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ORIGINAL PAPER

A Highly Selective Turn-on Fluorescent Chemodosimeter for Cu^{2+} Through a Cu^{2+}-Promoted Redox Reaction

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Abstract A highly sensitive and selective photoinduced electron transfer (PET) fluorescence chemodosimeter L for Cu^{2+} detection has been synthesized and characterized. This PET chemosensor composed of a butano-tethered electron-riched phenothiazine (Ptz) donor and acridine orange (AO) signalling element. Based on the Cu^{2+}-promoted oxidation of Ptz donor, the signalling element AO showed a unique fluorescent turn-on properties, which led to a highly Cu^{2+}-specific fluorescent chemodosimeter. A fluorescent enhancement factor over 8-fold can be reached by fully blocking the PET channel with a detection limit down to the 10^{-7} M range. Meanwhile, the reversibility of the chemodosimeter L can be realized by the addition of L-cysteine.

Keywords Fluorescence spectroscopy · Sensor · Acridine orange · Copper ion · Redox reaction

Introduction

A great deal of interest currently exists for the development of highly selective and sensitive sensors for the detection of environmentally and biologically important species, such as heavy metal ions, anions etc. [1–4]. Among the essential heavy metal ions in human body, Cu^{2+} is third in abundance after Fe^{3+} and Zn^{2+} and it is an important transition element in biological systems [5]. Deficiency or excessive levels of Cu^{2+} ions in the neuronal cytoplasm may cause some neurodegenerative diseases, such as Menkes and Wilson's diseases, gastrointestinal disorders, kidney damage, Alzheimer's disease and familial amyotropic lateral sclerosis [6–12]. In addition, copper is also considered as a significant environmental pollutant [13, 14]. Thus, design and development of highly selective luminescence based sensors for detection of copper ions for biological and environmental monitoring is significant for life sciences and environmental sciences [15–19]. According to Irving-Williams order of stability of transition metal ions, Cu^{2+} ion has the maximum stability [20, 21], however, the design of highly selective molecular sensors for metal ions is of great difficulty due to the paramagnetic nature of Cu^{2+} ions [22–32]. To date, a variety of Cu^{2+} probes exhibiting either fluorescence 'on-off' or 'off-on' signaling modes have been reported [33–40]. Although many of them showed binding selectivity to Cu^{2+} over other cations such as Fe^{3+} and Hg^{2+}, the interferences aroused from Co^{2+}, Fe^{2+}, Ni^{2+}, Zn^{2+} etc. could not be eliminated in many cases [41–48]. Significantly, the molecular design of highly sensitive and selective turn-on fluorescence chemosensor for copper is still a challenging but extremely attractive method because of their important features.

Among the reported sensing molecules, fluorophores with a fluorescent switching property driven by photoinduced electron transfer (PET) are often employed to signal metal ion binding. When a metal ion binds to the receptor module, the quenching interaction is cut off and shows a fluorescent enhancement via chemical reactions promoted by metal ions [49, 50]. However, the molecular design for Cu^{2+}-selective chemosensor via a chelate-binding module is still quite challenging by taking advantage of PET mechanism not only for the paramagnetic nature of Cu^{2+} ions, but also for it is difficult

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to eliminate the interferences aroused from other chemically close ions. Recently, fluorescence sensing method produced by the analyte-promoted specific reaction (chemodosimeter) has showed to be a promising way for highly sensitive and selective detections. For the fluoro- and chromogenic signal just released by the analyte-promoted specific reaction, this measurement may circumvent adverse effects on fluorescence signals promoted by other chemically close ions [51, 52]. Due to the fact that the fluorescent product does not coordinate to the analytes, this method is particularly important for producing high efficient turn-on fluorescent chemosensors for heavy metal ions and paramagnetic metal ions detection. However, Cu^{2+} specific chemodosimeters are still very rare [53, 54].

