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Synthesis and *In Vitro* anthelmintic activity of novel substituted oxadiazole bearing benzimidazole derivatives.

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ABSTRACT

Nitrogen containing heterocycles drawn special attention in pharmaceutical chemistry due to their excellent medicinal potential. A novel series of substituted oxadiazole derivatives of benzimidazole synthesize in the correlation of anthelmintic activity, all the products were assayed against Pheretima posthuma. Out of the twelve synthesized derivatives, five compounds (6d, 6c, 7a, 7c, 7d) showed anthelmintic activity in a dose-dependent manner giving shortest time of paralysis and death with different concentrations. Among these, two derivatives, 6c and 6d showed superior activity

Keywords: Chalcone, Benzimidazole, Anthelmintic activity, Pheretima posthuma

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INTRODUCTION

Benzimidazole and oxadiazole were reviewed for biological activity and found that both hetero systems possess a broad spectrum of biological activities viz antimicrobial[1-4], antiamoebic[5-6] antiprotozoal[7-8] cysticidal [9]anticancer.[10-11]

The chemistry of the fused ring heterocyclic compound is the fascinating field of investigation in medicinal chemistry as it has been found to exhibit enhanced biological profile. The present work has been directed to synthesize various substituted benzimidazoles containing oxadiazole ring through mild and facile synthetic route and the study has focused on the influence of the various substituents on anthelmintic activity of benzimidazole. The presence of oxadiazole ring reports potent pharmacological activities like antifungal, antibacterial. In view of the above observation, it was thought worthwhile to synthesize a new benzimidazole molecule in which it is linked with the oxadiazole ring and further investigate these compounds for their anthelmintic activities. Helminthiasis is among the most pervasive infection and a foremost degenerative disease, distressing a large proportion of the world's population. The anthelmintic drugs derived from benzimidazole 2-carbamates, such as albendazole and mebendazole are used mainly to treat endoparasitic diseases in domestic animals and humans. These types of compounds are characterized by a high therapeutic index and low toxicity; however, they find little use in tissue-dwelling parasites mainly due to poor solubility and absorption problems. Newly synthesized benzimidazoles were studied at the molecular level for the mode of action of anthelmintic drugs. These results constitute valuable information for the design or improvement of more potent and selective molecules.

MATERIALS AND METHODS

Chemistry: Chemicals were procured from Loba chem.pvt, new delhi (LR grade). Reactions were monitored and purity of the products was checked by thin layer chromatography (TLC) (Benzene: Toluene, 7:3). TLC was performed on Merck60 F-254 silica gel plates with visualization by UV-light. Melting points were determined on a Buchi Melting Point B-545 apparatus. IR spectra (KBr pellets) were recorded on a Nicolet 6700 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer instruments, in DMSO-d_6. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were recorded on time-of- flight (TOF) mass spectrometers. **Table 1, Table 2**

Methods of synthesis[12]

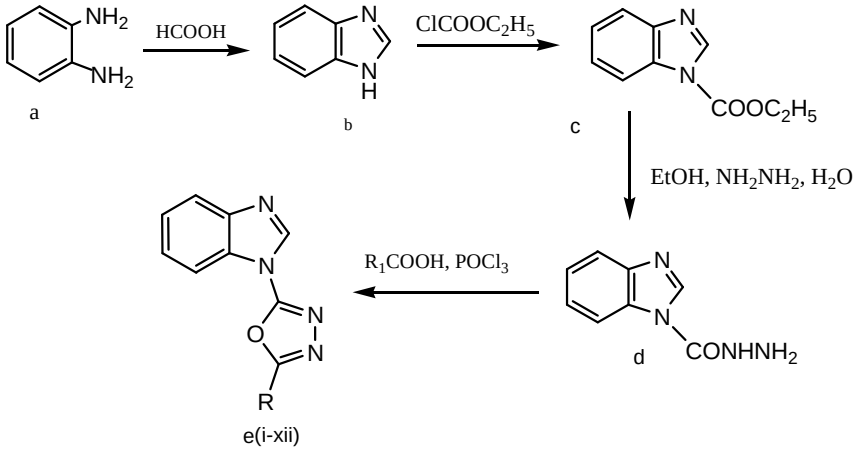
Synthesis of 1H-benzimidazole (b): 1H-benzimidazole was prepared by heating 0.24 mole of *o*-phenylenediamine in round bottomed flask with 0.48 mole of 90% formic acid on water bath at 100^{o}C for 2h, cooled, added 10% NaOH solution slowly with constant stirring until the mixture is just alkaline to litmus. Filtered off the product at the pump, cooled and washed with ice cold water, recrystallized with hot water, yield 90%, m.p. 171-173^{o} C.

