Chemistry & Biology Interface, 2018, 8, 5, 276-283

RESEARCH PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Etidronic acid catalyzed simple, facile and generalized synthetic protocol for preparation of 2-substituted-1*H*-benzo[*d*]imidazole-6-carboxylates

Pratik A. Ambasana,a,b,* Naval P. Kapuriya,a,b Pankajkumar B. Nariya,b Yogesh T. Naliyapara,a Rajesh G. Vaghasiya,a Anilkumar S. Patel a,b,*

[a]*Department of Chemistry, Saurashtra University, Rajkot – 360005*
[b]*Department of Chemistry, Shree M. & N. Virani Science College, Kalawad Road, Rajkot – 360005*
**Email: pratikambasana@gmail.com, patelanil32@gmail.com*
Received 20 June 2018; Accepted 4 September 2018

Abstract: A facile and efficient cyclo-condensation reaction of substituted ortho-phenylenediamines with an aldehyde or carboxylic acid using etidronic acid to furnish hitherto unreported Methyl 4-methyl-2-substituted-1*H*-benzo[*d*]imidazole-6-carboxylatederivatives was described. A new and efficient protocol was developed as a homogenous catalyst for the synthesis of benzimidazoles under conventional and microwave irradiated reaction atmosphere. This methodology has the advantage of excellent yields with short reaction time and highly robust & practical reaction arrangement.

Keywords: Homogenous catalyst, bisphosphonate, microwave assisted organic synthesis (MAOS), benzimidazoles, and fused heterocycles.

1. Introduction

Research in synthetic organic chemistry has observed ever continuing search for newer methodologies towards fused heterocycles; and benzimidazole core occupies central position in this search with many others, owing to its magnificent pharmaceutical properties.[1,2] The presence of the benzimidazole system in a natural productismost striking in the case of vitamin B_{12} (cyanocobalamin).[3]

Benzimidazole derivatives are potent inhibitors of TIE-2 and VEGFR-2 tyrosine kinase receptors[4], antitumor agents[5], gamma-aminobutyric acid (GABA) agonists[6], and 5-HT3 antagonists[7]. The scaffold is also known to inhibit the growth of gram-positive bacteria and is active against various transplantable tumors.[8] Moreover, these fused heterocycles have been studied as new non-nucleoside topoisomerase-I poisons, human immunodeficiency virus-1 reverse transcriptase inhibitors, potent DNA gyrase inhibitors and potent anti-breast cancer agents.[9] They can act as ligands to transition metals for modeling

biological systems.[10]

In drug research, benzimidazoles were originally developed as plant fungicides and later as veterinary anthelminthics. The first benzimidazole to be developed and licensed for human use was Thiabendazole in 1962. Then after countless drug molecules, including but not limited to most proton-pump inhibitors like Lansoprazole, Pantoprazole, Rabeprazole; and some blockbuster molecules like Omepreazole and Esomeprazole, have been developed around benzimidazole core.[11] Importance of having ester linkage at C6 position can be estimated from Structure Activity Relationship (SAR) profiles of Omepreazole and Esomeprazole. In continuation of our work for Etidronic Acid (EDA) catalysis and cyclo-condensation reactions[12-15], we herein report a highly simple, practical and efficient methodology towards hitherto unprepared benzimidazole derivatives.

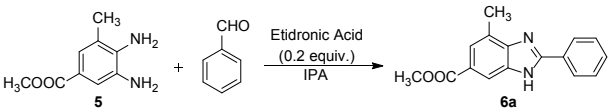
2. Result & Discussion

Etidronic acid, [(1-hydroxyethylidene) bisphosphonic acid], is one of the bisphosphonic acid derivative and also known as bisphosphonate having molecular formula $C_2H_8O_7P_2$. Etidronic acid is mild enough as compare to another strong acid such as polyphosphoric acid etc. Moreover, the catalyst did not affect acid sensitive aldehydes.

