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Synthesis and Biological Activity of (*Z*) –*n*-(5-Benzylidene-4-oxo-2-substituted-phenylthiazolidin-3-yl)-5-((1, 3-dioxoisoindolin-2-yl)methyl)-2-hydroxybenzamide

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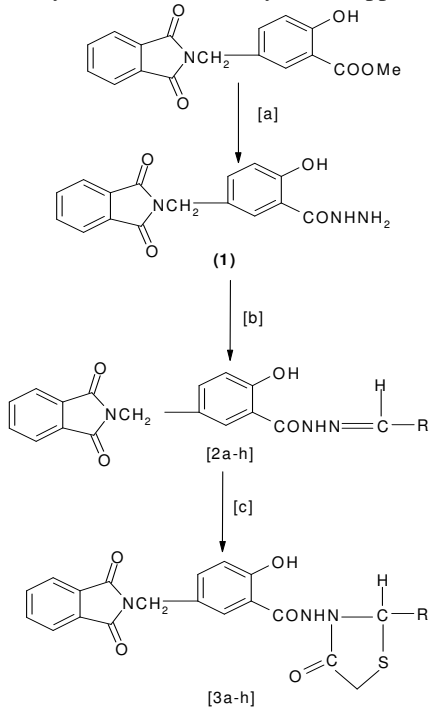
Abstract: 5-((1, 3-Dioxoisoindolin-2-yl)methyl-2-hydroxybenzohydrazide (**1**) undergoes facile condensation with aromatic aldehydes to afford the corresponding *N*'-substituted-phenyl-5-((1,3-dioxoisoindolin-2-yl) methyl)-2-hydroxybenzohydrazide (**2a-h**) in good yields. Cyclocondensation of compounds (**2a-h**) with thioglycolic acid yields 5-((1,3-dioxoisoindolin-2-yl) methyl)-2-hydroxy-*N*-(4-oxo-2-substituted phenylthiazolidin-3-yl)benzamide (**3a-h**). These (**3a-h**) compounds were further reacted with benzaldehyde in the presence of sodium ethanolate affords, (Z) –*N*-(5-benzylidene-4-oxo-2-substituted phenyl-thiazolidin-3-yl)-5-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxybenzamide(**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.

Keywords: 5-((1,3-Dioxoisoindolin-2-yl)methyl-2-hydroxybenzohydrazide, Thiazolidin, Antibacterial activity.

Introduction

Hydrazide and their heterocyclized 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, 5-((1,3-dioxoisoindolin-2-yl)methyl-2-hydroxybenzohydrazide 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 5-((1,3-dioxoisoindolin-2-yl)methyl-2-hydroxybenzohydrazide 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 salicylhydrazide containing thiazolidinone moiety. Hence the present communication comprises the synthesis of 5-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxy-*N*-(4-oxo-2-substituted phenylthiazolidin-3-yl)benzamide. The synthetic approach is shown in Scheme 1.



Scheme 1

(a) $NH_2NH_2.H_2O$ (b) RCHO (c) $SHCH_2COOH$, Anh. $ZnCl_2$

Where, R = (a) C_6H_5, (b) 4-OH-C_6H_4, (c) 2-OH-C_6H_4, (d) 4-OCH_3-C_6H_4, (e) 4-OH-3-OCH_3-C_6H_3, (f) 4- Cl- C_6H_4, (g) 2-No_2-C_6H_4, (h) 5-Br-2-OH-C_6H_3

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 ^1H 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 N'-Substituted phenyl-5-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxybenzohydrazide (**2a-h**)*

General procedure

An equimolecular mixture of 5-((1,3-dioxoisoindolin-2-yl)methyl-2-hydroxybenzohydrazide (**1**), (0.01 mole) and the aromatic aldehydes (**a-h**) in ethanol (20 mL) was refluxed on a water bath for 1.5-2.0 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.

