A new perimidine-based fluorescent turn-on chemosensor for selective detection of Cu$^{2+}$ ions

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Abstract
Two new molecules based on 2-(2-alkoxy-1-naphthyl)-2,3-dihydro-1H-perimidine are synthesized. The binding properties are investigated by fluorescence spectroscopy showing that one of the products (2a) can selectively bind Cu$^{2+}$ with fluorescence enhancement.

Keywords
chemosensor, Cu$^{2+}$, fluorescence enhancement, perimidine, selective

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Introduction
Perimidines are tricyclic heterocycles containing a dihydropyrimidine ring ortho- and peri-fused to the naphthalene structure.$^1$ These heterocyclic systems, which have been shown to be interesting candidates for biological studies, are widely applied in industry, agriculture and medicine.$^{2,3}$ Perimidines can also be used as dyes and have wide applications in industrial fields, with one notable perimidine-containing product being Solvent Black 3.$^4$ Perimidine derivatives are usually used as ligands with clamp carbon-nitrogen bond which have some advantages such as easy synthetic access to derived complexes.

Recently, perimidine derivatives have drawn more extensive examinations because of their diverse range of biological activity.$^{5-8}$ Because of the continuing interest in this field, investigations into new perimidine derivatives and their biological activities is of great importance. However, the biological activity of perimidine derivatives is mostly focused on applications in the biomedical field, while little attention has been paid to their application in the recognition field.$^9,10$

The dihydropyrimidine ring present in the structure of perimidine compounds can provide metal ion recognition sites. Based on this, we have introduced additional oxygen atoms and nitrogen atoms to improve the recognition ability of such compounds towards metal ions.$^{11,12}$ We now report the synthesis of perimidine-containing ethyl 2-{(1-(2,3-dihydro-1H-perimidin-2-yl)naphthalen-2-yl)oxy}acetate (2a) and 2-{(pyridin-3-ylmethoxy)naphthalen-1-yl}-2,3-dihydro-1H-perimidine (2b) and 2a’s utilization as a selective fluorescent chemosensor for Cu$^{2+}$ ions.

Results and discussion
The synthesis of the new perimidine derivatives 2a and 2b is shown in Scheme 1. The starting material, 1-(2,3-dihydro-1H-perimidin-2-yl)naphthalen-2-ol (1) was prepared...
according to the literature. Ethyl bromoacetate and 2-(bromomethyl)pyridine hydrobromide were subjected to the reaction with 1, respectively, in the presence of K2CO3 and KI in ethanol under reflux condition to furnish ethyl 2-((1-(2,3-dihydro-1H-perimidin-2-yl)naphthalen-2-yl)oxy)acetate (2a, 47% yield) and 2-(2-(pyridin-3-ylmethoxy)naphthalen-1-yl)-2,3-dihydro-1H-perimidine (2b, 43% yield). The structure and conformation of compound 2a were elucidated by single-crystal X-ray diffraction, as shown in Figure 1. The three-dimensional molecular-packing diagram of compound 2a is shown in Figure 2.

Crystals of 2a were obtained by slow evaporation from an ethanol solution. The crystal structure of 2a clearly revealed that it had a well-defined geometry due to the rigidity that the fused rings confer on the molecule. The dihedral angles are as follows: 88.57° between the two naphthalene rings, 46.95° between the naphthalene ring and the plane (C11, N1, N2), and 89.01° between the naphthalene ring with the hydroxy group and the plane (C11, N1, N2). The molecular conformation is stabilized by O–H...N hydrogen bonds and the crystal packing is governed by C–H...O and C–H...N hydrogen interactions, resulting in a three-dimensional network. These values are typical for the complexation of an aromatic ring by π–π stacking interactions.

The binding properties of molecules 2a and 2b with various metal ions were investigated by fluorescent spectroscopy titration experiments. For fluorescent titration experiments using metal ions, stock solutions of various metal ions were prepared using deionized water. 2a or 2b (2.5 mL) was added to a quartz cell with a path length of 1 cm. And we used a micro-syringe to increase the metal ion concentration. After each metal ion was added, the solution was stirred for 1 min. The metal ion stock solution was added in an amount of less than 10−7 M of various metal ions (Ag+, Bi3+, Cd2+, Cu2+, Fe3+, Hg2+, La3+, Mn2+, Ni2+, Pb2+, Sn4+, Sr2+) were added in an amount of less than 10−6 M to keep the total volume of the test solution unchanged.

Changes in the fluorescence properties of 2a and 2b in dimethylformamide (DMF) (1 × 10−4 M) solution caused by 6.7 × 10−7 M of various metal ions (Ag+, Bi3+, Cd2+, Cu2+, Fe3+, Hg2+, La3+, Mn2+, Ni2+, Pb2+, Sn4+, Sr2+) were measured once the emission intensity was constant. The result showed that 2a in DMF solution caused by Cu2+ ions produced significant enhancement in the fluorescent emission. Compound 2b and the other metal ions that were tested only showed relatively insignificant changes (Figure 3). Thus, it can be concluded that compound 2a has higher selectivity for the recognition of Cu2+ ions.

