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AN EFFICIENT SYNTHETIC APPROACH FOR THE DEVELOPMENT OF A NOVEL CLASS OF BENZIMIDAZOLE AMIDES

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Abstract: A series of substituted benzimidazole amides (**8a-h**) has been synthesized through the reaction of 2-amino benzimidazoles with substituted pyridine acid derivatives followed by Suzuki and Chan-Lam Couplings in a straight forward direction. The chemical structures of the newly synthesized compounds were characterized on the basis of analytical methods including ^{1}H NMR, Mass, IR and elemental analysis.

Keywords: 2-amino benzimidazoles; efficient synthesis; Suzuki coupling; Chan-Lam coupling.

INTRODUCTION

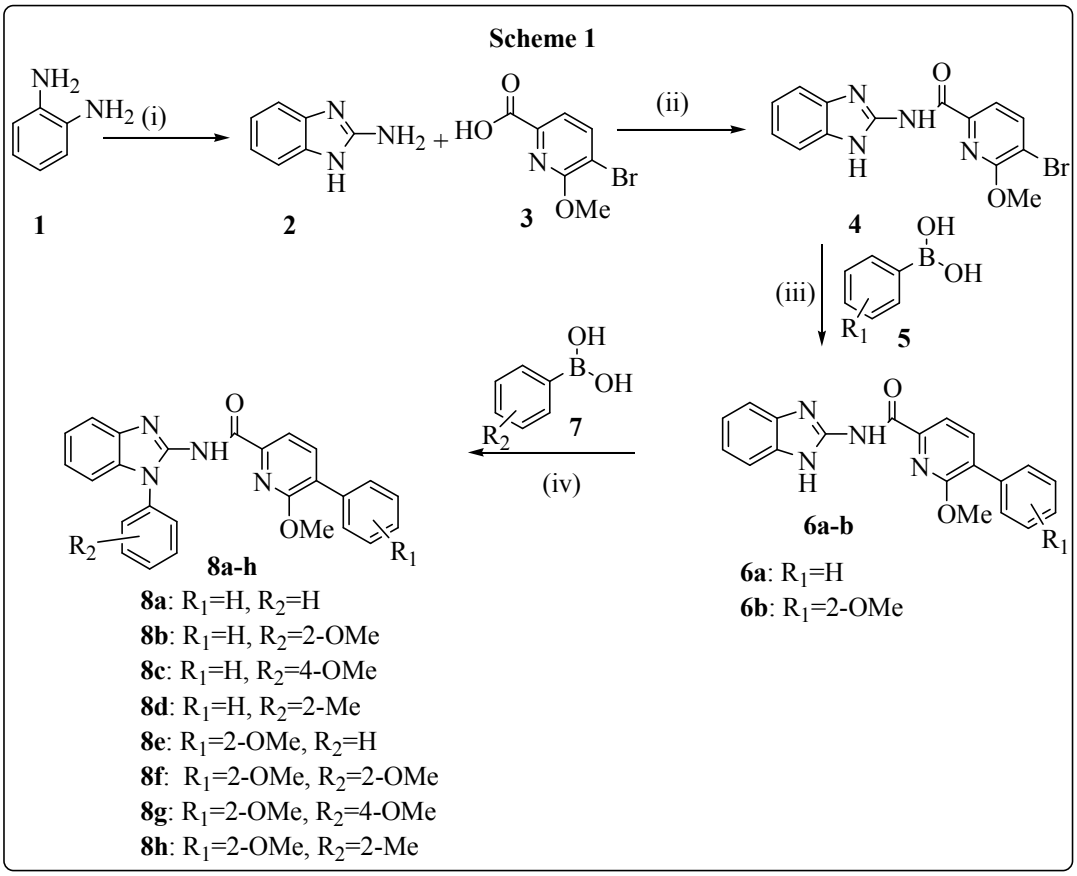
Benzimidazole nucleus is found in a variety of naturally occurring compounds and its derivatives; it is structurally similar to purine bases and these derivatives are associated with various types of pharmacokinetic and pharmacodynamic properties[i-iii]. Benzimidazoles and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities, and these are well documented in the literature[iv-vii]. Albendazole, Mebendazole and Thiabendazole are widely used as anthelmintic drugs.

