Tetrahedron Letters 49 (2008) 7391–7394

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A dual-function colorimetric chemosensor for thiols and transition metal ions based on ICT mechanism

Yan Zeng [a,b], Guanxin Zhang [a], Deqing Zhang [a,*], Daoben Zhu [a]

[a] Beijing National Laboratory for Molecular Sciences, Organic Solids Laboratory, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China
[b] Graduate School of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:
Received 31 July 2008
Revised 2 October 2008
Accepted 14 October 2008
Available online 17 October 2008

ABSTRACT

Remarkable absorption spectral changes were observed for compound **1** with *N*,*N*-bis(pyridin-2-yl-methyl) aniline and quinone units after either reaction with thiol-containing amino acids/peptides or coordination with Zn^{2+}/Co^{2+}. Therefore, compound **1** is a potential dual-function colorimetric chemosensor for thiol-containing amino acids/peptides and Zn^{2+}/Co^{2+}.

The rapid, sensitive, and selective sensing of thiols has aroused significant interest in many areas especially in biological systems.[1] Intracellular thiols such as glutathione (GSH), cysteine (Cys), and homocysteine (HCys) play a crucial role in maintaining biological redox homeostasis through the equilibrium established at a given electrical potential between reduced free thiols (RSH) and oxidized disulfides (RSSR). Thiols are also active in the catalytic sites of enzymes, and play important roles in metabolic pathways.[2] The levels of certain thiols have been linked to a number of diseases, including cancer, Alzheimer's, and cardiovascular disease.[3] The thiol-levels may also be affected in response to the oxidative stress that has been associated with some of these conditions. Consequently, the development of selective and sensitive chemosensors for thiols has received more attentions in recent years.[4] A wide variety of colorimetric[5] and fluorescent[6] sensors for thiol-containing amino acids and peptides have been developed. Most of the reported sensors are based on redox chemistry[7] or labeling with chromophores or fluorophores and a combination of separation technique.

Meanwhile, selective and sensitive assay for transition metal ions becomes highly desirable.[8] This is simply because transition metal ions have been widely used in different areas and they indeed pose an increasing environmental and health risk.[9] Besides, some transition metal ions have many important biological functions.[10] For instance, Zn^{2+} is of great interest in the field of neurobiology,[11] and the disorder of Zn^{2+} metabolism is closely associated with many severe neurological diseases, including Alzheimer's disease (AD), cerebral ischemia, and epilepsy.[12] Most of the colorimetric or luminescent chemosensors for transition metal ions are designed by employing intramolecular charge-transfer (ICT) or photoinduced electron transfer (PET) mechanisms.[13,14]

Although a number of chemosensors for different analytes such as thiols and transition metal ions have been described, dual-function chemosensors[15] which can be used to detect two analytes remain rare. In this Letter, we describe a dual-function colorimetric chemosensor for thiols and transition metal ions based on an electro donor–acceptor compound **1** (Scheme 1), which exhibits intramolecular charge-transfer absorption. The design rationale is explained as follows (see Scheme 1): (1) the intramolecular charge-transfer absorption would become weak by reducing either the electron-accepting ability of the quinone unit or the electron-donating ability of the aniline unit. It is known that the Michael reaction between quinone and thiol can take place easily as shown in Scheme 1. Accordingly, the electron-accepting ability of quinone would be reduced and the intensity of the ICT absorption band would decrease; (2) the incorporation of two pyridine units would allow the binding with metal ions and as a result, the electron-donating ability of aniline unit would be reduced; consequently, the ICT band would become gradually weak after binding with metal ions.

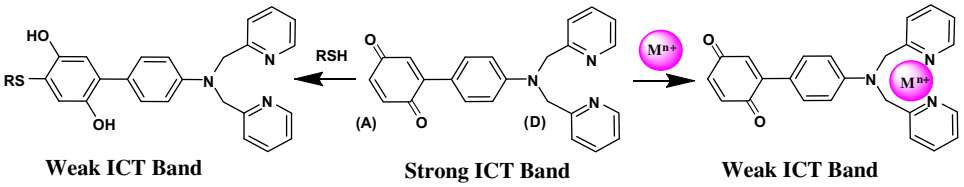
Herein, we will report the absorption spectral variation of compound **1** in the presence of thiols (Cys and GSH) and metal ions. The results show that compound **1** can be used as a dual-function colorimetric chemosensors for thiols and Zn^{2+}/Co^{2+}.

