



Highly water-soluble, near-infrared emissive BODIPY polymeric dye bearing RGD peptide residues for cancer imaging



Shilei Zhu^a, Jingtuo Zhang^a, Jagadeesh Janjanam^a, Jianheng Bi^a, Giri Vegesna^a, Ashutosh Tiwari^a, Fen-Tair Luo^b, Jianjun Wei^{c,*}, Haiying Liu^{a,*}

^a Department of Chemistry, Michigan Technological University, Houghton, MI 49931, United States

^b Institute of Chemistry, Academia Sinica, Taipei 11529, Taiwan, ROC

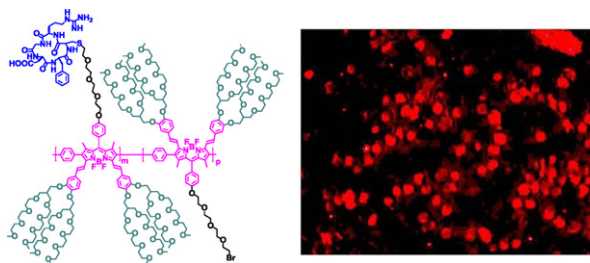
^c Biomedical Technology Branch, CFD Research Corporation, Huntsville, AL 35805, United States

HIGHLIGHTS

- ▶ Highly water-soluble near-infrared emissive BODIPY polymeric dye bearing bromide groups (polymer **A**) was prepared.
- ▶ BODIPY polymeric dye bearing RGD peptides (polymer **B**) was prepared by post-polymerization functionalization.
- ▶ Polymer **B** was used for specific near-infrared fluorescence imaging of breast cancer cells.

GRAPHICAL ABSTRACT

BODIPY polymeric dye bearing cancer-homing cyclic arginine–glycine–aspartic acid (RGD) peptide residues is used for selective near-infrared imaging of breast cancer cells (MDA-MB-231) through specific cooperative bindings of cancer-homing RGD peptides to $\alpha\beta3$ integrins of cancer cells.



ARTICLE INFO

Article history:

Received 29 June 2012

Received in revised form 12 October 2012

Accepted 14 October 2012

Available online 1 November 2012

Keywords:

BODIPY dye
Conjugated polymer
Cancer imaging
Fluorescence
RGD peptide

ABSTRACT

Near-infrared emissive BODIPY polymeric dye bearing cancer-homing cyclic arginine–glycine–aspartic acid (RGD) peptide residues (polymer **B**) was prepared by post-polymerization functionalization of BODIPY polymeric dye bearing bromo groups through tetra(ethylene glycol) tethered spacers (polymer **A**) with thiol-functionalized RGD cancer-homing peptide through thioether bonds under a mild basic condition. Polymer **B** possesses excellent water solubility, good photostability, biocompatibility and resistance to nonspecific interactions to normal endothelial cells, and can efficiently detect breast tumor cells through specific cooperative binding of cancer-homing RGD peptides to $\alpha\beta3$ integrins of cancer cells while its parent polymer **A** without RGD residues fails to target cancer cells.

© 2012 Elsevier B.V. All rights reserved.

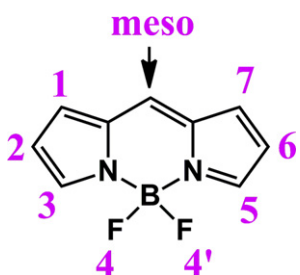
1. Introduction

Fluorescence-based optical imaging offers a convenient approach to monitor multiple biological processes simultaneously and in real time with high sensitivity, low tissue autoabsorption

and autofluorescence, low light scattering, operational simplicity, relatively low cost, potential miniaturization and mobility [1–4]. The demand for near-infrared (NIR) fluorescent dyes for noninvasive and simple diagnostic techniques such as in vivo imaging has been drastically growing as NIR dyes with emission wavelengths in the region between 700 nm and 900 nm can propagate through several centimeters of living tissues and may enable deep tissue imaging [1–4]. Functional bio-conjugated quantum dots (CdSe) could lead to a new generation of nanoparticle imaging probes

* Corresponding authors. Tel.: +1 906 487 3451; fax: +1 906 487 2061.

E-mail addresses: jjw@cfdr.com (J. Wei), hylu@mtu.edu (H. Liu).



Scheme 1. Chemical structure of BODIPY core.

for *in vivo* tumor imaging at high sensitivity and specificity [5], but their limited tissue penetration, lack of spatial resolution in tumor depth and potential toxicity concerns still restrict their clinical application. As a result, it is very important to develop a novel, highly water-soluble, near-infrared emissive agent with low cost, good biocompatibility, high intensity and photostability. In addition, high specificity for tumor cells, and tissue penetration and quantitative visualization for real time, *in vivo* detection of tumor will be highly desirable features in such a fluorescent dye. Numerous long-wavelength fluorophores such as 4,4'-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) dyes [6], rhodamine [7], squaraine [8], or cyanine dyes [9] have been recently reported. BODIPY dyes have received renewed interest for promising applications as imaging agents because of their many distinctive and desirable properties such as high absorption coefficients, narrow absorption bands, sharp emissions, high fluorescence quantum yields, and excellent chemical and photostabilities [6]. Functionalization of BODIPY dyes by the number and nature of the substituents at different positions (Scheme 1) has been used to tune to near-infrared emission. However, most reported studies have focused on small molecules of BODIPY dyes and only a few reported near-infrared emissive BODIPY dyes are soluble in aqueous solution [6,10,11]. Very recently, we and other groups reported some deep-red and near-infrared emissive polymeric BODIPY dyes [12–16]. However, all these BODIPY polymeric dyes are insoluble in aqueous solution [12–16].

