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Conventional and Microwave Assisted Synthesis of 5-phenyl-2-substituted-1,3,4-oxadiazole Derivatives and Evaluation of their Biological Studies

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ABSTRACT

In this study, conventional and microwave assisted synthesis of 5-phenyl-2-substituted-1,3,4-oxadiazole derivatives have been reported. The structures of synthesized compounds have been confirmed by Fourier transform infrared, ^{1}H nuclear magnetic resonance (NMR), $^{13}CNMR$, and mass spectroscopic methods. The title compounds were screened for antimicrobial and antioxidant activity followed by molecular docking studies. The compounds 3e and 3g were endowed with a high antibacterial activity when compared with standard antibacterial drugs and among docked compounds; the compound 3 g showed the best docking with 2-XCT protein. The antioxidant results revealed that the compounds exhibit dose-dependent antioxidant activity. Compounds 3a, 3b, 3c, 3e, and 3f have potential radical scavenging, while compounds 3a, 3b, 3c, 3h, and 3j have potential metal chelating ability as comparable with the standard used.

Key words: *1,3,4-Oxadiazole, Antibacterial, Antifungal, Antioxidant, 1,1-Diphenyl-2-picrylhydrazyl, Metal chelating.*

1. INTRODUCTION

In medicinal chemistry, 1,3,4-oxadiazolemoiety has great attraction as bioisosteres for a number of biological targets due to their metabolic stability, ability to bind with target peptides and can be engaged in hydrogen bond formation. The raltegravir and zibotentan are the drugs encompassing the 1,3,4-oxadiazole moiety and are currently used in clinical medicine as antiretroviral and anticancer drugs, respectively [1]. Setileuton[4-(4-fluorophenyl)-7-[({5-[(1S)-1-hydroxy-1-(trifluoromethyl)propyl]-1,3,4-oxadiazol-2-yl}amino)methyl]-2H-1-benzopyran-2-one] is used as an inhibitor of the 5-lipoxygenase enzyme [2]. Substituted 1,3,4-oxadiazoles have been found to exhibit wide range of pharmacological activities such as anticancer [3], anti-HIV [4], neurotoxic [5], antitubercular [6], antibacterial [7], antifungal [8], anti-inflammatory [9], antiviral [10], analgesic [11], insecticidal [12], antidepressant [13], anticonvulsant [14], hypoglycemic, and antimalarial activity [15].

The living organisms possessed enzymatic and non-enzymatic defense systems against overproduction of reactive oxygen species (ROS) and reactive nitrogen species. However, because of external factors like smoking, addiction of alcohol, stress, food nature, and aging will decrease the efficiency of defense system of living organisms [16]. In such cases, organisms need external antioxidants to establish redox equilibrium in the living system. A number of synthetic compounds such as derivatives of benzofuran, thiazoles, benzothiophene, pyrazole, oxadiazole, flavone, and quinazolinones have significant antioxidant properties [17-19].

On the other hand, the rising prevalence of multi-drug resistant of Gram-positive, Gram-negative bacteria, and fungi continues to provide momentum for search and development of novel active antimicrobial agents against these pathogens. Hence, antimicrobial agents are considered leading weapons in the treatment of infectious diseases. This will trigger the researcher effort is oriented toward to the design new antimicrobial agents with a high efficiency and minimal side effects.

The gyrase enzyme relieves strain while double strand DNA is being unwound by helicase [20,21]. It is an

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essential enzyme in all bacteria but absent in higher eukaryotes, hence making it a beautiful antibacterial target [22-25]. Hence, the molecular docking studies of gyrase with newly synthesized compounds were carried out and reported.

The extensive literature survey revealed that the presence of heterocyclic rings at the 2nd and 5th position of the oxadiazole ring increases the biological profile of these compounds to a greater extent [26-30]. These observations stimulated us to synthesize an array of substituted oxadiazoles by fusing phenyl ring at 5th position and heterocycles at the 2nd position with the intention to synthesize some novel derivatives with pharmacological relevance. Thus, herein, we report the design and synthesis of mutual prodrugs which contain 1,3,4-oxadiazole moiety with different heterocyclic aromatic substituents and aliphatic hydrocarbon chain to produce synergistic pharmacological activity.

2. MATERIALS AND METHODS

2.1. Synthesis of Acid Hydrazide (2)

The acid hydrazide 2 was prepared by reported method, and the melting point was checked and it is matched with literature value (174-176°C) [31].

2.2. General Procedure for the Synthesis of Compounds (3a-n)

Method A: By conventional heating:

A mixture of benzhydrazide 2 (0.01 mol) and appropriate carboxylic acids (0.015 mol) (a-n) was dissolved in 5 mL of $POCl_3$, and the reaction mixture was refluxed for 4-10 h at 110°C. The progress of the reaction was monitored by thin layer chromatography using petroleum ether:ethyl acetate (8:2 v/v %) as eluent. After completion of the reaction, the reaction mixture was cooled, poured onto a crushed ice, and neutralized using $NaHCO_3$. The obtained solid was filtered, dried and recrystallized from ethanol and purified by silica gel column chromatography eluting with petroleum ether:ethyl acetate mixture (80:20 v/v %).

Method B: By microwave irradiation:

A mixture of benzhydrazide 2 (0.01 mol) and appropriate carboxylic acids (0.015 mol) (a-n) were dissolved in 5 mL of $POCl_3$ and the reaction mixture was stirred under irradiate using micro oven for 4-10 min at 100°C at 110 W. After completion of the reaction, the reaction mixture was allowed to cool and poured into crushed ice. The resulting precipitate was filtered, washed with cold water and recrystallized from ethanol and further purification is done by silica gel column chromatography eluting with petroleum ether:ethyl acetate mixture (80:20 v/v %).

