Supporting Information

One-pot synthesis of 1,4-dihydroxy-2-((E)-1-hydroxy-4-phenylbut-3-enyl)anthracene-9,10-diones as novel shikonin analogs and evaluation of their antiproliferative activities

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Table of Contents

Experimental

1. Chemistry

β,γ-Unsaturated aldehydes were prepared by oxidation of the corresponding alcohol with Dess-Martin periodinane. Reactions were monitored using thin-layer chromatography (TLC) on silica gel plates. Flash column chromatography was performed on silica gel (200-300 mesh) for purification of the compounds. Melting points were measured on an X-4 melting-point apparatus and were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance spectrometer at 400 MHz and 100 MHz, respectively. Chemical shift values were reported as δ ppm relative to TMS as internal standard. HRMS were recorded on a Bruker TOF-Q Ⅱ spectrometer with electrospray ionization (ESI).

1.1. General procedure for the synthesis of **3**.

To a 0 °C solution of quinizarin (0.5 mmol) in MeOH (10 ml) and aqueous NaOH (1 N, 2.5 ml) was added a solution of $Na_2S_2O_4$ (1.0 mmol) in water under N_2. After 10 min, the aldehyde (1.0 mmol) was added via syringe. The reaction mixture was stirred for 3 h at 0 °C. The solution was poured into 10 ml of cold water, which contained 2 ml of 30% H_2O_2 and stirred for 10 min. The mixture was acidified by addition of HCl (3 N, 1 ml) and extracted with CH_2Cl_2, dried and concentrated. The residue was purified by flash column chromatography to afford **3** as an orange solid.

1.1.1. 1,4-Dihydroxy-2-((E)-1-hydroxy-4-phenylbut-3-enyl)anthracene-9,10-dione (**3a**). Yield 80%; mp 130-132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.48 (s, 1H), 12.91 (s, 1H), 8.33-8.35 (m, 2H), 7.82-7.84 (m, 2H), 7.51 (s, 1H), 7.36-7.38 (m, 2H), 7.29-7.32 (m, 2H), 7.21-7.24 (m, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 16.0, 8.0 Hz, 1H), 5.19 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.88-2.95 (m, 1H), 2.57-2.65 (m, 1H), 2.53 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.4, 157.9, 155.2, 145.1, 136.9, 134.6, 134.4, 134.1, 133.5, 133.4, 128.6, 127.5, 127.0, 126.2, 125.8, 125.1, 112.5, 111.8, 68.5, 40.6. HRMS (ESI): m/z caclcd for $C_{24}H_{17}O_5$ [(M-H$^+$)$^-$], 385.1076; found, 385.1075.

1.1.2. 1,4-Dihydroxy-2-((E)-1-hydroxy-4-*o*-tolylbut-3-enyl)anthracene-9,10-dione (**3b**). Yield 51%; mp 112-114 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 12.91 (s, 1H), 8.34-8.36 (m, 2H), 7.83-7.85 (m, 2H), 7.52 (s, 1H), 7.41-7.43 (m, 1H), 7.12-7.16 (m, 3H), 6.73 (d, *J* = 16.0 Hz, 1H), 6.16 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.20 (dt, *J* = 8.4, 4.4 Hz, 1H),

2.91-2.98 (m, 1H), 2.62-2.69 (m, 1H), 2.53 (d, *J* = 4.0 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 157.9, 155.3, 145.1, 136.1, 135.1, 134.6, 134.4, 133.6, 133.4, 132.1, 130.3, 127.4, 127.0, 127.0, 126.4, 126.1, 125.9, 125.6, 112.5, 111.8, 68.5, 40.8, 19.8. HRMS (ESI): m/z caclcd for $C_{25}H_{19}O_5$ [$(M\text{-}H^+)^-$], 399.1232; found, 399.1234.

1.1.3. 1,4-Dihydroxy-2-((E)-1-hydroxy-4-*m*-tolylbut-3-enyl)anthracene-9,10-dione (**3c**). Yield 90%; mp 147-149 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.48 (s, 1H), 12.91 (s, 1H), 8.33-8.35 (m, 2H), 7.82-7.84 (m, 2H), 7.51 (s, 1H), 7.15-7.21 (m, 3H), 7.04 (d, *J* = 4.0 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.18-5.20 (m, 1H), 2.88-2.94 (m, 1H), 2.53-2.63 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.4, 157.9, 155.2, 145.1, 138.1, 136.8, 134.6, 134.4, 134.3, 133.6, 133.4, 128.5, 128.3, 127.0, 127.0, 126.9, 125.8, 124.9, 123.4, 112.5, 111.8, 68.5, 40.6, 21.4. HRMS (ESI): m/z caclcd for $C_{25}H_{19}O_5$ [$(M\text{-}H^+)^-$], 399.1232; found, 399.1237.

1.1.4. 1,4-Dihydroxy-2-((E)-1-hydroxy-4-*p*-tolylbut-3-enyl)anthracene-9,10-dione (**3d**). Yield 70%; mp 95-97 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.47 (s, 1H), 12.91 (s, 1H), 8.32-8.35 (m, 2H), 7.82-7.84 (m, 2H), 7.50-7.54 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.25-7.27 (m, 3H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.22 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.18 (dt, *J* = 8.4, 4.0Hz, 1H), 2.88-2.94 (m, 1H), 2.54-2.62 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 186.4, 157.9, 155.2, 145.2, 137.3, 134.5, 134.4, 134.1, 133.5, 133.4, 129.3, 129.2, 127.0, 127.0, 126.8, 126.1, 125.8, 123.9, 112.4, 111.7, 68.4, 40.6, 21.2. HRMS (ESI): m/z caclcd for $C_{25}H_{19}O_5$ [$(M\text{-}H^+)^-$], 399.1232; found, 399.1236.

1.1.5. 1,4-Dihydroxy-2-((E)-1-hydroxy-4-(2-methoxyphenyl)but-3-enyl)anthracene-9,10-dione (**3e**). Yield 49%; mp 152-154 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 12.93 (s, 1H), 8.35-8.37 (m, 2H), 7.82-7.86 (m, 2H), 7.53 (s, 1H), 7.40-7.43 (m, 1H), 7.20-7.24 (m, 1H), 6.84-6.93 (m, 3H), 6.26 (dt, *J* = 16.0, 8.0 Hz, 1H), 5.20 (dt, *J* = 8.0, 4.0 Hz, 1H), 3.84 (s, 3H), 2.91-2.98 (m, 1H), 2.59-2.67 (m, 1H), 2.55 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 158.0, 156.5, 155.3, 145.3, 134.5, 134.4, 133.6, 133.4, 129.2, 128.6, 127.0, 127.0, 126.8, 125.9, 125.7, 120.6, 112.4, 111.7, 110.8, 68.4, 55.4, 41.0. HRMS (ESI): m/z caclcd for $C_{25}H_{19}O_6$ [$(M\text{-}H^+)^-$], 415.1182; found, 415.1175.

1.1.6. 1,4-Dihydroxy-2-((E)-1-hydroxy-4-(3-methoxyphenyl)but-3-enyl)anthracene-9,10-dione (**3f**). Yield 68%; mp 127-129 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 12.92 (s,

1H), 8.35-8.37 (m, 2H), 7.83-7.86 (m, 2H), 7.52 (s, 1H), 7.21-7.25 (m, 1H), 6.97 (d, *J* = 4.0 Hz, 1H), 6.90 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.24-6.32 (m, 1H), 5.19-5.21 (m, 1H), 3.82 (s, 3H), 2.90-2.94 (m, 1H), 2.60-2.65 (m, 1H), 2.49 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 159.8, 157.9, 155.2, 145.1, 138.4, 134.6, 134.4, 134.0, 133.6, 133.4, 129.5, 127.1, 127.0, 125.8, 125.5, 118.9, 113.2, 112.5, 111.8, 111.5, 68.5, 55.2, 40.6. HRMS (ESI): m/z caclcd for $C_{25}H_{19}O_6$ [$(M\text{-}H^+)^-$], 415.1182; found, 415.1177.

1.1.7. 1,4-Dihydroxy-2-((E)-1-hydroxy-4-(4-methoxyphenyl)but-3-enyl)anthracene-9,10-dione (**3g**). Yield 60%; mp 127-129 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.48 (s, 1H), 12.92 (s, 1H), 8.33-8.35 (m, 2H), 7.82-7.85 (m, 2H), 7.51 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.12 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.18 (dt, *J* = 8.0, 4.0 Hz, 1H), 3.80 (m, 3H), 2.87-2.93 (m, 1H), 2.57-2.61 (m, 1H), 2.54 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.4, 159.1, 157.9, 155.3, 145.2, 134.6, 134.4, 133.7, 133.6, 133.4, 129.7, 127.4, 127.0, 127.0, 125.8, 122.7, 114.0, 112.5, 111.7, 68.5, 55.3, 40.6. HRMS (ESI): m/z caclcd for $C_{25}H_{19}O_6$ [$(M\text{-}H^+)^-$], 415.1182; found, 415.1178.

1.1.8. 2-((E)-4-(2-Fluorophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3h**). Yield 49%; mp 140-142 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1H), 12.91 (s, 1H), 8.34-8.36 (m, 2H), 7.83-7.85 (m, 2H), 7.51 (s, 1H), 7.42-7.46 (m, 1H), 7.17-7.20 (m, 1H), 7.00-7.10 (m, 2H), 6.69 (d, *J* = 16.0 Hz, 1H), 6.36 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.22 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.91-2.97 (m, 1H), 2.62-2.70 (m, 1H), 2.52 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 157.9, 155.2, 145.0, 134.6, 134.4, 133.6, 133.4, 128.7, 128.0 (d, *J* = 4.6 Hz), 127.3 (d, *J* = 3.7 Hz), 127.0 (d, *J* = 3.1 Hz), 124.1 (d, *J* = 3.6 Hz), 126.4, 125.8, 115.8, 115.6, 112.5, 111.8, 68.6, 40.9. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5F$ [$(M\text{-}H^+)^-$], 403.0982; found, 403.0983.

1.1.9. 2-((E)-4-(3-Fluorophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3i**). Yield 79%; mp 172-174 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.48 (s, 1H), 12.90 (s, 1H), 8.33-8.35 (m, 2H), 7.83-7.85 (m, 2H), 7.50 (s, 1H), 7.23-7.25 (m, 1H), 7.05-7.13 (m, 2H), 6.89-6.94 (m, 1H), 6.50 (d, *J* = 15.6 Hz, 1H), 6.30 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.20 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.87-2.93 (m, 1H), 2.53-2.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 164.3, 157.9, 155.2, 144.9, 139.3 (d, *J* = 7.7 Hz), 134.6, 134.4, 133.6, 133.4,

132.8 (d, *J* = 2.5 Hz), 130.0, 127.0 (d, *J* = 2.1 Hz), 126.8, 125.8, 122.1 (d, *J* = 2.6 Hz), 114.4, 114.1, 112.8, 111.9, 68.6, 40.4. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5F$ [(M-H^+)$^-$], 403.0982; found, 403.0990.

1.1.10. 2-((E)-4-(4-Fluorophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3j**). Yield 67%; mp 176-178 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 12.93 (s, 1H), 8.35-8.37 (m, 2H), 7.84-7.86 (m, 2H), 7.52 (s, 1H), 7.31-7.35(m, 2H), 6.97-7.02 (m, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.20 (dt, *J* = 16.0, 7.2 Hz, 1H), 5.20 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.88-2.92 (m, 1H), 2.60-2.65 (m, 1H), 2.48 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 157.9, 155.2, 145.0, 134.6, 134.4, 133.6, 133.4, 133.1 (d, *J* = 3.4 Hz), 132.9, 127.7 (d, *J* = 7.9 Hz), 127.1 (d, *J* = 2.1 Hz), 125.8, 124.9, 115.6, 115.3, 112.5, 111.8, 68.6, 40.5. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5F$ [(M-H^+)$^-$], 403.0982; found, 403.0985.

1.1.11. 2-((E)-4-(2-Chlorophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3k**). Yield 60%; mp 128-130 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 12.91 (s, 1H), 8.34-8.36 (m, 2H), 7.83-7.85 (m, 2H), 7.52 (s, 1H), 7.32-7.34 (m, 1H), 7.16-7.21 (m, 2H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.27 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.22 (s, 1H), 2.92-2.98 (m, 1H), 2.67-2.74 (m, 1H), 2.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 157.9, 155.2, 144.9, 135.1, 134.6, 134.4, 133.6, 133.4, 132.7, 130.2, 129.6, 128.5, 128.2, 127.1, 127.0, 126.8, 125.9, 112.6, 111.9, 68.6, 40.6. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5Cl$ [(M-H^+)$^-$], 419.0686; found, 419.0683.

1.1.12. 2-((E)-4-(3-Chlorophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3l**). Yield 90%; mp 171-173 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 12.92 (s, 1H), 8.35-8.37 (m, 2H), 7.84-7.86 (m, 2H), 7.51 (s, 1H), 7.35 (s, 1H), 7.19-7.24 (m, 3H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.32 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.20 (dt, *J* = 8.0, 4.4 Hz, 1H), 2.88-2.94 (m, 1H), 2.60-2.67 (m, 1H), 2.48 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 186.5, 157.9, 155.2, 144.9, 138.9, 134.6, 134.4, 133.6, 133.4, 132.6, 132.6, 129.8, 127.4, 127.4, 127.1, 127.0, 126.2, 125.8, 124.4, 112.6, 111.9, 68.7, 40.5. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5Cl$ [(M-H^+)$^-$], 419.0686; found, 419.0702.

1.1.13. 2-((E)-4-(4-Chlorophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3m**). Yield 85%; mp 117-119 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 12.92 (s, 1H), 8.35-8.37 (m, 2H), 7.84-7.86 (m, 2H), 7.51 (s, 1H), 7.27-7.30 (m, 3H), 6.49 (d, *J* = 16.0

Hz, 1H), 6.26 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.20 (dt, *J* = 8.0, 4.4 Hz, 1H), 2.87-2.93 (m, 1H), 2.59-2.66 (m, 1H), 2.48 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 186.5, 157.9, 155.2, 145.0, 135.0, 134.6, 134.4, 133.6, 133.4, 133.1, 132.7, 128.7, 127.4, 127.1, 126.0, 125.8, 112.6, 111.9, 68.6, 40.5. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5Cl$ [$(M\text{-}H^+)^-$], 419.0686; found, 419.0679.

1.1.14. 2-((E)-4-(2-Bromophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3n**). Yield 65%; mp 140-142 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 12.92 (s, 1H), 8.35-8.37 (m, 2H), 7.83-7.86 (m, 2H), 7.48-7.53 (m, 3H), 7.24-7.26 (m, 1H), 7.07-7.11 (m, 1H), 6.84 (d, *J* = 15.6 Hz, 1H), 6.20 (dt, *J* = 16.0, 8.0 Hz, 1H), 5.24 (dt, *J* = 7.6, 4.4 Hz, 1H), 2.92-2.98 (m, 1H), 2.67-2.74 (m, 1H), 2.54 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 157.9, 155.2, 144.9, 136.9, 134.6, 134.4, 133.6, 133.4, 132.9, 132.8, 128.8, 128.4, 127.5, 127.1, 127.1, 127.0, 125.9, 123.3, 112.6, 111.9, 68.6, 40.5. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5Br$ [$(M\text{-}H^+)^-$], 463.0181; found, 463.0197.

