ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2018, *63*(1), 59-65

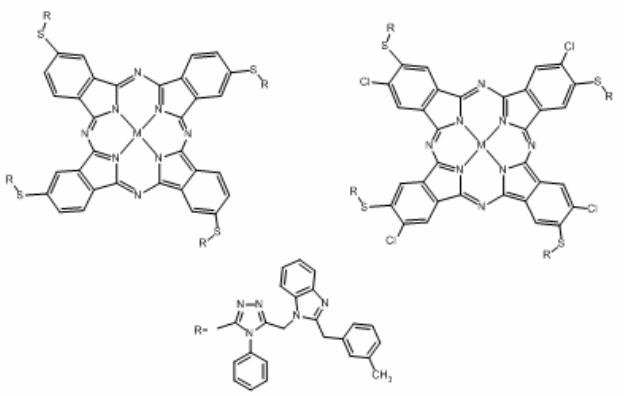
SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW TRIAZOLE BRIDGED BENZIMIDAZOLE SUBSTITUTED PHTHALONITRILE AND PHTHALOCYANINES**

Günay Kaya KANTAR,[a] Emre MENTEŞE,*[a] Fatih Şaban BERİŞ,[b] Selami ŞAŞMAZ[a] and Bahittin KAHVECİ[c]

[a] Department of Chemistry, Faculty of Arts and Sciences, Recep Tayyip Erdogan University, Rize 53100, Turkey
[b] Department of Biology, Faculty of Arts and Sciences, Recep Tayyip Erdogan University, Rize 53100, Turkey
[c] Department of Nutrition and Dietetics, Faculty of Health Sciences, Karadeniz Technical University, Trabzon 61100, Turkey

Received March 29, 2017

In this study, some new phthalonitriles and metallophthalocyanines (Zn, Ni, Co, and Cu) containing triazole bridged benzimidazole moieties were synthesized starting from 2-(3-methylbenzyl)-1*H*-benzimidazole. Newly synthesized compounds have been tested for their antimicrobial effects against four Gram positively (*Bacillus cereus* 702 Roma, *B. megaterium* DSM-32, *B. subtilis* ATCC 6633, and *Staphylococcus aureus* ATCC 25923) and four Gram negatively (*Escherichia coli* ATCC 25922, *Enterobacter cloaceae* ATCC13047, *Pseudomonas aeruginosa* ATCC 27853, and *Yersinia pseudotuberculosis* ATCC 911) bacteria. According to results, compounds **6**, **7b**, **7c**, and **8a** have the best activity with MIC values of 31.25 µg/mL to *B. subtilis*. The second best activity belongs to compounds **4**, **5**, **7**, **8**, **7a**, **8c**, and **8d** with the MIC value of 62.5 µg/mL on the same bacterium. Zinc (II) phthalocyanines have better antimicrobial activity than other metallophthalocyanines against Gram (+) bacteria.



INTRODUCTION

Phthalocyanines (Pcs) are an important class of macrocyclic compounds due to their wide range applications in different areas such as catalysts,[1] solar cells,[2] chemical sensors,[3] material devices,[4] optical data storage devices,[5] photovoltaic cells,[6] gas sensors,[7] organic semiconductors,[8] the photoinactivation of bacteria and viruses,[9, 10] and photosensitizers in photodynamic therapy.[11] During the last decades, great attention has been focused on the photophysical and photochemical behavior of Pcs bearing different heterocyclic moieties.[12-14] Also, antioxidant, xanthine oxidase, antibacterial, and anticancer properties of some phthalocyanine compounds have been previously reported.[15-17] Today, synthesis and investigation of biological properties of new phthalocyanines continues to be of interest.

Benzimidazole nucleus has an important role in the medicinal chemistry because of their diverse biological activities such as antibacterial, anti-inflammatory, anti-ulcer, antioxidant, antitumor and lipase inhibition.[18-22] Furthermore, benzimidazoles bearing triazole ring have demonstrated considerable biological activities.[23-25]

* Corresponding author: emre.mentese@erdogan.edu.tr
** Supplementary information on http://web.icf.ro/rrch or http://revroum.lew.ro

Although there are many publications about phthalonitrile and phthalocyanines containing triazole[26-29] or benzimidazole[30] rings at literature, any work has never been reported on the phthalocyanine containing triazole bridged benzimidazole moieties. In this work, we report the synthesis and antimicrobial activity of some novel metallophthalocyanines (M: Ni, Co, Zn, Cu) containing triazole bridged benzimidazole moieties.

EXPERIMENTAL

All the chemicals were supplied by Merck, Aldrich and Fluka. Melting points were determined on capillary tubes on Stuart SMP30 melting point apparatus and uncorrected. The IR spectra were recorded for KBr pellets on Perkin-Elmer 100 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were performed on Bruker 400 MHz spectrometer in DMSO-d_6 using TMS as internal. UV/vis spectra were recorded on Mattson UNICAM UV/vis spectrometer. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness).

4-Nitro-1,2-dicyanobenzene[31], 4,5-dichloro-1,2-dicyanobenzene[32], compound **1**[33] and **2**[21,34] were prepared by reviewing literature.

