Impact of The Arylation of N-Bridged Annulated BODIPY Dyes In Photophysical Properties

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Short Report

Keywords: BODIPY, heterocyclic fusion, arylation, batochromic effect

Posted Date: July 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-573621/v1

Abstract

Functionalization of BODIPY dyes is commonly used to modulate photophysical properties. Among the chemical modification of these dyes, ring fusion indifferent faces of dipyrromethene cores is gaining attention in the literature, due to the modulation ofemission/absorption properties and fluorophores with increased bright. N-bridged annulated BODIPYs were recently synthesized and shows intense bright and blu shifted emission. However, few examples of substituted compounds are described and none involving arylation with extention of the p-conjugation. In this manuscript, it is shown an optimized method for the synthesis of N-bridged annulated BODIPYs, including arylated derivatives, and the studies of molecular properties. It is also shown that fluorinated aryl substituted N-bridged annulated BODIPYs show high quantum yields and are red-shifted compared to unsubstituted examples. The work open opportunities for application of the new developed compounds as probes.

Introduction

BODIPY is a class of fluorescent dyes with several applications as probes within diverse areas, incuding in biology [1]. Compared to other fluorescent dyes as anthracenes, coumarins rhodamine, fluorescein, cyanine [2, 3], BODIPY is considered to be stable, versatile in terms of applications and reactivity. In fact, there are many examples of BODIPY functionalization in the literature, showing the modulation of fluorescence emission/absortion, quantum yields and other photophysical properties. Among the chemical modifications of BODIPY cores, the ring fusion to different faces of the dipyrromethene scaffold, is gaining attention in the literature, as shown in Fig. 1 [4–7, 8, 9].

N-bridged annulated BODIPY were recently described in the literature [10], showing an interesting method for developing new dyes with very high quantum yields and blue-shifted fluorescence absorption and emission compared to other general BODIPY dyes. However, little is known about the heterocyclization toward these N-bridged annulated BODIPY systems using substituted BODIPYs and the impact of this complex structures to photophysical properties. Arylation of BODIPYs is a commom chemical approach to produce red-shifted derivatives, which are useful as photosensitizers and biological applications [11]. To this purpose, we studied the synthesis of arylated quinoline-fused BODIPYs and the consequences of this functionalization on photophysical properties.

Experimental

Reagents were obtained from Sigma-Aldrich Brasil Ltd. (São Paulo, SP—Brazil) and were readily used in the synthetic procedures. Solvents were obtained from local suppliers and treated according to established purification protocols. The structures of the BODIPYs synthesized herein were determined by 75 MHz 13C-NMR and 300 MHz ^{1}H-NMR using a Bruker Ultrashield 300-MHz NMR system from Bruker Daltonics® (Billerica, MA, USA), and a high-resolution electrospray mass spectrometer (HRMS-ESI) using the ultrOTOFQ—ESI-TOF system from Bruker Daltonics ® (Billerica, MA, USA).

5,5-difluoro-10-(2-nitrophenyl)-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1, 3, 2]diazaborinine **1**.

2-Nitrobenzaldehyde (2.0 g, 13.2 mmol, 1.0 eq.) Was dissolved in distilled pyrrole (23 mL, 331 mmol, 25.0 eq.). TFA (100 µL, 1.3 mmol, 0.1 eq.) Was added and the mixture was stirred at room temperature for 10 minutes. The reaction was stopped by adding 0.1 M NaOH (45 ml). The organic phase was extracted with ethyl acetate (50 ml) and washed with distilled water (3 x 100 ml), dried over magnesium sulfate and concentrated under reduced pressure. 5- (2-nitrophenyl) XXXipyrromethene (3.21 g, 12 mmol, 1.0 eq.) Was dissolved in dichloromethane (150 ml). A solution of DDQ (2.73 g, 13 mmol, 1.0 eq.) in dichloromethane (100 mL) was added and the mixture was stirred at room temperature for 30 minutes. Triethylamine (10 mL, 72 mmol, 6.0 eq.) was added to the mixture and the reaction medium was kept under stirring for 1 hour. Boron trifluoride ether (13.3 mL, 108 mmol, 9.0 eq.) was added dropwise and the reaction medium stirred for an additional 2 hours. The reactional misture as washed with water (4x), saturated NaCl solution (1x), dried with sodium sulfate, filtered and evaporate the solvent. The product was purified over flash chromatographic column DCM / Hex 50–70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25–8.19 (m, 1H), 7.95 (s, 2H), 7.82–7.71 (m, 2H), 7.57 (dd, J = 6.9, 2.0 Hz, 1H), 6.67 (d, J = 4.1 Hz, 2H), 6.51 (d, J = 3.9 Hz, 2H). HRME (ESI) calculated for $C_{15}H_{10}BF_2N_3O_2$ $[M + Na]^+$: 336.0726, obtained: 336.0740 (S1).