The synthesis of compound **1** started from *N*,*N*-bis(pyridin-2-yl-methyl) aniline by a four-step synthesis in an overall 57% yield (Scheme 2). Bromination of *N*,*N*-bis(pyridin-2-yl-methyl) aniline with NBS led to compound **2**, which was transformed into compound **3** by Suzuki coupling reaction with compound **4**. Subsequently, demethoxylation of compound **3** with BBr_3 and then oxidation with PbO_2, compound **1** was obtained in good yield.[16]

As anticipated, compound **1** shows a strong ICT band in the range of 450–700 nm as shown in Figure 1. After addition of Cys, the intensity of ICT band started to decrease gradually. This is due to the fact that the reaction of thiol group of Cys toward the

* Corresponding author.
E-mail address: dqzhang@iccas.ac.cn (D. Zhang).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.055



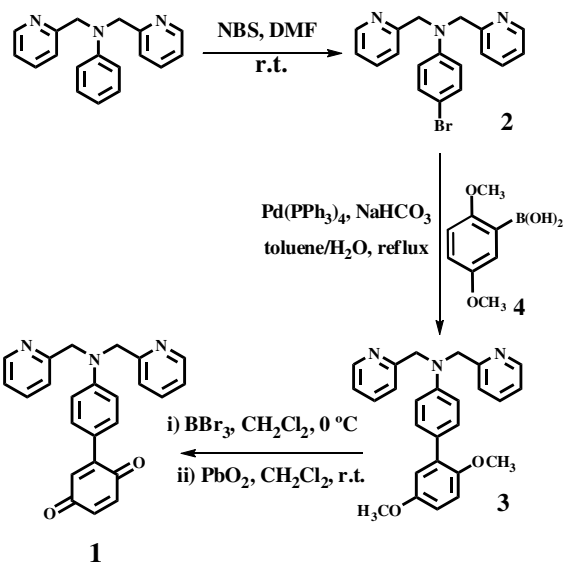
Scheme 1. Design rationale for the dual function chemosensor.

quinone unit of **1** results in the transformation of quinone into the corresponding hydroquinone as indicated in Scheme 1. The absorption intensity at 532 nm decreased with the concentration of Cys, and a nearly linear relation (I_{532nm} = 0.15339 − 0.00269 [Cys], r^2 = 0.9944, n = 8) was resulted as displayed in the inset of Figure 1. When more than 1.0 equiv of Cys was added, no further decrease of the intensity of ICT band was observed. This indicates that the reaction molar ratio between compound **1** and Cys is 1:1.[17]

As a tripeptide containing glutamate, cysteine, and glycine, glutathione (GSH) plays an important role in biological processes.[18] Developing new analytical probes for GSH becomes more and more appealing now. Compound **1** is a potentially useful colorimetric probe for GSH. As shown in Figure 2, the intensity of the ICT band of **1** decreased gradually after addition of GSH. Moreover, the intensity of the ICT band at 532 nm decreased linearly (I_{532nm} = 0.16287 − 0.00263 [GSH], r^2 = 0.9946, n = 5) with the increasing concentration of GSH in the solution (see inset of Fig. 2). These results indicate that a selective determination of GSH can be established with compound **1**. It is reasonably expected that compound **1** can also be employed to detect other thiol-containing peptides.

In order to examine the selectivity of compound **1** toward thiol-containing peptides and amino acids, competitive experiments were also carried out. The absorption spectra of **1** in the presence of other amino acids were recorded, and no obvious absorption spectral change was detected under the same conditions. Figure 3 illustrates the absorption intensity variation at 532 nm (ICT band) of 1 after addition of 1.0 equiv of the representative amino acids and GSH; the high intensity variation for the ICT band (at 532 nm) of **1** was observed only after addition of thiol-containing molecules (Cys and GSH). These results clearly show that the ICT band intensity of compound **1** was largely reduced after addition of either Cys or GSH, leading to contrasting color change of the solution of **1** (see inset of Fig. 3). Therefore, it can be concluded that compound **1** can be employed as a selective colorimetric visual probe for thiol-containing amino acids and peptides.

