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A NOVEL "TURN-ON" FLUORESCENT CHEMOSENSOR FOR THE SELECTIVE DETECTION OF ZN2+

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Abstract

The synthesis and evaluation of a novel 8-hydroxy quinoline derivatives based fluorescent chemosensor (L1, L2)for the detection of Zn2+ ions in THF/H2O. The fluorescent spectra changes observed upon addition of various metal ions show that L1, L2is highly selective for Zn2+ over other metal ions. Addition of Zn2+ to the solution of L1, L2 results in ratiometric measurement.The probe displayed an apparent color change, which could be observed by the naked eye under a UV lamp. Experimental results have been verified with DFT and TDDFT calculation. It's in vitro sensitivity to Zn2+was demonstrated in Hela cells with the use of confocal microscopy.

Introduction

Designing and synthesizing highly sensitive and selective chemo sensors for heavy metal ions have become increasingly important because of their close relationship with environmental, industrial, biological and human health.[1, 2]Chemosensors based on ion-induced changes in fluorescence appear to be particularly attractive due to their simplicity, high sensitivity and high selectivity response. [2] Therefore the detection of different metal ionssuch as Hg^{2+} [3], Pb^{2+} [4,5], Ni^{2+} [6,7], Cd^{2+}[8-10], etc..,cations[11,12]or neutral molecules[13,14]based on photoinduced electron transfer (PET) [15,16]have been reported.However, novel chemosensors are required to achieve the goal of extensively recognizing other heavy metal ions. Zinc is the second most abundant transition metal in the human body[17]since it is mostly trapped within proteins as a structural or catalytic cofactor, [18]and thereis a pool of Zn^{2+} which is loosely bound or present as chelate form in brain.[19] It is also known that the disturbance of Zn^{2+} metabolism is closely associated with severe neurological disease, including Alzheimer's disease(AD),[20]prostate cancer [21,22],cerebral ischemia,[23], and epilepsy.[24]In recent years the development of fluorescent sensors for zinc ions has become a very active area in the field of chemical biology.[13-22]

Fluorescence based sensing methodology has been preferred over other methods because of operational simplicity.[25]The common probes for Zn^{2+} are derivatives of zinquin, [26]8-aminoquinoline, [27]the Zinpyr family,[28] Zinbo-5,[29]coumarin,[30] and the TQEN[31] family. However, the development of fluorescent chemosensors does not have selectivity, it recognize one or more of the multiple analyst, especially species with similar chemical properties such as Mg^{2+}, Ca^{2+}, Zn^{2+}, Cd^{2+}, etc…,Biological imaging of specific molecules can provide direct information of molecular functions in living system. [32]The prostate Zn^{2+} concentrations are among the highest in the body, and a marked decrease in the level of these ions of these ions is observed in prostate cancer.[33]Among these recent publications of Zn^{2+} chemosensors, some Zn^{2+} chemosensors suffered from the cross interference of Cd^{2+} and/or Cu.[2+34-37] It is noteworthy that Lippard and coworkers have pioneered in this field by utilizing fluorescein as the fluorophoric platform for developing an array of Zn^{2+}chemosensors, allowing quantitative measurements of intracellular changes in zinc metal ion concentration.[38]Ratiometric sensor in which the ratio between one emission intensities can be used to evaluate the analyte concentrationand provide a built-in correction for environmental effects is a widely sought after sensing probe. To date, however, relatively few small-molecule ratiometric Zn^{2+} probes are available.[39-40]As a consequence, much focus has been devoted to the development of chemosensors for the recognition of Zn^{2+} (41–47). To best of our knowledge, there are few reports on zinc sensing based on 8-hydroxyquinoline-based multi-dentate ligand 2-(8-quinolinoxy) ethanohydrazide through imine formation mechanism.[48]

International Journal of Modern Agriculture, Volume 9, No. 4, 2020
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In this paper, we report a novel fluorescent sensor(L_1, L_2) based on fluorescein and 8-hydroxyquinoline as the receptor and highly selective, sensitive colorimetric fluorescent sensor for Zn^{2+}ions. The photo physical properties and recognition behaviors of the chemo sensor have been investigated in detail through UV−vis absorption spectra, fluorescence spectra, Mass, theoretical calculations and cell imaging were captured by Olympus FV-1000 laser scanning confocal fluorescence microscope.

