

## Synthesis, anticonvulsant activity and comparative QSAR study of some novel 1,2,5-trisubstituted benzimidazole derivatives

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### Abstract

In view of obtaining some potential anticonvulsant compounds we have synthesized a series of 1,2,5-trisubstituted benzimidazoles derivatives (6a-6j, 7a-7j, 8a-8j). The results of QSAR investigation and the study of various physicochemical properties indicates that the change in linker at position one (R<sub>1</sub>) does not change the activity of the synthesized compounds and optimum chain length at position two (R<sub>2</sub>) is responsible for the anti-convulsant activity. The results also showed that the synthesized compounds with electron withdrawing group at position five (R<sub>3</sub>) shows better anti-convulsant activity as predicted by QSAR studies.

**Keywords:** substituted benzimidazoles; synthesis; anti-convulsant activity; QSAR

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### Introduction

Substituted imidazoles are reported to possess a number of significant and diverse biological activities including antihistaminic, analgesic (Hunger et al. 1957), anti ulcer (Lindberg et al. 1986), antiviral (Galvao et al. 1977, Pandey et al. 2004), antihelmintic (Kholer 2001), anti-hypertensive (Rober et al. 1992, Levin et al. 1994, Bali et al. 2005), anti inflammatory and gout curing properties. A large number of therapeutic agents have been synthesized from imidazole nucleus which has demonstrated considerable potency (Hamor 1986, Rayemakers et al. 1988, Mishra et al. 1997, Saggu et al. 2002). As a part of our programme of synthesis and biological evaluation of novel imidazole derivatives, it was decided to synthesize some novel derivatives of imidazole by coupling them with  $\alpha$ ,  $\beta$  and  $\gamma$  picoline and evaluate them for anti-convulsant activity.

An extrathermodynamic approach in the analysis of quantitative structure activity relationships (QSAR) has been most widely and effectively used for theoretical drug design (Arpacı 2001). This method has also been called the Hansch approach and it assumes that the potency of a certain biological activity exerted by a series of congeneric compounds can be expressed in terms of a function of various physicochemical (electronic, steric and hydrophobic) effects.

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During the last 20 years quantitative structure activity relationship (QSAR) models have gained an extensive recognition in physical, organic, analytical, pharmaceutical and medicinal chemistry. The success of the QSAR approach can be explained by the insight offered based on the structural determination of chemical properties, and the possibility to estimate the properties of new chemical compounds without the need to synthesize and test them among the homologous series. In light of the above and in continuation of our efforts in the synthesis and QSAR studies of biologically active molecules, we hereby report the synthesis, anticonvulsant evaluation and QSAR studies of 1,2,5-trisubstituted benzimidazoles.

## Materials and Methods

All the chemicals and reagents used were of Analar grade and were procured from M/s S.D. Fine Ltd. and M/s Otto Ltd. All the solutions used for the synthesis were prepared by using distilled water. Melting points were determined by using open capillary method and are uncorrected. The IR spectra of compounds were recorded on Perkin Elmer Infra Red Spectrophotometer in KBr disc and absorption bands are expressed in  $\text{cm}^{-1}$ . NMR spectra were recorded on Bruker AC 300F (300 MHz) spectrometer using TMS as internal standard. Reactions were monitored by thin layer chromatography on pre-coated plates using different solvent systems. The purity of synthesized compounds was ascertained by TLC using iodine vapours as visualizing agents.

### Chemistry

*2-substituted Benzimidazoles 3a-3e:* *Ortho* phenylene diamine (1) (0.25 M) and appropriately substituted organic acids (2a-2e) were reacted by heating under reflux for 6-13 h. The reaction mixture was cooled and basified to a pH of 7-8. The crude product so obtained (3a-3e) was dissolved in 95% ethanol and was suitably digested with activated charcoal. The boiling water was then added to the filtrate till the appearance of slight turbidity. The solution was made clear by adding a few drops of ethanol and kept for recrystallization. Needle shaped crystals were obtained.

*5-nitro-2-substituted Benzimidazoles (3f-3j):* Concentrated nitric acid (7.5 mL) was placed in 3-necked RBF fitted with a mechanical stirrer. The flask was immersed in ice cold water and concentrated sulphuric acid (7.5 ml) was added slowly down the condenser with slow stirring. Afterwards, 2-substituted benzimidazole derivative (3a-3e) was added in portion over a period of 1h at such a rate that the temperature did not exceed  $35^{\circ}\text{C}$ . After continuous stirring for 10-13 h, the reaction mixture was poured very slowly over crushed ice with vigorous stirring. The product (3f-3j) was filtered and washed with cold water.

*Bromo methyl Pyridine (5):* Reaction of 2-methyl, 3-methyl, 4-methyl pyridine (4) (0.25 M) with N-bromo succinamide (NBS) (0.25 M) and benzoyl peroxide (0.25 M) in  $\text{CCl}_4$  for 8.3 h yielded the product (5), which was filtered and cooled overnight at room temperature.

