIAZOLIDINON DERIVATIVES

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ABSTRACT

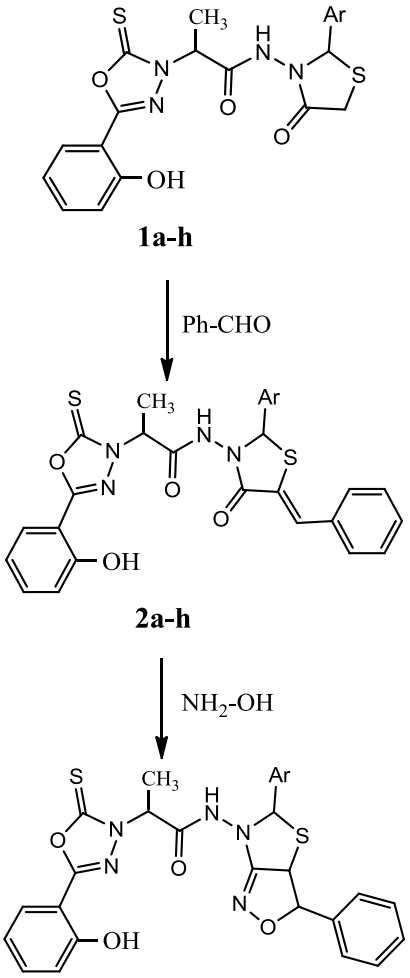
The Fused new heterocyclic compounds (3a-h) namely N-(3,5-diphenyl-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)-2-(5-(2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3 (2H)-yl)propanamide were prepared and characterized. First Oxadiazolo - thiazolidinones (1a-h) namely 2-(5-(2-hydroxyphenyl)-2-thioxo-1,3,4–oxadiazol-3(2H)-yl)-N-(4-oxo-2-phen ylthiazolidin-3-yl) propanamide on condensation with benzaldehyde gives the benzylidine der ivatives(2a-h) namely (z)-N-(5-benzylidene-4-oxo-2-phenylthiazolidin-3-yl)-2-(5-(2-hydroxy phenyl)-2-thioxo-1,3,4 -oxadiazol-3(2H)-yl) propanamide. Such compounds (2a-h) on condensation with hydroxyl amine gives the title compounds i.e. (3a-h). All the compounds were screened for their biological activities.

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

INTRODUCTION

The heterocyclic compounds thiazolidinones are of particular interest in pharmaceutical industry and medicinal chemistry.[1-3] Heterocyclic compounds containing the five membared oxadiazole nucleus which shows the diversity against useful biological effects.[4-8] 1,3,4-oxadiazol derivatives were comprehensively studied in recent years for their biological and pharmaceutical applications. 1,3,4-oxadiazol derivatives displayed broad range of biological activities such as anti- tubercular, antimicrobial, anticancer, anti-HIV, anthelmintic activities and anti-inflamatory activities.[9-13] These are also displays biochemical and physiochemical effects.[14,17] Hence, it was thought of interest to develop new 1,3,4-oxidiazol derivatives containing thiazolidinone nucleus which might be enhance the biological activity of compounds to some extent or they might be possess some of the above mentioned biological

activities. Hence the present communication comprises the synthesis of N-(3,5-diphenyl-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)-2-(5-(2-hydroxy phenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide (3a-h). The synthetic approach is to be shown below in scheme.



1a-h

2a-h

3a-h

Scheme: Synthetic approach of targeted derivatives.

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 -

EXPERIMENTAL

Materials and Methods

All chemicals used were of laboratory grade. 2-(5-(2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(4-oxo-2-phenylthiazolidin-3-yl)propanamide (1a-h) was prepared by

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 with TMS as internal standard on a Bruker spectrometer at 400 MHz.

Preparation of benzylidine derivatives (2a-h)

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

Synthesis of N-(3,5-diphenyl-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)-2-(5-(2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)propanamide (3a-h): A mixture of benzylidine derivatives **(2a-h)** (0.01 mole) in ethanol (50ml) with NH_2OH was refluxed for 6 hrs (Monitored by TLC). The crude product was left to cool at room temperature, then pured in the ice water, filtered, washed with water, dried and further crystallized from ethanol to get the target product named N-(3,5-diphenyl-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)-2-(5-(2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)yl)propanamide (3a-h), which obtained in good yield. The yields, melting points and other characterization data of these compounds are given in Table-2.

Biological Screening

Antibacterial activities

The newly synthesized heterocyclic compounds were tested for their antimicrobial activity 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. In similar conditions tetracycline was also used as a standard for comparison. The area of inhibition zone measured in mm. Compounds 3a and 3e were found more toxic for microbes. Other compounds found to be less or moderate active compared to tetracycline. According to their activities the results are shown in Table-3.

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2a	$C_{27}H_{22}N_4O_4S_2$ (530)	82	238-239	61.13	61.09	4.15	4.1	10.57	10.5	12.07	12.0
2b	$C_{27}H_{22}N_4O_5S_2$ (546)	78	228-229	59.34	59.3	4.03	4.0	10.25	10.2	11.72	11.69
2c	$C_{27}H_{22}N_4O_5S_2$ (546)	75	227-228	59.34	59.3	4.03	4.0	10.25	10.2	11.72	11.69
2d	$C_{28}H_{24}N_4O_5S_2$ (560)	77	230-231	60	59.8	4.29	4.2	10.0	9.8	11.43	11.4
2e	$C_{27}H_{21}ClN_4O_4S_2$ (565)	78	240-241	57.34	57.3	3.72	3.67	9.91	9.9	11.32	11.3
2f	$C_{28}H_{24}N_4O_4S_2$ (544)	71	227-228	61.76	61.6	4.41	4.39	10.29	10.2	11.76	11.7
2g	$C_{28}H_{24}N_4O_4S_2$ (544)	73	227-228	61.76	61.6	4.41	4.39	10.29	10.2	11.76	11.7
2h	$C_{27}H_{21}BrN_4O_4S_2$ (609)	70	246-247	53.20	53.18	3.45	3.4	9.2	9.1	10.50	10.0

