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Simple and efficient method for the synthesis of new 2-cyclohexyl-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole derivatives and their biological study

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Abstract: A derivatives of carboxamide and sulfonamide of new class of 2-cyclohexyl-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole have been synthesized via 3 steps cyclization, acid and sulfonyl chloride afforded in good yield. Moreover, these targets were synthesized by coupling of tert-butyl 4-aminopiperidine-1-carboxylate with 1-fluoro-2-nitrobenzene by using TEA in ACN at 70°C for 16 hrs. Reductive cyclization with cyclohexane carbaldehyde in the presence of 10% Pd/C, $H_{2(g)}$ in MeOH at rt for 16 hrs. obtained in good to excellent yield. Derivatives of the new 2-cyclohexyl-1-(piperidin-4-yl)-1*H*-benzo[*d*] imidazole hydrochloride with different acids and sulfonyl chloride were reported. The synthesized molecules were tested for their antimicrobial activity against Gram +*ve* and Gram -*ve* bacteria and for their fungi activity. Among them, compound **7d** and **7l** showed highest inhibition at 4.1 mm against *S.aureus* and 3.6 mm against *E.coli* Gram +*ve* and Gram –*ve* bacteria, respectively, which demonstrated moderate to good antimicrobial activity.

Keywords: Benzimidazole, Carboxamide, Sulfonamide, H2-Pd/C, Antimicrobial agents.

1. Introduction:

The Benzimidazole ring is a fellow of the class of heterocycles having heteroatoms at the 1st and 3rd positions also includes approxly one quarter of the top hundred selling drugs[1]. Precisely, *N*-2-arylaminobenzimidazoles have been an important component in intoxicating antihistamine drugs[2], and show local anaesthetic, adrenergic blocking, antispasmodic, sympathomimetic, analgesic, and antiserotonin activities[2-4]. Moreover, this course of molecules has recently shown selective nano-molar activity against human prostanoid DP receptor antagonists, which are supposed to be an important receptor aim in the treatment of allergic rhinitis[5-7]. In a new antimalarial method, *in vivo* studies have shown that the U.S. Food and Drug Administration approved antihistamine astemizole inhibits the malaria

parasite Plasmodium falciparum, perhaps permitting a streamlined treatment for the most lethal disease worldwide[8]. This wide ranging pharmaceutical activity is believed to derive from benzimidazole-mediated physicochemical properties; in particular, the relative acidity of *N*-aryl-2-aminobenzimidazoles facilitates favourable pharmacodynamics and pharmacokinetics, thereby making them ideal components of drug candidates[7, 9].

Heterocycles of benzimidazole is important substructure identified in the natural products and a pharmacologically active molecules.[10-14] Different derivative of imidazole act as an inhibitor of P-38 MAP kinase[15], glucagon receptors[16], plant growth regulators[8], therapeutic agents[17], antibacterial[18], and also antitumor[19]. Also used as a ionic liquid which highly benefits to green chemistry. The synthesis of benzimidazole derivatives play an important role in biological activities of these compounds induced by the heterocyclic ring. Benzimidazole derivative displays a wide range of biological and pharmaceutically active such as antiulcer activity, antimicrobial, antiviral, antidiabetic and anticancer activity[20-24]. Some of the marketed drugs are containing benzimidazole moiety. **(Figure 1)**

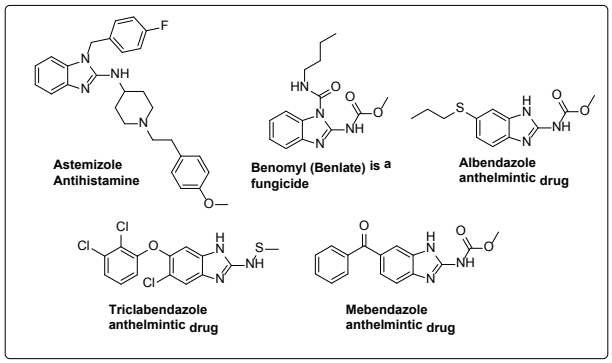


Figure 1: Some of the marketed drugs containing benzimidazole moiety.

