Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A new fluorescence chemosensor for selective detection of copper ion in aqueous solution

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ARTICLE INFO

Article history:
Received 28 January 2016
Revised 7 April 2016
Accepted 8 April 2016
Available online xxxx

Keywords:
2,5-Diphenylfuran
Di(2-picolyl)amine
Fluorescence sensor
Cu^{2+}

ABSTRACT

A new fluorescent chemosensor based upon 2,5-diphenylfuran and di(2-picolyl)amine (DPA) was designed and synthesized. Its structure was confirmed by single crystal X-ray diffraction and its photophysical properties were studied by absorption and fluorescence spectra. This compound can be used to determine Cu^{2+} ion with high selectivity among a series of cations in aqueous DMSO. This sensor forms a 1:1 complex with Cu^{2+} and displays fluorescent quenching.

The development of chemosensors for the detection of metal ions has received considerable attention because of their important roles in medicine, living systems, and the environment.[1,2] Among metals, copper is the third most abundant essential transition metal ion in the human body.[3] Many proteins use copper ions as a cofactor for electron transport, or as a catalyst in oxido-reduction reactions. Copper distribution in the human body is highly controlled, because of its cellular toxicity. An excess of copper ions in living cells can damage lipids, nucleic acids, and proteins. Several serious diseases, including Alzheimer's disease,[4] Indian childhood cirrhosis,[5] prion disease,[6] and Menkes and Wilson diseases,[7] have been associated with the cellular toxicity of copper ions. Due to its extensive applications in our daily lives, copper is also a common metal pollutant. For these reasons, much effort has been devoted to the design of various chemosensors specific for Cu^{2+} detection.[8–18]

In continuing of our study on developing molecular sensors for Cu^{2+} detection,[19–21] herein, we report a new fluorescent chemosensor **1**, which is constructed via two functional moieties: 2,5-diphenylfuran acts as a fluorophore for its excellent photophysical property, and di(2-picolyl)amine (DPA) linked to 2,5-diphenylfuran provides the recognition and binding site for metal ions. Sensor**1** displays high selectivity for Cu^{2+} ion among the metal ions examined and exhibits fluorescence quenching upon binding of Cu^{2+} ion with an 'on–off' type fluoroionophoric switching property. Moreover, its fluorescent signal can be revived by the addition of EDTA solution.

The new sensor **1** was synthesized as outlined in Scheme 1. 3-(Methylthio)-4-bromomethyl-2,5-diphenyl-furan (**5**) was synthesized according to the our reported procedure,[22] after reaction of compound **5** with DPA (**6**) in refluxing CH_3CN, the desired product **1** was obtained in 75.7% yields. The structure of compound **1** was fully characterized by ^1H NMR, ^{13}C NMR, ESI-MS (ESI, Figs. S1–S3),[23] and single crystal X-ray diffraction analysis[24] (Fig. 1).

To examine the binding properties of **1** with metal ions, the absorption spectra of **1** (10 μM) in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0) were first explored in the presence of 1 equiv of different metal ions and the results are depicted in Figure 2. The sensor **1** exhibited broad absorption in 326 nm. Upon binding of metal ions (K^+, Na^+, Ni^{2+}, Mg^{2+}, Mn^{2+}, Cr^{3+}, Pb^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Co^{2+}, Fe^{3+}, and Hg^{2+}) (as their chloride salts), it was found that only the Cu^{2+} ion causes the maximum absorption peak obvious change with a blue shift from 326 nm to 292 nm, other metal ions did not cause this change under the same conditions.

The UV/Vis titration of **1** with Cu^{2+} was shown in Figure 3. With the addition of increasing amounts of Cu^{2+} to a solution of **1** in DMSO/water (95:5, v/v), the maximum absorbance at 326 nm decreased gradually, and concomitantly, a rising new absorbance that peaked at 292 nm appeared. An isosbestic point was clearly observed at 314 nm, indicating the formation of a new complex between **1** and Cu^{2+}.

