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Synthesis of some novel benzimidazole derivatives and their biological evaluation

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ABSTRACT

A series of novel benzimidazole derivatives have been synthesized by the condensation of *o*-phenylenediamine with 4-bromophenoxy acetic acid and product obtained was alkylated at the benzimidazole -NH with different electrophilic reagents. Subsequent reactions of the products by the Suzuki Coupling between benzimidazole derivatives and phenylboronic acid derivatives were accomplished. All these compounds were characterized by FT-IR, ^{1}H NMR, MS and elemental analysis. These compounds were screened for their potential antibacterial and antifungal activities. This exhibited some promising results towards testing organism *in-vitro*.

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1. Introduction

The benzimidazole nucleus is a useful structure for research and development of new pharmaceutical molecules. Benzimidazole are among the important heterocyclic compounds found in several natural and non-natural products such as Vitamin B12 [1], marine alkaloid kealiiquinone [2], benzimidazole nucleosides [3,4] *etc*. Some of their derivatives are marketed as anti-fungal [5], anti-helmintic [6,7] and anti-psychotic [8,9] drugs and other derivatives have been found to possess some interesting bioactivities such as anti-tubercular [10], anti-cancer [11,12], HIV-inhibitors [13], anti-hypertensive agent [14], anti-inflammatory activity [15], anti-allergic activity [16], anti-diabetic activity [17], anticonvulsant activity [18], DNA inhibitory activity [19] *etc*. We have also published some series of biologically active benzimidazoles [20]. Owing to the immense biological importance of benzimidazole derivatives, we now synthesized some novel class of benzimidazole derivatives and their biological activity screening studies.

2. Experimental

2.1. Chemicals

Phenylboronic acid, 4-ethyl phenylboronic acid, palladium acetate, potassium fluoride and 18-crown-6 ether obtained from Aldrich. *o*-Phenylenediamine, 4-bromophenoxy acetic acid, alkylating agents and sodium hydride were obtained from commercial suppliers. All the solvents used were of commercial grade only.

2.2. Instrumentations

Melting points recorded on a MRVIS Series, Lab. India Instrument. TLC analysis was done using pre-coated silica gel plates and visualization was done using iodine/UV lamp. Infrared spectra were recorded on Perkin Elmer model FT-IR using the KBr disc. ^{1}H NMR spectra of the compounds were recorded on BRUKER Avance II 400 MHz NMR spectrometer with $CDCl_3$ as solvent unless otherwise mentioned. Elemental analysis was carried out on a Perkin Elmer Series II Elemental Analyzer 2400.

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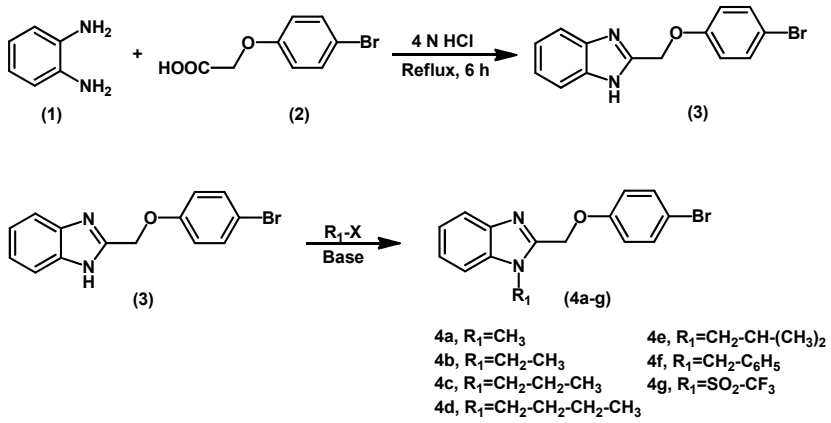


Scheme 1

2.3. Synthesis

2.3.1. Synthesis of 2-(4-bromo-phenoxymethyl)-1H-benzimidaziole by condensation of o-phenylenediamine (1) (OPDA) with 4-bromophenoxy acetic acid (2) under Philip's condition [21]

