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BODIPY derivatives: synthesis and evaluation of their optical properties †

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Abstract: Three BODIPY derivatives functionalized at *meso* and 2 position were synthesized in 22-59% yield. The compounds were characterized by the usual spectroscopic techniques and a photophysical study was also undertaken. The BODIPY derivatives presented absorption bands in the 494-512 nm range and were also emissive with fluorescence bands in the 512-514 nm interval. A preliminary study on the sensing ability of BODIPY functionalized at position 2 with a benzimidazole was carried out in acetonitrile and acetonitrile/water (75:25) solutions in the presence of anions and cations with environmental, biomedical and analytical relevance. A highly selective response was obtained for Hg^{2+} and Fe^{3+} in acetonitrile/water solution.

Keywords: BODIPY; Chemosensors; Fluorescence; Labelling

1. Introduction

3-Difluoroborodipyrromethene, commonly known as BODIPY, has been used in many innovative applications such as biological fluorescent labelling, electroluminescent devices, tunable laser dyes, components for solid state solar cells, photodynamic therapy and optical sensors (fluorimetric or colorimetric). The numerous desirable properties of BODIPY explain its growing success over recent years. It is endowed with chemical, structural and photochemical stability, both in solution and in solid state. Furthermore, it possesses a high coefficient of molar absorptivity, high quantum yield of fluorescence, negligible triplet formation and narrow band emission with high intensity peaks. Furthermore, its photophysical properties can be tuned/improved introducing groups at suitable positions in the BODIPY core [1-4].

In continuation of the work developed in our research group [5-6], we report in this communication the synthesis, characterization and evaluation of the optical properties of BODIPY derivatives having in mind their potential application as novel chromofluorogenic sensors and/or fluorescent probes for the detection of molecules, cations and anions with biological and medicinal relevance.

2. Experimental Section

2.1. Methods and Materials

NMR spectra were obtained on a Bruker Avance III 400 at an operating frequency of 400 MHz for ^{1}H and 100.6 MHz for ^{13}C, using the solvent peak as internal reference. The solvents are indicated in parenthesis before the chemical shifts values (δ relative to TMS). Peak assignments were made by comparison of chemical shifts, peak multiplicities and J values, and were supported by spin decoupling-double resonance and bidimensional heteronuclear techniques. All reagents were purchased from Sigma-Aldrich, Acros and Fluka and used as received. TLC analysis were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F254) and the spots were visualized under UV light. Chromatography on silica gel was carried out on Merck Kieselgel (230-

400 mesh). UV-visible absorption spectra were obtained using a Shimadzu UV/2501PC spectrophotometer. Fluorescence spectra were collected using a FluoroMax-4 spectrofluorometer. The relative fluorescence quantum yields were determined by using a 1×10^{-5} M solution of Rhodamine 6G in ethanol as standard ($\Phi_F = 0.95$) [7].

2.2 Synthesis of BODIPY derivatives

2.2.1 BODIPY derivative **1**

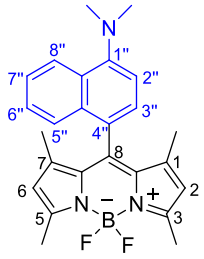


Figure 1. Structure of BODIPY derivative **1**.

2,4-Dimethylpyrrole (1.4 mmol) and 4-dimethylamino-1-naphthaldehyde (1.0 mmol) were dissolved in dry dichloromethane (100 mL). One drop of trifluoroacetic acid was added and the mixture was allowed to stir for 50 min at room temperature under a N_2 atmosphere. A solution of DDQ (1.5 mmol) in dry dichloromethane (100 mL) was added to the mixture. Stirring was continued for another 50 min and then triethylamine (12 mmol) was added. After stirring for 15 min, $BF_3.OEt_2$ (20 mmol) was added and further stirred for 30 min. The mixture was evaporated under reduced pressure and the crude residue was subjected to a dry flash chromatography (petroleum ether/ethyl acetate, 4:1). The product was obtained as a red brownish solid (0.063 g, 22%).

