Dyes and Pigments 162 (2019) 303–308

Contents lists available at ScienceDirect

Dyes and Pigments

journal homepage: www.elsevier.com/locate/dyepig

A simple and easy-to-prepare imidazole-based probe for the selective chromo-fluorogenic recognition of biothiols and Cu(II) in aqueous environments

Hazem Essam Okda[a,b,c], Sameh El Sayed[a,b,c], Ismael Otri[a,b,c], Rosa C.M. Ferreira[d], Susana P.G. Costa[d], M. Manuela M. Raposo[d,*], Ramón Martínez-Máñez[a,b,c,**], Félix Sancenón[a,b,c]

[a] Instituto Interuniversitario de Investigación de Reconocimiento Molecular y Desarrollo Tecnológico (IDM), Universitat Politècnica de València, Universitat de València, Spain
[b] Departamento de Química, Universitat Politècnica de València, Camino de Vera s/n, 46022, València, Spain
[c] CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Spain
[d] Centro de Química, Universidade do Minho, Campus de Gualtar, 4710-057, Braga, Portugal

ARTICLE INFO

Keywords:
Biothiols
Chromo-fluorogenic detection
Cu(II) complex
Displacement assay

ABSTRACT

A new simple and easy-to-prepare imidazole-based probe **1** was synthesized and used to detect Cu(II) and biothiols (Cys, Hcy and GSH) in aqueous environments. Addition of increasing amounts of Cu(II) to water (pH 7.4)-acetonitrile 90:10 v/v solutions of probe **1** induced the apperance of a red-shifted absorption together with a marked colour change from colorless to deep blue. In addition, probe **1** was fluorescent and a marked emission quenching in the presence of Cu(II) was observed. The optical response is selective and other cations tested do not induce significant chromo-fluorogenic modulations. Limits of detection for Cu(II) of 0.7 and 3.2 μM using UV–visible and fluorescence data were determined. On the other hand, addition of Cys, Hcy and GSH to the deep-blue water (pH 7.4)-acetonitrile 90:10 v/v solutions of the **1**-Cu(II) complex reulted in a marked bleaching together with the appearance of a highly emissive band centred at 475 nm. Other amino acids tested induced negligible response. The limits of detection for Cys, Hcy and GSH using **1**-Cu(II) and emission data are 6.5, 5.0 and 10.2 μM, respectively. These optical changes were ascribed to a biothiol-induced demetallation process of the **1**-Cu(II) complex that released the free probe. Besides, probe **1** is non-toxic and can be used for Cu(II) detection in HeLa cells.

1. Introduction

Transition metal cations are involved in several vital processes and are also used as diagnostic tools in medical, physiological and environmental fields [1–3]. In this scenario, the development of techniques for monitoring transition metal cations is an active area of research. Among transition metal cations, Cu(II) is the third most abundant essential element in the human body and plays vital roles in several physiological processes [4–9]. For instance, it has been reported that Cu(II) stimulates the proliferation of endothelial cells and is necessary for the secretion of several angiogenic factors by tumour cells [10,11]. Aside from its biological and environmental importance, copper is widely used in metallurgical, pharmaceutical and agrochemical industries [12]. As a result of the extensive applications of Cu(II) in life science and industry, it has become one of the first hazard environmental pollutants [13]. Despite the important role played by Cu (II) in several biological processes, abnormal levels of this cation can cause serious health problems on humans due to its ability to displace other vital metal ions in some enzyme-catalysed reactions [14]. In addition, high concentrations of Cu(II) in cells was documented to cause toxicity and different neurodegenerative diseases such as Menkes, Wilson's and Alzheimer [15]. Therefore, simple and rapid sensing tools to monitor Cu(II) levels in biological and environmental media is of importance.

In the past years, electrochemical methods, spectrometry and chromatography have been employed to detect Cu(II). However, these methods are limited by their relatively high costs, are time consuming and are not usually suitable for *in situ* and *on site* analysis. As an

* Corresponding author. Centro de Quimica, Universidadde do Minho, Braga, Portugal.
** Corresponding author. Instituto Interuniversitario de Investigación de Reconocimiento Molecular y Desarrollo Tecnológico (IDM), Universitat Politècnica de València, Universitat de València, Spain.
E-mail addresses: mfox@quimica.uminho.pt (M.M.M. Raposo), rmaez@qim.upv.es (R. Martínez-Máñez).

https://doi.org/10.1016/j.dyepig.2018.10.017
Received 22 May 2018; Received in revised form 11 July 2018; Accepted 11 October 2018
Available online 12 October 2018
0143-7208/

alternative to these classical methods, the use of chemical optical probes has attracted great attention in the last years and several Cu(II) sensors have been reported [16]. Some of these probes are able to detect Cu(II) both in solution (by colour and/or emission changes) and in living cells (by using confocal microscopy) [17–21]. In spite of these interesting features, some of these probes operate in organic solvents and often presented poor selectivity [22,23]. Thus, the preparation of selective probes that can detect Cu(II) in water or water/organic solvents mixtures is still a matter of interest.

On the other hand, biothiols (GSH, Cys and Hcy) are molecules that play fundamental roles in living systems because are involved in many important biological processes (such as tissue growth and defences) [24,25]. Dysregulation of biothiol levels could induce the appearance of certain diseases such as Alzheimer and cardiovascular disorders [26,27]. For the above mentioned reasons, the sensitive and selective detection of biothiols has been a matter of concern. In this respect, in the last years, several probes for the chromo-fluorogenic detection of biothiols have been published [28–31]. Most of the published examples are designed following the chemodosimeter paradigm, which makes use of the high nucleophilic reactivity of the thiol group. For example, biothiols reaction with fluorophores containing aldehyde [32–34], and 4-methoxythiophenol moieties [35,36] are recently reported. Besides, hydrolysis reactions induced by biothiols coupled with emission changes are also used [37,38]. However, among different approaches used for the design of biothiol chemosensors the use of Cu(II) complexes is perhaps one of the most promising. These probes worked using the well-known indicator displacement assay (IDA) paradigm [39,40]. These IDA assays are based on the use of fluorescent probes that coordinate selectively with Cu(II) (a highly effective quencher). As a consequence a non-emissive complex is formed. In the presence of biothiols, the non-emissive complex is demetallated (due to the preferential binding of Cu(II) with the thiol moieties in the biothiols) restoring the fluorescence of the free fluorophore. Using this IDA approach several systems for biothiols detection have been recently published [41–46].

