

## **SYNTHESIS AND CHARACTERISATION OF 2-( $\alpha$ -p - SUBSTITUTED PHENYL- $\alpha$ -BENZIMIDAZOLO) METHYL BENZIMIDAZOLE**

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### **ABSTRACT**

2-p-substituted phenyl-2-benzimidazolo acetonitriles (1a-5a) were prepared by the reaction of benzimidazole, p-substituted benzaldehydes and Sodium cyanide. A series of 2-( $\alpha$ -p -Substituted phenyl- $\alpha$ -benzimidazolo) methyl benzimidazoles (1b-5b) were synthesized by the reaction of 2-p-substituted phenyl-2-benzimidazolo acetonitrile(1a-5a) and o-phenylenediamine in presence of Conc. HCl. These compounds were characterized by IR, NMR and Mass spectroscopy.

**Key words:** Benzimidazole, o-phenylenediamine, acetonitrile

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### **INTRODUCTION**

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature.

The importance of imidazoline and benzimidazoles, units arises, because they are found in many biologically active compounds<sup>1-5</sup>. In addition, the benzimidazole moiety is found in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including anti-ulcer, anti-tumor and anti-viral effects<sup>6-9</sup>.

Almost all benzimidazole derivatives with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of these drugs. Tissue selectivity of this type of antiulcer drugs is based on both their pH dependent accumulation, as weak bases in the acidic compartment of secreting parietal cell, and the subsequent acid-induced rearrangement of the parent compound to the pharmacologically active principle<sup>10</sup>.

A series of benzimidazole derivatives have proven anti-ulcer activity as potential inhibitors of  $H^+/K^+$ -ATPase. Therapeutic significance of these clinically useful drugs in treatment of peptic ulcer and associated gastrointestinal diseases encouraged the development of some more potent and significant compounds<sup>11</sup>. These observations inspired us to synthesize the 2-( $\alpha$ -p -Substituted phenyl- $\alpha$ -benzimidazolo) methyl benzimidazoles

### **EXPERIMENTAL**

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (K Br) were recorded on a Perkin Elmer 1800(FTIR) spectrometer. PMR spectra (DMSO-d<sub>6</sub>) on a Varian EM-390 spectrometer using TMS as an internal standard (chemical shift in  $\delta$ ppm). Mass spectra were recorded on a Jeol JMS-D 300 Mass spectrometer operating at 70 eV. The purity of the compounds was confirmed by TLC using silica gel G. For TLC, Merck silica gel 60 G plate was used. The necessary chemicals were obtained from Merck and Fluka. All compounds showed satisfactory elemental analyses.

### Synthesis of 2-p-substituted phenyl-2-benzimidazoloacetonitriles (1a-5a):

#### *Synthesis of 2-benzimidazo-2-phenylacetonitrile (1a)*

To a stirred solution of sodiumbisulphite (4.16 g ; 0.04 mol) in 10 mL of water benzaldehyde (4.24 g; 0.04 mol) was added and then benzimidazole (4.72 g; 0.04 mol ) was added. The reaction mixture was stirred for 30 minutes and cooled in ice bath. A solution containing 1.96g (0.04 mol) of sodium cyanide was added dropwise into it . After 10 h the product was separated and filtered . The crude was recrystallized from chloroform-petroleum ether mixture. The pure sample melted at 183-184 °C.

#### *Synthesis of 2-p-chlorophenyl-2-benzimidazoloacetonitrile(2a)*

The 2-p-chlorophenyl-2-benzimidazoloacetonitrile (2a) was prepared by the reaction of p-chlorobenzaldehyde and benzimidazole in presence of NaH SO<sub>4</sub> as described above. The crude was recrystallized from chloroform-petroleum ether mixture .The pure sample melted at 158-159 °C.

#### *Synthesis of 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile(3a)*

The 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile(3a) was synthesized by the reaction of p-hydroxybenzaldehyde and benzimidazole. The crude was recrystallized from benzene-petroleum ether mixture . The pure compound melted at 192-193 °C.