The high profile of biological applications of the benzimidazole compounds has prompted the emergence of various studies on the synthesis of benzimidazole derivatives. In this context, various efforts have been made to synthesize benzimidazole derivatives. One of the most common methods for the preparation of benzimidazole derivatives involves the condensation of an *O*-phenylenediamine and carbonyl compounds such as aldehydes and acid derivatives. In most cases, the condensation of *O*-phenylenediamine with carboxylic acid requires strong acidic conditions and high temperatures [viii,ix]. The other method involves the oxidative cyclodehydrogenation of Schiff bases, which is obtained from *O*-phenylenediamine and aldehydes in the presence of various catalysts.
For last few decades, continuous efforts have been carried out on the structural modifications on the existing scaffolds for the identification of novels antibacterial agents as well as many other target diseases. On the basis of the above development of new hetero moieties, our group and other various research groups are intensively involved in the development of

various heterocyclic derivatives particularly benzimidazoles compounds which are important pharmacophores.

Chemistry

The preparation of 2-amino benzimidazole (**2**) was synthesized by the reaction of benzene-1,2-diamine (**1**) with cyanogen bromide, compound (**2)** was [x, xi] coupled with pyridine acid (**3**) in the presence of HATU and DIPEA [xii, xiii] to furnish compound (4) , which was further treated with boronic acids (**5**) using Suzuki coupling [xiv, xv] to give compound **6(a-b)**. Finally, compounds **6(a-b)** were reacted with arylboronic acids (**7)** using Chan-Lam Coupling [xvi, xvii] to accomplish the final targets **8(a-h)**.



Reaction and condition: Scheme 1 (i) cyanogen bromide, acetonitrile/water, 0^{o}C-RT, 16h. (ii) HATU, DIPEA, RT, 16h. (iii) Pd $(dppf)_2Cl_2$, $LiOH.H_2O$, Dioxane:H_2O, 30min,110^{o}C, microwave. (iv) $Cu(OAc)_2$, Pyridine, DCM,1h, 50^{o}C, Microwave.

CONCLUSION

In conclusion, we have reported the synthesis of novel 6-Methoxy-5-phenyl-pyridine-2-carboxylicacid (1-phenyl-1H-benzoimidazol-2-yl)-amide derivatives (**8a-h**) with moderate to good yields. The synthesis of these novel series of compounds involves various synthetic steps which are straightforward. This novel class of new benzimidazole derivatives reported to have a probability to emerge as a valuable lead series with great potential to be used as antibacterial and antifungal agents, and as promising candidates for further efficacy evaluation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

EXPERIMENTAL

Materials and Methods

All reagents and solvents were used as purchased without further purification. Crude products were purified by column chromatography on silica gel of 60–120 mesh. NMR spectra were recorded on a Varian 400 MHz and 500 MHz spectrometer for ^{1}H NMR. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Chemistry

Synthesis of 2-amino benzimidazole (2): To a stirred solution of benzene-1,2-diamine **1** (2.85 g, 0.026 mol) in acetonitrile (20 mL) & water (4 mL) at 0^{o}C, was added cyanogen bromide 5M in acetonitrile (6.45 mL, 0.032 mol),rection mixture was stirred at room temperature for 16h. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (120 mL), stirred for 10 min, the resulting solid was filtered and washed with water and dried under reduced pressure to obtained compound **2**.

2-Amino-benzimidazole (2): Off-white solid; yield: 72%, mp: 229- 231°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.58-4.60 (broad s, 2H, NH_2) 7.08-7.10 (m, 2H, Ar-H), 7.32-7.34 (m, 2H, Ar-H), 10.60-10.65 (broad s, 1H, NH); MS: m/z (%) 133.85 (M^{+ACN}]; HPLC purity (99.98%).

