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Synthesis and characterization of novel porphyrin-cinnamic acid conjugates

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Abstract

A series of novel porphyrin-cinnamic acid (porphyrin/CA) conjugates (**4a**-**4c**) have been synthesized by condensation of 5-(4-Hydroxyphenyl)-10,15,20-triphenyl-porphyrin (**1**) with different substituted cinnamic acids (CAs) through an alkyl linker due to the biological activities of CAs and the application of porphyrins in photodynamic therapy (PDT) of cancer. Their related Zinc (II) complexes (**5a**-**5c**) were also prepared. These novel compounds have been fully characterized by ^{1}H NMR, Infrared (IR), Mass spectra（Ms）and Elemental analysis. The photophysical properties of these target molecules were studied by absorption and Fluorescence spectroscopy. In solution，the effect of pH, ionic strength in acid media and concentration on the aggregation behaviors of **4a** has also been investigated by UV-Vis spectra. The broadened and red shifted Soret band indicated the formation of J-aggregates when the pH value was up to 2.0 in THF-aqueous solution. Furthermore, the higher ionic strength of 0.3 M NaCl in acid media resulted in the generation of J-aggregates in THF-aqueous solution. And the significant blue shift of Soret band also demonstrated the formation of H-aggregates of **4a** at 1.1×10^{-4} M in THF.

Keywords: Porphyrins; Cinnamic acids; Synthesis; Optical properties; Aggregation

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1. Introduction

One of the most important applications of porphyrin derivatives in biological system is photodynamic therapy (PDT) for either cancer or microbial pathogens. The common and effective way to acquire new porphyrin derivatives is to couple porphyrins with various functional molecules [1-3]. By this means, many biological porphyrin derivatives with improving efficiency and selectivity of photodynamic treatment have been achieved. For example, glycoporphyrins have not only better solubility in aqueous environment but also improved targeting [4]. In order to increase tumoral targeting ability of porphyrins, folic acid targeted tetraphenylporphyrin have been prepared [2]. Other related reports, such as a potential antibiotic of the porphyrin-vancomycin conjugate for drug-resistant Gram-positive pathogens [1], a potential PDT photosensitizer of porphyrin-profens derivative [5] and potential cancer diagnosis agent of the chalcone-porphyrin conjugates [6], also specified similar promising porphyrin derivatives. In addition, some reports pointed out that cinnamic acid derivatives (CAs) had diverse biological activities, including antitumor[7, 8], antimicrobial [9], antioxidant [10], antifungal [11] and so on. So far, porphyrin

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derivatives modified with CAs at their periphery have remained rather unexplored. Therefore, inspired by the reports above, we initiated the research on porphyrin/CA conjugates which might have the potential application in the field of medicine.

On the other hand, aggregation behaviors of porphyrin have received widespread attention in the porphyrin chemistry and their emergence has a significant effect on the physicochemical properties of these molecules [12,13]. It even affects the efficacy of porphyrins in applications, for example, in the field of medicine [14]. In recent years, much effort has been focused on the formation of J-aggregates for their promising applications such as pH sensors [15,16], PDT [17], nanophotonics [18,19].

In this work, we firstly report a series of novel unsymmetrical porphyrins bearing CAs at the periphery and the investigation of their photophysical properties by absorption and fluorescence spectroscopy. On the other hand, the influence of pH, ionic strength in acidic media and concentration on aggregation behaviors of porphyrin/CA conjugate **4a** has also been investigated.

2. Experimental section

2.1. General procedures

The ^{1}H NMR was recorded on a Bruker Avance 400/600 spectrometer with the indicated solvents operating at 400.15 MHz or 600.62 MHz, respectively. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (J) in Hertz (Hz) using residual solvent peaks as internal standards. Mass spectra were recorded on

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a Finnigan-LCQ DECA XP MAXspectrometer. Infrared spectra (IR) were recorded on a PerkineElmer SP2000 FT-IR spectrometer, using KBr disks technique. Elemental analyses were performed by Elementar Vario EL CUBE (in Institution State Key Lab Element Organic Chemistry, Nankai University, Tianjin, China).

Electronic absorption spectra were recorded on a Shimadzu UV-2450 spectrometer using quartz cells with a width of 1 cm, employing THF and DMF as solvent. Steady-state fluorescence spectra were recorded on a Hitachi F-7000 fluorescence spectrophotometer with a Xe-900 lamp and the emission slit widths were of 5 nm. Fluorescence quantum yields were determined as described in the previous reports [20].These experiments were conducted at room temperature in a dark room to avoid any impact of ambient light over the main light source.

2.2 Synthesis and purification

All reagents used in the synthesis were purchased from Sigma-Aldrich and used without further purification. For anhydrous reactions, the solvents were dried according to stated methods [21]. The dried solvents were then stored in flasks containing molecular sieves 4Å under nitrogen atmosphere. Yields refer to chromatographically pure compounds. 5-(4-Hydroxyphenyl)-10,15,20-triphenyl -porphyrin (**TPP-OH**) (**1**) [22] and 5-(4-(2-Bromoethoxy)phenyl)-10,15,20-triphenyl porphyrin (**H_2BTPP**) (**2**) (SI-Fig. 1) [23, 24] are known compounds and their spectroscopic data correspond to those reported previously.

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*2.2.1 Synthesis of 3-phenyl-acrylic acid 2-[4-(10,15,20-triphenyl-porphyrin-5-yl) -phenoxy]-ethyl ester (**4a**).*

