Electronic Supplementary Information

Attenuation of α-synuclein aggregation by catalytic photo-oxygenation

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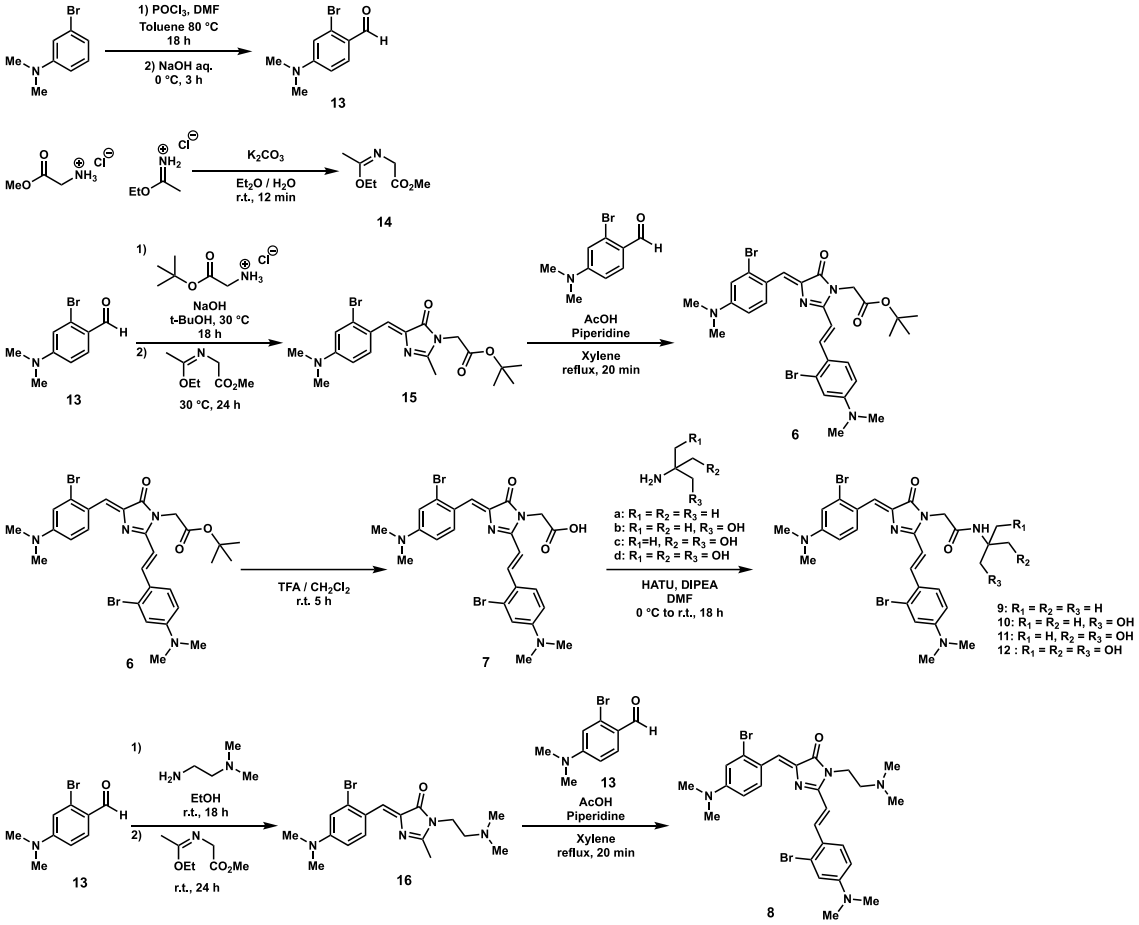
Experimental Procedures

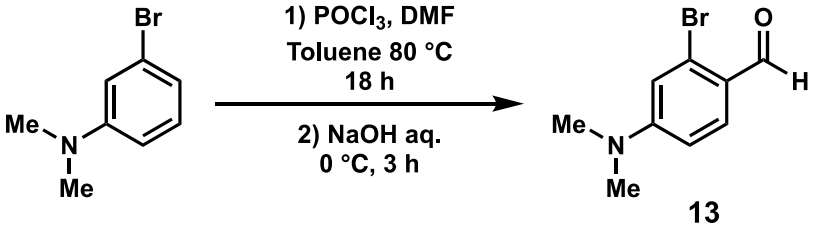
General

NMR spectra were recorded on JEOL ECX500 spectrometer operating at 500 MHz for ^{1}H NMR and 124.51 MHz for ^{13}C NMR, or JEOL ECS400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR) and DMSO (δ = 2.50 for ^{1}H NMR and δ = 39.5 for ^{13}C NMR) as an internal reference. Preparative HPLC was performed with Shimadzu HPLC system equipped with an SPD-20A UV−vis detector, LC-6AD pumps, a CTO-20AC column oven, an FRC-10A fraction collector, and a CBM-20A system controller. LC/MS (ESI) analysis was performed with Agilent Technologies LC/MS (ESI-Q) system equipped with a 1260 Infinity high-performance degasser, an Agilent 1260 Infinity binary pump, a 1260 Infinity standard autosampler, a 1290 Infinity thermostated column compartment, a 1260 Infinity variable wavelength detector, and an Agilent 6120 single quadrupole LC/MS. ESI-mass spectra were measured on a Bruker micrOTOF-II spectrometer. Photoreaction was performed with a Valore INSIGHT VAL-S light emitting diode (λ = 500, 595, 660 nm). Absorbance measurement was performed using a Shimadzu UV-1800 spectrometer with a rectangular quartz cell (5 mm pathlength). The fluorescence intensity and spectra were measured on a spectrofluorophotometer RF-5300PC (Shimadzu Co.) using a rectangular quartz cell (3 mm pathlength). All solvents and chemicals were purchased from commercial suppliers, Kanto Chemical Co., Inc., Sigma–Aldrich, Inc., Tokyo Chemical Industry Co., Ltd., Wako Pure Chemical Co., Inc., and Watanabe Chemical Industries, Ltd., and were used without further purification.

Synthesis



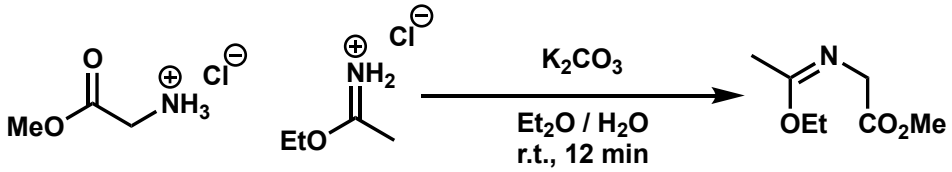
Compound 13



To a solution of 3-bromo-*N*,*N*-dimethylaniline (1.43 mL, 10.0 mmol) in toluene (10.0 mL), phosphoryl trichloride (1.12 mL, 12.0 mmol) and *N*,*N*-dimethylformamide (1.01 mL, 13.0 mmol) were added, and the mixture was stirred at 80 °C for 18 h. The reaction mixture was cooled in an ice bath, and treated with 1 N NaOH aq. After stirring the mixture for 3 h, products were extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on silica gel (Hexane/EtOAc =5/1 to 3/1) to afford **13** (1.87 g, 8.20 mmol, 82 %) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.06 (s, 1H), 7.77 (d, J = 8.9

Hz, 1H), 6.76 (s, 1H), 6.60 (d, J = 8.9 Hz, 1H), 3.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 190.3, 154.5, 131.0, 129.7, 122.0, 114.8, 110.5, 40.1. HRMS *m/z* Calcd for $C_9H_{10}BrNNaO^+$ [M + Na]$^+$: 249.9838. Found: 249.9838.

Compound 14

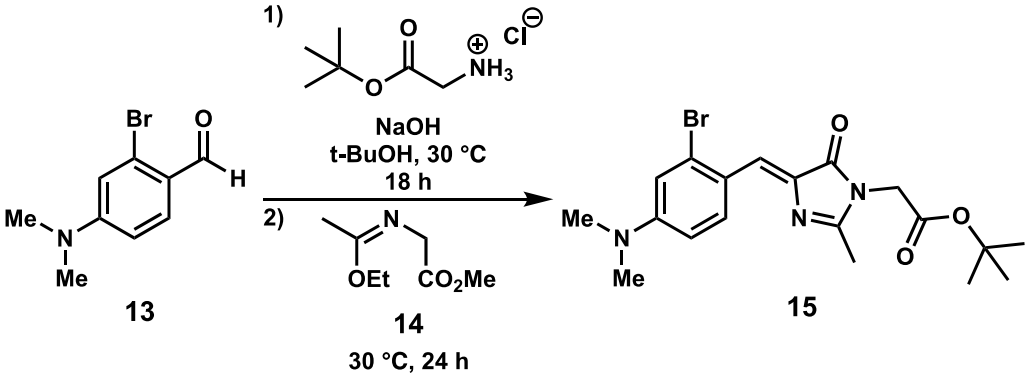


14

The reaction was performed according to reference[1].

To a solution of glycine methyl ester hydrochloride (1.00 g, 8.00 mmol) in Et_2O (20 mL) and H_2O (4 mL), K_2CO_3 (1.11 g, 8.00 mmol) and ethyl acetimidate hydrochloride (989 mg, 8.00 mmol) were added. The mixture was stirred at r.t. for 6 min, and then Et_2O was decanted off. After an additional portion of Et_2O (12 mL) was added, the reaction mixture was stirred for 6 min and the Et_2O was decanted off again. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator to afford **14** (560 mg, 3.52 mmol, 44 %) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.07 (q, J = 7.0 Hz, 2H), 4.01 (s, 2H), 3.70 (s, 3H), 1.84 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 171.6, 164.8, 60.9, 51.9, 51.1, 15.2, 14.1. HRMS *m/z* Calcd for $C_7H_{13}NNaO_3^+$ [M + Na]$^+$: 182.0788. Found:182.0788.

Compound 15

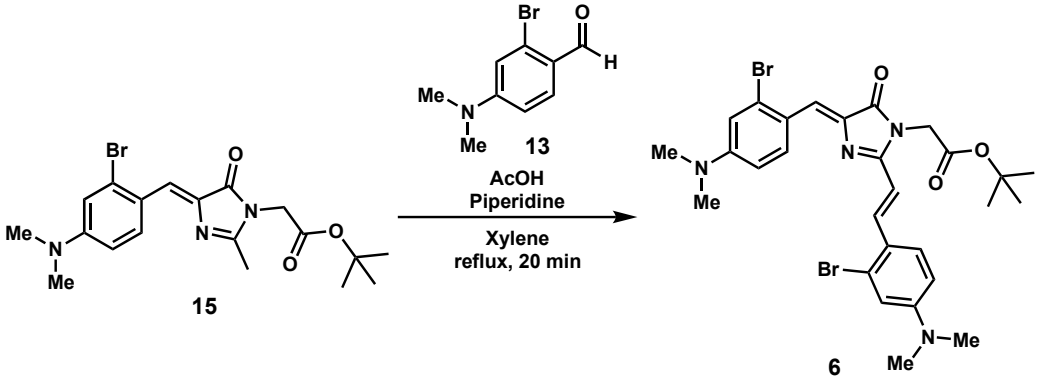


The reaction was performed according to references[1,2].

To a solution of glycine *tert*-butyl ester hydrochloride (184 mg, 1.10 mmol) in *tert*-BuOH (2.0 mL) was added sodium hydroxide (40 mg, 1.00 mmol), the reaction mixture was stirred at 30 °C for 1 h, and then was added **13** (228 mg, 1.00 mmol). The mixture was stirred at 30 °C for 18 h. Then, to the resulting mixture was added **14** (159 mg, 156 µL, 1.00 mmol) and stirred at 30 °C

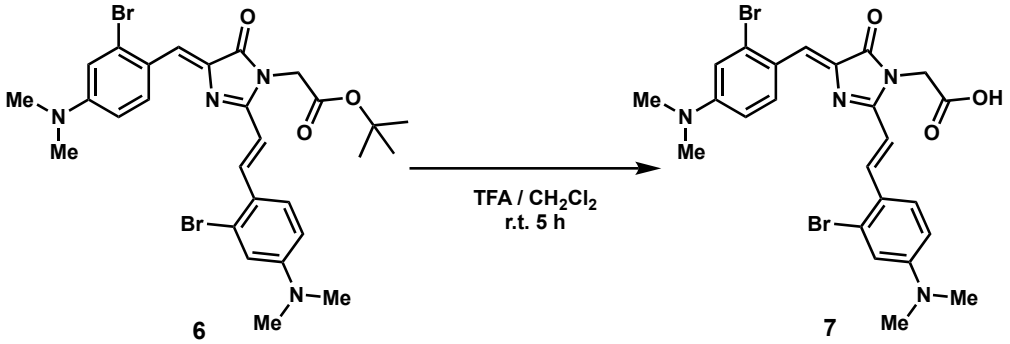
for 24 h. The reaction was quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on silica gel (Hexane/EtOAc = 3/1) to afford **15** (125 mg, 350 μmol, 35 %) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.80 (d, J = 8.9 Hz, 1H), 7.52 (s, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 8.9 Hz, 2.3 Hz, 1H), 4.26 (s, 2H), 3.01 (s, 6H), 2.27 (s, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.9, 166.8, 159.3, 151.7, 135.5, 134.4, 129.4, 126.9, 121.1, 115.3, 111.2, 42.1, 40.0, 28.0, 15.5. HRMS *m/z* Calcd for $C_{19}H_{24}BrN_3NaO_3^+$ $[M + Na]^+$: 444.0893. Found:444.0897.

Compound 6



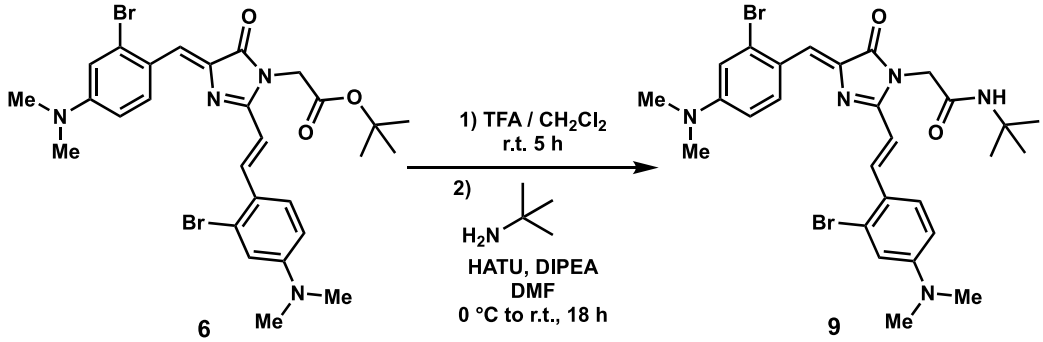
To a solution of **15** (63.3 mg, 150 μmol) in xylene (0.3 mL), **13** (34.2 mg, 150 μmol), acetic acid (90.1 mg, 85.8 μL, 1.50 mmol) and piperidine (128 mg, 148 μL, 1.50 mmol) were added, and the mixture was refluxed for 20 min. The reaction was cooled to r.t. and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on silica gel (Hexane/Acetone = 5/1 to 3/1) to afford **6** (41.3 mg, 65.3 μmol, 44 %) as a red-purple solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.06 (d, J = 9.2 Hz, 1H), 8.23 (d, J = 15.5 Hz, 1H), 7.54 (s, 1H), 7.50 (d, J = 9.2 Hz, 1H), 6.88 (d, J = 2.6 Hz, 1H), 6.87 (d, J = 2.6 Hz, 1H), 6.71 (dd, J = 9.2 Hz, 2.6 Hz, 1H), 6.62 (dd, J = 9.2 Hz, 2.6 Hz, 1H), 6.41 (d, J = 15.5 Hz, 1H), 4.43 (s, 2H), 3.03 (s, 6H), 3.00 (s, 6H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.2, 166.9, 157.2, 151.7, 151.6, 138.4, 136.5, 134.7, 129.6, 127.9, 127.4, 127.7, 122.3, 121.9, 115.5, 115.4, 111.4, 110.4, 82.8, 42.4, 40.1, 28.0. HRMS *m/z* Calcd for $C_{28}H_{33}Br_2N_4O_3^+$ $[M + H]^+$: 633.0893. Found:633.0893.

