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Synthesis and biological activity of 4-bromo-2-hydroxy-N-(5-methylene-4-oxo-2-aryl-thiazolidin-3-yl) benzamide

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ABSTRACT

4-bromo-2-hydroxy benzoic acid hydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding 4-bromo-2-hydroxy benzoic acid arylidene hydrazides (2a-h) in good yields. Cyclocondensation of compounds (2a-h) with thioglycolic acid yields 4-bromo-2-hydroxy- N (4-oxo-2-aryl- thiazolidin -3-yl) benzamides (3a-h). These (3a-h) compounds are for the reacted with benzaldehyde in the presence of sodium ethanolate affords, giving 4-bromo-2-hydroxy- N (5-methylene-4-oxo-2-aryl- thiazolidin -3-yl)benzamides (4a-h). 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.

Key words: 4-bromo-2-hydroxy benzoic acid hydrazide, thiazolidin, antibacterial activity.

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. One of the hydrazides, 4-bromo-2-hydroxy benzoic acid hydrazide and their condensed products play a vital role in medicinal chemistry [16-18]. 4-Thiazolidinones and its arylidene compounds give good pharmacological properties [19-23]. 4-thiazolidinones are also known to exhibit antitubercular [24], antibacterial [25], antifungal [26] and anticonvulsant activities. Hence, it was thought of interest to merge both of thiazolidinone and 4-bromo-2-hydroxy benzoic acid 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 4-bromo-2-hydroxy benzoic acid hydrazide containing thiazolidinone moiety. Hence the present communication comprises the synthesis of 4-bromo-2-hydroxy- N (5-methylene-4-oxo-2-aryl- thiazolidin -3-yl)benzamide. The synthetic approach is shown in scheme-1.

MATERIALS AND METHODS

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 of 4-bromo-2-hydroxy benzoic acid arylidene hydrazide (2a-h)

General procedure: – An equimolecular mixture of 4-bromo-2-hydroxy benzoic acid hydrazide (1), (0.01mole) and the aromatic aldehydes (a-h) in ethanol (15mL) was refluxed on a water bath for 1-2 h. 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 4-bromo-2-hydroxy- N-(4-oxo-2-aryl- thiazolidin -3-yl)benzamide (3a-h)

General procedure: A mixture 4-bromo-2-hydroxy benzoic acid arylidene hydrazide (2a-h) (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 h. 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 (3a-h), which were obtained in 50-60% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

Preparation of 4-bromo-2-hydroxy- N (5-methylene-4-oxo-2-aryl- thiazolidin -3-yl) benzamide (4a-h)

An equimolar solution of 4-bromo-2-hydroxy- N-(4-oxo-2-aryl- thiazolidin -3-yl)benzamide (3a-h) and benzaldehyde in dioxane (50mL) in the presence of C_2H_5ONa were refluxed for about 3 h. The solvent was removed in vacuo. The resulting product was recrystallized from methanol to yield compound (4a-h). The yields, melting points and other characterization data of these compounds are given in Table -3.

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 3f, 3g, 4f, and 4g were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -4 and 5.

Antifungal Activities

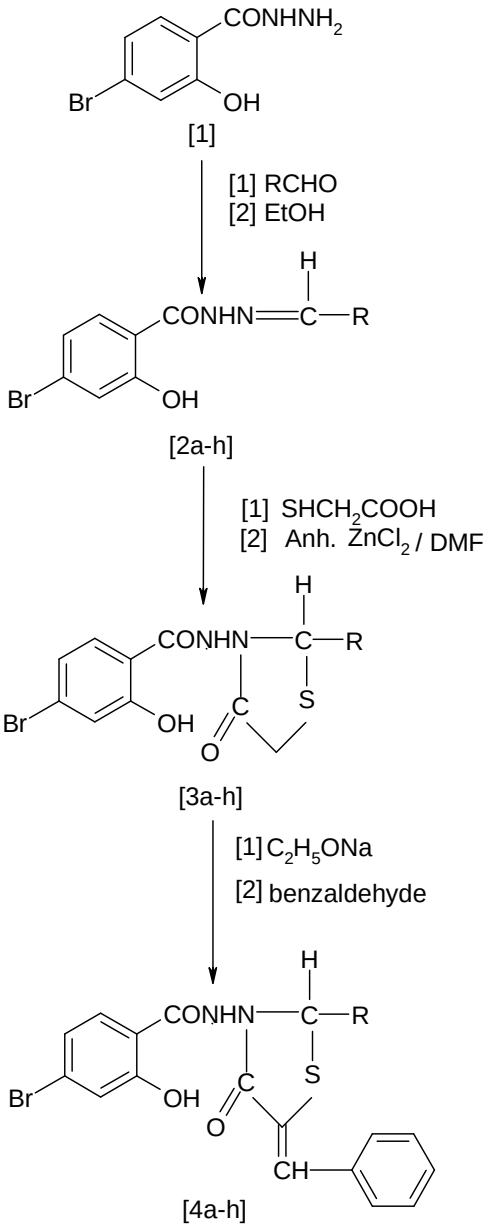
The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp*, *Aspergillus niger*, *Botrydepladia thiobromine*, and *Rhizopus nigricum***,** *Fusarium oxyporium*. The antifungal activity of all the compounds (3a-h) & (4a-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 1c. 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) and (4a-h) is shown in Tables-6 and 7.



