

## Synthesis of 4-Tetrahydropyridine-2-anilino-benzimidazoles

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A series of 2-anilinobenzimidazoles were derived from 2-chlorobenzimidazole. The condensation of methyl-1-benzyl-4-oxo-3-piperidinecarboxylate with 1,2-diamino-3,4-dimethoxybenzene in presence of xylene yielded dimethoxybenzimidazolinone compound, which was treated with phosphorous oxychloride to get 2-chlorobenzimidazole. This was reacted with anilines in presence of catalytic amount of dimethylformamide and concentrated hydrochloric acid yields 2-anilinobenzimidazoles.

**Key Words:** Synthesis, 4-Tetrahydro-pyridine-2-anilino benzimidazoles.

### INTRODUCTION

Although much work has been done in recent years on the synthesis of pyridinobenzimidazoles having neutroleptic activity<sup>1,2</sup>, but not much synthetic study has been carried out on pyridinobenzimidazoles substituted with 2-anilino groups. In the present paper, we describe the synthesis of 2-anilinobenzimidazole derivatives. Such type of substitution reaction was reported in other moiety<sup>3</sup>

### EXPERIMENTAL

Melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were determined with a FTIR spectrophotometer as KBr film unless otherwise mentioned. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> unless otherwise mentioned, on a 300 MHz spectrometer with TMS as internal standard. Chemical shift values are expressed in  $\delta$  (ppm). Mass spectra were mentioned as EI<sup>+</sup>. Petroleum ether refers to the fraction of b.p. 60–80°C. All compounds were homogeneous on TLC and gave proper spectral characteristics.

**3,4-Diamino veratrole (1):** As prepared as Ref. 4. Used directly in next step.

#### **1-Benzyl-4-[1,3-dihydro-2H-5,6-dimethoxy benzimidazole-2-one-1-yl]-1,2,5,6-tetrahydropyridine hydrochloride (3)**

A benzyl 4-piperidone hydrochloride (28 g, 0.098 mol) was dissolved in water (150 mL) and this solution was basified with 10% NaOH solution at 0°C and extracted with EtOAc. The EtOAc layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give free-base, which was dissolved in xylene (300 mL). This solution and 3,4-diamino veratrole compound<sup>4</sup> were refluxed with the aid of Dean

Stark apparatus under nitrogen atmosphere for 18 h. The reaction mixture was allowed to cool down and ethyl acetate was added. Then the organic layer was washed with dilute HCl. The aqueous acidic extract was separated and basified with 10% NaOH solution and extracted with EtOAc. The EtOAc layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. Residue was obtained which was crystallized from EtOAc (12.4 g) and mother liquor was concentrated and purified through silica gel column using MeOH- $\text{CHCl}_3$  (5 : 100) as eluent (4.0 g). Total yield 16.2 g (48.17%). Free base: m.p. 199°C. Analysis: Calcd. for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_3$  (363.41): C, 69.02, H, 6.34, N, 11.5. Found: C, 68.92, H, 6.14, N, 11.36. It was further converted into hydrochloride salt. m.p. 248–50°C;  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ): 2.7 (m, 2H), 3.15 (m, 4H); 3.64 (s, 2H,  $\text{CH}_2$  Ph), 3.88 (2s, 6H, 2OCH<sub>3</sub>), 5.86 (m, 1H), 6.68 (m, 2H, Ar—H), 7.38 (m, 5H, Ar—H). IR: 3088, 2961, 2820, 2341, 1685, 1489, 1384, 1195, 1023  $\text{cm}^{-1}$ . Mass,  $M^+$  = 365, 274, 246, 231, 172, 91. Analysis: Calcd. for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_3\cdot\text{HCl}$  (401.87): C, 62.76, H, 6.02, N, 10.46, Cl, 8.82%; Found: C, 63.14, H, 5.84, N, 10.4, Cl, 8.95%.