2-(3-Methylbenzyl)-1H-benzimidazole (**2**)

A mixture of 1,2-phenylenediamine (0.010 mol) and iminoester hydrochlorides (0.013 mol) (**1**) in methanol (30 mL) was taken in a round flask. The solution was stirred for 10 hours at room temperature. After the completion of the reaction, (monitored by TLC, ethylacetate:hexane, 3:1), the mixture was poured into water. The precipitate was collected by filtration and recrystallized from ethanol-water (1:3) to give pure compound **2.** Yield 90 %, mp: 151-152°C (lit.2 mp 152-153 °C).

Ethyl 2-(2-(3-methylbenzyl)-1H-benzimidazol-1-yl)acetate (**3**):

A mixture of compounds **2** (0.010 mol), ethylbromoacetate (0.010 mol) and K_2CO_3 (0.025 mol) in acetone (25 mL) was stirred for 12 hours at room temperature. After the completion of the reaction, (monitored by TLC, ethylacetate:hexane, 3:1), the mixture was poured into water. The precipitate was collected by filtration and recrystallized from acetone-water (1:3) to give pure compound **3.** Yield 95 %, mp: 109-110 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.11 (t, *J*= 7.2 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.97 (q, J= 7.2 Hz, 2H, O-CH_2), 4.20 (s, 2H, CH_2), 5.13 (s, 2H, N-CH_2), 7.00-7.13 (m, 3H, Ar-H), 7.16-7.18 (m, 3H, Ar-H), 7.43 (d, *J*= 8 Hz, 1H, Ar-H), 7.57 (d, *J*= 8 Hz, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.33, 21.41 (CH_3), 33.23 (CH_2), 44.59 (N-CH_2), 61.54 (O-CH_2), 110.61, 118.95, 122.10, 122.47, 126.38, 127.66, 128.77, 129.83, 136.10, 136.69, 137.93, 142.38 (Ar-C), 154.18 (C=N), 168.14 (C=O).

2-(2-(3-Methylbenzyl)-1H-benzimidazol-1-yl)acetohydrazide (**4**):

To a solution of compound **3** (0.010 mol) in ethanol (25 mL), hydrazine monohydrate (0.025 mol) was added and was refluxed for 8 hours (monitored by TLC, ethyl acetate-hexane, 3:1). Then, the mixture was cooled to room temperature. The precipitate was filtered off and recrystallized from ethanol to give pure compound **4**. Yield 83 %, mp: 168-169 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.25 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 4.30 (s, 2H, NH_2, D_2O exchangeable) 4.77 (s, 2H, N-CH_2), 7.01-7.18 (m, 6H, Ar-H),7.40 (d, J= 8, 1H, Ar-H), 7.54 (d, J= 8, 1H, Ar-H), 9.48 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 21.45 (CH_3), 33.35 (CH_2), 44.91 (N-CH_2), 110.45, 118.97, 121.87, 122.19, 126.43, 127.63, 128.78, 129.92, 136.07, 137.14, 142.69 (Ar-C), 154.57 (C=N), 166.38 (C=O).

1-(2-(2-(3-Methylbenzyl)-1H-benzimidazol-1-yl)acetyl)-4-phenylthiosemicarbazide (**5**):

A mixture of compound **4** (0.010 mol) and phenylisothiocyanate (0.010 mol) in ethanol (25 mL) was heated under reflux for 4 hours. Then, the mixture was cooled to room temperature and the crude product was observed by addition of water, filtered off and recrystallized from ethanol-water (2:1) to afford the desired product. Yield 85 %, mp: 175-177 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.25 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 4.95 (s, 2H, N-CH_2), 7.00-7.18 (m, 7H, Ar-H), 7.33-7.56 (m, 6H, Ar-H), 9.68, 9.80, 10.49 (s, 3H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 21.46 (CH_3), 33.31 (CH_2), 44.09 (N-CH_2), 110.60, 118.99, 122.25, 126.39, 127.68, 128.34, 129.89, 136.07, 137.10, 138.02, 139.40, 142.61 (Ar-C), 154.57 (C=N), 166.11 (C=O).

5-((2-(3-Methylbenzyl)-1H-benzo[d]imidazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**6**):

A solution of carbothioamide **5** (0.010 mol) in ethanol/water (1:1) was refluxed for 1 hour in the presence of 2N NaOH. Then, the resulting solution was cooled to room temperature and acidified to pH 5-6 with 37 % HCl. The crude product was filtered off, washed with water and recrystallized from ethanol to afford compound **6**. Yield 73%, mp: 276-278 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.21 (s, 3H, CH_3), 3.93 (s, 2H, CH_2), 5.28 (s, 2H, N-CH_2), 6.87-6.91 (m, 2H, Ar-H), 6.99-7.10 (m, 1H, Ar-H), 7.12-7.16 (m, 3H, Ar-H), 7.30-7.35 (m, 3H, Ar-H), 7.50-7.55 (m, 4H, Ar-H), 13.84 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 21.43 (CH_3), 33.02 (CH_2), 40.61 (N-CH_2), 110.81, 118.99, 122.47, 126.17, 127.68, 128.44, 128.74, 129.60, 129.95, 130.23, 133.34, 135.76, 136.53, 137.99, 142.37 (Ar-C), 147.94, 153.81 (C=N), 168.99 (C=S).

