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Synthesis and characterization of metallophthalocyanine with morpholine containing Schiff base and determination of their antimicrobial and antioxidant activities

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ABSTRACT

In this work, novel metallophthalocyanine compounds (M = Zn, Cu, Co) bearing four 2-methoxy-4-{(Z)-[(4-morpholin-4-ylphenyl)imino]methyl}phenol at the peripheral positions were sythesized starting from the new phthalonitrile derivative (**2**). These new compounds **(2–5)** have been characterized by a combination of FT-IR, ^{1}H NMR (for compounds 2 and 3), ^{13}C NMR (for compound 2), UV–Vis (for compounds 3,4 and 5) and mass spectrophotometry techniques. Antioxidant activities of the metallophthalocyanines were investigated by using DPPH free radical scavenging assay and FRAP (ferric ion reducing antioxidant power) method. The antimicrobial activity of the synthesized metallo phthalocyanine compounds **(3–5)** were determined against the selected different six standart bacteria isolates by microdilution broth assay with Alamar Blue Dye. Most affected bacteria from the compounds were standard *E. coli* and *S. typhimurium* (MIC 625 μg/ml). Standart *Y. enterocolitica* and *S. aureus* have been less affected by the compounds (MIC 10.000 μg/ml).

1. Introduction

Phthalocyanine compounds (Pcs) are heterocyclic compounds with thermal, chemical and photo-stability, chemical inertness and long wavelength absorption compatible with biological window. There are widely potential applications in technology and medicine owing to their physicochemical properties [1]. They have been used different application areas such as solar cell, dyes and pigments, catalysis, sensors, non-linear optical materials (NLO) and photodynamic therapy (PDT) [2–9]. The most interesting ones are peripherally substituted phthalocyanines bearing different metal cations into the macrocyclic core [10,11]. Phthalocyanines have to be soluble and pure in order to be used in these applications. In this regard, an important goal of Pc chemistry is to synthesize soluble Pcs.

According to the recent literature data, the scientific investigations related to the synthesis, conversions, and research of physiologically active substances with different application areas have been expanded [12]. Especially taking into account that the Schiff base, pyrimidine-thiones, natural or synthetic phenol compounds, morpholine are compounds with great pharmacological activity, the development of optimal synthesis method of these compounds are always in the spotlight of the researchers [13–15].

Novel and efficient methods for synthesis of phthalocyanines are an active area of research in industry and academia due to their applications in biological tests [16–20]. Many morpholine and its derivatives are important compounds with pharmacological and biological properties such as anticancer [21], tyrosinase inhibitory activities [22], antioxidant [23], antimicrobial [24,25], anti-inflammatory [26] and photodynamic therapy [27]. Furthermore, the most considerable properties of Schiff base exhibit antibacterial, antifungal and anticancer activities to have been submitted in the literature [28–30]. In addition to this Schiff bases containing morpholine have good antioxidant and antimicrobial activities [31].

For many years, antimicrobial activities, antibacterial and

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antifungal properties of compounds have been tried to determine. The Alamar Blue (resazurin) dye has been shown to provide a useful for investigation proliferation and cytotoxicity in lymphocytes and other cell lines. The Alamar Blue Dye for detection of metabolic activity works as a fluorometric/colorimetric growth indicator [32]. Alamar Blue Dye which non-toxic for cell even during long incubation times is an oxidation reduction indicator that changes colour from blue to pink in the presence of bacterial or fungal viability as a response to chemical reduction of the growth medium [33].

Recently, researchers have also researched the antioxidant and antimicrobial activities of Pc compounds [34–40]. The antimicrobial and antioxidant properties of phthalocyanine molecules vary according to the metal ion type and the types of substituted groups [41–46]. So, we purposed to determine the antibacterial activity by the microdilution broth assay with Alamar Blue Assay method in synthesized Pcs compounds.

In this study, new phthalonitrile derivative **(2)** and metallophthalocyanine complexes **(3, 4** and **5)** having morpholine moiety on their peripheral position were synthesized. The characterization of the novel compounds **(2–5)** were done by various spectroscopic techniques such as, FT-IR, NMR, UV–Vis and mass spectrometry. The antioxidant and antimicrobial properties of phthalocyanine compounds **(3–5)** were investigated.

2. Experimental

2.1. Materials and equipment

The used materials, antioxidant and antimicrobial procedure and equipments were supplied as supplementary information.