SCHEME – 1

Where, R =(a) C_6H_5 (b) 4-OCH_3-C_6H_4 (c) 4-OH-C_6H_4 (d) 2-OH-C_6H_4 (e) 4-CH_3-C_6H_4 (f) 3,4-CH_2O_2-C_6H_4 (g) 4-OH-3-OCH_3-C_6H_3 (h) 3,4-C_2H_5-C_6H_4

RESULTS AND DISCUSSION

It was observed that 4-bromo-2-hydroxy benzoic acid hydrazide (1), on condensation with aromatic aldehydes, yields 4-bromo-2-hydroxy benzoic acid arylidene hydrazides (2a-h). The structures of (2a-h) 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.), 3240-3260 cm^{-1} (-OH), 2815, 1250 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3). ^{1}H NMR : 6.85-7.84 (8H, m) (Ar - H), 11.70-11.80 (1H, s) (-OH), 11.84-11.95 (1H, s) (-CONH), 8.36-8.80 (1H, s) (-N=CH), 2e; 2.40 (3H, s) (-CH_3), 2b, 2g; 3.91 (3H, s) (-OCH_3), 2h; 4.15 (4H, q) (CH_2), 1.36 (6H, t) (CH_3), 2f; 6.14 (2H, s) (-OCH_2O- cyclic). ^{13}C NMR:111.8-160.8 (Ar-10C), 163.0-164 (-CONH), 146.4-147 (-CH); (2b,2g): 55.5-56.9 (-OCH_3); (2e): 21.3 (CH_3); (2f): 102.9 (OCH_2O cyclic); (2h): 65.5 (OCH_2), 15.4 (CH_3). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 4-bromo-2-hydroxy- N (4-oxo-2-aryl- thiazolidin -3-yl) -benzamides (3a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1630-1650cm^{-1} (C=O of thiazolidinone ring), 740-750 cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095cm^{-1} (CH_2 of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 3240-3260 cm^{-1} (-OH), 1660-1670 cm^{-1} (-CONH).

^{1}H NMR: 6.63-7.80 (8H, m) (Ar-H), 3.85-3.95 (2H, s) (-CH_2 of the ring), 5.90-5.95 (1H, s) (-CH), 11.84-11.98 (1H, s) (-CONH), 11.70-11.85 (1H, s) (-OH), 3e; 2.41 (3H, s) (-CH_3), 3b,3g; 3.92 (3H, s) (-OCH_3), 3h; 4.13 (4H q) (CH_2), 1.33 (6H, t) (CH_3), 3f; 6.11 (2H, s) (-OCH_2O- cyclic). ^{13}C NMR:112.3-160.8 (Ar-10C), 35.4-35.8 (–CH_2 of the ring), 64.0-64.8 (–CH), 164.5-165.2 (-CONH), 168.4-169 (-CO of the ring), (3b,3g): 55.2-56.2 (-OCH_3); (3e): 21.3 (CH_3); (3f): 102.5 (OCH_2O cyclic); (3h): 65.3 (OCH_2), 14.5 (CH_3). The C, H, N and S analysis data of all compounds are presented in Table-2.

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	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{14}H_{11}BrN_2O_2$ (319)	80	249	52.65	52.69	3.45	3.47	8.75	8.78
2b	$C_{15}H_{13}BrN_2O_3$ (349)	78	240	51.52	51.60	3.71	3.75	7.98	8.02
2c	$C_{14}H_{11}BrN_2O_3$ (335)	80	230	50.13	50.17	3.28	3.31	8.31	8.36
2d	$C_{14}H_{11}BrN_2O_3$ (335)	79	233	50.12	50.17	3.26	3.31	8.33	8.36
2e	$C_{15}H_{13}BrN_2O_2$ (333)	75	234	54.00	54.07	3.89	3.93	8.38	8.41
2f	$C_{15}H_{11}BrN_2O_4$ (363)	77	241	49.58	49.61	3.01	3.05	7.68	7.71
2g	$C_{15}H_{13}BrN_2O_3$ (365)	74	245	49.27	49.33	3.51	3.59	7.61	7.67
2h	$C_{18}H_{19}BrN_2O_4$ (407)	71	267	53.01	53.08	4.66	4.70	6.79	6.88

