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Synthesis of a Novel Benzimidazole derivative and It's evaluation for Anthelmintic activity

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ABSTRACT: Background: Benzimidazole derivatives act by interfering with metabolic pathways. This compound is most potent of a series of substituted 2-Amino derivatives. **Aim:** The present study was aimed to design a simple method for synthesis of a novel benzimidazole derivative and to screen the anthelmintic activity of that synthesized compound. **Method:** The benzimidazole derivative was synthesized by the reaction between o-phenylenediamine and lactic acid followed by self-condensation for obtaining a complex compound. The synthesized Benzimidazole derivative was evaluated for Anthelmintic activity by using Indian Earthworm *Pheretima postuma*. The test drug anthelmintic potency was compared with standard drug Albendazole. **Results:** The newly synthesized compound found to possess appreciable amount of anthelmintic activity as compare to the standard drug Albendazole. **Discussion:** When we increase the concentration of the synthesized compound the paralysis time as well as the death time also decreases accordingly. At a concentration of 50 µg/ml, the paralysis time was 30.43± 5.33 and death time was 0.56±5.32. **Conclusion:** It was concluded that our synthesized compound found to possess anthelmintic activity which may be used for anthelmintic drug formulation.

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INTRODUCTIONS:

The structural alteration of benzimidazole is so convenient for the development of molecules of pharmaceutical or biological interest. Applicably substituted benzimidazole derivatives have found diverse therapeutic applications such as in antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistaminics [1]. The alternated form of benzimidazole structures has been producing various drugs that are currently available on the market, such as omeprazole (Proton pump inhibitor), pimobendan (Ionodilator), and mebendazole (Anthelmintic). Since a number of new

methods for the synthesis of benzimidazoles have been discovered and reported; such work continues due to their wide range of pharmacological activities and their industrial and synthetic applications. Anthelmintics or antihelminthics are drugs that removed out parasitic worms (helminths) from the living body, by either stunning or killing them. They are also sometime called as vermifuges or vermicides [2,3].

MATERIALS AND METHODS:

The chemicals, o-phenylenediamine and lactic acid are purchased from S.D. Fine Chem. Ltd., Mumbai, India. The standard drug Albendazole was procured from Microlab, Chennai. All other chemicals and reagents used are of analytical grade and procured from a authorized dealer. Software used was ChemSketch.

Preparation of 2-hydroxy ethyl benzimidazole:

The equimolar fraction of o-phenylenediamine and lactic acid were refluxed for 7 h in the presence of 4N HCl and the completion of reaction was determined by performing TLC. Then the product was recrystallized with methanol. Melting point was determined by using digital melting point (Secor India) apparatus.

Preparation of 2- acetyl benzimidazole:

The 2-hydroxy ethyl benzimidazole was taken and it was oxidized in presence of potassium dichromate and refluxed for 4 h with glacial acetic acid. Completion of the reaction was determined by TLC. After refluxing the product, it was cooled and neutralized by adding ammonia solution. Then the product dried, recrystallized and the melting point was determined by using digital melting point (Secor India) apparatus.

Preparation of 1,3-bis(1*H*-benzimidazol-2-yl)-3-hydroxybutan-1-one:

The Acetyl benzimidazole was taken and 10 % NaOH was added and then refluxed for 4 h. After refluxing, glacial acetic acid was added. Then it was filtered, dried, recrystallized and melting point was determined by using digital melting point (Secor India) apparatus.

Preparation of 1,3-bis(1*H*-benzimidazol-2-yl)-3-hydroxy-5-phenyl-4-pentene-1-one:

This ketone was obtained from third step, was condensed with aryl aldehyde. The neutralization of the reaction mixture was carried out by dilute acetic acid followed by recrystallization, which gave the final compounds with yields 70 %. The chosen arylaldehyde (10 mmol) was added to 2-acetylbenzimidazole (1.5 g, 10 mmol) in ethanol solution of sodium hydroxide (75 mmol sodium hydroxide in 40 ml of ethanol). The reaction mixture was subsequently stirred at room temperature for 5 h and neutralized with a solution of 30 % acetic acid leading to a precipitate. It was filtered, dried and recrystallized in toluene and toluene/EtOH (4:1) to give final compound.

Physico-chemical evaluations:

The synthesized benzimidazole derivative drugs (1,3-bis(1*H*-benzimidazol-2-yl)-3-hydroxy-5-phenyl-4-pentene-1-one) was evaluated for its properties like molar refractivity, molar volume, parachor, refractive index, density, polarizability and surface tension. The physicho-chemical properties were determined by using FTIR and Mass spectroscopy (Shimadzu, Japan) [3].

Evaluation of Anthelmintic Activity:

The synthesized compound was tested for anthelmintic activity according to the method described by Dutta and others [4-6].

