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α- or *β*-Substituted functional phthalocyanines bearing thiophen-3-ylmethanol substituents: synthesis, characterization, aggregation behavior and antioxidant activity

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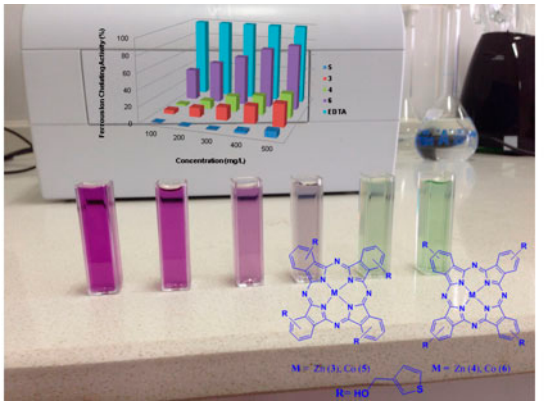

The tetra *α*- or *β*-thiophene substituted metal and metal-free phthalocyanines (Pcs) M[Pc(*α*-OCH_2Thiopen)$_4$] and M[Pc(*β*-OCH_2Thiopen)$_4$] {(***α*-ThMet-MPc**), (***β*-ThMet-MPc**) [ThMet: Thiophene methoxy], M = Zn(II), Co(II) and, 2H} were synthesized from the corresponding 3'-(thiophen-3-ylmethoxy)phthalonitrile or 4'-(thiophen-3-ylmethoxy)phthalonitrile (**ThMePN**). The structural characterization, spectral, and antioxidant properties of a series of new Pcs were also presented. Both *α*- and *β*-substituted Pc complexes increased solubility in polar solvents, such as THF, DMF, and DMSO. FT-IR, ^{1}H-NMR, ^{13}C-NMR, UV–vis, MALDI-TOF/MS spectral, and elemental analysis data were used to characterize the compounds. The aggregation behaviors of **3–8** were also investigated at different concentrations in THF. Antioxidant test methods, *α*,*α*-diphenyl-*β*-picrylhydrazyl radical scavenging activity, metal chelating activity, and reducing power, were used to determine the antioxidant activities. **6** showed very good ferrous ion chelating activity of 81 ± 1%. **6**, **5**, **4**, and **3** showed better reducing power than trolox, ascorbic, acid and butylated hydroxytoluene, commercially used antioxidants.

Keywords: Phthalocyanines; *α*- or *β*-Thiophene substitution; Antioxidant; Synthesis; Characterization

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1. Introduction

Phthalocyanines (Pcs) are macrocyclic complexes whose π systems (bonds in which the atomic orbitals overlap in parallel, forming an electron density cloud above and below the internuclear axis) are delocalized over an arrangement of conjugated carbon and nitrogen atoms, providing unique chemical and physical properties [1, 2]. Pcs based on an extensive delocalized 18-π electron system are modern functional materials in scientific research [3]. Pc dyes have been studied extensively due to their spectroscopic properties. They can be applied in chemistry, physics, medicine, and other sciences [4]. Some technological applications in fields such as liquid crystals [5], gas sensors [6], semiconductors [7], nonlinear optics [8], chemical sensors [9, 10], as photosensitizers in photodynamic therapy [11], selective metal cation extraction studies [12], and microanalysis [13] have shown importance of these macrocycles. Unsubstituted Pcs are insoluble and tend to aggregate (π–π stacking interactions) in polar and aqueous media. Nevertheless, solubility of Pcs in organic solvents can be improved by attaching substituents [14]. Peripheral substitution is used to enhance both the solubility of Pc compounds in aqueous and organic media, by altering the aggregation behavior and application targets [15–17]. If Pcs are modified with suitable functional groups, such as thiophen-3-ylmethanol in α or β positions, it could be induced to disaggregate by bulky structure and, therefore, results in significant changes of their optical properties. It is vitally important to control the aggregation. A few examples of Pcs bearing functionalized thiophene groups have been reported [18, 19]. According to these studies, Pcs bearing thiophene groups prevent aggregation and improve the solubility of tetra-substituted metallophthalocyanine complexes [20]. If Pc complexes have good solubility without aggregation in common organic solvents, Pcs have promising properties for antioxidant activity. The use of antioxidants in the food and pharmaceutical industries is particularly important to prevent decomposition of organic compounds present in prepared products. Toxicological and biological aspects, estimation, detection, development, and evaluation of antioxidants are important for food quality and food industries [21]. Antioxidant intake has emerged as an alternative therapeutic approach for several pathological conditions related to oxidative damage in the biological systems responsible for normal cell functions [22].

In this study, 3'-(thiophen-3-ylmethoxy)phthalonitrile or 4'-(thiophen-3-ylmethoxy)phthalonitrile (**ThMePN**) and their α- or β-substituted metallo and metal-free phthalocyanines M[Pc(α-OCH_2Thiopen)$_4$] {M = Zn(II)(**3**), Co(II)(**5**), 2H(**7**)} and M[Pc(β-OCH_2Thiopen)$_4$] {M = Zn(II)(**4**), Co(II)(**6**), 2H(**8**)} have been described. In addition, the antioxidant activities of the Pcs have been investigated using antioxidant assays.

2. Experimental

2.1. *Materials and equipment*

4-(Thiophen-3-ylmethoxy)phthalonitrile was prepared according to literature procedure [23]. 3-Nitrophthalonitrile, 4-nitrophthalonitrile, α,α-diphenyl-β-picrylhydrazyl (DPPH), trolox, ascorbic acid, butylated hydroxytoluene (BHT), and other reagents were obtained from Sigma-Aldrich and Fluka and used with/or without purification. *n*-Hexanol and THF were distilled from anhydrous $CaCl_2$ and acetophenone. All reagents were freshly distilled or recrystallized and dried under reduced pressure before use. Melting points were determined

using a Buchi melting apparatus. Chromatography was performed with silica gel (Merck grade 60) from Aldrich. Elemental analyses (C, H, and N) were performed at the instrumental Analysis Laboratory of Marmara University. FT-IR was recorded on a Shimadzu IR–prestige-2 spectrophotometer. Routine UV–vis spectra were recorded on an Agilent Model 8453 diode array spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker 300 spectrometer instruments. Mass spectra (MS) were acquired on a Voyager-DETM PRO MALDI-TOF mass spectrometer (Applied Biosystems, USA) equipped with a nitrogen UV-laser operating at 337 nm. Spectra were recorded in reflectron mode with average of 50 shots. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS were measured using a Bruker Autoflex III mass spectrometer equipped with a nitrogen UV–laser operating at 337 nm. α-Cyano-4-hydroxy-cinnamic acid was chosen as the best MALDI matrices.

