Supporting information

Synthesis of 1,4-naphthoquinone derivatives as antibacterial agents: activity and mechanistic studies

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1. Chemistry

1.1. ***General information***.

All NMR spectra were recorded on a Bruker Avance NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C or Varian Mercury NMR Spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C. All NMR measurements were carried out at room temperature and the chemical shifts are reported as parts per million (ppm) in unit relative to the resonance of $CDCl_3$ (7.26 ppm in the ^{1}H, 77.16 ppm for the central line of septet in the ^{13}C modes, respectively) or DMSO-d_6 (2.50 ppm in the ^{1}H, 39.52 ppm for the central line of septet in the ^{13}C modes, respectively). High-resolution mass spectra (HRMS) were recorded by electrospray ionization (ESI) with an Agilent 6500 Q/TOF-MS instrument. Melting points were determined on a SGW X-4 micro melting point apparatus. All reagents and solvents were reagent grade and were used without further purification unless otherwise stated. The plates used for thin-layer chromatography (TLC) were E. Merck Silica Gel GF254 (0.25-mm thickness) and they were visualized under short (254-nm) and long (365-nm) UV light. Chromatographic purifications were carried out using MN silica gel 60 (200-300 mesh). The purity of tested compounds was determined by HPLC, which was performed by using Agilent 1100 series installed with an analytic column of Agilent Prep-Sil Scalar column (4.6 mm x 250 mm, 5-μm) at UV detection of 254 nm (reference at 450 nm) with acetonitrile (25%) and water (75%) as the eluent at a flow rate of 1.0 mL/min.

1.2 Synthesis of ***5-Hydroxy-1,4-naphthoquinone*** (juglone,1a)

The H_2O_2 (225 mL, 30%) was placed in a 1000 mL dry three-neck flask which was cold by a water bath to keep the internal temperature no more than 40 °C, then acetic anhydride (125 mL, 97.5%) were added to the three-necked flask. The mixture was stirred at 40 ℃ for 4 hours. Then 45 g 1,5-naphthol (in methanol solution, 300 mL) was added to three-neck flask dropwise under stirring, and the dropping acceleration was controlled to keep the temperature of the reaction solution at 50 ~ 60 ℃. After dropping, the mixture solution was stirring for 1 hour. Then, the mixture solution was added to cold water (1000 mL) to precipitate a large amount of brown

precipitate. The precipitate was filtered, washed with cold water, and subjected to flash column chromatography to obtain the target compound as red needle crystal. Yield: 68%. Melting point: 153~157 °C. Ref. 154~156 °C(Bao et al., 2018). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 (s, 1H, OH), 7.67 – 7.55 (m, 2H), 7.26 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.94 (s, 2H). The results of ^{1}H-NMR are consistent with previous reports (Pancrazzi et al., 2021).

1.3 Synthesis of ***5-Methoxy-1,4-naphthoquinone*** (1b)

The title compound was prepared by the reduction-methylation of juglone and subsequent oxidation (Cui et al., 2015). Yield: 74%. Melting point: 184-186 °C. Ref. 183~185 °C (Rudolf et al., 2015). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.77 – 7.64 (m, 2H), 7.31 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.94 – 6.79 (m, 2H), 4.01 (s, 3H, OCH_3). The results of ^{1}H-NMR are consistent with previous reports (Mitchell et al., 2013).

1.4 Synthesis of ***5-Acetoxy-1,4-naphthoquinone*** (1c)

The title compound was prepared by the reported procedures with juglone as the starting material (Cui and Jia, 2021). Yield: 91%. Melting point: 151~153 °C. Ref. 151~152.5°C (Zhang et al., 2017). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (m, 1H), 7.77 (m, 1H), 7.40 (m, 1H), 6.94 (d, *J* = 10.3 Hz, 1H), 6.85 (d, *J* = 10.3 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.28 (C=O), 183.75 (C=O), 169.47 (C=O), 149.62, 140.01, 137.46, 134.94, 133.68, 129.86, 125.09, 123.40, 21.17.

1.5 Synthesis of ***5-Propionyloxy-1,4-naphthoquinone*** (1d)

The title compound was prepared by the reported procedures with juglone as the starting material (Cui and Jia, 2021). Propionyl juglone. Yield: 79%. Melting point: 114-115 °C. Ref. 113~114 °C (Maruo et al., 2011).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.76

(t, *J* = 7.9 Hz, 2H), 7.38 (dd, *J* = 7.9, 1.2 Hz, 2H), 6.93 (d, *J* = 10.3 Hz, 2H), 6.84 (d, *J* = 10.3 Hz, 2H), 2.77 (q, *J* = 7.5 Hz, 4H), 1.32 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 184.35 (C=O), 183.78 (C=O), 172.89 (C=O), 149.78, 140.04, 137.42, 134.91, 133.67, 129.93, 125.02, 123.47, 27.79, 8.85. HRMS (ESI^+): m/z Calcd. for $C_{13}H_{11}O_4$: 231.0657 $[M+H]^+$; Found: 231.0665.

1.6 Synthesis of ***2-Methyl-5- Hydroxy-1,4-naphthoquinone*** (1e)

The title compound was synthesized by the reported procedure with 1,5-naphthalenediol as the starting material (Möhrle and Folttmann, 1988). Yield: 31%. Melting point: 77~80 °C, Ref. 76~78 °C (Mathiyazhagan et al., 2018). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.98 (s, 1H, OH), 7.67 – 7.56 (m, 2H), 7.30 – 7.22 (m, 1H), 6.81 (q, *J* =1.6 Hz, 1H), 2.20 (d, *J* = 1.6 Hz, 3H, CH_3). The results of ^{1}H-NMR are consistent with previous reports (Chen et al., 2022) .

1.7 Synthesis of ***5,8-Dimethoxy -1,4-naphthoquinone*** (1f)

The title compound was obtained by the oxidation of 1,4,5,8-tetramethoxy naphthalene according to the reported procedures (Cui and Jia, 2021). Yield: 89%. Melting point: 159~160 °C. Ref. 157~159 °C (Brötz et al., 2014). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 2H), 6.77 (s, 2H), 3.95 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 184.99 (C=O), 153.82, 138.46, 121.10, 120.44, 57.00.

1.8 Synthesis of ***5-Benzyloxy -1,4-naphthoquinone*** (1g)

The title compounds were prepared by the reported procedures (Cui et al., 2020). Yield: 21%. Melting point: 113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.60 – 7.56 (m, 2H), 7.45 – 7.39 (m, 2H), 7.37 – 7.32 (m, 2H), 6.89 (s, 1H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.36, 184.28, 158.68, 141.05, 136.40, 136.19, 134.97, 134.31, 131.99, 128.86, 128.14, 126.85, 119.87, 119.66, 71.10.

1.9 Synthesis of ***1,4-naphthoquinone*** (2a)

The title compound was synthesized by the reported procedures with 1-naphthylamine as the starting material (Cui and Jia, 2021). Yield: 38%. Melting point: 121~123 °C, Ref.124~126 °C (Twum et al., 2015). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.04 (m, 2H), 7.81 – 7.71 (m, 2H), 6.98 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.14 (C=O), 138.82, 134.06, 132.08 (quat., C(1a), C(4a)), 126.56.

1.10 Synthesis of ***2-Hydroxy-1,4-naphthoquinone*** (2b)

The title compound was synthesized by the reported procedures with 2-methylnaphthalene as the starting material (Cui and Jia, 2021). Yield: 32%. Melting point: 189~191 °C, Ref. 188~192 °C (Zhou et al., 2018). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 7.99 (m, 2H), 7.71 (dd, *J* = 5.7, 3.3 Hz, 2H), 6.83 (q, *J* = 1.5 Hz, 1H), 2.18 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.64 (C=O), 185.07 (C=O), 148.28, 135.79, 133.75, 133.69, 132.38, 132.29, 126.63, 126.19, 16.58.

1.11 Synthesis of ***6-Methyl-1,4-naphthoquinone*** (2c)

The para-benzoquinone (54 g, 0.5 mol) was placed in a 1000 mL dry three-neck flask, then the glacial acetic acid (400 mL) and isoprene (40.8 g, 0.6 mmol) were added to the three-neck flask. The mixture was stirred at room temperature for 72 h under nitrogen protection. When the reaction finished and its color appeared red brown, the reacted solvent was filtered. After washing the filter cake, the filtrate was combined. At this point, the temperature was raised to 60 °C to remove the unreacted isoprene (isoprene distillation). In addition, na2Cr2O7.4H2O (212.0g, 0.74mmol) was added to a mixture of concentrated sulfuric acid and water (162 mL, V/V= 1:0.08) that preheated at 50 °C. The solvent was slowly added to the reaction system at 65-70 °C. After 2-3 h of reaction (until 4-5 compounds disappeared), the mixture was poured into ice water and stirred vigorously. The solid was filtered and cleaned with water and petroleum ether. The solvent was recrystallized

by ethanol to obtain yellow crystal, about 60.0 g. Yield: 71.0%. Melting point: 89 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 7.9 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 6.94 (s, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 185.51, 185.06, 145.26, 138.90, 138.64, 134.77, 132.01, 129.91, 126.92, 126.78, 22.02.

1.12 Synthesis of ***2-Methyl-1,4-naphthoquinone*** (2d)

The title compound was synthesized by the reported procedures with 2-methylnaphthalene as the starting material. Yield: 32%. Melting point: 109~110 °C, Ref.105~106 ℃ (Abu-Elfotoh, 2022).. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.13 – 7.99 (m, 2H), 7.71 (dd, J = 5.7, 3.3 Hz, 2H), 6.83 (q, J = 1.5 Hz, 1H), 2.18 (d, J = 1.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3): δ 185.64 (C=O), 185.07 (C=O), 148.28, 135.79, 133.75, 133.69, 132.38, 132.29, 126.63, 126.19, 16.58.

1.13 Synthesis of ***5,8-dihydroxy-2 - [(1R) - 1-hydroxy-4-methylpent-3-enyl] naphthalene-1,4 naphthoquinone*** (2e, shikonin)

The title compounds were prepared by the reported procedures (Wang et al., 2012). Yield: 41.9%. Melting point: 149~151 °C, Ref.148~149 ℃ (Rao et al., 2010). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 12.59 (s, 1 H, OH), 12.58 (s, 1 H, OH), 7.19 (s, 2 H, ArH), 7.16 (s,1 H), 5.20 (t, 1H, J = 8.1 Hz), 4.91 (d, 1 H, J = 7.2 Hz), 2.31-2.38 (m, 1 H), 2.62-2.66 (m, 1H), 1.75 (s, 3 H), 1.65 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 180.6, 180.1, 165.7, 165.1, 151.5, 137.7, 132.5, 132.3, 132.0, 118.6, 112.3, 111.7, 68.6, 35.1, 25.2, 18.3.

1.14 Synthesis of ***7-Methyl-5-Hydroxy-1,4-naphthoquinone*** (3a)

7-Methyl-5-Hydroxy-1,4-naphthoquinone (3a) was synthesized by the reported procedure with 2,5-dimethoxy benzaldehyde as a starting material (Cui et al., 2020). Yield:36.6%. Melting point: 120~122 °C, Ref.121~122 ℃ (Raps et al., 2020). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.84 (s, 1H), 7.43

(d, *J* = 1.5 Hz, 1H), 7.07 (s, 1H), 6.90 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.81, 184.66, 161.77, 148.58, 139.40, 138.86, 131.59, 124.23, 120.58, 113.06, 22.33.

1.15 Synthesis of ***7-Methyl-5-Methoxy-1,4-naphthoquinone*** (3b)

The title compounds were prepared by the reported procedures with 2,5-dimethoxy benzaldehyde as the starting material (Cui et al., 2020). Yield:47.6%. Melting point: 159~162 °C, Ref. 164~166 °C (Pullella et al., 2020). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.48 (m, 1H), 7.07 (s, 1H), 6.79 (s, 2H), 3.95 (s, 3H), 2.44 (s, 3H).The results of ^{1}H-NMR are consistent with previous reports(Xu et al., 2014).

