

## RESEARCH ARTICLE

## SYNTHESIS, ANTICONVULSANT ACTIVITY OF SOME NOVEL BENZIMIDAZOLE ACETOHYDRAZIDES

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## ABSTRACT:

A series of some novel benzimidazole aceto-hydrazone derivatives was synthesized and characterized by TLC, MP, elemental analysis, IR, Mass and <sup>1</sup>H NMR spectroscopy. These compounds were screened for anticonvulsant activities by Maximum Electroshock seizure model in male wistar rats and compared with the standard drug phenytoin.

**Keywords:** Benzimidazole, hydrazone, Anticonvulsant, MES

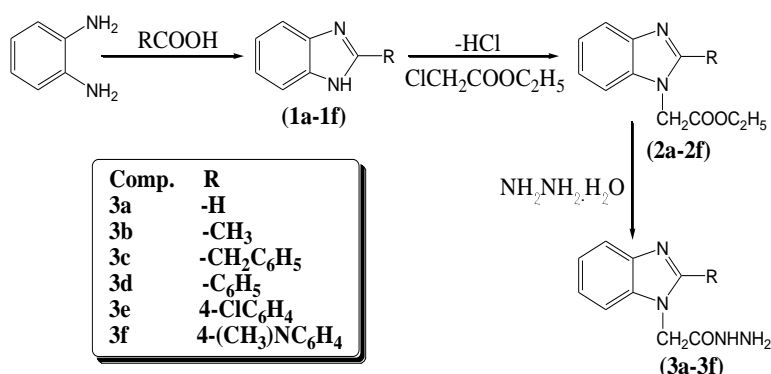
## INTRODUCTION:

Benzimidazole is very useful heterocyclic compound/intermediate for the development of molecules of pharmaceutical or biological interest.<sup>1</sup> Derivatives of benzimidazole possess a wide range of pharmacological activities such as Anti-neoplastic, analgesic, Anthelmintics, Anti-ulcer, anti-inflammatory, Antifungal, Anti-histaminic, Antiviral and Anti-diabetic.<sup>2-7</sup>

Numerous publications have shown that benzimidazole derivatives also have anticonvulsant activity.<sup>8-12</sup>

An attempt has been made in our study to synthesize Benzimidazole aceto-hydrazone derivatives to get as potent anticonvulsant compounds. The newly synthesized Benzimidazole aceto-hydrazone derivatives were evaluated for anticonvulsant activity by the MES method using phenytoin as standard.

## MATERIAL AND METHODS:



Scheme 1 Reaction Protocol for the synthesis of 3a-3f

*1H-benzimidazole (1a)*. A mixture of *o*-phenylenediamine (27 g, 0.25 mol) and formic acid (16 ml, 85 %) was refluxed on a water bath for 2 h. The reaction mixture was cooled and its pH was adjusted to 8 by addition of sodium hydroxide (10 %) solution. The crude product so obtained was filtered, thoroughly washed with ice cold water and dried. The dried product was boiled with decolorising charcoal (2 g) in water (400 ml) for 15 min and filtered while hot. The solution thus obtained was allowed to cool at 10 °C for 30 min, filtered and dried. The completion of reaction was monitored by running TLC.

Yield: 88 %, R<sub>f</sub> value: 0.46, M.p. 170-172 °C. IR (KBr in cm<sup>-1</sup>): 3115 (N-H), 3048 (Ar. C-H), 1362 (C=N). Anal. calcd. for C<sub>7</sub>H<sub>6</sub>N<sub>2</sub> (118.14): C, 71.17; H, 5.12; N, 23.71. Found: C, 71.22; H, 5.16; N, 23.31 %. LCMS m/z: 118.1 (M<sup>+</sup>).

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Similar procedure was used to prepare **1b-1f** by using corresponding aliphatic and aromatic carboxylic acid.