Table 1. Optimization of reaction condition for the synthesis of Methyl 4-methyl-2-phenyl-1*H*-benzo[*d*]imidazole-6-carboxylate **6a.**

Entry	Catalyst (equiv.)	Solvent	Isolated Yields (%)	Time
1	EDA (1.0)	THF	67[a]	4.0 hrs
2	EDA (1.0)	IPA	81[a]	4.0 hrs
3	EDA (0.5)	IPA	83[a]	4.0 hrs
4	**EDA (0.2)**	**IPA**	**82**[a]	**6.0 hrs**
5	EDA (0.2)	EtOH	72[a]	6.0 hrs
6	EDA (0.2)	MeOH	49[a,b]	6.0 hrs
7	**EDA (0.2)**	**IPA**	**79**[c]	**30.0 min**

[a] Conventional Heating, Refluxing temperature of the solvent used, [b] Incomplete conversion, [c] Microwave Heating



Scheme 1. Etidronic acid catalyzed synthesis of functionalized benzimidazoles under conventional/ microwave heating.

Indeed, cyclo-condensation of the methyl 3,4-diamino-5-methylbenzoate **5** with substituted benzaldehydes took place smoothly in the presence of EDA in Tetrahydrofuran (THF), and resulted in the formation of benzimidazole **6a** in 67% yield (Entry 1, Table 1). Detailed spectral analysis confirmed the isolated product as Methyl 4-methyl-2-phenyl-1*H*-benzo[*d*] imidazole-6-carboxylate **6a** (Scheme 1). The cyclo-condensation reaction was investigated under a variety of conditions (Table 1), as a test case, to optimize the yield, and the results are gathered in Table 1. The condensation took place even with a catalytic amount of EDA (0.2 equiv., Entry 4). Providentially, the reaction carried out under microwave irradiation gave excellent yields in very short reaction time. (Table 1, Entry 7). The yield of desired product **6a** was moderate when methanol and ethanol was used as solvent (Table 1, Entry 5,6).

With the optimized conditions in hand, the substrate scope was evaluated for cyclo-condensation reactions of methyl 3,4-diamino-5-methylbenzoate **5** with substituted benzaldehydes with 0.2 equiv. of etidronic acid in isopropyl alcohol (IPA). The synthesized compounds were characterized by spectroscopic analysis. The overall study indicates the catalytic system is efficient to synthesize diversely substituted 1*H*-benzo[*d*]imidazole-6-carboxylates.

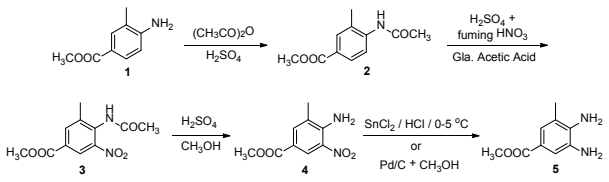
3. Conclusion

In summary, we have demonstrated a simple route for the synthesis of ester group containing benzimidazole via cyclo-condensation reactions using etidronic acid as an efficient homogeneous catalyst. The use of etidronic acid was well tolerated with a range of reactive substrates, including aliphatic, aromatic and heterocyclic. This protocol is general and provides substituted benzimidazoles in good to excellent yields depending on the reactivity of aldehydes/ carboxylic acids. Thus, the present methodology for the syntheses of benzimidazoles will serve as an exclusive method of preparative importance for this class of compounds.

4. Experimental

4.1 Materials and methods

Chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India) and used without purification. The solvents used were analytical grade. Analytical thin layer chromatography (TLC) was performed on Silica Gel 60 F_{254}precoated plates. Silica gel (Loba, 100–200 mesh, 60 Å) for column chromatography was used as received.^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$, and TMS was used as an internal reference on a Bruker AVANCE II spectrometer. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer. The syntheses were carried out in a Questron Technologies Corporation QPro-M microwave synthesizer. Melting points were measured in open capillaries and are uncorrected.



