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Multistep Synthesis and Structural Analysis of a BODIPY-Quinoline Compound

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Abstract

This article describes the design, synthesis, purification and characterization of a new BODIPY-quinoline compound (**6**). The molecular design strategy is based on the placement of azido substituents at the 3 and 5 positions of the BODIPY skeleton, preparation of propargyl-quinoline compound **(5)** and the click reaction between distyryl-BODIPY (**4**) and propargyl-quinoline **(5)**. The structures of all the new compounds were confirmed by MALDI-MS, ^{1}H and ^{13}C NMR spectroscopic techniques. This combination allows the formation of binding sites for metal ions. Thus, the BODIPY-quinoline compound presented in this study is promising for the development of novel fluorescent sensors. The presented synthetic strategy can also be used to synthesize other BODIPY derivatives needed for various applications.

Keywords: BODIPY, quinoline, click reaction

1. Introduction

The development of highly emissive dyes for a variety of applications has been the focus of scientific research for a long time. Among the many different types of fluorophores, BODIPY derivatives (Fig.1) are widely recognised for their strong emission intensity, large extinction coefficients, high quantum yields, and high stability under a variety of conditions [1,2]. These characteristics make BF_2 complexes highly valuable in a variety of applications, including photosensitizers [3,4], chemosensors [5,6], fluorescent biolabels [7,8], electron-transport materials [9,10], and photodynamic therapy [11–13]. Numerous investigations have been conducted on the synthesis, spectroscopic characteristics, and uses of these compounds since the description of the first boron difluoride complexes of the dipyrromethenes in 1968 [1,14]. One of the key characteristics of BODIPY compounds is that the ability of BODIPY compounds to be easily functionalized from a variety of positions [15]. Knoevenagel condensation reaction targeting the 3- and 5-position methyl groups to give a styryl-substituted BODIPY is a commonly used method for BODIPY functionalisation [14]. As a result of this interaction, which increases π-conjugation, a red shift in the absorption and emission wavelength of the dye occurs [16].

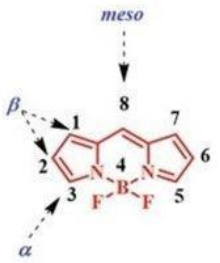

Figure 1. Numbering scheme of a BODIPY molecule [17]

Quinolines are a group of heterocyclic aromatic compounds, also known as benzo[b]pyridines, 1-azanaphthalenes and benzazines. They contain a nitrogen atom in their structure. The benzene ring is fused to the pyridine ring at the 2,3 position (Fig. 2) [18]. Due to their wide range of applications in medicinal and industrial chemistry, quinoline and its derivatives have become an attractive scaffold for chemists among the nitrogen-containing heterocycles. Quinolines are promising for a range of biological activities, including, anticancer, antibiotic, anti-inflammatory, anti-tuberculosis, anti-HIV [19–22]. Thanks to the extended π-electron system, quinolines also have exciting optical properties. They have the potential to be used as optical materials and fluorescent probes [23].

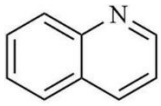

Figure 2. Chemical structure of quinoline

In this study, it is aimed to present an example of the design of fluorescence sensors by considering the coordination ability of the triazole ring formed as a result of the click reaction and the nitrogen atom in the quinoline compound with metal ions. Some examples of BODIPY-quinoline derivatives designed to bind specific metal ions can be found in the literature [24]. Herein, the synthesis and structural analysis of BF_2 complex bearing quinoline units at the 3- and 5-positions of the BODIPY core is demonstrated.

2. Materials and Methods

2.1. Chemicals

Merck silica gel plates (Kieselgel 60, F254 indicator, 0.25 mm) were used for thin-layer chromatography (TLC) and silica gel (Kieselgel 60, 230-400 mesh) for column chromatography. Deuterated solvent ($CDCl_3$) and the following chemicals were purchased from Merck; sodium azide, sodium sulfate, trifluoroacetic acid, p-chloranil, triethylamine (≥99%), piperidine (≥99%), copper(II) sulfate pentahydrate, sodium ascorbate, acetic acid (glacial), acetonitrile, dichloromethane, acetone, ethanol. Propargyl bromide (80% in toluene, stab. with MgO) and boron trifluoride diethyl etherate (more than 98%) were supplied by Alfa Aesar. 4-hydroxybenzaldehyde (99%) and 2,4-dimethylpyrrole (97%) were provided by Acros Organics. 1,4-dibromobutane, 8-hydroxyquinoline, potassium carbonate (≥99%), tetrahydrofuran, chloroform, benzene, and n-hexane were obtained from Sigma-Aldrich. All other chemicals were of the same quality as the analytical reagents and were used without further purification unless otherwise stated.

