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Synthesis, Characterization and Antibacterial Activity of Benzimidazole Derivatives

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Abstract

Derivatives of benzimidazole containing N-substituted benzyl, benzensuphonyl and acetyl were synthesized from a variety of amino acids such as Lysine and Leucine. The structures of all the synthesized compounds were elucidated by using IR, ^{1}H-NMR, ^{13}C-NMR.The synthesized target compounds were evaluated *in vitro* antibacterial activity against three bacterial strains by employing the disc diffusion method using Ciprofloxacin as a standard drug. The anti-bacterial assay revealed that the compounds (6` b) and (6'd) showed better activity 14, 9, 8 and 12, 9, 7 mm zone of inhibition against *S. auras*, *E. coli* and *K. pneumonia* respectively.

Keywords: Benzimidazole, Heterocycle, Leucine, Lysine, Antibacterial activity.

1. INTRODUCTION

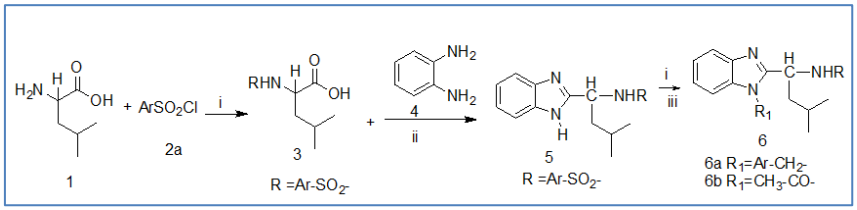
From time to time, heterocyclic compounds have continued to attract the interest of medicinal chemists, because of their numerous therapeutic applications and effective drug like property [1] among heterocyclic compounds Benzimidazole derivatives occupied a major part in the field of pharmaceutical chemistry and very important field of heterocyclic chemistry [2]. These substructures are often called 'privileged' due to their wide recurrence in bioactive compounds.[3] The Benzimidazole structure is part of the nucleotide portion of vitamin B12 and the nucleus of some drugs [4] Benzimidazole, versatile pharmacophore, have received considerable attention due to their association with diverse biological activities, The Benzimidazole nucleus is of significant importance in medicinal chemistry research, and many Benzimidazole containing compounds exhibit important biological activities such as antibacterial[5-9], antitubercular[10-14], Anti-inflammatory[15-18], antiviral[19,20] anticancer[21-23], antitumor[24] etc. activities.Various potent drugs that are now being currently practiced in the market, like albendazole, omeprazole, mebendazole, etc. contain benzimidazole ring [25].

Inspired by the importance biological activities of benzimidazole derivatives, we synthesized some 2-substituted benzimidazole derivatives and screened them for their antibacterial activity against three bacterial strain, S. auras, E. coli and K. pneumonia.

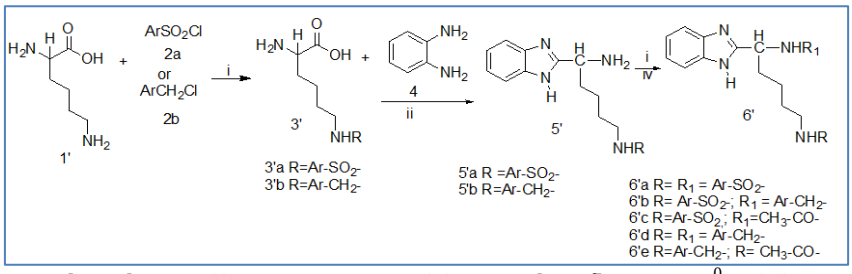
2. EXPERIMENTAL SECTION

2.1. Materials and Methods. All chemicals and reagents were analytical grade and used without further purification; Melting points of the synthesized compounds were measured on Gallenkamp melting point apparatus in open capillary tube and are uncorrected; Infrared spectra was recorded on Perk-Elmer BX infrared spectrometer in the range of 400-4000 cm^{-1}; Nuclear Magnetic Resonance (NMR) analysis was recorded on a Bruker avance 400MHz spectrometer with tetramethylsilane (TMS) as internal standard, $CDCl_3$ and DMSO-d_6 as solvent; Thin Layer Chromatography (TLC) was done using silica gel 60 F_{254} (type 60) pre-coated Aluminum sheets, Merck (Germany), the spots of the final compounds were visualized by irradiation with UV light at (254nm and 365nm) using LF-206 UV/Visible lamp. Column chromatography was performed on silica gel (60-120 mesh). All the Spectral analyses were carried out at the Department of Chemistry, Addis Ababa University, Ethiopia.