Herein, we report a selective 'turn-on' fluorescent chemodosimeter L for Cu^{2+} which acts by way of PET inhibition mechanism via a Cu^{2+}-promoted redox reaction. The chemodosimeter L is a butano-tethered conjugate of acridine orange (AO) and phenothiazine (Ptz). The choice of AO as fluorescence signal reporter was for construction of molecular sensors because of its advantageous characteristics, such as sharp absorption and fluorescence bands, high extinction coefficients, high fluorescence quantum yields, and high stability against light and chemical reactions [55, 56]. Indeed, AO is widely used in several areas such as photochemistry, photophysics, photocatalysis, chemiluminescence, energy transfer and photoinduced electron transfer [57]. Meanwhile, it has also been used extensively as a fluorescent signaling unit for nucleic acids in agarose and polyacrylamide gels and for cell staining of DNA in apoptosis studies [58–62]. On the other hand, as a stronger electron-donating unit, Ptz has been widely used in the field of photoelectronic devices. It has also been used for the treatment of neurodegenerative diseases [63, 64]. By combining the merits of the fluorescence signal reporter AO and the electron-donating Ptz, the chemodosimeter L showed excellent selectivity for Cu^{2+} over relevant competing metal ions with a fluorescent enhancement factor of 8-fold by inhibiting a photoinduced electron transfer (PET) quenching pathway via the Cu^{2+}-promoted oxidation of the electron-donating Ptz unit, thus resulting in the enhancement of fluorescence, and with the detection limit reaching the 10^{-7} M range.

Experimental

All cations in the form of nitrate salts, all anions in the form of sodium salts were purchased from Sigma-Aldrich Chemical Company and used without further purification. All other chemicals used were local products of analytical grade. All solvents (analytical grade and spectroscopic grade) were obtained commercially and used as received unless otherwise mentioned. NMR spectra were recorded on a Bruker spectrometer at 400 (^{1}H NMR) MHz and 100 (^{13}C NMR) MHz. Chemical shifts (δ values) were reported in ppm down field from internal Me4Si (^{1}H and ^{13}C NMR). High-resolution mass spectra (HRMS) were acquired on an Agilent 6510 Q-TOF LC/MS instrument (Agilent Technologies, Palo Alto, CA) equipped with an electrospray ionization (ESI) source. Elemental analyses were performed on a Vanio-EL elemental analyzer (Analysensystem GmbH, Germany). UV absorption spectra were recorded on a UV-2550 UV–VIS spectrophotometer (Shimadzu, Japan). Fluorescence measurements were performed using an F-4600 fluorescence spectrophotometer (Hitachi, Japan) and a quartz cell (1 × 1 cm). Melting point was recorded on a Boethius Block apparatus and was uncorrected.

Preparation of N-(4-Bromobutyl) Phenothiazine (1) Phenothiazine (2.06 g, 10.34 mmol) was stirred in a slurry of sodium hydride (60 % dispersion in mineral oil, 3.0 equivalents) in dry DMF (20 mL) at 0 °C for 1 h. 1,4-Dibromobutane (2.0 equivalents) was added dropwise and the suspension was stirred at 0 °C for 4 h. The reaction mixture was poured into water (200 mL). The crude product was extracted with CH_2Cl_2 (3 × 30 mL), and dried over Na_2SO_4. The crude product was then purified by column chromatography (SiO_2, petroleum ether 100 %) to give 1 (2.43 g, 70 % yield) as a colorless stick oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.01 (m, 4H), 3.43 (t, J=8.0 Hz, 2H), 3.94 (t, J=6.0 Hz, 2H), 6.90 (d, 2H), 6.96 (t, J=8.0 Hz, 2H), 7.18–7.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 27.6, 30.7, 33.4, 46.2, 115.4, 116.7, 122.4, 125.5, 127.6, 135.0. Anal. Calcd for $C_{16}H_{16}BrNS$: C: 57.49, H: 4.82, N: 4.19; Found: C: 57.61, H: 4.66, N: 4.25.

