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The Bromination on Methyl Pyropheophorbide-a for Constructing Chlorin-Bromine Building Block and Its Application

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The chlorin-bromine building block was constructed and applied to synthesize δ - bromo compounds of methyl pyropheophorbide-a. The visible spectra of the title compounds were discussed.

Key words: Chlorin-bromine building block, malignant tumor, methyl pyropheophorbide-a, Photo-dynamic Therapy (PDT)

INTRODUCTION

Photodynamic therapy (PDT) is a procedure for the treatment of various types of malignant tumors and involves local photochemical activation following accumulation of the photosensitizers in the tumors. For a photosensitizer to be clinically useful it should be nontoxic, selectively taken up and/or retained in malignant tissues, activated by penetrating light (λ_{max} > 600 nm) and photochemically efficient. So for, the most commonly used and studied photosensitizer to date is Photofrin II®, the only commercially available photosensitizer [1]. However, the application of this clinical photosensitizer on a routine basis were limited by weak absorption band in red region of spectrum (λ_{max} 630 nm), undetermined structure and long standing continuous photosensitivity [2]. In order to overcome these disadvantages, many new compounds have been synthesized in an attempt to create a better photosensitizer than Photofrin II®. Pyropheophorbide photosensitizers as chlorin analogues are promising new compounds because the chlorin analogues are activated with much longer red light at ~ 670 nm and produce less long-term normal tissue phototoxicity than Photofrin II® [3].

The variety of chlorin derivatives can be obtained by modifying peripheral substituted group, among which meso-H and vinyl group at 3-position are the most active points [4]. These characteristics prompted us to introduce bromine at meso-position and vinyl group for constructing chlorin-bromine building block. In this present study, bromine was introduced to methyl pyropheophorbide-a (MPP-a) to construct chlorin-bromine building block for synthesis of chlorin derivatives. The methyl pyropheophorbide-a was chosen as starting material and the brominated chlorin analogues were obtained from the reaction with bromine in carbon tetrachloride at −20 °C to give two products; meso-substituted compound **1**, and dibrominated at vinyl and tri-brominated compound **2**. The reaction of chlorin-bromine building block **2** with aminoethyl alcohol and glycol afforded morpholine and dioxane-substituted chlorin **3a** and **3b**.

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MATERIALS AND METHODS

Instrument. Ultra-Violet (UV) spectra were taken on a Varian model Cary-1 Spectrophotometer. ^{1}H-nuclear magnetic resonance spectra were recorded on a Bruker 300 MHz NMR spectrometer.

Materials.

Methyl Pyropheophorbide-a was obtained from *Spirulina maxima* according to K. M. Smith's method [4].

Methyl d-Bromopyropheophorbide-a (1)

Methyl pyropheophorbide-a (275 mg, 0.5 mmol) was dissolved in carbon tetrachloride (50 m*l*) and the mixture was cooled at −20°C. The bromine (0.2 m*l*) in carbon tetrachloride (5 m*l*) was added a dropwise such a rate that the temperature did not rise above −20 °C. The mixture was stirred for 5 min, and then H_2O (50 m*l*) was added. The organic layer was separated and was washed with 5% $NaHCO_3$. The product was purified on preparative TLC. Eluting with hexane: ethyl acetate = 2:1 gave a main brown title compound 102 mg (35%). mp 221-223°C; NMR: δ 9.47, 9.43(s, meso-H, each 1 H) 7.80(q, 2a-H, 1 H), 6.17, 6.10(dd, 2b-H, 2 H) 5.17(s, 10-H, 2 H), 4.78, 4.18 (m, 7, 8-H, 2 H), 3.61(m, 4a-H, 2 H), 3.58, 3.53, 3.52, 3.15(s, Me+OMe, each 3 H), 2.49, 2.15(m, 7a, 7b-H, 4 H), 1.62 (d, 8-Me, 3 H), 1.54(t, 4b-H, 3 H), -1.87(br, s, NH, 2 H). Vis(CH_2Cl_2) λ_{max} = 676.8 nm (relative intensity, 0.95), 618.6 (0.16), 551.8(0.32), 519.8(0.23), 489.4(0.12), 416.0(2.08).