1.16 Synthesis of ***7-Methyl-5-Acetoxy-1,4-naphthoquinone*** (3c)

The title compounds were prepared by the reported procedures with 2,5-dimethoxy benzaldehyde as the starting material (Cui et al., 2020). Yield:51.8%. Melting point: 149~151 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 1.7 Hz, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 6.89 (d, *J* = 10.4 Hz, 1H), 6.80 (d, *J* = 10.3 Hz, 1H), 2.48 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 185.51, 184.06, 157.46, 146.39, 141.04, 136.36, 133.91, 122.89, 121.60, 118.72, 95.30, 56.78, 22.32.

1.17 Synthesis of ***5-(Benzyloxy)- 7-Methyl-1,4-naphthoquinone*** (3d)

The title compounds were prepared by the reported procedures (Cui et al., 2020). Yield:48.2%. Melting point: 90~93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.57 (m, 2H), 7.55 – 7.52 (d, *J* = 1.6 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.35 – 7.29 (m, 1H), 7.13 (d, *J* = 1.6 Hz, 1H), 6.83 (s, 2H), 5.25 (s, 2H, CH_2), 2.43 (s, 3H, CH_3). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 185.62, 183.96, 158.77, 146.40, 141.05, 136.23, 136.14, 133.92, 128.75, 127.99, 126.72, 120.41, 120.06, 118.11, 70.87, 22.37.

1.18 Synthesis of ***5-(Methoxymethoxy)-7-methylnaphthalene-1,4-naphthoquinone*** (3e)

The title compounds were prepared by the reported procedures with 5,8-dimethoxy-3-methylnaphthalen-1-ol as the starting material (Cui et al., 2020). Melting point: 120 ~ 123 ℃^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.58 (m, 1H), 7.35 – 7.30 (m, 1H), 6.89 – 6.78 (m, 2H), 5.34 (s, 2H, CH_2), 3.54 (s, 3H, OCH_3), 2.46 (s, 3H, CH_3). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 185.51, 184.06, 157.46, 146.39, 141.04, 136.36, 133.91, 122.89, 121.60, 118.72, 95.30, 56.78, 22.32.

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Figure S1-S17. ^{1}H & ^{13}C-NMR Spectra of prepared compounds

Figure S1. ^{1}H-NMR Spectrum of ***Juglone*** (**1a**)
^{1}H-NMR ($CDCl_3$)

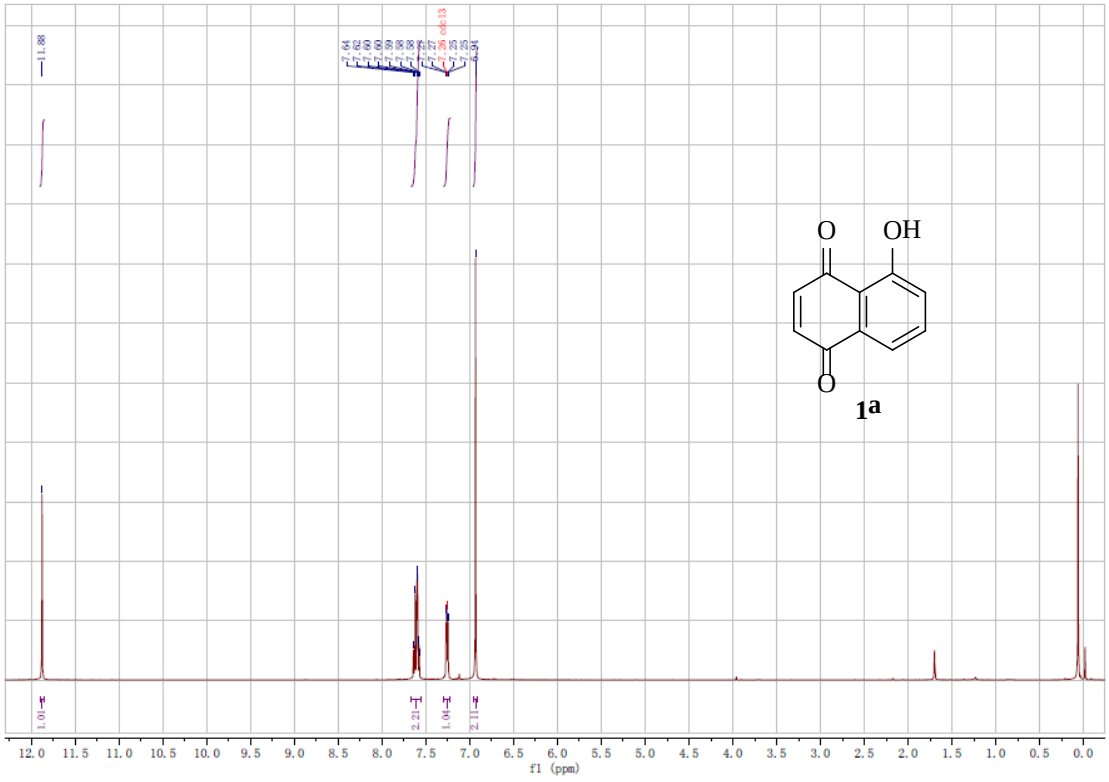


Figure S2. ^{1}H-NMR Spectrum of ***5-Methoxy-1,4-naphthoquinone*** (**1b**)

^{1}H-NMR ($CDCl_3$)

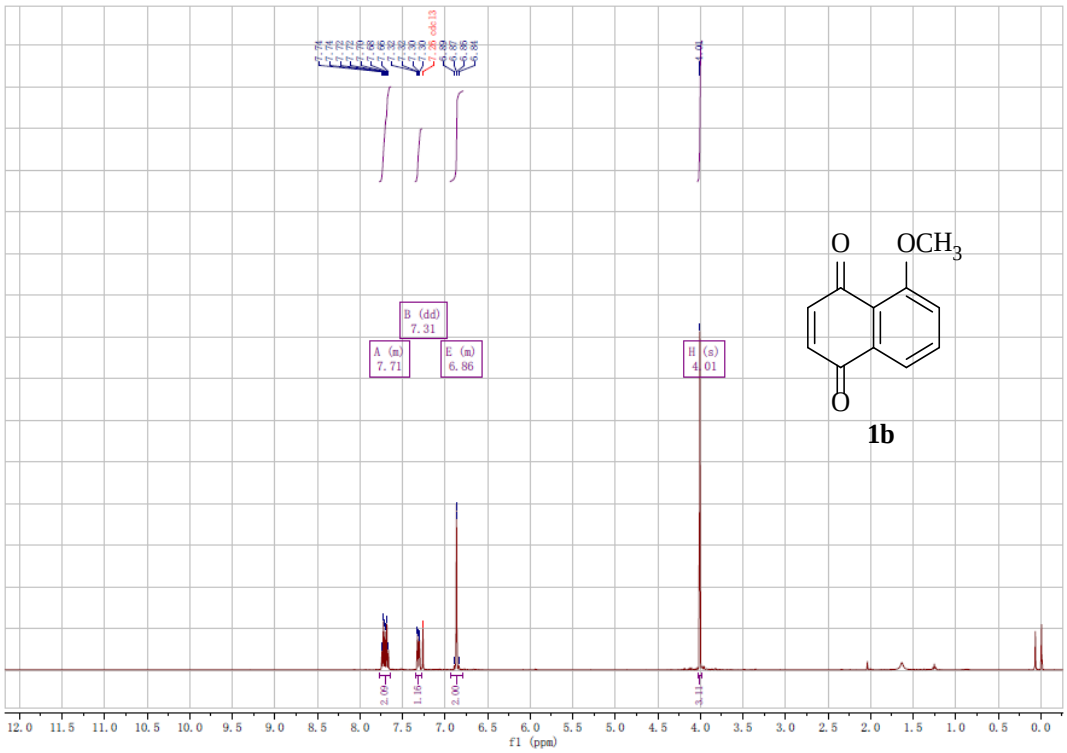
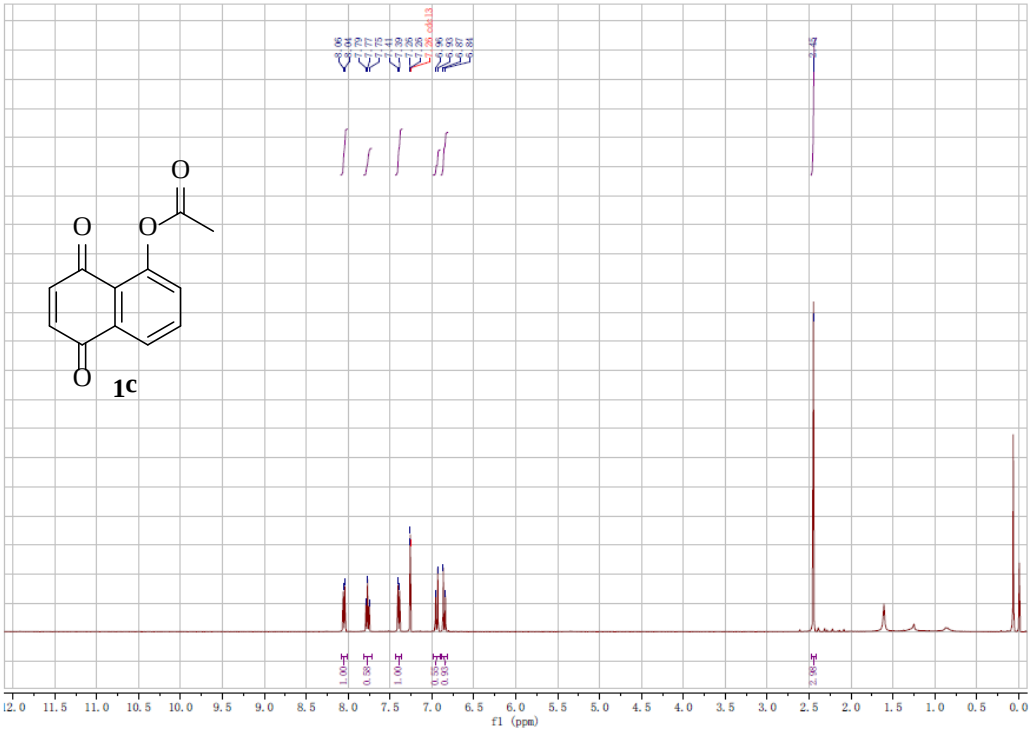

B (dd)
7.31
A (m)
7.71
E (m)
6.86
H (s)
4.01
O
OCH3
O
1b
f1 (ppm)

Figure S3. ^{1}H & ^{13}C-NMR Spectra of ***5-Acetoxy-1,4-naphthoquinone*** (**1c**)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