4-[5-((2-(3-Methylbenzyl)-1H-benzo[d]imidazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazole-3-thio]phthalonitrile (**7**):

Compound **6** (1.55 g, 2.88 mmol), 4-Nitro–1,2-dicyanobenzene (0.50 g, 2.88 mmol) were dissolved in DMF (50 mL) and anhydrous K_2CO_3 (1,4 g, 8.6 mmol) was added to this solution. Then, reaction mixture was stirred at 60 °C for 48 hours. After the reaction was completed, the mixture was filtered and poured into water bath. Formed solid material was filtered off and washed with water. The crude product was purified by recrystallization from ethanol. Yield 78 %, mp: 74-78 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.28 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 5.55 (s, 2H, N-CH_2), 6.94-7.08 (m, 2H, Ar-H), 7.18-7.27 (m, 4H, Ar-H), 7.32-7.40 (m, 3H, Ar-H), 7.47-7.63 (m, 4H, Ar-H), 7.63-8.07 (m, 3H, Ar-H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 21.53 (CH_3), 33.20 (CH_2), 64.90 (N-CH_2), 66.49, 110.83, 113.10, 115.77 (CN), 116.07 (CN), 119.12, 121.85, 122.47, 126.28, 127.73, 128.83, 129.25, 129.78, 130.30, 131.03, 132.24, 132.49, 134.84, 134.85, 136.67, 138.14, 141.47, 142.62, 146.25, 153.75, 153.86.

4-[5-((2-(3-Methylbenzyl)-1H-benzo[d]imidazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazole-3-thio] 5-chloro phthalonitrile (**8**):

Compound **6** (2.29g, 5.58 mmol), 4,5-dichloro-1,2-dicyanobenzene (0.55 g, 2.79 mmol) were dissolved in DMF (50 mL) and finely ground anhydrous K_2CO_3 (1,4 g, 13.2 mmol) was added to this solution. Then, the reaction mixture was stirred at 60 °C for 48 h. After the reaction was completed, the mixture was filtered and poured into water bath. Formed solid material was filtered off and washed with water. The crude product was purified by recrystallization from ethanol. Yield 71%, mp: 84-85 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.29 (s, 3H, CH_3), 3.93 (s, 2H, CH_2), 5.56 (s, 2H, N-CH_2), 6.94-7.08 (m, 2H, Ar-H), 7.17-7.21 (m, 4H, Ar-H), 7.23-7.40 (m, 4H, Ar-H), 7.49-7.62 (m, 3H, Ar-H), 7.71-8.48 (m, 2H, Ar-H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 21.56 (CH_3), 33.20 (CH_2), 94.83 (N-CH_2), 110.85, 115.10 (CN), 115.40 (CN), 118.66, 119.12, 122.21, 122.24, 122.49, 123.54, 126,33, 126.34, 127.69, 127.70 127.85, 128.94, 129.26, 129.33, 129.51, 129.80, 130.38, 132.54, 133.93, 136.13, 138.11, 154.32.

Microwave Assisted Synthesis of Phthalocyanines **(7a-7d** and **8a-8d)**:

The general method for the synthesis of various metallophthalocyanines (Co, Ni, Cu and Zn) is as follows. Compounds **7** and **8** (300 mg), metal salt for corresponding metallophthalocyanine ($CoCl_2$, $NiCl_2.6H_2O$, $CuCl_2.H_2O$, $Zn(CH_3COO)_2$ (0.060 mmol), DMF (5 mL) and 2 - 3 drops DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) were charged together into a round bottomed flask. The reaction flask was irradiated by a microwave apparatus at 300 W for 20 min. After cooling to room temperature, the mixture was poured into water to precipitate the substance. The obtained green product was purified by column chromatography (silica gel, EtOH - CH_2Cl_2, 10:1). All synthesized phthalocyanines are soluble in DMF and DMSO.

Yield, melting point, elemental analysis, FTIR and UV/vis spectra of the products were as follows.

Zinc phthalocyanine (**7a)**; Yield 27 mg (87.1 %) mp > 300 °C. FTIRν_{max}/cm^{-1} 3058 (Ar-CH), 1598 (C=C), 1275 (Ar-S-Ar), 1169, 1096, 907, 840, 743. UV/vis (DMSO) : λ_{max} /nm 329, 619, 687.

Nickel phthalocyanine **(7b)**; Yield 22 mg (70 %) mp > 300 °C. FTIRν_{max}/cm^{-1} 3060 (Ar-CH), 1587(C=C), 1361 (Ar-S-Ar), 1198, 1062, 847, 742. UV/vis (DMSO) : λ_{max} /nm 339, 605, 681.

Cobalt phthalocyanine (**7c**); Yield 23 mg (71%) mp > 300 °C. FTIRν_{max}/cm^{-1} 3062 (Ar-CH), 1593 (C=C), 1312 (Ar-S-Ar), 1261, 1178, 1140, 1101, 891, 741. UV/vis (DMSO) : λ_{max} /nm 338, 605, 678.

Copper phthalocyanine (**7d**); Yield 18 mg (58 %) mp > 300 °C. FTIRν_{max}/cm^{-1} 3051 (Ar-CH), 1595 (C=C), 1395 (Ar-S-Ar), 1309, 1141, 1100, 985, 918, 743. UV/vis (DMSO) : λ_{max}/nm 337, 615, 681.