**2-Methyl-1H-benzimidazole (1b)**: Yield: 76 %,  $R_f$  value: 0.39, M.p. 174-176 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3194 (N-H), 3066, 2998 (Ar. C-H), 1386 (C=N). Anal. calcd. for  $\text{C}_8\text{H}_8\text{N}_2$  (132.16): C, 72.70; H, 6.10; N, 21.20 %. Found: C, 72.57; H, 6.04; N, 21.12 %. LCMS m/z: 132.1 (M+).

**2-Benzyl-1H-benzimidazole (1c)**: Yield: 79 %,  $R_f$  value: 0.67, M.p. 192-194 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3023 (N-H), 2964 (Ar. C-H), 2614 (-CH<sub>2</sub>), 1418 (C=N). Anal. calcd. for  $\text{C}_{14}\text{H}_{12}\text{N}_2$  (208.26): C, 80.74; H, 5.81; N, 13.45 %. Found: C, 80.63; H, 5.92; N, 13.61 %. LCMS m/z: 208.1 (M+).

**2-Phenyl-1H-benzimidazole (1d)**: Yield: 81 %,  $R_f$  value: 0.57, M.p. 290-292 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3183 (N-H), 2943 (Ar. C-H), 1427 (C=N). Anal. calcd. for  $\text{C}_{13}\text{H}_{10}\text{N}_2$  (194.23): C, 80.39; H, 5.19; N, 14.42 %. Found: C, 80.51; H, 5.26; N, 14.23 %. LCMS m/z: 195.1 (M+).

**2-(4-Chlorophenyl)-1H-benzimidazole (1e)**: Yield: 87 %,  $R_f$  value: 0.77, M.p. 234-236 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3188 (N-H), 2971 (Ar. C-H), 1412 (C=N), 816 (C-Cl). Anal. calcd. for  $\text{C}_{13}\text{H}_9\text{ClN}_2$  (228.68): C, 68.28; H, 3.97; N, 12.25 %. Found: C, 68.39; H, 4.03; N, 12.36 %. LCMS m/z: 228.3.

**4-Dimethyl aminophenyl-1H-benzimidazole (1f)**: Yield: 83 %,  $R_f$  value: 0.66, M.p. 176-178 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3192 (N-H), 2987 (Ar. C-H), 1428 (C=N), 1293 (C-N). Anal. calcd. for  $\text{C}_{15}\text{H}_{17}\text{N}_3$  (239.32): C, 75.28; H, 7.16; N, 17.56 %. Found: C, 75.34; H, 7.23; N, 17.62 %. LCMS m/z: 239.6 (M+).

**Ethyl-2-(1H-benzimidazol-1-yl)ethanoate (2a)**: A solution of Benzimidazole **1a** (3.54 g, 0.03 mol) in acetone was refluxed with chloroethylacetate (3.69 g, 3.20 ml, 0.03 mol) and potassium carbonate (8.28 g, 0.06 mol) for 4 h. The reaction mixture was filtered while hot and evaporated to dryness. The completion of reaction was monitored by running TLC.

Yield: 74 %,  $R_f$  value: 0.49, M.p. 160-164 °C. IR (KBr in  $\text{cm}^{-1}$ ): 2978 (Ar H str), 1689 (C=O), 1396 (tert. N), 1226 (C-O). Anal. calcd. for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$  (204.23): C, 64.69; H, 5.92; N, 13.72 %. Found: C, 64.82; H, 5.76; N, 13.63 %. LCMS m/z: 205.1 (M+).

Similar procedure was used to prepare **2b-2f** by using corresponding 2-substituted benzimidazoles (**1b-1f**).

**Ethyl-2-(2-methyl-1H-benzimidazol-1-yl)ethanoate (2b)**: Yield: 79 %,  $R_f$  value: 0.68, M.p. 80-82 °C. IR (KBr in  $\text{cm}^{-1}$ ): 2998 (Ar H str), 1692 (C=O), 1387 (tert. N), 1248 (C-O). Anal. calcd. for  $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}$  (309.37): C, 66.00; H, 6.19; N, 22.64 %. Found: C, 65.91; H, 6.24; N, 22.55 %. LCMS m/z: 309.2 (M+).