2.2. Synthesis of the compounds 2,3,4,5

2.2.1. Synthesis of 4-(2-metoxy-4-{(E)-[(4-morpholin-4-ylphenyl) imino]methyl}phenoxy) phthalonitrile (2)

Schiff base compound **(1)** was prepared according to literature [24]. 4-(2-methoxy-4-{(E)-[(4-morpholin-4-ylphenyl)imino] methyl}phenol **(1)** (2.0 g, 6.41 mmol) and 4-nitrophthalonitrile (1.11 g, 6.41 mmol) were dissolved in dry DMF (dimethylformamide) (20 ml) and the solution was stirred at 60 °C. Then, dry K_2CO_3 (2.65 g, 19.20 mmol) was added into this solution the portion wise during 2 h. The system was stirred under N_2 at same temperature for 5 days. After this time, the reaction mixture was poured into ice-water and stirred at room temperature. The mixture was filtered and dried in vacuum over P_2O_5. The obtained yellow crude product was purified using column chromatography with silicon dioxide as the column material and a chloroform/ethanol (10:2) solvent system. Yield: 1.6 g (57%), mp: 197–200 °C. IR (ATR), ν_{max}/cm^{-1}: 3079 (Ar–H), 2969–2858 (Aliph. C–H), 2231 (C≡N), 1625–1591 (C=C), 1508–1487 (CH=N), 1414, 1319, 1240, 1116, 1033, 927, 860, 823, 723, 618, 582. ^{1}H NMR. (400 MHz, $CDCl_3$), (δ:ppm): 8.68 (s, 1H, C–H), 8.07–8.05 (d, 1H, Ar–H), 7.77–7.73 (d, 2H, Ar–H), 7.57–7.55 (d, 1H, Ar–H), 7.35–7.28 (m, 4H, Ar–H and $CDCl_3$), 7.01–6.99 (d, 2H, Ar–H), 6.99–6.49 (dd, 1H, Ar–H), 3.82 (s, 3H, O–CH_3), 3.75 (s, 4H, O–CH_2), 3.34 (s, 4H, N–CH_2). ^{13}C NMR. (400 MHz, $CDCl_3$), (δ:ppm): 161.45, 156.54, 151.72, 143.56, 142.76, 136.62, 136.22, 123.04, 123.00, 122.66, 121.80, 121.13, 118.05, 117.02, 116.40, 115.89, 115.23 (C≡N), 112.29 (C≡N), 108.33, 66.53 (O–CH_2), 56.33 (O–CH_3), 48.84 (N–CH_2). MALDI-TOF-MS, (m/z): Calculated: 438.84; Found: 438.65 $[M]^+$.

2.2.2. Synthesis of Zinc(II) phthalocyanine (3)

Phthalonitrile compound **(2)** (0.3 g, 0.68×10^{-3} mol), $Zn(CH_3COO)_2$ (0.044 g, 0.36×10^{-3} mol) and 1.8-diazabicyclo[5.4.0] undec-7-ene (DBU) (10 drops) in 3 ml of dry n-pentanol were stirred at 160 °C in a sealed glass tube for 24 h under $N_{2(g)}$. After cooling to room temperature, the solution was poured in ethanol. Green precipitate was filtered off. The obtained green product was purified by column chromatography on silicon oxide by using $CHCl_3$:CH_3OH as solvent system. Yield: 99 mg (32%). mp: >300 °C. IR (ATR) ν_{max}/cm^{-1}: 3070 (Ar–H), 2955–2852 (Aliph. C–H), 1617–1597 (C=N), 1506–1449 (C=C), 1260, 1115, 1087, 1030, 924, 821, 743. ^{1}H NMR. (400 MHz, $CDCl_3$), (δ:ppm): 8.68 (s, 4H, C–H), 7.40–7.28 (m, 20H, Ar–H), 7.02 (s, 16H, Ar–H), 6.65–6.53 (m, 4H, Ar–H), 3.76 (s, 12H, O–CH_3), 3.35 (s, 16H, O–CH_2), 3.15 (s, 16H, N–CH_2). UV–Vis (DMF): λ_{max}, nm (log ε): 681 (4.98), 612 (4.34), 362 (4.89). MALDI-TOF-MS, (m/z): Calculated: 1819.30; Found:1819.62 $[M]^+$.

2.2.3. Synthesis of copper (II) phthalocyanine (4)

4-(2-methoxy-4-{(E)-[(4-morpholin-4-ylphenyl)imino]methyl} phenoxy) phthalocyaninato copper (II) **(4)** was synthesized similarly to **(3)** by using anhydrous $CuCl_2$ instead of anhydrous $Zn(ac)_2$. Yield: 100 mg (32%). mp: > 300 °C. IR (ATR) ν_{max}/cm^{-1}: 3070(Ar–H), 2958–2853 (Aliph. C–H), 1618–1595 (C=N), 1505–1449 (C=C), 1260, 1219, 1115, 1093, 1029, 924, 822, 744. UV–Vis (DMF): λ_{max}, nm (log ε): 679 (4.88), 616 (4.58), 376 (5.19). MALDI-TOF-MS, (m/z): Calculated: 1817.47; Found: 1817.91 $[M]^+$.