Zinc phthalocyanine (**8a)**; Yield 24 mg (77 %) mp > 300 °C. FTIRν_{max}/cm^{-1} 3048 (Ar-CH), 1596, 1496 (C=C), 1288 (Ar-S-Ar), 1178, 1088, 1064, 942, 890, 742. UV/vis (DMSO) : λ_{max} /nm 326, 620, 687

Nickel phthalocyanine **(8b)**; Yield 21 mg (68 %) mp > 300 °C. FTIRν_{max}/cm^{-1} 3040 (Ar-CH), 1587 (C=C), 1416 (Ar-S-Ar), 1073, 741, 692. UV/vis (DMSO) : λ_{max} /nm 355, 612, 682.

Cobalt phthalocyanine (**8c**); Yield 24 mg (77 %) mp > 300 °C. FTIRν_{max}/cm^{-1} 3059 (Ar-CH), 1604 (C=C), 1414(Ar-S-Ar), 1387, 1289, 1132, 1071, 961, 883, 748. UV/vis (DMSO) : λ_{max} /nm 330, 619, 686.

Copper phthalocyanine (**8d**); Yield 21 mg (67 %) mp > 300 °C. FTIRν_{max}/cm^{-1} 3058 (Ar-CH), 1596 (C=C), 1380 (Ar-S-Ar), 1186, 1088, 1070, 951, 889, 743. UV/vis (DMSO) : λ_{max}/nm 328, 594, 685.

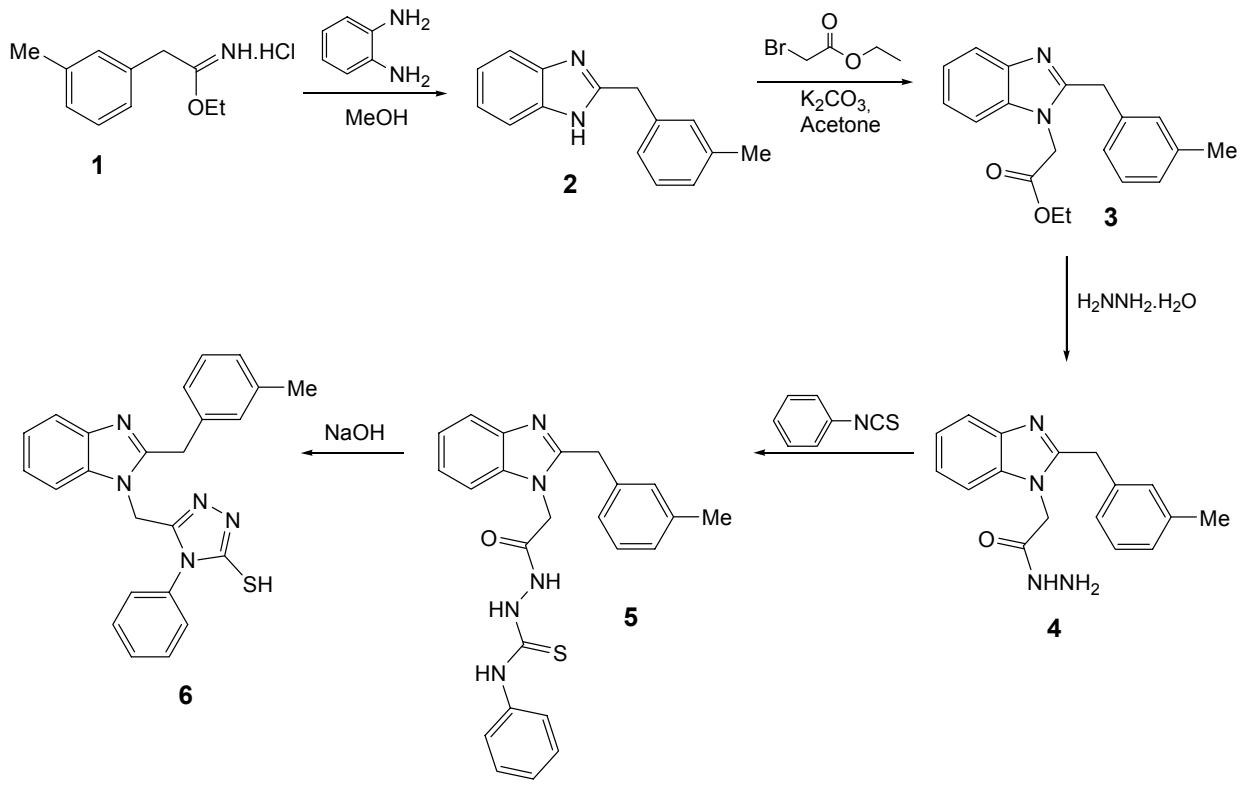
Anti-microbial Activity

The qualitative screening of the susceptibility spectra of different microbial strains to the complexes was performed by the quantitative assay of minimal inhibitory concentration (MIC, µg/mL) based on liquid medium serial microdilutions.[36,37] The MIC assays were performed in LB medium at pH 7.2. The stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO) at 2 mg/mL stock concentration. The dilution series of the chemical compounds to be tested were prepared from 1000 to 7.8 µg/mL concentrations in 100 µL medium. The broth cultures were incubated at 37.0 ± 1 °C for 18–24 h. Dimethysulphoxide, LB medium with or without antibiotic and ampicillin, were used as solvent control, positive, and negative control, respectively. The MIC was taken to be the last well in the dilution series that did not exhibit growth as determined on the basis of turbidity.