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http://dx.doi.org/10.1016/j.tetlet.2016.04.025
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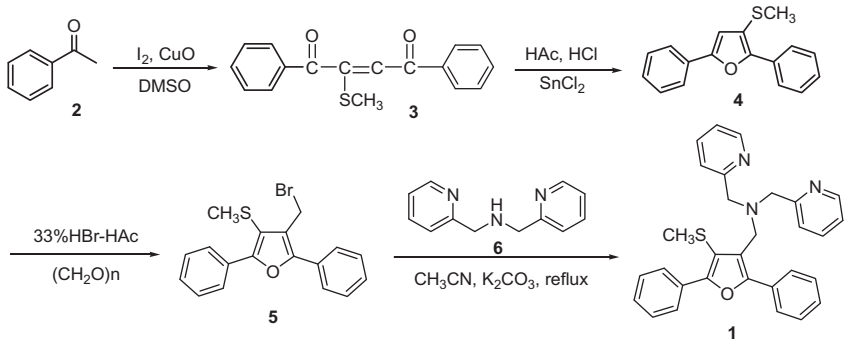


Scheme 1. Synthesis of chemosensor **1**.

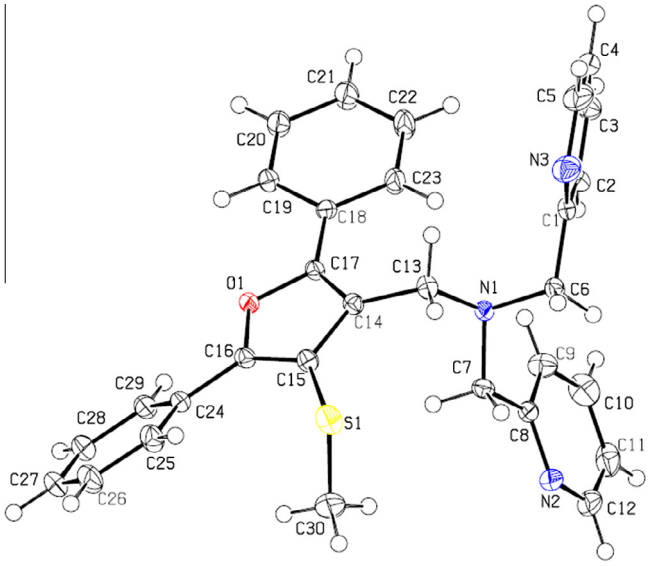


Figure 1. Crystal structure of compound **1**.

The selectivity of sensor **1** to Cu^{2+} was further investigated by fluorometric detection in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0). As shown in Figure 4, 1 exhibited a relatively strong fluorescence emission at 381 nm upon excitation at 326 nm. No significant changes of the spectra were observed for **1** upon addition of most of the metal ions, except for Co^{2+}, Ni^{2+}, and Cu^{2+}. Upon addition of 1 equiv of Co^{2+} and Ni^{2+}, the fluorescence intensity of **1** was reduced to 78.5% and 72.1% of the initial one, respectively. Compared with $Co^{2+}$and Ni^{2+}, upon addition of 1 equiv of Cu^{2+}, the fluorescence intensity of **1** could be reduced to 22.4% of the initial one. Such a significant difference in fluorescence intensity between Cu^{2+} and other metal ions indicates that the function group DPA of **1** is more suitable to bind Cu^{2+} than other metal ions observed.

The fluorescence titration of **1** toward Cu^{2+} was shown in Figure 5. The fluorescence intensity of compound **1** gradually decreased as Cu^{2+} was gradually titrated. When the amount of Cu^{2+} added was about 20 μM, the fluorescence intensity almost reached minimum. The fluorescence quantum yield of compound **1** in the absence of Cu^{2+} and in the presence of 20 μM Cu^{2+} with respect to quinine sulfate in 0.1 N H_2SO_4 solution ($\Phi_s = 0.54$)[25] was calculated to be 0.337 and 0.012, respectively.