2.2.4. Synthesis of cobalt (II) phthalocyanine (5)

4-(2-methoxy-4-{(E)-[(4-morpholin-4-ylphenyl)imino]methyl} phenoxy) phthalocyaninato cobat (II) **(5)** was synthesized similarly to **(3)** by using anhydrous $CoCl_2$ instead of anhydrous $Zn(ac)_2$. Yield: 79 mg (26%). mp: > 300 °C. IR (ATR) ν_{max}/cm^{-1}: 3068 (Ar–H), 2954–2853 (Aliph. C–H), 1619, 1595 (C=N), 1506–1449 (C=C),1413, 1260, 1217, 1114, 1095, 923, 822, 749. UV–Vis (DMF): λ_{max}, nm (log ε): 666 (4.86), 608 (4.47), 364 (5.14). MALDI-TOF-MS, (m/z): Calculated: 1812.85; Found: 1812.03 $[M]^+$.

3. Results and discussion

3.1. Synthesis and characterization

The synthetic pathway for the synthesis of phthalonitrile compound **(2)**, Zn(II) **(3)**, Cu(II) **(4)** and Co(II) **(5)** phthalocyanine complexes was shown in Fig. 1. The synthesis of phthalonitrile compound **(2)** was achieved by aromatic displacement of 2-methoxy-4-{(*Z*)-[(4-morpholin-4-ylphenyl)imino]methyl}phenol **(1)** with 4-nitrophthalonitrile in the presence of K_2CO_3 in dry DMF. The new vibration appeared at 2231 cm^{-1} (C≡N) verified the formation. The formation of compound **(2)** was confirmed by the combination of spectroscopic data. In the IR spectra of compound **(2)**, the peak due to phenolic O–H vibration of compound **(1)** disappeared. The new vibration (C≡N) appeared at 2231 cm^{-1} verified the formation of compound **(2).** In the ^{1}H NMR spectra of **(2)**, the phenolic OH signals of compound **(1)** disappeared and showed new aromatic protons signals. The characteristic new signals of carbon atom belonging to at 115.23 (C≡N) and 112.29 (C≡N) ppm in ^{13}C NMR spectra, supported the structure. The molecular ion peak of compound **(2)** was observed at m/z: 438.65 $[M]^+$, confirmed the proposed chemical structure.

The peripherally tetra-substituted Zn(II), Cu(II) and Co(II) phthalocyanines were accomplished in the presence of metal salts ($Zn(CH_3COO)_2$, $CuCl_2$ and $CoCl_2$) and DBU at 160 °C in n-pentanol in 24 h by cyclotetramerization of compound **(2).** These novel phthalocyanine derivatives were purified by column chromatography. The obtained phthalocyanines **(3–5)** are soluble in general organic solvents such as THF (Tetrahydrofuran), $CHCl_3$ (chloforom), DMF, CH_2Cl_2 (dichloromethane) and DMSO. The formation of Pc compounds **(3–5)** were clearly confirmed by the disappearance of

