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ORIGINAL ARTICLE

Synthesis and Characterization of Novel Benzimidazole Derivative as Potent Anthelmintic Agent.

Laxmi Keshwani[1], Kratika Daniel[*2], Vivek Daniel[3], Sachin K Jain[2]

[1]Research Scholar, Oriental College of Pharmacy & Research, Oriental University, Indore, MP.
[2]Professor, Oriental College of Pharmacy & Research, Oriental University, Indore, MP.
[3]Professor & Principal, NTVS Institute of Pharmacy, Nandurbar, Maharashtra

Corresponding Author: Ms. Laxmi Keshwani

Abstract:
The Chemistry of Heterocyclic compounds has been an interesting field of study, for a long time. The Benzo fused heterocyclic nucleus Benzimidazole founds an important class for new drug development. 4-((1H-benzimidazol-1-ylimino) methyl) phenol (**5d**) is the most effective among all derivatives as compared to albendazole standard and showed best anthelmintic potential at 0.1% concentration showed best paralysis time at 4.35±0.10, and death time at 09.33±0.63 respectively as compared to albendazole (Standard). Finally, it was concluded that all benzimidazole derivatives possess potent anthelmintic activities.
Keywords: Benzofused, Heterocyclic compounds, Anthelmintic, Benzimidazole

Introduction

A heterocyclic compound is any class of organic compounds in which at least one heteroatom (noncarbon element) is present i.e., oxygen, nitrogen, or sulphur [1]. Many Pharmacologically active heterocyclic drugs are commercially available. Only rings with at least one element picked from halogen, Nitrogen, oxygen, Sulphur, Phosphorus, or Selenium as a ring component are termed "heterocycles". Heterocyclic rings can exist as separate entities or condensed groups, either with carbocycles or among themselves [2].

In the present research work benzimidazole was selected for the study of benzo-fused five-membered nitrogen-containing heterocyclic compounds.

The biological use of benzimidazole was found in 1944 by Woolley hypothesized that benzimidazole had a purine-like structure.[3-4] Benzimidazole is an aromatic heterocyclic compound. It is a highly imperative pharmacophore and a preferred structure in Medicinal chemistry. 1,3 – benzimidazole (III) is produced when a benzene ring is fused to an imidazole ring by its 4 and 5 bonds shown in **Figure 1**.[5]

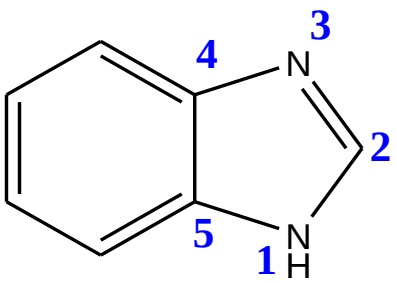


Figure 1 Structure of 1H-Benzimidazole

The bioactive heterocyclic aromatic compound exhibits a wide range of pharmacological actions. Some drugs already available in the market containing Benzimidazole pharmacophores such as Omeprazole, Lansoprazole, Albendazole, Mebendazole, Bendamustine, Nocodazole, mibefradil etc [6-8]. Benzimidazole derivatives have been developed for antihypertensive[8], antiviral[9] Antibacterial, Antifungal [10] Anticancer [11], Anthelmintic, Antifungal [12], H^+K^+ ATPase inhibitors [13 -14], and many more activities.

The main objective of this work is to Synthesize, Characterization, and anthelmintic activity of N-(aryl)-1H-benzimidazole-1-amine derivatives.

