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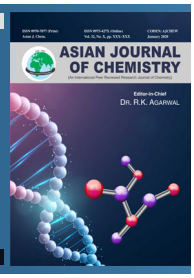

Synthesis, Characterization and Biological Activity of Novel 1,3,4-Oxadiazole Derivatives of 1,3-Dihydro-1-oxoisobenzofuran-5-carboxylic Acid

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This work relates to the synthesis of novel 1,3,4-oxadiazole derivatives (**5a-h**) from 1,3-dihydro-1-oxoisobenzofuran-5-carboxylic acid. The structure of the synthesized compounds were confirmed by using IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Further these synthesized derivatives were subjected to biological activity.

Keywords: 1,3-Dihydro-1-oxoisobenzofuran-5-carboxylic acid, 1,3,4-Oxadiazoles, Biological activity.

INTRODUCTION

Microbial infectious diseases became a great threat to people throughout the world. Recent results evidenced that less effect of conventional antibiotics on pathogenic bacterial species [1] is globally a major problem. However, the regular metabolism of cells are due to reactive nitrogen and oxygen species [2] (radicals) damage of biomolecules owing to radicals result in stress related diseases like diabetes mellitus [3-5], aging and cancer. For establishing the equilibrium, supplement the antioxidants to the body through either diet or medicine to prevent the above mentioned diseases.

In recent scenario, heterocycles play a major role in drug synthesis. In that respect, we design and synthesize a new series of benzofuranone oxadiazole motifs. Oxadiazoles play a significant role among other heterocycles. Oxadiazoles is an important heterocyclic compounds assisted with potent pharmacological activity due to the presence of -N=C-O- linkage. These moieties drawn considerable special attention in pharmaceutical chemistry due to their diverse medicinal potential. They have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields such as antimicrobial [6-8], anti-inflammatory [9,10], anticonvulsant [11-15], antimalarial [16], anticancer [17,18], antitubercular [19,20], antiallergic [21], anti-HIV [22,23], *etc*. The advantage of these particular moieties having intermolecular charge transfer properties due to the presence of π-conjugated system. In recent years, they have considerable attention in electric field [24] such as dye sensitized solar cells [25], organic photovoltaic cells, optical properties [26] and organic light emitting diodes. Therefore, 1,3,4-oxadiazoles have attracted the researchers to work in this area of new drug development and study their biological applications.

The detailed synthesis and medicinal importance of 5-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-2-benzofuran-1(3*H*)-ones (**5a-h**) are reported here. The proposed new class of heterocyclic moieties had impending bioactivity. The structure of the synthesized compounds is confirmed by IR, ^{1}H and ^{13}C NMR and mass spectral data. These compounds were screened for antibacterial and antifungal activities against different strains.

