IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

SYNTHESIS AND IN-VITRO BIOLOGICAL EVALUATION OF NOVEL 2-BROMO-1*H*-BENZIMIDAZOLE BEARING DIFFERENT TERTIARY AMINES DERIVATIVES AS POTENT ANTHELMINTIC AGENT

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ABSTRACT

When p-bromo benzoic acid and phenylenediamine are combined, a new 2-bromo-1h-benzimidazole is produced that contains a number of different tertiary amine derivatives. After that, amines were used to stop this reaction while aldehyde was present. To describe the finished items, spectral and physical studies were employed. Using the adult Indian earthworm Pheritima posthuma as a test subject, albendazole was used as a standard to assess the anthelmintic activity of the synthesized compounds. When compared to the norm, the synthesized substances show noteworthy activity as well.

Key words: benzimidazole, tertiary amines, anthelmintic activity.

INTRODUCTION

Benzimidazole is a well-known bioactive heterocyclic ring system that can be found in both natural and synthetic pharmaceuticals. It is made up of a phenyl ring fused to an imidazole ring. Benzimidazole [1] is a versatile scaffold

that may have anticancer, antitumor, and antiproliferative effects in addition to other beneficial biological functions. These heterocyclic compounds, like oxadiazole, thiadiazole, triazolo-thiadiazines, and triazolo-thiadiazoles, are a course group that have piqued medicinal chemists' interest due to their wide range of advantageous pharmacological actions, especially cytotoxic activities against DNA topoisomerase I [2]. Toxocariasis is a condition brought on by the worm Toxocara, which is frequently seen in the intestines of young and older dogs (Toxocara canis) and cats (T. cati). Humans become ill when they either unintentionally consume embryonated eggs or consume contaminated food that contains the soil that held the eggs (such as unwashed raw vegetables). The two clinical forms of human toxocariasis, referred to as Visceral Larva Migrants (VLM) and Ocular Larva Migrants (OLM), are, respectively [3]. The development of innovative chemotherapy has become urgently necessary due to the widespread load of parasite infections that affect both people and domestic animals [4]. In this regard, we have previously discovered several benzimidazole compounds that exhibit respectable action against Fasciola hepatica [5] and Trichinella spiralis [6]. In this paper, we describe the anthelmintic activity of 2 substituted benzimidazole derivatives (b1-3) prepared in our laboratory to enhance the anthelmintic activity of this compounds in order to gain further understanding into the anthelmintic efficacy of structurally related benzimidazole against worms Pheritima posthuma.

MATERIAL AND METHODS

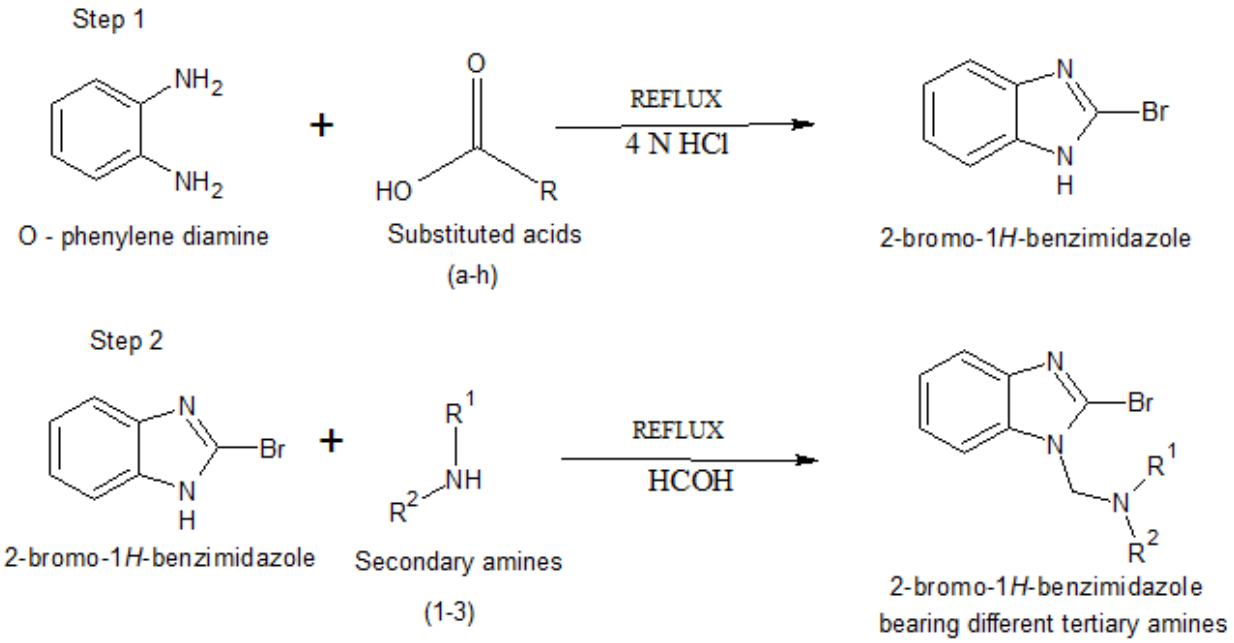
All chemicals and solvents were acquired from commercial sources, refined, and dried using recommended methods from the literature whenever necessary. Regents were purchased from S.D. Fine Research Laboratory in Mumbai and Marck Laboratory in Mumbai. The open capillary tube method was used to calculate the uncorrected melting points of the produced chemical. Thin layer chromatography was performed to confirm the reaction and the purity of the intermediate and end products by applying a single spot on a TLC plate (silica gel G) and using different solvents such butanol, chloroform, and water system. Under an iodine chamber, TLC plates were seen.

