Supplementary information for

Asymmetric bismuth-rhodamines as an activatable fluorogenic photosensitizer

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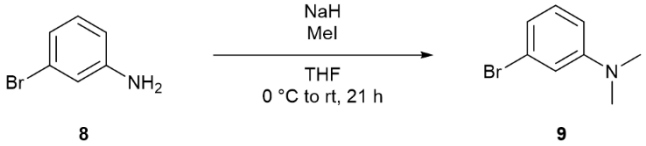
Contents

General

All chemicals used in this study were commercial products of the highest available purity. Anhydrous organic solvents were purchased. ^{1}H NMR spectra were obtained on a JEOL ECA-500 spectrometer at 500 MHz, a JEOL ECZ-400 spectrometer at 400 MHz and a JEOL JNM AL-400 spectrometer at 400 MHz. ^{13}C NMR spectra were obtained on a JEOL ECA-500 spectrometer at 125 MHz and a JEOL ECZ-400 spectrometer at 100 MHz. ^{19}F NMR spectra were obtained on a JEOL ECZ-400 spectrometer at 376 MHz. NMR spectra were obtained in $CDCl_3$, CD_3CN or d_6-DMSO. Chemical shifts of ^{1}H NMR were referenced to tetramethylsilane (0.00) or CH_3CN (1.94). Chemical shifts of ^{13}C NMR were referenced to $CDCl_3$ (77.0) or CD_3CN (118.0). Chemical shifts of ^{19}F NMR are referenced to hexafluorobenzene (−165.0). Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Data for ^{1}H NMR, ^{13}C NMR or ^{19}F NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens or fluorine). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), q (quartet), m (multiplet), br (broad). ESI-mass spectra were measured on a JEOL JMS-T100TD mass spectrometer. High-resolution mass spectra (HRMS) were measured on a JEOL JMS-T100TD by using polyethylene glycol (PEG) as an internal standard. Reactions were monitored by silica gel TLC (Silica gel 60 F_{254}, Merck) with visualization of components by UV light (254 nm), a visualization reagent (molybdophosphoric acid) or with visual observation of the dye spots. Products were purified on a silica gel column chromatography (AP-300S, Taiko-shoji) or a diol-functionalized silica gel (CHROMATOREX DIOL MB 100-40/75, FUJI SILYSIA CHEMICAL). Reversed phase HPLC analyses were performed on Chromaster series (Hitachi) equipped with TSKgel ODS-80Ts analytical column (5.0 μm, 4.6 × 75 mm, flow rate 0.5 mL min^{-1}, TOSOH). A solvent system consisting of 0.05% (v/v) formic acid in water (solvent A) and 0.05% (v/v) formic acid in acetonitrile (solvent B) was used, and the eluting products were detected by light absorption at 254, 526 or 615 nm. Reversed phase HPLC purification was performed on an HPLC system composed of pumps (PU-986, JASCO and PU-2086, JASCO), a dynamic mixer (MX-2080-32, JASCO), and a detector (UV-970, JASCO) equipped with a TSKgel ODS-80Ts preparative column (5.0 μm, 20.0 mm × 25 cm, flow rate 10.0 mL min^{-1}, TOSOH). A solvent system consisting of 0.05% (v/v) formic acid in water (solvent A) and 0.05% (v/v) formic acid in acetonitrile (solvent B) was used, and the eluting products were detected by light absorption at 254 nm.

1. Synthesis

3-Bromo-*N*,*N*-dimethylaniline (9)[1]

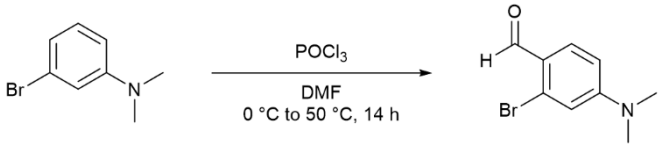


8 **9**

To a solution of 3-bromoaniline **8** (5.00 g, 29.1 mmol, 1.0 eq.) in THF (50 mL), NaH (5.82 g, 146 mmol, 5.0 eq. 60%w/w) was added at 0 °C. After stirring at the same temperature for 30 min, MeI (9.05 mL, 145 mmol, 5.0 eq.) was added and the reaction mixture was warmed to room temperature. After stirring for 21 h, the reaction was quenched by H_2O (50 mL), and the resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/*n*-hexane) to afford the title compound as a pale yellow oil (5.78 g, 28.9 mmol, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (t, *J* = 7.5 Hz, 1H), 6.82 (m, 2H), 6.63 (dd, *J* = 2.5, 8.5 Hz, 1H), 2.94 (s, 6H).

2-Bromo-4-(dimethylamino)benzaldehyde (1)[2]

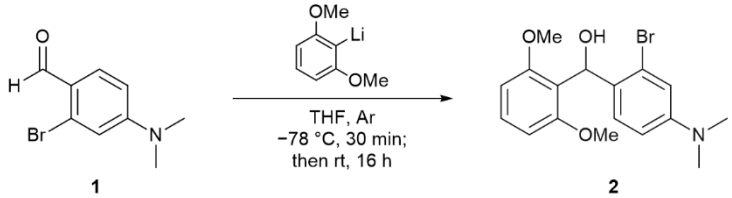


9 **1**

Under nitrogen atmosphere, phosphoryl chloride (752 μL, 8.09 mmol, 1.2 eq.) was dissolved in dry DMF (10 mL), and the mixture was stirred at 0 °C for 15 min. Compound **9** (1.35 g, 6.75 mmol, 1.0 eq.) was added to the mixture at 0 °C. After stirring at the same temperature for 10 min, the mixture was warmed to 50 °C and stirred for 14 h. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ (40 mL) and extracted with EtOAc/*n*-hexane (1/1, 40 mL × 3). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/*n*-hexane) to afford the title compound as a white solid (1.33 g, 5.83 mmol, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (d, *J* = 1.0 Hz, 1H), 7.81 (d, *J* = 9.2 Hz, 1H), 6.80 (d, *J* = 3.0 Hz, 1H), 6.64 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.08 (s, 6H).

[2-Bromo-4-(dimethylamino)phenyl](1,3-dimethoxyphenyl)methanol (2)



1 **2**

A solution of 2-bromo-1,3-dimethoxybenzene (1.60 g, 7.37 mmol, 1.0 eq.) in dry THF (10 mL) was cooled to −78 °C under an argon atmosphere. Then, *sec*-BuLi (7.70 mL, 8.09 mmol, 1.1 eq. 1.05 M in cyclohexane/*n*-

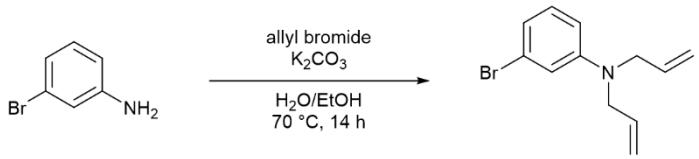
hexane) was added dropwise, and the mixture was stirred at −78 °C for 30 min. Then, the reaction mixture was added to a solution of compound **1** (1.68 g, 7.37 mmol, 1.0 eq.) in dry THF (20 mL) via a cannula at −78 °C. After stirring at the same temperature for 30 min, the mixture was warmed to room temperature. After stirring for 16 h, the reaction mixture was quenched by H_2O (50 mL) and extracted with $CHCl_3$ (50 mL × 3). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/*n*-hexane) to afford the title compound as a yellow amorphous (2.47 g, 6.74 mmol, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (t, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 2H), 6.49 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.46 (d, *J* = 10.9 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.82 (s, 6H), 2.90 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 150.5, 129.4, 128.9, 128.7, 125.7, 118.0, 116.5, 110.8, 104.4, 68.9, 55.7, 40.3.

HRMS (ESI^+) *m*/*z* calcd. for $[M+Na]^+$ $C_{17}H_{20}Br_2NNaO_3^+$ 388.0519; found 388.0496.

3-Bromo-*N*,*N*-diallylaniline (10)[3]

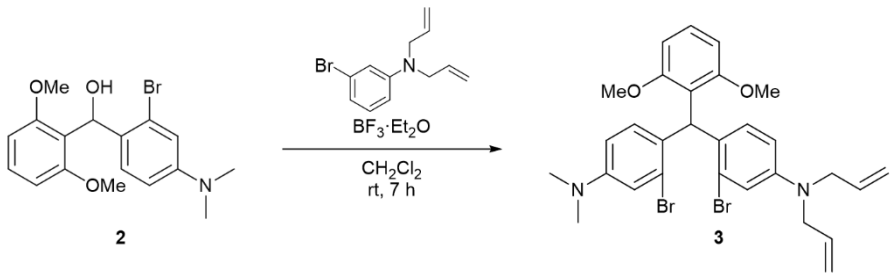


8 **10**

To a solution of 3-bromoaniline **8** (400 mg, 2.33 mmol, 1.0 eq.) in H_2O/EtOH (1/4, 25 mL), K_2CO_3 (1.28 g, 9.26 mmol, 4.0 eq) and allyl bromide (605 μL, 7.00 mmol, 3.0 eq.) were added, and the mixture was stirred at 70 °C for 14 h. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, and the filtrate was evaporated to dryness. The residue was suspended in H_2O (60mL), and the suspension was extracted with EtOAc (60 mL × 3). The organic layer was washed with brine (60 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/*n*-hexane) to give the title compound as a colorless oil (595 mg, quant.).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (t, *J* = 8.0 Hz, 1H), 6.80–6.77 (m, 2H), 6.59 (dd, *J* = 8.0, 2.3 Hz, 1H), 5.86–5.79 (m, 2H), 5.18–5.14 (m, 4H), 3.90–3.89 (m, 4H).

***N*, *N*-Diallyl-3-bromo-4-{[2-bromo-4-(dimethylamino)phenyl]1,3-dimethoxyphenylmethyl}aniline (3)**



2 **3**

To a solution of compound **2** (1.59 g, 4.34 mmol, 1.0 eq.) and compound **10** (1.31 g, 5.20 mmol, 1.2 eq.) in CH_2Cl_2 (20 mL), $BF_3 \cdot Et_2O$ (1.10 mL, 8.75 mmol, 2.0 eq.) was added. The reaction mixture was stirred at room

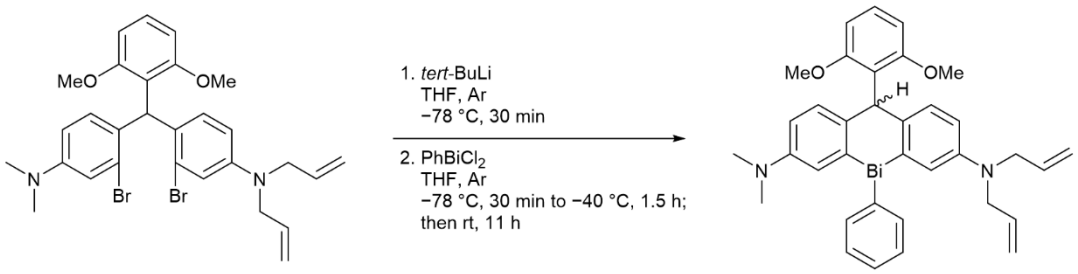
temperature for 7 h, then diluted with H_2O (50 mL), and extracted with $CHCl_3$ (50 mL × 3). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/*n*-hexane) to afford the title compound as a white amorphous (1.83 g, 3.05 mmol, 70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.87–6.84 (m, 3H), 6.56–6.54 (m, 3H), 6.50 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.21 (s, 1H), 5.85–5.77 (m, 2H), 5.16–5.12 (m, 4H), 3.84 (d, *J* = 5.2 Hz, 4H), 3.55 (s, 6H), 2.88 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 149.5, 147.8, 133.8, 131.9, 131.7, 130.4, 129.8, 127.8, 125.6, 125.5, 120.2, 116.1, 116.0, 115.8, 111.0, 110.9, 105.5, 56.2, 52.6, 45.4, 40.5.

HRMS (ESI$^+$) *m*/*z* calcd. for $[M+Na]^+$ $C_{29}H_{32}Br_2N_2NaO_2^+$ 623.0708; found 623.0710.

2-Diallylamino-9,10-dihydro-10-(2,6-dimethoxy)phenyl-7-dimethylamino-9-bismaanthracene (4)



3 **4**

A solution of compound **3** (1.81 g, 3.01 mmol, 1.0 eq.) in dry THF (40 mL) was cooled to −78 °C under an argon atmosphere. Then, *tert*-BuLi (7.90 mL, 12.6 mmol, 4.2 eq. 1.60 M in *n*-pentane) was added dropwise. The mixture was stirred at −78 °C for 30 min. Then, a suspension of dichlorophenylbismuthine[4] (1.08 g, 3.03 mmol, 1.0 eq.) in dry THF (10 mL) was added dropwise to the reaction mixture at −78 °C. After stirring at the same temperature for 30 min, the mixture was warmed to −40 °C over 1.5 h, and then warmed to room temperature. After stirring at room temperature for 11 h, the reaction was quenched by adding H_2O (80 mL), and the mixture was extracted with EtOAc (80 mL × 3). The combined organic layer was washed with brine (80 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (DIOL silica gel, EtOAc/*n*-hexane) to afford the title compound as a colorless amorphous diastereomer mixture (1.02 g, 1.40 mmol, 47%, diastereomer A : B = 1 : 1.3).

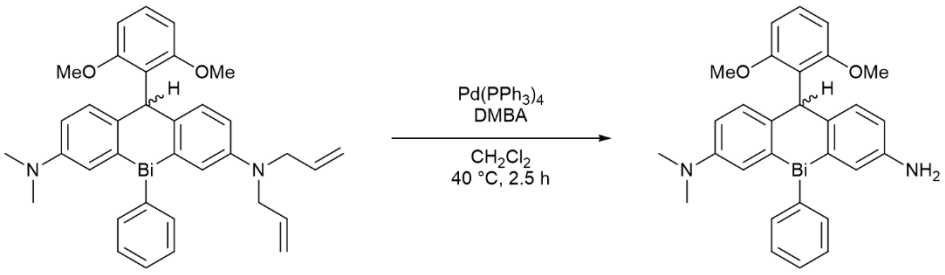
^{1}H NMR (500 MHz, $CDCl_3$): Diastereomer A: δ 8.01 (d, *J* = 6.3 Hz, 2H), 7.37–7.29 (m, 4H), 7.20–7.16 (m, overlapped, 1H), 7.10–7.03 (m, overlapped, 3H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.47 (dd, overlapped, *J* = 8.9, 2.6 Hz, 1H), 6.39 (dd, *J* = 8.6, 2.9 Hz, 1H), 5.71 (s, 1H), 5.72–5.65 (m, 2H), 5.10–5.05 (m, 4H), 3.85–3.74 (m, overlapped, 2H), 3.69–3.65 (m, 2H), 3.67 (s, 6H), 2.75 (s, 6H); Diastereomer B: δ 7.83 (dd, *J* = 8.0, 1.1 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 2H), 7.20–7.16 (m, overlapped, 1H), 7.10–7.03 (m, overlapped, 3H), 6.53 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.50 (d, *J* = 8.6 Hz, 2H), 6.47 (dd, overlapped, *J* = 8.9, 2.6 Hz, 1H), 6.39 (s, 1H), 5.79–5.75 (m, 2H), 5.03–4.97 (m, 4H), 3.85–3.74 (m, overlapped, 4H), 3.75 (s, 6H), 2.83 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 157.4, 154.5, 154.3, 154.0, 152.9, 152.8, 152.6, 152.5, 150.2, 149.3, 148.0, 147.3, 138.6, 137.6, 134.4, 134.3, 133.4, 132.8, 132.3, 131.4, 129.9, 129.8, 129.7, 129.5, 128.5, 128.2,

127.4, 126.9, 126.7, 124.2, 121.5, 120.9, 120.8, 120.6, 117.5, 115.9, 115.8, 113.4, 113.0, 112.0, 111.4, 104.8, 104.4, 56.0, 55.4, 52.9, 52.8, 52.1, 51.4, 41.0, 40.8.

HRMS (ESI$^+$) *m*/*z* calcd. for $[M+H]^+$ $C_{35}H_{38}BiN_2O_2^+$ 727.2332; found 727.2716.

2-Amino-9,10-dihydro-10-(2,6-dimethoxy)phenyl-7-dimethylamino-9-bismaanthracene (5)



4 **5**

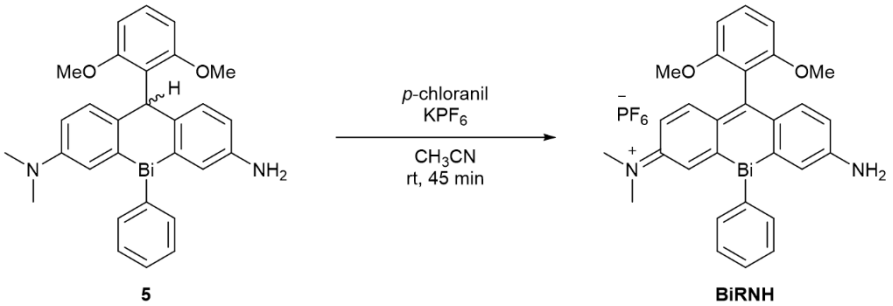
$Pd(PPh_3)_4$ (85.0 mg, 73.6 μmol, 5 mol%) and *N*, *N*-dimethylbarbituric acid (DMBA, 920 mg, 5.89 mmol, 4.0 eq.) were added to a solution of compound **4** (1.07 g, 1.47 mmol, 1.0 eq. dr = 1 : 1.3) in CH_2Cl_2 (30 mL) under argon atmosphere. The mixture was stirred at 40 °C for 2.5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (DIOL silica gel, EtOAc/*n*-hexane). The obtained material containing the diastereomers was suspended in Et_2O (20 mL). The precipitate was filtered, and the filtrate was evaporated to afford the title compound as a light blue amorphous (440 mg, 0.681 mmol, 46%, **5-*cis*** : **5-*trans*** = 1 : 0.16). The precipitate which remained on the filter paper was dried in vacuo to afford pure **5-*trans*** as white power (150 mg, 0.232 mmol, 16%).

^{1}H NMR: **5-*cis*** (500 MHz, CD_3CN): δ 7.91 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.42–7.30 (m, 4H), 7.08 (d, *J* = 2.9 Hz, 1H), 6.96–6.94 (m, 2H), 6.84 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.43 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.30 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.55 (s, 1H), 3.83 (brs, overlapped, 2H), 3.64 (s, 6H), 2.71 (t, *J* = 7.7 Hz, 6H); **5-*trans*** (400 MHz, d_6-DMSO): δ 7.76 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.21–7.24 (m, 2H), 7.15–7.19 (m, 1H), 7.09–7.05 (m, 2H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 2H), 6.48 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.48 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.30 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.25 (s, 1H), 4.76 (brs, 2H), 3.754 (s, 6H), 2.76 (s, 6H).