Material and Method

The melting point was determined by Thiel's tube method using liquid paraffin and which was uncorrected. Infrared (IR) spectra were recorded on Shimadzu 8400S FT-IR spectrophotometer model (υ_{max} in cm^{-1}). ^{1}HNMR spectra were recorded on Brucker multinuclear FTNMR spectrometer model AV-400, 400 MHz using deuterated-chloroform or deuterated dimethyl sulfoxide-containing tetramethyl silane (Me_4Si) as internal standard (chemical shifts in δ, ppm). The spin multiplicities are indicated by symbols, s (singlet), d (doublet), t (triplet), m (multiplet), and q (quartet). The purity of compounds was monitored by thin-layer chromatography (TLC) by using Petroleum ether and ethyl acetate (8:2) as a solvent system and Iodine was used to develop the TLC plates. All the solvents were distilled prior to use according to standard procedures. Anhydrous potassium carbonate was used as a drying agent.

The present work comprises of Synthesis, Characterization, and anthelmintic activity of N-(aryl)-1H-benzimidazole-1-amine derivatives of the following compounds as per scheme **figure** 2:

1. ortho phenylenediamine (**1**)
2. 1H-benzimidazole (**2**)
3. ethyl 2-(1H-benzimidazol-1-yl) acetate (**3**)
4. ethyl 2-(1H-benzimidazol-1-yl) hydrazide (**4**)
5. N-(**aryl**)-1H-benzimidazol-1-amine (**5a-e**)

a. N-benzylidene-1H-benzimidazol-1-amine (**5a**)
b. N-(4-chlorobenzylidene)-1H-benzimidazol-1-amine (**5b**)
c. N-(4-methoxybenzylidene)-1H-benzimidazol-1-amine (**5c**)
d. 4-((1H-benzimidazol-1-ylimino)methyl)phenol (**5d**)
e. 4-((1H-benzimidazol-1-ylimino)methyl)-3-methoxyphenol (**5e**)

Method of Synthesis

Synthesis of 1H-benzimidazole (2) from o-phenylenediamine (1) [15-16]

A mixture of 1gm (0.24 mol) of o-phenylenediamine and 5 mL (0.48 mol) of 90% formic acid was taken in a round-bottomed flask. Heat the mixture onto the water bath at 100^{o}C for 2 hrs. Cooled, the content and add 10% NaOH solution slowly with a constant rotation of the flask until the mixture is just alkaline to litmus. Filter out the crude benzimidazole, and wash with ice-cold water. Dissolve the crude product in 400 mL of boiling water, add 2 g of decolorizing carbon, and digest for 15 min, filter, cool the filtrate to about 10^{o}C, filter off the benzimidazole, wash with 25 mL of cold water, and dried at 100^{o}C. The completion of the reaction was monitored by TLC using petroleum ether and ethyl acetate (8:2) as eluent. Physical characteristics and spectral characteristics were summarized in **Table 1 & 2**

Synthesis of ethyl 2-(1H-benzimidazol-1-yl) acetate (3) from 1H-benzimidazole (2) [15-16]

A mixture of equimolar alkaline solution (0.5 mL, 4 N NaOH) of 1H-benzimidazole (**2**) (0.01 mol, 1.18 g) in methanol (50 mL) and ethyl bromoacetate (0.01 mol, 1 mL) in methanol (30 mL) was heated gently on boiling water bath for 0.5 hrs. The solid thus obtained on cooling was recrystallized from chloroform to give ethyl 2-(1H-benzimidazol-1-yl) acetate (**3**). The completion of the reaction was monitored by TLC using petroleum ether and ethyl acetate (8:2) as eluent. Physical characteristics and spectral characteristics were summarized in **Table 1 & 2**

Synthesis of ethyl 2-(1H-benzimidazol-1-yl) hydrazide (4) from ethyl 2-(1H-benzimidazol-1-yl) acetate (3) [15-16]

To a solution of ethyl 2-(1H-benzimidazol-1-yl) acetate (**3**).(1 g, 0.01 mol) dissolved in dry methanol (50 mL), 99% hydrazine hydrate (1 mL) was added and the mixture was refluxed for 4–5 h. The reaction mixture was cooled and the solid obtained was filtered, and washed with a small

quantity of cold methanol to give ethyl 2-(1H-benzimidazol-1-yl) hydrazide (**4**).The completion of the reaction was monitored by TLC using petroleum ether and ethyl acetate (8:2) as eluent. Physical characteristics and spectral characteristics were summarized in **Table 1 & 2**

