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Synthesis and spectral characteristics of halogen-substituted *meso*-carboxypropyl-BODIPYs as effective photosensitizers

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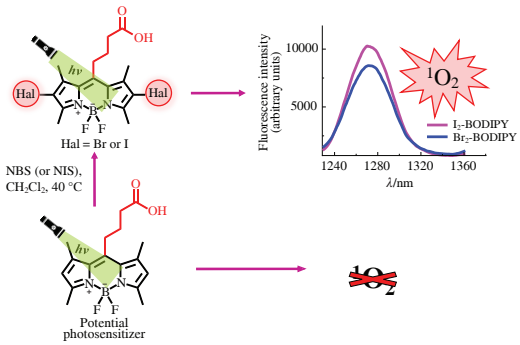
New luminophores, diiodo- and dibromo-substituted *meso*-BODIPY carboxylic acids, were synthesized. The compounds efficiently generate singlet oxygen and possess high affinity for hydrophilic biospheres, suggesting the dyes as potential photosensitizers for antimicrobial photodynamic therapy.



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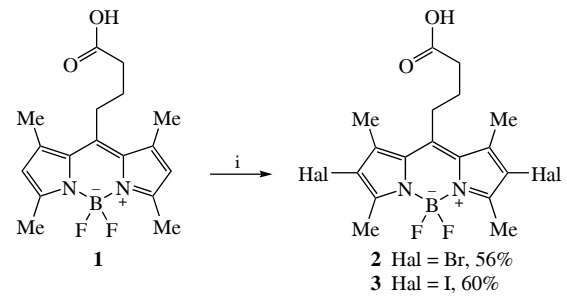
The global rise in antibiotic resistance is a major public health problem worldwide. The complexity of polymicrobial communities creates a scientific challenge to find an effective treatment strategy; thus, the development of new photosensitizers (PSs) for antimicrobial therapy of infective diseases is an urgent and demanding task. The method of antimicrobial photodynamic therapy is a potential treatment strategy providing elimination of pathogenic pathogens without resistance development. It is based on the selective accumulation and retention of PSs as triplet-excitable dyes directly in microorganism cells.[1–5] Recent studies[6–8] have shown that halogen-substituted borondipyrromethenates (BODIPYs, with boron oxidation state being B^{III}) endowed with the ability to efficiently generate singlet oxygen can be promising candidates for the role of PSs. The introduction of 'heavy' halogen atoms into the dipyrromethene core of BODIPY is the simplest and most convenient way to enhance the spin forbidden radiationless and radiative processes of the intersystem crossing and $T_1 \rightarrow S_0$, respectively, and allows one to shift the maxima of the absorption and fluorescence bands to the red region noticeably (by more than ~40–60 nm).[6,9] Structural modification of the dipyrromethene core by moving from *meso*-alkyl-substituted BODIPYs to relative carboxyalkyl analogues significantly increases the photostability of the luminophores[10] and increases their solubility in aqueous media, including physiological ones. This is important for biological studies.[11]

Previously,[10,12] we demonstrated that halogenated *meso*-BODIPY esters possessed high singlet oxygen generation efficiency and higher lipophilicity compared to the non-halogenated precursor. In order to address issues such as low water solubility and poor bioavailability of potential PSs, we focused on the preparation of diiodo- and dibromo-substituted BODIPYs containing a butanoic acid residue in a methine *meso*-spacer. In this work, the influence of the nature of the 'heavy' atom and the medium on the spectral and generation properties of halogen-containing BODIPY carboxylic acids were analysed and the affinity of the dyes for biosolids were evaluated.

The synthesis of the starting BODIPY carboxylic acid **1** has been published previously.[11] Dibromo- and diiodo-BODIPYs **2** and **3** were prepared by halogenation of compound **1** with *N*-halogenosuccinimides (Scheme 1).

The spectral properties of BODIPYs **2**, **3** were studied in different media, namely, non-polar (cyclohexane, toluene), aprotic polar (chloroform) and protic polar (ethanol, 1-propanol and 1-octanol). The initial *meso*-BODIPY butanoic acid **1** served as a reference. Quantitative spectral characteristics of the studied compounds are given in Table 1.

The electronic absorption spectra of BODIPYs **1**–**3** had two bands of different intensity due to $S_0 \rightarrow S_n$ electronic transitions: the first most intense S_0–S_1 absorption band (496–538 nm, $\lg\varepsilon$ from 4.65 to 4.89) with a shoulder on the left slope, and the second low intensity S_0–S_2 band in the range of 355–395 nm. The fluorescence spectra of the dyes have a single band with a



Scheme 1 *Reagents and conditions*: i, NBS (for **2**) or NIS (for **3**), CH_2Cl_2, 40 °C.