#### *Synthesis of 2-p -N, N'-Dimethylanilino -2-benzimidazoloacetonitrile(4a)*

The 2-p -N, N'-dimethylanilino -2-benzimidazoloacetonitrile(4a) was synthesized by the reaction of p -N, N'-dimethylaminobenzaldehyde and benzimidazole. The crude was recrystallized from benzene-petroleum ether mixture . The pure compound melted at 137-138 °C.

#### *Synthesis of 2--p-Anisyl-2-benzimidazoloacetonitrile (5a)*

2-p-Anisyl-2-benzimidazoloacetonitrile (5a) was synthesized by using p-Anisaldehyde. The crude was recrystallized from benzene and the pure compound melted at 163-164 °C.

### Synthesis of 2-( $\alpha$ -p -Substituted phenyl- $\alpha$ -benzimidazo) methyl benzimidazole(1b-5b):

#### *Synthesis of 2-( $\alpha$ -Benzimidazo- $\alpha$ -phenyl) methyl benzimidazole (1b)*

A mixture of 2-benzimidazo-2-phenylacetonitrile (1a) (4.66g; 0.02mol) and o-phenylenediamine(2.16g; 0.02mol) was taken in a 100 mL round bottom flask. About 5mL of concentrated hydrochloric acid was added .The contents were heated for 10 h in an oil bath maintained at 150-160 °C. The reaction mixture was kept over night . The precipitated hydrochloride was filtered and washed with ethanol ether mixture (1:5). The resulting hydrochloride was suspended in acetone and was made alkaline by adding 30 mL of strong ammonia solution .The base was liberated by diluting it with water .The benzimidazole was filtered, washed with excess of water and dried. It was recrystallised from methanol . The pure sample melted at 166-167 °C .

#### **Infra Red Spectral Data (KBr), $\lambda$ values in cm<sup>-1</sup>**

3482 (m) 3409(w) 3313(w) 3145 (m) 3116(s) 2983 (m) 2926 (m) 2853 (m) 2767 (s) 2566(w) 2366(m) 2050 (s) 1850 (m)1740 (w) 1626 (s) 1530 (m) 1500(s) 1455 (w ) 1402 (s ) 1318 (w) 1230 (m) 1200(w) 1153(w) 1113 (w) 1072 (w) 1022 (s) 926 (m) 838 (m) 749(s) 671 (w) 609 (m) 556 (w) 449(s)

#### **Proton Magnetic Resonance Spectral Data (CDCl<sub>3</sub> / TMS ), $\delta$ values in ppm**

4.6 (S) 1H C-H methine  
7.1-7.3 (m) 13H Aromatic proton  
8.1 (S) 1H C-H benzimidazole

#### **Mass Spectral Values ; m/z and %**

325 (8) 324 (30) 323 (42) 297 (20) 247 (15) 246(20) 234 (35) 210 (8) 207( 40 ) 206 (18)  
205 (40) 157 (15) 130 (60) 118 (100) 117 (35) 116 (20) 90 (65) 77 (45) 63 (22)

#### **Elemental Analysis C % H%**

C<sub>21</sub> H<sub>16</sub> N<sub>4</sub> Calculated : 77.77 4.93  
Mol.Wt. 324 found : 77.56 4.75

**Synthesis of 2-( $\alpha$ -p-Chlorophenyl - $\alpha$  - benzimidazolo)methyl benzimidazole (2b)**

To a mixture of 2-p-chlorophenyl-2-benzimidazoloacetonitrile(2a) (5.34g;0.02mol) and o-phenylenediamine(2.16g; 0.02mol) 10mL of concentrated hydrochloric acid was added .The mixture was heated for about 10 h in oil bath, maintained at 150 °C. The product obtained was cooled for 4 h and the precipitated hydrochloride was filtered.It was washed with ethanol- ether mixture (1:5) and the product was transferred to a beaker. The hydrochloride was suspended in acetone and made alkaline with strong ammonia solution . It was diluted with water and the solid was filtered, washed with water,dried and recrystallised from methanol. The pure sample melted at 138-139 °C.

