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SYNTHESIS AND BIOLOGICAL ACTIVITY OF PYRROLE AND PYRROLIDINE COMPOUNDS FROM 4-CHLORO-2-HYDROXYBENZOIC ACID HYDRAZIDE

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Abstract

4-chloro-2-hydroxy benzoic acid hydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding 4-chloro-2-hydroxy benzoic acid arylidene hydrazides (2a-h) in good yields. Cyclocondensation of compounds (2a-h) with maleic anhydride and succinic anhydride yields respectively 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h) and 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (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.

Introduction

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [1-13]. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the hydrazides, 4-chloro-2-hydroxy benzoic acid hydrazide and their condensed products play a vital role in medicinal chemistry [14-16]. Pyrrole and pyrrolidine compounds give good biological and pharmacological properties [17]. Hence, it was thought of interest to merge both of pyrrole and 4-chloro-2-hydroxy benzoic acid hydrazide, pyrrolidine and 4-chloro-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-chloro-2-hydroxy benzoic acid hydrazide containing pyrrole and pyrrolidine moiety. Hence the present communication comprises the synthesis of 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h) and 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (4a-h). The synthetic approach is shown in scheme-1.

Material and Method

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-chlro-2-hydroxy benzoic acid arylidene hydrazide **(2a-h)**

General procedure: – An equimolecular mixture of 4-chloro-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 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid **(3a-h)**

General procedure: A mixture 4-chloro-2-hydroxy benzoic acid arylidene hydrazide (2a-h) (0.1 mole) and Maleic anhydride (0.1 mole) were heated at reflux in chloroform (30ml) for about 5 hours with TLC monitoring. After the mixture was allowed to stand for 2 days, the solid was filtered. The product thus formed was recrystallized from ethanol to give pure 1-[4-pyridinylcarbonlyamino]-2-oxo-5-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid in (3a-h), which were obtained in 53-62% yield.

The yields, melting points and other characterization data of these compounds are given in Table -2.

Preparation of 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid **(4a-h)**

A mixture 4-chloro-2-hydroxy benzoic acid arylidene hydrazide (2a-h) (0.1 mole) and Succinic anhydride (0.1 mole) were heated at reflux in chloroform (30ml) for about 5 hours with TLC monitoring. After the mixture was allowed to stand for 2 days, the solid was filtered. The product thus formed was recrystallized from ethanol to give pure 1-[4-pyridinylcarbonyl amine]-2-oxo-5-aryl-2, 5-dihydro-1H-pyrrolidinone-3-carboxylic acid (3a-h) in good yield.

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, 3h, 4g, and 4h 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^{o} 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.

Results and Discussion

It was observed that 4-chloro-2-hydroxy benzoic acid hydrazide (1), on condensation with aromatic aldehydes, yields 4-chloro-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), 11.70-11.84 (1H, s) (-OH), 11.85-11.98 (1H, s) (-CONH), 8.36-8.80 (1H, s) (-N=CH), 2e; 2.39 (3H, s) ($-CH_3$), 2b, 2g; 3.89 (3H, s) ($-OCH_3$), 2h; 4.12 (4H, q) (CH_2), 1.34 (6H, t) (CH_3), 2f; 6.12 (2H, s) ($-OCH_2O-$ cyclic). ^{13}C NMR: 111.8-160.8 (Aromatic), 163.0-164 (-CONH), 146.3-147 (-CH); (2b,2g): 55.7-56.8 ($-OCH_3$); (2e): 21 (CH_3); (2f): 102.5 (OCH_2O cyclic); (2h): 65.4 (OCH_2), 15.2 (CH_3). The C, H, and N analysis data of all compounds are presented in Table -1.

The structures assigned to 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1667-1690cm^{-1} (C=O of -COOH), 1715-1720 (C=O of pyrrole-2-one), 3030-3080 cm^{-}

^{1} (C-H, of Ar.), 3240-3260 cm^{-1} (-OH). ^{1}H NMR: 6.62-7.82 (8H, m) (Ar-H), 5.50-5.60 (1H, s) (-C_5H of the ring), 7.10-7.15 (1H, s) (-C_3H), 12.90-12.98 (1H, s) (-COOH), 11.70-11.85 (1H, s) (-OH), 3e; 2.36 (3H, s) (-CH_3), 3b,3g; 3.93,3.90 (3H, s) (-OCH_3), 3h; 4.13 (4H q) (CH_2), 1.32 (6H, t) (CH_3), 3f; 6.11 (2H, s) (-OCH_2O- cyclic). ^{13}C NMR: 110-161 (Aromatic), 55.0-62.5 (-CH), 169.5-171.5 (-COOH), 164.5-165 (-CO of the ring), (3b,3g): 55.4-56.5 (-OCH_3); (3e): 21.5 (CH_3); (3f): 102.8 (OCH_2O cyclic); (3h): 65.3 (OCH_2), 14.6 (CH_3). The C, H, and N analysis data of all compounds are presented in Table-2.

