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Bifunctional fluorescent thiacalix[4]arene based chemosensor for Cu^{2+} and F^{-} ions

Vandana Bhalla,^{*} Rajesh Kumar, Manoj Kumar^{*} and Abhimanew Dhir*Department of Chemistry, Guru Nanak Dev University, Amritsar-143005, Punjab, India*

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Abstract—A new thiacalix[4]arene based fluorescent sensor bearing two dansyl groups has been synthesized in cone conformation. In $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$ (1:1), the presence of Cu (II) induces the formation of a 1:1 metal:ligand complex, which exhibits increasing emission at 433 nm at the expense of the fluorescent emission of **1** centered at 504 nm. The detection limit of the sensor for Cu^{2+} is $2 \times 10^{-7} \text{ mol L}^{-1}$. For anion sensing, **1** shows a high selectivity for fluoride ions over other anions tested.

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1. Introduction

The selective signaling of copper^{1,2} and fluoride^{3–5} ions has been a very important topic for the detection and treatment of these ions in various chemical systems including living systems.^{1–5} There are, however, relatively few examples of designed sensors for the copper ions in comparison with the large number of compounds developed for the alkali and alkaline earth metal ions.⁶ Copper is the third most abundant element (after Fe^{2+} and Zn^{2+}) amongst essential heavy metal ions present in human body. It plays an important role in fundamental physiological processes in organisms ranging from bacteria to mammals.¹ However copper can be toxic if the level exceeds cellular needs. It is also capable of displacing other metals, which act as co-factors in enzyme-catalyzed reactions.² On the other hand, among the biologically important anions, fluoride is of particular interest owing to its role in preventing dental caries,³ and in the treatment for osteoporosis.⁴ Furthermore, these ions are also associated with nerve gases, in the analysis of drinking water, and the refinement of uranium used in nuclear weapon manufacture. An excess of fluoride can lead to fluorosis,⁵ which is a type of fluoride toxicity that generally manifests itself clinically in terms of an increase in bone density. Thus, the diversity of their functions, both beneficial and otherwise, makes the detection of copper and fluoride ions important. The detection and monitoring of cations and anions by methods, which allow the development of selective and sensitive assays are in great demand. Fluorescence

signaling is one of the first choices due to its high detection sensitivity and simplicity. Thus, designing fluorescent sensors for copper⁷ and fluoride⁸ has recently drawn worldwide attention. The basic design of these fluorescent sensors consists of an ionophore for selective ion binding and a fluorophore capable of signaling the binding event through changes in fluorescence emission. In most of the fluorescent sensors reported for copper, so far, the binding of the copper with the ionophore results in nonspecific fluorescence quenching via photo-induced electron transfer.⁷ There are some reports in the literature where the binding of copper results in fluorescence enhancement.^{9–11} However, to increase the selectivity and sensitivity, ratiometric sensing has also been utilized. Ratiometric fluorescent probes have the important feature in that they permit signal rationing and thus increase the dynamic range and provide built-in correction for environmental effects.¹² Ratiometric fluorescent probes for Zn^{2+} ,¹³ Ag^+ ,¹⁴ Pb^{2+} ,¹⁵ Hg^{2+} ¹⁶ have been developed. In contrast to this there are only a few ratiometric sensors for Cu^{2+} reported in the literature^{11c,17} but none using calixarene scaffold, to the best of our knowledge. As far as the calixarene scaffold is concerned the fluorescent detection of Hg^{2+} ,¹⁸ Pb^{2+} ,^{15b,19} Tl^+ ,²⁰ alkali metal ions,²¹ Co^{2+} ,^{22a} Ni^{2+} ,^{22a} or Cd^{2+} ²² has been reported recently using the dansyl moiety as a reporter. The present manuscript is the first such report using the dansyl amido group as a fluorescent reporter on calixarene scaffold for the ratiometric fluorescent sensing of copper.

Recently, thiacalix[4]arene²³ reported as the second member of the calixarene family has been extensively used for the recognition of cations²⁴ and anions²⁵ and their potential applications as fluorescence sensing agents have received much interest.²⁴ Thiacalixarenes can be easily modified at

Keywords: Thiacalix[4]arene; Ratiometric sensing; Fluorescent Cu^{2+} sensor.

