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# Synthesis; Characterization and Anti-inflammatory Activity of *N*'-{4-[2-(1*H*-benzimidazol-2-YL)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and it's Derivatives

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## ABSTRACT

A fundamental structural feature of benzimidazoles, a group of heterocyclic, aromatic compounds, is the fusion of a six-membered benzene ring with a five-membered imidazole moiety. Formic acid, Acetyl chloride, hydrazine hydrate, Benzene-1,2-diol, Glycolic Acid, Benzoyl chloride, Methyl chloride, Ethyl chloride, Benzamide, and other chemicals were utilized in this research study. In this research study different methods were used such as TLC, IR spectra, 1H-NMR, and MS. These derivatives were tested for their anti-inflammatory activity determined by rat-paw- oedema method. It was determined that the synthetic chemicals ranged from BA to BK. When compared to common medicines like Indomethacin, the compounds Benzimidazole (BA), 1-(1H-benzimidazole-2-yl)-(3-hydrazinylphenyl) ethanone (BC), N'- {4- [2 - (1H-benzimidazol-2yl) -2- oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (3-nitrophenyl) acetamide (BK), N'- {4- [2 - (1H-benzimidazol-2yl) -2-oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (2-nitrophenyl) acetamide (BJ),N'- {4- [2- (1H–benzimidazol-2-yl) -2 -oxoethyl] phenyl} -2-hydroxyaceto hydrazide –N - phenylacetamide (BI) were found to be the most potent.

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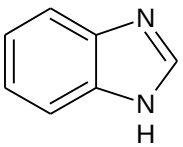
*Keywords: Benzimidazole; hydroxy acetic acid; benzene-1, 2-diol; 2- nitro aniline; indometacin; anti-inflammatory activity.*

## 1. INTRODUCTION

Inflammation is an important pathogenetic component in various diseases. It is an urgent problem in modern medicine. Now many people; about 20 % of the world's population regularly uses NSAIDs, they are having antipyretic, analgesic, and anti-inflammatory action. The benzimidazole nucleus was discovered in 1944. It contain benzene and imidazole ring fused together. Its structure is similar to purine [1]. Benzimidazole contain important heterocyclic nucleus due to its wide range of pharmacological applications. The first benzimidazole was prepared in 1872 by the scientist Hoebrecker [2]. Benzimidazoles contain a hydrogen atom which was attached to nitrogen at 1-position (see Fig. 1). Nowadays benzimidazole is a moiety of choice which possesses many pharmacological properties.




1*H*-benzimidazole

**Fig. 1. Benzimidazole heterocyclic nucleus**

The benzimidazoles are also known as Benzoglyoxalines. A compound containing benzimidazole and benzene rings have been used extensively for pharmaceutical purpose since 1960 [3-5]. 1-H-Benzimidazole rings, which exhibit remarkable basic characteristics due to their nitrogen content, comprise the active substances for several drugs. These derivatives have been also screened for their anti-inflammatory activity [6-9]. Mostly, five-membered-ring aromatic systems having 1 hetero atom at symmetrical position have been studied because of their physiological properties [10-11]. It is also well established that various derivatives of benzimidazole exhibit broad spectrum of pharmacological properties such as antibacterial; anti convulsion and antifungal activities.

Inflammation is an important part of human body's healing process. Inflammation occurs when inflammatory cells travel to the place of an injury or foreign body like Bacteria, Virus and other Pathogens. If inflammation stays for many days then it leads to chronic inflammation. The symptoms of chronic inflammation are rheumatoid arthritis. There are 2 types of inflammation; 1$^{st}$ is Acute inflammation and Chronic inflammation. In Acute inflammation occurs as body damage, such as cutting of finger. In Chronic inflammation, human body continues sending inflammatory cells even when there is no outside danger. For example; in rheumatoid arthritis inflammatory cells attack joint tissues leading to an inflammation which causes severe damage to joints with pain and deformities. Inflammation can be identified by 5 different signs like redness, swelling, heat, pain and loss of function [12-15]. From 19$^{th}$ century, the Research and Development (R and D) of Indian Pharmaceutical Company work on NSAID and to develop new non-steroidal anti-inflammatory drugs (NSAID). Indomethacin, the Fenamates, Ibuprofen drugs are used for the treatment of inflammation [16-17].

## 2. MATERIALS AND METHODS

### 2.1 Materials

Formic acid; Acetyl Chloride; Hydrazine, Benzene-1,2-diol; Glycolic Acid; Benzoyl Chloride; Methyl Chloride; Ethyl Chloride; Benzamide; Aniline; 2-Nitro Aniline; 3- Nitro Aniline All chemicals were of analytical grade. All chemicals were purchased from Modern Chemicals, Nashik and some chemicals are available in PRES's College of Pharmacy; Loni.

