Highly Efficient Green Synthesis and Photodynamic Therapeutic Study of Hypericin and Its Derivatives

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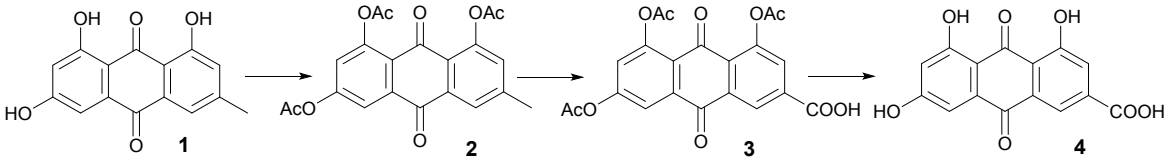
Supporting Information (pages)

1. *General information*

All reagents were purchased from commercial suppliers and used without further purification unless specified. Dimethyl sulfate, N-bromosuccinimide (NBS), 18-crown-6 and benzoyl peroxide (BPO) were purchased from Energy Chemical Reagent Co. Triphenyl phosphine and Tin (II) chloride dehydrate ($SnCl_2{\cdot}2H_2O$) were purchased from Sinopharm Chemical Reagent Co. Butyraldehyde was purchased from TCI. Benzaldehyde was purchased from Aladdin. Ferrous sulfate ($FeSO_4{\cdot}7H_2O$) was purchased from Tianjin Bodi Chemical Co., Ltd.. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from Kehao Biotech Co., Ltd.. Flash chromatography was performed using silica gel with a grain size of 40-63 μm (Qingdao Haiyang Co., Ltd). RPMI 1640 medium, Dulbecco's Modified Essential Medium (DMEM) and trypsin-EDTA solution were obtained from Gibco BRL Co., Ltd.. Penicillin/streptomycin was purchased from Nanjing KeyGen Biotech, fetal bovine serum was purchased from YuanhengJinma Co., Ltd.. NMR spectra were recorded on a Bruker 500 MHz Spectrometer with working frequencies of 500 MHz for ^1H and 125 MHz for ^{13}C, respectively, in DMSO-d_6, MeOH-d_4 or $CDCl_3$. The residual signals from DMSO-d_6 (^1H: δ 2.50 ppm; ^{13}C: δ 39.52 ppm), MeOH-d_4 (^1H: δ 3.31 ppm; ^{13}C: δ 49.00 ppm) or $CDCl_3$ (^1H: δ 7.26 ppm; ^{13}C: δ 77.00 ppm) were used as internal standards. HRMS (High Resolution Mass Spectrometer) analysis was performed on an Agilent 1290−6540 UHPLCQ-TOF-HRMS. UV-Vis spectra were recorded with Shimadzu 1750 UV-Visible spectrophotometer (Japan) at 298 K. MCF-7, HepG-2 and A431 cells were subcultured in an incubator with a humidified atmosphere of 5% CO_2 at 37 °C.

2. *Synthesis of the compounds*

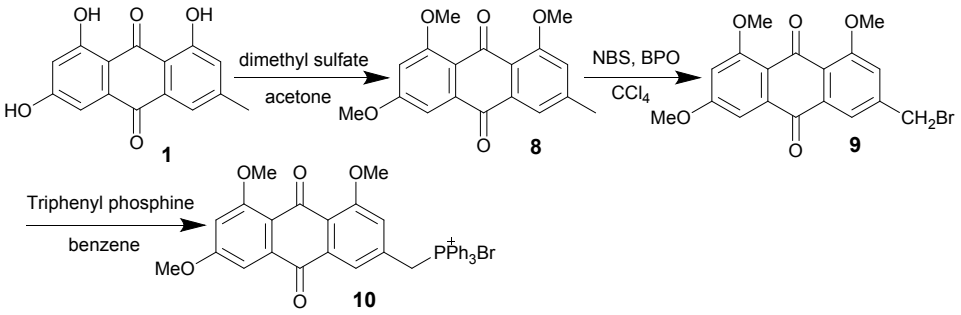


6-methyl-9,10-dioxo-9,10-dihydroanthracene-1,3,8-triyl triacetate (2)： To a 100 mL round-bottom flask, 4.05 g emodin (15.0 mmol) was charged and 40 mL acetic anhydride was added while stirring. To this solution, 750 μL sulfuric acid was added dropwise. The mixture was heated to 65 ^{o}C while stirring and led to react for 40 min. The solution was cooled and mixed with 200mL ice water. The precipitate formed was filtered, washed with water, and dried under vacuum to produce **2** (4.80 g, 82%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 1.0 Hz, 1 H),7.89 (d, J = 2.4 Hz, 1 H), 7.52 (d, J = 2.4 Hz, 1 H), 7.47 (d, J = 1.0 Hz, 1 H), 2.49 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H), 2.4 (s, 3H) ppm.[1]

4,5,7-triacetoxy-9, 10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (3)： To a 205mL flask, 1.19 g **2**(3.0 mmol) was mixed with glacial acetic acid and acetic anhydride (26 mL each) subsequently while stirring at 60 ^{o}C, followed by a solution of 2.55 g chromium trioxide in a mixture of 2.5 mL water and 30 mL glacial acetic acid, which was added dropwise over a 30 min period. The resulting mixture was stirred at 70 ^{o}C for 3 hrs, cooled and then poured into 1 L of ice water. The precipitate formed was filtered, washed with water, and dried under a vacuum to give **3** (1.15 g, 90%) as a yellow green powder.^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, J = 1.5 Hz, 1 H), 8.04 (d, J = 1.5 Hz, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 2.40 (s, 6H), 2.35 (s, 3H) ppm.[1]

4,5,7-trihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (4)： 1.28 g **3** (3.0 mmol) was refluxed in 300 mL 5% NaOH aqueous solution for 3hrs and the mixture was then cooled and acidified with concentrated hydrochloric acid.[5-6] The resulting precipitate was filtered, washed

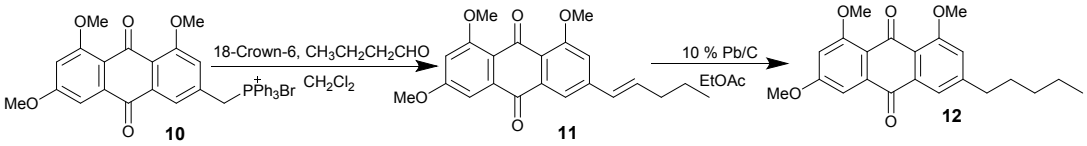
with water and dried to give **4** (828 mg, 92%) as a yellow green powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.71 (s, 1H), 12.00 (s, 1H), 11.93 (s, 1H), 11.56 (s, 1H), 7.99 (s, 1H), 7.64 (s, 1H), 7.05 (s, 1 H), 6.55 (s, 1H) ppm.[1]



1,3,8-Trimethoxy-6-methyl-anthraquinone (8)： To a stirred suspension of 4.32 g emodin (**1**, 6 mmol) and 44.2 g anhydrous K_2CO_3 (320 mmol) in 320 mL dry acetone, 45.5 mL dimethyl sulfate (480 mmol) were added dropwise. The mixture was stirred at room temperature for 30 min and then heated under reflux for 15hrs, cooled to room temperature, and diluted with 400 mLwater. After stirring for further 15 min, the mixture was extracted with 300 mL $CHCl_3$, washed with water, dried with Na_2SO_4, and evaporated. Crystallization from ethanol gave **8** (4.52 g, 91%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 0.8 Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 7.07 (s, 1H), 6.74 (d, J = 2.4 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 2.44 (s, 3H) ppm.[2]

6-Bromomethyl-I, 3, 8-trimethoxy-anthraquinone (9)： A mixture of 1.25 g **8** (2.64 mmol), 712 mg N-bromosuccinimide (4 mmol), 40 mg benzoyl peroxide, and 120 mL $CC1_4$ was refluxed for 46 hrs. After cooling to room temperature, the yellow solid was filtered, washed with $CC1_4$, hot water, and dried. Crystallization from benzene gave **9** (1.3 g, 83%) as a pale yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 1.5 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 4.51 (s, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H) ppm.[2]

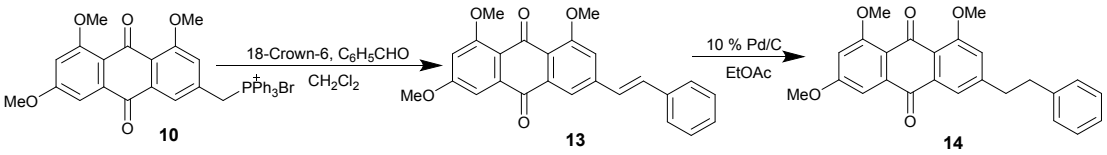
1,6,8-Trimethoxy-anthraquinon-3-yl-methyl-triphenylphosphoniumbromide (10)： A solution of 117 mg **9** (0.3 mmol) and 102 mg triphenylphosphine (0.39 mmol) in 10 mL anhydrous benzene was refluxed for 32 hrs. The yellow triphenylphosphonium salt was filtered and washed with benzene and dry ether. Purification of the crude by column chromatography on silica using a mixture of trichloromethane/methanol = 20:1 as eluent gave **10** (164 mg, 80%) as a yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.88 – 7.76 (m, 9H), 7.66 (dt, J = 7.8 and 3.5 Hz, 6H), 7.17 (d, J = 2.4 Hz, 1H), 7.10 – 7.03 (m, 1H), 6.72 (d, J = 2.4 Hz, 1H), 5.64 (d, J = 15.1 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H) ppm.[2]



1,3,8-trimethoxy-6-(pent-1-en-1-yl) anthracene-9,10-dione (11)： Compound **11** was synthesized by following a published procedure with some modification.[2] Briefly, a mixture of 297.5 mg **10** (0.46 mmol), 126 mg K_2CO_3 (0.9 mmol), and 48 mg 18-Crown-6 in 8 ml dry CH_2Cl_2 was refluxed for 15 min. To this refluxing dark blue ylide solution, 332 mg butyraldehyde (4.6 mmol) dissolved in 8 mL dry CH_2Cl_2 was added in 3 portions by 40 min intervals. During this time, the color changed from blue back to yellow. After refluxing for an additional 30 min, the reaction mixture was cooled to room temperature, diluted with benzene, and filtered to remove K_2CO_3. The filtrate was washed with saturated NaCl solution, dried with Na_2SO_4, and evaporated in vacuum. The purification of the crude by column chromatography on silica using a mixture of dichloromethane/petrol ether/ethyl acetate = 10:7:1 as eluent recovered the excess amount of unreacted butyraldehyde, and a mixture of dichloromethane/petrol ether/ethyl acetate = 10:5:1 gave **11** (95 mg, 56%) as a yellow powder. M.p.:159.8-160.3 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.81 (d, J = 1.3 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 1.1 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.53 – 6.39 (m, 2H), 3.99 (s, 3H), 3.94 (d, J = 7.3 Hz,3H), 2.25 (q, J = 6.9 Hz,2H), 1.53 (sextet, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4, 181.6, 163.8, 161.9, 160.2, 143.4, 136.6, 135.7, 134.9, 128.9, 122.3, 118.6, 116.6, 115.5, 105.4, 102.1, 56.6, 56.6, 55.9, 35.3, 22.3, 13.9 ppm. HRMS: *m/z* calculated for $C_{22}H_{22}O_5$ $[M + H]^+$ 367.1545. Found 367.1549.

1,3,8-trimethoxy-6-pentylanthracene-9,10-dione (12)： Compound **12** was synthesized by following a published procedure with some modification.[2, 6-9] Briefly, a mixture of 110 mg **11** (0.3 mmol), 129 mg 10% Pd/C in 60 mL ethyl acetate was hydrogenated at room temperature and atmospheric pressure for 12 hrs. The catalyst was then filtered off and washed with ethyl acetate. The combined organic solution were evaporated, and the residue was chromatographed on a dry silica column using a mixture of dichloromethane/petrol ether/ethyl acetate = 10:5:1 as eluent to give **12** (90 mg, 82%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.09 (s, 1H), 6.76 (d, J = 2.4 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 2.73 – 2.64 (m, 2H), 1.75 – 1.63 (m, 2H), 1.42 – 1.27 (m, 4H), 0.95 – 0.85 (m, 3H,) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 182.0, 163.9, 161.9, 159.9, 149.8, 136.7, 134.7, 122.0, 119.1, 118.6, 105.4, 102.1, 56.7, 56.6, 56.0, 36.5, 31.6, 30.7, 29.8, 22.6, 14.1 ppm. HRMS: *m/z* calculated for $C_{22}H_{24}O_5$ $[M + H]^+$ 369.1697. Found 369.1703. m.p.: 117.4-117.6 ^{o}C.



1,3,8-trimethoxy-6-styrylanthracene-9,10-dione(13)： A mixture of 351.9 mg **10** (0.54 mmol), 138 mg K_2CO_3 (1.08 mmol), and 98 mg 18-Crown-6 in 10 mL dry CH_2Cl_2 was refluxed for 15 min. To this refluxing dark blue ylide solution, 572.4 mg benzaldehyde (5.4 mmol) dissolved in 10 mL dry CH_2Cl_2 was added in 3 portions in 40 min intervals. During this time, the color changed from blue back to yellow. After refluxing for an additional 30 min, the reaction mixture was cooled to room temperature, diluted with benzene, and filtered to remove K_2CO_3. The filtrate was washed with saturated NaCl solution, dried with Na_2SO_4, and evaporated. Column chromatography on silica using first a mixture of dichloromethane/petrol ether/ethyl acetate = 10:7:1 as eluent recovered the excess amount of unreacted benzaldehyde, and then a mixture of dichloromethane/petrol ether/ethyl acetate = 10:5:1 gave **13** (201 mg, 93%) as a yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, J = 1.3 Hz, 1H), 7.68 (s, 1H), 7.52 (s, 1H), 7.44 – 7.40 (m, 3H), 7.35 – 7.23 (m, 3H), 7.16 (d, J = 2.4 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H) ppm.[3]

1,3,8-trimethoxy-6-phenethylanthracene-9,10-dione (14)： Compound **14** was synthesized by following a published procedure with some modification.[2, 4, 10] Briefly, a mixture of 378.3 mg **13** (0.95 mmol), 241 mg 10% Pd/C in 150 ml ethyl acetate was hydrogenated at room temperature and atmospheric pressure for 12 hrs. The catalyst was filtered off and washed with ethyl acetate. The combined organic solution was evaporated, and the residue was chromatographed on a dry silica column using a mixture of dichloromethane/ethyl acetate = 20:1 as eluent to give **14**

(320mg, 84%) as a yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 1.3 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 2H), 7.22 – 7.14 (m, 3H), 6.92 (s, 1H), 6.76 (d, J = 2.4 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H), 3.05 – 2.92 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 181.9, 163.9, 161.9, 159.8, 148.2, 140.9, 136.6, 134.8, 128.7, 128.6, 126.4, 122.1, 119.1, 118.8, 105.4, 102.1, 56.6, 56.6, 56.0, 38.3, 37.3 ppm. HRMS: *m/z* calculated for $C_{25}H_{22}O_5$ $[M + H]^+$ 403.1540. Found 403.1548. m.p.: 178.0-178.5 ^{o}C.

