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Der Chemica Sinica, 2011, 2 (1): 84-90

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and pharmacological evaluation of new benzimidazole derivatives

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ABSTRACT

Benzimidazole, a physiologically active nucleus, has attracted the attention of many researchers from the point of its chemistry and biological activity. 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. The schematic protocol is fusing the moieties of benzimidazole and thiazolidinones and synthesizing novel 3-[1H-benzimidazole-2-yl-amino]-2-phenyl-1,3-thiazolidin-4-one, such five compounds are synthesized and characterized by its physical data like Molecular formula, Melting point (°C), Molecular weight & Yield %. The spectral analysis is carried for the synthesized compounds by IR and Mass spectrum. These structures with screening them for possible CNS activity like gross behavioral studies and locomotion activity.

Keywords: Benzimidazole, Thiazolidinones, Gross behavior study & locomotory activity.

INTRODUCTION

Benzimidazole[1], a physiologically active nucleus possess antibacterial[2], antifungal,antiamoebic, antiviral, anthelmintic, analgesic, antineoplastic, antidiabetic, antihistaminic, hypotensive, diuretic, psychopharmacological and insecticidal agents. Thiazolidinones is also an important pharmacophore in many medicinally important moieties like in Antireterovirals, Anti-tubercular, Anti-microbial, Anti-convulsant[3], Anti-depressant[4] and many CNS drugs[5]. Hence, in the present study, we aimed at the synthesis of series of compounds having these two moieties fused together. Since benzimidazoles and thiazolidinones are associated with some CNS activities, the fused moiety is screened for their effects on locomotion and gross behavior. In Gross behavior study, parameters like alertness, visual placing, stereotype, passivity, writhing, grooming, vocalization, restlessness are studies which

reflect the awareness and mood of the experimental animal. In studying the tranquilizing and paralyzing effects of the synthesized compounds, the locomotory profile is studied using actophotometer.

In view of pharmacological significance of benzimidazole derivatives and thiazolidinone derivatives especially CNS activities it is planned to synthesize some new benzimidazole derivatives containing thiazolodinone moiety and these compounds will be screened for their CNS activity.

MATERIALS AND METHODS

Keeping in view an array of applications, it has been felt worthwhile 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.

Synthetic Procedures:

1.Synthesis of 2-Mercapto benzimidazole (II)

A mixture of orthophenylenediamine (OPDA), carbondisulphide 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 re-crystallized from suitable solvent M.P. 285-300°C.

2.Preparation of 2-Hydrazinobenzimidazole (III)

A mixture of 2-mercaptobenzimidazole (50g) and hydrazinehydrate (20 ml) was refluxed for 8-10 hr on a wire gauze and cooled. The separated crystals were filtered washed with a little amount of methanol, dried and re-crystallized from methanol. M.P. 200-201°C (lit 200-201°C)[6]

