

This document is the unedited Author's version of a Submitted Work that was subsequently accepted for publication in The Journal of Organic Chemistry, copyright © American Chemical Society after peer review. To access the final edited and published work see <https://pubs.acs.org/doi/10.1021/acs.joc.1c00586>. Access to this work was provided by the University of Maryland, Baltimore County (UMBC) ScholarWorks@UMBC digital repository on the Maryland Shared Open Access (MD-SOAR) platform.

Please provide feedback

Please support the ScholarWorks@UMBC repository by emailing [scholarworks-group@umbc.edu](mailto:scholarworks-group@umbc.edu) and telling us what having access to this work means to you and why it's important to you. Thank you.

**Amphiphilic Near-IR Emitting 3,5-Bis[2-Pyrrolylethenyl]BODIPY Derivatives:  
Synthesis, Characterization and Comparison with other (Hetero)Arylethenyl  
Substituted BODIPYs**

Sara Ansteatt, Adam Meares, Marcin Ptaszek\*

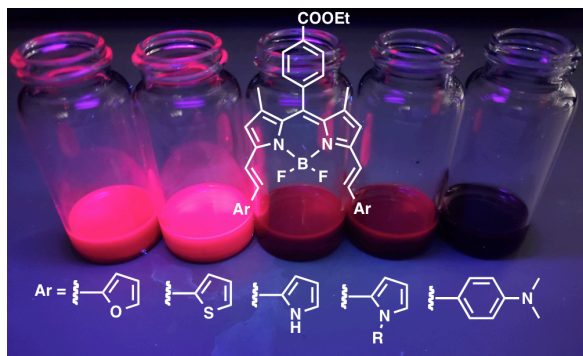
Department of Chemistry and Biochemistry

University of Maryland, Baltimore County

1000 Hilltop Circle

Baltimore, MD 21250

## TOC



## Abstract

A series of 3,5-bis(hetero)arylethenyl-substituted BODIPY derivatives has been prepared in Knoevenagel-type condensation of alkyl-substituted BODIPY with corresponding aldehydes. 2-Pyrrolylethenyl-substituted derivatives feature near-IR emission ( $\lambda_{\text{em}} > 700$  nm), with high fluorescence quantum yield. Both, emission maxima and fluorescence quantum yields are relatively insensitive to solvent polarity, contrary to corresponding near-IR emitting 4-(*N,N*-dimethylaminophenyl)ethenyl derivatives. Alkylation at the *N*-pyrrolic position of ethenyl substituent allows for installation of hydrophilic PEG group and afforded amphiphilic BODIPY derivatives. Overall, 2-pyrrolylethenyl-substituted BODIPY appears to be versatile fluorophores with potential application in near-IR imaging.

## Introduction

Near-IR fluorophores are of special interest, due to their potential applications for *in vivo* and deep-tissue fluorescence imaging.<sup>1-4</sup> Among various classes of organic fluorophores, BODIPY derivatives are relatively stable, with strong absorption, and high fluorescence quantum yield, and are reasonably straightforward to synthesize.<sup>5-7</sup> Simple BODIPY derivatives absorb and emit in

the visible region ( $\sim 500$  nm),<sup>5-6</sup> but there are several strategies to shift absorption and emission towards the deep-red or near-IR spectral windows.<sup>6</sup> The installation of arylethenyl (styryl) substituents at the 2,5-positions of BODIPY is synthetically straightforward and results in bathochromic shift of absorption and emission to  $\sim 650$  nm, and up to  $\sim 700$  nm, if a strongly electron donating *N,N*-dialkylamino substituent is present at the styryl moiety.<sup>8-12</sup>

For fluorescence deep-tissue imaging it is desirable to utilize fluorophores with wavelength of emission and excitation  $> 700$  nm because of the deeper tissue penetration by near-IR light, and diminished scattering for a longer-wavelength radiation.<sup>13</sup> Typically, distyryl-BODIPY derivatives absorb and emit  $\sim 650$  nm, and their absorption and emission shifts bathochromically with increasing electron-donating character of an aryl part of styryl substituent.<sup>5,6</sup> For example, BODIPY derivatives with 4-*N,N*-dialkylaminophenylethenyl substituents absorb and emit at  $\lambda > 700$  nm (e.g. **1**, Chart 1).<sup>8-12</sup> However, absorption and emission for these BODIPY derivatives are solvent- and pH sensitive.<sup>14</sup> Moreover, electron-rich aminoaryl substituents tend to quench fluorescence through internal charge transfer (ICT).<sup>14,15</sup> Overall, these characteristics can be problematic for certain *in vivo* imaging applications, when it is desirable that an optical probe behaves in predictable manner in complex, heterogenous biological environment. Therefore, we have been searching for alternative derivatives, which spectral properties are less solvent and pH dependent. Moreover, we were looking for a construct which enables easy installation of hydrophilic (e.g. PEG) groups to create amphiphilic derivatives, suitable for applications in biological media. Distyryl BODIPY derivatives are highly hydrophobic and notoriously undergo aggregation in aqueous media, though several water-soluble derivatives have been reported.<sup>16-18</sup> Nonetheless, both, hydrophilic and hydrophobic distyryl BODIPY derivatives have been employed as fluorophores for *in vivo* imaging and photosensitizers for photodynamic therapy.<sup>19-23</sup>

Previously, we have examined a series of amphiphilic energy transfer arrays, which utilized hydrophilic BODIPY derivatives for *in vivo* medicinal imaging.<sup>24,25</sup> We also examined BODIPY with (2,4,6-trialcoxyaryl)ethenyl substituents (**2**, Chart 1), which absorbs at 668 nm and functions as an excellent energy donor for bacteriochlorins.<sup>26</sup> However, this absorption and emission maxima are sub-optimal for *in vivo* application, therefore we envisioned, that 2-pyrrolylethenyl substituents should provide a desirable bathochromic shift, and nitrogen on pyrrole moiety should provide a convenient synthetic handle to attach hydrophilic group.

We also intended to compare the optical properties of 2-pyrrolylethynyl-substituted BODIPY with analogous derivatives comprising furan and thiophene since both the later are also considered electron-donating substituents (see below). While there are several reports on 3,5-bis(2-thienylethenyl),<sup>27-33</sup> 3,5-bis(2-furylethenyl)<sup>34</sup> as well as 3,5-bis(3-pyrrolylethenyl)BODIPY (e.g. **3**, Chart 1)<sup>35,36</sup> derivatives, to the best of our knowledge, there was only scarce reports on 3-(2-pyrrolylethenyl)BODIPY,<sup>37-39</sup> until recently, when during preparation of this manuscript a paper on synthesis of 3,5-di-(2-pyrrolyl)BODIPY (e.g. **4**, Chart 1) was published.<sup>40</sup> Reported derivatives **2** and **3** however, show a negligible fluorescence in polar solvent, which authors attributed to the photoinduced electron transfer from electron-rich dialkyl pyrrole substituents. Here we present a synthesis and characterization of a series of BODIPY derivatives with 3,5-bis(heteroarylethenyl) substituents (Scheme 1), including BODIPY with 2-thienylethenyl<sup>28</sup> (**BDP2**), 2-furylethenyl (**BDP-3**) 2-pyrrolylethynyl (**BDP4**), and *N*-alkyl-2-pyrrolylethenyl (**BDP5** and **BDP8**, Scheme 2) substituents. For comparison, we examined BODIPYs with 4-*N,N*-dimethylaminophenylethenyl (**BDP-6**<sup>1</sup> Scheme 1) and 4-alkoxyphenylethenyl (**BDP7** and **BDP9**, Schemes 1 and 3). Both **BDP6** and pyrrolylethenyl-substituted BODIPYs reported here show near-IR (> 700 nm) fluorescence, while the later show much less fluorescence dependence on solvent polarity. Thus, results reported

here also underpin the importance of the proper molecular design and subtle structural and electronic factors for achieving desired optical properties in BODIPY derivatives.

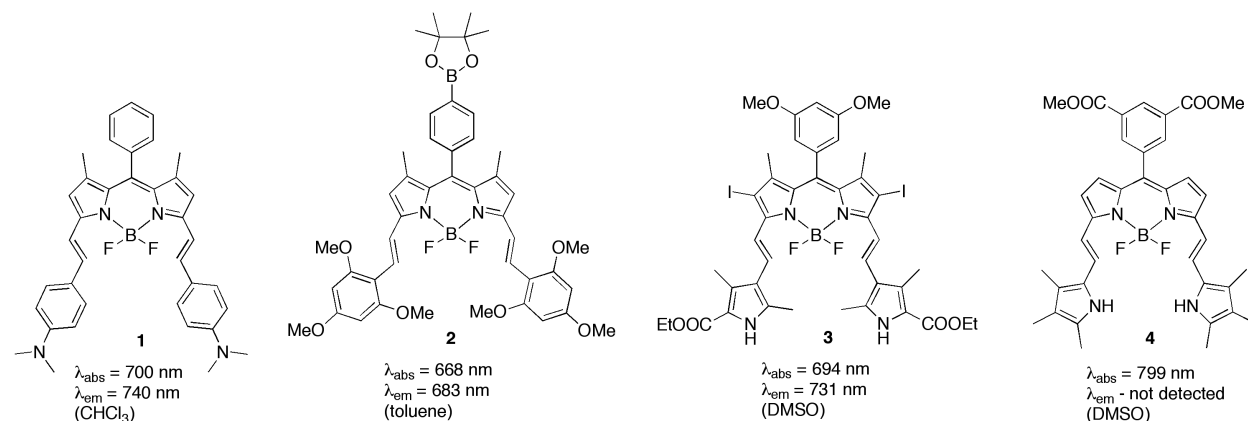
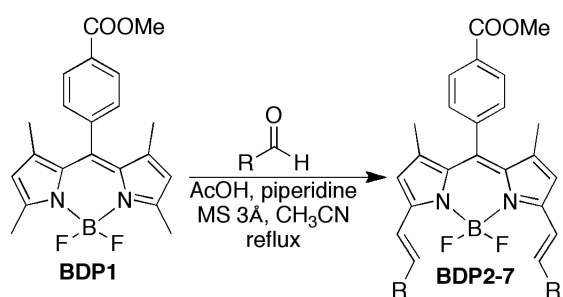


