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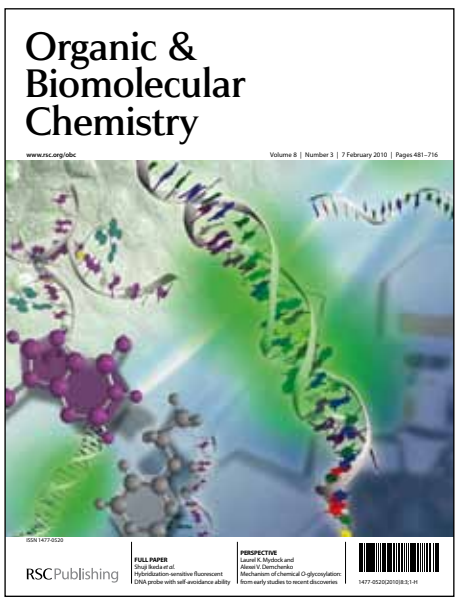

Syntheses and Photophysical Properties of BF_2 Complexes of Curcumin Analogs

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Abstract

Stable tetracoordinated organoboron complexes as classic fluorescent molecules have found various applications in material and medical sciences. A new class of curcumin-BF_2 complexes has been prepared from the condensation of 2,2-difluoro-1,3-dioxaborylpentadione with a variety of aldehydes, and characterized via photophysical properties. Systematic variations were observed in the absorption spectra of these curcumin-BF_2 dyes in solutions, which are well correlated with their structural features, including the characteristics of the aromatic groups and the presence of a *para* electron-donating substituent. A strong fluorescence that are tunable from 500 to 800 nm via the variation of the polarity of the solvent and a moderate to good fluorescence quantum yield ranging from 0.24 to 0.58 in dichloromethane were observed in curcumin-BF_2 complexes **1**. By contrast, their asymmetrical analog, curcumin-BF_2 complexes **3** exhibit much lower fluorescence quantum yields. Besides their excellent photostabilities, these curcumin-BF_2 dyes also show singlet oxygen generating capabilities.

Introduction

Stable organic fluorescent dyes, especially those with high absorption coefficients and fluorescence quantum yields, large Stokes shifts, and tunable absorption/emission profiles have attracted wide research interests, and found important applications in a variety of research fields for organic electronics, solar energy conversion, imaging, sensing, medical diagnosis, and photodynamic therapy.[1-3] Among those, stable tetracoordinated organoboron complexes as potential functional luminophores have received much attention,[4-6] as evidenced from significant research efforts dedicated towards boron dipyrromethene (BODIPY, **A** in Fig.1) dyes. Despite the excellent photophysical properties and the easy tunable spectroscopic properties through structural modification of the chromophore, BODIPY dyes often exhibit small Stokes shifts due to minimal reorganization of the molecules upon photoexcitation.[6h-i] Therefore, many research efforts have been devoted to the development of BODIPY analogs with larger Stokes shifts. A variety of N,N-bi-,[7-8] N,O-bi-,[9] O,N,O-tri-,[10] and N,N,O,O-tetradentated[11] boron complexes have been synthesized and some show larger Stokes shifts with remarkable photostabilities.

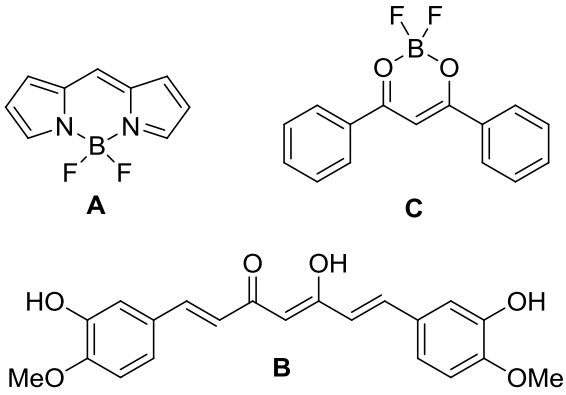


Figure 1. Chemical structures of BODIPY **A**, curcumin **B** and difluoroboron dibenzoylmethane **C**.