4,4-difluoro-4,7-dihydro-3a,4aλ^4,7-triaza-4λ^4-boracyclopenta[a]acephenanthrylene **2.**

(313 mg 1 mmol) of Bodipy-nitro was dissolved in a vial containing 2 ml of DMA. Then PPh3 (2.5 mmol, 2.5 eq., 655.25 mg) was added and the reaction medium was placed under constant stirring and at elevated temperature at 165 ° C for 1 hour, when the total consumption was verified of the starting product and formation of the new product by thin layer chromatography. The reaction medium was poured into water, the product extracted using chloroform (3x) and the chloroform washed with distilled water (3X). The organic phase was dried using magnesium sulfate, filtered, and the product purified using a classic chromatographic column (eluent DCM / EtOAc 4: 1). ^{1}H NMR (300 MHz, Acetone) δ 8.92 (d, J = 8.6 Hz, 1H), 8.11 (s, 1H), 8.01–7.91 (m, 1H), 7.79 (t, J = 7.7 Hz, 1H), 7.60 (dd, J = 9.2, 6.2 Hz, 2H), 7.47 (s, 1H), 6.58 (d, J = 2.5 Hz, 1H), 6.46 (s, 1H). ^{13}C NMR (75 MHz, Acetone) δ 142.44, 139.01, 137.62, 131.73, 131.47, 127.81, 125.38, 120.31, 119.16, 119.14, 117.86, 114.07, 114.01, 96.36, 96.33. HRMS (ESI): Calculated for $C_{15}H_{10}BF_2N_3$, $[M + K]^+$: 319.0495, obtained: 319.0647 (S2).

5,5-difluoro-10-(2-nitrophenyl)-3,7-bis(4-(trifluoromethyl)phenyl)-5H-4λ^4,5λ^4-dipyrrolo[1,2-c:2',1'-*f*][1, 3, 2]diazaborinine **5.**

0.64 mmol (200 mg) of nitro bodipy was dissolved in 6 ml of acetone and then (2.5 eq.; 1.6 mmol; 645 mg) of the corresponding phenyldiazonium tetrafluorborate salt was added. A solution of (60 mg, 0.32 mmol) of ferrocene in 1.28 ml of acetone was added to the reaction medium dropwise (64 microliters every 5 minutes) over the course of 100 min. The reaction medium was kept under constant stirring for 30 min. At the end of the reaction period, the reaction medium was poured into 100 ml of ethyl ether, washed with distilled water 3 times, dried over sodium sulfate, filtered and evaporated. The reaction mixture was purified on a flash chromatographic column with a concentration gradient of 30–50% DCM

in Hexane to isolate the diarylate product in 32% yield. ^{1}H NMR (300 MHz, Acetone-d6) δ 8.39 (s, 2H), 8.17 (d, J = 7.1 Hz, 2H), 7.99 (ddt, J = 21.6, 14.0, 7.4 Hz, 3H), 7.81 (d, J = 7.3 Hz, 2H), 7.71 (t, J = 7.8 Hz, 2H), 6.96 (s, 3H). ^{13}C NMR (75 MHz, Acetone) δ 157.44, 149.16, 141.79, 136.42, 133.77, 133.16, 133.04, 132.86, 131.70, 130.35, 129.98, 129.30, 127.97, 126.32, 125.24, 122.41, 121.79. HRME (ESI) calculated for $C_{29}H_{16}BF_8N_3O_2$ $[M + Na]^+$: 624,1100, obtained: 624,1133 (S3).

5,5-difluoro-3,7-bis(4-fluorophenyl)-10-(2-nitrophenyl)-5H-4λ^4,5λ^4-dipyrrolo[1,2-c:2',1'-*f*][1, 3, 2]diazaborinine **6**.