2.2. *Synthesis*

2.2.1. 3-(Thiophen-3-ylmethoxy)phthalonitrile (1) and 4-(thiophen-3 ylmethoxy)phthalonitrile (2). Thiophen-3-ylmethanol (1.15 g, 10.64 mmol) and 3- or 4-nitrophthalonitrile (1.00 g, 5.78 mmol) were dissolved in dry DMF (10 mL) and heated at 40 °C in N_2 for 1 h. Then, finely ground anhydrous potassium carbonate (~1.0 g excess) was added portionwise to mixture over the period of 0.5 h at 30 °C. After the reaction mixture was kept at this temperature under N_2 for 3 days, it was cooled to room temperature (rt.) and poured into 200 mL ice-water. The creamy precipitate formed was filtered and dissolved in $CHCl_3$ and washed with % 5 $NaHCO_3$ to remove starting unreacted compounds. The creamy solution was then dried with anhydrous Na_2SO_4 and filtered. It was chromatographed over a silica gel column using a mixture of $CHCl_3$: MeOH (100/5) as eluent, giving blue powder, **1**. Finally, the pure powder was dried in a vacuum.

Yield of **1**: 1.32 g (66%); m.p. = 96 °C; Anal. Calcd for $C_{13}H_8N_2OS$ (240 g mol^{-1}): C, 64.98; H, 3.36; N, 11.66. Found: C, 64.21; H, 3.32; N, 10.98. FT-IR (cm^{-1}); 3084 (w, Ar–CH), 2887 (w, Alip–CH), 2227 (C≡N, st), 1604(C=C), 1591 (C=N), 1471(st), 1249 (Ar–O–Alip–CH), 1266, 1184, 1035, 916, 858, 827, 800, 729, 768. ^{1}H-NMR (DMSO-d_6) ∑: 7.80 (t 1H, meta to Ar–OR and CN, Phenyl H5), 7.65 (d, 1H, ortho to Ar–OR, Phenyl H4), 7.59 (d, 1H ortho to S, thiophene) 7.20 (d, 1H, ortho to CN, Ar–H6), 6.45, 6.44 (m 2H ortho to S and meta to S thiophene) 5.21(s, 2H, CH_2OAr). ^{13}C-NMR (DMSO-d_6) δ: 192.38, 161.22, 116.45, 116.12, 136.77, 136.42, 128.07, 127.88, 125.65, 119.62, 103.84, 67.26, 56.71, EI/MS *m/z*: 241.02 [M]$^+$.

2.2.2. General procedure for the synthesis of metallophthalocyanines (3–6). **1** or **2**. (0.10 g, 0.4 mmol) anhydrous $Zn(O_2CMe)_2$ (0.4 g, 0.24 mmol) or $CoCl_2$ (0.04 g, 0.03 mmol), dry N,N-dimethylaminoethanol (2 mL) and DBU (0.05 mL) to a sealed tube was heated with efficient stirring at 150–155 °C for about 8 h under N_2. After cooling to room temperature, resulting powder was washed several times successively with hexane, MeOH, and acetonitrile and filtered to remove any inorganic and organic impurities until the filtrate was clear. The blue product was isolated by silica gel column chromatography with $CHCl_3$ to remove unreacted starting impurities and then with THF/$CHCl_3$ (1 : 2 v/v) as eluent to obtain main crude product and then dried in vacuo. The products are soluble in $CHCl_3$, acetone, THF, DMF, DMSO, and pyridine.

2.2.2.1. *1(4),8(11),15(18),22(25)-Tetrakis-3'-(thiophen3ylmethoxy)phthalocyaninatozinc(II) (3)*. Yield of **3**: 0.061 g (44%); m.p. > 200 °C; Anal. Calcd for $C_{52}H_{32}N_8O_4S_4Zn$ (1023.5 g mol^{-1}): C, 61.06; H, 3.48; N, 10.75. Found: C, 60.29; H, 3.21; N, 10.05%. FTIR (KBr) ν/cm^{-1}: 3097 (w, broad, Ar–H), 2926 (w, Alip–CH), 1716 (vw), 1600 (C=C), 1487, 1468, 1417, 1330, 1269 1234 (Ar–O–Alip), 1126, 1045, 868, 831, 795. ^{1}H NMR (DMSO-d_6) ∑: 8.10 (t 4H, meta to Ar–OR and CN, Phenyl H5), 7.98 (d, 4H, ortho to Ar–OR, Phenyl H4), 7.52 (d, 4H ortho to S, thiophene) 7.10 (d, 4H, ortho to CN, Ar–H6), 5.78 (d 4H ortho to S thiophene), 5.75 (d 4H meta to S thiophene) 5.17 (s, 8H, CH_2OAr). ^{13}C-NMR (DMSO-d_6) *δ*: 196.5, 168.3, 132.7, 131. 2, 129.5, 127.3, 124.5, 117.4, 116.4, 116.1, 102.4, 69.5, 55.1, UV–vis (THF), λ_{max}/nm: 694 (13.96), 623 (2.44), 310 (6.38); MS (MALDI-TOF, Dithranol as matrix) *m*/*z*: 1025.297 $[M + H]^+$.