^{*} Corresponding authors. Tel.: +91 183 2258802 09x3205; fax: +91 183 2258820; e-mail: mksharmaa@yahoo.co.in

the lower rim with various cation binding groups such as esters, amides, crown ethers.²⁴ For the selective binding of copper, nitrogen and sulfur binding sites are desirable as is well exemplified by copper proteins plastocyanin, rusticyanin, and cytochrome c oxidase.²⁶ Thus, a suitably designed thiacalix[4]arene with nitrogen binding sites might be a good candidate. On the other hand, it has been reported that amide groups complex cations through oxygen, but also anions through hydrogen bonding between anions and amide N–H.²⁷ Thus, we envisaged that derivatizing thiacalix[4]arene framework with amide group should give a host capable of interacting with both cations and anions. The dansyl group is one of the most attractive fluorophores due to its strong fluorescence, relatively long emission wavelength, and easy derivatization.²⁸

In continuation of our research program for the design and synthesis of calix[4]arene and thiacalix[4]arene derivatives for soft metal ions,²⁹ we recently reported³⁰ a convenient way of synthesizing thiacalix[4]arene-1,3-diamine **2**, which has sulfur and nitrogen ligating sites. Now, we have designed a fluoroionophore **1** in which compound **2** is combined with dansyl moieties. The fluoroionophore **1** shows high selectivity for copper with detection limit of 2×10^{-7} mol L⁻¹. The capture of Cu²⁺ by the receptor resulted in reduction in electron donating ability of the two nitrogen atoms; thus the receptor **1** showed a 71 nm blue shift of the fluorescence emission and provided high selectivity for Cu²⁺ over other heavy and transition metal ions. The fluorescence emission is considerably quenched in the presence of F⁻ ions. To the best of our knowledge this is the first report where thiacalix[4]arene-1,3-diamine scaffold has been combined with dansyl moiety to prepare fluorescent sensors for copper and fluoride ions.

2. Results and discussion

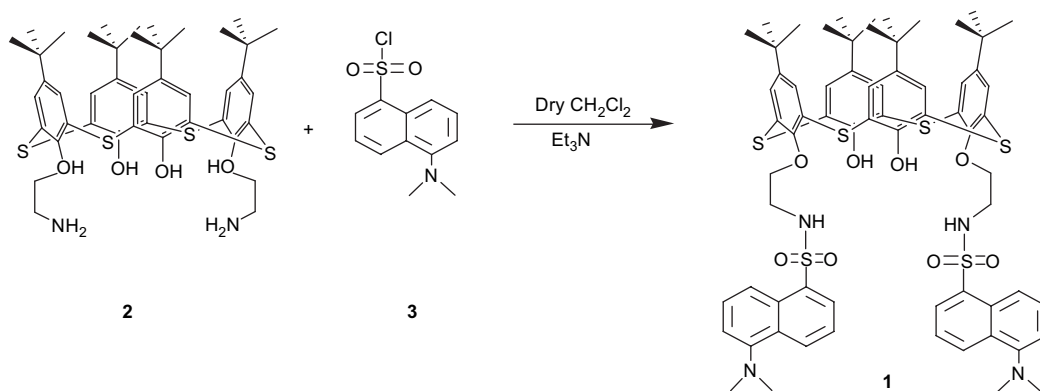
The thiacalix[4]arene-1,3-diamine **2** was prepared as reported in the literature.³⁰ Condensation of thiacalix[4]arene-1,3-diamine, **2**, with 2.0 mol equiv of dansyl chloride **3** in dichloromethane in the presence of triethylamine gave thiacalix[4]arene podand **1** in 45% yield (Scheme 1). The structure of compound **1** was confirmed from its spectroscopic and analytical data. The IR spectrum of **1** showed a stretching band at 1385 cm⁻¹ due to O=S=O and no absorption bands characteristic of free amino groups,

indicating that condensation has taken place. The ¹H NMR spectrum of this compound **1** showed two singlets (18H each) for the *tert*-butyl protons, two triplets (4H each) for the NCH₂ and OCH₂ protons, two singlets (4H each) for the aromatic protons, and one singlet (2H) for the amido protons, the magnetic equivalences suggesting a C_{2v}-symmetric structure that is in the cone conformation.

The cation binding properties of compound **1** were investigated by UV–vis absorption and fluorescence spectroscopy. All the titration experiments were carried out in CH₃CN:CH₂Cl₂ (1:1) by adding aliquots of different metal ions. The UV–vis absorption spectrum of the compound **1** exhibits typical dansyl absorption bands at λ 340 and 299 nm (Fig. 1). The addition of increasing amounts of Cu²⁺ from 0–10.0 μ M (0–1.0 equiv) resulted in a decrease in absorption at 340 nm and then a plateau was achieved (Fig. 1).

