Electronic Supplementary Material (ESI) for RSC Advances.

An Efficient Synthesis of 2-Thio-5-amino Substituted Benzoquinones *via* KI Catalyzed Cascade Oxidation/Michael addition/Oxidation Starting from Hydroquinone

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Content

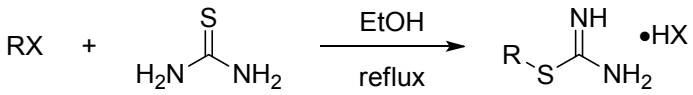
1. General information

All experiments were carried out under air unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AVIII-400/600 spectrometer at ambient temperature with $CDCl_3$, D_2O or DMSO-d_6 as the solvent using tetramethylsilane (TMS) as internal standard unless otherwise noted. High-resolution mass spectra were recorded by Bruker Apex IV Fourier Transform Ion Cyclotron Resonance Mass Spectrometer spectrometer (HRMS). All melting points were measured on a melting point apparatus with uncorrected thermometers.

2. Synthesis of isothiouronium salts (3)

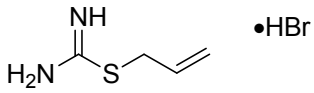
***S*-Methylisothiourea Hemisulfate Salt** (**3h**) was purchased from *accela*.

General preparation for isothiouronium salts (3)

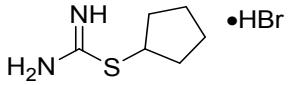


3

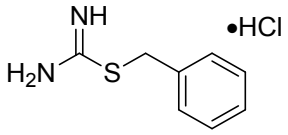
To the solution of thiourea (3.806 g, 50 mmol) in EtOH (50 mL) was added alkyl halide (55 mmol). The mixture was kept refluxing in oil bath. The completion of the reaction was monitored by TLC. The solvent was removed and the residue was recrystallized from EtOH/EtOAc.



***S*-Allylisothiouronium bromide (3a):** Obtained in 92% yield (9.062 g), white solid; m.p. 79.4-79.8°C (Lit.3 74-76°C); ^{1}H NMR (400 MHz, D_2O) δ 5.94 (ddt, J = 16.8, 10.1, 6.5 Hz, 1H), 5.44 (dd, J = 17.0, 1.0 Hz, 1H), 5.32 (dd, J = 10.2, 0.9 Hz, 1H), 3.82 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 170.9, 130.6, 120.3, 33.8

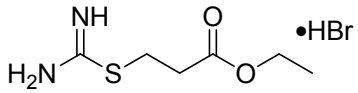


***S*-Cyclopentylisothiouronium bromide (3b):** Obtained in 92% yield (10.350 g), white solid; m.p. 140.4-141.2°C; ^{1}H NMR (400 MHz, D_2O) δ 4.01-3.69 (m, 1H), 2.29-2.08 (m, 2H), 1.66 (ddd, J = 15.7, 9.2, 5.1 Hz, 6H); ^{13}C NMR (101 MHz, D_2O) δ 171.7, 43.9, 32.9, 24.3

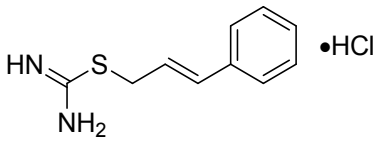


***S*-Benzylisothiouronium chloride (3c):** Obtained in 93% yield (9.393 g), white solid; m.p. 145.0-

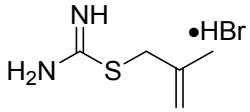
145.5°C(Lit.4 146-148°C); ^{1}H NMR (400 MHz, D_2O) δ 7.50-7.14 (m, 5H), 4.28 (s, 2H); ^{13}C NMR (101 MHz, D_2O) δ 170.5, 133.9, 129.2, 128.9, 128.5, 35.1



Ethyl 3-(carbamimidoylthio)propanoate hydrobromide (3e): Obtained in 86% yield (10.965 g), white solid; m.p. 85.6-86.2°C; ^{1}H NMR (400 MHz, D_2O) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.32 (t, *J* = 6.7 Hz, 2H), 2.80 (t, *J* = 6.7 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, D_2O) δ 173.4, 170.9, 62.3, 33.5, 26.0, 13.3

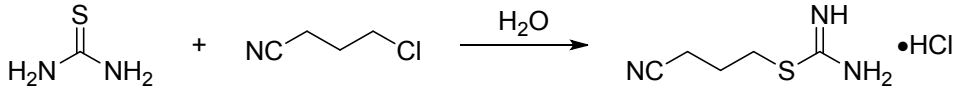


***S*-Cinnamylisothiouronium chloride (3f):** Obtained in 81% yield (9.234 g), white solid, m.p. 166.7-167.6°C; ^{1}H NMR (400 MHz, D_2O) δ 7.54-7.16 (m, 5H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.37-6.09 (m, 1H), 3.85 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (101 MHz, D_2O) δ 170.7, 135.9, 134.6, 129.0, 128.5, 126.6, 121.9, 33.5.



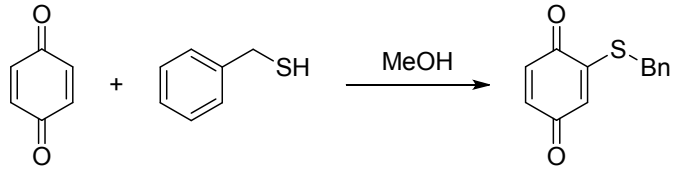
***S*-Methallylisothiouronium bromide (3g):** Obtained in 93% yield (9.811 g), white solid; m.p. 126.1-126.4°C; ^{1}H NMR (400 MHz, D_2O) δ 5.06 (s, 1H), 5.01 (s, 1H), 3.74 (s, 2H), 1.79 (s, 3H); ^{13}C NMR (101 MHz, D_2O) δ 139.0, 115.6, 38.0, 20.0

4-Isothioureidobutyronitrile hydrochloride (3d)



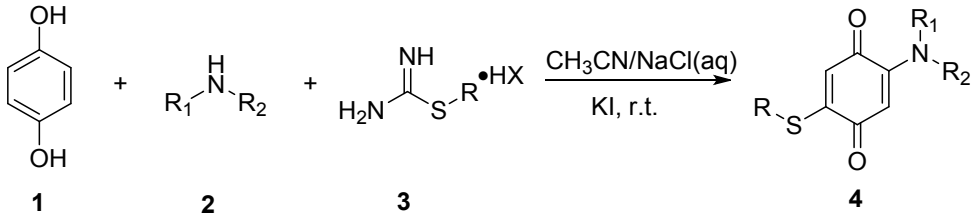
Redistilled 4-chlorobutyronitrile (7.663 g, 74 mmol) was added to a solution of thiourea (7.612 g, 100 mmol) in water (5.0 mL), and the mixture was refluxed for 3 h. Acetone (100 mL) was added to the solution, the mixture was filtered, and the cake was washed with acetone and diethyl ether and air-dried overnight.[1] Obtained **3d** in 83% yield (10.994 g), white solid; m.p. 130.1-130.9°C (Lit.2 125-127°C); ^{1}H NMR (400 MHz, D_2O) δ 3.20 (t, *J* = 7.2 Hz, 2H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.11-1.94 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 170.6, 120.6, 29.5, 24.0, 15.4

3. Synthesis of 2-(benzylthio)cyclohexa-2,5-diene-1,4-dione (7c)

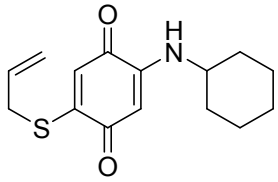


To a suspension of finely divided 1,4-benzoquinone (0.108 g, 1 mmol) in methanol (5 mL) was added a solution of benzyl mercaptan (0.124 g, 1 mmol) in methanol (1 mL). The mixture was stirred for 5 min and water (10 mL) was added, the solid was filtered off, which was then purified by silica gel column (EtOAc/petroleum ether) to give the orange solid in 68% yield (0.156 g).[5]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.29 (m, 5H), 6.82 (d, *J* = 10.1 Hz, 1H), 6.73 (dd, *J* = 10.1, 2.3 Hz, 1H), 6.48 (d, *J* = 2.2 Hz, 1H), 4.03 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 183.8, 152.4, 137.5, 136.1, 133.8, 129.0, 128.9, 128.1, 125.4, 35.3.

