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Infrared Absorbing Croconaine Dyes: Synthesis and Metal Ion Binding Properties

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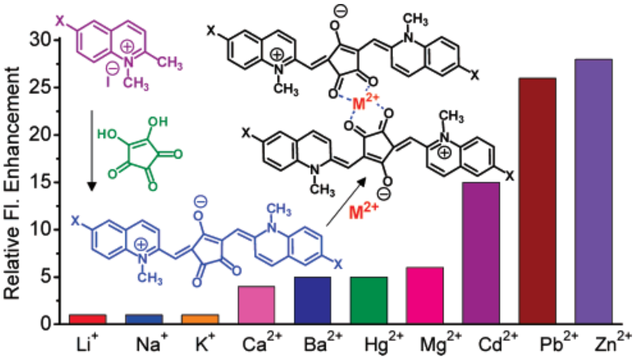

Quinaldine-based croconaine dyes synthesized by the condensation reaction between croconic acid and the respective quinaldinium salts are described. These dyes exhibit absorption maximum in the infrared region (840−870 nm) with high molar extinction coefficients (1−5 × 10^5 M^{-1} cm^{-1}) and have very low fluorescence quantum yields. Upon binding to divalent metal ions, these dyes were found to form complexes with a 2:1 stoichiometry having high association constants of the order of 10^{11}−10^{14} M^{-2}, while the monovalent metal ions showed negligible affinity. The binding of the croconaine dye **3d** with divalent metal ions especially Zn^{2+}, Pb^{2+}, and Cd^{2+} led to significant chelation-enhanced fluorescence emission. The broadening of the aromatic signals, vinylic and *N*-methyl protons and the negligible changes at the aliphatic region of the dye **3d** in the ^{1}H NMR spectrum in the presence of Zn^{2+}, indicate that the binding occurs at the carbonyl groups of the croconyl ring. The shift in the croconyl carbonyl stretching frequency in the [**3d**-Zn^{2+}] complex analyzed through FT-IR analysis further confirms the involvement of two electron-rich carbonyl groups of the croconyl moiety in the complexation. These results demonstrate that the binding of the divalent metal ions at the carbonyl oxygens of these infrared absorbing dyes can be favorably utilized for the development of potential sensors for the detection of metal ions and further can be exploited as sensitizers for photodynamic therapeutic applications.

Introduction

Dyes that absorb or emit in the long-wavelength (>650 nm) region of the optical spectrum have gained increasing attention in the past few years,[1] especially because of their potential optoelectronic[2] and biomedical[3] applications. Several attempts have been made toward developing compounds that absorb in the near-infrared region. One commonly employed approach is to increase the extent of π conjugation, which would eventually lead to its convergence limit.[4] Further, most of the near-infrared (NIR) absorbing dyes require tedious synthetic methodologies.[5] Of these, cyanine dyes have received considerable attention as NIR dyes due to their remarkable absorption and emission properties.[6] However, photobleaching and low chemical stability of these dyes has necessitated the development of alternate dyes with absorption in the NIR and infrared (IR) region. In this regard, the electron donor−acceptor−donor concept[7] has been utilized for the synthesis of long-wavelength absorbing dyes including squaraines and croconaines.[8]

Recently, we have reported the synthesis of phloroglucinol-based squaraine dyes[9] for photodynamic therapeutic (PDT) applications.[10] However, the absorption maximum of these dyes is in the short-wavelength region (600−650 nm) where most of the biological tissues have significant absorption. Since the

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tissue penetration of light increases with increasing wavelength, we were interested in the development of dyes having longer wavelength absorption. This was achieved by replacing the electron-donor phloroglucinol moiety with a quinaldine group. These quinaldine-based squaraine dyes were prepared by the condensation reaction between substituted quinaldinium salts and squaric acid in 2:1 equiv.[11] It was observed that quinaldinium salts with electron-donating substituents gave only the semisquaraine as the isolable product due to the reduced electrophilicity at the squaryl ring of the semisquaraine. However, the quinaldinium salts with electron-withdrawing substituents gave the corresponding squaraine dyes in quantitative yields. These dyes exhibit long-wavelength absorption (λ = 700−750 nm) and high molar extinction coefficients (ϵ = 1−3 × 10^5 M^{-1} cm^{-1}). We felt that if the squaryl moiety in these dyes is replaced with its higher homologue croconic acid having a stronger acceptor moiety, the absorption can be further shifted to longer wavelengths[12] and hence such longer wave-

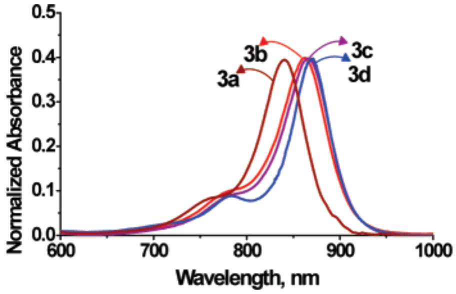

FIGURE 1. Normalized absorption spectra of the croconaine dyes **3a**−**d**.