2.2.1. 2-phenyl-5-(1H-1,2,4-triazol-3-yl)-1,3,4-oxadiazole(3a)

Brown solid (ethanol), m.p 222-224°C; infrared (IR) (KBr, υ cm^{-1}): 3214 (N-H), 3085 (C-H), 1605 (C=N), 1597 (C=C), 1157 (C-O-C); ^{1}H nuclear magnetic resonance (NMR) (400 MHz, DMSO, δ ppm): 7.32-7.35 (m, 3H Ar-H), 8.07 (d, *J*=7.2 Hz, 2H, Ar-H), 8.32 (s, 1H, triazole-H), 11.90 (s, 1H, triazole-NH); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 164.84, 158.31, 153.75, 150.35, 130.65, 129.74, 128.64, 127.54; $C_{10}H_7N_5O$, MS (LCMS): m/z 215[M+].

2.2.2. 2-(5-bromothiophen-2-yl)-5-phenyl-1,3,4-oxadiazole(3b)

Brown solid (ethanol), m.p 125-128°C; IR (KBr, υ cm^{-1}): 2927 (C-H), 1594 (C=N), 1547 (C=C), 1197 (C-O-C), 691(C-Br); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.04-7.08 (m, 3H, Ar-H), 7.82 (d, *J*=8.85 Hz, 2H, Ar-H), 7.90 (d, 1H, thiophene-H), 7.94 (d, 1H, thiophene-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 165.51, 162.23, 135.84, 132.26, 130.34, 130.17, 129.84, 127.54, 126.21, 121.83; $C_{12}H_7BrN_2OS$, MS (LCMS): m/z 310 [M+2], 308 [M+].

2.2.3. 2-(5-methyl-1,2-oxazol-3-yl)-5-phenyl-1,3,4-oxadiazole (3c)

Brown solid (ethanol), m.p 185-189°C; IR (KBr, υ cm^{-1}): 2918 (C-H), 1604 (C=N), 1551 (C=C), 1187 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.55 (s, 3H, methyl-H), 6.99 (s, 1H, oxazole-H), 7.62-7.68 (m, 3H Ar-H), 8.07 (d, *J*=8.40 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 171.58, 165.54, 157.23, 150.40, 132.35, 129.16, 127.38, 123.12, 101.15, 12.23; $C_{12}H_9N_3O_2$, MS (LCMS): m/z 229 [M+].

2.2.4. 2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)methyl] pyrazine (3d)

Brown solid (ethanol), m.p 228-230°C; IR (KBr, υ cm^{-1}): 2945 (C-H), 1615 (C=N), 1604 (C=C), 1209 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.90 (s, 2H), 7.29-7.31 (m, 3H, Ar-H), 7.53 (d, *J*=8.80 Hz, 2H, Ar-H), 8.42-8.44 (m, 2H, pyrazine-H) 8.46 (m, H, pyrazine-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 166.41, 164.21, 154.71, 145.64, 144.27, 143.37, 131.30, 130.38, 129.82, 128.57, 126.23, 38.45; $C_{13}H_{10}N_4O$, MS (LCMS): m/z 240 [M+].

2.2.5. 2-(3-Fluoro-5-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (3e)

Brown solid (ethanol), m.p 189-191°C; IR (KBr, υ cm^{-1}): 2978 (CH_3), 1598 (C=N), 1558 (C=C), 1425 (O-CH_3), 1209 (C-O-C), 1024 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.45 (s, 3H, O-CH_3), 6.73 (m, H, Ar-H), 6.75-6.78 (m, 3H, Ar-H), 7.32-7.34 (m, 3H, Ar-H), 7.60 (d, *J*=7.92 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 164.51, 160.84, 130.31, 130.14, 129.97, 128.71, 127.51, 126.26, 115.21, 112.23, 105.81, 60.34; $C_{15}H_{11}FN_2O_2$, MS (LCMS): m/z 270 [M+].

2.2.6. 1-methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1H-benzotriazole(3f)

Brown solid (ethanol), m.p 247-250°C; IR (KBr, υ cm^{-1}): 2919 (C-H), 1609 (C=N), 1578 (C=C), 1289

(C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.27 (s, 3H, triazole methyl), 7.44-7.51 (m, 3H, Ar-H), 7.60 (d, *J*=7.65, 1H, benztriazole-H), 8.07 (d, *J*=15.6 Hz, 2H, Ar-H), 8.28 (m, 1H, benztriazole-H), 8.71 (d, 1H, benztriazole-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 164.83, 164.24, 145.82, 134.98, 131.93, 129.17, 126.98, 126.09, 123.70, 120.06, 119.22, 110.37, 34.51; $C_{15}H_{11}N_5O$ MS (LCMS). m/z 279 [M+].

2.2.7. 2-[4-(1H-imidazol-1-yl)phenyl]-5-phenyl-1,3,4-oxadiazole(3g)

Brown solid (ethanol), m.p 212-215°C: IR (KBr, υ cm^{-1}): 3124 (C-H), 1612 (C=N), 1557 (C=C), 1238 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.51-7.53 (m, 5H, Ar-H), 7.54 (d, *J*=7.2 Hz, 2H), 7.60 (d, *J*=4.25 Hz, 2H, Ar-H), 7.72 (d, *J*=7.2 Hz 2H, imidazole-H), 8.12 (s, 1H, imidazole-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 162.564, 160.54, 140.56, 136.57, 130.87, 130.23, 129.81, 129.38, 127.84, 126.41, 126.01, 125.64, 122.67, 118.74; $C_{17}H_{12}N_4O$, MS (LCMS): m/z 290 [M+].

