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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY EVALUATION OF NOVEL OXADIAZOLE DERIVATIVES BEARING INDOLE AND BENZIMIDAZOLE MOIETIES

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ABSTRACT

A new series ofsixoxadiazole derivatives bearing indole and benzimidale moieties have been synthesized. The purity and the structures of all the synthesized compounds were confirmed using TLC, Column chromatography, IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.All the target compounds and four intermediates were screened for antimicrobial activities *against Staphylococcus aureus (*NTCC-6571), *Shigellasonnei (SG_4), Shigellaparatyphi A_2 (SL_2), Escherichia coli (TG_1)4 and Vibrio choleri* (NTCC-64) using Amoxycillin as a reference, compound **7b** and **8e** exhibit good activity against *Staphylococcus aureus*and compound **7a** against *Escherichia coli.*

Keywords: Oxadizaole, indole, benzimidazole, antimicrobial.

1. INTRODUCTION

For several decades antimicrobial resistance (AMR) has been a growing threat to the effective treatment and prevention of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi[1].To tackle this problem the attention of many researchers has been attracted toward designing and synthesizingof new and potent moleculesagainst drug resistant microbial pathogens. In this regard a wide variety of heterocyclic systems have been explored for developing pharmaceutically important molecules. Among them the derivatives of oxadiazoles, benzimidazole, indole etc. are intensively studied

The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial[2,3], antifungal[4],anti-inflammatory[5],anticancer[6,7] anti HIV[8].

Benzimidazole is also important heterocyclic ring; synthesis and biological screening of its derivatives have drawn continuing interest over the years because of their diverse biological activity and clinical applications. A large number of benzimidazole derivatives have been synthesized and evaluated for antimicrobial[9], antifungal[10], anti-inflammatory[11], anti cancer[12], antiviral[13], in the same way indole derivatives have also been synthesized and evaluated for antibacterial[14], antifungal[15], anti-malarial[16], antitumor[17], anti cancer[18].

We reported here the synthesis and antimicrobial evaluation of some novel structure hybrids incorporating indole and benzimidazole moieties with oxadizaole and screened for their antimicrobial activities

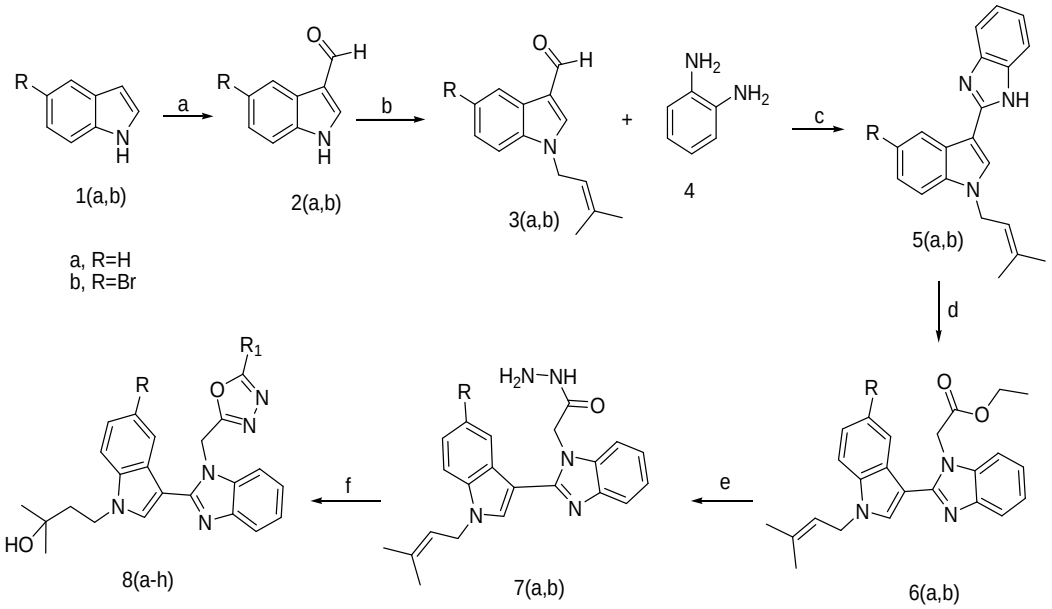
2. EXPERIMENTAL

All chemicals and solvents were purchased from Sigma Aldrich and used without further purification; the reaction process was monitored by TLC silica gel plates, the purification of the products was performed using column chromatography silica gel (100-