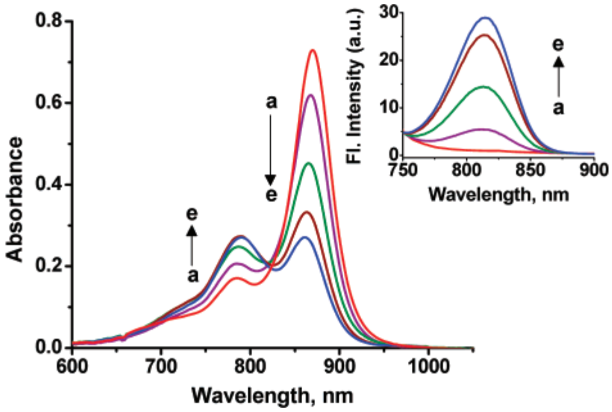

FIGURE 2. Changes in the absorption spectra of the croconaine dye **3d** (7.75 μM) in THF with the addition of Zn^{2+}: [Zn^{2+}] = 0 (a), 0.94 (b), 1.88 (c), 2.82 (d), and 3.87 μM (e). The inset shows the corresponding changes in the emission of **3d** on complexation with Zn^{2+}. Excitation wavelength, 700 nm.

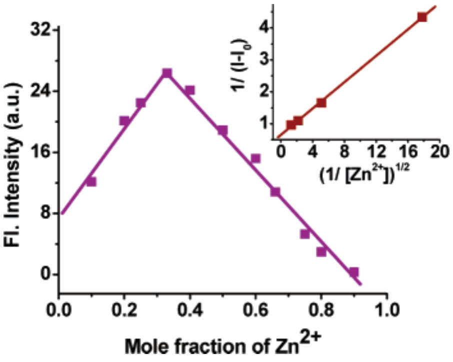

FIGURE 3. Job's plot for the complexation of the croconaine dye **3d** with Zn^{2+} in THF. The inset shows the Benesi−Hildebrand analysis of the emission changes for the complexation between the dye **3d** and Zn^{2+}.

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(1) (a) Fabian, J.; Nakazumi, H.; Matsuoka, M. *Chem. Rev.* **1992**, *92*, 1197−1226. (b) Ye, Y.; Li, W. P.; Anderson, C. J.; Kao, J.; Nikiforovich, G. V.; Achilefu, S. *J. Am. Chem. Soc.* **2003**, *125*, 7766−7767. (c) Tatsuura, S.; Tian, M.; Furuki, M.; Sato, Y.; Iwasa, I.; Mitsu, H. *Appl. Phys. Lett.* **2004**, *84*, 1450−1452. (d) Zhang, Z.; Achilefu, S. *Org. Lett.* **2004**, *6*, 2067−2070. (e) Zhao, W.; Carreira, E. M. *Chem. Eur. J.* **2006**, *12*, 7254−7263. (f) Kiyose, K.; Kojima, H.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2006**, *128*, 6548−6549. (g) Basheer, M. C.; Alex, S.; Thomas, K. G.; Suresh, C. H.; Das, S. *Terahedron* **2006**, *62*, 605−610. (h) Coskun, A.; Ylimaz, M. D.; Akkaya, E. U. *Org. Lett*. **2007**, *9*, 607−609. (i) Lee, P. H.-M.; Ko, C.-C.; Zhu, N.; Yam, V. W.-W. *J. Am. Chem. Soc.* **2007**, *129*, 6058−6059.

(2) (a) Tian, M.; Tatsuura, S.; Furuki, M.; Sato, Y.; Iwasa, I.; Pu, L. S. *J. Am. Chem. Soc*. **2003**, *125*, 348−349. (b) Wang, H.; Qian, G.; Wang, M.; Zhang, J.; Luo, Y. *J. Phys. Chem. B* **2004**, *108*, 8084−8088. (c) Kang, H.; Facchetti, A.; Jiang, H.; Cariati, E.; Righetto, S.; Ugo, R.; Zuccaccia, C.; Macchioni, A.; Stern, C. L.; Liu, Z.; Ho, S.-T.; Brown, E. C.; Ratner, M. A.; Marks, T. J. *J. Am. Chem. Soc*. **2007**, *129*, 3267−3286.

(3) (a) Achilefu, S.; Jimenez, H. N.; Dorshow, R. B.; Bugaj, J. E.; Webb, E. G.; Wilhelm, R. R.; Rajagopalan, R.; Johler, J.; Erion, J. L. *J. Med. Chem*. **2002**, *45*, 2003−2015. (b) Kim, K.; Lee, M.; Park, H.; Kim, J.-H.; Kim, S.; Chung, H.; Choi, K.; Kim, I.-S.; Seong, B. L.; Kwon, I. C. *J. Am. Chem. Soc*. **2006**, *128*, 3490−3491. (c) Leevy, W. M.; Gammon, S. T.; Jiang, H.; Johnson, J. R.; Maxwell, D. J.; Jackson, E. N.; Marquez, M.; Piwnica-Worms, D.; Smith, B. D. *J. Am. Chem. Soc*. **2006**, *128*, 16476−16472. (d) Chen, J.; Corbin, I. R.; Li, H.; Cao, W.; Glickson, J. D.; Zheng, G. *J. Am. Chem. Soc*. **2007**, *129*, 5798−5799.

(4) (a) Meier, H.; Petermann, R.; Gerold, J. *Chem. Commun*. **1999**, 977−978. (b) Adachi, M.; Nagao, Y. *Chem. Mater*. **2001**, *13*, 662−669.

(5) Kohl, C.; Becker, S.; Mullen, K. *Chem. Commun*. **2002**, 2278−2279.