The determination of minimum inhibitory concentration[37] was done with three of Gram-positive bacterial strains, namely *Bacillus cereus* 702 Roma, *B. megaterium* DSM-32, *B. subtilis* ATCC 6633, and *Staphylococcus aureus* ATCC 25923) and four Gram negative bacterial strains which were *Escherichia coli* ATCC 25922, *Enterobacter cloaceae* ATCC13047, *Pseudomonas aeruginosa* ATCC 27853, and *Yersinia pseudotuberculosis* ATCC 911. These were inoculated into Luria broth medium containing 1 % tryptone, 0.5 % yeast extract and 0.5 % sodium chloride. The pH of the medium was adjusted to 7.2 and incubated at 37 ºC for 18-24 hours. The optical density of the bacteria from mid-log phase of growth was measured at 600 nm and diluted in fresh medium so as to get an optical density of 0.004 (corresponding to 5 x 10^5 colony forming units/mL).

RESULTS AND DISCUSSION

Firstly, iminoester hydrochloride **1** was prepared according to the literature.[33] In order to synthesize benzimidazole derivative **2**,[21, 34] compound **1** was reacted with 1,2-phenylenediamine. By the treatment of compound **2** with ethyl bromoacetate in acetone was synthesized the compound **3** which was converted to afford the desired hydrazide derivative **4** by hydrazine hydrate. In the next step, compound **5** was obtained by the nucleophilic addition of **4** to phenylisothiocyanate. Finally, compound **6** was synthesized by intramolecular cyclization of compound **5** in present of 2N NaOH.[23] The synthetic route of the target compounds (**2-6**) can be seen in Scheme **1**. The chemical structures of new compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR spectroscopy. Spectroscopic investigations of newly synthesized compounds are accordance with the proposed structures.