200 mesh). Melting points were measured in open capillary tubes and were uncorrected; Infrared (IR) spectra were recorded using FT-IR Bruker Alpha spectrometer. NMR spectra were recorded on Bruker (400 MHz) spectrometer using TMS as the internal standard, mass spectra were recorded on an Agilent 110 Lc/MSD; the target compounds, 8a-8h and the intermediate 5a, 5b and 6a, 6b were investigated for antimicrobial activity against.

3. SYNTHETIC SCHEME

Formylindole (2) was obtained by a modified vilsmeier-haack method, which on prenylation with 3,3-dimethyl allylbromide gave the intermediate (3), condensation of (3) with phenylenediamine (4) yield the intermediate (5), in good yield. This was followed by the bromoacylation to give (6). The key intermediate hydrazide (7) was synthesized by the hydrazinolysis of compound (6)withhydrazine hydratedwhich was subsequently reacted with appropriate acid in the presence of phosphrousoxychloride to give the desired compounds 8(a-h) in good yield. The synthetic procedure was presented in scheme-1.



S. no	compounds	R	R_1
1	8a	H	$-CF_3$
2	8b	H	$-2BrC_6H_4$
3	8c	H	$-NO_2C_6H_4$
4	8d	H	$-4ClC_6H_4$
5	8e	Br	$-2BrC_6H_6$
6	8f	Br	$-4NO_2C_6H_4$

Scheme. 1: Reagent and Condition;

a) $POCl_3$, DMF, NaOH, b) 3,3-dimethyl allylbromide, NaH, DMF, 0 ^oC
c) PTSA, DMF, 100^oC, reflux d) ethyl 2-bromoacetate, NaH, DMF, 0^oC,
e) $NH_2NH_2\,H_2O$, MeOH, RT f) R_1COOH, $POCl_3$, reflux, H_2O

3.1 General procedure for the synthesis of 5-substituted 1*H*-indole-3-carboxaldehyde (2a/2b)

To a solution of substituted indoles**(1a /1b)** (42.6 mmol) in dry DMF (187.4 mmol) in an ice-salt bath, $POCl_3$ (47.1 mmol) was subsequently added with stirring over a period of 30 min. After completion of addition, the temperature was raised to 40 ^oC, the syrup was stirred for 1.5 h at same temperature. At the end of the reaction (as indicated by TLC) 25 gms crushed ice was added to the reaction mixture. The obtained solution was transferred into 250 mL RB flask, NaOH (470 mmol) dissolved in 50 mL water was added with constant stirring and the resultant suspension was heated rapidly to the boiling point and allowed to cool to room temperature, The

mixture was allowed to stand in refrigerator overnight. The precipitate was filtered off, washed thrice with 100 mL water, yielding 5-substituted 1*H*-indole-3-carboxaldehyd **(2a/b).**

3.1.1 1*H*-indole-3-carboxaldehyde (2a)

Yield: 92%., Brownish yellow solid; Mp: 196-198 ^{o}C; IR (KBr, cm^{-1}): 3442(N-H), 1632(C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.52 (s, 1H), 8.12 (s, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.52 (s, 1H), 7.34 (d, *J* = 8 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 22.4 MHz): *δ* 1882.7, 137.2, 131.82, 127.7, 122.4, 120.5, 119.4, 118.0, 111.4; ESI-MS: *m/z* 146.20 [M+H]$^{+}$.; Anal. Calc. for C_9H_7NO: C, 74.47, H, 4.86, N, 9.65 %, Found: C, 74.44, H, 4.91, N, 9.64 %.