Synthesis of N-(1H-benzo[d]imidazol-2-yl)-5-bromo-6-methoxypicolinamide (4): To a solution of compound **2** (500 mg, 0.0037 mol) in DCM (15 mL), cooled to 0^{o}C, compound **3** (953 mg, 0.0041 mol), HATU (2.130 g, 0.0056 mol) and DIPEA (1.3 mL, 0.0074 mol) were added, stirred at room temperature until TLC showed complete loss of Starting material (16 h), water was added and extracted with ethyl acetate (2x30 mL), dried over Na_2SO_4, organic layer concentrated under reduced pressure and purified by column chromatography using a gradient of hexane–EtOAc (8:2–5:5) to obtained compound.

N-(1H-Benzo[d]imidazol-2-yl)-5-bromo-6-methoxypicolinamide (4): Off-white solid; yield: 68%, mp: 188-190°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15 (s, 3H, OCH_3),7.25 (m, 2H, Ar-H), 7.45 (m, 1H, Ar-H), 7.62 (m, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 8.06 (d, 1H, Ar-H) 10.42 (broad s, 1H, NH), 11.02 (broad s, 1H, NH); MS: m/z (%) 348.7 [M^{+2}]; UPLC purity (98.9%).

Synthesis of 6-Methoxy-5-phenyl-pyridine-2-carboxylic acid (1H-benzoimidazol-2-yl)-amide (6): A mixture of Compound **4** (100 mg, 0.00028 mol), compound **5** (52.5 mg, 0.00043 mol), $Pd(dppf)_2Cl_2$ (8.1 mg, 0.000028 mol), $LiOH.H_2O$ (24.1 mg, 0.00056 mol), dioxane (1.6 mL) and Water (0.4mL), the mixture was stirred at 110^{o}C in microwave for 30 min, completion of starting material was identified by TLC, cooled to room temperature, water was added, extracted with EtOAc (2x30 mL), driedover Na_2SO_4, filtered and concentrated under reduced pressure, Crude was purified by column chromatography EtOAc:Hexane (1-9:2-8) to give pure compound **6**.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid (1H-benzoimidazol-2-yl)-amide (6a):

Off-white solid; yield : 75 %, mp: 194-198°C ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.12 (s, 3H, OCH_3),7.11-7.13(m, 2H, Ar-H), 7.42-7.50 (m, 5H, Ar-H), 7.59-7.62 (m, 2H, Ar-H), 7.89-7.91 (d, 1H, Ar-H), 8.01-8.03 (d, 1H, Ar-H),11.38 (bs, 1H, NH), 12.40 (bs, 1H, NH); MS: m/z (%) 345.0 [M^+], HPLC purity (98.9%).

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid (1H-benzoimidazol-2-yl)-amide (6b): Off-white solid; yield : 72%, mp: 196-198°C; ^{1}HNMR (500MHz, DMSO- d_6) δ:3.75(s,3H,OCH_3), 4.02 (s, 3H, OCH_3),7.01-7.03 (m, 1H, Ar-H), 7.14-7.16 (m, 3H, Ar-H), 7.21-7.23 (m, 1H, Ar-H), 7.38-7.41 (m, 1H, Ar-H), 7.70-7.72 (m, 2H, Ar-H),7.91-7.93 (m, 2H, Ar-H), 11.36 (bs, 1H, NH), 12.40 (bs, 1H, NH); MS: m/z (%) 375.1[M^+], HPLC purity (97.4 %).

