International Journal of Multidisciplinary Research and Growth Evaluation.

Synthesis and in vitro anthelmintic activity of "3-(2-[1h benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid and its derivatives"

Rohit Jaysing Bhor [1*], Shekhar Namdeo Kharde [2], Nayan Pandurang Shinde [3], Sonali Pawar [4]
[1-4] Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India

* Corresponding Author: **Rohit Jaysing Bhor**

Article Info

ISSN (online): 2582-7138
Impact Factor: 5.307 (SJIF)
Volume: 04
Issue: 06
November-December 2023
Received: 03-09-2023;
Accepted: 05-10-2023
Page No: 22-30

Abstract

Introduction: The six-membered benzene bonded to the five-membered imidazole molecule is a basic structural feature of the benzimidazole group of heterocyclic, aromatic chemicals. The application of molecules with benzimidazole motifs in medical and biological studies has demonstrated promise. The study's objective was assessing the pharmacological activity of synthesised substances. 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC) was investigated for its anthelmintic properties. The goal of this research was to evaluate the pharmacological activity of synthesised substances. 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC) was investigated in vitro for its anthelmintic properties. Using IR, 1H-NMR, mass spectrometry, and elemental analysis, the purity of the synthesised compounds was identified.

Materials & methods: Formic acid; Acetyl Chloride; Benzene-1,2-diol; Glycolic Acid; Benzoyl Chloride; Methyl Chloride; Ethyl Chloride; Benzamide etc and method is TLC, IR spectra, ^{1}H-NMR and MS. IR spectroscopic research proved the existence of a certain functional group. By using 1 H proton magnetic resonance, the structure of the synthesised molecules was determined. The derivatives'

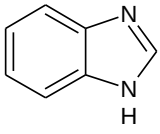
Results: The acquired results demonstrate that many active compounds at concentrations of 100 mg/mL in the compositions under investigation have been determined to be involved in the paralysis and death of earthworms, with paralysis occurring 20 minutes and death occurring 24 minutes afterwards.

Conclusion: Although the derivatives of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC) demonstrated moderate to good anthelmintic activity, IV was determined to be the most potent agent against Pheretima posthuma. Compound IV's anthelmintic activity was found to be comparable to that of the positive control drug Albendazole.

Keywords: Benzimidazole; Glycolic Acid; Benzene-1, 2-diol; 2- Nitro Aniline; Anthelmintic activity; Albendazole

Introduction

In 1944, the benzimidazole nuclei was identified. It has an integrated benzene and imidazole ring. Purine as well as its structure are identical [1]. Benzimidazole has a substantial heterocyclic nucleus owing to the broad spectrum of therapeutic applications it has. The chemical engineer Hoebrecker created the first benzimidazole in 1872 [2]. A hydrogen atom that was connected to nitrogen at the initial position is present in benzimidazole (see Figure 1). Today, benzimidazole is a favored moiety since it has an extensive list of pharmacological attributes.



1*H*-benzimidazole

Fig 1: Benzimidazole heterocyclic nucleus

Multiple studies demonstrate that heterocyclic compounds have medicinal properties. According to heterocyclic compounds characterized as bioactive molecules, the number of moieties [3]. This group of compounds additionally includes benzimidazole, whose derivatives have been demonstrated to possess a broad spectrum of biological and pharmacological characteristics [4]. According to research reports, benzimidazole derivatives have antiviral [5], antifungal [6], anticancer [7], anti-histaminic [8], antitubercular [9], antiallergic [10], antioxidant [11], antibacterial [12], and antiulcer [13] impacts besides other things. Specifically, at the second, fourth, and fifth positions, conjugated benzimidazole derivatives seem to be an indispensable scaffold for anti-parasitic, anti-anthelmintic, and pharmacological medicines. The anthelmintic activity of the substituted benzimidazole variant against the Indian earthworm is boosted [14]. Blocking the generation of reactive oxygen compounds, destroying free radicals whether directly or indirectly, and modifying the intracellular redox potential are also addressed [15]. Since apoptosis is believed to be triggered by oxidative stress, antioxidants indicate their effectiveness by reducing it. In the current the investigation, 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone has been generated by reacting several aromatic acids with o-phenylenediamine. At room temperature, further nitration has been undertaken to produce 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone derivatives. All synthetic chemicals are tested on Indian soil worms to determine their anti-anthelmintic activity [16]. likewise, all synthetic compounds have been examined for their antioxidant activity and contrasted with commercially available anti-oxidant prescription drugs moieties [17]. To figure out if these molecules are comparable with medication, the generated compounds' Insilco pharmacokinetic properties were evaluated as well. In deprived nations, especially those in Africa, worm infestation, also known as helminthiasis [18], is recognized as an extremely serious medical problem. The worms may penetrate the human body as larval or egg stages by a variety of means, including direct contact, contaminated food, mosquitoes (which in turn carry filarial worms), the ground, and water. Helminthiasis develops a number of sickness that are tied to it and is extremely dangerous to individuals as well as animals [19]. There aren't many anthelmintic medications on the market that can kill and get sick of all parasitic insects from the suffering host body. Many parasitic worms acquire resistance to treatment as a consequence of repeated administration of these therapies. Furthermore, routinely used anthelmintic pharmaceuticals, such as Albendazole, can have a number of adverse effects on hosts, including gastrointestinal distress, headaches, nausea, dizziness, and hair loss [20]. The failure of a reliable anthelmintic vaccination makes the issue considerably more difficult. Because of this, finding unusual anthelmintic chemicals that may be employed to address this issue is required. The majority of medications used in healthcare settings are synthetic and contain heterocyclic rings in their molecular structures [21].

