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Synthesis of 3-(1H-Benzimidazol-2-yl Amino) 2-Phenyl-1, 3-Thiazolidin -4-One as Potential CNS Depressant

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Abstract: A new series of 3-[1H-benzimidazole-2-yl-amino]-2-phenyl-1, 3-thiazolidin-4-one (V) were synthesized by the reaction of a mixture of 2-(2-benzylidenehydrazinyl)-1H-benzimidazole IV and thioglycolic acid in DMF containing a pinch of anhydrous zinc chloride. The chemical structures of the synthesized compounds were confirmed by IR, mass spectral and C, H, N analysis techniques. The synthesized compounds were screened for depressant activity by the gross behavioral studies and the loco motor activity method. The synthesized compounds were significantly showed their CNS depressant activity that of standard.

Keywords: Thiazolidinone, Benzimidazole, thioglycolic acid, CNS depressant,Loco motor activity.

INTRODUCTION

Benzimidazole, a physiologically active nucleus, has attracted the attention of many researchers from the point of its chemistry and biological activity. Hoebreker, in 1872 prepared Benzimidazole and since then thousands of Benzimidazole derivatives which are having the thiazolidinone moiety have been synthesized and tested for their biological activities. A few of them are of therapeutic importance. Parent benzimidazole it self possesses antibacterial, antifungal and antiamoebic activity, Literature survey reveals that in recent years several benzimidazole derivatives have been synthesized and reported to possess varied biological and pharmacological properties. They are found to be useful as antitubercular [1], antibacterial l[2, 8], depressant [3, anticonvulsant [4, 9], antimicrobial & antifungal [5], cardiovascular activity [6], anesthetic & hypnotic agents [7]. A good number of them have been also marked as drugs, albendazole (antihelmintic), carbenadazim (fungicide), emedastine (antihistamine), omeprazole (proton pump inhibitor), Droperidol and pimozide (psychopharmacological agent), etc. Also quite a large number of Benzimidazole is at various stages of screening in different laboratories throughout the world with an aim to develop them as future drugs. Some benzimidazole derivatives were found to be associated with anticonvulsant, tranquilizing and paralyzing properties. In view of pharmacological significance of benzimidazole derivatives and thiazolidinone derivatives especially CNS activities it is planed to synthesize some new benzimidazole derivatives containing thiazolidinone moiety and these compounds will be screened for their CNS activity.

Keeping in view an array of applications, it has been felt worth while to synthesize some new 3-[1H-benzimidazole-2-yl-amino]-2-phenyl-1,3-thiazolidin-4-one (V) as such reactions are not reported so for and also to screen for the central nervous system activity. The synthesis of title compounds could be achieved by the Scheme-I.

MATERIALS & METHODS:

EXPERIMENTAL

Step-1: Synthesis of 2-Mercapto benzimidazole (II)

A mixture of orthophenylenediamine (OPDA), carbon disulphide and alcoholic KOH was taken in a clean and dry R.B. flask and refluxed for 2 hr. using an electrical heating mantle. The reaction mixture was cooled to room temperature and poured into 200 ml of ice cold water and mixed thoroughly. To this concentrated HCl was added drop wise until the product precipitated out. The precipitate was collected by filtration. The product was recrystalized from suitable solvent m.p. 285-300°C.

Step-2: Synthesis of 2-Hydrazinobenzimidazole (III)

A mixture of 2-mercaptobenzimidazole (50g) and hydrazine hydrate (20 ml) was refluxed for 8-10 hr on wire gauze and cooled. The separated crystals were filtered washed with a little amount of methanol, dried and recrystallized from methanol. m.p. 200-201°C (lit 200-201°C)[10].

