ANTI INFLAMMATORY AND ANALGESIC ACTIVITY OF SOME NEW INDOLE DERIVATIVES

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Summary

In the present investigation, we have synthesized a novel series of (1, 3, 4) oxadiazino-[5, 6-b]indole derivatives(V). The synthesized compounds have been characterized by IR, ^{1}HNMR and their mass number by Mass Spectroscopy. They have screened for anti inlammatory and analgesic activity. The compounds which are the derivatives of methyl isatin (V (15)-V (21)) shows anti-inflammatory activity as good as the standard, all are statistically significant. Where as the compounds V (2), V (3), V (4), V (5), V (7), V (9), V (15) and V (19) showed good analgesic activity as the standard.

Key words: (1,3,4)oxadiazino-[5,6-b] Indole, Isatin derivatives, Anti inflammatory Activity, Analgesic activity

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Introduction

Isatin (2,3-dioxindole) is an endogenous compound identified in humans, and its effect has been studied in a variety of systems. Biological properties of isatin include a range of actions in the brain and offer protection against certain types of infections [1]. It is known from the literature that indole derivatives exhibit varied biological and pharmacological properties viz. anticonvulsant, analgesic, antiviral, anti-neoplastic, MAO-inhibitory activity, anti-HIV, spasmogenic, anti-microbial activity and anxiolytic [2-10]. In view of these observations the synthesis of New (1,3,4)oxadiazino-[5,6-b]- indole derivatives(V) has been carried out.

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). The data on anti-inflammatory and analgesic activity results are presented in Table-I and Table-II respectively.

Materials and Methods

Anti inflammatory activity

Carragennan - induced rat paw edema method [11] was employed for evaluating the anti inflammatory activity of the synthesized compounds. Wister Albino rats of either sex weighing approx 200- 350 gm, were housed in clean poly propylene cages and kept under room temperature (25±2^{O}C), and relative humidity 40-50% in a 12 hr light-day cycle. Food was withdrawn 12 hr before and during experimental hours. In this study, the animals were divided into groups as shown in the Table-I. Acute inflammation was produced by sub plantar injection of 0.1ml of 1% suspension of carragennan 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 at 1, 2, 3, and 4 hr intervals. Diclofenac sodium (10mg/ml) with 2% gum acacia in normal saline was used as standard drug. The results of anti-inflammatory activity were presented in the Table-I.

Analgesic activity

All the experiments were carried out using male, Swiss Albino mice (25-30 gm),which were obtained from animal house. On arrival the animals were placed at random and allocated to treatment groups in polypropylene cages with paddy husk as bedding. Animals were housed at a temperature of 24 ± 2^{o}C and relative humidity of 30-70 %. A 12:12 ratio of light and day cycle was followed. All animals were allowed for free access to water with standard commercial chaw pellets [12]. All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee. The Analgesic activity results were presented in the Table-II.

Hot Plate Method

Five groups of six mice each were selected for the present study. Group 1 served as control and received the vehicle. The drug concentration of 5 mg/kg was administered orally to groups 2, 3 and 4 respectively and group 5 received the standard drug pentazocine [30 mg/kg (i.p.)]. The mice were placed on Eddy's hot plate kept at a temperature of 55 ± 0.5^{0}C for a maximum time of 15 seconds. Reaction time was recorded when the animals licked their fore and hind paws and jumped; at before 0 and 15, 30, 45, and 60 min after administration of test drugs [13].

All the Statistical analysis results were expressed as Mean ± Standard Error (SEM). Data was analyzed using one-way ANOVA followed by Dunnett's t-test. P-values < 0.05 were considered as statistically significant.

Results and Discussion

The anti inflammatory data of 2-[(benzalamino-4-hydroxybenzyl) (1,3,4)-oxadiazino[6,5-b]] Indole derivatives (V) shown in the Table I indicate that these compounds exhibited a marginal activity , interestingly, the compounds which are the derivatives of Methyl isatin ($V_{(15)}$-$V_{(21)}$) showed activity as good as the standard, all are statistically significant and the p<0.0001***. While the remaining compounds V(11) ,V(12) , V(13) which are the chloro isatin derivatives showed moderate activity but remaining showed very less potency. The Compounds V (16) and V (17) have shown the activity almost equal to the standard drug.

The analgesic activity of the 2-[(benzalamine-4-hydroxybenzyl) (1,3,4)-oxadiazino(6,5-b)]indoles (V) has been presented in the Table II, indicating that the compounds V(2), V(3), V(4), V(5), V(7), V(9), V(15) and V(19) showed good analgesic activity and the remaining compounds showed very less to moderate analgesic activity.