In the fluorescence spectrum, compound **1** exhibited a typical emission band of the dansyl group at 504 nm (Fig. 2). Upon addition of small amounts of Cu²⁺ (0.5–4.0 μ M) to the solution of compound **1**, a significant decrease in the 504 nm emission and a blue-shifted emission band centered at 433 nm, which was attributed to **1**–Cu²⁺ complex was observed with an isoemission point at 454 nm (Fig. 2). The inset in Figure 2 shows the dependence of intensity ratios of emission at 433 nm to that at 504 nm (I_{433}/I_{504}) on Cu²⁺, which indicates the formation of complex between **1** and Cu²⁺. To rule out the possibility of oxidation of free phenolic groups of **1** by copper, we also carried out fluorescence experiment in the presence of an oxidizing agent such as silver oxide and it was observed that there was no change in the fluorescence emission spectrum of **1**. Thus, it may be concluded that the redox chemistry of copper is not involved in this process. Under the same conditions as used above for Cu²⁺, we also tested the fluorescence response of **1** to other metal ions such as Li⁺, Na⁺, K⁺, Ni⁺, Zn²⁺, Cd²⁺, Ag⁺, Hg²⁺, Pb²⁺ besides Cu²⁺, and as shown in Figure 3, no significant fluorescence change of **1** occurred in the presence of (0.5–100 μ M) these metal ions.

To test the practical applicability of compound **1** as a Cu²⁺ selective fluorescence sensor competitive experiments were carried out in the presence of Cu²⁺ at 4 μ M mixed with Li⁺, Na⁺, K⁺, Ni⁺, Zn²⁺, Cd²⁺, Ag⁺, Hg²⁺, and Pb²⁺ at 4 μ M, as shown in Figure 4, no significant variation in the



Scheme 1.

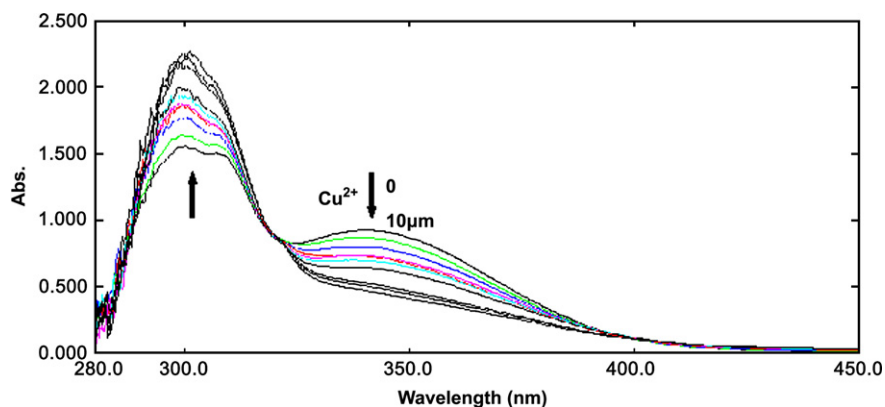


Figure 1. Absorption spectra of compound **1** on addition of Cu^{2+} (0–1.0 equiv) in $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$ (1:1, v/v).

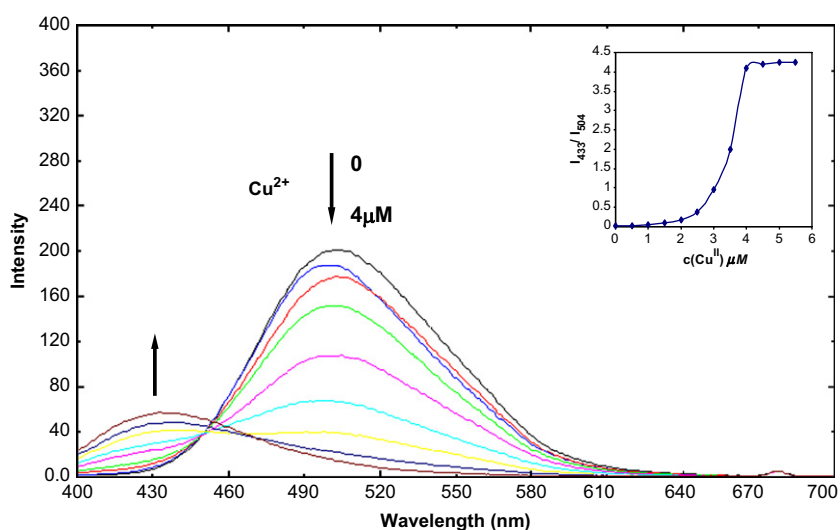


Figure 2. Fluorescent emission spectra of **1** in the presence of different concentration of Cu^{2+} (0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 μM) in $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$ (1:1, v/v). Excitation wavelength was 338 nm and emission was at 433 and 504 nm. The concentration of **1** was 10 μM . Inset: ratiometric calibration curve I_{433}/I_{504} as a function of Cu^{2+} concentration.

