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ORIGINAL ARTICLE

Synthesis, characterization and antimicrobial activity of 1,3,4-oxadiazole bearing 1H-benzimidazole derivatives

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Abstract 2-(Phenoxymethyl)-1H-benzimidazole **(3)** obtained by acidic condensation of o-phenylene diamine with phenoxyacetic acid, was reacted with ethyl chloroacetate under anhydrous condition to get ethyl [2-(phenoxymethyl)-1H-benzimidazol-1-yl]acetate (4). The ethyl [2-(phenoxymethyl)-1H-benzimidazol-1-yl]acetate (4) on treatment hydrazine hydrate gave 2-[2-(phenoxymethyl)-1Hbenzimidazol-1-yl]acetohydrazide (5). The acid hydrazide group of 5 was cyclocondensed with various aromatic acids in presence of phosphorous oxychloride to get the titled compounds (**6a–p**). The structures of all the compounds were established on the basis of elemental and spectral analysis. The synthesized compounds were evaluated for their antimicrobial activity. The compound **6d**, **6f**, **6h** and **6d**, **6h** and **6I** a is most active compounds against Escherichia coli and *Staphylococcus aureus* respectively. The compound **6d**, **6f** and **6l** is most active against *Candida albicans* and *Aspergillus flavus*.

1. Introduction

Benzimidazole and oxadiazole were reviewed for biological activity and found that both heterosystems possess a broad spectrum of biological activities viz Antimicrobial (Kumar et al., 2006; Shetgiri and Kokitkar, 2001; Kazimierczuk et al., 2002; Kilcigil et al., 1999; Tuncbilek et al., 2009; Ansari and Lal 2009a,b; Ozden et al., 2005; Kilcigil and Altanlar, 2003; Naik and Chikhalia 2007), anticonvulsant (Chimirri et al., 2002; Singh 1970; Chimirri et al., 1989), antitubercular (Foks et al., 2006; Gill et al., 2008), antiviral (Starcevic et al., 2007), anticancer (Demirayak et al., 2002), anti-inflammatory analgesic (Khan and Nandan 1997; Evans et al., 1996) etc. It was hypothesized that the chemical combination of both the systems in one compound may prove to be a breakthrough for antimicrobial activity. Further literature survey for the combined system showed a way as many workers reported biological properties of such compounds as antimicrobial (Ansari and Lal 2009a,b; El-masry et al., 2000), antitubercular (Kaghthara et al., 1999) etc. These evidence boosted us to carry out synthetic work for the titled compound to evaluate their antimicrobial/antibacterial potential.

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2. Experimental

o-Phenylenediamine, phenoxyacetic acid, chloroethylacetate, hydrazine hydrate, phosphorous oxychloride, methanol, ethanol, sodiumbicarbonate, aromatic acids, heating mantle, condenser, bacterial and fungal strains. Melting points were determined in open capillary using melting point apparatus and are uncorrected. The Proton Magnetic Resonance (^{1}HNMR) spectra were recorded on a Bruker 300 MHz instrument in DMSO-d_6 using tetramethylsilane as internal standard. The Infrared spectra of compounds were recorded in KBr on a Perkin–Elmer FTIR Spectrometer. To monitor the reactions and to confirm the purity of the compounds TLC (Solvent System Toluene: ethyacetate: formic acid 5:4:1) was performed and iodine/UV Chamber was used for visualization of spots.

2.1. Synthesis of 2-(phenoxymethyl)-1H-benzimidazole ***(3)***

A mixture of *o*-phenylenediamine 1 (0.05 mol; 5.40 g) and phenoxyacetic acid **2** (0.05 mol; 7.60 g) was refluxed in 4 N HCl for 4 h on a heating mantle. After completion of reaction, solution was poured onto crushed ice, ammonia solution was added drop wise to neutralize and the resulting solid was filtered, washed with cold water, dried and recrystallized. yield 85%, m.p. 160–164, IR (KBr) cm^{-1}: 1241 (C–O), 1545 (C═N), 3444 (N–H): ^{1}H-NMR (DMSO-d_6) δ ppm: 5.31 (s, 2H, OCH_2), 6.95–7.66 (m, 9H, aromatic), 12.68 (s, 1H, NH); EI-MS 224 (M^+); Anal calcd for $C_{14}H_{12}N_2O$: C, 74.98; H,5.39; N, 12.49; O, 7.13 Found: C, 74.99; H,5.36; N, 12.49; O, 7.11.

