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Research Article

# Synthesis and Antioxidant Activities of New 2-(4-methylphenylsulphonyl)-5-Aryl-1,3,4-Oxadiazole Compounds

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**Abstract**

In this study, it is aimed to synthesize some new heterocyclic oxadiazole derivatives with antioxidant activity. 1,3,4-oxadiazoles were obtained by condensation reaction with 4-methylphenylsulphonylhydrazide with different aromatic acids in the presence of $POCl_3$. The structures of the synthesized compounds were supported using $^1H$ NMR and $^{13}C$ NMR spectroscopy, and their purity was checked using thin layer chromatography. Elemental analyzes were performed on Carlo Erba 1106 elemental analysis device. Antioxidant activities of 2,5-disubstituted-1,3,4-oxadiazole derivatives (**1-5**), ABTS (2,2'-Azino-bis (3-ethylbenzenothiazoline-6-sulfonic acid), DPPH (1,1-diphenyl -2-picrilhydrazyl) radical removal activities and ferric reducing power antioxidant capacity were investigated. The obtained results showed that the synthesized compounds (**1-5**) had effective antioxidant activity.

**Keywords:** hydrazide, DPPH, ABTS, ferric reducing power

**Yeni 2-(4-metilfenilsülfonil)-5-Aril-1,3,4-Oksadiazol Bileşiklerinin Sentezi ve Antioksidan Aktiviteleri**

**Öz**

Bu çalışmada, antioksidan aktiviteye sahip bazı yeni heterosiklik oksadiazol türevlerinin sentezlenmesi amaçlanmıştır. 1,3,4-oksadiazoller, 4-metilfenilsülfonilhidrazidin farklı aromatik asitlerle $POCl_3$ varlığında kondenzasyon reaksiyonu sonucu elde edilmiştir. Sentezlenen bileşiklerin yapıları $^1H$ NMR ve $^{13}C$ NMR spektroskopisi kullanılarak desteklenmiş ayrıca ince tabaka kromotografisi kullanılarak saflıkları kontrol edilmiştir. Elementel analizleri Carlo Erba 1106 elementel analiz cihazında yapılmıştır. 2,5-disübstitüye-1,3,4-oksadiazol türevlerinin (**1-5**) antioksidan aktiviteleri, ABTS (2,2′-Azino-bis(3-etilbenzenotiyazolin-6-sülfonik asid), DPPH (1,1-difenil-2-pikrilhidrazil) radikal giderme aktiviteleri ve demir indirgeme gücü antioksidan kapasitesine göre incelenmiştir. Elde edilen sonuçlar, sentezlenen bileşiklerin (**1-5**) etkili antioksidan aktiviteye sahip olduğunu göstermiştir.

**Anahtar Kelimeler:** hidrazid, DPPH, ABTS, demir indirgeme gücü[1]

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## 1. Introduction

Pharmaceutical research is important for the development of more effective and new drugs and their more successful use in clinical practice. Accordingly, there is a search for new and original pharmaceuticals and preparations. This creates many advantages. These advantages may be qualitative or quantitative amelioration in activity, absence of unwanted side effects, lower toxicity, developed stability, or reduced cost. Oxadiazole derivatives attract the attention of chemists because of their various biological activities.

2,5-disubstituted-1,3,4-oxadiazoles have various pharmacological activities, such as antioxidant (Gumrukcuoglu and Sökmen, 2019), antibacterial (Maslat et al., 2002), anti-inflammatory (Ilango et al., 2009; Filho et al., 2009), amoebic killer (Kachroo et al., 1990), analgesic (Jayashankar et al., 2009; Amir and Shikha, 2004), antiviral and anticancer (Aboraia et al., 2006; Bhat et al., 2004), genotoxic (Maslat et al., 2004), anticonvulsant (Zarghi et al., 2008, Ali et al., 2004), antiproliferative (Akhilesh et al., 2009), antifungal (Zuhair et al., 2008), cardiovascular (Bankar et al., 2009), Antihypertensive (Ghania and Ullah, 2010), antiangiogenic (Abadi et al., 2003), monoamine oxidase (MAO) inhibitor (Shaoyong et al., 2008), insecticide (Mohan et al., 2004; Cao et al., 2002) antimycobacterial (Jha et al., 2009), antiasthymatic (Pandeya et al., 2000). Also, it was stated that oxadiazole derivatives were used as antitumor, anti-HIV, protease and anti-tyrosinase inhibitors (Kim et al., 2004; El-Emam et al., 2004; Rostom et al., 2003; Zarghi et al., 2005; Khan et al., 2005). In recent years, the importance of antioxidants against many diseases has increased enormously. With the discovery of free radicals, cancer, diabetes, heart diseases, autoimmune diseases, neurodegenerative diseases, etc. It has been associated with many diseases.