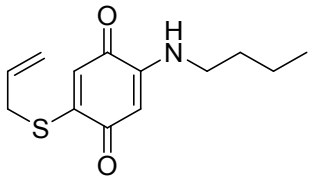
4. Preparation for 2-thio-5-amino substituted benzoquinones (4)



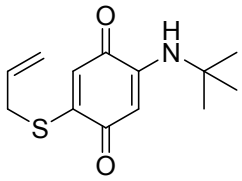
2-(Allylthio)-5-(cyclohexylamino)-2,5-cyclohexadiene-1,4-dione (4aa). Typical Procedure:



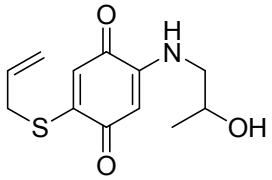
To the solution of hydroquinone (0.110 g, 1 mmol), *S*-Allylisothiouronium bromide (0.197 g, 1 mmol), potassium iodide (0.050 g, 0.3 mmol) in CH_3CN/NaCl (aq., saturated, 20 mL/5 mL) was added cyclohexylamine (0.297 g, 3 mmol). The mixture was stirred at room temperature for 12h until the consumption of hydroquinone on TLC indicated by iodine vapor, then diluted with saturated brine (20 mL), and extracted with EtOAc (3×20 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column (EtOAc/petroleum ether) to give the desired product **4aa** in 73% yield (0.202 g). red solid, m.p. 92.5-93.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.87 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 2H), 5.51 (s, 1H), 5.39 (dd, *J* = 17.0, 1.1 Hz, 1H), 5.28 (dd, *J* = 10.1, 1.0 Hz, 1H), 3.45 (d, *J* = 6.4 Hz, 2H), 3.33-3.16 (m, 1H), 2.08-1.88 (m, 2H), 1.90-1.72 (m, 2H), 1.66 (d, *J* = 5.8 Hz, 1H), 1.31 (ddd, *J* = 24.4, 14.5, 2.9 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.0, 179.4, 158.7, 146.2, 130.4, 120.3, 119.8, 96.8, 51.3, 33.4, 31.8, 25.4, 24.5; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}NO_2S$ $[M+H]^+$: 278.12093, found: 278.12107.



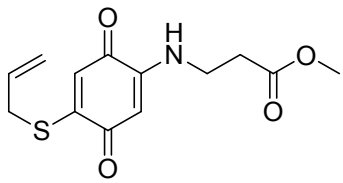
2-(Allylthio)-5-(butylamino)-2,5-cyclohexadiene-1,4-dione (4ab): Obtained in 71% yield (0.178 g), red solid, m.p. 83.5-84.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 6.12-5.73 (m, 2H), 5.49 (s, 1H), 5.40 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.29 (dd, *J* = 10.1, 1.0 Hz, 1H), 3.46 (d, *J* = 6.5 Hz, 2H), 3.13 (dd, *J* = 13.2, 6.9 Hz, 2H), 1.70-1.60 (m, 2H), 1.49-1.36 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1, 179.3, 158.7, 147.5, 130.4, 120.3, 119.8, 96.8, 42.3, 33.4, 30.2, 20.1, 13.6; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}NO_2S$ $[M+H]^+$: 252.10528, found: 252.10575.



2-(Allylthio)-5-(tert-butylamino)-2,5-cyclohexadiene-1,4-dione (4ac): Obtained in 50% yield (0.125 g), red solid, m.p. 113.9-114.6°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 5.96 (br, 1H), 5.91-5.80 (m, 1H), 5.71 (s, 1H), 5.39 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.28 (dd, *J* = 10.1, 1.0 Hz, 1H), 3.45 (d, *J* = 6.4 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.8, 179.7, 158.2, 145.2, 130.36, 120.4, 119.8, 98.8, 51.9, 33.3, 28.3; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}NO_2S$ $[M+H]^+$:252.10528, found: 252.10574.

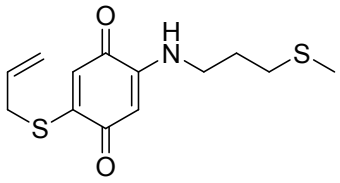


2-(Allylthio)-5-((2-hydroxypropyl)amino)-2,5-cyclohexadiene-1,4-dione (4ad): Obtained in 72% yield (0.182 g), red solid, m.p. 100.6-101.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 1H), 6.23 (s, 1H), 5.86 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.50 (s, 1H), 5.39 (d, *J* = 17.0 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 4.10 (s, 1H), 3.45 (d, *J* = 6.4 Hz, 2H), 3.20 (ddd, *J* = 13.7, 6.3, 3.7 Hz, 1H), 3.08 (ddd, *J* = 13.6, 7.8, 5.5 Hz, 1H), 2.23 (d, *J* = 37.2 Hz, 1H), 1.30 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3, 179.1, 158.5, 147.7, 130.3, 120.4, 119.9, 97.2, 65.6, 49.4, 33.4, 21.3; HRMS (ESI): *m/z* calcd for $C_{12}H_{16}NO_3S$ $[M+H]^+$: 254.08454, found: 254.08478.

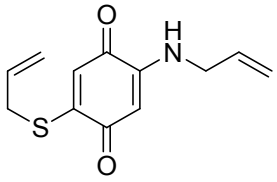


Methyl 3-((4-(allylthio)-3,6-dioxocyclohexa-1,4-dien-1-yl)amino)propanoate (4ae): Obtained

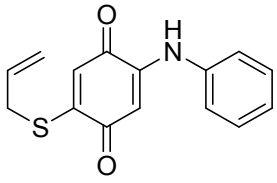
in 61% yield (0.171 g), red solid, m.p. 94.0-94.9°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.17 (s, 1H), 5.87 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.52 (s, 1H), 5.39 (dd, *J* = 17.0, 0.9 Hz, 1H), 5.29 (d, *J* = 10.1 Hz, 1H), 3.74 (s, 3H), 3.46 (q, *J* = 6.3 Hz, 4H), 2.66 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3, 179.0, 171.5, 158.3, 147.1, 130.3, 120.5, 119.9, 97.2, 52.1, 37.9, 33.4, 32.4; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}NO_4S$ $[M+H]^+$: 282.07946, found: 282.07982.



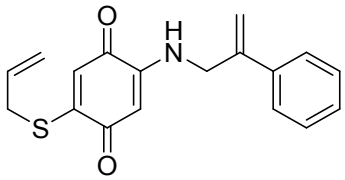
2-(Allylthio)-5-((3-(methylthio)propyl)amino)-2,5-cyclohexadiene-1,4-dione (4af): Obtained in 62% yield (0.175 g), red solid, m.p. 66.7-67.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 6.00 (s, 1H), 5.87 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.53 (s, 1H), 5.39 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.29 (dd, *J* = 10.1, 0.9 Hz, 1H), 3.46 (d, *J* = 6.5 Hz, 2H), 3.29 (q, *J* = 6.6 Hz, 2H), 2.58 (t, *J* = 6.9 Hz, 2H), 2.12 (s, 3H), 1.95 (p, *J* = 6.9 Hz, 2H); 13C NMR (101 MHz, CDCl3) δ 181.1, 179.2, 158.6, 147.4, 130.3, 120.4, 119.9, 97.1, 41.3, 33.4, 31.5, 27.1, 15. 6; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}NO_2S_2$ $[M+H]^+$: 284.07735, found: 284.07760.



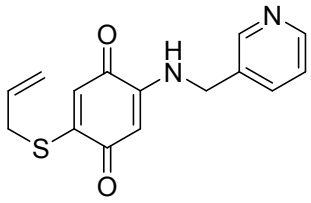
2-(Allylamino)-5-(allylthio)-2,5-cyclohexadiene-1,4-dione (4ag): Obtained in 60% yield (0.141 g), red solid, m.p. 108.5-109.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.99 (s, 1H), 5.94-5.78 (m, 2H), 5.51 (s, 1H), 5.40 (d, *J* = 17.0 Hz, 1H), 5.34-5.24 (m, 3H), 3.79 (t, *J* = 5.7 Hz, 2H), 3.46 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3, 179.2, 158.4, 147.2, 131.3, 130. 3, 120.4, 119.9, 118.4, 97.7, 44.9, 33.4; HRMS (ESI): *m/z* calcd for $C_{12}H_{14}NO_2S$ $[M+H]^+$: 236.07398, found: 236.07443.



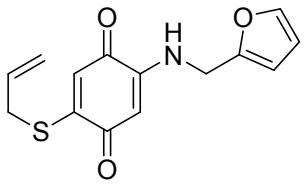
2-(Allylthio)-5-(phenylamino)-2,5-cyclohexadiene-1,4-dione (4ah): Obtained in 40% yield (0.108 g), red solid, m.p. 266.4-267.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.42 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 3H), 6.36 (s, 1H), 6.19 (s, 1H), 5.89 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.42 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.32 (dd, *J* = 10.1, 0.9 Hz, 1H), 3.50 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.4, 179.4, 157.9, 143.9, 137.2, 130.2, 129.7, 125.8, 122.4, 120.6, 112.0, 99.9, 33.4; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}NO_2S$ $[M+H]^+$: 272.07398, found: 272.07423.