### 2.2 Methods

All Benzimidazole derivatives were synthesized by conventional method. Melting points were determined by open tube capillary method. The purity of the compounds was checked on thin layer chromatography (TLC). IR spectra were obtained on a Perkin Elmer Spectrum FTIR instrument (KBr pellets). $^{1}$H-NMR spectra were recorded on a Bruker AVANCE III 500 MHz (AV 500) spectrometer using TMS as internal standard in DMSO-$d_6$/$CDCl_3$ and mass spectra was obtained on JEOL GCMATE II MS is presented as m/z. The synthetic route for the title compounds is shown in Scheme 1A and Scheme 1B.

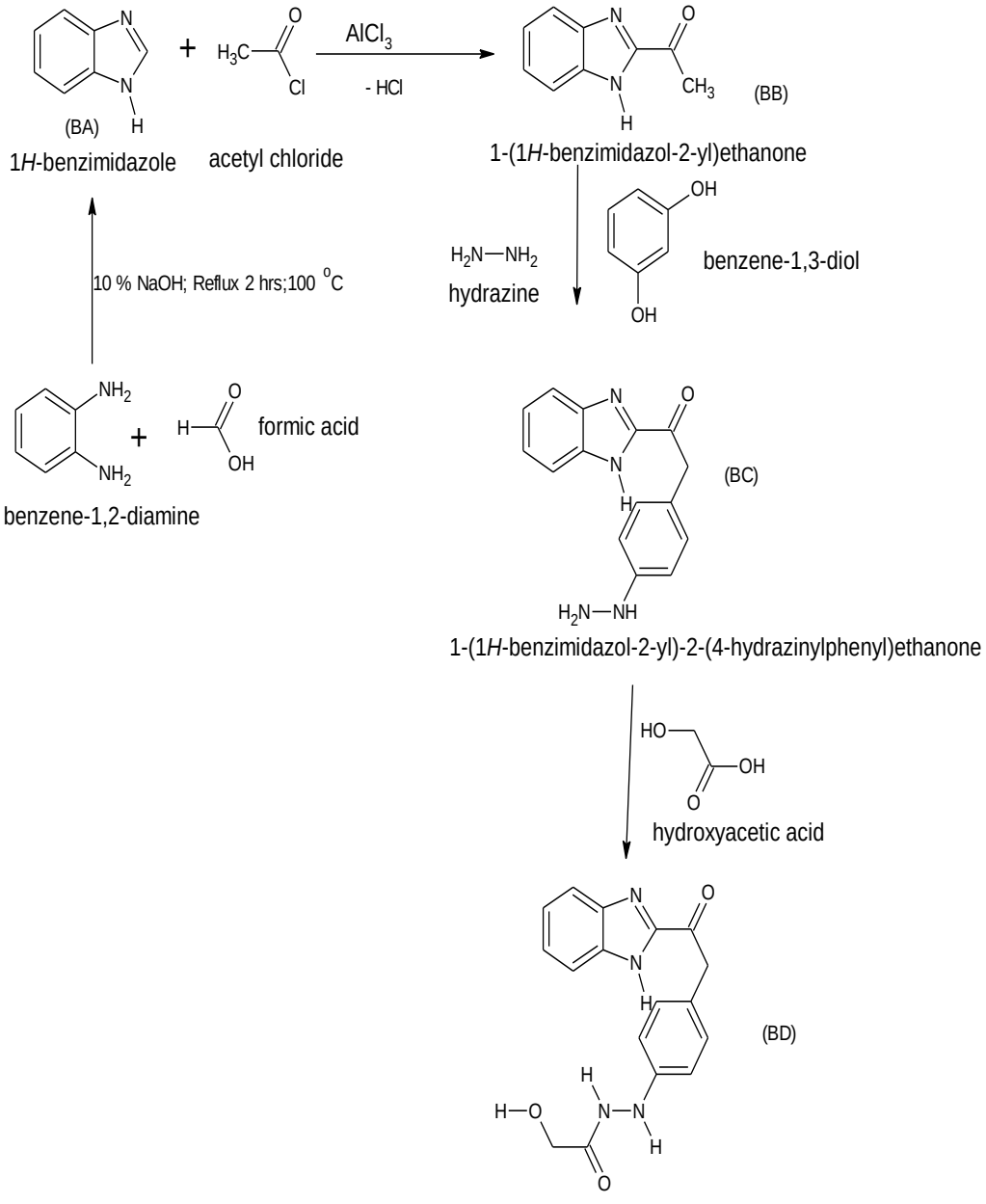
## 3. EXPERIMENTAL WORK

### 3.1 Chemistry: (Scheme IA)

#### 3.1.1 Synthesis of benzimidazole derivatives

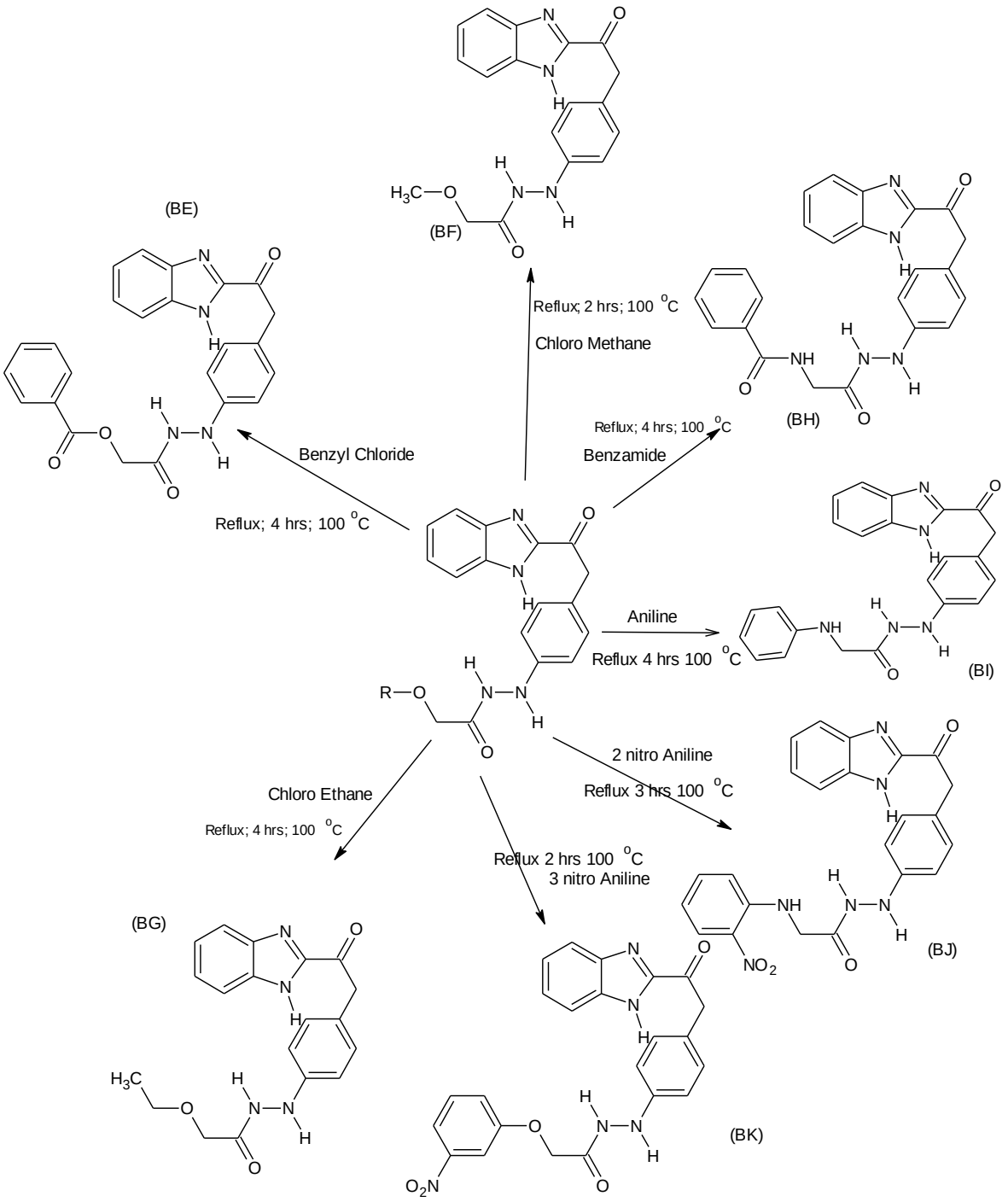
##### *3.1.1.1 Synthesis of Benzimidazole (BA): (Scheme 1A)*

In a round-bottomed flask 2gm of o-phenylenediamine reacted with 7ml of 90% formic acid. The mixture was heated in a water bath at 100°C for two hours. After cooling, 10% sodium hydroxide solution was added slowly, until the mixture is just alkaline to litmus. Ice-cold water was used to rinse solid products out of the reaction flask. The crude product was pressed thoroughly on the filter paper, washed with about 25 ml of cold water, and then recrystallization with Hot water.




**Scheme 1A. Synthesis of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide (BD)**

**(Scheme IB).**




**Scheme 1B. Synthesis of Synthesis of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide (BD) derivatives (BE- BK)**

#### *3.1.1.2 Synthesis of 1-(1H-benzimidazole-2-yl) ethanone (BB): (Scheme 1A)*

In a round-bottomed flask, take 2gm of 1H benzimidazole and 2 ml of Acetyl chloride and the reaction mixture were heated under reflux condition till (2 hrs). After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with

methanol to give 1-(1H-benzimidazol-2-yl) ethanone.