Synthesis of 6-Methoxy-5-phenyl-pyridine-2-carboxylic acid (1-phenyl-1H-benzoimidazol-2-yl)-amide (8): A mixture of Compound **6** (50 mg, 0.00014 mol), compound **7** (21.4mg, 0.00017mol), $Cu(OAc)_2$ (53.2mg, 0.00029 mol) and pyridine (0.035 mL, 0.00043 mol) in DCM (1.5 mL), stirred at 50^{o}C for 1 h in microwave, after completion of starting material, reaction mass quenched with Aq.Citric acid solution and water was added, extracted with ethyl acetate (2x30 mL), dried over Na_2SO_4, evaporated *in vacuo* to obtained the crude product which was purified by column chromatography using a gradient of Hexane–EtOAC (8:2-6:4) gave the title compound **8**.

6-Methoxy-5-phenyl-pyridine-2-carboxylicacid(1-phenyl-1H-benzoimidazol-2-yl)-amide (8a): Off-white solid ; yield : 65%, mp: 196-198°C; IR (KBr, cm-1): 3444 (N-H), 1730 (C=O), 1623 (C=N), 1539, 1379, 770; ^{1}H NMR (500 MHz, $CDCl_3$) δ:3.92 (s, 3H, OCH_3), 7.38-7.50 (m, 6H, Ar-H),7.52-7.70 (m, 7H, Ar-H), 7.72-7.88 (m, 2H, Ar-H), 8.02 (broad s, 1H, Ar-H), 11.40 (broad s, 1H, NH); MS: m/z (%) 421.0 [M^+]; HPLC purity (98.26%); Anal. Calcd. for $C_{26}H_{20}N_4O_2$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.21; H, 4.76; N, 13.30.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid [1-(2-methoxy-phenyl)-1H-benzoimidazol-2-yl]-amide(8b): Off-white solid; yield : 62%, mp: 198-202°C; 3443 (N-H), 1731 (C=O), 1622 (C=N), 1540, 1379, 722; ^{1}H NMR (500 MHz, $CDCl_3$) δ:3.92 (s,3H, OCH_3), 3.98 (s,3H, OCH_3), 7.16-7.22 (m, 2H, Ar-H), 7.40-7.48 (m, 4H, Ar-H), 7.50-7.58 (m, 4H, Ar-H),7.60-7.70 (m, 2H, Ar-H) 7.84-7.96 (m, 2H, Ar-H) 8.22 (broad s, 1H, Ar-H), 11.40 (broad s, 1H, NH); MS: m/z (%) 451.1[M^+]; HPLC purity (96.32%); Anal. Calcd. for $C_{27}H_{22}N_4O_3$: C, 71.99; H, 4.92; N, 12.44. Found: C, 71.82; H, 4.93; N, 12.48.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid [1-(4-methoxy-phenyl)-1H-benzoimidazol-2-yl]-amide(8c): Off-white solid ; yield : 66%, mp: 194-198°C; IR (KBr, cm-1) : 3429 (N-H), 1712 (C=O), 1618 (C=N), 1528, 1364, 744; ^{1}H NMR (500 MHz, $CDCl_3$) δ:3.90 (s,3H, OCH_3), 3.94 (s,3H, OCH_3), 7.16-7.20 (m, 2H, Ar-H),7.42-7.48 (m, 4H, Ar-H), 7.52-7.58 (m, 4H, Ar-H),7.60-7.68 (m, 2H, Ar-H) 7.84-7.92 (m, 2H, Ar-H) 8.20 (broad s, 1H, Ar-H), 11.38 (broad s, 1H, NH); MS: m/z (%) 451.0 [M^+]; HPLC purity (98.16%); Anal. Calcd. for $C_{27}H_{22}N_4O_3$: C, 71.99; H, 4.92; N, 12.44. Found: C, 71.83; H, 4.94; N, 12.48.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid (1-o-tolyl-1H-benzoimidazol-2-yl)-amide(8d): Off-white solid; yield: 62%, mp: 202-204°C; 3435 (N-H), 1726 (C=O), 1640 (C=N), 1535, 1365, 718; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 6.94-7.02 (m, 2H, Ar-H), 7.30-7.36 (m, 3H, Ar-H), 7.42-7.54 (m, 3H, Ar-H), 7.60-7.68 (m, 6H, Ar-H), 8.20 (broad s, 1H, Ar-H), 11.38 (broad s, 1H, NH); MS: m/z (%) 434.0 [M^+]; HPLC purity (95.41%); Anal. Calcd. for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89. Found: C, 74.60; H, 5.09; N, 12.81.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid (1-phenyl-1H-benzoimidazol-2-yl)-amide(8e): Off-white solid; yield : 66%, mp: 200-202°C; 3444 (N-H), 1716 (C=O), 1595 (C=N), 1540, 1242, 742; ^{1}H NMR (500 MHz, $CDCl_3$) δ:3.82 (s,3H, OCH_3), 4.02 (s,3H, OCH_3), 7.02 -7.04 (m, 2H, Ar-H),7.34-7.44 (m, 3H, Ar-H), 7.46-7.62 (m, 3H, Ar-H), 7.64-7.78 (m, 6H, Ar-H),8.18-8.20 (broad s, 1H, Ar-H), 11.42 (broad s, 1H, NH);

