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Short communication:

Two steps Synthesis of a BODIPY carboxylic-Curcumin

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- ✓ BODIPY
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Abstract

Boron dipyrromethene (BODIPY) carboxylic acid belong to a family of organoboron compounds and widely as fluorescent dye while curcumin is the traditional Chinese medicine to treat various diseases. Curcumin has a maximum absorption peak at wavelength 430 nm but its wavelength perhaps not long enough for photodynamic therapy or other biological applications. Organic synthesis is the major studied in this short communication, so we proposed a synthetic method linking the Boron dipyrromethene (BODIPY) carboxylic acid and curcumin to increase its absorption wavelength. The synthesized product, "BODIPY carboxylic-Curcumin" with 11% yield and characterized by ^{1}H NMR, ^{13}C NMR, HRMS and HPLC. It's also determined by Ultraviolet-visible (UV-Vis) spectroscopy. This preliminary results as an important starting to decide it for further investigation.

1. Introduction

Boron dipyrromethene (BODIPY) scaffold has been used in the application of biological systems such as dyes, fluorescent probes and photodynamic therapy because of the higher thermal and photochemical stability [1-4]. Its photophysical properties might be improved or modified by introducing functional groups to BODIPY core at suitable positions [5-11]. Boron dipyrromethene (BODIPY) carboxylic acid is a major core of the synthesis backbone (Figure 1) in this research.

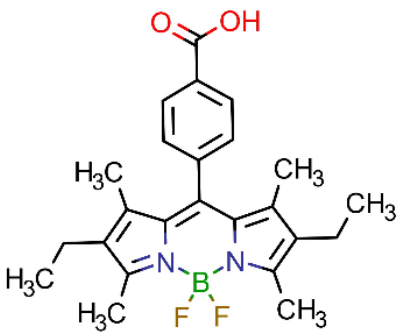


Figure 1. Boron dipyrromethene (BODIPY) carboxylic acid.

Curcumin is a traditional Chinese medicine which isolated from *Curcuma longa L*. Several pharmacological properties of curcumin have been reported such as antioxidants [12], anti-inflammatory [13], antibacterial [14], antifungal [15] and anticarcinogenic effects [16-17]. Curcumin has been used as a photosensitizer in photodynamic therapy with a broad absorption peak between 300 nm to 500 nm and the maximum absorption peak at wavelength 430 nm. To extend the absorption range of curcumin, boron dipyrromethene (BODIPY) carboxylic acid [18-20] was linked with curcumin and "BODIPY carboxylic-Curcumin" synthesized (Figure 2) in the present study.

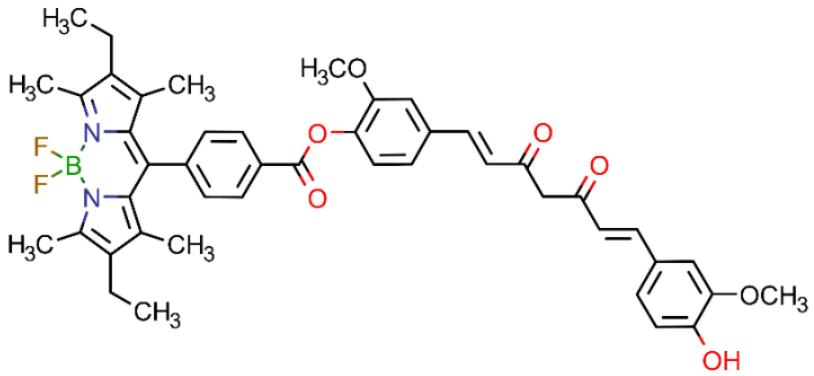


Figure 2. BODIPY carboxylic-Curcumin.

2. Material and Methods

All reagents and solvents were obtained from Sigma Aldrich without further purification unless otherwise stated. 3-Ethyl-2,4-dimethylpyrrole (97%), 4-Formylbenzonic acid (97%), Trifluoroacetic acid (99%), 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ, 98%), *N*,*N*′-dicyclohexylcarbodiimide (DCC, 99%) and 4-(Dimethylamino)pyridine (DMAP, 98%) were purchased from Sigma Aldrich. BODIPY was synthesized under the nitrogen atmosphere in oven-dried glassware. Anhydrous dichloromethane and dichloroethane were dried by calcium hydride. ^{1}H NMR and ^{13}C NMR spectrum were measured using Bruker AVANCE 400 spectrometer. The chemical shifts of NMR were given in ppm and coupling constants (*J*) in Hz. Mass spectrum was acquired using Bruker ultrafleXtreme MALDI-TOF/ESI spectrometer. Column chromatography was performed on silica gel (120-230 mesh). Thin-layer chromatography (TLC) was pre-coated with silica gel 60F_{254} (Merck) on aluminum sheets and visualized under 254 nm UV light.