General Procedure for synthesis of N-(aryl)-1H-benzimidazoles-1-amine (5a-e)[[15-16]

Ethyl 2-(1H-benzimidazol-1-yl) hydrazide (**4**) (1gm, 0.01 mol) was dissolved in ethanol (50 mL),addedsubstituted benzaldehyde(a-e) and 2-3 ml acetic acid in RBF. Refluxed the mixture for 2-3 hrs at 70-80^{o}Cto obtain Benzimidazole derivatives *i.e*.N-(Aryl)-1H-benzimidazol-1-amine (**5a-e**).

For CompoundN-benzylidene-1H-benzimidazol-1-amine (**5a**) Benzaldehyde was used.N-(4-chlorobenzylidene)-1H-benzimidazol-1-amine (**5b**) was obtained by using 4-chloro benzaldehyde. N-(4-methoxy benzylidene)-1H-benzimidazol-1-amine (**5c**) was obtained by using 4-methoxy benzaldehyde. 4-((1H-benzimidazol-1-ylimino) methyl) phenol (**5d**) was obtained by using 4-hydroxy benzaldehyde and 4-((1H-benzimidazol-1-ylimino) methyl)-3-methoxyphenol (**5e**) was obtained by using 2-methoxy,4-hydroxy benzaldehyde. The completion of the reaction was monitored by TLC using petroleum ether and ethyl acetate (8:2) as eluent. Physical characteristics and spectral characteristics were summarized in **Table 1 & 2.**

Anthelmintic Activity

Anthelmintic activity of all synthesized compounds was performed as per the method of Ajayieoba et al. [17-18]

Indian adult earthworm **(***Pheretima posthuma*) was used to study anthelmintic activity. The earthworms of nearly equal size (6±1 cm) were collected from moist soil (Oriental University, Indore) and washed to remove all fecal material acclimatized to laboratory conditions before experimentation. The earthworm resembles both anatomically and physiologically with intestinal roundworm parasites of human beings. [17] Albendazole was used as standard. Normal saline was used as a control.

The earthworms were divided into eight groups of six earthworms each. Albendazole diluted with normal saline to obtain 0.1% w/v was served as control. All synthesized compounds were suspended with normal saline and prepared at 0.1% w/v for each compound. Normal Saline served as control. Six earthworms were placed in different Petri dishes along with standard, control, and synthesized compound (**2, 5a-e**) respectively at room temperature.

The time taken for complete paralysis and death was observed and discussed in **Table 3.** The Mean paralysis time and mean lethal time for each compound were calculated (each reading taken in triplicate). The time taken for worms to become motionless was noted as paralysis and to ascertain death, each worm was frequently applied with external stimuli which stimulates and induced movement in earthworms, if alive. [19]

Statistical analysis - Experimental results were expressed as Mean ± SEM of all synthesized compounds. Analysis of variance (ANOVA) was used to determine the significance of the difference between treated groups ($p<0.05$). Means between treatment groups were compared for significance using the Student t-test.

Result and Discussion

The present work comprises of synthesis of new benzimidazole derivatives as an anthelmintic agent. It was reported in the literature that the presence of a heterocyclic ring increases the probability, good anthelmintic agent, so due to the presence of the above features in new compounds these compounds showed excellent anthelmintic activity.

