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SYNTHESIS AND IN-VITRO ANTI BACTERIAL ACTIVITY OF "{3-[2-(5-CHLORO-1*H*-BENZIMIDAZOL-2-YL)-2-OXOETHYL] PHENYL} ACETIC ACID AND ITS DERIVATIVES

BHOR RJ*, PAWAR S, WAYSE SS AND MORE DN

Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India

***Corresponding Author: Dr. Rohit Jaysing Bhor; E Mail: rohit.bhor69@gmail.com**

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ABSTRACT

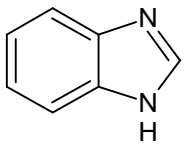
A series of novel {3-[2-(5-chloro-1H-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid and its derivatives were synthesized by treating various 1-(5-chloro-1*H*-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone with hydroxy acetic acid heat/ reflux this reaction for 4 hrs. The title compounds and its derivatives were investigated for *in vitro* antibacterial properties against some human pathogenic microorganisms by employing the agar dilution method using Gentamycin as standard drugs. All title compounds showed activity against some strains of microorganism. Structural activity relationship studies reveal that compounds possessing an electron-withdrawing group exhibit better activity than the compounds containing electron-donating groups. Based on the results obtained, When compared to common medicines like Gentamycin, the compounds *N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetyl)benzamide (AI);2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}-*N*-phenylacetamide (AJ); 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}-*N*-(2-nitrophenyl)acetamide (AK); 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}-*N*-(3-nitrophenyl) acetamide (AL) gives potent anti-bacterial activity. A group of heterocyclic, aromatic compounds, is the fusion of a six-

membered benzene ring with a five-membered imidazole moiety. The use of molecules with benzimidazole motifs in biological and medical research has shown promise. Formic acid, Acetyl chloride, Benzene-1,2-diol, Glycolic Acid, Benzoyl chloride, Methyl chloride, Ethyl chloride, Benzamide, and other chemicals were utilized in this study. The methods employed were TLC, IR spectra, 1H-NMR, and MS. The agar dilution method was used to conduct the pharmacological screening for antibacterial activity.

Keywords: Antibacterial, 5-chloro-1*H*-benzimidazole; hydroxy acetic acid; Glycolic Acid, Benzoyl chloride

INTRODUCTION:

The benzimidazole nucleus was discovered in 1944. It contains 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 **(Figure 1)**. Nowadays benzimidazole is a moiety of choice which possesses many pharmacological properties.



1*H*-benzimidazole

Figure 1: Benzimidazole heterocyclic nucleus

Benzimidazole and its derivatives are important heterocyclic in organic and biochemistry. Fungal and bacterial infections are most commonly affecting millions of people worldwide **[3-4]**. Heterocyclic compounds containing N give a variety of biological activities; antimicrobial activity. Similarly, Benzimidazole moiety constitutes the basic nucleus of nucleotides, which are most important and widespread natural product of plantsand display a large number of biological activities. Particularly, compound having both electronwithdrawing and electron donating groups attached with Benzimidazole ring showed more inhibitory potential against fungal strains and bacterial strains than standard drug. Benzimidazole gives broad spectrum activity such as Antimicrobial, Anti-inflammatory, Analgesic, Antitubercular, Antihypertensive, Anticonvulsant and Antiviral Activity **[5-7]**. The microbial bacterial or parasitic bacteria like *Staphylococcus aureus*, and *Escherichia coli* having moderate impact on the mucosal health of humans. These microbial growths give destruction of host tissue and life-threatening diseases. *Staphylococcus*

aureus and *Escherichia coli* bacterial parasites cause food poisoning, fever and diarrhea. It affects millions of individuals in developing countries also **[8-9]**. More than 60 million people worldwide are infected and up to 1,30,000 of people worldwide die from this infection every year. There are some antibiotic to treat these infection like Amoxicillin, Norfloxacin and Ciprofloxacin. They are the most commonly used drugs for this bacterial infection but they give severe side-effects. Therefore, significant efforts given by new scientist of whole world and they have been made by many research groups to find out new antimicrobial drug. On the other hand, pharmacologically, Benzimidazole and its derivatives represent one of the most important classes of organic heterocyclic compounds with anti-microbial activity like antibacterial **[10]**, antifungal, herbicidal and antiviral activities. Based on this contribution; we will continuation of our drug research program concerning synthesis of new, safer and more biologically active derivatives, so that it gives interest to synthesize a new series of benzimidazole so that it gives more active and less-toxic antimicrobial agents.

