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1,8-Naphthyridine Modified Naphthalimide Derivative: Ratiometric and Selective Sensor for Hg^{2+} in Organic Aqueous Solution

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A bottom-modified (4-position) naphthalimide derivative **1** with 1,8-naphthyridine as binding site has been designed and synthesized. Compound **1** is the first 1,8-naphthyridine-modified naphthalimide-based sensor that can detect Hg^{2+} selectively with respect to ratiometric fluorescent change and blue shift in organic aqueous solution. The Job's plot and FAB mass indicate that **1** formed a 1:1 complex with Hg^{2+}. A top-modified naphthalimide derivative **2** with 1,8-naphthyridin as binding site has also been synthesized for comparison.

Key Words : Fluorescent sensor, Naphthalimide, 1,8-Naphthyridine mercury, Ratiometric

Introduction

Fluorescent sensors for the detection and measurement of environment important ions are actively investigated because these ions play indispensable roles in vital processes.[1] In particular, the development of a high selective fluorescent probe for mercury ion in the presence of a variety of other metal ions has received great attention.[2] Mercury is a highly toxic and widely spread heavy metal pollutant, which damages DNA, impairs mitosis, and disrupts the central nervous and endocrine systems.[3] In this regard, many fluorescent probes for mercury ions have been extensively explored.[4] For instance, coordination of Hg^{2+} to S atom-based receptors and mercury-mediated desulfurization reactions have been widely used in development of reversible and irreversible Hg^{2+} fluorescent probes.[5-7] Compared to traditional S-containing receptors, *N*-containing receptor for effectively binding Hg^{2+} in a fluorescent probe is rare.[8]

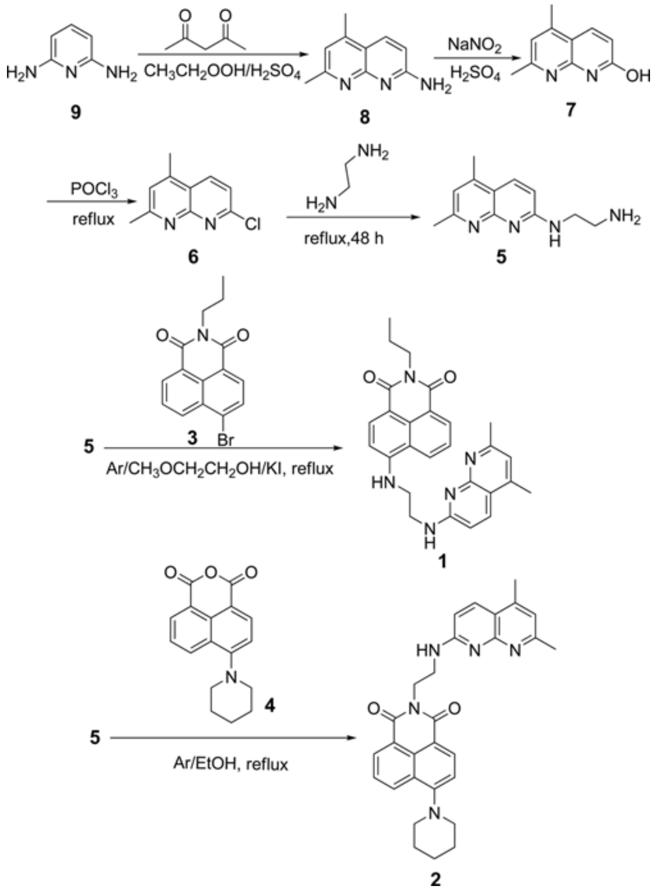
1,8-Naphthalimide (Naph) is well known for typical intramolecular charge transfer (ICT) fluorophore, strong absorption and emission in the visible region, high photostability, large Stokes' shift and insensitivity to pH.[9] Modifications of naphthalimide have given rise to a great number of derivatives with tunable binding properties and a variety of fluorescent properties.[10] Some of them have been reported in our previous works and proved to be effective fluorescent sensors for F^-,[11] Cu^{2+},[12] Zn^{2+},[13] and some other ions.[14] In the present work, the 1,8-naphthalimide fluorophore in conjunction with *N*-containing binding groups would facilitate the recognition of metal ions.

