

# Synthesis and Biological activities of 2-( $\alpha$ -p -Substituted phenyl- $\alpha$ -benzimidazolo) methyl benzoxazole

P.Jeyanthi<sup>1\*</sup>, K. Sheela<sup>1</sup> and P.Pazhanisamy<sup>2</sup>

<sup>1</sup>Department of Chemistry, Bharathi Women's College, Chennai-600108, India.

<sup>2</sup>Department of Chemistry, Sir Theagaraya College, Chennai – 600021, India

## Abstract

2-p-substituted phenyl-2-benzimidazolo acetonitriles (1a-3a) were prepared by the reaction of benzimidazole, p-substituted benzaldehydes and Sodium cyanide. The compounds (1a-3a) were also prepared by the reaction of benzimidazole, p-substituted benzaldehydes and trimethylsilyl cyanide in acetonitrile in the presence of bismuth tri chloride. The 2-( $\alpha$ -p -Substituted phenyl- $\alpha$ -benzimidazolo) methylbenzoxazoles (1b-3b) were synthesized by the reaction of 2-p-substituted phenyl-2-benzimidazolo acetonitrile(1a-3a) and o-aminophenol in presence of Conc. HCl. These synthesized (1b-3b) compounds showed both antibacterial and antifungal activities.

**Key words:** Benzimidazole, o-aminophenol, acetonitrile, benzoxazole

## INTRODUCTION

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. 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>.

The addition of cyanide to imines (Strecker reaction)<sup>10</sup> provides one of the most efficient methods for the synthesis of  $\alpha$ -aminonitriles.  $\alpha$ -Aminonitriles are important intermediates for the synthesis of amino acids<sup>11</sup> and various nitrogen containing heterocycles such as thiadiazoles and imidazoles<sup>12</sup>. The classical Strecker reaction is generally carried out with alkaline cyanides in aqueous solution. Among various cyanide ion sources,<sup>13</sup> trimethylsilyl cyanide is a safer and easily handled reagent compared to hydrogen cyanide, sodium cyanide, or potassium cyanide.

Recently, there has been considerable interest growing in the use of bismuth(III) halides as potential Lewis acids in various organic reactions<sup>14</sup> because they are inexpensive, relatively non-toxic, fairly insensitive to small amounts of water, and environmentally benign reagents. In this communication, we wish to report a simple and efficient method for the synthesis of  $\alpha$ -aminonitriles in the presence of a catalytic amount of bismuth(III) chloride in acetonitrile at room temperature.

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>15</sup>. The present study deals with synthesis and biological activities of 2-( $\alpha$ -p -Substituted phenyl- $\alpha$ -benzimidazolo) methyl benzoxazoles.

## 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- $d_6$ ) 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.

### Antimicrobial Activity

The synthesized compounds in the present investigation have been tested for antimicrobial activity by well diffusion method. The organisms selected for the antifungal activity was carried out by using *Aspergillus flavus*, *Candida albicans* and *Cryptococcus*. The organisms selected for the antibacterial activity was carried out by using *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The plates are prepared as per the standard methods<sup>16</sup>.

### Antimicrobial assay

Antibacterial analysis was followed using standard agar well diffusion method to study the antibacterial activity of compounds. Each bacterial and fungal isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately  $10^5$  colony forming unit (CFU) per mL. They were flood-

inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30  $\mu$ L (5 $\mu$ g compound in 500  $\mu$ L DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37°C for bacteria and at room temperature for fungi. Antimicrobial activity was evaluated by measuring the zone of inhibition in mm against the test microorganisms. DMSO was used as solvent control. Chloramphenicol was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent.

## 1. Synthesis of 2-p-substituted phenyl-2-benzimidazoloacetonitriles (1a-3a)

### 1.1 Synthesis of 2-p-Hydroxyphenyl-2-benzimidazoloacetonitrile (1a)

A mixture of 0.005mol p-Hydroxybenzaldehyde, 0.005mol benzimidazole and 0.0075mol trimethylsilylcyanide in 10 ml acetonitrile in the presence of 0.0005mol bismuth tri chloride was stirred at room temperature for 12hrs. After completion of the reaction, the reaction mixture was partitioned between 10 ml of ether and 50ml of water. The organic layer was washed with 50 ml brine, dried over sodium sulphate and concentrated. The crude was recrystallized from benzene-petroleum ether mixture. The pure compound melted at 192-193 °C.