MS: m/z (%) 451.0 [M^+]; HPLC purity (98.16%); Anal. Calcd. for $C_{27}H_{22}N_4O_3$: C, 71.99; H, 4.92; N, 12.44. Found: C, 71.90; H, 4.91; N, 12.38.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid [1-(2-methoxy-phenyl)-1H-benzoimidazol-2-yl]-amide(8f): Off-white solid; yield: 63%, mp: 195-198°C; 3422 (N-H), 1716 (C=O), 1633 (C=N), 1524, 1364, 718; ^{1}H NMR (500 MHz, $CDCl_3$) δ:3.80 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.01(s, 3H, OCH_3), 6.98-7.02 (m, 2H, Ar-H),7.30-7.38 (m, 2H, Ar-H), 7.42-7.58 (m, 3H, Ar-H), 7.60-7.74 (m, 6H, Ar-H), 8.20 (broad s, 1H, Ar-H),11.40 (broad s, 1H, NH); MS: m/z (%) 481.2[M^+]; HPLC purity (97.66%); Anal. Calcd. for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.91; H, 5.02; N, 11.60.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid [1-(4-methoxy-phenyl)-1H-benzoimidazol-2-yl]-amide(8g): Off-white solid ; yield : 62%, mp: 194-196 °C; 3436 (N-H), 1725 (C=O), 1615 (C=N), 1523, 1363, 716;^{1}H NMR (500 MHz, $CDCl_3$) δ:3.82 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.94-7.00 (m, 2H, Ar-H),7.24-7.32 (m, 2H, Ar-H), 7.42-7.52 (m, 3H, Ar-H), 7.56-7.68 (m, 6H, Ar-H), 8.20-8.22 (broad s, 1H, Ar-H), 11.36 (broad s, 1H, NH); MS: m/z (%) 481.1[M^+]; HPLC purity (96.53%); Anal. Calcd. for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.93; H, 5.02; N, 11.62.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid (1-o-tolyl-1H-benzoimidazol-2-yl)-amide(8h): Off-white solid; yield: 65%, mp: 198-200°C; 3433 (N-H), 1726 (C=O), 1614 (C=N), 1536, 1365, 714; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.92-7.00 (m, 2H, Ar-H),7.28-7.32 (m, 2H, Ar-H), 7.40-7.52 (m, 3H, Ar-H), 7.60-7.64 (m, 6H, Ar-H), 8.18 (broad s, 1H, Ar-H),11.38 (broad s, 1H, NH); MS: m/z (%) 466.0 [M^+]; HPLC purity (99.53%); Anal. Calcd. for $C_{28}H_{24}N_4O_3$: C, 72.40; H, 5.21; N, 12.06. Found: C, 72.46; H, 5.22; N, 12.08.

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