To a solution of cinnamic acid in distilled water was added dropwise a solution of sodium hydroxide (1.0 mol/L) in distilled water to adjust pH to 8-9. Then the resulting mixture was concentrated under vacuum and the crude product of sodium cinnamate (**3a**) was used directly without further purification. A mixture of sodium cinnamate (**3a**) (38.0 mg, 0.223 mmol) and 5-(4-(2-bromoethoxy)phenyl)-10,15,20-triphenyl porphyrin (**2**) (150.0 mg, 0.203 mmol) in dry DMF (15 mL)was stirred at 75ºC for 24 h. The reaction was monitored by thin layer chromatogrph (TLC) until it was completed. After completing the reaction, the unreacted solid salt was separated by filtering and the solvent was removed under vacuum, then the residue was dissolved in $CHCl_3$ and washed with H_2O. Finally, the solvent was removed under vacuum and the resulting residue was purified by silica gel chromatography with CH_2Cl_2/PE (1:1-1:0) as mobile phase. The main purple band was collected to give the desired product. Yield: 135.6 mg (83%); ^{1}H NMR (600 MHz, DMSO-d_6) (SI-Fig. 2) δ_H (ppm) 8.83 (m, 8H, β-pyrrole), 8.22 (d, J = 6.6 Hz 6H, *o*-phenyl), 8.13 (d, J = 7.8 Hz, 2H, *o*-phenyl), 7.83 (m, 12H, *o*- and *m*-phenyl), 7.43 (m, 5H, *p*-phenyl and acryloyl-H), 6.82 (d, J = 15.6 Hz, 1H, acryloyl-H), 4.68(m, 2H, CH_2), 4.58(m, 2H, CH_2), -2.93 (s, 2H, NH-pyrrole). UV-Vis (DMF) λ_{max} (log ε): 418.0 (5.46), 515.5 (4.05), 550.0 (3.76), 590.5 (3.52), 649.0 (3.43) nm; IR (KBr)/cm^{-1}: 3319 (υ_{N-H}, pyrrole), 2924(υ_{CH2}, -CH_2CH_2-), 2850(υ_{CH2}, -CH_2CH_2-), 1709 ($\upsilon_{C=O}$), 1248(υ_{C-O-C}), 964(δ_{N-H}, pyrrole); MS (ESI): m/z calc. for $[M+H]^+$, $C_{55}H_{41}N_4O_3$: 805.31, found: 805.49; elemental analysis

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calcd (%) for $C_{55}H_{40}N_4$ (756.33): C 87.27, H 5.33, N 7.40; Found C 87.19, H 5.35, N 7.47.

*2.2.2 Synthesis of 3-(4-chloro-phenyl)-acrylic acid 2-[4-(10,15,20-triphenyl-porphyrin- 5-yl)-phenoxy]-ethyl ester (**4b**)*

Sodium 3-(4-chloro-phenyl)-acrylate (**3b**) was prepared following a similar procedure to that described for the synthesis of **3a**. A mixture of sodium 3-(4-chloro-phenyl)-acrylate (**3b**) (45.6 mg, 0.223 mmol) and 5-(4-(2-bromoethoxy)phenyl)-10,15,20-triphenyl porphyrin (**2**) (150.0 mg, 0.203 mmol) in dry DMF (15 mL) was stirred at 75ºC for 8 h. The reaction was monitored by TLC until it was completed. After completing the reaction, the reaction mixture was poured into the solution of ice-water/MeOH(10:1) and a purple suspension was obtained which was further filtrated to give the purple crude product. Finally, the resulting crude product was purified by silica gel chromatography with CH_2Cl_2/PE (1:1-1:0) as mobile phase. The main purple band was collected to give the desired product. Yield: 126.8 mg (74.5%); ^{1}H NMR (600 MHz, DMSO-d_6) (SI-Fig. 4) δ (ppm) 8.86~8.84 (m, 8H, β-pyrrole), 8.22 (d, J = 6.6 Hz, 6H, *o*-phenyl), 8.13 (d, J = 7.8 Hz, 2H, *o*-phenyl), 7.79~7.75 (m, 10H, *o*- and *m*- phenyl and acryloyl-H), 7.50 (d, $J_{o\text{-}m}$ = 8.4 Hz, 2H, *m*-phenyl), 7.36 (d, J = 8.4 Hz, 2H, *m*- and *p*-phenyl), 7.31 (d, $J_{m\text{-}p}$ = 7.8 Hz, 2H, *p*-phenyl), 6.56 (d, J = 15.6 Hz, 1H, acryloyl-H), 4.74 (s, 2H, CH_2), 4.53 (d, J = 3.6, 2H, CH_2), -2.78(s, 2H, NH- pyrrole). UV-Vis (DMF) λ_{max} (log ε): 418.0 (5.10), 515.5 (3.67), 550.5 (3.36), 590.5 (3.06), 645.5 (2.94) nm; IR (KBr)/cm^{-1}: 3236 ($\upsilon_{N\text{-}H}$,

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pyrrole), 2926(υ_{CH2}, -CH_2CH_2-), 2852(υ_{CH2}, -CH_2CH_2-), 1716($\upsilon_{C=O}$), 1243υ_{C-O-C}), 966(δ_{N-H}, pyrrole); MS (ESI): m/z calc. for $[M+H]^+$, $C_{55}H_{40}ClN_4O_3$: 839.27, found: 839.47; elemental analysis calcd (%) for $C_{55}H_{39}N_4$ (755.32): C 87.39, H 5.20, N 7.41; Found C 87.42, H 5.17, N 7.42.

*2.2.3 Synthesis of 3-(4-methoxy-phenyl)-acrylic acid 2-[4-(10, 15, 20-triphenyl-porphyrin-5-yl)-phenoxy]-ethyl ester (**4c**)*

Sodium 3-(4-methoxy phenyl) acrylate (**3c**) was prepared following a similar procedure to that described for the synthesis of **3a**. A mixture of sodium 3-(4-methoxy phenyl) acrylate (**3c**) (44.0 mg, 0.223 mmol) and 5-(4-(2-bromoethoxy)phenyl)-10,15,20-triphenyl porphyrin (**2**) (150.0 mg, 0.203 mmol) in dry DMF (15 mL) was stirred at 60^{o}C for 5 h. The reaction was monitored by TLC until it was completed. After completing the reaction, the unreacted solid salt was separated by filtering and the solvent was removed under vacuum, then the residue was dissolved in $CHCl_3$ and washed with H_2O. Finally, the solvent was removed under vacuum and the resulting residue was purified by silica gel chromatography with CH_2Cl_2/PE (1:1-1:0) as mobile phase. The main purple band was collected to give the desired product. Yield: 120 mg (71.2 %); ^{1}H NMR (600 MHz, $CDCl_3$) (SI-Fig. 6) δ_H (ppm) 8.85 (m, 8H, β-pyrrole), 8.21 (d, *J* = 6.6 Hz, 6H, *o*-phenyl); 8.13 (d, *J* = 7.8 Hz, 2H, *o*-phenyl), 7.76 (m, 10H, *o*-,*m*-phenyl and acryloyl-H), 7.53 (d, J_{o-m} = 9.0 Hz, 2H, *m*-phenyl), 7.31 (d, *Jm-p* = 8.4 Hz, 2H, *m*- and *p*-phenyl), 6.90 (d, J_{m-p} = 8.4 Hz, 2H, *p*-phenyl), 6.47 (d, *J* = 15.6 Hz, 1H, acryloyl-H),