Synthesis of 6a in large scale

To a microwave 10 mL tube, **5a** (5.0 mmol, 1.28 g), pyridine-N-oxide (26.3 mmol, 2.51 g), $FeSO_4{\cdot}7H_2O$ (107 mg, 0.38mmol), and NaOH (203 mg, 5.0 mmol) were dissolved in 20 mL ultrapure water. The mixture was irradiated in a microwave unit at 10 W, 105 ^{o}C under argon atmosphere for 70 min. The reaction mixture was cooled to room temperature, and was acidified with 3% hydrochloric acid. The precipitate was filtered, washed with deionized water, and vacuum dried. The purification with column chromatography in silica gel by using petroleum ether/ethyl acetate/methanol (4:8:1 in volume) as eluent gave **6a** as a purple solid (1.15 g, 91.6%).

Synthesis of 7a in large scale

To a 50 mL flask, **6a** (1.0g, 2.0 mmol) dissolved in 200 mL acetone was irradiated for 60 min by means of a 575 nm monochromatic lamp. The color of mixture changed from hyacinthine to prunosus. The solvent was concentrated under vacuum. The crude product was purified by flash column chromatography to give **7a** as a purple solid (895 mg, 89.8%).

3. Cell culture

The breast cancer cell line (MCF-7), Human hepatoma cell line (HepG-2), Human skin Basal cell carcinoma (A431) were obtained from American Type Culture Collection. MCF-7 and A431 cells were cultured at 37 ^{o}C under a humidified 5% CO_2 in DMEM medium supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin; and HepG-2 cells were cultured in 1640 containing 10% fetal bovine serum, 1% penicillin/streptomycin.

4. Cell viability assay

HepG-2, A431 and MCF-7 cells were seeded in 96-well plates at a density of 1×10^4 cells/well and incubated for 24hrs, respectively. The cells were treated with a range of compound **7a-d** doses (0.2 μM, 0.4 μM, 0.6 μM, 0.8 μM, 1.0 μM). Cell viability was assessed using the MTT method at 24hrs post-compound **7a-d** treatment and irradiation with visible light for 30 min.

5. *UV-Vis spectra of 7a-d*

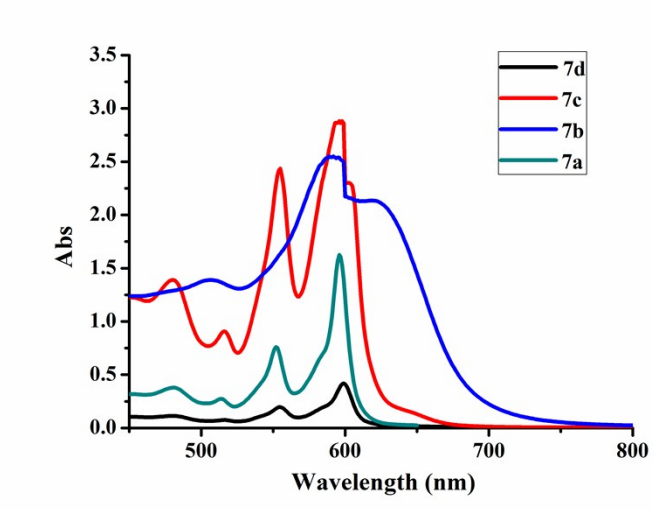


Figure S1. UV-Vis absorption spectra of 7a-d (1 mM, DMSO).

6. NMR spectra and HRMS spectra

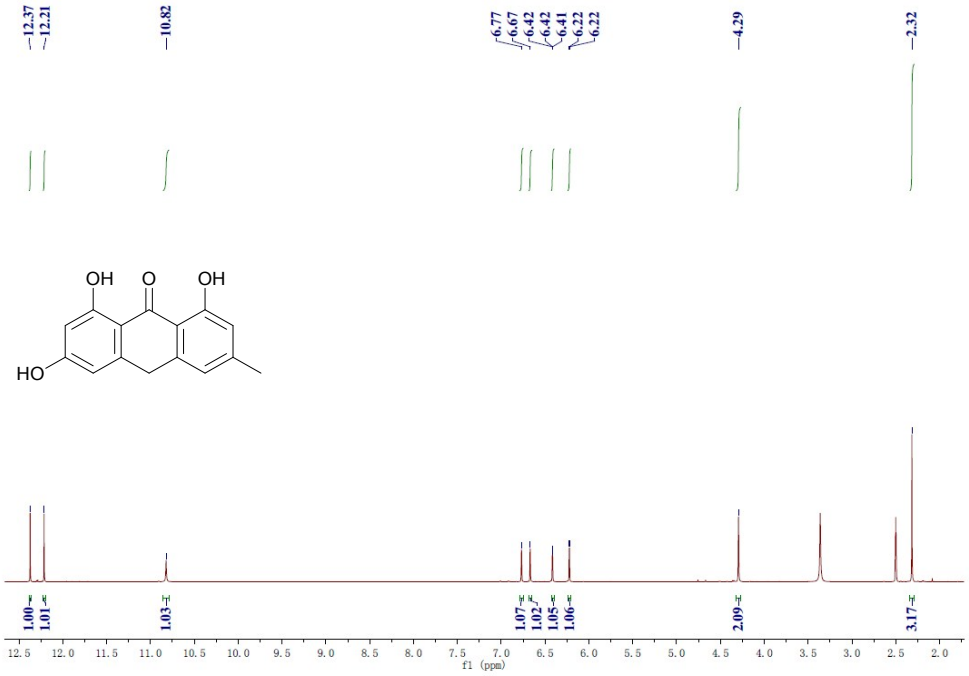


Figure S2. ^{1}H NMR spectrum of Compound 5a in $CDCl_3$.

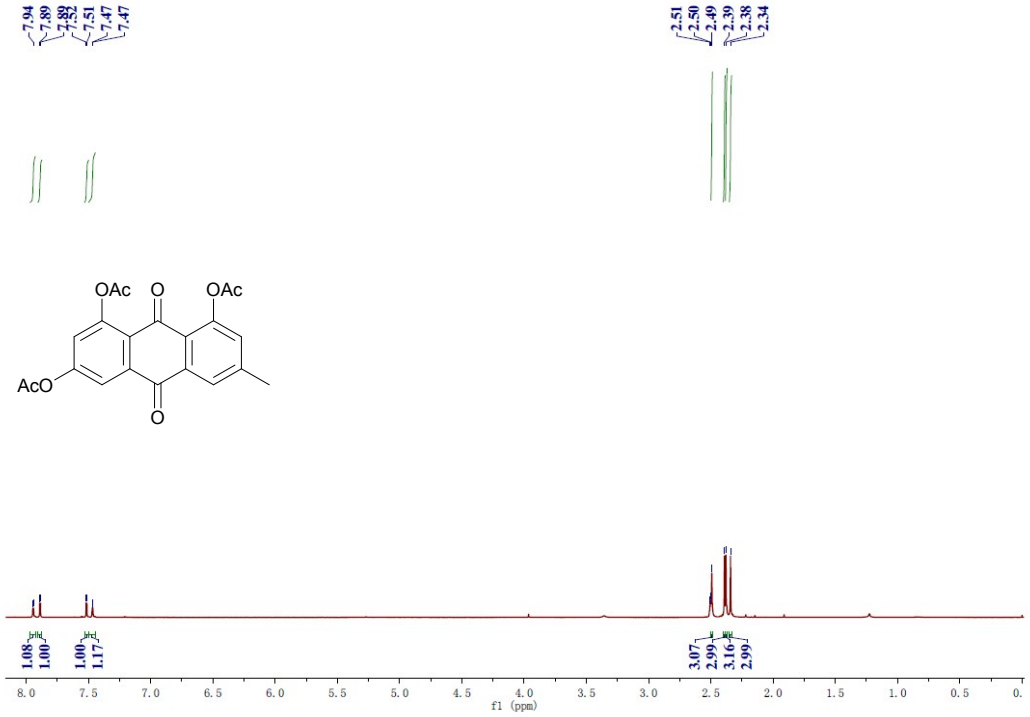


Figure S3. ^{1}H NMR spectrum of Compound 2 in $CDCl_3$.

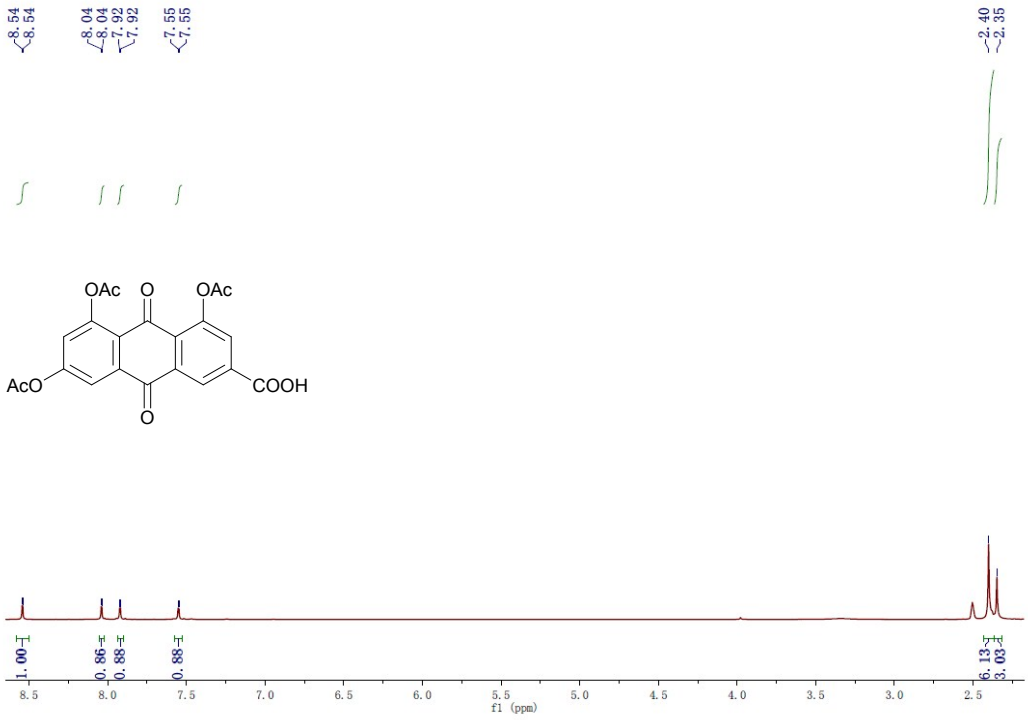


Figure S4. ^{1}H NMR spectrum of Compound 3 in DMSO.

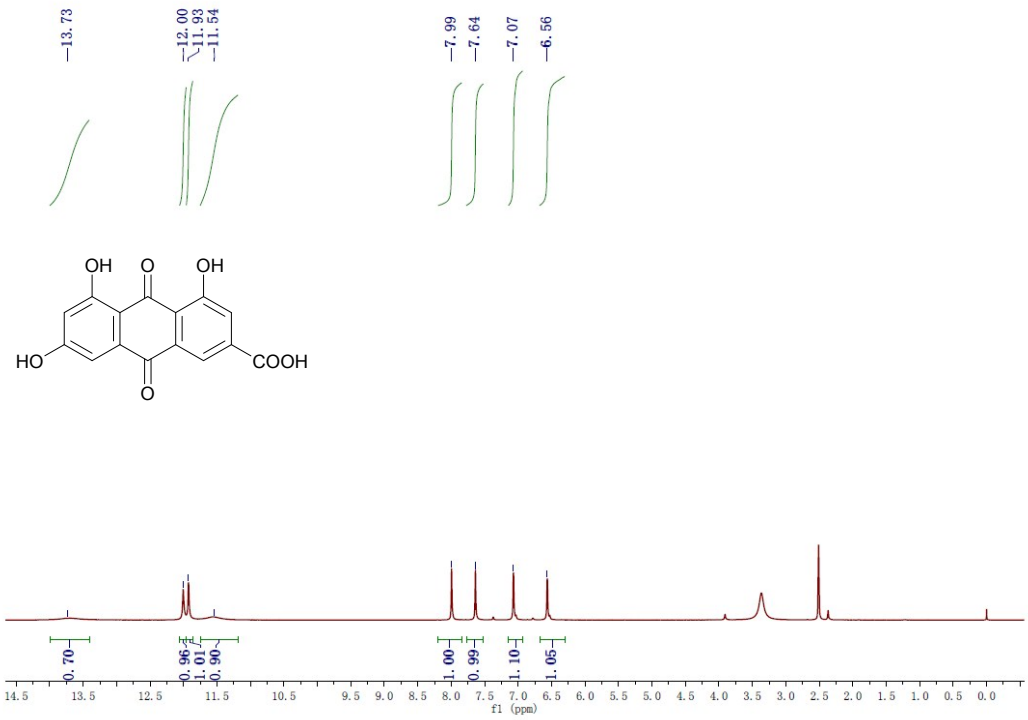


Figure S5. ^{1}H NMR spectrum of Compound 4 in DMSO.