Table 1 Spectral characteristics of BODIPY **1** and its halogenated analogues **2**, **3** in organic solvents.

Solvent	λ^{abs}_{max}/nm,[a] (lg ε)[b]	λ^{fl}_{max}/nm[a]	$\Delta\nu_{St}$/cm^{-1} [c]	φ^{fl} [d]
		1[11]		
Cyclohexane	361–367; 503 (s. s.) [e]	518	575	0.85
Toluene	356–363; 502 (4.89)	517	578	0.82
Chloroform	359–365; 502 (4.85)	517	577	0.90
1-Octanol	359–362; 500 (4.87)	513	507	0.93
1-Propanol	359–368; 499 (4.86)	512	509	0.83
Ethanol	355–375; 496 (4.80)	510	553	0.80
Water	353–365; 493 (4.82)	508	599	0.70
		2		
Cyclohexane	373–380; 536 (s. s.) [e]	550	475	0.26
Toluene	377–383; 534 (4.78)	549	512	0.25
Chloroform	377–385; 534 (4.68)	549	511	0.25
1-Octanol	374–380; 528 (4.72)	543	523	0.25
1-Propanol	373–377; 526 (4.73)	542	561	0.23
Ethanol	371–378; 525 (4.68)	541	563	0.20
Water/Ethanol (1 : 1)	374–380; 526 (–)	543	595	0.17
		3		
Cyclohexane	384–388; 538 (s. s.)[e]	554	537	0.04
Toluene	391–395; 537 (4.83)	553	539	0.03
Chloroform	536 (4.80)	552	541	0.02
1-Octanol	384–390; 531 (4.79)	548	584	0.02
1-Propanol	380–389; 529 (4.80)	546	589	0.02
Ethanol	380–386; 531 (4.80)	549	617	0.02
Water/Ethanol (1 : 1)	381–388; 530 (–)	549	653	0.01

[a] λ^{abs}_{max} and λ^{fl}_{max} stand for absorption maximum wavelength and emission, respectively. [b] lg ε stands for the logarithm of the molar extinction coefficient. [c] $\Delta\nu_{St}$ stands for the Stokes shift. [d] φ^{fl} stands for the fluorescence quantum yield. [e] (s. s.) is slightly soluble.

maximum at 510–554 nm, mirroring the intense absorption band (Figure 1).

The presence of 'heavy' bromine or iodine atoms at the positions 2 and of the BODIPY moiety in luminophores **2** and **3** causes a noticeable bathochromic shift of the absorption (up to ~35 nm) and fluorescence (up to ~42 nm) band maxima compared to BODIPY **1** (see Figure 1, Table 1). This probably relates to the enhancement polarisation of the dipyrromethene chromophores due to the manifestation of the total electronic effects of bromine or iodine atoms. At the same time, the influence of the nature of halogen atoms leads to a small (2–6 nm) bathochromic shift of the intense absorption band when bromine is replaced by iodine.

Dibromination of luminophore **2** is accompanied by a decrease in the fluorescence quantum yield up to ~4-fold compared to BODIPY **1** (see Table 1). More effective (up to ~40 times) fluorescence quenching is registered in the case of diiodo BODIPY **3**. This is obviously caused by the enhancement of intersystem crossing due to an increase in spin–orbit interactions as a consequence of the effect of a heavier iodine atom.[13–15] The introduction of a butanoic acid residue into the *meso*-position of

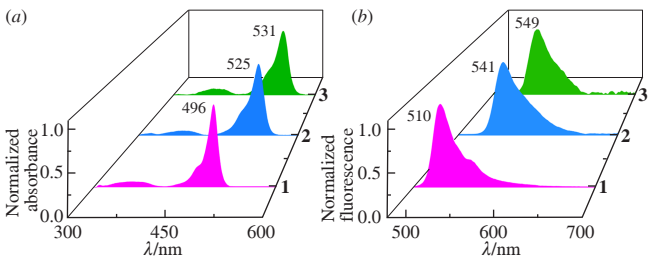


Figure 1 Normalized (*a*) electronic absorption and (*b*) fluorescence spectra of BODIPY **1** and its halogenated analogues **2**, **3** in ethanol.

the BODIPY core leads to a blue shift (by ~1–9 nm) of the absorption band maximum compared to the *meso*-unsubstituted tetramethylated analogues.[16] This may result from depolarisation of the BODIPY chromophore system due to the manifestation of the total electronic effect from the bulky carboxy substituent and a slight distortion of the plane of the aromatic system of the chromophore. A similar effect was recorded previously for the structurally related diiodinated *meso*-BODIPY ester.[17]

