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Synthesis, Characterization ofBenzimidazole Moeity as antihelmenthics activity.

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ABSTRACT
Benzimidazole is Hetrocyclic compound . This bicyclic compound may be viewed as fused rings of the aromatic compounds benzene and imidazole. It is a white solid that appears in form of tabular crystals.Benzimidazole and its derivatives are regarded as an important heterocyclic compound that exhibits a wide range of pharmaceutical applications including Anticancer , antihypertensive ,antiviral…etcEven though benzimidazole derivatives are widely used to treat various infection, including helmintics infection , they show some side effects, low potential and physicochemical problems. Therefore, discovering new, safer and more potent anthelmintics benzimidazoles with reduced side effects .
A review of the literature thus suggests that there is the scope for the design of additional benzimidazole derivatives with antimicrobial activity, by examining the effect of a number of different functional groups.
In this paper, we report on the synthesis of benzimidazole derivatives (Halogen derivative) and their antihelmintics .
Keywords: Benzimidazole, heterocyclic compound , halogen , Antihelmenthics bromine, Acetic acid

I. INTRODUCTION

Soil-transmitted helminth (STH) infections are among the most common infections worldwide with an estimated 1.5 billion infected people or 24% of the world's population. These infections affect the poorest and most deprived communities with poor access to clean water, sanitation and hygiene in tropical and subtropical areas, with the highest prevalence reported from sub-Saharan Africa, China, South America and Asia. They are transmitted by eggs present in human faeces, which in turn contaminate soil in areas where sanitation is poor. Over 260 million preschool-age children, 654 million school-age children,108 million adolescent girls and 138.8 million pregnant and lactating women live in areas where these parasites are intensively transmitted, and are in need of treatment and preventive interventions.

Globally over 600 million people are estimated to be infected by S. stercoralis; however, since also this parasite is transmitted in areas where sanitation is poor, its geographical distribution overlaps with the one of the other soil-transmitted helminthiases.

Types of species

The main species that infect people are the roundworm (Ascaris lumbricoides), the whipworm (Trichuris trichiura) and hookworms (Necator americanus and Ancylostoma duodenale). These STH species are normally addressed as a group because they need similar diagnostic procedures and respond to the same medicines.

