ORIGINAL ARTICLE

Synthesis, characterization and pharmacological evaluation of (Z)-2-(5-(biphenyl-4-yl)-3-(1-(imino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol derivatives as potent antimicrobial and antioxidant agents

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Abstract The oxadiazole pharmacophore is considered a viable lead structure for the synthesis of more efficacious and broad spectrum antimicrobial agents. The significance of this study was to pre-pare various oxadiazole derivatives by introducing the 1,3,4 oxadiazole core into several molecules to explore the possibilities of some altered biological activities. Therefore, the study presents the synthesis, antimicrobial and antioxidant evaluation of a series of 1,3,4 substituted oxadiazole deriv-atives. Antimicrobial evaluation revealed that eighteen compounds were able to display variable growth inhibitory effects on the tested Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, Gram-negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli* and fungal strains *Candida albicans* and *Aspergillus niger*. Among the synthesized derivative analogues **6f**, **6l** and **6r** were found to be the most effective antibacterial agents. While the compounds **6c**, **6l** and **6q** were found to be the most promising antifungal agents. On the other hand, all the synthesized com-pounds **6a–6r** were subjected to antioxidant activity but only analogues **6l** and **6q** were found to exhibit potent antioxidant activity. Further compound **6l** containing *p*-nitro phenyl moiety along with oxadiazole pharmacophore proved to be the most active antimicrobial and antioxidant agent.
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1. Introduction

One of the main objectives of organic and medicinal chemists is to design and synthesize molecules having therapeutic values (Verma and Saraf, 2008). The dramatically rising prevalence

of multi-drug resistant microbial infection in the past few decades has become a serious health care problem. In, the past 25 years, the incidence of microbial infection has increased in alarming levels all over the world as a result of antimicrobial resistance. A growing number of immuno-compromised patients (immune response attenuated by administration of immunosuppressive drugs) as a result of cancer chemotherapy, organ transplantation and HIV infection are the major factors contributing to this increase (Koca et al., 2005; Bonde and Gaikwad, 2004; Yu and Huiyuan, 2002; Ram, 1988). Hence there will always be a vital need to discover new chemotherapeutic agents to avert the emergence of resistance and ideally shorten the duration of therapy (Dolman et al., 2006; Murphy et al., 2007).

A wide variety of heterocyclic systems have been explored for developing pharmaceutically important molecules. Nitrogen containing heterocyclic molecules constitutes the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals (Khalil et al., 1980). Among them the derivatives of oxadiazoles played a very important role in the medicinal chemistry. Oxadiazoles have been described as bio-isosteres for amides and esters (Jonathan and Robert, 1998). Due to increased hydrolytic (Clapp, 1976) and metabolic stabilities of the oxadiazole ring, improved pharmacokinetic and *in vivo* performance is often observed, which make these heterocycles an important structural motif for the pharmaceutical industry. 1,3,4-oxadiazoles are an important class of heterocyclic compounds with a variety of biological activities. Substituted 1,3,4-oxadiazoles have shown antibacterial and antifungal (Gaonkar et al., 2006), antioxidant (Padmavathi et al., 2011), anticancer (Bhatt et al., 1994), antimycobacterial (Tangallapally et al., 2007), antimalarial (Kagthara et al., 1999), antihypoglycemic (Hussian et al., 1986), anti-inflammatory (Palaska et al., 2002), anticonvulsant (Zarghi et al., 2005) and muscle relaxant (Yale and Losee, 1966), genotoxic (Maslat et al., 2002), and insecticidal activities (Shi et al., 2001). They are also used extensively in the symptomatic treatment of rheumatic fever, arthritis (rheumatoid, osteo and jaundice arthritis), and management of primary dysmennorrhoea (Cao et al., 2003). Oxadiazole pharmacophore has the key property that influences the ability of a drug to reach the target by transmembrane diffusion and show potent antimicrobial activity (Testa et al., 2000).

The wide range of therapeutic values of 1,3,4-substituted oxadiazole ring systems promoted us to synthesize the title compounds and screen them for their antimicrobial and antioxidant activities. Therefore, it was envisaged that chemical entities with Schiff base and oxadiazole moieties would result in compounds of interesting biological activities. In view of these findings, we have attempted to incorporate all two biologically active components together to give the title compounds for evaluating their antimicrobial and antioxidant activities inspired by the above facts and in continuation of our ongoing research programme in the field of synthesis and antimicrobial activity of medicinally important compounds (Deep et al., 2010, 2012; Madhukar et al., 2009). In this communication we are reporting the synthesis of 1,3,4-substituted oxadiazole derivatives and evaluated them for antimicrobial and antioxidant activities.

2. Materials and methods

Melting points of the synthesized compounds were determined in open-glass capillaries on a Stuart SMP10 melting point apparatus and were recorded as uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC). Silica gel plates kieselgel 0.25 mm, 60 GF$_{254}$, precoated sheets obtained from Merck, Darmstadt (Germany) were used for TLC and the spots were visualized by iodine vapours/ultraviolet light as visualizing agent. The IR spectra (v, cm^{-1}) were obtained with a Perkin-Elmer 1600 FTIR spectrometer in KBr pellets. ^{1}H-NMR spectra (δ, ppm) were recorded in DMSO-d6 solutions on a Varian–Mercury 300 MHz spectrometer using tetramethylsilane as the internal reference. ^{13}C-NMR spectra were recorded in dimethylsulphoxide (DMSO)-d6 solutions on a Bruker Avance II 400 spectrometer at 400 MHz using tetramethylsilane as the internal reference. Elemental analyses were performed on an ECS 4010 Elemental Combustion System. The necessary chemicals were purchased from Loba Chemie, Fluka and Sigma Aldrich.