The Indian earthworm *Pheretima posthuma* of approximately equal size (6±1 cm) were selected randomly for the present study due to their anatomical and physiological resemblance to the intestinal roundworm parasites in humans. The worms were acclimatized to laboratory conditions before experimentation. The earthworms were divided into six groups of six earthworms each. The group 1 was served with normal saline water. The group 2 was served with standard drug Albendazole. The Albendazole was diluted with normal saline to obtain a dose of 20 µg/ml, which served as the standard and was poured into Petri dishes. The groups 3 to 6 were served with test drug that is benzimidazole derivative compounds at doses of 20, 30, 40 and 50 µg/ml respectively. The test drug was dissolved in a minimum quantity of ethanol and diluted to prepare 20 µg/ml. The paralysis time and lethal time were calculated for the benzimidazole derivative. The time taken for worms to become motionless was noted as paralysis time. To ascertain death, each worm was frequently subjected to external stimuli that stimulate and induce movement in earthworms, if alive. Paralysis occurred when the worms did not revive even in normal saline. Death was declared when the worms lost motility, followed by fading away of their body colors.

Statistical Analysis:

All data are verified with mean and standard deviation analyzes the statistical significance [7].

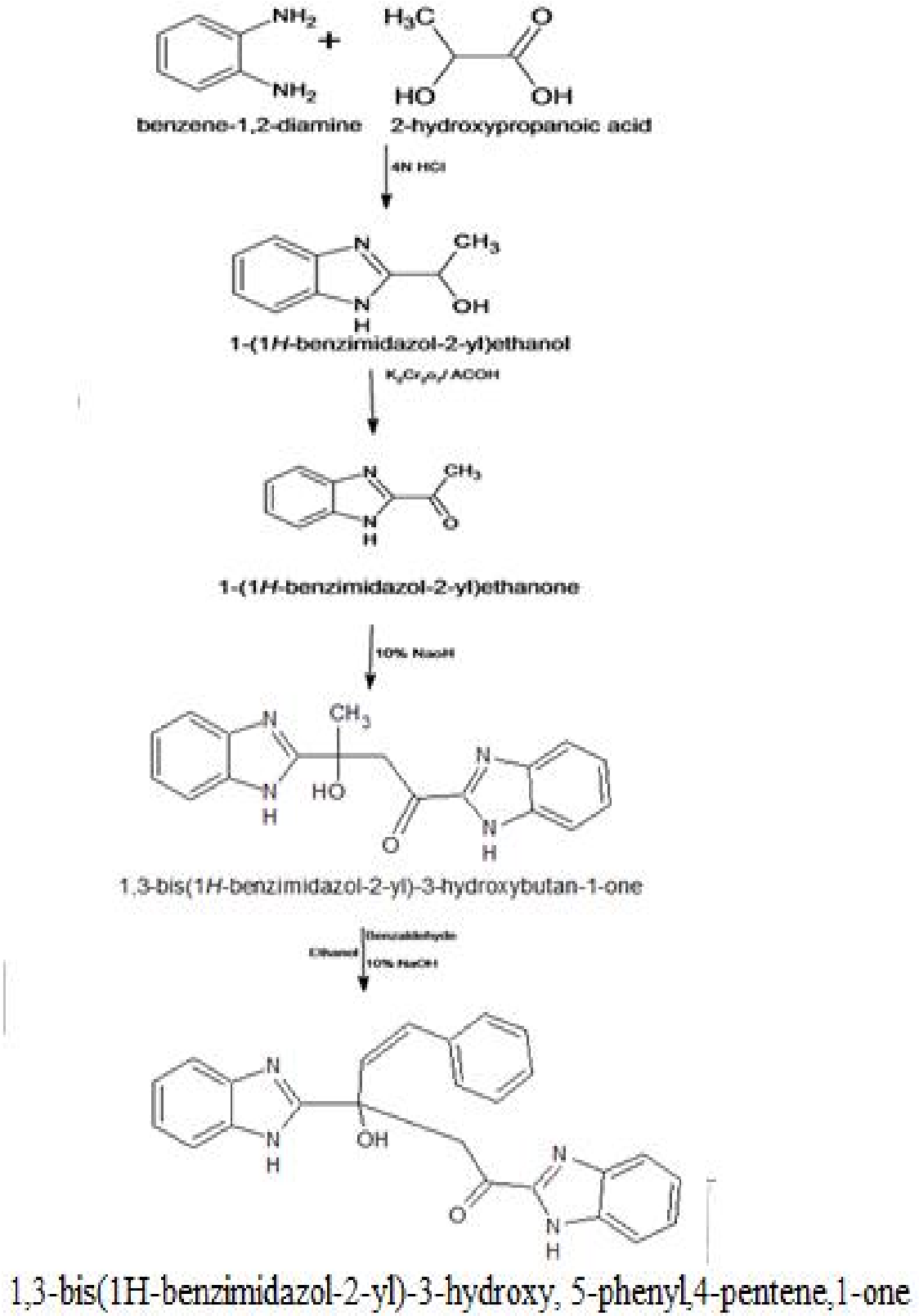

Fig 1. Synthetic scheme for Benzimidazole derivatives.

