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Short Communication

Benzimidazoles with biphenyls: Synthesis of 5-substituted-2-*n*-propyl-1-[(2'-carboxybiphenyl-4-yl-)methyl]benzimidazoles

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Abstract

A one-step coupling of substituted benzimidazoles with biphenylcarboxylic moiety mediated by potassium carbonate is described. The biphenylcarboxylic moiety was prepared from 9-H-fluorenone and substituted benzimidazoles were synthesized from *o*-phenylenediamine and butyric acid.

Keywords: Benzimidazoles, biphenyls, angiotensin II, hypertension.

1. Introduction

Substituted biphenyls and benzimidazoles constitute important chemical classes of compounds having a number of biological, pharmacological and microbiological activities [1]–[5]. Out of these, antihypertensive activity of these compounds is of major concern, which they produce by acting as angiotensin-II receptor antagonists [6]–[11].

In this paper, we report a method for the synthesis of 5-substituted-2-*n*-propyl-1-[(2'-carboxybiphenyl-4-yl) methyl]benzimidazoles via coupling of substituted benzimidazoles with substituted biphenyl, which may produce an antihypertensive activity by acting as potential angiotensin-II receptor antagonist. The present series of compounds have been designed and synthesized employing benzimidazole replacement for the imidazole ring in the lead compound losarten. These compounds are intended to explore the substitution possibilities at 5-position of benzimidazole system, which can be instrumental in designing novel, potent and orally active angiotensin-II antagonists.

2. Experimental

All melting points were determined by open capillary method and were uncorrected. IR spectra were recorded on Hitachi 230–50 IR spectrophotometer and ^{1}H NMR spectra on Bruker AC 300F (300 MHz) spectrometer with TMS as internal standard. Mass spectra were recorded on JEOL-JMS D300 mass spectrometer.

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2.1. *2-Propylbenzimidazole (AJ_1)*

o-Phenylenediamine (0.25 mole) and butyric acid (0.50 mole) were placed in a round bottom flask and refluxed for 13 h. The reaction mixture was then cooled and basified (pH 7–8) with 20% sodium hydroxide solution. The crude product was dissolved in 95% ethanol and digested with activated charcoal for 45 min. Boiling water was then added to the filtrate till slight turbidity appeared. The solution was then made clear by the addition of a few drops of ethanol and kept for recrystallization. The product was obtained as white, needle-shaped crystals in 72% yield, m.p. 148°C (Found, C, 74.89; H, 7.61; N, 17.43; $C_{10}H_{12}N_2$ requires C, 74.97; H, 7.55; N, 17.48%). IR (KBr): 3625–3162 (broad N-H stretching), 3082 and 3053 (aromatic C-H stretching), 2928 and 2834 (aliphatic C-H stretching), 1480 (N-H bending), 1421 (C=C and C=N ring stretching), 899 (N-H wagging), 727 cm^{-1} (out of plane C=C bending); ^1H NMR ($CDCl_3$): δ 4.58 (1H, s, NH), 1.01 (3H, t, J = 7.34 Hz, terminal methyl of propyl chain), 1.89 (2H, sextet, J = 7.5 Hz, central CH_2); Mass (*m*/*z*): 160 (M^+), 132 (M-CH_2=CH_2).

2.2. *5-Nitro-2-propyl benzimidazole (AJ_2)*

Concentrated nitric acid (7.5 ml) was placed in a three-necked RBF fitted with a mechanical stirrer. The flask was immersed in ice-cold water and concentrated sulphuric acid (7.5 ml) was added slowly down the condenser with slow stirring. 2-Propylbenzimidazole (AJ_1) (0.028 mole) was then added in portions over 1 h at such a rate that the temperature did not exceed 35°C. After continuous stirring for 12 h at room temperature, the reaction mixture was poured very slowly over crushed ice with vigorous stirring. The precipitated product was filtered out and washed with cold water (90.6% yield, m. p.140°C) (Found, C, 58.48; H, 5.38; N, 20.52; $C_{10}H_{11}N_3O_2$ requires C, 58.53; H, 5.40; N, 20.48%). IR (KBr): 3677–3100 (broad N-H stretching), 1636 and 1384 (C=C and C=N ring stretching), 1530 and 1346 cm^{-1} (NO_2 asymmetrical and symmetrical stretching); ^1H NMR ($CDCl_3$): δ 8.69 (1H, s), 8.34, (1H, d, J=8.7 Hz), 3.21 (2H, t, J=7.2Hz), 1.97 (2H, sextet, J=7.2 Hz), δ 1.06 (3H, t, J=7.2Hz); Mass (*m*/*z*): 205 (M^+), 177 (M-CH_2= CH_2), 160 (M-NO_2).