2.1.1. Synthesis of ethyl [2-(phenoxymethyl)-1H-benzimidazol-1-yl]acetate ***(4)***

To a suspension of 2-(phenoxymethyl)-1H-benzimidazole **3** (0.01 mol; 2.24 g), anhydrous potassium carbonate (2 g) in dry acetone, ethyl chloroacetate (0.01 mol; 1.2 ml) was added drop wise at room temperature for a period of 20–30 min. The reaction mixture was stirred at room temperature for 10–12 h. The inorganic solid was filtered off and the filtrate was concentrated under reduced pressure. Yield 73%, mp 88–92, IR (KBr) cm^{-1}: 1241 (C–O), 1550 (C═N), 1650 (C═O): ^{1}H-NMR (DMSO-d_6) δ ppm: 5.21 (s, 2H, OCH_2), 6.95–7.63 (m, 9H, aromatic), 4.120 (m, 2H, CH_2), 1.45 (m, 3H, CH_3), EI-MS 310 (M^+); Anal calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; O, 15.47. Found: C, 69.65; H, 5.84; N, 9.06; O, 15.45.

2.1.2. Synthesis of 2-[2-(phenoxymethyl)-3H-indol-3-yl] acetohydrazide ***(5)***

To an ethanolic solution of ethyl [2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetate **4** (0.01 mol; 3.10 g), hydrazine hydrate (98%) (0.01 mol; 0.49 ml) was added and the mixture was refluxed for 3 h. After completion of the reaction, the mixture was cooled and the solid so obtained was filtered, washed with cold water and recrystallized from methanol. Yield 82%; m.p. 178–180, IR (KBr) cm^{-1}: 1032 (N–N), 1240 (C–O), 1600 (C═N); 1666 (C═O), 3044 (CH–Ar), 3291 (N–H); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.54 (s, 1H, NH_2), 4.95 (s, 2H, CH_2), 5.38 (s, 2H, OCH_2), 6.94–7.66 (m, 9H, aroamtic), 9.51 (s, 1H, CONH), EI-MS 296 (M^+); Anal calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91; O, 10.80 Found: C, 64.81; H, 5.43; N, 18.94; O, 10.82.

2.1.3. General procedure for the synthesis of compounds ***(6a–p)***

A mixture of 2-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetohydrazide **5** (0.0025 mol; 0.738 g) and suitable aromatic acid (0.0025 mol) was refluxed in the presence of $POCl_3$ (5 ml) for 5 h at a temperature of 110–120 °C. After completion of reaction, the mixture was cooled at room temperature and poured onto crushed ice. On basification with sodium bicarbonate (5%), a solid mass was so separated out which was filtered to get crude product. Finally the product was heated with charcoal in hydrated ethanol and then re-crystallized from ethanol to obtain **6a–p**.

2.1.3.1. Synthesis of 2-(phenoxymethyl)-1-[(5-phenyl-1,3,4-oxadiazol-2-yl) methyl] -1H-benzimidazole ***(6a)***. Percentage yield 84% m.p. 148–152 °C IR (KBr) cm^{-1}: 1034 (N–N), 1241 (C–O), 1602 (C═N); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.52 (s, 2H, CH_2), 6.04 (s, 2H, OCH_2), 7.00–7.81 (m, 14H, aromatic); EI-MS 382 (M^+); Anal calcd for $C_{23}H_{18}N_4O_2$: C, 72.24; H, 4.74; N, 14.65; O, 8.37 Found: C, 72.21; H, 4.72; N, 14.60; O, 8.36.