Bearing in mind our experience in the development of molecular probes for detection of anions, cations and neutral molecules of biological and environmental significance [47–52], we report herein the synthesis and sensing behaviour of a new imidazole-based easy-to-prepare chromo-fluorogenic probe **1** able to detect Cu(II) in water (pH 7.4)-acetonitrile 90:10 v/v mixtures. Besides, the complex formed between probe **1** and Cu(II) was used for the selective chromo-fluorogenic detection of relevant biothiols (Cys, Hcy and GSH). Probe **1** was also successfully used for detection of Cu(II) in living cells.

2. Experimental section

Chemicals: Commercially available reagents 4-(dimethylamino) benzaldehyde (**1a**), 1,2-di(thiophen-2-yl)ethane-1,2-dione (**1b**), ammonium acetate, $Na_2S_2O_3$, and I_2 were purchased from Sigma-Aldrich and Acros and used as received. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel $60F_{254}$) and spots were visualized under UV light. Chromatography on silica gel was carried out on Merck Kieselgel (230–240 mesh). All the metal salts used for the UV–visible and fluorescence experiments are nitrates.

Materials and methods: All melting points were measured on a Stuart SMP3 melting point apparatus. IR spectra were determined on a BOMEM MB 104 spectrophotometer using KBr discs. NMR spectra were obtained on a Bruker Avance III 400 at an operating frequency of 400 MHz for ^1H and 100.6 MHz for ^{13}C using the solvent peak as internal reference at 25 °C. All chemical shifts are given in ppm using $^{\delta}H$ Me_4Si = 0 ppm as reference. Assignments were supported by spin decoupling-double resonance and bi-dimensional heteronuclear correlation techniques. High resolution mass spectrometry (HRMS) data were obtained with a TRIPLETOF T5600 (ABSciex, USA) spectrometer. UV/visible titration profiles were carried out with JASCO V-650 spectrophotometer (Easton, MD, USA). Fluorescence measurements were recorded with a JASCO FP-8500 spectrophotometer.

Synthesis of probe 1 (method A): 4-(Dimethylamino) benzaldehyde (**1a**, 0.15 g, 1 mmol), 1,2-di(thiophen-2-yl)ethane-1,2-dione (**1b**, 0.2 g, 1 mmol) and NH_4OAc (20 mmol) were dissolved in glacial acetic acid (5 mL), followed by stirring and heating at reflux for 8 h. Then, the reaction mixture was cooled to room temperature, ethyl acetate (15 mL) was added and the mixture was washed with water (3 × 10 mL). After, the organic phase was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 100:1), given the pure product as a pink solid: yield (70 mg, 59%). ^1H NMR (400 MHz, DMSO-d_6): δ = 2.96 (s, 6H, NMe_2), 6.77 (dd, J = 7.2 and 2.4 Hz, 2H, H3 and H5), 6.99 (dd, J = 5.2 and 3.6 Hz, 1H), 7.13 (dd, J = 3.6 and 1.2 Hz, 1H), 7.19 (dd, J = 5.2 and 3.6 Hz, 1H), 7.36–7.39 (m, 2H), 7.65 (dd, J = 5.2 and 1.2 Hz, 1H), 7.84 (dd, J = 7.2 and 2.0 Hz, 2H, H2 and H6), 12.46 (s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 40.12 (NMe_2), 111.86 (C3 and C5), 117.51 (C1), 119.51, 123.08, 124.52 (C2 and C6), 126.40, 126.98, 127.24, 127.51, 128.04, 131.27, 133.01, 137.87, 146.70 (C4), 150.45 ppm. IR (Nujol): ν = 2855, 1615, 1510, 1201, 1167, 1116, 1078, 905, 841, 822, 687 cm^{-1}. HRMS-EI m/z: calcd for $C_{19}H_{17}N_3S_2 + H^+$: 352.0942; measured: 352.0936.

Synthesis of probe 1 (method B): 4-(Dimethylamino) benzaldehyde (**1a**, 0.15 g, 1 mmol), 1,2-di(thiophen-2-yl)ethane-1,2-dione (**1b**, 0.2 g, 1 mmol), NH_4OAc (20 mmol) and I_2 (5 mol %) were dissolved in ethanol (5 mL), followed by stirring and heating at reflux for 27 h. Then, the reaction mixture was diluted with water (15 mL) having a small amount of $Na_2S_2O_3$ and was cooled in an ice bath. The resulting crude product which precipitated was purified by recrystallization from ethanol given the pure compound **1** as a pink solid: yield (100 mg, 84%).

Synthesis of complex 1-Cu(II): Probe **1** dissolved in acetonitrile (1.0 mmol) was mixed with $Cu(NO_3)_2$ (1.0 mmol) followed by stirring and heating at reflux for 4 h. Then $[NH_4][PF_6]$ was added and the solid product formed was collected, washed with cold acetonitrile and dried: yield (0.8 mmol, 80%). Elemental analysis, [**1**-Cu(II)]$[PF_6]_2$, Calculated: C, 54.98; H, 4.13; N, 10.12; Cu, 15.31; Found: C, 55.05; H, 4.06; N, 10.17; Cu, 15.25.

3. Results

Probe **1** is not completely water soluble and, for this reason, the spectroscopic behaviour was studied in water (pH 7.4)-acetonitrile 90:10 v/v mixture. In this respect, water (pH 7.4)-acetonitrile 90:10 v/v solutions of probe **1** (1.0×10^{-5} mol L^{-1}) presented an absorption band centred at ca. 320 nm with a molar extinction coefficient of 28000 M^{-1} cm^{-1} (see Fig. 1). Next, UV–visible changes in probe **1** upon addition of 10 eq. of Cu(II), Pb(II), Mg(II), Ge(II), Ca(II), Zn(II), Co (II), Ni(II), Ba(II), Cd(II), Hg(II), Fe(III), In(III), As(III), Al(III), Cr(III), Ga(III), K(I), Li(I) and Na(I) was studied. As could be seen in Fig. 1, among all cations tested, only Cu(II) was able to induce the appearance of a new absorption band centred at 555 nm (ε = 32000 M^{-1} cm^{-1}). The marked changes in the UV–visible spectrum of probe **1** upon addition of 10 eq. of Cu(II) is reflected in a clear colour modulation from colourless to deep blue (see also Fig. 1).