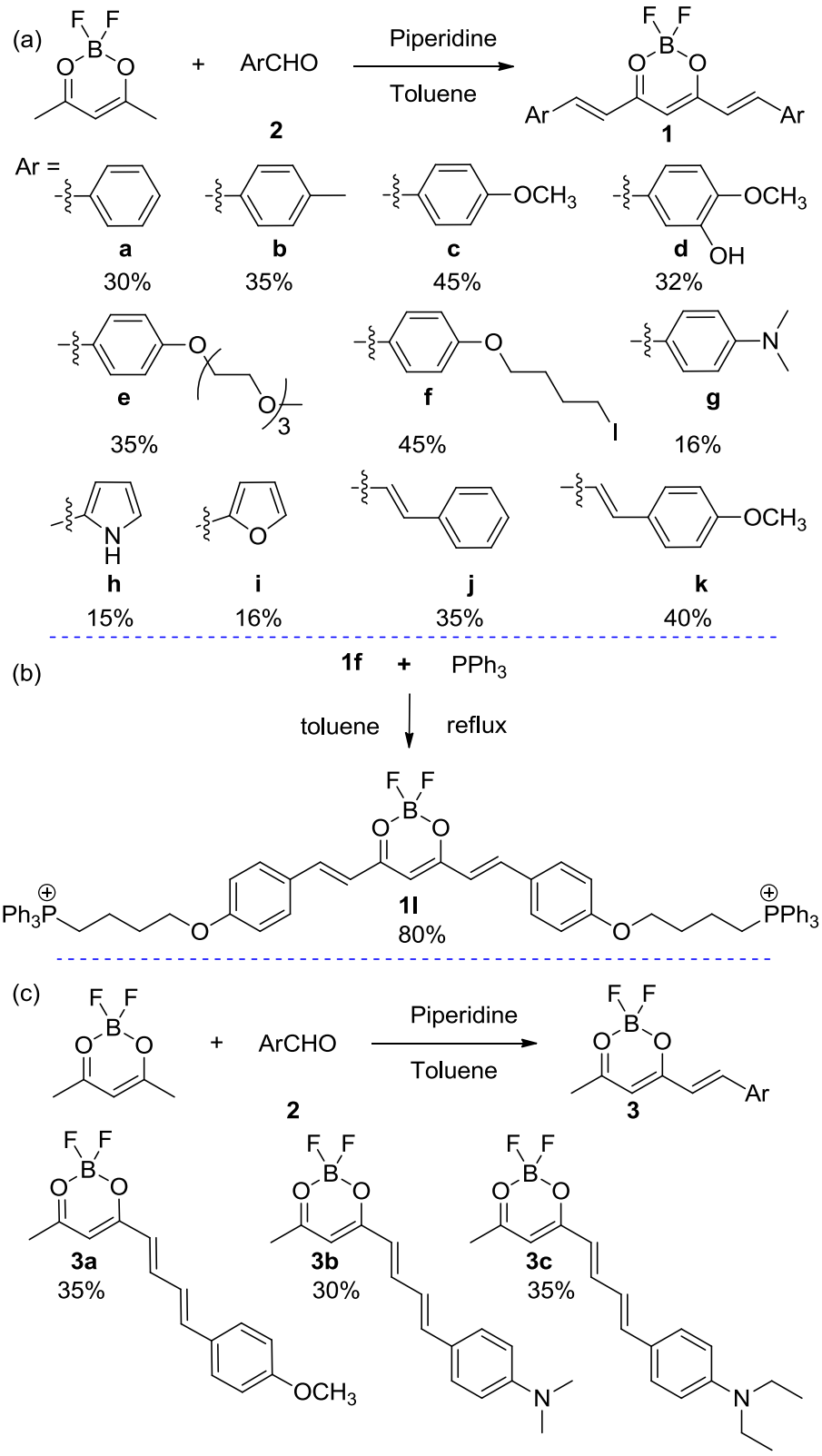
Curcumin (**B** in Fig.1), a natural diphenolic β-diketone compound extracted from the rhizome of turmeric (Curcuma longa), shows low dark toxicity, and multiple therapeutic effects, including the prevention and therapy effects for various cancers.[12] Although the enhancement of the phototoxicity of curcumin have been achieved[13] via the localized delivery of curcumin with effective vehicle (micelles,

cyclodextrin, liposomes)[13d] or via the complexation with metal cations[14], their short wavelength absorption (within 410-430 nm), and poor chem- and photostability stability (rapid decomposition at pH above 7 and severe fading upon illumination)[13] limited their further applications as fluorescent dyes.

The BF_2 complexes of β-diketonates have been used for the generation of fluorescent molecules like the well-known difluoroboron dibenzoylmethane derivatives (**C** in Fig.1), which typically show blue fluorescence and have limited applications in biosensing and bioimaging.[15-16] The incorporation of BF_2 into the curcumin chromophore may shift their absorption out of the UV region, reducing the photodamaging to biological systems. So far, only limited BF_2 complexes of curcumin analogs have been reported, one by Moore[17a] as a novel NIR Aβ plaque-specific fluorescent probe, and the other by Tomapatanaget[17b] as a promising cyanide chemical sensor, respectively. While we were in preparing this manuscript, the synthesis of *meso*-phenyl curcuminoid-BF_2 complexes[17c] via a different synthetic route came out. Herein, we present the synthesis and properties of a series of photostable curcumin-BF_2 complexes. The incorporation of BF_2 to curcumin moiety enhanced rigidity of the 1,3-diketone unit, resulting in the enhancement of the stabilities, red shift of the absorption and emission spectra, and reduced nonradiative relaxation rates.

Results and Discussion

Knoevenagel condensation of 3,5-methyl groups on BODIPYs with electron-deficient aldehyde to extend the conjugation of BODIPY has been well documented in the rich chemistry of BODIPYs. In comparison with BODIPYs, the 1,3-methyl groups of 2,2-difluoro-1,3-dioxaborylpentadione show much higher reactivity toward Knoevenagel reaction. By reacting it with corresponding electron-rich aldehydes **2a-k** respectively in toluene at room temperature, curcumin-BF_2 complexes **1a-k** were straightforwardly synthesized in good yields (Scheme 1a). In a similar way, their asymmetrical analogs (**3a-c**) were also prepared (Scheme 1c). Triphenylphosphine (TPP) ion is non-toxic for cells and can facilitate the cytoplasm uptake of non-permeable drugs.[18] For the specific cell-targeting, curcumin BF_2 complex **1f** was further applied for the nucleophilic substitution with TPP to generate curcumin-BF_2 complex **1l** in 80% yield (Scheme 1b).



Scheme 1. Syntheses of curcumin-BF_2 complexes **1** and **3** and their corresponding yields.

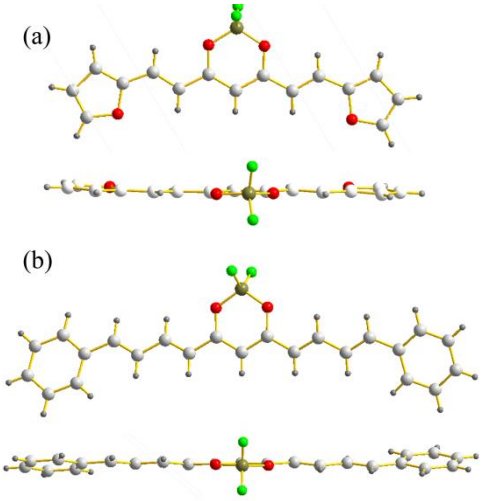


Figure 2. Top view (top) and side view (bottom) of X-ray structures of curcumin BF_2 complexes **1i** (a) and **1j** (b). C, light gray; H, gray; O, red; B, dark yellow; F, light green.

Curcumin-BF_2 complexes **1** and **3** were characterized by NMR and HRMS. The structures for curcumin-BF_2 complexes **1f** and **1g** were also confirmed by X-ray analysis results (Figure 2), in which the double bonds all adopt *a trans* geometry. Crystals of curcumin-BF_2 complexes suitable for X-ray analysis were obtained by slow evaporation of their dichloromethane solutions and show a nearly planar structure. The plane defined by F-B-F atoms for curcumin-BF_2 complexes **1f** and **1g** is perpendicular to that of the core of curcumin-BF_2 complexes with the B-O distance for these curcumin-BF_2 complexes within 1.46-1.48 Å. This indicates the usual delocalization of the positive charge.