Compound 7



To a solution of **6** (20.0 mg, 31.6 μmol) in CH_2Cl_2 (0.2 mL) was added TFA (0.1 mL), and the reaction mixture was stirred at r.t. for 5 h. The mixture was concentrated on a rotary evaporator and the resulting crude residue was purified by preparative HPLC (YMC Triart Phenyl column, MeCN/0.1 % TFA = 50/50 to 100/0) to afford **7** (17.2 mg, 29.8 μmol, 94 %) as a red-purple solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.98 (d, J = 9.2, 1H), 8.21 (d, J = 15.5, 1H), 7.93 (d, J = 9.2, 1H), 7.17 (s, 1H), 6.97-6.93 (m, 3H), 6.89 (dd, J = 9.2 Hz, 2.9 Hz, 1H), 6.79 (dd, J = 9.2 Hz, 2.9 Hz, 1H), 4.59 (s, 2H), 3.03 (s, 6H), 3.00 (s, 6H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ =169.7, 169.6, 158.2, 152.0, 151.6, 137.6, 136.1, 133.8, 128.8, 128.7, 127.1, 122.1, 120.9, 120.3, 115.0, 114.7, 111.8, 110.0, 41.2. HRMS *m/z* Calcd for $C_{24}H_{25}Br_2N_4O_3^+$ $[M + H]^+$: 577.0267. Found:577.0269.

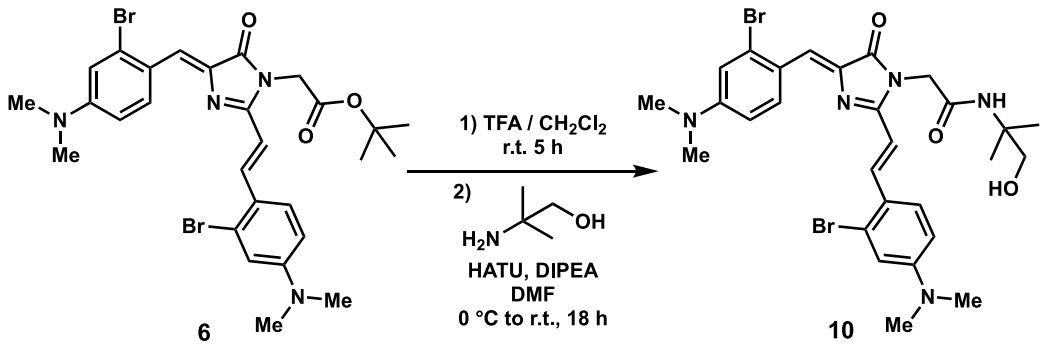
Compound 9



To a solution of **6** (20.0 mg, 31.6 μmol) in CH_2Cl_2 (0.2 mL) was added TFA (0.1 mL), and the reaction mixture was stirred at r.t. for 5 h, then concentrated on a rotary evaporator. The residue was dissolved in DMF (0.2 mL), and HATU (24.1 mg, 63.3 μmol) and *N*,*N*-diisopropylethylamine (22.0 μL, 127 μmol) were added to the solution. The reaction mixture was stirred at 0 °C for 30 min. To the resulting mixture was added *tert*-butylamine (10.1 μL, 94.9 μmol) and the reaction mixture was stirred at r.t. for 18 h. After concentration on a rotary evaporator, the residue was dissolved in EtOAc and washed with H_2O, 0.01 M HCl aq., sat. $NaHCO_3$ aq., and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on silica gel (Hexane/Acetone=5/1 to 3/1) to

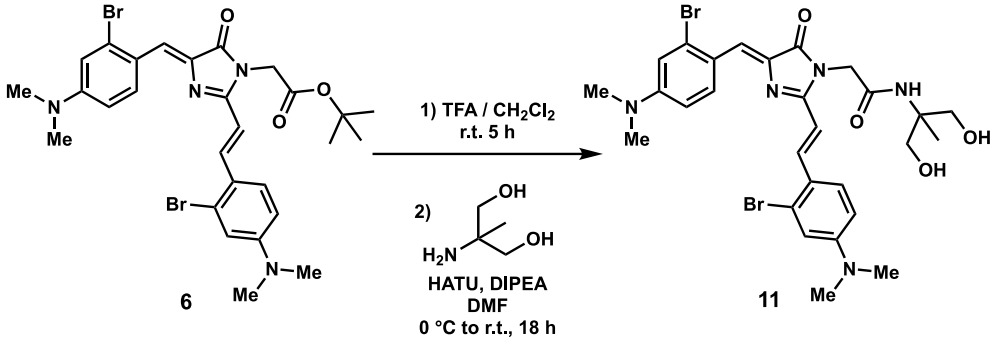
afford **9** (18.0 mg, 28.5 μmol, 90 %) as a red-purple solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.07 (d, J = 9.2 Hz, 1H), 8.32 (d, J = 15.5 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.56 (s, 1H), 6.89 (d, J = 2.6 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H), 6.72 (dd, J = 9.2 Hz, 2.6 Hz, 1H), 6.62 (dd, J = 9.2 Hz, 2.6 Hz, 1H), 6.56 (d, J = 15.5 Hz, 1H), 5.80 (s, 1H), 4.28 (s, 2H), 3.05 (s, 6H), 3.01 (s, 6H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.4, 166.5, 156.9, 151.83, 151.75, 139.2, 136.0, 134.8, 129.9, 128.2, 127.6, 126.3, 122.2, 121.7, 115.44, 115.42, 111.50, 111.46, 109.5, 51.7, 45.4, 40.1, 28.6. HRMS *m/z* Calcd for $C_{28}H_{33}Br_2N_5NaO_2^+$ $[M + Na]^+$: 654.0873. Found:654.0880.

Compound 10



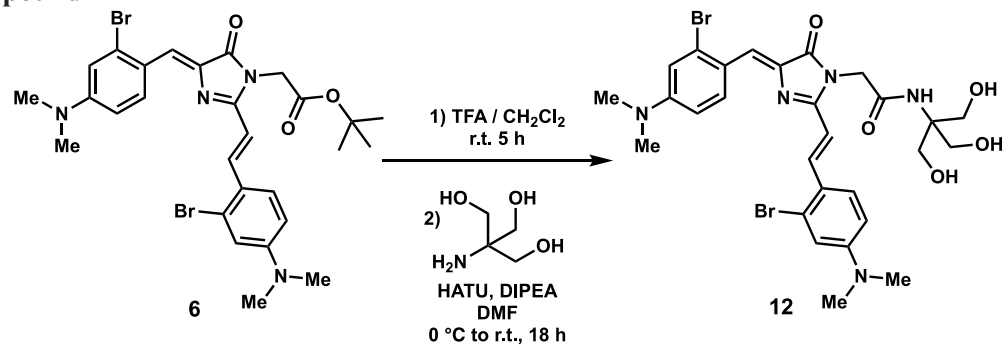
To a solution of **6** (20.0 mg, 31.6 μmol) in CH_2Cl_2 (0.2 mL) was added TFA (0.1 mL).The reaction mixture was stirred at r.t. for 5 h and concentrated on a rotary evaporator. The residue was dissolved in DMF (0.2 mL). HATU (24.1 mg, 63.3 μmol) and *N*,*N*-diisopropylethylamine (22.0 μL, 127 μmol) were added, and the reaction mixture was stirred at 0°C for 30 min. To the resulting mixture was added 2-amino-2-methyl-1-propanol (9.05 μL, 94.9 μmol) and the reaction mixture was stirred at r.t. for 18 h. After concentration on a rotary evaporator, the residue was dissolved in EtOAc. The organic layer was washed with H_2O, 0.01 M HCl aq., sat. $NaHCO_3$ aq., and brine, which was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on silica gel (CH_2Cl_2/Acetone=9/1 to 1/1) to afford **10** (18.2 mg, 28.1 μmol, 89 %) as a red-purple solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.06 (d, J = 9.2 Hz, 1H), 8.29 (d, J = 15.5 Hz, 1H), 7.57 (d, J = 9.2 Hz, 1H), 7.54 (s, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.71 (dd, J = 9.2 Hz, 2.3 Hz, 1H), 6.62 (dd, J = 9.2 Hz, 2.3 Hz, 1H), 6.53 (d, J = 15.5 Hz, 1H), 6.23 (s, 1H), 4.35 (s, 2H), 3.55 (s, 2H), 3.04 (s, 6H), 3.01 (s, 6H), 1.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.6, 168.1, 156.4, 151.9, 151.8, 139.4, 135.7, 134.9, 130.0, 128.2, 127.7, 126.7, 122.1, 121.6, 115.5, 111.6, 111.5, 109.2, 56.7, 45.1, 40.2, 40.1, 24.6. HRMS *m/z* Calcd for $C_{28}H_{33}Br_2N_5NaO_3^+$ $[M + Na]^+$: 670.0822. Found:670.0818.

Compound 11



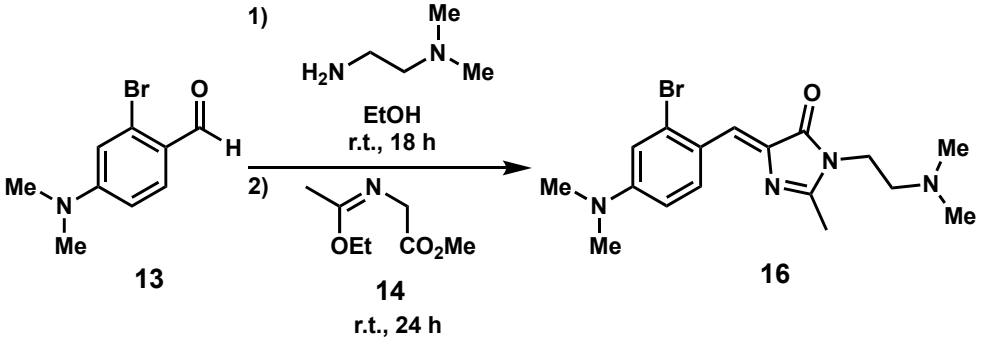
To a solution of **6** (20.0 mg, 31.6 μmol) in CH_2Cl_2 (0.2 mL) was added TFA (0.1 mL). The reaction mixture was stirred at r.t. for 5 h and concentrated on a rotary evaporator. The residue was dissolved in DMF (0.2 mL). HATU (24.1 mg, 63.3 μmol) and *N*,*N*-diisopropylethylamine (22.0 μL, 127 μmol) were added to the solution, and the reaction mixture was stirred at 0°C for 30 min. To the resulting mixture was added 2-amino-2-methyl-1,3-propanediol (10.0 mg, 94.9 μmol) and the reaction mixture was stirred at r.t. for 18 h. After concentration on a rotary evaporator, the residue was dissolved in EtOAc and washed with H_2O, 0.01 M HCl aq., sat. $NaHCO_3$ aq., and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on silica gel (CH_2Cl_2/Acetone=4/1 to 1/3) to afford **11** (16.6 mg, 25.0 μmol, 79 %) as a red-purple solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.98 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 15.5 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.64 (s, 1H), 7.16 (s, 1H), 6.96-6.93 (m, 2H), 6.89 (dd, J = 9.2 Hz, 2.3 Hz, 1H), 6.79 (dd, J = 9.2 Hz, 2.3 Hz, 1H), 6.75 (d, J = 15.5 Hz, 1H), 4.71 (t, J = 5.5, 2H), 4.43 (s, 2H), 3.47 (dq, J = 24.3 Hz, 5.5 Hz, 4H), 3.03 (s, 6H), 3.00 (s, 6H), 1.14 (s, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ = 169.6, 166.7, 158.8, 151.9, 151.6, 137.0, 136.5, 133.7, 128.6, 128.5, 127.0, 121.9, 121.0, 120.4, 114.9, 114.7, 111.83, 111.79, 110.6, 68.5 , 63.3, 58.7, 42.4, 18.5. HRMS *m/z* Calcd for $C_{28}H_{33}Br_2N_5NaO_4^+$ $[M + H]^+$: 686.0771. Found:686.0769.

Compound 12



To a solution of **6** (20.0 mg, 31.6 μmol) in CH_2Cl_2 (0.2 mL) was added TFA (0.1 mL). The reaction mixture was stirred at r.t. for 5 h and concentrated on a rotary evaporator. The residue was dissolved in DMF (0.2 mL). HATU (24.1 mg, 63.3 μmol) and *N*,*N*-diisopropylethylamine (22.0 μL, 127 μmol) were added to the solution, and the mixture was stirred at 0°C for 30 min. To the resulting mixture was added tris(hydroxymethyl)aminomethane (11.5 mg, 94.9 μmol) and the reaction mixture was stirred at r.t. for 18 h. After concentration on a rotary evaporator, the residue was dissolved in EtOAc and washed with H_2O, 0.01 M HCl aq., sat. $NaHCO_3$ aq., and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on silica gel (CH_2Cl_2/Acetone=2/1 to 1/4) to afford **12** (20.7 mg, 30.5 μmol, 96 %) as a red-purple solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.98 (d, J = 9.2 Hz, 1H), 8.17 (d, J = 15.5 Hz, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.57 (s, 1H), 7.16 (s, 1H), 6.97-6.92 (m, 2H), 6.89 (dd, J = 9.2 Hz, 2.3 Hz, 1H), 6.78 (dd, J = 9.2 Hz, 2.3 Hz, 1H), 6.75 (d, J = 15.5 Hz, 1H), 4.63 (t, J = 5.7, 3H), 4.47 (s, 2H), 3.57 (d, J = 5.7 Hz, 4H), 3.03 (s, 6H), 3.00 (s, 6H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ = 169.6, 167.3, 158.8, 151.9, 151.6, 137.1, 136.4, 133.7, 128.7, 128.5, 127.0, 121.9, 121.0, 120.4, 114.9, 114.7, 111.9, 111.8, 110.6, 62.5, 60.0, 42.4. HRMS *m/z* Calcd for $C_{28}H_{33}Br_2N_5NaO_5^+$ $[M + Na]^+$: 702.0720. Found:702.0715

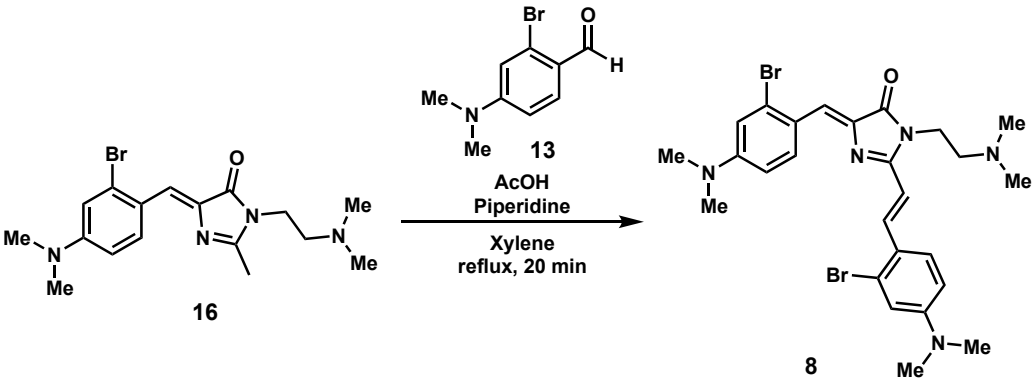
Compound 16



The reaction was performed according to references[1,2].