Having assessed the highly selective response of probe **1** toward Cu (II) we studied, in the next step, the changes in the UV–visible spectra upon addition of increasing amounts of Cu(II). Addition of different amounts of Cu(II) to water (pH 7.4)-acetonitrile 90:10 v/v solutions of **1** (1.0×10^{-5} mol L^{-1}) induced the progressive decrease of the absorption centred at 320 nm together with the growth of the visible band at 555 nm. From the obtained titration profile a limit of detection of 0.7 μM was determined (see Supporting Information) which is almost 100 times lower than the limit prescribed by the World Health

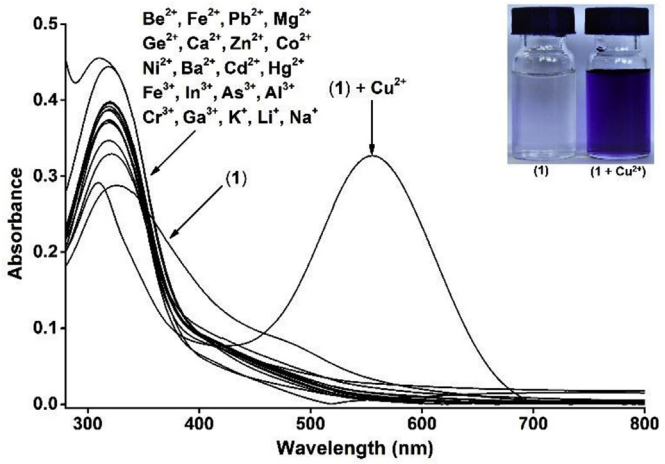


Fig. 1. UV–visible spectra of probe **1** in water (pH 7.4)-acetonitrile 90:10 v/v (1.0×10^{-5} mol L^{-1}) alone and in the presence of 10 eq. of selected metal cations. The inset shows the change in colour of probe **1** in the presence of Cu (II). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

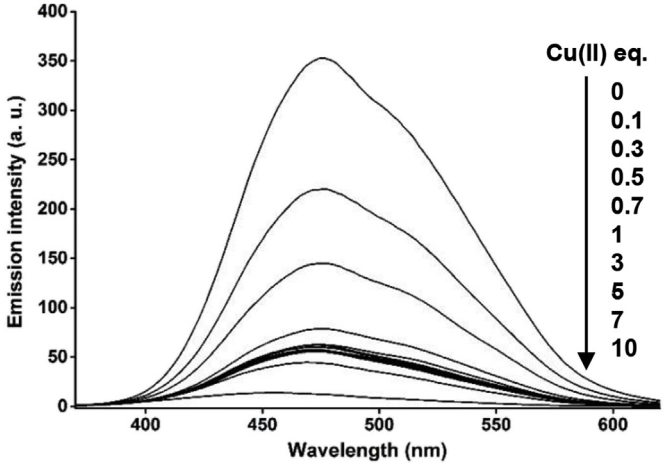


Fig. 3. Fluorescence spectra of probe **1** in water (pH 7.4)-acetonitrile 90:10 v/v (1.0×10^{-5} mol L^{-1}) upon addition of increasing amounts of Cu(II) (from 0 to 10 eq.).

Organization (WHO) guideline for drinking water (30 mM) [53,54].

In order to understand the mode of coordination between probe **1** and Cu(II) Job's plot were determined. As could be seen in Fig. 2, probe **1** clearly forms a 1:1 stoichiometry complex with Cu(II). From the UV–visible titration shown in Fig. 3 a logarithm of the stability constant for the formation of the **1**-Cu(II) complex of 3.50 ± 0.15 was determined.

Probe **1** is also fluorescent. Excitation at 324 nm (one of the isosbestic points observed in the Cu(II) UV–visible titration profile) of water (pH 7.4)-acetonitrile 90:10 v/v of probe **1** (1.0×10^{-5} mol L^{-1}) showed a marked emission band centred at 475 nm (quantum yield of 0.26). Among all cations tested, only Cu(II) induced emission quenching as could be seen in Fig. 3. From the emission titration profile (see Supporting Information) a linear ratio between the emission intensity and the amount of Cu(II) added was observed. Besides, a limit of detection of 3.7 μM of Cu(II) was determined. On the other hand, the emission of probe **1** in water-acetonitrile 90:10 v/v mixtures at acidic pH (5.0 and 6.0) remained nearly unchanged upon addition of Cu(II) cation (see Supporting Information).

The observed emission quenching is remarkable, especially when compared with the results previously published obtained with a structurally related probe **2** (see Scheme 1). In this respect, ethanol solutions

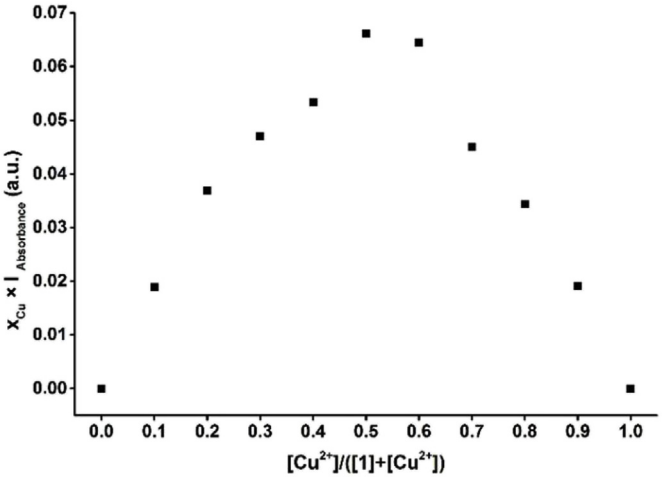
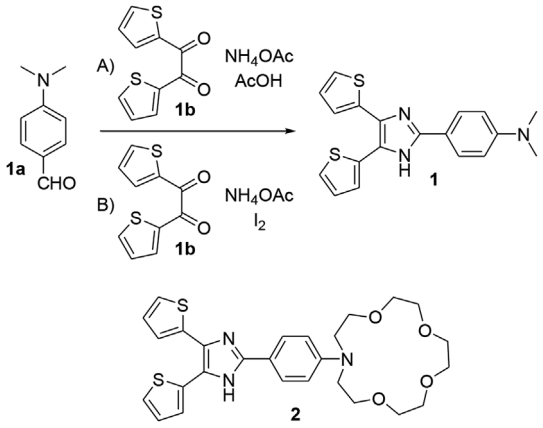


Fig. 2. Job's plot of probe **1** and Cu(II) in water (pH 7.4)-acetonitrile 90:10 v/v. Total concentration of **1** and Cu(II) of 2.0×10^{-5} mol L^{-1}.



