Supplementary Materials

Synthesis of water-soluble BODIPYs: BODIPY-PEG †

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General Remarks

All reactions were performed with dry glassware under nitrogen atmosphere, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates. Column chromatography was conducted using silica-gel (Aldrich Chemical CO., LLC., Silica gel, technical grade, pore size 60 A, 70-230 mesh, particle size 63-200 mm).

The glassware was pre-dried in an oven at 100 °C for 12 hours. The solvents used as reaction media (THF) were dried on a 4 Å molecular sieve under a nitrogen atmosphere and deoxygenated before use. The remaining reagent-grade solvents were used as purchased. Tetrahydrofuran (CAS 109-99-9 Sigma Aldrich).

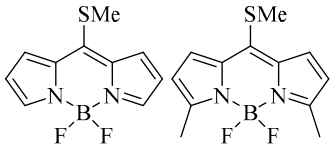
^{1}H NMR and ^{13}C NMR spectra were acquired, with a Bruker 400 (400 MHz) and Bruker 500 (500 MHz). $CDCl_3$ was used as a solvent for obtaining NMR spectra. Chemical shifts (d) are given in parts per million (ppm) from $(CH_3)_4Si$ (d 0.00 ppm for ^{1}H NMR in $CDCl_3$) or the solvent peak (*d* 7.26 ppm for ^{1}H NMR in $CDCl_3$). The solvent peak (D_2O (*d* 4.79 ppm for ^{1}H NMR) as internal reference. The solvent peak (*d* 77.0 ppm for ^{13}C NMR in $CDCl_3$) as an internal reference with coupling constants (*J*) in hertz (Hz). The abreviations s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). High-resolutioin mass spectra (HRMS) were measued a Bruker Maxis Impact II mass spectrometer.

Unless otherwise noted, materials obteined from comercial suppliers were used without further purification. Triethylene glycol monomethyl ether (CAS 112-35-6 Sigma Aldrich), Sodium carbonate (CAS 497-9-8 J. T. Baker).

Experimental Procedures.

Starting materials.

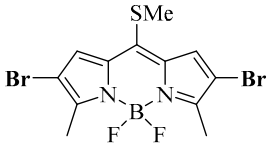
8-thiomethyl-BODIPY 1a and 3,5-dimethyl-8-methylthio-BODIPY 1b, were prepared according to procedures reported in the literature [1].



1a

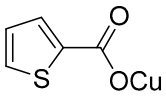
1b

3,5-dimethyl-2,6-dibromo-8-thiomethyl-BODIPY 1c was prepared according to procedure reported in the literature [2].



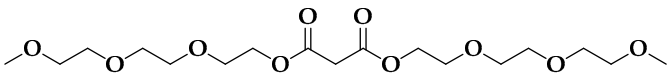
1c

CuTC (Copper(I) thiophene-2-carboxylate) was prepared according to procedures reported in the literatura [3].



CuTC

Malonic glycol ester 6 was prepared according to procedures reported in the literatura [4].



6

Typical procedure (TP1) for the pegylation of 8-thiomethyl borondipyrromethene 1a.

All reactions were initiated under an N_2 atmosphere. 1a (1.0 equiv) and 2 mL of dry THF dry were added to a Schlenk tube that had been vacuum-dried and purged three times; the mixture was then purged for 5 min. Next, CuTC (2.0 equiv) was added, and the mixture was stirred for 2 min. Finally, malonic glycol ester 6 and Na_2CO_3 (2.0 equiv) were added, and the mixture was purged for 5 min. The reaction was then left stirring at room temperature. Once the starting material was consumed, the mixture was quenched with an AcO-/AcOH buffer (pH 4, 5 mL), extracted with EtOAc (5 × 5 mL), dried over anhydrous

magnesium sulfate, filtered, and the solvent was evaporated. Silica gel (58 Å) column chromatography was performed for all compounds using gradients of EtOAc/Hex (5:8), EtOAc. Viscous liquids were obtained and subsequently placed under high vacuum for 24 h.

Typical procedure (TP2) for the pegylation of 3,5-dimethyl-8-methylthio-BODIPY 1b.