The absorption spectrum of **1** was also measured in the presence of transition metal ions and other ions such as Fe^{3+}, Ba^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, K^+, Mg^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, and Zn^{2+}. Among the tested metal ions, large absorption spectral changes were observed for **1** after addition of Zn^{2+} or Co^{2+}. The intensities of the absorption bands around 532 nm (ICT band) were gradually reduced after introducing either Zn^{2+} or Co^{2+}. Simultaneously, a new absorption band around 394 nm emerged and increased gradually. As a result, an isosbestic absorption point appeared at 444 nm (Fig. 4). After addition of either Zn^{2+} or Co^{2+}, the dark purple solution of **1** turned out to be yellow as shown in the insets of Figure 4. A linear relation



Scheme 2. Synthetic approach for compound **1**.

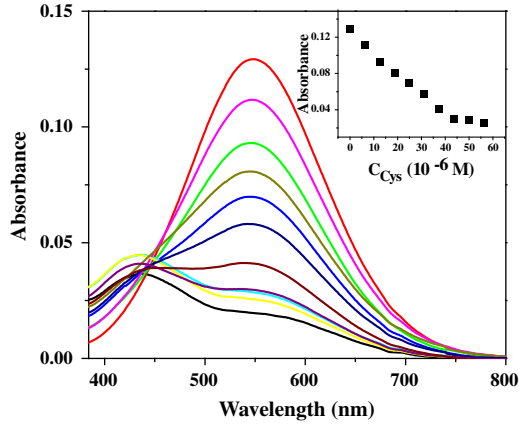


Figure 1. Absorption spectra of compound **1** (40 μM) in CH_3CN/H_2O (v/v, 1:1) after addition of Cys; inset shows the variation of absorption intensity at 532 nm vs. the concentration of Cys; The absorption spectra were recorded after the mixture solution was kept at 40 °C for 20 min.

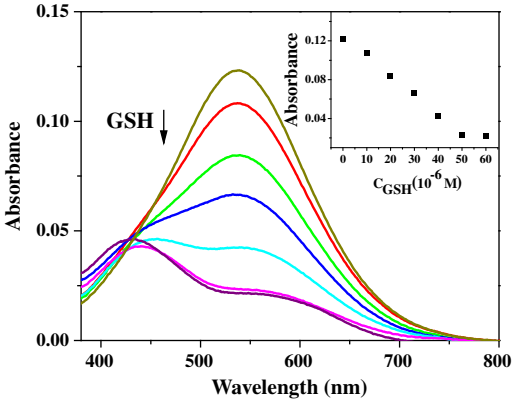


Figure 2. Absorption spectra of compound **1** (40 μM) in CH_3CN/H_2O (v/v, 1:1) after addition of GSH; inset shows the variation of absorption intensity at 532 nm versus the concentration of GSH. The absorption spectra were recorded after the mixture solution was kept at 40 °C for 20 min.

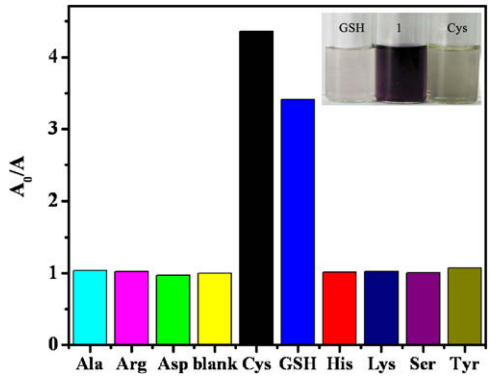


Figure 3. Absorbance variation (A_0/A) of compound **1** (40 μM in CH_3CN and H_2O, v/v = 1/1) at 532 nm before (A_0) and after (A) addition of 1.0 equiv of several representative amino acids and GSH; inset shows the color change of **1** (400 μM) in the absence and presence of 1.0 equiv of Cys or GSH.

