



Antioxidant activity of phthalonitrile derivatives bearing different chalcone groups

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Abstract

This work presents the synthesis of four phthalonitrile compounds (3_{a-d}) bearing different chalcone moiety which have biological activities. Phthalonitrile compounds are a considerable pioneer in the synthesis of novel photoactive phthalocyanine derivatives. Antioxidant activity of the new phthalonitrile compounds (3_a and 3_b) and those of one's synthesized previously (3_c and 3_d) have been studied after the determination of their spectroscopic properties. Ferric reducing/antioxidant power (FRAP) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) methods have been used to determine the antioxidant activities of the compounds. According to the DPPH radical scavenging activity values, the antioxidant activity of 4-[3-[(2E)-3-(4-nitrophenyl)prop-2-enoyl]phenoxy]phthalonitrile 3_b is significantly higher than the counterparts.

Keywords: Phthalonitrile, chalcone, DPPH, antioxidant

1. Introduction

Phthalonitrile derivatives are known as phthalocyanine building blocks. They have proper properties for the development of dye-sensitized solar cells [1], usage as imaging probes, and environmental and biological sensing [2]. Their liquid crystal properties are another important research subject [3]. Moreover, phthalonitrile polymers are good components in a wide variety of applications as composite matrices [4], adhesives [5], electronic conductors [6], and solar panels because of having high thermal resistivity [7,8]. Phthalonitrile compounds can have one, two, or four substituents which can be diverse for particular purposes [9,10]. Their synthesis depends on nucleophilic substitution [11]. Organometallic couplings, click reactions, reductions, amidifications which are offer all-purpose functionalization opportunities, making the possible combination of phthalonitrile substitution almost limitless [12-15].

Many plants have a few bioactive substances such as flavonoids [16]. The α , β -unsaturated ketones known as chalcone are coming from the flavonoid family [17]. In recent years, chalcones have been investigated as sensors and biologically active compounds. They have various biological activities such as antioxidant [18], cytotoxic

[19], antiviral [20], antimalarial [21], anti-inflammatory [22], antibacterial [23] and tyrosinase inhibitory [24]. In addition, chalcones are used as initial materials for synthesizing many compounds such as flavones, isoxazoles, quinolinones, thiadiazines, benzothiazepines, benzodiazepines, benzofuranones, etc [25,26].

Internal and external factors exposed in a lifetime, cause the formation of free radicals in the body. The formation of oxygen-centered free radicals such as hydroxyl, superoxide, and hydrogen peroxide, which are named reactive oxygen species (ROS) bring about damages to the human body [27]. Free radicals may induce many diseases such as cardiovascular diseases, cancer, diabetes, neurodegenerative disorders, and many other diseases [28,29]. In addition, free radicals are one of the main causes of disease formation and the aging process in the person [30]. The antioxidant substances protect the body from the detrimental effects of free radicals (ROS). Antioxidants that are considered protective agents are synthetic or natural compounds that lessen the harmful effects of ROS [31,32]. Therefore, there has been increasing interest in potential antioxidative compounds in recent years [33].

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Synthesis of phthalonitrile derivatives with different functional groups increases with their need in new application areas [34]. Thus, in this paper, the phthalonitriles having the chalcone groups with the different substituted groups were obtained. It is thought that the electron-rich structure of chalcones positively contributes to the antioxidant effect of the phthalonitriles. Also, it is thought that the differences in the atoms and positions of the chalcone compounds are changed the antioxidant properties of the phthalonitrile derivatives.