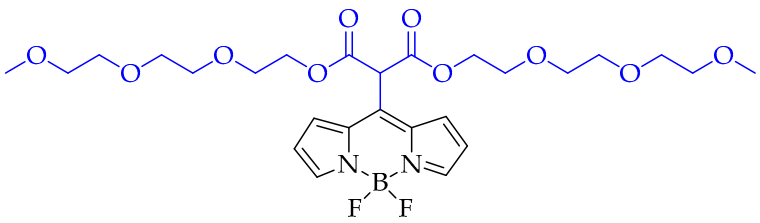
All reactions were initiated under an N_2 atmosphere. 1b (1.0 equiv) and 2 mL of dry THF dry were added to a Schlenk tube that had been vacuum-dried and purged three times; the mixture was then purged for 5 min. Next, CuTC (2 equiv.) was added, and the mixture was stirred for 2 min. Finally, malonic glycol ester 6 and Na_2CO_3 (2.0 equiv) were added, and the mixture was purged for 5 min. The reaction was then left stirring at room temperature. Once the starting material was consumed, the mixture was quenched with an AcO-/AcOH buffer (pH 4, 5 mL), extracted with EtOAc (5 × 5 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. Silica gel (58 Å) column chromatography was performed for all compounds using gradients of EtOAc/Hex (5:8), EtOAc. Viscous liquids were obtained and subsequently placed under high vacuum for 24 h.

Typical procedure (TP3) for the pegylation of 2,6-dibromo-3,5-dimethyl-8-methylthio-BODIPY 1c.

All reactions were initiated under an N_2 atmosphere. 1c (1.0 equiv) and 2 mL of dry THF dry were added to a Schlenk tube that had been vacuum-dried and purged three times; the mixture was then purged for 5 min. Next, CuTC (3 equiv.) was added, and the mixture was stirred for 2 min. Finally, malonic glycol ester 6 and Na_2CO_3 (2.0 equiv) were added, and the mixture was purged for 5 min. The reaction was then left stirring at room temperature. Once the starting material was consumed, the mixture was quenched with an AcO-/AcOH buffer (pH 4, 5 mL), extracted with EtOAc (5 × 5 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. Silica gel (58 Å) column chromatography was performed for all compounds using gradients of EtOAc/Hex (5:8), EtOAc. Viscous liquids were obtained and subsequently placed under high vacuum for 24 h.

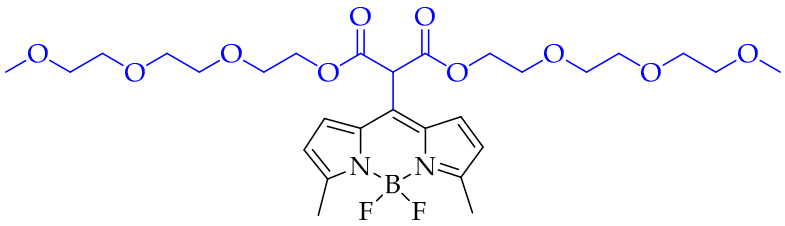
Characterization data of new Compounds.

BDP-PEG01.



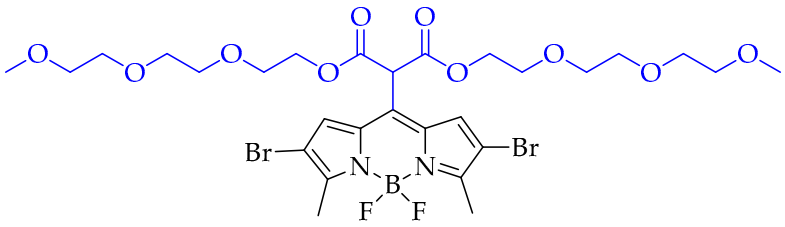
According to TP1. SMe-BODIPY 1a (50 mg, 0.21 mmol, 1.0 equiv.), 6 (166.50 mg, 0.42 mmol, 2.0 eq), Na_2CO_3 (44.5 mg, 0.42 mmol, 2.0 equiv), THF (3.5 mL, 0.06M), BODIPY-PEG01 (60 mg, 0.1 mmol). TLC (EtOAc, R*f* = 0.35); red viscous liquid; 22 h, %R= 50%; IR (KBr, cm-1): 2876 (m), 1736 (s), 1565 (s), 1451 (w), 1416 (m), 1395 (s), 1355 (m), 1259 (s), 1085 (s), 1040 (w), 965 (m), 851 (w), 779 (m), 710 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (s, 2H), 7.37 (d, J = 4.3 Hz, 2H), 6.58 (dd, J = 22.6, 4.3 Hz, 2H), 5.16 (s, 1H), 4.43 – 4.20 (m, 4H), 3.68 – 3.61 (m, 4H), 3.62 – 3.56 (m, 4H), 3.57 – 3.49 (m, 12H), 3.36 (d, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ: 165.75, 145.41, 136.60, 135.31, 130.29, 118.97, 71.88, 70.56, 70.51, 68.51, 65.90, 59.02, 53.48. HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{26}H_{37}BF_2N_2O_{10}$, M+nNa (MW 609.2407) found: 609.2406.

