ANTIHELMINTHIC AND ANALGESIC ACTIVITY OF SOME NOVEL INDOLE DERIVATIVES

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Summary

In the present investigation, we have synthesized a novel series of (1, 3, 4) oxadiazino-[6, 5-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 antihelmenthic activity and analgesic activity. Compounds V(2),V(9), V(12), showed good paralytic time V(10), V(14), V(16) showed moderate paralytic time when compared with the standard Albendazole drug. Compounds V(24),V(25),V(26),V(28),V(30),V(40) showed good analgesic activity when compared with the standard drug pentazocine.

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

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-[6,5-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). Twenty one compounds(**V(1)-V(21)**) were screened for anti helminthic activity and the compounds (**V(22)-V(42)**) were screened for analgesic activity, the results are presented in Table-I and Table-II respectively.

Materials and Methods

Anti helminthic activity [11,12]:
The synthesized compounds (V1-V) are screened for Antihelminthic 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 adjusted the volume up to 15ml 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 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 were tabulated in 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 [13]. 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 ± 0.5^0C 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.

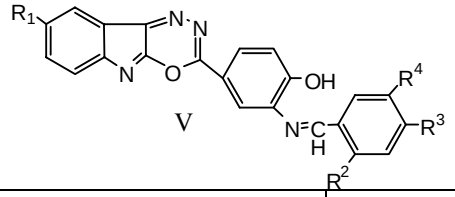
Results and Discussion

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

The investigation of anti helminthic activity revealed that the tested compounds V(2), V(9), V(12) showed good paralytic time, where as V(10),V(14),V(16) showed moderate paralytic time of earthworms compared to standard Albendazole drug at 0.1%, 0.2%, 0.5% concentration of compounds and results are presented in Table-I

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(24), V(25), V(26), V(28), V(30), V(40) showed good analgesic activity and the remaining compounds showed very less to moderate analgesic activity.

Table I: Data on Anti helminthic Activity of New (1,3,4)oxadiazino-[6,5-b]indole derivatives.



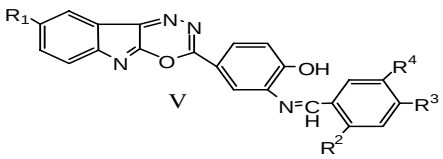
V

Compound	Substitutents				Concentration	Time in Minutes	
	R1	R2	R3	R4		For Paralysis	For Death
Control	-	-	-	-	0.9%	-	-
Albendazole	-	-	-	-	0.1%	49±0.46	68±0.34
					0.2%	44±0.18	62±0.24
					0.5%	38±0.43	53±0.16
V(1)	F	H	H	H	0.1%	51±0.21	160±0.24
					0.2%	50±0.16	149±0.34
					0.5%	48±0.32	140±0.19
V(2)	F	H	Cl	H	0.1%	40±0.41	135±0.13
					0.2%	38±0.25	130±0.24
					0.5%	30±0.15	118±0.38
V(3)	F	OH	H	H	0.1%	49±0.31	161±0.22
					0.2%	45±0.29	150±0.34
					0.5%	44±0.16	142±0.11
V(4)	F	H	OCH_3	H	0.1%	50±0.24	164±0.22
					0.2%	48±0.31	158±0.15
					0.5%	45±0.35	149±0.19
V(5)	F	H	OCH_3	OCH_3	0.1%	51±0.19	160±0.36
					0.2%	47±0.11	151±0.31
					0.5%	42±0.23	142±0.22
V(6)	F	H	$N(CH_3)_2$	H	0.1%	53±0.33	165±0.18
					0.2%	50±0.21	160±0.27