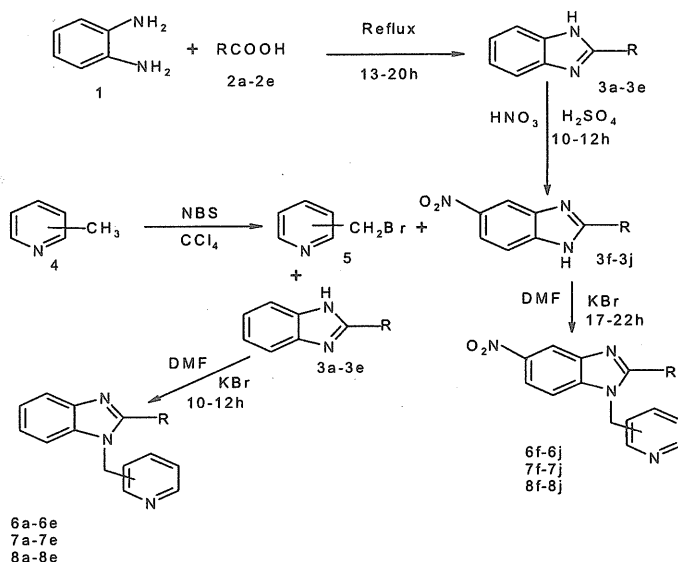
### Title compounds

*(6a-6j):* Appropriately substituted benzimidazole (3) (0.1 M) was dissolved in Dimethyl formamide (DMF) and 2.5 g potassium carbonate were stirred vigorously at room temperature on a mechanical stirrer for 1 h. To the reaction mixture, a suspension of 2-bromomethyl pyridine (5) (0.1M) in DMF was added dropwise with stirring for 1h. The reaction mixture was allowed to proceed further for 10-23 h and the excess solvent was removed under vacuum. The residue thus obtained treated with 20 ml dilute HCl and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous

sodium sulphate. The solvent was evaporated under reduced pressure to afford the product (6) as a brownish amorphous solid (Scheme 1).

(7a-7j): Appropriately substituted benzimidazole (3) (0.1 M) was dissolved in Dimethyl formamide (DMF) and 2.5 g potassium carbonate were stirred vigorously at room temperature on a mechanical stirrer for 1 h. To the reaction mixture, a suspension of 3-bromomethyl pyridine (5) (0.1M) in DMF was added dropwise with stirring for 1h. The reaction mixture was allowed to proceed further for 10-23 h and the excess solvent was removed under vacuum. The residue thus obtained treated with 20 ml dilute HCl and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the product (7) as a brownish amorphous solid (Scheme 1).

(8a-8j): Appropriately substituted benzimidazole (3) (0.1 M) was dissolved in Dimethyl formamide (DMF) and 2.5 g potassium carbonate were stirred vigorously at room temperature on a mechanical stirrer for 1 h. To the reaction mixture, a suspension of 4-bromomethyl pyridine (5) (0.1M) in DMF was added dropwise with stirring for 1h. The reaction mixture was allowed to proceed further for 10-23 h and the excess solvent was removed under vacuum. The residue thus obtained treated with 20 ml dilute HCl and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the product (8) as a brownish amorphous solid (Scheme 1).



Scheme 1. Synthesis of substituted benzimidazoles

Physical, analytical data and physicochemical properties of synthesized compounds are summarized in Table 1, Table 2 and Table 3, respectively.

Table 1. Physical and analytical data of synthesized compounds

Comp. No.	R	M.P. (°C)	Yield (%)	Molecular Formula	Molecular Weight	R <sub>f</sub> value*
6a	-H	82	53%	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub>	210	0.8
6b	-CH <sub>3</sub>	168	61%	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub>	224	0.81
6c	-C <sub>2</sub> H <sub>5</sub>	104	48%	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub>	238	0.89
6d	-C <sub>3</sub> H <sub>7</sub>	134	51%	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub>	252	0.92
6e	-C <sub>4</sub> H <sub>9</sub>	110	38%	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub>	266	0.69
6f	-H	104	60%	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub>	255	0.7
6g	-CH <sub>3</sub>	152	59%	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub>	269	0.9
6h	-C <sub>2</sub> H <sub>5</sub>	148	53%	C <sub>15</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	283	0.84
6i	-C <sub>3</sub> H <sub>7</sub>	58	52%	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	297	0.9
6j	-C <sub>4</sub> H <sub>9</sub>	66	51%	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>	311	0.8
7a	-H	130	57%	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub>	210	0.7
7b	-CH <sub>3</sub>	116	61%	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub>	224	0.84
7c	-C <sub>2</sub> H <sub>5</sub>	76	48%	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub>	238	0.89
7d	-C <sub>3</sub> H <sub>7</sub>	88	51%	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub>	252	0.89
7e	-C <sub>4</sub> H <sub>9</sub>	70	38%	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub>	266	0.91
7f	-H	98	50%	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub>	255	0.67
7g	-CH <sub>3</sub>	74	59%	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub>	269	0.92
7h	-C <sub>2</sub> H <sub>5</sub>	54	53%	C <sub>15</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	283	0.84
7i	-C <sub>3</sub> H <sub>7</sub>	72	52%	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	297	0.9
7j	-C <sub>4</sub> H <sub>9</sub>	52	51%	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>	311	0.75
8a	-H	50	59%	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub>	210	0.72
8b	-CH <sub>3</sub>	78	60%	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub>	224	0.8
8c	-C <sub>2</sub> H <sub>5</sub>	74	58%	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub>	238	0.85
8d	-C <sub>3</sub> H <sub>7</sub>	79	59%	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub>	252	0.87
8e	-C <sub>4</sub> H <sub>9</sub>	108	51%	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub>	266	0.9
8f	-H	68	55%	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub>	255	0.6
8g	-CH <sub>3</sub>	76	57%	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub>	269	0.93
8h	-C <sub>2</sub> H <sub>5</sub>	58	60%	C <sub>15</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	283	0.84
8i	-C <sub>3</sub> H <sub>7</sub>	60	57%	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	297	0.88
8j	-C <sub>4</sub> H <sub>9</sub>	64	54%	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>	311	0.75

\*Solvent System: Chloroform: Methanol (97:3)