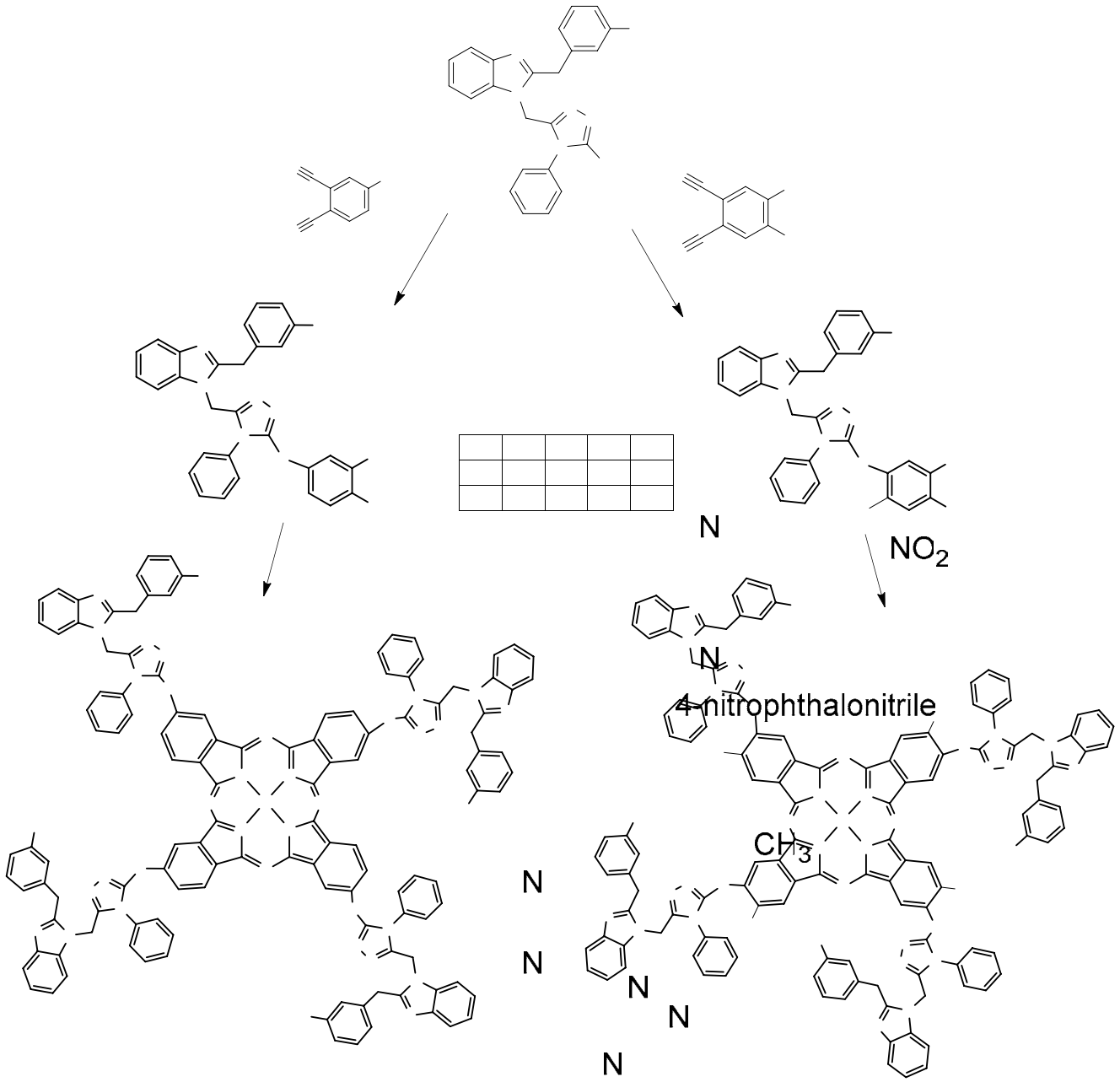


Scheme 1 – The synthetic path of the target compounds (**2-6**).

The synthesis of phthalonitrile compounds (**7** and **8**) was the most important step in these reaction sequences. For this purpose, compounds **7** and **8** were synthesized by the treatment compound **6** with 4-nitro-1,2-dicyanobenzene[31] and 4,5-dichloro-1,2-dicyanobenzene[32] respectively, in DMF using K_2CO_3 as base. At the last step, metallophthalocyanines were synthesized from the corresponding phthalonitrile compounds and $CoCl_2$, $NiCl_2.6H_2O$, $CuCl_2.H_2O$, $Zn(CH_3COO)_2$, respectively, in DMF by microwave irradiation for 10 min. The synthetic route of the phthalonitrile compounds and phthalocyanines can be seen in Scheme 2.

The FT-IR spectra of compounds **7** and **8** showed the presence of nitrile group at 2231 and 2236 cm^{-1}, respectively. In the ^1H NMR spectrum of **6,** SH peak appears at 13.84 ppm. In compounds **7** and **8**, this peak disappears. The ^{13}C NMR spectral data of compounds **7** and **8** are also in accordance with the expected structure. The ^{13}C NMR spectrum of compounds **7** and **8** showed the presence of C≡N carbon atom at (115.77, 116.07) and (115.10, 115.40) ppm, respectively. FT-IR spectra of the phthalocyanines (**7a-d, 8a-d)** clearly indicate the cyclotetramerization of the phthalonitrile derivatives with the disappearance of the C≡N peak at 2231 and 2236 cm^{-1}, respectively.

The best indication for the phthalocyanine systems is their UV-vis spectra in solutions. The phthalocyanines exhibit typical electronic spectra with two strong absorption regions. One of them is in the UV region at about 200–350 nm (B band), and the other one is in the visible region at 600–700 nm (Q band). The Q band was attributed to $\pi \rightarrow \pi^*$ transitions from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the Pc ring. The other bands (B) in the UV region are observed due to the transitions from the deeper π levels to the LUMO[35.] The novel synthesized metallophthalocyanines showed typical electronic spectra with two strong absorption regions. One of them is in UV region at about **7a-d** (326-355 nm), **8a-d** (329-339 nm) (B band) and the other is in the visible region at about **7a-d** (605-687 nm), **8a-d** (594-687 nm) (Q band) in DMSO, respectively. Aggregation describes coplanar association of phthalocyanine compounds from monomer to dimer or higher order complexes. For the Q band regions, sharper and more intense Q-bands than the bathochromically shifted shoulders are evidence of monomeric behaviour[13]. According to UV/vis spectra the metallophthalocyanines **7a** and **8a** are monomeric form in DMSO at 1 x 10^{-5} concentration. The UV-vis spectra of newly synthesized phthalocyanines can be seen in figure 1.



Scheme 2 – Synthesis route of compounds **7**, **8** and phthalocyanines (**7a-d** and **8a-d**)

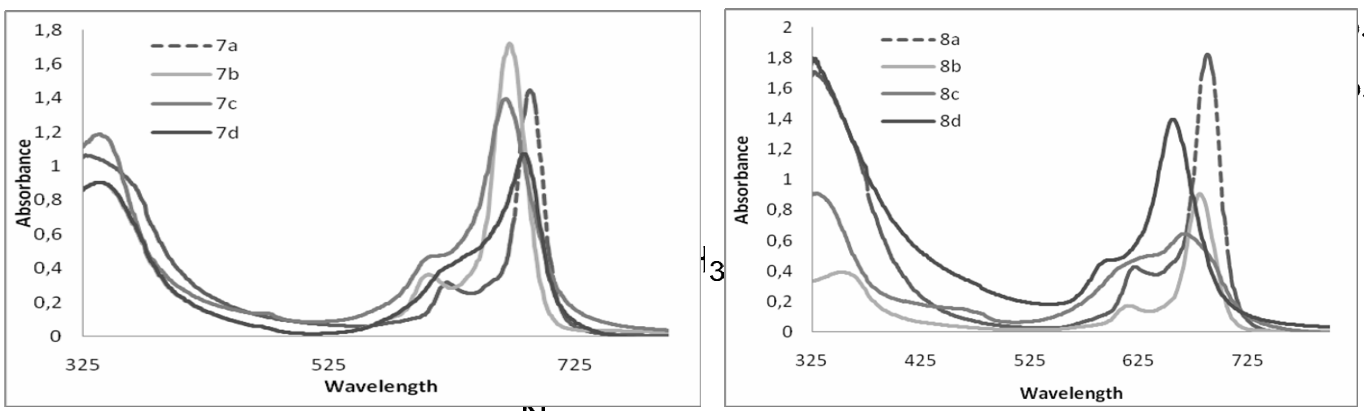


Fig. 1 – UV/vis spectra of compounds **7a-d** and **8a-d** in DMSO.

