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A novel approach to synthesis of flibanserin

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Abstract

The 1,3-dihydro-1-(2-bromoethyl)-3-isopropenyl-2H-benzimidazol-2-one was used as a starting material for making of the title compound. This compound treated with piperazine in the presence of TBAB as a catalyst which is treated with m-trifluoromethyl bromobenzene, in the presence of base and palladium acetate than followed by passing HCl gas to produced corresponding title compound in good yield with high purity. The structures of all the synthesized compounds were confirmed by IR, ¹H NMR, C¹³ NMR and Mass Spectral data.

Keywords: TBAB, trifluoromethyl bromo benzene, benzimidazole, piperazine.

Introduction

Aryl piperazine derivatives possess anti-histaminic, anti-hypertensive, adrenergic and anti-inflammatory activities [1]. They are also an important class of compounds in the field of neuropharmacology [2]. They bind with high affinity to serotonin sites [3, 4]. The compounds like 1-[3-(trifluoromethyl) phenyl]piperazine and 1-[3-(chloro)phenyl] piperazine are peripheral 5-HT agonists [5] and in addition have been shown to bind at central 5-HT sites [6].

The benzimidazole ring is an important pharmacophore in modern drug discovery. A variety of benzimidazoles are in use, like Thiabendazole, Flubendazole (anti-helminthic), Omeprazole, Lansoprazole (anti-ulcerative) and Astemizole (anti-histaminic). The chemistry and pharmacology of benzimidazoles have been of great interest to medicinal chemistry [7,8], because of its derivatives possessed various biological activities such as anti-oxidant [9,10], anti-microbial [11-16], anti-helminthic [17-19], anti-cancer [20], anti-hypertensive [21], anti-neoplastic [22], anti-inflammatory [23,24],

analgesic [25], anti-protozoal [26,27], anti hepatitis activities [28] and also shows anti-depressant activity [29].

The biological importance and considerable therapeutic potential of benzimidazol-2-ones and aryl piperazines generate considerable interest to us in designing the novel method of synthesis of 1-(2-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-2,3-dihydro-2-benzimidazol-2-one (Flibanserin).

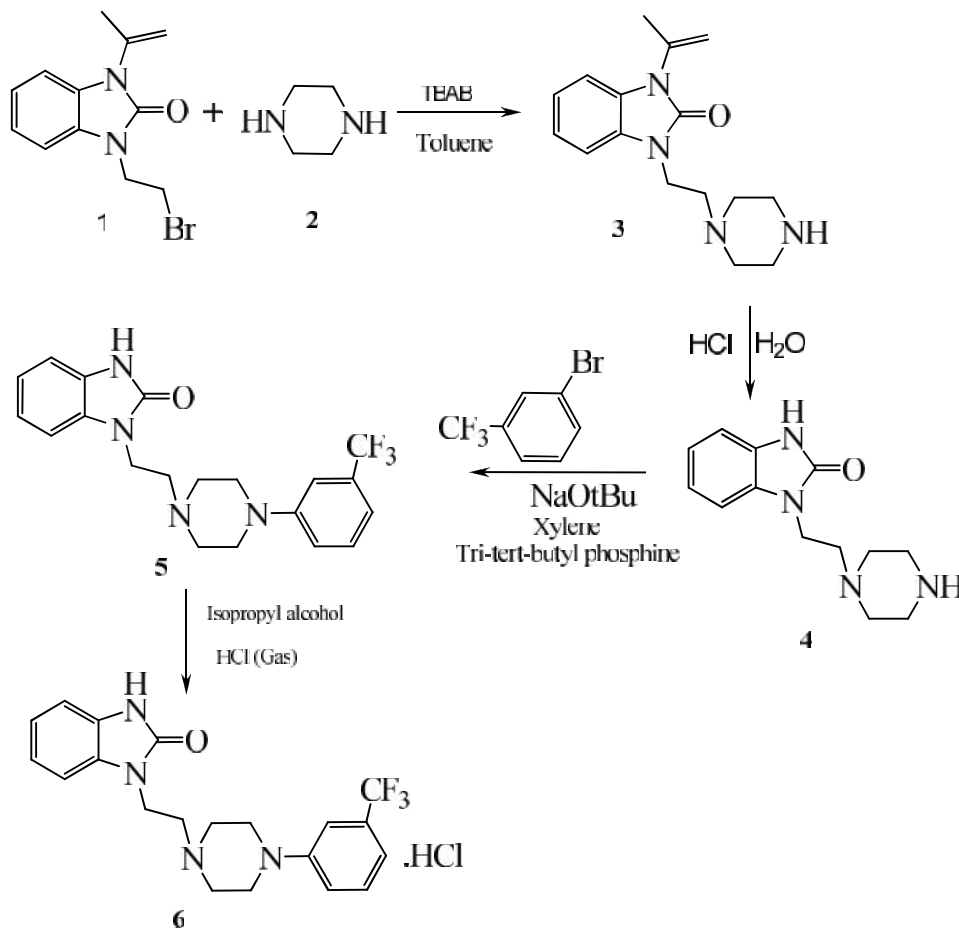
Results and Discussion

The synthetic strategy is shown in **Scheme-1**. The 1,3-dihydro-1-(2-bromoethyl)-3-isopropenyl-2H-benzimidazol-2-one **1** was used as a starting material for making the title compound. The compound **1** treated with piperazine in the presence of TBAB as a catalyst in toluene to form compound **2** which is reacted with m-trifluoromethyl bromo benzene, sodium tert. butoxide, palladium acetate

in xylene as solvent and added tri tertiary butylphosphine as catalyst than followed by passing HCl gas in isopropyl alcohol to produced

corresponding title compound in good yield. The structures of all the compounds were confirmed by IR, ¹H NMR, C¹³ NMR and Mass Spectral data.

