Tetrahedron Letters 54 (2013) 2766–2769

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New calix[4]arene based oxalylamido receptors for recognition of copper(II)

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ARTICLE INFO

Article history:
Received 28 October 2012
Revised 11 February 2013
Accepted 13 February 2013
Available online 20 February 2013

Keywords:
Calix[4]arenes
Oxalylamido looping
Recognition
Fluorescence
Color change

ABSTRACT

New calix[4]arene derivatives with oxalylamido loops on their upper and lower rim (**7**, **8**) have been designed and synthesized. It has been determined that molecular receptor **8** is more efficient than **7** for recognition of copper ions in preference to other metal ions through distinct 'naked eye' color change and a significant change in absorption spectra and fluorescence characteristics. The reported work paves the way for development of novel sensor materials for ubiquitous ions like copper at low concentrations.

Calix[4]arenes represent one of the most widely employed molecular scaffolds for applications in ionic and molecular recognition.[1] Selective ionic and molecular sensing through colorimetric and change in fluorescence intensity have received considerable attention from the scientific community due to comparative ease of such operations and high selectivity and sensitivity.[2,3] For instance, while the former technique is useful to obtain '*use and throw type*' indicator strips,[4] the latter is used to measure much low concentrations present in biological samples.

We report herein the synthesis and evaluation of new oxalylamidocalix[4]arene derivatives with loops at their upper and the lower rim for ubiquitous ion recognition such as that of copper ions. These ions are essential at low concentrations for sustenance of important biological processes but are extremely toxic when present in higher concentrations.[5]

Most sensors developed so far for detection of metal ions show only fluorescence changes.[6] Sensors based on both naked eye detection and fluorescence changes are rare especially the ones which show specific selectivity toward a target metal ion(s) over other competing metal ions with high efficiency in the spectral visible region. There is an urgent demand for the development of novel fluorescent chemosensors with improved efficiency. The advantage associated with the designed molecular receptor being reported here is that it acts as a dual fluorescence and visible light sensing probe. It has a large Stoke shift, induces a color change visible to the naked eye, has high binding constant, and emits in the visible region to promote least interference from background emissions.[7]

Calixarenes are known to undergo rapid conformational tranformations.[8] When the target application is ionic or molecular recognition, it is essential that the designed molecular receptor possesses a judicious balance of rigidity and flexibility to interact with the target ion or a molecule. Since calix[4]arene cavity is not large enough to accommodate ions and molecules, the calixarene macrocycle usually provides a rigid support system in which the recognition elements could be incorporated through functionalization at their upper or the lower rim.[9] In this Letter we describe our attempts at functionalization of calix[4]arene macrocycle to provide oxalylamidocalix[4]arene derivatives which have shown an excellent promise to develop molecular receptors for copper ions in preference to many other related ions when present alone or in mixtures without loss of selectivity.

A survey of the literature indicates that hydrazine derived Schiff's bases are useful for both colorimetric and fluorometric metal ion detection.[10] These two properties prompted us to take up the design and synthesis of molecular receptors **7**–**8** which was accomplished by a series of reactions given in Scheme 1.[11–14]

Diethyl *o*-phenylenedioxamate[11] required for the designed molecular receptors was synthesized by stirring the solution of *o*-phenylenediamine with ethyl oxalyl chloride and Et_3N in dry DCM. This was further reacted with hydrazine hydrate in ethanol to give **1**.[11] Reaction of bis-formyl derivative of calix[4]arene (**5** and **6**) with **1** in the presence of glacial acetic acid in ethanol yielded products which were further washed with methanol to give **7** and **8** in 82% and 75% yields, respectively.

