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Synthesis of novel long wavelength cationic chlorins via stereoselective aldol-like condensation

Jia Zhu Li [a], Jin Jun Wang [a,b], Il Yoon [a], Bing Cun Cui [a,c], Young Key Shim [a,*]

[a] PDT Research Institute, School of Nano System Engineering, Inje University, Gimhae 621-749, Republic of Korea
[b] College of Chemistry and Chemical Engineering, Yantai University, Yantai 264005, China
[c] College of Medicine, Huangshi Institute of Technology, Huangshi 435003, China

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ABSTRACT

Using stereoselective aldol-like condensation as a key methodology, a series of chlorophyll *a*-based long wavelength cationic chlorins were synthesized using methyl pyropheophorbide *a* (MPP*a*) and purpurin-18-*N*-methoxylimide methyl ester as starting materials. Such long wavelength cationic chlorins possess covalently linked cationic moieties (pyridinium or quinolinium) on the peripheral of their tetrapyrrole macrocycles. It was found that all long wavelength cationic chlorins showed their longest absorption maxima in the range of 712–763 nm, making them potential photosensitizers in photodynamic therapy. The results of preliminary experiments probing in vitro photodynamic effects showed that the purpurin-imide derivatives exhibit relatively high phototoxicity in HeLa cells as compared to MPP*a* derivatives.

Cationic porphyrins or chlorins have recently attracted considerable attention because of their potential applications as DNA binding and photocleavage agents[1–4], chemical nucleases[5,6], human telomerase inhibitors[7–9], and photosensitizers in photodynamic therapy (PDT).[10–12] The high uptake and retention of such compounds as well as their DNA targeting and photodynamic anticancer capabilities have led to the synthesis of a number of novel cationic derivatives, such as tetra-cationic meso-porphyrins[13], tetrahydroporphyrin tetratosylate (THPTS)[14], cationic water-soluble esters of chlorin e_6[15], and monocationic cycloimide derivatives of chlorin p_6 (CICD).[16] It is known that cationic dyes can efficiently cross cell membranes and accumulate to a much greater extent in the mitochondria of carcinoma cells relative to that of most normal cells.[16–19] Also, it has recently been revealed that late stage apoptosis was introduced in the mitochondria during PDT.[20,21] On the other hand, maximum long wavelength absorption of the photosensitizer was considered as one of the most important factors and must be taken into account in the rational design of new photosensitizers used in PDT, because irradiation of the tumor is necessary for the photophysical reaction that occurs in PDT. In the range of 600–800 nm, the light absorption of tissues decreases with increasing wavelength, and therefore penetration of light in tissue increases with wavelength.[22] Formyl-possessing chlorophyll derivatives have attracted increasing attention because of the high reactivity of the formyl group and their potential application to the construction of artificial photosynthetic pigments and the new generation of photosensitizers for PDT.[23–26] In the present work, we report the efficient synthesis of a series of novel chlorophyll *a*-based long wavelength cationic chlorins using stereoselective aldol-like carbon–carbon condensation of formyl chlorins as a key methodology.

4-Picoline and quinaldine are known to undergo stereoselective aldol-like condensations with carbonyl compounds upon treatment with acid or base.[27,28] Such reactivity is due to the deprotonation of the alkyl group at the carbon adjacent to the ring.[29] The use of *N*-alkylpyridiniums or *N*-alkylquinoliniums allows the reaction to occur under milder conditions as a consequence of the electron withdrawing effect exerted on the ring by the presence of the positive charge.[30]

