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Synthesis and biological studies of benzimidazole derivatives

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ABSTRACT

1-(1H-benzo[d]imidazol-2-yl)-N,N-dimethylmethanamine (1) react with chloro acetic acid and hydrazine hydrate gives 2-(2-((dimethylamino)methyl)-1H- benzo[d]imidazol-1-yl)acetohydrazide (2),Which on reaction with CS2/KOH gives 5-((2-((dimethylamino)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (3). The compound (3) on Mannich reaction gives different 3-((dialkylamino)methyl)-5-((2-((dimethylamino) methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (4a-e). The structures of these compounds were established on basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: Benzimidazole, Oxadiazole, Mannich reaction, Spectral studies, antibacterial and antifungal activities.

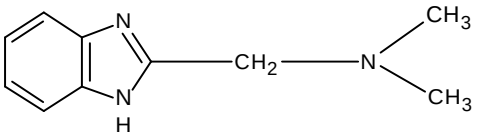
INTRODUCTION

The heterocyclic compounds are an important class of compounds [1-3]. One of the other compounds says, oxadiazoles and their condensed products play a vital role in medicinal chemistry [4-6]. Substituted 1,3,4-oxadiazole are the heterocyclic system that have been found to exhibit diverse biological activities such as antibacterial, antifungal, anti-inflammatory, analgesic and anticancer activity[7-10]. Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [11-14]. Hence, it was thought of interest to merge both of benzimidazole and oxadiazole 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 oxadiazole containing benzimidazole moiety. Hence the current communication covers the study of 3-((dialkylamino)methyl)-5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione. The synthetic approach is shown in scheme-1.

EXPERIMENTAL SECTION

Materials:
1-(1*H*-benzo[*d*]imidazol-2-yl)-N,N-dimethylmethanamine (1) was prepared by method reported [15]. All other chemicals used were of analytical grade.

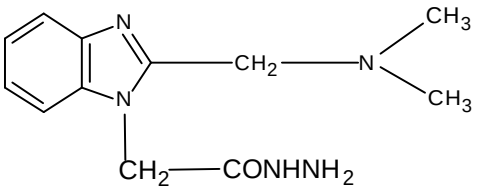
Analysis:
Melting points were determined in open capillary tubes and were uncorrected. Elemental analysis was carried out by Thermo finnigan CHN analyzer (Italy). The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively.



1-(1*H*-benzo[*d*]imidazol-2-yl)- *N,N*-dimethyl methan amine (1)

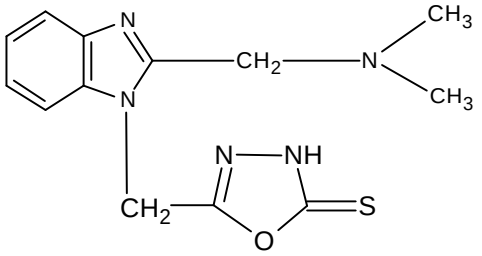
(i) $ClCH_2COOC_2H_5$ /dry acetone/anhy. K_2CO_3 8.5 hr.

(ii) hydrazine hydrate / 1,4 dioxane



2-(2-((dimethylamino)methyl)-1 *H*-benzo[*d*]imidazol-1-yl)acetohydrazide (2)

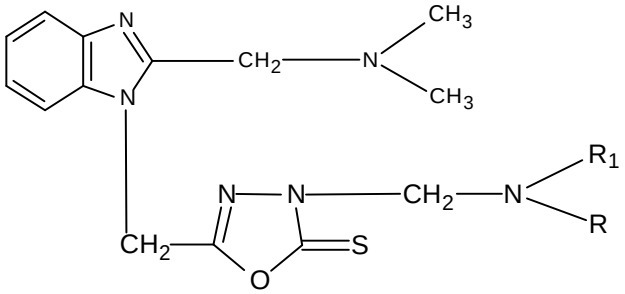
CS_2 / KOH / C_2H_5OH



5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione(3)

Mannich Reaction

CH_2O / $NH(CH_3)_2$ / THF



3-((dialkylamino)methyl)-5-((2-((dimetylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl) methyl)-1,3,4-oxadiazole-2(3 *H*)-thione (4a-e)

Where,

	4a	**4b**	**4c**	**4d**	**4e**
R	CH_3	CH_3	Et	Et	Ph
R1	CH_3	Et	Et	Ph	Ph

SCHEME – 1

Antimicrobial activities of all compounds were monitored against common bio species by using cup plate method.

