



SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF NOVEL PYRROLE COMPOUNDS

Dharmesh R. Dhameliya* and Mukesh C. Patel

P.S.Science and H. D. Patel Arts College, Kadi, Gujarat, India.

*E-mail: dharmeshdhameliya11@yahoo.com

ABSTRACT

5-((1, 3-dioxoisindolin-2-yl) methyl-2-hydroxybenzohydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding N'-Substitutedphenyl-5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxy benzo hydrazides (2a-h) in good yield. Cyclocondensation of compounds (2a-h) with maleic anhydride yields 1-(5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzamido) -5-oxo-2-substituted phenyl-2, 5-dihydro-1H-pyrrole-3-carboxylic acid (3a-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: substituted benzohydrazide, pyrrole, antibacterial activity.

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INTRODUCTION

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties¹⁻¹⁵. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the hydrazides, benzohydrazide and their condensed products play a vital role in medicinal chemistry¹⁶⁻¹⁸. 2-pyrrole and its arylidene compounds give good pharmacological properties¹⁹⁻²⁶. Hence, it was thought of interest to merge both of pyrrole and benzohydrazide 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 pyrrole moiety. Hence the present communication comprises the synthesis of 1-(5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzamido) -5-oxo-2-substituted phenyl-2, 5-dihydro-1H-pyrrole-3-carboxylic acid. 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 ¹H NMR and ¹³C 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.

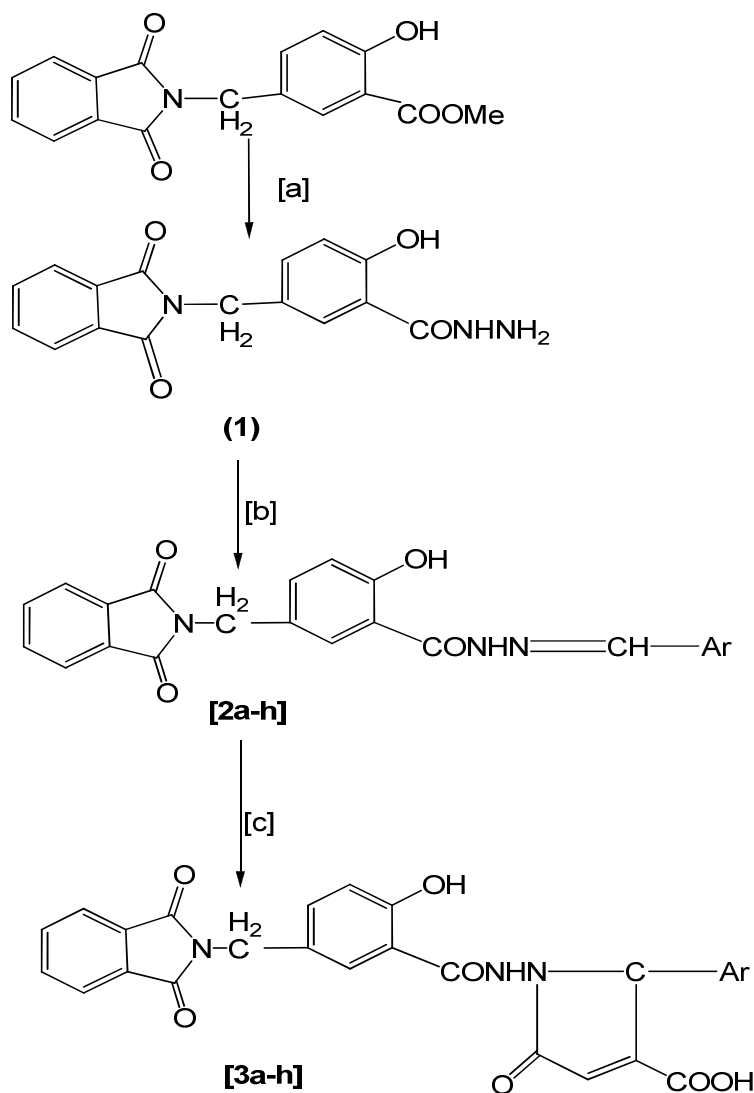
Preparation of N'-Substituted phenyl-5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzohydrazide (2a-h)

An equimolecular mixture of 5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzohydrazide (1), (0.01mole) and the aromatic aldehydes (a-h) in ethanol (20ML) 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.

Preparation of 1-(5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzamido) -5-oxo-2-substituted phenyl-2, 5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h)

A mixture of Maleic anhydride (0.01mole) and N'-Substituted phenyl-5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzohydrazide (2a-h) (0.01 mole) in chloroform (50ML) was refluxed for 6hrs. The reaction mixture was allowed to stand for 2 days, the solid was filtered. The product thus formed was recrystallized from ethanol to give pure 1-(5-((1,3-dioxoisindolin-2-yl) methyl)-2-

hydroxybenzamido)-5-oxo-2-substituted phenyl -2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h), which were obtained in 54-68% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.