Scheme 1



Experimental Section

All the melting points mentioned were determine in capillaries using Polman digital melting point apparatus (Model MP-96) and reported in degree centigrade. Reactions were monitored by TLC on silica gel-protected aluminum sheets (Type 60 F 254, Merck) and visualization was done using Iodine/UV lamp. The IR spectra were recorded in the solid state as K Br dispersion medium using Perkin-Elmer Spectrum One FT-IR spectrophotometer. The LC-MS has been performed on AB-4000 Q-trap LC-MS/MS mass spectrometer. ¹H NMR was recorded using 400 MHz Varian Mercury plus 400 MHz NMR spectrometer. The ¹H chemical shift values were reported on the scale in ppm,

Synthesis of 1, 3-dihydro-1-(2-piperazinyl)ethyl-3-isopropenyl-2H-benzimidazol-2-one (3):

Piperazine (12 gm), toluene (60 ml) and tetra butyl ammonium bromide (1 gm) mixture was heated to 60°C, added 1,3-dihydro-1-(2-bromoethyl)-3-isopropenyl-2H-benzimidazol-2-one (10 gm) and stirred for 4 h at 90 to 95°C. The reaction was monitored by TLC. The mixture was cooled to 60°C and added water (50 mL). The separated toluene layer distilled off under vacuum to get compound 3 as a white solid.

IR (K Br, cm⁻¹): 3287, 3088, 3063, 2946, 2860, 1686, 1610, 1370, 1357, 1118, 997, 951, 872, 842; ¹H NMR (DMSO-d₆) ppm: 7.1 (m, 1H), 6.8-6.9 (m, 3H), 5.0 (s, 1H), 4.75 (s, 1H), 3.2-3.3 (t, 2H), 2.8-3.1 (m, 4H), 2.6 (m, 2H), 2.3-2.5 (m, 4H), 2.1 (s, 3H). MS: 286 (M⁺).

Synthesis of 1,3-dihydro-1-(2-piperazinyl ethyl)-2H-benzimidazol-2-one (4):

To the mixture of concentrated hydrochloric acid (20 mL) and water (100 mL) was added 1,3-dihydro-1-(2-piperazinylethyl)-3-isopropenyl-2H-benzimidazol-2-one **3** (10 gm) and heated to 60 to 65 °C for 1 h. The mixture was cooled to room temperature and pH of the solution was adjusted to 9-10 with 10% sodium hydroxide solution, extracted with ethyl acetate and the organic layer was washed with water. After drying the solvent was removed under vacuum to get the compound **4** as a white solid in good yield.

IR (K Br, cm⁻¹): 3260, 3079, 3025, 2942, 2807, 1686, 1509; ¹H NMR (DMSO-d₆) ppm: 7.0 (m, 4H), 3.2 (t, 2H), 2.8 (m, 4H), 2.6 (m, 2H), 2.4 (s, 2H); ¹³C NMR (DMSO-d₆) ppm: 121, 120, 109, 108, 55, 52, 51; MS: 246 (M⁺).

Synthesis of 1-[2-(4-(3-trifluoromethyl phenyl)piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazole-2-one (6):

To a mixture of 1,3-dihydro-1-(2-piperazinyl ethyl)-2H-benzimidazol-2-one **4** (10 gm), m-trifluoromethylbromobenzene (9 gm), sodium tertiary butoxide (5.5 gm), palladium acetate (4.5 mg) and xylene (80 mL) was added tri tertiary butylphosphine (0.2 mL). The mixture was heated to 120°C and stirred for 3 h. The reaction mass was cooled, added water (100 mL) and extracted with ethyl acetate and the organic layer was washed with water. After drying the solvent was removed under vacuum to yield the compound **5** in good yield. The compound is dissolved in isopropyl alcohol and passed HCl gas to get corresponding Flibanserin hydrochloride as salt with high purity.


IR (K Br, cm⁻¹): 3399, 3198, 3147, 2979, 2957, 16863, 1590, 1490, 1450, 1354, 1310, 1167, 1111, 946, 779; ¹H NMR (DMSO-d₆) ppm: 11.5 (s, 1H), 11.05 (br, s, 1H), 7.47-7.01 (m, 8H), 4.33-4.30 (t, 2H), 4.00-3.98 (t, 2H), 3.72-3.71 (t, 2H), 3.45 (t, 2H), 3.24-3.23 (t, 4H); ¹³C NMR (DMSO-d₆) ppm: 154.23, 151.13, 130.30, 129.84, 128.49, 123.32, 120.62, 118.55, 114.46, 110.72, 108.62, 107.81, 55.35, 52.43, 47.54, 37.50; MS: 391 (M+H).

