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An aniline bearing hemicyanine derivative serves as a mitochondria selective probe

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A B S T R A C T

Mitochondria play key roles in a variety of pathologies, such as Alzheimer's disease and cancer. Because of this, the development of mitochondria staining probes has attracted great attention. In the current study, we designed, prepared and explored the properties of the hemicyanine derivative, **HCA-Mito**, bearing an aniline moiety. The results show that this substance serves as a mitochondria staining probe. **HCA-Mito**, which is insensitive to pH and has a low cytotoxicity, shows a high coincidence with the mitochondria specific dyes, MitoTracker Red and MitoTracker Deep Red. More importantly, the fibrous network structure of mitochondria is clearly stained by using **HCA-Mito**.

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1. Introduction

A large effort has been devoted to uncovering stains that are specific for organelles in complex cellular systems. Moreover, the organelle selective staining probes have played a significant role in development of diagnostic and therapeutic tools [1]. Among various organelles, mitochondria are the primary producers of cellular ATP. In addition, mitochondria play a key role in various pathologies, such as Alzheimer's disease and cancer [2,3], and they are also involved in apoptosis and programmed cell death [4]. Furthermore, cell damage can induce changes in the sizes and structures of mitochondria [5]. Owing to these important features, numerous investigations in the past decade have focused on the development of staining [6–15] and fluorescent probes that target specific analytes in mitochondria [16–24].

Fluorescence spectroscopy is a highly attractive tool to study biological processes because of its high sensitivity and, more importantly, its compatibility with direct imaging using confocal microscopy [25–30]. Owing to the complicated nature of the cellular environment, especially at the molecular level, it is challenging to design selective fluorescent mitochondrial markers in a rational manner. Most mitochondria staining dyes developed to date are cationic fluorescent compounds, which interact electrostatically with the negative potential gradient of mitochondrial membranes. For example, substances containing the triphenylphosphonium (TPP) group have been used as mitochondria staining dyes and for sensing analytes in mitochondria [2,31]. In the current study, we designed the new, positively charged hemicyanine derivative, **HCA-Mito**, which contains an aniline moiety, and demonstrated that it serves as a practical staining probe for mitochondria. In contrast to many other staining probes that require extensive and/or complicated routes for their synthesis, **HCA-Mito** is readily prepared in a moderate yield using a simple two-step sequence. In addition, **HCA-Mito** has a 94% of Pearson's coefficient and a high overlap index. Finally, this sensor is not sensitive to pH, it is highly soluble in aqueous environments and it displays low cytotoxicity, which are sought after characteristics of mitochondria staining probes.

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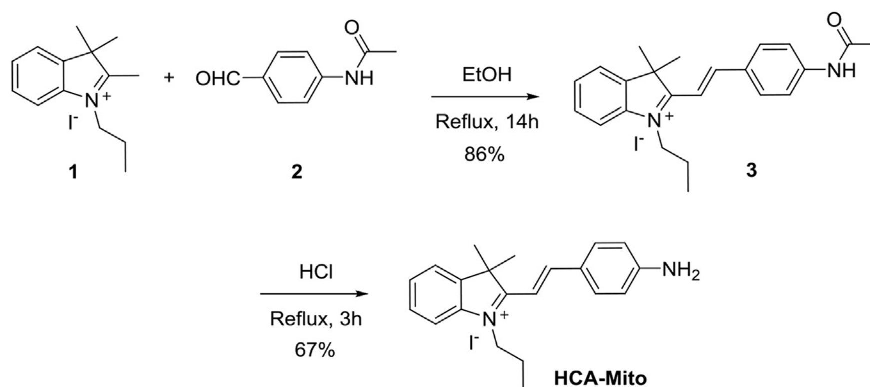

Scheme 1. Route for synthesis of **HCA-Mito**.

2. Experimental section

2.1. Materials and apparatus

Unless otherwise noted, materials were obtained from Aldrich and were used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker 300 MHz instrument. Chemical shifts are given in ppm. UV absorption spectra were obtained using a UVIKON 933 Double Beam UV/VIS Spectrometer. Fluorescence emission spectra were obtained using RF-5301/PC Spectro-fluorophotometer (Shimadzu).

