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Synthesis, Characterization and Biological studies of Novel Heterocyclic compounds

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Abstract

Reaction of N-((1H-benzoimidazol-2-yl)methyl)-N-methylethanamine(1) with chloro acetic acid and hydrazine hydrate gives 2-(2-((ethyl(methyl)amino)methyl)-1H-benzoimidazol-1-yl)acetohydrazide(2),Which react with CS2/KOH gives 5-((2-((ethylmethylamino)methyl)-1H-benzoimidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione(3). The product (3) on Mannich reaction gives different 3-((dialkyl amino)methyl)-5-((2-((ethyl (methyl)amino)methyl)-1H-benzoimidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (4a-e). The structures of these newly synthesized compounds were established on the basis of analytical studies as well as spectral studies. The final products were examined for their antibacterial studies and antifungal studies.

Keywords: Oxadiazole, benzimidazole, Mannich reaction, spectral studies, antibacterial and antifungal Activities.

Introduction

In recent time, the research done on hydrazide and its derivatives, because of their heterocyclic products show medicinal properties like, analgesic, anti-inflammatory, antibacterial, antifungal properties[1-3]. The heterocyclic compounds containing nitrogen and oxygen atom are an important class of compounds[4-6]. Some of the compounds like, Oxadiazole and their derivatives play a significant role in medicinal chemistry[7-10]. Oxadiazole is 5 member heterocyclic compound having 2 nitrogen atoms and 1 oxygen atom. 1,3,4-oxadiazole and their substituted derivative have been found to exhibit diverse biological activities like, anticancer, antifungal, antibacterial, antioxidant, analgesic and anti-inflammatory[11-18]. Oxadiazole work as bioisosteres of carbonyls and thioguanidines in H3 antagonists[19-20]. In continuation of our earlier work[21-22]. It is thought to fuse both, Benzimidazole and oxadiazole compound which may increase the drug potency to some extent or they might exhibit some of the above mentioned biological activities. From this hope, the objective of the current research work is to synthesize new derivatives of oxadiazole containing Benzimidazole moiety. Hence the current work covers the synthesis of 3-((dialkylamino)methyl)-5-((2-((ethyl(methyl)amino)methyl)-1H-benzoimidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (4a-e). The route of synthesis is shown in scheme-1.

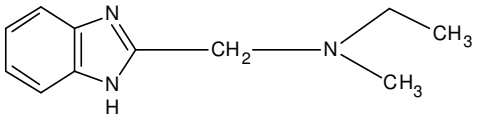
Material and Methods

N-((1H-benzoimidazol-2-yl) methyl)-N-methylethanamine (1) was prepared by method shown in[23].All other chemicals were used of analytical grade. In open capillary tube, Melting points were determined and were uncorrected. The Infra Red spectra were studied in potassium bromide pellets on a Nicolet 400D spectrometer and PMR spectra were studied in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. Antimicrobial activities of all compounds were examined against common bio species by using cup plate method.

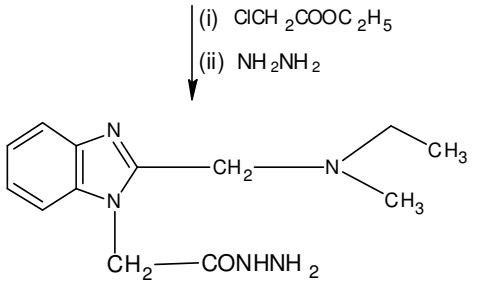
Preparation of N-((1H-benzoimidazol-2-yl)methyl)-N-methylethanamine (1): 2-(chloromethyl)-1H-benzoimidazole (0. 01 mole) was added to the mixture of the methyl ethyl amine (0.01mole) and anhy. K_2CO_3 (0.05 mole) in ethyl methyl ketone (15 ml). At ambient temperature the whole reaction mixture was stirred for 7- 8.5 hrs and ethyl methyl ketone was then evaporated. After addition of Distilled water to the residue, precipitate formed. This precipitate was filtered, washed with water and after removal of excess solvent, the product crystallized from CH_3OH. Yield is about 72%, M.P.171°C. Infra Red spectra cm^{-1}: 3150(NH) 1620-1648(C=N), 3020-3080(C-H,of Ar.), 2950, 2885, 1370(-CH_3,CH_2). PMR: 7.24-7.65 (multiplet,4H,Ar-H), 5.40(singlet,1H,NH), 4.46(singlet,2H,CH_2), 2.66(quartet,2H, CH_2), 1.12(triplet,3H,CH_3), 2.28 (singlet,3H,CH_3). Analysis Calculated for $C_{11}H_{15}N_3$ (189gm/mole): C, 69.81; H, 7.99; N, 22.20. Found: C, 69.79; H, 7.96; N, 22.18.