Scheme 2. Step-wise synthesis of methyl 3,4-diamino-5-methylbenzoate **5.**

4.2 Preparation of methyl 4-(acetylamino)-3-methylbenzoate (2)

Methyl 4-amino-3-methylbenzoate **1** (5g, 0.03mol) was charged in a 250 mL round bottom flask, and acetic anhydride (4.6mL, 0.045mol) was introduced with constant stirring. Subsequently, catalytic amount of concentrated sulphuric acid was added, resulting to clear solution. Stir the reaction mixture vigorously for 30-35 minute at room temperature. The reaction was monitored by TLC. (Hexane:Ethyl Acetate :: 5:5) After completion of reaction, the reaction mixture was poured onto crushed ice leading to precipitation of solid product. The product was allowed to stand at room temperature for 15 minute, filtered and washed with cold water until free from acids. The product was recrystallized from ethanol, filtered, and dried by air drying. The yield of methyl 4-(acetylamino)-3-methylbenzoate **2**, a light pink crystalline solid of MP 134°C, was 5.8g, 92.5%.

4.3 Preparation of methyl 4-(acetylamino)-3-methyl-5-nitrobenzoate (3)

Methyl 4-(acetylamino)-3-methylbenzoate **2** (3g, 0.0145mol) was charged with glacial acetic acid (6 mL) in a 50mL flat bottom flask. Subsequently, concentrated sulphuric acid (3mL) was added, resulting to clear solution. The reaction mixture was cooled in ice bath, and stirred while maintaining the temperature 0-2°C. To this reaction mixture, previously cooled mixture of fuming nitric acid (3mL) and sulphuric acid (6mL) was portion wise introduced. After all the mixed acid was added, the reaction mixture was allowed to stir for about 3 hours at 0-2°C. The reaction was monitored by TLC. (Hexane:Ethyl Acetate :: 5:5) After completion of reaction, reaction mixture was poured onto crushed ice, resulting in to the

precipitation of solid product. The product was allowed to stand at room temperature for 15 minute, filtered and washed with cold water until free from acids. The product was recrystallized from ethanol, filtered, and dried by air drying. The yield of methyl 4-(acetylamino)-3-methyl-5-nitrobenzoate **3**, a pale yellow solid of MP 162°C, was 3.2g, 88.89%.

4.4 Preparation of Methyl 4-amino-3-methyl-5-nitrobenzoate (4)

Methyl 4-(acetylamino)-3-methyl-5-nitrobenzoate **3** (3g, 0.012mol) was charged with methanol (30mL) in a 250mL round bottom flask. Subsequently, concentrated sulphuric acid (12mL) was added, resulting in to the clear solution. The reaction mixture was refluxed in water bath for 3-4 hours. The reaction was monitored by TLC. (Hexane:Ethyl Acetate :: 5:5) After completion of reaction, reaction mixture was poured onto crushed ice, resulting in to the precipitation of solid product. The product was allowed to stand at room temperature for 15 minute, filtered and washed with cold water until free from acids. The product was recrystallized from ethanol, filtered, and dried by air drying. The yield of methyl 4-amino-3-methyl-5-nitrobenzoate **4**, a bright yellow crystalline solid, was 2.2g, 88%.

4.5 Preparation of Methyl 3,4-diamino-5-methylbenzoate (5)

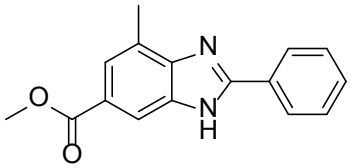
Methyl 4-amino-3-methyl-5-nitrobenzoate **4** (3g, 0.014 mol) was charged with methanol (30mL) in a 250mL round bottom flask. Catalytic amount of palladized charcoal was added to the reaction mixture, and was allowed to reflux in boiling water bath. The reaction was monitored by TLC. (Hexane:Ethyl Acetate :: 5:5) After completion of reaction, reaction mixture was filtered to recover the catalyst. Subsequently, methanol was evaporated from filtrate to afford solid crystalline product, which was recrystallized from methanol, filtered, and dried by air drying. The yield of methyl 3,4-diamino-5-methylbenzoate **5**, a light brown crystalline solid of MP 158°C, was 2.1g, 84%.

4.6 General procedure for preparation of 2-substituted-1*H*-benzo[*d*]imidazole-6-carboxylates

4.6.1 Conventional method. Methyl 3,4-diamino-5-methylbenzoate **5** (1g, 0.005mol) was dissolved in isopropyl alcohol (15mL) in a 250mL round bottom flask. Equimolar amount of substituted carboxylic acid or aldehyde, and catalytic amount of etidronic acid (20 mol%) were introduced to the reaction mixture. The reaction mixture was allowed to reflux under conventional heating and progress of the reaction was monitored by TLC (Hexane:Ethyl Acetate :: 5:5). After completion of reaction, reaction mixture was neutralized with aqueous sodium bicarbonate solution, allowed to stand at room temperature for 15 minute, filtered and washed thoroughly with cold water. The product was recrystallized from methanol, filtered, and dried by air drying.

