Supporting information for

An Esterase-activated Click and Release Approach to Metal-free CO-prodrugs

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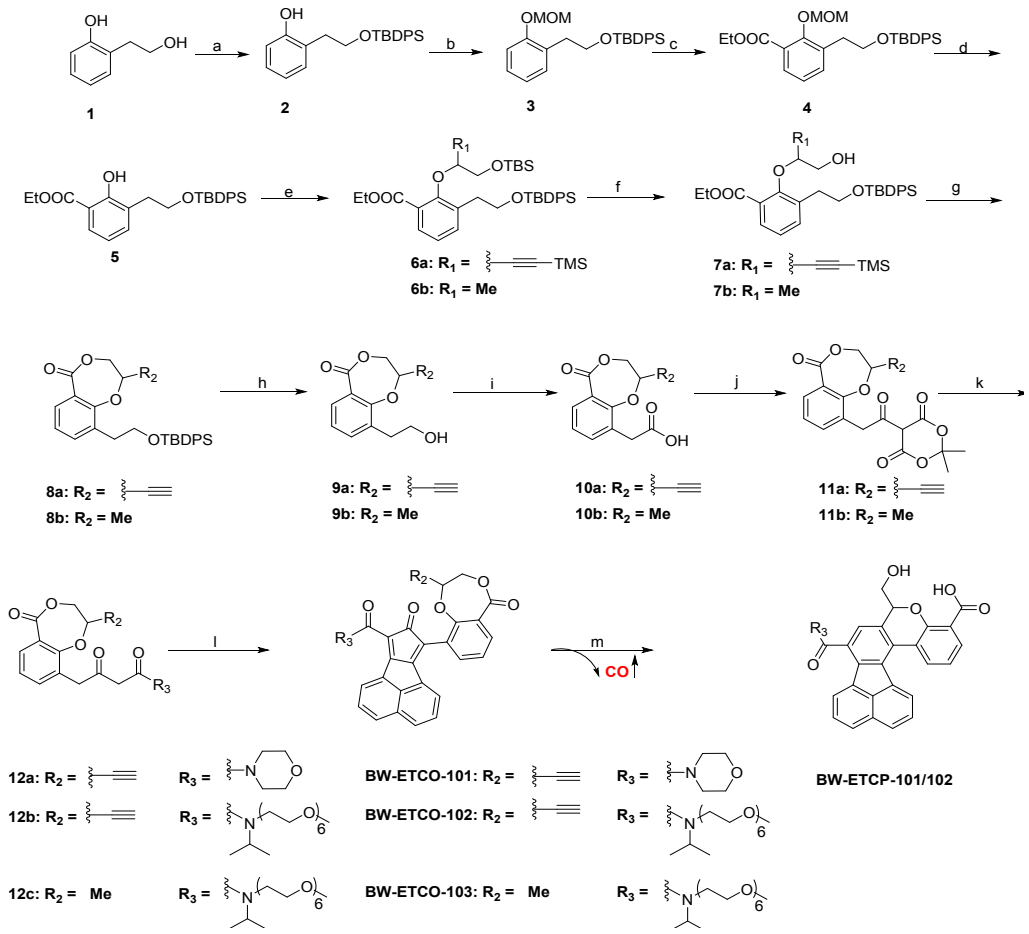
1. Synthetic procedure for the CO prodrugs

General information

All reagents and solvents were of reagent grade. Column chromatography was carried out using flash silica gel (Sorbent 230–400 mesh) and P-2 Gel (Bio-Gel, particle size range 45- 90 μm). TLC analysis was conducted on silica gel plates (Sorbent Silica G UV254). NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C on an Avance Bruker instrument. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and hertz, respectively, using the respective solvent (^{1}H NMR, ^{13}C NMR) as the internal reference.



Scheme S1. Synthetic route to esterase sensitive CO prodrugs. Reagents and conditions: a) imidazole, DMF, TBDPSCl, r.t., 90%; b) NaH, MOMCl, DMF, 0 °C-r.t., 90%; c) *n*-BuLi, TMEDA, r.t., 1h, then EtOCOCl, -78 °C-r.t., 78%; d) CBr_4, *i*-PrOH, reflux, 70%; e) DIAD, PPh_3, THF, 0 °C-r.t., 75-76%; f) 10% HCl, THF/H_2O, r.t., 82-84%; g) KOH, MeOH/H_2O; then Ac_2O, reflux, 70-74%; h) TBAF, THF, r.t., 85-90%; i) Jones' reagent, acetone/H_2O, 0 °C-r.t., 65-68%; j) EDC, DMAP, r.t., 73-75%; k) amines, TMSCl, chlorobenzene, reflux, 70-75%; l) Et_3N, THF/MeOH, r.t.; then Ac_2O, H_2SO_4, 60-68%; m) 5% DMSO/PBS, porcine liver esterase (10 U/mL), 37 °C.

Synthesis of compound 2

Compound **1** (2.0 g, 14.5 mmol) and imidazole (1.5 g, 21.7 mmol) were dissolved in anhydrous DMF (10 mL) under N_2. Then TBDPSCl (4.2 g, 15.2 mmol) was added dropwise at room temperature. The resulting mixture was stirred for another 1 h at room temperature. Then the mixture was poured into water, and extracted with ethyl acetate (3 × 40 mL). The obtained organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was triturated with hexane, and the formed precipitate was filtered as the title compound **2**. Yield: 90%. ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1H), 7.66 (d, *J* = 6.8 Hz, 4H), 7.51 – 7.39 (m, 6H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.90 (t, *J* = 7.2 Hz, 1H), 3.92 (t, *J* = 5.2 Hz, 2H), 2.98 (t, *J* = 5.2 Hz, 2H), 1.13 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 155.8, 135.6, 132.0, 130.9, 130.1, 128.4, 127.9, 126.9, 120.4, 117.1, 66.8, 35.1, 26.7, 18.9. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{24}H_{28}O_2SiNa$ 399.1756, found 399.1744.

Synthesis of compound 3

To a solution of compound **2** (1.5 g, 4 mmol) in dry DMF (25 mL) at 0 °C was added NaH (191 mg, 4.8 mmol) portion wise. Then the resulting mixture was stirred at 0 °C for another 0.5 h, followed by the dropwise addition of MOMCl (480 mg, 6 mmol). The resulting mixture was stirred for another 4 h at room temperature. The reaction mixture was poured into ice-water, and extracted with ethyl acetate (3 × 40 mL). The obtained organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After filtration and concentration, the obtained residue was purified on a silica gel column to afford compound **3** as a colorless oil (yield: 90%). ^{1}H NMR ($CDCl_3$): δ 7.76 – 7.61 (m, 4H), 7.54 – 7.37 (m, 6H), 7.28 – 7.20 (m, 2H), 7.17 – 7.06 (m, 1H), 6.99 (td, *J* = 7.4, 1.1 Hz, 1H), 5.14 (s, 2H), 3.96 (t, *J* = 7.2 Hz, 2H), 3.40 (s, 3H), 3.05 (t, *J* = 7.2Hz, 2H), 1.13 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 155.4, 135.6, 134.0, 131.4, 129.5, 127.6, 127.5, 121.4, 113.6, 94.1, 63.8, 55.9, 34.1, 26.8, 19.2. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{26}H_{32}O_3SiNa$ 443.2025, found 443.2018.

Synthesis of compound 4

To a solution of compound **3** (1.0 g, 2.4 mmol) in anhydrous THF (30 mL) at 0 °C was added TMEDA (417 mg, 3.6 mmol), followed by the dropwise addition of *n*-BuLi (1.8 mL, 3.6 mmol, 2M in hexane) under N_2. The resulting solution was stirred for another 1 h at room temperature. The obtained brownish solution was cooled to -78 °C, followed by dropwise addition of ethyl chloroformate (520 mg, 4.8 mmol). A white precipitate was formed immediately. The resulting mixture was stirred with temperature slowly warming to room temperature (around 1 h). Then the reaction mixture was poured into saturated solution of NH_4Cl, and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the obtained residue was purified on a silica gel column to afford compound **4** as a colorless oil (yield: 78%).

^{1}H NMR ($CDCl_3$): δ 7.74 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.6 Hz, 4H), 7.49 – 7.33 (m, 7H), 7.10 (t, *J* = 7.6 Hz, 1H), 5.03 (s, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.95 (t, *J* = 6.8 Hz, 2H), 3.54 (s, 3H), 3.06 (t, *J* = 6.8 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 166.4, 156.2, 135.6, 135.4, 133.9, 133.8, 129.7, 129.6, 127.6, 124.9, 123.6, 101.4, 63.8, 61.0, 57.4, 33.7, 26.9, 19.2, 14.3. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{29}H_{36}O_5SiNa$ 515.2238, found 515.2230.

Synthesis of compound 5

A solution of compound **4** (500 mg, 1.0 mmol) and CBr_4 (497 mg, 1.5 mmol) in isopropanol (20 mL) was heated under reflux for 3 h. Then the reaction mixture was dried, and purified on a silica gel column to afford compound **5** as a colorless oil (yield: 70%).

^{1}H NMR ($CDCl_3$): δ 10.99 (s, 1H), 7.75 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.69 – 7.56 (m, 4H), 7.50 – 7.31 (m, 7H), 6.80 (t, *J* = 7.7 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.92 (t, *J* = 6.7 Hz, 2H), 2.96 (t, *J* = 6.7 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 170.6, 160.1, 137.2, 135.6, 133.9, 129.5, 128.0, 127.6, 127.4, 118.3, 112.1, 62.9, 61.3, 33.3, 26.9, 19.2, 14.3. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{27}H_{32}O_4SiNa$ 471.1968, found 471.1984.

General procedure for the synthesis of compound 6a-b

To a solution of compound **5** (1 equiv.), substituted alcohol (1.5 equiv.) and PPh_3 (1.5 equiv.) in dry THF under N_2 was added DIAD (1.5 equiv.) dropwise at 0 ^oC. The resulting solution was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford compound **6a**/**6b** as a pale-yellow oil.

6a (yield: 75%). ^1H NMR ($CDCl_3$): δ 7.77 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.71 – 7.56 (m, 4H), 7.49 – 7.34 (m, 7H), 7.10 (t, *J* = 7.6 Hz, 1H), 4.91 (t, *J* = 5.6 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.10 – 3.79 (m, 4H), 3.39 (dt, *J* = 13.3, 6.5 Hz, 1H), 2.87 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 9H), 0.94 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.08 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 166.6, 155.2, 135.7, 135.6, 135.2, 135.1, 133.9, 133.8, 129.9, 129.5, 127.7, 127.6, 125.4, 123.6, 101.8, 93.2, 75.0, 65.7, 63.9, 60.9, 33.7, 26.9, 25.9, 19.2, 18.4, 14.3, -0.4, -5.2, -5.2. HRMS (ESI) $[M+H]^+$ calcd. for $C_{40}H_{58}O_5Si_3Na$ 725.3490, found 725.3500.

6b (yield: 76%). ^1H NMR ($CDCl_3$): δ 7.65 – 7.61 (m, 5H), 7.48 – 7.32 (m, 8H), 7.02 (t, *J* = 7.6 Hz, 1H), 4.38 (q, *J* = 6.8 Hz, 2H), 4.16 – 4.03 (m, 1H), 3.91 – 3.72 (m, 3H), 3.59 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.08 – 2.95 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 167.2, 155.7, 135.6, 134.8, 134.1, 133.9, 129.5, 127.6, 125.0, 122.6, 81.0, 66.1, 63.8, 60.9, 33.4, 26.8, 25.8, 21.6, 19.2, 18.2, 16.9, 14.3, -5.4. HRMS (ESI) $[M+H]^+$ calcd. for $C_{36}H_{52}O_5Si_2$ Na 643.3251, found 643.3243.

General procedure for the synthesis of 7a-b

To a solution of **6a**/**6b** (6 mmol) in THF (30 mL) was added 10% HCl (5 mL), and the resulting solution was stirred for 3 h at room temperature. The reaction mixture was extracted with ethyl acetate. The combine organic layer was washed with $NaHCO_3$ solution and brine successively, and was dried over anhydrous Na_2SO_4. After filtration

and concentration, the residue was purified on a silica gel column to afford compound **6a**/**6b** as a colorless oil.

7a (Yield: 82%). ^{1}H NMR ($CDCl_3$): δ 7.79 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.65 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.60 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.49 – 7.33 (m, 7H), 7.12 (t, *J* = 7.7 Hz, 1H), 4.86 (dd, *J* = 6.3, 3.9 Hz, 1H), 4.42 – 4.35 (m, 2H), 3.99 – 3.81 (m, 4H), 3.48 – 3.36 (m, 2H), 2.89 – 2.82 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.08 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 166.5, 155.6, 135.6, 135.5, 135.1, 133.7, 133.7, 129.9, 129.6, 129.6, 127.7, 127.6, 124.8, 123.9, 100.2, 94.4, 75.6, 65.6, 63.9, 61.3, 34.2, 26.8, 19.2, 14.3, -0.5. HRMS (ESI) $[M+H]^+$ calcd. for $C_{34}H_{44}O_5Si_2Na$ 611.2625, found 611.2635.

7b (Yield: 84%). ^{1}H NMR ($CDCl_3$): δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.65 – 7.60 (m, 4H), 7.50 – 7.32 (m, 7H), 7.08 (t, *J* = 7.6 Hz, 1H), 4.48 – 4.34 (m, 2H), 4.25 – 4.09 (m, 1H), 3.95 – 3.86 (m, 2H), 3.74 (d, *J* = 11.8 Hz, 1H), 3.60 (dd, *J* = 11.9, 5.6 Hz, 1H), 3.09 – 2.89 (m, 2H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 167.0, 155.8, 135.6, 135.3, 134.2, 133.7, 133.6, 129.7, 129.6, 127.7, 127.6, 125.0, 123.2, 81.5, 65.9, 63.7, 61.4, 33.5, 26.8, 19.2, 16.0, 14.2. HRMS (ESI) $[M+H]^+$ calcd. for $C_{30}H_{38}O_5SiNa$ 529.2386, found 529.2360.

General procedure for the synthesis of **8a**-**b**

A solution of **7a**/**7b** (1 equiv.) and KOH (2 equiv.) in methanol and water was stirred at room temperature for 4 h at room temperature. The reaction mixture was poured into ice/water, and was acidified with 10% HCl to adjust the pH value to around 2. Then the mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layer was washed with $NaHCO_3$ solution and brine successively, and was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was dissolved in Ac_2O, and was heated under reflux for 1 h. Then reaction mixture was dried, and the residue was purified on a silica gel column to afford compound **8a**/**8b** as colorless oil.

8a (Yield: 70%). ^{1}H NMR ($CDCl_3$): δ 7.65 – 7.62 (m, 3H), 7.56 – 7.53 (m, 3H), 7.47 – 7.29 (m, 6H), 7.20 (t, *J* = 7.6 Hz, 1H), 5.22 (ddd, *J* = 10.0, 4.4, 2.0 Hz, 1H), 4.35 (dd, *J* = 13.6, 4.4 Hz, 1H), 4.23 (dd, *J* = 13.6, 10.0 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.88 – 3.82

(m, 1H), 3.32 (dt, *J* = 12.5, 6.0 Hz, 1H), 2.88 (dt, *J* = 13.8, 7.1 Hz, 1H), 2.50 (d, *J* = 2.0 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 169.2, 149.8, 136.9, 135.6, 135.5, 133.8, 133.6, 133.5, 129.9, 129.6, 127.7, 124.8, 124.5, 70.3, 66.8, 63.7, 33.4, 26.9, 19.2. HRMS (ESI) $[M+H]^+$ calcd. for $C_{29}H_{30}O_4SiNa$ 493.1811, found 493.1829.

8b (Yield: 74%). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.48 – 7.31 (m, 7H), 7.11 (t, *J* = 7.6 Hz, 1H), 4.50 (br, 1H), 4.21 (d, *J* = 13.4 Hz, 1H), 4.04 (dd, *J* = 13.4, 5.5 Hz, 1H), 3.87 (q, *J* = 6.0 Hz, 2H), 3.03 – 2.98 (m, 1H), 2.91 – 2.86 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 169.9, 151.9, 136.5, 135.5, 133.7, 133.6, 131.9, 130.6, 129.6, 127.6, 123.3, 122.7, 99.9, 68.7, 63.6, 33.5, 26.8, 19.2, 17.7. HRMS (ESI) $[M+H]^+$ calcd. for $C_{28}H_{32}O_4SiNa$ 483.1968, found 483.1965.

General procedure for the synthesis of 9a-b

To a solution of **8a**/**8b** (1 equiv.) in THF was added a solution of TBAF (1.5 equiv.) in THF, and the resulting solution was stirred for 2-3 h. The reaction mixture was poured into ice/water, and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford compound **9a**/**9b** as colorless oil.

9a (Yield: 90%).^{1}H NMR ($CDCl_3$): δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 5.39 – 5.22 (m, 1H), 4.38 (dd, *J* = 13.6, 4.3 Hz, 1H), 4.24 (dd, *J* = 13.4, 10.3 Hz, 1H), 3.89 – 3.74 (m, 2H), 3.29 – 3.23 (m, 1H), 2.85 – 2.79 (m, 1H), 2.66 (s, 1H), 2.23 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 169.2, 149.8, 136.2, 133.3, 129.9, 125.2, 124.6, 77.3, 70.5, 66.8, 62.6, 33.2. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{12}O_4Na$ 255.0633, found 255.0632.

9b (Yield: 85%). ^{1}H NMR ($CDCl_3$): δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 4.71 – 4.67 (m, 1H), 4.31 (dd, *J* = 13.5, 2.8 Hz, 1H), 4.14 (dd, *J* = 13.5, 5.8 Hz, 1H), 3.82 (t, *J* = 6.5 Hz, 2H), 3.00 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.86 (dt, *J* = 13.4, 6.5 Hz, 1H), 1.43 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 169.9, 151.8,

135.9, 131.9, 130.6, 123.8, 123.2, 68.7, 62.6, 33.5, 17.7. HRMS (ESI) $[M+H]^+$ calcd. for $C_{12}H_{14}O_4Na$ 245.0790, found 245.0794.

General procedure for the synthesis of 10a-b

To a solution of **9a**/**9b** (1 equiv.) in acetone was added Jones' reagent (Prepared from 250 mg CrO_3, 0.25 mL H_2SO_4, and 0.75 mL H_2O) till the reaction mixture gave a reddish solution at 0 ^oC. Then reaction mixture was stirred for another 3 h at room temperature. The reaction mixture was then poured into icy water, and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford compound **10a**/**10b** as white solid.

10a (Yield: 65%). ^1H NMR (CD_3OD): δ 7.65 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.41 (ddd, *J* = 9.0, 4.2, 2.2 Hz, 1H), 4.52 (dd, *J* = 13.7, 4.2 Hz, 1H), 4.31 (dd, *J* = 13.7, 9.0 Hz, 1H), 4.01 (d, *J* = 16.8 Hz, 1H), 3.70 (d, *J* = 16.8 Hz, 1H), 3.23 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (CD_3OD): δ 173.5, 169.7, 150.2, 136.4, 130.2, 129.4, 124.6, 124.4, 77.8, 77.1, 70.8, 66.9, 34.8. HRMS (ESI) $[M-H]^-$ calcd. for $C_{13}H_9O_5$ 245.0450, found 245.0444.

10b (Yield: 68%). ^1H NMR ($CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 4.78 – 4.65 (m, 1H), 4.35 (d, *J* = 13.6 Hz, 1H), 4.21 (dd, *J* = 13.6, 5.4 Hz, 1H), 3.77 (d, *J* = 16.4 Hz, 1H), 3.66 (d, *J* = 16.4 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 177.0, 169.4, 152.3, 136.2, 132.3, 126.7, 123.3, 121.9, 77.8, 68.8, 35.8, 17.7. HRMS (ESI) $[M-H]^-$ calcd. for $C_{12}H_{11}O_5$ 235.0606, found 235.0617.

General procedure for the synthesis of 11a-b

To a solution of compound **10a**/**b** (1 equiv.), 2, 2-dimethyl-1,3-dioxane-4,6-dione (1.4 equiv.), and DMAP (1.4 equiv.) in DCM was added EDC (1.4 equiv.) portion wise at 0 ^oC. The resulting mixture was stirred overnight at room temperature. Then the reaction mixture was diluted with DCM (30 mL), and washed with HCl 5% solution and brine

successively. The obtained organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford compound **11a**/**11b** as yellow solid.

11a (Yield: 75%).^{1}H NMR ($CDCl_3$) δ 15.46 (s, 1H), 7.73 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 5.33 – 5.30 (m, 1H), 4.88 (d, *J* = 17.5 Hz, 1H), 4.46 – 4.42 (m, 2H), 4.33 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.67 (d, *J* = 2.2 Hz, 1H), 1.80 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (CD_3OD): δ 171.6, 170.2, 150.6, 136.7, 129.4, 124.4, 124.1, 101.9, 77.7, 77.4, 70.8, 67.3, 60.2, 25.0, 19.5, 13.1. HRMS (ESI) $[M-H]^-$ calcd. for $C_{19}H_{15}O_8$ 371.0767, found 371.0760.

11b (Yield: 73%). ^{1}H NMR (CD_3OD): δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.38 (br, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 4.63 (br, 1H), 4.39 – 4.31 (m, 2H), 4.16 – 4.05 (m, 2H), 1.64 (s, 6H), 1.35 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (CD_3OD): δ 195.7, 171.6, 171.1, 166.8, 152.5, 136.2, 131.3, 130.8, 129.6, 123.0, 102.2, 101.7, 89.3, 77.6, 68.9, 60.1, 42.5, 24.9, 19.5, 16.7, 13.1. HRMS (ESI) $[M-H]^-$ calcd. for $C_{18}H_{17}O_8$ 361.0923, found 361.0915.

General procedure for the synthesis of 12a-c

A solution of compound **11a**/**b** (1 equiv.), amine (2 equiv.), and TMSCl (3 equiv.) in toluene was heated under reflux for 2 h, then the reaction mixture was diluted with ethyl acetate (30 mL), and washed with $NaHCO_3$ solution and brine successively. The obtained organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford compound **12a-c** as yellowish oil.

12a (Yield: 75%). ^{1}H NMR ($CDCl_3$): δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.08 (m, 1H), 5.37 – 5.17 (m, 1H), 4.44 (dd, *J* = 13.6, 4.1 Hz, 1H), 4.35 – 4.18 (m, 2H), 3.85 (d, *J* = 17.1 Hz, 1H), 3.68 – 3.61 (m, 8H), 3.45 – 3.30 (m, 2H), 2.72 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 200.9, 168.5, 164.9, 149.9, 136.9, 131.3, 128.3, 125.4, 124.4, 78.1, 70.7, 66.7, 66.7, 66.6, 48.4, 46.8, 44.3, 42.2. HRMS (ESI) $[M+H]^+$ calcd. for $C_{19}H_{19}NO_6Na$ 380.1110, found 380.1110.

12b (Yield: 70%). ^{1}H NMR (CD_3OD): δ 7.66 (t, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 6.7 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 5.42 – 5.39 (m, 1H), 4.70 – 4.40 (m, 2H), 4.41 – 4.19 (m, 2H), 4.05 – 3.71 (m, 3H), 3.70 – 3.56 (m, 19H), 3.51 – 3.39 (m, 2H), 3.36 (s, 3H), 3.33 (br, 3H), 1.25 – 1.18 (m, 6H). ^{13}C NMR (CD_3OD): δ 202.6, 201.7, 169.5, 169.5, 168.9, 167.7, 150.2, 136.8, 136.7, 130.6, 130.5, 129.0, 128.8, 124.8, 124.7, 124.4, 124.3, 78.4, 78.2, 77.3, 77.2, 71.6, 70.4, 70.2, 70.1, 70.0, 69.9, 68.4, 66.9, 57.71, 49.7, 49.1, 48.3, 44.2, 43.8, 43.6, 40.4, 20.0, 19.9, 19.1, 19.0. HRMS (ESI) $[M+H]^+$ calcd. for $C_{31}H_{45}NO_{11}Na$ 630.2890, found 630.2878.