Chart 1. Examples of previously reported long-wavelength absorbing di(heter)arylethynyl-substituted BODIPY derivatives: **1**,<sup>9</sup> **2**,<sup>26</sup> **3**,<sup>35</sup> and **4**.<sup>40</sup>

## Results and Discussion.

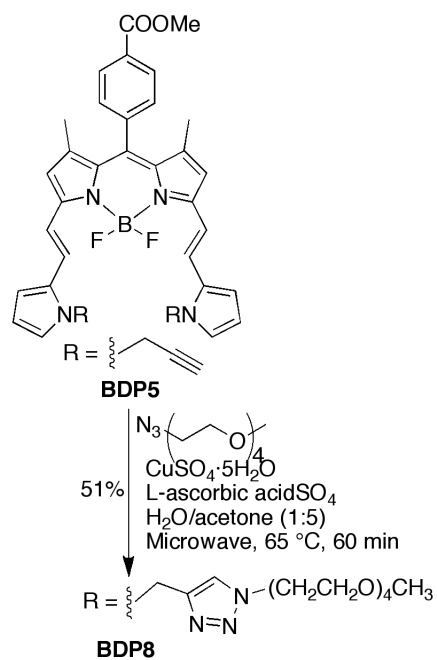
**Synthesis.** BODIPY **BDP1** was synthesized following reported procedure.<sup>41</sup> Several different conditions have been reported for the Knoevenagel condensation, leading to installation of arylethenyl substituents at 3 and 5 positions.<sup>8-12,42</sup> We found, the moderate to good yields have been obtained when mixture of **BDP1** and corresponding aldehyde was treated with piperidine and acetic acid, in the presence of molecular sieves 3Å, in DMF or CH<sub>3</sub>CN.<sup>42</sup> Resulting products were easily purified on column chromatography. Under these conditions only minute amount of the corresponding monosubstituted product was detected, however substantial amount of material more polar than product was formed, which was not characterized. Trimethyleneglycol moiety was subsequently installed on **BDP-5** through microwave-assisted 1,3-dipolar cycloaddition reaction with of pre-installed propargyl substituent with corresponding azide under microwave irradiation,<sup>24</sup> to obtain **BDP8** and **BDP9** in 51% and 71%, respectively (Schemes 1 and 2).

New BODIPY was characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and HRMS. The corresponding data are consistent with the expected structures. The installation of new arylethenyl moiety is indicated by the presence of two doublets at  $\sim 7\text{-}8$  ppm, with a coupling constants  $\sim 16$  Hz, which is consistent with vinyl substituent in *trans* configuration.

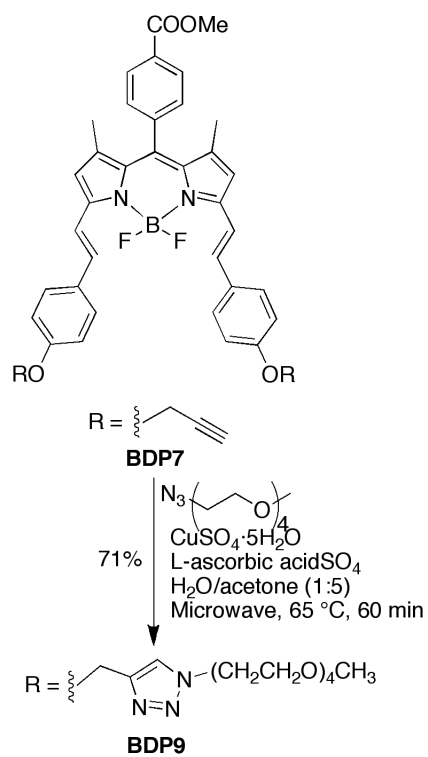


R	Product	Yield
	<b>BDP2</b>	62%
	<b>BDP3</b>	21%
	<b>BDP4</b>	55%
	<b>BDP5</b>	67%
	<b>BDP6</b>	45%
	<b>BDP7</b>	63%

Scheme 1. Synthesis of diarylethenyl-substituted BODIPY through Knoevenagel-type condensation.



Scheme 2. Synthesis of **BDP8**.





Scheme 3. Synthesis of **BDP9**.

**Absorption and emission properties.** Absorption and emission properties for all reported BODIPYs were first determined in toluene (Table 1). As expected, absorption spectrum for each dirylethenyl-BODIPY is dominated by a very strong band between 600-700 nm, corresponding to  $S_0 \rightarrow S_1$  transition, with a distinctive vibronic band on the blue onset of the manifold, and a weaker band  $\sim 400$  nm, corresponding to  $S_0 \rightarrow S_2$  transition. The position of the long-wavelength band is progressively bathochromically shifted with increasing electron-donating ability of aryl part of substituent. In particular,  $\lambda_{\max}$  for furyl and thiophene-substituted **BDP2** and **BDP3** are nearly identical (657 nm and 658 nm), while for pyrrole-substituted **BDP3**  $\lambda_{\max}$  is shifted to 686 nm. *N*-substitution pyrrole by alkyl group (**BDP5**, **BDP8**), causes additional bathochromic shift (695-697 nm), consistently with an electron-donating character of alkyl groups. The most bathochromically shifted derivative is a dimethylaminophenyl-substituted **BDP6** (708 nm), that derivative features also elaborated manifold between 300-500 nm.

Emission spectra of new BODIPY derivatives in toluene are similar to these reported for analogous styryl derivatives and consist predominantly 0-0 transition, with much weaker 0-1 transition. Stokes' shift varies from  $\sim 10$  nm for derivatives absorbing at shorter wavelength (**BDP2,3,7** and **BDP9**), and gradually increases for derivatives absorbing  $\sim 700$  nm, ranging from 16 nm for **BDP4** to 18 nm for **BDP5** and to 29 nm for **BDP6**. Fluorescence quantum yield  $\Phi_f$  in toluene is relatively high, ranging from 0.74 for **BDP7** to 0.40 for **BDP8**. Reduction of  $\Phi_f$  for long-wavelength emitting derivatives is consistent with an energy-gap rule.<sup>43</sup> *N*-substitution of pyrrole causes minute decrease in  $\Phi_f$  (0.46 for **BDP4**, 0.43 for **BDP5** and 0.40 for **BDP8**). Alkyl groups likely impose conformational flexibility, which enhances internal conversion. It is worth noting,

that thiophene-substituted **BDP3** has identical  $\Phi_f$  as furan-substituted **BDP2**. Apparently, thiophene did not substantially enhance  $S_1 \rightarrow T_1$  intersystem crossing. Previous reports indicate that thiophene may or may not affect the ISC in BODIPY, depending on manner how thiophene is attached.<sup>44</sup>

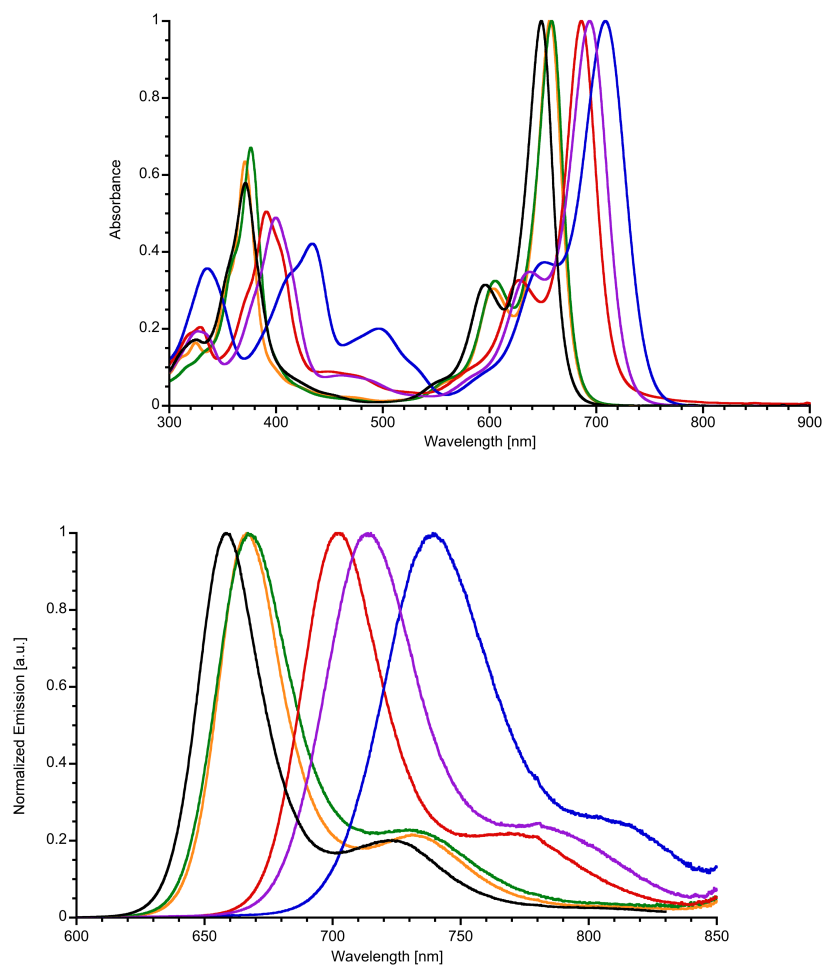


Figure 1. Absorption (upper panel) and emission (lower panel) spectra of **BDP2** (orange), **BDP3** (green), **BDP4** (red), **BDP5** (purple), **BDP6** (blue), **BDP7** (black). All spectra are taken in toluene and normalized at the maximum of absorption/emission.

