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Synthesis and photophysical properties of a new glycoconjugate based on *meso*-arylporphyrin

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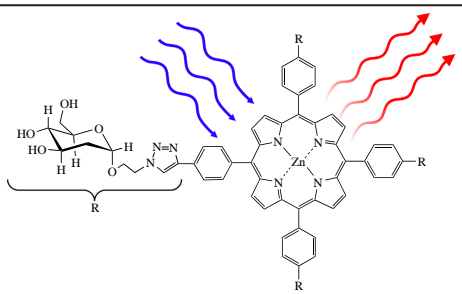
New conjugate of *meso*-aryl-substituted porphyrin and 2-deoxy-D-glucose was synthesized *via* the Cu-catalyzed azide–alkyne cycloaddition between azido-containing sugar and tetraethynyl-substituted porphyrin. The conjugate exhibits nanomolar photoinduced toxicity, namely, the IC_{50} for MCF7 cells is 42 nM, and the IC_{50} dark/IC_{50} light ratio is 71.



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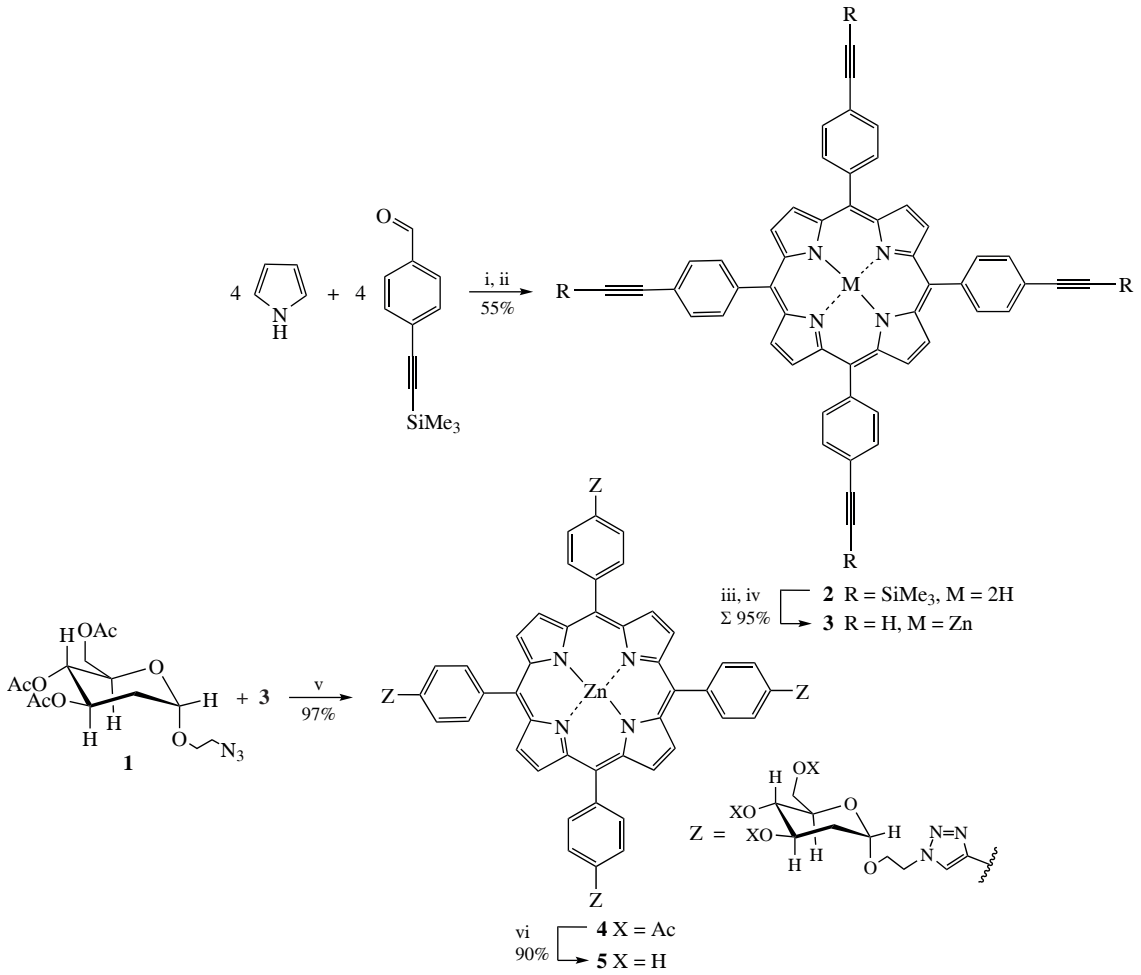
Photodynamic therapy (PDT) is a minimally invasive antitumor therapy that combines a photosensitizer (PS) and irradiation with a specific light wavelength to generate reactive oxygen species to eradicate cancer cells. The PS, as a key element of PDT, plays a pivotal role in the practical application of PDT.[1–4] Glucose metabolism in tumors is a promising target because of high level of glucose consumption by cancer cells as compared to the normal tissues.[5] 2-Deoxy-D-glucose (2DG), a modified form of D-glucose, decreases energy production by inhibiting glycolysis and induces cancer cell autophagy and apoptosis.[5,7] Analogs of 2-DG are readily taken up into cells *via* the normal facilitated glucose transporters and competitively inhibit glucose uptake.[8,10] Clinical trials of 2-DG have demonstrated the challenges in its use in monotherapy due to poor drug-like characteristics, however combined with other potent cytotoxic agents, novel glucose analogs could synergistically eliminate cancer cells.[5,11]