12c (Yield: 74%). ^{1}H NMR ($CDCl_3$): δ 7.79 – 7.55 (m, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.15 – 7.10 (m, 1H), 4.63 – 4.55 (m, 1H), 4.33 (dd, *J* = 13.6, 5.2 Hz, 1H), 4.16 (dd, *J* = 13.6, 5.2 Hz, 1H), 4.0 – 3.81 (m, 2H), 3.71 – 3.45 (m, 26H), 3.45 – 3.14 (m, 5H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.16 (d, *J* = 5.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 202.4, 201.8, 171.9, 169.5, 169.4, 167.4, 166.3, 152.3, 152.2, 136.6, 136.5, 131.9, 131.8, 127.7, 127.4, 123.6, 123.5, 122.5, 122.4, 77.8, 77.7, 71.9, 70.8, 70.7, 70.6, 70.5, 70.4, 68.8, 68.7, 68.6, 59.02 49.4, 48.9, 48.6, 46.4, 44.8, 44.7, 43.7, 40.7, 21.2, 20.4, 17.7. HRMS (ESI) $[M+H]^+$ calcd. for $C_{30}H_{47}NO_{11}Na$ 620.3047, found 620.3043.

General procedure for the synthesis of BW-ETCO-101-103

A solution of compound **12a-c** (1 equiv.), acenaphthylene-1, 2-dione (1 equiv.), and Et_3N (1.5 equiv.) in THF/MeOH (1:1) was stirred at room temperature overnight. The reaction mixture was then dried under vacuum, and the obtained residue was dissolved in Ac_2O (2 mL). The obtained solution was cooled to 0 ^{o}C, then 1-2 drops of concentrated sulfuric acid was added. The resulting dark purple solution was diluted with ethyl acetate, washed with $NaHCO_3$ solution and brine successively. The obtained organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford compound **BW-ETCO-101-103**.

BW-ETCO-101 (Dark solid. Yield: 64%). ^{1}H NMR ($CDCl_3$): δ 8.08 (d, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 7.1 Hz, 1H), 7.81 – 7.67 (m, 2H), 7.61 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 5.13 (s, 1H), 4.39 (s, 1H), 4.25 (s,

1H), 3.94 – 3.70 (m, 6H), 3.58 (d, *J* = 3.0 Hz, 2H), 2.46 (d, *J* = 1.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 198.8, 171.2, 168.8, 163.5, 162.6, 155.2, 145.6, 136.2, 131.6, 129.7, 129.6, 128.8, 128.0, 125.4, 124.8, 67.2, 66.9, 65.8, 60.4, 47.9, 42.7, 21.7, 15.3, 14.2. HRMS (ESI) $[M+H]^+$ calcd. for $C_{31}H_{22}NO_6$ 504.1442, found 504.1429.

BW-ETCO-102 (Dark sticky oil. Yield: 60%). ^{1}H NMR (CD_3CN): δ 8.05 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.90 – 7.56 (m, 6H), 7.49 (t, *J* = 7.7 Hz, 1 H), 5.19 (br, 1H), 4.55 – 4.41 (m, 1H), 4.26 – 4.17 (m, 1H), 3.82 – 3.37 (m, 22H), 3.31 (d, *J* = 5.7 Hz, 5H), 2.95 (s, 0.3H), 2.71 (s, 0.6H), 1.40 (d, *J* = 6.7 Hz, 2H), 1.30 (d, *J* = 7.0 Hz, 0.4H), 1.23 – 1.17 (m, 3.6H). ^{13}C NMR (CD_3CN): δ 198.9, 168.7, 163.9, 157.7, 150.0, 144.8, 136.0, 131.8, 130.9, 129.6, 128.9, 128.8, 128.0, 125.2, 123.1, 71.6, 70.2, 70.0, 69.8, 68.6, 66.7, 57.9, 50.6, 40.2, 20.9, 20.8, 19.8. HRMS (ESI) [M+H]+ calcd. for $C_{43}H_{48}NO_{11}$ 754.3222, found 754.3210.

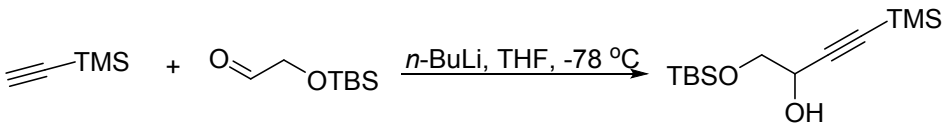
BW-ETCO-103 (Dark sticky oil. Yield: 68%). ^{1}H NMR ($CDCl_3$): δ 8.00 – 7.81 (m, 4H), 7.77 (dd, *J* = 17.7, 7.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.63 – 7.49 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 4.78 – 4.55 (m, 2H), 4.23 – 4.01 (m, 2H), 3.82 (t, *J* = 6.2 Hz, 2H), 3.79 – 3.50 (m, 20H), 3.50 – 3.31 (m, 5H), 1.45 – 1.06 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 198.8, 169.56 164.3, 159.9, 155.2, 145.3, 136.1, 132.8, 131.7, 130.9, 129.9, 128.9, 128.7, 127.9, 123.6, 117.3, 78.1, 71.9, 70.6, 70.5, 68.9, 59.0, 50.8, 40.6, 21.7, 21.6, 20.6. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{42}H_{49}NO_{11}Na$ 766.3203, found 766.3241.

The CO release of BW-ETCO-101/102 in the presence of porcine liver esterase

A solution of **BW-ETCO-101**/**102** (10 mg) and porcine liver esterase (15 mg) in 30% DMSO/PBS (50 mL) was incubated at 37 °C for 48 h. Then MeOH (60 mL) was added, and the solution was centrifuged to get rid of the protein. The obtained solution was dried under vacuum, and the residue was acidified and extracted with ethyl acetate. The obtained organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford the cyclized compound.

BW-ETCP-101. ^{1}H NMR (DMSO-d_6): δ 8.46 (d, J = 7.6 Hz, 1H), 8.37 (d, J = 7.1 Hz, 1H), 8.06 (d, J = 8.0 Hz, 2H), 7.91 (d, J = 7.0 Hz, 1H), 7.73 (m, 3H), 7.36 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 5.37 (s, 1H), 3.95 – 3.75 (m, 4H), 3.60 (m, 4H), 3.39 (s, 1H), 3.19 (d, J = 12.3 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 167.9, 136.6, 133.9, 132.3, 131.7, 130.3, 128.9, 128.6, 128.5, 128.4, 127.6, 123.9, 123.8, 122.9, 121.9, 79.5, 66.4, 61.7, 47.5, 42.0. HRMS (ESI) $[M+H]^+$ calcd. for $C_{30}H_{24}NO_6$ 494.1598, found 494.1583.

BW-ETCP-102. ^{1}H NMR (CD_3OD): δ 8.45 (d, J = 7.2 Hz, 1H), 8.38 (t, J = 8.4 Hz, 1H), 7.99 – 7.93 (m, 3H), 7.69 – 7.58 (m, 3H), 7.33 – 7.22 (m, 2H), 5.39 (br, 1H), 4.11 – 3.90 (m, 2H), 3.88 – 3.54 (m, 17H), 3.50 – 3.38 (m, 4H), 3.28 – 3.23 (m, 8H), 1.56-1.52 (m, 1.6 H), 1.33 (d, J = 6.9 Hz, 0.4 H), 1.24 (d, J = 6.5 Hz, 1H), 1.20 (d, J = 6.5 Hz, 1H), 1.14 (d, J = 6.5 Hz, 1H), 0.98 (d, J = 6.4 Hz, 1H). ^{13}C NMR (CD_3OD): δ 171.2, 150.2, 136.4, 136.1, 135.9, 135.2, 135.2, 134.8, 133.8, 132.5, 131.3, 131.1, 130.9, 130.3, 128.2, 127.9, 127.8, 127.7, 127.4, 123.7, 123.5, 122.4, 122.2, 121.7, 121.4, 79.6, 76.8, 71.4, 70.2, 70.1, 70.0, 69.9, 69.9, 69.8, 69.7, 69.6, 68.7, 68.6, 65.5, 61.3, 57.7, 57.7, 54.8, 51.2, 51.2, 40.5, 33.9, 20.4, 20.3, 20.0, 19.9, 19.4, 19.2, 18.8. HRMS (ESI) $[M+H]^+$ calcd. for $C_{42}H_{50}NO_{11}$ 744.3378, found 744.3367.



Scheme S2. The synthesis of the linker

To a solution of ethynyltrimethylsilane (2.0 g, 20.4 mmol) in THF (30 mL) was added *n*-BuLi (10.7 mL, 21.4 mmol) at -78 °C under N_2. Then the resulting solution was stirred for another 1 h, followed by the dropwise addition of 2-((tert-butyldimethylsilyl)oxy) acetaldehyde (2.3 g, 13.6 mmol). Then the stirring was continued for another 2 h. The reaction mixture was poured into a solution of NH_4Cl (50 mL), and extracted with ethyl acetate (3 × 60 mL). The combined organic layer was washed with water and brine, and was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified on a silica gel column to afford the title

compound as a colorless oil (yield: 80%). ^{1}H NMR ($CDCl_3$): δ 4.40 – 4.36 (m, 1H), 3.76 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.65 (dd, *J* = 10.0, 6.8 Hz, 1H), 2.72 (d, *J* = 4.8 Hz, 1H), 0.91 (s, 9H), 0.16 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 103.6, 90.0, 66.9, 63.5, 25.8, 18.3, -5.3. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{28}O_2Si_2Na$ 295.1526, found 295.1526.

2. The amide rotamers for BW-ETCO-102

BW-ETCO-102/103 were obtained as a mixture of amide rotamers. Take **BW-ETCO-102** as an example, because there are one chiral centre and one rotation restricted amide bond, there are 4 possible isomers, including (R, E), (R, Z), (S, E), (S, Z). For each one, the dimethyl group of *iso*-propyl should appear as two doublet peaks. Therefore, 8 doublet peaks should be observed theoretically for **BW-ETCO-102**. However, only four doublet peaks were observed due to peak overlapping in CD_3CN at room temperature (Figure S1). The peaks begin to coalesce at elevated temperature (60 ^{o}C). These results supported the existence of amidic rotamers for **BW-ETCO-102**.

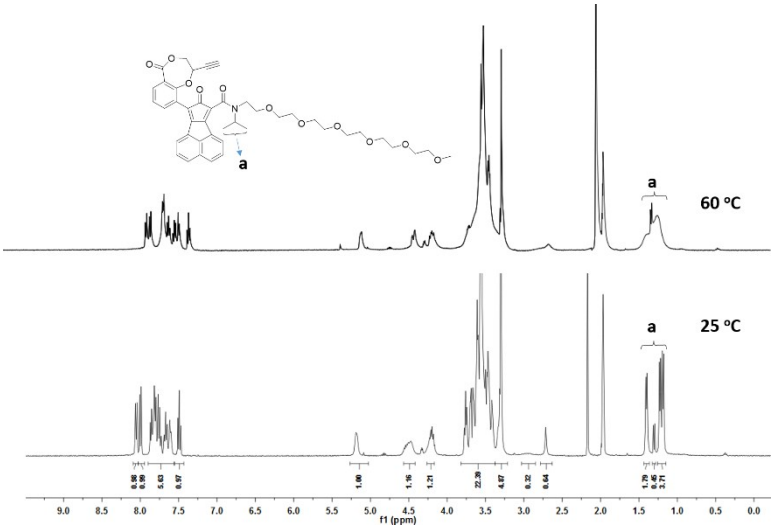


Figure S1. The amide rotamers of **BW-ETCO-102**

3. CO-myoglobin Assay

In order to further confirm CO release, **BW-ETCO-101** were chosen for CO-myoglobin assay. For such purpose, a solution of myoglobin (0.5 mg/ml) and esterase (10 Unit/mL) in PBS (10 mL, pH = 7.4) was degassed by bubbling with nitrogen for at

least 20 min. To this degassed solution was added a solution of **BW-ETCO-101** (0.45 mg) in DMSO (1 mL), and the resulting solution was incubated at 37 °C for 4 h. Then a solution of sodium dithionite (1 mL, 22 mg/mL) was added, and a red solution was obtained, which was cooled down to 0 °C with an ice bath, and was stirred for another 1 h. Afterwards, the UV-vis spectra of the resulting pinkish red solution was taken to confirm CO release. The results are shown in Figure S2.

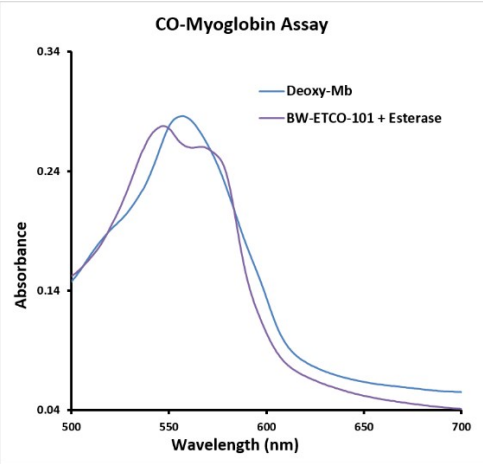


Figure S2. The CO-myoglobin assay

4. CO release kinetics

CO release kinetics were studied indirectly using HPLC to monitor the disappearance of the prodrug and the formation of the cyclized product. Specifically, a solution of **BW-ETCO-101**/**102** (20 μM) in DMSO/PBS (5%) was incubated with or without porcine liver esterase (10 Unit/mL) at 37 °C. The sample was analysed using HPLC on a column with 50% of CH_3CN/H_2O (containing 0.3% of TFA, pH = 3) as eluent at intervals. The prodrug remaining was plotted against time to obtain CO release kinetic curves. As shown in Figure S3-6, with or without esterase, the cyclized product **BW-ETCP-101**/**102** came as the sole product (confirmed by HRMS), and the hydrolysis of the lactone ring is much faster in the presence of esterase, as compared to the one without esterase.

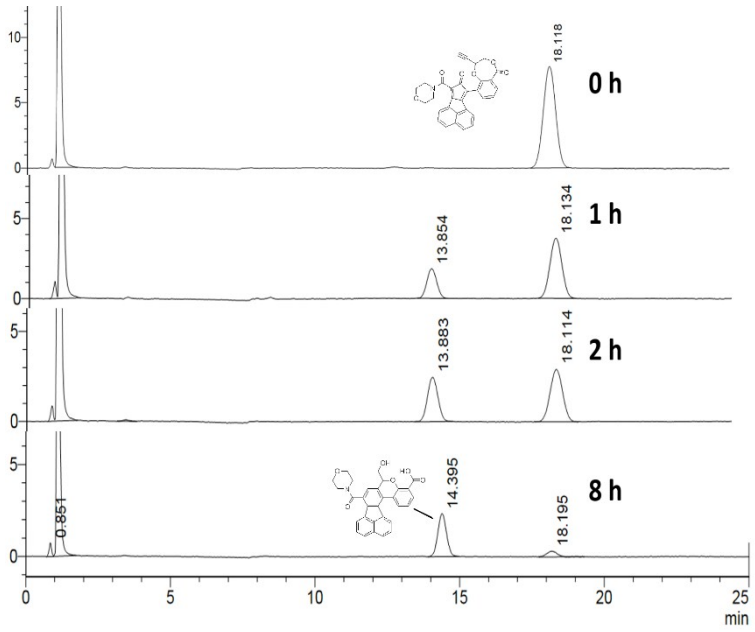


Figure S3. The hydrolysis and cyclization of **BW-ETCO-101** in the presence of the esterase

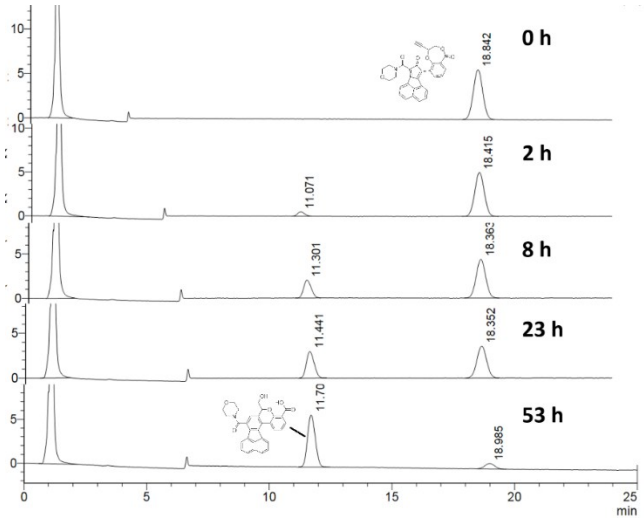


Figure S4. The hydrolysis and cyclization of **BW-ETCO-101** in the absence of the esterase

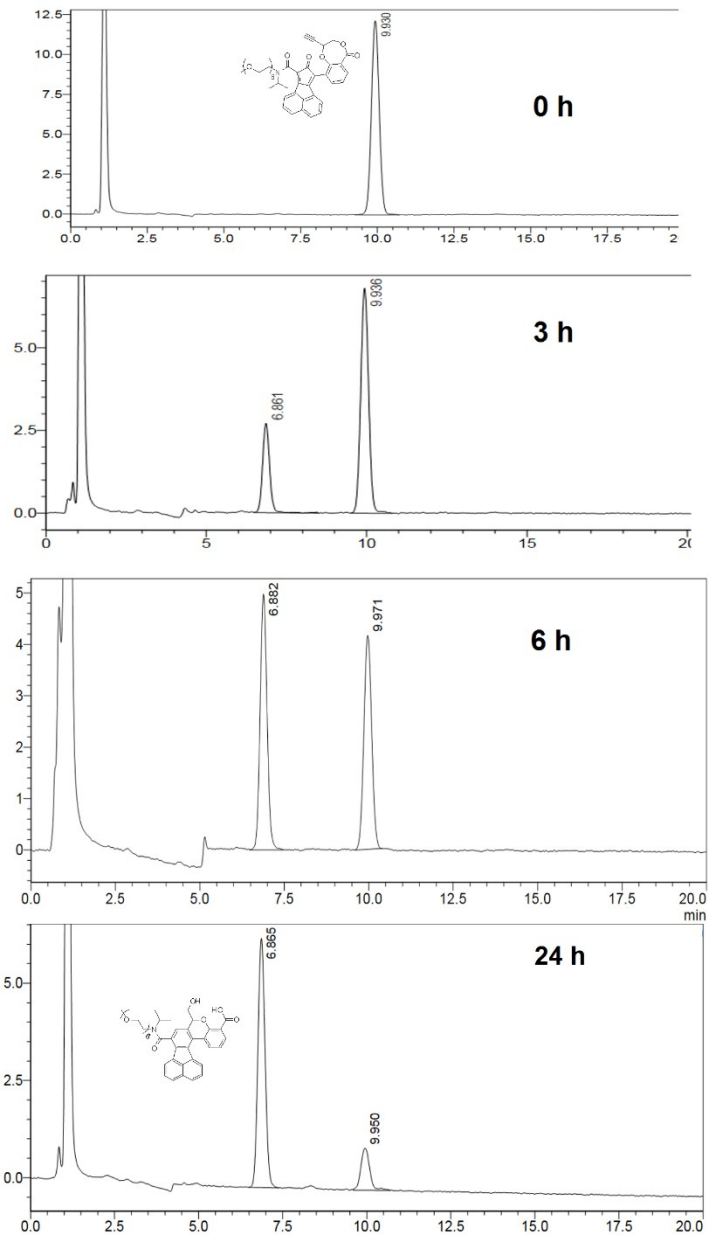


Figure S5. The hydrolysis and cyclization of **BW-ETCO-102** in the presence of the esterase

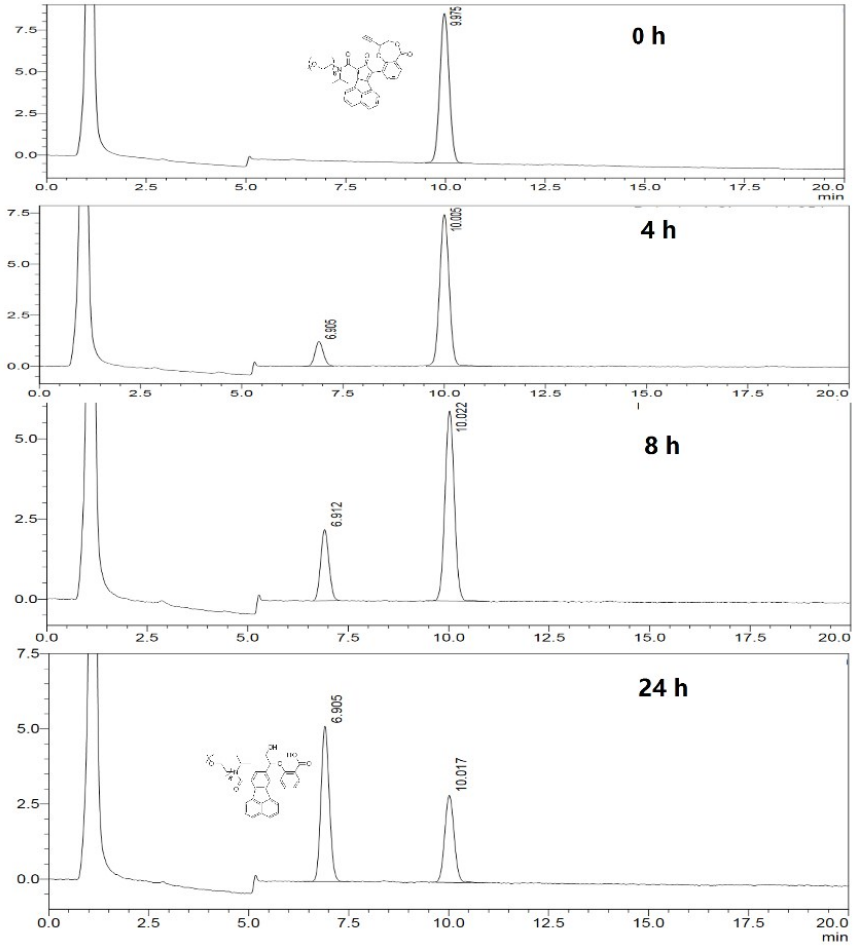


Figure S6. The hydrolysis and cyclization of **BW-ETCO-102** in the absence of the esterase

5. MTT assay

Raw 264.7 cells were seeded in 96-well plates and cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin at 37 °C under 5% CO_2 for 24 h. Then RAW 264.7 cells were incubated in DMEM containing 1% DMSO and compounds (0 – 50 μM) for 24 hours. Then 10 μL of MTT solution was added to each well and incubated for another three hours at 37 °C. The absorbance at 570 nm was measured by using a microplate reader. The cell viability was measured and the results were shown in Figure S7-8.