The structures assigned to 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (4a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1667-1690cm^{-1} (C=O of -COOH), 1715-1720 (C=O of pyrrole-2-one), 3030-3080 cm^{-1} (C-H, of Ar.), 3240-3260 cm^{-1} (-OH). ^{1}H NMR: 6.65-7.85 (8H, m) (Ar-H), 5.52-5.60 (1H, s) (-C_5H), 3.33-3.36 (1H, s) (-C_4H), , 2.50-2.54, 2.75-2.80 (2H, s) (-C_3H), 11.70-11.85 (1H, s) (-OH), 12.90-12.95 (1H, s) (-COOH), 4e; 2.38 (3H, s) (-CH_3), 4b, 4g; 3.86 (3H, s) (-OCH_3), 4h; 4.06, (4H, q) (-CH_2), 1.35 (6H, t) (-CH_3), 4f; 6.08 (2H, s) (-OCH_2O cyclic). ^{13}C NMR: 110-161 (Aromatic), 50.0-57.0 (-CH of the ring), 37.0.-37.5 (-CH_2), 172.0-172.5 (-CO), 178.0-179 (-COOH), (4b,4g): 55.5-56.5 (-OCH_3); (4e): 21.6 (CH_3); (4f): 101.5 (OCH_2O); (4h): 65.3 (OCH_2), 15.0 (CH_3). The C, H, and N 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 of 3d and 4f compounds are 391 and 422 respectively.

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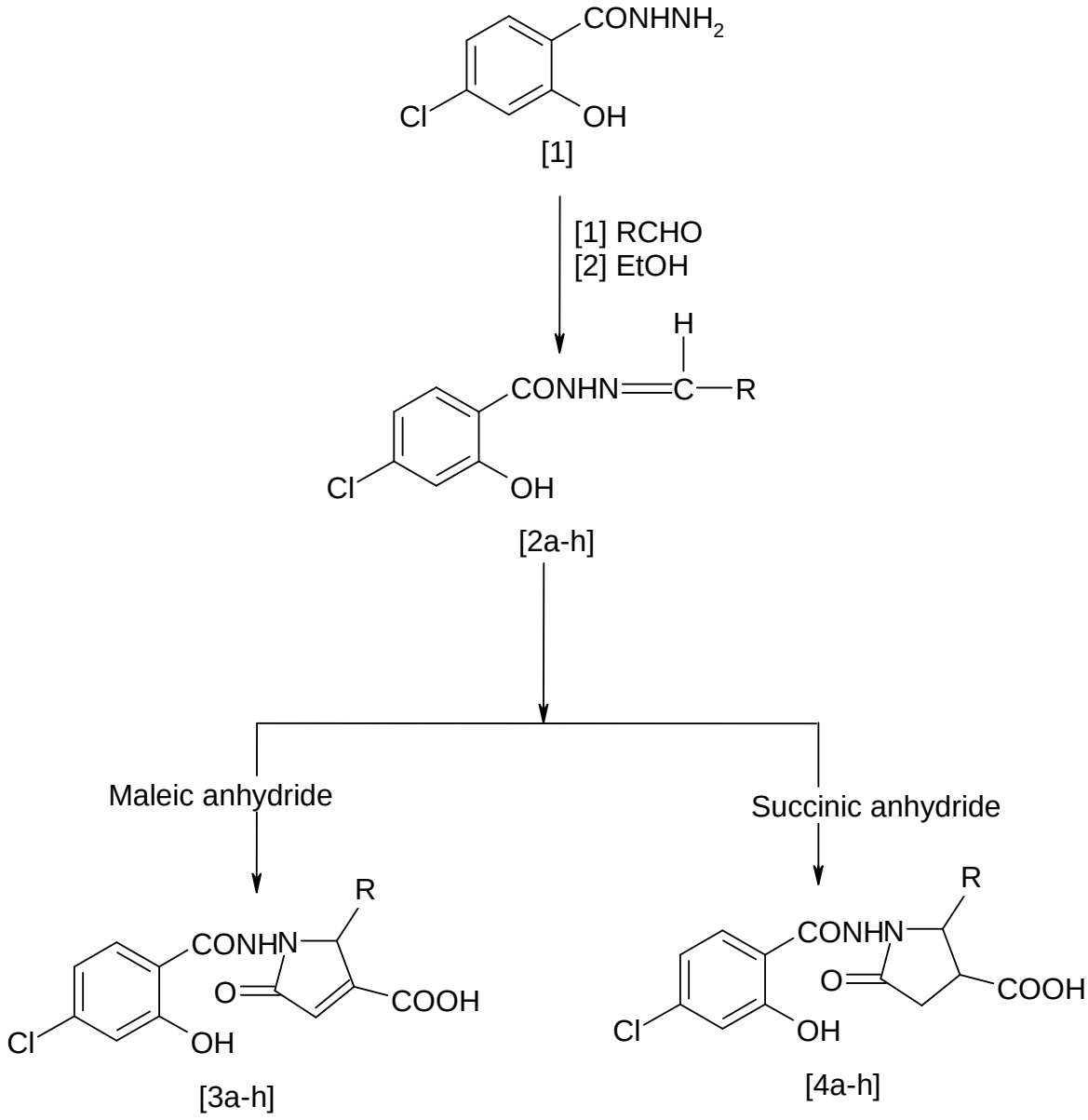