The Stokes shift ($\Delta\nu_{St}$) of *meso*-BODIPYs **1**–**3** increases ~1.3–2.5 times (see Table 1) compared to that of the *meso*-unsubstituted analogue ($\Delta\nu_{St}$ = 191–461 cm^{-1}). The observed effect may be caused by structural differences in the geometry of the ground and excited states of luminophore molecules due to conformational mobility of the bulk *meso*-substituent.[18]

The influence of the nature of the solvent on the spectral properties of BODIPYs **1**–**3** is manifested in a slight hypsochromic shift (up to ~11 nm) of the intense absorption band in the transition from hydrocarbons (cyclohexane, toluene) to polar proton-donor alcohols (see Table 1). The fluorescence of BODIPY **1** is practically independent of the solvent properties. On the contrary, the quantum yield of fluorescence of dibromo and diodo luminophores **2**, **3** is maximal in cyclohexane and insignificantly decreases (up to ~1.3 times) in toluene. A more marked fall in values is recorded in alcohols (up to ~2 times), especially in ethanol. It should be noted that, in contrast to BODIPY **1**, the $\Delta\nu_{St}$ values for halogenated analogues **2** and **3** increase markedly (up to ~1.2 times) upon transition from nonpolar to polar media. The observed effect is probably due to an increase in the dipole moment of the luminophore molecule in the excited state and an increase in its solvation by polar solvents.[19]

To evaluate the possibility of using dibromo and diiodo BODIPYs **2**, **3** in biological studies, we performed additional experiments to obtain the spectral-luminescent characteristics of the luminophores in a binary 1 : 1 ethanol–water mixture. In both cases, the addition of water (f_w = 50%) to ethanol solutions of BODIPYs **2**, **3** has almost no effect on the position of the band maxima in the absorption (fluorescence) spectra and results in lower φ^{fl} values (1.17 and 1.42 times) compared to the fluorescence quantum yield in pure ethanol (see Table 1 and Figure S9 of the Online Supplementary Materials). According to the literature,[11] the observed changes are probably due to the partial formation of non-fluorescent aggregated forms, which is the topic of our further studies.

The quantum yield values of singlet oxygen (Φ_Δ) in ethanol were determined as reported[20] using the intensity values of the phosphorescence spectrum of $^1O_2$ at 1270 nm (see Online Supplementary Materials, part 'Singlet oxygen generation'). At the same time, the quantum yield values of singlet oxygen generation of photosensitizers **2**, **3** were quite high and were Φ_Δ ~66 and ~78%, respectively. The intensity of the emission band at 1270 nm (Figure S10) and the Φ_Δ values increase (up to ~1.2 times) on moving from bromo BODIPY **2** to its iodo analogue **3** due to intersystem crossing enhancement and photochemical reaction with energy transfer from phosphor to molecular oxygen.[14]

To evaluate the affinity of dyes **2**, **3** to bio-environments, the log*P* distribution coefficient values of BODIPYs **1**–**3** in a two-phase water-octanol model system were determined. All studied BODIPYs **1**–**3** partially transferred from the octanol solution to the aqueous phase, giving it weak colouration and luminescence. The values of log*P* distribution coefficients increased in the sequence: **1** (0.97), **3** (0.99), **2** (1.10). The results obtained allow us to conclude that the introduction of butanoic acid residue into the dipyrromethene core **1**–**3** significantly (~1.7–1.9 times) increases the affinity of luminophores to hydrophilic media

compared to structurally related dibromo and diiodo BODIPY esters.[12]

To conclude, the optimal combination of spectral characteristics with high singlet oxygen generation efficiency and affinity for hydrophilic media allow us to propose dibromo- and diiodo-*meso*-carboxypropyl BODIPYs as promising photosensitizers for biological and medical applications.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7573.

References

1 C. Garapati, S. H. Boddu, S. Jacob, K. M. Ranch, C. Patel, R. J. Babu, A. K. Tiwari, and H. Yasin, *Arab. J. Chem.*, 2023, **16**, 104583; https://doi.org/10.1016/j.arabjc.2023.104583.

2 P. Dharmaratne, D. N. Sapugahawatte, B. Wang, C. L. Chan, K.-M. Lau, C. B. Lau, K. P. Fung, D. K. Ng and M. Ip, *Eur. J. Med. Chem.*, 2020, **200**, 112341; https://doi.org/10.1016/j.ejmech.2020.112341.

3 M. Klausen, M. Ucuncu and M. Bradley, *Molecules*, 2020, **25**, 5239; https://doi.org/10.3390/molecules25225239.

4 R. Youf, M. Müller, A. Balasini, F. Thétiot, M. Müller, A. Hascoët, U. Jonas, H. Schönherr, G. Lemercier, T. Montier and T. Le Gall, *Pharmaceutics*, 2021, **13**, 1995; https://doi.org/10.3390/pharmaceutics13121995.

