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A versatile strategy for the synthesis of crown ether-bearing heterocycles: Discovery of calcium-selective fluoroionophore

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Abstract—Heterocycles have been modified in various ways in the search for new functions, but few examples are known of crown ethers incorporating heterocycles in macro-ring systems. Here we report a simple and versatile synthesis of crown ether-bearing heterocycles. An acylurea moiety in the heterocycles is efficiently transformed to 'crown ether' of various ring sizes. The products included a Ca^{2+}-selective fluoroionophore. Our simple methodology is expected to provide many novel functional heterocyclic compounds, including fluoroionophores and candidate pharmaceuticals.

1. Introduction

Cyclic acylurea structure, represented by uracil derivatives, hydantoins and barbitals, is often seen in both natural and synthetic heterocycles. Many of these major heterocycles have significant functions, for example, as pharmacophores, redox-active molecules, acid–base catalysts, metal ion chelators, intercalators to DNA, nucleic acid analogs, and fluorophores.[1] Therefore, novel types of cyclic acylurea modification have the potential to generate new functional molecules.

Crown ethers have the remarkable property of selectively recognizing and binding metal cations, especially alkali metal and alkaline earth metal cations, in complex mixtures.[2] Various modifications of crown ether structure have been made in the search for new functions, but few examples are known of crown ethers incorporating heterocycles in macro-ring systems.[3,4] Such compounds have multiple complexation centers, which influence the rigidity of the macro-cycle, and are therefore expected to have unique selectivity and complex formation characteristics. Here we present a new strategy for modification of acylurea-type heterocycle scaffolds based on polyether-linked macro-cyclization. We also report the discovery of a selective fluoroionophore for calcium ion in a library of compounds constructed with the present synthetic method.

2. Results and discussion

Our synthetic approach is outlined in Table 1. We previously tried to link two uracils with an oligo(ethylene glycol) chain by using oligo(ethylene glycol) diiodide and cesium carbonate as a base, but unexpectedly obtained a cyclized product almost exclusively, even when a large excess of uracil was used. It was found that intramolecular linking of the oligo(ethylene glycol) chain at ^{1}N and ^{3}N of uracil predominantly occurred. This non-symmetrical type of cyclization has not previously been reported, so we examined the reaction of various acylurea-containing heterocycles (uracil **1a**, lumazine **2a**, lumichrome **3a**, phenobarbital **4a**, and phenytoin **5a**) with oligo(ethylene glycol) diiodides ($n = 1$–4) to ascertain the generality of this reaction. As shown in Table 1, each combination successfully afforded a novel cyclized product. Phenytoin **5a** also afforded a cyclized product, even though it has substantial steric hindrance

Keywords: Heterocycle; Crown ether; Acylurea; One-step synthesis; Fluoroionophore; Metal sensor; Crystal structure; Fluorescence; Uracil; Lumazine; Lumichrome; Phenobarbital; Phenytoin; Calcium; Magnesium; Cesium effect; Selectivity; Coordination.
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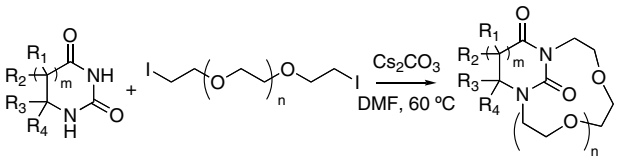
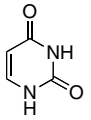
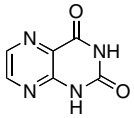
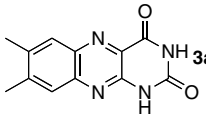
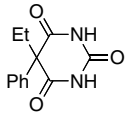
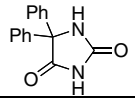
Table 1. Synthesis of crown ether bearing heterocycles



Heterocycle		Cyclized product and its isolated yield			
		$n = 1$	$n = 2$	$n = 3$	$n = 4$
	**1a**	**1b** 33%	**1c** 73%	**1d** 64%	**1e** 70%
	**2a**	**2b** 32%	**2c** 30%	**2d** 20%	**2e** 68%
	**3a**	**3b** 28%	**3c** 40%	**3d** 31%	**3e** 42%
	**4a**	**4b** 30%	**4c** 62%	**4d** 72%	**4e** 71%
	**5a**	**5b** 16%	**5c** 37%	**5d** 52%	**5e** 66%

Heterocycle = 5.56 mM; oligoethylene glycol diiodide 6.67 mM. Four equivalents of Cs_2CO_3 was used with respect to the heterocycle. Reactions were carried out in DMF at 60 °C for 23 h.

at the 5 position. The cyclized products were also obtained in the case of $n = 1$, even though an 11-membered ring size is unfavorable for cyclization. In the NMR spectra of **2b**, for example, each proton of the ether moiety gives very sharp, well-defined signals showing couplings with the neighboring protons. On the other hand, the protons at the ether moieties of **2c–e** show broad, overlapped peaks. The results indicate that compounds **1b–5b** have rigid structures.

The driving force for this cyclization is considered to be the cesium ion's assistance.[5] The intramolecular process should be preferred when Cs_2CO_3 is used in DMF. Acylurea should be deprotonated to form the corresponding cesium salt, and the cesium salt should exhibit special reactivity characteristics that have been called the 'cesium effect'. This term refers to either or both of two different synthetic phenomena. As first employed, the term applied to the readiness with which cesium salt dissolved in DMF could be alkylated with alkyl halides. Cesium salts have been shown to be well suited for S_N2 displacement on primary and secondary halides. 'Cesium effect' also refers to the phenomenon that many macro-cycles can be obtained by ring closure via an intramolecular anionic S_N2 substitution of an appropriate precursor. Intermolecular substitution is known to be suppressed relative to the intramolecular process.