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4.74(t, 2H, CH_2), 4.52(t, *J* = 4.2 Hz, 2H, CH_2), 3.82(s, 3H, -OMe), -2.78 (s, 2H, NH-pyrrole); UV-Vis (DMF) λ_{max} (log ε): 418.5 (5.38), 516.0 (3.99), 550.0 (3.73), 592.0 (3.59), 646.0 (3.52) nm; IR (KBr)/cm^{-1}: 3240 (υ_{N-H}, pyrrole), 2924(υ_{CH2}, -CH_2CH_2-), 2850(υ_{CH2}, -CH_2CH_2-), 1712($\upsilon_{C=O}$), 1250(υ_{C-O-C}), 966(δ_{N-H}, pyrrole); MS (ESI): m/z calc. for $[M+H]^+$, $C_{56}H_{43}N_4O_4$: 835.32, found: 835.54; elemental analysis calcd (%) for $C_{56}H_{42}N_4$ (770.34): C 87.24, H 5.49, N 7.27; Found C 87.26, H 5.43, N 7.32.

*2.2.4 Synthesis of zinc(II) 3-phenyl-acrylic acid 2-[4-(10,15,20-triphenyl-porphyrin-5-yl)-phenoxy]-ethyl ester (**5a**)*

A mixture of $Zn(OAc)_2 \bullet 2H_2O$ (2.66 g, 11.3 mmol) and the free 3-Phenyl-acrylic acid 2-[4-(10,15,20-triphenyl-porphyrin-5-yl)-phenoxy]-ethyl ester (**4a**) (100.0 mg, 0.124 mmol) in DMF (25 ml) was heated to 70 ºC under nitrogen for ca. 3h. The reaction was monitored by TLC until it was completed. The solvent was then removed in vacuo and the residue was subjected to chromatography on Al_2O_3 column using PE/CH_2Cl_2 (1:5) as eluent. Repeated chromatography gave pure target compound as a light purple compound. Yield: 83.9 mg (78%); ^{1}H NMR (600 MHz, $CDCl_3$) (SI-Fig. 3) δ_H (ppm) 8.84 (d, *J* = 15.0, 8H, β-pyrrole), 8.15 (d, *J* = 5.4 Hz 6H, *o*-phenyl), 8.06 (d, *J* = 6.6 Hz, 2H, *o*-phenyl), 7.74 (d, *J* = 15.6 Hz, 1H, acryloyl-H), 7.66 (d, *J* = 6.6 Hz, 9H, *o- and m*-phenyl), 7.52 (s, 2H, *m*-phenyl), 7.33 (s, 3H, *m*- and *p*-phenyl), 7.23 (d, J_{m-p} = 6.6 Hz, 2H, *p*-phenyl), 6.52 (d, *J* = 15.6 Hz, 1H, acryloyl-H), 4.67(s, 2H, CH_2), 4.47(s, 2H, CH_2); UV-Vis (DMF) λ_{max} (log ε): 426.5 (5.46), 559.0 (4.00), 599.0 (3.71)

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nm; IR (KBr)/cm^{-1}: 2919(υ_{CH2}, -CH_2CH_2-), 2853(υ_{CH2}, -CH_2CH_2-), 1708($\upsilon_{C=O}$), 1242(υ_{C-O-C}), 1169($\delta_{C\beta-H}$), 992(υ_{N-Zn}); MS (ESI): m/z calc. for [M + H]$^+$, $C_{55}H_{39}N_4O_3Zn$: 867.23, found: 867.43; elemental analysis calcd (%) for $C_{55}H_{38}N_4$ (754.31): C 87.50, H 5.07, N 7.42; Found C 87.56, H 4.98, N 7.45.

*2.2.5 Synthesis of zinc (II) 3-(4-chloro-phenyl)-acrylic acid 2-[4-(10,15,20-triphenyl-porphyrin-5-yl)-phenoxy]-ethyl ester (**5b**)*

A mixture of $Zn(OAc)_2 \cdot 2H_2O$ (3.03 g, 11.3 mmol) and 3-(4-chloro-phenyl)-acrylic acid 2-[4-(10,15,20-triphenyl-porphyrin-5-yl)-phenoxy]-ethyl ester (**4b**) (100.0 mg, 0.124 mmol) in DMF (25 ml) was heated to 120 ^{o}C under nitrogen for ca. 2h. The reaction was monitored by TLC until it was finished. The solvent was then removed in vacuo and the residue was subjected to chromatography on Al_2O_3 column using PE/CH_2Cl_2 (1:3) as eluent to give pure the product as a purple compound. Yield: 83.8 mg (75%); ^{1}H NMR (600 MHz, $CDCl_3$) (SI-Fig. 5) δ_H (ppm) 8.95 (d, *J* =10.8 Hz, 8H, β-pyrrole) 8.22 (d, *J* = 3.6 Hz, 6H, *o*-phenyl), 8.13 (d, *J* = 6.6 Hz, 2H, *o*-phenyl), 7.75 (d, *J* = 6.0 Hz, 9H, *o*- and *m*-phenyl), 7.62 (d, *J* = 16.2 Hz, 1H, acryloyl-H), 7.47 (d, J_{o-m} = 7.8 Hz, 2H, *m*-phenyl), 7.35 (d, *J* = 7.2 Hz, 2H, *m*- and *p*- phenyl), 7.29 (d, J_{m-p} = 6.6 Hz, 2H, *p*-phenyl), 6.47 (d, *J* = 15.6 Hz, 1H, acryloyl-H), 4.63(s, 2H, CH_2), 4.46(s, 2H, CH_2); UV-Vis (DMF) λ_{max} (log ε) : 426.5 (5.58), 559.0 (4.18), 598.5 (3.96) nm; IR (KBr)/cm^{-1}: 2926(υ_{CH2}, -CH_2CH_2-), 2854(υ_{CH2}, -CH_2CH_2-), 1716($\upsilon_{C=O}$), 1243(υ_{C-O-C}), 1166($\delta_{C\beta-H}$), 993(υ_{N-Zn}); MS (ESI): m/z calc. for [M + H]$^+$, $C_{55}H_{38}ClN_4O_3Zn$(isotope): 901.19, found: 901.30; elemental analysis calcd (%) for

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$C_{55}H_{37}N_4$ (753.30): C 87.62, H 4.95, N 7.43; Found C 87.65, H 4.89, N 7.46.