2.2. Instrumentations

A Varian 500 MHz spectrometer was used for compound **4** and a Bruker Avance III HD 600 MHz spectrometer was used for compound **6** to record ^1H and ^{13}C NMR spectra at 20°C in $CDCl_3$ solutions. ^1H chemical shifts were recorded in ppm relative to the internal standard TMS (δ=0.00 ppm). The ^{13}C chemical shifts were given in ppm. They were referenced to the shift of $CDCl_3$ (δ=77 ppm). Coupling constants (*J*) were given in Hz. Mass spectrometry (MS) was performed using the MALDI-TOF technique. A Bruker Daltonics Microflex mass spectrometer was used.

2.3. Synthesis

Compound **1** [25], compound **2** [26], compound **3** [27] and compound **5** [28] were synthesized in accordance with their respective literature reports.

2.3.1. Synthesis of compound 4

Compound 3 (0.2 g, 0.58 mmol) and compound 2 (0.38 g, 1.76 mmol) were dissolved in 30 mL of benzene. 0.2 mL of glacial acetic acid and 0.2 mL of piperidine were introduced. The resulting mixture was refluxed for 2 hours. A Dean-Stark apparatus was used to remove the water formed during the reaction. The mixture was allowed to concentrate. The reaction was monitored by TLC until the main product was blue. After cooling to room temperature, the mixture was extracted with dicholoromethane-water. The water remaining in the organic phase was dried with Na_2SO_4. Column chromatography was used to purify the reaction mixture (n-hexane/ethyl acetate, 33%) (0.117 g, 0.16 mmol, 54%).
Spectral data of compound **4**: ^1H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.61 (d, *J* = 16.3 Hz, 2H, trans C=CH), 7.56 (d, *J* = 8.6 Hz, 4H, ArH), 7.20 (d, *J* = 16.2 Hz, 2H, trans C=CH), 7.16 (d, *J* = 8.1 Hz, 2H, ArH), 6.96 (d, *J* = 8.0 Hz, 2H, ArH), 6.91 (d, *J* = 8.3 Hz, 4H, ArH), 6.61 (s, 2H, pyrrole-CH), 4.04 (t, *J* = 6.0 Hz, 4H, $-CH_2N_3$), 3.39 (t, *J* = 6.7 Hz, 4H, $-OCH_2$), 1.90 (m, 4H, $-CH_2$-), 1.82 (m, 4H, $-CH_2$-), 1.50 (s, 6H, $-CH_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K, δ ppm) δ 159.66, 156.23, 152.60, 141.81, 135.67, 133.53, 129.94, 129.62, 129.04, 127.49, 117.46, 117.24, 116.01, 114.77, 109.98, 67.28, 51.21, 26.49, 25.75, 14.83. MALDI-TOF MS (DIT) m/z Calc.: 742.34; found: 741.159 $[M-H]^+$ (Fig. 3a).