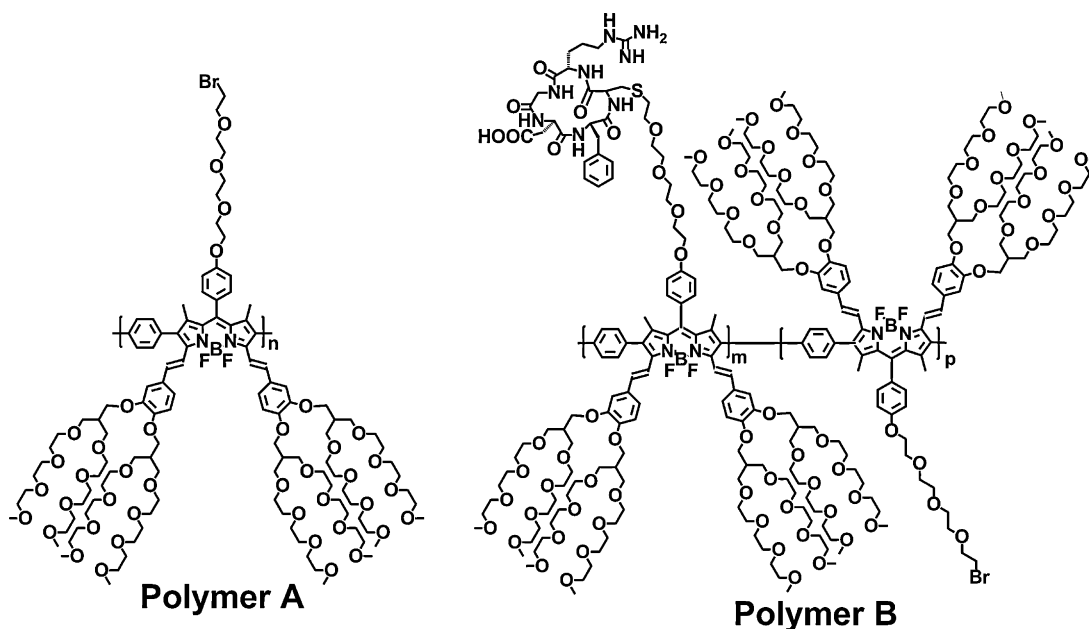
In this paper, we report a facile, convenient and versatile approach to prepare highly water-soluble, near-infrared emissive BODIPY polymeric dye bearing RGD cancer-homing peptide residues for cancer imaging application (Scheme 2). We prepared highly water-soluble BODIPY polymeric dye (polymer A) through the palladium-catalyzed Suzuki polymerization of highly water-soluble 2,6-diiodo-3,5-distyryl-BODIPY dye bearing bromide residue at the meso-position with 1,4-phenyldiboronic acid because this polymer is expected to display the relatively weak π - π stacking interactions among different polymer backbones. Incorporation of new branched oligo(ethylene glycol)methyl ether residues to distyryl units of BODIPY core at 3,5-positions effectively enhances enthalpic interactions of BODIPY dye with water, significantly increases water solubility of BODIPY polymeric dyes and prevents potential non-specific interactions of BODIPY dyes with other proteins through intermolecular interactions. RGD cancer-homing peptide residues were covalently attached to BODIPY cores at the meso positions through tetra(ethylene glycol) tethered spacers. This BODIPY polymeric dye functions as intrinsic near-infrared fluorophore with high water solubility, good photostability, biocompatibility and resistance to nonspecific interactions to biomolecules, targeting efficacy to tumor cells and easy-to-use during imaging detection.

2. Experimental

2.1. Materials

Unless otherwise indicated, all reagents and solvents were obtained from commercial suppliers (Aldrich, Sigma, Fluka, Acros Organics, Fisher Scientific, Lancaster) and used without further purification. Air- and moisture-sensitive reactions were conducted in oven-dried glassware using a standard Schlenk line or drybox techniques under an inert atmosphere of dry nitrogen.

BODIPY dye 3. The aldehyde **3** (2.0 g, 5.56 mmol) and 2,4-dimethylpyrrole (1.16 g, 12.23 mmol) were dissolved in 1000 mL of dry CH_2Cl_2 in a 2000 mL three-neck flask. Five drops of trifluoroacetic acid (TFA) were added to the reaction mixture, and the resulting mixture was stirred in the dark for 12 h under a nitrogen



Scheme 2. Chemical structures of highly water-soluble, near-infrared BODIPY polymeric dyes.

Download English Version:

<https://daneshyari.com/en/article/1165645>

Download Persian Version:

<https://daneshyari.com/article/1165645>

[Daneshyari.com](https://daneshyari.com)