In the study conducted by Palaska et al., 1-acylthiosemicarbazide, 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole-3-thione derivatives were used to reduce fever and stomach pain (ulcer, gastritis). It has been found to have a healing effect. In addition, no side effects were found in these synthesized compounds (Palaska et al., 2002).

In this study, it was aimed to synthesize new 1,3,4-oxadiazole derivative compounds containing heterocyclic ring, which are considered as potential biological active substances, and to investigate their antioxidant activities.

## 2. Materials and Methods

### 2.1. General

Shimadzu UV Mini-1240 model UV-VIS Spectrophotometer was used for absorbance measurements. pH meter Butech, precision balance Sartorius, magnetic stirrer Chiltern Hotplate HS 31, vortex Velp Scientifica, shaking water bath Memmert, sonic water bath Selectra brand were used.

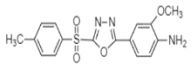
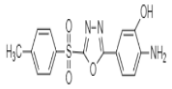
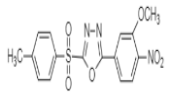
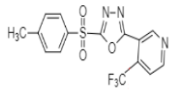
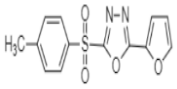
### 2.2. General Method for the Synthesis of 1,3,4-Oxadiazole Compounds

4-methylphenylsulfonylhydrazide (0.01 mol) and different aromatic carboxylic acids (0.01 mol) were refluxed with a phosphoroxychloride solution (10 mL) for 10 hours. After the reaction was complete (controlled by TLC), the reaction mixture was poured into ice water with cooling at room temperature and neutralized with

sodium bicarbonate solution. Then, the product was extracted with ethyl acetate, washed with water (2 x 10 mL) and dried with sodium sulfate, removing the solvent in vacuo. The final product was purified using column chromatography.

The open structures and naming of the compounds synthesized in this study are given in Table 1.

**Table 1.** Synthesized oxadiazole compounds (**1-5**).

| Compounds | Chemical Structure | Systematic Name |
|---|---|---|
| **1** |  | 2-(4-amino-3-methoxyphenyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole |
| **2** |  | 2-(4-amino-3-hydroxyphenyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole |
| **3** |  | 2-(3-methoxy-4-nitrophenyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole |
| **4** |  | 2-(4-trifluoromethylpyridyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole |
| **5** |  | 2-(2-furyl)-5-(4-methylphenyl-sulfonyl)-1,3,4-oxadiazole |

***2-(4-amino-3-methoxyphenyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole (1):*** Yield (2.38g, 69%), M.p. 218-219 °C; Proton Spectrum: 2.31 (s, 3H, Aromatic-$CH_3$), 3.34 (s, 3H, $OCH_3$), 6.23 (s, 2H, $NH_2$), Ar–H [7.26 (d, 2H, *J*=7.94 Hertz), 7.41 (d, 1H, *J*=7.45 Hertz), 7.54 (s, 1H), 7.70 d, 2H, *J*=8.10 Hertz), 7.83 (d, 1H, *J*=7.45 Hertz]; Carbon Spectrum: 153.62, 151.46 (2C=N), Ar–C [143.51 (2CH), 139.20 (C), 137.46 (2 CH), 136.12 (C), 134.77 (C), 131.00 (CH), 129.02 (CH), 127.66 (C), 123.35 (CH), 16.48 (C)], 41.02 ($OCH_3$), 21.09 (Ar-$CH_3$). ($C_{16}H_{15}N_3O_4S$); Elemental Analysis % (Calculated / Found): C: 55.64 (55.91); H: 4.38 (4.29); N: 12.17 (12.86).