Table 2. Spectral data of Synthesized Compounds

Compound	IR (KBr) cm <sup>-1</sup>	<sup>1</sup> H NMR (CDCl <sub>3</sub> )
6a	3097 (Aromatic C-H Stretch); 2944 (Aliphatic C-H Stretch); 1933, 1896 (Di-substituted benzene); 1703 (C=N Stretch); 1587 (C=C Stretch); 1458 (CH <sub>2</sub> bending); 1245 (C-N Stretch); 746 (Ortho disubstituted benzene (oop))	δ = 8.90 (1H, s, -CH Imidazole); 8.31 (1H, d, -CH at α to nitrogen in pyridine ring); 4.76 (2H, s, -CH <sub>2</sub> linker); 6.9-7.74 (7H, m, Aromatic protons)

<b>6b</b>	3114 (Aromatic C-H Stretch); 2980 (Aliphatic C-H Stretch); 1918, 1876 (Di-substituted benzene); 1655 (C=N Stretch); 1555 (C=C Stretch); 1450 (CH <sub>2</sub> bending); 1350.9(CH <sub>3</sub> bending); 1270 (C-N Stretch); 734 (oop)	$\delta = 8.31$ (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.76 (2H, s, -CH <sub>2</sub> linker); 7.0-7.64 (7H, m, Aromatic protons); 2.66 (s, 3H, -CH <sub>3</sub> )
<b>6c</b>	3053 (Aromatic C-H Stretch); 2973 (Aliphatic C-H Stretch); 1919, 1771 (Di-Substituted benzene); 1621 (C=N Stretch); 1588 (C=C Stretch); 1456 (CH <sub>2</sub> bending); 1378 (CH <sub>3</sub> bending); 1270 (C-N Stretch); 741 (oop)	$\delta = 8.03$ (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.74 (2H, s, -CH <sub>2</sub> linker); 6.8-7.55 (7H, m, Aromatic protons); 2.97 (q, 2H, -CH <sub>2</sub> ), 1.43 (t, 3H, -CH <sub>3</sub> )
<b>6d</b>	3050 (Aromatic C-H Stretch); 2928 (Aliphatic C-H Stretch); 1923, 1771 (Di-Substituted benzene); 1622 (C=N Stretch); 1537 (C=C Stretch); 1452 (CH <sub>2</sub> Bending); 1315(CH <sub>3</sub> bending); 1260 (C-N Stretch); 747 (oop)	$\delta = 8.60$ (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.76 (2H, s, -CH <sub>2</sub> linker); 6.70-7.54 (7H, m, Aromatic protons); 2.92 (t, 2H, -CH <sub>2</sub> ), 1.88 (m, 2H, -CH <sub>2</sub> ), 1.04 (t, 3H, -CH <sub>3</sub> )
<b>6e</b>	3140 (Aromatic C-H Stretch); 2928 (Aliphatic C-H Stretch); 1929, 1889 (Di-substituted benzene); 1622 (C=N Stretch); 1579 (C=C Stretch); 1417 (CH <sub>2</sub> Bending); 1311(CH <sub>3</sub> bending); 1271 (C-N Stretch); 745 (oop)	$\delta = 8.60$ (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.77 (2H, s, -CH <sub>2</sub> linker); 6.82-7.57 (7H, m, Aromatic protons); 2.97 (t, 2H, -CH <sub>2</sub> ), 1.85 (m, 2H, -CH <sub>2</sub> ), 1.43 (m, 2H, -CH <sub>2</sub> ), 0.91 (t, 3H, -CH <sub>3</sub> )
<b>6f</b>	3103 (Aromatic C-H Stretch); 2815 (Aliphatic C-H Stretch); 1901, 1773 (Di-substituted benzene); 1623 (C=N Stretch); 1591 (C=C Stretch); 1513, 1480 (-N=O aromatic stretch); 1345 (C-N Stretch); 741 (oop)	$\delta = 8.60$ (1H, s, -CH imidazole), 8.16 (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 7.90 (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.72 (2H, s, -CH <sub>2</sub> linker); 6.32-7.60 (5H, m, Aromatic protons)
<b>6g</b>	3107 (Aromatic C-H Stretch); 2919 (Aliphatic C-H Stretch); 1901, 1706 (Di-Substituted benzene); 1630 (C=N Stretch); 1592 (C=C Stretch); 1512, 1490 (-N=O aromatic stretch); 1418 (CH <sub>2</sub> bending); 1383 (CH <sub>3</sub> bending); 1270 (C-N Stretch); 738 (oop)	$\delta = 8.50$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.10 (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.2 (2H, s, -CH <sub>2</sub> linker); 6.30-7.44 (5H, m, Aromatic protons); 2.95 (3H, s, -CH <sub>3</sub> )
<b>6h</b>	3095 (Aromatic C-H Stretch); 2982 (Aliphatic C-H Stretch); 1895, 1755 (Di-Substituted benzene); 1671 (C=N Stretch); 1591 (C=C Stretch); 1517, 1490 (-N=O aromatic stretch); 1474 (CH <sub>3</sub> bending); 1490 (CH <sub>2</sub> bending); 1274 (C-N Stretch); 737 (oop)	$\delta = 8.45$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.12 (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.55 (2H, s, -CH <sub>2</sub> linker); 6.09-7.57 (5H, m, Aromatic protons); 2.90 (2H, q, -CH <sub>2</sub> ); 1.45 (3H, t, -CH <sub>3</sub> )
<b>6i</b>	3102 (Aromatic C-H Stretch); 2965 (Aliphatic C-H Stretch); 1912, 1772 (Di-substituted benzene); 1628 (C=N Stretch); 1595 (C=C Stretch); 1517, 1441 (-N=O stretch); 1440 (CH <sub>2</sub> bending); 1384 (CH <sub>3</sub> Bending); 1265(C-N-stretch); 738 (oop)	$\delta = 8.45$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.10 (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.85 (2H, s, -CH <sub>2</sub> linker); 6.1-7.58 (5H, m, Aromatic protons); 2.69 (2H, q, -CH <sub>2</sub> ); 1.94 (2H, m, -CH <sub>2</sub> ); 1.03 (3H, t, -CH <sub>3</sub> )
<b>6j</b>	3140 (Aromatic C-H Stretch); 2960 (Aliphatic C-H Stretch); 1889, 1363 (Di-substituted benzene); 1672 (C=N Stretch); 1594 (C=C Stretch); 1513, 1441 (NO <sub>2</sub> Stretch); 1470 (CH <sub>2</sub> bending); 1310 (CH <sub>3</sub> Bending); 1223(C-N stretch); 737 (oop)	$\delta = 8.47$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.15 (1H, d, -CH at $\alpha$ to nitrogen in pyridine ring); 4.1 (2H, s, -CH <sub>2</sub> linker); 5.9-7.57 (5H, m, Aromatic protons); 2.94 (2H, q, -CH <sub>2</sub> ); 2.45 (2H, m, -CH <sub>2</sub> ); 1.98 (2H, m, -CH <sub>2</sub> ); 1.05 (3H, t, -CH <sub>3</sub> )
<b>7a</b>	3114 (Aromatic C-H Stretch); 2941 (Aliphatic C-H Stretch); 1932, 1895 (Di-substituted benzene); 1675 (C=N Stretch); 1585 (C=C Stretch); 1458 (CH <sub>2</sub> bending); 1245 (C-N Stretch); 746 (Ortho disubstituted benzene (oop))	$\delta = 8.37$ (1H, s, -CH Imidazole); 7.68 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.2 (2H, s, -CH <sub>2</sub> linker); 6.51-7.0 (6H, m, Aromatic protons)
<b>7b</b>	3060 (Aromatic C-H Stretch); 2990 (Aliphatic C-H Stretch); 1919, 1773 (Di-substituted benzene); 1622 (C=N Stretch); 1554 (C=C Stretch); 1448 (CH <sub>2</sub> bending); 1350 (CH <sub>3</sub> bending); 1268 (C-N Stretch); 734 (oop)	$\delta = 8.30$ (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.41 (2H, s, -CH <sub>2</sub> linker); 6.7-7.57 (6H, m, Aromatic protons); 2.8 (s, 3H, -CH <sub>3</sub> )