2.3.2. Synthesis of compound 6

A solution of compound **4** (0.05 mmol, 34 mg), compound **5** (0.20 mmol, 40 mg), sodium ascorbate (0.11 mmol, 21 mg) and $CuSO_4.5H_2O$ (0.06 mmol, 14 mg) in dichloromethane, ethanol and water (14 mL) was stirred for 48 h. Column chromatography was used to purify the reaction mixture (CH_2Cl_2/MetOH, 4%) (18 mg, 0.016 mmol, 32%).
Spectral data of compound **6**: ^1H NMR (600 MHz, $CDCl_3$) δ 8.93 (dd, *J* = 4.2, 1.7 Hz, 2H, ArH), 8.17 (dd, *J* = 8.3, 1.7 Hz, 2H, ArH), 7.85 (s, 2H, triazole-H), 7.57 (d, *J* = 16.1 Hz, 2H, trans C=CH), 7.51 – 7.43 (m, 8H, ArH), 7.42 (dd, *J* = 8.3, 1.4 Hz, 2H, ArH), 7.32 (dd, *J* = 7.6, 1.4 Hz, 2H, ArH), 7.12 (d, *J* = 16.2 Hz, 2H, trans C=CH), 7.07 – 7.02 (m, 2H, ArH), 7.02 – 6.97 (m, 2H, ArH), 6.82 – 6.77 (m, 4H, ArH), 6.52 (s, 2H, pyrrole-CH), 5.55 (s, 4H, $-OCH_2$), 4.43 (t, *J* = 7.1 Hz, 4H, $-CH_2N$), 3.95 (t, *J* = 5.9 Hz, 4H, $-OCH_2$), 2.15 – 2.07 (m, 4H, $-CH_2$-), 1.80 (m, 4H, $-CH_2$-), 1.43 (s, 6H, $-CH_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.38, 153.76, 152.48, 149.21, 144.36, 144.19, 144.08, 141.72, 140.07, 138.45, 136.36, 135.56, 133.60, 129.84, 129.76, 129.60, 129.02,

126.91, 123.15, 121.76, 120.28, 117.48, 117.29, 116.18, 114.64, 110.03, 66.97, 63.11, 50.13, 27.20, 26.19, 14.82. MALDI-TOF MS (DHB) m/z Calc.: 1108.47; found: 1109.195 $[M+H]^+$, $[M-F]^+$ calc.: 1091.07; found: 1090.379, $[M+Na]^+$ calc.: 1131.04; found: 1132.011 (Fig. 3b).

3. Results and Discussion

Figure **4** illustrates the multiple steps that were involved in the synthesis of the BODIPY-quinoline molecule. Briefly, unsubstituted BODIPY (**3**) and aldehyde derivatives **1** and **2** were synthesized. The following Knoevenagel reaction between BODIPY (**3**) and compound **2** gave distyryl-BODIPY (**4**) bearing functional azido groups for click reactions. The desired BODIPY-quinoline molecule was then obtained by click reaction between BODIPY **4** and propargyl quinoline (**5**). All products were purified by column chromatography and structural characterization of **4** and **6** were successfully identified by mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy techniques.