***2-(4-amino-3-hydroxyphenyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole (2):*** Yield (2.08g, 63%), M.p. 228-229 °C; Proton Spectrum: 2.35 (s, 3H, Ar-$CH_3$), 6.25 (s, 2H, $NH_2$), Ar–H [7.22 (d, 2H, *J*=7.94 Hertz), 7.38 (d, 1H, *J*=7.53 Hertz), 7.54 (s, 1H), 7.73 (d, 2H, *J*=8.10 Hertz), 7.80 (d, 1H, *J*=7.53 Hertz], 10.36 (s, 1H, OH); Carbon Spectrum: 151.02, 150.00 (2C=N), Ar–C [144.12 (2CH), 139.90 (C), 138.00 (2CH), 137.44 (C), 134.53 (C), 132.58 (CH), 129.15 (CH), 126.66 (C), 122.78 (CH), 115.89 (C)], 21.48 (Ar-$CH_3$). ($C_{15}H_{13}N_3O_4S$); Elemental Analysis % (Calculated / Found): C: 54.38 (54.46); H: 3.95 (3.82); N: 12.68 (12.59).

***2-(3-methoxy-4-nitrophenyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole (3):*** Yield (2.21g, 59%), M.p. 192-193°C; Proton Spectrum: 3.44 (s, 3H, $OCH_3$), Ar–H [7.21 (d, 2H, *J*=7.94 Hertz), 7.51 (d, 1H, *J*=7.92 Hertz), 7.60 (s, 1H), 7.77 d, 2H, *J*=8.10 Hertz), 7.90 (d, 1H, *J*=7.92 Hertz]; Carbon Spectrum: 152.67, 150.31 (2C=N), Ar–C [139.97 (2CH), 137.44 (C), 135.00 (2CH), 134.89 (C), 133.20 (C), 131.56 (CH), 128.72 (CH), 125.93 (C), 121.45 (CH), 113.56 (C)], 21.36 (Ar-$CH_3$), ($C_{16}H_{13}N_3O_6S$); Elemental Analysis % (Calculated / Found): C: 51.20 (51.23); H: 3.49 (3.42); N: 11.19 (11.23).

***2-(4-trifluoromethylpyridyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole (4):*** Yield (3.14g, 85%), M.p. 228-229 °C; Proton Spectrum: 2.35 (s, 3H, Ar-$CH_3$), Aromatic–H [7.14 (d, 2H, *J*=7.94 Hertz), 7.49 (d, 1H, *J*=8.42 Hertz), 7.63 (d, 1H, *J*=8.42 Hertz), 7.80 (s, 1H, *J*=7.45 Hertz), 7.90 (d, 2H, *J*=8.10 Hertz]; Carbon Spectrum: 154.00, 152.73 (2C=N), Ar–C [138.67 (2CH), 137.00 (CH), 136.44 (2CH), 136.13 (C), 134.96 (C), 133.18 (CH), 132.48 (C), 117.89 (CH), 113.71 (C)], 22.47 (Ar-$CH_3$), ($C_{15}H_{10}F_3N_3O_3S$); Elemental Analysis % (Calculated

/ Found): C: 48.78 (48.82); H: 2.73 (2.71); N: 11.38 (11.36).

***2-(2-furyl)-5-(4-methylphenylsulfonyl)-1,3,4-oxadiazole (5):*** Yield (1.89g, 65%), M.p. 163-164°C; Proton Spectrum: 2.40 (s, 3H, Ar-$CH_3$), Aromatic–H [7.38 (d, 2H, *J*=7.94 Hertz), 7.43 (d, 1H, *J*=7.54 Hertz), 7,70 (m, 1H), 7.83 (d, 1H, *J*=8.45 Hertz), 7.93 (d, 2H, *J*=8.10 Hertz]; Carbon Spectrum: 153.12, 151.68 (2C=N), Ar–C [138.45 (2CH), 137.36 (C), 136.20 (2CH), 134.18 (CH), 128.87 (CH), 125.60 (C), 121.40 (CH), 119.17 (C)], 23.00 (Ar-$CH_3$), ($C_{13}H_{10}N_2O_4S$); Elemental Analysis % (Calculated / Found): C: 53.79 (53.82); H: 3.47 (3.44); N: 9.65 (9.59).

