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1,8-Naphthalimide-based 'turn-on' fluorescent sensor for the detection of zinc ion in aqueous media and its applications for bioimaging

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ABSTRACT

A 1,8-naphthalimide derivative (**1**) was intentionally designed and synthesized as a new turn-on fluorescent probe for the detection of zinc ion with high selectivity over other metal ions at pH 7.4 in aqueous media (CH_3CN/HEPES, V/V = 6:4). The reaction mechanism is attributed to the replacement of the protons of the O–H groups by zinc ion at the binding site and production of fluorescence which is blocked in the photo-induced electron transfer (PET) process. Remarkable enhancement of up to 13-fold in fluorescence intensity with a 38 nm red-shift was achieved in the detection of zinc ion. Compound **1** was successfully applied to the fluorescence imaging of zinc ion, with a fluorescence emission color produced in the cell nucleus different from that produced in the cytoplasm, in A549, BEAS-2B, CHO, Hela, and HepG2 cells. Furthermore, cytokinesis-block micronucleus (CBMN) assay was carried out in CHO cells using **1** and zinc ion as the imaging agents, showing that the **1**-Zn^{2+} agent is a nucleic acid selective stain, which could be applied in MN assays in different kinds of cell lines.

1. Introduction

Because of the high sensitivity, specificity, simplicity of implementation, and fast response time, fluorescent probes for detecting metal ions possess innate advantages over other detection methods developed, such as high performance liquid chromatography[1] and capillary electrophoresis.[2] Fluorescent probes also offer applications for both in vitro assays and in vivo imaging studies.[3] In particular, the development of a fluorescent probe for zinc ion in the presence of a variety of other metal ions has received considerable attention.[4,5] Zn^{2+} is involved in a variety of physiological and pathological processes, such as Alzheimer's disease, epilepsy, ischemic stroke, and infantile diarrhea.[6] It is also reported that zinc ion is a potent killer of neurons via oxidative stress.[7] A decrease in the concentration of Zn^{2+} can cause a reduction in the ability of the islet cells of the pancreas to produce and secrete insulin.[8] Accordingly, development of Zn^{2+} selective fluorescent sensors and convenient methods to detect intracellular Zn^{2+} ion are certainly important issues in recent years. The total concentration of Zn^{2+} in different cells varies from the nanomolar range up to about 0.3 mM,[9] which means that optimized chemical probes are required to monitor zinc concentration over that broad range.

Most of the fluorescence-based probes for Zn^{2+} suffer from limitations due to tight binding affinity or lack of sufficient selectivity to detect intrinsic levels of Zn^{2+} in pancreatic islets. Therefore, it remains a challenge to develop efficient fluorescent probes with high sensitivity and selectivity for the detection of metal ions in biological applications. Recently, a rhodamine-based derivative bearing a *N*-butyl-1,8-naphthalimide group was reported in our work, in which it displayed a selective colorimetric and fluorescence change toward Cu^{2+} based on the rhodamine ring-opening approach.[10] Meanwhile, some simple but efficient fluorescent sensors based on Shift base, which displayed selective optical responses, were reported.[11] In order to further explore the sensing mechanism of this series of 1,8-naphthalimide-based compounds and their biological applications, the introduction of new ligands with different binding points has attracted considerable interest.

Herein, we describe the synthesis and the photophysical properties of a new 1,8-naphthalimide-based chemosensor **1**, which has been designed for the sensitive and selective 'turn-on' fluorescence detection of Zn^{2+} in aqueous solvents (CH_3CN/HEPES, V/V = 6:4, 0.02 M HEPES buffer, pH 7.4) as well as in intracellular media. As expected, upon addition of 20 equiv of various metal ions, only Zn^{2+} leads to a significant enhancement of up to 13-fold in fluorescence intensity with a 38 nm red-shift, and no obvious

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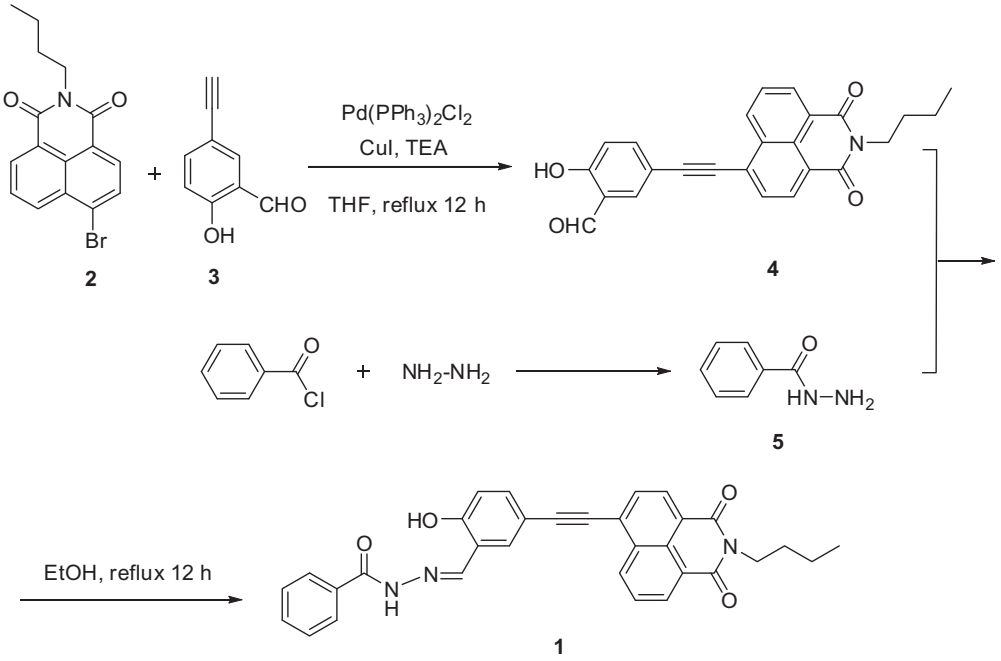

Scheme 1. The synthetic route of compound **1**.