Next, we surveyed metal sensor function in our compound library, since these compounds are crown ether-type potential chelators with various heterocycles built in. Among the compounds in Table 1, **2b** showed highly selective fluorogenicity with calcium ion. As shown in Figure 1, the fluorescence emission of compound **2b** was greatly enhanced by the addition of Ca^{2+} ion, with a slight red shift (~15 nm). Little change was observed on absorption before and after the addition of Ca^{2+} to **2b** (Fig. 2). Other metal ions (Li^+, Na^+, K^+, Rb^+, Mg^{2+}, and Zn^{2+}) did not affect the fluorescence spectrum of **2b**. The fluorescence enhancement by Ca^{2+} was unaffected by an equal concentration of Mg^{2+} or alkali metal ions, which indicates that the affinity of **2b** for Ca^{2+} is much greater than those for Mg^{2+} and the other metal ions. Representative results with Mg^{2+} and Na^+ are shown in Figure 3. The increase in the fluorescence of **2b** was dependent on Ca^{2+} concentration (Fig. 4). Compounds **2c–e** and **3b–e** showed no fluorescence change in the presence of metal ions, although all of them exhibited fluorescence.

The full molecular geometry of the **2b**–Ca^{2+} complex was elucidated by single-crystal X-ray diffraction analysis, and the ORTEP diagram is given in Figure 5. The complex formation of lumazine derivatives with metal ions through the C4=O and N5 atoms is well known, whereas the C2=O atom generally does not coordinate.[6] In the case of **2b**, the C2=O functional group does coordinate to metal ions, and this property is likely to be important for the metal selectivity of the fluorescence. Shifts of the ν(C=O) stretching modes of carbonyls in the presence or absence of metal ions provide useful information. Compound **2b** showed a shift in the bands of C=O at both the 2 and 4 positions on addition of Ca^{2+} (from 1728 to 1733 cm^{-1}, C2=O; from 1685 to 1652 cm^{-1}, C4=O), suggesting that complex formation occurs through these carbonyls. The

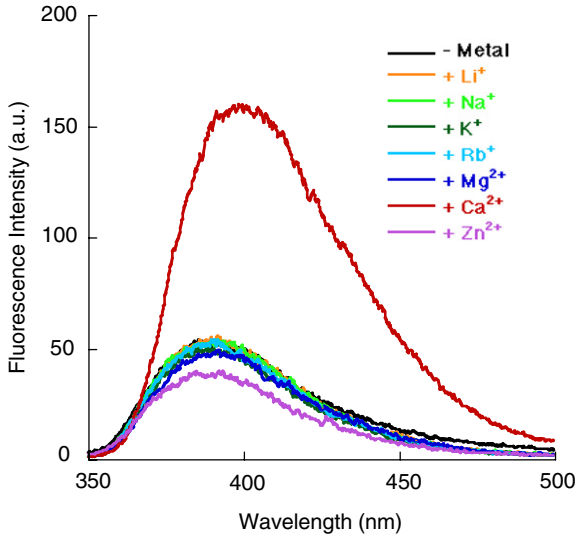


Figure 1. Calcium selective fluorescence enhancement of **2b** upon titration with various metal ions. All fluorescence spectra were acquired at 20 μM in CH_3CN. Metals were added as the ClO_4^- salt in CH_3CN at the concentration of 2 mM. λ_{ex} = 340 nm.

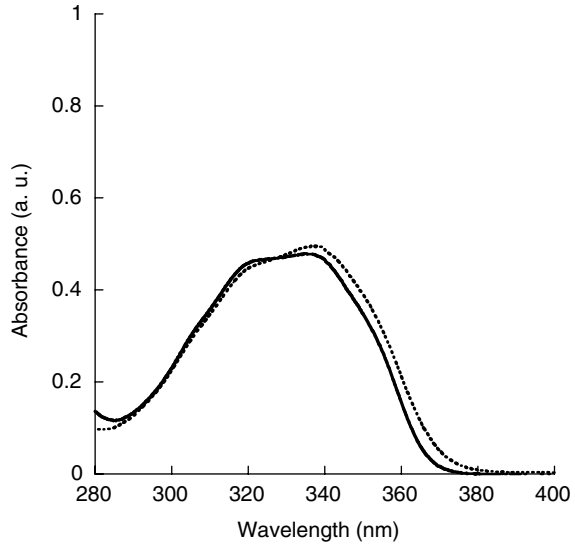


Figure 2. Absorption spectra of **2b** (90 μM in CH_3CN) in the absence (solid line) or presence (dotted line) of Ca^{2+} (360 μM).

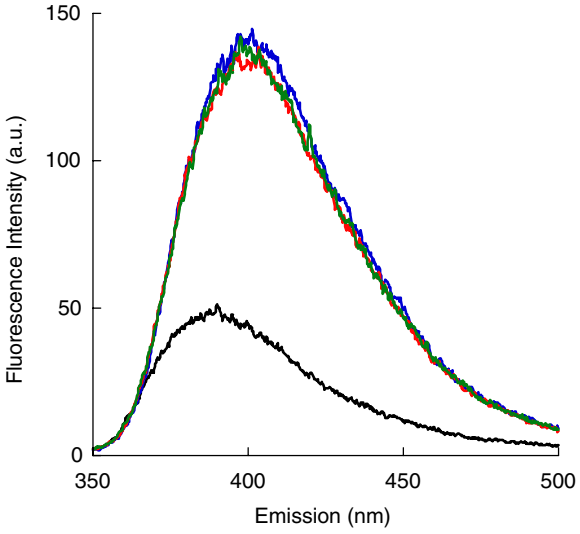


Figure 3. Emission spectra (excitation at 340 nm) of **2b** (20 μM in CH_3CN) in the presence of various cations. Black, **2b**; blue, **2b** + Ca^{2+} (2 mM); red, **2b** + Ca^{2+} (2 mM) + Na^{+} (2 mM); green, **2b** + Ca^{2+} (2 mM) + Mg^{2+} (2 mM).