Table 1. Photophysical properties of BODIPY derivatives.<sup>a</sup>

Compound	$\lambda_{\text{abs}}$	$\lambda_{\text{em}}$	$\Phi_f(\text{toluene})$	$\Phi_f(\text{DMF})$
<b>BDP2</b>	657 nm	667 nm	0.66	0.46
<b>BDP3</b>	658 nm	668 nm	0.57	0.46
<b>BDP4</b>	686 nm	702 nm	0.46	0.31
<b>BDP5</b>	695 nm	713 nm	0.43	0.34
<b>BDP6</b>	708 nm	737 nm	0.41	$\sim 0.08^c$
<b>BDP7</b>	648 nm	658 nm	0.74	0.72
<b>BDP8</b>	697 nm	721 nm	0.40	0.32
<b>BDP9</b>	644 nm <sup>b</sup>	656 nm <sup>b</sup>	- <sup>d</sup>	0.57

<sup>a</sup>Absorption and emission wavelength were determined in toluene, unless noted otherwise. Only the longest wavelength band is reported. Fluorescence quantum yield was determined in air-equilibrated solvents, using tetraphenylporphyrin in air-equilibrated toluene ( $\Phi_f = 0.070^{45}$ ).

<sup>b</sup>Determined in DMF. <sup>c</sup>Fluorescence quantum yield could not be accurately determined, due to the limitation in detector sensitivity for  $\lambda > 850$  nm <sup>d</sup> Insoluble in toluene.

**MOs calculation.** DFT calculations (Table 2, see *Supporting Information* for more details) show the effect of (hetero)aromatic substituents on HOMO and LUMO energies of the resulting derivatives. Energies of both HOMO and LUMO progressively increase in order of **BDP3** < **BDP7** < **BDP2** < **BDP4** < **BDP5** < **BDP6**, compared to benchmark phenylethenyl-BODIPY **BDP10**. Increase in MOs energies is accompanied by reduction of HOMO-LUMO energy gap, which is congruent with shift of  $S_0 - S_1$  absorption band. Overall, both effects, increase in HOMO/LUMO energies and reduction of HOMO-LUMO gap are significantly larger for (2-pyrrolylethenyl)-substituted BODIPY than for corresponding furan or thiophene derivatives. This probably reflects the greater electron-donating ability of pyrrole, compared to thiophene or furan. Electron donating

ability can be quantified, for example, by ionization potential, which is equal to 8.2 eV,<sup>46,47</sup> 7.94 eV,<sup>47</sup> 8.87 eV,<sup>48</sup> 8.89 eV,<sup>49</sup> and 7.14 eV<sup>48</sup> for pyrrole, *N*-methylpyrrole, thiophene, furan, and *N,N*-dimethylpyrrole respectively. Interestingly, 4-methoxyphenylethenyl-substituted BODIPY **BDP7** features much lower HOMO/LUMO energies and larger HOMO-LUMO gap, despite having ionization energy (~8.2-8.4 eV)<sup>50</sup> comparable with that of pyrrole. Apparently, pyrrole is a greater contributor of an electron density through resonance than methoxybenzene (see below).

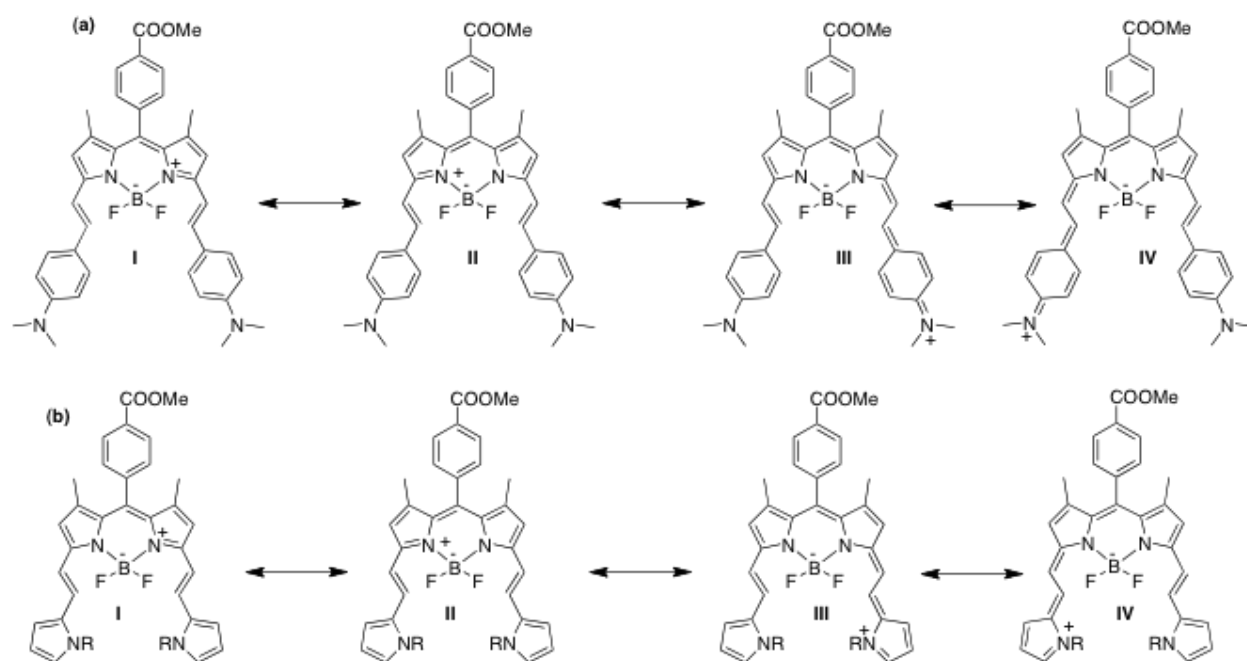
Table 2. MOs for selected BODIPY derivatives.<sup>a</sup>

Compound	HOMO [eV]	LUMO [eV]	LUMO-HOMO [eV]
<b>BDP1</b>	-5.43	-2.44	2.99
<b>BDP2</b>	-4.71	-2.60	2.11
<b>BDP3</b>	-4.79	-2.67	2.12
<b>BDP4</b>	-4.55	-2.49	2.06
<b>BDP5</b>	-4.54	-2.48	2.06
<b>BDP6</b>	-4.29	-2.26	2.03
<b>BDP7</b>	-4.75	-2.58	2.17
<b>BDP10<sup>b</sup></b>	-4.90	-2.68	2.22

<sup>a</sup> Calculations were performed in vacuum, employing the DFT B3LYP 6-31G\* method. <sup>b</sup> **BDP-10** is 3,5-diphenylethynyl-BODIPY (see *Supporting Information* for the structure).

***Solvent-dependent absorption and emission properties of diarylethenyl-BODIPY derivatives.*** 4-(*N,N*-dimethylamino)phenylethenyl-substituted BODIPYs shows a remarkable dependence of emission maxima and  $\Phi_f$  on solvent polarity which is manifested by a significant bathochromic shift of emission band and reduction of  $\Phi_f$  when solvent dielectric constants

increases,<sup>14</sup> This behavior is attributed to significant contribution of internal charge transfer (ICT) state to  $S_1$ , due to the presence of non-bonding electron pairs on amino nitrogen, which donates electrons via relevant resonance structures (structures **III** and **IV**, Scheme 4a).<sup>14</sup> Corresponding resonance structures can be drawn for 2-pyrrolylethenyl substituted BODIPY (Scheme 4b), therefore it can be expected, that **BDP5** and **BDP8** will exhibit a similar solvent dependence. Moreover, recently a nearly complete fluorescence quenching in DMSO was reported for analogous pyrrolylethenyl-substituted BODIPY derivatives, which was attributed to photoinduced electron transfer, from pyrrole substituents, which efficiently quenches BODIPY excited state.<sup>40</sup>



Scheme 4. Possible resonance structures for (a) **BDP6**<sup>14</sup> and (b) **BDP5** or **BDP8**.