2.1.3.2. Synthesis of 2-(phenoxymethyl)-1-[{5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl}methyl]-1H-benzimidazole ***(6b)***. Percentage yield 60%; m.p. 138–140 °C, IR (KBr) cm^{-1}: 1034 (N–N), 1239 (C–O), 1593 (C═N), 3056 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.48 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 5.93 (s, 2H, OCH_2), 6.83–7.59 (m, 13H, aromatic), EI-MS 397 ($M^+ + 1$). Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13; O, 8.07 Found: C, 72.74; H, 5.11; N, 14.15; O, 8.10.

2.1.3.3. Synthesis of 2-(phenoxymethyl)-1-[{5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl}methyl]-1H-benzimidazole ***(6c)***. Percentage yield 60%; m.p. 170–172 °C, IR (KBr) cm^{-1}: 1031 (N–N), 1238 (C–O), 1600 (C═N), 3032 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.21–3.38 (s, 3H, CH_3, Merged with H_2O in DMSO), 5.50 (s, 2H, CH_2), 6.03 (s, 2H, OCH_2), 6.99–7.72 (m, 13H, aromatic), EI-MS 397 ($M^+ + 1$). Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13; O, 8.07 Found: C, 72.74; H, 5.14; N, 14.12; O, 8.16.

2.1.3.4. Synthesis of 2-(phenoxymethyl)-1-[{5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl}methyl]-1H-benzimidazole ***(6d)***. Percentage yield 66%; m.p. 164–168 °C, IR (KBr) cm^{-1}: 1237 (N–N),1277 (C–O), 1654 (C═N); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.37 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 6.02 (s, 2H, OCH_2), 6.91–7.71 (m, 13H, aromatic); EI-MS 397 ($M^+ + 1$); Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13; O, 8.07 Found: C, 72.75; H, 5.16; N, 14.09; O, 8.05.

2.1.3.5. Synthesis of 1-[{5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl}methyl]-2-(phenoxymethyl)-1H-benzimidazole ***(6e)***. Percentage yield 72%; m.p. 170–173 °C, IR (KBr) cm^{-1}: 737 (C–Cl), 1239 (C–O), 1600 (C═N), 2982 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.50 (s, 2H, CH_2), 6.07 (s, 2H, OCH_2), 6.91–7.78 (m,13H, aromatic), EI-MS 417 ($M^+ + 1$); Anal calcd for $C_{23}H_{17}ClN_4O_2$: C, 66.27, H, 4.11; Cl, 8.50; N, 13.44; O, 7.68 Found: C, 66.23, H, 4.13; Cl, 8.55; N, 13.46; O, 7.69.

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2.1.3.6. Synthesis of 1-[{5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl}methyl]-2-(phenoxymethyl)-1H-benzimidazole ***(6f)***. Percentage yield 69%; m.p.236–244 °C, IR (KBr) cm^{-1}: 740 (C–Cl), 1092 (N–N), 1238 (C–O), 1608 (C═N), 3155 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.47 (s, 2H, CH_2), 6.01 (s, 2H, OCH_2), 6.87–7.78 (m, 13H, aromatic), EI-MS 417 (M^+ + 1). Anal calcd for $C_{23}H_{17}ClN_4O_2$: C, 66.27, H, 4.11; Cl, 8.50; N, 13.44; O, 7.68 Found: C, 66.28, H, 4.10; Cl, 8.52; N, 13.45; O, 7.70.

2.1.3.7. Synthesis of 1-[{5-(2-bromophenyl)-1,3,4-oxadiazol-2-yl}methyl]-2-(phenoxymethyl)-1H-benzimidazole ***(6g)***. Percentage yield 80%; m.p. 160–164 °C, IR (KBr) cm^{-1}: 738 (C-Br), 1082 (N–N), 1240 (C–O), 1592 (C═N), 3062 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.50 (s, 2H, CH_2), 6.08 (s, 2H, OCH_2), 6.88–7.83 (m, 13H, aromatic), EI-MS 461 (M^+ + 1). Anal calcd for $C_{23}H_{17}BrN_4O_2$: C, 59.88; H, 3.71; Br, 17.32; N, 12.15; O, 6.94 Found: C, 59.85; H, 3.74; Br, 17.30; N, 12.14; O, 6.91.