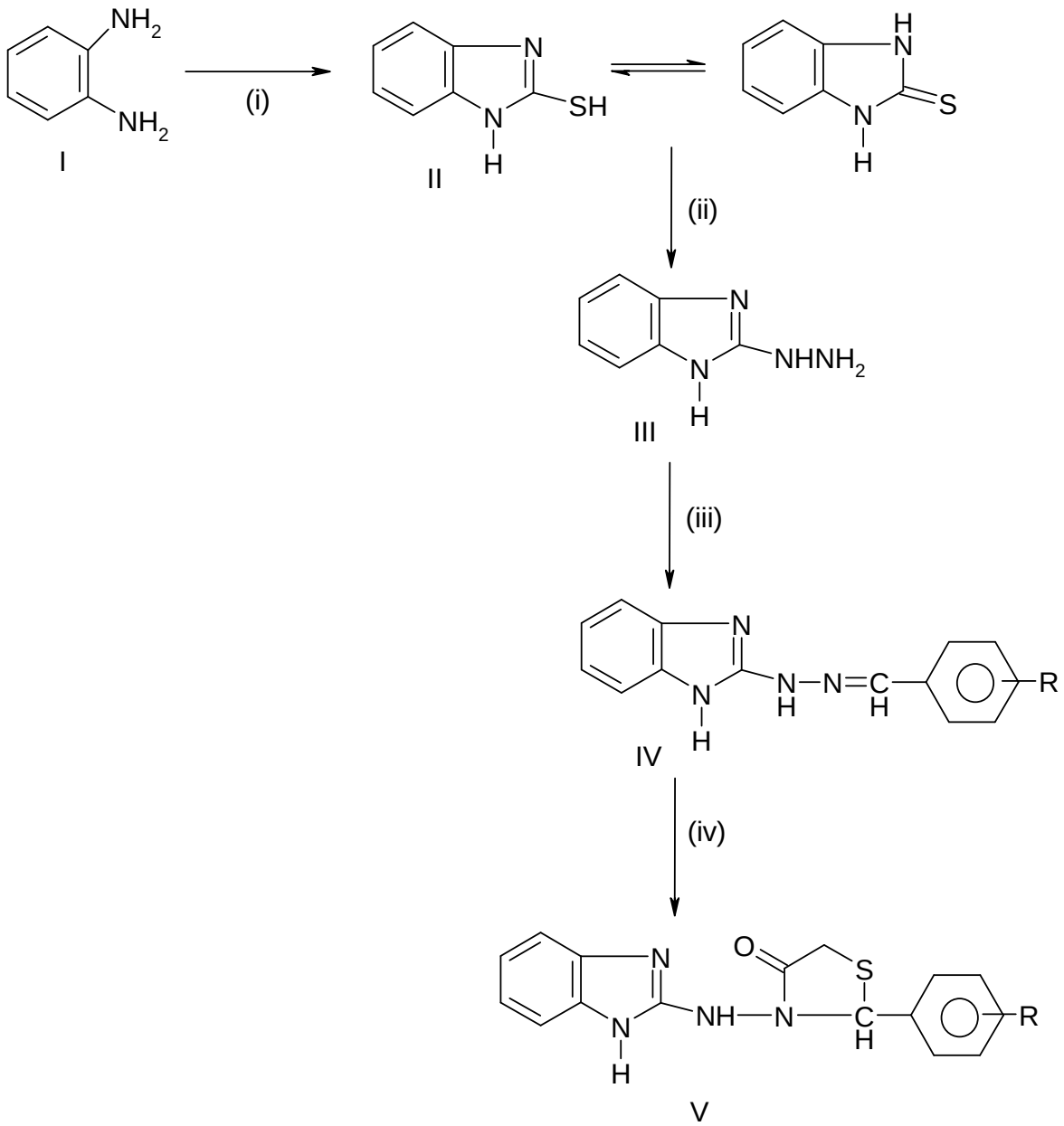
3.Preparation of 2-[2-benzylidenehydrazinyl]-1H-benzimidazole (IV)

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(s). The compound has been characterized by physical and spectral data.

4.Preparation 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. The compound has been characterized by physical and spectral data.

SCHEME - 1



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

Pharmacological evaluation procedures:

1.Locomotory Activity:[7]

The locomotor 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 overnight 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.

2.*Gross Behavioural Study*:[8]
Action on central nervous system gross behavioural studies
Materials: 0.1% Sodium CMC, Test compounds.
Instruments: Sonicator. **Animals:** Mice
Method:
In the gross behavioural study, the test compound is sonicated with 0.1% sodium CMC. All the compounds tested for acute toxicity studies were observed for gross behavioural changes, 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 behavioural profile, the animals have been observed for changes in their:
i) Awareness (Alertness, Visual placing, Stereotype, Passivity, Writhing)
ii) Mood (Grooming, Vocalization, Restlessness, Irritability).
The results are presented in Table-II

RESULTS AND DISCUSSION

Compound II, 2-Mercapto benzimidazole is confirmed by the single spot in the TLC system and IR spectral peaks at 3454 (N-H str), 2959.5 (=C-H str) and 1637 (C=C str), 1558 (C=N str). Compound III, 2-Hydrazinobenzimidazole is confirmed by single spot in TLC system and IR spectral peaks at 3378(N-H), 3298 (NH_2), 1613 (C=N).