3. Chemistry

The syntheses of targeted compounds were carried out as outlined in synthetic scheme. Compounds (**6a–6r**) were readily prepared in good yields and purity. Initially biphenyl-4-carboxylic acid (1) and excess of methanol with a catalytic amount of sulphuric acid were refluxed for 5 h to form biphenyl-4-carboxylic acid methyl ester (2) which on treatment with excess of hydrazine hydrate forms biphenyl-4-carboxylic acid hydrazide (3). Then biphenyl-4-carboxylic acid hydrazide and 2-hydroxybenzaldehyde were refluxed to form N′-(2-hydroxybenzylidene)biphenyl-4-carbohydrazide (4) which on reaction with acetic anhydride results in the formation of 1-(5-(biphenyl-4-yl)-2-(2-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (5). Finally an equimolar amount of 1-(5-(biphenyl-4-yl)-2-(2-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone and appropriate aromatic amines were refluxed with a catalytic amount of glacial acetic acid to form substituted oxadiazole derivatives (**6a–6r**). The purity of the compounds was checked by thin layer chromatography (TLC) and elemental analyses. The physical constants of synthesized compounds are given in Table 1.

### 3.1. Synthesis of biphenyl-4-carboxylic acid methyl ester (2)

A mixture of (50 g, 0.25 mol) biphenyl-4-carboxylic acid and excess of methanol (250 ml) with 1 mL of sulphuric acid was refluxed for 5 h in a round bottom flask. The mixture was cooled; the solid was separated by filtration and recrystallized from methanol.

3.2. Synthesis of biphenyl-4-carboxylic acid hydrazide (3)

A mixture of (42.4 g, 0.2 mol) biphenyl-4-carboxylic acid methyl ester and excess of hydrazine hydrate (15 ml, 0.30 mol) and ethanol (250 ml) were refluxed for about 3 h and cooled. The solid was separated by filtration and recrystallized from ethanol to afford biphenyl-4-carboxylic acid hydrazide.

3.3. Synthesis of N′-(2-hydroxybenzylidene)biphenyl-4-carbohydrazide (4)

A mixture of (5.3 g, 0.025 mol) biphenyl-4-carboxylic acid hydrazide and 2-hydroxybenzaldehyde (3.05 g, 0.025 mol)

Table 1 Physical constants of the synthesized compounds.

(6a-6r)
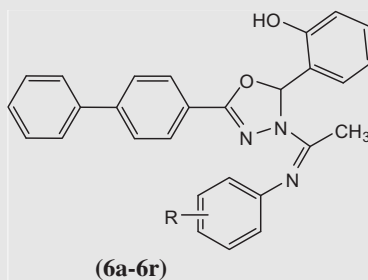
Compound no.	R	Molecular formula	Molecular weight	Yield (%)	Mp (°C)
6a	2F	$C_{28}H_{22}FN_3O$	451.49	72	192–194
6b	3F	$C_{28}H_{22}FN_3O$	451.49	69	183–185
6c	4F	$C_{28}H_{22}FN_3O$	451.49	64	214–216
6d	2Cl	$C_{28}H_{22}ClN_3O_2$	467.95	65	177–179
6e	3Cl	$C_{28}H_{22}ClN_3O_2$	467.95	58	182–184
6f	4Cl	$C_{28}H_{22}ClN_3O_2$	467.95	68	219–221
6 g	2Br	$C_{28}H_{22}BrN_3O_2$	512.40	75	227–229
6 h	3Br	$C_{28}H_{22}BrN_3O_2$	512.40	63	211–213
6i	4Br	$C_{28}H_{22}BrN_3O_2$	512.40	61	217–219
6j	2NO$_2$	$C_{28}H_{22}N_4O_4$	478.50	77	225–227
6 k	3NO$_2$	$C_{28}H_{22}N_4O_4$	478.50	63	208–210
6 l	4NO$_2$	$C_{28}H_{22}N_4O_4$	478.50	73	224–226
6 m	2CH$_3$	$C_{29}H_{25}N_3O_2$	447.23	58	197–199
6n	3CH$_3$	$C_{29}H_{25}N_3O_2$	447.23	63	209–211
6o	4CH$_3$	$C_{29}H_{25}N_3O_2$	447.23	65	206–208
6p	2OCH$_3$	$C_{29}H_{25}N_3O_3$	463.53	55	214–216
6q	3OCH$_3$	$C_{29}H_{25}N_3O_3$	463.53	63	207–209
6r	4OCH$_3$	$C_{29}H_{25}N_3O_3$	463.53	67	231–233

was refluxed in methanol (50 mL) for 5 h in the presence of a catalytic amount of glacial acetic acid. The mixture was cooled; the solid was separated by filtration and recrystallized from methanol to give the corresponding hydrazide hydrazone.

3.4. Synthesis of 1-(5-(biphenyl-4-yl)-2-(2-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (5)

A mixture of N′-(2-hydroxybenzylidene)biphenyl-4-carbohydrazide (0.01 mol, 3.16 g) with 5 ml of acetic anhydride was refluxed for 7 h until the completion of the reaction which was monitored by TLC.

Phenols, unlike amines cannot be acetylated satisfactorily with acetic anhydride. Usually phenols get acetylated with acetic anhydride/acetyl chloride in the presence of catalyst (HgCl$_2$, TMS-Cl, Zncl$_2$, ZnO, Mg (Clo$_4$), SmI$_2$). On the other hand N-acetylation is more feasible as compared to phenol acetylation. That is why only –NH gets acetylated and the residue was poured onto crushed ice (Mulla et al., 2012). The solid thus obtained was filtered; washed with water and was then recrystallized with aqueous methanol. Yield 77 %; m.p. 175–177 °C; IR (KBr; cm^{-1}): 3452, 2951, 2862, 2840, 1681, 1568, 1179, and 1143. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.82 (s,1H, OH, D_2O exchangeable), 7.91–7.58 (m, 9H, biphenyl H), 6.85–6.62 (m, 4H, phenol), 5.72 (s, 1H, oxadiazole), 2.11 (s, 3H, O=C–CH$_3$); ^{13}C-NMR (400 MHz, DMSO d_6, δ ppm): 167.59, 155.38, 154.17, 142.12, 139.85, 130.55, 129.74, 129.57, 128.03, 127.91, 127.65, 120.82, 114.74, 67.33, and

22.72. Anal.: Calcd. for $C_{22}H_{18}N_2O_3$. (358.39) C 73.73, H 5.06, N 7.82. Found: C 73.65, H 5.11, and N 7.85.

3.5. General procedure for synthesis of substituted oxadiazole derivatives (6a–6r)

A mixture of 1-(5-(biphenyl-4-yl)-2-(2-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (1.79 g, 0.005 mol) and an equimolar amount of appropriate aromatic amines (0.01 mol) were added to 25 ml of absolute ethanol (99.9%) with a drop of glacial acetic acid, and were heated under reflux for 9–11 h until the completion of the reaction that was monitored by TLC. The obtained precipitate was filtered-off; washed with cold ethanol and recrystallized from absolute ethanol.