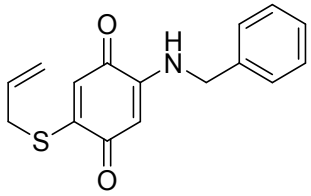
2-(Allylthio)-5-((2-phenylallyl)amino)-2,5-cyclohexadiene-1,4-dione (4ai): Obtained in 69% yield (0.214 g), red solid, m.p. 129.7-130.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.30 (m, 5H), 6.24 (s, 1H), 6.03 (s, 1H), 5.94-5.79 (m, 1H), 5.59 (s, 1H), 5.56 (s, 1H), 5.39 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.31-5.28 (m, 1H), 5.28 (s, 1H), 4.18 (d, *J* = 5.9 Hz, 2H), 3.46 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3, 179.1, 158.3, 147.2, 141.8, 138.0, 130.3, 128.7, 128.4, 126.0, 120.5, 119.9, 115.1, 97.9, 46.5, 33.4; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}NO_2S$ $[M+H]^+$: 312.10528, found: 312.10531.



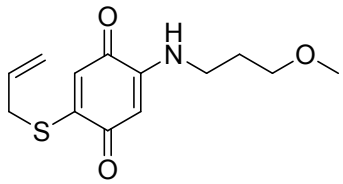
2-(Allylthio)-5-((pyridin-3-ylmethyl)amino)-2,5-cyclohexadiene-1,4-dione (4aj): Obtained in 73% yield (0.208 g), red solid, m.p. 117.2-118.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71-8.56 (m, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.8, 4.9 Hz, 1H), 6.28 (s, 1H), 6.18 (s, 1H), 5.87 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.54 (s, 1H), 5.40 (d, *J* = 17.0 Hz, 1H), 5.30 (d, *J* = 10.1 Hz, 1H), 4.37 (d, *J* = 5.9 Hz, 2H), 3.47 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 179.0, 158.2, 149.7, 149.1, 147.0, 135.2, 131.3, 130.2, 123.8, 120.6, 112.0, 98.4, 44.2, 33.4; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}N_2O_2S$ $[M+H]^+$: 287.08487, found: 287.08508.



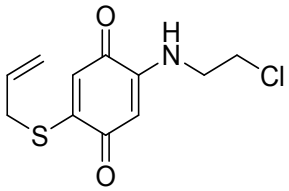
2-(Allylthio)-5-((furan-2-ylmethyl)amino)-2,5-cyclohexadiene-1,4-dione (4ak): Obtained in 61% yield (0.166 g), red solid, m.p. 124.4-124.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.37 (d, *J* = 2.6 Hz, 1H), 6.32 (d, *J* = 3.1 Hz, 1H), 6.26 (s, 1H), 6.12 (s, 1H), 5.87 (ddt, *J* = 16.5, 9.9, 6.4 Hz, 1H), 5.63 (s, 1H), 5.40 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 10.1 Hz, 1H), 4.31 (d, *J* = 5.8 Hz, 2H), 3.46 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 179.1, 158.2, 148.7, 146.9, 142.9, 130.3, 120.5, 119.9, 110.6, 108.8, 97.9, 39.6, 33.4; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}NO_3S$ $[M+H]^+$: 276.06889, found: 276.06957.



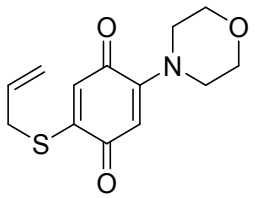
2-(Allylthio)-5-(benzylamino)-2,5-cyclohexadiene-1,4-dione (4al): Obtained in 69% yield (0.196 g), red solid, m.p. 109.0-109.9°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 6.26 (s, 1H), 6.19 (s, 1H), 5.87 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.55 (s, 1H), 5.40 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.29 (dd, *J* = 10.1, 0.8 Hz, 1H), 4.32 (d, *J* = 5.8 Hz, 2H), 3.46 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3, 179.2, 158.4, 147.2, 135.6, 130.3, 129.0, 128. 2, 127.7, 120.5, 119.9, 97.9, 46.8, 33.4; HRMS (ESI): *m/z* calcd for $C_{16}H_{16}NO_2S$ $[M+H]^+$: 286.08963, found: 286.08984.



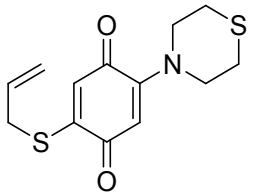
2-(Allylthio)-5-((3-methoxypropyl)amino)-2,5-cyclohexadiene-1,4-dione (4am): Obtained in 65% yield (0.173 g), red solid, m.p. 77.3-77.6°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (br, 1H), 6.23 (s, 1H), 5.87 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 5.49 (s, 1H), 5.39 (d, *J* = 17.0 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 3.50 (t, *J* = 5.6 Hz, 2H), 3.46 (d, *J* = 6.4 Hz, 2H), 3.38 (s, 3H), 3.25 (dd, *J* = 12.4, 6.3 Hz, 2H), 1.97-1.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1, 179.2, 158.6, 147.7, 130.4, 120.4, 119.8, 96.63, 70.7, 58.9, 40.8, 33.4 28.0; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}NO_3S$ $[M+H]^+$: 268.10019, found: 268.10042.



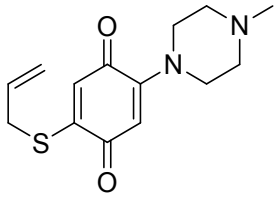
2-(Allylthio)-5-((2-chloroethyl)amino)-2,5-cyclohexadiene-1,4-dione (4an): Obtained in 48% yield (0.123 g), red solid, m.p. 102.9-103.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (s, 1H), 6.13 (br, 1H), 5.87 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.53 (s, 1H), 5.40 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 10.1 Hz, 1H), 3.72 (t, *J* = 5.8 Hz, 2H), 3.52 (dd, *J* = 11.8, 5.9 Hz, 2H), 3.47 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 178.8, 158.1, 147.0, 130.2, 120.6, 120.0, 97.8, 43.9, 41.3, 33.4; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}ClNO_2S$ $[M+H]^+$: 258.03500, found: 258.03482.



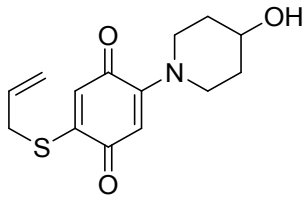
2-(Allylthio)-5-morpholino-2,5-cyclohexadiene-1,4-dione (4ao): Obtained in 82% yield (0.217 g), red solid, m.p. 120.3-121.1°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1H), 5.87 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.77 (s, 1H), 5.39 (d, *J* = 16.9 Hz, 1H), 5.29 (d, *J* = 10.1 Hz, 1H), 3.86-3.81 (m, 4H), 3.53-3.49 (m, 4H), 3.46 (d, *J* = 6.4 Hz, 2H); 13C NMR (101 MHz, CDCl3) δ 182.2, 181.0, 153.9, 152.1, 130.4, 123.7, 119.8, 107.6, 66.4, 49.0, 33.2; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}NO_3S$ $[M+H]^+$: 266.08454, found: 266.08469.



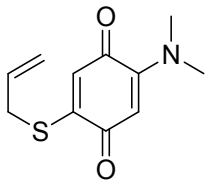
2-(Allylthio)-5-thiomorpholino-2,5-cyclohexadiene-1,4-dione (4ap): Obtained in 79% yield (0.222 g), red solid, m.p. 105.9-106.9°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H), 5.86 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.77 (s, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 3.84 (dd, *J* = 6.3, 3.8 Hz, 4H), 3.45 (d, *J* = 6.4 Hz, 2H), 2.81-2.70 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.9, 181.1, 154.1, 151.7, 130.4, 123.5, 119.8, 107.21, 51.8, 33.2, 27.1; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}NO_2S_2$ $[M+H]^+$: 282.06170, found: 282.06208.



2-(Allylthio)-5-(4-methylpiperazin-1-yl)-2,5-cyclohexadiene-1,4-dione (4aq): Obtained in 79% yield (0.219 g), red solid, m.p. 172.4-173.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (s, 1H), 5.87 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H), 5.77 (s, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 3.58-3.50 (m, 4H), 3.45 (d, *J* = 6.4 Hz, 2H), 2.59-2.50 (m, 4H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0, 181.2, 154.0, 152.3, 130.5, 123.6, 119.7, 107.3, 54.6, 48.8, 45.9, 33.2; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_2O_2S$ $[M+H]^+$: 279.11617, found: 279.11656.

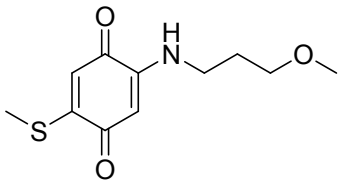


2-(Allylthio)-5-(4-hydroxypiperidin-1-yl)-2,5-cyclohexadiene-1,4-dione (4ar): Obtained in 75% yield (0.209 g), red solid, m.p. 84.4-85.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H), 5.93-5.83 (m, 1H), 5.80 (s, 1H), 5.39 (d, *J* = 16.9 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 4.13-3.92 (m, 1H), 3.92-3.75 (m, 2H), 3.43 (d, *J* = 14.9 Hz, 2H), 3.32 (ddd, *J* = 35.5, 19.4, 15.1 Hz, 2H), 2.07-1.94 (m, 2H), 1.72-1.65 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.9, 181.2, 154.2, 152.3, 130.5, 123.5, 119.7, 106.6, 66.5, 46.3, 33.9, 33.2; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}NO_3S$ $[M+H]^+$: 280.10019, found: 280.10053.

