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BODIPY Derivatives: Synthesis and Evaluation of Their Optical Properties †

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Abstract: Three 3-difluoroborodipyrromethene (BODIPY) derivatives functionalized at the *meso* and 2 positions were synthesized with 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 a BODIPY derivative 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; labeling

1. Introduction

3-Difluoroborodipyrromethene, commonly known as BODIPY, has been used in many innovative applications such as biological fluorescent labeling, 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 the 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 by 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 **1**-**3** (Figures 1–3) with respect to 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 parentheses before the chemical shift values [(δ relative to trimethylsilane (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. Thin layer chromatography (TLC) analyses 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 ($\Phi_F = 0.95$) [7–8].

2.2. Synthesis of BODIPY Derivatives

2.2.1. BODIPY Derivative **1**

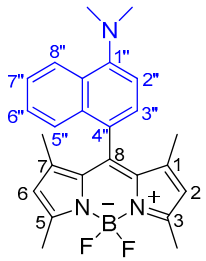


Figure 1. Structure of 3-difluoroborodipyrromethene (BODIPY) derivative **1**.

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 (TFA) was added and the mixture was allowed to stir for 50 min at room temperature under an N_2 atmosphere. A solution of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (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 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**

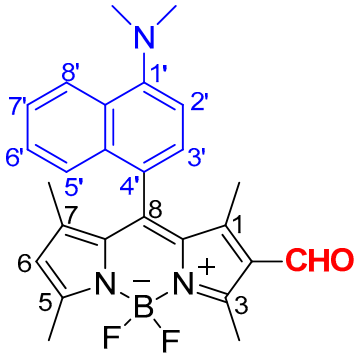


Figure 2. Structure of BODIPY derivative **2**.

A mixture of dimethylformamide (DMF) (23 mmol) and $POCl_3$ (18.2 mmol) was stirred for 5 min at 0 °C under an N_2 atmosphere. Once the mixture reached room temperature, it was allowed to stir for 30 min. 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 for 30 min at room temperature. Ethyl acetate (5 mL) was added to the reaction mixture, and the resulting organic layer was 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**

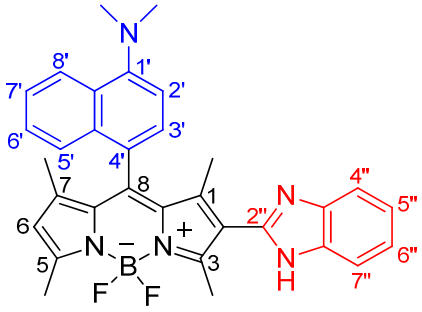


Figure 3. Structure of BODIPY derivative **3**.

The previously prepared compound **2** (0.11 mmol), ethanol (10 mL), and $NaHSO_3$ (0.10 mmol) were added to 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.

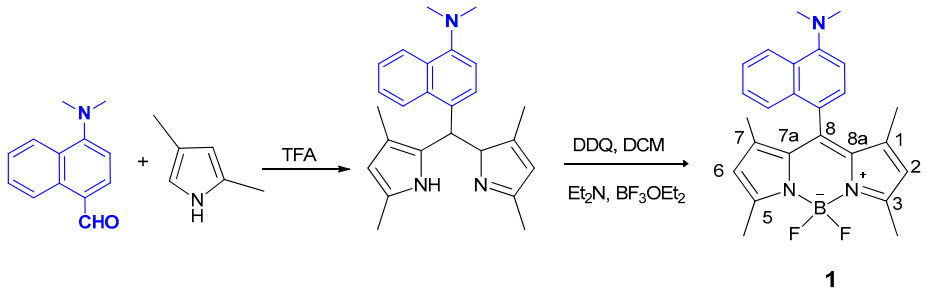
2.3. Study on the Sensing Ability of BODIPY Derivative 3

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 the mixture of acetonitrile/water.