3.6. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(2-fluorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6a)

IR (υ, cm^{-1}): 3452, 2955, 2865, 2838, 1688, 1578, 1277, 1185, and 1165. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.86 (s, 1H, OH, D_2O exchangeable), 7.87-7.55 (m, 9H, Ar H), 7.62-7.39 (m, 4H, phenyl), 6.89-6.67 (m, 4H, phenol), 5.64 (s, 1H, oxadiazole), 2.25 (s, 3H, N=C–CH$_3$); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.72, 155.35, 153.18, 143.36, 139.25, 135.27, 130.35, 129.74, 127.15, 126.88, 125.18, 122.78, 120.73, 117.91, 114.25, 68.95, and 20.53. Anal.: Calcd. for $C_{28}H_{22}FN_3O_2$ (451.49): C 74.49, H 4.91, N 9.31. Found: C 74.82, H 4.87, and N 9.22.

3.7. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(3-fluorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6b)

IR (v, cm^{-1}): 3455, 2988, 2861, 2840, 1685, 1569, 1256, 1183, and 1155. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.92 (s, 1H, OH, D_2O exchangeable), 8.19-7.89 (m, 9H, Ar H), 7.54-7.38 (m, 4H, phenyl), 6.95-6.68 (m, 4H, phenol), 5.69 (s, 1H, oxadiazole), 2.37 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.18, 162.83, 155.28, 153.25, 149.29, 142.34, 140.87, 130.74, 129.75, 128.59, 127.84, 120.81, 118.82, 114.77, 114.22, 108.91, 69.32, and 22.72. Anal.: Calcd. for $C_{28}H_{22}FN_3O_2$ (451.49): C 74.49, H 4.91, N 9.31. Found: C 74.43, H 4.94, and N 9.34.

3.8. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-fluorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6c)

IR (v, cm^{-1}): 3439, 2979, 2863, 2843, 1688, 1567, 1252, 1175, and 1162. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.95 (s, 1H, OH, D_2O exchangeable), 8.25-7.92 (m, 9H, Ar H), 7.59-7.34 (m, 4H, phenyl), 6.87-6.55 (m, 4H, phenol), 5.55 (s, 1H, oxadiazole), 2.35 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.59, 160.35, 155.26, 154.38, 153.39, 146.38, 142.18, 130.83, 129.78, 128.75, 127.15, 122.59, 120.38, 115.85, 114.64, 69.72, and 22.36. Anal.: Calcd. for $C_{28}H_{22}FN_3O_2$ (451.49): C 74.49, H 4.91, N 9.31. Found: C 74.55, H 4.93, and N 9.23.

3.9. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(2-chlorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6d)

IR (v, cm^{-1}): 3438, 2975, 2860, 2840, 1679, 1562, 1188, 1159, and 739. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.87 (s, 1H, OH, D_2O exchangeable), 8.25-7.83 (m, 9H, Ar H), 7.69-7.32 (m, 4H, phenyl), 6.90-6.71 (m, 4H, phenol), 5.72 (s, 1H, oxadiazole), 2.35 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.53, 155.39, 153.89, 143.27, 139.75, 138.29, 130.88, 129.63, 129.17, 128.74, 128.11, 127.89, 127.43, 121.37, 119.74, 115.75, 69.74, and 22.87. Anal.: Calcd. for $C_{28}H_{22}ClN_3O_2$ (467.95): C 71.87, H 4.74, N 8.98. Found: C 71.94, H 4.79, and N 8.86.

3.10. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(3-chlorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6e)

IR (v, cm^{-1}): 3435, 2972, 2861, 2843, 1675, 1566, 1184, 1133, and 725. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.88 (s, 1H, OH, D_2O exchangeable), 8.39-7.85 (m, 9H, Ar H), 7.65-7.29 (m, 4H, phenyl), 6.86-6.68 (m, 4H, phenol), 5.71 (s, 1H, oxadiazole), 2.32 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.85, 154.39, 153.93, 149.95, 143.29, 139.75, 133.81, 130.75, 129.75, 128.19, 128.05, 127.91, 127.45, 121.63, 119.78, 114.87, 69.71, and 22.78. Anal.: Calcd. for $C_{28}H_{22}ClN_3O_2$ (467.95): C 71.87, H 4.74, N 8.98. Found: C 71.83, H 4.77, and N 8.99.

3.11. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-chlorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6f)

IR (v, cm^{-1}): 3439, 2965, 2865, 2837, 1683, 1565, 1182, 1121, and 735. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.81 (s, 1H, OH, D_2O exchangeable), 8.49-8.03 (m, 9H, Ar H), 7.61-7.39 (m, 4H, phenyl), 6.91-6.68 (m, 4H, phenol), 5.76 (s, 1H, oxadiazole), 2.39 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.28, 155.38, 154.19, 149.85, 142.18, 139.77, 133.87, 130.85, 129.47, 128.46, 127.41, 126.48, 126.15, 121.29, 119.87, 114.75, 69.75, and 22.81. Anal.: Calcd. for $C_{28}H_{22}ClN_3O_2$ (467.95): C 71.87, H 4.74, N 8.98. Found: C 71.83, H 4.78, and N 8.98.