To a solution of 4-bromophenoxy acetic acid (**2**) (10.8 g, 50 mmol) and 4 N HCl (50 mL), *o*-phenylenediamine (**1**) (5.40 g, 50 mmol) was added. The reaction mixture was heated slowly to reflux temperature for 6 hours (TLC monitoring). The reaction mixture was then cooled to room temperature and neutralized with 10% aq. $NaHCO_3$ till the neutral pH. The reaction mixture was stirred for 30 min resulted free flowing suspension. The solid separated out was filtered, washed with water (3 × 30 mL) and dried under vacuum to afford an off-white solid. The crude product was recrystallized from hot aq. ethanol to obtain the pure white crystalline compound **3** (Scheme 1). Yield: 13.5 g, 89 %. M.p.: 260-262 °C (Lit. [22]: 260 °C).

2.3.2. Synthesis of compound 3 via microwave irradiation

To a solution of 4-bromophenoxy acetic acid (**2**) (10.8 g, 50 mmol) and 4 N HCl (50 mL), *o*-phenylenediamine (**1**) (5.40 g, 50 mmol) was added. The reaction mixture was irradiated in a microwave oven at 100 W for 3 min at 100 °C. The reaction mixture was then cooled to room temperature and neutralized with aq. $NaHCO_3$ (10%) till the neutral pH. The reaction mixture was stirred for 30 min resulted free flowing suspension. The solid separated out was filtered, washed with water (3 × 30 mL) and dried under vacuum to afford an off-white solid. The crude product was recrystallized from hot aq. ethanol to obtain the pure white crystalline compound **3**. Yield: 13.0 g, 87%. M.p.: 260-262 °C (Lit. [22]: 260 °C).

2.3.3. General procedure for the synthesis of N-alkylated derivatives of 2-(4-bromo-phenoxymethyl)-1H-benzimidaziole (4a-g) [23]

To a solution of 2-(4-bromo-phenoxymethyl)-1*H*-benzimidazole (2 mmol) (**3**) in dimethylformamide (10 mL) was added sodium hydride (60 %, 2.4 mmol) lot wise at 0 °C. After completion of addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred at this temperature for 1 h. The reaction mixture was again cooled to 0 °C and the respective alkyl halide (2.4 mmol) was added at 0 °C. The temperature of the reaction mixture was then allowed to warm to room temperature and stirred for 2 h. After completion of the reaction, (TLC monitoring) water (50 mL) was slowly added to reaction mixture and extracted with ethyl acetate (2 × 25 mL). The organic layer was washed with water (2 × 25 mL), brine and dried over anhydrous sodium sulfate and concentrated under vacuum to yield the corresponding *N*-substituted derivatives (**4a**-**g**) the crude compounds were recrystallized from hot aq. ethanol to obtain pure products. Scheme 1.

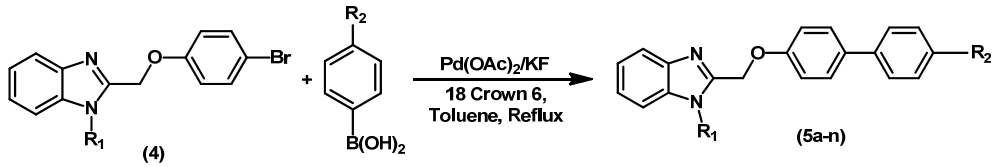
2.3.4. General procedure for the synthesis of Suzuki coupling [24-26] *compounds 5a-n*

To a solution of *N*-alkylated benzimidazole compounds **4a**-**g** (2.5 mmol) in toluene (50 mL) was added phenylboronic acid and 4-ethylphenylboronic acid (3 mmol), presence of potassium fluoride (5 mmol), 18-crown-6 ether (1.25 mmol) and palladium acetate (0.125 mmol). The reaction mixture was then refluxed and maintained for 3 h (TLC monitored). Upon completion, reaction mixture was allowed to cool to room temperature and filtered through hyflo. The toluene filtrate was washed with 5% $NaHCO_3$ (25 mL), brine (25 mL) and water (25 L and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded crude products, which were subjected to column chromatography to isolate the pure products **5a**-**n**, Scheme 2.