To determine the binding stoichiometry of the **1**–Cu^{2+} complex, the Job plot[26] for the system was performed in aqueous solution by keeping the total concentration of **1** and Cu^{2+} at 10 μM and changing the molar ration of Cu^{2+} ($[Cu^{2+}]/[Cu^{2+} + \mathbf{1}]$) from 0 to 1. As shown in Figure 5, the result shows a maximum at a molar fraction of 0.5, indicating the formation of 1:1 complex of **1** and Cu^{2+}. The ESI mass spectrum of a mixture of **1** and $CuCl_2$ also revealed the formation of a 1:1 metal–ligand complex through the metal coordination interaction where there is a major signal at *m*/*z* 575.24

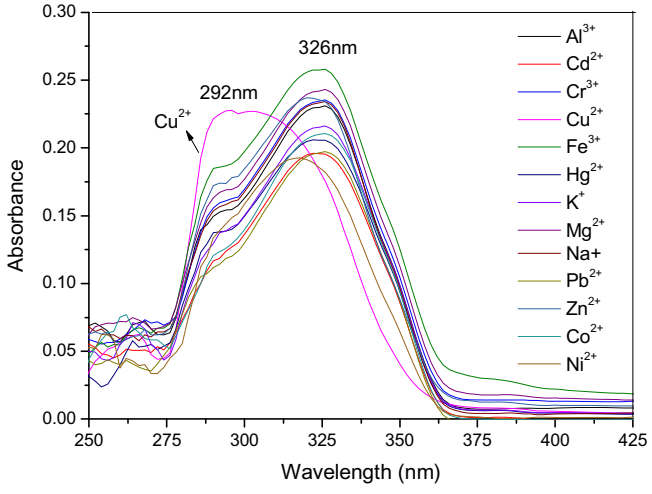


Figure 2. UV–vis spectral changes of compound **1** (10 μM) in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0) upon additions of various metal ions (10 μM).

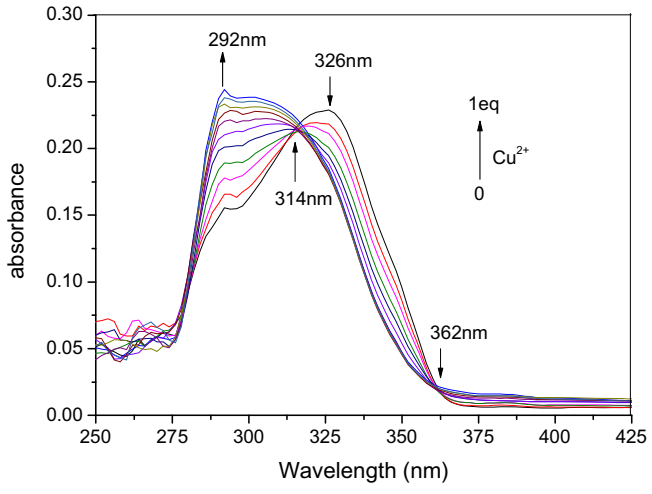


Figure 3. UV–vis spectral changes of compound **1** (10 μM) in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0) with increasing amount of Cu^{2+} (as its chloride salt).

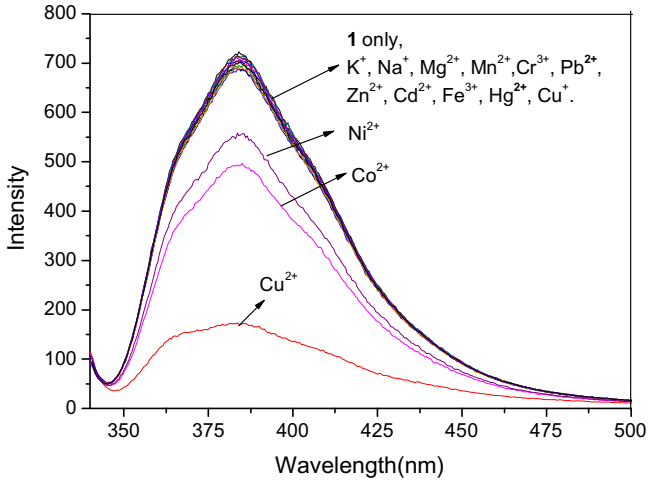


Figure 4. Emission spectral changes of compound **1** (10 μM) in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0) upon additions of various metal ions (10 μM). λ_{ex} = 326 nm.

