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RESEARCH ARTICLE

Studies of Novel Pyrrole and their Biological Studies

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ABSTRACT

2-(1H-benzo[d]imidazol-2-ylthio)-N-arylidene aceto hydrazide (**4a-f**) was synthesized in good yields by facile condensation of 2-(1H-benzo[d]imidazol-2-ylthio) acetohydrazide**(3)** with aromatic aldehydes to afford the corresponding. Cyclocondensation of compounds (**4a-f**) with maleic anhydride yields 1-(2-(1H-benzo[d]imidazol-2-ylthio)acetamido)-5-oxo-2-subsituted phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (**5a-f**). The structures of these compounds were established on the basis of analytical and spectral data. The synthesized compounds were tested for their antibacterial and antifungal activities.

KEYWORDS

2-(1H-benzo[d]imidazol-2-ylthio) acetohydrazide, Pyrrole, Antibacterial activity and antifungal activity

INTRODUCTION

The heterocyclic systems find wide use in medicine, agriculture and industry. One of the other compounds says, oxadiazoles and their condensed products play a vital role in medicinal chemistry[1-3]. Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties[4-13]. Another heterocyclic moiety says, pyrrole and its substituted derivatives furnish good pharmacological properties[14-19]. Hence, it was thought of interest in merging of both pyrrole and benzimidazole moieties may enhance the drug activity of compounds up to some extent or might posses some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of imidazole containing a pyrrole moiety.

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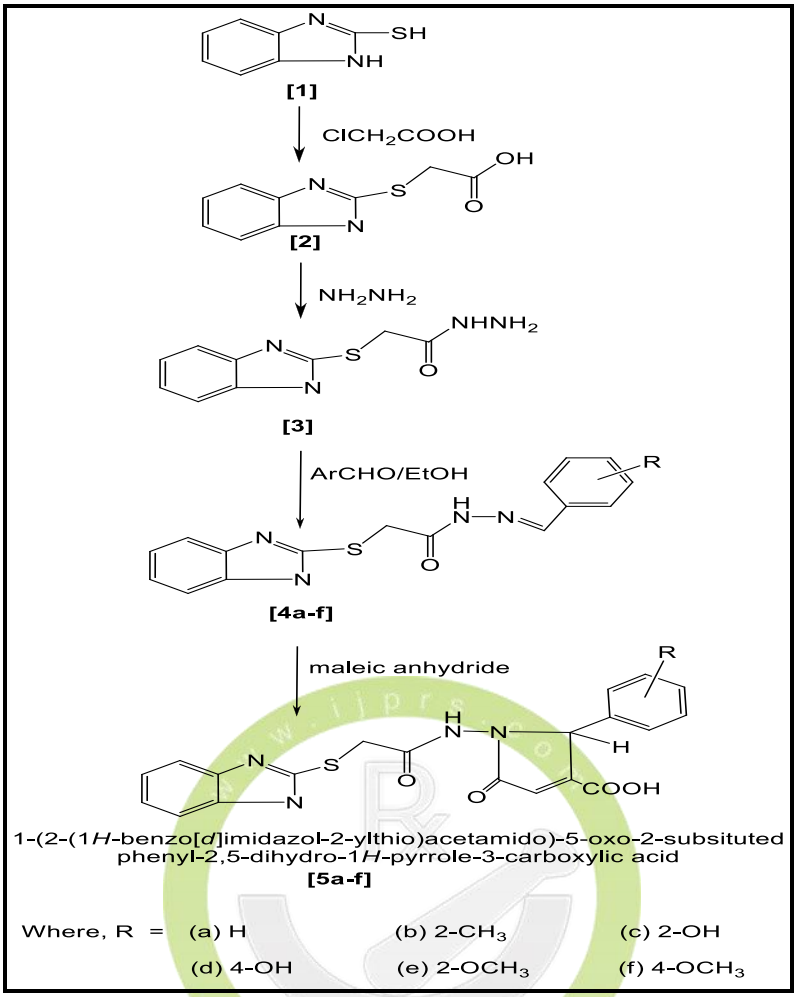
Hence the present communication comprises the synthesis of 1-(2-(1H-benzo[d]imidazol-2-ylthio)acetamido)-5-oxo-2-subsituted phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid(5a-f). The research work is scanned in Scheme-1.

