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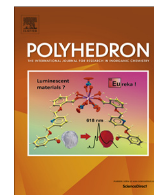

A highly selective fluorescent sensor for zinc ion based on quinoline platform with potential applications for cell imaging studies

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ABSTRACT

An 8-aminoquinoline based fluorescent Zn^{2+} sensor, 2-methoxy-6-((quinolin-8-ylimino)methyl)phenol (**HL**), was synthesized. It has been found to display quick responses through fluorogenic properties on selective 2:1 binding to Zn^{2+}, as delineated by absorption and fluorescence titrations as well as by Job's method and X-ray crystallography studies. This probe features visible light excitation (461 nm) and emission (594 nm) profiles, excellent selectivity responses for Zn^{2+} over other competing biological metal ions with high binding constant and about 17-fold enhancement in fluorescence quantum yield (Φ) upon half equivalent of Zn^{2+} binding under physiological pH window. The low detection limit in micromolar range (1.3×10^{-7} M) for Zn^{2+}, makes **HL** a suitable candidate for the development of a potential probe. It also exhibits cell permeability and intracellular Zn^{2+} sensing in HeLa cells from human cervical cancer cell and rat hippocampal slices.

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1. Introduction

Design and exploration of fluorescent probes for the detection of biologically important transition metal ions have received extensive interest because fluorescent chemosensors have several advantages such as high selectivity, sensitivity and real-time monitoring over other methods [1,2]. It is highly demanding the development of a fluorescent probe to selectively sense zinc ion in the presence of other transition-metal ions [3,4–10].

Zinc ion is the second most abundant transition metal ion in the human body (2–3 g in total), and it plays diverse roles in human physiopathology, where it can be found in both tightly bound and mobile forms [11,12]. The intracellular concentration of mobile zinc is tightly regulated and varies from picomolar to millimolar, depending on the organ [13]. The mobile form, alternatively referred to as loosely bound, chelatable or free zinc, occurs in organs such as brain, intestine, pancreas, retina, prostate, olfactory bulb, and spermatic sac [14,15]. Failure of mobile zinc homeostasis has been linked to pathological states, including Alzheimer's disease, epilepsy, ischemic stroke and infantile diarrhea [16]. Zinc plays a critical role in numerous cellular functions [17], such as gene expression, apoptosis, neurotransmission and accumulation of Zn^{2+} ions to toxic levels leads to cell death [18–20]. These findings have evoked great interest in mobile zinc biology, but much is still unknown about the molecular mechanisms of its homeostasis and pathophysiology. So many conventional spectroscopic tools cannot be applied to study spectroscopically silent Zn^{2+} ions because of its $3d^{10}$ electronic configurations. It is believed that the use of fluorescence technique among various analytical tools is one of the most promising by transuding chemical information about biological events thereby providing a better understanding to the fundamental and essential mechanism of many pathophysical process [21–23]. However, little is known about the distribution, accumulation and mobility of intracellular zinc. The major challenge is to apply a Zn-sensor to real time situations. To apply a luminescence probe to biomedical imaging, one needs to access them intracellularly and optimize the photophysical properties.

Among various fluorescent sensors, 8-aminoquinoline and its derivatives were the first class of probes to be developed for Zn^{2+} ion [24]. They exhibit good photostability, high affinity to metal ions, and satisfactory membrane permeability [25]. The common probes are aryl sulfonamide derivatives of 8-aminoquinoline, such as 6 methoxy-(8-*p* toluenesulfonamido)quinoline (TSQ), Zinquin, as well as Zinbo-5, the Zinpyr (ZP) family [26,27] and the ZnAF

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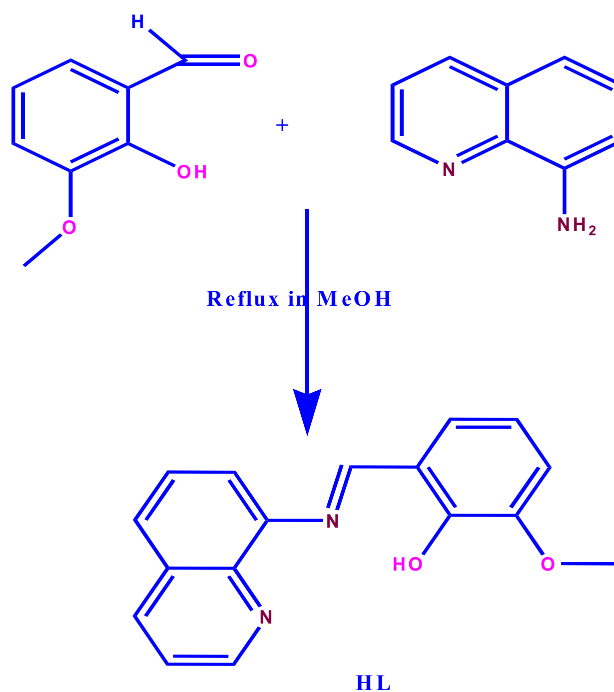
molecules [28]. One of these probes, Zinquin can detect intracellular Zn^{2+} ions in living cells [29]. Despite the availability of some commercial fluorescent probes for Zn^{2+} ion [26,30], the design of easy-to-synthesize, low-toxicity, extremely high affinity for zinc ions and good selectivity over other relevant metal ions is still a challenging task [31].