2.2.8. 2-phenyl-5-undecyl-1,3,4-oxadiazole(3h)

Yellow solid (ethanol); m.p 151-154 °C; IR (KBr, υ cm^{-1}): 1603 (C=N), 1541(C=C), 1230 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.91 (t, 3H), 1.24-1.81 (m, 20H), 2.14 (t, 2H), 7.64 (m, 3H Ar-H), 8.02 (m, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 161.43, 130.34, 129.95, 127.41, 123.62, 35.52, 30.73, 28.71, 26.92, 25.62, 24.43, 14.11; $C_{19}H_{28}N_2O$, MS (LCMS): m/z 302 [M+].

2.2.9. 2-pentadecyl-5-phenyl-1, 3, 4-oxadiazole(3i)

Yellow solid (ethanol), m.p 158-162 °C; IR (KBr, υ cm^{-1}): 1586 (C=N), 1455 (C=C), 1136 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.83 (t, 3H), 1.09-1.24 (m, 23H), 3.07 (t, 2H), 7.22-7.26 (m, 5H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 160.87, 130.54, 129.34, 128.42, 128.04, 34.67, 32.54, 31.12, 29.78, 29.41, 29.41, 29.32, 29.08, 22.87, 16.43; $C_{21}H_{32}N_2O$, MS (LCMS): m/z 328 [M+].

2.2.10. 2-phenyl-5-tetradecyl-1,3,4-oxadiazole(3j)

Yellow solid (ethanol), m.p 121-124°C; IR (KBr, υ cm^{-1}): 1607 (C=N), 1542 (C=C), 1213 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.930 (t, 3H), 1.28-1.34 (m, 24H), 2.91 (t, 2H), 7.31-7.35 (m, 5H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 163.54, 130.31, 129.84, 128.56, 128.04, 127.21, 34.74, 32.94, 29.74, 29.43, 29.31, 23.82, 16.19; $C_{22}H_{34}N_2O$, MS (LCMS): m/z 344 [M+].

2.2.11. 1-heptadecyl-5-phenyl-1,3,4-oxadiazole(3k)

Yellow solid (ethanol), m.p 114-117 °C: IR (KBr, υ cm^{-1}): 1586 (C=N), 1573 (C=C), 1528, 1238 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.80 (m, 3H), 1.17 (m, 25H), 1.32-1.37 (m, 2H), 1.73-1.74 (m, 2H), 2.27-2.87 (m, 2H), 7.42-7.45 (m, 3H, Ar-H), 7.95-7.97 (m, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 167.07, 164.67, 131.49, 128.99, 126.76, 124.08, 31.92, 29.41, 26.60, 25.45, 22.69, 14.11; $C_{25}H_{40}N_2O$ MS (LCMS): m/z 385 [M+].

2.2.12. 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazole (3l)

Yellow solid (ethanol), m.p 124-128 °C; IR (KBr, υ cm^{-1}): 1600 (C=N), 1498 (C=C), 1123 (C-O-C), 725 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.54-7.57 (m, 3H, Ar-H), 7.81 (d, *J*=7.25 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 162.34, 161.05, 133.27, 130.37, 128.31, 126.34, 124.34, 100.34; $C_9H_5C_{l3}N_2O$, MS (LCMS): m/z 270 [M+6], 268 [M+4], 266 [M+2], 264 [M+].

2.2.13. 2-phenyl-5-(3,3,3-trifluoropropyl)-1,3,4-oxadiazole (3m)

Yellow solid (ethanol), m.p 142-148 °C; IR (KBr, υ cm^{-1}): 3064 (C-H), 1582 (C=N), 1552 (C=C), 1233 (C-O-C), 1139 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.68 (m, 2H), 3.14 (d, 2H), 7.42-7.50 (m, 3H, Ar-H), 7.95 (d, *J*=7.2 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 165.27, 163.97, 131.88, 129.26, 126.85, 124.87, 123.59, 99.99, 30.69, 29.69, 18.99; $C_{11}H_9F_3N_2O$, MS (LCMS). m/z 242 [M+].

2.2.14. 2-phenyl-5-(4,4,4-trifluorobutyl)-1,3,4-oxadiazole (3n)

Yellow solid (ethanol): m.p 154-157 °C: IR (KBr, υ cm^{-1}): 2923 (C-H), 1612 (C=N), 1501 (C=C), 1212 (C-O-C), 1143 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.33 (m, 2H), 2.55 (m, 2H), 2.69 (d, 2H), 7.48-7.54 (m, 3H, Ar-H), 7.77 (d, *J*=7.24 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 163.57, 161.41, 130.34, 130.28, 128.87, 127.64, 127.29, 126.31, 40.74, 33.67, 12.64; $C_{21}H_{11}F_3N_2O$, MS (LCMS): m/z 256 [M+].