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 ^{1}H 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 2-(1H-benzo[d]imidazol-2-ylthio)- N'-arylidene aceto hydrazide (4a-f)
An equimolecular mixture of 2-(1H-benzo[d]imidazol-2-ylthio) acetohydrazide (3), (0.01mole) and the aromatic aldehydes (a-f) in ethanol (15ml) was refluxed on a water bath for 1.5-2 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol.



Scheme 1

Table: 1 Analytical Data and elemental analysis of compounds **(4a-f)**

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		% H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{16}H_{14}N_4OS$ (310)	313	87	241-243	61.90	61.92	4.52	4.55	18.04	18.05	10.31	10.33
4b	$C_{17}H_{16}N_4OS$ (324)	344	83	236-238	62.92	62.94	4.95	4.97	17.26	17.27	9.86	9.88
4c	$C_{16}H_{14}N_4O_2S$ (326)	329	82	238-240	58.85	58.88	4.30	4.32	17.15	17.17	9.80	9.82
4d	$C_{16}H_{14}N_4O_2S$ (326)	328	80	239-241	58.86	58.88	4.31	4.32	17.16	17.17	9.81	9.82
4e	$C_{17}H_{16}N_4O_2S$ (340)	344	83	236-238	59.96	59.98	4.72	4.74	16.44	16.46	9.40	9.42
4f	$C_{17}H_{16}N_4O_2S$ (340)	344	83	236-238	59.96	59.98	4.72	4.74	16.44	16.46	9.40	9.42

***** Uncorrected

The yields, melting points and other characterization data of these compounds are given in Table -1.

Preparation of 1-(2-(1H-benzo[d]imidazol-2-ylthio)acetamido)-5-oxo-2-subsituted phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (5a-f:-)

A mixture of Maleic anhydride (0.01mole) and *2-(1H-benzo[d]imidazol-2-ylthio)- N'-arylidene aceto hydrazide* ***(4a-f)*** (0.01 mole) in chloroform (50ml) was refluxed for 4-5.5 hrs. The reaction mixture was allowed to stand for 36hrs, the solid was filtered. The product thus formed was recrystallized from ethanol to give 1-(2-(1H-benzo[d]imidazol-2-ylthio) acetamido)-5-oxo-2-subsituted phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid(**5a-f**),which were obtained in good yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

RESULTS AND DISCUSSION

It was observed that 2-(1H-benzo[d]imidazol-2-ylthio) acetohydrazide **(3)**, on condensation with aromatic aldehydes, yields 2-(1H-benzo[d]imidazol-2-ylthio)- N-arylidene aceto hydrazide **(4a-f)**. The structures of **(4a-f)** 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.), 1720-1750 cm^{-1} (-CO), 2620-2560 cm^{-1} (-CS), 2815-2850 cm^{-1} ($-OCH_3$), 2950, 1370 cm^{-1} ($-CH_3$). ^1H NMR : 6.98 – 7.95 (10H, m) (Ar-H), 11.79-11.80 (1H, s) (-CONH), 8.43-8.80 (1H, s) (-N=CH),4b,1.56(3H,s)($-CH_3$); 4c,4d; 4.22-4.24 (1H,s) (-OH),4e,4f:3.65-3.69(3H,s)($-CH_3$). The C, H, N analysis data of all compounds are presented in Table -1.