intensity ratio (I_{433}/I_{504}) was found by comparison with that without the other metal ions besides Cu^{2+} . This means that compound **1** has a high selectivity for Cu^{2+} . However, Zn^{2+} , Cd^{2+} , and Pb^{2+} strongly interfere when competitive experiments were carried out in the presence of Cu^{2+} at 4 μM mixed with Li^+ , Na^+ , K^+ , Ni^+ , Zn^{2+} , Cd^{2+} , Ag^+ , at

40 μM and Hg^{2+} , Pb^{2+} at 20 μM . The detection limit³¹ of **1** as a fluorescent sensor for the analysis of Cu^{2+} was determined from a plot of fluorescence intensity as a function of the concentration of the added metal ions. It was found that **1** has a detection limit of $2 \times 10^{-7} \text{ mol L}^{-1}$ for Cu^{2+} , which is sufficiently low for the detection of submillimolar

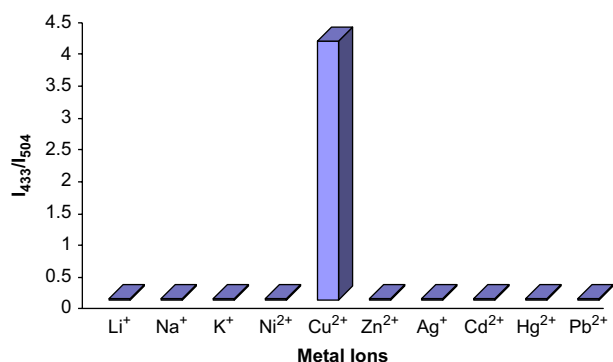


Figure 3. Ratiometric (I_{433}/I_{504}) selectivity of **1** (10 μM) upon addition of different cations (100 μM).

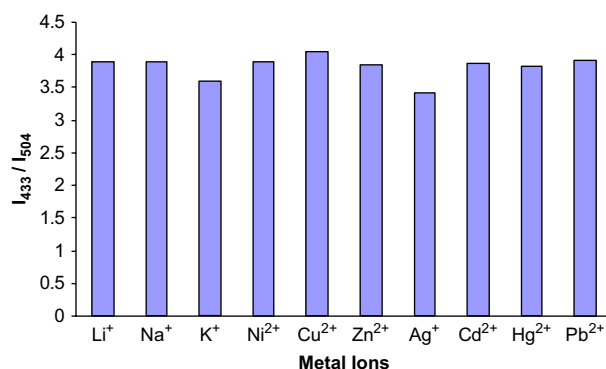


Figure 4. Ratiometric fluorescent response of sensor **1** (10 μM) to Cu^{2+} (4.0 μM) over the selected metal ions (4.0 μM).

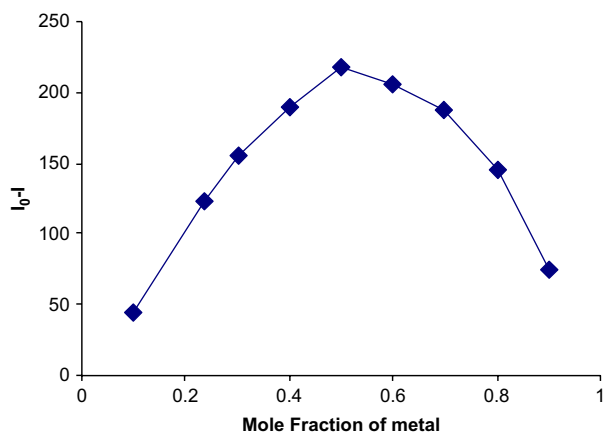


Figure 5. Job's plot for **1** and Cu^{2+} $[\text{1} + \text{Cu}^{2+}] = 2.5 \times 10^{-5}$ M in $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{CN}$ (1:1).

also used. The total concentration of the compound **1** and Cu^{2+} was constant (2.5×10^{-5} M), with a continuous variable molar fraction of guest ($[\text{Cu}^{2+}]/[\text{1}] + [\text{Cu}^{2+}]$). Figure 5 shows the Job plot of compound **1** with Cu^{2+} at 504 nm. The **1**– Cu^{2+} complex concentration approaches a maximum when the molar fraction of Cu^{2+} is 0.5, which means **1** and Cu^{2+} formed a 1:1 complex.