Preparation of 2-(2-((ethyl(methyl)amino)methyl)-1H-benzoimidazol-1-yl)acetohydrazide(2): A solution of N-((1H-benzoimidazol-2-yl) methyl)-N-methylethanamine **(1)** (0.01mole) in dry CH_3COCH_3 (60 ml) and ethylchloroacetate (0.01 mole) in the presence of anhy.K_2CO_3 (5 g) was refluxed for 9-9.5 hrs., after cooling the solid was filtered, dried and crystallized from C_2H_5OH, yield is 69%. M.P. 167°C. This compound (0.05mole) with hydrazine hydrate (0.05mole) and 1,4-dioxane (35 ml) was refluxed for 5 hrs. On heating coil .After removal of excess solvent, the product was crystallized from CH_3OH to give (2),

yield is 73%, M.P 182°C. Infra Red spectra cm^{-1}: 3350(NH_2), 1620-1648 (C=N), 3020-3080 (C-H, of Ar.), 2950, 2885, 1370(-CH_3,CH_2), 1660-1670 (-CONH). PMR : 7.24–7.65(multiplet, 4H, Ar-H), 4.86-4.38(singlet,4H,CH_2),2.66 (quartet,2H,CH_2), 1.12 (triplet,3H,CH_3), 2.28 (singlet,3H,CH_3), 7.8 (singlet,1H, CONH), 4.6(singlet, 2H, NH_2). *Analysis.* Calculated for $C_{13}H_{19}N_5O$(261): C, 59.75; H, 7.33; N, 26.80. Found: C, 59.73; H, 7.30; N, 26.78.



N-((1H-benzoimidazol-2-yl)methyl)-N-methylethanamine (1)



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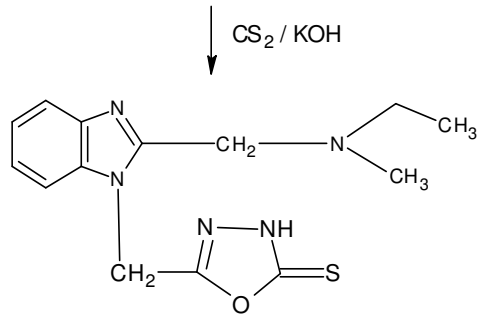
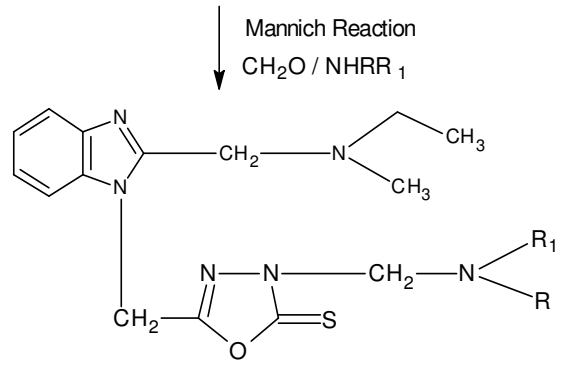


5-((2-((ethylmethylamino)methyl)-1H-benzoimidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione(3)



3-((dialkylamino)methyl)-5-((2-((ethyl(metyl)amino)methyl)-1H-benzoimidazol-1-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione (4a-e)

