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A new far-red naphthorhodamine dye: Synthesis, fluorescent probe and bioimaging applications

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ABSTRACT

A new extended-π-conjugated naphthorhodamine dye, 9′-diethylamino-2′-hydroxyl-benzo[*a*]fluoran (**1**) with a carboxylic acid-functional group was designed and synthesized. Compared to Rhodamine B, the emission wavelength of **1** was extended to ca. 600 nm, and its fluorescence properties could be controlled by the key carboxylic acid-functional group. By taking advantage of **1**, we synthesized a new far-red bioimaging dye 2-ethyl-9′-diethylimino-2′-hydroxyl- benzo[*a*]fluoran (**2**) by esterification of **1**, which could selectively stain mitochondria. Moreover, encouraged by the spirocyclization switching mechanism platform, we successfully constructed a new fluorescent probe 9′-diethylamino-2′-hydroxyl-benzo[*a*]fluoran hydrazine (**3**), the hydrazide derivative of **1**, for Hg^{2+} with good selectivity. These results suggest that the new naphthorhodamine dye could be used as a platform to construct fluorescent probes and bioimaging reagents.

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1. Introduction

Fluorescent imaging have been recognized as a facile and powerful tool for the detection of biologically relevant species with the ability to visualize morphological details and monitor various physiological processes in living systems [1–5]. The imaging technique is highly dependent on the photophysical and photochemical properties of the fluorescent dyes being used [6,7]. To date, various fluorophores with different excitation and emission wavelengths have been employed as signal reporters of chemosensors, such as coumarin, pyrene, 1,8-naphthalimide, boron dipyrromethene difluoride (BODIPY), xanthenes, squaraine, cyanine, etc. [8,9]. Among the fluorophores developed, xanthenes, especially rhodamine and fluorescein derivatives, are highly favorable because of their excellent photophysical properties, such as high extinction coefficients, great photostability, and relatively long emission wavelength. More importantly, the fluorescence behavior of rhodamine and fluorescein dyes can be controlled by the unique spirolactam ring opening and closing process [10–12]. Due to these favorable properties, rhodamine and fluorescein dyes have been used as a platform for constructing fluorescent probes and biomarkers for a wide variety of targets [13–17].

However, the absorption and emission wavelengths of most rhodamine derivatives are below 600 nm, which is sometimes unsuitable for biological applications [18,19]. Moreover, these derivatives have small Stokes shifts (typically less than 35 nm), that is often detrimental for practical applications either due to reduced emission intensity by self-absorption and inner filter effect or fluorescence detection errors because of excitation backscattering effects [20]. In fact, it is well established that fluorescent dyes operating in the far-red to NIR region with large Stokes shifts have many advantages for biological applications, including low phototoxicity, low autofluorescence, good tissue penetration, and low detection limits [21,22]. Therefore, there is a strong interest in the development of the rhodamine-inspired NIR dyes with large Stokes shifts.

In this work, we have designed and synthesized a new far-red fluorescent dye **1** by the strategy of extending the π-conjugation of the xanthene ring with the substituted naphthalene, while keeping the favorable properties of the well-known Rhodamine dyes. The emission wavelength of dye **1** was extended to the far-red region (>600 nm) along with a large Stokes shifts (>40 nm). Furthermore, we designed a new mitochondria biomarker and a new Hg^{2+} fluorescent probe based on the new dye **1**, and verify their practical applicability.

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2. Experimental

2.1. Materials and instruments

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC). Flash chromatography (FC) was performed using silica gel 60 (230–400 mesh). Deionized water was used throughout all experiments. Solutions of Fe^{2+} and Ca^{2+} were prepared from their chloride salts; Solutions of Hg^{2+}, Na^{+}, K^{+}, Mg^{2+}, Mn^{2+}, Fe^{2+}, Ca^{2+}, Zn^{2+}, Co^{2+}, Pb^{2+}, Cu^{2+}, Cd^{2+}, Ni^{2+} and Ag^{+} were prepared from their nitrate salts. Absorption spectra were taken on a Varian Carry 4000 spectrophotometer. Fluorescence spectra were taken on Hitachi F-7000 fluorescence spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 and 150 MHz, respectively. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiple; br = broad. Mass spectra were obtained using Thermo Scientific Q Exactive LC-MS/MS. The fluorescence images were acquired through Zeiss LSM 880 confocal microscope.

2.2. Synthesis and characterization

The synthetic routes to compounds **1**, **2** and **3** are shown in Scheme 1. Compound **1** was prepared by a simple one-step procedure in good yield from the reaction of 2-(4-diethyl-amino-2-hydroxybenzoyl)-benzoic acid and naphthalene-2, 7-diol in trifluoroacetic acid as a red brown powder. The starting material **4** was prepared according to the reported procedure [23]. Compound **2** was synthesized by esterification of **1** with concentrated sulfuric acid as the catalyst [24]. Condensation of **1** with hydrazine in refluxing ethanol afforded the desired product **3** as a white solid. The structures of **1**, **2** and **3** were characterized by ESI-MS, ^{1}H and ^{13}C NMR and the corresponding spectra are shown in Supplementary information.