Table 1

In-vitro antibacterial activity data of all compounds

Compound No.	Stock Solution (μg/mL)	Bacteria and Minimal Inhibitory Concentrations (MIC)							
		Gram Negative				Gram Positive			
		Ec	Eclo	Pae	Yp	Bc	Bm	Bs	Sau
3	1000	1000	1000	1000	500	500	1000	250	1000
4	1000	500	250	250	62,5	125	62,5	62,5	500
5	1000	250	250	250	250	125	62,5	62,5	500
6	1000	250	250	125	62,5	125	125	31,25	250
7	1000	250	125	250	125	62,5	125	62,5	250
8	1000	250	250	250	125	250	125	62,5	500
7a	1000	250	250	250	125	125	125	62,5	250
7b	1000	250	250	250	125	125	125	31,25	250
7c	1000	250	250	250	125	125	125	31,25	250
7d	1000	1000	1000	1000	1000	1000	1000	1000	1000
8a	1000	125	125	500	500	62,5	62,5	31,25	125
8b	ND	ND	ND	ND	ND	ND	ND	ND	ND
8c	1000	250	250	250	125	125	125	62,5	250
8d	1000	250	250	250	125	125	125	62,5	500
DMSO	ND	ND	ND	ND	ND	ND	ND	ND	ND
P + amp.	100 μg/mL	-	-	-	-	-	-	-	-
P		+	+	+	+	+	+	+	+

Bc: *B. cereus* 702 Roma, Bm: *B. megaterium* DSM-32, Bs: *B. subtilis* ATCC 6633, Sau: *S. aureus* ATCC 25923, Ec: *E. coli* ATCC 25922, Eclo: *E. cloaceae* ATCC 13047, Pae: *P. aeruginosa* ATCC 27853, Yp: *Y. pseudotuberculosis* ATCC 911; DMSO: dimethyl sulfoxide; P: positive control (just medium, LB); ND: not determined; amp: ampicilline as the negative control agent.

Antimicrobial Activity

All of the synthesized compounds were tested against four of Gram-positive and of Gram-negative bacteria in accordance with the published protocols.[13, 14] The results were compared with the standard drug, ampicillin (Table 1). As can be seen from the table 1, all newly synthesized compounds showed anti-bacterial effect, ranging from good to moderate, with a minimum inhibitory concentration of 7.8-1000 μg/mL in dimethyl sulfoxide.

According to all microbial results, compounds **6**, **7b**, **7c**, and **8b** have the best activity with MIC values of 31.25 μg/mL to *B. subtilis*. The second best activity belongs to compounds **4**, **5**, **7**, **8**, **7a**, **8c**, and **8d** with the MIC value of 62.5 μg/mL on the same bacterium. Compound **8a** has the MIC value of 31.25 μg/mL to *B. subtilis*, of 62.5 μg/mL to *B. cereus* and *B. megaterium*, of 125 μg/mL to *S. aureus*, *E. coli*, and *E. cloaceae*. As is seen from Table 1, the second best effect was the 62.5 μg/mL with compound **4** to *Y. pseudotuberculosis* and *B. megaterium*, **5** to *B. megaterium*, **6** to *Y. pseudotuberculosis*, and **7** to *B. cereus*. The other compounds have a moderately effect on the bacteria, *i.e.* 125 and 250 μg/mL. Compounds **7d, 3 and 8b** haven't got any effect on all bacteria at used concentrations.

CONCLUSION

In conclusion, some new phthalonitrile and metallophthalocyanines (Zn, Ni, Co, and Cu) containing both benzimidazole and 1,2,4-triazole rings have been synthesized for the first time. The antibacterial activity of the target compounds varied for the bacterial strains tested. The compounds **6**, **7b**, **7c**, and **8a** showed the best antibacterial activity against all bacteria tested. Compounds **4**, **5**, **7**, **8**, **7a**, **8c**, and **8d** have the same activity as compounds above on the bacteria

used in the experiments. Zinc phthalocyanine derivatives have better antimicrobial activity than the other metallophthalocyanines (Ni, Co, and Cu) against Gram (+) bacteria. Antimicrobial activity results indicated that metallophthalocyanines have good activity against Gram (+) bacteria compared to the Gram (-) bacteria.