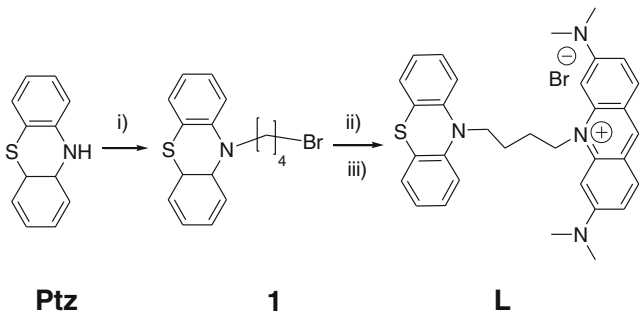
Preparation of 10-[4-(4a,10a-Dihydrophenothiazin-10-yl)-Butyl]-3,6-Bisdimethylaminoacridinium (L) Commercial available acridine orange base (5.0 g) was washed with concentrated ammonia (10 mL) three times to remove the coordinated zinc salt. The insoluble solid materials were collected by filtration, and then dried over Na_2SO_4. Then, a mixture of acridine orange (531 mg, 2.01 mmol) and *N*-(4-bromobutyl) phenothiazine (1) (700 mg, 2.08 mmol) in 30 mL toluene was refluxed for 20 h. After cooling to room temperature, the solid product was filtered and washed with toluene (3 × 5 mL) and ether (3 × 5 mL), respectively. The solid product was dissolved in dichloromethane (15 mL) and ethanol (15 mL), and then KBF_4 (1.0 g) was added in one portion. The suspension was refluxed for 3 h in dark for anion exchange. The insoluble inorganic salts were filtered out. The filtrate was condensed to dryness. The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5:1, v/v) to give L as red powder (668 mg, 60 % yield); m.p. 248–250 °C; HRMS: 519.2577 $(M\text{-}BF_4^-)^+$; cald: 519.2577; ^{1}H NMR (300 MHz, DMSO-d_6, ppm): 1.98 (m, 4H), 3.23 (s, 12H), 3.97 (t, J=5.3 Hz, 2H), 4.75 (t, J=5.0 Hz, 2H), 6.60 (s, 2H), 6.90 (t, J=7.5 Hz, 2H), 6.99 (d, 2H), 7.08–7.15 (m, 4H), 7.26 (d, 2H) 7.90 (d, 2H), 8.75 (s, 1H); ^{13}C NMR (100 MHz,

DMSO-d_6, ppm): 23.4, 24.2, 39.8, 40.4, 46.7, 114.7, 116.5, 116.9, 123.0, 124.4, 127.6, 127.9, 128.0, 133.4, 142.5, 143.2, 145.1. Anal. Calcd for $C_{33}H_{35}BF_4N_4S\cdot 2H_2O$: C: 61.68, H: 6.12, N: 8.72; Found: C: 61.91, H: 6.05, N: 8.74.

Results and Discussion

As shown in Scheme 1, 1 was prepared in 70 % yield by the reaction of phenothiazine with 1,4-dibromobutane in sodium hydride (60 % dispersing in mineral oil) in dry DMF at 0 °C. Then, L was facilely obtained by the reaction of acridine orange with 1 in 60 % yields. The anion exchange was achieved by refluxing the ethanol solutions L with excess KBF_4. The structure of L was confirmed by HRMS, NMR and elemental analysis (Fig. S1-S5, ESI).