In this study we represented synthesis of phthalonitrile derivatives by nucleophilic aromatic substitution reaction of 4-nitrophthalonitrile with different chalcone compounds. Antioxidant activity of the chalcone substituted phthalonitrile compounds, 4 - {3 - [(2E) - 3 - (4-fluorophenyl)prop-2-enoyl]phenoxy}phthalonitrile 3a, 4 - {3 - [(2E) - 3 - (4-nitrophenyl)prop-2-enoyl]phenoxy}phthalonitrile 3b, 4 - {3 - [(2E) - 3 - (3-fluorophenyl)prop-2-enoyl]phenoxy}phthalonitrile 3c and 4 - {3 - [(2E) - 3 - (3-bromophenyl)prop-2-enoyl]phenoxy}phthalonitrile 3d were investigated. While the characterization of newly synthesized phthalonitriles 3a and 3b are presented in this paper, the characterization of phthalonitrile 3c and 3d were explained in our previous work [35]. The purpose of the present work was to compare the different chalcone substituted phthalonitriles and to study the antioxidant activities of all phthalonitrile derivatives. The novel compounds were characterized by instrumental techniques such as FT-IR, NMR spectroscopy, and mass spectrometry. The antioxidant properties of phthalonitrile compounds 3a, 3b, 3c, and 3d were investigated by using DPPH and FRAP method.

2. Experimental

2.1. Materials and Equipment

All reagents, solvents, and 4-nitrophthalonitrile were obtained from commercial suppliers. Chalcone compounds (1a and 1b) [36] and phthalonitriles (3c and 3d) [35] were prepared according to literature. All reactions were achieved under a dry and nitrogen atmosphere using the Schlenk system. ^{13}C $\{^1\text{H}\}$ NMR spectra were registered on a Bruker AVANCE III 400 MHz NMR spectrophotometer in CDCl_3 . IR spectra were recorded on an FT-IR spectrometer. MALDI-TOF-MS (Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) measurements were carried out on a BRUKER Microflex. The melting point was recorded on a Gallenkamp melting point apparatus. DPPH and Trolox were bought from Sigma-Aldrich.

2.2. Synthesis

2.2.1. General procedure for the synthesis of phthalonitrile compounds 3a and 3b

Chalcone-based phthalonitrile derivatives were produced by the nucleophilic substitution reaction between 4-nitrophthalonitrile with chalcone compounds (2E)-3-(4-fluorophenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one 1a and (2E)-1-(3-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one 1b. Compounds (1a-b) and 4-nitrophthalonitrile (2) were dissolved in dry DMF at 60 °C. Dry K_2CO_3 as a basic catalyst was added to the solution in portion during 2 h. The mixture was stirred under N_2 (g) for 4 days at the same temperature. After 4 days, the reaction mixture was poured into ice-water and stirred at room temperature to yield the product. The reaction pathway of the phthalonitrile derivatives was shown in Figure 1.

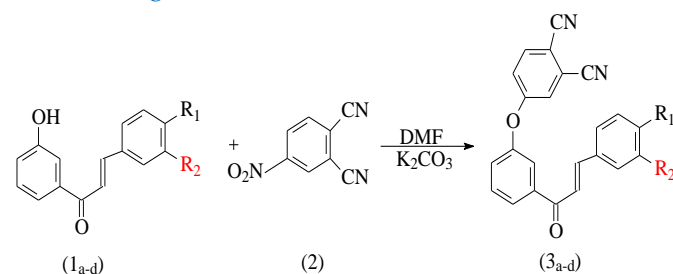


Figure 1. The synthesis route of compounds 3a-d. (3a:R₁=F, R₂=H, 3b:R₁=NO₂, R₂=H, 3c:R₂=F, R₁=H [32], 3d:R₂=Br, R₁=H [32])

2.2.1.1. 4-{3-[(2E)-3-(4-fluorophenyl)prop-2-enoyl]phenoxy}phthalonitrile (3a)