Synthesis of ethyl 1H-benzo[d]imidazole-1-carboxylate (c): An equimolar solution of of 1H-benzimidazole (b) (1.18g, 0.01mole) and ethylechloroformate (0.95ml, 0.01mole) in dry acetone (4ml) in the presence of K_2CO_3 (1g) was refluxed on a water bath for 6h. The solvent was removed by vacuum distillation and the residue was dried and recrystallized from chloroform to give (c). Yield 90% , m.p. 170^{o}C.

Synthesis of 1H-benzo[d]imidazole-1-carbohydrazide(d): Compound (c) (1.9g, 0.01mole) dissolved in methanol (50ml) and 99% hydrazine hydrate (1ml) was refluxed for 4-5h. The reaction mixture was cooled and solid was filtered off, washed with methanol to obtain (d). Yield 85%, m.p. 180^{o}C.

Synthesis for 5- substituted 1-(1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (e[i-xii])

General method: A solution of hydrazide (4) (1.6g, 0.01mole) and the corresponding acid (0.01mole) in $POCl_3$ (30ml) was refluxed for 18-20h. Excess solvent was removed by steam distillation and the solution poured on ice with stirring and the product was precipitated by neutralization by ammonia, filtered, washed with water and recrystallized by chloroform to get respective oxadiazole. **Scheme 1**[14]



Scheme 1. Synthetic route for oxadiazole substituted benzimidazole derivatives

Methodology for in vitro anthelmintic activity[13]

Anthelmintic activity was studied with minor modifications to the standard Albendazole (Bandy Mankind Pharma Ltd., New Delhi) A group of six earthworms was released in each of 15 ml of control drugs and the test suspensions (1, 2.5 and 5% w/v each). Observations were made for the time taken to paralysis and death of individual worms up to 1 h of the test period. Each Petri dish was placed with 6 worms and observed for paralysis (or) death. The mean time for paralysis was noted when no movement of any sort could be observed, except when the worm was shaken

vigorously. The death time of worm (min) was recorded after ascertaining that worms neither moved when shaken nor when given external stimuli. Death was concluded when the worms lost their motility followed with fading away of their body colour. **Table. 3**

RESULTS

Table . 1 Characterization data (5i-xii)

Compound no.	R	Molecular formulae	% Yield	MP (^{0}C)
(5-(1H-benzo[d]imidazol-1-yl)-1,3,4-oxadiazol-2-yl)methanamine (5i)	$-CH_2NH_2$	$C_{10}H_9N_5O$	60	160 – 62
4-(5-(1H-benzo[d]imidazol-1-yl)-1,3,4-oxadiazol-2-yl)-3- ydroxybenzenesulfonic (5ii)	$-C_6H_3(OH)(SO_3H)$	$C_{15}H_{10}N_4O_5S$	89	172 – 74
1-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (5iii)	$-C_5H_4N$	$C_{14}H_9N_5O$	50	167- 69
1-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (5iv)	$4\text{-}NO_2C_6H_4$	$C_{15}H_9N_5O_3$	55	178- 80
1-(5-phenyl-1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (5v)	$-C_6H_5$	$C_{15}H_{10}N_4O$	70	196 – 98
1-(5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (5vi)	$2\text{-}ClC_6H_5$	$C_{15}H_9N_4OCl$	45	188 – 90
1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (VII)	$4\text{-}ClC_6H_5$	$C_{15}H_9N_4OCl$	46	196 – 98
(Z)-1-(5-styryl-1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (viii)	$-CH{=}CH\text{-}C_6H_5$	$C_{17}H_{12}N_4O$	49	159 – 61
4-(5-(1H-benzo[d]imidazol-1-yl)-1,3,4-oxadiazol-2-yl)benzenamine (ix)	$4\text{-}NH_2C_6H_5$	$C_{15}H_{11}N_5O$	43	179 – 81
1-(1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (x)	H	$C_9H_6N_4O$	46	193 – 95
1-(5-(1H-benzo[d]imidazol-1-yl)-1,3,4-oxadiazol-2-yl)ethanol (xi)	$-CH(OH)(CH_3)$	$C_{14}H_{10}N_4O_2$	71	186 – 88
1-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)-1H-benzo[d]imidazole (xii)	$-CH_2Cl$	$C_{10}H_7N_4OCl$	67	194- 96

