



**Makale / Research Paper**

**Synthesis, Characterization, and Antioxidant Activities of New 1,3,4-Thiadiazoles Based on Benzoic Acid**

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Received/Geliş: 13.09.2020

Accepted/Kabul: 21.10.2020

**Abstract:** *N*-aryl-1,3,4-thiadiazole derivatives were obtained by cyclization reaction of benzoic acid and *N*-aryltiosemicarbazides in the presence of phosphorous oxychloride (POCl<sub>3</sub>). FT-IR, <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR, spectroscopic methods, and elemental analysis were used to elucidate the identification of the synthesized molecules. The *in vitro* antioxidant activity of the synthesized molecules was analyzed with the 1,1-diphenyl-2-picryl hydrazyl (DPPH) free-radical-trapping process. IC<sub>50</sub> values of these molecules were measured from 25.17 to 43.55 μM. Among the synthesized compounds, compound II had the best antioxidant activity. Moreover, this work explained the structure-activity relationship of the obtained molecules with different substituents in radical trapping reactions.

**Keywords:** 1,3,4-Thiadiazoles; DPPH; structure-activity relationship; spectroscopic methods.

**Benzoik Asit Temelli Yeni 1,3,4-Tiyadiazollerin Sentezi, Karakterizasyonu ve Antioksidan Aktiviteleri**

**Öz:** *N*-aril-1,3,4-tiyadiazol türevleri benzoik asit ile *N*-ariltiyosemikarbazitlerin fosforoksiklorür varlığında halkalaşma tepkimesi sonucu elde edildi. Sentezlenen bileşiklerin yapısı FT-IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR, spektroskopik yöntemler ve elementel analiz ile aydınlatılmıştır. Sentezlenen bileşiklerin antioksidan özellikleri laboratuvar ortamında DPPH yöntemi ile analiz edildi. IC<sub>50</sub> değerleri 25.17-43.55 μM arasında değişmektedir. Bileşik II, sentezlenen bileşikler arasında en iyi antioksidan aktivite göstermiştir. Ayrıca bu çalışmada, farklı fonksiyonel gruplara sahip bileşiklerin radikal yakalama tepkimelerinde yapı-aktivite ilişkisi açıklandı.

**Anahtar kelimeler:** 1,3,4-Tiyadiazoller, DPPH, yapı-aktivite ilişkisi, spektroskopik yöntemler.

**1. Introduction**

Heterocyclic compounds are one of the most significant fields of synthetic organic chemistry. Thiadiazole is a heterocyclic compound covering both two nitrogen atoms and sulfur atom as part of the five-membered aromatic ring [1]. 1,3,4-Thiadiazole compounds have shown numerous medicinal properties and biological activities such as antituberculosis [1], anticancer [2], urease inhibitory [3], anti-inflammatory [4], antibacterial [5], antimicrobial [6], anti-leishmanial [7], and antioxidant activity [3,8–10]. Furthermore, they are largely used in agricultural applications, such as herbicides, fungicides, pesticides, insecticides, and bactericides [11].

The significance of free radicals and reactive oxygen species (ROS) in the pathogenicity of various diseases such as metabolic disorders, reperfusion damage, inflammatory diseases, cellular aging, and cancer has attracted substantial consideration [12,13]. Many of these diseases have occurred

*Bu makaleye atf yapmak için*

Yakan, H, "Benzoik Asit Temelli Yeni 1,3,4-Tiyadiazollerin Sentezi, Karakterizasyonu ve Antioksidan Aktiviteleri" El-Cezeri Fen ve Mühendislik Dergisi 2021, 8(1); 155-163.

*How to cite this article*

Yakan, H, "Synthesis, Characterization, and Antioxidant Activities of New 1,3,4-Thiadiazoles Based on Benzoic Acid" El-Cezeri Journal of Science and Engineering, 2021, 8(1); 155-163.