2.2. Chemistry. The target compounds were synthesized starting from amino acids such as Leucine (**1**) which depicted in **Scheme-1** and starting from Lysine(**1'**) which is also indicated in **Scheme-2.** The amino acids were reacted with benzenesulfonyl chloride or benzyl chloride in dimethylformamide (DMF) and sodium hydride (NaH), to give the intermediate (3) and (3') respectively, the intermediates condenses with o-phenylenediamine (4) using 4N HCl, to give 2-substituted benzimidazole derivatives (5) and (5') respectively, and further reaction of (5) and (5') with benzenesulfonyl chloride, benzyl chloride or acetyl chloride gave the target compounds, N-substituted benzimidazole derivatives.



Scheme-1: Reagents and conditions: (i) NaH, DMF, RT; (ii) 4N HCl, Reflux 90-100^{0}C; (iii) $ArCH_2Cl$, CH_3COCl, NaH, DMF



Scheme-2: Reagents and conditions: (i) NaH, DMF, RT; (ii) 4N HCl, Reflux 90-100^{0}C; (iv) $ArSO_2Cl$, $ArCH_2Cl$, or CH_3COCl, NaH, DMF

2.3. Synthesis and Characterization

Synthesis of 2-amino-6-(benzenesulphonylamino) hexanoic acid (3'a) and 5-(1H-benzo[d]imidazol-2-yl)-N^1-(benzenesulphonyl) pentane-1, 5-diamine (5'a)

To a solution of Lysine (0.5g, 3.42m.mol) in 10ml of DMF sodium hydride (500mg) was added and stirred at room temperature for 30 minutes, then benzenesulfonyl chloride (603.60 mg 3.42 mmol) was added drop wise in to the reaction mixture. The reaction mixture was stirred at room temperature for 5 hrs. The progress of the reaction was monitored using TLC, after completion of the reaction; the mixture was allowed to cool, extracted with chloroform. Then the organic layer was collected and dried with anhydrous sodium sulfate and concentrated using rotary evaporator. The product was further purified using column chromatography.The intermediate (3'a') was refluxed with 300mg o-phenylenediamine (4), in 10ml of 4N HCl at 90-100^{0}C for 4 hours and 5-(1H-benzo[d]imidazol-2-yl)-N^1-(benzenesulphonyl)pentane-1,5-diamine(5'a') was obtained as yellow waxy solid.

Yellow waxy; Yield 61.3%, m.p 142-144 ^{o}C; FT-IR (KBr, cm^{-1}): 3428(-NH), 3050(C-H, aromatic), 2918 (C-H, aliphatic), 1684(C=O, carbonyl), 1385 and 1018(S=O of benzene sulfonyl); ^{1}H-NMR (DMSO-d_6, 400MHz), δ 8.23 (s, 2H, NH_2), 7.96 (d, J =7.6Hz, 2H, Ar-H), 7.79 (dd, J=7.2Hz, 2H, Ar-H), 7.41(d, J=2.2Hz, 1H, Ar-H), 3.57(t, 1H, NCH), 2.91 (t, 2H, NCH_2), 1.52 (m, 2H, CH_2), 1.21 (m, 2H, CH_2); [13] C-NMR(DMSO-d_6, 100MHz)**:** δ 174.2, 141.4, 132.7, 129.3, 126.8, 54.6, 42.2, 36.2, 31.1, 21.3

Synthesis of 2-amino-6-(benzylamino) hexanoic acid (3'b) and 5-(1H-benzo[d]imidazol-2-yl)-N^1-(benzyl) pentane-1, 5-diamine (5'b)

Lysine (1.0g, 3.42 mmol) dissolved in 15ml of DMF, 1.0g NaH was added and stirred at room temperature for 30 minutes, then benzyl chloride (862mg, 3.42m.mol) was added drop wise in to the reaction mixture. The completion of the reaction was confirmed after 15 hrs using TLC, after completion the reaction the reaction mixture was allowed to cool, extracted with chloroform and washed with water. Then the organic layer was collected, dried using anhydrous Na_2SO_4 and concentrated on rotary evaporator. The product was further purified by column chromatography then, the purified product was concentrated using rotary evaporator. The compound 3'b was refluxed at 90-100^{o}C with o-phenylenediamine (4), in 12.5 ml of 4N HCl and 5-(1H-benzo[d]imidazol-2-yl)-N^1-(benzyl) pentane-1, 5-diamine (5b) was obtained