BDP-PEG02.



According to TP2**.** SMe-BODIPY 1b (30 mg, 0.113 mmol, 1.0 equiv), 6 (50 mg, 0.226 mmol, 2.0 equiv.), Na_2CO_3 (24 mg, 0.226 mmol, 2.0 equiv), CuTC (43 mg, 0.226 mmol, 2.0 equiv.), THF (2 mL, 0.06M), BDP-PEG02 (56 mg, 0.091 mmol). TLC (EtAcO, R*f* = 0.2); red viscous liquid; 26 h, %R= 80%; IR (KBr, cm^{-1}): 2923 (m), 1732 (s), 1573 (s), 1452 (w), 1242 (m), 1131 (s), 1099 (s), 1007 (m), 849 (w), 728 (m), 673 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, J = 4.2 Hz, 2H), 6.29 (d, J = 4.2 Hz, 2H), 5.03 (s, 1H), 4.43 – 4.20 (m, 4H), 3.69 – 3.62 (m, 4H), 3.62 – 3.58 (m, 4H), 3.57 – 3.50 (m, 12H), 3.37 (s, 6H), 2.78 – 2.42 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.64, 166.40, 158.96, 134.80, 131.59, 128.99, 127.98, 120.07, 119.69, 77.16, 76.84, 72.01, 71.97, 70.69, 70.66, 70.61, 68.94, 68.64, 65.80, 64.70, 59.17, 59.15, 52.94, 41.37, 29.81, 15.11. HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd to $C_{28}H_{41}BF_2N_2O_{10}$ M+nNa (MW 637.2720) found: 637.2023 M+nNa.