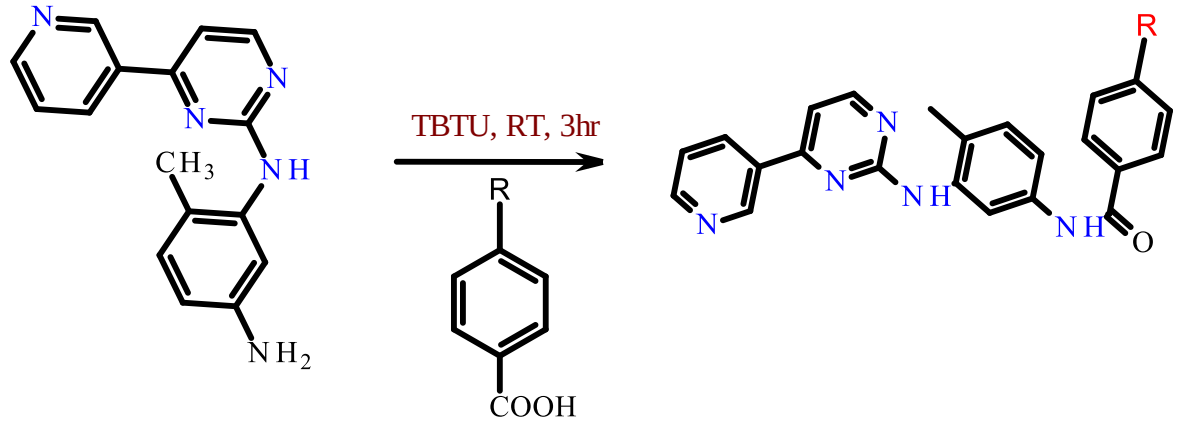
Experimental

Materials and methods

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H-NMR, ^{13}C-NMR were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as an internal standard and DMSO as asolvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz.Absorption spectra were determined on a JASCO V-550 UV–vis spectrophotometer equipped with an ETC-505 peltier thermos tatted single cell holder. Fluorescence spectra were determined on a JASCO FP-6500 spectrofluorimeter equipped with an ETC-273T peltier thermos tatted single cell holder. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. ESI mass was recorded using a Thermo Fleet-LC mass instrument.Fluorescence imaging was carried on an Olympus FV-1000 confocal microscope.

Result and discussion

The target compounds were synthesized from 6-methyl- N-(4-(pyridin-3-yl) pyrimidin-2-yl) benzene-1,3-diamine 8 (2 mmol), DMF (10 mL), and DIPEA (4 mmol) followed by substituted aromatic acid (2 mmol) was added and stirred at room temperature for 1 hr. After completion of the reaction mixture was poured into ice-cold water. The obtained yellow precipitate washed with water and dried to get target titled product pyrimidine scaffold benzamide derivatives (9 a-k). Yellow solid, Yield 90 %, FTIR (KBr, ν cm-1): 2360 (-C–H), 1644 (-C=O), 1585 (-N–H), 1549 (C=N), 1132 (C–N). 1H-NMR (300MHz, CDCl3) δ 9.80 (s, 1H), 9.01(s, 1H), 8.50-8.45 (m, 2H), 8.37-8.30 (m, 2H), 8.29-8.27 (m, 2H), 8.07 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.24 - 7.16 (m, 2H), 7.00 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 5.2 Hz, 1H), 2.10 (s, 3H). ES-MS (M+1) Calculated (m/z) 382.15, Found 383.1. Anal. Calcd. For C22H18N6O: C, 69.10; H, 4.74; N, 21.98%; Found: C, 69.06; H, 4.72; N, 21.99%.