3.12. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(2-bromophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6g)

IR (v, cm^{-1}): 3432, 2962, 2855, 2842, 1688, 1566, 1185, 1127, and 639. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.85 (s, 1H, OH, D_2O exchangeable), 8.59-8.17 (m, 9H, Ar H), 7.66-7.31 (m, 4H, phenyl), 6.87-6.54 (m, 4H, phenol), 5.68 (s, 1H, oxadiazole), 2.35 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.37, 155.39, 154.86, 145.29, 142.77, 139.48, 131.84, 130.73, 129.71, 128.85, 128.37, 127.32, 126.54, 120.81, 118.52, 117.59, 114.35, 69.22, and 22.89. Anal.: Calcd. for $C_{28}H_{22}BrN_3O_2$ (512.40): C 65.63, H 4.33, N 8.20. Found: C 65.81, H 4.21, and N 8.14.

3.13. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(3-bromophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6h)

IR (v, cm^{-1}): 3439, 2968, 2859, 2839, 1685, 1569, 1184, 1118, and 645. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.87 (s, 1H, OH, D_2O exchangeable), 8.67-8.24 (m, 9H, Ar H), 7.61-7.34 (m, 4H, phenyl), 6.89-6.73 (m, 4H, phenol), 5.87 (s, 1H, oxadiazole), 2.42 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.81, 155.29, 154.42, 150.48, 142.85, 139.87, 131.87, 130.15, 129.38, 128.54, 127.53, 124.18, 123.19, 122.71, 121.87, 114.82, 69.55, and 22.85. Anal.: Calcd. for $C_{28}H_{22}BrN_3O_2$ (512.40): C 65.63, H 4.33, N 8.20. Found: C 65.57, H 4.32, and N 8.27.

3.14. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-bromophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6i)

IR (v, cm^{-1}): 3436, 2958, 2863, 2845, 1682, 1563, 1182, 1119, and 637. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.85 (s, 1H, OH, D_2O exchangeable), 8.62-8.23 (m, 9H, Ar H), 7.77-7.31 (m, 4H, phenyl), 6.84-6.75 (m, 4H, phenol), 5.83 (s, 1H, oxadiazole), 2.49 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.56, 155.39, 154.17, 150.35, 142.11, 140.39, 132.31, 130.87, 129.79, 129.62, 128.75, 127.94, 127.55, 121.38, 120.93, 114.73, 69.81, and 22.64. Anal.: Calcd. for $C_{28}H_{22}BrN_3O_2$ (512.40): C 65.63, H 4.33, N 8.20. Found: C 65.60, H 4.27, and N 8.29.

3.15. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(2-nitrophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6j)

IR (v, cm^{-1}): 3431, 2975, 2855, 2843, 1680, 1572, 1552, 1358, 1181, and 1129. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.83 (s, 1H, OH, D_2O exchangeable), 8.55-8.15 (m, 9H, Ar H), 7.78-7.56 (m, 4H, phenyl), 6.87-6.76 (m, 4H, phenol), 5.44 (s, 1H, oxadiazole), 2.35 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.59, 155.83, 154.11, 144.55, 142.91, 141.88, 140.15, 131.38, 129.24, 128.45, 128.09, 127.94, 127.65, 124.75, 120.58, 114.91, 69.58, and 22.75. Anal.: Calcd. for $C_{28}H_{22}N_4O_4$ (478.50): C 70.28, H 4.63, N 11.71. Found: C 70.35, H 4.60, and N 11.67.

3.16. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(3-nitrophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6k)

IR (v, cm^{-1}): 3455, 2990, 2858, 2846, 1686, 1575, 1557, 1335, 1192, and 1135. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.89 (s, 1H, OH, D_2O exchangeable), 8.59-8.21 (m, 9H, Ar H), 7.81-7.59 (m, 4H, phenyl), 6.85-6.69 (m, 4H, phenol), 5.54 (s, 1H, oxadiazole), 2.39 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.94, 155.84, 154.37, 148.75, 148.13, 142.11, 140.19, 131.94, 130.88, 129.84, 128.53, 127.84, 127.43, 121.48, 120.59, 117.75, 114.73, 69.53, and 22.81. Anal.: Calcd. for $C_{28}H_{22}N_4O_4$ (478.50): C 70.28, H 4.63, N 11.71. Found: C 70.35, H 4.66, and N 11.61.

3.17. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-nitrophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6l)

IR (v, cm^{-1}): 3443, 2972, 2856, 2841, 1683, 1575, 1555, 1351, 1177, and 1139. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.79 (s, 1H, OH, D_2O exchangeable), 8.51-8.22 (m, 9H, Ar H), 7.75-7.38 (m, 4H, phenyl), 6.89-6.73 (m, 4H, phenol), 5.59 (s, 1H, oxadiazole), 2.38 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.84, 157.64, 155.65, 154.32, 145.91, 142.18, 139.72, 130.29, 129.83, 129.65, 128.54, 127.85, 127.64, 125.57, 123.25, 120.55, 114.73, 69.57, and 22.45. Anal.: Calcd. for $C_{28}H_{22}N_4O_4$ (478.50): C 70.28, H 4.63, N 11.71. Found: C 70.22, H 4.65, and N 11.75.

3.18. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(o-tolylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6m)

IR (v, cm^{-1}): 3425, 2969, 2858, 2845, 1681, 1564, 1183, and 1128. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.72 (s, 1H, OH, D_2O exchangeable), 8.48-8.15 (m, 9H, Ar H), 7.77-7.33 (m, 4H, phenyl), 6.87-6.64 (m, 4H, phenol), 5.60 (s, 1H, oxadiazole), 2.42 (s, 3H, CH$_3$), 2.15 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.52, 155.46, 153.97, 142.35, 139.87, 135.27, 130.77, 129.58, 129.11, 128.51, 127.79, 127.17, 126.25, 120.59, 114.29, 70.12, 22.27, and 19.35. Anal.: Calcd. for $C_{29}H_{25}N_3O_2$ (447.23): C 77.83, H 5.63, N 9.39. Found: C 77.88, H 5.65, and N 9.32.