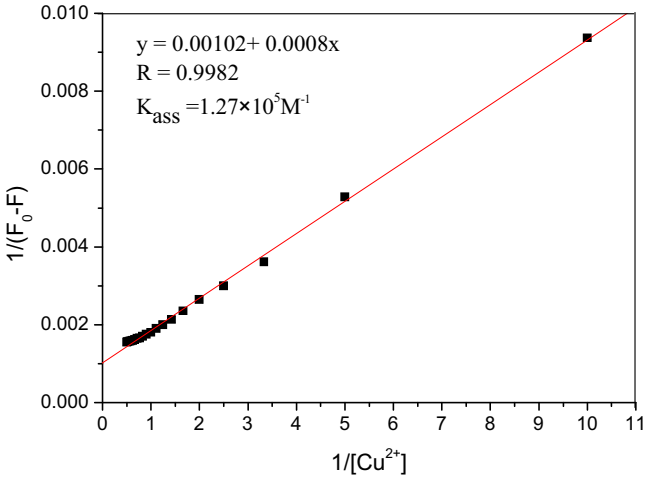


Figure 6. Benesi–Hildebrand plot of sensor **1** with Cu^{2+}.

(calculated value, 575.09) assigned to the species [Cu (**1**)Cl]$^+$ with the loss of one Cl^- anion (ESI, Fig. S4).

The association constant as determined by fluorescence titration method following the Benesi–Hildebrand equation[27] is found to be 1.27 × 10^5 M^{-1} (Fig. 6). The detection limit, based on the definition of IUPAC (C_{DL} = 3Sb/m),[28] was found to be 1.68 × 10^{-7} M from 10 blank solutions, lower than the limit of copper in drinking water (~20 μM). These results suggest that compound **1** has a high selectivity to Cu^{2+}, and could be exploited as a fluorescence sensor for Cu^{2+}.

Additionally, the effects of anionic counterions on the sensing behavior of compound **1** to Cu^{2+} were also investigated. The separate concomitant additions of different copper salts, such as Cu $(NO_3)_2$, Cu$(AcO)_2$, and $CuSO_4$ to the receptor **1**, gave rise to the same fluorescence profiles in its response to Cu^{2+} (Fig. 7) indicating a negligible effect of the counter anions on the recognition ability and photo physical properties of receptor **1**.

The effect of pH on the emission spectrum of **1** and **1**–Cu^{2+} complex was depicted in Figure 8. At a low (2.0–6.0) pH, decreasing pH protonates the nitrogen of DPA moiety of **1** and inhibits the PET to

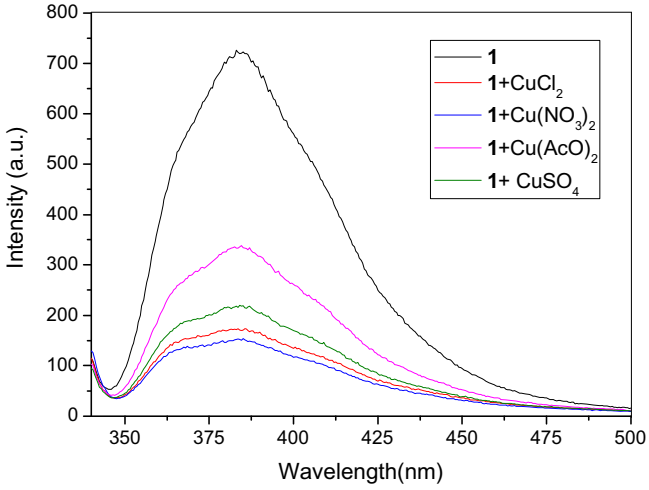


Figure 7. Emission spectra of **1** (10 μM) in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0) in the presence of different copper salts (10 μM). λ_{ex} = 325 nm.

