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Synthesis and Characterization of Benzimidazole Derivatives and Evaluation of Antimicrobial activity

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ABSTRACT

A series of benzimidazole derivatives were synthesized for this investigation. NMR and IR spectrum analysis as well as carbon, hydrogen, and nitrogen studies were used to characterize these novel synthesized derivatives. Antibacterial and antifungal tests were conducted on all of the newly synthesized compounds. Ciprofloxacin and fluconazole were utilized as reference medications in antibacterial and antifungal research, respectively. The microbiological assay revealed that the compounds show promising antibacterial and antifungal activity.

Keywords: Benzimidazole, Antibacterial, Antifungal.

INTRODUCTION

All the heterocyclic compounds are of great interest in pharmaceutical chemistry. Out of these heterocyclic compounds the benzofused heterocyclic compound, i.e. benzimidazole and its derivatives have wide variety of biological activities. The synthesis of benzimidazole derivatives is a topic of much research and discussion. The two carbon-nitrogen bonds in benzimidazole when disconnected give O-phenylenediamine and formic acid. Therefore benzimidazole synthesized by condensation of diamine and a carboxylic acid or carbonyl compound. Ammonium salt can be used as catalyst[1]. Fig. 1. Transition metal catalysts namely copper(II) acetate and lead tetra acetate can also be used. Antimicrobial activity[2-6], antiinflammatory-analgesic[7-9], anticancer[10], CNS depressant[11], androgen receptor antagonist[12], antitubercular[13,14] and anticonvulsant[15-19] properties have been found for benzimidazole and their derivatives. Benzimidazole nucleus is present in vitamin-B12 (Merck index 2001), albendazole, mebendzole and thiabendazole. In this present study some novel derivatives of amino acid containing benzimidazole nucleus have been synthesized and their antimicrobial and antifungal activity have been established.

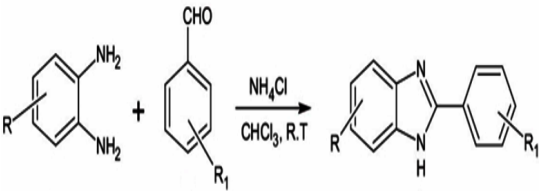


Fig. 1. General synthesis of Benzimidazole derivatives

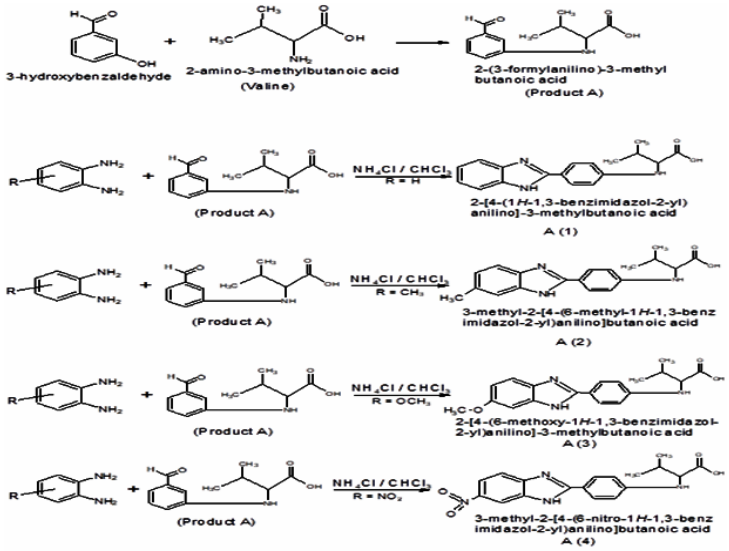
MATERIAL AND METHOD

Both the reagents and the solvents were obtained from commercial sources.The open capillary technique was used to get all of the melting points, without any adjustments being made. Recrystallization was used to improve the quality of the final products. Thin films mounted on KBr pellets were used to capture IR spectra using a PERKIN ELMER FT-IR Spectrophotometer. Chloroform was used to collect ^{1}HNMR spectra, and the resulting chemical shift values are presented in ppm with respect to TMS (δ=0) as the internal standard.