White solid, Yield 77.4%, m.p 185-187 ^{o}C; FT-IR (KBr, cm^{-1}): 3428 (-NH), 3061(C-H, aromatic), 2840 (C-H aliphatic), 1684(C=O, carbonyl); 1018 (C-N stretch); [1] H-NMR (DMSO-d_6, 400MHz): δ 7.98 (s,

2H, -NH_2), 7.32 (dd, J=6.4Hz, 2H, Ar-H), 7.27 (dd, J=6.8Hz, 1H, Ar-H) 7.21 (d, J=6.2Hz, 2H, Ar-H), 3.72 (s, 2H, NCH_2), 2.91 (s, 1H, CH), 2.50 (t, 2H, NCH_2), 1.43 (m, 2H, CH_2), 1.23 (m, 2H, CH_2); [13] C-NMR (DMSO-d_6, 100MHz): δ 175.1, 140.7, 128.5, 128.3, 127.1, 57.9, 53.2, 51.3, 36.2, 31.2

Synthesis of N-benzenesulphonyl-1-(1-benzyl-1H-benzo[d]imidazol-2-yl)-3-methylbutan-1-amine (6a)

To a solution of (5) (300mg, 0.87 mmol) in10 ml of DMF, NaH (500mg) was added and stirred at room temperature for 30 minutes. Then benzyl chloride (2.0ml, 0.87m.mol) was added drop wise in to the reaction mixture. The reaction was stirred at room temperature for 5 hrs, after completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool, extracted with chloroform and washed with water. Then the organic layer was collected, dried by anhydrous Na_2SO_4 and concentrated using rotary evaporator. The product was further purified using column chromatography.

White solid, Yield 85.8%, m.p 194-196 ^oC; FT-IR (KBr, v in cm^{-1}): 3428 (N-H) 3130(C-H, aromatic), 2972 (C-H, sp^3 stretching), 1452 (C=N), 1374 and 1254 (R-SO_2-R' and S=O stretch respectively), 1074 and 741 (C-N and C-S stretch respectively); ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.99 (d, J=7.6Hz, 2H, Ar-H), 7.82 (2H, d, J=5.3Hz, 2H, Ar-H), 7.54 (dd, J=1.8Hz, 2H, Ar-H), 7.30 (dd, J=1.5Hz, 1H, Ar-H), 7.26 (d, J=11.4Hz, 2H, Ar-H), 7.20 (dd, J=7.8Hz, 2H, Ar-H), 5.41 (s, 2H, NCH_2), 3.21 (s, 1H, NH), 1.83 (m, 1H, CH), 1.24 (d, J=4.6Hz, 6H, $2CH_3$); [13] C-NMR ($CDCl_3$, 100MHz): δ143.9, 143.2, 135.4, 133.9, 133.4, 129.4, 129.2, 128.2, 127.1, 123.1, 122.2, 113.7, 51.6, 48.8

Synthesis of N-benzenesulphonyl-1-(1-acetyl-1H-benzo[d]imidazol-2-yl)-3-methylbutan-1-amine (6b)

To a solution of (5) (300mg, 0.87mmol) in 10ml of DMF, NaH (500mg) was added and stirred at room temperature for 30 minutes, then acetyl chloride (2.0ml, 0.87 m chloride (2.0ml, 0.87 mmol) was added drop wise and stirred at room temperature for 5 hrs, after completion of the reaction monitored by TLC, the reaction mixture was cooled, extracted with dichloromethane and washed with water. Then the organic layer was collected, dried over anhydrous sodium sulfate and concentrated using rotary evaporator. The product was further purified using column chromatography.