The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS (SI, Fig. 1). For example, **8** showed a >C=N– signal at 1600 cm^{-1} in IR and a sharp pair of doublets at δ 3.52 and δ 4.24 in the ^{1}H NMR spectrum which could be attributed to axial

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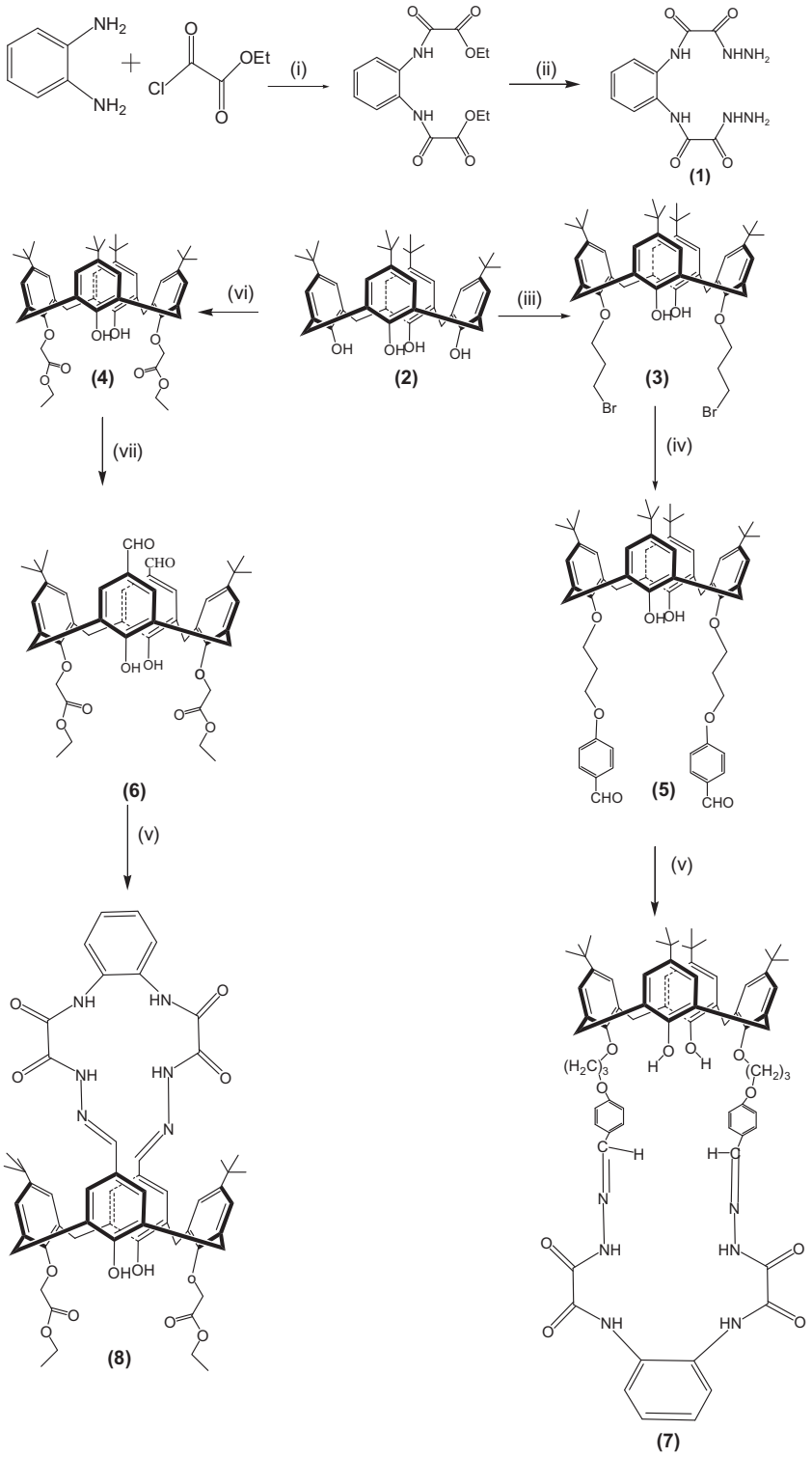
http://dx.doi.org/10.1016/j.tetlet.2013.02.034



Scheme 1. Synthesis of novel calixarene derivatives. Reagents and conditions: (i) Et_3N, anhyd DCM, 0 °C, N_2 atm; (ii) $NH_2NH_2{\cdot}2H_2O$, ethanol, reflux; (iii) 1,3-dibromopropane, K_2CO_3, reflux; (iv) p-hydroxy-benzaldehyde, K_2CO_3, reflux; (v) (**1**),[11] acetic acid, ethanol reflux; (vi) ethyl bromoacetate, K_2CO_3, reflux; (vii) HMTA, TFA, reflux.

and equatorial protons respectively. A distinct signal at δ 30.83 for the methylene carbons in its ^{13}C NMR spectrum indicated a symmetric cone conformation for the calix[4]arene scaffold. It was further confirmed by observing two D_2O exchangeable singlets at δ 10.70 and δ 12.06 for –NH and –OH protons, respectively. The azo-methine (–N=CH) proton was observed as a non-deuterable singlet at δ 8.44 (Scheme 1).