2.1. Synthesis of BODIPY carboxylic acid

(8-(4-carboxyphenyl)-4,4-difluoro-1,3,5,7-tetramethyl-3a,4a-diazepine-4-benzodiazepine boron-S-indene)

3-Ethyl-2,4-dimethylpyrrole (10.3 g, 83.9 mmol) and 4-Formylbenzonic acid (6.3 g, 42.0 mmol) were dissolved in dichloromethane (2.60 L). Trifluoroacetic acid (328 µL) was then added and the mixture stirred at room temperature for 48 h. A solution of 2,3-dichloro-5,6-dicyano-p-benzoquinone (9.53 g, 42.0 mmol) in dichloromethane was added to the reaction mixture and further stirred for 50 min. Triethylamine (84.0 mL, 630 mmol), BF_3Et_2O (85.0 mL, 672 mmol) were added and the resulting solution turned purple. After stirring for 2 h, the reaction mixture was washed with water, dried over magnesium sulfate and the solvent was evaporated. The residue was purified by silica gel column chromatography through 9:1 ethylacetate-hexane followed by recrystallization in the same ratio mixture of dichloromethane and hexane to afford the pure red solid (1.00 g, 30%).

2.2. Synthesis of BODIPY carboxylic-Curcumin

DCC (0.48 g) was added to a solution of Curcumin (0.9 g). BODIPY (1.0 g) and DMAP (25 mg) were dissolved in CH_2Cl_2 (500 mL). It was maintained at 0°C under argon gas. The mixture was allowed to warm up to ambient temperature over 12 h and stirred for a further 36 h. The solvent was distilled off under reduced pressure and the residue purified by column chromatography repeatedly to afford the BODIPY carboxylic-Curcumin (200 mg, 11%) as a red solid.

3. Results and discussion

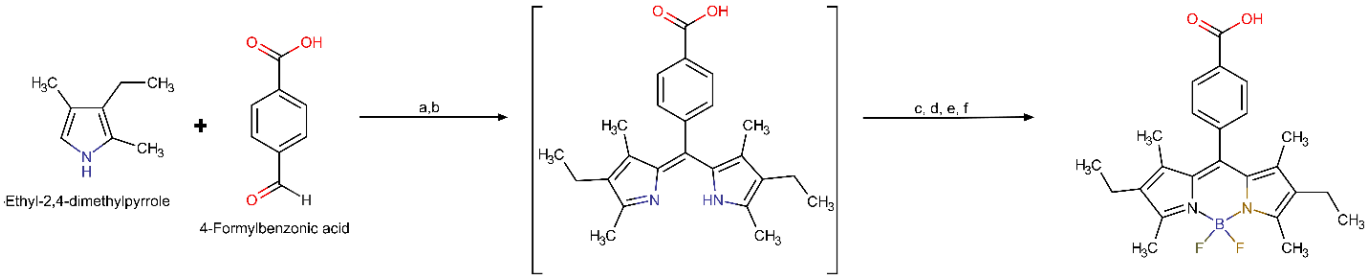
Boron dipyrromethene (BODIPY) carboxylic acid was synthesized in two reactional steps including condensation and oxidation. Firstly, 3-Ethyl-2,4-dimethylpyrrole reacted with 4-Formylbenzonic acid through the condensation reaction and the aldehyde was carried out in the presence of a catalyst, trifluoroacetic acid (TFA). Second, the intermediate product was oxidized by 2,3-dichloro-5,6-dicyano-p-benzoquinone then reacted with BF_3Et_2O. Triethylamine was acted as a catalyst for the neutralization (Scheme 1). The crude residue was purified by silica gel column chromatography column. Boron dipyrromethene (BODIPY) carboxylic acid was obtained as a pure red solid with a 30% yield. The ^1H NMR, ^{13}C NMR, HRMS and HPLC were confirmed the proposed structure.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.26-8.28 (m, *J*=7.1 Hz, 2H), 7.47-7.49 (d, *J*=7.1 Hz, 2H), 2.57 (s, 6H), 2.30-2.36 (q, 4H), 1.30 (s, 6H), 0.99-1.03(t, *J*=7.0 Hz, 6H) (Figure S1).