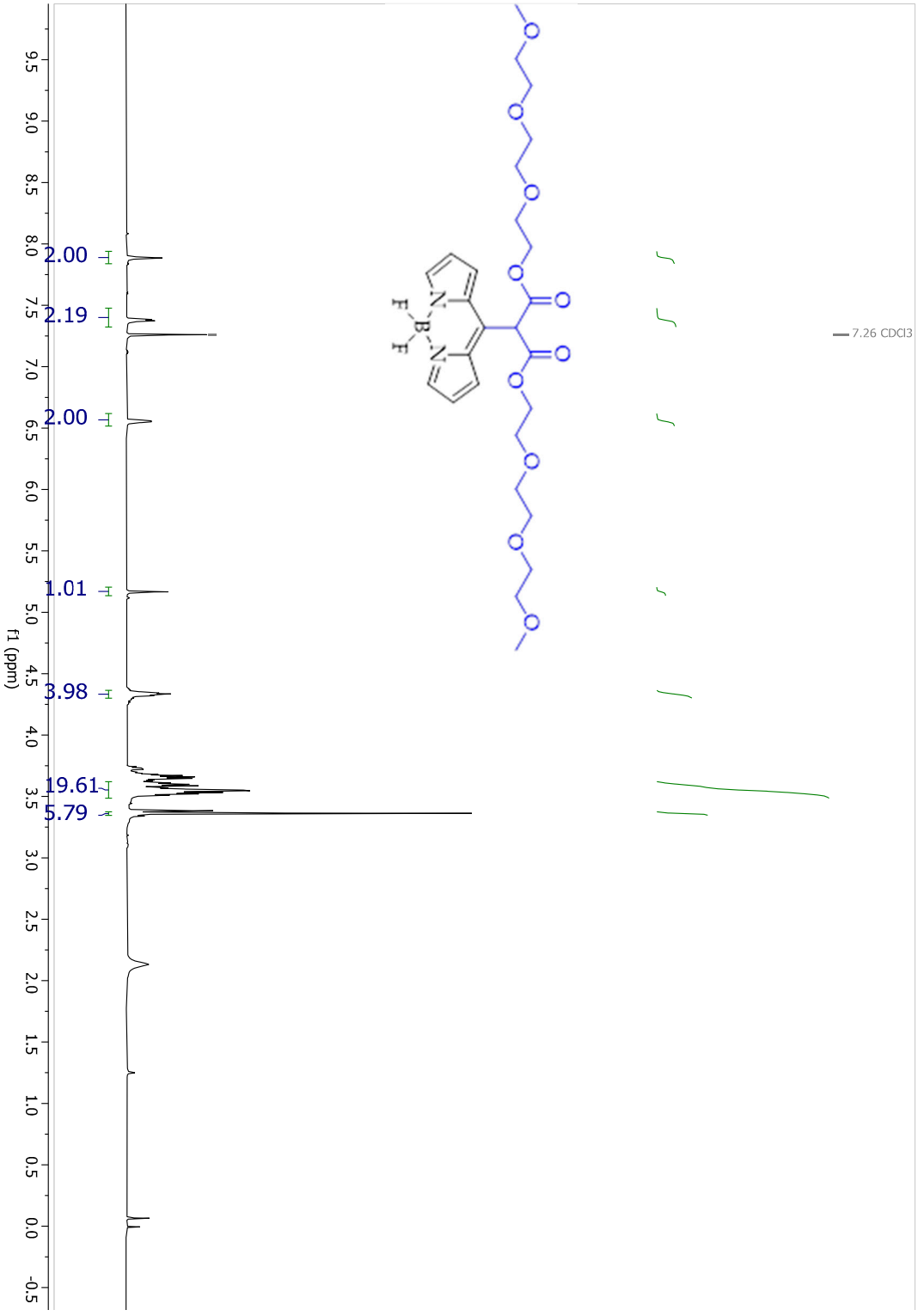
BODIPY-PEG03.

