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Synthesis and characterization of novel flavonoid-substituted phthalocyanines using (±)naringenin

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ABSTRACT

In this study, novel unsymmetrical mono- and di-substituted metal free and metallo phthalocyanines containing peripheral naringeninoxy moieties have been prepared. The naringenin-substituted phthalonitrile was synthesized from 4-nitrophthalonitrile and (±)naringenin in dimethylsulfoxide. Preparation of unsymmetrical mono- and di-substituted phthalocyanines, 2-naringenin-7-O-phthalocyaninatozinc, 2,9-bis-naringenin-7-O-phthalocyaninatozinc, 2,9-bis-naringenin-7-O-phthalocyaninatocobalt and 2,9-bis-naringenin-7-O-phthalocyanine was performed at 120–140 °C using the corresponding phthalonitrile in the presence of N,N-dimethylethanolamine (DMAE), $ZnCl_2$, $CoCl_2$ and LiCl, respectively. Synthesized new phthalocyanine compounds have been characterized by elemental analysis and ^1H NMR, ^{13}C NMR, FT-IR, MS and UV–vis spectroscopy. These are the first known examples of flavonoid-substituted phthalocyanines.

1. Introduction

Since their first synthesis in 1928, phthalocyanines (Pcs) have gained considerable industrial importance for use in dyestuffs, paints, colorants for metal surfaces, fabrics and plastics [1]. Applications in the fields of chemical sensors, liquid crystals, semiconductors, nonlinear optics, and photodynamic therapy (PDT) have been demonstrated the increase due to the importance of these macrocyclic coordination compounds [2].

Flavonoids are a group of natural products present in a wide variety of plants. They are ubiquitous in photosynthesizing cells and therefore occur widely in the plant kingdom. They are found in flowers, vegetables, nuts, seeds, citrus fruits, olive oil, tea and red wine and are commonly consumed with the human diet [3,4]. Flavonoids, with several phenolic hydroxyl groups, exhibit a broad range of biological activities, including antiviral, anti-inflammatory, antioxidant, anti-allergic and anti-tumoral properties [5–7]. Furthermore, these compounds are used in bacteriology, pharmacology and medicine due to their bactericidal activities [8]. It is also known that amino-substituted flavone derivatives exhibit strong antitumour activity in breast cancer cells [9]. Moreover, flavone imines show antimicrobial and antimalarial activities [10,11].

The basic structural feature of flavonoid compounds is the 2-phenylchroman or flavane nucleus, which consists of two benzene rings (A and B), linked through a heterocyclic pyrane ring (C) (Fig. 1).

Flavonoids are classified with the rings named as A, B and C, and/or the positions numbered. Based on the flavanone structure, all other flavonoid species can be generated, including flavanols, anthocyanidins, flavonols, flavonones and flavones [12]. Naringenin is a member of the flavonoid family. It bears three hydroxyl groups at the 5, 7 and 4′ positions and may exhibit protective effects against several types of cancers. Cell culture experiments have shown inhibitory effects of naringenin on tumor growth in human cancer cell lines deriving from breast, colon, liver, cervix, and pancreas or stomach cancers [13].

Phthalocyanine derivatives have attracted much interest as PDT candidates because they possess certain advantages over their porphyrin analogues. Phthalocyanines generally have larger extinction coefficients, absorptions in the therapeutically convenient 650–800 nm range and they have no dark toxicity. The photosensitizing properties of aluminum, gallium, zinc, and silicon phthalocyanines and naphthalocyanines have been investigated, as well as a series of hydroxy-phthalocyanines. The latter was prepared by Leznoff's group as both single isomers and as statistical mixtures of the isomers, and their efficacy as sensitizers for PDT was examined in vitro and in vivo on some tumor species [14]. Some unsymmetrical benzylic-hydroxysubstituted phthalocyanines were prepared in 2003 by Cosimelli and co-workers and their photodynamic activity was tested against *Candida albicans* [15]. Hydroxyphenyl porphyrins have been found to be among the most active compounds in photodynamic therapy studies. Another porphyrin-based substance, Photofrin®, a mixture of porphyrin oligomers, is currently in use as an effective treatment against esophageal and endobronchial cancer [16].

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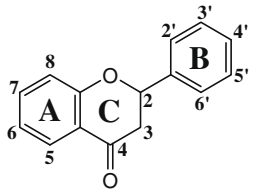


Fig. 1. The skeleton structure of favonoids (Flavanone).

In this work, we report the synthesis, characterization and investigation of some spectroscopic properties of novel phthalocyanines containing naringenin groups as substituents. The phthalocyanines were prepared as both metal free and metalated compounds, substituted either mono- or di-peripherally. To our knowledge, these are the first examples of naringenin-substituted phthalocyanine compounds which may poses unique biological activity properties.

2. Experimental

2.1. Materials and characterization techniques

(±)Naringenin **1** was purchased from Sigma–Aldrich Company. Deuteriated solvents ($CDCl_3$ and DMSO-d_6) for NMR spectroscopy and the following chemicals were obtained from Merck; hexane, MeOH, N,N-dimethylaminoethanol (DMEA), anhydrous $ZnCl_2$, anhydrous $CoCl_2$, LiCl, THF, DMSO, HCl (37% sol.), CH_2Cl_2, K_2CO_3. All other reagents and solvents were reagent grade quality and were obtained from commercial suppliers. All solvents were dried and purified as described by Perrin et al. [17], and the solvents stored over molecular sieves (4 Å). 4-Nitro phthalonitrile **2** was prepared according to literature procedure [18]. All reactions were carried out under an atmosphere of argon, using standard Schlenk techniques. Thin-Layer chromatography (TLC) was performed using silica gel 60 HF_{254} as an adsorbent. Hot solvent extraction was performed using a Soxhlet extractor. Flash silica with particle size 20–45 μm was used as solid phase dispersion during extraction. Melting points (mp) were determined using a Barnstad-Electrotermel 9200 apparatus and are uncorrected. Electronic spectra were recorded on a Shimadzu UV-2401 Pc-spectrophotometer using a 1 cm quartz cell. Infrared spectra were recorded on a Shimadzu FTIR IRPrestige-21 spectrophotometer equipped with PIKE MIRacle™ diamond ATR and corrected by applying IR solution software's ATR-correction function. ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ and DMSO-d_6 solutions on a Varian Mercury Plus 300 MHz spectrometer. Mass analyses were measured on a Micro-Mass Quatro LC/ULTIMA LC–MS/MS spectrometer. For Maldi-TOF spectra, the experiments were carried out using a Bruker micrOTOF (Germany) electrospray ionisation-mass spectrometer (ESI-MS). Samples were run in positive ion mode (ESI+). ChemDraw Ultra version 7.0 was also used to calculate and examine the mass fragments.