^{13}C NMR: **5-*cis*** (100 MHz, CD_3CN): δ 159.7, 157.7, 154.2, 153.0, 151.1, 147.8, 138.7, 132.5, 132.1, 130.6, 130.2, 129.3, 129.2, 129.0, 128.3, 123.2, 122.0, 114.2, 112.6, 105.5, 55.8, 52.0, 40.6 (the peaks of **5-*trans*** were not detected); **5-*trans*** (125 MHz, $CDCl_3$): δ 157.3, 154.9, 152.7, 152.4, 149.4, 144.7, 137.9, 135.0, 133.1, 130.0, 129.8, 129.7, 127.0, 126.9, 124.4, 123.1, 120.9, 115.8, 113.5, 104.9, 56.1, 52.2, 40.8.

HRMS (ESI$^+$) *m*/*z* calcd. for $[M+H]^+$ $C_{29}H_{30}BiN_2O_2^+$ 647.2106; found 647.2099.

BiRNH



To a solution of compound **5** (40.1 mg, 62.0 μmol, 1.0 eq. *cis* : *trans* = 1 : 0.16) in CH_3CN (3 mL), KPF_6 (22.5 mg, 0.122 mmol, 2.0 eq.) and *p*-chloranil (30.5 mg, 0.124 mmol, 2.0 eq.) were added. After stirring at room temperature for 45 min, insoluble material was removed by filtration with a pad of celite. After evaporation, the residue was purified by column chromatography (DIOL silica gel, acetone/$CHCl_3$) to afford the title compound as dark blue solid (21.4 mg, 27.1 μmol, 44%).

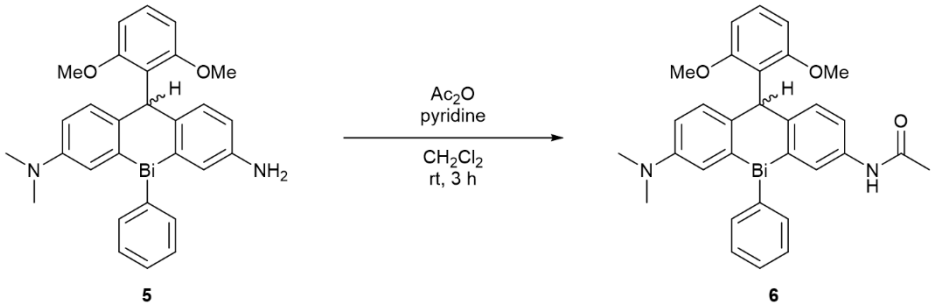
^{1}H NMR (500 MHz, CD_3CN): δ 7.87 (dd, *J* = 8.0, 1.1 Hz, 2H), 7.72 (d, *J* = 2.9 Hz, 1H), 7.62 (d, *J* = 9.7 Hz, 1H), 7.57 (d, *J* = 9.7 Hz, 1H), 7.53 (t, *J* = 8.6 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.25 (tt, *J* = 7.4, 1.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.61 (dd, *J* = 9.7, 2.9 Hz, 1H), 6.49 (dd, *J* = 9.5, 2.6 Hz, 1H), 6.23 (brs, 2H), 3.65 (s, 3H), 3.57 (s, 3H), 3.25 (s, 6H).

^{13}C NMR (100 MHz, CD_3CN): δ 176.4, 168.2, 167.5, 157.7, 157.7, 156.6, 155.8, 144.0, 143.9, 137.3, 131.5, 131.2, 128.5, 126.1, 125.9, 125.4, 125.2, 116.0, 114.9, 105.0, 104.7, 56.4, 56.4, 41.0.

^{19}F NMR (376 MHz, CD_3CN): δ −73.5 (d, *J* = 707 Hz, 6F).

HRMS (ESI+) *m*/*z* calcd. for $C_{29}H_{28}BiN_2O_2^+$ $[M-PF_6^-]^+$ 645.1949, found 645.1923.

2-Acetylamino-9,10-dihydro-10-(2,6-dimethoxy)phenyl-7-dimethylamino-9-bismaanthracene (6)



To a solution of compound **5** (120 mg, 0.186 mmol, 1.0 eq. *cis* : *trans* = 1 : 0.16) in CH_2Cl_2 (5 mL), pyridine (150 μL, 1.86 mmol, 10 eq.) and acetic anhydride (88.0 μL, 0.931 mmol, 5.0 eq.) was added. After stirring for 3 h at room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (10 mL × 3). The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (DIOL silica gel, EtOAc/*n*-hexane) to afford the title compound as a light purple solid (82.4 mg, 0.120 mmol, 64%, **6-*cis*** : **6-*trans*** = 1 : 0.16).

^{1}H NMR (500 MHz, $CDCl_3$): **6-*cis***: δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.38–7.35 (m, 2H), 7.30–7.09 (m, 5H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.50–6.45 (m, 2H), 5.68 (s, 1H), 3.64 (s, 6H), 2.74 (s, 6H), 1.87

(s, 3H); **6-*trans***: δ 7.78 (d, *J* = 6.3 Hz, 2H), 7.64–7.61 (m, 3H), 7.30–7.09 (m, 7H), 7.02–7.01 (m, 2H), 6.54 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.72 (s, 6H), 2.80 (s, 6H), 1.91 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.3, 159.1, 157.2, 154.4, 153.0, 152.4, 150.3, 149.4, 140.6, 139.6, 138.8, 137.8, 137.1, 136.3, 132.5, 131.1, 130.0, 129.8, 129.7, 128.7, 128.6, 128.5, 127.9, 127.7, 123.7, 121.3, 120.6, 120.1, 119.1, 116.9, 113.5, 112.1, 104.7, 104.5, 56.0, 55.4, 52.5, 52.1, 40.8, 40.7, 24.2 (several peaks were overlapped).

HRMS (ESI+) *m*/*z* calcd. for $C_{31}H_{32}BiN_2O_3^+$ $[M+H]^+$ 689.2211, found 689.2209.

BiRAc

To a solution of compound **6** (75.0 mg, 0.109 mmol, 1.0 eq. *cis* : *trans* = 1 : 0.16) in CH_3CN (2 mL), KPF_6 (40.2 mg, 0.218 mmol, 2.0 eq.) and *p*-chloranil (40.2 mg, 0.163 mmol, 1.5 eq.) were added. After stirring at room temperature for 30 min, insoluble material was removed by filtration with a pad of celite. After evaporation of the filtrate, the residue was purified by column chromatography (DIOL silica gel, acetone/$CHCl_3$) to afford the title compound as dark purple solid (52.8 mg, 63.4 μmol, 58%).

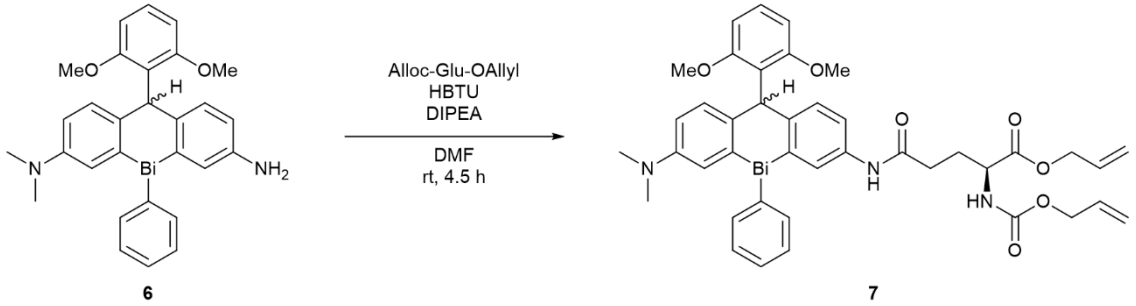
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.26 (d, *J* = 2.3 Hz, 1H), 7.78–7.75 (m, 3H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 2.6 Hz, 1H), 7.63 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.47 (t, *J* = 8.6 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 6.63 (dd, *J* = 9.6, 2.6 Hz, 1H), 3.69 (s, 3H), 3.51 (s, 3H), 3.36 (s, 3H), 3.28 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 172.1, 170.3, 162.8, 157.2, 157.0, 156.9, 156.4, 146.7, 144.4, 140.4, 136.7, 131.9, 131.4, 130.9, 128.9, 128.1, 127.6, 126.4, 120.1, 117.0, 116.1, 104.2, 103.9, 56.1, 56.0, 41.8, 41.5, 24.6.

^{19}F NMR (376 MHz, CD_3CN): δ −73.5 (d, *J* = 706 Hz, 6F).

HRMS (ESI+) *m*/*z* calcd. for $C_{31}H_{30}BiN_2O_3^+$ $[M-PF_6^-]^+$ 687.2055, found 687.2030.

Compound 7



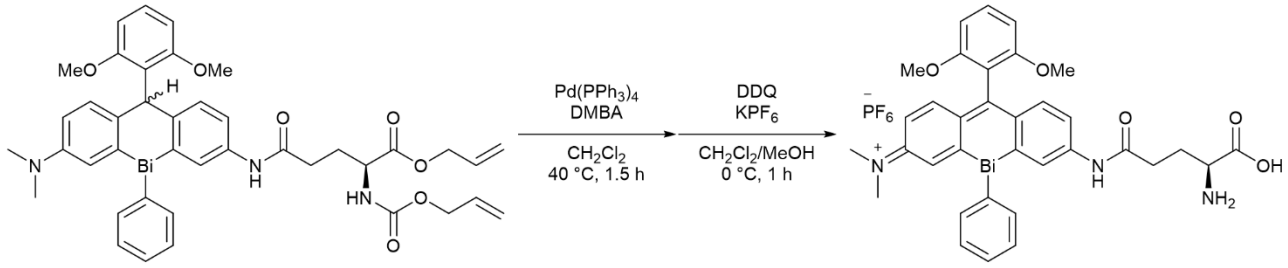
Alloc-Glu-OAllyl[5] (240 mg, 0.885 mmol, 1.1 eq. *cis* : *trans* = 1 : 0.16) and *N*,*N*-diisopropylethylamine (DIPEA, 280 µL, 1.61 mmol, 2.0 eq.) were dissolved in DMF (3 mL). The mixture and HBTU (335 mg, 0.885 mmol, 1.1 eq.) were added to a solution of compound **6** (120 mg, 0.186 mmol, 1.0 eq.) in DMF (5 mL). After stirring at room temperature for 4.5 h, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc/*n*-hexane (4/1, 25 mL × 3). The organic layer was washed with brine (25 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (DIOL silica gel, EtOAc/*n*-hexane) to afford the title compound as a light purple amorphous (545 mg, 0.605 mmol, 75%, dr = 1 : 0.24).

^{1}H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 8.00 (d, *J* = 7.4 Hz, 2H), 7.65–7.61 (m, 1H), 7.56–7.52 (m, 1H), 7.40–7.33 (m, 4H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.11–7.13 (m, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.48-6.51 (m, 1H), 5.93–5.76 (m, 2H), 5.69 (s, 1H), 5.54 (br, 1H), 5.31–5.15 (m, 4H), 4.60–4.59 (m, 2H), 4.53–4.43 (m, 2H), 4.41–4.32 (m, 1H), 3.68 (s, 6H), 2.77 (s, 6H), 2.42–2.31 (m, 2H), 2.31–2.21 (m, 1H), 2.04–1.93 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 169.8, 159.1, 157.2, 156.2, 154.3, 152.9, 152.4, 152.4, 150.3, 149.4, 139.7, 139.6, 138.7, 137.8, 137.1, 137.1, 136.3, 132.4, 131.3, 130.0, 129.8, 129.7, 128.8, 128.6, 127.6, 127.4, 127.2, 126.9, 123.7, 121.3, 120.6, 119.9, 119.1, 118.8, 118.0, 1167.0, 113.5, 112.1, 104.7, 104.5, 66.1, 65.9, 56.0, 55.4, 53.5, 52.5, 52.1, 40.8, 40.7, 33.4, 28.8, 28.7.

HRMS (ESI+) *m*/*z* calcd. for $C_{41}H_{45}BiN_3O_7^+$ $[M+H]^+$ 900.3056, found 900.3037.

BiRGlu



7 **BiRGlu**

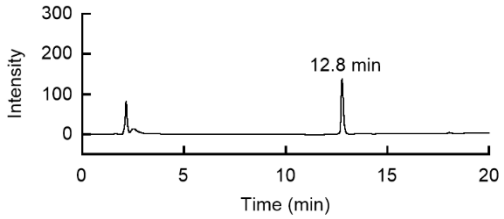
$Pd(PPh_3)_4$ (18.1 mg, 15.7 µmol, 5 mol%) and *N*,*N*-dimethylbarbituric acid (DMBA, 195 mg, 1.25 mmol, 4.0 eq.) were added to a solution of compound **7** (282 mg, 0.313 mmol, 1.0 eq. dr = 1 : 0.24) in CH_2Cl_2 (3 mL) under argon atmosphere. The mixture was stirred at 40 °C for 1.5 h. After evaporation, the residue was purified by column chromatography (DIOL silica gel, MeOH/$CHCl_3$) to obtain the deprotected compound as a light purple solid. The deprotected compound (196 mg, 0.252 mmol, 1.0 eq.) was dissolved in in CH_2Cl_2/MeOH (1/1, 5 mL). KPF_6 (92.8 mg, 0.504 mmol, 2.0 eq.) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 86.0 mg, 0.379 mmol, 1.5 eq.) were added to the solution. After stirring at 0 °C for 1 h, the solvent was evaporated. The residue was purified by preparative HPLC to afford the title compound as a purple powder (15.7 mg, 17.1 µmol, 5.5%)

^{1}H NMR (500 MHz, d_6-DMSO): δ 8.53 (s, 1H), 8.27 (d, *J* = 2.3 Hz, 1H), 7.90 (d, *J* = 6.9 Hz, 2H), 7.60–7.54 (m, 3H), 7.43 (s, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 6.97–6.94 (m, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 3.66 (s, 3H), 3.60 (s, 1H), 3.56 (s, 3H), 3.49 (s, 3H), 3.37 (overlapped with H_2O, 3H), 2.54 (s, 2H), 1.96 (s, 2H).

^{19}F NMR (376 MHz, d_6-DMSO): δ −72.5 (d, *J* = 711 Hz, 6F).

HRMS (ESI+) *m/z* calcd. for $C_{34}H_{35}BiN_3O_5^+$ $[M-PF_6^-]^+$ 774.2375, found 774.2347.

HPLC analysis of the purified **BiRGlu**



HPLC conditions: Solvent A: 0.05% (v/v) formic acid in ultra-pure water, Solvent B: 0.05% (v/v) formic acid in acetonitrile (solvent B). Solvent A/B = 20/80 for 5 min, and then 20/80–80/20 for 15 min. The eluate was monitored at 254 nm. Retention time = 12.8 min.

2. Absorption and fluorescence measurements

The UV-vis absorption spectra were recorded on an Agilent 8453 photodiode array spectrometer equipped with a UNISOKU thermo-static cell holder (USP-203). Fluorescence spectra were recorded using a JASCO FP6600 with a slit width of 5 nm and 6 nm for excitation and emission, respectively. To reduce fluctuation in the excitation intensity during measurement, the lamp was kept on for 30 min prior to the experiment. The path length was 1 cm with a cell volume of 3.0 mL. Quantum yields (Φ_{FL}) were measured in HEPES buffer (50 mM, pH 7.4, 0.05% DMSO) by using a Quantaurus-QY absolute photo-luminescence quantum yields measurement system (C11347-01, Hamamatsu Photonics).

3. $^1O_2$ generation study[6]

$^1O_2$ generation study was performed with a red LED light (625 nm, M625L3, Thorlabs) or a green LED light source (530 nm, M530L3, Thorlabs) equipped with a liquid light guide (1.2 m, ϕ = 5 mm, LLG-0538-4, Thorlabs) and a T-cube light source driver (Thorlabs). Absorption spectra of mixed solutions of photosensitizer (**BiRNH**, **BiRAc** or **BiRGlu**) and DPBF (1,3-diphenylbenzofuran, a colorimetric scavenger of $^1O_2$) were measured as above every 60 sec under irradiation (1.1 mW cm^{-2}) in acetonitrile. The quantum yield ($\Phi(^1O_2)_{BiRX}$) of BiRX for $^1O_2$ generation was calculated from an initial photooxidation rate (k) of DPBF by using the equation as follows:

$$\Phi(^1O_2)_{BiRX} = \Phi(^1O_2)_{SP} \bullet (k_{BiRX}/k_{SP}) \bullet (F_{SP}/F_{BiRX})$$

where SP means a standard photosensitizer, which indicates methylene blue or rose bengal, $\Phi(^1O_2)_{SP}$ and F indicates quantum yield of methylene blue for $^1O_2$ generation (0.52 in acetonitrile)[7] or that of rose bengal for $^1O_2$ generation (0.54 in acetonitrile)[8] and the absorption cofactor given by $F = 1-10^{-OD}$, respectively; OD is an optical density at the irradiation wavelengths. The initial concentration of DPBF was adjusted to 60 μM and those of **BiRNH**, **BiRAc**, and **BiRGlu** were adjusted to 1.7 μM.

For the photostability tests, absorption spectra of **BiRNH**, **BiRAc** and **BiRGlu** were acquired in the dark or under the continuous irradiation condition without DPBF in HEPES buffer (50 mM, pH 7.4, 0.5% DMSO).

4. Product analysis of the reaction between BiRGlu and GGT by HPLC

BiRGlu (10 μM) was incubated with GGT (10 U mL^{-1}) in HEPES buffer (50 mM, pH 7.4, 5% DMSO). After 5 min, 1 h, 2.5 h, the reaction mixture was analyzed by HPLC (solvent A/B = 20/80 to 80/20 for 5–20 min). Solvent A: 0.05% (v/v) formic acid in water, Solvent B: 0.05% (v/v) formic acid in acetonitrile. Eluates were monitored at 254, 526 and 615 nm.

5. Cell culture

Human lung adenocarcinoma (A549, purchased from RIKEN Bioresource Center) cells and Human ovarian adenocarcinoma (SKOV3ip1,[9] kindly provided from Prof. Ken-ichiro Morishige, Department of Obstetrics and Gynecology, Gifu University School of Medicine, Gifu, Japan) were cultured in Dulbecco's modified Eagle medium with L-glutamine and phenol red (D-MEM, Wako) containing 10% fetal bovine serum (FBS, SIGMA), 1 mM sodium pyruvate solution (Wako), 50 U mL^{-1} penicillin, 50 ng mL^{-1} streptomycin and 50 ng mL^{-1} kanamycin at 37 °C in a 5% CO_2/ 95% air incubator.

6. Confocal fluorescence microscopy

Confocal fluorescence images were acquired with an Olympus IX83 microscope equipped with a laser diode illuminator (LDI with 7 laser lines, 89 North), an EMCCD camera (ImagEM, Hamamatsu Photonics), a stage incubator with a gas controlling system (STX series, TOKAI Hit), and a disk scan confocal unit (DSU). Images were obtained with appropriate filter sets for each dye as follows.