3.1.2 5-bromo-1*H*-indole-3-carboxaldehyde (2b)

Yield: 90%., Cream coloured solid, Mp: 192 ^{o}C.; IR (KBr, cm^{-1}): 3312(N-H), 1643(C=O) ^{1}H NMR (DMSO-d_6, 400 MHz): *δ* 9.94 (s, 1H)**,** 8.32 (s, 1H), 8.25 (s, 1H), 7.75 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 22.4 MHz): *δ* 183.9, 144.4,136.7, 135.2, 125.6, 123.1, 117.3, 114.8, 113.0; ESI-MS: *m/z* 245.95 [M+Na]$^{+\cdot}$; Anal. Calc. for C_9H_6BrNO: C, 48.25, H, 2.70, N, 6.25 %, Found: C, 48.22, H, 2.76, N, 6.24 %.

3.2 General procedure for the synthesis of substituted 1-(3-methylbut-2-enyl)-1*H*-indole-3-carboxaldehyde (3a/ b)

To a solution of substituted 1*H*-indole-3-carboxaldehyd**(2a/b)** (2.20 mmol) in dry DMF (5 mL) (2.64 mmol, 60% oil dispersion) of NaH was added and the resulting mixture was stirred for 10 min in an ice bath, 3,3-dimethylallyl bromide (2.20 mmol) was added and the resulting mixture was stirred for 90 min at 0 ^{o}C. The mixture was diluted with EtOAc (20 mL), washed five times with distilled water (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to get crude residue which was purified by column chromatography (silica gel 100-200 mesh) using 8:2 (Hexane : EtOAc) as eluents affording **3a/b** in good yield.

3.2.1 1-(3-methylbut-2-enyl)-1*H*-indole-3-carboxaldehyde (3a)

Yield: 87%., Brownish yellow crystals., Mp: 79-81 ^{o}C; IR (KBr, cm^{-1}): 1640, (C=O) 1224; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 9.99 (s, 1H), 7.76 (s, 1H), 7.28-7.41 (m, 4H), 5.44 (t, *J* = 7.2 Hz, 1H), 4.74 (d, *J* = 7.2 Hz, 2H), 1.86 (s, 3H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 22.4 MHz): *δ* 184.3, 138.7, 137.5, 137.3, 125.5, 123.6, 122.7, 121.8, 117.9, 110.0, 117.7, 44.6, 25.4, 17.9; ESI-MS: *m/z* 214.20 [M+H]$^{+}$; Anal. Calc. for $C_{14}H_{15}NO$: C, 78.84, H, 7.09, N, 6.57 %, Found: C, 78.80, H, 7.16, N, 6.55 %

3.2.2 5-bromo-1-(3-methylbut-2-enyl)-1*H*-indole-3-carboxaldehyde (3b)

Yield: 89%., Pale pink solid., Mp: 95-98 ^{o}C; IR (KBr, cm^{-1}): 1654(C=O), 1162; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 9.96 (s, 1H)., 8.47 (d, *J* = 2.0 Hz, 1H), 7.73 (s, 1H), 7.43 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.25 (d, *J* = 9.6 Hz, 1H), 5.42 (t, *J* =7.2 Hz, 1H), 4.71 (d, *J* =7.2 Hz, 2H), 1.86 (s, 3H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 22.4 MHz): *δ* 178.6, 133.8, 132.8, 132.6, 130.3, 121.4, 121.1, 119.0, 111.7, 110.8, 106.0, 39.4, 20.1, 12.7; ESI-MS: *m/z* 314.01 [M+Na]$^{+}$.; Anal. Calc. for $C_{14}H_{14}BrNO$: C, 57.55, H, 4.83, N, 4.79 %, Found: C, 57.53, H, 4.90, N, 4.77.

3.3 Synthesis of 2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazole/2-(5-bromo-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazole (5a/5b)

Equivalent of 1-(3-methylbut-2-enyl)-1*H*-indole-3-carboxaldehyde /5-bromo-1-(3-methylbut-2-enyl)-1*H*-indole-3-carboxaldehyde (3a, 3b) and 1 equivalent of o-phenylenediamine (4) were thoroughly dissolved in DMF, 40 mol % of PTSA was added, and the solution was refluxed at 100 °C for appropriate time, After completion of the reaction, (monitored by TLC). The solution was cooled to RT and extracted with ethyl acetate; the combined organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure, the crude product was purified by column chromatography over silica gel (hexane: ethyl acetate, 7:3).