Significant dependence of  $\lambda_{em}$  and  $\Phi_f$  on local polarity can be problematic for application of given derivatives in biological imaging, since brightness of the probe would significantly be affected by a complex intracellular media. Therefore, here we determined absorption and emission properties of *N*-alkyl-2-pyrrolylethenyl-substituted derivatives in series of solvents of high

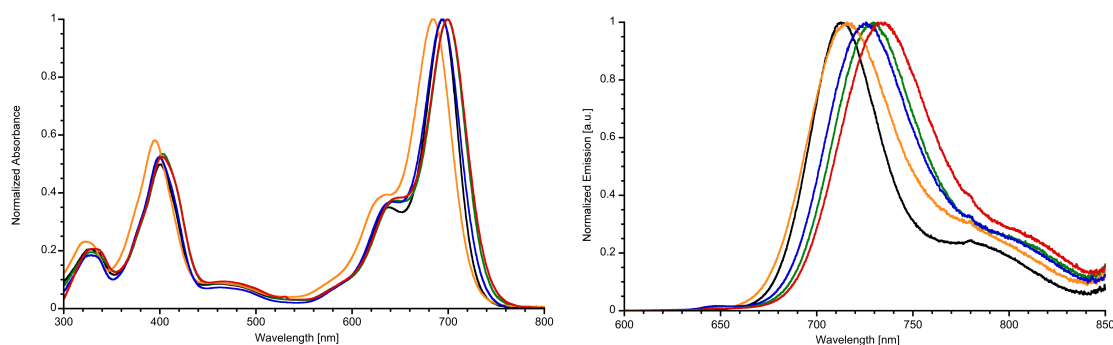
dielectric constants, and compared these with the same for *N,N*-dimethylaminophenylethenyl-substituted derivative (Figure 2, Table 3).

Absorption spectra of **BDP5**, **BDP6**, and **BDP8** show comparable, very minor solvent polarity dependence, manifested by a small ( $< 10$  nm) shift of the  $S_0 - S_1$  absorption band, and even smaller shift for  $S_0 - S_2$  transition. Interestingly, these spectral shifts do not correlate with solvent dielectric constants (e.g. the largest bathochromic shift is observed in PhCN).

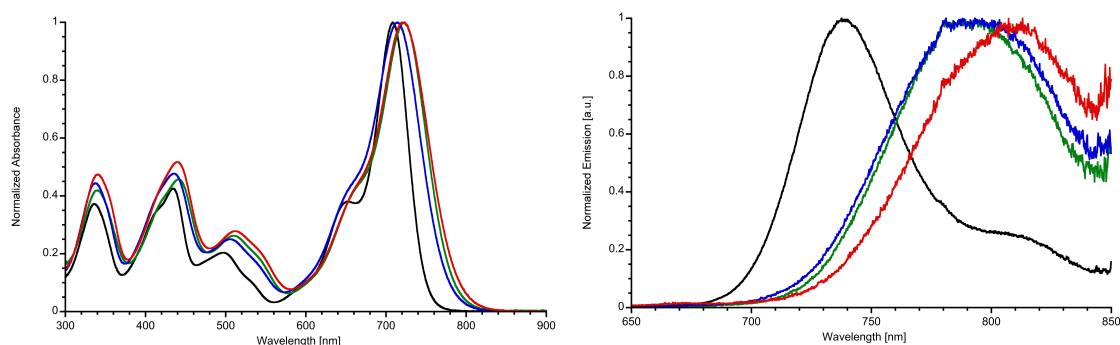
Emission spectra in solvents of high dielectric constants are distinct for dimethylaminophenylethenyl-BODIPY **BDP6** and *N*-alkyl-2-pyrrolylethenyl-BODIPY **BDP5** and **BDP8**. **BDP6** exhibits significant broadening and bathochromic shift in emission (44 – 75 nm, compared to toluene), when solvent dielectric constant increases (Figure 2b). This observation indicates a huge change in dipole moment in the excited state for **BDP6** and it is consistent with substantial contribution of ICT (i.e. structures **III** and **IV**) to the excited state.<sup>14</sup> On the other hand **BDP5** and **BDP8** exhibit a small bathochromic shift in polar solvent (maximum 21 nm compared to toluene), and without significant broadening. Stokes' shift increases parallel to increase of dielectric constant of solvent, but this increase is substantially smaller than for **BDP6**.  $\Phi_f$  for **BDP5** and **BDP8** are moderately reduced ( $\sim 1.3$ -fold) in polar solvents. Larger reduction (1.8-fold compared to that in toluene) is observed in MeOH. This reduction is much smaller than that reported for 4-*N,N*-dimethylaminophenylethenyl substituted BODIPY reported previously (e.g.  $>10$ -fold reduction of  $\Phi_f$  for monostyryl-substituted BODIPY in DMSO compared to toluene).<sup>14</sup> In our case, an accurate determination of  $\Phi_f$  for **BDP6** in polar solvents was impossible due to the limitation in detector sensitivity for  $\lambda > 850$  nm). Our results also contrast with that reported recently for other pyrrolylethenyl-substituted BODIPY, where a negligible emission was observed

in DMSO, due to the photoinduced electron transfer from pyrrole to photoexcited BODIPY.<sup>40</sup> Apparently, PET does not operate efficiently for **BDP5** and **BDP8**, even in highly polar DMSO. We are attributing less efficient PET to (a) lower electron-donating ability of pyrrole substituent for **BDP5** and **BDP8**, compared to that in **2** and **3**, where more electron rich dialkylpyrrole was used, and (2) lower electron-accepting ability of BODIPY core of **BDP5** and **BDP8**, due to the presence of two methyl groups at 1 and 8 positions.<sup>51</sup> Overall, these results underpin the importance of an electronic balance, achieved by a substitution pattern, to achieve a high fluorescence quantum yield. We anticipate that further modification of BODIPY structure allows for both greater bathochromic shift and high fluorescence quantum yield in pyrrolylethenyl substituted BODIPY.

(a)



(b)



(c)

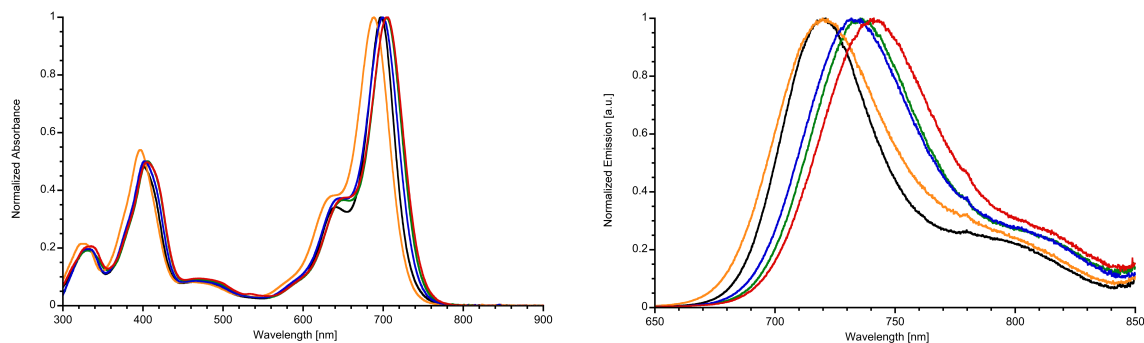


Figure 2. Absorption and emission spectra of **BDP5** (a), **BDP6** (b), and **BDP8** (c) in different solvents: toluene (black), MeOH (orange), PhCN (green), DMF (blue), DMSO (red).

Table 3. Absorption and emission data for BODIPY derivatives in solvents of different dielectric constants.

Solvent (dielectric constant)	$\lambda_{\text{abs}}$	$\lambda_{\text{em}}$	Stokes' shift ( $\text{cm}^{-1}$ )	$\Phi_f$
<b>BDP5</b>				
Toluene ( $\epsilon = 2.38$ )	695 nm	713 nm	363	0.43
PhCN ( $\epsilon = 26.00$ )	699 nm	729 nm	589	0.36
MeOH ( $\epsilon = 33.00$ )	684 nm	716 nm	653	0.24
DMF ( $\epsilon = 36.71$ )	694 nm	722 nm	748	0.34
DMSO ( $\epsilon = 47.24$ )	699 nm	732 nm	645	0.32
<b>BDP6</b>				
Toluene	708 nm	737 nm	556	0.41
PhCN	732 nm	781 nm	857	$\sim 0.13^b$
MeOH <sup>a</sup>	-	-	-	N/A
DMF	714 nm	793 nm	1395	$\sim 0.08^b$
DMSO	723 nm	813 nm	1531	$\sim 0.07^b$
<b>BDP8</b>				
Toluene	697 nm	721 nm	478	0.40



PhCN	705 nm	736 nm	597	0.35
MeOH	689 nm	720 nm	625	0.23
DMF	699 nm	732 nm	645	0.32
DMSO	705 nm	741 nm	689	0.31

<sup>a</sup> **BDP6** is not soluble in MeOH. <sup>b</sup> Fluorescence quantum yield cannot be accurately determined, due to the limitation in sensitivity of detector at wavelength > 850 nm.

