Electronic Supplementary Information

Activator-induced quencher-detachment-based turn-on probe with a cationic substrate moiety for acetylcholinesterase

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1. Experimental Section

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1.1. Materials and Methods

Potassium carbonate (K_2CO_3), *N*,*N*-dimethylformamide (DMF), acetone, methanol (MeOH), hexane, ethyl acetate (AcOEt) *N*,*N*-diisopropylethylamine (EtN(*i*-Pr)$_2$), and sodium hydroxide (NaOH) were purchased from Nacalai Tesque (Japan). Pyridine, dimethylsulfoxide (DMSO), chloroform ($CHCl_3$), acetonitrile (MeCN), acetic acid (AcOH), choline chloride, Dulbecco's modified Eagle's medium (DMEM), Dulbecco's Phosphate-Buffer Saline (-) (D-PBS(-)), trifluoroacetic acid (TFA) and tetra-*n*-butylammonium hexafluorophosphate were purchased from FUJIFILM Wako Pure Chemicals Inc. (Japan). Dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) was purchased from Kishida Chemical Co., Ltd. (Japan). 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-Oxide Hexafluorophosphate (HATU) and 1-hydroxybenzotriazole (HOBt) were purchased from WATANABE CHEMICAL IND., LTD. (Japan). Silica gel (SiO_2, 230–400 mesh) and Al_2O_3 (neutral, 40–160 μm) for column chromatography was purchased from Silicycle (Canada) and Oakwood Chemical (USA), respectively. Pyridine and DMF were distilled over CaH_2 under N_2 before use. MeOH was distilled over Mg under N_2 before use. All other materials were purchased and used without further purification.

Buffer aqueous solutions (pH 2.0–2.2) were prepared by dissolving hydrochloric acid (HCl) and potassium chloride (KCl) in water (MilliQ). Buffer aqueous solutions (pH 3.1–6.9) were prepared by dissolving citric acid and sodium dihydrogenphosphate (NaH_2PO_4) in water (MilliQ). Buffer aqueous solutions (pH 7.5–8.7) were prepared by dissolving NaH_2PO_4 and disodium hydrogenphosphate (Na_2HPO_4) in water (MilliQ). Buffer aqueous solutions (pH 9.0–11.0) were prepared by dissolving sodium bicarbonate ($NaHCO_3$) and sodium carbonate (Na_2CO_3) in water (MilliQ). All buffer aqueous solutions were stored in refrigerator and used within one week.

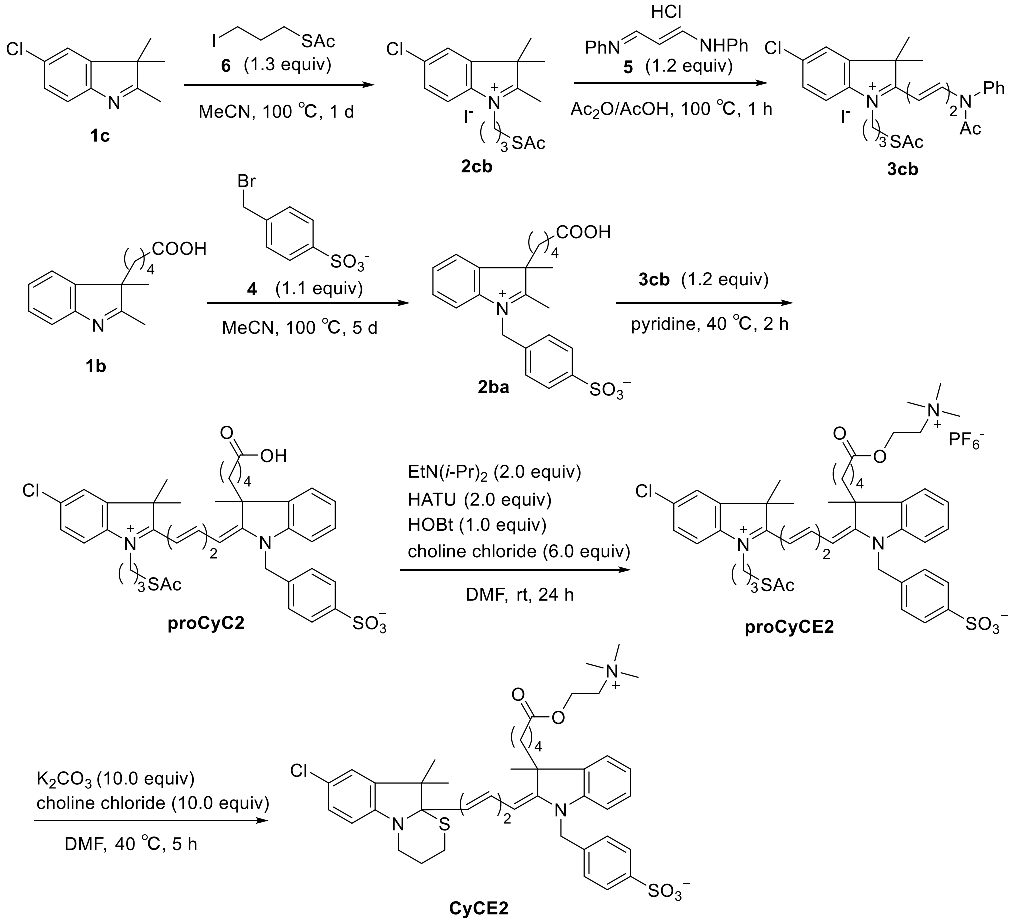
Purification of probes was performed by the instrument equipped with HPLC column oven, UV detector (GL-7450, GL Sciences Inc., Japan) and HPLC pump (GL-7410, GL Sciences Inc., Japan). Liquid chromatography-mass spectrometer (LC-MS) was carried out with LCMS-2020 (absorbance at 700 nm) with a reversed-phase column (Shim-pack XR-ODS II, 150 × 2.0 mm) (Shimadzu Industrial System Co., Ltd., Japan).

UV-vis absorption spectra of dyes were measured by UV-vis-NIR spectrophotometer (UH5300, Hitachi High-Technologies Co., Japan). Emission spectra of dyes were measured by fluorescence spectrophotometer (RF-6000, Shimadzu Co., Japan). High-resolution mass spectra were measured by Exactive Plus Orbitrap (ESI, Thermo Fisher Scientific Inc., USA). NMR spectra were recorded on JEOL JNM-ECZ 400 (400 MHz) or JEOL JNM-ECX 400 spectrometer (400 MHz). LSM 710 (Zeiss, Germany) was used for laser scanning confocal microscopy of SUIT-2 cells.

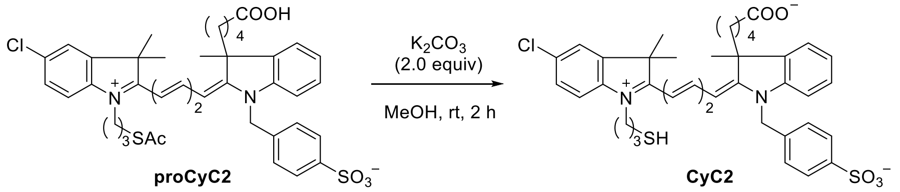
1.2. Synthesis

Synthesis of CyCE2 and CyC2

Scheme S1



Scheme S2



To a flame-dried Schlenk flask, **1c**[1] (1.5 g, 7.5 mmol), *S*-3-iodopropyl thioacetate (**6**)[2] (2.4 g, 9.8 mmol), and MeCN (8.0 mL) were successively added at room temperature under nitrogen atmosphere. After refluxing for 1 d, the organic solvent was removed under reduced pressure. The residue was dissolved in a small amount of CH_2Cl_2. After the solution was added to Et_2O, the product was gradually precipitated. The precipitate was washed with Et_2O. The volatiles were removed under reduced pressure to afford indole **2cb** (2.0 g, 4.6 mmol, 61%) as a red solid.

2cb: mp 135.5−137.0 °C; IR(ATR) 2999, 2869, 2829, 1688, 1622, 1604, 1469, 1417, 1356, 1299, 1205, 1176, 1130, 10333, 958, 928, 836, 823, 771, 667, 623, 552, 511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.70 (s, 6H), 2.21−2.29 (m, 2H), 2.31 (s, 3H), 3.02 (t, J = 7.3 Hz, 2H), 3.14 (s, 3H), 4.89 (t, J = 7.3 Hz, 2H), 7.52−7.57 (m, 2H), 7.94 (t, J = 8.7 Hz, 1H). HRMS (ESI) calcd for $C_{16}H_{21}ClNOS$ ([M^+]) 310.1027, found 310.1027.

To a solution of indole **1b**[3] (0.41 g, 1.6 mmol) in MeCN (0.8 mL) was added **4**[4] (0.46 g, 1.8 mmol) at room temperature. After refluxing for 5 d, the organic solvent was removed under reduced pressure. The residue was dissolved in a small amount of MeOH. After the solution was added to AcOEt, the product was gradually precipitated. The precipitate was washed with AcOEt. The volatiles were removed under reduced pressure to afford indole **2ba** (0.62 g, 1.5 mmol, 91%) as a green solid.

2ba: mp 142.5−144.0 °C; IR(ATR) 3450, 3028, 2868, 1721, 1616, 1562, 1439, 1407, 1168, 1120, 1033, 1008, 822, 765, 689, 613, 565 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$, 25 °C) δ 0.49−0.60 (m, 1H), 0.68−0.81 (m, 1H), 1.26−1.40 (m, 2H), 1.58 (s, 3H), 2.17 (t, J = 7.3 Hz, 2H), 2.24−2.33 (m, 2H), 2.98 (s, 3H), 5.80 (d, J = 17.0 Hz, 1H), 5.87 (d, J = 15.6 Hz, 1H), 7.37 (d, J = 7.8 Hz, 2H), 7.52−7.64 (m, 4H), 7.77−7.85 (m, 2H). HRMS (ESI) calcd for $C_{22}H_{25}NO_5S$ ([M + H]$^+$) 416.1526, found 416.1530.

To a solution of indole **2cb** (1.4 g, 3.2 mmol) in AcOH/Ac$_2$O (18 mL/7.8 mL) was added malonaldehyde dianilide hydrochloride (**5**)[5] (1.0 g, 3.9 mmol) at room temperature. After stirring at 100 °C for 1 h, the crude solution was cooled to room temperature. After the solution was added to cold Et$_2$O, and kept it at 0 °C for 12 h. The precipitate was filtered. The volatile was removed under reduced pressure to afford **3cb** (1.4 g) as a purple solid. **3cb** was used for the next step without further purification.

In a flame-dried Schlenk flask, indole **2ba** (0.36 g, 0.87 mmol), **3cb** (0.64 g, 1.0 mmol), and pyridine (8.5 mL) were successively added at room temperature under nitrogen atmosphere. After stirring at 40 °C for 2 h, the organic solvent was removed under reduced pressure and the residue was subjected to column chromatography on SiO$_2$ (eluent: CH$_2$Cl$_2$-MeOH, v:v = 15:1) to afford a crude product. The organic solvents were removed under reduced pressure and the residue was dissolved in a small amount of MeOH. After adding Et$_2$O slowly, the product was gradually precipitated. The precipitate was washed with Et$_2$O. The volatiles were removed under reduced pressure to afford Cy5 derivative **proCyC2** (0.12 g, 0.16 mmol, 18%) as a red solid.

proCyC2: mp 120.0−122.0 °C; IR(ATR) 3421, 2972, 2867, 2827, 1683, 1573, 1488, 1455, 1373, 1327, 1212, 1171, 1100, 1033, 1007, 925, 792, 718, 674, 595, 562 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD, 25 °C) δ 0.59−0.70 (m, 1H), 0.91−1.02 (m, 1H), 1.42−1.52 (m, 2H), 1.73 (s, 3H), 1.73 (s, 3H), 1.75 (s, 3H), 2.03 (t, J = 7.3 Hz, 2H), 2.07−2.04 (m, 2H), 2.25 (dt, J = 12.8, 3.2 Hz, 1H), 2.31 (s, 3H), 2.51 (dt, J = 12.4, 3.7 Hz, 1H), 2.95 (t, J = 7.3 Hz, 2H), 4.13 (t, J = 7.3 Hz, 2H), 5.41 (s, 2H), 6.28 (d, J = 13.8 Hz, 1H), 6.33 (d, J = 13.8 Hz, 1H), 6.56 (dd, J = 12.4, 12.4 Hz, 1H), 7.26−7.30 (m, 3H), 7.35−7.41 (m, 4H), 7.50 (d, J = 7.3 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 7.83 (d, J = 8.7 Hz, 2H), 8.21−8.29 (m, 2H). ^{13}C NMR (100 MHz, CD$_3$OD, 25 °C) δ 25.9, 26.3, 26.9, 26.9, 27.8, 28.4, 28.8, 30.6, 42.1, 44.1, 48.2, 50.8, 55.3, 105.1, 105.8, 112.1, 113.2, 123.6, 124.1, 126.5, 127.8, 127.9, 129.8, 130.0, 131.8, 138.5, 140.7, 142.3, 144.6, 144.8, 145.1, 146.2, 155.5, 156.1, 156.2, 174.0, 174.7, 197.0. HRMS (ESI) calcd for $C_{41}H_{44}ClN_2O_6S_2$ ([M – H]$^-$) 759.2335, found 759.2331.

To a flame-dried Schlenk flask, Cy5 derivative **proCyC2** (88 mg, 0.12 mmol) and DMF (1.1 mL) were successively added at room temperature under nitrogen atmosphere. To this solution were added EtN(*i*-Pr)$_2$ (40 µL, 0.23 mmol), HATU (88 mg, 0.23 mmol), HOBt (16 mg, 0.12 mmol) and choline chloride (97 mg, 0.70 mmol) in order at 0 °C. After stirring at room temperature for 24 h, the reaction mixture was diluted with AcOEt. The precipitate was subjected to column chromatography on Al$_2$O$_3$ (eluent: CH$_3$Cl-MeOH, v:v = 15:1) to afford a crude product. The organic solvents were removed under reduced pressure and the residue was dissolved in a small amount of a solution

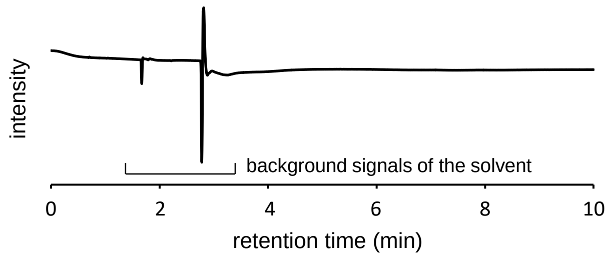
(CH_3Cl-MeOH, v:v = 15:1). After adding Et_2O slowly, the product was gradually precipitated. The precipitate was washed with Et_2O. The volatiles were removed under reduced pressure to afford Cy5 derivative **proCyCE2** (0.35 g, 35 μmol, 30%) as a red solid.

proCyCE2: mp 135.0−137.0 °C; IR(ATR) 3649, 2968, 2867, 2828, 1734, 1685, 1489, 1455, 1374, 1328, 1217, 1100, 1052, 1033, 1007, 926, 794, 718, 685, 595, 563, 552 cm^{-1}; ^1H NMR (400 MHz, CD_3OD, 25 °C) δ 0.43−0.52 (m, 1H), 0.71−0.81 (m, 1H), 1.26−1.40 (m, 2H), 1.64 (s, 6H), 1.66 (s, 3H), 1.91−1.98 (m, 2H), 2.04−2.19 (m, 3H), 2.22 (s, 3H), 2.40 (dt, J = 9.1, 4.1 Hz, 1H), 2.86 (t, J = 6.9 Hz, 2H), 3.03 (s, 9H), 3.52 (t, J = 4.6 Hz, 2H), 4.05 (t, J = 6.9 Hz, 2H), 4.29−4.32 (m, 2H), 5.28 (d, J = 16.5 Hz, 1H), 5.34 (d, J = 16.9 Hz, 1H), 6.20 (d, J = 13.7 Hz, 1H), 6.28 (d, J = 13.3 Hz, 1H), 6.48 (dd, J = 12.3, 12.3 Hz, 1H), 7.18−7.26 (m, 3H), 7.31 (d, J = 7.8 Hz, 4H), 7.41 (d, J = 7.3 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 8.15 (dd, J = 13.7, 12.3 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD, 25 °C) δ 25.4, 26.1, 26.9, 27.7, 28.2, 28.8, 30.6, 34.3, 42.5, 44.1, 48.1, 50.8, 54.4, 55.2, 58.7, 66.0, 71.4, 105.1, 105.8, 112.1, 113.2, 126.6, 124.1, 126.5, 127.7, 127.8, 128.3, 129.8, 130.0, 131.9, 138.6, 140.7, 142.2, 144.5, 144.8, 146.5, 155.3, 156.0, 173.6, 173.7, 174.8, 197.0. HRMS (ESI) calcd for $C_{46}H_{57}ClN_3O_6S_2$ ([M^+]) 846.3372, found 846.3379.

To a flame-dried Schlenk flask, Cy5 derivative **proCyCE2** (5.2 mg, 5.2 μmol), K_2CO_3 (7.5 mg, 54 μmol), choline chloride (7.3 mg, 52 μmol) and DMF (0.35 mL) were successively added at room temperature under nitrogen atmosphere. After stirring at 40 °C for 5 h, the crude was purified by HPLC analysis (YMC-Triart Phenyl column 250 × 4.6 mm, acetonitrile/ammonium acetate buffer (pH 4.8)) to afford **CyCE2** (Figure S1b). HRMS (ESI) of **CyCE2** calcd for $C_{44}H_{54}ClN_3O_5S_2$ ([M + H]$^+$) 804.3266, found 804.3263.

The similar deprotection procedure for **proCyC2** in MeOH was conducted to afford **CyC2**. HRMS (ESI) of **CyC2** calcd for $C_{39}H_{42}ClN_2O_5S_2$ ([M – H]$^-$) 717.2222, found 717.2229.

(a) without **CyCE2**



(b) with **CyCE2**

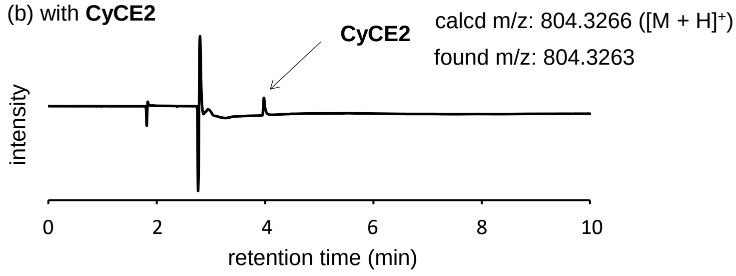
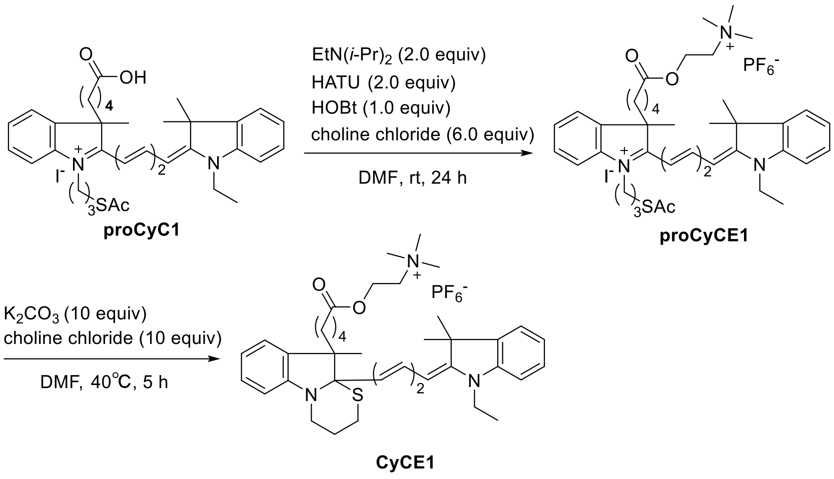


Fig. S1 LC-MS analysis of (a) a blank solution (MeCN-ammonium acetate buffer (pH 4.8), v:v = 1:1) and (b) a solution of **CyCE2** (MeCN-ammonium acetate buffer (pH 4.8), v:v = 1:1). Mobile phase: ammonium acetate buffer (pH 4.8) (phase A) and MeCN (phase B). The gradient program was set as follows: 0–6 min, 0–95% B; 6–7 min, 95–100% B; 7–9 min, 100% B; 9–10 min, 100–0% B (0.4 mL/min).

