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Design, synthesis and characterization of 3-alkyl substituted chlorin derivatives

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ABSTRACT

The novel 3-alkyl substituted chlorin derivatives exhibiting good lipophilicity were obtained from methyl pheophorbide-a by modification of the peripheral functional groups. The vinyl group at 3-position was oxidized with OsO4 and NaIO4 to form the formyl group and the Grignard reaction of this aldehyde with the alkyl magnesium bromide was carried out to give the corresponding 3-(1-hydrroxylalkyl) pheophorbide-a. The 3-(1-hydrroxylalkyl) functional group was converted into 3-alkyl chain by dehydration and hydrogenation. The Qy band of prepared photosensitizers were affected by the substituent on the Qy axis (N^{21}-N^{23}). The structures of new photosensitizers were characterized by elemental analysis, UV-vis and ^{1}H NMR spectra.

Key words: Chlorin, Methyl pheophorbide-a, Photosensitizer, Photodynamic therapy

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INTRODUCTION

Photpdynamic therapy (PDT) is an innovative and attractive treatment for the destruction of various types of solid tumorous and non-tumorous diseases. PDT utilizes the ability of a selectively retained photosensitizer to elicit an efficient photodynamic reaction upon activation with tissue penetrating light. [1-2]

In continuing efforts to develop new phtosensitizers for PDT, the design and synthesis of chlorin derivatives having well-defined structure with amphiphilic properties, high selectivity for tumor cell, quick elimination from health cells and strong absorption in the red region of visible spectrum is an important challenge in the PDT field. Recently interest has been aroused in natural chlorins and their derivatives which contain an additional exocyclic ring in the lower part (ring C and D) of the macrocycle such as five-membered E-ring of methyl pheophorbide-a (MPa) and six-membered anhydride ring of purpurin-18 methyl ester.[3-7] The modifications of these naturally occurring chlorins have been the focus of developing new photsensitisers for use in photodynamic therapy (PDT), particularly for 3-position and exocyclic ring because the Qy bands of chlorin, the longest absorption band, were strongly affected by the substituents along the Qy axis (N^{21}-N^{23}, Scheme 1). [8]

In the study of MPa derivatives, Dougherty and co-workers found that HPPH, which has a secondary n-hexyl ether group at 3 position, exhibits excellent PDT efficacy. [9-10] Among the optimal photosensitizers, different lengths of alkyl ethers were regioselectively introduced at their 3-position. According to quantitative structure-activity relationship(QSAR) for the analogues of MPa series, we expanded this approach to photosensitizers with various alkyl chains, which improved their lipophilicity more efficiently comparing to alkoxy chain.

EXPERIMENTAL SECTION

General Methods.
The UV-vis absorption spectra were recorded on Scinco S-3100 spectrophotometer using CH_2Cl_2 as a solvent. Thin

layer chromatography (TLC) was performed on silica gel 60 F254 (E. Merck). Routine nuclear magnetic resonance (NMR) spectra were recorded on a Varian-500MHz spectrometer. Chemical shifts are given as δ values using TMS as the internal standard and J values in Hz. Chemical shifts are quoted in ppm on the δ scale and coupling constants (J) are expressed in Hertz (Hz). Samples for NMR spectroscopic studies were prepared using solvents purchased from Aldrich. Elemental analysis data were measured on Flash 2000 series (Thermo). All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled. Methylpheophorbide-a (MPa) 1 was obtained according to Smith's method 11.

3-(1-Hydroxy-1-ethyl)-3-devinyl-pheophorbide-a methyl ester 3a.