0.64 mmol (200 mg) of nitro bodipy was dissolved in 6 ml of acetone and then (2.5 eq.; 1.6 mmol; 336 mg) of the corresponding phenyldiazonium tetrafluorborate salt was added. A solution of (60 mg, 0.32 mmol) of ferrocene in 1.28 ml of acetone was added to the reaction medium dropwise (64 µl every 5 minutes) over the course of 100 min. The reaction medium was kept under constant stirring for 30 min. At the end of the reaction period, the reaction medium was poured into 100 ml of ethyl ether, washed with distilled water 3 times, dried over sodium sulfate, filtered and evaporated. The reaction mixture was purified on a flash chromatographic column with a concentration gradient of 30–50% DCM in Hexane to isolate the diarylate product in 24% yield. ^{1}H NMR (300 MHz, Acetone-d6) δ 8.37 (dd, J = 7.9, 1.5 Hz, 1H), 8.04–7.95 (m, 6H), 7.90 (dd, J = 7.3, 1.7 Hz, 1H), 7.27 (t, J = 8.9 Hz, 2H), 6.89 (d, J = 4.3 Hz, 2H), 6.82 (d, J = 4.4 Hz, 2H). ^{13}C NMR (75 MHz, Acetone) δ 165.26, 161.97, 158.08, 149.29, 140.31, 136.00, 133.64, 132.89, 131.94, 131.51, 129.69, 128.78, 128.18, 125.11, 121.47, 115.35, 115.06. HRME (ESI) calculated for $C_{27}H_{16}BF_4N_3O_2$ $[M + Na]^+$: 524,1164, obtained: 524,1187 (S4).

4,4-difluoro-3,5-bis(4-(trifluoromethyl)phenyl)-4,7-dihydro-3a,4aλ^4,7-triaza-4λ^4-boracyclopenta[*a*]acephenanthrylene **7.**

In a vial containing 115 mg of BODIPY (1 eq.; 0.19 mmol), 253 mg of triphenylphosphine (5 eq,; 0.96 mmol) and 200 µl of dimethylacetamide were added. The atmosphere of the vial was replaced by N_2 and, later, sealed. The temperature of the reaction medium was raised to 180 ° C and maintained at that temperature and constant stirring for 120 min. After checking in TLC the total consumption of the starting product, the reaction medium was poured into ethyl ether and the resulting solution was washed with deionized water (3X), dried over sodium sulfate, filtered and evaporated. The product was isolated by flash chromatographic column using DCM: hexane 8: 1 as eluent in 25% yield. ^{1}H NMR (300 MHz, Acetone-d6) δ 9.06 (d, J = 8.5 Hz, 1H), 8.45 (s, 1H), 8.30–8.25 (m, 4H), 8.11–8.05 (m, 2H), 7.94 (t, J = 7.7 Hz, 1H), 7.82–7.61 (m, 8H), 6.97 (s, 1H), 6.78 (d, J = 3.9 Hz, 1H). ^{13}C NMR (75 MHz, Acetone) δ 200.82, 186.55, 169.15, 155.11, 144.25, 138.04, 136.79, 136.22, 133.83, 133.28, 132.50, 132.47, 131.03, 129.17, 128.76, 128.51, 127.78, 127.06, 126.32, 126.26, 125.88, 125.58, 124.73, 123.68, 123.63, 119.35, 117.45, 116.20, 96.88. HRME (ESI) calculated for $C_{29}H_{16}BF_8N_3$ $[M + Na]^+$: 592,1202, obtained: 592,1254 (S5).

4,4-difluoro-3,5-bis(4-fluorophenyl)-4,7-dihydro-3a,4aλ^4,7-triaza-4λ^4-boracyclopenta[a]acephenanthrylene **8.**