**Optical properties in micelles.** Optical properties of PEG-derivatized **BDP8** were investigated in series of aqueous micelles formulated from surfactants Pluronic F127, Tween 20, and Triton X100. Absorption spectra of **BDP8** at concentration of ~ 10  $\mu$ M are presented in Figure 3 and Table 4. Wavelengths of absorption maxima in micelles vary only slightly, compared to that observed in toluene (Table 4) A moderate broadening (~ 50% compared to toluene) of  $S_0 \rightarrow S_1$  band is observed in Triton X100 and Tween 20, suggesting a partial aggregation of BODIPY in these media. In Pluronic P127 significant lowering of the ratio of the intensities of 0-0 to 0-1 vibronic bands as well as ratio of intensities of  $S_0 \rightarrow S_1$  to  $S_0 \rightarrow S_2$  absorption bands is observed, in addition to broadening of the longest wavelength absorption band. Emission bands in micelles are slightly shifted (~10 nm) compared to that in toluene. The magnitude of a Stokes' shift suggests, that micelles BODIPY is localized in environment of dielectric constants between that of toluene, and PhCN. Emission band in each micelle is moderately broader (~1.3-fold), compared to that in toluene. However,  $\Phi_f$  in micelles is reduced significantly compared to that in toluene, from ~2-fold (in Tween 20 and Triton X100), up to 10-fold (in Pluronic F127).

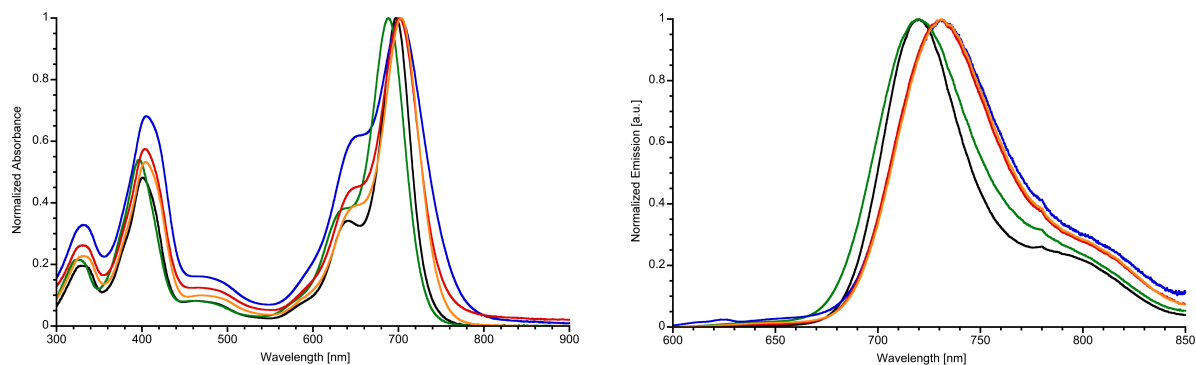


Figure 3. Normalized absorption and emission spectra of **BDP8** in aqueous micelles and selected organic solvents: toluene (black), MeOH (green), Pluronic F127 (blue), Tween 20 (red), and Triton X100 (orange).

Table 4. Optical properties of **BDP8** in micelles.<sup>a</sup>

Medium	$\lambda_{\text{abs}}$ (FWHM)	$\lambda_{\text{em}}$ (FWHM)	Stokes' shift ( $\text{cm}^{-1}$ )	$\Phi_f$
Toluene	697 nm (42.5 nm)	721 nm (47 nm)	478	0.40
Pluronic F127	702 nm (104 nm)	731 nm (64 nm)	565	0.03
Tween 20	701 nm (61 nm)	731 nm (60 nm)	585	0.21
Triton X100	704 nm (55)	730 nm (61 nm)	506	0.23

<sup>a</sup> Measurements performed in 3 mM Triton X-100, 0.15 mM of Pluronic F127, and 0.1% (v/v) of Tween-20 all in PBS (pH = 7.4).  $\Phi_f$  ( $\pm 10\%$ ) was determined in air-equilibrated solvents, using tetraphenylporphyrin in toluene as a standard ( $\Phi = 0.070^{45}$ ) and corrected for refractive index  $n$  of

the medium. For all measurements done in aqueous surfactant  $n = 1.45$  was used,<sup>52</sup> as an average between that for pure hydrocarbons (1.49) and pure water (1.39).

## Conclusion

Substitution of BODIPY at 3,5-positions with 2-pyrrolylethenyl substituents causes a significant bathochromic shift of absorption and emission bands, pushing them in near-IR window. This shift in absorption/emission is much larger than in case of analogous derivatives bearing furan or thiophene substituents. *N*-Pyrrolic positions can be easily derivatized through a click chemistry and allow for introducing hydrophilic substituents and producing amphiphilic derivatives. Novel near-IR emitting BODIPY derivatives show limited dependence of emission properties of microenvironment and show good fluorescence quantum yield in polar and non-polar environment as well as in aqueous micelles, thus they appear to be excellent candidates for near-IR fluorophores for biological applications. The results of initial *in vivo* testing of BODIPY s described here are described elsewhere.<sup>53</sup> The research on incorporation of BODIPY derivatives described here into energy transfer arrays to develop fluorophores for multicolor imaging are currently ongoing in our laboratory.

## Experimental Section

**General. Synthesis.** All reagents, solvents, etc. not prepared in house were purchased through either Sigma-Aldrich or Fisher Scientific and used without further purification. All solvents used are ACS grade, unless noted otherwise.

**Microwave Reactions** Microwave reactions were performed in CEM Discover CEM, Mathew, NC) microwave instrument. All reactions were performed in 80 mL CEM microwave vessel, with continuous monitoring of pressure and temperature. Temperature was monitored using

built-in IR sensor. Microwave reactions involves three stages: (1) “Run time” - reaction mixture was irradiated with 150 W until it reaches designated temperature (30-120 sec); (2) “Hold time” – reaction mixture was maintained at designated temperature for set time, (3) “Cooling time” – reaction mixture was kept in closed reaction vials until reaches 50 °C (approximately 5-10 min).

*Characterization* All NMR spectra were acquired on either 400 MHz NMR or 500 MHz NMR. All HRMS data acquired on FT-ICR MS.

*Spectroscopic Studies.* Fluorescence measurements were performed with a sample absorbance of approximately 0.1. All measurements were performed in HPLC grade solvents.

DFT calculations were performed, and results were visualized using Spartan 10 for Windows (Wavefunction Inc, Irvine, CA).

Known compounds **1**,<sup>54</sup> and **BDP1**<sup>41</sup> were synthesized following the reported procedure.

**BDP2.** A mixture of **BDP1** (150 mg, 0.392 mmol), furfural (377 mg, 3.92 mmol), and molecular sieves (3Å, ~1.0 g) in acetonitrile (15 mL) was treated with acetic acid (15 µL) and piperidine (30 µL). The resulting mixture was protected from light and refluxed for 18 hours. The reaction mixture was diluted with ethyl acetate and washed (water and brine), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Column chromatography [silica, hexanes/CH<sub>2</sub>Cl<sub>2</sub> (1:10), first band (blue)] provided a green-gold solid. (130 mg, 62%). <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>): δ 1.44 (s, 6H), 3.94 (s, 3H), 6.59 (dd, *J* = 1.8 Hz, 3.4 Hz, 2H), 6.67 (d, *J* = 3.4 Hz, 2H), 6.84 (s, 2H), 7.31 (d, *J* = 16.3 Hz, 2H), 7.59 (d, *J* = 16.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.73 (m, 2H), 8.22 (d, *J* = 8.5 Hz, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 15.1, 52.6, 57.5, 60.8, 112.5, 112.7, 117.7, 117.7 118.3, 119.9, 123.5, 128.4, 129.3, 129.3, 130.6, 144.4, 153.3, 181.6; HRMS (ESI-TOF) *m/z* [M+Cs]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>25</sub>BF<sub>2</sub>N<sub>2</sub>O<sub>4</sub>, 671.0930; Found: 671.0928.

**BDP3.** **BDP3** was reported previously<sup>28</sup> and here it was prepared following a slightly modified procedure. A mixture of **BDP1** (30 mg, 0.078 mmol), 2-thiophenecarboxaldehyde (88.3 mg, 0.784 mmol), and molecular sieves (3 Å, ~1.0 g) in acetonitrile (5 mL) was treated with acetic acid (3 µL) and piperidine (6 µL). The resulting mixture was refluxed, protected from light, for 18 hours. The reaction mixture was diluted with ethyl acetate, washed (water and brine), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (5:1), first band (blue)] provided a dark blue-purple film (9.6 mg, 21%). Characterization data (<sup>1</sup>H NMR, HRMS) are consistent with the one reported previously.<sup>N2</sup> <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>): δ 1.51 (s, 6H), 4.00 (s, 3H), 6.93 (s, 2H), 7.19 (dd, *J* = 3.6 Hz, 5.1 Hz, 2H), 7.38 (d, *J* = 3.6 Hz, 2H), 7.55 (d, *J* = 16.6 Hz, 2H), 7.63 (d, *J* = 5.7 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 16.1 Hz, 2H), 8.28 (d, *J* = 8.5 Hz, 2H); HRMS (ESI-TOF) *m/z* [M+Cs]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>25</sub>BF<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>, 703.0473, Found 703.0477.