1,8-Naphthyridine and its derivatives have been applied in the coordination chemistry,[15] pharmaceutical[16] and molecular recognition fields,[17] because of their intriguing structures and bonding properties, as well as the biocompatibility and spectroscopic properties.[18] It exhibit various coordination modes and interesting spectroscopic properties.[19] A distinguishing feature of this ligand working as a sensor is the sensitive response toward D-glucoside or D-glucopyranoside with a significant blue shift in emission,[20] which provides the potential to form a ratiometric fluorescent sensor that exhibits a spectral shift upon binding to the analytes of interest. Therefore, 1,8-naphthyridine, as a typical *N*-containing receptor, was introduced to form the ratiometric sensing system in **1**.

This paper reports the design and synthesis of a new naphthalimide derivative bearing a 1,8-naphthyridine binding group (**1**), which displays a ratiometric fluorescent change toward Hg^{2+} among the other examined metal ions in organic aqueous solution. After addition Hg^{2+} to **1** in CH_3CN-HEPES buffer (0.02 M, pH 7.4) (1:1, v/v), **1** showed obvious blue shift from 547 nm to 534 nm in emission spectra, which allowed **1** to selectively detect Hg^{2+} ion by the naked eye over a great number of environmental ions including Ag^+, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{3+}, Cr^{3+} and other alkali metal and alkaline earth metal cations. For comparison, a top-modified naphthalimide derivative **2** with 1,8-naphthyridin as binding site has also been designed and synthesized. To the best of our knowledge, **1** is the first example of 1,8-naphthyridine-modified naphthalimide-based compounds used as Hg^{2+} fluorescent chemosensor with ratiometric fluorescent changes and blue shift.

Results and Discussion

Coumpound **1** and **2** were synthesized as shown in Scheme 1. *N*-(2-aminoethyl)-5,7-dimethyl-1,8-naphthyridin-2-amine (**5**) was first synthesized by displacement reaction between ethanediamine and 7-chloro-2,4-dimethyl-1,8-naphthyridine (**6**) with a moderate yield of 74%. Compound **5** was then reacted with *N*-propyl-4-bromo-1,8-naphthalimides (**3**) in 2-methoxyethanol to give **1** in 46% yield. When compound **5** was reacted with 4-(*N*-piperidine)-1,8-naphthalic anhydride in ethanol, **2** was obtained in 70% yield.



Scheme 1. Synthesis route of compound **1** and **2**.

The detailed experimental procedures and the characterization of the new compounds are described in Supporting Information.

The structures of **1** and **2** were further confirmed by X-ray analysis (Figure 1). The single crystal of **1** and **2** suitable for X-ray diffraction studies were grown by the vapor diffusion of diethyl ether into a CH_2Cl_2 solution of **1** and **2**, respectively. In crystal **1**, the distances between N2 and N1, N2 and N3, N2 and N4 are 3.039, 2.995 and 4.417 Å, respectively. The naphthalimide plane defined by C24-C25-N5 atoms has a dihedral angle of 46.8° with the naphthyridine C2-C11-N4 mean plane. While in crystal **2**, the distances between N1 and N2, N1 and N3, N1 and N4 are 3.758, 5.709 and 7.927 Å, respectively. The naphthalimide plane defined by C1-N1-C2 atoms has a dihedral angle of 155.3° with the naphthyridine C15-C16-C17 mean plane. These data indicate that the uncoordinated N atoms in crystal **1** are more appropriate to bind a metal ion than that in crystal **2**.