					0.5%	48±0.22	156±*0.28*
V(7)	F	H	OH	OCH_3	0.1%	52±0.16	157±0.19
					0.2%	49±0.34	153±0.24
					0.5%	46±0.26	148±0.37
V(8)	Cl	H	H	H	0.1%	48±0.31	146±0.28
					0.2%	46±0.18	138±0.34
					0.5%	42±0.11	135±0.21
V(9)	Cl	H	Cl	H	0.1%	39±0.34	131±0.31
					0.2%	35±0.21	114±0.36
					0.5%	30±0.31	102±0.29
V(10)	Cl	OH	H	H	0.1%	46±0.26	144±0.37
					0.2%	43±0.18	136±0.11
					0.5%	42±0.34	128±0.16
V(11)	Cl	H	OCH_3	H	0.1%	47±0.22	150±0.24
					0.2%	45±0.35	146±0.33
					0.5%	41±0.44	138±0.44
V(12)	Cl	H	OCH_3	OCH_3	0.1%	48±0.36	145±0.38
					0.2%	44±0.49	137±0.19
					0.5%	39±0.25	124±0.24
V(13)	Cl	H	$N(CH_3)_2$	H	0.1%	49±0.09	153±0.36
					0.2%	48±0.16	147±0.29
					0.5%	45±0.22	140±0.15
V(14)	Cl	H	OH	OCH_3	0.1%	48±0.24	142±0.18
					0.2%	45±0.34	138±0.14
					0.5%	43±0.36	134±0.34
V(15)	CH_3	H	H	H	0.1%	63±0.42	172±0.28
					0.2%	60±0.19	169±0.34
					0.5%	57±0.35	162±0.34
V(16)	CH_3	H	Cl	H	0.1%	49±0.26	152±0.15

					0.2%	46±0.19	145±0.16
					0.5%	37±0.14	131±0.34
V(17)	CH_3	OH	H	H	0.1%	68±0.15	180±0.15
					0.2%	65±0.35	173±0.17
					0.5%	60±0.24	164±0.16
V(18)	CH_3	H	OCH_3	H	0.1%	71±0.31	185±0.34
					0.2%	67±0.15	179±0.15
					0.5%	64±0.31	171±0.33
V(19)	CH_3	H	OCH_3	OCH_3	0.1%	75±0.22	189±0.15
					0.2%	71±0.43	181±0.34
					0.5%	63±0.19	170±0.26
V(20)	CH_3	H	$N(CH_3)_2$	H	0.1%	77±0.17	191±0.31
					0.2%	71±0.24	183±0.25
					0.5%	64±0.18	172±0.13
V(21)	CH_3	H	OH	OCH_3	0.1%	79±0.31	195±0.22
					0.2%	73±0.19	187±0.18
					0.5%	68±0.16	179±0.17

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



V

Standard: Pentozocine

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					4.42 ± 0.16	NA	4.27± 0.19	NA	4.33 ± 0.11	NA
Standard					11.1 ± 0.89	159.25*	12.1 ± 0.05	183.37*	13.2 ± 0.34	204.89*
V(22)	H	H	H	H	4.95 ± 0.22	12	5.7 ± 0.45	33.48	6.15 ± 0.82	42.03
V(23)	H	H	Cl	H	5.13 ± 0.12	16	6.3 ± 0.53	47.54	7.2 ± 0.61	66.28
V(24)	H	OH	H	H	5.38 ± 0.14	21.7	7.2 ± 0.12	68.61	8.72 ± 0.46	101.38*
V(25)	H	H	OCH_3	H	7.23 ± 0.25	63.5	8.2 ± 0.23	92.03	9.12 ± 0.22	110.62*
V(26)	H	H	OCH_3	OCH_3	8.56 ± 0.09	93.66*	9.42 ± 0.22	120.60*	10.65 ± 0.43	145.40*
V(27)	H	H	$N(CH_3)_2$	H	5.11 ± 0.43	15.6	5.83 ± 0.17	36.53	6.37 ± 0.51	47.11
V(28)	H	H	OH	OCH_3	9.00 ± 0.22	103.61*	10.02 ± 0.15	134.6*	11.50 ± 0.44	165.58*
V(29)	Br	H	H	H	5.45 ± 0.51	23	6.27 ± 0.38	46.83	7.21 ± 0.21	66.51
V(30)	Br	H	Cl	H	7.09 ± 0.02	67.15	11.0 ± 0.51	57.6	11.80 ± 0.24	172.5*
V(31)	Br	OH	H	H	6.05 ± 0.15	36.87	6.17 ± 1.00	44.4	7.15 ± 0.32	65.12
V(32)	Br	H	OCH_3	H	5.01 ± 0.15	13.34	5.43 ± 0.23	27.16	6.11 ± 0.81	41.10
V(33)	Br	H	OCH_3	OCH_3	4.85 ± 0.05	9.72	5.31 ± 0.32	24.35	6.17 ± 0.28	42.49
V(34)	Br	H	$N(CH_3)_2$	H	5.34 ± 0.16	20.8	5.81 ± 0.32	36.29	6.61 ± 0.51	52.65
V(35)	Br	H	OH	OCH_3	6.14 ± 0.19	38.91	6.37 ± 0.21	49.18	7.15 ± 0.43	65.12
V(36)	NO_2	H	H	H	5.63 ± 0.22	27.3	6.52 ± 0.11	52.69	7.91 ± 0.21	82.67
V(37)	NO_2	H	Cl	H	7.67 ± 0.21	73.52	6.13 ± 0.79	43.55	5.91 ± 0.21	36.48
V(38)	NO_2	OH	H	H	5.65 ± 0.21	27.82	6.82 ± 0.23	59.7	7.75 ± 0.23	78.98
V(39)	NO_2	H	OCH_3	H	6.67 ± 0.16	50.90	7.56 ± 0.45	77.04	8.59 ± 0.34	98.38
V(40)	NO_2	H	OCH_3	OCH_3	9.15 ± 0.19	107.01*	10.18 ± 0.14	138.90*	12.08 ± 0.23	178.98*
V(41)	NO_2	H	$N(CH_3)_2$	H	5.19 ± 0.29	17.42	6.89 ± 0.84	61.35	7.38 ± 0.21	70.43
V(42)	NO_2	H	OH	OCH_3	4.93 ± 0.52	11.53	5.83 ± 0.81	36.53	6.78 ± 0.18	56.58