3. Results and Discussion

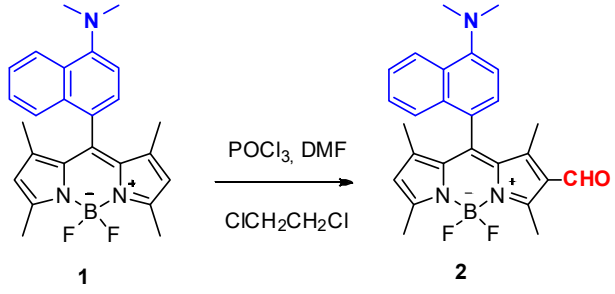
3.1. Synthesis of BODIPY Derivatives

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 of the oxidation of the condensed precursor by DDQ, followed by reaction with $BF_3.OEt_2$. The residue was purified by a dry flash chromatography column. The product was obtained as a red-brownish solid in 22% yield (Scheme 1). ^{1}H and ^{13}C NMR spectroscopy of compound **1** confirmed the proposed structure.



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

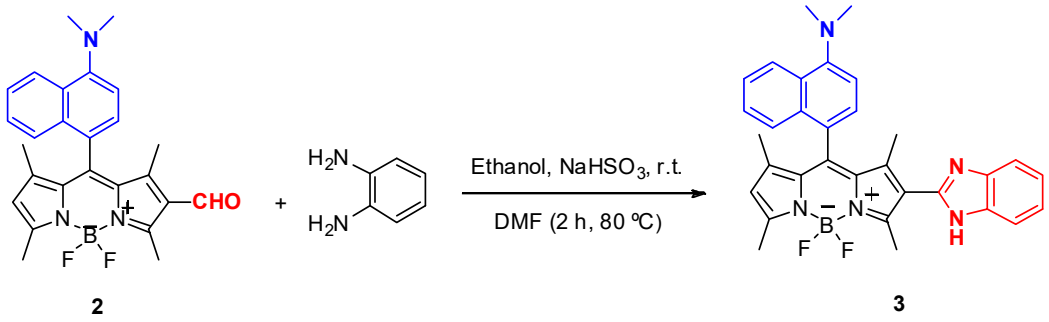
The synthesis of BODIPY derivative **2** was obtained through Vilsmeier formylation of BODIPY **1** using DMF/ $POCl_3$ as the Vilsmeier–Haack reagent, giving the corresponding formylated BODIPY derivative **2** as a dark red solid in 59% yield (Scheme 2).



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

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

The synthesis of BODIPY derivative **3** consisted of a condensation reaction of *o*-phenylenediamine with compound **2** in the presence of $NaHSO_3$ as the 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.



2 **3**

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, it 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 depend 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 the standard (Φ_F = 0.95) [7-8]. 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 the addition of up to 50 equivalents of each ion to the solution of compound **3** in acetonitrile. It was observed that the compound displayed marked color changes from pale pink to orange upon interaction with Cu^{2+}, Pd^{2+}, Zn^{2+}, and Co^{2+}, and from pale pink to yellow with Fe^{2+}, Hg^{2+},

Fe^{3+}, and Ni^{2+}. The same solutions were analyzed under a 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).

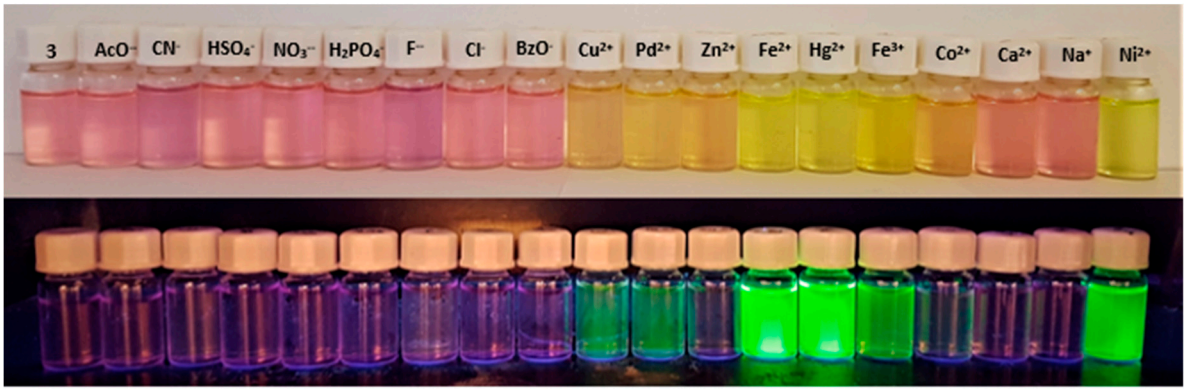


Figure 4. Evaluation of BODIPY derivative **3** as a colorimetric (top) and fluorimetric (bottom) chemosensor for several ions in acetonitrile solutions.