2.3. Biological Activity

2.3.1. In vitro antimicrobial activity and minimum inhibitory concentration (MIC)

Antimicrobial activity of the synthesized compounds was tested against four bacterial strains and two fungal stains using agar well diffusion method [32]. All bacterial strains were maintained on nutrient agar medium at ±37°C and fungi strains were maintained on potato dextrose agar at ±25°C. The test compounds were dissolved in DMSO to get a concentration of 1000 µg/mL and 100 µL of this sample was loaded into the wells of agar plates directly. Plates inoculated with the bacteria were incubated at 37°C for 24 h and the fungal culture was incubated at 25°C for 72 h. All determinations were done in triplicates. Ciprofloxacin (1000 µg/mL) and fluconazole (1000 µg/mL) were used as standard drugs for antibacterial and antifungal activities, respectively. MIC was performed by serial broth dilution method at different concentrations such as 250, 500, 750, and 1000 µg/mL. After the incubation period, the minimum Inhibition zone at which the

micro-organism growth was inhibited was measured in mm.

2.3.2. In silico molecular docking studies

An entirely in house developed drug discovery informatics system OSIRIS was used to perform ADMET based calculations. It is a Java based library layer that provides reusable cheminformatics functionality and was used to predict the toxicity risks and overall drug score via *in silico* [33]. The structure of synthesized molecules and the standards was drawn in ChemBioDraw tool (ChemBioOffice Ultra 14.0 suite) assigned with proper two-dimensional (2D) orientation and structure of each was checked for structural drawing error. The energy of each molecule was minimized using ChemBio3D (ChemBioOffice Ultra 14.0 suite).The energy minimized ligand molecules were then used as input for AutoDockVinain order to carry out the docking simulation [34]. The Protein Data Bank (PDB) coordinate file entitled "2XCT.pdb" was used as receptor protein molecule, which is a structure of *Staphylococcus aureus* gyrase in complex with ciprofloxacin and DNA. All the water molecules were removed from the receptor and SPDBV deep view was used to automatically rebuild the missing side chains in receptor. The Graphical User Interface program "MGL Tools" was used to set the grid box for docking simulations. The grid was set so that it surround the region of interest active site in the macromolecule.

In this study, the active site was selected based on the amino acid residues of 2XCT, which are involved in binding with Ciprofloxacin. Therefore, the grid was centered at the region including the two amino acid residues (Arg 458 and Gly 459) and four nitrogenous bases from DNA, i.e. guanine (G), adenine (A), thymine (T) orcytosine (C) as evidenced by the work of Bax [35], this surrounds the active site.

The grid box volume was set to 8, 14 and 14 Å for x, y and z dimensions and the grid center was set to 3.194, 43.143 and 69.977 for x, y and z center, respectively, which covered the two amino acid residues and four nitrogenous bases in the considered active pocket. Auto Grid 4.0 Program, supplied with Auto Dock 4.0 was used to produce grid maps [36]. The docking algorithm provided with Auto Dock Vina was used to search for the best docked conformation between ligand and protein. During the docking process, a maximum of 10 conformers were considered for each ligand. All the AutoDock docking runs were performed in Corei7 Intel processor CPU with 8 GB DDR3l RAM. Auto Dock Vina was compiled and run under Windows 8.0 professional operating system. LigPlot+ [37] and PyMol [38] were used to deduce the pictorial representation of the interaction between the ligands and the target protein.

2.3.3. Antioxidant activity

2.3.3.1. 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity

All the synthesized compounds were screened for free radical scavenging activity by DPPH method of Kenchappa *et al*., [39]. Briefly, compounds in methanol at different concentrations (20-100 µg/mL) were added to each test tube and volume was made up to 4 mL using methanol. To this, 3 mL of 0.004% DPPH in methanol was added, and the mixtures were incubated at room temperature under dark condition for 30 min. The scavenging activity on the DPPH radical was determined by measuring the absorbance at 517 nm. Radical scavenging activity was calculated using the formula:

$$\% \text{ of radical scavenging activity} = ([(A_{control} - A_{test})/A_{control}]) \times 100$$

Where $A_{control}$ is the absorbance of the control sample and A_{test} is the absorbance of the test sample. The DPPH radical scavenging activity of ascorbic acid was also assayed for comparison. The test was performed in triplicate, and the results were averaged.

2.3.3.2. Metal chelating activity

The chelating activity of ferrous ions by the synthesized compounds and standard was estimated by the method of Dinis *et al*. [40]. Briefly, 3 mL of sample solution at different concentrations (20-100 µg/mL) was taken and 0.05 mL of 2 mM $FeCl_2$ was added. The reaction was initiated by adding 0.2 mL 5 mM ferrozine, mixed vigorously and incubated at room temperature for 10 min. The absorbance of the solution was measured at 562 nm. The percentage of inhibition of ferrozine-Fe^{2+} complex formation was calculated using the formula:

$$\% \text{ of inhibition} = ([(A_{control} - A_{test})/A_{control}]) \times 100$$

Where $A_{control}$ is the absorbance of the control sample and A_{test} is the absorbance of the test sample. The test was performed in triplicate, and the results were averaged.

3. RESULT AND DISCUSSION

3.1. Chemistry

The most common synthetic strategy for the synthesis of 5-pheny-2-substituted-1,3,4-oxadiazoles (3a-n) involves the dehydrative cyclization of N,N-diacylhydrazines using strong acids as dehydration agent such as $POCl_3$ [41], $SOCl_2$ [42], P_2O_5 [43], H_2SO_4 [44], and also by mild cyclodehydrating agents such as Burgess reagent [45], triflic anhydride [46], CDI [47], BF_3–OEt_2 [48], and triphenylphospine [49]. In our study, we coupled some heterocyclic aromatic carboxylic acids and fatty acids with benzohydrazide to design 5-pheny-2-substituted-1,3,4-oxadiazole derivatives as prodrug under conventional method

and microwave method in presence of $POCl_3$ as cyclodehydrating agent.

