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ANTIHELMINTHIC AND ANTIINFLAMMATORY ACTIVITY OF A NOVEL SERIES OF NEW (1,3,4) OXADIAZINO-[6,5-b]INDOLE DERIVATIVES

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ABSTRACT

In the present investigation, a novel series of 2-[(benzalamino-4-hydroxybenzyl) (1,3,4)-oxadiazino[6,5-b] Indole derivatives (**V**) has been synthesized. The synthesized compounds have been characterized by IR, ^{1}H NMR and their mass number by mass spectroscopy. It was screened for anti-helminthic activity using earthworms at 0.1%, 0.2%, 0.5% concentration of compounds compared to standard albendazole drug. Compounds **V_2, V_9** and **V_{16}** showed good paralytic time, where as **V_3, V_8, V_{10}** and **V_{11}** showed moderate paralytic time of earthworms. Further, the synthesized compounds were screened for antiinflammatory activity by using Carrageenan–induced paw edema rat model. The results showed that the compounds significantly ($p < 0.0001$) reduced the inflammation, thereby showed a promising antiinflammatory activity. The synthesized compounds **V_2, V_3, V_4, V_5, V_7, V_9, V_{11}, V_{14}, V_{15}, V_{16}, V_{18}, V_{19}, V_{20}** and **V_{21}** showed potent activity ($p < 0.0001$), where as compound **V_1, V_6, V_8, V_{10}, V_{12}, V_{13}** and **V_{17}** showed moderate activity ($p < 0.05$) in Carrageenan paw edema model on comparison with the standard drug diclofenac Sodium (10 mg/mL).

Key words: (1,3,4)-Oxadiazino-[6,5-b]indole, Isatin derivatives, Antihelminthic activity, Albendazole, Antiinflammatory activity.

INTRODUCTION

Recent observations suggest that indole derivatives and related heterocyclic compounds, possess potential activity with lower toxicities in the chemotherapeutic approach in man [1,2] .The good biological profile of indole derivatives have been reported to possess a wide variety of biological properties viz.. anticonvulsant[3], cardiovascular[4], anti-

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bacterial[5], antiviral[6], antineoplastic[7], antihypertensive[8], antihistaminic[9], analgesic[10] and anti-inflammatory[11] activity. In view of these observations, the synthesis of new series of indole derivatives **(V)** has been carried out.

EXPERIMENTAL

Materials and methods

For this purpose, the required indole-2,3-diones **(I)** were prepared and condensed with 3-amino-4-hydroxybenzoicacidhydrazide **(II)** in ethanol to get the respective 3-amino-4-hydroxy-benzoic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide **(III)**. These compounds were cyclized using concentrated sulphuric acid to get respective 2-amino-4-[(1,3,4)oxadiazino[6,5-b]indole-3-yl]-phenol (**IV**). These compounds were refluxed with aromatic aldehyde, ethanol and few drops of acetic acid to get the title compounds. The compounds were characterized by their physical, analytical and spectral data (IR, PMR and Mass).

Antihelmintic activity[13,14]

The synthesized compounds are screened for antihelmintic activity by using earth worms. Five earth worms of nearly equal size were placed in standard drug solution and test compound solutions at room temperature. Normal saline was used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and the volume was adjusted up to 15 mL with normal saline solution to get the concentration of 0.1% w/v, 0.2% w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated for the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of motionless worms, they were frequently applied with external stimuli, which stimulate and induces movement in the worms, if alive. The mean lethal time and paralysis time of the earth worms for different test compounds and standard drug are given in Table 1.

Antiinflammatory activity

Carrageenan-induced rat paw edema method[12] was employed for evaluating the anti-inflammatory activity of the synthesized compounds. Wister Albino rats of either sex weighing approx 200- 350 g, were housed in clean polypropylene cages and kept under room temperature. In this study, the animals were divided into groups. Acute inflammation

was produced by sub plantar injection of 0.1 mL of 1% suspension of Carrageenan with 2% gum acacia in normal saline, in the right hind paw of the rats. After oral administration of the test compounds, the paw volume was measured plethysmometrically. Diclofenac sodium (10 mg/mL) with 2% gum acacia in normal saline was used as the standard drug. The data on anti-inflammatory activity are reported in Tables 2 (a) and 2 (b).