Synthesis of CyCE1

Scheme S3



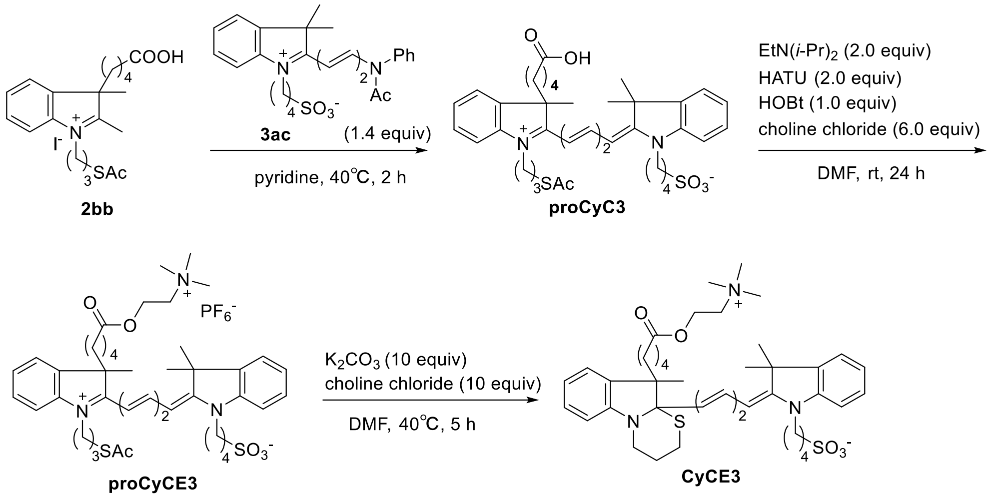
To a flame-dried Schlenk flask, Cy5 derivative **proCyC1**^{6} (0.13 g, 0.18 mmol) and DMF (0.9 mL) were successively added at room temperature under nitrogen atmosphere. To this solution were added EtN(*i*-Pr)$_2$ (63 µL, 0.36 mmol), HATU (0.14 g, 0.37 mmol), HOBt (26 mg, 0.19 mmol) and choline chloride (0.16 g, 1.2 mmol) in order at 0 °C. After stirring at room temperature for 24 h, the reaction mixture was diluted with CH_2Cl_2. The organic solutions was washed with saturated $NaHCO_3$ aqueous solution (10 mL×3) and dried over Na_2SO_4. The organic solvents were removed under reduced pressure and the residue was subjected to column chromatography on SiO_2 (eluent: CH_2Cl_2-MeOH, v:v = 7:1) to afford a crude product. The organic solvents were removed under reduced pressure and the residue was dissolved in a small amount of CH_2Cl_2. After adding Et_2O slowly, the product was gradually precipitated. The precipitate was washed with Et_2O. The volatiles were removed under reduced pressure to afford Cy5 derivative **proCyCE1** (0.17 g, 0.16 mmol, 86%) as a red solid.

proCyCE1: mp 61.0–62.5 °C; IR(ATR) 3670, 2971, 2869, 2826, 1739, 1480, 1448, 1374, 1332, 1228, 1217, 1148, 1103, 1063, 1042, 1016, 998, 924, 833, 772, 708, 626, 555 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$, 25 °C) δ 0.46–0.56 (m, 1H), 0.79–0.91 (m, 1H), 1.29 (t, J = 6.9 Hz, 3H), 1.34–1.42 (m, 2H), 1.68 (s, 3H), 1.69 (s, 6H), 1.89–1.96 (m, 2H), 2.14–2.21 (m, 3H), 2.34 (s, 3H), 2.42 (t, J = 13.3 Hz, 1H), 2.92 (t, J = 7.3 Hz, 2H), 3.05 (s, 9H), 3.54–3.57 (m, 2H), 4.11–4.20 (m, 4H), 4.32–4.35 (m, 2H), 6.28 (d, J = 13.7 Hz, 1H), 6.37 (d, J = 14.2 Hz, 1H), 6.57 (dd, J = 12.4, 12.4 Hz, 1H), 7.22–7.30 (m, 2H), 7.34–7.44 (m, 4H), 7.56 (d, J = 7.3 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 8.27–8.38 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d$_6$, 25 °C) δ 12.2, 23.7, 24.1, 26.7, 26.9, 27.0, 27.3, 27.3, 30.6, 32.9, 42.3, 49.2, 52.9, 53.1, 57.6, 63.7, 79.2, 103.0, 103.5, 110.5, 111.2, 122.4, 122.6, 124.5, 125.1, 125.7, 128.6, 128.6, 139.0, 141.4, 141.5, 142.9, 153.1, 154.6, 170.4, 172.0, 173.1, 195.2. HRMS (ESI) calcd for $C_{41}H_{57}N_3O_3S$ ([M^{2+}]) 335.7055, found 335.7059.

Cy5 derivative **CyCE1** was synthesized in a similar manner to **CyCE2** using Cy5 derivative **proCyCE1** instead of **proCyCE2**. HRMS (ESI) of **CyCE1** calcd for $C_{39}H_{54}N_3O_2S$ ([M^{+}]) 628.3931, found 628.3931.

Synthesis of CyCE3

Scheme S4



In a flame-dried Schlenk flask, indole **2bb**[6] (0.27 g, 0.56 mmol), **3ac**[7] (0.36 g, 0.78 mmol), and pyridine (6.0 mL) were successively added at room temperature under nitrogen atmosphere. After stirring at 40 °C for 2 h, the organic solvent was removed under reduced pressure and the residue was subjected to column chromatography on SiO_2 (eluent: CH_2Cl_2-MeOH, v:v = 15:1) to afford a crude product. The organic solvents were removed under reduced pressure and the residue was dissolved in a small amount of MeOH. After adding Et_2O slowly, the product was gradually precipitated. The precipitate was washed with Et_2O. The volatiles were removed under reduced pressure to afford Cy5 derivative **proCyC3** (0.29 g, 0.42 mmol, 75%) as a red solid.

proCyC3: mp 165.0−166.5 °C; IR(ATR) 3423, 2971, 2907, 2828, 1738, 1685, 1565, 1489, 1449, 1374, 1333, 1216, 1179, 1128, 1101, 1085, 1034, 1016, 924, 796, 750, 708, 603, 553 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$, 25 °C) δ 0.42−0.53 (m, 1H), 0.75−0.85 (m, 1H), 1.28−1.36 (m, 2H), 1.63−1.80 (m, 15H), 1.86−1.94 (m, 2H), 1.96−2.06 (m, 2H), 2.14 (t, J = 12.8 Hz, 1H), 2.32 (s, 3H), 2.40 (t, J = 11.9 Hz, 1H), 2.92 (t, J = 7.8 Hz, 2H), 4.09−4.14 (m, 4H), 6.29 (d, J = 13.7 Hz, 1H), 6.44 (d, J = 13.7 Hz, 1H), 6.57 (dd, J = 12.4, 12.3 Hz, 1H), 7.19−7.28 (m, 2H), 7.31−7.42 (m, 3H), 7.46 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 8.28 (dd, J = 12.8, 12.3 Hz, 1H), 8.34 (dd, J = 13.3, 12.8 Hz, 1H). HRMS (ESI) calcd for $C_{38}H_{48}N_2O_6S_2$ ([M – H]$^-$) 691.2881, found 691.2872.

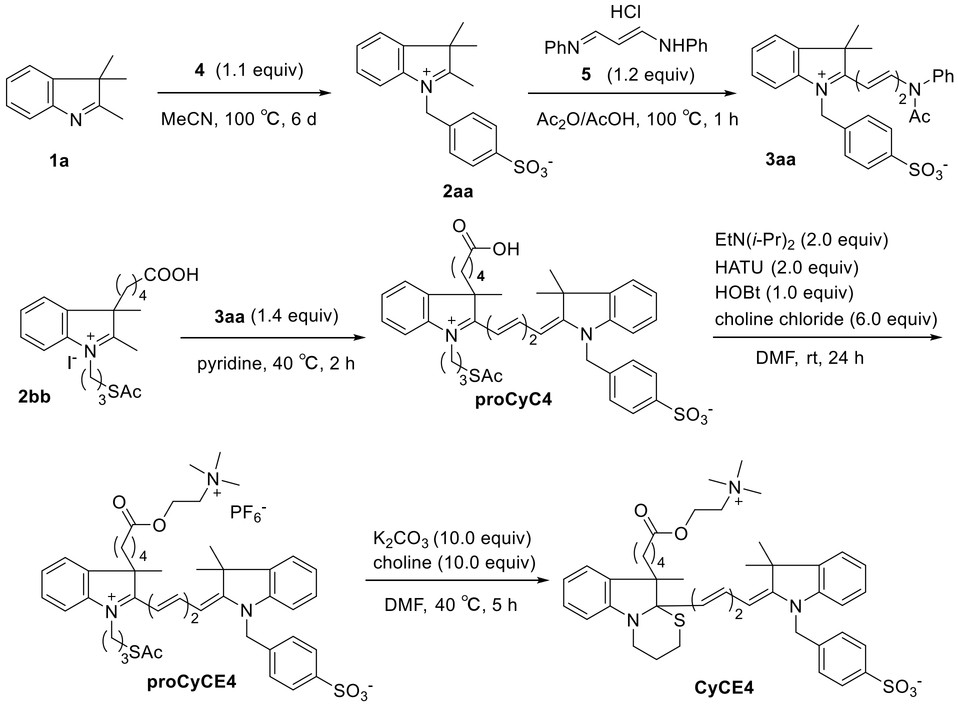
Cy5 derivative **proCyCE3** was obtained in the similar manner to **proCyCE2** using Cy5 derivative **proCyC3** instead of **proCyC2**.

proCyCE3: a red solid (85%): mp 88.0−89.5 °C; IR(ATR) 3386, 2969, 2936, 2868, 1735, 1682, 1573, 1479, 1447, 1375, 1332, 1215, 1176, 1127, 1099, 1055, 1033, 999, 923, 840, 794, 752, 707, 600, 557 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 0.57−0.70 (m, 1H), 0.89−0.98 (m, 1H), 1.46−1.54 (m, 2H), 1.71 (s, 3H), 1.73 (s, 3H), 1.76 (s, 3H), 1.89−1.95 (m, 2H), 1.99−2.08 (m, 4H), 2.16−2.27 (m, 3H), 2.36 (s, 3H), 2.46 (t, J = 13.3 Hz, 1H), 2.83−2.92 (m, 2H), 2.98 (t, J = 7.3 Hz, 2H), 3.15 (s, 9H), 3.63−3.66 (m, 2H), 4.13 (t, J = 7.4 Hz, 2H), 4.18−4.26 (m, 2H), 4.41−4.44 (m, 2H), 6.28 (d, J = 13.7 Hz, 1H), 6.46 (d, J = 13.8 Hz, 1H), 6.65 (dd, J = 12.8, 12.4 Hz, 1H), 7.23−7.31 (m, 3H), 7.37−7.46 (m, 4H), 7.51 (d, J = 7.3 Hz, 1H), 8.19 (dd, J = 13.3, 13.3 Hz, 1H), 8.28 (dd, J = 13.3, 12.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD, 25 °C) δ 23.5, 25.2, 25.5, 27.1, 27.4, 27.9, 28.0, 28.2, 28.8, 30.7, 30.7, 34.2, 41.8, 43.7, 45.0, 50.9, 51.8, 54.4, 54.8, 58.8, 66.0, 71.5, 104.2, 105.5, 111.5, 112.6, 123.4, 123.5, 125.9, 126.7, 127.1, 129.8, 129.9, 140.5, 142.9, 143.4, 144.5, 154.3, 156.2, 172.1, 173.7, 175.8, 197.0. HRMS (ESI) calcd for $C_{43}H_{60}N_3O_6S_2$ ($[M^+]$) 778.3918, found 778.3918.

Cy5 derivative **CyCE3** was synthesized in a similar manner to **CyCE2** using Cy5 derivative **proCyCE3** instead of **proCyCE2**. HRMS (ESI) of **CyCE3** calcd for $C_{41}H_{57}N_3O_5S_2$ ($[M + H]^+$) 736.3812, found 736.3816.

Synthesis of CyCE4

Scheme S5



Indole **2aa** was obtained in the similar manner to **2ba** using indole **1a**[8] instead of **1b**.

2aa: a green solid (90%): mp 258.0−260.0 °C; IR(ATR) 3133, 3039, 1606, 1453, 1405, 1175, 1121, 1034, 1009, 826, 764, 687, 657, 612, 600, 553 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ, 1.59 (s, 6H), 2.97 (s, 3H), 5.82 (s, 2H), 7.36−7.41 (m, 2H), 7.52-7.63 (m, 4H), 7.78-7.87 (m, 2H). HRMS (ESI) calcd for $C_{18}H_{19}NO_3S$ ($[M + H]^+$) 330.1158, found 330.1162.

To a solution of indole **2aa** (0.61 g, 1.9 mmol) in AcOH/Ac_2O (3.6 mL/8.1 mL) was added **5** (0.57 g, 2.2 mmol) at room temperature. After stirring at 100 °C for 1 h, the crude solution was cooled to room temperature. After the solution was added to cold Et_2O, and kept it at 0 °C for 12 h. The precipitate was filtered. The volatile was removed under reduced pressure to afford **3aa** (0.69 g) as a red solid. **3aa** was used for the next step without further purification.

In a flame-dried Schlenk flask, indole **2bb** (0.22 g, 0.45 mmol), **3aa** (0.31 g, 0.62 mmol), and pyridine (4.8 mL) were successively added at room temperature under nitrogen atmosphere. After stirring at 40 °C for 3 h, the organic solvent was removed under reduced pressure and the residue was subjected to column chromatography on SiO_2 (eluent: CH_3Cl-MeOH, v:v = 15:1) to afford a crude product. The organic solvents were removed under reduced pressure and the residue was dissolved in a small amount of MeOH. After adding Et_2O slowly, the product was gradually precipitated. The precipitate was washed with Et_2O. The volatiles were removed under reduced pressure to afford Cy5 derivative **proCyC4** (80 mg, 0.11 mmol, 25%) as a red solid.

proCyC4: mp 113.0−115.0 °C; IR(ATR) 3427, 2973, 2868, 2827, 1681, 1628, 1561, 1449, 1374, 1331, 1212, 1129, 1101, 1034, 1006, 919, 790, 750, 708, 681, 595, 553 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 0.62−0.70 (m, 1H), 0.94−1.02 (m, 1H), 1.40−1.53 (m, 2H), 1.73 (s, 3H), 1.73 (s, 3H), 1.74 (s, 3H), 2.01−2.04 (m, 4H), 2.21 (dt, *J* = 13.3, 3.6 Hz, 1H), 2.31 (s, 3H), 2.50 (dt, *J* = 12.3, 4.1 Hz, 1H), 2.96 (t, *J* = 7.3 Hz, 2H), 4.18 (t, *J* = 7.3 Hz, 2H), 5.32−5.41 (m, 2H), 6.24 (d, *J* = 13.8 Hz, 1H), 6.34 (d, *J* = 13.7 Hz, 1H), 6.53 (dd, *J* = 12.3, 12.3 Hz, 1H), 7.24 (dd, *J* = 7.8, 6.4 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 5.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.38−7.44 (m, 2H) 7.49 (d, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 8.18−8.29 (m, 2H). HRMS (ESI) calcd for $C_{41}H_{46}N_2O_6S_2$ ($[M - H]^-$) 725.2725, found 725.2723.

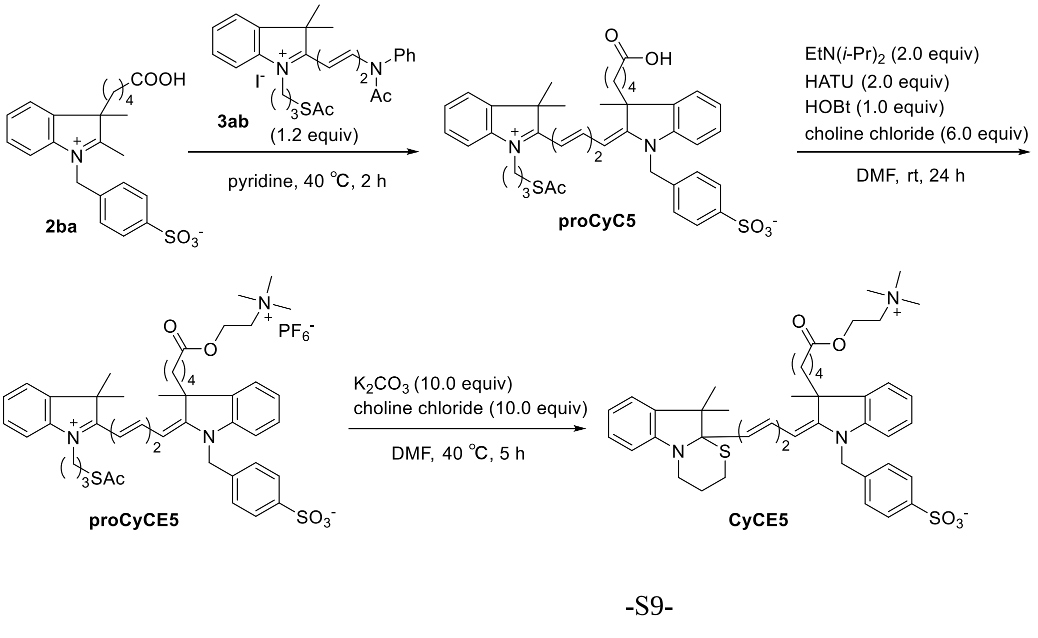
Cy5 derivative **proCyCE4** was obtained in the similar manner to **proCyCE2** using Cy5 derivative **proCyC4** instead of **proCyC2**.

proCyCE4: a red solid (44%): mp 125.0−127.0 °C; IR(ATR) 3417, 2948, 2868, 2827, 1735, 1685, 1573, 1480, 1449, 1375, 1331, 1216, 1174, 1130, 1100, 1033, 1006, 920, 790, 750, 707, 681, 589, 555, 564 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 0.41−0.52 (m, 1H), 0.72−0.83 (m, 1H), 1.29−1.39 (m, 2H), 1.60 (s, 3H), 1.66 (s, 6H), 1.89−1.96 (m, 2H), 2.02−2.14 (m, 3H), 2.21 (s, 3H), 2.33 (t, *J* = 12.8 Hz, 1H), 2.85 (t, *J* = 7.3 Hz, 2H), 3.02 (s, 9H), 3.50−3.52 (m, 2H), 4.07 (t, *J* = 7.3 Hz, 2H), 4.26−4.31 (m, 2H), 5.24 (d, *J* = 16.9 Hz, 1H), 5.36 (d, *J* = 16.9 Hz, 1H), 6.10 (d, *J* = 13.7 Hz, 1H), 6.26 (d, *J* = 13.7 Hz, 1H), 6.44 (dd, *J* = 12.3, 12.3 Hz, 1H), 7.13−7.35 (m, 8H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 2H), 8.08−8.16 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD, 25 °C) δ 25.2, 25.4, 27.0, 27.9, 28.0, 28.2, 28.9, 30.6, 34.2, 41.9, 44.1, 47.7, 50.5, 54.4, 55.3, 58.7, 65.9, 71.3, 104.9, 105.7, 111.8, 112.1, 123.5, 123.6, 126.2, 126.7, 127.4, 127.6, 127.8, 129.9, 129.9, 138.6, 140.9, 142.2, 144.0, 144.2, 146.3, 155.3, 155.6, 173.7, 174.0, 174.3, 197.0. HRMS (ESI) calcd for $C_{46}H_{58}N_3O_6S_2$ ($[M^+]$) 812.3762, found 812.3758.