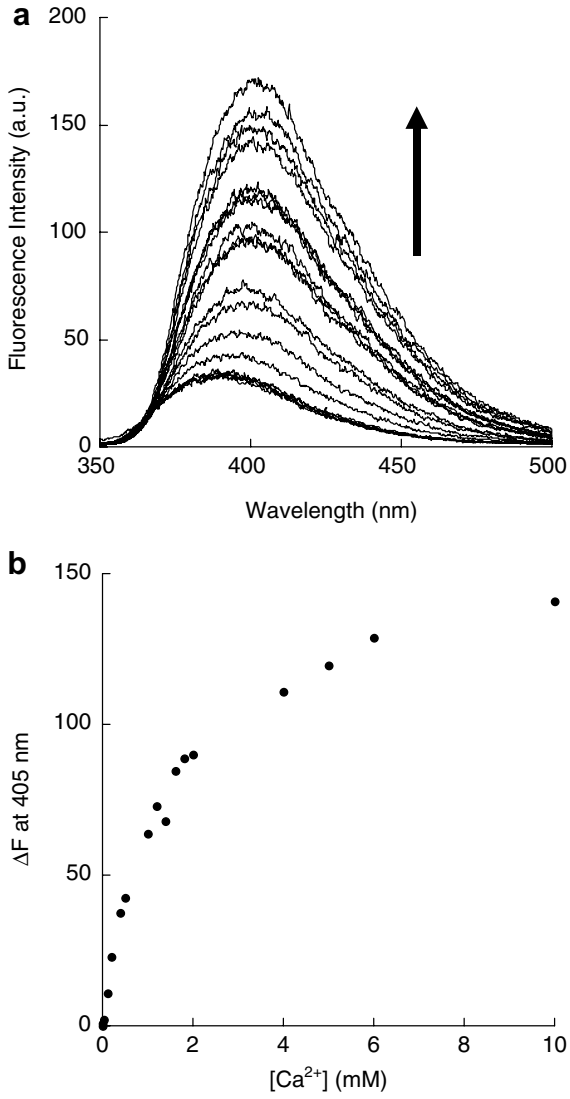


Figure 4. (a) Emission spectra (excitation at 340 nm) of **2b** (20 μM in CH_3CN) upon titration with Ca^{2+} (0–10 mM). (b) Fluorescence enhancement of **2b** at 405 nm upon titration with Ca^{2+}. ΔF was calculated as follows: $\Delta F = F - F_0$. F, fluorescence intensity in the presence of metal ion; F_0, fluorescence intensity in the absence of metal ion.

high Ca^{2+} selectivity of fluorescence enhancement of **2b** is considered to be due to coordination of Ca^{2+} to both C4═O and C2═O with the assistance of the rigid ethylenedioxy ether, which has often been used as a selectivity-providing moiety in Ca^{2+}-selective chelators and probes.

With regard to the origin of the fluorescence enhancement, a possible mechanism is that metal binding alters the rate of one or more of the relaxation processes from the excited state, that is, radiative decay, internal conversion, or intersystem crossing.[7,8] The emission wavelength shift of **2b** upon addition of Ca^{2+} ion is consistent with this idea. Such a mechanism could reasonably explain the fluorescence response of **2b**.

3. Conclusion

In summary, we have provided a simple and versatile synthetic strategy to construct heterocyclic compounds with various sizes of crown ether moiety. This method afforded a wide variety of novel compounds, of which one is a new fluoroionophore, **2b**, that responds selectively to Ca^{2+}. Compound **2b**, which has low molecular weight (Mw 278), is one of the smallest Ca^{2+}-selective fluorescent chemosensors known.[7,8] Many heterocyclic compounds possess interesting properties other than fluorescence; for example, phenobarbital (**4a**) and phenytoin (**5a**) used in this study are well-known pharmaceuticals. Besides the complex-forming ability of crown ether, the introduction of amphiphilic fragments into pharmacophore heterocycles will affect the biological activity and the distribution of the

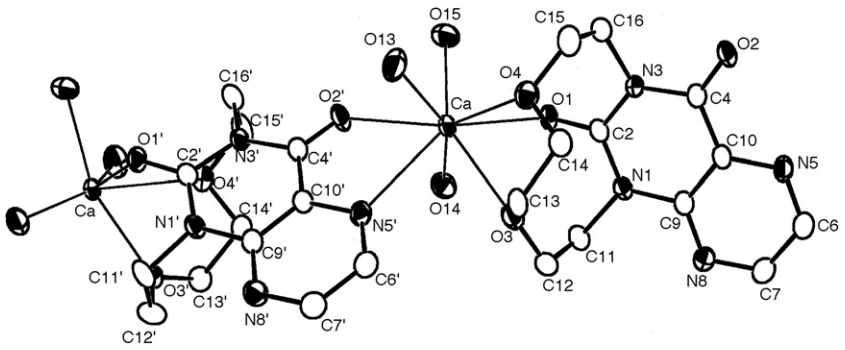


Figure 5. Solid-state structure of **2b**–Ca^{2+} complex. The non-coordinated ClO_4^- ions and hydrogens are omitted for clarity.

resulting compound. Compounds obtained by this method could be interesting drug candidates for various targets.

