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Synthesis and Optical Properties of Fluorine-Containing Phthalocyanine Conjugated with Glucofuranose and its Application to Photo-Dynamic Therapy

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Abstract

A novel fluorinated phthalocyanine **1a** with four glucofuranoses at its peripheral positions was designed as a photosensitizer for photodynamic therapy of cancer. The target fluorinated phthalocyanine/glucofuranose conjugate **1a** was synthesized by tetramerization of corresponding glucofuranose-attached fluorinated phthalonitrile **4** in the presence of zinc (II) acetate when heated. The optical and chemical properties of the target conjugate **1a** were investigated by UV/Vis spectra, fluorescence, HPLC, MALDI-TOF MS, and partition coefficients. The biological (PDT) property of **1a** was also examined via an *in vitro* assay using HT-1080 cells after exposure to light. All the properties of **1a** were compared to the acetal analogue **2a** and non-fluorinated counterparts **1b** and **2b**. Of note, the perfluorinated conjugate **1a** showed a more efficient photo-dynamic effect than its non-fluorinated analogue **1b** and their acetal analogues **2a**,**b** in the *in vitro* cell assay.

Key-words*: Phthalocyanine, Fluorine, PDT, Sugar, Cancer*

1. Introduction

Photodynamic therapy (PDT) is laser cancer treatment that uses photosensitizers under nontoxic visible light[1,2]. The photosensitizers are activated *in situ* by exposure to a specific wavelength of light, leading to the destruction of nearby cancer cells by generation of singlet oxygen. Phthalocyanines, desk-like aromatic macrocyclic dyes consisting of four isoindoline units, are particularly attractive photosensitizers for PDT because of their unique optical properties[3-5]. Phthalocyanines, which display intense absorption at 600-750 nm, are easy to transmit to the human body where they effectively produce singlet oxygen. We have been engaged for several years in the development of novel fluorinated molecules expected as pharmaceuticals and agrochemicals[6-8]. Fluorine, the most electronegative element, induces polarization and hydrophobicity in original molecules. Furthermore, replacement of hydrogen by fluorine effectively improves their stability against oxidation. Therefore, the introduction of fluorine(s) into biologically active molecules is a reasonable strategy to develop novel drug candidates[9,10]. In this context, fluorine-containing phthalocyanines have been gaining attention. Fluorinated phthalocyanines[11,12] are expected to improve cell permeability and metabolic stability[13,14]. Recently, we reported that a fluorinated phthalocyanine/*galactopyranose* conjugate shows a much more efficient PDT property than that its non-fluorinated phthalocyanine/galactopyranose counterpart[15]. As part of an ongoing research program committed to phthalocyanine/sugar conjugates as PDT agents[16,17], and encouraged by the success of a fluorinated phthalocyanine/galactopyranose conjugate, we have newly designed perfluorinated phthalocyanine conjugated with *glucofuranose* **1a** and **2a** instead of galactopyranose (**Fig. 1**). Similar to our previous report on the phthalocyanine/galactopyranose conjugate, four *glucofuranose* units at peripheral positions are expected to improve water solubility while fluorine at these positions affects cellular affinity by a hydrophobic effect. Besides, the replacement of galactopyranoses by *glucofuranoses* should alter the interaction with target cells, rendering them as complementary choices as PDT drugs. Herein, the synthesis, optical properties and photodynamic activities

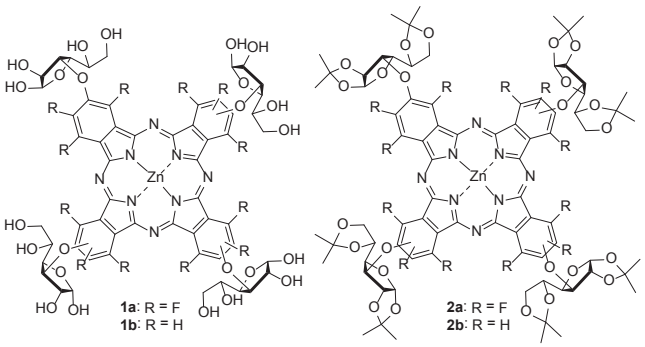

Fig. 1 Phthalocyanine/*glucofuranose* conjugates **1** and **2**.