The K_a values of **1**– M^{n+} complexes for these metal ions were calculated from the fluorescence titration experiments by the Benesi and Hildebrand method³² and the results are summarized in Table 1. These observations indicate that apart from Cu^{2+} , Pb^{2+} also binds to compound **1** though with a much lower binding constants (Table 1).

In addition to cation binding properties, we also investigated the sensing properties of **1** toward different anions (F^- , Cl^- ,

Table 1. Stability constant (K_a) values ($\times 10^3$) of 1:1 complexes of **1**– M^{n+}

M^{n+}	Li^+	Na^+	K^+	Ni^{2+}	Cu^{2+}	Zn^{2+}	Ag^+	Cd^{2+}	Hg^{2+}	Pb^{2+}
K_a	— ^a	— ^a	— ^a	— ^a	6.77	— ^a	— ^a	— ^a	— ^a	0.8

^a Not available because of minor spectral changes.

Table 2. Fluorescence changes ($I-I_0$) of **1** upon addition of various tetrabutylammonium anions^a

Ligand	λ_{em} (nm)	Fluorescence changes ($I-I_0$)							
		F^-	Cl^-	Br^-	I^-	HSO_4^-	CH_3COO^-	NO_3^-	CN^-
1	504	–168.0	–35.0	–9.0	–30.0	–58.0	–9.0	–10.0	–9.0

^a Conditions: **1**, 10.0 μM in $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$ (1:1), excitation at 338 nm, anions 50 equiv in $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$ (1:1). I_0 : fluorescence emission intensity of free ligand. I : fluorescence emission intensity of anion complexed **1**.

concentration range of Cu^{2+} ions found in many chemical systems.

In order to determine the stoichiometry of the **1**– Cu^{2+} complex, the method of continuous variation (Job's plot) was

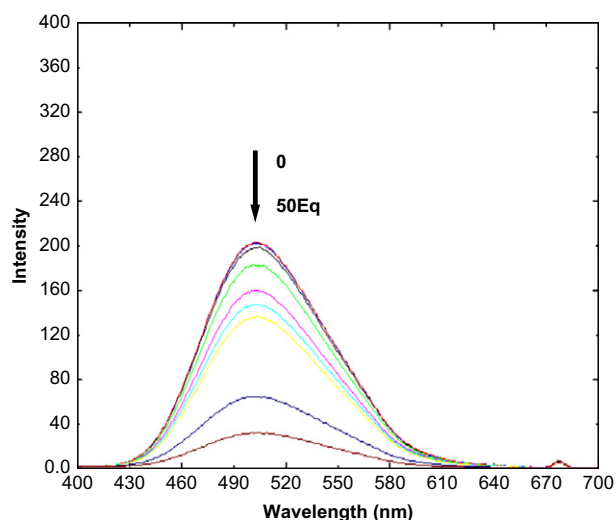


Figure 6. Fluorescent emission spectra of **1** in the presence of different equivalents of F^- ion as tetrabutylammonium salt in $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$ (1:1, v/v). Excitation wavelength was 338 nm and emission was 504 nm. The concentration of **1** was 10 μM .

Br^- , I^- , HSO_4^- , CH_3COO^- , NO_3^- , and CN^-) using tetrabutylammonium as counter cation. The fluorescence intensity changes ($I-I_0$) of **1** upon addition of anions are listed in Table 2. The results indicate that compound **1** has a high selectivity for F^- ion. When fluoride ion is added, the fluorescence emission band of the dansyl group was considerably quenched. For I^- ion, well-known as a quenching heavy anion, the fluorescence intensity was expected to decline. Figure 6 shows the fluorescence changes on addition of fluoride ions.