Scheme 1. Synthesis of probe **1** and structure of closely related macrocycle-containing imidazole-derivative **2**.

of macrocycle-containing probe **2** presented a weak emission band that was markedly increased upon addition of Cu(II) [55]. The marked emission enhancement observed with **2** was ascribed to an increase in the rigidity of the probe upon formation of 2:1 metal-probe complexes in which one Cu(II) coordinated with the macrocycle and the other with the nitrogen atoms of the imidazole with a logarithm of the stability constant of 11.58 ± 0.01. In our case, the fluorescence experiments were carried out in a more competitive media (water-acetonitrile 90:10 v/v) and probe **1** lacks the macrocycle binding domain presented in **2**. Taking into account the red shift observed in the UV–visible titration profile of probe **1** with Cu(II), and also the formation of 1:1 complexes, assessed from the Job's plot, we proposed that for **1**, the Cu(II) coordinates with one of the nitrogen atoms of the imidazole heterocycle. The observed quenching of the emission intensity of **1** upon Cu(II) binding is most likely due to an electron or energy transfer process between the probe and the cation.

Taking into account the non-emissive nature of **1**-Cu(II) complex (quantum yield of 0.07) and the high affinity of thiol moieties for Cu(II) we tested the possible use of this complex in an IDA assay for biothiols detection. As stated above, water (pH 7.4)-acetonitrile 90:10 v/v solutions of **1**-Cu(II) complex (6.2×10^{-6} mol L^{-1}) presented a marked deep blue colour due to a remarkable absorption band centred at 555 nm. In a first step, the chromogenic response of **1**-Cu(II) complex was tested in the presence of amino acids (Val, Leu, Thr, Lys, Trp, His, Phe, Ile, Arg, Met, Ala, Pro, Gly, Ser, Cys, Asn, Gln, Tyr, Asp, Glu and

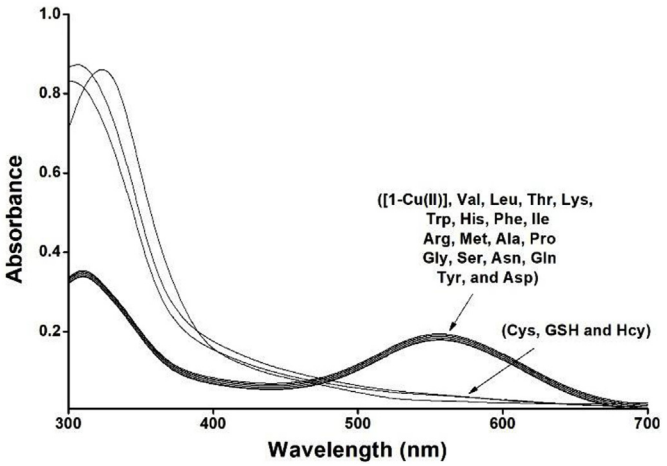


Fig. 4. UV–visible changes of **1**-Cu(II) (6.2×10^{-6} mol L^{-1}) in water (pH 7.4)-acetonitrile 90:10 v/v in the presence of selected amino acids (0.2 eq.) and biothiols (0.2 eq.).

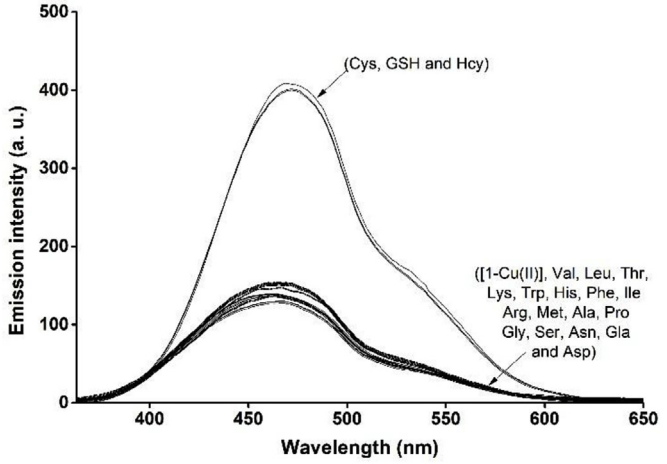


Fig. 5. Changes in the emission band of **1**-Cu(II) complex (6.2×10^{-6} mol L^{-1}) in water (pH 7.4)-acetonitrile 90:10 v/v upon addition of biothiols (0.2 eq.) and selected amino acids (0.2 eq.).

Hcy) and relevant biothiols (GSH). As could be seen in Fig. 4 only Cys, Hcy and GSH were able to induce the bleaching of the solution of the **1**-Cu(II) complex reflected in the disappearance of the 555 nm band together with the appearance of an absorption centred at 320 nm. Besides, water (pH 7.4)-acetonitrile 90:10 v/v solutions of **1**-Cu(II) complex (6.2×10^{-6} mol L^{-1}) were weakly emissive and only addition of Cys, Hcy and GSH induced an emission enhancement (ca. 2.7-fold) at 475 nm (see Fig. 5). From the emission titration profiles obtained upon addition of increasing quantities of biothiols (see Supporting Information) limits of detection of 6.5, 5.0 and 10.2 μM for Cys, Hcy and GSH were obtained. The chromo-fluorogenic changes observed upon addition of biothiols to the aqueous solutions of **1**-Cu(II) complex were ascribed to a demetallation complex, due to the high affinity of Cu(II) cation for thiol moieties, that released the free probe **1**.

