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Near-infrared fluorescent pyrrolopyrrole cyanine derivatives and colloidal nanoparticles with tunable optical properties for in vivo bioimaging

Shuo Huang, Cangjie Yang, Jing Huang, Xiaochen Wang, Mingfeng Wang*

School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, Singapore, 637459, Singapore

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ABSTRACT

Near infrared (NIR) fluorescent molecules with light absorption and emission above 700 nm are important for noninvasive and deep-tissue imaging for disease diagnosis and imaging-guided surgery. Nevertheless, currently available NIR fluorophores with high fluorescence quantum yields and robust photostability remain rather limited. Here we report a series of π-extended pyrrolopyrrole cyanine (PPCy) derivatives with tunable light absorption and emission in the NIR spectral region. The extent of the intramolecular charge transfer shows significant effect on the optical bandgap, the Stokes shift and the fluorescence quantum yield. These hydrophobic PPCy derivatives were dispersed as colloidal nanoparticles into water via a nanoprecipitation process. The nanoparticles composed of spirofluorene-flanked PPCy derivatives exhibit the optimal optical properties, effective tumor-targeting, and high fluorescence contrast for in vivo bioimaging of xenografted tumor-model mice.

Fluorescent molecules with light absorption and emission in the near-infrared (NIR) spectral window (700–2500 nm) are important for non-invasive diagnosis and treatment of diseases such as cancers [1–3]. As NIR fluoresence imaging offers several advantages such as large tissue-penetration depth and high contrast with minimal interference of autofluorescence background [4], a large number of inorganic materials, such as gold nanomaterials [5,6] and single wall carbon nanotubes (SWCNT) [7–9], have been explored as in vivo NIR imaging probes. Although most of these materials have shown strong NIR signal and efficacy for cancer treatment, concerns with the poor biodegradability and long-term toxicity limit their further clinical applications. Recently, a few NIR organic fluorophores such as methylene blue, porphyrin derivatives [10,11], and indocyanine green (ICG) [12–14] have been used in both preclinical cell/animal imaging and clinical image-guided cancer surgery [15]. However, ICG suffered from its poor photostability, short life-time of blood-circulation and nonspecific interaction with cells and tissues [16]. The porphysomes formed by self-assembly of porphyrin-attached lipid derivatives showed dramatic aggregation-caused fluorescence quenching and remained as relatively fragile as conventional liposomes [10,11].

During our exploration of new organic fluorophores with light absorption and emission both in NIR region while high-fluorescence quantum yield in water for in vivo deep-tissue bioimaging applications, we have been interested in a group of pyrrolopyrrole cyanines (PPCys) [17–19] with strong light-absorption coefficients, high fluorescence quantum yields up to 70%, and robust photostability that are attractive for biolabeling applications [20], fluorescence lifetime imaging in vivo [21], and photoacoustic imaging [16,22,23,28]. A few PPCy fluorophores with the light absorption and emission wavelengths extended to NIR region (> 800 nm) have been reported [24]. Particularly, Zumbusch and coworkers [20,25,26] have synthesized π-extended PPCy-based derivatives or dimers with strong NIR fluorescence in organic solvents. Nevertheless, the synthesis appeared tedious and the yield was often low. While the majority of the reported PPCy derivatives are hydrophobic, a few water-soluble derivatives [27] have been reported but dramatic fluorescence quenching occurred in water.

Recently, we discovered that some PPCy chromophores form strongly fluorescent J-aggregates when they co-precipitate with macromolecular surfactants such as amphiphilic diblock copolymers poly(ε-caprolactone)-*b*-poly(oligoethylene glycol methyl methacrylate) (PCL-*b*-POEGMA) to form colloidal nanoparticles (NPs) in water [16]. The formation of such J-aggregates is quite sensitive to minor change of the chemical structures in the π-conjugated core. For instance, conjugation of a phenyl group at both ends of the PPCy core only resulted in non-fluorescent H-aggregates in the colloidal NPs. Despite the strong NIR fluorescence of these J-aggregate colloidal NPs, the small Stokes shift of only a few nanometers limits their bioimaging applications due to the crosstalk between the light absorption and the light emission.

Herein, we report an alternative post-modification approach towards facile functionalization of PPCy-based fluorophores in order to

* Corresponding author.
E-mail address: mfwang@ntu.edu.sg (M. Wang).

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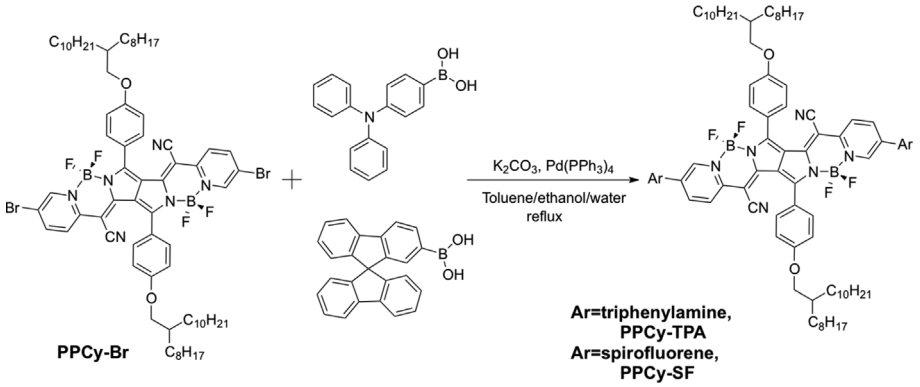

Scheme 1. Synthetic route to π-extended PPCy derivatives via Suzuki coupling.