EXPERIMENTAL

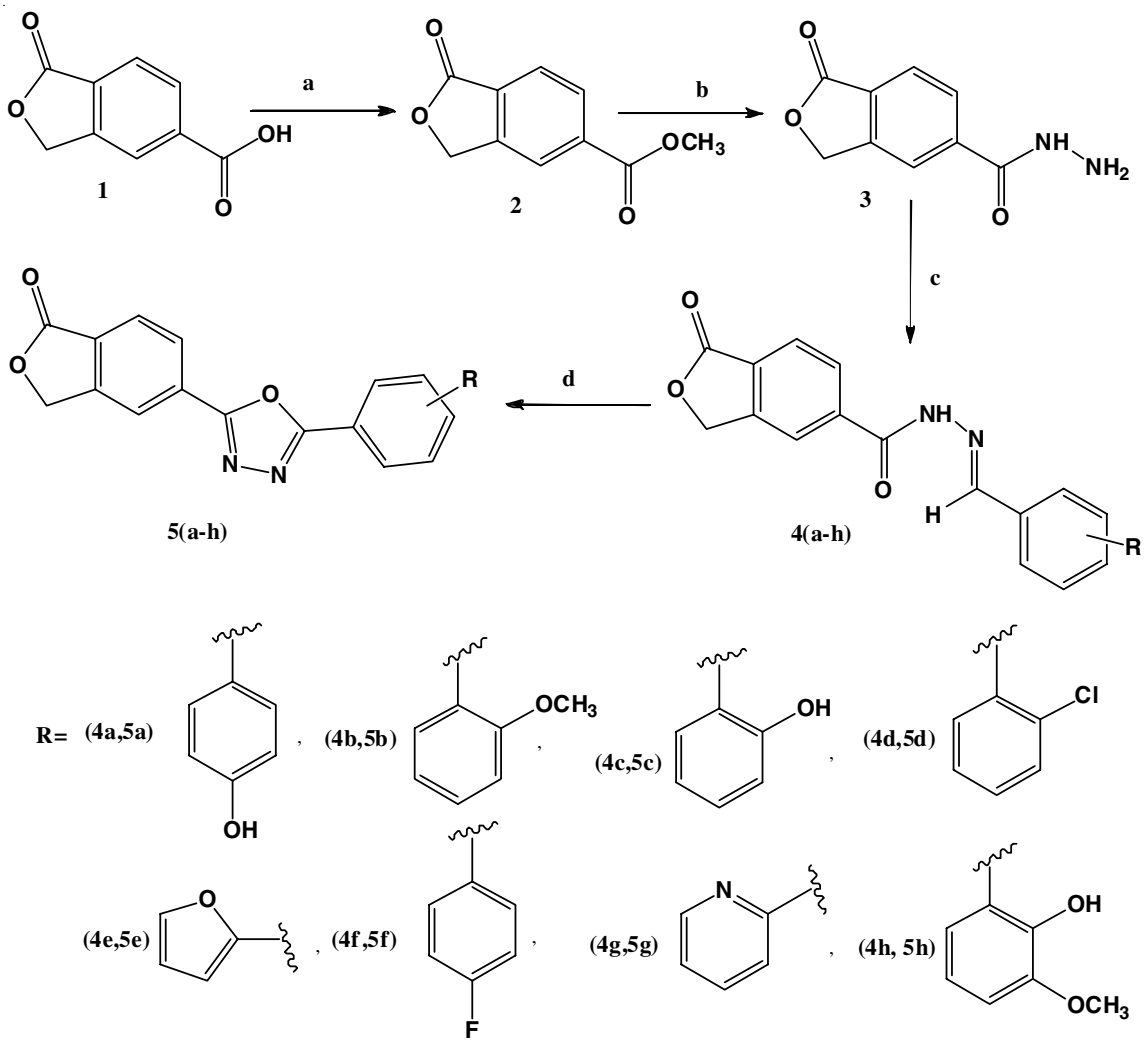
All chemicals, solvents and reagents used in the present study were of analytical and commercial grade. The purity of the compounds was checked by using precoated TLC plates (Merck). IR spectra were recorded using KBr on Perkin-Elmer spectrophotometer. ^{1}H and ^{13}C NMR spectra in DMSO on a Bruker FT-NMR instrument using TMS as an internal standard and chemical shift values were expressed in ppm.

Synthesis of methyl-1,3-dihydro-1-oxoisobenzofuran-5-carboxylate (2): 1,3-Dihydro-1-oxoisobenzofuran-5-carboxylic acid (**1**) was converted into methyl-1,3-dihydro-1-oxoisobenzofuran-5-carboxylate by esterification. The mixture of 1,3-dihydro-1-oxoisobenzofuran-5-carboxylic acid (5.6 mmol) was taken in methanol (10 mL), thionyl chloride (1.33 g) was added slowly at 5-10 ºC. The reaction mass was refluxed for 2 h and then cooled to room temperature and poured into crushed ice. The solid mass was filtered,dried and the white colour solid was obtained (Yield: 90 %).

