Research Article

Synthesis and Analgesic Activity of Novel Derivatives of 1,2-Substituted Benzimidazoles

Shobhit Srivastava, S. N. Pandeya, Meena K. Yadav, and B. K. Singh

Department of Pharmaceutical Chemistry, Saroj Institute of Technology & Management, Lucknow, UP 226002, India

Correspondence should be addressed to Shobhit Srivastava; shobhit_pharma@yahoo.co.in

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A series of novel 2-phenylhydrazinomethyl and 2-(2-hydroxyphenyl)-benzimidazole derivatives substituted at the N1-position of benzimidazole nucleus were synthesized as well as screened for analgesic activity. Some of these compounds showed promising analgesic activity when compared with the standard drug diclofenac sodium. The incorporation of a phenylhydrazinomethyl nucleus at 2-position of benzimidazole compound gave a biologically active pharmacophore.

1. Introduction

Benzimidazole derivatives are well-known biologically active N-containing heterocycles [1], widely used as drugs such as proton pump inhibitor (Omeprazole [2, 3]), antihelminthic (Albendazole [4, 5]), antidopaminergic (Domperidone [6, 7]), and antipsychotic agent (Pimozide). Specifically, the 2-substituted analogs of benzimidazoles are known to be potent biologically active compounds [8–10]. Moreover, benzimidazole derivatives are structural isosteres of naturally occurring nucleotides, which allows them to interact easily with the biopolymers of the living systems.

2. Experimental

Melting points were determined with an electrothermal melting point apparatus and are uncorrected Table 1. The homogeneity of the synthesized compounds was monitored by thin layer chromatography on Merck Silica Gel precoated plates and visualization was done by exposure to iodine vapour. Unless stated, room temperature was approximately 25°C. Separation of pure compound was done by column chromatography by using hexane and ethylacetate. ¹H NMR was recorded on BRUKER DRX-300 spectrometer (operating

at 300 MHz) using DMSO as solvent. Tetramethyl silane (0.00 ppm) served as an internal standard in ¹H NMR. IR spectra were recorded as thin films with a Shimadzu FT-IR spectrophotometer. Elemental analysis was done on Elementar Vario EL III machine at Central Drug Research Institute (CDRI). All the chemicals were commercially purchased from LOBA CHEMIE and were used as received.

2.1. General Procedure for the Synthesis of 2-(Chloromethyl)-1H-benzimidazole. Mixture of o-phenylenediamine (5.4 g, 0.05 mol), chloroacetic acid (7.1 g, 0.08 mol), and 4N hydrochloric acid (17.17 mL) was heated at reflux for 45 minutes (Scheme 1). The mixture was allowed to stand overnight, filtered, diluted with 100 mL of distilled water, cooled, and carefully neutralized with 6N ammonium hydroxide solution. The solution was kept cold during the neutralization and stirred vigorously to prevent the formation of gums. Product formed was filtered, washed well with cold water and then was placed in vacuum desiccators until dry [11–13]. Recrystallization was done using ethyl alcohol. Yield: 4 g (48%), MP: 160–162°C, R_f: 0.33; IR(KBr) cm⁻¹: 3150(CH, str, ar), 2976(CH, str, ali), 3320(–NH, str), 1657(C=N, str), 492(C=C, str), 787(C–Cl, str); elemental analysis (%) (calculated/found):

Compounds	Secondary amines	Substituents (R)
1a	Diethylamine	
1b	Piperazine	
1c	Piperidine	
1d	Morpholine	
1e	Dimethylamine	

SCHEME 1

TABLE 1: Physicochemical data for synthesized compounds.

Compound code	Molecular formula	Molecular weight	Yield (%)	Melting point (°C)	Rf value	Solubility in DMSO
1a	C ₂₀ H ₂₇ N ₅	337.46188	92.0	120–122	0.44	soluble
1b	C ₂₀ H ₂₆ N ₆	350.46064	73.0	183–185	0.19	soluble
1c	C ₂₁ H ₂₇ N ₅	349.47258	23.0	218–220	0.29	soluble
1d	C ₂₀ H ₂₅ N ₅ O	351.4454	43.0	118–120	0.24	soluble
1e	C ₁₈ H ₂₃ N ₅	309.40872	37.50	230–232	0.31	soluble
2	C ₁₈ H ₂₀ N ₄ O	308.3776	22.0	238–240	0.39	soluble

* Eluants for TLC were ethyl acetate: benzene (1: 4).