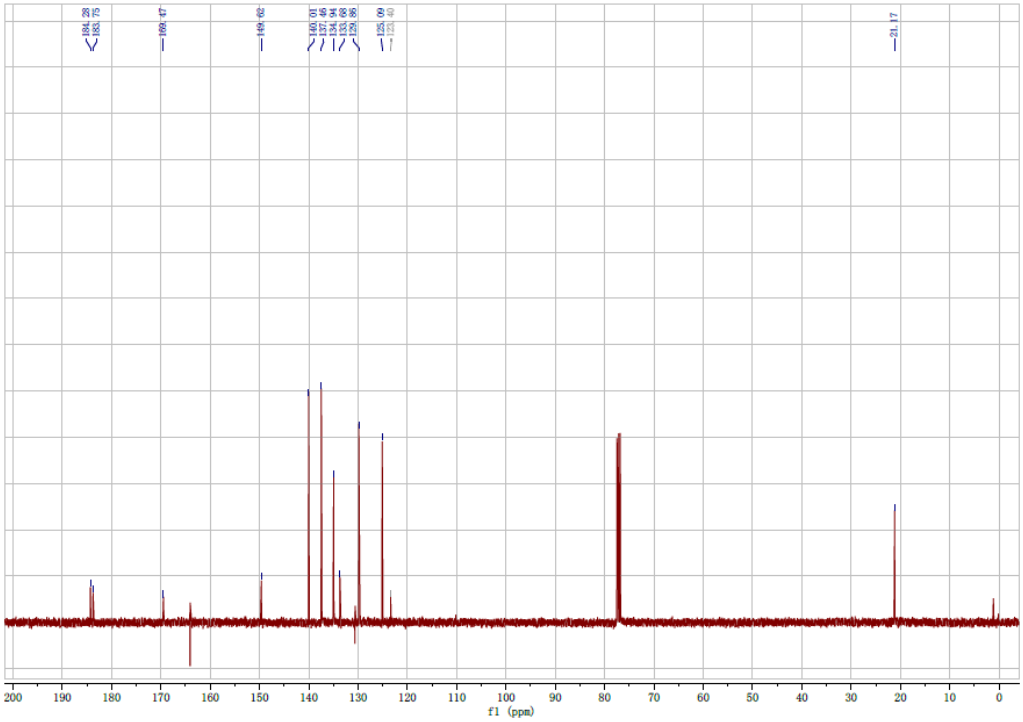
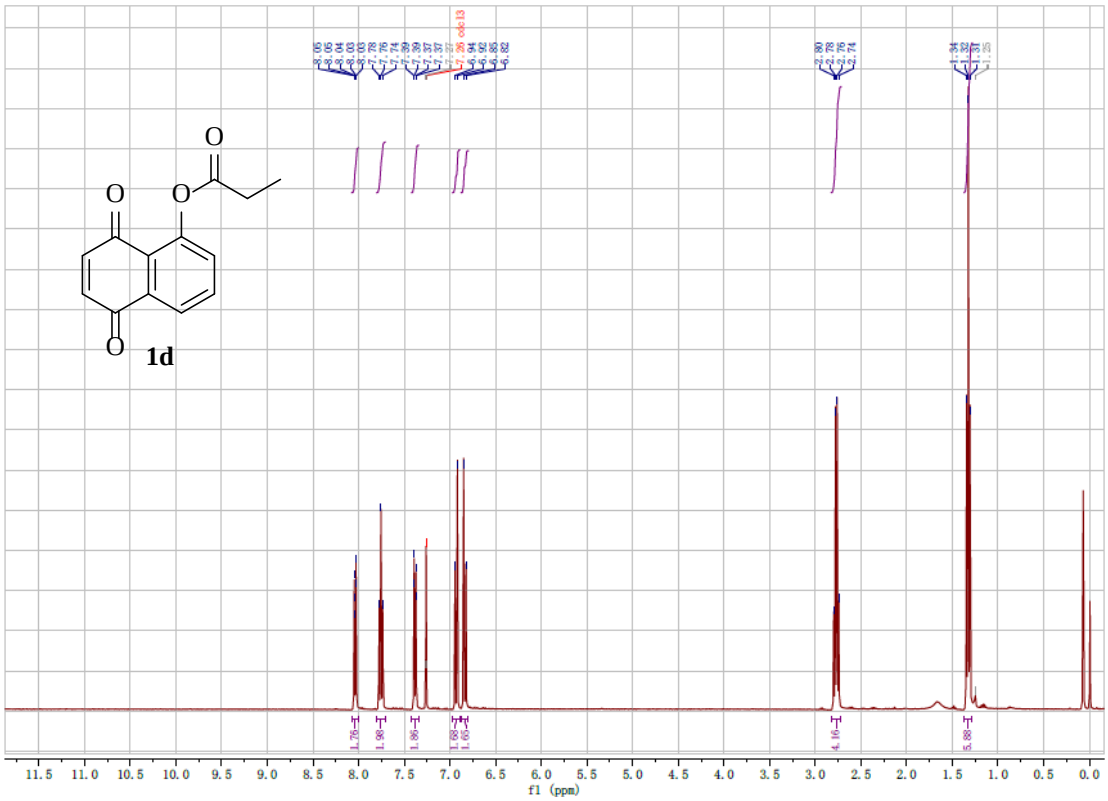


Figure S4. ^{1}H & ^{13}C-NMR Spectra of **Propionyl Juglone** (**1d**)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

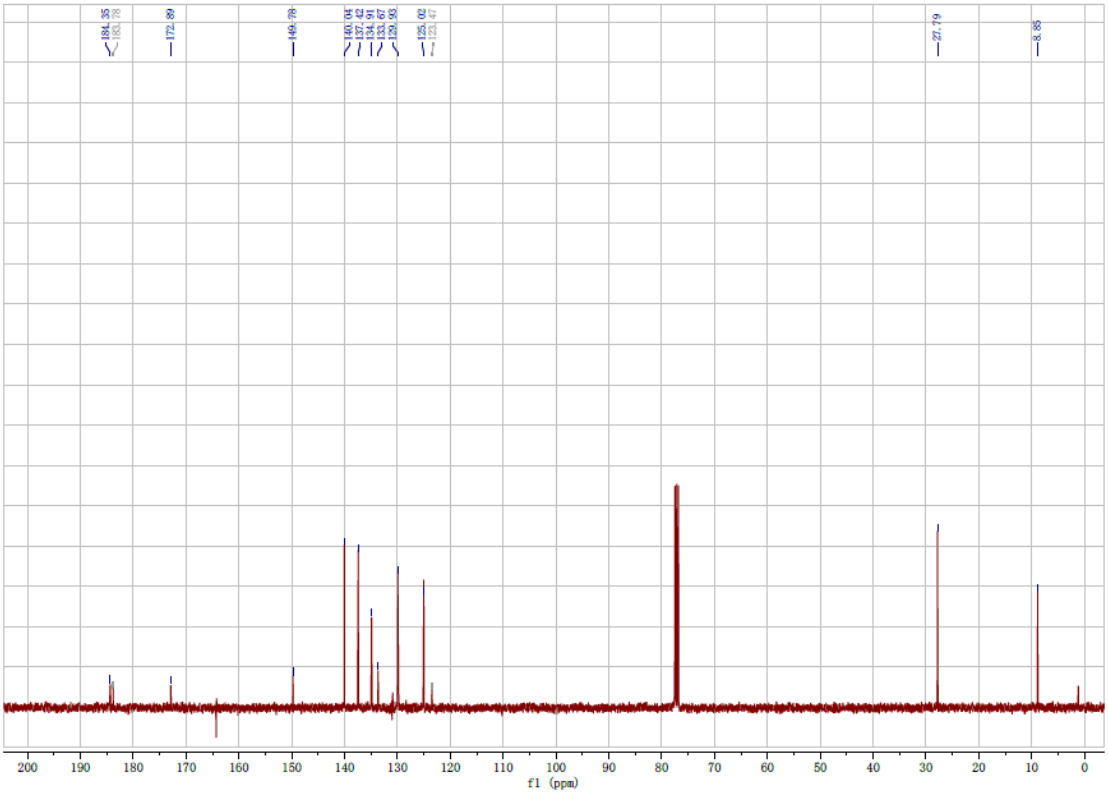


Figure S5. ^{1}H & ^{13}C-NMR Spectra of ***2-Methyl-5- Hydroxy-1,4-naphthoquinone*** (**1e**)

^{1}H-NMR ($CDCl_3$)

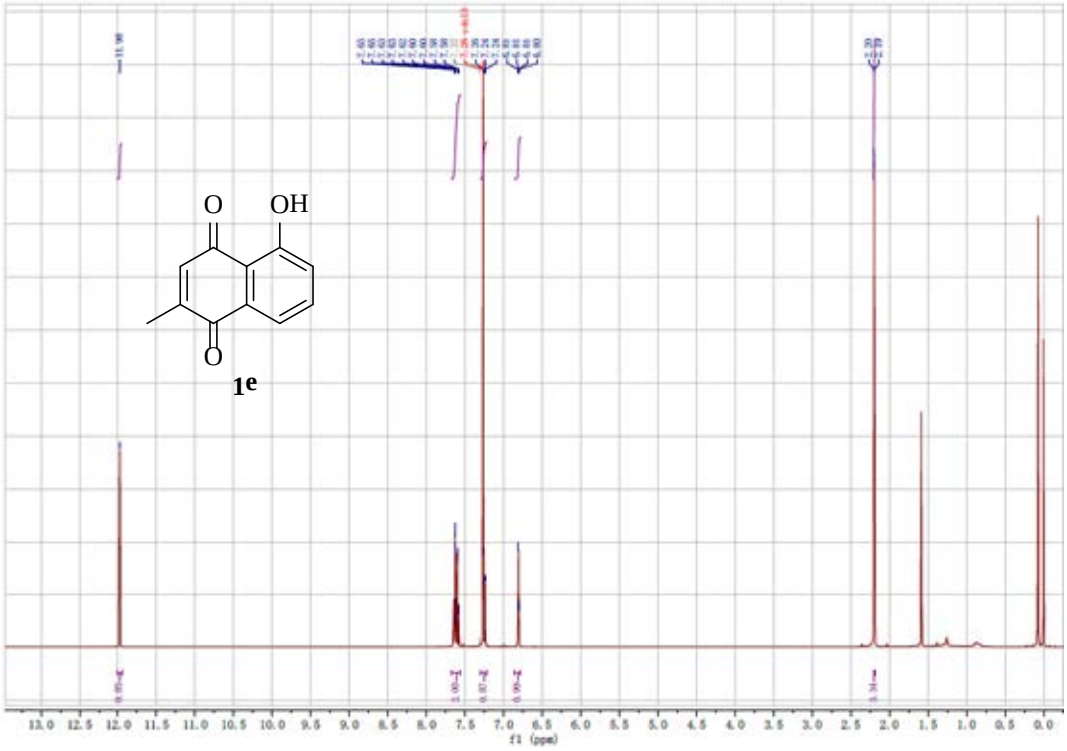
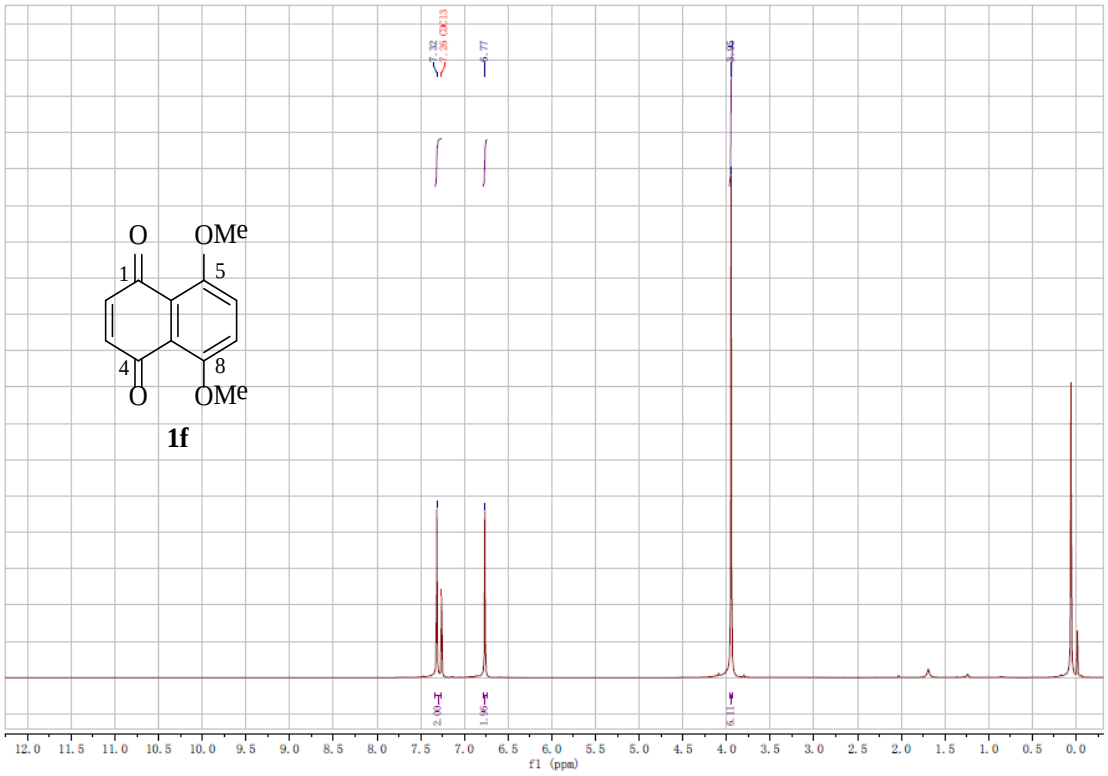


