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Peripherally and non-peripherally tetra-benzothiazole substituted metal-free zinc (II) and lead (II) phthalocyanines: Synthesis, characterization, and investigation of photophysical and photochemical properties

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ABSTRACT

In this study, novel phthalonitrile compounds bearing 2-methylbenzo[d]thiazol-5-yloxy groups (**4** and **5**) and their peripherally and non-peripherally tetra-substituted metal-free (**6** and **7**), zinc (II) (**8** and **9**), and lead (II) (**10** and **11**) phthalocyanine derivatives were synthesized and characterized for the first time. These novel compounds showed extremely good solubility in most common organic solvents. The novel phthalocyanine compounds presented excellent results from photophysical and photochemical examinations in DMF solution. Especially, the singlet oxygen quantum yield (Φ_{Δ}) values of the substituted zinc (II) phthalocyanines indicate that these compounds have significant potential as photosensitizers in cancer treatment by the photodynamic therapy (PDT) technique. The fluorescence quenching behaviour of these novel phthalocyanine compounds by 1,4-benzoquinone (BQ) was also examined in DMF solution.

1. Introduction

Phthalocyanine compounds present visible optical properties and good thermal stability due to having delocalized 18 π-electronic structure. For this reason, they are very useful in various technological areas ranging from chemical sensors to photodynamic therapeutic (PDT) agents [1–14].

Benzothiazole derivatives are one of the most important heterocyclic compounds due to their pharmacological and biological properties, such as antifungal, antiviral, antidiabetic, and anti-inflammatory activities [15]. In addition, the photophysical and photochemical properties of benzothiazoles have been discussed in some studies and they are used as photosensitizers [16,17].

Metallophthalocyanine compounds are known to show generally low solubility properties in most common organic solvents. Substitution of different groups on the phthalocyanine skeleton could be performed the solubility of these compounds. Due to the formation of constitutional isomers and their high dipole moments, tetra-substituted phthalocyanine compounds are more soluble than their octa-substituted counterparts [18,19]. Furthermore, due to having an extensively planar aromatic π system, phthalocyanines could exhibit a high aggregation tendency, which leads to low solubility and lower efficiency in their use in PDT [20,21].

PDT is one of the cancer therapy methods that include the combination of light and a photosensitizer. Phthalocyanine compounds have been mostly used for the treatment of various cancers and photo-inactivation of viruses as they have excellent properties such as intense absorption in the visible region, generation of reactive oxygen species with high efficiency, and low dark toxicity [22,23].

Various substituted phthalocyanine compounds showing a high singlet oxygen quantum yield, which is one of the most important properties for photosensitizer in PDT applications, have already been reported in our previous studies [24–28]. In this work, novel

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metal-free (**6** and **7**), zinc (II) (**8** and **9**), and lead (II) (**10** and **11**) phthalocyanines that are non-peripherally and peripherally substituted with four 2-methyl-5-benzothiazol groups were synthesized and characterized. In this case, to determine their potential viability in PDT applications as photosensitizer, the aggregation behaviour, photophysical (fluorescence lifetime and quantum yields), and photochemical (singlet oxygen and photodegradation quantum yields) properties of these phthalocyanine compounds were investigated in DMF solution. Moreover, the effects of the substituents and the nature of the central metal atom (Zn and Pb) on the photophysical and photochemical parameters of the studied phthalocyanine derivatives in DMF solution are also reported in this work. Lastly, this study also demonstrates the fluorescence properties and the quenching of the novel phthalocyanines by 1,4-benzoquinone (BQ) using the Stern–Volmer relationship.

2. Experimental

The equipment, materials, photochemical and photophysical formulas, and parameters used are given as supplementary materials.

2.1. Synthesis

2.1.1. 4-(2-Methylbenzo[d]thiazol-5-yloxy)phthalonitrile (4)