We evaluated the possibility of using such aldol-like reactions between methyl pyropheophorbide *d* (MPP*d*) **2** and 1,4-dimethyl pyridinium iodide (or 1,2-dimethyl quinolinium iodide) in order to afford the desired monosubstituted cationic derivatives **3b** and **3d** in a one-step process. Indeed, such aldol-like reactions could produce the desired compounds, however, the yield was very low (22% for **3b** and 18% for **3d**). To improve the yields of the desired pyridinium or quinolinium substituted chlorins, we proposed a two-step procedure as shown in Scheme 1: for compound **3b**, MPP*d* **2** prepared from methyl pyropheophorbide *a* (MPP*a*) **1** was refluxed for 5 h under nitrogen atmosphere with 4-picoline in acetic anhydride with several drops of acetic acid to afford the pyridyl substituted chlorin **3a** in 65% yield, which was methylated by excess iodomethane to give the desired pyridinium substituted

* Corresponding author. Tel.: +82 55 320 3871; fax: +82 55 320 3872.
E-mail address: ykshim@inje.ac.kr (Y.K. Shim).

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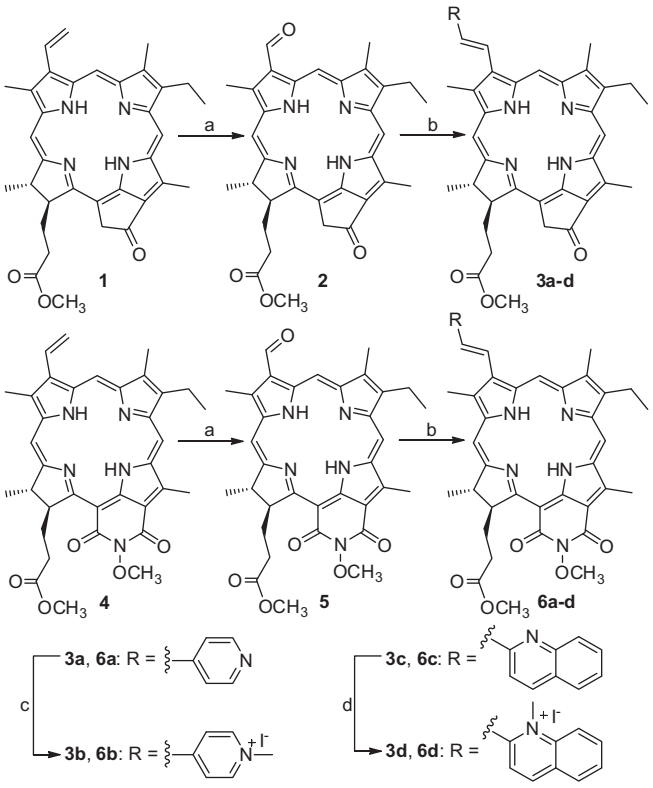

Scheme 1. Synthetic route of long wavelength cationic chlorins. Reaction conditions: (a) OsO_4, $NaIO_4$, 6 h; (b) 4-picoline (or quinaldine), Ac_2O, AcOH, reflux, 5 h; (c) MeI, rt, 20 h; (d) MeI, 40 °C, 3 days.

chlorin **3b** in quantitative yield. To produce compound **3d**, quinaldine was used instead of 4-picoline in the refluxing step with MPP*d* in acetic anhydride to afford the quinolyl substituted chlorin **3c**, and after iodomethane methylation at 40 °C for 3 days, the final product **3d** was obtained in 57% overall yield. For the synthesis of pyridinium or quinolinium substituted derivatives of purpurinimide, *N*-methoxyl purpurinimide **4** was first oxidized by osmium tetroxide (OsO_4) and sodium periodate ($NaIO_4$) to a 3-formyl derivative **5** (92%), which was refluxed with 4-picoline in acetic anhydride with several drops of acetic acid to afford the 3^2-quinolyl substituted purpurinimide **6a** in 60% yield. After methylation,