4. Experimental

4.1. General

Column chromatography was carried out using BW-200 (Fuji Silysia, Japan) as the stationary phase, and TLC was performed on precoated silica gel plates (0.25 mm thick, $60F_{254}$, Merck, Germany) and observed under UV light. Melting points were determined using a Yanaco MP apparatus and are not corrected. Infrared spectra were determined on a JASCO FTIR-680 spectrophotometer and were reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on a JEOL JNM GSX-400 spectrometer (400 MHz, FT) in $CDCl_3$ as a solvent. Chemical shifts were reported in parts per million (ppm) and referenced to TMS. Coupling constants (J) were reported in Hertz. Standard abbreviations indicating multiplicity were used as follows: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. FAB mass spectra were recorded on a JEOL JMS-LCmate spectrometer. High-resolution ESI mass spectra were recorded on a Bruker FT MS APEX II spectrometer. EI mass spectroscopy (JEOL JMS-SX 102A), ^{13}C NMR spectroscopy (JEOL JNM Alpha 500, JEOL JNM Lambda 500) and elemental analysis (Yanaco CHN Corder MT-5) were carried out by the central services laboratory at the Nagoya City University.

4.2. Synthesis

4.2.1. General procedure for the synthesis of oligoethylene glycol diiodides. The oligoethylene glycol di-*p*-tosylate (13.0 mmol) was dissolved in acetone (50 mL), and KI (8.30 g, 50.0 mmol) was added to the solution. The mixture was stirred at 40 °C for 4–5 days. The solvent was removed under reduced pressure, and water (10 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (4× 50 mL), and then the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (CH_2Cl_2) gave the product.

4.2.2. Triethylene glycol diiodide. Triethylene glycol di-*p*-tosylate (5.97 g, 13.0 mmol) was used as the starting material. Yield: 90% (4.33 g, 11.7 mmol) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.22 (t, 4H, J = 6.8 Hz), 3.63 (s, 4H), 3.73 (t, 4H, J = 6.8 Hz). FAB-MS: 371 m/z $[M+H]^+$.

4.2.3. Tetraethylene glycol diiodide. Tetraethylene glycol di-*p*-tosylate (6.54 g, 13.0 mmol) was used as the starting material. Yield: 88% (4.72 g, 11.4 mmol) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.27 (t, 4H, J = 6.8 Hz), 3.68 (s, 8H), 3.77 (t, 4H, J = 6.8 Hz). FAB-MS: 415 m/z $[M+H]^+$.

4.2.4. Pentaethylene glycol diiodide. Pentaethylene glycol di-*p*-tosylate (7.11 g, 13.0 mmol) was used as the starting material. Yield: 98% (5.82 g, 12.7 mmol) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.27 (t, 4H, J = 7.1 Hz), 3.67 (s, 12H), 3.76 (t, 4H, J = 7.1 Hz). FAB-MS: 459 m/z $[M+H]^+$.

4.2.5. Hexaethylene glycol diiodide. Hexaethylene glycol di-*p*-tosylate (7.68 g, 13.0 mmol) was used as the starting material. Yield: 99% (6.48 g, 12.9 mmol) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.28 (t, 4H, J = 6.8 Hz), 3.68 (s, 16H), 3.77 (t, 4H, J = 6.8 Hz). FAB-MS: 503 m/z $[M+H]^+$. Anal. Calcd for $C_{12}H_{24}I_2O_5$: C, 28.70; H, 4.82. Found: C, 28.98; H, 4.92.

4.2.6. General procedure for the synthesis of heterocyclic crown ethers. The heterocyclic compound (1.00 mmol) was dissolved in DMF (180 mL). Cs_2CO_3 (1.30 g, 3.99 mmol) and oligoethylene glycol diiodide (1.20 mmol) were added to the solution, and the mixture was stirred at 60 °C for 23 h. The solvent was removed under reduced pressure, and water (20 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3× 100 mL), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography afforded the product.

4.2.7. Compound 1b. The synthesis was performed using uracil **1a** (0.112 g, 1.00 mmol) and triethylene glycol diiodide (0.444 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from acetone to give a colorless solid. Yield: 33% (0.074 g,

0.327 mmol). R_f: 0.46 (CH_2Cl_2/MeOH, 9:1). Mp 128–131 °C. IR (KBr): 1711, 1658, 1448, 1142, 1114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.24–3.27 (m, 1H), 3.40–3.43 (m, 1H), 3.46–3.50 (m, 1H), 3.53–3.57 (m, 2H), 3.65–3.76 (m, 2H), 3.96–4.00 (m, 1H), 4.09–4.13 (m, 1H), 4.33–4.36 (m, 2H), 4.50–4.53 (m, 1H), 5.74 (d, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.23, 51.55, 68.25, 68.36, 72.20, 73.69, 101.01, 143.74, 153.25, 163.45. EI-MS: 226 *m/z* $[M]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{10}H_{14}N_2O_4Na$): 249.0846. Found: 249.0851.

4.2.8. Compound 1c. The synthesis was performed using uracil **1a** (0.112 g, 1.00 mmol) and tetraethylene glycol diiodide (0.497 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from acetone to give colorless rods. Yield: 73% (0.196 g, 0.726 mmol). R_f: 0.42 (CH_2Cl_2/MeOH, 9:1). Mp 89.5–90.0 °C. IR (KBr): 1710, 1656, 1657, 1357, 1231, 1124, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.27–3.34 (m, 1H), 3.39–3.44 (m, 2H), 3.45–3.48 (m, 2H), 3.56–3.59 (m, 1H), 3.65–3.72 (m, 5H), 3.78–3.82 (m, 1H), 4.03–4.06 (m, 1H), 4.12–4.16 (m, 1H), 4.33–4.36 (m, 1H), 4.44–4.48 (m, 1H), 5.68 (d, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.37, 50.63, 66.99, 67.53, 69.26, 70.19, 70.25, 71.64, 99.97, 144.38, 151.75, 163.52. FAB-MS: 271 *m/z* $[M+H]^+$. Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.16; H, 6.70; N, 10.38. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{12}H_{18}N_2O_5Na$): 293.1108. Found: 293.1104.