On the other hand, we also tested the chromo-fluorogenic behaviour of water (pH 7.4)-acetonitrile 90:10 v/v solutions of **1**-Cu(II) complex (3.2×10^{-6} mol L^{-1}) in the presence of selected anions (F^-, Cl^-, Br^-, I^-, AcO^-, BH_4^-, ClO_4^-, $H_2PO_4^-$, CN^-, HS^-, SCN^-, NO_3^-, HCO_3^- and $P_2O_7^{4-}$). Of all the anions tested only $P_2O_7^{4-}$ was able to induce the disappearance of the absorption band of the complex centred at 555 nm (with a marked bleaching of the solution) and an enhancement in the emission at 475 nm (see Supporting Information). These chromo-fluorogenic changes were also ascribed to a demetallation of **1**-Cu(II) complex, induced by $P_2O_7^{4-}$ anion, that produced the free probe [56].

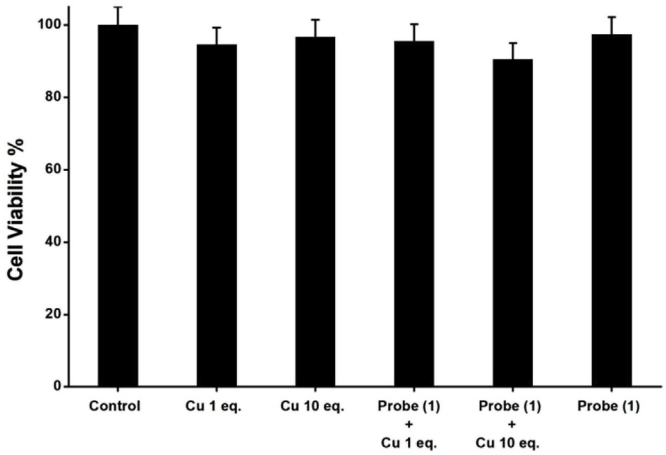


Fig. 6. Cell viability assays. HeLa cells were treated with probe **1** (5 μM) for 30 min in the absence or in the presence of Cu(II) (1 and 10 eq.). Then, cell viability was quantified by means of WST-1 assay.

The selective emission quenching of **1** in the presence of Cu(II) and the recovery observed with GSH suggests that the probe can be used for the imaging of these species in living cells. Based on these observations, the cytotoxicity of **1** was first evaluated. HeLa cells were treated with **1** (5 μM) over half an hour period and cell viability was determined by a WST-1 assay. Moreover, the viability of probe **1** in the presence of Cu (II) (1 and 10 eq.) was also assessed. The obtained results are shown in Fig. 6. As could be seen, probe **1** was non-toxic to HeLa cells at the concentration tested. Besides, the concentrations of Cu(II) added (alone and in the presence of probe **1**) were also non-toxic to HeLa cells.

Then, in order to verify the feasibility of the developed probe to detect Cu(II) and GSH in highly competitive environments, we prospectively used probe **1** for the fluorescence imaging of both species in living cells. In a typical experiment, HeLa cells were incubated in DMEM supplemented with 10% fetal bovine serum. To conduct fluorescence microscopy studies, HeLa cells were seeded in 24 mm glass coverslips in 6-well plates and were allowed to settle for 24 h. Cells were treated with probe **1** in DMSO (1%) at a final concentration of 5 μM. After 30 min, the medium was removed and solutions of different concentrations of $Cu(NO_3)_2$ in PBS were added (5 μM and 50 μM) and cells were incubated for another 10-min period. Finally, treated cells were incubated overnight in order to ascertain the intracellular GSH effect. As seen in the confocal fluorescence microscope images shown in Fig. 7a, the control experiment (HeLa cells without probe **1**) showed a weak fluorescence, and cells treated with **1** (5 μM) showed a marked intracellular emission (Fig. 7b). Moreover, a significant quenching in intracellular emission was observed in the Cu(II)-treated cells (Fig. 7c), clearly indicating the possible use of **1** to detect this divalent metal cation in complex biological settings. Finally, after incubation overnight, a remarkable emission enhancement could be observed probably due to a intracellular GSH-induced demetallation of complex **1**-Cu(II) which generated the free probe (Fig. 7d). Besides, the emission intensity of the HeLa cells after each treatment was measured and the obtained results are presented in Fig. 7e.

4. Conclusions

In summary, we report herein an easy-to-prepare imidazole-based chromo-fluorogenic probe **1** for the selective and sensitive optical detection of Cu(II) and biothiols. Probe **1** was able to selectively detect Cu (II) in a highly competitive media (water-acetonitrile 90:10 v/v) by a marked colour change from colourless to deep blue. Besides, a significant quenching of the probe emission in the presence of Cu(II) was observed. Moreover, real-time fluorescence imaging measurements