(6) (a) Mishra, A.; Behera, R. K.; Behera, P. K.; Mishra, B. K.; Behera, G. B. *Chem. Rev*. **2000**, *100*, 1973−2011. (b) Peng, X.; Song, F.; Lu, E.; Wang, Y.; Zhou, W.; Fan, J.; Gao, Y. *J. Am. Chem. Soc*. **2005**, *127*, 4170−4171.

(7) (a) Konig, W. *J. Prakt. Chem*. **1925**, *112*, 1. (b) Ismailsky, W. Dissertation, Universität Dresden, 1913. (c) Dilthey, W.; Wizinger, R. *J. Prakt. Chem*. **1928**, *118*, 321. (d) Wizinger, R. *Chimia* **1961**, *15*, 89. (e) Griffiths, J. *Colour and Constitution of Organic Molecules*; Academic Press: London, UK, 1976. (f) Dähne, S.; Kulpe, S. *Structural Principles of Unsaturated Organic Compounds*; Akademic Verlag: Berlin, Germany, 1977 (*Abh. Akad. Wiss. DDR 8*). (g) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*, 1st ed.; Plenum: New York, 1975; pp 410−418. (h) Langhals, H. *Angew. Chem., Int. Ed*. **2003**, *42*, 4286−4288.

(8) (a) Meier, H.; Dullweber, U. *J. Org. Chem*. **1997**, *42*, 4821−4826. (b) Prabhakar, C.; Chaitanya, G. K.; Sitha, S.; Bhanuprakash, K.; Rao, V. J. *J. Phys. Chem. A* **2005**, *109*, 8604−8616. (c) Prabhakar, C.; Chaitanya, G. K.; Sitha, S.; Bhanuprakash, K.; Rao, V. J. *J. Phys. Chem. A* **2005**, *109*, 2614−2622.

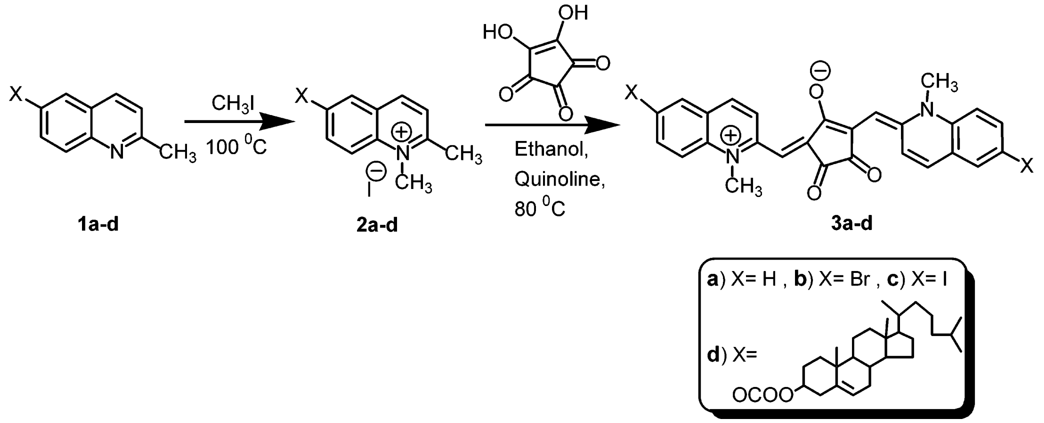
(9) (a) Arun, K. T.; Epe, B.; Ramaiah, D. *J. Phys. Chem. B* **2002**, *106*, 11622−11627. (b) Arun, K. T.; Ramaiah, D. *J. Phys. Chem. A* **2005**, *109*, 5571−5578. (c) Jisha, V. S.; Arun, K. T.; Hariharan, M.; Ramaiah, D. *J. Am. Chem. Soc*. **2006**, *128*, 6024−6025.

(10) (a) Ramaiah, D.; Joy, A.; Chandrasekhar, N.; Eldho, N. V.; Das, S.; George, M. V. *Photochem. Photobiol*. **1997**, *65*, 783−790. (b) Ramaiah, D.; Eckert, I.; Arun, K. T.; Weidenfeller, L.; Epe, B. *Photochem. Photobiol.* **2002**, *76*, 672−677. (c) Ramaiah, D.; Eckert, I.; Arun, K. T.; Weidenfeller, L.; Epe, B. *Photochem. Photobiol*. **2004**, *79*, 99−104.

(11) (a) Jyothish, K.; Arun, K. T.; Ramaiah, D. *Org. Lett.* **2004**, *6*, 3965−3968. (b) Jyothish, K.; Avirah, R. R.; Ramaiah, D. *Org. Lett*. **2006**, *8*, 111−114. (c) Jyothish, K.; Avirah, R. R.; Ramaiah, D. *Arkivoc* **2007**, *8*, 296−310. (d) Jyothish, K.; Hariharan, H.; Ramaiah, D. *Chem. Eur. J*. **2007**, *13*, 5944−5931.