2.3.5. Synthesis of Suzuki coupling compounds 5a-n via microwave irradiation

To a solution of *N*-alkylated benzimidazole compounds **4a**-**g** (2.5 mmol) in toluene (50 mL) was added phenylboronic acid and 4-ethylphenylboronic acid (3 mmol), presence of potassium fluoride (5 mmol), 18-crown-6 ether (1.25 mmol) and palladium acetate (0.125 mmol) was heated under microwave conditions at 150 °C and 200 Watt for 2 minutes. It was allowed to cool to room temperature and filtered through hyflo. The toluene filtrate was washed with 5% $NaHCO_3$ (25 mL), brine (25 mL) and water (25 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded crude products, which were subjected to column chromatography to isolate the pure products **5a**-**n**, Scheme 2.

2-(Biphenyl-4-yloxymethyl)-1-methyl-1H-benzoimidazole (**5a**): Colour: White. Yield: 60%. M.p.: 83-85 °C. FT-IR (KBr, ν, cm^{-1}): 2961 (C-H), 1683 (C=N), 1011 (C-O). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.80 (s, 3H, CH_3-N-), 5.29 (s, 2H, CH_2-O-), 6.86-6.90 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.18-7.34 (m, 8H, Ar-H), 7.43-7.45 (d, 1H, *J* = 8 Hz, Ar-H), 7.71-7.75 (dd, 2H, *J* = 8.7 Hz, Ar-H). MS (EI, *m/z* (%)): 315.2 (M+1). Anal. calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.10; H, 5.90; N, 9.04%.



5a, R_1=CH_3, R_2=H
5b, R_1=CH_2-CH_3, R_2=H
5c, R_1=CH_2-CH_2-CH_3, R_2=H
5d, R_1=CH_2-CH_2-CH_2-CH_3, R_2=H
5e, R_1=CH_2-CH-$(CH_3)_2$, R_2=H
5f, R_1=CH_2-C_6H_5, R_2=H
5g, R_1=SO_2-CF_3, R_2=H
5h, R_1=CH_3, R_2=CH_2-CH_3
5i, R_1=CH_2-CH_3, R_2=CH_2-CH_3
5j, R_1=CH_2-CH_2-CH_3, R_2=CH_2-CH_3
5k, R_1=CH_2-CH_2-CH_2-CH_3, R_2=CH_2-CH_3
5l, R_1=CH_2-CH-$(CH_3)_2$, R_2=CH_2-CH_3
5m, R_1=CH_2-C_6H_5, R_2=CH_2-CH_3
5n, R_1=SO_2-CF_3, R_2=CH_2-CH_3

Scheme 2

2-(Biphenyl-4-yloxymethyl)-1-ethyl-1H-benzoimidazole (**5b**): Colour: White. Yield: 70.27%. M.p.: 88-90 °C. FT-IR (KBr, ν, cm^{-1}): 2902 (C-H), 1674 (C=N), 1045 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.46-1.50 (t, *J* = 7.24 Hz, 3H, CH_3-CH_2), 4.33-4.38 (q, *J* = 7.24 Hz, 2H, CH_2-N), 5.41 (s, 2H, CH_2-O-), 7.14-7.17 (m, 2H, Ar-H), 7.25-7.33 (m, 3H, Ar-H), 7.38-7.42 (m, 3H, Ar-H), 7.51-7.53 (d, *J* = 8.84 Hz, 4H, Ar-H), 7.79-7.81 (dd, *J* = 6.92 Hz, 1H, Ar-H). MS (EI, *m/z* (%)): 329.2 (M+1). Anal. calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.56; H, 6.20; N, 8.65. MS (*m/z*): (M+1) 329.2%.