Materials and Methods

Materials

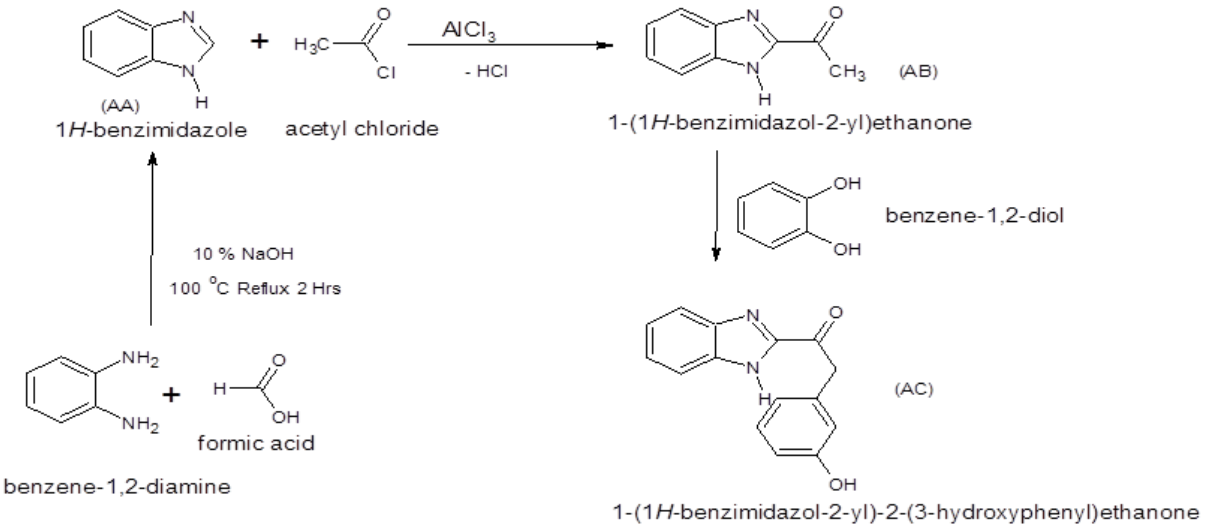
Formic acid; Acetyl Chloride; Benzene-1,2-diol; Glycolic Acid; Benzoyl Chloride; Methyl Chloride; Ethyl Chloride; Benzamide; Aniline; 2-Nitro Aniline; 3- Nitro Aniline was used for novel benzimidazole derivatives. Research grade reagents were used altogether. Some chemicals are readily available at educational institutions; however, all have been purchased from Modern Chemicals in Nashik.

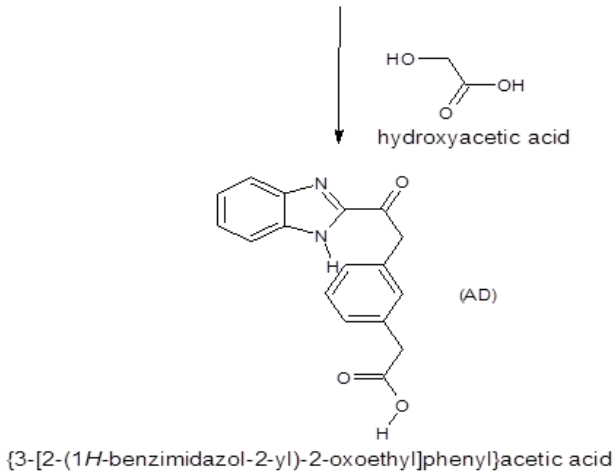
Methods

Every benzimidazole derivative has been synthesised using traditional techniques. The open tube capillary technique was employed to determine melting points. On thin layer chromatography (TLC) plates (silica gel G) in chloroform: ethanol (6:4) and chloroform: methanol (8:2) carrier systems, the purity of the compounds was investigated. The flecks were found under iodine vapours and UV light. IR spectra were collected using KBr pellets and a Perkin Elmer Horizon FTIR spectrometer. TMS was used as the internal standard for the 1H-NMR spectra on the Bruker AVANCE III 500 MHz (AV 500) spectrometer, and the mass spectra from the JEOL GCMATE II MS are shown as m/z. Scheme 1 demonstrates the title compounds' synthesis approach.