Compound 2 (150 mg) and 0.35 mL of ethyl magnesium bromide in THF (1mol/L) were dissolved in THF (15mL) at 0 ^{o}C. The mixture was stirred for 25 min. The mixture was poured into saturated solution of NH_4Cl, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and evaporated in vacuuo to dryness. The residue was purified by chromatography to give the title compound **3a** in 67% yield. Mp 220-222^{o}C, UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 647.0 (0.38), 596.6 (0.05), 566.6 (0.06), 528.0 (0.07), 398.1 (1.48). ^{1}H NMR (500MHz, $CDCl_3$) δ: -1.34 (brs, 2H, NH), 0.86 (t, J=7.0 Hz, 3H, 33-Me), 1.47 (m, 2H, 32-H), 1.79 (t, J=7.0Hz, 3H, 8-Me), 1.86 (d, J=7.5 Hz, 3H, 18-Me), 2.20-2.82 (m, 2H, 171-H and 17^2-H), 3.55 (m, 2H, 8-H), 3.10, 3.36, 3.58, 3.67, 3.82 (each s, each 3H, 15H, Me+OMe), 4.21 (m, 1H, 17-H), 4.42 (m, 1H, 18-H), 6.18 (m, 1H, 3^1-H), 6.32 (s, 1H, 13^2-H), 8.57, 9.36, 9.65 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{36}H_{40}N_4O_6$: C, 69.21; H, 6.45; N, 8. 97. Found: C, 69.25; H,6.46; N, 8. 96.

3-(1-Hydroxy-1-propyl)-3-devinyl-pheophorbide-a methyl ester 3b.

Followed the same procedure for the synthesis of **3a**. Yield: 70%. Mp 221-223^{o}C, UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 647.3 (0.25), 596.1 (0.04), 566.5 (0.05), 528.3 (0.06), 398.7 (1.18). ^{1}H NMR (500MHz, $CDCl_3$) δ: -1.74 (brs, 2H, NH), 0.88 (t, J = 7.0 Hz, 3H, 3^3-Me), 1.49 (m, 4H, 3^2, 3^3-H), 1.68 (t, J = 7.0Hz, 3H, 8-Me), 1.86 (d, J = 7.5 Hz, 3H, 18-Me), 2.10-2.80 (m, 2H, 17^1-H and 17^2-H), 3.56 (m, 2H, 8-H), 3.11, 3.35, 3.59, 3.68, 3.80 (each s, each 3H, 15H, Me + OMe), 4.20 (m, 1H, 17-H), 4.41 (m, 1H, 18-H), 6.22 (m, 1H, 3^1-H), 6.34 (s, 1H, 13^2-H), 8.55, 9.32, 9.67 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{37}H_{42}N_4O_6$: C, 69.57; H, 6.63; N, 8. 77. Found: C, 69.53; H, 6.60; N, 8.81.

3-(1-Hydroxy-1-butyl)-3-devinyl-pheophorbide-a methyl ester 3c.

Followed the same procedure for the synthesis of **3a**. Yield: 62%. Mp 230-231^{o}C, UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 648.2 (0.20), 596.0 (0.03), 566.1 (0.05), 527.6 (0.05), 399.2 (1.09). ^{1}H NMR (500MHz, $CDCl_3$) δ: -1.80 (brs, 2H, NH), 0.89 (t, J = 7.0 Hz, 3H, 3^5-Me), 1.41 (m, 6H, 3^2, 3^3 and 3^4-H), 1.69 (t, J = 7.0Hz, 3H, 8-Me), 1.81 (d, J = 7.5 Hz, 3H, 18-Me), 2.29-2.76 (m, 2H, 17^1-H and 17^2-H), 3.58 (m, 2H, 8-H), 3.16, 3.35, 3.59, 3.61, 3.88 (each s, each 3H, 15H, Me + OMe), 4.20 (m, 1H, 17-H), 4.43 (m, 1H, 18-H), 6.18 (m, 1H, 3^1-H), 6.24 (s, 1H, 13^2-H), 8.45, 9.30, 9.61 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{38}H_{44}N_4O_6$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.942; H, 6.78; N, 8.61.

3-(1-Hydroxy-1-pentyl)-3-devinyl-pheophorbide-a methyl ester 3d.