White solid, Yield 80.2%, m.p 175-177 ^oC; FT-IR (KBr, v in cm^{-1}): 3428 (N-H) 3128(C-H, aromatic), 2928(sp^3 C-H), 2961(C-H stretch), 1673(C=O, carbonyl), 1441(C=N) 1374 and 1129 (R-SO_2-R' and S=O stretch respectively), 962 and 797 (C-N and C-S stretch respectively); ^{1}H-NMR($CDCl_3$, 400MHz): δ 8.22 (d, J=2.4Hz, 2H, Ar-H), 7.80 (d, J=5.6Hz, 2H, Ar-H), 7.45 (dd, J=1.6Hz, 2H, Ar-H), 7.41 (dd, J=2.4Hz, 1H, Ar-H), 7.26 (d, J=3.2Hz, 2H, Ar-H), 2.74 (s, 3H, $COCH_3$), 1.45 (t, 2H, CH_2), 0.83 (d, J=4.2Hz, 6H, $2CH_3$); [13]C-NMR ($CDCl_3$, 100MHz): δ 167.2, 143.9, 141.3, 131.4, 125.9, 125.1, 120.5, 115.5, 31.9, 29.7, 23.7, 14.1

Synthesis of N-(5-(1H-benzo[d]imidazol-2-yl)-5-(benzenesulphonylamino)pentyl)benzene sulphonylamine (6'a)

To a solution of 5'a' (500mg, 1.4mmol) in15ml of DMF, NaH (600mg) was added and stirred at room temperature for 30 minutes, then benzenesulfonyl chloride (2.5ml, 1.4m.mol) was added drop wise and stirred at room temperature for 3 hrs, the progress of the reaction was monitored using TLC, after completion of the reaction, the reaction mixture was allowed to cool, extracted with chloroform and washed with water. The organic layer was collected, dried over anhydrous sodium sulfate and concentrated using rotary evaporator. The product was further purified using column chromatography.

Brown crystal, Yield 68.3%, m.p 172-174 ^oC; FT-IR (KBr, cm^{-1}): 3428 (N-H stretch), 3039(C-H aromatic), 2851(C-H aliphatic), 1518 (C-N stretch), 1385 and 1129 (R-SO_2-R' and S-O stretch respectively); ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.15 (d, J=8.0Hz, 4H, Ar-H), 7.71 (d, J=7.2Hz, 2H, Ar-H), 7.63 (dd, J=3.2Hz, 4H, Ar-H), 7.32 (dd, J=2.8Hz, 2H, Ar-H), 7.28 (d, J=12.8Hz, 2H, Ar-H), 5.1 (s, 1H, N-H), 3.01 (t, 2H, NCH_2), 2.55 (s, 2H), 1.29 (m, 2H, CH_2); [13]C-NMR ($CDCl_3$, 100MHz): δ 140.4, 137.23, 132.9, 129.9, 123.1, 115.4, 108.7, 103.3, 26.0

Synthesis of N-(5-(1H-benzo[d]imidazol-2-yl)-5-(benzylamino) (pentyl) benzenesulphonylamine (6'b)

To a solution of (5'a) (300mg, 0.84m.mol) in10ml of DMF, 400mg NaH was added and stirred at room temperature for 30 minutes, then benzyl chloride (1.75ml, 0.84m.mol) was added drop wise in to the reaction mixture and stirred at room temperature for 3 hrs, the progress of the reaction was monitored using TLC, after completion of the reaction, the reaction mixture was allowed to cool, extracted with chloroform and washed with water. Then the organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated using rotary evaporator. The product was further purified using column chromatography. Finally, the purified product was concentrated by using rotary evaporator.

White crystal, Yield 79.5%, m.p 198 ^oC; FT-IR (KBr, Cm^{-1}): 3406 (N-H stretch) 3117(C-H, aromatic), 2873(C-H, aliphatic), 1452 (C-N), 1374 and 1185 (R-SO_2-R' and S-O stretch); ^{1}H-NMR($CDCl_3$, 400MHz): δ 8.21 (d, J=8.02Hz, 2H, Ar-H), 7.87 (d, J=6.8Hz, 2H, Ar-H), 7.55 (dd, J=8.5Hz, 2H, Ar-H), 7.30 (d, J=2.74Hz, 1H, Ar-H), 7.26 (d, J=12Hz, 2H, Ar-H), 7.19 (dd, J=9.1Hz, 2H, Ar-H), 5.5 (s, 1H, N-H), 5.05 (t, 1H, N-CH), 3.16 (t, 2H, N-CH_2), 2.2 (s, 2H), 1.29 (m, 2H,

CH_2); [13] C-NMR ($CDCl_3$, 100MHz): δ 142.8, 135.0, 133.3, 129.4, 129.2, 129.1, 128.4, 128.2, 127.2, 127.0, 123.5, 119.9, 49.1, 45.3, 34.6