### 1.2 Synthesis of 2-p-Methylphenyl-2-benzimidazoloacetonitrile (2a)

The 2-p-methylphenyl-2-benzimidazoloacetonitrile (2a) was prepared by the reaction of p-methylbenzaldehyde and benzimidazole as described above. The crude was recrystallized from chloroform-petroleum ether mixture. The pure sample melted at 158-159 °C.

### 1.3 Synthesis of 2-p-Anisyl-2-benzimidazoloacetonitrile (3a)

2-p-Anisyl-2-benzimidazoloacetonitrile (3a) was synthesized by using p-Anisaldehyde. The crude was recrystallized from benzene and the pure compound melted at 163-164 °C.

## 2. Synthesis of 2-(a-p -Substituted phenyl- $\alpha$ -benzimidazolo) methyl benzoxazoles(1b-3b)

### 2.1 Synthesis of 2-(a-p Hydroxyphenyl - $\alpha$ -benzimidazolo) methyl benzoxazole(1b)

A mixture of 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile (0.02 mol) and o-aminophenol(0.02mol) was taken in a 100mL round bottomed flask and 5mL of concentrated hydrochloric acid was added. It was heated for 12

hours in an oil bath maintained at 150-180°C. The reaction mixture was kept overnight and the precipitated hydrochloride was filtered. It was washed using ethanol- ether mixture (1:5) and the hydrochloride was suspended in acetone. It was made alkaline by adding strong ammonia solution. The base was liberated by diluting with excess of water. The crude product was filtered, washed with water, dried. It was recrystallized from benzene. The compound melted at 163-165°C. **Infra Red Spectral Data (KBr),  $\lambda$  values in  $\text{cm}^{-1}$ :** 3775(w) 3448 (w) 3083 (m) 2924 (m) 2854 (m) 2743 (s) 2666(w) 2583 (w) 1833(w) 1699 (s) 1632 (w) 1571 (s) 1472 (s) 1420 (s) 1410 (w) 1393 (m) 1301 (m) 1288 (m) 1250 (s) 1203 (w) 1168 (w) 1135 (w) 1049 (w) 1023 (w) 928 (w) 852 (m) 756 (m) 615 (w) 570 (m) 449 (w) **Proton Magnetic Resonance Spectral Data (CDCl<sub>3</sub> / TMS),  $\delta$  in ppm:** 4.6 s 1H C-H methane 6.7 - 7.3 m 12H Aromatic protons 7.8 s 1H - OH phenolic, 8.1 s 1H C -H benzimidazole **Mass Spectral Values ; m/z (%)** 343 (20) 342 (10) 341 (25) 324 (18) 323 (40) 297 (12) 286 (15) 256 (8) 248 (100) 236 (16) 224 (65) 222(20) 205 (28) 180 (10) 178 (24) 168 (25) 158(24) 156 (36) 150 (30) 149 (6) 132 (12) 131 (20) 127 (18) 120 (40) 119 (45) 118 (60) 117 (30) 105(15) 92 (35) 91 (10) 90(28) 63 (44)

### 2.2 Synthesis of 2-(a-p-Methylphenyl- $\alpha$ -benzimidazolo) methyl benzoxazole (2b)

A mixture of 2-benzimidazolo-2-phenylacetonitrile (0.02mol) and o-aminophenol(0.02 mol) was taken in a 100mL round bottomed flask. Added 5mL of concentrated hydrochloric acid and was heated for 12 hours in an oil bath maintained at 150-160°C. The reaction mixture was kept overnight. The precipitated hydrochloride was filtered and washed with ethanol-ether mixture (1:5). The hydrochloride was suspended in acetone and it was made alkaline by adding strong ammonia solution. The base was liberated by diluting it with water. The benzoxazole was filtered, washed with excess of water and dried. It was recrystallized from methanol. The pure sample melted at 195-197 °C. **Infra Red Spectral Data (KBr),  $\lambda$  values in  $\text{cm}^{-1}$ :** 3429 (m) 3366(m) 3181 (m) 3116(m) 2950 (w) 2924 (w) 2853 (m) 2050(m) 1920 (m) 1816 (m) 1799 (s) 1750 (s) 1700 (m) 1665 (w) 1568 (s) 1477 (s) 1291 (m) 1266 (m) 1240 (m) 1169(m) 1100(s) 1066 (w) 1025 (w) 966 (m) 928 (w) 852 (m) 755(s) 683 (w) 613 (w) 569 (m) 447(w) **Proton Magnetic Resonance Spectral Data (CDCl<sub>3</sub> / TMS),  $\delta$  in ppm:** 4.6 s 1H C-H methane, 7.1-7.3 m

