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SYNTHESIS AND ANTI CONVULSANT ACTIVITY OF "3-(2-[1H BENZIMIDAZOLE-2-YL)-2-OXETHYL] PHENYL) ACETIC ACID AND ITS DERIVATIVES

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ABSTRACT

Introduction: Benzimidazoles are a class of heterocyclic, aromatic compounds which share a fundamental structural characteristic of six-membered benzene fused to five-membered imidazole moiety. Molecules having benzimidazole motifs showed promising application in biological and clinical studies. **Objective:** Synthesis and biological activity of benzimidazole derivatives. **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 **Results & Conclusion**: The pharmacological screening was done by using PTZ Induced Convulsion Method for anticonvulsant activity. The synthesize compounds were establish to be AA to AL. The compound AA, AC, AJ, AK and AL were established to be the most potent compound through compare to standard drugs phenytoin.

Keywords: Benzimidazole; Glycolic Acid; Benzene-1, 2-diol; 2- Nitro Aniline, PTZ; Anti Convulsant Activity

INTRODUCTION

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 **(Figure 1)**. Nowadays benzimidazole is a moiety of choice which possesses many pharmacological properties.

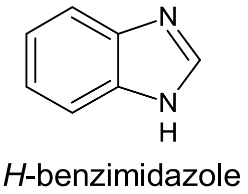


Figure 1: Benzimidazole heterocyclic nucleus

Epilepsy is common disorders of the brain, which affects 60 million people worldwide according to epidemiological studies (Husain *et al*., 2010; Scheurer and Pedley, 1990) **[3-5]**. Every year approximately 2, 40,000 new cases are added to this figure (Husain *et al*., 2009). In Indian Market; more than 40 different anti-epileptic drugs are available but only 30 % of patients have been cure with uncontrolled seizures **[6-9]**. So that, now a day's currently much researcher work on antiepileptic derivatives. It is main focus on investigation of new anticonvulsant agents. Benzimidazole derivatives identification was conducted via in vivo screening tests on the basis of seizure type **[10]**. Anticonvulsant activity of different derivatives depends on the presence of aryl binding site with aryl/alkyl group, hydrogen bonding domain and electron donor group, which are the essential requirements for potential anticonvulsant activity **[11]**.

MATERIALS AND METHODS:

Materials:

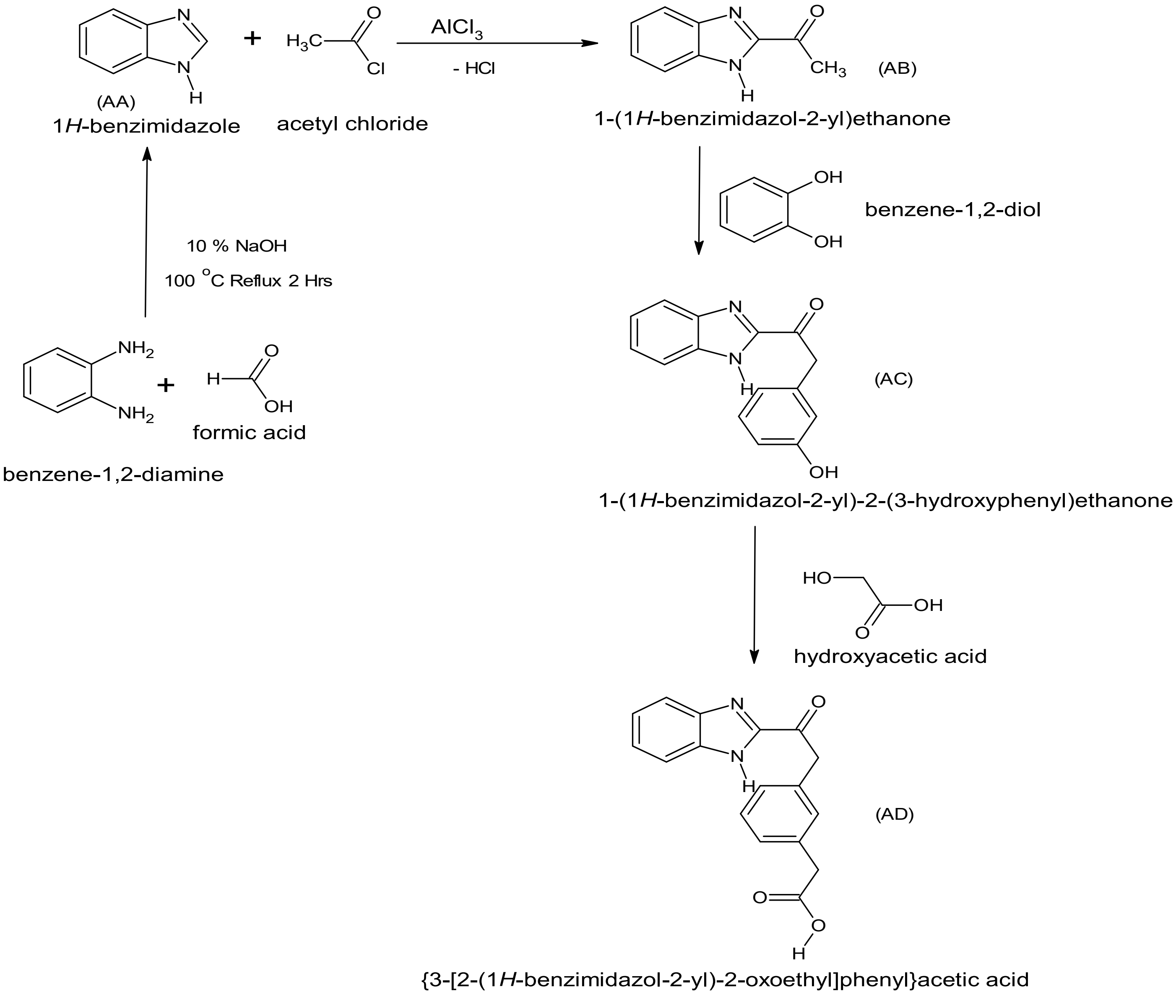
Formic acid; Acetyl Chloride; Benzene-1,2-diol; Glycolic Acid; Benzoyl Chloride; Methyl Chloride; Ethyl Chloride; Benzamide; Aniline; 2-Nitro Aniline; 3-Nitro Aniline All chemicals were of analytical grade. All chemicals were of purchased from Modern Chemicals, Nashik and Some chemicals are available 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) plates (silica gel G) in Chloroform: Ethanol (6:4) and chloroform: methanol (8:2) solvent systems, the spots were located under iodine vapors and UV light. 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 1**.

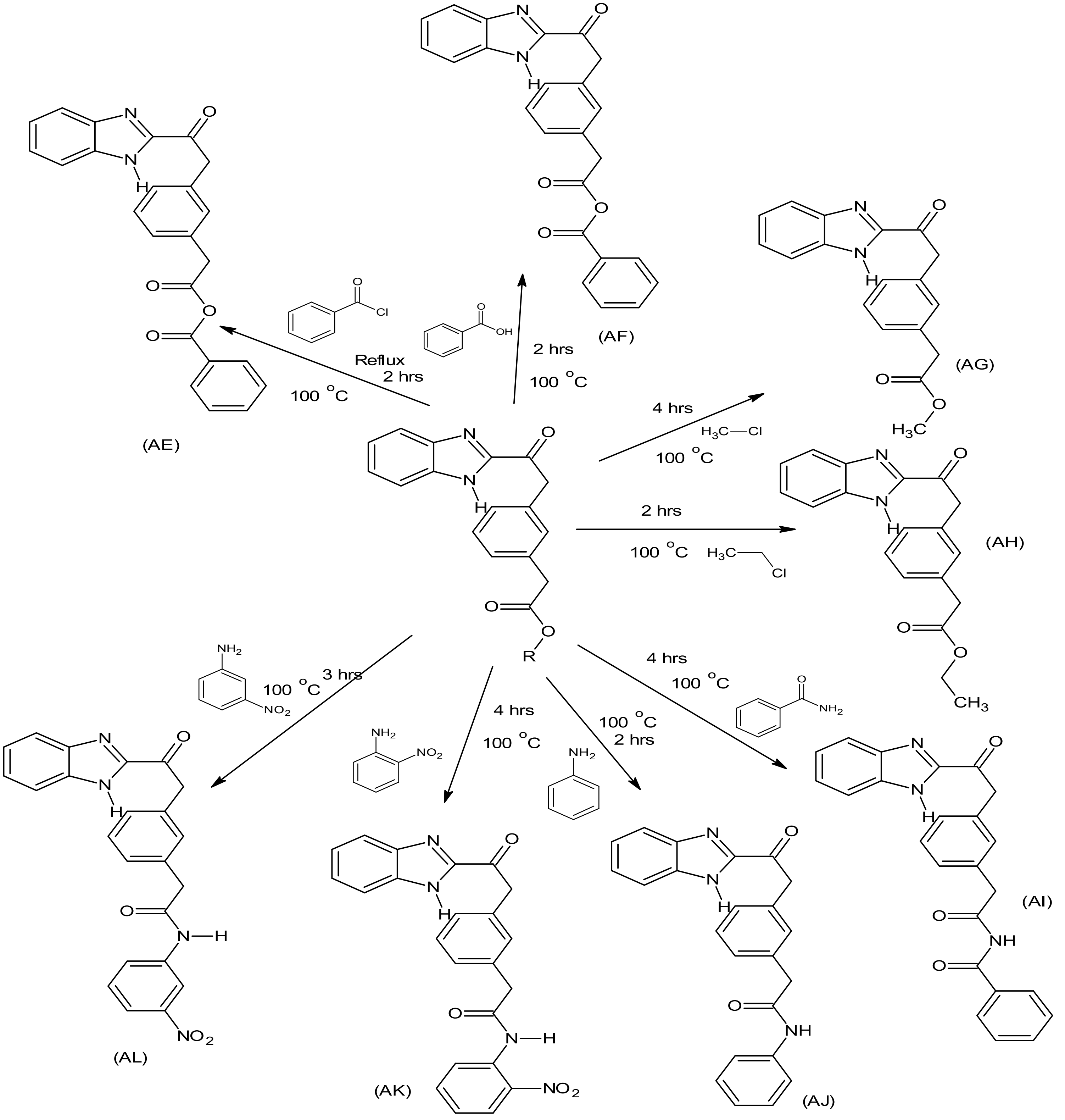
EXPERIMENTAL WORK:

Chemistry: (Scheme IA)



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

(Scheme IB):



Scheme 1B: Synthesis of 3-(2-1H benzimidazole 2yl)-2-oxethyl) phenyl) acetic acid derivatives (AE- AL)

Synthesis of Benzimidazole Derivatives:

Synthesis of Benzimidazole (AA): (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 (AB) : (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. Cool at room temperature; filter the product. Wash with cold water.

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

In a round-bottomed flask take 2gm of 1-(1-H benzimidazol-2-yl) ethanone and 2gm Benzene-1,2-diol and 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-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl)ethanone. Cool at room temperature; filter the product. Wash with cold water.

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

In a round-bottom flask take 2gm of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone and 2ml Glycolic acid. 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 3-(2-[1H benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid Cool at room temperature, filter the product. Wash with cold water. Filter the product.

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

In a round-bottomed flask; take 2gm of {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and 4 ml benzoyl chloride and then heated for 2hr. 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(1H benzimidazol-2-yl)-2-oxoethyl phenyl) acetic benzoic anhydride . Cool at room temperature; filter the product. Wash with cold water.

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

In a round-bottomed flask; take 2gm of {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetic acid and benzoic acid 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 {3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetic benzoic anhydride. Cool at room temperature; filter the product. Wash with cold water.

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

In a round-bottomed flask; take 2 gm of {3-2(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl} acetic acid and chloromethane 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 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-(1*H*-benzimidazol-2-yl)-2-oxoethyl]phenyl}acetate (AH): (Scheme 1B)

In a round-bottomed flask; take 2 gm of {3-2(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl} acetic acid and 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-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl} acetate. Cool at room temperature; filter the product. 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)

In a round-bottomed flask; take 2 gm of {3-2(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl} acetic acid and 2ml 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-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide. Cool at room temperature; filter the product. Wash with cold water.

Synthesis of 2-{3-[2-(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(1-H benzimidazole-2-yl)-2-oxoethyl) phenyl} acetic acid and 2ml 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-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(2-nitrophenyl)acetamide. Cool at room temperature; filter the product. Wash with cold water.

Synthesis of 2-{3-[2-(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(1-H benzimidazole-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-(1-H benzimidazole-2yl)2oxoethyl) 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	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

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

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 NMR (500 MHz) CDCl3 δ ppm: 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); 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 NMR (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 NMR (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 (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 (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 NMR (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 NMR (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 NMR (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 NMR (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 NMR (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 NMR (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 NMR (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 NMR (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:

Synthesized newer benzimidazole derivatives were screened for Anti-convulsant activity. Total 12 compounds (4 Step Products + 8 Benzimidazole Derivatives) were evaluated for their biological screening. The following section describes, in brief the anticonvulsant activity.