#### *3.1.1.3 Synthesis of 1-(1H-benzimidazol-2-yl)-2-(4-hydrazinylphenyl) ethanone (BC): (Scheme 1A)*

In a round-bottomed flask, take 2gm of 1-(1-H benzimidazol-2-yl) ethanone, 2gm Benzene-1,2-diol and 10 ml of hydrazine and the reaction mixture were heated under reflux condition till (4 hrs). After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give 1-(1*H*-benzimidazol-2-yl)-2-(4-hydrazinylphenyl) ethanone.

#### *3.1.1.4 Synthesis of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxy aceto hydrazide (BD): (Scheme 1A)*

In a round-bottom flask, take 2gm of 1-(1*H*-benzimidazol-2-yl)-2-(4-hydrazinylphenyl) ethanone and 2ml Hydroxy Acetic Acid were heated under reflux condition till for 2hr. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxy aceto hydrazide.

#### *3.1.1.5 Synthesis of {N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl]phenyl}-2-hydroxyaceto hydrazide (BE): (Scheme 1B)*

In a round-bottomed flask 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide reacted with 5 ml benzoyl chloride. The mixture was heated in a water bath at 100°C for 4hrs under reflux condition. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give {N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide.

#### *3.1.1.6 Synthesis of N'- {4- [2- (1H-benzimidazol-2yl) -2-oxoethyl] phenyl} – 2 –methoxy aceto hydrazide (BF): (Scheme 1B)*

In a round-bottomed flask (RBF) 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide reacted with 5 ml Methyl Chloride. The mixture was heated in a water bath at 100°C for 2hrs under reflux condition. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give N'- {4- [2- (1H-benzimidazol-2yl) -2-oxoethyl] phenyl} – 2 –methoxyacetoydrazide.

#### *3.1.1.7 Synthesis of N' {4- [2- (1H-benzimidazol- 2yl} – 2 - oxoethyl] phenyl} – 2 – ethoxy aceto hydrazide (BG): (Scheme 1B)*

In a round-bottomed flask (RBF) 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide reacted with 5 ml chloroethane. The mixture was heated in a water bath at 100°C for 4hrs under reflux condition. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give N' {4- [2- (1H-benzimidazol- 2yl} – 2 - oxoethyl] phenyl} – 2 – ethoxy aceto hydrazide.

#### *3.1.1.8 Synthesis of N'{4-[2-(1H-benzimidazol-2-yl) -2-oxoethyl] phenyl}-2-hydroxy acetyl benzamide (BH): (Scheme 1B)*

In a round-bottomed flask (RBF) 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide reacted with 2gm of benzamide. The mixture was heated in a water bath at 100°C for 2hrs under reflux condition. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give N'{4-[2-(1H-benzimidazol-2-yl) -2-oxoethyl] phenyl}-2-hydroxy acetyl benzamide.

#### *3.1.1.9 Synthesis of N'- {4- [2 - (1H – benzimidazole-2-yl) – 2 - oxoethyl] phenyl} -2-hydroxyaceto hydrazide-N-phenylacetamide (BI): (Scheme 1B)*

In a round-bottomed flask (RBF) 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide reacted with 5ml of aniline. The mixture was heated in a water bath at 100°C for 4hrs under reflux condition. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give *N*-({3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) Benzamide.

#### *3.1.1.10 Synthesis of N' - {4 [2,- (1H-benzimidazol-2-yl) -2 - oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (2-nitrophenyl) acetamide (BJ): (Scheme 1B)*

In a round-bottomed flask (RBF) 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide reacted with 5ml of 2-nitroaniline. The mixture was heated in a water bath at 100°C for 2hrs under reflux condition. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give N' - {4 [2, - (1H-benzimidazol - 2yl) -2 - oxoethyl] phenyl} -2-hydroxyacetohydrazide N- (2-nitrophenyl) acetamide.

#### *3.1.1.11 Synthesis of N'-{4- [2- (1H – benzimidazol-2-yl) -2 - oxoethyl] phenyl} -2- hydroxyaceto hydrazide - N- (3-nitrophenyl) acetamide (BK): (Scheme 1B)*

In a round-bottomed flask (RBF) 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide reacted with 5ml 3-nitroaniline. The mixture was heated in a water bath at 100°C for 4hrs under reflux condition. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol to give N'-{4- [2- (1H – benzimidazol-2-yl) -2 - oxoethyl] phenyl} -2- hydroxyaceto hydrazide - N- (3-nitrophenyl) acetamide.

