March 2010 ISSN: 0974 - 7516 Volume 6 Issue 1

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Short Communication

OCAIJ, 6(1), 2010 [13-15]

CNS activity of some new 2-{(benzalamino-4-hydroxybenzyl) (1,3,4)-oxadiazino[6,5-b]} indole derivatives

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Received: 16th November, 2009 ; Accepted: 26th November, 2009

ABSTRACT

Twenty one New 2-{(benzalamino-4-hydroxybenzyl) (1,3,4)-oxadiazino[6,5-b]} Indole derivatives **(V)** have been synthesized by condensing 2-Amino-4-[(1,3,4)oxadiazino[6,5-b]indole-3-yl]-phenol **(IV)** with various aromatic aldehydes. The intermediates, on the other hand, have been synthesized by the cyclization of 3-Amino-4-hydroxy-benzoic acid (2-oxo-1, 2-dihydro-indol-3-ylidene)-hydrazide **(III)** in presence of Concentrated H_2SO_4. The title compounds have been purified and characterized by their analytical and spectral data. They have screened for their gross behavioral studies, effects on locomotor activity and effect on pentobarbitone sodium induced sleeping time. All the test compounds exhibited reduction in locomotor activity, compound **(V)(9)** exhibited more effect among all the test compounds and potentiation of pentobarbitone sodium induced sleeping time ranges from 167.40 per cent to 276.60 per cent. The compound **(V) (6)** showed more activity with a potentiation of 276.60 per cent in experimental animals.

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KEYWORDS

(1, 3, 4) oxadiazino-[5,6-b] Indole;
Isatin derivatives;
Locomotor activity;
Pentobarbitone sodium.

INTRODUCTION

It is known from the literature that Indole derivatives exhibit varied biological and pharmacological properties[1-7] viz. anti-microbial, anti-viral, anti neoplastic, analgesic, CNS activities. 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 sulfuric 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 as shown in Scheme 1. The compounds were characterized by their physical, analytical and spectral data (IR and PMR, MASS). The data on locomotor activity and effect on pentobarbitone sodium induced sleeping time activities is presented in TABLE 1.

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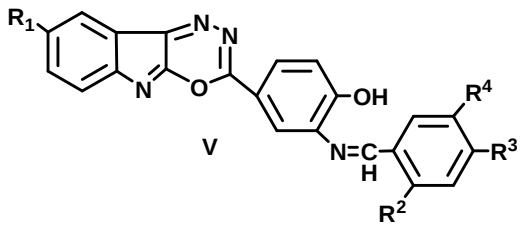

Scheme 1

MATERIALS AND METHODS

Action on central nervous system gross behavioral studies

Healthy albino mice weighing between 20 to 25gm were fasted for 24 hours and divided into groups of six animals each. Each of the test compounds 10mg was suspended in 0.3ml of tween solution (one drop dissolved in 1 ml of distilled water) and the volume made up with saline solution to get 10 mg/ml concentration. The suspension of test compounds was administered, intraperitoneally in dose of 100 mg/kg (body weight). The control group of animals received only the vehicle. The animals were observed for gross behavioral changes, continuously, for 7 hours starting from the administration of compounds[8]. The locomotor activity was studied with Actophotomotor after half an hour of administration of the test compounds. The results are presented in TABLE 1.