**1-Benzyl-4-[2-chloro-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (4)**

A solution of benzyl dimethoxybenzimidazole (17 g, 0.0455 mol) in  $\text{CHCl}_3$  (15 mL) was added to phosphorous oxychloride (500 mL) at room temperature over a period of 30 min. The reaction mixture was refluxed for 20 h. Then poured into ice, neutralized with 10% NaOH solution and extracted with  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated to give crude compound, which was crystallized from  $\text{CH}_2\text{Cl}_2$ -petroleum ether and mother liquor was purified through silica gel column using MeOH- $\text{CHCl}_3$  (2 : 100) as eluent. Total yield 13 g (87.6%). m.p. 161°C;  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ): 2.4 (m, 2H), 2.8 (m, 2H); 3.23 (m, 2H), 3.68 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 3.85 (2s, 6H, 2OCH<sub>3</sub>), 6.1 (m, 1H), 6.88 (s, 1H, Ar—H), 7.2 (s, 1H, Ar—H), 7.4 (m, 5H, Ar—H). IR: 2927, 2815, 2281, 1491, 1451, 1437, 1349, 1197, 1116, 1009  $\text{cm}^{-1}$ . Mass  $M^+$  = 383, 348, 264, 172, 146, 91. Analysis: Calcd. for  $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_2$  (383.86): C, 65.70, H, 5.78, N, 10.95, Cl, 9.24%; Found: C, 65.78, H, 6.29, N, 10.45, Cl, 9.32%.

**1-Benzyl-4-[2-(4-methoxyanilino)-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (5)**

To a solution of chloro compound 4 (0.4 g, 1.042 mmol) and *p*-anisidine (0.128 g, 1.04 mmol) in MeOH (10 mL), catalytic amount of conc. HCl and dry DMF were added. The reaction mixture was stirred at 70°C for 16 h. The solvent was evaporated and water was added. It was basified with 10% NaOH and extracted with ethyl acetate. The solvent layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. The residue obtained was passed through silica gel column using 50% ethyl acetate-petroleum ether as eluting agent. Yield 0.26 g (53.06%). m.p. 82–84°C; IR: 3419, 3063, 2926, 2361, 1610, 1556, 1510, 1485, 1235, 1031  $\text{cm}^{-1}$ . Mass,  $M^+$  = 470, 351, 336, 298, 283, 172, 91. Analysis: Calcd. for  $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_3$  (470.59): C, 71.47, H, 6.43, N, 11.91%; Found: C, 71.63, H, 6.47, N, 12.23%.

**1-Benzyl-4-[2-(2,4-dimethoxyanilino)-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (6)**

The title compound was prepared as the representative procedure for **5**. The reactants were chloro compound **4** (0.4 g, 1.042 mmol) and 2,4-dimethoxyaniline (0.16 g, 1.04 mmol). Yield 0.24 g (46.15%). m.p. 65–67°C; <sup>1</sup>H NMR: 2.5 (m, 2H), 2.9 (m, 2H), 3.2 (m, 2H); 3.76 (s, 2H, CH<sub>2</sub>Ph), 3.82 (s, 3H, OCH<sub>3</sub>), 3.95 (3s, 9H, 3-OCH<sub>3</sub>), 6.1 (m, 1H), 6.24 (s, 1H, Ar—H), 7.0 (m, 3H, Ar—H), 7.18 (s, 1H, Ar—H), 7.24 (m, 5H, Ar—H). IR: 3430, 3060, 2941, 2582, 2361, 1643, 1511, 1498, 1348, 1210, 1032 cm<sup>-1</sup>. Mass, M<sup>+</sup> = 500, 406, 381, 366, 349, 172, 91. Analysis: Calcd. for C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub> (500.595); C, 69.58, H, 6.44, N, 11.91%; Found: C, 69.32, H, 6.52, N, 11.70%.

**1-Benzyl-4-[2-(3,4-dimethoxyanilino)-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (7)**

The title compound was prepared as the representative procedure for **5**. The reactants were chloro compound **4** (0.4 g, 1.042 mmol) and 3,4-dimethoxyaniline (0.16 g, 1.04 mmol). Yield 0.28 g (53.85%). m.p. 134°C; IR: 3407, 3058, 2953, 2361, 1623, 1561, 1512, 1447, 1228, 1029 cm<sup>-1</sup>. Mass, M<sup>+</sup> = 500, 409, 393, 381, 366, 172, 91. Analysis: Calcd. for C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub> (500.595): C, 69.58, H, 6.44, N, 11.91%; Found: C, 69.32, H, 6.52, N, 11.70%.