**Infra Red Spectral Data (KBr),  $\lambda$  values in  $\text{cm}^{-1}$**

3450(m) 3369 (m) 3250(m) 3176 (m) 3116 (w) 3027 (w) 2924 (s) 2854 (s) 2700 (m) 2500 (w)  
2349 (m) 2099(m) 1747 (w) 1630 (m) 1610 (w) 1501 (s) 1457 (m) 1402 (s) 1320(w) 1273 (s)  
1200(w) 1151(m) 1120(w) 1025(s) 929(m) 842(m) 750(s) 664(w) 595(w) 541(w) 506(w)  
453(m)

**Proton Magnetic Resonance Spectral Data ( $\text{CDCl}_3$  / TMS ),  $\delta$  in ppm**

4.3 (S) 1H C-H methine  
6.8-7.3 (m) 12H Aromatic protons  
8.2 (S) 1H C-H benzimidazole

**Mass Spectral Values ; m/z and %**

359(32) 358(8) 323 (40) 269 (60) 247 (18) 246(55) 242(40) 241 (28) 210 (6 5) 157  
(35) 152(35) 151(25) 118 (10) 117 (22) 90 (100) 76 (18) 63 (5)

**Elemental Analysis C% H%**

$\text{C}_{21}\text{H}_{15}\text{N}_4$  CI Calculated : 70.29 4.18  
Mol.Wt. 358 found : 70.18 4.13

**Synthesis of 2-( $\alpha$ -p-Hydroxyphenyl - $\alpha$  benzimidazolo)methylbenzimidazole (3b)**

A mixture of 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile (4.98g;0.02mol) and o-phenylenediamine(2.16g; 0.02mol) 10L of concentrated hydrochloric acid was added .The mixture was heated for about 10 hours in an oil bath, maintained at a temperature of 150 °C. The product obtained was cooled for 4 h and the precipitated hydrochloride was filtered. It was washed with ethanol- ether mixture (1:5) and the product was transferred to a beaker. The hydrochloride was suspended in acetone and made alkaline with strong ammonia solution . It was diluted with water and the solid was filtered, washed with water,dried and recrystallised from chloroform. The pure sample melted at 155-156 °C.

**Infra Red Spectral Data (KBr),  $\lambda$  values in  $\text{cm}^{-1}$**

3452 (m) 3198 (w) 3110 (w) 2924 (s) 2854 (s) 2798 (m) 2666(w) 2500 (w) 2000 (w) 1820(w)  
1743 (m) 1620 (m) 1500 (w) 1458 (s) 1405 (s) 1247 (m) 1208 (m) 1120 (m) 1021 (s) 845 (m)  
751 (s) 670 (m) 589 (m) 543 (m) 460 (s)

**Proton Magnetic Resonance Spectral Data ( $\text{CDCl}_3$  / TMS ),  $\delta$  in ppm**

4.6 (S) 1H C-H methine  
6.7 -7.3 (m) 12H Aromatic protons  
7.8 (S) 1H - O-H phenolic  
8.1 (S) 1H C-H benzimidazole

**Mass Spectral Values ; m/z and %**

341 (5) 340 (40) 322 (26) 250 (60) 247 (15) 223 (32) 222(18) 205 (25) 204 (35) 157  
(55) 133 (45) 132 (30) 118 (38) 117 (100) 93 (53) 90(45) 63 (20)

**Elemental Analysis C% H %**

$\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}$  Calculated : 74.1 4.70  
Mol.Wt. 340 found : 74.00 4.55

**Synthesis of 2-( $\alpha$ -p -N, N'-Dimethylanilino - $\alpha$  - benzimidazolo)methyl benzimidazole (4b)**

2-p-N,N'-Dimethylamino-2-benzimidazolo acetonitrile (5.52g;0.02 mol ) was mixed with o-phenylenediamine (2.16g; 0.02mol). About 10 mL of concentrated hydrochloric acid was added to it

The reaction mixture was heated for 10 h in an oil bath, maintained at 150-160 °C. The reaction mixture was cooled for 4 h. The precipitated hydrochloride was filtered, washed with ethanol- ether mixture (1:5) and transferred to a beaker. The resulting hydrochloride was suspended in acetone and made alkaline with strong ammonia solution. The base was liberated by the addition of excess of water. Filtered the solid washed with water, dried and recrystallised from methanol. The pure sample melted at 127-129 °C.