The cation binding ability of the synthesized receptors **7** and **8** was first investigated by examining their UV–Vis spectrum in dry THF solution in the presence of various metal ions (Na^+, Li^+, K^+, Cs^+, Ag^+, Ca^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+}, Fe^{3+}, Ni^{2+}, and Cu^{2+}) as their perchlorate salts. While selectivity observed through **7** was limiting (see later discussion and Supplementary information), **8** showed a strong absorption band at 327 nm which on addition of

a solution of various metal ions exhibited negligible shift for Na^+, Li^+, K^+, Cs^+, Ag^+, Ca^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+}, Fe^{3+}, and a little shift for Ni^{2+}. However, a significant change in the absorption profile of **8** was observed on addition of Cu^{2+} (SI, Fig. 2).

Upon gradual addition of Cu^{2+} ion to receptor **8**, the absorption at 327 nm gradually decreased with the concurrent increase in the intensity in the new absorption band centered at 345 nm with appearance of an isosbestic point at 350 nm (Fig. 1) accompanied by a noticeable color change from colorless to light yellow. Thus, it could be used as a naked eye visible sensor for Cu^{2+}. Job's continuous variation plot was deduced to determine the stoichiometry of the interaction between the Cu^{2+} ion and receptor **8**. Analysis of the data obtained from Job's plot revealed the formation of a 1:1 molecular complex (Fig. 2).

Sensitivity and selectivity of the synthesized receptor **8** were evaluated by observing changes in their fluorescence emission spectra in THF solution. The fluorescence emission spectrum of **8** was recorded from 350 to 800 nm by exciting it at 327 nm when the emission maximum was observed at 443 nm. From this data, we inferred that it could be employed as a fluorescence sensor which required a thorough study of **8** through fluorescence spectroscopy in the presence of various ions. The spectral measurements were accomplished in the presence of competing metal ions in THF solution to evaluate the utility of synthesized molecular receptors to function as fluorescence based cation sensors. Figure 3 shows a relative change in the fluorescence intensity of molecular receptor **8** upon addition of various metal ions. It has been observed from the data given in Figure 3 that while other metal ions do not confer significant change in the emission spectra of the receptor **8**, addition of Cu^{2+} induces a remarkable quenching on its emission band. The observed quenching might be due to electron transfer in the excited state as reported earlier.[15]

To analyze the mode of interaction between Cu^{2+} and **8**, fluorescence titration was performed by using increasing concentration of Cu^{2+} (Fig. 4). A plot of F_0/F versus $[Cu^{2+}]$ was found to be linear thereby confirming the interaction to be of 1:1 type interaction (inset Fig. 3). These data sets were further confirmed by mass spectrometric analysis. A peak at m/z 1170.5413 in ESI-MS data showed the formation of 1:1 complex $[8+Cu^{2+}+ClO_4]^+$ (SI, Fig. 1). Moreover, the quenching of fluorescence intensity occurring in this case seems to be static quenching[15] which could be inferred from a careful examination of the absorption spectra of synthesized receptor **8**. The detection limit[16] calculated by using the semi-logarithmic plot of $(F_0-F)/F_0$ (where F_0 and F are emission intensities at 443 nm) against log $[Cu^{2+}]$ was found to be 6.02×10^{-6} M (SI, Fig. 3). Using the fluorescence titration data, the Stern Volmer quenching constant[15] K_{sv} of **8**–Cu^{2+} complex in THF solution was