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with the bulking of free radicals in human bodies. Therefore, antioxidants have been noted to play a key role in preserving humans from many potentially serious diseases [12].

In consideration of these pieces of proof, 1,3,4-thiadiazole derivatives are significant not only in possessing biological activities but also in pharmacological chemistry. In this study, *N*-substituted-aryl-1,3,4-thiadiazole derivatives were prepared through the reaction of benzoic acid, *N*-substituted-aryl-thiosemicarbazides, and phosphorous oxychloride ( $\text{POCl}_3$ ). The synthesized compounds were new. The structures of the compounds were characterized by FT-IR,  $^1\text{H-NMR}$ , and  $^{13}\text{C-NMR}$  spectroscopic techniques, and elemental analysis. Antioxidants are vital reagents because they can trap free radicals and diminish the destruction effects in our bodies. Thus, the *in vitro* antioxidant activity of all the structures were tested by the DPPH· free radical scavenging method. The activity results were presented with calculated  $\text{IC}_{50}$  values. Furthermore, the present paper clarified the structure-activity relationship of the obtained molecules with different substituents in radical scavenging-reactions.

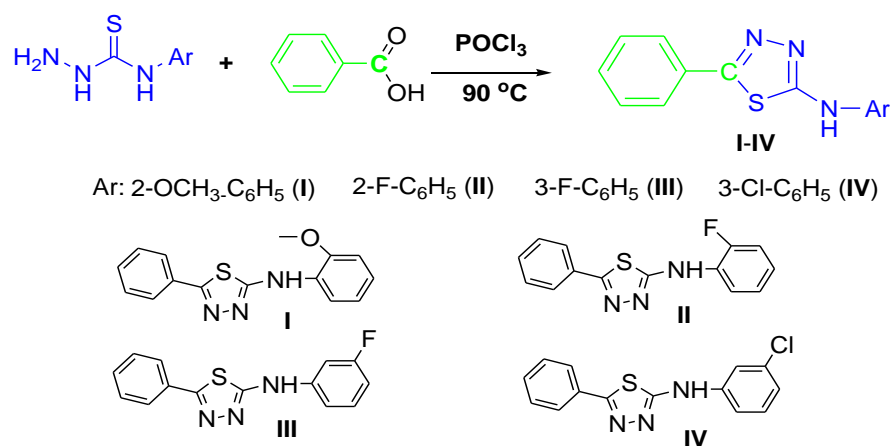
## 2. Experimental Methods

### 2.1. Materials

All the substances were used without further purification and bought from Merck, Sigma, or Aldrich Chemical Company. The spectroscopic grade was used as the solvent. The elemental analysis was measured on Eurovector EA3000-Single. Melting points were recorded with a Stuart SMP30 melting point apparatus and were not corrected. A Bruker Alpha FT-IR spectrometer was used for IR spectra. A Bruker Avance DPX-400 (400 MHz) in  $\text{DMSO-d}_6$  spectrophotometer was used for  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. A Shimadzu Pharmaspec 1700 UV-visible spectrophotometer was used for absorption measurements. The splitting patterns are indicated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplied).

### 2.2. Synthesis

A mixture of *N*-arylthiosemicarbazides ( $n$  mol) and benzoic acid ( $n$  mol) was chilled in a refrigerator and phosphorous oxychloride ( $3n$  mol) was added drop-wise by stirring. Then, refluxing was continued  $90^\circ\text{C}$  for 4 h. After completion of the reaction, the mixture was cooled to room temperature, poured into ice-cold water with stirring, and then neutralized with ammonia. The precipitated product was filtered, washed with water, and crystallized in a suitable solvent. New 1,3,4-thiadiazoles were synthesized according to the method [5] illustrated in Figure 1.