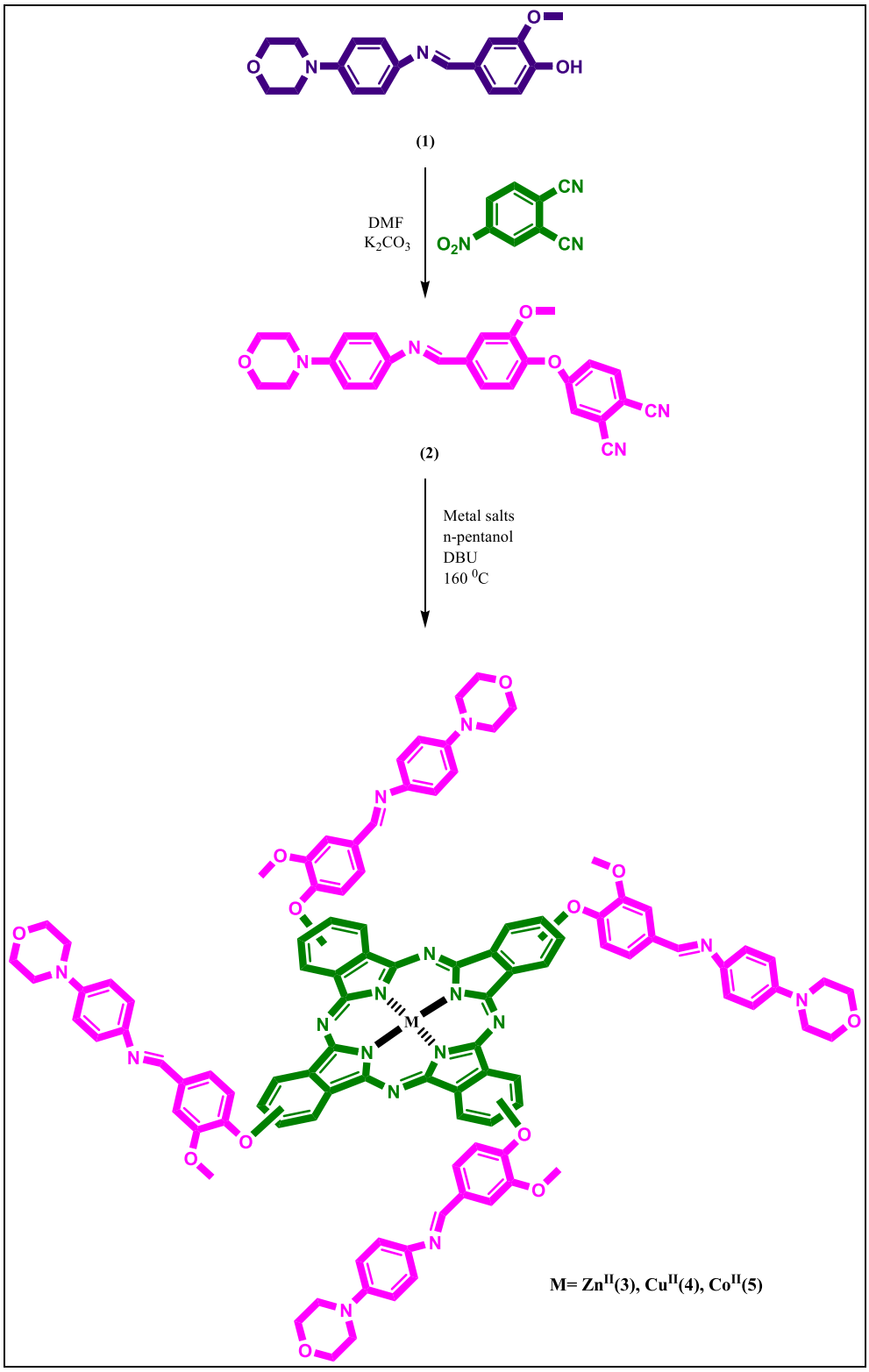

Fig. 1. The synthesis route of compounds **2**–**5.**

the C≡N band in the IR spectra. The ^{1}H NMR spectrum of zinc (II) phthalocyanine (**3**) was similar with phthalonitrile compound (**2**). This similarity is another evidence of the formation of wanted compounds. In the MALDI-TOF mass spectrum of compound (**3**) showed a peak at $m/z = 1819.62$ $[M]^{+}$, confirmed the proposed formula (Fig. 2). The NMR measurements of complexes copper(II)Pc (**4**) and cobalt(II)Pc (**5**) could not be obtained due to the paramagnetic nature [47]. Their molecular ion peaks at $m/z = 1817.91$ $[M]^{+}$ (Fig. 3) and 1812.03 $[M]^{+}$ respectively in mass spectra, are in accordance with the expected values.