2-(Biphenyl-4-yloxymethyl)-1-propyl-1H-benzoimidazole (**5c**): Colour: White. Yield: 64.86%. M.p.: 95-98 °C. FT-IR (KBr, ν, cm^{-1}): 2947 (C-H), 1672 (C=N), 1045 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.02-1.05 (t, *J* = 7.40 Hz, 3H, CH_3-CH_2), 1.90-2.00 (m, 2H, CH_2-CH_3), 4.27-4.31 (t, *J* = 7.30 Hz, 2H, CH_2-N), 5.44 (s, 2H, CH_2-O-), 7.17-7.19 (d, *J* = 8.64 Hz, 2H, Ar-H), 7.28-7.34 (m, 3H, Ar-H), 7.40-7.45 (m, 3H, Ar-H), 7.54-7.56 (d, *J* = 8.32 Hz, 4H, Ar-H), 7.80-7.84 (dd, *J* = 8.28 Hz, 1H, Ar-H). MS (EI, *m/z* (%)): 343.2 (M+1). Anal. calcd. for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.60; H, 6.60; N, 8.12%.

2-(Biphenyl-4-yloxymethyl)-1-butyl-1H-benzoimidazole (**5d**): Colour: White. Yield: 68.91%. M.p.: 100-103 °C. FT-IR (KBr, ν, cm^{-1}): 2961 (C-H), 1683 (C=N), 1011 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.94-0.98 (t, *J* = 7.40 Hz, 3H, CH_3-CH_2) , 1.38-1.46 (m, 2H, CH_2-CH_3), 1.82-1.89 (m, 2H, CH_2-CH_2-CH_3), 4.27-4.31 (t, *J* = 7.64 Hz, 2H, CH_2-N), 5.42 (s, 2H, CH_2-O), 7.13-7.17 (m, 2H, Ar-H), 7.25-7.33 (m, 3H, ArH), 7.37-7.42 (m, 3H, Ar-H), 7.50-7.53 (m, 4H, Ar-H), 7.79-7.84 (dd, *J* = 6.8 Hz, 1H, Ar-H). MS (EI, *m/z* (%)): 357.2 (M+1). Anal. calcd. for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.70; H, 6.85; N, 7.81%.

2-(Biphenyl-4-yloxymethyl)-1-isobutyl-1H-benzoimidazole (**5e**): Colour: White. Yield: 66.21%. M.p.: 99-102 °C. FT-IR (KBr, ν, cm^{-1}): 2937 (C-H), 1676 (C=N), 1037 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.97-0.99 (d, *J* = 6.68 Hz, 6H, $(CH_3)_2$-CH), 2.33-2.38 (m, 1H, CH-CH_2), 4.11-4.13 (d, *J* = 7.64 Hz, 2H, CH_2-N), 5.42 (s, 2H, CH_2-O), 7.14-7.16 (d, *J* = 8.72 Hz 2H, Ar-H), 7.25-7.32 (m, 3H, Ar-H), 7.36-7.42 (m, 3H, Ar-H), 7.51-7.54 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.79-7.81 (dd, *J* = 6.52 1H, Ar-H). MS (EI, *m/z* (%)): 357.2 (M+1). Anal. calcd. for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.70; H, 6.90; N, 7.80%.

1-Benzyl-2-(Biphenyl-4-yloxymethyl)-1H-benzoimidazole (**5f**): Colour: White. Yield: 70.27%. M.p.: 158-161 °C. FT-IR (KBr, ν, cm^{-1}): 2961 (C-H), 1677 (C=N), 1011 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.39 (s, 2H, CH_2-O), 5.56 (s, 2H, CH_2-N), 7.05-7.08 (m, 2H, Ar-H), 7.10-7.13 (m, 2H, Ar-H), 7.28-7.31 (m, 7H, Ar-H), 7.41-7.44 (m, 2H, Ar-H), 7.49-7.55 (m, 4H, Ar-H), 7.85-7.87 (dd, *J* = 7.40, 1H, Ar-H). MS (EI, *m/z* (%)): 391.2 (M+1). Anal. calcd. for $C_{27}H_{22}N_2O$: C, 80.05; H, 5.68; N, 7.17. Found: C, 79.85; H, 5.80; N, 7.12%.