Synthesis of 1,3-dihydro-1-oxoisobenzofuran-5-carboxylic acid hydrazide (3): Compound **2** was converted to 1,3-dihydro-1-oxoisobenzofuran-5-carbohydrazide (**3**) by reacting with hydrazine hydrate in methanol. To a mixture of methyl-1,3-dihydro-1-oxoisobenzofuran-5-carboxylate (**2**, 5.2 mmol) and methanol (5 mL) at 20-25 ºC, hydrazine hydrate (5 mL) was added. The reaction mass was refluxed for 4 h and the reaction completion was monitored by TLC. The reaction mass was filtered, washed with water followed by methanol and finally dried to get the pure product. White colour solid, yield: 98 %, m.p.: 220-230 ºC. IR (KBr, ν_{max}, cm^{-1}): 3284 (-NH), 3178 (-NH_2), 3053 (-CH), 1759 (lactone C=O), 1644 (amide C=O), 1045 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.44 (2H, d, CH_2), 7.41 (1H, m, ArH), 7.72 (1H, m, ArH), 8.01 (1H, dd, ArH), 9.81 (1H, s, CONH), 4.50 (2H, -NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.2, 164.5, 144.8, 134.8, 128.7, 127.6, 126.4, 123.8, 60.6. LC-MS: *m/z*: 192 $[M]^+$, 193 $[M+1]^+$. Elemental analysis of $C_9H_8N_2O_3$ calcd. (found) %: C, 56.28 (56.23); H, 4.20 (4.20); N, 14.58 (14.58); O, 24.98 (24.99).

General procedure for the synthesis of N′-[(*E*)-(substituted aryl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazides (4a-i): A mixture of 1,3-dihydro-1-oxoisobenzofuran-5-carboxylic acid hydrazide (**3**, 2.6 mmol) and required aromatic aldehyde (3.12 mmol) was refluxed in methanol (5 mL) in the presence of catalytic amount of glacial acetic acid for 3-4 h. The completion of reaction was confirmed by TLC. After completion of the reaction, the reaction mass was cooled to room temperature and the solid obtained was filtered and washed with methanol. The purity of dried pure products was checked by TLC. The synthetic pathway of title compounds is shown in **Scheme-I**. Yield varied from 90-95 %.

***N′*-[(*E*)-(4-Hydroxyphenyl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazide (4a):** White solid, yield: 90.2 %, m.p.: 190-193°C; IR (KBr, ν_{max}, cm^{-1}): 3587 (-OH),



(a) $SOCl_2$, Methanol, reflux, 2 h. (b) $NH_2NH_2{\cdot}H_2O$, methanol, glacial acetic acid, reflux for 3-4 h.
(c) Aromatic aldehyde, methanol, glacial acetic acid (catalyst) reflux for 3-4 h. (d) $PhI(OAc)_2$, $CHCl_3$, reflux, 4-6 h

Scheme-I: Synthesis of 5-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-2-benzofuran-1(3*H*)-ones

3278 (-NH), 3059 (-CH), 1751 (lactone C=O), 1631 (amide C=O), 1598 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.46 (2H, d, CH_2), 7.22-7.47 (2H, m, ArH), 7.56-7.64 (3H, m, ArH), 7.89 (1H, dd, ArH), 8.06 (1H, dd, ArH), 8.21 (1H, s, N=CH), 8.11 (1H, s, CONH), 10.76 (1H, s, ArOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 169.8, 162.2, 159.4, 148.4, 141.3, 134.7, 128.9, 127.5, 127.5, 126.2, 124.7, 115.7, 60.6. LC-MS: *m/z*: 296 $[M]^+$, 295 $[M-1]^+$. Elemental analysis of $C_{16}H_{12}N_2O_4$ calcd. (found) %: C, 64.86 (64.85); H, 4.08 (4.08); N, 9.46 (9.46); O, 21.60 (21.61).

***N′*-[(*E*)-(2-Methoxyphenyl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazide (4b):** Pale yellow solid; yield: 91.2 %; m.p.: 186-189 ºC. IR (KBr, ν_{max}, cm^{-1}): 3284 (-NH), 3048 (-CH), 2925 (-CH), 1759 (lactone C=O), 1647 (amide C=O), 1570 (C=N), 1279 (=C-O), 1046 (O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.88 (3H, s, CH_3), 5.48 (2H, d, CH_2), 7.56 (1H, dd, ArH), 7.99 (1H, dd, ArH), 8.06 (1H, dd, ArH), 6.94 (1H, m, ArH), 7.31-7.35 (2H, m, ArH), 7.59 (1H, m, ArH), 8.20 (1H, s, N=CH), 8.17 (1H, s, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 169.8, 161.8, 159.8, 145.2, 144.9, 142.5, 132.2, 131.2, 128.8, 128.4, 127.7, 126.2, 123.8, 119.5, 119.1, 111.2, 60.3, 55.5. LC-MS: *m/z*: 310 $[M]^+$, 311 $[M+1]^+$. Elemental analysis of $C_{17}H_{14}N_2O_4$ calcd. (found) %: C, 65.80 (65.79); H, 4.55 (4.55); N, 9.03 (9.03); O, 20.62 (20.63).