2.2.2.2. *2(3),9(10),16(17),23(24)-Tetrakis-4'-(thiophen-3-ylmethoxy)phthalocyaninatozinc (II) (4)*. Yield of **4**: 0.067 g (48%); m.p. > 200 °C; Anal. Calcd for $C_{52}H_{32}N_8O_4S_4Zn$ (1023.5 g mol^{-1}): C, 61.05; H, 3.42; N, 10.76. Found: C, 60.30; H, 3.20; N, 10.10%. FTIR (KBr) ν/cm^{-1}: 3099 (w, broad, Ar–H), 2917 (w, Alip–CH), 1709 (vw), 1605 (C=C), 1484, 1457, 1393, 1335, 1279 (Ar–O–Alip), 1118, 1047, 857, 831, 777. ^{1}H-NMR (DMSO-d_6) *δ*: 8.28 (d 4H, meta to Ar–OR and ortho to CN, Phenyl H6), 7.81(s, 4H, ortho to Ar–OR and CN, Phenyl H3), 7.73 (d, 4H ortho to S, thiophene), 7.35 (d 4H, ortho to Ar–OR and meta to CN, Phenyl H5), 6.72 (d 4H ortho to S thiophene), 6.70 (d 4H meta to S thiophene), 5.15 (s, 8H, CH_2OAr). ^{13}C-NMR (DMSO-d_6) *δ*: 191.91, 162.21, 136.86, 136.43, 128.38, 127.73, 125.94, 121.038, 116.91, 116.41, 106.74, 66.56, 56.71, UV–vis (THF), λ_{max}/nm: 666 (7.67), 604 (2.59), 324 (8.91); MS (MALDI-TOF, Dithranol as matrix) *m*/*z*: 1025.297 $[M + H]^+$.

2.2.2.3. *1(4),8(11),15(18),22(25)-Tetrakis-3'-(thiophen-3-ylmethoxy)phthalocyaninatocobalt (II) (5)*. Yield of **5**: 0.056 g (40%); m.p. > 200 °C; Anal. Calcd for $C_{52}H_{32}N_8O_4S_4Co$ (1020.05 g mol^{-1}): C, 61.76; H, 3.65; N, 10.67. Found: C, 60.19; H, 3.31; N, 10.02%. FTIR (KBr) ν/cm^{-1}: 3091 (w, broad, Ar–H), 2927 (w, Alip–CH), 1721 (vw), 1600 (C=C), 1487, 1454, 1409, 1328, 1269, 1234 (Ar–O–Alip), 1126, 1063, 868, 831, 765. UV–vis (THF), λ_{max}/nm: 697 (8.67), 628 (2.95), 312 (5.57); MS (MALDI-TOF, Dithranol as matrix) *m*/*z* (100%): 1021.29 $[M + H]^+$.

2.2.2.4. *2(3),9(10),16(17),23(24)-Tetrakis-4'-(thiophen-3-ylmethoxy)phthalocyaninatocobalt (II) (6)*. Yield of **6**: 0.063 g (45%); m.p. > 200 °C; Anal. Calcd for $C_{52}H_{32}N_8O_4S_4Co$ (1020.05 g mol^{-1}): C, 61.76; H, 3.65; N, 10.67. Found: C, 60.19; H, 3.31; N, 10.12%. FTIR (KBr) ν/cm^{-1}: 3097 (w, broad, Ar–H), 2918 (w, Alip–CH), 1724 (vw), 1606 (C=C), 1477, 1460, 1396, 1273 (Ar–O–Alip), 1118, 1095, 852, 827, 750. UV–vis (THF), λ_{max}/nm: 678 (8.49), 610 (1.801), 351 (3.97); MS (MALDI-TOF, Dithranol as matrix) *m*/*z* (100%): 1021.15 $[M + H]^+$.

2.2.3. General procedure for the synthesis of metal-free Pcs (7 and 8). **1** or **2** (0.10 g, 0.4 mmol) and DBU (0.05 mL) in dry N,N-dimethylaminoethanol were heated to 160 °C under N_2 for 8 h (1.00 mL). After cooling to room temperature and diluting with MeOH several times to remove any inorganic and organic impurities, it was filtered. The dark-blue crude product was treated several times with MeCN and filtered off. It was then successively washed with MeOH, diethylether and dried. Further purification by column

chromatography with silica gel (eluent: $CHCl_3$/MeOH; 10/1, and then THF) and dried in vacuo. These compounds are less soluble than the metallophthalocyanines.

2.2.3.1. *1(4),8(11),15(18),22(25)-Tetrakis-3'-(thiophen-3-ylmethoxy)phthalocyaninatofree (7)*. Yield of **7**: 0.033 g (35%); m.p. > 200 °C; Anal. Calcd for $C_{52}H_{34}N_8O_4S_4$ (963 g mol^{-1}): C, 64.85; H, 3.56; N, 11.63. Found: C, 65.11; H, 3.85; N, 11.52%. FT-IR (KBr) ν/cm^{-1}: 3305 (NH), 3085 (w, broad, Ar–H), 2932 (w, Alip–CH), 1708 (vw), 1609 (C=C), 1481, 1458, 1380, 1271 (Ar–O–Alip), 1129, 1011, 851, 830, 777. ^{1}H-NMR (DMSO-d_6) δ: 8.25 (d 4H, meta to Ar–OR and ortho to CN, Phenyl H6), 7.91 (s, 4H, ortho to Ar–OR and CN, Phenyl H3), 7.59 (d, 4H ortho to S, thiophene), 7.21 (d 4H, ortho to Ar–OR and meta to CN, Phenyl H5), 6.72 (d 4H ortho to S thiophene), 6.59 (d 4H meta to S thiophene), 5.12 (s, 8H, CH_2OAr). ^{13}C-NMR (DMSO-d_6) δ: 190.12, 160.11, 133.78, 131.43, 129.01, 127.03, 125.09, 121.61, 116.98, 115.73, 105.12, 65.51, 57.01, UV–vis (THF), λ_{max}/nm: Qx 698 (4.54), Qy 724 (4.39) 629 (1.55), 334 (5.18); MS (MALDI-TOF, Dithranol as matrix) *m*/*z*: 964.6 $[M + H]^+$.