In a vial containing 71 mg of BODIPY (1 eq.; 0.14 mmol) 176 mg of triphenylphosphine (5 eq.; 0.71 mmol) and 200 µl of dimethylacetamide were added. The atmosphere of the vial was replaced by N_2 and subsequently sealed. The temperature of the reaction medium was raised to 180 ° C and maintained at that temperature and constant stirring for 120 min. After checking in TLC the total consumption of the starting product, the reaction medium was poured into ethyl ether and the resulting solution was washed with deionized water (3X), dried over sodium sulfate, filtered and evaporated. The product was isolated by flash chromatographic column using DCM / hexane 8 : 1 as eluent in 15% yield. ^{1}H NMR (300 MHz, Acetone-d6) δ 9.02 (d, J = 8.6 Hz, 1H), 8.09–8.02 (m, 4H), 7.92–7.80 (m, 3H), 7.71 (dd, J = 15.6, 5.6 Hz, 2H), 7.24 (t, J = 8.9 Hz, 1H), 7.15 (t, J = 8.9 Hz, 1H), 6.79 (s, 1H), 6.61 (d, J = 3.9 Hz, 1H). ^{13}C NMR (75 MHz, Acetone) δ 159.11, 159.08, 152.46, 142.23, 138.67, 137.55, 136.81, 132.96, 132.39, 131.97, 131.71, 128.04, 125.37, 124.64, 120.09, 116.49, 116.10, 115.81, 115.36, 115.08. HRME (ESI) calculated for $C_{27}H_{16}BF_4N_3$ $[M + Na]^+$: 492.1266, obtained: 492.1293 (S6).

Absorption spectra were obtained on an Agilent 8453 UV-Visible spectrophotometer at room temperature in the solvents described above. Steady state fluorescence spectra were obtained on a Shimadzu RF5301PC spectrofluorimeter with a xenon arc lamp as the light source while using an excitation wavelength (λ_{exc}) of 470 nm.

Quantum yields were obtained by a comparative method [12] using fluorescein in 0.1 M NaOH(aq) as the standard (φ = 0.91, λ_{exc} = 470 nm) [13] The quantum yield of the tested compound (φ_x) was calculated using Eqs. (1), where φ_{st} is the quantum yield of the standard, m_x and m_{st} are the slopes for the test compound and standard compound, and η_x and η_{st} are the refractive indexes of the solvents.

$$\varphi_x = \varphi_{st}\left[\frac{m_x}{m_{st}}\right]\left[\frac{\eta_x}{\eta_{st}}\right] \quad (1)$$

Results And Discussion

Synthesis

The synthesis of 8-(2-nitrophenyl)-BODIPY **1** was carried out according classical methods. To prepare the planned N-bridged annulated BODIPY **2** the heterocyclization method was optimized the previously described method [10], by modifying solvent, reaction time and amount of triphenylphosphine (Table 1, Scheme 1).

***Table 1*: Optimization study.**

Entry	Solvents	Time (h)	Temp. (°C)	Yield (%)
1	**DMF**	1	153	30
2	**DMSO**	1	190	5
3	p-**DCB**	5	174	66
4	**DMA**	24	25	n/c
5	**DMA**	24	40	n/c
6	**DMA**	24	80	n/c
7	**DMA**	24	120	5
8	**DMA**	0,5	165	75
*n/c = no convertion was observed.				

Using the optimized method, the simpler fused BODIPY **2** was obtained in good yiels (75%, entry 8) using DMA, triphenylsphosphine (2.5 equivalents) and high temperature (165 ºC) under inert atmosphere for 0.5h, improving the yields and reaction time considerably compared topreviously published method (48%, 24h) [10]. However, attempt to arylate compound **2** with diazonium salts (**3** and **4**), using ferrocene, was unsuccessful (Scheme 2).

So, the strategy was modified by attempting to arylate **1** prior to the heterocyclization. Using the same arylation approach, BODIPYs **5** and **6** were synthesized and used as starting materials for the heterocyclization to produce the correspondet fused BODIPYs **7** and **8** (25% and 15%, respectively, (Scheme 3).

PHOTOPHYSICAL PROPERTIES

We tested the photophysical properties of BODIPYs **5**, **6**, **7** and **8** in dichloromethane, investigating by UV-Vis spectar and fuorescence spectra as shown in Fig. 2 and summarized in Table 2. We used published fluorescence data of **1** to compare with those prepared in this work. The quinoline-BODIPY **2** showed a maximum absorption at λ_{abs} 458 nm and maximum emission at λ_{em} 478 nm [10]. Compared to **1**, the heterocyclization towards **2** resuted in hypsochromic shift for λ_{abs} 48 nm and for λ_{em} 54 nm. Diarylated derivatives **5** and **6** showed λ_{abs} 486 nm and λ_{abs} 490 nm of absortion, respectively, while the emission was found in λ_{em} 542 for **5** and λ_{em} 547 nm for **6**. It is noticeable the bathochromic shift, as a result of the introduction of the aryl group in the core, specially for λ_{em} wavelengths, due to expansion of the *p*-conjugated system [14].