Chemistry

The present work comprises the synthesis of the benzimidazole derivatives. The steps involved in the synthesis was shown in Scheme **Figure 2.**

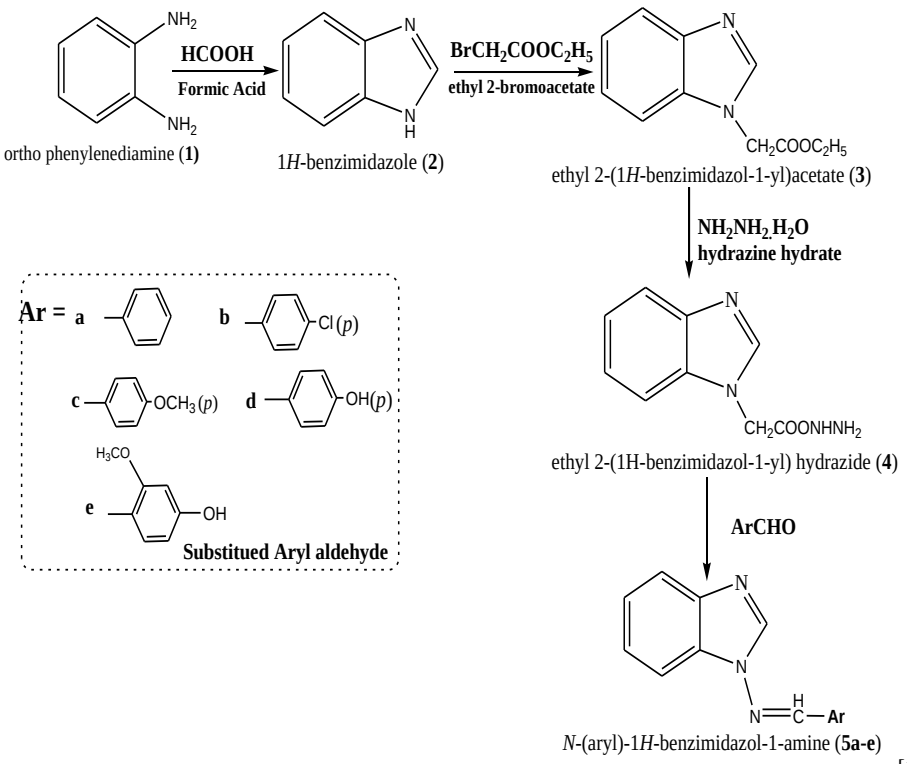


Figure 2. Synthetic pathway of proposed Benzimidazole Derivatives [15]

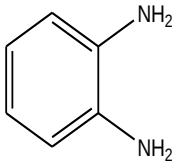
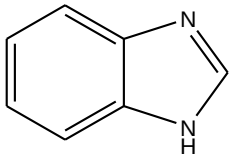
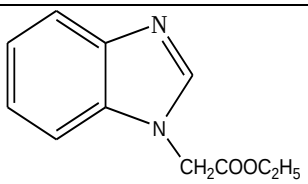
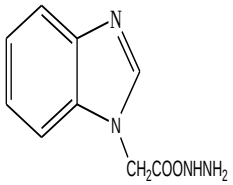
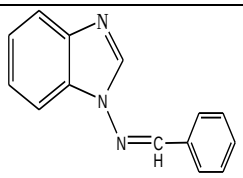
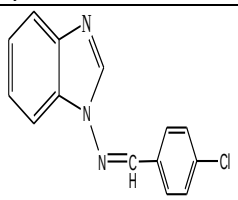
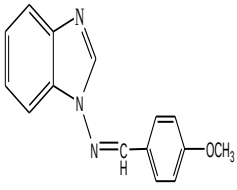
O-phenylenediamine (**1**) was used as starting material to synthesize 1H-benzimidazole (**2**) with formic acid and compound (**2**) was further reacted with Ethy-2-bromo acetate to obtain ethyl 2-(1H-benzimidazol-1-yl) acetate (**3**) which was further reacted with hydrazine hydrate to obtain ethyl 2-(1H-benzimidazol-1-yl) hydrazide (**4**). Compound 4 was reacted with N Aryl Substituted Benzaldehyde to yield N-(**aryl**)-1H-benzimidazol-1-amine (**5a-e**). Completion of the reaction was monitored by using TLC and Petroleum ether and Ethyl acetate (8:2) was used as a solvent and Iodine was used to develop the TLC plates. All Physical characteristics and spectral analysis such as Melting Point, Colour, Yield, *rf*, were summarized in **Table 1**.