## 3.2 Characterization

TLC plates were used to check the products purity, and melting point apparatus was used to detect the M.P. Different solvent such as chloroform, ethanol, methanol, and benzene were used to verify and to perform TLC work. An IR lamp was employed as a visualization tool. Various spectroscopic methods, including 1H NMR, IR, and MS, were used to describe and to detect molecules. Table 1 displays the physical characteristics of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxy aceto hydrazide (BD) derivatives.

## 3.3 Spectral Data

### 3.3.1 Synthesis of Benzimidazole (BA): (Scheme1A)

% yield:80%; Melting point: 170°C; Rf Value :0.9; benzene :Ethanol (4:1); FTIR (KBr) v $cm^{-1}$: 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); 1H NMR 12.3 (N-H ), 7.2 (Ar C-H),7.5 (Ar C-H), 7.7 (Ar C-H), 7.9 (Ar C-H), 6.6 (C-H); Mol.Wt. 118.

#### *3.3.1.1 Synthesis of 1-(1H-benzimidazole-2-yl) ethanone (BB): (Scheme1A)*

% yield:92%; Melting point: 230°C; Rf Value :0.8; benzene :Ethanol (9:1); FTIR (KBr) v $cm^{-1}$: 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 NMR 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); Mol.Wt. 161.

#### *3.3.1.2 Synthesis of 1-(1H-benzimidazole-2yl)-(3hydrazinylphenyl) ethanone (BC): (Scheme1A)*

% yield:96%; Melting point: 270°C; Rf Value :0.9; benzene :Ethanol (7:1); FTIR (KBr): v $cm^{-1}$ : 3089.97 (C-H Aromatic), 2797.24 (C-H Aliphatic), 1682.95 (C=C Aromatic), 1170.58 (C-C Aromatic), 3356.50 (N-H Aromatic), 1717.30 (C=O ketone), 1280.50 (C-N Aromatic); 1H NMR 11.9 (N-H), 11.4 (N-H), 8.2 (Ar C-H), 8.0 (Ar C-H), 7.5 (Ar C-H), 7.4 (Ar C-H), 7.3 (Ar C-H), 7.0 (Ar C-H), 6.8 (Ar C-H), 6.7 (Ar C-H), 6.4 (C-H); Mol.Wt. 161.

#### *3.3.1.3 Synthesis of N' {4- [2 - (1H–benzimidazole–2-yl) – 2 oxoethyl] phenyl} -2-hydroxyaceto hydrazide (BD): (Scheme1A)*

% yield:79%; Melting point: 280°C; Rf Value :0.8; benzene :Ethanol (5:1); FTIR (KBr) v $cm^{-1}$ : 2977.55 (C-H Aromatic), 2881.13 (C-H Aliphatic), 1698.02 (C=C), 1247.72 (C-C), 3413.72 (N-H); 1340.28 (C-N Ar), 3026.73 (N-H Ar), 1725.98 (C=O ketone), 1193.72 (C-O Aliphatic), 3428.10(C-O Aliphatic); 1H NMR: 12.8 (N-H), 12.2 (N-H), 7.9 (Ar C-H), 7.8 (Ar C-H), 7.7 (Ar C-H), 7.5 (Ar C-H), 7.3 (Ar C-H),6.9 (Ar C-H), 6.8 ( Ar C-H), 6.6 (Ar C-H), 6.3 (C-H), 6.1 (C-H), 5.4 (O-H); GC-MS(m/z): 322; Mol.Wt. 324.

#### *3.3.1.4 Synthesis of N'-{4- [2 - (1H – benzimidazol-2-yl) -2 - oxoethyl] phenyl} -2- hydroxyaceto hydrazide (BE): (Scheme1B)*

% yield: 80%; Melting point ($^0$C) : 290°C; Rf Value: 0.7;Benzene:Ethanol (9:1);FTIR (KBr) v $cm^{-1}$ : 3031.55 (C-H Ar), 2986.23 (C-H Aliphatic),

**Table 1. Physical Data of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxy aceto hydrazide (BD) derivatives**

| Sr. No. | Compounds | Colors of compounds | Molecular formula | Melting Point | % yields | Molecular weight |
|---|---|---|---|---|---|---|
| 1 | BA | WHITE | C7H6N2 | 170°C | 80% | 118 |
| 2 | BB | BROWN | C9H9N2O | 230°C | 92% | 161 |
| 3 | BC | WHITE | C15H14N4O | 270°C | 96% | 266 |
| 4 | BD | BROWN | C17H16N4O3 | 280°C | 79% | 324 |
| 5 | BE | WHITE | C24H20N4O4 | 290°C | 80% | 412 |
| 6 | BF | BROWN | C18H18N4O3 | 320°C | 95% | 338 |
| 7 | BG | WHITE | C19H20N4O3 | 290°C | 90% | 352 |
| 8 | BH | WHITE | C24H21N5O3 | 250°C | 85% | 427 |
| 9 | BI | WHITE | C23H21n5O2 | 280°C | 88% | 399 |
| 10 | BJ | BROWN | C23H20N6O4 | 340°C | 85% | 444 |
| 11 | BK | WHITE | C23H20N6O4 | 340°C | 85% | 444 |