Figure S6. ^{1}H & ^{13}C-NMR Spectra of **5,8-Dimethoxy-1,4-Naphthoquinone** (**1f**)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

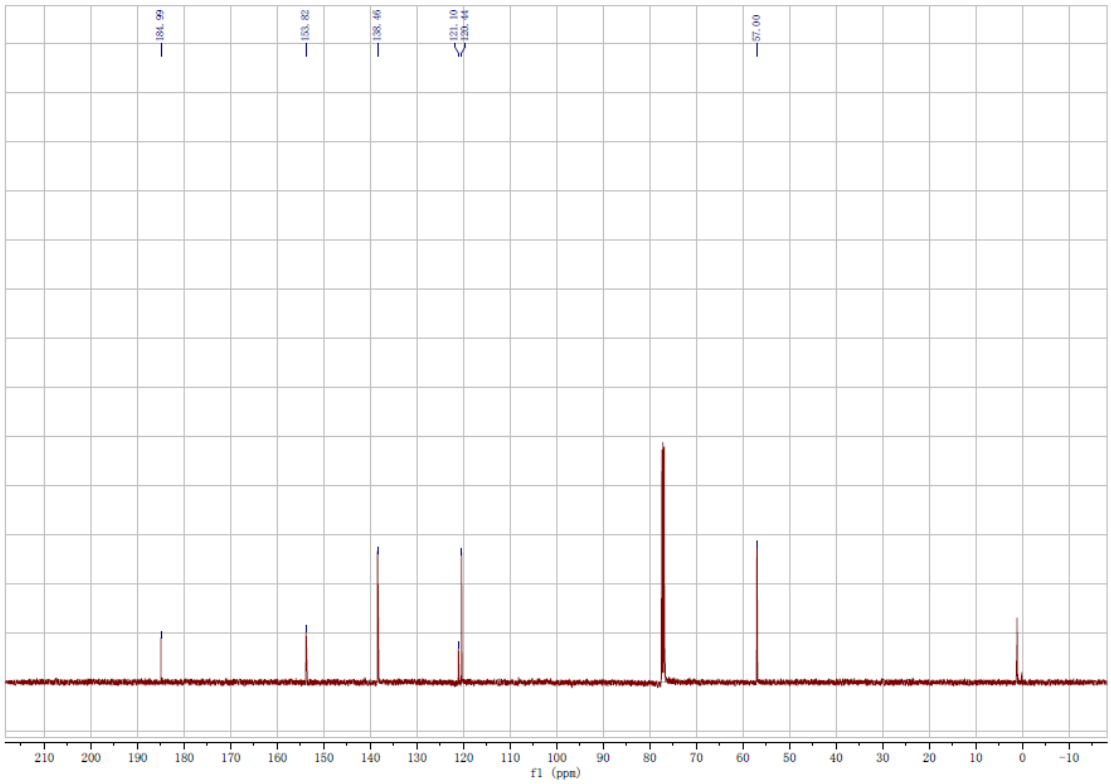
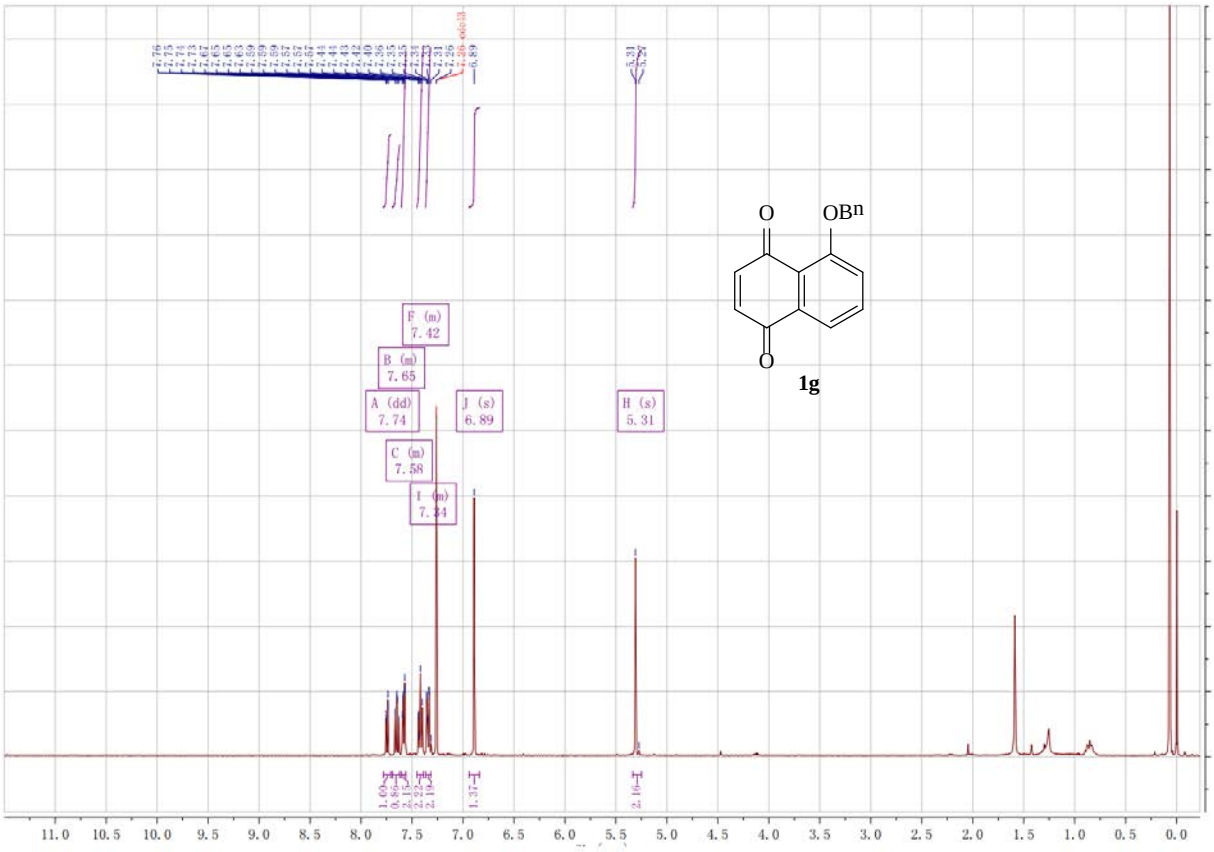


Figure S7. ^{1}H & ^{13}C-NMR Spectra of ***5-Benzyloxy -1,4-naphthoquinone*** (**1g**)



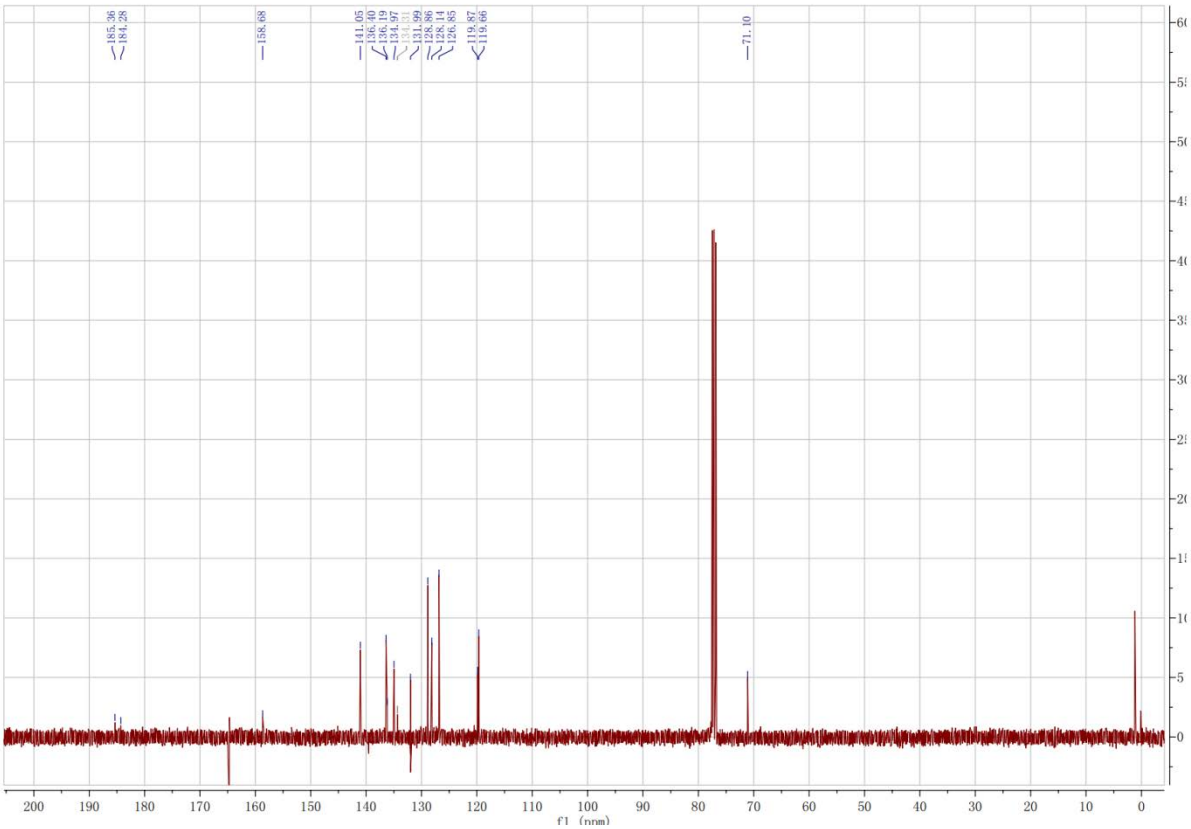
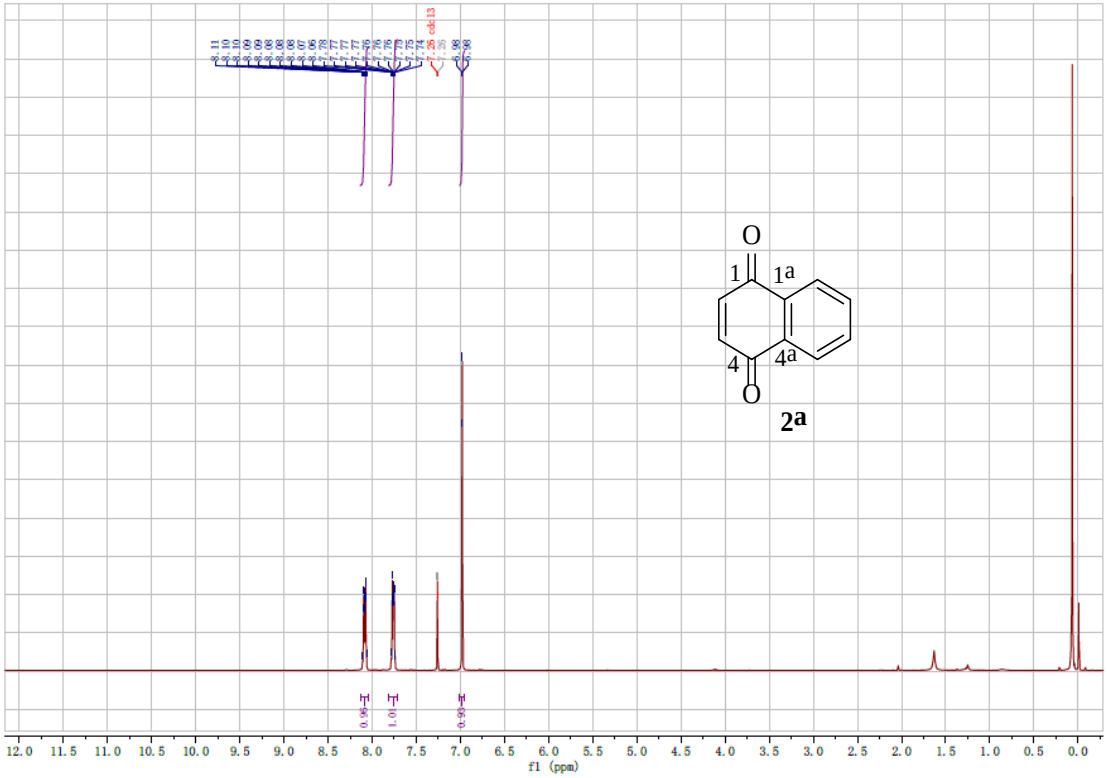