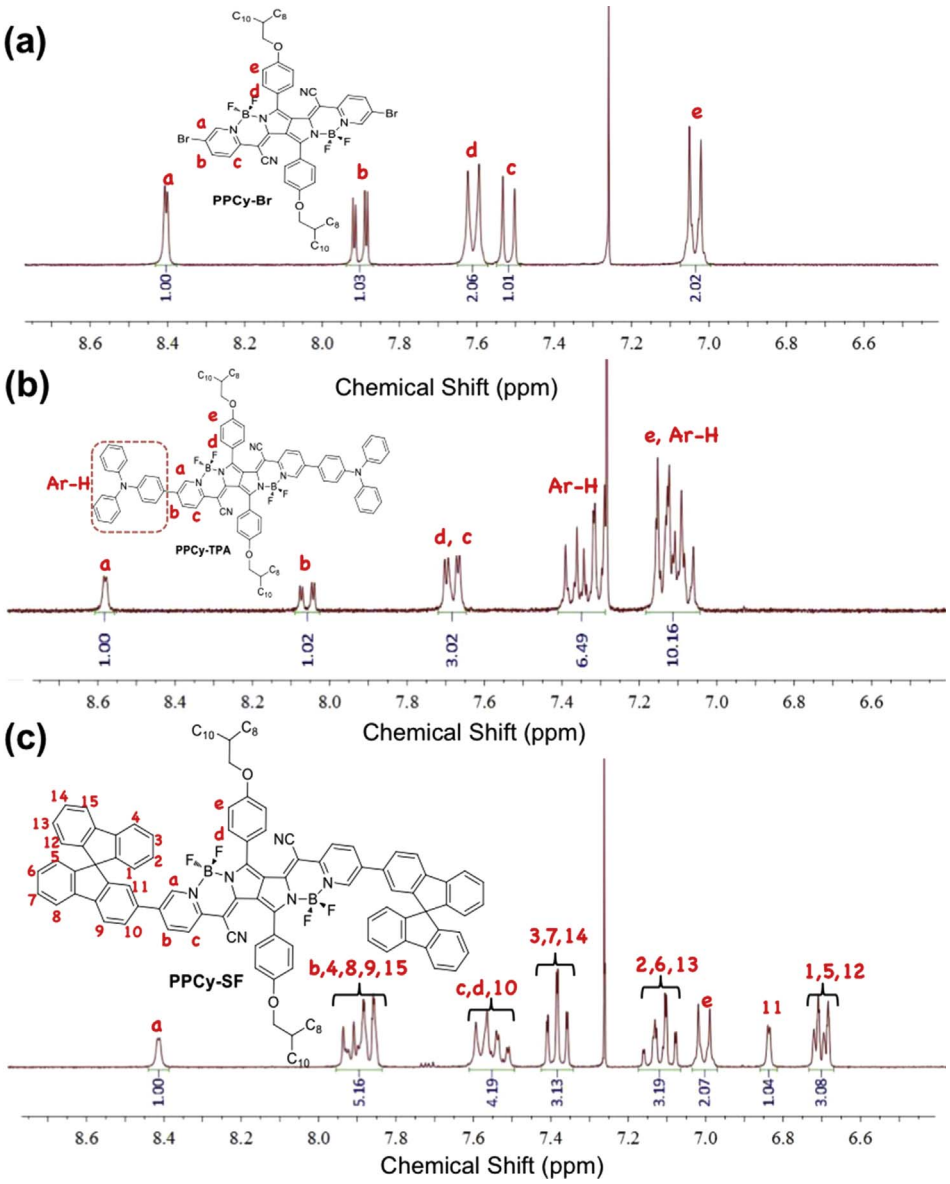

Fig. 1. ^{1}H-NMR (300 MHz, $CDCl_3$) spectra of PPCy-based derivatives: PPCy-Br (A) PPCy-TPA (B) and PPCy-SF (C).

extend the π-conjugation and further redshift the light absorption and emission wavelengths. In particular, two PPCy-based derivatives, PPCy-TPA and PPCy-SF, were synthesized with intrinsically extended conjugation lengths, by decorating BF_2-PPCy with triphenylamine (TPA) or spirofluorene (SF)(Scheme 1). At the same time, the intramolecular charge transfer (ICT) between the donor (TPA or SF) and the acceptor (PPCy) could reduce the optical bandgap and enlarge the Stokes shift. In particular, we illustrate how the chemical structures and the intramolecular charge transfer affect the optical properties in both organic solvents and PEGylated colloidal NPs in aqueous media. We