2.2. Synthesis

2.2.1. Synthesis of **3**

To a solution of 2,3,3-trimethyl-1-propyl-3H-indol-1-ium iodide (**1**) (329 mg, 1.0 mm) in dry EtOH (10 mL) was added *p*-acetamidobenzaldehyde (**2**) (163 mg, 1.0 mm). The mixture was stirred under a nitrogen atmosphere at reflux for 14 h. After cooling to room temperature, the solvent was removed by evaporation. The crude product was subjected to silica gel column chromatography (eluent: MeOH/dichloromethane 1:40), affording the desired product **3**. Yield, 86%. ^{1}H NMR (300 MHz, $CDCl_3$) 8.50 (d, $J = 15.9$ Hz, 1H), 8.11 (d, $J = 8.4$ Hz, 2H), 7.85 (m, 4H), 7.67 (m, 3H), 4.67 (t, $J = 7.5$ Hz, 2H), 2.22 (s, 3H), 2.06 (q, $J = 7.5$ Hz, 2H), 1.90 (s, 6H), 1.14 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 182.3, 170.7, 154.5, 144.3, 143.7, 140.9, 131.7, 129.4, 119.5, 114.7, 110.1, 52.4, 25.4, 22.8, 21.8, 9.9; FAB-MS $m/z = 347.2124$ $[M-I^-]^+$, calcd for $C_{23}H_{27}N_2O = 347.2118$.

2.2.2. Synthesis of compound ***HCA-Mito***

A solution of **3** (474 mg, 1.0 mm) in hydrochloric acid (37%, 10 mL) under a nitrogen atmosphere was stirred at reflux for 3 h. After cooling to room temperature, the solvent was removed by evaporation. The crude product was subjected to silica gel column chromatography (eluent: MeOH/dichloromethane 1:20), affording **HCA-Mito**. Yield, 67%. ^{1}H NMR (300 MHz, $CDCl_3$) 8.02 (d, $J = 15.3$ Hz, 2H), 7.85 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 6.9$ Hz, 3H), 7.38 (m, 1H), 7.12 (d, $J = 15.3$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 2H), 6.15 (NH_2), 4.59 (t, $J = 6.9$ Hz, 2H), 1.95 (q, $J = 6.9$ Hz, 2H), 1.75 (s, 6H), 1.05 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.1, 157.6, 155.0, 141.8, 141.4, 129.1, 127.3, 123.0, 122.4, 116.1, 112.3, 103.0, 50.7, 47.2, 27.9, 21.6, 11.5; FAB-MS $m/z = 305.2021$ $[M-I^-]^+$, calcd for $C_{21}H_{25}N_2 = 305.2012$.

2.3. Cell culture

HeLa cell (human epithelial adenocarcinoma) lines were purchased from Korean Cell Line Bank (Seoul, Korea). Cells were grown in DMEM (Dulbecco Modified Eagle Medium, high glucose) supplemented with 10% heat-inactivated fetal bovine serum, 100 U/mL penicillin and 100 U/mL streptomycin. All cells were maintained in an incubator at 37 °C and a 5% CO_2 air environment.

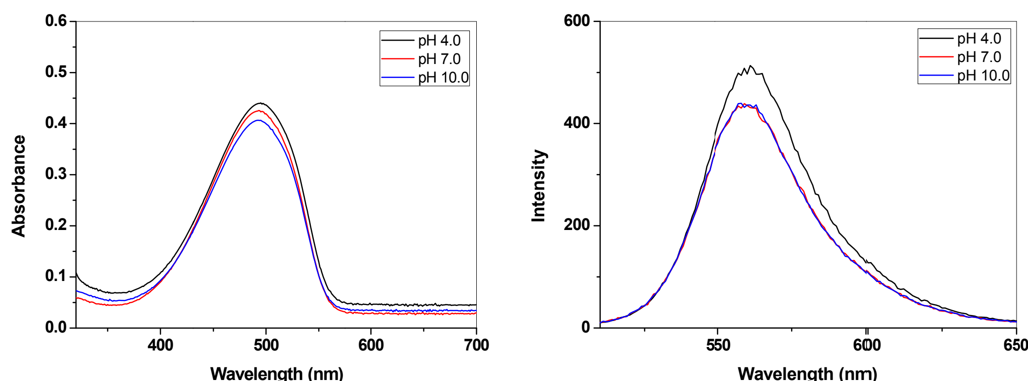

Fig. 1. UV–Vis absorption (Left) and fluorescence emission spectra (Right) of **HCA-Mito** (10 μM) in citric acid-Na_2HPO_4 (10 mM) buffer solution containing 10% CH_3CN at pH values of 10.0, 7.0, and 4.0. (excitation wavelength = 495 nm).

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