	4a	**4b**	**4c**	**4d**	**4e**
R	CH_3	CH_3	C_2H_5	C_2H_5	C_6H_5
R1	CH_3	C_2H_5	C_2H_5	C_6H_5	C_6H_5

Scheme–1

Preparation of 5-((2-((ethylmethylamino)methyl)-1H-benzoimidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione(3): To a cold stirred solution of 2-(2-((ethyl (methyl) amino) methyl)-1H-benzoimidazol-1-yl) acetohydrazide **(2)** (0.01mole) in C_2H_5OH (50 ml) containing KOH (0.01mole) and CS_2 (0.05mole) was added gradually. The reaction mixture was heated on a steam-bath under reflux until H_2S evolution ceased. C_2H_5OH was removed under reduced pressure by distillation and the residue was stirred with distilled water, after filtration the filtrate was neutralized with dil.HCl. The product after filtration, washed with water and recrystallized from C_2H_5OH to get the compound *5-((2-((ethylmethylamino)methyl)-1H-benzoimidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione**(3)**,* which were obtained in 66% yield. Infra Red spectra cm^{-1}: 1620-1648(C=N), 3020-3080 cm^{-1}(C-H, of Ar.), 2950, 2878, 1370 cm^{-1} (-CH_3, CH_2), 1185 (C=S), 765(C-O-C ring). PMR: 7.24–7.65 (multiplet, 4H, Ar-H), 9.40 (singlet,1H, NH), 4.86-4.38 (singlet, 4H,CH_2), 2.66 (quartet,2H,CH_2), 1.12 (triplet,3H,CH_3), 2.28(singlet ,3H,CH_3). Analysis. Calculated for $C_{14}H_{17}N_5OS$(303): C, 55.42; H, 5.65; N, 23.08; S, 10.57. Found: C, 55.41; H, 5.63; N, 23.06; S, 10.55.

Preparation of 3-((dialkylamino)methyl)-5-((2-((ethyl (methyl) amino)methyl)-1H-benzoimidazol-1-yl) methyl) -1,3,4-oxadiazole-2(3H)-thione (4a-e): In a R.B.flask, the mixture of 5-((2-((ethylmethylamino) methyl)-1H-benzoimidazol-1-yl) methyl)-1, 3, 4-oxadiazole-2(3H)-thione **(3)** (0.01mole) in THF (100ml), HCHO (0.01mole) and secondary amine (a-e) (0.12mole) was refluxed on water bath for 3-3.5 hrs. This mixture was concentrated, cooled and poured into ice-cold water. After air-dried, this product was recrystallized by n-hexane and gave 3-((dialkylamino) methyl)-5-((2-((ethyl (methyl) amino) methyl)-1H-benzoimidazol-1-yl) methyl)-1, 3, 4-oxadiazole-2(3H) -thione (4a-e), which was obtained in 65-76% yield. The Yields, M.P and other analytical data of these compounds are presented in table-1

Biological Activities: Antibacterial screening: The antibacterial screening of all the compounds (4a-e) were studied for gram-positive (*Bacillus subtilis and Staphylococcus aureus*) and gram-negative (*klebsiella promioe and E.coli*) bacteria at a concentration of 50µg/ml by agar cup plate method. As a control, the methanol system was used. Tetracycline used as standard for comparison in similar conditions. The area of zone inhibition measured in mm. The antibacterial screening of all the compounds (4a-e) is shown in table-2.

Table-1
Elemental and Analytical data of Compounds (4a-e)

Compd.	Molecular Formula (Mol.Wt.)	Yield %	M.P. ^0C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{17}H_{24}N_6OS$ (324)	67	197	56.62	56.64	6.69	6.71	23.29	23.31	8.88	8.90
4b	$C_{18}H_{26}N_6OS$ (374)	76	186	57.70	57.73	6.98	7.00	22.43	22.44	8.55	8.56
4c	$C_{19}H_{28}N_6OS$ (388)	74	187	58.71	58.74	7.25	7.26	21.61	21.63	8.23	8.25
4d	$C_{23}H_{28}N_6OS$ (436)	69	195	63.25	63.28	6.43	6.46	19.24	19.25	7.32	7.34
4e	$C_{27}H_{28}N_6OS$ (484)	65	182	66.91	66.92	5.80	5.82	17.32	17.34	**6.61**	6.62

Table-2
Antibacterial screening of Compounds (4a-e)