- **BiRGlu** and **BiRNH**: excitation = 640 nm, emission = 672–712 nm, and dichroic mirror = 660 nm.
- ProteoGREEN-gGlu[10]: excitation = 470 nm, emission = 516–556 nm, and dichroic mirror = 495 nm.
- ER-Tracker Green: excitation = 470 nm, emission = 516–556 nm, and dichroic mirror = 495 nm.
- Hoechst: excitation = 405 nm, emission = 423–467 nm, dichroic mirror = 414 nm.
- Propidium iodide (PI): excitation = 555 nm, emission = 572–642 nm, dichroic mirror = 562 nm.

For all imaging experiments, Hank's Balanced Salt Solution (HBSS, Gibco) containing calcium and magnesium without Phenol-Red was used.

One day before use, the cells were seeded on Advanced TC glass-bottomed dishes (CELLview Cell Culture Dish, Greiner) at 5.0×10^4 cells/well. The cells were incubated in the appropriate media for 24 h.

For confirmation of GGT expression, after washing A549 cells with HBSS (× 2), cells were treated with ProteoGREEN-gGlu (1 μM, from 0.1 mM stock solution in DMSO, Goryo Chemical) for 30 min. Then, the cells were washed with HBSS and imaged.

For GGT inhibition experiment, after washing A549 cells with HBSS (× 2), GGT inhibitor (GGsTOP, 100 μM, from 10 mM stock solution in water, Wako) was added. After incubation for 1 h, the cells were treated with **BiRGlu** (1 μM, from 0.2 mM stock solution in DMSO) at 37 °C for 2 h, and then imaged.

For co-staining experiments, after washing A549 cells with HBSS (× 2), A549 cells were treated with ER-Tracker Green (0.2 μM, from 20 μM stock solution in DMSO, Thermo Fisher) and **BiRNH** (1 μM, from 0.1 mM stock solution in DMSO) in HBSS for 30 min. Then, the cells were washed with HBSS and imaged. Colocalization analysis was performed by calculation of Pearson's correlation values (R_{coloc}) for the corresponding channels using Coloc2 program of Fiji. R_{coloc} values were obtained for each field of view, and the means of R_{coloc} values were calculated (n = 3).

For in-cell photostability test of **BiRNH**, A549 cells were washed with HBSS (× 2) and then treated with **BiRNH** (1 μM, from 0.1 mM stock solution in DMSO) in HBSS for 30 min. Then, the cells were washed with HBSS and imaged. Then, the cells were irradiated with excitation light (640 nm, 14.1 mW cm^{-2}) of the microscope for 1 min and imaged.

7. Cell death assay by PI/Hoechst staining

After washing cells with HBSS (× 2), the cells were incubatted with **BiRGlu** (1 μM, from 0.2 mM stock solution in DMSO) for 0.5, 1, 2 or 4 h. Then, the cells were irradiated with excitation light (640 nm, 14.1 mW cm^{-2}) of the microscope for 1 min. Then, PI (5 μM, from 500 μM stock solution in DMSO) and Hoechst 33342 (1 μg mL^{-1}, from 0.1 mg mL^{-1} stock solution in water) were added to the cells. After incubation for 30 min, the cells were imaged. The numbers of nucleus stained by PI and Hoechst were counted, and the cell death rate were evaluated by calculating the ratio of PI-positive cells/Hoechst-positive cells.

8. Cell viability assay by MTT assay

For phototoxicity test, the cells were seeded on 96-well cell plates (Techno Plastic Products AG) at 1.0×10^4 cells/well. The cells were incubated in the appropriate media for 24 h. The cells were treated with various concentreation of BiR series under the dark condition at 37 °C. After 2 h incubation, the cells were irradiated with red LED light (625 nm, 20 J cm^{-2}, M625L3, Thorlabs) or green LED light (530 nm, 20 J cm^{-2}, M530L3, Thorlabs). Then, the cells were incubated with 0.5 mg mL^{-1} MTT reagent for 4 h. Then, the media was removed, and the cells were lysed with DMSO. For 24 h cytotoxicity test, the cells were seeded on 96-well cell plates (Techno Plastic Products AG) at 5.0×10^3 cells/well. The cells were incubated in the appropriate media for 24 h. The cells were treated with various concentration of **BiRNH** and **BiRAc** series under the dark condition at 37 °C for 24 h. Then, the cells were incubated with 0.5 mg mL^{-1} MTT reagent for 4 h. Then, the media was removed, and the cells were lysed with DMSO. Absorption at 560 nm of each wells were measured on a microplate reader (SpectraMax iD3, Molecular Devices) to calculate cell viability.

Supplementary Figures

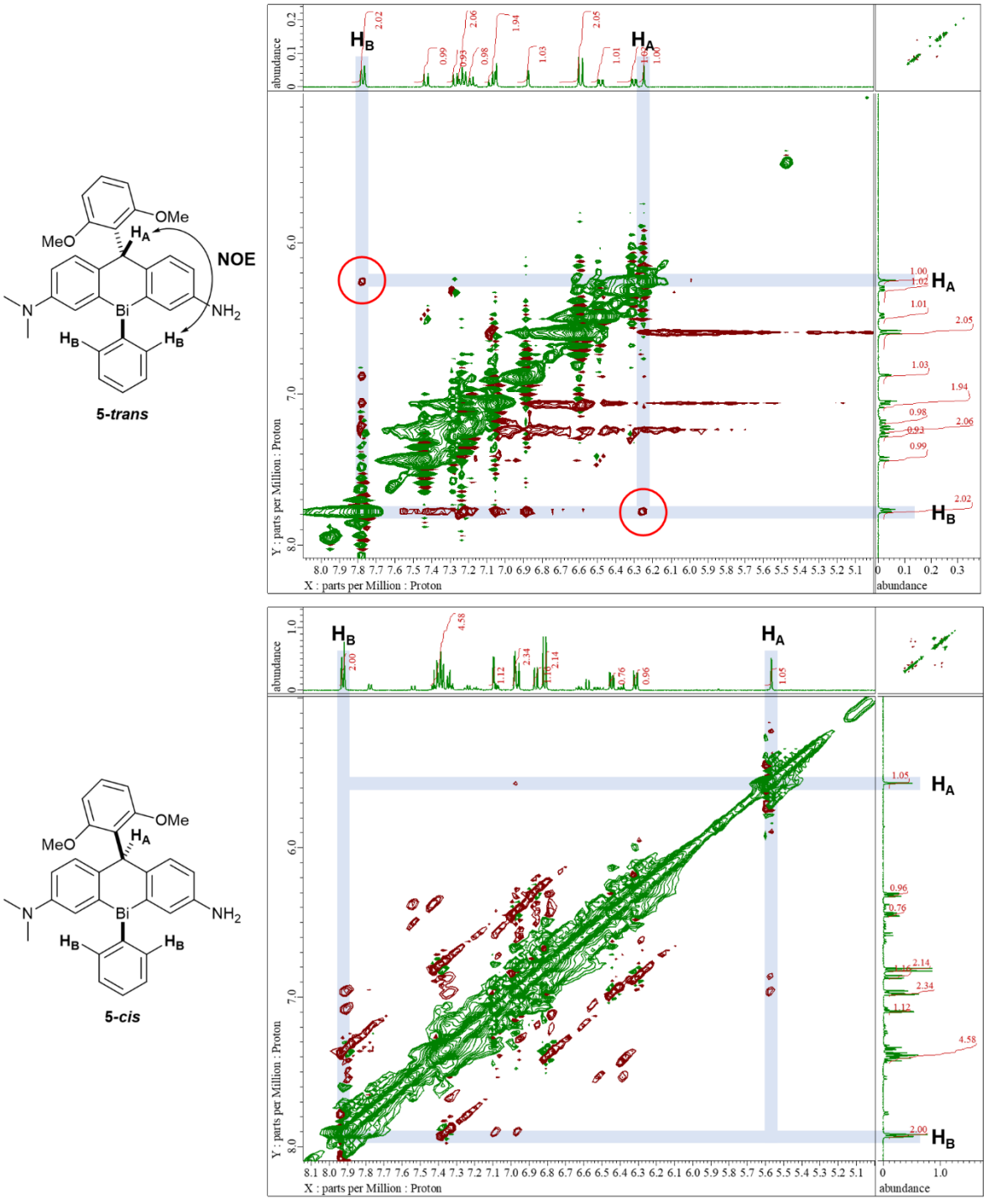


Figure S1. NOESY spectra of **5-*cis*** and **5-*trans***.

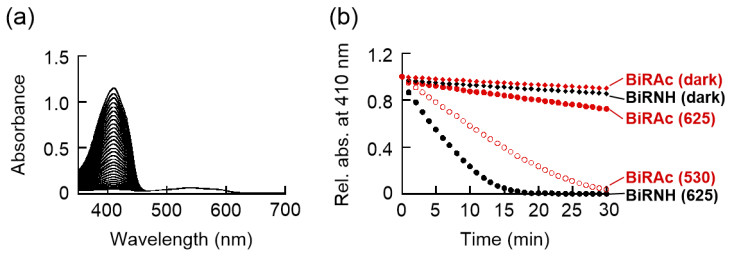


Figure S2. (a) Absorption spectral change of DPBF (60 μM) with green light irradiation (530 nm, 1.1 mW cm^{-2}) in the presence of **BiRAc** (1.7 μM). (b) Plots of absorption at 410 nm measured in (a) (**BiRAc** (530), red open circles) and comparison with those measured in Figure 1a–d.

Table S1. Photophysical properties of the bismuth-rhodamines.

	λ_{abs} (nm)	ε (M^{-1} cm^{-1})	λ_{em} (nm)	Φ_{Fl}	$\Phi(^1O_2)$ (at 625 nm)	$\Phi(^1O_2)$ (at 530 nm)
BiRNH	615	90400	634	0.033	0.74	n.d.[b]
BiRAc	526	31700	n.d.[b]	n.d.[b]	n.d.[b]	0.66
BiRGlu	525	48000	n.d.[b]	n.d.[b]	n.d.[b]	0.45
BiR[a]	635	77600	658	0.039	0.66	n.d.[b]

[a]Ref. 4. [b]Not determined

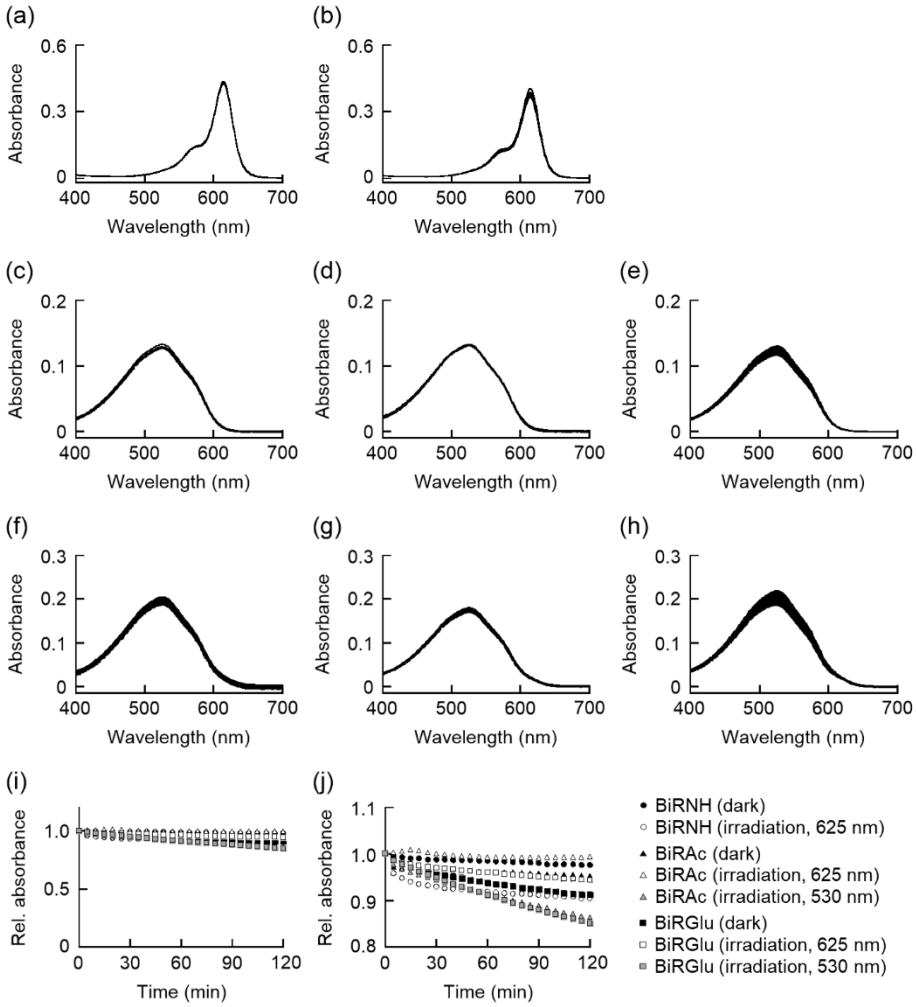


Figure S3. Photostability tests of **BiRNH**, **BiRAc** and **BiRGlu**. Absorption spectra of (a) **BiRNH** in the dark, (b) **BiRNH** under continuous irradiation with a red LED light (625 nm, 1.1 mW cm^{-2}) (c) **BiRAc** in the dark, (d) **BiRAc** under continuous irradiation with the red LED light (625 nm, 1.1 mW cm^{-2}), (e) **BiRAc** under continuous irradiation with a green LED light (530 nm, 1.1 mW cm^{-2}), (f) **BiRGlu** in the dark, (g) **BiRGlu** under continuous irradiation with with the red LED light (625 nm, 1.1 mW cm^{-2}), and (h) **BiRGlu** under continuous irradiation with with green LED light (530 nm, 1.1 mW cm^{-2}). The absorption spectra were acquired with the sample concentration of 5 μM every 5 min for 2 h in HEPES buffer (50 mM, pH 7.4, 0.5% DMSO). (i) Plots of the relative absorption at each maximum (615 nm for **BiRNH**, 526 nm for **BiRAc**, and 525 nm for **BiRGlu**) measured in (a)–(h). (j) A magnified graph of (i).

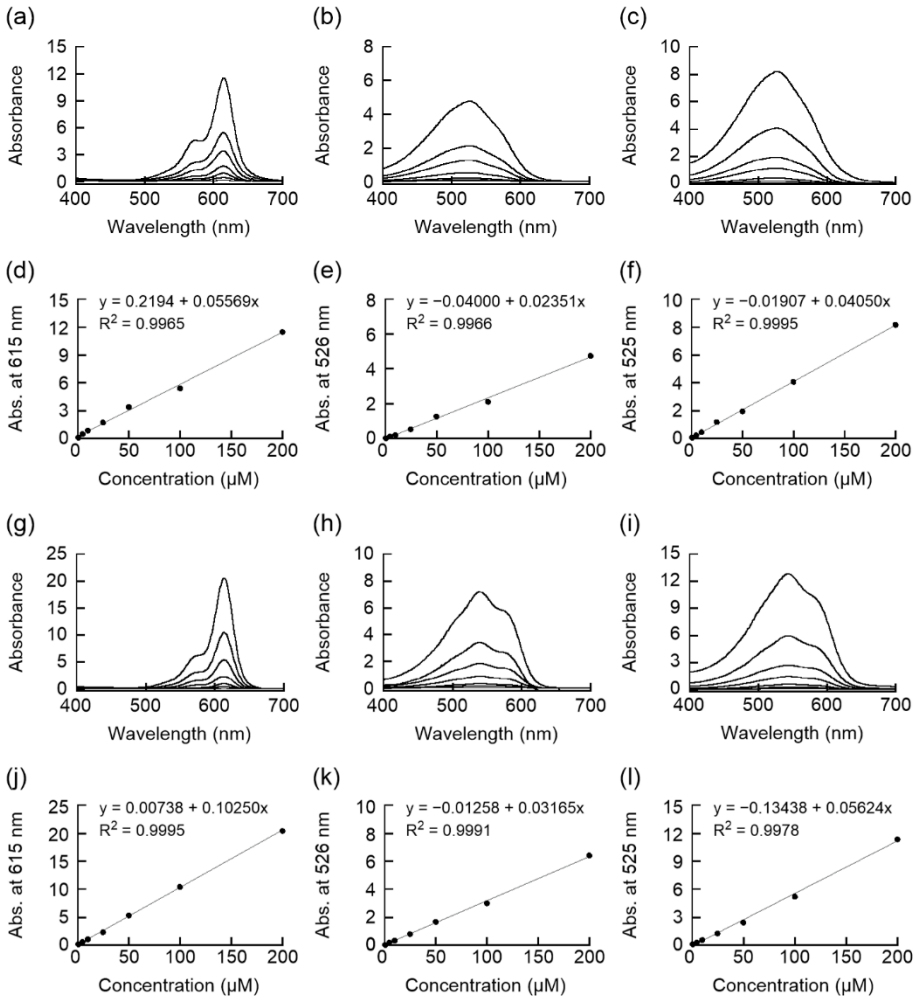


Figure S4. Solubility tests of **BiRNH**, **BiRAc**, and **BiRGlu**. Absorption spectra of (a) **BiRNH** (1, 5, 10, 25, 50, 100, 200 μM), (b) **BiRAc** (1, 5, 10, 25, 50, 100, 200 μM) and (c) **BiRGlu** (1, 5, 10, 25, 50, 100, 200 μM) in HEPES buffer (50 mM, pH 7.4, 1% DMSO). Plots of absorbance of (d) **BiRNH**, (e) **BiRAc**, and (f) **BiRGlu** at the maximum (615 nm for **BiRNH**, 526 nm for **BiRAc**, 525 nm for **BiRGlu**) against concentration measured in (a)–(c). Absorption spectra of (g) **BiRNH** (1, 5, 10, 25, 50, 100, 200 μM), (h) **BiRAc** (1, 5, 10, 25, 50, 100, 200 μM) and (i) **BiRGlu** (1, 5, 10, 25, 50, 100, 200 μM) in acetonitrile. Plots of absorbance of (j) **BiRNH**, (k) **BiRAc** and (l) **BiRGlu** at the maximum (615 nm for **BiRNH**, 526 nm for **BiRAc**, 525 nm for **BiRGlu**) against concentration measured in (g)–(i).