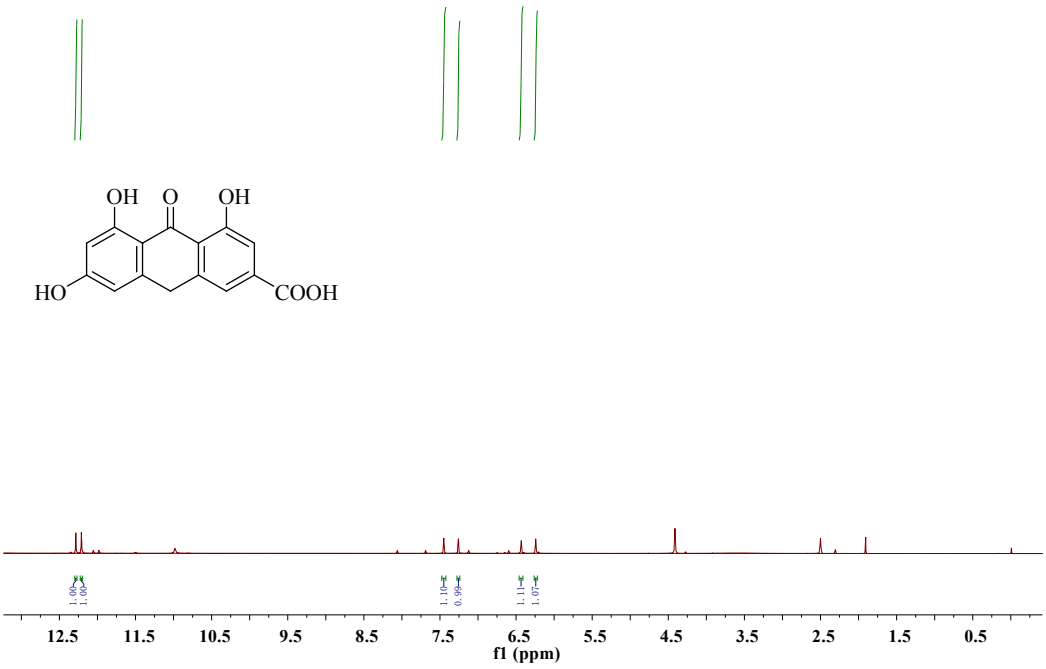


Figure S6. ^{1}H NMR spectrum of Compound 5b in DMSO.

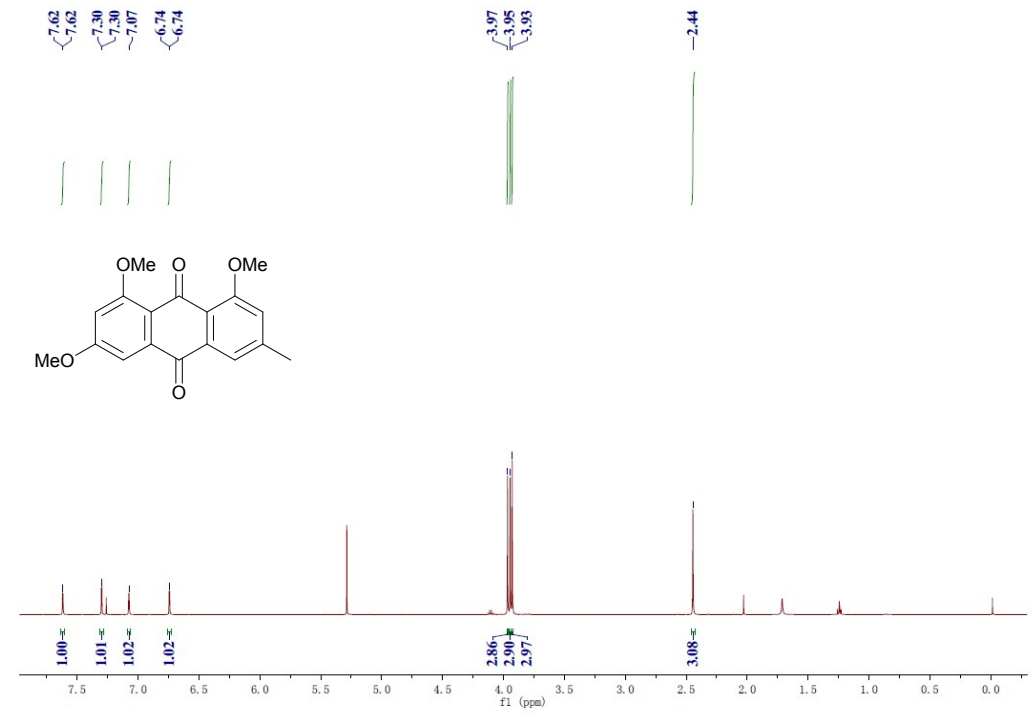


Figure S7. ^{1}H NMR spectrum of Compound 8 in $CDCl_3$。

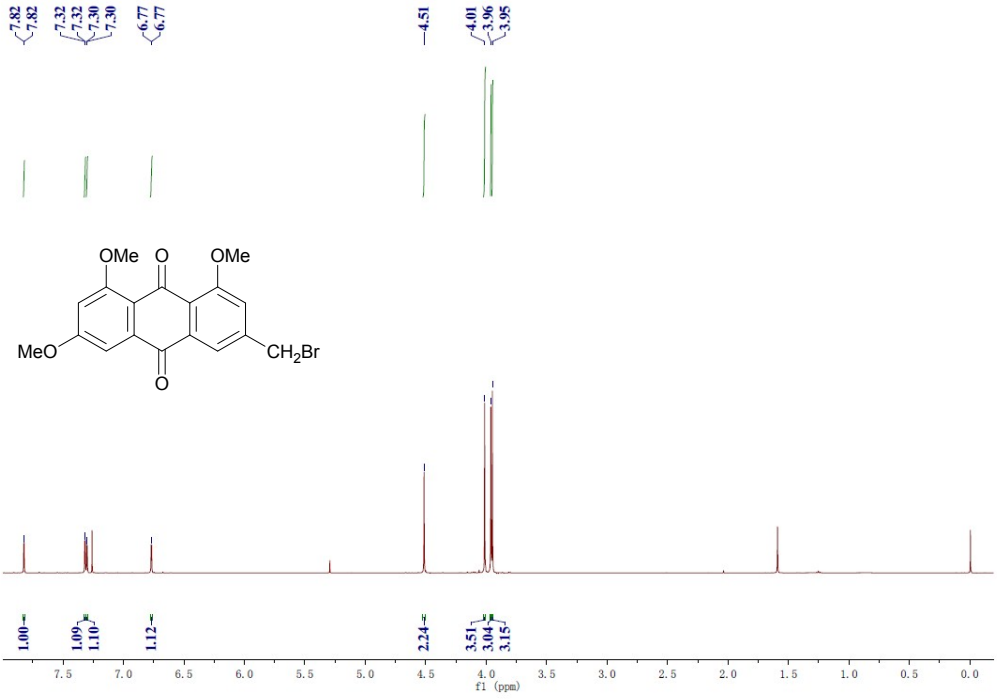


Figure S8. ^{1}H NMR spectrum of Compound 9 in $CDCl_3$.

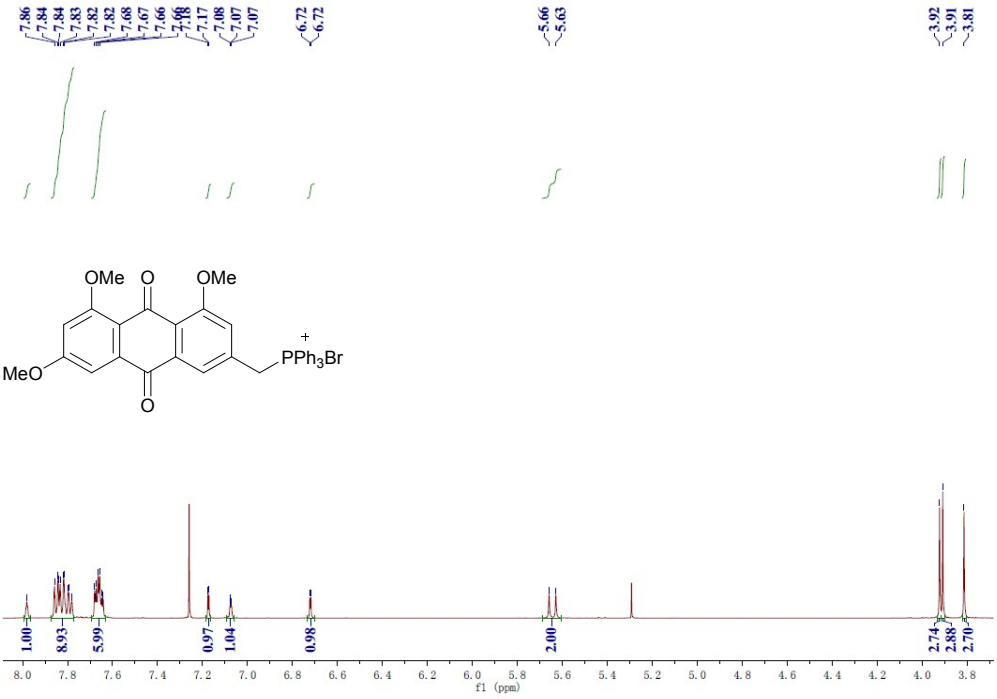


Figure S9. ^{1}H NMR spectrum of Compound 10 in $CDCl_3$.

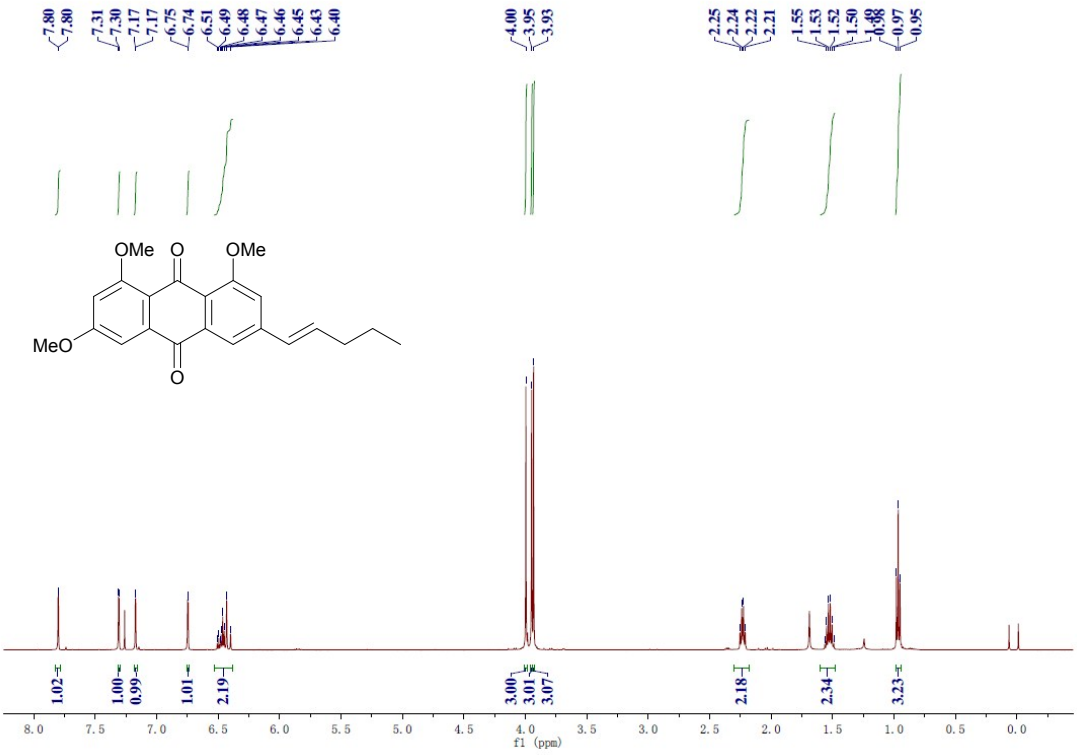


Figure S10. 1H NMR spectrum of Compound 11 in $CDCl_3$.

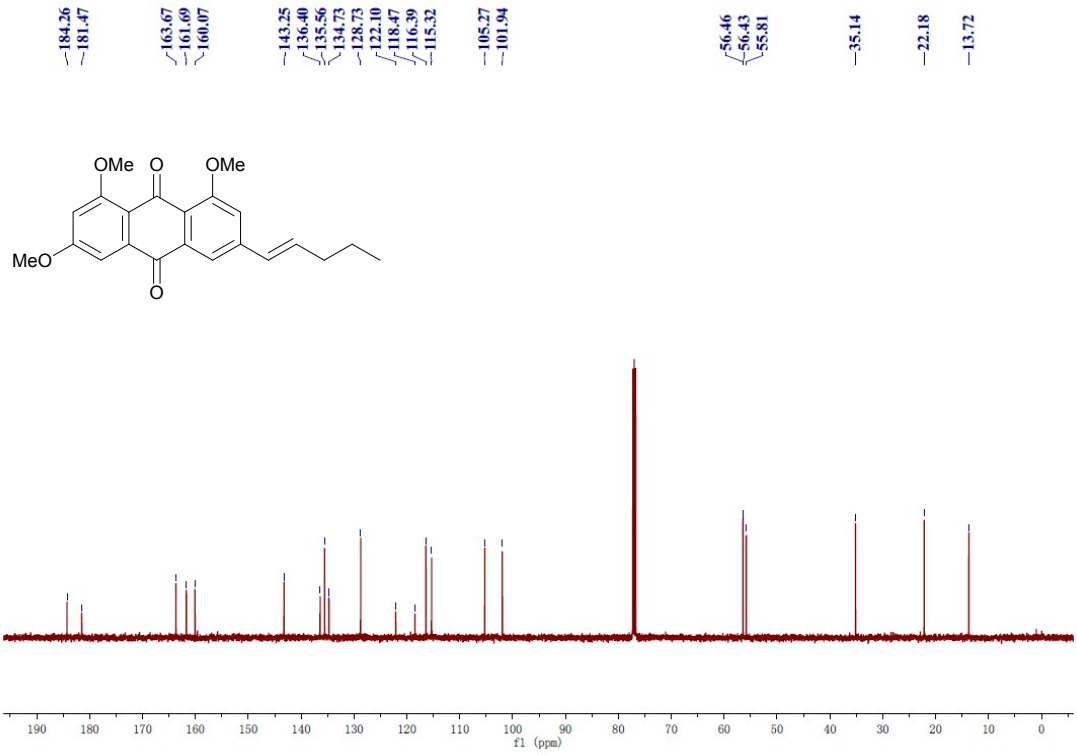


Figure S11. ^{13}C NMR spectrum of Compound 11 in $CDCl_3$.