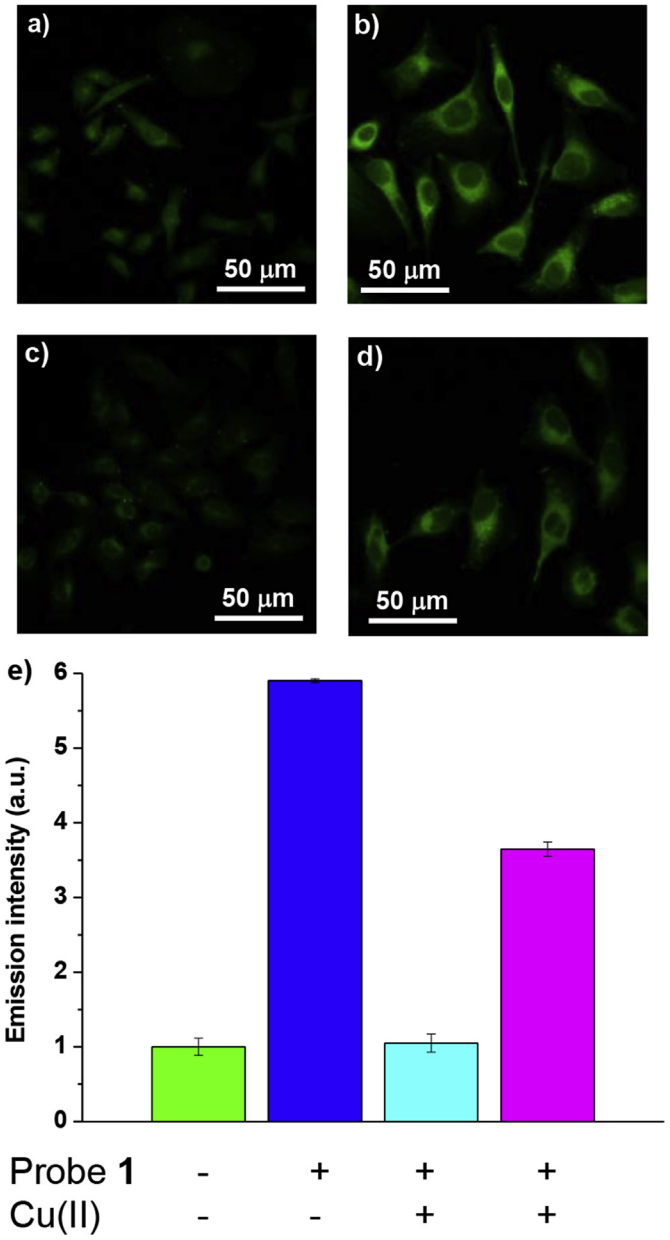


Fig. 7. Confocal microscopy images of probe **1** in HeLa cells. HeLa cells were incubated with **1** (5 μM) for 30 min at 37 °C in DMEM. Cells images obtained using an excitation wavelength of 405 nm. (a) Fluorescence images of Hela cells, (b) Fluorescence images of Hela cells incubated with **1** (5 μM) for 30 min. (c) Fluorescence images of Hela cells incubated with probe **1** and pre-treated with Cu(II) 10 eq. (50 μM) for 10 min. (d) Fluorescence images of HeLa cells after the pre-treatment with probe **1** and Cu(II) and after incubation overnight. (e) Emission intensity quantification by the confocal images analysis.

confirmed that probe **1** can be used to detect intracellular Cu(II) at micromolar concentrations. Moreover, **1**-Cu(II) complex was used for the development of an IDA assay for the selective chromo-fluorogenic sensing of biothiols (Cys, Hcy and GSH). Biothiols were able to demetallate **1**-Cu(II) complex with the subsequent release of free probe **1** assessed by a marked colour change from deep blue to colorless and by a significant emission enhancement. The sensing behaviour of probe **1** toward Cu(II) and of the **1**-Cu(II) complex toward biothiols are comparable to other sensing probes recently published (see Supporting Information for a comparative table). Besides, the results presented here showed the sequential detection of two analytes, which is an emerging area inside the design and synthesis of new molecular probes [41–46,57–59].

Acknowledgments

The authors thank the financial support from the Spanish Government (projects MAT2015-64139-C4-1-R and AGL2015-70235-C2-2-R) and the Generalitat Valenciana (project PROMETEOII/2014/047). Thanks are also due to Fundação para a Ciência e a Tecnologia for financial support to the Portuguese NMR network (PTNMR, Bruker Avance III 400-Univ. Minho), FCT and FEDER (European Fund for Regional Development)-COMPETEQREN-EU for financial support to the research centre CQ/UM (Ref. UID/QUI/00686/2013 and UID/QUI/0686/2016), and a PhD grant to R. C. M. Ferreira (SFRH/BD/86408/2012).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dyepig.2018.10.017.

References

[1] Maity D, Raj A, Karthigeyan D, Kundu TK, Govindaraju T. A switch-on near-infrared fluorescence-ready probe for Cu(II): live cell imaging. Supramol Chem 2015;27:589–94.
[2] Ghosh S, Ganguly A, Bhattacharyya A, Alam MA, Guchhait N. Selective chromo-fluorogenic molecular sensor for dual channel recognition of Cu^{2+} and F^-: effect of functional gropu on selectivity. RSC Adv 2016;6:67693–700.
[3] Nandre J, Patil S, Patil V, Yu F, Chen L, Sahoo S, Prior T, Redshaw C, Mahulikar P, Patil U. A novel fluorescent "turn-on" chemosensor for nanomolar detection of Fe (III) from aqueous solution and its application in living cells imaging. Biosens Bioelectron 2014;61:612–7.
[4] Xu H, Wang X, Zhang C, Wu Y, Liu Z. Coumarin-hydrazone based high selective fluorescence sensor foe copper(II) detection in aqueous solution. Inorg Chem Commun 2013;34:8–11.
[5] Chereddy NR, Thennarasu S. Synthesis of a highly selective bis-rhodamine chemosensor for naked-eye detection of Cu^{2+} ions and its application in bio-imaging. Dyes Pigments 2011;91:378–82.
[6] Lee HG, Kim KB, Park GJ, Na YJ, Jo HY, Lee SA, Kim C. An anthracene-based fluorescent sensor for sequential detection of zinc and copper ions. Inorg Chem Commun 2014;39:61–5.
[7] Dong M, Ma TH, Zhang AJ, Dong YM, Wang YW, Peng Y. A series of highly sensitive and selective fluorescent and colorimetric "off-on" chemosensors for Cu(II) based on rhodamine derivatives. Dyes Pigments 2010;87:164–72.
[8] Chen X, Pradhan T, Wang F, Kim JS, Yoon J. Fluorescent chemosensors based on spiroring-opening of xanthenes and related derivatives. Chem Rev 2012;112:1910–56.
[9] Kim H, Na YJ, Song EJ, Kim KB, Bae JM, Kim C. A single colorimetric sensor for multiple target ions: the simultaneous detection of Fe^{2+} and Cu^{2+} in aqueous media. RSC Adv 2014;4:22463–9.
[10] Swaminathan S, Gangadaran P, Venkatesh T, Ghosh M. Association between serum copper and tumor markers CEA and CA 125. J Pharmaceut Biomed Sci 2011;9:1–15.
[11] Kamble S, Utage B, Mogle P, Kamble R, Hese S, Dawane B, Gacche R. Evaluation of curcumin capped copper nanoparticles as possible inhibitors of human breast cancer cells and angiogenesis: a comparative study with native curcumin. AAPS Pharm Sci Tech 2016;17:1030–41.
[12] Jain AK, Singh RK, Jain S, Raisoni J. Copper(II) ion selective electrode based on a newly synthesized Schiff-base chelate. Transition Met. Chem. 2008;33:243–9.
[13] Goswami S, Sen D, Das NK, Hazra G. Highly selective colorimetric fluorescence sensor for Cu^{2+}: cation-induced "switching-on" of fluorescence due to excited state internal charge transfer in the red/near-infrared region of emission spectra. Tetrahedron Lett 2010;51:5563–6.
[14] Xie Q, Zhou T, Yen L, Shariff M, Nguyen T, Kami K, Gu P, Liang L, Rao J, Shi R. Effects of Arthro-7 in relieving symptoms of osteoarthritis with mild to moderate arthralgia. Nutr Diet Suppl 2013;5:1–6.
[15] Choo XY, Alukaidey L, White AR, Grubman A. Neuroinflammation and copper in Alzheimer's disease. Int J Alzheimer's Dis 2013;2013:145345.
[16] Udhayakumari D, Naha S, Velmathi S. Colorimetric and fluorescent chemosensors for Cu^{2+}. A comprehensive review from the years 2013-15. Anal. Methods 2017;9:552–78.
[17] Na YJ, Park GJ, Jo HY, Lee SA, Kim C. A colorimetric chemosensor based on a Schiff base for highly selective sensing of cyanide in aqueous solution: the influence of solvents. New J Chem 2014;38:5769–76.
[18] Divya KP, Sreejith S, Balakrishna B, Jayamurthy P, Anees P, Ajayaghosh A. A Zn^{2+}-specific fluorescent molecular probe for the selective detection of endogenous cyanide in biorelevant samples. Chem Commun (J Chem Soc Sect D) 2010;46:6069–71.
[19] Yu H, Fu M, Xiao Y. Switching off FRET by analyte-induced decomposition of squaraine energy acceptor: a concept to transform "turn off" chemodosimeter into