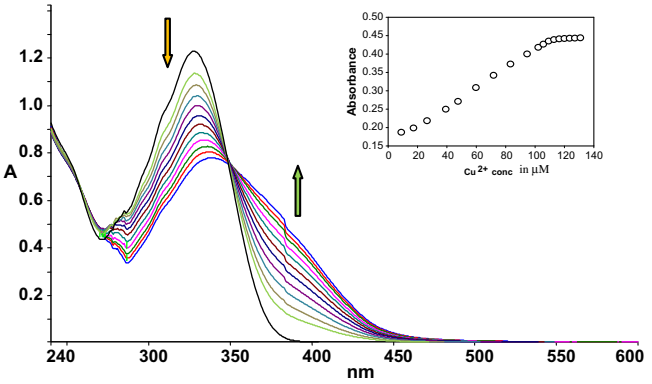


Figure 1. Change in the UV–Vis spectra of **8** (20 µM) upon addition of 7.5 equiv of Cu^{2+} in THF. Inset: changes in the absorption as a function of Cu^{2+} added.

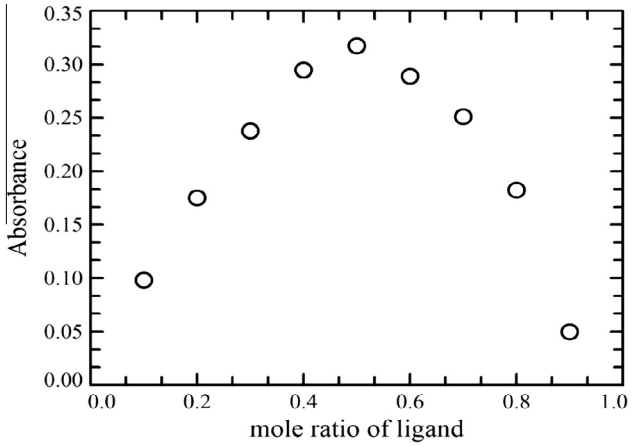


Figure 2. Job's plot of Cu^{2+} complex formation. {[8]/[8]+[Cu^{2+}]} is the mole fraction of ligand **8**}.

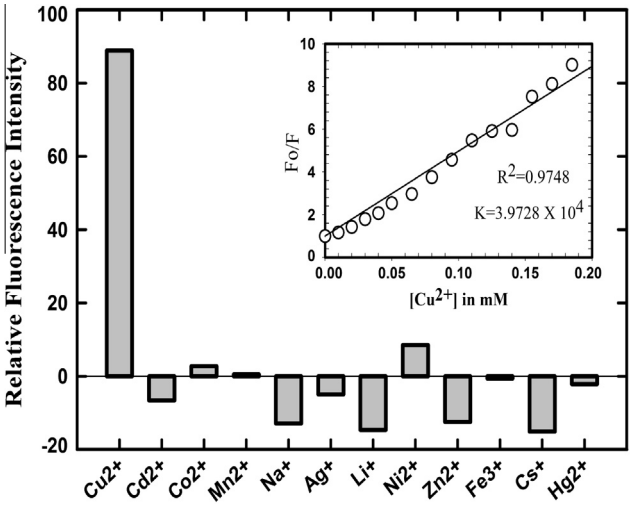


Figure 3. Change in the fluorescence intensity of **8** upon addition of 7.5 equiv of various metal ions in THF ($\lambda_{excitation}$ = 327 nm). Inset: a plot of F_0/F versus $[Cu^{2+}]$ for ligand **8**.

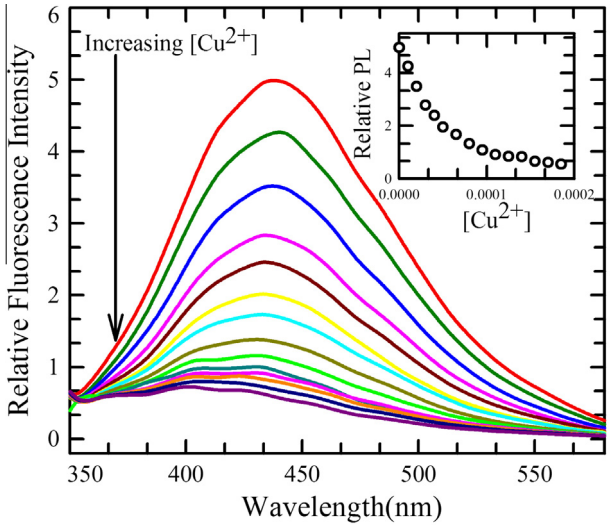


Figure 4. Quenching of fluorescence intensity of **8** (20 µM) in THF in the presence of Cu^{2+} ($\lambda_{excitation}$ = 327 nm). Inset: shows change in the fluorescence intensity of the ligand **8** with varying concentrations of Cu^{2+}.