^{13}C NMR (400 MHz, $CDCl_3$): δ=10.83, 11.55, 13.57, 16.05, 127.90, 128.53, 129.19, 129.86, 132.13, 137.00, 140.74, 153.39, 169.69 (Figure S2).

HPLC: 260 nm and 520 nm, 0.04% TFA/H_2O: 0.04% TFA/ACN, >94% and >97% (Figure S3 & S4).

ESI-MS (*m*/*z*): calculated for $C_{24}H_{27}BF_2N_2O_2$: 424.21; Found: 424.21 (Figure S5).



Scheme 1. Synthetic pathway of the Boron dipyrromethene (BODIPY) carboxylic acid. Reagents and conditions: (a) Trifluoroacetic acid (TFA); (b) Dichloromethane 24h / r.t.; (c) 2,3-dichloro-5,6-dicyano-p-benzoquinone; (d) Dichloromethane 50 min / r.t.; (e) BF_3Et_2O; (f) Triethylamine 1 h / r.t.

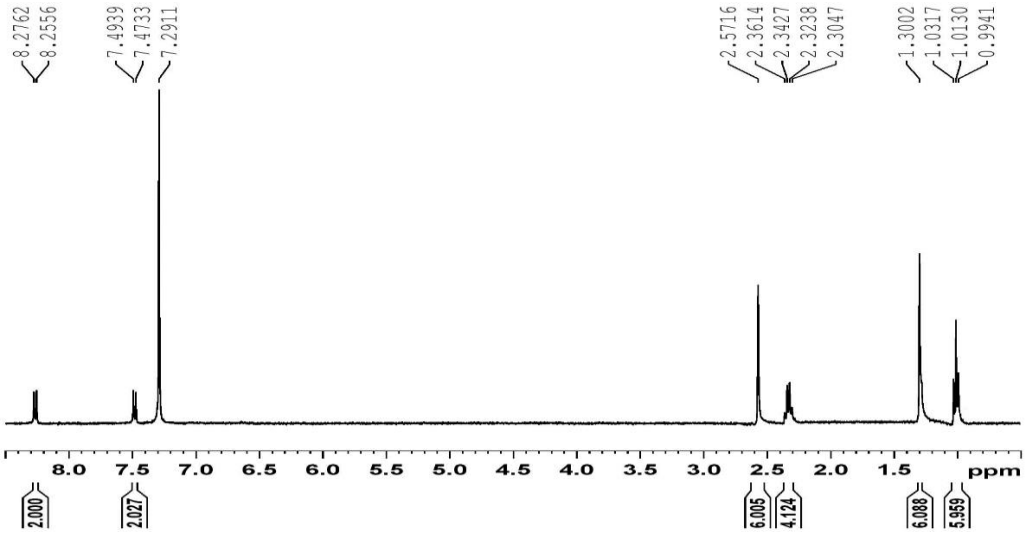


Figure S1. ^1H NMR of BODIPY carboxylic acid.

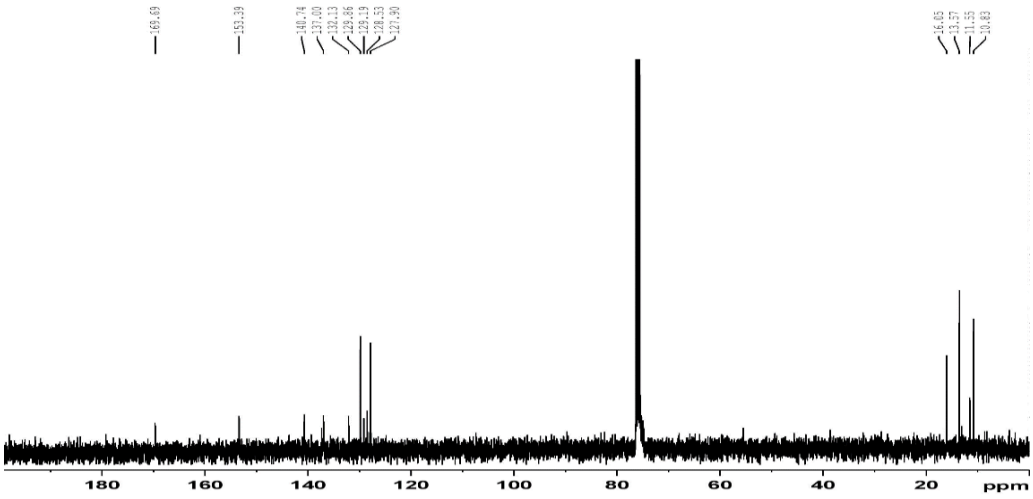


Figure S2. ^{13}C NMR of BODIPY carboxylic acid.