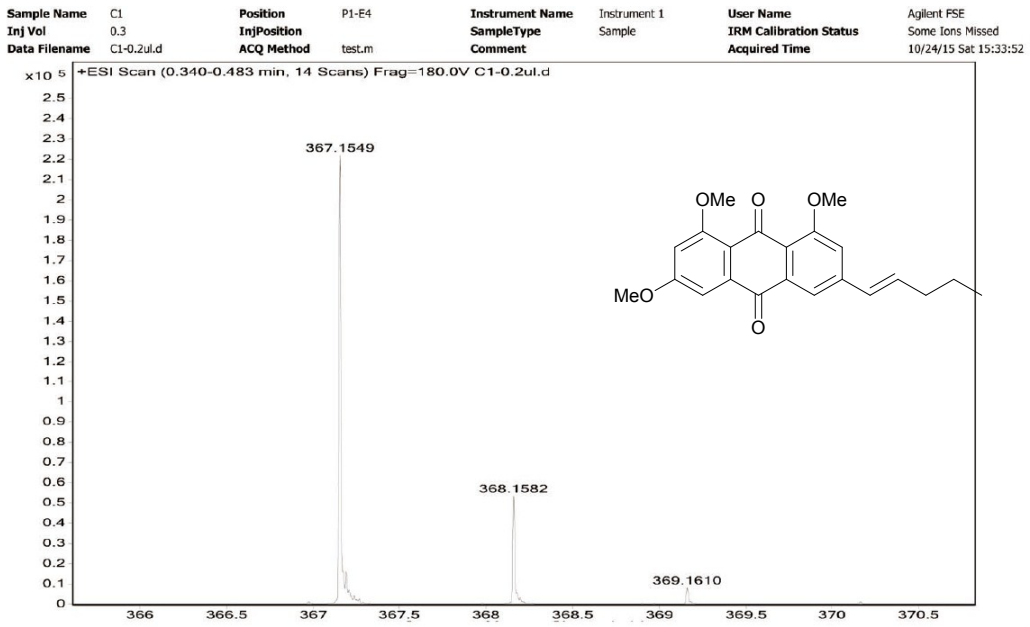


Figure S12. HRMS spectrum of Compound 11.

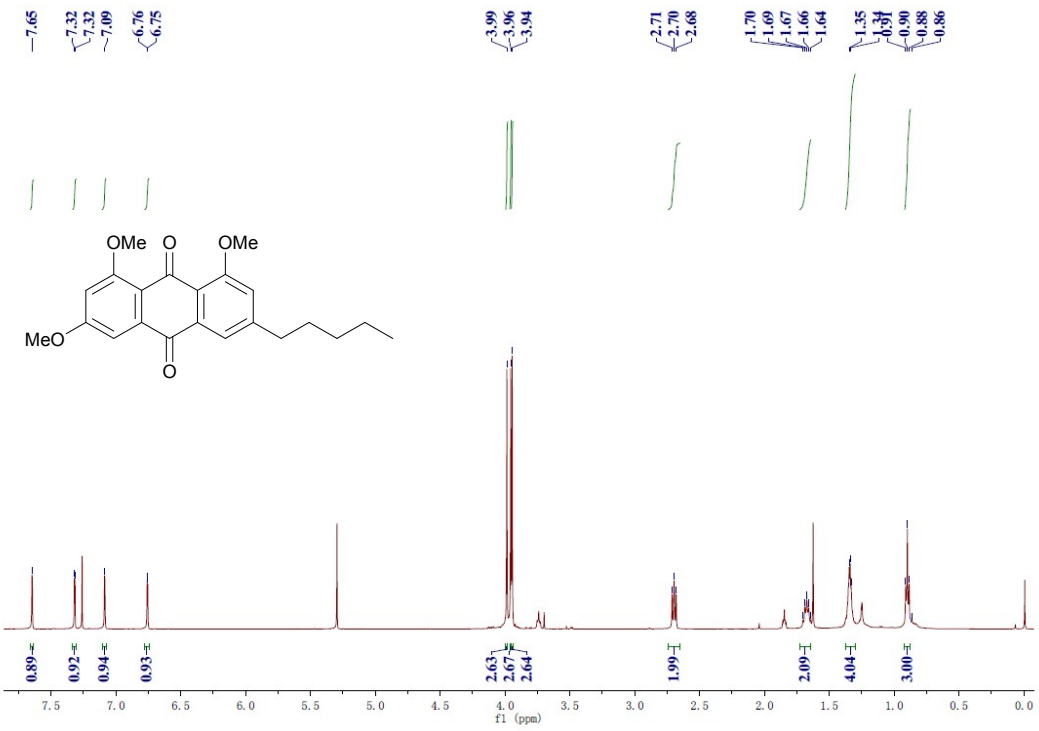


Figure S13. ^{1}H NMR spectrum of Compound 12 in $CDCl_3$.

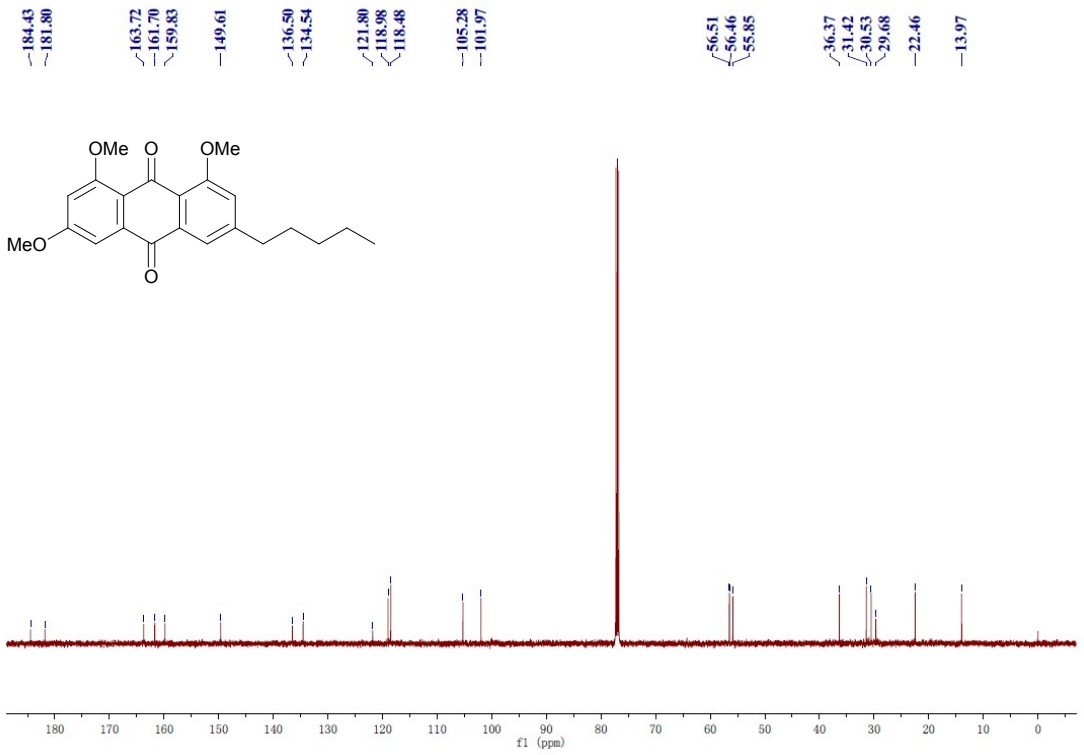


Figure S14. ^{13}C NMR spectrum of Compound 12 in $CDCl_3$.

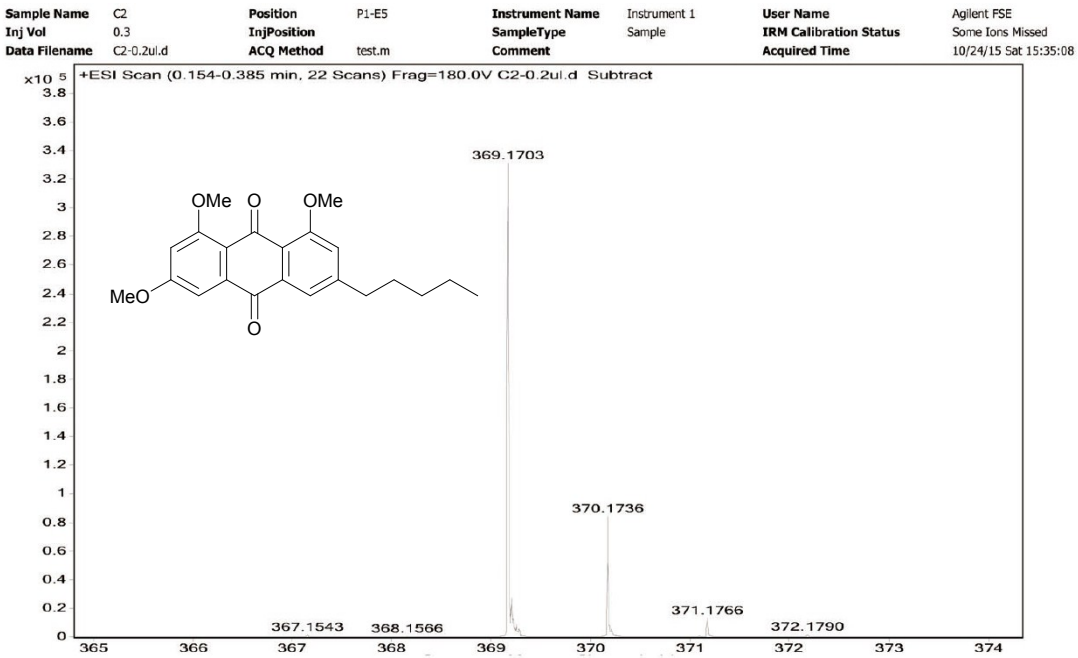


Figure S15. HRMS spectrum of Compound 12.

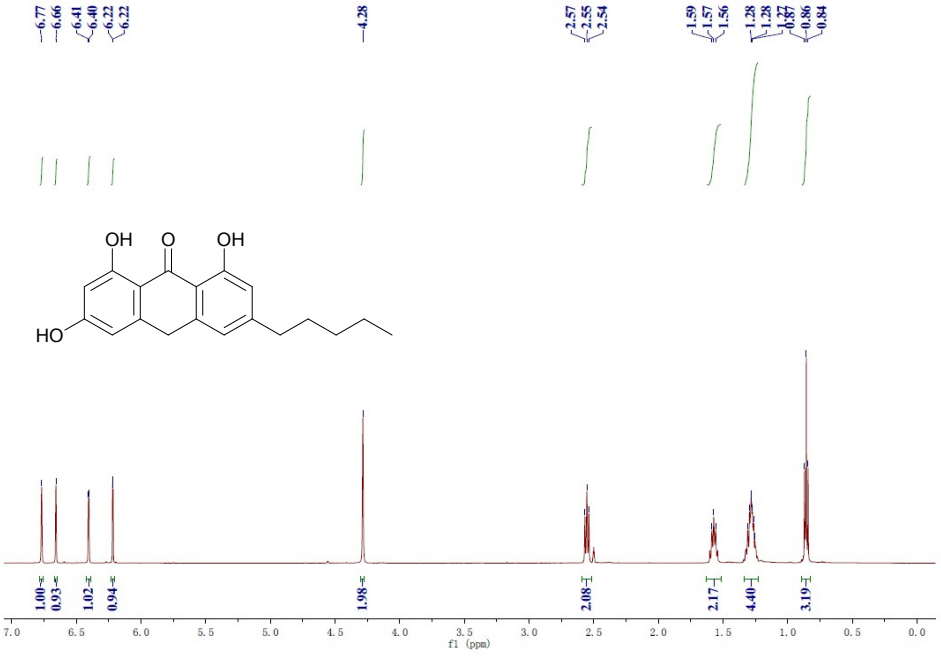


Figure S16. ^{1}H NMR spectrum of Compound 5c in DMSO.

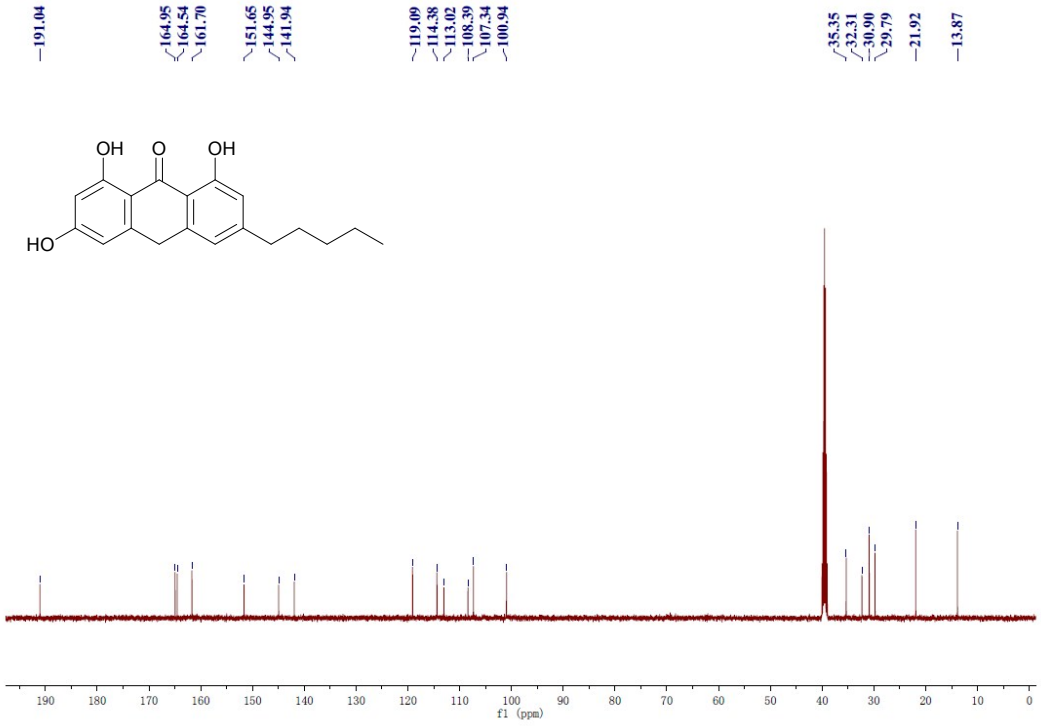


Figure S17. ^{13}C NMR spectrum of Compound 5c in DMSO.