To a solution of **13** (228 mg, 1.00 mmol) in EtOH (2.0 mL) was added *N1*,*N1*-dimethylethane-1,2-diamine (120 μL, 1.10 mmol), and the reaction mixture was stirred at r.t. for 18 h. Then, the resulting solution was added **14** (158 μL, 1.00 mmol) and stirred at r.t. for 24 h. The reaction was quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude residue was purified by column chromatography on amino silica gel (eluent: Hexane/Acetone = 4/1 to 1/1) to afford **16** (328 mg, 865 μmol, 87 %) as an orange solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.79 (d, J = 8.7 Hz, 1H), 7.47 (s, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.65 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 3.65 (t, J = 6.6 Hz, 2H), 2.99 (s, 6H), 2.46 (t, J = 6.6 Hz, 2H), 2.35 (s, 3H), 2.25 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.4, 160.5, 151.6, 135.9, 134.2, 129.3, 126.1, 121.2, 115.3, 111.2, 58.1, 45.7, 40.0, 38.9, 15.7. HRMS *m/z* Calcd for $C_{17}H_{24}BrN_4O^+$ [M + H]$^+$: 379.1128. Found:379.1120.

Compound 8



To a solution of **16** (27.5 mg, 72.5 μmol) in xylene (0.200 mL), **13** (16.5 mg, 72.5 μmol), acetic acid (41.5 μL, 725 μmol) and piperidine (71.6 μL, 725 μmol) were added, and the reaction mixture was refluxed for 20 min. The reaction was cooled to r.t., concentrated on a rotary evaporator, and the resulting crude residue was purified by preparative HPLC (YMC Triart Phenyl column, MeCN/0.1 % TFA = 50/50 to 100/0) to afford **8** (11.5 mg, 19.5 μmol as a TFA salt, 27 %) as a red-purple solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.52 (d, J = 15.5, 1H), 8.05-8.03 (m, 2H), 7.49 (s, 1H), 6.78-6.74 (m, 3H), 6.69 (dd, J = 9.2, 2.3, 1H), 6.61 (dd, J = 9.2, 2.3, 1H), 4.39 (t, J = 7.0, 2H), 3.45 (t, J = 7.0, 2H), 3.07 (s, 6H), 3.03 (s, 6H), 2.97 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 163.9, 160.9, 155.4, 154.0, 153.1, 133.8, 131.5, 131.1, 131.0, 126.7, 121.3, 118.4, 115.8, 115.7, 111.7, 54.9, 43.5, 40.18, 40.16, 40.1, 40.0, 35.8. HRMS *m/z* Calcd for $C_{26}H_{32}Br_2N_5O^+$ [M + H]$^+$: 590.0948. Found: 590.0949.

Preparation of Recombinant α-synuclein

Recombinant human α-synuclein was expressed in *E. coli* BL21 (DE3) and purified by a boiling treatment and then Q-Sepharose ion-exchange chromatography followed by ammonium sulfate precipitation and dialysis against phosphate-buffered saline (PBS; pH 7.4).

Photo-oxygenation of α-synuclein

The reaction was performed according to reference[3].

PBS containing α-synuclein (69 μM; aggregated sample was prepared via incubation at 37 °C for 24 h) and catalyst (20 μM) was photo-irradiated with an LED at 37 °C for 30 min. The reaction mixture was treated with Trypsin Gold and analyzed using LC-MS. Power of the light source for LED was 20 mW, and photoirradiation was performed at a distance of approximately 10 cm away from the samples. The degrees of oxygenation were expressed as the intensity ratio of oxygenation (%) = (sum of MS intensities of n[O] adducts)/(sum of MS peak intensities for remained starting material and n[O] adducts) × 100.

Absorbance spectrum of catalysts

Catalysts (10 mM in DMSO) were diluted with PBS (final concentration: 20 μM), and the absorbance spectra were measured.

Absorbance spectrum of catalysts in the presence of α-synuclein

A PBS (pH 7.4) containing catalyst (20 μM) with or without aggregated α-synuclein (20 μM) was incubated at 37 °C for 10 min, and the absorbance spectra were measured.

Fluorescence spectrum of catalysts in the presence of α-synuclein

The solution for "Absorbance spectrum of catalysts in the presence of α-synuclein" was diluted 10-folds with PBS, and the fluorescence spectra were measured. Catalysts were excited at 530 nm.

Fluorescence spectrum of 11 in glycerol

To each ratio of glycerol-PBS mixed solvents (glycerol: 0, 12.5, 25, 50, 62.5, and 75 %) catalyst **11** was added with the final concentration to 2 μM, and the fluorescence spectra were measured.

Oxygenation selectivity experiment

Stock solutions of aggregated α-synuclein, Angiotensin IV, Leuprorelin and Met-enkephalin were diluted with PBS to final peptide concentrations of 20 μM. To each solution, catalyst **11**

(100 μM in DMSO) was added to the final concentration of 4 μM. The mixture was irradiated with LED (λ = 500 nm) at 37 °C for 30 min. The reaction mixture of α-synuclein was treated with Trypsin Gold. The reactions were monitored and analyzed using LC-MS.

Thioflavin-T (ThT) assay

To a 50 mM glycine-NaOH buffer (383 μL, pH 8.5), 69 μM α-synuclein solution (7.25 μL, final concentration: 1.25 μM) and 50 μM ThT solution (10 μL, final concentration: 1.25 μM; ThT was purchased from Sigma-Aldrich Inc.) were added. The fluorescence intensity of the solution (400 μL) was measured with 440 nm of the excitation wavelength and 480 nm of the emission wavelength at room temperature.

Aggregation inhibition assay

To PBS containing monomer α-synuclein (69 μM) was added 20 μM of catalyst **11** or DMSO. The samples were photo-irradiated with LED (λ = 500 nm) at 37 ℃ for 24 h. To evaluate the amounts of α-synuclein fibril, ThT fluorescence was measured as above.

Seeding activity assay

Aggregated α-synuclein solution (69 μM) was centrifuged at 50,000 rpm for 20 min and the pellet was resuspended with PBS. After sonication of the suspended α-synuclein solution, the α-synuclein concentration was calculated by BCA protein assay. The seed α-synuclein solution was irradiated at 500 nm at 37 ℃ overnight with catalyst **11** (69 μM) or DMSO. This photo-oxygenated α-synuclein was added to a monomer α-synuclein solution with 1 mol% ratio and the mixture was shaken at 1,000 rpm at 37 °C under dark conditions. To evaluate the amounts of α-synuclein fibril, ThT fluorescence was measured as above.

Low aggregated α-synuclein oxygenation

PBS containing monomer α-synuclein (69 μM) was shaken at 37 ℃, 1000 rpm for 60 h (for small aggregates) and 120 h (for large aggregates). The aggregation propensities were checked by ThT fluorescence with the above method. The ThT fluorescence of small aggregates is 106 and the ThT fluorescence of large aggregates is 1015.

To each aggregated state of α-synuclein solution (69 μM), was added 20 μM catalyst (catalyst **11**, **2-4**). The mixture was photo-irradiated with LED (catalyst **11**: λ = 500 nm, **2** and **3** catalysts: λ = 660 nm, **4**: λ = 595 nm) at 37 °C for 30 min. The reaction mixture was treated with Trypsin Gold and analyzed using LC-MS.

Photo-oxygenation of amyloid β

10 mM Phosphate buffer containing amyloid β (20 μM; aggregated sample was prepared via incubation at 37 °C for 2 h) and catalyst (4 μM) was photo-irradiated with an LED at 37 °C for 30 min. The reactions were monitored and analyzed using MALDI-TOF MS.

Assessment of $^1O_2$ production

A glycerol/methanol = 1/1 solvent containing **11** (20 μM) and furfuryl alcohol (FurA; 2 mM) was photo-irradiated with the LED (λ = 500 nm) at room temperature for certain time periods, and the remaining FurA was quantified by ultraviolet (UV) absorbance.

$^1O_2$ Quantum yields of catalysts

The quantum yields for the singlet oxygen production [$\Phi(^1O_2)$] of catalyst **6 - 12** were determined using the following equation:

$$\Phi(1O_2)^{cat.} = \Phi(1O_2)^{RB} \cdot \frac{k^{cat.}}{k^{RB}} \cdot \frac{F^{RB}}{F^{cat.}}$$

$$F = 1 - 10^{-A}$$

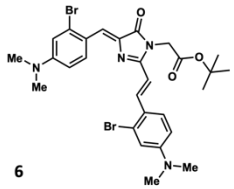
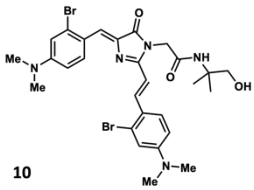
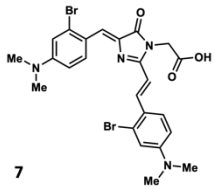
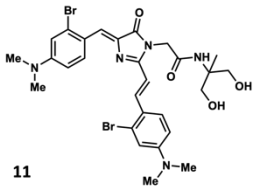
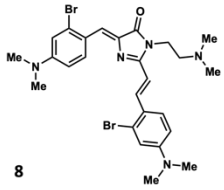
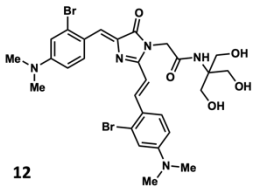
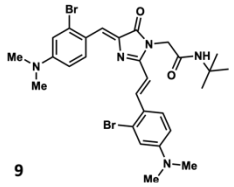
where $\Phi(^1O_2)^{RB}$ is the quantum yield of rose bengal (standard sample, $\Phi(^1O_2) = 0.76$),[4] k is the slope of a plot for the conversion of furfuryl alcohol *versus* reaction time in 50 % glycerol in methanol (λ = 500 nm; furfuryl alcohol: 2 mM; rose bengal and catalysts: 20 μM; room temperature), and A is the absorbance at 500 nm. Results are summarized in Fig. S8.

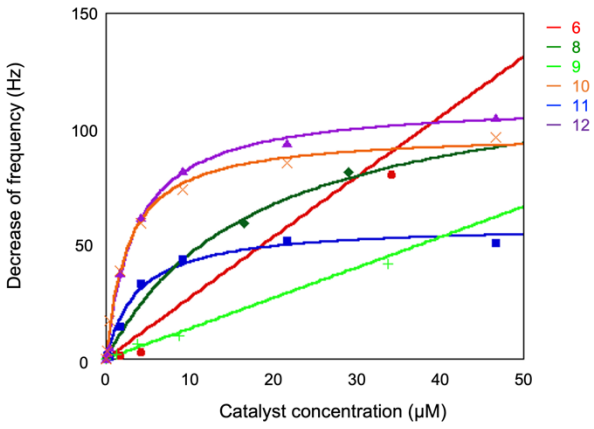
Quartz crystal microbalance

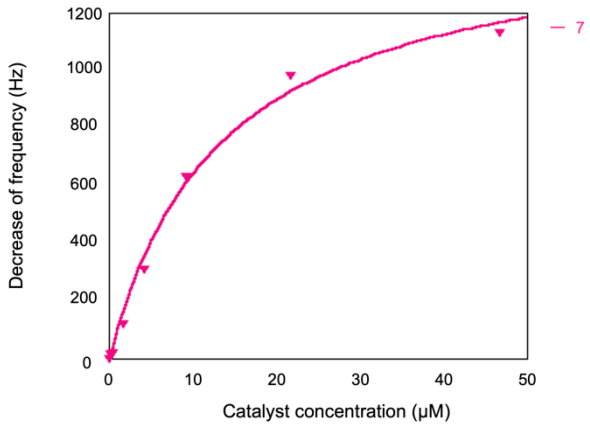
To a gold electrode sensor housed in the cell, 10 μL of 5% EtOH/water including 0.1 mM 20-(11-mercaptoundecanyloxy)-3,6,9,12,15,18-hexaoxaeicosanoic acid was added, and the solution was allowed to stand at room temperature for 1 h. The sensor was rinsed with water and dried with air blow. Then, to the resulting sensor with self-assembled monolayer on the surface, 50 μL of an aqueous solution including *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (50 mg ml^{-1}) and *N*-hydroxy succinimide (50 mg ml^{-1}) was added, the solution was allowed to stand at room temperature for 15 min, and the sensor was rinsed with water and dried with air blow. After the sensor cell was installed into the quartz crystal microbalance apparatus, preaggregated α-synuclein in 10 times diluted PBS was added to the sensor unit (final volume: 20 μL, 50 μM α-synuclein). The solution was stirred at 25 °C until the frequencies become stable. After the sensor was washed with water, 200 μL of 10 times diluted PBS was added. When a stable baseline was attained, 0.5 μl of DMSO solution containing catalyst (0.05, 0.1, 0.5, 1, 2, 5, or 10 mM) was added consecutively, and the change of the frequency was measured. The binding curves were generated using KaleidaGraph 4.5. The

concentration of catalyst that elicited one-half of the maximum change of the frequency was calculated and assigned as K_d value.

Fig. S1 K_d values of catalysts.

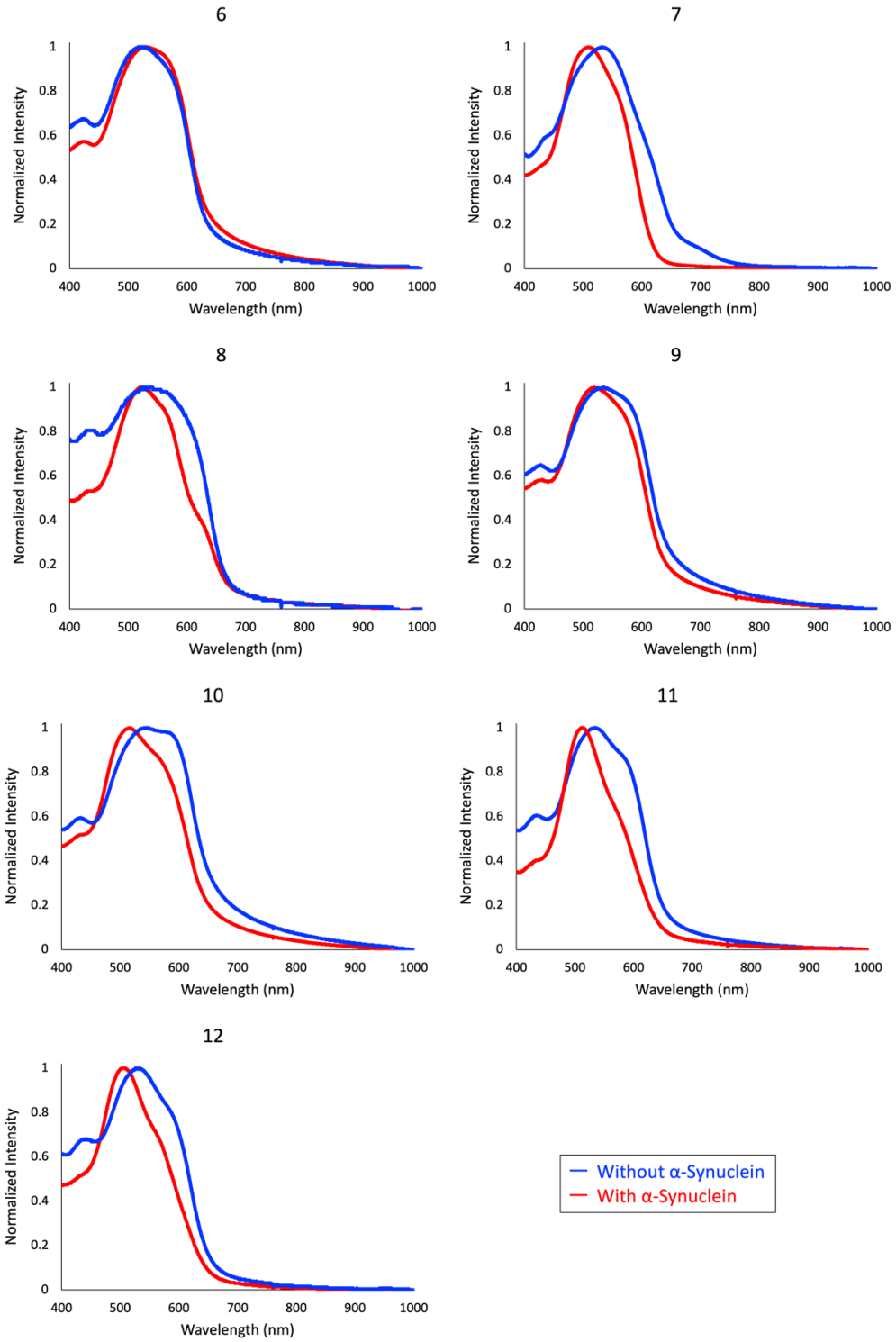
Catalyst	K_d value measured by QCM [μM]	Catalyst	K_d value measured by QCM [μM]
 **6**	N.D.	 **10**	2.64 ±0.55
 **7**	14.3 ±2.2	 **11**	3.80 ±0.69
 **8**	38.9 ±7.0	 **12**	3.72 ±0.18
 **9**	N.D.		





