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Mechanochemical synthesis of 2,2-difluoro-4,6-bis(β-styryl)-1,3,2-dioxaborines and their use in cyanide ion sensing

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Abstract: The conversion of arylaldehydes to 1,7-diaryl-5-hydroxyhepta-1,4,6-trien-3-ones (curcuminoids) and the mechanochemical cyclization of these products to 2,2-difluoro-4,6-bis(β-styryl)-1,3,2-dioxaborines using BF_3-Et_2O are described. Investigation of the cyanide ion sensing ability of the 2,2-difluoro-4,6-bis(β-styryl)-1,3,2-dioxaborines, in relation to the substituent groups on the aryl ring, showed that a hydroxy susbstituent is required, preferably *para* to the intervening carbon bridge.

Keywords: cyanide; 2,2-difluoro-4,6-bis(β-styryl)-1,3,2-dioxaborines; mechanochemical.

Introduction

The design and development of 1,3,2-dioxaborine based fluorophores is a growing area of research with applications in sensing and biomedical imaging [1–4]. 1,3-Diketones form stable 2,2-difluoro-1,3,2-dioxaborines, also termed as difluoroboron complexes, that exhibit interesting photophysical properties. Curcuminoids are 1,3-diketones, existing preferentially as enol tautomers [5], and belong to the diarylheptanoid class of natural products. These (*1E,4Z,6E*)-1,7-diaryl-5-hydroxyhepta-1,4,6-trien-3-ones have served as useful precursors for the synthesis of 2,2-difluoro-1,3,2-dioxaborine scaffold based cyanide sensing fluoroprobe [6], NIR probes for amyloid β-deposits [7–9], inhibitors for HIV proteases [10] and NIR luminophores [11]. Recently, BF_2 complexes of π-extended curcuminoids have been described that show solvatochromic and solvatofluorochromic properties [12].

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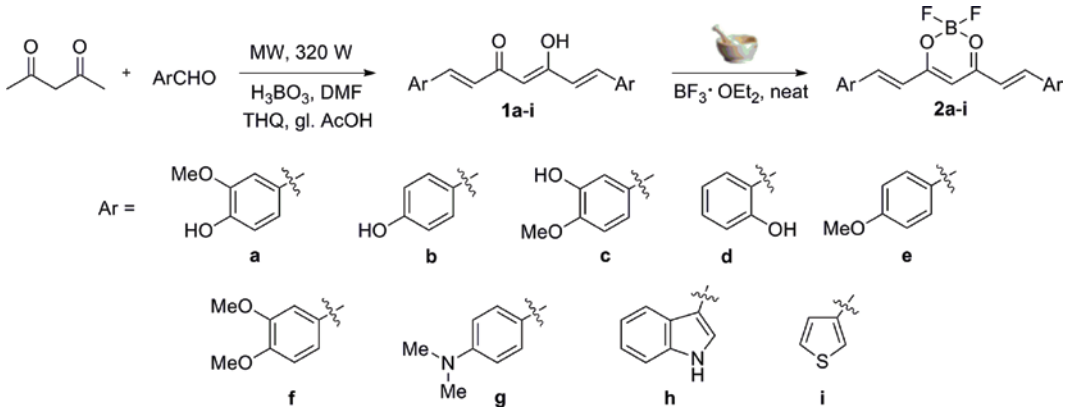
Reported methods for the synthesis of curcuminoid-BF_2 complexes include the reaction of the natural curcuminoids, or synthetic ones obtained from arylaldehyde, boric acid and 1,3-pentanedione, with boron trifluoride etherate. These complexes can also be prepared by condensation of arylaldehydes with 2,2-difluoro-1,3-dioxaborylpentadione. Both routes however, afford these complexes in generally low yields. For example, Ran and co-workers [7, 8] have reported yields in the range of 14–20% for 2,2-difluoro-1,3,2-dioxaborines obtained by the bis-condensation of arylaldehydes with 2,2-difluoro-1,3-dioxaborylpentadione at 60°C overnight. More recently, Bai et al. [12] have prepared BF_2 complexes, including π-extended systems, by reacting arylaldehydes, hetarylaldehydes and cinnamaldehydes with 2,2-difluoro-1,3-dioxaborylpentadione in toluene at room temperature for 2 h in 15–45% yield. Feloaut and co-workers [13] obtained two curcuminoid-BF_2 complexes in 61 and 74% yield by reacting the curcuminoids and boron trifluoride etherate in dichloromethane at reflux for 24 h. In a similar way, a long reaction time has been reported by Sui and co-workers [10] in seemingly the first report of the synthesis of a curcumin-BF_2 complex. With our interest in the synthesis and bioactivity of curcuminoids [14–16], we now report a mild two-stage synthetic route to access curcumin templated 1,3,2-dioxaborines.