Figure S8. ^{1}H & ^{13}C-NMR Spectra of **1,4-Naphthoquinone** (**2a**)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

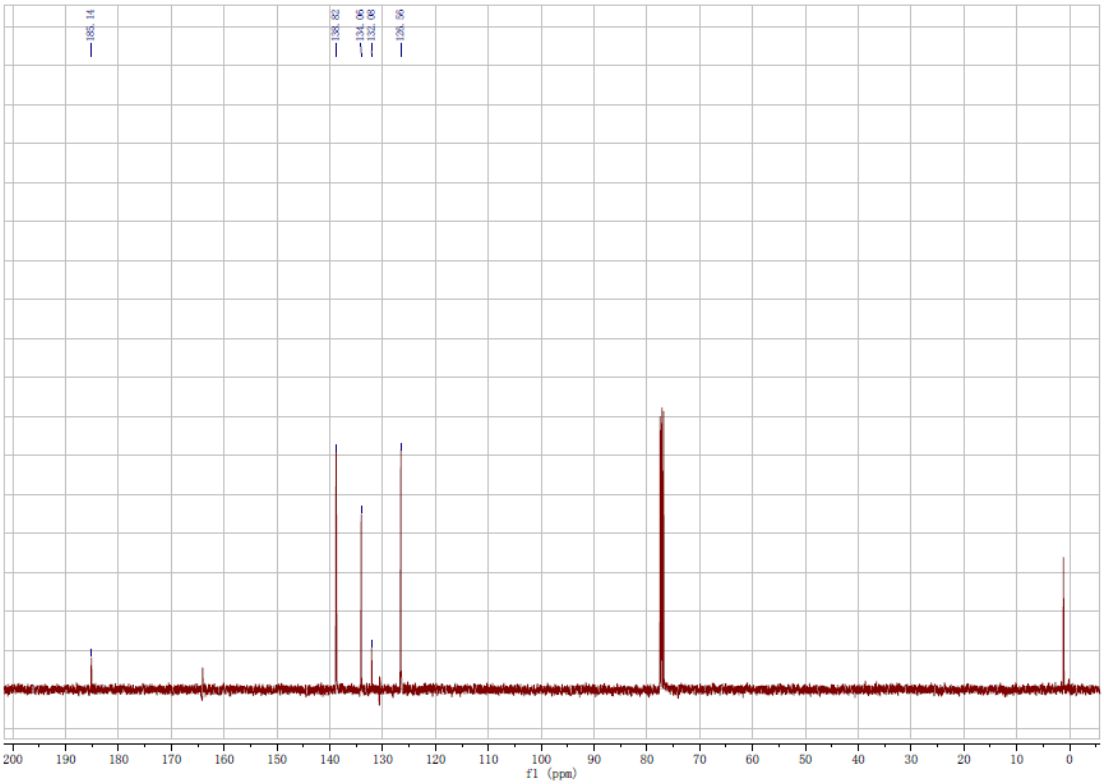
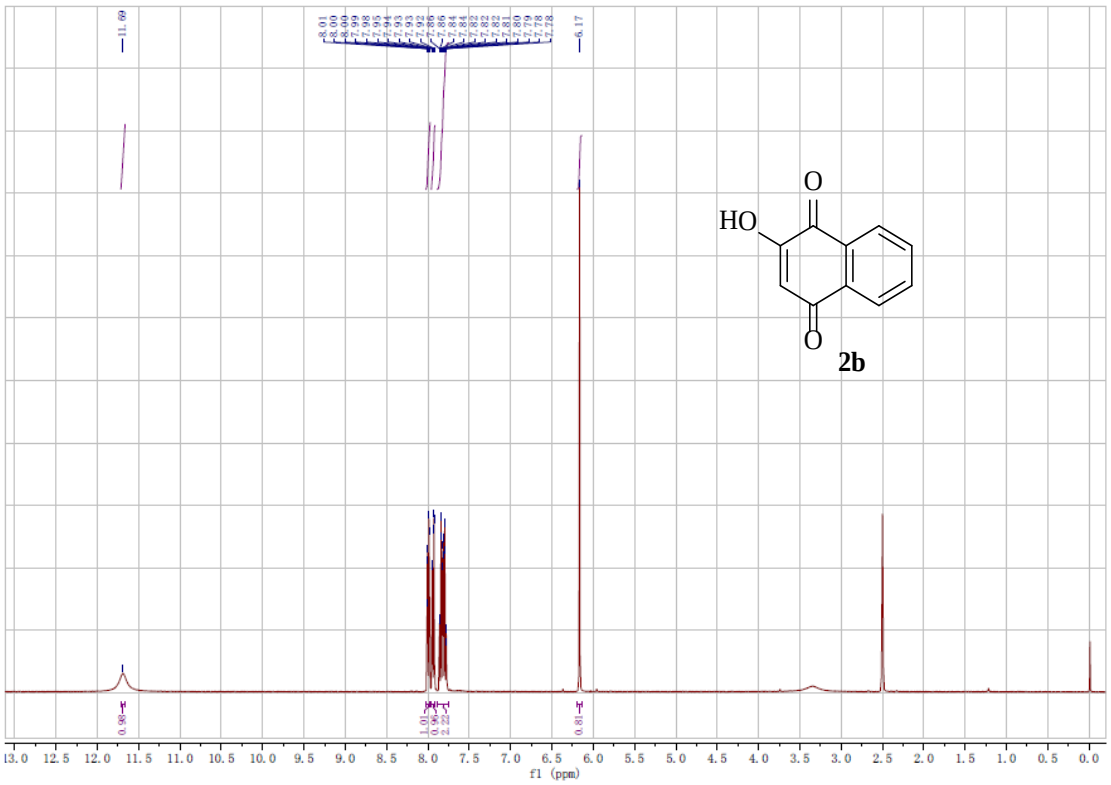


Figure S9. ^{1}H & ^{13}C-NMR Spectra of **2-Hydroxy-1,4-Naphthoquinone** (**2b**)

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



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

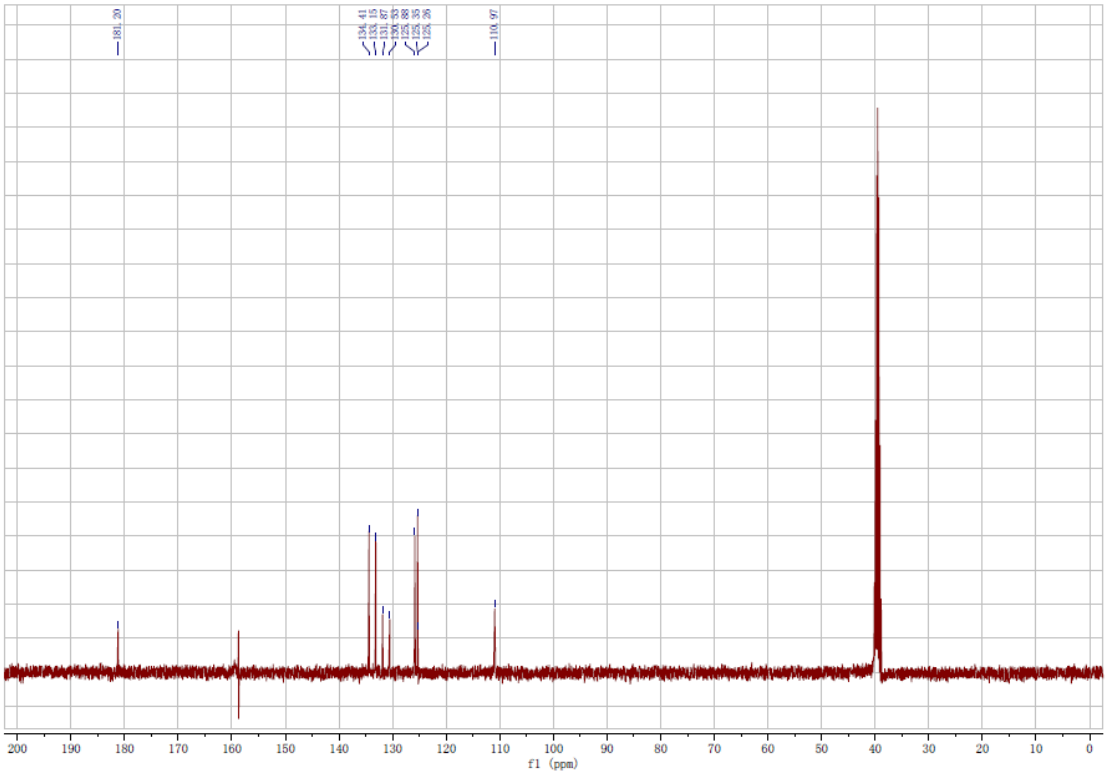
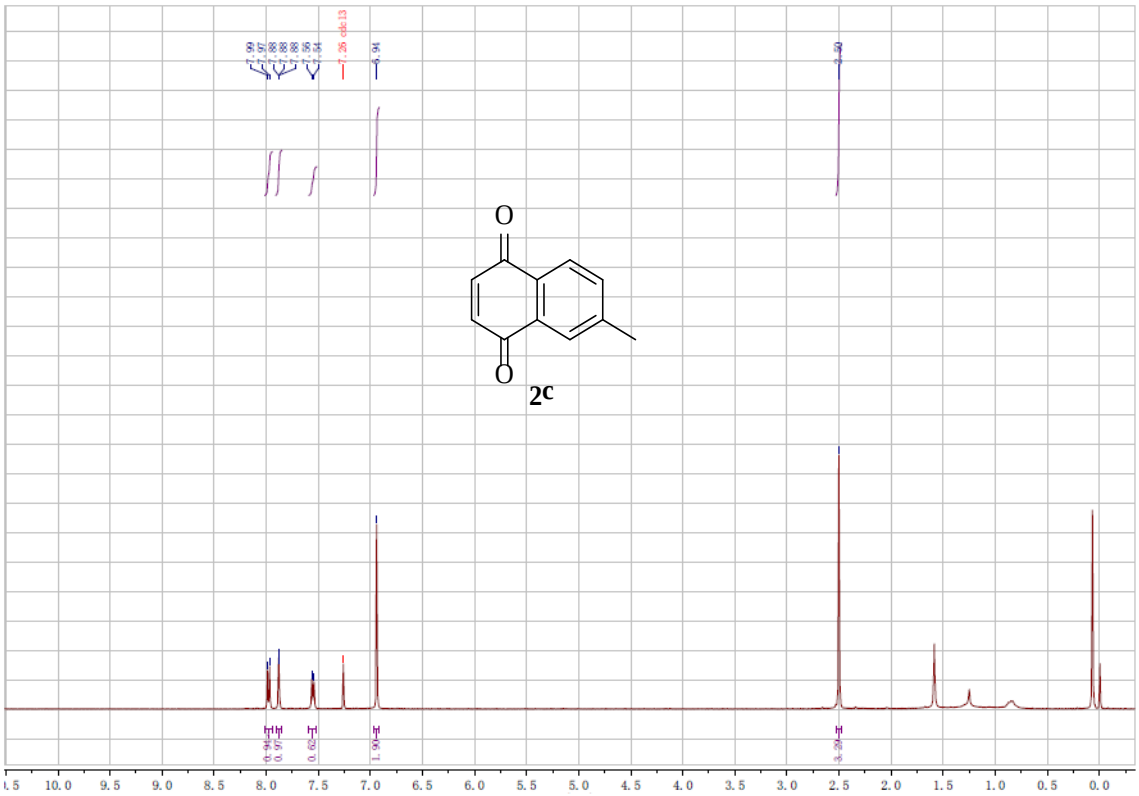