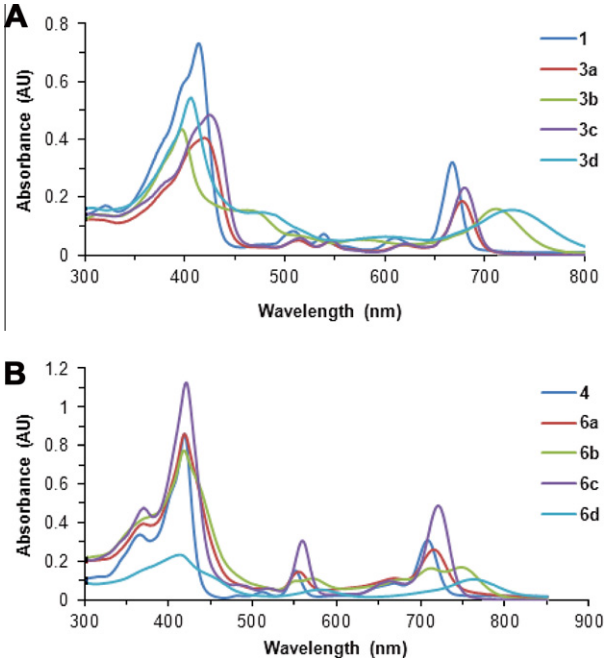

Figure 2. Electronic absorption spectra (10 μM in CH_2Cl_2) of 3^2-substituted MPP*a* (A), and 3^2-substituted purpurinimide (B).

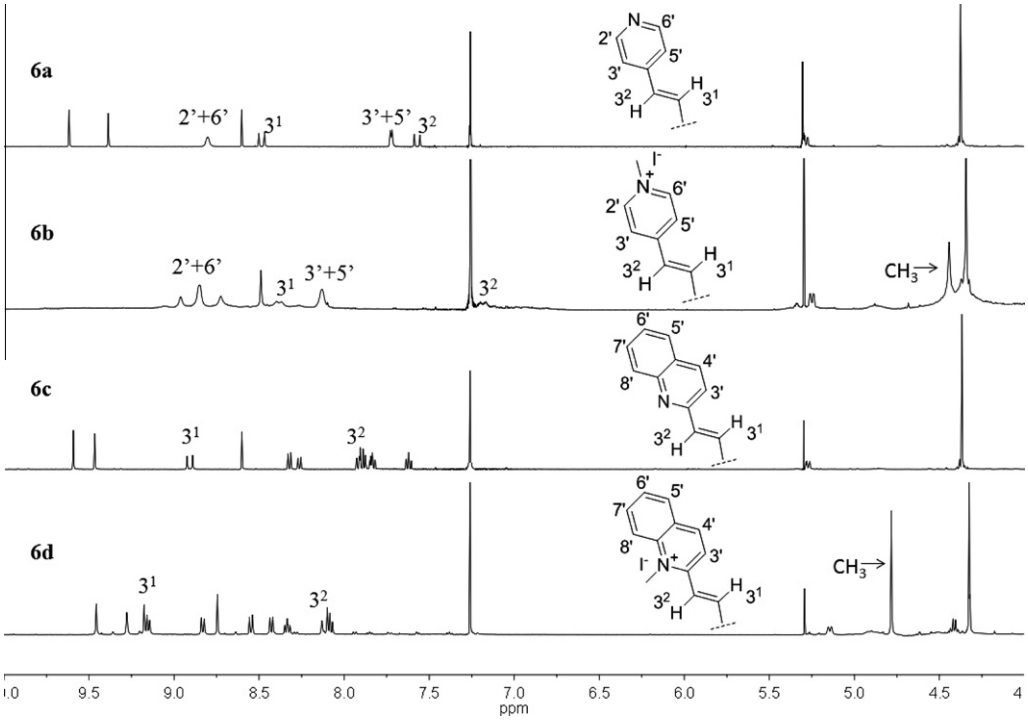

Figure 1. The comparative ^1H NMR spectra ($CDCl_3$, 500 MHz) in the region δ 4.0–10.0 ppm of pyridyl substituted derivative **6a**, pyridinium substituted derivative **6b**, quinolyl substituted derivative **6c**, and quinolinium substituted derivative **6d**.