***** *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	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{16}H_{13}BrN_2O_3S$ (393)	65	224	48.81	48.87	3.23	3.33	7.08	7.12	8.11	8.15
3b	$C_{17}H_{15}BrN_2O_4S$ (423)	61	229	48.21	48.24	3.51	3.57	6.58	6.62	7.50	7.58
3c	$C_{16}H_{13}BrN_2O_4S$ (409)	60	178	46.90	46.96	3.15	3.20	6.78	6.84	7.74	7.83
3d	$C_{16}H_{13}BrN_2O_4S$ (409)	61	155	46.91	46.96	3.16	3.20	6.79	6.84	7.72	7.83
3e	$C_{17}H_{15}BrN_2O_3S$ (407)	62	179	50.08	50.13	3.13	3.17	6.80	6.88	7.81	7.87
3f	$C_{17}H_{13}BrN_2O_5S$ (437)	64	189	46.66	46.70	2.92	3.00	6.38	6.41	7.23	7.33
3g	$C_{17}H_{15}BrN_2O_5S$ (439)	55	172	46.39	46.48	3.36	3.44	6.35	6.38	7.26	7.30
3h	$C_{20}H_{21}BrN_2O_5S$ (481)	60	218	49.84	49.90	4.30	4.40	5.78	5.82	6.61	6.66

*****Uncorrected*

Table:-3 Analytical Data and Elemental Analysis of Compounds (4a-h)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{17}H_{13}BrN_2O_3S$ (405)	68	230	50.30	50.38	3.18	3.23	6.89	6.91	7.85	7.91
4b	$C_{18}H_{15}BrN_2O_4S$ (435)	62	229	49.59	49.67	3.41	3.47	6.36	6.44	7.31	7.37
4c	$C_{17}H_{13}BrN_2O_4S$ (421)	67	218	48.40	48.47	3.08	3.11	6.60	6.65	7.55	7.61
4d	$C_{17}H_{13}BrN_2O_4S$ (421)	68	220	48.42	48.47	3.09	3.11	6.59	6.65	7.54	7.61
4e	$C_{18}H_{15}BrN_2O_3S$ (419)	59	218	51.52	51.56	3.59	3.61	6.61	6.68	7.61	7.65
4f	$C_{18}H_{13}BrN_2O_5S$ (449)	60	218	48.09	48.12	2.89	2.92	6.18	6.24	7.10	7.14
4g	$C_{18}H_{15}BrN_2O_5S$ (451)	65	223	47.89	47.91	3.30	3.35	6.18	6.21	7.07	7.11
4h	$C_{21}H_{21}BrN_2O_5S$ (493)	66	226	51.07	51.12	4.17	4.29	5.60	5.68	6.48	6.50

*****Uncorrected*

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

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E. coli***	***Klebsiella promioe***
3a	10	10	12	14
3b	13	12	11	19
3c	11	12	17	13
3d	12	15	14	16
3e	13	13	15	12
3f	17	17	18	19
3g	18	16	17	20
3h	15	12	14	13
Tetracycline	22	18	21	23

The IR spectra of (4a-h) are almost resemble those of the corresponding (3a-h) only discernable difference observed that the new band (but not strong) at 1628cm^{-1} (-C=CH-Ar) is observed in all the spectra of (4a-h) Which might be responsible.

^{1}H NMR: 6.63-7.80 (8H, m) (Ar-H), 5.97 (1H, s) (-CH), 11.84-11.98 (1H, s) (-CONH), 11.70-11.85 (1H, s) (-OH), 4e; 2.40 (3H, s) (-CH_3), 4b, 4g; 3.85 (3H, s) (-OCH_3), 4h; 4.08, (4H, q) (-CH_2), 1.38 (6H, t) (-CH_3), 4f; 6.10 (2H, s) (-OCH_2O cyclic). ^{13}C NMR:112.9-160.8 (Ar-10C), 140.0-140.5 (-C- of the ring), 70.0-70.6 (-CH of the ring), 112.5-113.5 (-CH_2), 164.0-164.9 (-CO), 164.8-165.2 (-CONH), (4b,4g): 55.5-56.0 (-OCH_3); (4e): 21.8 (CH_3); (4f): 101.5 (OCH_2O); (4h): 65.4 (OCH_2), 15.3 (CH_3). The C, H, N and S analysis data of all compounds are presented in Table-3.

Table:-5 Antifungal Activity of Compounds (3a-h)

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Nigrospora Sp.***	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Rhizopus Nigricum***	***Fusarium oxyporium***
3a	67	61	67	61	70
3b	59	59	62	64	68
3c	64	65	64	68	69
3d	60	60	66	70	68
3e	61	62	61	71	62
3f	63	60	64	64	71
3g	65	68	70	61	69
3h	58	72	71	70	60

Table:-6 Antibacterial Activity of Compounds (4a-h)

Compounds	**Gram +Ve**		**Gram -Ve**	
	Staphylococcus aureus	***Bacillus subtilis***	***E. coli***	***Klebsiella promioe***
4a	11	12	11	09
4b	13	09	10	11
4c	15	14	11	13
4d	11	14	13	14
4e	12	15	11	15
4f	17	17	19	17
4g	19	18	19	20
4h	12	17	13	17
Tetracycline	22	19	21	23

Table:-7 Antifungal Activity of Compounds (4a-h)

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Nigrospora Sp.***	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Rhizopus Nigricum***	***Fusarium oxyporium***
4a	69	70	70	58	68
4b	63	62	67	61	69
4c	62	68	64	62	70
4d	60	63	68	70	69
4e	61	61	65	74	61
4f	62	58	69	68	70
4g	70	60	70	66	70
4h	61	65	72	71	64

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 of 3c and 4e compounds are 415 and 426 respectively.

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