IR spectrum of the compound 2-Hydrazinobenzimidazole (III) (in KBr) exhibited characteristics absorption bonds (in cm^{-1}) at 3378, 3298 (NH_2), 1613 (C=N)

Step-3: Synthesis of 2-[2-benzylidenehydrazinyl]-1H-benzimidazole (IV)

A mixture of 2-Hydrazinobenzimidazole (III, 0.001 mol) and an appropriate aromatic aldehyde (0.002 mol) in methanol (50 ml) containing 3-4 drops of glacial acetic acid was refluxed on water bath for 30 min and cooled. The crystalline solid which separated out during reaction, was filtered and recrystalised from suitable solvent.

IR spectrum of the compound 2-[2-(4-chlorobenzylidene) hydrazinyl]-1H-benzimidazole (IV) (in KBr) exhibited characteristic absorption bands (in cm^{-1}) at 3457 (N-H), 2956.5 (=C-H) and 1641 (C=C), 1561 (C=N). The mass spectrum of the compound 2-[2-(4-chlorobenzylidene) hydrazinyl]-1H-benzimidazole (IV) showed its molecular ion (M^+) peak at m/z. 269.8 as a base peak. M^{+1} and M^{+2} peaks are also observed.

Step-4: Synthesis of 3-(1H-benzimidazol-2-yl amino)2-phenyl-1,3-thiazolidin -4-one (V)

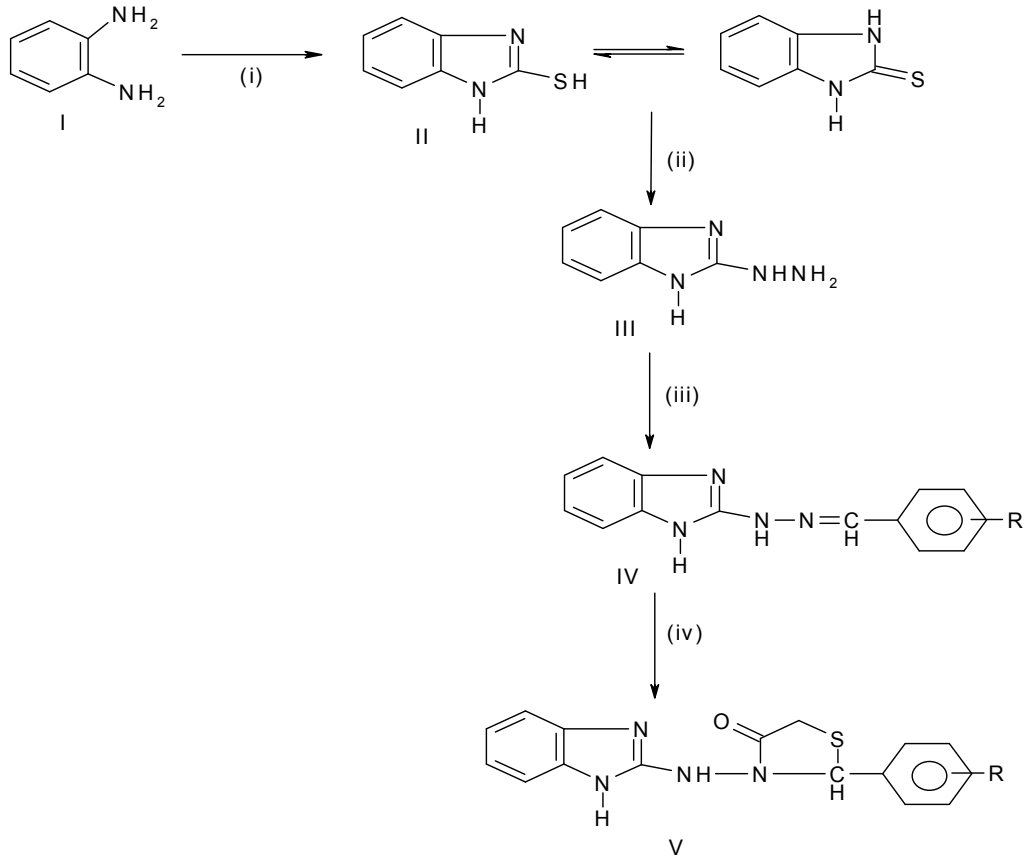
A mixture of 2-(2-benzylidenehydrazinyl)-1H-benzimidazole IV(R=H, 0.01 mol) and thioglycolic acid (0.01 mol) in DMF containing a pinch of anhydrous zinc chloride was refluxed for 8-10hr. The reaction mixture was cooled to room temperature and poured into ice cold water. The resultant compound thus obtained was filtered, washed and dried. The purity of the compound was checked by TLC.