Most of these resultant curcumin-BF_2 derivatives have electron donating moieties at both ends of the conjugated π-system with an electron accepting moiety in the middle of the molecules (D-A-D system), differing by virtue of the degree of conjugations and the substitution patterns at the *para*-aromatic units. These resultant curcumin-BF_2 complexes generally show high absorption coefficients in the range of 400-700 nm (Table 1), which are desirable for fluorescent dyes and photosensitizers. The absorption maximum can be finely tuned simply through the variations of the starting electron-rich aromatic aldehydes (Figure 3). In another word, the electron donating abilities of the aromatic groups greatly affect the spectroscopic behavior of the resultant curcumin-BF_2 complexes. For example, **1g** containing *N, N'*-dimethyl moieties gives the longest wavelength absorption (597 nm), while **1c**, **1b** and **1a**

containing methoxyl, methyl and hydrogen moieties absorbs at relatively shorter wavelength (488, 463 and 424 nm, respectively). Adding an extra double bond also leads to a large red-shift of the absorption as demonstrated in compounds **1j-k** and **3** (Figure 4).

Table 1. Photophyscial properties of curcumin-BF_2 complexes **1** and **3** at room temperature in dichloromethane.

Dyes	λ_{abs} (nm) (logε)	λ_{em} (nm)	Stokes-shift (cm^{-1})	ϕ[a]	τ[b] (ns)	K_f[c] (10^7 s^{-1})	K_{nr}[d] (10^8 s^{-1})
1a	424,447(4.65)	484	2924	0.24	1.31	0.18	0.58
1b	439,463 (4.71)	506	1835	0.26	0.90	0.29	0.82
1c	489 (4.88)	546	2135	0.49	1.64	0.30	0.31
1d	497 (4.80)	557	2167	0.58	1.60	0.36	0.26
1e	491 (4.83)	549	2152	0.56	1.50	0.37	0.29
1f	490 (4.85)	548	2160	0.57	1.48	0.39	0.29
1g	597 (4.65)	681	2066	0.47	2.99	0.16	0.18
1h	531(4.91)	583	1680	0.35	2.03	0.17	0.32
1i	464,490 (4.90)	535	1717	0.33	1.21	0.27	0.55
1j	476,499 (4.91)	556	3023	0.27	1.09	0.25	0.67
1k	523 (4.92)	625	3120	0.24	1.25	0.19	0.61
1l	488 (4.78)	543	2076	0.33	1.31	0.25	0.51
3a	435 (4.49)	553	4905	0.01	0.63	0.02	1.57
3b	534 (4.50)	664	3666	0.10	1.50	0.07	0.60
3c	551 (4.49)	670	3223	0.08	1.50	0.05	0.61

[a] fluorescence quantum yield was obtained using fluorescein as reference compound ($\phi = 0.85$ in 0.1N NaOH solution), the standard errors are less than 5%. [b] fluorescence lifetime, [c] $K_f = \phi/\tau$, [d] $K_{nr} = (1-\phi)/\tau$.

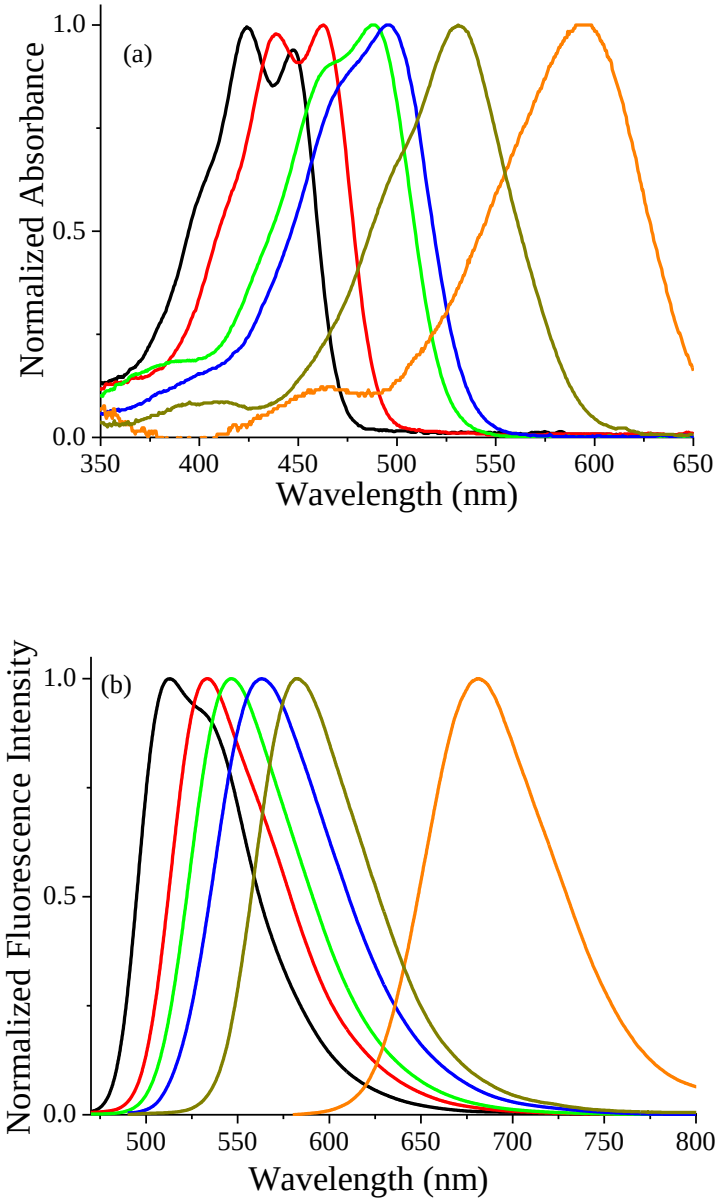
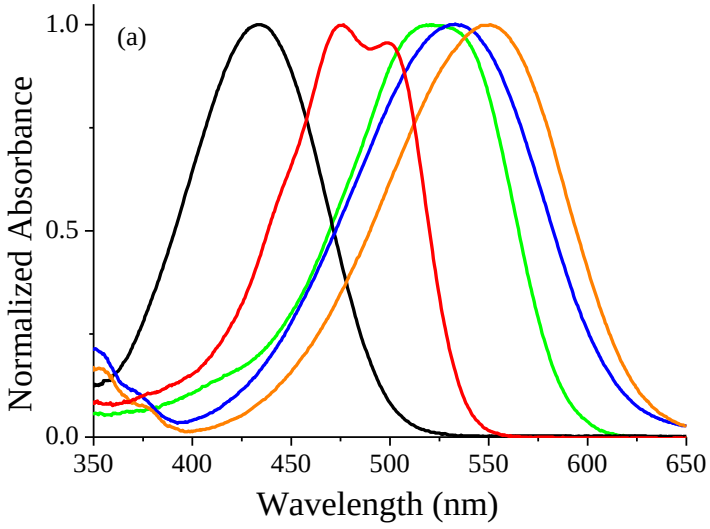