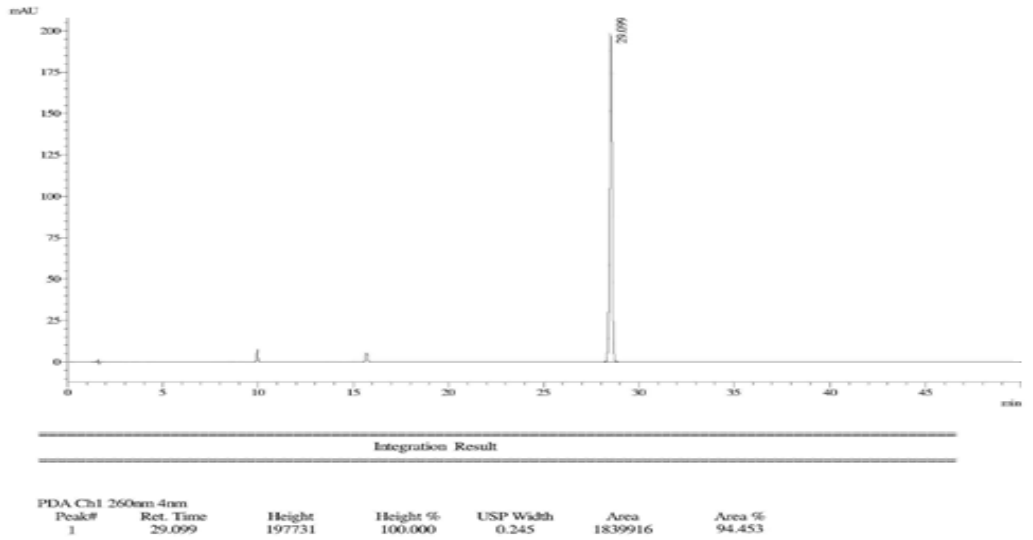


Figure S3. HPLC 260 nm of BODIPY carboxylic acid.

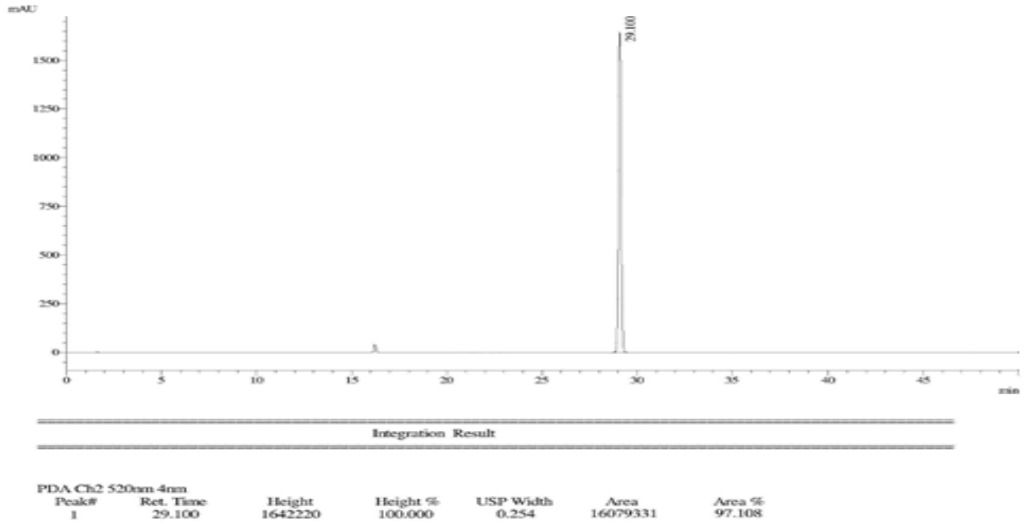


Figure S4. HPLC 520 nm of BODIPY carboxylic acid.