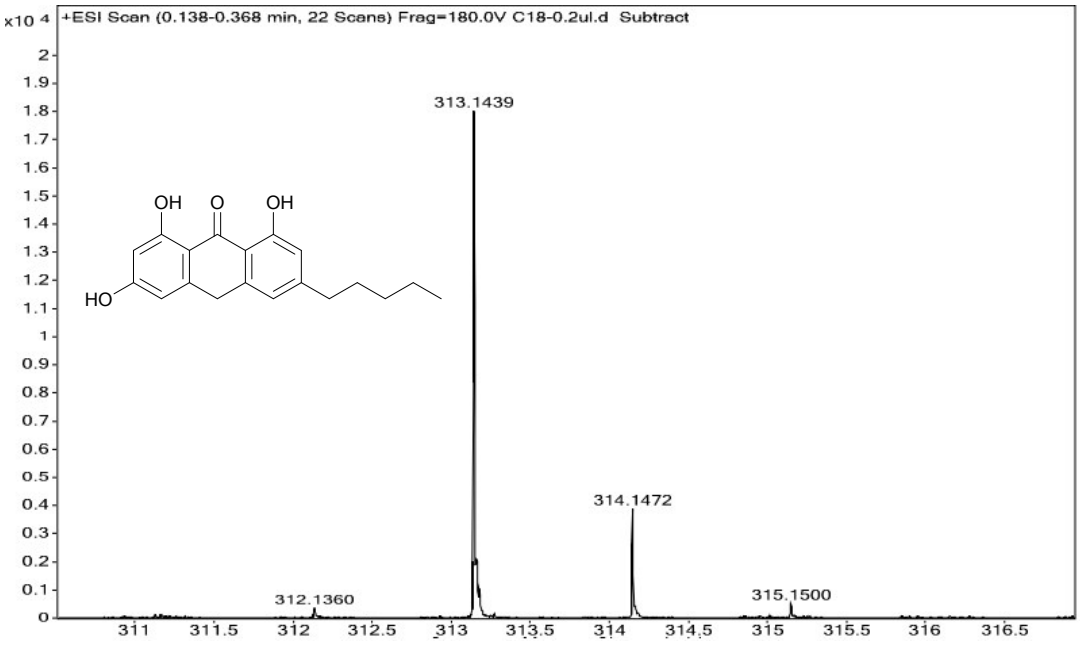


Figure S18. HRMS spectrum of Compound 5c.

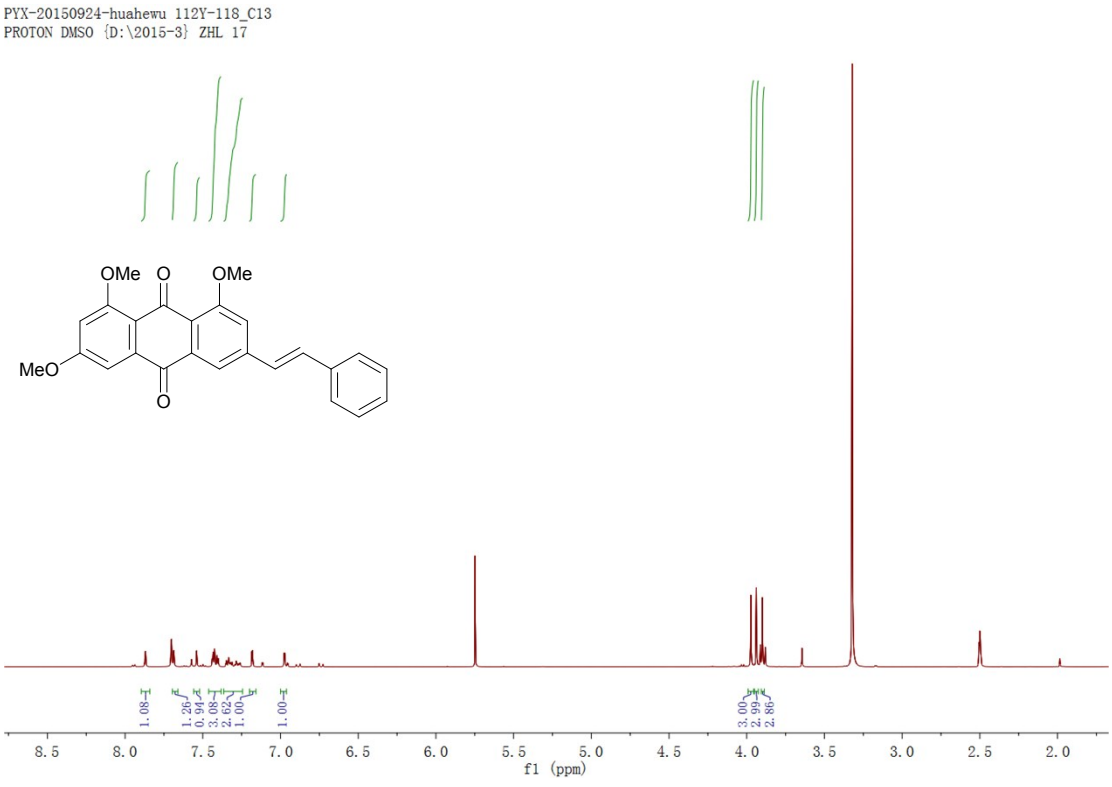


Figure S19. ^{1}H NMR spectrum of Compound 13 in DMSO.

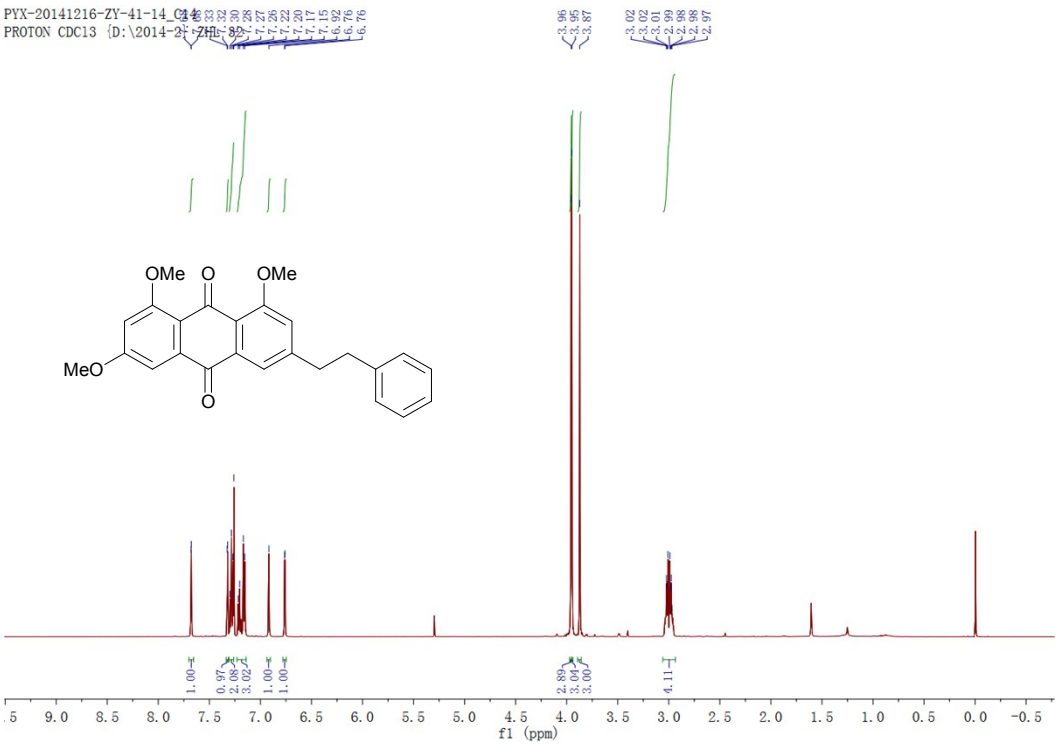


Figure S20. ^{1}H NMR spectrum of Compound 14 in $CDCl_3$.

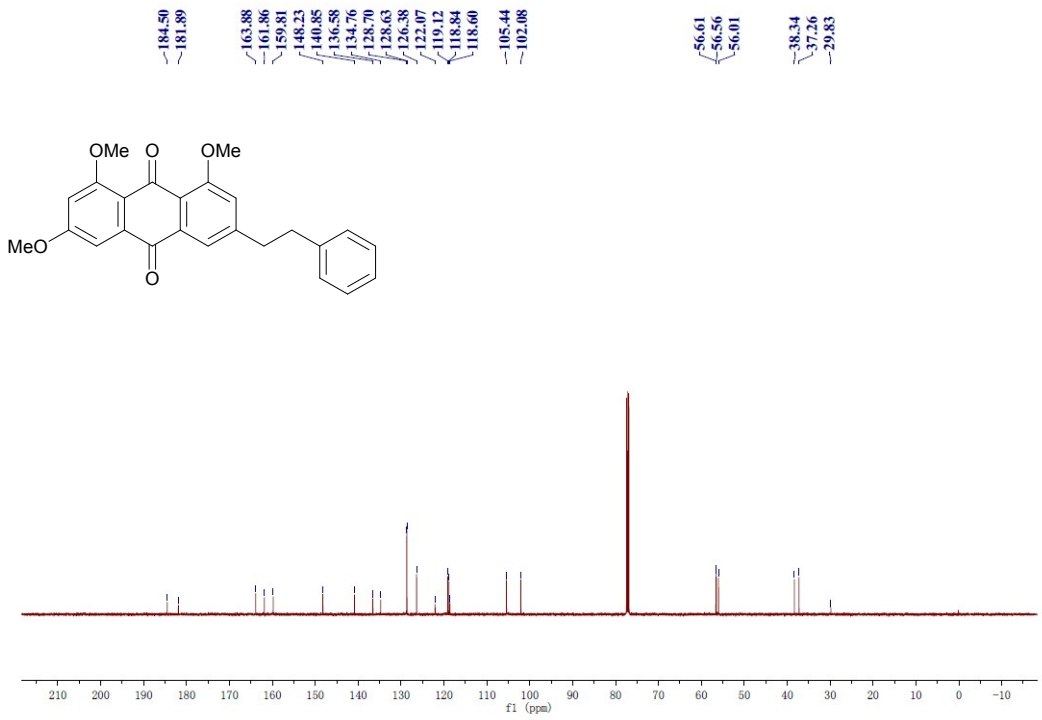


Figure S21. ^{13}C NMR spectrum of Compound 14 in $CDCl_3$.

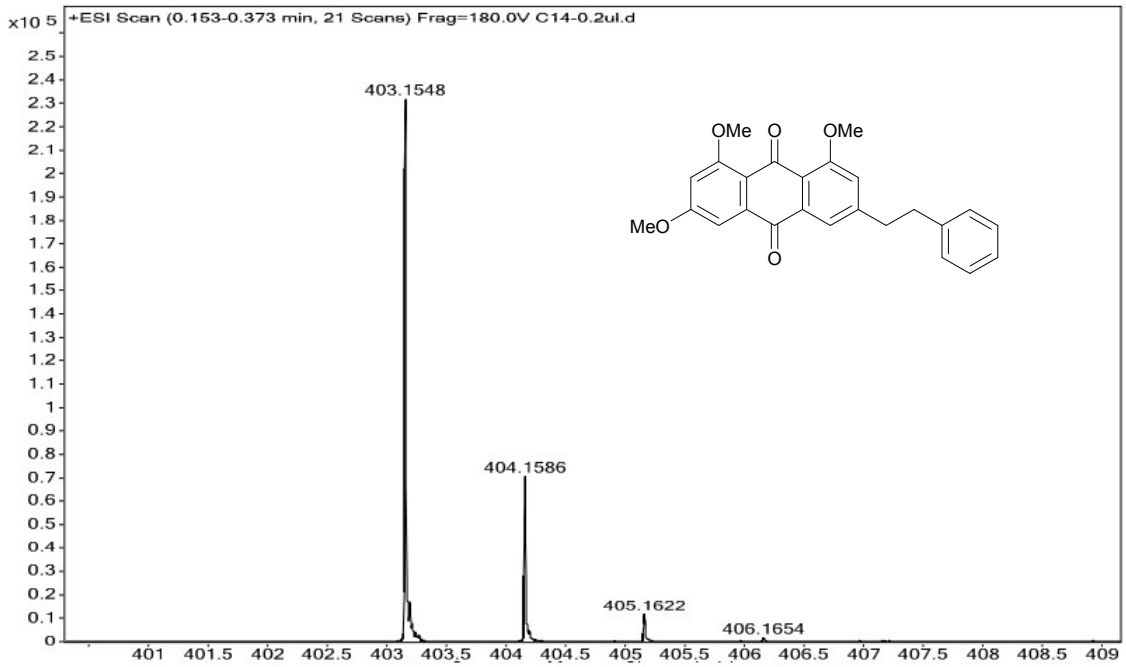


Figure S22. HRMS spectrum of Compound 14.

Figure S23. ^{1}H NMR spectrum of Compound 5d in DMSO.

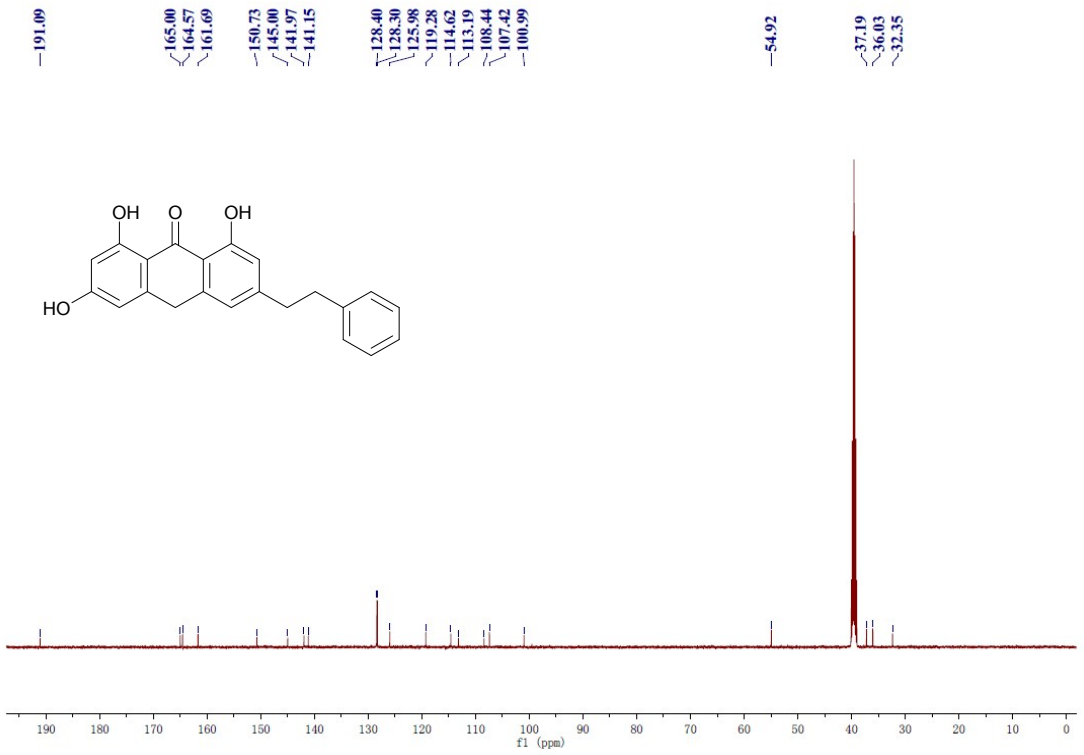


Figure S24. ^{13}C NMR spectrum of Compound 5d in DMSO.