Synthesis of sensor probe L1

International Journal of Modern Agriculture, Volume 9, No. 4, 2020
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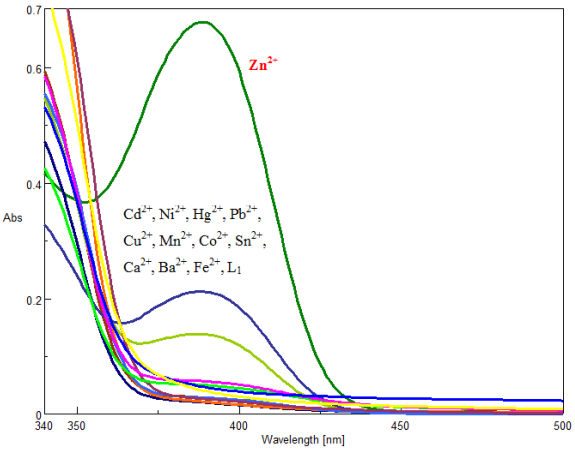

Figure-1UV-visible absorption spectra of compound L_1 (10 µM) in the presence of various metals perchlorate salts of Cd^{2+}, Ni^{2+}, Hg^{2+}, Pb^{2+}, Cu^{2+}, Mn^{2+}, Co^{2+}, Sn^{2+}, Ca^{2+}, Ba^{2+}, Fe^{2+} and Zn^{2+} (1 x 10^{-5}M) in(THF/H_2O).

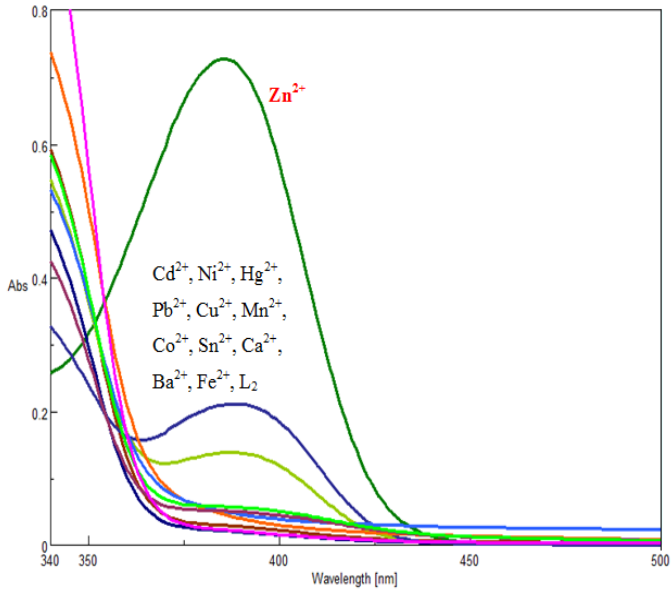

Figure-2UV-visible absorption spectra of compound L_2 (10 µM) in the presence of various metals perchlorate salts of Cd^{2+}, Ni^{2+}, Hg^{2+}, Pb^{2+}, Cu^{2+}, Mn^{2+}, Co^{2+}, Sn^{2+}, Ca^{2+}, Ba^{2+}, Fe^{2+} and Zn^{2+} (1 x 10^{-5}M) in (THF/H_2O).

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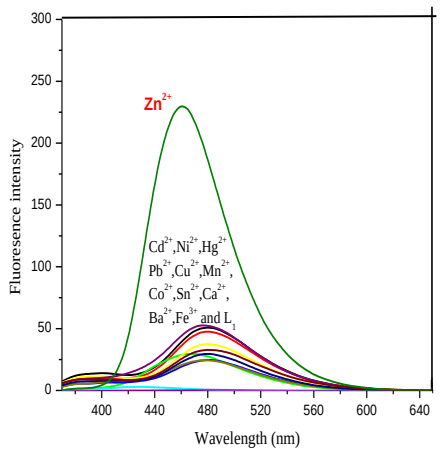


Figure-5Fluorescence emission profile of compound L_1(10 µM) in the presence of various metals perchlorate salts of Cd^{2+}, Ni^{2+}, Hg^{2+}, Pb^{2+}, Cu^{2+}, Mn^{2+}, Co^{2+}, Sn^{2+}, Ca^{2+}, Ba^{2+}, Fe^{2+} and Zn^{2+}(1 x 10^{-5}M) in (THF/H_2O). Excitation wavelength was 330 nm with 5cm slit width.