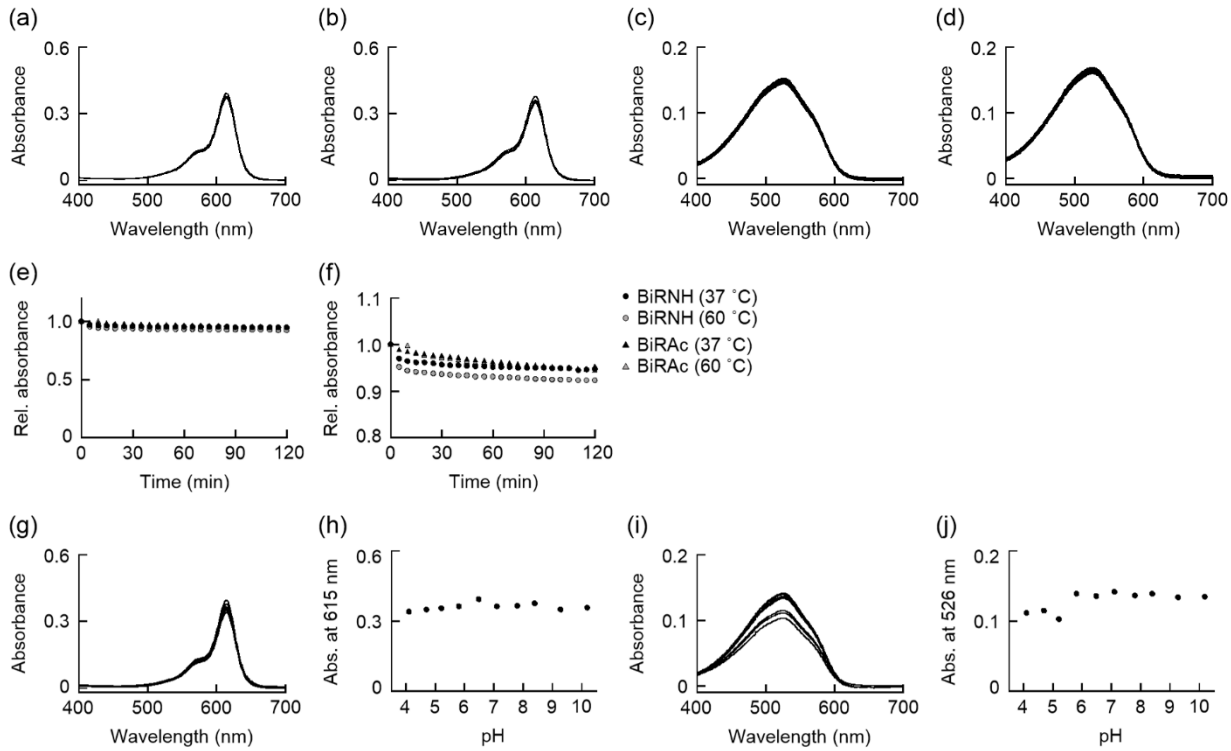


Figure S5. Stability tests of **BiRNH** and **BiRAc** in the dark. Absorption spectra of (a) **BiRNH** at 37 °C, (b) **BiRNH** at 60 °C, (c) **BiRAc** at 37 °C and (b) **BiRAc** at 60 °C in HEPES buffer (50 mM, pH 7.4, 0.5% DMSO). Absorption spectra were obtained every 5 min for 2 h. (e) Time course plots of relative absorbance at the maximum (615 nm for **BiRNH** and 526 nm for **BiRAc**) obtained in (a)–(d). (f) Magnified graph of (e). Absorption spectra of (g) **BiRNH** (5 μM) and (i) **BiRAc** (5 μM) in phosphate buffer (200 mM, 0.5% DMSO) at various pH (4.1, 4.7, 5.2, 5.8, 6.5, 7.1, 7.8, 8.4, 9.3, 10.2). Plots of absorbance of (h) **BiRNH** and (j) **BiRAc** at the maximum (615 nm for **BiRNH**, 526 nm for **BiRAc**) against pH obtained in (g) and (i).

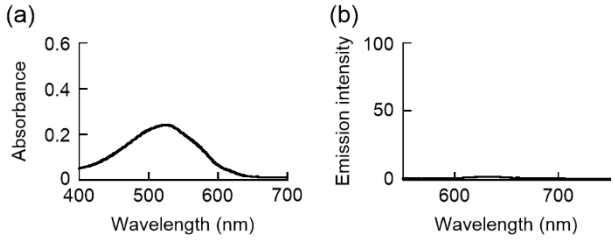


Figure S6. Absorption spectrum of **BiRGlu** (5 μM) in HEPES buffer (50 mM, pH 7.4, 0.5% DMSO). (b) Fluorescence spectrum of **BiRGlu** (1 μM) in in HEPES buffer (50 mM, pH 7.4, 0.5% DMSO). Excitation was provided at 526 nm.

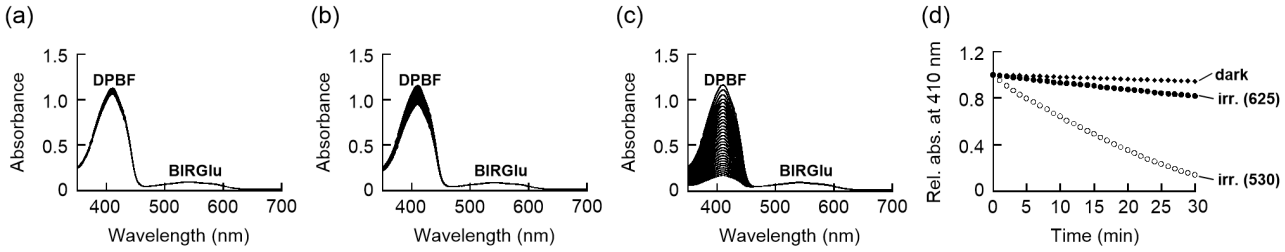


Figure S7. Absorption spectral change of DPBF (60 μM) without irradiation (a), with red light irradiation (625 nm, 1.1 mW cm^{-2}) (b) and with green light irradiation (530 nm, 1.1 mW cm^{-2}) (c) in the presence of **BiRGlu** (1.7 μM) in acetonitrile. (d) Plots of absorption at 410 nm measured in (a), (b) and (c). The data were collected every 1 minute.

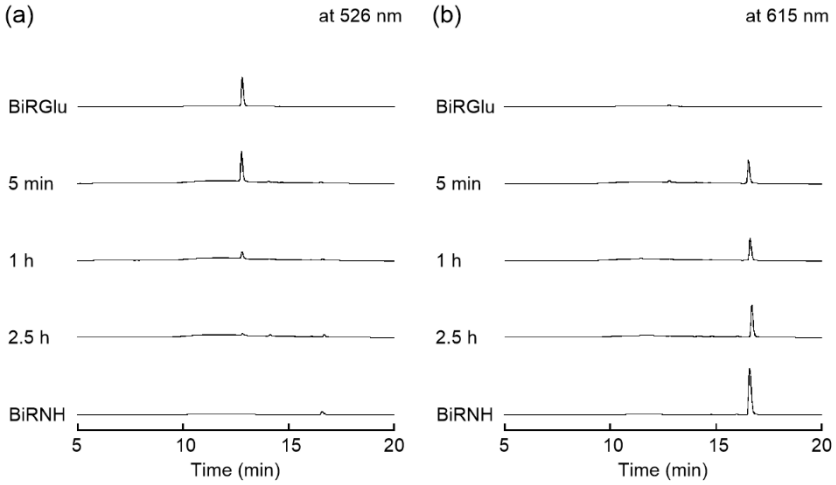


Figure S8. HPLC analysis of the reaction between **BiRGlu** (10 μM) and GGT (10 U mL^{-1}) in HEPES buffer (50 mM, pH 7.4, 5% DMSO). The reaction mixture was analyzed at each time point (5 min, 1 h, and 2.5 h) by reversed phase HPLC (A: 0.05% formic acid in water, B: 0.05% formic acid in acetonitrile, A/B = 20/80 to 80/20 for 5–20 min). Elutes were monitored at (a) 526 nm and (b) 615 nm. Pure samples of **BiRGlu** and **BiRNH** were also analyzed at the same concentrations.

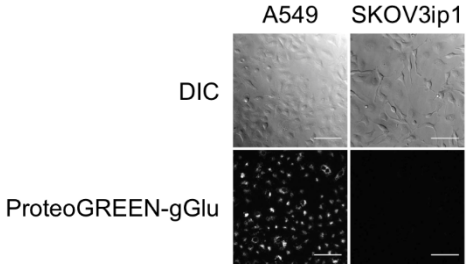


Figure S9. (Upper) Differential interference contrast (DIC) images of the same field of view of the fluorescence images. (Lower) Fluorescence microscopic images of A549 cells (left) and SKOV3ip1 cells (right) stained with ProteoGREEN-gGlu (GGT probe, referred as to gGlu-HMRG in the literature[10]). The images were acquired using an FITC filter set (excitation = 470 nm, emission = 516–556 nm). Scale bars indicate 100 μm.

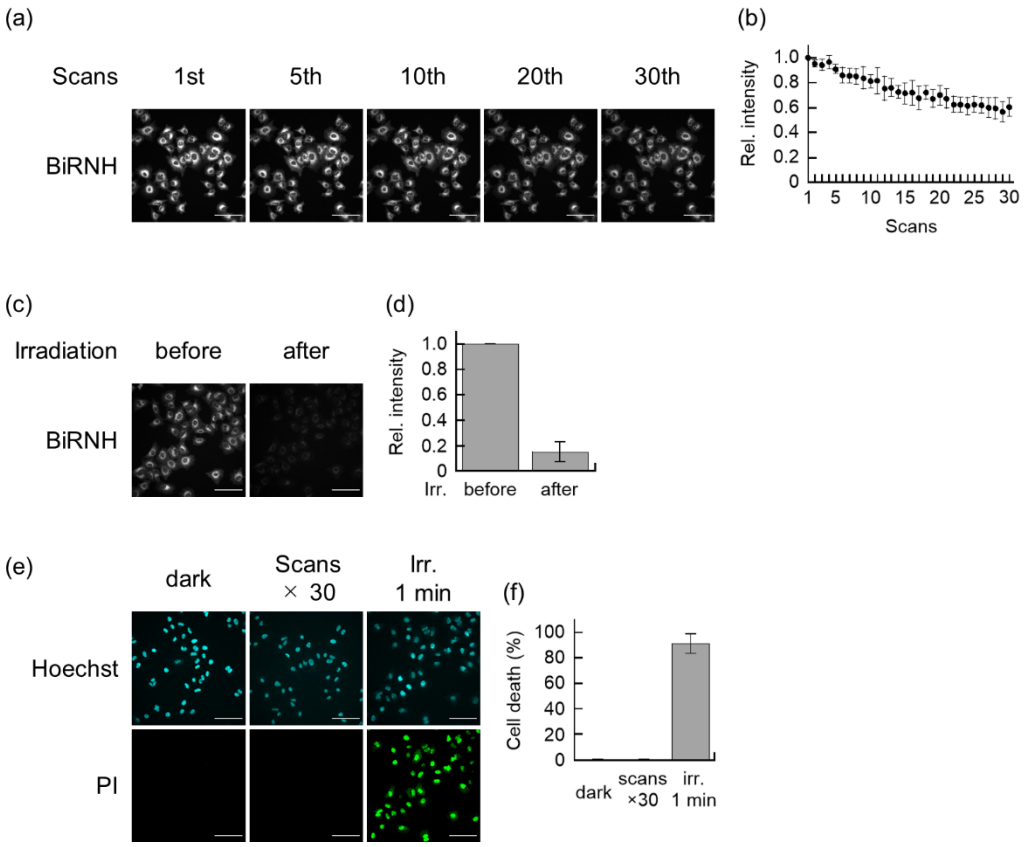


Figure S10. (a) Fluorescence microscopic images of A549 cells stained with **BiRNH** (1 μM). Scanning with excitation (640 nm, < 2 mW/cm^{-2}, 150 ms) was repeated 30 times. Scale bars indicate 100 μm. (b) Plot of relative fluorescence signal intensities from **BiRNH**. Each value indicates the mean ± SD (n = 3). (c) Fluorescence microscopic images of A549 cells stained with **BiRNH** (left) before and (right) after irradiation with red light (640 nm, 14.1 mW cm^{-2}, 1 min) for photosensitization. Scale bars indicate 100 μm. (d) Plot of relative fluorescence signal intensities from **BiRNH** before and after irradiation with red light. Each value indicates the mean ± SD (n = 3). (e) Fluorescence microscopic images of A549 cells stained with propidium iodide (PI) and Hoechst 33342 after the treatment with **BiRNH** (1 μM) followed by (left) no irradiation, (middle) scans repeated 30 times, or (right) irradiation with red light (640 nm, 14.1 mW cm^{-2}, 1 min). Scale bars indicate 100 μm. (f) Plot of the populations of PI-positive cells in the total cells (Hoechst-stained cells) under each condition in (a). Each value indicates the mean ± SD (n = 3).

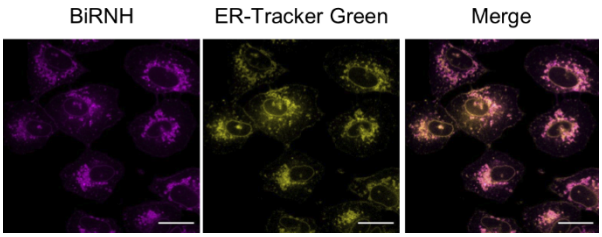


Figure S11. Colocalization assay of **BiRNH** (1 μM) and ER-Tracker Green (0.2 μM) in A549 cells. Left and middle images were acquired using a Cy5 filter (**BiRNH**, excitation = 640 nm, emission = 672–712 nm) and a FITC filter (ER-Tracker Green, excitation = 470 nm, emission = 516–556 nm), respectively. The right image is the merged image of the left and middle images. Scale bars indicate 25 μm. Pearson's correlation value (R_{coloc}) was calculated to be 0.87 ± 0.05 (n = 3).

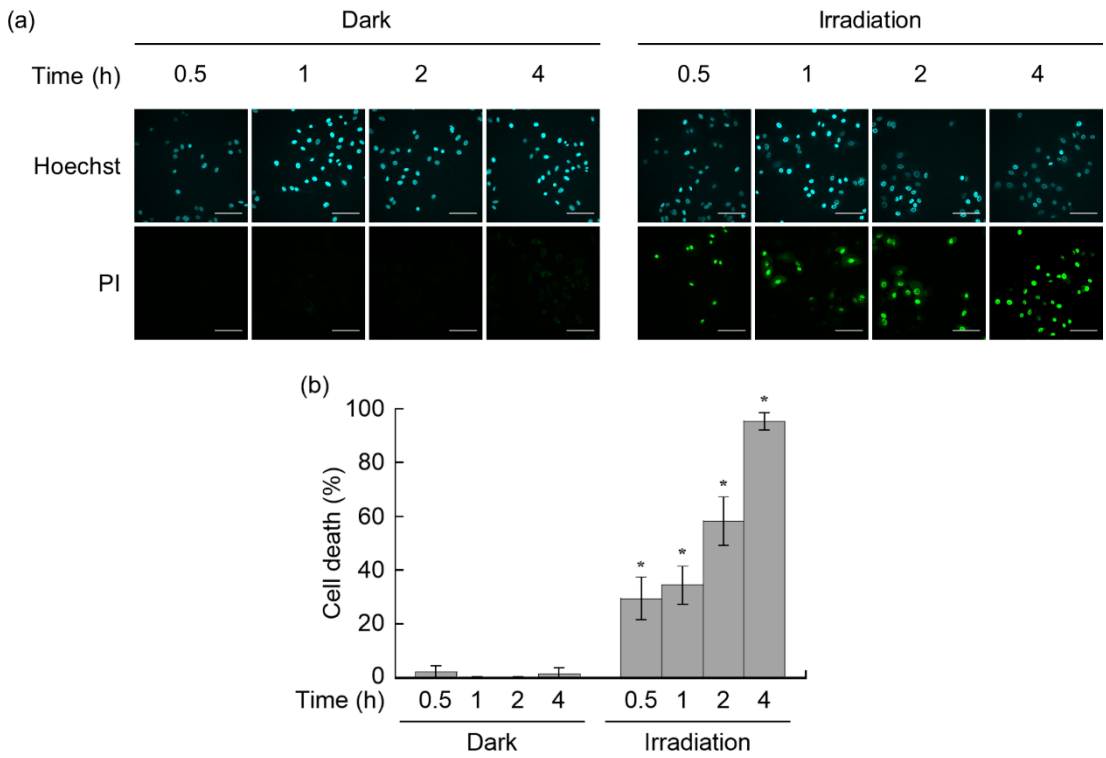


Figure S12. (a) Fluorescence microscopic images of A549 cells stained with propidium iodide (PI) and Hoechst 33342 after the treatment with **BiRGlu** (1 μM) for the indicated times (0.5, 1, 2, and 4 h) followed by (right) irradiation with red light (640 nm, 14.1 mW cm^{-2}, 1 min) or (left) no irradiation. Scale bars indicate 100 μm. (b) Plot of the populations of PI-positive cells in the total cells (Hoechst-stained cells) under each condition in (a). Each value indicates the mean ± SD (n = 4). Statistical analysis was performed with Student's *t*-test (vs dark condition of the corresponding incubation times). **P* < 0.005.

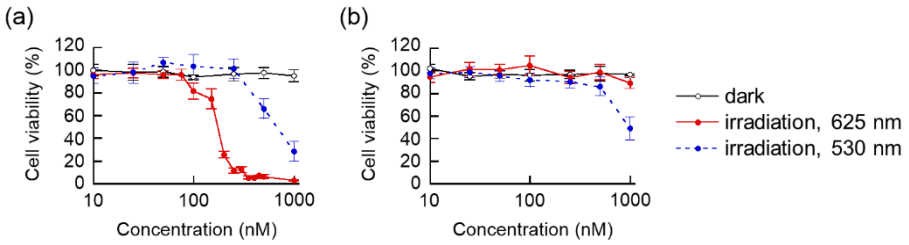


Figure S13. (a) Cell viability assay of A549 cells and (b) SKOV3ip1 cell after the treatment with the indicated concentrations of **BiRGlu** for 2 h followed by irradiation with a red light (625 nm, 20 J cm^{-2}) or a green light (530 nm, 20 J cm^{-2}) and by no irradiation. Each value indicates the mean ± SD (n = 6).

