Original Research Article

SYNTHESIS; CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF "*N*'-{4-[2-(1*H*-BENZIMIDAZOL-2-YL)-2-OXOETHYL] PHENYL}-2-HYDROXYACETOHYDRAZIDE AND IT'S DERIVATIVES"

ABSTRACT:

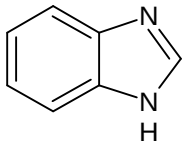
A series of five-membered heterocyclic rings like Benzimidazole were synthesized by the reaction between benzene-1, 2 diamine and formic acid to form various Benzimidazole derivatives (BD- BK) compounds and was tested for their anti-inflammatory activity determined by rat-paw- oedema method. All the synthesis compounds have been characterized by ^{1}HNMR, IR and some Mass spectral data. The compounds were purified by recrystallization method. The entire compound gives good response for the anti-inflammatory activity: 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). For this anti-inflammatory activity, Indometacin was used as a standard drug and compared to new synthesized drugs. Some new synthesized drugs have shown better activities for the anti-inflammation.

KEYWORDS:

Benzimidazole; Hydroxy acetic acid; Benzene-1, 2-diol; 2- Nitro Aniline; Indometacin; Anti-inflammatory activity

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.

MATERIALS AND METHODS:

Materials:

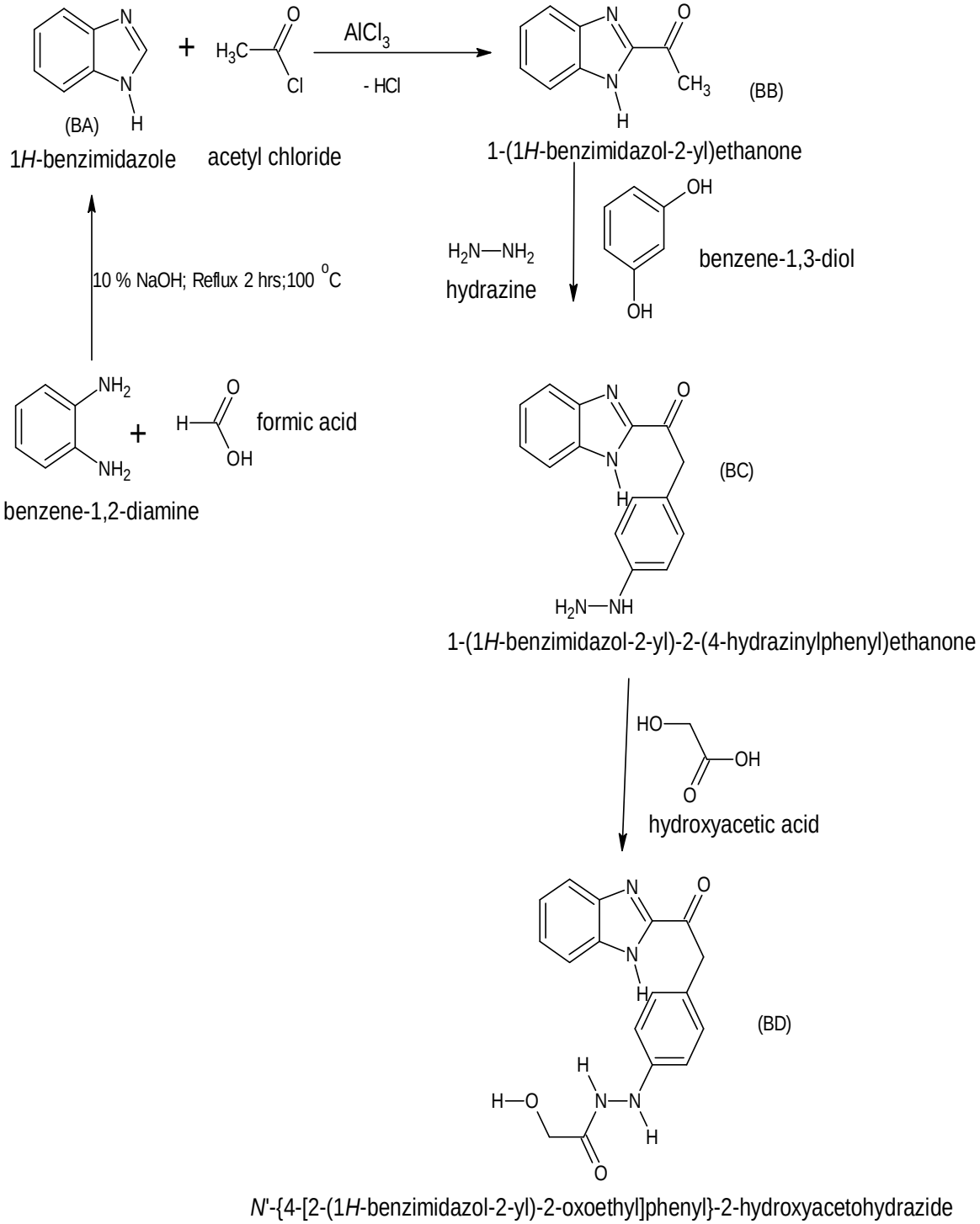
Formic acid; Acetyl Chloride; Hydrazine, Benzene-1,2-diol; Glycolic Acid; Benzoyl Chloride; Methyl Chloride; Ethyl Chloride; Benzamide; Aniline; 2-Nitro Aniline; 3- Nitro Aniline All chemicals were of analytical grade. All chemicals were of purchased from Modern Chemicals, Nashik and Some chemicals are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