Figure 3. Normalized absorption (a) and emission (b) spectra of curcumin-BF_2 complexes **1a** (black), **1b** (red), **1c** (green), **1d** (blue), **1g** (orange) and **1h** (dark yellow) in dichloromethane at room temperature.

Most of the symmetrical curcumin-BF_2 complexes **1** show a strong fluorescence in the range of 500-800 nm with fluorescence quantum yields range from 0.24 to 0.58 in dichloromethane as summarized in Table 1. The emission bands of these curcumin-BF_2 complexes can be further tuned through the variation of the polarity of solvents. The absorption bands also show positive solvatochromism and lose their vibronic structure in more polar solvents as shown in Figure 5 and Figures S1-S15 in supporting

information. For example, the emission maximum of **1k** is red-shifted from 538 to 572, 587, 625, 632 and 634 nm by simply changing the solvent from cyclohexane to toluene, tetrahedrofuran, dichloromethane, acetonitrile and methanol (Figure 5). The solvatochromic shifts of the fluorescence emission found here are similar to those observed in BODIPYs with electron donating groups at 3,5-positions as reported by Boens and coworkers.[19] A broad absorption spectrum was observed for compound **1l** in PBS buffer (including 1% DMSO) as shown in Figures S16 in supporting information. Compared to that in dichloromethane, a lower fluorescence quantum yield (0.19) was observed for compound **1l** in this PBS buffer solution. In addition, large decrease of fluorescence quantum yields was observed in this PBS buffer system with reducing of the water-solubility of these dyes. For example, only negligible fluorescence could be observed for low to non water-soluble dyes **1e** (0.08), **1h** (0.02) and **1i** (0.02) in this PBS buffer solutions. This dramatic decrease of fluorescence yield in PBS buffer system may be attributed to the aggregation effects of these dyes in aqueous system.



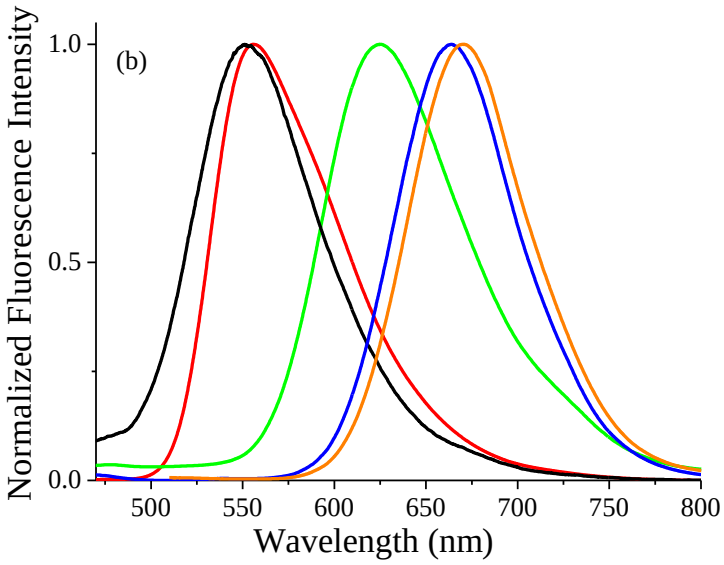
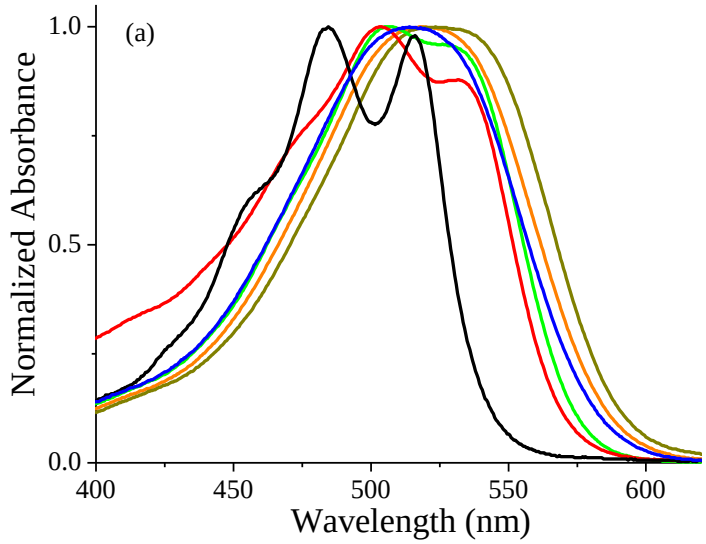


Figure 4. Normalized absorption (a) and emission (b) spectra of curcumin-BF_2 complexes **3a** (black), **1j** (red), **1k** (green), **3b** (blue) and **3c** (orange) in dichloromethane at room temperature.