Followed the same procedure for the synthesis of a **3a**. Yield: 61%. Mp 221-223^{o}C, UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 647.3 (0.25), 596.1 (0.04), 566.5 (0.05), 528.3 (0.06), 398.7 (1.18). ^{1}H NMR (500MHz, $CDCl_3$) δ: -1.38, -1.90 (brs, 2H, NH), 0.80 (t, J = 7.5 Hz, 3H, 3^6-Me), 1.33 (m, 8H, 3^2, 3^3, 3^4, 3^5-H), 1.69 (t, J = 7.0Hz, 3H, 8-Me), 1.80 (d, J = 7.5 Hz, 3H, 18-Me), 2.19-2.86 (m, 2H, 17^1-H and 17^2-H), 3.78 (m, 2H, 8-H), 3.16, 3.34, 3.44, 3.58, 3.67 (each s, each 3H, 15H, Me + OMe), 4.40 (m, 1H, 17-H), 4.64 (m, 1H, 18-H), 6.18 (s, 1H, 13^2-H), 8.79, 9.64, 9.93 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{39}H_{46}N_4O_6$: C, 70.25; H, 6.95; N, 8.40. Found: C, 70.21; H, 6.92; N, 8.46.

3-(1-ethylene)-3-devinyl-pheophorbide a methyl ester 4a.

Compound **3** (100 mg) was dissolved in benzene (25 mL), and then TsOH (3 mg) was added. This mixture was allowed to stir for 1 h at 90 ^{o}C before water (20 mL) and dichloromethane (25mL) was added. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by chromatography to give the title compound **4a** in 68% yield. UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 662.8 (0.23), 604.8 (0.05), 535.9 (0.06), 505.2(0.06), 409.0 (1.12). ^{1}H NMR (500MHz, $CDCl_3$) δ: 0.08, -1.78 (each br s, 1H, NH), 0.96 (t, *J* = 7.5 Hz, 3H, 3^3-Me), 1.65 (t, J = 7.0Hz, 3H, 8-Me), 1.79 (d, *J* = 7.5 Hz, 3H, 18-Me), 2.10-2.66 (m, 2H, 17^1-H and 17^2-H), 3.68 (m, 2H, 8-H), 3.16, 3.31, 3.60, 3.66 (each s, each 3H, 15H, Me + OMe), 4.24 (m, 1H, 17-H), 4.46 (m, 1H, 18-H), 6.68 (td, *J* = 16.0 and 7.0 Hz, 1H, 3^2-H), 7.51(d, *J* = 16.0 Hz, 1H, 3^1-H), 8.48, 9.23, 9.36 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{36}H_{38}N_4O_5$: C, 71.27; H, 6.31; N, 9.23. Found: C,

71.29; H, 6.34; N, 9.24.

3-(1-propylene)-3-devinyl-pheophorbide a methyl ester 4b.
Followed the same procedure for the synthesis of **4a**. Yield: 66%. UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 664.0 (0.66), 605.3 (0.15), 510.4 (0.17), 414.8 (1.89). ^{1}H NMR (500MHz, $CDCl_3$) δ: 0.48, -1.70 (each br s, 1H, NH), 0.92 (t, *J* = 7.5 Hz, 3H, 3^4-Me), 1.40 (m, 2H, 3^3-H), 1.66 (t, J = 7.0Hz, 3H, 8-Me), 1.78 (d, *J* = 7.5 Hz, 3H, 18-Me), 2.10-2.68 (m, 2H, 17^1-H and 17^2-H), 3.66 (m, 2H, 8-H), 3.12, 3.30, 3.62, 3.69 (each s, each 3H, 15H, Me ₊ OMe), 4.22 (m, 1H, 17-H), 4.41 (m, 1H, 18-H), 6.69 (td, *J* = 16.0 and 7.5 Hz, 1H, 3^2-H), 7.51 (d, *J* = 16.5 Hz, 1H, 3^1-H), 8.55, 9.28, 9.45 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{37}H_{40}N_4O_5$: C, 71.59; H, 6.50; N, 9.03. Found: C, 71.56; H, 6.41; N, 8.91.