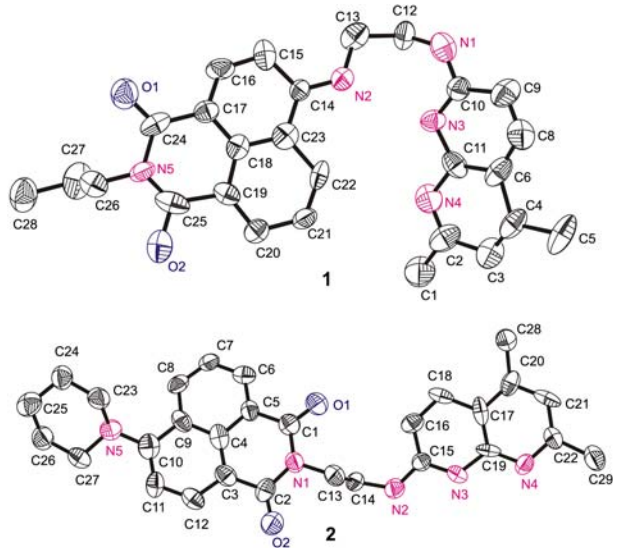


Figure 1. Crystal structures of compound **1** and **2**.

The photophysical properties of **1** and **2** were evaluated in CH_3CN-HEPES buffer (0.02 M, pH = 7.4) (1:1, v/v) solution. As shown in Figure S1, S2, both of compound **1** and **2** showed strong absorption at around 445 nm with the presence of the ICT band of Naph. Addition of Li^+, Na^+, K^+, Ag^+, Fe^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+} and Cr^{3+} did not change the absorption spectra, while only a slight blue shift was observed upon the addition of Hg^{2+}, Cu^{2+} and Fe^{3+} in **1**. Studies on the UV-vis absorption revealed that **1** and **2** showed no obvious selectivity toward a great number of environmental ions including Ag^+, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{3+}, Cr^{3+} and other alkali metal and alkaline earth metal cations.

The changes in the fluorescence emission of **1** and **2** were next investigated. For **1**, excitation of the ICT absorption bands gave rise to long wavelength emission, centered at 547 nm. Addition of Li^+, Na^+, K^+, Mg^{2+}, Ag^+, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{3+} and Cr^{3+} showed little or no effect on the emission of **1**. However in the case of Hg^{2+}, a new emission peak centered at 534 nm appeared (Figure 2). A 13 nm blue-shift of the emission spectra from 547 nm to 534 nm was probably due to the weakened ICT effect caused by the coordination of the nitrogen atom of the naphthalimide with Hg^{2+}. In contrast, **2** showed a very weak emission peak centered at 550 nm. A slightly fluorescence quenching was observed, with no changes in max, upon the addition of Hg^{2+} in **2** solutions (Figure S3). These results demon-

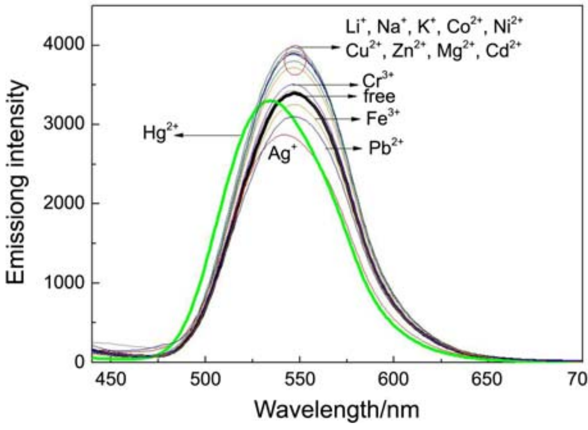


Figure 2. Fluorescence spectra of **1** (10 μM) in CH_3CN-HEPES buffer (0.02 M, pH = 7.4) (1:1, v/v) in the presence of different metal perchlorates (5 equiv.). Excitation wavelength was 360 nm.

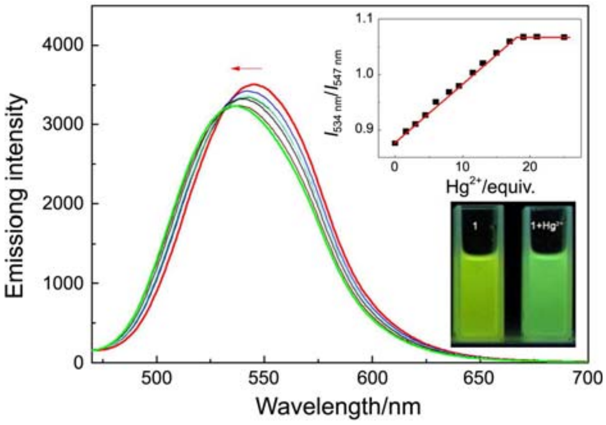


Figure 3. Fluorescence spectra of **1** (10 μM) in CH_3CN-HEPES buffer (0.02 M, pH 7.4, v/v, 1:1) in the presence of different amounts of Hg^{2+}. Inset: the ratio of emission intensity at 547 nm and 534 nm as a function of Hg^{2+} concentration.