Results and discussion

The (*1E,4Z,6E*)-1,7-diaryl-5-hydroxyhepta-1,4,6-trien-3-ones **1a–i** were prepared by microwave irradiation of a mixture of arylaldehyde, acetylacetone and boric acid in a mixed solvent consisting of a small amount of *N,N*-dimethylformamide (DMF), glacial acetic acid and 1,2,3,4-tetrahydroquinoline (THQ) as catalyst for 20 min. This method is a great improvement over the method reported previously which required heating at 85°C for 4 h [14]. Among different solvents tried, including DMF, dimethyl sulfoxide, *N*-methylpyrrolidine and *N,N*-dimethylacetamide, DMF was the best and with



Scheme 1 Synthetic route for curcuminoid 1,3,2-dioxaborines.

various amines tried as catalyst, THQ was found to work best, followed by diethanolamine, on the basis of yield and purity of the crude product. This use of THQ-acetic acid in curcumin synthesis has been adopted by others [9, 17]. We also observed that boric acid could also serve as the boron source and the addition of a tri-*n*-butyl borate did not improve the yield [9, 17]. The reaction mixture was worked up by a dropwise addition to 20% aqueous acetic acid under very rapid stirring to afford a crude product, which was further purified by planar preparative chromatography (PTLC). The curcuminoids **1a–i**, obtained in yields of 61–79%, were then efficiently converted to the corresponding BF_2 complexes in yields of 87–93% by neat grinding of these compounds with BF_3-etherate for a few minutes (Scheme 1 and Table 1). The resultant complexes **2a–i** were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS. The products **2b–d, 2h** and **2i** have not been described previously. The synthesized BF_2 complexes are excellent D-A-D molecules having electron donor (D) moieties at both ends of the conjugated system and an electron acceptor (A) moiety in the middle of the molecule.

Chaicham and co-workers have reported the cyanide ion sensing ability of curcumin-BF_2 complex **2a**. These workers have attributed the selective detection of cyanide to the deprotonation of the two phenolic groups, followed by an intramolecular charge transfer process, as well as to the basicity of cyanide ion [6]. We examined the cyanide anion sensing ability of **2a–i** and concluded that a hydroxy group on the aryl rings, *para* to the intervening seven carbon bridge, is a structural feature that imparts a good cyanide ion sensing ability.

Thus, the 2,2-difluoro-1,3,2-dioxaborines **2a** and **2b**, both having a 4-hydroxyaryl moiety, show an excellent ability to sense cyanide ion under the conditions of this work (Figures 1 and 2). Between compounds **2a** and **2b**, the former compound exhibits a stronger response. Since the response of **2a** to cyanide ion is stronger than that of **2b,** factors other than pKa of the phenolic hydroxyl group may also play a role in the sensing mechanism, since the phenolic group in **2b** would be expected to be deprotonated easier. The compound **2c,** with a

Table 1 Yields of 2,2-difluoro-4,6-bis[β-(styryl)]-1,3,2-dioxaborines.

2,2-Difluoro-4,6-bis[β-(styryl)]-1,3,2-dioxaborine	Yield (%)	Reported yield (%)
2a	93	32 [12]
2b	91	–
2c	87	–
2d	92	–
2e	89	45 [12]
2f	90	73 [6]
2g	89	15 [7], 24 [12]
2h	90	–
2i	88	–

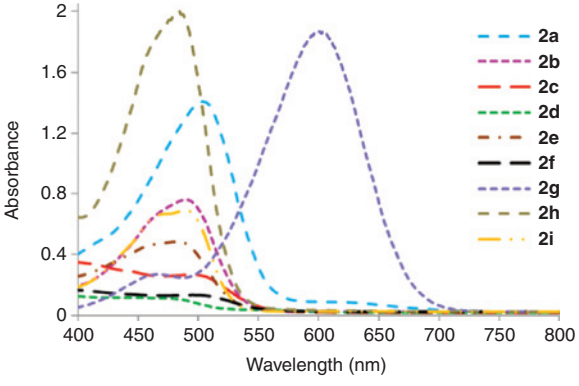


Figure 1 Absorption spectra of 5×10^{-6} M solutions of curcuminoid 2,2-difluoro-1,3,2-dioxaborines **2a–i** in MeCN/H_2O (4:1).