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.

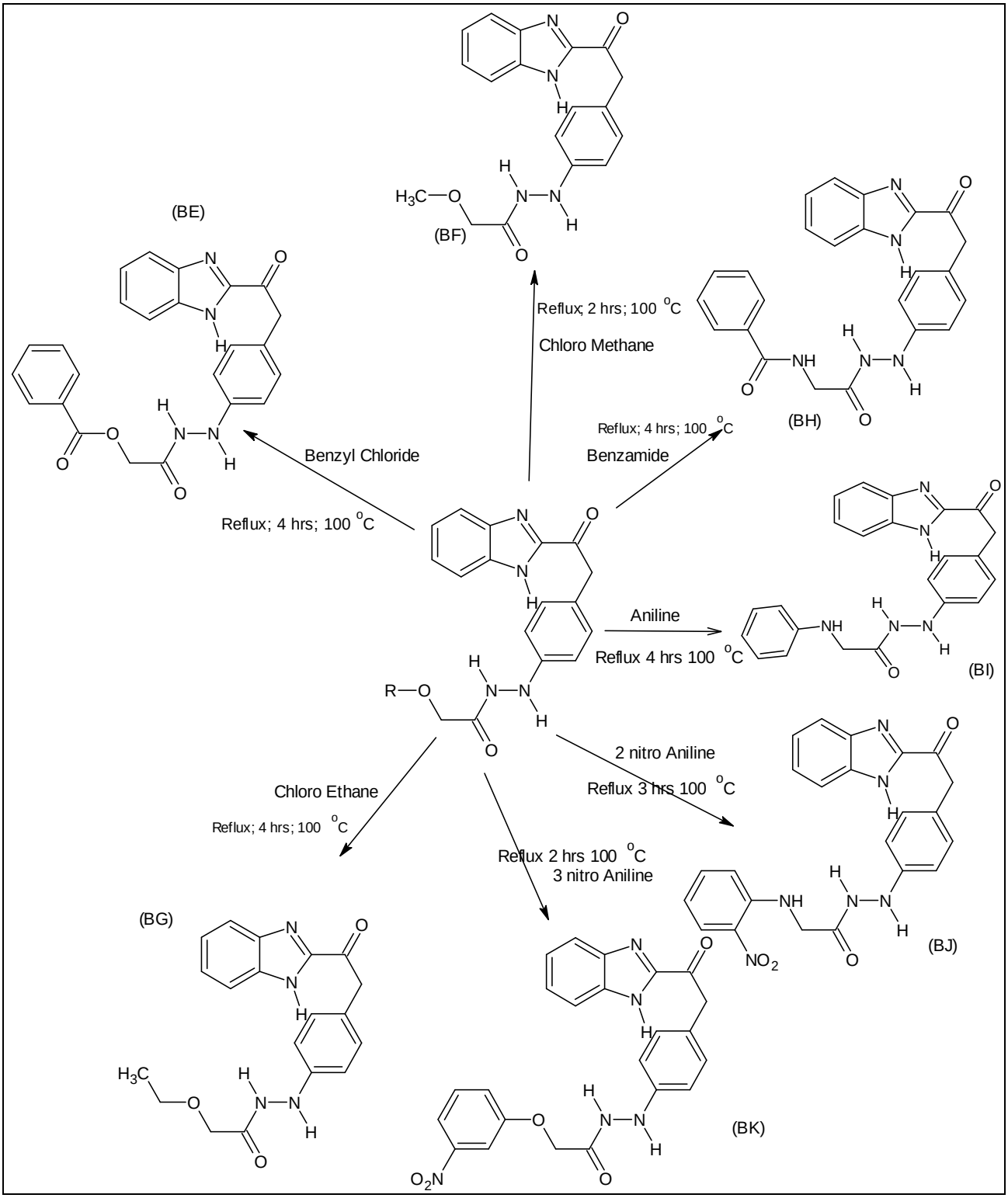
EXPERIMENTAL WORK:

Chemistry: (Scheme IA)



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)

Synthesis of Benzimidazole Derivatives:

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

In a round-bottomed flask 2gm of o-phenylenediamine was react with 7ml of 90%formic acid. The mixture was heated in a water bath at 100° 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 all solid 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.

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 was heated under reflex condition till (after 2 hrs) completion of reaction (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 1-(1H-benzimidazol-2-yl)ethanone..

Synthesis of 1-(1*H*-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 and 2gm Benzene-1,2-diol and 10 ml of hydrazine was heated under reflex condition till (after 4 hrs) completion of reaction (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 1-(1*H*-benzimidazol-2-yl)-2-(4-hydrazinylphenyl) ethanone.

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 was heated and reflux for 2hr.cool the completion of reaction 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'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxy aceto hydrazide

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

In a round-bottomed flask; take 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and 5 ml benzoyl chloride was heated for 4hrs. Completion of reaction (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'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide.

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

In a round-bottomed flask; take 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and 5 ml Methyl Chloride in RBF; reaction mixture was heated under reflex condition at 100° till (after 2 hrs) completion of reaction (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'- {4- [2- (1H-benzimidazol-2yl) -2-oxoethyl] phenyl} – 2 –methoxyacetoydrazide.

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

In a round-bottomed flask; take 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and 5 ml chloroethane was heated together under reflux condition till (after 4 hrs) completion of reaction (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' {4- [2- (1H-benzimidazol- 2yl} – 2 - oxoethyl] phenyl} – 2 – ethoxy aceto hydrazide.

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

In a round-bottomed flask; take 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and 2gm of benzamide was heated under reflex condition till (after 2 hrs) completion of reaction (Checked by TLC).After completion of reaction the contents were allowed to cool, the solid obtained was filtered recrystalized from methanol to give N'{4-[2-(1H-benzimidazol-2-yl) -2-oxoethyl] phenyl}-2-hydroxy acetyl benzamide.

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; take 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and 5ml of aniline 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 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; take 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and 5ml of 2-nitroaniline was heated under reflux condition for 2hr cool at room temperature, (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' - {4 [2,- (1H-benzimidazol - 2yl) -2 - oxoethyl] phenyl} -2-hydroxyacetohydrazide N- (2-nitrophenyl) acetamide.