2.2.3.2. *2(3),9(10),16(17),23(24)-Tetrakis-4'-(thiophen-3-ylmethoxy)phthalocyaninatofree (8)*. Yield of **8**: 0.038 g (40%); m.p. > 200 °C; Anal. Calcd for $C_{52}H_{34}N_8O_4S_4$ (963 g mol^{-1}): C, 64.85; H, 3.56; N, 11.63. Found: C, 64.72; H, 3.78; N, 11.78%. FT-IR (KBr) ν/cm^{-1}: 3299 (NH), 3088 (w, broad, Ar–H), 2941 (w, Alip–CH), 1702 (vw), 1615 (C=C), 1480, 1455, 1387, 1270 (Ar–O–Alip), 1129, 1010, 851, 830, 777. ^{1}H-NMR (DMSO-d_6) δ: 8.21 (d 4H, meta to Ar–OR and ortho to CN, Phenyl H6), 7.98 (s, 4H, ortho to Ar–OR and CN, Phenyl H3), 7.57 (d, 4H ortho to S, thiophene), 7.28 (d 4H, ortho to Ar–OR and meta to CN, Phenyl H5), 6.72 (d 4H ortho to S thiophene), 6.52 (d 4H meta to S thiophene), 5.20 (s, 8H, CH_2OAr). ^{13}C-NMR (DMSO-d_6) δ: 191.58, 160.03, 131.54, 131.89, 130.05, 128.19, 124.87, 121.43, 116.88, 114.97, 105.56, 65.32, 57.56, UV–vis (THF), λ_{max}/nm: Qx 682 (4.15), Qy 708 (3.72) 615 (1.47), 314 (5.23); MS (MALDI-TOF, Dithranol as matrix) *m*/*z*: 964.2 $[M + H]^+$.

2.3. *DPPH radical scavenging assay*

DPPH scavenging activity was determined using the method of Blois [24]. Two milliliters of methanol solution of DPPH (0.004%) was added to 500 µL of different concentrations (100–500 µg mL^{-1}) of Pc compound (with and without metal) solution. These solutions were vortexed vigorously and incubated in the dark for 30 min at room temperature; 30 min later, the absorbance was measured at 517 nm using a UV–vis spectrophotometer. The control was prepared without any Pc compound. The ability to scavenge DPPH radical was calculated by the following equation:

$$\text{DPPH scavenging activity}\,(\%) = (1 - A_{\text{sample517}}/A_{\text{control517}}) \times 100$$

where $A_{\text{control517}}$ is the absorbance of the control (containing all reagents except the tested Pc) and $A_{\text{sample517}}$ is the absorbance in the presence of Pc compound or standards. Trolox and BHT were used as standards and their scavenging ability was compared with our results.

IC_{50} (50% inhibition concentration) values of Pc compounds (with and without metal) and standards (BHT and Trolox) were also calculated for comparison. IC_{50} (mg mL^{-1}) is the amount of antioxidant necessary to decrease by 50% the absorbance of DPPH. The

percentage of remaining DPPH radical against the Pc compound concentration was plotted to obtain the amount of antioxidant necessary to decrease DPPH radical by 50%.

2.4. *Ferrous ion chelating activity*

Ferrous ion chelating effects of Pc compounds (with and without metal) were estimated by the method of Dinis *et al.* [25]. Briefly, the reaction mixture contained 1.0 mL of various concentrations (100–500 μg mL^{-1}) of the compound solution, 0.1 mL of $FeCl_2$ (2 mM), and 3.7 mL of distilled water. The mixture was vortexed and incubated at room temperature for 30 min. Ferrozine (0.2 mL, 5 mM) solution was added to this mixture, mixed, and incubated at room temperature for 10 min. Absorbance of the solution was then measured spectrophotometrically at 562 nm. The control contains only $FeCl_2$ and ferrozine. The percentage of inhibition of ferrozine–Fe^{2+} complex formation was calculated using the equation given below:

$$\text{Ferrous ion chelating effect}\,(\%) = (1 - A_{\text{sample562}}/A_{\text{control562}}) \times 100$$

where $A_{\text{control562}}$ is the absorbance of the control and $A_{\text{sample562}}$ is the absorbance in the presence of Pc compound or standard. Ethylenediaminetetraacetic acid (EDTA) was used as standard.

2.5. *Reducing power*

The reducing power of Pc compounds (with and without metal) was determined as described by Oyaizu [26]. Briefly, 2.5 mL of sample solution at different concentrations (5–100 μg mL^{-1}) was mixed with 2.5 mL of phosphate buffer (0.2 M, pH 6.6) and 2.5 mL of potassium ferricyanide (1%). The reaction mixture was incubated at 50 °C for 20 min. After 20 min incubation, 2.5 mL of trichloroacetic acid (10%) was added to the mixture to terminate the reaction. The mixture was centrifuged at 2500 rpm for 10 min. Then, 2.5 mL of the supernatant was mixed with 2.5 mL of distilled water and 0.5 mL of $FeCl_3$ (0.1%), and the absorbance was measured at 700 nm. Ascorbic acid, BHT, and Trolox were used as standards. Increased absorbance of the reaction mixture indicated increased reducing power.

2.6. *Statistical analysis*

All the assays were carried out in triplicate. The results were expressed as mean values and standard deviation (SD).

3. Results and discussion

3.1. *Synthesis and characterization*

In this study, zinc, cobalt, and metal-free Pcs bearing thiophen-3-ylmethanol substituents at the peripheral and nonperipheral positions were synthesized and characterized by elemental analysis, FT-IR, UV–vis, ^{1}H-NMR, ^{13}C-NMR, and MALDI-TOF mass spectroscopy. We have used the cyclotetramerization technique of the ligands, 3-(thiophen-3-ylmethoxy)phthalonitrile (**1**); 4-(thiophen-3-ylmethoxy)phthalonitrile (**2**) with corresponding metal free or metal salts in the presence of DMAE for 8 h in moderate yields (44% for **3**, 48% for **4**,

40% for **5**, 45% for **6**, 35% for **7,** and 40% for **8**) (scheme 1). Newly synthesized Pcs **3–8** are moderately soluble in $CHCl_3$ and soluble in acetone, THF, DMF, DMSO, and quinoline.