*2.2.6 Synthesis of zinc (II) 3-(4-methoxy-phenyl)-acrylic acid 2-[4-(10, 15, 20-triphenyl-porphyrin-5-yl)-phenoxy]-ethyl ester (***5c***)*

A mixture of $Zn(OAc)_2 \cdot 2H_2O$ (2.66 g, 11.3 mmol) and the free 3-(4-methoxy-phenyl)-acrylic acid 2-[4-(10, 15, 20-triphenyl-porphyrin-5-yl)-phenoxy]-ethyl ester (**4c**) (100.0 mg, 0.199 mmol) in DMF (25 ml) was heated to 70 ^oC under nitrogen for ca. 4h. The reaction was monitored by TLC until it was completed. The solvent was then removed in vacuo and the residue was subjected to chromatography on Al_2O_3 column using PE/CH_2Cl_2 (1:5) as eluent. Repeated chromatography gave pure target compound as a light purple compound. Yield: 76 mg (71%); ^1H NMR (600 MHz, $CDCl_3$) (SI-Fig. 7) δ_H (ppm) 8.96 (m, 8H, β-pyrrole and phenyl), 8.22 (d, *J* = 6.6 Hz, 6H, *o*-phenyl); 8.13 (d, *J* = 7.2 Hz, 2H, *o*-phenyl), 7.75 (m, 9H, *o*- and *m*-phenyl), 7.61 (d, *J* = 16.2 Hz, 1H, acryloyl-H), 7.47 (d, $J_{o\text{-}m}$ = 7.8 Hz, 2H, *m*-phenyl), 7.29 (d, *J* = 7.8 Hz, 2H, *m*- and *p*-phenyl), 6.86 (d, $J_{m\text{-}p}$ = 7.8 Hz, 2H, *p*-phenyl), 6.34 (d, *J* = 15.6 Hz, 1H, acryloyl-H), 4.60(m, 2H, CH_2), 4.44(m, 2H, CH_2), 3.80(s, 3H, -OMe); UV-Vis (DMF) λ_{max} (log ε) : 426.0 (5.65), 559.5 (4.19), 598.5 (3.92) nm. IR (KBr)/cm^{-1}: 2926(υ_{CH2}, -CH_2CH_2-), 2852(υ_{CH2}, -CH_2CH_2-), 1716($\upsilon_{C=O}$), 1243($\upsilon_{C\text{-}O\text{-}C}$), 1163($\delta_{C\beta\text{-}H}$), 991($\upsilon_{N\text{-}Zn}$); Elemental analysis calcd (%) for $C_{56}H_{40}N_4$ (768.33): C 87.47, H 5.24, N 7.29; Found C 87.44, H 5.26, N 7.30.

2.3 Aggregation studies

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The concentration of porphyrin/CA conjugates **4a** in the THF-aqueous solution was varied from 1.0 to 110 μM. The pH variation was carried out by addition of 0.1 M HCl or NaOH concentrated stock solutions. The pH values were measured with a digital pH-meter Corning 430. The ionic strength was 0.1, 0.2, and 0.3 M NaCl respectively and changes in ionic strength were made by addition of NaCl in dry form.

The resulted solutions were then measured by means of UV-Vis absorption spectra to study the aggregation behaviors of the porphyrin/CA conjugate **4a**. As previously described [25, 26], porphyrins self-assembling behaviors were evaluated through changes of the UV-Vis spectra including the maximum absorption wavelength, intensity and the band shape of the Soret bands under different measurement conditions.

3. Results and discussions

3.1 Synthesis

A series of porphyrin/CA conjugates have been prepared by coupling **TPP-OH** (**1**) with cinnamic acid derivatives through alkyl linker (Scheme 1). Although attempts to directly couple **TPP-OH** with cinnamic acid derivatives were made, desired products failed to be obtained either by using DCC/DMAP as condensing agent or converting cinnamic acids into corresponding acyl chlorides. All this maybe resulted from the lower nucleophilicity of hydroxyl group of **TPP-OH**. We then opted to couple the cinnamic acid derivatives with **TPP-OH** through an alkyl linker and prepare the building block 5-[4-(2-bromo-ethoxy)-phenyl]-10,15,20-triphenyl-porphyrin

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(**H_2BTPP**) (**2**). For comparisons, we chose cinnamic acid derivatives substituted at 4-position with chloro- (-Cl), methoxy (-OCH_3) groups and without any substitutents (-H). The cinnamic acid derivatives were then transformed into corresponding sodium cinnamates. Having both **H_2BTPP** and sodium cinnamate **3a** as starting materials, the coupling reaction was performed using DMF as solvent at 75^{o}C to afford the desired product **4a** in an excellent yield 83%. Compounds **4b, 4c** were also synthesized with similar methods in yields 75%, 71%, respectively [27].

After chelating with zinc acetate dihydrate ($Zn(OAc)_2 \cdot 2H_2O$) [28, 29], compound **4a** was converted into its zinc complex (**5a)**. And the other target complexes **5b, 5c** were obtained in a similar way.

3.2 ^{1}H NMR spectral Analysis

^{1}H NMR spectra of compounds **4a**~**4c** and their zinc complexes of **5a**~**5c** were shown in Fig 1. As seen from Fig 1, all of the free bases **4a**~**4c** gave the characteristic signals at -2.8 ppm which were attributed to NH-pyrrole of the porphyrin ring. However, as to the zinc complexes **5a**~**5c**, the corresponding signals disappeared indicating the formation of N-metal bond of the metalloporphyrins. Moreover, all the compounds gave doublets at about 6.5 ppm with typical coupling constants of 15.6 Hz which suggested the double bond of acryloyl group in *E*-configuration. And the multiplets at about 8.8 ppm were assigned to the hydrogens of *β*-pyrrole.