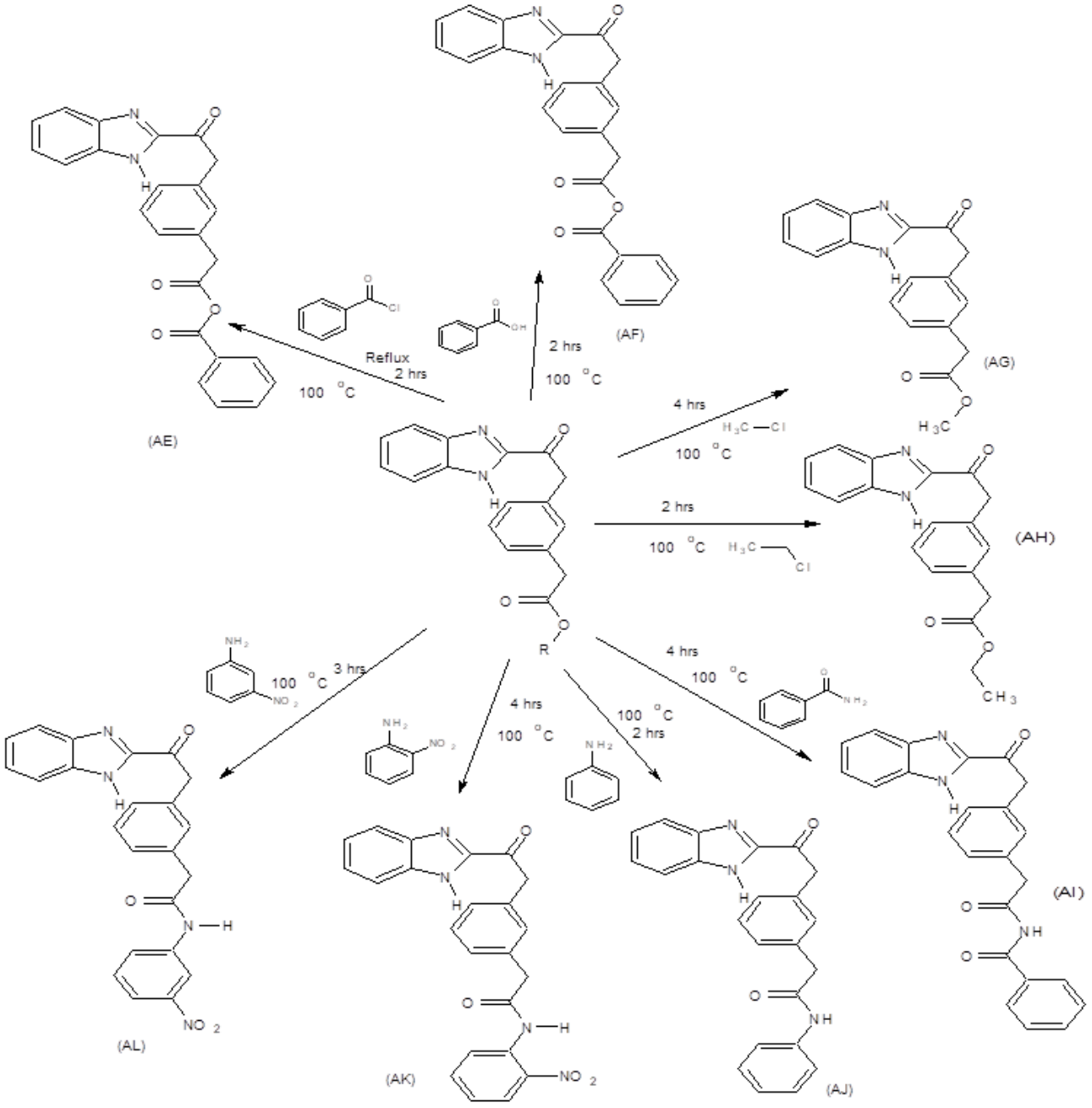
Experimental Work

Chemistry: (Scheme IA)





Scheme 1A: Synthesis of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC)
(Scheme IB)



Scheme 1B: Synthesis of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AE- AL) Derivatives

Synthesis of Benzimidazole Derivatives

Synthesis of Benzimidazole (AA): (Scheme 1A)

In a flask with a round bottom, two grammes of o-phenylenediamine was react with seven millilitres of 90%formic acid. The combination was heated in a bath of water at 100℃ for two hours. After cooling, a solution of 10% sodium hydroxide was then added carefully, until the mixture is simply alkaline to litmus. Ice-cold water was used to flush every single solid out of the reaction flask. The crude product was squeezed thoroughly on the filter cloth, washed with approximately twenty-five millilitres of cold water, and then recrystallization with Hot water.

Synthesis of 1-(1H-benzimidazole-2-yl) ethanone (AB): (Scheme 1A)

2 grammes of 1H benzimidazole and 2 millilitres of acetyl chloride were put together in a round-bottomed flask, and the resulting mixture was heated under rebound conditions until the reaction finished (checked by TLC) after a period of two hours.Following the reaction was finished, the mixture's contents were allowed to cool, and the solid that generated was filtered and then crystallised afresh from methanol to create 1-(1H-benzimidazol-2-yl)ethanone. Cool the product at room temperature and filter it. Apply cold water for washing.

Synthesis of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC): (Scheme 1A)

Take 2 grammes of 1-(1-H benzimidazol-2-yl) ethanone and 2 grammes of benzene-1,2-diol and insert them into a flask employing a round bottom. Heat the solution under reflex conditions for four hours before checking the reaction's completion using a TLC. Following the reaction was finished, the mixture's contents were allowed to cool, and the solid that was produced was filtered and reconstituted from methanol to get 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl)ethanone. Cool the product at room temperature and filter it. Apply cold water for washing.

Synthesis of 3-(2-[1H benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid (AD): (Scheme 1A)

Take two grammes of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone and two millilitres of glycolic acid and place both of them in a flask with a spherical bottom. Two hours of reflux.TLC was used to verify that the reaction had fully cooled. After the reaction was finished, the mixture's contents were allowed to cool. The solid that emerged was filtered and recrystallized from the methanol to produce 3-(2-[1H benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid. Filter the product and let it cool at room temperature. Apply cold water to wash.

Synthesis of {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic benzoic anhydride (AE): (Scheme 1B)

2 grammes of 3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenylacetic acid and 4 millilitres of benzoyl chloride should be boiled for twenty minutes in a flask with an oval bottom. Reactions completion (which can be verified by TLC). After the reaction had concluded, the mixture's contents were allowed to cool to create a solid. This solid was subsequently purified and recrystallized from methanol to generate 3-2(1H benzimidazol-2-yl)-2-oxoethyl phenyl) acetic benzoic anhydride. Cool the product at room temperature and filter it. Apply cold water for washing.

Synthesis of {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic benzoic anhydride (AF): (Scheme 1B)

2 grammes of 3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl]phenylacetic acid and benzoic acid were mixed together in a round-bottomed flask, and the resultant mixture was heated under reflex conditions at 100° til the reaction finished (checked by TLC) after a period of two hours. After the reaction concluded, the mixture was obtained by allowing the contents to cool. The solid that was generated was then filtered and then came together from methanol to generate 3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl acetic benzoic anhydride. Cool the product at room temperature as well as filter it. Apply cold water to wash.

Synthesis of methyl {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AG): (Scheme 1B)

A total of two grammes of 3-2(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl acetic acid and chloromethane were subjected to heating together under conditions of reflux till the reaction finished (checked by TLC) after a period of four hours. Following the reaction completed, the mixture's contents were allowed to cool. The resulting solid was filtered and then crystallised from methanol to generate methyl 3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl acetate. Refrigerate the product at room temperature as well as filter it. Apply cold water to wash.

Synthesis of ethyl {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetate (AH): (Scheme 1B)

In a flask with a round bottom and under reflex circumstances, a total of two grammes of 3-(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl acetic acid and two grammes of chloroethane were heated until the reaction was complete (confirmed by TLC) after two hours. The reaction mixture was created by allowing the contents to cool once the reaction was complete. The resulting solid was filtered, and ethyl 3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl acetate was produced by re-crystallizing it from methanol. The product is filtered and then cooled at room temperature. Wash with cold water.

Synthesis of *N*-({3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) Benzamide (AI): (Scheme 1B)

In a round-bottomed flask; take 2 gm of {3-2(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl} acetic acid and Benzamide was. heated under reflux for 4hr (Checked by TLC).After completion of reaction the contents were allowed to cool obtain reaction mixture, the solid obtained was filtered recrystalized from methanol to give *N*-({3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) Benzamide.