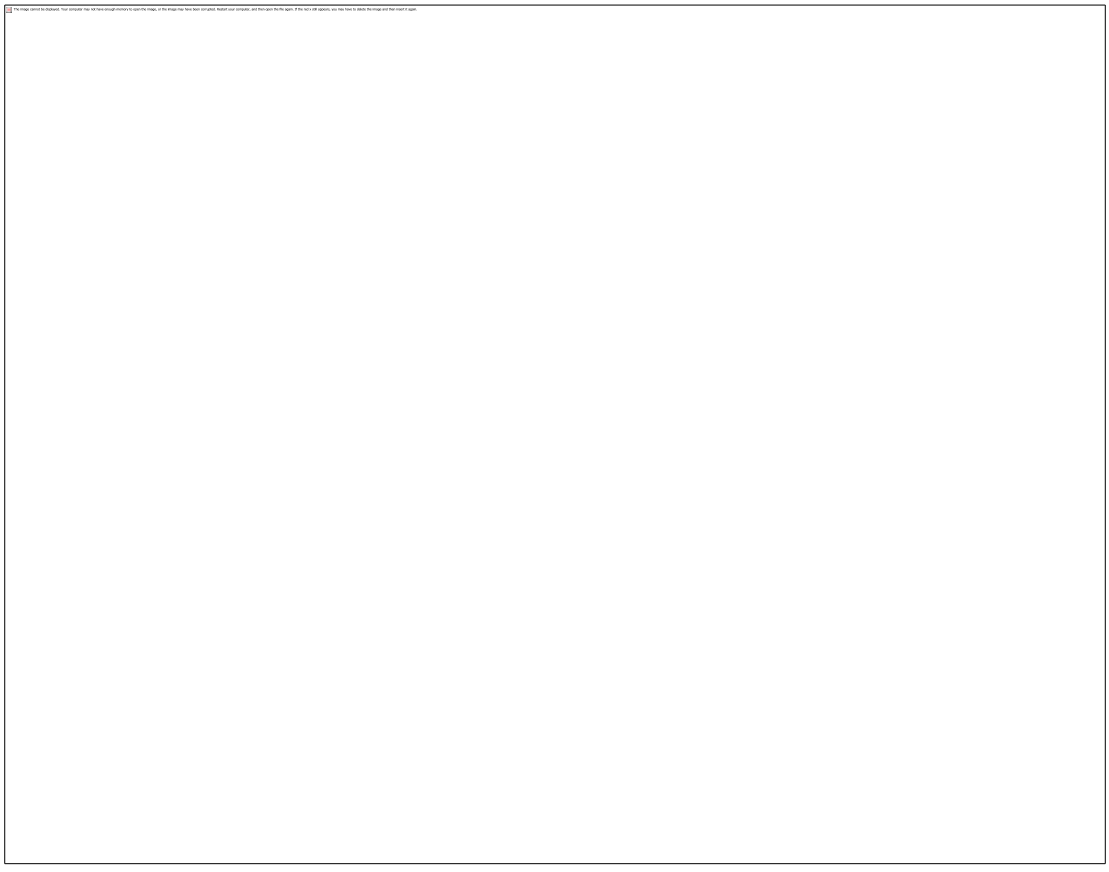
Strongyloides stercoralis is an intestinal helminth with peculiar characteristics: the parasite requires different diagnostic methods than other soil-transmitted helminthiases, and for this reason is frequently not identified. In addition, the parasite is not sensitive to albendazole or mebendazole and therefore not impacted by large-scale preventive treatment campaigns targeting other soil-transmitted helminthiases.

Benzimidazole (BIM) is a heterocyclic aromatic molecule. The benzimidazole core consists of the imidazole subgroup, of which the nitrogen at position 1 binds aromatic group substituents in the ability of an N-donor ligand. For example, in the coordination of metal heterocyclic complexes that exhibit optoelectronic properties with attractive redox behavior, exhibiting specific low oxidation potentials. BIM is often found in

biomolecules and has significant biological activities, such as the inhibition of microtubule assembly and tubulin interactions with microtubule-associated proteins, human mitotic arrest, as well as potent cytotoxicity towards human tumor cells, inhibition of tubulin assembly in osteosarcoma cells, non-specific anti-inflammatory/analgesic/antidepressant agent, and histaminic and gastric anti-secretory agent.

Microbial drug resistance is a serious issue, especially as increasing numbers of strains are becoming resistant to multiple antimicrobial agents, with some bacteria now being resistant to all available antibiotics. There is thus a critical need to develop new drugs with novel mechanisms of action. However, the investment available for such development is frequently lower than the required level. The development of new drug entities is hampered by several issues, notably the high cost and length of time required, as well as the logistical and regulatory challenges of performing the necessary clinical evaluations across multiple geographical areas. Therefore, a few new classes of antimicrobials have been developed since the late 1980s [.and much research has focused only on the chemical modification of existing drugs to improve their potency and/or ability to overcome antibiotic resistance mechanisms. Even if this approach does not improve antimicrobial activity directly, it may lead to derivatives that can usefully inhibit virulence mechanisms .

Compounds having benzimidazole as a Nucleus have been widely used in medicinal chemistry and drug development, and researchers are actively seeking new uses and applications of this heterocycle . Benzimidazole-containing compounds have numerous medical and biological activities, such as Antiulcer , antihypertensive ,antiparasitic , antihistaminic activity.