2-(Biphenyl-4-yloxymethyl)-1-trifluoromethanesulfonyl-1H-benzoimidazole (**5g**): Colour: Yellow. Yield: 80%. M.p.: 85-88 °C. FT-IR (KBr, ν, cm^{-1}): 2825 (C-H), 1621 (C=N), 1352 (S=O), 1069 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.41 (s, 2H, CH_2-O), 7.14-7.17 (m, 2H, Ar-H), 7.25-7.33 (m, 3H, Ar-H), 7.38-7.42 (m, 3H, Ar-H), 7.51-7.53 (d, *J* = 8.84 Hz, 4H, Ar-H), 7.79-7.81 (dd, *J* = 6.92 Hz, 1H, Ar-H). MS (EI, *m/z* (%)): 433.2 (M+1). Anal. calcd. for $C_{21}H_{15}F_3N_2O_3S$: C, 58.33; H, 3.50; N, 6.48. Found: C, 58.25; H, 3.60; N, 6.42%.

2-(4'-Ethyl-biphenyl-4-yloxymethyl)-1-methyl-1H-benzoimidazole (**5h**): Colour: White. Yield: 61.04%. M.p.: 84-87 °C. FT-IR (KBr, ν, cm^{-1}): 2948 (C-H), 1623 (C=N), 1024 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.17-1.21 (t, *J* = 7.64 Hz, 3H, CH_3-CH_2), 2.57-2.63 (q, *J* = 7.64 Hz, 2H, CH_2-CH_3), 3.83(s, 3H, CH_3-N), 5.35 (s, 2H, CH_2-O), 7.04-7.08 (m, 2H, Ar-H), 7.15-7.19 (m, 2H, Ar-H), 7.21-7.31 (m, 3H, Ar-H), 7.36-7.38 (m, 2H, Ar-H), 7.41-7.45 (m, 2H, Ar-H), 7.69-7.72 (dd, *J* = 7.12 Hz ,1H, Ar-H). MS (EI, *m/z* (%)): 343.2 (M+1). Anal. calcd. for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.52; H, 6.60; N, 8.10%.

2-(4'-Ethyl-biphenyl-4-yloxymethyl)-1-ethyl-1H-benzoimidazole (**5i**): Colour: White. Yield: 71.20%. M.p.: 90-93 °C. FT-IR (KBr, ν, cm^{-1}): 2902 (C-H), 1639 (C=N), 1043 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.24-1.28 (t, *J* = 7.60 Hz, CH_3-CH_2), 1.47-1.51 (t, *J* = 7.2 Hz, 3H, CH_3-CH_2-N), 2.64-2.70 (q, *J* = 7.60 Hz, 2H, CH_2-CH_3), 4.34-4.39(q, *J* = 7.2 Hz, 2H, N-CH_2-CH_3), 5.41 (s, 2H, CH_2-O), 7.13-7.16 (m, 2H, Ar-H), 7.23-7.27 (m, 2H, Ar-H), 7.28-7.34 (m, 2H, Ar-H), 7.37-7.41 (m, 1H, Ar-H), 7.44-7.46 (d, *J* = 8.16 Hz, 2H, Ar-H), 7.49-7.53 (m, 2H, Ar-H), 7.79-7.81 (dd, *J* = 6.96, 1H, Ar-H). MS (EI, *m/z* (%)): 357.2 (M+1). Anal. calcd. for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.90; H, 6.90; N, 7.82%.