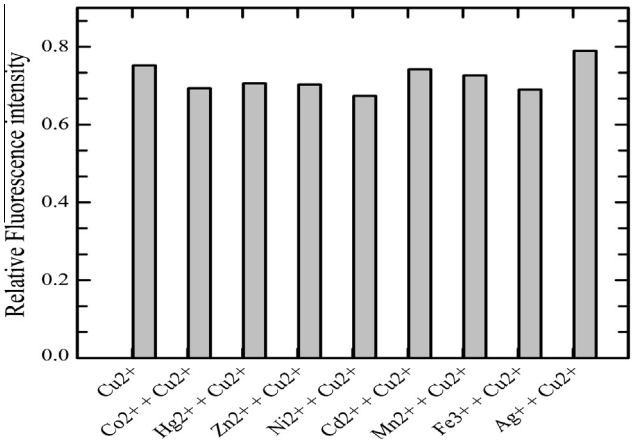


Figure 5. Comparative study of molecular receptor **8** in THF of peak at 443 nm in the presence of 7.5 equiv of various metal ions + 7.5 equiv of Cu^{2+} by exciting at 327 nm.

calculated to be $3.92 \times 10^4\ M^{-1}$ (Inset Fig. 3). To calculate association constant,[17] a plot of log (F_0-F/F) versus log $[Cu^{2+}]$ yielded the value of K as $1.655 \times 10^6\ M^{-1}$ which represents efficient binding of Cu^{2+} and **8** (SI, Fig. 10).

Under identical conditions, addition of Cu^{2+} to **7** resulted in 80% quenching of the fluorescence intensity of the synthesized receptor (SI, Fig. 5) with less K_{sv} and binding constant $(1.981 \times 10^4\ M^{-1})$ as compared to **8** (SI, Figs. 6 and 11) revealing superiority of **8** over **7** for binding Cu^{2+}.

The practical application of synthesized receptor **8** as fluorescence 'turn off' probe for Cu^{2+} was examined by recording its fluorescence response to Cu^{2+} in the presence of other competing ions. As shown in Figure 5, most of the competing ions such as Co^{2+}, Hg^{2+}, Zn^{2+}, Ni^{2+}, Cd^{2+}, Mn^{2+}, Fe^{3+}, Ag^{+}, exhibited negligible interference in the detection of Cu^{2+} in the presence of other metal ions. Thus **8** can be used for selective detection of Cu^{2+} even in the presence of these competing ions. The same selectivity was determined by UV–Vis spectroscopic studies (SI, Fig. 8).

The binding of Cu^{2+} with receptor **8** could not be monitored through NMR titrations owing to the paramagnetic nature of copper which leads to the broadening of peaks.

In conclusion, we have designed, synthesized and evaluated novel calix[4]arene based oxalylamide receptors (**7**, **8**) as chemosensors for Cu^{2+} ions through fluorescence and chromogenic probes. The detection has been found to be selective in the micromolar range without interference from other competing ions in coexisting systems. It appears that upper rim oxalylamido looping of the calixarene scaffold is advantageous for Cu^{2+} recognition.

Acknowledgments

P.G. and R.S. thank UGC and CSIR, India for a research fellowship. Financial assistance from DST, MoFPI, MoEF, and MoRD is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.034.