Figure S10. ^{1}H & ^{13}C-NMR Spectra of **6-Methyl-1,4-naphthoquinone** (**2c**)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

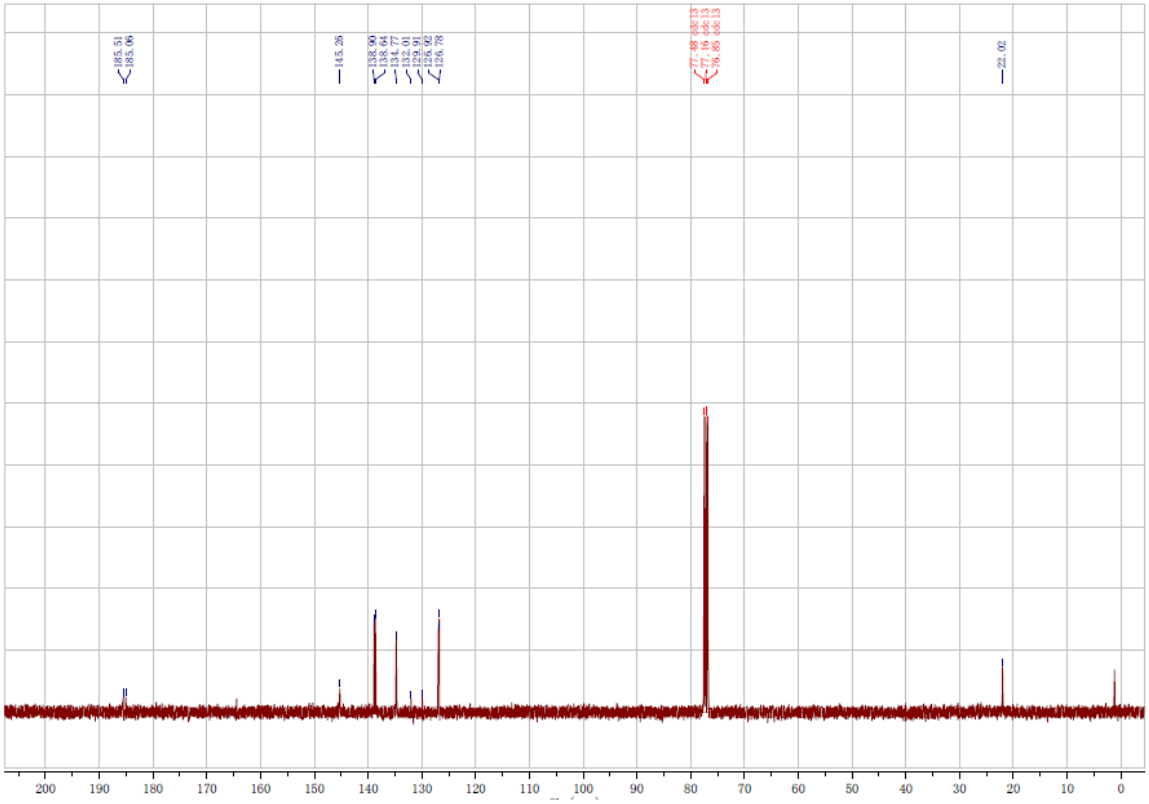
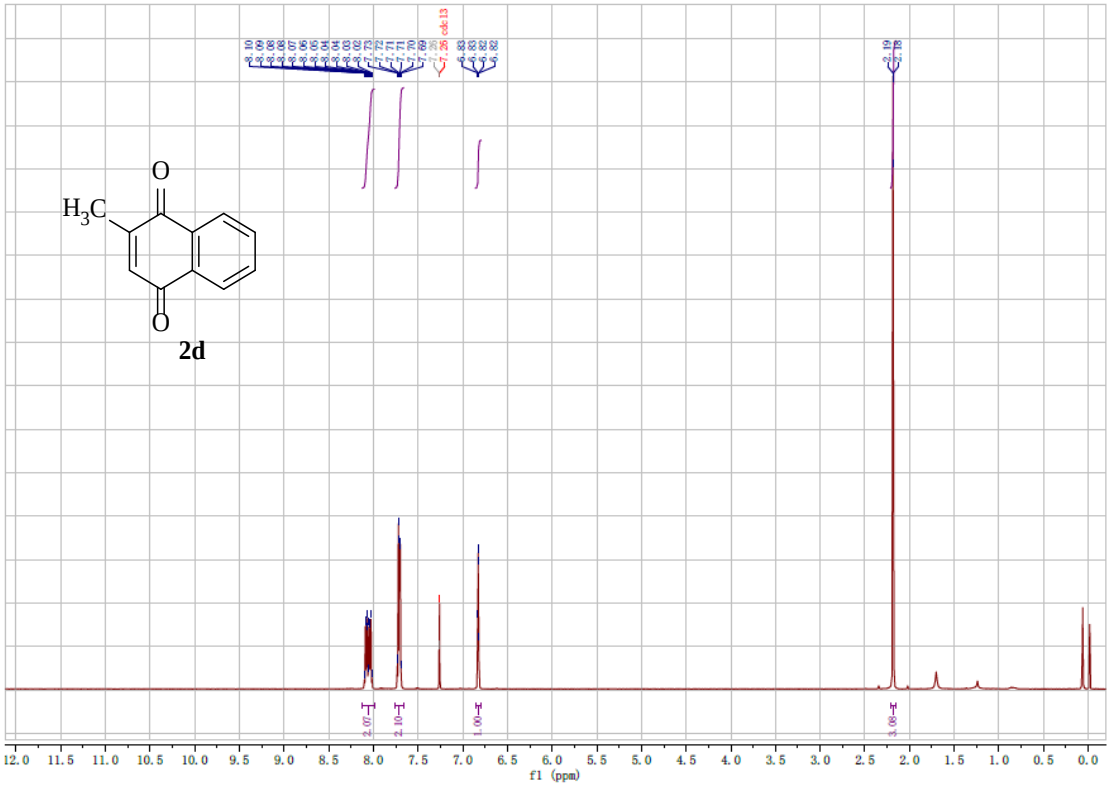


Figure S11. ^{1}H & ^{13}C-NMR Spectra of **2-Methyl-1,4-Naphthoquinone** (**2d**)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

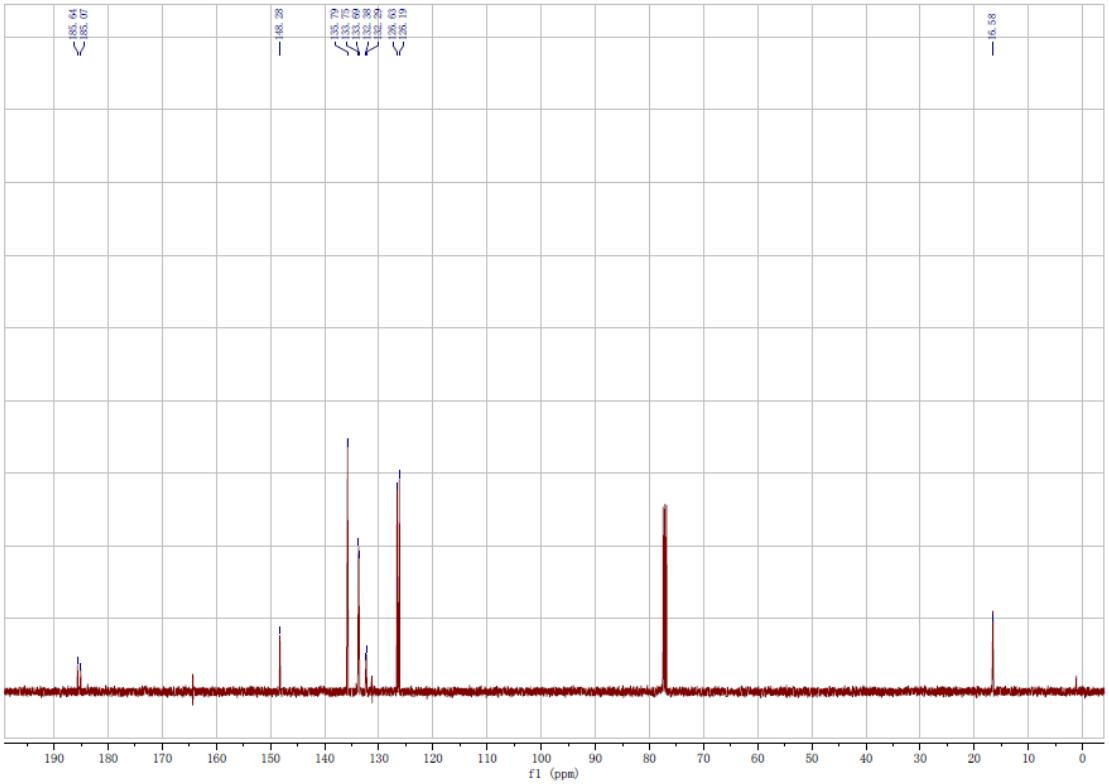
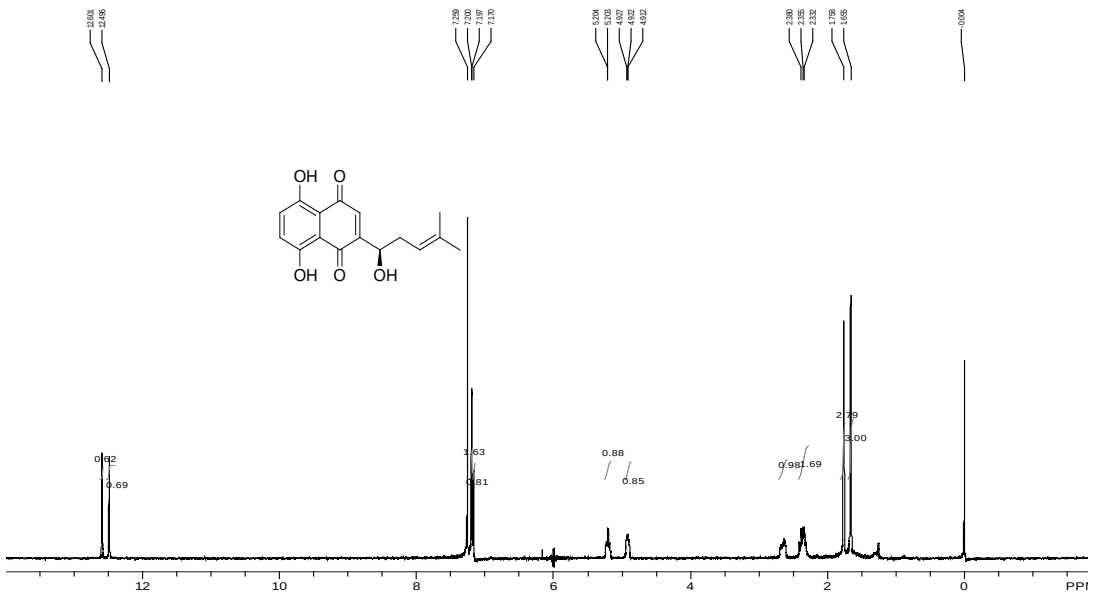