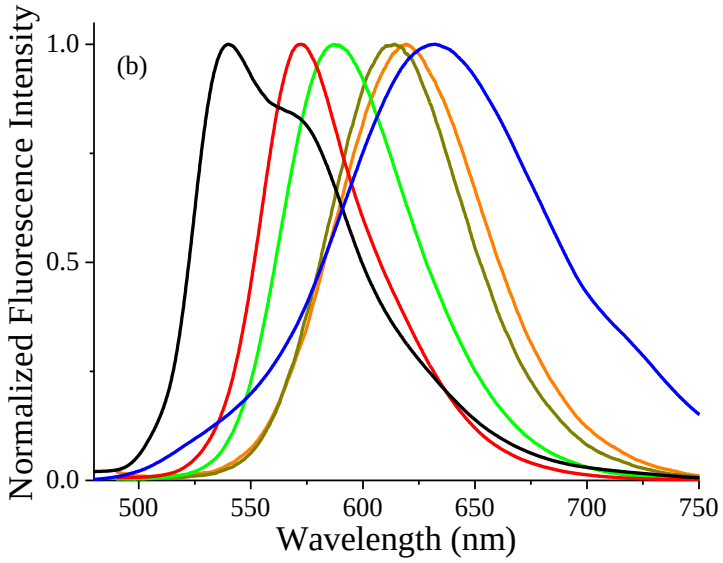


Figure 5. Normalized absorption (a) and emission (b) spectra of curcumin-BF_2 **1k** in six different solvents at room temperature. Cyclohexane (black), toluene (red), tetrahedrofuran (green), methanol (blue), acetonitrile (orange) and dichloromethane (dark yellow).

Time-resolved emissions of these dyes were studied and the fluorescence lifetimes (τ) via TCSPC (Time-Correlated-Single-Photon-Counting) were determined in dichloromethane (Table 1). Most of these dyes gave a monoexponential decay function with lifetimes in the range of 0.63-2.99 ns which are shorter in comparison to that of classical BODIPYs, while comparable to that of difluoroboron dibenzoylmethane **C** reported.[15c]

To test the capabilities of these curcumin-BF_2 complexes as fluorescent dyes, the photostabilities of curcumin-BF_2 complexes **1d**, **1k** and **1e** were studied by continuous irradiation with a Xe lamp (500 W) and were compared with that of the well-known Rose Bengal (Figure 6). Our curcumin-BF_2 complexes show much better photostability than Rose Bengal. Degradation of organic dyes can be partially attributed to their oxidation by reactive oxygen species. The high photostability observed here may be attributed to the enhanced rigidity of the chromophore through BF_2 complexation of the diketone structure in curcumin derivatives.

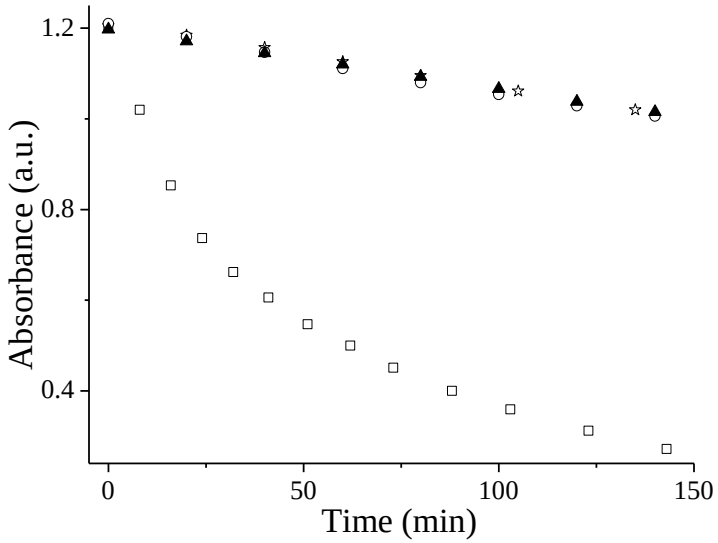


Figure 6. Comparison of the photostability of curcumin-BF_2 complexes (2×10^{-5} M) **1d** (☆), **1k** (○), **1e** (△) and Rose Bengal (4×10^{-5} M, □) in toluene (1% DMF) under continuous irradiation with a 500 W Xe lamp.

To demonstrate the potential application of these dyes as novel fluorescent dyes for cell image, amphiphilic **1l** was applied for the cell imaging in Human gastric cancer SGC7901 living cells. SGC7901 cells were treated with **1l** in Dulbecco's Modified Eagle Medium (DMEM) containing 0.1% dimethyl sulfoxide. After incubation with 10 μM **1l** for 30 min, cells showed strong green fluorescence (Figure 7b) when imaged with a fluorescence microscope using FITC (green channel) filter set. Bright-field transmission images of cells confirmed that cells were viable throughout the imaging experiments (Figures 7a). These preliminary results suggest these dyes can be easily taken up by cells and are nontoxic to the living cells.

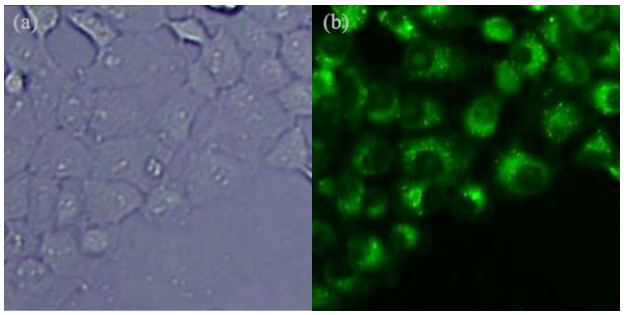


Figure 7. Brightfield (a) and fluorescence (b) images of living SGC7901 cells incubated with 10 μM **1l** for 30 min.