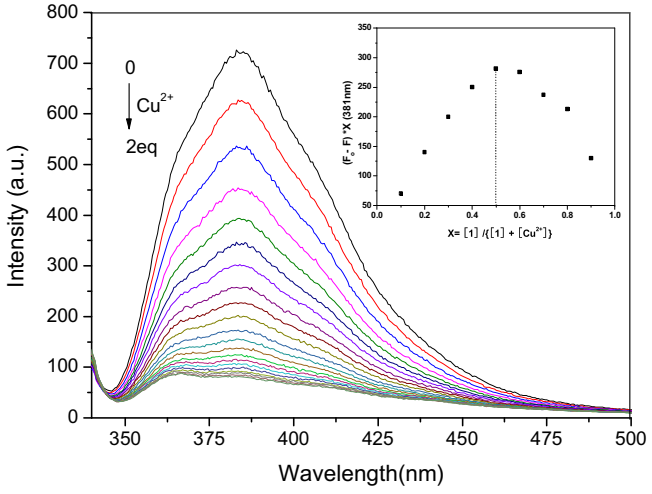


Figure 5. Emision spectra of **1** (10 μM) in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0) upon the addition of Cu^{2+} (0–2 equiv) at 25 °C. Inset: Job's plot of **1** and Cu^{2+}. The total concentration of **1** and Cu^{2+} was kept at a fixed 10 μM.

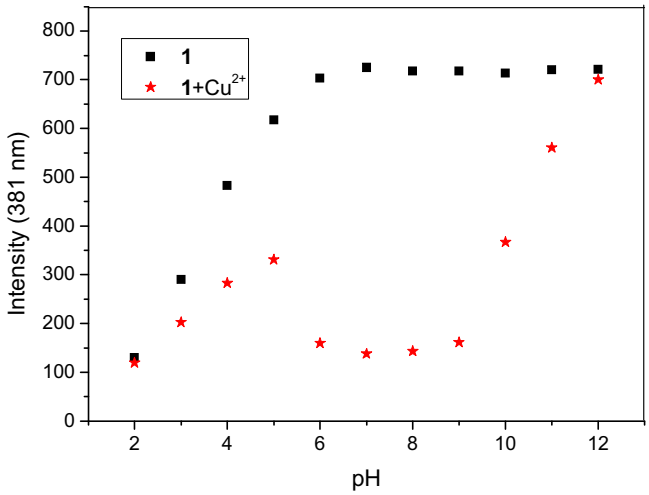


Figure 8. Fluorescence response (381 nm) of free **1** (10 μM) and after addition of Cu^{2+} (10 μM) in DMSO /H_2O (v/v 95:5, 10 mM buffer) solution as a function of different pH values.

the fluorophore resulting in a decrease in fluorescence of **1**. At pH 6.0, **1** shows a maximum intensity and it remains unchanged at higher pH (>6.0). The effect of pH on **1**–Cu^{2+}complex shows that the increase in pH increases the amount of quenching, reaching its maximum at pH 6.0 after which it displayed no pH-sensitivity in the pH range of 6.0–9.0. With a further increase in pH, the fluorescence intensity was gradually restored with the pH increase. This response was due to the stronger complexation of OH^- with Cu^{2+} than the complexation of **1** with Cu^{2+} and formation of $Cu(OH)_2$. Thus **1** displayed virtually no physiological pH-sensitivity and fluorescence on–off can be controlled by Cu^{2+} binding within the pH range of 6.0–9.0.

Competitive binding experiments with different metal ions and Cu^{2+} were carried out from fluorescence spectra and the result is shown in Figure 9. When **1** (10 μM) was treated with 1 equiv of Cu^{2+} in the presence of the same concentration of other metal ions, the Cu^{2+}- induced fluorescence response of **1** was almost unaffected by the presence of the other metal ions. The results indicate that the binding of Cu^{2+} ion to **1** is much stronger than that of other metal ions.