strated that the 1,8-naphthyridin in the bottom part (4-position) in **1** could efficiently be involved in the formation of Hg^{2+} complex in the recognition of metal ions; however, the 1,8-naphthyridin in the top part cannot work like that in **2**.

To get further insight into the binding of Hg^{2+} with **1**, the fluorescence spectra of **1** upon titration with Hg^{2+} were recorded (Figure 3). Upon addition of increasing amounts of Hg^{2+}, the emission intensity at 547 nm decreased slowly with a 13 nm blue-shift. With 20 equivalent of Hg^{2+}, the maximum of emission band shifted to 534 nm. The linear dependence of the intensity ratio within the equivalent range of Hg^{2+} ion testified that **1** forms a 1:1 complex with Hg^{2+}, whose association constant (Ka) was determined to be about 2.3×10^3 from the titration experiments. Moreover, the Job's plot (Figures 4) and FAB mass (Figures S4) confirmed the 1:1 stoichiometry for the **1**-Hg^{2+} complex, which also strongly supports the above conclusions.

To explore the possibility of using **1** as a Hg^{2+} selective fluorescent chemosensor, competition experiments were carried out. **1** (10 μM) was first mixed with 20 equivalent of Hg^{2+}, followed by adding 40 equivalent of various metal ions including Li^+, Na^+, K^+, Mg^{2+}, Ag^+, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{3+} and Cr^{3+}. Fluorescence emission spectroscopy was used to monitor the competition events. As shown in Figure 5, in the presence of Li^+, Na^+, K^+, Mg^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Cr^{3+}, the emission spectra were almost identical to which was obtained in the presence of Hg^{2+} alone. In the case of Ag^+, Pb^{2+} and Fe^{3+}, the emission intensities diminished to different extents, but they still had sufficient detections of Hg^{2+}. Therefore, **1** was proved to be a promising selective fluorescent sensor for Hg^{2+} in the presence of most competing metal.

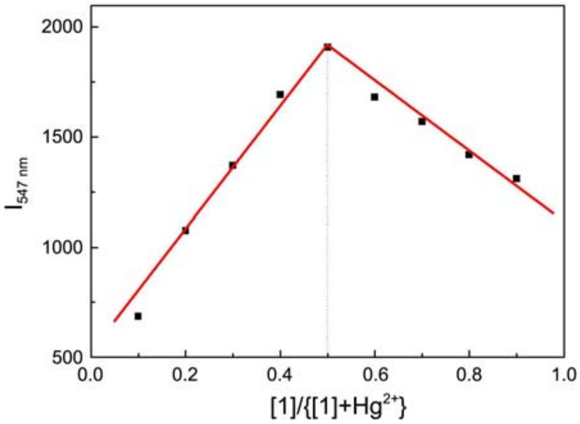


Figure 4. The Job's plot showing the 1:1 binding of **1** to Hg^{2+} ions.