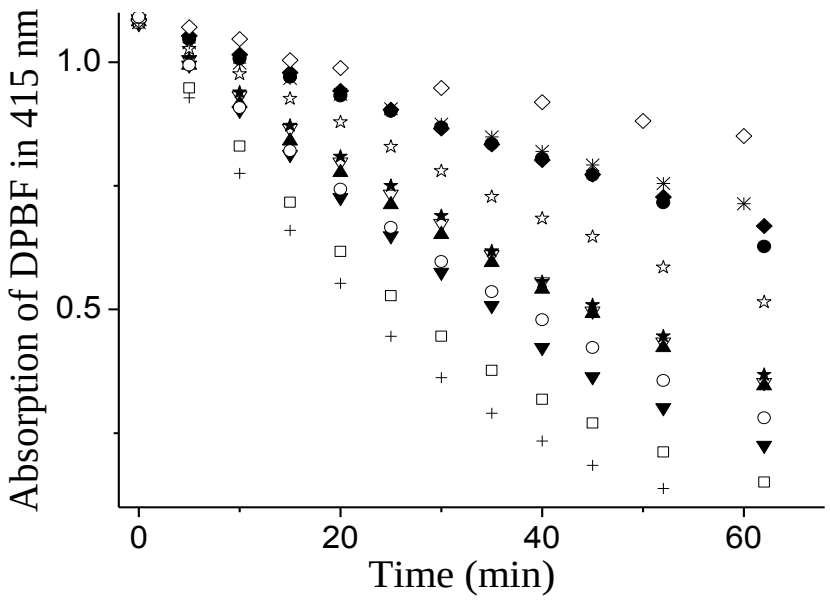


Figure 8. Comparative DPBF (initial concentration at 5×10^{-5} M) degradation profiles in toluene (1% DMF) by curcumin-BF_2 complexes (1×10^{-6} M): **1b** (●), **1c** (☆), **1d** (+), **1e** (▼), **1f** (○), **1g** (◆), **1h** (▽), **1i** (▲), **1j** (★), **1k** (□), **3b** (*), and **3c** (◇). Filtered light > 455 nm used.

Some metal complexes of curcumin derivatives have been reported with good singlet oxygen generating abilities due to their enhanced stabilities upon chelation with metal ions.[14] Encouraged by these positive results, the relative singlet oxygen generating efficiency of our curcumin-BF_2 complexes were investigated in toluene by using 1,3-diphenylisobenzofuran (DPBF) as a trap molecule (Figure 8 and Figures S16–29 in supporting information). Interestingly, most of our dyes have singlet oxygen generation ability in toluene. Among those, the highest singlet oxygen generating efficiency was observed in **1d**, the second and third highest efficiency were observed in **1k** and **1e** containing extra double bonds or ethylene glycol soluble groups. The capabilities of these dyes to generate $^1O_2$ coupled with their reasonable fluorescence emission suggest a possible application as theranostic drugs for dual-functioning PDT and imaging.[20]

Conclusions

In summary, we have designed and synthesized a series of novel highly photostable π-extended curcumin-BF_2 complexes with strong absorption and fluorescence ranged from 400 to 800 nm. Systematically fine tuning of their spectroscopic properties was achieved through the structural variations (e.g. the variation of the electron donating abilities on the starting aromatic aldehydes and the number of conjugated double bonds) and even solvents for the tunable of emission band. These dyes may found potential application as fluorescent dyes for cell image as demonstrated by dye **1l**, and photosensitizers as indicated in this work for their singlet oxygen generating capabilities and excellent photostabilities.

Experimental Section

General: Reagents and solvents were used as received from commercial suppliers unless noted otherwise. All reactions were performed in oven-dried or flame-dried glassware, and were monitored by TLC using 0.25 mm silica gel plates with UV indicator (60F-254). ^{1}H and ^{13}C NMR were recorded on a 300 MHz NMR spectrometer at room temperature. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm for ^{1}H and 77 ppm for ^{13}C) or to internal TMS. High-resolution mass spectra (HRMS) were obtained using APCI-TOF in positive mode.

Fluorometric analysis: UV-visible absorption and fluorescence emission spectra were recorded on a commercial spectrophotometer (190-900 nm scan range). Relative fluorescence quantum efficiencies of dyes were obtained by comparing the areas under the corrected emission spectrum of the test sample in various solvents with fluorescein (ϕ = 0.85 in 0.1 N NaOH aqueous solution) or Rhodamin B (ϕ = 0.49 in EtOH) [21] as standards. Non-degassed, spectroscopic grade solvents and a 10 mm quartz cuvette were used. Dilute solutions ($0.01<A<0.05$) were used to minimize the reabsorption effects. Quantum yields were determined using the following equation[22]:

$$\Phi_X = \Phi_S (I_X/I_S) (A_S/A_X) (\eta_X/\eta_S)^2$$

Where Φ_S stands for the reported quantum yield of the standard, I stands for the integrated emission spectra, A stands for the absorbance at the excitation wavelength and η stands for the refractive index of

the solvent being used (η = 1 when the same solvent was used for both the test sample and the standard). X subscript stands for the test sample, and S subscript stands for the standard.

Fluorescence lifetimes were measured on a combined steady-state lifetime fluorescence spectrometer and the fluorescence lifetimes were obtained from deconvolution and distribution lifetime analysis. Details of the instrumentation and experimental procedures used have been described elsewhere.[23] When the fluorescence decays were single exponential, the rate constants of radiative (k_f) and nonradiative (k_{nr}) deactivation were calculated from the measured fluorescence quantum yield and fluorescence lifetime using the following equation: $k_f = \phi/\tau$ and $k_{nr} = (1- \phi)/\tau$.

X-ray crystallography for 1i and 1j: Crystals of curcumin-BF_2 complexes **1i** (CCDC 950204) and **1j** (CCDC 950205) suitable for X-ray analysis were obtained by slow evaporation of their dichloromethane solutions. Data were collected using a diffractometer equipped with a graphite crystal monochromator situated in the incident beam for data collection at room temperature. Cell parameters were retrieved using SMART[24] software and refined using SAINT on all observed reflections. The determination of unit cell parameters and data collections were performed with Mo Kα radiation (λ) at 0.71073 Å. Data reduction was performed using the SAINT software,[25] which corrects for Lp and decay. The structure was solved by the direct method using the SHELXS-974 program and refined by least squares method on F2, SHELXL-97,[26] incorporated in SHELXTL V5.10.[27]

Syntheses: 2,2-difluoro-1,3-dioxaborylpentadione was synthesized according to literature.[17a]

General procedure for the synthesis of curcumin-BF_2 complex 1: To a solution of **2** (2.0 mmol) and 2,2-difluoro-1,3-dioxaborylpentadione (120 mg, 0.8 mmol) in 10 mL dry toluene was added a drop of piperidine. The mixture was left stirred for 2 h at room temperature, quenched by adding water, and extracted with CH_2Cl_2. Organic layers were combined and reduced under vacuum. The crude product was washed with ether for several times or purified by silica gel column chromatography to afford the desired product.