(12) (a) Yasui, S.; Matsuoka, M.; Kitao, T. *Dyes Pigm*. **1988**, *10*, 13−22. (b) In *Topics in Applied Chemistry*: *Infrared Absorbing Dyes*; Matsuoka, M., Ed.; Plenum Press: New York, 1990; pp 19−33. (c) Kim, S. H.; Hwang, S. H.; Song, H. C.; Yoon, N. S. *J. Korean Chem. Soc*. **1996**, *40*, 741−747. (d) Simard, T. P.; Yu, J. H.; Zebrowski-Young, J. M.; Haley, N. F.; Detty, M. R. *J. Org. Chem*. **2000**, *65*, 2236−2238. (e) Encinas, C.; Otazo, E.; Rivera, L.; Miltsov, S.; Alonso, J. *Tetrahedron Lett*. **2002**, *43*, 8391−8393. (f) Li, Z.; Jin, Z.-h.; Kasatani, K.; Okamoto, H. *Phys. B* **2006**, *382*, 229−234. (g) Puyol, M.; Encinas, C.; Rivera, L.; Miltsov, S.; Alonso, J. *Dyes Pigm*. **2007**, *73*, 383−389.

SCHEME 1. Synthesis of Croconaine Dyes 3a−d



length absorbing dyes can have potential PDT applications.[13] Further, as observed previously with the semisquaraines,[14] these dyes could also act as a bidentate ligand and form stable complexes with metal ions. Due to the higher penetration and minimal autofluorescence of infrared light by the tissues, these dyes could function as novel metal ion sensors in biological applications. Our results demonstrate that the appropriately substituted quinaldine derivatives undergo efficient condensation reaction with croconic acid yielding the dyes in quantitative yields. These dyes exhibit absorption in the infrared region (λ_{max} = 800−900 nm) and were found to undergo selective complexation with divalent metal ions, indicating thereby their potential use as sensors for metal ions and sensitizers in PDT applications.

Results and Discussion

Synthesis and Photophysical Properties of the Croconaine Dyes. With the objective of preparing the croconic acid-based dyes, we synthesized the substituted quinaldines by modifying the reported procedure.[15] Since heavy atom substitution would result in higher intersystem crossing efficiency as well as higher triplet yields, we introduced heavy atoms like iodine in the quinaldine ring. Besides, as observed previously for the squaraine dyes, the incorporation of electronegative and electron-withdrawing groups in the quinaldine ring would facilitate the formation of croconaine dyes in quantitative yields. As shown in Scheme 1, the reaction of the substituted quinaldines **1a−c** with methyl iodide at 100 °C in a sealed tube yielded the corresponding quinaldinium salts **2a−c** (Figures S1−S7, Supporting Information). The condensation reaction between 2:1 equiv of the quinaldinium salts **2a−c** and croconic acid in ethanol at 80 °C with quinoline as catalyst gave the corresponding croconaine dyes **3a−c** in 80−90% yields. With a view to improving the solubility and cellular permeability of the dyes, cholesterol-anchored croconaine dye **3d** was synthesized from the corresponding quinaldinium salt **2d**, following the same synthetic strategy as in the previous cases. The reaction mixture after evaporation of the solvent was subjected to column chromatography to yield the cholesterol-linked croconaine dye **3d** in 75% yield.

The croconaine dyes **3a−d** exhibited sharp and intense absorption in the IR window with absorption maximum ranging from 800 to 900 nm and have high molar extinction coefficients in the range $\epsilon = 1{-}5 \times 10^5$ M^{-1} cm^{-1}. Figure 1 shows the absorption spectra of the various croconaine dyes. The unsubstituted croconaine dye **3a** showed absorption maximum at 840 nm in DMF, while the halogenated dyes **3b** and **3c** exhibited absorption maximum, which is ca. 20 nm red-shifted from the parent unsubstituted derivative, at 860 and 865 nm, respectively (Table S1, Supporting Information). The dyes **3a−c** have low solubility in common organic solvents. However, substitution of the quinaldine ring with the cholesterol moiety resulted in increased solubility of the dye **3d** in THF and $CHCl_3$. The dye **3d** showed an absorption maximum at 871 nm in THF. All these dyes were found to have negligible fluorescence quantum yields.

Metal Ion Binding Properties of the Croconaine Dyes. With a view to investigate the ability of these dyes as bidentate ligands and thereby their potential use as probes, we have carried out their interactions with various mono- and divalent metal ions. The derivative **3d** was selected as a representative example because of its higher solubility and stability. Figure 2 shows the changes in the absorption spectrum of the dye **3d** on addition of Zn^{2+}. With increasing concentration of Zn^{2+}, we observed a decrease in the absorption band at 871 nm, with the concomitant formation of a new band at 788 nm. The corresponding changes in the fluorescence spectra of the dye **3d** with increasing addition of the metal ion are shown in the inset. The dye **3d** alone is weakly fluorescent. With the addition of Zn^{2+} a significant increase in the fluorescence intensity was observed with an emission maximum at 814 nm. The progressive increase in the fluorescence intensity reached saturation with the addition of 0.5 equiv of the metal ion and ca. 28-fold fluorescence enhancement could be observed with Zn^{2+} ($\Phi = 2.5 \times 10^{-3}$). The stoichiometry of the complex formed between the croconaine dye **3d** and the representative metal ion Zn^{2+} was found to be 2:1 as evidenced from the Job's plot (Figure 3). Benesi−Hildebrand analysis of the fluorescence titration data of complexation between the dye **3d** and Zn^{2+} gave a binding constant of $2.2 \pm 0.3 \times 10^{14}$ M^{-2}, which is in good agreement with the value obtained from the absorption changes.