2.2. Synthesis

2.2.1. Synthesis of substituted phthalonitriles

*2.2.1.1. Naringenin-7-O-4-phtalonitrile (**3**).* (±)Naringenin **1** (0.602 g, 4.43 mmol) and 4-nitro phthalonitrile **2** (0.808 g, 4.67 mmol) were dissolved in 40 mL dry DMSO. After stirring for 15 min at 30–40 °C, finely powdered anhydrous potassium carbonate (0.555 g, 4 mmol) was added portion wise over 12 h with efficient stirring and the system was kept under vacuum. The reaction was stirred for 72 h and monitored by TLC using THF/hexane (3/4) as eluent. The reaction mixture was poured into ice-distilled water (200 g), dilute HCl (1/3) was added to adjust the pH ≈ 3 and the mixture was stirred until all the ice had melted. The precipitated crude product was collected by vacuum filtration, washed with distilled water until pH 7, and then dried under vacuum. The crude product was treated with hot diethyl ether (3 × 20 mL) to remove some oily residues, and than it was re-crystallized from acetone. The yield was 1.48 g (84%), m.p. 153–158 °C. Anal. Calc. for $C_{22}H_{14}N_2O_5$: C, 69.34; H, 3.54; N, 7.03. Found: C, 69.17; H, 3.73; N, 6.85%. FT-IR (PIKE MIRacle™ ATR) ν_{max}, cm^{-1}: 3421, 3085, 2955, 2927, 2233, 1774, 1693, 1616, 1592, 1249, 1200, 1126. ^1H NMR (DMSO): δ, ppm 12.14 (1H, s, Ar–OH), 10.92 (1H, s, Ar–OH), 8.15 (1H, d, Ar–H), 7.81 (1H, s, Ar–H), 7.65 (2H, d, Ar–H), 7.48 (1H, d, Ar–H), 7.23 (2H, d, Ar–H), 5.95 (2H, d, Ar–CH), 5.85 (1H, d, Alip–CH), 3.30 (2H, d, Alip–CH_2) and 2.78 (2H, d, Alip–CH_2), ^{13}C (DMSO): δ, ppm 207.22, 196.58, 167.41, 164.18, 163.35, 161.48, 154.60, 137.02, 129.75, 123.57, 122.90, 121.02, 117.43, 116.59, 116.07, 109.08, 102.45, 96.68, 95.73, 78.53, 31.38. MS(FAB) (*m*/*z*): 437 (Calc. for $[M+2H_2O+3]^+$ 437), 417 (Calc. for $[M+H_2O+1]^+$ 417), 399 (Calc. for $[M+1]^+$ 399) and 269.

*2.2.1.2. 4′,5-Dibenzyl-naringenin-7-O-4-phtalonitrile (**4**).* Compound **3** (0.398 g, 1 mmol) was dissolved in 50 mL acetone. Benzoyl chloride (0.260 mL, 2 mmol), potassium iodide (0.015 g, 0.09 mmol) and potassium carbonate (1.380 g, 10 mmol) were added to the solution. The reaction mixture was refluxed for 48 h and then poured into distilled water (250 mL). Dilute HCl was added to the mixture until pH ≈ 4. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The extracts were combined, washed with water until pH ≈ 7, dried over anhydrous sodium sulfate, and then filtered. The solvent was evaporated and the product was purified by column chromatography on silica gel using THF/hexane (4/3) as mobile phase. Compound **4** is solid; yield 0.167 g (34%). Anal. Calc. for $C_{30}H_{20}N_2O_5$: C, 73.76; H, 4.13; N, 5.73. Found: C, 75.85; H, 4.02; N, 5.49%. FT-IR (PIKE MIRacle™ ATR) ν_{max}/cm^{-1}: 3066, 3030, 2922, 2850, 2235, 1720, 1633, 1591, 1485, 1247, 1150, 1090, 833. ^1H ($CDCl_3$) δ = 12.15 (1H, s, Ar–OH), 7.84–6.22 (14H, m, Ar–H), 5.43 (1H, d, cyclic-CH), 5.15 (2H, s, benzylic-CH_2), 3.20–2.82 (2H, m, cyclic-CH_2). ^{13}C (DMSO): δ, ppm 225.92, 195.02, 188.89, 187.46, 185.17, 177.14, 175.16, 166.45, 159.39, 157.06, 146.00, 134.86, 128.99, 127.70, 123.91, 121.25, 118.35, 114.87, 113.85, 110.00, 101.41, 99.69, 94.07, 65.39, 52.19, 29.95. MS(FAB) (*m*/*z*): 527 (Calc. for $[M+2H_2O+3]^+$ 527), 489 (Calc. for $[M+1]^+$ 489), 438, 413 and 400.

2.2.2. Synthesis of phthalocyanines

*2.2.2.1. 2-Naringenin-7-O-phthalocyaninatozinc (**5**).* Substituted phthalonitrile **3** (24 mg, 0.06 mmol) or **4** (32 mg, 0.06 mmol), anhydrous $ZnCl_2$ (14 mg, 0.1 mmol) and phthalonitrile (0.128 g 1 mmol) were dissolved in dry DMAE (10 mL). The reaction mixture was heated at 135 °C for 4 h under an Ar atmosphere. The resulting green reaction mixture was cooled to room temperature and precipitated by pouring into 1:1 MeOH/H_2O mixture. The precipitate was collected by centrifuge and washed with 1:1 MeOH/H_2O and then distilled water. The precipitate was dried under vacuum. The crude product was dissolved in THF (10 mL), adsorbed onto silica gel (20 g) and then Soxhlet-extracted with hot THF (125 mL) for 12 h. The solvent was evaporated and the product was chromatographed by preparative TLC on silica gel using THF/hexane (3/2) as mobile phase. Compound **5** was obtained as a blue-green solid in both cases, with the melting point >300 °C and the yield 0.025 g (48%) or 0.030 g (55%), respectively. Anal. Calc. for $C_{47}H_{26}N_8O_5Zn$: C, 66.56; H, 3.09; N, 13.21. Found: C, 66.27; H, 3.15; N, 13.54%. FT-IR (PIKE MIRacle™ ATR) ν_{max}/cm^{-1}: 3186, 3060, 2953, 2922, 2855, 1720, 1605, 1483, 1330, 1285, 1088, 725. MS(FAB) (*m*/*z*): 843 (Calc. for $[M-3]^+$ 843), 718, 507,

129. UV–vis (THF): λ, nm (log ε) 667.5 (5.46), 638.0 (4.55), 602.0 (4.60), 341.5 (4.91), 238.5 (4.83).

*2.2.2.2. 2,9-Bis-naringenin-7-O-phthalocyaninatozinc (**6**). (Reaction with L/M: 1/10 ratio)*: Substituted phthalonitrile **3** (40 mg, 0.1 mmol), anhydrous $ZnCl_2$ (0.136 g, 1 mmol) and phthalonitrile (0.128 g, 1 mmol) were dissolved in dry DMAE (4 mL). The reaction mixture was stirred at 130–140 °C for 2.5 h under an Ar atmosphere.

(Reaction with L/M: 1/3 ratio): Substituted phthalonitrile **3** (40 mg, 0.1 mmol), anhydrous $ZnCl_2$ (41 mg, 0.3 mmol) and phthalonitrile (38.5 mg, 0.3 mmol) were dissolved in dry DMAE (4 mL). The reaction mixture was stirred at 130 °C for 3.5 h under an Ar atmosphere.

(Reaction with L/M: 1/1 ratio): Substituted phthalonitrile **3** (40 mg, 0.1 mmol), anhydrous $ZnCl_2$ (14 mg, 0.1 mmol) and phthalonitrile (13 mg, 0.1 mmol) were dissolved in dry DMAE (3 mL). The reaction mixture was stirred at 130 °C for 4 h under an Ar atmosphere.