Methyl d-Bromo-3(1,2-dibromoethyl)-2-devinylpyropheophorbide -a (2)

The same reaction for preparing compound **1** was performed and was purified on preparative TLC plates to give the title

compound 48 mg (12%). mp 231-233°C; NMR: δ 10.20, 9.70(s, meso-H, each 1 H) 6.20(m, 2a-H, 1 H), 5.18 (s, 10-H, 2 H), 4.70(d, 2b-H, 2 H), 4.30, 4.15 (m, 7, 8-H, 2 H), 3.73, 3.69, 3.50, 3.26(s, Me+Ome, each 3 H), 3.66(m, 4a-H, 2 H), 2.70, 2.50(m, 7a, 7b-H, 4 H), 1.69 (d, 8-Me, 3 H), 1.62(t, 4b-H, 3 H), -1.87(br, s, NH, 2 H). Vis(CH_2CI_2) λ_{max} = 676.6 nm (relative intensity, 0.72), 619.6 (0.21), 551.6(0.31), 519.4(0.25), 487.0(0.20), 414.2(1.33).

Meyhyl 2-Morpholine-d-bromopyropheophorbide-a (3a)

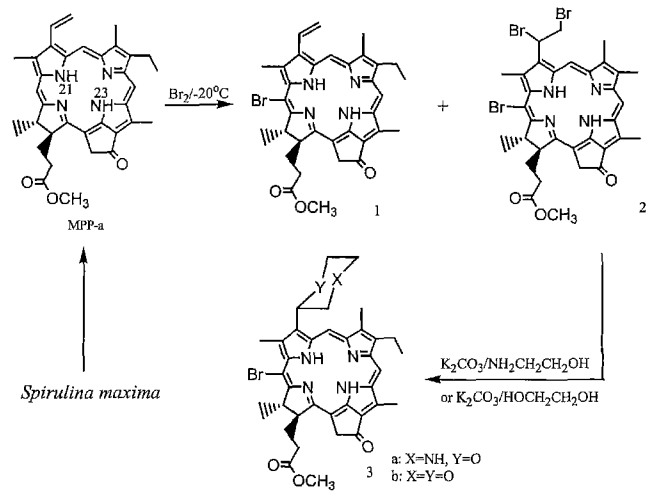
After adding aminoethyl alcohol (2 m*l*) and anhydrous potassium carbonate (40 mg) the mixture was stirred under room temperature for 2 h, and then diluted with dichloromethane (100 m*l*). The organic layer was separated, washed with water. The dichloromethane was removed by distillation and diazomethane was treated to give crude product which was chromatographed by silica gel eluting with hexane : ethyl acetete 2:1 to give title compound **3a** 35 mg (10%). mp 221-223°C; NMR: δ 10.30, 9.55(s, meso-H, each 1 H), 5.80(m, 2a-H, 1 H), 5.21(s, 10-H, 2 H), 4.91, 4.87, 4.10(m, morpholine-H, 6 H), 4.45, 4.23(m, 7, 8-H, 2 H), 3.70, 3.63, 3.39 and 3.31(s, Me+OMe), 3.57(m, 4a-H, 2 H), 2.50, 2.20(m, 7b, 7aH, 4 H), 1.73(d, 8-Me, 3 H), 1.56(t, 4b-H, 3 H), -1.19, -1.20(br, s, each 1 H). Vis(CH_2CI_2) λ_{max} = 677.4 nm (relative intensity, 0.68), 619.8(0.10), 551.2(0.21), 519.2(0.14), 495.6(0.08), 414.6(1.28).