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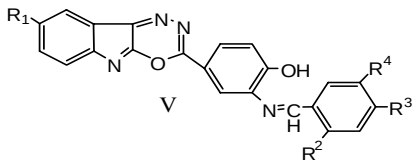
Table I: Anti inflammatory activity of New (1,3,4)oxadiazino[5,6-b]indole (V) derivatives

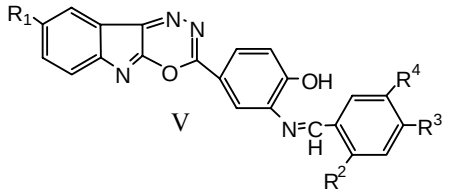


V

Compound Mean ±SD	Substituents				1hr		2hr		3hr		4hr	
	R^1	R^2	R^3	R^4	Mean ±SD	% red	Mean ±SD	% red	Mean ±SD	% red	Mean ±SD	% red
Control					3.42 ± 0.16	NA	3.57± 0.16	NA	3.63 ± 0.1	NA	3.47± 0.10	NA
Standard					2.38 ± 0.13	30.40*	2.13± 0.12	40.33*	1.93± 0.12	46.83*	1.72± 0.13	50.43*
V(1)	F	H	H	H	3.28±0.09	2.95	3.20±0.08	8.57	3.10±0.11	13.40	2.90±0.08	15.20
V(2)	F	H	Cl	H	3.25±0.08	3.84	3.15±0.10	10.0	3.05±0.10	14.80	2.95±0.10	13.74
V(3)	F	OH	H	H	3.15±0.08	6.80	3.05±0.08	12.85	2.95±0.08	17.59	2.82±0.04	17.54
V(4)	F	H	OCH_3	H	3.02±0.07	10.65	2.85±0.10	18.57	2.75±0.10	23.18	2.67±0.08	21.92
V(5)	F	H	OCH_3	OCH_3	2.93±0.05	13.31	2.77±0.05	20.85	2.63±0.05	26.53	2.55±0.05	25.43**
V(6)	F	H	$N(CH_3)_2$	H	3.22±0.11	4.73	3.13±0.10	10.57	3.03±0.10	15.36	2.93±0.08	14.32
V(7)	F	H	OH	OCH_3	2.67±0.10	21.00	2.53±0.08	27.71	2.45±0.10	31.56	2.35±0.10	31.28**
V(8)	Cl	H	H	H	3.25±0.08	3.84	3.18±0.07	9.14	3.10±0.08	13.40	2.95±0.05	13.74
V(9)	Cl	H	Cl	H	2.51±0.19	24.04	2.33±0.13	31.39	2.21±0.11	37.78	2.08±0.08	35.64**
V(10)	Cl	H	OCH_3	H	2.52±0.19	24.09	2.38±0.13	31.41	2.22±0.11	37.81	2.10±0.08	35.78**
V(11)	Cl	OH	H	H	2.87±0.16	13.55	2.73±0.10	21.32	2.83±0.11	20.72	2.52±0.09	22.93
V(12)	Cl	H	OCH_3	OCH_3	2.53±0.17	23.79	2.42±0.09	30.25	2.27±0.1	36.41	2.12±0.09	35.16**
V(13)	Cl	H	$N(CH_3)_2$	H	2.65±0.21	20.18	2.45±0.21	29.39	2.33±0.24	34.73	2.2±0.25	32.72**
V(14)	Cl	H	OH	OCH_3	3.17±0.15	4.51	3.02±0.13	12.96	2.93±0.1	17.92	2.78±0.11	14.98
V(15)	CH_3	H	H	H	2.8±0.17	15.66	2.7±0.2	22.19	2.62±0.16	26.61	2.48±0.18	44.15***
V(16)	CH_3	H	Cl	H	2.82 ± 0.11	17.54	2.83 ± 0.08	20.72	2.72 ±0.07	25.06	2.45 ± 0.10	49.39***
V(17)	CH_3	OH	H	H	3.27 ± 0.17	4.38	3.17 ± 0.17	11.20	3.01 ± 0.15	17.07	2.93 ± 0.12	45.56***
V(18)	CH_3	H	OCH_3	H	2.72 ± 0.09	20.46	2.55 ± 0.05	28.57	2.45 ± 0.05	32.50	2.25 ± 0.05	39.15***
V(19)	CH_3	H	OCH_3	OCH_3	2.93 ± 0.15	14.32	2.83 ± 0.1	20.72	2.72 ±0.07	25.06	2.57 ± 0.08	42.93***
V(20)	CH_3	H	$N(CH_3)_2$	H	3.28±0.09	2.95	3.20±0.08	8.57	3.10±0.11	13.40	2.90±0.08	15.20
V(21)	CH_3	H	OH	OCH_3	3.25±0.08	3.84	3.15±0.10	10.0	3.05±0.10	14.80	2.95±0.10	13.74

Standard: Diclofenac Sod.