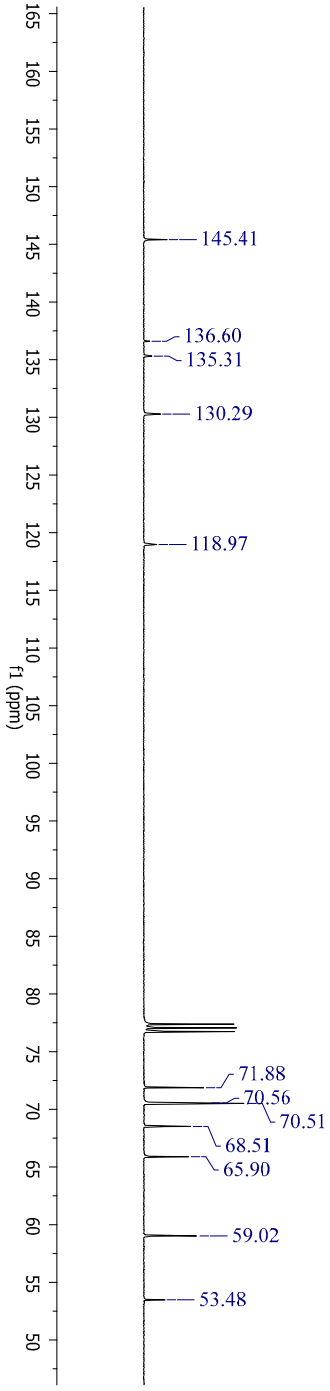


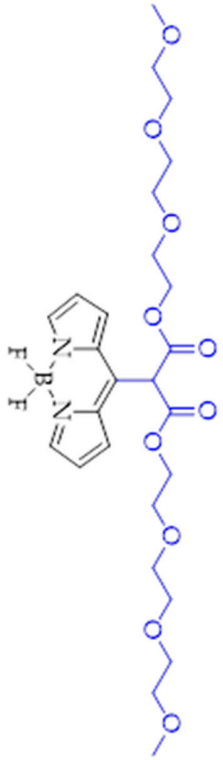
According to TP3**.** 1c (69 mg, 0.16 mmol, 1.0 eq), **6** (127 mg, 0.32 mmol, 2.0 eq), Na_2CO_3 (34 mg, 0.32 mmol, 2.0 eq), CuTC (61 mg, 0.32 mmol, 2.0 eq), THF (2.6 mL, 0.06M), BODIPY-PEG03 (100 mg, 0.129 mmol). TLC (EtOAc, R*f* = 0.1); red viscous liquid; 18 h, %R= 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (s, 2H), 4.96 (s, 1H), 4.47 – 4.20 (m, 4H), 3.68 (m, 4H), 3.69 – 3.53 (m, 21H), 3.37 (s, 6H), 2.60 (s, 6H. HRMS (ESI+) *m*/*z*: $[M + H]^+$ Calcd to $C_{28}H_{39}BBr_2F_2N_2O_{10}$, M+nNa (MW 771.1105) found: 771.1111, M+nNa.