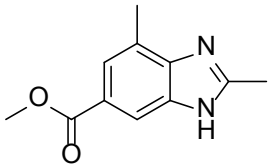
4.6.2 Microwave irradiated method. Methyl 3,4-diamino-5-methylbenzoate **5** (0.2g, 0.001mol) was dissolved in isopropyl alcohol (3mL) in a glass vial. Equimolar amount of substituted carboxylic acid or aldehyde, and catalytic amount of etidronic acid (20 mol%) were to the reaction mixture. The reaction was heated at refluxing temperature under microwave irradiation for 30 to 60 min., and monitored by TLC. (Hexane:Ethyl Acetate :: 5:5) After completion of reaction, reaction mixture was neutralized with aqueous sodium bicarbonate solution, allowed to stand at room temperature for 15 minute, filtered and washed thoroughly with cold water. The product was recrystallized from methanol, filtered, and dried by air drying.

4.7 Spectral Analysis



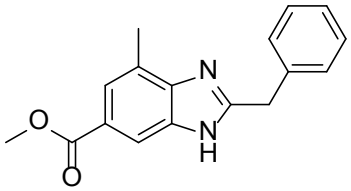
Methyl 4-methyl-2-phenyl-1*H*-benzo[*d*] imidazole-6-carboxylate **6a.**

Yield 82%, M.P. 222-224°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 8.09 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 7.29 -7.26 (m, 5H, Ar-H), 5.04 (s, 1H, -NH), 3.83 (s, 3H, -CH_3 ester), 2.55 (s, 3H, -CH_3); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 167.57, 143.21, 140.96, 137.55, 125.12, 124.02, 123.73, 115.64, 51.98, 17.06; **MS** *m/z*: 266; **Anal.** Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52; O, 12.02; Found: C, 71.20; H, 5.28; N, 9.88%.



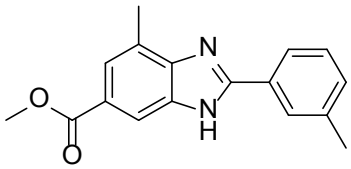
Methyl 2,4-dimethyl-1*H*-benzo[*d*]imidazole-6-carboxylate **6b.**

Yield 76%, M.P. 188-190°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 8.04 (s, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 5.04 (bs, 1H, NH), 3.88 (s, 3H, -CH_3 ester), 2.61 (s, 3H, -CH_3), 2.56 (s, 3H, -CH_3); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 163.06, 148.88, 137.18, 133.04, 119.28, 118.64, 118.44, 109.35, 47.01, 12.08, 9.98; **MS** *m/z*: 204; **Anal.** Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72; O, 15.67; Found: C, 64.20; H, 5.50; N, 14.10%.



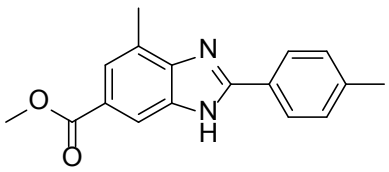
Methyl 2-benzyl-4-methyl-1*H*-benzo[*d*] imidazole-6-carboxylate **6c.**

Yield 81%, M.P. 236-238°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 8.08 (s, 1H), 7.64 (s, 1H), 7.26 -7.22 (m, 5H), 5.04 (s, 1H), 3. 98 (s, 2H), 3.82 (s, 3H), 2.55 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.45, 147.27, 136.02, 135.70, 131.66, 131.15, 128.65, 128.44, 127.66, 124.08, 114.23, 52.02, 34.07, 18.35; **MS** *m/z*: 280; **Anal.** Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99; O, 11.42; Found: C, 70.34; H, 5.48; N, 9.11%.