1.1.15. 2-((E)-4-(3-Bromophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3o**). Yield 85%; mp 179-181 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 12.93 (s, 1H), 8.35-8.38 (m, 2H), 7.84-7.86 (m, 2H), 7.51 (s, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.15-7.19 (m, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J* = 16.0, 8.0 Hz, 1H), 5.21 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.88-2.94 (m, 1H), 2.60-2.68 (m, 1H), 2.47 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 186.5, 157.9, 155.2, 144.9, 139.2, 134.6, 134.4, 133.6, 133.4, 132.5, 130.3, 130.1, 129.1, 127.1, 127.1, 127.0, 125.8, 124.9, 122.8, 112.6, 111.9, 68.6, 40.5. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5Br$ [$(M\text{-}H^+)^-$], 463.0181; found, 463.0172.

1.1.16. 2-((E)-4-(4-Bromophenyl)-1-hydroxybut-3-enyl)-1,4-dihydroxyanthracene-9,10-dione (**3p**). Yield 74%; mp 180-182 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1H), 12.91 (s, 1H), 8.34-8.36 (m, 2H), 7.83-7.86 (m, 2H), 7.50 (s, 1H), 7.41-7.43 (m, 2H), 7.21-7.23 (m, 2H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.27 (dt, *J* = 16.0, 8.0 Hz, 1H), 5.20 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.86-2.92 (m, 1H), 2.60-2.66 (m, 1H), 2.50 (d, *J* = 4.0 Hz,1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.5, 157.9, 155.2, 144.9, 135.9, 134.6, 134.4, 133.6, 133.4, 132.8, 131.7, 127.7, 127.1, 126.1, 125.8, 121.2, 112.6, 111.9, 68.6, 40.5. HRMS (ESI): m/z caclcd for $C_{24}H_{16}O_5Br$ [$(M\text{-}H^+)^-$], 463.0181; found, 463.0170.

1.2. General procedure for the synthesis of **4**.

Compounds **4a-c** was synthesized by a recently described procedure[28].

1.2.1. 1,2-Dihydro-3,4,11-trihydroxy-1-phenyl-1H-cyclopenta[b]anthracene-5,10-dione (**4a**). Yield 70%. The spectra data obtained for **4a** are in agreement with previously reported values[28].

1.2.2. 7/8-Bromo-1,2-dihydro-3,4,11-trihydroxy-1-phenyl-1H-cyclopenta[b]anthracene-5, 10-dione (**4b**/**4b'**). Prepared using the method for the preparation of **4a** from 6-bromo-1,4-dihydroxyanthraquinone and cinnamaldehyde, affording an inseparable regioisomeric mixture of **4b** and **4b'** (72:28, ratio obtained from ^{1}H NMR spectra) as an orange solid in 79% yield; mp 229-230 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.01 (s, 1H), 12.88 (s, 1H), 8.41-8.45 (m, 1H), 8.14-8.19 (m, 1H), 7.90-7.93 (m, 1H), 7.32-7.36 (m, 5H), 5.60-5.63 (m, 1H), 4.50-4.53 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.07-3.15 (m, 1H), 2.88 (s, 1H), 2.14-2.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 185.7, 155.8, 155.1, 146.4, 143.8, 143.1, 137.5, 134.6, 132.2, 130.1, 129.9, 128.7, 128.5, 127.9, 126.8, 113.2, 112.9, 73.3, 48.3, 43.0. HRMS (ESI): m/z caclcd for $C_{23}H_{14}BrO_5$ [$(M\text{-}H^{+})^{-}$], 449.0025; found, 449.0006.

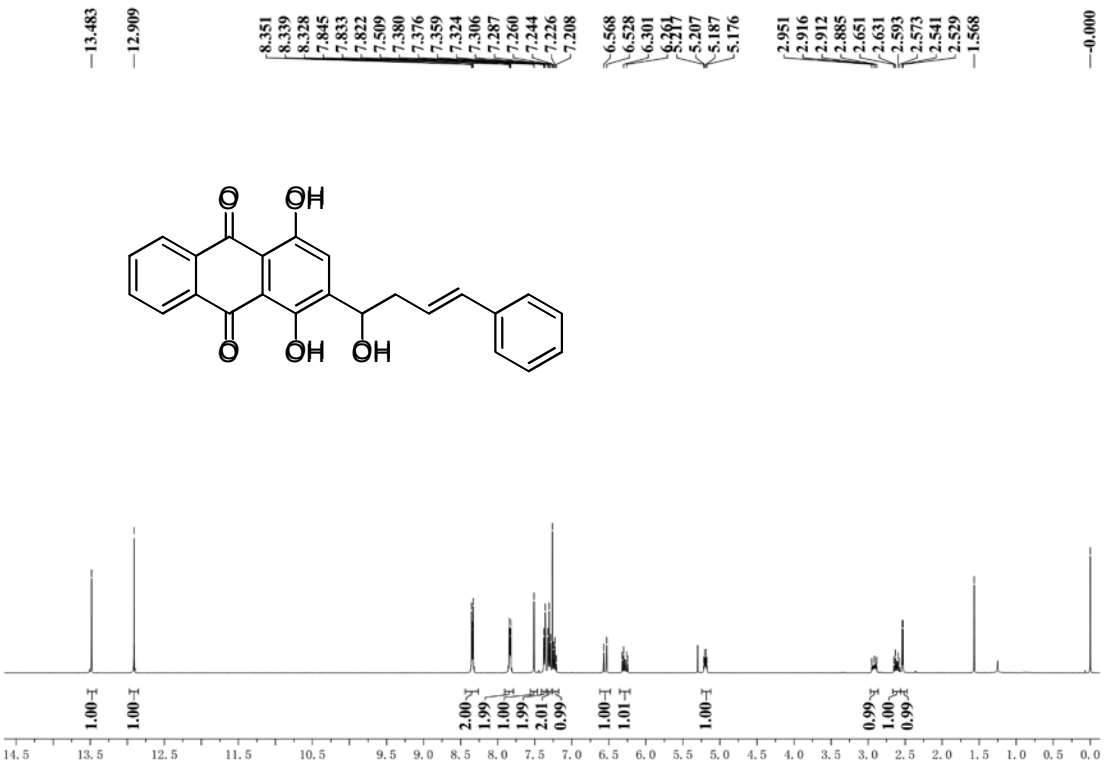
1.2.3. 7/8-Bromo-1,2-dihydro-3,4,11-trihydroxy-1-*m*-tolyl-1H-cyclopenta[b]anthracene-5,10-dione (**4c**/**4c'**). Prepared using the method for the preparation of **4a** from 6-bromo-1,4-dihydroxyanthraquinone and 3-*m*-tolylacrylaldehyde, affording an inseparable regioisomeric mixture of **4c** and **4c'** (72:28, ratio obtained from ^{1}H NMR spectra) as an orange solid in 81% yield; mp 219-220 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.18 (s, 1H), 12.82 (s, 1H), 8.43-8.46 (m, 1H), 8.15-8.20 (m, 1H), 7.92-7.94 (m, 1H), 7.05-7.26 (m, 4H), 5.59-5.61 (m, 1H), 4.45-4.49 (m, 1H), 3.05-3.13 (m, 1H), 2.84 (s, 1H), 2.33 (s, 3H), 2.12-2.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.26, 185.70, 155.90, 155.19, 146.13, 143.12, 138.18, 137.41, 134.75, 132.10, 130.08, 128.61, 128.55, 128.43, 127.61, 124.87, 113.34, 112.76, 73.31, 48.17, 43.20, 21.51. HRMS (ESI): m/z caclcd for $C_{24}H_{16}BrO_5$ [$(M\text{-}H^{+})^{-}$], 463.0181; found, 463.0170.

2. Cell culture and cytotoxicity assays

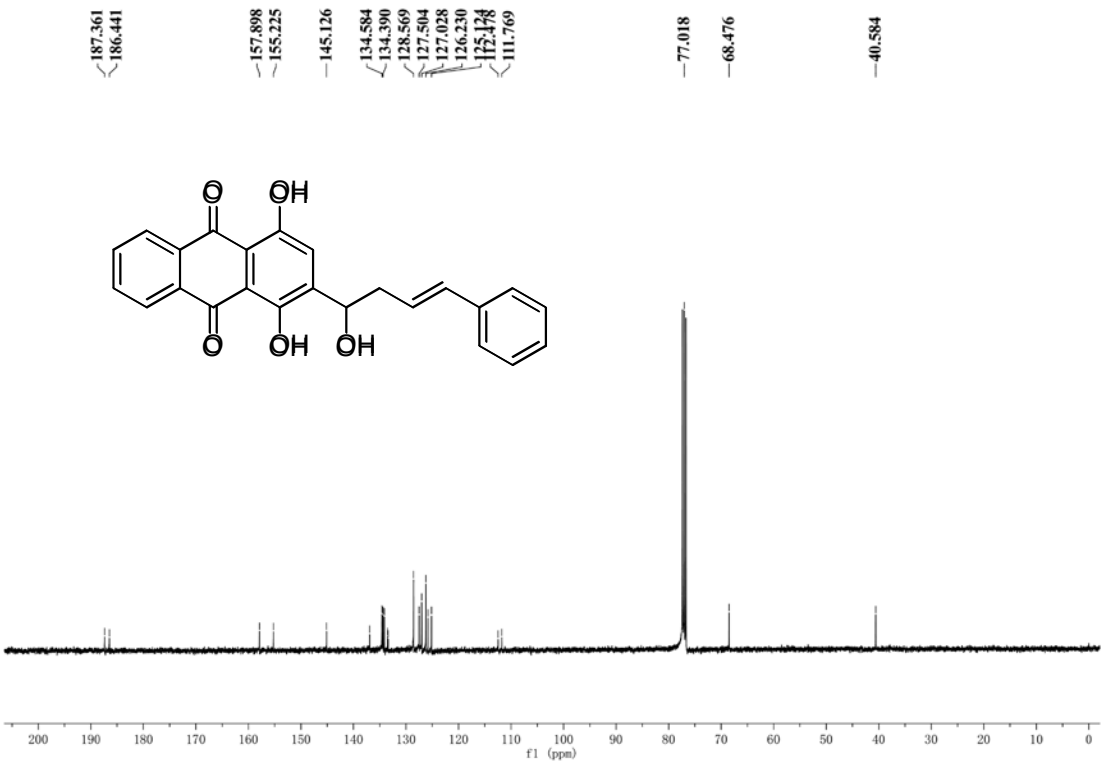
Human cancer cell lines, HeLa, MDA-MB-231, MCF-7, and MiaPaca-2 were obtained from ATCC and maintained in either DMEM (HeLa, MDA-MB-231, MiaPaca-2) or RPMI (MCF-7) media supplemented with 10% FBS and 1% Penicillin-Streptomycin. MCF-10 cells were cultured in DMEM/F-12 supplemented with 5% horse serum, 20 ng/mL epidermal

growth factor (EGF), 0.5 mg/mL hydrocortisone, 100 ng/mL cholera toxin, and 10 µg/mL insulin.. Cells were plated at varying densities (2000-4000 cells/well) in 3 96-well plates and allowed to adhere overnight at 37° C. Compounds were diluted to desired concentrations in DMSO then serum-free RPMI media, then added to cells and incubated at 37° C for 72 hrs. Effects on cell proliferation were assessed using the CellTiter Glo assay. Each value was normalized to cells treated with DMSO and IC_{50}s were determined using Microsoft Excel.

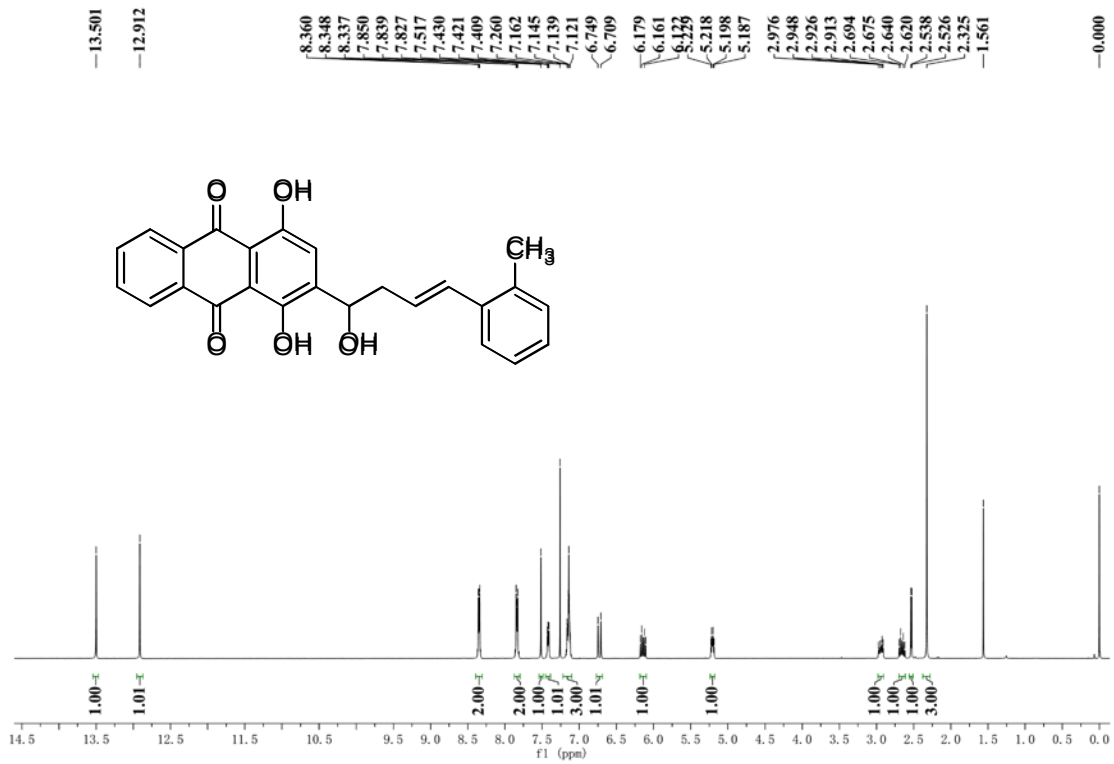
Copies of ^{1}H and ^{13}C NMR Spectra for Compounds **3a-p** and **4a-c**



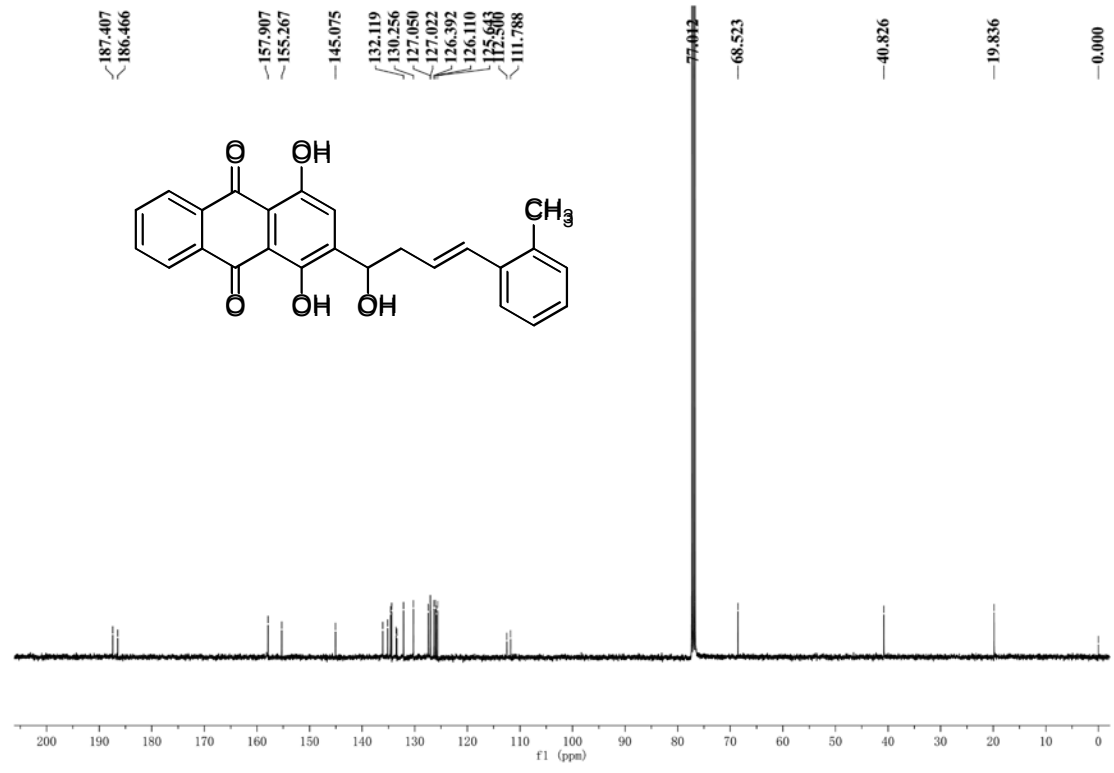
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3a**