**Figure 1.** General synthesis pathway of 1,3,4-thiadiazole compounds.

### 2.3. Antioxidant Activity

To determine antioxidant activity of the synthesized compounds was used previously reported method with slight modifications by Brand-Williams [14]. 1.0 mL of DPPH solution (0.1 mM) was mixed with compound solutions in acetone (3.0 mL) of different concentrations. After incubating in dark at 30 min, the absorbance of the mixture was monitored at 517 nm [15]. Butylated hydroxyanisole (BHA) were used as standards. The lower absorbance in the reaction indicates a higher free radical (DPPH $\cdot$ ) scavenging property. The sample compounds were calculated percentage inhibition of the free radical concentration and subsequently compared to the standard. The percentage of inhibition of radical scavenging activity was calculated by using the formula (Equation 1) shown below:

$$\text{Radical scavenging activity (\%)} = [(A_c - A) / A_c \times 100] \quad (1)$$

where  $A_c$  is the absorbance of the control and  $A$  is the absorbance of the test compound or standard [16].

Besides,  $IC_{50}$  values were calculated from the calibration curve. The  $IC_{50}$  value is determined as the concentration of all compounds required obtaining half-maximum inhibition, and the low  $IC_{50}$  value shows more antioxidant activity [17].

## 3. Results and Discussion

### 3.1. Physical Properties

The current experimental results for the physical data, melting points, yields, and elemental analyses are presented in Table 1.

**Table 1.** The physical data for the synthesized compounds

Comp.	M.P. (°C)	Colour	Solubility	Yield (%)	Mol. formula	Calculated			Experimental		
						C %	H %	N %	C %	H %	N %
I	95-96	Light Brown	DMSO (+)	85	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS	63.58	4.62	14.83	63.41	4.55	14.89
II	117-118	Yellow	DMSO (+)	78	C <sub>14</sub> H <sub>10</sub> FN <sub>3</sub> S	61.98	3.72	15.49	61.90	3.76	15.55
III	71-73	Dark Brown	DMSO (+)	72	C <sub>14</sub> H <sub>10</sub> FN <sub>3</sub> S	61.98	3.72	15.49	61.85	3.77	15.52
IV	193-194	Brown	DMSO (+)	83	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> S	58.43	3.50	14.60	58.35	3.53	14.55

### 3.2. IR Spectral Analysis

At the end of the reaction, the -C=O (carbonyl group) vibration on the starting material (carboxylic acid) was neither observed about 1700 cm<sup>-1</sup> nor the -OH stretching band observed at 3450–2820 cm<sup>-1</sup>. Furthermore, asymmetric and symmetric amino group (-NH<sub>2</sub>) peaks of *N*-substituted-aryl-thiosemicarbazides were not observed at 3550–3150 cm<sup>-1</sup>. Instead, new peaks for the amine group (-NH) stretching vibrations were observed at 3200-3182 cm<sup>-1</sup>, vibration peaks for -C=N group on the thiadiazole ring were observed at 1608-1543 cm<sup>-1</sup>, the -C-N group peaks were observed at 1290-1219 cm<sup>-1</sup>, and -C-S vibrations from the thiadiazole ring were observed at 714-678 cm<sup>-1</sup> for the products. The other remarkable very strong vibrational bands were in the spectrum of the obtained compounds resulting from the -C-O, Ar-F, and Ar-Cl functions, respectively. The -C-O group vibration of compound I was observed at 1246 cm<sup>-1</sup> as shown in Figure 2. For compounds II and III cm<sup>-1</sup>, Ar-F stretching vibrations were shown at 1089 and 1101 cm<sup>-1</sup>, Ar-Cl stretching

vibration of compound IV was observed at  $878\text{ cm}^{-1}$ . These results agree with the values of previously reported for similar compounds [6,18,19]. Table 2 lists the key IR stretching vibrations of the synthesized compounds.