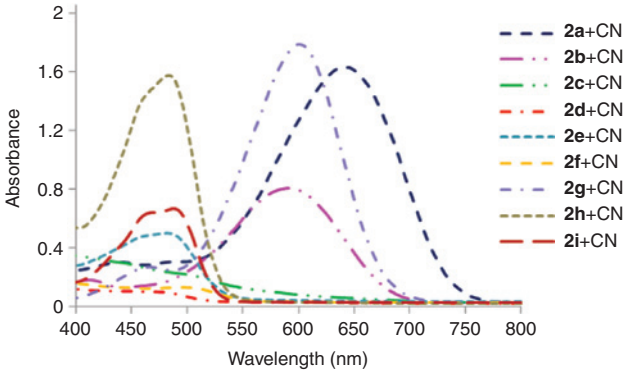


Figure 2 Absorption spectra of 5×10^{-6} M solutions of curcuminoid 2,2-difluoro-1,3,2-dioxaborines **2a–i** in presence of 100 molar excess of cyanide ion in MeCN/H_2O (4:1).

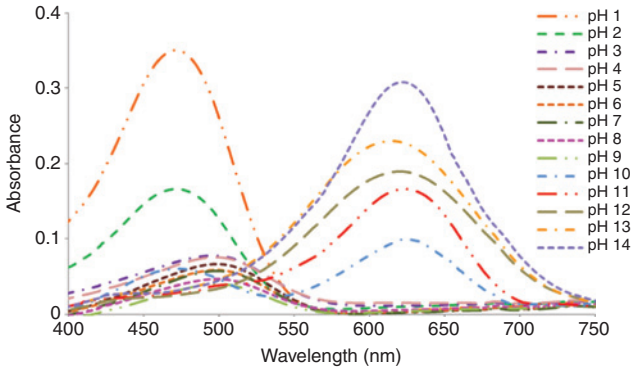


Figure 4 Absorption spectra of 2,2-difluoro-4,6-bis[β-(4-hydroxy-3-methoxystyryl)]-1,3,2-dioxaborine (**2a**) in MeCN/H_2O (4:1) solutions of pH range 1–14.

3-hydroxyaryl group, and **2d** with a 2-hydroxyaryl group respond very poorly, whereas those 2,2-difluoro-1,3,2-dioxaborines with no hydroxyaryl group, such as **2e–i**, do not respond markedly. The sensing of cyanide anion by 2,2-difluoro-1,3,2-dioxaborines **2a** and **2b** is insensitive to the presence of other anions including chloride, fluoride, phosphate, nitrite, nitrate and sulfate (Figure 3).

We also examined the response of the curcumin-BF_2 complex **2a** to pH using MeCN/H_2O solution in the pH range 1–14 (Figure 4). This study revealed that a change in pH is paralleled by a change in color. This observation indicates that the basis for cyanide ion sensing by curcumin-BF_2 complex **2a** is probably due to an acid-base reaction between cyanide ion and **2a,** as suggested by Chiacham and co-workers [6]. It appears that in order to analyze the presence of cyanide ion using **2a** as a sensor, the pH of the analyte aqueous solution should preferably be in the range of 7–9.

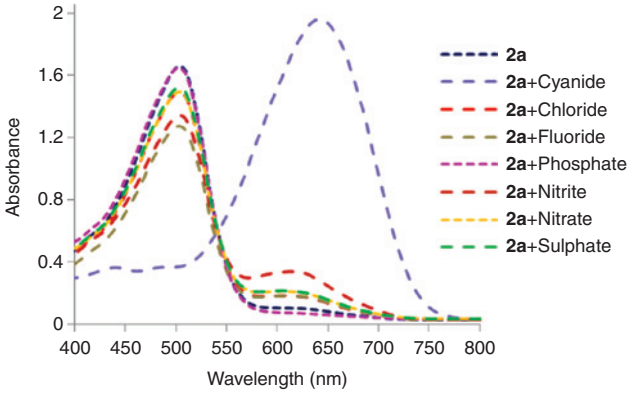


Figure 3 Absorption spectra of 5×10^{-6} M solutions of 2,2-difluoro-4,6-bis[β-(4-hydroxy-3-methoxystyryl)]-1,3,2-dioxaborine (**2a**) in presence of 100 molar excess of various ions in MeCN/H_2O (4:1).