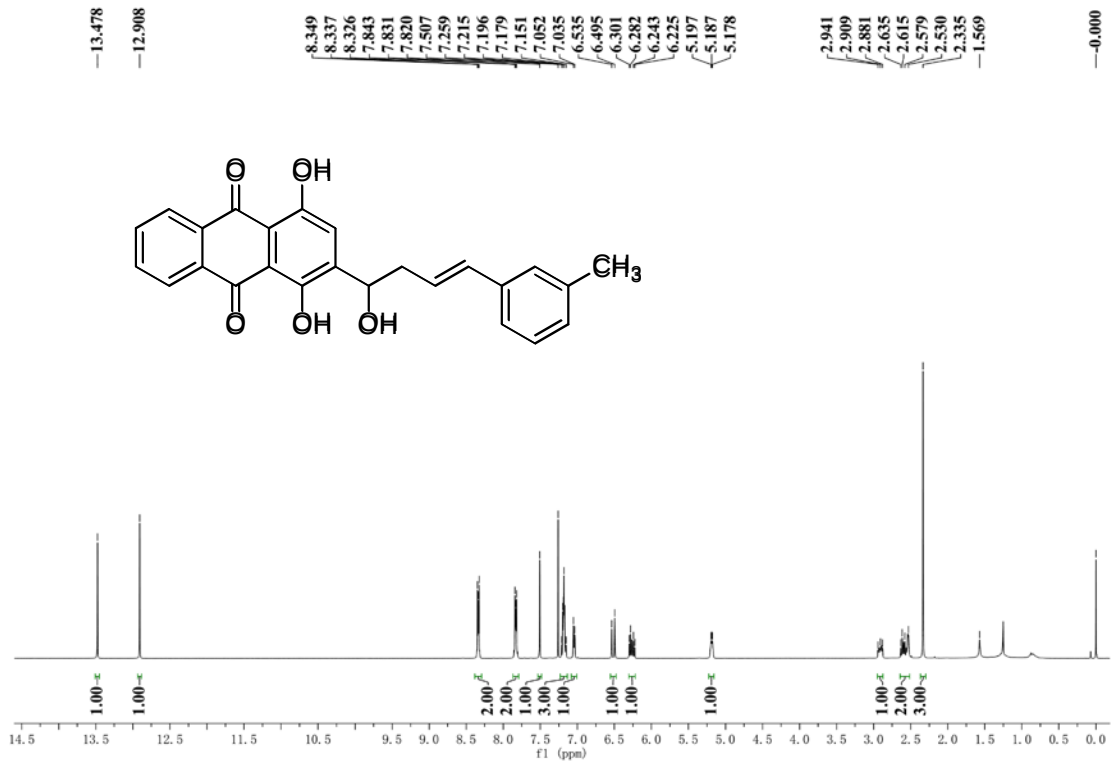
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3a**



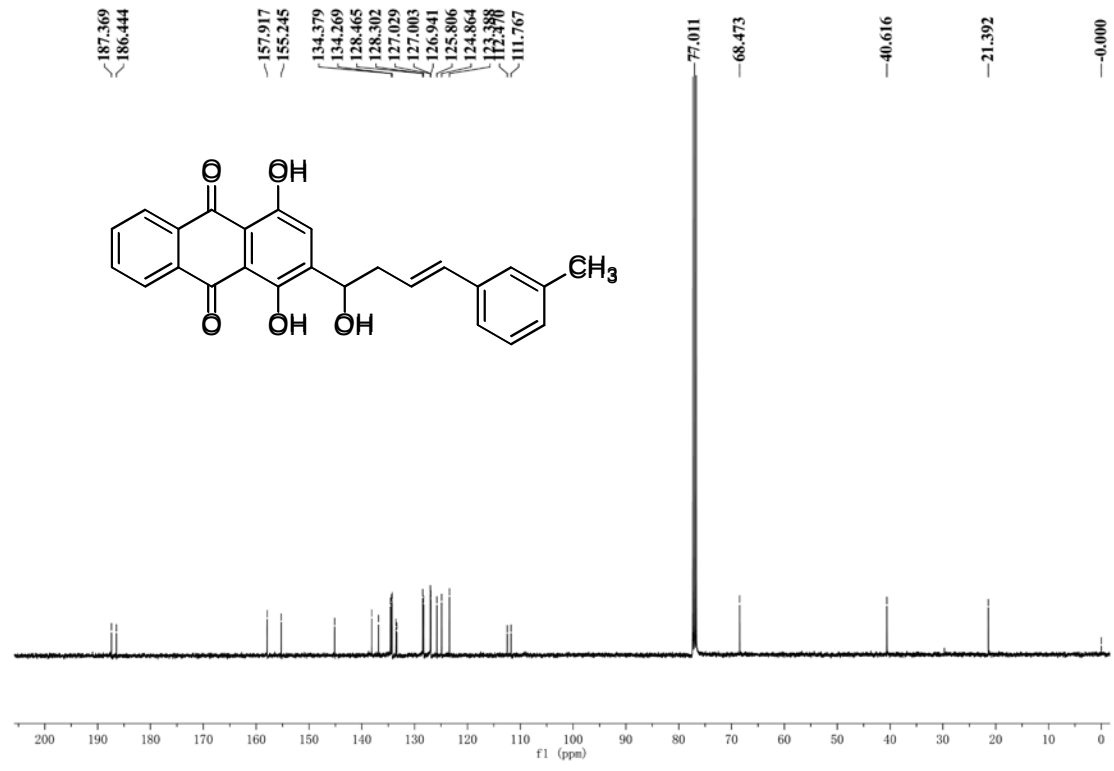
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3b**



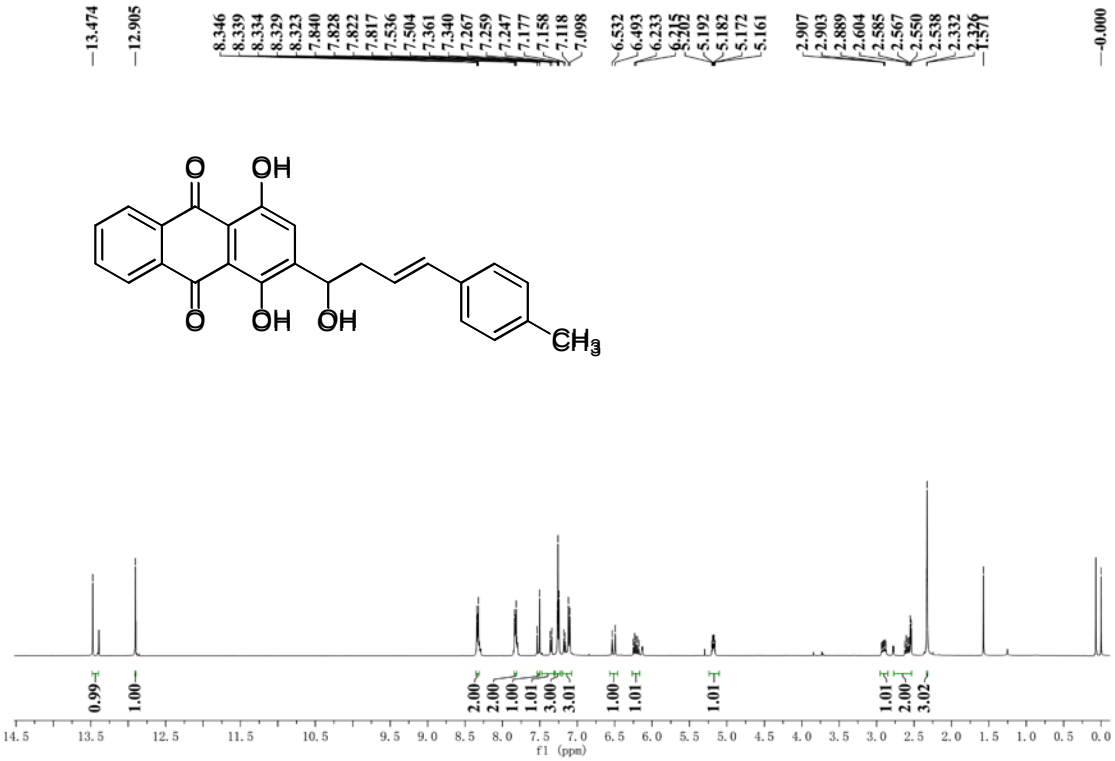
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3b**



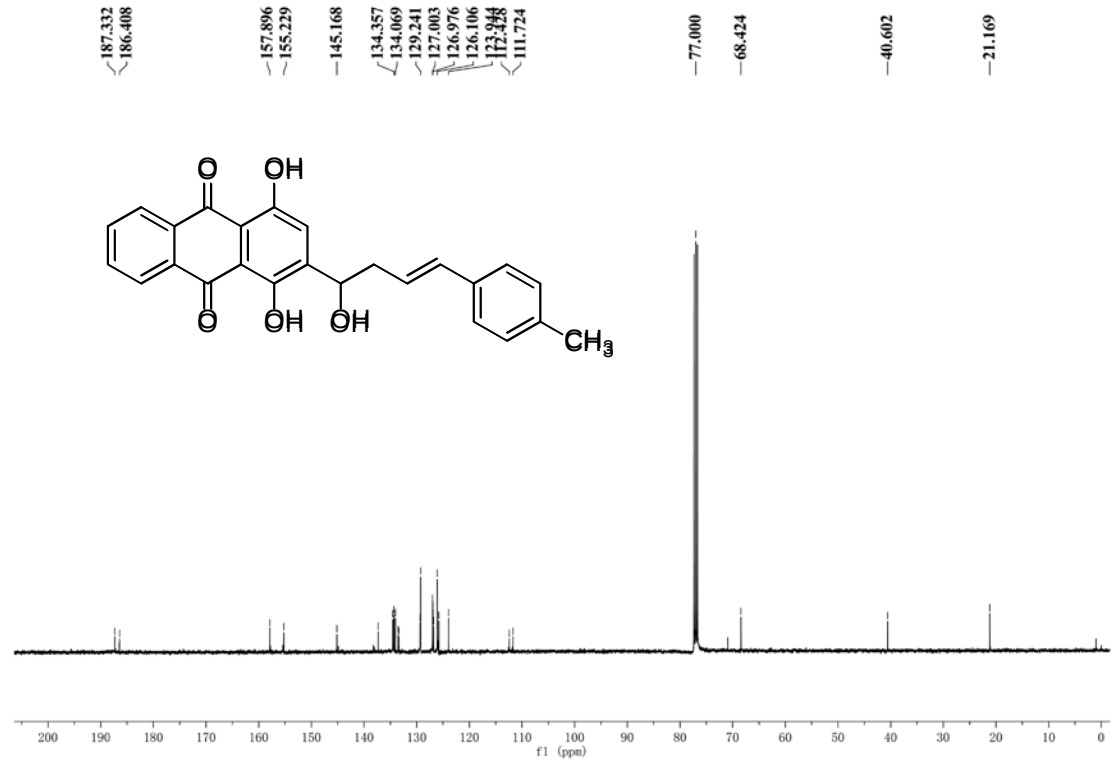
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3c**



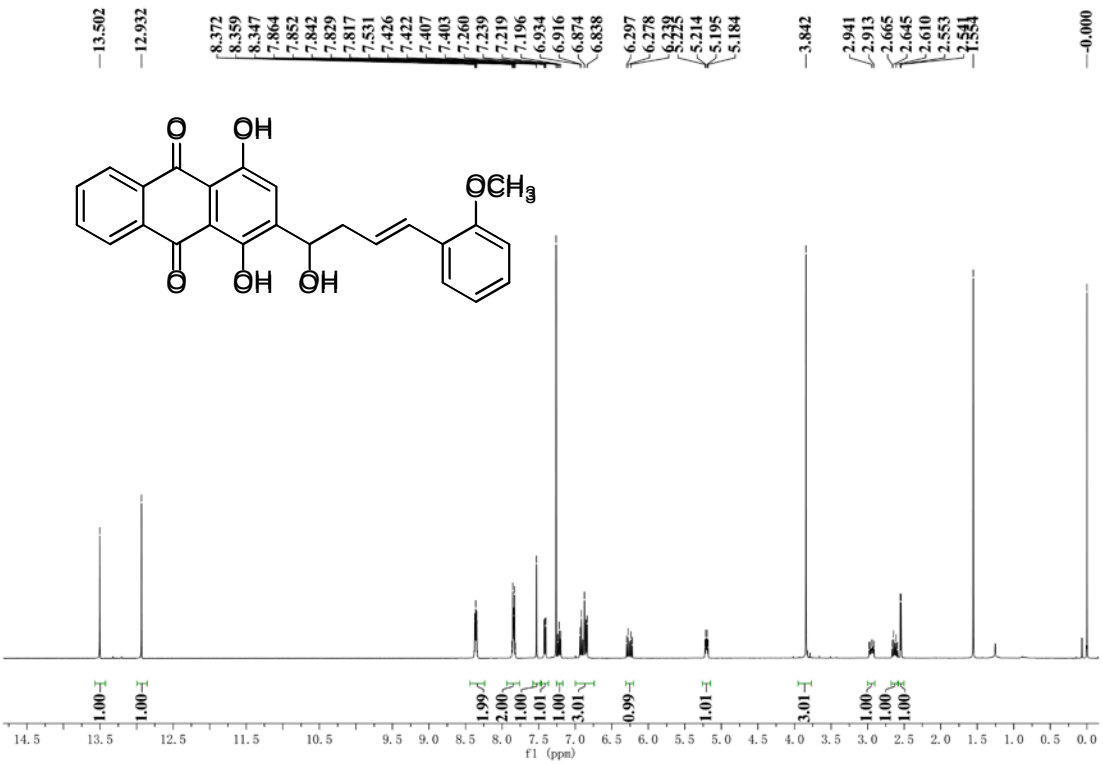
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3c**