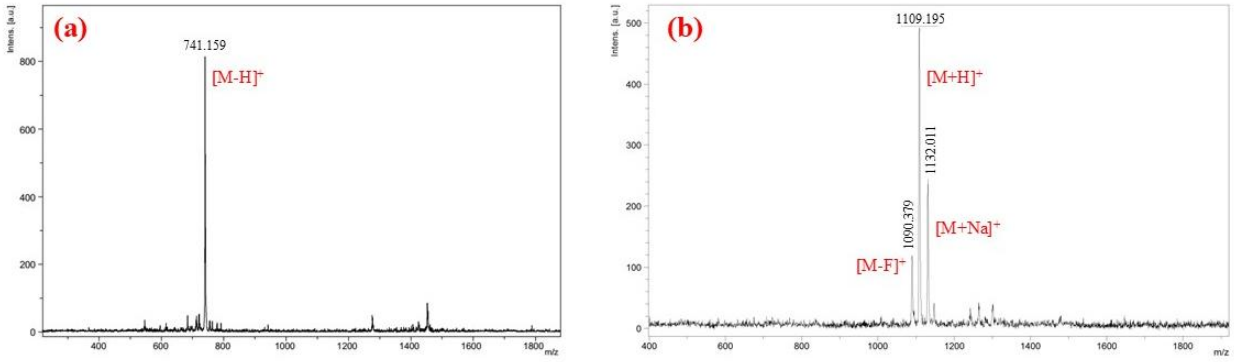

Figure 3. MALDI- MS spectra of (a) compound 4, (b) compound 6

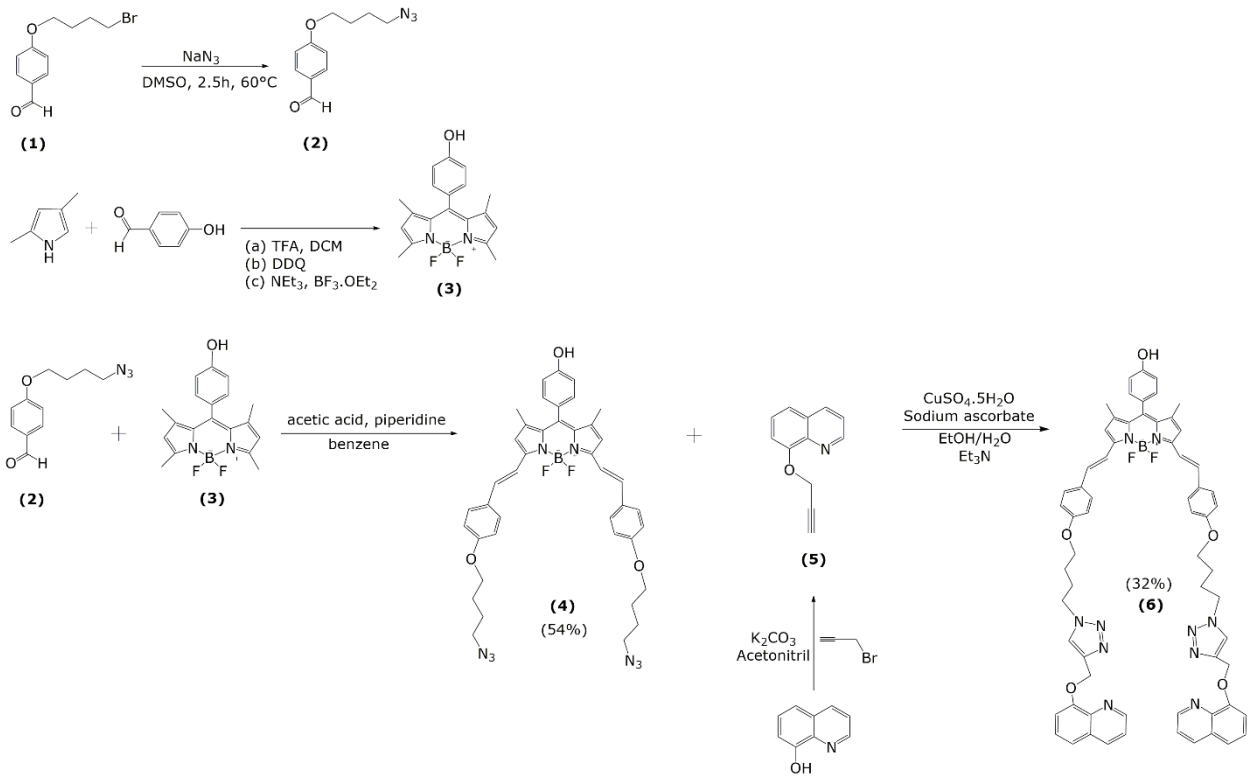

Figure 4. Synthesis route of the BODIPY-quinoline compound.

The results were in line with the formulations assigned to them. The molecular ion peak of the azido-BODIPY unit (**4**) was marked as 741.159 while that of the BODIPY-quinoline derivative (**6**) was measured as

1109.195 by MALDI-TOF mass spectrometer. The spectra of compound **6** revealed the peak groups representing the $[M]^+$, $[M-F]^+$ and $[M+Na]^+$ ions (Fig.3).

The ^{1}H NMR spectra of the compound **6** was evaluated in comparison to that of the BODIPY unit (**4**). In the well-resolved ^{1}H NMR spectra of compound **6**, the singlet signal at δ 7.85 corresponding to the triazole ring proton confirmed the formation of 1,2,3-triazole. *trans*=CH with the *E* conformation on the styryl units were detected as doublets at 7.12 and 7.57 ppm with coupling constant of ~16 Hz. The β-pyrrole protons appeared as a singlet at 6.52 ppm as expected. The quinoline protons were observed at 7.31, 7.42, 8.17 and 8.93 ppm as doublet to doublet. The other aromatic protons in both BODIPY and quinoline units were marked between 7.43-7.51 ppm. The aliphatic $-CH_2$ moieties on the structure were distinguished as singlet, triplet and multiplet where $-CH_3$ protons on the BODIPY core were detected at 1.44 ppm as a singlet (Fig. 6).