(***β*-ThMet-MPc**) and (***α*-ThMet-MPc**) were purified by silica gel column chromatography in two steps after solvent purification. All the analytical and spectral data are in agreement with the theoretical requirements of **3–8**.

In the FT-IR spectra, the major strong –CN band at 2227 cm^{-1} of **1** and 2222 cm^{-1} of **2** disappeared after conversion to **3–8**. In the FT-IR spectra of all the MPcs, the most intense bands of the spectra are the absorptions between 2950 and 2850 cm^{-1}, which are due to the antisymmetric C–H stretching vibrations of the $–CH_2$ groups of the 3-thiophene methoxy and 4-thiophene moieties. A very weak band in all the MPcs above 3000 cm^{-1} is due to aromatic C–H stretching. The most instinctive indicators for the formation of **1** and **2** are the signals belonging to the aromatic carbons, between 110 and 150 ppm in the ^{13}C NMR spectra.

The ^1H-NMR spectra of **3** and **4** were recorded at room temperature in (DMSO-d_6). Well resolved ^1H-NMR spectra were recorded for Pcs functionalized with thiophen-3-ylmethanol moieties. The substitution of the Pc rings with thiophen-3-ylmethanol results in the formation of positional isomers, which causes splitting of the signals for the peripheral aromatic protons in the downfield aromatic region [27].

Aromatic protons in the peripheral and nonperipheral positions of Pc rings were obtained as broad signals. This broadening is likely due to chemical exchange caused by aggregation–disaggregation equilibria. The aromatic region protons of Pc rings were observed as a broad signal at $\delta = 8.10$, 7.98, and 7.10 ppm for **3**, $\delta = 8.28$, 7.81, and 7.35 ppm for **4**, respectively.

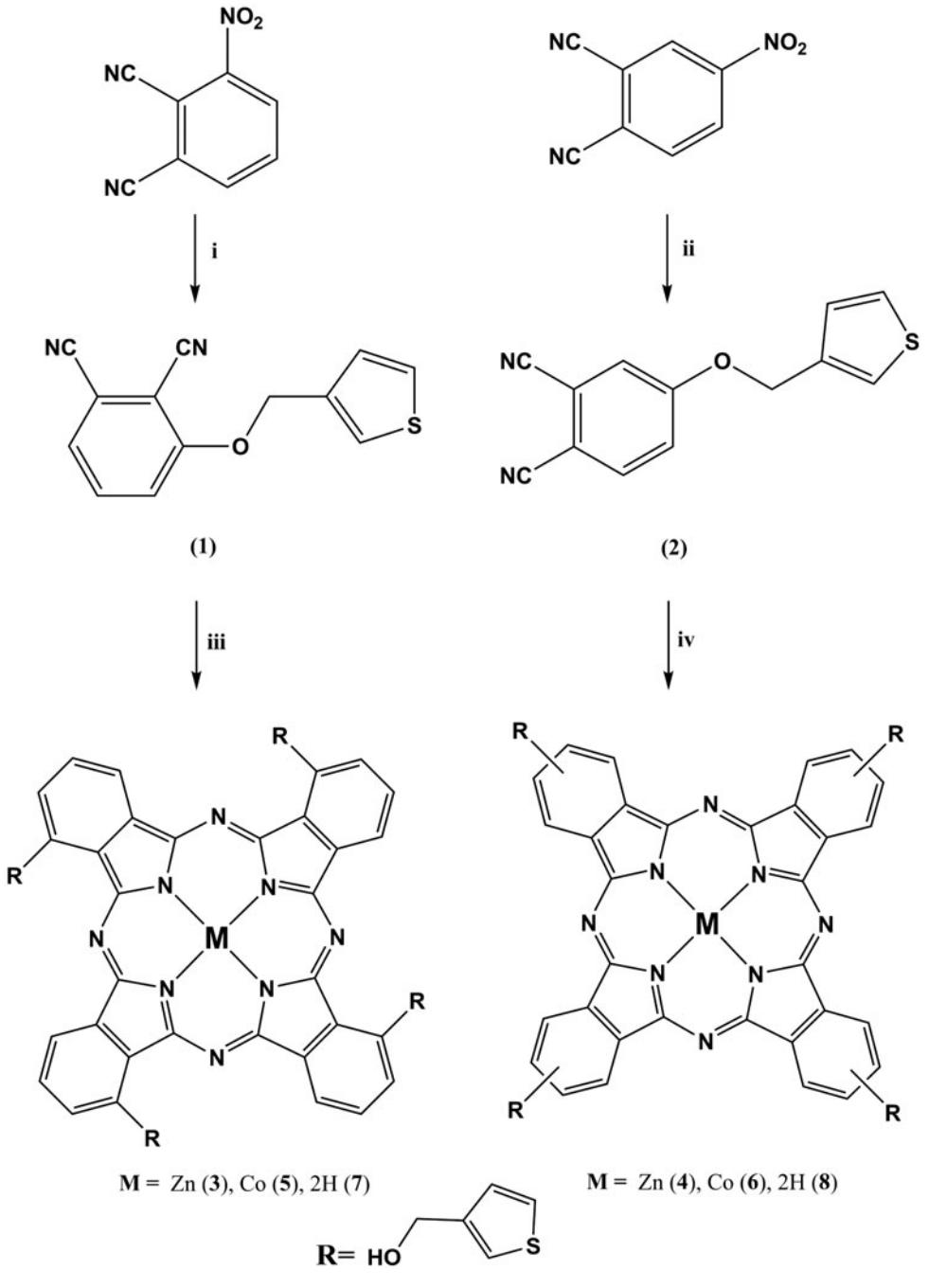
The other resonances related to S*CH*, *CH*S, SCH*CH*, and *CH_2*OAr protons in the ^1H-NMR spectra of complexes were obtained $\delta = 7.52$, 5.78, 5.75, and 5.17 ppm for **3**, $\delta = 7.73$, 6.72, 6.70, and 5.15 ppm for **4**, respectively.