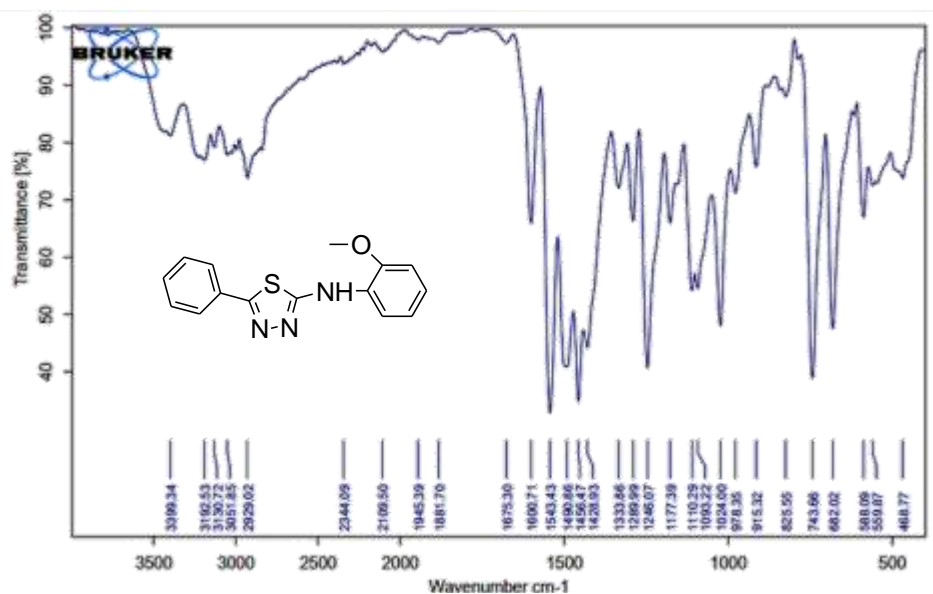


Figure 2. IR spectrum of compound I

Table 2. IR vibration frequencies of the synthesized compounds

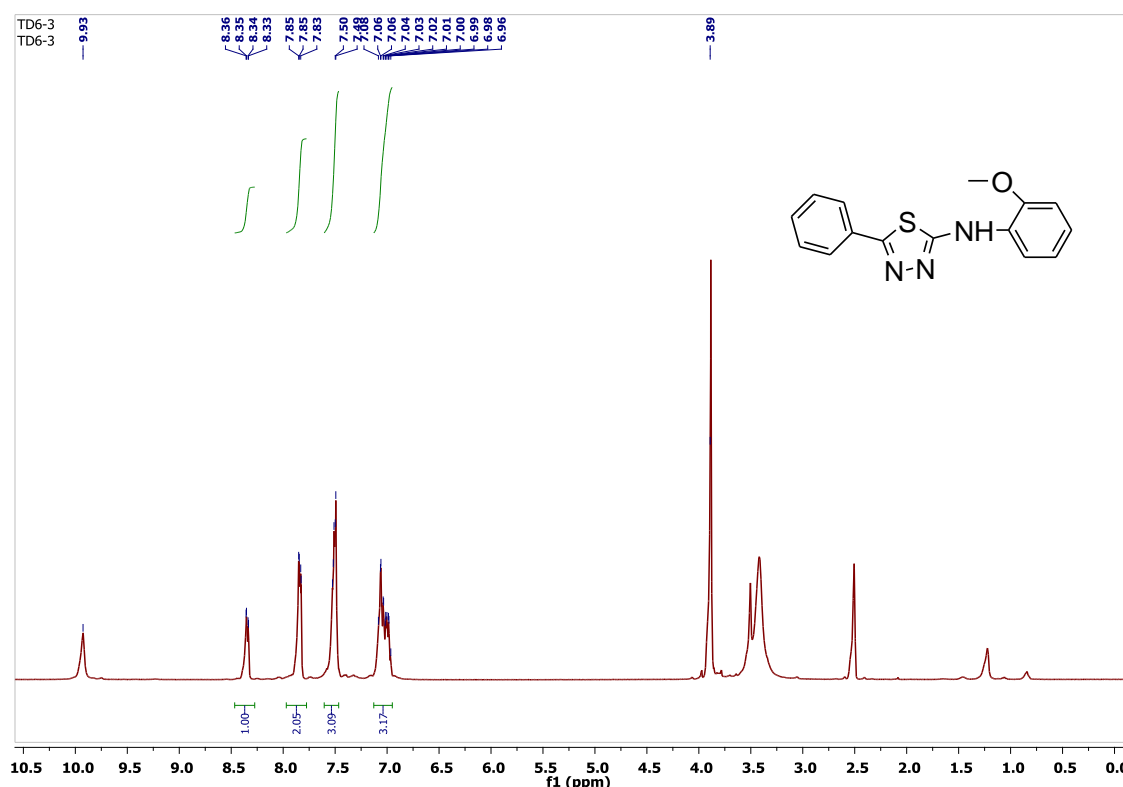
Compounds	$\nu_{\text{NH}}$ stretching	$\nu_{\text{C-H}}$ (Aromatic)	$\nu_{\text{C=N}}$ (thiadiazole)	$\nu_{\text{C-N}}$	$\nu_{\text{C-S}}$	Specific Vib.
I	3192	3130	1601, 1543	1290	682	Alip.CH: 2929 C-O: 1246
II	3182	3130	1605, 1598	1243	687	Ar-F:1089
III	3200	3044	1608, 1568	1241	678	Ar-F:1101
IV	3185	3046	1587, 1554	1219	714	Ar-Cl:878