The interaction of the dye **3d** with different alkali, alkaline earth, transition, and heavy metal ions was also examined. Figure 4 shows the changes in the absorption spectra of the dye **3d**

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[13] (a) Hilmey, D. G.; Abe, M.; Nelen, M. I.; Stilts, C. E.; Baker, G. A.; Baker, S. N.; Bright, F. V.; Davies, S. R.; Gollnick, S. O.; Oseroff, A. R.; Gibson, S. L.; Hilf, R.; Detty, M. R. *J. Med. Chem.* **2002**, *45*, 449−461. (b) Gorman, A.; Killoran, J.; O'Shea, C.; Kenna, T.; Gallagher, W. M.; O'Shea, D. F. *J. Am. Chem. Soc.* **2004**, *126*, 10624−10625. (c) Stefflova, K.; Li, H.; Chen, J.; Zheng, G. *Bioconj. Chem.* **2007**, *18*, 379−388.

[14] Avirah, R. R.; Jyothish, K.; Ramaiah, D. *Org. Lett.* **2007**, *9*, 121−124.

[15] Doebner, A.; von Miller, W. *Ber.* **1884**, *17*, 708.

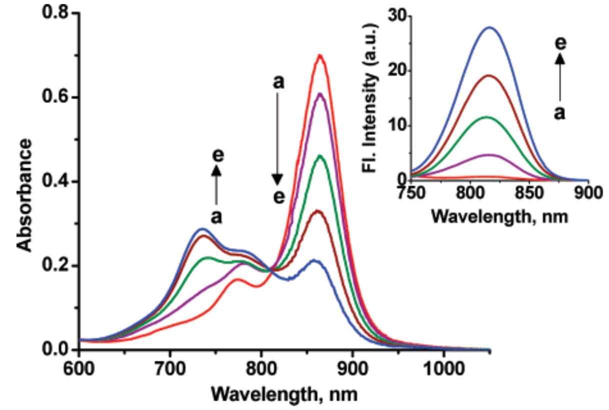

FIGURE 4. Changes in the absorption spectra of the dye **3d** (7.75 μM) in THF with the addition of Pb^{2+}: $[Pb^{2+}] = 0$ (a), 0.94 (b), 1.88 (c), 2.82 (d), and 3.87 μM (e). The inset shows the corresponding changes in fluorescence intensity. Excitation wavelength, 700 nm.

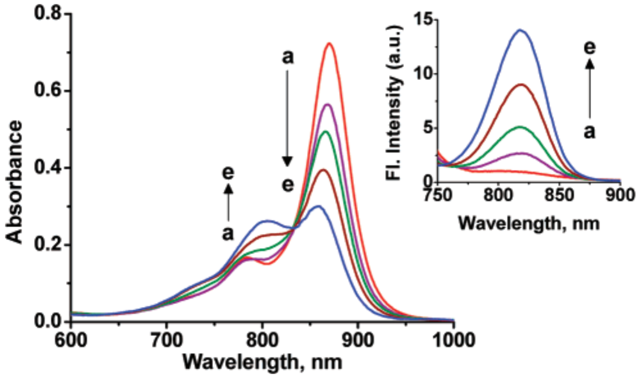

FIGURE 5. Changes in the absorption spectra of the dye **3d** (7.75 μM) in THF with the addition of Cd^{2+}: $[Cd^{2+}] = 0$ (a), 0.94 (b), 1.88 (c), 2.82 (d), and 3.87 μM (e). The inset shows the corresponding changes in fluorescence intensity. Excitation wavelength, 700 nm.

with the addition of Pb^{2+}. With the addition of Pb^{2+} to the dye solution in THF, we observed a decrease in the absorption band of the dye at 871 nm, with the concomitant formation of a new band at 735 nm. The corresponding change in the fluorescence spectra of the dye on addition of Pb^{2+} is shown in the inset. With increasing concentration of Pb^{2+}, the initially weakly fluorescent dye shows ca. 26-fold enhancement in fluorescence intensity ($\Phi = 2.2 \times 10^{-3}$) with the emission maxima at 816 nm. Figure 5 shows the changes in the absorption spectra of the dye **3d** with increasing concentration of Cd^{2+}. As observed in the case of Pb^{2+}, the addition of Cd^{2+} resulted in the decrease of the absorption band of the dye at 871 nm. However, the new band corresponding to the [**3d**-Cd^{2+}] complex was observed at 804 nm. In the fluorescence spectra a ca. 14-fold fluorescence enhancement ($\Phi = 1.4 \times 10^{-3}$) was observed with the emission maxima at 818 nm (inset, Figure 5). On the basis of the fluorescence data, we calculated the binding constants for Pb^{2+} and Cd^{2+} and these values are found to be $1.3 \pm 0.5 \times 10^{13}$ and $5.3 \pm 0.3 \times 10^{12}$ M^{-2}, respectively.

The relative changes in the fluorescence intensity of the croconaine dye **3d** upon the addition of different metal ions are shown in Figure 6. The monovalent metal ions such as Li^{+}, Na^{+}, and K^{+} caused negligible changes in absorption and fluorescence emission. In contrast, the addition of other divalent metal ions like Pb^{2+}, Cd^{2+}, Mg^{2+}, Hg^{2+}, Ca^{2+}, and Ba^{2+} to the dye solution in THF resulted in a decrease in absorption and chelation-enhanced fluorescence intensity. However, the relative changes were found to vary with different metal ions (Figures S8 and S9, Supporting Information). Similar, but lower effects were observed in the absorption and emission spectra of the dye **3d** upon adding other divalent metal ions like Mg^{2+}, Hg^{2+}, Ba^{2+}, and Ca^{2+} (Table 1). With the addition of a strong chelating agent such as ethylenediaminetetraacetic acid (EDTA) to the dye−metal ion complex, we observed the disappearance of the new band formed during metal ion complexation as well as the quenching of the fluorescence, indicating thereby the reversibility of the complex formation between **3d** and various divalent metal ions.