Literature survey supported that only few methods have been reported for one-pot synthesis of benzimidazole by *in situ* reductive cyclization of o-phenelyne diamne (OPD) and aldehyde or ester or acids in the presence of aq. HCl or $Na_2S_2O_4$ in methanol/water condition. However, this methods suffer from low yield and reaction temperature. Thus, there is a need for simple and efficient methods to synthesized derivative of benzimidazole under mild condition. Herein, we report the simple and efficient reaction of functionalized benzimidazole derivatives and their antimicrobial and antifungal screening.

2. Materials and Method:

2.1 Chemistry

All reagents and solvents were obtained from Aldrich and local suppliers are used without any purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F254 precoated on aluminium plates of 0.5 mm thickness, obtained from Merck. TLC spots were visualized by UV-light irradiation (254 nm). Melting point was determined using a Buchi B-540 capillary apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on bruker FT-400 using tetramethylsilane (TMS) as internal standard. ^{1}H NMR ($CDCl_3$ 7.26 and DMSO-d_6 2.5). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constant in Hz. IR data were recorded on a Shimadzu FT-IR-8400 instrument and are expressed in cm^{-1} (KBr). LCMS analysis was recorded. The compounds were purified by column chromatography using silica gel (60-120 mesh size).

2.2 Synthesis of tert-butyl 4-((2-nitrophenyl) amino)piperidine-1-carboxylate (3): 1-Fluoro-2-nitrobenzene, **1** (3.0 gm, 21.26 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate, **2** (5.32 gm, 26.58 mmol) was heated in the presence of TEA (9.2 mL, 63.82 mmol) in ACN (30 mL) at 70°C for 16 hrs. Afterwards

H_2O (100 mL) was added and resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer were dried over (Na_2SO_4) and concentrated to dryness. The remaining crude mixture was chromatographed on silica gel column using EtOAc/Hexane (3:7) to give tert-butyl 4-((2-nitrophenyl)amino) piperidine-1-carboxylate as a yellow liquid (**Yield:** 4.7 gm, 70%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.073 - 8.097 (dd, 1H, J = 1.2, 8.8 Hz), 7.921 - 7.968 (t, 1H), 7.539 - 7.576 (t, 1H), 7.201 (d, 1H, J = 8.8 Hz), 3.836 - 3.925 (m, 3H), 2.905 - 2.989 (m, 4H), 1.924 - 1.980 (m, 2H), 1.23 (s, 9H); **Ms:** *m/z* [M^-] 321.3.

2.3 Synthesis of tert-butyl 4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carboxylate (5): Tert-butyl 4-((2-nitrophenyl) amino)piperidine-1-carboxylate, **3** (1.0 g, 3.11 mmol) in MeOH (10 mL), 0.1 g of 10% Pd/C (50% wt.) under the presence of $H_{2(g)}$, stirred for 3 hrs., cyclohexylaldehyde (0.35 gm, 3.11 mmol) was added to a solution of methanol (5 mL), then added cat. Acetic acid. Reaction was stirred under $H_{2(g)}$ for 16 hrs. TLC shows the completion of the reaction, filer the reaction mixture through celite and distilled out it the filtrate under vacuum to obtained tert-butyl 4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl) piperidine-1-carboxylate, **5** (**Yield:** 1.0 gm, 90%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6): □ 7.483 - 7.568 (m, 2H), 7.119 - 7.140 (t, 2H), 4.620 (s, br, 1H), 4.119 (s, br, 1H), 3.028 - 3.055 (m, 4H), 2.249 - 2.334 (m, 2H), 1.721 - 1.902 (m, 8H), 1.596 - 1.657 (m, 2H), 1.470 (s, 9H), 1.239 - 1.292 (m, 2H); **Ms:** *m/z* [M^+] 383.5.