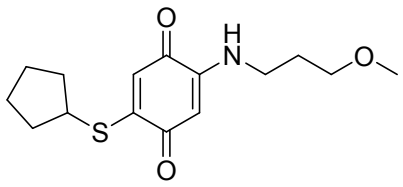


2-(Allylthio)-5-(dimethylamino)-2,5-cyclohexadiene-1,4-dione (4as): Obtained in 49% yield (0.109 g), red solid, m.p. 112.9-113.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 5.86 (ddt, *J*

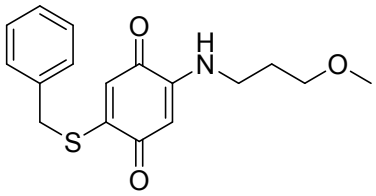
= 16.7, 10.2, 6.5 Hz, 1H), 5.59 (s, 1H), 5.38 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 3.44 (d, *J* = 6.4 Hz, 2H), 3.18 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 180.9, 155.1, 151.0, 130.6, 122.64, 119.6, 102.8, 42.7, 33.2; HRMS (ESI): *m/z* calcd for $C_{11}H_{14}NO_2S$ $[M+H]^+$: 224.07398, found: 224.07432.



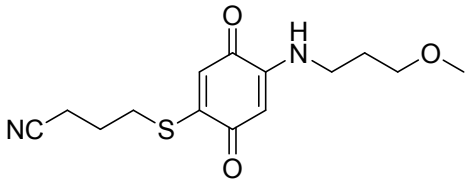
2-((3-Methoxypropyl)amino)-5-(methylthio)-2,5-cyclohexadiene-1,4-dione (4mh): Obtained in 62% yield (0.149 g), red solid, m.p. 77.9-78.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 6.7 Hz, 1H), 6.16 (s, 1H), 5.50 (s, 1H), 3.51 (t, *J* = 5.6 Hz, 2H), 3.38 (s, 3H), 3.26 (dd, *J* = 12.5, 6.2 Hz, 2H), 2.31 (s, 3H), 2.00-1.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.9, 179.1, 160.6, 147.9, 119.6, 96.5, 70.7, 58.9, 40.8, 28.0, 13.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{16}NO_3S$ $[M+H]^+$: 242.08454, found: 242.08504.



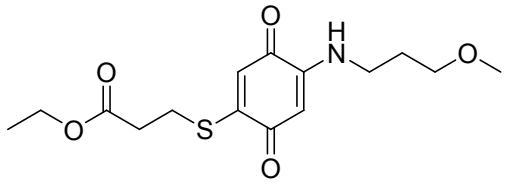
2-(Cyclopentylthio)-5-((3-methoxypropyl)amino)-2,5-cyclohexadiene-1,4-dione (4mb): Obtained in 68% yield (0.201 g), red solid, m.p. 82.8-83.7°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (br, 1H), 6.26 (s, 1H), 5.46 (s, 1H), 3.49 (t, *J* = 5.6 Hz, 2H), 3.43-3.37 (m, 1H), 3.36 (s, 3H), 3.23 (dd, *J* = 12.5, 6.3 Hz, 2H), 2.22-2.10 (m, 2H), 1.95-1.86 (m, 2H), 1.83-1.71 (m, 4H), 1.66 (dd, *J* = 8.5, 6.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3, 179.2, 160.0, 147.8, 120.5, 96.6, 70.7, 58.8, 42.6, 40.7, 32.8, 28.0, 25.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}NO_3S$ $[M+H]^+$: 296.13149, found: 296.13188.



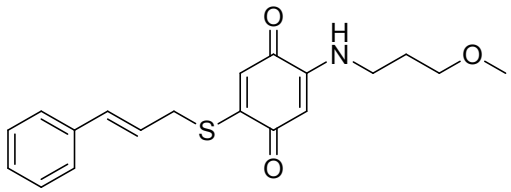
2-(Benzylthio)-5-((3-methoxypropyl)amino)-2,5-cyclohexadiene-1,4-dione (4mc): Obtained in 68% yield (0.216 g), red solid, m.p. 141.3-142.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (ddd, *J* = 20.3, 13.0, 7.2 Hz, 5H), 6.37 (br, 1H), 6.27 (s, 1H), 5.49 (s, 1H), 4.00 (s, 2H), 3.50 (t, *J* = 5.6 Hz, 2H), 3.38 (s, 3H), 3.25 (q, *J* = 6.3 Hz, 2H), 2.02-1.85 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.0, 179.2, 158.9, 147.7, 134.2, 128.9, 128.9, 127.9, 120.3, 96. 6, 70.7, 58.9, 40.8, 35.6, 28.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{20}NO_3S$ $[M+H]^+$: 318.11584, found: 318.11637.



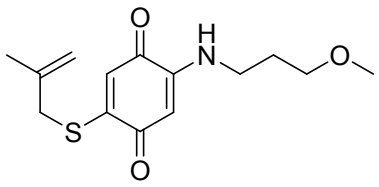
4-((4-((3-Methoxypropyl)amino)-3,6-dioxocyclohexa-1,4-dien-1-yl)thio)butanenitrile (4md): Obtained in 71% yield (0.209 g), red solid, m.p. 111.5-112.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (br, 1H), 6.21 (s, 1H), 5.50 (s, 1H), 3.51 (t, *J* = 5.6 Hz, 2H), 3.38 (s, 3H), 3.26 (dd, *J* = 12.4, 6.2 Hz, 2H), 2.91 (t, *J* = 7.1 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.12 (p, *J* = 7.0 Hz, 2H), 1.97-1.88 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 179.1, 158.0, 147.7, 120.2, 118.3, 96.6, 70.7, 58.9, 40.9, 28.7, 28.0, 23.4, 16.5; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_2O_3S$ $[M+H]^+$: 295.11109, found: 295.11135.



Ethyl 3-((4-((3-methoxypropyl)amino)-3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate (4me): Obtained in 70% yield (0.229 g), red solid, m.p. 108.0-108.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (br, 1H), 6.23 (s, 1H), 5.49 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.50 (t, *J* = 5.6 Hz, 2H), 3.37 (s, 3H), 3.25 (dd, *J* = 12.4, 6.2 Hz, 2H), 3.04 (t, *J* = 7.4 Hz, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 1.97-1.87 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.8, 179.2, 170.9, 158.6, 147.7, 119.9, 96.6, 70.7, 61.2, 58.9, 40.8, 32.2, 28.0, 25.3, 14.2; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}NO_5S$ $[M+H]^+$: 328.12132, found: 328.12148.



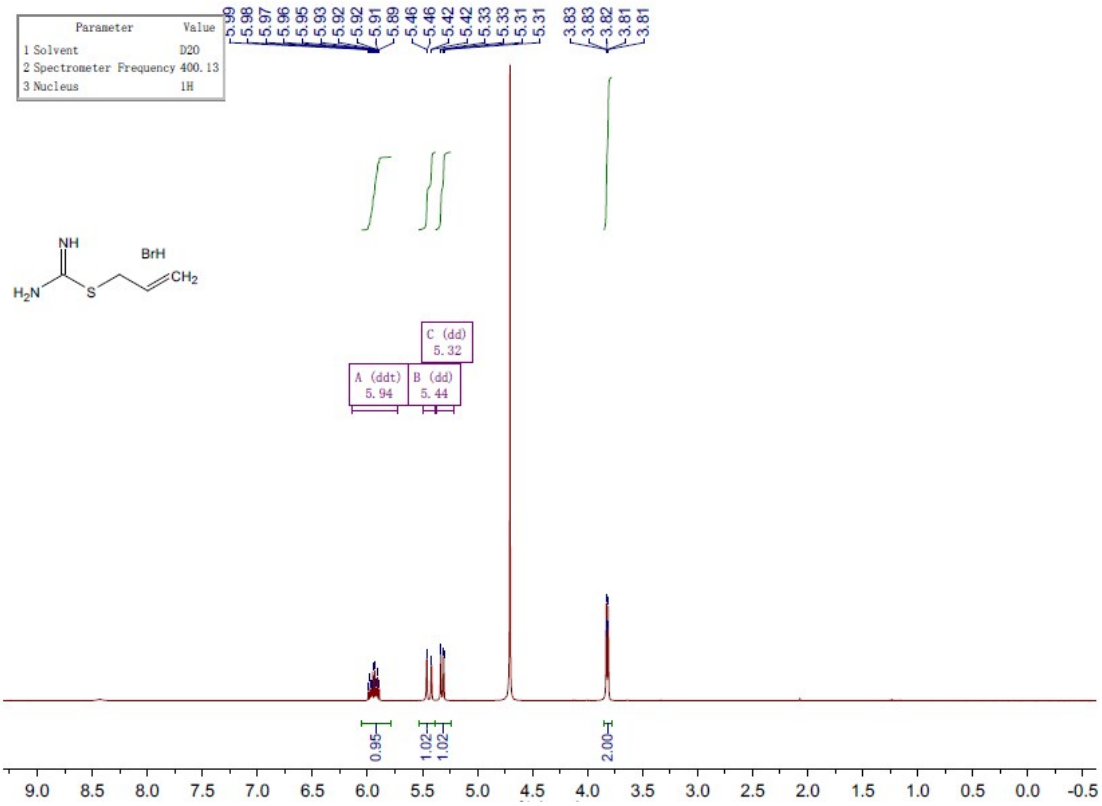
2-(Cinnamylthio)-5-((3-methoxypropyl)amino)-2,5-cyclohexadiene-1,4-dione (4mf): Obtained in 63% yield (0.216 g), red solid, m.p. 102.0-102.7°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.39 (br, 1H), 6.30 (s, 1H), 6.22 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.50 (s, 1H), 3.66-3.59 (m, 2H), 3.50 (t, *J* = 5.6 Hz, 2H), 3.37 (s, 3H), 3.25 (dd, *J* = 12.4, 6.2 Hz, 2H), 1.96-1.85 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1, 179.2, 158.7, 147.7, 136.1, 134.7, 128.6, 128.1, 126.5, 121.5, 120.4, 96.6, 70.7, 58.9, 40.8, 33.1, 28.0; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}NO_3S$ $[M+H]^+$: 344.13149, found: 344.13150.