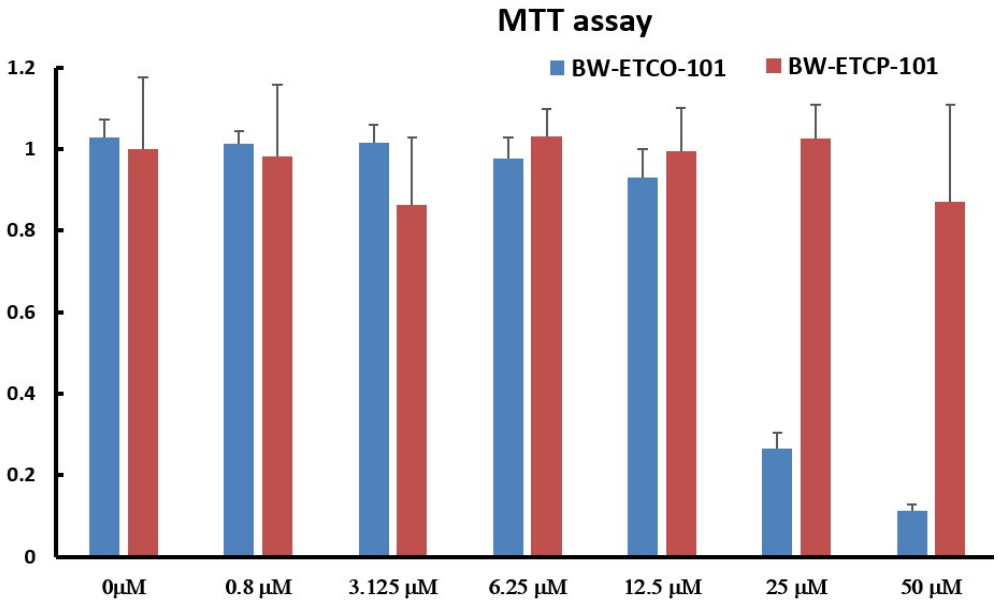


Figure S7. The cytotoxicity results of **BW-ETCO/CP-101** to Raw264.7 cells

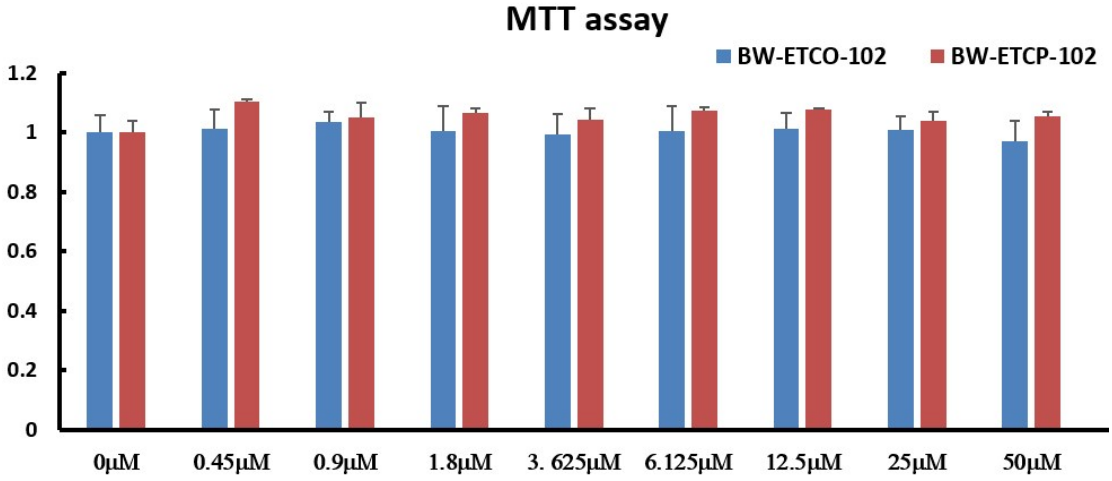


Figure S8. The cytotoxicity results of **BW-ETCO/CP-102** to Raw264.7 cells

6. Anti-inflammation effects of BW-ETCO-101 – 102

RAW 264.7 cells were seeded in 48-well plates one day before the experiment. LPS was used to initiate the inflammatory response in RAW 264.7 cells. RAW 264.7 cells were pre-treated with different concentrations of **BW-ETCO-101/102/103** or **BW-ETCP-101/102** for 4 hours. Thereafter, 1 μg/mL LPS was added into the cell culture media. For the TNF-α test, the cell culture supernatant was collected 1 hour after LPS treatment. Cell culture without LPS treatment was used as the control. The concentrations of cytokine in the cell culture supernatant were measurement by a

commercial ELISA kit (ELISA Ready-SET-Go!®-eBioscience).

7. The fluorescent imaging of CO release

RAW 264.7 cells were seeded in the 6-well plate one day before the imaging experiment. Compounds were dissolved in DMSO as stock solution. Final concentration of 1 μM **COP-1** and different concentrations of **BW-ETCO-102/103** (25 μM, 50 μM) were added into the cell culture. After adding the compound, the cells were incubated under 37 °C for 5 hours. The cell samples were then fixed for imaging study under FITC channel (excitation: 490 nm, emission: 525 nm) for the fluorescence of **COP-1**, using a Zeiss fluorescent microscope.

8. NMR spectra

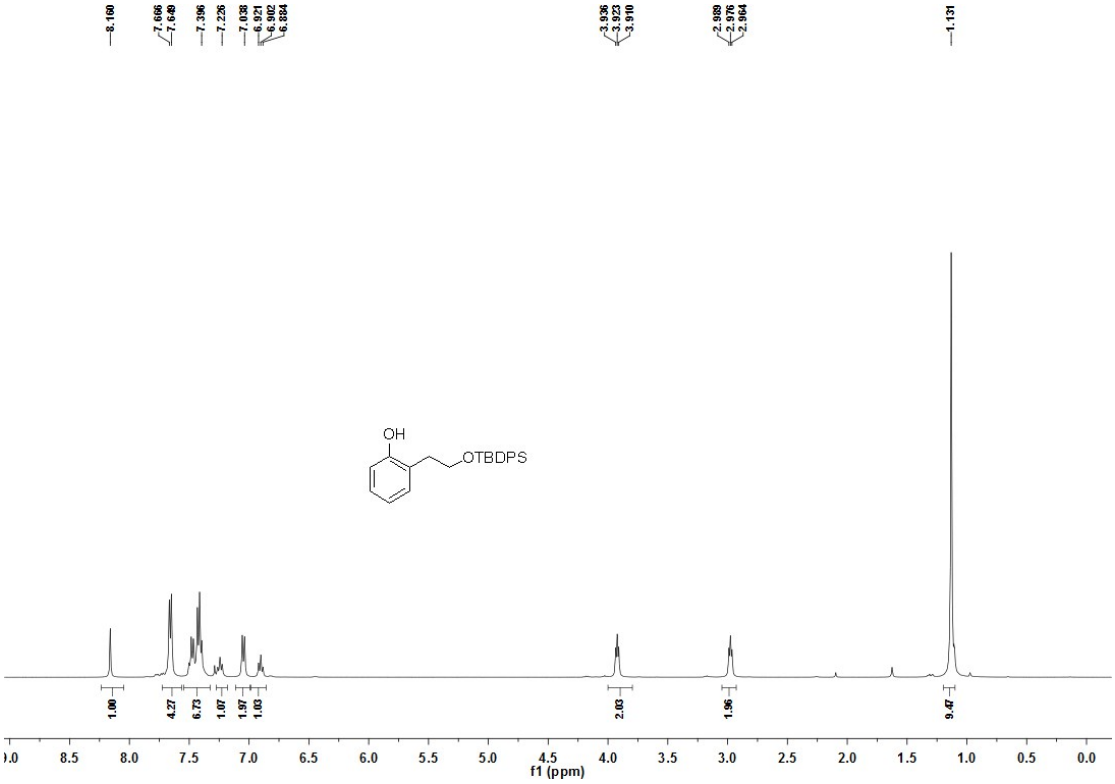


Figure S9. The ^{1}H NMR spectrum of compound **2** in $CDCl_3$.

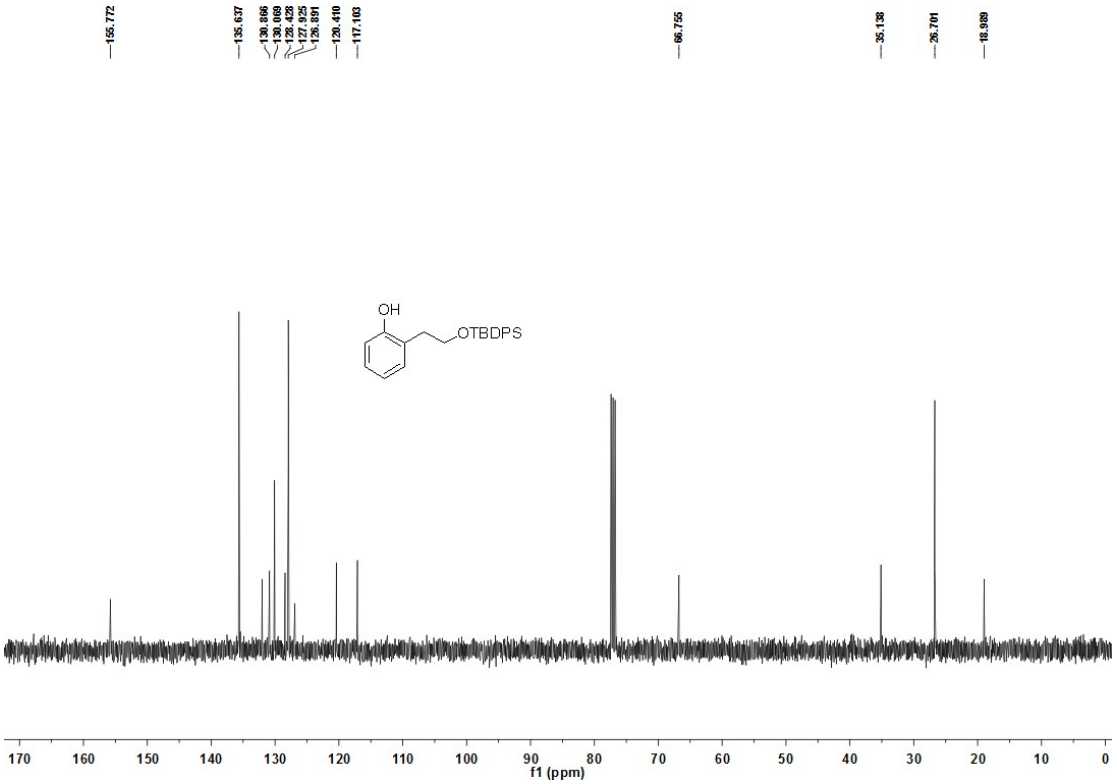


Figure S10. The ^{13}C NMR spectrum of compound **2** in $CDCl_3$.

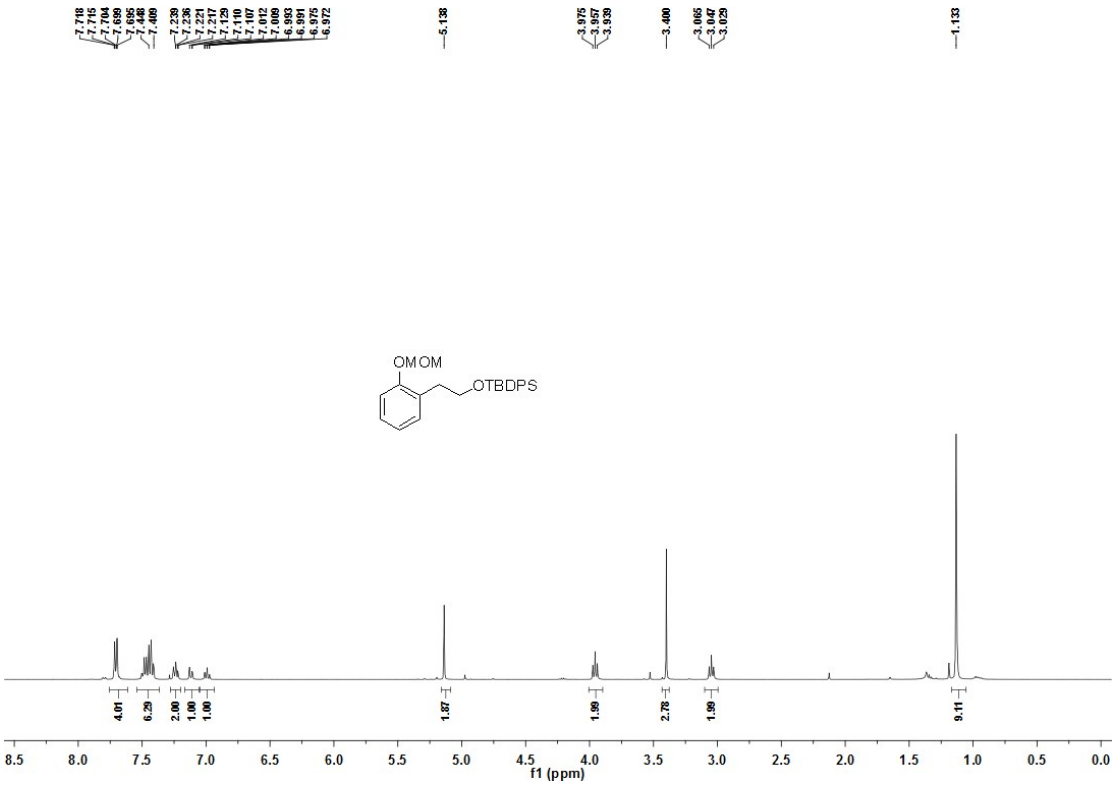


Figure S11. The ^{1}H NMR spectrum of compound **3** in $CDCl_3$.

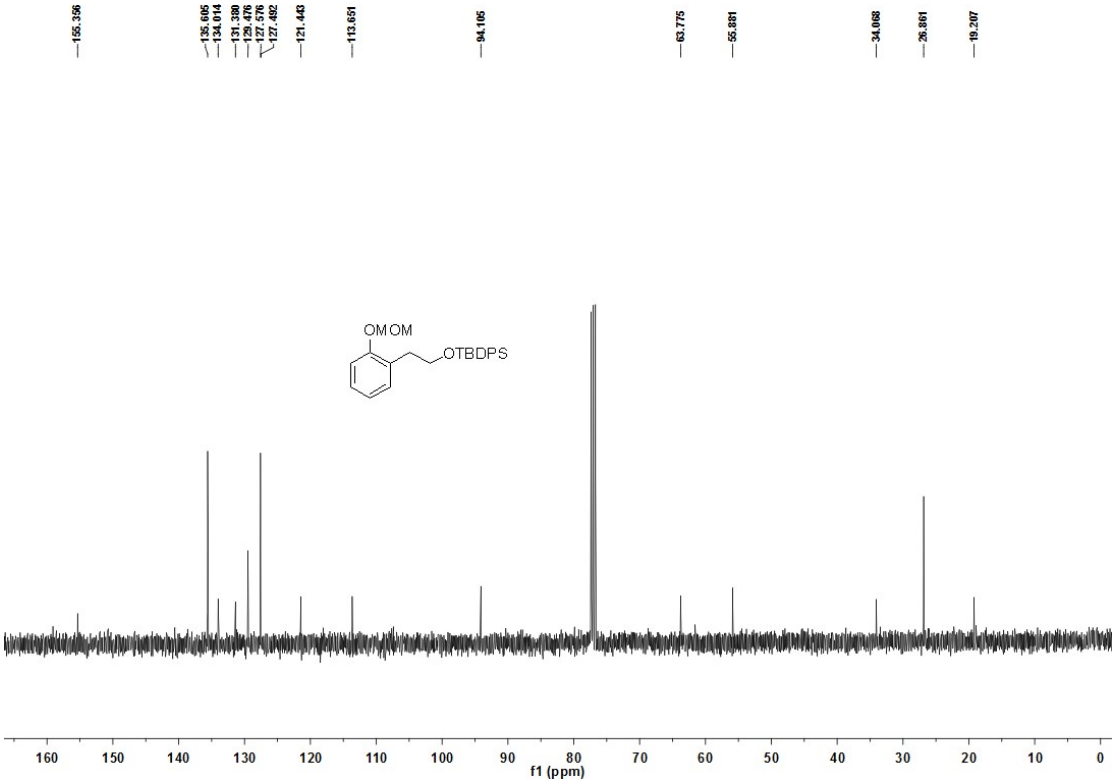


Figure S12. The ^{13}C NMR spectrum of compound **3** in $CDCl_3$.

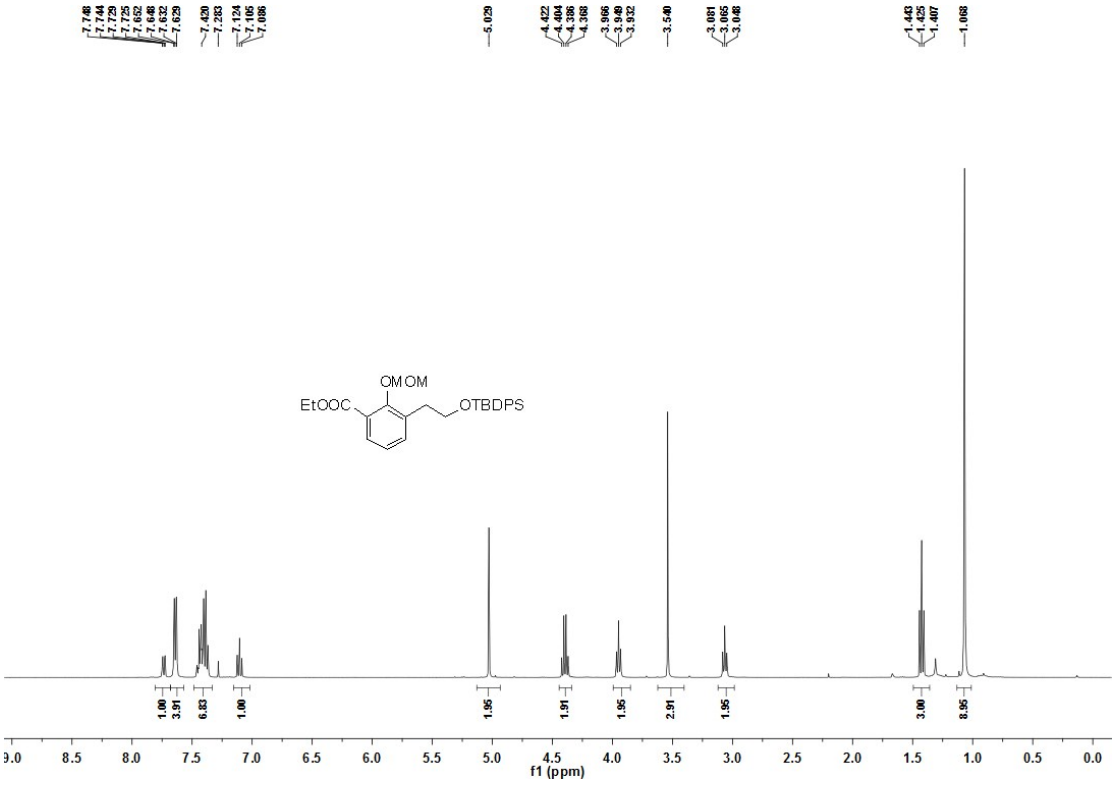


Figure S13. The ^{1}H NMR spectrum of compound **4** in $CDCl_3$.

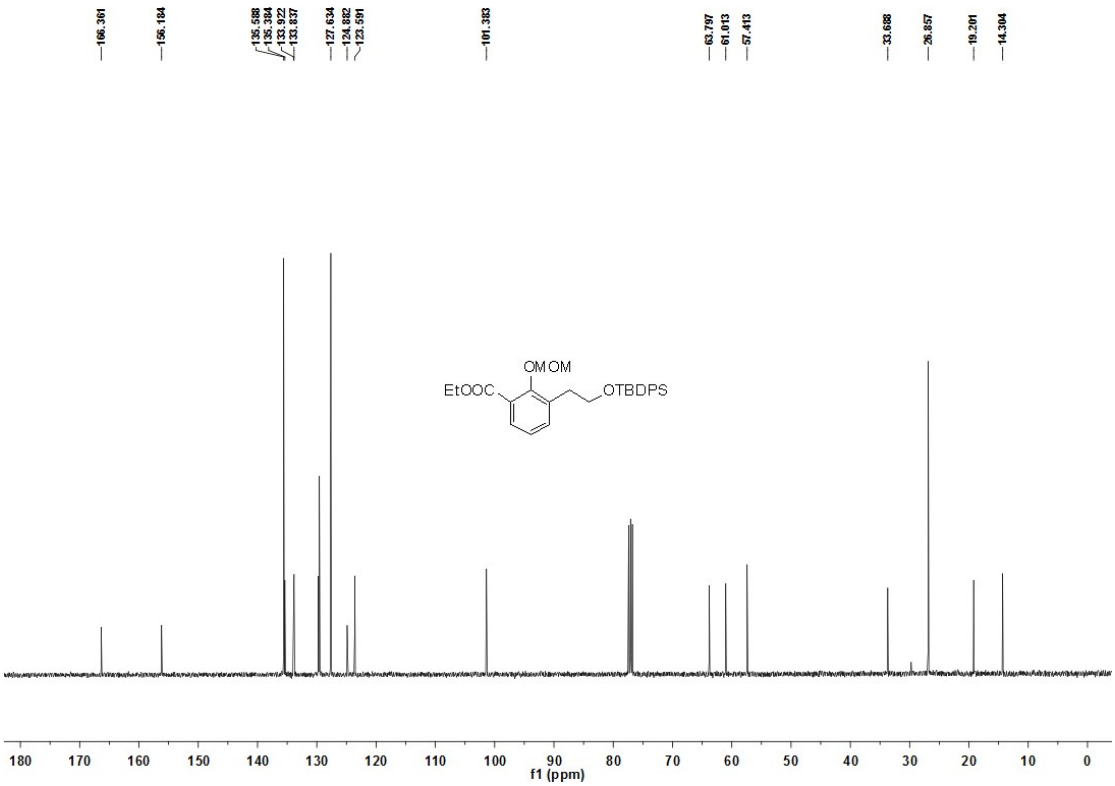


Figure S14. The ^{13}C NMR spectrum of compound **4** in $CDCl_3$.

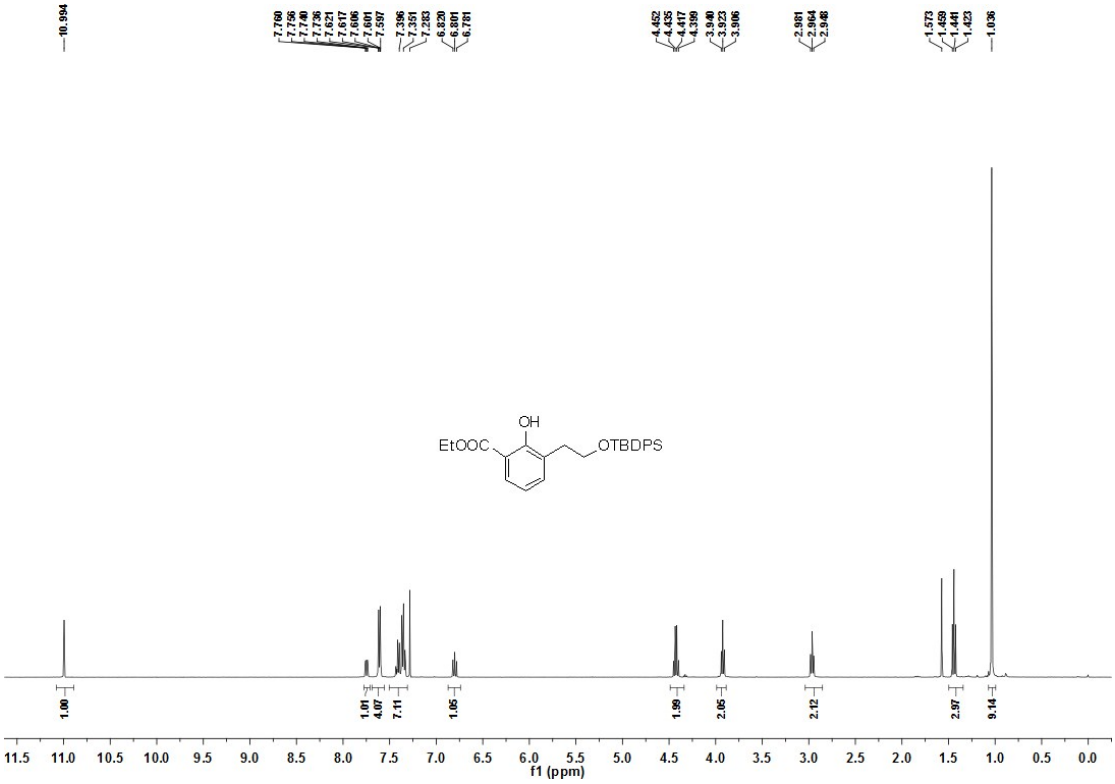


Figure S15. The ^{1}H NMR spectrum of compound **5** in $CDCl_3$.