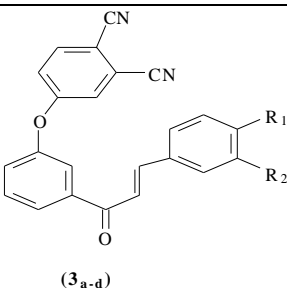
After 3h, the reaction mixture was filtered and washed with water. After washing, the product dried in vacuum over P_2O_5 and recrystallized from methanol to white product. Yield: 1.28 g, (85%), mp= 144-148 °C. IR (ATR), $\nu_{\text{max}}/\text{cm}^{-1}$: 3073 (Ar-H), 2231 ($\text{C}\equiv\text{N}$), 1661 ($\text{C}=\text{O}$), 1576-1480 ($\text{C}=\text{C}$), 1287, 1247-1226 (Ar-O-Ar), 1160, 1089, 957, 831, 802. ^1H NMR (CDCl_3), (δ :ppm): 7.98 (d, $J=8\text{Hz}$, 1H, Ar-H), 7.86-7.75 (m, 3H, Ar-H), 7.69-7.63 (m, 3H, Ar-H), 7.45-7.31 (m, 4H, Ar-H), 7.17 (t, $J=17\text{Hz}$, 2H, =C-H). ^{13}C NMR (CDCl_3), (δ :ppm): 188.64 ($-\text{C}=\text{O}$), 165.58 (C-F), 163.07, 161.24, 154.18, 144.71, 140.83, 135.57, 131.04, 130.61, 130.53, 126.09, 124.83, 121.77, 121.63, 120.90, 120.37, 117.90, 116.40, 116.19, 115.21 ($\text{C}\equiv\text{N}$), 114.80 ($\text{C}\equiv\text{N}$), 109.53. MALDI-TOF-MS, (m/z): Calculated: 368.36; Found: 395.71 [$\text{M}+\text{Na}+4\text{H}$]⁺.

2.2.1.2. 4-{3-[(2E)-3-(4-nitrophenyl)prop-2-enoyl]phenoxy}phthalonitrile (3b)

After the mixture was stirred in 3h, the mixture was washed with 35 ml of CHCl_3 . The organic content was dried over MgSO_4 (magnesium sulfate), filtered, and evaporated. The obtained dark brown oily crude dried in vacuum over P_2O_5 and recrystallized from methanol to brown product. Yield: 0.65 g (44%), mp: 140-142 °C. IR

(ATR), $\nu_{\max}/\text{cm}^{-1}$: 3076 (Ar-H), 2232 (C≡N), 1666 (C=O), 1565-1516 (C=C), 1343, 1276-1247 (Ar-O-Ar), 1090, 953, 853, 695. $^1\text{H NMR}$ (CDCl_3), (δ :ppm): 8.43-8.38 (m, 1H, Ar-H), 8.22-8.16 (m, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 7.90-7.88 (d, $J=8\text{Hz}$, 1H, Ar-H), 7.79-7.75 (m, 3H, Ar-H), 7.51-7.49 (m, 1H, Ar-H), 7.35-7.32 (m, 5H, =CH and Ar-H). $^{13}\text{C NMR}$ (CDCl_3), (δ :ppm): 181.72 (-C=O), 177.56, 169.57, 162.62, 154.35, 149.13, 148.43, 140.85, 139.45, 135.62, 131.16, 130.79, 126.62, 124.22, 123.90, 122.47, 122.14, 121.80, 119.72, 117.98, 115.15 (C≡N), 114.85 (C≡N), 108.98. MALDI-TOF-MS, (m/z): Calculated: 395.37; Found: 391.43 $[\text{M}-4\text{H}]^+$.

Table 1. Structure and chemical data comparison of the compounds 3a-d



Compound	R ₁	R ₂	Formula	Melting point (°C)	Yield (%)
3a	-F	-H	C ₂₃ H ₁₃ N ₂ O ₂ F	144-149	85
3b	-NO ₂	-H	C ₂₃ H ₁₃ N ₃ O ₄	140-144	45
3c	-H	-F	C ₂₃ H ₁₃ N ₂ O ₂ F	98-101	60 [32]
3d	-H	-Br	C ₂₃ H ₁₃ N ₂ O ₂ Br	76-79	60 [32]

2.3. Antioxidant activities of new phthalonitrile derivatives using DPPH, and FRAP assay

The free radical scavenging activities of new phthalonitrile derivatives were measured using the method described by Molyneux with some modification. A 100 μM solution of DPPH in methanol was used. For each sample, 0.75 mL of the samples at six different concentrations were mixed with 0.75 mL of the DPPH solution. The decrease in absorbance at 517 nm was measured after 2 hours. The SC_{50} (mg sample per mL), described as the amount of antioxidant required to reduce the initial DPPH concentration by 50%, was calculated from the results obtained.