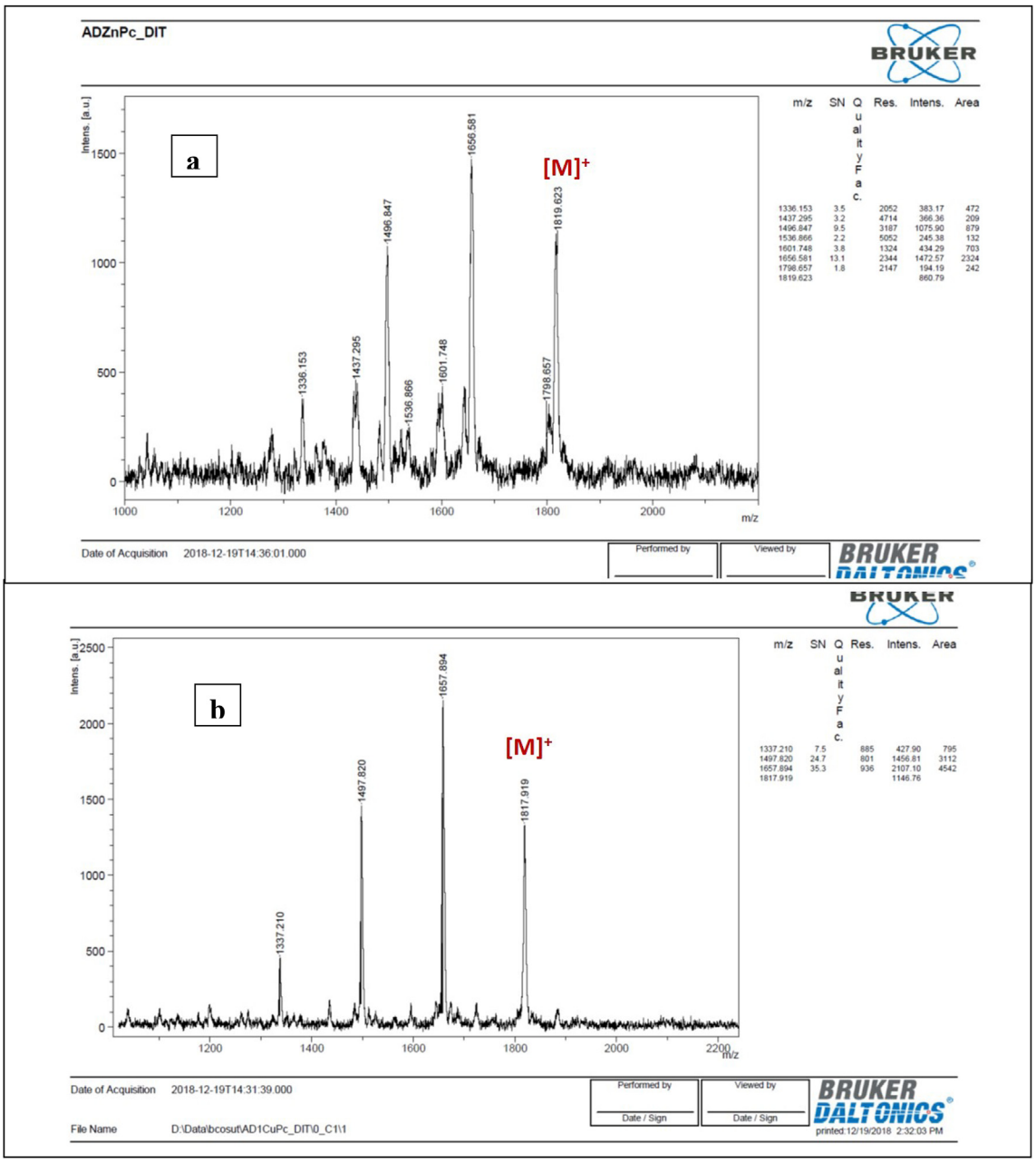

Fig. 2. MALDI-TOF-MS spectrum of ZnPc; b) MALDI-TOF-MS spectrum of CuPc.

3.2. Absorption properties of phthalocyanine compounds (3–5)

The UV–Vis spectra of the phthalocyanines show two strong absorption regions. One is B bands at 300–500 nm in the UV region. The other is Q band at near 600–700 nm which is more intense and energetic absorption [48]. Fig. 2 shows UV–Vis absorption spectrum of the metallophthalocyanine (**3**–**5**) in DMF at 1×10^{-5} mol dm^{-3} concentration. In the UV–Vis absorption spectra of (**3**), (**4**) and (**5**) intense Q band absorptions were observed at 681, 679 and 666 nm, respectively, while the B band absorptions were observed at 362, 376 and 364 nm, respectively. Metallophthalocyanines belonging to D_{4h} symmetry exhibits only an intense Q band absorption in their UV–Vis spectra [49].

Metallophthalocyanines (**3**), (**4**) and (**5**) have the same peripherally group, but have different metal center. This similarity in molecular structure resulted in similar shaped Q bands with small shifts in the wavelength (Fig. 4). The Q band positions of metallophthalocyanines (**3**–**5**) were observed in the order of ZnPc > CuPc > CoPc.

3.3. Antioxidant activity

In this study, FRAP and DPPH tests were followed to evaluate the antioxidant activities of three compounds (Co, Cu and Zn) and the results are presented in Fig. 5 [50–53]. In the FRAP and DPPH tests, the increasing $FeSO_4 \cdot 7H_2O$ equivalent and the decreasing SC_{50} value are indicative of more effective activity. When the results were compared with the results obtained from the standard antioxidant compound (Trolox), it was determined that the activities obtained from compound CoPc (**5**) and ZnPc (**3**) were quite high