Conclusions

In summary, we have synthesized several curcuminoids and converted these compounds to 2,2-difluoro-4,6-bis[β-(styryl)]-1,3,2-dioxaborines with a D-A-D motif under mild conditions in a very good overall yield. The structural feature required for conferring a cyanide ion sensing ability by these compounds is a 4-HOC_6H_4 functionality.

Experimental

Reagents and solvents used were of analytical grade. Analytical thin layer chromatography (TLC) and preparative thin layer chromatography (PTLC) were performed on glass plates (20 mm×75 mm and 20 cm×20 cm, respectively) coated with TLC grade silica gel-G (E. Merck, India). Preparative chromatography was conducted using dry columns as reported earlier by us [14]. The spots or bands were visualized directly or under UV light. The elemental analyses were carried out on a Vario EL elemental analyzer. The ^1H and ^{13}C NMR spectra were recorded on Bruker Topspin and Bruker AV spectrometers at room temperature. HRMS were recorded on JEOL JMS 600H mass spectrometer. The UV-Vis absorption spectra of the complexes in the presence and absence of ions were recorded on a HALO DB-20 UV-Vis spectrophotometer.

General procedure for the synthesis of curcuminoids (1a–i)

To a mixture of arylaldehyde (2 mmol), acetylacetone (1 mmol) and boric acid (0.2 g), a small amount of DMF (1 mL) was added to obtain a pasty mass. The mixture was then subjected to MW irradiation at 320 W in a multimode microwave oven for 5 min. To the clear mixture thus obtained, glacial acetic acid (60 μL) and 1,2,3,4-tetrahydroquinoline (20 μL) in DMF (0.5 mL) were added and MW irradiation was continued for 15 min. During irradiation, the mixture was cooled for

short periods at regular intervals. After the reaction was completed, the deeply colored mixture was diluted with DMF (1 mL) and added slowly to 20% aqueous acetic acid (10 mL) under rapid stirring. The precipitate obtained after stirring for 2 h was filtered and dried. The purity of the product was checked by TLC and it was further purified by preparative TLC ($CHCl_3$/MeOH, 95:5). The identity of the curcuminoids **1a–g** were established by comparison (TLC, IR) with samples prepared earlier in our laboratories [14].

(*1E,4Z,6E*)-5-Hydroxy-1,7-bis(indol-3-yl) hepta-1,4,6-trien-3-one (1h) This compound was obtained as red solid in 65% yield; mp 210°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.15 (s, 1H, 4-H), 6.71 (d, 2H, 2,6-H, J = 16 Hz), 7.19–7.25 (m, 4H, ArH), 7.48 (d, 2H, ArH, J = 7.5 Hz), 7.85 (d, 2H, 1,7-H, J = 16 Hz), 7.96 (s, 2H, ArH), 7.98 (d, 2H, ArH, J = 7.5 Hz), 11.81 (s, 2H, Ar-NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 183.2, 137.5, 134.3, 131.8, 124.9, 122.6, 120.9, 120.0, 118.2, 112.7, 112.4, 100.0. ESI-HRMS. Calcd for $C_{23}H_{18}N_2O_2$ (M+Na)$^+$: *m/z* 377.1266. Found: *m/z* 377.1266. Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.89; H, 5.13; N, 7.89.

(*1E,4Z,6E*)-5-Hydroxy-1,7-bis(thiophen-3-yl)hepta-1,4,6-trien-3-one (1i) This compound was obtained as yellowish brown solid in 69% yield; mp 189°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.19 (s, 1H, 4-H), 6.58 (d, 2H, 2,6-H, J = 15.5 Hz), 7.18 (s, 2H, ArH), 7.54 (d, 2H, ArH, J = 4.5 Hz), 7.75 (d, 2H, ArH, J = 4.5 Hz), 7.82 (d, 2H, 1,7-H, J = 15.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 182.5, 139.8, 133.2, 132.0, 130.0, 128.8, 122.7, 101.5; ESI-HRMS. Calcd for $C_{15}H_{12}S_2O_2$ (M+Na)$^+$: *m/z* 311.0176. Found: *m/z* 311.0179. Anal. Calcd for $C_{15}H_{12}S_2O_2$: C, 62.47; H, 4.19. Found: C, 62.35; H, 4.02.

General procedure for synthesis of curcuminoid 2,2-difluoro-1,3,2-dioxaborines 2a–i

BF_3·OEt_2 (0.12 mL, 1 mmol) was added to the curcuminoid **1a–h** (1 mmol) in an agate mortar and the mixture was ground with an agate pestle for a few seconds whereupon the mixture changed its color rapidly. The whole pasty mass soon solidified and further turned into a solid that had the appearance of a crystalline material. The crude product was purified by preparative TLC ($CHCl_3$/MeOH, 95:5).