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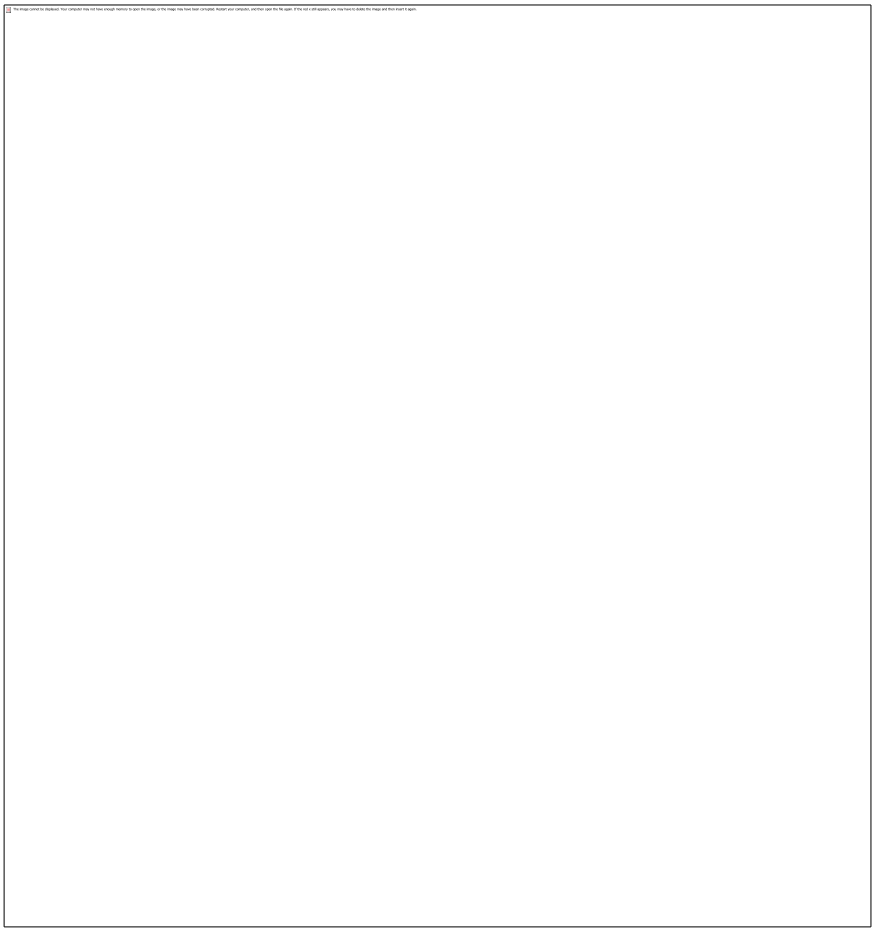


Benzimidazoles selectively bind with beta-tubulin & inhibit microtubule polymerization. This results in the destruction of cell structure and consequent death of the parasite

II. MATERIALS AND METHODS:

Materials)

Acetic acid ,bromine o-phenylene diamine were purchased from the Scientific Systems & Chemicals Pvt. Ltd.All other chemicals were of analytical grade purchased from local suppliers bhopal.

METHODS

Synthesis

1**. General procedure for preparation of the key intermediates**

Place 27 g (0.25 mol) of o-phenylene diamine in a Round bottom flask of 250 ml and add 17.5 g (16 ml, 0.34 mol) of 90% formic acid. Heat the mixture on a water bath at 100 °C for 2 h. Cool and add 10% sodium hydroxide solution slowly, with constant rotation of the flask, until the mixture is just alkaline to litmus.Benzimidazole were separated by filtration and recrystallized from a Ethanol/water mixture.