BODIPY carboxylic-curcumin was one step synthesis only (Scheme 2). Curcumin was reacted to the carboxylic group of BODIPY through the DCC/DMAP coupling reaction with the elimination of water.

The crude residue was purified by silica gel column chromatography column. BODIPY carboxylic-curcumin was obtained as a red solid with an 11% yield. The ^{1}H NMR, ^{13}C NMR, HRMS and HPLC were confirmed the proposed structure. The product yield was a little bit low due to the incomplete reaction.

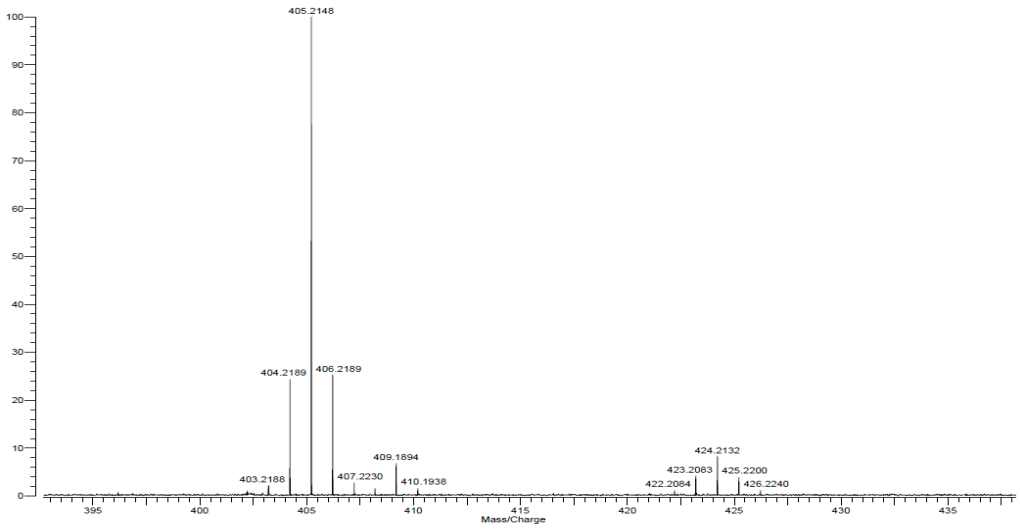
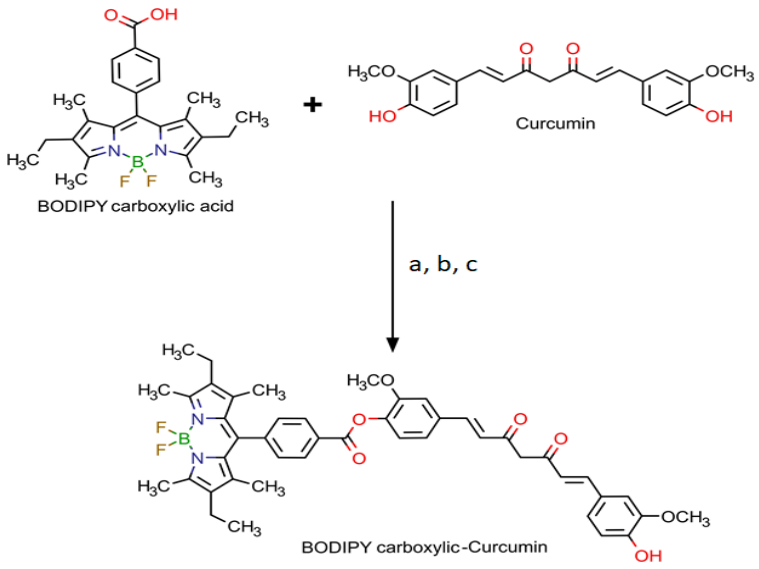


Figure S5. ESI-MS of BODIPY carboxylic acid.



Scheme 2. Synthetic pathway of the BODIPY carboxylic-Curcumin.
Reagents and conditions: (a) DCC/DMAP, 0°C; (b) Dichloroethane; (c) 48 h / r.t.

Curcumin still remained in the reaction mixture since it was difficult to dissolve at room temperature. Meanwhile, esterification cannot occur at high temperature, otherwise, curcumin would be decomposed itself.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.33 (m, *J*=7.1 Hz, 2H), 6.95-7.64 (m, *J*=7.1 Hz, 9H), 6.49-6.62 (m, *J*=7.1 Hz, 2H), 5.85-5.94 (d, *J*=7.1 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 2.55 (s, 6H), 2.33 (q, 4H), 1.32 (m, 7H), 1.00 (m, *J*=7.0 Hz, 6H) (Figure S6).