**BDP4.** A mixture of **BDP1** (150 mg, 0.392 mmol), pyrrole-2-carboxaldehyde (373 mg, 3.92 mmol), and molecular sieves (3Å, ~1.0 g) in acetonitrile (15 mL) was treated with acetic acid (15 µL) and piperidine (30 µL). The resulting mixture was refluxed for 18 hours, protected from light. The reaction mixture was diluted with ethyl acetate, washed (water and brine), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Column chromatography [silica, CH<sub>2</sub>Cl<sub>2</sub>, second band (green)] provided a dark green solid. The semi-pure product was dissolved in the minimum amount of CH<sub>2</sub>Cl<sub>2</sub> and small portions of cold hexanes were added to remove residual impurities. The resulting dark-red solid was collected (115 mg, 55% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.45 (s, 6H) 4.00 (s, 3H), 6.14 (m, 2H), 6.29 (s, 2H), 6.54 (s, 2H), 6.57 (m, 2H), 6.99 (d, *J* = 16.3 Hz, 2H), 7.46 (d, *J* = 16.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 8.22 (d, *J* = 8.4 Hz, 2H), 9.54 (s, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 14.9, 52.5, 100.0, 110.3, 112.1, 114.5, 117.5, 122.5, 126.8, 129.4, 130.3,

130.8, 132.4, 137.7, 140.3, 140.9, 153., 166.; HRMS (ESI-TOF)  $m/z$  [M] Calcd for  $C_{31}H_{27}BF_2N_4O_2$ , 536.2195, Found; 536.2191.

**BDP5.** A mixture of **BDP1** (580 mg, 1.52 mmol), 1-(prop-2-yn-1-yl)-1H-pyrrole-2-carboxaldehyde (2.02 g, 15.2 mmol), and molecular sieves (3 Å, ~1.0 g) in acetonitrile (46 mL) was treated with acetic acid (58 µL) and piperidine (116 µL). The resulting mixture was refluxed for 18 hours, protected by light. Upon reaction completion, the mixture was concentrated. Column chromatography [silica, hexanes/ $CH_2Cl_2$  (1:2), second band (green)] provided a dark green solid. The semi-pure product was washed with hexanes to remove excess aldehyde. Product is a dark green solid (612.6 mg, 67% yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  1.41 (s, 6H), 2.47 (t,  $J$  = 2.5 Hz, 2H), 3.98 (s, 3H), 4.78 (d,  $J$  = 2.5 Hz, 4H), 6.26 (m, 2H), 6.57 (s, 2H), 6.83 (dd,  $J$  = 1.1 Hz, 3.9 Hz, 2H), 6.89 (dd,  $J$  = 1.6 Hz, 2.6 Hz, 2H), 7.19 (d,  $J$  = 16.0 Hz, 2H), 7.46 (m, 4H), 8.18 (d,  $J$  = 8.5 Hz, 2H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta$  14.9, 36.9, 52.5, 74.9, 77.8, 110.2, 111.8, 116.4, 117.6, 123.4, 124.8, 129.3, 130.3, 130.7, 131.5, 132.9, 135.2, 140.5, 141.0, 152.8, 166.7; HRMS (ESI-TOF)  $m/z$  [M] Calcd for  $C_{37}H_{31}BF_2N_4O_2$ , 612.2509, Found; 612.2501.

**BDP6.** A mixture of **BDP1** (80 mg, 0.209 mmol), *p*-*N,N*-dimethylaminobenzaldehyde (312 mg, 2.09 mmol), and molecular sieves (4 Å, ~1.0 g) in acetonitrile (8 mL) was treated with acetic acid (96 µL) and piperidine (248 µL). The reaction was refluxed for two days, protected from light. The resulting mixture was dissolved in ethyl acetate, washed (water and brine), dried ( $Na_2SO_4$ ), and concentrated. Column chromatography [silica, hexanes/ $CH_2Cl_2$  (1:5), third band (green)] provided a dark red solid (60.2 mg, 45% yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  1.39 (s, 6H), 3.03 (s, 12H), 3.97 (s, 3H), 6.59 (s, 2H), 6.71 (d,  $J$  = 8.9 Hz, 4H), 7.19 (d,  $J$  = 16.1 Hz, 2H), 7.45 (d,  $J$  = 8.5 Hz, 2H), 7.53 (m, 6H), 8.16 (d,  $J$  = 8.5 Hz, 2H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta$  14.9, 40.4, 52.4, 112.2, 114.9, 117.5, 125.1, 129.3, 129.4, 129.4, 130.2, 130.6, 130.6, 136.8, 140.6, 140.8,

151.0, 153.2, 166.8; HRMS (ESI-TOF)  $m/z$  [M] Calcd for  $C_{39}H_{39}BF_2N_4O_2$ , 644.3135, Found; 644.3132.

**BDP7.** A mixture of **BDP1** (0.668g, 1.75 mmol), *p*-propargyloxybenzaldehyde (0.617 g, 3.85 mmol), and molecular sieves (3Å ~1g) in anhydrous MeCN (70 mL) was treated dropwise with AcOH (2.1 mL, 0.25 mmol) and piperidine (3.5 mL, 0.25 mmol) and refluxed under  $N_2$ . After 21 hours, the reaction mixture was concentrated to dryness. Column chromatography [silica, hexanes/ $CH_2Cl_2$  (1:1)→(2:3)→(1:2)→(0:1)] yielded a blue-gold solid, with a minor impurity visible on TLC, located just beneath product. This impurity was removed by dissolving product in  $CH_2Cl_2$  and precipitating through addition of hexanes. Precipitate was filtered and dried, yielding a blue-gold solid (732 mg, 63%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  1.42 (s, 6H), 2.56 (t,  $J$  = 2.3 Hz, 2H), 3.98 (s, 3H), 4.74 (s, 4H), 6.62 (s, 2H), 7.02 (d,  $J$  = 8.8 Hz, 4H), 7.22 (d,  $J$  = 16.1 Hz, 2H), 7.46 (d,  $J$  = 8.1 Hz, 2H), 7.59-7.64 (m, 6H), 8.19 (d,  $J$  = 8.1 Hz, 2H);  $^{13}C$  NMR ( $CDCl_3$ , 126 MHz):  $\delta$  15.1, 52.8, 56.2, 76.2, 78.6, 115.8, 118.0, 118.2, 129.3, 129.4, 130.6, 131.1, 133.1, 136.3, 137.1, 140.5, 141.9, 153.4, 158.7, 166.9; HRMS (ESI-TOF)  $m/z$   $[M+H]^+$  Calcd for  $C_{41}H_{34}BF_2N_2O_4$  666.2503; Found 666.2501.

**BDP8.** A mixture of **BDP5** (613 mg, 1.00 mmol), azide **1** (1.87 g, 8.00 mmol),  $CuSO_4 \cdot 5H_2O$  (335 mg, 1.34 mmol), and L-ascorbic acid (266 mg, 1.34 mmol) in acetone/water ((5:1), 6 mL). Was placed in a microwave tube and irradiated at 65 $^{\circ}C$  for one hour, as described in *General Experimental Section*. The resulting mixture was diluted with ethyl acetate, washed (water and brine), dried ( $Na_2SO_4$ ) and concentrated. Column chromatography [ethyl acetate/ $CH_3OH$  (10:1), third band (green, red fluorescent)] provided a dark green sticky solid (544 mg, 51% yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  1.37 (s, 6H), 3.33 (s, 6H), 3.54 (m, 27H), 3.80 (m, 4H), 3.96 (s, 3H), 4.46 (m, 4H), 5.33 (s, 4H), 6.25 (dd,  $J$  = 2.7 Hz, 3.7 Hz, 2H), 6.53 (s, 2H), 6.83

(dd,  $J = 1.4$  Hz, 3.9 Hz, 2H), 6.88 (dd,  $J = 1.6$  Hz, 2.6 Hz, 2H), 7.19 (d,  $J = 16.1$  Hz, 2H), 7.38 (d,  $J = 16.0$  Hz, 2H), 7.42 (d,  $J = 8.5$  Hz, 2H), 7.48 (s, 2H), 8.16 (d,  $J = 8.45$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  15.0, 43.4, 50.7, 52.7, 59.3, 69.6, 70.8, 72.2, 110.6, 111.7, 116.2, 118.0, 123.6, 124.1, 125.6, 129.5, 130.5, 131.0, 131.6, 133.1, 135.2, 140.7, 141.2, 145.1, 152.9, 166.9.; HRMS (ESI-TOF)  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{55}\text{H}_{69}\text{BF}_2\text{N}_{10}\text{O}_{10}$ , 1079.5341, Found; 1079.5329.

**BDP9.** A suspension of **BDP7** (150.0 mg, 0.225 mmol), azide **1** (136.5 mg, 0.585 mmol),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (28.1 mg, 0.113 mmol), L ascorbic acid sodium salt (22.4 mg, 0.113 mmol) in acetone/ $\text{H}_2\text{O}$  (5:1, 48 mL) was placed in 80 mL microwave vessel. The contents of the vessel were then subjected to two microwave irradiation cycles of, 30-minute hold time, power of 150W at 65 °C. TLC indicated reaction was incomplete, thus another batch of **1** (136.5 mg, 0.585 mmol) was added, and a third microwave exposure was performed. After third exposure reaction was still incomplete, another batch of **1** (136 mg, 0.585 mmol)  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (28.1 mg, 0.113 mmol) and sodium ascorbate 22.4 mg (0.113 mmol) were added, and the contents were exposed to two further irradiation cycles for a total of five cycles (2.5 hours). Once the reaction was determined to be complete (TLC), the reaction was diluted with  $\text{CH}_2\text{Cl}_2$ , washed (water and brine), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Column chromatography [silica,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (1:0)  $\rightarrow$  (40:1)  $\rightarrow$  (30:1)  $\rightarrow$  (20:1)] yielded a dark blue oil, that solidified upon prolonged drying under high vacuum.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.39 (s, 6H), 3.33 (s, 6H), 3.48-3.52 (m, 4H), 3.58-3.62 (m, 20H), 3.87 (t,  $J = 5.0$  Hz, 4H), 3.96 (s, 3H), 4.55 (t,  $J = 5.0$  Hz, 4H), 7.02 (d,  $J = 8.8$  Hz, 4H), 7.20 (d,  $J = 16.2$  Hz, 2H), 7.43 (d,  $J = 8.4$  Hz, 2H), 7.53-7.62 (m, 6H), 7.86 (s, 2H), 8.17 (d,  $J = 8.5$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  15.1, 50.6, 52.7, 59.3, 62.3, 69.7, 70.7, 70.76, 70.82, 70.83, 72.2, 115.5, 117.6, 118.1, 124.5, 129.2, 129.4, 130.2, 130.5, 131.0, 133.0, 136.3, 136.9, 140.4, 141.8, 143.9,



153.3, 159.4, 166.8; HRMS (ESI-TOF)  $m/z$   $[M+Na]^+$  Calcd for  $C_{59}H_{71}BF_2N_8O_{12}Na$  1155.5154; Found 1155.5170.