NMR spectra of Compounds

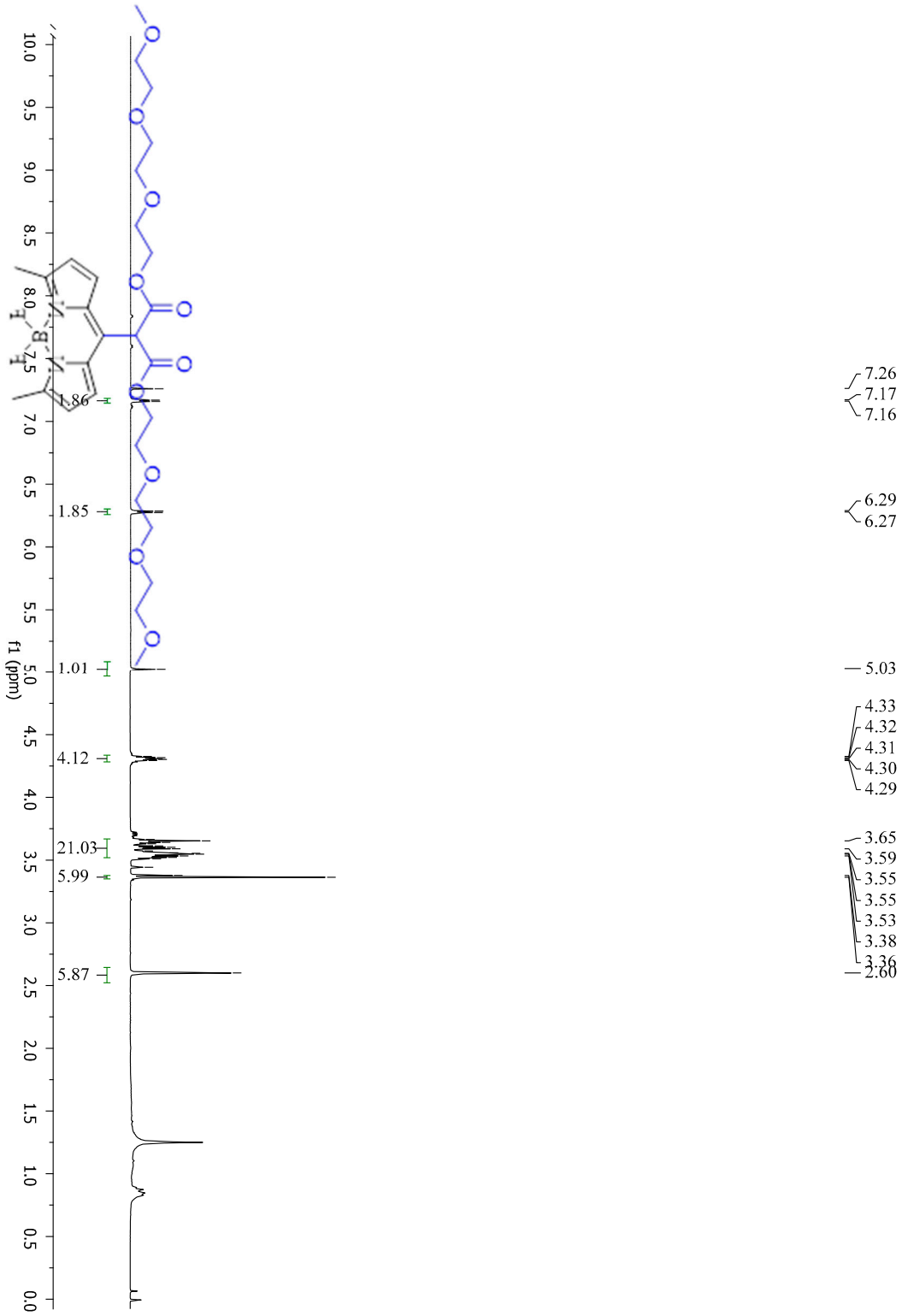
BDP-PEG01



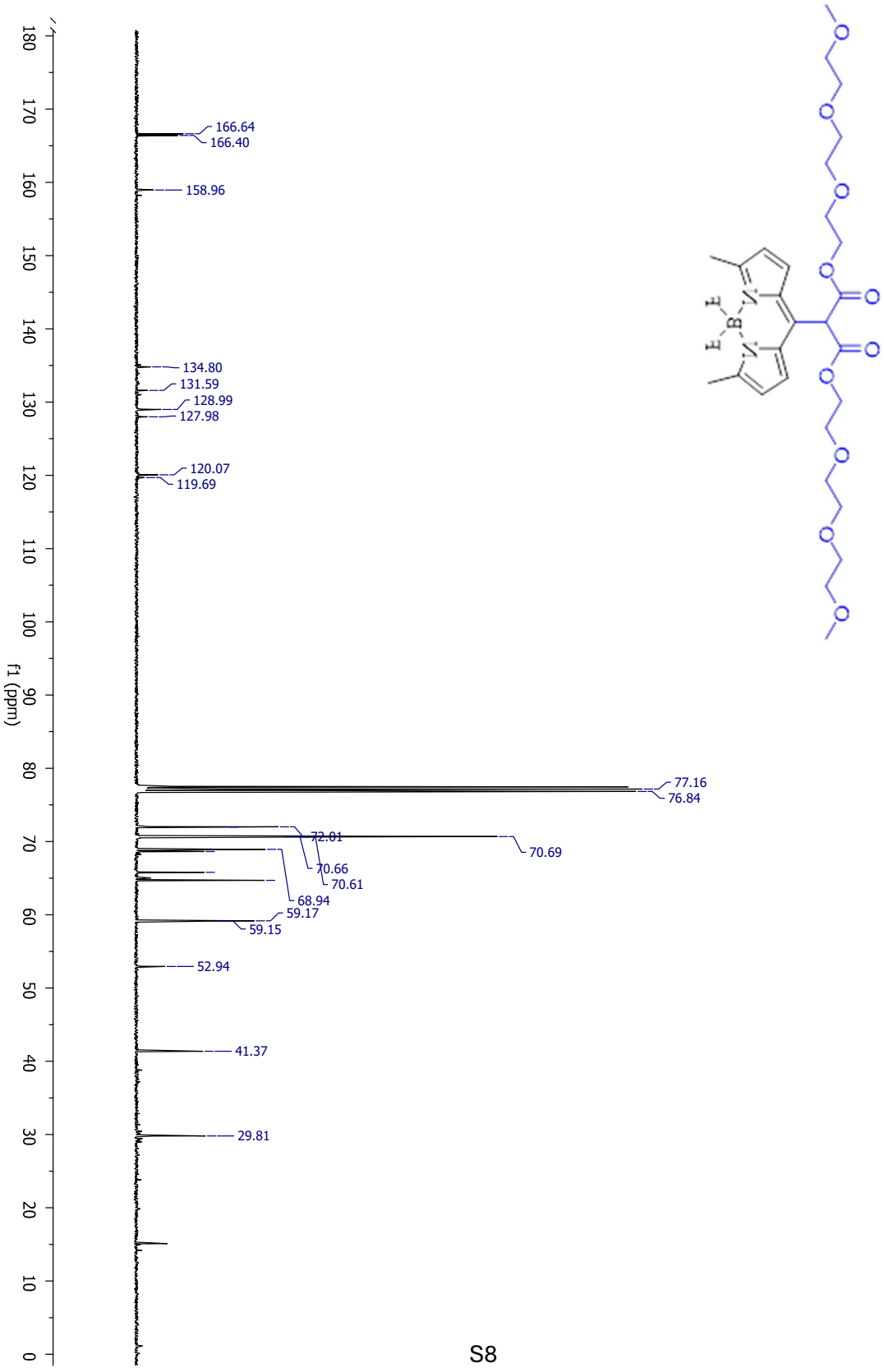

145.41
136.60
135.31
130.29
118.97
71.88
70.56
70.51
68.51
65.90
59.02
53.48
f1 (ppm)