Methyl 4-methyl-2-(*m*-tolyl)-1*H*-benzo[*d*] imidazole-6-carboxylate **6d.**

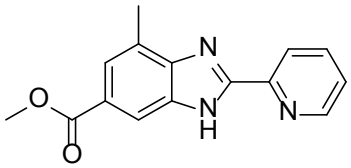
Yield 79%, M.P. 244-246°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 8.09 (s, 1H), 7.66 (s, 1H), 7.82 (s, 1H), 7.31 - 7.28 (m, 3H), 5.05 (s, 1H), 3.86 (s, 3H), 2.57 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.09, 151.24, 137.86, 136.41, 136.33, 130.73, 130.66, 130.54, 129.67, 127.69, 127.15, 126.46, 124.41, 116.35, 52.34, 19.80, 17.67; **MS** *m/z*: 280; **Anal.** Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99; O, 11.42; Found: C, 70.34; H, 5.48; N, 9.11%.



Methyl 4-methyl-2-(*p*-tolyl)-1*H*-benzo[*d*] imidazole-6-carboxylate **6e.**

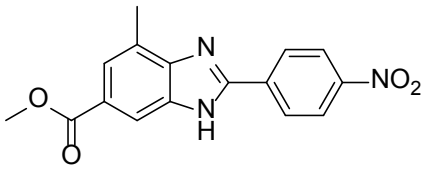
Yield 86%, M.P. 232-236°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm):8.02 - 7.93 (m, 3H), 7. 62 (s, 1H), 7.37 (s, 2H), 5.05 (s, 1H), 3.86 (s, 3H), 2.57 (s, 3H), 2.21 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.13, 149.92, 139.44, 139.36, 131.79, 131.37, 131.05, 129.01, 128.61,

125.48, 114.15, 52.03, 21.37, 18.22; **MS** *m/z*: 280; **Anal.** Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99; O, 11.42; Found: C, 70.34; H, 5.48; N, 9.11%.



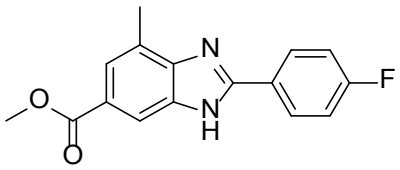
Methyl 4-methyl-2-(pyridin-2-yl)-1*H*-benzo[*d*] imidazole-6-carboxylate **6f.**

Yield 68%, M.P. 252-254°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm):8.69 (bs, 1H), 8.07 - 7.90 (m, 3H), 7.61 - 7.41 (m, 2H), 5.02 (bs, 1H), 3.84 (s, 3H), 2.52 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.10, 152.61, 147.33, 146.87, 139.32, 136.68, 131.37, 129.61, 128.88, 125.89, 120.99, 115.62, 52.18, 18.53; **MS** *m/z*: 267; **Anal.** Calcd.for $C15H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72; O, 11.97; Found: C, 67.34; H, 4.82; N, 15.85%.



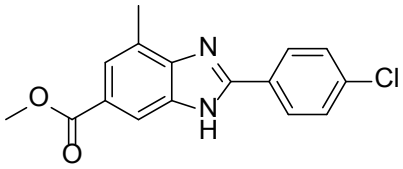
Methyl 4-methyl-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole-6-carboxylate **6g.**

Yield 68%, M.P. 214-216°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 8.31 – 8.23 (m, 2H), 7.87 – 7.78 (m, 3H), 7.53 (m, 1H), 5.05 (s, 1H), 3.92 (s, 3H), 2.53 (m, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.25, 148.90, 138.71, 136.80, 129.76, 129.03, 128.51, 126.69, 125.78, 123.90, 115.62, 52.08, 18.53; **MS** *m/z* : 311; **Anal.** Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50; O, 20.56; Found: C, 61.60; H, 4.02; N, 13.76%.