Synthesis of 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ): (Scheme 1B)

Take a total of two grammes of benzamide and 3-2(1-H benzimidazole-2-yl)-2-oxoethyl) acetic acid and insert them into a flask with a spherical bottom. A total of four hours of reflux warming was employed (TLC checked). After the reaction concluded, the mixture's contents were allowed to cool. The solid that resulted was passed through filters and then recrystallized from solvent to generate N-(3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl] acetyl) benzamide.

Synthesis of 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(2-nitrophenyl) acetamide (AK): (Scheme 1B)
Two grammes of 3-2(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl acetic acid and 2 millilitres of aniline were subjected to heating in a flask with a round bottom under reflux over a period of two hours before cooling at room temperature (TLC checked). After the process of reaction concluded, the contents were allowed to cool in order to generate the reaction mixture. The resulting solid was filtered and subsequently re-crystallized from methanol to obtain 2-[3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl-N-phenylacetamide. Cool the product at room temperature as well as filter it. Apply cold water to wash.

Synthesis of 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(3-nitrophenyl) acetamide (AL): (Scheme 1B)
A total of two grammes of 3-2(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl acetic acid and 3-nitro aniline were subjected to heating under reflux conditions for three hours, cooled in a freezer, and then permitted to cool at the ambient temperature. After the reaction concluded, the mixture's contents were allowed to cool. The solid that resulted was filtered and reconstructed from methanol to produce 2- 3-(2-(1-H benzimidazole-2yl)2oxoethyl) phenylN-(3-nitrophenyl) acetamide.

Characterization

Table 1: Physical Data of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone derivatives

Sr. No.	Compounds	Colors Of Compounds	Molecular Formula	Melting Point	% yields	Molecular Weight
1	AA	White	$C_7H_6N_2$	170°C	80%	118
2	AB	Yellowish	$C_9H_9N_2O$	180°C	92%	161
3	AC	White	$C_{15}H_{14}N_2O_2$	181°C	51%	236
4	AD	Brown	$C_{17}H_{14}N_2O_2$	192°C	82%	278
5	AE	White	$C_{24}H_{18}N_2O_4$	198°C	82%	398
6	AF	Yellowish	$C_{18}H_{16}N_2O_3$	200°C	75%	338
7	AG	White	$C_{19}H_{18}N_2O_3$	195°C	89%	308
8	AH	White	$C_{24}H_{19}N_3O_3$	197°C	95%	322
9	AI	White	$C_{23}H_{19}N_3O_2$	201°C	89%	397
10	AJ	Yellowish	$C_{23}H_{18}N_4O_4$	202°C	65%	369
11	AK	Grey	$C_{23}H_{18}N_4O_4$	205°C	72%	414
12	AL	White	$C_{23}H_{18}N_4O_4$	202°C	72%	354

TLC plates were employed for verifying the products' purity, and melting point apparatus was used for figuring out what they were. Usually, solvent media such as chloroform, ethanol, methanol, and benzene were utilized for confirming the response on plates with TLC. Thin layer chromatography was used to keep an eye on the reaction's progress. A ultraviolet (UV) light was utilized as a visualization tool. The entire process was carried out in clean glassware under specified catalyst conditions that may be either basic or acidic. Various spectroscopic methods, including 1H NMR, IR, and MS, were used for analyzing all synthesised substances. Table 1 displays the physical information of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone derivatives.

Result

Spectral Data

Synthesis of Benzimidazole (AA): (Scheme 1 A)
% yield:80%; Melting point (^{0}C) : 170°C; Rf Value :0.9; Benzene :Ethanol (4:1); FTIR (KBr) ν cm^{-1} : 3051.80 (Ar C-H), 2809.78 (Ar C-H), 1699.33 (Ar C=C),1003.77 (Ar C-C), 1216.86 (Ar C-N), 3277.83 (Ar N-H)28; 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 12.3 (N-H), 7.9-7.2 (Ar C-H), 6.6 (C-H); JEOL GCMATE II MS (m/z): 117 (M^+), 118 (M^++1) Mol.Wt. 118.

Synthesis of 1-(1H-benzimidazole-2-yl) ethanone (AB): (Scheme 1 A)
% yield:92%; Melting point (^{0}C) : 230°C; Rf Value :0.8; Benzene :Ethanol (9:1); FTIR (KBr) ν cm^{-1} : 3048.91 (C-H Stretch); 2881.13 (C-H Stretch); 1694.16 (C=C); 1191.79 (C-C); 1260.25 (C-N), 3482.81 (N-H), 1718.34 (C=O ketone); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.7 (N-H), 7.6 (Ar C-H), 7.5 (Ar C-H), 7.3 (Ar C-H), 7.1 (Ar C-H), 2.3(Methyl C-H); JEOL GCMATE II MS (m/z): 160 (M^+), 161 (M^++1); Mol.Wt. 161.

Synthesis of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC): (Scheme 1 A)
% yield:51%; Melting point (^{0}C) : 187°C; Rf Value :0.5; Chloroform: Methanol (7:1); FTIR (KBr) ν cm^{-1} : 3089.97 (C-H Aromatic); 2797.24 (C-H Aliphatic); 16.8295 (C=C Aromatic); 2943.58 (C-C Aromatic); 1641.50 (N-H Aromatic); 1286.30 (C=O ketone); 1710.50 (C-N Aromatic), 3347 (C-OH), 2797 (C-H), 1340 (C-C), 3468 (N-H), 1008 (C-O); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.7 (N-H), 11.4 (N-H), 8.2 (Ar C-H), 8.0 (Ar C-H), 7.5 (Ar C-H), 7.3 (Ar C-H), 6.8 (Ar C-H), 7.0 (Ar C-H), 6.7 (Ar C-H), 6.4 (C-H), 5.3 (O-H) JEOL GCMATE II MS (m/z): 235 (M^+), 236 (M^++1);Mol.Wt. 236