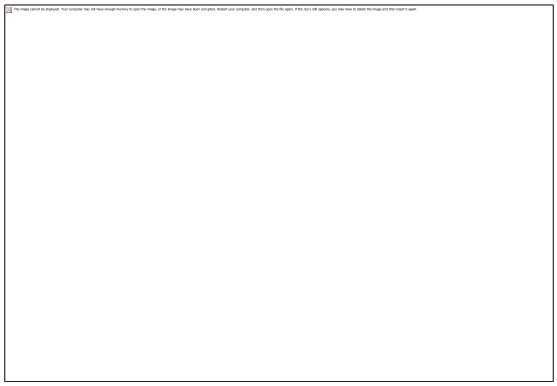
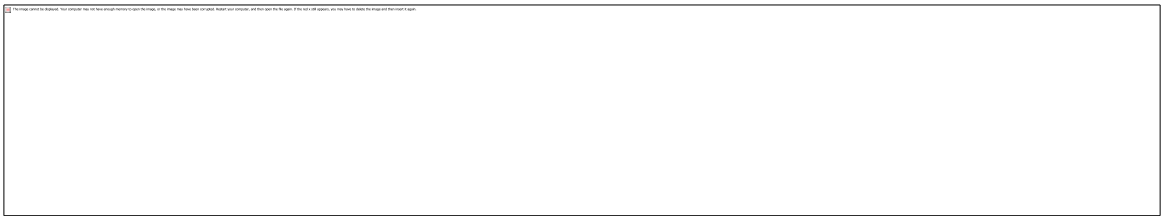
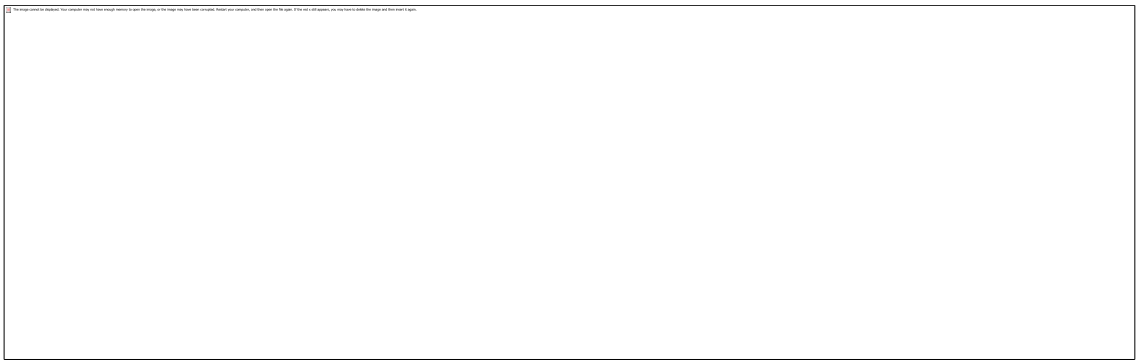


Fig.Crude Benzimidazole (Before Purification)

Reaction:



Mechanism:



2.2. **General procedure for the synthesis of N-bromo benzimidazole**

Glacial acetic acid into 250 ml conical flask (beaker) adddropwise by burette 3.5 ml Bromine. dissolve in glacialaceticacidwithconstantshaking.allowtostandatorange colour reaction . mix at room temperature for halfan hour then pour the content in cool water stir well . addsufficientamountofsodiumbisulphatetodischarge orange colour filter the crude product wash with coldwater and recrystalized with dilute ethanol to obtain withwhitecrystallinecompound.