The use of microwave heating greatly reduced reaction time as well as improved product yields over the conventional method. The cyclization reaction of heterocyclic aromatic carboxylic acids required prolonged heating under normal conventional method but in microwave irradiation, reaction completed within 10 min, the purity and yield of product also dramatically increases. In the case of long-chain fatty acids, in the conventional method, the yield and product purity is very less and it required prolonged heating, while in microwave method, product yield and purity increased significantly. The yield of oxadiazole derivatives is high in microwave method probably due to high energy heating sensitivity of our substrates and product purity increased as a result of decreased side-products. The comparison between results of conventional method and microwave method is summarized in the Table 1.

The structures of the newly synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic methods. In the IR spectrum of compound 3c, the characteristic absorption band at 1187 cm^{-1} confirmed the presence of C-O-C oxadiazole ring. ^{1}H NMR spectrum of compound 3c showed singlet at δ 2.55 ppm assigned for three protons of methyl group attached to the oxazole ring. Another singlet at δ 6.99 ppm assigned for the oxazole proton. The multiplet between δ 7.62 and 7.68 ppm assigned for three aromatic protons of phenyl ring and another triplet at 8.07 ppm assigned for two aromatic protons of phenyl ring. Further, ^{13}C NMR spectrum of compound 3c confirmed the proposed structure by the appearance of signal at δ 171.58 ppm due to the C of oxadiazole ring and another signal at δ 12.23 ppm correspond to CH_3 carbon, and other signals are in well agreement with the suggested structures. Mass spectrum of compound 3c displayed a molecular ion peak at m/z 229 [M+] corresponding to the molecular mass of the compound. The reaction pathway used for the synthesis of title compounds (3a-n) has been shown in Scheme 1.

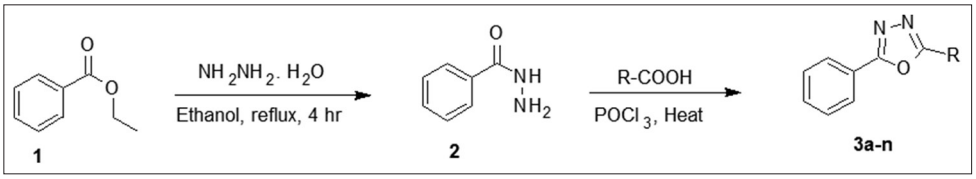
3.1.1. In vitro antimicrobial activity and MIC

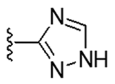
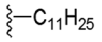
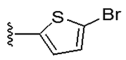
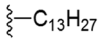
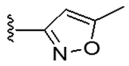
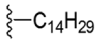
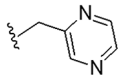
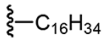
The synthesized molecules exhibited promising and encouraging antibacterial and antifungal activities. The results of these studies are given in Table 2. From antibacterial screening results, it has been observed that compound 3g showed antibacterial activity with MIC values ranging between 250 and 750 µg/mL against tested micro-organisms. Compounds 3e and 3c showed very good activity against all tested micro-organisms. Compound 3d possessed good activities against *Pseudomonas aeruginosa* and *Aspergillus flavus* with MIC values 500 µg/mL. The compound 3n showed promising activity against *Escherichia coli* and moderate activity against *S. aureus* with MIC values 500 and 750 µg/mL, respectively.

All synthesized compounds were screened for the antifungal activity against two fungal stains *Chrysosporium keratinophilum* and *Candida albicans*. Among all tested compounds, compound 3d and 3n showed significant activity against both tested fungal pathogens with MIC values 750 µg/mL, remaining synthesized compounds almost inactive against tested fungal pathogens.

Table 1: Comparison between conventional method and microwave assisted method for the synthesis of 5-phenyl-2-substituted-1,3,4-oxadiazole derivatives 3(a-n).

Compound	Conventional		Microwave	
	Time (min)	Yield (%)	Time (min)	Yield (%)
3a	360	66	10	83
3b	360	65	10	82
3c	360	85	10	90
3d	360	72	10	85
3e	480	71	10	82
3f	480	70	10	85
3g	600	69	10	87
3h	240	64	5	94
3i	240	68	5	95
3j	240	63	5	91
3k	240	60	5	93
3l	240	72	4	89
3m	240	70	4	94
3n	240	71	4	87



Comp Code	R	Code	R
3a		3h	
3b		3i	
3c		3j	
3d		3k	
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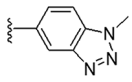
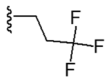
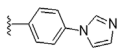
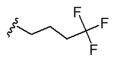
3f		3m	
3g		3n	

Scheme 1: Synthesis of 5-phenyl-2-substituted-1,3,4-oxadiazole derivatives 3(a-n).

Table 2: Antimicrobial and MIC values of synthesized compounds 3(a-n).