Synthesis of N-(5-benzenesulphonylamino-1-(1H-benzo[d]imidazol-2-yl) (pentyl) acetamide (6'c)

To a solution of (5'a') (300mg, 0.84m.mol) in10ml of DMF, 500mg NaH was added and stirred at room temperature for 30 minutes, then acetyl chloride (1.0ml, 0.84m.mol) was added drop wise in to the reaction mixture. The reaction was stirred at room temperature for 5 hrs, the progress of the reaction was monitored using TLC after completion the reaction, the reaction mixture was cooled, extracted with chloroform and washed with water. Then the organic layer was collected, dried by anhydrous sodium sulfate and concentrated using rotary evaporator. The product was further purified using column chromatography.

Brown crystal, Yield 62.7%, m.p 173-176 ^oC; FT-IR (KBr, Cm^{-1}): 3439 (N-H stretch) 3061(C-H, aromatic), 2928 (C-H stretch), 1707(C=O, carbonyl), 1463(C-N), 1385 and 1087(R-SO_2-R' and S-O); ^{1}H-NMR($CDCl_3$, 400MHz): δ 9.20 (s, N-H), 7.93 (2H, d, J=15.2Hz, Ar-H), 7.61 (2H, d, J=3.6Hz, Ar-H), 7.59 (2H, dd, J=7.6Hz, Ar-H), 7.35 (d, 1H, J=2.4Hz, Ar-H), 7.27 (d, 2H, J=3.2Hz, Ar-H), 2.5 (t, 2H, N-CH), 2.14 (s, 3H, $COCH_3$), 1.29 (m, 2H, CH_2); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 170.2, 140.6, 136.9, 130.6, 126.1, 125.5, 123.1, 115.3, 114.1, 39.1, 29.7, 28.5

Synthesis of N-(1-(1H-benzo[d]imidazol-2-yl)-5-(benzylamino) (pentyl)benzylamine(6'd)

To a solution of 5'b (300mg, 0.98 mmol) in10ml DMF, 500mg NaH was added and stirred at room temperature for 30 minutes, then benzyl chloride (2.0ml, 0.98m.mol) was added drop wise. The progress of the reaction was monitored using TLC, after completion of the reaction; the mixture was allowed to cool, extracted with chloroform and washed with water. Then the organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated using rotary evaporator. The product was further purified using column chromatography.

White solid, Yield 83.9%, m.p 197-199^oC; FT-IR (KBr, cm^{-1}): 3428 (N-H) 3039(C-H, aromatic), 2918(C-H stretch), 1463 (C=N), 741 (C-S stretch); ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.85 (d, J=4.1Hz, 2H, Ar-H), 7.65 (d, J=3.42 Hz, 2H, Ar-H), 7.32 (dd, J=7.32 Hz, 4H, Ar-H), 7.19 (dd, J=6.93Hz, 2H, Ar-H), 5.09 (s, 1H, N-H), 4.59 (t, 1H, NC-H), 3.15 (s, 4H, $2CH_2$), 2.67 (t, 2H, CH_2), 2.0 (t, 2H,), 1.25 (m, 2H, CH_2); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 143.1, 135.3, 133.3, 129.4, 128.3, 127.8, 123.2, 113.7, 52.3, 48.9, 48.4, 34.6

Synthesis of N-(1-(1H-benzo[d]imidazol-2-yl)-5-(benzylamino) (pentyl)acetamide (6'e)

To a solution of (5'b) (300mg, 0.98m.mol) in 10ml of DMF, NaH (500mg) was added and stirred at room temperature for 30 minutes, then acetyl chloride (1.5ml, 0.98 mmol) was added drop wise and stirred at room temperature for 6 hrs, the progress of the reaction was monitored using TLC, after completion of the reaction, the reaction mixture was allowed to cool, extracted with dichloromethane and washed with water, the organic layer was collected, dried over anhydrous sodium sulfate and concentrated using rotary evaporator. The product was further purified using column chromatography.