MATERIALS AND METHODS:

Materials:

5-chloro-1*H*-benzimidazole; 4-chlorobenzene-1,2-diamine; Formic acid; Acetyl Chloride; 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 reflux method. Melting points were determined by open tube capillary method. The purity of the compounds was checked by thin layer chromatography (TLC) plates by using silica gel G in different solvents like Chloroform: Ethanol (6:4) and chloroform: methanol (8:2) solvent systems, the spots were located under iodine vapors and UV light. Our FTIR 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) with solvents like DMSO-d_6/$CDCl_3$. Mass spectra was obtained on JEOL GCMATE II MS is presented as m/z. The synthetic scheme of these benzimidazole derivatives is shown in **Scheme 1A (Figure 2)**.

EXPERIMENTAL WORK:

(Scheme IA):

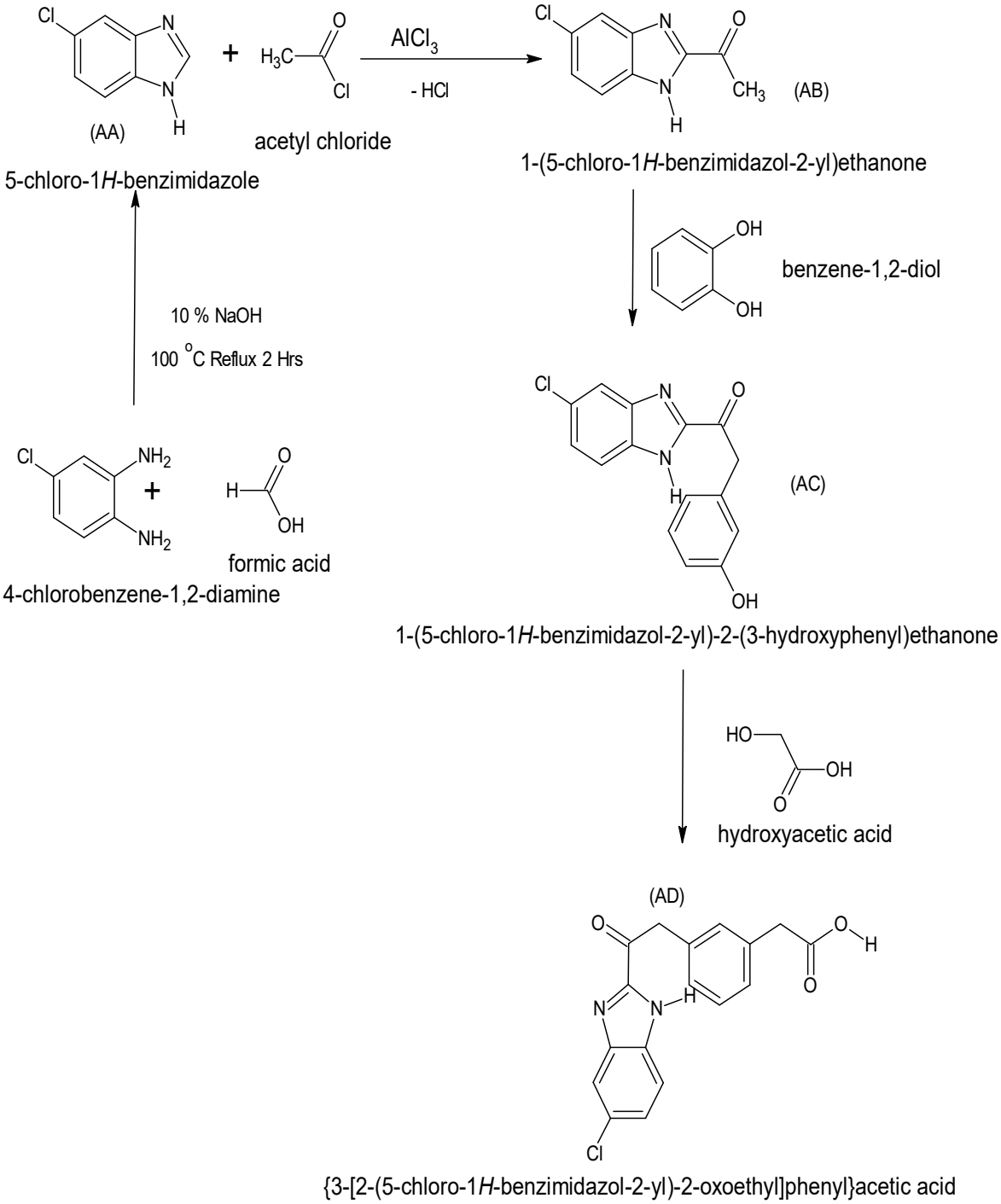


Figure 2: **Scheme 1A: Synthesis of {3-[2-(5-chloro-1H-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid (AD)**

(Scheme IB):