Herein, we introduced an easily synthesizable Salen-based receptor with potential N_2O donor atoms equipped with 8-aminoquinoline moiety for sensitive and selective recognition of Zn^{2+} ions in mixed organo-aqua media. It was looking quite interesting that our synthesized fluorescent sensor fulfill almost all the crucial characteristic that a intracellular fluorescent sensor should have (1) a signal with high quantum yield (Φ) to permit the use of glass microscope objectives, (2) excitation wavelengths exceeding 340 nm to prevent UV–induced cell damage, (3) emission wavelength approaching 500 nm to avoid autofluorescence from species native to the cell and to facilitate use with typical fluorescence microscopy optical filter sets [32]. In a recent work Rajak et al. have reported similar type of ligand system based on 8-aminoquinoline and salicylaldehyde and its derivatives. Their ligands also exhibited significant enhancement of the fluorescence intensity and quantum yield in presence of Zn^{2+} ion [33]. However to the best of our knowledge, application of Zn(II) fluorescent probe 2-methoxy-6-((quinolin-8-ylimino)methyl)phenol (**HL**) for cellular imaging in living cells is still unexplored.



Scheme 1. Synthetic route of fluorescent probe **HL**.

2. Experimental

Materials and synthesis: All the analytical grade chemicals and solvents were purchased from commercial sources and used as received. 8-Aminoquinoline, *o*-vanillin, sodium azide and zinc(II) nitrate hexahydrate were purchased from Sigma–Aldrich. All buffers were prepared in quartz-distilled deionized water from a Milli-Q source (Millipore, USA). Solvents used for spectroscopic studies were purified and dried by standard procedures before use [34].

2.1. Synthesis

2.1.1. Synthesis of 2-methoxy-6-((quinolin-8-ylimino)methyl)phenol (HL)

The tridentate Schiff base ligand (**HL**) was prepared by a slight modification of the procedure described previously (Scheme 1) [33,35]. Briefly, 1.0 mmol (0.144 g) of 8-aminoquinoline was mixed with 1.0 mmol (0.152 g) of *o*-vanillin in 20 ml of methanol. The resulting solution was heated to reflux for ca. 1 h, and allowed to cool. The solution was then filtered, concentrated on a rotary evaporator to dryness. The ligand was further purified on a silica gel column. A red band was eluted using 5% ethylacetate in toluene solution. A red colored solid was obtained as pure solid by removal of solvent under reduced pressure. Yield: 236 mg (85%). *Anal.* Calc. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 72.87; H, 5.41; N, 9.74%. IR (cm^{-1}, KBr): ν(C=N) 1610 cm^{-1}. ^{1}H NMR {300 MHz, $CDCl_3$, δ (ppm), J (Hz)}: 14.49 (OH, s), 8.1 (—CH=N, s) 8.97–6.82 (9H, ArH), 3.95 (OCH_3, s) (Fig. S1). ESI mass spectrum of **HL** shows a peak at m/z 279.1273, which can be assigned to $[M+H]^+$, where M = $C_{17}H_{14}N_2O_2$ (Fig. S2).

2.1.2. Synthesis of [Zn(L)2] (1)

A 10 ml methanolic solution of zinc(II) nitrate hexahydrate (0.297 g, 1.0 mmol) was added slowly to a magnetically stirred 10 ml methanolic solution of ligand (**HL**) (0.556 g, 2.0 mmol). The mixture was stirred for 3 h, whereby an orange solution was formed. Single crystals suitable for X-ray diffraction were obtained from orange color solution after several days, which was collected by filtration and washed with ether and air dried. Yield: 495 mg (80%). *Anal.* Calc. for $C_{34}H_{26}N_4O_4Zn$: C, 65.87; H, 4.23; N, 9.04. Found: C, 65.41; H, 4.87; N, 9.57%. IR (KBr, cm^{-1}): ν(C=N) 1606; ν(C–$O_{phenoxo}$) 1211 cm^{-1}. ^{1}H NMR {300 MHz, DMSO–d_6, δ (ppm), J (Hz)}: 8.89 (—CH=N, s) 10.25–6.89 (9H, ArH), 3.83 (OCH_3, s).

2.2. Physical measurements

Elemental analyses for C, H and N were carried out using a Perkin–Elmer 240 elemental analyzer and ^{1}H spectra were measured on Bruker FT 300 MHz spectrometer. Infrared spectra (400–4000 cm^{-1}) were recorded from KBr pellets on a Nickolet Magna IR 750 series-II FTIR spectrophotometer. Fluorescence and absorption spectral studies were performed using Shimadzu spectrofluorimeter, model RF-5301PC (Shimadzu Corporation, Japan) and Shimadzu model UV-1800 spectrophotometer (Shimadzu Corporation, Japan) in matched quartz cells of 1 cm path length respectively. A thermo programmer was attached to both these instruments to maintain the temperature by peltier effect. Fluorescence lifetimes were determined from time-resolved intensity decay by the method of time-correlated single-photon counting (TCSPC) measurements using a picosecond diode laser (IBH Nanoled-07) in an IBH fluorocube apparatus. The fluorescence decay data were collected on a Hamamatsu MCP photo multiplier (R3809) and were analyzed by using IBH DAS6 software and a nano LED at 370 nm was used as the light source.

2.3. X-ray crystal structure determination

Single crystal X-ray data of complex **1** was collected on a Bruker SMART APEX-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at room temperature. Data processing, structure solution, and refinement were performed using the Bruker Apex-II suite program. All available reflections to $2\theta_{max}$ were harvested and corrected for Lorentz and polarization factors with Bruker SAINT Plus [36]. Absorption corrections, inter-frame scaling, and other systematic errors were performed with SADABS

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