Zone of inhibition in mm (1 µg/mL)							MIC (µg/mL)					
Antibacterial				Antifungal								
Comp	***E. c.***	***S. a.***	***P. a.***	***A. f.***	***C. k.***	***C. a.***	***E. c.***	***S. a.***	***P. a.***	***A. f.***	***C. k.***	***C. a.***
3a	03±0.2	02±0.2	01±0.2	01±0.2	02±0.2	03±0.5	500	500	500	500	1000	1000
3b	08±0.2	10±0.1	08±0.1	07±0.2	04±0.1	04±0.2	750	500	750	500	750	1000
3c	10±0.3	17±0.4	14±0.2	12±0.3	04±0.2	04±0.3	500	500	500	500	750	750
3d	07±0.1	10±0.1	12±0.1	13±0.2	11±0.4	13±0.5	500	500	500	500	750	500
3e	13±0.5	12±0.2	14±0.5	10±0.3	02±0.5	04±0.4	500	500	500	500	1000	1000
3f	05±0.3	03±0.2	05±0.2	01±0.1	-	-	500	500	750	500	-	-
3g	15±0.1	13±0.2	14±0.3	11±0.3	02±0.4	-	250	500	500	250	750	-
3h	04±0.2	06±0.2	03±0.2	01±0.2	03±0.2	04±0.2	500	750	750	750	750	750
3i	03±0.7	04±0.1	02±0.1	03±0.4	-	04±0.2	500	500	500	500	-	1000
3j	02±0.2	01±0.0	01±0.2	01±0.1	-	-	500	500	750	750	-	-
3k	-	-	-	-	-	-	-	-	-	-	-	-
3l	04±0.1	01±0.1	02±0.4	01±0.4	01±0.1	01±0.1	500	500	500	500	750	750
3m	05±0.3	03±0.2	05±0.2	01±0.1	-	-	500	500	750	500	-	-
3n	10±0.3	08±0.1	06±0.1	04±0.3	06±0.2	05±0.6	500	750	750	750	750	750
Stnd[a]	14±0.2	13±0.2	13±0.2	10±0.1	-	-	250	250	250	250	-	-
Stnd[b]	-	-	-	-	14±0.2	20±0.2	-	-	-	-	250	250

Each value is expressed as mean±standard deviation of three replicates for zone of inhibition, Stnd[a]: Ciprofloxacin, Stnd[b]: Fluconazole, *E. c: Escherichia coli, S. a: Staphylococcus aureus, P. a: Pseudomonas aeruginosa, A. f: Aspergillus flavus, C. k: Chrysosporium keratinophilum, C. a: Candida albicans, MIC: Minimum inhibitory concentration*

The structural activity study of the newly synthesized compounds revealed that the high antibacterial activity of compound 3g may be attributed due to the phenyl imidazole ring on the oxadiazole ring at fifth position. The activity of compound 3e due to electron-withdrawing fluorine atom on meta-position of phenyl substituent on the fifth position of oxadiazole ring and compound 3c is due to oxazole ring on the fifth position of oxadiazole ring. The antibacterial activity of compound 3d may be attributed due to the pyrazine ring and compound 3n showed antibacterial activity due to the presence of fluorine atoms on the aliphatic hydrocarbon side chain. Here, we examined that, as the length of hydrocarbon chain increases, the activity of synthesized compound decreases (3h-k), when the length of the hydrocarbon chain increases along with electron withdrawing group the antibacterial activity increases (3i-n).

3.2. In Silico Molecular Docking Studies

Considering the results obtained from antimicrobial study, it was thought worthy to perform molecular docking studies by substantiating the *in vivo* results with *in silico* studies. The comparative docking of receptor gyrase with compounds 3c, 3d, 3e, 3g, and 3n and the standard ciprofloxacin exhibited good affinity. Figure 1 depicts the 2D representation of the synthesized ligands 3c, 3d, 3e, 3g, 3n and the standard ciprofloxacin. Figure 2 represents the 3D interaction of 3g and ciprofloxacin, respectively, with gyrase by using educational version of PyMol.

The molecular docking of ligand molecules 3c, 3d, 3e, 3g, and 3nwith gyrase revealed that all the tested ligand molecules showed encouraging binding energy and the compounds exhibited hydrogen bonding with one or the other amino acids in the active pockets as shown in Figure 1. The docked compounds 3c, 3d, 3e, 3g, and 3nwere found best-docked confirmation with a least binding affinity (−5.6, −5.7, −5.8, −6.0 and −5.3 kJ mol^{-1}) than the standard drugs used for docking (Table 3).

The compound 3c established three hydrogen bonds with Glu435, His1081 and Glu435 amino acids in the active site of the target protein with bond length 2.98, 3.30 and 3.35 Å. The compound 3d established three hydrogen bonds with Glu435, Glu435andAsp512 amino acids with bond length 3.08, 3.25 and 2.99 Å, respectively. Further compounds 3e exhibited one hydrogen bonding with bond length 3.13 Å with Glu435 amino acid. Compound 3g exhibited two hydrogen bonding with Asp510 and Gly459 amino acids with bond length 3.12 and 3.18 Å, respectively. Among docked molecules compound 3n did not show hydrogen bonding with protein. In this study, all the docked molecules 3c, 3d, 3e, 3g, and 3n showed more hydrophobic interaction than the standard

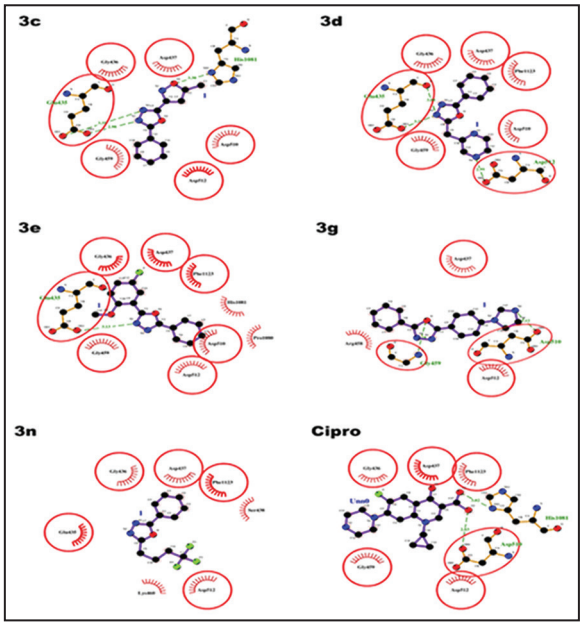


Figure 1: Two-dimensional representation of the interaction of the synthesized molecules 3c, 3d, 3e, 3g, 3n and ciprofloxacin with 2-XCT.