### 3.3. $^1\text{H}$ NMR Analysis

The  $^1\text{H}$  NMR spectra of the synthesized compounds were detected in  $\text{DMSO-d}_6$  and the chemical shifts are given in Table 3.

Table 3.  $^1\text{H}$  NMR data of compounds for I–IV, ( $\delta$ /ppm).

Comp.	H1, H2, H2'	H3, H3'	H4	H5	H6	H7	H8	NH
I	7.50-7.49 (3H, dd)	7.85-7.83 (2H, d)	OMe:3.89 (3H, s)	8.36-8.33 (1H, dd)		7.08-6.96 (3H, m)		9.93
II	7.52-7.50 (3H, dd)	7.87-7.85 (2H, d)	-	8.44-8.40 (1H, dd)	7.32-7.22 (2H, m)		7.10-7.05 (1H, dd)	10.38
III	7.53-7.51 (3H, dd)	7.89-7.87 (2H, d)	6.87-6.82 (1H, dd)	-	7.40-7.32 (2H, m)		7.74-7.71 (1H, m)	10.81
IV	7.53-7.52 (3H, dd)	7.89-7.87 (2H, d)	7.97-7.96 (1H, s)	-	7.49-7.47 (1H, dd)	7.42-7.37 (1H, m)	7.09-7.06 (1H, dd)	10.80



**Figure 3.**  $^1\text{H}$  NMR spectrum of compound I

For compounds I-IV, aromatic proton signals of the substituted aryl region were detected at 8.44-6.96 ppm, and aromatic proton signals of the phenyl ring were showed at 7.89-7.49 ppm. The  $-\text{NH}$  proton signals were observed as singlets in the range of 10.81-9.93 ppm for all the compounds. As seen in compound I, while aromatic protons (H1-H3) of phenyl ring were observed at 7.85-7.49 ppm, aromatic protons (H4-H8) of substituted aryl ring were observed at 8.36-6.96 ppm. The H1 and H2 proton detected doublet of doublets peaks at 7.50-7.49 ppm. The H3 proton coupled to the H2 proton and detected doublet peaks at 7.85-7.83 ppm. The  $-\text{OCH}_3$  proton signals were observed as a singlet in the range of 3.89 ppm; the  $-\text{NH}$  proton signals were observed as a singlet 9.93 ppm in Figure 3. DMSO- $d_6$  and water in DMSO (HOD,  $\text{H}_2\text{O}$ ) signals were seen around at 2.50 (quintet) and 3.30 (variable, based on the solvent and its concentration) ppm, respectively [20]. These observed are agree with the values of earlier reported for similar compounds [6,18,19].