3.3.1 2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*- benzo[*d*]imidazole (5a)

Yield: 79.6 %; Yellow solid; Mp: 142-144^{o}C.; IR (KBr Cm^{-1}):3443 (N-H), 3095, (C-H aromatic), 2966(C-H, aliphatic), 1625(C=N).; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 7.6Hz, 1H, Ar-H), 7.89 (s, 1H, H-2′), 7.58-7.56 (m, 2H, Ar-H), 7.31-7.15 (m, 5H, Ar-H), 5.19 (t, *J* = 6.8 Hz, 1H), 4.48 (d, *J* = 6.8 Hz, 2 H), 1.65 (s, 3H), 1.62 (s, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 149.1, 138.2, 137.8, 136.6, 129.3, 129.2, 125.5, 122.3, 121.2, 121.2, 120.3, 120.3, 118.5, 114.3, 110.2, 110.2, 105.2, 44.3, 25.5, 17.9; MS m/z: 302 [M + H]$^{+}$; Anal. Calc. (%) for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94; found: C, 79.12; H, 6.33; N, 13.92.

3.3.2 2-(5-bromo-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazole (5b)

Yield: 78.7 %; Light brown solid; Mp: 238-240 ^{o}C.; IR (KBr Cm^{-1}):3423 (N-H), 3084, (C-H aromatic) 2924 (C-H aliphatic) 1625(C=N); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37(s, 1H, Ar-H), 7.55(s, 1H, H-2′), 7.27-7.06 (m, 6H, Ar-H), 5.17(t, *J* = 6.8Hz, 1H), 4.53 (d, *J* = 5.2Hz, 2 H), 1.69(s, 3H), 1.65(s, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 148.5, 138.4, 136.7, 130.9, 127.1, 125.5, 122.3, 118.2, 114.7, 111.6, 110.8, 106.5, 44.5, 25.6, 18.0; ESI-MS: *m/z* 382.1/380.1 (M^+ + H)(for ^{81}Br/^{79}Br, 100%, 99%); Anal. Calc. (%) for $C_{20}H_{18}BrN_3$: C, 63.17; H, 4.77; Br, 21.01; N, 11.05; found: C, 62.88; H, 4.76; N, 11.02

3.4 Synthesis of ethyl 2-(2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*] imidazol-1-yl) acetate/ ethyl 2-(2-(5-bromo-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo [*d*]imidazol-1-yl) acetate (6a/ 6b)

1 equivalent of (5a/5b) were dissolved in DMF, 1.2 equivelents of NaH was added and stirred on ice-bath for 20-30 minutes and then 1.2 equivelents of ethyl 2-bromoacetate was added, the mixture was stirred at RT for 6-7 hrs after completion of the reaction, (monitored by TLC) the reaction mixture was diluted with water and extracted with ethyl acetate the combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel (hexane: ethyl acetate, 8:2)

3.4.1 Ethyl 2-(2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl) acetate (6a)

Yield: 84 Mp: 185-187 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, *J* =7.6Hz1H, Ar-H), 7.86-7.83 (m, 1H, Ar-H), 7.64(s, 1H, H-2′), 7.47-7.32 (m, 5H, Ar-H), 5.33 (t, *J* = 7.2 Hz, 1H), 4.90(s, 2H), 4.64(d, *J* = 7.2 Hz, 2H), 4.27(q, *J* = 7.2 Hz, 2H), 1.79(s, 3H), 1.76(s, 3H), 1.23 (t, *J*, 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 165.6, 148.2, 141.4, 138.6, 136.1, 134.4, 128.9, 128.5, 123.4, 123.1, 121.0, 119.1, 117.8, 114.3, 111.7, 109.7, 104.5, 61.2, 45.7, 44.4, 18.3, 14.5