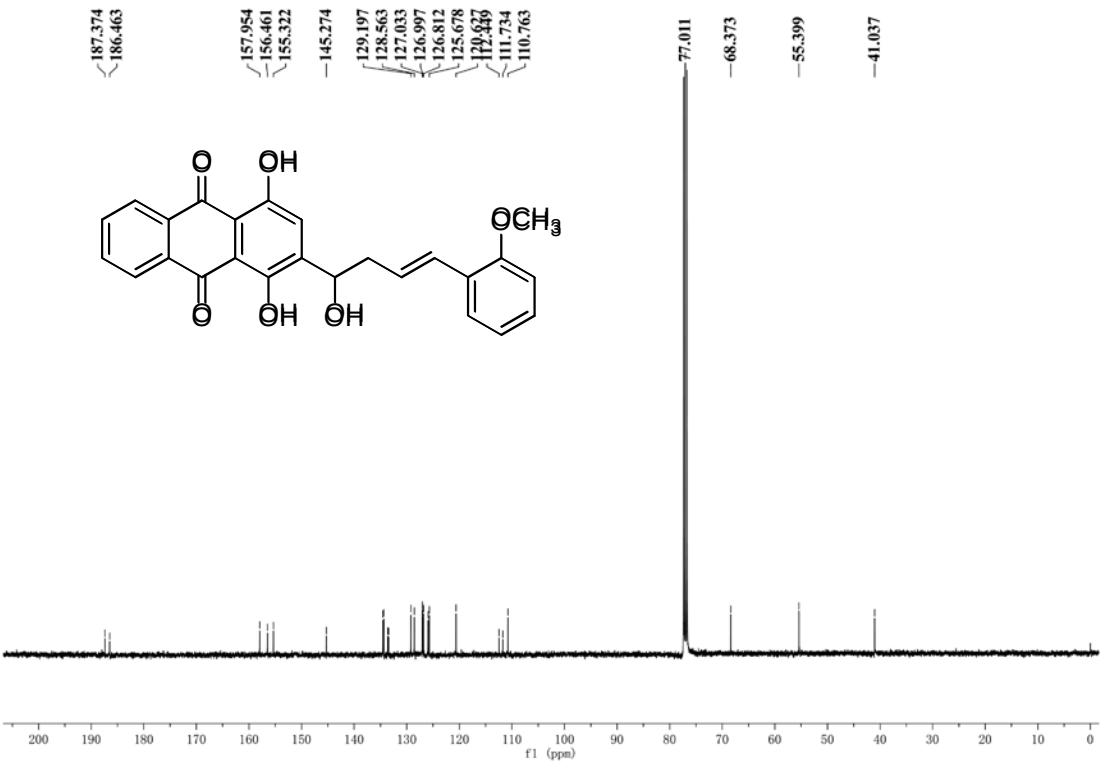
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3d**



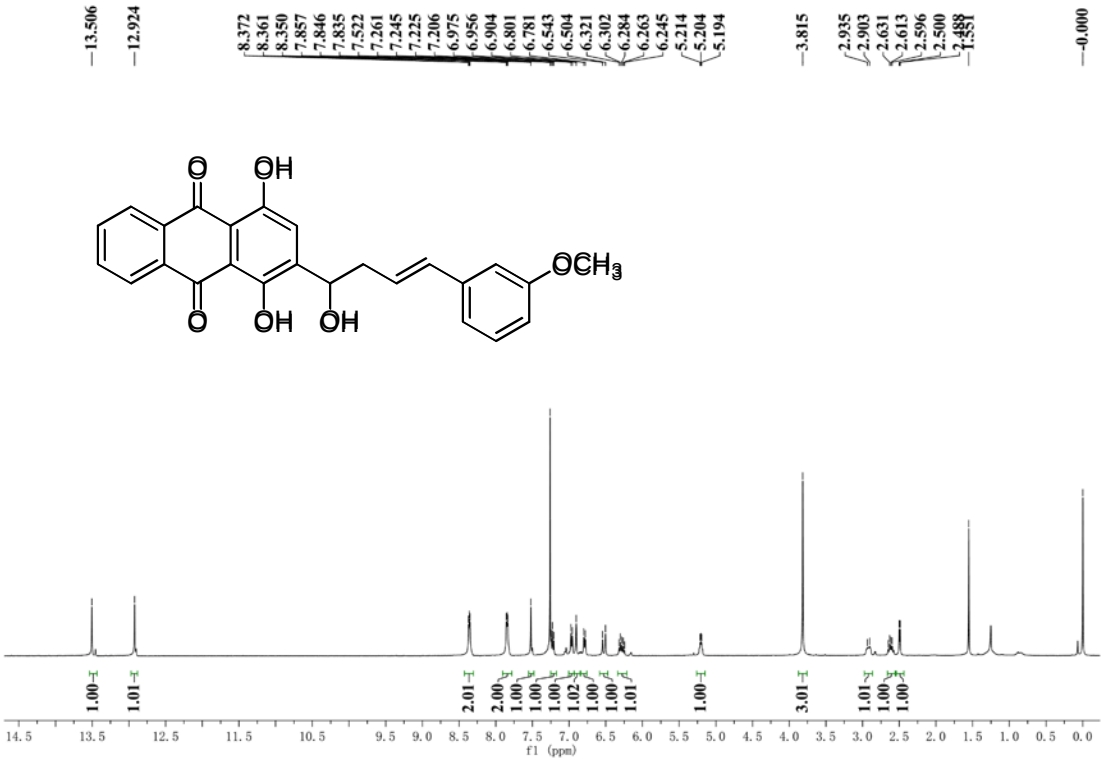
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3d**



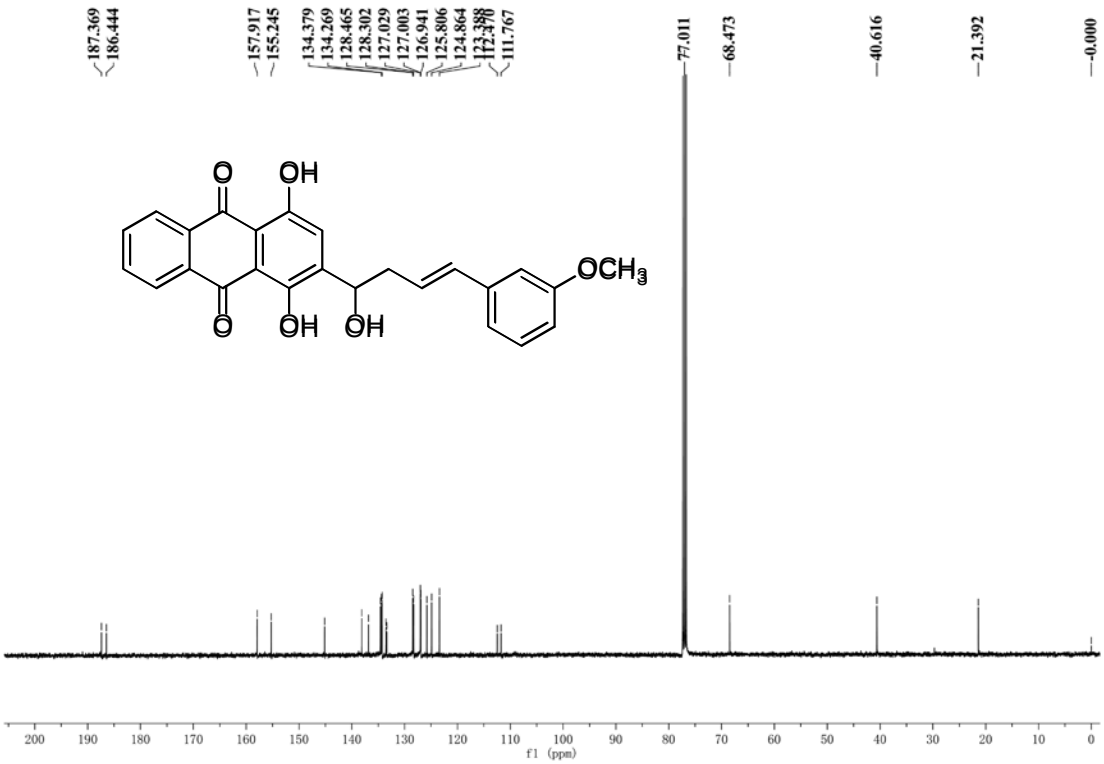
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3e**



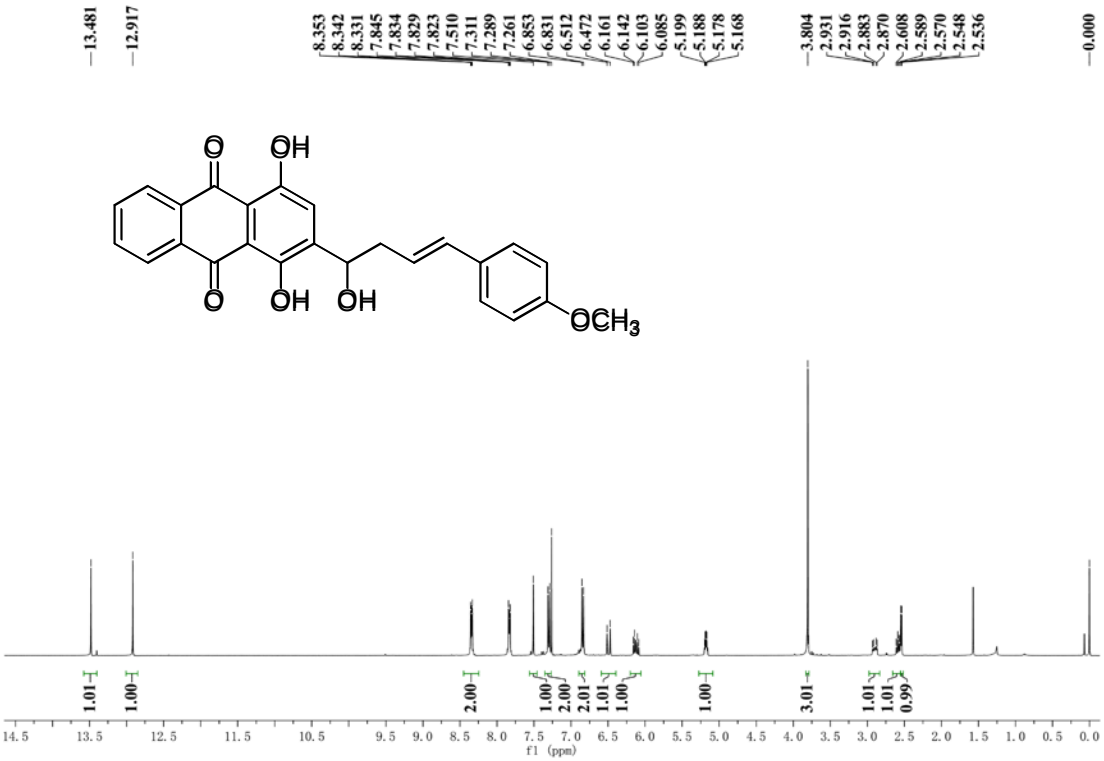
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3e**



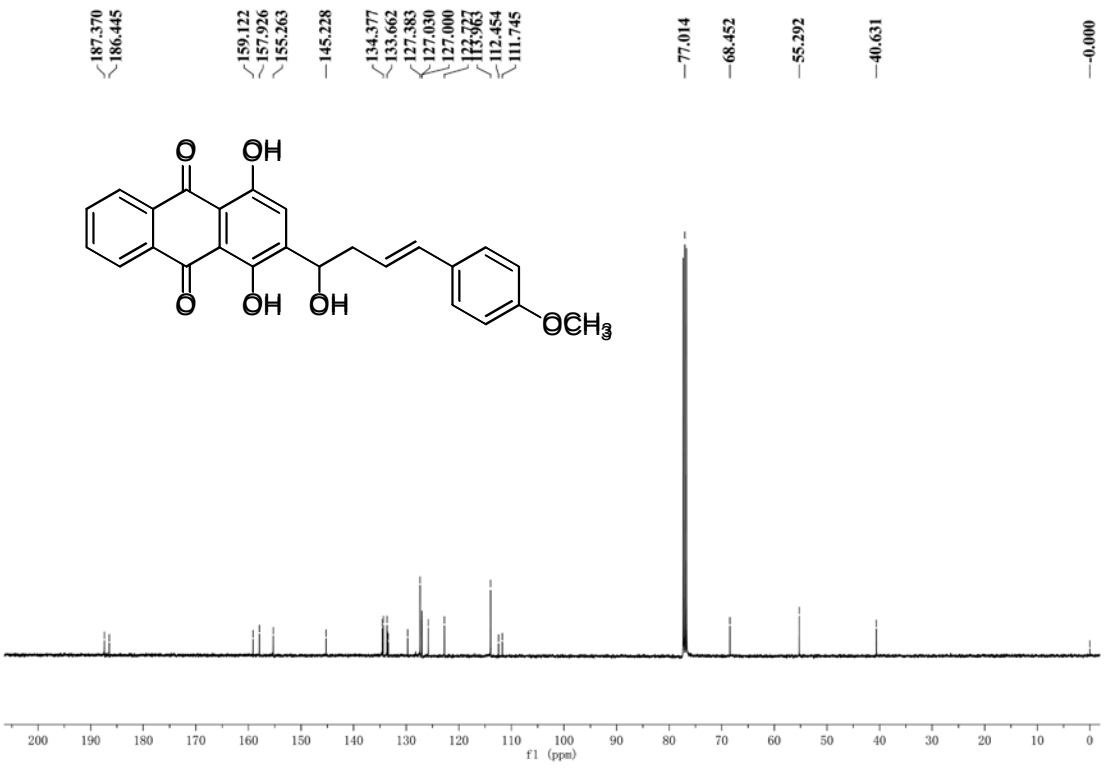
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3f**



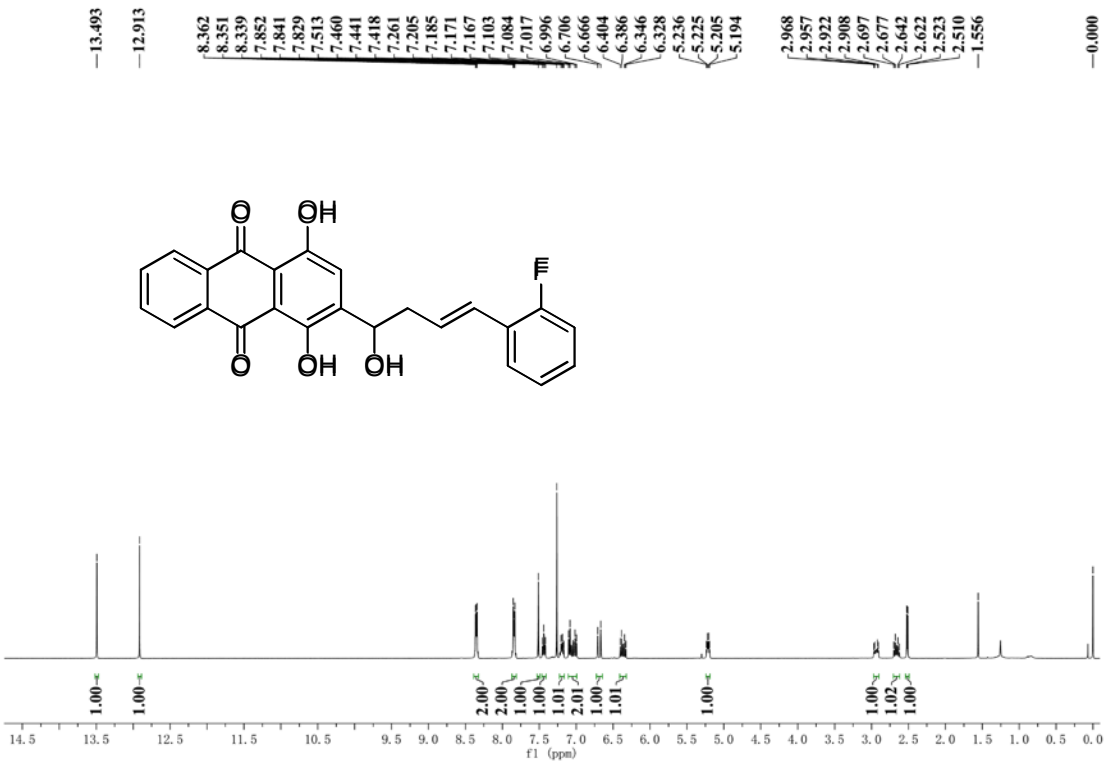
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3f**