**Infra Red Spectral Data (KBr),  $\lambda$  values in  $\text{cm}^{-1}$**

3420 (m) 3408(8) 3333(s) 3251 (w) 3150 (w) 2973 (w) 2919(m) 2859 (m) 2700 (m) 2598 (s) 2500 (m) 2366(m) 2100 (m) 1956 (w) 1750 (w) 1623 (s) 1563 (m) 1496 (s) 1458(w) 1403 (s) 1316(w) 1291 (w) 1238 (w) 1188 (w) 1095 (w) 1043(w) 940 (w) 861 (w) 761 (s) 644 (m) 525 (m) 448 (s)

**Proton Magnetic Resonance Spectral Data ( $\text{CDCl}_3$  / TMS ),  $\delta$  in ppm**

2.9 (S) 6 H -N -(CH<sub>3</sub>)<sub>2</sub>  
4.6 (S) 1 H C-H methine  
6.7 -7.7 (m) 12 H Aromatic protons  
8.1 (S) 1 H C -H benzimidazole

**Mass Spectral Values ; m/z and %**

367 (20) 366 (30) 323 (40) 277(35) 250 (8) 249(15) 247 (5) 210 (18) 206 (20) 205 (38) 183(12) 160(50) 159(25) 157 (25) 120 (100) 118 (60) 117 (32) 90(28) 76(42) 63 (40)

**Elemental Analysis C% H%**

C<sub>23</sub> H<sub>21</sub> N<sub>5</sub> Calculated : 75.2 5.72  
Mol.Wt . 367 found : 74.8 5.68

**Synthesis of 2-(*o*-p Anisyl-*a* – benzimidazolo) methyl benzimidazole (5b)**

A mixture of 2-p-Anisyl-2-benzimidazoloacetonitrile (5b) (5.26g; 0.02mol) and *o*-phenylenediamine(2.16g; 0.02mol) was taken in a 100ml.round bottomed flask. About 5mL of concentrated hydrochloric acid was added and heated for 10 h in an oil bath maintaining the temperature at 160-165 °C. The reaction mixture was cooled and the precipitated hydrochloride was filtered. It was washed with ethanol ether mixture (1:5). and transferred to a beaker. Addition of excess of water liberated the base. The resulting solid was filtered, and washed with water and dried. It was recrystallised from benzene. The pure sample melted at 188-189 °C.

**Infra Red Spectral Data (KBr),  $\lambda$  values in  $\text{cm}^{-1}$**

3455 (m) 3366 (m) 3141 (m) 3026(w) 2959 (w) 2863 (w) 2805 (w) 2690 (m) 2598 (s) 2430 (m) 2366(m) 2043 (m) 1918 (w) 1774 (w) 1683 (w) 1625(m) 1531 (m) 1501(w) 1465 (w) 1402 (s) 1273 (m) 1236 (m) 1148 (m) 1025 (m) 930 (w) 878 (w) 837(m) 748 (s) 606 (m) 442(m)

**Proton Magnetic Resonance Spectral Data ( $\text{CDCl}_3$  / TMS ),  $\delta$  in ppm**

3.9 (S) 3H - CH<sub>3</sub> anisyl  
4.6 (S) 1 H C-H methine  
6.8 -7.4 (m) 12 H Aromatic protons  
8.2 (S) 1H C -H benzimidazole

**Mass Spectral Values ; m/z and %**

355 (8) 354 (42) 347(16) 323 (45) 297(6) 284 (58) 264 (20) 237 (20) 236(6) 224(18) 210 (15) 205 (30) 195(65) 182 (12) 157 (50) 147 (25) 146(42) 130 (35) 118 (25) 117 (40) 107(100) 90(36) 63 (10)

**Elemental Analysis C% H%**

C<sub>22</sub> H<sub>18</sub> N<sub>4</sub> O Calculated : 74.57 5.08  
M.W . 354 found : 74.34 5.03