Porphyrins have become versatile and efficient PSs, and their conjugates with various targeting ligands can be used as targeted PSs in the PDT.[12–14] Porphyrin-based PDT offers the prospect of combinatorial therapy to overcome anticancer resistance and combat metastatic cancerous tumors.[15–17] Particularly exciting are the third-generation PDT agents based on glycoporphyrins, which are selective and highly specific for cancer cells.[18–22]

In the present work, we synthesized a new glycoporphyrin containing four 2DG moieties. It should be noted that conjugates of porphyrins with 2DG have not been previously reported. Photochemical and photophysical properties were also studied for the target compound. The synthetic strategy for the new porphyrin conjugates with 2DG was to attach a carbohydrate moiety to the porphyrin using a 'click'-reaction.[23] For this purpose, it was necessary to modify the 2DG molecule synthesized according to the described method.[24] Bromo derivative of 2DG was obtained by the reaction between 2DG and 2-bromoethanol, followed by treatment with NaN_3 to yield azide **1** (Scheme 1). The pyrrole condensation with 4-(2-trimethylsilylethynyl)benzaldehyde using the Lindsey method with the catalyst $BF_3 \cdot OEt_2$ and DDQ oxidation[25] was chosen for the synthesis of *meso*-aryl-substituted porphyrin **2**. The Zn^{II} complex of **2** was prepared by the reaction of free base of porphyrin **2** with $Zn(OAc)_2 \cdot 2H_2O$ (the completion of the complexation was monitored by spectrophotometry; the reaction was completed when only two Q-bands remained). Subsequently, the trimethylsilyl protection was removed using Bu_4NF in THF to afford the tetraalkyne porphyrin derivative **3** in high yield. Then the conjugate of *meso*-arylporphyrin and 2DG was synthesized using the Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC) with $CuSO_4 \cdot 5H_2O$ and sodium ascorbate (NaAsc) in THF/water solution at 66 °C. The yield of the click reaction product **4** was 90%. The last step was the removal of acetoxy groups from the sugar moiety using MeONa/MeOH system. The reaction mixture was neutralized with Dowex 50WX8 (H^+ form), and the product **5** was purified by recrystallization. The structure of all the obtained compounds was confirmed using ^1H, ^{13}C, ^1H–^1H–COSY NMR and UV-VIS spectroscopy, as well as MALDI-TOF and HRMS mass spectrometry.