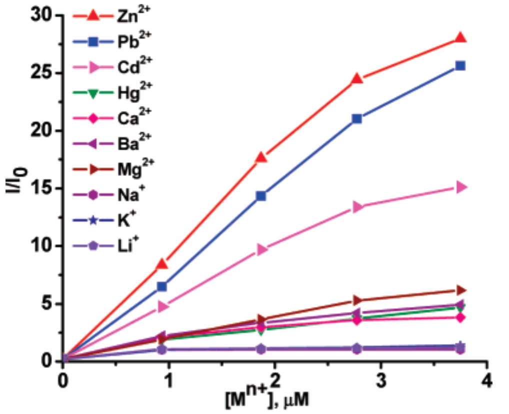

FIGURE 6. Relative fluorescence enhancement of the croconaine dye **3d** (7.75 μM) upon interaction with different metal ions.

TABLE 1. Absorption and Fluorescence Maxima, Association Constants, and Quantum Yields of the Various Metal Ion Complexes of 3d in THF[a]

	λ_{max}, nm			
complex	absorption	emission	Φ_F[b]	association constant (K_{ass}),[c] M^{-2}
[**3d**-Zn^{2+}]	788	814	2.5×10^{-3}	$1.9 \pm 0.4 \times 10^{14}$ $(2.2 \pm 0.3 \times 10^{14})$
[**3d**-Pb^{2+}]	735	816	2.2×10^{-3}	$1.0 \pm 0.3 \times 10^{13}$ $(1.3 \pm 0.5 \times 10^{13})$
[**3d**-Cd^{2+}]	804	818	1.4×10^{-3}	$5.2 \pm 0.4 \times 10^{12}$ $(5.3 \pm 0.3 \times 10^{12})$
[**3d**-Mg^{2+}]	805	815	5.5×10^{-4}	$6.0 \pm 0.5 \times 10^{12}$ $(6.5 \pm 0.4 \times 10^{12})$
[**3d**-Ba^{2+}]	750	818	4.7×10^{-4}	$2.7 \pm 0.3 \times 10^{11}$ $(3.1 \pm 0.2 \times 10^{11})$
[**3d**-Hg^{2+}]	735	812	4.2×10^{-4}	$5.1 \pm 0.5 \times 10^{11}$ $(5.9 \pm 0.3 \times 10^{11})$
[**3d**-Ca^{2+}]	755	820	3.2×10^{-4}	$3.1 \pm 0.3 \times 10^{11}$ $(3.5 \pm 0.4 \times 10^{11})$

[a] Average of more than 2 experiments and the error is ca. ±5%. [b] Fluorescence quantum yields were calculated by using the IR-125 as the standard ($\Phi = 0.13$, in DMSO). [c] Association constants were calculated based on fluorescence changes while the values obtained from absorption changes are given in parentheses.

Characterization of the Metal Ion Complexation. The complexation between the metal ion and the dye **3d** was further confirmed through the ^{1}H NMR titrations and the infrared (FT-IR) spectral analysis of the [**3d**-Zn^{2+}] complex. The ^{1}H NMR spectrum of the croconaine dye **3d** in $CDCl_3$ showed five aromatic protons as multiplets in the region between δ 7 and 9.1, while the olefinic and *N*-methyl protons appeared as singlets at δ 6.4 and 3.9 ppm, respectively (Figure 7). With the addition of Zn^{2+}, a broadening of the aromatic signals as well as the vinylic and *N*-methyl protons could be observed. However, no significant changes were observed in the aliphatic region,

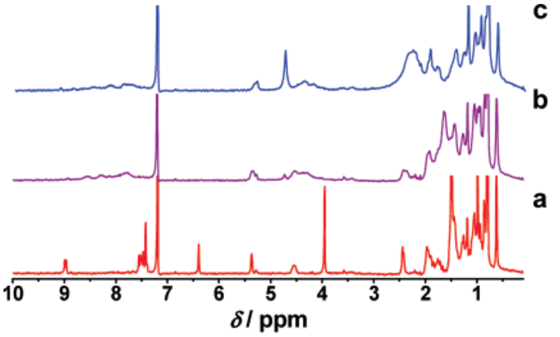

FIGURE 7. ^{1}H NMR spectra of the dye **3d** in $CDCl_3$ with increasing concentration of Zn^{2+} in CD_3CN. The mole ratio of [Zn^{2+}] to [**3d**] is 0 (a), 0.25 (b), and 0.5 (c).