2.2.1. Synthesis of *1*

2-(4-Diethylamino-2-hydroxy-benzoyl)-benzoic acid (1.50 g, 5.00 mmol) and naphthalene-1,4-diol (0.80 g, 5.0 mmol) (0.8 g, 5.0 mmol) were added to a pressure flask and dissolved in 20 mL of TFA. The reaction was stirred for 12 h at 100 °C. After cooling, the solvent was removed under reduced pressure to give the crude product, which was purified by silica gel flash chromatography using CH_2Cl_2/EA as eluent to afford **1** as pink solid (yield, 72%). 1H NMR (DMSO-d_6, 600 MHz) δ (ppm): 9.80 (s, 1H), 8.12 (d, 1H, J = 7.2 Hz), 7.96 (d, 1H, J = 9.0 Hz), 7.77 (d, 1H, J = 8.4 Hz), 7.69 (t, 2H, J = 8.4 Hz), 7.28 (d, 1H, J = 9.0 Hz), 7.15 (d, 1H, J = 6.6 Hz), 6.92 (d, 1H, J = 9.0 Hz), 6.47 (d, 1H, J = 9.0 Hz), 6.45 (s, 1H), 6.36 (d, 1H, J = 9.0 Hz), 6.25 (s, 1H), 3.33 (d, 4H, J = 6.6 Hz), 1.07 (t, 6H, J = 6.6 Hz); 13C NMR (150 MHz, DMSO-d_6, ppm): δ 169.87, 156.68, 155.04, 151.49, 150.53, 149.12, 136.16, 133.06, 131.37, 130.16, 128.30, 126.86, 125.78, 125.52, 123.68, 116.58, 115.04, 109.56, 107.09, 106.94, 106.18, 96.74, 84.26, 44.20, 12.79; HRMS [ESI]: m/z, calcd for $[(M+H)]^{+}$ 438.1700; Found 438.1703.

2.2.2. Synthesis of *2*

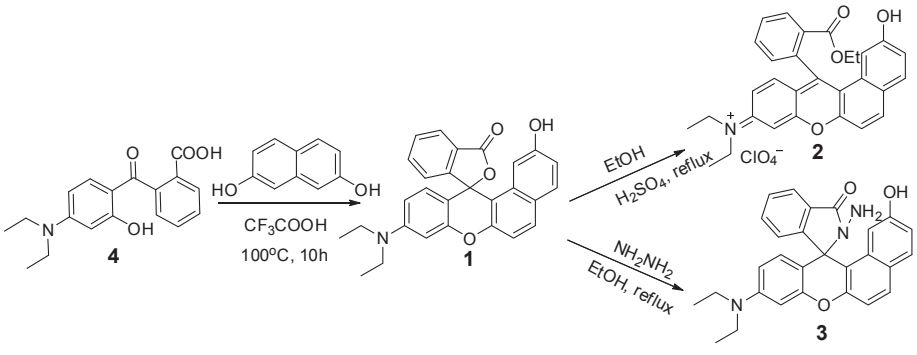
Concentrated H_2SO_4 (0.5 mL) was added to ethanol solution of compound **1** (0.21 g, 4.8 mmol), and heated to reflux for 4 h. After cooling, ethanol was removed under vacuum, and the residue was neutralized with 20 mL of 10% NaOH aqueous solution to collect the resulting precipitate. After drying, it was purified by silica gel chromatography using CH_2Cl_2:CH_3OH = 100:1 (v/v) as the eluent to give compound **2** as a dark green solid (0.19 g, 85%);^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm): 9.79 (s, 1H), 8.12 (d, 1H, J = 6.6 Hz), 7.96 (d, 1H, J = 9.0 Hz), 7.77 (d, 1H, J = 9.0 Hz), 7.72–7.67 (m, 2H), 7.28 (d, 1H, J = 8.4 Hz), 7.15 (d, 1H, J = 7.2 Hz), 6.93–6.91 (m, 1H), 6.44 (d, 1H, J = 2.4 Hz), 6.36 (d, 1H, J = 9.0 Hz), 6.24 (s, 1H), 3.36–3.33 (s, 6H), 1.14 (t, 3H, J = 7.2 Hz), 1.08 (t, 6H, J = 6.6 Hz).

2.2.3. Synthesis of *3*

Compound **1** (0.20 g, 1.07 mmol) was dissolved in EtOH (30 mL) and $NH_2NH_2 \cdot H_2O$ (200 μL). The reaction solution was heated and kept under reflux for 4 h. The ethanol was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (50 mL × 3). The organic solution was washed with distilled water (50 mL × 3), dried over anhydrous magnesium sulfate and then filtered. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (dichloromethane:EA = 2:1) to obtain a white solid of compound **3** (0.16 g, 80.5%).^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm): 9.61 (s, 1H), 7.92 (d, 1H, J = 7.8 Hz), 7.84 (d, 1H, J = 8.4 Hz), 7.69 (d, 1H, J = 8.4 Hz), 7.52 (t, 1H, J = 8.4 Hz), 7.44 (t, 1H, J = 8.4 Hz), 7.20 (d, 1H, J = 8.4 Hz), 6.96 (d, 1H, J = 7.8 Hz), 6.873–6.854 (dd, 1H, J = 9.0 Hz, J = 2.4 Hz), 6.38–6.35 (m, 3H), 6.17–6.15 (m, 1H), 4.27 (s, 2H), 3.31 (q, 4H, J = 7.2 Hz), 1.07 (t, 6H, J = 7.2 Hz); 13C NMR (150 MHz, DMSO-d_6, ppm): δ 166.42, 156.48, 152.03, 151.89, 151.70, 148.31, 133.49, 133.22, 131.73, 130.91, 130.70, 128.78, 127.30, 125.52, 123.48, 116.25, 115.21, 109.04, 107.56, 106.85, 106.46, 97.22, 65.95, 56.50, 44.11, 12.92; HRMS [ESI]: m/z, calcd for $[(M+H)]^{+}$ 452.1969; Found 452.1971.

2.3. Crystallography of *1*

A single crystal of **1** was grown from a MeOH/EtOAc solution and was characterized using X-ray crystallography (Fig. 1). The crystal structure clearly represents the unique spirolactam-ring formation. Intensity data of **1** were collected on a Siemens SMART-CCD



Scheme 1. Chemical structures and synthetic routes of the compounds **1**, **2** and **3**.

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