2-(4'-Ethyl-biphenyl-4-yloxymethyl)-1-propyl-1H-benzoimidazole (**5j**): Colour: White. Yield: 60.13%. M.p.: 85-89 °C. FT-IR (KBr, ν, cm^{-1}): 2960 (C-H), 1675 (C=N), 1010 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.89-0.93 (t, *J* = 7.64 Hz, 3H, CH_3-CH_2), 1.17-1.21 (t, *J* = 7.6 Hz, 3H, CH_3-CH_2), 1.78-1.86 (m, 2H, CH_2-CH_3), 2.57-2.63 (q, *J* = 7.64 Hz, 2H, CH_2-CH_3), 4.13-4.17 (t, *J*= 7.64 Hz, 2H, CH_2-CH_2-CH_3), 5.30 (s, 2H, CH_2-O), 6.87-6.90 (m, 2H, Ar H), 7.16-7.26 (m, 5H, Ar H), 7.29-7.33 (m, 4H, Ar H) 7.75-7.77 (dd, *J* = 6.64 Hz, 1H, Ar-H). MS (EI, *m/z* (%)): 371.2 (M+1). Anal. calcd. for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.25; N, 7.56. Found: C, 80.92; H, 7.25; N, 7.45%.

2-(4'-Ethyl-biphenyl-4-yloxymethyl)-1-butyl-1H-benzoimidazole (**5k**): Colour: White. Yield: 63.22%. M.p.: 101-104 °C. FT-IR (KBr, ν, cm^{-1}): 2947 (C-H), 1660 (C=N), 1031 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.87-0.89 (t, *J* = 7.64 Hz, 3H, CH_3-CH_2), 1.18-1.20 (t, *J* = 7.64 Hz, 3H, CH_3-$(CH_2)_3$), 1.32-1.34 (m, 2H, CH_2-CH_3), 1.78-1.84 (m, 2H, CH_2-CH_3), 2.57-2.63 (q, *J* = 7.64 Hz, 2H, CH_2-CH_2-CH_3), 4.13-4.17 (t, *J* = 7.64 Hz, 2H, CH_2- CH_2-CH_2-CH_3), 5.30 (s, 2H, CH_2-O), 6.87-6.90 (m, 2H, Ar H), 7.16-7.26 (m, 5H, Ar H), 7.29-7.33 (m, 4H, Ar H), 7.75-7.77 (dd, *J* = 6.64 Hz, 1H, Ar H).

Table 1. Antibacterial activity of compound **5a-n** (Minimal inhibition concentration, MIC).

Compound	Antibacterial activity (MIC, µg/mL)			
	E. coli	*P. Aeruginosa*	*S. Aureus*	*S. Pyogenus*
5a	100	62.5	200	100
5b	125	100	62.5	200
5c	100	100	200	250
5d	62.5	100	125	250
5e	125	200	125	100
5f	250	100	250	125
5g	100	200	100	125
5h	100	100	250	250
5i	250	200	250	250
5j	250	125	100	250
5k	100	125	125	200
5l	200	250	250	500
5m	150	200	250	250
5n	125	250	250	100
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	-	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Table 2. Antifungal activity of compound **5a-n** (Minimal inhibition concentration, MIC).

Compound	Antifungal activity (MIC, µg/mL)		
	C. Albicans	*A. Niger*	*A. Clavatus*
5a	250	>1000	>1000
5b	>1000	500	500
5c	500	500	500
5d	>1000	>1000	>1000
5e	1000	250	500
5f	500	>1000	>1000
5g	1000	1000	1000
5h	250	500	500
5i	1000	250	250
5j	500	500	500
5k	1000	500	1000
5l	>1000	>1000	>1000
5m	>1000	>1000	>1000
5n	500	500	500
Nystatin	100	100	100
Greseofulvin	500	100	100

MS (EI, *m/z* (%)): 385.2 (M+1). Anal. calcd. for $C_{26}H_{28}N_2O$: C, 81.25; H, 7.34; N, 7.29. Found: C, 81.35; H, 7.50; N, 7.25%.