General method for the Synthesis of 2-bromo-1*h*-benzimidazole

A solution of P-bromo benzoic acid acid (0.01 mol) and o-phenylene diamine (0.01 mol) in 20 ml 4N Hydrochloric acid was refluxed for few hr, the precipitate obtained after cooling was recrystallized from ethanol The reaction was monitored by TLC using chloroform: methanol (9:1) as mobile phase.

General method for the Synthesis of 2-bromo-1*h*-benzimidazole bearing different tertiary amines

2-bromo-1*h*-benzimidazole bearing different tertiary amines were prepared by a solution of 2-substituted benzimidazole (0.005 mol) in 10 ml ethanol, 0.005 mol of secondary amine and 0.005 mol of formaldehyde and then the reaction mixture was refluxed for few hours. On cooling, the product formed was filtered and dried. The reaction was monitored by TLC using butane: chloroform: water (7:2:1) as mobile phase. The solid product was washed with water and recrystallized with methanol.



Where,

1- Diethylamine

2-Dimethylamine

3-ethyl aniline

Scheme 1: Synthetic route for the preparation of the title compound (b1-3)

Biological evaluation:

Anthelmintic activity:

Earthworms from the sangli area were gathered and identified. On the adult Indian earthworm Pheritima posthuma, the anthelmintic procedure was carried out. [7,8] To obtain 25, 50, and 100 mg/ml concentrations of albendazole, the typical medication, it was diluted with sterile saline and then placed into Petri dishes. To produce concentrations of 25, 50, and 100 mg/ml, manufactured compounds were diluted with ordinary saline. 0.9% NaCl solution of regular saline. These dilutions were all appropriately poured into the Petri dishes. Earthworms were divided into six groups (n = 6) for the study. Each Petri dish was filled with earthworms that were roughly the same size (approximately 8 cm). When there was no movement visible other than when the worms were violently agitated, that period of paralysis was recorded. After determining that the worms did not move when shook vigorously or dunked in warm water, the time of death for the worms was recorded (50oC). Minutes were used to calculate both the paralysis time and the death time.

RESULTS AND DISCUSSION

Chemistry

mixture of P-bromo benzoic acid (0.01 mol) and o-phenylene diamine (0.01 mol) in 20 ml 4N in the first stage After few hours of refluxing hydrochloric acid, the precipitate was cooled and then recrystallized from ethanol. Using chloroform : methanol (9:1) as the mobile phase, the reaction was seen using TLC. A reaction mixture consisting of 0.005 mol of 2-substituted benzimidazole, 10 ml of ethanol, 0.005 mol of secondary amine, and 0.005 mol of formaldehyde was then refluxed for few hours. The created product underwent filtering and drying after cooling. Using butane, chloroform, and water (7:2:1) as the mobile phase, the reaction was seen using TLC. Water was used to clean the solid product, and methanol was used to recrystallize it. In Scheme 1, the reaction sequence is displayed. Open tube capillary technique is used to measure melting point.

Anthelmintic Activity

In order to determine the time before paralysis and death, the anthelmintic activity of the synthesised 2-bromo-1h-benzimidazole bearing various tertiary amines (b1-3) was assessed on the adult Indian earthworm Pheritima posthuma. The novel compounds' capacity to paralyse or kill the worm was examined in this experiment at concentrations of 25, 50, and 100 mg/ml. The data shown in (Table 1) demonstrated that all investigated drugs had better paralysing or killing warms activity compared to conventional albendazole. In comparison to normal albendazole, which showed a 20 2 min. time necessary to kill the worm at the same dose, compound b1 required the shortest time to kill the worm (25 2 min.) at 100 mg/ml.

Table 1: Anthelmintic activity of the synthesized compounds and standard drug (albendazole)

Compound code	25 mg/ml		50 mg/ml		100 mg/ml	
	Paralyzing time (min.)	Death time (min.)	Paralyzing time (min.)	Death time (min.)	Paralyzing time (min.)	Death time (min.)
b1	25 ± 2	28 ± 2	23 ± 2	24 ± 2	20 ± 2	25 ± 2
b2	30 ± 2	32 ± 2	29± 2	30 ± 2	28 ± 2	29 ± 2
b3	36 ± 2	37 ± 2	34 ± 2	35 ± 2	32 ± 2	33 ± 2
albendazole	21 ± 2	22 ± 2	20 ± 2	22 ± 2	18 ± 2	20 ± 2

CONCLUSION:

The usual procedure was used to create every synthetic derivative of the novel series. The chemical code b1 demonstrated the most noticeable anthelmintic activity out of all the manufactured substances that were tested for it.

ACKNOWLEDGEMENT

I express my sincere thanks to Principal Prof. Dr. S. K. Mohite and guide C. S. Magdum for providing me all necessary facilities.

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