2.1.3.8. Synthesis of 1-[{5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl}methyl]-2-(phenoxymethyl)-1H-benzimidazole ***(6h)***. Percentage yield 76%; m.p.204–210 °C, IR (KBr) cm^{-1}: 738 (C-Br), 1083 (N–N), 1241 (C–O), 1604 (C═N), 2917 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.57 (s, 2H, CH_2), 5.85 (s, 2H, OCH_2), 6.99–7.82 (m, 13H, aromatic), EI-MS 461 (M^+ + 1). Anal calcd for $C_{23}H_{17}BrN_4O_2$:C, 59.88; H, 3.71; Br, 17.32; N, 12.15; O, 6.94 Found: C, 59.91; H, 3.69; Br, 17.28; N, 12.15; O, 6.87.

2.1.3.9. Synthesis of 1-[{5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl}methyl]-2-(phenoxymethyl)-1H-benzimidazole ***(6i)***. Percentage yield 58%; m.p.226-230 °C, IR (KBr) cm^{-1}: 1035 (N–N), 1239 (C–O), 1566 and 1350 (NO_2), 1685 (C═N), 3063 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.38 (s, 2H, CH_2), 5.61 (s, 2H, OCH_2), 6.88–8.09 (m, 13H, aromatic), EI-MS 428 (M^+ + 1). Anal calcd for $C_{23}H_{17}N_5O_4$: C, 64.63; H, 4.01; N, 16.39; O, 14.97 Found: C, 64.60; H, 4.04; N, 16.42; O, 14.95.

2.1.3.10. Synthesis of 1-[{5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl}methyl]-2-(phenoxymethyl)-1H-benzimidazole ***(6j)***. Percentage yield 70%; m.p. 232–236 °C, IR (KBr) cm^{-1}: 1036 (N–N) 1237 (C–O), 1287 and 1349 (NO_2), 1598 (C═C); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.50 (s, 2H, CH_2), 6.04 (s, 2H, OCH_2), 6.96–7.76 (m,13H, aromatic), EI-MS 428 (M^+ + 1). Anal calcd for $C_{23}H_{17}N_5O_4$: C, 64.63; H, 4.01; N, 16.39; O, 14.97 Found: C, 64.65; H, 4.0; N, 16.36; O, 14.98.

2.1.3.11. Synthesis of 2-(phenoxymethyl)-1-[{5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl}methyl]-1H-benzimidazole ***(6k)***. Percentage yield 80%; m.p. 168–174 °C, IR (KBr) cm^{-1}: 1028 (N–N), 1256 (C–O), 1610 (C═N); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.82 (s, 3H, OCH_3), 5.51 (s, 2H, CH_2), 6.01 (s, 2H, OCH_2), 6.94–7.73 (m, 13H, aromatic), EI-MS 413 (M^+ + 1). Anal calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58; O, 11.64 Found: C, 69.92; H, 4.87; N, 13.54; O, 11.61.

2.1.3.12. Synthesis of 2-(phenoxymethyl)-1-[{5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl}methyl]-1H-benzimidazole ***(6l)***. Percentage yield 85%; m.p.182–186 °C, IR (KBr) cm^{-1}: 1025 (N–N), 1240 (C–O), 1600 (C═N), 3025 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.83 (s, 6H, OCH_3), 5.50 (s, 2H, CH_2), 6.00 (s, 2H, OCH_2), 6.92–7.75 (m, 12H, aromatic), EI-MS 443 (M^+ + 1). Anal calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 5.01; N, 12.66; O, 14.46. Found: C, 67.83; H, 5.05; N, 12.67; O, 14.48.