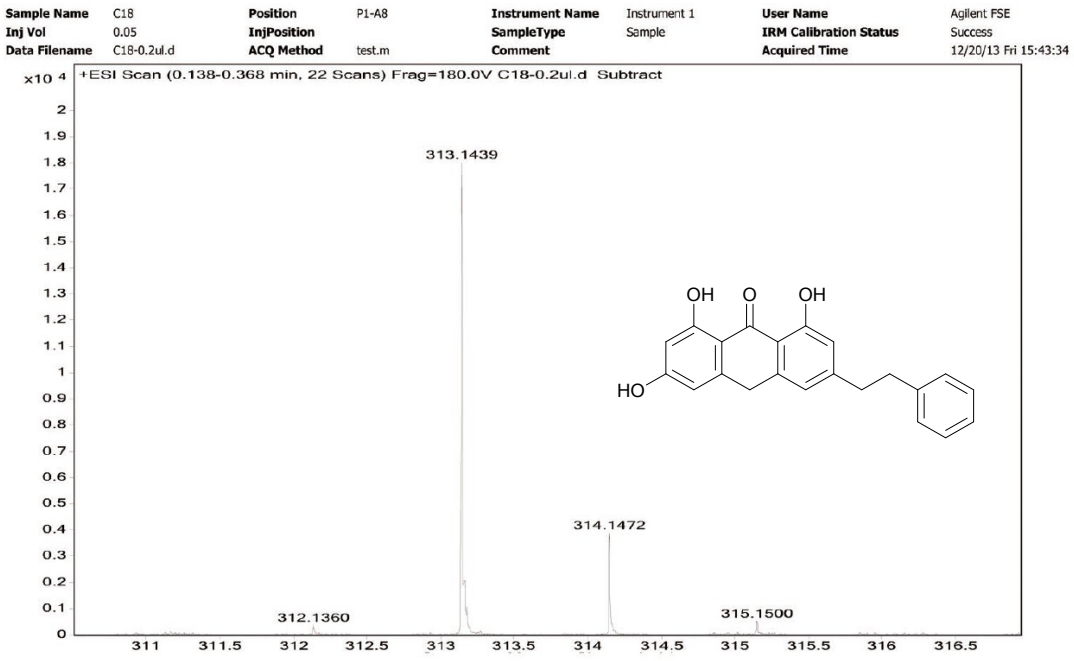


Figure S25. HRMS spectrum of Compound 5d.

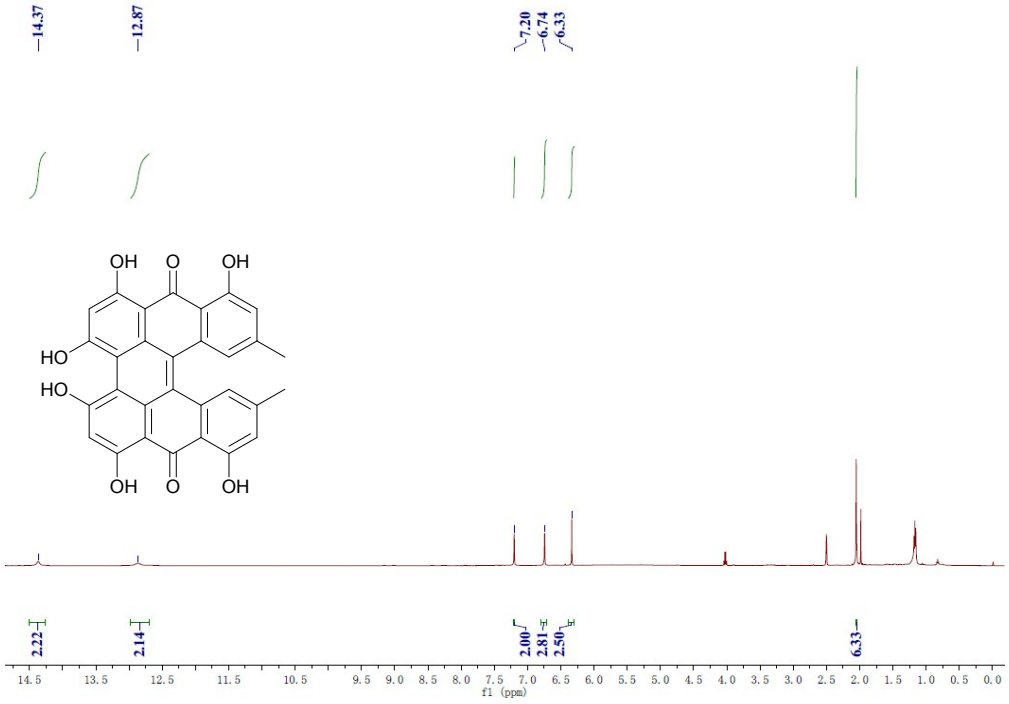


Figure S26. ^{1}H NMR spectrum of Compound 6a in DMSO.

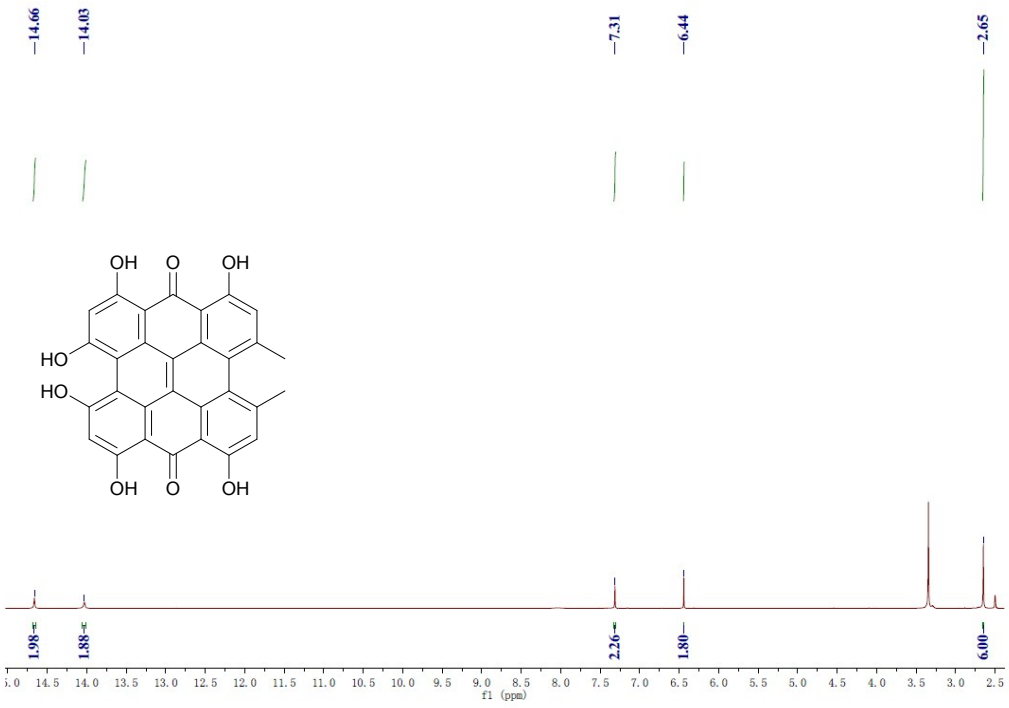


Figure S27. ^{1}H NMR spectrum of Compound 7a in DMSO.

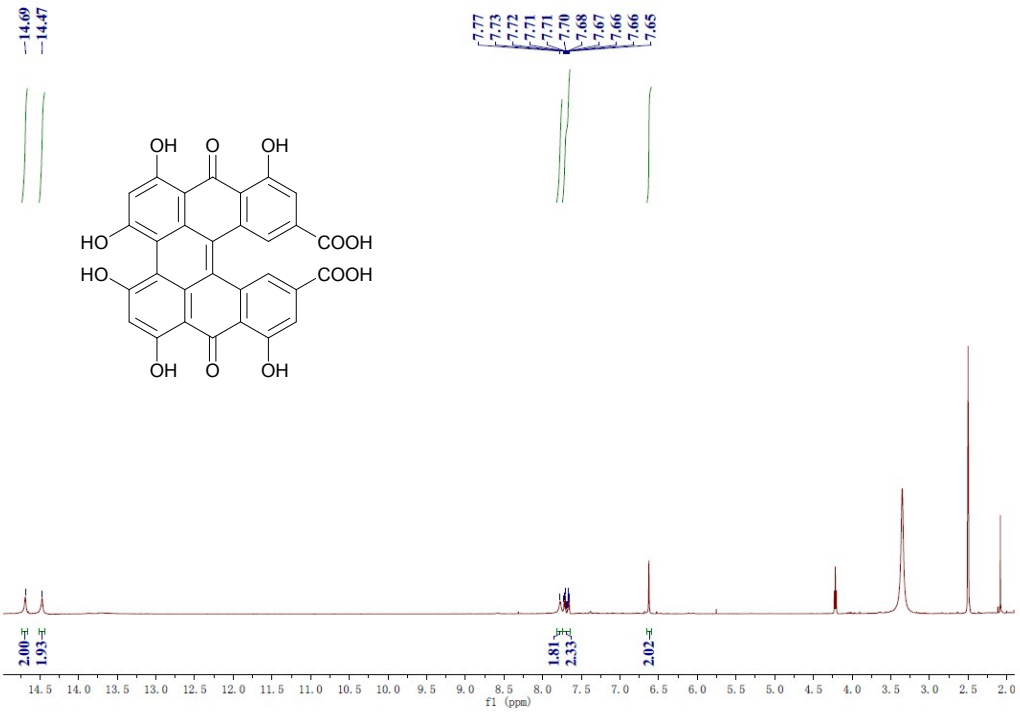


Figure S28. ^{1}H NMR spectrum of Compound 6b in DMSO.

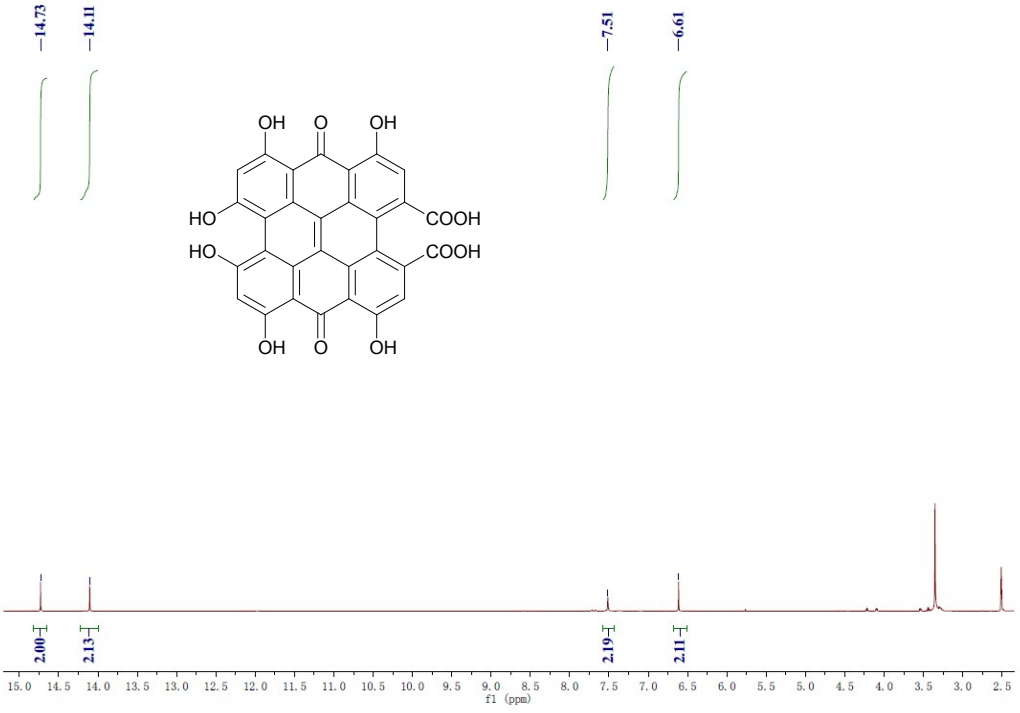


Figure S29. ^{1}H NMR spectrum of Compound 7b in DMSO.

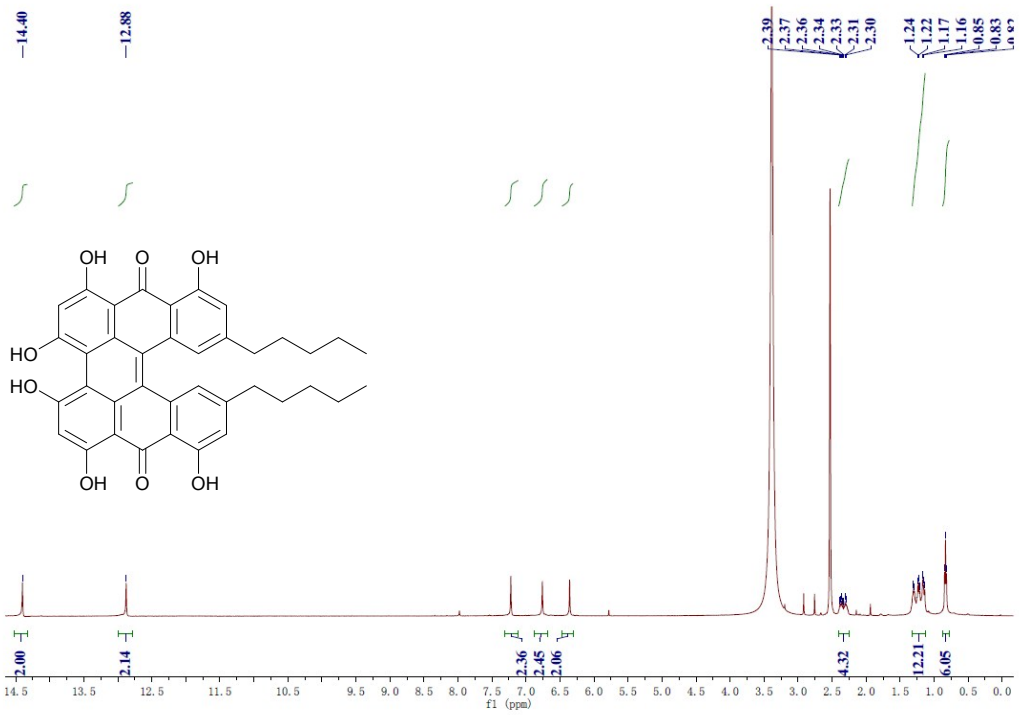


Figure S30. ^{1}H NMR spectrum of Compound 6c in DMSO.