**Ethyl-2-(2-benzyl-1H-benzimidazol-1-yl)ethanoate (2c)**: Yield: 83 %,  $R_f$  value: 0.49, M.p. 92-96 °C. IR (KBr in  $\text{cm}^{-1}$ ): 2974 (Ar H str), 1678 (C=O), 1392 (tert. N), 1253 (C-O). Anal. calcd. for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$  (294.35): C, 73.45; H, 6.16; N, 9.52 %. Found: C, 73.61; H, 6.19; N, 9.67 %. LCMS m/z: 294.14 (M+).

**Ethyl-2-(2-phenyl-1H-benzimidazol-1-yl)ethanoate (2d)**: Yield: 81 %,  $R_f$  value: 0.69, M.p. 74-78 °C. IR (KBr in  $\text{cm}^{-1}$ ): 2963 (Ar H str), 1689 (C=O), 1374 (tert. N), 1265

(C-O). Anal. calcd. for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$  (280.32): C, 72.84; H, 5.75; N, 9.99 %. Found: C, 72.79; H, 5.81; N, 9.79 %. LCMS m/z: 280.1 (M+).

**Ethyl-2-(2-(4-chloro)phenyl-1H-benzimidazol-1-yl)ethanoate (2e)**: Yield: 67 %,  $R_f$  value: 0.53, M.p. 88-90 °C. IR (KBr in  $\text{cm}^{-1}$ ): 2943 (Ar H str), 1678 (C=O), 1381 (tert. N), 1272 (C-O), 8-24 (C-Cl). Anal. calcd. for  $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2$  (314.77): C, 64.87; H, 4.80; N, 8.90 %. Found: C, 64.92; H, 4.89; N, 8.78 %. LCMS m/z: 314.1 (M+).

**Ethyl 2-(2-(4-dimethyl amino)phenyl-1H-benzimidazol-1-yl)ethanoate (2f)**: Yield: 88 %,  $R_f$  value: 0.76, M.p. 102-106 °C. IR (KBr in  $\text{cm}^{-1}$ ): <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): . Anal. calcd. for  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_2$  (323.39): C, 70.57; H, 6.55; N, 12.99 %. Found: C, 70.72; H, 6.61; N, 12.93 %. LCMS m/z: 323.2 (M+).

**2-(1H-Benzimidazol-1-yl) acetohydrazide (3a)**: A mixture of Ethyl-2-(1H-benzimidazol-1-yl) ethanoate **2a** (2.04 g, 0.01 mol) and hydrazine hydrate (0.75 g, 0.73 ml, 0.015 mol) in ethanol (25 ml) was refluxed on a water bath for 3 h. The reaction mixture was cooled, made acidic to get precipitate. The separated solid was filtered and purified by recrystallisation from ethanol. The completion of reaction was monitored by running TLC. Yield: 73 %,  $R_f$  value: 0.65, M.p. 180-182 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3362 (NH), 2972 (Ar C-H str), 1689 (C=O), 1391 (tert. N). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 7.92 (s, 1H, Ar-CH), 7.23-7.73 (m, 4H, Ar-CH), 6.34 (s, 1H, NH), 5.29 (s, 2H, CH<sub>2</sub>), 3.39-3.44 (s, 2H, NH<sub>2</sub>). Anal. calcd. for  $\text{C}_9\text{H}_{10}\text{N}_4\text{O}$  (190.2): C, 56.83; H, 5.30; N, 29.46 %. Found: C, 56.63; H, 5.23; N, 29.29 %. LCMS m/z: 190.1 (M+).

Compounds (**2b-2f**) were used to prepare **3b-3f** by using similar procedure.