White solid, Yield 74.8%; m.p 175-178 ^oC; FT-IR (KBr, cm^{-1}): 3428 (N-H), 3050(C-H, aromatic), 2928 (C-H, aliphatic), 1695 (C=O, carbonyl), 1453 (C=N), 940 (C-N stretch); ^{1}HNMR ($CDCl_3$, 400MHz): δ 8.03 (s, 1H, N-H), 7.83 (d, J=4.5Hz, 2H, Ar-H), 7.63 (d, 2H, J=3.8Hz, Ar-H), 7.31 (dd, J=7.4Hz, 2H, Ar-H), 7.26 (dd, J=2.2Hz, 1H, Ar-H), 7.14 (d, J=6.7Hz, 2H, Ar-H), 3.55 (s, 2H, NCH_2), 2.71 (t, 2H, NCH_2), 2.14 (s, 3H, $COCH_3$), 1.31 (m, 2H, CH_2); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 170.1, 140.6, 137.2, 130.6, 128.9, 128.2, 127.7, 123.0, 115.4, 37.5, 29.6

3. RESULT AND DISCUSSION

3.1. Antibacterial Activity of the Synthesized Compounds

The antimicrobial activity of newly synthesized compounds were evaluated against three bacterial strains, Staphylococcus auraes (S. auraes), Escherichia coli (E. coli) and Klebsiella pneumonia (K. pneumonia) using Ciprofloxacin (5µg/disc) as a standard drug.

3.2. Culture Media and Disc Preparation

Nutrient agar, Muller Hinton agar and Nutrient broth were prepared according to the manufacturer instruction in which the prepared media was autoclaved at 121^0C for 15 minutes. Then the prepared culture media was checked for the sterility for 24 hours at 37^0C. Quality control stains of Staphylococcus auraes (S. auraes), Escherichia coli (E. coli) and Klebsiella pneumonia (K. pneumonia) known American type culture collection committee (ATCC) was used to perform the antibacterial activities of the agents. Whatman filter paper was used to prepare a disc of 6 mm diameter using manual paper punching.

3.3. Preparation of chemical solution and media for the antibacterial activity

Preparation of solution was conducted as recommended by Hoda P. et al., with slight modification to concentration. [26] Analytical balance was used to measure a 20µg and 10µg of each chemical powder and added to 150µl dimethylsulfoxide (DMSO) and mixed to form a homogenous solution. A 10µl of solution was added to the sterile disc prepared before using sterile micropipette. Quality control strains obtained from Hawassa University College of medicine and health science was inoculated on nutrient agar plate using sterile loop. The plate was incubated for 24 hours

at 37 ^{o}C. A 3-5 colonies was picked and suspended in 5ml nutrient broth to form 0.5 McFarland standards. From the suspension by using sterile swab deepen and swab on Muller Hinton agar plate in three directions to form uniform inoculum. Then a disc with a control gentamicin and solution impregnated disc was placed on the plate and incubated for 24 hours at 37^{0}C. Each disc was labeled with its unique ID number on the back of the Petri-dish. Antibacterial activity was considered if there is zone of inhibition around the disc. The synthesized compounds were evaluated in vitro for antimicrobial activity against three bacterial strains, Staphylococcus auraes (S. auraes), Escherichia coli (E. coli) and Klebsiella pneumonia (K. pneumonia) using Ciprofloxacin as a standard. Gentamicin was used as a control in this study and DMSO used as a solvent. Disc diffusion method was used for the sensitivity testing and the diameter of zones of inhibition (ZOI) was documented in millimeter (Table-1).

Table-1: Antimicrobial activity of compounds with zones of inhibition in millimeter

Compound code	Bacteria		
	S. auraes	E. coli	K. pneumonia
6a-10µg	10	7	6
6a-20µg	11	8	7
6b-10µg	6	7	6
6b-20µg	6	7	6
6'a-10µg	6	6	6
6'a-20µg	6	6	6
6'b-10µg	9	8	6
6'b-20µg	14	9	8
6'c	ND	ND	ND
6'd-10µg	11	8	6
6'd-20µg	12	9	7
6'e-10µg	10	7	6
6'e-20µg	11	8	7
Ciprofloxacin	24	34	6

ND: Not determined

4. CONCLUSION

In the present study, biologically active of 1, 2-disubstituted benzimidazole derivatives were synthesized and evaluated for antimicrobial activity. All the newly synthesized compounds were evaluated in vitro for antimicrobial activity by the disc diffusion method and its zone of inhibition was determined against three different bacterial strains. Among the synthesized compounds, compounds (6'b) and (6'd) showed better antimicrobial activity against S. auras bacterial strain. Compound (6a) and (6'e) exhibited moderate activity against all the bacterial strains. Compounds (6 b) and (6' a) exhibited no activity against all the tested bacterial strains.

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