We investigated the spectral properties of L and optimized its reaction conditions with Cu^{2+} by electronic absorption spectra and fluorescence spectra. As shown in Fig. 1, L showed a weak fluorescence emission intensities in acetonitrile, ethanol, water and the mixture solvents of acetonnitrile/water (1:1, v/v), and ethanol/water (1:1, v/v). Upon addition of Cu^{2+}, L showed a prominent fluorescence enhancement in acetonitrile, however, only weak fluorescence changes were observed in other solvents systems, indicated that acetonitrile is the best solvent to adjust the redox potential between Cu^{2+} ions and the Ptz unit within L. Meanwhile, L in acetonitrile exhibited a maximal absorption at 498 nm ($\varepsilon = 5.21\times 10^4\ M^{-1}\ cm^{-1}$). The absorbance at 498 nm decreased smoothly in the presence of different concentrations of Cu^{2+} (0–100 equivalents). The decrease of the absorption intensity at 498 nm in this concentration range complied with the equation y = 0.46018–0.00314× and with correlation coefficient R= −0.9902 (Fig. S6, ESI). At the same time, upon the addition of Cu^{2+}, the color of the solution immediately changed from pink-red to light-green, indicating that L can serve as a 'naked-eye' chemodosimeter for Cu^{2+} (Fig. 1).



Scheme 1 Structure and the synthesis of the chemodosimeter L. Reagents and conditions: i) 1,4-dibromobutane, NaH, 0 °C, 1 h; ii) 1 and AO in toluene, 110 °C, 20 h; iii) KBF_4, refluxed for 3 h in ethanol

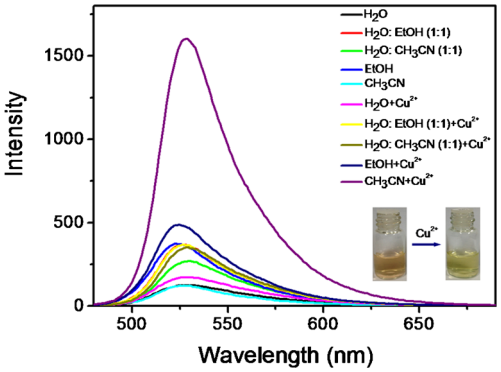


Fig. 1 Fluorescence spectra of the chemodosimeter L (10.0 μM) upon addition of Cu^{2+} (10 equivalents) in different solvents. Inset shows the characteristic color change of L from *pink-red* to *light-green* in acetonitrile. λ_{ex}=460 nm, Slit: 2.5 nm; 5.0 nm

Figure 2 shows the fluorescence spectrum of the chemodosimeter L and those in the presence of different amounts of Cu^{2+}. As displayed in Fig. 2, the chemodosimeter L showed a very weak emission band centered at 528 nm due to the fluorescence of the chemodosimeter L being quenched by the efficient PET process from the strong electron-donating Ptz unit to the electron-accepting AO unit. The titration of Cu^{2+} into L triggered a strong fluorescence enhancement with the increase of Cu^{2+} concentration, indicated that the PET channel from the electron-donating Ptz unit to the electron-accepting AO unit can be efficiently blocked by the Cu^{2+}-promoted oxidation of electron-riched Ptz donor. The enhancement of emission intensity in Cu^{2+} titrations saturated at the addition of about 40 equiv. of Cu^{2+}. The increase of the fluorescence intensity at 528 nm followed the sigmoidal curves and the fluorescence turn-on constant ($K_{turn\text{-}on}$) was calculated as 115±18 μM (with correlation coefficient R= 0.996) where $K_{turn\text{-}on}$ represents the conversion of the weak fluorescent L to the high fluorescent oxidized form of AOPtzO by the Cu^{2+}-promoted oxidation of Ptz donor (Fig. S7, ESI) [65]. The HRMS mass spectra showed clear