***** Uncorrected.

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{27}H_{23}N_5O_4S_2$ (545)	73	242-243	59.44	59.5	4.22	4.2	12.84	12.8	11.74	11.7
3b	$C_{27}H_{23}N_5O_5S_2$ (561)	71	230-231	57.75	57.7	4.09	4.0	12.47	12.4	11.41	11.4
3c	$C_{27}H_{23}N_5O_5S_2$ (561)	69	232-233	57.75	57.7	4.09	4.0	12.47	12.4	11.41	11.4
3d	$C_{28}H_{25}N_5O_5S_2$ (575)	70	235-236	58.43	58.4	4.35	4.3	12.17	12.1	11.13	11.10
3e	$C_{27}H_{22}ClN_5O_4S_2$ (580)	68	245-246	55.86	55.8	3.79	3.9	12.07	12.0	11.13	11.1
3f	$C_{28}H_{25}N_5O_4S_2$ (559)	64	230-231	60.10	60.1	4.47	4.4	12.52	12.5	11.45	11.4
3g	$C_{28}H_{25}N_5O_4S_2$ (559)	66	229-230	60.10	60.1	4.47	4.4	12.52	12.5	11.45	11.4
3h	$C_{27}H_{22}BrN_5O_4S_2$ (624)	61	248-249	51.92	51.9	3.53	3.5	11.28	11.2	10.26	10.2

*****Uncorrected.

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

Compounds	Gram +Ve		Gram –Ve	
	Staphylococcus aureus	Bacillus subtilis	Escherichia coli	Klebsiella promioe
3a	59	72	69	78
3b	52	68	62	71
3c	49	59	61	70
3d	50	70	63	75
3e	55	71	65	78
3f	45	60	60	69
3g	47	61	61	71
3h	49	63	62	72
Tetracycline	60	80	75	85

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used where Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine and Rhizopus nigricum. The antifungal activities of all the compounds (3a-h) 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 1ml. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) 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:

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

Where, X = Area of colony in control plate

Y = Area of colony in test plate The fungicidal activity displayed by various compounds (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	69	50	60	51
3b	61	54	57	53
3c	63	57	54	56
3d	66	60	57	58
3e	68	62	60	54
3f	58	53	55	50
3g	60	54	55	52
3h	63	54	58	53

RESULTS AND DISCUSSION

The 2-(5-(2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(4-oxo-2-phenyl thiazolidin-3-yl)propanamide (1a-h) undergoes in a facile condensation with benzaldehyde to afford the corresponding benzylidine derivatives (2a-h). The structures of (2a-h) were confirmed by elemental analysis and IR spectra showing an absorption bands at around 1640-1660cm^{-1}(C=N), 3390cm^{-1}(NH), 2950cm^{-1}(CH_2), 1720-1740cm^{-1} (CO), 1680cm^{-1}(C=O of thiazolidinone ring), 720cm^{-1}(C-S-C of thiazolidinone ring), 3040-3090cm^{-1}(C-H of Ar), 3400cm^{-1}(OH), 2830cm^{-1}(-OCH_3), and 1550-1570cm^{-1} (C=C). ^{1}H NMR: δ 7.16-7.90 (15H, m) (Ar-H), δ 4.5 (2H, d) (CH_2), δ 7.05 (1H, s) (oxadiazole ring N=CH), δ 8.10 (1H, s) (CH), δ 10.52 (1H, s) (NH), 2b; δ 5.30 (1H, s) (-OH). 2c; δ 5.36 (1H, s) (-OH), 2d; δ 3.80 (1H, s) (-OCH_3), 2f; δ 2.30 (3H, s) (-CH_3) and 2g; δ 2.34 (3H, s) (-CH_3). The C, H, N analysis data of all compounds are presented in Table-1.

The structures assigned for N-(3,5-diphenyl-3,3a-dihydrothiazolo[4,5-c]isoxazol-6(5H)-yl)-2-(5-(2-hydroxy phenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) propanamide (3a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1640-1660cm^{-1}(C=N), 3390cm^{-1}(NH), 2950cm^{-1}(CH_2), 720cm^{-1}(C-S-C of thiazolidinone ring), 3040-3090cm^{-1}(C-H of Ar), 3400cm^{-1}(OH), 2830cm^{-1}(-OCH_3) and 600cm^{-1}(C-X). Only difference found that missing of thiazolidinone ring containing C=O group in these derivatives. ^{1}H NMR: δ 7.30-7.92 (15H, m) (Ar - H), δ 4.5 (2H, d) (CH_2), δ 5.7 (1H, s) (oxadiazole ring N=CH), δ 10.52 (1H, s) (NH), 3b; δ 5.29 (1H, s) (-OH). 3c; δ 5.36 (1H, s) (-OH), 3d; δ 3.82 (1H, s) (-OCH_3), 3f; δ 2.32 (3H, s) (-CH_3) and 3g; δ 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 elemental contents are consistence with the predicted structure shown in Scheme. The IR data also equivalent for assignment of the predicted structure.

CONCLUSION

All the novel synthesized compounds were shown moderate antibacterial and antifungal activities. Thiazolidinone derivatives, were synthesized and characterized for their structure elucidation. Antibacterial and antifungal activities of these compounds indicated that compounds were found to be showing comparable activity against some bacteria compared to standard antibiotic drug.

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