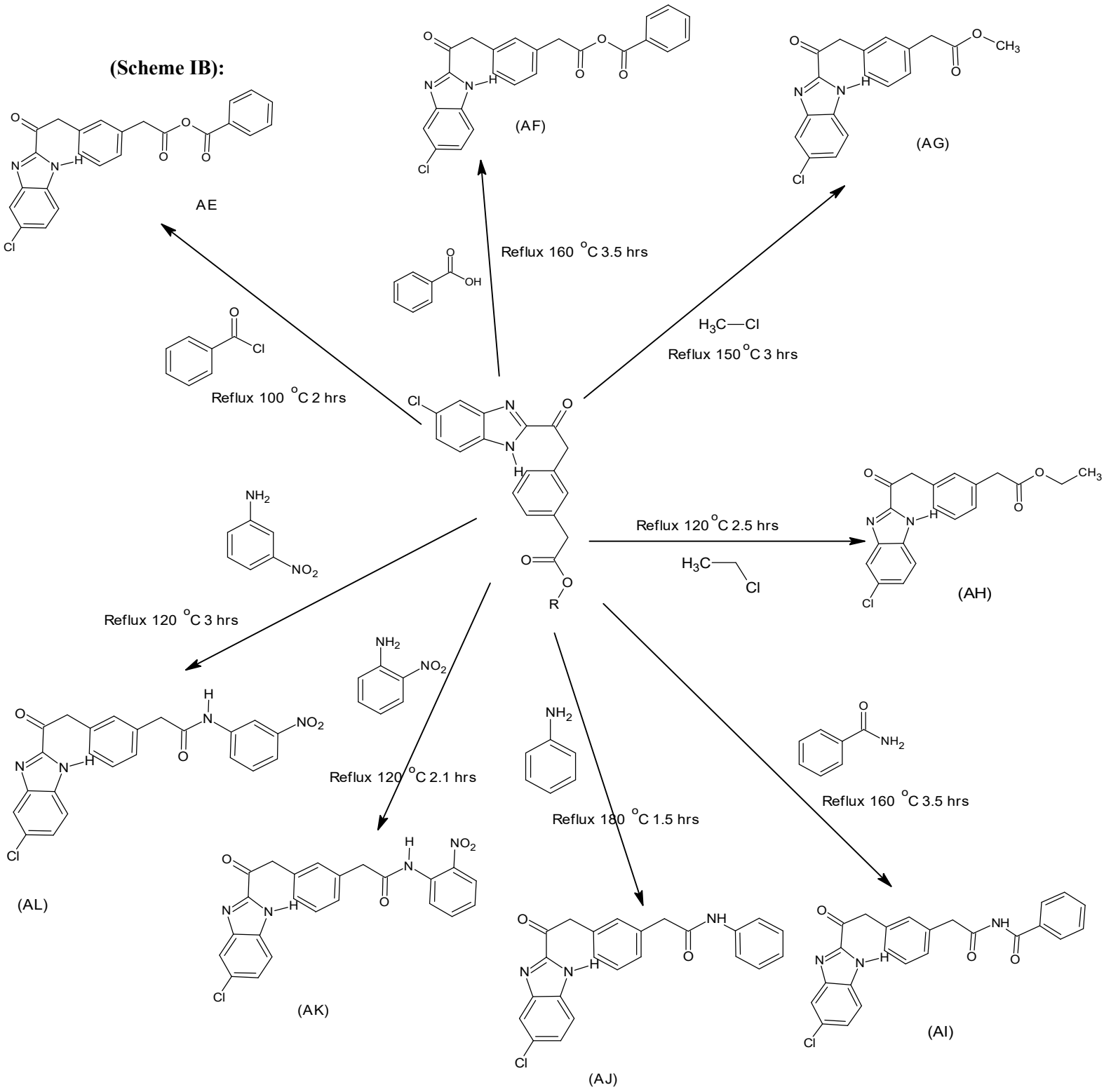


Figure 3: **Scheme 1B: Synthesis of {3-[2-(5-chloro-1H-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid derivatives (AE-AL)**

Procedure:

Synthesis of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid (AD) Derivatives:

Synthesis of 5-chloro-1*H*-benzimidazole (AA) :(Scheme 1A):

In a round-bottomed flask 2gm of 4-chlorobenzene-1,2-diamine was reacted with 7ml of 90%formic acid. The mixture was heated under reflux condition in a water bath at 120° for near 2 hours. After cooling, 10% sodium hydroxide (NaOH) 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-(5-chloro-1*H*-benzimidazol-2-yl)ethanone (AB) : (Scheme 1A)

In a round-bottomed flask take 2gm of 5-chloro-1*H*-benzimidazole and 10 ml of Acetyl chloride and the reaction mixture was heated 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 , filter the product. Wash with cold water. The solid obtained was filtered recrystalized from methanol to give 1-(5-chloro-1*H*-benzimidazol-2-yl) ethanone.

Synthesis of 1-(5-chloro-1*H*-benzimidazol-2-yl)-2-(3-hydroxyphenyl)ethanone (AC): (Scheme 1A)

In a round-bottomed flask take 2gm of 1-(5-chloro-1*H*-benzimidazol-2-yl) ethanone and 2gm Benzene-1,2-diol and heated under reflex condition till (after 5 hrs) completion of reaction (Checked by TLC). After completion of reaction the contents were allowed to cool obtain reaction mixture, Cool at room temperature; the solid obtained was filtered and recrystalized from methanol to give 1-(5-chloro-1*H*-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone.

Synthesis of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid (AD): (Scheme 1A)

In a round-bottom flask take 2gm of 1-(5-chloro-1*H*-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone and 2ml Glycolic acid. and heated under reflex condition till 4 hrs. Completion of reaction (Checked by TLC). After completion of reaction the contents were allowed to cool obtain reaction mixture, Cool at room temperature; the solid obtained was filtered and recrystalized from ethanol to give {3-[2-(5-chloro-1*H*-

benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid

Synthesis of {benzoic {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic anhydride (AE): (Scheme 1B)

In a round-bottomed flask; take 2gm of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 4 ml benzoyl chloride and then heated for 3hr. 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 {benzoic {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic anhydride .

Synthesis of benzoic {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic anhydride (AF): (Scheme 1B)