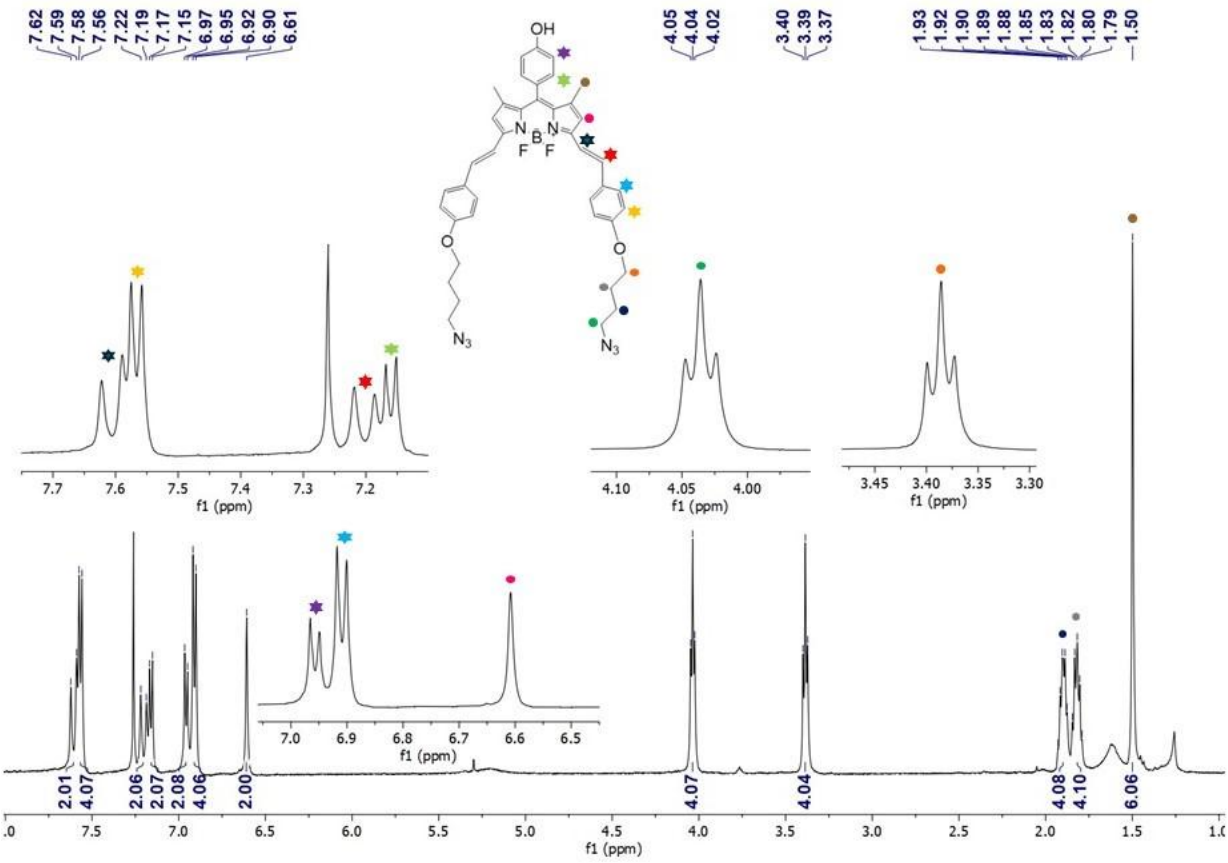

Figure 5. ^{1}H- NMR spectra of compound 4 in $CDCl_3$.