The sensitivity of the fluorescence emission response of 2a towards Cu2+ was also examined under the same conditions with various Cu2+ concentrations (Figure 4(a)). The fluorescence intensity of 2a was enhanced continually upon addition of Cu2+. When the concentration of Cu2+ was increased to 10 equivalents, the fluorescence intensity of 2a was enhanced to 477% of the initial value. From a Stern–Volmer plot (Figure 4(b)), the quenching constant was estimated to be 1.441 × 105 M−1.

A proposed mechanism for the fluorescence enhancement of 2a is shown in Figure 5. Two pathways have been suggested for the fluorescence enhancement. (1) When the receptor molecule is coordinated to Cu2+, the rigidity of 2a is enhanced and the fluorescence intensity of 2a increases. (2) When the receptor molecule is in coordination with Cu2+, the energy of the lowest excited state and the fluorescence quantum yield increased significantly, such that the fluorescence intensity is enhanced.

To understand more clearly the structure of the Cu2+–2a complex, a Job plot indicated a stoichiometry of Cu2+–2a. Figure 6 shows the relationship between the fluorescence intensity at 365 nm and the Cu2+ mole fraction at a constant concentration of [2a] + Cu2+. As shown in Figure 6, when the molar fraction of [Cu2+]/([2a] + [Cu2+]) is about 0.5, the Cu2+–2a complex has the strongest fluorescence intensity, and it is evident that the stoichiometric ratio of acceptor 2a to Cu2+ is 1:1. In addition, the 1H NMR spectrum of the sensor had after complexation with copper ions showed that the two amine proton (Ha) signals at 6.7 ppm had completely disappeared (Figure 7) and that the shape of the signal for Hb had also changed, indicating that the copper ions were bound to the nitrogen atoms on the perimidine.

**Scheme 1.** Synthetic route to 1, 2a and 2b. Reagents and conditions: (i) EtOH, 70 °C, 4 h; (ii) ethyl bromoacetate, K2CO3, KI, EtOH, reflux, 5 h, yield: 47%; (iii) 2-(bromomethyl)pyridine hydrobromide, K2CO3, KI, EtOH, reflux, 3.5 h, yield: 43%.
According to the Job plot and nuclear magnetic resonance (NMR) spectroscopy, the chemosensor 2a is likely to chelate Cu\(^{2+}\) by way of oxygen on the ether, oxygen on the carbonyl group, and nitrogen on the perimidine. The Cu\(^{2+}\)–2a complex may be composed of the mechanism and coordination mode of deprotonation of the receptor.

**Conclusion**

In conclusion, two new perimidine products had been designed and synthesized. The structures of 2a and 2b were identified by mass spectroscopy (MS), \(^1\)H NMR and \(^{13}\)C NMR. One of the compounds (2a) displayed high selectivity for Cu\(^{2+}\) revealed by fluorescence enhancement, and the recognition mechanism of 2a compound for copper ions was verified by \(^1\)H NMR and fluorescence.

**Experimental**

**General**

All reagents were obtained from commercial sources and were of AR (Analytical Reagent) grade. Melting points were determined with a XT4A micromelting point apparatus and are uncorrected. The \(^1\)H NMR spectra were recorded on a Mercury Plus-400 spectrometer with tetramethylsilane (TMS) as the internal reference and CDCl\(_3\) as the solvent. MS was performed with Finnigan Trace MS instrument.

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![Figure 1. The crystal structure of compound 2a.](image1)

![Figure 2. (a) View of 2a along the b axis, (b) view of 2a along the c axis, and (c) 2a structure along the view between the a and b axes.](image2)

![Figure 3. (a) Fluorescence emission changes of 2a (1 × 10^{-6} M) in DMF in the presence of 6.7 × 10^{-7} M aqueous solutions of various metal ions (excitation at 365 nm). (b) Fluorescence emission of 2b (1 × 10^{-6} M) in DMF in the presence of 6.7 × 10^{-7} M aqueous solutions of metal ions (excitation at 350 nm).](image3)
using the electron ionization (EI) method. Elemental analyses were carried out on a Vario EL III instrument.

1-(2,3-dihydro-1H-perimidin-2-yl)naphthalen-2-ol (1): To a solution of naphthalene-1,8-diamine (632 mg, 4 mmol) in ethanol (30 mL) was added 2-hydroxy-1-naphthaldehyde (688 mg, 4 mmol), and the reaction mixture was heated at 70 °C for 4 h. Subsequently, it was cooled to room temperature. The resultant orange solution was filtered and a yellow precipitate was obtained. The precipitate was purified by recrystallization from ethanol/ethyl acetate (2:1) to give 749 mg of compound 1 as a 60% solid. M.p.: 145–147 °C. 