C(57.67/57.27); H(4.23/3.83); Cl(21.28/20.88); N(16.81/17.21); ¹H NMR (DMSO-*d*₆): δppm 5.0(1s, 1H, N-H), 7.7(m, 2H, Ar-CH), 4.6(s, 2H, CH₂-Cl).

2.2. Procedure for the Synthesis of 2-[(2-Phenylhydrazinyl)methyl]-1H-benzimidazole(1) (Scheme 1). A mixture of the above synthesized substituent (0.02 mole) and phenylhydrazine (0.0217 mole) was heated at reflux in methanol for 5 hours. The hot mixture was poured in crushed ice with constant stirring, the solid was filtered, dried, and recrystallized from absolute ethanol [14]. Yield: 2.0 g (40%); MP: 80°C–82°C; Rf: 0.81; IR(KBr) cm⁻¹: 3053 (CH, str, ar), 2978(CH, str, ali), 3487, 3350(NH, str), 1655(C=N, str), 1456 (C=C, str); elemental analysis(%) (calculated/found): C(70.57/70.17); H(5.92/5.52); N(23.51/23.11); ¹H NMR (DMSO-*d*₆): δppm 5.0(1s, 1H, N-H), 7.7(1s, 2H, Ar-CH), 3.81(1s, 2H, CH₂-N), 4.0 (1s, 1H, Ar-N-H).

2.3. Procedure for the Preparation of Mannich Bases of (1) with Different Secondary Amines

- (a) Synthesis of *N*-ethyl-*N*-({2-[(2-phenylhydrazinyl)methyl]-1H-benzimidazole-1 yl)methyl} ethanamine (1a): a mixture of compound 1 (1 g, 0.004 mol), formaldehyde (5 mL, 0.004 mol), diethylamine(0.5 mL, 0.004 mol), and HCl (2 mL) was heated at reflux in methanol for 2.5 hours. The hot mixture was filtered and the filtrate obtained was cooled in cold water [15]. Crystals obtained were separated by filtration and purified by column chromatography and recrystallized from absolute ethanol. Yield: 1.230 g (92%); MP: 120°C–122°C; Rf: 0.44; IR(KBr) cm⁻¹: 3040(CH, str, ar), 2978(CH, str, ali), 3320, 3405(-NH, str), 1557(C=N, str); elemental analysis (%) (calculated/found): C(70.56/70.16); H(7.79/7.39); N(21.65/21.25); ¹H NMR (DMSO-*d*₆): δppm 7.7(1s, 2H, Ar-CH), 3.81(1s, 2H, CH₂-NH), 4.0(1s, 1H, Ar-N-H), 2.0(1s, 1H, N-H), 1.0(1s, 6H, CH₃).
- (b) Synthesis of 2-[(2-phenylhydrazinyl)methyl]-1-(piperazin-1-ylmethyl)-1H-benzimidazole (1b): a mixture of compound 1 (1 g, 0.004 mol), formaldehyde (5 mL, 0.004 mol), piperazine (360 mg, 0.004 mol), and HCl (2 mL) was heated at reflux in methanol for 3 hours. The hot mixture was filtered and the

filtrate obtained was cooled in cold water. Crystals obtained were separated by filtration and purified by column chromatography and recrystallized from absolute ethanol. Yield: 0.950 g (73%); MP: 183°C–185°C; Rf: 0.19; IR(KBr) cm⁻¹: 3180(CH, str, ar), 2979(C H, str, ali), 3358, 3340(-NH, str), 1667(C=N, str), 1250(-CN, str); elemental analysis (%) calculated/found: C(67.83/67.43); H(7.19/7.59); N(16.45/16.05); ¹H NMR (DMSO-*d*₆) spectra: δppm 2.0(1s, 1H, N-H), 7.7(1s, 4H, Ar-CH), 3.81(1s, 2H, CH₂-N), 4.0(1s, 1H, Ar-N-H), 2.0(1s, 1H, amine N-H)