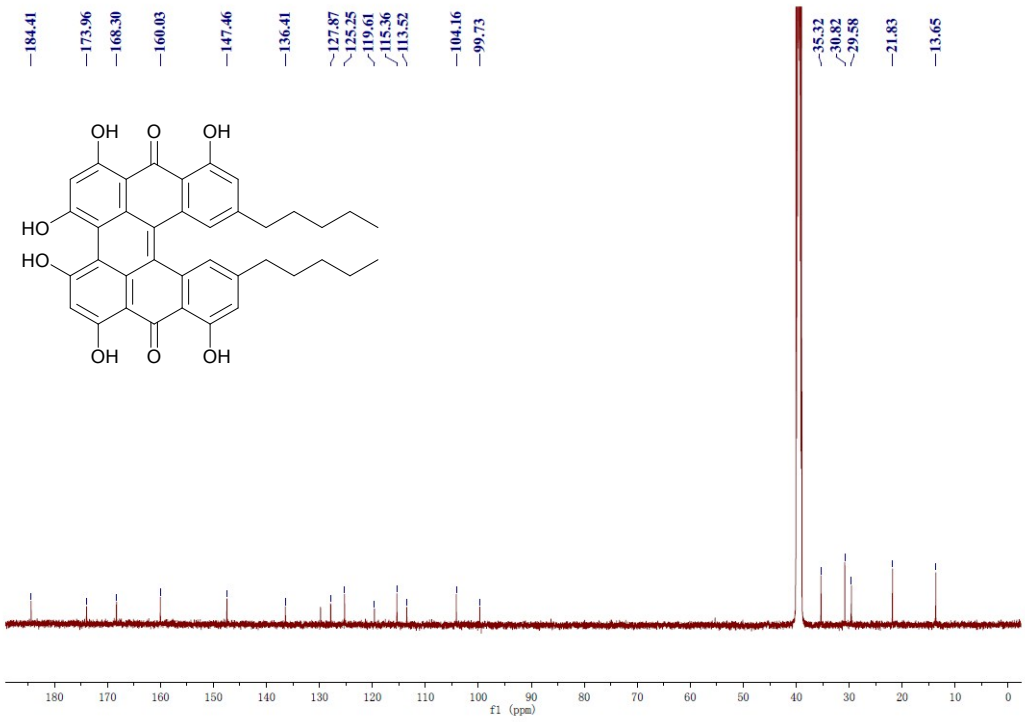


Figure S31. ^{13}C NMR spectrum of Compound 6c in DMSO.

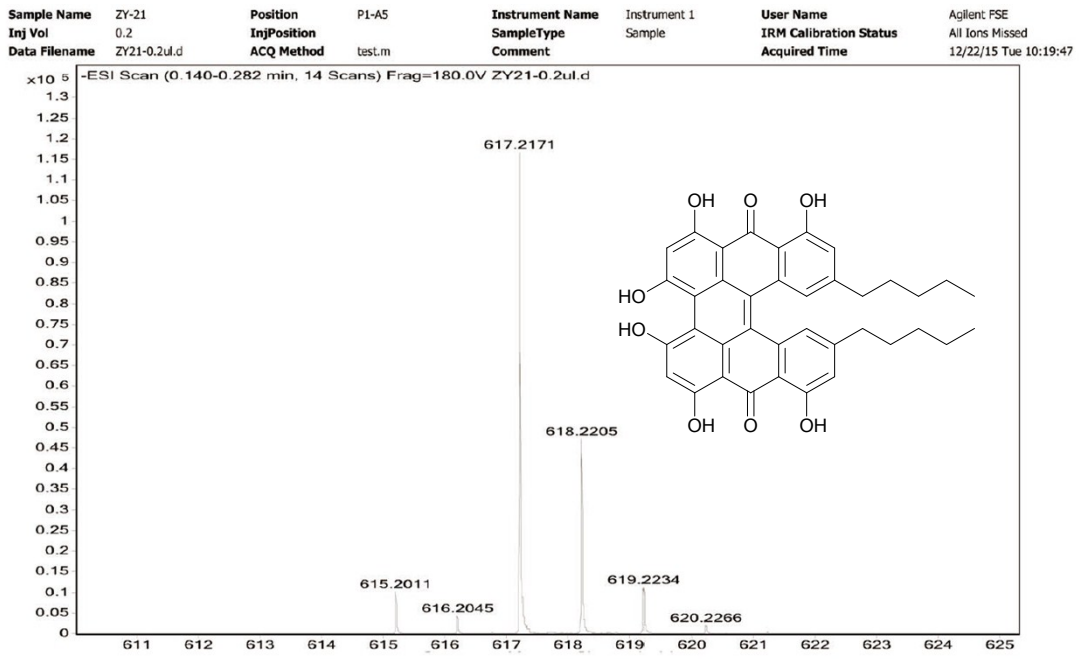


Figure S32. HRMS spectrum of Compound 6c.

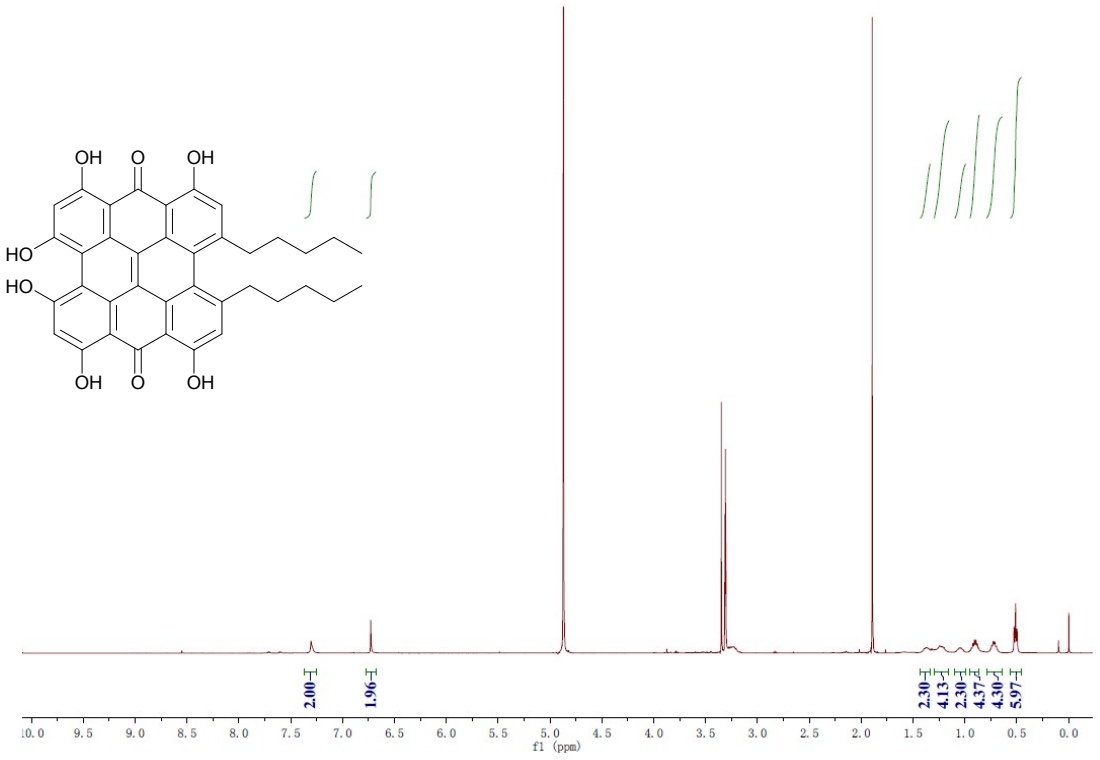


Figure S33. ^{1}H NMR spectrum of Compound 7c in MeOD.

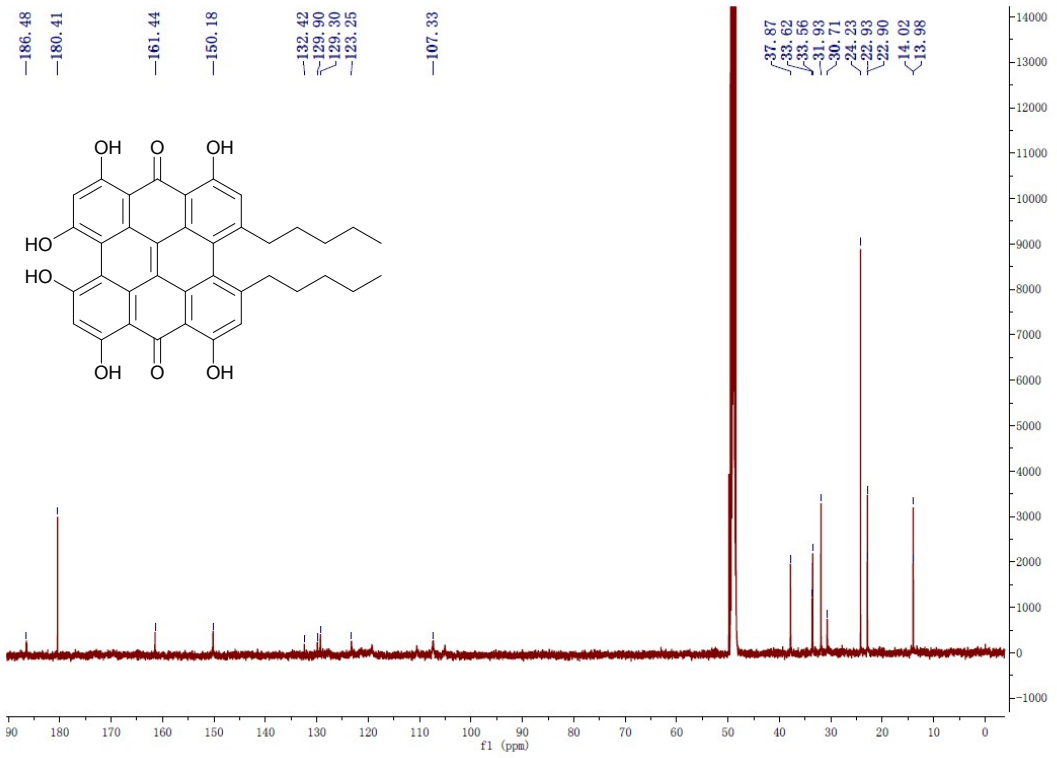


Figure S34. ^{13}C NMR spectrum of Compound 7c in MeOD.

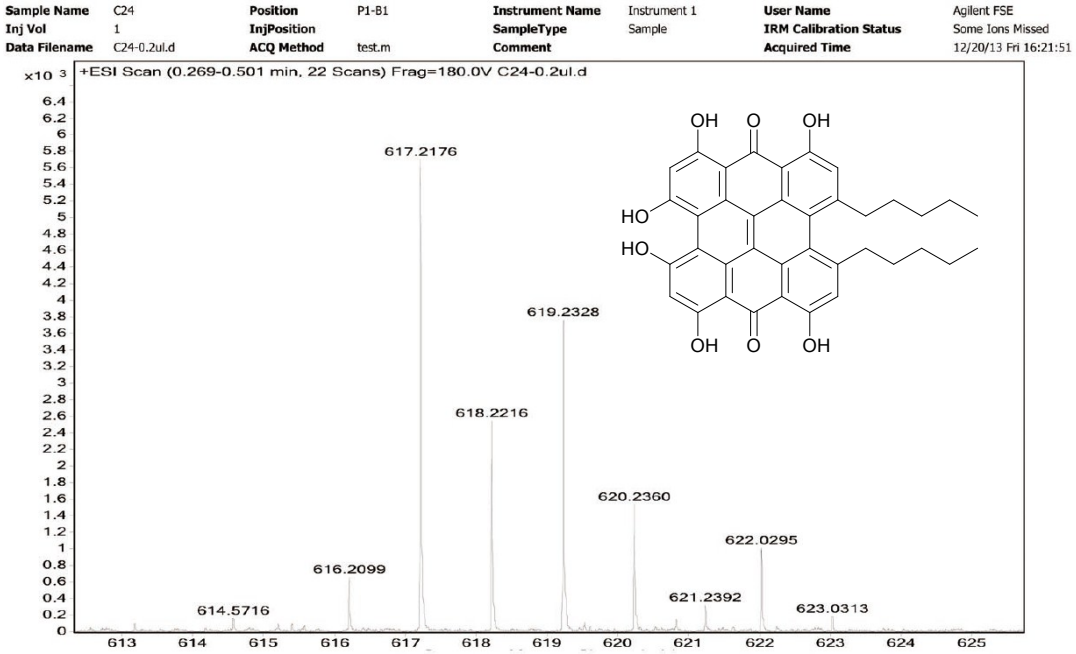


Figure S35. HRMS spectrum of Compound 7c.