The progress of the reactions was monitored by UV–vis spectroscopy for the samples prepared dissolving 5 μL reaction media in 25 mL THF. Upon completion, the reaction mixtures were cooled to room temperature and precipitated by pouring into 1:3 MeOH/H_2O. For each reaction, the precipitate was collected by centrifuge and washed with 1:2 MeOH/H_2O and then distilled water. The precipitate was dried under vacuum. The crude product was adsorbed onto silica gel (20–50 g) and then purified by Soxhlet extraction with hot THF (150–200 mL) according to the previously described method for **5**. The solvent was evaporated to dryness and the product was chromatographed by preparative TLC on silica gel using THF/hexane (3/2) as mobile phase. After re-precipitated by methanol, collected by centrifuge and dried under vacuum, the phthalocyanine **6** was obtained as statistical mixture of isomers with different yield for each reaction condition. The product is a blue-green solid, melting point > 300 °C and the yield for 1/10 reaction ratio 0.042 g (63%), for 1/3 reaction ratio 0.036 g (54%) and for 1/1 reaction ratio 0.020 g (30%). Anal. Calc. for $C_{62}H_{36}N_8O_{10}Zn$: C, 66.58; H, 3.24; N, 10.02. Found: C, 66.65; H, 3.18; N, 9.95%. FT-IR (PIKE MIRacle™ ATR) ν_{max}/cm^{-1}: 3196, 3059, 2953, 2924, 2855, 1717, 1651, 1605, 1483, 1385, 1333, 1284, 1116, 1088, 1053, 738. MS(MALDI-TOF) (m/z): 1116 (Calc. for $[M]^+$ 1116), 1026, 830, 753, 864. UV–vis (THF): λ, nm (log ε) 665.5 (5.57), 637.5 (4.71), 601.5 (4.76), 341.5 (5.01), 239.0 (4.78).

*2.2.2.3. 2,9-Bis-naringenin-7-O-phthalocyaninatocobalt (**7**).* Substituted phthalonitrile **3** (48 mg, 0.12 mmol), anhydrous $CoCl_2$ (0.130 g, 1 mmol) and phthalonitrile (0.128 g 1 mmol) were dissolved in dry DMAE (4 mL). The reaction mixture was heated at 135 °C for 4 h under an Ar atmosphere. The resulting green reaction mixture was cooled to room temperature and precipitated by pouring into ice-distilled water (50 g). The precipitate was collected by centrifuge and washed with 1:1 MeOH/H_2O solution until no-yellow colored washing solution remained. After drying under vacuum, the crude product was dissolved in THF (10 mL), adsorbed onto silica gel (20 g) and then Soxhlet-extracted with hot THF (125 mL) for 12 h. The solvent was evaporated and the product was chromatographed by TLC on silica gel using THF/hexane (3/2) as mobile phase to check the purity of the compound. Without future purification, compound **7** was obtained pure enough as a greenish-blue solid with the melting point > 300 °C and the yield 0.025 g (38%). Anal. Calc. for $C_{62}H_{36}N_8O_{10}Co$: C, 66.97; H, 3.26; N, 10.08. Found: C, 66.32; H, 3.16; N, 10.54%. FT-IR (PIKE MIRacle™ ATR) ν_{max}/cm^{-1}: 3194, 3061, 2955, 2918, 2870, 1736, 1605, 1475, 1427, 1333, 1163, 1121, 1094, 736. MS(MALDI-TOF) (m/z): 1135 (Calc. for $[M+Na]^+$, 1134), 901, 579. UV–vis (THF): λ, nm (log ε) 655.5 (5.31), 594.0 (4.65), 323.5 (5.05), 238.0 (4.87).

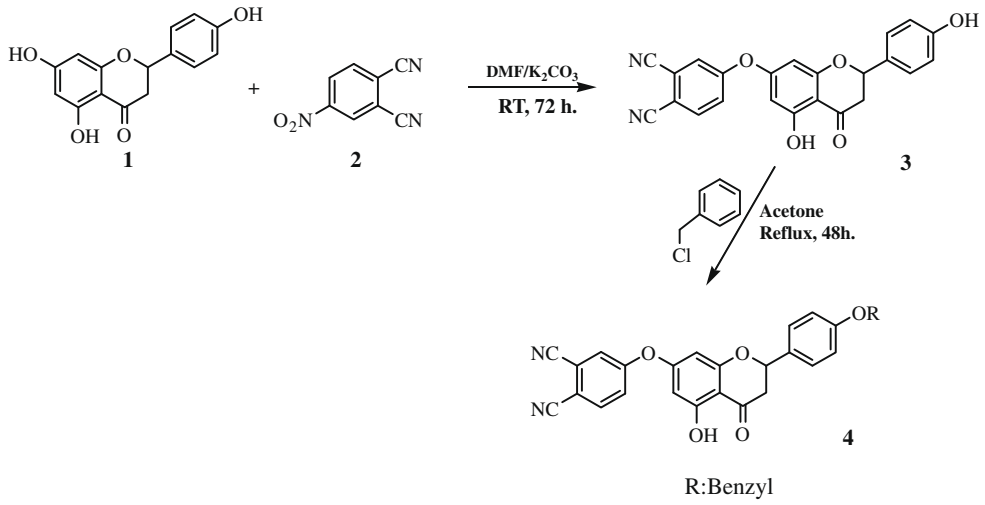
*2.2.2.4. 2,9-Bis-naringenin-7-O-phthalocyanine (**8**).* Substituted phthalonitrile **3** (48 mg, 0.12 mmol), phthalonitrile (0.128 g 1 mmol) and LiCl (78 mg, 1 mmol) were dissolved in dry DMAE (4 mL). The reaction mixture was heated at 120 °C for 4 h under an Ar atmosphere. The progress of the reactions was monitored by UV–vis spectroscopy according to the previously motioned method for **6**. The resulting green reaction mixture was cooled to room temperature and precipitated by pouring into H_2O (50 mL). The precipitate was collected by centrifuge and washed with 1:3 MeOH/H_2O solution until no-yellow colored washing solution remained. The precipitate was dried under vacuum. The crude product was dissolved in THF (10 mL), adsorbed onto silica gel (20 g) and then Soxhlet-extracted with hot THF (125 mL) for 12 h. The solvent was evaporated and the slurry was chromatographed by preparative TLC on silica gel using THF/hexane (3/2) as mobile phase. The purified compound **8** was collected as a frontier phase and re-precipitated with methanol. After collected by centrifuge and dried under vacuum, the compound **8** could be obtained as a greenish-blue solid with the melting point > 300 °C and the yield 0.027 g (42%). Anal. Calc. for $C_{62}H_{38}N_8O_{10}$: C, 70.58; H, 3.63; N, 10.62. Found: C, 70.52; H, 4.26; N, 10.31%. FT-IR (PIKE MIRacle™ ATR) ν_{max}/cm^{-1}: 3289, 3150, 3071, 2950, 2914, 2870, 1741, 1699, 1595, 1506, 1437, 1302, 1275, 1238, 1163, 1007, 741, 716. MS(MALDI-TOF) (m/z): 1074 (Calc. for $[M+H_2O]^+$, 1074), 950, 799, 544. UV–vis (THF): λ, nm (log ε) 689.0 (5.21), 652.5 (5.16), 635.5 (4.74), 593.0 (4.51), 338.0 (5.02), 236.5 (4.97).

2.3. Spectroscopic measurement

Stock solutions were prepared in 1×10^{-4} mol dm^{-3} by dissolving 30 mg, 2,9-bis-naringenin-7-O-phthalocyaninatozinc (**6**) in 250 mL THF, EtOH and DMSO, respectively. The solutions were diluted to 7.5×10^{-5} mol/dm^3, 5.0×10^{-5} mol/dm^3, 2.5×10^{-5} mol/dm^3, 1.0×10^{-5} mol/dm^3, 7.5×10^{-6} mol/dm^3, 5.0×10^{-6} mol/dm^3, 1.0×10^{-6} mol/dm^3 and 5.0×10^{-7} mol/dm^3 by adding related solvent. UV–vis spectra of the prepared solutions were taken in a 1×1 cm quartz tub at the range of 850–200 nm. UVPC39 software program was used to record the results. The collected results were plotted as absorptions against to concentration on the graphics to examine the changes of the aggregation properties with the varying concentration.