References and notes

1. (a) Chawla, H. M.; Pant, N.; Kumar, S.; Kumar, N.; St. Black david, C. Calixarene – Based Materials for Chemical Sensors In *Chemical Sensors Fundamentals of Sensing Materials*; Korotcenkov, G., Ed.; Momentum Press: New York, 2010; Vol. 3, p 300; (b) Joseph, R.; Rao, C. P. *Chem. Rev.* **2011**, *111*, 4658–4702; (c) Chawla, H. M.; Shukla, R.; Pandey, S. *Tetrahedron Lett.* **2012**, *53*, 2996–2999; (d) Shaabani, B.; Shaghaghi, Z.; Khandar, A. A. *Spectrochim. Acta A* **2012**, *98*, 81–85; (e) Sap, A.; Tabakci, B.; Yilmaz, A. *Tetrahedron* **2012**, *68*, 8739–8745; (f) Wang, N.-J.; Sun, C.-M.; Chung, W. S. *Sens. Actuators, B* **2012**, *171–172*, 984–993; (g) Echabaane, M.; Rouis, A.; Bonnamour, I.; Quada, H. B. *Mater. Sci. Eng., C* **2012**, *32*, 1218–1221; (h) Pandey, S.; Azam, A.; Pandey, S.; Chawla, H. M. *Org. Biomol. Chem.* **2009**, *7*, 269–279.
2. (a) Kumar, A.; Kumar, V.; Neeraj; Upadhyay, K. K.; Roychowdhury, P. K. *J. Mol. Struct.* **2013**, *1035*, 174–182; (b) Wang, M.; Xu, Z.; Wang, X.; Cui, J. *Dyes Pigm.* **2013**, *96*, 333–337; (c) Hu, S.; Zhang, S.; Hu, Y.; Tao, Q.; Wu, A. *Dyes Pigm.* **2013**, *96*, 509–515; (d) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3–40.
3. (a) Haung, J.; Xu, Y.; Qian, X. *Dalton Trans.* **2009**, 1761–1766; (b) Kim, H. J.; Kim, S. H.; Anh, L. N.; Lee, J. H.; Lee, C.; Kim, J. S. *Tetrahedron Lett.* **2009**, *50*, 2782–2786.
4. (a) Udhayakumari, D.; Saravanamoorthy, S.; Velmathi, S. *Mater. Sci. Eng., C* **2012**, *32*, 1878–1882; (b) Maity, D.; Govindaraju, T. *Inorg. Chem.* **2011**, *50*, 11282–11284.
5. (a) de Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Coord. Chem. Rev.* **2000**, *205*, 41–57; (b) Mahendra, N.; Gangaiya, P.; Subramaniam, S.; Narayanaswamy, R. *Sens. Actuators, B* **2003**, *90*, 113–118; (c) Xiang, Y.; Tong, A. J.; Jin, P. Y.; Ju, Y. *Org. Lett.* **2006**, *8*, 2863–2866; (d) Georgopoulos, P. G.; Roy, A.; Yonone-Lioy, M. J.; Opiekun, R. E.; Lioy, P. J. *J. Toxicol. Environ. Health Part B* **2001**, *4*, 341–394; (e) Koval, I. A.; Gamez, P.; Belle, C.; Selmeczi, K.; Reedijk, J. *Chem. Soc. Rev.* **2006**, *35*, 814–840; (f) Zhang, L.; Zhu, J.; Ai, J.; Zhou, Z.; Jia, X.; Wang, E. *Biosens. Bioelectron.* **2013**, *39*, 268–273; (g) He, G.; Zhang, X.; He, C.; Zhao, X.; Duan, C. *Tetrahedron* **2010**, *66*, 9762–9768; (h) Viswanathan, K. *Sens. Actuators, A* **2012**, *175*, 15–18; (i) Kaur, P.; Sareen, D.; Singh, K. *Talanta* **2012**, *83*, 1695–1700; (j) Xu, Z.; Zhang, L.; Guo, R.; Xiang, T.; Wu, C.; Zheng, Z.; Yang, F. *Sens. Actuators, B* **2011**, *156*, 546–552; (k) Tang, L.; Li, F.; Liu, M.; Nandhakumar, R. *Spectrochim. Acta A* **2011**, *78*, 1168–1172.
6. (a) Li, G.; Xu, Z.; Chen, C.; Huang, Z. *Chem. Commun.* **2008**, 1774–1776; (b) Aksuner, N.; Henden, E.; Yilmaz, I.; Cukurovali, A. *Dyes Pigm.* **2009**, *83*, 211–217; (c) Joseph, R.; Ramanujam, B.; Acharya, A.; Rao, C. P. *Tetrahedron Lett.* **2009**, *50*, 2735–2739; (d) Liang, Z.; Liu, Z.; Jiang, L.; Gao, Y. *Tetrahedron Lett.* **2007**, *48*, 1629–1632; (e) Baghel, G. S.; Ramanujam, B.; Rao, C. P. *J. Photochem. Photobiol. A Chem.* **2009**, *202*, 172–177.