3.19. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(m-tolylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6n)

IR (v, cm^{-1}): 3431, 2965, 2855, 2841, 1685, 1562, 1184, and 1125. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.77 (s, 1H, OH, D_2O exchangeable), 8.52-8.19 (m, 9H, Ar H), 7.76-7.31 (m, 4H, phenyl), 6.77-6.69 (m, 4H, phenol), 5.62 (s, 1H, oxadiazole), 2.39 (s, 3H, CH$_3$), 2.09 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.59, 155.39, 154.21, 151.18, 142.27, 139.71, 139.15, 130.19, 129.94, 129.73, 129.35, 128.18, 127.59, 123.88, 120.93, 118.85, 114.71, 69.71, and 22.78. Anal.: Calcd. for $C_{29}H_{25}N_3O_2$ (447.23): C 77.83, H 5.63, N 9.39. Found: C 77.81, H 5.55, and N 9.49.

3.20. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(p-tolylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6o)

IR (v, cm^{-1}): 3432, 2965, 2861, 2841, 1683, 1563, 1185, and 1132. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.74 (s, 1H, OH, D_2O exchangeable), 8.41-8.11 (m, 9H, Ar H), 7.69-7.44 (m, 4H, phenyl), 6.65-6.37 (m, 4H, phenol), 5.62 (s, 1H, oxadiazole), 2.53 (s, 3H, CH$_3$), 2.19 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.83, 155.39, 154.15, 148.29, 142.17, 139.77, 137.15, 130.72, 130.12, 129.72, 129.13, 128.15, 127.87, 127.57, 125.74, 120.19, 114.72, 69.74, and 22.55. Anal.: Calcd. for $C_{29}H_{25}N_3O_2$ (447.23): C 77.83, H 5.63, N 9.39. Found: C 77.89, H 5.61, and N 9.35.

3.21. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(2-methoxyphenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6p)

IR (v, cm^{-1}): 3459, 2976, 2852, 2846, 1687, 1571, 1176, and 1165. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.86 (s, 1H, OH, D_2O exchangeable), 8.58-8.19 (m, 9H, Ar H), 7.79-7.31 (m, 4H, phenyl), 6.68-6.51 (m, 4H, phenol), 5.47 (s, 1H, oxadiazole), 3.84 (s, 3H, OCH_3), 2.27 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.83, 155.77, 154.73, 151.18, 142.53, 139.77, 134.48, 130.75, 129.81, 129.44, 128.37, 127.93, 127.35, 124.33, 122.43, 120.62, 116.84, 69.71, 56.82, and 22.78. Anal.: Calcd. for $C_{29}H_{25}N_3O_3$ (463.53): C 75.14, H 5.44, N 9.07. Found: C 75.23, H 5.37, and N 9.05.

3.22. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(3-methoxyphenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6q)

IR (v, cm^{-1}): 3443, 2976, 2860, 2842, 1684, 1566, 1171, and 1143. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.75 (s, 1H, OH, D_2O exchangeable), 8.54-8.19 (m, 9H, Ar H), 7.71-7.28 (m, 4H, phenyl), 6.83-6.66 (m, 4H, phenol), 5.51 (s, 1H, oxadiazole), 3.81 (s, 3H, OCH_3), 2.34 (s, 3H, N=C–CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.82, 160.91, 155.38, 153.29, 149.74, 142.73, 139.64, 131.69, 129.38, 128.11, 127.92, 127.54, 127.05, 120.79, 114.75, 113.67, 107.55, 105.19, 69.54, 54.11, and 22.72. Anal.: Calcd. for $C_{29}H_{25}N_3O_3$ (463.53): C 75.14, H 5.44, N 9.07. Found: C 75.25, H 5.39, and N 9.01.

3.23. (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-methoxyphenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (6r)

IR (v, cm^{-1}): 3437, 2971, 2863, 2843, 1685, 1561, 1175, and 1143. ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 9.71 (s, 1H, OH, D_2O exchangeable), 8.51-8.20 (m, 9H,biphenyl H), 7.82-7.33 (m, 4H, phenyl), 6.87-6.59 (m, 4H, phenol), 5.45 (s, 1H, oxadiazole), 3.89 (s, 3H, OCH$_3$), 2.39 (s, 3H, N=C-CH_3); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.48, 158.41, 154.51, 153.35, 143.92, 142.18, 139.74, 130.83, 129.61, 128.26, 127.73, 127.41, 127.03, 121.20, 119.77, 114.62, 69.75, 54.11, 22.68. Anal.: Calcd. for C$_{29}$H$_{25}$N$_3$O$_3$ (463.53): C 75.14, H 5.44, N 9.07. Found: C 75.07, H 5.48, N 9.10.

4. Antimicrobial Evaluation

The newly synthesized compounds were screened for their antibacterial activity against *Bacillus subtilis* (MTCC 96), *Staphylococcus aureus* (MTCC 121), *Pseudomonas aeruginosa* (MTCC 2453) and *Escherichia coli* (MTCC 40) bacterial strains by the disc-diffusion method (Cruickshank et al., 1975; Collins, 1976). A standard inoculum ($1-2 \times 10^7$ c.f.u./ml 0.5 McFarland standards) was introduced on the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. A disc measuring 6.25 mm in diameter was prepared from Whatman No. 1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile disc previously soaked with the test compound solution in DMSO of specific concentrations 100 μg and 200 μg/disc was carefully placed on the agar culture plates. The plates were inverted and incubated for 24 h at 37 °C. Ciprofloxacin was used as a standard drug. Inhibition zones were measured and compared with the controls. The bacterial zones of inhibition were given in Table 2. Minimum inhibitory concentrations (MICs) were determined by the broth dilution technique. The nutrient broth, which contained logarithmic serially two fold diluted amount of the test compound and control was inoculated with approximately 5×10^5 c.f.u (colony forming unit) of actively dividing bacteria cells. The cultures were incubated for 24 h at 37 °C and the growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC).