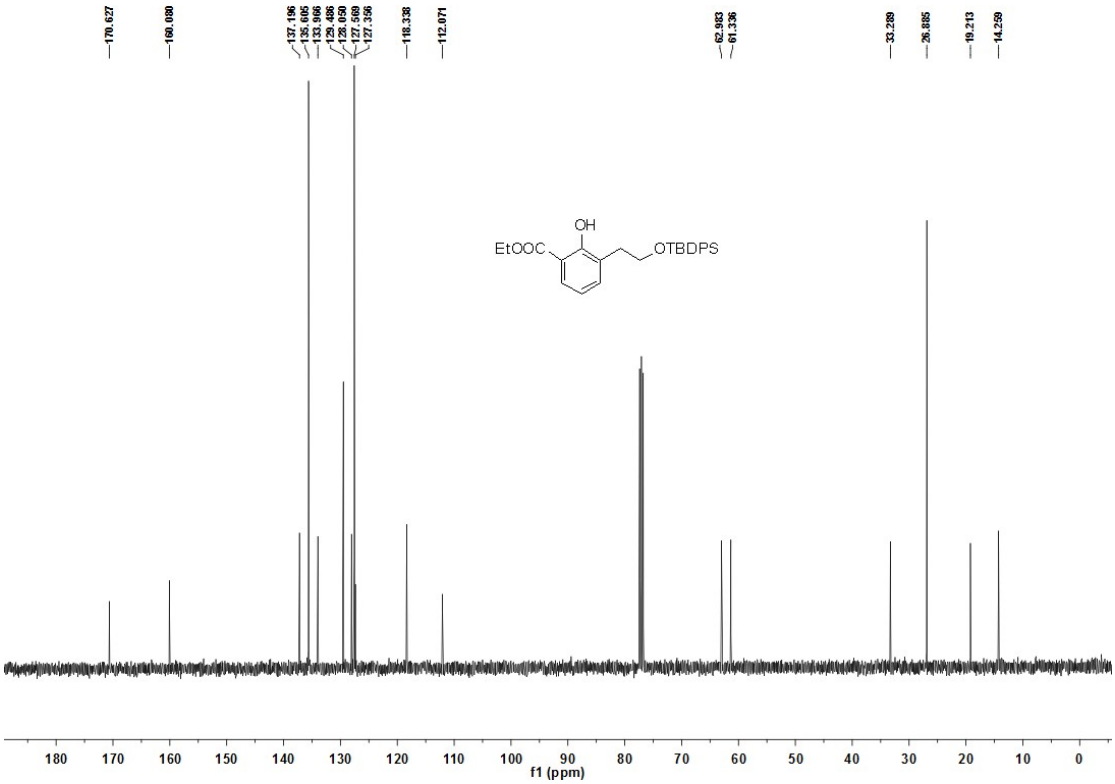


Figure S16. The ^{13}C NMR spectrum of compound **5** in $CDCl_3$.

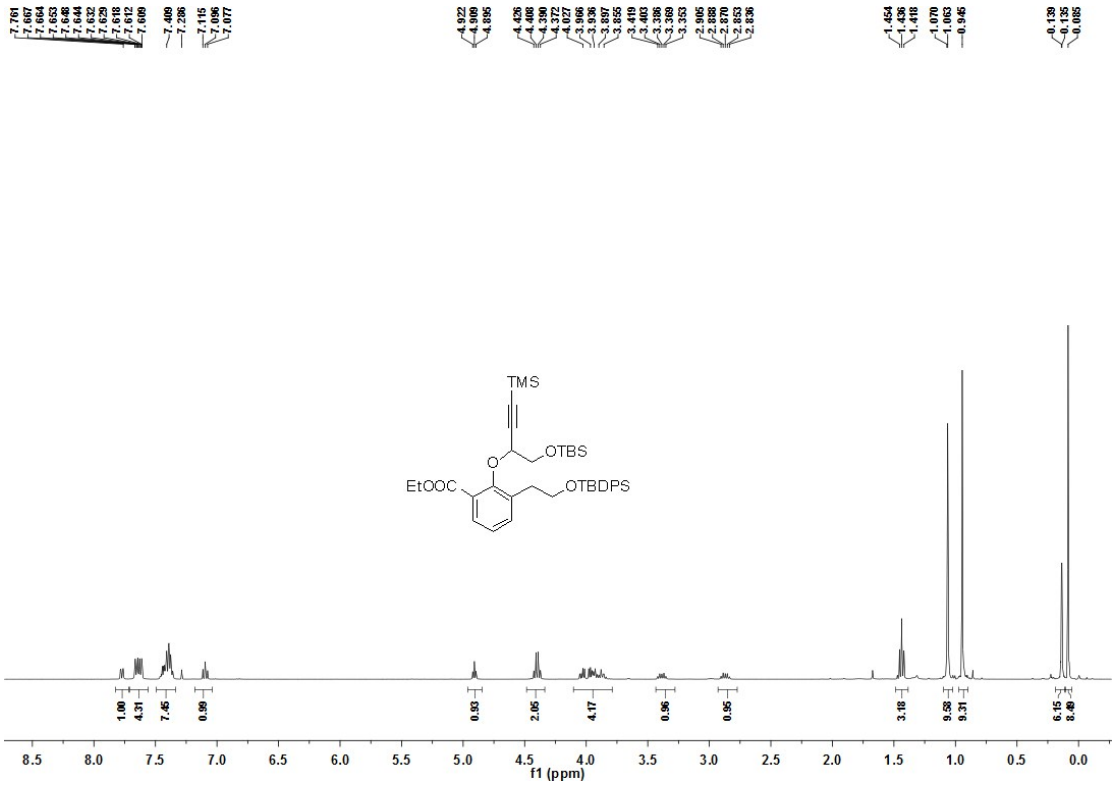


Figure S17. The ^{1}H NMR spectrum of compound **6a** in $CDCl_3$.

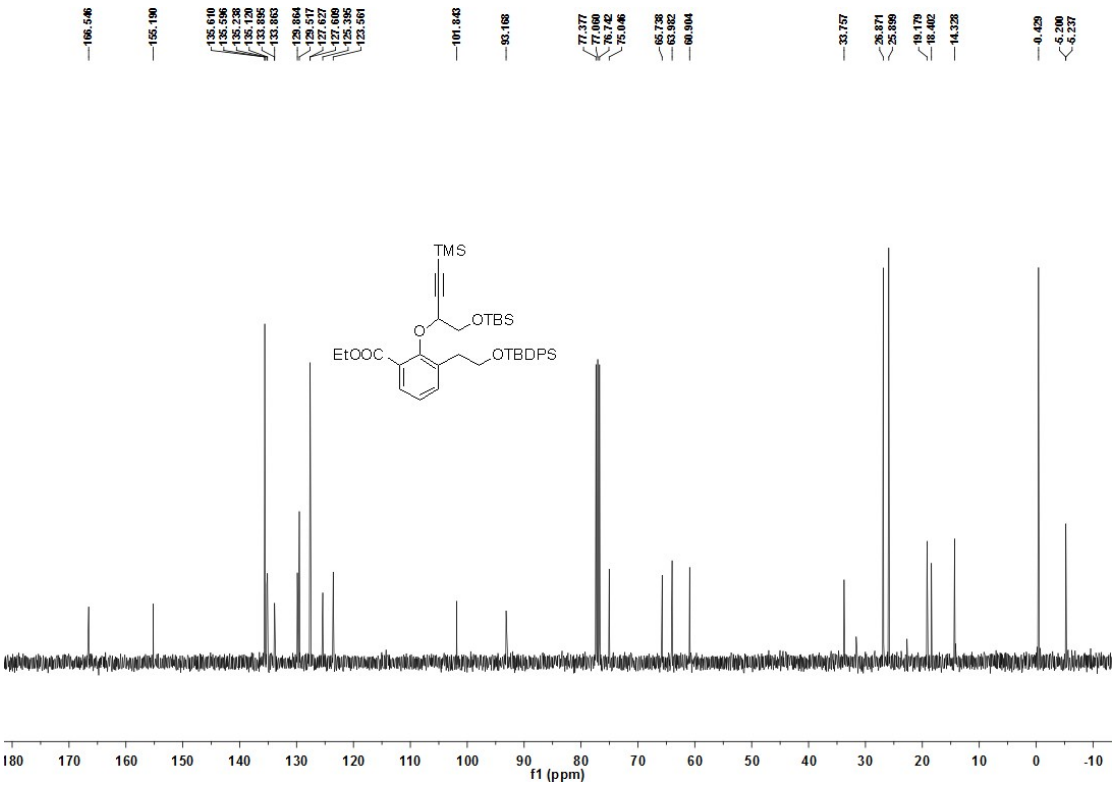


Figure S18. The ^{13}C NMR spectrum of compound **6a** in $CDCl_3$.

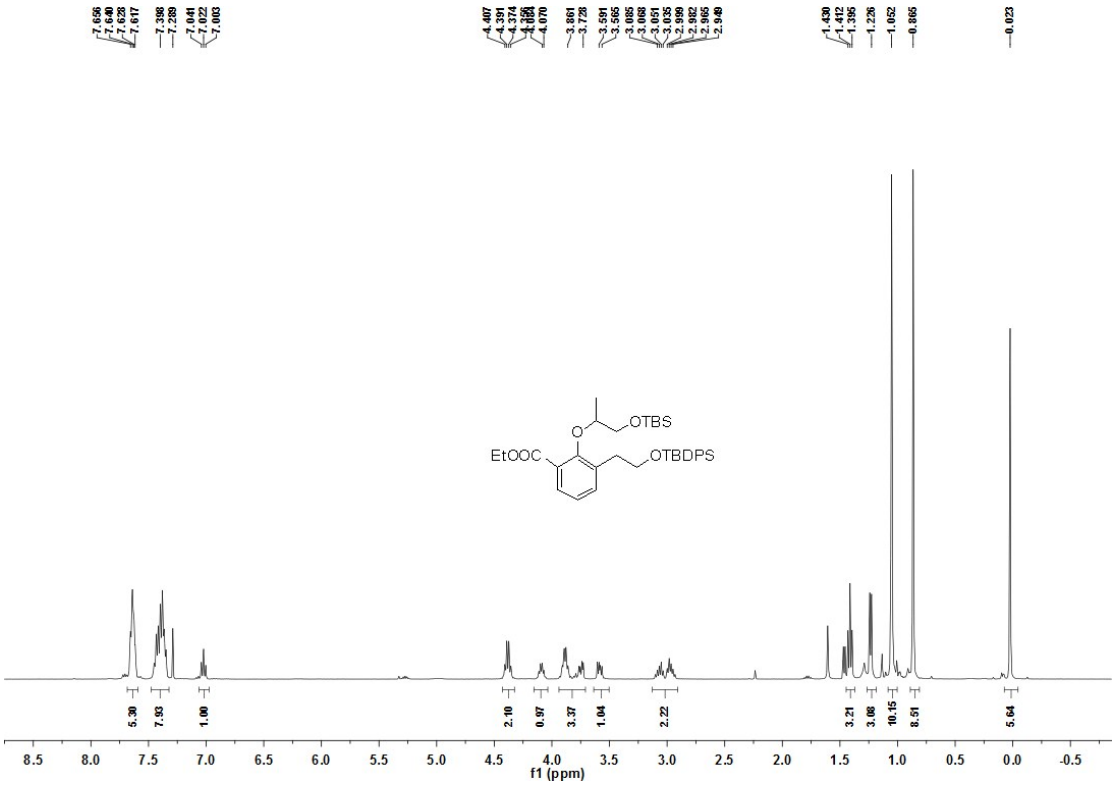


Figure S19. The ^{1}H NMR spectrum of compound **6b** in $CDCl_3$.

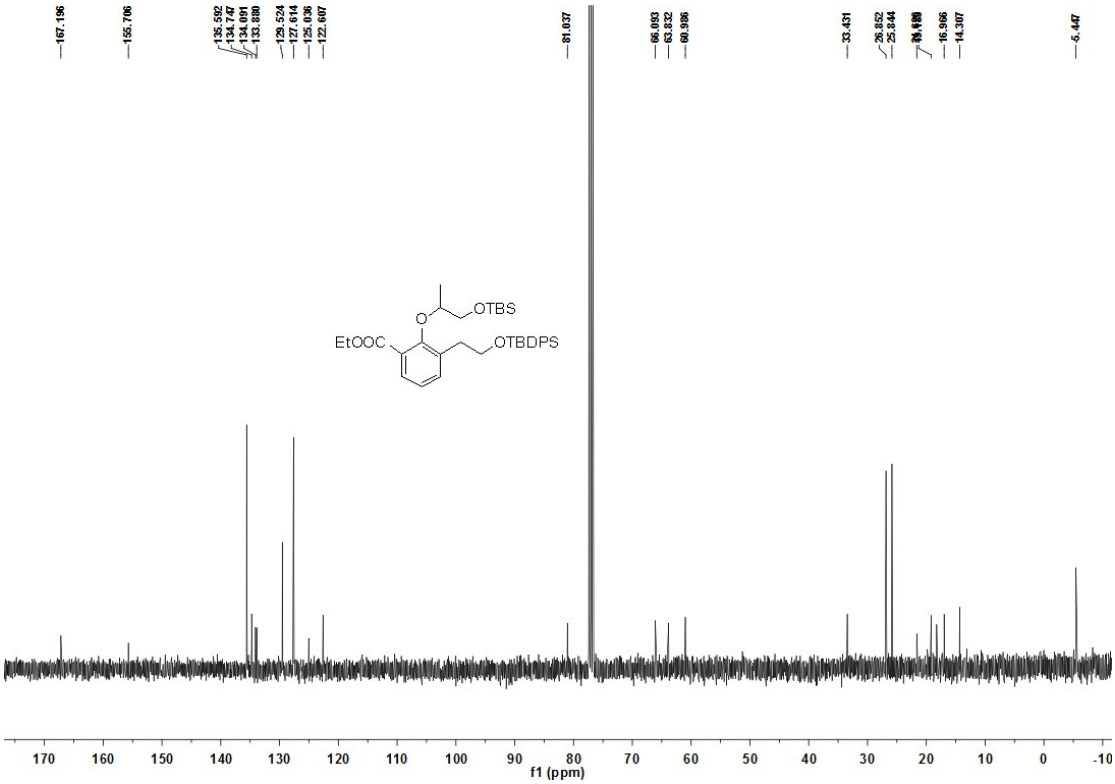


Figure S20. The ^{13}C NMR spectrum of compound **6b** in $CDCl_3$.

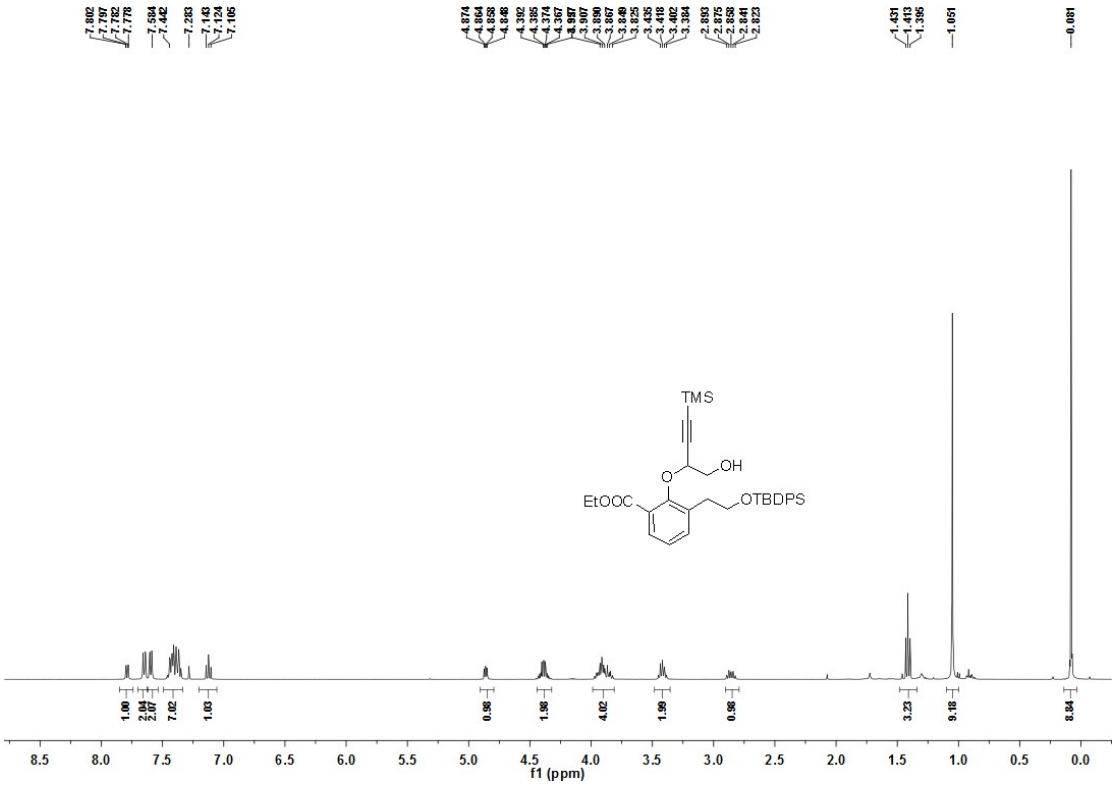


Figure S21. The ^{1}H NMR spectrum of compound **7a** in $CDCl_3$.