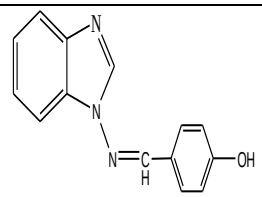
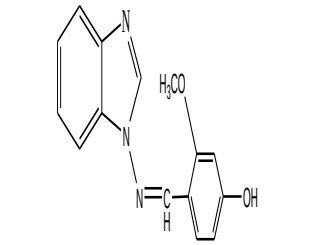
Table 1 - Physical Characteristics and Spectral Data of all Compounds

S. No.	Compound Name with code	Color	M.P. (^oC)	% Yield	R_f
1.	*o*-phenylenediamine **(1)**	Brown	99	-	0.82
2.	1H-benzimidazole **(2)**	White	168 -170	70.08	0.67
3.	Ethyl 2-(1H-benzimidazol-1-yl) acetate (**3**)	Pale Yellow	208 -210	58.55	0.78
4.	Ethyl 2-(1H-benzimidazol-1-yl) hydrazide **(4)**	Off White	230 - 232	43.26	0.62
5.	N-benzylidene-1H-benzimidazol-1-amine **(5a)**	Pale brown	210 -212	54.39,	0.53
6.	N-(4-chloro benzylidene)-1H-benzimidazol-1-amine **(5b)**	Off white	235 -237	56.88	0.67
7.	N-(4-methoxy benzylidene)-1H-benzimidazol-1-amine **(5c)**	Off white	<230	32.08	0.79
8.	4-((1H-benzimidazol-1-yl imino) methyl) phenol **(5d)**	Pale Yellow	226-228	40.89	0.53
9.	4-((1H-benzimidazol-1-yl imino) methyl) -3-methoxy phenol **(5e)**	Off white	230 -232	50.76	0.58

Spectral analysis – All FTIR Peaks and H NMR data were summarised in a Table 2

Table 2 – Spectral Analysis of all Compounds

S. No	Name and Structure of Compound	IR Spectra (ν_{max} cm^{-1})	^{1}H NMR (DMSO): δ ppm
1.	 ortho phenylenediamine (**1**)	3033.82 C-H (stretching aromatic) 1591.16, 1461.94 C = C (stretching aromatic) 3382.91 N-H stretching, 1325.01 C-N Stretching	-
2.	 1*H*-benzimidazole (**2**)	2987.9 C-H (stretching aromatic) 1558.8, 1460.0 C = C (stretching aromatic) 3427.27 N-H stretching (Heterocyclic).	-
3.	 ethyl 2-(1*H*-benzimidazol-1-yl)acetate (**3**)	2821.06 C-H (stretching aromatic) 1454 C = C (stretching aromatic) 3500.6 N-H stretching (Heterocyclic) 782.4, C=O stretching for ester 1012.30, C - O stretching for ester cm^{-1}.	-
4.	 ethyl 2-(1H-benzimidazol-1-yl) hydrazide (**4**)	3051.1 C-H (stretching aromatic) 1402.1 C = C (stretching aromatic) 3500.9 N-H (stretching Amide) 1672.4 C=O (stretching amide) 1487.0 C-N (stretching amide)	-
5.	 *N*-benzylidene-1*H*-benzimidazol-1-amine (5a)	3101 C-H (stretching aromatic) 1415 C = C (stretching aromatic), 1253 ring stretching due to C = C & C = N 2052 CH=N-N stretching for diazo cm^{-1}.	7.78 – 7.69 (d, *J* = 5.7 Hz, 4H, Ar-H), 7.43 – 7.38 (d, *J* = 5.7 Hz 4H, Ar-H), 7.34 (s, 1H, CH), 7.25 (s, 1H, CH).
6.	 *N*-(4-chlorobenzylidene)-1*H*-benzimidazol-1-amine (5b)	3000 C-H (stretching aromatic) 1442 C = C (stretching aromatic) 1282 ring stretching due to C = C & C = N 2058 CH=N-N stretching for diazo 757 C- Cl aromatic cm^{-1}.	7.84 (d, *J* = 5.7 Hz, 2H, Ar-H), 7.57 (s, 1H), 7.48 – 7.43 (m, 2H, Ar-H), 7.38 – 7.33 (m, 2H, Ar-H).
7.	 *N*-(4-methoxybenzylidene)-1*H*-benzimidazol-1-amine (5c)	2910 C-H (stretching aromatic) 1400 C = C (stretching aromatic) 1237 ring stretching due to C = C & C = N 2081 CH=N-N stretching for diazo 1135, C - O -C Stretching 1720 C= O stretching for Ester cm^{-1}.	δ 7.85 (d, *J* = 4.0 Hz, 2H), 7.44 – 7.39 (m, 2H, Ar-H), 7.27 (s, 1H, CH), 6.93 – 6.88 (d, *J* = 4.0 Hz, 2H, Ar-H), 3.80 (s, 3H, OCH_3).