3-(1-butylene)-3-devinyl-pheophorbide a methyl ester 4c.
Followed the same procedure for the synthesis of **4a**. Yield: 66%. UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 665.1 (0.45), 605.4 (0.10), 510.8 (0.12), 415.0 (1.69). ^{1}H NMR (500MHz, $CDCl_3$) δ: 0.08, -1.88 (each br s, 1H, NH), 0.91 (t, *J* = 7.5 Hz, 3H, 3^5-Me), 1.40 (m, 4H, 3^3 ,3^4-H), 1.69 (t, J = 7.0Hz, 3H, 8-Me), 1.86 (d, *J* = 7.5 Hz, 3H, 18-Me), 2.11-2.75 (m, 2H, 17^1-H and 17^2-H), 3.66 (m, 2H, 8-H), 3.10, 3.30, 3.60, 3.72 (each s, each 3H, 15H, Me ₊ OMe), 4.28 (m, 1H, 17-H), 4.46 (m, 1H, 18-H), 6.65 (td, *J* = 16.0 and 7.5 Hz, 1H, 3^2-H), 7.50 (d, *J* = 16.5 Hz, 1H, 3^1-H), 8.45, 9.22, 9.48 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{38}H_{42}N_4O_5$: C, 71.90; H, 6.67; N, 8.83. Found: C, 71.79; H, 6.72; N, 8.72.

3-(1-pentylene)-3-devinyl-pheophorbide a methyl ester 4d.
Followed the same procedure for the synthesis of **4a**. Yield: 60%. UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 665.0 (0.65), 605.0 (0.13), 510.2 (0.16), 415.0 (1.78). ^{1}H NMR (500MHz, $CDCl_3$) δ: 0.46, -1.78 (each br s, 1H, NH), 1.06 (t, *J* = 7.5 Hz, 3H, 3^6-Me), 1.40 (m, 6H, 3^3 , 3^4 ,3^5-H), 1.66 (t, J = 7.0Hz, 3H, 8-Me), 1.78 (d, *J* = 7.5 Hz, 3H, 18-Me), 2.12-2.71 (m, 2H, 17^1-H and 17^2-H), 3.68 (m, 2H, 8-H), 3.12, 3.35, 3.61, 3.72 (each s, each 3H, 15H, Me ₊ OMe), 4.22 (m, 1H, 17-H), 4.41 (m, 1H, 18-H), 6.68 (td, *J* = 16.0 and 7.5 Hz, 1H, 3^2-H), 7.52 (d, *J* = 16.5 Hz, 1H, 3^1-H), 8.47, 9.23, 9.38 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{39}H_{44}N_4O_5$: C, 72.20; H, 6.84; N, 8.64. Found: C, 72.30; H, 6.92; N, 8.51.