Cy5 derivative **CyCE4** was synthesized in a similar manner to **CyCE2** using Cy5 derivative **proCyCE4** instead of **proCyCE2**. HRMS (ESI) of **CyCE4** calcd for $C_{44}H_{55}N_3O_5S_2$ ($[M + H]^+$) 770.3656, found 770.3638.

Synthesis of CyCE5

Scheme S6



Cy5 derivatives **proCyC5** was obtained in the similar manner to **proCyC3** using indole **2ba** and **3ab**[6] instead of **2bb** and **3ac**, respectively.

proCyC5: a red solid (19%): mp 115.0−116.0 °C; IR(ATR) 3435, 2972, 2907, 2828, 1724, 1626, 1479, 1452, 1376, 1331, 1212, 1171, 1132, 1102, 1037, 1008, 925, 791, 752, 709, 596, 553 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 0.60−0.71 (m, 1H), 0.93−1.02 (m, 1H), 1.40−1.52 (m, 2H), 1.73 (s, 9H), 2.01−2.10 (m, 4H), 2.22 (t, J = 14.1 Hz, 1H), 2.30 (s, 3H), 2.49 (t, J = 12.3 Hz, 1H), 2.96 (t, J = 6.4 Hz, 2H), 4.18 (t, J = 6.9 Hz, 2H), 5.36 (s, 2H), 6.24 (d, J = 13.3 Hz, 1H), 6.33 (d, J = 13.3 Hz, 1H), 6.52 (dd, J = 11.9, 11.8 Hz, 1H), 7.21−7.29 (m, 3H), 7.31−7.44 (m, 5H), 7.47−7.52 (m, 2H), 7.83 (d, J =8.2 Hz, 2H), 8.17−8.28 (m, 2H). HRMS (ESI) calcd for $C_{41}H_{46}N_2O_6S_2$ ([M – H]$^{-}$) 725.2725, found 725.2728.

Cy5 derivative **proCyCE5** was obtained in the similar manner to **proCyCE2** using Cy5 derivative **proCyC5** instead of **proCyC2**.

proCyCE5: a red solid (36%): mp 131.0−133.0 °C; IR(ATR) 3425, 2965, 2927, 2861, 1734, 1683, 1574, 1479, 1451, 1375, 1331, 1215, 1130, 1099, 1033, 1006, 923, 790, 752, 708, 684, 595, 553 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 0.55−0.65 (m, 1H), 0.83−0.94 (m, 1H), 1.38−1.51 (m, 2H), 1.73 (s, 3H), 1.74 (s, 3H), 1.74 (s, 3H), 2.02−2.09 (m, 2H), 2.14−2.25 (m, 3H), 2.31 (s, 3H), 2.50 (dt, J = 8.2, 5.0 Hz, 1H), 2.97 (t, J = 7.3 Hz, 2H), 3.12 (s, 9H), 3.61 (t, J = 4.6 Hz, 2H), 4.20 (t, J = 7.3 Hz, 2H), 4.38−4.41 (m, 2H), 5.33 (d, J = 16.5 Hz, 1H), 5.39 (d, J = 16.9 Hz, 1H), 6.30 (d, J = 13.7 Hz, 1H), 6.37 (d, J = 13.7 Hz, 1H), 6.56 (dd, J = 12.3, 12.3 Hz, 1H), 7.24−7.45 (m, 8H), 7.49 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 8.17−8.30 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD, 25 °C) δ 25.4, 26.1, 26.9, 27.8, 28.3, 28.9, 30.6, 30.8, 34.3, 42.5, 44.1, 47.9, 51.0, 54.4, 54.8, 58.7, 66.0, 71.3, 104.9, 105.6, 111.6, 112.4, 123.5, 126.1, 126.8, 127.3, 127.6, 127.8, 128.3, 129.8, 129.9, 138.8, 140.4, 142.9, 143.3, 145.0, 146.4, 154.5, 156.4, 172.4, 173.6, 176.0, 196.9. HRMS (ESI) calcd for $C_{46}H_{58}N_3O_6S_2$ ([M^{+}]) 812.3762, found 812.3762.

Cy5 derivative **CyCE5** was synthesized in a similar manner to **CyCE2** using Cy5 derivative **proCyCE5** instead of **proCyCE2**. HRMS (ESI) of **CyCE5** calcd for $C_{44}H_{55}N_3O_5S_2$ ([M + H]$^{+}$) 770.3656, found: 770.3641.

1.3. UV-vis and Fluorescence Spectra

For UV-vis and fluorescence spectra measurements, the sample solutions (5.0×10^{-6} M) were prepared by mixing a solution of probes in DMSO (30 μL, 5.0×10^{-4} M) with deoxygenated buffer aqueous solution (2970 μL). To estimate R_c of probes, the normalized absorbance of the open-ring structure (λ = 640 nm) was fitted to sigmoid curve (Figure S3). Since it is assumed that the equilibrium shifts to the open-ring form under acidic conditions, the maximum absorbance of each probe in an acidic solution is defined as 1. R_c was calculated by using the following equation,

$$R_c = 1 - A_{640}$$

where A_{640} is the normalized absorbance of open-ring structure of a probe at pH 7.4 estimated by utilizing the sigmoid curve.

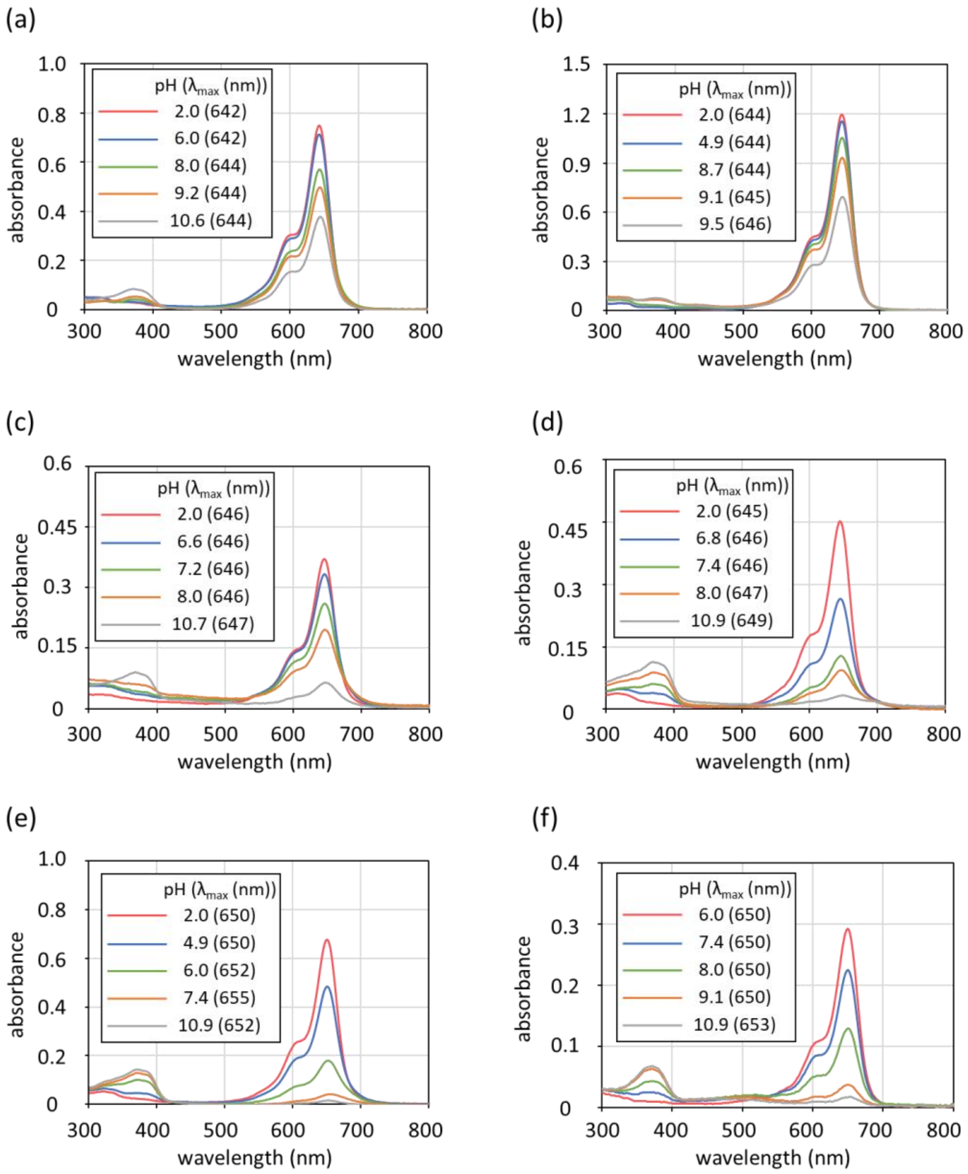


Fig. S2 UV-vis absorption spectra of (a) **CyCE1**, (b) **CyCE3**, (c) **CyCE4**, (d) **CyCE5**, (e) **CyCE2**, and (f) **CyC2** (5.0×10^{-6} M) in buffer solutions.

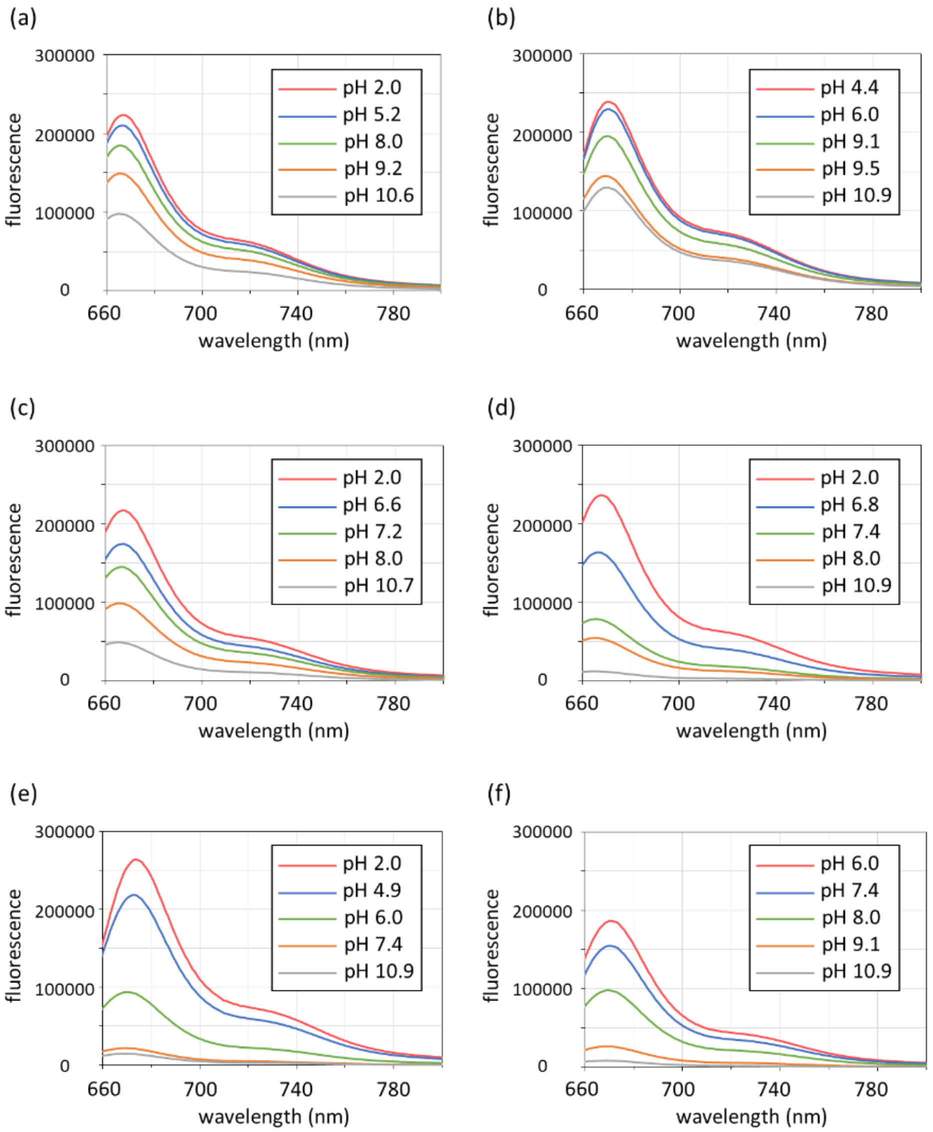


Fig. S3 Fluorescence spectra of (a) **CyCE1**, (b) **CyCE3**, (c) **CyCE4**, (d) **CyCE5**, (e) **CyCE2**, and (f) **CyC2** (5.0×10^{-6} M) in buffer solutions. Excitation wavelength is 650 nm.

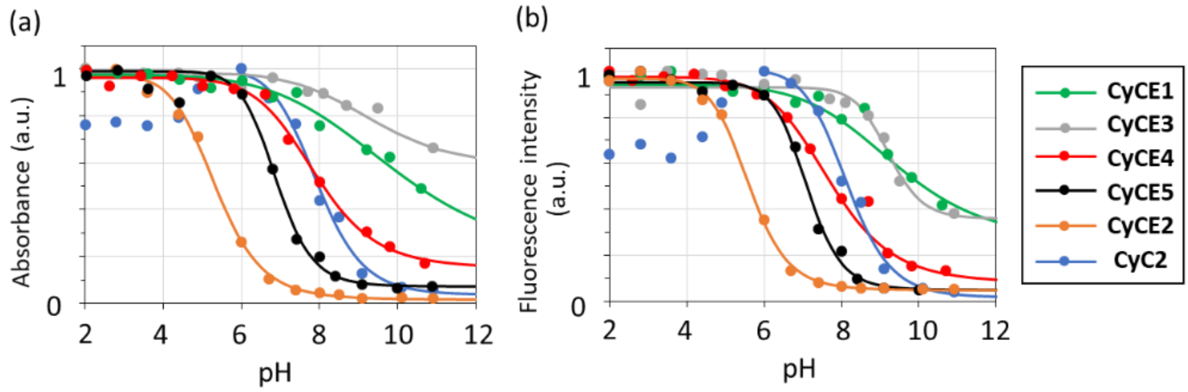
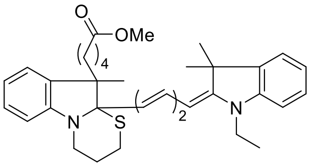


Fig. S4 (a) Normalized absorbance at 640 nm and (b) normalized fluorescence intensity at 670 nm (λ_{ex} = 650 nm) of **CyCE1–5** and **CyC2** (5.0×10^{-6} M) in buffer solutions.

Table S1. Photophysical properties of **CyCE1–CyCE5**, **CyC2** and **CyME4** and their band gap estimated from absorption edge.

probe	buffered solution (pH = 2.0)			CH_3CN (0.1% TFA)	
	ε (cm^{-1} M^{-1})	λ_{max} (nm)	$E_{g,abs}$ (eV)	λ_{max} (nm)	$E_{g,abs}$ (eV)
CyCE1	1.5×10^5	642	1.87	644	1.86
CyCE2	1.4×10^5	650	1.85	651	1.85
CyCE3	2.4×10^5	644	1.86	646	1.86
CyCE4	7.4×10^4	646	1.86	647	1.85
CyCE5	9.0×10^4	645	1.86	646	1.86
CyC2	4.3×10^4	650	1.84	651	1.84
CyME4	1.8×10^5	652	1.84	644	1.86

The HOMO-LUMO band gap was estimated from the absorption edge. The $(h\nu \times \alpha)^2$ values, where α is absorption coefficient, were plotted against $h\nu$ (eV). The absorption edge (eV) was determined as a cross point ($E_{g,abs}$, band gap) of a tangent line and $(h\nu \times \alpha)^2 = 0$, see Fig. S5.



CyME4 (reported in ref. 6)

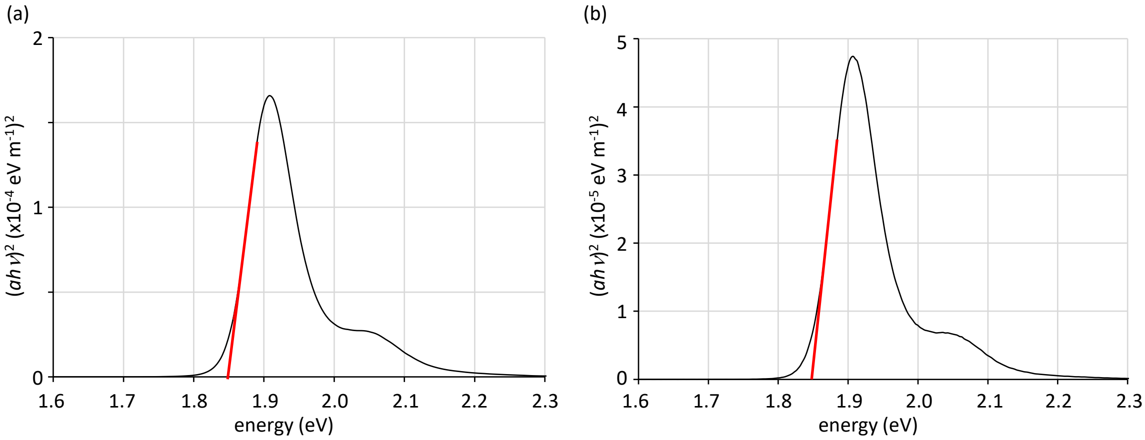


Fig. S5 Tauc plot of (a) a buffered solution (pH 2.0) and (b) CH_3CN solution (0.1% TFA) of **CyCE2**.

1.4. Electrochemical Measurements

A solution of **CyCE1–CyCE5** and **CyME4** (30 μL, 1.0×10^{-2} M) in DMF and tetra-*n*-butylammonium hexafluorophosphate (2970 μL, 0.1 M) in CH_3CN (0.1% TFA) was well mixed prior to measurement. Pt electrode (counter), glassy carbon electrode (working), and Ag/AgCl electrode were used. In order to shift the equilibrium to their open-ring forms, TFA (0.1%) was added to the sample solution. The cyclic voltammogram and differential pulse voltammogram were measured at a rate of 25 mV/sec by electrochemical analyzer (610C-S, ALS Co., Ltd., Japan) (Fig. S6). The one-electron reduction potential (E_{red} [V]) of probes was determined by differential pulse voltammetry because the clear reversible signal was not detected in cyclic voltammetry.