2,2-Difluoro-4,6-bis[β-(4-hydroxy-3-methoxystyryl)]-1,3,2-dioxaborine (2a) This compound was obtained as red solid in 93% yield; mp 147°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 6H, OMe), 6.01 (s, 1H, 5-H), 6.54 (d, 2H, 2,6-H, J = 15.2 Hz), 6.95–7.21 (m, 6H, ArH) 7.95 (d, 2H, 1,7-H, J = 15.2 Hz), 9.60 (s, 2H, ArOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 183.2, 178.7, 151.3, 149.3, 148.1, 148.0, 146.9, 140.7, 126.3, 126.0, 125.2, 123.1, 121.1, 117.8, 115.9, 115.7, 112.4, 111.3, 101.1, 100.8, 55.7, 55.7. ESI-HRMS. Calcd for $C_{21}H_{19}BF_2O_6$ (M+Na)$^+$: *m/z* 439.1140. Found: *m/z* 439.1139.

2,2-Difluoro-4,6-bis[β-(4-hydroxystyryl)]-1,3,2-dioxaborine (2b) This compound was obtained as red solid in 91% yield; mp 169°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.05 (s, 1H, 5-H), 6.54 (d, 2H, 2,6-H, J = 15.2 Hz), 6.96–7.20 (m, 8H, ArH) 7.96 (d, 2H, 1,7-H, J = 15.2 Hz), 9.03 (s, 2H, ArOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.0, 179.2, 155.8, 150.0, 130.7, 129.3, 128.2, 126.6, 114.2, 98.7. ESI-HRMS. Calcd for $C_{19}H_{15}BF_2O_4$ (M+H)$^+$: *m/z* 357.1110. Found: *m/z* 357.2402.

2,2-Difluoro-4,6-bis[β-(3-hydroxy-4-methoxystyryl)]-1,3,2-dioxaborine (2c) This compound was obtained as red solid in 87% yield; mp 162°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 6H, OMe), 5.98 (s, 1H, 5-H), 6.53 (d, 2H, 2,6-H, J = 15.2 Hz), 6.95–7.21 (m, 6H, ArH), 7.96 (d, 2H, 1,7-H, J = 15.2 Hz), 9.46 (s, 2H, ArOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 179.1, 150.5, 148.7, 147.7, 146.9, 140.5, 126.3, 125.8, 125.2, 123.1, 121.1, 117.6, 115.7, 112.3, 111.3, 100.8, 55.6, 55.6. ESI-HRMS. Calcd for $C_{21}H_{19}BF_2O_6$ (M+Na)$^+$: *m/z* 439.1140. Found: *m/z* 439.1137.

2,2-Difluoro-4,6-bis[β-(2-hydroxystyryl)]-1,3,2-dioxaborine (2d) This compound was obtained as red solid in 92% yield; mp 158°C; ^{1}H NMR (400 MHz, DMSO-d_6): 5.81 (s, 1H, 5-H), 6.80 (d, 2H, 2,6-H, J = 16.0 Hz), 6.88–7.41 (m, 8H, ArH), 7.49 (d, 2H, 1,7-H, J = 16.0 Hz), 9.80 (s, 2H, ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.8, 180.2, 155.1, 150.1, 131.4, 130.4, 129.2, 126.6, 125.5, 114.0, 98.1. ESI-HRMS. Calcd for $C_{19}H_{15}BF_2O_4$ (M+H)$^+$: *m/z* 357.1110. Found: *m/z* 357.2404.

2,2-Difluoro-4,6-bis[β-(4-methoxystyryl)]-1,3,2-dioxaborine (2e) This compound was obtained as red solid in 89% yield; mp 150°C, Lit. [13] mp 247–249°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.85 (s, 6H, OMe), 6.57 (s, 1H, 5-H), 6.73 (d, 2H, 2,6-H, J = 15.4 Hz), 7.20 (d, 4H, ArH, J = 8.2 Hz), 7.88 (d, 4H, ArH, J = 8.2 Hz), 8.14 (d, 2H, 1,7-H, J = 15.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.6, 161.8, 147.3, 130.6, 130.5, 128.8, 128.6, 128.4, 128.3, 127.9, 127.1, 114.4, 101.7, 55.7. ESI-HRMS. Calcd for $C_{21}H_{19}BF_2O_4$ (M+H)$^+$: *m/z* 385.1423. Found: *m/z* 385.1489.