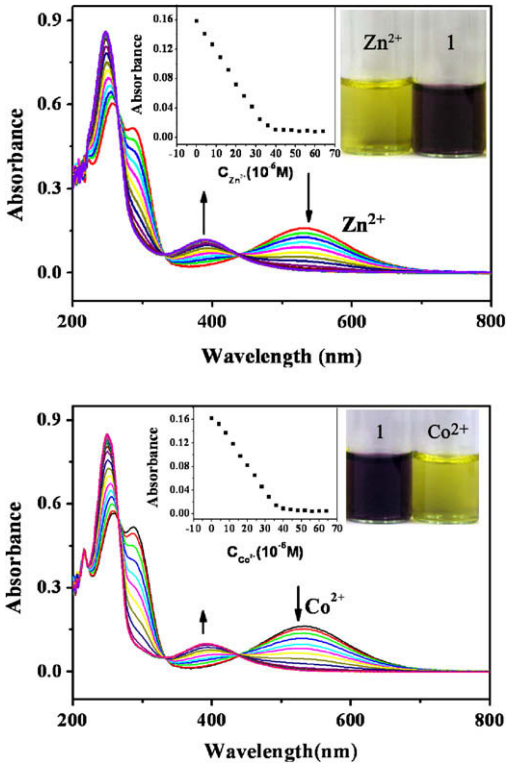


Figure 4. Absorption spectra change of compound 1 (40 μM, CH_3CN) by addition of Zn^{2+} (up) and Co^{2+} (below). Insets: left the variation of absorption intensity at 532 nm versus the concentration of the respective metal ion; right the color change of **1** (400 μM) in the presence of 1.0 equiv of the respective metal ion.

was observed for the absorption intensity at 532 nm versus the concentration of Zn^{2+} or Co^{2+} as shown in the insets of Figure 4 too. The spectrum of **1** kept almost unchanged when more than 1.0 equiv of Zn^{2+} or Co^{2+} were added to the solution, implying a 1:1 complex was formed between **1** and Zn^{2+} or Co^{2+}. ^1H NMR and mass spectroscopic data also supported this conclusion (see Supplementary data). The binding constants of **1** with Zn^{2+} and Co^{2+} were estimated to be 2.49×10^4 for Co^{2+} and 2.28×10^4 for Zn^{2+}, respectively, based on the corresponding absorption spectral changes.

Figure 5 shows the absorption intensity variation at 532 nm of **1** in the presence of 1.0 equiv of representative metal ions. Clearly, other transition metal ions cannot induce such obvious absorption

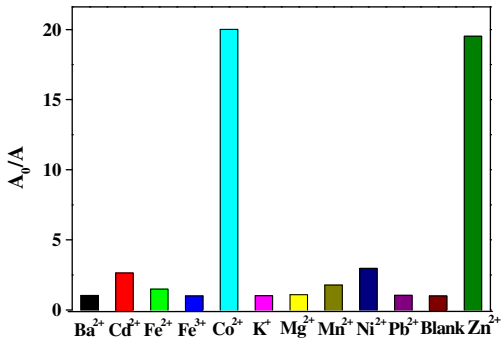


Figure 5. Absorbance variation (A_0/A) of compound **1** (40 μM,CH_3CN) at 532 nm before (A_0) and after (A) addition of 1.0 equiv of several metal ions.

spectral variation for **1** under the same conditions in comparison with Zn^{2+} and Co^{2+}. These results indicate that compound **1** can act as a colorimetric visual sensor for Zn^{2+} and Co^{2+}.

In summary, a donor–acceptor compound **1** bearing *N*,*N*-bis (pyridin-2-yl-methyl) aniline and quinone units was designed and synthesized for development of colorimetric chemosensors for thiols and metal ions. The reaction of the quinone unit with thiol-containing amino acids and peptides weakens the electron-accepting ability of the quinone unit in **1** and as a result the ICT band intensity decreases gradually. Similarly, the coordination between **1** and metal ions reduces the electron-donating ability of the aniline unit in **1** and accordingly the ICT band becomes weak gradually. Remarkable absorption spectral changes were observed for **1** after addition of either thiol-containing amino acids/peptides or Zn^{2+}/Co^{2+}. Therefore, compound **1** can be employed as a dual-function colorimetric chemosensor for thiols and Zn^{2+}/Co^{2+}.

Supplementary data

Supplementary data contains experimental details of the synthesis and characterization. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.055.