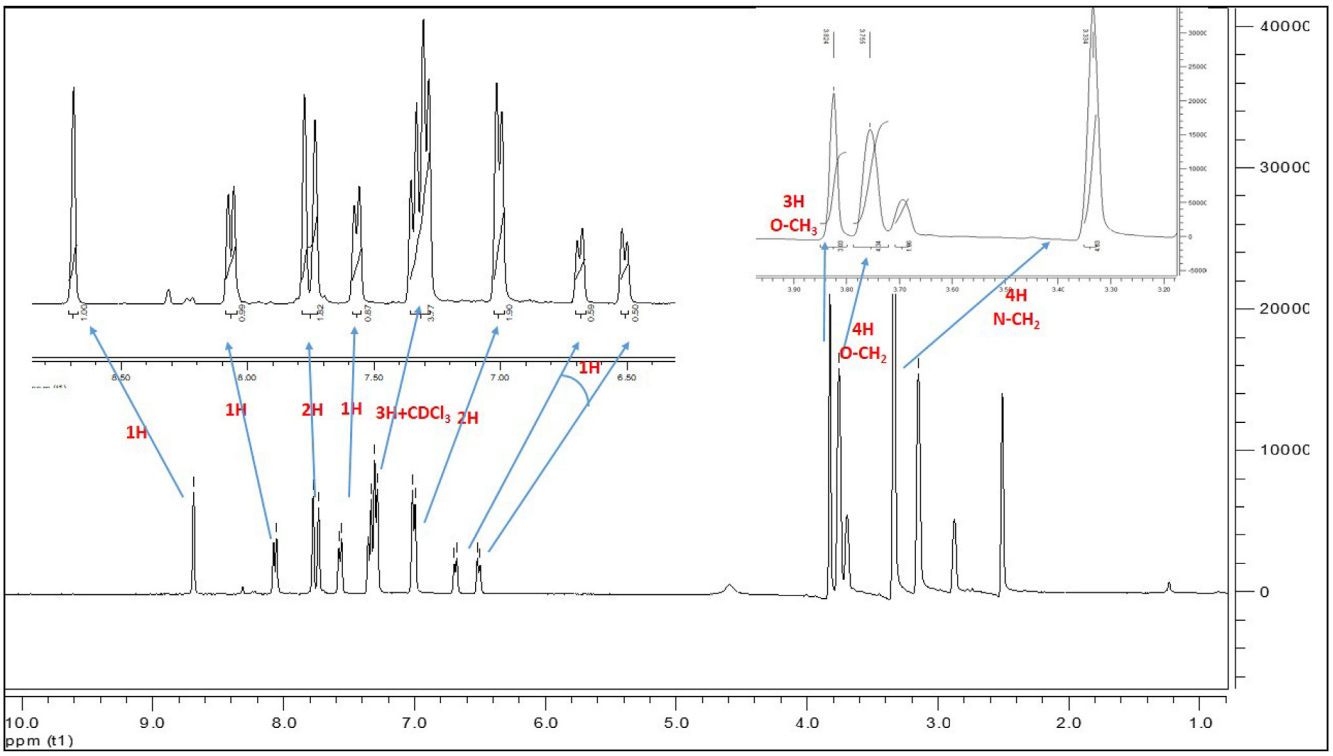

Fig. 3. ^{1}H NMR spectrum of phthalonitrile compound 2.