### 3.4. $^{13}\text{C}$ NMR Analysis

The  $^{13}\text{C}$  NMR spectra of the synthesized compounds were detected in DMSO- $d_6$  and the chemical shifts are given in Table 4. The aromatic C signals from the substituted aryl ring (C7-C12) were observed between 164.5 and 104.7 ppm for all compounds, those from the phenyl ring (C1-C4) were observed between 134.0 and 121.2 ppm, and from the thiadiazole ring (C5 and C6) were observed between 165.2 and 158.6 ppm.

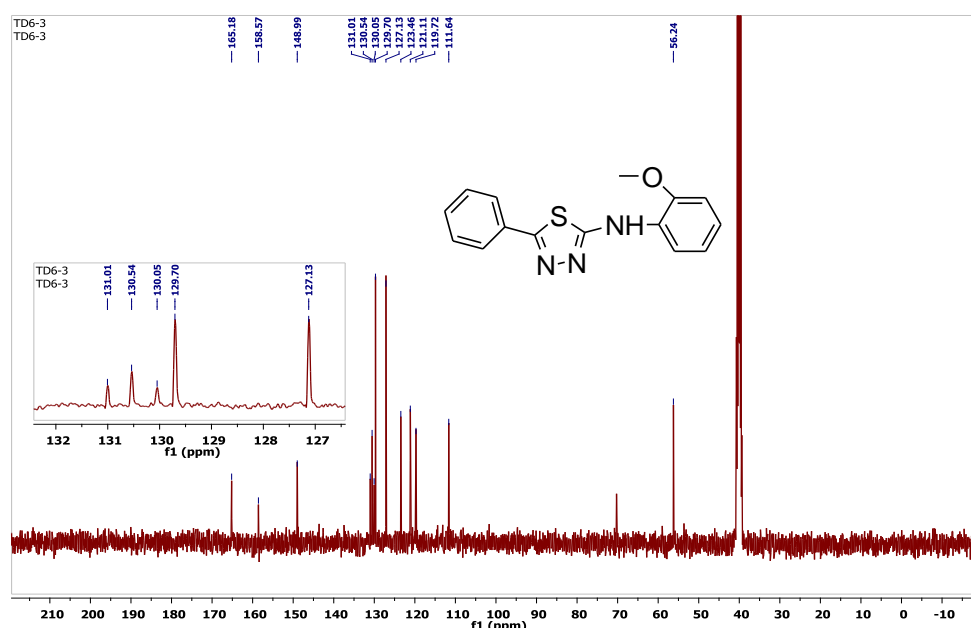
In compound I, the methoxy carbon atoms ( $-\text{OCH}_3$ ) resonated at 56.2 ppm. The C7-C12 carbon atoms were affected by both methoxy ( $-\text{OCH}_3$ ) and amino ( $-\text{NH}$ , C7) groups. The C8 carbon atom was shifted down-field (high values of  $\delta$ ) relative to the signal of benzene (128.5 ppm) due to the presence of 2- $\text{OCH}_3$  (149.0 ppm). The C6 signal was up-field (low values of  $\delta$ ) compared to the C5 due to the increase in the electron density from the mesomeric effect of the amino group ( $-\text{NH}$ ).

**Table 4.**  $^{13}\text{C}$  NMR data of the obtained compounds, ( $\delta/\text{ppm}$ )

Comp.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
I	129.7	130.1	127.1	131.0	165.2	158.6	130.5	149.0	111.6	121.1	123.5	119.7
II <sup>a</sup>	121.2	128.1	127.2	129.7	164.7	159.2	130.76 130.75	153.7 151.3	115.8 115.6	125.25 125.21	128.9	123.7 123.6
III <sup>a</sup>	129.7	130.6	127.3	130.8	161.8	158.7	142.6 142.5	105.0 104.7	164.24 164.15	108.9	131.2	113.86 113.84
IV	130.9	131.2	127.3	134.0	164.1	158.8	130.6	117.4	142.2	122.0	129.8	116.4

<sup>a</sup> C7-C12 atoms were observed split into doublets by interacting with the atomic nucleus of F.