Anticonvulsant activity:

The anticonvulsant activity of synthesized compound was determined by screening them against pentylenetetrazole (PTZ) by using sc PTZ model **[12-15]**. The basic principal of Anti-convulsant assay lies in the comparison between the synthesized compounds with the standard phenytoin. It should be concluded by comparing the percentage of protection (%protection), the onset of action in seconds (Sec.), the duration of convulsions, etc. Pentylenetetrazole is used as a negative control in this sc PTZ model. The selection of dose for of standard and negative control was done by referring S.K. Kulkarni book of practical.

PTZ Induced Convulsion Method:

Wistar Rats will be dividing into six groups. Each group contains of six animals (n=6) and treated for 10 days. The first group will be served as control vehicle treating with distilled water and the second group will receive the standard drug **[16-17]**. Phenytoin 100mg/kg is used. The group third will be receiving lower dose (a) of novel substituted benzimidazole derivatives, fourth group will be receiving middle dose (b) of novel substituted benzimidazole derivatives, fifth group will be receiving Higher dose (c) of novel substituted benzimidazole derivatives resp. one's a day for 10 days, on 10th day 60 min after administration of last dose of convulsions were induced in rats by injection of PTZ 85mg/kg to all the groups. Each animal will be observed individually for convulsive behavior for next 30 min **[18]**. In this method we are used; we used 36 Wistar rats and they having body weight around 150-250 gm. In this PTZ Induced Convulsion Method; Wistar rats were divided into 6 groups like Group 1is Vehicle control; Group 2 is Negative control (PTZ 85mg/kg); Group 3 is Standard (Phenytoin 100mg/kg); Group 4 is Novel substituted Benzimidazole derivatives (a) Lower dose; Group 5 is Novel substituted Benzimidazole derivatives (b) Middle dose; Group 6 is Novel substituted Benzimidazole derivatives (c) Higher dose. The results of Anticonvulsant Activity testing of the prepared compounds were shown in **Table 2 and Figure 2**.

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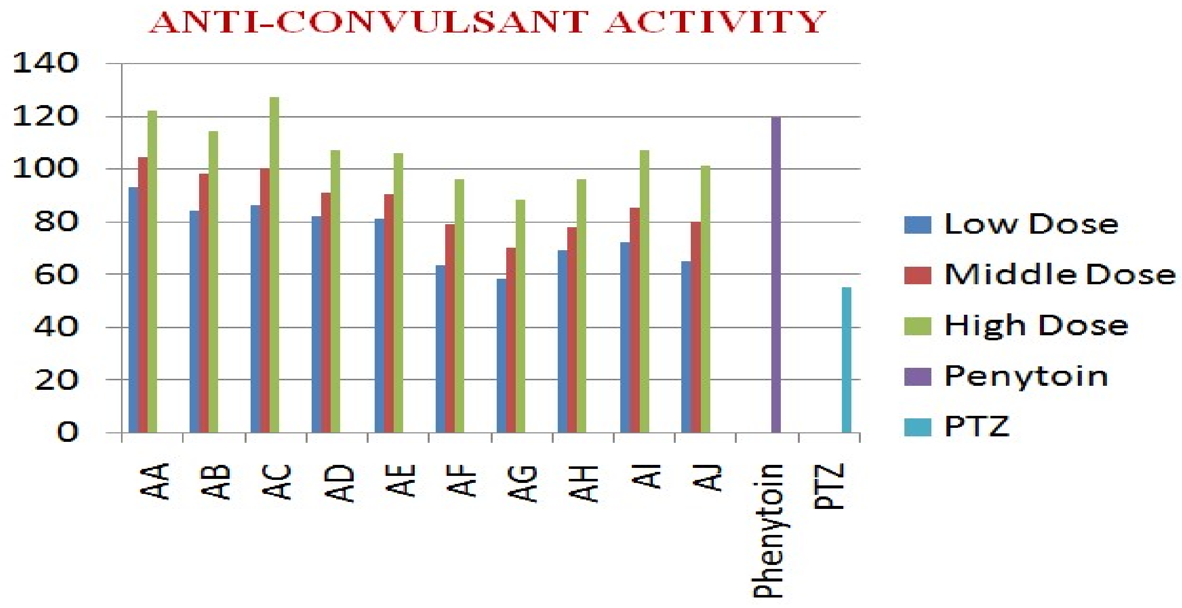