The ^1H-NMR spectra of **7** and **8** were almost identical with starting compounds except small shifts and core NH signal. The NH protons in the inner core of **7** and **8** were very well characterized by ^1H NMR spectroscopy, which showed a peak at −1.58 and −1.51 ppm, respectively [16].

The most pronounced characterization data for the Pcs are given by their UV–vis spectra in solution. The UV–vis spectra of Pcs **3–8** can be readily interpreted using Gouterman's four orbital model [28]. There are two principle π–π* transitions, a lower energy "Q-band" (~600–700 nm) and a higher energy B band {~300–350 nm, deeper π–π* transition) [29]. The Q-band absorptions for **3–6** in THF were observed as a single band of high intensity at 694 nm for **3**, 666 nm for **4**, 697 nm for **5,** and 678 nm for **6**. There was also a shoulder at the slightly higher energy side of the Q band for each Pc. B band absorptions of the metallophthalocyanines **3–6** were observed at 310, 324, 312, and 351 nm, respectively (figures 1 and 2).

The metal-free Pcs show splitting of the Q band. Splitting Q bands of free based metal Pcs were observed (Qx = 698 nm and Qy = 724 nm for **7** and Qx = 682 nm and Qy = 708 for **8**) and also B band absorptions of **7** and **8** were observed at 334 and 314 nm, respectively (figure 3).

In this study, the aggregation behaviors of **3–6** were also investigated at different concentrations (from 2×10^{-6} to 12×10^{-6}) in THF (**4** as an example) (figure 4). As shown in the figure, the Q band increases in intensity with increasing concentration of **4**; no new bands were observed due to the aggregated species.



Scheme 1. Synthetic route for 3-(thiophen-3-ylmethoxy)phthalonitrile (**1**); 4-(thiophen-3-ylmethoxy)phthalonitrile (**2**) and their α- or β-tetra-substituted phthalocyanines, {M[Pc(α-OCH_2Thiopen)$_4$] and M[Pc(β-OCH_2Thiopen)$_4$] {(α-**ThMet-MPc**) [ThMet: Thiophene methoxy], M = Zn(II), Co(II), 2H)} (**3–8**). i, ii: K_2CO_3, Thiophen-3-yl-methanol, DMF, 30 °C, 3 days. iii, iv: Anhydrous $Zn(acac)_2$, $CoCl_2$, NNDMAE reflux temperature.

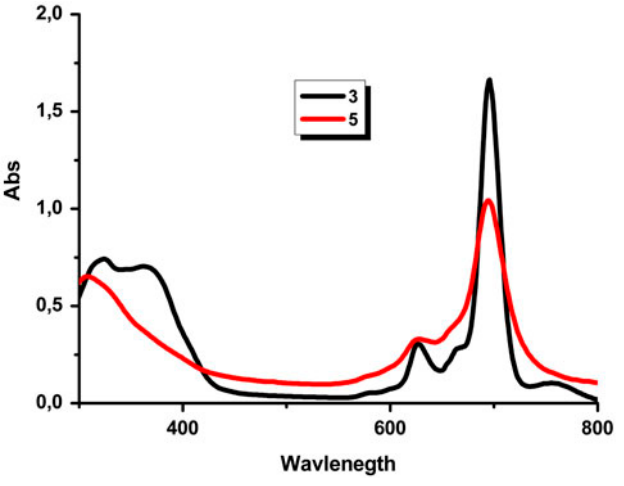


Figure 1. UV–vis spectra of **3** and **5** in THF at 1.2×10^{-5} molar concentration.

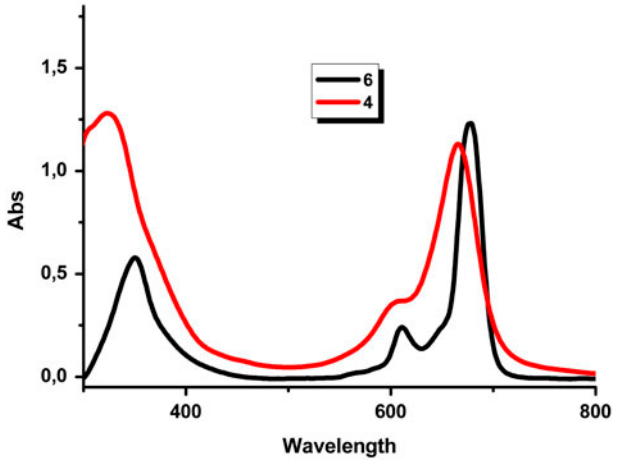


Figure 2. UV–vis spectra of **4** and **6** in THF at 1.2×10^{-5} molar concentration.

3.2. *DPPH radical scavenging activity*

Free radical scavenging is one mechanism by which antioxidants slow or inhibit lipid oxidation by interfering with either chain initiation and/or propagation. The method of scavenging DPPH-free radicals has been used to evaluate the antioxidant activity of specific compounds or extracts. It is considered a valid and easy assay to evaluate the scavenging activity of antioxidants since the radical compound is stable and does not have to be generated, as is necessary in other radical scavenging assays [30].

The scavenging activities on DPPH radicals by **3–8** are given in figure 5. Among the compounds, maximum radical scavenging effect was 37.94% for **5**. Agirtas *et al.* also found that a water soluble phenoxy phenyl diazenyl benzoic acid substituted Pc derivatized

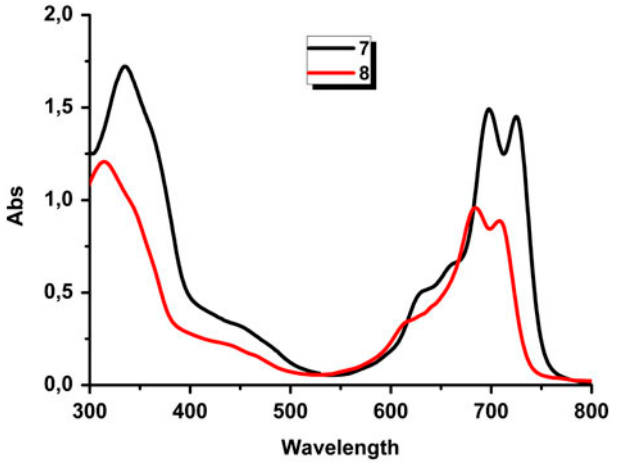


Figure 3. UV–vis spectra of **7** and **8** in THF at 1.2×10^{-5} molar concentration.