Synthesis of 3-(2-[1H benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid (AD): (Scheme 1 A)
% yield:82%; Melting point (^{0}C) : 192°C; Rf Value :0.8; Chloroform :Ethanol (7:3); FTIR technique (KBr) ν cm^{-1} : 3059.55 (C-H Aromatic); 2881.13 (C-H Aliphatic); 1637.02 (C=C); 1000.72 (C-C); 3352.72 (N-H); 1340.28 (C-N Ar); 3026.73 (N-H Ar); 1719.98 (C=O ketone); 3537.72; 1193.10(C-O Aliphatic); acid anhydride1751; 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.7 (N-H), 8.9 (Ar C-H), 8.8 (Ar C-H), 8.7 (Ar C-H), 8.5 (Ar C-H), 8.4 (Ar C-H), 8.3 (Ar C-H), 8.1 (Ar C-H), 8.0 (Ar C-H), 7.7 (C-H), 7.5 (C-H), 7.3, 6.4(C-H), (C-H), 6.3 (C-H); Mol.Wt. 278

Synthesis of {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic benzoic anhydride (AE): (Scheme 1 B)
% yield: 75%; Melting point (^{0}C) : 198°C; Rf Value:

(0.6);Chloroform: Ethanol (9:1); FTIR (KBr) ν cm^{-1} : 3051.85 (C-H Ar); 2797.23 (C-H Aliphatic); 1687.41 (C=C Ar); 1000.19 (C-C Ar); 1340.00 (C-N Ar); 3352.64(N-H Ar); 1719.83(C=O Ketone); 1193.72 (C-O); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.7 (N-H); 12.0 (N-H); 8.9 (Ar C-H); 8.8 (Ar C-H); 8.7 (Ar C-H); 8.5 (Ar C-H); 8.4 (Ar C-H); 8.3 (Ar C-H); 8.1(Ar C-H); 8.0(Ar C-H); 7.7(Ar C-H); 7.5 (Ar C-H); 7.3(Ar C-H); 7.0(Ar C-H); 7.0 (Ar C-H); 6.4 (C-H); 6.3(C-H); Mol. Wt. 398.

Synthesis of {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic benzoic anhydride (AF): (Scheme 1 B)
% yield: 89; Melting point (^{0}C) : 200°C; Rf Value: 0.8; Chloroform: Ethanol 7:3); FTIR (KBr) ν cm^{-1} : 3051.80 (C-H Ar); 2797.24 (C-H Aliphatic); 1695.12 (C=C Ar); 1178.29 (C-C Ar); 1340.28(C-N Ar); 3460.63(N-H Ar); 1725.88 (C=O)ketone; 1263.60(C-O Aliphatic); acid anhydride 1746.46; 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.7 (N-H); 11.6 (N-H); 11.3 (N-H); 8.9 (Ar C-H); 8.8 (Ar C-H); 8.7 (Ar C-H); 8.5 (Ar C-H);8.4 (Ar C-H); 8.3 (Ar C-H); 8.1(Ar C-H); 8.0 (Ar C-H); 7.7 (C-H); 7.5 (C-H); 7.3 (Methyl C-H);7.0 (Ar C-H); 7.0 (Ar C-H);6.4 (C-H); Mol.Wt. 338

Synthesis of methyl {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AG): (Scheme 1 B)
% yield: 95%; Melting point (^{0}C) : 199°C; Rf Value: 0.7; chloroform: Ethanol (8:2); FTIR (KBr) ν cm^{-1} : 2975.53 (C-H Ar); 2881.30(C-H)1698C=C) Aliphatic); 1247 (C=C Ar); 1340.28 (C-C Ar); 3026.73 (N-H Aliphatic); 1725.98(C-N Ar); 1219.16 (N-H Ar); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 12.1 (N-H); 8.0 (Ar C-H); 8.0 (Ar C-H); 7.8 (Ar C-H); 7.6(Ar C-H); 7.4 (Ar C-H); 7.3 (Ar C-H); 7.2(Ar C-H); 6.9(Ar C-H); 6.7 (Ar C-H); 6.2(C-H); 6.4 (C-H); 2.4 Methyl (C-H); Mol.Wt. 308.

Synthesis of ethyl {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetate (AH): (Scheme 1 B)
% yield: 95%; Melting point (^{0}C) : 202°C; Rf Value: 0.6; Chloroform: Ethanol(9:1); FTIR (KBr) ν cm^{-1} : 3067.23(C-H Ar); 2997.80(C-H Aliphatic); 1594.84 (C=C Ar); 1201.43 (C-C Ar); 1270.40 (C-N Ar); 3295.50(N-H Ar);1695.12 (C=O) ketone; 1000.87 (C-O); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.5 (N-H); 8.6 Ar C-H); 8.5(Ar C-H); 8.4 (Ar C-H); 8.2(Ar C-H); 8.1 (Ar C-H); 7.8 (Ar C-H); 7.7 (Ar C-H); 7.2(Ar C-H); 6.6 (Ar C-H); 6.4 (Ar C-H); 6.2 (Ar C-H); 3.0 (Ar C-H); Mol.Wt. 322.

Synthesis of *N*-({3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) Benzamide (AI): (Scheme 1 B)
% yield: 89%; Melting point (^{0}C) : 204°C; Rf Value: 0.7; Chloroform: Ethanol (8:2); FTIR (KBr) ν cm^{-1} : 3005.52 (C-H Ar); 2997.80 (C-H); 1594.84 (C=C Ar); 1201.43(C-C Ar); 3098.08 (C-N); 1337.27 (N-H Ar); 3420.59 (N-H),1707(C=O),1278.57(C-O),3352.64(N-H); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 12.2 (N-H); 11.6 (N-H), 9.2(Ar C-H); 9.1 (Ar C-H); 9.0(Ar C-H); 8.8 (Ar C-H); 8.6(Ar C-H); 8.5 (Ar C-H); 8.3(Ar C-H); 8.0 (Ar C-H); 7.8 (Ar C-H); 7.6 (Ar C-H); 7.3 (Ar C-H); 7.2 (C-H); 7.1 (C-H);6.3(C-H);6.4(C-H); Mol.Wt. 397.