7c	3079 (Aromatic C-H Stretch); 2915 (Aliphatic C-H Stretch); 1927, 1769 (Di-Substituted benzene); 1618 (C=N Stretch); 1570 (C=C Stretch); 1430 (CH <sub>2</sub> Bending); 1310(CH <sub>3</sub> bending); 1250 (C-N Stretch); 760 (oop)	$\delta$ = 8.30 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 3.80 (2H, s, -CH <sub>2</sub> linker); 7.1-7.57 (6H, m, Aromatic protons); 2.77 (q, 2H, -CH <sub>2</sub> ), 1.42 (t, 3H, -CH <sub>3</sub> )
7d	3050 (Aromatic C-H Stretch); 2928 (Aliphatic C-H Stretch); 1929, 1774 (Di-Substituted benzene); 1621 (C=N Stretch); 1589 (C=C Stretch); 1408 (CH <sub>2</sub> Bending); 1323(CH <sub>3</sub> bending); 1170 (C-N Stretch); 742 (oop)	$\delta$ = 8.34 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.1 (2H, s, -CH <sub>2</sub> linker); 7.03-7.53 (6H, m, Aromatic protons); 2.90 (t, 2H, -CH <sub>2</sub> ), 2.37 (m, 2H, -CH <sub>2</sub> ), 1.09 (t, 3H, -CH <sub>3</sub> )
7e	3050 (Aromatic C-H Stretch); 2815 (Aliphatic C-H Stretch); 1928, 1775 (Di-substituted benzene); 1622 (C=N Stretch); 1588 (C=C Stretch); 1453 (CH <sub>2</sub> Bending); 1311(CH <sub>3</sub> bending); 1272 (C-N Stretch); 742 (oop)	$\delta$ = 8.30 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.2 (2H, s, -CH <sub>2</sub> linker); 6.9-7.55 (6H, m Aromatic protons); 2.90 (t, 2H, -CH <sub>2</sub> ), 2.78 (m, 2H, -CH <sub>2</sub> ), 1.85 (m, 2H, -CH <sub>2</sub> ), 1.1 (t, 3H, -CH <sub>3</sub> )
7f	3097 (Aromatic C-H Stretch); 2819 (Aliphatic C-H Stretch); 1901, 1773 (Di-substituted benzene); 1626 (C=N Stretch); 1512 (C=C Stretch); 1505, 1447 (-N=O aromatic stretch); 1125 (C-N Stretch); 734 (oop)	$\delta$ = 8.90 (1H, s, -CH imidazole), 8.30 (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.68 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.10 (2H, s, -CH <sub>2</sub> linker); 6.80-7.90 (4H, m, Aromatic protons)
7g	3073 (Aromatic C-H Stretch); 2955 (Aliphatic C-H Stretch); 1901, 1706 (Di-Substituted benzene); 1700 (C=N Stretch); 1539 (C=C Stretch); 1695, 1590 (-N=O aromatic stretch); 1418 (CH <sub>2</sub> bending); 1393 (CH <sub>3</sub> bending); 1191 (C-N Stretch); 641 (oop)	$\delta$ = 8.60 (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.32 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.0 (2H, s, -CH <sub>2</sub> linker); 6.6-7.80 (4H, m, Aromatic protons); 2.89 (3H, s, -CH <sub>3</sub> )
7h	3085 (Aromatic C-H Stretch); 2984 (Aliphatic C-H Stretch); 1901, 1706 (Di-Substituted benzene); 1774 (C=N Stretch); 1516 (C=C Stretch); 1597, 1440 (-N=O aromatic stretch); 1423 (CH <sub>3</sub> bending); 1375 (CH <sub>2</sub> bending); 1191 (C-N Stretch); 640 (oop)	$\delta$ = 8.53 (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.21 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.23 (2H, s, -CH <sub>2</sub> linker); 7.3-7.80 (4H, m, Aromatic protons); 2.97 (2H, q, -CH <sub>2</sub> ); 1.60 (3H, t, -CH <sub>3</sub> )
7i	3183 (Aromatic C-H Stretch); 2900 (Aliphatic C-H Stretch); 1910, 1740 (Di-substituted benzene); 1741 (C=N Stretch); 1537 (C=C Stretch); 1617, 1490 (-N=O stretch); 1435 (CH <sub>2</sub> bending); 1390 (CH <sub>3</sub> Bending); 1185(C-N-stretch); 659 (oop)	$\delta$ = 8.50 (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.23 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.27 (2H, s, -CH <sub>2</sub> linker); 7.4-7.90 (4H, m, Aromatic protons); 2.77 (2H, q, -CH <sub>2</sub> ); 2.20 (2H, m, -CH <sub>2</sub> ); 1.56 (3H, t, -CH <sub>3</sub> )
7j	3082 (Aromatic C-H Stretch); 2929 (Aliphatic C-H Stretch); 1889, 1363 (Di-substituted benzene); 1699 (C=N Stretch); 1628 (C=C Stretch); 1514, 1440 (NO <sub>2</sub> Stretch); 1468 (CH <sub>2</sub> bending); 1310 (CH <sub>3</sub> Bending); 1191 (C-N stretch); 736 (oop)	$\delta$ = 8.32 (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 7.99 (2H, m, -CH at $\alpha$ to nitrogen in pyridine ring); 4.0 (2H, s, -CH <sub>2</sub> linker); 7.28-7.57 (4H, m Aromatic protons); 2.84 (2H, q, -CH <sub>2</sub> ); 2.45 (2H, m, -CH <sub>2</sub> ); 1.73 (2H, m, -CH <sub>2</sub> ); 0.94 (3H, t, -CH <sub>3</sub> )
8a	3097 (Aromatic C-H Stretch); 2944 (Aliphatic C-H Stretch); 1933, 1896 (Di-substituted benzene); 1703 (C=N Stretch); 1587 (C=C Stretch); 1458 (CH <sub>2</sub> bending); 1245 (C-N Stretch); 746 (Ortho disubstituted benzene (oop))	$\delta$ = 8.47 (1H, s, -CH Imidazole); 8.22 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.10 (2H, s, -CH <sub>2</sub> linker); 6.9-7.3 (6H, m, Aromatic protons)
8b	3114 (Aromatic C-H Stretch); 2980 (Aliphatic C-H Stretch); 1918, 1876 (Di-substituted benzene); 1655 (C=N Stretch); 1555 (C=C Stretch); 1450 (CH <sub>2</sub> bending); 1350.9(CH <sub>3</sub> bending); 1270 (C-N Stretch); 734 (oop)	$\delta$ = 8.46 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.23 (2H, s, -CH <sub>2</sub> linker); 7.2-7.56 (6H, m, Aromatic protons); 2.85 (s, 3H, -CH <sub>3</sub> )
8c	3053 (Aromatic C-H Stretch); 2973 (Aliphatic C-H Stretch); 1919, 1771 (Di-Substituted benzene); 1621 (C=N Stretch); 1588 (C=C Stretch); 1456 (CH <sub>2</sub> Bending); 1378(CH <sub>3</sub> bending); 1270 (C-N Stretch); 741 (oop)	$\delta$ = 8.47 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.40 (2H, s, -CH <sub>2</sub> linker); 7.10-7.60 (6H, m, Aromatic protons); 2.90 (q, 2H, -CH <sub>2</sub> ), 1.60 (t, 3H, -CH <sub>3</sub> )