2-Methyl-5-benzothiazolol **(1)** (2.00 g, 12.10 mmol) and 4-nitrophthalonitrile (**2**) (2.10 g. 12.10 mmol) were dissolved in dried DMF (20 mL). Under an inert nitrogen atmosphere, anhydrous K_2CO_3 (5.01 g 36.30 mmol) was added portion by portion to the reaction mixture within 2 h and stirred at 60 °C for 3 days. The mixture was poured into 200 mL of ice-water, stirred for 1 h at room temperature, and then filtered off. The solid product was crystallized from ethanol. Yield: 2.29 g (65%), mp: 204–206 °C, $C_{16}H_9N_3OS$. IR (KBr pellet) υ_{max}/cm^{-1}: 3073, 3042, 2997, 2225 (C≡N), 1587–1556, 1483–1449, 1318, 1275, 1244, 1171, 1129, 1089, 870, 824, 704.^{1}H NMR ($CDCl_3$), (δ: ppm): 7.90–7.88, 7.73–7.71 (dd, 2H, Ar-H), 7.65–7.64 (d, 1H, Ar-H), 7.30–7.26 (m, 2H, Ar-H), 7.11–7.08 (dd, 1H, Ar-H), 2.87 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$), (δ: ppm): 170.11 (C=N), 161.85, 154.75, 152.09, 135.43, 133.44, 123.12, 121.46, 121.37, 117.85, 117.72, 115.31 (C≡N), 114.86 (C≡N), 114.27, 109.05, 20.32 (CH_3). MS (ESI), (m/z): calculated: 291.05; found: 291.20 $[M]^+$.

2.1.2. 3-(2-Methylbenzo[d]thiazol-5-yloxy)phthalonitrile (5)

2-Methyl-5-benzothiazolol **(1)** (2.00 g, 12.10 mmol) and 3-nitrophthalonitrile (**3**) (2.10 g. 12.10 mmol) were dissolved in dried DMF (20 mL). Under an inert nitrogen atmosphere, anhydrous K_2CO_3 (5.01 g 36.30 mmol) was added portion by portion to the reaction mixture within 2 h and stirred at 60 °C for 3 days. After that, the mixture was poured into 200 mL of ice-water, stirred for 1 h at room temperature, and filtered off. The solid product was crystallized from ethanol. Yield: 1.86 g (53%), mp: 196–198 °C, $C_{16}H_9N_3OS$. IR (KBr pellet) υ_{max}/cm^{-1}: 3083, 3033, 2923, 2232 (C≡N), 1573, 1561, 1468, 1450, 1309, 1261, 1176, 1147, 1132, 1067, 884, 800, 621.^{1}H NMR ($CDCl_3$), (δ: ppm): 7.89–7.87 (d, 1H, ArH), 7.65–7.64 (d, 1H, Ar-H), 7.58–7.54 (m, 1H, Ar-H), 7.49–7.46 (dd, 1H, Ar-H), 7.15–7.10 (m, 2H, Ar-H), 2.85 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$), (δ: ppm): 170.03 (C=N), 160.88, 154.59, 152.43, 134.45, 133.27, 127.21, 123.00, 120.55, 117.72, 117.36, 115.06 (C≡N), 113.85 (C≡N), 112.64, 106.22, 20.32 (CH_3). MS (ESI), (m/z): calculated: 291.05; found: 291.07 $[M]^+$.

2.1.3. General procedure for synthesis of phthalocyanines (6–11)

The mixture of phthalonitrile compound **(4** or **5)** (0.2 g. 0.69 mmol), dried n-pentanol (5 mL), 1,8-diazabicyclo [4.5.0] undec-7-ene (DBU) (6 drops), and no metal salts for compounds **6** and **7** or equivalent amounts of anhydrous $Zn(CH_3COO)_2$ for compounds **8** and **9** or $Pb(CH_3COO)_2$ for compounds **10** and **11** was heated to 160 °C and stirred for 24 h. After cooling to room temperature, the mixture was precipitated by the addition of ethanol and filtered off. After washing with hot ethanol, acetone, and ethyl acetate, the green solid product was subjected to chromatography by using silica gel and a chloroform-methanol solvent system.

2.1.3.1. Peripherally tetra-2-methylbenzothiazole substituted metal-free phthalocyanine (6). A chloroform:methanol (100:1.5) solvent system was used for column chromatography. Yield: 60 mg (30%), mp > 300 °C, $C_{64}H_{38}N_{12}O_4S_4$. IR (KBr pellet) υ_{max}/cm^{-1}: 3286 (N–H), 3062, 2920, 2850, 1598, 1558, 1474, 1448, 1308, 1262, 1174, 1129, 1090, 951, 741.^{1}H NMR ($CDCl_3$), (δ: ppm): 7.89–7.85 (m, 4H, Ar-H), 7.78–7.76 (m, 4H, Ar-H), 7.68–7.66 (m, 4H, ArH), 7.57–7.52 (m, 4H, ArH), 7.21–7.10 (m, 6H, ArH), 6.87 (bs, 2H, ArH), 2.96 (s, 12H, CH_3), −6.64 (bs, 2H, NH). UV–*vis* (DMSO, 1×10^{-5} M): λ_{max}/nm (log ε): 700 (4.04), 671 (4.20), 638 (3.90), 609 (3.77), 343 (4.11). MS (ESI), (m/z): calculated: 1166.20, found: 1166.20 $[M]^+$.