References

- Mull, R.P, Tannenbaum, C, Dapero. M.R, Bernier, M, Yost, W, DeStevens. G. J. Med. Chem. 8, **1965**, 332.
- Fuller, R. W, Maso. N.R, Molloy. B.B. Biochem. Pharmacol. 29, **1980**, 833.
- Martin, G.E, Elgin, R. J, Jr, Kesslick, J.M, Badly, W.J, Mathiasen, J.R, Shank. R.P, Scott, M.K. Eur. J. Pharmacol. 156, **1988**, 223.

- Lyon, R.A, Titeler, M, McKenney, J.D, Magee, P.S, Glennon, R.A. J. med. Chem. 29, **1986**, 630.
- Fuller, R.W.; Snoddy, H.D.; Mason, N.R.; Molloy, B.B.; Eur. J. Pharmacol. 52, **1978**, 11.
- Fuller, R.W.; Mason, N.R.; Molloy, B.B.; Biochem. Pharmacol. 29, **1980**, 833.
- Wright JB **1951** Chem. Rev. 48 397; (b) Preston P N **1974** Chem. Rev. 74, 279.
- Preston PN **1980** In Benzimidazole and congeneric tricyclic compounds (eds) A Weissberger and E C Taylor (New York: John Wiley and Sons), Part-2 pp.63-147; (b) Grimmett M R **1984** In Comprehensive heterocyclic chemistry (ed.) K T Pots (Oxford: Pergamon) pp. 345-498; (c) Hoffman K **1953** In Imidazole and its derivatives (ed.) A Weissberger; The chemistry of heterocyclic compounds (New York: Inter science Publishers, Inc) pp. 247-317.
- Kus C, Ayhan-Kilcigil G, Can Eke B and Iscan M, Arch. Pharm. Res. 27, **2004**, 156.
- Ates-Alagoz Z, Kus C and Coban T, J. Enzyme Inhib. Med. Chem. 20, **2005**, 325.
- Goker H, Kus C, Boykin D W, Yildiz S and Altanlar N, Bioorg. Med. Chem. 10, **2002**, 2589.
- Goker H, Ozden S, Yildiz S and Boykin D W, Eur. J. Med. Chem. 40, **2005**, 1062.
- Desai K G and Desai K R, Bioorg. Med. Chem. 14, **2006**, 8271.
- Kazimierczuk Z, Upcroft J A, Upcroft P, Gorska A, Starosciak B and Laudy A, Acta Biochim. Polon. 49, **2002**, 185.
- Mohammad B G, Hussien M A, Abdel-Alim A A and Hashem M, Arch. Pharm. Res. 29, **2006**, 26.
- Pawar N S, Dalal D S, Shimpi S R and Mahulikar P P, Eur. J. Pharm. Sci. 21, **2004**, 115.
- Dubey R, Abuzar S, Sharma S, Chatterjee R K and Katiyar J C, J. Med. Chem, 28, **1985**, 1748.
- Mavrova A T, Denkova P S, Tsenov Y A, Anichina K K and Vutchev D L, Bioorg. Med. Chem 15, **2007**, 6291.
- Ravina E, Sanchez-Alonso R, Fueyo J, Baltar M P Bos J, Iglesias R and Sanmartin M L, Arzneim, Forsch. 43, **1993**, 684.
- Starcevic K, Kralj M, Ester K, Sabol I, Grce M, Pavelic K and Karminski-Zamola G, Bioorg. Med. Chem. 15, **2007**, 4419.
- Kubo K Inada Y, Kohara Y, Sugiura Y, Ojima M, Itoh K, Furukawa Y, Nishikawa Y K and Naka T, J. Med. Chem. 36, **1993**, 1772.
- Ram S, Wise D S, Wotring L L, McCall J W and Townsend L B, J. Med. Chem. 35, **1992**, 539.
- Lazer E S, Matteo M R and Possanza G J, J. Med. Chem. 30, **1987**, 726.
- Lackner T E and Clissold S P, Drugs 38, **1989**, 204.
- Ito K, Kagaya H, Fukudat, Yoshino K and Nose T, Arzneim. Forsch. Drug Res. 32, **1982**, 49.
- Navarette- Vazquez G, Cedilla R, Hernandez-Campos A, Yopez A, Hernandez-Luis F, Valdez J,

- Morales R, Cortes R, Hernandez M and Castillo R, Bioorg. Med. Chem. 11, **2001**, 187.
27. Katiyar S K, Gordon V R, McLaughlin G L and Edlind T D, Antimicrob. Agents Chemother. 38, **1994**, 2986.
28. Li Y F, Wang G F, He P L, Huang W G, Zhu F H, Gao H Y, Tang W, Luo Y, Feng C L, Shi L P, ren Y D, Lu W and Zuo J P, J. Med. Chem. 49, **2006**, 4790.
29. Drugs of the future, 23(1), **1998**, 9-16.

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