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A 1,8-Naphthyridine-Based Fluorescent Chemodosimeter for the Rapid Detection of Zn^{2+} and Cu^{2+}

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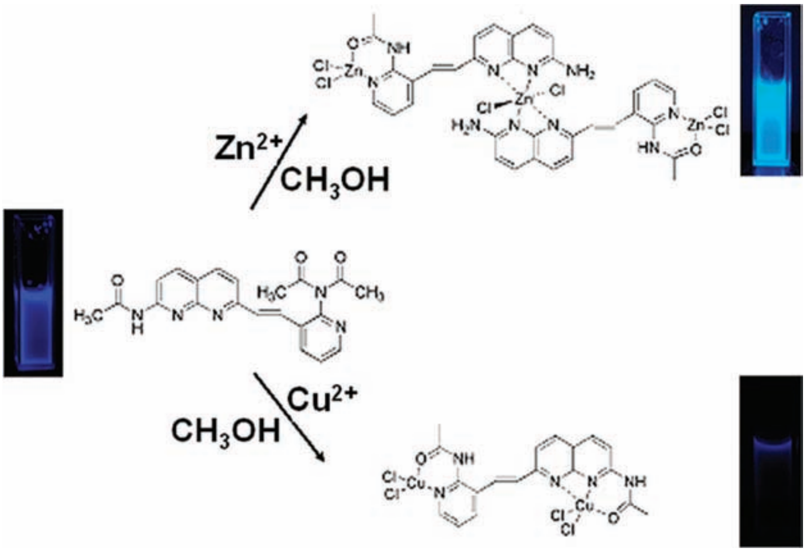
ABSTRACT



A novel fluorescent chemodosimeter based on 1,8-naphthyridine exhibits high selectivity to Zn^{2+} and Cu^{2+}. When 1-(7-acetamino-1,8-naphthyridyl)-2-(6-diacetaminopyridyl)ethene was mixed with $CuCl_2$, hydrolysis of the acetamino group catalyzed by Cu^{2+} complex was first observed. Resulting from coordination and hydrolysis catalyzed by the corresponding complex of Zn^{2+} or Cu^{2+}, the highly effective fluorescent detection of Zn^{2+} and Cu^{2+} is realized with Zn^{2+}-selective dual-emission and Cu^{2+}-selective ON−OFF behavior.

The design and synthesis of fluorescent probes with desirable properties are of considerable importance in supermolecular chemistry due to their fundamental role in medical, environmental, and biological applications.[1] As the second metal ion in abundance among the essential heavy metal elements in the human body, zinc ion plays an important role in various fundamental biological processes, such as gene transcription, regulation of metalloenzymes, and neural signal transmission.[2] Zn^{2+} does not show distinct spectroscopic or magnetic signals necessary for application of many common analytical techniques such as UV−vis spectrometry, Mössbauer spectroscopy, nuclear magnetic resonance (NMR), and electron paramagnetic resonance (EPR) spectroscopy for its $3d^{10}4s^0$ electronic configuration. These features make it hard to detect Zn^{2+}. Due to great changes in the absorption and/or fluorescent spectra of many fluorescent organic molecules after they are coordinated with metal ions, the colorimetric and fluorescence methods are very important and effective ways to detect metal ions.[3] Recently, some zinc ion-selective chemosensors have been reported.[4] On the other

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(1) (a) Komatsu, K.; Urano, Y.; Kojima, H.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 13447. (b) Peng, X.; Du, J.; Fan, J.; Wang, J.; Wu, Y.; Zhao, J.; Sun, S.; Xu, T. *J. Am. Chem. Soc.* **2007**, *129*, 1500. (c) He, Q.; Miller, E. W.; Wong, A. P.; Chang, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 9316. (d) Liu, L.; Zhang, D.; Zhang, G.; Xiang, J.; Zhu, D. *J. Org. Chem.* **2008**, *10*, 2271.

(2) (a) Carol, P.; Sreejith, S.; Ajayaghosh, A. *Chem. Asian J.* **2007**, *2*, 338. (b) Rhee, H. W.; Choi, H. Y.; Han, K.; Hong, J. I. *J. Am. Chem. Soc.* **2007**, *129*, 4524. (c) Chang, C. J.; Nolan, E. M.; Jaworski, J.; Okamoto, K.; Hayashi, Y.; Sheng, M.; Lippard, S. J. *Inorg. Chem.* **2004**, *43*, 6774.