To obtain the minimum bactericidal concentration (MBC), 0.1 ml volume was taken from each tube and spread on agar plates. The number of c.f.u was counted after 18–24 h of incubation at 35 °C. MBC was defined as the lowest drug concentration at which 99.9% of the inoculum was killed. The minimum inhibitory concentration and minimum bactericidal concentrations are given in Table 3.

The newly synthesized compounds were screened for their antifungal activity against *Candida albicans* (MTCC 8184) and *Aspergillus niger* (MTCC 8189) in DMSO by the agar diffusion method (Khan, 1997; Varma, 1998) Sabouraud's agar medium was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawing. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of the corresponding species. Twenty millilitres of agar media was

Table 2 Antibacterial zone of inhibition (mm) of synthesized oxadiazoles.

Compound[b]	Conc. (μg/ml)	Zone of inhibition (mm)			
		B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
6a	100	11	12	14	15
	200	13	14	16	17
6b	100	10	11	15	16
	200	12	13	18	18
6c	100	12	15	23	18
	200	14	17	24	21
6d	100	14	12	18	19
	200	16	15	20	21
6e	100	15	14	21	18
	200	17	16	23	20
6f	100	17	18	24	22
	200	19	20	27	25
6 g	100	11	13	15	17
	200	13	15	18	19
6 h	100	11	14	19	18
	200	12	16	22	20
6i	100	13	17	25	21
	200	15	18	27	23
6j	100	16	14	22	19
	200	18	17	24	22
6 k	100	15	16	25	22
	200	17	18	28	24
6 l	100	18	21	30	25
	200	20	23	32	26
6 m	100	9	8	15	12
	200	11	10	18	14
6n	100	10	10	19	15
	200	12	13	22	17
6o	100	12	15	23	19
	200	14	16	25	21
6p	100	10	11	19	15
	200	12	13	22	16
6q	100	11	15	22	17
	200	13	17	24	19
6r	100	12	16	25	21
	200	14	18	26	23
Ciprofloxacin[a]	100	21	23	32	26
	200	22	24	33	27

[a] Ciprofloxacin (100, 200 μg per disc) was used as positive reference standard antibiotic discs and Synthesized compounds (100, 200 μg per disc).
[b] Synthesized compounds 6a–6r.

poured into each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch, wells were made and each well was labelled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. The fungal activity of each compound was compared with voriconazole as a standard drug. Inhibition zones were measured and compared with the controls. The fungal zones of inhibition values are given in Table 4.

The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls was inoculated with approximately 1.6×10^4–6×10^4 c.f.u./ml. The cultures were incubated for 48 h at 35 °C and the growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as mini-

Table 3 MIC and MBC results of oxadiazoles.

Compounds	B. subtilis		S. aureus		P. aeruginosa		E. coli	
	MIC[a]	MBC[b]	MIC[a]	MBC[b]	MIC[a]	MBC[b]	MIC[a]	MBC[b]
6a	25	50	12.5	50	25	50	12.5	25
6b	50	100	25	50	12.5	25	25	50
6c	12.5	25	12.5	25	50	100	25	50
6d	6	12.5	25	50	12.5	25	12.5	25
6e	12.5	25	25	50	12.5	25	6	12.5
6f	6	12.5	6	12.5	6	12.5	12.5	25
6 g	12.5	50	12.5	25	6	12.5	6	12.5
6 h	25	50	12.5	25	6	12.5	6	12.5
6i	12.5	25	12.5	25	6	12.5	6	12.5
6j	12.5	50	12.5	25	6	12.5	25	50
6 k	12.5	25	12.5	25	6	12.5	6	12.5
6 l	6	12.5	6	12.5	12.5	25	6	12.5
6 m	25	50	25	50	25	50	50	100
6n	12.5	25	25	50	25	50	12.5	25
6o	12.5	25	12.5	25	25	50	12.5	25
6p	25	50	12.5	25	6	12.5	12.5	25
6q	12.5	25	12.5	25	6	12.5	12.5	25
6r	12.5	25	6	12.5	6	12.5	12.5	25
Std[c]	6	12.5	6	12.5	6	12.5	6	12.5

[a] MIC (µg/ml) = minimum inhibitory concentration, i.e., the lowest concentration to completely inhibit bacterial growth.
[b] MBC (µg/ml) = minimum bactericidal concentration, i.e., the lowest concentration to completely kill bacteria.
[c] Ciprofloxacin is used as standard drug.

mum inhibitory concentration (MIC). To obtain the minimum fungicidal concentration (MFC), 0.1 ml volume was taken from each tube and spread on agar plates. The number of c.f.u was counted after 48 h of incubation at 35 °C. MFC was defined as the lowest drug concentration at which 99.9% of the inoculum was killed. The minimum inhibitory, minimum bactericidal and minimum fungicidal concentrations are given in Table 5.

5. Antioxidant activity

Antioxidant activity is determined in terms of hydrogen peroxide scavenging activity. The solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (pH 7.4). Different concentrations (100, 300, and 500 µg/mL) of all the synthesized compounds were added to a hydrogen peroxide solution (0.6 mL, 40 mM). The absorbance of hydrogen peroxide at 230 nm was determined after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage scavenging of hydrogen peroxide of the synthesized compounds and the standard compounds was calculated using the following formula: Percentage scavenging $[H_2O_2] = [(A_0 - A_1)/A_0] \times 100$, where A_0 was the absorbance of the blank, and A_1 was the absorbance in the presence of the sample and standards (Gulcin et al., 2005). The percentage scavenging of hydrogen peroxide by the synthesized compounds at 100, 300 and 500 µg/mL concentrations was calculated and results are summarized in Table 6.