3. Results and discussion

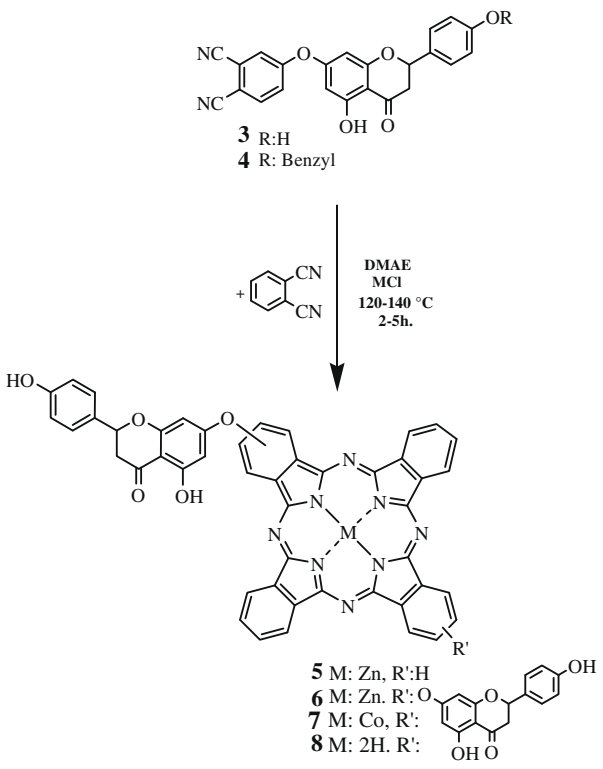
Naringeninoxy-substituted phthalonitrile **3** was synthesized from (±)naringenin **1** and 4-nitrophthalonitrile **2** via displacement of the nitro group with the 7-hydroxy group on (±)naringenin as shown in Scheme 1. This reaction was performed in the presence of K_2CO_3 and DMF using a well established procedure and gave one product almost exclusively, and in very good yield due to the higher reactivity of the hydroxyl group at the 7 position compared to those at the 5 and 4′ positions [18–20]. Water was added to the reaction mixture to precipitate the crude phthalonitrile **3**, but the alkaline constitution of the reaction mixture resulted in emulsions due to the formation of partially-soluble phenolate salts. The crude product was eventually isolated by simply adjusting the pH of the mixture to ≈3. Substituted phthalonitrile **3** was purified by crystallization from acetone to obtain a light brownish micro-crystalline product. After investigating various protecting groups for the free hydroxyls on **3**, it was found that only the benzylated derivative could be prepared. Refluxing compound **3** with benzyl chloride in acetone for 48 h gave compound **4**, but in poor yield. A mixture of mono-benzyl and di-benzyl derivatives was obtained, and was separated by column chromatography on silica gel using THF/hex-



Scheme 1. Preparation steps of substituted phthalonitrile.

ane (4/3) as eluent. Due to the di-benzyl derivative of **3** was obtained in very low yield, it is unaccepted as product.

Preparation of the corresponding metallo phthalocyanines (**5**–**7**) was achieved by fusing of phthalonitrile and the naringeninoxy-substituted phthalonitrile in different ratios in the presence of DMAE and the related MCl_2 salt at 120–140 °C for 2–4 h. In the preparation of the metal free phthalocyanine **8**, LiCl was used as metal salt and the lityum phthalocyanine $PcLi_2$ was obtained initially, and than it hydrolyzed to metal free species, PcH_2, with water during work up. Naringeninoxy-phthalonitrile **3** and its benzyl derivative **4** were both combined with phthalonitrile in various ratios to determine the optimum reaction conditions of either the mono- or di- substituted zinc-phthalocyanines. It was found that the benzyl protecting groups of **4** unexpectedly cleaved under these reaction conditions, therefore only the free-hydroxyl naringeninoxy-substituted zinc-phthalocyanines were prepared. Mono-substituted Zn-Pc **5** could be obtained under dilute reaction conditions, when the ratio of **3** or **4** to phthalonitrile was applied as 1:17 or higher, respectively. On the other hand, using ratios of 1:1, 1:3, or 1:10 **3** to phthalonitrile, the same di-substituted Zn-Pc **6** was obtained each time (Scheme 2). It was found that the highest yield was achieved using a ratio of 1:10. This reaction was found to be essentially complete within 30 min, but when left to heat for extended periods of time, lower yields were obtained. In the preparation of the other di-substituted phthalocyanines **7** and **8**, the same 1:10 ratio was applied by using phthalonitrile **3**. Reaction completion was monitored by UV–vis spectroscopy with samples taken at half hour intervals. The samples were diluted to prepare 2.5×10^{-6} M solutions in THF (5 μL/25 mL THF) and the Q band absorptions at 600–700 nm region were checked to establish the optimal reaction time. For all phthalocyanines **5**–**8**, a slightly longer reaction time was necessary (2–4 h) to reach completion. A number of attempts were made to synthesize the tetrasubstituted phthalocyanines by self tetramerization of **3** using a variety of conditions, but unfortunately all attempts were unsuccessful. The reaction conditions and yields are summarized in Table 1.



Scheme 2. Synthesis of naringeninoxy-substituted Pcs.

Separation of the substituted Pcs from un-substituted Pc was able to achieve due to the higher solubility of naringeninoxy-substituted Pcs in organic solvents. The crude products were dissolved in THF and adsorbed onto flash silica gel (1 mg/1 g) and then isolated by Soxhlet extraction using THF as the solvent. The extracted naringeninoxy-substituted phthalocyanines were purified by preparative TLC on silica gel using THF/hexane (3/2) as mobile phase except Co-Pc **7**.

The new compounds are characterized by a combination of elemental analysis and spectroscopic data involving FT-IR, ^{1}H NMR, ^{13}C NMR, ESI MS-MS and UV–vis spectra. The data for all the new compounds appear to be consistent with the proposed structures.

The elemental analysis result of the starting materials **3**, **4** and the phthalocyanines **5**, **6**, **7** and **8** show good agreements with the calculated values (Table 2). Comparison of the IR spectral data clearly indicates the formation of **3** and **4** with the appearance of absorption bands at 3421 cm^{-1} (Ar–OH), 3085 cm^{-1} (Ar–H), 2927 cm^{-1} (C–H), 2233 cm^{-1} (C≡N), 1774 cm^{-1} (C=O) and 1200 cm^{-1} (C–O–C) for compound **3**, and at 3066–3030 cm^{-1} (Ar–H), 2922–2850 cm^{-1} (C–H), 2235 cm^{-1} (C≡N), 1720 cm^{-1}

Table 1
Preparation conditions of substituted phthalocyanines and their yields.

Metal salt (mmol)		Substituted PN (mmol)		PN[a] (mmol)	Reaction time (h)	Reaction temp. (°C)	Pc	Yield (%)
$ZnCl_2$	17	**3**	1	20	4	130–140	**5**	48
$ZnCl_2$	17	**4**	1	20	4	130–140	**5**	55
$ZnCl_2$	10	**3**	1	10	2.5	135–140	**6**	63
$ZnCl_2$	3	**3**	1	3	3.5	130–135	**6**	54
$ZnCl_2$	1	**3**	1	1	4	130–135	**6**	30
$ZnCl_2$	3	**3**	4	–	12	135–140	–	–
$CoCl_2$	10	**3**	1	10	4	135–140	**7**	38
LiCl	10	**3**	1	10	4	120–125	**8**	42

[a] PN: phthalonitrile.