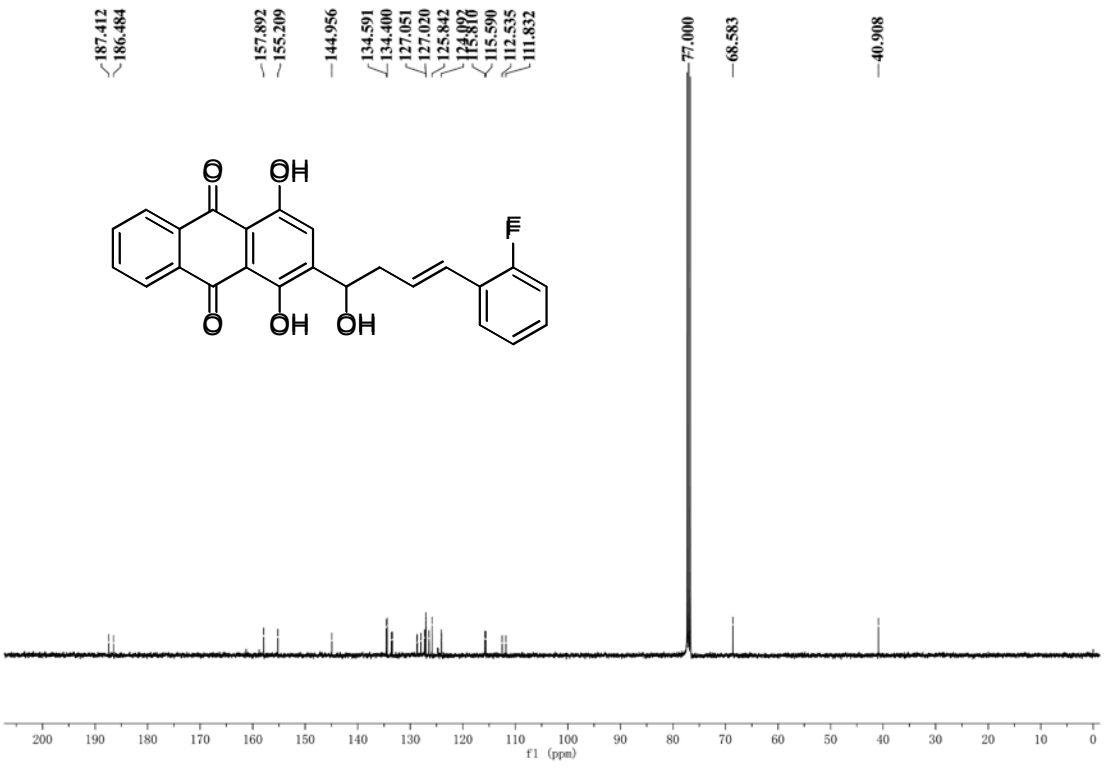
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3g**



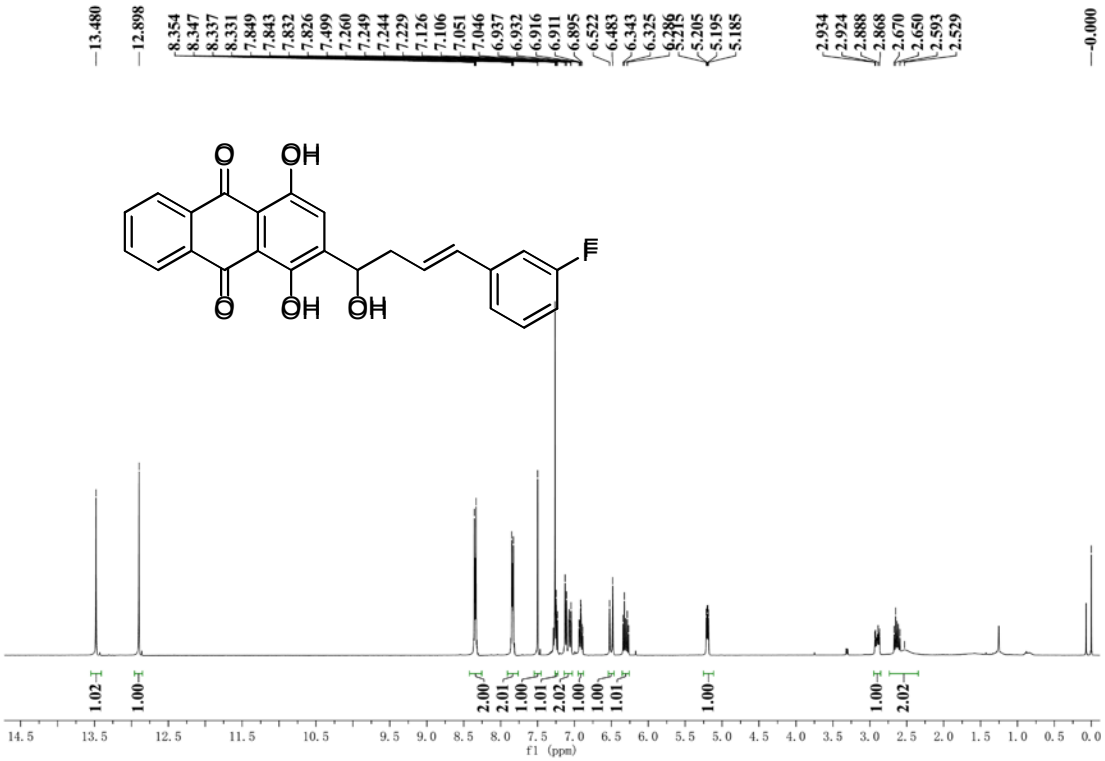
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3g**



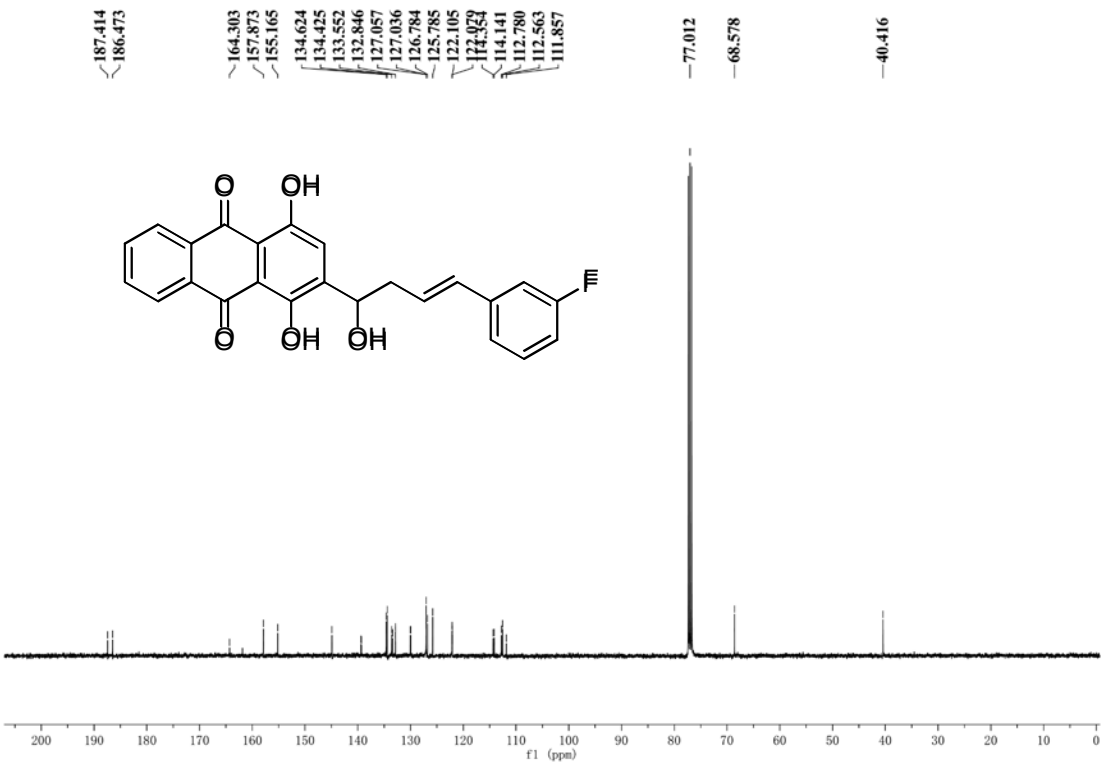
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3h**



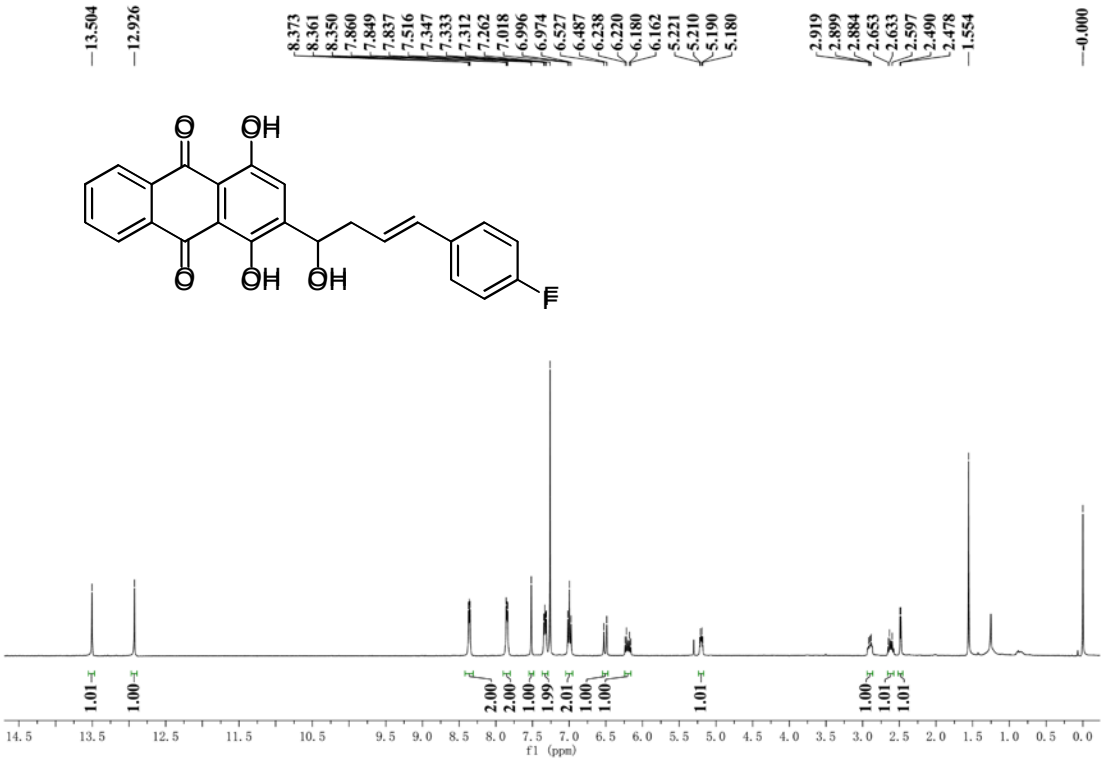
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3h**



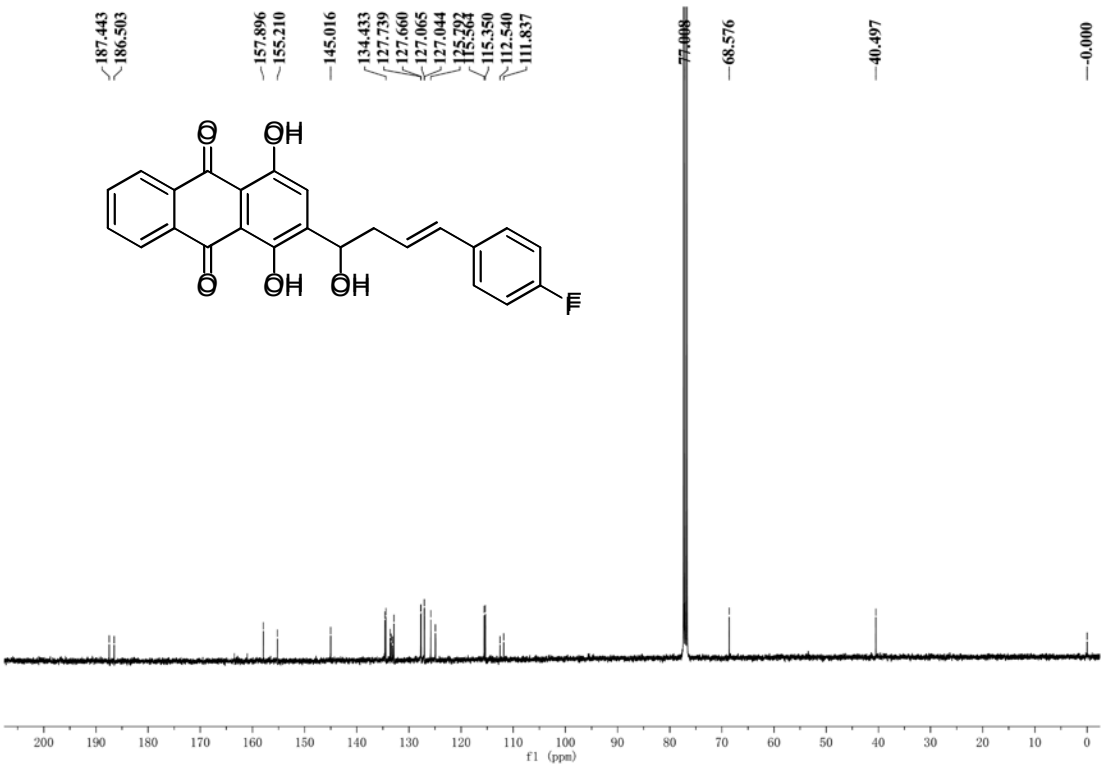
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3i**



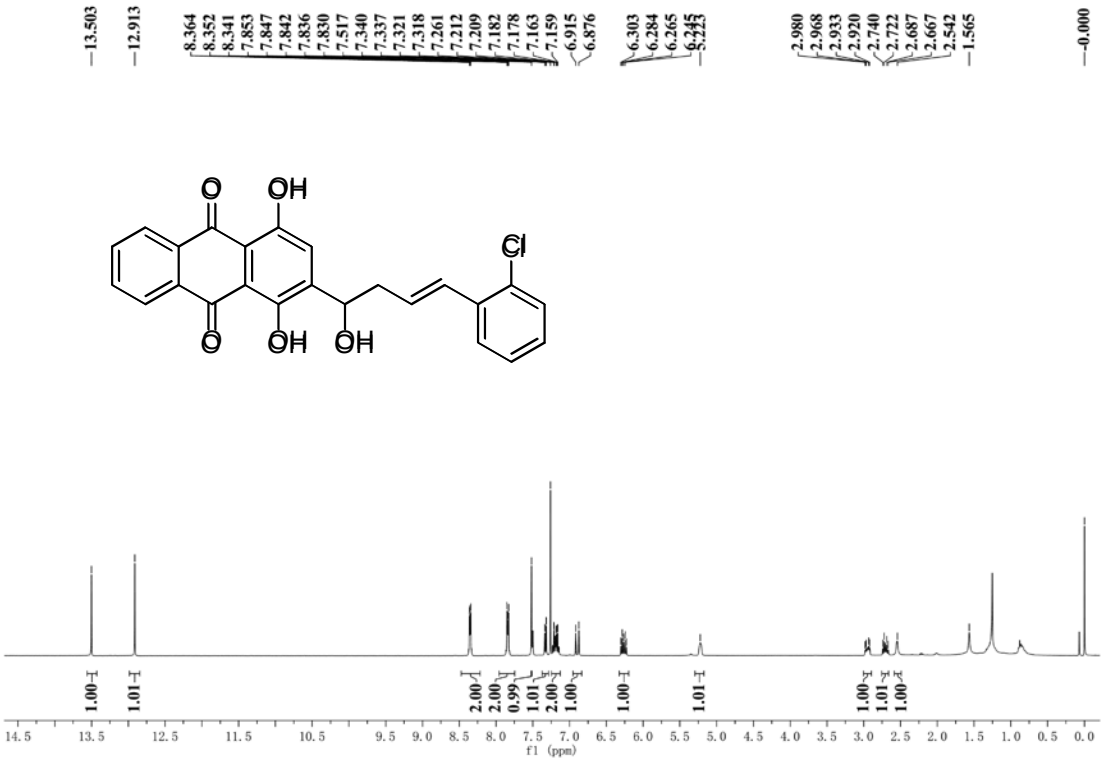
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3i**