6. Result and discussion

Nevertheless, the structures of all new compounds synthesized were confirmed by (IR, ^{1}H NMR and ^{13}C NMR) spectra. The IR spectra of all compound **(6a–6r)** showed absorption band at around 3459-3425, 2995-2958, 2865-2835, 1688-1675, 1578-1561, 1188-1171, and 1173-1118 cm^{-1} regions, conforming the presence of OH, CH, CH$_2$, C=N, C=C, C–O, and C–N respectively. In the ^{1}H NMR spectra, the signals of the respective prepared derivatives were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The spectra of most compounds showed the characteristic 1H proton of OH at around δ 9.95-9.71, 9H proton of biphenyl at around δ 8.69-7.55, characteristic protons of phenyl at δ 7.82-7.28 ppm, 3H proton of phenol appearing at 6.95-6.37, 1H proton of oxadiazole at 5.87-5.43, and 3H proton of N=C–CH$_3$ around δ 2.49-2.09 ppm. ^{13}C-NMR spectra of compounds showed characteristic signals appearing for N=C–CH$_3$ at δ 163.94-163.18, oxadiazole ring at δ 155.84-68.95, phenyl ring at δ 162.83-108.91, biphenyl moiety at δ 131.94-127.03, phenol at δ 160.35-114.22 and N=C–CH$_3$ at δ 22.89-19.35 ppm.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good antibacterial and antifungal activities against B. subtilis, S. aureus, P. aeruginosa, E. coli, C. albicans and A. niger respectively. The compounds **6f**, **6l** and **6r** displayed excellent antibacterial activity while **6e**, **6j** and **6k** showed moderate antibacterial activity and the compounds **6b**, **6m** and **6p** are less active as compared to standard drug ciprofloxacin. In case of antifungal activity compounds **6c**, **6l** and **6q** exhibit significant activity while the compounds **6h**, **6j**, **6m**, **6o** and **6k** showed moderate activity. Among all the synthesized derivatives the compound **6n** was found to be the least active compound against fungal strain. All the synthesized compounds exhibited potent hydrogen peroxide scavenging activities. From all the synthesized compound analogues **6l** with nitro moiety was the most active with scavenging of hydrogen peroxide of 58.18 at 500 µg/mL concentration, followed by compound **6q** with methoxy group with hydrogen peroxide scavenging of 57.36 at 500 µg/mL.

Table 4 Antifungal zone of inhibition (mm) of oxadiazoles.

Compounds[b]	Conc. (μg/ml)	Zone of inhibition (mm)	
		C. albicans	*A. niger*
6a	100	15	18
	200	17	20
6b	100	16	17
	200	18	19
6c	100	21	25
	200	23	26
6d	100	12	13
	200	15	15
6e	100	13	15
	200	14	17
6f	100	15	20
	200	15	20
6 g	100	12	18
	200	15	20
6 h	100	19	23
	200	21	25
6i	100	16	22
	200	18	24
6j	100	16	15
	200	19	18
6 k	100	18	23
	200	20	25
6 l	100	21	27
	200	24	29
6 m	100	17	19
	200	20	22
6n	100	11	16
	200	14	18
6o	100	16	20
	200	19	23
6p	100	16	20
	200	18	21
6q	100	20	23
	200	23	26
6r	100	18	20
	200	19	22
Voriconazole[a]	100	25	24
	200	27	26

[a] Voriconazole (100, 200 μg per disc) was used as positive reference standard antibiotic discs, and Synthesized compounds (100, 200 μg per disc).
[b] Synthesized compounds 6a–6r.

Table 5 MIC and MFC results of oxadiazoles.

Compounds	*C. albicans*		*A. niger*	
	MIC[a]	MFC[b]	MIC[a]	MFC[b]
6a	25	100	6	12.5
6b	12.5	25	25	100
6c	6	12.5	6	12.5
6d	25	50	-	-
6e	-	-	6	25
6f	12.5	25	25	50
6 g	25	50	12.5	25
6 h	6	12.5	12.5	25
6i	12.5	25	6	12.5
6j	6	12.5	12.5	25
6 k	6	12.5	12.5	25
6 l	6	12.5	6	12.5
6 m	12.5	25	12.5	25
6n	12.5	25	6	12.5
6o	25	50	25	50
6p	6	25	25	50
6q	6	12.5	6	12.5
6r	6	12.5	25	50
Std[c]	6	12.5	25	50

[a] MIC (μg/ml) = minimum inhibitory concentration, i.e., the lowest concentration to completely inhibit fungal growth;
[b] MFC (μg/ml) = minimum fungicidal concentration, i.e., the lowest concentration to completely kill the fungi.
[c] Voriconazole is used as standard drug.

Table 6 Hydrogen peroxide scavenging activity of synthesized compounds.

Comp.	Scavenging of hydrogen peroxide at different concentrations (%)		
	100 μg	300 μg	500 μg
6a	41.55	39.84	41.22
6b	46.34	44.55	45.77
6c	51.11	48.12	44.59
6d	41.92	42.33	41.72
6e	45.65	46.19	45.91
6f	51.21	43.12	39.57
6 g	39.58	42.61	43.18
6 h	43.45	41.37	45.27
6i	41.88	45.19	48.11
6j	47.52	54.15	53.18
6 k	45.35	50.27	52.15
6 l	51.15	52.27	58.18
6 m	45.87	41.37	41.93
6n	42.98	39.72	39.57
6o	41.03	43.06	44.14
6p	51.62	52.18	52.91
6q	54.18	53.76	57.36
6r	49.87	51.35	48.74
BHA	63.27	66.19	68.25
Ascorbic Acid	51.47	53.45	55.38