Table 2
Elemental analysis results of the substituted phthalonitriles (**3**, **4**) and the phthalocyanines (**5**–**8**).[a]

Compound	C%	H%	N%
3	69.17(69.34)	3.73(3.54)	6.85(7.03)
4	75.85(73.76)	4.02(4.13)	5.49(5.73)
5	66.27(66.56)	3.15(3.09)	13.54(13.21)
6	66.65(66.58)	3.18(3.24)	9.95(10.02)
7	66.52(66.97)	3.16(3.26)	10.54(10.08)
8	70.52 (70.58)	4.26 (3.63)	10.31(10.62)

[a] Theoretical calculated values are given in parentheses.

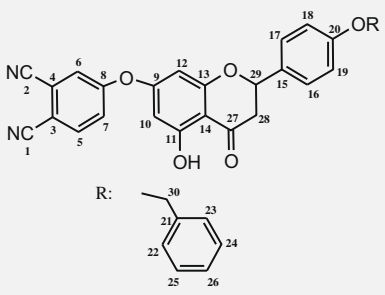
(O–H–O) 1683 cm^{-1} (C=O) and 1150 cm^{-1} (C–O–C) for compound **4**.

Cyclotetramerizations of the dinitriles **3** and **4** to obtain mono-substituted phthalocyanine **5** and di-substituted phthalocyanines **6**, **7** and **8** were confirmed by the disappearance of the sharp –C≡N vibrations at 2233 cm^{-1} and 2235 cm^{-1}, respectively. In the IR spectra of mono-substituted phthalocyanine **5** and di-substituted phthalocyanines **6**, **7** all the peaks are located the same, but the intensities have some differences. The stretching vibration which belongs to free –OH group at 4′ position of the naringenin moiety appears at 3196–3184 cm^{-1} as broad band and the intramolecular hydrogen bond at 1717 cm^{-1}. Because of this hydrogen bond, the stretching vibration of the C=O group shifted to 1651 cm^{-1} in all phthalocyanines. Weak bands at above 3000 cm^{-1} and the absorptions at 2953–2855 $cm^{-1}$are due to the aromatic =C–H stretchings of the substituted phthalocyanines and the anti-symmetric C–H stretching vibrations of the heterocyclic ring of the naringenin substituent, respectively. In the range of 1605–1284 cm^{-1}, the pyrrole, benzene, isoindol ring and aza group stretching of the molecules are prominent, and the in-place C–H bending vibrations are in between 1116 and 1053 cm^{-1} in the spectra. Additionally, the resonances at 3289 and 1006 cm^{-1} are assigned to the N–H stretching and bending vibrations for **8**. All the IR results of the substituted phthalonitriles and the phthalocyanines are in good agreement with the previous literature [15,16,20–23].

The ^1H NMR of the compound **3** in deuterated DMSO indicates two different D_2O exchangeable phenolic Ar–OH protons appeared at δ 12.14 ppm and 10.92 ppm with 1H integrated values. The intra-molecular hydrogen bond between the phenolic proton at 5 position and the carbonyl group at 4 in the flavanone ring made the Ar–OH group more acidic, and the peak shifted to lower field. As well as, all the aromatic protons appeared in between δ 8.15 and 5.95 ppm with the 9H integrated values and the identified splitting, the aliphatic protons belong to the heterocyclic ring appeared at δ 5.85 ppm, 3.30 ppm and 2.78 ppm as doublets due to geminal and vicinal interactions with the justifying integrals. In the ^1H NMR spectra of **4,** as the benzylated product of **3**, the singlet at δ 10.92 ppm disappeared. The aromatic proton region became more complicated with the addition of the benzyl group, and the $-CH_2-$ protons of this group appeared as singlet at δ 5.15 ppm. Because of the extremely low solubility of naringeninoxy-substituted phthalocyanines (**5**–**8**), we were unable to record their ^1H and ^{13}C NMR spectra. However, appeared decoupled peaks in the ^{13}C NMR spectra of **3** and **4** support the proposed structures. Some characteristic shifts which belong to the compounds can be seen at Table 3. In addition, the ^1H and ^{13}C NMR results of the compound **3** and **4** are in good agreement with the published literature [24–26].

ESI MS-MS and MALDI-TOF spectra identify the structures of the prepared compounds. Interpretation of MS spectra of **3** has been done according to peaks which appeared at *m*/*z* 437, 417, and 399. Corresponding molecular ion and the fragment ions were calculated as $[M+2H_2O+3]^+$, $[M+H_2O+1]^+$ and $[M+1]^+$. Additionally, the basic peak of the spectrum, which appears at 269, could be commented as three hydrogen lost naringenin moiety. The MS spectra of **4** were interpreted according to peaks which appeared at *m*/*z* 527, 489, 413 and 400. The molecular ion and the fragment ion molecules were calculated as $[M+2H_2O+3]^+$, $[M+1]^+$, $[M-Bzyl+H_2O-2]$ and $[M-Bzyl+3]$, respectively. The peak appear-

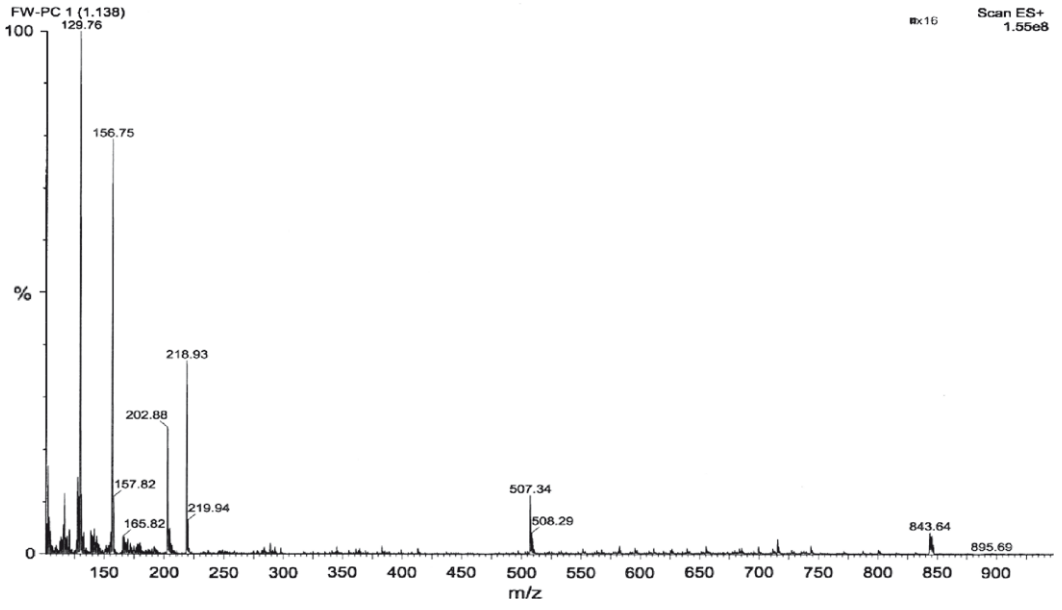
Table 3
Some characteristic ^{13}C NMR shifts of **3** and **4**.