2.1.3.13. Synthesis of 1-[(5-benzyl-1,3,4-oxadiazol-2-yl)methyl]-2-(phenoxy methyl)-1H-benzimidazole ***(6m)***. Percentage yield 75%; m.p.234-238 °C, IR (KBr) cm^{-1}: 1034 (N–N), 1239 (C–O), 1610 (C═N), 3178 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.17 (s, 2H, CH_2-benzilic), 4.96 (s, 2H, CH_2), 5.29 (s, 2H, OCH_2), 6.96–7.66 (m, 14H, aromatic), EI-MS 396 (M^+); Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13; O, 8.07 Found: C, 72.68; H, 5.11; N, 14.15; O, 8.11.

2.1.3.14. Synthesis of 1-[{5-(phenoxymethyl-1,3,4-oxadiazol-2-yl)methyl}]-2-(phenoxymethyl)-1H-benzimidazole ***(6n)***. Percentage yield 73%; m.p.224-230 °C, IR (KBr) cm^{-1}: 1079 (N–N), 1220 (C–O), 1623 (C═N), 3055 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 4.61 (s, 2H, OCH_2-phenoxy), 5.12 (s, 2H, CH_2), 5.39 (s, 2H, OCH_2), 6.97–7.67 (m, 14H, aromatic), EI-MS 412 (M^+). Anal calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58; O, 11.64 Found: C, 69.90; H, 4.85; N, 13.56; O, 11.67.

2.1.3.15. Synthesis of 1-[{5-(naphthylmethyl-1,3,4-oxadiazol-2-yl)methyl}]-2-(phenoxymethyl)-1H-benzimidazole ***(6o)***. Percentage yield 70%; m.p. 138–142 °C, IR (KBr) cm^{-1}: 1036 (N–N), 1201 (C–O), 1711 (C═N), 3158 (CH–Ar); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.99 (s, 2H, CH_2-naphthyl), 5.24 (s, 2H, CH_2), 5.51 (s, 2H, OCH_2), 7.00–8.10 (m, 16H, aromatic), EI-MS 446 (M^+). Anal calcd for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55; O, 7.17 Found: C, 75.29; H, 4.95; N, 12.59; O, 7.20.

2.1.3.16. Synthesis of 1-[{5-(diphenylmethyl-1,3,4-oxadiazol-2-yl)methyl}]-2-(phenoxymethyl)-1H-benzimidazole ***(6p)***. Percentage yield 79%; m.p. 152–158, IR (KBr) cm^{-1}: 1036 (N–N), 1240 (C–O), 1613 (C═N); ^{1}H-NMR (DMSO-d_6) δ ppm: 5.16 (s, 2H, CH_2-biphenyl), 5.42 (s, 2H, CH_2), 5.96(s, 2H, OCH_2), 6.82–7.71 (m, 20H, aromatic), EI-MS 472 (M^+); Anal calcd for $C_{30}H_{24}N_4O_2$: C, 76.25; H, 5.12; N, 11.86; O, 6.77 Found: C, 76.26; H, 5.15; N, 11.90; O, 6.80.

3. Result and discussion

3.1. Chemistry

The reaction sequence for the titled compound is outlined in Scheme 1. o-Phenylenediamine **(1)** and phenoxyacetic acid **(2)** were used as starting material for the formation of 2-(phenoxymethyl)-1*H*-benzimidazole **(3)**. The compound **3** on treatment with ethylchloroacetate in the presence of anhydrous potassium carbonate in dry acetone gave ethyl [2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetate **(4)**, which on treatment with hydrazine hydrate resulted in the formation of 2-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetohydrazide **(5)**, final intermediate **5** on condensation with various aromatic acids in the presence of phosphorous oxychloride at a temperature of 110–120 °C resulted in the formation of