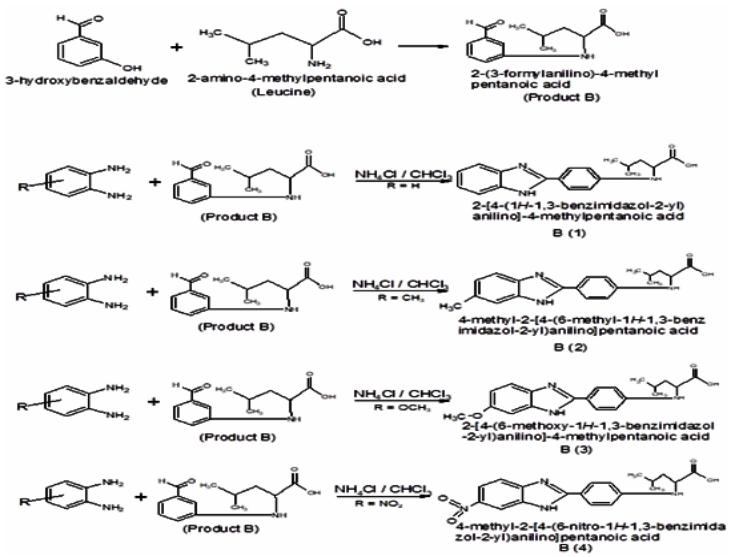
EXPERIMENTAL

Synthesis and Characterization

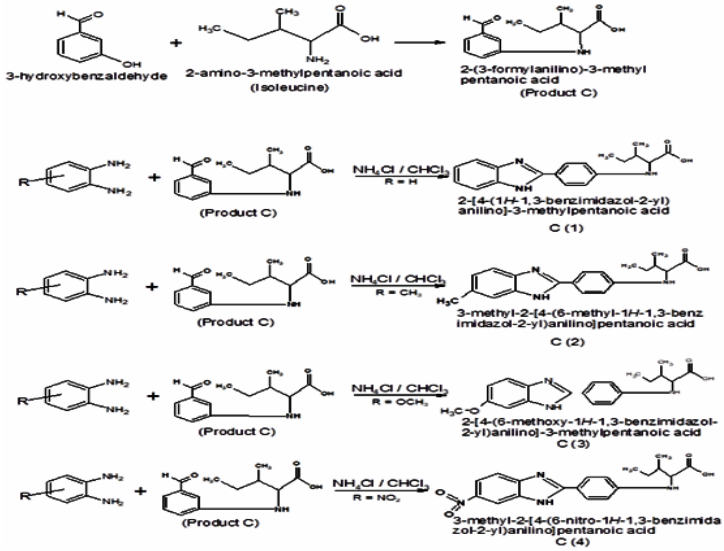
Three amino named Valine, Leucine and Isoleucine were used to synthesis of amino acid derivatives of benzimidazoles. In first step amino acid has been reacted with carbonyl compound (0.01 mol) and form parent compound. In second step parent compound reacted with differently substituted O-phenylenediamine (0.01 mol) in presence of NH_4Cl and $CHCl_3$ as catalyst at 80-90^{0}C which results in the formation of various benzimidazole derivatives.



Scheme 1. By using Valine



Scheme 2. By using Leucine



Scheme 3. By using Isoleucine

In all total 12 derivatives were formed A (1-4), B (1-4) and C (1-4).