4.2.9. Compound 1d. The synthesis was performed using uracil **1a** (0.112 g, 1.00 mmol) and pentaethylene glycol diiodide (0.550 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) to give product as a colorless oil. Yield: 64% (0.202 g, 0.643 mmol). R_f: 0.42 (CH_2Cl_2/MeOH, 9:1). IR (KBr): 1705, 1659, 1456, 1393, 1355, 1236, 1112, 926, 809, 767, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.57–3.59 (m, 4H), 3.62–3.66 (m, 8H), 3.75–3.80 (m, 4H), 3.91–3.95 (m, 2H), 4.22–4.25 (m, 2H), 5.68 (d, 1H, J = 8.0 Hz), 7.22 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.39, 50.04, 67.28, 68.90, 70.17, 70.93, 70.01, 71.08, 71.20, 71.51, 100.45, 143.92, 151.47, 163.43. FAB-MS: 315 *m/z* $[M+H]^+$, 337 *m/z* $[M+Na]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{14}H_{22}N_2O_6Na$): 337.1370. Found: 337.1372.

4.2.10. Compound 1e. The synthesis was performed using uracil **1a** (0.112 g, 1.00 mmol) and hexaethylene glycol diiodide (0.602 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) to give product as a colorless oil. Yield: 70% (0.251 g, 0.701 mmol). R_f: 0.42 (CH_2Cl_2/MeOH, 9:1). IR (KBr): 1704, 1656, 1457, 1351, 1237, 1119, 913, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.60–3.67 (m, 8H), 3.75–3.82 (m, 8H), 3.95 (t, 4H, J = 5.2 Hz), 4.23 (t, 4H, J = 5.2 Hz), 5.70 (d, 1H, J = 7.6 Hz), 7.30 (d, 1H, J = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.27, 49.53, 67.55, 68.96, 70.62, 70.69, 70.71, 70.75, 70.81, 70.96, 100.71, 143.81, 151.66, 163.36. EI-MS: 358 *m/z* $[M]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{16}H_{26}N_2O_7Na$): 381.1632. Found: 381.1621.

4.2.11. Compound 2b. The synthesis was performed using lumazine **2a** (0.164 g, 1.00 mmol) and triethylene glycol diiodide (0.444 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from acetone to give colorless rods. Yield: 32% (0.090 g, 0.324 mmol). R_f: 0.46 (CH_2Cl_2/MeOH, 9:1). Mp 169.5–170.0 °C. IR (KBr): 1724, 1686, 1544, 1486, 1453, 1225, 1131, 1105, 915, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.21–3.30 (m, 2H), 3.53–3.66 (m, 4H), 4.00–4.08 (m, 2H), 4.33–4.39 (m, 1H), 4.43–4.49 (m, 1H), 4.60–4.64 (m, 1H), 4.89–4.95 (m, 1H), 8.58 (d, 1H, J = 2.0 Hz), 8.60 (d, 1H, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.15, 42.52, 67.72, 68.15, 72.25, 72.88, 128.18, 140.15, 147.43, 148.68, 151.59, 159.95. FAB-MS: 279 *m/z* $[M+H]^+$. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.54; H, 5.07; N, 19.90.

4.2.12. Compound 2c. The synthesis was performed using lumazine **2a** (0.164 g, 1.00 mmol) and tetraethylene glycol diiodide (0.497 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from acetone to give a colorless solid. Yield: 30% (0.097 g, 0.301 mmol). R_f: 0.42 (CH_2Cl_2/MeOH, 9:1). Mp 162–163 °C. IR (KBr): 1723, 1682, 1544, 1492, 1454, 1400, 1348, 1226, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.42–3.49 (m, 3H), 3.51–3.56 (m, 3H), 3.62–3.66 (m, 2H), 3.85–3.88 (m, 3H), 3.93–3.97 (m, 1H), 4.35–4.39 (m, 1H), 4.53–4.58 (m, 1H), 4.64–4.67 (m, 2H), 8.58 (d, 1H, J = 2.0 Hz), 8.60 (d, 1H, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.58, 41.63, 66.94, 67.13, 69.80, 70.03, 70.19, 70.23, 128.15, 140.09, 147.20, 148.45, 150.53, 159.95. FAB-MS: 323 *m/z* $[M+H]^+$. Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.38. Found: C, 51.88; H, 5.74; N, 17.28.

4.2.13. Compound 2d. The synthesis was performed using lumazine **2a** (0.164 g, 1.00 mmol) and pentaethylene glycol diiodide (0.550 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from acetone to give a colorless solid. Yield: 20% (0.072 g, 0.197 mmol). R_f: 0.42 (CH_2Cl_2/MeOH, 9:1). Mp 98–100 °C. IR (KBr): 1720, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.39–3.40 (m, 2H), 3.49–3.51 (m, 2H), 3.56–3.57 (m, 2H), 3.60–3.65 (m, 6H), 3.87–3.92 (m, 4H), 4.42 (t, 2H, J = 5.0 Hz), 4.61 (t, 2H, J = 5.0 Hz), 8.57 (d, 1H, J = 2.0 Hz), 8.61 (d, 1H, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.71, 41.73, 67.78, 67.98, 70.71, 70.86, 70.89, 70.92, 71.01, 128.20, 140.18, 147.17, 148.46, 150.37, 159.97. FAB-MS: 367 *m/z* $[M+H]^+$. Anal. Calcd for $C_{16}H_{22}N_4O_6$: C, 52.45; H, 6.05; N, 15.29. Found: C, 52.37; H, 5.95; N, 15.31.