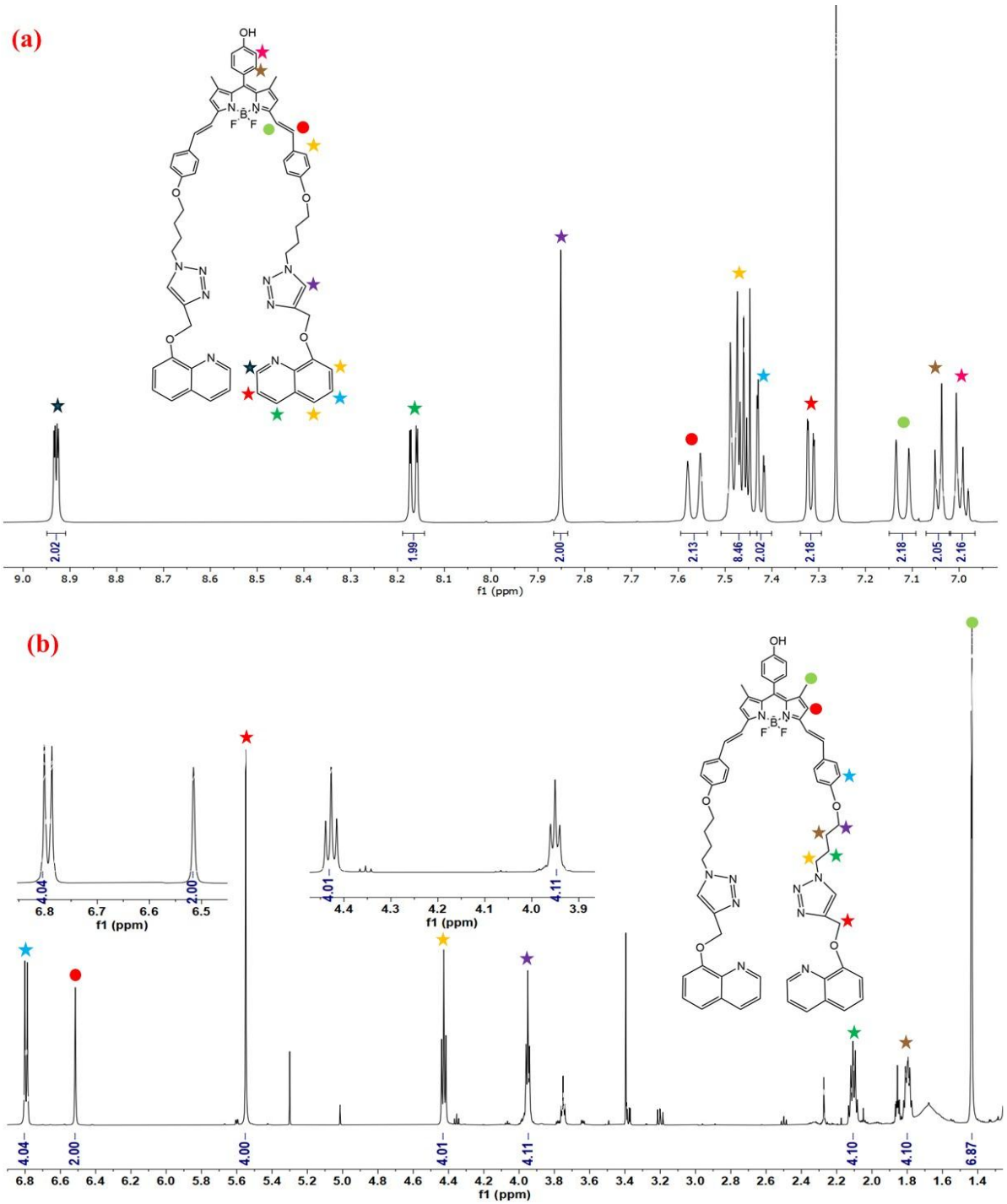

Figure 6. ^{1}H- NMR spectra of (a) compound 6 (7-9 ppm), (b) compound 6 (1-7 ppm) in $CDCl_3$.

The 13C NMR spectral data of the compounds were also consistent with the molecular structures (Fig. 7). In the spectra, the signals of sp2 carbon atoms belonging to aromatic and alkene groups in the structures appeared in the range of 110-160 ppm. It can be seen that the number of peaks in this region for compound 6 increases with the addition of quinoline groups to the structure. Methyl groups in the BODIPY moiety and other aliphatic sp3 carbon atoms resonated in the range of 14-67 ppm. In the 13C NMR spectrum of compound 6, the number of peaks in the alphatic region increases by one due to the methylene groups remaining between the triazole ring formed by the click reaction and quinoline (quinoline-CH2-triazole).