1696.09 (C=C Ar), 1046.19 (C-C Ar), 1294.00 (C-N Ar), 3344.93 (N-H Ar), 1718.26 (C=O Ketone), 1014.90 (C-O Aliphatic); 1H NMR:12.3 (N-H), 12.0 (N-H), 11.7 (N-H), 9.3 (Ar C-H), 9.2 (Ar C-H), 9.0 (Ar C-H), 8.9 (Ar C-H), 8.7 (Ar C-H), 8.6 (Ar C-H), 8.3(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. 412.

#### *3.3.1.5 Synthesis of N'- {4- [2- (1-H – benzimidazol-2-yl) -2 -oxoethyl] phenyl} -2-methoxyaceto hydrazide (BF) :( Scheme1B)*

% yield: 95%; Melting point ($^0$C) : 320°C; Rf Value: 0.9;Benzene:Ethanol 7:1);FTIR (KBr) v $cm^{-1}$:3048.91 (C-H Ar), 2820.38 (C-H Aliphatic), 1633.41 (C=C Ar), 1137.06 (C-C Ar), 1267.97 (C-N Ar), 3497.27 (N-H Ar), 1708.62 (C=O) ketone, 1249.20 (C-O Aliphatic); 1H NMR: 12.3 (N-H), 11.6 (N-H), 11.3 (N-H), 8.0 (Ar C-H), 7.8 (Ar C-H), 7.7 (Ar C-H), 7.4 (Ar C-H), 7.3 (Ar C-H), 7.2 (Ar C-H), 6.9 (Ar C-H), 6.8 (Ar C-H), 6.4 (C-H), 6.1 (C-H), 2.4 (Methyl C-H); Mol.Wt. 338.

#### *3.3.1.6 Synthesis of N' {4- [2- (1H – benzimidazol-2-yl} -2 -oxoethyl] phenyl} - 2-ethoxyaceto hydrazide (BG): (Scheme1B)*

% yield: 90%; Melting point ($^0$C) : 290°C; Rf Value: 0.7;Benzene:Ethanol 8:1);FTIR (KBr) v $cm^{-1}$:3067.23 (C-H Ar), 2820.38 (C-H Aliphatic), 1632.20 (C=C Ar), 1139.72 (C-C Ar), 3363.39 (N-H Aliphatic), 1232.20 (C-N Ar), 3236.93 (N-H Ar), 1718.26 (C=O) ketone, 1070.30 (C-O aliphatic), 1157.39 (Ether R-O-R Aliphatic); 1H NMR: 12.3 (N-H), 11.8 (N-H), 11.4 (N-H), 8.6 (Ar C-H), 8.5 (Ar C-H), 8.4 (Ar C-H), 8.3 (Ar C-H), 8.0 (Ar C-H), 7.9 (Ar C-H), 7.8 (Ar C-H), 7.3 (Ar C-H), 6.7 (C-H), 6.4 (C-H), 6.1 (C-H), 3.0 Methyl (C-H); GC-MS(m/z): 354; Mol.Wt. 352.

#### *3.3.1.7 Synthesis of N' {4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl]phenyl}-2-hydroxy acetyl benzamide (BH): (Scheme1B)*

% yield: 85%; Melting point ($^0$C) : 250°C; Rf Value: 0.6;Benzene:Ethanol 9:1);FTIR (KBr) v $cm^{-1}$ : 3051.26 (C-H Ar), 2874.38 (C-H Aliphatic), 1671.98 (C=C Ar), 1139.72 (C-C Ar), 1332.57 (C-N Ar), 3406.64 (N-H Ar), 1718.26 (C=O) ketone, 1167.70 (C-O); 1H NMR: 12.0 (N-H), 11.7 (N-H), 11.3 (N-H), 10.8 (N-H), 8.8 (Ar C-H), 8.7 (Ar C-H), 8.6 (Ar C-H), 8.5 (Ar C-H), 8.4 (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), 7.0 (Ar C-H), 6.4 (C-H), 6.3 (C-H); Mol.Wt. 427.