Curcumin-BF_2 complex **1a** was isolated as a red solid in 30% yield (78 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 15.3 Hz，2H), 7.63 (s, 4H), 7.47 (s, 6H), 6.75 (d, J = 15.6 Hz, 2H), 6.12 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.3, 147.6, 134.0, 131.9, 129.3, 129.2, 120.6, 102.2. HRMS (APCI) Calcd. for $C_{19}H_{15}O_2BF$ $[M-F]^+$ 305.1144, found 305.1144. HRMS (APCI) Calcd. for $C_{19}H_{16}O_2BF_2$ $[M + H]^+$ 325.1206, found 325.1201.

Curcumin-BF_2 complex **1b** was isolated as a red solid in 35% yield (99 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 14.1 Hz, 2H), 7.50 (s, 4H), 7.24 (s, 4H), 6.68 (d, *J* = 14.1 Hz, 2H), 6.07 (s, 1H), 2.41 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 147.5, 142.8, 131.4, 130.0, 129.3, 119.6, 102.0, 22.0. HRMS (APCI) Calcd. for $C_{21}H_{19}O_2BF$ $[M-F]^+$ 333.1457, found 333.1461; HRMS (APCI) Calcd. for $C_{21}H_{20}O_2BF_2$ $[M + H]^+$ 353.1519, found 353.1513.

Curcumin-BF_2 complex **1c** was isolated as a brown solid in 45% yield (138 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 15.6 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 4H), 6.95 (d, *J* = 8.1 Hz, 4H), 6.58 (d, *J* = 15.6 Hz, 2H), 6.01 (s, 1H), 3.87 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 162.8, 146.9, 131.2, 126.9, 118.0, 114.7, 101.7, 55.5.. HRMS (APCI) Calcd. for $C_{21}H_{19}O_4BF$ $[M-F]^+$ 365.1355, found 365.1355; HRMS (APCI) Calcd. for $C_{21}H_{20}O_4BF_2$ $[M + H]^+$ 385.1417, found 385.1410.

Curcumin-BF_2 complexes **1d** was isolated as red powder in 32 % yield (106 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 2H), 7.90 (d, *J* = 15.6 Hz, 2H), 7.46(s, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 15.3 Hz, 2H), 6.86(d, *J* = 8.1 Hz, 2H), 6.43(s, 1H), 3.83 (s, 6H). The data was in agreement with literature.[17a]

Curcumin-BF_2 complex **1e** was isolated as a brown solid in 35% yield (91 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 14.7 Hz, 2H), 7.52 (d, *J* = 5.7 Hz, 4H), 6.94 (d, *J* = 5.1 Hz, 4H), 6.57 (d, *J* = 15.0 Hz, 2H), 6.03 (s, 1H), 4.18 (s, 4H), 3.88 -3.57 (m, 20H), 3.39 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.3, 161.8, 146.6, 131.1, 126.9, 118.1, 115.2, 101.6, 71.8, 70.7, 70.5, 69.4, 67.6, 59.0. HRMS (APCI) Calcd. for $C_{33}H_{43}O_{10}BF$ $[M-F]^+$ 629.2928, found 629.2926; HRMS (APCI) Calcd. for $C_{33}H_{43}O_{10}BF_2$ $[M^+]$ 648.2912, found 648.2914.

Curcumin-BF_2 complex **1f** was isolated as a brown solid as a brown solid in 45% yield (128 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 15.6 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 4H), 6.91 (d, *J* = 8.7 Hz, 4H), 6.57 (d, *J* = 15.3 Hz, 2H), 6.00 (s, 1H), 4.05(t, *J* = 6.0 Hz, 4H), 3.27 (t, *J* = 6.9 Hz, 4H), 2.07-

1.91(m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 161.9, 146.6, 131.1, 126.8, 118.0, 115.0, 101.6, 66.9, 29.9, 6.0. HRMS (APCI) Calcd. for $C_{27}H_{29}O_4BFI_2$ $[M-F]^+$ 701.0227, found 701.0228; HRMS (APCI) Calcd. for $C_{27}H_{30}O_4BF_2I_2$ $[M + H]^+$ 721.0289, found 721.0285.

Curcumin-BF_2 complex **1g** was synthesized according above general procedure and was isolated as black powder in 24% yield (79 mg). ^{1}H NMR (DMSO-d_6): δ (ppm) 3.04 (s, 12H), 6.26 (s, 1H), 6.77-6.75(m, 6H), 7.66 (4H, d, J = 8.0 Hz), 7.78 (1H, s), 7.83 (1H, s). The data was in agreement with literature.[17b]

Curcumin-BF_2 complex **1h** was isolated as a brown solid in 15% yield (36 mg): ^{1}H NMR (300 MHz , DMSO-d_6) δ 11.91 (s, 2H), 7.80 - 7.71 (m, 2H), 7.29 (s, 2H), 6.89 (s, 2H), 6.65 - 6.56 (m, 2H), 6.32 (s, 2H), 6.11 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.4, 135.5, 130.1, 127.7, 118.9, 113.9, 112.5, 100.4. HRMS (APCI) Calcd. for $C_{15}H_{13}O_2N_2BF$ $[M-F]^+$ 283.1049, found 283.1047. HRMS (APCI) Calcd. for $C_{15}H_{14}O_2N_2BF_2$ $[M + H]^+$ 303.1111, found 303.1107.