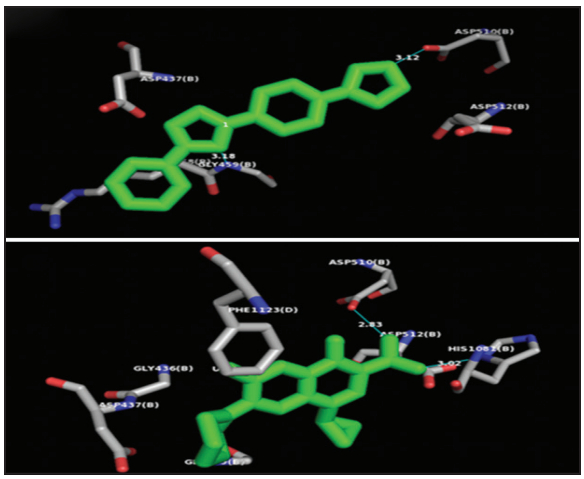


Figure 2: Three-dimensional representation of the interaction of the synthesized molecules 3g and ciprofloxacin with 2-XCT.

ciprofloxacin. Further the root mean square deviation (RMSD) has often been used to measure the quality of reproduction of a known binding pose by molecules with ligands. All docked molecules have zero RMSD values; this indicated the true binding pose of molecules with protein.

3.3. Antioxidant Activity

3.3.1. Free radical scavenging activity by DPPH method

Nowadays search for a safer new molecule with antioxidant potentiality is a very active domain of research, since they can protect the living tissue of the body from free radical damage and they retard the

Table 3: The binding affinity (kcal/mol), H-bonds, H-bond length and H-bond formation of the standards and the synthesized molecules after *in silico* docking.

Ligand	Affinity (kcal/mol)	H-bonds	H-bond length (Å)	H-bond with	Hydrophobic interaction
3c	−5.6	3	2.98	2XCT: Glu435::3c:N3	Gly436, Asp437, Gly459, Asp510, Asp510
			3.30	2XCT: His1081::3c:O1	
			3.35	2XCT: Glu435::3c:N2	
3d	−5.7	3	3.08	2XCT: Glu435::3d:N2	Gly436, Asp437, Gly459, Asp510, Phe1123
			3.25	2XCT: Glu435::3d:N2	
			2.99	2XCT: Asp512::3d:N4	
3e	−5.8	1	3.13	2XCT: Glu435::3e:N1	Asp437, Gly436, Gly459, Asp510, Asp512, Pro1080, His1081, Phe1123
3g	−6.0	2	3.12	2XCT: Asp510::3g:N4	Asp437, Arg458, Asp512
			3.18	2XCT: Gly459::3g:O	
3n	−5.3	0	-	-	Glu435, Gly436, Asp437, Ser438, Lys460, Asp512, Phe1123
Ciprofloxacin	-	2	2.84	2XCT: Asp510::Cipro:O3	Cys300, Ser347, Gln348, Val399, Lys603
			3.02	2XCT: His10810::Cipro:O2	

progress of many chronic diseases, cancer, diabetes, and vascular diseases.

DPPH radical scavenging ability was measured by quenching of stable DPPH radical, purple color solution changes to a stable yellow on reacting with an antioxidant.

The newly synthesized 1,3,4-oxadiazole derivatives exhibited inhibition of DPPH radical scavenging in a dose-dependent manner. The results were tabulated in Table 4 and Figure 3. The results obtained clearly indicated the compound 3a has very good radical scavenging activity with IC_{50} value 75.99±3.46 µg/mL as compared to the standard butylated hydroxyl anisole (57.05±0.64 µg/mL). The compounds 3b, 3f, 3e, and 3c have potential radical scavenging activity with IC_{50} values 96.99±2.45, 95.66±1.68, 96.90±2.77 and 80.72±1.35 µg/mL, respectively, and other compounds showed promising radical scavenging activity with IC_{50} values ranging between 156.9±2.46 and 273.0±1.78 µg/mL as compared to the standard.

DPPH is a stable free radical that can accept an electron or hydrogen atom and stabilized that can be observed by decrease in its absorbance at 517 nm, which is induced by antioxidants. The higher activity of compound 3a may be due to the presence of labile hydrogen of triazole (NH) ring in the structure. The promising scavenging radical property of compound 3f and 3c may be attributed due to the presence of benzotriazole and oxazole ring respectively. Due to the presence of electron withdrawing atom like bromine on thiophene ring of compound 3b and methoxy group

Table 4: Antioxidant activity of synthesized compounds.