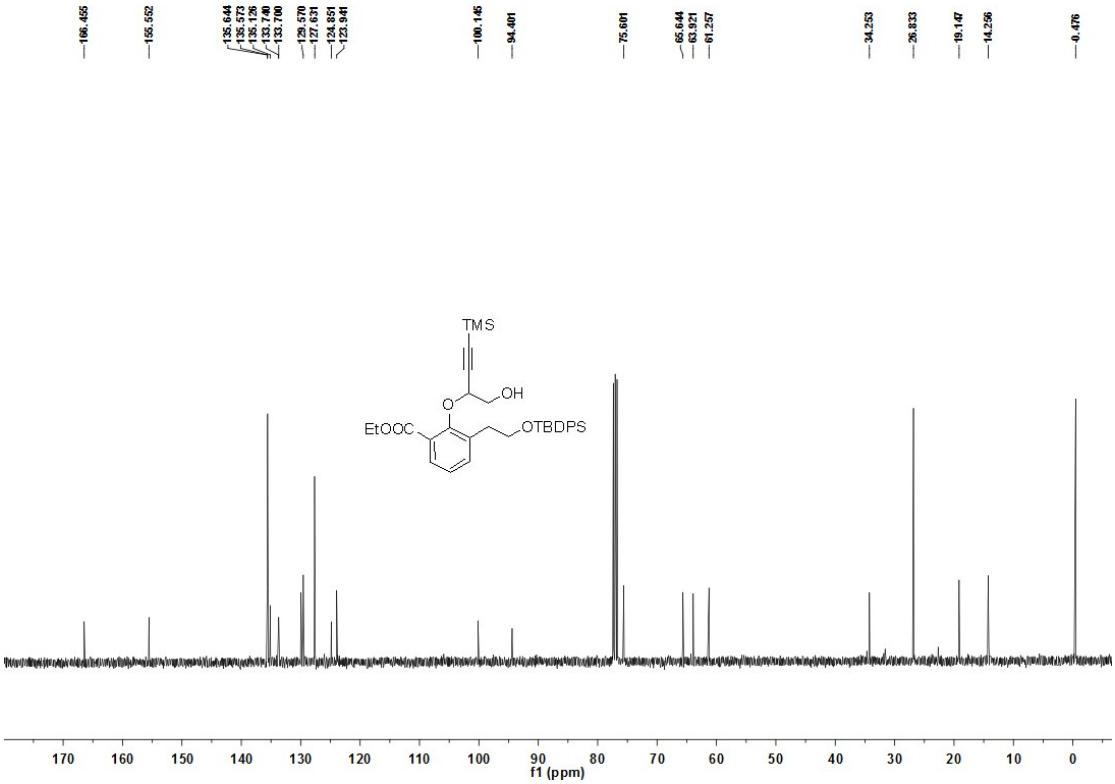


Figure S22. The ^{13}C NMR spectrum of compound **7a** in $CDCl_3$

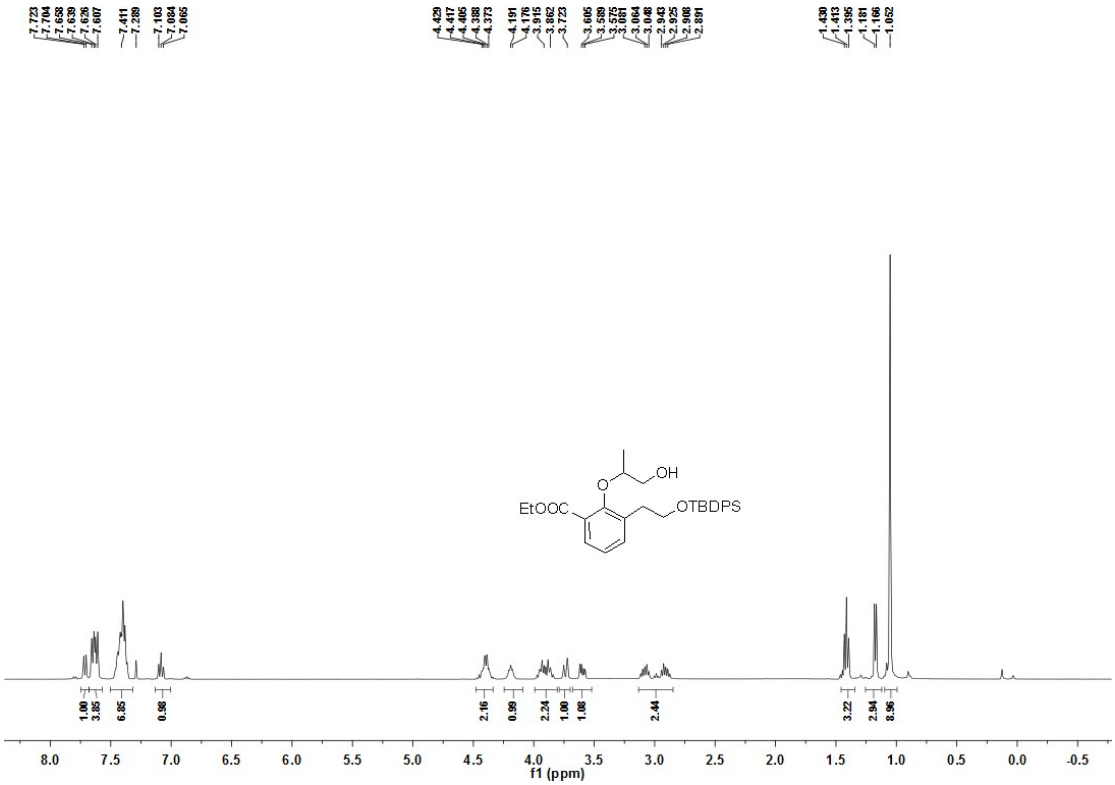


Figure S23. The ^{1}H NMR spectrum of compound **7b** in $CDCl_3$

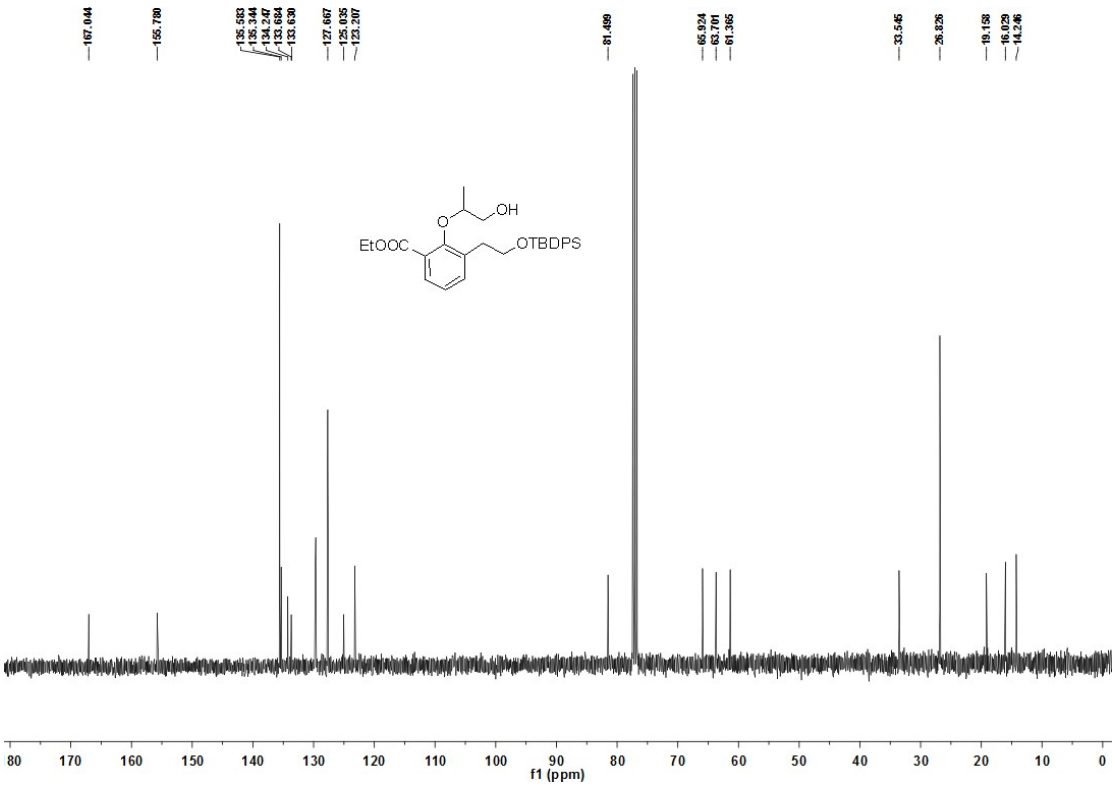


Figure S24. The ^{13}C NMR spectrum of compound **7b** in $CDCl_3$

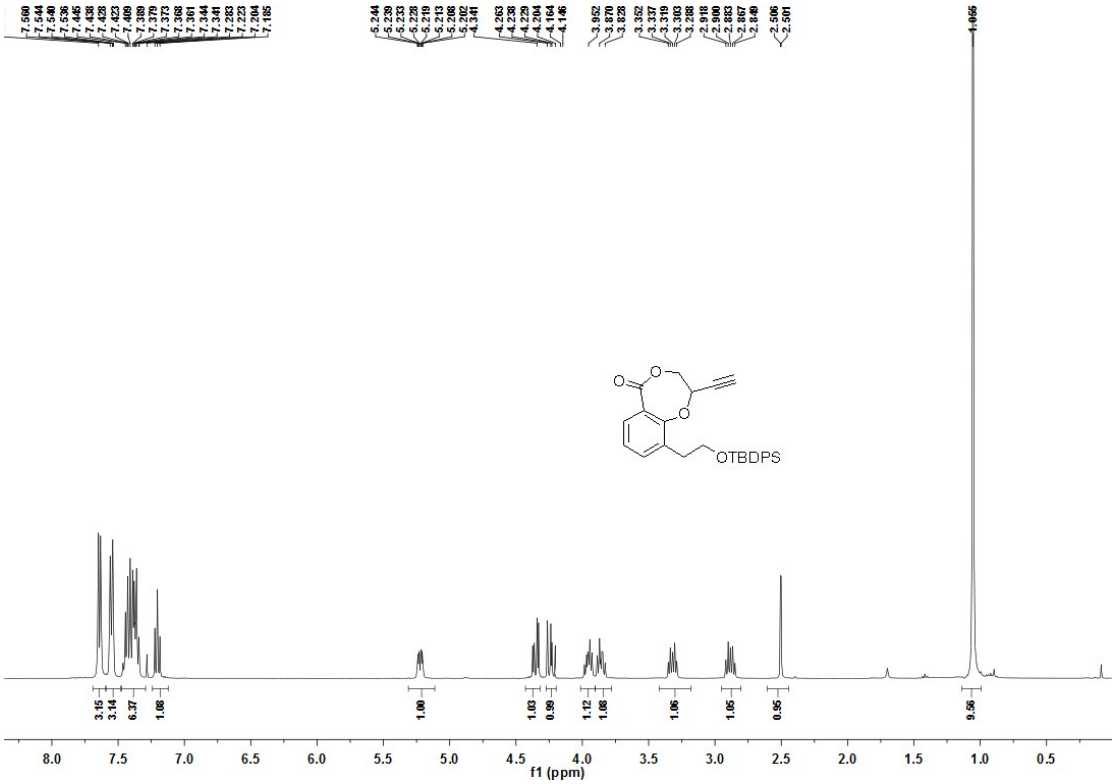


Figure S25. The ^{1}H NMR spectrum of compound **8a** in $CDCl_3$

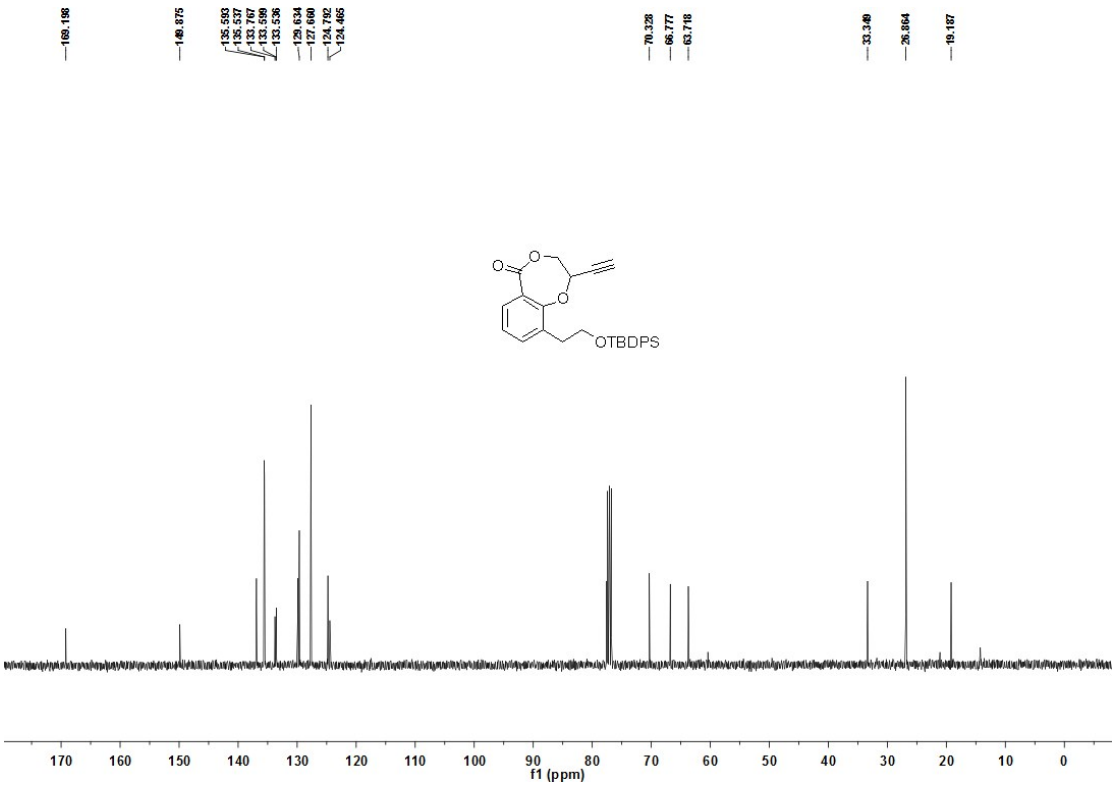


Figure S26. The ^{13}C NMR spectrum of compound **8a** in $CDCl_3$

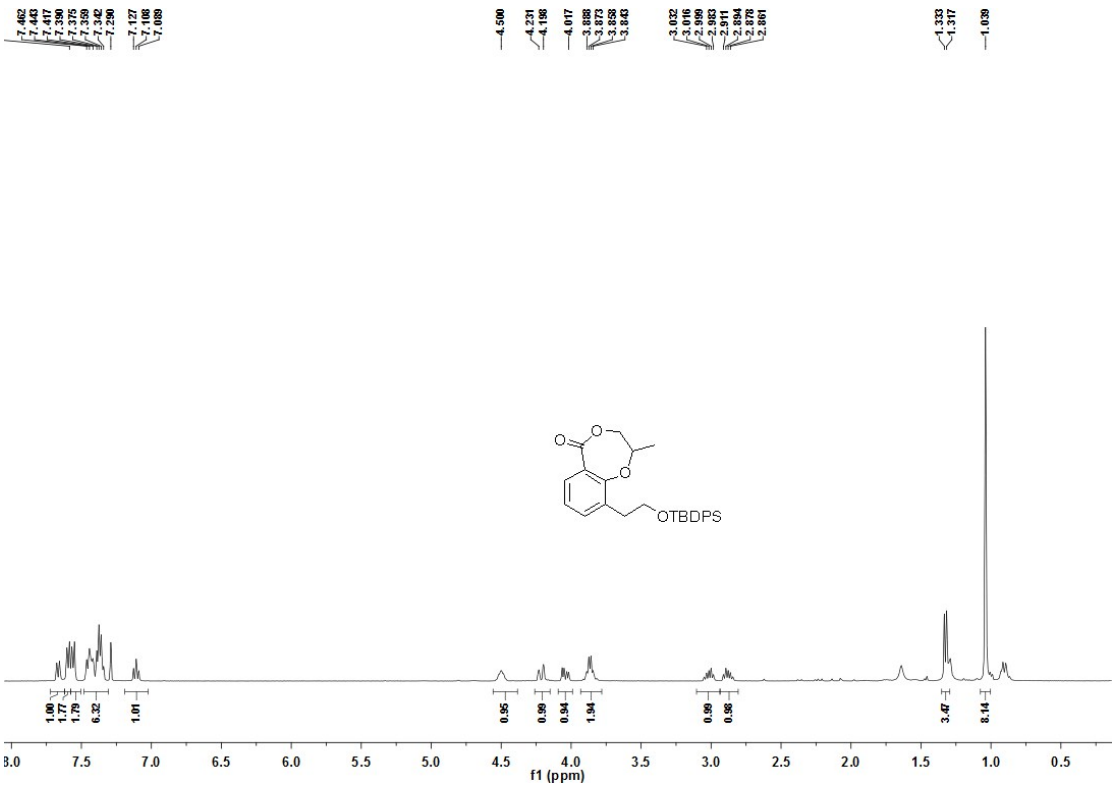


Figure S27. The ^{1}H NMR spectrum of compound **8b** in $CDCl_3$

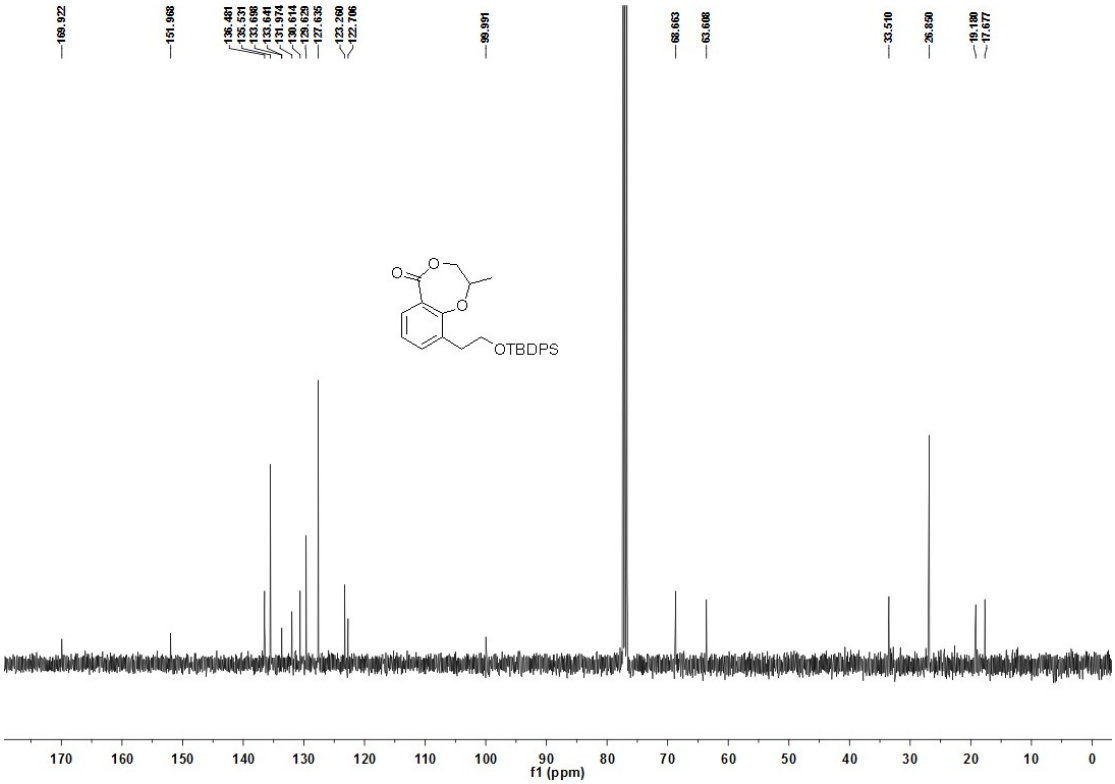


Figure S28. The ^{13}C NMR spectrum of compound **8b** in $CDCl_3$

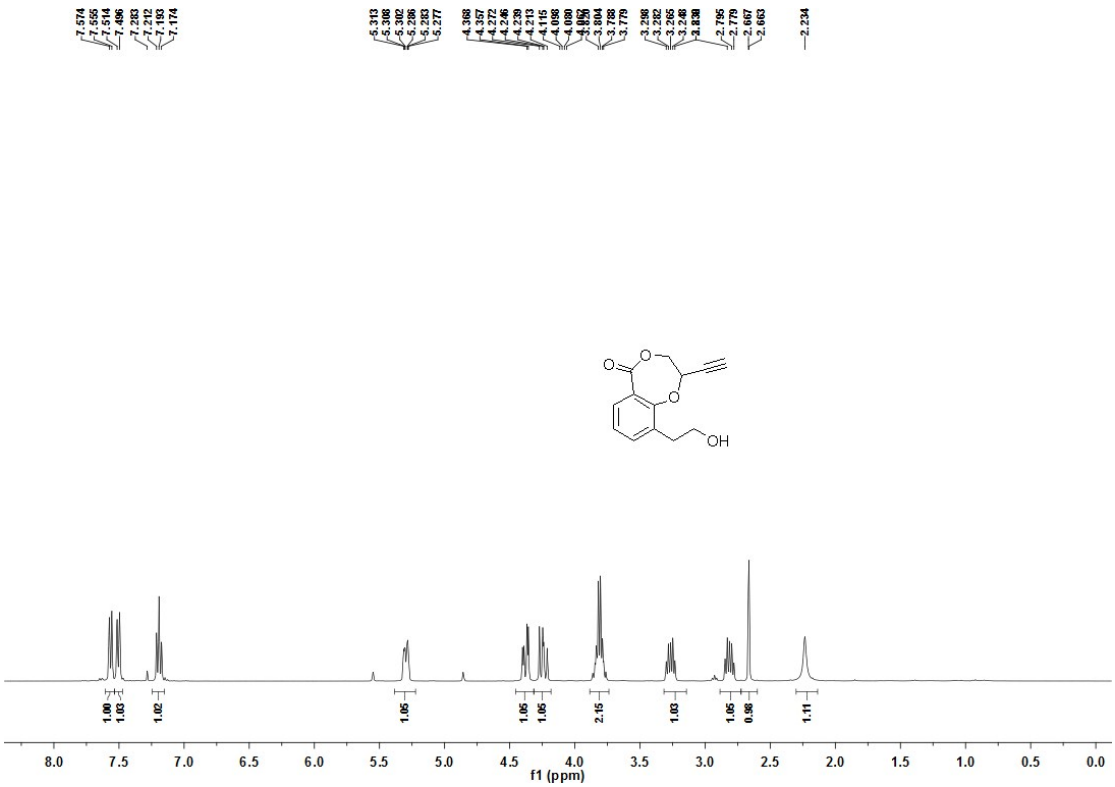


Figure S29. The ^{1}H NMR spectrum of compound **9a** in $CDCl_3$

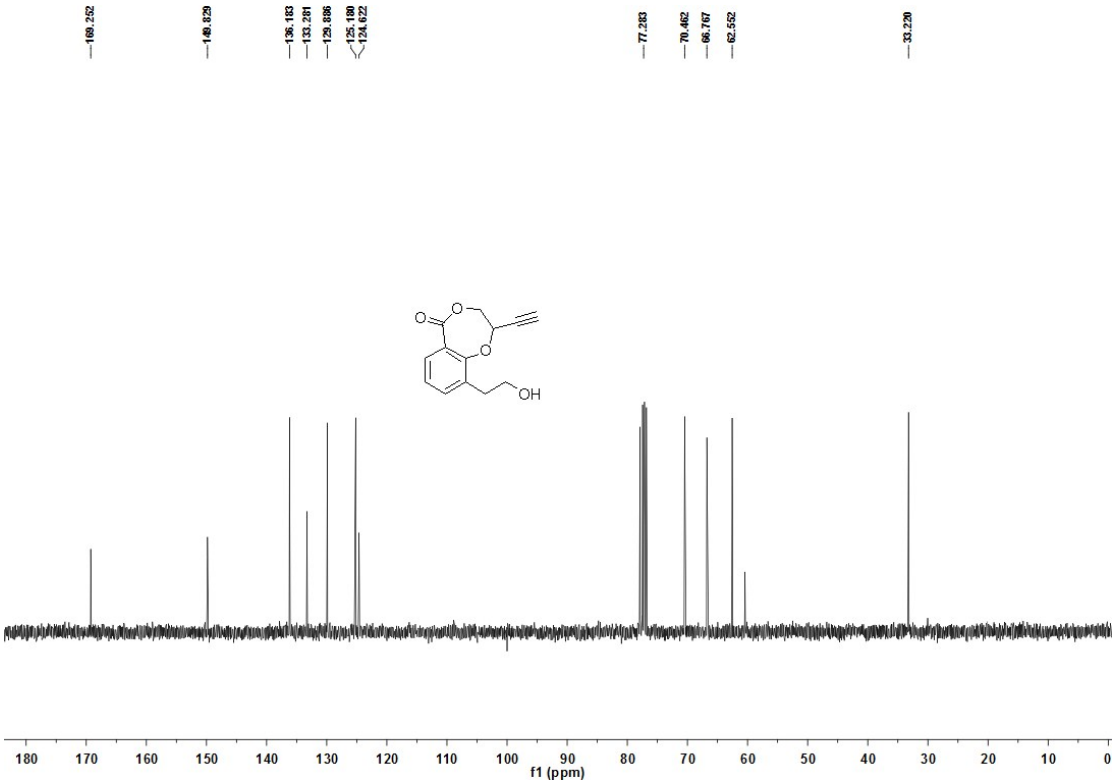


Figure S30. The ^{13}C NMR spectrum of compound **9a** in $CDCl_3$

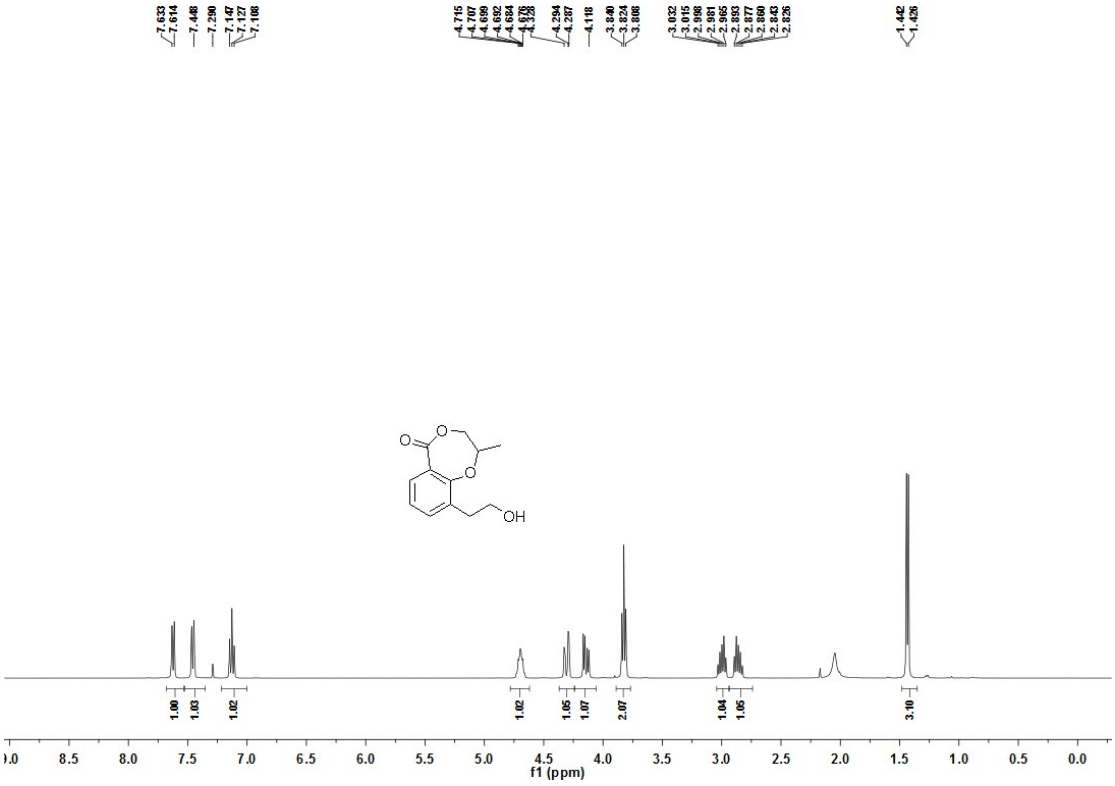


