



The photoacoustic effect of near-infrared absorbing porphyrin derivatives prepared via click chemistry



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ARTICLE INFO

Article history:

Received 15 March 2017

Received in revised form

31 July 2017

Accepted 3 August 2017

Available online 12 August 2017

Keywords:

Near-infrared

Photoacoustic imaging

Photothermal treatment

ABSTRACT

A great demand of near-infrared (NIR) light-absorbing agents has recently arisen, as they are employed to enhance photoacoustic (PA) imaging and photothermal therapy (PTT) technologies. In this study, applications of a series of NIR absorbing porphyrin derivatives to PA and PT were carefully examined. Among other interesting results, it was found that the click reagent F₄-TCNQ showed a higher PA intensity than those of TCNE and TCNQ. Moreover, the PA intensity remained high when R33 was dispersed in water. The toxicity of R33 molecules embedded into hydrophobic phospholipid bilayer of liposomes (R33@L) was low. Systematic research of the NIR dyes not only allowed for a more educated design of NIR absorbing dyes for PA signal enhancement, but also provided us with a way to reduce the solution toxicity of oil soluble organic NIR dyes.

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1. Introduction

Photoacoustic (PA) imaging provides deeper tissue imaging penetration and higher spatial resolution than traditional optical imaging techniques. In PA imaging, ultrasonic waves are detected as result of photon absorption by biomolecules [1–4]. Gold-based particles have been the most widely used nonorganic materials in PA imaging [5–8]. However, gold-based particles need to be modified to shift their absorption profiles into the NIR range, as it is necessary for PA imaging; unfortunately, modification of gold particles always results in peak broadening, which can be problematic in multiplexed PA imaging [9–11]. In comparison, low molecular weight organic dyes with sharp absorption peaks in the NIR region,

such as indocyanine green (ICG) [12,13] and others [14], have proved to be good contrast agents for PA imaging. Furthermore, they can also be used as photothermal agents employable in the generation of heat from optical energy for the burning of cancer cells [15]. An ideal drug would be able to be activated within the range of wavelengths of the “therapeutic window”(700–950 nm) [16]. Among all dyes, porphyrin and its derivatives have been the focus of biochemical applications [17,18], not only because of their well-described photosensitizing properties but also thanks to their capability to selectively accumulate and persist longer in tumorous tissues [19]. Therefore, porphyrins have great potential for employment in medical imaging and cell treatment.

Previous studies reported that some porphyrins can be used as photothermal [20] and contrast [21] agents for PA imaging. Besides, porphyrins are the most popular photosensitizers (PSs) for photodynamic therapy (PDT) [22]. When irradiated, PSs generate reactive oxygen species (ROS) used to kill cancer cells [23]; their cytotoxic response is known to be limited to the irradiated areas because of the high reactivity and short lifetime of singlet oxygen [24]. However, their complicated preparation and single applications restrict

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the development of porphyrin derivatives. Recently, Chung and co-workers [25] prepared a dendrimeric porphyrin-coated golden shell for the synergistic combination of PDT and PTT treatments, improving the therapeutic effect. Huynh and co-workers [26] also prepared new porphyrin shell microbubbles with PA signal enhancing properties. While integrating imaging and treatment would be desirable for biomedical therapy, Lovell and co-workers [27] were able to prepare porphyrin nanovesicles from porphyrin bilayers and use them in PA imaging and PTT treatment. Thus, it is urgent to find NIR functional, low molecular weight porphyrin derivatives that would be easy to prepare and have high efficiency for both, imaging and therapy. For these reasons, our lab [28] focused on the development of a series of easy to prepare porphyrin derivatives bearing high yield and strong absorption in the NIR region. Several click-chemistry agents (tetracyanoethene (TCNE), 7,7,8,8-tetracyanoquidimethane (TCNQ), 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquidimethane (F₄-TCNQ) [29–31]), which would be suitable for using in PA imaging and PTT treatment, were employed.

In this study, we measured the PA and PT effect of the porphyrin derivatives. The tested molecules showed good potential as PA and PT contrast agents and as photothermal agents. Moreover, the compounds with click agent F₄-TCNQ showed a red shift in the wavelength of the signals. Low aqueous solubility of the molecules was addressed by dissolving R33 in co-solvent, such as tetrahydrofuran and water, and the PA intensity was still high. Furthermore, the R33 mixed solution was loaded into a hydrophobic phospholipid bilayer of liposomes (R33@L) and internalized into MCF-7 cell. The PA intensity of MCF-7 cell with R33@L was high despite low toxicity. This study provided guidelines for the design of NIR absorbing agents for PA imaging and PTT treatment and pioneers application of porphyrin derivatives in the biomedical field.