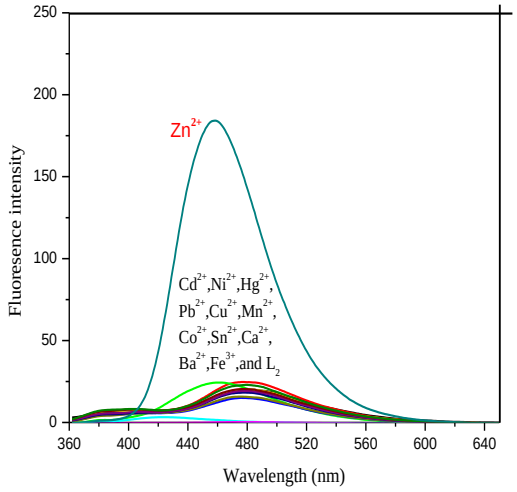
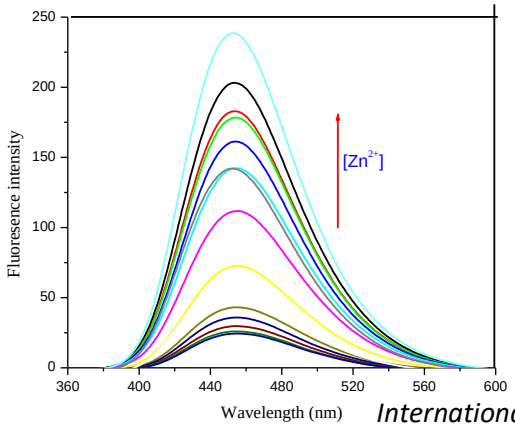


Figure-6 Fluorescence emission profile of compound L_2 (10 µM) in the presence of various metals perchlorate salts of Cd^{2+}, Ni^{2+}, Hg^{2+}, Pb^{2+}, Cu^{2+}, Mn^{2+}, Co^{2+}, Sn^{2+}, Ca^{2+}, Ba^{2+}, $Fe^{2+}$and Zn^{2+}(1 x 10^{-5}M) in (THF/H_2O). Excitation wavelength was 330 nm with 5cm slit width.



International Journal of Modern Agriculture, Volume 9, No. 4, 2020
ISSN: 2305-7246

Figure-7.Concentration-dependent fluorescence spectra of L_1(10 μM) on the addition of various amounts of Zn^{2+}(1.0×10^{-5}M) 0-1equivalents (THF/ H_2O). Excitation wavelength was 330 nm with 5cm slit width.