2-(4'-Ethyl-biphenyl-4-yloxymethyl)-1-isobutyl-1H-benzoimidazole (**5l**): Colour: White. Yield: 61.77%. M.p.: 103-105 °C. FT-IR (KBr, ν, cm^{-1}): 2960 (C-H), 1683 (C=N), 1011 (C-O). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.95-0.99 (d, *J* = 6.68 Hz, 6H, $(CH_3)_2$-CH_2), 1.24-1.28 (t, *J* = 7.64 Hz, 3H, CH_3-CH_2) 2.33-2.40 (m, 1H, CH-$(CH_3)_2$, 2.65-2.70 (q, *J* = 7.6 Hz, 2H, CH_2-CH_3), 4.11-4.13 (d, *J* = 7.6 Hz, 2H, -N-CH_2), 5.41 (s, 2H, -O-CH_2), 7.12-7.15 (m, 2H, Ar-H), 7.23-7.32 (m, 4H, Ar-H), 7.36-7.39 (m, 1H, Ar-H), 7.44-7.44 (d, *J* = 8.16 Hz, 2H, Ar-H), 7.49-7.53 (m, 2H, Ar-H), 7.78-7.80 (dd, *J* = 6.64 Hz, 1H, Ar-H). MS (EI, *m/z* (%)): 385.3 (M +1). Anal. calcd. for $C_{26}H_{28}N_2O$: C, 81.25; H, 7.34; N, 7.29. Found: C, 81.15; H, 7.50; N, 7.24%.

1-Benzyl-2-(4'-ethyl-biphenyl-4-yloxymethyl)-1H-benzoimidazole (**5m**): Colour: White. Yield: 62.50%. M.p.: 160-164 °C. FT-IR (KBr, ν, cm^{-1}): 2963 (C-H), 1693 (C=N), 1008 (C-O). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.17-1.20 (t, *J* = 7.6 Hz, 3H, CH_3-CH_2), 2.57-2.63 (q, *J* = 7.52 Hz, 2H, -CH_2-CH_3), 5.46 (s, 2H, -O-CH_2), 5.56 (s, 2H, -N-CH_2), 6.93-6.96 (m, 2H, Ar-H), 7.00-7.02 (m, 2H, Ar-H), 7.17-7.24 (m, 8H, Ar-H), 7.35-7.41 (m, 4H, Ar-H), 7.74-7.76 (dd, *J* = 7.12 Hz, 2H, Ar-H). MS (EI, *m/z* (%)): 319.3 (M +1). Anal. calcd. for $C_{29}H_{26}N_2O$: C, 83.22; H, 6.26; N, 6.69. Found: C, 83.32; H, 7.41; N, 6.60%.

2-(4'-ethyl-biphenyl-4-yloxymethyl)-1-trifluoromethane sulfonyl-1H-benzoimidazole (**5n**): Colour: Yellow. Yield: 75.63%. M.p.: 80-83 °C. FT-IR (KBr, ν, cm^{-1}): 2945 (C-H), 1656 (C=N), 1348 (S=O), 1026 (C-O). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.24-1.28 (t, *J* = 7.60 Hz, 3H, CH_3-CH_2), 2.64-2.70 (q, *J* = 7.60 Hz, 2H, CH_2-CH_3), 5.41 (s, 2H, -O-CH_2), 7.13-7.16 (m, 2H, Ar-H), 7.23-7.27 (m, 2H, Ar-H), 7.28-7.34 (m, 2H, Ar-H), 7.37-7.41 (m, 1H, Ar-H), 7.44-7.46 (d, *J* = 8.16 Hz, 2H, Ar-H), 7.49-7.53 (m, 2H, Ar-H), 7.79-7.81 (dd, *J* = 6.96 Hz, 1H, Ar-H). MS (EI, *m/z* (%)): 461.07 (M +1). Anal. calcd. for $C_{23}H_{19}F_3N_2O_3S$: C, 59.99; H, 4.16; N, 6.08. Found: C, 60.05; H, 4.25; N, 6.02%.