8.	 4-((1*H*-benzimidazol-1-ylimino)methyl)phenol (5d)	3078 C-H (stretching aromatic) 1407 C = C (stretching aromatic), 1249 ring stretching due to C = C & C = N 2055 CH=N-N stretching for diazo; 3311, 1159 stretching for alcohol O-H	8.46 (s, 1H, OH), 7.92 (s, 1H, CH), 7.85 (d, *J* = 6.1 Hz, 2H, Ar-H), 7.57 (s, 1H, Ar-H), 7.42 – 7.37 (m, 2H, Ar-H), 6.91 – 6.86 (d, *J* = 6.1 Hz, 2H, Ar-H).
9.	 4-((1*H*-benzimidazol-1-ylimino)methyl)-3-methoxyphenol (5e)	3086 C-H (stretching aromatic) 1421 C = C (stretching aromatic), 1209 ring stretching due to C = C & C = N 2088 CH=N-N stretching for diazo, 1130 C - O - C Stretching, 3304 O- H stretching for alcohol, 1182 C - O stretching for alcohol 1730 C = O stretching for Ester cm^{-1}.	8.67 (s, 1H, OH), 8.24 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.99 (s, 1H, CH), 7.63 (s, 1H), 7.26 (d, *J* = 19.9 Hz, 2H, Ar-H), 6.57 (d, *J* = 9.5 Hz, 2H, Ar-H), 3.83 (s, 3H, OCH_3).

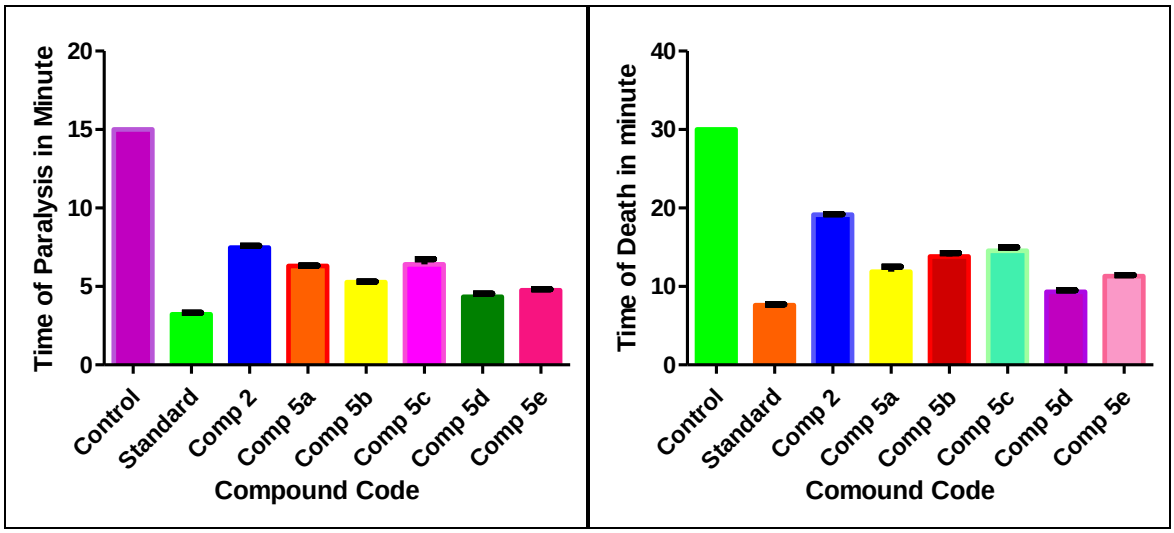
Anthelmintic activity:

All the synthesized benzimidazole derivative were screened for in-vitro anthelmintic activity against *Pheretima posthuma* having similar anatomical and physiological resemblance with the intestinal human being's roundworm parasite [17-19]. All results were summarized in **Table** 3 and it has been observed that all compounds possess anthelmintic potency. A closer inspection of **Table 3** and **Figure 3** indicates that compounds 4-((1H-benzimidazol-1-yl imino) methyl) phenol (**5d**) and 4-((1H-benzimidazol-1-yl imino) methyl) -3-methoxy phenol (**5e**) of 0.1% concentration showed best paralysis time at 4.35±0.10 and 4.75±0.28 respectively, and death time at 09.33±0.63 and 11.33±0.66 respectively as compared to albendazole (Standard) as 3.21±0.32 and 7.60±0.01. other compounds such as **2, 5a, 5b** and **5c** had interestingly low level of anthelmintic activity.

Table 3 - Anthelmintic potency of synthesized Benzimidazole Derivatives

S. No	**Compound Name (Code)**	**Concentration (%w/v)**	**Time in min. (Mean ± SEM)**	
			Paralysis (P)	**Death** (D)
1.	Control	-	No paralysis was observed	No Death was observed
2.	1H-benzimidazole **(2)**	0.1	7.46±0.02	19.16±0.01
3.	N-benzylidene-1H-benzimidazol-1-amine **(5a)**	0.1	6.30±0.28	11.90±0.26
4.	N-(4-chloro benzylidene)-1H-benzimidazol-1-amine **(5b)**	0.1	5.28±0.23	13.80±0.46
5.	N-(4-methoxy benzylidene)-1H-benzimidazol-1-amine **(5c)**	0.1	6.41±0.36	14.56±0.48
6.	4-((1H-benzimidazol-1-yl imino) methyl) phenol **(5d)**	0.1	4.35±0.10	09.33±0.63
7.	4-((1H-benzimidazol-1-yl imino) methyl) -3-methoxy phenol **(5e)**	0.1	4.75±0.28	11.33±0.66
8.	Albendazole (Standard)	0.1	3.21±0.32	7.60±0.01

All values represent Mean ± SEM; n=6 in each group.



A **B**

Figure 3. Anthelmintic Activity of synthesized derivatives A. Time of paralysis B. Time of Death

Conclusion

The present work has been comprised of the synthesis and characterization of benzimidazole derivatives. In this view, have made an attempt in reviewing the literature on substituted benzimidazole nuclei for their medicinal significance with help of chemical abstracts, journals, and various search engines. All proposed compounds were synthesized and tested for the preliminary tests, physical constants, and TLC. All structures of the final compound were confirmed by IR and ^{1}HNMR spectra. All compounds were subjected to Invitro Anthelmintic activity. Finally, it was concluded that compound 4-((1H-benzimidazol-1-ylimino) methyl) phenol (**5d**) is the most effective and showed excellent anthelmintic potential at 0.1% concentration and showed the best paralysis time at 4.35±0.10, and the death time at 09.33±0.63 respectively as compared to albendazole (Standard).

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