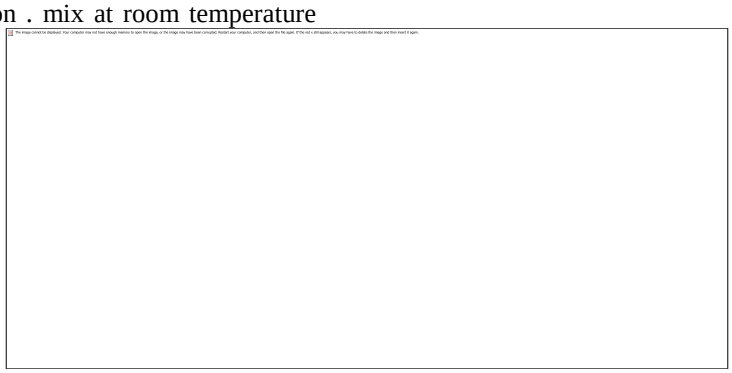


Fig.Synthesis of benzimidazole at Laboratory of IES UNIVERSITY BHOPAL

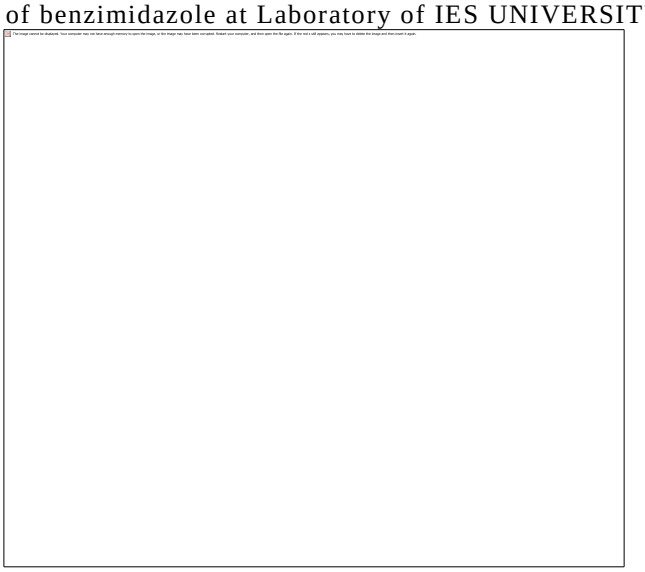


Fig.Bromination of benzimidazole at Laboratory of IES UNIVERSITY BHOPAL

Characterization

A) By Physical properties

Molecular Formula	**Molecularweight (g.mol^{-1})**	**MeltingPoint (^{o}C)**	**MeltingPoint (^{o}C)**	**%Yield**
$C_7H_5BrN_2$	**195.96**		**215**	**84**

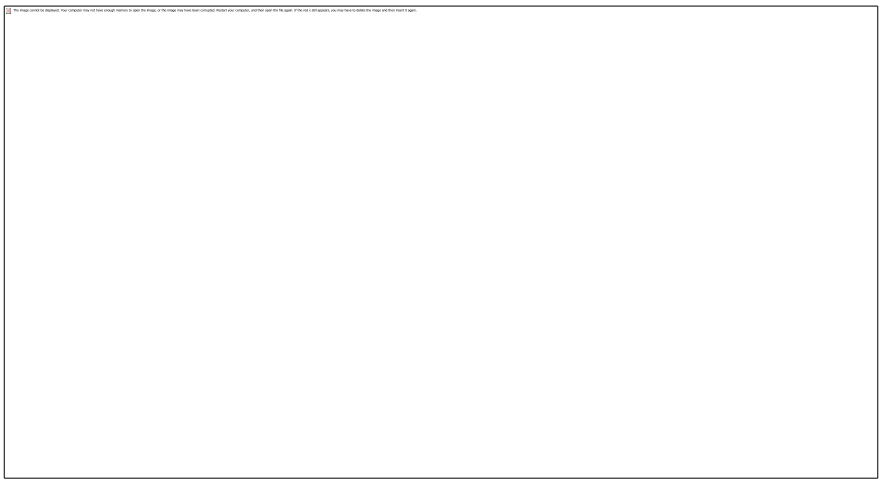
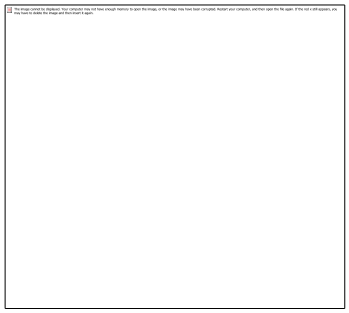


Fig. Determination of melting point of bromobenzimidazole at Laboratory of IES UNIVERSITY BHOPAL

b**) By optical properties**

The refractive index (or refraction index) of an optical medium is a dimensionless number that gives the indication of the light bending ability of that medium.