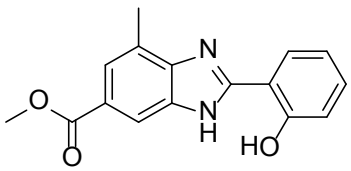
Methyl 2-(4-fluorophenyl)-4-methyl-1*H*-benzo[*d*]imidazole-6-carboxylate **6h.**

Yield 72%, M.P. 188-190°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 7.85 – 7.73 (m, 3H), 7.49 (m, 1H), 7.25 – 7.16 (m, 2H), 5.04 (s, 1H), 3.93 (s, 3H), 2.54 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.13, 163.36, 149.75, 139.44, 138.58, 131.37, 131.15, 129.70, 125.78, 115.60, 114.25, 52.10, 18.12; **MS** *m/z*: 284; **Anal.** Calcd. for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; F, 6.68; N, 9.85; O, 11.26; Found: C, 67.52; H, 4.42; N, 9.98%.



Methyl 2-(4-chlorophenyl)-4-methyl-1*H*-benzo[*d*]imidazole-6-carboxylate **6i.**

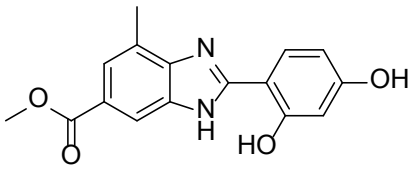
Yield 72%, M.P. 260-262°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 8.07 (s, 1H), 7.81 - 7.78 (m, 4H), 7.67 (s, 1H), 5.04 (s, 1H), 3.84 (s, 3H), 2.54 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.13, 149.46, 139.44, 138.58, 131.37, 131.15, 129.34, 127.11, 125.78, 115.62, 52.10, 18.53; **MS** *m/z*: 300; **Anal.** Calcd. for $C16H_{13}ClN_2O_2$: C, 63.90; H, 4.36; Cl, 11.79; N, 9.31; O, 10.64; Found: C, 63.90; H, 4.32; N, 9.56%.



Methyl 2-(2-hydroxyphenyl)-4-methyl-1*H*-

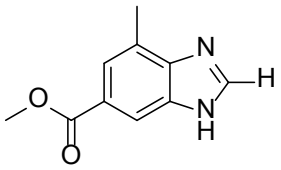
benzo[*d*]imidazole-6-carboxylate **6j.**

Yield 88%, M.P. 258-260°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm):8.08 (s, 1H), 7.79 - 7.32 (m, 4H), 7.02 (m, 1H), 5.05 (bs, 1H), 3.82 (s, 3H), 2.54 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.10, 157.42, 153.29, 140.74, 136.80, 133.66, 131.37, 131.15, 128.45, 126.48, 124.70, 114.60, 114.00, 113.61, 52.10, 18.53; **MS** *m/z*: 282; **Anal.** Calcd. for $C16H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92; O, 17.00; Found: C, 68.22; H, 5.03; N, 9.65%.



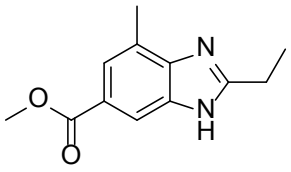
Methyl 2-(2,4-dihydroxyphenyl)-4-methyl-1*H*-benzo[*d*]imidazole-6-carboxylate **6k.**

Yield 89%, M.P. 276-278°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 9.61 (s, 1H), 8.06 (s, 1H), 7.64 - 7.53 (m, 2H), 6.51 - 6.46 (m, 2H), 5.05 (bs, 1H), 3.82 (s, 3H), 2.54 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.13, 163.09, 158.97, 151.52, 140.74, 136.53, 131.37, 131.15, 130.20, 126.48, 115.19, 113.39, 108.56, 102.52, 52.08, 18.68; **MS** *m/z*: 298; **Anal.** Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39; O, 21.45; Found: C, 64.20; H, 4.72; N, 9.22%.



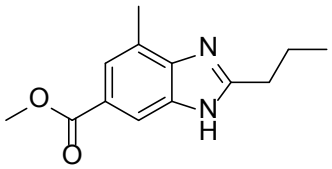
Methyl 4-methyl-1*H*-benzo[*d*]imidazole-6-carboxylate **6l.**

Yield 92%, M.P. 174-176°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm):8.89 (d, *J* = 1.8 Hz, 1H), 7.96 (m, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 3.89 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.56, 143.32, 143.30, 140.72, 131.86, 130.34, 129.73, 112.91, 52.10, 18.12; **MS** *m/z*: 190; **Anal.** Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73; O, 16.82; Found: C, 63.35; H, 5.12; N, 14.75%.