***N′*-[(*E*)-(2-Hydroxyphenyl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazide (4c):** White solid; yield: 91.25 %; m.p.: 205-207 ºC. IR (KBr, ν_{max}, cm^{-1}): 3539 (-OH), 3416 (-NH), 3012 (-CH), 1766 (lactone C=O), 1685 (amide C=O), 1595 (C=N); ^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 5.46 (2H, d, CH_2), 7.46 (1H, dd, ArH), 7.99 (1H, dd, ArH), 8.06 (1H, dd, ArH), 6.93 (1H, m, ArH), 7.14 (1H, m, ArH), 7.20 (1H, m, ArH), 7.52 (1H, m, ArH), 8.23 (1H, s, N=CH), 8.13 (1H, s, CONH), 10.47 (1H, s, Ar-OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 169.8, 162.1, 158.8, 146.5, 134.6, 131.8, 131.6, 128.4, 127.6, 126.2, 123.8, 119.3, 117.4, 116.8, 60.50; LC-MS: *m/z*: 296 $[M]^+$, 295$[M-1]^+$. Elemental analysis of $C_{16}H_{12}N_2O_4$ calcd. (found) %: C, 64.86 (64.85); H, 4.08 (4.08); N, 9.46 (9.46); O, 21.61 (21.61).

***N′*-[(*E*)-(2-Chlorophenyl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazide (4d):** Yellow solid; yield: 92.4 %; m.p.: 178-180 ºC. IR (KBr, ν_{max}, cm^{-1}): 3261 (-NH), 3032 (-CH), 1764 (lactone C=O), 1627 (amide C=O), 1541 (C=N); ^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 5.49 (2H, d, CH_2), 7.27-8.23 (7H, m, ArH), 8.76 (1H, s, N=CH), 8.49 (1H, s, CONH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.3, 162.8, 143.8, 141.7, 135.8, 134.4, 133.2, 131.5, 131.3, 127.6, 126.8, 126.6, 126.2, 125.8, 125.4, 60.3. LC-MS: *m/z*: 314 $[M]^+$, 316 $[M+2]^+$; Elemental analysis of $C_{16}H_{11}N_2O_3Cl$ calcd. (found) %: C, 61.06 (61.04); H, 3.52 (3.52); Cl, 11.26 (11.27); N, 8.90 (8.90); O, 15.25 (15.26).

***N′*-[(*E*)-(Furan-2-yl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazide (4e):** Brown solid; yield: 90.8 %; m.p.: 199-202°C. IR (KBr, ν_{max}, cm^{-1}): 3170 (-NH), 3028 (-CH), 1756 (lactone C=O), 1629 (amide C=O), 1546 (-C=N), 1292 (=C-O). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.46 (2H, d, CH_2), 7.47 (1H, dd, ArH), 7.87 (1H, dd, ArH), 8.00 (1H, dd, ArH), 6.66 (1H, dd, ArH), 6.96 (2H, dd, ArH), 7.13 (2H, dd, ArH), 8.22 (1H, s, N=CH), 8.17 (1H, s, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.09, 162.8, 144.9, 141.5, 140.2, 137.9, 137.6, 127.5, 126.5, 125.7, 125.2, 113.8, 112.2, 60.3. LC-MS: *m/z*: 270$[M]^+$, 271$[M+1]^+$. Elemental analysis of $C_{14}H_{10}N_2O_4$ calcd. (found) %: C, 62.22 (62.21); H, 3.73 (3.73); N, 10.37 (10.37); O, 23.68 (23.69).