References and notes

1. (a) Tang, B.; Xing, Y. L.; Li, P.; Zhang, N.; Yu, F. B.; Yang, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 11666; (b) Matsumoto, T.; Urano, Y.; Shoda, T.; Kojima, H.; Nagano, T. *Org. Lett.* **2007**, *9*, 3375; (c) Shimada, T.; Ookubo, K.; Komuro, N.; Shimizu, T.; Vehara, N. *Langmuir* **2007**, *23*, 11225.
2. (a) Finkelstein, J. D.; Martin, J. J. *Int. J. Biochem. Cell Biol.* **2000**, *32*, 385; (b) Poole, L. B.; Karplus, P. A.; Claiborne, A. *Annu. Rev. Pharmacol. Toxicol.* **2004**, *44*, 325.
3. (a) Refsum, H.; Ueland, P. M.; Nygard, O.; Vollset, S. E. *Annu. Rev. Med.* **1998**, *49*, 31; (b) Shahrokhian, S. *Anal. Chem.* **2001**, *73*, 5972; (c) Wolfe, M. S.; de Los Angeles, J.; Miller, D. D.; Xia, W.; Selkoe, D. *J. Biochem.* **1999**, *38*, 11223.
4. (a) Wang, W. H.; Escobedo, J. O.; Lawrence, C. M.; Strongin, R. M. *J. Am. Chem. Soc.* **2004**, *126*, 3400; (b) Lu, C.; Zu, Y. B. *Chem. Commun.* **2007**, *37*, 3871; (c) Lee, J. S.; Ulmann, P. A.; Han, M. S.; Mirkin, C. A. *Nano Lett.* **2008**, *8*, 529.
5. (a) Ros-Lis, J. V.; Garcia, B.; Jimenez, D.; Martinez-Manez, R.; Sancenon, F.; Soto, J.; Gonzalvo, F.; Valldecabres, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 4064; (b) Rusin, O.; Luce, N. N.; Agbaria, R. A.; Escobedo, J. O.; Jiang, S.; Warner, I. M.; Dawan, F. B.; Lian, K.; Strongin, R. M. *J. Am. Chem. Soc.* **2004**, *126*, 438; (c) Shao, N.; Jin, J. Y.; Cheung, S. M.; Yang, R. H.; Chan, W. H.; Mo, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4944; (d) Li, S. H.; Yu, C. W.; Xu, J. G. *Chem. Commun.* **2005**, *4*, 450.
6. (a) Tanaka, F.; Mase, N.; Barbas, C. F. *Chem. Commun.* **2004**, *15*, 1762; (b) Zhang, M.; Yu, M. X.; Li, F. Y.; Zhu, M. W.; Li, M. Y.; Gao, Y. H.; Li, L.; Liu, Z. Q.; Zhang, J. P.; Zhang, D. Q.; Tao, Y.; Huang, C. H. *J. Am. Chem. Soc.* **2007**, *129*, 10322; (c) Chen, H. L.; Zhao, Q.; Wu, Y. B.; Li, F. Y.; Yang, H.; Yi, T.; Huang, C. H. *Inorg. Chem.* **2007**, *46*, 11075; (d) Bouffard, J.; Kim, Y.; Swager, T. M.; Weissleder, R.; Hilderbrand, S. A. *Org. Lett.* **2008**, *10*, 37.
7. (a) Inoue, T.; Kirchhoff, J. R. *Anal. Chem.* **2000**, *72*, 5755; (b) Zen, J.-M.; Kumar, A. S.; Chen, J.-C. *Anal. Chem.* **2001**, *73*, 1169; (c) Pacsial-Ong, E. J.; McCarley, R. L.; Wang, W. H.; Strongin, R. M. *Anal. Chem.* **2006**, *78*, 7577.
8. (a) De Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515; (b) Valeur, B.; Leray, I. *Coord .Chem. Rev.* **2000**, *205*, 3; (c) Rurack, K.; Resch-Genger, U.