3.4.2 Ethyl 2-(2(5-bromo-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl) acetate (6b)

Yield: 78 %; Mp: 160-162 ^{o}C; IR (KBr, cm^{-1}): 3086(C-H aromatic), 2927 (C-H aliphatic), 1730 (C=O, ester), 1680(-C=N); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, *J* = 1.6 Hz1H, Ar-H), 7.86-7.83 (m, 1H, Ar-H), 7.54(s, 1H, H-2′), 7.37-7.22 (m, 5H, Ar-H), 5.37 (t, *J* = 7.2 Hz, 1H), 4.89(s, 2H), 4.67(d, *J* = 7.2 Hz, 2H),), 4.27(q, *J* = 7.2 Hz, 2H), 1.80(s, 3H), 1.78(s, 3H), 1.25 (t, *J* = 7.2Hz, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 167.9, 149.1, 142.5, 138.3, 135.0, 134.8, 129.9, 128.7, 123.8, 123.1, 122.9, 119.2, 118.5, 114.7, 111.5, 109.4, 103.3, 60.8, 46.6, 44.9, 18.1, 14.1

3.5 Synthesis of2-(2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl) acetohydrizide/2-(2-(5-bromo-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*benzo[*d*] imidazol-1-yl) acetohyderazide (7a/ 7b)

To a solution of compounds **6(a/ b)**(0.02 mol) in methanol, hydrazine hydrate(3 ml) was added and stirred at RT overnight after completion of the reaction, (as indicated by TLC) the methanol was removed under reduced pressure, the crude product obtained was crystallized from cold ethanol.

3.5.1 2-(2-(1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)aceto hydrazide(7a)

Yield: 76%, Mp; 172-174 ^{o}C; IR (KBr Cm^{-1})3383 (N-H), 3045(C-H aromatic), 2970 (C-H aliphatic), 1686(-CONH amide), 16516(C=N); ^{1}H NMR ($CDCl_3$, 400 MHz): **δ** 9.65 (s, 1H, NH), 8.29 (d, *J* = 8 Hz1H, Ar-H), 7.94(s, 1H, H-2′), 7.70-7.19 (m, 7H, Ar-H), 5.43 (t, *J* = 6.8 Hz, 1H), 4.98(s, 2H), 4.89 (d, *J* = 6.8 Hz, 2 H), 4.42 (s, 2H, NH_2), 1.88(s, 3H), 1.76(s, 3H);^{13}CNMR ($CDCl_3$, 100 MHz): δ 166.5, 149.6, 143.1, 136.2, 135.9, 135.8, 129.1, 129.0, 127.1, 121.5, 121.5, 119.8, 118.3, 118.2, 110.3, 109.9, 104.0, 45.4, 44.0, 25.3, 17.9; MS m/z: 374.44 $(M + H)^{+\cdot}$

3.5.2 2-(2(5-bromo-1-(3-methylbut-2-enyl)-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)aceto hydrazide(7b)

Yield: 72 %; Mp: 168-170 ^{o}C; ^{1}H NMR (DMSO-d_6 400 MHz): **δ** 9.8 (s, 1H, NH), 8.48 (s, 1H, Ar-H), 7.99(s, 1H, H-2′), 7.74-7.20 (m, 6H, Ar-H), 5.38 (t, *J* = 6.8 Hz, 1H), 4.97(s, 2H), 4.87 (d, *J* = 6.8 Hz, 2 H), 1.82(s, 3H), 1.73(s, 3H); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 166.4, 149.67, 142.9, 136.7, 135.8, 134.5, 130.3, 128.8, 124.9, 123.7, 121.7, 119.5, 113.2, 112.5, 109.9, 103.7, 45.5, 44.2, 25.3, 17.9

3.6 Synthesis of derivatives of 4-(3-(1-((1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*] imidazol-2-yl)-1*H*-indol-1-yl)-2-methylbutan-2-ol/4-(5-bromo-3-(1-((1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1H-indol-1-yl)-2-

methylbutan-2-ol (8a-h)

An equimolar mixture of compounds 7(a / b) and substituted carboxylic acid in phosphrous oxy chloride was refluxed at 100 ^{0}C for 6h., after completion of the reaction, (monitored by TLC)The reaction mixture was cooled, poured into ice water and kept until precipitate was formed, up to 5-6 hrs., and then washed with $NaHCO_3$ solution. The product obtained was filtered, and recrystallized from ethanol.