RESULTS AND DISCUSSION:

A novel Benzimidazole derivative was synthesized with good yields using an ambient reaction conditions in a simple work-up procedure. Physicochemical data of title compounds are shown in Table 1.

Table 1. General properties of 1,3-bis(1*H*-benzimidazol-2-yl)-3-hydroxy-5-phenyl-4-pentene-1-one.

Parameters	Values
Molecular Formula	$C_{25}H_{20}N_4O_2$
Formula Weight	408.4519
Composition	C(73.51%) H(4.94%) N(13.72%) O(7.83%)
Molar Refractivity	122.70±0.3 cm^3
Molar Volume	293.2±3.0 cm^3
Parachor	866.4±4.0 cm^3
Index of Refraction	1.777±0.02
Surface Tension	76.2±3.0 dyne/cm
Density	1.392±0.06 g/cm^3
Polarizability	48.64±0.5 $10^{-24}cm^3$
Monoisotopic Mass	408.158626 Da
Nominal Mass	408 Da
Average Mass	408.4519 Da

Values are presented as mean±standard error of mean, n = 3.

The structure of compounds was confirmed on the basis of FTIR (Fig 2). The data obtained from Fig 2 was as follows that are IR (KBr, cm^{-1})1056(O-H bending), 1022(C-N vibration), 2925(C-H stretching), 2854(C-H stretching), 1640(C=N stretching), 1582(C=C stretching), 1408 (C-O stretching), 3409 (N-H stretching) and 750 (C-H bending).

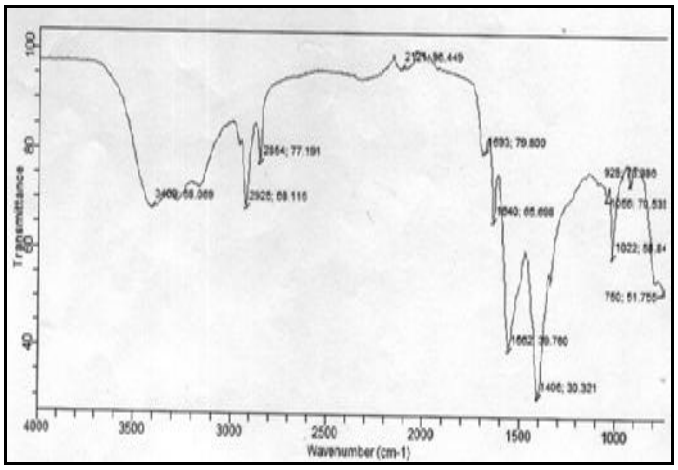

Fig 2. IR of 1,3-bis(1*H*-benzimidazol-2-yl)-3-hydroxy-5-phenyl-4-pentene-1-one.

The purpose of the present study was to synthesize a novel Benzimidazole derivative expected to have good anthelmintic activity (Fig 1). The synthesized drug was compare with one of the effective anthelmintic standard drug Albendazole with different concentration (Table 2). When 20 µg/ml solutions of the standard drug Albendazole and our synthesized drug sample was tested, then it was found that Albendazole took 25.43±1.16 min for paralysis whereas synthesized drug took 35.43± 3.22 min for paralysis and death time for both are found to be 1.10±1.65 and 1.23±2.26 h respectively. From this we can say that our synthesized compound has definitely some anthelmintic activity. According to that when we increase the concentration of the synthesized compound the paralysis time as well as the death time also decreases accordingly.

Table 2. Anthelmintic activity study data of synthesized Benzimidazole derivative.

Gro-ups	Drug	Dose (µg/ml)	Paralysis time (min)	Death time (h)
1	NSW	20	>24	>24
2	SD	20	25.4±1.16	01.1±1.65
3	TD	20	35.4±3.22	01.2±2.16
4		30	34.4±1.17	01.1±1.21
5		40	33.7±4.01	0.6±3.54
6		50	30.4±5.33	0.56±5.32

NSW – Normal saline water, SD – Standard drug (Albendazole) and TD – Test drug (1,3-bis(1*H*-benzimidazol-2-yl)-3-hydroxy-5-phenyl-4-pentene-1-one). Values are expressed as mean ± SEM, *n* = 6.

CONCLUSION:

Benzimidazole derivatives have an important place in the field of synthetic chemistry. Presence of benzimidazole nucleus in the ultimate compound plays an important role for its therapeutic activity. We tried for a new, simple synthetic method for the synthesis of benzimidazole derivative which showed significant anthelmintic activity. In future it may be effectively used for the formulation of anthelmintic drugs.

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