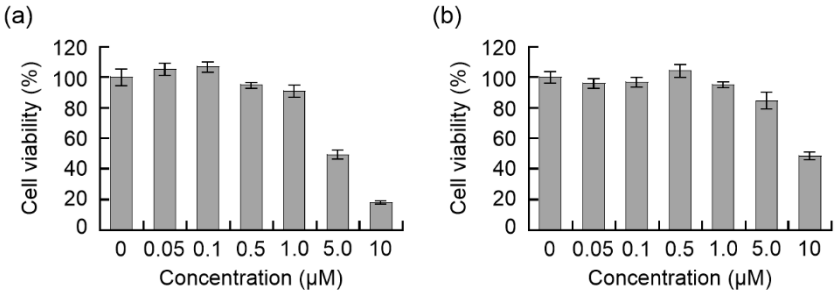
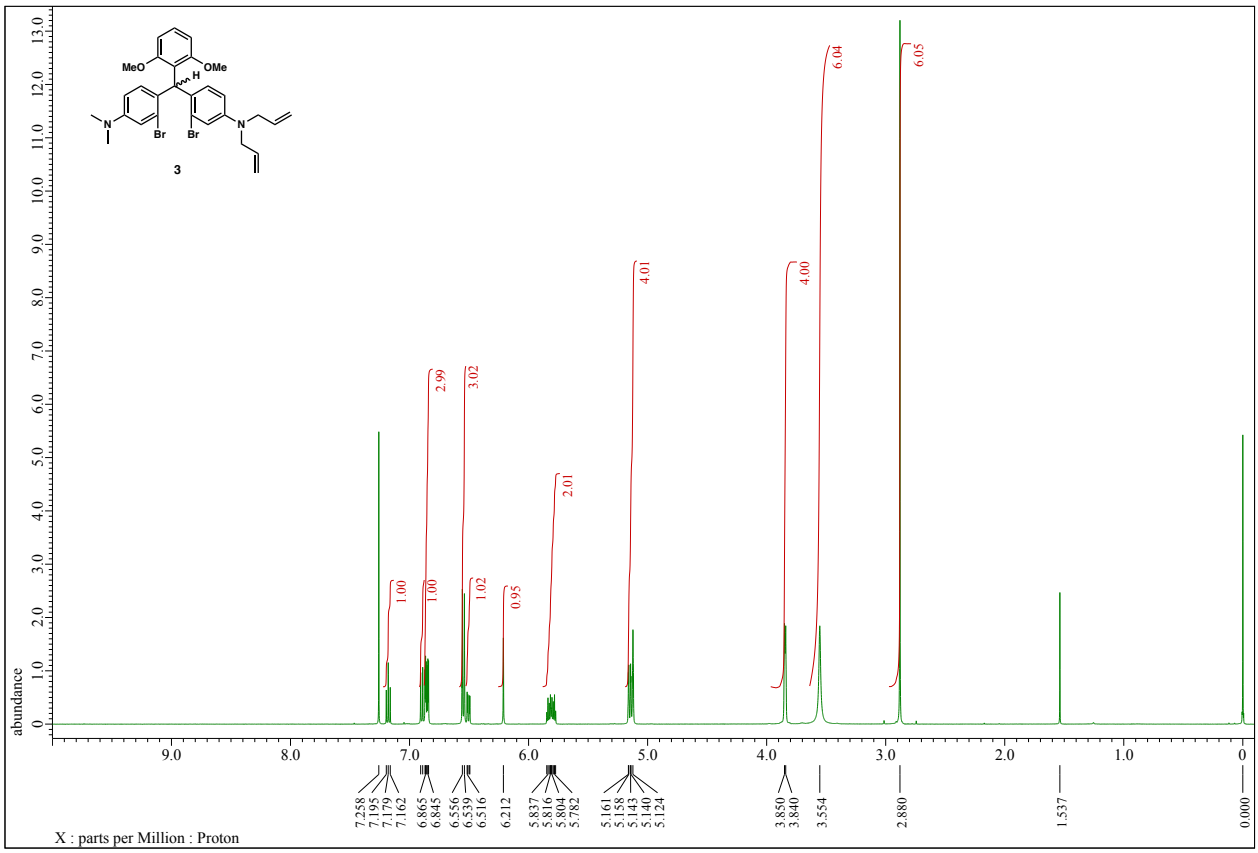


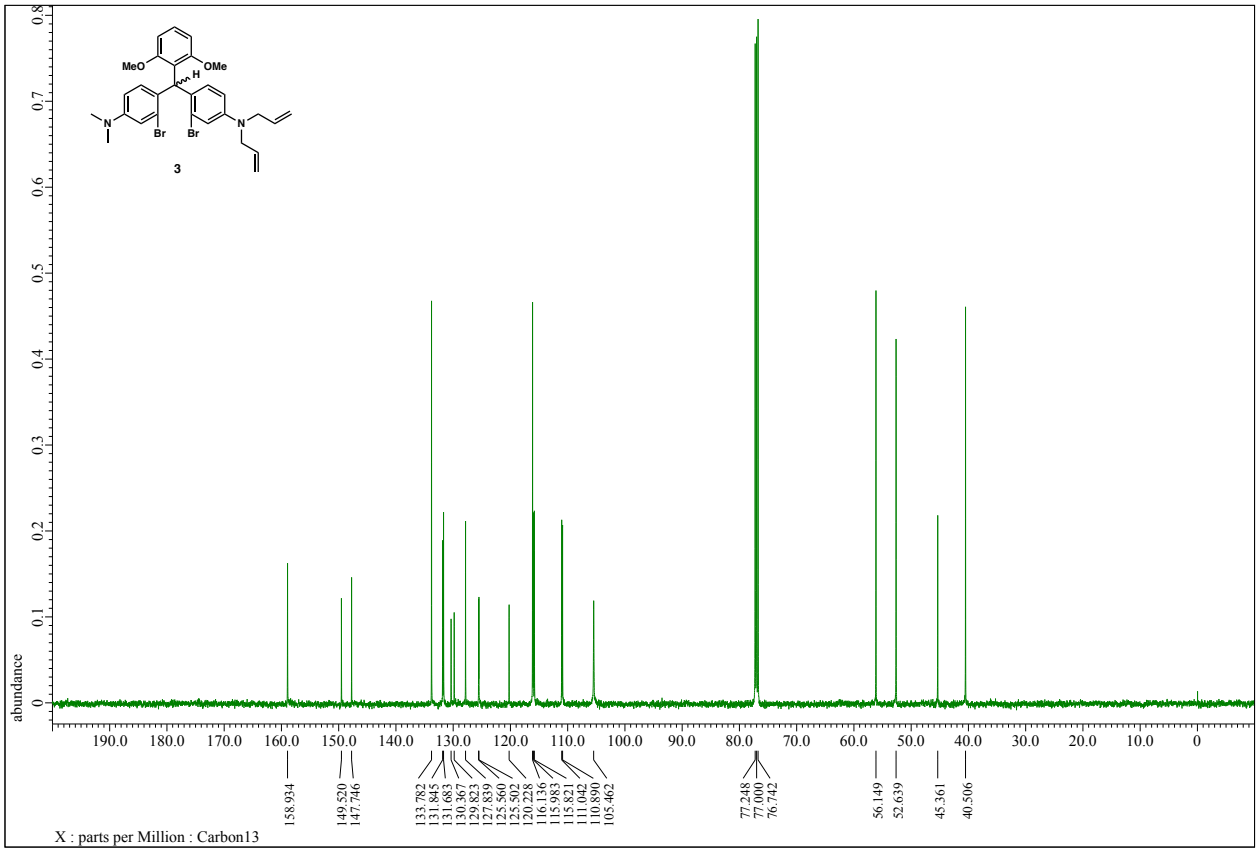
Figure S14. Cell viability assay (MTT assay) of (a) A549 and (b) SKOV3ip1 cells after 24 h treatment with various concentrations of **BiRGlu**. Each value indicates the mean ± SD (n = 6).