ratiometric sensors. Phys Chem Chem Phys 2010;12:7386–91.
[20] Kim H, Na YJ, Park GJ, Lee JJ, Kim YS, Lee SY, Kim C. Synthesis, crystal structure, luminescence and thermal behavior of a new energetic Zn(II) compound. Inorg Chem Commun 2014;49:68–71.
[21] Noh JY, Park GJ, Na YJ, Jo HY, Lee SA, Kim C. A colorimetric "naked-eye" Cu(II) chemosensor and pH indicator in 100% aqueous solution. J Chem Soc, Dalton Trans 2014;43:5652–6.
[22] Trigo-López M, Muñoz A, Ibeas S, Serna F, García FC, García JM. Colorimetric detection and determination of Fe(III), Co(II), Cu(II) and Sn(II) in aqueous media by acrylic polymers with pendant terpyridine motifs. Sensor Actuator B Chem 2016;226:118–26.
[23] Kim KB, Park GJ, Kim H, Song EJ, Bae JM, Kim C. A novel colorimetric chemosensor for multiple target ions in aqueous solution: simultaneous detection of Mn(II) and Fe(II). Inorg Chem Commun 2014;46:237–40.
[24] Townsend DM, Tew KD, Tapiero H. The importance of glutathione in human disease. Biomed Pharmacother 2003;57:145–55.
[25] Miller JW, Beresford SA, Neuhouser ML, Cheng TY, Song X, Brown EC, Zheng Y, Rodriguez B, Green R, Ulrich CM. Homocysteine, cysteine, and risk of incidental colorectal cancer in the women's health initiative observational cohort. Am J Clin Nutr 2013;97:827–34.
[26] Dorszewska J, Prendecki M, Oczkowska A, Dezor M, Kozubski W. Molecular basis of familial and sporadic Alzheimer's disease. Curr Alzheimer Res 2016;13:952–63.
[27] Rozycka A, Jagodzinski PP, Kozubski W, Lianeri M, Dorszewska J. Homocysteine levels and mechanisms of injury in Parkinson's disease as related to MTHFR, MTR, and MTHFD1 genes polymorphisms and LDopa treatment. Curr Genom 2013;14:534–42.
[28] Isik M, Ozdemir T, Turan IS, Kolemen S, Akkaya EU. Chromogenic and fluorogenic sensing of biological thiols in aqueous solution using BODIPY-based reagents. Org Lett 2013;15:216–9.
[29] Liao YC, Venkatesan P, Wei LF, Wu SP. A coumarin-based fluorescent probe for thiols and its application in cell imaging. Sensor Actuator B Chem 2016;232:732–7.
[30] Liu T, Huo F, Yin C, Jianfang L, Jianbin C, Yongbin Z. A triphenylamine as a fluorophore and maleimide as a bonding group selective turn-on fluorescent imaging probe for thiols. Dyes Pigments 2016;128:209–14.
[31] Lee KS, Park J, Park HJ, Chung YK, Park SB, Kim HJ, Shin IS, Hong JI. Regenerative fluorescence "turn-on" probe for biothiols through Cu(II)/Cu(I) redox conversion. Sensor Actuator B Chem 2016;237:256–61.
[32] Kong F, Liu R, Chu R, Wang X, Xu K, Tang B. A highly sensitive near-infrared fluorescent probe for cysteine and homocysteine in living cells. Chem Commun (J Chem Soc Sect D) 2013;49:9176–8.
[33] Zhang J, Jiang XD, Shao X, Zhao J, Su Y, Xi D, Yu H, Yue S, Xiao LJ, Zhao W. A turn on NIR fluorescent probe for the detection of homocysteine over cysteine. RSC Adv 2014;4:54080–3.
[34] Wang YW, Liu SB, Ling WJ, Peng Y. A fluorescent probe for relay recognition of homocysteine and group IIIA ions including Ga(III). Chem Commun (J Chem Soc Sect D) 2016;52:827–30.
[35] Liu J, Sun YQ, Zhang H, Huo Y, Shi Y, Guo W. Simultaneous fluorescent imaging of Cys/Hcy and GSH from different emission channels. Chem Sci 2014;5:3183–8.
[36] Guan YS, Niu LY, Chen YZ, Wu LZ, Tung CH, Yang QZ. A near-infrared fluorescent sensor for selective detection of cysteine and its application in live cell imaging. RSC Adv 2014;4:8360–4.
[37] Fu ZH, Han X, Shao Y, Fang J, Zhang ZH, Wang YW, Peng Y. Fluorescein-based chromogenic and ratiometric fluorescence probe for highly selective detection of cysteine and its application in bioimaging. Anal Chem 2017;89:1937–44.
[38] Yang YL, Zhang FM, Wang YW, Zhang BX, Fang R, Fang JG, Peng Y. An imino-coumarin sulfonamide based turn-on fluorescent probe for the detection of biothiols in aqueous solution. Chem Aust J 2015;10:422–6.
[39] Zhao CC, Chen Y, Zhang HY, Zhou BJ, Lv XJ, Fu WF. A BODIPY-based fluorescent chemosensor for Cu^{2+} and biological thiols, and its application as a Cu^{2+} probe in living cell imaging. J Photochem Photobiol A 2014;282:41–6.
[40] Guangjie H, Meng Q, Zhao X, Cheng H, Zhoub P, Duan C. A new Cu(II) selective fluorescence probe based on naphthalimide: synthesis, mechanism and application in living cells. Inorg Chem Commun 2016;65:28–31.