In a round-bottomed flask; take 2gm of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 5 gm benzoic acid in RBF; reaction mixture was heated under reflex condition at 100°C till (after 3 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 {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic anhydride.

Synthesis of methyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AG): (Scheme 1B)

In a round-bottomed flask; take 2 gm of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 10 ml chloromethane was heated together under reflux condition till (after 5 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 methyl {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate. Cool at room temperature; filter the product. Wash with cold water.

Synthesis of ethyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AH): (Scheme 1B)

In a round-bottomed flask; take 2 gm of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 10 ml chloroethane 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 ethyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetate

Synthesis of *N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) benzamide (AI): (Scheme 1B)

In a round-bottomed flask; take 2 gm of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid and 2 gm Benzamide was. heated under reflux for 5 hrs (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-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetyl)benzamide

Synthesis of 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ): (Scheme 1B)

In a round-bottomed flask; take 2 gm of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 10 ml aniline 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 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}-*N*-phenylacetamide

Synthesis of 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(2-nitrophenyl)acetamide (AK): (Scheme 1B)

In a round-bottomed flask; take 2 gm of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 10 ml 2-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 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}-*N*-(2-nitrophenyl)acetamide

Synthesis of 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(3-nitrophenyl)acetamide (AL): (Scheme 1B)

In a round-bottomed flask; take 2 gm of{{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 3-nitro aniline was heated under reflux condition for 3 hr , cool in ice bath ,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 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}-*N*-(3-nitrophenyl)acetamide.

