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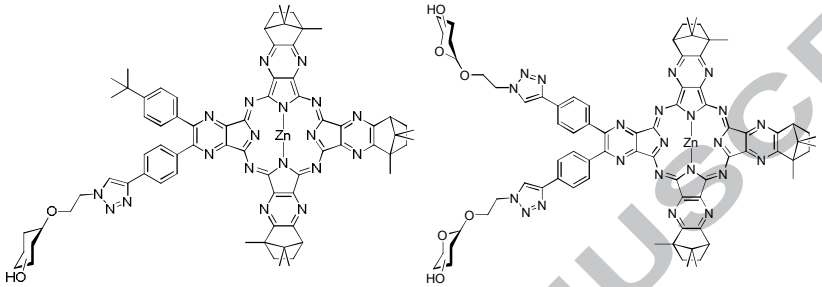

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Synthesis of carbohydrate-conjugated azaphthalocyanine complexes for PDT

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ABSTRACT

A series of azaphthalocyanine (AzaPc) complexes conjugated with one or two carbohydrate groups for photodynamic therapy (PDT) were synthesized by the alkyne – azide click chemistry reaction with previously-developed AzaPc complexes incorporating the bornane group.

Phthalocyanines (Pcs) are remarkable compounds possessing photophysical, semiconducting, and photoconducting properties due to their 18π-electron aromatic macrocyclic structures[1]. Among the phthalocyanines, azaphthalocyanines (AzaPcs), in which nitrogens replace some of the carbons with the four fused benzo- substituents of the phthalocyanine, have unique physical properties including color, oxidation potential, and stability[2, 3]. Moreover, 2,3-dicyanopyrazines, the precursors of AzaPcs, are comparatively easy to prepare, and their numerous derivatives have been designed and prepared for potential use as biologically active materials[4]. The classical synthesis of 2,3-dicyanopyrazines involves the condensation of diaminomalonitrile with 1,2-dicarbonyl compounds. The reaction is facile and it's the most widely used synthetic method for 1,2-dicyanopyrazine derivatives[5].

The potential applications of phthalocyanines (Pcs) have been explored for decades in various fields including photodynamic therapy (PDT)[6], the dyeing industry[7], semiconducting device[8], liquid crystals[9], chemosensors[10] and solar cells[11].

The solubility of Pc in various solvents is critical for application in PDT; however, many phthalocyanines are not soluble in common organic solutions, though their solubility can be improved by peripheral or axial substituents such as long alkyl[12], alkoxy[13], and other bulky groups[14].

Recent research has focused on the use of biomolecules with specific selectivity for tumor-associated antigens, receptors, or specific structural features of tumor morphology. The use of biomolecules with an affinity for tumor tissue as targeting agents for PDT sensitizers has grown together with methods for bioconjugation to porphyrins and related molecules, which represent the majority of PDT agents. Sugars are an attractive type of biomolecule to conjugate with photosensitizers, because they are not only biologically active, but also improve water solubility[15].

In this paper, we synthesized asymmetric A_3B-type AzaPc complexes incorporating bornanes and two distinct carbohydrate units, *β*-D-glucose and *β*-D-galactose, to investigate important properties with applications in PDT sensitizers. Carbohydrate groups were introduced at the periphery of the AzaPcs to enhance their hydrophilicity. As bornane groups have bulky three-dimensional structures, their introduction into the overall structure was expected to aid in prevention of the axial or peripheral approach between photosensitizers (PSs) without altering optical properties, because of the fully sp_3 structure of bornane[16].