Chem. Soc. Rev. **2002**, *31*, 116; (d) Jiang, P.; Guo, Z. *Coord. Chem. Rev.* **2004**, *248*, 205.
9. (a) Needleman, H. L. *Human Lead Exposure*; CRC Press: Boca Raton, FL, 1992; (b) Renzoni, A.; Zino, F.; Franchi, E. *Environ. Res.* **1998**, *77*, 68; (c) Turner, F. *Science* **2000**, *290*, 1315.
10. (a) Crick, O. R.; Othmer, F. D. *Encyclopedia of Chemical Technology* **1982**, *5*, 851; (b) Que, E. L.; Domaille, D. W.; Chang, C. J. *Chem. Rev.* **2008**, *108*, 1517.
11. (a) Frederickson, C. J. *Int. Re. Neurobiol.* **1989**, *31*, 145; (b) Berg, J. M.; Shi, Y. *Science* **1996**, *271*, 1081; (c) Huang, E. P. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 13386.
12. (a) Koh, J. Y.; Suh, S. W.; Gwag, B. J.; He, Y. Y.; Hsu, C. Y.; Choi, D. W. *Science* **1996**, *272*, 1013; (b) Frederickson, C. J.; Hernandez, M. D.; McGinty, J. F. *Brain Res.* **1989**, *480*, 317.
13. (a) Wang, J. B.; Qian, X. H.; Qian, J. H.; Xu, Y. F. *Chem. Eur. J.* **2007**, *13*, 7543; (b) Gunnlaugsson, T.; Leonard, J. P.; Murray, N. S. *Org. Lett.* **2004**, *6*, 1557; (c) Xu, Z. C.; Xiao, Y.; Qian, X. H.; Cui, J. N.; Cui, D. W. *Org. Lett.* **2005**, *7*, 889; (d) Wang, J. B.; Qian, X. H.; Cui, J. N. *J. Org. Chem.* **2006**, *71*, 4308; (e) Zhang, H.; Wang, Q. L.; Jiang, Y. B. *Tetrahedron Lett.* **2007**, *48*, 3959; (f) Zhang, H.; Han, L. F.; Zachariasse, K. A.; Jiang, Y. B. *Org. Lett.* **2005**, *7*, 4217.
14. (a) Walkup, G. K.; Burdette, S. C.; Lippard, S. J.; Tsien, R. Y. *J. Am. Chem. Soc.* **2000**, *122*, 5644; (b) Burdette, S. C.; Walkup, G. K.; Spingler, B.; Tsien, R. Y.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 7831; (c) Burdette, S. C.; Frederickson, C. J.; Bu, W.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 1778; (d) Wang, J. B.; Qian, X. H. *Org. Lett.* **2006**, *8*, 3721; (e) Liu, B.; Tian, H. *Chem. Commun.* **2005**, 3156; (f) Zhang, G.; Zhang, D.; Yin, S. W.; Yang, X. D.; Shuai, Z. G.; Zhu, D. B. *Chem. Commun.* **2005**, 2161; (g) Wang, Z.; Zhang, D. Q.; Zhu, D. B. *Anal. Chim. Acta* **2005**, *549*, 10.
15. (a) Collado, D.; Perez-Inestrosa, E.; Suau, R.; Desvergne, J-P.; Bouas-Laurent, H. *Org. Lett.* **2002**, *4*, 855; (b) Mello, J. V.; Finney, N. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1536; (c) El-Safty, S. A.; Ismail, A. A.; Matsunaga, H.; Hanaoka, T.; Mizukami, F. *Adv. Funct. Mater.* **2008**, *18*, 1485.
16. *Characterization data for* **1**: mp 139–140 °C, ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.61 (d, 2H, J = 4 Hz), 7.64 (t, 2H, J = 7.6 Hz), 7.40 (d, 2H, J = 8.8 Hz), 7.24 (d, 2H, J = 7.6 Hz), 7.19 (t, 2H, J = 6.8 Hz), 6.78 (d, 2H, J = 7.6 Hz), 6.76 (3H, m) 4.88 (4H, s); ^{13}CNMR (100 MHz, $CDCl_3$): δ 187.63, 187.57, 157.85, 150.01, 149.85, 144.995, 136.89, 136.25, 130.58, 129.03, 122.25, 121.13, 120.70, 112.38, 57.09. HR-MS (ESI): Anal. Calcd for $C_{24}H_{20}N_3O_2$ $(M+1)^+$, 382.15499; found, 382.15501. EA: Anal. Calcd for $C_{24}H_{19}N_3O_2{\cdot}CH_3COOC_2H_5$: C, 71.62; H, 5.80; N, 8.95. Found: C, 71.27; H, 5.44; N, 9.26.
17. This is in agreement with previous reports (see *J. Med. Chem.*, **1986**, *29*, 1714–1720; *Analyst*, **2001**, *126*, 353–357; *Electrochem. Commun.* **2003**, *5*, 732–736) about the transformation of quinone into the corresponding hydroquinone unit upon reaction with Cys.
18. (a) Samiec, P. S.; Drews-Botsch, C.; Flagg, E. W.; Kurtz, J. C.; Sternberg, P.; Reed, R. L.; Jones, D. P. *Free Radic. Biol. Med.* **1998**, *24*, 699; (b) Finkel, T.; Holbrook, N. J. *Nature* **2000**, *408*, 239.