#### *3.3.1.8 Synthesis of N'- {4- [2- (1H– benzimidazol-2-yl) -2 -oxoethyl] phenyl} -2-hydroxyaceto hydrazide –N - phenylacetamide (BI): (Scheme1B)*

% yield: 88%; Melting point ($^0$C) : 280°C; Rf Value: 0.8;Benzene:Ethanol(8:1);FTIR (KBr) v $cm^{-1}$ : 3033.48 (C-H Ar), 2736.49 (C-H), 1655.59 (C=C Ar), 1077.05 (C-C Ar), 1261.30 (C-N); 3489.55 (N-H Ar), 1776.34 (C=O) ketone, 1130.32 (C-O), 1H NMR: 12.0 (N-H), 11.7 (N-H), 11.3 (N-H), 10.8 (N-H), 8.8 (Ar C-H), 8.7 (Ar C-H), 8.6 (Ar C-H), 8.5 (Ar C-H), 8.4 (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), 7.0 (Ar C-H), 6.4 (C-H), 6.3 (C-H); Mol.Wt. 399.

#### *3.3.1.9 Synthesis of N'- {4- [2 - (1H-benzimidazol-2yl) -2- oxoethyl] phenyl} -2-hydroxyaceto hydrazide N-(2-nitrophenyl) acetamide (BJ): (Scheme1B)*

% yield: 85%; Melting point ($^0$C) : 340°C; Rf Value: 0.8;Benzene:Ethanol(4:1);FTIR (KBr) v $cm^{-1}$: 3051.80 (C-H Stretch Aromatic), 2743.24 (C-H Aliphatic), 1658.55 (C=C Ar), 1008.59 (C-C Ar), 3433.24 (N-H Ar), 1268.15 (C-N Ar), 3241.70 (N-H Ar), 1729.58 (C=O) ketone, 1124.30 (C-O ); 1H NMR :11.4 (N-H), 11.3 (N-H), 11.0 (N-H), 10.9 (N-H), 8.8 (Ar C-H), 8.7 (Ar C-H), 8.6 (Ar C-H), 8.5 (Ar C-H), 8.4 (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), 7.0 (Ar C-H), 6.3 (C-H), 6.1 (C-H); Mol.Wt. 444.

#### *3.3.1.10 Synthesis of N'- {4- [2 - (1H-benzimidazol-2yl) -2- oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (3-nitrophenyl) acetamide (BK): (Scheme1B)*

% yield: 85%; Melting point ($^0$C) : 340°C; Rf Value: 0.8;Benzene:Ethanol(4:1);FTIR (KBr) v $cm^{-1}$: 3050.80 (C-H Stretch Aromatic), 2742.24 (C-H Aliphatic), 1668.55 (C=C Ar), 1008.59 (C-C Ar), 3433.24 (N-H Ar), 1268.15 (C-N Ar), 3241.70 (N-H Ar), 1729.58 (C=O) ketone, 1124.30 (C-O ); 1H NMR :11.4 (N-H), 11.3 (N-H), 11.0 (N-H), 10.9 (N-H), 8.8 (Ar C-H), 8.7 (Ar C-H), 8.6 (Ar C-H), 8.5 (Ar C-H), 8.4 (Ar C-H), 8.2 (Ar C-H), 7.9 (Ar C-H), 7.7 (Ar C-H), 7.4 (Ar C-H), 7.3 (Ar C-H), 7.0 (Ar C-H), 6.3 (C-H), 6.2 (C-H); Mol.Wt. 444.

## 3.4 Biological Evaluation

Synthesized newer benzimidazole derivatives were screened for Anti-inflammatory activity. Total 11 compounds (4 Step Products + 7 Benzimidazole Derivatives) were evaluated for their biological screening. The following section describes, in brief the Anti-inflammatory activity.

## 3.5 Anti-inflammatory Activity

The carrageenan-induced rat paw oedema model was used to assess the anti-inflammatory activity of all synthesized benzimidazole derivatives (BA to BK). Wister rats (weighing between 100 and 200 gm) were separated into three groups for control, test, and standard [18–20]. There are six animals per group in each category. Animals that had been fasting overnight were employed in the experiment, and only distilled water was supplied to them at that time. Indomethacin was typically used as a routine medication. Both the test and control medications were dissolved in 1 percent carboxymethyl cellulose (CMC) and ingested using a Gavage needle. In the control group, carboxymethyl cellulose (CMC) at 1% was given [16–18]. We administered carrageenan (1%) by the sub planner surface of the animals for one hour after administering the chemical. The percentage of paw oedema inhibition for benzimidazole derivatives was determined after 3hr and 6 hrs [21-22].