The reaction pathways for the preparation of the complexes are shown in Scheme 1. The synthesis procedures of compounds **1**[17] and **6**[18] have been explained by previous researchers. Dicyanopyrazines **2,** substituted with the triisopropylsilyl (TIPS) acetylene group, were obtained through the Heck reaction between diketones **1** and TIPS-acetylene with $Pd(OAc)_2$ and PPh_3 as the catalyst, followed by a condensation reaction with diaminomaleonitrile (DAMN) in the presence of *p*-toluenesulfonic acid as a catalyst. The metal free AzaPc complexes **4** were obtained in two steps. First, 3.5 equivalents of **3** and 1 equivalent of **2** were reacted in the presence of Mg turnings in *n*-butanol to give the AzaPc Mg complexes, and then the crude AzaPc Mg complexes were treated with excess *p*-

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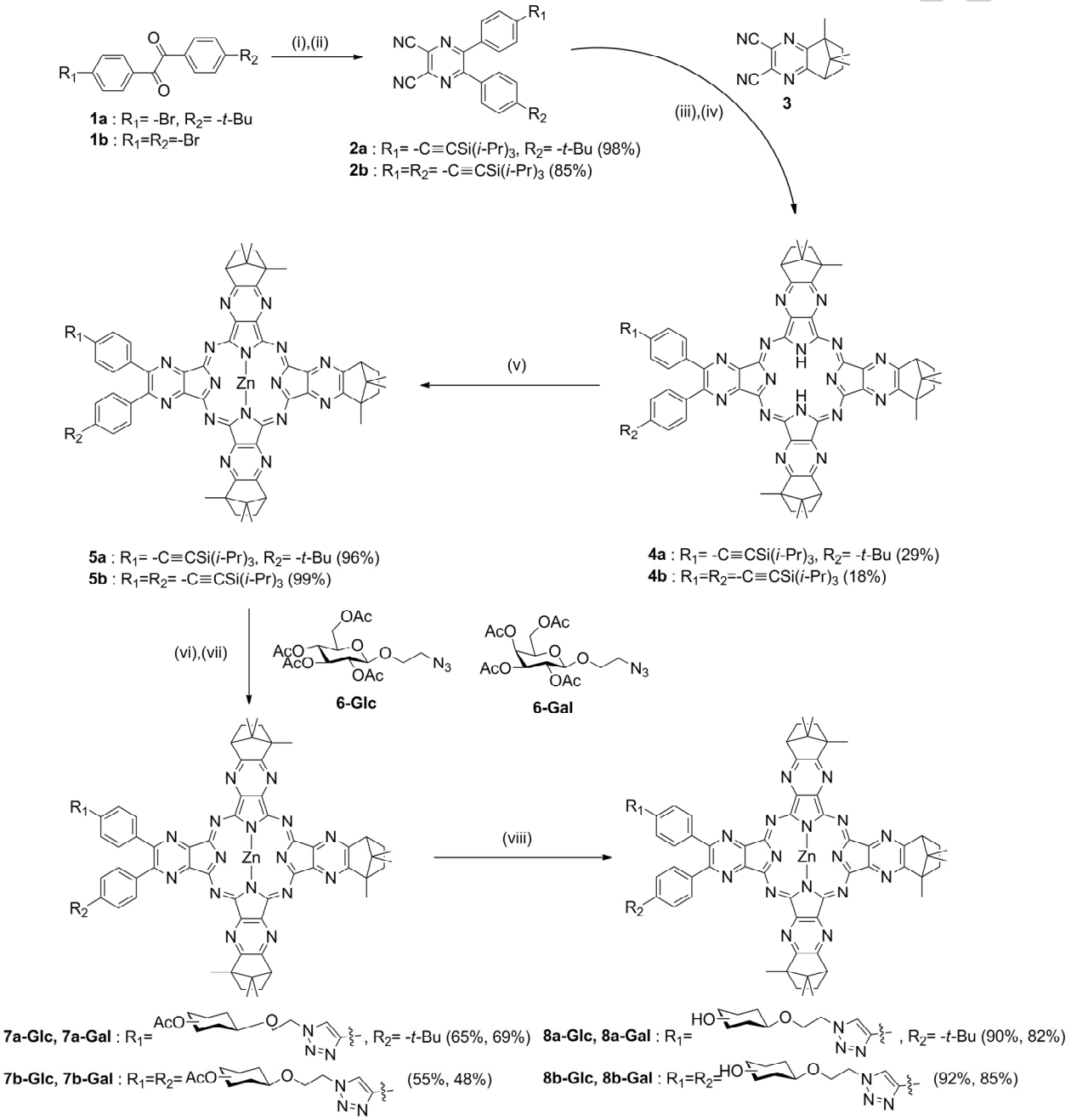
toluenesulfonic acid to remove the complexed Mg. After purification via chromatography on silica gel with the appropriate solvent, the pure A_3B-type, metal-free AzaPc was treated with $Zn(OAc)_2$ in DMF/toluene solvent (1/1) at reflux to obtain AzaPc Zn complexes **5**. To obtain the carbohydrate-conjugated AzaPc complexes **7**, the TIPS groups were removed using excess tetrabutylammonium fluoride, and then the unprotected AzaPc was reacted with compound **6** through click chemistry using a catalytic amount of CuI and *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDTA) in THF at reflux. The final products **8** were obtained through deacetylation of the AzaPc complexes **7** using sodium methoxide in methanol.