Table 3. Anthelmintic activities of substituted benzimidazole

Compound Code	Concentration (% W/V)	Time taken in minutes (+-SD)	
		Paralysis Time	Death Time
5i	1.0	13.12+_0.25	40.12+-0.46
	2.5	11.13+_0.29	35.24+_0.33
	5.0	10.23+_0.30	20.22+_0.38
5ii	1.0	25.35+_0.14	45.23+_0.16
	2.5	20.34+_0.14	40.35+_0.23
	5.0	12.20+0.38	25.23+_0.12
5iii	1.0	11.12+_0.23	60.45+_0.42
	2.5	9.23+_0.12	50.36+_0.45
	5.0	8.29+_0.24	40.40+_0.38
5iv	1.0	8.25+_0.40	38.39+_0.24
	2.5	6.23+_0.46	31.15+_0.16
	5.0	5.17+_0.35	25.46+_0.27
5v	1.0	15.32+_0.14	30.24+_0.32
	2.5	12.36+_0.65	27.14+_0.29
	5.0	10.32+_0.14	22.15+_0.24
5vi	1.0	11.15+_0.16	35.32+_0.12
	2.5	9.65+_0.25	32.12+_0.36
	5.0	8.23+_0.39	19.38+_040
5vii	1.0	10.20+_0.21	38.15+_0.25
	2.5	9.39+_0.17	36.17+-0.38
	5.0	5.40+_0.50	30.14+_0.39
5viii	1.0	14.39+_0.32	42.32+_0.14
	2.5	10.26+_0.16	45.33+_0.25
	5.0	8.17+_0.28	32.15+_0.63
5ix	1.0	9.36+_0.45	30.29+_0.36
	2.5	9.44+_0.34	25.39+_0.47
	5.0	8.54+_0.17	20.56+_0.21
5x	1.0	11.32+_0.30	12.14+_0.25
	2.5	9.41+_0.26	18.12+_0.47
	5.0	8.12+_0.38	25.44+_0.16
5xi	1.0	16.21+_0.14	36.32+_0.16
	2.5	13.36+_0.39	30.54+_0.12
	5.0	10.25+_0.39	21.12+_0.36
5xii	1.0	12.14+_0.32	30.21+_0.23
	2.5	10.25+_0.29	29.23+_0.44
	5.0	9.54+_0.12	21.14+_0.27
Albendazole	2.5	8.14+_0.38	15.38+_0.18
Normal saline	--	--	--

CONCLUSION

Newer substituted oxadiazole and phenyl pyrazoline derivatives of benzimidazole were synthesized .All the synthesized compounds were tested for anthelmintic activity against adult arthworms (P. posthuma) due to their anatomical and physiological resemblance with the intestinal roundworm parasites of human being. Albendazole,

one of the reference compounds in the present study is effective in a broad range of helminth infections, including roundworms, hookworms, whipworms, pinworms and its mechanism of action involves inhibition of the glucose uptake system leading to a lethal depletion of energy reserves in the helminths. Synthesized benzmidazole anthelmintic derivatives arrest cell division in metaphase by interfering with microtubule assembly. They exhibit high affinity for tubulin, the precursor protein for microtubule synthesis. From the observations made in the present study, lower concentration of the synthesized derivatives exhibited the paralytic effect much earlier and the time of death was shorter for worms. Out of the twelve synthesized derivatives, five compounds (6d, 6c, 7a, 7c, 7d) showed good anthelmintic activity in a dose-dependent manner, giving the shortest time of paralysis (P) and death (D) with all three concentrations of the derivatives.

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