2.4 Synthesis of 2-cyclohexyl-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride (6): Tert-butyl 4-(2-cyclohexyl-1*H*-benzo[*d*] imidazol-1-yl)piperidine-1-carboxylate, **5** (1.0 gm, 2.61 mmol) was added in 1,4-dioxane (10 mL) cool at 0°C was added 4M HCl in dioxane (20 mL) drop wise and stirred at room temperature for 16 hrs. Filtered the solid and dry it under vacuum to obtained 2-cyclohexyl-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride, **6** (**Yield:** 0.8 gm, 95%) as an off white solid. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.859 - 7.877 (d , 1H, J = 7.2 Hz), 7.551 - 7.661 (m, 3H), 5.173 (s, br, 1H), 3.462 - 3.491 (m, 2H), 3.221 - 3.249 (m, 2H), 2.894 - 2.922 (m, 2H), 2.127 - 2.158 (m, 1H), 2.006 - 2.035 (m, 2H), 1.846 - 1.879 (m, 2H), 1.721 - 1.800 (m, 4H), 1.527 - 1.598 (m, 2H), 1.239 - 1.348 (m, 2H); **Ms:** *m/z* [M^+] 283.4.

2.5 General procedure for the synthesis of compound 7a and 7i to 7l: 2-Cyclohexyl-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride, **6** (100 mg, 3.12 mmol) was added in THF (3 mL), trimethylamine (0.25 mL) cool to 0°C. 3,5-dichlorobenzoyl chloride (72.03 mg, 3.43 mmol) was dilute with THF (1 mL) added drop wise at 0°C, stirred for 16 hrs. at room temperature. Extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel using Hexane/EtOAc as an eluent to afford the analytically pure product in all cases.

2.6 General procedure for the synthesis of compound 7b to 7h: Acid substrate (3.12 mmol) was added in DMF (3 mL) cool to 0°C, HATU (117 mg, 4.70 mmol) was added and stirred for 30 min. at 0°C. 2-cyclohexyl-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole hydrochloride, **6** (100 mg, 3.12 mmol) was added portion wise and stirred for 30 min at 0°C. DIPEA (0.3 mL, 1.56 mmol) was added dropwise at 0°C and stirred for 16 hrs. Extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel using Hexane/EtOAc as an eluent to afford the analytically pure product in all cases.

2.7 Spectral data for representative of

compounds:

(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(3,5-dichlorophenyl) methanone (7a): Off white solid (**Yield:** 98 mg, 68%). **mp.:** 210°C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.83 - 7.85 (d, 1H, *J* = 8.0 Hz), 7.73 (s, 1H), 7.64 (suedo, d, 2H), 7.54 - 7.56 (d, 1H, *J* = 8.0 Hz), 7.15 (m, 2H), 4.69 - 4.81 (m, 2H), 3.52 - 3.63 (m, 1H), 3.08 - 3.16 (m, 3H), 1.16 - 1.88 (m, 14H); **IR** (KBr, υ in cm^{-1}): 3409, 2927, 2848, 1610, 1450, 1270, 1090, 990, 841, 725, 680 cm^{-1}. **LC-MS:** RT: 2.415 min, 98.93%, λ_{max}: 210 nm; **Ms:** *m/z* [M^+] 456.4.

(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(2,5-dimethylphenyl) methanone (7b): White solid (**Yield:** 100 mg, 76%). **mp.:** 155°C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.43 - 7.70 (m, 2H), 6.97 - 7.22 (m, 5H), 4.72 (br, 2H), 4.09 - 4.11 (m, 1H), 3.28 - 3.40 (m, 1H), 3.02 - 3.16 (m, 2H), 2.35 (s, 6H), 2.15 - 2.28 (m, 6H), 1.22 - 1.86 (m, 9H); **IR** (KBr, υ in cm^{-1}): 3411, 2920, 2848, 1615, 1375, 1270, 1090, 980, 841, 790 cm^{-1}. **LC-MS:** RT: 1.714 min, 91.84%, λ_{max}: 218 nm; **Ms:** *m/z* [M^+] 415.5.