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+} (color change from pink to pale yellow) and for Fe^{3+} (color change from pink to orange). As a fluorimetric chemosensor, a change of emission for both cations from the blue to green region (Figure 5) was observed.

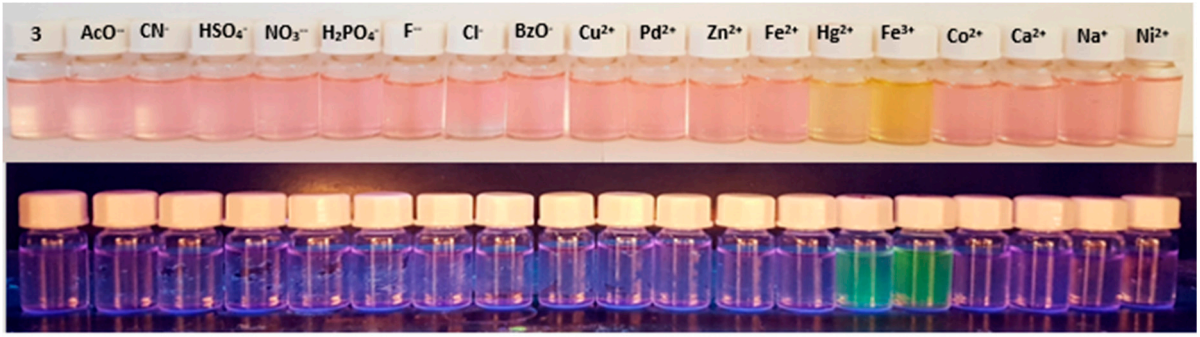


Figure 5. Evaluation of BODIPY derivative **3** as colorimetric (top) and fluorimetric (bottom) chemosensor for several ions in acetonitrile/water (75:25) solution.

These results demonstrated the potential of BODIPY derivative **3** to act as an efficient optical chemosensor for Hg^{2+} and Fe^{3+} in environmental 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.

References

1. Boens, N.; Leen, V.; Dehaen, W. Fluorescent indicators based on BODIPY. *Chem. Soc. Rev.* **2012**, *41*, 1130–1172. 10.1039/C1CS15132K.
2. Loudet, A.; Burgess, K. BODIPY dyes and their derivatives: Syntheses and spectroscopic properties. *Chem. Rev.* **2007**, *107*, 4891–4932. 10.1021/cr078381n.
3. Wu, D.; Sedgwick, A.C.; Gunnlaugsson, T.; Akkaya, E.U.; Yoon, J.; James, T.D. Fluorescent chemosensors: The past, present and future. *Chem. Soc. Rev*. **2017**, *46*, 7105–7123. 10.1039/c7cs00240h.
4. Freidus, L.G.; Pradeep, P.; Kumar, P.; Choonara, Y.E.; Pillay, V. Alternative fluorophores designed for advanced molecular imaging. *Drug Discov. Today* **2018**, *23*, 115–133. 10.1016/j.drudis.2017.09.008.
5. Presti, M.L.; Martínez-Máñez, R.; Ros-Lis, J.V.; Batista, R.M.F.; Costa, S.P.G.; Raposo, M.M.M., Sancenón, F. A dual channel sulphur-containing macrocycle functionalised BODIPY probe for the detection of Hg(II) in mixed aqueous solution. *New J. Chem.* **2018**, *42*, 7863–7868. 10.1039/c7nj04699e.
6. Collado, D.; Casado, J.; González, S.R.; Navarrete, J.T.L.; Suau, R.; Perez-Inestrosa, E.; Pappenfus, T.M.; Raposo, M.M.M. Enhanced functionality for donor-acceptor oligothiophenes via inclusion of BODIPY: Synthesis, electrochemistry, photophysics and model chemistry. *Chem. Eur. J.* **2011**, *17*, 498–507. 10.1002/chem.201001942.
7. Montalti, M.; Credi, A.; Prodi, L.; Gandolfi, M.T. *Handbook of Photochemistry*, 3rd ed.; CRC Press: Boca Raton, FL, USA, 2006.
8. Demas, J.N.; Crosby, G.A. Measurement of photoluminescence quantum yields. Review. *J. Phys. Chem.* **1971**, *75*, 991–1024. 10.1021/j100678a001.