2.3. *Biphenyl-2-carboxylic acid (AJ_4)*

Potassium hydroxide (0.53 mole) was fused at 180–200°C in a two-necked RBF fitted with a mechanical stirrer. Finely powdered 9H-fluorenone (AJ_3) (0.055 mole) was added in six portions over 30 min with vigorous stirring and the temperature was maintained at 180–200°C for further 30 min. The hot slurry was then poured in ice-cold water with vigorous stirring. The resulting suspension was filtered at pump. The filtrate was acidified with concentrated HCl to pH 5.0 resulting in precipitation of byproduct, which was filtered under suction, washed with distilled water, and the filtrate was again acidified with concentrated HCl. The precipitated product was filtered under suction and dried in air. The product was recrystallized from CCl_4 (Yield 81%, m.p. 110°C) (Found, C, 78.79; H, 5.15; $C_{13}H_{10}O_2$ requires C, 78.77; H, 5.09%). IR (KBr):3600–2750 (broad O-H stretching), 1760 (C=O stretching), 1400 cm^{-1} (C-OH in-plane bending); ^1H NMR ($CDCl_3$): δ 9.03 (1H, s, COOH), 7.9 (1H, d, J=9.0 Hz); Mass (*m*/*z*): 198 (M^+), 181 (M-OH), 153 (M-COH), 152 (M-H_2O, CO).

2.4. *4-Acetamidomethyl-biphenyl-2'-carboxylic acid (AJ_5)*

Biphenyl-2-carboxylic acid (AJ_4) (0.05 mole) was dissolved in concentrated H_2SO_4 (12.12 ml). Acetamide (0.15 mole) was added in one portion followed by the addition of paraformaldehyde

(0.05 mole) in portions. The solution was heated at 55°C along with stirring for 3 h and the hot mixture was poured over ice water. The resulting solid was filtered out (Yield 21%, m.p.145°C); (Found, C, 71.31; H, 5.62; N, 5.26; $C_{16}H_{15}NO_3$ requires C, 71.36; H, 5.61; N, 5.20%). IR (KBr): 3500–3300 (broad O-H and N-H stretching), 3070 (aromatic C-H stretching), 2925 (aliphatic C-H stretching), 1636 (C=O stretching of amide), 1553 (N-H bending of amide), 1456 cm^{-1} (C-N stretching); ^1H NMR ($CDCl_3$): δ 8.1 (1H, s, COOH), 4.46 (2H, s, CH_2 of acetamide), 2.10 (3H, s, CH_3); Mass (*m*/*z*): 269 (M^+), 180 (M-CH_3CHO, COOH), 180 (M- CH_3CO, COOH).

2.5. *4-Chloromethylbiphenyl-2'-carboxylic acid (AJ_6)*

4-Acetamidomethyl-biphenyl-2'-carboxylic acid (AJ_5) (0.03 mole) and phosphorous oxychloride (0.063 mole) were taken in a RBF. DMF (2 ml) and xylene (2 ml) were added and the reaction mixture was refluxed for 7 h, cooled and washed with water. It was evaporated to give a light yellow crystalline product. (Yield 4%, m.p. 125°C); (Found, C, 68.24; H, 4.48; $C_{14}H_{11}ClO_2$ requires C, 68.16; H, 4.44%). IR (KBr): 650 (C-Cl stretching), 1296 (C-H wagging of CH_2Cl), 2875–2800 cm^{-1} (aliphatic C-H stretching); ^1H NMR ($CDCl_3$): δ 8.1 (1H, s, COOH), 4.01 (2H, s, CH_2Cl); Mass (*m*/*z*): 246 (M^+), (*m*/*z*) 210 (M-HCl), 126 (M-C_6H_4COOH).