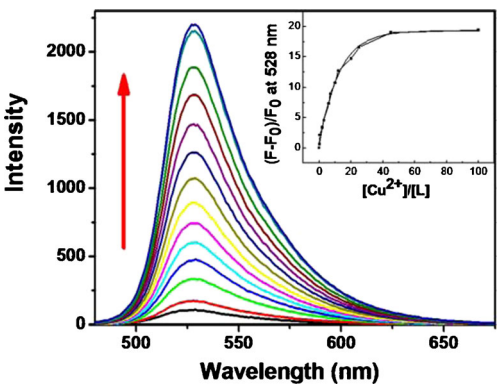
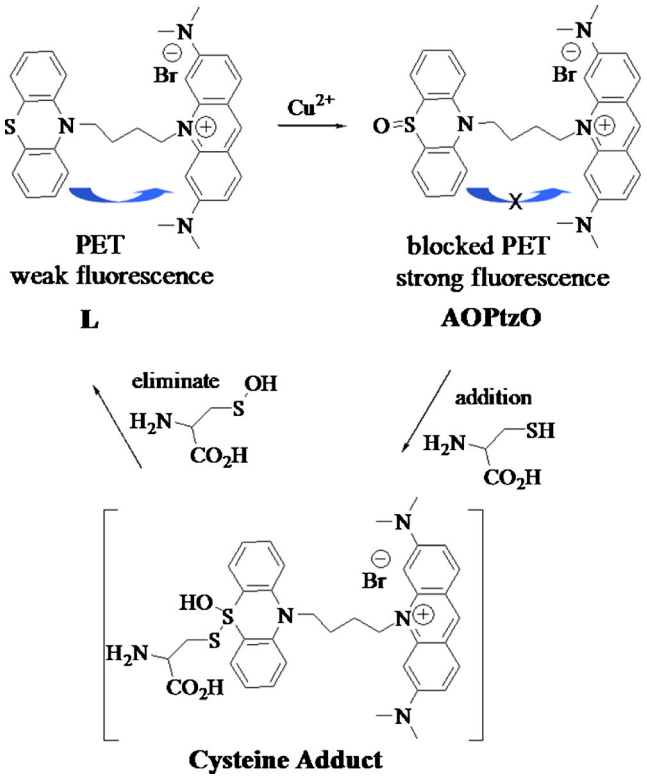


Fig. 2 Fluorescent titration spectra of the chemodosimeter L (10.0 μM) in the presence of different concentrations of Cu^{2+} in CH_3CN, Inset: the fluorescence at 528 nm of L (10.0 μM) as a function of the Cu^{2+} concentration. λ_{ex}=460 nm, Slit: 2.5 nm; 5.0 nm

peaks (m/z) of the oxidized form of L (AOPtzO-BF_4^-) at 535.2577 (Fig. S8, ESI). The stoichiometric ratio of the reaction between the chemodosimeter L and Cu^{2+} was estimated to be 1:1 by Job's plot yielded from fluorescence spectrum (Fig. S9, ESI) [66]. From the changes in Cu^{2+}-dependent fluorescence intensity (Fig. S10, ESI), the detection limit was estimated to be 2.3×10^{-7} M [67, 68], indicating that the limit of detection of L for Cu^{2+} accorded with the requirement for the limit of heavy metals of raw medicine in the Chinese pharmacopoeia, which should be 10 μg/g (approximately 156 μM for Cu^{2+}) [69]. Similar fluorescence enhancement was observed for L after the addition of Cu^{2+} salts with different counteranions (AcO^-, BF_4^-, Br^-, ClO^-, ClO_4^-, F^-, $H_2PO_4^-$, HCO_3^-, HO_4^{2-}, HSO_4^-, NO_2^-, NO_3^-, and SO_4^{2-}) (Fig. S11, ESI), suggesting that the counteranions don't influence the Cu^{2+}-promoted reaction and L can be used as a selective fluorescent chemodosimeter for copper ions in the presence of a wide range of the environmentally relevant anions.