CHARACTERIZATION:

Table 1: Physical Data of 3-(2-[1H benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid (AD) derivatives

Sr. No.	Compounds	Colors Of Compounds	Molecular Formula	Melting Point	% yields
1	AA	White	$C_7H_4N_2Cl$	170°C	80%
2	AB	Yellowish	$C_9H_8N_2OCl$	180°C	92%
3	AC	White	$C_{15}H_{13}N_2O_2Cl$	181°C	51%
4	AD	Brown	$C_{17}H_{14}N_2O_2Cl$	192°C	82%
5	AE	White	$C_{24}H_{17}N_2O_4$ Cl	198°C	82%
6	AF	Yellowish	$C_{18}H_{15}N_2O_3$ Cl	200°C	75%
7	AG	White	$C_{19}H_{17}N_2O_3$ Cl	195°C	89%
8	AH	White	$C_{24}H_{18}N_3O_3$ Cl	197°C	95%
9	AI	White	$C_{23}H_{18}N_3O_2$ Cl	201°C	89%
10	AJ	Yellowish	$C_{23}H_{17}N_4O_4$ Cl	202°C	65%
11	AK	Grey	$C_{23}H_{17}N_4O_4$ Cl	205°C	72%
12	AL	White	$C_{23}H_{17}N_4O_4$ Cl	202°C	72%

The physical data of 3-(2-[1H benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid (AD) derivatives were shown in **Table 1**.

Spectral Data:

Synthesis of 5-chloro-1*H*-benzimidazole (AA) :(Scheme 1A):

% 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 NMR (500 MHz) CDCl3 δ ppm: 12.3 Ar N-H (s, 1H, *J* = 11.1 Hz), 7.2-7.90 Ar C-H, (m, 3H, *J* = 16.9 Hz), 6.6 C-H (s, 1H, *J* = 14.7 Hz); JEOL GCMATE II MS (m/z): 117 (M^+), 118 (M^++1) Mol.Wt. 118.

Synthesis of 1-(5-chloro-1*H*-benzimidazol-2-yl)ethanone (AB) : (Scheme 1A):

% 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 NMR (500 MHz) CDCl3 δ ppm: 11.7 Ar N-H (s, 1H, *J* = 11.1 Hz),7.6-7.1 (m, 3H, *J* = 16.8 Hz), 2.3 C-H(s, 3H, *J* = 14.7 Hz); JEOL GCMATE II MS (m/z): 160 (M^+), 161 (M^++1); Mol.Wt. 161.

Synthesis of 1-(5-chloro-1*H*-benzimidazol-2-yl)-2-(3-hydroxyphenyl)ethanone (AC): (Scheme 1A)

% 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 NMR (500 MHz) CDCl3 δ ppm: 11.7 Ar N-H (s, 1H, *J* = 11.1 Hz),11.4 Ar N-H (s, 1H, *J* = 11.3 Hz),8.2-6.7 Ar C-H (m, 7H, *J* = 15.8 Hz), 6.4 C-H (s, 1H, *J* = 14.7 Hz), 5.3 O-H (s, 1H, *J* = 17.7 Hz); JEOL GCMATE II

MS (m/z): 235 (M^+), 236 (M^++1);Mol.Wt. 236

Synthesis of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid (AD): (Scheme 1A)

% yield:82%; Melting point (^{0}C) : 192°C; Rf Value :0.8; Chloroform :Ethanol (7:3); FTIR (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 NMR (500 MHz) CDCl3 δ ppm: 11.7 Ar N-H (s, 1H, *J* = 11.1 Hz),8.9-8.0 Ar C-H (m, 7H, *J* = 13.7 Hz), 5.3 O-H (s, 1H, *J* = 17.7 Hz), 6.4 C-H (s, 1H, *J* = 13.7 Hz), 6.3 C-H (s, 1H, *J* = 14.7 Hz), Mol.Wt. 278

Synthesis of {benzoic {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic anhydride (AE): (Scheme 1B)

% 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 NMR (500 MHz) CDCl3 δ ppm: 11.7 Ar N-H (s, 1H, *J* = 11.1 Hz), 12.0 Ar N-H (s, 1H, *J* = 10.1 Hz),8.9-7.0 Ar C-H (m, 15H, *J* = 13.7 Hz), 6.4 C-H (s, 1H, *J* = 13.7 Hz); 6.3 C-H (s, 1H, *J* = 12.9 Hz);; Mol. Wt. 398.