3.3 IR Spectral analysis

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FT-IR spectra of free bases of **4a**~**4c** and their zinc complexes of **5a**~**5c**, with the appearance of C=O vibration around 1710 cm^{-1}, signified the successful coupling of CA derivatives with **HBTPP**. Furthermore, the disappearance of N-H vibration around 3236, 3540 cm^{-1} and the emergence of metal-dependent band at around 990-1030 cm^{-1} for the divalent metal derivatives for the tetraphenylporphines implied that zinc complexes were also successfully prepared[30, 31]. The IR spectra of **4b** and its zinc complex **5a** well showed the characteristic signals in Fig 2.

3.4 Electronic Spectral analysis

Similar to the spectra of starting material **TPP-OH** (λ_{max}=418 nm) and the intermediate **H_2BTPP** (**2**) (λ_{max}=418 nm) (Fig. 3), the UV-Vis spectra of free base porphyrin/CA conjugates **4a**~**4c** showed intense Soret bands at 418 nm, arising from $S_0 \rightarrow S_2$ transition, followed by a series of low intensity bands (*Q* bands) at 516, 550, 592, 646 nm (Table 1, Fig. 4) due to the $S_0 \rightarrow S_1$ transition. Remarkably, the electronic effect from $-OCH_2CH_2Br$ and $-OCH_2CH_2$-CA groups was comparable to that of the hydroxyl group in **TPP-OH** although CA derivatives showed their typical absorption bands, respectively (CA λ_{max}: 274 nm； 4-OCH_3-CA λ_{max}: 299 nm； 4-Cl-CA λ_{max}: 279 nm) (SI-Fig.11). That was to say, the CA moieties had little effect on π-electron transferring in the conjugated porphyrin rings. Furthermore, the similar absorption spectra for **4a**-**4c** also indicated that the outermost substituents, including -H, -OCH_3, -Cl, almost had no influence on the π→π* transitions in the obtained porphyrin/CA conjugates.

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The similarities of the absorption spectra between compounds **4a-4c, H_2BTPP** and **TPP-OH** might result from the saturated alkyl linker between the CA moieties and the porphyrin rings. A large conjugate system between the porphyrin ring and the CA moieties failed to form because of the introduction of the saturated alkyl linker. And no electronic effect from CAs or -OCH_2CH_2Br could be passed onto the porphyrin chromophores.

In addition, the absorption spectra of zinc complexes of **5a-5c** all exhibited a Soret band at 426 nm, rooting from the $S_0 \rightarrow S_2$ transition, followed by two *Q* bands at 559 and 598 nm, caused by $S_0 \rightarrow S_1$ transition (Table 1). The electronic spectra of **5a-5c** were also similar to each other (Fig. 5). Moreover, all the absorption bands of the metallated complexes **5a-5c** showed a red shift compared with those of corresponding ligands **4a-4c**. The metallated complexes **5a-5c** also exhibited two *Q* bands instead of four, due to their higher symmetry.

3.5 Fluorescence spectral analysis

The main fluorescence emission of these porphyrin/CA conjugates was the usual $^1(\pi \leftarrow \pi^*)$ or also was described as $^1(S_0 \leftarrow S_1)$ transition [32]. The peripheral substituents around the porphyrin chromophores almost had no electronic effect on the emission spectra of **4a-4c**, **H_2BTPP** and **TPP-OH** (Fig. 4 and Fig. 3) because they nearly had no influence on the UV-Vis spectra of **4a-4c**, **H_2BTPP** and **TPP-OH** [31]. And the emission spectra of **4a-4c** exhibit two emission peaks of 656 and 723 nm (excited at 418 nm), respectively (Table 2) (Fig. 4). As CA derivatives showed their

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emission peaks as follows: 620 nm (CA, excited at 274 nm)； 580 nm (4-OCH_3-CA, excited at 299 nm); 646 nm (4-Cl-CA, excited at 279 nm) (SI-Fig.11), the mutual overlap effect could only be found in the emission spectrum of **4b**. Furthermore, fluorescence quantum yields were calculated compared with the standard **H_2TPP**, irradiating at 513 nm in deaerated DMF. Results in Table 2 showed that compounds **4a**-**4c** had lower Φ_f (0.13-0.15) which suggested that the singlet excited state was deactivated largely by processes other than fluorescence [20].

Similarly, the fluorescence emission spectra of zinc complexes **5a**-**5c** (Fig. 5) also showed same emission peaks of 611 and 662 nm which demonstrated a significant blue shift compared with those of free bases **4a**-**4c**, separately. In the case of zinc-ion (II), the insertion of metal ion could improve the coplanarity of porphyrins which ascends the energy difference between HOMO and LUMO and makes emission peaks blue shift [33]. Their fluorescence quantum yields (Φ_f = 0.08-0.10) were also lower than that of **H_2TPP** (Φ_f = 0.12).

3.6 Aggregation studies

3.6.1 Influence of the acid medium

As previously reported, most of free porphyrin bases showed significant aggregation behaviors in acid aqueous solutions with changes of the position, the shape and the intensity of the characteristic absorption bands [34].

The changes appeared in the UV-Vis spectra of **4a** in THF-aqueous solution at different values of pH have been studied as exhibited in Fig. 6. When the acidity of

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the solutions was increased, the protonation of the inner nitrogen atom of the porphyrin ring was formed and partial positive charge was induced in the central part of the molecule. Compared with the broadened and unresolved curve at pH 5.5 in Fig. 6, the curve at pH 4.5 slightly splitted into the main peak at 417.5 nm and a shoulder band at 440.0 nm which showed a tendency to form aggregates. Among them, the band at 417.5 nm was unequivocally assigned to the monomer.

It was shown from Fig. 7, by increasing the acidity of the solution, the absorption of Soret bands of the monomer at 417 nm was gradually decreased while the absorption of shoulder bands related to the formation of aggregates was gradually increased. The formation of aggregates was further evidenced by a broadened and bathochromically shifted from 417 nm to 430 nm Soret band when the value of pH was up to 2.0. Moreover, the Q bands didn't show any obvious changes at different values of pH.

As formerly presented, diprotonation of meso-tetraarylporphyrins led to the saddling of the porphyrin core and to an enhanced coplanarity of the *meso*-aryl groups with the porphyrin core [35]. As a consequence of the saddling of the porphyrin core, because of greater stabilization of e_g orbital with respect to a_{1u} orbital, a bathochromic shift of the Soretband was displayed [34].

According to the excitonic splitting theory, side-to-side J-aggregates are characterized by a broadened and red shifted absorption band [34, 36].