4.2.14. Compound 2e. The synthesis was performed using lumazine **2a** (0.164 g, 1.00 mmol) and hexaethylene glycol diiodide (0.602 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from acetone to give a colorless solid. Yield: 68% (0.280 g, 0.683 mmol). R_f: 0.42 (CH_2Cl_2/MeOH, 9:1). Mp 69–70 °C. IR (KBr): 1722, 1678, 1548, 1490, 1348, 1231, 1116, 916, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.36–3.38 (m, 2H), 3.42–3.48 (m, 4H), 3.53–3.57 (m, 4H), 3.60–3.66 (m, 6H), 3.85–3.90 (m, 4H), 4.39 (t, 2H, J = 5.6 Hz), 4.60 (t, 2H, J = 5.6 Hz), 8.55 (d, 1H, J = 2.4 Hz), 8.60 (d, 1H, J = 2.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.47, 41.65, 67.61, 67.82, 70.59, 70.67, 70.71, 70.77, 70.81, 70.85, 128.30, 140.08, 147.10, 148.51, 150.36, 160.02. EI-MS: 410 m/z $[M]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{18}H_{26}N_4O_7$Na): 433.1694. Found: 433.1688.

4.2.15. Compound 3b. The synthesis was performed using lumichrome **3a** (0.242 g, 1.00 mmol) and triethylene glycol diiodide (0.444 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from CH_2Cl_2 to give a yellow solid. Yield: 28% (0.100 g, 0.281 mmol). R_f: 0.42 (CH_2Cl_2/MeOH, 9:1). Mp 280–281 °C. IR (KBr): 1720, 1679, 1553, 1388, 1102 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H), 2.53 (s, 3H), 3.21–3.26 (m, 2H), 3.53–3.69 (m, 4H), 4.03–4.11 (m, 2H), 4.38–4.34 (m, 1H), 4.53–4.55 (m, 1H), 4.64–4.69 (m, 1H), 5.06–5.11 (m, 1H), 7.75 (s, 1H), 8.06 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.28, 20.85, 42.27, 42.54, 68.01, 68.44, 72.42, 72.81, 126.77 129.00, 129.46, 139.31, 139.78, 142.46, 145.31, 145.47, 151.87, 160.05. FAB-MS: 357 m/z $[M+H]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{18}H_{20}N_4O_4$Na): 379.1377. Found: 379.1386.

4.2.16. Compound 3c. The synthesis was performed using lumichrome **3a** (0.242 g, 1.00 mmol) and tetraethylene glycol diiodide (0.497 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from CH_2Cl_2 to give a yellow solid. Yield: 40% (0.160 g, 0.400 mmol). R_f: 0.38 (CH_2Cl_2/MeOH, 9:1). Mp 219 °C. IR (KBr): 1718, 1677, 1555, 1480, 1459, 1389, 1361, 1229, 1130, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.52 (s, 3H), 3.37–3.56 (m, 5H), 3.62–3.70 (m, 4H), 3.85–4.00 (m, 4H), 4.36–4.40 (m, 1H), 4.57–4.64 (m, 1H), 4.72–4.78 (m, 1H), 7.75 (s, 1H), 8.06 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.08, 20.82, 41.65, 41.73, 67.22, 67.37, 70.07, 70.29, 70.35, 126.79, 128.94, 129.47, 139.15, 139.69, 142.30, 145.03, 145.31, 150.83, 160.04. FAB-MS: 401 m/z $[M+H]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{20}H_{24}N_4O_5$Na): 423.1639. Found: 423.1638.

4.2.17. Compound 3d. The synthesis was performed using lumichrome **3a** (0.242 g, 1.00 mmol) and pentaethylene glycol diiodide (0.550 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from CH_2Cl_2 to give a yellow solid. Yield: 31% (0.139 g, 0.313 mmol). R_f: 0.35 (CH_2Cl_2/MeOH, 9:1). Mp 205–207 °C. IR (KBr): 1720, 1681, 1557, 1483, 1362, 1230, 1118, 912, 743, 651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.53 (s, 3H), 3.42–3.47 (m, 2H), 3.52–3.54 (m, 2H), 3.58–3.62 (m, 2H), 3.63–3.66 (m, 6H), 3.90 (t, 2H, J = 5.2 Hz), 3.98 (t, 2H, J = 5.2 Hz), 4.46 (t, 2H, J = 5.2 Hz), 4.71 (t, 2H, J = 5.2 Hz), 7.78 (s, 1H), 8.06 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.31, 20.86, 41.61, 41.67, 67.80, 68.01, 70.54, 70.60, 70.84, 70.99, 71.10, 126.82, 128.81, 129.45, 139.17, 139.86, 142.28, 144.94, 145.45, 150.66, 160.05. FAB-MS: 445 m/z $[M+H]^+$, 467 $[M+Na]^+$. Anal. Calcd For $C_{22}H_{28}N_4O_6 \cdot 1/2CH_2Cl_2$: C, 55.49; H, 6.01; N, 11.51. Found: C, 55.65; H, 6.06; N, 11.39.

4.2.18. Compound 3e. The synthesis was performed using lumichrome **3a** (0.242 g, 1.00 mmol) and hexaethylene glycol diiodide (0.602 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) followed by recrystallization from CH_2Cl_2 to give a yellow solid. Yield: 42% (0.204 g, 0.418 mmol). R_f: 0.35 (CH_2Cl_2/MeOH, 9:1). Mp 125–127 °C. IR (KBr): 1718, 1681, 1557, 1458, 1363, 1107, 912, 742, 651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H), 2.53 (s, 3H), 3.48–3.50 (m, 4H), 3.57–3.61 (m, 4H), 3.62–3.74 (m, 8H), 3.89 (t, 2H, J = 5.6 Hz), 3.96 (t, 2H, J = 5.6 Hz), 4.44 (t, 2H, J = 5.6 Hz), 4.70 (t, 2H, J = 5.6 Hz), 7.78 (s, 1H), 8.06 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.30, 20.85, 41.47, 41.65, 67.81, 70.53, 70.60, 70.63, 70.72, 70.75, 70.79, 126.83, 128.89, 129.42, 139.23, 139.85, 142.30, 145.04, 145.41, 150.66, 160.09. EI-MS: 488 m/z $[M]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{24}H_{32}N_4O_7$Na): 511.2163. Found: 511.2159.