We propose that the fluorescence quenching of **1** on addition of fluoride ions probably occurs by the deprotonation of the amide moiety, which results in the formation of an anion, which then transfers electron to the dansyl moiety. To confirm this assumption and evaluate the intermolecular interactions between the compound **1** and fluoride ion, we also carried out NMR studies in CDCl_3 . It was found that on addition of small amounts of tetrabutylammonium fluoride to a solution of compound **1** in CDCl_3 , the weakening of signal due to NH protons takes place, which indicates that interaction of these protons is taking place with fluoride ions. On adding 1 equiv of tetrabutylammonium fluoride to a solution of compound **1** in CDCl_3 , the NH protons completely disappeared. This indicates that the deprotonation of the amide proton is taking place in the presence of fluoride ions. Similar results were obtained when strong base such as Bu_4NOH was specifically employed. Other examples of deprotonation

of neutral hydrogen bond donor anion receptor systems with fluoride ions have been reported by Gale et al.,³³ Fabbri et al.,³⁴ Gunnlaugsson et al.,³⁵ Liu and Tian,³⁶ etc.

In conclusion, we developed a highly selective fluorescent sensor for Cu²⁺ and F⁻ based on thiacalix[4]arene armed with dansyl moieties. The recognition of Cu²⁺ gave rise to ratiometric change at the ratio of the fluorescent intensity of 433 and 504 nm for the complexation. The detection limit for Cu²⁺ was found to be 2 × 10⁻⁷ mol L⁻¹. Thus **1** may be considered as a potential bifunctional fluorescent chemosensor for Cu²⁺ and F⁻ ions. Work is in progress to explore sensors for other heavy metal ions and anions based on thiacalix[4]-arenes/calix[4]arenes armed with different fluorophores.

3. Experimental

3.1. General

Melting points were determined in capillaries and are uncorrected. Most of the chemicals and reagents were obtained from Sigma–Aldrich and were used as such without further purification. ¹H and ¹³C NMR spectra were recorded on Bruker AC 200 MHz spectrometer using TMS as an internal standard and CDCl₃ as solvent. FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using xenon (6 kV, 10 mA) as the FAB gas. Infrared spectra were recorded on a Pye Unicam SP3-3—infrared spectrophotometer. UV spectra were recorded on UV-1601 spectrophotometer. Fluorescence spectra were recorded on Shimadzu 5301 spectrofluorophotometer.

3.2. Synthesis of **1**

Dansyl chloride (167.5 mg, 0.620 mmol) was added dropwise to a stirred solution of thiacalix[4]arene-1,3-diamine **2** (200.0 mg, 0.248 mmol) and Et₃N (50.0 mg, 0.496 mmol) in dry dichloromethane. The reaction was stirred at room temperature for 12 h. After completion of reaction (TLC), the reaction mixture was washed with water. The organic layer was separated, dried over anhydrous sodium sulfate and distilled under reduced pressure to give a crude residue, which was recrystallized from CHCl₃:MeOH (1:1) to give compound **1**. Yield 63%; mp 142–144 °C, ¹H NMR (300 MHz, CDCl₃): δ 1.07 (18H, s, C(CH₃)₃ × 2), 1.26 (18H, s, C(CH₃)₃ × 2), 2.88 (12H, s, CH₃ × 4), 2.99 (4H, q, J=4.8 Hz, NCH₂ × 2), 4.15 (4H, t, J=4.5 Hz, OCH₂ × 2), 7.07 (2H, d, J=8.4 Hz, ArH × 2), 7.29 (2H, t, J=7.8 Hz, ArH × 2), 7.46 (6H, m, J=7.2 Hz, ArH × 4, ArH × 2), 7.60 (4H, s, ArH), 8.10 (2H, d, J=6.0 Hz, ArH × 2), 8.35 (2H, d, J=8.7 Hz, ArH × 2), 8.50 (2H, d, J=8.4 Hz, ArH × 2), 8.58 (2H, s, NH × 2). ¹³C NMR (300 MHz, CDCl₃): δ 30.9 (C(CH₃)₃), 31.4 (C(CH₃)₃), 34.1 (CH₃), 34.4 (CH₃), 45.5 (N(CH₃)₂), 52.3 (NCH₂), 70.6 (OCH₂), 114.9 (ArC), 119.8 (ArC), 120.8 (ArC), 123.3 (ArC), 128.1 (ArC), 128.5 (ArC), 128.7 (ArC), 128.9 (ArC), 129.8 (ArC), 135.6 (ArC), 136.0 (ArC), 143.4 (ArC), 145.1 (ArC), 149.2 (ArC), 151.6 (ArC), 156.6 (ArC), 156.8 (ArC), 177.6 (ArC) 6.6, 156.8, 177.6.; FAB-MS: m/z 1273 (M+H)⁺. Anal. Calcd for C₆₈H₈₄N₄O₁₀S₆: C, 62.32; H, 6.42. Found: C, 62.02; H, 6.16.

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