IR spectrum of the compound 3-(1H-benzimidazol-2-yl amino)-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (Vb) exhibited characteristic absorption bands (in cm^{-1}) at: 3361 (NH), 2920 ($-CH_2$), 1672 (C=O), and 1590 (C=N), 708 (C-S-C). The mass spectrum of the compound (Vb) showed its molecular ion (m+) peak at m/z 344, m^{+2} peak is also found in mass spectra. The physical data results are presented in Table-I.

Table-I: Physical data of 3-(1H-benzimidazol-2-yl amino)-2-phenyl-1,3-thiazolidin-4-one (V)

S.No.	Compound	Substituent R	Molecular formula	Melting point (°C)	Molecular weight	Yield %
1	Va	H	$C_{16}H_{13}N_4SO$	250-254	309	58
2	Vb	4-Cl	$C_{16}H_{13}N_4SOCl$	245-247	344	60
3	Vc	4-$N(CH_3)_2$	$C_{18}H_{17}N_5SO$	240-244	353	55
4	Vd	4-OCH_3	$C_{17}H_{13}N_4SO$	246-248	340	42
5	Ve	3-CH_3,4-OH	$C_{17}H_{17}N_4SO_2$	260-262	341	40

SCHEME



i) CS_2/Alcoholic KOH
ii) Hydrazine hydrate (99%)
iii) Aromatic aldehydes /methanol
iv) HS-CH_2-COOH, DMF and anhydrous $ZnCl_2$

SCREENING METHODS

Action on central nervous system gross behavioral studies[11]:

All the compounds tested for acute toxicity studies were also observed for gross behavioral changes in mice, continuously for 5 hours at 1 hour interval after administration of the compounds. There after the observations were recorded intermittently for 24 hours and compared with that of control group. In the behavioral profile, the animals have been observed for changes in their Awareness and Mood. The results are presented in Table-II.

Loco motor activity[11]:

The loco motor activity was studied by using actophotometer, which operates on photoelectric cells, which are connected in circuit with a counter. When animals cut of beam of light falling on the photocells, a count was recorded. Healthy male mice weighing between 20-25 gm were used. Animals were fasted for over night and divided into groups of six animals each group. The test compounds suspended in 0.1% Sodium CMC are administered at a dose of 100 mg/kg body weight i.p. The control group animal received only vehicle (0.1% sodium CMC). The response (counts) was recorded after 30 minutes of administration of drug or test compounds. The animals were placed in actophotometer for 10 minutes and scores were recorded (no. of deflections) and compared the results with control. The results are presented in Table-III.

Table-II: Gross behavioral studies of 3-(1H-benzimidazol-2-yl amino)-2-phenyl-1,3 thiazolidin-4-one (V)