Due to the reversibility is a prerequisite in fabrication of novel chemosensors for practical application, the reversibility of the recognition process of the chemodosimeter L toward Cu^{2+} was performed by adding the reducing reagent L-cysteine. Scheme 2 illustrated the redox cycling capacity of S atom between the conversions of S (II) in L and S (IV) in AOPtzO via cysteine addition and cysteine sulfenic acid elimination procedures [70]. As shown in Fig. 3, the addition of L-cysteine to a mixture of L and Cu^{2+} resulted in diminution of the fluorescence intensity at 528 nm, which indicated that the oxidized probe (AOPtzO) was reduced to the weak fluorescent L by L-cysteine. The fluorescence was recovered by the addition of Cu^{2+} again. This observation indicates the reversibility of L, which is important for the fabrication of devices to sense the Cu^{2+} ion.



Scheme 2 Schematic representation of the reversibility of L among the conversions between S (II) in L and S (IV) in AOPtzO

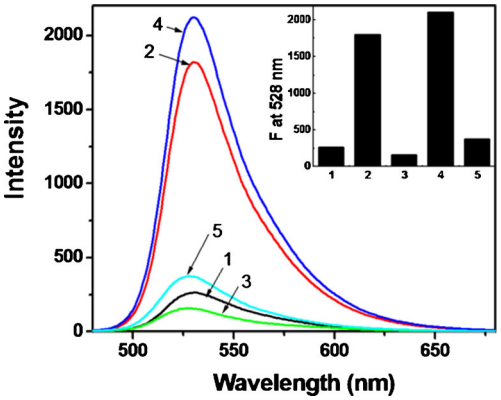


Fig. 3 The reversibility reaction of the chemodosimeter L and Cu^{2+} with the addition of L-Cysteine. Fluorescence spectra of L (10.0 μM) upon the addition of 20 equivalents of Cu^{2+} in CH_3CN. L-Cysteine (60 equivalents) was added to L + Cu^{2+} mixture to show the reversible binding nature of Cu^{2+} with L. Inset: Histogram representing the fluorescence intensity of L and Cu^{2+} with the addition of L-Cysteine at 528 nm in the presence of copper catalysts (*bottom*). (1) L; (2) L+20 equivalents Cu^{2+}; (3) L+20 equivalents Cu^{2+}+60 equivalents Cys; (4) L+40 equivalents Cu^{2+}+60 equivalents Cys; (5) L+40 equivalents Cu^{2+}+120 equivalents Cys. λ_{ex}=460 nm, Slit: 2.5 nm; 5.0 nm

Subsequently, we evaluated the response of the chemodosimeter L to other metal ions. As shown in Fig. 4, the addition of 20 equivalents of Ag^+, Al^{3+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Fe^{3+}, Hg^{2+}, K^+, Mg^{2+}, Na^+, NH_4^+, Ni^{2+}, Pb^{2+}, and Zn^{2+} has no obvious effect on the fluorescence emission. Among

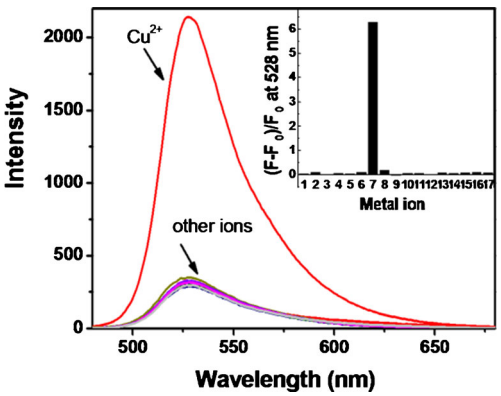


Fig. 4 Fluorescence spectra of the chemodosimeter L (10.0 μM) upon the addition of the nitrate salts (20.0 equivalents) of metal ions in CH_3CN. Inset: histogram representing the fluorescence enhancement and quenching of L in the presence of metal ions. (1) Ag^+; (2) Al^{3+}; (3) Ca^{2+}; (4) Cd^{2+}; (5) Co^{2+}; (6) Cr^{3+}; (7) Cu^{2+}; (8) Fe^{2+};(9) Fe^{3+}; (10) Hg^{2+}; (11) K^+; (12) Mg^{2+}; (13) Na^+; (14) NH_4^+; (15) Ni^{2+}; (16) Pb^{2+}; (17) Zn^{2+}. For the entire test, excitation and emission were performed at 460 and 528 nm