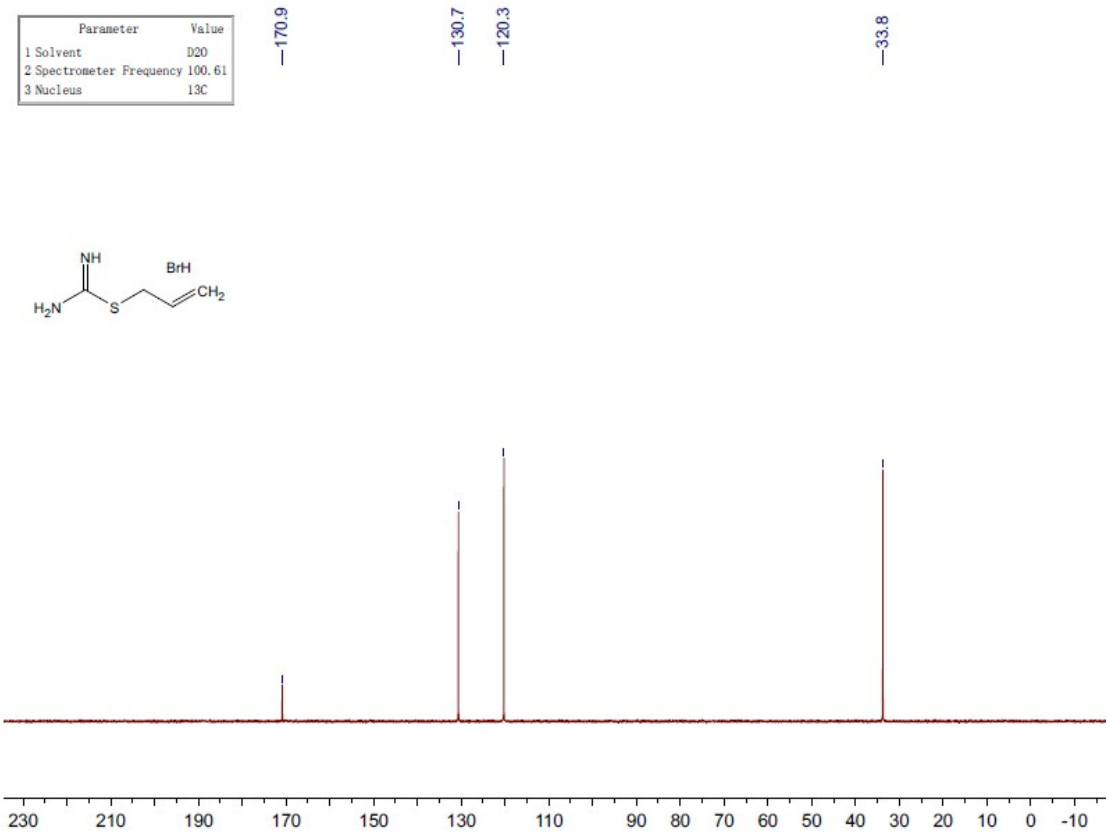
2-((3-Methoxypropyl)amino)-5-((2-methylallyl)thio)-2,5-cyclohexadiene-1,4-dione (4mg): Obtained in 65% yield (0.182 g), red solid, m.p. 103.5-104.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (br, 1H), 6.22 (s, 1H), 5.48 (s, 1H), 5.09 (s, 1H), 5.02 (s, 1H), 3.50 (t, *J* = 5.6 Hz, 2H), 3.42 (s, 2H), 3.37 (s, 3H), 3.24 (dd, *J* = 12.4, 6.2 Hz, 2H), 1.92 (dd, *J* = 12.1, 6.0 Hz, 2H), 1.88 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1, 179.2, 159.1, 147.7, 138.0, 120.5, 115.5, 96.6, 70.7, 58.9, 40.80, 37.9, 28.0, 21.8; HRMS (ESI): *m/z* calcd for $C_{14}H_{20}NO_3S$ $[M+H]^+$: 282.11584, found: 282.11581.