Synthesis of 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ): (Scheme 1 B)
% yield: 65%; Melting point (^{0}C) : 206°C; Rf Value: 0.6; Chloroform: Ethanol (9:1); FTIR (KBr) ν cm^{-1} : 3074.98 (C-H Stretch Aromatic); 2997.50 (C-H Aliphatic); 1671.98(C=C Ar); 1139.72 (C-C Ar); 3096.24(N-H Al); 1340.28 (C-N Ar); 3236.98 (N-H Ar); 1710.55 (C=O) ketone; 1276.20 (C-O), 3304.52(N-H); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.2 (N-H); 10.9 (N-H); 8.9 (Ar C-H); 8.8 (Ar C-H); 8.7 (Ar C-H); 8.5 (Ar C-H); 8.4 (Ar C-H); 8.3 (Ar C-H); 8.2 (Ar C-H); 8.0 (Ar C-H); 7.7 (Ar C-H); 7.4 (Ar C-H); 7.3(Ar C-H); 7.1 (C-H); 7.0 (C-H); 6.3(C-H),6.4(C-H), Mol.Wt. 369.

Synthesis of 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(2-nitrophenyl) acetamide (AK): (Scheme 1B)
% yield: 95%; Melting point (^{0}C) : 199°C; Rf Value: 0.8; chloroform: Ethanol (9:1); FTIR (KBr) ν cm^{-1} : 2975.53 (C-H Ar); 2881.30(C-H)1698C=C) Aliphatic); 1247 (C=C Ar); 1340.28 (C-C Ar); 3026.73 (N-H Aliphatic); 1735.98(C-N Ar); 1215.16 (N-H Ar); 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 12.1 (N-H); 8.0 (Ar C-H); 8.0 (Ar C-H); 7.8 (Ar C-H); 7.6(Ar C-H); 7.4 (Ar C-H); 7.3 (Ar C-H); 7.2(Ar C-H); 6.9(Ar C-H); 6.7 (Ar C-H); 6.2(C-H); 6.4 (C-H); 2.4 Methyl (C-H); Mol.Wt. 308.

Synthesis of 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(3-nitrophenyl) acetamide (AL): (Scheme 1B)
% yield: 92; Melting point (^{0}C) : 200°C; Rf Value: 0.8; Chloroform: Ethanol 7:3); FTIR (KBr) ν cm^{-1} : 3051.80 (C-H Ar); 2795.24 (C-H Aliphatic); 1696.12 (C=C Ar); 1178.29 (C-C Ar); 1340.28(C-N Ar); 3460.63(N-H Ar); 1725.88 (C=O)ketone; 1263.60(C-O Aliphatic); acid anhydride 1756.46; 1H Nuclear magnetic resonance (500 MHz) CDCl3 δ ppm: 11.8 (N-H); 11.6 (N-H); 11.3 (N-H); 8.9 (Ar C-H); 8.8 (Ar C-H); 8.7 (Ar C-H); 8.4 (Ar C-H);8.4 (Ar C-H); 8.3 (Ar C-H); 8.1(Ar C-H); 8.0 (Ar C-H); 7.7 (C-H); 7.5 (C-H); 7.3 (Methyl C-H);7.0 (Ar C-H); 7.0 (Ar C-H);6.4 (C-H); Mol.Wt. 338.

Biological evaluation

In vitro anthelmintic activity

Earth worm gathering Indian earthworms from moist soil were utilized for the anthelmintic investigation after being cleaned with the standard solution. Due to their pharmacological and anatomical connections with the human abdominal roundworm parasites, Indian earthworms approximately 3-5 cm in length and 0.1–0.2 cm in width were utilized.

Preparation of test solutions

Here the synthesized compounds were prepared by using the 5% Methanol alcoholic solutions.

In vitro anthelmintic activity

The anthelmintic activity of the freshly synthesised substances has been assessed. For the current examination, eight nearly identical Pheretima posthuma the earthworms (obtained from our institution's Botanical Garden, Loni) were chosen at random [22]. Pheretima posthuma and Perionyx excavatus, two species of worms, have been evaluated for their anthelmintic activity against the title components or analogues (AA to AL) at a concentration of 2 mg/mL. For the purpose of getting rid of soil and faeces, collected earthworms have been washed in regular saline water. Synthesised compounds (100 mg) were triturated with 0.5 percent Tween 80 and normal saline solution, and the

resultant mixtures were agitated for twenty minutes for generating sample suspensions. In order to achieve a level of concentration of 0.2% w/v for the test samples, the suspensions of each sample were diluted. The reference medicine Albendazole (0.2% w/v) suspension was made in the same manner. Earthworms of approximately two inches in length, in three batches of five, had been placed in Petri plates having a diameter of 4 inches that contained 50 mL of a suspension of specimens to be tested and a reference medication. In a suspension of distilled water and 0.5% Tween 80 in 50 mL, a different group of five earthworms have been preserved as a control [23]. For sets of three, the times required for both types of worms to become paralysed and to die were noted, and their means were calculated. Each measurement was taken in triplicate, and the mean paralysis time and mean lethal time for each sample were determined (Table No. 2). Each worm was regularly exposed to external stimuli that stimulate +and promote movement in the earthworms, if they were alive, for the purpose to verify death. The time it took for the worms to become motionless was measured as the paralysis period. Three different concentrations of the benzimidazole compounds (25 mg/mL, 50 mg/mL, and 100 mg/mL) were used to investigate the anthelmintic behavior [24].