Figure S31. The ^{1}H NMR spectrum of compound **9b** in $CDCl_3$

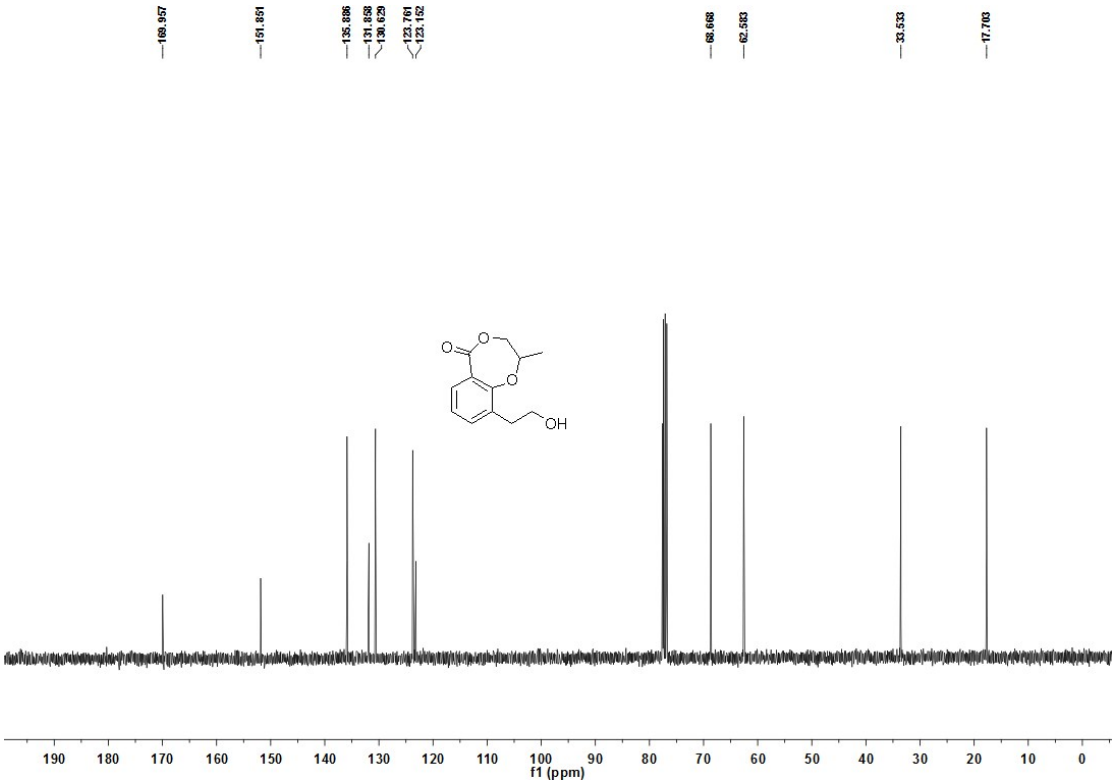


Figure S32. The ^{13}C NMR spectrum of compound **9b** in $CDCl_3$

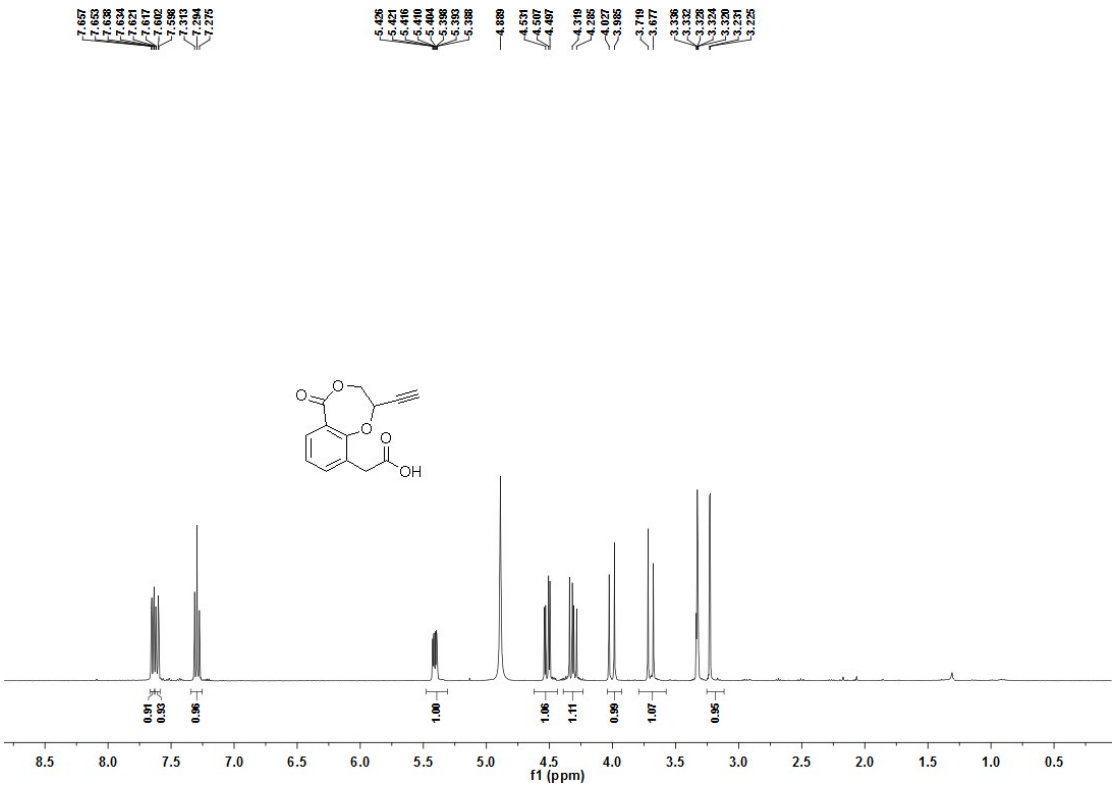


Figure S33. The ^{1}H NMR spectrum of compound **10a** in MeOD

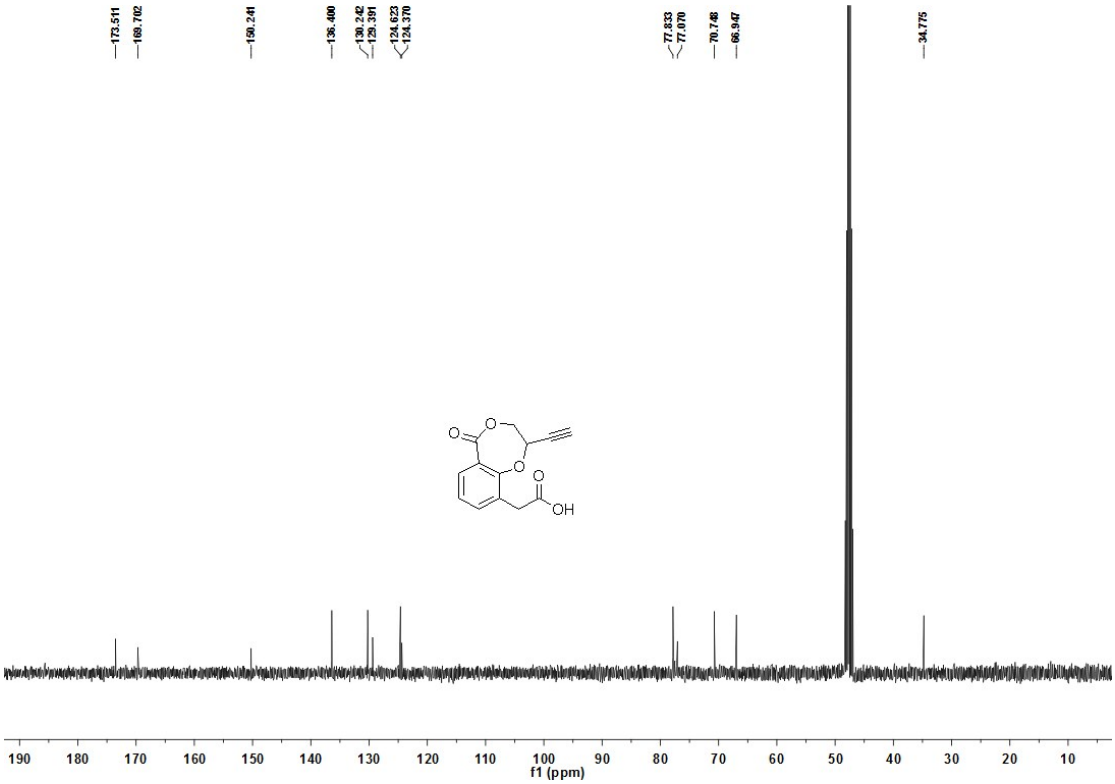


Figure S34. The ^{13}C NMR spectrum of compound **10a** in MeOD

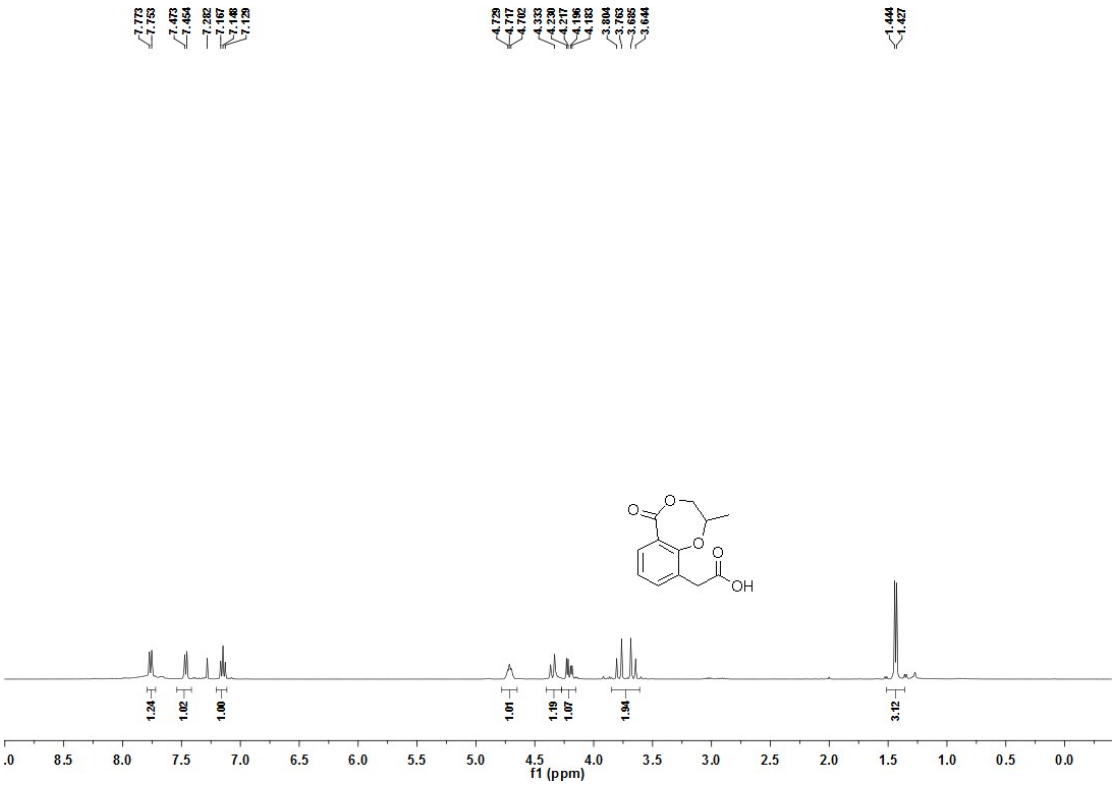


Figure S35. The ^{1}H NMR spectrum of compound **10b** in $CDCl_3$

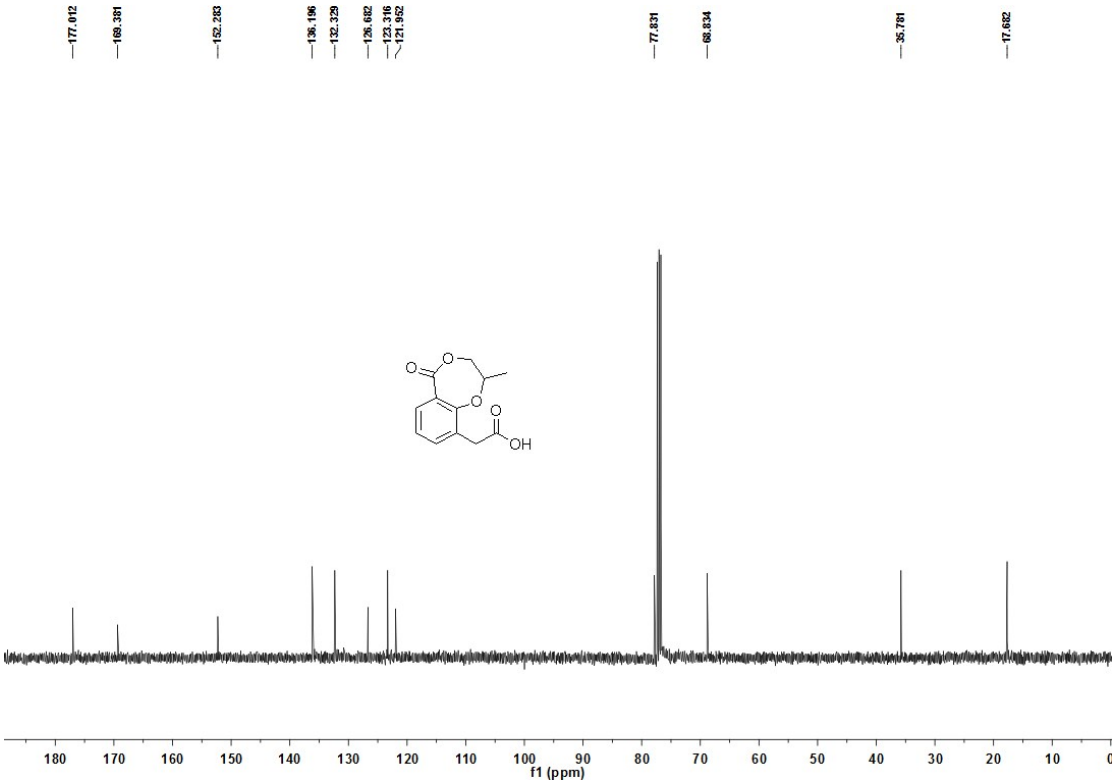


Figure S36. The ^{13}C NMR spectrum of compound **10b** in $CDCl_3$

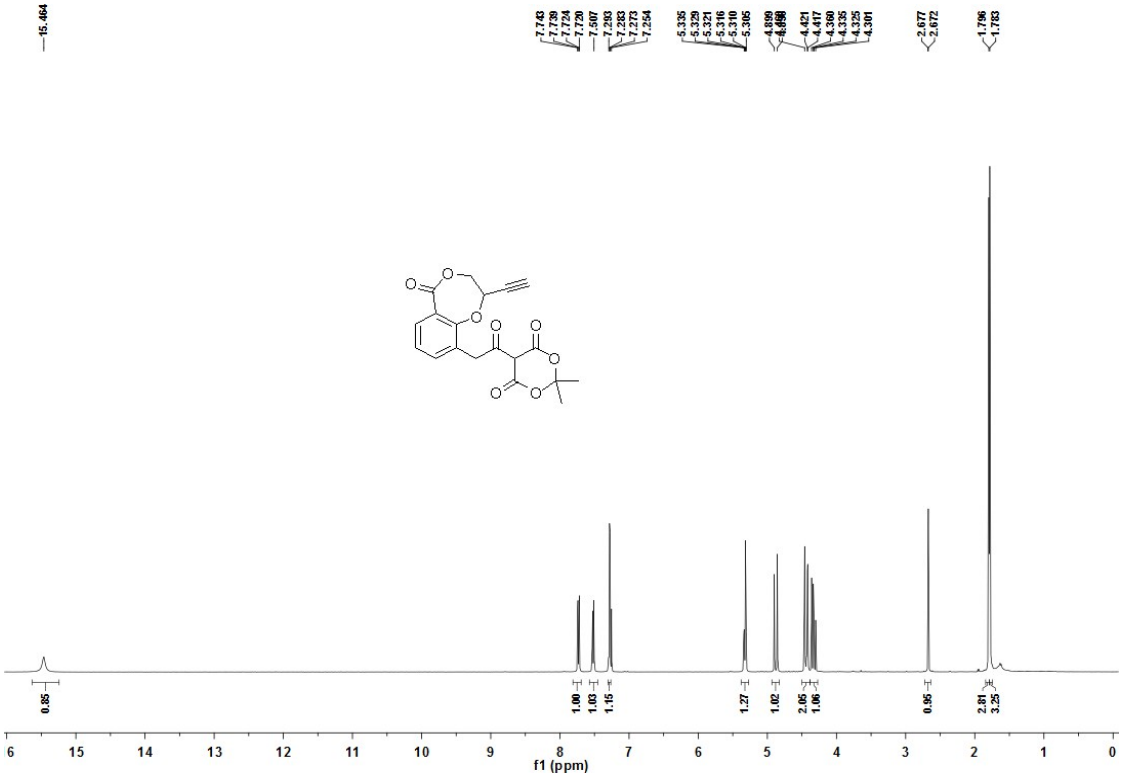


Figure S37. The ^{1}H NMR spectrum of compound **11a** in $CDCl_3$

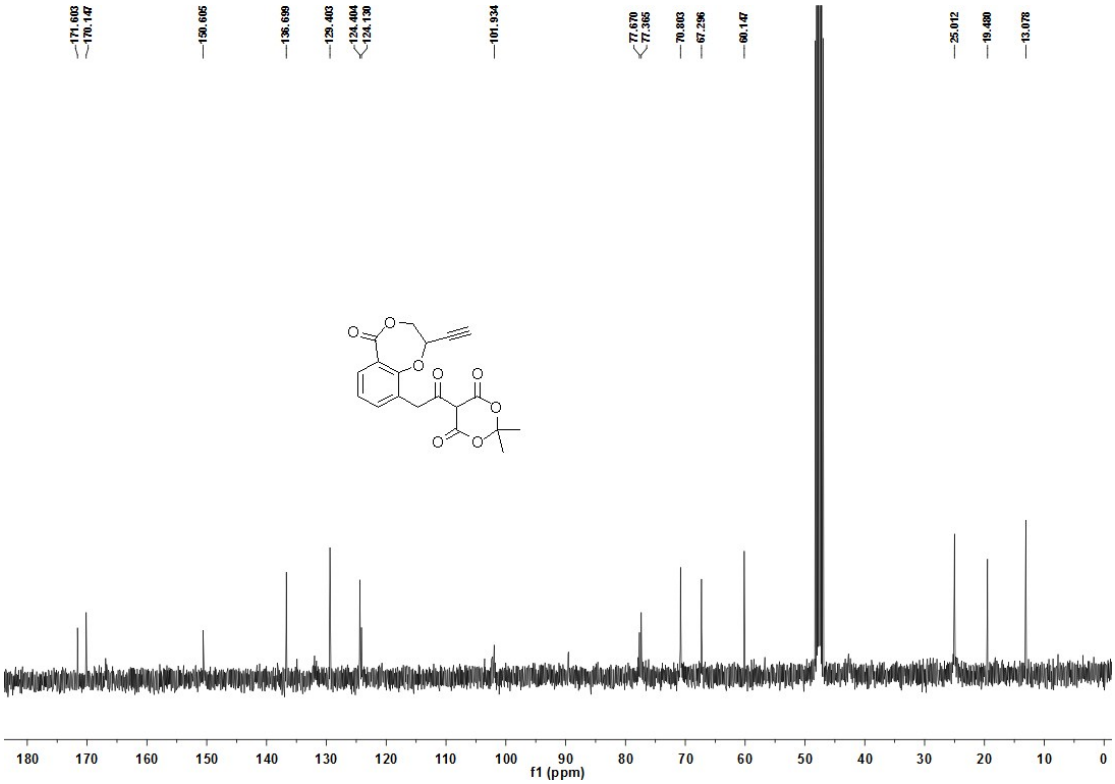


Figure S38. The ^{13}C NMR spectrum of compound **11a** in MeOD

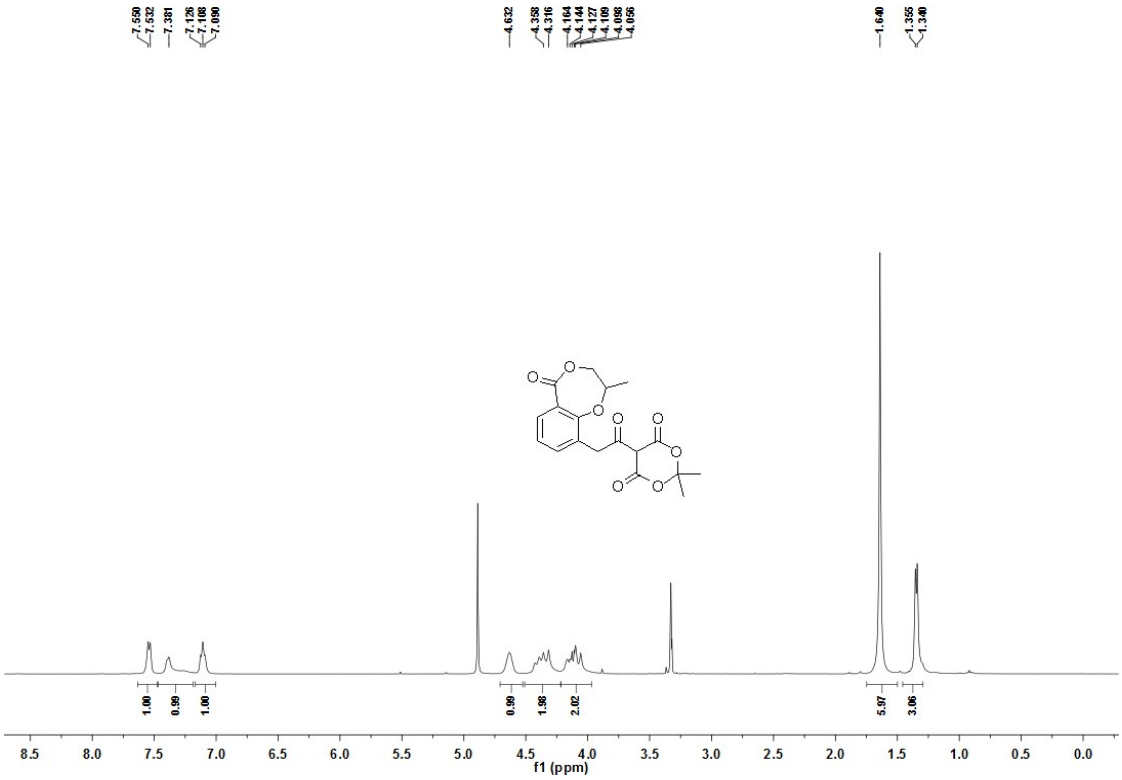


Figure S39. The ^{1}H NMR spectrum of compound **11b** in MeOD

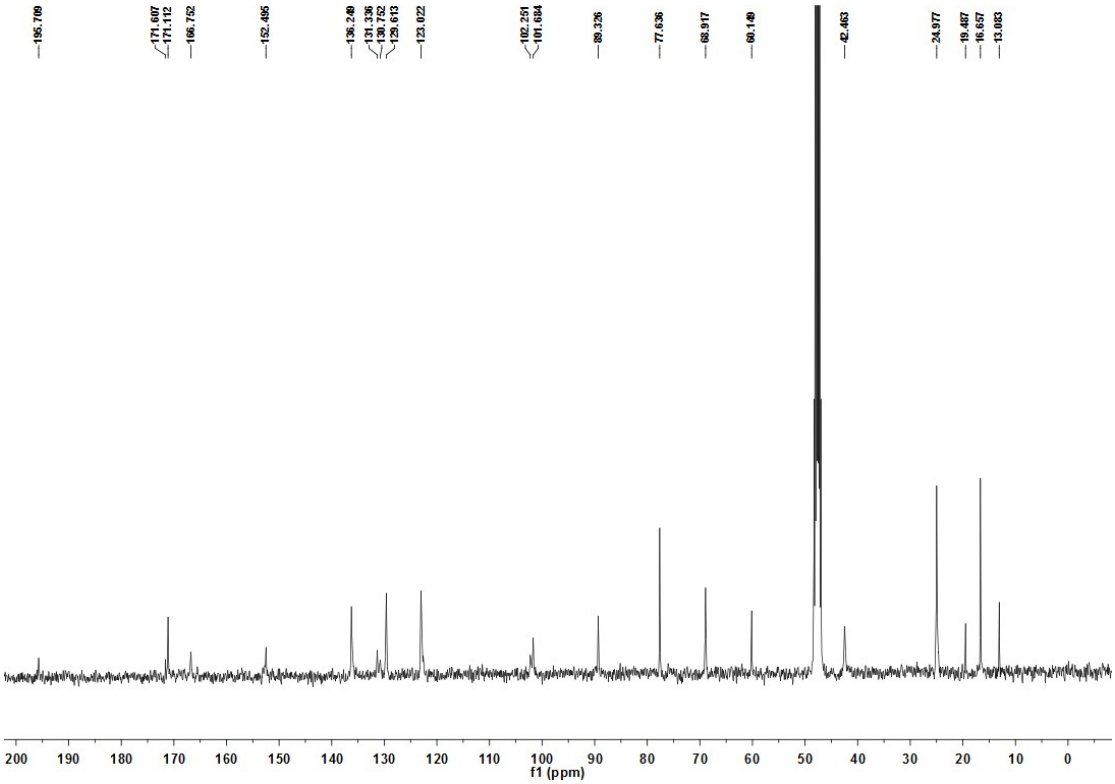


Figure S40. The ^{13}C NMR spectrum of compound **11b** in MeOD