**Table 2. Anti-inflammatory activities of compounds BA to BK**

| Code | Dose Mg/Kg | Inhibition of paw oedema after 3 h (%)1 | Inhibition of paw oedema after 6 h (%)2 |
|---|---|---|---|
| BA | 30 mg/Kg | 3.28 ± 0.28 | 58.24 |
| BB | 30 mg/Kg | 2.48 ± 0.23 | 56.48 |
| BC | 30 mg/Kg | 3.46 ± 0.22 | 51.16 |
| BD | 30 mg/Kg | 1.62 ± 0.27 | 70.98 |
| BE | 30 mg/Kg | 3.26 ± 0.241 | 59.48 |
| BF | 30 mg/Kg | 3.22 ± 0.281 | 53.98 |
| BG | 30 mg/Kg | 1.52 ± 0.271 | 69.54 |
| BH | 30 mg/Kg | 2.48 ± 0.23 | 58.24 |
| BI | 30 mg/Kg | 3.26 ± 0.241 | 56.48 |
| BJ | 30 mg/Kg | 3.22 ± 0.281 | 51.16 |
| BK | 30 mg/Kg | 1.52 ± 0.271 | 70.98 |
| Control | - | 0 .36 ± 0.28 | _ |
| Indomethacin | 40 | 1.78 ± 0.340 | 66.44 |

*1: Dose for 1-7: 30 mg/Kg; 2: Dose for indomethacin 40 mg/Kg b.wt; mean ± SEM; n+6*

## 4. RESULTS AND DISCUSSION

The syntheses of benzimidazole derivatives from BE to BK were undertaken as per the Scheme 1B. The required N' {4- [2 - (1H–benzimidazole–2-yl) – 2 oxoethyl] phenyl} -2-hydroxyaceto hydrazide (BD) was prepared by using 2gm of 1-(1H-benzimidazole-2yl)-(3hydrazinylphenyl) ethanone and 2ml Hydroxy acetic acid reacted with each other under the reflux condition for 2hr. After completion of reaction, add ice-cold water to rinse solid products out of the reaction flask. Solid product was filtered and recrystalized with methanol. N' {4- [2 - (1H–benzimidazole–2-yl) – 2 oxoethyl] phenyl} -2-hydroxyaceto hydrazide (BD) reacted with different reagent so it gives different benzimidazole derivatives (BE-BK). IR spectra were taken on a Perkin Elmer Spectrum. FTIR work was done in Dr. Vithalrao Vikhe Patil foundation's College of Pharmacy; Vilad; Ahmednagar. 1H-NMR spectra were recorded on a Bruker AVANCE III 500 MHz (AV 500) spectrometer using TMS as an internal standard in DMSO-d6/CDCl3. 1H-NMR spectra and MS work were done in IIT Bombay (Sophisticated Analytical Instrument Facility). At the end of the experiment, the compounds synthesized in the project have good yield value. The synthesized benzimidazole compounds were identified and characterized by IR, $^{1}$H NMR and MASS spectra. The all benzimidazole derivatives have a good response for Anti-inflammatory activity: Benzimidazole (BA), 1-(1H-benzimidazole-2yl)-(3hydrazinylphenyl) ethanone (BC), N'- {4- [2 - (1H-benzimidazol-2yl) -2- oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (3-nitrophenyl) acetamide (BK), N'- {4- [2 - (1H-benzimidazol-2yl) -2- oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (2-nitrophenyl) acetamide (BJ),N'- {4- [2- (1H–benzimidazol-2-yl) -2 -oxoethyl] phenyl} -2-hydroxyaceto hydrazide –N - phenylacetamide (BI) derivatives have a good response for Anti-inflammatory activity. The results of Anti-inflammatory activity testing of the prepared compounds were shown in Table 2.

## 5. CONCLUSION

N' {4- [2 - (1H–benzimidazole–2-yl) – 2 oxoethyl] phenyl} -2-hydroxyaceto hydrazide (BD}) and other reagents were used to produce various benzimidazole derivatives. At the end of the experiment, the compounds synthesized in the project have good yield value and RF value. By using FTIR, NMR spectroscopy, and MS, synthetic compounds' structures were verified. Wister rats (weighing between 100 and 200 gm) were separated into three groups for control, test, and standard [12–15]. There are six animals per group in each category. Animals that had been fasting overnight were employed in the experiment, and only distilled water was supplied to them at that time. Indomethacin was typically used as a routine medication. According to this study, benzimidazole derivatives have more potent anti-inflammatory effects. Thus, it can be said that benzimidazole compounds have the potential to be turned into effective anti-inflammatory medications. The compound Benzimidazole (BA), 1-(1H-benzimidazole-2yl)-(3hydrazinylphenyl) ethanone (BC), N'- {4- [2 - (1H-benzimidazol-2yl) -2- oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (3-nitrophenyl) acetamide (BK), N'- {4- [2 - (1H-benzimidazol-2yl) -2- oxoethyl] phenyl} -2-hydroxyaceto hydrazide N- (2-nitrophenyl) acetamide (BJ),N'- {4- [2- (1H–benzimidazol-2-yl) -2 -oxoethyl] phenyl} -2-hydroxyaceto hydrazide –N - phenylacetamide (BI) derivatives have a good response for Anti-inflammatory activity.

## ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s). Animal ethical approval number was 1942/PO/Re/S/17/CPCSEA/2022/01/3.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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