^{13}C NMR (400 MHz, $CDCl_3$): δ=12.02, 12.59, 14.63, 17.10, 24.96, 25.62, 33.96, 55.98, 56.06, 101.63, 109.67, 111.59, 114.88, 121.05,121.76, 123.07, 123.35, 124.43, 127.54, 128.95, 129.54, 130.25, 131.01, 133.16, 134.38, 138.10, 138.46, 139.33, 141.21, 141.54, 146.83, 148.04, 151.57, 154.41, 164.10, 181.74, 184.61 (Figure S7).

HPLC: 260 nm and 520 nm, 0.04% TFA/H_2O: 0.04% TFA/ACN, >95% and >96% (Figure S8 & S9).

ESI-MS (*m*/*z*): calculated for $C_{45}H_{45}BF_2N_2O_2$: 774.32; Found: 774.30 (Figure S10).

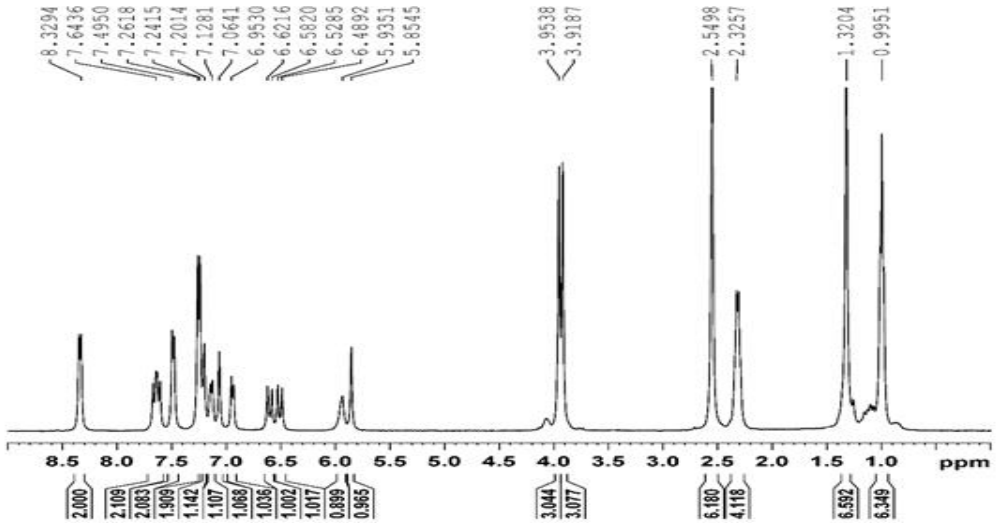


Figure S6. ^{1}H NMR of BODIPY carboxylic-Curcumin.