To establish the reversibility of **1**–Cu^{2+} complexes, EDTA titration was conducted as shown in Figure 10. Upon addition of EDTA to the solution containing **1** and Cu^{2+} mixture, the original fluorescence could be reproduced again. When Cu^{2+} was added to the system again, the fluorescence intensities of solution decrease again. The results indicated that sensor **1** could be easily regenerated for repeating use.

Based on above studies, a proposed binding model for **1** with Cu^{2+} is shown in Scheme 2. The complexation of Cu^{2+} ion requires the coordination of three N atoms of DPA and one S atom of methylthio group of **1,** which was supported by Cu^{2+} induced chemical shift of **l** changes in the ^1H NMR spectra (ESI, Fig. S5). In the presence of 1.0 equiv of Cu^{2+} ions, chemical shifts of proton NMR signals corresponding to the methylthio-CH_3 was downfield shifted by 0.0017 ppm. In the same way, obvious change in the chemical shifts of proton of pyridine-H and three bridged-CH_2 groups also can be observed owing to the binding of the Cu^{2+}. These results suggest that the DPA and methylthio group are involved in the complexation with Cu^{2+}. When the DPA and methylthio group coordinated to Cu^{2+}, the electron density of the DPA and methylthio group would be decreased, lowering their electrondonating ability. While **1** was excited, the electron was probably transferred from the fluorophore to the receptor, and a PET process occurred.[1,29] Thus, the quenching phenomena of the fluorescence of **1** by Cu^{2+} were observed.

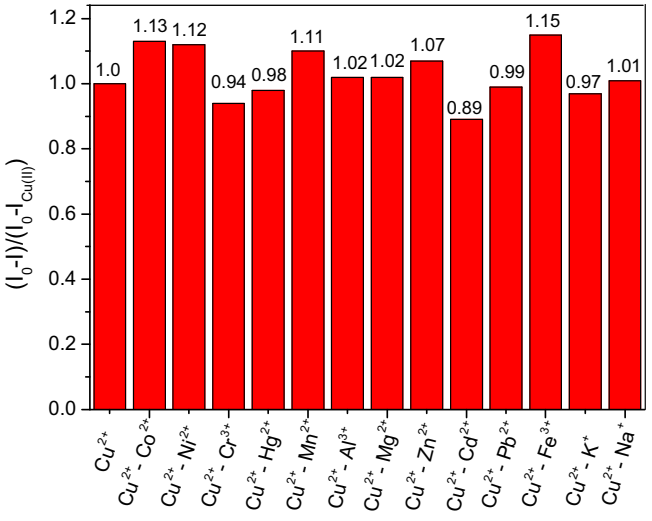


Figure 9. Competitive experiments in the **1** + Cu^{2+} system with interfering metal ions. [**1**] = 10 μM, [Cu^{2+}] = 10 μM, and [M^{n+}] = 10 μM. λ_{ex} = 326 nm.

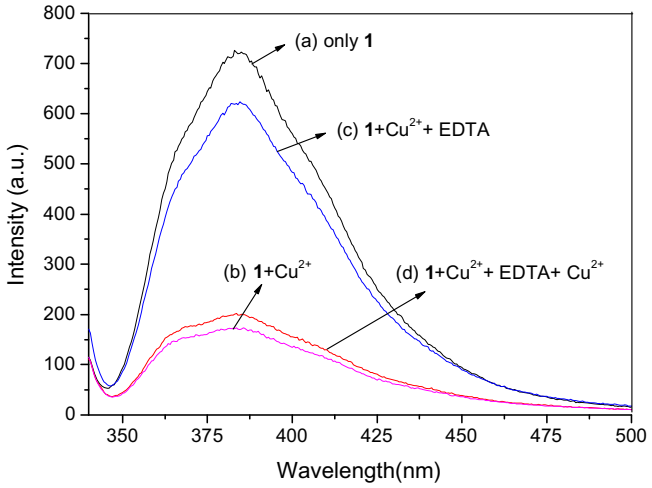
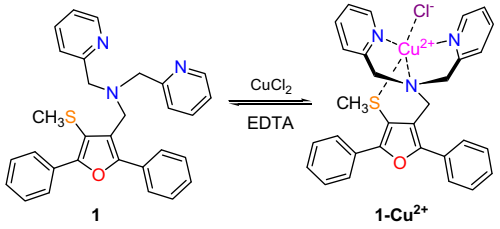