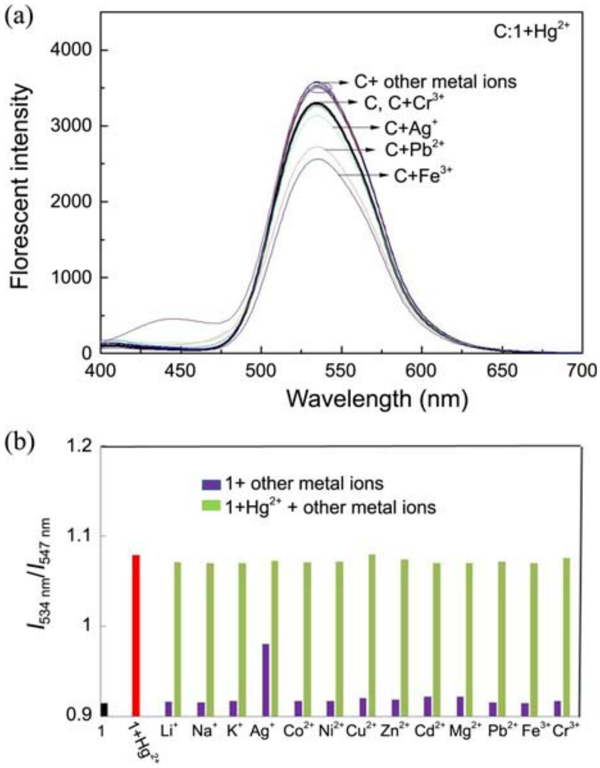


Figure 5. (a) Emission spectra of **1** (10 μM) mixed with 20 equiv. of Hg^{2+} and 40 equiv. of various metal ions in CH_3CN-HEPES buffer (0.02 M, pH 7.4) (1:1, v/v). (b) Histogram representing emission intensity of **1** to various metal ions (purple bars) and fluorescence intensity change of the mixture of **1** and Hg^{2+} after addition of an excess of the appropriate other metal ions (green bars), its wavelength is I_{534nm} and I_{547nm} of the fluorescence intensity ratios. Excitation at 360 nm (slit = 5/5).

Conclusions

In conclusion, we have developed a novel ratiometric fluorescent sensor **1** for Hg^{2+}. It displays a 13 nm blue-shift of fluorescence emission, with dramatic fluorescence color change from yellow to green yellow upon addition of Hg^{2+} in organic aqueous solution, as a result of the weakened ICT effect caused by the coordination of the nitrogen atom of the naphthalimide with Hg^{2+}. The Job's plot and FAB mass indicate that **1** formed a 1:1 complex with Hg^{2+}. Moreover, as far as we are aware, **1** is the first 1,8-naphthyridine-modified naphthalimide-based chemosensor that can selectively detect Hg^{2+} with ratiometric fluorescent change.

Experimental

Materials and Measurement.

General Methods – Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Flash chromatography was carried out on silica gel (100-200 mesh). ^{1}H NMR spectra were recorded using 500 MHz and ^{13}C NMR was recorded using 150 MHz. Chemical shifts were expressed in ppm and coupling constants (*J*) in Hz.

UV-Vis and Fluorescence Titration of 1 with Metal Ions. The UV-Vis spectra were obtained using U-3010 spectrophoto meter. The fluorescence spectra were obtained with F-4500 FL spectrometer with a 1 cm standard quartz cell. Stock solutions (0.01 M) of the perchlorate salts of Li^+, Na^+, K^+, Ag^+, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Mg^{2+}, Hg^{2+}, Pb^{2+}, Fe^{3+}, Cr^{3+} in CH_3CN were prepared. Stock solutions of host (10 μM) were prepared in CH_3CN/HEPES (0.02 M, pH 7.4) (1:1, v/v). Test solutions were prepared by placing 50 μL of each ions stock, and diluting the solution to 3 mL with CH_3CN/HEPES (0.02 M, pH 7.4) (1:1, v/v). All of the titration experiments were recorded at room temperature.

Structural Determination. Crystals suitable for X-ray diffraction were obtained by diffusion of diethyl ether into a CH_2Cl_2 solution. All complexes reported here were structurally characterized by X-ray crystal analysis. Diffraction date were collected on a Rigaku RAXIS-RAPID X-Ray diffractometer using a graphite monochromator with Mo Kα radiation (=0.71073 nm) at 298(2) k. Structures were solved by direct methods (SHELXS-97) and refined (SHELXS-97) by full-matrix least-squares methods on all F^2 date.[21] The unweighted and weighted agreement factors (R_f, R_w) and the goodness of fit were calculated. Crystal data and details on data collection and refinement are summarized in Table S1.