The quantum yield of the fused-quinoline BODIPY **1** is Φ_F 0.99 [10]. The increase of the molecular rigidity decreases the non radiative decay of the fluorophore, increasing his brightness. Interestingly, diarylation

with *p*-fluor-phenyl resulted in a lower quantum yield (Φ_F 0,60) compared to unsubstituted, due to while, diarylation with *p*-trifluormethyl-phenyl keep the quantum yield in the same level (Φ_F 0.95).

Table 2: maximum absorption and emission values

Compounds	λ_{abs}(nm)*	λ_{em}(nm)*
2	507	533
9	558	590
10	564	600
11	486	542
12	490	547

*λ_{abs} = maximum absortion (nm); *λ_{em} = maximum emission.

Conclusion

In conclusion, in this work it was shown that heterocyclization toward quinoline-fused BODIPY using higher boiling point solvent can increase yields and reaction time, and also, reduce the amount of triphenylphosphine needed. Interesting, this N-bridged annulated BODIPYs is very stable, including under arylative conditions. Introduction of aryl groups to N-bridged annulated BODIPYs demonstrated to be a very useful strategy to produce new red-shifted fluorophores with high quantum yields, which could be very useful for further studies and applications. An optimized protocol for the production of the fused quinoline-BODIPY derivative was achieved and a library of unpublished derivatives was built. As planned, these derivatives have a significant red shift, however, due to the decrease in molecular rigidity, the derived probes showed a decrease in brightness. It was also found that CF_3 in the aryl moiety of the probe were able to recover the probe's brightness lost due to decreased rigidity mainteining the red-shift. Finally, the evolutive process of non-annulated to arylated annulated BODIPY derivatives showed a way to modulate photophysical properties within a series of fluorophores.

Declarations

-Funding:

1. Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

2. Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

-Conflict of interest: There is no conflict of interests.

-Ethics approval/declarations: Not applicable

-Consent to participate: Not applicable

-Consent for publication: Not applicable

-Availability of data and material: Data available as supporting material to this manuscript.

-Code availability: Not applicable

-Authors' contributions:

1. Rodrigo Brito de Mello: Planning, synthesys, Analysis

2. Flavio da Silva Emery: Planning, Advisor, Review.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Grants numbers 165417/2014-5 and 168073/2017-0) and CAPES (This work was carried out with the support of the Coordination of Improvement of Higher Education Personnel - Brazil (CAPES - Financing code 001). We also would like to acknowledge the Analytical Centre of NPPNS (FCFRP-USP, Brazil) for the Mass Spectrometry analysis.