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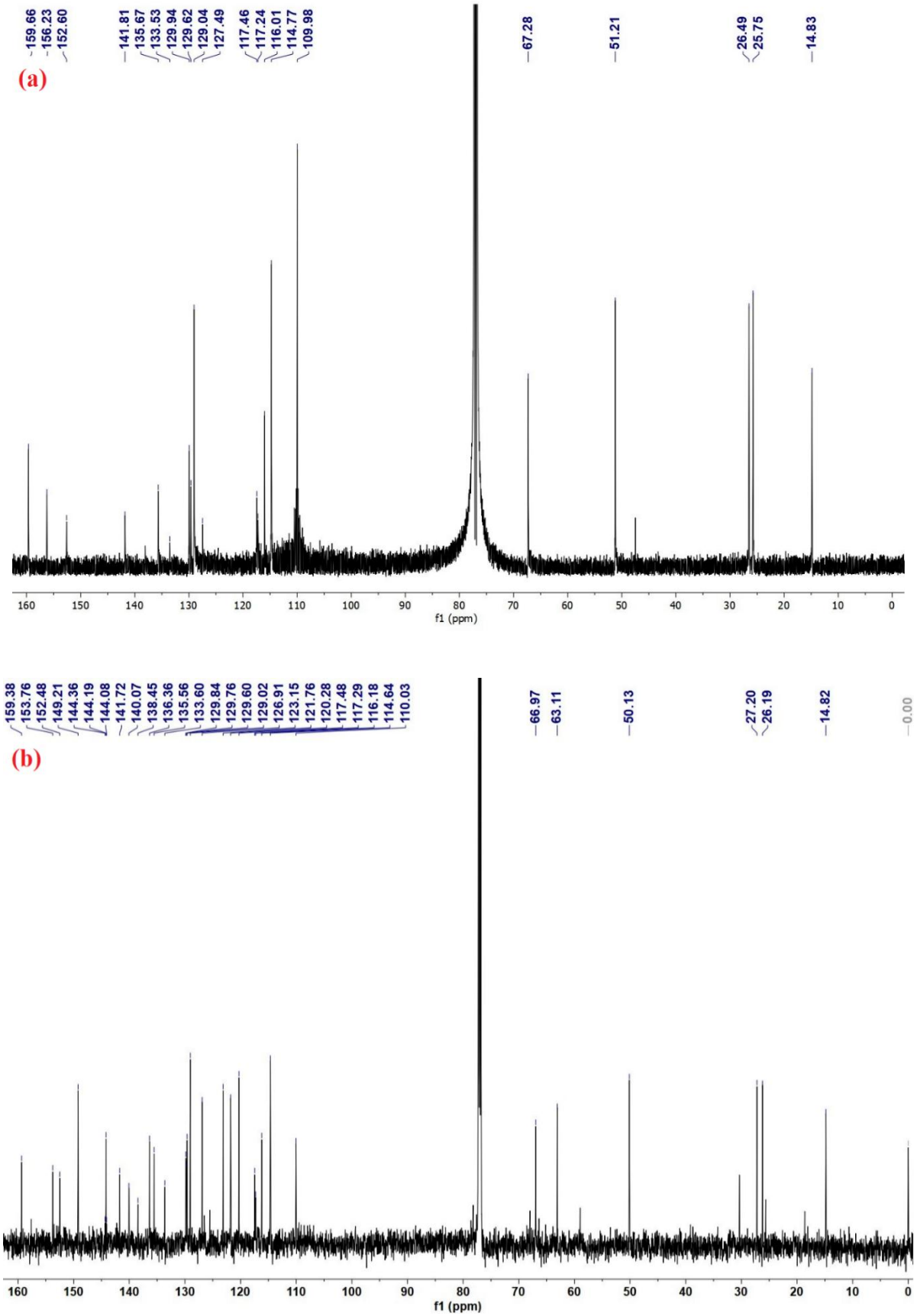

Figure 7. ^{13}C- NMR spectra of (a) compound 4, (b) compound 6 in $CDCl_3$

4. Conclusion

This study presents the synthesis and characterisation of a novel BODIPY quinoline compound. A synthetic strategy based on well-known reactions is presented for the design of this BODIPY derivative. The introduction of quinoline substituents at positions 3 and 5 of the BODIPY by click reaction allows the formation of binding sites for metal ions. So, the findings of this study may contribute to the development of new materials for sensor applications. In future work, we will synthesize the water-soluble derivative of the BODIPY-quinoline molecule introduced in this paper and study its photophysical properties and applications as sensors.

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Author's Contributions

Semiha Yıldırım Sarıkaya: The design of the molecule, performing experiments, interpreting the results, project administration and writing – original draft.

Ethics

There are no ethical issues after the publication of this manuscript.

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