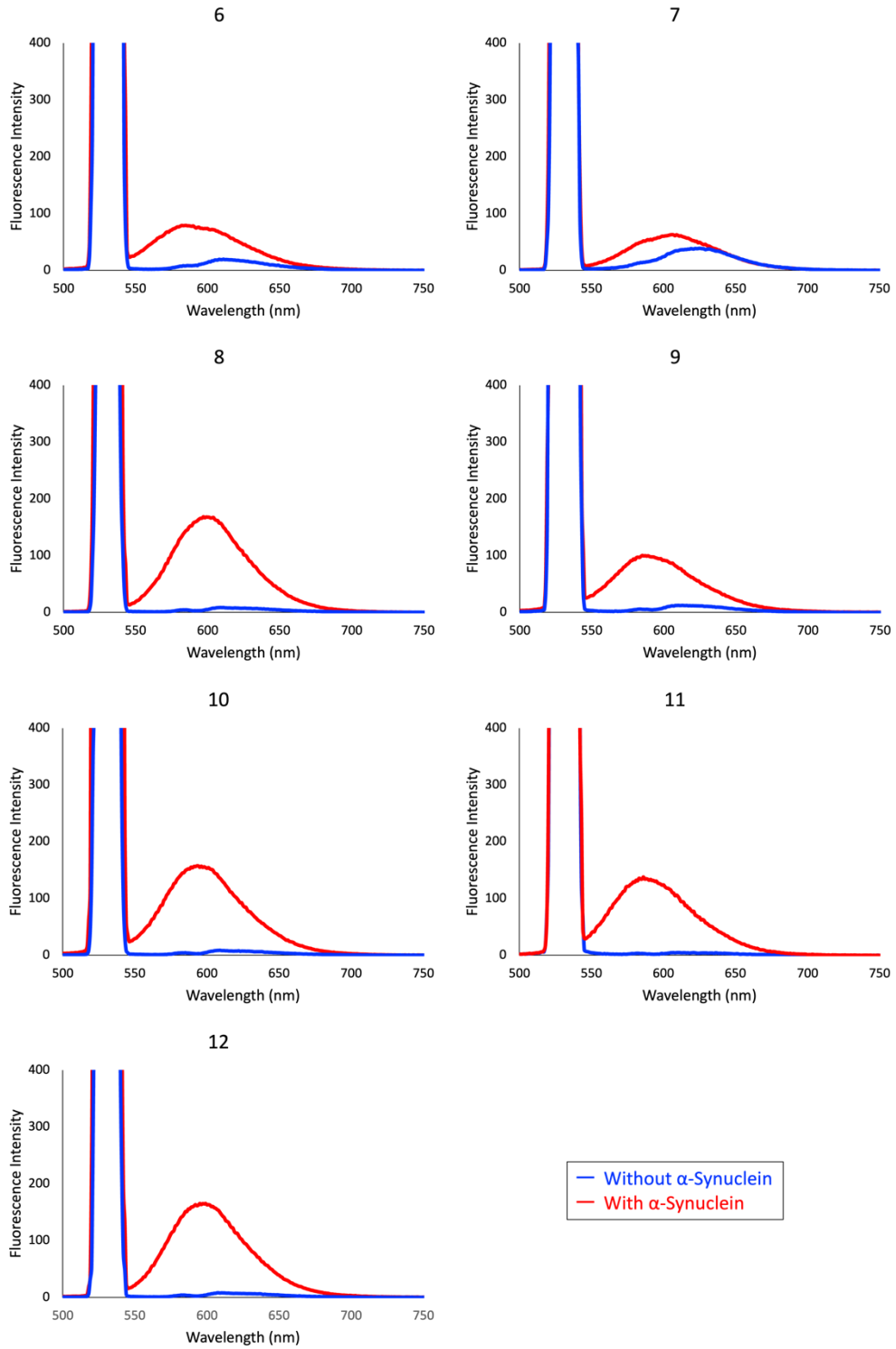
The K_d value of catalyst **6** and **9** was not obtained under the identical conditions (= N.D.). The low water solubility may have caused the catalyst to bind the sensor nonspecifically, resulting in a linear plot.

Fig. S2 Absorption spectra of catalysts 6 - 12.



A phosphate buffer solution (pH 7.4) containing catalyst (20 μM) in the presence or absence of aggregated α-synuclein (20 μM) was incubated at 37 °C for 10 min and absorbance spectra were measured.

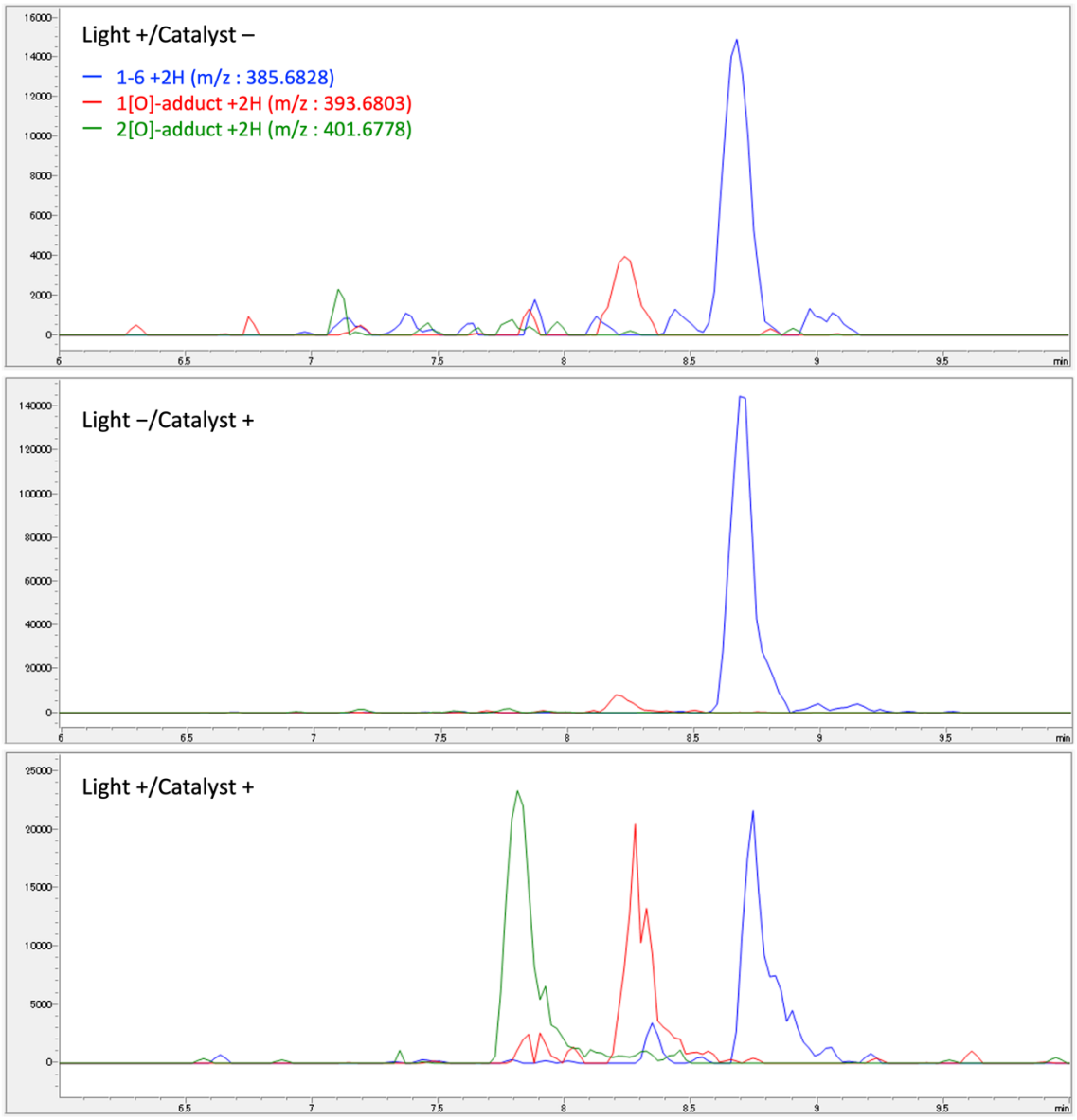
Fig. S3 Fluorescence spectra of catalysts 6 – 12 with or without aggregated α-synuclein.



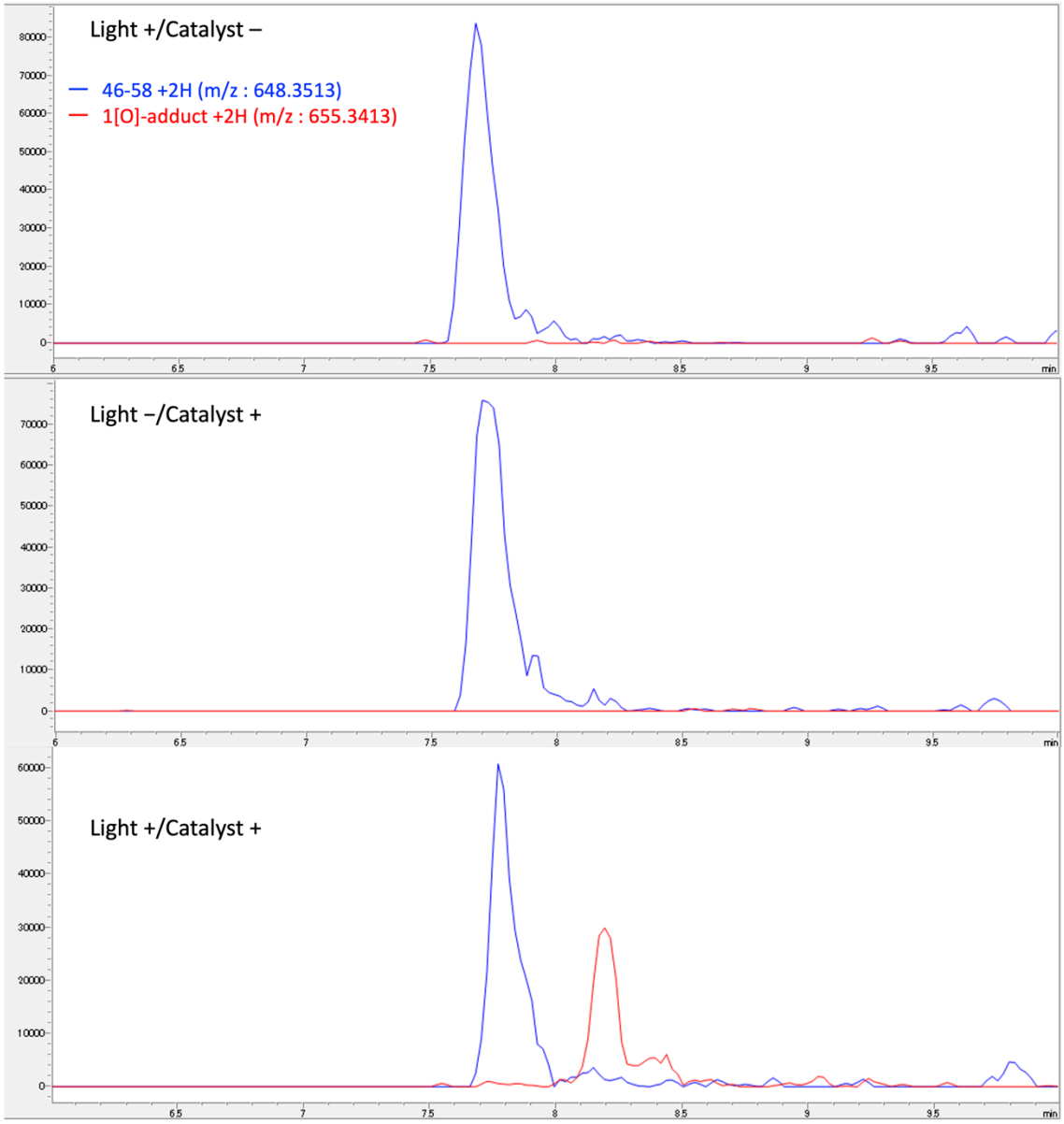
A phosphate buffer solution (pH 7.4) containing catalyst (2 μM) with or without aggregated α-synuclein (2 μM) was incubated at 37 °C for 10 min. Catalysts were excited at λ = 530 nm.

Fig. S4 LC-MS charts of each peptide fragments of α-synuclein after trypsin digestion.