13H Aromatic protons, 8.1 s 1H C-H benzimidazole  
**Mass Spectral Values ; m/z( %)**  
 :325 (30) 324 (25) 297 (6) 284 (24) 248 (40)  
 235(42) 233 (28) 208 (20) 206 (100) 205  
 (65) 158 (48) 156 (32) 131 (15) 192 (32) 128  
 (10) 118 (10) 117 (50) 116 (20) 92 (45) 91 (35)  
 90 (55) 89 (20)63 (28)

### 2.3. Synthesis of 2-( $\alpha$ -p Anisyl- $\alpha$ - benzimidazolo) methyl benzoxazole (3b)

A mixture of 2-p-Anisyl-2-benzimidazolo acetonitrile (0.02mol) and o-aminophenol (0.02mol) was taken in a 100mL round bottomed flask. Added about 5mL of concentrated hydrochloric acid it was heated for 10 hours in an oil bath maintained at 150-160°C until the evolution of ammonia gas ceased. The reaction mixture was kept overnight. 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 diluting with excess of water. The resulting solid was filtered, and washed with water and dried. It was recrystallised from chloroform. The pure sample

melted at 125-126°C.  
**Infra Red Spectral Data (KBr),  $\lambda$  values in  $\text{cm}^{-1}$ :** 3416 (m) 3376 (m) 3066(w) 2949 (w) 2925 (m)2853 (m) 2799 (w) 2449 (w) 1783 (m) 1742 (s) 1620 (s) 1580 (s) 1480(s) 1397 (w) 1295 (m) 1252 (s) 1172(m) 1132 (w) 1026 (m) 926 (w) 850 (w) 831(w) 753 (m) 704 (w) 634(w) 567 (m) 450(m)

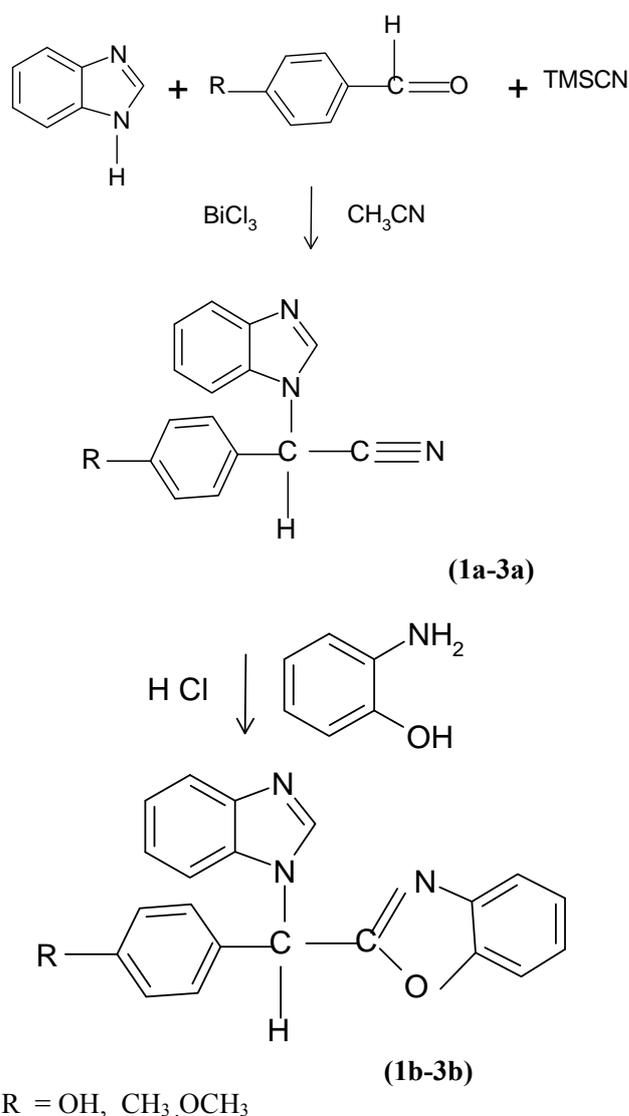
**Proton Magnetic Resonance Spectral Data (CDCl<sub>3</sub> / TMS ),  $\delta$  in ppm:** 3.9 s 3H -OCH<sub>3</sub>, 4.6 s 1H C-H methane, 6.7 -7.7 m 12H Aromatic protons 8.0 s 1H C-H benzimidazole  
**Mass Spectral Values ; m/z( %)** 355 (40) 354 (18) 324 (28) 285 (12) 265 (35) 263 (42) 248 (36)238 (55) 236(45) 158 (40) 156 (20)146(25) 144(16) 129 (38) 119 (20) 118 (28) 117 (30) 107(18) 92 (50) 91 (100) 90(28) 63(35)