8d	3050 (Aromatic C-H Stretch); 2928 (Aliphatic C-H Stretch); 1923, 1771 (Di-Substituted benzene); 1622 (C=N Stretch); 1537 (C=C Stretch); 1452 (CH <sub>2</sub> Bending); 1315(CH <sub>3</sub> bending); 1260 (C-N Stretch); 747 (oop)	$\delta = 8.40$ (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.50 (2H, s, -CH <sub>2</sub> linker); 7.20-7.61 (6H, m, Aromatic protons); 2.90 (t, 2H, -CH <sub>2</sub> ), 2.34 (m, 2H, -CH <sub>2</sub> ), 1.80 (t, 3H, -CH <sub>3</sub> )
8e	3140 (Aromatic C-H Stretch); 2928 (Aliphatic C-H Stretch); 1929, 1889 (Di-substituted benzene); 1622 (C=N Stretch); 1579 (C=C Stretch); 1417 (CH <sub>2</sub> Bending); 1311(CH <sub>3</sub> bending); 1271 (C-N Stretch); 745 (oop)	$\delta = 8.44$ (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.20 (2H, s, -CH <sub>2</sub> linker); 7.18-7.75 (6H, m, Aromatic protons); 3.0 (t, 2H, -CH <sub>2</sub> ), 2.67 (m, 2H, -CH <sub>2</sub> ), 1.72 (m, 2H, -CH <sub>2</sub> ), 0.98 (t, 3H, -CH <sub>3</sub> )
8f	3103 (Aromatic C-H Stretch); 2815 (Aliphatic C-H Stretch); 1901, 1773 (Di-substituted benzene); 1623 (C=N Stretch); 1591 (C=C Stretch); 1513, 1480 (-N=O aromatic stretch); 1345 (C-N Stretch); 741 (oop)	$\delta = 8.64$ (1H, s, -CH imidazole), 8.40 (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.10 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.20 (2H, s, -CH <sub>2</sub> linker); 7.3-7.80 (4H, m, Aromatic protons)
8g	3107 (Aromatic C-H Stretch) ; 2919 (Aliphatic C-H Stretch); 1901, 1706 (Di-Substituted benzene); 1630 (C=N Stretch); 1592 (C=C Stretch); 1512, 1490 (-N=O aromatic stretch); 1418 (CH <sub>2</sub> bending); 1383 (CH <sub>3</sub> bending); 1270 (C-N Stretch); 738 (oop)	$\delta = 8.65$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.38 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.0 (2H, s, -CH <sub>2</sub> linker); 7.30-8.0 (4H, m, Aromatic protons); 2.90 (3H, s, -CH <sub>3</sub> )
8h	3095 (Aromatic C-H Stretch); 2982 (Aliphatic C-H Stretch); 1895, 1755 (Di-Substituted benzene); 1671 (C=N Stretch); 1591 (C=C Stretch); 1517, 1490 (-N=O aromatic stretch); 1474 (CH <sub>3</sub> bending); 1490 (CH <sub>2</sub> bending); 1274 (C-N Stretch); 737 (oop)	$\delta = 8.64$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.33 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.5 (2H, s, -CH <sub>2</sub> linker); 7.32-7.90 (4H, m, Aromatic protons); 2.87 (2H, q, -CH <sub>2</sub> ); 1.49 (3H, t, -CH <sub>3</sub> )
8i	3102 (Aromatic C-H Stretch); 2965 (Aliphatic C-H Stretch); 1912, 1772 (Di-substituted benzene); 1628 (C=N Stretch); 1595 (C=C Stretch); 1517, 1441 (-N=O stretch); 1440 (CH <sub>2</sub> bending); 1384 (CH <sub>3</sub> Bending); 1265(C-N-stretch); 738 (oop)	$\delta = 8.49$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.17 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.34 (2H, s, -CH <sub>2</sub> linker); 7.20-7.65 (4H, m, Aromatic protons); 2.57 (2H, q, -CH <sub>2</sub> ); 1.86 (2H, m, -CH <sub>2</sub> ); 1.13 (3H, t, -CH <sub>3</sub> )
8j	3140 (Aromatic C-H Stretch); 2960 (Aliphatic C-H Stretch); 1889, 1363 (Di-substituted benzene); 1672 (C=N Stretch); 1594 (C=C Stretch); 1513, 1441 (NO <sub>2</sub> Stretch); 1470 (CH <sub>2</sub> bending); 1310 (CH <sub>3</sub> Bending); 1223(C-N stretch); 737 (oop)	$\delta = 8.51$ (1H, s, -CH at $\beta$ to nitrogen of imidazole & $\alpha$ to carbon containing nitro group), 8.20 (2H, dd, -CH at $\alpha$ to nitrogen in pyridine ring); 4.27 (2H, s, -CH <sub>2</sub> linker); 7.26-7.86 (4H, m Aromatic protons); 2.99 (2H, q, -CH <sub>2</sub> ); 2.55 (2H, m, -CH <sub>2</sub> ); 1.88 (2H, m, -CH <sub>2</sub> ); 1.02 (3H, t, -CH <sub>3</sub> )