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; take 2gm of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxyacetohydrazide and 5ml 3-nitroaniline was heated under reflux condition for 4 hr (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'-{4- [2- (1H – benzimidazol-2-yl) -2 - oxoethyl] phenyl} -2- hydroxyaceto hydrazide - N- (3-nitrophenyl) acetamide.

Characterization:

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

The purity of products was monitored through TLC plates and melting point was determined through melting point apparatus. Generally, Chloroform, ethanol, methanol and Benzene solvent medium was used for checking of reaction through TLC plates. Progress of reaction was monitored by thin layer chromatography. Ultra Violet lamp was used as visualizing agent. The whole reactions were carried out in clean glassware with specific catalysts, basic or acidic conditions. All synthesized compounds were characterized by using different spectroscopic techniques such as 1H NMR; IR and MS. The physical data of N'-{4-[2-(1H-benzimidazol-2-yl)-2-oxoethyl] phenyl}-2-hydroxy aceto hydrazide (BD) derivatives were shown in Table 1.

Spectral Data:

S**ynthesis 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.

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.

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.

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.

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), 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.

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.

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.

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.

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.

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.

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.

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.

Anti-inflammatory activity:

Anti-inflammatory activity of all synthesized benzimidazole derivatives was determined by the carrageen an- induced rat paw oedema model. Wister rats (100-200 g) were divided into 3 groups as control, test and standard [12-15]. In each group there are six animals per group. During experiment; overnight fasted animals were used and during that period only distilled water was given to animals. Generally, Indomethacin was used as standard drug. Both test and standard drugs were suspended in 1% carboxymethyl cellulose (CMC) and administered orally through the Gavage needle. 1% of Carboxymethyl cellulose (CMC) was administered in control group [16-18]. After 1 hr of administrating the compound, we induced the carrageen an (1%) by the sub planner surface of the right hind paws of animals. The initial paw volume and also the paw volume after 3 and 6 h of administrating carrageen a were measured. Percent paw oedema inhibition was calculated for benzimidazole derivatives [19-20].

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

RESULT 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 mixture of 2gm of 1-(1H-benzimidazole-2yl)-(3hydrazinylphenyl) ethanone and 2ml Hydroxy acetic acid reflux for 2hr. After completion of reaction the contents were allowed to cool obtains reaction mixture, the solid product was obtained. N' {4- [2 - (1H–benzimidazole–2-yl) – 2 oxoethyl] phenyl} -2-hydroxyaceto hydrazide react with different reagent so it gives different benzimidazole derivatives. IR spectra were obtained on a Perkin Elmer Spectrum1 FT-IR instrument (KBr pellets). Perkin Elmer Spectrum1 FT-IR instrument consists of globar and mercury vapor lamp as sources. 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 and mass spectra was obtained on JEOL GCMATE II. At the end of the experiment, it has been concluded that the compounds synthesized in the project have good yield value. The synthesized oxadiazole compounds were identified and characterized by IR, ^{1}H NMR and MASS spectra. Then, the pharmacological activity was done. The entire compound had 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). The results of Anti-inflammatory activity testing of the prepared compounds were shown in Table 2.

CONCLUSION:

Various benzimidazole derivatives was synthesized by N' {4- [2 - (1H–benzimidazole–2-yl) – 2 oxoethyl] phenyl} -2-hydroxyaceto hydrazide (BD}). The total 11 benzimidazole derivatives were synthesized. All of the compounds were prepared in good yields. The structure confirmations of synthesized compounds were done by IR, NMR spectroscopy and MS. Biological activity of Anti-inflammatory activity was taken by using Wistar rats and it having body weight 150-200 gm. In this research; benzimidazole derivatives had stronger Anti-inflammatory activity against inflammation. Synthesized compounds exhibited more activity when compared to other benzimidazole. Hence, it can be concluded that the benzimidazole derivatives can be potentially developed into useful anti-convulsant agents. The synthesize compounds were establish to be BA to BK. 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) were established to be the most potent compound as compared to standard drugs Indomethacin.

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