2.4. Biological evaluation-antibacterial and antifungal activity studies

The microbial activity was undertaken to evaluate the effect of the synthesized compounds on different bacteria and fungal strains. The compounds **5a-n** were screened for their antibacterial activity [27,28] against human pathogenic Gram negative bacteria such as *Escherichia coli* MTCC442, *Pseudomonas aeruginosa* MTCC441 and Gram positive bacteria *Staphylococcus aureus* MTCC96, and *Streptococcus pyogenes* MTCC443. DMSO was used as diluents and Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin as standard. The compounds **5a-n** were also screened for their antifungal activity [29] against *Candida albicans* MTCC227, *Aspergillus Niger* MTCC282 and *Aspergillus clavatus* MTCC1323. Broth dilution method was used to evaluate the antibacterial activity. It is carried out in tubes. Mueller Hinton Broth [30] was used as nutrient medium. Serial dilutions were prepared in primary and secondary screening. Each synthesized drug was diluted obtaining 2000 µg/mL concentration, as a stock solution. In primary screening 1000, 500 and 250 µg/mL concentrations of the synthesized drugs were taken. The drugs found active in primary screening were similarly diluted to obtain 200, 100, 50, 25, 12.5, and 6.250 µg/mL, and concentrations. The highest dilution showing at least 99% inhibition zone was taken as MIC.

3. Results and discussion

We have synthesized a series of novel benzimidazoles; initially we have carried out the condensation of *o*-phenylene diamine (OPDA) (**1**) with 4-bromophenoxy acetic acid (**2**) in 4 N HCl at reflux temperature for 6 h. After simple workup gives 2-(4-bromo-phenoxymethyl)-1*H*-benzimidaziole (**3**) [22] (Scheme 1).

Having obtained compound **3**, we have carried out *N*-alkylation to get compounds **4a-g** (Scheme 1). Compounds **4a-g** were then reacted phenyl boronic acid and 4-ethylphenyl boronic acid in presence of potassium fluoride, palladium acetate and 18-crown-6 under suzuki coupling condition to get compounds *N*-substituted 2-(biphenyl-4-yloxymethyl)-1*H*-benzimidazole, 2-(4'-ethyl-biphenyl-4-yloxymethyl)-1*H*-benzimidazole derivatives (**5a-n**) (Scheme 2). It is noteworthy to mention here that we have synthesized compound **3** and **5a-n** alternatively by microwave irradiation in comparable yield, which give the scope of alternative route to synthesis benzimidazoles at low temperature and in less reaction time. The structures of all the synthesized compounds were characterized by spectroscopic data, and allowed these molecules for study of antibacterial and antifungal activities.

The examination of the data reveals that compounds **5a**, **5c**, **5d**, **5g**, **5h** and **5k** possess high activity against *Escherichia coli* whereas compounds **5a-n** were highly active against *Staphylococcus aureus* and compound **5a**, **5e**, and **5n** have also exerted very good activity against *Streptococcus pyogenes* employed for screening, the results are presented in Table 1. The compounds **5a** and **5h** show excellent activity against *Candida albicans.* But rests of other compounds are not displayed significant anti-fungal activity when compared to the standard Nystatin and Greseofulvin; the results are presented in Table 2.

4. Conclusion

Newly synthesized *N*-substituted 2-(biphenyl-4-yloxy methyl)-1*H*-benzimidazole, 2-(4'-ethyl-biphenyl-4-yloxymeth yl)-1*H*-benzimidazole derivatives by using Suzuki coupling conditions were thoroughly characterized and some of them exhibited antibacterial activity. The compounds **5a** and **5h** exhibited antifungal activity. However, antifungal activity of the other synthesized compounds was unsatisfactory.

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