7. Kumar, S.; Luxami, V.; Kumar, A. *Org. Lett.* **2008**, *10*, 5549–5552.
8. Chawla, H. M.; Hundal, G.; Singh, S. P.; Upreti, S. *Cryst. Eng. Comm.* **2007**, *9*, 119–122.
9. (a) Gutsche, C. D. In *Calixarenes: Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: London, 1989; (b)*Calixarene: An Introduction*; Gutsche, C. D., Ed., 2nd ed.; Royal Society of Chemistry: Cambridge, 2008.
10. Narayanaswamy, N.; Govindaraju, T. *Sens. Actuators, B* **2012**, *161*, 304–310.
11. Padilla-Martinez, I. I.; Martinez-Martinez, F. J.; Guillen-Hernandez, C. I.; Chaparro-Huerta, M.; Caberera-Perez, L. C.; Gomez-Castro, C. Z.; Lopez-Romero, B. A.; Garcia-Baez, E. V. *ARKIVOC* **2005**, *205*, 401–415.
12. (a) Iqbal, M.; Mangiafico, T.; Gutsche, C. D. *Tetrahedron* **1987**, *43*, 4917–4930; (b) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234; (c) Gutsche, C. D.; Iqbal, M.; Steward, D. *J. Org. Chem.* **1986**, *51*, 742–745; (d) Chawla, H. M.; Shrivastava, R.; Sahu, S. N. *New J. Chem.* **2008**, *32*, 1999–2005; (e) Chawla, H. M.; Pant, N.; Srivastava, B.; Upreti, S. *Org. Lett.* **2006**, *8*, 2237–2240.
13. *Procedure for the synthesis of* ***8***: To a solution of bis formyl calix[4]arene (**6**) in ethanol was added **1** and a catalytic amount of acetic acid. The reaction mixture was refluxed for 24 h. After completion of the reaction (TLC), the precipitate was filtered and washed with water. The structure of **4** was confirmed by ^1H NMR and ^{13}C NMR spectra as well as ESI MS analysis.
14. *Analytical data for* ***8***: White solid; melting point: 340 °C (decomposed); UV (λ_{max}, THF): 327 nm. IR (KBr pellet, cm^{-1}): 3445, 1682, 1600, 756; ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 12.065 (s, 2H, N*H*, D_2O exchangeable), 10.704 (s, 2H, N*H*, D_2O exchangeable), 8.440 (s, 2H, =C*H*), 8.12 (s, 2H, O*H*, D_2O exchangeable), 7.628(d, 2H, ArH_1), 7.520(s, 4H, Ar*H*), 7.311 (d, 2H, ArH_1), 6.916 (s, 4H, Ar*H*), 4.754 (s, 4H, $-OCH_2$), 4.252–4.229 (m, 8H, $-CH_2$+$-OCH_2CH_3$), 3.517 (dd, 4H, CH_2), 1.266 (t, 6H, $-CH_3$), 0.999 (s, 18H, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm): 168.89, 158.55, 155.58, 155.14151.78, 150.49, 146.75, 131.80, 129.94, 128.79, 128.01, 126.14, 125.71, 124.69, 71.90, 60.84, 33.69, 30.93, 30.83, 13.94; HRMS (ESI-MS) *m/z*: calcd 1031.4161, found 1031.4173 ($M+Na^+$).
15. Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*, 3rd ed.; Kluwer Academics/Plenum: New York, 2006.
16. Mashraqui, S. H.; Ghorpade, S. S.; Tripathi, S.; Britto, S. *Tetrahedron Lett.* **2012**, *53*, 765–768.
17. (a) Mishra, B.; Barik, A.; Priyadarsini, K. I.; Mohan, H. *J. Chem. Sci.* **2005**, *117*, 641–647; (b) Ding, J.; Yuan, L.; Gao, L.; Chen, J. *J. Lumin.* **2012**, *132*, 1987–1993.