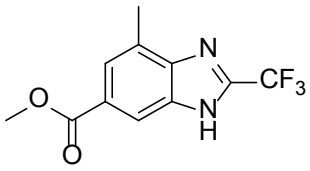
Methyl 2-ethyl-4-methyl-1*H*-benzo[*d*] imidazole-6-carboxylate**6m.**

Yield 77%, M.P. 224-224°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 7.78 (s, 1H), 7.63 (s, 1H), 3.89 (s, 3H), 2.92 - 2.86 (m, 2H), 2.32 (d, *J* = 0.5 Hz, 3H), 1.21 (m, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.35, 146.00, 142.19, 139.33, 131.86, 129.73, 112.91, 52.07, 29.05, 18.12, 12.77; **MS** *m/z*: 218; **Anal.** Calcd.for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84; O, 14.66; Found: C, 65.94; H, 6.62; N, 13.01%.



Methyl 4-methyl-2-propyl-1*H*-benzo[*d*] imidazole-6-carboxylate**6n.**

Yield 74%, M.P. 202-204°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm): 7.87 (s, 2H), 3.89 (s, 3H), 3.01 (t, *J* = 6.4 Hz, 2H), 2.30 (s, 3H), 1.84 (m, 2H), 0.98 (m, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.35, 146.43, 142.28, 139.32, 130.02, 129.52, 112.96, 52.08, 27.90, 21.74, 18.12, 13.78; **MS** *m/z*: 232; **Anal.** Calcd. for $C13H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.78; Found: C, 67.23; H, 6.81; N, 11.95%.



Methyl 4-methyl-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-6-carboxylate**6o.**
Yield 86%, M.P. 200-204°C; **^{1}H NMR** 400 MHz: ($CDCl_3$, δ ppm):8.02 (m, 1H), 7.53 (d, *J* = 2.1 Hz, 1H), 3.88 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** 100 MHz: ($CDCl_3$, δ ppm): 166.07, 148.08, 140.05, 139.97, 131.37, 130.02, 128.08, 122.99, 115.62, 52.16, 18.68; **MS** *m/z*: 258; **Anal.** Calcd. for $C_{11}H_9F_3N_2O_2$: C, 51.17; H, 3.51; F, 22.07; N, 10.85; O, 12.39; Found: C, 51.03; H, 3.37; N, 10.96%.

Acknowledgement

The authors are thankful to FIST-DST and SAP-UGC for their financial and instrumentation support. Special thanks are due to "National Facility for Drug Discovery through New Chemical Entities (NCE's) Development & Instrumentation Support to Small Manufacturing Pharma Enterprises" Programme under Drug & Pharma Research Support (DPRS) jointly funded by Department of Science & Technology, New Delhi, Government of Gujarat Industries Commissionerate & Saurashtra University, Rajkot