Compounds	Time (hr)	Awareness					Mood			
		Alertness	Visual placing	Stereo type	Passivity	Writhing	Grooming	Vocalization	Restlessness	irritability
Va R = H	½	-	-	-	+	-	+	-	-	-
	1	-	-	-	+	-	-	-	-	-
	2	-	-	-	+	-	-	-	-	-
	3	+	-	-	+	-	-	-	-	-
	4	+	+	-	+	-	-	-	-	-
	5	+	+	-	-	-	-	-	-	-
	24	+	+	-	-	-	-	-	-	-
Vb R=4-Cl	½	-	-	-	+	-	-	-	-	-
	1	-	-	-	+	-	+	-	-	-
	2	-	-	-	+	-	-	-	-	-
	3	-	-	-	+	-	-	-	-	-
	4	-	-	-	-	-	-	-	-	-
	5	+	-	-	-	-	-	-	-	-
	24	+	-	-	-	-	-	-	-	-
Vc R = 4 - $N(CH_3)_2$	½	-	+	-	+	-	+	-	-	-
	1	-	-	-	+	-	-	-	-	-
	2	-	-	-	+	-	-	-	-	-
	3	-	-	-	-	-	-	-	-	-
	4	+	-	-	-	-	-	-	-	-
	5	+	-	-	-	-	-	-	-	-
	24	+	-	-	-	-	-	-	-	-
Vd R=4- OCH_3	½	-	+	-	+	-	-	-	-	-
	1	-	-	-	+	-	-	-	-	-
	2	-	-	-	+	-	-	-	-	-
	3	-	-	-	-	-	-	-	-	-
	4	+	-	-	-	-	-	-	-	-
	5	+	-	-	-	-	-	-	-	-
	24	+	-	-	-	-	-	-	-	-
Ve R=3- CH_3, 4-OH	½	-	+	-	+	-	-	-	-	-
	1	-	-	-	+	-	-	-	-	-
	2	+	-	-	-	-	-	-	-	-
	3	+	-	-	-	-	-	-	-	-
	4	+	-	-	-	-	-	-	-	-
	5	+	-	-	-	-	-	-	-	-
	24	+	-	-	-	-	-	-	-	-

Dose = 100mg/kg body weight; + - positive response, - -negative response

Table-III: Loco motor activity of 3-[1H-benzimidazol-2-yl amino]-2-phenyl-1,3-thiazolidin-4-one (V)

Compound *	Substituent R	Loco motor activity (scores) in 10 minutes, n=6		% Change in activity (↓)
		Before administration	After administration	
Va	H	410	180	56.09
Vb	4-Cl	397	86	78.34
Vc	4-$N(CH_3)_2$	307	97	68.40
Vd	4-OCH_3	430	185	56.33
Ve	3-CH_3, 4-OH	376	171	54.52

*The compounds were tested at a dose of 100mg/kg(I.P) , n= number of animals

RESULTS AND DISCUSSION

3-[1H-benzimidazol-2-ylamino]-2-phenyl-1,3-thiazolidin-4-one were schematically synthesized as planned. All the compounds are authentically identified by physical and spectroscopic data. All the new compounds were screened for gross behavioral studies. The gross behavioral studies of the test compounds revealed that all the test compounds exhibited central nervous system depression in the mice. Table-II pertaining to the gross behavioral studies of 3-[1H-benzimidazol-2-yl amino] 2-phenyl-1, 3-thiazolidin-4-one (V) shows that all the compounds did not show alertness. Among the test compounds, Vb, Vc and Vd showed more depressant activity than the rest of the compounds. Table-III pertaining to the results of the loco motor activity of the 3-[1H-benzimidazol-2-yl amino] 2-phenyl-1,3-thiazolidin-4-one (V) in mice shows that all the test compounds reduced the loco motor activity. The loco motor activity was studied by actophotometer. The compound Vb (R=4-Cl) exhibited more effect among all the compounds with 78.34% reduction in the loco motor activity. The compound Vc (R=4-N$(CH_3)_2$) reduced the loco motor activity by 68.40% and the compounds Vd, Va, Ve were next in the order of reduction of loco motor activity.

CONCLUSIONS:

The following conclusions have been drawn from the results of this investigation. Synthetic work of this study have positively undergone as per the planning and as such in all the reactions carried, the expected compounds are obtained. From gross behavioral studies and loco motor activity, all the test compounds were showed depression of the central nervous system in mice. Compound with 4-Chloro substitution on phenyl ring showed more promising depressant activity among all the test compounds. It has been felt necessary, from the result of preliminary investigations that there is a need for further screening on those test compounds, which had shown promising activity.

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