



Highly efficient organic photosensitizer with aggregation-induced emission for imaging-guided photodynamic ablation of cancer cells

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ABSTRACT

We design an organic photosensitizer with a donor- π -acceptor configuration. The photosensitizer exhibits aggregation-induced emission characteristics and efficient singlet oxygen production in the aggregated state. It is then enveloped into the water-soluble micelle to afford a nanoprobe. The water-soluble nanoprobe keeps the photosensitizer in the aggregation state and is used for imaging-guided photodynamic ablation of cancer cells.

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Introduction

Cancer remains one of the most commonly diagnosed diseases and causes a high death rate.¹ Up to now, the clinic treatments for cancer mainly rely on surgery, chemical therapy and radiation therapy,² which aim to remove the tumor tissues and reduce the recurrence rate in patients. These treatments have their merits and demerits. Surgery is rendered as the most directly therapeutic option to remove the tumor tissues, but the effectiveness is usually dependent on the healthy condition of the individual patient and the stage of the cancer,^{2c} thus giving rise to the unpredictable recurrence rate. The chemical therapy and radiation therapy are also commonly used in the clinic applications, but they induce the unavoidable invasiveness and systemic toxicity.³ In contrast, photodynamic therapy (PDT) has emerged as a novel measurement for cancer therapy. It utilizes photosensitizers to generate reactive oxygen species (ROS) to damage the tumorous cells or tissues under light activation.⁴ Since the phototoxicity towards cancer cells is only triggered under irradiation, the PDT process exhibits specific spatiotemporal selectivity and minimal invasiveness.

Photosensitizers are involved in the PDT process as the primary element that not only generates cytotoxic singlet oxygen (¹O₂) for cancer therapy but also can serve as an imaging agent to label the distribution of the tumor. The reported photosensitizers include

phosphorescent transition-metal complexes,⁵ nanoparticles⁶ and organic compounds.⁷ Organic compounds have attracted great research interest because of large molar extinction coefficient and easy metabolism.⁸ However, compared to transition-metal complexes, organic compounds have relatively lower intersystem crossing (ISC) efficiency, resulting in the decreased generation of ¹O₂. The introduction of halogen atoms into the molecular structure is one of the most widely used methods to improve the ISC efficiency,⁹ but these halogen atoms cause the increased dark toxicity.¹⁰ Additionally, since most hydrophobic photosensitizers suffer from the aggregation in the aqueous media through π - π stacking, the remarkable emission quenching and decreased production of ¹O₂ are observed.¹¹

Fortunately, fluorophores with aggregation-induced emission (AIE) that were originally reported by Tang's group have recently utilized for biological applications.¹² These fluorophores exhibit weak emission when soluble in solution, while emit brightly in the aggregated state. Some of these fluorophores have been reported to show efficient ISC efficiency in the aggregation state,¹³ which paves the way for the development of photosensitizers with AIE for PDT. For example, tetraphenylethene derivatives are the most commonly employed as scaffolds to build AIE-active photosensitizers.¹⁴

In this work, we proposed to prepare an organic AIE-active photosensitizer (**1**) with donor- π -acceptor (D- π -A) configuration. We anticipate that the introduction of quinoline-malononitrile moiety in **1** will give rise to AIE characteristics and the spatially separated electron donor and acceptor moieties will result in the efficient ¹O₂

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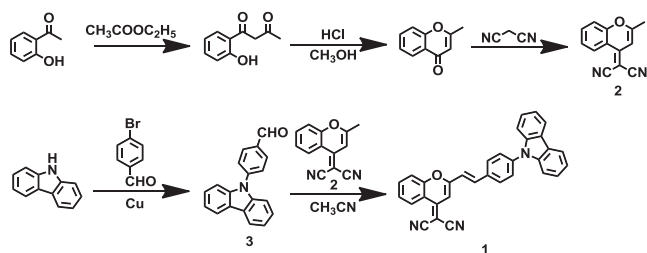
generation in the aggregation state. By encapsulating into amphiphilic molecules, **1** was easily enveloped into the water-soluble micelle to afford a nanoprobe. The nanoprobe bearing **1** has been demonstrated to show bright emission and efficient PDT efficiency. It can be used for imaging and photodynamic ablation of cancer cells. The unique properties of the nanoprobe warrant it as a novel photosensitizer for imaging-guided cancer therapy.

Results and discussion

The synthesis route is shown in Scheme 1 by a six-step procedure. **2** was prepared according to a reported method.¹⁵ **3** was synthesized by the coupling of carbazole and 4-bromobenzaldehyde through Ullmann reaction. The reaction of **2** with **3** in acetonitrile catalyzed by piperidine afforded **1**. In **1**, the quinoline-malononitrile (QM) moiety (electron donor) and carbazole (electron acceptor) were modified to obtain the donor- π -acceptor system. The introduction of QM moiety aimed at retaining the AIE characteristics. The intramolecular charge transfer within **1** is feasible to lower the energy gap between the S_1 and T_1 states, which will facilitate the increased ISC efficiency, resulting in the increasing efficiency of 1O_2 generation (Fig. S1 in Supporting information).¹⁶

The AIE characteristics of **1** was investigated by monitoring the emission spectra in the mixture of dimethyl sulfoxide and water (DMSO/H₂O). As illustrated in Fig. 1a, the emission intensity was observed to be gradually enhanced along with an increased fraction of water in DMSO/H₂O mixture. Interestingly, when the fraction of water was increased, the bathochromic effect was enhanced. The fraction of water reached to be 90%, the emission spectrum of **1** was bathochromically shifted to far-red region ($\lambda_{em} = 639$ nm), which is advantageous to deep tissue penetration and minimize noise from the autofluorescence in biological applications. The absorption spectrum of **1** was observed to localize in the white light (>400 nm), which paves the way for minimized photo-damage (Fig. 1b). In order to better understand the optical properties of **1**, the density functional theory (DFT) calculations were carried out using the Gaussian 09 package at the B3LYP level. The HOMO and LUMO distribution are respectively localized in carbazole and malononitrile (Fig. 1c), which demonstrated intramolecular charge transfer within molecular systems. The spatially separated electron donor and acceptor moieties resulted in small ΔE_{ST} value that was estimated to be 0.61 eV, which makes it possible to enhance ISC efficiency for 1O_2 generation.