5. Spectra of compounds

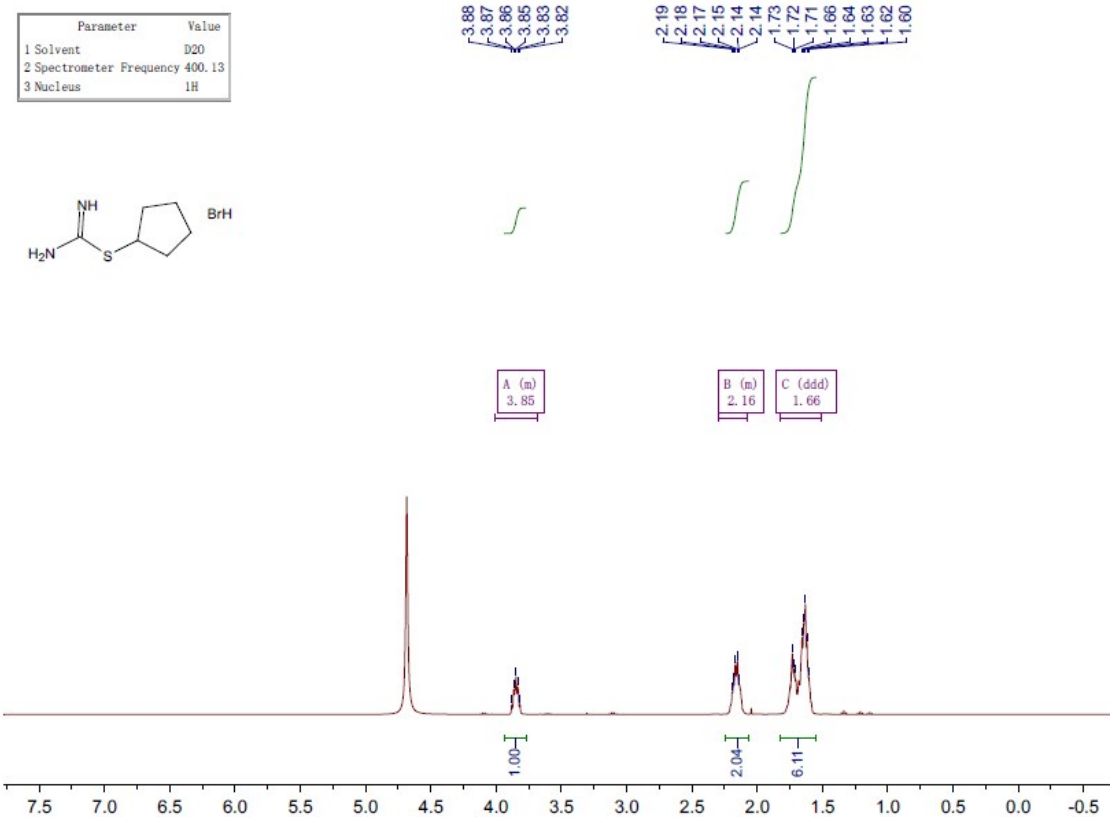
^{1}H NMR (400 MHz, D_2O) of **3a**



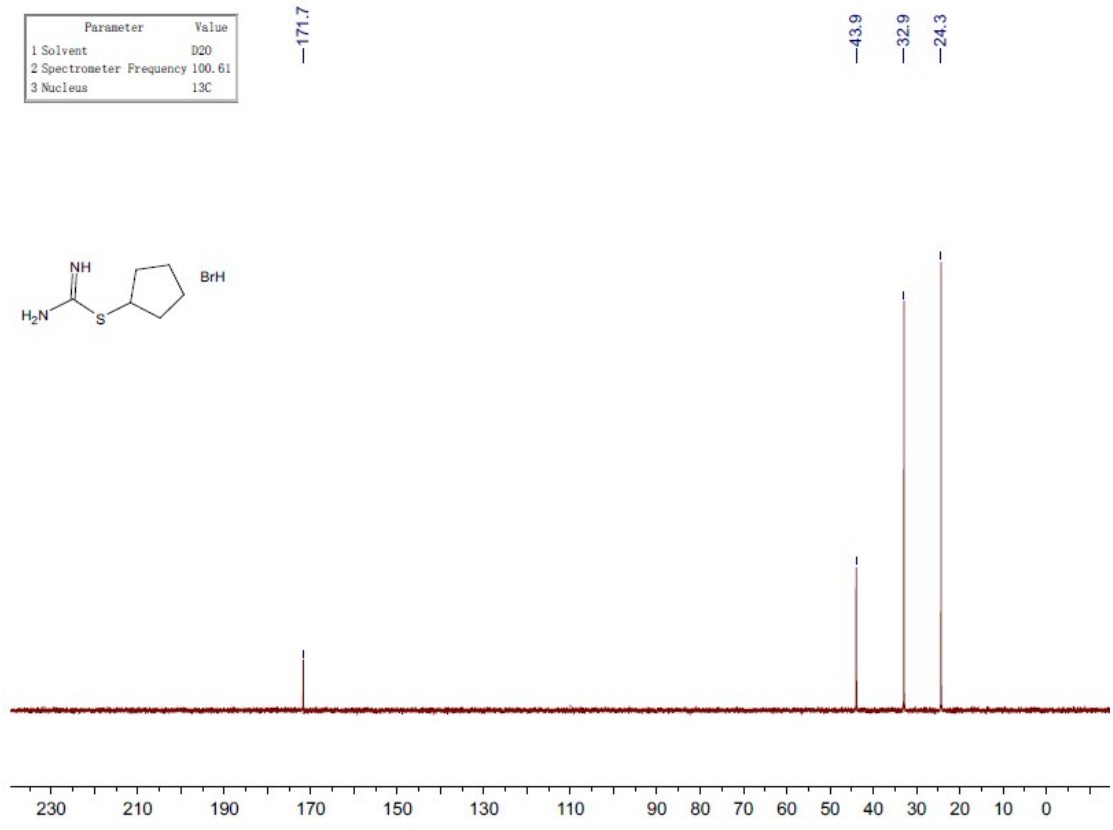
^{13}C NMR (101 MHz, D_2O) of **3a**



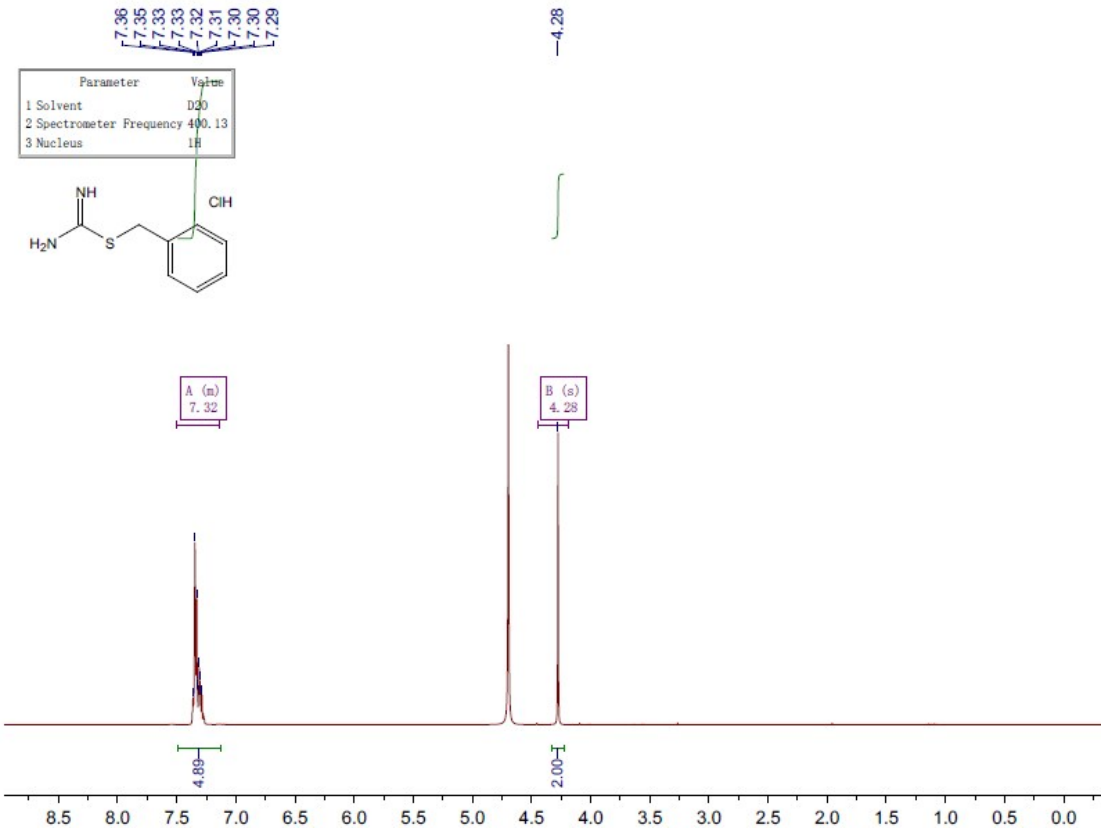
^{1}H NMR (400 MHz, D_2O) of **3b**