Peptide fragment 1-6: MDVFMK



Peptide fragment 46-58: EGVVH GVATV AEK



Peptide fragment 103-140: GKNEE GAPQE GILED MPVDP DNEAY EMPSE EGYQD YEPEA

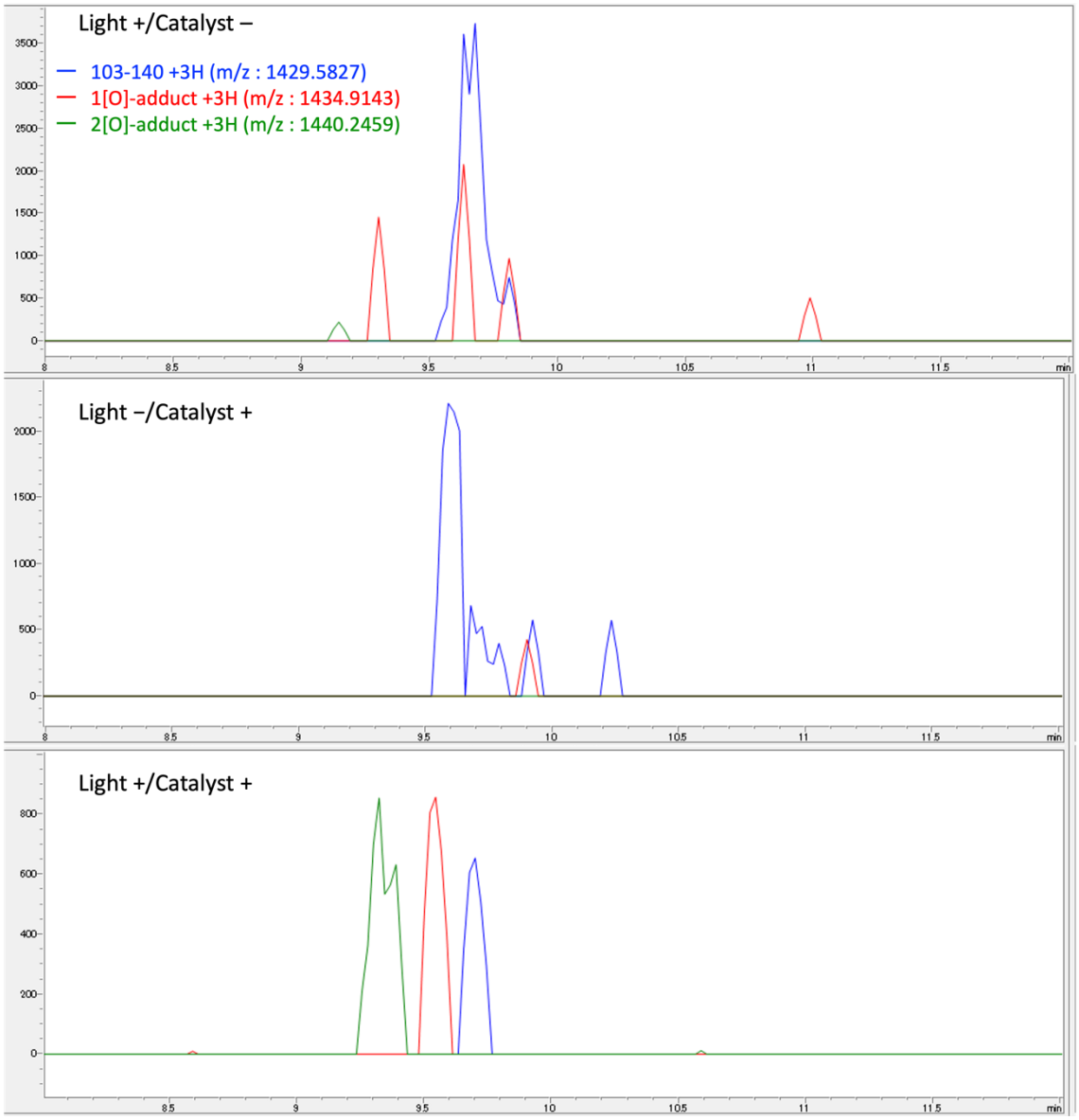
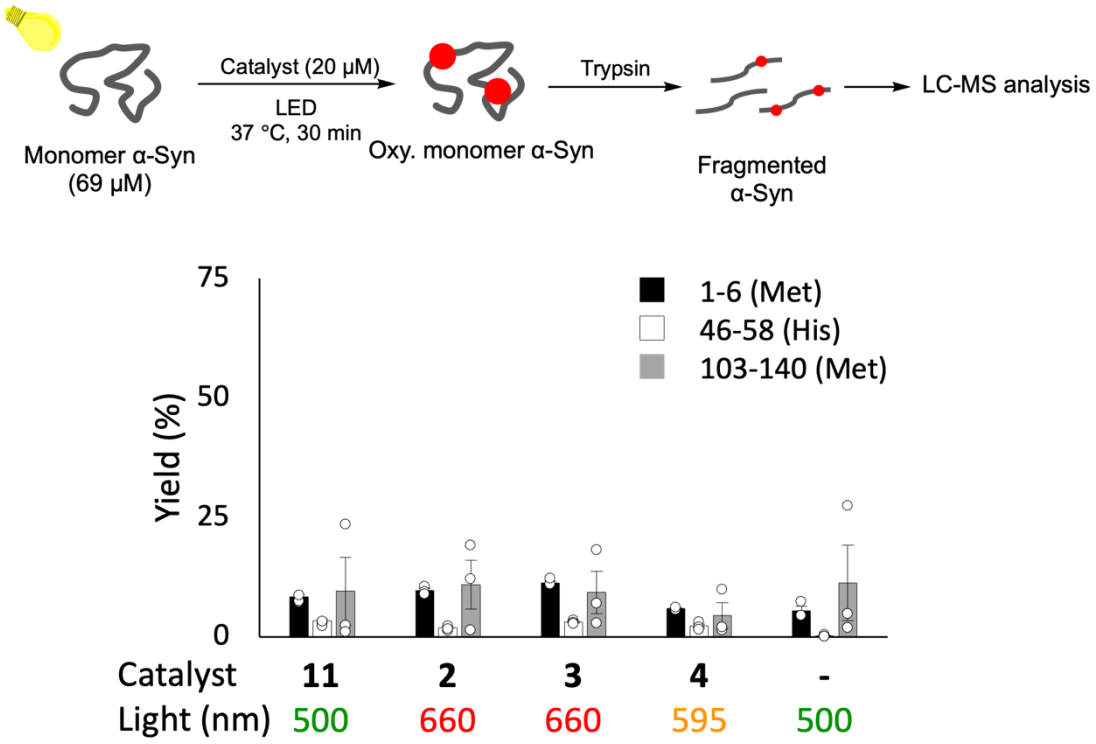
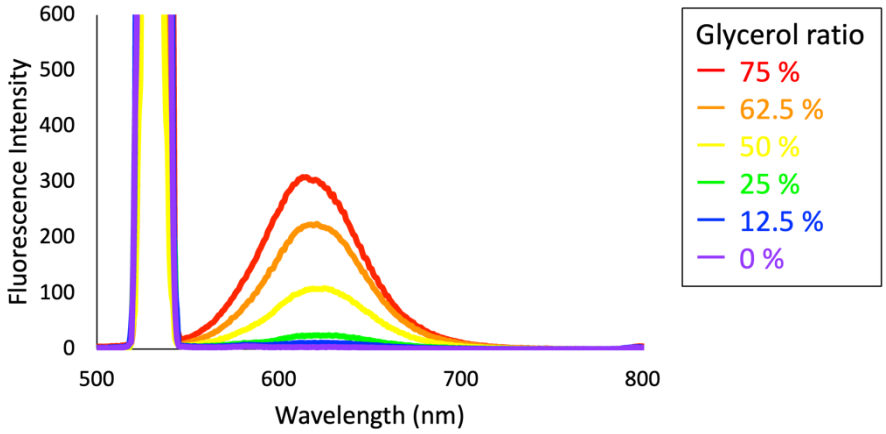


Fig. S5 Monomer α-synuclein photo-oxygenation



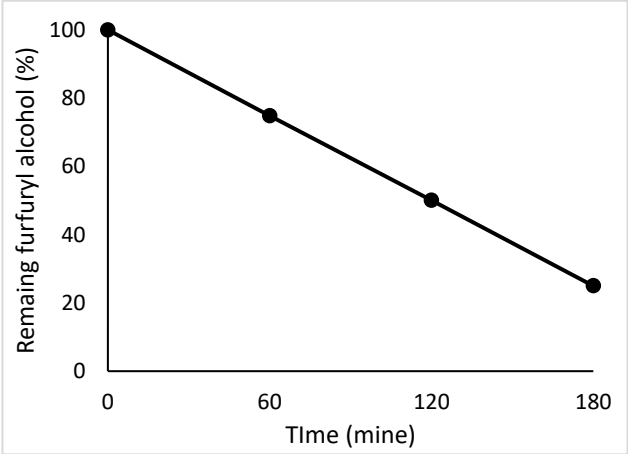
To monomer α-synuclein solution (69 μM), was added 20 μM catalyst (catalyst **11**, **2-4**). The mixture was photo-irradiated with LED (catalyst **11**: λ = 500 nm, **2** and **3** catalysts: λ = 660 nm, **4**: λ = 595 nm) at 37 °C for 30 min. The reaction mixture was treated with Trypsin Gold and analyzed using LC-MS. All catalysts oxygenate little monomer α-synuclein.

Fig. S6 Fluorescence spectra of 11 in glycerol.



To each ratio of glycerol-PBS mixed solvents (glycerol: 0, 12.5, 25, 50, 62.5, and 75 %) catalyst **11** was added at the final concentration of 2 μM, and the fluorescence spectra were measured.

Fig. S7 Assessment of $^1O_2$ production.



Glycerol/methanol = 1/1 solvent containing **11** (20 μM) and furfuryl alcohol (FurA; 2 mM) was photo-irradiated (λ = 500 nm) at room temperature for certain time periods, and the remaining FurA was quantified by ultraviolet (UV) absorbance.

Fig. S8 $^1O_2$ quantum yields of catalysts.

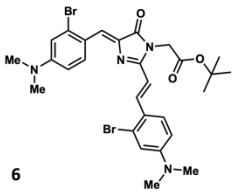
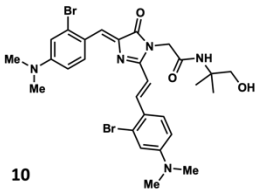
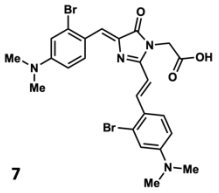
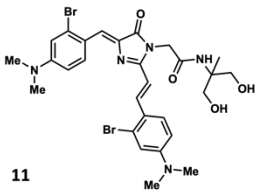
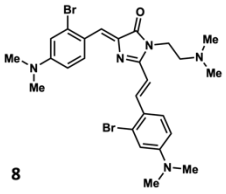
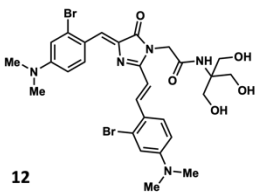
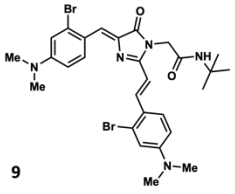
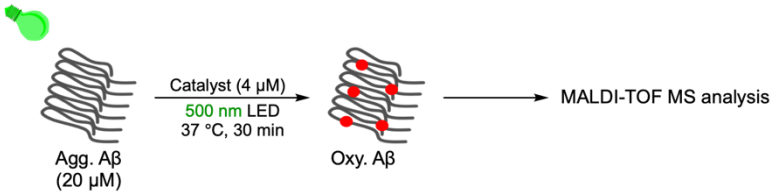
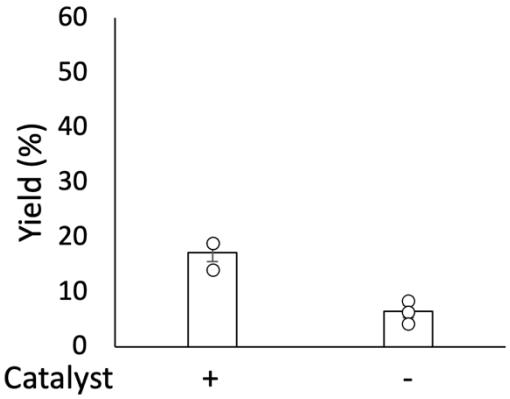
Catalyst	$^1O_2$ quantum yield	Catalyst	$^1O_2$ quantum yield
 **6**	0.0018	 **10**	0.0016
 **7**	0.0018	 **11**	0.0016
 **8**	0.0017	 **12**	0.0017
 **9**	0.0016		

Fig. S9 Amyloid β photo-oxygenation



DAEFR HDSGY EVHHQ KLVFF AEDVG SNKGA IIGLM VGGVV IA



10 mM Phosphate buffer containing amyloid β (20 μM; aggregated sample was prepared via incubation at 37 °C for 2 h) and catalyst **11** (4 μM) was photo-irradiated with 500 nm LED at 37 °C for 30 min. The reactions were monitored and analyzed using MALDI-TOF MS.
The oxygenating activity of catalyst **11** on amyloid β (19% yield) is lower than that on α-synuclein (51% yield, Fig. 2d).

References

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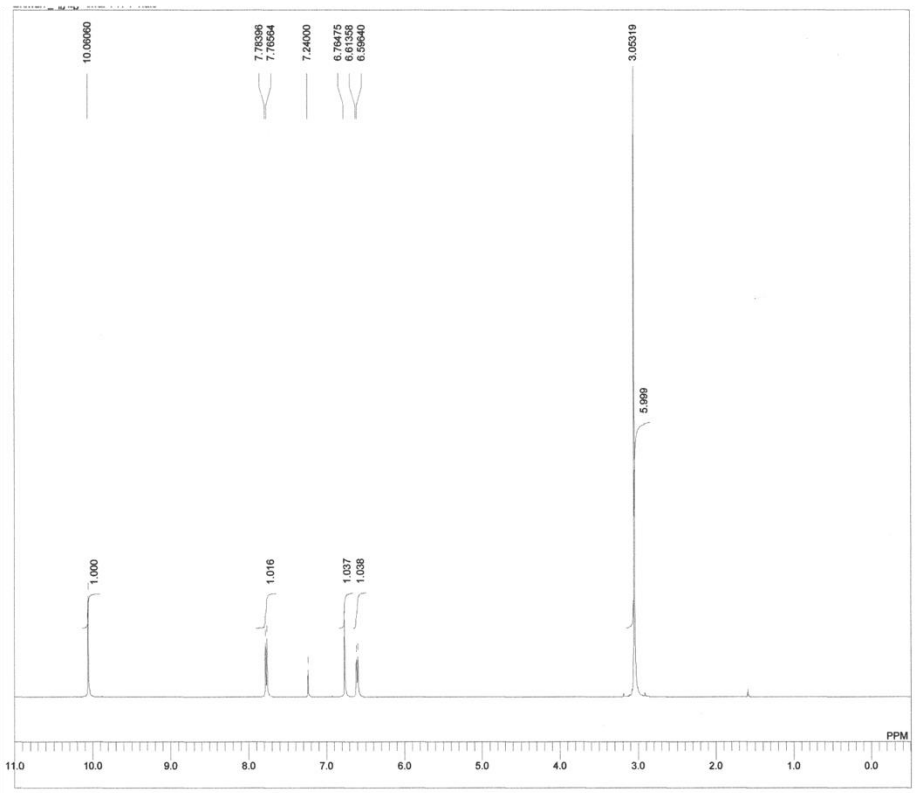
(2) Liu, Y.; Wolstenholme, C. H.; Carter, G. C.; Liu, H.; Hu, H.; Grainger, L. S.; Miao, K.; Fares, M.; Hoelzel, C. A.; Yennawar, H. P.; Ning, G.; Du, M.; Bai, L.; Li, X.; Zhang, X. *J. Am. Chem. Soc.* **2018**, *140*, 7381-7384.

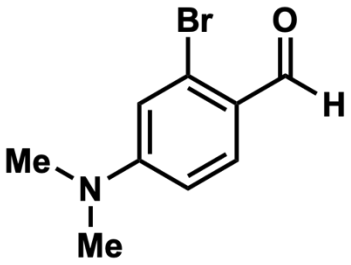
(3) Taniguchi, A.; Shimizu, Y.; Oisaki, K.; Sohma, Y.; Kanai, M. *Nat. Chem.* **2016**, *8*, 974-982.

(4) Redmond, R. W., Gamlin, J. N. *Photochem. Photobiol*. **1999**, *70*, 391-475.