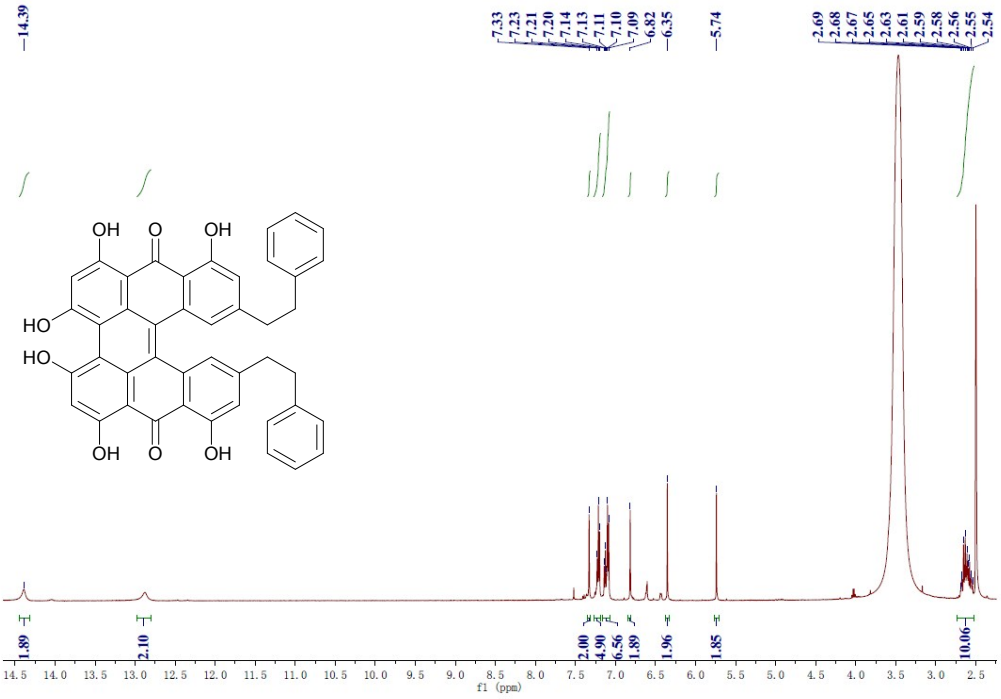


Figure S36. ^{1}H NMR spectrum of Compound 6d in DMSO.

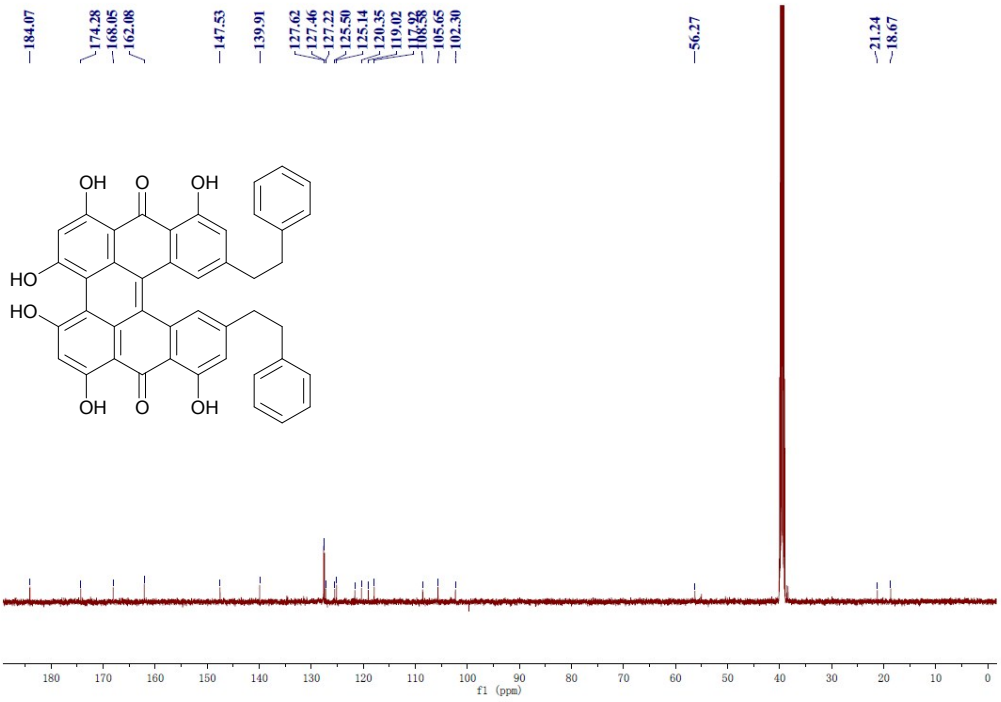


Figure S37. ^{13}C NMR spectrum of Compound 6d in DMSO.

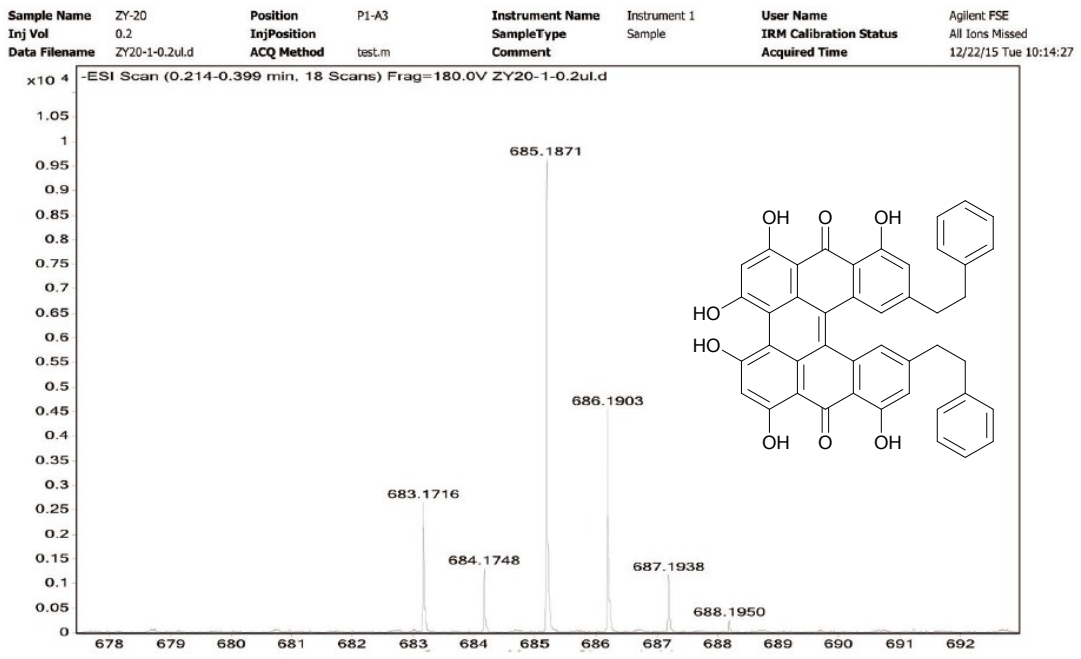


Figure S38. HRMS spectrum of Compound 6d.

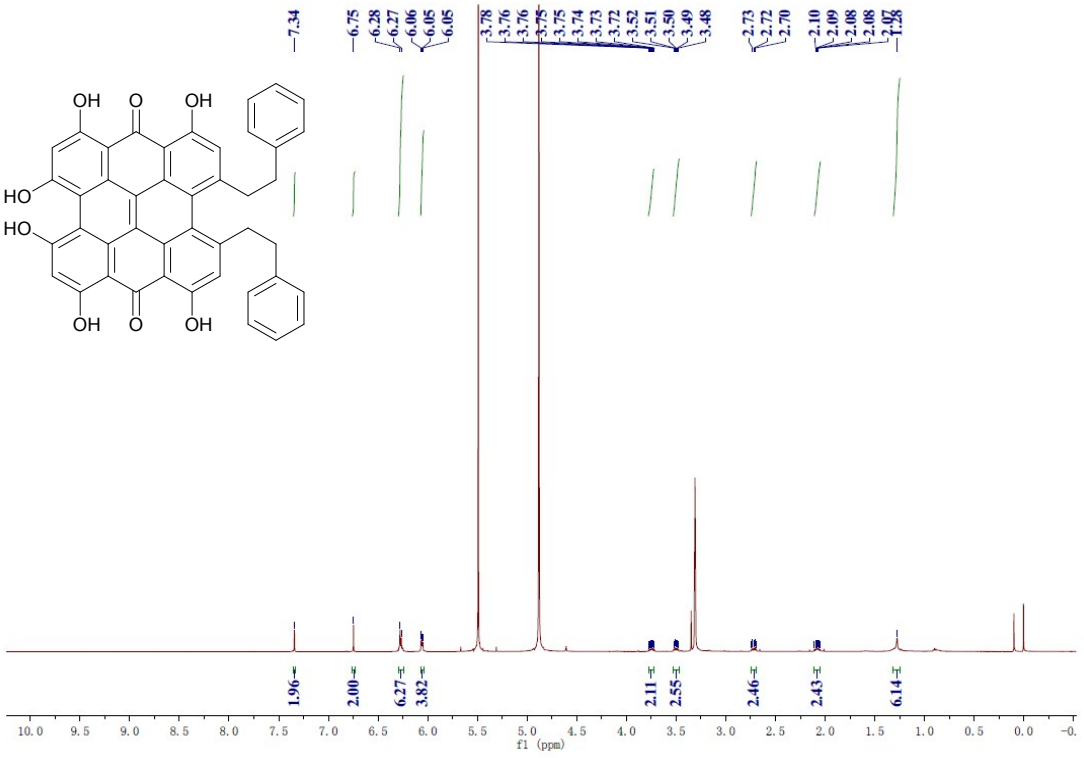


Figure S39. ^{1}H NMR spectrum of Compound 7d in MeOD.

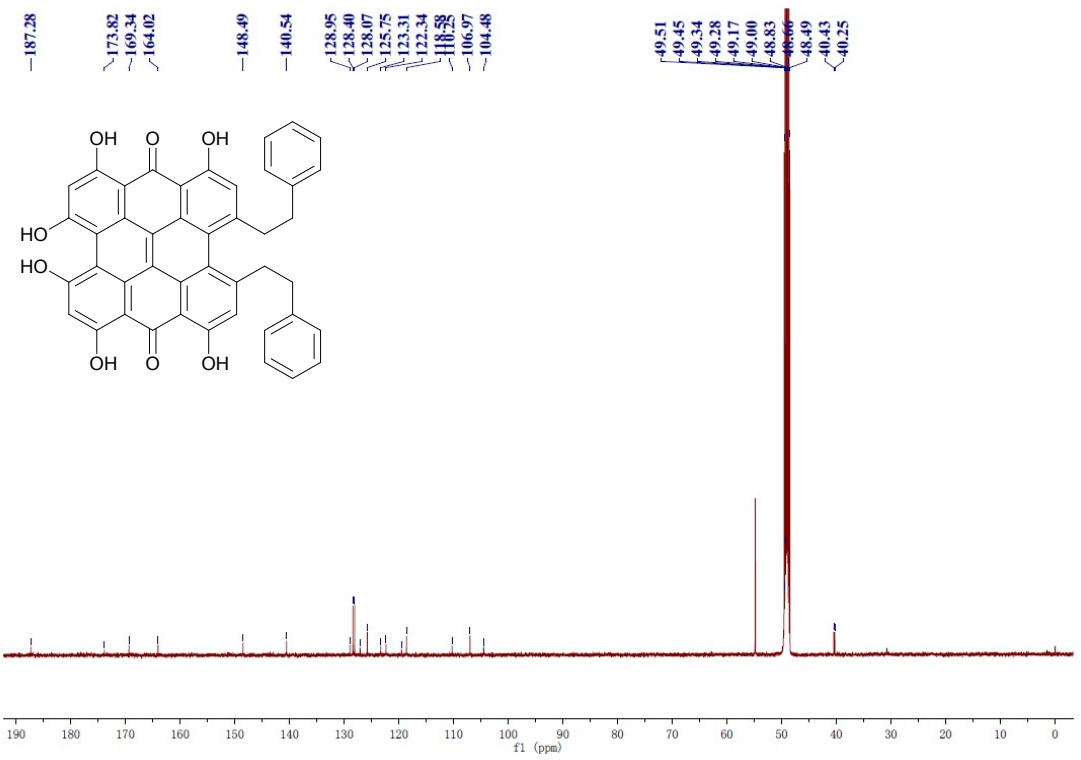


Figure S40. ^{13}C NMR spectrum of Compound 7d in MeOD.

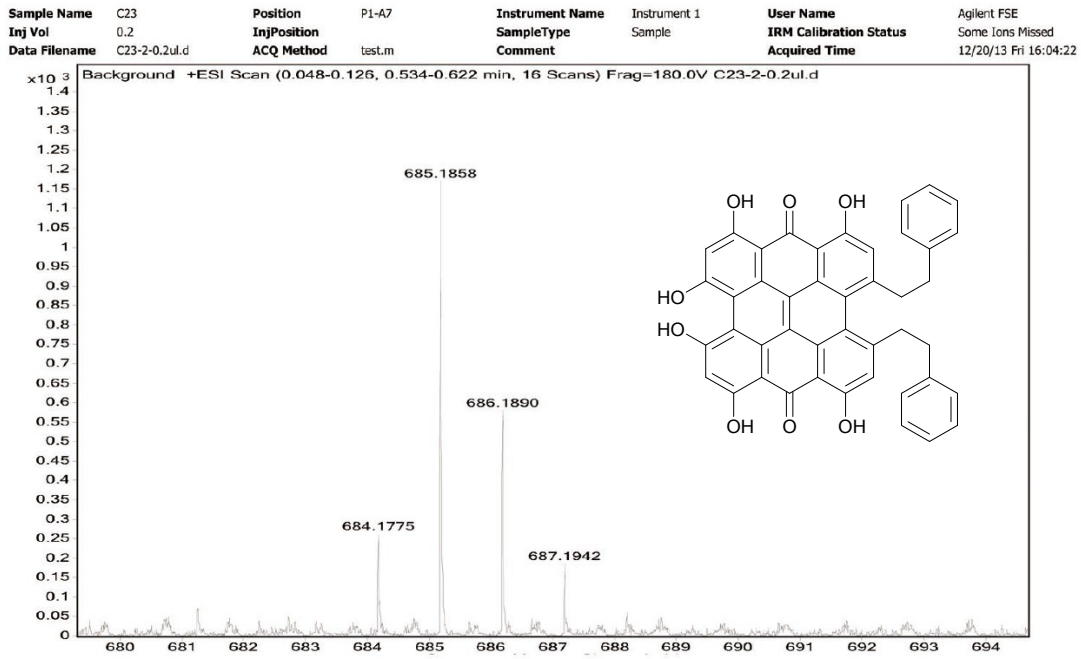


Figure S41. HRMS spectrum of Compound 7d.

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