Figure S12. ^{1}H & ^{13}C-NMR Spectra of **Shikonin (2e)**

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

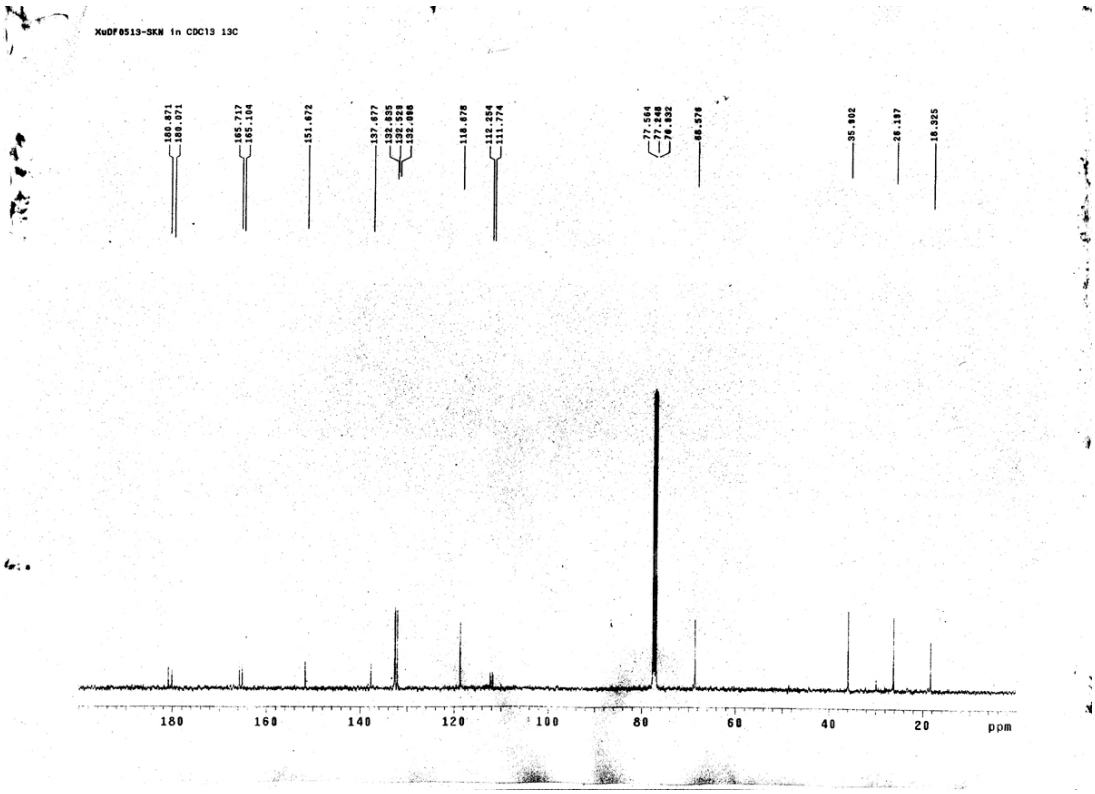
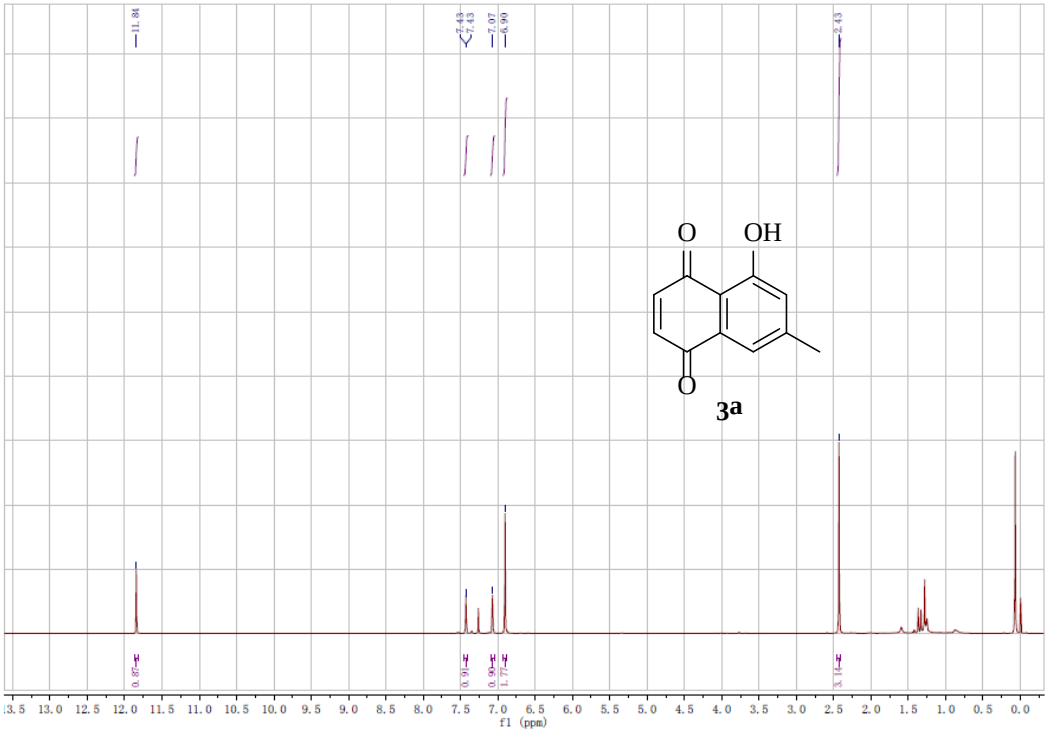


Figure S13. ^{1}H-NMR Spectra of ***7-Methyl Juglone*** (**3a**)^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

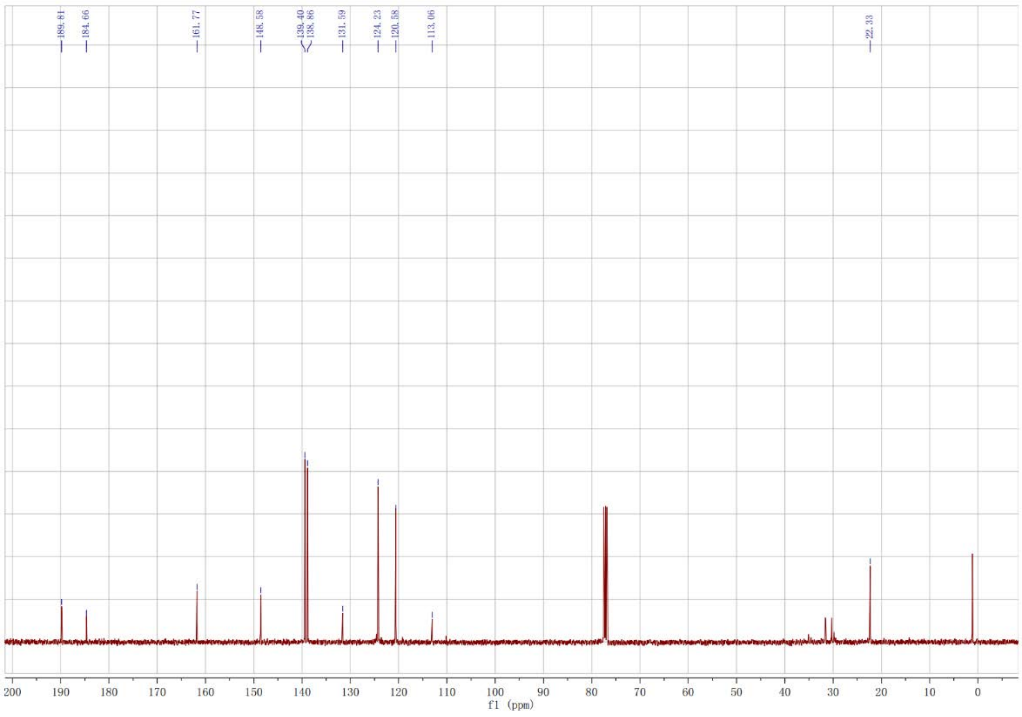


Figure S14. ^{1}H-NMR Spectra of ***7-Methyl-5-Methoxy-1,4-naphthoquinone*** (**3b)**

^{1}H-NMR ($CDCl_3$)

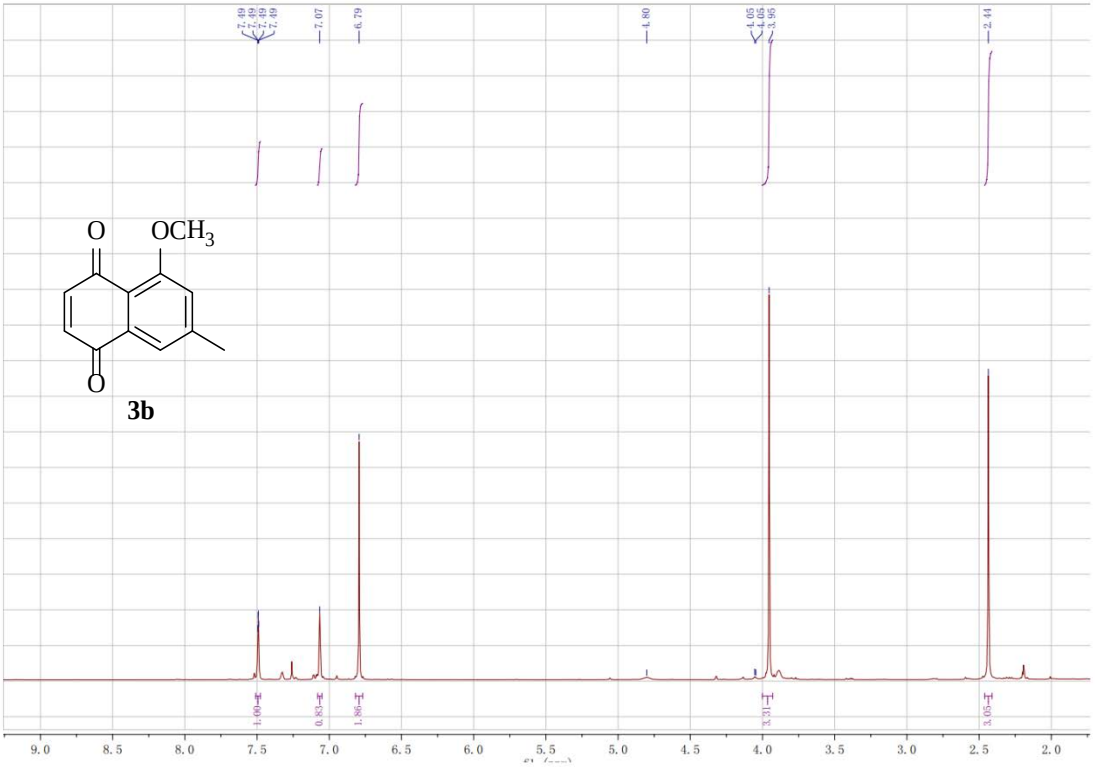
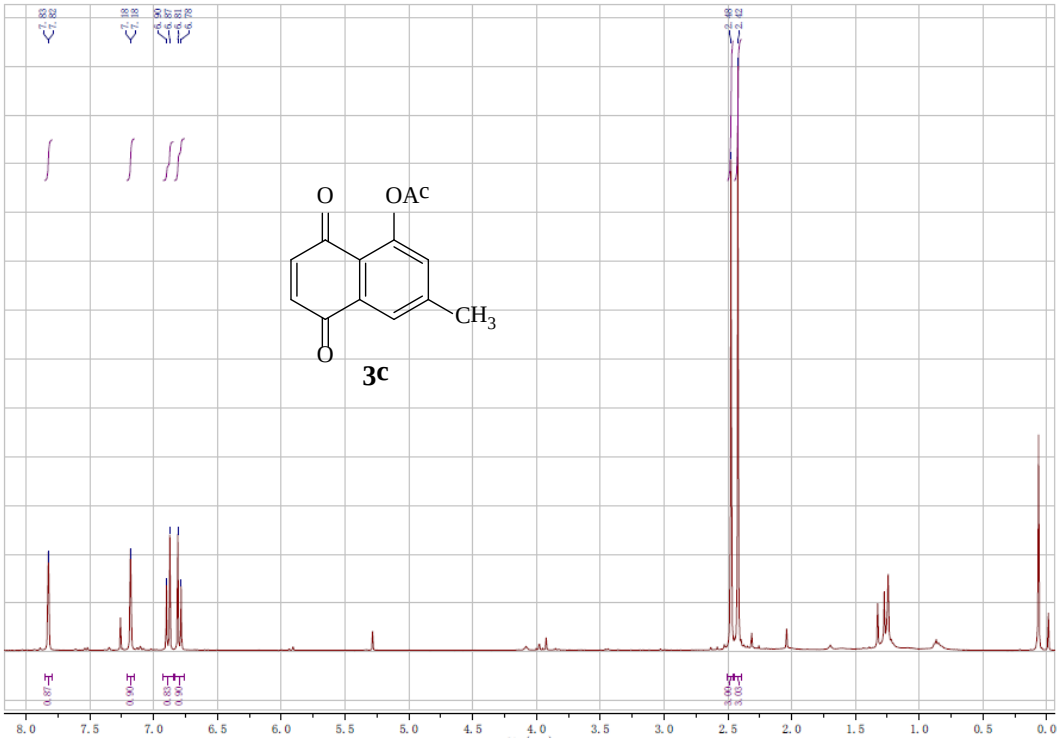