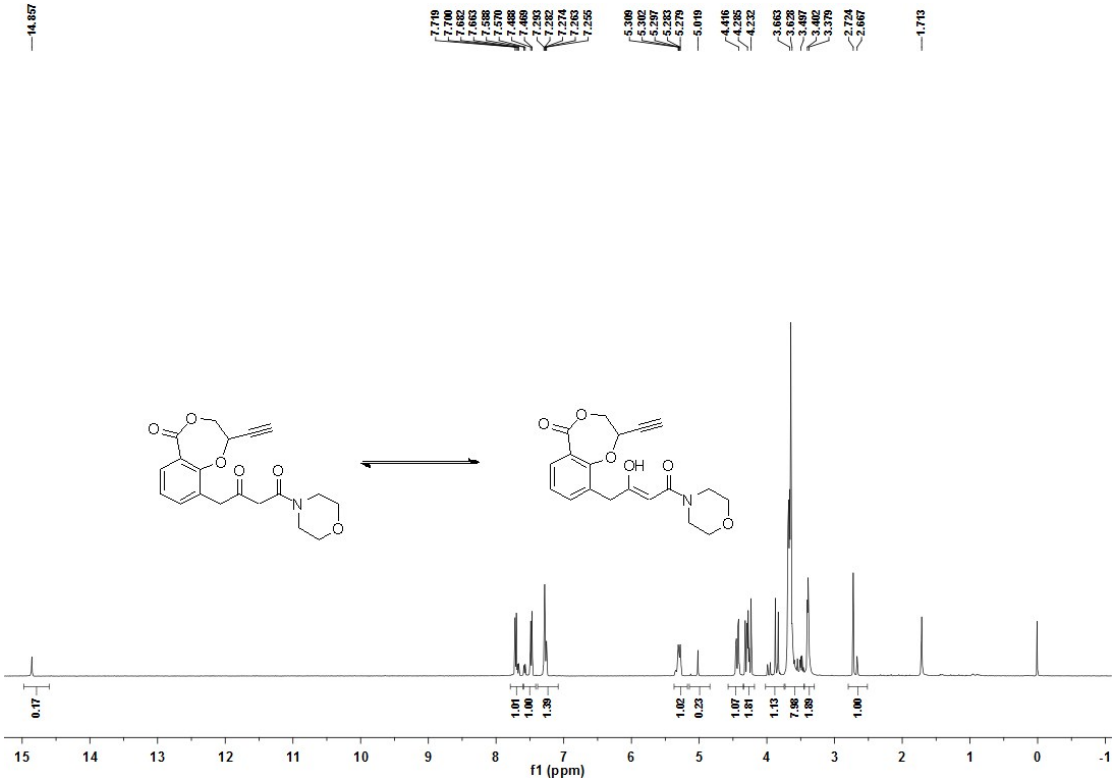


Figure S41. The ^{1}H NMR spectrum of compound **12a** in $CDCl_3$

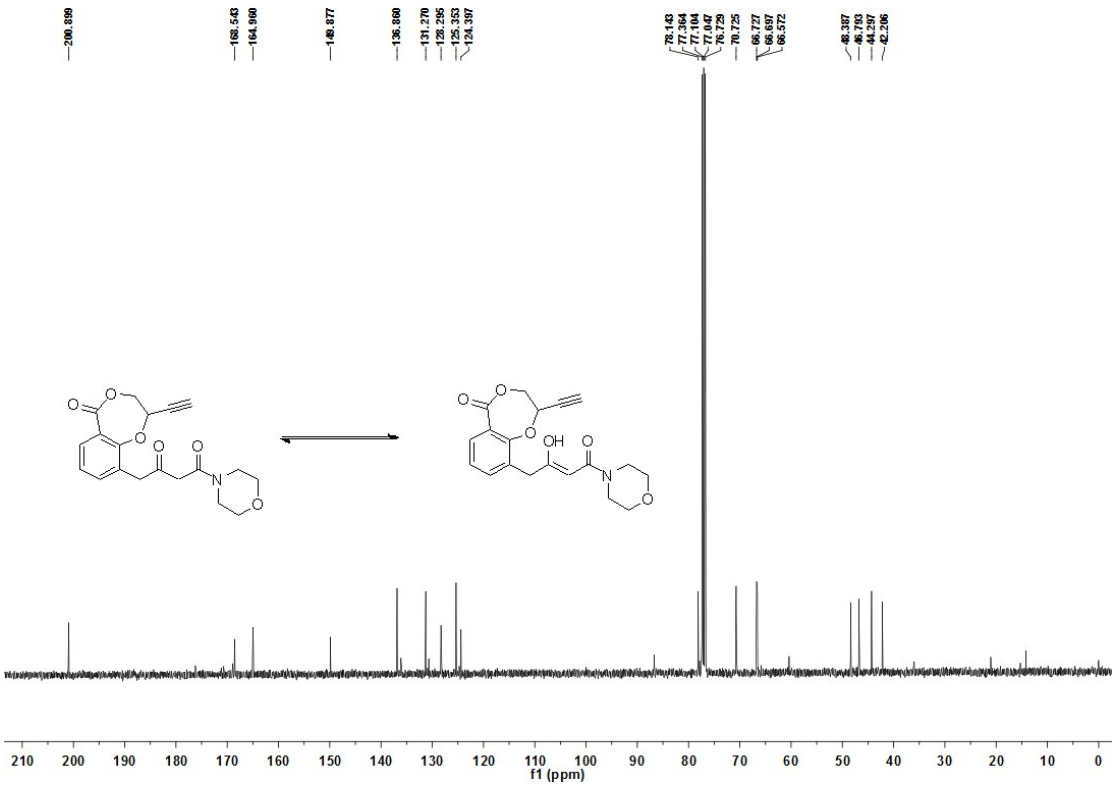


Figure S42. The ^{13}C NMR spectrum of compound **12a** in $CDCl_3$

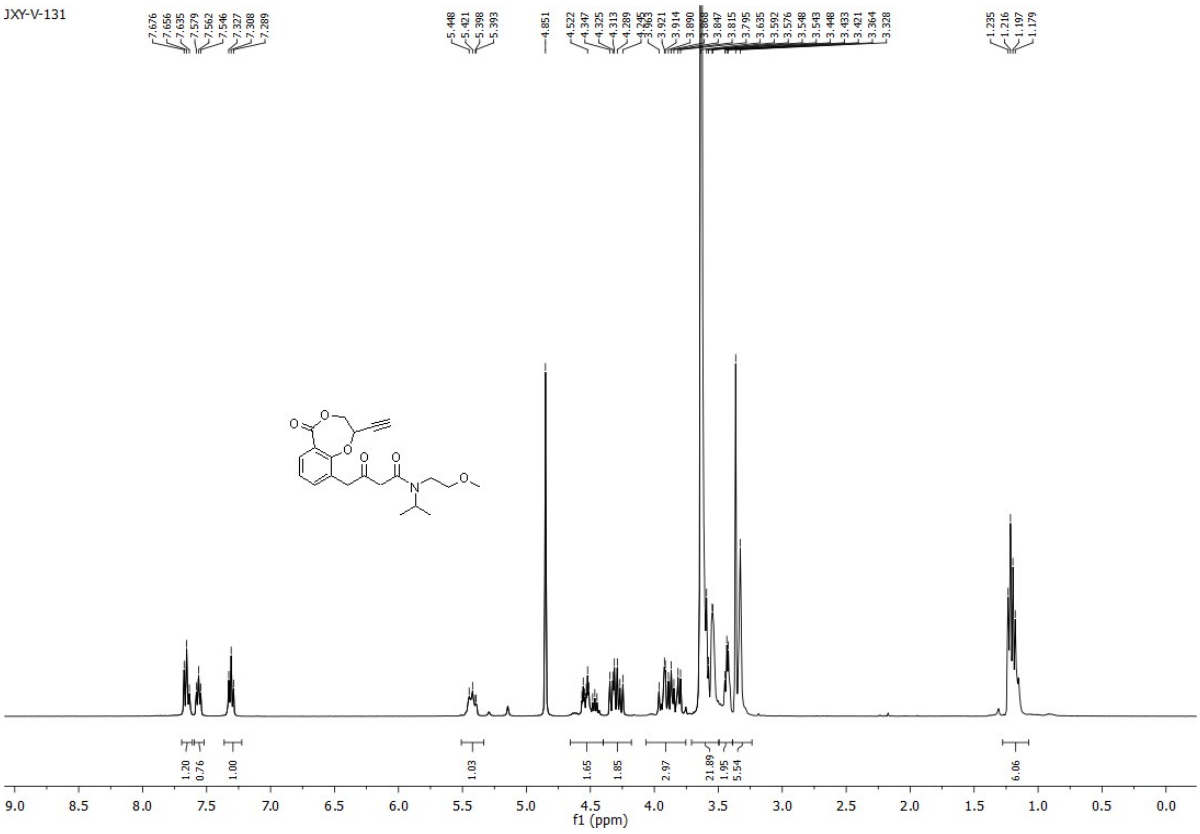


Figure S43. The ^{1}H NMR spectrum of compound **12b** in MeOD

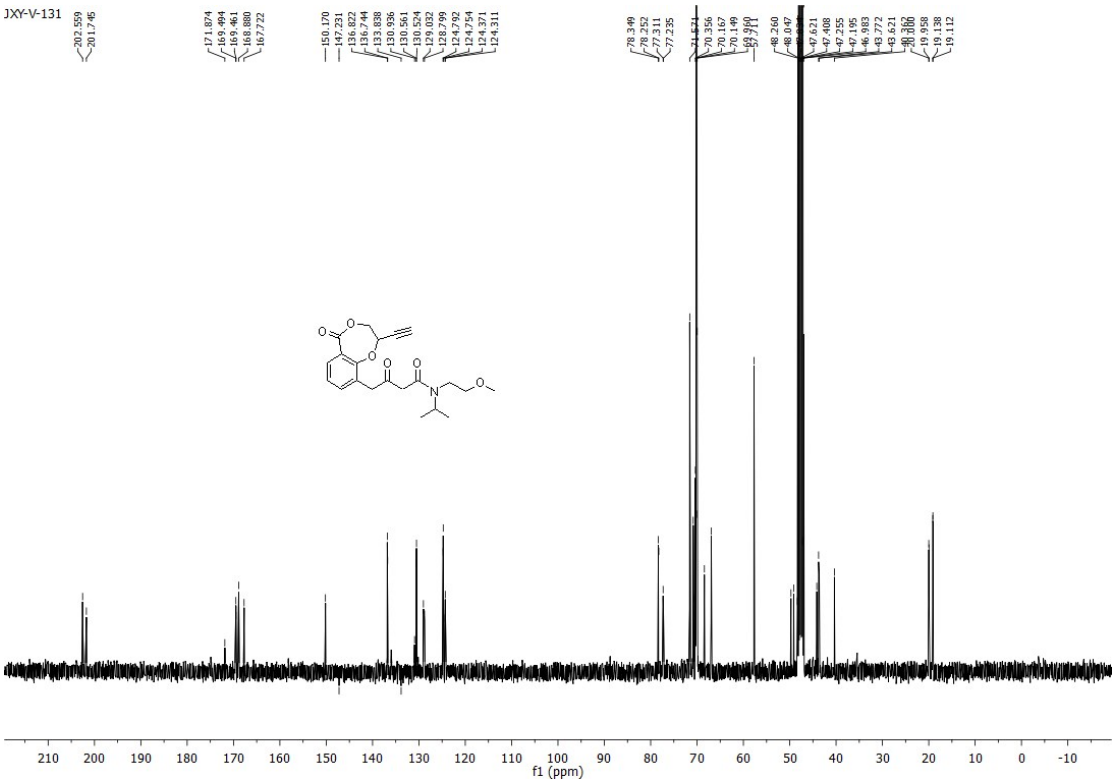


Figure S44. The ^{13}C NMR spectrum of compound **12b** in MeOD

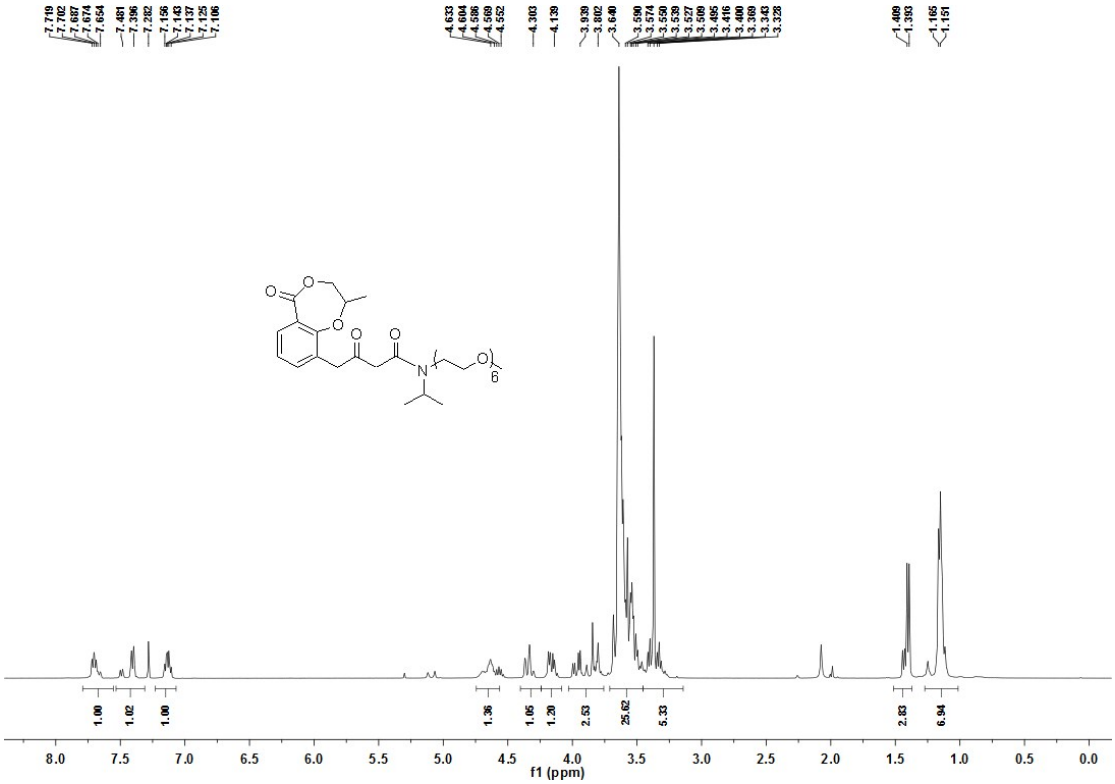


Figure S45. The ^{1}H NMR spectrum of compound **12c** in $CDCl_3$

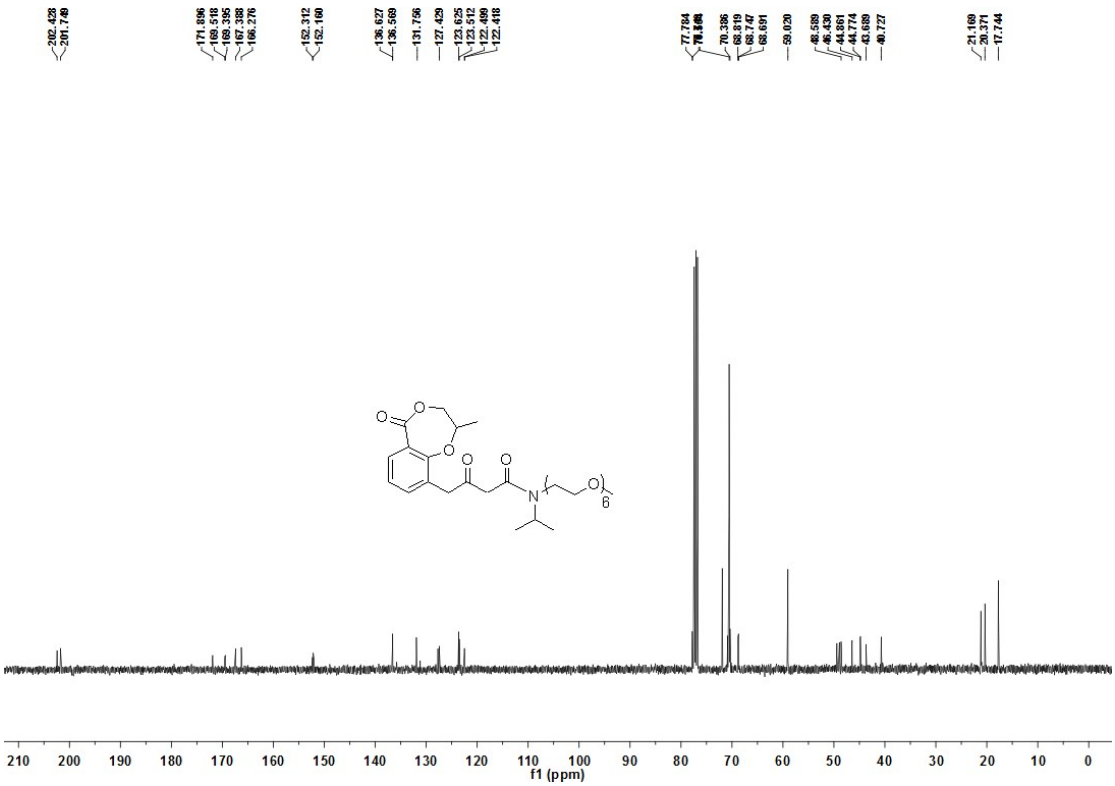


Figure S46. The ^{13}C NMR spectrum of compound **12c** in $CDCl_3$

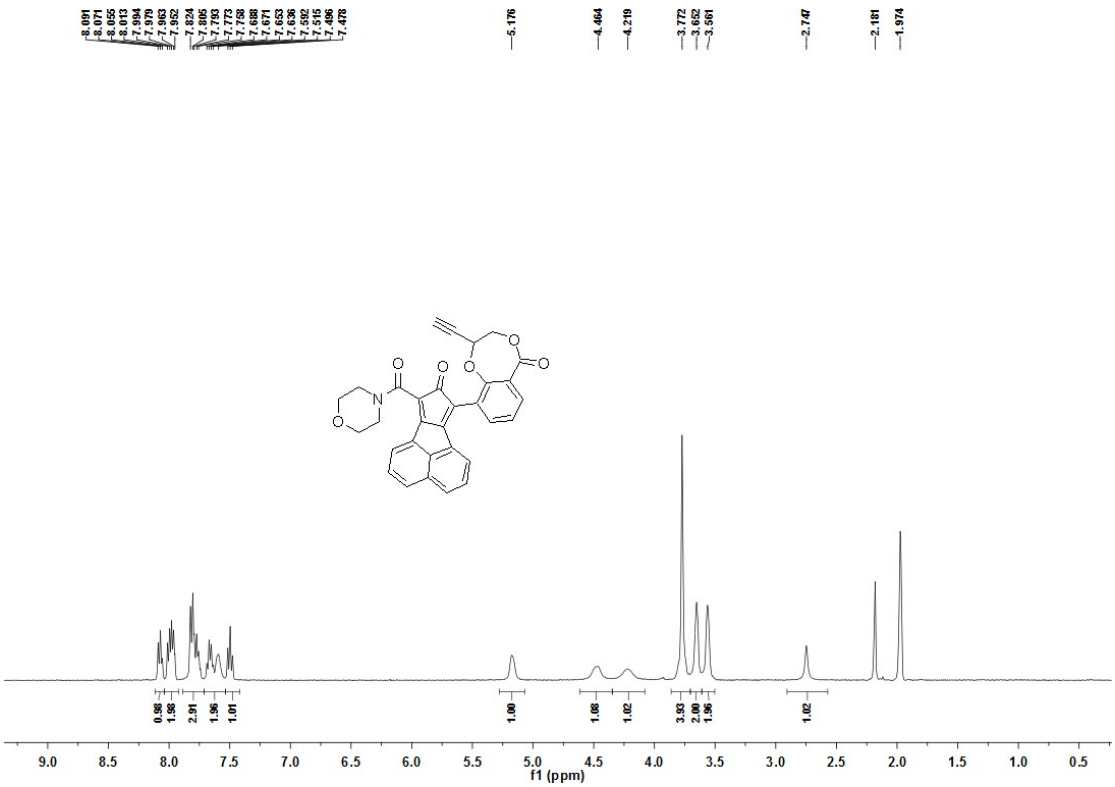


Figure S47. The ^{1}H NMR spectrum of compound **BW-ETCO-101** in CD_3CN

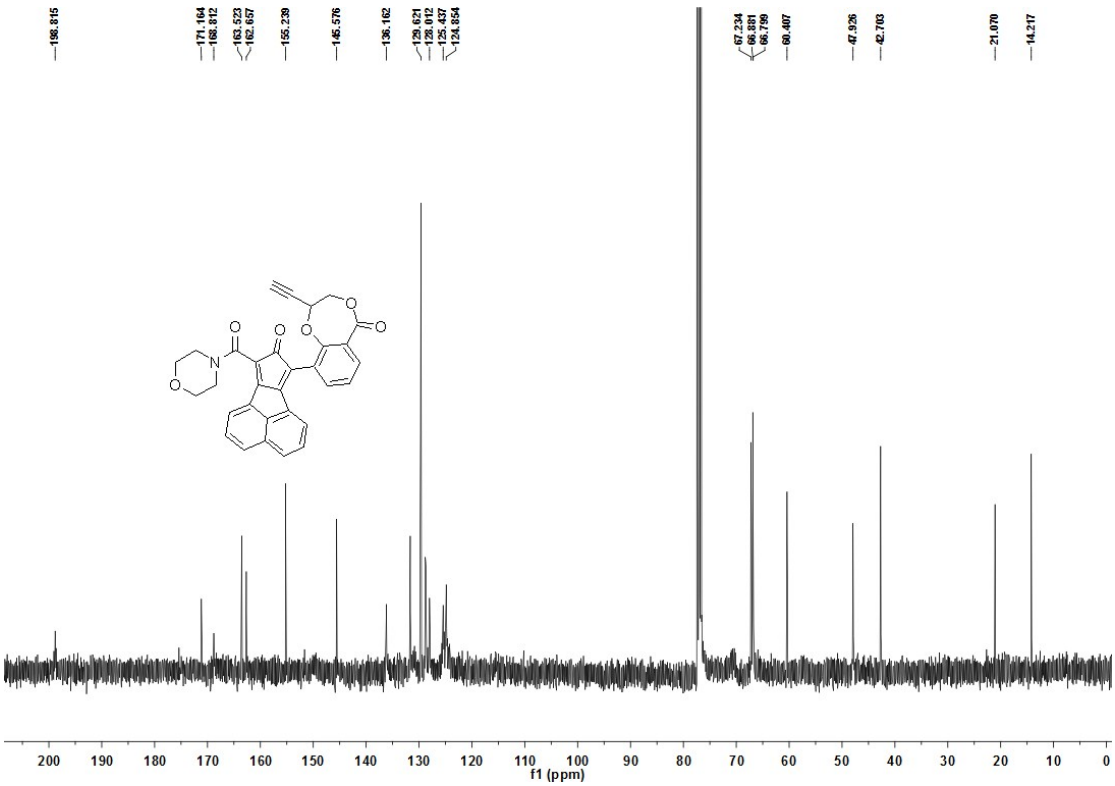


Figure S48. The ^{13}C NMR spectrum of compound **BW-ETCO-101** in CD_3CN

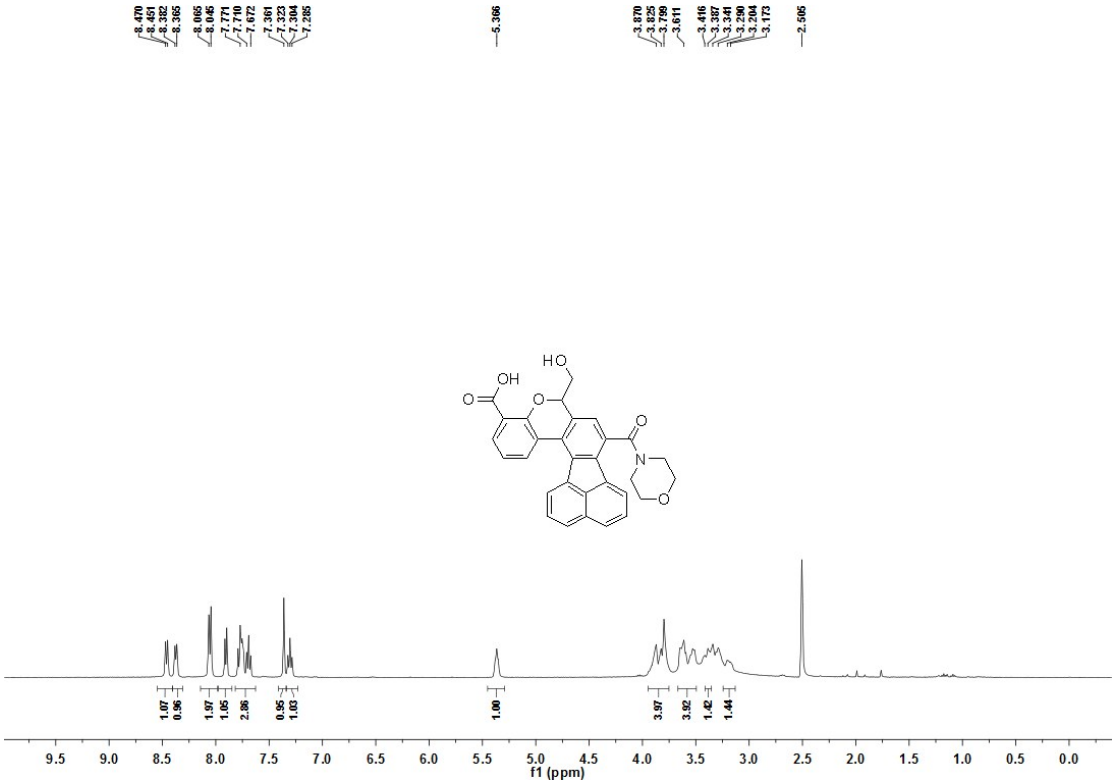


Figure S49. The ^{1}H NMR spectrum of compound **BW-ETCP-101** in DMSO-d_6