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.09 (s, 6H, CH_3-1 and CH_3-7), 2.58 (s, 6H, CH_3-3 and CH_3-5), 3.05 (s, 6H, $N(CH_3)_2$), 5.94 (s, 2H, H-2 and H-6), 7.24 (d, J=7.6 Hz, 1H, H-2′), 7.30 (d, J=7.6 Hz, 1H, H-3′), 7.44 (dt, J=1.2 and 7.2 Hz, 1H, H-7′), 7.54 (dt, J=1.2 and 7.4 Hz, H-6′), 7.77 (d, J=8.4 Hz, 1H, H-5′), 8.31 (d, J=8.4 Hz, 1H, H-8′) ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ =13.89, 14.60, 45.53, 114.08, 121.07, 123.80, 125.45, 125.83, 126.16, 127.18, 127.80, 128.04, 132.19, 132.95, 140.36, 143.01, 155.43 ppm.

2.2.2. BODIPY derivative **2**

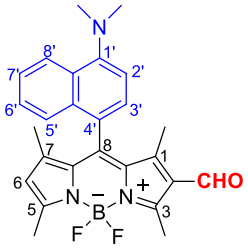


Figure 2. Structure of BODIPY derivative **2**.

A mixture of DMF (23 mmol) and $POCl_3$ (18.2 mmol) was stirred for 5 minutes at 0 °C under a N_2 atmosphere. Once the mixture reached room temperature, it was allowed to stir for 30 minutes. Then, compound **1** (0.127 mmol) dissolved in dichloroethane (7 mL) was added dropwise with stirring. The reaction mixture was then heated for 2 h at 50 °C. After cooling, the solution was poured slowly into 40 mL of saturated sodium bicarbonate solution at 0 °C and stirred during 30 min at room temperature. Ethyl acetate (5 mL) was added to the reaction mixture and the resulting organic layer separated and washed with water (2 × 50 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated. The crude residue was purified through a silica gel

chromatography column, using dichloromethane as eluent. The product was obtained as a dark red solid (0.032 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.12 (s, 3H, CH_3-7), 1.37 (s, 3H, CH_3-1), 2.64 (s, 3H, CH_3-5), 2.84 (s, 3H, CH_3-3), 3.13 (s, 6H, $N(CH_3)_2$), 6.11 (s, 1H, H-6), 7.33 (m, 2H, H-2′ and H-3′), 7.48 (t, J=7.6 Hz, 1H, H-7′), 7.62 (t, J=7.6 Hz, H-6′), 7.72 (d, J=8.4 Hz, 1H, H-5′), 8.31 (s, 1H, H-8′), 9.94 (s, 1H, CHO) ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ=10.99, 13.03, 14.12, 15.09, 45.69, 124.01, 125.21, 125.60, 127.90, 132.75, 134.79, 142.51, 156.58, 162.77, 171.15, 175.26, 185.87 ppm.

2.2.3. BODIPY derivative **3**

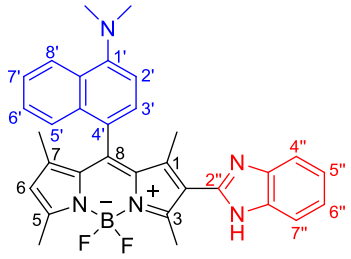


Figure 3. Structure of BODIPY derivative **3**.

