Journal of Fluorine Chemistry 174 (2015) 137–141

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Short Communication

Design, synthesis, spectral investigations and biological activity of fluorinated phthalocyanine conjugated with galactose and comparison to its non-fluorinated counterpart

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ARTICLE INFO

Article history:
Received 17 October 2014
Received in revised form 8 November 2014
Accepted 11 November 2014
Available online 20 November 2014

Dedicated to Professor Iwao Ojima for his 70th birthday.

Keywords:
Fluorine
Phthalocyanine
Photodynamic therapy
Galactose
Amphipathicity

ABSTRACT

Photofrin® is a clinically useful photosensitizer of photodynamic therapy (PDT) used for cancer treatment, but has some disadvantages, including its weak absorbance when excited at 630 nm. Hence, the development of novel photosensitizers with greater than 630 nm absorbance is required. In addition, photosensitizers must have suitable balance between lipophilicity and hydrophilicity to allow for selective accumulation in tumor cells. Herein, we describe the design and synthesis of a novel perfluorinated phthalocyanine/galactose conjugate **1a** suitable for use as a PDT agent. Our novel phthalocyanine/galactose conjugate **1a** displays absorption at 600–750 nm. Four of its peripheral galactopyranosyl moieties resulted in improved water solubility confirmed by a 1-octanol/water partition coefficient log *P* value. Moreover, 12 fluorine atoms at the peripheral position of **1a** simultaneously endowed the macrocycle with suitable hydrophobicity. *In vitro* biological activity of our perfluorinated phthalocyanine/galactose conjugate **1a** showed a much more efficient photo-dynamic effect than the non-fluorinated phthalocyanine/galactose counterpart **1b**. This is one of the clear examples of fluorine effect on biological activity.

1. Introduction

Photodynamic therapy (PDT) is one of the most important therapeutic methods for the treatment of cancer and infectious diseases [1]. Photosensitizers and visible light are required for PDT. Photosensitizers are activated *in situ* after exposure to a specific wavelength of light, leading to the destruction of nearby cancer cells. Although the mechanism by which cancer cells are killed by PDT is not very clear, two types of photoreactions involving free radicals and/or singlet oxygen are highly likely to be involved. A porphyrin-type photosensitizer, Photofrin® is a commercially available drug used for the PDT of cancer [2]. Despite its long clinical history, Photofrin® is not effective enough for damaging cancer cells due to its low absorption in the red region of the light spectrum. In this context, phthalocyanines have been gaining attention as potential alternatives [3]. While the main absorption of porphyrins is at around 400 nm [4], phthalocyanines display an intense absorption at 600–750 nm. This is particularly desirable because photosensitizers in PDT should be activated under manageable and permeable red light. On the other hand, phthalocyanines have one disadvantage, their poor hydrophilicity. In order to add suitable hydrophilicity to phthalocyanines, anionic functional groups such as carboxylic acids, sulfonic acids, and phosphoric acids or cationic substituents like quaternary ammonium salts are commonly introduced [5]. Another important aspect of photosensitizers for PDT is tumor localization, which is highly related to the balance of lipophilicity and hydrophilicity [6]. To fulfill both requirements, phthalocyanine/carbohydrate conjugates have emerged [7]. Recently, we have been interested in the synthesis and spectral investigation of fluoro-functionalized phthalocyanines [8], and a series of fluoro-functionalized phthalocyanine-nucleoside conjugates were demonstrated for PDT agents [9]. We disclose herein the synthesis and photodynamic activities of novel, water-soluble fluorinated phthalocyanine/galactopyranose conjugate **1a**. Four peripheral

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http://dx.doi.org/10.1016/j.jfluchem.2014.11.003
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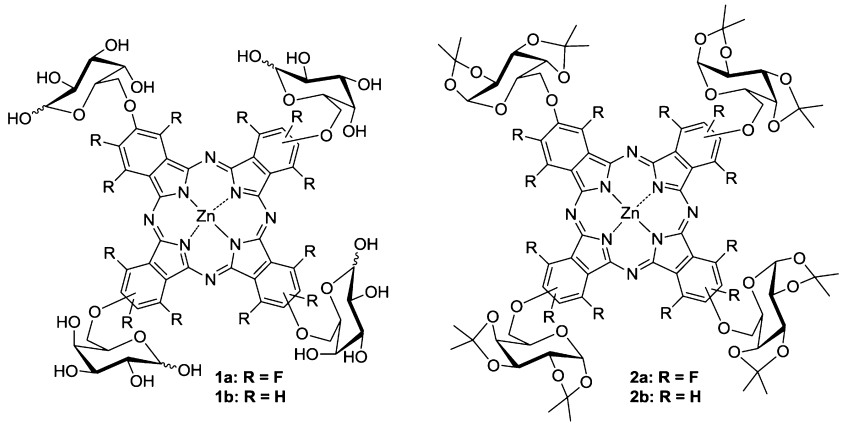
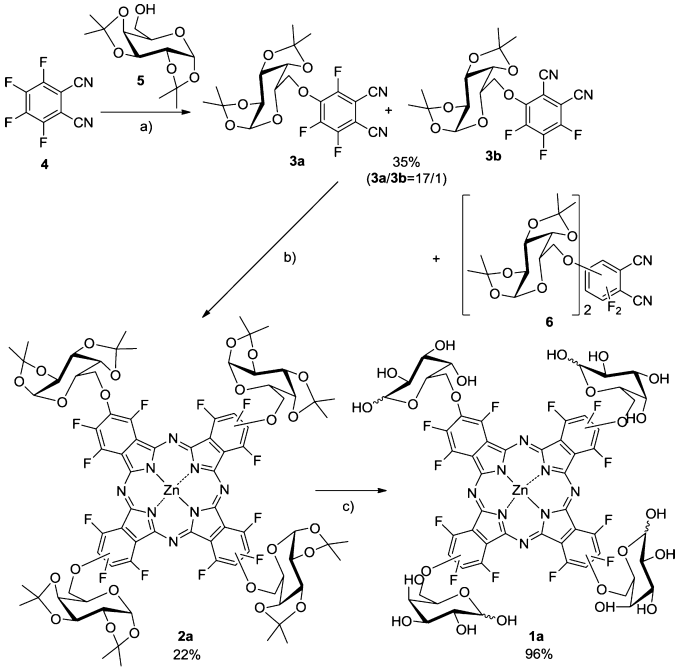