the metal ions examined, L showed a selective fluorescence increase only with Cu^{2+}. The addition of 20 equivalents Cu^{2+} resulted in a prominent enhancement of the emission intensity (with an enhancement factor over 6-fold) positioned at 528 nm. Even though Cu^{2+} ion has the maximum stability through receptor/ligand interactions according to Irving-Williams order [20, 21], many of chemosensors based on the receptor-Cu^{2+} binding mode exhibited low to moderate affinity for other chemically close metal ions, such as Co^{2+}, Fe^{2+}, Ni^{2+}, Hg^{2+}, Zn^{2+} etc. Comparatively, chemodosimeters based on the ions-promoted chemical reaction normally provided a very highly specific detection method [51, 52]. Thus, the method by blocking of the PET channel of L via this type specific Cu^{2+}-promoted oxidization of the electron-donating Ptz unit can function as a highly selective fluorescence PET chemodosimeter for Cu^{2+} ions.

To further explore the utility of L as an ion-selective fluorescent chemodosimeter for Cu^{2+}, the competition experiments were performed in which L (10.0 μM) was first mixed with 20 equivalents of various metal ions, and then 20 equivalents of Cu^{2+} was added. The fluorescence spectra were exploited to monitor the competition events. As can be seen from Fig. 5, no strong interference was observed in the presence of 20 equivalents of a series of metal ions. Upon the addition of Ag^{+}, Al^{3+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Fe^{3+}, Hg^{2+}, K^{+}, Mg^{2+}, Na^{+}, NH_4^{+}, Ni^{2+}, Pb^{2+}, and Zn^{2+}, the emission spectra are almost identical to that obtained in the presence of Cu^{2+} alone. The results demonstrated that the chemodosimeter L is able to discriminate between Cu^{2+} and chemically close ions, especially Co^{2+}, Fe^{2+}, Ni^{2+}, Hg^{2+}, Zn^{2+} which are common interfering ions in many cases are eliminated [33–40].

As copper salts have been widely used as novel catalyst in the manufactures of dyes, pharmaceuticals, and many other fine chemicals [71], the detection of residual Cu^{2+} in pharmaceuticals and these chemicals is very necessary. For practical

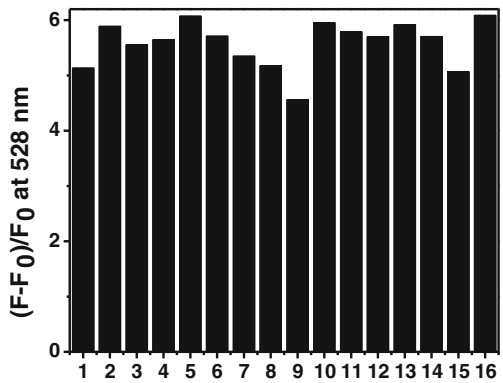


Fig. 5 Change ratio ((F - F_0)/F_0) of fluorescence intensity of L upon the addition of 20 equiv. Cu^{2+} in the presence of 20 equiv. background metal ions in CH_3CN. (1) Cu^{2+}; (2) Cu^{2+} + Ag^{+}; (3) Cu^{2+} + Al^{3+}; (4) Cu^{2+} + Ca^{2+}; (5) Cu^{2+} + Cd^{2+}; (6) Cu^{2+} + Co^{2+}; (7) Cu^{2+} + Cr^{3+}; (8) Cu^{2+} + Fe^{3+}; (9) Cu^{2+} + Hg^{2+}; (10) Cu^{2+} + K^{+}; (11) Cu^{2+} + Mg^{2+}; (12) Cu^{2+} + Na^{+}; (13) Cu^{2+} + NH_4^{+}; (14) Cu^{2+} + Ni^{2+}; (15) Cu^{2+} + Pb^{2+}; (16) Cu^{2+} + Zn^{2+}