2.3.1. FRAP assay

The total antioxidant potential of each sample solution was defined using the FRAP assay as a measure of antioxidant power [37]. Briefly, the FRAP reagent was prepared by mixing acetate buffer (300 μM , pH3.6) a solution of 10 μM TPTZ in 40 μM HCl and 20 μM FeCl_3 . 100 μL of each sample and 3 mL of the reagent were added to each mixed. The absorbance value was taken at 593 nm after 20 min. The standard curve was prepared using different concentrations of $\mu\text{mol FeSO}_4 \cdot 7\text{H}_2\text{O/g}$ and the results were expressed as $\mu\text{mol FeSO}_4 \cdot 7\text{H}_2\text{O/g}$.

2.3.2. DPPH % scavenging activity assay

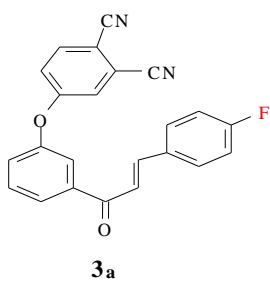
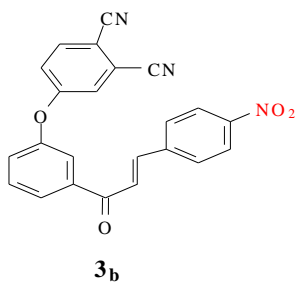
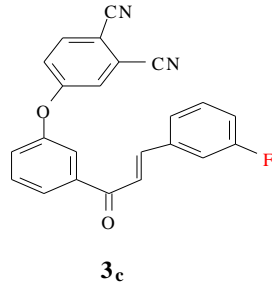
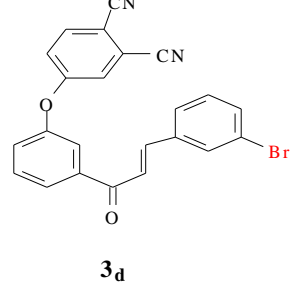
DPPH radical scavenging assay was performed according to the method described by Molyneux [38]. Each extract solution (0.75 ml) was added to 0.75 ml of a freshly prepared 0.1 mM DPPH solution dissolved in methanol. The mixture was shaken and left to stand at room temperature for 50 min in the dark. The absorbance was read at 517 nm against a control using a spectrophotometer. The values were shown as an SC_{50} mg/mL sample representing the concentration of each sample that resulted in a 50% scavenging of DPPH radicals.

3. Results and Discussion

3.1. Synthesis and Characterization

The synthesis of the chalcone containing phthalonitrile derivative has been performed by the procedure shown in Figure 1. Chalcone compounds 1a and 1b were synthesized according to the literature [36]. After a simple nucleophilic displacement, compounds 3a and 3b were obtained. Phthalonitrile compounds 3c and 3d were studied in our previous paper [35]. Novel chalcone derivative phthalonitrile compounds 3a and 3b were obtained by nucleophilic substitution of 4-nitrophthalonitrile with (2E)-3-(4-fluorophenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one 1a for compound 3a, (2E)-1-(3-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one 1b for compound 3b in the presence of K_2CO_3 as a catalyst at 60 °C in DMF (Figure 1). After purification, the FT-IR, $^1\text{H NMR}$, $^{13}\text{C NMR}$, and mass techniques were used to identify the structure of phthalonitrile compounds 3a and 3b. Structures and chemical data of the synthesized compounds are given in Tables 1 and 2. The FT-IR spectra of phthalonitrile compounds (3a-b) were clearly supported with the disappearance of the OH group of (1a-b) (3380 cm^{-1}) and the existence of characteristic stretching bands for C≡N group presented at 2231 and 2232 cm^{-1} , respectively. Other IR stretching vibrations of (3a-b) were similar to the compound (1a-b). In the $^1\text{H NMR}$ spectra of phthalonitrile compounds, the peaks at $\delta=12.8$ ppm (OH group) were disappeared and the aromatic protons appeared at around $\delta=7.98-7.17$ ppm for 3a and $\delta=8.43-7.32$ ppm for 3b (Figure 2 was an example of 3a). The $^{13}\text{C NMR}$ spectra of phthalonitriles 3a and 3b indicate carbonyl carbon atoms (C=O) at 188.64 ppm (for 3a) and 181.72 ppm (for 3b), the nitrile carbon atoms (C≡N) at 115.21 and 114.80 ppm for 3a, 115.15 and 114.85 ppm for 3b. In the mass spectra of phthalonitrile compounds 3a and 3b, the molecular ion peaks are given in Table 1. Due to the non-ionization of compounds when receiving mass spectra, we couldn't obtain a clear ion peak. All the analytical data confirmed the expected chemical structure of phthalonitriles.