### 2.3. Antioxidant Activity Assays

Stock solutions were prepared by dissolving oxadiazole compounds in dimethyl sulfoxide (DMSO). Prior to, antioxidant activities were determined by making certain dilutions from the prepared stock solutions.

#### 2.3.1. Assay of DPPH Radical Scavenging Activity

The DPPH radical scavenging activity of the samples was measured using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical according to the method developed by Brand-Williams et al. (Brand Williams et al., 1995). The solution of DPPH in methanol was prepared daily at a concentration of 20 mg/L. 0.75 mL of sample or standard solution (250-1000 µg/mL) was added onto 1.5 mL DPPH solution. After 30 minutes in the dark, the absorbance values were read at 517 nm against the blank and calculations were made according to the formula below.

DPPH Radical Scavenging Activity (%) = $[(A_0-A_1) / (A_0)] \times 100$

$A_0$ = Control absorbance value
$A_1$ = Absorbance value of sample or standard

$SC_{50}$ values (the amount of substance required for the compounds to show 50% inhibition effect) abscissa concentration was calculated from the regression equation obtained from the linear part of the curve drawn by applying % radical scavenging activity values to the ordinate.

#### 2.3.2. Assay of ABTS Radical Scavenging Activity

The ABTS scavenging activity of the samples was determined according to the method developed by Arnao (Arnao et al., 2001). Solutions of 7.4 mM ABTS (2,2'-azino-bis (3-ethylbenzenothiazoline-6-sulfonic acid) and 2.6 mM potassium persulfate in water were mixed and kept in the dark for 12-16 hours at room temperature. 1 mL of this mixture was taken and 60 mL of methanol was added on it and the absorbance of this solution was read against methanol at 734 nm spectrophotometer. 2850 µL of the prepared ABTS solution with methanol was taken and 150 µL of the sample or standard solution (250-1000 µg/mL) was added. After being kept in the dark for 2 hours, absorbance values against blank were read at 734 nm. Calculations were made according to the formula below.

ABTS Radical Scavenging Activity (%) = $[(A_0-A_1) / (A_0)] \times 100$

$A_0$ = Control absorbance value
$A_1$ = Absorbance value of sample or standard

$SC_{50}$ values were calculated as in DPPH method.

### 2.3.3. Assay of Ferric Reducing Antioxidant Power

The Ferric reducing power of the samples was determined by Oyaizu method (Oyaizu, 1986). Each sample or standard substance with a concentration range of 250-1000 µg/mL was added 1% potassium ferricyanide in 0.2 M phosphate buffer with pH 6.6 and incubated in a water bath at 50°C for 30 minutes. After the incubation, 10% TCA was added and centrifuged at 3000 rpm for 10 minutes. It was taken from the upper phase of the solution, 0.1% $FeCl_3$ was added and the absorbance values against blank were read at 700 nm. The results were interpreted as an absorbance concentration table (Table 2).

## 3. Results and Discussion

The reaction mechanism of the synthesized compounds is shown in Figure 1.

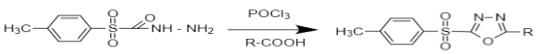



**Figure 1.** Synthesis scheme of 2- (4-methylphenylsulfonyl)-5-aryl-1,3,4-oxadiazole compounds

The original compounds were obtained by refluxing for 10 hours with 4-methylphenylsulfonylhydrazide (0.01 mol) and phosphoroxychloride solution (10 mL) of different aromatic carboxylic acids (0.01 mol). The carboxylic acids used are; 4-amino-3-methoxybenzoic acid (1), 4-amino-3-hydroxybenzoic acid (2), 3-methoxy-4-nitrobenzoic acid (3), 4- (trifluoromethyl) -pyridine-3-carboxylic acid (4) and furan-2-carboxylic acid (5). The structures of the compounds were verified by $^1H$ NMR, $^{13}C$-NMR and elemental analysis data.

DPPH is often used as a reagent to evaluate the free radical scavenging efficiency of antioxidant substances (Oyaizu, 1986). DPPH radical scavenging activity of 2,5-disubstituted-1,3,4-oxadiazole derivatives is presented in Table 2. BHT (Butylated hydroxy toluene) was used as the standard antioxidant in the study. All compounds tested showed DPPH free radical scavenging activity. Their comparable scavenging activities are expressed as $SC_{50}$ values in Table 2. Among all the oxadiazole derivatives tested, the compound **1** the highest activity ($SC_{50}$ = 4056 ± 186.2 µM); Compound **4** showed the lowest activity ($SC_{50}$ = 9217 ± 261.7 µM).