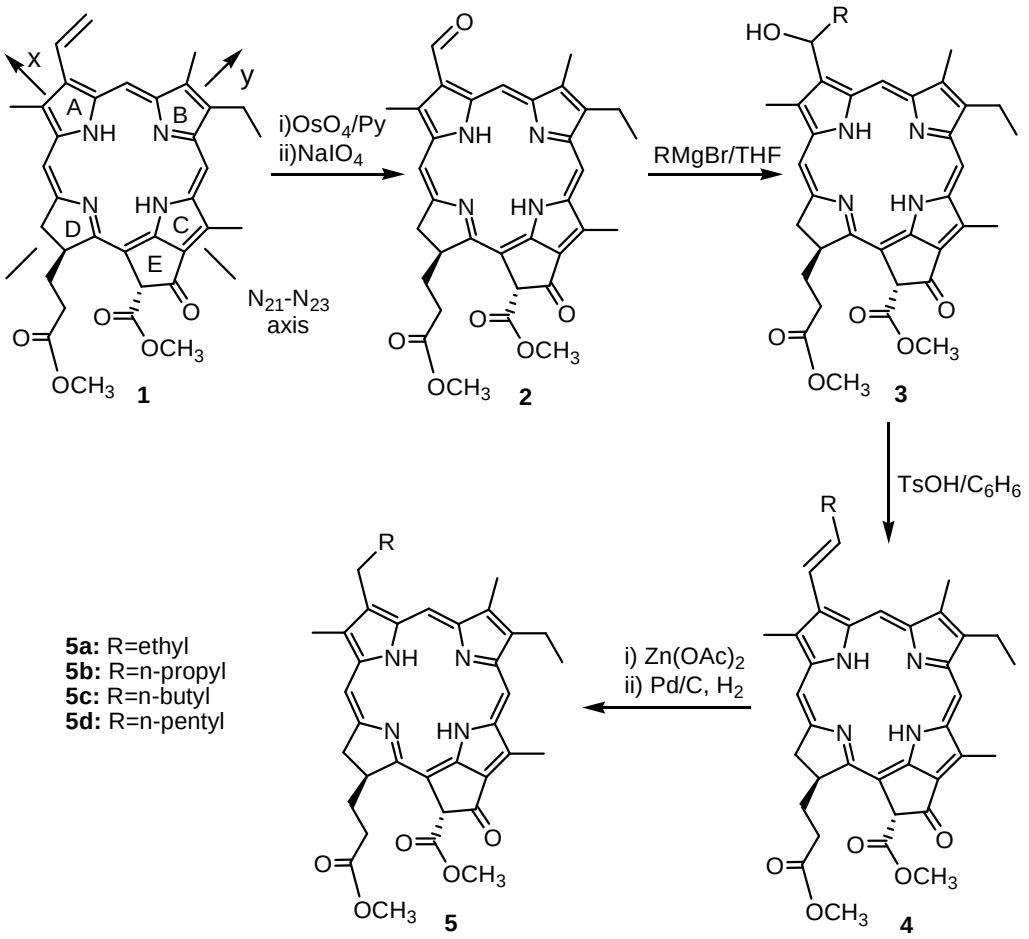
3-Propyl-3-devinyl-pheophorbide-a methyl ester 5a.
Znic complex of **4a** (490mg) was dissolved in 100ml of distilled THF. Et_3N (0.1ml) and Pd/C(10%, 300mg) were added to the reaction mixture. The reaction mixture was stirred for 20h under H_2 atmosphere. After completion of the reaction, the reaction mixture was filtered. The filtrate was concentrated, and the residue was treated with TFA (15ml) for 2h at room temperature. The reaction mixture was poured in to ice and extracted with dichloromethane . The organic layer was collect, and washed with water (3x100ml). The organic layer was separated,dried over anhydrous Na_2SO_4, and concentrated. The solvent was removed, and The residue was purified by chromatography to give the title compound **5a** in 92% yield . UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 646.6 (0.30), 596.1 (0.05), 527.2 (0.07), 399.1 (1.02). ^{1}H NMR (500MHz, $CDCl_3$) δ: -1.77 (brs, 2H, NH), 0.86 (t, J = 7.0 Hz, 3H, 3^3-Me), 1.46 (m, 4H, 3^1 , 3^2-H), 1.64 (t, J = 7.0Hz, 3H, 8-Me), 1.80 (d, J = 7.5 Hz, 3H, 18-Me), 2.10-2.66 (m, 2H, 17^1-H and 17^2-H), 3.56 (m, 2H, 8-H), 3.12, 3.31, 3.52, 3.64, 3.77 (each s, each 3H, 15H, Me ₊ OMe), 4.20 (m, 1H, 17-H), 4.42 (m, 1H, 18-H), 8.55, 9.23, 9.65 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{36}H_{40}N_4O_5$: C, 71.03; H, 6.62; N, 9.20. Found: C, 70.91; H, 6.45; N, 9.14.