The C5 was observed at 165.2 ppm, whereas C6 was observed between 158.6 ppm as shown in Figure 4. Additionally, in compounds II and III, the C atoms (for C7-C12) were also split into doublets due to interacting with the atomic nucleus of F. These results were shown 13 different resonances in good agreement with the proposed structure and are consistent with similar compounds [6,18,19].

**Figure 4.**  $^{13}\text{C}$  NMR spectrum of compound I

### 3.5. Evaluation of Antioxidant Activity

Antioxidants are substances that considerably retarding inhibiting or preventing oxidation of a substrate at low concentrations and have numerous physiological roles in the human body [21,22]. Antioxidant structures can react with DPPH free radicals by giving hydrogen atoms or by electron donation via a free radical attack on these molecules [23,24]. According to this reaction ( $\text{DPPH}^{\bullet} + \text{R-NH} \rightarrow \text{DPPH-H} + \text{R-N}^{\bullet}$ ), weaker hydrogen bonds are essential for higher antioxidant activity in a compound. The strength of these hydrogen bonds is proportional to electron density. Thus, the structure of the obtained products and electronic effects of groups/substituents in structures plays a significant role in antioxidant activity [25,26]. Subsequently, antioxidant activities depend on two

things: the first being the capacity/skill of compounds to lose hydrogen atoms, and the second being the stability of the formed radical [25-27].

**Table 5.** IC<sub>50</sub> values for the compounds

Compounds	DPPH activity IC <sub>50</sub> (μM)*
<b>I</b>	43.55 ± 0.65
<b>II</b>	25.17 ± 0.52
<b>III</b>	30.43 ± 0.46
<b>IV</b>	37.87 ± 0.72
<b>BHA</b>	20.83 ± 0.37

\*IC<sub>50</sub> = the concentration (μM) exhibiting 50% inhibition of DPPH radical. Values are expressed as means (n = 3).

In the present work, IC<sub>50</sub> values were calculated at the end of DPPH analysis for the obtained products and BHA as shown in Table 5. The IC<sub>50</sub> values of tested products were between 25.17 and 43.55 μM. The obtained products exhibited low activity compared to a standard BHA. Compound II had the strongest antioxidant activity among the synthesized compounds and followed the order BHA>II>III>IV>I. Compound II has a fluorine atom (-F) which had strong electron-withdrawing through inductive effect, reducing electron density in the structure, which reasons easier loss of the hydrogen atom. Compound IV has lower activity than compounds II and III due to a fluorine atom is stronger electron-withdrawing than a chlorine atom. Compound I (-OCH<sub>3</sub>) has an electron-donating group, it is exhibited the lowest activity due to increased electron density in the structure with mesomeric effect. That is, the loss of the hydrogen atom in the compound gets difficult.

#### 4. Conclusions

In this study, new 1,3,4-thiadiazole derivatives were prepared in excellent yields of 72–85%. The obtained compounds were elucidated by using IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectroscopic methods and elemental analysis. The *in vitro* antioxidant activities of the compounds were determined by the DPPH free radical scavenging method. IC<sub>50</sub> values of the new compounds ranged from 25.17 to 43.55 μM. Compound II of among the tested molecules showed the best satisfactory antioxidant activity against the DPPH radical. Besides, the structure-activity relationships were studied concerning the presence and types of substituents. As a result, a compound which possesses electron-withdrawing groups has mostly higher antioxidant activity against DPPH free radicals compared to electron-donating groups in structures.

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