Figure 2: Comparison of Anticonvulsant activity of Benzimidazole Derivatives at different concentrations

RESULT AND DISCUSSION

The syntheses of benzimidazole derivatives from AE to AJ were undertaken as per the **scheme 1B**. The required 3-(2-[1H Benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid (AD) was prepared by mixture. 2gm of 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone and 2ml Glycolic acid reflux for 2hr. After completion of reaction the contents were allowed to cool obtain reaction mixture, the solid product was obtained. 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.

The newly synthesized 3-(2-[1H Benzimidazole-2-yl)-2-oxethyl] phenyl) acetic acid (AD) derivatives were subjected to anticonvulsant screening by using standard model PTZ Induced Convulsion. There is comparison Chart **(Figure 2)** of Anticonvulsant activity of Benzimidazole Derivatives at different concentrations like Low dose; Middle Dose and High Dose Method for their ability to reduce seizure spread **(Table 2)**. Phenytoin was used as standard drugs. Each animal will be observed individually for convulsive behavior for next 30 min. The anticonvulsant data of titled compounds (AA-AL) was summarized in **Table 2**, compounds AA and AC showed protection at maximum dose level of 300 mg/kg and each animal will be observed individually for convulsive behavior for next 30 min. Compound AI and AJ displayed protection at maximum dose level (300 mg/kg) and each animal will be observed individually for convulsive behavior for next 30 min. Compound AK and AL containing 2-Nito Aniline and 3-Nitro Aniline groups, showed protection against induced seizures at lower dose level (30 mg/kg). Compound AH and AG containing Aliphatic group like Methyl and Ethyl groups, showed less protection against induced seizures at lower dose level (30 mg/kg). The results of Anticonvulsant Activity testing of the prepared compounds were shown in **Table 2 and Figure 2**.

Table 2: Anti convulsant result of 3-(2-1H benzimidazole 2yl) 2-oxethyl) phenyl) acetic acid (AD) derivatives

Compounds	Doses (mg/kg)	Onset of Convulsions (sec)	Duration of Convulsions (sec)	Avg. % Protection	Recovery/Death
AA	50	93	148	87.52%	Recovery
	100	104	52		
	200	122	26		
AB	50	84	119	82.63%	Recovery
	100	98	90		
	200	114	46		
AC	50	86	183	84.16%	Recovery
	100	100	103		
	200	127	41		
AD	50	82	139	76.35%	Recovery
	100	91	89		
	200	107	53		
AE	50	81	119	75.63%	Recovery
	100	90	80		
	200	106	66		
AF	50	63	163	66.38%	Recovery
	100	79	101		
	200	96	63		
AG	50	58	142	59.10%	Recovery
	100	70	99		
	200	88	73		
AH	50	69	150	66.10%	Recovery
	100	78	91		
	200	96	52		
AI	50	72	148	71.56%	Recovery
	100	85	84		
	200	107	50		
AJ	50	65	165	67.50%	Recovery
	100	80	89		
	200	101	39		
AK	50	70	172	62.88%	Recovery
	100	75	105		
	200	99	38		
AL	50	58	187	63.57%	Recovery
	100	75	104		
	200	105	46		
Std. Phenytoin	100	119	11	100	Recovery

CONCLUSION

Various benzimidazole derivatives was synthesized by 3-(2-1H benzimidazole 2yl)-2-oxethyl) phenyl) acetic acid (AD). The total 12 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-convulsant was taken by using Wistar rats and it having body weight 150-200 gm. In this research; derivatives had stronger anticonvulsant activity against different types of convulsions. Some of the synthesized compounds were found to have potent anti-convulsant activity. Synthesized compounds exhibited more activity when compared to other benzimidazole derivatives. 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 AA to AL. The compound Benzimidazole (AA), 1-(1H-benzimidazol-2-yl)-2-(3-hydroxyphenyl) ethanone (AC), 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-phenylacetamide (AJ), 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(2-nitrophenyl) acetamide (AK) and 2-{3-[2-(1*H*-benzimidazol-2-yl)-2-oxoethyl] phenyl}-*N*-(3-nitrophenyl) acetamide (AL) were established to be the most potent compound as compared to standard drugs phenytoin.

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