Molecular structures	Carbon num. C_n	Comp. **3** δ (ppm)	Comp. **4** δ (ppm)
	C_1, C_2	116.59, 116.07	114.87, 113.85
	C_3–C_{20}	196.58–95.73	–
	C_3–C_{26}	–	195.02–94.07
	C_{27}	207.22	225.92
	C_{28}	31.38	29.95
	C_{29}	78.53	52.19
	C_{30}	–	65.39

ing at *m*/*z* 413 was the basic peak of the spectrum, as well. ESI MS-MS spectra of mono-substituted zinc-phthalocyanine **5** were examined in detail and the peaks appeared at m/z 843, 718, 507 and 129 were determined to be molecular ion peak and derived fragment peaks. The MS spectra of **5** and the structures of the corresponding molecular ion and the fragment ions can be seen in Fig. 2. The basic peak of the spectrum appeared at *m*/*z* 129 belongs to an iminoisoindoline moiety. MALDI-TOF spectra of **6** were also interpreted and the chemical structures of the molecular ion and the fragment ions were determined from the peaks which appeared at *m*/*z* 1116, 1026, 830, 753 and 663. The considered MS peaks in the determination of the structures and the molecular species matched with are given in Fig. 3. The molecular ion peak of the di-substituted zinc-phthalocyanine **6** appeared at *m*/*z* 1116 was expanded to see the distributions of the peaks in the region. It is obvious that the main peak fractionated in to the five due to the isotopes of the zinc ion bearing in the tetrabenzotetraazaporphyrin ring [19]. Zinc has five stable isotopes with the mass numbers 64, 66, 67, 68 and 70, and their abundances are 48.6%, 27.9%, 4.1%, 18.8%, and 0.6%, respectively [27–29]. However, MS spectra of Co-Pc **7** is simpler due to, the stable isotope of cobalt is only one [30]. Accordingly, in the MALDI-TOF spectra of **7**, the molecular ion peak emerged at *m*/*z* 1135 was calculated as $[M+Na]^+$. Finally, the MS spectra of PcH_2 **8** was examined as MALDI-TOF and the peak appeared at *m*/*z* 1074 was interpreted as the molecular ion ($[M+H_2O]^+$). The chemical structures of the molecular ions of the phthalocyanines (**5**–**8**) and their fragments were determined using ChemDraw Ultra version 7.0.

UV–vis spectra of **6** were recorded from 1×10^{-5} M solutions in THF, DMSO and ethanol (Fig. 4). The significant wavelengths and the calculated extinction coefficients of the prepared compound are given in Table 4. As shown in Table 4, the molar extinction coefficients of **6** in THF solutions have prominently higher values at the Q and B band regions than those found in DMSO and ethanol solution due to less aggregation effects in non polar solvents. However, the aggregation properties of **6** changing with the increased concentrations were examined by using mentioned solvents in 5×10^{-5}–5×10^{-7} mol/L concentration range. The increase of the aggregation properties with the rising concentration in the related solvents was determined in the order of THF > DMSO > EtOH, and the Q band appeared at 665 nm was found as the much affected one (Fig. 5). The typical Q and B bands correspond to the transitions $a_{1u} \rightarrow e_g$ or HOMO–LUMO and a_{2u}-LUMO at wavelengths around 700 nm and 380 nm, respectively [31]. The single Q bands observed for THF solutions **6** at 667.5 and 665.0 nm are characteristic of metallo phthalocyanines. The nature and the symmetrical positions of the peripheral substituents and the molecular environment of the Pc macro-ring affect the Q and B bands of the electronic spectrum by splitting or shifting the peaks [32,33].

Polyhydroxyl-containing substituents such as glucose and phenol derivatives cause blue-shifting in the Q bands and shorter wavelength shifting in the B bands owing to the electron



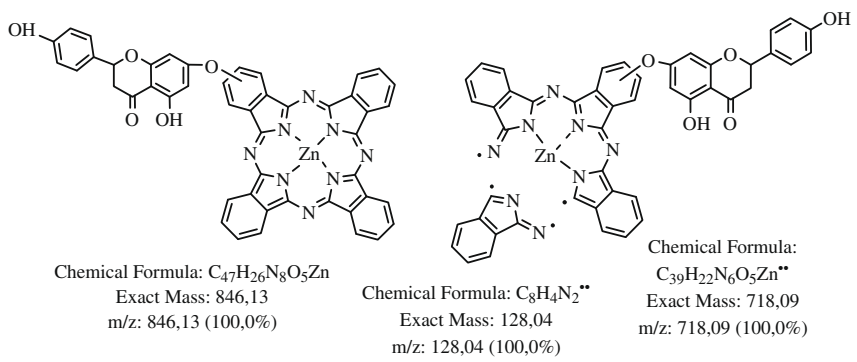


Fig. 2. (a) ESI MS-MS spectra of **5** and (b) molecular ion and some fragment ions structures of **5** examined by using ChemDraw Ultra 7.0 version.

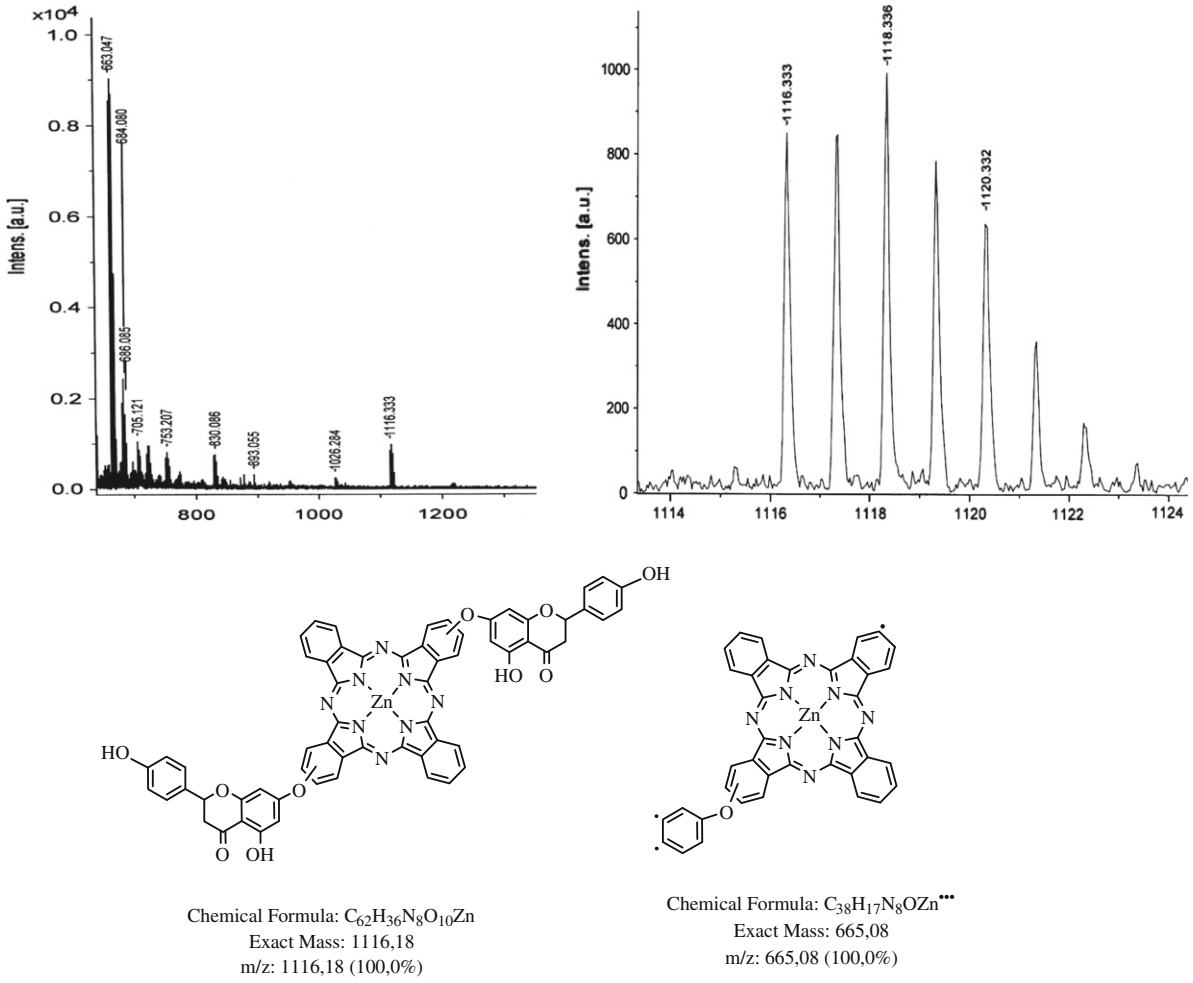


Fig. 3. (a) MALDI-TOF spectra of **6** and (b) molecular ion and basic fragment ion structures of **6** examined by using ChemDraw Ultra 7.0 version.