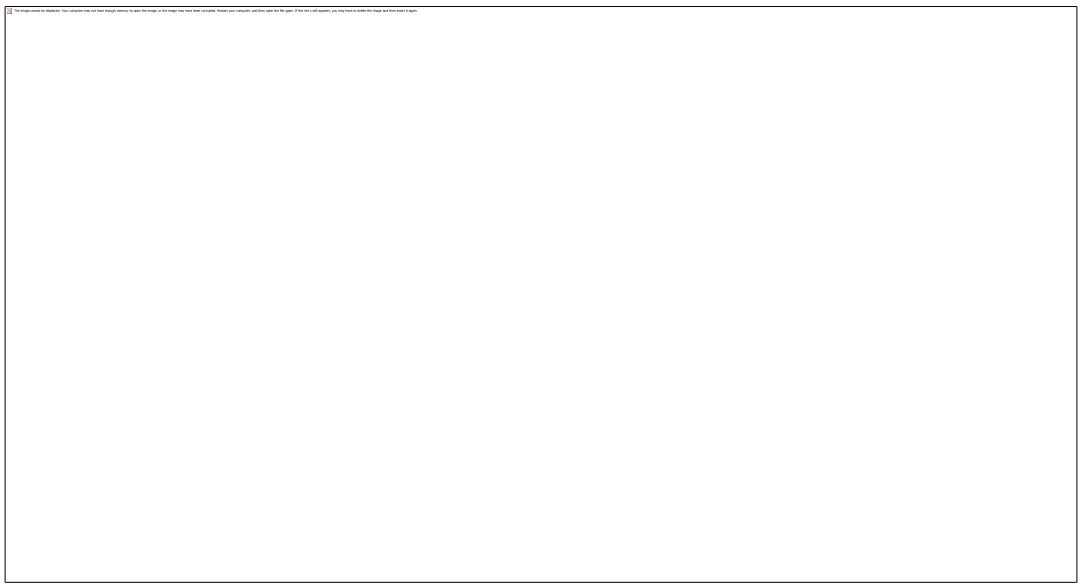
The refractive index determines how much the path of light is bent, or refracted, when entering a material. This is described by Snell's law of refraction, $n_1 \sin \theta_1 = n_2 \sin \theta_2$, where θ_1 and θ_2 are the angle of incidence and anglerefraction, respectively, of a ray crossing the interface between two media with refractive indices n_1 and n_2. The refractive indices also determine the amount of light that is reflected when reaching the interface, as well as the critical angle for total internal reflection, their intensity (Fresnel equations) and Brewster's angle.
Refractive Index of N-bromobenzimidazole is : 1.728

AnthelminticActivity

N-bromobenzimidazole were tested for anthelmintic activity against two different worms species; Pheretima posthuma and Perionyx excava tus, at a 2 mg/mL concentration Earthworms collected from local marshy areas were washed with normal saline water to remove adhering soil and fecal matter. Suspensions of the synthesized compounds (100 mg) were prepared by triturating with Tween 80 (0.5%) and normal saline solution and stirring the resulting mixtures for 30 min. These suspensions were suitably diluted to obtain conc. of 0.2% w/v of the test samples. The suspension (0.2% w/v) of the standard drug albendazole was prepared in the same manner. Three sets of five earthworms of almost similar sizes (approx. 2 inches in length) were placed in Petri dishes of 4 inches diameter containing 50 mL of a suspension of prepared test samples and albendazole. Another petri dish containing 50 mL suspension of distilled water and tween 80 (0.5%) was kept as control and a set of five earthworms was placed in it. The paralyzing and death times for each synthesized compound and standard drug were noted, and their mean was calculated for triplicate sets. The death time was ascertained by placing the earthworms in warm water (500 C) which stimulated the movement, if the worm was alive.