The previous prepared compound **2** (0.11 mmol), ethanol (10 mL) and $NaHSO_3$ (0.10 mmol) were added in a round bottomed flask. The reaction mixture was stirred at room temperature for 4 h. Then, dry DMF (5 mL) and o-phenylenediamine (0.08 mmol) were added and the solution was heated for 2 h at 80 °C. The reaction mixture was cooled to room temperature, ethyl acetate was added (10 mL) and the mixture was washed with water (3 × 10 mL). The organic phase was dried with anhydrous $MgSO_4$, the solution was filtered and the solvent was evaporated to dryness. The resulting crude product was purified by a silica gel chromatography column using dichloromethane as eluent and was obtained as a red solid (0.015 g, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.10 (s, 3H, CH_3-7), 1.25 (s, 3H, CH_3-1), 2.63 (s, 3H, CH_3-5), 2.76 (s, 3H, CH_3-3), 2.90 (s, 6H, $N(CH_3)_2$), 6.05 (s, 1H, H-6), 7.03 (d, J=7.6 Hz, 1H, H-2′), 7.08 (d, J=7.6 Hz, 1H, H-3′), 7.21-7.25 (m, 2H, H-5′′ and H-6′′), 7.27 (s, 1H, H-7′), 7.40 (t, J=1.2 and 7.6 Hz, H-6′), 7.51-7.53 (m, 2H, H-4′′ and H-7′′), 7.58 (d, J=8 Hz, 1H, H-5′), 8.19 (d, J=8.4 Hz, 1H, H-8′) ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ =12.36, 13.57, 14.21, 14.93, 45.07, 113.44, 114.57, 122.88, 123.43, 124.51, 124.98, 125.54, 125.82, 127.06, 131.22, 132.61, 134.12, 136.41, 139.91, 142.28, 145.75, 146.19, 152.35, 152.46, 159.54 ppm.

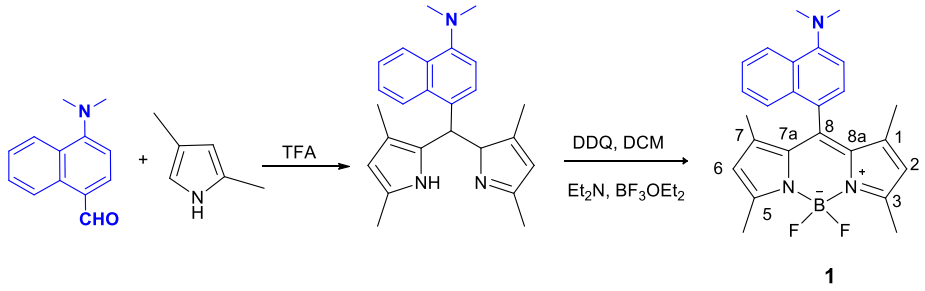
2.3. Study on the sensing ability of BODIPY derivative ***3***

Evaluation of BODIPY derivative **3** as a colorimetric chemosensor was carried out in the presence of several ions (AcO^-, F^-, Cl^-, CN^-, NO_3^-, BzO^-, $H_2PO_4^-$, HSO_4^-, Cu^{2+}, Co^{2+}, Pd^{2+}, Ni^{2+}, Ca^{2+}, Hg^{2+}, Zn^{2+}, Fe^{2+}, Fe^{3+} and Na^+) with environmental, biomedical and analytical relevance. Solutions of the compound (1×10^{-5} M) and of the ions under study (1×10^{-2} M) were prepared in acetonitrile and acetonitrile/water (75:25). Preliminary tests were carried out by addition of up to 50 equivalents of each ion to the solution of BODIPY derivative **3** in acetonitrile and in mixture of acetonitrile/water.

3. Results and Discussion

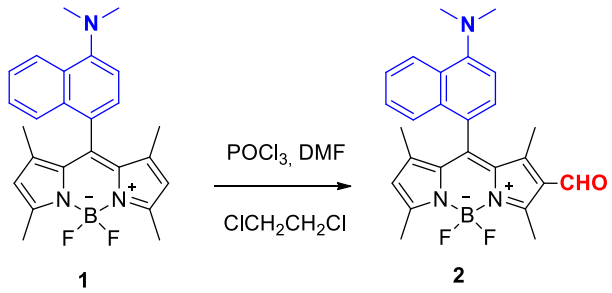
3.1. Synthesis of BODIPY derivatives

BODIPY derivative **1** functionalized at the *meso* position was synthesized in two reactional steps. Initially, the condensation reaction of 2,4-dimethylpyrrole and 4-dimethylamino-1-naphthaldehyde in the presence of TFA as catalyst was carried out. The second reactional step consisted in the oxidation of the condensed precursor by DDQ followed by reaction with BF_3OEt_2. The residue was purified by a dry flash chromatography column. The product was obtained as a red brownish solid in 22% yield (Scheme 1). ^1H and ^{13}C NMR spectroscopy of compound **1** confirmed the proposed structure.