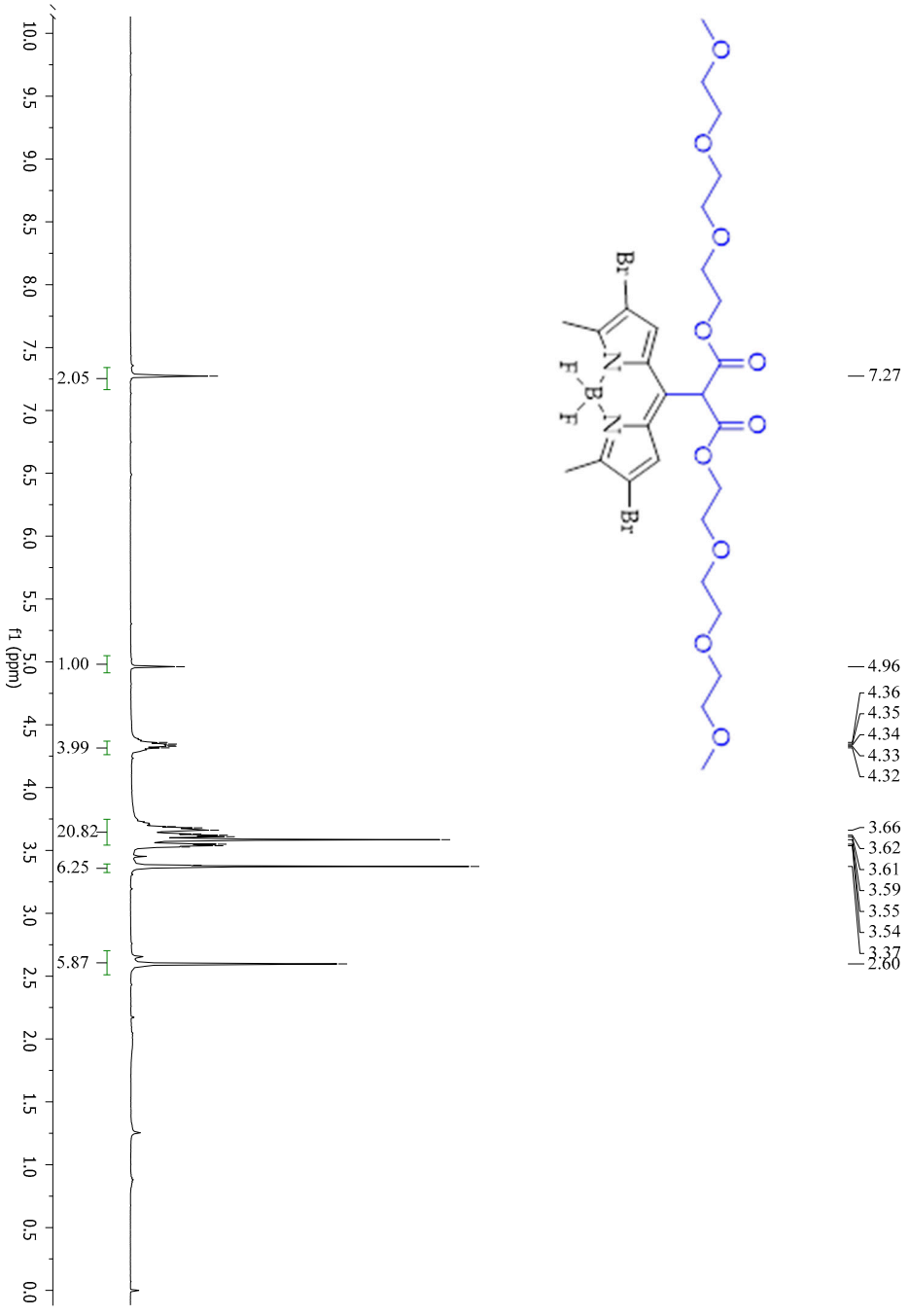
BDP-PEG02


1.86
1.85
1.01
4.12
21.03
5.99
5.87
f1 (ppm)
7.26
7.17
7.16
6.29
6.27
5.03
4.33
4.32
4.31
4.30
4.29
3.65
3.59
3.55
3.55
3.53
3.38
3.36
2.60

BDP-PEG02.