### RESULTS AND DISCUSSION

The formation of 2-p-substituted phenyl-2-benzimidazolo acetonitriles (1a-3a) was confirmed by spectral values of IR and NMR and are presented in **Table 1**. In the present study, 2-( $\alpha$ -p-Substituted phenyl- $\alpha$ -benzimidazolo) methyl benzoxazoles were synthesized by condensation of 2-p-substituted phenyl-2-benzimidazolo acetonitriles (1a-3a) and o-aminophenol in the presence of hydrochloric acid. The synthetic route of these compounds were represented as Scheme-I.

**Table 1: Spectral data of the compounds (1a-3a)**

Sample No	IR (KBr) $\text{cm}^{-1}$ (Nitriles)	<sup>1</sup> H-NMR (CDCl <sub>3</sub> ) $\delta$ ppm
1a	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)
2a	2240	4.6(s,1H, -CH methine), 7.0-7.4 (m,8H,Ar-H), 8.2(s,1H,C-H, Benzimidazole)
3a	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 benzoxazoles**

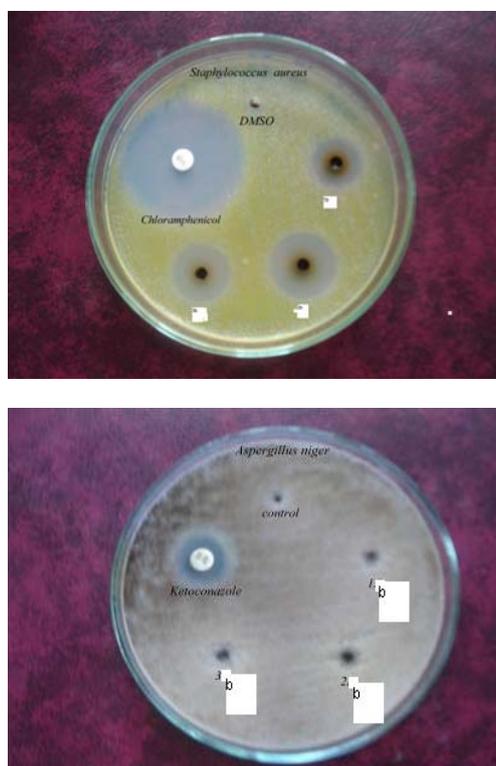
**Biological activities:**

The antibacterial screening of 1b, 2b and 3b compounds inhibited the activity of the following bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus Aureus*(Table 2& Figure 1). Thus, compound **3b** showed a higher activity against all the screened bacteria. This activity was more pronounced against Gram-negative than Gram-positive bacteria. This could be as a result of the

morphological differences between these micro-organisms. The antifungal screening of 1b, 2b and 3b compounds for the following fungi : *Aspergillus niger*, *Candida albicans* and *Candida tropicalis*(Table 2 Figure 1). The compound 3b only showed activities against all fungi and the compound 2b showed some activity against *Candida albicans*. The compound 1b inactive against all the fungi. Some selected photographs were shown.

**Table 2. Antibacterial and Antifungal activities of 1b,2b and 3b compounds.**

Bacteria(ORGANISM)	Zone of inhibition in mm				
	Chloramphenicol	Control(DMSO)	1b	2b	3b
<i>Escherichia coli</i>	27	-	8	11	13
<i>Pseudomonas aeruginosa</i>	37	-	12	27	25
<i>Staphylococcus aureus</i>	31	-	15	20	27
Fungus(ORGANISM)	Zone of inhibition in mm				
	Ketoconazole	Control(DMSO)	1b	2b	3b
<i>Aspergillus niger</i>	17	- -	6	6	
<i>Candida albicans</i>	15	-	-	6	6
<i>Candida tropicalis</i>	12	-	-	-	6



**Figure 1. Antibacterial and antifungal activities of 1b,2b and 3b compounds. (Selected Organism only shown)**

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