^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **3**

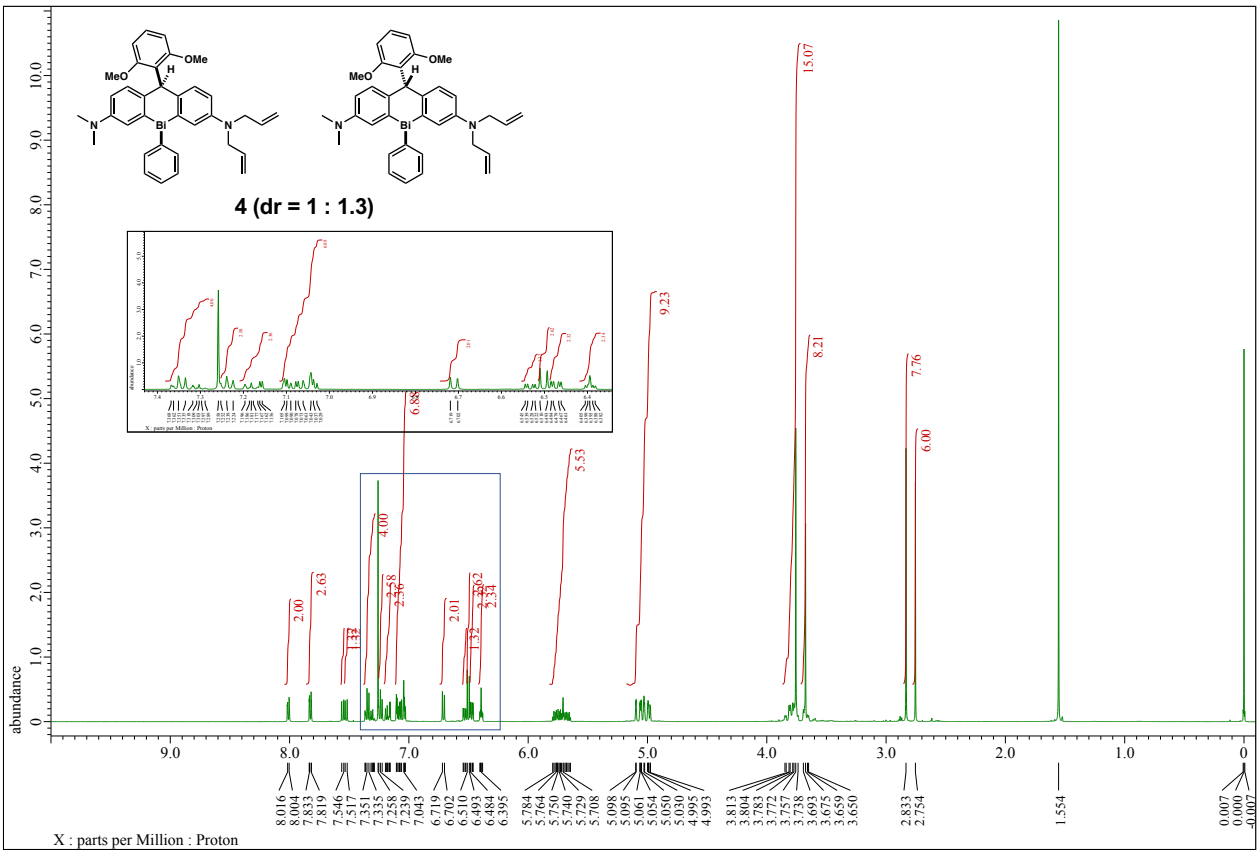


^{13}C NMR spectrum of **3**

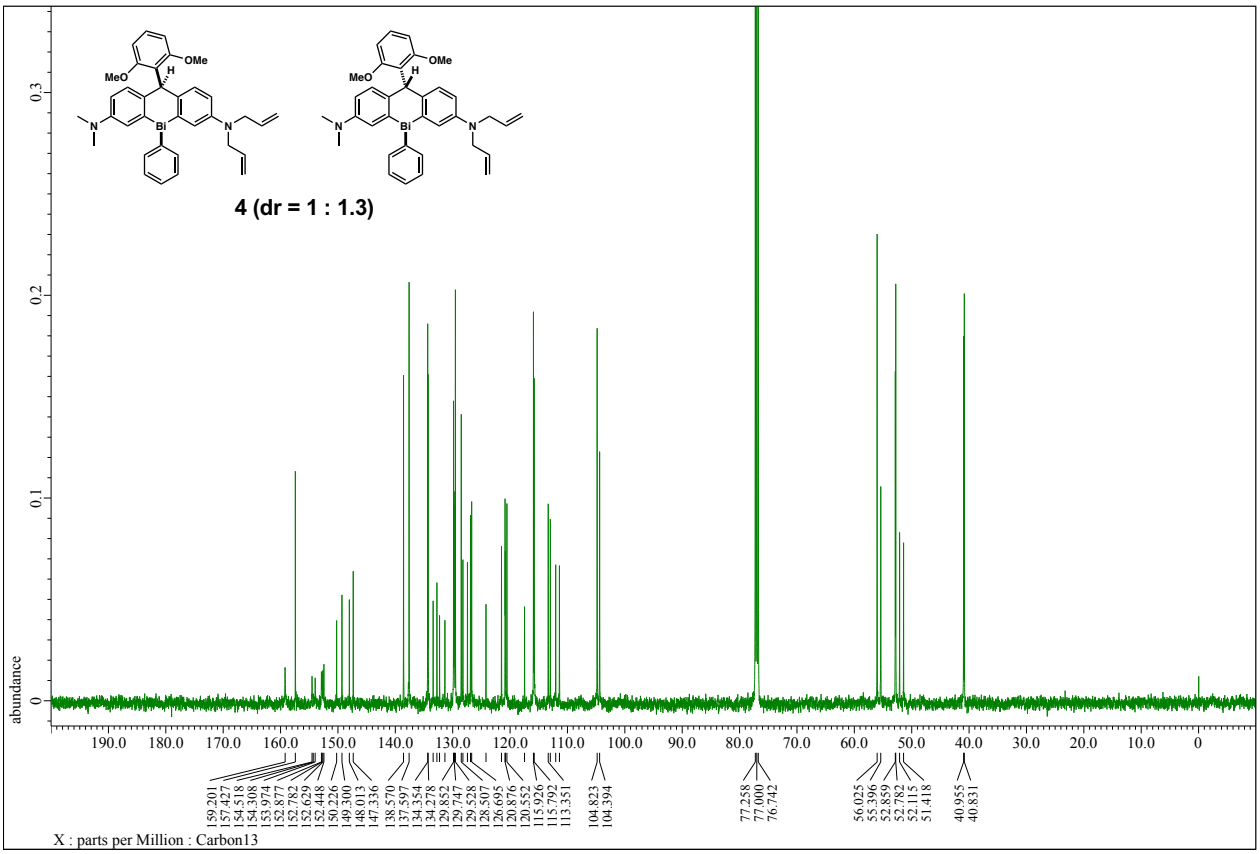


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **4**

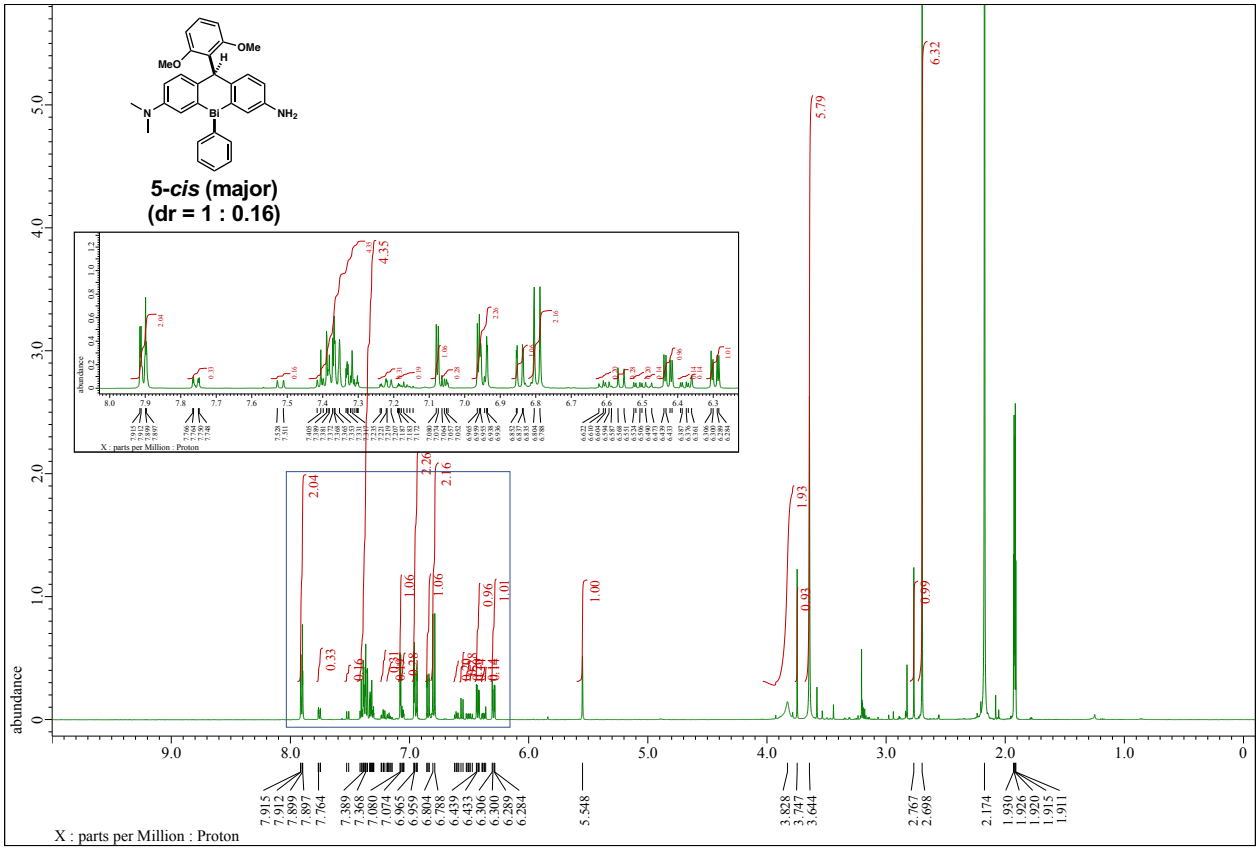


^{13}C NMR spectrum of **4**

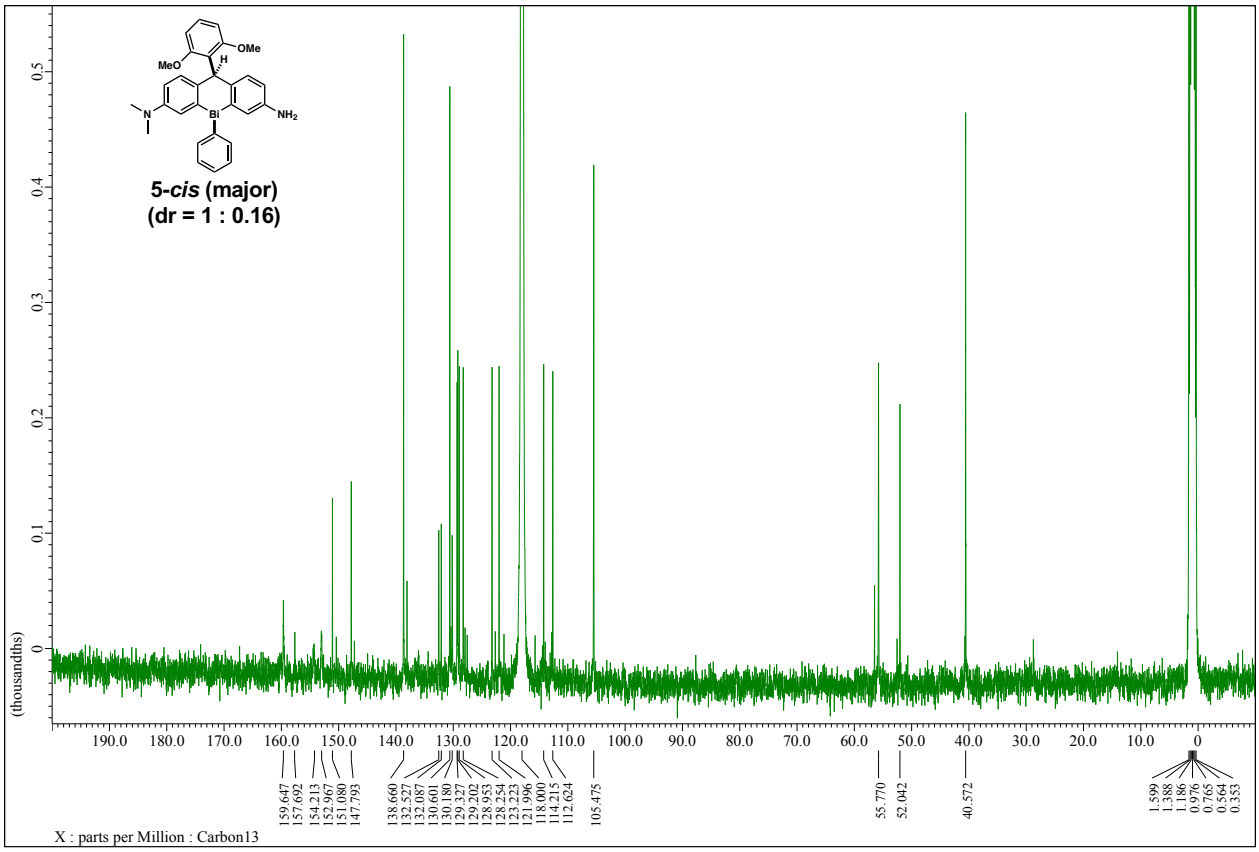


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **5-*cis***

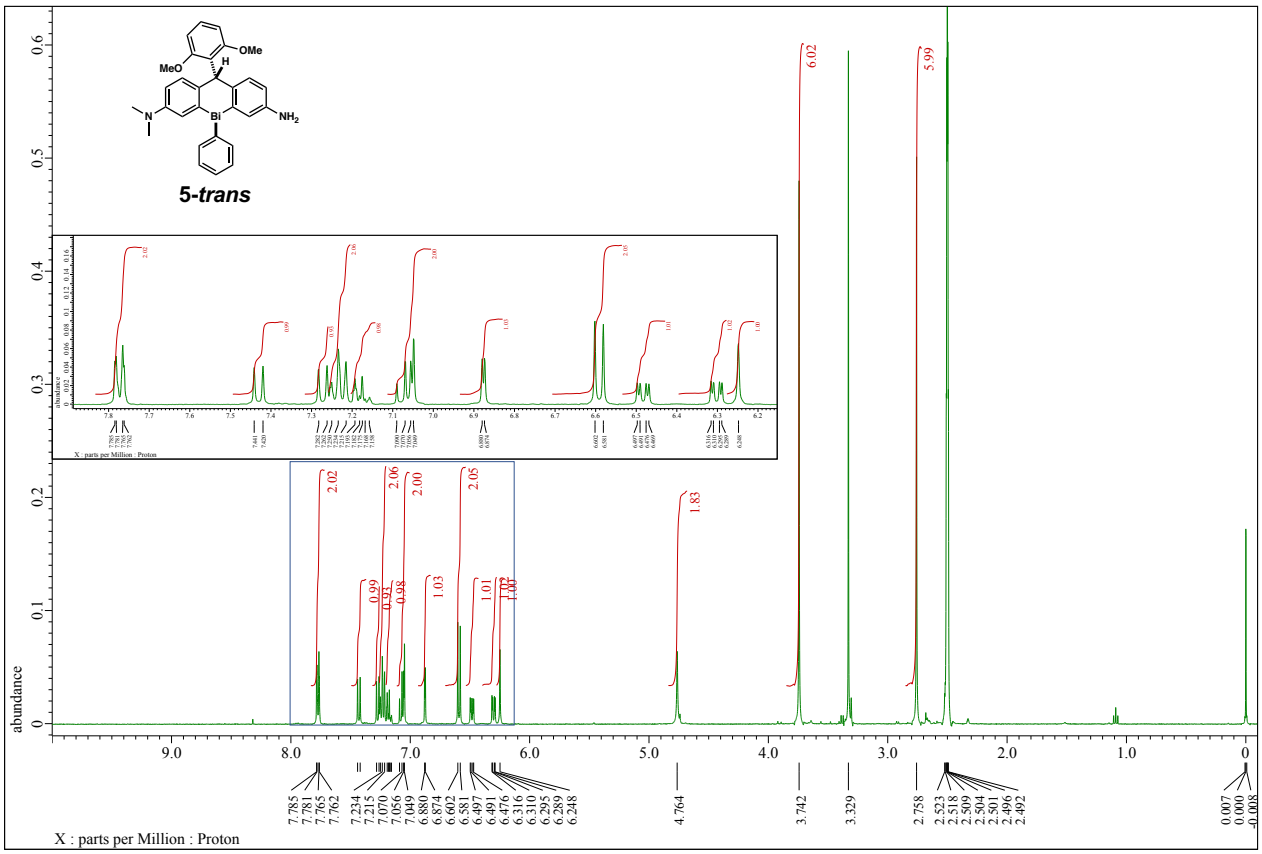


^{13}C NMR spectrum of **5-*cis***

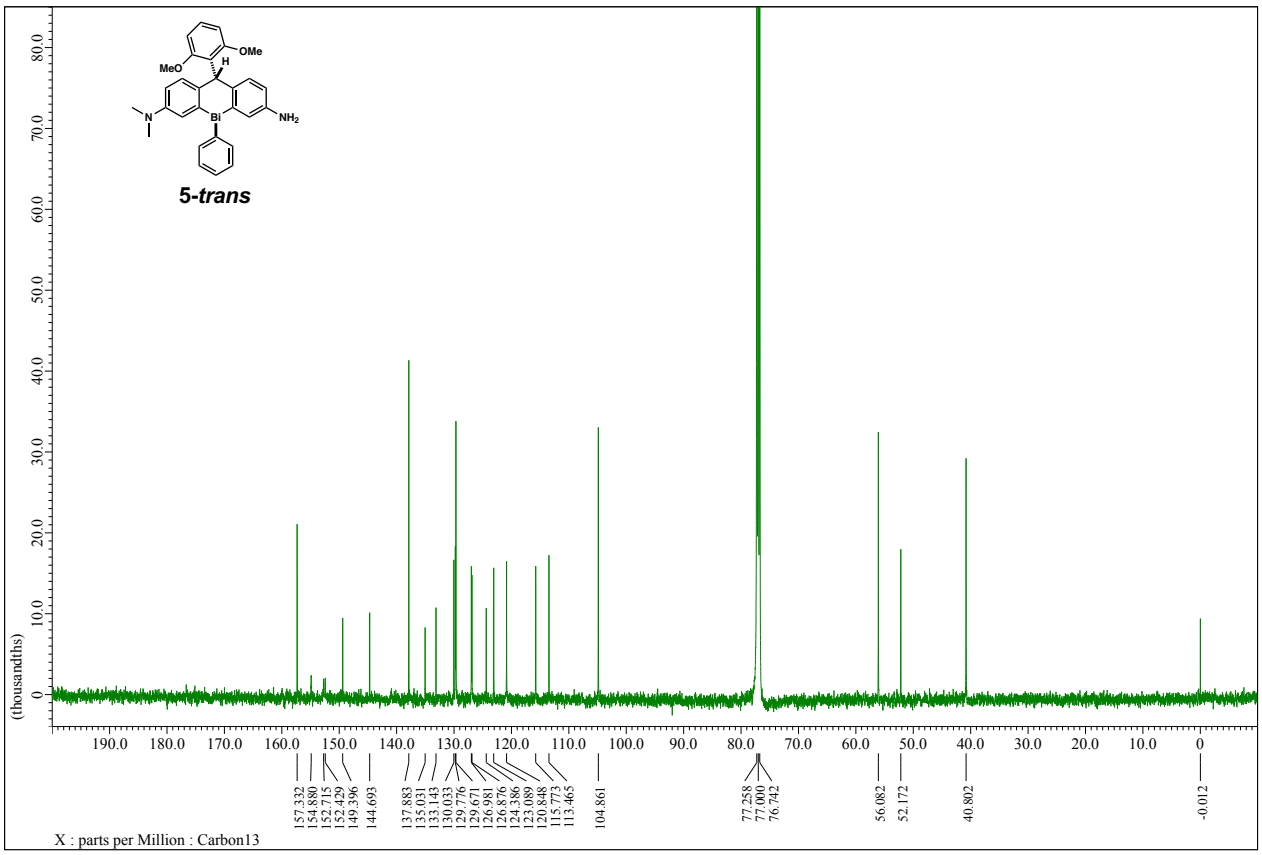


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **5-*trans***

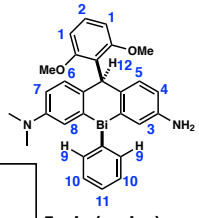


^{13}C NMR spectrum of **5-*trans***

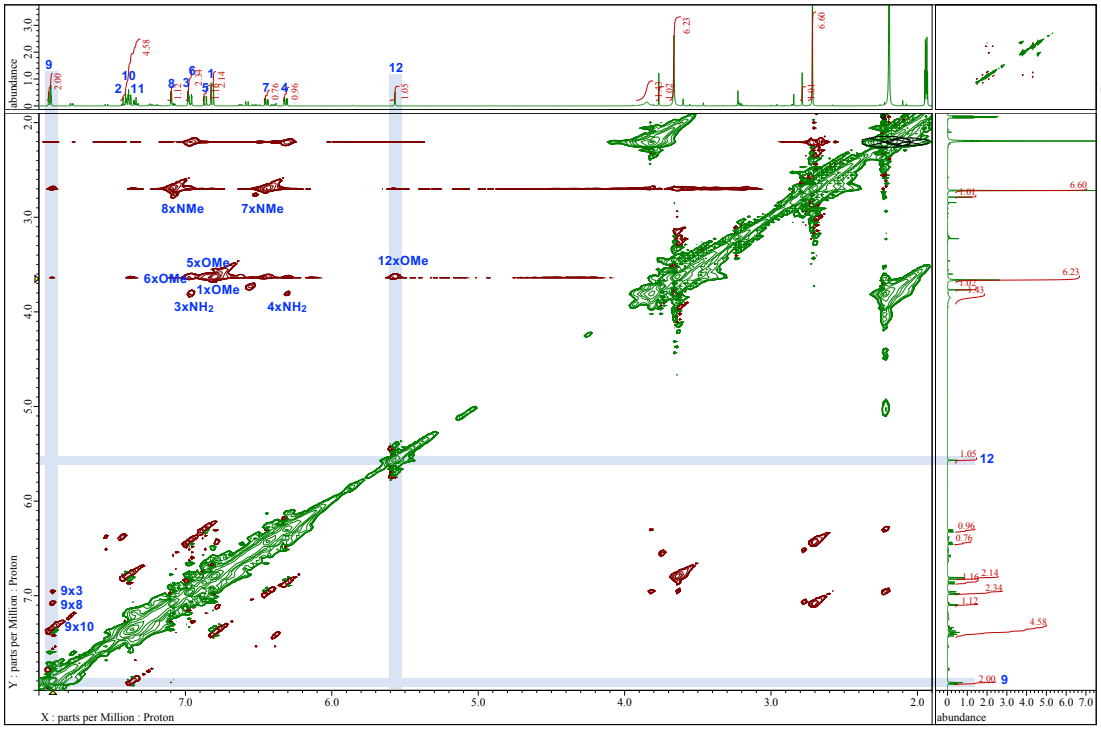


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

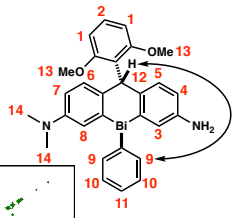
NOESY spectrum of **5-*cis***



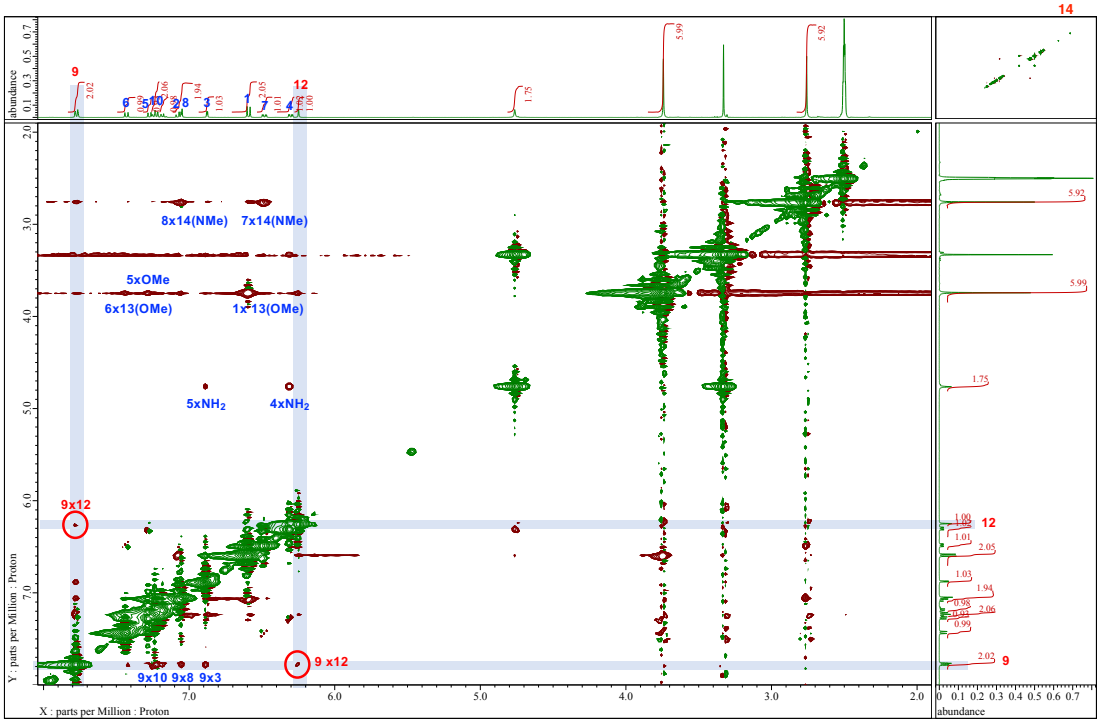
5-*cis* (major)
(dr = 1 : 0.16)