**1-Benzyl-4-[2-(3,4,5-trimethoxyanilino)-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (8)**

The title compound was prepared as the representative procedure for **5**. The reactants were chloro compound **4** (0.4 g, 1.042 mmol) and 3,4,5-trimethoxyaniline (0.19 g, 1.04 mmol). Yield 0.29 g (54.4%). m.p. 74°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 2.35 (m, 2H), 2.82 (m, 2H), 3.28 (m, 2H), 3.67 (s, 2H, CH<sub>2</sub>Ph), 3.85 (5s, 15H, 5OCH<sub>3</sub>), 6.1 (m, 1H), 6.75 (s, 1H, AR—H), 7.05 (s, 1H, Ar—H), 7.4 (m, 7H, Ar—H). IR: 3329, 2995, 2936, 2361, 1609, 1538, 1508, 1462, 1234, 1127, 1026 cm<sup>-1</sup>. Mass, M<sup>+</sup> = 530, 439, 411, 396, 172, 91. Analysis: Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub> (530.62): C, 67.91, H, 6.46, N, 10.56%; Found: C, 70.20, H, 6.51, N, 10.50%.

**1-Benzyl-4-[2-(2,4-dimethylanilino)-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (9)**

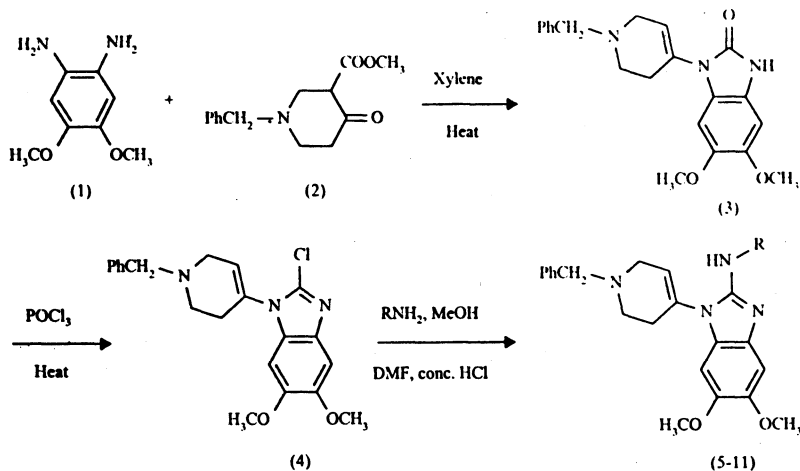
The title compound was prepared as the representative procedure for **5**. The reactants were chloro compound **4** (0.4 g, 1.042 mmol) and 2,4-dimethylaniline (0.126 g, 1.04 mmol). Yield 0.27 g (56.14%). m.p. 65°C; <sup>1</sup>H NMR: 2.28 (2s, 6H, 2CH<sub>3</sub>), 2.5 (m, 2H), 2.88 (m, 2H), 3.34 (m, 2H), 3.78 (s, 2H, CH<sub>2</sub>Ph), 3.92 (2s, 6H, 2OCH<sub>3</sub>), 6.05 (m, 1H), 6.65 (m, 2H, Ar—H), 7.2 (s, 1H, Ar—H), 7.3 (m, 6H, Ar—H). IR: 3357, 3063, 2921, 2813, 2361, 1620, 1574, 1539, 1485, 1357, 1237, 1166 cm<sup>-1</sup>. Mass, M<sup>+</sup> = 468, 377, 348, 334, 282, 229, 172, 91. Analysis: Calcd. for C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub> (468.597): C, 74.33, H, 6.88, N, 11.96%; Found: C, 74.19, H, 6.42, N, 11.72%.