1H NMR (300 MHz, CDCl3): δ 9.69 (s, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.84–7.80 (m, 2H), 7.49 (t, J = 7.1 Hz, 1H), 7.37–7.29 (m, 5H), 7.2 (d, J = 8.9 Hz, 1H), 6.66 (dd, J1 = 6.7 Hz, J2 = 1.2 Hz, 2H), 6.45 (s, 1H), 4.72 (s, 2H). ESI-MS: m/z = 312.97 [M+H]+; 646.82 [2M+Na]+.

Ethyl 2-((1-(2,3-dihydro-1H-perimidin-2-yl)naphthalen-2-yl)oxy)acetate (2a): Ethanol (30 mL) was added to a flask containing compound 1 (62.5 mg, 0.2 mmol), K2CO3 (72.2 mg), KI (98.6 mg) and ethyl bromoacetate (0.0244 mL, 0.22 mmol).15,16 The resulting mixture was stirred at 70 °C for 5 h. After removal of the solvent, a yellow precipitate was obtained, and the precipitate was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give 2a as a yellow solid; yield 37.6 mg (47%). 1H NMR (300 MHz, DMSO-d6) δ 9.09 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 9.1 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.49–7.33 (m, 3H), 7.18 (t, J = 7.8 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 6.70 (s, 2H), 6.49 (d, J = 7.3 Hz, 2H), 6.42 (s, 1H), 4.93 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H), 13C NMR (75 MHz, CDCl3) δ 168.9, 154.1, 143.0, 135.0, 132.9, 131.7, 130.4, 128.1, 127.6, 126.7, 126.2, 124.5, 120.7, 117.5, 114.2, 113.4, 105.9, 66.9, 61.7, 61.4, 14.1. ESI-MS: m/z = 312.97 [M+H]+; 421.07 [M+Na]+; 796.49 [2M+H]+; 818.47 [2M+Na]+.
2-(2-(pyridin-3-ylmethoxy)naphthalen-1-yl)-2,3-dihydro-1H-perimidine (2b): Ethanol (30 mL) was added to a flask containing compound 1 (62.5 mg, 0.2 mmol), K₂CO₃ (72.2 mg), KI (98.6 mg) and 2-(bromomethyl)pyridine hydrobromide (55.6 mg, 0.22 mol). The resulting mixture was stirred at 70 °C for 3.5 h. After removal of the solvent, a brown precipitate was obtained, and the precipitate was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 6:1) to give 2b as a brown solid; yield 35.1 mg (44%). ¹H NMR (300 MHz, DMSO-d₆), δ 9.10 (d, J = 9.3 Hz, 1H), 8.56 (d, J = 4.8 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.92–7.84 (m, 1H), 7.77 (td, J = 7.7, 1.8 Hz, 1H), 7.53 (dd, J = 13.1, 8.5 Hz, 2H), 7.44–7.34 (m, 2H), 7.30 (dd, J = 7.5, 4.9 Hz, 1H), 7.17 (t, J = 7.8 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 6.77 (s, 2H), 6.56–6.42 (m, 3H), 5.37 (s, 2H), 1.3C NMR (75 MHz, CDCl₃) δ 156.4, 154.6, 149.1, 142.9, 137.1, 135.0, 132.9, 131.8, 130.1, 128.1, 127.4, 126.8, 126.2, 124.2, 122.9, 121.7, 119.2, 117.4, 114.4, 113.3, 105.8, 72.47, 61.37. ESI-MS: m/z = 404.16 [M+H]+; 426.16 [M+Na]+; 828.50 [2M+Na]+.

X-ray diffraction study of 2a

A white crystal of 2a was mounted on a glass fibre in a random orientation at 296(2)K. The determination of the unit cell and data collection were performed with Mo-Kα radiation (λ = 0.71073 Å) on a Bruker Smart Apex-CCD diffractometer with a ψ-ω scan mode. The structure was solved by direct methods with the SHELXS-97 program and expanded by the Fourier technique. The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were placed at the calculated positions. Crystal data for 2a: C₂₅H₂₂N₂O₃, M = 398.44, triclinic, space group P-1, a = 5.189(4)Å, b = 11.912(8)Å, c = 16.929(11)Å, α = 70.225°, β = 87.153°, γ = 81.378°, V = 974.4(11)Å³, Z = 2, Dc = 1.358 mg/ml, reflections collected: 7585, independent reflections: 2669 [R(int) = 0.1027], final R indices [I > 2σ(I)]: R1 = 0.0624, wR2 = 0.1307. R indices (all data): R1 = 0.1842, wR2 = 0.1825.

The Cambridge Crystallographic Data Centre (CCDC) deposition number is 1957498 for compound 2a.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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