Table 2. Spectral data of new compounds 3_{a-d}

Compound	IR (ATR, cm ⁻¹)	¹ H NMR (CDCl ₃ , ppm) ^a	¹³ C NMR (CDCl ₃ , ppm)	MALDI-TOFF-MS
	3073 (Ar-H), 2231 (C≡N), 1661 (C = O), 1576-1480 (C = C), 1287, 1247-1226 (Ar-O-Ar), 1160, 1089, 957, 831, 802	7.98 (d, J= 8Hz, 1H, Ar-H), 7.86-7.75 (m, 3H, Ar-H), 7.69-7.63 (m, 3H, Ar-H), 7.45-7.31 (m, 4H, Ar-H), 7.17 (t, J= 17Hz, 2H, =C-H).	188.64 (-C=O), 165.58 (C-F), 163.07, 161.24, 154.18, 144.71, 140.83, 135.57, 131.04, 130.61, 130.53, 126.09, 124.83, 121.77, 121.63, 120.90, 120.37, 117.90, 116.40, 116.19, 115.21 (C≡N), 114.80 (C≡N), 109.53	395.71 [M+Na+4H] ⁺
	3076 (Ar-H), 2232 (C≡N), 1666 (C = O), 1565-1516 (C = C), 1343, 1276-1247 (Ar-O-Ar), 1090, 953, 853, 695	8.43-8.38 (m, 1H, Ar-H), 8.22-8.16 (m, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 7.90-7.88 (d, J= 8Hz, 1H, Ar-H), 7.79-7.75 (m, 3H, Ar-H), 7.51-7.49 (m, 1H, Ar-H), 7.35-7.32 (m, 5H, =CH and Ar-H)	181.72 (-C=O), 177.56, 169.57, 162.62, 154.35, 149.13, 148.43, 140.85, 139.45, 135.62, 131.16, 130.79, 126.62, 124.22, 123.90, 122.47, 122.14, 121.80, 119.72, 117.98, 115.15 (C≡N), 114.85 (C≡N), 108.98	441.03 [M-4H] ⁺
				
				

3_c and 3_d [32] ^as, singlet; d, doublet; t, triplet; m, multiplet.

3.2. DPPH radical scavenging assay

3.2.1. Radical-Scavenging Ability

It is known that free radical scavenging is one of the most popular methods of antioxidants inhibiting lipid oxidation. The DPPH method is an easy and fast method for determining radical cleaning activity. The DPPH and FRAP results of the synthesized compounds are given in mg/mL Table 3. The DPPH value for compound 3_b was significantly higher than the other compounds. FRAP values of all compounds were very low. According to the FRAP values, all synthesized phthalonitrile compounds did not exhibit any activity. But, according to the DPPH values, compound 3_b has highest antioxidant activity. Çolak et al. reported phthalonitrile and phthalocyanines did not exhibit any scavenging activity [27]. Çolak et al. determined 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid (ABTS) activity in the same study [27]. It was founded that none of the tested compounds displayed ABTS radical activity. Barut et al. investigated DPPH radical scavenging effects of the 3-(5-chloro-2-(2,4-dichlorophenoxy)phenoxy)phthalonitrile and their non-peripheral phthalocyanine complexes [39]. DPPH radical scavenging value (IC₅₀) of phthalonitrile compound was determined as 237.80 ± 6.92 (µM). Yakan et al. investigated DPPH radical scavenging effects of 4-(benzo[d]imidazole-2-ylthio)phthalonitrile and its IC₅₀ value was 15.61 [40]. Sağlam et al. investigated DPPH radical scavenging effects of 4-[4-(trifluoromethoxy)-thiophenyl]phthalonitrile and their cobalt and zinc phthalocyanine complexes [41]. DPPH radical scavenging value (IC₅₀) of 4-[4-(trifluoromethoxy)thiophenyl]phthalonitrile compound