4.2.19. Compound 4b. The synthesis was performed using phenobarbital (**4a**) sodium salt (0.254 g, 1.00 mmol) and triethylene glycol diiodide (0.444 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2 to give a colorless solid. Yield: 30% (0.105 g, 0.303 mmol). R_f: 0.60 (CH_2Cl_2/MeOH, 19:1). Mp 164–165 °C. IR (KBr): 1693, 1439, 1399, 1281, 1200, 1137, 1107, 1060, 903, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, 3H, J = 7.2 Hz), 2.37 (q, 2H, J = 7.2, 14 Hz), 3.40–3.45 (m, 2H), 3.57–3.66 (m, 4H), 3.89–3.93 (m, 2H), 4.01–4.06 (m, 2H), 4.36–4.40 (m, 2H), 7.29–7.33 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.77, 30.71, 42.40, 62.79, 68.45, 72.62, 125.49, 128.46, 129.22, 152.29, 169.23. FAB-MS: 347 m/z $[M+H]^+$. Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.06; H, 6.39; N, 8.14.

4.2.20. Compound 4c. The synthesis was performed using phenobarbital (**4a**) sodium salt (0.254 g, 1.00 mmol) and tetraethylene glycol diiodide (0.497 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2 to give a colorless solid. Yield: 62% (0.242 g, 0.621 mmol). R_f: 0.46 (CH_2Cl_2/MeOH, 19:1). Mp 109–110 °C. IR (KBr): 1751, 1681, 1435, 1399, 1361, 1291, 1197, 1136, 1097, 918, 752,

716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, 3H, J = 7.2 Hz), 2.61 (q, 2H, J = 7.2, 14 Hz), 3.37–3.43 (m, 2H), 3.51–3.58 (m, 7H), 3.68–3.78 (m, 2H), 3.84–3.88 (m, 1H), 4.19–4.23 (m, 3H), 4.34–4.41 (m, 1H), 7.28–7.37 (m, 3H), 7.36 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.05, 31.05, 41.92, 60.46, 61.49, 66.47, 67.28, 69.79, 69.96, 70.02, 70.09, 126.41, 128.35, 129.27, 139.03, 150.93, 170.70. FAB-MS: 391 m/z $[M+H]^+$. Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.28; H, 6.64; N, 7.21.

4.2.21. Compound 4d. The synthesis was performed using phenobarbital (**4a**) sodium salt (0.254 g, 1.00 mmol) and pentaethylene glycol diiodide (0.550 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2 to give a colorless solid. Yield: 72% (0.314 g, 0.724 mmol). R_f: 0.38 (CH_2Cl_2/MeOH, 19:1). Mp 85–86 °C. IR (KBr): 1685, 1401, 1356, 1298, 1199, 1124, 929, 780, 755, 725, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, J = 7.2 Hz), 2.53 (q, 2H, J = 7.2, 15 Hz), 3.50–3.63 (m, 12H), 3.66–3.71 (m, 2H), 3.74–3.80 (m, 2H), 4.17–4.26 (m, 4H), 7.29–7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.98, 30.07, 41.58, 61.35, 67.65, 70.40, 70.59, 70.96, 71.11, 126.15, 128.30, 129.11, 138.45, 150.79, 170.25. FAB-MS: 435 m/z $[M+H]^+$. Anal. Calcd for $C_{22}H_{30}N_2O_7$: C, 60.82; H, 6.96; N, 6.45. Found: C, 60.77; H, 6.88; N, 6.65.

4.2.22. Compound 4e. The synthesis was performed using phenobarbital (**4a**) sodium salt (0.254 g, 1.00 mmol) and hexaethylene glycol diiodide (0.602 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2, to give colorless cubes. Yield: 71% (0.340 g, 0.711 mmol). R_f: 0.38 (CH_2Cl_2/MeOH, 19:1). Mp 41–42 °C. IR (KBr): 1686, 1437, 1397, 1353, 1295, 1199, 1113, 912, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3H, J = 7.2 Hz), 2.51 (q, 2H, J = 7.2, 15 Hz), 3.51–3.61 (m, 16H), 3.62–3.76 (m, 4H), 4.15–4.25 (m, 4H), 7.26–7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.04, 30.34, 41.37, 61.51, 67.45, 70.59, 70.66, 70.81, 71.00, 126.12, 128.37, 129.13, 138.45, 150.70, 170.24. FAB-MS: 479 m/z $[M+H]^+$. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{24}H_{34}N_2O_8$Na): 501.2207. Found: 501.2210.

4.2.23. Compound 5b. The synthesis was performed using phenytoin **5a** (0.252 g, 1.00 mmol) and triethylene glycol diiodide (0.444 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2 to give a colorless solid. Yield: 16% (0.058 g, 0.158 mmol). R_f: 0.38 (CH_2Cl_2/MeOH, 19:1). Mp 152–153 °C. IR (KBr): 1728, 1653, 1459, 1413, 1331, 1279, 1148, 1027, 882, 755, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.59–3.61 (m, 4H), 3.72–3.76 (m, 4H), 3.87–3.89 (m, 2H), 4.72–4.74 (m, 2H), 7.27–7.34 (m, 6H), 7.50–7.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.12, 67.91, 68.78, 69.74, 69.81, 71.28, 127.25, 127.58, 128.32, 140.76, 159.22, 180.42. FAB-MS: 367 m/z $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.57; H, 6.23; N, 7.77.