Synthesis of benzoic {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic anhydride (AF): (Scheme 1B)

% 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 NMR (500 MHz) CDCl3 δ ppm: 11.7 (N-H); 11.6 Ar N-H (s, 1H, *J* = 15.4 Hz), 11.3 Ar N-H (s, 1H, *J* = 12.1 Hz), 8.9-7.7 Ar C-H (m, 12H, *J* = 11.1 Hz), 2.4 C-H(s, 3H, *J* = 14.7 Hz); 6.4 C-H(s, 1H, *J* = 17.9 Hz); Mol.Wt. 338

Synthesis of methyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AG): (Scheme 1B)

% 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 NMR (500 MHz) CDCl3 δ ppm: 12.1 Ar N-H (s, 1H, *J* = 11.0 Hz),8.0-6.7 Ar C-H (m, 17H, *J* = 11.1 Hz), 6.2 C-H (s, 1H, *J* = 19.1

Hz), 6.4 C-H (s, 1H, *J* = 18.7 Hz), 2.4 C-H (s, 3H, *J* = 14.7 Hz); Mol.Wt. 308.

Synthesis of ethyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AH): (Scheme 1B)

% 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 NMR (500 MHz) CDCl3 δ ppm: 11.5 Ar N-H (s, 1H, *J* = 11.1 Hz),8.6-7.2 Ar C-H (m, 13H, *J* = 11.1 Hz), 6.4 C-H (s, 1H, *J* = 19.1 Hz), 6.2 C-H (s, 1H, *J* = 18.7 Hz),3.0 C-H (s, 3H, *J* = 14.7 Hz); Mol.Wt. 322.

Synthesis of *N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) benzamide (AI): (Scheme 1B)

% 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 NMR (500 MHz) CDCl3 δ ppm: 12.2 Ar N-H (s, 1H, *J* = 11.1 Hz),11.6 Ar N-H (s, 1H, *J* = 11.0 Hz), 8.8-7.1 Ar C-H (m, 13H, *J* = 11.1 Hz), 6.3C-H (s, 1H, *J* = 18.7 Hz),6.4C-H (s, 1H, *J* = 18.7 Hz); Mol.Wt. 397.

Synthesis of 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ): (Scheme 1B)

% 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 NMR (500 MHz) CDCl3 δ ppm: 11.2 Ar N-H (s, 1H, *J* = 10.3 Hz),10.9 Ar N-H (s, 1H, *J* = 10.1 Hz),8.9-7.0 Ar C-H (m, 14H, *J* = 11.1 Hz), 6.3 C-H (s, 1H, *J* = 18.7 Hz),6.4C-H (s, 1H, *J* = 18.1 Hz); Mol.Wt. 369.

Synthesis of 2-{3-[2-(5-chloro-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 NMR (500 MHz) CDCl3 δ ppm: 12.1 Ar N-H (s, 1H, *J* = 11.1 Hz),8.0-6.9 Ar C-H (m, 14H, *J* = 11.1 Hz), 6.2C-H (s, 1H, *J* = 18.7 Hz), 6.4 C-H (s, 1H, *J* = 19.7 Hz), 2.8 C-H(s, 3H, *J* = 14.8 Hz); Mol.Wt. 308.

Synthesis of 2-{3-[2-(5-chloro-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 NMR (500 MHz) CDCl3 δ ppm: 11.8 Ar N-H (s, 1H, *J* = 11.1 Hz),11.6 Ar N-H (s, 1H, *J* = 11.4 Hz),11.3 (s, 1H, *J* = 11.3 Hz),8.9-7.0 Ar C-H (m, 14H, *J* = 11.1 Hz), 6.4 C-H(s, 1H, *J* = 18.2 Hz); Mol.Wt. 338.