## RESULTS AND DISCUSSION

The formation of 2-p-substituted phenyl-2-benzimidazoacetonitriles (1a-5a) was conformed by spectral values of IR and NMR and is presented in Table-1. In the present study, 2-phenylacetonitrile(1a) and other nitriles(2a-5a) have been condensed with o-phenylenediamine in the presence of hydrochloric acid. The synthetic route of these compounds was represented as Scheme-1. Nitriles make ring closure in the presence of acids<sup>12</sup> and it follows the mechanism:

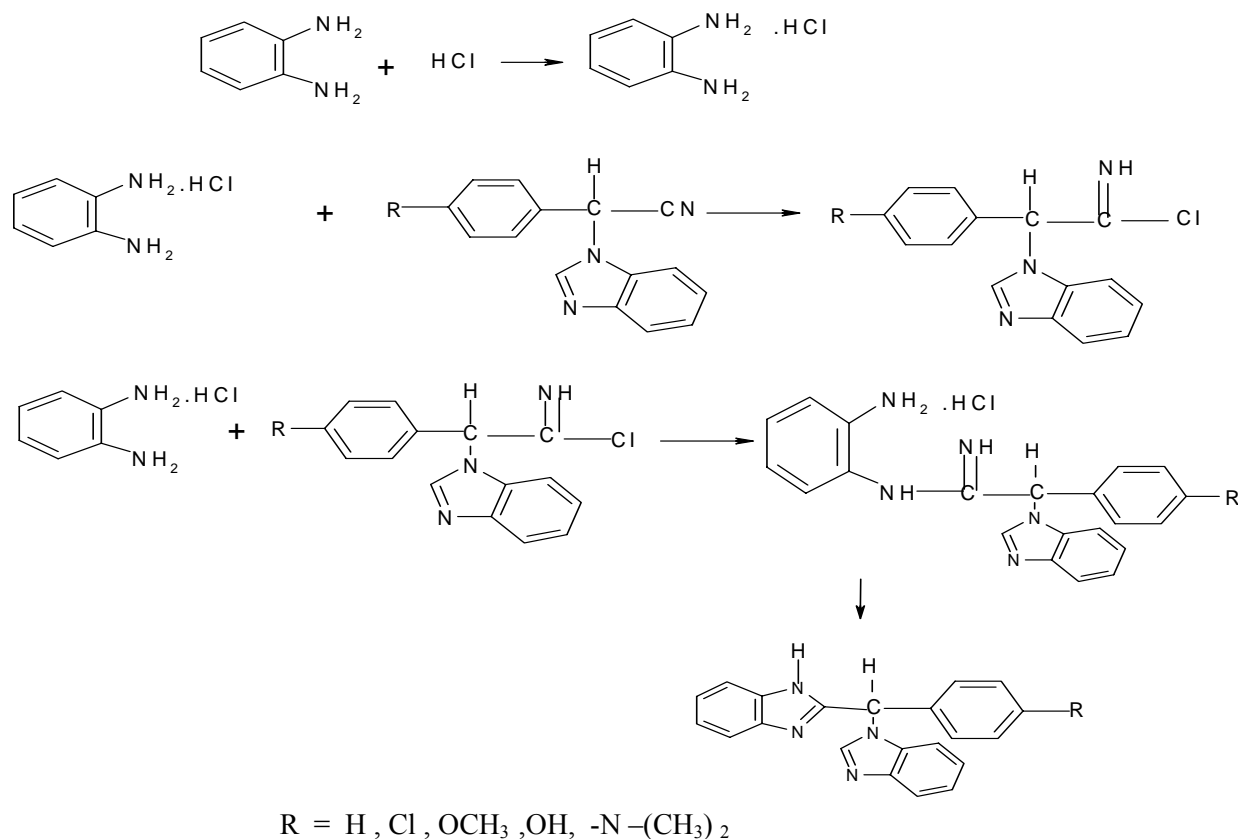
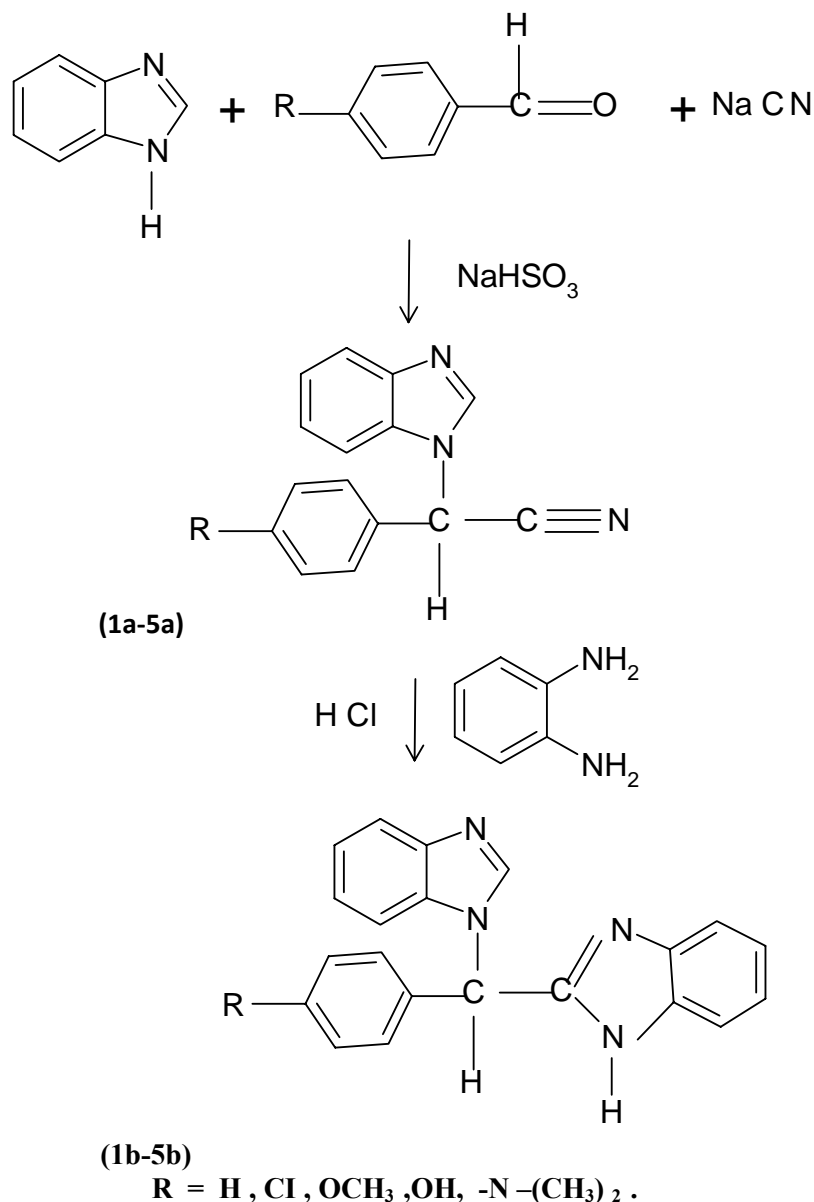