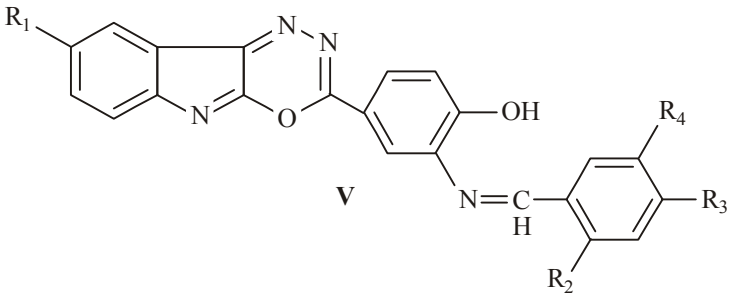

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Table 1: Antihelminthic activity of (1,3,4)oxadiazino-[6,5-b]indole derivatives

Compd.	Substitutents				Concentration (% w/v)	Time (min) *Mean* ± *SD*	
	R_1	R_2	R_3	R_4		For paralysis	For death
Control	-	-	-	-	0.9	-	-
					0.1	49 ± 0.56	68 ± 0.21
Standard	-	-	-	-	0.2	44 ± 0.15	62 ± 0.31
					0.5	38 ± 0.21	53 ± 0.24
					0.1	60 ± 0.18	158 ± 0.19
V_1	H	H	H	H	0.2	57 ± 0.14	145 ± 0.24
					0.5	53 ± 0.32	139 ± 0.34
					0.1	49 ± 0.26	152 ± 0.17
V_2	H	H	Cl	H	0.2	42 ± 0.35	137 ± 0.34
					0.5	39 ± 0.29	128 ± 0.21
					0.1	57 ± 0.34	162 ± 0.18
V_3	H	OH	H	H	0.2	55 ± 0.51	143 ± 0.26
					0.5	52 ± 0.28	135 ± 0.27

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Compd.	Substitutents				Concentration (% w/v)	Time (min) *Mean ± SD*	
	R_1	R_2	R_3	R_4		For paralysis	For death
V_4	H	H	OCH_3	H	0.1	61 ± 0.31	170 ± 0.36
					0.2	58 ± 0.25	157 ± 0.15
					0.5	55 ± 0.36	145 ± 0.34
V_5	H	H	OCH_3	OCH_3	0.1	63 ± 0.42	178 ± 0.28
					0.2	59 ± 0.25	162 ± 0.31
					0.5	57 ± 0.51	149 ± 0.27
V_6	H	H	N $(CH_3)_2$	H	0.1	65 ± 0.24	182 ± 0.54
					0.2	62 ± 0.32	167 ± 0.51
					0.5	60 ± 0.29	151 ± 0.34
V_7	H	H	OH	OCH_3	0.1	67 ± 0.14	168 ± 0.26
					0.2	63 ± 0.51	149 ± 0.19
					0.5	59 ± 0.26	140 ± 0.34
V_8	Br	H	H	H	0.1	53 ± 0.34	165 ± 0.28
					0.2	51 ± 0.31	152 ± 0.35
					0.5	48 ±0.24	143 ± 0.34
V_9	Br	H	Cl	H	0.1	42 ± 0.52	142 ± 0.21
					0.2	39 ± 0.26	137 ± 0.51
					0.5	30 ± 0.41	125 ±0.18
V_{10}	Br	OH	H	H	0.1	52 ± 0.52	167 ± 0.34
					0.2	50 ± 0.32	155 ± 0.51
					0.5	47 ± 0.42	149 ± 0.42
V_{11}	Br	H	OCH_3	H	0.1	55 ± 0.32	170 ± 0.31
					0.2	52 ± 0.28	163 ± 0.57
					0.5	49 ± 0.34	156 ± 0.35