2-[4-(1H-1,3-benzimidazol-2-yl)anilino]-3-methylbutanoic acid (A 1)

Yield 78.88%, m.p. 463.4^{0}C, Mol. Wt. 309.36, IR (cm^{-1})-2830.47-(-NH) stretching, 1718.75-(C=O) stretching, 1702.14-(C=N) stretching, 1669.56-(Ar C=C) stretching, 1574.54-(-NH) bent, 1140.17-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.57 (3 CH), 7.58 (4 CH), 7.24 (5 CH), 7.25 (6 CH), 7.53 (8 NH), 1.06 (16, 19 CH_3), 5.12 (20 NH), 10.64 (23 OH), Anal. calcd. for $C_{18}H_{19}N_3O_2$:N, 13.58; H, 6.19; C, 69.88; O, 10.34.

3-methyl-2-[4-(6-methyl-1H-1,3-benzimidazol-2-yl)anilino]butanoic acid (A 2)

Yield 89.34%, m.p. 487.19^{0}C, Mol. Wt. 323.39, IR (cm^{-1})-2834.33-(-NH) stretching, 2778.63-(Ar-CH) stretching, 1713.53-(C=O) stretching, 1701.03-(C=N) stretching, 1673.51-(Ar C=C) stretching, 1570.1-(-NH) bent, 1132.14-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.53 (3 CH), 7.55 (4 CH), 7.11 (5 CH), 7.49 (8 NH), 6.65 (10 CH), 7.5 (11 CH), 1.1(16,19 CH_3), 4.69 (20 NH), 10.1 (23 OH), Anal. calcd. for $C_{19}H_{21}N_3O_2$:N, 12.99; H, 6.55; C, 70.57; O, 9.89.

2-[4-(6-methoxy-1H-1,3-benzimidazol-2-yl) anilino]-3-methylbutanoic acid (A 3)

Yield 83.89%, m. p. 509.42^{0}C, Mol. Wt. 339.39, IR (cm^{-1})-2830.2-(-NH) stretching, 2769.51-(Ar-CH) stretching, 1751.66-(C=O) stretching, 1697.61-(C=N) stretching, 1668.41-(Ar C=C) stretching, 1580.68-(-NH) bent, 1149.26-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.56 (3 CH), 7.27 (4 CH), 6.88 (5 CH), 7.45 (8 NH),6.73 (10 CH), 1.07 (16,19 CH_3), 5.08 (20 NH), 10.09 (23 OH), 3.83 (25 CH_3), Anal. calcd. for $C_{19}H_{21}N_3O_3$:N, 12.38; H, 6.24; C, 67.24; O, 14.14.

3-methyl-2-[4-(6-nitro-1H-1,3-benzimidazol-2-yl) anilino]butanoic acid (A 4)

Yield 81.79%, m. p. 619.53^{0}C, Mol. Wt. 354.36, IR (cm^{-1})-2856.74-(-NH) stretching, 2783.21-(Ar-CH) stretching, 1738.4-(C=O) stretching, 1694.17-(C=N) stretching, 1664.08-(Ar C=C) stretching, 1569.06-(-NH) bent, 1450.33-(NO_2) stretching, 1147.26-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.84 (3 CH), 8.57 (4 CH), 8.08 (5 CH), 7.62 (8 NH), 6.74 (10 CH), 1.07 (16, 19 CH_3), 5.22 (20 NH), 10.09 (23 OH), Anal. calcd. for $C_{18}H_{18}N_4O_4$: N, 15.81; H, 5.12; C, 61.01; O, 18.06.

2-[4-(1H-1,3-benzimidazol-2-yl)anilino]-4-methylpentanoic acid (B 1)

Yield 91.09%, m. p. 474.67^{0}C, Mol. Wt. 323.39, IR (cm^{-1})-2830.96-(-NH) stretching, 1718.95-(C=O) stretching, 1703.33-(C=N) stretching, 1673.39-(Ar C=C) stretching, 1580.44-(-NH) bent, 1142.62-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.63 (3 CH), 7.6 (4 CH), 7.26 (5 CH), 7.26 (6 CH), 7.56 (8 NH), 6.75 (10 CH), 5.67 (17 NH), 9.6 (20 OH), 1.05(23, 14 CH_3), Anal. calcd. for $C_{19}H_{21}N_3O_2$: N, 12.99; H, 6.55; C, 70.57; O, 9.89.