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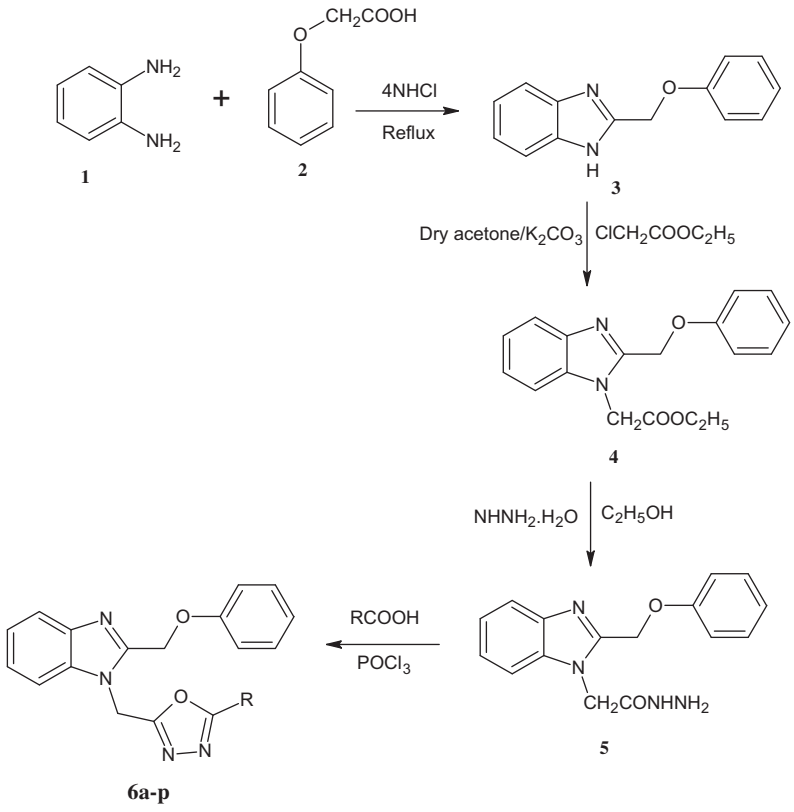

Scheme 1 R = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4,, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$, 3,4-di$OCH_3C_6H_3$, $C_6H_5CH_2$, $C_6H_5OCH_2$, $C_{10}H_7CH_2$, $C_{12}H_9CH_2$.

Table 1 Antibacterial activity of compounds against *Escherichia coli*.

Compounds	Concentrations						
	1 μg/ml	10 μg/ml	50 μg/ml	100 μg/ml	200 μg/ml	500 μg/ml	App. MIC μg/ml
6a	–	–	–	+	+ +	+ +	200
6b	–	–	+	+	+ +	+ +	200
6c-	–	–	+	+	+ +	+ +	200
6d	–	–	+	+ +	+ + +	+ + +	100
6e	–	–	–	–	+	+ +	500
6f	–	–	+	+ + +	+ + +	+ + +	100
6g	–	–	–	–	+	+	200
6h	–	–	–	+ + +	+ + +	+ + +	100
6i	–	–	–	–	–	+	500
6j	–	–	–	+	+ +	+ +	200
6k	–	–	–	–	+	+	200
6l	–	–	–	+	+	+	100
6m	–	–	–	+	+ +	+ +	200
6n	–	–	–	–	+	+	200
6o	–	–	–	+	+ +	+ +	200
6p	–	–	+	+ +	+ +	+ + +	500
Ofloxacin	–	+	+	+ + +	+ + +	+ + +	100

Symbols: (–), no inhibition; (+), weakly active; (+ +), moderately active; (+ + +), highly active.

2-(phenoxymethyl)-1-[(5-substituted-1,3,4-oxadiazol-2-yl)methyl] -1*H*-benzimidazole **(6a–p)**.

3.2. Antibacterial activity test

The synthesized compounds **6a–p** were screened for antibacterial activity against *S. aureus* and *E. coli* by agar diffusion technique using ofloxacin as reference. The diameter of the zone of inhibition exhibited by the compounds was measured. It was found that compounds **6d, 6f and 6h** were the most active against *E. coli* at a concentration of 100 μg/ml. The compounds screened against *S. aureus*, compounds **6d, 6h and 6l** were the most active against *S. aureus* at a concentration of 100 μg/ml.

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Table 2 Antibacterial activity of compounds against *S. aureus*.