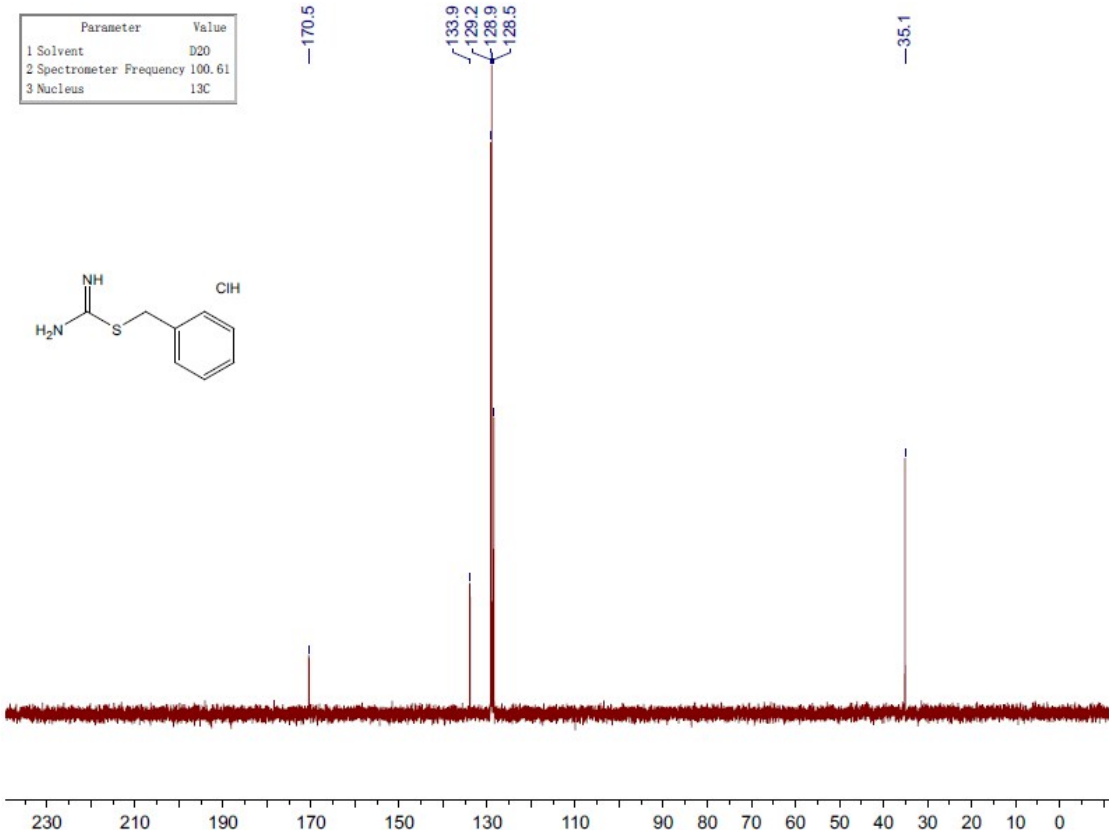
^{13}C NMR (101 MHz, D_2O) of **3b**



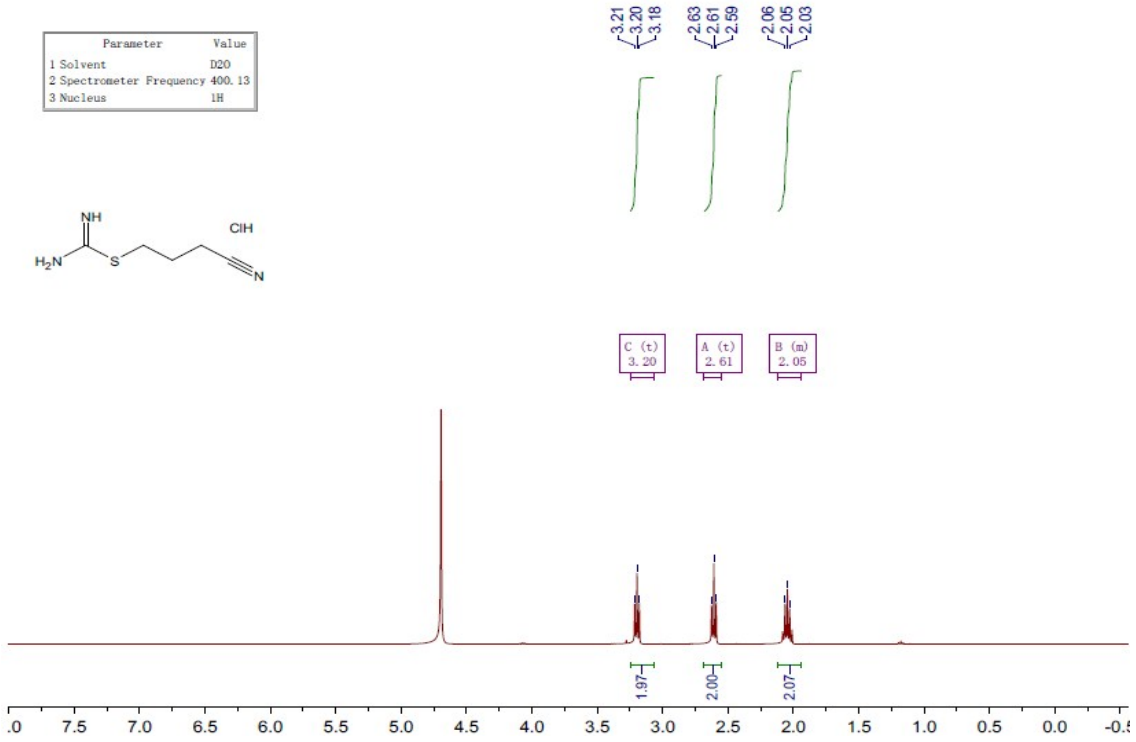
^{1}H NMR (400 MHz, D_2O) of **3c**



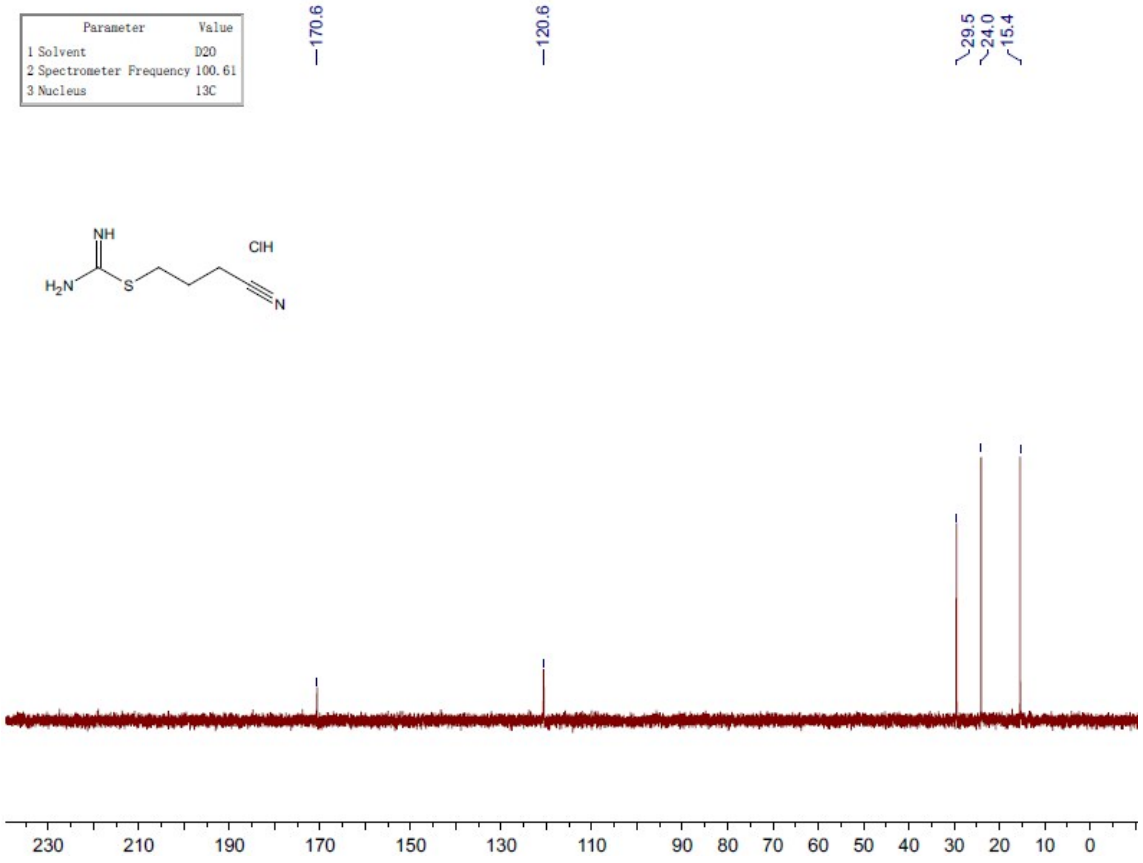
^{13}C NMR (101 MHz, D_2O) of **3c**



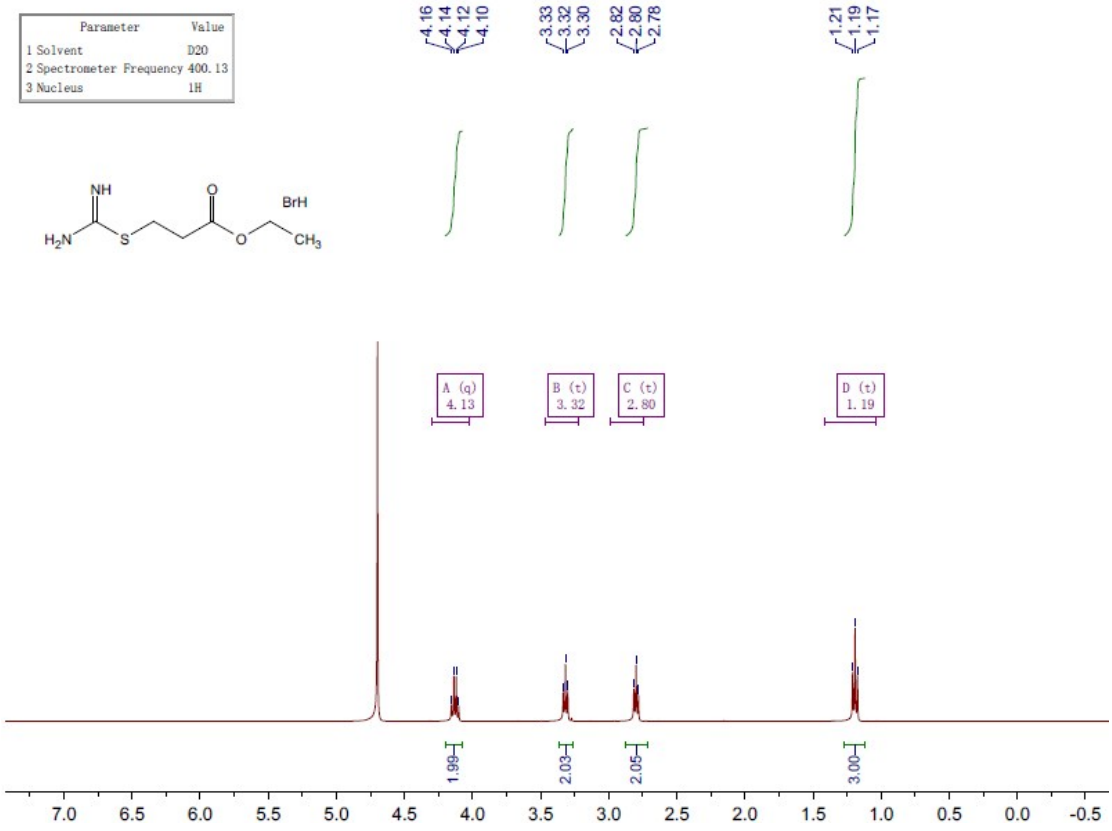