was determined as 23.71 ± 0.03%. According to these literature, when compared with this study, it was seen that DPPH radical scavenging activity of synthesized phthalonitrile compounds bearing different chalcone group (3_{a-d}) were higher than counterpart in literature. In this sense, this study has reached its aim and contributed to the literature.

The results revealed that compounds bearing electron-withdrawing groups such as fluoro-, nitro- and bromo- on the aromatic rings at position meta- (3) and para- (4) of chalcones, considerably effected the antioxidant activity.

Table 3. The antioxidant activities of phthalonitrile derivatives 3_{a-d}

Compound	DPPH SC ₅₀ (mg/mL)	FRAP µMFeSO ₄ ·7H ₂ O/g compound
3 _a	8.82 ± 1.42	0.06 ± 0.01
3 _b	0.60 ± 0.02	0.07 ± 0.01
3 _c	5.98 ± 0.21	0.05 ± 0.01
3 _d	8.36 ± 1.11	0.05 ± 0.01

According to the results, compound bearing NO₂ group on the chalcone aromatic rings at para position 3_b enhanced the antioxidant activity when compared to the counterparts. Also, Table 3 was showed that the antioxidant activity of phthalonitrile derivative bearing fluoro- on the meta-position 3_c was higher than on the para-position 3_a. When compared to the phthalonitriles possessing halogen atom on meta-position on chalcone, the antioxidant activity of compound bearing bromo-3_d was higher than compound bearing fluoro-3_c.

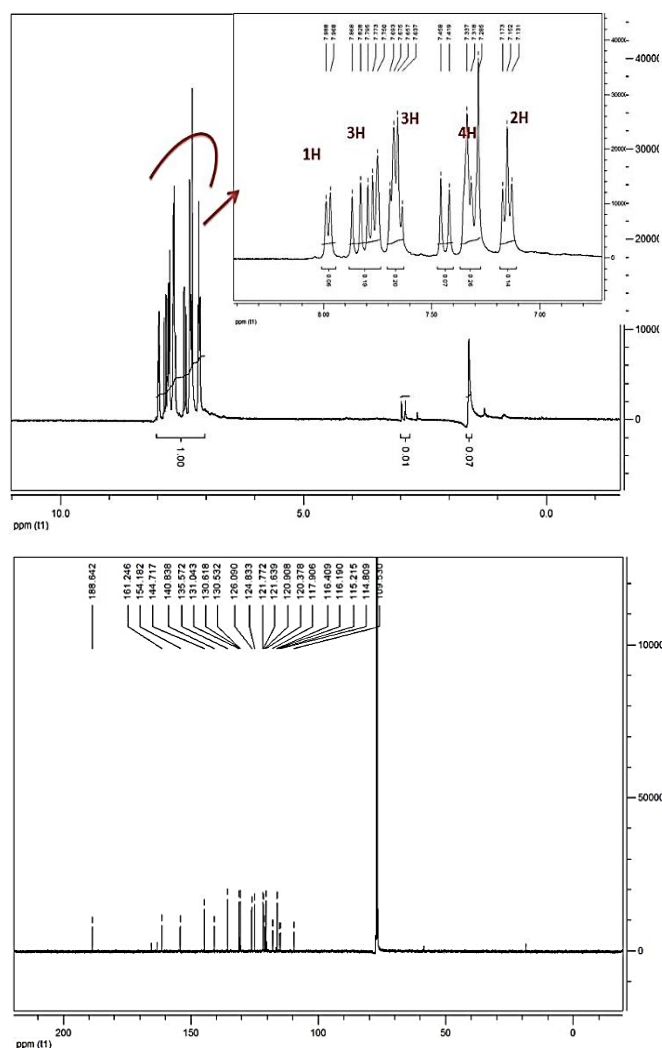


Figure 2. ^1H and ^{13}C NMR spectra of phthalonitrile compound 3_a .