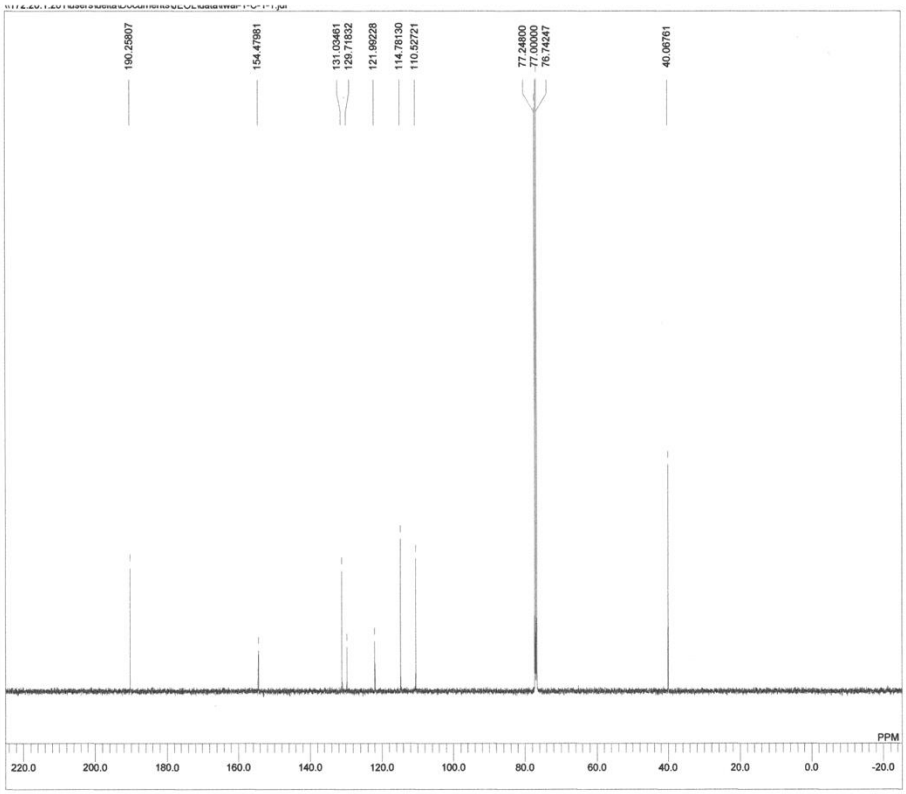
NMR charts

^{1}H NMR

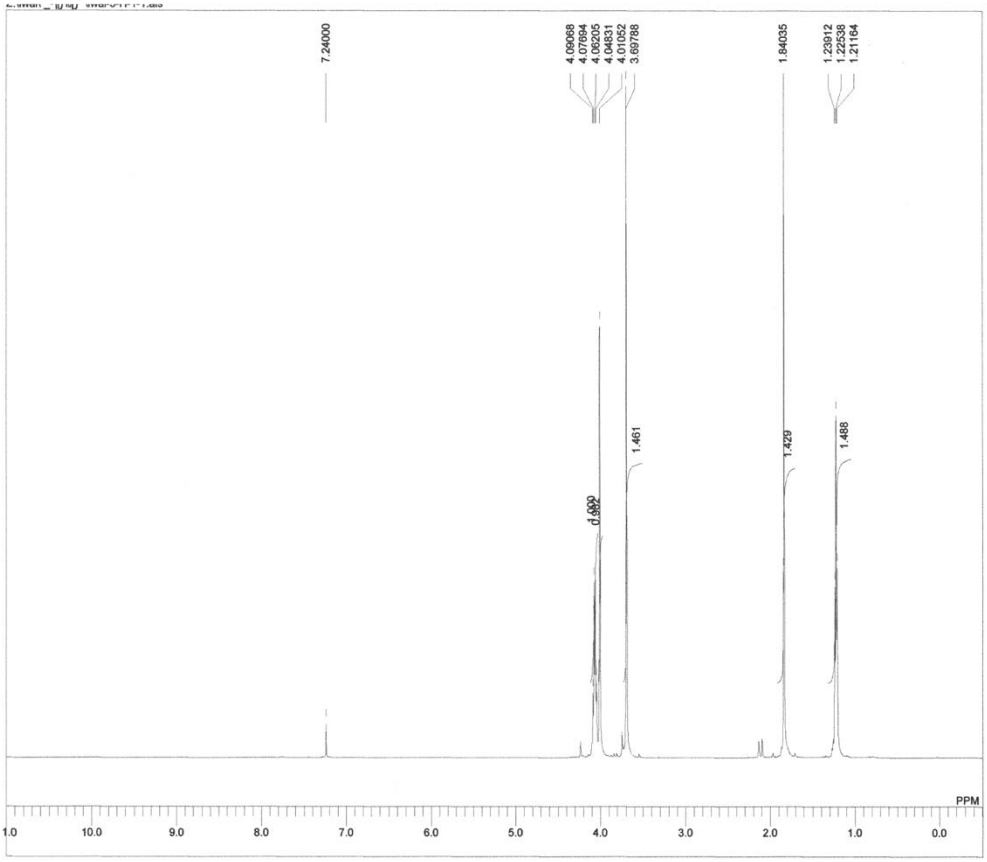


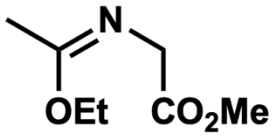


^{13}C NMR

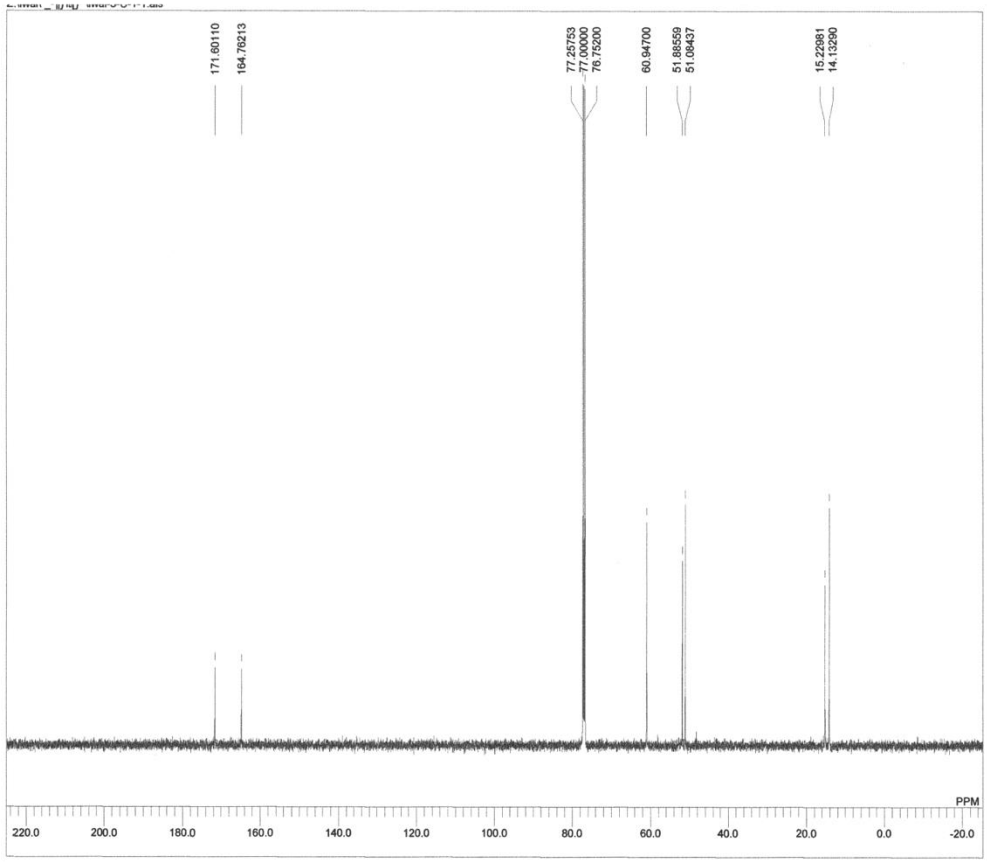


^{1}H NMR





^{13}C NMR



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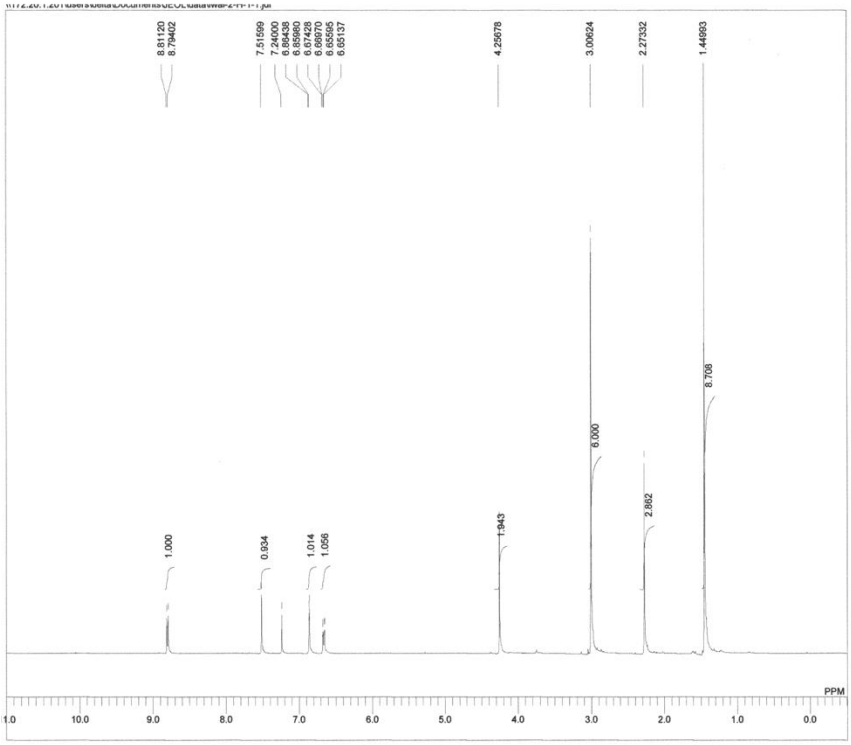

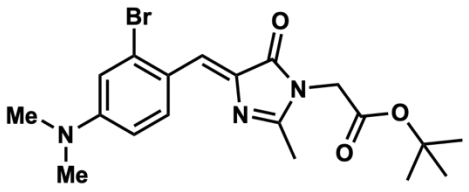

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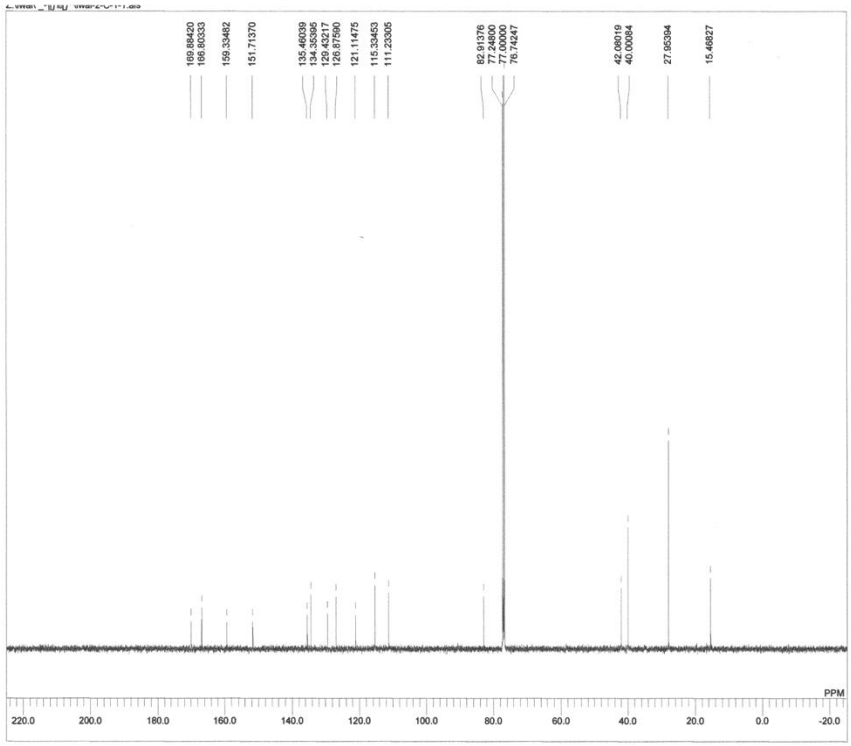

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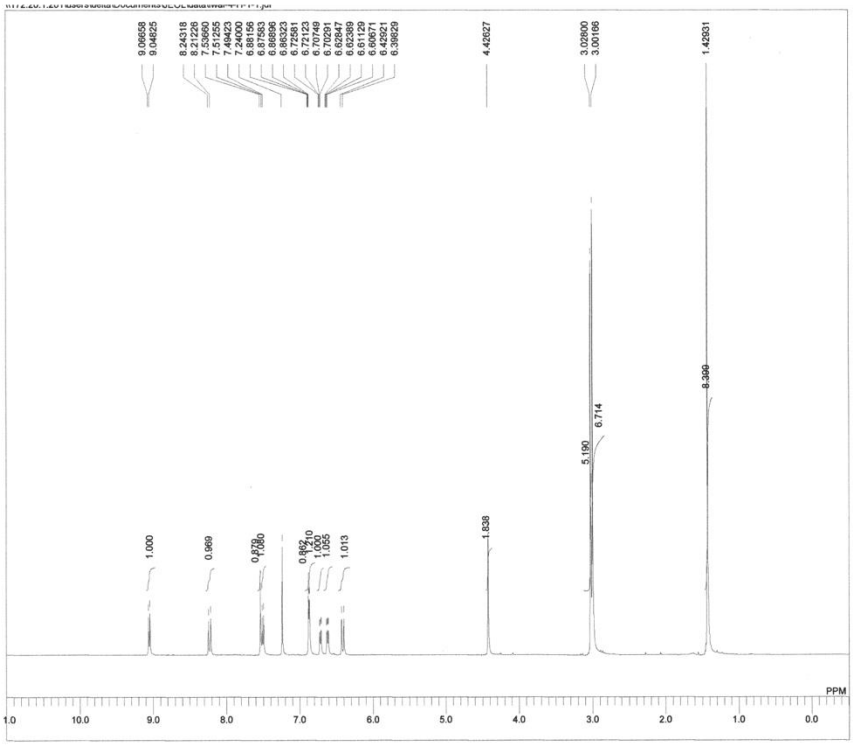

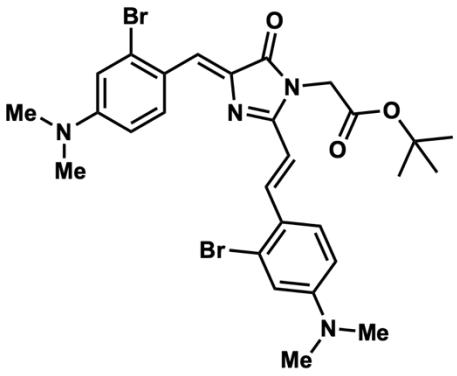

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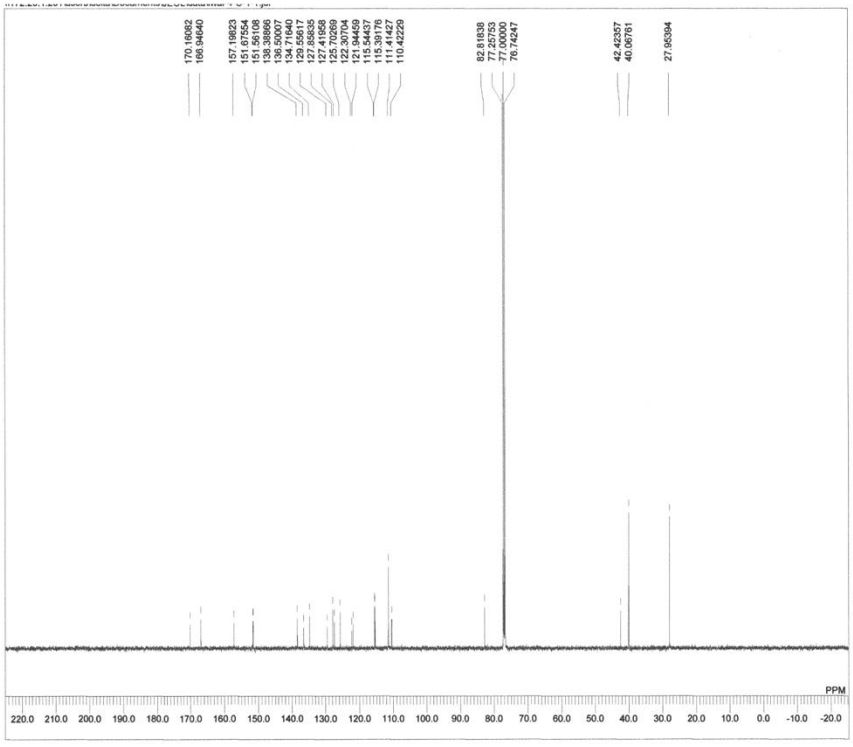