SCHEME – 1

Where, R =(a) C6H5 (b) 4-OCH3-C6H4 (c) 4-OH-C6H4 (d) 2-OH-C6H4 (e) 4-CH3-C6H4 (f) 3,4-CH2O2-C6H4 (g) 4-OH-3-OCH3-C6H3 (h) 3,4-C2H5-C6H4

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	$C_{14}H_{11}ClN_2O_2$ (274)	85	243	61.18	61.21	3.99	4.04	10.15	**10.20**
2b	$C_{15}H_{13}ClN_2O_3$ (304)	80	246	59.08	59.12	4.25	4.30	9.14	**9.19**
2c	$C_{14}H_{11}ClN_2O_3$ (290)	75	240	57.79	57.84	3.77	3.81	9.58	**9.64**
2d	$C_{14}H_{11}ClN_2O_3$ (290)	81	243	57.78	57.84	3.75	3.81	9.57	**9.64**
2e	$C_{15}H_{13}ClN_2O_2$ (288)	79	244	62.36	62.40	4.51	4.54	9.64	**9.70**
2f	$C_{15}H_{11}ClN_2O_4$ (318)	75	247	56.49	56.53	3.44	3.48	8.73	**8.79**
2g	$C_{15}H_{13}ClN_2O_3$ (320)	77	249	56.14	56.17	3.04	4.09	8.68	**8.73**
2h	**$C_{18}H_{19}ClN_2O_4$ (362)**	**73**	**261**	**59.55**	**59.59**	**5.24**	**5.28**	**7.68**	**7.72**

* 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	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{18}H_{13}ClN_2O_5$ (372)	60	224	58.00	57.88	3.52	3.45	7.52	**7.48**
3b	$C_{19}H_{15}ClN_2O_6$ (402)	62	220	56.66	56.58	3.75	3.70	6.95	**6.87**
3c	$C_{18}H_{13}ClN_2O_6$ (388)	58	174	55.61	55.56	3.37	3.30	7.21	**7.18**
3d	$C_{18}H_{13}ClN_2O_6$ (388)	59	170	55.61	55.54	3.37	3.31	7.21	**7.19**
3e	$C_{19}H_{15}ClN_2O_5$ (386)	62	164	59.00	58.90	3.91	3.88	7.24	**7.20**
3f	$C_{19}H_{13}ClN_2O_7$ (416)	59	179	54.76	54.71	3.14	3.09	6.72	**6.68**
3g	$C_{19}H_{15}ClN_2O_7$ (418)	53	185	54.49	54.40	3.61	3.58	6.69	**6.61**
3h	**$C_{22}H_{21}ClN_2O_7$ (460)**	**57**	**218**	**57.33**	**57.23**	**4.59**	**4.54**	**6.08**	**6.02**

* Uncorrected

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. ^0C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{18}H_{15}ClN_2O_5$ (374.78)	60	225	57.69	57.59	4.03	4.00	7.47	**7.39**
4b	$C_{19}H_{17}ClN_2O_6$ (404.80)	64	228	56.37	56.30	4.23	4.21	6.92	**6.82**
4c	$C_{18}H_{15}ClN_2O_6$ (390)	62	212	55.32	55.27	3.87	3.81	7.17	**7.09**
4d	$C_{18}H_{15}ClN_2O_6$ (390)	66	215	55.32	55.28	3.87	3.83	7.17	**7.12**
4e	$C_{19}H_{17}ClN_2O_5$ (388)	59	214	58.69	58.59	4.41	4.38	7.21	**7.18**
4f	$C_{19}H_{15}ClN_2O_7$ (418)	55	218	54.49	54.40	3.61	3.58	6.69	**6.63**
4g	$C_{19}H_{17}ClN_2O_7$ (420)	54	215	54.23	54.19	4.07	4.01	6.66	**6.61**
4h	**$C_{22}H_{23}ClN_2O_7$ (462)**	**56**	**221**	**57.09**	**57.01**	**5.01**	**4.94**	**6.05**	**5.98**

* Uncorrect

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

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

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	61	61	63	62	**64**
3b	57	59	64	61	**67**
3c	64	66	66	65	**70**
3d	65	61	59	70	**66**
3e	63	63	61	71	**70**
3f	58	60	64	66	**71**
3g	60	67	70	62	**69**
3h	**59**	**70**	**69**	**70**	**68**

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

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
4a	12	10	11	**10**
4b	14	13	13	**15**
4c	17	17	14	**14**
4d	11	15	17	**16**
4e	12	13	11	**18**
4f	15	11	12	**11**
4g	19	18	19	**20**
4h	17	16	17	**19**
Tetracycline	**21**	**20**	**19**	**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	66	64	59	55	**60**
4b	63	67	64	60	**62**
4c	62	69	61	64	**68**
4d	60	60	60	63	**61**
4e	64	64	63	70	**65**
4f	61	56	65	63	**69**
4g	68	60	68	58	**66**
4h	**60**	**62**	**70**	**71**	69

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