References

1. (a) Senem Akkoç, Veysel Kayser, Ilhan Ozer, Ilhan, David E. Hibbs, Yetkin Gok, Peter A. Williams, Bryson Hawkins, Felcia Lai, J. Organometallic Chem., **2017,** 839, 98-107. (b) Shadia A. Galal, Ahmed S. Abdelsamie, Samia A. Shouman, Yasmin M. Attia, Hamed I. Ali, Ashraf Tabll, Reem El-Shenawy, Yasmine S. El Abd, Mamdouh M. Ali, Abeer E. Mahmoud, Abeer H. Abdel-Halim, Amal A. Fyiad, Adel S. Girgis, Hoda I. El-Diwani, Eur. J. Med. Chem., **2017**, 134, 392-405. (c) Vikas S. Padalkar, Bhushan N. Borse, Vinod D. Gupta, Kiran R. Phatangare, Vikas S. Patil, Prashant G. Umape, N. Sekar, Arab. J. Chem., **2016**, 9, S1125-S1130. (d) José Miguel Velázquez-López, Alicia Hernández-Campos, Lilián Yépez-Mulia, Alfredo Téllez-Valencia, Paulina Flores-Carrillo, Rocío Nieto-Meneses, Rafael Castillo, Bioorg. Med. Chem. Lett., **2016,** 26(17), 4377-4381. (e) Mohammad Shaharyar, Avijit Mazumder, Salahuddin, Ruchika Garg, Rishabh D Pandey, Arab. J. Chem., **2016,** 9, S342-S347. (f) L Ravithej Singh, Srinivasa Rao Avula, Sneha Raj, Akanksha Srivastava, Gopala Reddy Palnati, CKM Tripathi, Mukesh Pasupuleti and Koneni V Sashidhara, The Journal of Antibiotics, **2017**, 1–8.
2. Monika Gaba and Chander Mohan, Med. Chem. Res., **2016**, 25(2), 173–210.
3. R. B. Woodward, Pure Appl. Chem. **1973**, 33, 145; Pure Appl. Chem. **1971**, 25, 283; A. Es-chenmoser in: 23rd IUPAC Congress Boston, **1971**, 2, 69, Butterworth, London.
4. M. Hasegawa, N. Nishigaki, Y. Washio, K. Kano, P. A. Harris, H. Sato, I. Mori, R. I. West, M. Shibahara, H. Toyoda, L. Wang, R. T. Nolte, J. M. Veal, M. Cheng, J. Med. Chem.,**2007**, 50, 4453.
5. M. Hranjec, M. Kralj, I. Piantanida, M. Sedic, L. Suman, K. Pavelic, G. K. Zamola, J. Med. Chem.,**2007**, 50, 5696.
6. Falco, J. Pique, M. Gonzalez, M. Buira, I. Mendez, E. Terencio, J. Perez, C. Princep, M. Palomer, A. Guglietta, Eur. J. Med. Chem., **2006**, 41, 985.
7. M. L. R. Lopez, B. Benhamu, M. J. Morcillio, I. D. Tejada, L. Orensanz, L. Alfaro, M. I. Martin, J. Med. Chem., **1999**, 33, 814.
8. A. Dell, D. H. William, H. R. Morris, G. A. Smith, J. Feeney, G. C. Roberts, J. Am. Chem. Soc., **1975**, 97, 2497.
9. (a) C. Hubschwerlen, P. Pflieger, J. L. Specklin, J. Med. Chem., **1992**, 35, 1385. (b) J. S. Kim, Q. Sun, B. Gatto, Bioorg. Med. Chem., **1996**, 4, 621. (c) D. F. Shi, T. D. Bradshaw, S. Wrigley, J. Med. Chem., **1996**, 39, 3375. (d) Chandrabose Karthikeyan, Viswas Raja Solomon, Hoyun Lee, Piyush Trivedi , Arab. J. Chem., **2017**, 10, S1788-S1794.
10. (a) H. Yun, J. Yang, W. Baogen, L. Risen, E. E. Swayze, Bioorg. Med. Chem. Lett., **2004**, 14, 1217. (b) Z. H. Zhan, Y. Liang, W. M. Yong, Catal. Commun., **2007**, 8, 1126. (c) I. Y. Oren, I. Yalcin, E. A. Sener, N. Ucarturk, Eur. J. Med. Chem., **2004**, 39, 291. (d) J. M. Gardiner, R. Colin, A. B. Loyns, A. Khan, N. Mahmood, Bioorg. Med. Chem. Lett., **1995**, 5, 1251.
11. Jie Jack Li, Blockbuster Drugs: The Rise and Fall of the Pharmaceutical Industry, OUP USA, 2014.
12. Vicky Jain, Sabera Bijani, Pratik Ambasana, Umed Bhoya, Anamik Shah, Chem. Bio. Interface, **2015**, 5(6), 347-364.
13. Akshay M. Pansuriya, Mahesh M. Savant, Chirag V. Bhuva, Jyoti Singh, and Yogesh T. Naliapara, Arkivoc, **2009,** vii, 79-85.
14. Mahesh M. Savant, Akshay M. Pansuriya, Chirag V. Bhuva, Naval P. Kapuriya, Yogesh T. Naliapara, Catal. Lett., **2009**, 132, 281–284.
15. Mahesh M. Savant, Akshay M. Pansuriya, Chirag V. Bhuva, Naval Kapuriya, and Yogesh T. Naliapara, Org. Chem. Int., **2014**, 567053.