Scheme 1. Synthesis of BODIPY derivative **1**.

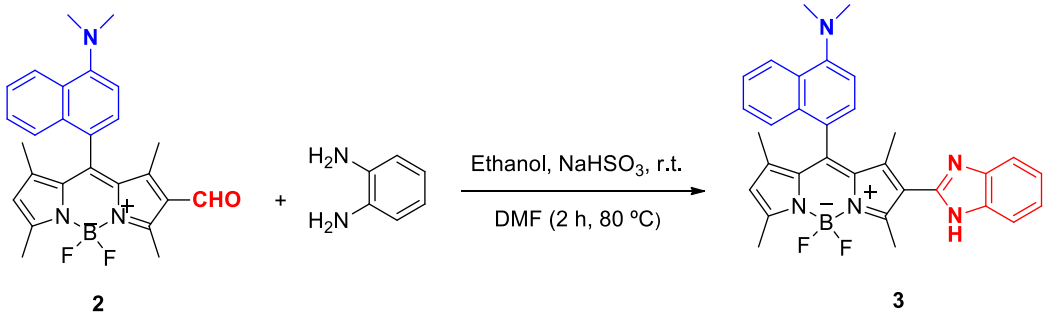
The synthesis of BODIPY derivative **2** was obtained through Vilsmeier formylation of BODIPY **1** using DMF/ $POCl_3$ as Vilsmeier- Haack reagent giving the corresponding formylated BODIPY derivative **2** as a dark red solid in 59% yield (Scheme 2).



Scheme 2. Synthesis of BODIPY derivative **2**.

The presence of formyl group at position 2 of the BODIPY nucleus was confirmed by ^1H NMR spectroscopy, with the appearance of a singlet at δ 9.94 ppm.

The synthesis of BODIPY derivative **3** consisted in a condensation reaction of *o*-phenylenediamine with compound **2** in the presence of $NaHSO_3$ as activating agent of the diamine (Scheme 3). The pure BODIPY derivative **3** functionalized with a benzimidazole group was obtained as a red solid in 31% yield after purification through dry flash chromatography.



Scheme 3. Synthesis of BODIPY derivative **3**.

The presence of the benzimidazole ring in compound **3** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum was possible to identify the signals corresponding to the aromatic protons of the benzimidazole moiety, with two multiplets in the range 7.21-7.25 ppm due to the 5'' and 6'' protons and at 7.51-7.53 ppm due to the 4'' and 7'' protons.

3.2. Photophysical characterization of BODIPY derivatives

The spectroscopic characterization of the three compounds was carried out in of acetonitrile solutions. The BODIPY derivatives showed intense absorption bands (log ε = 4.58-4.75) in the range of 494-512 nm (Table 1).

Table 1. UV-visible absorption and emission data for BODIPY derivatives **1-3**.

BODIPY derivatives	**UV-vis**		**Fluorescence**		
	λ_{max} (nm)	log ε	λ_{em} (nm)	Φ_F	Stokes' shift (nm)
1	500	4.58	512	0.117	12
2	494	4.75	512	0.148	15
3	512	4.75	514	0.031	2

The position of the absorption bands depended on the structure and electronic character of the substituent groups at position 2 of the BODIPY nucleus. The results showed that the functionalization of the BODIPY moiety with an electron-deficient heterocycle (compound **3**) gave rise to a bathochromic shift of 12 nm compared to BODIPY **1**, which can be attributed to the increase of extension of the π-conjugated system. Moreover, upon excitation at the corresponding maximum wavelength of absorption, the compounds showed emission bands in the 512-514 nm range. The relative fluorescence quantum yields were determined using a solution of Rhodamine 6G in ethanol as standard (Φ_F = 0.95) [7]. The BODIPY derivative **3** exhibited weak emissive properties (Φ_F = 0.031), while compound **2** showed a higher relative quantum fluorescence yield (Φ_F = 0.148).