2. Result and discussion

A variety of derivatives were prepared from the symmetric parent molecule R. The long alkylic chains on the anilino groups A [32] enhance the solubility [33,34] of the porphyrin system and the electron-cloud density. The series of symmetric and asymmetric derivatives R-XY was synthesized by using click reagents TCNE, TCNQ or F₄-TCNQ. X and Y were different groups and the nature of

which was reported in Fig. 1. The introduction of long alkyl chains and click reagents changed the spectral properties of the materials simplifying the process of separating the products.

As shown in Fig. 2a, all the NIR dyes afforded high PA intensities, except for R. Since R did not have any absorption in the NIR region, it did not produce any PA or photothermal effects. To further study the PA intensity of the porphyrin derivatives, the molar extinction coefficients (ϵ), and the thermal conversion efficiency (η) were measured according to the photothermal mechanism equation for the PA effect:

$$q \propto \Gamma \epsilon \eta F \quad (1)$$

where Γ is the Grüneisen parameter (dimensionless), ϵ is the optical absorption coefficient (cm^{-1}), η is the thermal conversion efficiency (%), and F is the local optical fluence ($\text{J} \cdot \text{cm}^{-2}$) [35]. The parameters that mostly influence the PA signals are the optical absorption coefficient (ϵ) and the thermal conversion efficiency (η). The UV/Vis/NIR absorbances of porphyrin derivatives were not in accordance with the wavelength-dependent PA intensity (Fig. 2a and c). In the NIR region, ϵ of R33 was maximum ($5.6 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$), and the PA effect was the highest (12.4×10^4). Whereas, the PA intensity of R12 (4.7×10^4) is the lowest, although its ϵ was not the lowest ($0.9 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$). The same phenomenon occurred in the thermal conversion efficiency (η) of R-XY dyes, the values of which were calculated through fitting curves of time-dependent temperature variations (Fig. S1, Table 1) [36]. R2, despite having the highest η value (46.6%), showed a low PA intensity (7.7×10^4). On the other hand, R33 afforded the highest PA intensity (12.4×10^4) while also showed the lowest η (23.7%). The result was not supported by photothermal Eqs. S1 and S2. For a series of porphyrin derivatives, the photoacoustic waves might be also related to the electrostriction of the solvent, which is induced by charge transfer of the molecules [37]. The wavelengths of PA intensity peaks of the R2, R12 and R22 substrates with F₄-TCNQ were all in range of near 710 nm (710, 708 and 708, respectively). In contrast, the peaks of R3 (866 nm), R13 (866 nm), R23 (822 nm), R33 (866 nm) with F₄-TCNQ substitution were all above 820 nm (Fig. 2a). Results matching with ϵ support the correspondence of the mechanism. The presence of a quinone moiety in the structure of TCNQ increases conjugation, causing a red shift in the wavelength of the signal. The strong

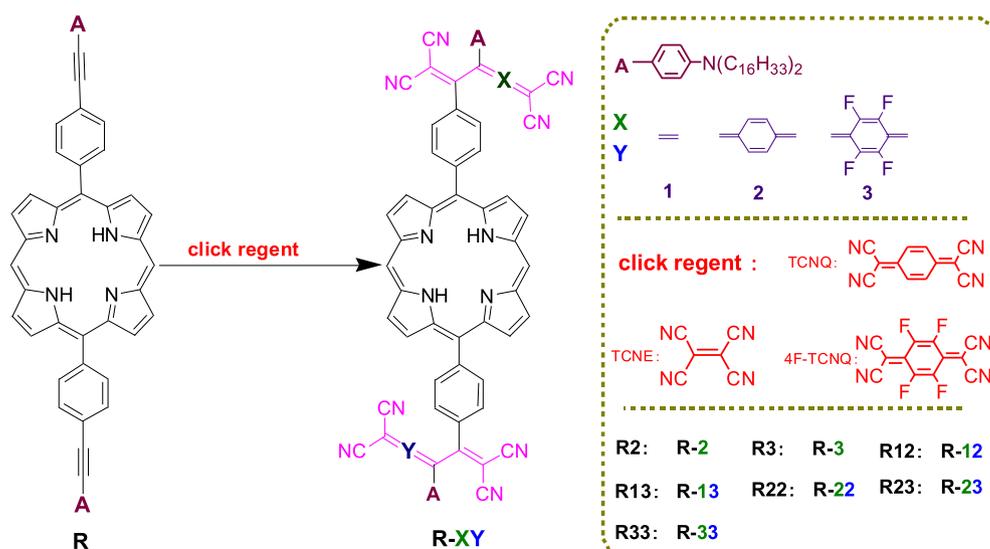


Fig. 1. Preparation of porphyrin derivatives via click chemistry.

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