- (c) Synthesis of 2-[(2-phenylhydrazinyl)methyl]-1-(piperidin-1-ylmethyl)-1H-benzimidazole (1c): a mixture of compound 1 (1 g, 0.004 mol), formaldehyde (5 mL, 0.004 mol), piperidine (0.42 mL, 0.004mol), and HCl (2 mL) was heated at reflux in methanol for 3 hours. The hot mixture was filtered and the filtrate obtained was cooled in cold water. Crystals obtained were separated by filtration. The residue was separated. Yield: 0.300 g (23%); MP: 218°C–220°C; Rf: 0.38; IR(KBr) cm⁻¹: 3252(CH, str, ar), 2976 (CH, str, ali), 3380, 3410 (-NH, str), 1658(C=N, str), 1205(-CN, str); elemental analysis (%) calculated/found: C(71.61/71.21); H(7.51/7.11); N(20.88/20.48); ¹H NMR (DMSO-*d*₆) spectra: δppm 2.0(1s, 1h, N-H), 7.7(1s, 4H, Ar-CH), 3.81(1s, 2H, CH₂-N), 4.0(1s, 1H, Ar-N-H), 1.05(1s, 4H, amine CH₂), 4.08(1s, 2H, meth CH₂).
- (d) Synthesis of 1-(morpholin-4-ylmethyl)-2-[(2 phenylhydrazinyl)methyl]-1H-benzimidazole (1d): a mixture of compound 1(1 g, 0.004 mol), formaldehyde (5 mL, 0.004 mol), morpholine (0.37 mL, 0.004 mol), and HCl (2 mL) was heated at reflux in methanol for 3 hours. The hot mixture was filtered and the filtrate obtained was cooled in cold water. Crystals obtained were separated by filtration and purified by column chromatography and recrystallized by absolute ethanol. Yield: 0.550 g (43%); MP: 118°C–120°C; Rf: 0.24; IR(KBr) cm⁻¹: 3150(CH, str, ar), 2980 (CH, str, ali), 3310(-NH, str), 1657(C=N, str), 1620(C-O, str), 1240(-CN, str); elemental analysis (%) calculated/found: C(67.63/67.23); H(6.87/6.47); N(20.76/20.36); ¹H NMR (DMSO-*d*₆) spectra: δppm 2.0(1s, 1H,

SCHEME 2

N-H), 7.2(m, 4H, Ar-CH), 3.81(1s, 2H, CH₂-N), 4.0(1s, 1H, Ar-N-H), 3.6(1s, 4H, amine O-CH).

- (e) Synthesis of *N,N*-dimethyl-1-{2-[(2-phenylhydrazinyl)methyl]-1*H*-benzimidazol-1-yl}methanamine (1e): a mixture of compound 1(1 g, 0.004 mol), formaldehyde (5 mL, 0.004 mol), dimethylamine (0.21 mL, 0.004 mol), and HCl (2 mL) was heated at reflux in methanol for 3 hours. The hot mixture was filtered and the filtrate obtained was cooled in cold water [16]. Crystals obtained were separated by filtration and purified by column chromatography and recrystallized by absolute ethanol. Yield: 0.450 g (37.5%); MP: 230°C–232°C; Rf: 0.29; IR(KBr) cm⁻¹: 3180(CH, str, ar), 2978 (CH, str, ali), 3350(-NH, str), 1658(C=N, str); elemental analysis (%) calculated/found: C(69.12/69.57); H(7.17/7.57); N(23.71/23.31); ¹H NMR (DMSO-*d*₆) spectra: δppm 2.0(1s, 1H, N-H), 7.2(m, 4H, Ar-CH), 3.81(1s, 2H, CH₂-N), 4.0(1s, 1H, Ar-N-H), 2.27(1s, 6H, amine N-CH₃).

2.4. Procedure for the Synthesis of 2-(1*H*-benzimidazol-2-yl)phenol (Scheme 2). A mixture of o-phenylenediamine (2.70 g, 0.05 mol), salicylic acid (3.55 g, 0.05 mol), and 4N hydrochloric acid (25 mL) was heated at reflux for 5 hours. The completion of the reaction was monitored through TLC. The mixture was allowed to stand over-night, filtered, diluted with 50 mL of distilled water, cooled, and carefully neutralized with 6N ammonium hydroxide solution. The solution was kept cold during the neutralization and stirred

vigorously to prevent the formation of gums. Product formed was filtered, washed well with cold water, and then was placed in vacuum desiccator until dry [17]. Yield: 3.20 g (32%); MP: 208°C–210°C; Rf: 0.24; IR(KBr) cm⁻¹: 3180 (CH, str, ar), 3310 (-NH, str), 1657(C=N, str), 3404(OH, str); elemental analysis (%) calculated/found: C(74.27/74.67); H(4.79/4.39); N(13.33/13.73); ¹H NMR (DMSO-*d*₆) spectra: δppm 5.0(1s, 1H, N-H), 7.7(1s, 2H, Ar-CH), 5.1(1s, OH).