Figure S15. ^{1}H & ^{13}C-NMR spectra of *7-Methyl-5-Acetoxy-1,4-naphthoquinone* (3c)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

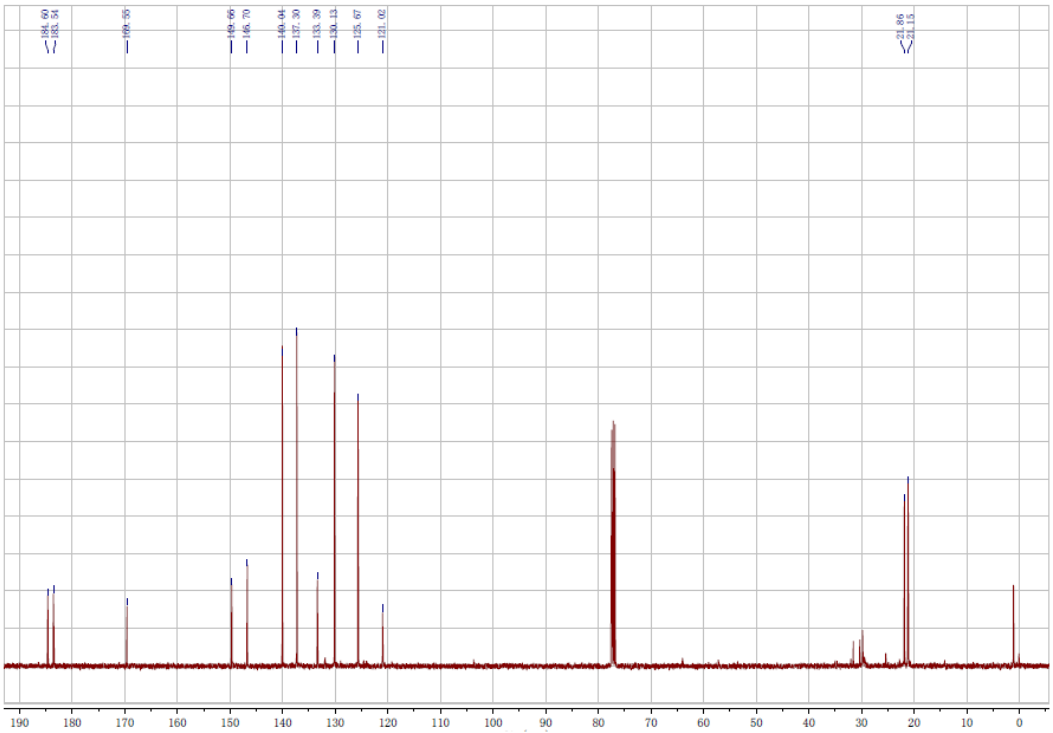
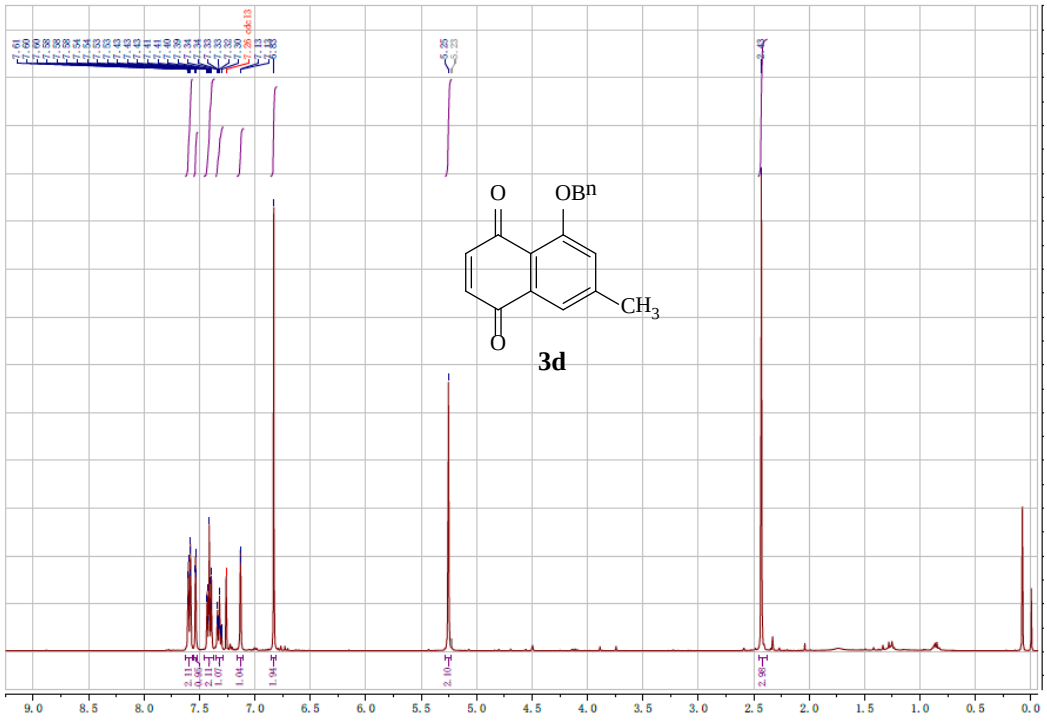


Figure S16. ^{1}H & ^{13}C-NMR spectra of 5-(benzyloxy)-7-methylnaphthalene-1,4-dione (3d)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

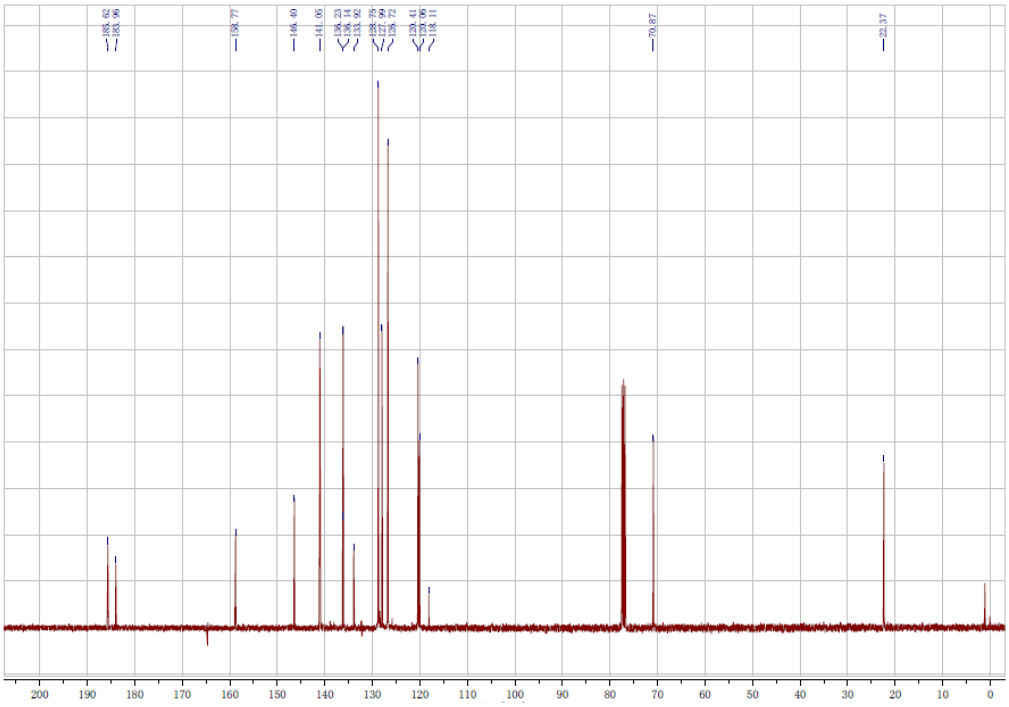
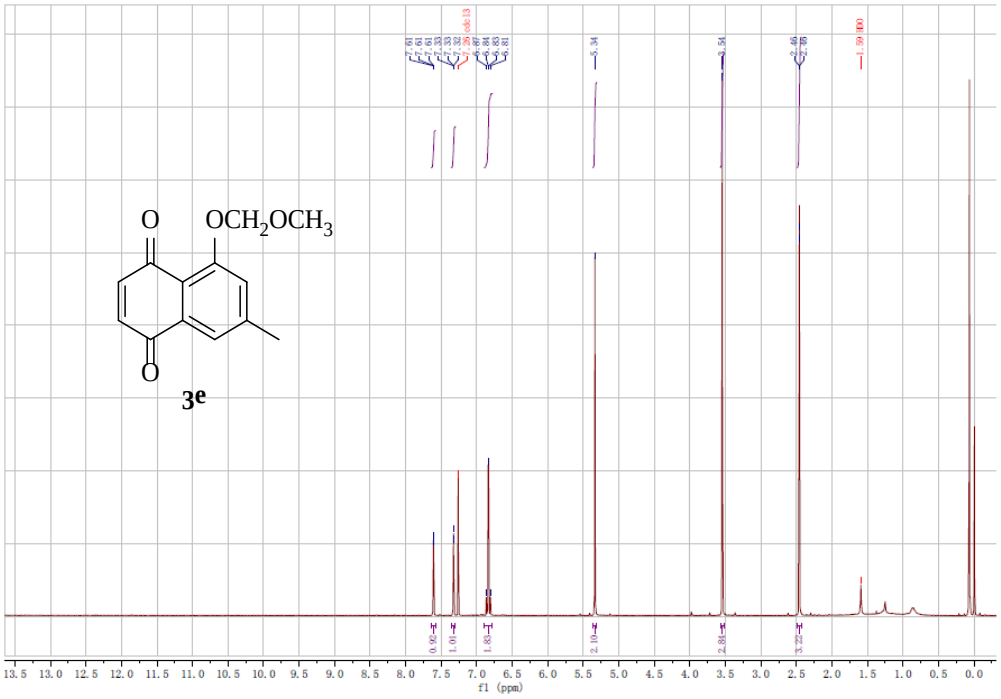


Figure S17. ^{1}H-NMR Spectrum of **5-(Methoxymethoxy)-7-Methylnaphthalene-1,4-Dione** (**3e**)

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)