[41] Fu ZH, Yan LB, Zhang X, Zhu FF, Han XL, Fang J, Wang YW, Peng Y. A fluorescein-based chemosensor for relay fluorescence recognition of Cu(II) ions and biothiols in water and its applications to a molecular logic gate and living cell imaging. Org Biomol Chem 2017;15:4115–21.
[42] Singh Y, Arun S, Singh BK, Dutta PK, Ghosh T. Colorimetric and ON-OFF-ON fluorescent chemosensor for the sequential detection of Cu(II) and cysteine and its application in imaging of living cells. RSC Adv 2016;6:80268–74.
[43] Lee SH, Lee JJ, Shin JW, Min KS, Kim C. A colorimetric chemosensor for the sequential detection of Cu(II) and cysteine. Dyes Pigments 2015;116:131–8.
[44] Maheshwaran D, Nagendraraj T, Manimaran P, Ashokkumar B, Kumar M, Mayilmurugan R. A highly selective and efficient Cu(II) "turn-on" fluorescence imaging probe for L-cysteine. Eur J Inorg Chem 2017:1007–16.
[45] Kim YS, Park GJ, Lee SA, Kim C. A colorimetric chemosensor for the sequential detection of copper ion and amino acids (cysteine and histidine) in aqueous solution. RSC Adv 2015;5:31179–88.
[46] You GR, Lee JJ, Choi YW, Lee SY, Kim C. Experimental and theoretical studies for sequential detection of copper(II) and cysteine by a colorimetric chemosensor. Tetrahedron 2016;72:875–81.
[47] Santos-Figueroa LE, Llopis-Lorente A, Royo S, Sancenón F, Martínez-Máñez R, Costero AM, Gil S, Parra M. A chalcone-based highly selective and sensitive chromofluorogenic probe for trivalent metal cations. ChemPlusChem 2015;80:800–4.
[48] Marín-Hernández C, Santos-Figueroa LE, El Sayed S, Pardo T, Raposo MMM, Batista RMF, Costa SPG, Sancenón F, Martínez-Máñez R. Synthesis and evaluation of the chromo-fluorogenic recognition ability of imidazoquinoline derivatives toward ions. Dyes Pigments 2015;122:50–8.
[49] Lo Presti M, El Sayed S, Martínez-Máñez R, Costero AM, Gil S, Parra M, Sancenón F. Selective chromo-fluorogenic detection of trivalent cations in aqueous environments using a dehydration reaction. New J Chem 2016;40:9042–5.
[50] El Sayed S, de la Torre C, Santos-Figueroa LE, Pérez-Paya E, Martínez-Máñez R, Sancenón F, Costero AM, Parra M, Gil S. A new fluorescent "turn-on" chemodosimeter for the detection of hydrogen sulfide in water and living cells. RSC Adv 2013;3:25690–3.
[51] El Sayed S, de la Torre C, Santos-Figueroa LE, Martínez-Máñez R, Sancenón F. 2,4-dinitrophenyl ether-containing chemodosimeters for the selective and sensitive "*in vitro*" and "*in vivo*" detection of hydrogen sulfide. Supramol Chem 2015;4:244–54.
[52] Marín-Hernández C, Santos-Figueroa LE, Moragues ME, Raposo MMM, Batista RMF, Costa SPG, Pardo T, Martínez-Máñez R, Sancenón F. Imidazoanthraquinone derivatives for the chromofluorogenic sensing of basic anions and trivalent metal cations. J Org Chem 2014;79:10752–61.
[53] Sarkar B. Treatment of Wilson and Menkes diseases. Chem Rev 1999;99:2535–44.
[54] Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. Nat Rev Drug Discov 2004;3:205–14.
[55] Oliveira E, Baptista RMF, Costa SPG, Raposo MMM, Lodeiro C. Exploring the emissive properties of new azacrown compouds bearing aryl, furyl, or thienyl moieties: a special case of chelation enhanced fluorescence upon interaction with Ca^{2+}, Cu^{2+}, or Ni^{2+}. Inorg Chem 2010;49:10847–57.
[56] Huang X, Guo Z, Zhu W, Xie Y, Tian H. A colorimetric and fluorescent turn-on sensor for pyrophosphate anion based on a dicyanomethylene-4*H*-chromene framework. Chem Commun (J Chem Soc Sect D) 2008:5143–5.
[57] Dong YM, Peng Y, Dong M, Wang YW. A selective, sensitive, and chromogenic chemodosimeter for cyanide based on the 1,1'-binaphthyl scaffold. J Org Chem 2011;76:6962–6.
[58] Peng Y, Dong YM, Dong M, Wang YW. A selective, sensitive, colorimetric, and fluorescence probe for relay recognition of fluoride and Cu(II) ions with "off-on-off" switching in ethanol-water solution. J Org Chem 2012;77:9072–80.
[59] Dong M, Peng Y, Dong YM, Tang N, Wang YW. A selective, colorimetric, and fluorescent chemodosimeter for relay recognition of fluoride and cyanide anions based on 1,1'-binaphthyl scaffold Org. Letture 2012;14:130–3.