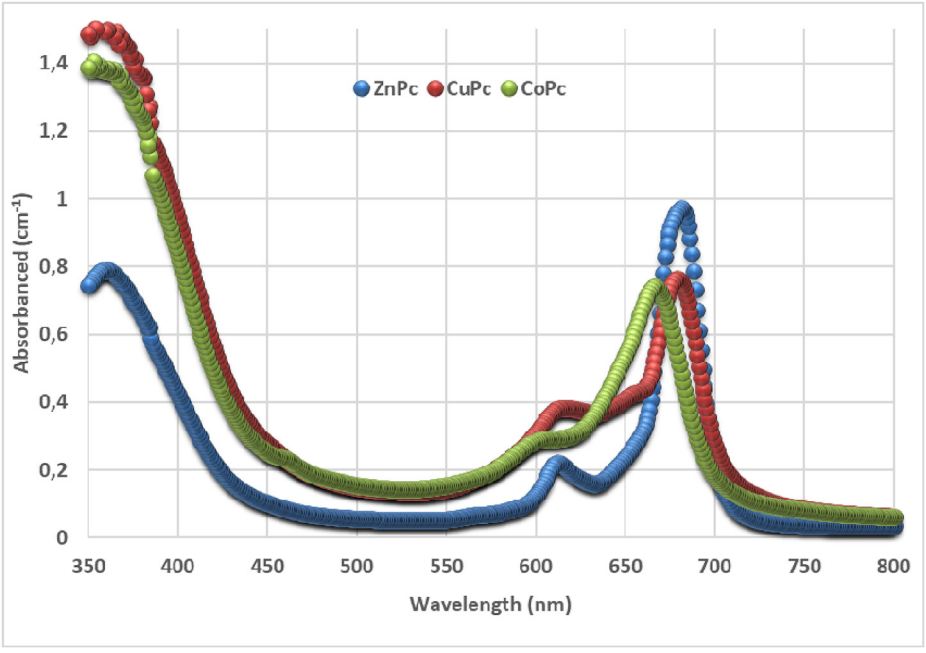

Fig. 4. UV–Vis absorption spectrum of ZnPc, CoPc and CuPc in DMF at 1×10^{-5} M.

and the activity of compound CuPc **(4)** was moderate. In the ferric reducing power test, the FRAP values were defined as 5948.3, 3084.4 and 4709.4 μM $FeSO_4 \cdot 7H_2O$ equivalent/g sample. The highest FRAP value (i.e. the highest activity) and the lowest FRAP value (i.e. lowest activity) was measured in compound CoPc and CuPc, respectively. In the DPPH assay, the compounds have a significant free radical scavenging effect (against the DPPH radical) with SC_{50} values of 23.31, 63.15 and 23.52 μg/mL. The strongest activity was observed in compound CoPc **(5)** (SC_{50}: 23.31 μg/mL) and the weakest activity in compound CuPc **(4)** (SC_{50}: 63.15 μg/mL). The SC_{50} value of standard antioxidant compound (trolox) was found as 5.11 μg/mL. The lower IC_{50} means higher antioxidant power [54]. According to this, the descending order of IC_{50} values of phthalocyanine compounds was **4 > 3 > 5**.

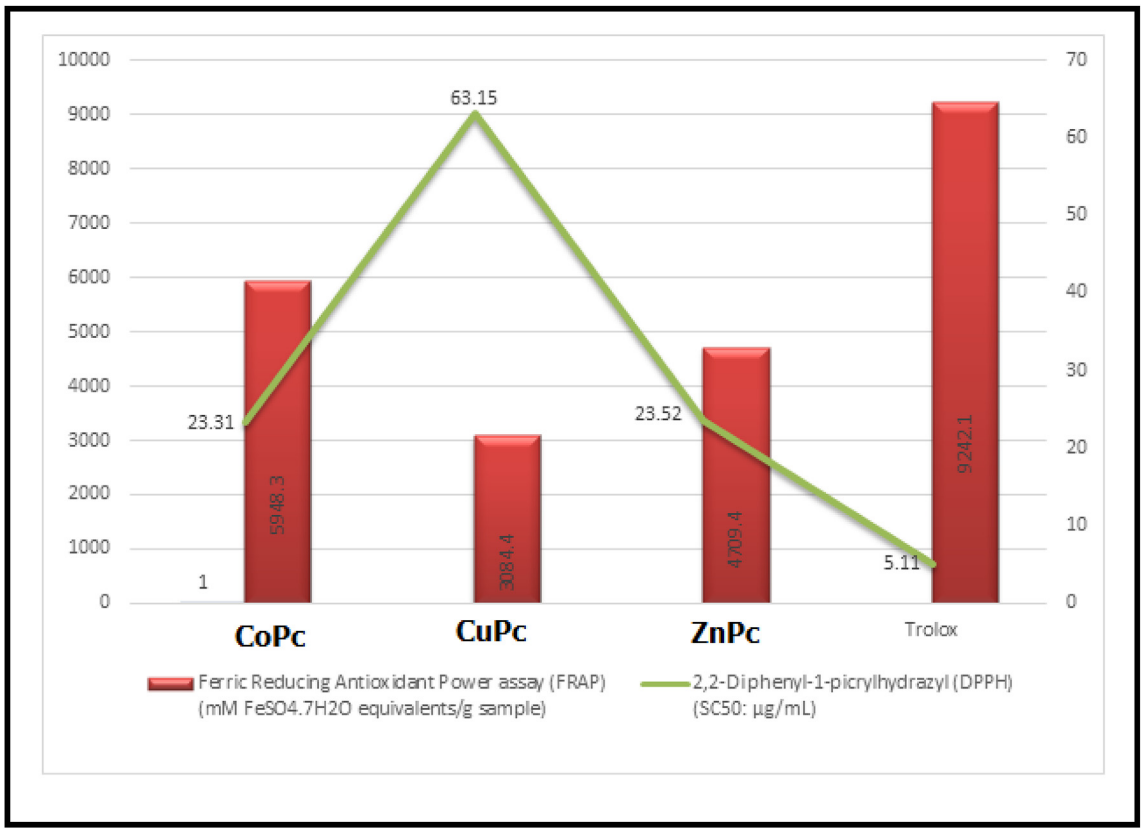

Fig. 5. Ferric reducing antioxidant power (FRAP), and radical scavenging activities (DPPH) of phthalocyanine compounds (3–5).