4-methyl-2-[4-(6-methyl-1H-1,3-benzimidazol-2-yl)anilino]pentanoic acid (B 2)

Yield 79.74%, m. p. 498.46^{0}C, Mol. Wt. 337.42, IR (cm^{-1})-2835.54-(-NH) stretching, 2767.08- (Ar-CH) stretching, 1722.05-(C=O) stretching, 1694.78-(C=N) stretching, 1581.81-(Ar C=C) stretching, 1520.43-(-NH) bent, 1141.24-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.6 (3 CH),7.57 (4 CH), 7.12 (5 CH), 7.55 (8 NH), 6.72 (10 CH), 5.14 (17 NH), 12.54 (20 OH), 1.03 (24, 25 CH_3), Anal. calcd. for $C_{20}H_{23}N_3O_2$: N, 12.45; H, 6.87; C, 71.19; O, 9.48.

2-[4-(6-methoxy-1H-1,3-benzimidazol-2-yl) anilino]-4-methylpentanoic acid (B 3)

Yield 81.65%, m. p. 520.69^{0}C, Mol. Wt. 353.41, IR (cm^{-1})-2836.46-(-NH) stretching, 2773. 7-(Ar-CH) stretching, 1720.63-(C=O) stretching, 1699.14-(C=N) stretching, 1579.86-(Ar C=C) stretching, 1527.86-(-NH) bent, 1181.29-(C-O-C) stretching, 1138.6-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.62 (3 CH),7.29 (4 CH), 6.89 (5 CH), 7.49 (8 NH), 6.72 (10 CH), 5.11 (17 NH), 12.54 (20 OH), 1.03 (25,26 CH_3), Anal. calcd. for $C_{20}H_{23}N_3O_3$: N, 11.89; H, 6.56; C, 67.97; O, 13.58.

4-methyl-2-[4-(6-nitro-1H-1,3-benzimidazol-2-yl) anilino]pentanoic acid (B 4)

Yield 68.99%, m. p. 657.8^{0}C, Mol. Wt. 368.39, IR (cm^{-1})-2860.97-(-NH) stretching, 2766.97-(Ar-CH) stretching, 1722.04-(C=O) stretching, 1692.46-(C=N) stretching, 1581.48-(Ar C=C) stretching, 1520.57-(-NH) bent, 1441.29-(NO_2) stretching, 1141.74-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.9 (3 CH), 8.62 (4 CH), 8.12 (5 CH), 7.68 (8 NH), 6.73 (10 CH), 5.24 (17 NH), 12.52 (20 OH), 1.03 (26. 27 CH_3), Anal. calcd. for $C_{19}H_{20}N_4O_4$: N, 15.21; H, 5.47; C, 61.95; O, 17.37.

2-[4-(1H-1,3-benzimidazol-2-yl)anilino]-3-methylpentanoic acid (C1)

Yield 86.92%, m. p. 474.67^{0}C, Mol. Wt. 323.39, IR (cm^{-1})-2834.7- (-NH) stretching, 1716.61-(C=O) stretching, 1699.85-(C=N) stretching, 1672.65-(Ar C=C) stretching, 1580.22-(-NH) bent, 1148.65-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.58 (3 CH), 7.58 (4 CH), 7.24 (5 CH), 7.25 (6 CH), 7.53 (8 NH), 6.72 (10 CH), 5.39 (17 NH), 10.66 (20 OH), 1.1 (24 CH_3) Anal. calcd. for $C_{19}H_{21}N_2O_2$: N, 12.99; H, 6.55; C, 70.57; O, 9.89.