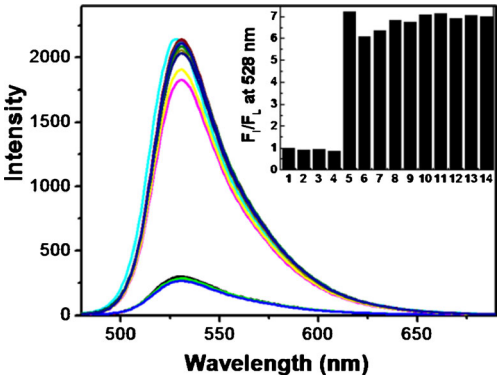


Fig. 6 Fluorescence intensity changes of L (10.0 μM) in the presence of commonly found copper catalysts (20 equivalents) in CH_3CN. Inset: Histogram representing the fluorescence enhancement (F_i / F_L) of L at 528 nm in the presence of copper catalysts (*bottom*). (1) L; (2) L + A_1; (3) L + A_2; (4) L + A_3; (5) Cu $(NO_3)_2$; (6) Cu $(NO_3)_2$ + A_1; (7) Cu $(OAc)_2$ + A_1; (8) $CuCl_2$ + A_1; (9) Cu $(NO_3)_2$ + A_2; (10) Cu $(OAc)_2$ + A_2; (11) $CuCl_2$ + A_2; (12) Cu $(NO_3)_2$ + A_3; (13) Cu $(OAc)_2$ + A_3; (14) $CuCl_2$ + A_3. λ_{ex}=460 nm, Slit: 2.5 nm; 5.0 nm

applicability, L was used to the analog detecting of copper residual in chemicals which might be obtained by the reaction of amine with aryl halide under copper catalytic conditions. Thus, we chose amines, such as *N*,*N*-dimethyl aniline (A1), aniline (A2) and triphenylamine (A3) to mimic the detecting of copper residual (Fig. 6). At the first step, we tested the ability of the chemodosimeter L to respond to Cu^{2+} in the above amines A1-A3. In the absence of the Cu^{2+} ions, no remarkable emission intensity enhancement were observed, which means the absence of the Cu^{2+} ions in these chemicals. Next, the responses of L to Cu^{2+} ions in samples spiked with Cu $(NO_3)_2$, Cu $(OAc)_2$ and $CuCl_2$ were investigated. In each case, L showed prominent fluorescence turn-on effect of the emission band at 528 nm. For further considering the chemodosimeter L can quantization detecting the Cu^{2+}-contaminated chemical samples, A3-spiked samples and those in the presence of an incremental amount of Cu^{2+} were analyzed by fluorescence titrations. The intensity of the fluorescence emission band at 528 nm showed a steady and smooth linear increase with the increase of the Cu $(NO_3)_2$ concentration (0–10 equivalents) (Fig. S12, ESI). This result indicated that L could detect of Cu^{2+} residual in these chemicals with significantly more complex composition than laboratory conditions.

Conclusion

In summary, we have successfully developed a highly selective and sensitive chemodosimeter L for Cu^{2+} detection. Based on the blocking of PET channel from the electron donating Ptz unit to the AO fluorophore by the specific Cu^{2+}-promoted oxidation of the Ptz unit, it shows a

remarkably high ability to discriminate between Cu^{2+} and other chemically close ions and with a detection limit down to the 10^{-7} M range. The reversibility of L can be realized by the addition of L-cysteine, which is important for the fabrication of devices to sense the Cu^{2+} ion. Furthermore, L was shown to be a promising potential selective fluorescent chemodosimeter for the direct quantitative measurement of residual copper species in drug chemicals.

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