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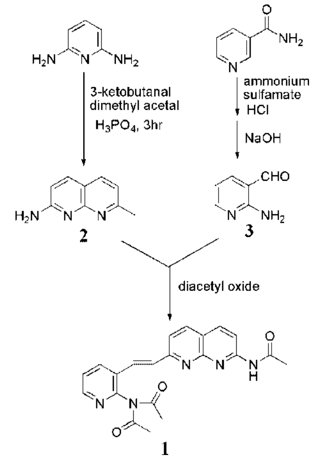
hand, the design of colorimetric or fluorescent sensor with specific response to Cu^{2+} has been extensively studied[5] as it is a significant metal pollutant due to its widespread use,[6] and it is also an essential trace element in biologic systems.[7] Although great achievement in the field of metal ion-chemosenors has been obtained, there is still a demand for new indicators with improved properties, especially fluorescent probes with high efficiency in the spectral visible region.

This work is aimed at the design and construction of a fluorometric assay to highly effective detection of Zn^{2+} and Cu^{2+}. For their various photoluminescent properties and short metal···metal distance formed in their metal building blocks, 1,8-naphthyridine (napy) and its derivatives have been widely used as guanine recognition regents and bidentate ligands.[8] However, there are very few reports about the derivatives of 1,8-naphthyridine as fluorescent sensors for transition metals. In order to shift the emission bands to a visible region, a larger conjugated molecule 1-(7-acetamino-1,8-naphthyridyl)-2-(6-diacetaminopyridyl)ethene (**1**) was selected. In this paper, we report the Zn^{2+}- and Cu^{2+}-selective recognizing properties of fluorophore **1**. Compound **1** possesses efficient Zn^{2+}-selective dual-emission and Cu^{2+}-slective ON−OFF behavior.

Compound **1**[9] was synthesized by the reaction of compounds **2** and **3** in diacetyl oxide. Compounds 2-methyl-7-amino-1,8-naphthyridine (**2**),[10] 2-amino-3-aldehyde−pyridine (**3**),[11] 2-diacetamino-3-methyl-pyridine (**4**), and 2-methyl-7-acetamino-1,8-naphthyridine (**5**) were synthesized acording to modified reported methods.[12] The crystals of **1** were obtained by slow volatilization of their DMF solution in air. The synthetic route is shown in Scheme 1, the detailed synthetic procedure, X-ray crystal structure of **1**, and characterization of **1**−**5** are shown in the Supporting Information.

Scheme 1. Synthetic Route of Compound **1**



Compound **1** exhibits relative strong fluorescence emission at 411 nm ($\Phi_f = 0.07$)[13] in methanol upon excitation at 362 nm (Figure 1A). Upon titration of Zn^{2+}, a new fluorescence emission peak at about 458 nm appeared and the intensity dramatically enhanced with 411 nm emission intensity decreased, indicating a Zn^{2+}-selective dual-emissive-type signaling behavior. However, when Cu^{2+} ion was added, the

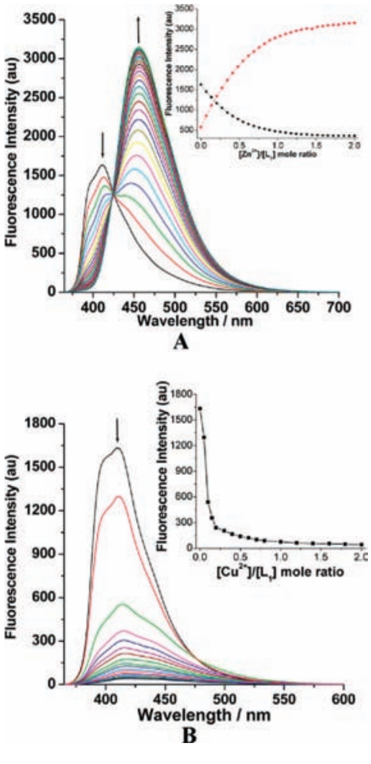


Figure 1. Changes in fluorescence emission spectra of **1** (5.0×10^{-5} M) in methanol upon addition of Zn^{2+} (A) and Cu^{2+} (B). The ratio of metal ions to **1** is 2 equiv to 1. Inset: Emission intensities of compound **1** at 411 nm (black dot) and 458 nm (red dot) as a function of addition of Zn^{2+} (A)/Cu^{2+} (B). The concentration of Zn^{2+}/Cu^{2+} changed from 0 to 1.0×10^{-4} M and excitation was at 362 nm.