Table 3. Physicochemical Properties of Synthesized compounds \*\*

Compound	Molar Refractivity (cm <sup>3</sup> )	Molar Volume (cm <sup>3</sup> )	Parachor (cm <sup>3</sup> )	Index of refraction	Density (g/cm <sup>3</sup> )	Polarizability (cm <sup>3</sup> )	Surface Tension (dyne/cm)
6a, 7a, 8a	64.87±0.5	176.5±7.0	465.5±8.0	1.656±0.05	1.18±0.1	25.71±0.5*10 <sup>-24</sup>	48.3±7.0
6b, 7b, 8b	69.29±0.5	191.7±7.0	496.6±8.0	1.642±0.05	1.16±0.1	27.47±0.5*10 <sup>-24</sup>	44.9±7.0
6c, 7c, 8c	73.90±0.5	207.8±7.0	535.2±8.0	1.629±0.05	1.14±0.1	29.29±0.5*10 <sup>-24</sup>	43.9±7.0
6d, 7d, 8d	78.51±0.5	223.9±7.0	573.8±8.0	1.618±0.05	1.12±0.1	31.12±0.5*10 <sup>-24</sup>	43.0±7.0
6e, 7e, 8e	83.12±0.5	240.0±7.0	612.4±8.0	1.608±0.05	1.10±0.1	32.95±0.5*10 <sup>-24</sup>	42.3±7.0
6f, 7f, 8f	75.14±0.5	198.0±7.0	549.6±8.0	1.683±0.05	1.35±0.1	29.78±0.5*10 <sup>-24</sup>	59.3±7.0
6g, 7g, 8g	79.56±0.5	213.2±7.0	580.6±8.0	1.668±0.05	1.32±0.1	31.54±0.5*10 <sup>-24</sup>	54.9±7.0
6, 7h, 8h	84.17±0.5	229.3±7.0	619.3±8.0	1.655±0.05	1.29±0.1	33.36±0.5*10 <sup>-24</sup>	53.1±7.0
6i, 7i, 8i	88.78±0.5	245.4±7.0	657.9±8.0	1.643±0.05	1.26±0.1	35.19±0.5*10 <sup>-24</sup>	51.6±7.0
6j, 7j, 8j	93.39±0.5	261.5±7.0	696.5±8.0	1.633±0.05	1.24±0.1	37.02±0.5*10 <sup>-24</sup>	50.3±7.0