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References

[1] Surendra Nath Pandeya, Sivakumar Smitha, Mayank Jyoti, Seshaiah Krishnan Sridhar. *Acta Pharm.* 2005; 55: 27–46.

[2] Bhattacharya SK and Chakraborti A. Dose related proconvulsant and anticonvulsant activity of isatin, a putative biological factor in rats, *Indian J Exp Biol.*1998; 36:118–121.

[3] Sharaf OA. Some pharmacological activities of new substituted pyrollo indoles, indolothiazepineand azole derivatives. *Bull Fac Pharm.* 1997; 35:79–82.

[4] Sarangapani M, Jessy Jacob, Srinivas B and Raghunandan N, Synthesis and CNS Activity of New Indole Derivatives. *Indian Drugs*. 2001; 38(5):264-268.

[5] Pandeya SN, Laximi VS and Pandeya A. Biological Activity of Mannich Bases. *Indian J Pharma Sci*. 2003; 65(3):213-222.

[6] Medvedev AE, Goodwin A, Clow A, Halket J, Glover V and Sandler M. Inhibitory potency of some isatin analogues on human monoamine oxidase A and B, *Biochem. Pharmacol*. 1992; 44:590–592.

[7] Pandeya SN, Sriram D, Nath G and De Clercq E. Synthesis, antibacterial, antifungal and anti-HIV activity of Schiff and Mannich bases of isatin with N-6-chlorobenzthiazol-2-yl-thiosemicarbazide, *Indian J. Pharm. Sci.* 1999; 61: 358–361.

[8] Hota D and Acharya SB, Studies on peripheral actions of isatin. *Indian J. Exp. Biol.*1994; 32:710–717.

[9] Varma RS and Nobles WL. Substituted *N*-amino methyl isatins. *J. Med. Chem*. 1967;10: 510-513.

[10] Palit G, Kumar R, Patnaik GK and Bhattacharya SK. Behavioral effects of isatin, a putative biological factor, in rhesus monkeys. *Biogenic. Amines.* 1997;13:131–142.

[11] Sreenivasa Murthy V, E.Jayachandra,LVG Nargund ,Indian Drugs, 36(2):137-139.

[12] Grover J.K Experiments in Pharmacy and Pharmacology II nd ed.1993;II

[13] Prinz W, Kayle A and Levy PR. *J. Chem. Res.* 1978; 116.

[14] Prinz W, Kayle A and Levy PR. *J. Chem. Res.* 1978;1347.