4.2.24. Compound 5c. The synthesis was performed using phenytoin **5a** (0.252 g, 1.00 mmol) and tetraethylene glycol diiodide (0.497 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2 to give colorless plates. Yield: 37% (0.150 g, 0.366 mmol). R_f: 0.35 (CH_2Cl_2/MeOH, 19:1). Mp 154–155 °C. IR (KBr): 1771, 1714, 1447, 1363, 1322, 1133, 1077, 769, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.79–2.85 (m, 1H), 2.98–3.05 (m, 1H), 3.29–3.34 (m, 2H), 3.50–3.52 (m,2H), 3.66–3.71 (m, 5H), 3.75–3.86 (m, 3H), 3.93–3.97 (m, 1H), 4.29–4.37 (m, 1H), 7.37–7.43 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.01, 40.90, 65.47, 67.32, 69.22, 69.72, 70.21, 74.23, 127.85, 128.57, 128.76, 130.16, 136.31, 138.54, 156.54, 174.42. FAB-MS: 411 m/z $[M+H]^+$. Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.21; H, 6.45; N, 6.74. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{23}H_{26}N_2O_5$Na): 433.1734. Found: 433.1726.

4.2.25. Compound 5d. The synthesis was performed using phenytoin **5a** (0.252 g, 1.00 mmol) and pentaethylene glycol diiodide (0.550 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2 to give colorless plates. Yield: 52% (0.237 g, 0.522 mmol). R_f: 0.31 (CH_2Cl_2/MeOH, 19:1). Mp 101–102 °C. IR (KBr): 1766, 1714, 1455, 1357, 1118, 761, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.41–3.53 (m, 4H), 3.57–3.62 (m, 6H), 3.63–3.69 (m, 6H), 3.70–3.81 (m, 4H), 7.39 (s, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.97, 41.29, 66.79, 67.67, 70.08, 70.35, 70.81, 70.87, 70.98, 71.07, 74.58, 127.09, 128.69, 128.74, 128.76, 137.09, 156.29, 174.02. FAB-MS: 455 m/z $[M+H]^+$. Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.70; H, 6.66; N, 6.34. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{25}H_{30}N_2O_6$Na): 477.1996. Found: 477.1985.

4.2.26. Compound 5e. The synthesis was performed using phenytoin **5a** (0.252 g, 1.00 mmol) and hexaethylene glycol diiodide (0.602 g, 1.20 mmol). The crude compound was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) followed by recrystallization from CH_2Cl_2 to give a colorless solid. Yield: 66% (0.330 g, 0.663 mmol). R_f: 0.31 (CH_2Cl_2/MeOH, 19:1). Mp 89–90 °C. IR (KBr): 1771, 1715, 1451, 1355, 1267, 1117, 913, 734, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.98–3.01 (m, 2H), 3.39–3.41 (m, 2H), 3.51–3.55 (m, 4H), 3.57–3.60 (m,2H), 3.66–3.71 (m, 10H), 3.80 (s, 4H), 7.34–7.37 (m, 4H), 7.39–7.41 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.77, 41.21, 66.83, 67.54, 70.38, 70.44, 70.57, 70.72, 70.77, 70.93, 70.96, 71.05, 71.22, 74.61, 128.52, 128.78, 128.85, 137.10, 156.04, 173.95. EI-MS: 498 m/z $[M]^+$. Anal. Calcd for $C_{27}H_{34}N_2O_7$: C, 65.04; H, 6.87; N, 5.62. Found: C, 65.33; H, 6.97; N, 5.47. HRMS (ESI-FTMS) Calcd for $[M+Na]^+$ ($C_{27}H_{34}N_2O_7$Na): 521.2258. Found: 521.2252.

4.3. X-ray crystallographic analyses for 2b and 2b–Ca^{2+} complex

Crystals suitable for X-ray analysis were obtained by slow evaporation of the solvent (chloroform–methanol) solution for both compounds. Data collections were made on an Enraf-Nonius CAD4 diffractometer with a graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Diffracted intensities were reduced to a set of relative structure factors by the application of the standard Lorentz and polarization factors. No absorption correction was made. The molecular structures of two compounds were solved by the direct method (MULTAN82),[9] and refined by the difference Fourier (DF) and least-squares techniques. The programs used in the refinement and plot were modified versions of Busing and Levy's ORFLS, and Johnson's ORTEP II. DF syntheses revealed all non-hydrogen atomic positions of both compounds. Complex **2b**–Ca^{2+} suffered some positional disorders in the perchlorate and crown ether moiety. The disorders were treated by the fraction of oxygen or carbon atoms with appropriate occupancy in the DF maps. The non-hydrogen atoms of the molecule were refined with anisotropic thermal parameters, and hydrogen atoms bound to carbons were included in calculated positions as fixed parameters. Four hydrogen atoms bound to three water ligands of **2b**–Ca^{2+} complex were found in a final DF map and refined isotropically in part. Final cycles of full-matrix least-squares refinement of the molecular models were carried to convergence at $R = 0.043$ and $R_w = 0.045$ for **2b**, and $R = 0.086$ and $R_w = 0.083$ for **2b**–Ca^{2+} complex, respectively. The final DF map showed residual peaks of 0.3 e/Å^3 level for both compounds, but these were judged to be essentially featureless.

4.4. Fluorometric analysis

Fluorescence spectra were measured with a Hitachi F4500. The slit width was 5.0 nm for excitation and emission. Excitation at 340 nm was used for **2b**. All emission spectra were recorded over the range 350–500 nm.

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