Fig. 1. Galactopyranosyl phthalocyanine conjugates **1** and **2**.



Scheme 1. Synthesis of fluorinated phthalocyanine/galactopyranose conjugate **1a**; (a) potassium carbonate, *N*,*N*-dimethylformamide, r.t.; (b) zinc acetate dehydrate, neat, 180 °C; (c) trifluoroacetic acid, H_2O, 40 °C.

galactopyranose substituents appending phthalocyanine nuclei are expected to improve the solubility of perfluorinated phthalocyanine in water. Besides, beneficial effects on biological activity by these fluorinated groups are also expected [10]. Eventually, our fluorinated phthalocyanine **1a** was found to be more effective as a PDT agent than the non-fluorinated counterpart **1b** and their hydrophobic analogs **2a**,**b** (Fig. 1).

2. Results and discussion

The target phthalocyanine/galactopyranose conjugate **1a** was synthesized by tetramerization of 4-galactopyranosyl trifluorophthalonitrile **3a** followed by deprotection under acidic conditions (Scheme 1). First, treatment of 3,4,5,6-tetrafluorophthalonitrile (**4**) with 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5**) [11] in the presence of K_2CO_3 in DMF at room temperature provided **3a** accompanied with 3-galactopyranosyl-trifluorophthalonitrile **3b** and bis(galactopyranosyl)-difluorophthalonitrile **6**. The desired phthalonitrile **3a** was isolated by silica–gel column chromatography using benzene/AcOEt (98/2) in 35% yield. Compound **3a** obtained still contained a trace amount of regioisomer **3b** (**3a**/**3b** = 17/1), but it was used as such without further purification due to the difficulty in separating both. Tetramerization of **3a** in the presence of zinc acetate gave phthalocyanine acetal **2a** in 22% yield, which was finally treated with trifluoroacetic acid, affording desired **1a** in 96% yield. Although a 17:1 mixture of **3a** and **3b** was used for the synthesis of **2a**, phthalocyanines **2a** and **1a** were obtained single isomers by chromatographic separation of **2a**. This was confirmed by reverse phase HPLC analyses (Fig. 2). Non-fluorinated analogs **1b** and **2b** (Fig. 1) were also synthesized for comparisons according to a procedure described in the literature [7f].

The UV–vis spectra of conjugates **1a**,**b** and **2a**,**b** were recorded in DMSO with a concentration range of 1×10^{-6} M to 1×10^{-4} M (Fig. 3). Conjugates **1a**,**b** showed a broadened Q-band in the 600–700 nm region. The Q-band of fluorinated conjugate **1a** became sharp as its concentration decreased. This result suggests that **1a**

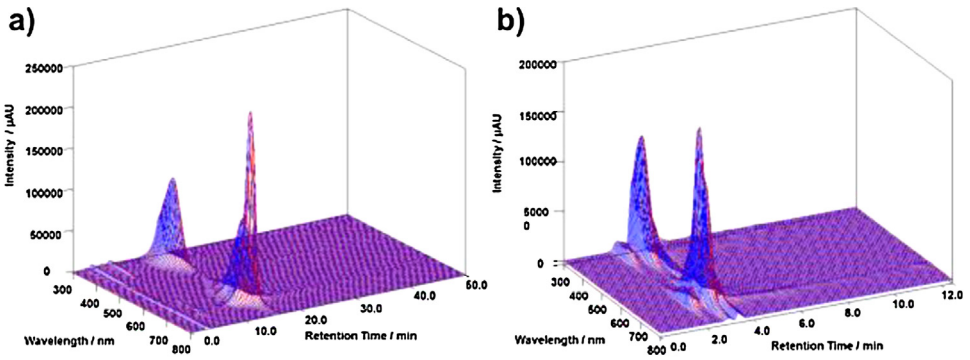


Fig. 2. Reverse phase HPLC analyses of (a) **2a** (H_2O:MeCN:THF = 5:25:70, 0.7 mL/min, t_R = 15.9 min) and (b) **1a** (H_2O:MeCN:THF = 5:25:70, 0.3 mL/min, t_R = 3.0 min).