Figure 10. Emission spectra in DMSO/water (95:5, v/v) containing HEPES buffer (10 mM, pH = 7.0). (a) Only **1** (10 μM); (b) **1** (10 μM) with Cu^{2+} (10 μM); (c) **1** (10 μM) with Cu^{2+} (10 μM) and then addition of EDTA (20 μM); (d) **1** (10 μM) with Cu^{2+} (10 μM) and EDTA (20 μM) then addition of Cu^{2+} (25 μM).



Scheme 2. Proposed binding model for **1** with Cu^{2+}.

In conclusion, a new selective fluorescent sensor based on 2,5-diphenylfuran and di(2-picolyl)amine (DPA) was designed and synthesized which was capable to detect Cu^{2+} ion with high selectivity in aqueous DMSO. This sensor formed a 1:1 complex with Cu^{2+} and showed a fluorescent quenching.

Acknowledgments

This study was supported by the Science Technology Foundation for Creative Research Group of HBDE (Grant No. T201311) and the National Natural Science Foundation of China (Grant No. 21501055).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.025.

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23. *Procedures for the synthesis of compound* ***1***: To a 50 mL flask, Compound **5** (0.358 g, 1.0 mmol) and di(2-picolyl)amine (**6**) (0.199 g, 1.0 mmol) was dissolved in CH_3CN (20 mL) and K_2CO_3 (0.55 g, 4.0 mol) was added. The resultant mixture was refluxed for 3 h, cooled to room temperature, diluted with 2 N HCl (50 mL) and extracted with EtOAc (3 × 20 mL). The extracts were washed with brine (2 × 20 mL) and dried over anh. $MgSO_4$. After filtration and rotary evaporation, the residue was purified by flash chromatography with petroleum as elust to give compound **1** (0.36 g, 75.7%) as a pale solid. Mp: 128–129 °C; IR (KBr, cm^{-1}): 3059, 2827, 1594, 1479, 147, 760. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.51 (dd, J = 9 Hz, 9 Hz, 2H), 8.19–8.2 (m, 2H), 7.83 (d, J = 15 Hz, 1H), 7.64 (d, J = 15 Hz, 1H), 7.30–7.43 (m, 8H), 3.95 (s, 2H), 3.88 (s, 4H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 152.1, 149.9, 148.7, 136.2, 130.7, 130.4, 128.4, 127.9, 127.4, 126.3, 125.7, 123.6, 122.5, 121.9, 117.7, 60.5, 48.0, 19.3. ESI-MS: m/z 478.14 ($[M+H]^+$). Anal. Calcd for $C_{30}H_{27}N_3OS$: C, 75.44; H, 5.70; N, 8.80. Found C, 75.23; H, 5.35; N, 8.67.
24. *Crystal data for* ***1***. $C_{30}H_{27}N_3OS$, M = 477.61, Triclinic, space group P-1, a = 10.5773(12), b = 11.1121(12), c = 12.1339(13) Å, α = 110.1090(10), β = 98.237(2), γ = 107.317(2)°, V = 1229.6(2) $Å^3$, Z = 2, Dc = 1.339 g cm^{-3}, Reflections collected: 11208, independent reflections: 6970 [R(int) = 0.0215], Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0418, wR_2 = 0.1239. R indices (all data): R_1 = 0.0466, wR_2 = 0.1307. CCDC 924966.
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