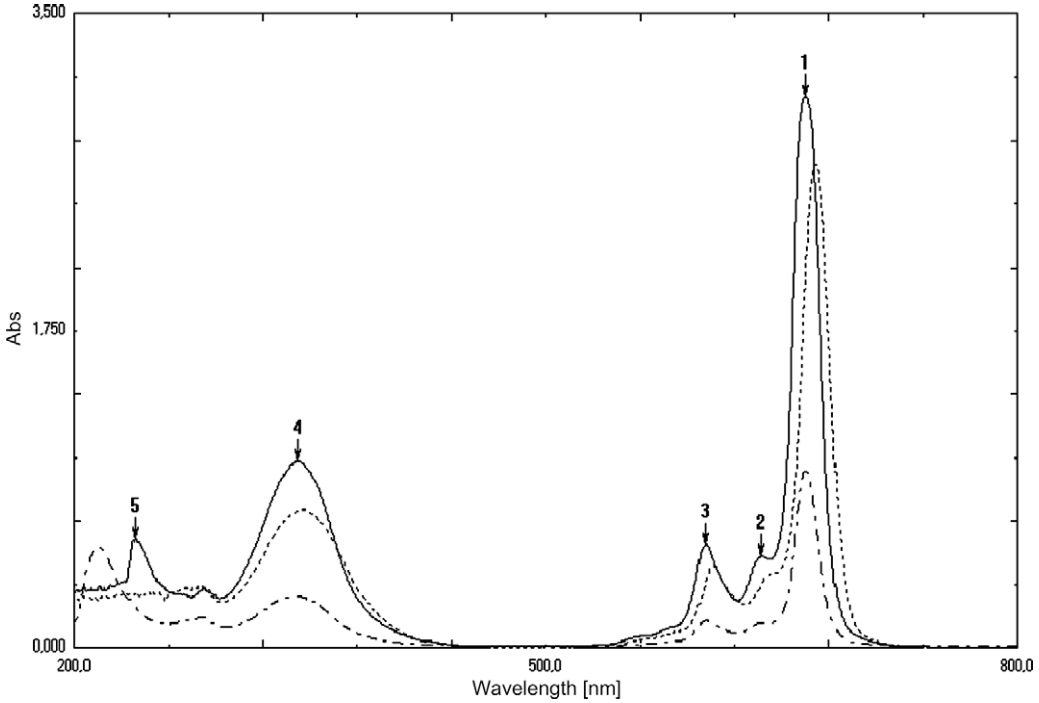


Fig. 4. UV–vis spectra of Pc–Zn **6** in THF (—), DMSO (···) and ethanol (– –).

Table 4
Wavelengths and the extinction coefficients of 1×10^{-5} M solutions of **6** in THF, DMSO and ethanol.

Solution($1x10^{-5}$M)	THF		DMSO		Ethanol	
Peaks	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
1	665.0	5.48	671.5	5.43	665.5	4.99
2	637.5	4.71	606.0	4.66	637.5	4.15
3	601.5	4.76	345.0	4.88	602.0	4.18
4	341.5	5.01	281.0	4.53	341.5	4.46
5	239.0	4.78	253.0	4.49	282.0	4.24

withdrawing properties of the substituents. The same effect was observed with the substitutions of the naringenin groups as polyphenolic species, thus the bands appeared at lower wavelengths when they compared with the un-substituted phthalocyanines [16,34,35]. Addition of a second naringenin group to the macroring did not appreciably affect the electronic spectrum. However, approximately 2.5 nm shifts were observed in the Q bands as well as a decrease in the intensity in the B bands due to the increasing aggregation effects by the rising of the number of the substituted hydroxyl groups. These changes can be seen in the UV–vis spectra of **3**, **5** and **6**, which were recorded from 1.3×10^{-6} M solutions in

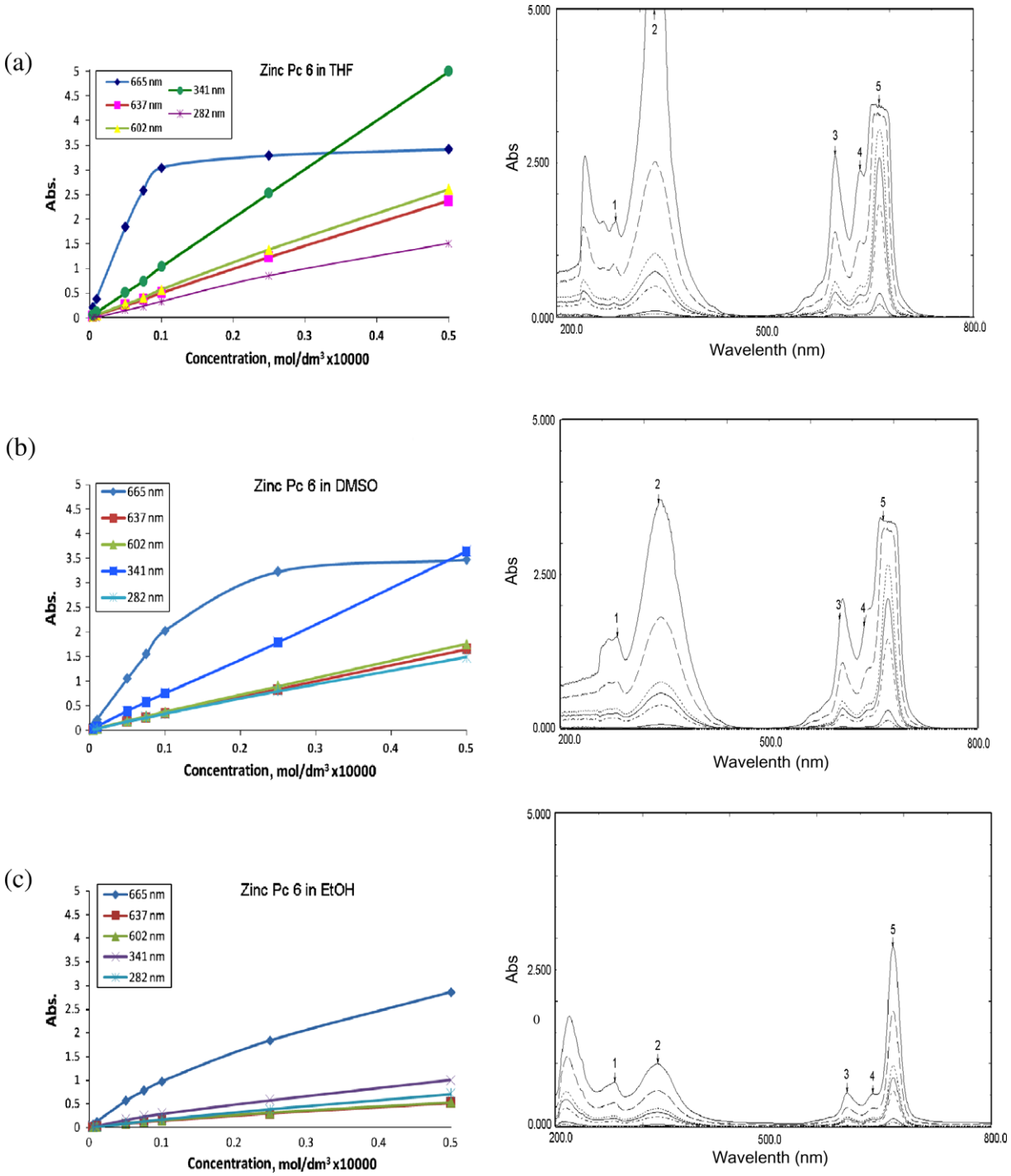


Fig. 5. The aggregation properties of Zinc Pc **6** in (a) THF, (b) DMSO and (c) EtOH.