***N′*-[(*E*)-(4-Fluorophenyl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazide (4f):** White solid; yield: 94.2 %; m.p.: 186-188 ºC; IR (KBr, ν_{max}, cm^{-1}): 3280 (-NH), 3060 (-CH), 1770 (lactone C=O), 1637 (amide C=O), 1568 (C=N), 1300 (C-F); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.49 (2H, d, CH_2), 7.48 (1H, dd, ArH), 7.96 (H, dd, ArH), 8.08 (1H, dd, ArH), 7.49 (2H, m, ArH), 6.99 (2H, m, ArH), 8.26 (1H, s, N=CH), 8.15 (1H, s, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.1, 162.9, 161.8, 144.9, 142.5, 134.6, 134.2, 130.2, 128.6, 127.7, 126.2, 123.6, 115.4, 60.4; LC-MS: *m/z*: 298$[M]^+$, 299 $[M+1]^+$. Elemental analysis of $C_{16}H_{11}N_2O_3F$ calcd. (found) %: (64.43) 64.41; H, 3.72 (3.72); F, 6.37 (6.37); N, 9.39 (9.40); O, 16.09 (16.10).

1-Oxo-*N′*-[(*E*)-(pyridin-4-yl)methylidene]-1,3-dihydro-2-benzofuran-5-carbohydrazide (4g): Pale yellow solid; yield: 92.8 %; m.p.: 192.195 ºC. IR (KBr, ν_{max}, cm^{-1}): 3194 (-NH), 3057 (-CH), 1762 (lactone C=O), 1657 (amide C=O), 1552 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.48 (2H, d, CH_2), 7.49 (1H, dd, ArH), 8.04 (1H, dd, ArH), 8.16 (1H, dd, ArH), 7.55 (2H, m, ArH), 8.63 (2H, m, ArH), 8.44 (1H, s, N=CH), 8.33 (1H, s, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.4, 161.8, 152.8, 149.7, 145.5, 144.9, 137.3, 134.6, 128.3, 127.6, 126.3, 123.8, 123.5, 120.1, 60.3; LC-MS: *m/z*: 281 $[M]^+$, 282 $[M+1]^+$. Elemental analysis of $C_{15}H_{11}N_3O_3$ calcd. (found) %: C, 64.05 (64.04); H, 3.94 (3.95); N, 14.94 (14.94); O, 17.07 (17.07).

***N′*-[(*E*)-(2-Hydroxy-3-methoxyphenyl)methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazide (4f):** Light brown solid; yield: 93.8 %; m.p.: 175-177 ºC. IR (KBr, ν_{max}, cm^{-1}): 3416 (-OH), 3201 (-NH), 3003 (-CH), 1758 (lactone C=O), 1641 (amide C=O), 1566 (-C=N), 1249 (=C-O), 1076 (O-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.83 (3H, s, $ArOCH_3$), 5.49 (2H, d, CH_2), 7.52 (1H, dd, ArH), 7.93 (1H, dd, ArH), 8.01 (1H, dd, ArH), 6.73 (1H, dd, ArH), 6.84-6.94 (2H, m, ArH), 8.33 (1H, s, N=CH), 8.21 (1H, s, CONH), 8.55 (1H, s, ArOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.8, 162.3, 148.4, 147.9, 146.1, 141.7, 135.7, 134.2, 127.9, 127.2, 126.6, 126.2, 125.8, 120.5, 113.8, 60.3, 55.7. LC-MS: *m/z*: 326 $[M]^+$, 327 $[M+1]^+$. Elemental analysis of $C_{17}H_{14}N_2O_5$ calcd. (found) %: C, 62.57 (62.56); H, 4.32 (4.33); N, 8.59 (8.59); O, 24.52 (24.53).

General procedure for the synthesis of 5-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-2-benzofuran-1(3*H*)-ones (5a-h): The desired oxadiazoles (**5a-h**) were prepared by oxidative cyclization of N′-[(*E*)-(substituted aryl) methylidene]-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazides (**4a-h**, 0.5g) using non-toxic hypervalent iodine reagent, diacetoxyiodo benzene (1 eq.) in the presences of methylene dichloride (5 mL) were refluxed for 4-6 h. The completion of the reaction was confirmed by TLC. After completion of the reaction, the reaction mas was cooled to room temperature and the solid obtained was filtered and washed with water and methanol. The product was then dried and purified by column chromatography eluted by ethyl acetate/hexane (5-10 %) (**Scheme-I**).