Table-1: Spectral data of the compounds (1a-5a)

Sample No	IR (KBr) cm <sup>-1</sup>	<sup>1</sup> H-NMR (CDCl <sub>3</sub> ) δ ppm
1a	2230	4.6(s,1H, -CH methine),7.0-7.4 (m,9H,Ar-H),8.2(s,1H,C-H, Benzimidazole)
2a	2240	4.6(s,1H, -CH methine),7.0-7.4 (m,8H,Ar -H), 8.2(s,1H,C-H, Benzimidazole)
3a	2220	4.6(S,1H, -CH methine),6..6-7.4 (m,8H,Ar-H),7.8, (S, 1H,OH Phenolic ),8.1(s,1H,C-H, Benzimidazole)
4a	2240	3.0 (s,6H-N -(CH <sub>3</sub> ) <sub>2</sub> ) 4.6(s,1H, -CH methine),6.6-7.3(m,8H,Ar-H),8.2(s,1H,C-H, Benzimidazole)
5a	2232	3.9(s,3H, - CH <sub>3</sub> anisyl ), 4.6(s,1H, -CH methine),7.0-7.4 (m,8H,Ar-H),8.2(s,1H,C-H, Benzimidazole)



Scheme-1: Synthesis of 2-( $\alpha$ -p-Substituted phenyl- $\alpha$ -benzimidazolo) methyl benzimidazole

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