TABLE 1 : CNS activity of new (1,3,4)-oxadiazino-[5,6-b] indole (V) derivatives

Compound	Substituents				Locomotor activity on mice		Pentobarbitone induced sleeping time	
	R^1	R^2	R^3	R^4	Before admin. of drug (for 1 min)	After half an hour of admin. of drug (for 1 min)	Duration f action (min)	Percent effect (%)
V(1)	H	H	H	H	33.46	18.26	80.00	266.66
V(2)	H	H	Cl	H	31.33	14.22	68.23	227.43
V(3)	H	OH	H	H	34.00	20.12	65.55	218.50
V(4)	H	H	OCH_3	H	33.86	18.66	69.00	230.00
V(5)	H	H	OCH_3	OCH_3	30.55	13.72	54.62	182.06
V(6)	H	H	$N(CH_3)_2$	H	34.28	10.66	82.98	276.60
V(7)	H	H	OH	OCH_3	36.74	10.33	50.36	167.86
V(8)	Br	H	H	H	42.77	9.96	65.00	216.66
V(9)	Br	H	Cl	H	44.83	8.12	73.32	244.44
V(10)	Br	OH	H	H	43.00	10.00	61.00	203.33
V(11)	Br	H	OCH_3	H	42.64	12.66	72.99	243.30
V(12)	Br	H	OCH_3	OCH_3	40.32	11.98	53.33	177.76
V(13)	Br	H	$N(CH_3)_2$	H	36.91	10.01	75.00	250.00
V(14)	Br	H	OH	OCH_3	37.11	11.89	71.22	237.40
V(15)	NO_2	H	H	H	32.99	15.26	62.00	206.66
V(16)	NO_2	H	Cl	H	36.71	12.48	60.26	200.80
V(17)	NO_2	OH	H	H	30.91	14.87	50.23	167.40
V(18)	NO_2	H	OCH_3	H	31.62	18.34	58.33	194.44
V(19)	NO_2	H	OCH_3	OCH_3	32.66	20.66	55.26	184.20
V(20)	NO_2	H	$N(CH_3)_2$	H	33.34	21.03	64.21	214.00
V(21)	NO_2	H	OH	OCH_3	30.26	20.96	68.11	227.00
Control							30	100

***The test compounds were administered in a dose of 100 mg/kg (body weight)**

Effect on pentobarabitone sodium induced sleeping time

Healthy albino mice weighing between 20 and 28gm were fasted for 24 hours before the experiment and were divided into groups of six animals each. The test compounds were administered intraperitoneally at a

dose of 100mg/kg (body weight). The control group of animals was given only the vehicle. After 30 minutes, pentobarbitone sodium was administered intraperitoneally to all groups of animals at a dose of 35 mg/kg (body weight). The time of administration of test compounds and pentobarbitone sodium, the time of loss and gain of righting reflex were recorded in all the groups of test animals and percentage effect on pentobarbitone sodium induced sleeping time by the test compounds was calculated using the formula given below[9], considering righting reflex in control an 100%. The results are presented in TABLE 1.

$$\% \text{ Effect} = \frac{\text{Average duration of loss of righting reflex in test group}}{\text{Average duration of loss of righting reflex in control group}}$$

RESULTS AND DISCUSSION

The gross behavioral studies of the test compounds revealed that all the test compounds exhibited the CNS depression in the mice. The other features observed that of frequent excretion of urine. The data pertaining to the results of the effect of the test compound on locomotor activity shows that all the test compounds reduced locomotor activity. Compound **(V)(9)** exhibited more effect among all the test compounds. Compound **(V)(8)**, **(V)(10)** and **(V)(12)** were next to the compound **(V)(9)** in the order of reduction in the locomotor activity.

The results of effect on pentobarbitone sodium induced narcosis showed that all the test compounds potentiated the pentobarbitone sodium induced sleeping time from 166.66 per cent to 276.60 per cent. The compound **(V)(6)** showed more activity with a potentiation of 276.60 per cent. Compound **(V)(1)**, **(V)(13)**, **(V)(9)**, **(V)(10)** , **(V)(14)** and **(V)(4)** were found to be next in the order of potentiation of pentobarbitone sodium sleeping time with 26.66, 250.00, 244.44, 243.30, 237.40, 233.00 per cent respectively and rest of the compounds showed moderate percentage of potentiation of pentobarbitone sodium sleeping time.

ACKNOWLEDGEMENTS

The authors are thankful to the Prof. Dr.B.Agaiah, Principal, SRR College of Pharmaceutical Sciences for providing necessary facilities to carry out this Research Work.

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