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

Satoru Mori*, Etsuko Tokunaga*, Masamichi Hayashi*, Tohru Obata**, Motohiro Tanaka*** and Norio Shibata*†

* Department of Nanopharmaceutical Sciences, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan
** Department of Bioorganic Chemistry, School of Pharmacy, Aichi Gakuin University, 1-100 Kasumoto-cho, Chikusa-ku, Nagoya 464-8650, Japan
†Corresponding Author, E-mail: noshiba@nitech.ac.jp

(Received December 28, 2015; Accepted May 9, 2016)

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 fluorocyanine/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 light1,2. 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 properties3-5. 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 agrochemicals6-8. 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 candidates9,10. In this context, fluorine-containing phthalocyanines have been gaining attention. Fluorinated phthalocyanines11,12 are expected to improve cell permeability and metabolic stability13,14. Recently, we reported that a fluorinated phthalocyanine/galactopyranose conjugate shows a much more efficient PDT property than that of its non-fluorinated phthalocyanine/galactopyranose counterpart15. As part of an ongoing research program committed to phthalocyanine/sugar conjugates as PDT agents16,17, 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...