**Supporting Information Available.** Structure of model compound **BDP10**, details of calculations, and copies of  $^1H$  and  $^{13}C$  spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>

**Acknowledgement.** This work was supported by the National Cancer Institute of the National Institutes of Health under Award Number U01CA181628. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## References

- (1) Ptaszek, M. Rational Design of Fluorophores for In Vivo Applications. *Prog. Mol. Biol. Transl. Sci.* **2013**, *113*, 59–108.
- (2) Escobedo, J. O., Rusin, O, Lim, S. and Strongin, R. M. NIR dyes for bioimaging applications. *Curr. Opin. Chem. Biol.* **2010**, *14*, 64-70.
- (3) Won, M.; Li, M.; Kim, H. S.; Liu, P.; Koo, S.; Son, S.; Seo, J. H.; Kim, J. S. Visible to Mid IR: A Library of Multispectral Diagnostic Imaging. *Coord. Chem. Rev.* **2021**, *426*, 213608.
- (4) Hong, G.; Antaris, A. L.; Dai, H. Near-Infrared Fluorophores for Biomedical Bioimaging. *Nature Biomed. Eng.* **2017**, *1*, Article Number 0010.
- (5) Loudet, A.; Burgess K. BODIPY Dyes and Their Derivatives: Synthesis and Spectroscopic Properties. *Chem. Rev.* **2007**, *107*, 4891-4932.

- (6) Lu, H.; Mack, J.; Yang, Y.; Shen, Z. Structural Modification Strategies for the Rational Design of Red/Near-IR Region BODIPYs. *Chem. Soc. Rev.* **2014**, *43*, 4778-4823.
- (7) Qin, W.; Rohand, T.; Dehaen, W.; Clifford, J. N.; Driesen, K.; Beljonne, D.; Van Aeverbeke, B.; Van der Auweraer, M.; Boens, N. Boron Dipyrromethane Analogs with Phenyl, Styryl, and Ethynylphenyl Substituents: Synthesis, Photophysics, Electrochemistry, and Quantum-Chemical Calculations. *J. Phys. Chem. A* **2007**, *111*, 8588-8597.
- (8) Dost, Z.; Atilgan, S.; Akkaya, E. U. Distyryl-boradiazaindacenes: Facile Synthesis of Novel Near IR Emitting Fluorophores. *Tetrahedron*, **2006**, *62*, 8484-8488.
- (9) Deniz, E.; Isbasar, C.; Bozdemir, Ö. A.; Yildirim, L. T.; Siemierczuk, A.; Akkaya, E. U. Bidirectional Switching of Near IR Emitting Boradiazaindacene Fluorophores. *Org. Lett.* **2008**, *10*, 3401-3403.
- (10) Galangan, O.; Dumas-Verdes, C.; Méallet-Renault, R.; Clavier, G. Rational Design of Visible and NIR Distyryl-BODIPY Dyes from a Novel Fluorinated Platform. *Org. Biomol. Chem.* **2010**, *8*, 4546-4553.
- (11) Jiang, X.-D.; Fang, T.; Liu, X.; Xi, D. Synthesis of meso-CF<sub>3</sub>-Substituted BODIPY Compounds with Redshifted Absorption. *Eur. J. Org. Chem.* **2017**, *34*, 5074-5079.
- (12) Yang, J.; Cai, F.; Desbois, N.; Huang, L.; Gros, C. P.; Bolze, F.; Fang, Y.; Wang, S.; Xu, H.-J. Synthesis, Spectroscopic Characterization, One and Two-photon Absorption Properties and Electrochemistry of  $\pi$ -expanded BODIPY Dyes. *Dyes and Pigments*. **2020**, *175*, 108173.

- (13) Kobayashi, H.; Ogawa, M.; Choyke, Alford, R. Choyke, P. L. Urano, Y. New Strategies for Fluorescence Probe Design in Medical Diagnostic Imaging. *Chem. Rev.* **2010**, *110*, 2620-2640.
- (14) Baruah, M.; Qin, W.; Flors, C.; Hofkens, J.; Valée, R. A. L.; Beljonne, D.; Van der Auweraer, M.; De Borggraeve, W. M.; Boens, N. Solvent and pH Dependent Fluorescent Properties of a Dimethylaminostyryl Borondipyrromethene Dye in Solution. *J. Phys. Chem. A*, **2006**, *110*, 5998-6009.
- (15) Bozdemir, O. A.; Guliyev, R.; Buyukcakil, O.; Selcuk, S.; Koleman, S.; Gulseren, G.; Nalbantoglu, T.; Boyaci, H.; Akkaya, E. U. Selective Manipulation of ICT and PET Processes in Styryl-BODIPY Derivatives: Applications in Molecular Logic and Fluorescence Sensing of Metal Ions. *J. Am. Chem. Soc.* **2010**, *132*, 8029-8036.
- (16) Niu, S.-l.; Massif, C.; Ulrich, G.; Renard, P.-Y.; Romieu, A.; Ziessel, R. Water-Soluble Red-Emitting Distyryl-Borodipyrromethane (BODIPY) Dyes for Biolabeling. *Chem. Eur. J.* **2012**, *18*, 7229-7242.
- (17) Zhu, S.; Zhang, J.; Vegesna, G.; Luo, F.-T.; Green, S. A.; Liu, H. Highly Water-Soluble Neutral BODIPY Dyes with Controllable Fluorescence Quantum Yields. *Org. Lett.* **2011**, *13*, 438-441.
- (18) Leoage, M. L.; Mirloup, A.; Ripoll, M.; Stauffert, F.; Bodlenner, A.; Ziessel, R.; Compain, P. Design, Synthesis and Photochemical Properties of the First Examples of Iminosugar Clusters Based on Fluorescence Core. *Beilstein J. Org. Chem.* **2015**, *11*, 659-667.

- (19) He, H.; Lo, P.-C.; Yeung, S.-L.; Fong, W.-P.; Ng, D. K. P. Synthesis and In Vitro Photodynamic Activities of Pegylated Distyryl Boron Dipyrromethene Derivatives. *J. Med. Chem.* **2011**, *54*, 3097-3102.
- (20) Gibbs, J. H.; Zhou, Z.; Kessel, D.; Fronczek, F. R.; Pakhomova, S.; Vicente, M. G. H. Synthesis, Spectroscopic, and In Vitro Investigation of 2,6-Diiodo-BODIPYs with PDT and Bioimaging Applications. *J. Photochem. Photobiol. B*, **2015**, *145*, 35-47.
- (21) Uppal, T.; Bhupathiraju, N. V. S. D. K.; Vicente, M. G. H. Synthesis and Cellular Properties of Near-IR BODIPY-PEG and Carbohydrate Conjugates. *Tetrahedron*, **2013**, *69*, 4697-4693.
- (22) Zhang, Q.; Cai, Y.; Wang, X.-J.; Xu, J.-L.; Ye, Z.; Wang, S.; Seeberger, P. H.; Yin, J. Targeted Photodynamic Killing of Breast Cancer Cells Employing Heptamannosylated *b*-Cyclodextrin-Mediated Nanoparticle Formation of an Adamantane-Functionalized BODIPY Photosensitizer. *ACS Appl. Mater. Interfaces* **2016**, *8*, 33405-33411.
- (23) Liu, X.; Wu, M.; Hu, Q.; Bai, H.; Zhang, S.; Shen, Y.; Tang, G.; Ping, Y. Redox-Activated Light-Up Nanomicelle for Precise Imaging-Guided Cancer Therapy and Real-Time Pharmacokinetic Monitoring. *ACS Nano* **2016**, *10*, 11385-11396.
- (24) Meares, A.; Satraitis, A.; Akhigbe, J.; Santhanam, N.; Swaminathan, S.; Ehudin, M.; Ptaszek, M. Amphiphilic BODIPY-Hydroporphyrin Energy Transfer Arrays with Broadly Tunable Absorption and Deep Red/Near-Infrared Emission in Aqueous Micelles. *J. Org. Chem.* **2017**, *82*, 6054-6070.
- (25) Ogata, F.; Nagaya, T.; Maruoka, Y.; Akhigbe, J.; Meares, A.; Lucero, M.; Satraitis, A.;