Compounds	Gram-positive		Gram-negative	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E.coli***
4a	53	47	66	61
4b	52	49	65	60
4c	55	48	58	65
4d	63	56	69	70
4e	64	57	71	72
Tetracycline	68	60	77	80

Antifungal screening: The antifungal screening of all the compounds was studied in vitro at 1000 ppm concentration. Plant pathogenic organisms *Rhizopus nigrican, Nigrospora Sp and Aspergillus niger* were used. The antifungal activities of all the synthesized compounds **(4a-e)** were studied on each of these plant pathogenic strains on a PDA (potato dextrose agar) medium. This PDA medium is a mixture of potato 200g, dextrose 20g, agar 20g and water 1c. Old cultures of five days were employed. The compounds to be screen were suspended (1000ppm) in a PDA medium which autoclaved at 120^{o} C for 15 min. at 15atm. pressure. After cooling the Petri plates these media were poured into it and the organisms were inoculated. Ketoconazole was used as a standard in same condition. After 5 days the percentage inhibition for fungi was calculated using the formula given below.

Percentage of inhibition = 100(X-Y) ÷ X
Where, Area of colony in control plate = X. Area of colony in test plate = Y.

The fungicidal screening by compounds (4a-e) is shown in table-3.

Table-3
Antifungal screening of Compounds (4a-e)

	Zone of Inhibition at 1000 ppm (%)		
Compounds	***Rhizopus Nigrican***	***Nigrospora Sp.***	***Aspergillus Niger***
4a	58	63	62
4b	56	62	60
4c	62	61	59
4d	66	69	63
4e	69	67	67
Ketoconazole	78	75	72

Results and Discussion

The analytical data shows that the elemental compositions are consistence with predicted structure. (shown in Scheme-1). The Infra Red and PMR spectral data also support to the predicted structure. The structures assigned to 3-((dialkylamino)methyl)-5-((2-((ethyl(methyl)amino)methyl)-1H-benzoimidazol-1-yl) methyl) -1,3,4-oxadiazole-2(3H)-thione **(4a-e)** were supported by the analytical data. Infra Red and PMR spectra showing an absorption bands at 1620-1648(C=N), 3020-3080cm^{-1}(C-H of Ar.), 2950, 2878, 1370cm^{-1} (-CH_3,CH_2),1185(C=S), 765(C-O-C ring). PMR: 7.24–7.65(multiplet, 4H,Ar-H),4.86-4.38(singlet,4H,CH_2), 2.66(quartet,2H,CH_2),1.12(triplet,3H,CH_3), 2.28(singlet,3H,CH_3),3.82 (singlet,2H,CH_2), 4a;2.17(singlet, 6H,CH_3),4b;2.26(singlet,3H,CH_3),1.08(triplet,3H,CH_3), 2.67(quartet,2H,CH_2),4c;1.08(triplet,6H,CH_3),2.67(quartet,4H,C H_2),4d;1.08(triplet,3H,CH_3),2.67(quartet,2H,CH_2),6.82–7.27(multiplet, 5H,Ar-H),4e;6.82–7.27 (multiplet,10H, Ar-H). The data of all compounds including C, H, N and S analysis are in table-1.

The antibacterial screenings of all synthesized compounds (4a-e) were studied for gram-positive (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative (*E.coli and klebsiella promioe*) bacteria. Compounds 4d and 4e were more toxic for these bacteria, rest of the compounds found less or moderate active as a antibacterial agent than tetracycline. The activity is shown in table -2.

The fungicidal screenings of all synthesized compounds (4a-e) were studied in vitro Plant pathogenic organisms like *Nigrospora Sp, Rhizopus nigricum and Aspergillus Niger*. After 5 days the percentage inhibition for fungi was calculated. Compounds 4d and 4e were more active, other compounds show less or moderate active. The activity is displayed in table-3

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Conclusion

The fused derivatives of novel heterocyclic compound (4a-e) were successfully synthesized. With the help of analytical and spectral data the structures of new compounds were established. The novel compounds were examined for their antibacterial and antifungal activities. Among all the synthesize compounds 4d and 4e are more active as antibacterial and antifungal agent.

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