2.6. *2-Propyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-benzimidazole (AJ_7)*

2-Propylbenzimidazole (AJ_1) (0.068 mole) was dissolved in DMF (35 ml) and stirred vigorously with potassium carbonate (0.081 mole) at room temperature for 1 h. To the resulting suspension, 4-chloromethylbiphenyl-2'-carboxylic acid (AJ_6) (0.0056 mole), previously dissolved in DMF (20 ml), was added dropwise with stirring over a period of 1 h. The reaction was allowed to proceed for further 20 h and the solvent was removed under vacuum. Residue was treated with dilute HCl (20 ml) and extracted with ethylacetate. The organic layer was washed with brine, distilled water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the product as brownish amorphous solid. (Yield 51%, m.p. 126°C); (Found, C, 77.74; H, 6.02; N, 7.51; $C_{24}H_{22}N_2O_2$ requires C, 77.81; H, 5.99; N, 7.56%). IR (KBr): 3625–2625 (broad O-H stretching), 1760 (carboxylic C=O stretching), 1387 cm^{-1} (C-OH in-plane bending); ^1H NMR ($CDCl_3$): δ 7.64 (2H, d, J=8.9 Hz), 7.52 (2H, d, J=8.9 Hz), 7.27 (4H, m), 1.9 (2H, sextet, J=7.5 Hz); Mass (*m*/*z*): 370 (M^+), 76.

2.7. *2-Propyl-5-nitro[(2'-carboxybiphenyl-4-yl)methyl]benzimidazole (AJ_8)*

5-Nitro-2-propyl-benzimidazole (AJ_2) (0.0045 mole) was dissolved in DMF (40 ml) and stirred vigorously with potassium carbonate (0.0217 mole) at room temperature for 1 h. To the resulting suspension, 4-chloromethylbiphenyl-2'-carboxylic acid (AJ_6) (0.0045 mole), previously dissolved in DMF (20 ml), was added dropwise with stirring over a period of 1 h. The reaction was allowed to proceed for further 11 h and the solvent was removed under vacuum. Residue was treated with dilute HCl (20 ml) and extracted with ethylacetate. The organic layer was washed with brine, distilled water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the product as brownish amorphous solid (Yield 67%, m.p. 160°C); (Found, C, 69.44; H, 5.12; N, 10.09; $C_{24}H_{21}N_3O_4$ requires C, 69.39; H, 5.10; N, 10.11%). IR (KBr): 3625–3200 (broad O-H stretching), 1750 (carboxylic C=O stretching), 1457 and 1384 (asymmetric and symmetric NO_2 stretching), 1206 cm^{-1} (C-N stretching); ^1H NMR ($CDCl_3$): δ 8.27 (2H, s), δ 7.65

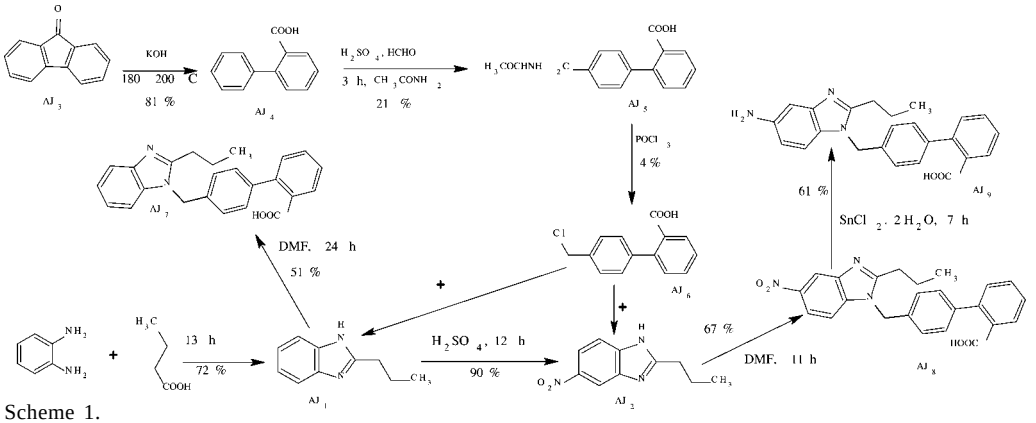
(2H, d, J=8Hz), 7.55–7.35 (3H, m), 7.30 (2H, d, J=8Hz), 2.92 (2H, t, J=7.5Hz), 1.05 (3H, t, J=7.34 Hz), Mass (m/z): 415 (M^+), 205, 177 (m/z 205-CH_2=CH_2).