Scheme-1
(a) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (b) ArCHO (c) Maleic anhydride/chloroform

Where, Ar = (a) C_6H_5 (b) $4\text{-OH-C}_6\text{H}_4$ (c) $2\text{-OH-C}_6\text{H}_4$
(d) $4\text{-OCH}_3\text{-C}_6\text{H}_4$ (e) $4\text{-OH-3-OCH}_3\text{-C}_6\text{H}_3$ (f) $4\text{-Cl-C}_6\text{H}_4$
(g) $2\text{-NO}_2\text{-C}_6\text{H}_4$ (h) $5\text{-Br-2-OH-C}_6\text{H}_3$

RESULTS AND DISCUSSION

It was observed that 5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzohydrazide (1), on condensation with aromatic aldehydes, yields N'-Substitutedphenyl-5-((1, 3-dioxoisindolin-2-yl) methyl)-2-hydroxy benzo hydrazide (2a-h). The structures of (2a-h) were confirmed by elemental analysis and IR spectra showing an absorption band at $3030\text{-}3080\text{ cm}^{-1}$ (C-H, of Ar.), $1620\text{-}1640\text{ cm}^{-1}$ (C=N), $1660\text{-}1670\text{ cm}^{-1}$ (-CONH), $3450\text{-}3550\text{ cm}^{-1}$ (-OH), $2810\text{-}2852\text{ cm}^{-1}$ (-OCH₃). ¹H 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) (CH₂). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 1-(5-((1,3-dioxoisindolin-2-yl) methyl)-2-hydroxybenzamido) -5-oxo-2-substituted phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1720cm⁻¹ (C=O of pyrrole ring), 3040-3058 cm⁻¹ (C-H, of Ar.), 3450-3550 cm⁻¹ (-OH), 1660-1670 cm⁻¹ (-CO of -COOH) for (3a) compound. ¹H NMR: 6.18-8.16 (12H, m) (Ar-H), 4.72(1H, s) (-C₅H of the ring), 5.19(1H, s) (-C₃H), 8.20-8.22 (1H, s) (-CONH), 5.33-5.45 (1H, s) (-OH), 4.80 (2H, s) (CH₂), 12.96(1H, s) (-COOH). 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 consistency 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 3b and 3e gives the molecular ion peak (m/z) at 526 and 558 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 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 3c, 3e and 3g were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -3.

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. * °C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	C ₂₄ H ₁₉ N ₃ O ₃ (397.43)	80	252	72.44	72.53	4.77	4.82	10.45	10.57
2b	C ₂₄ H ₁₉ N ₃ O ₄ (413.43)	72	260	69.65	69.72	4.58	4.63	10.04	10.16
2c	C ₂₄ H ₁₉ N ₃ O ₄ (413.43)	76	259	69.69	69.72	4.56	4.63	10.05	10.16
2d	C ₂₅ H ₂₁ N ₃ O ₄ (249)	79	253	70.14	70.25	4.88	4.95	9.78	9.83
2e	C ₂₅ H ₂₁ N ₃ O ₅ (443.45)	70	258	67.65	67.71	4.69	4.77	9.39	9.48
2f	C ₂₄ H ₁₈ ClN ₃ O ₃ (431.87)	64	255	66.70	66.75	4.19	4.20	9.75	9.83
2g	C ₂₄ H ₁₈ N ₄ O ₅ (442.42)	70	261	65.10	65.15	4.05	4.10	12.56	12.66
2h	C ₂₄ H ₁₈ BrN ₃ O ₄ (492.32)	78	257	58.49	58.55	3.61	3.69	8.51	8.54

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 activities of all the compounds (3a-h) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium.

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* °C	Elemental Analysis					
				%C		%H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	C ₂₇ H ₁₉ N ₃ O ₇ (497)	58	247	65.1	65.19	3.8	3.85	8.4	8.45
3b	C ₂₇ H ₁₉ N ₃ O ₈ (513)	64	242	63.1	63.16	3.7	3.73	8.1	8.18
3c	C ₂₇ H ₁₉ N ₃ O ₈ (513)	58	238	63.1	63.16	3.7	3.73	8.1	8.18
3d	C ₂₈ H ₂₁ N ₃ O ₈ (527)	67	250	63.7	63.76	4.0	4.01	7.9	7.97
3e	C ₂₈ H ₂₁ N ₃ O ₉ (543)	68	246	61.8	61.88	3.8	3.89	7.7	7.73
3f	C ₂₇ H ₁₈ N ₃ O ₇ Cl (531)	62	251	60.9	60.97	3.4	3.41	7.8	7.90
3g	C ₂₇ H ₁₈ N ₄ O ₉ (542)	55	249	59.7	59.78	3.3	3.34	10.3	10.33
3h	C ₂₇ H ₁₈ N ₃ O ₈ Br (591)	63	248	54.7	54.75	3.0	3.06	7.0	7.09

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

Compounds	Gram -Ve		Gram +Ve	
	<i>E.coli</i>	<i>Klebsiella promioe</i>	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>
3a	66	51	52	48
3b	53	64	51	57
3c	59	60	60	66
3d	58	53	51	54
3e	66	70	62	62
3f	60	68	59	51
3g	67	66	68	57
3h	552	61	61	60
Tetracycline	80	77	60	68

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

Compounds	Zone of Inhibition at 1000 ppm (%)				
	<i>Aspergillus Niger</i>	<i>Botrydepladia Thiobromine</i>	<i>Fusarium oxyporium</i>	<i>Nigrospora Sp.</i>	<i>Rhizopus Nigricum</i>
3a	68	58	64	69	64
3b	55	56	66	60	56
3c	57	70	67	56	57
3d	58	62	60	58	66
3e	60	67	66	57	60
3f	55	65	62	67	67
3g	59	61	66	60	61
3h	65	66	65	59	65

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:

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

Where, X = Area of colony in control plate; Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (3a-h) is shown in Tables-4.

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