- Fujimura, D.; Okada, R.; Inagaki, F.; Choyke, P.; Ptaszek, M.; Kobayashi, H. Activatable Near-Infrared Fluorescence Imaging Using PEGylated Bacteriochlorin-Based Chlorin and BODIPY-Dyads as Probes for Detecting Cancer. *Bioconjugate Chem.* **2019**, *30*, 169-183.
- (26) Meares, A.; Satraitis, A.; Ptaszek, M. BODIPY–Bacteriochlorin Energy Transfer Arrays: Toward Near-IR Emitters with Broadly Tunable, Multiple Absorption Bands. *J. Org. Chem.* **2017**, *82*, 13068-13075.
- (27) Bura, T.; Leclerc, N.; Fall, S.; Lévêque, P.; Heiser, T.; Retailleau, P.; Rihn, S.; Mirloup, A.; Ziessel, R. High-Performance Solution-Processed Solar Cells and Ambipolar Behavior I Organic Field-Effect Transistors with Thienyl-BODIPY Scaffold. *J. Am. Chem. Soc.* **2012**, *134*, 17404-17407.
- (28) Harris, J.; Gai, L.; Kubheka, G.; Mack, J.; Nnyokong, T.; Shen, Z. Optical Limiting Properties of 3,5-Dithienylenevinylene BODIPY Dyes at 532 nm. *Chem. Eur. J.* **2017**, *23*, 14507-14517.
- (29) Teng, K.-X.; Niu, L.-Y.; Li, J.; Jia, L.; Yang, Q.-Z. An Unexpected Coupling-Reduction Tandem Reaction for the Synthesis of Alkenyl-Substituted BODIPYs. *Chem. Comm.* **2019**, *55*, 13761-13764.
- (30) Brzeczek, A.; Piwowar, K.; Domagala, W.; Mikolajczyk, M. N.; Walczak, K.; Wagner, P. Systematic Elongation of Thienyl Linkers and Their Effects on Optical and Electrochemical Properties in Carbazole-BODIPY Donor-Acceptor Systems. *RSC Adv.*, **2016**, *6*, 36500-36509.

- (31) Dixit, S.; Awasthi, A.; Ash, S.; Singh, P. K.; Agarwal, N. Synthesis and Photophysical Properties of Near Infra-Red Absorbing BODIPY Derivatives and their Nanoaggregates. *J. Photochem. Photobiol. A*, **2018**, *365*, 1-6.
- (32) Thumugants, G.; Gupta, V.; Singh, S. P. New Dithienosilole- and Dithienogermanole-based BODIPY for Solar Cell Applications. *New J. Chem.* **2019**, *43*, 8735-8740.
- (33) Kurowska, A.; Brzeczek-Szafran, A.; Zassowski, P.; Lapkowski, M.; Domagala, W.; Wagner, P.; Wagner, K. Mono and Di-substituted BODIPY with Electron Donating Carbazole, Thiophene, and 3,4-Ethylenedioxythiophene Units. *Electrochimica Acta* **2018**, *271*, 685-698.
- (34) Kim, S.; Ohulchansky, T. Y.; Baev, A.; Prasad, P. N. Synthesis and Nanoparticle Encapsulation of 3,5-Difuranyl-boradiaza-s-indacenes for Near-infrared Fluorescence Imaging. *J. Mater. Chem.* **2009**, *19*, 3181-3188.
- (35) Gibbs, J. H.; Zhou, Z.; Kessel, D.; Fronczek, F. R.; Pakhomova, S.; Vicente, M. G. H. Synthesis, Spectroscopic, and *in vitro* Investigation of 2,6-diiodo-BODIPYs with PDT and Bioimaging Applications. *J. Photochem. Photobiol. B.*, **2015**, *145*, 35-47.
- (36) Gotor, R.; Costero, A. M.; Gil, S.; Gaviña, P.; Rurack, K. On the Ion-Pair Recognition and Indication Features of a Fluorescent Heteroditopic Host Based on BODIPY Core. *Eur. J. Org. Chem.* **2014**, 4005-4013.
- (37) Iv, Y.; Xu, J.; Guo, Y.; Shao, S. A Novel Calorimetric and Fluorometric Anion Sensor Based on BODIPY-Calix[4]pyrrole Conjugate. *J. Incl. Phenom. Macrocycl. Chem.* **2012**, *72*, 95-101.

- (38) Lee, J.-S.; Kang, N.-y.; Kim, Y. K.; Samanta, A.; Feng, S.; Kim, H. K.; Vendrell, M.; Park, J. H.; Chang, Y.-T. Synthesis of a BODIPY Library and its Application to the Development of Live Cell Glucagon Imaging Probe. *J. Am. Chem. Soc.* **2009**, *131*, 10077-10082.
- (39) Lee, J.-S.; Kim, H. K.; Feng, S.; Vendrell, M.; Chang, Y.-T. Accelerating Fluorescent Sensor Discovery: Unbiased Screening of a Diversity-Oriented BODIPY Library. *Chem. Commun.* **2011**, *47*, 2339-2341.
- (40) Merkes, J. M.; Lammers, T.; Kancherla, R.; Rueping, M.; Kiessling, F.; Banala, S. Tuning Optical Properties of BODIPY Dyes by Pyrrole Conjugation for Photoacoustic Imaging. *Adv. Optical. Mater.* **2020**, *8*, 1902115.
- (41) Nguyen, A. L.; Bobadova-Parvanova, P.; Hopfinger, M.; Fronczek, F. R.; Smith, K. M.; Vicente, M. G. H. Synthesis and Reactivity of 4,4-Dialkoxy-BODIPYs: An Experimental and Computational Study. *Inorg. Chem.* **2015**, *54*, 3228-3236.
- (42) Fedeli, S.; Paoli, P.; Brandi, A.; Venturini, L.; Giambastiani, G.; Tuci, G.; Cicchi, S. Azido-Substituted BODIPY Dyes for the Production of Fluorescent Carbon Nanotubes. *Chem. Eur. J.* **2015**, *21*, 15349-15353.
- (43) Valeur, B., *Molecular fluorescence: principles and applications*. Weinheim; New York: Wiley-VCH, 2002.
- (44) Ji, S.; Ge, J.; Escudero, D.; Wang, Z.; Zhao, J.; Jacquenin, D. Molecular-Structure-Intersystem Crossing Relationship of Heavy-Atom-Free BODIPY Triplet Photosensitizer. *J. Org. Chem.* **2015**, *80*, 5958-5963.

- (45) Mandal, A. K.; Taniguchi, M.; Diers, J. R.; Niedzwiedzki, D. M.; Kirmaier, C.; Lindsey, J. S.; Bocian, D. F.; Holten, D. Photophysical Properties and Electronic Structure of Porphyrins Bearing Zero to Four meso-Phenyl Substituents: New Insights into Seemingly Well Understood Tetrapyrroles *J. Phys. Chem. A*, **2016**, *120*, 9719-9731.
- (46) Lubman, D. M.; Kronick, M. N. Multiwavelength-Selective Ionization of Organic Compounds in an Ion Mobility Spectrometer. *Anal. Chem.* **1983**, *55*, 867-873.
- (47) Cooper, C. D.; Williamson, A. D.; Miller, J. C.; Compton, R. N. Resonantly Enhanced Multiphoton Ionization of Pyrrole, *N*-Methyl Pyrrole and Furan. *J. Chem. Phys.* **1980**, *73*, 1527-1537.
- (48) Hsu, C.-W.; Liao, C.-L.; Ma, Z.-X.; Ng, C. Y. Direct Identification of Photofragment Structures Formed in the 193 nm Photodissociation of Thiophene. *J. Phys. Chem.* **1995**, *99*, 1760-1767.
- (49) Distefano, G.; Jones, D.; Guerra, M.; Favaretto, L.; Modelli, A.; Mengoli, G. Determination of the Electronic Structure of Oligofurans and Extrapolation to Polyfuran. *J. Phys. Chem.* **1991**, *95*, 9746-9753.
- (50) Data taken from NIST:  
  
<https://webbook.nist.gov/cgi/cbook.cgi?ID=C100663&Mask=20>
- (51) Sunahara, H.; Urano, Y.; Kojima, H.; Nagano, T. Design and Synthesis of a Library of BODIPY-based Environmental Polarity Sensors Utilizing Photoinduced Electron-transfer-controlled Fluorescence ON/OFF Switching. *J. Am. Chem. Soc.* **2007**, *129*, 5597-5604.



- (52) Sahin, T.; Harris, M. A.; Vairaprakash, P.; Niedzwiedzki, D. M.; Subramanian, V.; Shreve, A. P.; Bocian, D. F.; Holten, D.; Lindsey, J. S. Self-Assembled Light-Harvesting System from Chromophores in Lipid Vesicles. *J. Phys. Chem. B* **2015**, *119*, 10231-10243.
- (53) Inagaki, F. F.; Fukimura, D.; Ansteatt, S.; Okada, R.; Furusawa, A.; Choyke, P. L.; Ptaszek, M.; Kobayashi, H. Effect of Short PEG on Near-Infrared BODIPY-Based Activatable Optical Probes. *ACS Omega*, **2020**, *5*, 15657-15665.
- (54) Dan, K.; Bose, N.; Ghosh, S. Vesicular Assembly and Thermo-responsive Vesicle-to-micelle Transition from an Amphiphilic Random Copolymer. *Chem. Commun.* **2011**, *47*, 12491-12493.