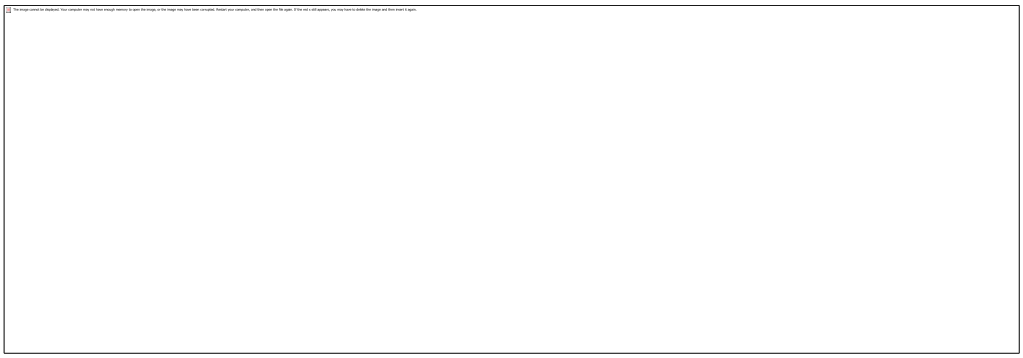
III. RESULTS

FTIR OF BENZIMIDAZOLE



Functional group	Frequency in cm-1
C=N stretching	1603.88
CH=N stretching	1501.65
Aromatic C-H stretching	2570.26

FTIR OF 2-BROMO BENZIMIDAZOLE



Functional group	Frequency in cm-1
C=N stretching	1594.23
CH=N stretching	1499.72
C-H stretching	3119.03
Aromatic C-H stretching	2850.91

The compounds N-bromobenzimidazole were obtained by the reaction between bromine solution and benzimidazole in the presence of acetic acid as a solvent . The synthesized compounds were confirmed by thin layer chromatography (TLC), Melting Point (mp), Boiling point solubility . The yields and melting points for all the synthesized compounds are listed in below

Table .

Benzimidazole

IUPACName	1H-benzo[d]imidazole
Mol.F	$C_7H_6N_2$
Mol.wt	188.14 $gmol^{-1}$
M.P	163 ^oC
Solubility	Methanol andethanol
TLCsolvent	Methanol:Water:Tetrahydrofuran-2:2:1
$R_f$value	0.65
%Yield	86%

N-bromobenzimidazole

IUPACName	2-bromo-1H-benzo[d]imidazole
Mol.F	$C_7H_5BrN_2$
Mol.wt	195.96
M.P	185-190^oC
Solubility	Tetrahydrofuran
TLCsolvent	Methanol: Water:Tetrahydrofuran-2:2:1
$R_f$value	0.56
%Yield	70%

Antihelmenthics

The synthesized compounds were evaluated for anthelmintic Pheretima posthuma and Perionyx excava tus, at a 2 mg/mL concentration .Allcompoundsshowedanthelminticactivity.Amongt he compounds tested, all the compounds showed significantparalytic time for earthworms compared to standard drugalbendazole at (0.2% and 0.5%) concentration ofcompounds.

IV. DISCUSSION

Several researchers reported a synthesis of benzimidazole derivatives, but in our present study we synthesized the benzimidazole derivatives by using acetic acid as polar solvent, which were inexpensive and decreased the reaction time, with very good yields. This method could be easily practiced in laboratories within the stipulated time.

A simple and efficient procedure for the synthesis N-bromobenzimidazoles through a one-pot reaction of Benzimidazole & bromine solution in the presence of acetic acid at room temperature features short reaction time, easy and quick isolation of the products, and excellent yields.

V. CONCLUSION

The present study describes a simple, inexpensive, and easy method for synthesis of benzimidazole derivatives in a stipulated time, without using any drastic conditions. The yield of all benzimidazole derivatives were found to be in 70%. The purity of the compounds were ascertained by a melting point and TLC.

From the present study, it can be concluded that the benzimidazole derivatives can potentially be developed into useful anthelmintic, which can prompt future researchers to synthesize a series of benzimidazole derivatives containing a wide variety of substituent's, with the aim of producing a novel heterocyclic system, with enhanced activity.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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