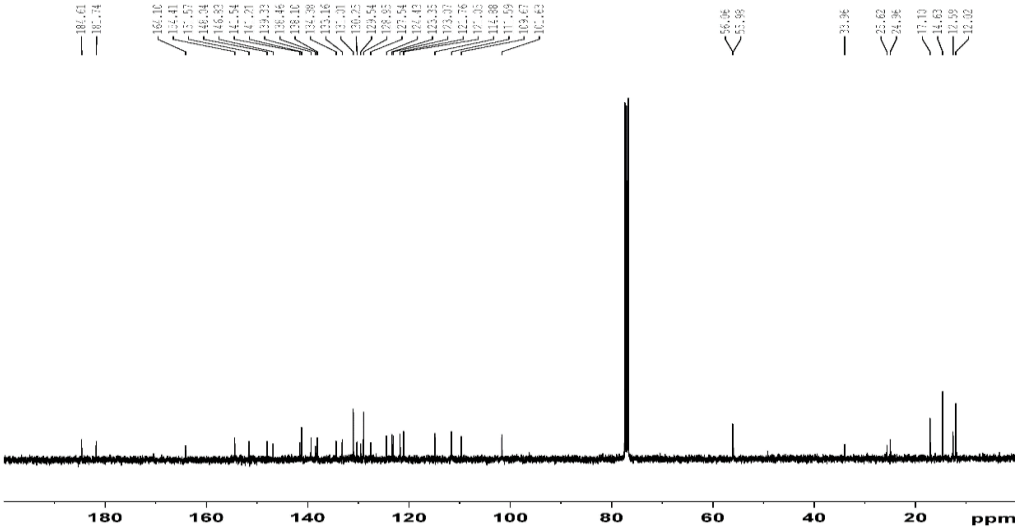
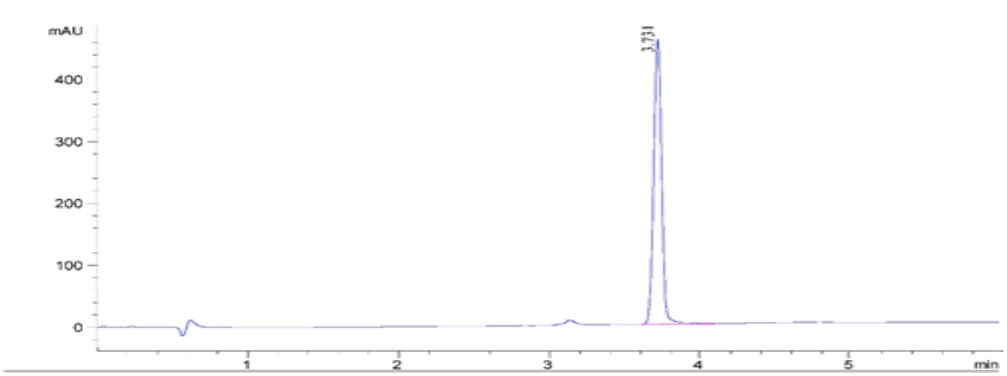


Figure S7. ^{13}C NMR of BODIPY carboxylic-Curcumin.



Integration Results

Signal : DAD1 A, Sig=260,4 Ref=off

#	Ret. Time	Height	Height %	Area	Area %
1	3.731	95.516	95.516	1.646e3	95.592

Figure S8. HPLC 260 nm of BODIPY carboxylic-Curcumin.

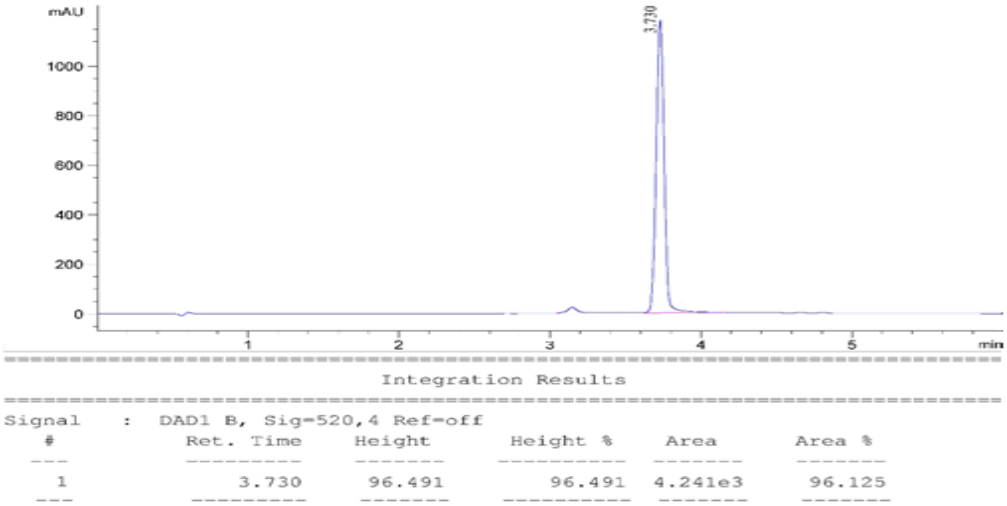


Figure S9. HPLC 520 nm of BODIPY carboxylic-Curcumin.