3.6.2 4-(3-(1-((5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-indol-1-yl)-2-methylbutan-2-ol (8a)

Yield: 72 %; Mp: 176-178 ^{o}C;IR (KBr Cm^{-1}) 3345(OH), 2984 (C-H aliphatic), 1677 (C=N of Oxadiazole ring), 1586(C=N of benzimidazole ring), 1201(C-O-C), 1018 (C-F); ^{1}H NMR (DMSO-d_6 400 MHz): δ 8.31-8.01 (m, 1H, Ar-H), 7.99-7.71(m, 3H., Ar-H), 7.59-7.35 (m, 5H, Ar-H), 5.43 (s, 2H), 4.58 (t, *J* = 7.6 Hz, 2H), 2.48 (s, 1H), 2.37(t, *J* = 8 Hz, 2H), 1.66(s, 6H); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 165.6, 158.5(q, $^2J_{CF}$ = 36 Hz), 156.3, 147.6, 136.5, 133.7, 126.2, 125.8, 124.3, 124.1, 122.5, 122.5, 120.6, 120.4, 117.5, (q, CF_3, *J* = 260), 114.9, 114.7, 112.9, 111.9, 70.7, 47.1, 44.8, 43.9, 32.5.

3.6.3 4-(3-(1-((5-(2-bromophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-indol-1-yl) 2-methylbutan-2-ol (8b)

Yield: 56 %; Mp: 226-228 ^{o}C; IR (KBr Cm^{-1}): 3342(OH), 2984(C-H aliphatic), 1677(C=N of Oxadiazole ring), 1621(C=N of benzimidazole ring), 1244(C-O-C); ^{1}H NMR (DMSO-d_6 400MHz): δ 8.54-8.18 (m, 2H, Ar-H), 7.78-7.42 (m, 11H, Ar-H), 5.23 (s, 2H), 4.56(t, *J* = 8.4 Hz, 2H), 2.40 (s, 1H), 2.38(t, *J* = 7.6 Hz, 2H), 1.68(s, 6H); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 167.3, 164.3, 144.2, 137.3, 136.5, 134.5, 133.6, 132.8, 132.1, 131.2, 129.6, 128.3, 126.5, 123.6, 122.3, 119.4, 118.7, 112.4, 110.2, 70.7, 44.6, 42.8, 40.6, 30.6.

3.6.4 2-methyl-4-(3-(1-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-indol-1-yl)butan-2-ol (8c)

Yield: 74 %; Mp: 184-186 ^{o}C;IR (KBr Cm^{-1}): 3424(OH), 3118(C-H aromatic), 2928 (C-H aliphatic), 1693 (C=N of Oxadiazole ring), 1606(C=N of benzimidazole ring), 1350(NO_2), 1251, 1014(C-O-C); ^{1}H NMR (DMSO-d_6 400 MHz): δ 8.55-8.11 (m, 7H, Ar-H), 7.74-7.23(m, 6H, Ar-H), 5.26 (s, 2H), 4.57(t, *J* = 8.4 Hz, 2H), 2.61 (s, 1H), 2.40(t, *J* = 8 Hz, 2H), 1.67(s, 6H); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 166.4, 161.4, 149.0, 136.8, 136.2, 135.0, 132.5, 131.8, 129.9, 128.1, 127.9, 125.8, 125,6, 124.2, 123.7, 122.8, 118.3, 114.0, 112.7, 110.8, 103.3, 70.9, 46.2, 45.0, 43.6, 32.6.