Synthesis. *N*-propyl-4-bromo-1,8-naphthalimides (**4**) and 7-chloro-2,4-dimethyl-1,8-naphthyridine (**6**) were synthesized by an improved method according to the literature.[22-24] Synthesis of other compounds is described below.

5: Under argon, 7-choro-2,4-dimethy-1,8-naphthyridine (**6**) (0.2 g, 1.04 mmol) was dissolved in excess ethane diamine (10 mL), the reaction mixture were refluxed for 48 h, after which the solution was clear and the solvent was evaporated under reduced pressure, the crude product was purified by silica gel column chromatography using CH_2Cl_2/MeOH (12:1, v/v) as eluent to afford a white solid product **5** (0.1661 g, 7% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.98 (d, 1H, *J* = 7.2 Hz), 7.37 (s, 1H), 6.90 (s, 1H), 6.76 (d, *J* = 8.8, 1H), 2.85 (t, *J* = 6.15, 2H), 2.49 (S, 6H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ 160.06, 159.43, 156.58, 145.03, 133.53, 118.97, 114.44, 112.68, 42.86, 40.93, 17.81. FAB mass calcd for $C_{12}H_{16}N_4$ $[M + H]^+$: 217.14, found 217.13.

2: Under argon, a solution of **3** (100 mg, 0.35 mmol)[25] and **5** (120 mg, 0.55 mmol) in EtOH (20 mL) were refluxed for 24 h. The volatile was evaporated under reduced pressure and a yellow solid was obtained. The crude product was purified by column chromatography (silica, CH_2Cl_2/MeOH, 15:1, v/v) to afford 103 mg of **2** (70% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.59 (d, *J* = 7.2 Hz, 1H), 8.51 (d, *J* = 8.1 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 9.9 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 5.81 (s, 1H), 4.60-4.54 (m, 2H), 4.00 (s, 2H), 3.24 (s, 4H), 2.61 (d, *J* = 14.5 Hz, 3H), 2.50 (d, *J* = 10.6 Hz, 3H), 1.90 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.21, 164.77, 161.01, 158.94, 157.54, 144.80, 133.84-133.23 (m), 133.00, 131.30, 130.87, 130.01, 126.17, 125.34, 122.84, 119.39, 115.51, 114.70, 54.53, 53.44, 41.84, 39.46, 26.21, 25.13, 24.34, 17.90.

1: [12] Under argon, a solution of **4** (367.5 mg, 1.16 mmol), **5** (250.4 mg, 1.16 mmol), and potassium iodide (50 mg) in 2-methoxyethanol (30 mL) were refluxed for 24 h. The solvent was evaporated under reduced pressure, a yellow solid was obtained, the crude product was purified by column chromatography (silica, CH_2Cl_2/MeOH, 100:1, v/v) to afford 85 mg of **1** (46% yield). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.91 (d, *J* = 8.4 Hz, 1H), 8.60 (s, 1H), 8.40 (d, *J* = 7.3 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.80 (t, *J* = 5.8 Hz, 1H), 7.59-7.48 (m, 1H), 7.03 (d, *J* = 4.6 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 4.00-3.93 (m, 2H), 3.83 (dd, *J* = 11.4, 5.8 Hz, 2H), 3.59 (dd, *J* = 10.3, 5.2 Hz, 2H), 2.65 (s, 3H), 2.52 (s, 3H), 1.68-1.52 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ 164.19, 163.40, 160.51, 160.26, 156.38, 151.05, 145.47, 134.76, 134.29, 131.02, 129.66, 129.47, 124.50, 122.14, 120.31, 119.53, 114.89, 112.91, 108.14, 104.31, 55.38, 45.81, 41.21, 25.48, 21.45, 17.97, 11.89. FAB mass calcd for $C_{28}H_{27}N_5O_2$ $[M + H]^+$: 454.22, found 454.3.

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Notes and References

†Electronic Supplementary Information (ESI) available: CCDC 878377 (**1**) & 878378 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif. ^{1}H NMR, ^{13}C NMR, Mass spectra and other supplementary data associated with this article. See DOI: 10.1039/b000000x/

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