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



V

Compound Mean ±SD	Substituents				0.5hr		1hr		2hr	
	R^1	R^2	R^3	R^4	Mean ±SD	%Protection	Mean ±SD	%Protection	Mean ±SD	%Protection
Control					*3.42 ± 0.16*	NA	*3.57± 0.16*	NA	*3.63 ± 0.1*	NA
Standard					11.1 ± 0.89	146.66*	13.0 ± 0.5	188.88*	14.2 ± 0.34	215.55*
V(1)	F	H	H	H	4.83 ± 0.82	7.3	5.7 ± 1.01	26.66	6.5 ± 1.02	44.44
V(2)	F	H	Cl	H	5.33 ± 0.82	18.44	6.3 ± 0.8	40.0	7.2 ± 0.6	60.0*
V(3)	F	OH	H	H	6.33 ± 0.82	40.66	7.2 ± 0.8	60.0*	8.0 ± 0.6	77.77*
V(4)	F	H	OCH_3	H	7.17 ± 0.75	59.33	8.2 ± 0.8	82.22*	9.2 ± 0.8	104.44*
V(5)	F	H	OCH_3	OCH_3	9.17 ± 0.75	103.77*	10.02 ± 0.8	122.66*	11.2 ± 0.8	148.88*
V(6)	F	H	$N(CH_3)_2$	H	4.91 ± 1.03	9.11	5.8 ± 0.8	28.88	6.7 ± 0.5	48.88
V(7)	F	H	OH	OCH_3	9.33 ± 0.52	107.33*	11.0 ± 0.5	144.44*	12.0 ± 0.4	166.66*
V(8)	Cl	H	H	H	5.17 ± 0.98	14.88	6.17 ± 0.98	37.11	7.2 ± 1.01	60.0*
V(9)	Cl	H	Cl	H	9.33 ± 0.52	107.33*	11.0 ± 0.5	144.44*	12.0 ± 0.4	166.66*
V(10)	Cl	OH	H	H	5.03 ± 0.75	11.77	5.7 ± 1.01	26.66	6.5 ± 1.02	44.44
V(11)	Cl	H	OCH_3	H	5.31 ± 0.75	18.0	5.03 ± 0.75	11.77	4.82 ± 0.8	7.1
V(12)	Cl	H	OCH_3	OCH_3	4.81 ± 0.55	6.88	5.31 ± 0.75	18.0	4.8 ± 0.8	6.6
V(13)	Cl	H	$N(CH_3)_2$	H	5.17 ± 0.41	14.88	4.81 ± 0.55	6.88	5.5 ± 0.5	22.22
V(14)	Cl	H	OH	OCH_3	7.02 ± 0.11	56.0	5.17 ± 0.41	14.88	6.2 ± 0.4	37.77
V(15)	CH_3	H	H	H	5.13 ± 0.75	14.0	7.02 ± 0.11	56.0	8.8 ± 0.8	95.55*
V(16)	CH_3	H	Cl	H	7.83 ± 0.41	74.0*	5.13 ± 0.75	14.0	4.8 ± 0.8	6.6
V(17)	CH_3	OH	H	H	5.33 ± 0.82	18.44	7.83 ± 0.41	74.0*	8.8 ± 0.4	95.55*
V(18)	CH_3	H	OCH_3	H	6.01 ± 0.11	33.55	5.33 ± 0.82	18.44	5.5 ± 0.8	22.22
V(19)	CH_3	H	OCH_3	OCH_3	11.1 ± 0.89	146.66*	6.01 ± 0.11	33.55	8.3 ± 0.8	84.44*
V(20)	CH_3	H	$N(CH_3)_2$	H	4.9 ± 0.89	8.0	4.9 ± 0.89	8.0	5.0 ± 0.9	11.11
V(21)	CH_3	H	OH	OCH_3	4.83 ± 0.82	7.3	4.83 ± 0.82	7.3	5.5 ± 0.5	22.22

Standard: Pentozocine