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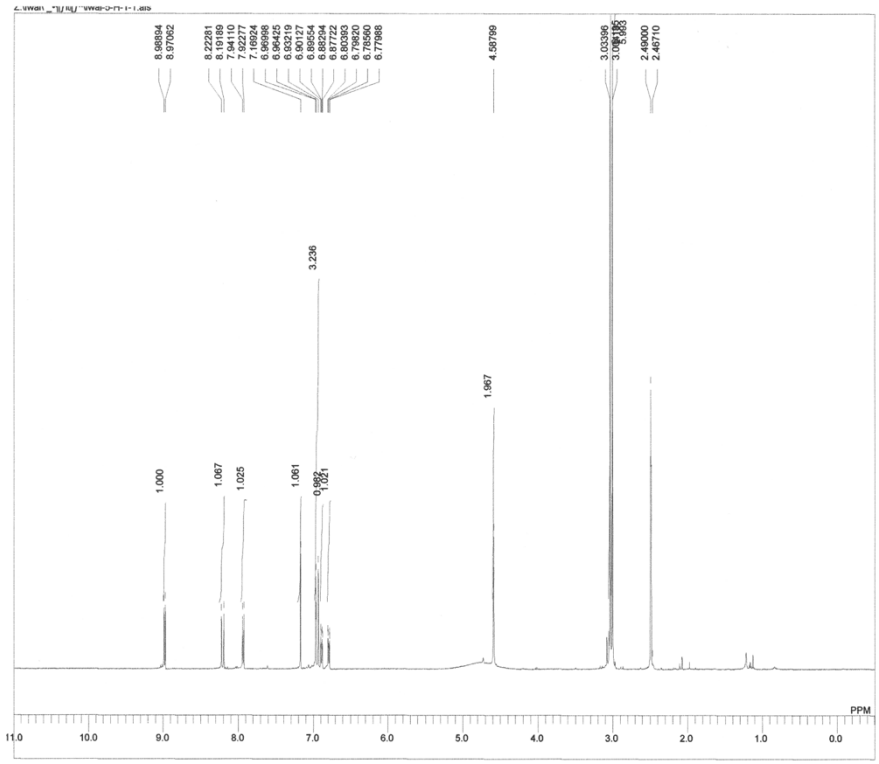

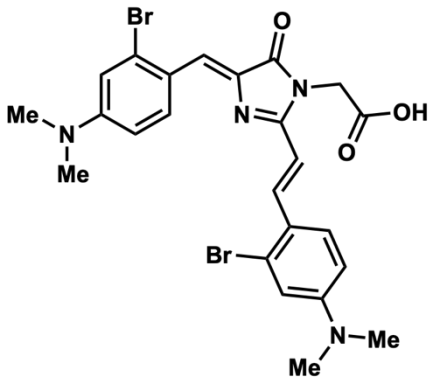

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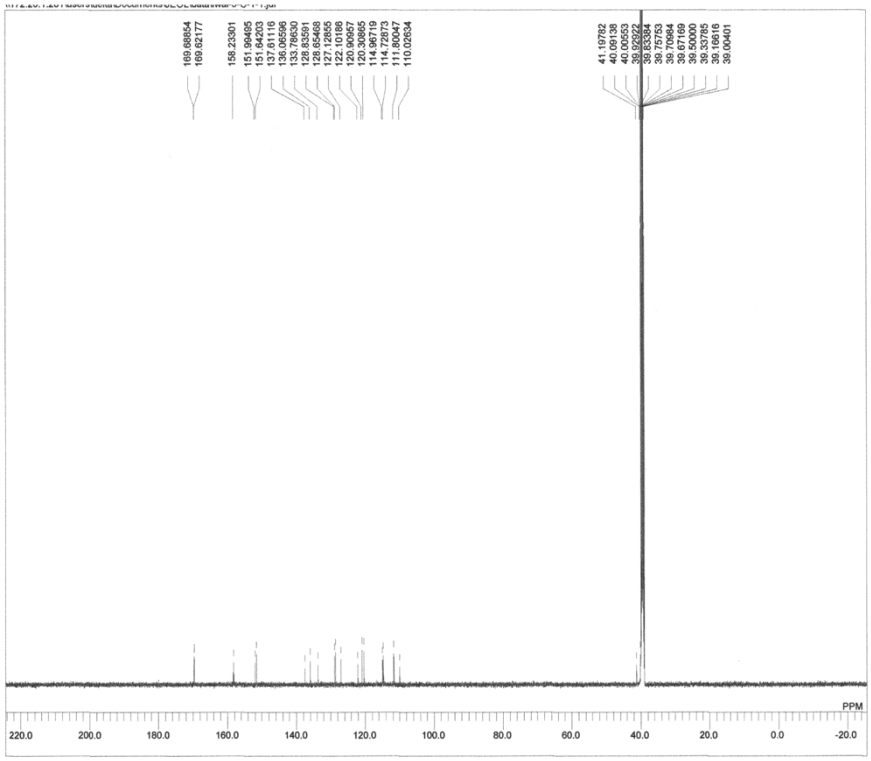

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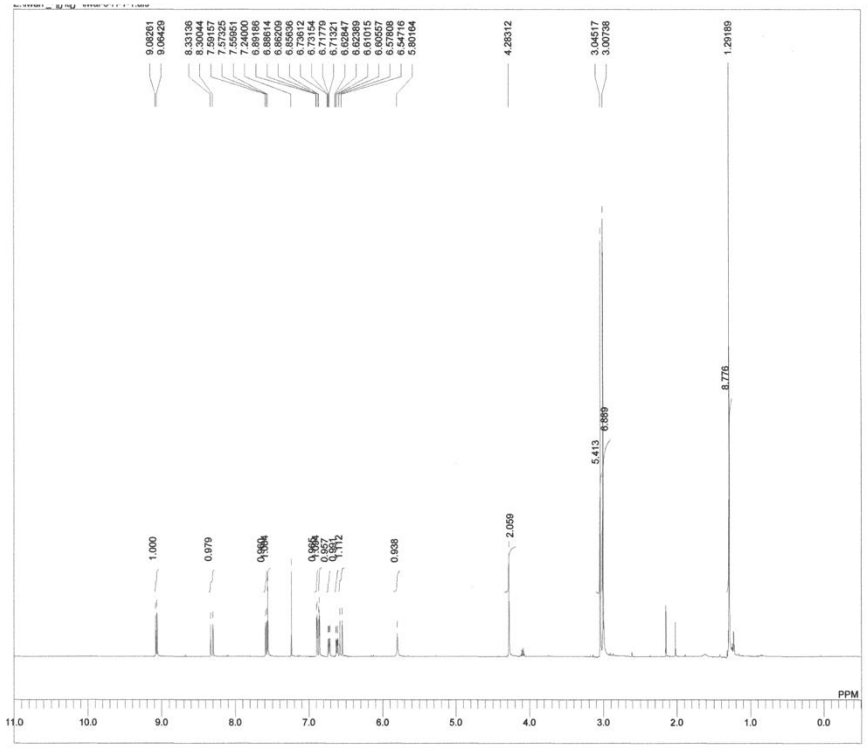

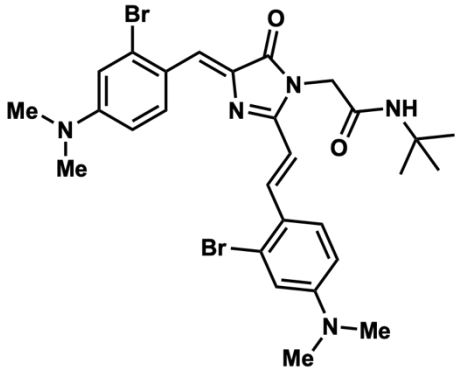

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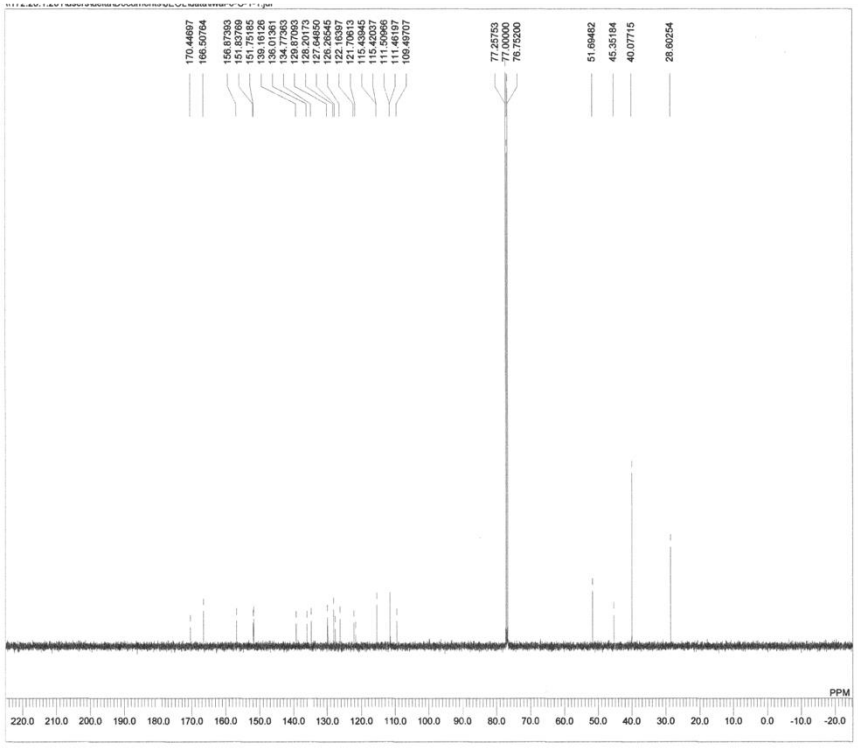

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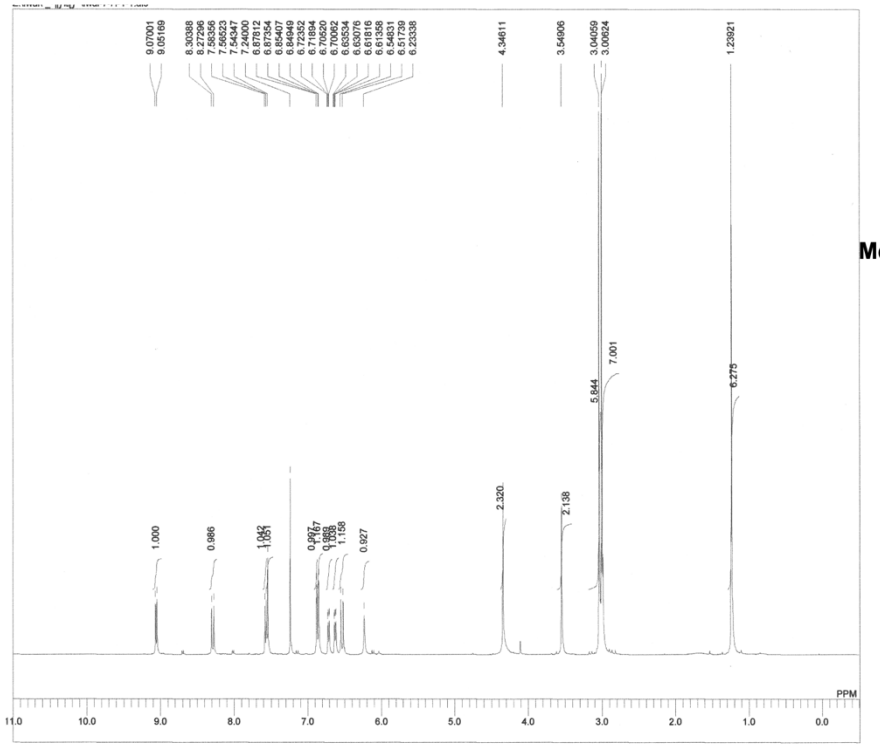

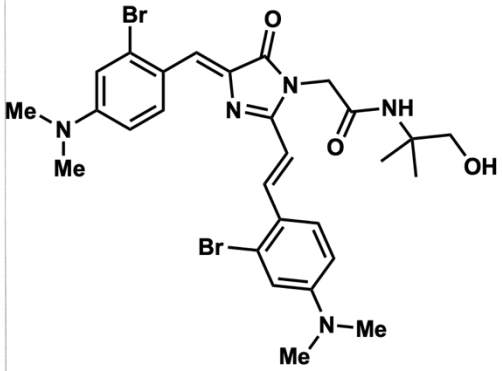

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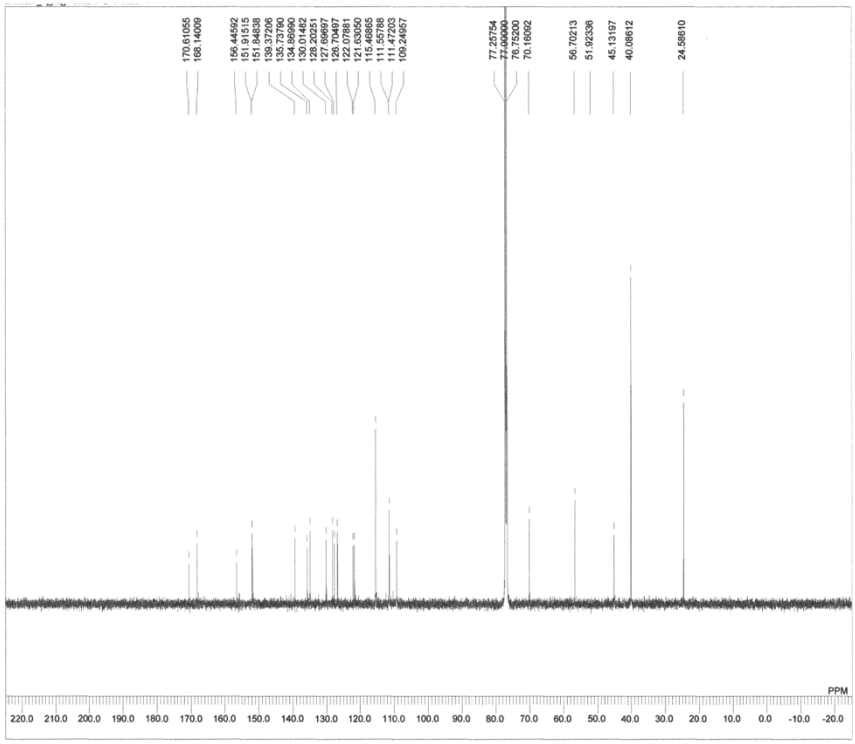