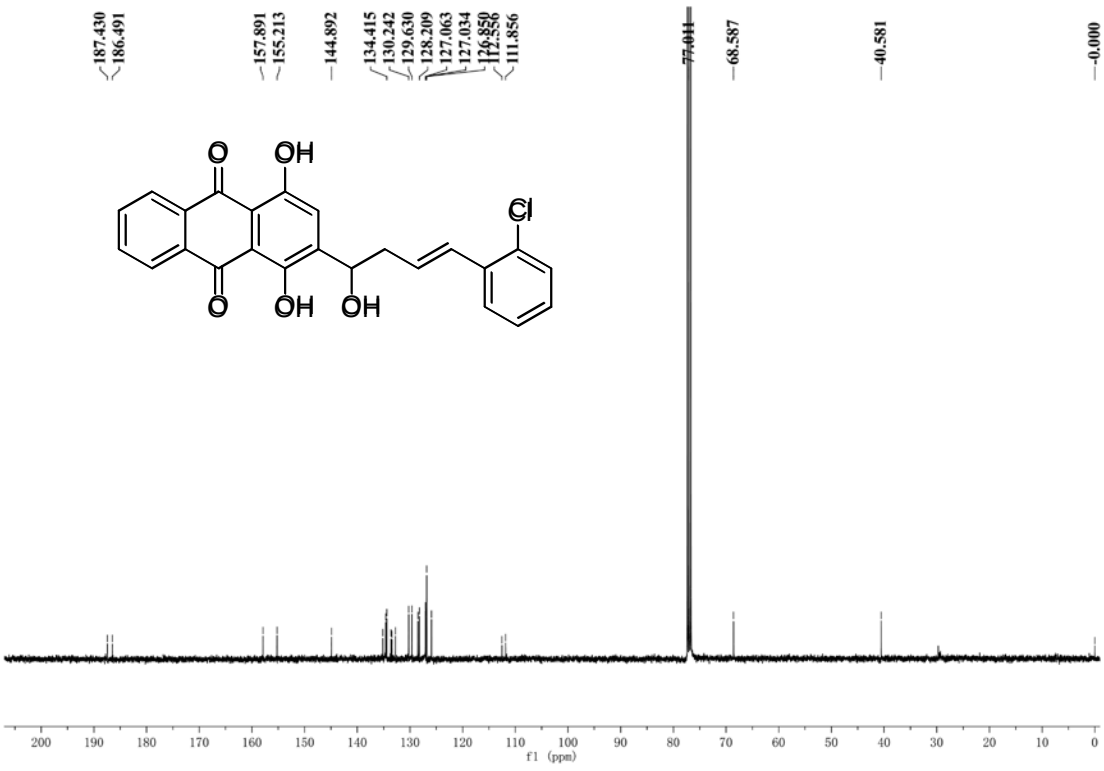
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3j**



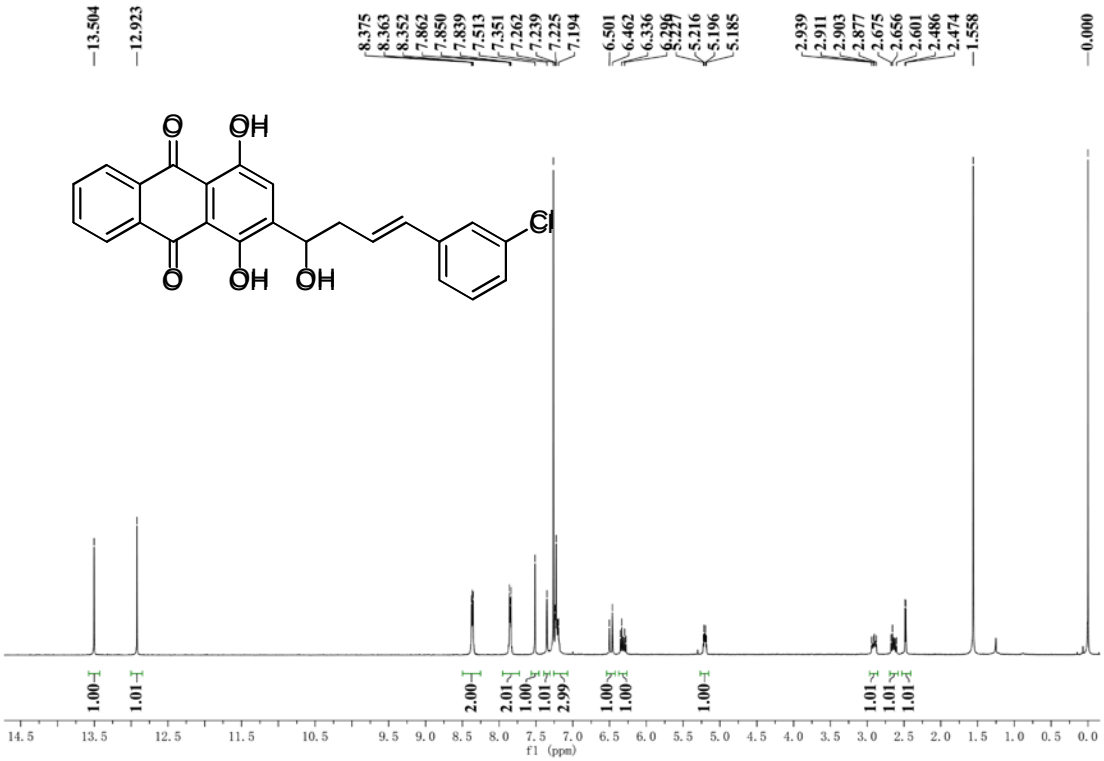
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3j**



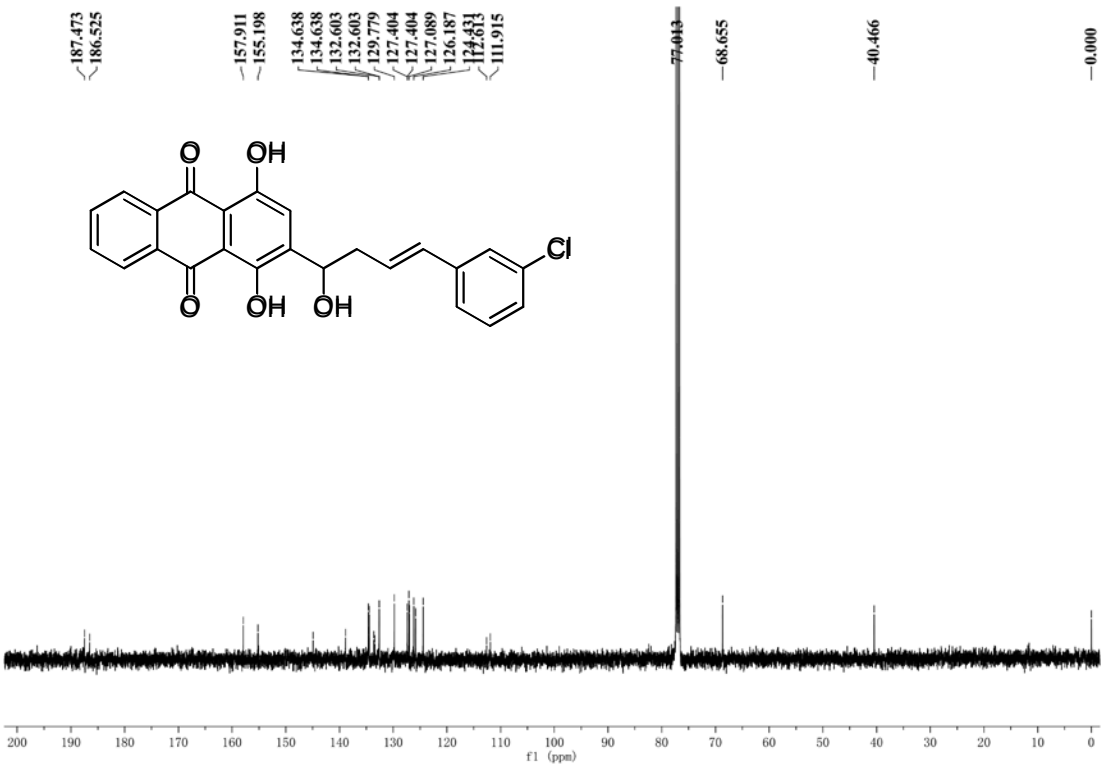
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3k**



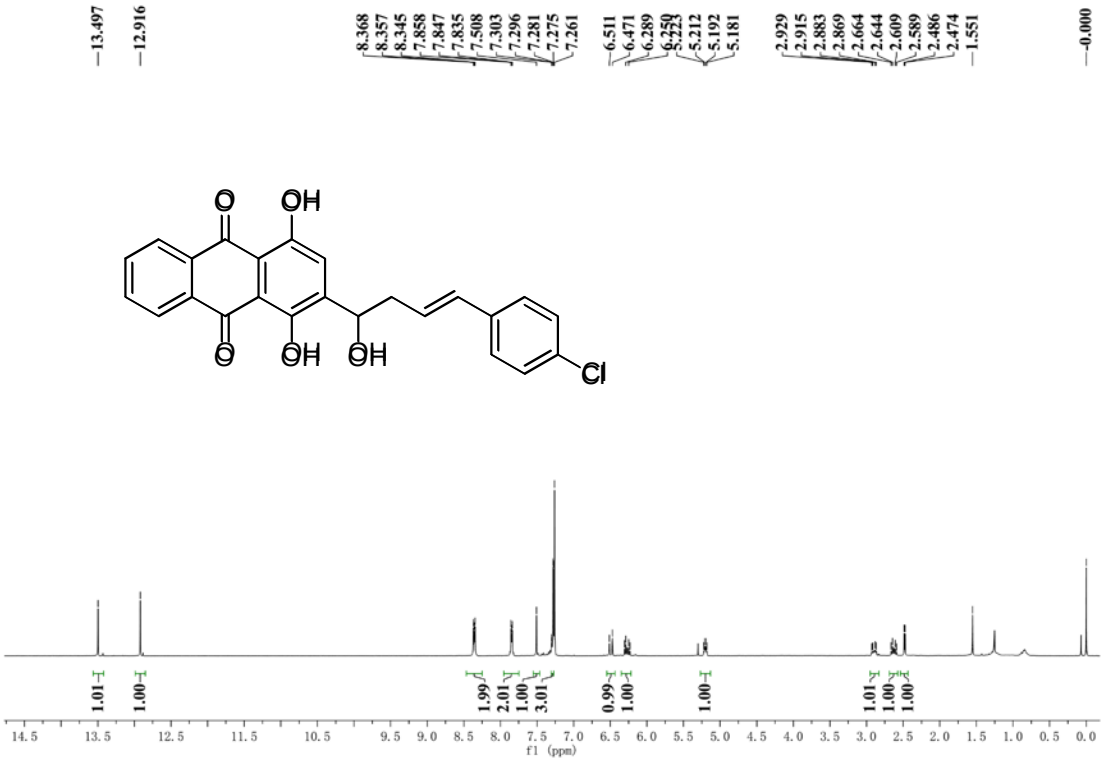
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3k**



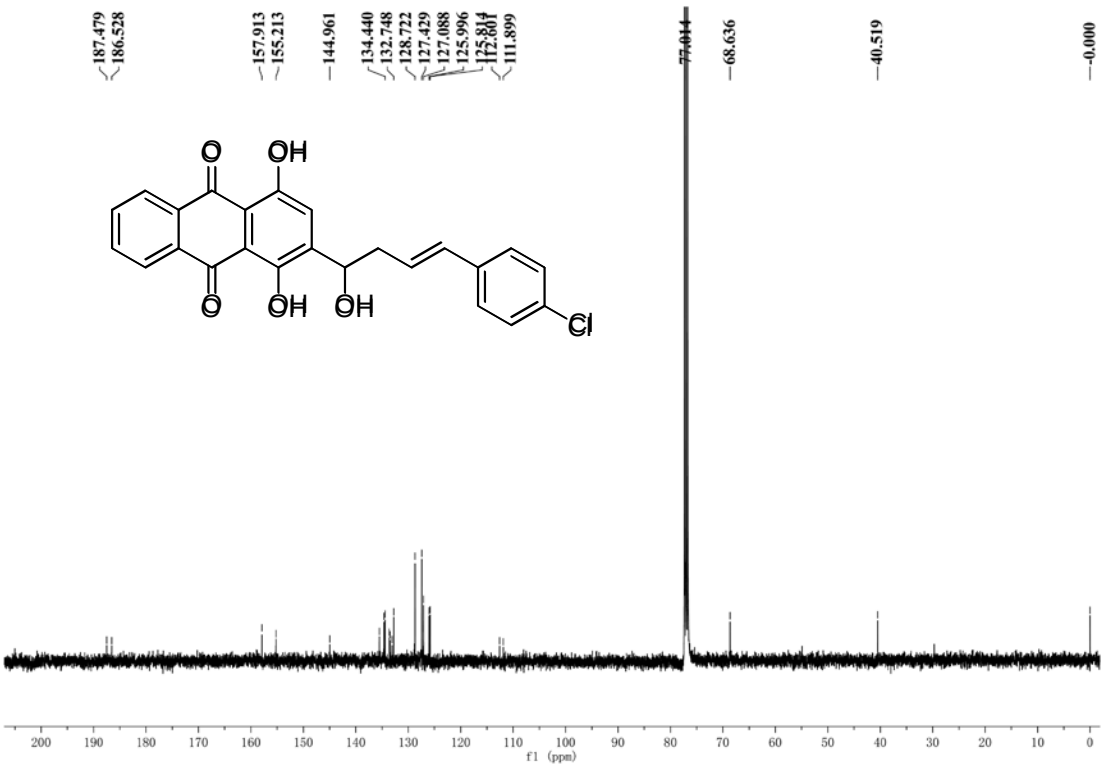
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3l**