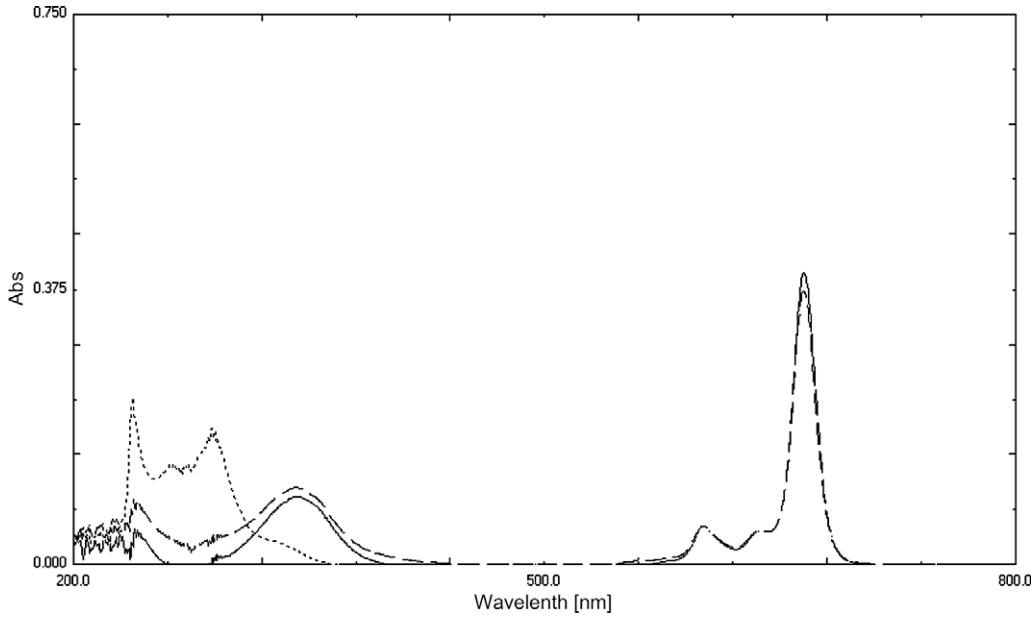


Fig. 6. UV–vis spectra of **3** (···), **5** (- - -) and **6** (—) in THF.

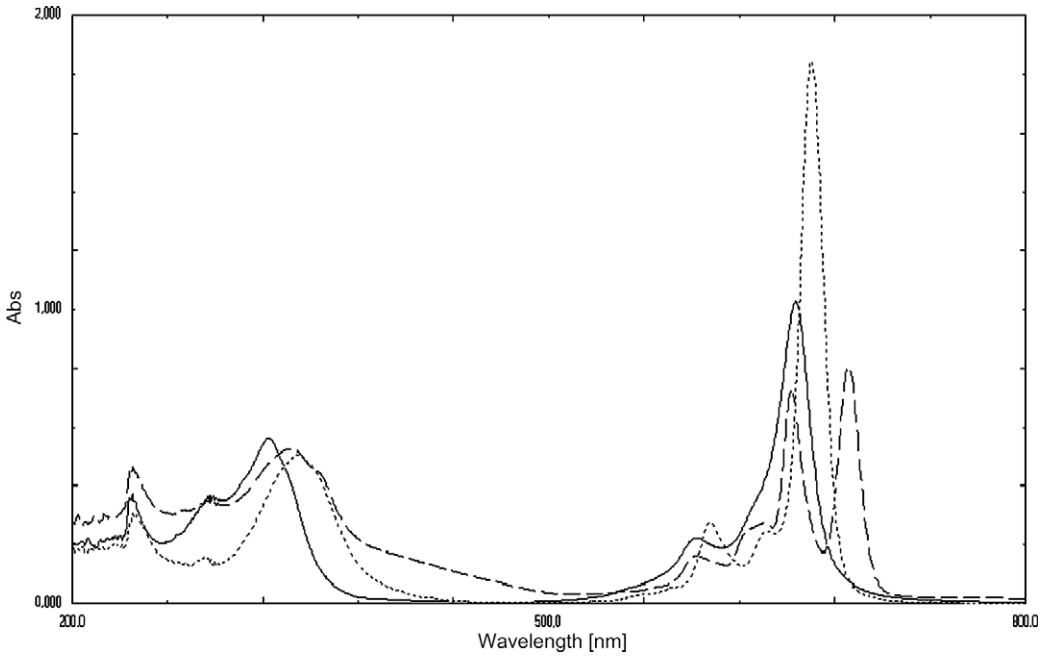


Fig. 7. UV–vis spectra of Pc–Zn **6** (···), Pc–Co **7** (—) and Pc–H_2 **8** (- - -) in THF.

THF (Fig. 6). The extinction coefficients of the intense Q bands of **5** and **6** are also higher than known many symmetrical and unsymmetrical phthalocyanines [24]. Mono-substituted zinc-phthalocyanine **5** gives rise to a single Q band at 667.5 nm, similar to some other mono-functional phthalocyanines due to the degeneracy of the LUMO (e_g) in the molecules with D_{4h} symmetry [15,33–37]. Steric hindrance of the naringeninonxy group gives opposite type di-substituted phthalocyanines. However, the metallo phthalocyanines **6** and **7** consist of the mixture of isomers (C_{2v}, Cs and D_{2h}) and give single Q bands at 665 and 655 nm, respectively. Compound **8** has split Q absorption bands which appear at 689 and 652 nm as shown in Fig. 7. These results are consistent with the published literature [38–40]. The UV–vis spectra of **6**, **7** and **8** which were taken in THF can be seen at Fig. 7.

4. Conclusion

Novel naringenin-substituted zinc-phthalocyanines have been prepared by reacting 4-naringeninoxyphthalonitrile **3** and its benzylated derivative **4** with an excess of phthalonitrile in the presence of DMAE and $ZnCl_2$. By varying the amount of phthalonitrile, either the mono-substituted ZnPc **5** or the di-substituted ZnPc **6** could be obtained. During this tetramerization reaction protecting group (benzyl) cleaved. Therefore, in the preparation of the other phthalocyanines **7** and **8**, phthalonitrile **3** was used directly in the same reaction conditions together with $CoCl_2$ and LiCl, respectively. The starting naringenin-substituted phthalonitrile **3** was prepared by reacting 4-nitrophthalonitrile with naringenin in DMSO in the presence of K_2CO_3. Due to the substantially higher

reactivity of the 7-hydroxy group, as compared to the 5 or 4′-hydroxy groups on naringenin, this nucleophilic aromatic displacement was performed selectively without the need for protecting groups. To our knowledge, these are the first known examples of flavonoid-substituted phthalocyanines.

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