**2-(2-Methyl-1H-benzimidazol-1-yl)acetohydrazide (3b)**: Yield: 79 %,  $R_f$  value: 0.29, M.p. 240-242 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3455 (NH), 3138 (NH), 3051, 2905 (Ar CH str), 1635 (C=O), 1510 (C=N), 1323 (tert. N), 1290 (C-N). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 7.14-7.59 (m, 4H, Ar-CH), 6.28 (s, 1H, NH), 5.23 (s, 2H, CH<sub>2</sub>), 3.29-3.31 (s, 2H, NH<sub>2</sub>), 2.58 (s, 3H, CH<sub>3</sub>). Anal. calcd. For  $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}$  (204.23): C, 58.81; H, 5.92; N, 27.43; O, 7.83 %. Found: C, 58.81; H, 5.87; N, 27.53; O, 7.69 %. LCMS m/z: 204.6 (M+).

**2-(2-Benzyl-1H-benzimidazol-1-yl)acetohydrazide (3c)**: Yield: 82 %,  $R_f$  value: 0.36, M.p. 184-186 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3342 (-NH), 2894 (Ar CH str), 1652 (C=O), 1509 (C=N), 1328 (tert. N), 1310 (C-N). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 7.09-7.64 (m, 9H, Ar-CH), 6.47 (s, 1H, NH), 5.16 (s, 2H, CH<sub>2</sub>), 3.94 (s, 2H, CH<sub>2</sub>), 3.29-3.31 (s, 2H, NH<sub>2</sub>). Anal. calcd. for  $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}$  (280.32): C, 68.55; H, 5.75; N, 19.99 %. Found: C, 68.73; H, 5.82; N, 19.86 %. LCMS m/z: 280.1 (M+).

**2-(2-Phenyl-1H-benzimidazol-1-yl)acetohydrazide (3d)**: Yield: 79 %,  $R_f$  value: 0.36, M.p. 294-298 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3358 (NH), 3051, 2961 (Ar H str), 1696 (C=O), 1380 (tert. N). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 7.11-7.86 (m, 9H, Ar-CH), 6.29 (s, 1H, NH), 5.27 (s, 2H, CH<sub>2</sub>), 3.08 (s, 2H, NH<sub>2</sub>). Anal. calcd. for  $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}$  (266.3): C, 67.65; H, 5.30; N, 21.04 %. Found: C, 67.75; H, 5.49; N, 21.14 %. LCMS m/z: 266.1 (M+).

2-(2-(4-Chloro) phenyl-1H-benzimidazol-1-yl)acetohydrazide (**3e**): Yield: 74 %,  $R_f$  value: 0.29, M.p. 252-256 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3369 (NH), 2914 (Ar H str), 1699 (C=O), 1375 (tert. N), 733 (C-Cl).  $^1\text{H-NMR}$  (DMSO  $\delta$  ppm): 7.03-7.68 (m, 8H, Ar-CH), 6.34 (s, 1H, NH), 5.19 (s, 2H,  $\text{CH}_2$ ), 3.13 (s, 2H,  $\text{NH}_2$ ). Anal. calcd. for  $\text{C}_{15}\text{H}_{13}\text{ClN}_4\text{O}$  (300.74): C, 59.91; H, 4.36; Cl, 11.79; N, 18.63 %. Found: C, 59.82; H, 4.24; N, 18.48 %. LCMS  $m/z$ : 300.1(M+).

2-(2-(4-Dimethyl amino) phenyl-1H-benzimidazol-1-yl)acetohydrazide (**3f**): Yield: 85 %,  $R_f$  value: 0.73, M.p. 204-206 °C. IR (KBr in  $\text{cm}^{-1}$ ): 3380 (NH), 2924 (Ar H str), 1681 (C=O), 1384 (tert. N).  $^1\text{H-NMR}$  (DMSO  $\delta$  ppm): 7.01-7.61 (m, 8H, Ar-CH), 6.42 (s, 1H, NH), 5.28 (s, 2H,  $\text{CH}_2$ ), 3.18 (s, 2H,  $\text{NH}_2$ ), 2.89 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ). Anal. calcd. for  $\text{C}_{17}\text{H}_{19}\text{N}_5\text{O}$  (309.37): C, 66.00; H, 6.19; N, 22.64 %. Found: C, 66.11; H, 6.12; N, 22.52 %. LCMS  $m/z$ : 309.2 (M+).