2.8. *5-Amino-2-propyl-1-[-(2'-carboxybiphenyl-4-yl)methyl]benzimidazole (AJ_9)*

2-Propyl-5-nitro[(2'-carboxybiphenyl-4-yl)-methyl]benzimidazole (AJ_8) (0.023 mole) was placed in three-necked RBF fitted with a mechanical stirrer and dissolved in anhydrous ethanol and heated to 70°C under reflux. To the resulting solution was added stannous chloride dihydrate (0.0115 mole) with slow stirring during 45 min and the reaction conditions were maintained for further 7 h. The mixture was cooled to room temperature and pH was adjusted to 7.0 with 5% sodium hydroxide solution. Ethanol was removed under reduced pressure and the residue was extracted with dichloromethane. The organic layer was washed with brine, distilled water and dried over anhydrous sodium sulphate. Solvent was removed under vacuum yielding amorphous mass, which was subjected to preparative TLC. The solvent system was $CHCl_3$: MeOH (95:5) affording the product as a yellow crystalline powder (Yield 61%, m.p. 120°C); (Found, C, 74.76; H, 6.04; N, 10.87; $C_{24}H_{23}N_4O_2$ requires C, 74.78; H, 6.01; N, 10.90%). IR (KBr): 3625–2725 (broad O-H and N-H stretching), 1755 (carboxylic C=O stretching), 1412 (C-OH in-plane bending), 1261 cm^{-1} (C-N stretching); ^1H NMR ($CDCl_3$): δ 8.0 (1H, s), 7.62 (1H, m), 7.55 (5H, m), 7.45 (3H, m), 3.47 (2H, s, NH_2)), 2.75 (2H, t, J=7.74 Hz); Mass (m/z): 385 (M^+), 264 ($^+C_{17}H_{18}N_3$), and 77 ($^+C_6H_5$).

3. Results and discussion

The synthetic scheme employed involved the synthesis of carboxybiphenylmethylbenzimidazole-based compounds with varying substituents at 5-position. The incorporation of optimal grouping at 5-position is expected to increase the binding affinity of compounds. Synthesis has been carried out of selected benzimidazole derivatives having electron donor and acceptor substituents at 5-position and their authencity and purity have been established through appropriate spectral and chromatographic techniques. Scheme 1 outlines a procedure followed for generation of benzimidazole system. *o*-Phenylendiamine was refluxed with twice molar quantity of butyric acid forming 2-propyl-benzimidazoles (AJ_1) in 72.5% yield. AJ_1 was further subjected to nitration using a mixture of nitric acid and sulphuric acid (1:1). Studies with benzimidazoles suggest that in acetic anhydride, nitration products generated depend upon the temperature employed. At 30°C, specifically, the 5-nitro derivative is obtained, whereas at 70°C, 5,6-dinitro product is formed [5]. On this basis, we have carried out nitration of AJ_1 under controlled temperature conditions at 35°C resulting in the exclusive 5-nitrobenzimidazole derivative (AJ_2) in 90% yield. Scheme 1 also outlines the synthesis of (2'-carboxybiphenyl-4-yl)methyl chloride system and its coupling to the benzimidazole derivative. Biphenyl-2-carboxylic acid (AJ_4) was prepared in 81% yield from 9H-fluorenone (AJ_3) by potassium hydroxide fusion [12]. AJ_4 was then subjected to Friedel–Crafts alkylation to introduce chloromethyl substituent at 4-position giving 4-chloromethylbiphenyl-2'-carboxylic acid (AJ_6). This involves a two-step process. The first step involves amidomethylation of AJ_4 by reaction with paraformaldehyde and acetamide in the presence of concentrated sulphuric acid. This yields an intermediate, AJ_5, i. e. 4-acetamidomethylbiphenyl-2'-carboxylic acid. AJ_5 was then treated with phosphorous oxychloride in DMF and xylene and converted into chloromethylated product AJ_6. The last step in the synthesis of target compounds is coupling of benzimidazole nucleus to the biphenyl carboxylic moiety. AJ_1, the unsubstituted benzimidazole-based compound was allowed to react with AJ_6 to give coupled product AJ_7. This



Scheme 1.

reaction was carried out in DMF in the presence of potassium carbonate at room temperature and the coupled product AJ_7 was obtained in 51% yield. The coupling reaction of AJ_2, the 5-nitro derivative of AJ_1, occurred much faster (almost twice the rate) than the AJ_1 and the resulting coupled product AJ_8 was obtained in 67% yield. AJ_8 was finally reduced to its amino derivative AJ_9 in the presence of stannous chloride dihydrate in ethanol in 61% yield [13]–[14].

In conclusion, 5-substituted 2-*n*-propyl-1-[(2'-carboxybiphenyl-4-yl)methyl]benzimidazoles may be a potential angiotensin II receptor antagonist.

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