(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)(2,5-dimethoxyphenyl) methanone (7c): Yellow solid (**Yield:** 105 mg, 75%); **mp.:** 195°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 - 7.79 (m, 1H), 7.59 - 7.61 (m, 1H), 7.23 - 7.24 (t, 2H), 6.87 - 6.99 (m, 3H), 5.10 - 5.12 (m, 2H), 4.46 - 4.49 (m, 1H), 3.93 (s, 3H), 3.81 - 3.84 (d, 3H, *J* = 12.0 Hz), 3.25 - 3.235 (m, 1H), 3.13 - 3.19 (m, 1H), 2.83 - 2.93 (m, 2H), 2.73 - 2.76 (m, 2H), 1.81 - 2.07 (m, 8H), 1.37 - 1.48 (m, 3H); **IR** (KBr, υ in cm^{-1}): 3408, 2900, 2818, 1610, 1370, 1280, 1050, 970, 840, 790 cm^{-1}. **LC-MS:** RT: 1.588 min, 100%, λ_{max}: 224 nm; **Ms:** *m/z* [M^+] 447.5.

4-(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carbonyl) benzenesulfonamide (7d): Yellow solid (**Yield:** 125 mg, 85%); **mp.:** 250°C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.24 - 1.32 (m, 2H), 1.46 - 1.50 (m, 2H), 1.63 - 1.65 (m, 2H), 1.73 - 1.90 (m, 6H), 2.33 - 2.45 (m, 2H), 3.07 - 3.16 (m, 2H), 3.33 (br, 1H), 3.62 (br, 1H), 4.72 (br, 2H), 7.16 (br, 2H), 7.48 (s, 2H), 7.55 - 7.57 (d, 1H, *J* = 7.2 Hz), 7.73 - 7.78 (m, 3H), 7.90 - 7.92 (d, 1H, *J* = 8.0 Hz); **IR** (KBr, υ in cm^{-1}): 3349, 2911, 2810, 1600, 1335, 1285, 1010, 960, 870, 770 cm^{-1}. **LC-MS:** RT: 1.961 min, 96%, λ_{max}: 254 nm; **Ms:** *m/z* [M^+] 466.6.

[1,1'-biphenyl]-4-yl(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl) methanone (7e): Off white solid (**Yield:** 95 mg, 65%); **mp.:** 130°C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.19 - 125 (m, 2H), 1.48 - 1.54 (m, 2H), 1.64 - 1.67 (d, 2H, *J* = 12.8 Hz), 1.74 - 2.00 (m, 7H), 2.46 (br, 2H), 3.09 - 3.11 (m, 2H), 3.90 (br, 1H), 4.74 (br, 2H), 7.13 - 7.21 (m, 2H), 7.39 - 7.43 (m, 1H), 7.49 - 7.53 (t, 2H), 7.56 - 7.58 (d, 1H, *J* = 7.2 Hz), 7.63 - 7.65 (d, 2H, *J* = 8.0 Hz), 7.72 - 7.80 (m, 5H); **IR** (KBr, υ in cm^{-1}): 3410, 2924, 2850, 1620, 1454, 1280, 1097, 993, 842, 738, 696 cm^{-1}; **LC-MS:** RT: 1.947 min, 97.5%, λ_{max}: 270 nm; **Ms:** *m/z* [M^+] 463.6.

1-(3-(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carbonyl)phenyl)ethan-1-one (7f): Off white solid (**Yield:** 105 mg, 78%); **mp.:** 215°C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.25 - 1.33 (m, 2H), 1.48 - 1.51 (m, 2H), 1.64 - 1.67 (m, 3H), 1.74 - 2.0 (m, 8H), 2.68 (s, 3H), 3.10 - 3.12 (m, 2H), 3.70 (br, 1H), 4.74 (br, 2H), 7.18 (br, 2H), 7.57 - 7.58 (d, 1H, *J* = 6.8 Hz), 7.64 - 7.68 (t, 1H), 7.81 - 7.83 (m, 2H), 8.05 - 8.08 (m, 2H); **IR** (KBr, υ in cm^{-1}): 3500, 2930, 2830, 1650, 1330, 1275, 1015, 725, 680 cm^{-1}; **LC-MS:** RT: 2.130 min, 96.7%, λ_{max}: 254 nm; **Ms:** *m/z* [M^+] 429.5.