Compounds	Concentrations						
	1 μg/ml	10 μg/ml	50 μg/ml	100 μg/ml	200 μg/ml	500 μg/ml	App. MIC μg/ml
6a	–	–	–	+	+	+ +	500
6b	–	–	+	+	+ +	+ +	200
6c	–	–	–	–	+	+ +	500
6d	–	–	+	+ + +	+ + +	+ + +	100
6e	–	–	–	–	+ +	+ +	200
6f	–	–	+	+ +	+ +	+ +	100
6g	–	–	–	+	+	+ +	500
6h	–	–	+	+ + +	+ + + +	+ + +	100
6i	–	–	–	–	–	+	500
6j	–	–	–	+	+ +	+ +	200
6k	–	–	–	+	+ +	+ +	200
6l	–	–	+	+ + +	+ + +	+ + +	100
6m	–	–	–	+	+ +	+ + +	500
6n	–	–	–	+ +	+ +	+ +	100
6o	–	–	–	–	+ +	+ +	200
6p	–	–	+	+ +	+ +	+ + +	500
Ofloxacin		+	+	+ + +	+ + +	+ + +	100

Symbols: (–), no inhibition; (+), weakly active; (+ +), moderately active; (+ + +), highly active.

3.3. Antifungal activity test

For the antifungal activity the synthesized compounds **6a–p** were tested for antifungal activity against *Aspergillus flavus* and *Candida albicans* by agar diffusion technique using ketoconazole as reference. The diameter of the zone of inhibition exhibited by the compounds was measured and it was found that the compounds **6d, 6f and 6l** were the most active.

4. Conclusion

The development of oxadiazole bearing benzimidazole system has new potentially active antibacterial and antifungal agents. The results of in vitro antimicrobial activities showed that the compounds having deactivating group (electron withdrawing group like NO_2, Br and Cl) and weakly activating group i.e., CH_3 group were the most active against *E. coli* and *S. aureus*. The antifungal activity confirmed that the compound having Cl, NO2, Br and methyl group in the oxadiazole system (Table 3) is the most potent against *A. flavus* and *C. albicans* respectively.

5. Biological activities

The synthesized compound **(6a–p)**, were screened for antibacterial activity against *S. aureus* and *E. coli* by agar diffusion technique using ofloxacin as the reference (50 μg/ml), antifungal activity against *A. flavus* and *C. albicans* by agar diffusion technique using ketoconazole as reference (50 μg/ml). Six concentrations of test compounds i.e., 1, 10, 50, 100 200 and 500 μg/ml were chosen for evaluation. The diameter of the zone of inhibition exhibited by the compounds was measured. The observations are outlined in Tables 1–3.

The antifungal activity of compounds **(6a–p)** was evaluated by using a cup plate agar diffusion method against *Aspergillus niger* and *A. flavus* fungal strains using ketoconazole as standard. The zone of inhibition exhibited standard with MIC (ofloxacin) was considered as the highest growth inhibition and indicated by + + + and all the test compounds were evaluated on the same scale.

Table 3 Antifungal activity of compounds against *Candida albicans* and *Aspergillus flavus*.

Compounds	Zone of inhibition (50 and 100 μg/ml)			
	Candida albicans		*Aspergillus flavus*	
	50 μg/ml	100 μg/ml	50 μg/ml	100 μg/ml
6a	+	+ +	–	+
6b	+ +	+ +	+	+ +
6c	+	+	–	+
6d	+ +	+ + +	+ +	+ + +
6e	–	+ +	+	+ +
6f	+	+ + +	+ + +	+ + +
6g	+ +	+ +	+	+ +
6h	+ +	+ +	+ +	+ +
6i	+ +	+ +	+ +	+ +
6j	+	+ +	+ +	+ +
6k	–	+	–	–
6l	+ +	+ + +	+ +	+ + +
6m	+	+	–	+
6n	–	+	+	+ +
6o	+	+ +	+	+ +
6p	+ +	+ +	+	+ +
Ketoconazole	+ +	+ + +	+ +	+ + +

Symbols: (–), no inhibition (> 10 mm); (+), weakly active (10–14 mm); (+ +), moderately active (15–20 mm); (+ + +), highly active (20–30 mm); (+ + +), ketoconazole.

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