The experimentally determined energy (E_{LUMO} [eV]) at the LUMO was estimated according to the reported equation:

$$E_{\mathrm{LUMO}} = -\,(E_{\mathrm{red}} + E_{\mathrm{abs}}(\mathrm{Fc}^+/\mathrm{Fc}))$$

where the value of $E_{\mathrm{abs}}(\mathrm{Fc}^+/\mathrm{Fc})$: 4.970 V was used.[9]

The energy (E_{HOMO} [eV]) at the HOMO was calculated by using the energy gap (E_{g}) determined from absorption edge in CH_3CN (Table S1).

Table S2. Experimentally determined energy levels of **CyCE1–CyCE5** and **CyME4**.

dye	E_{red} (V vs $\mathrm{Fc}^+/\mathrm{Fc})^b$	E_{LUMO} (eV)^c	E_{HOMO} (eV)	$E_{\mathrm{g,abs}}$ (eV)
CyCE1	–1.18	–3.79	–5.65	1.86
CyCE2	–1.11	–3.86	–5.71	1.85
CyCE3	–1.15	–3.82	–5.68	1.86
CyCE4	–1.15	–3.82	–5.67	1.85
CyCE5	–1.14	–3.83	–5.69	1.86
CyME4	–1.19	–3.78	–5.64	1.86

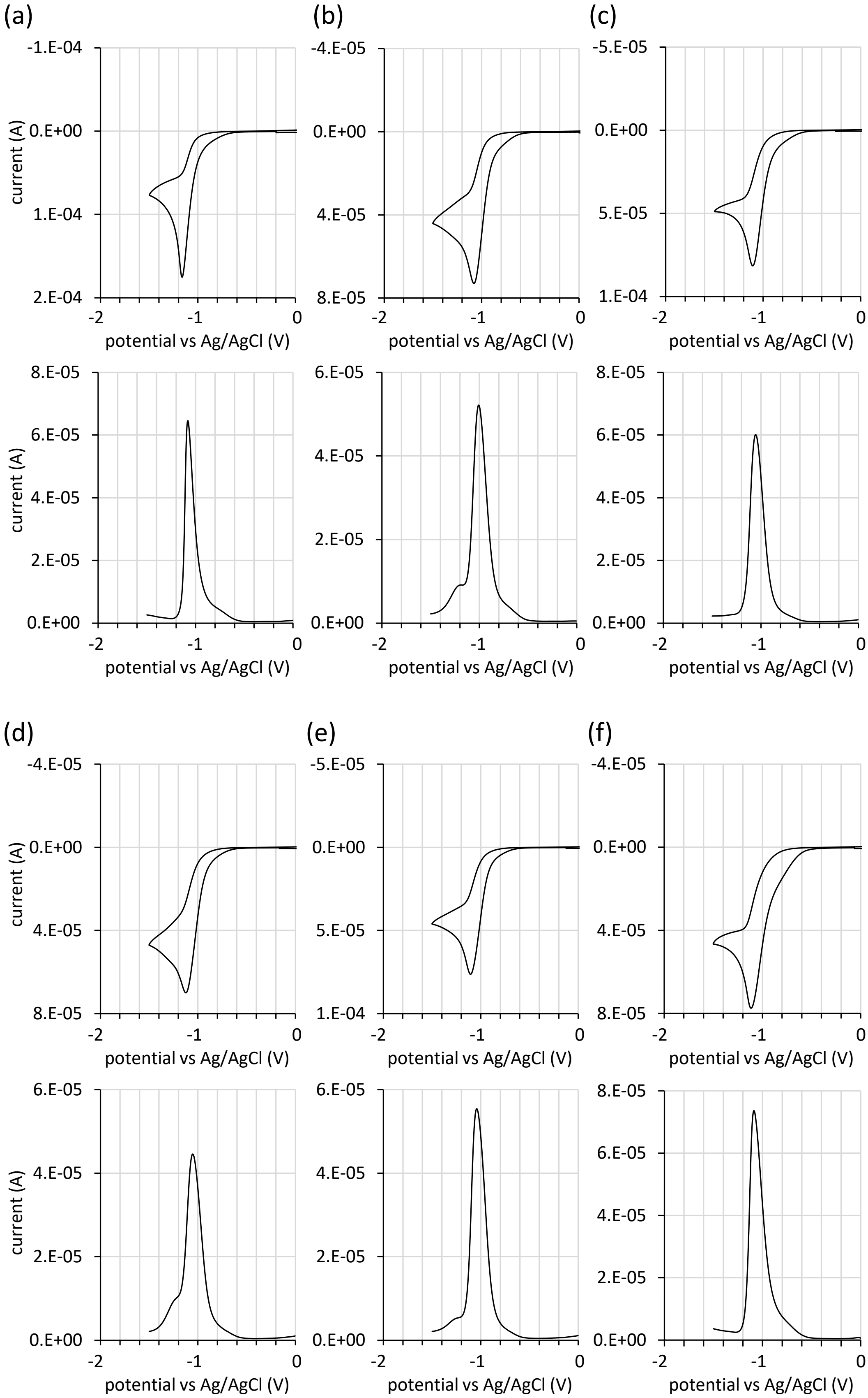


Fig. S6 Cyclic voltammograms and differential pulse voltammograms of (a) **CyCE1**, (b) **CyCE2**, (c) **CyCE3**, (d) **CyCE4**, (e) **CyCE5**, and (f) **CyME4**.

1.5. Theoretical Calculation

The density functional theory (DFT) calculation was performed for the geometry optimization of **CyCE1–5** at the B3LYP/6-31G(d,p)[10] level by using Gaussian 16 package.[11] The energy-minimized structures at the ground state estimated are summarized in Fig. S7. The ground states of **CyCE1–5** were calculated by the time-dependent (TD) DFT calculations at the CAM-B3LYP/6-31G(d)[12] level by using Gaussian 16 package. The optimized structures with frontier orbitals were visualized by Avogadro software.[13] The cartesian coordinates of the optimized structures are summarized at the end of the ESI (section 3).

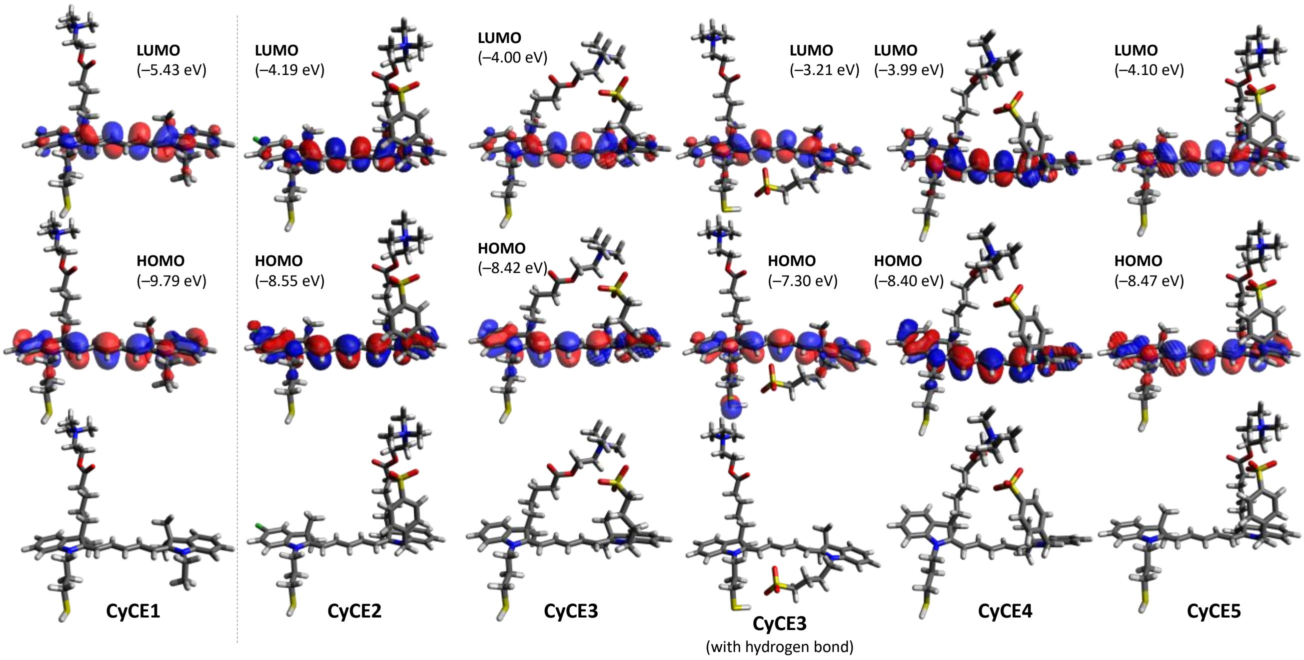


Fig. S7 Kohn-Sham HOMO and LUMO energy levels for the optimized structures at the ground (S_0) state (TD-CAM-B3LYP/6-31G(d)//B3LYP/6-31G(d)) of **CyCE1–5**. Top: LUMO, middle: HOMO, bottom: without electron density distribution.

1.6. Enzyme Assay

Enzyme assay with acetylcholineesterase (AChE)

AChE from Electrophorus electricus (Aldrich) was diluted with 0.1 M phosphate buffer solution to make different AChE concentrations. AChE solution (200 μL) was diluted with the mixture of a probe (20 μL, dissolved in DMSO) solution and a phosphate buffer solution (pH 8.0, 1780 μL) at 37 °C. Final concentration of the probes were 1.0 μM. The AChE concentration was 0–50 U/mL for the assay. Fluorescence intensity excited at 650 nm was recorded for 600 min at 37 °C. The fluorescence intensity at 0 min is defined as 1.

Inhibition assay by using neostigmine

For inhibition assay of enzyme activity, final concentration of probe **CyCE2** was fixed to 1.0 μM (Fig. S8) or 5.0 μM (Fig. 2c). Final concentration of AChE was 10 U/mL (Fig. S8) or 50 U/mL (Fig. 2c) for the assay. AChE inhibitor, neostigmine (FUJIFILM Wako Pure Chemicals Inc.), was dissolved in 10 μL DMSO at different concentrations, and then mixed with the phosphate buffer solution (190 μL) of AChE. The mixed solutions were incubated at 37 °C for 30 min to inhibit enzyme activity. To the inhibitor-treated AChE solution was then added the probe (20 μL, dissolved in DMSO) solution in the phosphate buffer solution (1780 μL). Enzymatic reaction was performed at 37 °C. Excitation wavelength for measurement was 640 nm.

Michaelis-Menten kinetics

Michaelis constant K_m and maximum rate V_{max} were determined by monitoring the time-dependent increment of absorbance of **CyCE2**. The initial rate V (μM min^{-1}) of AChE-mediated reaction was determined from the absorbance increment ($[AChE]_0$ = 25 U/mL, temp.: rt). The absorbance increment was monitored every 1 sec for 3.5 min and the initial reaction rate V was obtained from the slope of the linear fitting (conc. (μM) vs time (min)). The relationship between the initial reaction rate V and the concentration of **CyCE2** ($[S]_0$, μM) was plotted. From the Lineweaver-Burk plot ($1/V$ vs $1/[S]_0$), Michaelis constant K_m and maximum rate V_{max} were calculated.

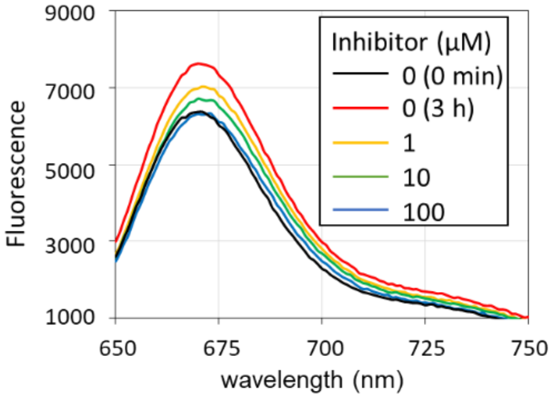


Fig. S8 Fluorescence spectra (λ_{ex} = 640 nm) of **CyCE2** solution incubated for 3 h with AChE (10 U/mL) and neostigmine (0 μM, 1 μM, 10 μM, 100 μM, 1000 μM) as an inhibitor of AChE at 37 °C. AChE was pretreated with neostigmine for 30 min at 37 °C.

From the absorbance measurement, the linear relationship of absorbance at 640 nm in **CyC2/CyCE2** solution (pH = 8.0) was confirmed.

$\Delta I_{\mathrm{abs}} = 2.77 \times 10^{-2}$ [$\mu\mathrm{M}^{-1}$]

, in which ΔI_{abs} is the absorbance change when 1 μM of **CyCE2** converts to 1 μM of **CyC2**.

Based on this linear relationship, the initial rate V_0 ($\mu\mathrm{M}\ \mathrm{min}^{-1}$) of the AChE-mediated reaction was determined.

$V_0 = (6.60 \times 10^{-5} \times 60) / 0.0277 = 0.143$ [$\mu\mathrm{M}\ \mathrm{min}^{-1}$]

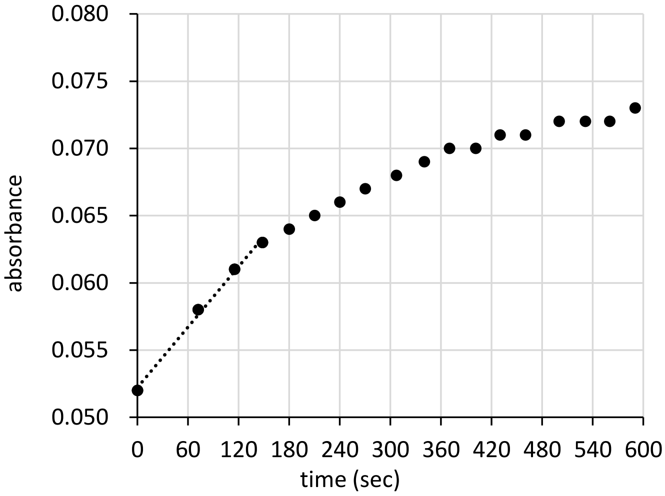


Fig. S9 Time-dependent absorbance change at 640 nm of **CyCE2** (5.0 μM) with 50 U/mL AChE. The fitting line is $I_{\mathrm{abs}} = 6.60 \times 10^{-5} \times t$ [sec] $+ 0.0533$ ($R^2 = 0.9985$)

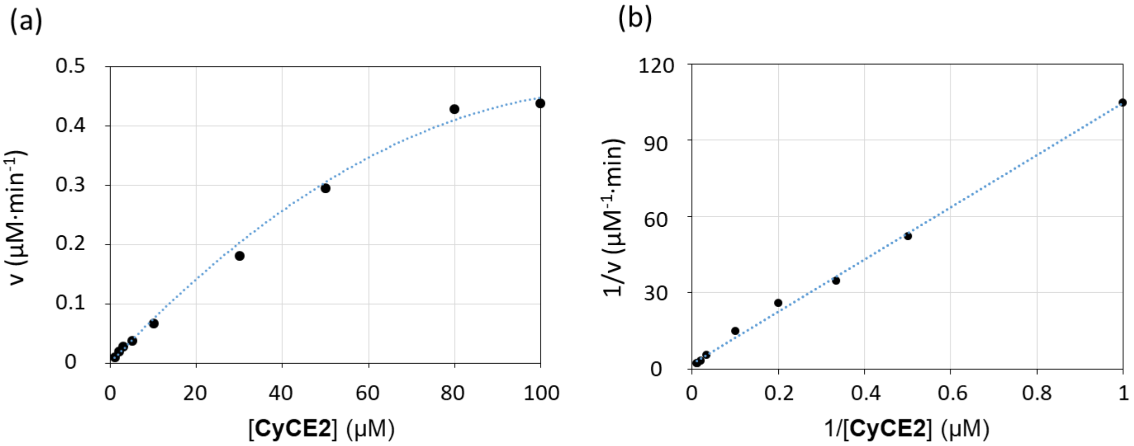
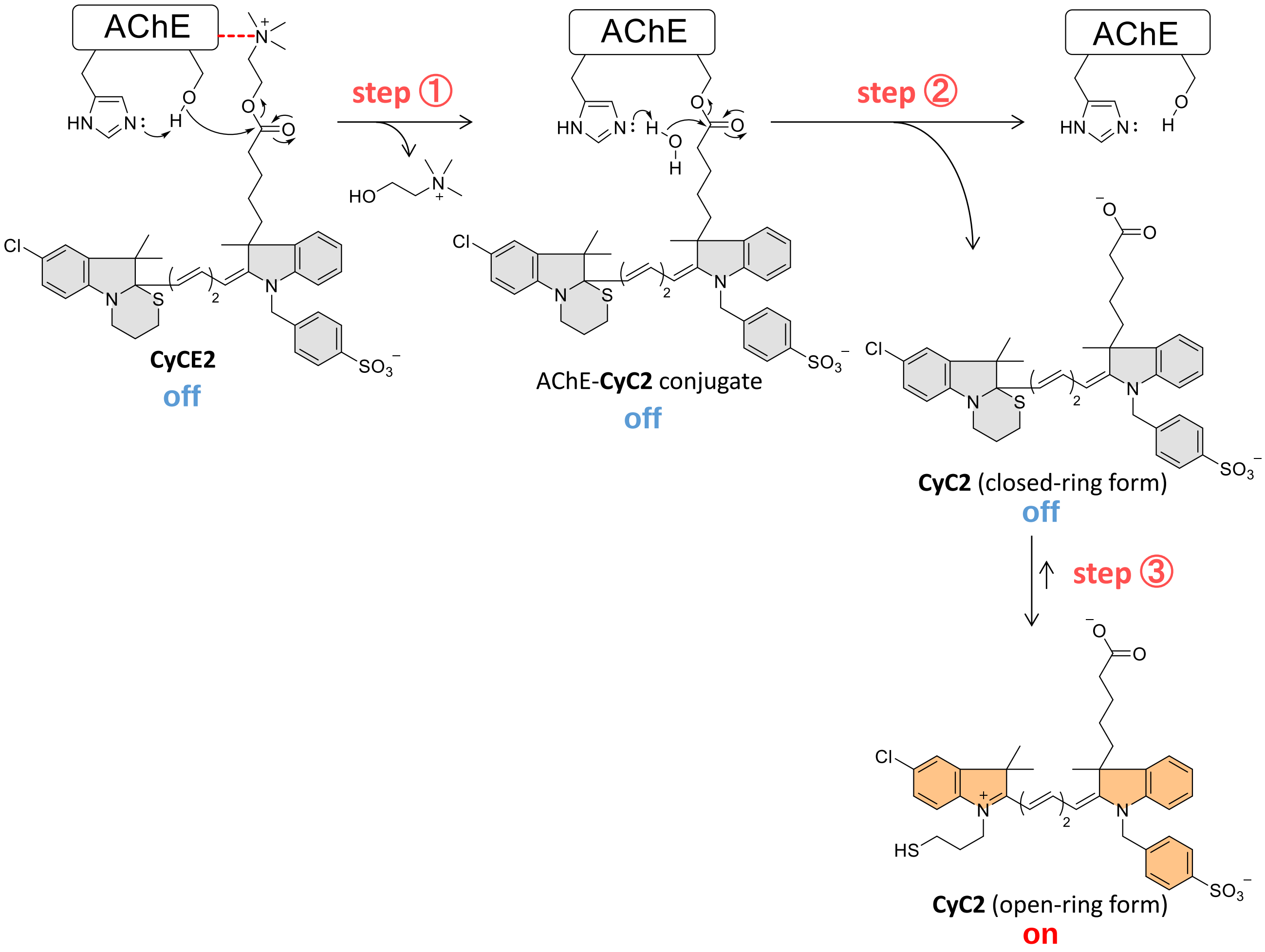


Fig. S10 (a) Michaelis-Menten kinetics and (b) Lineweaver-Burke plot for AChE-catalyzed reaction of **CyCE2**. Conditions: AChE (25 U/mL) with different concentration (1.0 μM, 2.0 μM, 3.0 μM, 5.0 μM, 10.0 μM, 30.0 μM, 50.0 μM, 80.0 μM, 100.0 μM) of **CyCE2** in phosphate buffer solution (pH 8.0).