Preparation of 2-(2-((dimethylamino)methyl)- 1*H*-benzo[d]imidazol-1-yl)acetohydrazide (2) :–Equimolar solution of 1-(1*H*-benzo[*d*]imidazol-2-yl)-*N*,*N*-dimethylmethanamine (1) (0.1 mole) in the dry acetone (60 ml) and ethylchloroacetate (0.1 mole) in the presence of anhydrous K_2CO_3 (5 gm) was refluxed for 8.5 hrs., cooled and the solid thus obtained was filtered, dried and crystallized from ethanol yield is about 74%. m.p. 158 C, and this compound (0.05 mole) and hydrazine hydrate (0.05mole) in 1,4-dioxane (35 ml) was refluxed on heating coil for 5 hrs. The excess of solvent was removed and the product crystallized from methanol to give (2), yield is about 78%, m.p.178 C. IR cm^{-1}: 3350(NH_2)1620-1648(C=N),3020-3080(C-H,of Ar.), 2950, 1370 (-CH_3),1660-1670(-CONH). ^{1}HNMR : 7.24–7.65(m, 4H, Ar-H), 9.40 (s,1H, NH), 4.86-4.38(s,4H,CH_2), 2.22(s,6H, CH_3),7.8(s,1H,CONH), 4.6(s,2H,NH_2). *Anal.* Calcd for $C_{12}H_{17}N_5O$(247): C, 58.28; H, 6.93; N, 28.32. Found: C, 58.26; H, 6.91; N, 28.30.

Preparation of 5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione(3):-

To a cold stirred solution of 2-(2-((dimethylamino)methyl)- 1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (2) (0.1 mole) in ethanol (50 ml) containing potassium hydroxide (0.01 mole), carbon disulphide (0.05 mole)was added gradually. The reaction mixture was heated under reflux on a steam-bath until hydrogen sulphide evolution ceased. Ethanol was removed by distillation under reduced pressure and the residue was stirred with water, filtered and the filtrate was neutralized with dilute hydrochloric acid. The product was filtered, washed with water and recrystallized from ethanol to get the compound 5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione (3),which were obtained in 69% yield. IR cm^{-1}: 1620-1648(C=N), 3020-3080 cm^{-1}(C-H, of Ar.), 2950, 1370 cm^{-1} (-CH_3), 1185 (C=S),765(C-O-C ring).^{1}H NMR : 7.24–7.65(m, 4H, Ar-H), 9.40 (s,1H, NH), 4.86-4.38 (s,4H,CH_2),2.22(s,6H,CH_3). *Anal.* Calcd for $C_{13}H_{15}N_5OS$(289): C, 53.96; H, 5.23; N,24.20,S,11.08. Found: C, 53.95; H, 5.21; N,24.17, S, 11.06.

Preparation of 3-((dialkylamino)methyl)-5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl) methyl)-1,3,4-oxadiazole-2(3*H*)-thione (4a-e):-

In a round bottom flask, the mixture of 5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione(3) (0.1mole) in THF (100ml), formaldehyde (0.1mole) and secondary amine **(a-e)** (0.12mole) was reflux on water bath for 3 hrs. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air-dried. recrystallization from n-hexane gave 3-((dialkylamino)methyl)-5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione(4a-e), which was obtained in 54-73% yield. 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 (4a-e)