The 1O_2 generation of **1** was assessed by using 9,10-anthracenediyl-bis(methylene) dimaleonic acid (ABDA), as an indicator and Ru(bpy)₃²⁺ as the standard photosensitizer. The mixture of **1** or Ru(bpy)₃²⁺ in the ABDA solution was irradiated with a white light lamp at 100 mW cm⁻². The absorption band of ABDA was observed to be gradually decreased in the presence of photosensitizer under irradiation, indicating the degradation of ABDA when 1O_2 was generated in solution. The decomposition rate constant of **1** was estimated to be $3.39 \times 10^{-3} s^{-1}$ (Fig. 2). The 1O_2 quantum yields of **1** was calculated to be 0.12. The capacity of **1** to produce 1O_2 agreed



Scheme 1. Synthetic route of **1**.

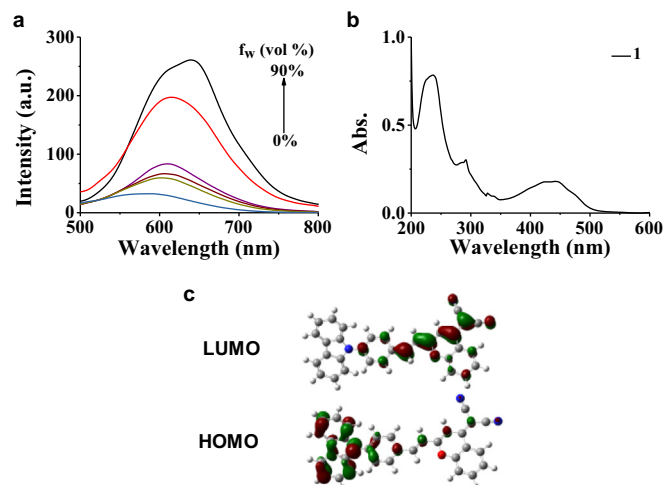


Fig. 1. (a) Photoluminescence spectra of **1** (8 μ M) in DMSO/water mixtures with different fraction of water; (b) The absorption spectrum of **1** (8 μ M) in DMSO; (c) Chemical structure and HOMO-LUMO distribution of **1**.

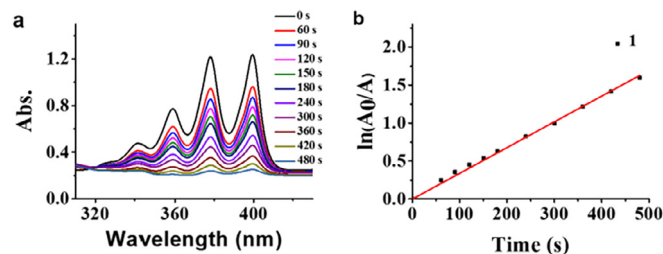


Fig. 2. (a) The absorption spectra of ABDA in the presence of **1** in the mixture containing DMSO and water (1:200, v/v) under irradiation (white light, 100 mW cm⁻²) over different periods of time; (b) The decomposition rate of ABDA by **1**; A₀ and A are the absorption of ABDA monitored at 400 nm in the presence of **1** before and after irradiation, respectively.

well with small ΔE_{ST} value in the results of DFT calculation, suggesting the possibility to utilize **1** as a photosensitizer in intracellular environments. The nanoprobe was then obtained by

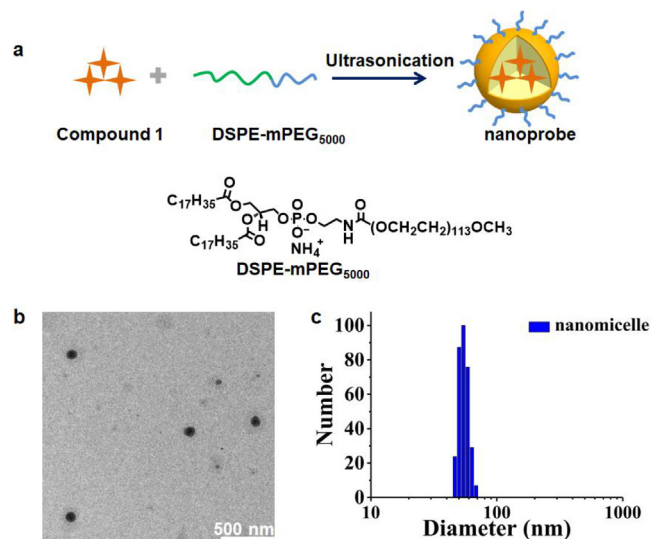


Fig. 3. (a) Schematic illustration of the formation of the nanoprobe through nanoprecipitation method; (b) TEM image of the nanoprobe; (c) Hydrodynamic size distribution of the nanoprobe.

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