Scheme S7


AChE
HN
N
H
O
O
O
N
Cl
N
S
2
N
SO3−
CyCE2
off
step ①
HO
N
AChE
AChE-CyC2 conjugate
off
step ②
AChE
CyC2 (closed-ring form)
off
step ③
HS
CyC2 (open-ring form)
on

1.7. *In Vitro* Cell Experiments

Cell culture

PC-12 cell line was purchased from RIKEN BioResource Research Center (Tsukuba, Japan). PC-12 cells was cultured in RPMI-1640 with 10% FBS and 1% penicillin/streptomycin. Cells were cultured well-humidified incubator with 5% CO_2 and 95% air at 37 °C.

MTT cytotoxicity Assay

PC-12 cells was seeded into a 96-well microtiter plate at a density of 1×10^5 cells per well. The cells were incubated for 24 h for cell attachment. PC-12 cells were incubated at 37 °C for an additional 12 h with different concentrations of **CyCE2** (0, 1, 5, 10, 50, 100 and 500 µM). Then the cells were washed with PBS. Subsequently, MTT (200 µL, 0.5 mg/mL) was added to each well and the cells were incubated at 37 °C. After 4 h, the remaining MTT solution was removed, and the formazan crystals were dissolved in 200 µL of DMSO with gentle agitation for 5 min. The absorbance at 550 nm was measured using 800TS^{TM} Absorbance Microplate Reader (BioTek Instruments, USA).

Confocal fluorescence imaging

PC-12 cells were seeded in a 35 mm dish (µ-Dish$^{35\ mm,\ high}$, ibidi, Germany) at a density of 8×10^5 cells. The cells were incubated for 24 h for cell attachment. **CyCE2** dissolved in DMSO (0.2 mM) was diluted in the cell culture medium without phenol red to have a final concentration of 5 µM. PC-12 cells were incubated with the medium at 37 °C for 90 min. Fluorescence images of the cells were acquired by confocal laser scanning microscope (63× objective lens). Excitation lasers of 633 nm (emission: 647–759 nm) was used for detecting fluorescence signals. For positive control, before **CyCE2** was added to the medium, PC-12 cells were treated with 10 µM Phorbol 12-myristate 13-acetate (PMA, Adipogen) for 60 min. For negative control, PC-12 cells were pretreated with neostigmine (10 µM) for 30 min and also incubated with the inhibitor (10 µM) during the treatment of **CyCE2**.

2. References

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3. Cartesian Coordinates of the Optimized Geometry

CyCE1

C	3.24464	-5.46146	1.81482
C	2.69809	-6.44048	0.9829
C	1.57684	-6.16944	0.19258
C	1.04226	-4.88589	0.2592
C	1.58803	-3.88368	1.06645
C	2.68771	-4.17653	1.86436
N	-0.10203	-4.37891	-0.39577
C	-0.37144	-3.0993	-0.01339
C	0.76984	-2.60825	0.90403
C	1.56627	-1.50715	0.12051
C	0.26127	-2.11116	2.27575
C	2.84904	-0.98884	0.78602
C	3.54538	0.08079	-0.06896
C	4.87991	0.52804	0.53842
C	5.57185	1.59115	-0.28057
O	6.86356	1.792	0.15662
O	5.11098	2.22287	-1.19928
C	-1.5092	-2.42345	-0.44458
C	-0.92427	-5.20038	-1.28755
C	-1.91319	-1.12046	-0.12086
C	-3.10671	-0.55809	-0.56253
C	-3.53866	0.72219	-0.2008
C	-4.74917	1.27561	-0.61556
C	-5.25867	2.53297	-0.27139
N	-6.43885	2.99541	-0.7475
C	-6.75437	4.26919	-0.21321
C	-5.71822	4.67255	0.63039
C	-4.65146	3.5911	0.66785
C	-7.88253	5.05211	-0.44109
C	-7.94306	6.28741	0.21132
C	-6.91234	6.71028	1.05527
C	-5.78916	5.9017	1.27108
C	-3.31203	4.13905	0.11678
C	-4.48957	3.04847	2.1087
C	-7.33965	2.2875	-1.66725
C	7.57732	2.80072	-0.56201
C	8.98012	2.74062	0.04272
N	9.99452	3.71491	-0.54776
C	10.2083	3.45281	-2.0201
C	11.30648	3.50766	0.17562
C	9.55418	5.14608	-0.34945
C	-8.3524	1.39944	-0.94048
C	-2.04588	-5.94492	-0.54588
C	-2.86732	-6.81859	-1.49735
S	-4.23421	-7.60744	-0.54317
H	4.10008	-5.70073	2.43771
H	3.13506	-7.43333	0.95887
H	1.14156	-6.94585	-0.4262
H	3.10613	-3.4339	2.53588
H	0.89027	-0.66428	-0.06418
H	1.82214	-1.91396	-0.86537
H	1.10277	-1.96094	2.95648
H	-0.27783	-1.16433	2.19987
H	-0.40443	-2.84756	2.7324
H	3.54118	-1.82287	0.9446
H	2.62486	-0.57168	1.77616
H	2.89574	0.95389	-0.19471
H	3.72572	-0.31018	-1.07727
H	5.57068	-0.31484	0.65799
H	4.73754	0.93713	1.54817
H	-2.19176	-2.97478	-1.08394
H	-0.2541	-5.90646	-1.78475
H	-1.3295	-4.55573	-2.07188
H	-1.28374	-0.50755	0.5183
H	-3.75117	-1.15457	-1.20645
H	-2.88353	1.29711	0.44755
H	-5.36086	0.65283	-1.26095
H	-8.69151	4.7313	-1.08751
H	-8.80822	6.92406	0.05875
H	-6.98479	7.67282	1.55035
H	-4.99442	6.2367	1.93107
H	-2.52986	3.37624	0.11233
H	-2.97354	4.96728	0.74556
H	-3.43001	4.51546	-0.90262
H	-4.17019	3.85999	2.76841
H	-5.43568	2.65668	2.49066
H	-3.74276	2.25318	2.1645
H	-7.8464	3.04999	-2.26294
H	-6.72819	1.70931	-2.36301
H	7.56358	2.57383	-1.63192
H	7.09427	3.77216	-0.41839
H	8.93204	2.95165	1.11326
H	9.39538	1.73938	-0.09096
H	10.49733	2.41014	-2.15455
H	11.00338	4.10764	-2.37706
H	9.28982	3.66237	-2.56561
H	11.16029	3.70562	1.23754
H	11.63304	2.47816	0.02823
H	12.04582	4.19594	-0.23403
H	9.3732	5.31579	0.7123
H	10.34811	5.80532	-0.70086
H	8.64621	5.33094	-0.92095
H	-9.00796	0.91656	-1.67033
H	-7.85216	0.61951	-0.35999
H	-8.97433	1.987	-0.26015
H	-2.69852	-5.21632	-0.05192
H	-1.6086	-6.56548	0.2437
H	-2.23859	-7.59586	-1.94142
H	-3.28994	-6.21409	-2.3059
H	-4.72732	-8.34675	-1.55614

CyCE2

C	4.635	-4.76639	-3.34826
C	4.84819	-5.50693	-2.18308
C	4.01036	-5.36115	-1.07352
C	2.96458	-4.44799	-1.17612
C	2.74067	-3.69355	-2.32983
C	3.57545	-3.8542	-3.42888
N	1.94743	-4.16017	-0.23034
C	1.01557	-3.32476	-0.76188
C	1.53377	-2.7967	-2.11222

C	1.98172	-1.31937	-1.79137
C	0.54574	-2.88567	-3.28851
C	2.84874	-0.57849	-2.81886
C	3.16898	0.82305	-2.27476
C	4.15718	1.63701	-3.13976
C	4.43626	2.93197	-2.41094
O	5.56658	2.84009	-1.6563
O	3.71848	3.9059	-2.40271
C	-0.15709	-2.99174	-0.07882
C	2.16846	-4.35966	1.22873
C	-1.13541	-2.08488	-0.48098
C	-2.30403	-1.82136	0.24112
C	-3.25337	-0.89604	-0.17836
C	-4.43389	-0.60531	0.51984
C	-5.41463	0.30733	0.1464
N	-6.52127	0.54931	0.90509
C	-7.38293	1.48036	0.28414
C	-6.80936	1.89768	-0.91831
C	-5.4808	1.18575	-1.11834
C	-8.61318	1.9617	0.72241
C	-9.26858	2.89827	-0.0816
C	-8.69318	3.32243	-1.28121
C	-7.45707	2.82756	-1.71624
C	-5.52298	0.33198	-2.4088
C	-4.32408	2.21469	-1.15966
C	-6.8373	-0.08389	2.18596
C	5.70122	3.85002	-0.64634
C	6.80965	3.30676	0.24904
N	7.14357	4.17058	1.46513
C	8.10135	3.37493	2.32478
C	7.80207	5.4512	1.03929
C	5.9216	4.49615	2.29651
C	-7.59645	-1.41023	2.02273
C	2.86882	-3.13228	1.78045
C	4.24312	-2.95733	1.56609
C	4.84638	-1.72458	1.80599
S	-8.79571	-3.64062	3.09781
C	-7.93561	-2.03329	3.37896
C	2.13099	-2.07996	2.3422
C	2.73069	-0.84635	2.59012
C	4.07674	-0.6585	2.27159
Cl	-9.53549	4.49652	-2.26958
S	4.76982	1.00817	2.26682
O	6.25591	0.81685	2.22804
O	4.28454	1.69682	3.48735
O	4.24516	1.6075	1.00064
H	5.29203	-4.90345	-4.20074
H	5.66917	-6.21499	-2.13708
H	4.17313	-5.95672	-0.18239
H	3.41218	-3.2904	-4.34167
H	2.52902	-1.3339	-0.84236
H	1.0743	-0.73388	-1.60486
H	0.16169	-3.90277	-3.40219
H	-0.30323	-2.20916	-3.17364
H	1.05219	-2.61446	-4.21828
H	2.33925	-0.5034	-3.78863
H	3.78133	-1.12848	-2.98737
H	3.58468	0.73746	-1.26374
H	2.24259	1.40193	-2.17754
H	3.72261	1.87294	-4.11547
H	5.0876	1.08129	-3.28625
H	-0.3348	-3.49854	0.86454
H	1.20851	-4.54264	1.71247
H	2.76287	-5.26682	1.34373
H	-0.9957	-1.52692	-1.40165
H	-2.475	-2.36232	1.17049
H	-3.04812	-0.37351	-1.1081
H	-4.58931	-1.15805	1.44141
H	-9.07085	1.63197	1.64811
H	-10.22908	3.29725	0.22276
H	-7.03442	3.17207	-2.65372
H	-4.58868	-0.21028	-2.56895
H	-6.33851	-0.39493	-2.37398
H	-5.6869	0.9832	-3.27196
H	-3.35247	1.73054	-1.27958
H	-4.46946	2.89305	-2.00507
H	-4.29676	2.81393	-0.24597
H	-5.9041	-0.22932	2.7365
H	-7.42827	0.63144	2.76422
H	5.93834	4.81228	-1.11321
H	4.75507	3.93016	-0.10956
H	6.50852	2.3321	0.63518
H	7.74311	3.20669	-0.31088
H	8.35736	3.97484	3.19903
H	8.99767	3.1679	1.73842
H	7.60453	2.44257	2.60742
H	8.08653	6.01416	1.92894
H	7.10538	6.03831	0.44201
H	8.68956	5.21528	0.45126
H	6.25662	5.07759	3.15652
H	5.23229	5.09152	1.70017
H	5.43696	3.57903	2.63469
H	-8.51603	-1.23351	1.45416
H	-6.98731	-2.10561	1.43444
H	4.83939	-3.7732	1.1692
H	5.90113	-1.56615	1.61178
H	-9.01373	-3.93098	4.39562
H	-7.02466	-2.20665	3.96
H	-8.58857	-1.3687	3.95231
H	1.07528	-2.21354	2.55993
H	2.15945	-0.02244	3.00456

CyCE3

C	7.81893	2.98473	1.65678
C	8.52388	2.42291	0.59068
C	7.94353	1.4422	-0.22
C	6.63663	1.06234	0.07184
C	5.90817	1.62289	1.12523
C	6.50573	2.58201	1.93355
N	5.84221	0.08591	-0.57052
C	4.63339	-0.05754	0.04226
C	4.52323	0.9928	1.16867
C	3.41187	2.00776	0.73216
C	4.26047	0.36949	2.55882
C	3.10643	3.17462	1.68104

C	1.99041	4.08308	1.13004
C	0.59511	3.44767	1.15799
C	-0.39693	4.15264	0.25562
O	-1.65183	3.67417	0.4604
O	-0.13201	5.00135	-0.56545
C	3.67626	-0.96975	-0.39005
C	6.32227	-0.69794	-1.70849
C	2.419	-1.19857	0.18923
C	1.44605	-2.04187	-0.33258
C	0.22219	-2.26036	0.3117
C	-0.81569	-3.02466	-0.21253
C	-2.02248	-3.33562	0.42448
N	-3.03201	-3.99945	-0.1917
C	-4.08439	-4.29082	0.71173
C	-3.76798	-3.75998	1.9623
C	-2.4213	-3.06275	1.88675
C	-5.25902	-5.00028	0.47573
C	-6.13395	-5.16359	1.55392
C	-5.83622	-4.63251	2.81185
C	-4.64675	-3.92446	3.02384
C	-2.59387	-1.54175	2.15321
C	-1.4266	-3.70051	2.88444
C	-3.18249	-4.22896	-1.63592
C	-2.65232	4.13418	-0.46747
C	-3.98332	3.8709	0.23264
N	-5.16167	4.63481	-0.37409
C	-5.13845	6.06364	0.08648
C	-6.43356	3.97248	0.10619
C	-5.14818	4.5977	-1.88864
C	-4.15874	-3.22308	-2.27901
C	6.97858	-2.0213	-1.28421
C	7.49182	-2.80642	-2.49344
S	8.22085	-4.39644	-1.90741
C	-4.8995	-0.77997	-2.36893
C	-3.76303	-1.75551	-2.06582
S	-4.60922	0.85356	-1.62117
O	-5.88013	1.61108	-1.87485
O	-3.42854	1.44935	-2.3084
O	-4.38495	0.59983	-0.16137
H	8.29345	3.73452	2.281
H	9.54221	2.74005	0.39083
H	8.50845	0.99561	-1.0305
H	5.97536	3.01229	2.77667
H	2.49779	1.43293	0.55751
H	3.69927	2.41724	-0.24401
H	3.24351	-0.0151	2.66122
H	4.95748	-0.44921	2.75495
H	4.40643	1.12239	3.33692
H	4.00584	3.78311	1.81785
H	2.82394	2.80177	2.67404
H	2.22498	4.37225	0.10019
H	1.96706	5.01546	1.70439
H	0.18274	3.4095	2.17269
H	0.61616	2.4063	0.81204
H	3.90999	-1.5628	-1.2692
H	5.48179	-0.87566	-2.38496
H	7.03154	-0.07273	-2.25687
H	2.16817	-0.68803	1.11393
H	1.63412	-2.54213	-1.28103
H	0.0887	-1.77988	1.27637
H	-0.66256	-3.41483	-1.21348
H	-5.49733	-5.41737	-0.49594
H	-7.05839	-5.7124	1.40664
H	-6.53242	-4.77182	3.63227
H	-4.42113	-3.5162	4.00451
H	-1.63336	-1.02078	2.14245
H	-3.03267	-1.40806	3.14651
H	-3.24913	-1.06009	1.42147
H	-1.79869	-3.56814	3.90424
H	-1.31492	-4.77259	2.70167
H	-0.43861	-3.2388	2.82319
H	-2.20026	-4.16779	-2.10286
H	-3.53709	-5.25479	-1.77343
H	-2.47108	5.19014	-0.68767
H	-2.5797	3.54277	-1.38444
H	-4.22103	2.80362	0.2014
H	-3.92458	4.18927	1.27642
H	-5.23421	6.08889	1.17249
H	-5.9737	6.59439	-0.37128
H	-4.20015	6.52815	-0.21541
H	-6.47371	2.97218	-0.33435
H	-6.40861	3.93028	1.19597
H	-7.27962	4.57623	-0.22568
H	-5.16998	3.55334	-2.2077
H	-6.04313	5.11639	-2.23539
H	-4.26111	5.11711	-2.24827
H	-4.2221	-3.46594	-3.34656
H	-5.15841	-3.39214	-1.8637
H	7.8065	-1.81007	-0.59865
H	6.2505	-2.62364	-0.7296
H	6.67372	-3.01812	-3.18868
H	8.25636	-2.23261	-3.02543
H	8.61854	-4.84182	-3.11562
H	-5.84368	-1.12261	-1.93515
H	-5.05186	-0.61463	-3.43853
H	-2.8809	-1.49649	-2.66125
H	-3.49168	-1.60297	-1.01782

CyCE3 with hydrogen bond

C	3.72632	-5.28575	1.89816
C	2.97855	-6.12866	1.07338
C	1.84854	-5.66028	0.39654
C	1.50678	-4.32008	0.56614
C	2.25791	-3.45276	1.36911
C	3.36412	-3.94038	2.05353
N	0.40624	-3.6281	0.02962
C	0.3634	-2.34287	0.48054
C	1.61982	-2.07088	1.33036
C	2.50066	-1.04648	0.53974
C	1.27263	-1.58195	2.75346
C	3.88198	-0.72653	1.12512
C	4.63369	0.29456	0.25988
C	6.05674	0.55394	0.76703
C	6.79122	1.58256	-0.05456
O	8.15629	1.51057	0.15649