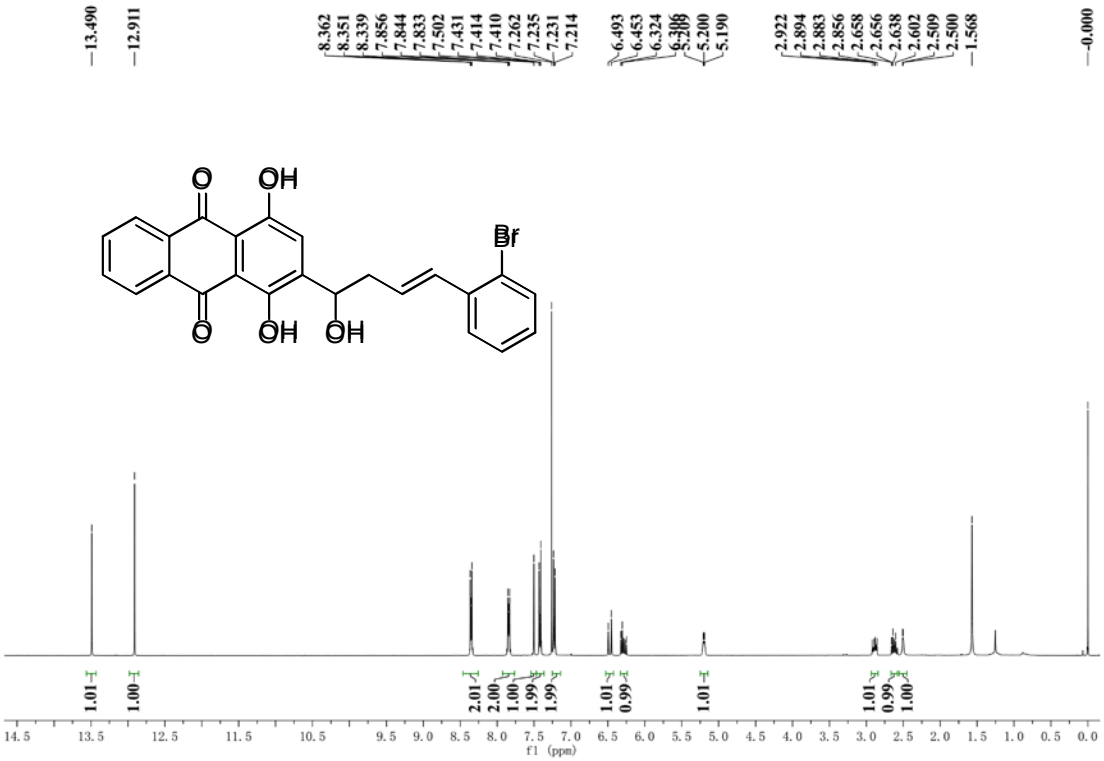
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3l**



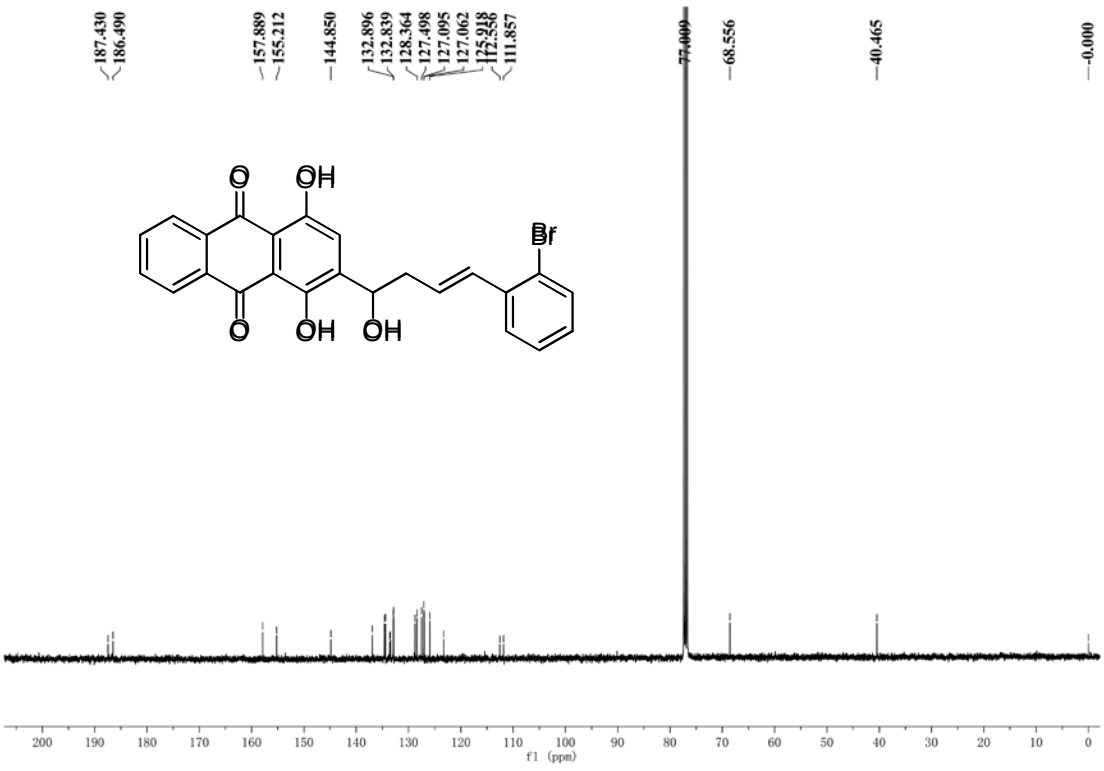
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3m**



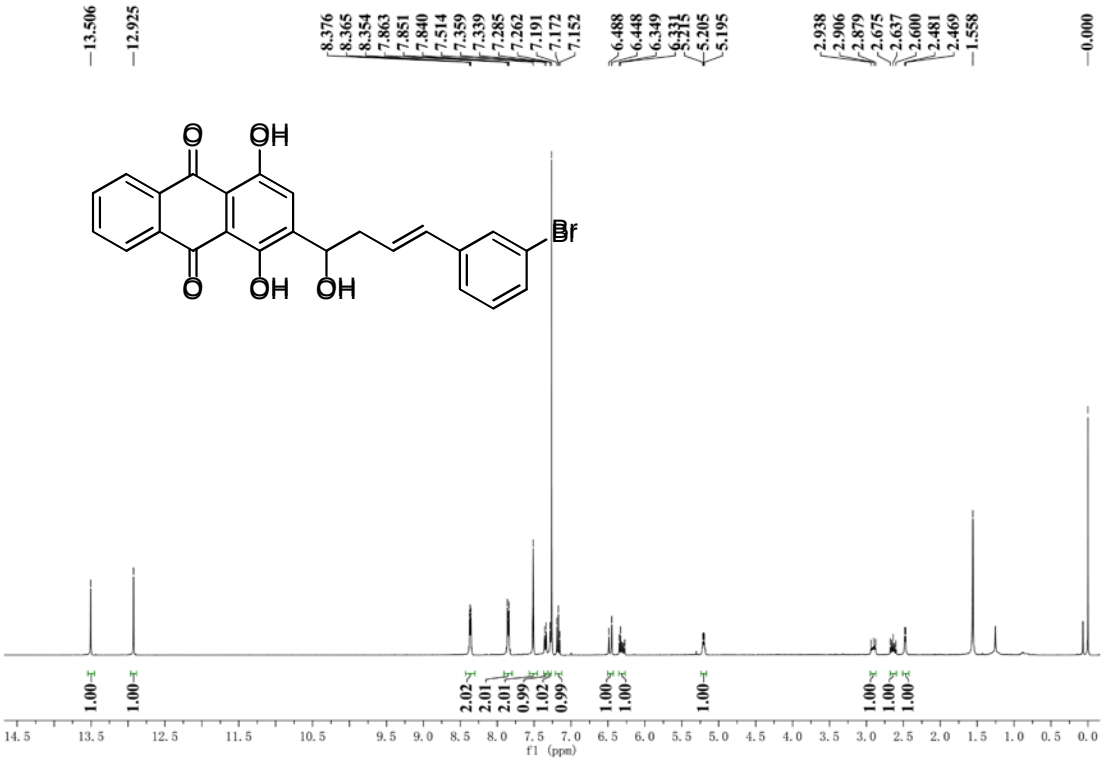
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3m**



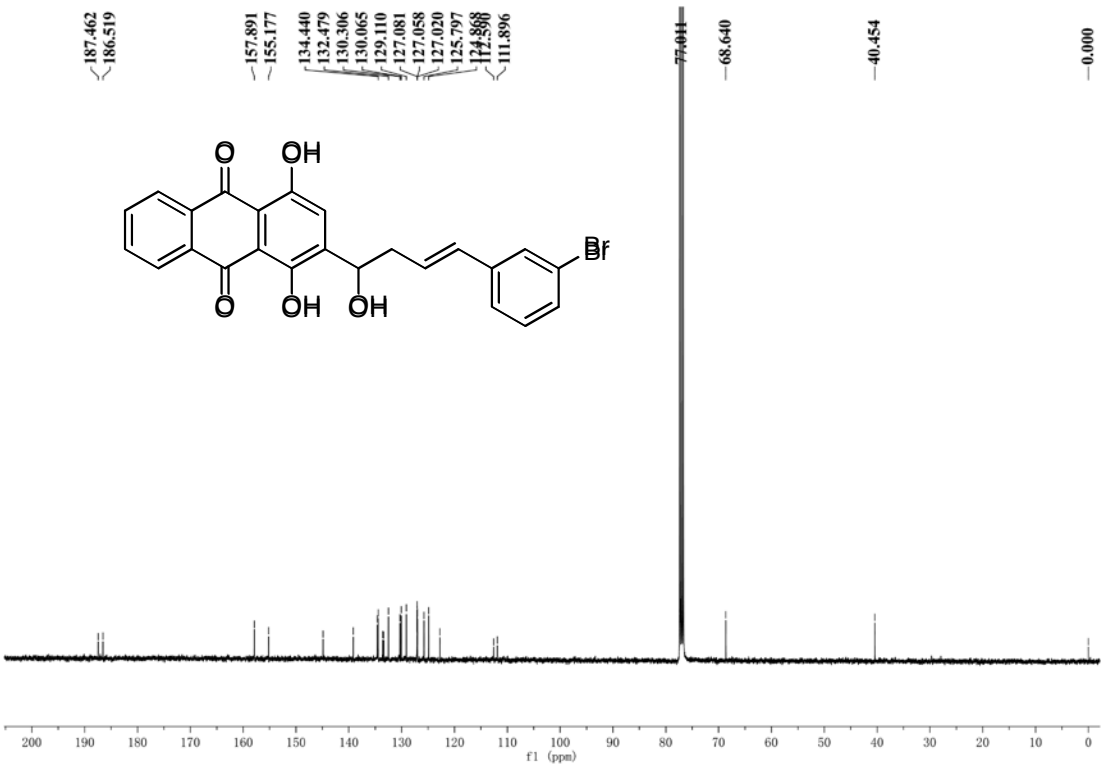
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3n**



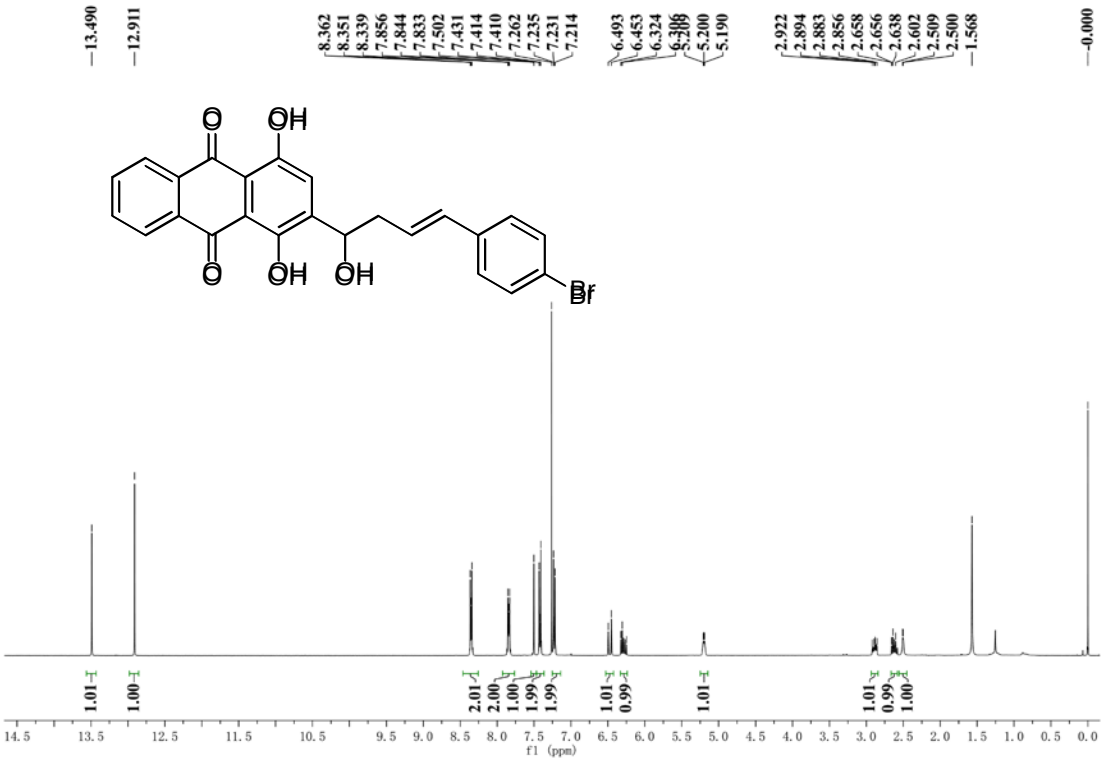
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3n**



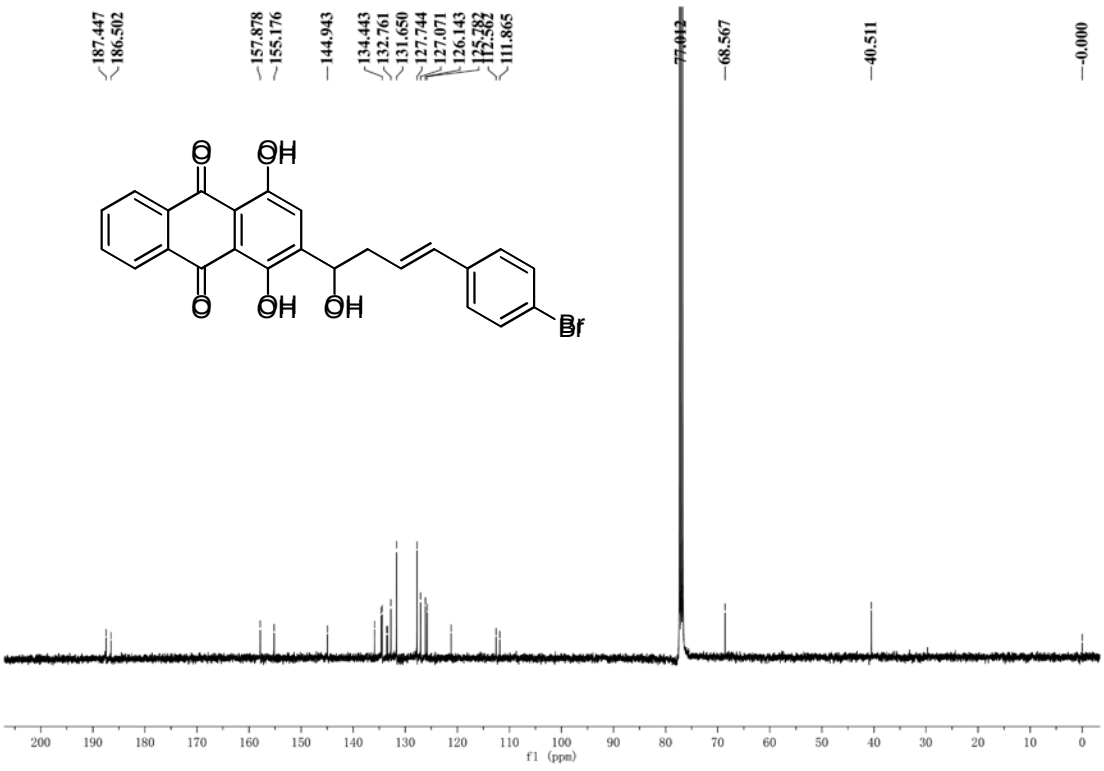
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3o**