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Compd.	Substitutents				Concentration (% w/v)	Time (min) *Mean* ± *SD*	
	R_1	R_2	R_3	R_4		For paralysis	For death
V_{12}	Br	H	OCH_3	OCH_3	0.1	57 ± 0.39	166 ± 0.29
					0.2	55 ± 0.48	157 ± 0.18
					0.5	50 ± 0.19	148 ± 0.15
V_{13}	Br	H	N $(CH_3)_2$	H	0.1	59 ± 0.42	173 ± 0.36
					0.2	57 ± 0.51	164 ± 0.24
					0.5	54 ± 0.32	157 ± 0.36
V_{14}	Br	H	OH	OCH_3	0.1	57 ± 0.55	163 ± 0.33
					0.2	54 ± 0.46	158 ± 0.25
					0.5	52 ± 0.52	152 ± 0.34
V_{15}	NO_2	H	H	H	0.1	60 ± 0.51	169 ± 0.16
					0.2	57 ± 0.19	165 ± 0.36
					0.5	54 ± 0.33	158 ± 0.44
V_{16}	NO_2	H	Cl	H	0.1	46 ± 0.52	148 ± 0.43
					0.2	42 ± 0.24	141 ± 0.48
					0.5	34 ± 0.43	122 ± 0.24
V_{17}	NO_2	OH	H	H	0.1	65 ± 0.15	177 ± 0.35
					0.2	61 ± 0.35	169 ± 0.29
					0.5	57 ± 0.42	160 ± 0.17
V_{18}	NO_2	H	OCH_3	H	0.1	67 ± 0.16	181 ± 0.34
					0.2	63 ± 0.42	175 ±0.21
					0.5	59 ± 0.33	168 ± 0.36
V_{19}	NO_2	H	OCH_3	OCH_3	0.1	72 ± 0.53	186 ± 0.29
					0.2	67 ± 0.17	179 ± 0.46
					0.5	59 ± 0.45	166 ± 0.37

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Compd.	Substitutents				Concentration (% w/v)	Time (min) *Mean ± SD*	
	R_1	R_2	R_3	R_4		For paralysis	For death
V_{20}	NO_2	H	N $(CH_3)_2$	H	0.1	74 ± 0.43	189 ± 0.31
					0.2	68 ± 0.27	180 ± 0.28
					0.5	61 ± 0.31	169 ± 0.19
V_{21}	NO_2	H	OH	OCH_3	0.1	75 ± 0.24	191 ± 0.33
					0.2	69 ± 0.19	183 ± 0.24
					0.5	65 ± 0.11	176 ± 0.15
Standard : Albendazole							

Table 2(a): Antiinflammatory activity of (1,3,4)oxadiazino-[6,5-b]indole derivatives

Initial mean ± SD (1.58 ± 0.07)	1 hr		2 hr	
	Mean ± SD	% Red.	Mean ± SD	% Red.
Control	3.32 ± 0.18	NA	3.47 ± 0.19	NA
Standard	2.33 ± 0.16	29.81*	2.13 ± 0.16	38.61*
V_1	3.17 ± 0.15	4.51	3.02 ± 0.13	12.96
V_2	2.8 ± 0.17	15.66	2.7 ± 0.2	22.19
V_3	2.73 ± 0.16	17.77	2.63 ± 0.15	24.20*
V_4	2.53 ± 0.17	23.79*	2.42 ± 0.09	30.25*
V_5	2.65 ± 0.21	20.18	2.45 ± 0.21	29.39*
V_6	3.1 ± 0.11	6.62	2.95 ± 0.1	14.98
V_7	2.45 ± 0.15	26.20*	2.25 ± 0.19	35.15*
V_8	2.87 ± 0.16	13.55	2.73 ± 0.10	21.32
V_9	2.52 ± 0.19	24.09*	2.38 ± 0.13	31.41*
V_{10}	3.28 ± 0.11	4.09	3.20 ± 0.08	9.09
V_{11}	3.22 ± 0.07	5.84	3.12 ± 0.10	11.36
V_{12}	3.15 ± 0.10	7.89	3.07 ± 0.12	12.78