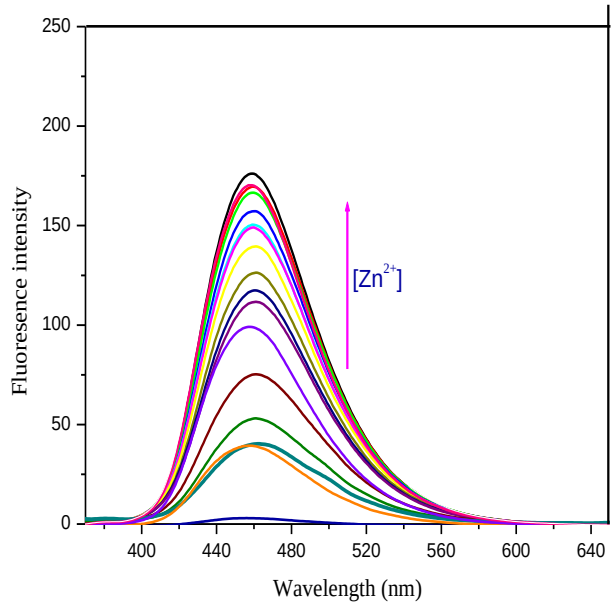


Figure-8.Concentration-dependent fluorescence spectra of L_2(10μM) on the addition of various amounts of Zn^{2+}(1.0×10^{-5}M) 0-1equivalents (THF/ H_2O). Excitation wavelength was 330 nm with 5cm slit width.

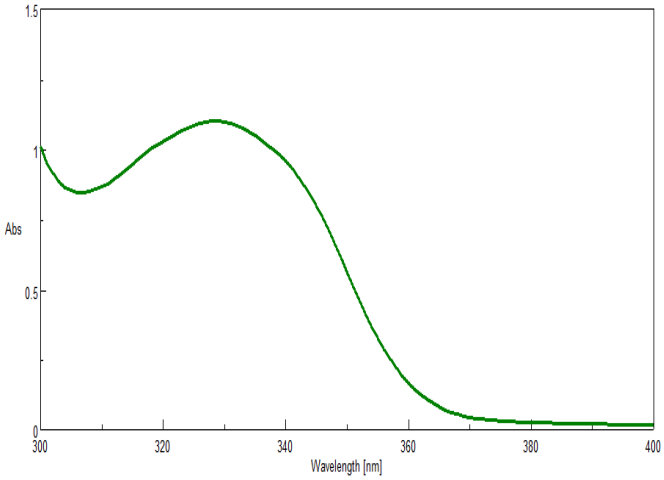


Figure-9UV-visible absorption spectra of compound L_1 (1.0×10^{-6}M) in THF solution.

Result and discussion

The probe L_1, $L_2$was synthesized one step condensation of pyrimidine scaffold benzamide derivatives in good yield (scheme 1). L_1, $L_2$was characterized by ^{1}H-NMR, ^{13}C-NMR and ESI-MS, (L_1, L_2) forms colorless and non-fluorescent solutions in organic solvent mixtures.

International Journal of Modern Agriculture, Volume 9, No. 4, 2020
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The absorption spectrum of (L_1,) shows absorption bands at 230 nm. Upon addition of 1equiv of Zn^{2+}ions to the(L_1,) the most significant changes were broadening of the absorption bands around 380–390 nm observed with hypochromism (Fig.1). This is also accountable for the color change from white to yellow. The absorption spectra of the (L_1) with several metal cations (Ca^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, and Sn^{2+}) using their Chloride salts in H_2O-THF (30: 70, v/v) are shown in (Fig.1). The UV-absorption studies of the probe L_1, clearly showed the selective response for Zn^{2+}. We checked the changes in its fluorescence properties of the probe L_1, $L_2$with the addition of metal ions like Cd^{2+}, Ni^{2+}, Cu^{2+}, Mn^{2+}, Pb^{2+}, Fe^{2+}, Hg^{2+}, Ca^{2+}, Sn^{2+}, Ba^{2+}, Co^{2+}, and Zn^{2+}(fig.5). Up on addition of Zn^{2+}, the probe becomes strongly fluorescent besides probe L_1, L_2 is non-fluorescent. Whereas addition other metal ions do not affect the photophysical properties of the probe. The increase absorbance and fluorescence intensity of the probe effected by the addition of Zn^{2+} ions not interfered with the other competing metal ions (fig.7). Increase the addition of Zn^{2+} ions also leads to increase in fluorescence maximum.