The connected substituent on Pc and centrally located metal atom effect antioxidant activity [54,55]. The increase in redox activity of the central metal atom in the phthalocyanine compounds also increases the antioxidant property. According to the DPPH and FRAP tests, the order of the antioxidant effect of Pc compounds was CoPc **(5)** > ZnPc **(3)** > CuPc **(4)**. These results showed a higher antioxidant effect compared with Pcs in the literature [56].

3.4. Antimicrobial activity

The antibacterial activity of the synthesized Pc compounds were screened against Gram positive strains (*S. aureus* [MRSA]), Gram negative strains (*E. coli, S.typhimurium, Y. enterocolitica, S.flexneri*) and Gram negative nonfermenter strain (*P. aeruginosa*). MIC interpretation criteria of standard bacteria isolates against standard amikacin antibiotic were made according to the CLSI (Clinical and Laboratory Standards Institute, CLSI M100-S25) [57]. MIC values of the compounds were given in Table 1. Antibacterial activities assessed with Alamar Blue Dye were shown in Fig. 6. In the study were assessed negative control in 7th wells and positive control in 8th wells (Fig. 6). The highest antibacterial activity were observed for *E.coli* and *S.typhimurium* (minimum inhibitory concentrations (MIC) 625 µg/mL). All negative and positive controls were working properly.

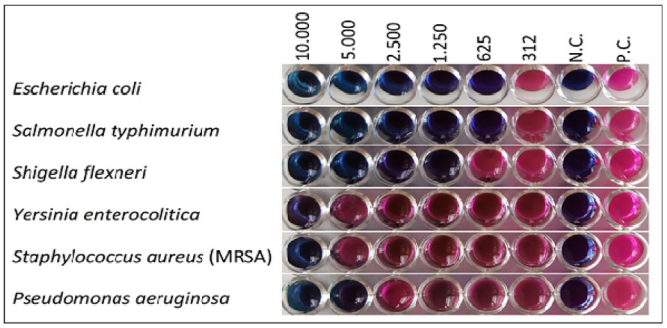

Fig. 6. Antibacterial activity shown in microplate of the compound CoPc (5).

CoPc **(5)** was found to have antimicrobial activity at different concentrations against all standard bacteria. In vitro studies have showed that the especially compounds CoPc **(5)** and CuPc **(4)** have remarkable antibacterial activity for *S. typhimurium*, and E. Coli (Table 1). Therefore, this study can contribute to new drug development on based the compound.

Table 1
The antibacterial activities of five compounds against bacterial isolates (MIC value µg/ml).

Complexes	Bacteria					
	Escherichia coli	*Salmonella typhimurium*	*Shigella flexneri*	*Yersinia enterocolitica*	*Staphylococcus aureus* (MRSA)	*Pseudomonas aeruginosa*
$Co^{II}Pc$	625	625	1.250	10.000	10.000	5.000
$Cu^{II}Pc$	625	625	5.000	10.000	>10.000	5.000
$Zn^{II}Pc$	1.250	1.250	2.500	>10.000	10.000	5.000

4. Conclusion

The phthalonitrile derivative (**2**), Zn(II), Cu(II) and Co(II) phthalocyanine compounds **(3–5)** which are substituted with morpholine bearing schiff base group have been synthesized for the firstly. All compounds were characterized by different spectroscopic method for the secondly. These synthesized phthalocyanine complexes **(3–5)** exhibit high solubility in common organic solvents owing to the addition of 4-(2-methoxy-4-{(E)-[(4-morpholin-4-ylphenyl)imino]methyl}phenol groups on the structure. Antioxidant activities were determined by using, FRAP (ferric reducing antioxidant power) and DPPH free radical scavenging systems. In all antioxidant assays, CoPc **(5)** showed higher activities than other Pcs **(3** and **4).** The order of the antioxidant activity was CoPc > ZnPc > CuPc. Finally antimicrobial activities of metallo Pcs were determined using microdilution broth assay with Alamar Blue Dye. According to in vitro studies, especially compounds CoPc **(5)** and CuPc **(4)** have remarkable antibacterial activity for *S. typhimurium*, and *E. coli*. Therefore, this work can contribute to new drug development on based the compound. Besides, due to these encouraging in vitro antimicrobial activity results, after further studies, the compound can be evaluated as new therapeutic agent against for the bacteria.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.120936.

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