3-methyl-2-[4-(6-methyl-1H-1,3-benzimidazol-2-yl)anilino]pentanoic acid (C2)

Yield 76.29%, m. p. 498.46^{0}C, Mol. Wt. 337.42, IR (cm^{-1})-2830.05-(-NH) stretching, 2773.62-(Ar-CH) stretching, 1716.19-(C=O) stretching, 1696.72-(C=N) stretching, 1675.66-(Ar C=C) stretching, 1576.09-(-NH) bent, 1143.18-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.53 (3 CH), 7.55 (4 CH), 7.11 (5 CH), 7.51 (8 NH), 6.74 (10 CH), 4.91 (17 NH), 9.77 (20 OH), 1.09 (25 CH_3), Anal. calcd. for $C_{20}H_{23}N_3O_2$: N, 12.45; H, 6.87; C, 71.19; O, 9.48.

2-[4-(6-methoxy-1H-1,3-benzimidazol-2-yl) anilino]-3-methylpentanoic acid (C 3)

Yield 78.74%, m. p. 520.69^{0}C, Mol. Wt. 353.41, IR (cm^{-1})-2832.77-(-NH) stretching, 2776.57-(Ar-CH) stretching, 1718.07-(C=O) stretching, 1701.43-(C=N) stretching, 1675.97-(Ar C=C) stretching, 1582.57-(-NH) bent, 1183.86-(C-O-C) stretching, 1140.18-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.56 (3CH), 7.27 (4 CH), 6.87 (5 CH), 7.41 (8 NH), 6.69 (10 CH), 4.91 (17 NH), 9.97 (20 OH), 1.09 (26 CH_3), Anal. calcd. for $C_{20}H_{23}N_3O_3$: N, 11.89; H, 6.56; C, 67.97; O, 13.58.

3-methyl-2-[4-(6-nitro-1H-1,3-benzimidazol-2-yl) anilino]pentanoic acid (C 4)

Yield 88.13%, m. p. 630.8^{0}C, Mol. Wt. 368.39, IR (cm^{-1})-2857.99-(-NH) stretching, 2776.44-(Ar-CH) stretching, 1711.23-(C=O) stretching, 1695.05-(C=N) stretching, 1668.87-(Ar C=C) stretching, 1575.22-(-NH) bent, 1441.33-(NO_2) stretching, 1146.81-(C-N) stretching, ^{1}H-NMR ($CDCl_3$, 500 MHz, ppm): 7.84 (3 CH), 8.56 (4 CH), 8.07 (5 CH), 7.6 (8 NH), 6.69 (10 CH), 5.72 (17 NH), 10.63 (20 OH), 1.12 (27 CH_3), Anal. calcd. for $C_{19}H_{20}N_4O_4$: N, 15.21; H, 5.47; C, 61.95; O, 17.37.

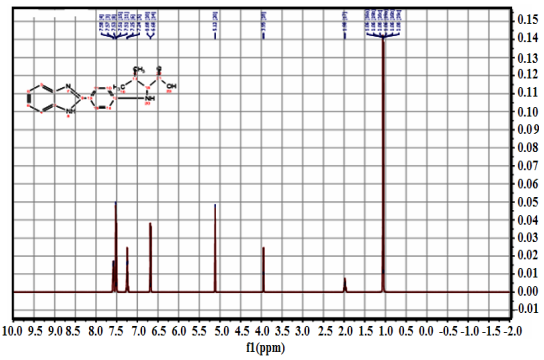


Fig. 2. NMR Spectra of compound A(1)

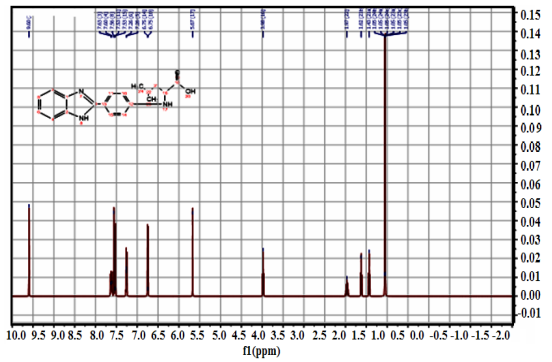


Fig. 3. NMR Spectra of compound B(1)