O	6.31943	2.39914	-0.80649
C	-0.67274	-1.48205	0.13886
C	-0.57658	-4.2838	-0.85014
C	-0.85836	-0.14046	0.49509
C	-1.9907	0.52084	0.01319
C	-2.44051	1.79768	0.32821
C	-3.66629	2.21404	-0.22232
C	-4.45479	3.32251	0.03168
N	-5.68926	3.45349	-0.54394
C	-6.32274	4.64076	-0.12452
C	-5.4727	5.32765	0.75175
C	-4.19315	4.5276	0.94197
C	-7.5799	5.13293	-0.46691
C	-7.96982	6.35431	0.09238
C	-7.13121	7.0533	0.96335
C	-5.87233	6.53742	1.2996
C	-2.95497	5.3236	0.46902
C	-4.03683	4.09434	2.41947
C	-6.28199	2.45648	-1.44985
C	8.90799	2.47807	-0.57429
C	10.35609	2.05577	-0.33211
N	11.4132	2.90501	-1.03241
C	11.25153	2.84453	-2.53285
C	12.76888	2.34509	-0.66884
C	11.3442	4.34259	-0.57565
C	-6.62527	1.10832	-0.75241
C	-1.65879	-5.05746	-0.07856
C	-2.51554	-5.89543	-1.0329
S	-3.87883	-6.77822	-0.17192
C	-5.85615	-1.32363	-0.54454
C	-6.06924	-0.13424	-1.48413
S	-4.69717	-2.57896	-1.20212
O	-4.55048	-3.53496	-0.06204
O	-3.4233	-1.81559	-1.47045
O	-5.31915	-3.13338	-2.42256
H	4.58563	-5.67733	2.43309
H	3.2639	-7.17051	0.96719
H	1.25356	-6.32824	-0.21496
H	3.93603	-3.30104	2.71899
H	1.92939	-0.11713	0.43813
H	2.63272	-1.43369	-0.47796
H	0.83551	-0.58089	2.74589
H	0.55894	-2.25962	3.22807
H	2.17031	-1.55461	3.37755
H	4.47513	-1.64537	1.19368
H	3.78582	-0.33507	2.14621
H	4.08652	1.24268	0.22458
H	4.68412	-0.06545	-0.77483
H	6.65353	-0.36459	0.78937
H	6.04062	0.92352	1.80229
H	-1.48305	-1.89053	-0.46358
H	-1.03831	-3.52615	-1.48563
H	-0.00574	-4.95184	-1.50408
H	-0.1602	0.3864	1.14273
H	-2.62583	-0.07858	-0.63978
H	-1.87893	2.42833	1.01496
H	-4.08596	1.49147	-0.90916
H	-8.24519	4.59988	-1.1367
H	-8.9447	6.76097	-0.15747
H	-7.45723	7.9988	1.38417
H	-5.22406	7.08057	1.98162
H	-2.04367	4.72537	0.55499
H	-2.83336	6.22136	1.08276
H	-3.06227	5.636	-0.57304
H	-3.95362	4.97952	3.05731
H	-4.90194	3.51579	2.75346
H	-3.14145	3.48444	2.56371
H	-7.16385	2.91618	-1.89575
H	-5.57177	2.29197	-2.26762
H	8.62466	2.44872	-1.63034
H	8.69141	3.48297	-0.19738
H	10.58294	2.09408	0.73561
H	10.50144	1.02991	-0.67745
H	11.27278	1.80094	-2.84782
H	12.07625	3.38917	-2.99287
H	10.306	3.30282	-2.81695
H	12.89437	2.39637	0.41276
H	12.82439	1.30883	-1.0025
H	13.53857	2.93828	-1.1628
H	11.42737	4.37171	0.51112
H	12.1715	4.89059	-1.02706
H	10.39912	4.78053	-0.89204
H	-6.21034	1.13842	0.26013
H	-7.71019	1.02659	-0.62854
H	-1.19484	-5.70906	0.6705
H	-2.3103	-4.34774	0.43855
H	-2.96182	-5.26851	-1.80868
H	-1.91598	-6.66962	-1.52456
H	-4.60415	-5.64982	0.01968
H	-6.78568	-1.85205	-0.31716
H	-5.41125	-0.99908	0.40159
H	-5.0979	0.10343	-1.93438
H	-6.7191	-0.42527	-2.3154

CyCE4

C	-7.20217	1.60097	-2.12528
C	-7.87319	1.21266	-0.96398
C	-7.26463	0.37076	-0.0278
C	-5.96515	-0.0501	-0.29616
C	-5.27057	0.33823	-1.44539
C	-5.89606	1.15967	-2.37508
N	-5.14789	-0.91706	0.46414
C	-3.96077	-1.15883	-0.15873
C	-3.88538	-0.29105	-1.43334
C	-2.76333	0.77341	-1.16905
C	-3.6469	-1.09693	-2.73045
C	-2.53305	1.8488	-2.23752
C	-1.36175	2.75525	-1.82927
C	-1.09186	3.87826	-2.84788
C	0.15794	4.66379	-2.5166
O	0.06468	5.23818	-1.28105
O	1.13194	4.78509	-3.22051
C	-2.97216	-1.96329	0.40077
C	-5.59049	-1.51838	1.72214
C	-1.75269	-2.3169	-0.1926

C	-0.68514	-2.89856	0.48277
C	0.51531	-3.22939	-0.15342
C	1.6985	-3.52302	0.52209
C	2.92793	-3.85594	-0.0492
N	4.08258	-3.81166	0.66287
C	5.17216	-4.3186	-0.08855
C	4.71209	-4.67786	-1.35845
C	3.23142	-4.35245	-1.47108
C	6.50187	-4.47649	0.29179
C	7.37935	-5.01857	-0.65302
C	6.93561	-5.38351	-1.92631
C	5.59366	-5.21023	-2.28838
C	3.03233	-3.22251	-2.51789
C	2.3949	-5.5983	-1.83315
C	4.23197	-3.10737	1.95133
C	1.27739	5.82291	-0.79036
C	1.0345	5.93747	0.71252
N	2.09395	6.73523	1.47242
C	3.49549	6.38009	1.02448
C	1.95761	6.38582	2.93624
C	1.87122	8.20806	1.28697
C	3.89354	-1.63074	1.82389
C	-6.22577	-2.90375	1.52511
C	-6.69785	-3.49955	2.85329
S	-7.41121	-5.17129	2.53782
C	4.49174	-0.85611	0.82086
C	4.10374	0.46636	0.62308
C	3.1189	1.02779	1.43855
C	2.56228	0.28903	2.48173
C	2.94859	-1.03873	2.66801
S	2.48677	2.67546	1.05553
O	3.60126	3.36809	0.34138
O	2.16632	3.30081	2.37802
O	1.28127	2.45918	0.21326
H	-7.69836	2.24414	-2.8445
H	-8.88696	1.55661	-0.78629
H	-7.80372	0.05563	0.85856
H	-5.39105	1.45411	-3.28912
H	-1.82448	0.2327	-1.00926
H	-2.98831	1.26825	-0.21651
H	-2.62094	-1.46125	-2.81406
H	-4.32529	-1.95173	-2.79243
H	-3.83459	-0.46114	-3.59879
H	-3.4379	2.45388	-2.37005
H	-2.31539	1.38595	-3.2089
H	-0.45229	2.16045	-1.69312
H	-1.5622	3.20367	-0.85097
H	-1.94337	4.57002	-2.87794
H	-0.94963	3.47802	-3.85507
H	-3.13391	-2.32617	1.41175
H	-4.73531	-1.5726	2.40147
H	-6.30258	-0.82708	2.17958
H	-1.6034	-2.10717	-1.24706
H	-0.75539	-3.02837	1.56131
H	0.52398	-3.18466	-1.23898
H	1.67647	-3.40096	1.5998
H	6.86112	-4.20471	1.27792
H	8.42174	-5.15832	-0.38587
H	7.63571	-5.80455	-2.64018
H	5.25504	-5.49169	-3.28118
H	1.97715	-2.9823	-2.66495
H	3.43645	-3.55	-3.47972
H	3.55499	-2.30984	-2.22105
H	2.68585	-5.96538	-2.82148
H	2.55294	-6.40394	-1.1115
H	1.32735	-5.36494	-1.85748
H	3.59801	-3.5895	2.70207
H	5.26428	-3.25595	2.2724
H	2.11776	5.16157	-1.00953
H	1.44269	6.78995	-1.28105
H	0.08117	6.43508	0.907
H	1.01429	4.93937	1.15141
H	3.61645	5.2924	1.03038
H	4.19342	6.86496	1.70825
H	3.64802	6.76281	0.01543
H	0.93786	6.61372	3.25043
H	2.16293	5.31752	3.04447
H	2.66615	6.99243	3.50197
H	0.89237	8.47386	1.68742
H	2.65085	8.75197	1.8215
H	1.91716	8.45039	0.22567
H	-7.07132	-2.81726	0.83396
H	-5.49503	-3.57123	1.05524
H	-5.86062	-3.58973	3.55213
H	-7.46053	-2.8614	3.30937
H	-7.76478	-5.43419	3.81148
H	5.25123	-1.29267	0.17716
H	4.55184	1.07319	-0.15597
H	1.82594	0.75208	3.12959
H	2.49628	-1.62234	3.46686

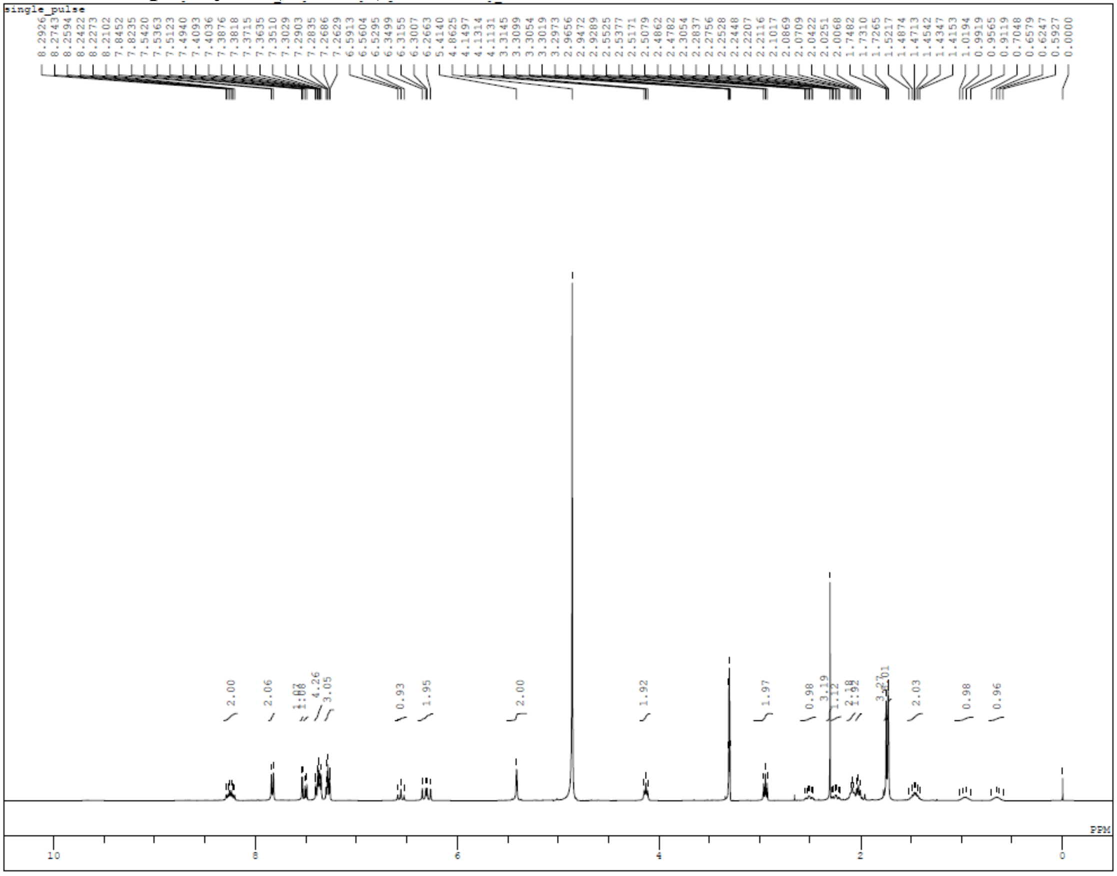
CyCE5

C	3.99085	5.27346	2.70962
C	4.1028	5.889	1.4607
C	3.24206	5.55214	0.41179
C	2.27815	4.57904	0.66088
C	2.15628	3.94767	1.90067
C	3.0124	4.2977	2.9375
N	1.25609	4.10755	-0.20174
C	0.41291	3.26945	0.46087
C	1.01914	2.9418	1.83811
C	1.57304	1.47572	1.66789
C	0.06813	3.09161	3.03857
C	2.53306	0.9281	2.73318
C	2.94821	-0.49806	2.33752
C	4.02717	-1.12775	3.24675
C	4.38749	-2.47286	2.65797
O	5.48154	-2.38174	1.8515
O	3.75225	-3.49412	2.78989
C	-0.75133	2.7723	-0.12751
C	1.41223	4.14954	-1.68161
C	-1.63952	1.84449	0.41594
C	-2.80553	1.41096	-0.22041
C	-3.66239	0.46823	0.34044
C	-4.83614	0.00866	-0.2696

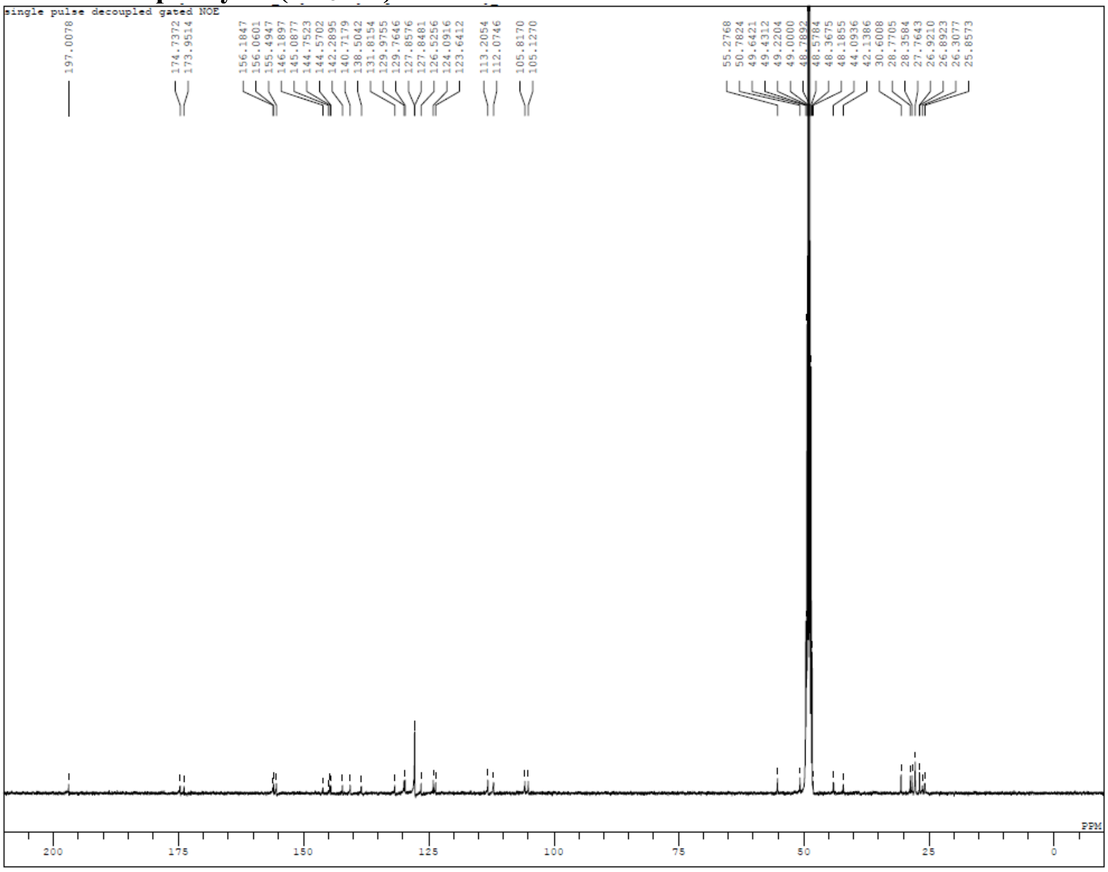
C	-5.72633	-0.93018	0.24564
N	-6.8312	-1.34385	-0.43347
C	-7.5946	-2.26327	0.32421
C	-6.94955	-2.49123	1.54108
C	-5.67943	-1.65821	1.6027
C	-8.79434	-2.88385	-0.01194
C	-9.34072	-3.76891	0.92336
C	-8.70528	-4.01415	2.14304
C	-7.50078	-3.3728	2.46006
C	-5.74971	-0.66513	2.78801
C	-4.43957	-2.57972	1.71238
C	-7.23925	-0.89064	-1.76353
C	5.66514	-3.48796	0.95672
C	6.69618	-2.96758	-0.03916
N	7.06012	-3.93723	-1.16341
C	7.92144	-3.17389	-2.14557
C	7.83434	-5.10521	-0.62387
C	5.84292	-4.4501	-1.90213
C	-8.10479	0.3786	-1.71895
C	2.19208	2.92378	-2.11856
C	3.58259	2.8825	-1.94538
C	4.27686	1.68094	-2.06959
S	-9.52849	2.36218	-2.98765
C	-8.53866	0.81136	-3.12142
C	1.52478	1.75875	-2.52432
C	2.21515	0.55507	-2.65622
C	3.58229	0.51119	-2.37763
H	-9.14975	-4.70471	2.85195
S	4.41027	-1.08425	-2.21477
O	5.87621	-0.77396	-2.25776
O	3.94607	-1.94457	-3.33018
O	3.97706	-1.57434	-0.86946
H	4.66335	5.55788	3.51215
H	4.86126	6.64824	1.29998
H	3.32502	6.0519	-0.54672
H	2.92695	3.83161	3.91384
H	2.08324	1.42084	0.69988
H	0.7097	0.8052	1.58977
H	-0.39148	4.08331	3.05335
H	-0.72789	2.34465	3.03703
H	0.62588	2.9685	3.97041
H	2.06556	0.92695	3.72677
H	3.42283	1.56439	2.79743
H	3.32218	-0.4981	1.30679
H	2.06935	-1.15406	2.34494
H	3.64522	-1.28193	4.26012
H	4.91341	-0.48851	3.29081
H	-1.00247	3.15154	-1.11321
H	0.4252	4.19919	-2.14243
H	1.9263	5.08001	-1.92567
H	-1.42318	1.40859	1.38637
H	-3.05182	1.82629	-1.19636
H	-3.38371	0.07374	1.31323
H	-5.06727	0.43788	-1.23983
H	-9.30134	-2.69565	-0.95167
H	-10.27591	-4.26914	0.69388
H	-7.0135	-3.566	3.41127
H	-4.85832	-0.0369	2.84843
H	-6.6228	-0.0129	2.70392
H	-5.83355	-1.2227	3.72507
H	-3.50775	-2.01044	1.73881
H	-4.50295	-3.16602	2.63337
H	-4.39097	-3.27612	0.87132
H	-6.33972	-0.73292	-2.36439
H	-7.78433	-1.71385	-2.23292
H	5.99474	-4.36883	1.51851
H	4.71174	-3.70203	0.47198
H	6.30437	-2.07008	-0.51956
H	7.63602	-2.73197	0.46688
H	8.19734	-3.84863	-2.95697
H	8.81628	-2.83188	-1.62365
H	7.341	-2.32163	-2.51003
H	8.13587	-5.74292	-1.45556
H	7.20719	-5.67207	0.06326
H	8.71754	-4.73488	-0.10242
H	6.19679	-5.09955	-2.70398
H	5.22354	-5.02383	-1.21485
H	5.27481	-3.61842	-2.32161
H	-8.98725	0.19262	-1.0971
H	-7.54007	1.18488	-1.23756
H	4.12278	3.78301	-1.66972
H	5.34701	1.62878	-1.90417
H	-9.80588	2.48513	-4.30072
H	-7.6647	0.99327	-3.75433
H	-9.14754	0.0328	-3.59034
H	0.45479	1.7834	-2.70932
H	1.69965	-0.35355	-2.94873

4. NMR spectra

^{1}H NMR of proCyC2 (CD_3OD)



^{13}C NMR of proCyC2 (CD_3OD)