(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl) piperidin-1-yl)(furan-3-yl)methanone (7g): Off white solid (**Yield:** 90 mg, 76%); **mp.:**

190°C; **^{1}H NMR** (400 MHz, DMSO-d^6): δ 1.24 - 1.33 (m, 2H), 1.47 - 1.54 (m, 3H), 1.61 - 1.67 (m, 4H), 1.70 - 1.92 (m, 6H), 2.34 - 2.39 (m, 3H), 3.08 - 3.13 (m, 1H), 4.70 - 4.76 (m, 1H), 6.77 (s, 1H), 7.13 - 7.15 (t, 2H), 7.55 - 7.57 (t, 1H), 7.62 - 7.64 (t, 1H), 7.78 (s, 1H), 8.15 (s, 1H); **IR** (KBr, υ in cm^{-1}): 3500, 3300, 2930, 1640, 1334, 1270, 1010, 778 cm^{-1}; **LC-MS:** RT: 2.081 min, 98.7%, λ_{max}: 254 nm; **Ms:** *m/z* [M$^+$] 377.5.

(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl) piperidin-1-yl)(thiophen-3-yl)methanone (7h): Off white solid (**Yield:** 100 mg, 81%); **mp.:** 210°C; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 1.26 - 1.32 (m, 4H), 1.43 - 1.50 (m, 2H), 1.60 - 1.91 (m, 9H), 2.34 - 2.51 (m, 3H), 3.07 - 3.13 (m, 2H), 4.69 - 4.75 (m, 2H), 7.11 - 7.17 (m, 2H), 7.31 - 7.33 (dd, 1H, *J* = 1.2, 4.8 Hz), 7.54 - 7.57 (m, 1H), 7.64 - 7.70 (t, 2H), 7.90 - 7.91 (dd, 1H, *J* = 0.8, 2.8 Hz); **IR** (KBr, υ in cm^{-1}): 3480, 3310, 2900, 1620, 1330, 1250, 1000, 770 cm^{-1}; **LC-MS:** RT: 2.167 min, 95.45%, λ_{max}: 202 nm; **Ms:** *m/z* [M$^+$] 393.5.

cyclohexyl(4-(2-cyclohexyl-1*H*-benzo[*d*] imidazol-1-yl)piperidin-1-yl)methanone (7i): Yellow solid (**Yield:** 92 mg, 74%); **mp.:** 190°C; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 1.19 - 1.52 (m, 10H), 1.65 - 1.92 (m, 11H), 2.117 - 2.19 (m, 1H), 2.31 - 2.34 (m, 2H), 2.68 - 2.76 (m, 2H), 3.083 (m, 2H), 4.2 (br, 1H), 4.61 - 4.69 (m, 2H), 7.12 - 7.14 (m, 2H), 7.48 - 7.57 (m, 2H); **IR** (KBr, υ in cm^{-1}): 3000, 1620, 1330, 1210, 770 cm^{-1}; **LC-MS:** RT: 2.023 min, 94.69%, λ_{max}: 254 nm; **Ms:** *m/z* [M$^+$] 393.5.

(4-(2-cyclohexyl-1*H*-benzo[*d*]imidazol-1-yl) piperidin-1-yl)(cyclopropyl)methanone (7j): Yellow solid (**Yield:** 80 mg, 72%); **mp.:** 250°C; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 0.77 - 0.86 (m, 4H), 1.25 - 1.33 (m, 2H), 1.43 - 1.53 (m, 2H), 1.65 - 1.92 (m, 9H), 2.08 - 2.11 (m, 1H), 2.22 (br, 1H), 2.34 (br, 2H), 2.84 (br, 1H), 3.06 - 3.18 (m, 2H), 4.45 - 4.59 (m, 2H), 4.71 (t, 1H), 7.10 - 7.16 (m, 2H), 7.49 - 7.57 (m, 2H); **IR** (KBr, υ in cm^{-1}): 3412, 2927, 2854, 1610, 1327, 1135, 880, 730 cm^{-1}; **LC-MS:** RT: 1.426 min, 100%, λ_{max}: 215 nm; **Ms:** *m/z* [M$^+$] 351.5.