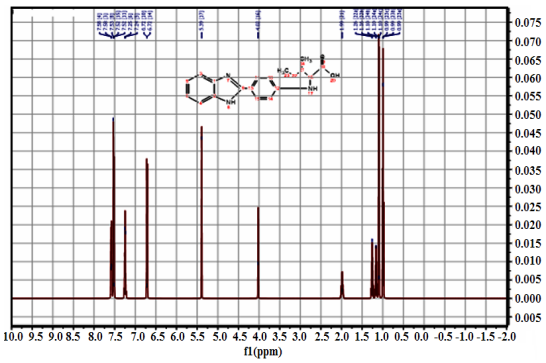


Fig. 4. NMR Spectra of compound C(1)

Antimicrobial evaluation

For antibacterial investigations, two *Gram+ve* i.e. *Staphylococcus aureus* and *Bacillus subtilis* while, two *Gram-ve* bacteria i.e. *Escherichia coli* and *Pseudomonas aureginosa* were used. Two fungal species i.e. *Aspergillus niger* and *Candida albicans* were taken for antifungal examinations. The concentrations 100 µg/mL of the compounds were used. For antibacterial and antifungal studies, Ciprofloxacin and Fluconazole were used as standard drugs separately. The 20 µg/mL of concentration of each standard drug was used.

Table 1: Antibacterial activity of benzimidazole derivatives (Zone of inhibition, ZOI and % inhibition)

S. No	Comp Code	*S. aureus*			*B. substilis*			*E. coli*			*P. aureginosa*		
		ZOI±SD	% Inhib	t-value#	ZOI±SD	% Inhib	t-value#	ZOI±SD	% Inhib	t-value#	ZOI±SD	% Inhib	t-value#
1	A (1)	16.82±0.78	91.3	2.628	17.90±1.05	89.8	2.675	16.09±0.59	80.0	8.579*	12.26±0.60	68.1	14.50*
2	A (2)	12.16±0.79	68.2	11.06*	13.10±0.38	67.6	22.11*	12.19±0.68	61.5	16.56*	11.32±0.50	58.5	22.63*
3	A (3)	16.32±1.51	88.8	2.035	17.91±1.13	90	2.460	16.86±1.51	81.5	2.746*	12.32±0.68	68.4	12.83*
4	A (4)	10.66±0.56	60.7	19.02*	11.82±0.23	61.7	36.40*	10.66±0.40	50.2	22.05*	10.00±0.38	52.0	31.47*
5	B (1)	16.69±0.85	90.6	2.478	18.49±0.68	92.5	2.625	18.00±1.06	87.5	2.493	16.86±0.91	90.7	2.510
6	B (2)	16.79±0.84	91.1	2.416	18.12±0.93	90.8	2.614	14.86±0.65	73.4	12.10*	13.59±0.65	74.6	10.32*
7	B (3)	17.16±0.60	92	2.48	18.14±0.93	90.8	2.56	13.72±0.60	68.3	14.68*	11.42±0.68	60.2	17.23*
8	B (4)	10.06±0.34	57.7	29.34*	11.26±0.40	60.1	27.76*	10.76±0.33	55.1	34.42*	11.32±0.43	64.5	21.10*
9	C (1)	10.26±0.56	58.7	19.70*	11.52±0.27	60.3	34.81*	10.79±0.58	50.7	26.36*	8.31±0.31	43.8	43.66*
10	C (2)	10.46±0.63	54.8	20.07*	11.86±0.23	62	36.20*	10.42±0.40	50.1	35.97*	10.70±0.35	51.5	33.61*
11	C (3)	16.94±0.71	92	2.48	18.09±0.93	90.7	2.667	15.26±1.51	75.2	5.527*	16.69±1.18	90.7	2.194
12	C (4)	16.86±0.79	91.4	2.415	18.16±0.90	91.0	2.652	18.88±0.88	91.5	2.517	16.96±0.80	91.2	2.658
13	Cipro	18.16±0.27	100	0.000	19.66±0.23	100	0.000	20.32±0.27	100	0.000	19.31±0.27	100	0.000
14	DMF	-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Antifungal activity of benzimidazole derivatives (Zone of inhibition, ZOI and %inhibition)