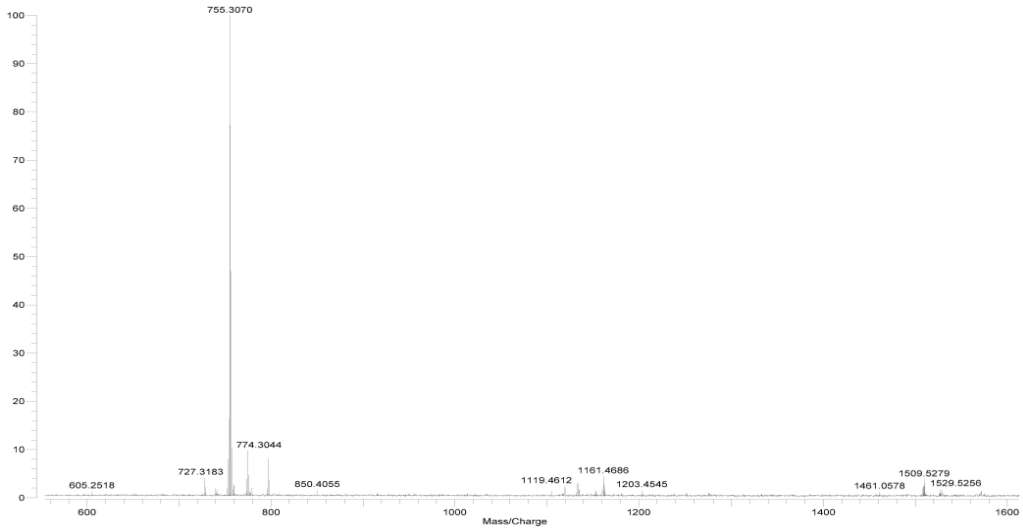


Figure S10. ESI-MS of BODIPY carboxylic-Curcumin.

The absorption spectrum of curcumin, BODIPY carboxylic acid and BODIPY carboxylic-Curcumin were measured using Ultraviolet-visible (UV-Vis) spectroscopy (Figure 3).

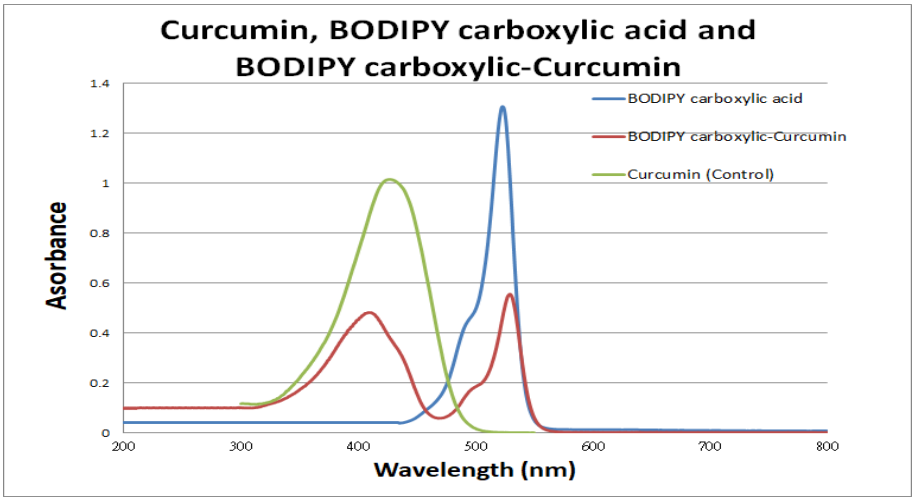


Figure 3. Ultraviolet-visible (UV-Vis) absorption spectrum of Curcumin, BODIPY carboxylic acid and BODIPY carboxylic-Curcumin.

This was shown that curcumin and BODIPY carboxylic acid with the maximum absorption peak at wavelength 430 nm and 525 nm respectively. BODIPY carboxylic-Curcumin consisted of two absorption peaks at wavelength 413 nm and 532 nm which were curcumin and BODIPY carboxylic acid. There was a little red shift for BODIPY carboxylic-Curcumin since the absorption wavelength increased from 525 nm to 532 nm after BODIPY carboxylic acid linked to curcumin.

Conclusion

BODIPY carboxylic-Curcumin was synthesized successfully with 11% yield and characterized by ^{1}H NMR, ^{13}C NMR, HRMS and HPLC. Curcumin reacted to the carboxylic group of BODIPY through the DCC/DMAP coupling reaction. However, there is a low product yield because of the curcumin solubility problem lead to incomplete reaction. The absorption peak of BODIPY carboxylic acid was increased to 532 nm after conjugated with curcumin. BODIPY carboxylic-Curcumin might be a potential candidate for photodynamic therapy if it presents a good photodynamic behaviours such as extinction coefficients, narrow absorption, emission bands and quantum efficiencies of fluorescence in further development.

Conflicts of interest statement - The authors declare no conflict of interest.

Author contributions - All authors contributed to the concept, drafting of the article, and critical revision for important intellectual content.

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