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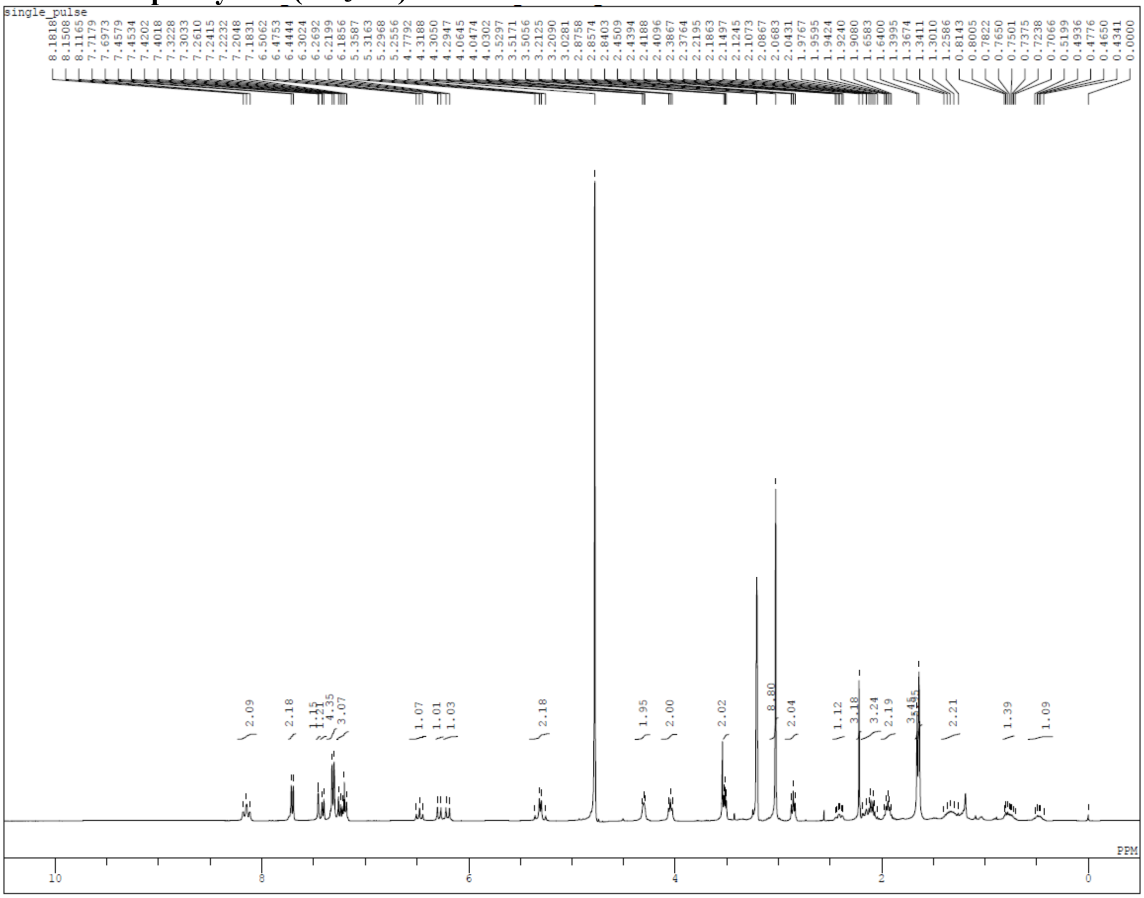
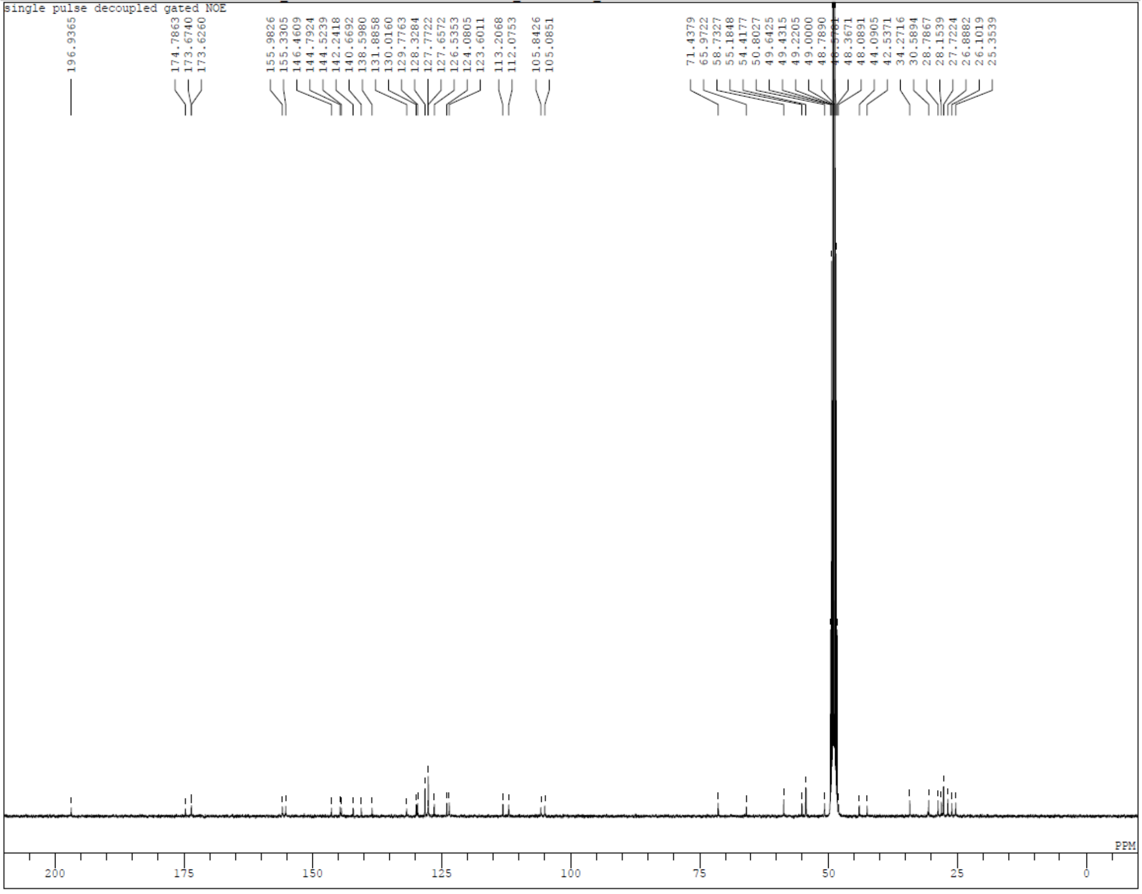
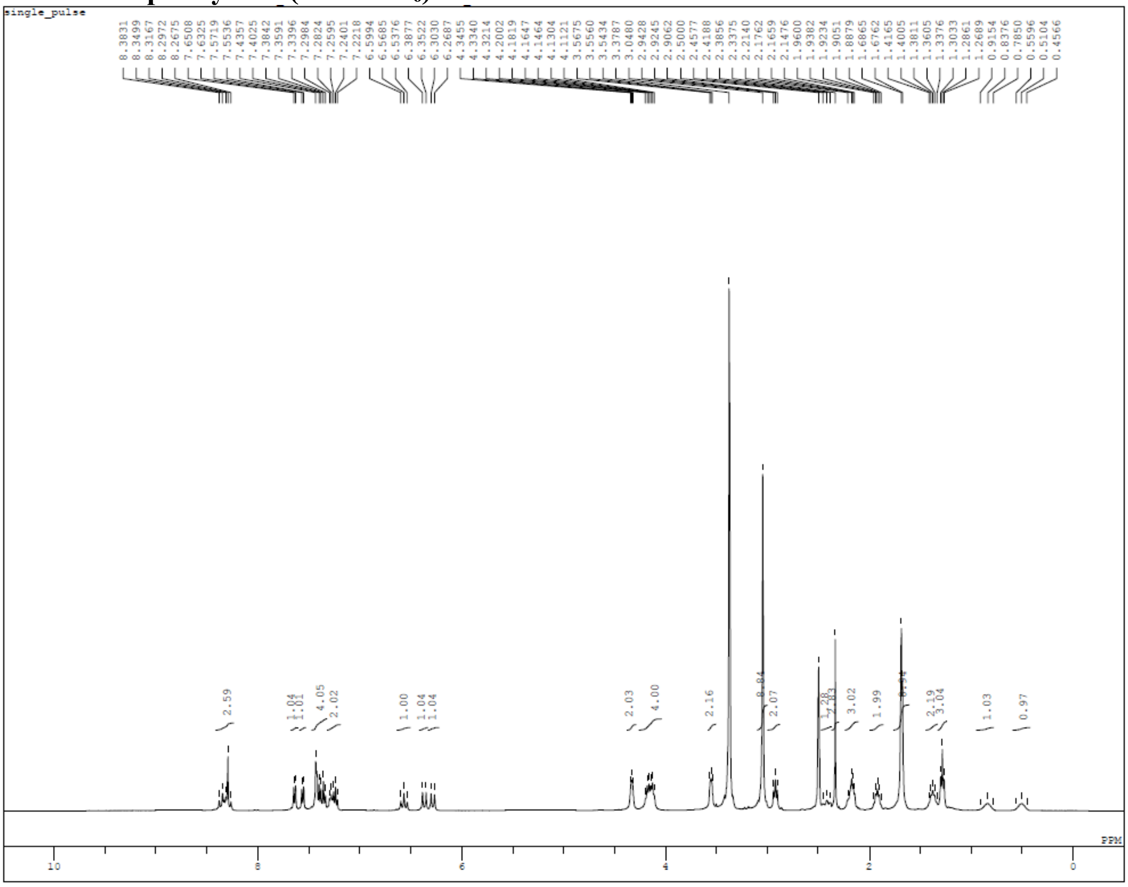


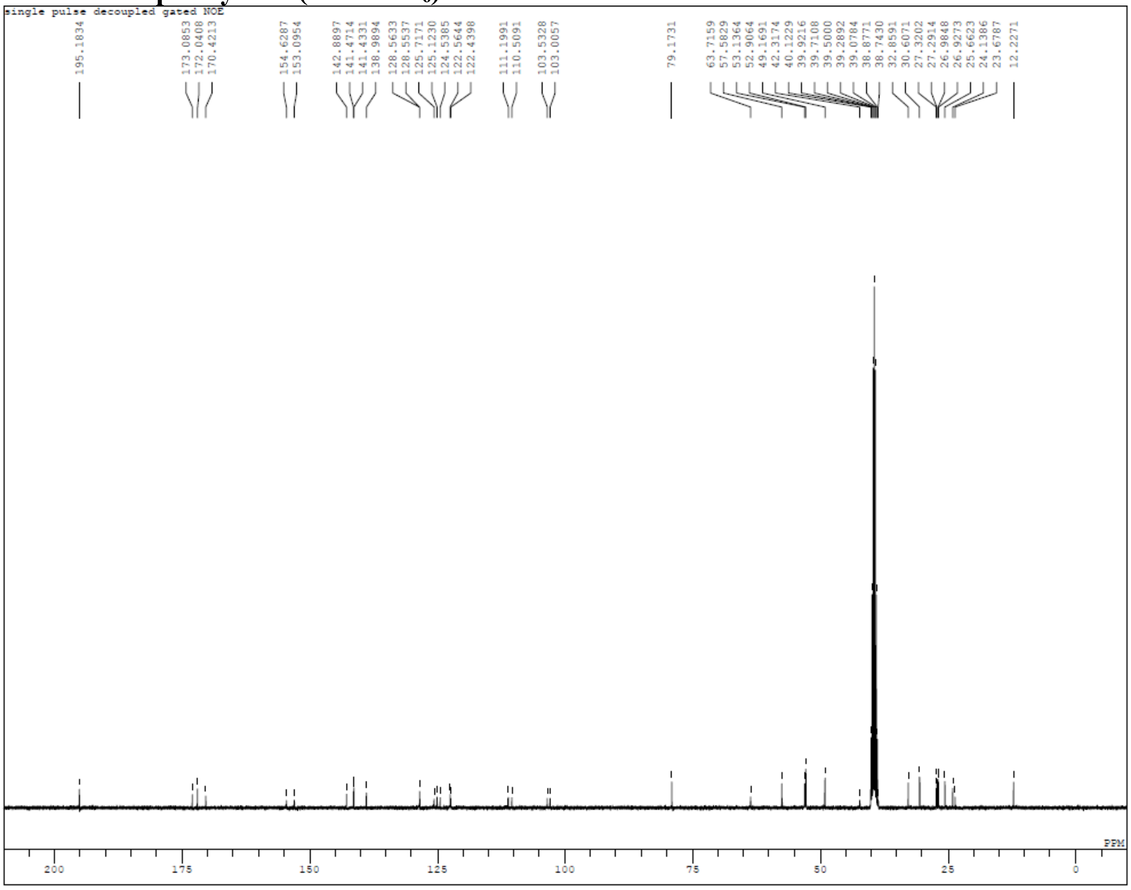
^{13}C NMR of proCyCE2 (CD_3OD)



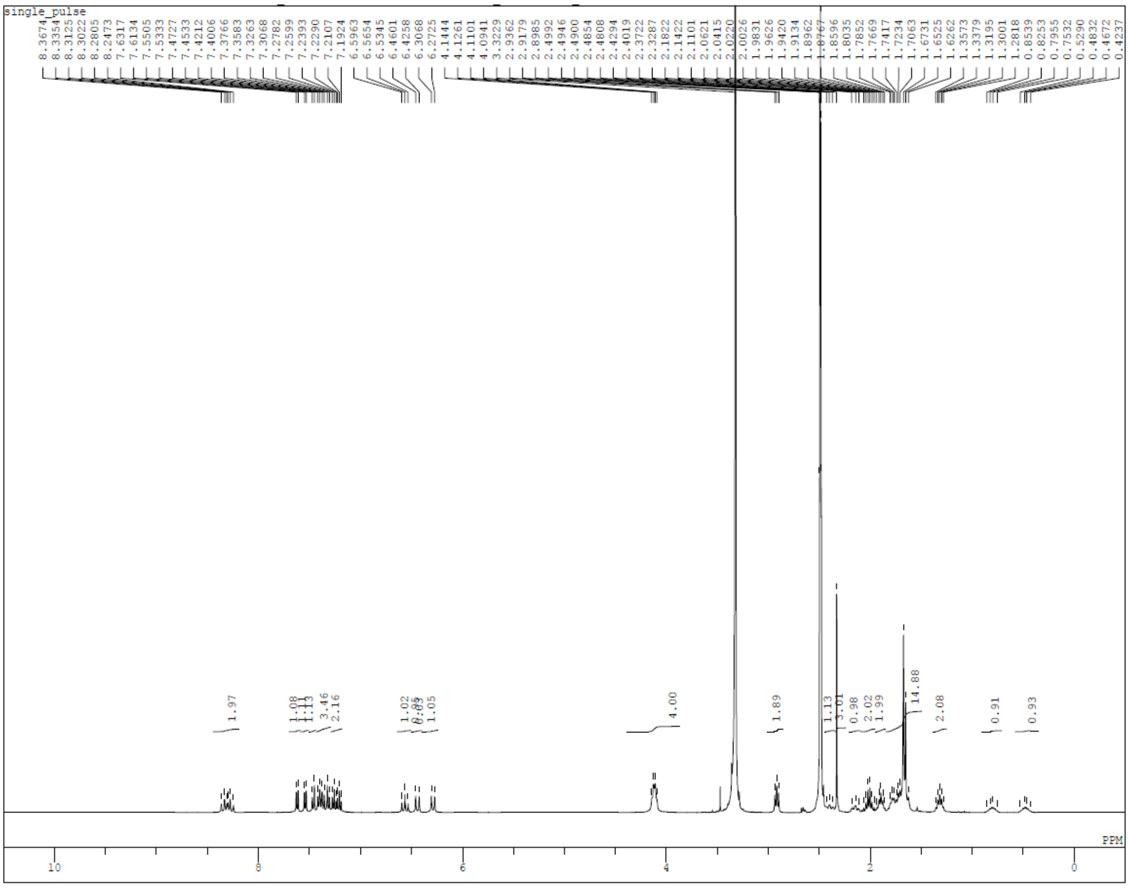
^{1}H NMR of proCyCE1 (DMSO-d_6)



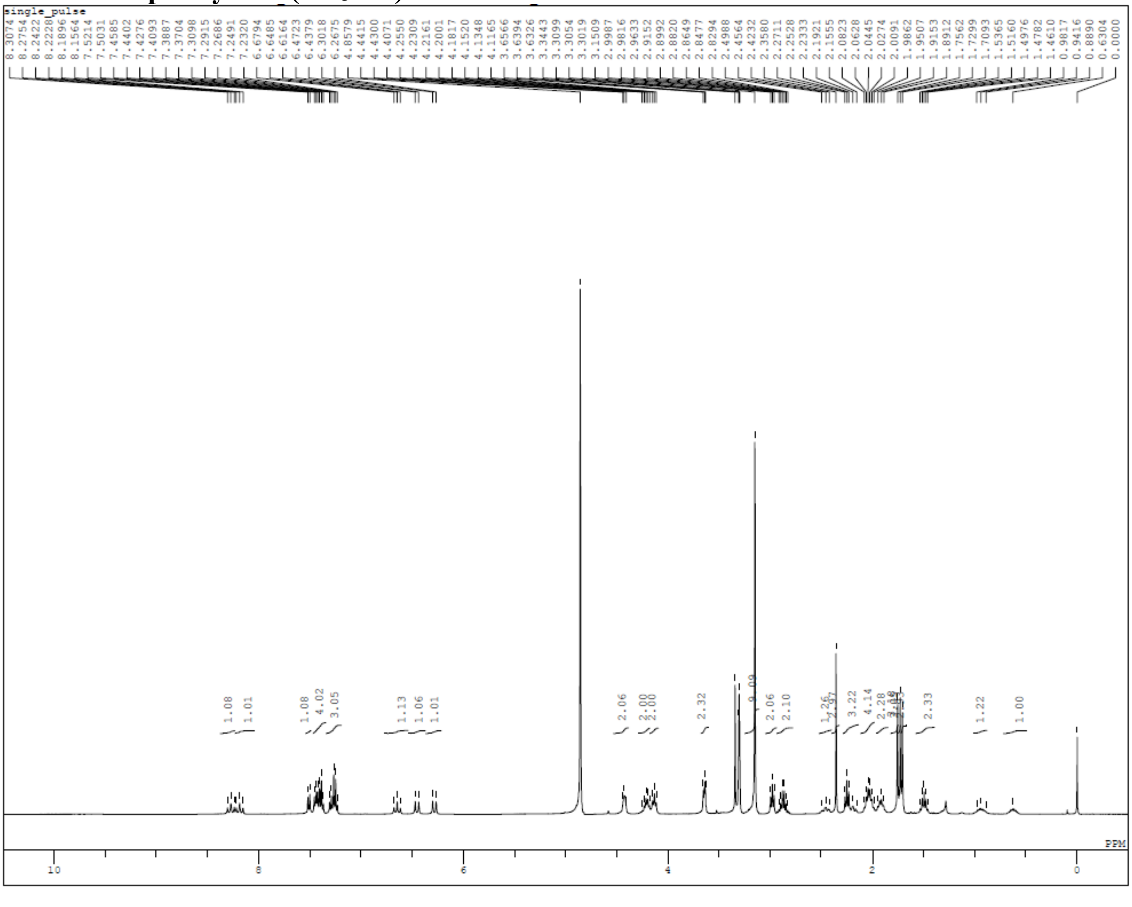
^{13}C NMR of proCyCE1 (DMSO-d_6)