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	$C_{24}H_{19}N_3O_3$(397.43)	80	252	72.44	72.53	4.77	4.82	10.45	10.57
2b	$C_{24}H_{19}N_3O_4$(413.43)	72	260	69.65	69.72	4.58	4.63	10.04	10.16
2c	$C_{24}H_{19}N_3O_4$(413.43)	76	259	69.69	69.72	4.56	4.63	10.05	10.16
2d	$C_{25}H_{21}N_3O_4$(249)	79	253	70.14	70.25	4.88	4.95	9.78	9.83
2e	$C_{25}H_{21}N_3O_5$(443.45)	70	258	67.65	67.71	4.69	4.77	9.39	9.48
2f	$C_{24}H_{18}ClN_3O_3$(431.87)	64	255	66.70	66.75	4.19	4.20	9.75	9.83
2g	$C_{24}H_{18}N_4O_5$(442.42)	70	261	65.10	65.15	4.05	4.10	12.56	12.66
2h	$C_{24}H_{18}BrN_3O_4$(492.32)	78	257	58.49	58.55	3.61	3.69	8.51	8.54

*Preparation of 5-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxy-N-(4-oxo-2-substituted phenylthiazolidin-3-yl)benzamide (**3a-h**)*

General procedure

A mixture *N*'-substituted phenyl-5-((1,3-dioxoisoindolin-2-yl) methyl)-2-hydroxybenzo hydrazide (**2a-h**) (0.01 mole) in THF (50 mL) 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 52-65% yield. The yields, melting points and other characterization data of these compounds are given in Table 2.

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	$C_{25}H_{19}N_3O_5S$ (473.50)	55	265	63.28	63.41	3.95	4.04	8.79	8.87	6.68	6.77
3b	$C_{25}H_{19}N_3O_6S$ (489.50)	61	262	61.25	61.34	3.81	3.91	8.46	8.58	6.44	6.55
3c	$C_{25}H_{19}N_3O_6S$ (489.50)	54	259	61.27	61.34	3.80	3.91	8.47	8.48	6 .43	6.55
3d	$C_{26}H_{21}N_3O_6S$ (503.53)	64	260	61.95	62.02	4.11	4.20	8.32	8.35	6.31	6.37
3e	$C_{26}H_{21}N_3O_7S$ (519)	65	264	60.02	60.11	3.98	4.07	8.02	8.09	6.11	6.17
3f	$C_{25}H_{18}ClN_3O_5S$ (507.95)	58	263	59.04	59.11	3.47	3.57	8.21	8.27	6.25	6.31
3g	$C_{25}H_{18}N_4O_7S$ (518.50)	52	261	56.58	56.67	3.42	3.50	10.75	10.81	6.04	6.18
3h	$C_{25}H_{18}N_3O_6S$ (568.40)	60	258	52.79	52.83	3.07	3.19	7.26	7.39	5.58	5.64

*Preparation of (Z) –N-(5-benzylidene-4-oxo-2-substituted phenylthiazolidin-3-yl)-5-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxybenzamdie (**4a-h**)*

An equimolar solution of 5-((1,3-dioxoisoindolin-2-yl) methyl)-2-hydroxy-*N*-(4-oxo-2-substituted phenylthiazolidin-3-yl)benzamide (**3a-h**) and benzaldehyde in dioxane (40 mL) in the presence of C_2H_5ONa were refluxed for about 3.5 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.

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	$C_{32}H_{23}N_3O_5S$ (514.61)	73	269	68.30	68.44	4.09	4.13	7.41	7.48	5.63	5.71
4b	$C_{32}H_{23}N_3O_6S$ (577.61)	68	270	66.39	66.54	3.94	4.01	8.09	8.19	5.45	5.55
4c	$C_{32}H_{23}N_3O_6S$ (577.61)	70	273	66.41	66.54	3.93	4.01	7.20	7.27	5.48	5.55
4d	$C_{33}H_{25}N_3O_6S$ (591.63)	55	277	66.89	66.99	4.11	4.26	7.02	7.10	5.33	5.42
4e	$C_{33}H_{25}N_3O_7S$ (607.63)	68	272	65.19	65.23	4.08	4.15	6.83	6.92	5.19	5.28
4f	$C_{32}H_{22}ClN_3O_5S$ (596.05)	59	267	64.37	64.48	3.65	3.72	6.94	7.05	5.27	5.38
4g	$C_{32}H_{22}N_4O_7S$ (606.60)	62	268	63.25	63.36	3.58	3.66	9.19	9.24	5.18	5.29
4h	$C_{32}H_{22}BrN_3O_6S$ (656.50)	59	275	58.42	58.54	3.27	3.38	6.32	6.40	4.79	4.88