2.5. Synthesis of 2-(1-Piperazin-1-ylmethyl-1*H*-benzimidazol-2-yl)-phenol (2). a mixture of the above synthesized compound(1 g, 0.004 mol), formaldehyde (5 mL, 0.004 mol), piperazine (0.410 g, 0.004 mol) and HCl(2 mL) was heated at reflux in methanol for 3 hours. The hot mixture was filtered and cooled in cold water. Crystals obtained were separated by filtration and purified by column chromatography and recrystallized by absolute ethanol. Yield: 0.300 g (22%); MP: 238°C–240°C; Rf: 0.39; IR(KBr) cm⁻¹: 3158(CH, str, ar), 2978(CH, str, ali), 3340(-NH, str), 1668(C=N, str), 3347(OH, str), 1278(-CN, str); elemental analysis (%) calculated/found: C(70.11/70.51); H(6.54/6.94); N(18.17/18.37); ¹H NMR(DMSO-*d*₆): δppm 1.2(s, 2H, CH₂), 3.4(s, 1H, Pipera-H), 9.83(s, O-H), 7.4(t, 4H, ar-H).

2.6. Biological Activity (Analgesic Activity by Acetic Acid Induced Writhing Test). Analgesic activity was determined by calculating total number of writhings, followed by intraperitoneal (IP) administration of 0.6% (0.1 mL/10 g) acetic acid in mice. 7 Albino mice of either sex (25–30 g) were used. Synthesized compounds (1a, 1b, 1c, 1d, 1e, 2) were administered

TABLE 2: Acetic-acid-induced writhing response in mice.

S. no.	Derivative	Dosage	No. of writhings in 20 min (mean $\pm$ S.E.M)	% Analgesic activity*
1	Control	Vehicle	75.66 $\pm$ 2.15	0
2	1a	20 mg/kg	19.00 $\pm$ 1.84	74.88**
3	1b	20 mg/kg	33.66 $\pm$ 1.83	55.51**
4	1c	20 mg/kg	33.33 $\pm$ 1.27	55.94**
5	1d	20 mg/kg	26.83 $\pm$ 1.41	64.53**
6	1e	20 mg/kg	23.33 $\pm$ 2.00	69.16**
7	2	20 mg/kg	22.83 $\pm$ 1.42	70.12**
8	Diclofenac	20 mg/kg	08.16 $\pm$ 0.85	89.21***

N = 6; Student's *t*-test;

* $P \leq 0.05$;

** $P \leq 0.01$;

*** $P \leq 0.0001$ when compared with control.

IP (0.5 mL) as a suspension in sterile 0.9% DMSO solution as vehicle. Diclofenac (10 mg/kg) was used as the standard drug under same conditions. Acetic acid solution was administered IP 30 min after administration of the compounds. 10 min after intraperitoneal injection of acetic acid solution, the

number of writhings per animal was recorded for 20 min. Control animals received an equal volume of vehicle [17]. Results of percentage Analgesic activity of compounds was calculated using the following formula and the results are shown in Table 2:

$$\% \text{ Analgesic activity} = \frac{\text{No. of writhings for control} - \text{No. of writhings for test compound}}{\text{No. of writhings for control}} * 100. \quad (1)$$

3. Results and Discussion

The series of above synthesized compounds (1a, 1b, 1c, 1d, 1e, 2) in Table 1 were evaluated for analgesic activity by acetic-acid-induced writhing test *in vivo* on albino mice. Diclofenac sodium was used as the standard drug in above-cited test. In Table 2 The compounds (1a, 2) showed good activity and compounds (1b, 1c, 1d, 1e) showed moderated activity when compared with the standard drug. Compound 1a was almost equal in activity to the standard drug diclofenac and was considered the lead molecule. The results were evaluated by measuring the mean $\pm$ S.E.M and *P* value. Thus, 2-substitution of phenylhydrazinomethyl on benzimidazole moiety and use of different secondary amines for preparation of Mannich bases at N1 of 2-substituted benzimidazole ring increases the compound's activity against peripheral analgesia.

4. Conclusion

The present work has clearly demonstrated that 2-chloromethylbenzimidazole moiety may be successfully used to synthesize a wide variety of benzimidazole derivatives of pharmaceutical interest. Moreover, in general the desired compounds are obtained in a single step with clean high yields. Six derivatives of 2-substituted benzimidazole were prepared out of that compounds 1a and 2 possess potent analgesic activity as shown in the acetic-acid-induced writhing test. Hence, the focus is on the synthesis of potent

1,2-substituted benzimidazole derivatives as potential drug-like scaffolds for future development.

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