The structures of the target compounds were confirmed via ^{1}H NMR, ^{13}C NMR, elemental analysis, and MALDI-TOF mass spectra. The ^{1}H NMR peaks from the AzaPc macrocycles were broad due to the nonsymmetrical structure of the AzaPc complexes and the shielding and deshielding effects in the complicated heterocyclic structure. In the ^{1}H NMR spectrum of **8a**, the protons of the bornane groups appeared near δ 0.85 ppm ~ 2.60 ppm, and the local protons of the carbohydrate and ethylene glycol groups were observed as multiples near δ 3.08 ppm ~ 5.32 ppm. The protons of the aromatic and triazole groups were observed as broad peaks around δ 7.67 ppm ~ 8.08 ppm and δ 8.86 ppm, respectively. In the ^{13}C NMR spectrum, carbon peaks of bornane, carbohydrate, and ethylene glycol groups were observed as a strong peak below δ 100 ppm; however, the peaks



Scheme 1. Synthesis of AzaPc complexes **8**. (i) PPh_3, $Pd(OAc)_2$, $(i\text{-Pr})_3SiC{\equiv}CH$, TEA, reflux, 4h, (ii) DAMN, *p*-TsOH, EtOH, reflux, 3h, (iii) Mg turnings, I_2, reflux, 4h, (iv) *p*-TsOH, THF, r.t., 1h, (v) $Zn(OAc)_2$, DMF/Toluene(1:1), reflux, 4h, (vi) TBAF, THF, r.t., 3h, (vii) **6**, CuI, PMDTA, THF, reflux, 5h, (viii) CH_3ONa, MeOH, r.t. 4h.

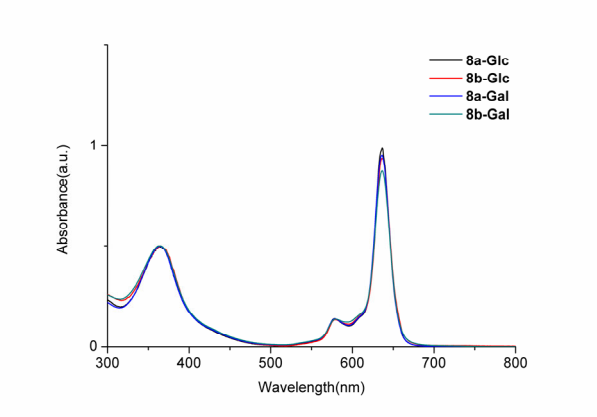


Figure 1. UV-Vis absorption spectra of **8** in DMSO normalized at B-band

of the aromatic and central carbons were exhibited weakly above δ 100 ppm. In the MALDI-TOF mass spectra of **8a-Glc**, the peaks were observed at 1391.96 and 1180.01. The peak at 1391.96 corresponded with the original molecular weight of **8a-Glc**. The peak at 1180.01 corresponded with triazole ring fragmented form of **8a-Glc**. Due to the fragmentation of triazole ring, the conjugated parts including ethylene glycol and carbohydrate fell off from AzaPc complexes[19]. Other compounds (**8a-Gal**, **8b-Glc** and **8b-Gal**) showed similar behaviors with ^{1}H NMR, ^{13}C NMR, and MALDI-TOF mass spectra as well.