\*\*Calculated using ACDLABS 12.0 software

Pharmacology

Anticonvulsant activity

The convulsions were induced in mice by administering Pentylene-tetrazole (PTZ-Sigma Co.) in the doses of 80 mg/kg intraperitoneally (Dhir et al. 2006). Each animal was placed into an individual plastic cage for observation lasting 1hour. The injections of test compounds (40mg/kg; i.p.) were prepared by dissolving the compounds in dimethylsulphoxide (DMSO) solvent. The test compounds were administered 30 min before PTZ challenge. Phenobarbitone was used as a standard anticonvulsant drug. The biological activity of these compounds was studied in 32 groups of six animals each as under:

Group 1- Served as control group. These animals were treated with vehicle, DMSO, 1mL/100g body weight intraperitoneally. These animals also received PTZ (80mg/kg) intraperitoneally after 30 min of injection of DMSO solution.

Table 4. Anti-convulsant activity of synthesized compounds

Group	Onset time of convulsion (sec)	% recovery/death
Control	47±5.15	0**
6a	46.6±4.9	0**
6b	108.2±8.23*	33.2
6c	51±4.42	0**
6d	56±2.63	0**
6e	56.6±5.35	0**
6f	91±8.27*	16.6
6g	81±7.67*	0**
6h	93±7.8*	16.6
6i	91±4.85*	16.6
6j	48.2±3.06	0**
7a	53.2±4.8	0**
7b	61.2±6.72	0**
7c	54.2±5.8	0**
7d	52.6±5.16	0**
7e	61.4±5.23	0**
7f	66.8±5.4	0**
7g	57.6±6.63	0**
7h	55.4±5.1	0**
7i	51.4±5.43	0**
7j	62.8±6.17	0**
8a	66.4±4.9	0**
8b	47.2±3.82	0**
8c	47.6±4.52	0**
8d	57.6±5.88	0**
8e	46.6±4.43	0**
8f	62±6.54	0**
8g	55.2±5.28	0**
8h	49.6±4.53	0**
8i	49.4±4.72	0**
8j	65.6±6.5	0**
Phenobarbitone	183.6± 9.7*	>80

Phenobarbitone was used as standard drug. Values are expressed as Mean ± SEM.  
 \* p<0.05 in comparison to control (n=6); \*\*100% death. No recovery.

Group 2 to group 31- Served as test groups. The animals of these groups were used for observing the influence of test compounds on PTZ induced convulsions or recovery or death. These animals were administered DMSO solution of test compounds 1 ml/100g by intraperitoneal route. Thirty min later these



animals were administered PTZ (80 mg/kg; i.p.) as a challenging agent. The animals were observed for a period of 30 min each (post-PTZ administration). The parameters noted were mean onset time of convulsions, recovery or death. Percentage recovery or Percentage survival after PTZ administration was recorded. The increase in onset time of convulsions and percentage recovery was taken as parameter for anticonvulsant activity.

The animals of Group number 32 received phenobarbitone (20 mg/kg; i.p.) 30 min before administration of PTZ (80 mg/kg; i.p.). These animals also were observed in above referred manner for onset-time of convulsions and percentage recovery or death.

Albino rats of either sex were obtained from CCS HA University, Hisar. All the compounds exhibited mild to moderate activities. All the values were expressed as mean $\pm$ SEM. The data was analyzed using Student's t-test followed by Dunnett's test. In all tests, the criterion for statistical significance was  $p < 0.05$ . Biological activity data of synthesized compounds is summarized in Table 4.

## Results and Discussion

### QSAR Analysis

The anti-convulsant activity data of 30 compounds after the injection of irritant was used in this analysis. General structure of the compounds is shown in Fig.1. 3D of structure of compound substituted with electron withdrawing group (-NO<sub>2</sub>) at position 5 and with picoline at position 1 with varying chain length at position 2 is shown in Fig.2.

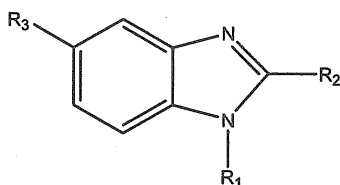


Figure 1. General structure of 1,2,5-trisubstituted benzimidazole

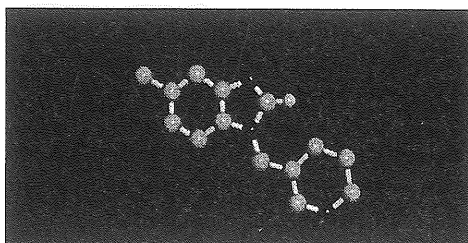


Figure 2. 3D Structure of 1,2,5-trisubstituted benzimidazole with geometry optimization (Fetcher Reeves method) (Using Hyper Chem Professional 7.0)

The biological activity values [BA] was converted to  $-\log$  scale and subsequently used as a response variable for QSAR analysis (Table 5, 6 and 7).

In order to identify the substituent effect on anti-convulsant activity, quantitative structure activity relationship (QSAR) studies of title compounds were performed. Biological activity data

(BA) in their negative logarithmic values are listed in Table 4. The compounds were analyzed by physicochemical-based QSAR (Hansch) approach using different physicochemical parameters (Table 5, 6 and 7) as independent and pBA values as dependent variables. These QSAR descriptors of substituted benzimidazoles were calculated using the multiple regression techniques.