Results and Discussion

It was observed that 5-((1,3-dioxoisoindolin-2-yl)methyl-2-hydroxybenzohydrazide (**1**), on condensation with aromatic aldehydes, yields *N*'-substitutedphenyl-5-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxybenzohydrazide (**2a-h**). The structures of (**2a-h**) were confirmed by elemental analysis and IR spectra showing an absorption band at 3030-3080 cm^{-1} (C-H, of Ar.), 1620-1640 (C=N), 1660-1670 cm^{-1} (-CONH), 3450-3550 cm^{-1} (-OH), 2810-2852 cm^{-1} ($-OCH_3$). ^{1}H NMR: 6.90 – 7.95 (9H, m) (Ar - H), 5.30-5.50 (1H, s) (-OH), 8.40-8.78 (1H, s) (-CONH), 8.40-8.70 (1H, s) (-N=CH), 3.90 (3H, s) (-OCH3), 4.85 (2H, s) (CH_2). The C, H, N analysis data of all compounds are presented in Table 1.

The structures assigned to 5-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxy-*N*-(4-oxo-2-substituted phenylthiazolidin-3-yl)benzamide (**3a-h**) were supported by the elemental analysis and IR spectra showing an absorption bands at 718 cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095 cm^{-1} (CH_2 of thiazolidinone ring), 1690 cm^{-1} (C=O of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 3450-3550 cm^{-1} (-OH), 1660-1670 cm^{-1} (-CONH) for (**3a**) compound. ^{1}H NMR: 6.90-7.95 (9H, m) (Ar-H), 3.85-3.95 (2H, s) ($-CH_2$ of the ring), 5.950-5.959 (1H, s) (-CH), 8.20-8.22 (1H, s) (-CONH), 5.33-5.45 (1H, s) (-OH), 4.80 (2H, s) (CH_2), 3.92 (3H, s) (-OCH3). The C, H, N, S analysis data of all compounds are presented in Table 2.

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 1625 cm^{-1} (-C=CH-Ar) is observed in all the spectra of (**4a-h**) Which might be responsible. ^1H NMR: 6.90-7.95 (9H, m) (Ar-H), 7.75 (1H, s) (-CH), 8.20-8.28 (1H, s) (-CONH), 5.30-5.45 (1H, s) (-OH), 4.88 (2H, s) (CH_2), 3.95 (3H, s) (-OCH3). The C, H, N, S analysis data of all compounds are presented in Table 3.

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 samples **4b** and **4e** give the molecular ion peak (*m/z*) at 579 and 610 respectively. These values are corresponds to their molecular weight.

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 50 µg/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 **3c, 3e, 3g, 4b, 4d** and **4f** were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables 4 & 5.

Table 4. Antibacterial activity of compounds (**3a-h**)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
3a	55	51	68	53
3b	53	60	55	65
3c	63	70	61	62
3d	54	57	60	56
3e	64	65	68	71
3f	63	54	61	67
3g	70	59	69	68
3h	63	61	55	64
Tetracycline	62	69	81	78

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

Compounds	Zone of Inhibition at 1000 ppm, %				
	Nigrospora Sp.	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*	*Fusarium oxyporium*
3a	72	71	61	67	67
3b	63	58	59	60	69
3c	59	60	73	59	70
3d	61	61	65	69	63
3e	60	63	71	63	69
3f	70	58	68	70	65
3g	63	62	64	64	69
3h	62	68	69	68	68

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, Rhizopus nigricum* and *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 200 g, dextrose 20 g, agar 20 g and water. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120 ^{o}C for 15 min. at 15 atm. 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:

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

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.

Table 6. Antibacterial activity of compounds (**4a-h**)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
4a	54	56	62	56
4b	70	68	69	68
4c	67	61	64	60
4d	64	69	71	68
4e	57	54	63	61
4f	68	70	71	69
4g	63	61	60	62
4h	61	69	56	55
Tetracycline	60	69	68	76

Table 7. Antifungal activity of compounds (**4a-h**)

Compounds	Zone of Inhibition at 1000 ppm, %				
	Nigrospora Sp.	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*	*Fusarium oxyporium*
4a	61	58	63	52	61
4b	64	64	70	63	59
4c	62	71	68	74	68
4d	59	62	60	60	71
4e	61	59	68	71	63
4f	59	64	68	73	69
4g	66	73	67	69	68
4h	71	63	64	65	69

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