5-(5-(4-Hydroxyphenyl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3*H*-one) (5a): Pale yellow solid, yield: 82.5 %, m.p.: 209-212 ºC. IR (KBr, ν_{max}, cm^{-1}): 3605 (-OH), 3032 (-CH), 1756 (-C=O), 1558 (C=N), 1254 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.42 (2H, d, CH_2), 7.14 (2H, m, ArH), 7.85 (2H, m, ArH), 7.89 (1H, dd, ArH), 8.27 (1H, dd, ArH), 8.65 (1H, m, ArH), 10.96 (1H, s, Ar-OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.6, 163.7, 157.8, 147.1, 128.9, 127.7, 126.8, 126.2, 125.5, 120.9, 115.8, 115.0, 69.5; LC-MS: *m/z*: 294 $[M]^+$, 293 $[M-1]^+$. Elemental analysis of $C_{16}H_{10}N_2O_4$ calcd. (found) %: C, 65.31 (65.29); H, 3.43 (3.43); N, 9.52 (9.52); O, 21.75 (21.76).

5-(5-(2-Methoxyphenyl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3H-one) (5b): Pale yellow solid, yield: 80.2 %, m.p.: 218-220 ºC. IR (KBr, ν_{max}, cm^{-1}): 3033 (-CH), 1765 (-C=O), 1558 (C=N), 1232 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.40 (2H, d, CH_2), 3.85 (3H, s, $-OCH_3$), 7.29-7.7 (4H, m, ArH), 77.89 (1H, dd, ArH), 8.27 (1H, dd, ArH), 8.64 (1H, dd, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.4, 163.6, 160.4, 147.1, 128.7, 127.7, 126.8, 126.2, 125.5, 120.6, 115.8, 114.8, 69.5, 55.6. LC-MS: *m/z*: 308 $[M]^+$, 309 $[M+1]^+$. Elemental analysis of $C_{16}H_{10}N_2O_4$ calcd. (found) %: C, 66.23 (66.22); H, 3.92 (3.93); N, 9.09 (9.09); O, 20.76 (20.77).

5-(5-(2-Hydroxyphenyl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3*H*-one) (5c): Pale yellow solid, yield: 81.8 %, m.p.: 213-215 ºC. IR (KBr, ν_{max}, cm^{-1}): 3624 (-OH), 3024 (-CH), 1756 (-C=O), 1589 (C=N), 1247 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.45 (2H, d, CH_2), 7.22-7.78 (4H, m, ArH), 7.89 (1H, dd, ArH), 8.28 (1H, dd, ArH), 8.66 (1H, m, ArH), 11.22 (1H, s, ArOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.5, 163.7, 158.1, 147.1, 131.9, 127.7, 127.3, 126.8, 126.2, 125.5, 120.6, 119.9, 117.3, 112.6, 69.5; LC-MS: *m/z*: 294 $[M]^+$, 293 $[M-1]^+$. Elemental analysis of $C_{16}H_{10}N_2O_4$ calcd. (found) %: C, 65.31 (65.29); H, 3.43 (3.43); N, 9.52 (9.52); O, 21.75 (21.76)

5-(5-(2-Chlorophenyl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3*H*-one) (5d): Light brown solid, yield: 82.94 %; m.p.: 221-223 ºC. IR (KBr, ν_{max}, cm^{-1}): 3016 (-CH), 1766 (-C=O), 1579 (C=N), 1239 (C-O-C), ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.47 (2H, d, CH_2), 7.51-7.87 (4H, dd, ArH), 8.00-8.05 (2H, m, ArH), 8.65 (1H, dd, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.0, 163.8, 147.1, 133.2, 132.9, 131.4, 131.3, 128.8, 127.7, 126.8, 127.4, 127.2, 126.5, 120.9, 69.5; LC-MS: *m/z*: 312 $[M]^+$, 314 $[M+2]^+$. Elemental analysis of $C_{16}H_9N_2O_3Cl$ calcd. (found) %: C, 61.45 (61.44); H, 2.90 (2.90); Cl, 11.34 (11.34); N, 8.96 (8.96); O, 15.35 (15.35).