3.6.2 Influence of the ionic strength in acid media

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It's known that changes of the ionic strength in acid media could affect the aggregation of porphyrins [13, 37].

Studies have been carried out on the changes in the UV-vis spectra of **4a** in THF-aqueous solutions with different ionic strength in acid media.

As seen from Fig. 8, the curve (1) showed a broadened and slightly split Soret band without NaCl at pH 4.5, but with addition of 0.1 M NaCl at pH 4.5, the curve (2) showed a remarkable tendency to split into two bands at 417.5 and 453.5 nm respectively.

By increasing the ionic strength with varying concentration of NaCl from 0.1 M to 0.3 M with the fixed concentration of porphyrin **4a**, the generation of aggregates was achieved and confirmed by the clear splitting of the broadened Soret band into two individual Lorentzian bands located around 417 nm and 456 nm, respectively (Fig. 9, curve (2) and (3)). Obviously, the band at 417 nm could be exactly assigned to the monomer while the red shift of the Soret band to 456 nm should be attributed to formation of side-by-side J-aggregates.

As expeted, the addition of salt could reduce the solubility of porphyrins in the acidic THF-aqueous media through salting-out effect and change the micro-environment in which the porphyrin existed. Then the hydrophobic-lipophilic interaction among hydrophobic molecules of porphyrin was improved which contributed to aggregation of porphyrins. As already presented, in the aggregation complex, the adjacent porphyrin molecules interact by hydrophobic interaction or electrostatic attraction [13, 38].

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3.6.3 Influence of the concentration

It can be observed that, from Fig. 10, with increasing the concentration of **4a**, the maximum of Soret band was blue shifted from 417.0 to 398.5 nm, and a shoulder band [39] appeared around 422.0 nm, while the four Q bands did not show significant changes in shape and location. And the significant blue shift was not present until the concentration was up to 1.093×10^{-4} mol/L.

According to Kasha's exciton theory [40], the obvious blue shift with respect to the Soret monomer band resulted from the formation of face-to-face H-aggregates, while the red shift arised from the generation of side by side J-aggregates. Moreover, experimental data on the dihedral angle between the porphyrin planes indicated that the hypsochromic shift component of the Soret band should have a dihedral angle of 0^{o} and manifest a dipole-forbidden transition [41].

4. Conclusions

In this paper, a new series of porphyrin/CA conjugates **4a**-**4c** and their zinc complexes **5a**-**5c** were synthesized and fully characterized. These new compounds exhibited the typical bands of the porphyrin core in the absorption and emission spectra which were not significantly affected by the introduction of the alkyl linker and CA moieties. The characteristic Soret band of the porphyrin/CA conjugates **4a**-**4c** was at ca. 418 nm followed by four Q bands situated at 516, 550, 591 and 646 nm.. Furthermore, the Soret bands of metallated porphyrins **5a**-**5c** were red-shifted to ca.

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426 nm followed by two Q bands located at 559 and 599 nm. The emissive bands of the free bases appeared at ca. 656 and 722 nm while the bands of the metallated porphyrins are blue-shifted to ca. 611 and 662 nm. Moreover, the aggregation behaviors of porphyrin/CA conjugates **4a** in solutions were explored under different conditions by UV-vis spectra, icluding: different pH values, various ionic strengths in the acidic media and diverse concentrations. As pH values were decreased with fixed concentration of **4a** in THF-aqueous solution, UV-vis bands showed obvious changes in the shape and location. J aggregates were clearly present when pH value was up to 2.0. Additionally, increase of ionic strength under acidic conditions led to the splitting of broadened Soret band into two distinct Lorentzian bands which suggested the formation of J aggregates. When the concentration was increased to 1.093×10^{-4} mol/L, the maximum of Soret band was obviously blue shifted from 417.0 nm to 398.5 nm which indicated the formation of H aggregates. Furthermore, the investigation of the photodynamic biological activity of these compounds is currently under investigation in our laboratories at present.

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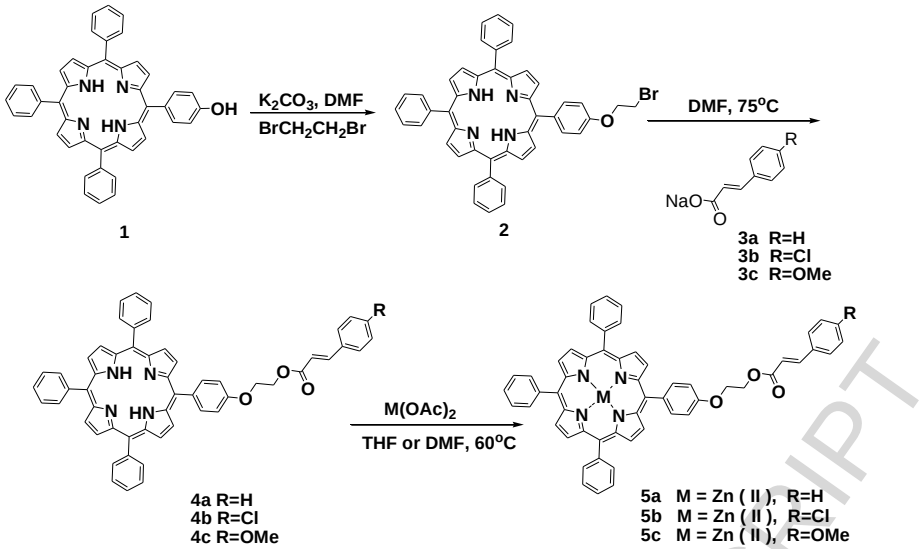

Scheme 1. Synthesis of CA / porphyrin conjugates **4a-4c** and their Zn complexes **5a-5c**.