**Table 2.** The antioxidant activities of 2,5-disubstitue-1,3,4-oxadiazole derivatives and standards (**1-5**).

| Compounds | DPPH $SC_{50}$ (µM)* | ABTS $SC_{50}$ (µM)* | Reducing Power Absorbance* |
|---|---|---|---|
| | | | 0.312±0.004 |
| **1** | 4056±186.2 | 1892±7.45 | 0.386±0.006 |
| | | | 0.497±0.004 |
| | | | 0.411±0.007 |
| | | | 0.105±0.004 |
| **2** | 8539±317.6 | 15176±92.18 | 0.138±0.026 |
| | | | 0.147±0.018 |
| | | | 0.165±0.042 |
| | | | 0.045±0.003 |
| **3** | 8214±184.8 | 14521±181.2 | 0.117±0.008 |
| | | | 0.163±0.012 |
| | | | 0.198±0.021 |
| | | | 0.069±0.006 |
| **4** | 9217±261.7 | 17542±212.5 | 0.076±0.007 |
| | | | 0.086±0.007 |
| | | | 0.118±0.017 |
| | | | 0.136±0.004 |
| **5** | 7318±56.13 | 13371±132.7 | 0.159±0.006 |
| | | | 0.243±0.008 |
| | | | 0.271±0.010 |
| | | | 0.116±0.024 |
| BHT | 216.24±23.13 | 317.11±28.82 | 0.183±0.012 |
| | | | 0.249±0.015 |
| | | | 0.387±0.014 |

*Values were the means of three replicates ± Standard Deviation (SD).

ABTS radical scavenging activity values of 1,3,4-oxadiazole derivatives are given in Table 2. ABTS radical scavenging activity increased with increasing concentration. Lower $SC_{50}$ values mean higher ABTS radical scavenging capability. The highest and lowest activity was observed in

compound **1** ($SC_{50}$ = 1892 ± 7.45 μM) and compound **3** ($SC_{50}$ = 17542 ± 212.5 μM), respectively. All compounds showed lower ABTS radical scavenging activity than BHT ($SC_{50}$= 317.11±28.82 μM).

The reducing powers of oxadiazole derivatives were examined at different concentrations (250-1000 μg/mL) and the results were compared with the standard antioxidant BHT (Table 2). In this study, the reducing power of the synthesized oxadiazole compounds increased with increasing sample concentration. The highest and lowest activity was observed in compounds **1** and **4**, respectively, at the same concentration.

According to these data, it can be said that the presence of electron donor groups on both sides of the 1,3,4-oxadiazole ring increases the activity while the electron withdrawing groups decrease the activity. In a study, Zheng et al. reported that ABTS radical scavenging activity $SC_{50}$ values ranged from 0.07 to 17.2 mM (Zheng et al., 2020). The results in our article are consistent with these values. Maa et al. investigated DPPH and ABTS radical scavenging activity, ferric reducing power activities in a study they conducted with 1,3,4-oxadiazoles and reported that most oxadiazole compounds in the series had better antioxidant activity than standard antioxidants (Maa et al., 2013).

## 4. Conclusion and Recommendations

The findings obtained in this study showed that the new series of 2,5-disubstituted-1,3,4-oxadiazole derivatives (**1-5**) have antioxidant activity. As a result, it is thought that these new derivatives can be used as an antioxidant source in industrial areas such as pharmaceuticals, cosmetics and agriculture. Since the increase of free radicals in metabolism leads to cell damage, from cardiovascular diseases to respiratory and excretory system disorders. It can increase susceptibility to a wide variety of ailments, from gastrointestinal diseases to infertility. In order to prevent these diseases, it should be ensured that oxidant substances that cause the formation of free radicals are in balance with antioxidants. With a balanced diet and adequate intake of antioxidants, it may be possible to get rid of the negative effects of free radicals. Therefore, antioxidants can be recommended as an important defense mechanism for reducing the risk of oxidant-induced diseases and for a better quality and longer life.

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