### Pharmacology

Animals: Male wistar rats procured from BN College of Pharmacy, Udaipur (150-200 g) were used in the present study. The animals were housed in colony cages, conditions of constant temperature ( $22 \pm 2$  °C), a 12 h light/dark schedule, and allowed free access to standard diet and tap water except during the experiment. The animals were allowed to habituate to the laboratory environment for 24 h before the experiments were initiated.

All the experimental procedures were carried out in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. The protocol of the study was approved by Institutional Animal Ethical Committee.

### Anticonvulsant activity

Maximal Electroshock Seizure Model (MES): Maximal electroshock seizure model was used in the present study to evaluate the anticonvulsant activity of the compounds on male wistar rats. Seizures were induced in rats by delivering electroshock of 150 mA for 0.2 sec by means of an electro-convulsimeter through a pair of ear clip electrodes. The test compounds (100 mg/kg) were administered by oral route in the form of solution (The compounds were dissolved in 1% sodium carboxymethyl cellulose), 30 min before the maximal electroshock seizure (MES) test.<sup>13</sup> Phenytoin (100 mg/kg) was used as a standard drug. The reduction in time or abolition of tonic extensor phase of MES- convulsions was noted.<sup>14</sup> The data are calculated & expressed as mean extensor phase duration in sec. followed by % protection and % potency in comparison with the standard as shown in Table 1 using the following formula:

$$\% \text{ Protection} = (\text{MEPD}_{\text{nc}} - \text{MEPD}_{\text{sample}} / \text{MEPD}) \times 100$$

Where  $\text{MEPD}_{\text{nc}}$  is the mean extensor phase duration of normal control in sec. and  $\text{MEPD}$  is the mean extensor phase duration of sample or standard in sec.

$$\% \text{ Potency} = (\text{MEPD}_{\text{nc}} - \text{MEPD} / \text{MEPD}_{\text{nc}} - \text{MEPD}_{\text{std}}) \times 100$$

Where  $\text{MEPD}_{\text{std}}$  is the mean extensor phase duration of standard control in sec.

### Statistical analysis

The results are expressed as the mean  $\pm$  SEM per group and the data were analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as post hoc test.  $p$  value  $< 0.05$  was considered statistically significant.

**Table 1** Anticonvulsant activity of title compounds

Compound Nos.	Dose (mg/kg)	Extensor phase duration (Sec.)	Protection (%)	Potency (%)
Control	-	18.4 $\pm$ 0.927	-	-
Phenytoin	100	7.6 $\pm$ 0.509**	58.69	100
<b>3a</b>	100	14.8 $\pm$ 0.860**	19.56	33.33
<b>3b</b>	100	13.0 $\pm$ 0.447**	29.35	50.00
<b>3c</b>	100	12.6 $\pm$ 0.678**	31.52	53.70
<b>3d</b>	100	17.6 $\pm$ 0.812 <sup>ns</sup>	4.35	7.41
<b>3e</b>	100	15.6 $\pm$ 1.116 <sup>ns</sup>	15.22	25.92
<b>3f</b>	100	15.2 $\pm$ 0.374*	17.39	29.63

Data analyzed by one way ANOVA followed by Dunnett's test, (n = 6), \* $P < 0.05$ , \*\* $P < 0.01$  significant from control; ns, not significant.

### RESULTS & DISCUSSION:

All title compounds were synthesized as per Scheme 1 and their structure was confirmed by IR,  $^1\text{H}$  NMR, LCMS, and elemental analysis. The anticonvulsant activity was determined by MES method on wistar rats using phenytoin as standard drug (Table 1). Compounds **3a**, **3b**, **3c** and **3f** showed significant protection against

maximum electroshock seizures. Compounds **3b** and **3c** exhibited more potent activity than that of other compounds. Compound **3c** was found to be most potent among all the compounds.

### ACKNOWLEDGEMENTS:

The authors are thankful to the BN College of Pharmacy, Udaipur, India for providing laboratory facility for carrying out research work. The authors also deeply appreciate the Punjab University, Punjab, India for providing the spectral studies.

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