Table 1 UV-Vis spectral data for **TPP-OH**, **H_2BTPP**, and compounds **4a-4c**, **5a-5c** [a]

Compounds	Soret band/nm(ε)	Qy(1,0)/nm (ε)	Qy(0,0)/nm (ε)	Qx(1,0)/nm (ε)	Qx(0,0)/nm (ε)
1 (TPP-OH)	418.0（3.37×10^5）	516.0（1.6×10^4）	550.0（8.0×10^3）	591.0（4.0×10^3）	647.0（4.13×10^3）
2 (H_2BTPP)	418.0（3.59×10^5）	516.0（1.2×10^4）	550.5（5.0×10^3）	591.0（1.8×10^3）	646.0（1.5×10^3）
4a (R = H))	418.0（2.87×10^5）	515.5(1.1×10^4）	550.0（5.7×10^3）	590.5（3.3×10^3）	646.0（2.7×10^3）
4b (R = Cl)	418.0（1.26×10^5）	515.5（4.6×10^3）	550.5（2.3×10^3）	590.5（1.15×10^3）	645.5（0.87×10^3）
4c (R = OMe)	418.5（2.42×10^5）	516.0（9.8×10^3）	550.0（5.4×10^3）	592.0（3.87×10^3）	646.0（3.3×10^3）
5a (M= Zn, R= H)	426.5（2.91×10^5)		559.0(9.97×10^3)	599.0(5.1×10^3)	
5b (M = Zn, R= Cl)	426.5（3.84×10^5）		559.5（1.53×10^4）	598.5(9.03×10^3)	
5c (M = Zn, R= OMe)	426.0（4.47×10^5）		559.5（1.56×10^4）	598.5（8.3×10^3）	

a A solution of DMF was used in UV-Vis spectral determinations. The concentrations for the porphyrins and their derivatives were 3×10^{-6} mol/L.

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Table 2 Emission data for H_2TBPP and compounds **4a**-**4c**, **5a**-**5c**.[a]

Compounds	Q(0,0)/nm (intensity)	Q(0,1)/nm (intensity)	Φ_f(513nm)[b]	Compounds	Q(0,0)/nm (intensity)	Q(0,1)/nm (intensity)	Φ_f(513nm)[b]
4a	656 (4762)	722（1310）	0.15	**5a**	611 (2138)	662 (1195)	0.09
4b	656 (3572)	722（981）	0.13	**5b**	611 (2052)	662 (1338)	0.08
4c	656 (4734)	722（1284）	0.15	**5c**	611 (2144)	662 (1198)	0.10
TPP-OH	657(4963)	722(1248)	0.12	**H_2TBPP**	657(4785)	721(1279)	0.10

a A solution of DMF was used in fluorenscence emission spectral determinations. The concentrations for the porphyrin-CA conjugates and the intermediates were 3×10^{-6} mol/L.

b Using H_2TPP in DMF (Φ_f = 0.12) as a reference.

THF:CH_2Cl_2 30:70 (blue line), THF: water 30:70 (magenta line) and THF (red line)at room temperature (conc = 1μM).

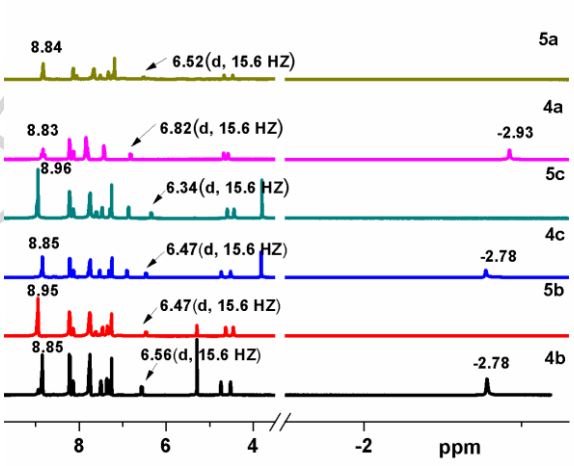

Fig. 1. ^{1}H NMR spectra of prophyrins/CA conjugates **4a**~**4c** and their zinc complexes **5a**~**5c**

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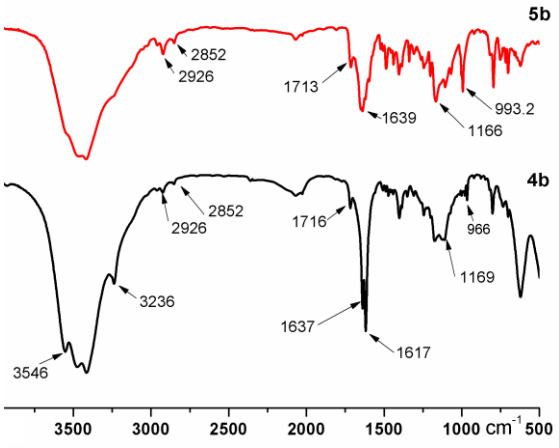

Fig. 2. IR spectra of free base of **4b** and its zinc complex of **5b**

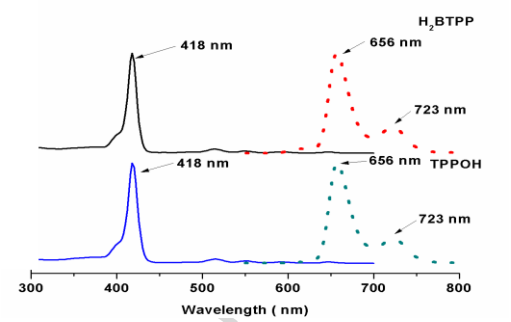

Fig. 3. Normalized Absorption (solid) and Fluorescence spectra (dotted) of compounds **TPP-OH**, **H_2BTPP** in DMF.

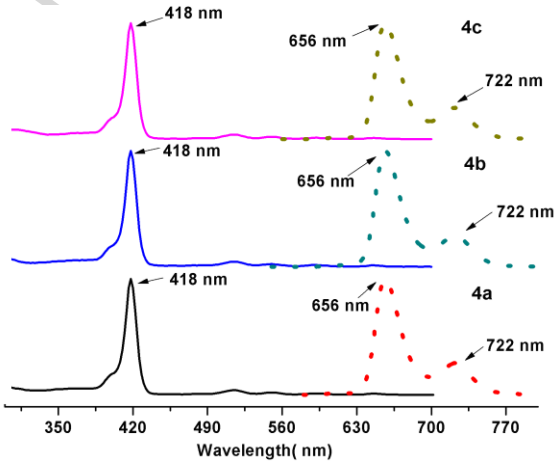

Fig. 4. Normalized Absorption (solid) and Fluorescence spectra (dotted) of the metal free porphyrins **4a**-**4c** in DMF.