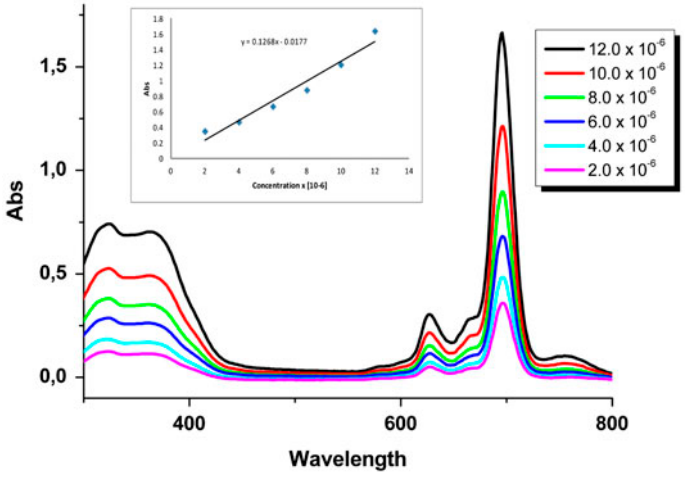


Figure 4. Absorption spectra of ZnPc (**4**) in THF at different concentrations (inset: plot of absorbance *vs*. concentration).

compound showed 35.6% scavenging activity at 100 mg mL^{-1} [31]. The order of radical scavenging effect of compounds was **5** > **6** > **3** > **4**. However, all tested metallophthalocyanine compounds showed lower DPPH activity than the BHT and Trolox standards (figure 5). The radical scavenging effect of metal-free Pc compounds was also determined. They did not show any activity. These results suggest that the metals play an important role in DPPH scavenging activity of this kind of metallophthalocyanine compound.

In addition to the concentration effect of the Pc compounds, IC_{50} values of metallo Pc compounds, metal-free Pc compounds, and standards (BHT and Trolox) were also calculated for comparison (table 1). Overall, metalloPc compounds were associated with higher IC_{50} values than the standards. The higher IC_{50} values represent lower antioxidant ability.

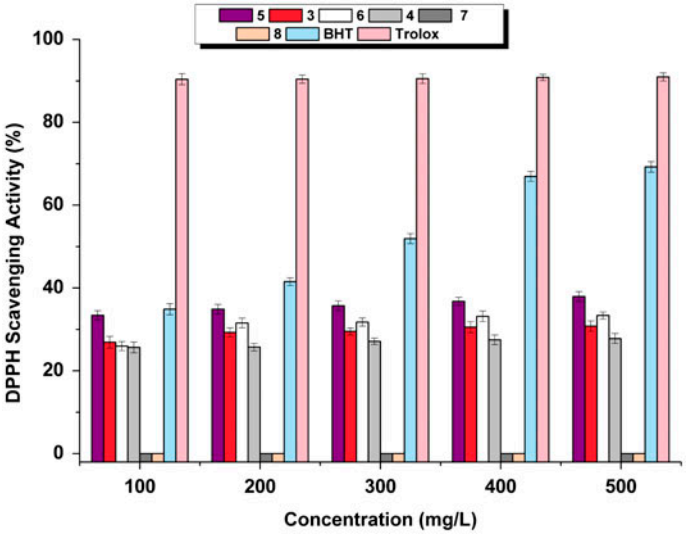


Figure 5. Free radical scavenging activity on DPPH radicals (%) of the compounds. Radical scavenging activity was determined by DPPH assay in the presence of different concentrations of Pc compounds (with and without metal). Vertical bars represent the SD.

Table 1. IC_{50} values of Pc compounds (with and without metal) for DPPH scavenging assay.

Pc compounds/standards	IC_{50} (mg mL^{-1})
3	2.0 ± 0.2
4	4.2 ± 0.7
5	1.57 ± 0.07
6	1.37 ± 0.03
7	ND[a]
8	ND[a]
BHT	0.27 ± 0.001
Trolox	0.02 ± 0.0003

Notes: DPPH 50% inhibition values of Pc compounds. The results are presented in IC_{50} values, what means that higher values correspond to lower antioxidant potential. IC_{50} inhibition concentration corresponding to 50% of antioxidant activity for DPPH (2,2-diphenyl-1-picrylhydrazyl radical) scavenging assay. Trolox (commercial standard) was used as positive control. The number of replications was $n = 3$.
[a]ND means "not detected"; metal-free Pc compounds did not show DPPH scavenging activity.

Thus, IC_{50} results in table 1 support the DPPH results of the tested compounds at different concentrations with having low DPPH scavenging activity.

3.3. *Metal chelating activity on ferrous ions*

Another antioxidant mechanism is based on the ability of some of these compounds to chelate transition metals ions (especially iron and copper), giving stable complexes that,

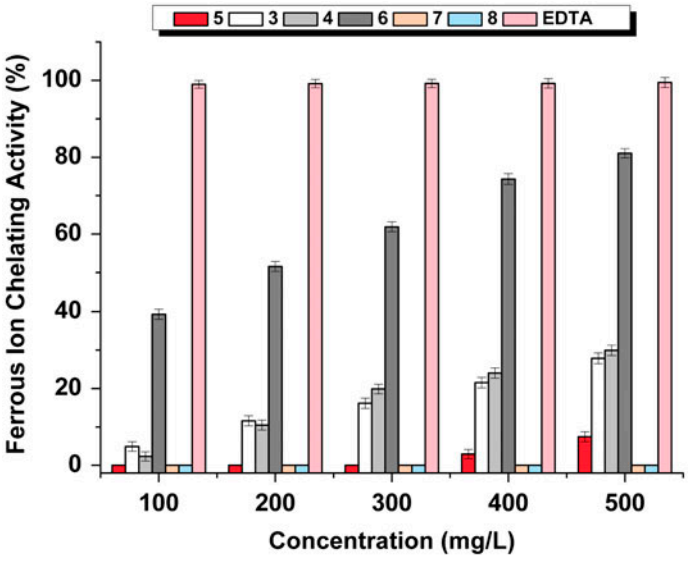


Figure 6. Ferrous ion chelating ability of **3–8** showing the comparison of Pc compounds (with and without metal) with EDTA for their metal ion chelating activity. Vertical bars represent the SD.