3.6.5 2-methyl-4-(3-(1-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-indol-1-yl)butan-2-ol (8d)

Yield: 69.4 %; Mp: 198-200 ^{o}C;IR (KBr Cm^{-1}): 3452(OH), 3051 (C-H aromatic), 2924 (C-H aliphatic), 1680 (C=N of Oxadiazole ring), 1591(C=N of benzimidazole), 1238, 1092(C-O-C), 761(C-Cl); ^{1}H NMR (DMSO-d_6 400 MHz): δ 8.31-8.06 (m, 2H, Ar-H), 7.92-7.86(m, 3H) 7.68-7.53 (m, 4H, Ar-H), 7.52-7.17(m, 4H, Ar-H), 5.20 (s, 2H), 4.95(t, *J* = 7.2 Hz, 2H), 2.48 (s, 1H), 2.06(t, *J* = 7.6 Hz, 2H), 1.86(s, 6H); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 167.6, 167.5, 150.1, 143.5, 137.4, 136.5, 136.3, 136.2, 131.3, 130.0, 129.8, 129.1, 127.5, 121.0, 120.5, 118.8, 113.0, 110.2, 71.1, 45.1, 44.7, 43.3, 31.1.

3.6.6 4-(5-bromo-3-(1-((5-(2-bromophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*] imidazol-2-yl)-1*H*-indol-1-yl)-2-methylbutan-2-ol (8e)

Yield: 52%, Mp: 218-220 ^{o}C**;** IR (KBr Cm^{-1})3402 (OH),3045(C-H aromatic), 2970 (C-H aliphatic), 1596(C=N) 1236(C-O-C), 561(C-Br)**;** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.54-7.78(m, 2H, Ar-H), 7.76-7.42(m, 10H, Ar-H), 5.24(s, 2H), 4.56 (t, *J* = 7.2 Hz, 2 H), 2.51(s, 1H), 2.38(t, *J* = 8Hz, 2H), 1.68 (s, 6H); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 167.3, 166.6, 144.5, 136.2, 134.5, 134.5, 133.7, 133.7, 133.0, 131.0, 130.5, 128.5, 127.6, 123.9, 122.2, 119.9, 119.2, 113.5, 110.3, 70.4, 46.0, 43.8, 42.6, 32.1.

3.6.7 4-(5-bromo-3-(1-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*- benzo[*d*] imidazol-2-yl)-1*H*-indol-1-yl)-2-methylbutan-2-ol (8f)

Yield: 58 %; Mp: 162-164 ^{o}C; IR (KBr Cm^{-1})3424 (OH),3118(C-H aromatic), 2938 (C-H aliphatic), 1606(C=N) 1251(C-O-C), 1311(NO_2), 561(C-Br**);** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.55 (d, *J* = 1.6 Hz, 1H, Ar-H), 8.45-8.11 (m, 5H, Ar-H), 7.74-7.23 (m, 6H, Ar-H), 5.26(s, 2H), 4.57 (t, *J* = 7.6 Hz, 2 H), 2.6(s, 1H), 2.40(t, *J* = 8Hz, 2H), 1.67 (s, 6H); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 166.4, 165.6, 144.6, 136.3, 134.4, 134.2, 133.7, 133.5, 133.3, 131.0, 130.3, 128.9, 126.9, 123.2, 122.1, 119.6, 118.2, 113.5, 110.3, 70.5, 47.2, 44.6, 43.4, 31.8.

4. BIOLOGICAL EVALUATION

4.1 Antibacterial activity

The antibacterial activity of the synthesized compounds was performed by adopting cup plate method[19].

Conical flask with the medium was cooled to 46ºC and inoculated with test organism (20ml of subculture medium/100ml of the assay medium) 30 ml of inoculated media distributed into Petri dishes. Four cups (8mm diameter) per plate were made by using a sterile cork borer. The whole operation was carried out under the laminar flow aseptically.

Cups were filled with 50 µl of test solution and 50 µl of standard solution (100µg/ml, 250µg/ml,) and blank (DMF) were placed in each cups separately under aseptic condition. Then the Petri dishes uniform diffusion of drug into the agar medium. All the Petri dishes were then incubated at 37°C for 24 hours. After 24 h the activity of sample i.e. zone of inhibition was observed for each compound against five (2 Gram positive and 3 Gram negative) microorganisms, namely *Staphylococcus aureus*NTCC-6571, *Shigellasonnei (SG$_4$), ShigellaparatyphiA$_2$(SL$_2$), Escherichia coli (TG$_1$)4, Vibrio choleri* NTCC-64 and zones of inhibition were measured and results are presented in table.1 and Figure 1.