5-(5-(Furan-2-yl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3*H*-one) (5e): Brown solid, yield: 82.7 %, m.p.: 205-215 ºC. IR (KBr, ν_{max}, cm^{-1}): 3048 (-CH), 1756 (-C=O), 1588 (C=N), 1221 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.31 (2H, d, CH_2), 6.74 (1H, dd, ArH), 7.33 (1H, dd, ArH), 7.82 (1H, dd, ArH), 8.04-8.06 (2H, dd, ArH), 8.38 (1H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.7, 157.5, 147.0, 146.9, 139.6, 127.7, 126.8, 126.2, 125.5, 120.9, 116.7, 113.9, 69.5; LC-MS: *m/z*: 268$[M]^+$, 269 $[M+1]^+$. Elemental analysis of $C_{14}H_8N_2O_4$ calcd. (found) %: C, 62.69 (62.68); H, 3.01 (3.01); N, 10.44 (10.45); O, 23.86 (23.87).

5-(5-(4-Fluorophenyl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3*H*-one) (5f): Pale pink solid, yield: 83.5 %, m.p.: 210-213°C. IR (KBr, ν_{max}, cm^{-1}): 3038 (-CH), 1772 (-C=O), 1593 (C=N), 1249 (C-O-C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.46 (2H, d, CH_2), 7.44 (2H, m, ArH), 7.86-7.95 (4H, m, ArH), 8.68 (1H, dd, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.6, 163.5, 163.4, 147.1, 133.4, 127.7, 126.8, 126.2, 125.5, 120.3, 122.8, 116.5, 69.5. LC-MS: *m/z*: 296$[M]^+$, 297 $[M+1]^+$. Elemental analysis of $C_{16}H_9N_2O_3F$ calcd. (found) %: C, 64.87 (64.85); H, 3.06 (3.06); F, 6.41 (6.41); N, 9.46 (9.46); O, 16.20 (16.21).

5-(5-(Pyridine-2-yl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3*H*-one) (5g): Pale brown solid; yield: 83.5 %, m.p.: 218-221 ºC. IR (KBr, ν_{max}, cm^{-1}): 3048 (-CH), 1763 (-C=O), 1589 (C=N), 1240 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.35 (2H, d, CH_2), 7.61 (1H, m, ArH), 7.91-8.50 (4H, m, ArH), 8.74 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.5, 162.3, 149.6, 147.1, 145.8, 136.4, 127.7, 126.8, 126.2, 125.5, 124.0, 120.6, 123.4, 69.5; LC-MS: *m/z*: 279 $[M]^+$, 280 $[M+1]^+$. Elemental analysis of $C_{15}H_9N_3O_3$ calcd. (found) %: C, 64.52 (64.50); H, 3.25 (3.25); N, 15.05 (15.05); O, 17.19 (17.19). Nature:

5-(5-(2-Hydroxy-3-methoxyphenyl)-1,3,4-oxadiazole-2-yl)isobenzofuran-1(3*H*-one) (5h): Pale yellow solid, yield: 83.5 %; m.p.: 215-218 ºC. IR (KBr, ν_{max}, cm^{-1}): 3605 (-OH), 3032 (-CH), 1756 (-C=O), 1558 (C=N), 1254 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.29 (2H, d, CH_2), 3.74 (3H, s, OCH_3), 6.92 (1H, m, ArH), 7.29 (1H, m, ArH), 7.86 (1H, dd, ArH), 7.90 (1H, dd, ArH), 8.24 (1H, m, ArH), 8.65 (1H, m, ArH), 10.99 (1H, s, ArOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 164.5, 163.7, 148.6, 147.1, 146.5, 128.8, 127.7, 127.3, 126.8, 126.2, 125.5, 120.6, 113.2, 112.3, 69.5, 56.2; LC-MS: *m/z*: 324$[M]^+$, 325 $[M+1]^+$. Elemental analysis of $C_{17}H_{12}N_2O_5$ calcd. (found) %: C, 62.96 (62.95); H, 3.73 (3.73); N, 8.64 (8.64); O, 24.67 (24.68).