Curcumin-BF_2 complex **1i** was isolated as a brown solid in 16% yield (40 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 15.3 Hz, 2H), 7.59 (s, 2H), 6.81 (d, J = 3.3 Hz, 2H), 6.58 (d, J = 14.1 Hz, 4H), 6.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 151.3, 146.9, 132.1, 119.1, 118.2, 113.5, 102.6; HRMS (APCI) Calcd. for $C_{15}H_{11}O_4BF$ $[M-F]^+$ 285.0729, found 285.0725. HRMS (APCI) Calcd. for $C_{15}H_{12}O_4BF_2$ $[M + H]^+$ 305.0791, found 305.0786.

Curcumin-BF_2 complex **1j** was isolated as a reddish brown solid in 35% yield (105 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.76 (m, 2H), 7.49 (s, 4H), 7.38 (d, J = 5.1 Hz，6H), 7.10-6.92(m, 4H), 6.26 (d, J = 14.7 Hz，2H), 5.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 147.5, 145.0, 135.7, 130.1, 128.9, 127.9, 126.5, 124.1, 102.0. HRMS (APCI) Calcd. for $C_{23}H_{19}O_2BF$ $[M-F]^+$ 357.1457, found 357.1457; HRMS (APCI) Calcd. for $C_{23}H_{20}O_2BF_2$ $[M + H]^+$ 377.1519, found 377.1514.

Curcumin-BF_2 complex **1k** was isolated as a black solid in 40% yield (140 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (br, 2H), 7.46 (d, J = 8.4 Hz, 4H), 7.05 (d, J = 15.0 Hz, 2H), 6.92-6.80 (m, 6H), 6.19 (d, J = 14.4 Hz, 2H), 5.87 (s, 1H), 3.84 (s, 6H). HRMS (APCI) Calcd. for $C_{25}H_{23}O_4BF$ $[M-F]^+$ 417.1668, found 417.1670.

Synthesis of Curcumin-BF_2 complex **1l**: Curcumin-BF_2 complex **1l** (36 mg, 0.05 mmol) and PPh_3 (262 mg, 1 mmol) were dissolved in 5 mL toluene. The mixture was refluxed for 36 h, cooled to room temperature, and removed solvent under vacuum. The residue was washed with dry toluene for several times to afford the desired product as a red solid in 80% yield (40 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.49 (m, 36H), 6.87 (d, *J* = 6.3 Hz, 4H), 6.62 (d, *J* = 14.7 Hz, 4H), 6.15 (s, 1H), 4.16 (s, 4H), 3.82 (s, 4H), 2.23 (s, 4H),1.87 (s, 4H). HRMS (ESI) Calcd. for $C_{63}H_{59}O_4BFP_2$ $[M]^+$ 495.1969, found 495.1967. HRMS (ESI) Calcd. for $C_{63}H_{60}O_4BF_2P_2$ $[M + H]^+$ 495.7009, found 495.6973.

General procedure for the synthesis of Curcumin-BF_2 complex 3: To a solution of **2** (0.8 mmol) and 2,2-difluoro-1,3-dioxaborylpentadione (120 mg, 0.8 mmol) in 10 mL dry toluene was added a drop of piperidine. The mixture was stirred under argon for 3 h at room temperature, quenched by adding water, and extracted with CH_2Cl_2. Organic layers were combined and concentrated under vacuum. Then the crude product was purified by silica gel column chromatography to afford the desired product.

Curcumin-BF_2 complex **3a** was isolated as a bluish black solid in 35% yield (79 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.91 (m, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 15.3 Hz, 1H), 6.93 - 6.81 (m, 3H), 6.14 (d, *J* = 14.7 Hz, 1H), 5.90 (s, 1H) , 3.85 (s, 3H), 2.30(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 180.5, 161.6, 149.6, 145.8, 129.7, 128.3, 124.1, 121.7, 114.6, 101.0, 55.5, 24.2. HRMS (APCI) Calcd. for $C_{15}H_{15}O_3BF$ $[M - F]^+$ 273.1093, found 273.1095.

Curcumin-BF_2 complex **3b** was isolated as a black solid in 30% yield (72 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (br, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 15.0 Hz, 1H), 6.80 (br, 1H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.04 (d, *J* = 14.7 Hz, 1H), 5.83 (s, 1H), 3.05 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.9, 180.5, 152.0, 151.0, 147.9, 130.2, 123.4, 121.6, 119.3, 111.9, 100.6, 40.1, 24.0. HRMS (APCI) Calcd. for $C_{16}H_{18}O_2NBF$ $[M-F]^+$ 286.1409, found 286.1410. HRMS (APCI) Calcd. for $C_{16}H_{19}O_2NBF_2$ $[M + H]^+$ 306.1471, found 306.1470.

Curcumin-BF_2 complex **3c** was isolated as a bluish black solid in 35% yield (94 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.93 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 15.0 Hz, 1H), 6.77-6.81 (m, 1H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.03 (d, *J* = 14.1 Hz, 1H), 5.82 (s, 1H), 3.42 (q, *J* = 6.9 Hz, 4H), 2.25 (s,

3H), 1.21 (t, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 180.4, 151.3, 149.8, 148.1, 130.6, 122.7, 121.1, 118.8, 111.5, 100.5, 44.6, 23.9, 12.6. HRMS (APCI) Calcd. for $C_{18}H_{22}O_2NBF$ $[M\text{-}F]^+$ 314.1722, found 314.1723. HRMS (APCI) Calcd. for $C_{18}H_{23}O_2NBF_2$ $[M + H]^+$ 334.1784, found 334.1785.

Fluorescence Imaging: Human gastric cancer SGC7901 cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS), penicillin (100 U/ml), streptomycin sulfate (100 μg/ml), and maintained at 37 °C with 5% CO_2 in a humidified incubator. One day before imaging, cells were seeded in 6-well flat-bottomed plates in an atmosphere of 5% CO_2, 95% air at 37 °C. Fluorescence imaging of intracellular dyes was observed under OLYMPUS-IX71 inverted fluorescence microscope and imaged using FITC channel or TRITC channel. The cells were treated with 10 μM of dyes in culture media for 30 min at 37 °C with 5% CO_2 in a humidified incubator. Fluorescence imaging was then carried out after washing the cells with the PBS. For the control experiment, the cells without treatment of dyes did not show any noticeable fluorescence under the same conditions.

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