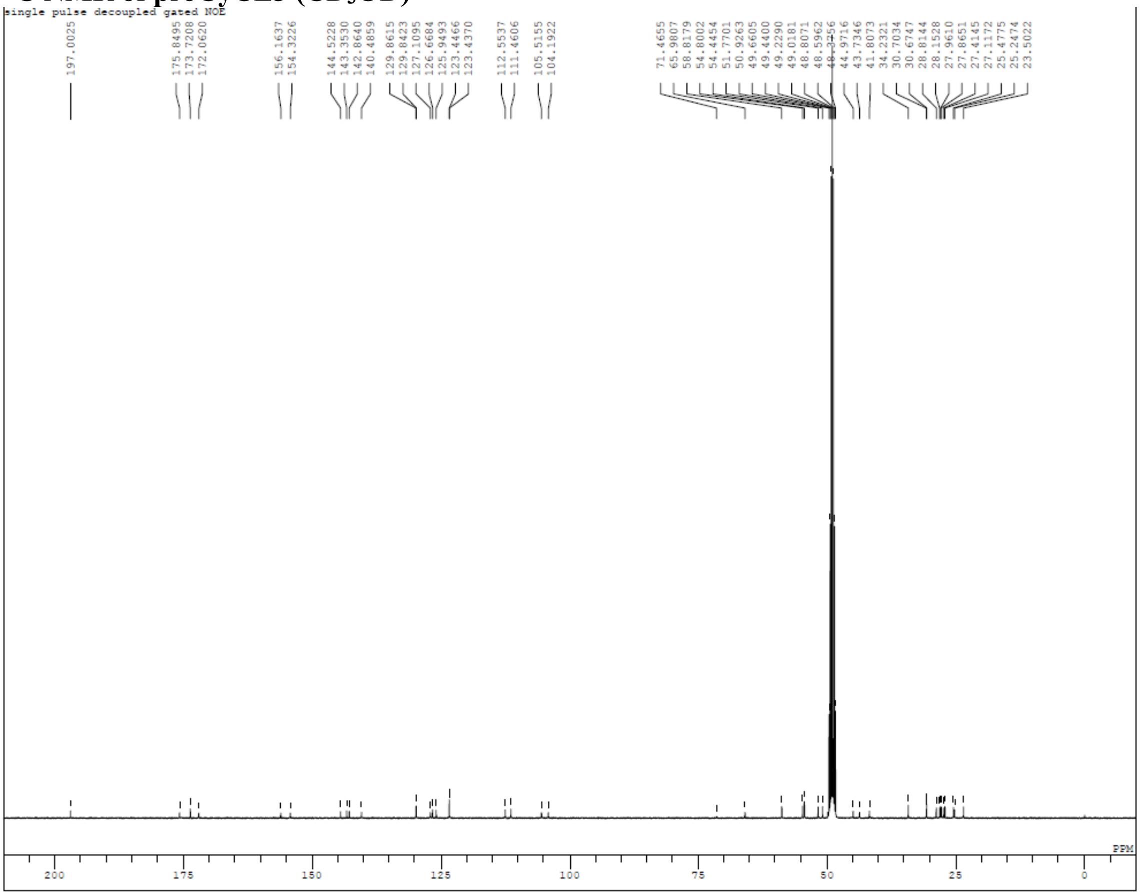
^{1}H NMR of proCyC3 (DMSO-d_6)



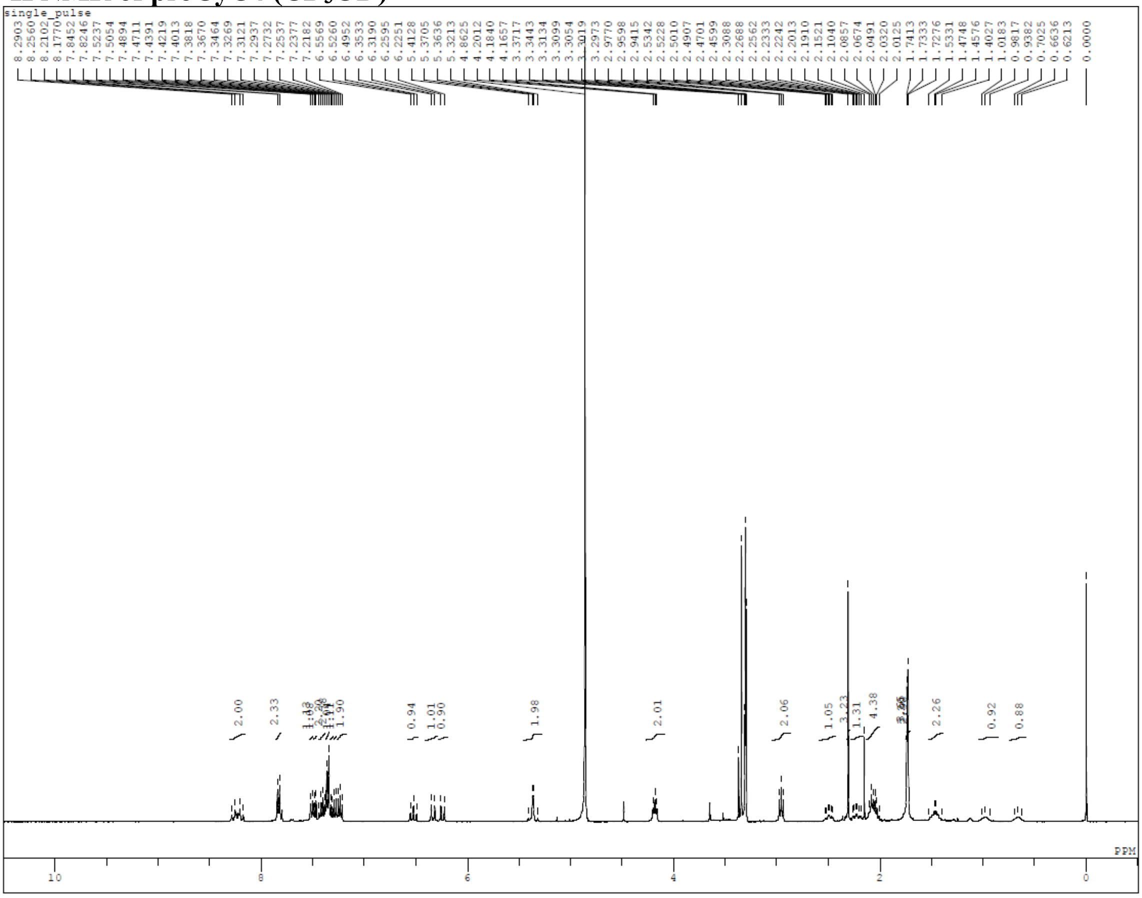
^{1}H NMR of proCyCE3 (CD_3OD)



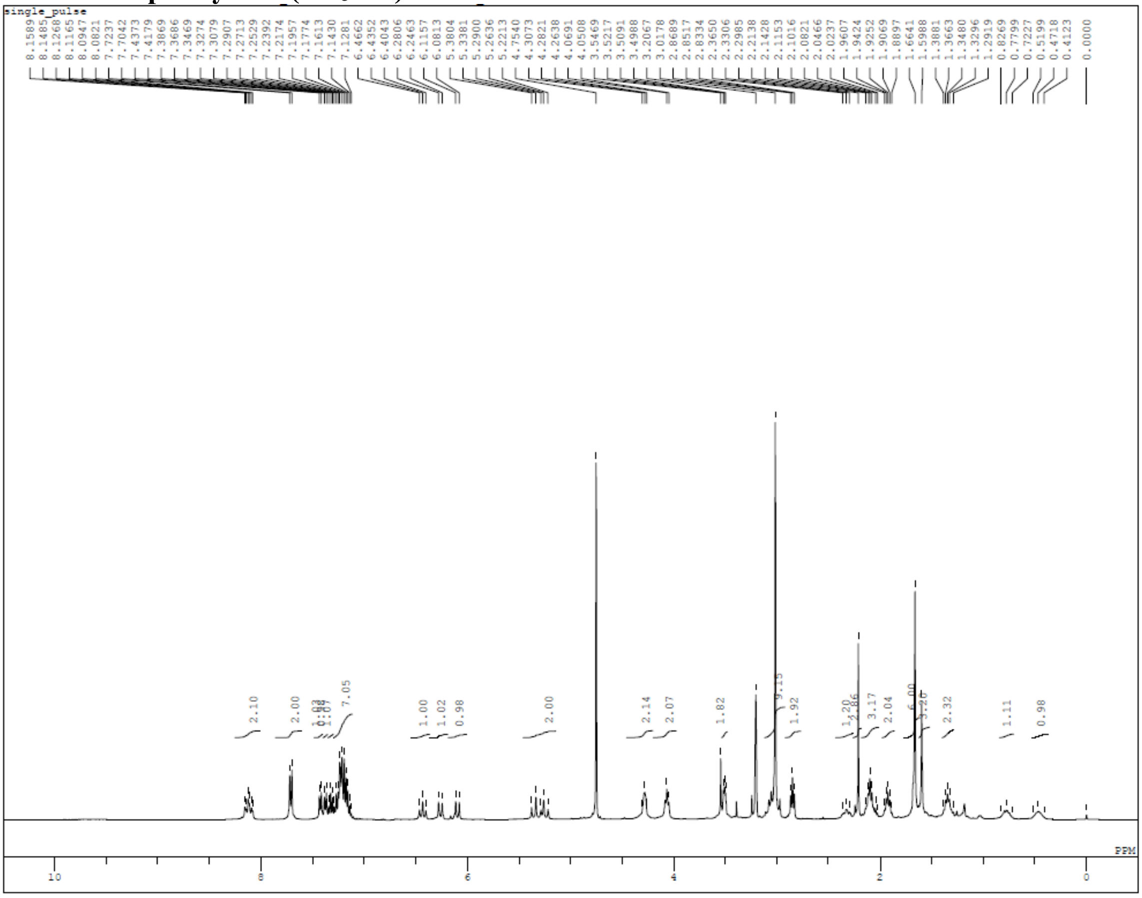
^{13}C NMR of proCyCE3 (CD_3OD)



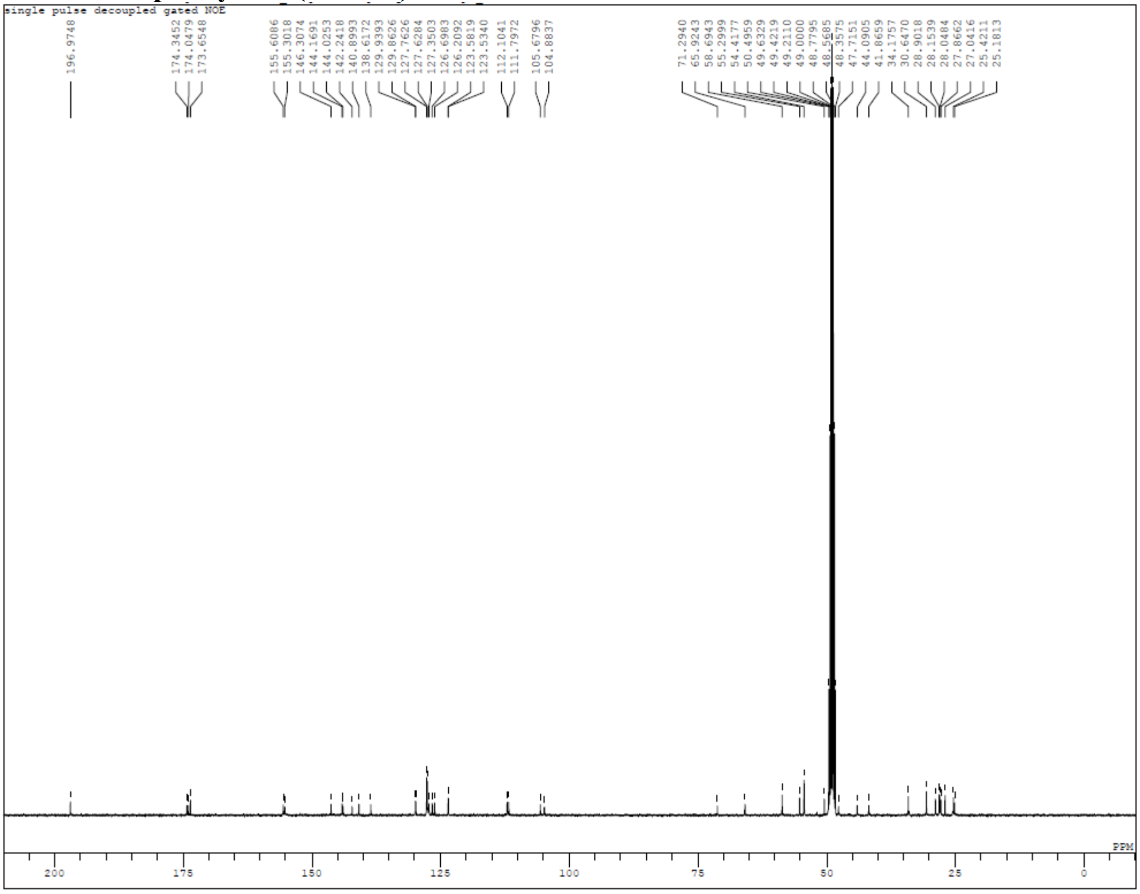
^{1}H NMR of proCyC4 (CD_3OD)



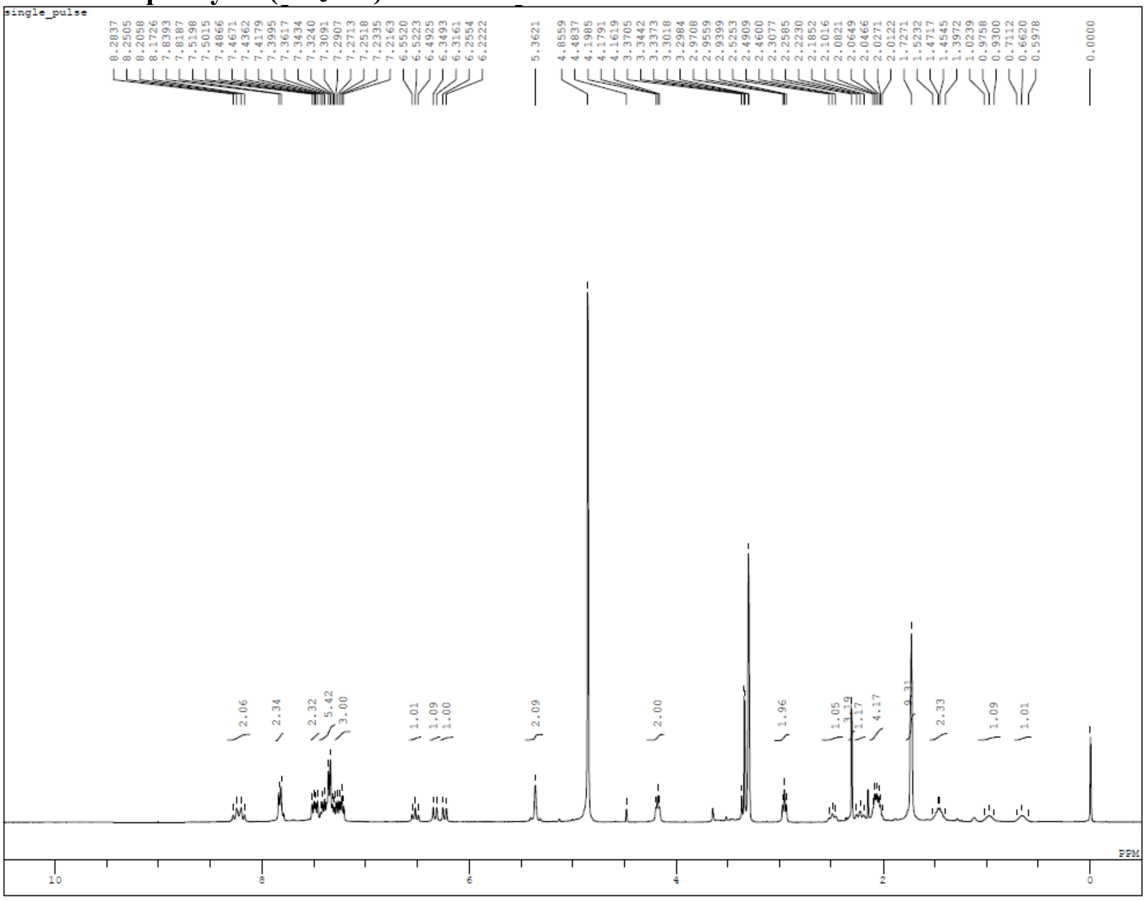
^{1}H NMR of proCyCE4 (CD_3OD)



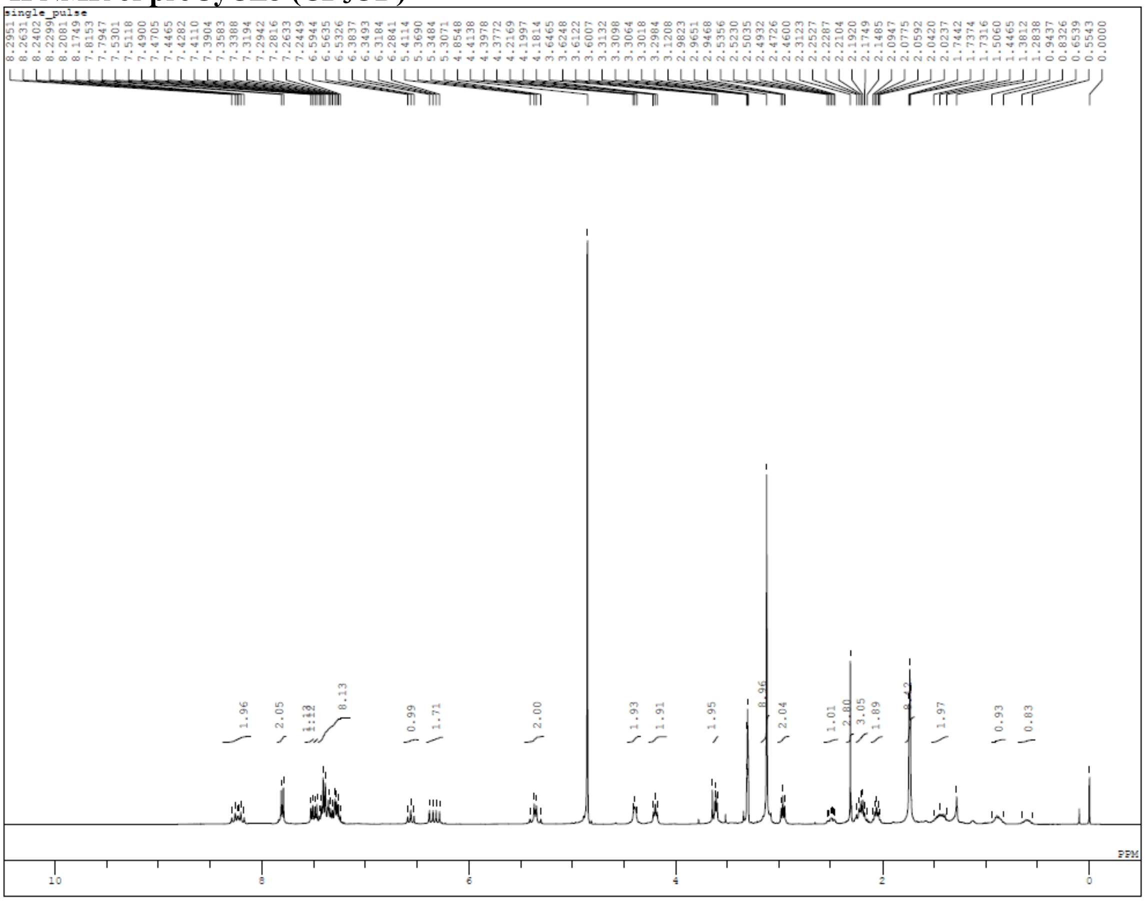
^{13}C NMR of proCyCE4 (CD_3OD)



^{1}H NMR of proCyC5 (CD_3OD)



^{1}H NMR of proCyCE5 (CD_3OD)



^{13}C NMR of proCyCE5 (CD_3OD)