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Initial mean ± SD (1.58 ± 0.07)	1 hr		2 hr	
	Mean ± SD	**% Red.**	**Mean ± SD**	**% Red.**
V_{13}	3.02 ± 0.07	11.69	2.90 ± 0.08	17.61
V_{14}	2.9 ± 0.07	15.20	2.80 ± 0.08	20.45
V_{15}	3.18 ± 0.07	7.01	3.10 ± 0.08	11.93
V_{16}	2.68 ± 0.07	21.63	2.55 ± 0.08	27.55*
V_{17}	3.10 ± 0.16	9.35	3.0 ± 0.12	14.77
V_{18}	2.77 ± 0.05	19.00	2.62 ± 0.07	25.56*
V_{19}	2.72 ± 0.09	20.46	2.55 ± 0.05	28.57*
V_{20}	3.27 ± 0.17	4.38	3.17 ± 0.17	11.20
V_{21}	2.82 ± 0.11	17.54	2.83 ± 0.08	20.72

Table 2(b): Antiinflammatory activity of (1,3,4)oxadiazino-[6,5-b]indole derivatives

Initial Mean ± SD (1.58 ± 0.07)	3 hr		4 hr	
	Mean ± SD	**% Red.**	**Mean ± SD**	**% Red.**
Control	3.57 ± 0.17	NA	3.27 ± 0.25	NA
Standard	2.07 ± 0.1	42.01*	1.83 ± 0.13	44.03*
V_1	2.93 ± 0.1	17.92	2.78 ± 0.11	14.98
V_2	2.62 ± 0.16	26.61*	2.48 ± 0.18	34.15*
V_3	2.5 ± 0.11	29.97*	2.37 ± 0.15	37.52*
V_4	2.27 ± 0.1	36.41*	2.12 ± 0.09	35.16*
V_5	2.33 ± 0.24	34.73*	2.2 ± 0.25	32.72*
V_6	2.83 ± 0.15	20.72	2.7 ± 0.16	17.43
V_7	2.15 ± 0.13	39.77*	2.02 ± 0.04	38.22*
V_8	2.83 ± 0.11	20.72	2.52 ± 0.09	22.93
V_9	2.22 ± 0.11	37.81*	2.10 ± 0.08	35.78*

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Initial Mean ± SD (1.58 ± 0.07)	3 hr		4 hr	
	Mean ± SD	% Red.	Mean ± SD	% Red.
V_{10}	3.12 ± 0.09	13.33	3.0 ± 0.07	12.28
V_{11}	3.08 ± 0.07	14.44	2.98 ±0.07	32.86*
V_{12}	2.93 ± 0.08	18.61	2.9 ± 0.11	15.20
V_{13}	2.80 ± 0.12	22.22	2.68 ± 0.11	21.63
V_{14}	2.72 ± 0.11	24.44*	2.6 ± 0.14	33.97*
V_{15}	3.0 ± 0.07	16.66	2.9 ± 0.07	35.20*
V_{16}	2.44 ± 0.08	32.22*	2.3 ± 0.08	32.74*
V_{17}	3.0 ± 0.11	16.66	2.92 ± 0.11	14.61
V_{18}	2.53 ± 0.05	29.72*	2.43 ±0.05	28.94*
V_{19}	2.45 ± 0.05	32.50*	2.25 ± 0.05	35.15*
V_{20}	3.01 ± 0.15	17.07	2.93 ± 0.12	32.56*
V_{21}	2.72 ± 0.07	25.06*	2.45 ± 0.10	36.39*

RESULTS AND DISSCUSION

The synthesized compounds of novel series of (1,3,4)oxadiazino-[6,5-b]indole derivatives were tested for antihelminthic activity and antiinflammatory activities.

The results of antihelminthic activity studies revealed that the compounds **V_2, V_9** and **V_{16}** showed good paralytic time, where as **V_3, V_8, V_{10}** and **V_{11}** showed moderate paralytic time of earthworms as compared to standard albendazole drug at 0.1%, 0.2%, 0.5% (w/v) concentration of compounds (Table 1).

The results of antiinflammatory acivity studies revealed that the compounds **V_2, V_3, V_4, V_5, V_7, V_9, V_{11}, V_{14}, V_{15}, V_{16}, V_{18}, V_{19}, V_{20}** and **V_{21}** showed potent activity ($p < 0.0001$), where as compounds **V_1, V_6, V_8, V_{10}, V_{12}, V_{13}** and **V_{17}** showed moderate activity ($p < 0.05$) in Carrageenan paw edema model, when compared to the standard drug diclofenac sodium (10 mg/mL) (Table 2).

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