Compound code	IC_{50} µg/mL	
	DPPH scavenging	Metal chelating
3a	75.99±3.46	80.94±2.34
3b	96.99±2.45	98.28±1.78
3c	80.72±1.35	76.82±2.45
3d	172.86±3.25	100.86±3.33
3e	96.90±2.77	112.23±2.02
3f	95.66±1.68	104.04±2.65
3g	156.9±2.46	119.86±2.44
3h	206.59±1.46	77.66±8.65
3i	228.62±1.01	80.45±1.38
3j	236.83±1.65	92.35±2.45
3k	273.04±1.78	132.18±4.24
3l	182.0±2.78	161.94±2.34
3m	184.87±2.34	137.86±3.78
3n	177.10±3.46	103.35±3.96
Std	57.05±0.64*	35.27±3.12**

*BHA: Butylated hydroxyl anisole,
**EDTA: Ethylenediamine tetraacetic acid,
DPPH: 1,1-diphenyl-2-picrylhydrazyl

at meta position of phenyl ring of compound 3e lead to the higher radical scavenging activity

3.3.2. Metal chelating ability

In nature, iron can be found in either ferrous (Fe^{2+}) or ferric ion (Fe^{3+}) form. In living systems, ferrous iron can facilitate the production of ROS, hence the ability of substances to chelate iron can be a valuable antioxidant. The compounds with more than two functional groups with favorable structural configurations can show the metal chelation activity. The ferrous ion chelating activity of the newly synthesized compounds is represented in Table 4 and Figure 4. Compounds 3a, 3c, 3i, and 3n showed higher chelating activity with IC_{50} values 80.94±2.34, 76.82±2.45, 80.45±1.38, and 77.66±8.65 µg/mL as compared to the standard ethylenediaminetetraacetic acid (35.27±3.12 µg/mL).

The chelating compounds exhibit their antioxidant activity by forming σ bond with metal ion and form stable complex. In the compounds 3a and 3c, their chelating ability is attributed due to the lone pair of electrons on hetero atoms, which involved in the complex formation by forming σ bond with the ferrous ion. In compounds 3h, 3i, 3j, and 3k the chelating ability were diminished as the length of hydrocarbon chain increase, while in case of compounds 3l, 3m, and 3n due to the presence of electron withdrawing groups, as length of carbon chain increases the chelating ability of compound significantly increases.

4. CONCLUSION

In summary, a series of novel 1,3,4-oxadiazole derivatives 3(a-n) were prepared under conventional heating and microwave heating. The use of microwave heating reduced reaction time, improved product yields and minimized the byproducts over conventional heating. The antimicrobial activity of synthesized compounds revealed that the compounds 3c, 3d, 3e, 3g, and 3n were active against bacterial stains, while compounds 3d and 3n were active against

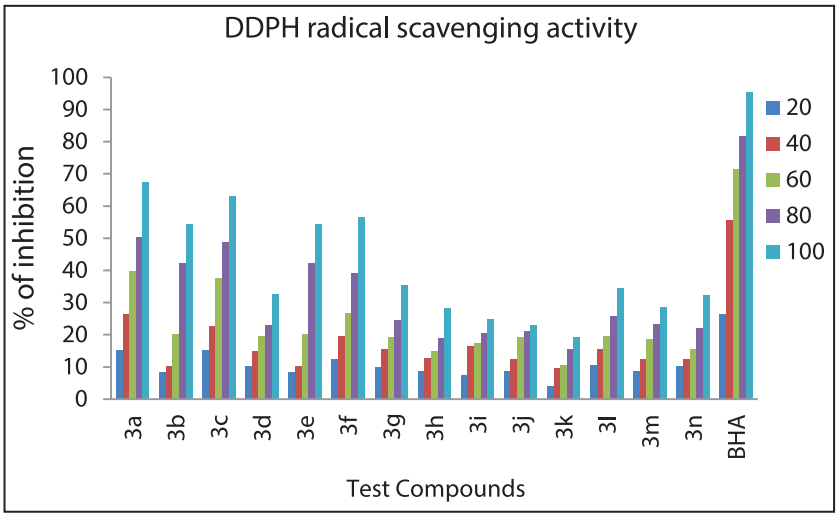


Figure 3: 1,1-diphenyl-2-picrylhydrazyl free radial scavenging activity of test compounds 3(a-n).

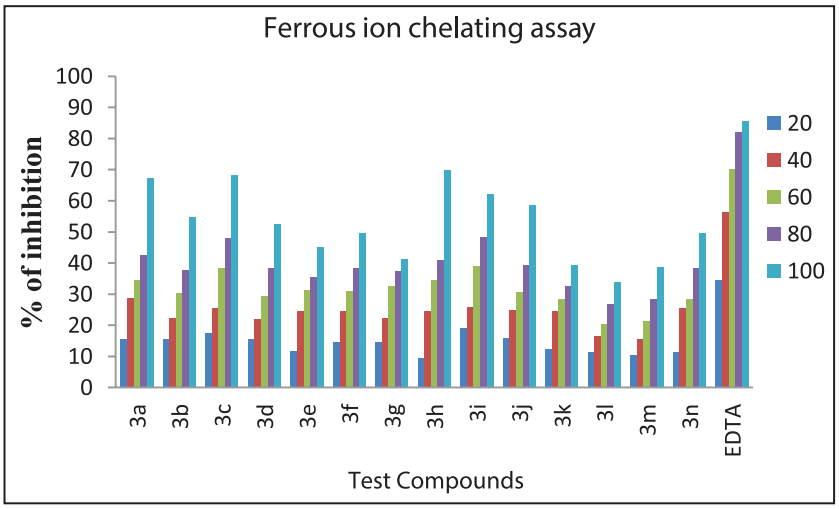


Figure 4: Ferrous ion chelating assay of test compounds 3(a-n).

fungal stains. The docking study revealed that the compounds 3g showed good binding energy with the target protein. The antioxidant results revealed that compound 3a exhibits significant antioxidant activity in dose-dependent manner.

5. ACKNOWLEDGMENTS

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