Antimicrobial activity: The antibacterial assay was carried out by performing pour plate method in which 1 mL bacterial active cultures per plate were mixed into agar media before solidifying temperature and poured into plates. Herein, *Bacillus* and *Klebsiella* were selected as Gram-positive and Gram-negative bacteria. A 5 mm diameter wells were made using a sterile well borer and 100 µL samples were loaded in each well respectively in Gram-positive and Gram-negative plates. Plates were incubated at 37 ºC for 24 h.

Antifungal assay: The antifungal assay was performed by taking the potato dextrose agar plates preplaced with 5 mm diameter fungal plugs of *Fusarium oxysoprum lycopersici* and *Phytophthora nicotiana* at the center. Wells were made based on the number of samples to be analyzed. Samples were loaded into the respective wells (100 µL each) and incubated at 25 ºC for 96 h.

RESULTS AND DISCUSSION

1,3-Dihydro-1-oxoisobenzofuran-5-carboxylic acid (**1**) was esterified in methanol and thoinyl chloride under reflux for 2 h afforded methyl-1,3-dihydro-1-oxoisobenzo furan-5-carboxylic methyl ester (**2**). Compound **2** when reacted with hydrazine hydrate in methanol under reflux for 4 h obtained the compound **3**. It was condensed under reflux with different aromatic aldehydes in methanol in the presence of catalytic

TABLE-1
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **5(a-h)**

Compound	Zone of inhibition (mm)			
	Gram-positive	Gram-negative	Antifungal assay	
	Bacillus	*Klebsiella*	*Fusarium oxysoprum lycopersici*	*Phytophthora nicotiana*
5a	4	3	26	10
5b	5	4	26	10
5c	4	4	26	10
5d	4	3	26	10
5e	5	4	28	15
5f	5	4	28	15
5g	6	5	28	15
5h	6	6	28	15
Streptomycin	19	16	–	–
Mancozeb 75 % WP	–	–	16	10

amount of glacial acetic acid to give the corresponding Schiff base derivatives (**4a-h**), respectively. Finally, desired oxadiazoles (**5a-h**) were prepared by refluxing the oxidative cyclization of N′-[(*E*)-(substituted aryl)methylidene-1-oxo-1,3-dihydro-2-benzofuran-5-carbohydrazides (**4a-h**) using non-toxic hypervalent iodine reagent, diacetoxyiodobenzene in the presence of methylene dichloride for 4-6 h.

The structure of the isolated compounds was substantiated based on spectral data. The ^{1}H NMR spectra revealed in each case, a singlet at δ 5.46-5.49 ppm -CH protons, a singlet at δ 8.20-8.76 ppm which attributed to the imine (-N=CH) proton. The structure of the compounds was confirmed by the appearance of hydrazone-NH band at 3280-3170 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum revealed the -NH proton (D_2O exchangeable) peaks appears at the range of δ 8.11-8.49 ppm as singlet for all the compounds. All the compounds were confirmed by ^{1}H , ^{13}C NMR, IR and mass spectral data.

The final synthesized compounds 5-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-2-benzofuran-1(3*H*)-ones (**5a-h**) were identified by the peaks appears at 1589-1558 cm^{-1} (C=N), 1254-1221 cm^{-1} (C-O-C) in IR spectrum. The -NH peaks disappears, oxadiazole ring formation takes place and their structure conformed by ^{13}C NMR.

Biological activity: All the compounds exhibit excellent inhibitory effect against *Fusarium oxysoprum lycopersici*, while the compounds **5e**, **5f**, **5g** and **5h** compounds have excellent activity against *Phytophthora nicotiana* remaining compounds **5a**, **5b**, **5c** and **5d** show good activity against the same (Table-1). Moreover, all the compounds are found to exhibit poor activity against Gram-positive and Gram-negative bacteria (Table-1).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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