S. No	Compound	*A. niger*			*C. albicans*		
		ZOI±SD	% Inhib	t-value#	ZOI ± SD	% Inhib	t-value#
1	A (1)	14.26±0.64	70.2	14.39*	13.32±0.73	61	14.59*
2	A (2)	10.12±0.68	46.5	24.23*	11.16±0.64	49	21.54*
3	A (3)	10.32±0.94	47.5	18.60*	10.48±0.38	41.1	30.02*
4	A (4)	8.82±0.80	42.1	24.73*	8.50±0.68	38	25.68*
5	B (1)	14.62±0.24	66.4	29.11*	15.19±0.25	64.5	17.74*
6	B (2)	11.49±0.40	52.7	32.00*	13.42±0.64	57.2	16.35*
7	B (3)	12.38±0.27	56.5	36.16*	12.26±0.80	52.3	17.32*
8	B (4)	19.49±1.48	87.7	2.526	20.92±1.51	88.0	2.394
9	C (1)	20.31±0.90	91.3	2.532	20.54±0.93	90.5	2.563
10	C (2)	19.43±1.43	87.5	2.671	20.06±1.13	88.6	2.535
11	C (3)	13.49±0.28	65.7	26.45*	12.71±0.64	58.3	15.80*
12	C (4)	10.41±0.31	52.2	36.58*	11.56±0.80	53.6	15.82*
13	Fluconazole	21.81±0.31	100	0.000	23.32±0.64	100	0.000
14	DMF	-	-	-	-	-	-

RESULTS AND DISCUSSION

The primary focus of this study was the synthesis of a number of substituted benzimidazole derivatives (Scheme 1, 2 and 3). Excellent yields of 60-90% were obtained for all of the synthesized compounds. Spectroscopic (IR and ^{1}H-NMR) approaches were used to verify the structures of all freshly synthesized derivatives. All synthesized derivatives had analytical and spectral data that agreed completely with their postulated structures. Antibacterial and antifungal properties were tested for all synthesized compounds. The inhibitory effects ranged from mild to strong across all of the substances. From what we can tell from the screening findings, several of these compounds have far stronger antibacterial and antifungal properties than the standard medications.

When compared to Ciprofloxacin, the inhibitory activity of compounds A(1), A(3), B(1), B(2), B(3), C(3) and C(4) was shown to be between 75% and 95% more effective against Staphylococcus aureus and Bacillus substilis. The inhibitory effects of compounds A(2) were moderate, at 65-74%, while those of compounds A(4), B(4), C(1) and C(2) were weak, at 50-64%.

Inhibitory action against *Escherichia coli* was increased by 75-95% when comparing compounds A(1), A(3), B(1), B(2), C(3) and C(4) to Ciprofloxacin. Compound B(3) exhibited moderate activity (66-77 percent inhibition), whereas compounds A(2), A(4), B(4), C(1) and C(2) all shown inhibitory effects in the 50-64 percent range.

Inhibitory activity against *Pseudomonas aeruginosa* was greatest for compounds B(1), B(2), C(3) and C(4) Table 1, whereas the other compounds exhibited moderate to weak activity.

Aspergillus niger and *Candida albicans* were shown to be susceptible to killing by some of the chemicals in the aforementioned series. Compounds B(4), C(1), and C(2) showed the greatest effectiveness (75-95% inhibition). Inhibition rates between 50% and 74% were observed with other drugs against the aforementioned fungal species Table 2.

According to the results shown above, antimicrobial activity are modified by the presence of a heterocyclic nucleus.

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Conflict of interest

The authors declare no conflict of interest in the present work.

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