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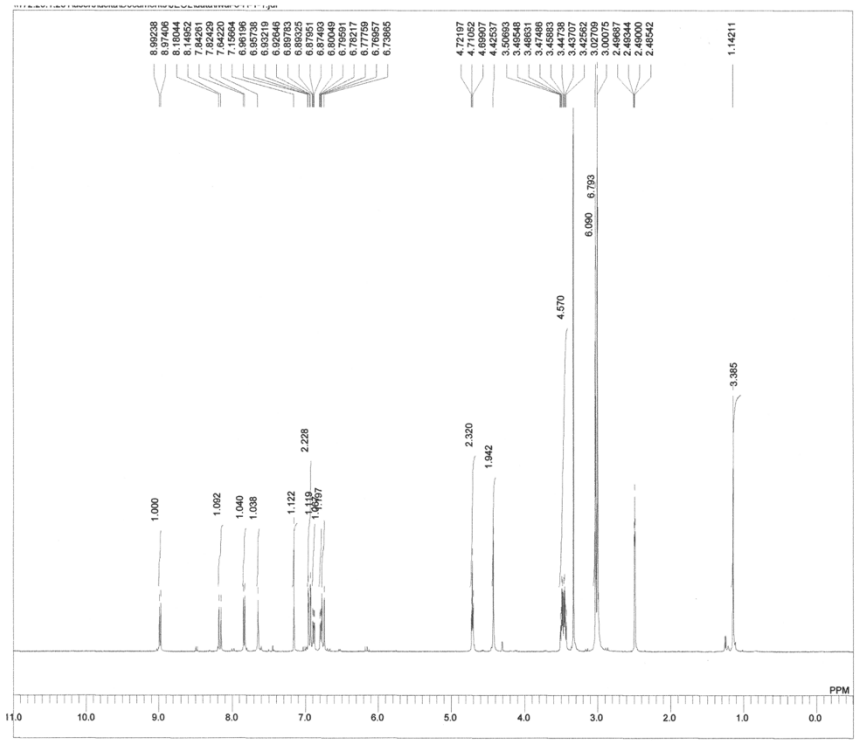

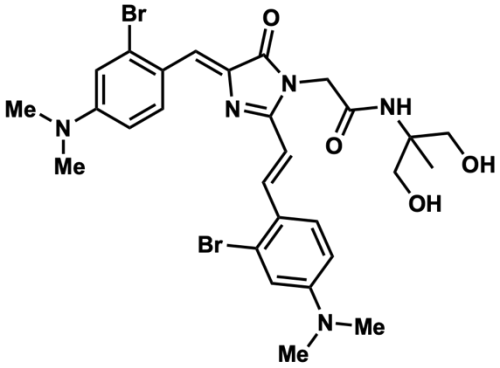

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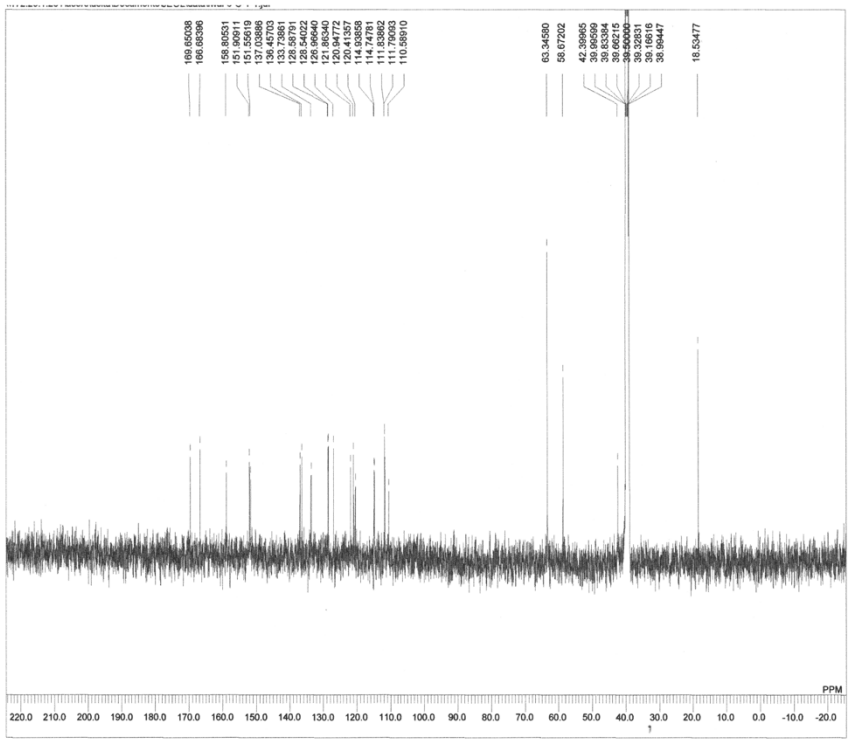

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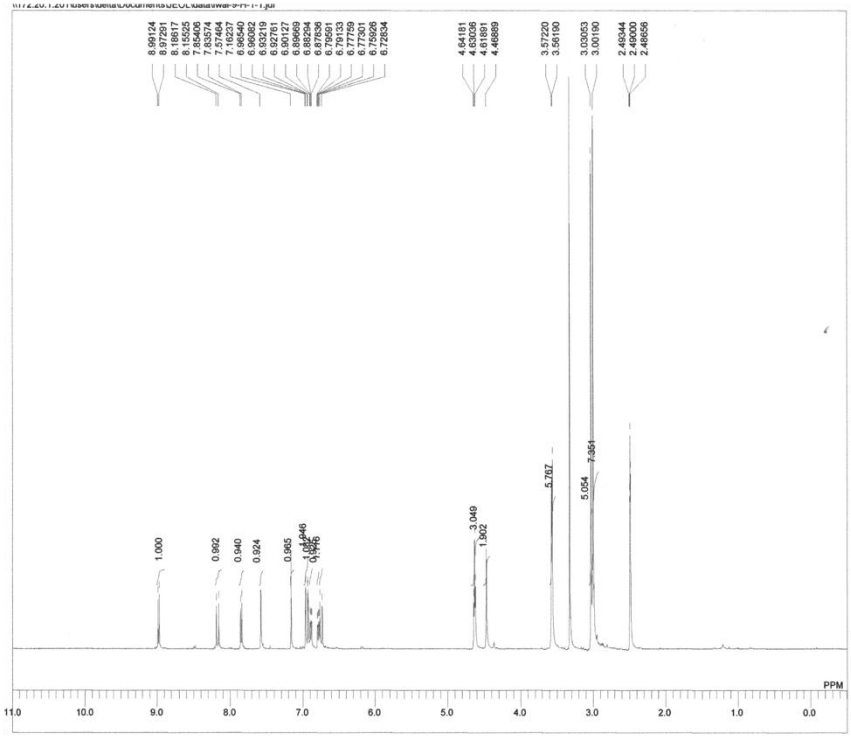

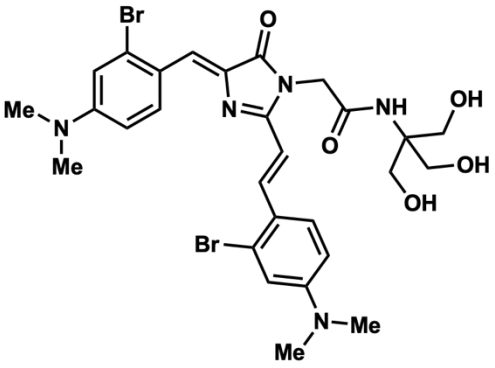

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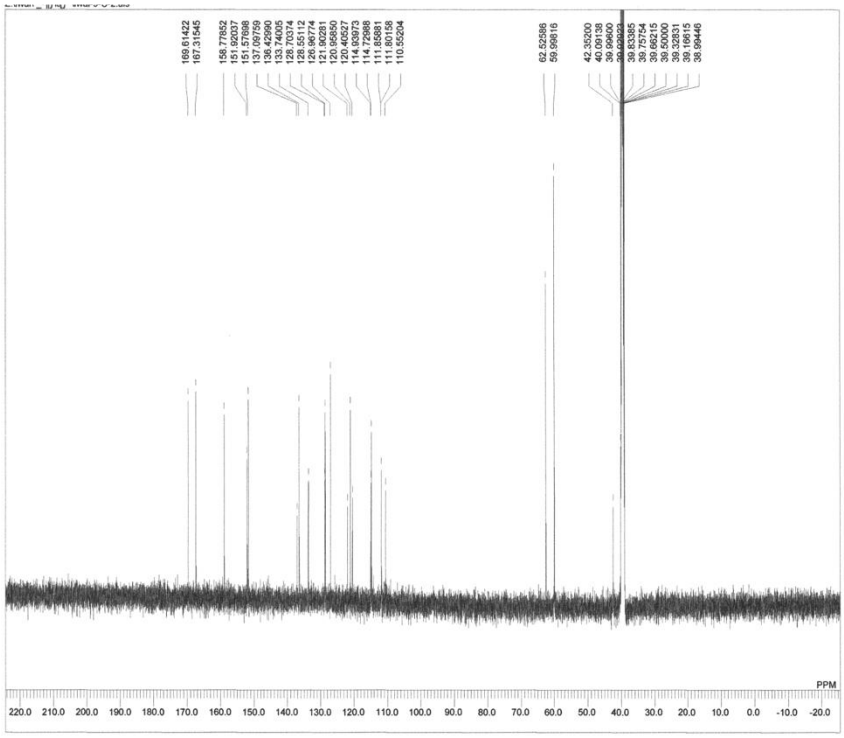

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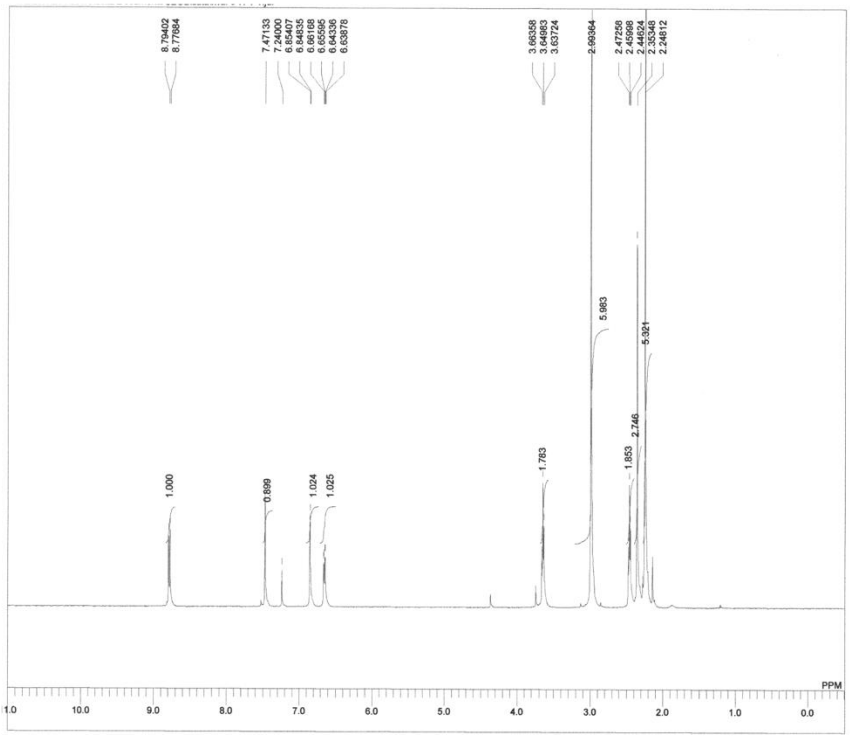

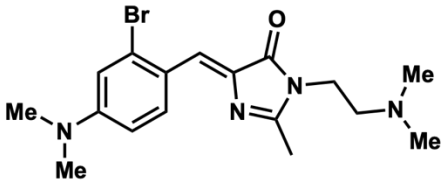

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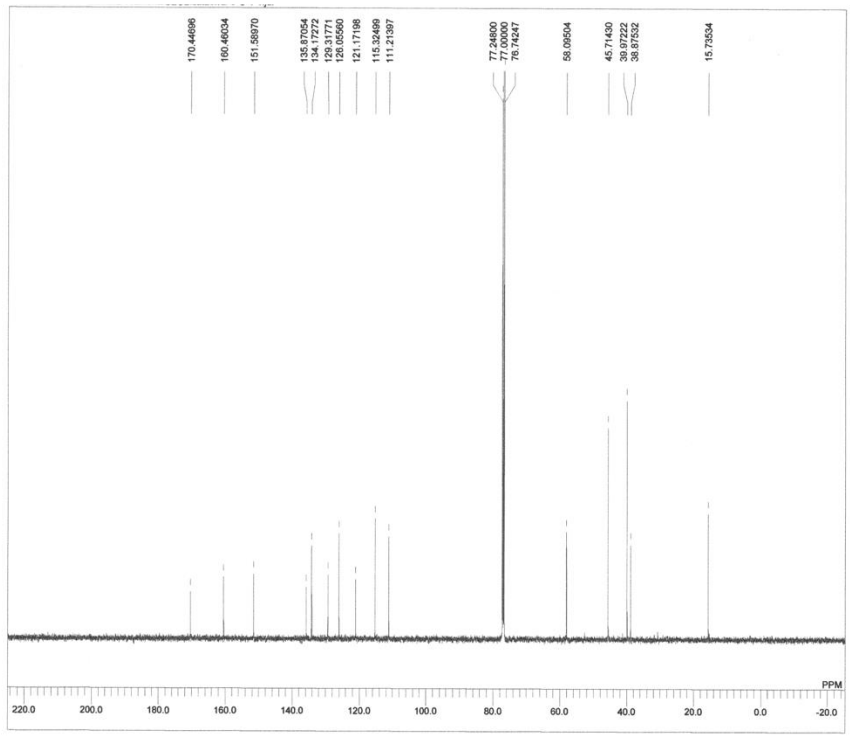

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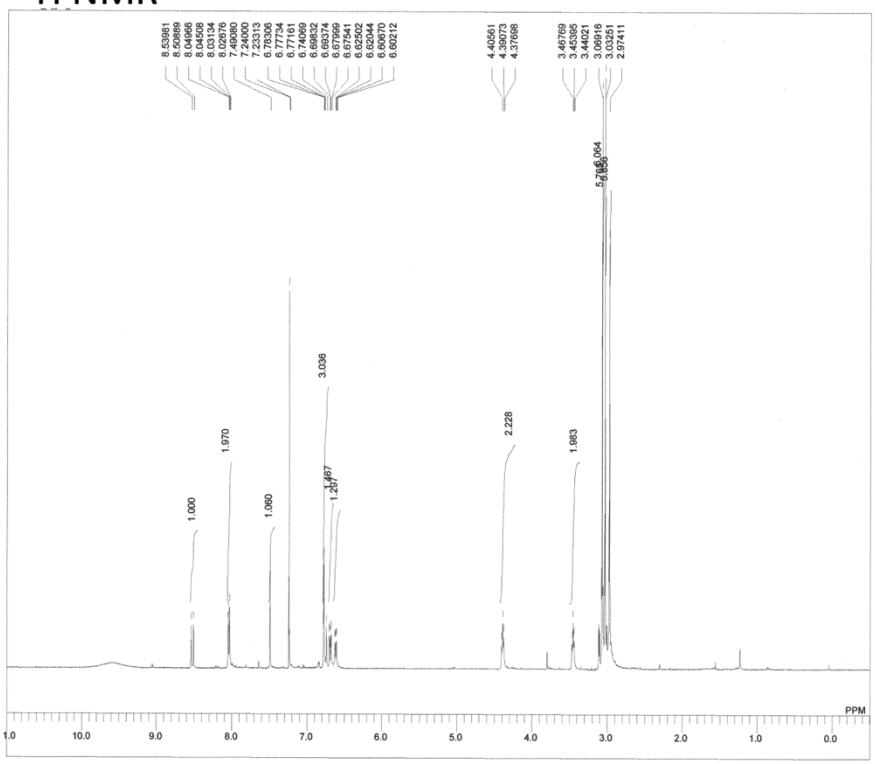

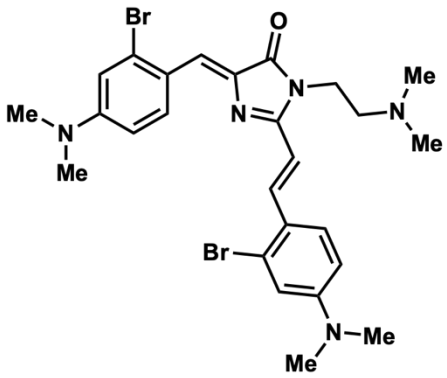

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