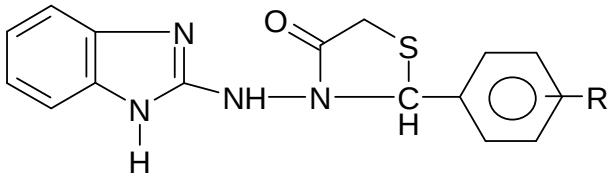
Compound IV, 2-[2-(4-chlorobenzylidene)hydrazinyl]-1H-benzimidazole is confirmed by single spot in TLC system, IR spectral peaks at 3457 (N-H str), 2956.5 (=C-H str) and 1641 (C=C str) and extra peak at 1561 corresponding to (C=N str) and further confirmed by molecular ion (M^+) peak at m/z. 269.8. as a base peak and M^{+1}, M^{+2} peaks corresponding to m/z. 270.7 and 271.9 respectively.

Compound V(a-e), 3-(1H-benzimidazol-2-yl amino)2-substituted phenyl-1,3-thiazolidin -4-one are confirmed by single spot in TLC system, IR spectral peaks and mass spectra corresponding to the extra thiazolidinone moiety.

Compound V(b), 3-(1H-benzimidazol-2-yl amino)-2-(4-chlorophenyl)-1,3-thiazolidin-4-one exhibited characteristic absorption bands (in cm^{-1}) at: 3361 (NH), 2920 (-CH_2 str), 1672 (C=O), and 1590 (C=N), 708 (C-S-C of thiazolidinone) and further confirmed by molecular ion (m+) peak at m/z 344, and m^{+2} peak at m/z 346 in mass spectrum.

The physical data of the compounds Va-e were shown in table-I.

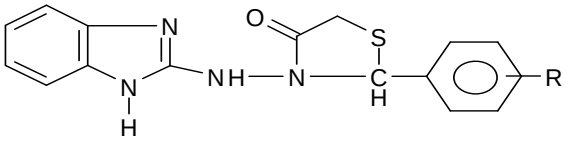
Table-I {Physical data of 3-(1H-benzimidazol-2-yl amino)-2-phenyl-1,3-thiazolidin-4-one (V)}



V

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

Table-II{Gross behavioural studies of 3-(1H-benzimidazol-2-yl amino)-2-(4-chloro phenyl)-1,3-thiazolidin-4-one (Vb)}



V R= Cl

Compound	Time (in Hrs)	Awareness					Mood			
		A	**VP**	**S**	**P**	**W**	**G**	**V**	**R**	**I**
Vb R = 4-Cl	½	-	-	-	+	-	-	-	-	-
	1	-	-	-	+	-	+	-	-	-
	2	-	-	-	+	-	-	-	-	-
	3	-	-	-	+	-	-	-	-	-
	4	-	-	-	-	-	-	-	-	-
	5	+	-	-	-	-	-	-	-	-
	24	+	-	-	-	-	-	-	-	-

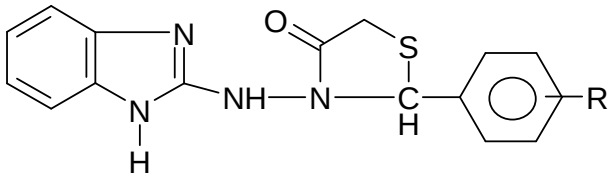
Dose = 100mg/kg body weight; + - positive response, - -negative response

A: Alertness; VP: Visual Placing; S: Stereotype; P: Passivity; W: Writhing; G: Grooming; V: Vocalization; R: Restless ness; I: Irritability

All the new compounds were screened for gross behavioural studies. The gross behavioural 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 behavioural studies of 3-[1H-benzimidazol-2-yl amino]2-phenyl-1,3-thiazolidin-4-one (Va-e) 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{Locomotor activity of 3-[1H-benzimidazol-2-yl amino]-2-phenyl-1,3-thiazolidin-4-one (V)}



V

Compound[a]	Substituent R	Locomotor 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

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

Table-III pertaining to the results of the locomotor 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 locomotor activity. The locomotor activity was studied by actophotometer. The compound Vb (R=4-Cl) exhibited more effect among all the compounds with 78.34% reduction in the locomotor activity. The compound Vc (R=4-$N(CH_3)_2$) reduced the locomotor activity by 68.40% and the compounds Vd, Va, Ve were next in the order of reduction of locomotor activity.

CONCLUSION

The structures of the synthesized compounds were confirmed by the analytical data. From gross behavioural studies and locomotor activity, all the test compounds showed depression on 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.

Acknowledgements
We are thankful to IICT, Hyderabad for providing Mass spectra and thankful to the assistance provided from Talla Padmavathi College of Pharmacy for providing all the requirements. I also thank the governing body, AICTE.

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