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Figures

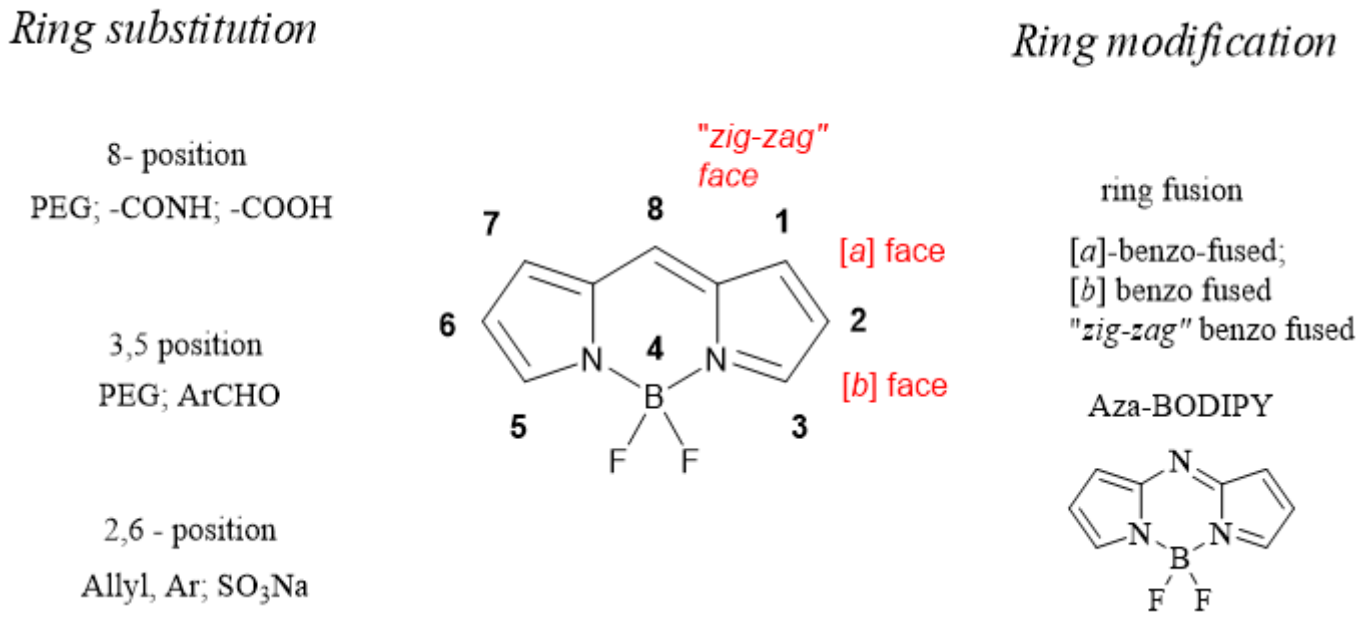

Figure 1

Structural formula of the BODIPY core and main structural modifications.

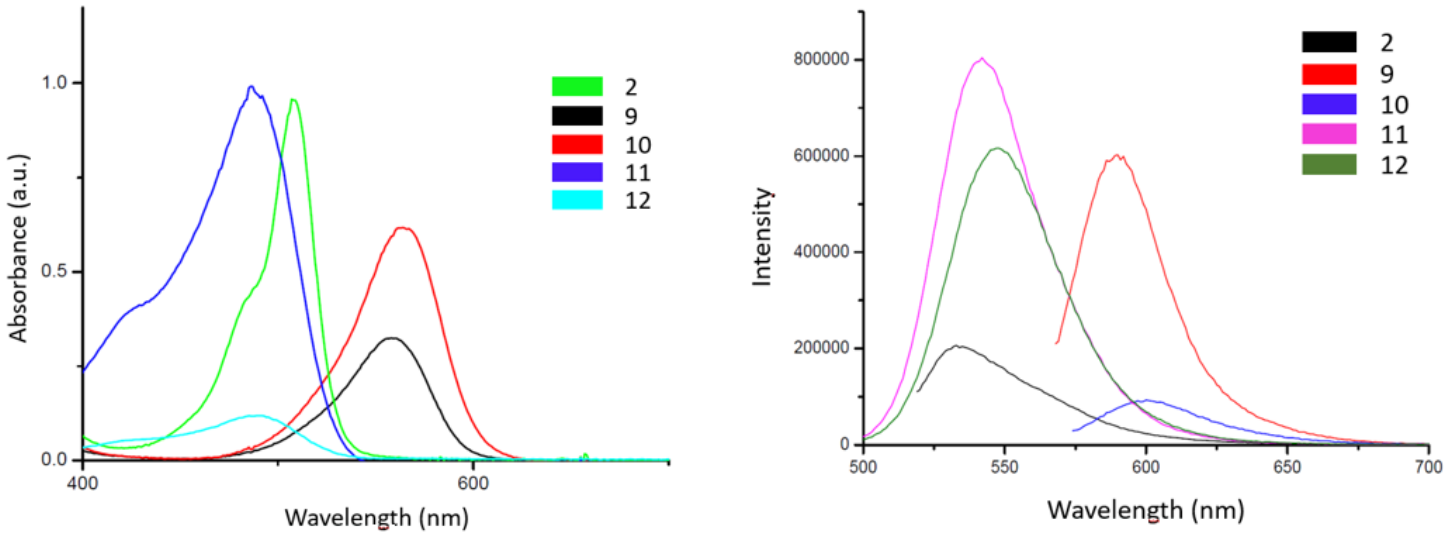

Figure 2

UV-Vis absortion spectra (left) and fluorescence (right).

Supplementary Files

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- SUPPLEMENTARYINFORMATION.docx
- Scheme1.png
- Scheme2.png
- Scheme3.png