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(3) (a) Chen, Y.; Han, K. Y.; Liu, Y. *Bioorg. Med. Chem.* **2007**, *15*, 4537. (b) Partha, R.; Koushik, D.; Mario, M.; Jagnyeswar, R.; Pradyot, B. *Inorg. Chem.* **2007**, *46*, 6405. (c) Royzen, M.; Durandin, A.; Young, V. G.; Geacintov, N. E.; Canary, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 3854. (d) Komatsu, K.; Kikuchi, K.; Kojima, H.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 10197. (e) Woodroofe, C. C.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 11458.

(4) (a) Wang, H. H.; Gan, Q.; Wang, X. J.; Xue, L.; Liu, S. H.; Jiang, H. *Org. Lett.* **2007**, *9*, 4995. (b) Zhou, X.; Yan, J.; Pei, J. *Macromolecules* **2004**, *37*, 7078. (c) Maruyama, S.; Kikuchi, K.; Hirano, T.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2002**, *124*, 10650. (d) Pearce, D. A.; Jotterand, N.; Carrico, I. S.; Imperiali, B. *J. Am. Chem. Soc.* **2001**, *123*, 5160. (e) Lu, C.; Xu, Z.; Cui, J.; Zhang, R.; Qian, X. *J. Org. Chem.* **2007**, *72*, 3554. (f) Henary, M. M.; Wu, Y.; Fahrni, C. J. *Chem.*−*Eur. J.* **2004**, *10*, 3015.

(5) (a) Weng, Y.-Q.; Yue, F.; Zhong, Y.-R.; Ye, B.-H. *Inorg. Chem.* **2007**, *46*, 7749. (b) Rurack, K.; Kollmannsberger, M.; Resch-Genger, U.; Daub, J. *J. Am. Chem. Soc.* **2000**, *122*, 968. (c) Royzen, M.; Dai, Z.; Canary, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 1612. (d) Qi, X.; Jun, E. J.; Xu, L.; Kim, S.-L.; Hong, J. S. J.; Yoon, Y. J.; Yoon, J. *J. Org. Chem.* **2006**, *71*, 2881. (e) Xu, Z.; Xiao, Y.; Qian, X.; Cui, D. *Org. Lett.* **2005**, *7*, 889. (f) Wen, Z.-C.; Yang, R.; He, H.; Jiang, Y.-B. *Chem. Commun.* **2006**, 106.

(6) Rurack, K. *Spectrochim. Acta Part A* **2001**, *57*, 2161.

(7) (a) Kramer, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 772.

(8) (a) Djurdjevic, S.; Leigh, D. A.; McNab, H.; Parsons, S.; Teobaldi, G.; Zerbetto, F. *J. Am. Chem. Soc.* **2007**, *129*, 476. (b) Quinn, J. R.; Zimmerman, S. C.; Del Bene, J. E.; Shavitt, I. *J. Am. Chem. Soc.* **2007**, *129*, 934. (c) Cristian, S. C.; Lisa, M. T.; José, R. G.; Xiang, O.; Kim, R. D. *Inorg. Chem.* **2002**, *41*, 1523.

(9) (a) Newkome, G. R.; Koppersmith, D. L. *J. Org. Chem.* **1973**, *38*, 4461. (b) Liang, F. S.; Xie, Z. Y.; Wang, L. X.; Jing, X. B.; Wang, F. S. *Tetrahedron Lett.* **2002**, *43*, 3427.

(10) Satake, H.; Nishizawa, S.; Teramae, N. *Anal. Sci.* **2006**, *22*, 195.

(11) Majewicz, T. G.; Caluwe, P. *J. Org. Chem.* **1974**, *39*, 721.