Biological evaluation:

Synthesized newer benzimidazole derivatives were screened for Anti-Bacterial Activity. Total 12 compounds (4 Step Products and 8 {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid (AD) Derivatives were evaluated for their biological screening. The following section describes, in brief the Anti-Bacterial Activity.

***In vitro* Antibacterial activity by disc diffusion method:**

i) Antibacterial Activity:

The compounds like AF to AK were evaluated for their *in vitro* antibacterial activity against various microorganisms such as gram-positive *Staphylococcus aureus*, gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* by *in vitro* method like disc diffusion method was performed using Mueller Hinton Agar (M173) medium. This anti-bacterial activity was done in college level. Each compound was tested at concentration 100µg/mL by using DMSO solvents. The zone of inhibition was measured after 24 hrs incubation at 37ºC. Standard: Gentamycin (100µg/mL of DMSO) **[14]**.

Table 2: Antibacterial activity screening result of synthesized compound measuring the zone of inhibition in millimeter of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid (AD) Derivatives

CompoundNo.	Diameter of zone of inhibition (mm)		
	Escherichia coli ATCC 25922	*Staphylococcus aureus* ATCC 25923	*Pseudomonasaeruginosa* ATCC 27853
AA	12	18	10
AB	08	15	09
AC	13	19	22
AD	16	22	20
AE	16	21	21
AF	14	21	20
AG	17	19	19
AH	17	20	21
AI	13	21	19
AJ	11	22	21
AK	14	24	20
Gentamycin	20	36	28

Figure 3: Zone of Inhibition of Benzimidazole derivatives *(In vitro* Antibacterial activity by disc diffusion method) of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid (AD) Derivatives

RESULT AND DISCUSSION:

The syntheses of benzimidazole derivatives code name from AE to AK were undertaken as per the scheme 1B. The required {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid (AD) was prepared by mixture 2gm of 1-(5-chloro-1*H*-benzimidazol-2-yl) ethanone and 2gm Benzene-1,2-diol reflux for 2hr. After completion of reaction the contents were allowed to cool obtain reaction mixture, the solid product was obtained. 1H-NMR spectra and MS spectra were done in SPPU university Pune. The results revealed that most of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the tested some gram-positive bacteria gives higher inhibition than some gram-negative bacteria. Moreover, the compounds code name like {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid (AD), benzoic {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic anhydride (AE) and 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ) having the side chain showed higher activity than benzoic {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic anhydride (AF) and methyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AG) against *S. aureus* and *Pseudomonas aeruginosa.* The replacement of oxygen atom to nitrogen atom resulted in a slightly increased antimicrobial activity. Our study revealed that all the compounds had stronger antibacterial activity against Gram-positive bacteria when compared to Gram-negative bacteria. Antimicrobial activity revealed that newly synthesized compound ethyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AH), *N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) benzamide (AI) and 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl]

phenyl}-*N*-phenylacetamide (AJ) showed good significant activity. The results of the preliminary antimicrobial testing of the prepared compounds, the typical broad spectrum antibacterial drug like Gentamycin was shown in **Table 2**.

The synthesized compounds were screened for their antibacterial activity and Zone of Inhibition of {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid (AD) derivatives *(In vitro* Antibacterial activity by disc diffusion method) as showed in **Figure 2 and Figure 3**. The derivatives like {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AH), *N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) benzamide (AI) and 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ) showed highly active compound against *E. coli, Staphylococcus aureus* and *Pseudomonas aureus.* Ethyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AH) showed moderately active compound against *E. coli* and *S. aureus. N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) benzamide (AI) and 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ) showed moderately active compound against *E. coli* and *S. aureus*. Standard (Gentamycin) showed highly active against *E. coli, Pseudomonas aeruginosa* and *S. aureus*

CONCLUSION:

Synthesized compounds exhibited more activity when compared to other benzimidazole derivatives. Hence, it can be concluded that the {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic acid (AD) derivatives can be potentially developed into useful as a antibacterial agents. The derivatives like {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AH), *N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) benzamide (AI) and 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ) showed highly active compound against *E. coli, Staphylococcus aureus* and *Pseudomonas aureus.* Ethyl {3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate (AH) showed moderately active compound against *E. coli* and *S. aureus. N*-({3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetyl) benzamide (AI) and 2-{3-[2-(5-chloro-1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ) showed moderately active compound against *E. coli* and *S. aureus* and they were

established to be the most potent compound as compared to standard drugs Gentamycin.