**Table 5.** Observed and predicted activities of substituted benzimidazoles (6a-6j) using QSAR studies

Compound No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	BA	-log BA (Observed activity)	Calculated activity	Residual activity*
6a	1-picoline	H	H	46.6	-1.668	-1.765	0.097
6b	1-picoline	CH <sub>3</sub>	H	108.2	-2.034	-1.915	-0.119
6c	1-picoline	C <sub>2</sub> H <sub>5</sub>	H	51	-1.708	-1.801	0.093
6d	1-picoline	C <sub>3</sub> H <sub>7</sub>	H	56	-1.748	-1.740	-0.008
6e	1-picoline	C <sub>4</sub> H <sub>9</sub>	H	56.6	-1.752	-1.689	-0.063
6f	1-picoline	H	NO <sub>2</sub>	91	-1.959	-5.537	3.578
6g	1-picoline	CH <sub>3</sub>	NO <sub>2</sub>	81	-1.908	-5.686	3.778
6h	1-picoline	C <sub>2</sub> H <sub>5</sub>	NO <sub>2</sub>	93	-1.968	-5.586	3.618
6i	1-picoline	C <sub>3</sub> H <sub>7</sub>	NO <sub>2</sub>	91	-1.959	-5.511	3.552
6j	1-picoline	C <sub>4</sub> H <sub>9</sub>	NO <sub>2</sub>	48.2	-1.683	-5.460	3.777

\*Residual activity is the difference in predicted activity and experimental activity

**Table 6.** Observed and predicted activities of substituted benzimidazoles (7a-7j) using QSAR studies

Compound No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	BA	-log BA (Observed activity)	Calculated activity	Residual activity
7a	2-picoline	H	H	53.2	-1.726	-1.756	0.030
7b	2-picoline	CH <sub>3</sub>	H	61.2	-1.787	-1.749	-0.038
7c	2-picoline	C <sub>2</sub> H <sub>5</sub>	H	54.2	-1.734	-1.751	0.017
7d	2-picoline	C <sub>3</sub> H <sub>7</sub>	H	52.6	-1.721	-1.751	0.030
7e	2-picoline	C <sub>4</sub> H <sub>9</sub>	H	61.4	-1.788	-1.750	-0.038
7f	2-picoline	H	NO <sub>2</sub>	66.8	-1.825	-5.230	3.405
7g	2-picoline	CH <sub>3</sub>	NO <sub>2</sub>	57.6	-1.760	-5.223	3.463
7h	2-picoline	C <sub>2</sub> H <sub>5</sub>	NO <sub>2</sub>	55.4	-1.744	-5.226	3.482
7i	2-picoline	C <sub>3</sub> H <sub>7</sub>	NO <sub>2</sub>	51.4	-1.711	-5.225	3.514
7j	2-picoline	C <sub>4</sub> H <sub>9</sub>	NO <sub>2</sub>	62.8	-1.798	-5.225	3.427

**Table 7.** Observed and predicted activities of substituted benzimidazoles (8a-8j) using QSAR studies

Compound No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	BA	-log BA (Observed activity)	Calculated activity	Residual activity
8a	3-picoline	H	H	66.4	-1.822	-1.779	-0.043
8b	3-picoline	CH <sub>3</sub>	H	47.2	-1.674	-1.676	0.002
8c	3-picoline	C <sub>2</sub> H <sub>5</sub>	H	47.6	-1.678	-1.711	0.033
8d	3-picoline	C <sub>3</sub> H <sub>7</sub>	H	57.6	-1.760	-1.717	-0.043
8e	3-picoline	C <sub>4</sub> H <sub>9</sub>	H	46.6	-1.668	-1.718	0.050
8f	3-picoline	H	NO <sub>2</sub>	62.0	-1.792	-5.222	3.430
8g	3-picoline	CH <sub>3</sub>	NO <sub>2</sub>	55.2	-1.742	-5.119	3.377
8h	3-picoline	C <sub>2</sub> H <sub>5</sub>	NO <sub>2</sub>	49.6	-1.695	-5.170	3.475
8i	3-picoline	C <sub>3</sub> H <sub>7</sub>	NO <sub>2</sub>	49.4	-1.694	-5.160	3.466
8j	3-picoline	C <sub>4</sub> H <sub>9</sub>	NO <sub>2</sub>	65.6	-1.817	-5.161	3.344

## Conclusion

A novel series of a disubstituted benzimidazole derivatives have been synthesized successfully in appreciable yields and screened for their *in vivo* anti-convulsant activity. The QSAR studies and physicochemical parameters indicate that the change in linker at position one does not change the activity of synthesized 1,2,5-trisubstituted benzimidazole. Optimum chain length of the carbon at position 2 is responsible for the anti-convulsant activity. Pentylenetetrazole (PTZ 80mg/kg, i.p.) induced convulsion in all animals of the control group. Four (6b, 6f, 6h and 6i) out of thirty synthesized compounds which were tested for their influence on PTZ induced convulsions showed significant protective action. These four compounds had caused increased in onset time of clonus phase as well as significant increase in percentage recovery of the animals. Phenobarbitone (20 mg/kg; i.p.) used as a standard drug showed a significant prevention of PTZ-induced convulsions in all the tested mice.

Synthesized compounds with electron withdrawing group at position five shows better anti-convulsant activity as predicted by QSAR studies.

The study will be helpful in the design of better analogs of benzimidazole derivatives for anti-convulsant activity.

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