166.64
166.40
158.96
134.80
131.59
128.99
127.98
120.07
119.69
77.16
76.84
72.01
70.69
70.66
70.61
68.94
59.17
59.15
52.94
41.37
29.81
f1 (ppm)

BDP-PEG03


f1 (ppm)
2.05
1.00
3.99
20.82
6.25
5.87
7.27
4.96
4.36
4.35
4.34
4.33
4.32
3.66
3.62
3.61
3.59
3.55
3.54
3.37
2.60
Br
Br
F
B
F

Photophysical properties of BODIPY-peg derivatives.

Procedure for determining the quantum yield.

• Evaluate the solubility of the sample.

• Prepare a $1x10^{-6}$ solution of the sample.

• Obtain the absorption spectrum of the sample using a UV-visible spectrophotometer.

• Perkin Elmer Lambda 40; which will provide the λmax data of the sample and the absorbance at that wavelength.

• From the absorption spectrum, measure the excitation λ at which the sample will be excited in the fluorimeter, and the absorbance at that wavelength.

• Obtain the fluorescence spectrum on the F-7000 Hitachi fluorescence spectrophotometer: which will provide the maximum emission λ data and calculate the area under the maximum emission curve.

• The reference is chosen depending on the excitation wavelength at which the sample will be excited; for example, if the excitation wavelength is 500 nm, then a standard within that emission range will be selected, such as fluorescein or parent BODIPY (4,4-difluoro-4-bora-3a, 4a-diaza-s-indaceno).

• Measure the absorbance of the reference.

• Obtain the fluorescence spectrum of the reference using the F-7000 Hitachi fluorescence spectrophotometer: this will provide the maximum emission wavelength data, and the area under the maximum emission curve is calculated.

• Check the refractive indices of the solvent for both the sample and the reference.

• Calculate the quantum yield [5].

Φx = Quantum yield of the sample.

Φst = Reported quantum yield of the reference.

Ix = Integrated fluorescence spectrum (area under the curve of the maximum emission obtained in the fluorimeter) of the sample.

Ist = Integrated fluorescence spectrum (area under the curve of the maximum emission obtained in the fluorimeter) of the reference.

Ast = Absorbance (area under the curve) at the excitation **λ** of the reference obtained with the UV-vis spectrophotometer.

Ax = Absorbance (area under the curve) at the excitation λ of the sample obtained with the UV-vis spectrophotometer.

ηx = Refractive index of the sample's solvent.

ηst = Refractive index of the reference solvent.

Table S1. Quantum yield calculation for BDP-PEG01, BDP-PEG02, BDP-03.

Entry	BODIPY-PEG	λ_{em} (nm)	A_X	A_{ST}	η_{ST}[a]	η_X[b]	I_X	I_{ST}	Φ_{ST}	Φ_X
1	BODIPY-PEG01	525	0.088	0.088	1.335	1.330	849.1	2595	0.87	0.28
2	BODIPY-PEG02	533	0.068	0.068	1.335	1.330	393	2119	0.87	0.16
3	BODIPY-PEG03	560	0.055	0.050	1.335	1.330	312.3	1676	0.87	0.15

[a] The solvent for fluorescein (reference standard) is in 0.1 M NaOH solution, ηst=1.335 [5].
[b] The solvent for the sample is in water, ηx=1.330.

References for Supplementary materials

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3. [3] Zhang, S.; Zhang, D.; Liebeskind, L.S. Ambient Temperature, Ullmann-like Reductive Coupling of Aryl, Heteroaryl, and Alkenyl Halides. *J. Org. Chem.* **1997**, *62*, 2312–2313. https://doi.org/10.1021/jo9700078.
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