Table 1: Zone of inhibition (in mm) 100µg/ml against bacteria

Compd. No.	Zone of Inhibition(in mm)100µg/ml				
	S.p	***S.a***	***E.c***	***S.s***	***V1***
5a	13.2	12.3	9.2	13.1	14.5
5b	16	19.8	18	13.5	12
7a	16	18	25.5	18.3	15
7b	18.3	23	21	17.8	15.6
8a	15	22	20.5	15	14.5
8b	11.5	12	8.5	14	--
8c	13	11	12.8	14.9	--
8d	21	23.5	18.7	13	---
8e	12	14.2	10.9	17.3	13.8
8f	15	18	18	13.9	11.5
Amoxycillin	24.5	32.8	31.6	29.3	27.8
DMF	--	--	--	--	--

*Average of three readings

S .a*: Staphylococcus aureus*- NTCC-6571, E.c; *Escherichiacoli-(TG$_1$)4* S.s; *Shigellasonnei*- SG$_4$, S.p; *Shigella paratyphi-A$_2$, Vibriocholeri(V1)*

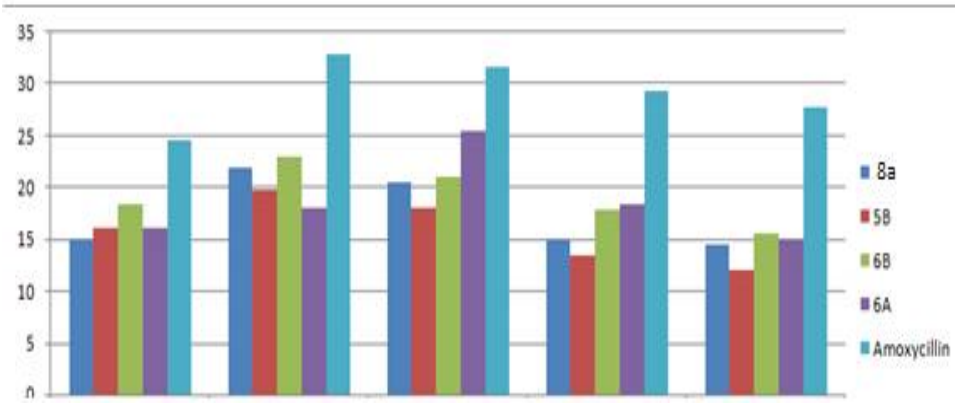


Figure. 1: Graphical Presentation for Zone Of Inhibition

5. RESULTS AND DISCUSSION

From the **resulttable 1** it was observed that compounds 5a, 5b, 7a, and 7b found to be active against both gram positive and gram negative bacteria, they exhibited zone of inhibition ranged from 9.2 to 25.5 Compound 7a exhibited maximum zone of inhibition against *Escherichiacoli(TG$_1$)4* (25.5mmin in 100µg/ml), Compounds 8b, 8c and 8d exhibited no activity against Vibriocholeri(V1) but they exhibited from moderate to good activity against all other bacterial strain. Generally the intermediates 5a, 5b, 7a, and 7b were not less active than the target compounds 8a-8f; in some cases even they are more active.

Compound 5b is more active than compound 5a against *Staphylococcus aureus*- NTCC-6571, *Escherichiacoli-(TG$_1$), Shigellasonnei*-SG$_4$, *Shigella paratyphi-A$_2$,* 5b has Br substituent at 5-position of indole ring, similarly 7b is more active than 7a against*Staphylococcus aureus*- NTCC-6571, *Shigella paratyphi-A$_2$, Vibrio choleri(V1),* which has also Br substituent at 5-position of indole ring generally it can be concluded that bromine substituent on indole ring enhance activity against certain bacterial strain.

Among 8a-8f compounds, 8d is more active against two bacterial strain; *Staphylococcus aureus*- NTCC-6571, and *Escherichiacoli-(TG$_1$)4* than all other, 8d has Cl substituent at para position of phenyl ring attached to oxadiazole ring.

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