Table 2: Anthelmintic Activity Data of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone derivatives

Compounds Code	Earthworm species			
	Perionyx excavatus		Pheretima posthuma	
AA	21.50±0.71	35.14±0.39	21.11±0.22	30.09±0.51
AB	15.12±0.32	20.22±0.12	14.29±0.61	20.74±0.31
AC	20.22±0.12	27.17±0.76	23.16±0.32	28.10±0.22
AD	28.35±0.16	20.35±0.86	33.23±0.61	34.53±0.43
AE	14.33±0.98	24.54±1.48	34.41±0.66	28.7±0.2
AF	20.50±0.71	28.65±0.54	20.43±0.21	27.29±0.22
AG	29.15±0.76	37.54±0.98	16.32±0.6	15.4±0.82
AH	14.33±0.98	24.54±0.48	34.41±2.66	28.7±1.2
AJ	24.11±0.5	24.65±0.12	39.23±3.65	30.86±2.65
AI	28.35±0.16	20.35±0.86	33.23±0.61	34.53±0.43
AK	30.22±0.12	37.17±0.76	33.16±0.32	38.10±0.22
AL	34.35±0.16	31.35±1.86	30.23±0.61	31.53±0.43
Albendazole	10.13±0.69	15.72±0.52	11.53±0.85	17.92±0.59
Control	------	-------	--------	-------

Discussion

The newly created substances have been tested for how well they were able to kill helminthes, or worms. Parasitic problems are frequently brought on by helminthes or worms. Anthelmintic medications kill and remove the worms from the plagued host body, but because of their widespread usage, a resistance has developed, prompting the development of safe and effective anthelmintic drugs. Due to their morphological ones such and physiological similarity to human intestinal roundworm parasites, the Indian earthworms Pheretima posthuma and Perionyx excavatus were employed to assess the anthelmintic activity of the synthetic drugs. At a concentration of 2 mg/mL, the benzimidazole derivatives displayed moderate to good anthelmintic performance. In terms of mean paralysing and mean fatal times, the results indicated that all of the looked into drugs were effective versus Perionyx excavatus and Pheretima posthuma. The standard deviation of the mean paralysing time (min) of the compounds tested against Perionyx excavatus and Pheretima posthuma was found to be shorter than the values of 10.13 and 11.53 minute for novel Benzimidazole derivatives demonstrated by the reference drug Albendazole (Table 2). The outcomes were comparable to those of the widely used medication Albendazole. In the control group, every single worm was present and active. Albendazole caused Pheretima posthuma and Perionyx excavatus perished on average in 17.92 and 15.72 minutes, respectively. The two compounds AL and AK were found to be effective at killing worms. Compound AL killed worms in an average of 34.350.16 and 30.230.61 a minute against Perionyx excavatus and Pheretima posthuma, respectively, while compound AK killed worms in an average of 30.220.12 min and 33.160.32 min. The most potent compound likes 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(3-nitrophenyl) acetamide (AL) and 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(2-nitrophenyl) acetamide (AK) having nitro groups in their structure. Based on Table 3; The Benzimidazole compounds exhibit superior anthelmintic action in vitro. Three distinct concentrations of the benzimidazole molecules (25 mg/mL, 50 mg/mL, and 100 mg/mL) were used to investigate the anthelmintic behavior. The earthworms were paralyzed and killed in a shorter amount of time, showing the 100 mg/mL's high level of activity. Here, 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC), 2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl-N-phenylacetamide (AJ), and 2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl-N-phenylacetamide (At a concentration of 100 mg/mL, N-(2-nitrophenyl) acetamide (AK) and 2-3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenylN-(3-nitrophenyl) acetamide (AL) had the highest degree of anti-earthworm activity. All of these derivatives exhibit a variety of readings, ranging from 20 to 30 minutes for paralysis and 24-33 minutes for death.

Conclusion

In the current investigation, Indian earthworms were utilised as the test subject for 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone's anthelmintic effectiveness. According to the findings, benzimidazole derivatives may be able to paralyse and kill parasitic worms. For the development of safe and effective anthelmintic medicines based on this heterocyclic moiety, it should be tried to synthesised novel analogues and derivatives with electron-donating Benzimidazole. The results of the present study showed that synthetic 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AA-AL) has left good

anthelmintic ability against both kinds of worms. Two compound likes, 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(3-nitrophenyl) acetamide (AL) and 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(2-nitrophenyl) acetamide (AK) were promising in their anthelmintic action. According to the outcomes, benzimidazole derivatives may be able to immobilise and kill parasitic worms. The active chemicals may be further derived in order to create safer and possibly more efficient anthelmintic medicines. The current study highlights the significance of benzimidazole derivatives that possess distinct heterocyclic moiety features that are responsible for the 2-3-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl-N-(2-nitrophenyl) acetamide (AK) and may serve as a lead molecule for further modification to obtain clinically useful novel entities.

Acknowledgement
The authors are thankful to Dr. S.B. Bhawar, Pravara Rural College of Pharmacy, Pravaranagar.

Conflict of Interest
The authors declare no conflict of interest.

Abbreviations
FTIR: Fourier transform infrared spectroscopy; NMR spectroscopy: Nuclear magnetic spectroscopy; MS: Mass spectroscopy; KBr: Potassium Bromide; % yield: Percentage yields; M.P.: Melting point; mg/kg: Milligram/ kilograms; sec: seconds; δ: Chemical shift; Mol. Wt: Molecular Weight; gm: Gram.