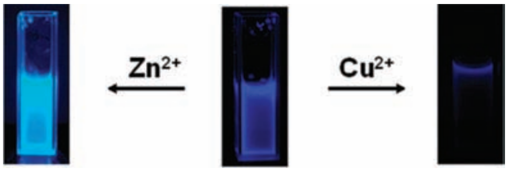


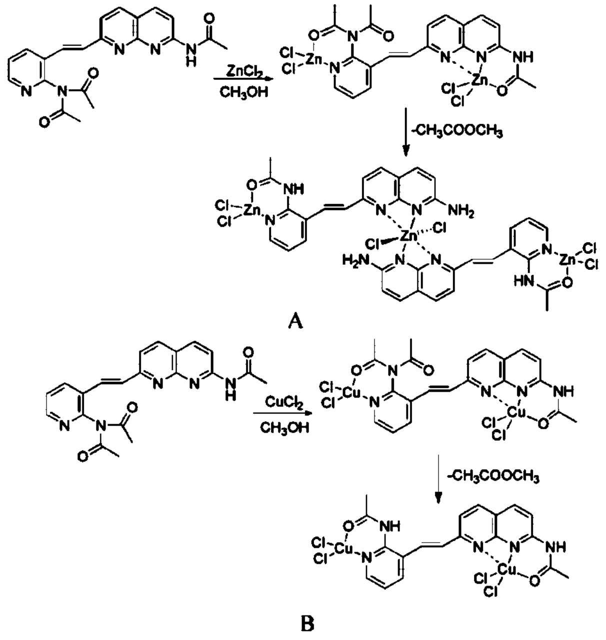
Figure 2. Photograph of **1** in methanol under the irradiation at 365 nm (left: after addition of Zn^{2+}, middle: **1** only, right: after addition of Cu^{2+}).

fluorescence of **1** was significantly quenched (Figure 1B), indicating an efficient Cu^{2+}-selective ON−OFF behavior.[14] The different fluorescence spectra change of compound **1** upon addition of Zn^{2+} and Cu^{2+} may be explained as below: as for the fluorescence change resulted from addition of Zn^{2+}, the red-shift of the emission peak can be ascribed to the recombination of the orbitals, and the increase of emission intensity is most likely the result of rigidification and coplanarity of the compound 1-(7-amino-1,8-naphthyridyl)-2-(6-acetaminopyridyl)ethene; as for the addition of Cu^{2+} into the methanol solution of compound **1**, the d orbitals of Cu^{2+} in the final reaction product of Cu^{2+} and compound **1** might show partial contribution to the LUMO, which led to the quench of the fluorescence of 1-(7-acetamino-1,8-naphthyridyl)-2-(6-acetaminopyridyl)ethene by Cu^{2+} through the electron- and/or energy-transfer processes.[15] The fluorescence decay curves of compound **1** in methanol are fitted to double-exponential decays no matter whether Zn^{2+} or Cu^{2+} was added (Figures S15 and S17, Supporting Information). The changes of fluorescence lifetimes indicate that new fluorescence decay processes were formed after addition of Zn^{2+} or Cu^{2+}. The insets in Figures 1A,B demonstrate the relationship between the molar ratio of Zn^{2+}/Cu^{2+} to that of **1** and the emission intensity at special wavelength.

To study the emission change resulting from the addition of Zn^{2+} and Cu^{2+}, electron spectroscopic imaging (ESI) of **1** was measured after addition of Zn^{2+}/Cu^{2+}. ESI data[16] show that Zn^{2+} and Cu^{2+} play different roles when reacted with **1**. The absorption spectra change of **1** in methanol upon addition of Zn^{2+} and Cu^{2+} are shown inparts A and B of Figure S1 (see the Supporting Information), respectively. Upon gradual addition of Zn^{2+} into the methanol solution of **1**, a new absorption peak at about 369 nm appeared and its intensity increased while the original absorption peak at 360 nm weakened ($\varepsilon = 4.01 \times 10^4$ M^{-1} cm^{-1}). As for addition of Cu^{2+} into methanol solution of **1**, a similar absorption change was observed.

With addition of Zn^{2+}, **1** coordinated first with metal ions to form the coordination complex, and then the complex formed made acetamino group of **1** hydrolyze.[17] In the case of Cu^{2+}, a similar reaction occurred; Cu^{2+} coordinated with **1**, and then the complex formed catalyzed the hydrolysis of acetamino group. The hydrolysis of the two acetamino groups resulting from the complex of Zn^{2+} and **1** may be ascribed to the stronger Lewis acid ZnCl$_2$ compared with CuCl$_2$. The possible reaction mechanism of Zn^{2+}/Cu^{2+} and **1** is depicted in Scheme 2.