NOESY spectrum of **5-*trans***

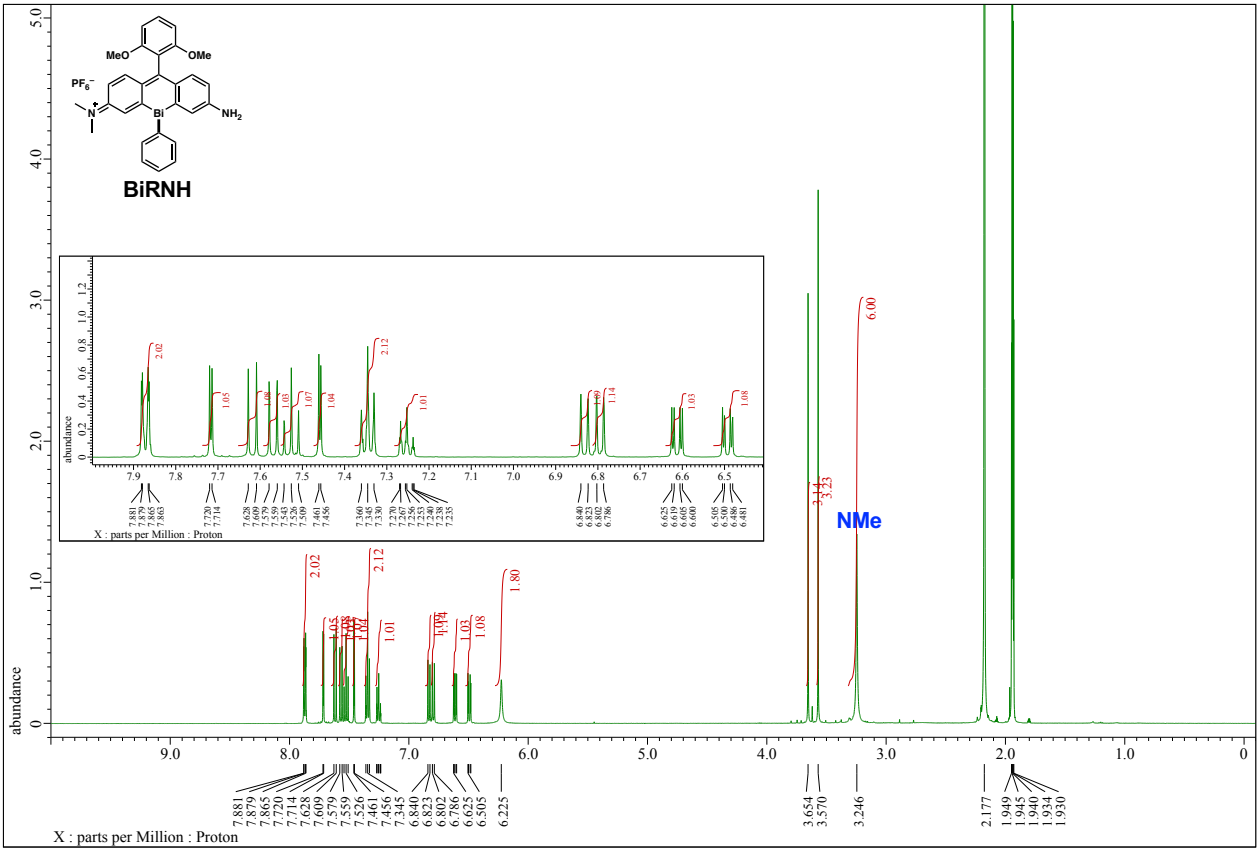


5-*trans*

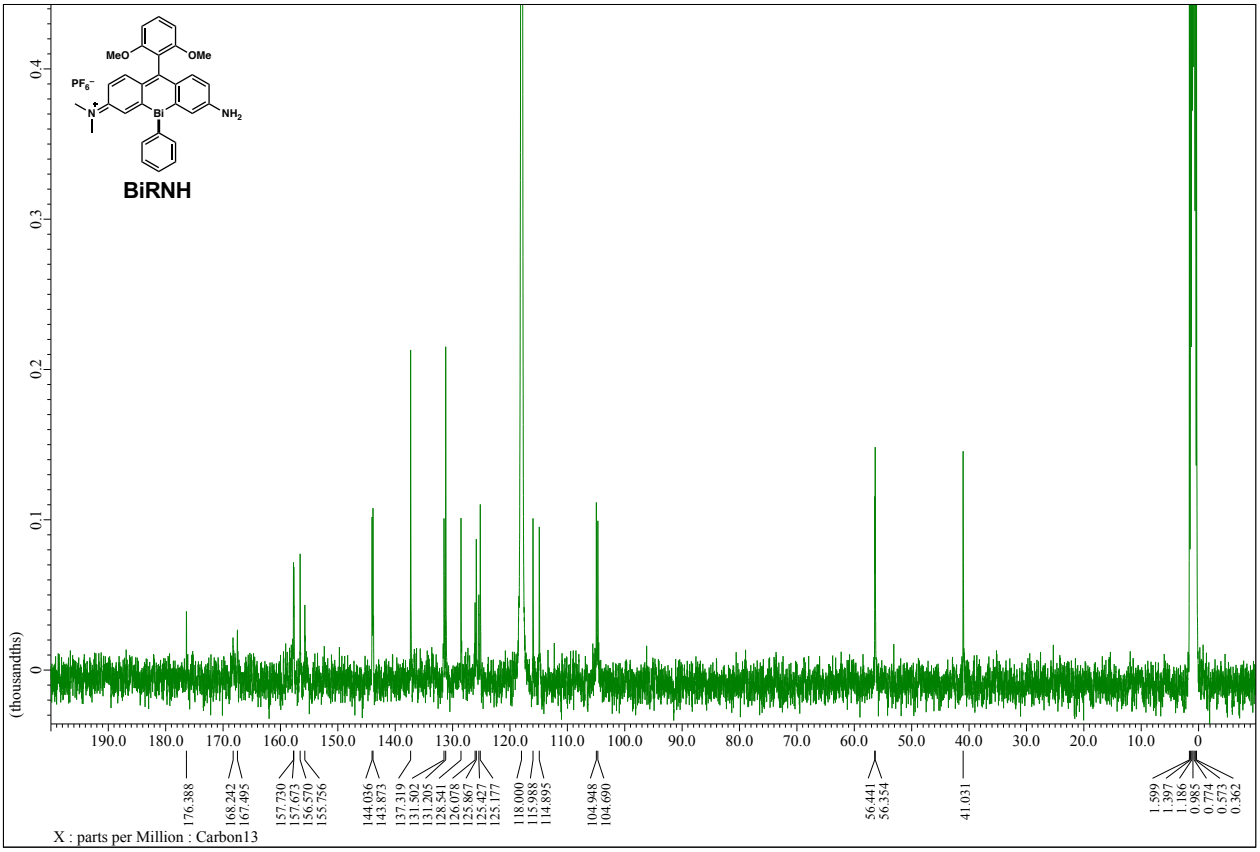


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **BiRNH**

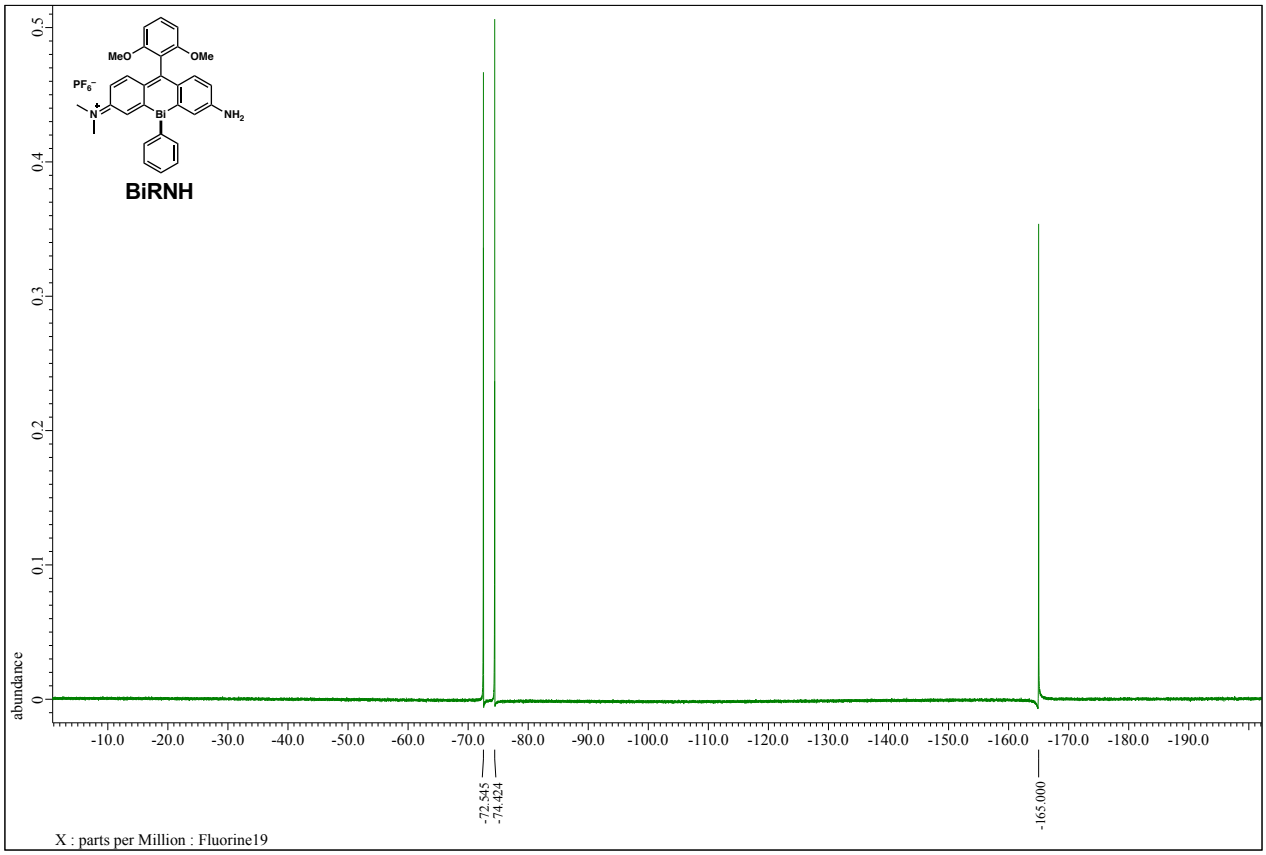


^{13}C NMR spectrum of **BiRNH**



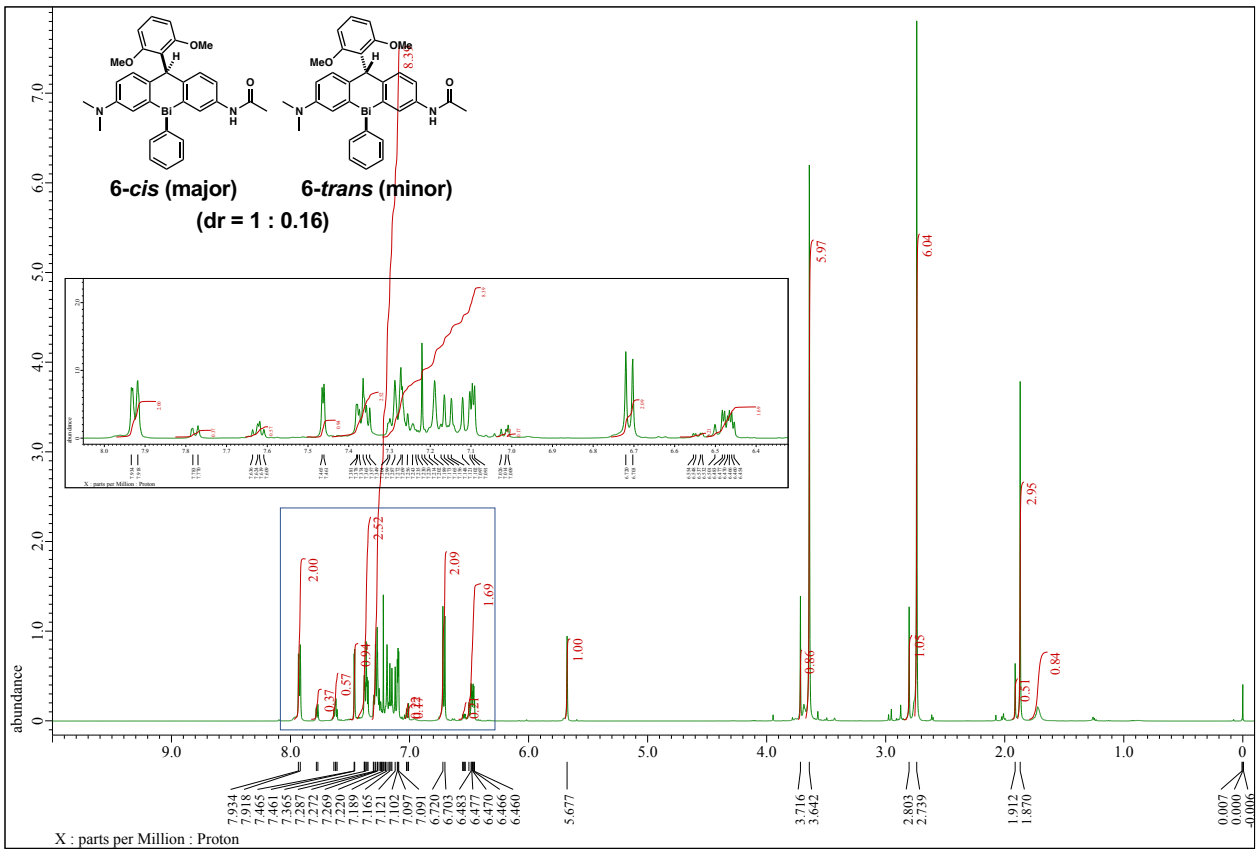
^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{19}F NMR spectrum of **BiRNH**