The UV-VIS absorption spectrum of compound **5** in DMSO is typical for the zinc porphyrins and characterized by the Soret band at 432 nm (logε = 5.8) and two Q-bands at 563 and 604 nm, which are slightly red-shifted by 5 nm compared to those for non-substituted zinc tetraphenylporphyrin (ZnTPP). The corresponding fluorescence spectrum of conjugate **5** shows two emission bands with maxima at 614 and 665 nm. It is noteworthy that despite the lower molar extinction coefficient for conjugate



Scheme 1 *Reagents and conditions*: i, $BF_3 \cdot Et_2O$, CH_2Cl_2, dark, inert atmosphere; ii, DDQ; iii, $Zn(OAc)_2$, CH_2Cl_2/MeOH; iv, Bu_4NF, THF; v, $CuSO_4 \cdot 5H_2O$, NaAsc, THF/H_2O, 60 °C; vi, MeONa, MeOH.

5, the fluorescence quantum yield is significantly higher ($\Phi_F = 0.055$) than that for ZnTPP. Singlet oxygen quantum yield for conjugate **5** in DMSO determined by the chemical trapping method using 1,3-diphenylisobenzofuran as a selective $^1O_2$ acceptor was also found to be rather high ($\Phi_\Delta = 0.78$) and close to that for ZnTPP.

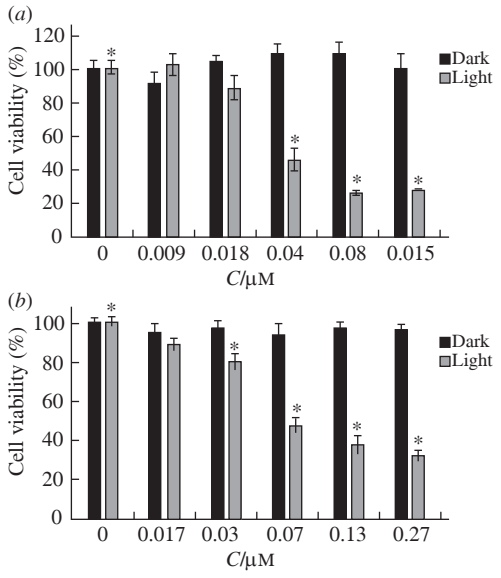


Figure 1 The effect of compound **5** on the viability of MCF7(*a*) and NKE (*b*) cell lines. Cells were irradiated for 90 min using the Medical Therapy Philips TL 20W/52 lamp (irradiation dose of 8.073 J cm^{-2}). Incubation of cells with the compound was performed for 24 h. Asterisks * stand for statistically significant differences in cell survival relative to the values with zero concentration of the compound ($p < 0.05$).

The octanol–water partition coefficient was experimentally determined for porphyrin **5**, the glycoconjugate was found to be amphiphilic ($P = 2.02$); therefore, for *in vitro* tests, the porphyrin was encapsulated in Pluronic-F127 micelles.

As a result of this study, the dark and light-induced toxicity of compound **5** was determined using two cell lines such as MCF7 (breast ductal adenocarcinoma) and NKE (normal kidney epithelial) (Figure 1, see also Table S1 in Online Supplementary Materials). Dark toxicity was found to be lacking in both cell lines at $IC_{50} > 3$ μM, further increasing the concentration of compound **5** resulted in precipitation. The glycoconjucate was more toxic against MCF7 cell line (IC_{50} light = 42 nM) by a factor of 1.6 compared to NKE cell line (IC_{50} light = 67 nM). The ratio of dark and light toxicity (IC_{50} dark/IC_{50} light) was >71, which is a good ratio for photosensitizers.

In conclusion, we have synthesized novel photosensitizer based on porphyrin bearing four 2-deoxy-D-glucose residues. The proposed approach is characterized by the high yields and convenient methodology. The data obtained indicate the prospect of further study of this conjugate as a potential drug for photodynamic therapy due to the presence of targeting 2DG groups.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7791.

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