3-Butyl-3-devinyl-pheophorbide-a methyl ester 5b.
Followed the same procedure for the synthesis of **5a**. Yield: 91%. UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 645.0 (0.32), 595.0 (0.06), 526.1 (0.06), 398.5 (1.02). ^{1}H NMR (500MHz, $CDCl_3$) δ: -1.79, 0.09 (br s, 2H, NH), 0.88 (t, J = 7.0 Hz, 3H, 3^4-Me), 1.49 (m, 6H, 3^1, 3^2, 3^3-H), 1.69 (t, J = 7.0Hz, 3H, 8-Me), 1.88 (d, J = 7.5 Hz, 3H, 18-Me), 2.15-2.66 (m, 2H, 17^1-H and 17^2-H), 3.55 (m, 2H, 8-H), 3.12, 3.31, 3.54, 3.60, 3.72 (each s, each 3H, 15H, Me ₊ OMe), 4.28 (m, 1H, 17-H), 4.44 (m, 1H, 18-H), 8.57, 9.38, 9.58 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{37}H_{44}N_4O_5$: C, 71.36; H, 6.80; N, 9.00. Found: C, 71.33; H, 6.94; N, 8.87.

3-Pentyl-3-devinyl-pheophorbide-a methyl esterc 5c.
Followed the same procedure for the synthesis of **5a**. Yield: 94%. UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 646.2 (0.35), 595.2 (0.07), 526.6 (0.08), 399.9 (1.32). ^{1}H NMR (500MHz, $CDCl_3$) δ: -0.08, -1.88 (br s, 2H, NH), 0.88 (t, J = 7.5 Hz, 3H, 3^5-Me), 1.45 (m, 8H, 3^1,3^2, 3^3, 3^4-H), 1.66 (t, J = 7.0Hz, 3H, 8-Me), 1.86 (d, J = 7.5 Hz, 3H, 18-Me), 2.10-2.70 (m, 2H, 17^1-H and 17^2-H), 3.78 (m, 2H, 8-H), 3.15 3.35, 3.42, 3.56, 3.60 (each s, each 3H, 15H, Me ₊ OMe), 4.44 (m, 1H, 17-H), 4.68 (m, 1H, 18-H), 8.60, 9.28, 9.46 (each s, each 1H, 3H, meso-H). Anal. calcd.

For $C_{38}H_{44}N_4O_5$: C, 71.67; H, 6.96; N, 8.80. Found: C, 71.75; H, 7.01; N, 8.76.

3-Hexyl-3-devinyl-pheophorbide-a methyl ester 5d.
Followed the same procedure for the synthesis of **5a**. Yield: 92%. UV-vis in CH_2Cl_2, λ max (nm, rel. intensity log ε): 645.8 (0.20), 594.5 (0.04), 525.0 (0.06), 398.8 (0.86). ^{1}H NMR (500MHz, $CDCl_3$) δ: -0.18, -1.78 (br s, 2H, NH), 0.84 (t, J = 7.5 Hz, 3H, 3^6-Me), 1.33 (m, 10H, 3^1, 3^2, 3^3, 3^4, 3^5-H), 1.69 (t, J = 7.0Hz, 3H, 8-Me), 1.86 (d, J = 7.5 Hz, 3H, 18-Me), 2.12-2.76 (m, 2H, 17^1-H and 17^2-H), 3.78 (m, 2H, 8-H), 3.10, 3.35, 3.44, 3.55, 3.62 (each s, each 3H, 15H, Me + OMe), 4.40 (m, 1H, 17-H), 4.60 (m, 1H, 18-H), 8.64, 9.48, 9.76 (each s, each 1H, 3H, meso-H). Anal. calcd. For $C_{39}H_{46}N_4O_5$: C, 71.97; H, 7.12; N, 8.61. Found: C, 71.92; H, 7.17; N, 8.67.