4. Conclusion

In this paper, the new phthalonitrile derivatives bearing chalcone moiety, 3_a and 3_b , were synthesized and characterized by spectroscopic methods. Furthermore, the antioxidant properties of phthalonitriles 3_a , 3_b , 3_c , and 3_d were investigated. The new structures were characterized by FT-IR, ^1H NMR, ^{13}C NMR, and MALDI-TOF-MS spectroscopy technique. We have determined the antioxidant activities of newly synthesized phthalonitrile compounds for their use in biological applications. In this study, DPPH and FRAP, which are the antioxidant determination methods, were used. While samples showed DPPH radical scavenging activity, no activity was observed in the FRAP method. According to the test, the radical scavenging activities of compound 3_b were higher than those of other samples 3_a , 3_c , and 3_d . Because the nitro groups stabilize the phenolate ion by resonance electron withdrawal that allows the negative charge to be moved to an electronegative oxygen atom in the nitro group and make the compound more acidic. A nitro group is strongly withdrawing due to resonance, a fluoro and

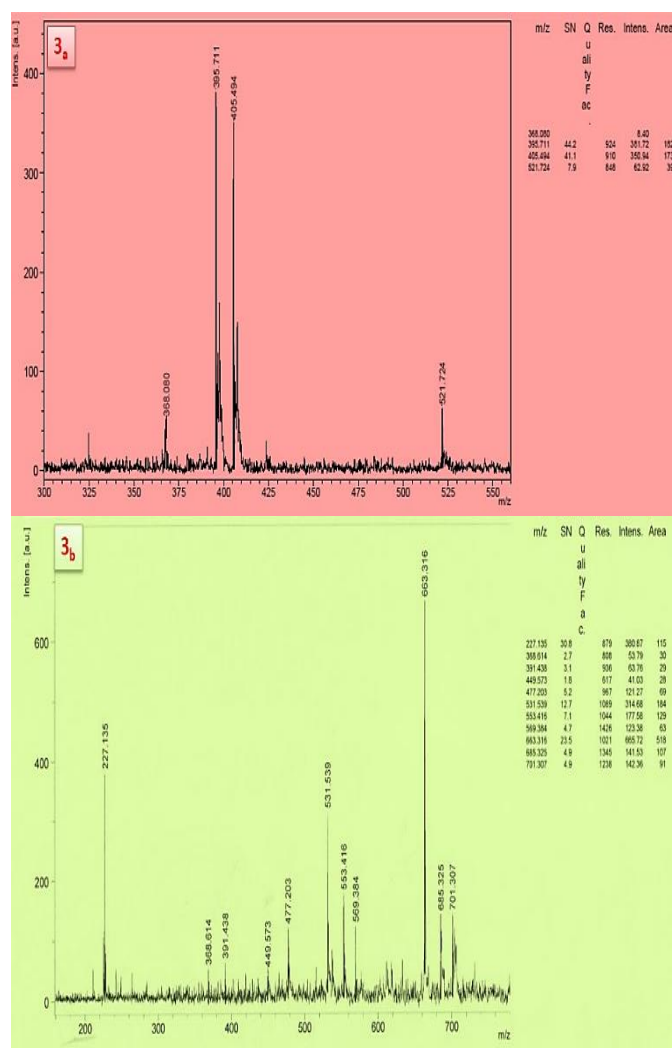


Figure 3. Mass spectra of phthalonitrile derivatives 3_a and 3_b

bromo groups are weakly electron withdrawing due to inductive effects. So, as a result, when the antioxidant activities of the compounds (3_a - d) were compared, the ranking was found as $3_b > 3_c > 3_d > 3_a$.

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