Methyl 2-Dioxane-d-bromopyropheophorbide-a (3b)

Title compound was synthesized using glycol as reagent by the same method of **3a**. mp 210-212°C; NMR: δ 10.0, 9.54(s, meso-H, each 1 H), 6.18(m, 2a-H, 1 H), 5.19(s, 10-H, 1 H), 4.80, 4.42, 4.10(m, dioxane-H, 6 H), 4.40, 4.20(m, 7, 8-H, 2 H), 3.62, 3.60, 3.51, 3.24(s, Me+OMe, each 3 H), 3.54(m, 4a-H, 2 H), 2.50, 2.20 (m, 7a, 7b-H, 2 H), 1.65(d, 8-Me, 3 H), 1.53(t, 4b-H, 3 H), -1.19, -2.00(br, s, NH, each 1 H). Vis(CH_2CI_2) λ_{max} = 676.2 nm (relative intensity, 0.70), 615.2(0.01), 551.0(0.20), 518.6(0.13), 413.2(1.55).

RESULTS AND DISCUSSION

In our study, the first example demonstrating the utility of bromination in preparing a chlorin-bromine system as a novel versatile building block was shown. The bromination of MPP-a underwent two processes, substitution and addition, to give mono-substituted product **1** at meso-position, and tri-substituted product **2** at both-position, respectively. In the absorption spectra (Qy band), the δ - bromino derivative **1** (676 n), **3a** (677 nm) and **3b** (676 nm) showed a red shift in comparison with MPP-a (668 nm) due to introducing an electron-withdrawing group at meso-position(see Fig. 1). This difference in visible spectra was explained by the fact that converting vinyl group to dibromoethyl in compound **2** decrease conjugation of peripheral substituted group with chlorin chromophore because the Qy band of chlorin compound were strongly affected by the substituents on the Qy axis (N_{21} -N_{23}, see Scheme 1), i.e. position at 3-and 13-position. The substitution on meso-position



Scheme 1.

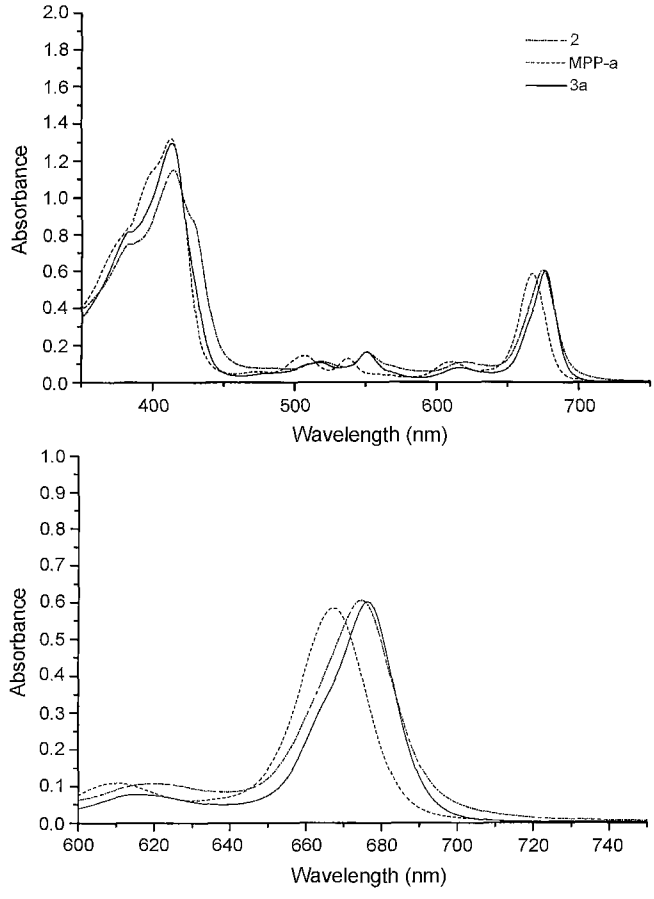


Figure 1. The Visible spectra of compounds **2**, MPP-a, and **3a** in dichloromethane, normalized at Qy peak.

and addition to vinyl group caused dual influence with Qy band in visible spectra of compound **2** (676 nm) and **3a** (677 nm), **3b**(676 nm). These results suggest that introducing electron -withdrawing group at δ - meso position generated red-shifted in visible spectra.

The application of chlorin-bromine building block **2** was performed by cyclization with ethylene-diamine and ethylene glycol to offer chlorin-heterocycle dyad, a kind of new pyropheophorbide-a derivatives. The other application using chlorin-bromine building blocks, such as various coupling reactions are under investigation.

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