The cyclocondensation of **(4a-f)** with maleic anhydride resulted in formation of 1-(2-(1H-benzo[d]imidazol-2-ylthio)acetamido)-5-oxo-2-subsituted phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (**5a-f**). The structures assigned to **(5a-f)** were supported by the elemental analysis and IR spectra showing absorption bands at 1720 cm^{-1} (C=O of pyrrole ring),3035-3090cm^{-1}(C-H, of Ar.), 3450-3550 cm^{-1} (-OH), 2820-2850 cm^{-1} ($-OCH_3$), 2950, 1370 cm^{-1} ($-CH_2$), 1670 cm^{-1} (-CO of -COOH), 1628-1645 cm^{-1} (C=N). ^1H NMR: 7.64 – 6.98 (8H,m)(Ar-H),11.79-11.80(1H,s)(-CONH),7.8(1H,s)(-NH),4.72(1H,s,C_2H of the ring), 5.19 (1H, s,C_4H),12.96(1H,s)(-COOH),4.1(s,1H,CH_2); 5c,5d; 4.22-4.24 (1H,s)(-OH),5e,5f:3.65-3.69(3H,s)($-CH_3$). The C, H, N analysis data of all compounds are presented in Table -2.

Table: 2 Analytical Data and elemental analysis of compounds **(5a-f)**

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^0C	Elemental Analysis							
					%C		% H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
5a	$C_{20}H_{16}N_4O_4S$ (408)	441	56	186-187	58.80	58.81	3.93	3.95	13.70	13.72	7.84	7.85
5b	$C_{21}H_{18}N_4O_4S$ (422)	468	60	202-204	59.83	59.85	4.05	4.07	13.27	13.29	7.58	7.61
5c	$C_{20}H_{16}N_4O_5S$ (424)	462	69	196-199	56.58	56.60	3.78	3.80	13.17	13.20	7.54	7.55
5d	$C_{20}H_{16}N_4O_5S$ (424)	466	68	205-208	56.59	56.60	3.78	3.80	13.18	13.20	7.52	7.55
5e	$C_{21}H_{18}N_4O_5S$ (438)	474	70	212-213	57.51	57.53	4.11	4.14	12.76	12.78	7.29	7.31
5f	$C_{21}H_{18}N_4O_5S$ (438)	479	66	200-200	57.52	57.53	4.12	4.14	12.76	12.78	7.30	7.31

***** Uncorrected

The examination of data reveals that the elemental contents are consistence with the predicted structure shown in Figure-1.The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS data of selected samples. The LC-MS of samples **5a** and **5d** give the molecular ion peak (m/z) at 441 and 466 respectively. These values are corresponds to their molecular weight.

Biological Screening

Antibacterial Activities

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.

Methanol system was used as control in this method. Under similar condition using tetracycline as a standard for comparison carried out control experiment. The area of inhibition of zone measured in mm.

Compound 5e and 5f were found more active against the above microbes. Other compounds found to be less or moderate active than tetracycline (Table -3).

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Rhizopus nigricum***,** *Aspergillus niger, Fusarium oxyporium and Botrydepladia thiobromine*. The antifungal activity of all the compounds (**5a-f**) was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200gm, dextrose 20gm, agar 20gm and water one liter. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120º C for 15 min. at 15atm.pressure. These medium 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:

Table: 3 Antibacterial Activities of Compounds **(5a-f)**

Compounds	**Gram +Ve**		**Gram -Ve**	
	Bacillus subtilis	***E.coli***	***Klebsiella promioe***	***Staphylococcs aureus***
5a	48	64	54	51
5b	53	65	49	57
5c	59	54	55	58
5d	57	59	56	52
5e	70	62	59	67
5f	67	68	58	63
Tetracycline	79	78	86	67

Table: 4 Antifungal Activities of Compounds (5a-f)

Zone of Inhibition at 1000 ppm (%)				
Compounds	***Rhizopus Nigricum***	***Aspergillus niger***	***Fusarium oxyporium***	***Botrydepladia Thiobromine***
5a	50	57	62	58
5b	61	53	60	56
5c	62	58	63	58
5d	64	47	62	59
5e	69	65	64	63
5f	71	62	66	62

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 (**5a-f**) is shown in Table-4.

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