2-cyclohexyl-1-(1-(cyclopropylsulfonyl) piperidin-4-yl)-1*H*-benzo[*d*]imidazole (7k): White solid (**Yield:** 75 mg, 61%); **mp.:** 210°C; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 1.01 - 1.07 (m, 4H), 1.17 - 1.20 (m, 2H), 1.27 - 1.30 (m, 1H), 1.44 - 1.53 (m, 2H), 1.61 - 1.70 (m, 2H), 1.73 - 1.76 (m, 1H), 1.81 - 1.95 (m, 6H), 2.42 (br, 1H), 2.72 - 2.76 (m, 1H), 3.06 - 3.10 (m, 2H), 3.17 - 3.22 (m, 1H), 3.79 - 3.82 (m, 2H), 4.66 (m, 1H), 7.19 (m, 2H), 7.58 - 7.64 (m, 2H); **IR** (KBr, υ in cm^{-1}): 3412, 2927, 2854, 1452, 1327, 1155, 889, 732 cm^{-1}; **LC-MS:** RT: 1.493 min, 100%, λ_{max}: 220 nm; **Ms:** *m/z* [M$^+$] 387.5.

2-cyclohexyl-1-(1-((3,5-dichlorophenyl) sulfonyl)piperidin-4-yl)-1*H*-benzo[*d*] imidazole (7l): White solid (**Yield:** 140 mg, 91%); **mp.:** 234°C; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 1.40 - 1.49 (m, 2H), 1.58 - 1.67 (m, 2H), 1.72 - 1.90 (m, 7H), 2.35 - 2.41 (m, 2H), 3.00 - 3.10 (m, 1H), 3.14 - 3.19 (m, 3H), 3.97 - 4.0 (m, 2H), 4.67 - 4.70 (m, 1H), 7.13 - 7.15 (m, 2H), 7.30 (br, 1H), 7.55 - 7.57 (m, 1H), 7.85 - 7.90 (m, 2H), 8.075 - 8.079 (d, 1H, *J* = 1.6 Hz); **IR** (KBr, υ in cm^{-1}): 3300, 2920, 2830, 1450, 1270, 1090, 990, 841, 725, 680 cm^{-1}; **LC-MS:** RT: 1.76 min, 97.0%, λ_{max}: 202 nm; **Ms:** *m/z* [M$^+$] 492.4.

Antimicrobial activity:

In these experiments, five microorganisms were used. This group included two Gram +*ve* bacteria: *Bacillus subtilis* and *Staphylococcus aureus*; two Gram -*ve* bacteria: *Escherichia coli* and *Pseudomonas aeruginosa* for antibacterial activity; and Fungi *Aspergillus niger* was used for antifungal activity. Taking Ampicillin and Nystatin as standard drugs. Nutrient agar or