The UV-Vis absorption spectra of AzaPc complex **8** in DMSO is shown in Figure 1. All compounds are monomeric in DMSO, which axially bind to Pc Zn(II) macromolecules, reducing their aggregation behavior[20]. Thus, a sharp and strong Q-band and a broad and weak B-band in aprotic polar solvents were observed near 637 nm and 336 nm, respectively. Moreover, **8b-Glc** obeyed Lambert-Beer's law in concentration ranging from 1 μM to 15 μM. As the concentration of **8b-Glc** was increased, the Q-band absorption intensity increased as well, and the new bands, induced by aggregation, were not found in DMSO (Figure 2). The other AzaPc complexes **8** also showed a similar behavior in DMSO. The solubility of AzaPc **8** in water showed variation, based on the number of carbohydrate groups. **8a** were insoluble in water because the inter-force between the carbohydrate group and water is most likely insufficient for **8a** to dissolve. In comparison to **8a**, **8b** were dissolved in water. To research for aggregation behavior, the UV-Vis absorption spectra of **8b-Glc**

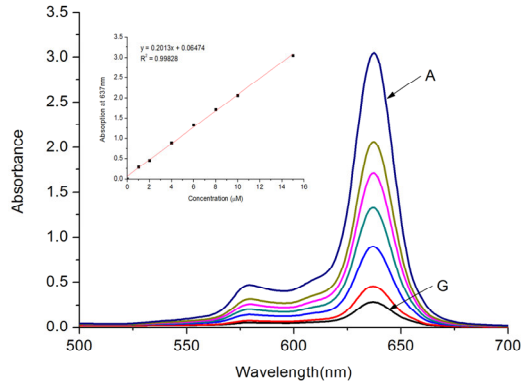


Figure 2. UV-Vis absorption spectra of **8b-Glc** at different concentration in DMSO. Concentration rage: (A) 15 μM, (B) 10 μM , (C) 8 μM , (D) 6 μM , (E) 4 μM , (F) 2 μM (G) 1 μM. Inset : Lambert-Beer law plot

was investigated in DMSO and DMSO / water mixture as solvent. As mentioned above, the absorption spectra of **8b-Glc** indicated that they existed as monomeric state in DMSO. On the other hand, as the water ratio was increased, the new band was found near 602 nm, caused by aggregation, and below 25% of water ratio, obvious isosbestic point was exhibited, indicating that monomer and aggregate (probably dimer) are in equilibrium. **8b-Gal** showed similar spectral behavior in the same condition.

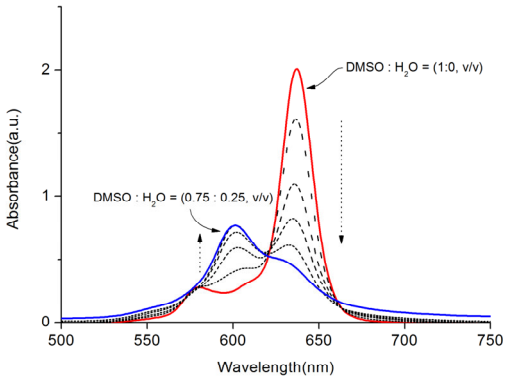


Figure 3. UV-Vis absorption spectra of **8b-Glc** in DMSO and DMSO / water mixture. The specific concentrations are 10 μM.

In summary, we have synthesized A_3B-type AzaPc complexes conjugated with one or two carbohydrate groups, and have confirmed their structure using ^{1}H NMR, ^{13}C NMR, Elemental analysis, and MALDI-TOF mass spectra. The synthesized compounds did not show aggregation in DMSO. **8b** was slightly soluble and aggregated in water. Future testing of the AzaPc complexes against different cancer cell lines is being perused to determine their potential targeting selectivity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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