2.1.3.2. Non-peripherally tetra-2-methylbenzothiazole substituted metal-free phthalocyanine (7). A chloroform:methanol (100:1) solvent system was used for column chromatography. Yield: 55 mg (28%), mp > 300 °C. $C_{64}H_{38}N_{12}O_4S_4$. IR (KBr pellet) υ_{max}/cm^{-1}: 3286 (N–H), 3059, 2923, 1583, 1557, 1486, 1448, 1333, 1309, 1267, 1237, 1128, 1068, 1021, 957, 865, 745.^{1}H NMR ($CDCl_3$), (δ: ppm): 7.88–7.73 (m, 10H, Ar-H), 7.72–7.42 (m, 6H, Ar-H), 7.34–7.26 (m, 8H, ArH), 2.86 (s, 12H, CH_3), −1.50 (s, 2H, NH). UV–vis (DMSO, 1×10^{-5} M): λ_{max}/nm (log ε): 717 (5.02), 671 (5.03), 638 (4.56), 609 (4.46), 343 (4.76). MS (ESI), (m/z): calculated: 1166.20, found: 1167.44 $[M+H]^+$.

2.1.3.3. Peripherally tetra-2-methylbenzothiazole substituted zinc (II) phthalocyanine (8). A chloroform:methanol (50:1) solvent system was used for column chromatography. Yield: 74 mg (35%). mp > 300 °C. $C_{64}H_{36}N_{12}O_4S_4Zn$. IR (KBr pellet) υ_{max}/cm^{-1}: 3062, 2969, 1599, 1558, 1484, 1448, 1309, 1263, 1162, 1130, 1085, 1042, 953, 744, 728.^{1}H NMR ($CDCl_3$), (δ: ppm): 8.57–7.82 (m, 18H, Ar-H), 7.67–7.57 (m, 4H, Ar-H), 7.32–7.23 (m, 2H, ArH), 2,83 (s, 12H, CH_3). UV–vis (DMSO, 1×10^{-5} M): λ_{max}/nm (log ε): 678 (5.37), 611 (4.63), 357 (4.96). MS (ESI), (m/z): calculated: 1228.12, found: 1228.84 $[M]^+$.

2.1.3.4. Non-peripherally tetra-2-methylbenzothiazole substituted zinc (II) phthalocyanine (9). A chloroform:methanol (25:1) solvent system was used for column chromatography. Yield: 64 mg (30%). mp > 300 °C. $C_{64}H_{36}N_{12}O_4S_4Zn$. IR (KBr pellet) υ_{max}/cm^{-1}: 3061, 2919, 1581, 1558, 1481, 1448, 1330, 1267, 1230, 1111, 1087, 1045, 966, 877, 743.^{1}H NMR ($CDCl_3$), (δ: ppm): 9.09–8.82 (m, 2H, Ar-H), 8.54–8.37 (m, 2H, Ar-H), 8.09–8.06 (m, 6H, ArH), 7.75–7.57 (m, 8H, ArH), 7.29–7.22 (m, 6H, ArH), 2.78 (s, 12H, CH_3). UV–vis (DMSO, 1×10^{-5} M): λ_{max}/nm (log ε): 693 (5.30), 623 (4.53), 329 (4.67). MS (ESI), (m/z): calculated: 1228.12, found: 1229.67 $[M+H]^+$.

2.1.3.5. Peripherally tetra-2-methylbenzothiazole substituted lead (II) phthalocyanine (10). A chloroform:methanol (100:1.5) solvent system was used for column chromatography. Yield: 66 mg (28%). mp > 300 °C. $C_{64}H_{36}N_{12}O_4PbS_4$. IR (KBr pellet) υ_{max}/cm^{-1}: 3057, 2992, 2919, 1596, 1557, 1479, 1447, 1384, 1324, 1210, 1162, 1129, 1076, 1039, 952, 930, 724.^{1}H NMR ($CDCl_3$), (δ: ppm): 8.99 (bs, 4H, Ar-H), 8.68 (bs, 4H, Ar-H), 8.15 (s, 2H, ArH), 7.95–7.91 (d, 4H, ArH), 7.78–7.52 (m, 6H, ArH), 7.50–7.44 (m, 2H, ArH), 7.30 (s, 2H, ArH), 2.81 (s, 12H, CH_3). UV–vis (DMSO, 1×10^{-5} M): λ_{max}/nm (log ε): 709 (5.08), 639 (4.34), 361 (4.65). MS (ESI), (m/z): calculated: 1372.16, found: 1373.67 $[M+H]^+$.

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