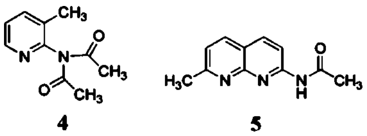
Scheme 2. Proposed Reaction Mechanism of Zn^{2+} (A) and Cu^{2+} (B) with **1**, Respectively



In order to confirm that hydrolysis of acetamino group occurred during the reaction of Zn^{2+} and **1**, we studied reaction of compound **4** and **5** with Zn^{2+}. The crystal structure of complex **5**−Zn (Figure 3) shows that acetamino group was hydrolyzed to amino group during the reaction process of **5** and Zn^{2+}, validating our proposed mechanism. After compound **4** or **5** reacted with Zn^{2+} and Cu^{2+} respectively, the ESI measurement also shows that same reactions occur as those of **1** and Zn^{2+} or Cu^{2+}.[18]

The sensing experiments on Zn^{2+} and Cu^{2+} in ethanol show that recognizing results are similar with those in methanol (Figures S2 and S3, Supporting Information). The experiments of the nitrate anion effect on the selective properties of Zn^{2+} and Cu^{2+} demonstrate that counterions have little influence on the selective effect of fluorophore **1** on Zn^{2+} and Cu^{2+} (Figures S4 and S5, Supporting Informa-

Scheme 3. Molecular Structures of **4** and **5**



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(12) (a) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 3744. (b) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024.

(13) Demas, J. N.; Crosby, G. A. *J. Phys. Chem.* **1971**, *75*, 991.

(14) Fahrni, C. J.; O’flHalloran, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 11448.

(15) Gong, H. Y.; Zheng, Q. Y.; Zhang, X. H.; D.; Wang, X.; Wang, M. X. *Org. Lett.* **2006**, *8*, 4895.

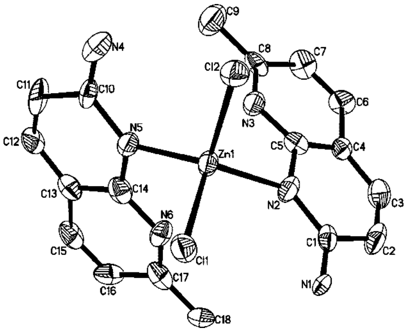

Figure 3. X-ray crystal structure of complex **5**−Zn; solvent molecules were omitted for clarity.

tion). As for sulfate anion, addition of $CuSO_4$ made the fluorescence of **1** quench less strongly than that of $CuCl_2$ and $Cu(NO_3)_2$ (Figure S6, Supporting Information). The weaker quenching intensity of **1** resulting from $CuSO_4$ may be ascribed to the uncoordinated ability of sulfate anion.

The selectivities of **1** to the specific metal ions were examined in methanol. Compound **1** shows extraordinarily different selectivities toward Zn^{2+} and Cu^{2+}. As illustrated in Figure 4A and in the left part from Zn^{2+} in Figure 4B, upon addition of the same amount of the various metal ions, respectively, only Zn^{2+} simultaneously quenched the emission of **1** and a new stronger emission peak appears at about 458 nm. While Cu^{2+} quenched the most significiently fluorescent emission of **1**, no new emission emerged. Compound **1** did not respond distinctly to alkali and alkaline earth metal ions such as Ca^{2+}, Mg^{2+}, Na^+, and K^+. Besides, little influence on the fluorescence intensity of compound **1** was observed for the first-row transition-metal ions such as Cr^{2+}, Ni^{2+}, and Mn^{2+}. The different selectivity of **1** toward Zn^{2+} and Cu^{2+} suggests that **1** has potential application in sensing Zn^{2+} and Cu^{2+}.

Because Ca^{2+}, Mg^{2+}, Na^+, and K^+ exist at high concentration under physiological conditions, it is necessary to measure the disturbance of such metal ions on the detection of Zn^{2+} with compound **1**. The titration of Zn^{2+} and compound **1** in the presence of various metal ions was conducted, and the experimental results (the right part in Figure 4B) illuminate that the fluorescence of the complex resulting from the reaction of Zn^{2+} and compound **1** was not influenced by the alkali and alkaline earth metal ions, even at concentration as high as 5 mM.