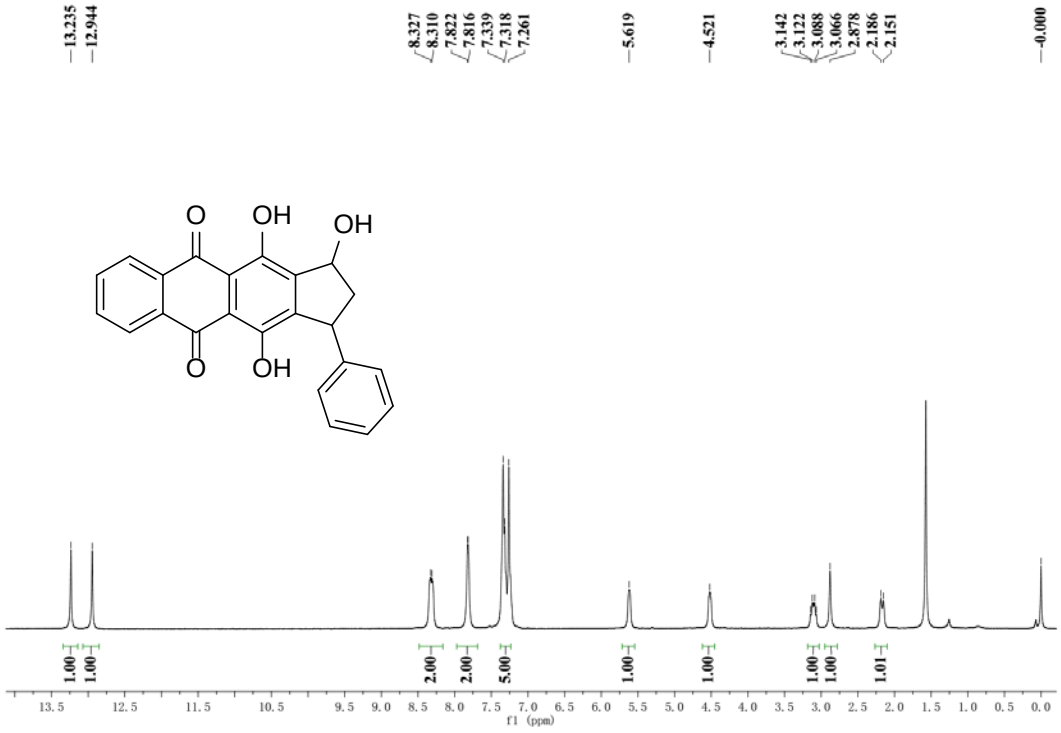
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3o**



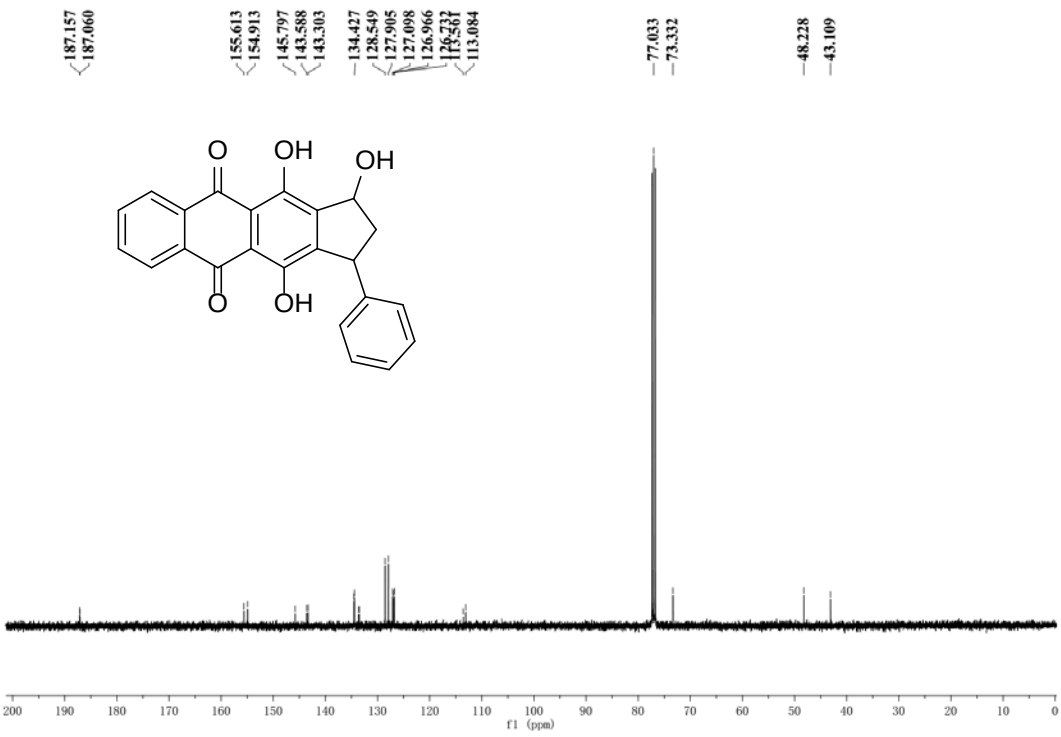
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **3p**



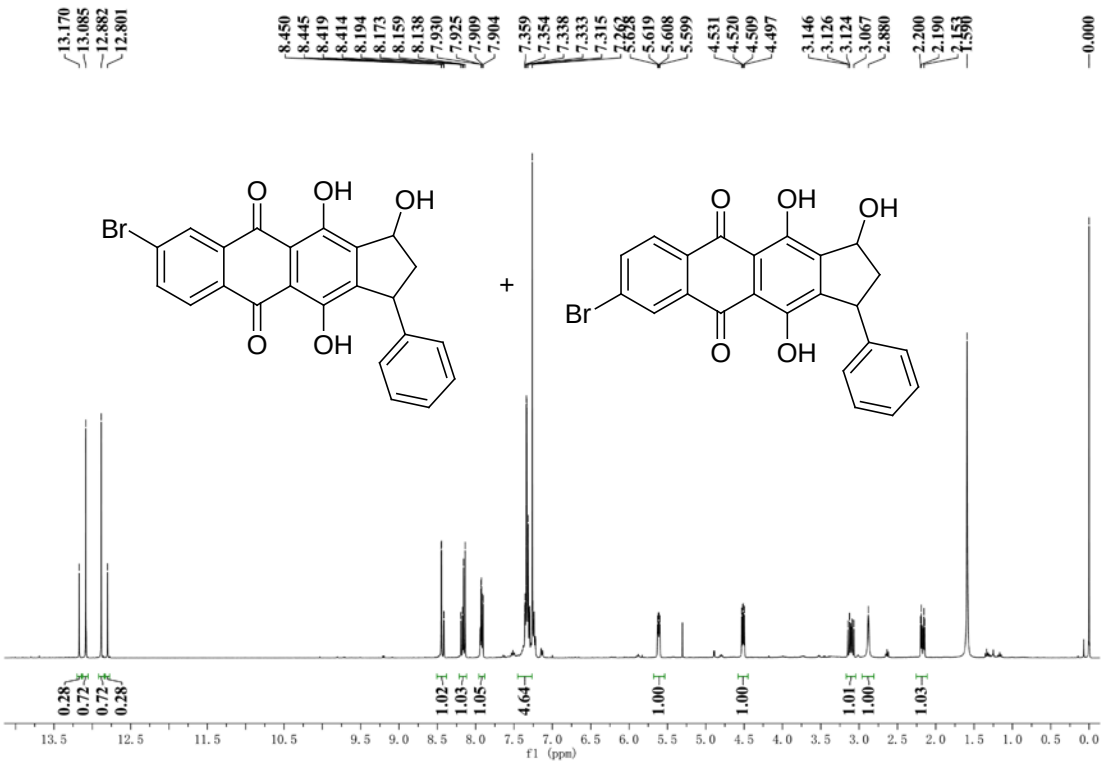
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **3p**



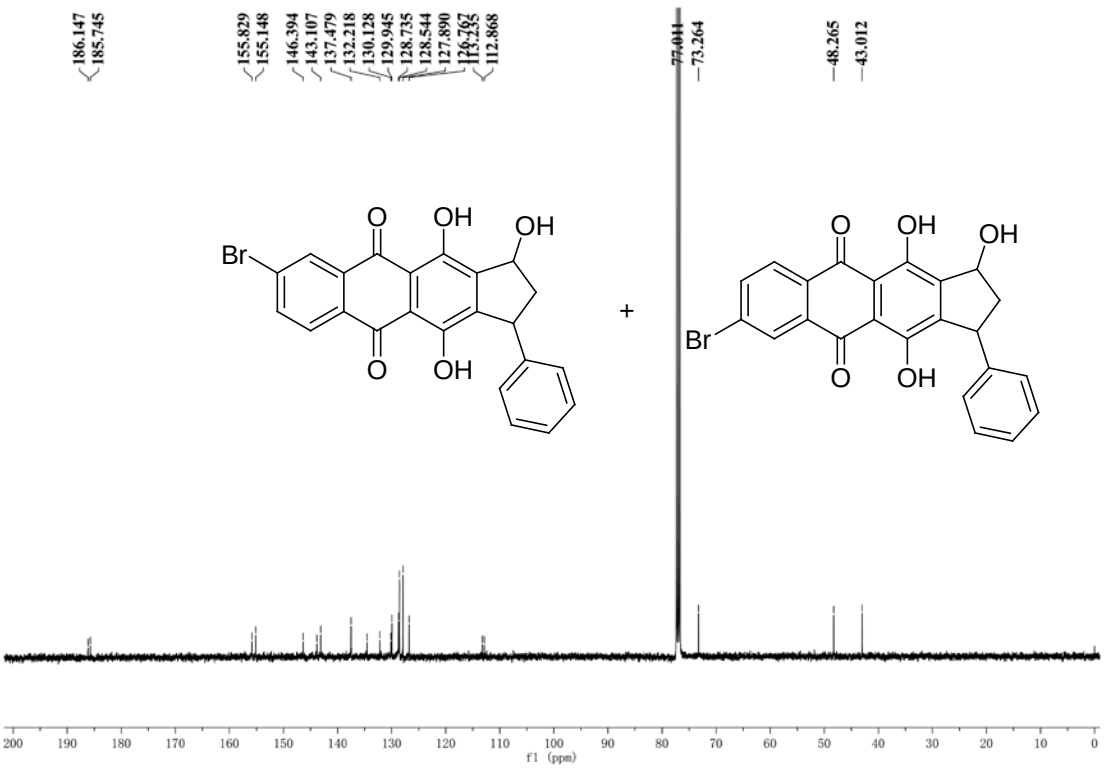
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4a**



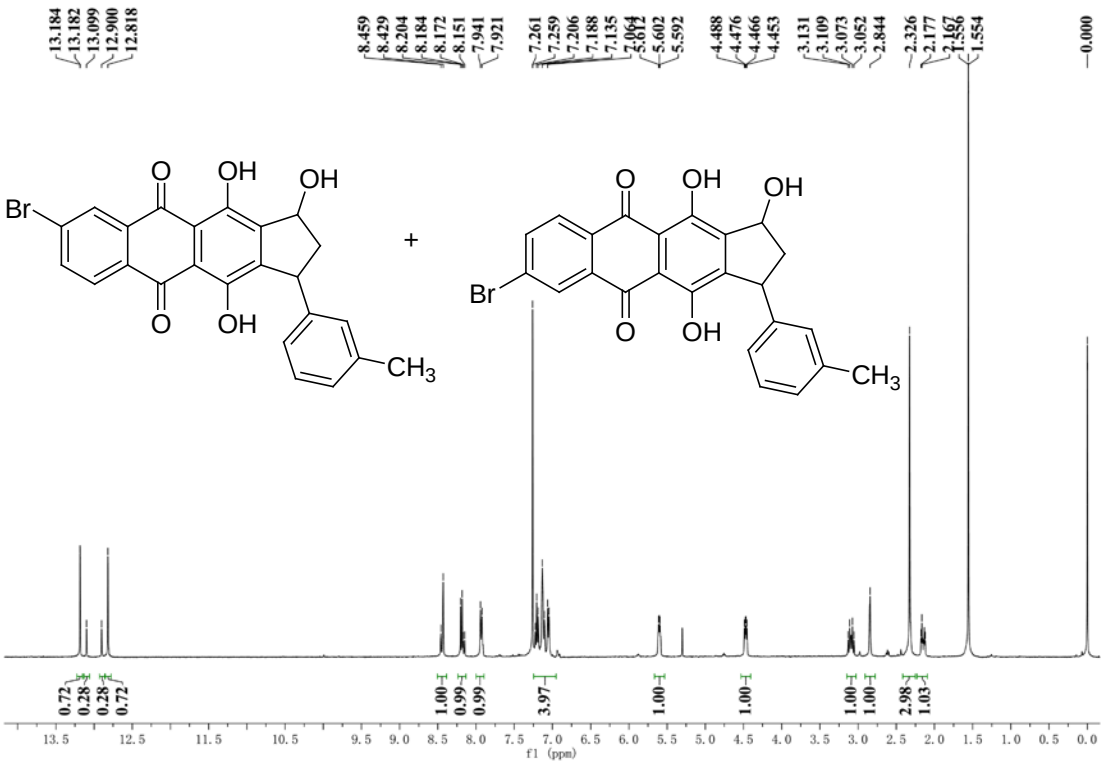
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4a**



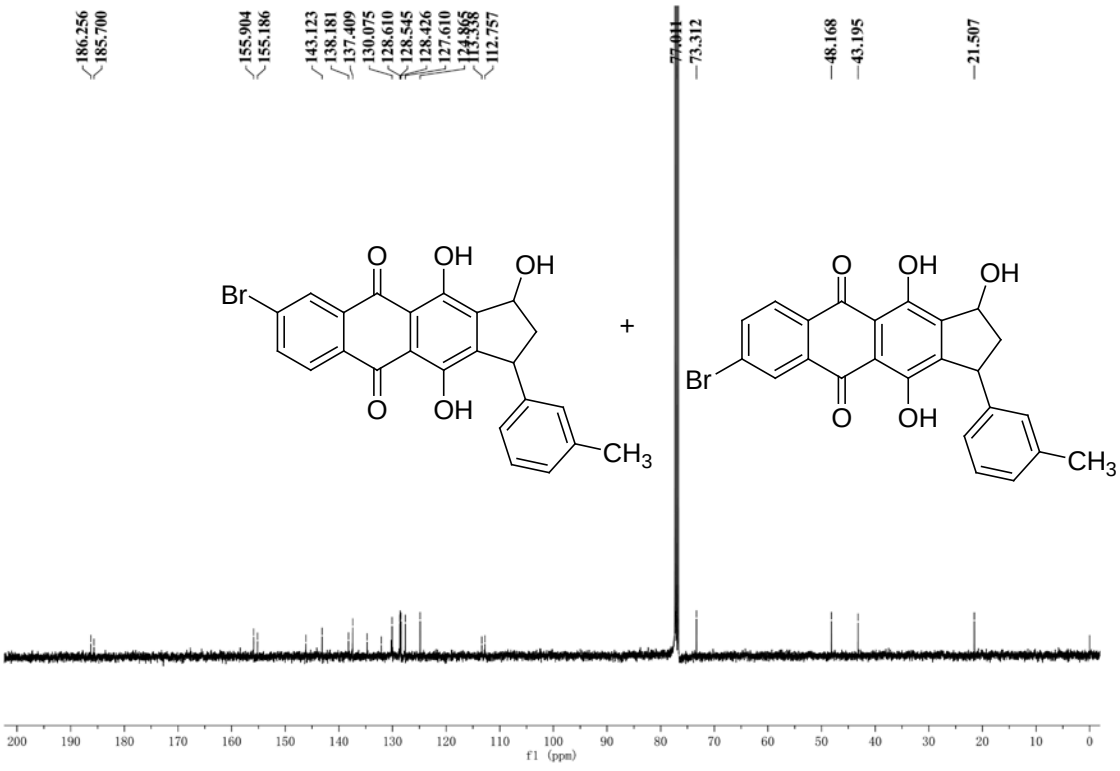
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compounds **4b/4b'**



^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compounds **4b/4b'**



^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compounds **4c**/**4c'**



^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compounds **4c**/**4c'**