In the fluorescence titration spectra of L_1, L_2 with Zn^{2+} (0.1-1equiv) excited at 330 nm (fig.7), L_1, L_2 alone shows a weak fluorescence emission band at 468 nm with a quite weak fluorescence. When adding the Zn^{2+} to the solution, a gradual increase in fluorescence with a color change from colorless to blue is found.The sensing property of L_1, $L_2$for Zn^{2+} ion could be explained by the inhibition of isomerization of the C=N double bond. Imines are mainly non-fluorescent, in part due to the isomerization of the C=N double bond in the excited state.[33] The C=N isomerization may be inhibited upon the complexation with certain metal ions. Therefore, the stable chelation of L with zinc ions makes the C=N isomerization of L_1, L_2 inhibited (Scheme1), resulting in fluorescence enhancement. Moreover, the complexation of Zn^{2+} ion with L_1, L_2 induces rigidity in the resulting molecule and tends to produce a large chelation-enhanced fluorescence detection effect which induces the large enhancement of fluorescence. From the absorption and fluorometric results it is revealed that the probe L_1 is very selective and sensitive over other metal ions (Fig.8).In order to understand the binding ratio of Zn^{2+} with L_1 we carried out Jobs plot, this suggests 1:1 binding stoichiometry for the Zn^{2+}-L1 complex (Fig.9). The proposition is further augmented by the peak in the ESI-mass spectrum at m/z 458.45 corresponding to (L1+ Zn^{2+}-H^+).

To further understand the photophysical properties of L_1/Zn^{2+}, density functional theory (DFT) were carried out using a Gaussian 09 program.[49] Full geometry optimization of L_1 and its Zn complex were carried out using the DFT method at the B3LYP level of theory.[50, 51]The optimized configuration showed that one Zn^{2+} was occupied at the coordination center of L_1suitably and the complex formed a (Fig.10). The TDDFT calculations of L_1 and L_1 + Zn^{2+}, showed the possible transitions with their corresponding oscillator strength. In L_1 the transition at 333 nm (f=0.1143) with the major contribution from HOMO-1 to LUMO, whereas HOMO to LUMO transition at 308 nm (f=0.0021) is very weak. In L_1 + Zn^{2+} the HOMO- LUMO transition is observed at 477 nm (f=0.3040) whereas HOMO-1 to LUMO transition is observed at 360 nm (f = 0.0015) to very weak. In Probe L_1, HOMO-1 to LUMO is strong, it is reason for PET. In case of L_1-Zn^{2+} the HOMO-1 to LUMO transition is too weak, hence the photo induced electron transfer effect was arrested by Zn^{2+} coordination. The sensor must be capable of imaging the analyst specifically in living cells without the interference with other intra

cellular materials. We have measured the sensitivity of L_1 for Zn^{2+} in living Hela cells by fluorescence microscopy. First, HeLa cells incubated with the probe L_1 did not showed a fluorescence image (Fig.11). After incubation of the Probe treated cells with Zn^{2+} the bright blue fluorescence was observed when imaged through the confocal fluorescent microscope. The overlapping of the fluorescence and bright field images reveals that the fluorescence signals are localized in the intracellular area, indicating good cell membrane permeability of chemo sensor L_1. After further treatment with Zn^{2+}, the fluorescence vanished. The significant blue fluorescence from the intracellular region proves that the probe L_1 is applicable for imaging Zn^{2+} in living cells. The bio imaging in the Hela cells confirms the fluorescence enhancement with excellent cell permeability. It shows that L_1 is biocompatible in nature and used for detecting Zn^{2+} ions in cells rapidly.

International Journal of Modern Agriculture, Volume 9, No. 4, 2020
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Conclusion

In conclusion, we have reported a new fluorescence chemo sensor ($L_{1,}$) to detect $Zn^{2+}$with a good selectivity. The complexation of $L_1$with Zn^{2+} exhibited a pronounced enhancement in the fluorescence emission spectrum in THF/ H_2O, while many other ions such as Mn^{2+} ,Co^{2+} ,Ni^{2+} ,Cd^{2+} ,Hg^{2+} ,$Mg^{2+,}Ca^{2+}$ and Sn^{2+}etc... have no influence.

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International Journal of Modern Agriculture, Volume 9, No. 4, 2020
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