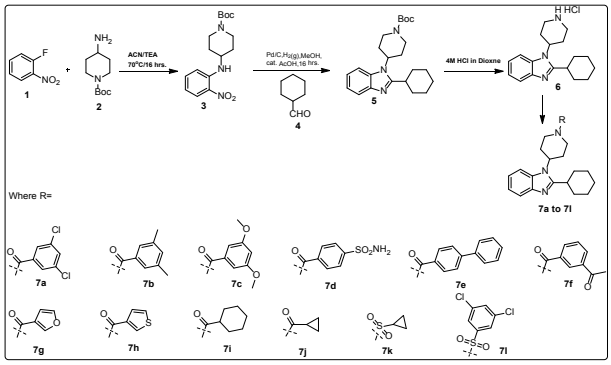
broths (Himedia PVT Ltd., India) were used for bacterial cultivation. Before the experiments, all bacteria were subcultured on fresh media and then incubated for 24 hour in temperature 30°C (*P. aeruginosa* and *S. aureus*) and 37°C (remaining bacteria). *A. niger* culture was inoculated in Potato dextrose agar, and then, spore suspension was made by using tween 80 surfactant. Next, suspensions of microorganisms in Saline/Tween 80 water were prepared, and their density was established at a level of 0.5 according to McFarland Standard. Antimicrobial activity of aqueous solutions of substrates and products of chemical synthesis was determined by well diffusion assay. Suspensions of microorganisms were overlaid with agar media and after medium solidification; the wells (10 mm in diameter) were cut with sterile cork borer. To the wells, 100 µL of substrates and surfactants solutions were introduced. The plates were incubated for 24 hour at the temperature of 30°C or 37°C depending on the indicator microorganism. After incubation, the diameter of inhibition zones were measured in millimeters. Tests were performed in triplicate, and the mean values are presented. The results are shown in **Table 1.**

Table 1: Antimicrobial and antifungal screening of some selected compounds:

Entry	Antibacterial activity				Antifungal activity
	Antibacterial activity (zone of inhibition in mm), concentration: 1000 µg/mL				Antifungal activity (zone of inhibition in mm), concentration: 1000 µg/mL
	Gram +*ve* Bacteria		Gram -*ve* Bacteria		
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*
7a	3.1	NIL	4.0	NIL	3.75
7d	3.2	**4.1**	3.6	NIL	3.8
7g	3.3	NIL	3.2	3.0	3.1
7h	3.4	NIL	NIL	NIL	3.1
7k	3.2	NIL	3.5	NIL	3.2
7l	NIL	4.0	3.6	1.5	3.7
Ampicillin	5.0	5.0	5.0	5.0	-
Nystatin	-	-	-	-	5.0

3. Result and discussion

Tert-butyl-4-(2-cyclohexyl-1*H*-benzo[*d*] imidazol-1-yl)piperidine-1-carboxylate was synthesized by the modification of literature procedure and in good yield[25, 26]. However to make the benzimidazole there are various methods was reported from o-phenelene diamne (OPD). Here we have change the reaction strategy and synthesized the new biologically active molecules. We have used 1-fluoro-2-nitrobenzene and tert-butyl 4-aminopiperidine-1-carboxylate coupling reaction in acetonitrile in triethyl amine instead of DMF, DIPEA, with 80% yield[25]. Cyclohexane carbaldehyde reacted with tert-butyl 4-((2-nitrophenyl) amino)piperidine-1-carboxylate in the presence of Pd/C in methanol and cat. acetic acid under $H_{2(g)}$ pressure instead of aq. HCl at 100°C or $Na_2S_2O_4$ in methanol[27]. Followed by de-protection by using trifluoro acetic acid in methanol and various acid and sulfonyl chloride coupling by using DCM, TEA and acid amine coupling reactions by HATU, DIPEA and DMF condition. Here we report the new method for the cyclization of benzimidazole by Pd/C in methanol under $H_{2(g)}$, cat. acetic acid with new class of biologically active of benzimidazole derivatives. Also further development of this series in process we will report soon for this development. All over the route of synthesis are shown in **Scheme 1.**



Scheme 1

4. Conclusions

In summary, we have established an efficient and simple method for the synthesis of benzimidazole derivatives system. The yields were good to excellent of all compounds. Among the synthesized compounds, selected compounds were screened for *in vitro* antimicrobial activity against anti-bacterial and anti-fungal strain examined in zone of inhibition. From the results of *in vitro* antimicrobial activity data reveals that, compound **7d** has shown 4.1 mm inhibition in against *S. aureus*, Gram +*ve* bacteria as compared to Ampicillin as a standard drug and 3.8 mm inhibition against *A. niger*, Gram -*ve* bacteria. However, all compounds have shown inhibition at 3 to 3.75 mm against *A. niger* as compare with Nystatin as a standard drug.

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