References

1. Arora RK, Kaur N, Bansal Y, Bansal G. Novel coumarin–benzimidazole derivatives as antioxidants and safer anti-inflammatory agents. Acta Pharmaceutica Sinica B. 2014; 4(5):368-375. https://doi.org/10.1016/j. apsb.2014.07.001.
2. Habib NS, Soliman R, Ashour FA, El-Taiebi M. ChemInform Abstract: Synthesis and Antimicrobial Testing of 4H-1,2,4-Triazole, 1,2,4-Triazolo[3,4-b][1,3,4] thiadiazole, and 1,2,4-Triazolo[3,4-b][1,3,4] thiadiazine Derivatives of 1H-Benzimidazole. ChemInform, 2010, 29(11), https://doi. org/10.1002/chin.199811142
3. Karaburun AA, Kaya Çavuşoğlu B, Acar Çevik U, Osmaniye D, Sağlık BN, Levent S, *et al*. Synthesis and Antifungal Potential of Some Novel Benzimidazole1,3, 4-Oxadiazole Compounds. Molecules. 2019; 24(1):191. https://doi.org/10.3390/ molecules24010191.
4. Karmaker N, Lira DN, Das BK, Kumar U, Rouf ASS. Synthesis and Antioxidant Activity of Some Novel Benzimidazole Derivatives. Dhaka University Journal of Pharmaceutical Sciences. 2018; 16(2):245-249. https://doi.org/10.3329/dujps. v16i2.35263.
5. Kenchappa R, Bodke YD, Telkar S, Aruna Sindhe M. Antifungal and anthelmintic activity of novel benzofuran derivatives containing thiazolo benzimidazole nucleus: an in vitro evaluation. Journal of Chemical Biology. 2016; 10(1):11-23. https://doi. org/10.1007/s12154-016-0160-x.
6. Küçükbay H, Gönül Z, Küçükbay FZ, Tekin Z, Angeli A, Bartolucci G, *et al*. Synthesis of new 7-amino-3,4-dihydroquinolin-2(1 H)-one-peptide derivatives and their carbonic anhydrase enzyme inhibition, antioxidant, and cytotoxic activities. Archiv Der Pharmazie. 2021; 354(11):2100122. https://doi.org/10.1002/ardp.202100122.
7. Meher CP, Sahu AK, Dash SK, Sahoo RK, Sahu SC, Gupta DK. Designing and Synthesis of some Novel 2-Substituted Benzimidazole Derivatives and their Evaluation for Antimicrobial and Anthelmintic Activity. Asian Journal of Research in Chemistry. 2019; 12(2):58. https://doi. org/10.5958/0974-4150.2019.00013.0.
8. Nemoto S, Takeda K, Yu ZX, Ferrans VJ, Finkel T. Role for Mitochondrial Oxidants as Regulators of Cellular Metabolism. Molecular and Cellular Biology. 2000; 20(19):7311-7318. https://doi.org/10.1128/ mcb.20.19.7311-7318.2000.
9. Ramprasad J, Nayak N, Dalimba U, Yogeeswari P, Sriram D, Peethambar S, *et al*. Synthesis and biological evaluation of new imidazo[2,1-b] [1,3,4]thiadiazole-benzimidazole derivatives. European Journal of Medicinal Chemistry. 2015; 95:49-63. https://doi.org/10.1016/j. ejmech.2015.03.024.
10. Roth T, Morningstar ML, Boyer PL, Hughes SH, Buckheit RWJ, Michejda CJ. ChemInform Abstract: Synthesis and Biological Activity of Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2-Aryl-Substituted Benzimidazoles. ChemInform, 2010, 29(20). https://doi. org/10.1002/chin.199820150.
11. Sabah Matrood Mezaal, & Shaimaa Adnan. Synthesis, identification and evaluation of antibacterial activity for some new heterocyclic derivatives from 4-methoxy2-nitroaniline. Al-Qadisiyah Journal of Pure Science, 2021, 26(4). https://doi. org/10.29350/qjps.2021.26.4.1383.
12. Shaker YM, Omar MA, Mahmoud K, Elhallouty SM, El-Senousy WM, Ali MM, *et al*. Synthesis, In vitro and In vivo antitumor and antiviral activity of novel 1-substituted benzimidazole derivatives. Journal of Enzyme Inhibition and Medicinal Chemistry. 2015; 30(5):826-845. https://doi. org/10.3109/14756366.2014.979344
13. Shrivastava N, Naim MJ, Alam MJ, Nawaz F, Ahmed S, Alam O. Benzimidazole Scaffold as Anticancer Agent: Synthetic Approaches and Structure-Activity Relationship. Archiv Der Pharmazie. 2017; 350(6):e201700040. https://doi.org/10.1002/ ardp.201700040. 15. Tahlan, S.; Ramasamy, K.; Lim, S. M.; Shah, S. A. A.; Mani, V., & Narasimhan, B. Design, synthesis and therapeutic potential of 3-(2-(1H-benzo[d]imidazol-2-ylthio)acetamido)- N-(substituted phenyl)benzamide analogues. Chemistry Central Journal., 2018, 12(1). https:// doi.org/10.1186/s13065-018-0513-3.
14. Vinodkumar R, Vaidya SD, Kumar BVS, Bhise UN, Bhirud SB, Mashelkar UC. Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted 2-(4-styrylphenyl)-1H-benzimidazole and N-substituted-3[4-(1H-benzimidazole-2-yl)- phenyl]-acrylic acid tert-butyl ester. Arkivoc. 2008; 14:37-49. https://doi.org/10.3998/ ark.5550190.0009.e05.
15. Selvam TP, Ramu P, Kumar AS. Synthesis, characterization and anthelmintic activity of novel 3-benzyl-2-(4'-substituted phenyl)-4(5H)-(4"-nitrophenyl amino)-1,3-oxazolidines derivatives. J Pharm. Res. Health Care. 2011; 3(1):9-14.

16. Newton SE, Munn EA. The development of vaccines against gastrointestinal Nematode parasites, particularly Haemonchus contortus. Parasitol Today. 1999; 15(3):116-22.
17. Bansal RK. Heterocyclic chemistry-synthesis, reaction and mechanism. 2nd Edition, New Delhi, Wiley Eastern Ltd., 1996.
18. Shillinger JE. Anthelmintic properties of Santonin. J Agr Res. 1927; 34(9):839-45.
19. Husain A, Khan MSY, Hasan SM, Alam MM. 2-arylidene4 (4-phenoxy-phenyl)but-3-en-4-olides. Eur J Med Chem., 2005; 40:1394-404.
20. Khan MSY, Husain A, Sharma S. Studies on butenolides: 2- arylidene-4-(substituted aryl)but-3-en-4-olides. Indian J Chem. 2002; 41B:2160-71.
21. Khokra SB, Monga J, Husain A, Vij M, Saini R. Docking studies on butenolide derivatives as Cox-II inhibitors. Med Chem Res. 2013; 22:5536–44.
22. Husain A, Lal S, Alam MM, Shaharyar M. Antimicrobial activity of some synthetic butenolides& their pyrrolone derivatives. J Enz Inhib Med Chem. 2010; 25:54-61.
23. Chimchi S, Boccalini M, Cosimelli B, Viola G, Vedaldi D, Dall' Acqua F. New geiparvarin analogues from 7-(2-oxoethoxy) coumarins as efficient in vitro antitumoral agents. Tetrahedron Lett. 2002; 43:7473-76.
24. Azam F, Lal S, Prakash O, Ismail A. Synthesis of some novel N4-(naphtha[1,2-d]thiazol-2-yl)semicarbazides as potential anticonvulsants. Eur J Med Chem. 2009; 44:203-21.