Scheme 1. Synthetic route to 3-alkyl Substituted Chlorin Derivatives

RESULTS AND DISCUSSION

The Grignard reaction into the carbonyl group is an important method for introducing alkyl group. Like other aromatic ring, the carbonyl group conjugated with chlorin chromophore can take place this nucleophilic addition. In this approach, Mpa **1** was used as a starting material, which was oxidized with OsO_4 in THF containing catalytic pyridine at 0 ^{o}C to give the aldehyde **2**. To introduce the mono-alkyl structure on chlorin parent ring, aldehyde **2** was reacted with alkyl magnesium bromide in THF at 0 ^{o}C to form sec-alcohol chlorin **3a**-**3d**, respectively. And then the alkylidene-substituted pheophorbide a derivatives **4a**-**4d** was obtained as only product by dehydration of **3a**-**3d** in benzene with TsOH as a catalyst, respectively. After hydrogenation for alkylidene chlorin **4a**-**4d** to yield mono-alkyl methyl pheophorbide a derivatives **5a**-**5d**, respectively.

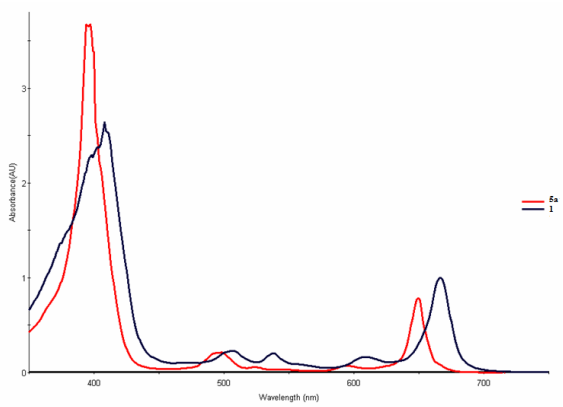


Figure 1. Electronic absorption spectra of 1 and 5a in dichloromethane

Compound	Absorption λ_{max} (nm) (log ε)[a]			
	Soret	ΔSoret (Δε)	Q_y	ΔQ_y (Δε)
1	406.2 (1.00)	0	666.0 (0.38)	0
5a	399.1(1.02)	-7.1 (0.02)	646.6 (0.30)	-19.4 (-0.08)
5b	398.5 (1.02)	-7.7 (0.02)	645.0 (0.32)	-21.0 (-0.06)
5c	398.5 (1.02)	-7.7 (0.02)	646.2 (0.35)	-19.8 (-0.03)
5d	398.8 (0.86)	-7.4 (-0.14)	645.8 (0.20)	-20.2 (-0.18)

Table 1. Absorption properties of 1 and 5a-5d in dichloromethane.

In the UV-vis spectra, all compounds showed the same pyrrole-type visible spectra in dichloromethane, but the peaks in max of Qy and Soret bands are different. The Qy absorption (>600nm are useful for PDT) maxima of 3-alkyl substituted chlorin derivatives **5a-5d** in dichloromethane are in the range of 645-646.6 nm. As can be seen from Figure 1, the Qy peak at 646.6 nm of 5a was blue-shifted in comparison with 666.0 nm. This difference in UV-vis spectra was explained by the fact that the vinyl group at 3 position was transformed to decrease conjugation region of peripheral substituted alkyl group with macrocycle. In the ^{1}H-NMR spectra, the structure of the intermediates and title photosensitizers were clearly indicated. The proton signals of the 3-methyl groups of the 3-alkyl substituted chlorin derivatives **5a-5d** were observed as triplets as δ 0.86, 0.88, 0.88, 0.84ppm, respectively. The 3^1, 3^2-CH_2 protons of **5a** appears as a multiplets at δ 1.46ppm.

CONCLUSION

A series of 3-alkyl substituted chlorin derivatives were designed and synthesized to develop novel and potent photosensitizer. The Grignard reaction thus proved to be an effective way of producing chlorins with 3-substituted alkyl groups with excellent control of E-stereoselectivity. This method provided a generalizable strategy for modifying the amphiphilicity of the tetrapyrrolic macrocyles. Such reaction by reconstruction for these chemical groups performed the synthesis of some new chlorophyll-a derivatives conveniently, and these modification may be valuable in the generation of novel photosensitisers for PDT.

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