Tetrahedron Letters 55 (2014) 6311–6314

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis and cell phototoxicity of a triply bridged fused diporphyrin appended with six thioglucose units

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ARTICLE INFO

Article history:
Received 23 July 2014
Revised 16 September 2014
Accepted 18 September 2014
Available online 28 September 2014

Keywords:
Porphyrin
Thioglucose
Photodynamic therapy
Fluorescence
Click chemistry

ABSTRACT

A triply bridged fused diporphyrin appended with six thioglucose units is reported. This new, chemically, and photochemically stable amphiphilic compound is taken up by breast cancer cells and causes cell death upon light exposure. Photophysical studies reveal absorption bands in the near IR region, and photosensitized formation of singlet oxygen in high quantum yields.

Introduction

There are many applications of dyes in biochemistry, imaging, and therapy that require appended, robust biotargeting motifs. Since there is a wide range of biotargeting motifs available for all of these applications, core dye platforms with appropriate photophysical properties that can be rapidly and efficiently appended with the targeting motif avoid the complex redesign of synthetic strategies. Photodynamic therapy (PDT), for example, is a non-invasive treatment for cancer involving the interaction of light, a photosensitizer and oxygen to result in generation of singlet oxygen and other reactive oxygen species that cause necrosis or apoptosis.[1,2] There are many cancer targeting motifs, including sugars and peptides.

The photophysics of porphyrin and phthalocyanine derivatives can be tuned for many of the above applications. For example, those with good triplet quantum yields can serve as photosensitizers for PDT, while those with good fluorescence quantum yields can serve as imaging agents and biochemical trackers. Thus there is a need for a palate of these core dye platforms with different photophysical properties. Porphyrinoids are generally non-toxic under dark conditions.[3,4] Imaging and PDT of various forms of cancers are more efficient if the dye absorbs light in the therapeutic window (ca. 700–1100 nm) especially for deep cancers,[5–7] so biotargeted dye systems with longer wavelength absorptions are needed for next-generation imaging and PDT agents.[8,9]

Direct, covalent linking of porphyrins (e.g., **2** and **3** in Fig. 1) yields systems with photophysical properties such as high polarizability and high nonlinear optical character[10] that arise from strong electronic coupling of the macrocycles. Compounds such as **1** and **2** are fluorescent. Fused (β–β, *meso–meso*, β–β) triply bridged porphyrins have low energy absorption bands in the infrared region because of extended conjugation and coplanar geometries.[11] Compounds such as **3** are minimally fluorescent but exhibit large two-photon absorption (2PA) cross sections (σ) where two low energy 1400–2000 nm photons are simultaneously absorbed and have good triplet quantum yields.[12,13] Sugar moieties appended to porphyrinoids increase the selective uptake by cancer cells.[14] The number, type, and position of the sugar moieties effect cell uptake,[15,16] but the hydrolysis of *O*-glyco linkages of many reported conjugates can diminish in vivo effectiveness compared to non-hydrolysable derivatives.[14]

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http://dx.doi.org/10.1016/j.tetlet.2014.09.085
0040-4039/

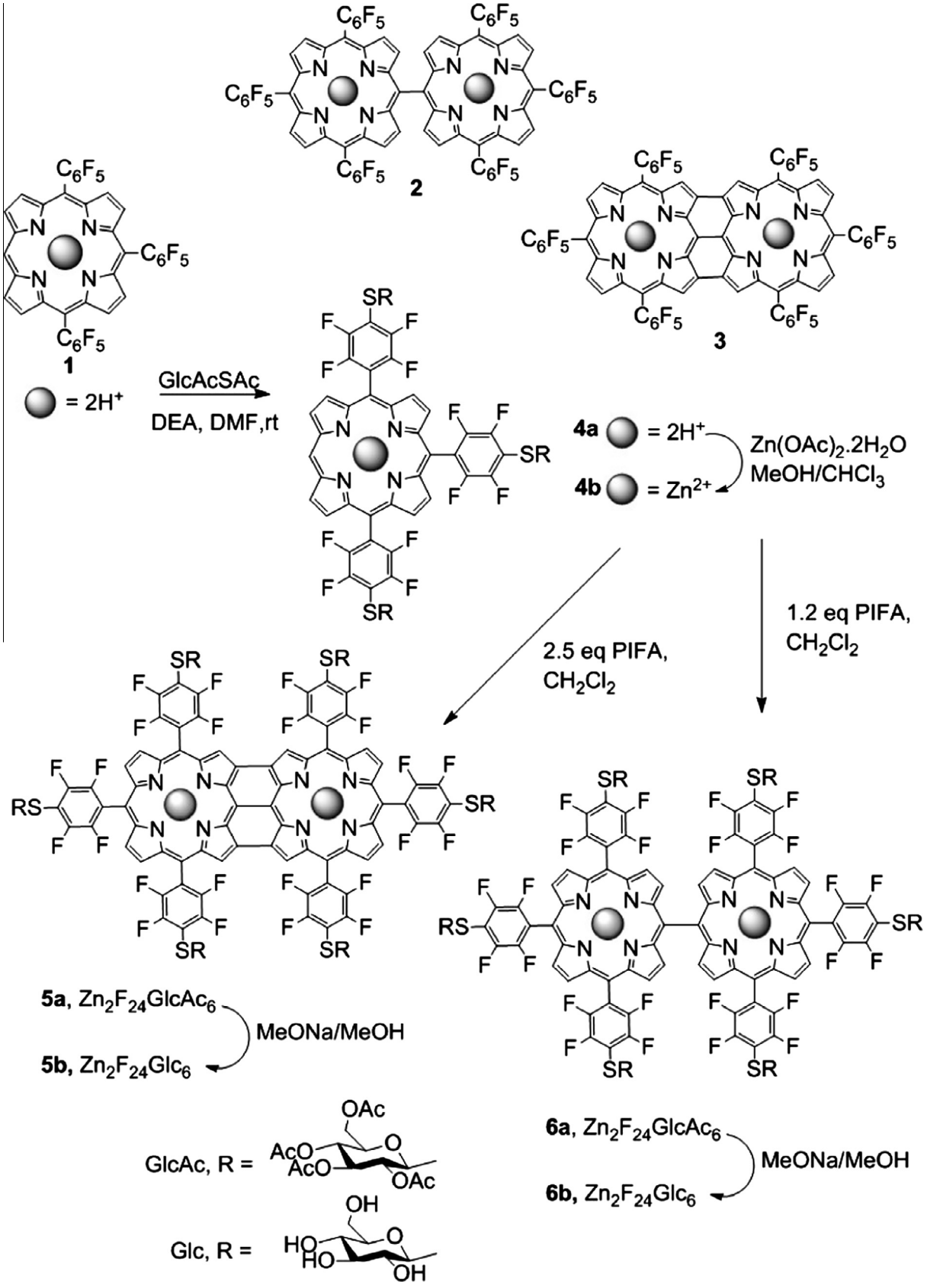

Figure 1. Oxidative coupling of **1** with DDQ/$Sc(OTf)_3$ yields **2** and **3**,[13] but substitution of the *para* fluoro groups **2** or **3** is inefficient. Adding the sugars to compound **1** proceeds in high yields, followed by oxidative coupling of **4b** with PIFA efficiently yields **5a** and **6a**, which are readily deprotected to yield **5b** and **6b**.