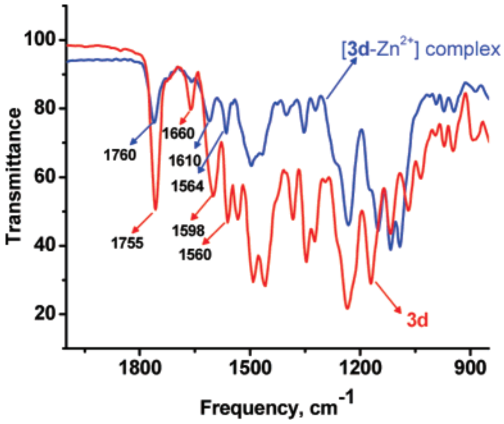

FIGURE 8. IR spectra of the croconaine dye **3d** and the [**3d**-Zn^{2+}] complex.

indicating that the cholesterol moiety has no significant interaction with the metal ion. The IR spectrum of the dye showed four carbonyl bands of the dye **3d** (Figure 8). The bands at 1660, 1598, and 1560 cm^{-1} are characteristic of the carbonyl groups of the croconyl moiety, while the band at 1755 cm^{-1} is assigned to the carbonyl group attached to the cholesterol moiety. However, in the IR spectrum of the [**3d**-Zn^{2+}] complex, the carbonyl band at 1660 cm^{-1} shifted to 1610 cm^{-1}, while the bands at 1598 and 1560 cm^{-1} merged to give a new band at 1564 cm^{-1}. This clearly indicates the involvement of two carbonyl groups of the croconyl moiety of **3d** in the complexation with Zn^{2+}. As expected, the band at 1755 cm^{-1} corresponding to the carbonyl group attached to the cholesterol moiety showed negligible changes. Figure 9 shows the mode of binding of the divalent metal ions to the croconaine dye **3d**. As shown in the figure, the croconaine dye **3d** binds to the divalent metal ions through the electron-rich carbonyl group of the croconyl ring in a 2:1 binding mode.

The binding of the metal ion at the carbonyl groups results in the broadening of the peaks of the aromatic protons and vinylic and *N*-methyl groups seen in the ^{1}H NMR titration data. Moreover, the binding of the positively charged metal ions at the carbonyl group reduces the bond energy of the conjugated C═O bond and reduces the carbonyl stretching frequency in the [**3d**-Zn^{2+}] complex.

The ground (S_0) and excited state (S_1) of the croconaine dyes are intramolecular D-A-D charge transfer (ICT) states.[16] The S_0-S_1 electronic excitation in these systems involves a CT process that is primarily confined to the central C_5O_3 cyclopentane ring, with the major contribution from the oxygen atoms. The intramolecular charge-transfer character (ICT) of this transition, combined with an extended π conjugation, is responsible for the sharp and intense absorption bands of these dyes. The strong binding of the divalent metal ions at the croconyl ring could be attributed to the presence of two electron-rich carbonyl groups in the croconyl ring that can act as a bidentate ligand for various divalent metal ions. The interaction of the metal ions at the carbonyl group lowers the π conjugation as well as the CT character, resulting in the formation of a hypsochromically shifted absorption band for the dye−metal complex. This interaction of the metal ion with the carbonyl groups of the dye **3d** is strongly supported by the clear shifts in the stretching frequency of the croconyl carbonyl groups in the [**3d**-M^{2+}] complex. Further, the possibility of the metal ion binding with a keto−enol tautomeric form can be ruled out, since such an interaction of the metal ion with the keto−enol form of the dye would have resulted in the loss of conjugation and thereby a much lower wavelength absorption band than observed for the [**3d**-M^{2+}] complex. On the basis of this evidence we propose that the metal ion binding is through the dicarbonyl rather than through a keto−enolate tautomer. The presence of electron-rich carbonyl oxygens allows only the interaction with divalent metal ions and the sensitivity of the binding follows the order $Zn^{2+} > Pb^{2+} \gg Cd^{2+} \gg Mg^{2+} \approx Hg^{2+} \approx Ca^{2+} \approx Ba^{2+}$.

Conclusions

In conclusion, a new class of substituted quinoline-based croconaine dyes have been synthesized in quantitative yields by the condensation reaction between croconic acid and the corresponding quinaldinium salts, and their interactions with metal ions have been investigated. These dyes show sharp and intense absorption in the IR region (λ_{max} = 800−900 nm) with high extinction coefficients ($\epsilon_{max} = 1-5 \times 10^5$ M^{-1} cm^{-1}). Due to the presence of a stronger acceptor moiety, these

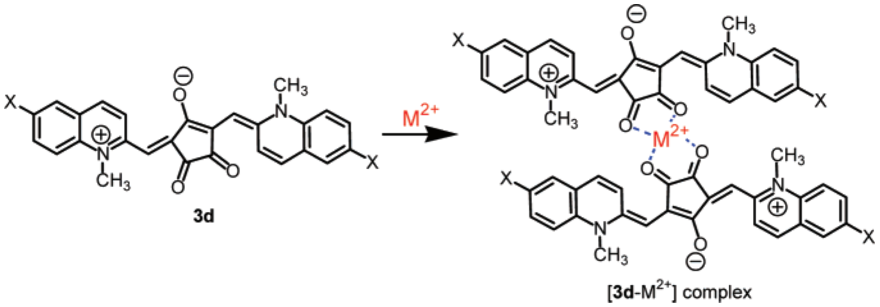

FIGURE 9. Schematic representation of the complexation between divalent metal ion, M^{2+}, and the croconaine dye **3d**.

croconaine dyes exhibited around 100 nm red-shifted absorption compared to the corresponding squaraine dyes. The presence of the two carbonyl groups facilitates complex formation of the croconaine dyes with divalent metal ions. The lowered ICT character and decreased conjugation in the ring resulted in the formation of a new absorption band at the shorter wavelength region for the dye−metal ion complex and the metal binding is signaled through "turn on" fluorescence intensity and high association constants (10^{14}−10^{11} M^{-2}). The broadening of the aromatic, vinylic, and *N*-methyl peaks during the ^{1}H NMR titrations indicates binding of the metal ion at the carbonyl group of the croconyl moiety. This was further substantiated by the clear shifts in the carbonyl stretching frequency of the croconyl ring upon metal ion binding. These features, together with the high affinity and sensitivity of the dyes for Zn^{2+}, Pb^{2+}, and Cd^{2+}, could be exploited for the design of IR absorbing metal ion sensors and sensitizers for PDT applications.