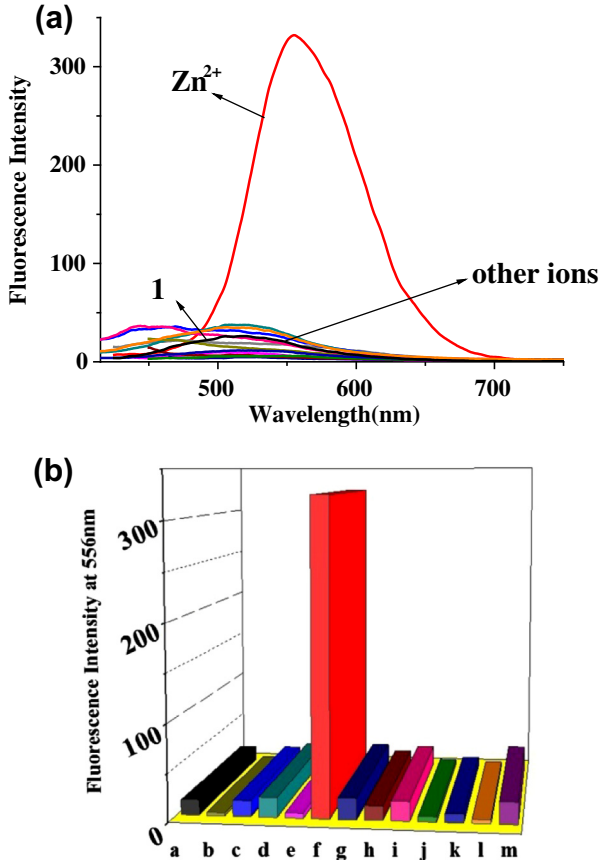

Figure 1. (a) Fluorescence emission spectra of **1** (2.0×10^{-5} M) in CH_3CN–HEPES buffer (0.02 M, pH 7.4) (V/V = 6:4) with 20 equiv of Na^+, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Cd^{2+}, Ag^+, Hg^{2+}, Fe^{2+}, Mg^{2+}, and Cr^{3+}. (b) Fluorescence intensity of **1** (2.0×10^{-5} M) at 556 nm after addition of 20 equiv of selected ions in CH_3CN–HEPES buffer (0.02 M, pH 7.4) (V/V = 6:4) (a: **1**, b: Co^{2+}, c: Cd^{2+}, d: Hg^{2+}, e: Cu^{2+}, f: Zn^{2+}, g: Na^+, h: Ag^+, i: Pb^{2+}, j: Fe^{2+}, k: Mg^{2+}, l: Ni^{2+}, m: Cr^{3+}).

fluorescence change was observed for other tested metal ions. Furthermore, chemosensor **1** presents high sensitivity and selectivity in the fluorescence imaging of Zn^{2+} in A549, BEAS-2B, CHO, Hela, and HepG2 cells. With differing binding capacities toward different nucleic acids (DNA and RNA), not characteristic of most of other imaging agents, **1** exhibits a fluorescence emission color in the cell nucleus different from that in the cytoplasm. It provides a clear fluorescence image of the tested cells. Cytokinesis-block

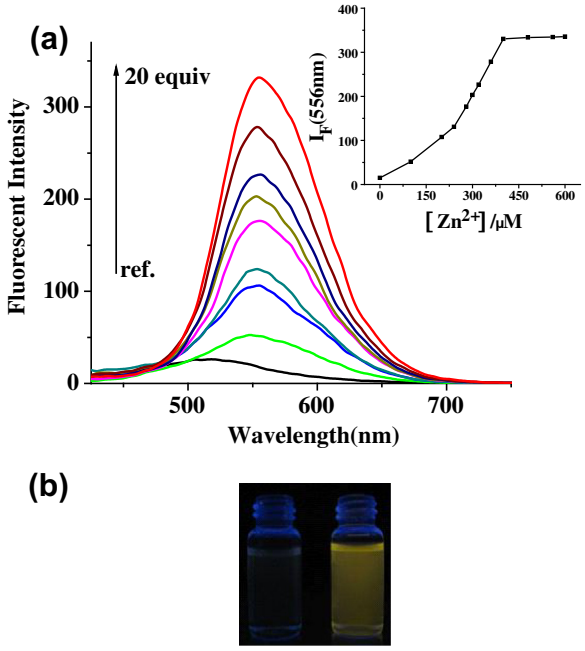

Figure 2. (a) Fluorescence emission titration spectra of **1** (2.0×10^{-5} M) in the presence of varying concentrations of Zn^{2+} in CH_3CN–HEPES buffer (0.02 M, pH 7.4) (V/V = 6:4). Excitation wavelength was 410 nm. Inset: fluorescence intensity of **1** (2.0×10^{-5} M) at 556 nm as a function of varying concentrations of Zn^{2+}. (b) Fluorescence picture of compound **1** (left) and compound **1** upon the addition of 20 equiv of Zn^{2+} (right).