entrapping metals, prevent these from participating in free radical generation [32]. The ferrozine test was used to determine metal chelating activity of compounds in this work. The method is based on complex formation of Fe^{2+} with Ferrozine, a strong ferrous iron chelating compound, or antioxidant compounds. In the presence of other chelating agents, the complex formation is disrupted with the result that the complex formation is decreased [33]. In the present work, chelating activities of metallophthalocyanine, metal-free Pc compounds, and EDTA which is an excellent chelating compound as a standard were investigated and the results are indicated in figure 6.

The chelating activities are 7 ± 1%, 28 ± 1%, 30 ± 1%, and 81 ± 1% for **5**, **3**, **4,** and **6**, respectively, at 500 μg mL^{-1} concentration. However, metal-free Pc compounds did not show any chelating activity in the experimental conditions. Compound **6** showed the maximum chelating activity with 81% among the other metallophthalocyanine compounds. This might arise from the differences of absorbance energy and electrovalent behavior of the metallophthalocyanine complexes. The absorbance energy of **6** is higher than the absorbance energy of **5** which is nonperipheral. Chelating and antioxidant properties of Co Pc when comparing to Zn Pc are from electrovalent behavior of redox active cobalt center in Co Pc. All tested compounds showed less Fe^{2+} chelating activity than EDTA. Our results showed similar activities with previous studies [34–36].

3.4. *Reducing power*

The reducing power assay is usually used to analyze the ability of an antioxidant to donate an electron. Thus, the more antioxidant compounds in solution convert the iron (Fe + 3) in ferric chloride to ferrous (Fe + 2), thereby changing the solution into various shades from green to blue, depending on the reducing power of the compounds. Strong reducing agents, however, formed Perl's Prussian blue color and absorbed at 700 nm. With higher amount of

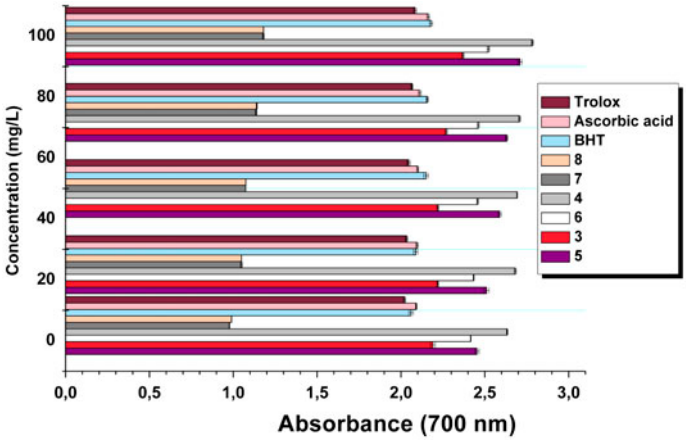


Figure 7. Reducing power assay absorbance changes at 700 nm in the presence of different concentrations of Pc compounds (with and without metal). Vertical bars represent the SD.

reducing agents or antioxidants, they can react with free radicals to stabilize and terminate radical chain reactions in living systems [37]. Figure 7 shows the reducing power of the metallophthalocyanine, metal-free Pc compounds, and three different positive controls trolox, BHT, and ascorbic acid. According to the obtained results, all tested Pc compounds showed very high reduction capacity; the higher the absorbance of the reaction mixture, the higher would be the reducing power. Reducing power of the compounds increased with increased concentrations (figure 7). All tested metallophthalocyanine compounds showed higher reducing power than trolox, BHT, and ascorbic acid which are known conventional antioxidants at all concentrations. Metal-free Pc compounds showed much lower reducing power activity (figure 7). According to the results, there are no pronounced differences among the metallophthalocyanine complexes, in the order **4** (2.78 ± 0.006) > **5** (2.71 ± 0.01) > **6** (2.52 ± 0.007) > **3** (2.37 ± 0.008) > **BHT** (2.18 ± 0.01) > **ascorbic acid** (2.16 ± 0.008) > **trolox** (2.08 ± 0.01) metal-free Pc4' (1.18 ± 0.001) ≥ metal-free Pc3' (1.17 ± 0.005) at all concentrations. These results were also higher than literature values [38–40]. Our results suggest that the four Pc compounds are slightly more sensitive than the known compounds as reducing agents. As a result, all four compounds can be used as positive control for metal chelating.

4. Conclusion

We have prepared and characterized tetrakis α- or β-substituted metal and metal-free Pcs MPcs M[Pc(α-OCH_2Thiopen)$_4$] {M = Zn(II) (**3**), Co(II) (**5**), 2H(**7**)}, M[Pc(β-OCH_2Thiopen)$_4$]{M = Zn(II) (**4**), Co(II) (**6**), 2H(**8**)}, bearing 3'-(thiophen-3-ylmethoxy)phthalonitrile, and 4'-(thiophen-3-ylmethoxy)phthalonitrile on the nonperipheral or peripheral sites. Structures of the newly synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR, MALDI-TOF, and UV–vis spectral data. Additionally, metallophthalocyanine and metal-free Pcs were tested for antioxidant activities using free radical scavenging (DPPH), ferrous ion chelating, and reducing power methods. The results of our work

suggest that **6** had higher chelating activity on ferrous ions than the other complexes. All metallophthalocyanine compounds showed good and strong reducing power, better than commercial antioxidants. Thus, the tested metallophthalocyanines can be used instead of BHT and Trolox for reducing power activity. For comparison, the antioxidant effect of metal-free Pc compounds was also determined; the metals in tested Pcs play an important role in antioxidant activity.

Disclosure statement

No potential conflict of interest was reported by the authors.

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