Experimental Section

Calculation of Quantum Yield of the [3d-M^{2+}] Complexes. The fluorescence quantum yields were determined by using optically matched solutions with IR-125 as the standard (Φ DMSO = 0.13).[6b] The quantum yields of the [**3d**-M^{2+}] complexes have been determined by measuring the integrated fluorescence intensity after the addition of 0.5 equiv of the M^{2+} ion to 1 equiv of the dye **3d** and substituting in the equation

$$\Phi_u = \frac{\Phi_s A_s F_u {n_u}^2}{A_u F_s {n_s}^2}$$

where Φ_u and Φ_s are the quantum yield of the unknown and standard, A_u and A_s are the absorbance at the excitation wavelength of the unknown and standard, F_u and F_s are the integrated fluorescence intensity of the unknown and standard, and n_u and n_s are the refractive index of the solvent of the unknown and standard, respectively.

General Procedure for the Synthesis of Croconaine Dyes. A mixture of the corresponding quinaldinium salt (0.06 mmol), croconic acid (0.03 mmol), and quinoline (0.5 mL) was refluxed in ethanol (6 mL) for 24 h. The solvent was distilled off under reduced pressure to obtain a residue, which was washed with methanol and DMSO to give the corresponding croconaine dyes **3a**−**c**.

3a (80%, based on conversion): mp >300 °C; IR (KBr) ν_{max} (cm^{-1}) 3035, 1604, 1558, 1454; ^{1}H NMR (DMF, 300 MHz) δ 9.14 (1H, d, J = 9.4 Hz), 7.9 (2H, d, J = 9.4 Hz), 7.82 (2H, m), 7.53 (1H, m), 6.46 (1H, s), 4.14 (3H, s); FAB-MS *m/z* calcd for $C_{27}H_{20}N_2O_3$ 420.46, found 420.24. Anal. Calcd for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 76.92; H, 4.65; N, 6.54.

3b (85%): mp >300 °C; IR (KBr) ν_{max} (cm^{-1}) 3055, 1654, 1608, 1543; FAB-MS *m/z* calcd for $C_{27}H_{18}Br_2N_2O_3$ 578.25, found 579.35. Anal. Calcd for $C_{27}H_{18}Br_2N_2O_3$: C, 56.08; H, 3.14; N, 4.84. Found: C, 55.74; H, 2.97; N, 5.10.

3c (85%): mp >300 °C; IR (KBr) ν_{max} (cm^{-1}) 3055, 1653, 1606, 1546; FAB-MS *m/z* calcd for $C_{27}H_{18}I_2N_2O_3$ 672.25, found 672.31. Anal. Calcd for $C_{27}H_{18}I_2N_2O_3$: C, 48.04; H, 2.70; N, 4.17. Found: C, 48.21; H, 2.90; N, 4.16.

Procedure for the Synthesis of Dye 3d. A mixture of the cholesterol-linked quinaldinium salt **2d** (0.06 mmol), croconic acid (0.03 mmol), and quinoline (0.5 mL) was refluxed in ethanol (6 mL) for 24 h. The solvent was distilled off under reduced pressure to obtain a residue, which was then subjected to column chromatography over silica gel. Elution of the column with a mixture (1:9) of methanol and chloroform gave 75% of the croconaine dye **3d**: mp 290−292 °C; IR (KBr) ν_{max} (cm^{-1}) 2947, 1755, 1660, 1598, 1560; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.99 (2H, d, J = 9.4 Hz), 7.55−7.39 (8H, m), 6.39 (2H, s), 5.37 (2H, s), 4.55 (2H, s), 3.95 (6H, s), 2.44 (4H, s), 1.96−0.75 (82H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.6, 188.3, 186.8, 183.2, 154.1, 153.1, 140.4, 130.3, 128.2, 124.9, 123.2, 121.4, 118.2, 117.5, 114.3, 111.1, 108.4, 103.3, 81, 73.3, 72.1, 58.2, 57.7, 51.5, 43.8, 41, 37.7, 37.3, 33.4, 31.2, 30.9, 29.7, 29.5, 25.8, 25.4, 24.4, 24.2, 24.1, 22.6, 20.8, 20.3, 13; FAB-MS *m/z* calcd for $C_{83}H_{108}N_2O_9$ 1277.75, found 1277.69. Anal. Calcd for $C_{83}H_{108}N_2O_9$: C, 78.02; H, 8.52; N, 2.19. Found: C, 77.85; H, 8.30; N, 2.13.

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Supporting Information Available: Synthetic details, spectroscopic data, and photophysical properties of the croconaine dyes, ^{1}H and ^{13}C NMR spectra of the representative dyes, and Figures S1−S10 showing the changes in NMR, absorption, and fluorescence spectra of **3d** in the presence of various metal ions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Bigelow, R. W.; Freund, H.-J. *Chem. Phys.* **1986**, *107*, 159−174.