2,2-Difluoro-4,6-bis[β-(3,4-dimethoxystyryl)]-1,3,2-dioxaborine (2f) This compound was obtained as red solid in 90% yield; mp 152°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.34 (s, 12H, OMe), 6.57 (s, 1H, 5-H), 6.73 (d, 2H, 2,6-H, J = 15.9 Hz), 7.10 (s, 2H, ArH), 7.19 (d, 2H, ArH, J = 8.35 Hz), 7.71 (d, 2H, ArH, J = 8.6 Hz), 8.14 (d, 2H, 1,7-H, J = 15.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.3, 181.1, 150.0, 147.8, 146.2, 130.5, 128.8, 119.1, 114.1, 112.0, 99.1, 56.3. ESI-HRMS. Calcd for $C_{23}H_{23}BF_2O_6$ (M+H)$^+$: *m/z* 445.1634. Found: *m/z* 445.1807.

2,2-Difluoro-4,6-bis[β-(4-*N*,*N*-dimethylaminostyryl)]-1,3,2-dioxaborine (2g) This compound was obtained as dark blue solid in 89% yield; mp 144°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.09 (s, 12H, NMe_2), 6.26 (s, 1H, 5-H), 6.78 (d, 4H, ArH, J = 7.5 Hz), 7.66 (d, 4H, ArH, J = 8.4 Hz), 7.80 (d, 2H, 2,6-H, J = 15.6 Hz), 7.95 (d, 2H, 1,7-H, J = 15.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.6, 153.3, 145.7, 131.2, 129.2, 124.0, 116.0, 112.2, 99.2, 44.3. ESI-HRMS. Calcd for $C_{23}H_{25}BF_2N_2O_2$ (M+Na)$^+$: *m/z* 433.1875. Found: *m/z* 433.1870.

2,2-Difluoro-4,6-bis[β-(indol-3-yl)ethenyl]-1,3,2-dioxaborine (2h) This compound was obtained as red solid in 90% yield; mp 161°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.30 (s, 1H, 5-H), 6.41 (d, 2H, ArH, J = 8.6 Hz), 6.75 (d, 2H, 2,6-H, J = 15.7 Hz), 6.80 (d, 2H, ArH, J = 8.6 Hz), 6.86–6.92 (dd, 4H, ArH), 7.68 (s, 2H, ArH), 7.84 (d, 2H, 1,7-H, J = 15.7 Hz), 8.27 (s, 2H, Ar-NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 178.8, 151.3, 137.3, 136.1, 132.1, 128.3, 126.9, 126.0, 125.3, 123.4, 121.1, 112.4, 111.7, 101.1, 100.8. ESI-HRMS. Calcd for $C_{23}H_{17}BF_2N_2O_2$ (M+Na)$^+$: *m/z* 425.1249. Found: *m/z* 425.1245.

2,2-Difluoro-4,6-bis[β-(thiophen-3-yl)ethenyl]-1,3,2-dioxaborine (2i) This compound was obtained as red solid in 88% yield; mp 171°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.76 (d, 2H, ArH, J = 7.5 Hz), 6.92 (s, 1H, 5-H), 6.99 (d, 2H, ArH, J = 7.5 Hz), 7.18 (d, 2H, 2,6-H, J = 13.1 Hz), 7.34 (s, 2H, ArH), 7.35 (d, 2H, 1,7-H, J = 13.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 178.8, 140.0, 139.5, 139.3, 135.3, 133.6, 129.8, 129.4, 128.7,

119.4, 101.9. ESI-HRMS. Calcd for $C_{15}H_{11}BF_2S_2O_2$ $(M+Na)^+$: *m/z* 359.0159. Found: 359.01554.

UV-Vis spectrophotometric study of the interaction of curcuminoid 2,2-difluoro-1,3,2-dioxaborines 2a–i with anions

Stock solutions of the 2,2,-difluoro-1,3,2-dioxaborines **2a–i** (5 μM) and solutions of sodium cyanide, chloride, fluoride, phosphate, nitrite, nitrate and sulfate (0.5 mM) were freshly prepared in MeCN/H_2O (4:1). Absorption spectra of **2a–i** were recorded in the absence of any anions and in the presence of a 100-molar excess of sodium cyanide, chloride, fluoride, phosphate, nitrite, nitrate or sulfate. For the pH study, the solutions of **2a** were prepared in MeCN/H_2O (4:1).

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