Compd.	Molecular formula	Yield	M.P. ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{16}H_{22}N_6OS$	65	195	55.45	55.47	6.38	6.40	24.25	24.26	9.25	9.26
4b	$C_{17}H_{24}N_6OS$	72	189	56.62	56.64	6.70	6.71	23.30	23.31	8.87	8.90
4c	$C_{18}H_{26}N_6OS$	71	185	57.70	57.73	6.98	7.00	22.42	22.44	8.54	8.56
4d	$C_{22}H_{26}N_6OS$	64	196	62.51	62.53	6.17	6.20	19.87	19.89	7.57	7.59
4e	$C_{26}H_{26}N_6OS$	54	175	66.34	66.36	5.55	5.57	17.84	17.86	6.80	6.81

***** *Uncorrected*

The structures assigned to 3-((dialkylamino)methyl)-5-((2-((dimethylamino)methyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione (4a-e) were supported by the elemental analysis , IR &NMR spectra showing an absorption bands at 1620-1648(C=N), 3020-3080 cm^{-1}(C-H, of Ar.), 2950, 1370 cm^{-1} (-CH_3), 1185

(C=S),765(C-O-C ring)^{1}H NMR : 7.24–7.65(m,4H,Ar-H),4.86-4.38(s,4H,CH_2),2.22(s,6H,CH_3), 3.82(s,2H,CH_2), 4a;2.17(s,6H, CH_3),3b;2.26(s,3H,CH_3),1.08(t,3H,CH_3),2.67(q,2H,CH_2),3c;1.08(t,6H,CH_3),2.67(q,4H, CH_2), 4d; 1.08(t,3H,CH_3),2.67(q,2H,CH_2), 6.82–7.27(m,5H,Ar-H), 4e; 6.82–7.27(m,10H,Ar-H).The C, H, N, S analysis data of all compounds are presented in Table-1.

BIOLOGICAL SCREENING:

Antibacterial activities

The antibacterial activities of all the compounds (4a-e) were studied against gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and gram-negative bacteria (*klebsiella promioe , and E.coli,*) 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. The antibacterial activities of all the compounds are shown in Tables -2.

Table:-2 Antibacterial Activity of Compounds (4a-e)

Compounds	Gram +Ve		Gram -Ve	
	Bacillus subtilis	*Staphylococcus aureus*	*Klebsiella promioe*	*E.coli*
4a	50	46	64	59
4b	51	47	65	60
4c	53	48	56	66
4d	62	53	68	71
4e	63	55	72	73
Tetracycline	68	60	77	80

Antifungal Activities

The fungicidal activity of all the compounds (4a-e) were studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Rhizopus nigricum ,Nigrospora Sp,and Aspergillus niger,*. The antifungal activities of all the compounds 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:

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

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

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

Table:-3 Antifungal Activity of Compounds (4a-e)

Zone of Inhibition at 1000 ppm (%)			
Compounds	***Rhizopus Nigricum***	***Nigrospora Sp.***	***Aspergillus Niger***
4a	57	62	61
4b	56	63	59
4c	61	60	58
4d	65	70	64
4e	70	69	66

RESULTS AND DISCUSSION

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR & NMR data also direct for assignment of the predicted structure.

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*). All Compounds were found toxic for microbes. Compound 4d and 4e were found more toxic, other compounds found to be less or moderate active than tetracycline, is shown in Tables -2.

The fungicidal activity of all the compounds were studied in vitro. Plant pathogenic organisms used were *Rhizopus nigricum ,Nigrospora Sp,and Aspergillus niger,* . The percentage inhibition for fungi was calculated after five days

using the formula given. The fungicidal activity displayed by various compounds is shown in Tables-3. Compound 4d and 4e were found more active, Other compounds found to be less or moderate active

CONCLUSION

The proposed Benzimidazole derivatives (4a-e) were successfully synthesized And the structures of these compounds were established on basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities. Among all the active compounds of Benzimidazole derivatives ,Compound 4d and 4e shown more active as antibacterial and antifungal agent.

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