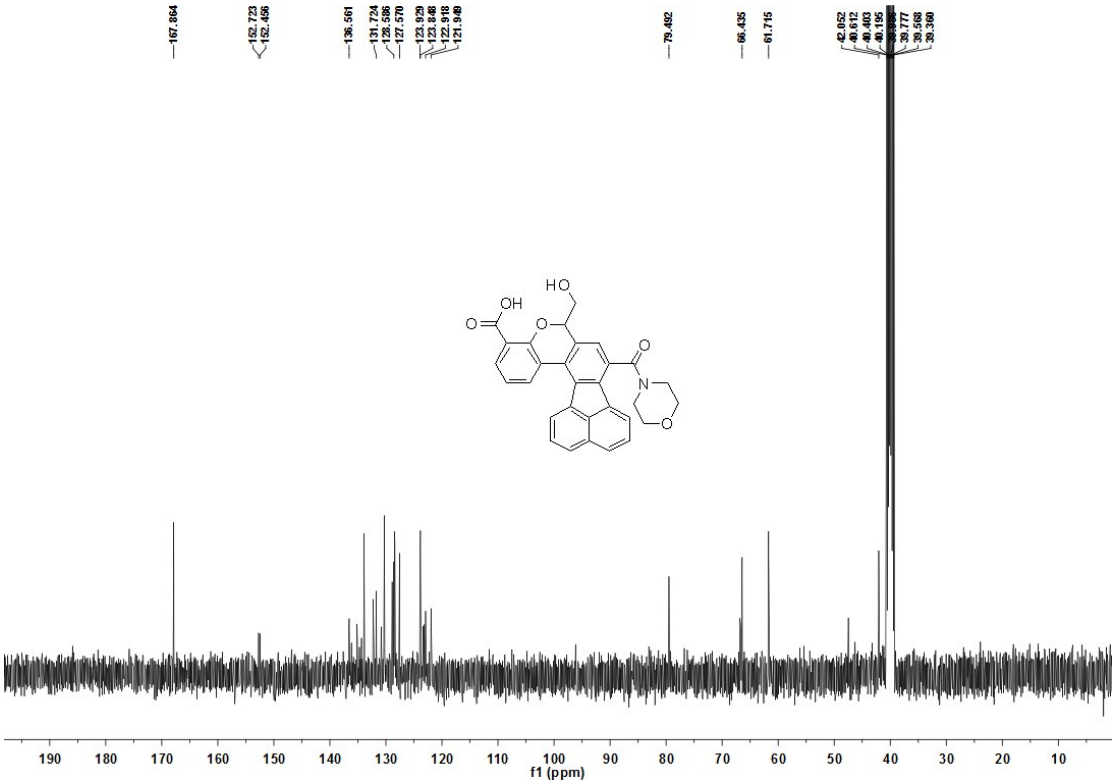


Figure S50. The ^{13}C NMR spectrum of compound **BW-ETCP-101** in DMSO-d_6

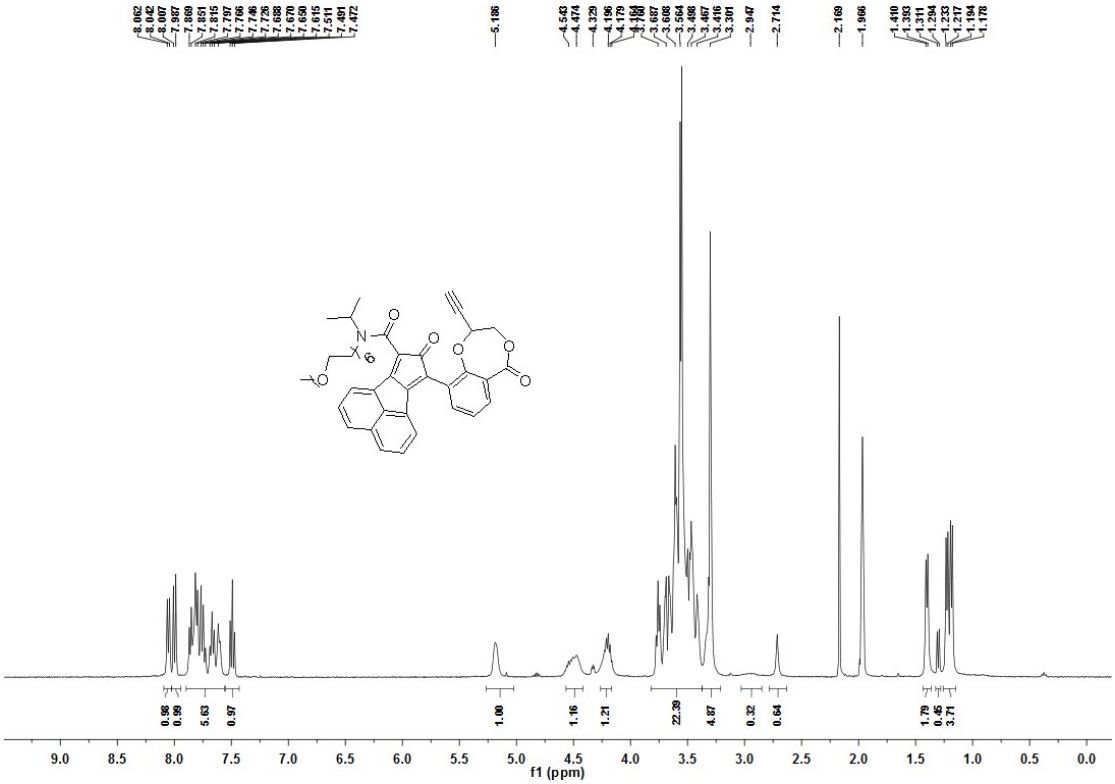


Figure S51. The ^{1}H NMR spectrum of compound **BW-ETCO-102** in CD_3CN

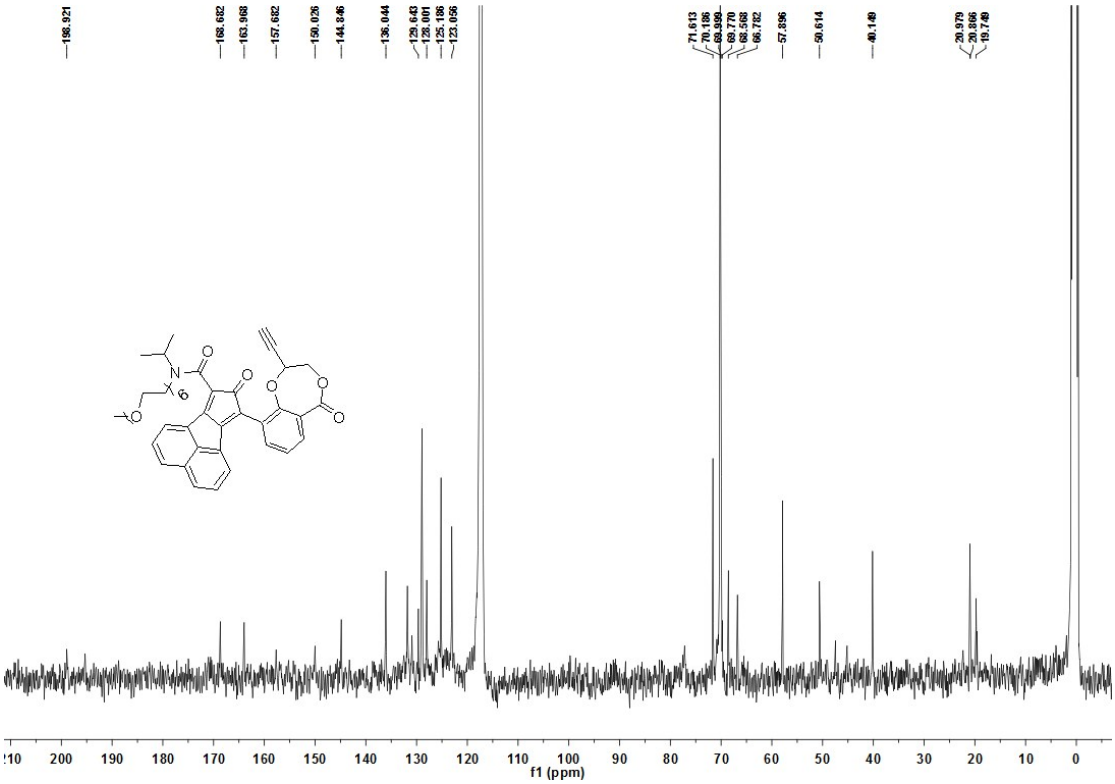


Figure S52. The ^{13}C NMR spectrum of compound **BW-ETCO-102** in CD_3CN

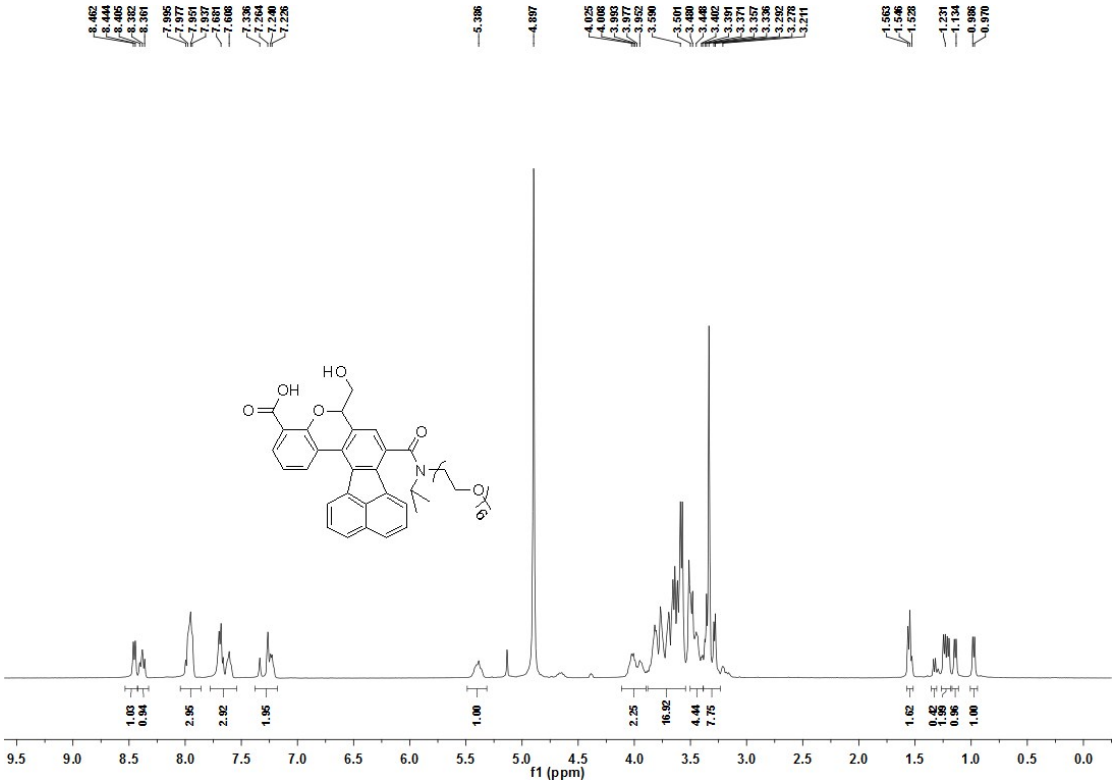


Figure S53. The ^{1}H NMR spectrum of compound **BW-ETCP-102** in CD_3OD

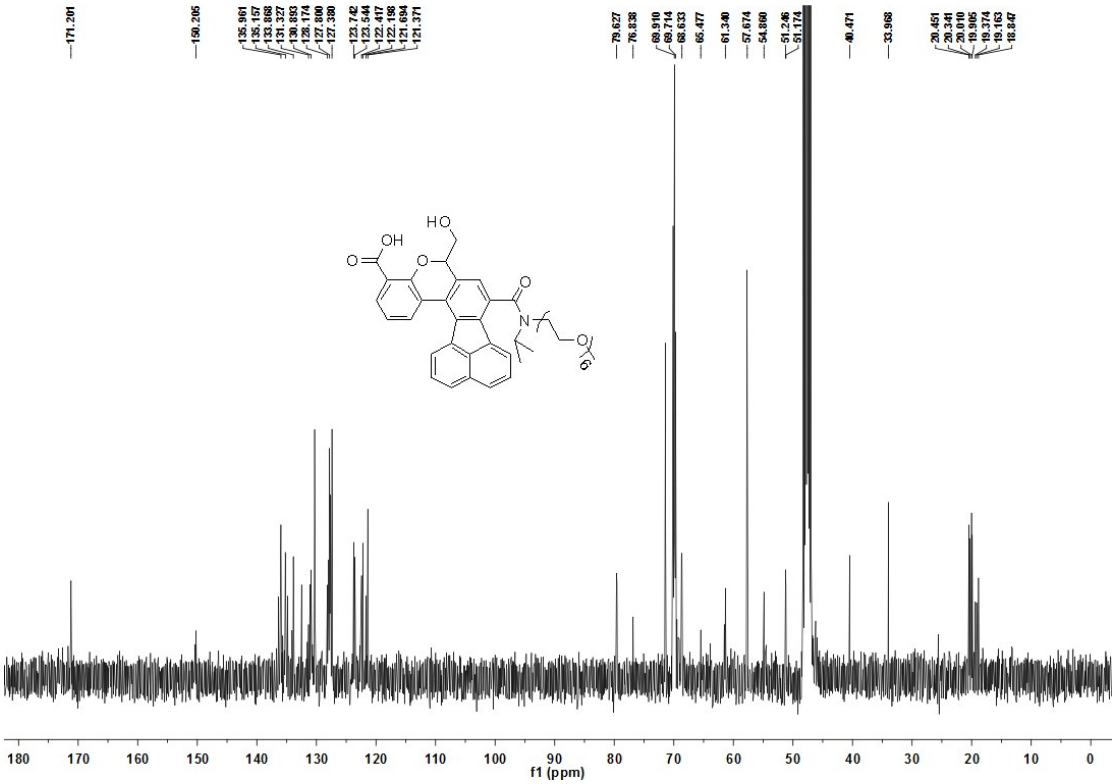


Figure S54. The ^{13}C NMR spectrum of compound **BW-ETCP-102** in CD_3OD

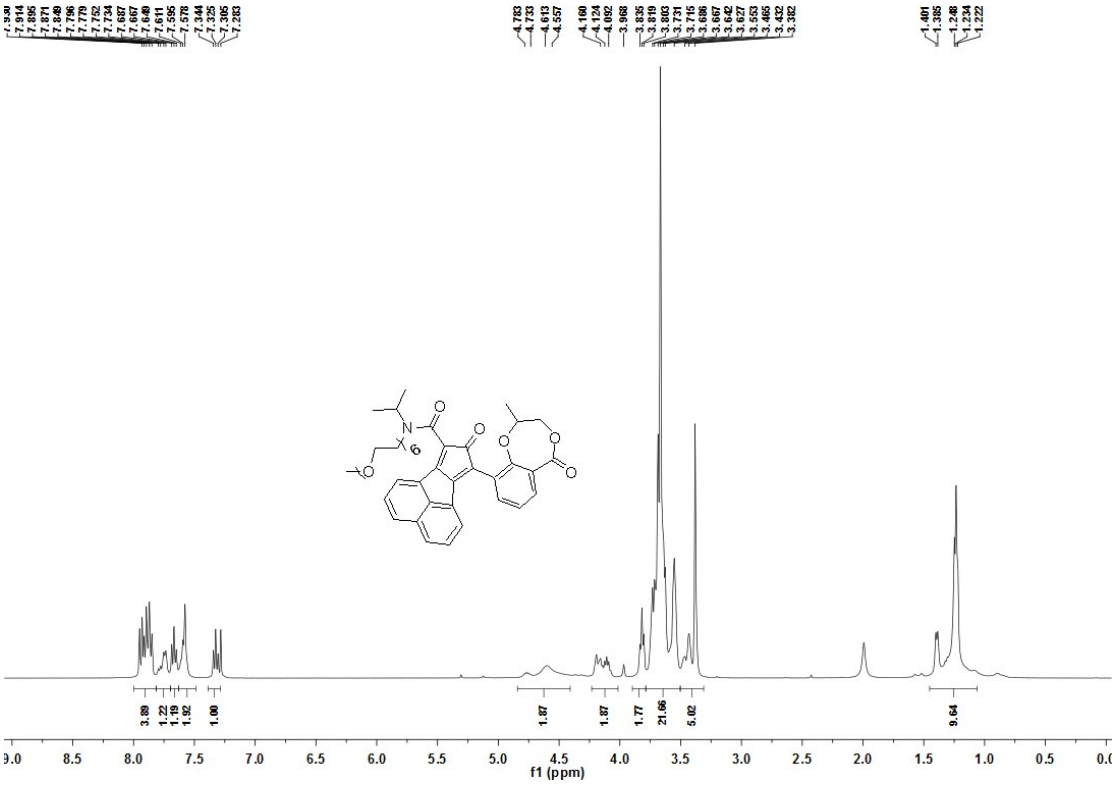


Figure S55. The ^{1}H NMR spectrum of compound **BW-ETCO-103** in $CDCl_3$

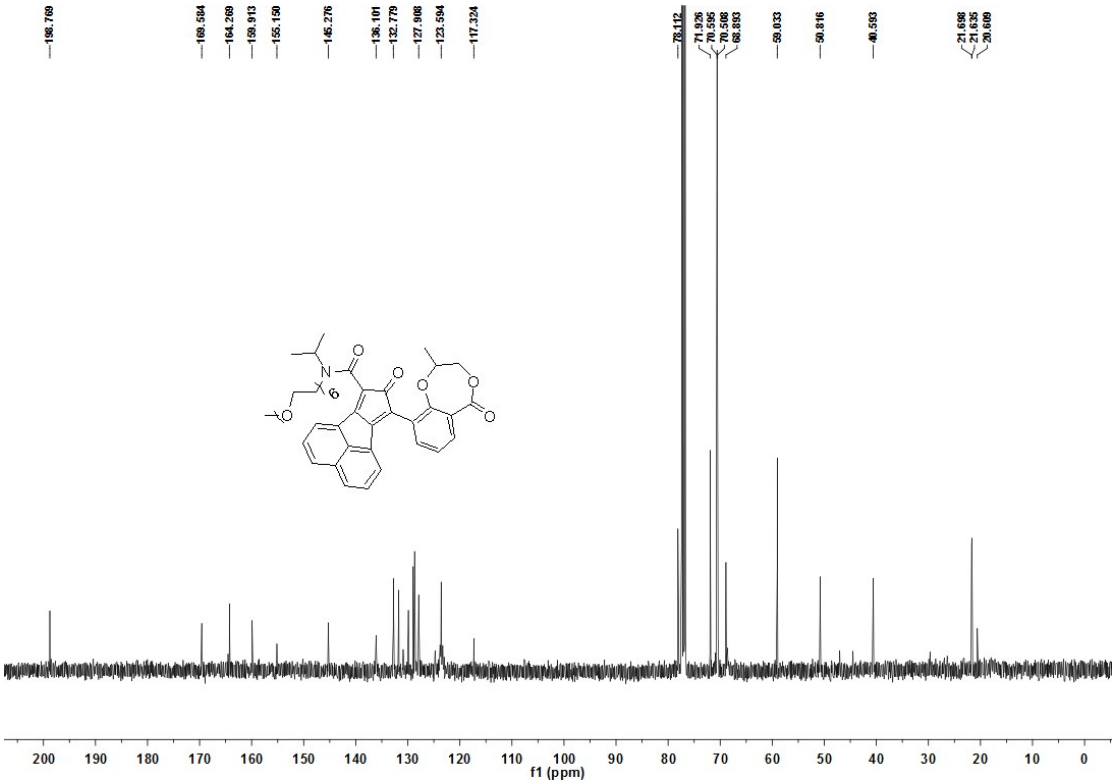


Figure S56. The ^{13}C NMR spectrum of compound **BW-ETCO-103** in $CDCl_3$

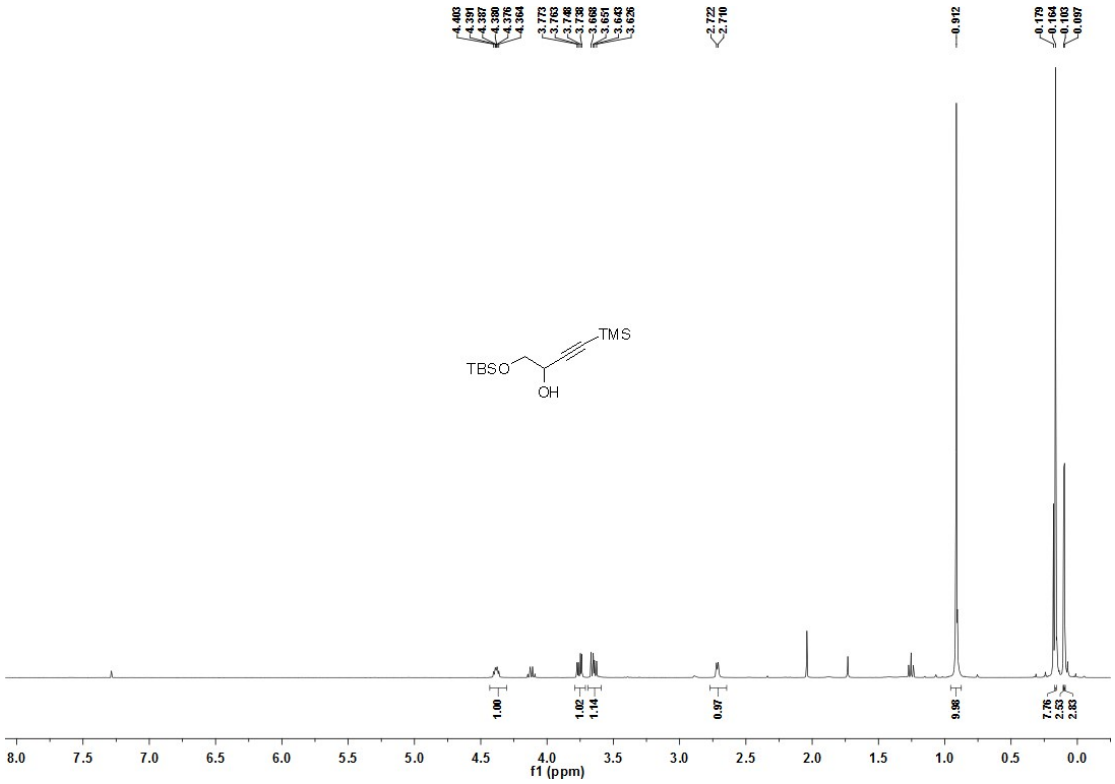


Figure S57. The ^{1}H NMR spectrum of compound **13** in $CDCl_3$

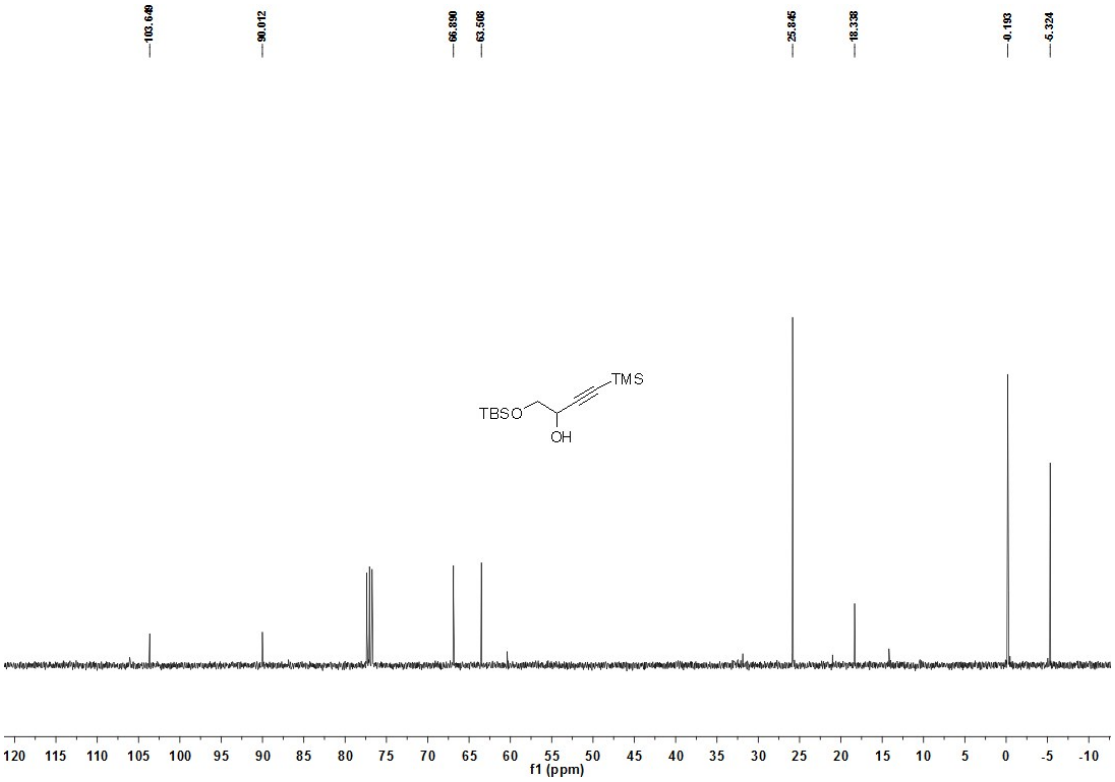


Figure S58. The ^{13}C NMR spectrum of compound **13** in $CDCl_3$