REFERENCES

1. Z. F. Huang, H. W. Bao, Y. Y. Yao, W. Y. Lu and W. X. Chen, *Appl. Catal. B*, **2014**, *154*, 36.
2. F. Yang and S. R. Forrest, *ACS Nano*, **2008**, *2*, 1022.
3. D. D. Erbahar, G. Gümüş, O. Pamir, E. Musluoglu, V. Ahsen, I. Gürol, *Sens. Actuators B,* **2016**, *227*, 277.
4. S. Schumann, R. A. Hatton and T. S. Jones, *J. Phys. Chem. C.*, **2011**, *115*, 4916.
5. M. Emmelius, G. Pawlowski and H. W. Vollmann, *Angew. Chem. Int. Ed.*, **1989**, *28*, 1445.
6. P. Peumans, S. Uchida and F. R. Forrest, *Nature*, **2003**, *425*, 158.
7. A. Kumar, J. Brunet, C. Varenne, A. Ndiaye, A. Pauly, M. Penza and M. Alvisi, *Sen. Act. B Chem.,* **2015**, *210*, 39.
8. J. Z. Jiang and D. K. Ng, *Acc. Chem. Res.*, **2009**, *42*, 79.
9. T. N. Demidova and M. R. Hamblin, *Int. J. Immunopathol. Pharmacol.*, **2004**, *17*, 245.
10. M. R. Hamblin and T. Hasan, *Photochem. Photobiol. Sci.*, **2004**, *3*, 436.
11. H. Ali and J. E. van Lier, *Chem. Rev.*, **1999**, *99*, 2379.
12. H. T. Akçay, M. Piskin, Ü. Demirbas, R. Bayrak, M. Durmus, E. Menteşe and H. Kantekin, *J. Organomet. Chem.*, **2013**, *745-746*, 379.
13. R. Bayrak, M. Durmus, S. Meydanal and K. Sancak, İ. Değirmencioğlu, *Polyhedron*, **2012**, *48*, 1.
14. P. Khoza, E. Antunes and T. Nyokong, *Polyhedron*, **2013**, *61*, 119.
15. G. Kaya Kantar, N. Baltaş, E. Menteşe and S. Şaşmaz, *J. Organomet. Chem.*, **2015**, *787*, 8.
16. C. Kantar, H. Akal, B. Kaya, F. Islamoglu, M. Türk and S. Şaşmaz, *J. Organomet. Chem.*, **2015**, *783*, 28.
17. S. Çolak, S. Kahraman and S. Z. Yıldız, *J. Organomet. Chem.*, **2016**, *823*, 83.
18. A. H. El-Masry, H. H. Fahmy and H. A. Abdelwahed, *Molecules*, **2000**, *5*, 1429.
19. M. Ramla, M. A. Omar, A. M. El-Khamry and H. I. El-Diwani, *Bioorg. Med. Chem.*, **2006**, 14, 7324.
20. R. Wubulikasimu, Y. Yang, F. Xue, X. Luo, D. Shao, Y. Li, R. Gao and W. Ye, *Bull. Korean Chem. Soc.*, **2013**, *34*, 2297.
21. E. Menteşe, H. Bektas, O. Bekircan and B. Kahveci, *Enzym. Inh. Med. Chem.,* **2014**, *29*, 64.
22. E. Menteşe, S. Ulker and B. Kahveci, *Chem. Heterocycl. Comp.,* **2015**, *50,* 1671.
23. E. Menteşe, N. Karaali, F. Yılmaz, S. Ülker and B. Kahveci, *Arch. Pharm.*, **2013**, 346, 556.
24. N. Baltaş, F. Yılmaz and E. Menteşe, *Hacettepe J. Biol. & Chem.*, **2016**, *44*, 293.
25. M, Ozil, M. Emirik, S. Ülker and B. Kahveci, *Bioorganic Chem.*, **2016**, *68*, 226.
26. K. Serbest, İ. Değirmencioğlu, Y. Unver, M. Er, C. Kantar and K. Sancak, *J. Organomet. Chem.,* **2007**, *692*, 5646.
27. Y.V. Romanenko, E.A. Danilova, O.G. Khelevina and M.K. Islyaikin, *Russ. Chem. B.,* **2009**, *58*, 1408.
28. O. Bekircan, Z. Bıyıklıoğlu, I. Acar, H. Baktas and H. Kantekin, *J. Organomet. Chem*. **2008,** *693*, 3425.
29. M. Juricek, P.H.J. Kouwer, J. Rehak, J. Sly and A.E. Rowan, *J. Org. Chem.* **2009**, *74*, 21.
30. R. N. Tantry, K. Jathi , M.N.K. Harish, S.A.R. Angadi, and K.K.T. Chinnagiri, *Res. J. Chem. Sci.* **2013**, *11*, 36.
31. J.G. Young and W. Onyebuagu, *J. Org. Chem*., **1990**, *55,* 2155.
32. D. Wohrle, M. Eskes, K. Shigehara and A. Yamada, *Synth. Stuttg*., **1993**, 194.
33. A. Pinner, "Die imidoether und ihre Derivate", 1. Auflage, Oppenheim, Berlin, 1892.
34. R. C. Elderfield and K. L. Burgess, *J. Am. Chem. Soc.*, **1960**, *82*, 1975.
35. A. Bilgin, B. Ertem and Y. Gok, *Eur. J. Inorg. Chem.*, **2007**, *12*, 1703.
36. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standart – Eight Edition.* CLSI document M07-A8. Clinical and Laboratory Standards Institue. 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2009.
37. M. Kaspady, V. K. Narayanaswamy, M. Raju and G. K. Rao, *Lett. Drug Design Disc.***2009***, 6,* 21.