3.3. Preliminary study on the sensing ability of BODIPY derivative 3

Evaluation of the BODIPY derivative **3** as an optical chemosensor was carried out in acetonitrile and acetonitrile/water (75:25) solutions, in the presence of several ions. The preliminary study was carried out by addition of up to 50 equivalents of each ion to the solution of compound **3** in acetonitrile. It was observed that the compound displayed a marked colour change, from pale pink to orange, upon interaction with Cu^{2+}, Pd^{2+}, Zn^{2+} and Co^{2+}, from pale pink to yellow with Fe^{2+}, Hg^{2+}, Fe^{3+} and Ni^{2+}. The same solutions were analyzed under UV lamp at 365 nm and solutions containing

Fe^{2+}, Hg^{2+} and Ni^{2+} exhibited an intense fluorescence. The interaction of the BODIPY derivative **3** with Cu^{2+}, Pd^{2+} and Fe^{3+} also resulted in an increase of fluorescence but with lower intensity (Figure 4).

Figure 4. Evaluation of BODIPY derivative **3** as colorimetric (top) and fluorimetric (bottom) chemosensor for several ions in acetonitrile solutions.

A similar preliminary chemosensor study was performed in an acetonitrile/water (75:25) solution, confirming the selectivity of compound **3** as a colorimetric chemosensor for Hg^{2+} (colour change from pink to pale yellow) and for Fe^{3+} (colour change from pink to orange). As a fluorimetric chemosensor, it was observed a change of emission for both cations from the blue to green region (Figure 5).

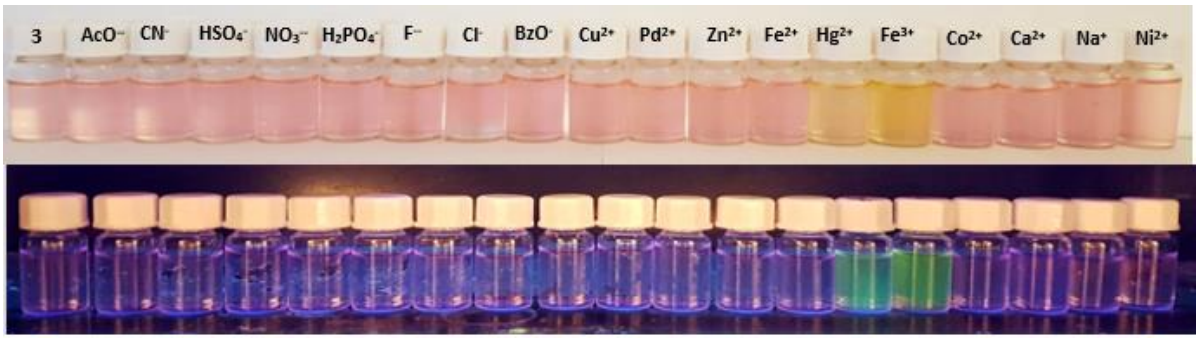


Figure 5. Evaluation of BODIPY derivative **3** as colorimetric (top) and fluorimetric (bottom) chemosensor for several ions in acetonitrile/water (75:25) solution.

These results demonstrated the potential of BODIPY derivative **3** to act as an efficient optical chemosensor for Hg^{2+} and Fe^{3+} in environment and biological samples, considering that the analysis should be carried out in aqueous solutions.

4. Conclusions

Three BODIPY derivatives **1**-**3** were synthesized in fair to moderate yields. Compound **1** was synthesized through a condensation reaction between 2,4-dimethylpyrrole and 4-dimethylamino-1-naphthaldehyde. Functionalization of compound **1** through Vilsmeier formylation gave BODIPY derivative **2**. Moreover, BODIPY **3** was prepared through condensation-cyclization reaction between formyl precursor **2** and *o*-phenylenediamine. All the compounds were characterized by the usual spectroscopic techniques and a photophysical study was also undertaken.

The chemosensory ability of BODIPY derivative **3** was evaluated for several ions in acetonitrile and acetonitrile/water (75:25) solutions revealing its selectivity as a colorimetric and a fluorimetric chemosensor for Hg^{2+} and Fe^{3+} in aqueous solution. This result might be of interest for applications with environmental and biological samples.

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Conflicts of Interest: The authors declare no conflict of interest.

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