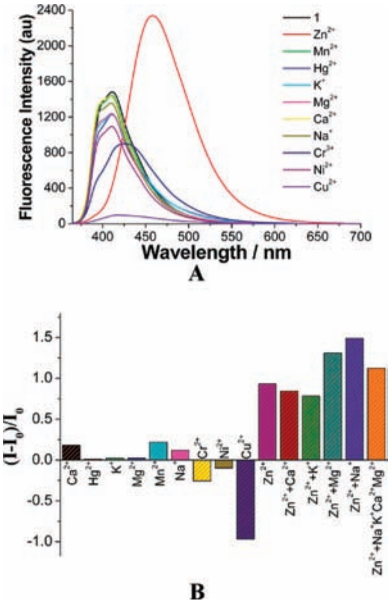

Figure 4. (A) Fluorescence spectra change of **1** (5.0×10^{-5} M) upon addition of different metal cations (2 equiv) in methanol solution. (B) Fluorescence responses of **1** to various metal ions (left part from Zn^{2+} represented in Figure 4B) and fluorescence change of the mixture of **1** and Zn^{2+} after addition of an excess of the appropriate metal ions (5 mM for Ca^{2+} Mg^{2+}, Na^+, K^+) (right part from Zn^{2+} represented in Figure 4B). Bars represent the ratio of the difference between I and I_0 to I_0. I represents the emission intensity at 458 nm, and I_0 is equal to the emission intensity at 441 nm. The overall emission spectra were measured at excitation of 362 nm.

In conclusion, based on the 1,8-naphthyridyl moiety, we have developed a highly selective fluorescent chemodosimeter for Zn^{2+} and Cu^{2+}, which possesses Zn^{2+}-slective dual-emissive-type signaling and Cu^{2+}-selective ON−OFF behaviors. Detection of both Zn^{2+} and Cu^{2+} is realized through fluorescence change resulting from the coordination and hydrolysis of the acetamino group catalyzed by the corresponding complexes of **1** with Zn^{2+} and Cu^{2+}, respectively. In addition, the hydrolysis of the acetamino group induced by Cu^{2+} was first observed herein. Studies of the Zn^{2+}- and Cu^{2+}-selective recognizing properties of fluorophore **1** provide a new type of chemodosimeter to metal ions.

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Supporting Information Available: Experimental procedures, characterization data including mp, ^1H, ^{13}C spectral, and elemental analysis data of the compounds, changes in absorption and emission spectra of **1** upon addition of various metal ions, radiative decay curves of **1** in methanol before, after addition of Zn^{2+} and Cu^{2+}, and crystallographic data of **1** and **5-Zn** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) ESI data of the final compound from reaction of **1** and $ZnCl_2$: $m/z = 1019$ $[M^+ + 1]$, 306 $[M^+ + 1 - 3ZnCl_2$ − compound **5**]. ESI data of the final compound from reaction of **1** and $CuCl_2$: $m/z = 619$ $[M^+ + 1]$, 348 $[M^+ + 1 - 2CuCl_2]$, 306 $[M^+ + 1 - 2CuCl_2 - CH_2CO]$.

(17) (a) Ewa, S.; Gajendrasingh, K. I.; Rex, W. W.; Atta, M. A.; Lisa, M. B. *Inorg. Chem.* **2007**, *46*, 2353. (b) Akira, W.; Yasutaka, H.; Syuhei, Y.; Shigenori, N.; Teizo, K.; Koichiro, J.; Hideki, M. *Inorg. Chem.* **2004**, *43*, 5725. (c) Lisa, M. B.; Magdalena, M. M.; Atta, M. A. *Inorg. Chem.* **2001**, *40*, 2212.

(18) ESI data of the final compound from reaction of **4** and $ZnCl_2$: $m/z = 285$ $[M^+ + 1]$, 249 $[M^+ + 1 - Cl]$, 151 $[M^+ + 1 - ZnCl_2]$. ESI data of the final compound from reaction of **4** and $CuCl_2$: $m/z = 284$ $[M^+ + 1]$, 248 $[M^+ + 1 - Cl]$, 151 $[M^+ + 1 - ZnCl_2]$. ESI data of the final compound from reaction of **5** and $ZnCl_2$: $m/z = 455$ $[M^+ + 1]$, 419 $[M^+ + 1 - Cl]$, 160 $[M^+ + 1 - ZnCl_2]$. ESI data of the final compound from reaction of **4** and $CuCl_2$: $m/z = 301$ $[M^+ + 1]$, 336 $[M^+ + 1 - Cl]$, 202 $[M^+ + 1 - CuCl_2]$, 160 $[M^+ + 1 - CuCl_2 - CH_2CO]$.