### 1-Benzyl-4-[2-(4-fluoroanilino)-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (10)

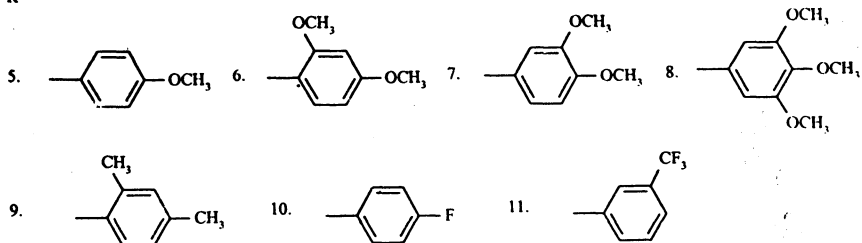
The title compound was prepared as the representative procedure for **5**. The reactants were chloro compound **4** (0.4 g, 1.042 mmol) and 4-fluoroaniline (0.116 g, 1.04 mmol). Yield 0.26 g (54.5%). m.p. 108°C; <sup>1</sup>H NMR: 2.5 (m, 2H), 2.9 (m, 2H), 3.32 (m, 2H), 3.76 (s, 2H, CH<sub>2</sub>Ph), 3.94 (2s, 6H, 2OCH<sub>3</sub>), 6.08 (m, 1H), 6.6 (s, 1H, Ar—H), 7.0 (m, 2H, Ar—H), 7.16 (s, 1H, Ar—H), 7.5 (m, 5H, Ar—H), 7.7 (m, 2H, Ar—H). IR: 3289, 3062, 2925, 2360, 1616, 1557, 1506, 1419, 1209, 1167 cm<sup>-1</sup>. Mass M<sup>+</sup> = 458, 351, 339, 229, 172, 91. Analysis: Calcd. for C<sub>27</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>2</sub> (458.533): C, 70.72, H, 5.93, N, 12.22%; Found: C, 70.43, H, 5.81, N, 11.93%.

### 1-Benzyl-4-[2-(3-trifluoromethylanilino)-5,6-dimethoxybenzimidazole-1-yl]-1,2,5,6-tetrahydropyridine (11)

The title compound was prepared as the representative procedure for **5**. The reactants were chloro compound **4** (0.4 g, 1.042 mmol) and 3-(trifluoromethyl) aniline (0.168 g, 1.04 mmol). Yield 0.29 g (54.71%). m.p. 84–86°C; <sup>1</sup>H NMR: 2.55 (m, 2H), 2.9 (m, 2H), 3.35 (m, 2H), 3.75 (s, 2H, CH<sub>2</sub>Ph), 3.95 (2s, 6H, 2OCH<sub>3</sub>), 6.1 (m, 1H), 6.62 (s, 1H, Ar—H), 7.2 (m, 2H, Ar—H), 7.5 (m, 6H, Ar—H), 7.9 (m, 1H, Ar—H), 8.1 (m, 1H, Ar—H). IR: 3396, 3085, 2932, 2832, 2361, 1606, 1572, 1540, 1487, 1458, 1336, 1114 cm<sup>-1</sup>. Mass, M<sup>+</sup> = 508, 401, 389, 374, 229, 172, 91. Analysis: Calcd. for C<sub>28</sub>H<sub>27</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub> (508.541): C, 66.13, H, 5.35, N, 11.02%; Found: C, 66.32, H, 5.5, N, 11.42%.



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## RESULTS AND DISCUSSION

The synthesis has been started with commercially available piperidone (**2**) and dimethoxy diaminobenzene (**1**), which was prepared by 3,4-dinitroveratrole hydrogenated with raney nickel<sup>4</sup> in the presence of xylene to afford (**3**) in 48% yield. Reaction of (**3**) with phosphorous oxychloride gave 2-chlorobenzimidazole (**4**) in 87% yield, which upon treatment with catalytic amount of dimethylformamide and concentrated hydrochloric acid with anilines afforded benzimidazoles in 46–56% yield. The structures (**3–12**) were confirmed by their elemental analysis, IR, NMR and mass spectra.

In conclusion, we have found an efficient method for preparation of a variety of 2-anilino benzimidazole derivatives.

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### DEVELOPMENTS IN MOLECULAR MECHANISMS OF BIOLOGICAL SIGNIFICANCE

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