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REFERENCES

[1] Mckellar Q A and Scott E W 1990. The benzimidazole anthelmintic agents-a review. *J. Veter. Pharmacol and Ther.*, 13(3): 223-247.

[2] Richards ML, Lio SC, Sinha A, Banie H, Thomas RJ, Major M, Tanji M and Sircar JC. 2006. Substituted 2- phenyl-benzimidazole derivatives: novel compounds that suppress key markers of allergy. *Eur. J. Med. Chem*. 41(8): 950-969.

[3] Smith K, Yang Y, Anova L, Roncal N, Gerena L, Kyle D, Navarrete-Vazquez G, Castillo R, Hernandez-Luis F, Hernandez-Campos A, Yepez L and Melendez V 2004. *IN VITRO* Antimalarial Efficacy and Metabolic Stability of Benzimidazole Derivatives. *Am.J. Trop. Med. Hyg*., 71(6): 711-714.

[4] Nakano H, Inoue T, Kawasaki N, Miyataka H, Matsumoto H, Taguchi T, Inagaki N and Satoh T 1999. Synthesis of Benzimidazole Derivatives as Antiallergic Agents with 5-Lipoxygenase Inhibiting Action. *Chem. Pharm. Bull*, 47(11); 1573-1578.

[5] Aragón-Muriel A., Liscano Y., Upegui Y., Robledo S.M., Ramírez-Apan M.T., Morales-Morales D., Oñate-Garzón J., Polo-Cerón D 2021. In Vitro Evaluation of the Potential Pharmacological Activity and Molecular Targets of New Benzimidazole-Based Schiff Base Metal Complexes. *Antibiotics.* 10(1):728.

[6] Zhang H.-Z., He S.-C., Peng Y.-J., Zhang H.-J., Gopala L., Tangadanchu V.K.R., Gan L.-L., Zhou C.-H. Design 2017, synthesis and antimicrobial evaluation of novel benzimidazole-incorporated sulfonamide analogues. *Eur. J. Med. Chem.* 136:165–183.

[7] Marinescu M. 2019 *Chemistry and Applications of Benzimidazole and Its Derivatives.* Intech Open; London, UK 14: 110–130

[8] Bansal Y., Silakari O. 2012 The therapeutic journey of benzimidazoles: A review. *Bioorg. Med. Chem.*; **20**: 6208–6236.

[9] Kim T.H., Yang H.Y., Park B.G., Jung S.Y., Park J.H., Park K.D., Min S.J., Tae J., Yang H., Cho S., *et al*. 2017 Discovery of benzimidazole derivatives as modulators of mitochondrial function: A potential treatment for Alzheimer's

disease. *Eur. J. Med. Chem.*; 125: 1172–1192.

[10] Khalifa M.E., Gobouri A.A., Kabli F.M., Altalhi T.A., Almalki A.S.A., Mohamed M.A. 2018; Synthesis, antibacterial, and anti HepG2 cell line human hepatocyte carcinoma activity of some new potentially benzimidazole-5-(aryldiazenyl)thiazole derivatives. *Molecules.* 23: 3285.

[11] Hadole C.D., Rajput J.D., Bendre R.S. 2018 Concise on some biologically important 2-substituted benzimidazole derivatives. *Curr. Chem. Curr. Res.; 7:195*.

[12] Kumbhar S.S., Choudhari P.B., Bhatia M.S. 2017; 3D QSAR and Pharmacophore modelling of selected benzimidazole derivatives as factor IXa inhibitors. *Indian J. Pharm. Sci.* 79: 813–819.

[13] Desai N.C., Pandya D.D., Joshi V.V., Rajpara K.M., Vaghani H.V., Satodiya H.M. (2012) Synthesis, characterization and antimicrobial screening of hybrid molecules containing benzimidazole-pyrazole and pyridine nucleus. *Med. Chem. Res.* 21:4463–4472.

[14] Rajora J., Srivastava Y.K. 2009 Synthesis and antimicrobial activities of some benzimidazolyl pyrazoles. *Rasayan J. Chem.*; 2:655–658.