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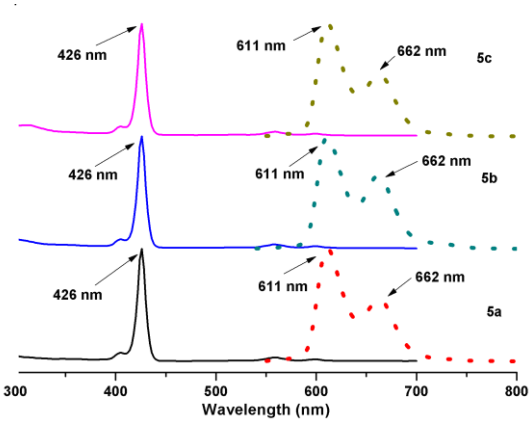

Fig. 5. Normalized Absorption (solid) and Fluorescence spectra (dotted) of zinc complexes **5a-5c** in DMF.

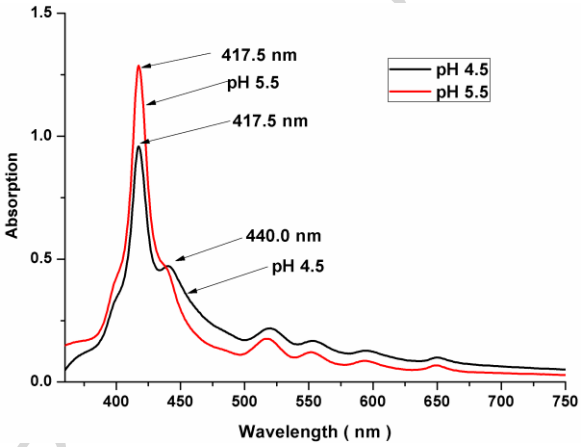

Fig. 6. The UV-vis spectra of **4a** in THF-aqueous solution, at pH 5.5 (red line) and pH 4.5 (black line).

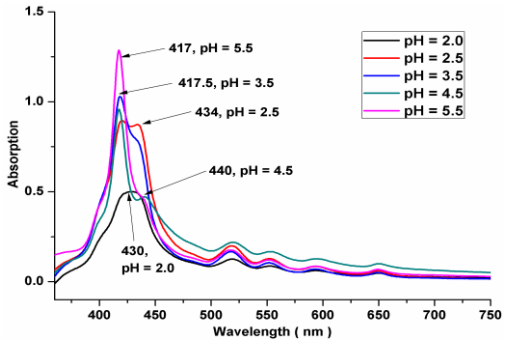

Fig. 7. The UV-vis spectra of **4a** in THF-aqueous solution by modifying pH value from 5.5 to 2.0.

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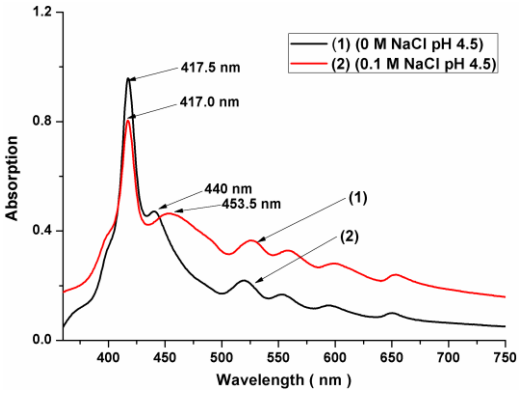

Fig. 8. The UV-vis spectra of **4a** in THF-aqueous solution without NaCl at pH 4.5 (black line) and in the presence of 0.1 M NaCl at pH 4.5 (red line).

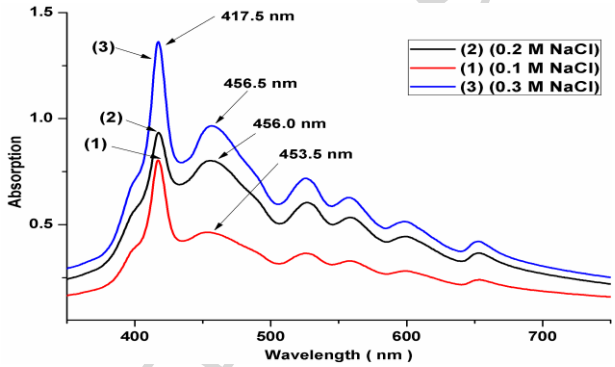

Fig. 9. The UV-vis spectra of **4a** in THF-aqueous solution with different ionic strength of 0.1, 0.2, 0.3 M NaCl at pH 4.5.

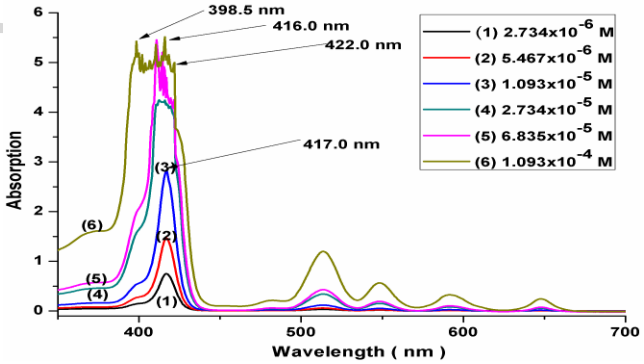

Fig. 10. The superposed UV-vis spectra of **4a** in THF at different concentrations.

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Synthesis and characterization of novel porphyrin-cinnamic acid conjugates

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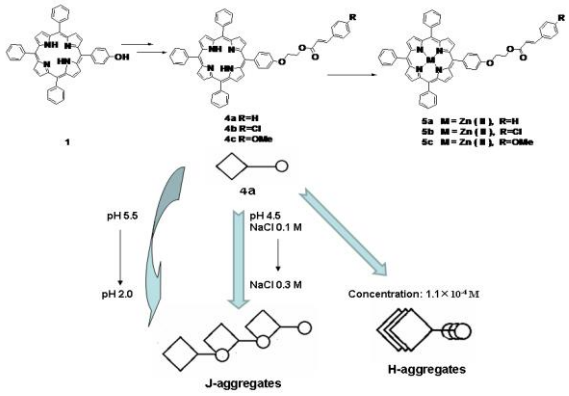
Graphical Abstract:



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Highlights

Synthesis and characterization of novel porphyrin-cinnamic acid conjugates

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Contents

- Porphyrin cinnamic acid conjugates were synthesized and characterized.
- Znic complexes of these conjugates were prepared and characterized
- Photophysical properties of these conjugates were studied by UV-Vis and Fluorescence.
- Aggregation behaviors of a conjugate in THF-aqueous and THF solutions were explored.