5 K. G. Pavlov, D. A. Guk, R. O. Burlutsky, A. A. Moiseeva, O. O. Krasnovskaya, D. A. Lemenovskiy, N. V. Zyk and E. K. Beloglazkina, *Mendeleev Commun*., 2024, **34**, 552; https://doi.org/10.1016/j.mencom.2024.06.027.

6 M. L. Agazzi, M. B. Ballatore, A. M. Durantini, E. N. Durantini and A. C. Tomé, *J. Photochem. Photobiol., C*, 2019, **40**, 21; https://doi.org/10.1016/j.jphotochemrev.2019.04.001.

7 L. Huang and G. Han, *Small Methods*, 2018, **2**, 1700370; https://doi.org/10.1002/smtd.201700370.

8 L. Yuan, Y. Su, H. Cong, B. Yu and Y. Shen, *Dyes Pigm.*, 2023, **208**, 110851; https://doi.org/10.1016/j.dyepig.2022.110851.

9 F. Cieplik, D. Deng, W. Crielaard, W. Buchalla, E. Hellwig, A. Al-Ahmad and T. Maisch, *Crit. Rev. Microbiol.*, 2018, **44**, 571; https://doi.org/10.1080/1040841X.2018.1467876.

10 G. B. Guseva, E. N. Nuraneeva, M. B. Berezin and E. V. Antina, *J. Photochem. Photobiol., A*, 2022, **423**, 113620; https://doi.org/10.1016/j.jphotochem.2021.113620.

11 G. B. Guseva, M. M. Lukanov, A. A. Ksenofontov, E. V. Antina, S. Lisovskaya, L. E. Nikitina, A. R. Galembikova and S. V. Boichuk, *J. Photochem. Photobiol., A*, 2023, **444**, 114926; https://doi.org/10.1016/j.jphotochem.2023.114926.

12 G. B. Guseva, E. N. Lapshina, E. V. Antina, Y. V. Eremeeva, S. A. Lisovskaya, A. A. Izmailov and L. E. Nikitina, *J. Photochem. Photobiol., A*, 2024, **454**, 115700; https://doi.org/10.1016/j.jphotochem.2024.115700.

13 E. G. Azenha, A. C. Serra, M. Pineiro, M. M. Pereira, J. Seixas de Melo, L. G. Arnaut, S. J. Formosinho and A. M. d'A. Rocha Gonsalves, *Chem. Phys*., 2002, **280**, 177; https://doi.org/10.1016/S0301-0104(02)00485-8.

14 A. Karatay, M. C. Miser, X. Cui, B. Küçüköz, H. Yılmaz, G. Sevinç, E. Akhüseyin, X. Wu, M. Hayvali, H. G. Yaglioglu, J. Zhao and A. Elmali, *Dyes Pigm.*, 2015, **122**, 286; https://doi.org/10.1016/j.dyepig.2015.07.002.

15 P. P. Kiran, N. K. M. Naga Srinivas, D. R. Reddy, B. G. Maiya, A. Dharmadhikari, A. S. Sandhu, G. R. Kumar and D. N. Rao, *Opt. Commun.*, 2002, **202**, 347; https://doi.org/10.1016/S0030-4018(02)01112-4.

16 E. N. Nuraneeva, G. B. Guseva, E. V. Antina, O. A. Lodochnikova, D. R. Islamov and L. E. Nikitina, *Dyes Pigm.*, 2022, **201**, 110202; https://doi.org/10.1016/j.dyepig.2022.110202.

17 E. N. Nuraneeva, G. B. Guseva, E. V. Antina and A. I. V'yugin, *J. Photochem. Photobiol., A*, 2023, **439**, 114611; https://doi.org/10.1016/j.jphotochem.2023.114611.

18 G. B. Guseva, A. A. Ksenofontov, P. S. Bocharov, E. V. Antina and L. E. Nikitina, *J. Mol. Liq.*, 2023, **371**, 121078; https://doi.org/10.1016/j.molliq.2022.121078.

19 C. Reichardt, *Solvents and Medium Effects in Organic Chemistry*, 2nd edn., VCH, Weinheim, 1988; https://books.google.ru/books?id=hm0vAQAAIAAJ&dq=editions:ISBN0895736845&hl.

20 W. Hu, R. Zhang, X.-F. Zhang, J. Liu and L. Luo, *Spectrochim. Acta, Part A*, 2022, **272**, 120965; https://doi.org/10.1016/j.saa.2022.120965.

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