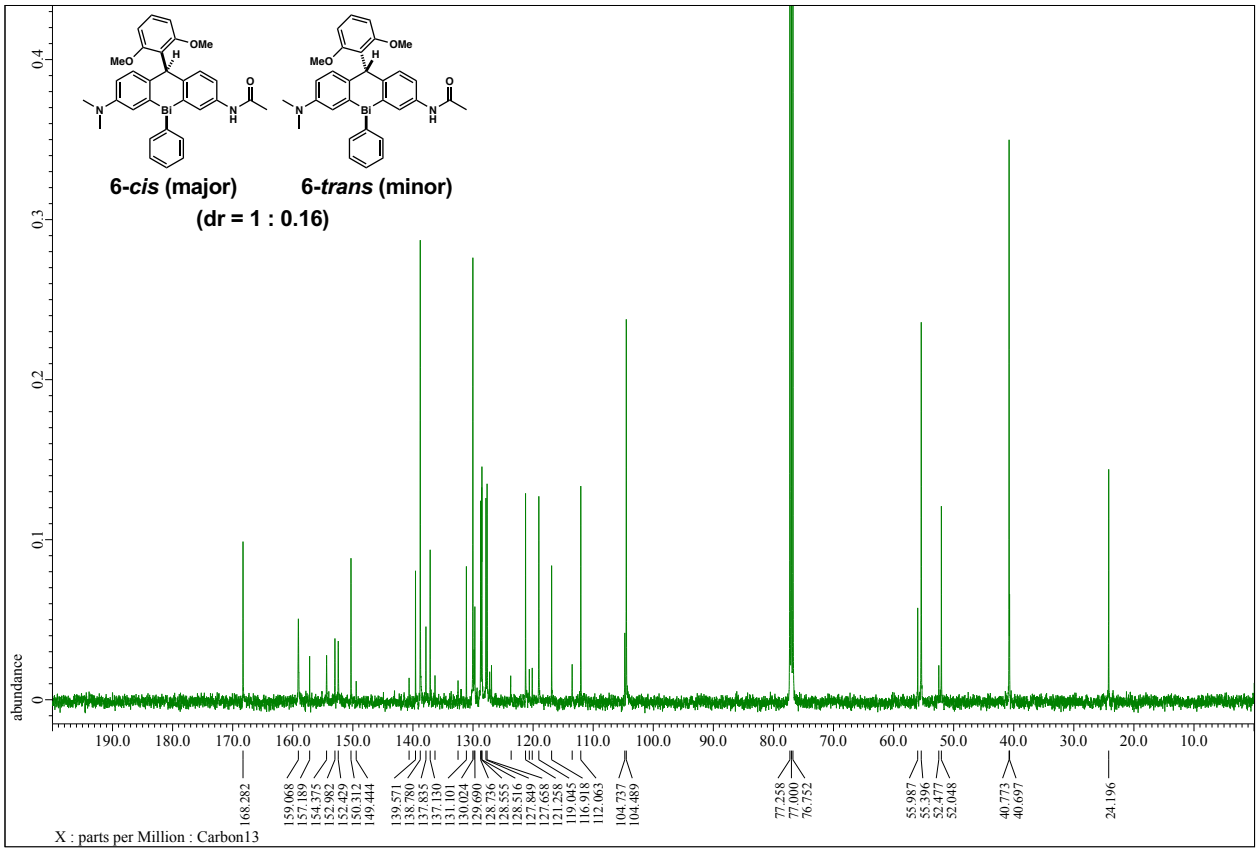


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **6**

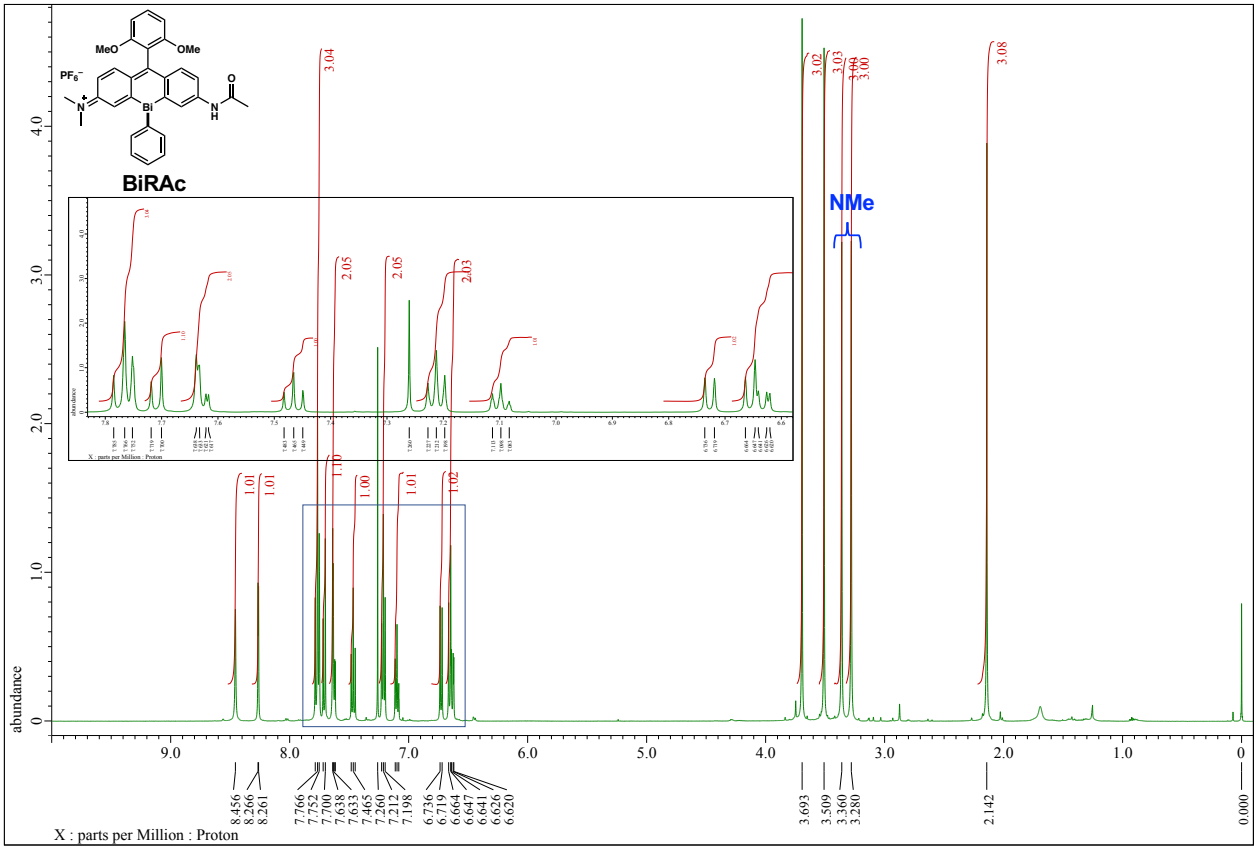


^{13}C NMR spectrum of **6**

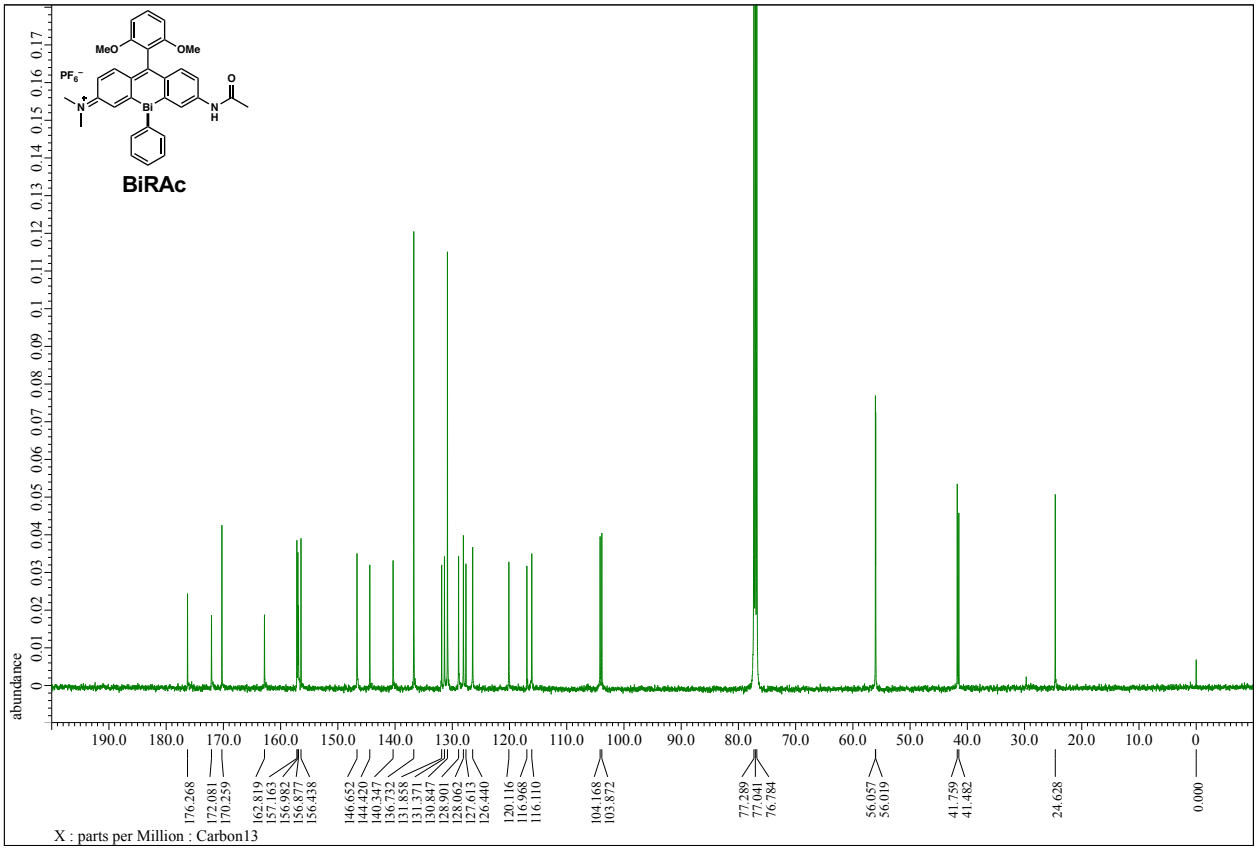


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **BiRAc**

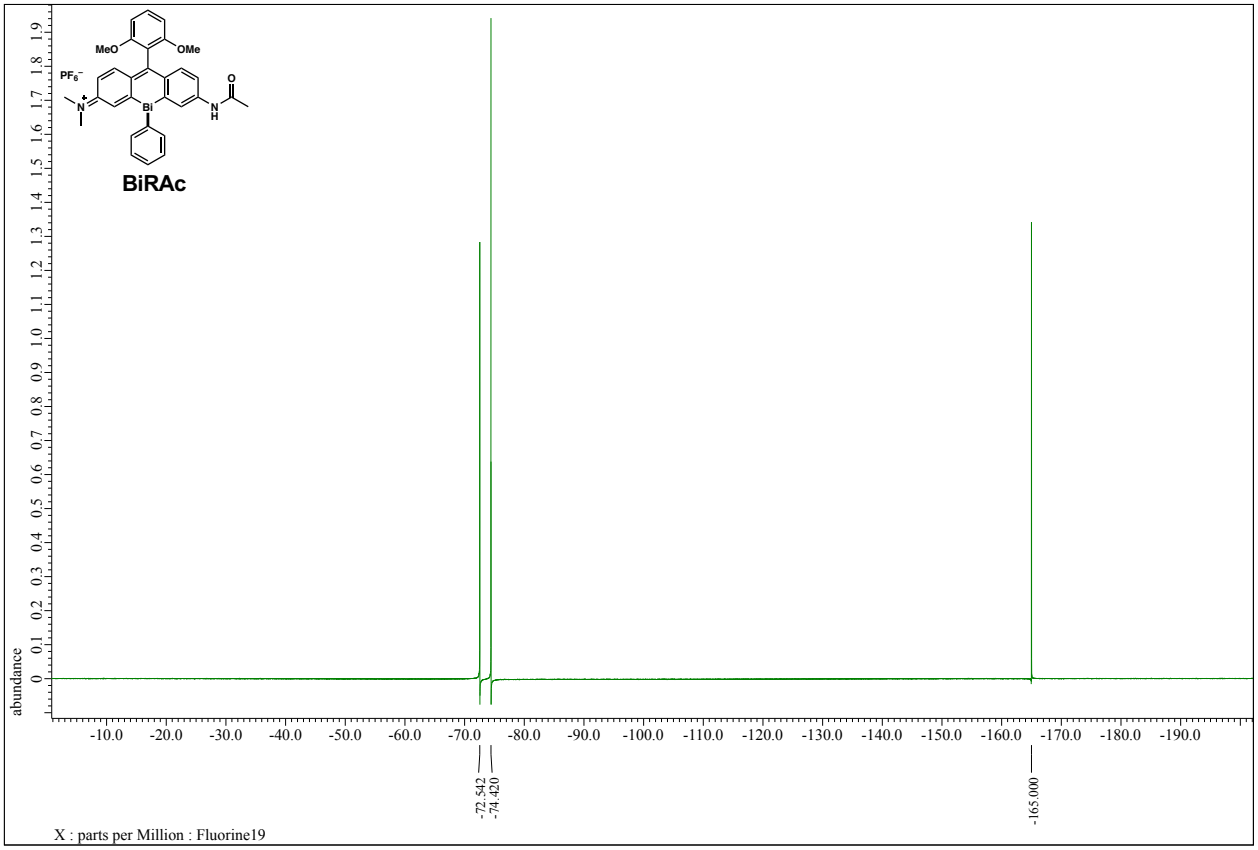


^{13}C NMR spectrum of **BiRAc**



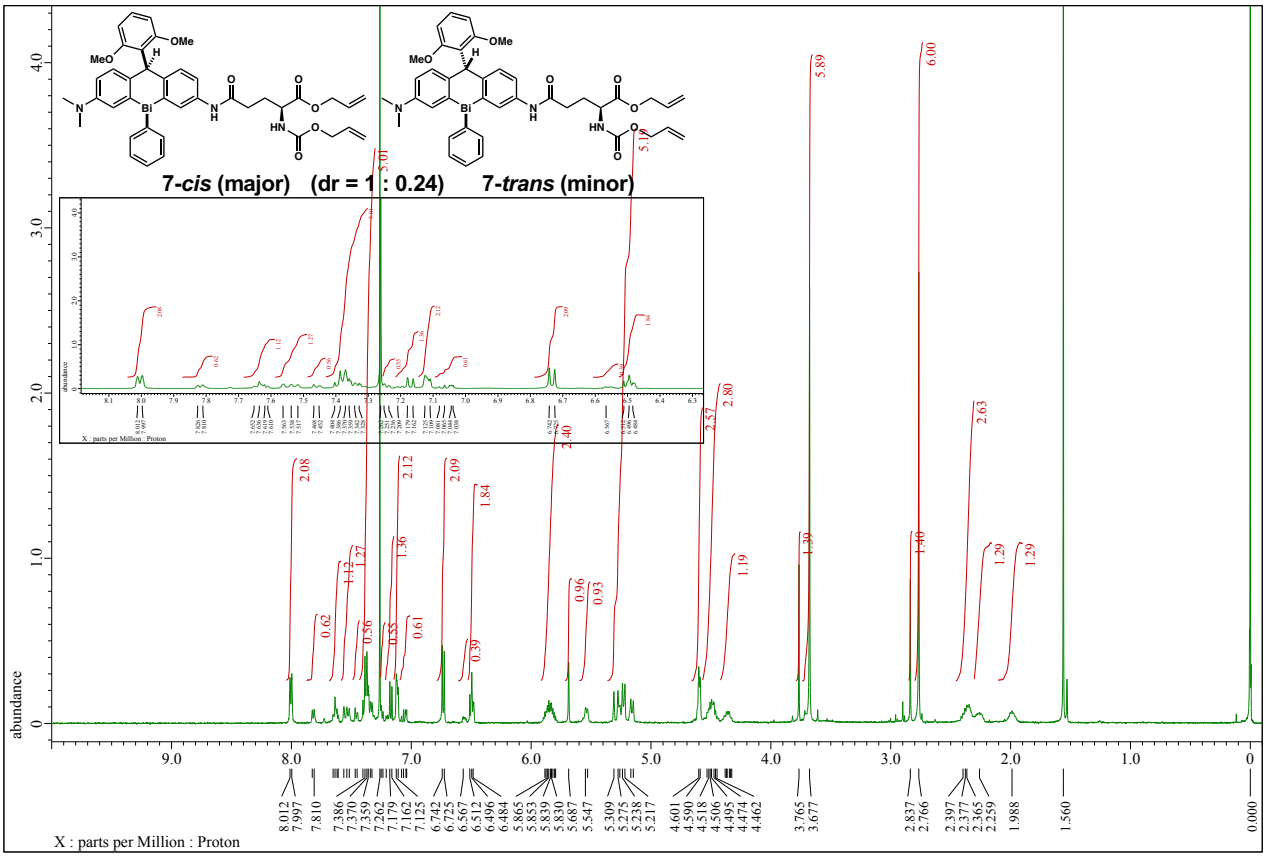
^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{19}F NMR spectrum of **BiRAc**

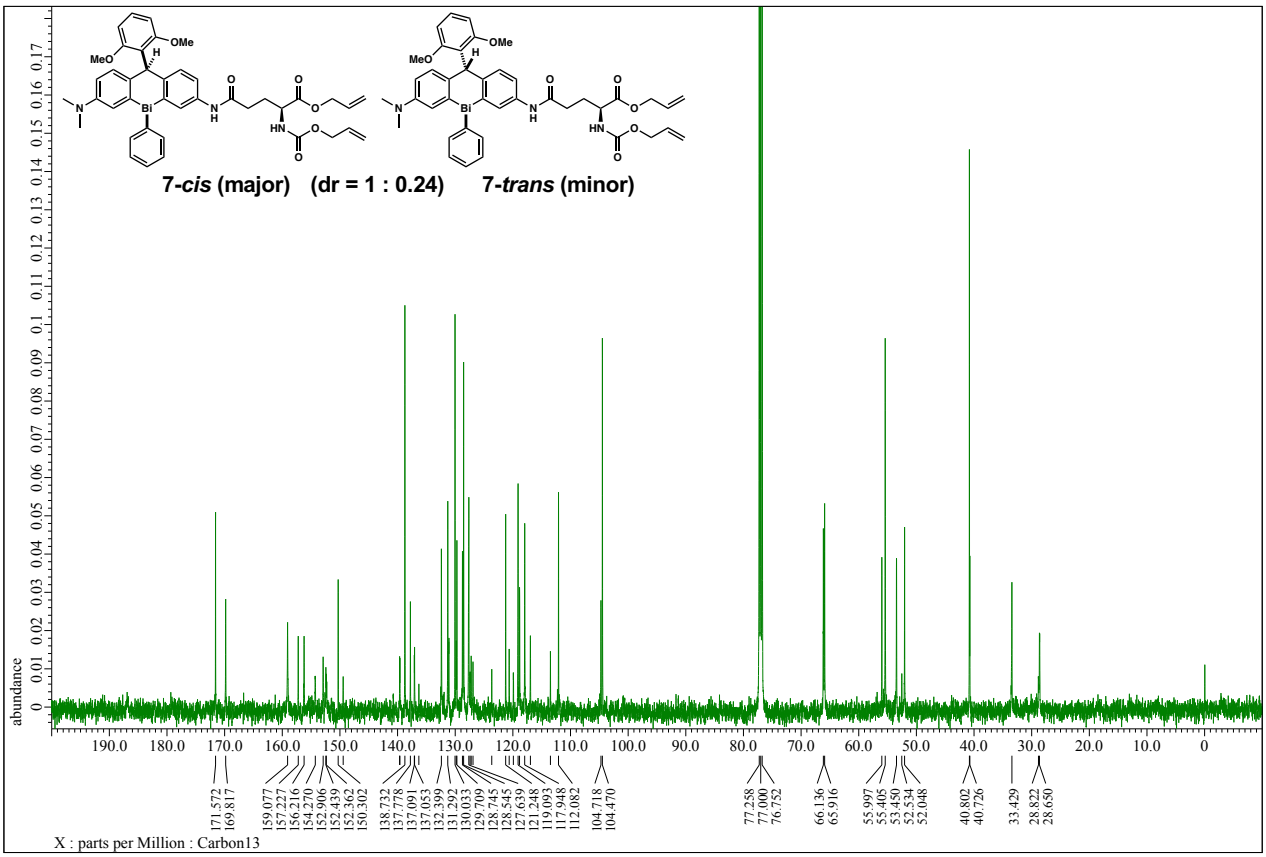


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **7**

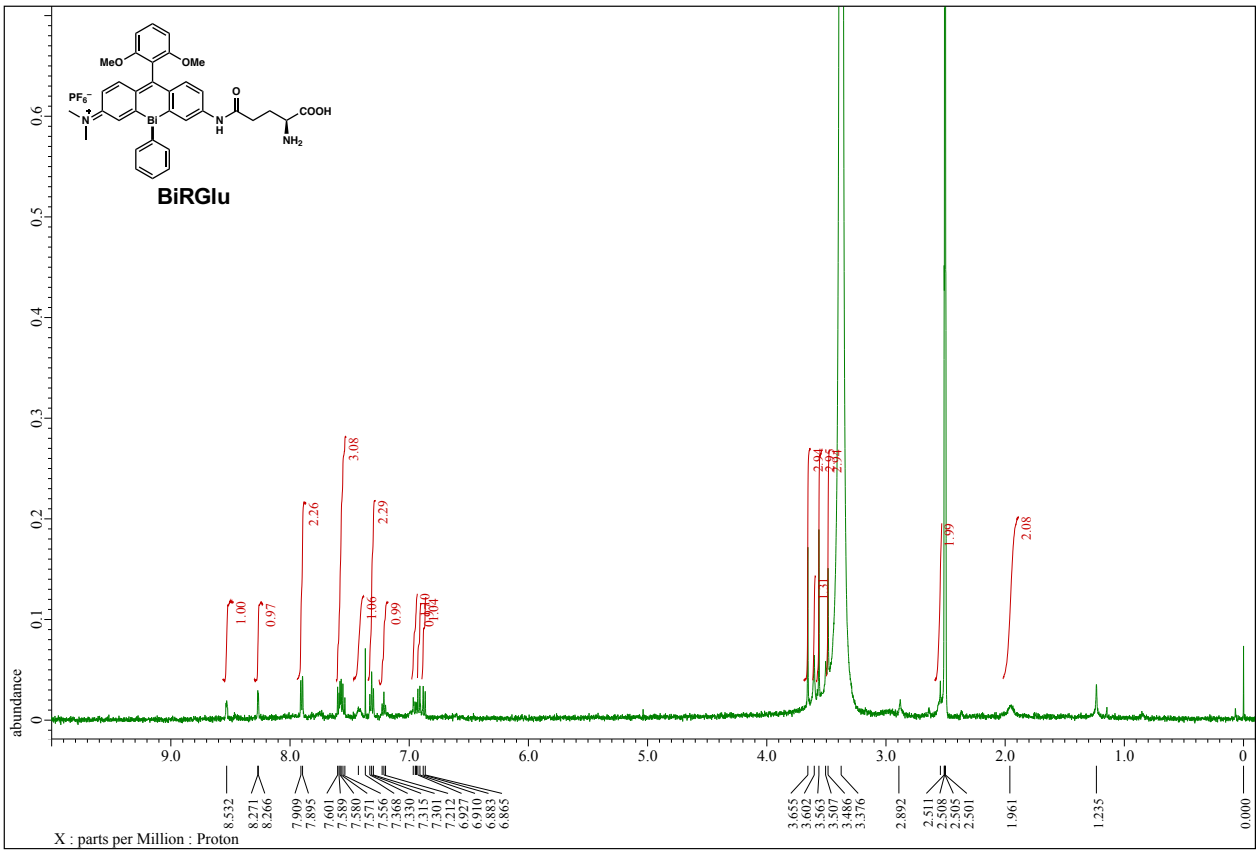


^{13}C NMR spectrum of **7**

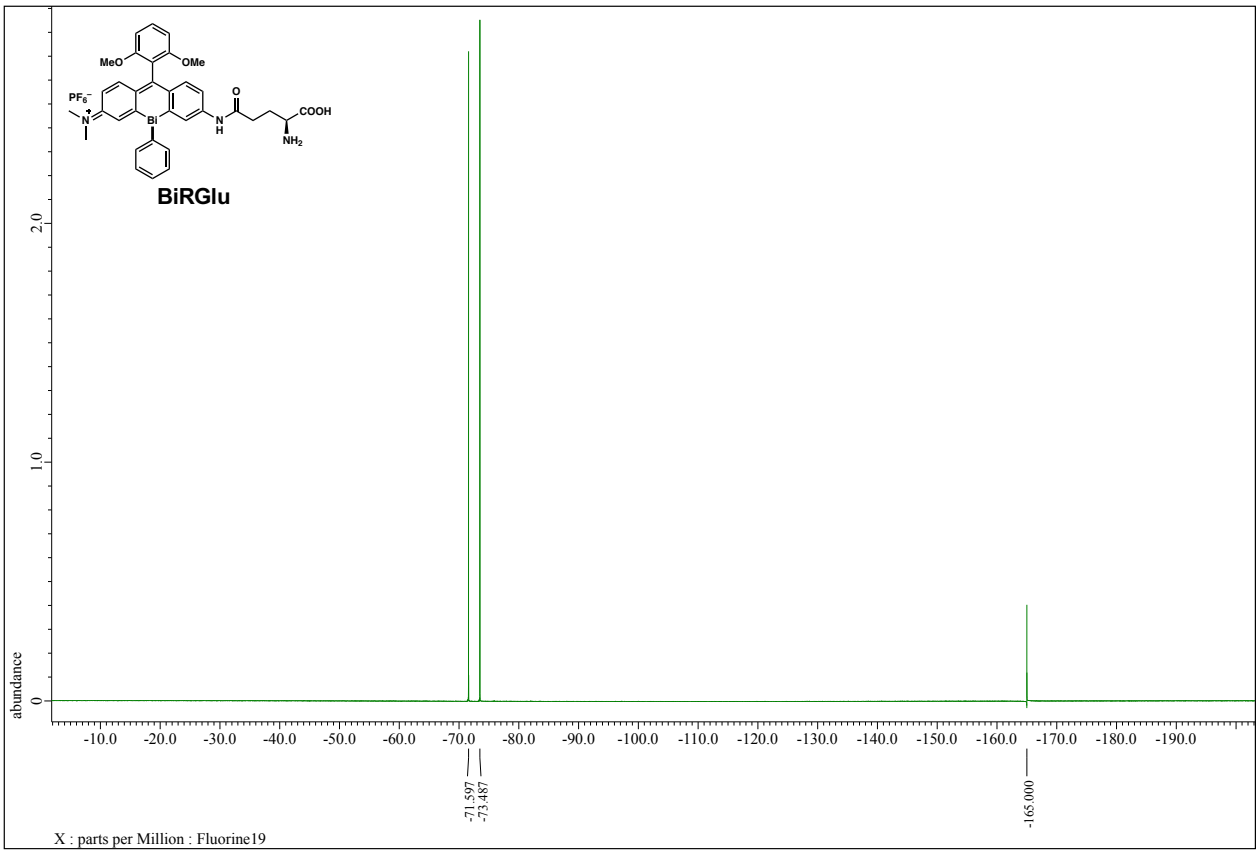


^{1}H, ^{13}C, ^{19}F NMR spectra and NOESY spectra of the newly synthesized compounds

^{1}H NMR spectrum of **BiRGlu**



^{19}F NMR spectrum of **BiRGlu**



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