The main aim of the present investigation is to synthesize and investigate the antimicrobial and antioxidant activity of newly synthesized oxadiazole containing compounds that are structurally related to the famous antimicrobial oxadiazole pharmacophore, with the hope of discovering new structure leads serving as potential broad spectrum antimicrobial and antioxidant activities. The obtained results revealed that 18 compounds were able to display growth inhibitory effects on the tested Gram-positive *B. subtilis*, *S. aureus* and Gram-negative bacteria *P. aeruginosa*, *E. coli*. Meanwhile, three compounds **6f**, **6l** and **6r** displayed excellent activity against Gram-positive bacteria and Gram-negative bacteria meanwhile, three compounds **6c**, **6l** and **6q** exhibit promising antifungal activity against *C. albicans* and *A. niger*. Structurally, the antimicrobial and antioxidant potential of the active compound depends on the nature of the substituents: remarkabe antibacterial and antifungal activities were encountered with the *p*-nitro phenyl moiety of the oxadiazole counterpart **6l**, while the obtained antifungal activity conformed to those comprising compounds having *p*-fluoro, *p*-nitro and *m*-methoxy
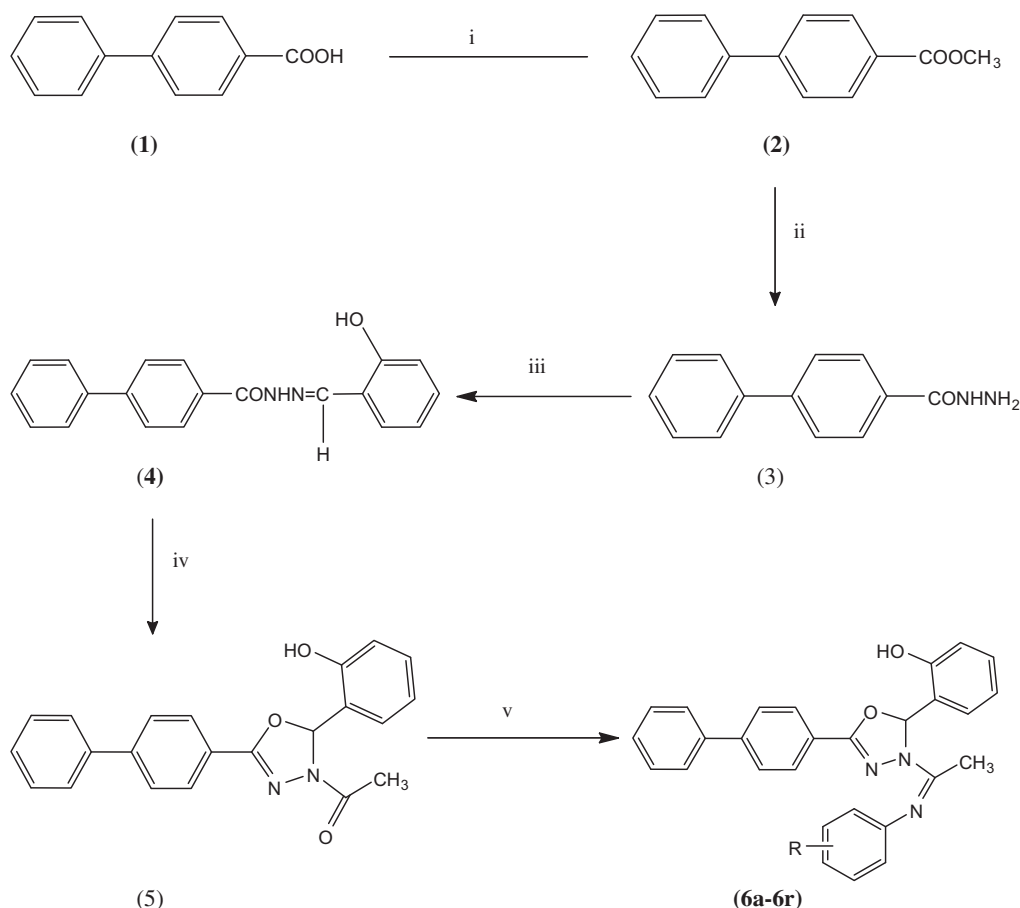
Scheme 1 Reagents and conditions: (i) Methanol, reflux, 5 h, 84.43%; (ii) NH₂NH₂.H₂O, reflux, 3 h, 86.79%; (iii) 2-OHC₆H₄, ethanol, CH₃COOH, reflux, 5 h, 81% (iv) (CH₃CO)₂O, reflux, 7 h, 77% (v) Ethanol, CH₃COOH, aromatic amines, reflux, 9–11 h, 55–77%.

substituted oxadiazole derivatives **6c**, **6l** and **6q**. While the compound **6l** proved to be the most active antimicrobial member within this study with a considerable broad spectrum activity against all bacterial and fungal strains. From the results it is concluded that the introduction of *p*-nitro phenyl moiety along with oxadiazole pharmacophore **6l** resulted in potent hydrogen peroxide scavenging activity. It may be due to nitro substitution at the para position of phenyl nucleus along with oxadiazole moiety which supports its therapeutic activity. So, from the results it has revealed that the nature and position of the substituent has shown a marked effect on antimicrobial and antioxidant activities. (See Scheme 1).

7. Conclusion

This study reports the synthesis of (Z)-2-(5-(biphenyl-4-yl)-3-(1-(imino)ethyl)-2,3-dihydro-1,3,4 oxadiazol-2-yl)phenol derivatives as potent antimicrobial and antioxidant agents **(6a–6r)** and were characterized by spectral analysis. The obtained results revealed that most of the synthesized analogues have shown prominent antimicrobial and antioxidant activities. It was observed that the analogues **(6f)** (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-chlorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol and **(6l)** (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-nitrophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol have shown excellent antibacterial activity rather in case of

antifungal activity the analogues **(6c)** (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-fluorophenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol, **(6l)** and **(6q)** (Z)-2-(5-(biphenyl-4-yl)-3-(1-(3-methoxyphenylimino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol exhibit prominent activity. Among all the synthesized compounds the analogue **6l** exhibits potent antioxidant activity. So, these new therapeutic agents could be considered as lead molecule for the future development of drugs which could be used as antimicrobial and antioxidant agents.

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