^{1}H NMR (400 MHz, D_2O) of **3d**



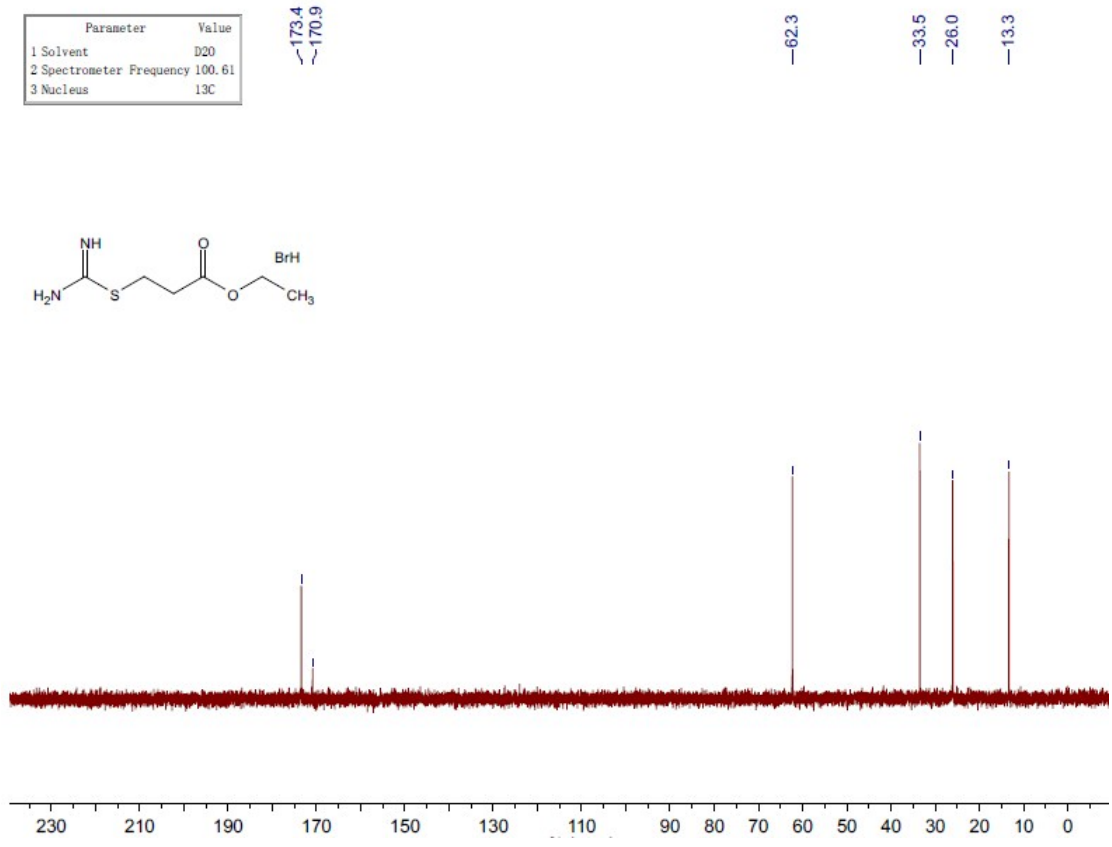
^{13}C NMR (101 MHz, D_2O) of **3d**



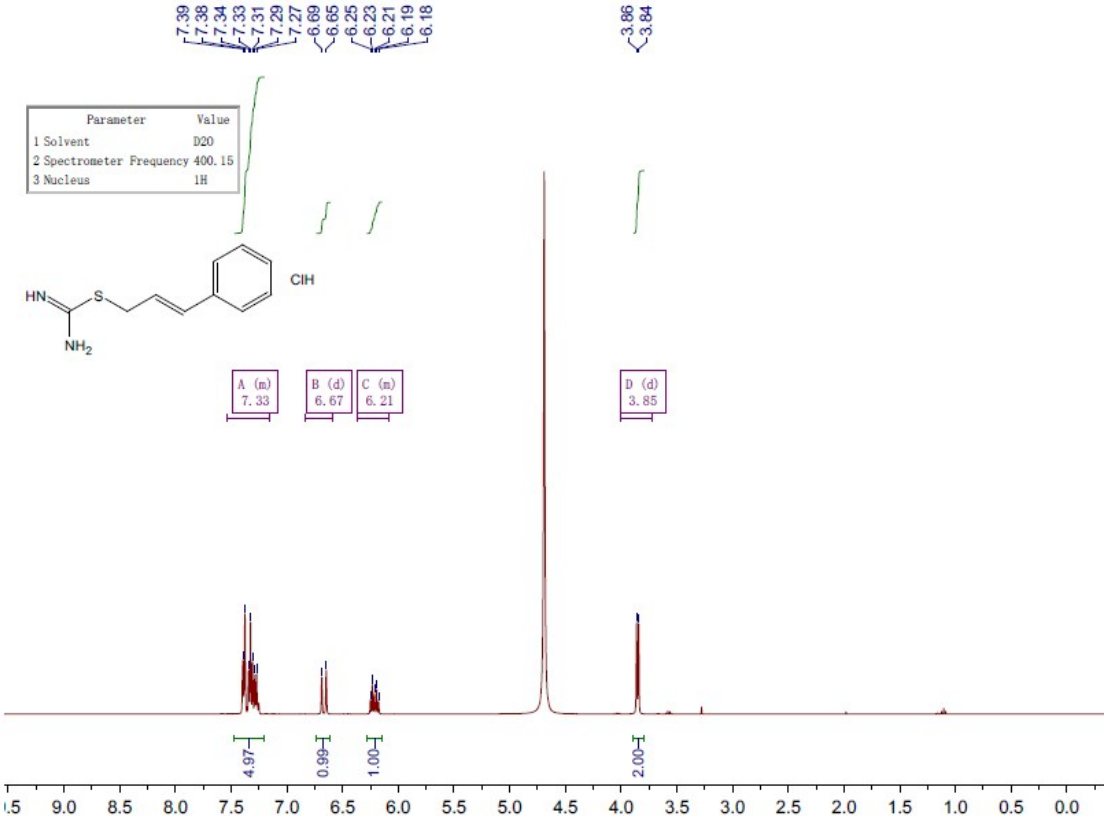
^{1}H NMR (400 MHz, D_2O) of **3e**



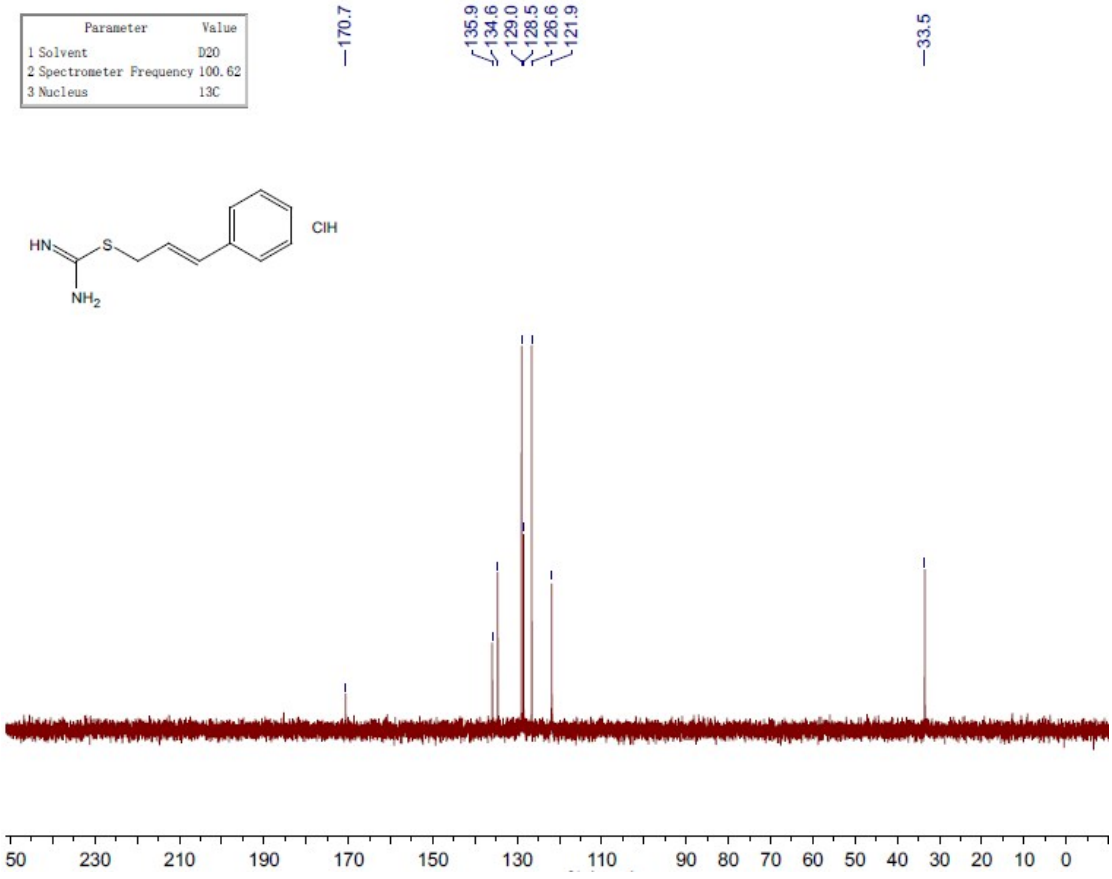
^{13}C NMR (101 MHz, D_2O) of **3e**



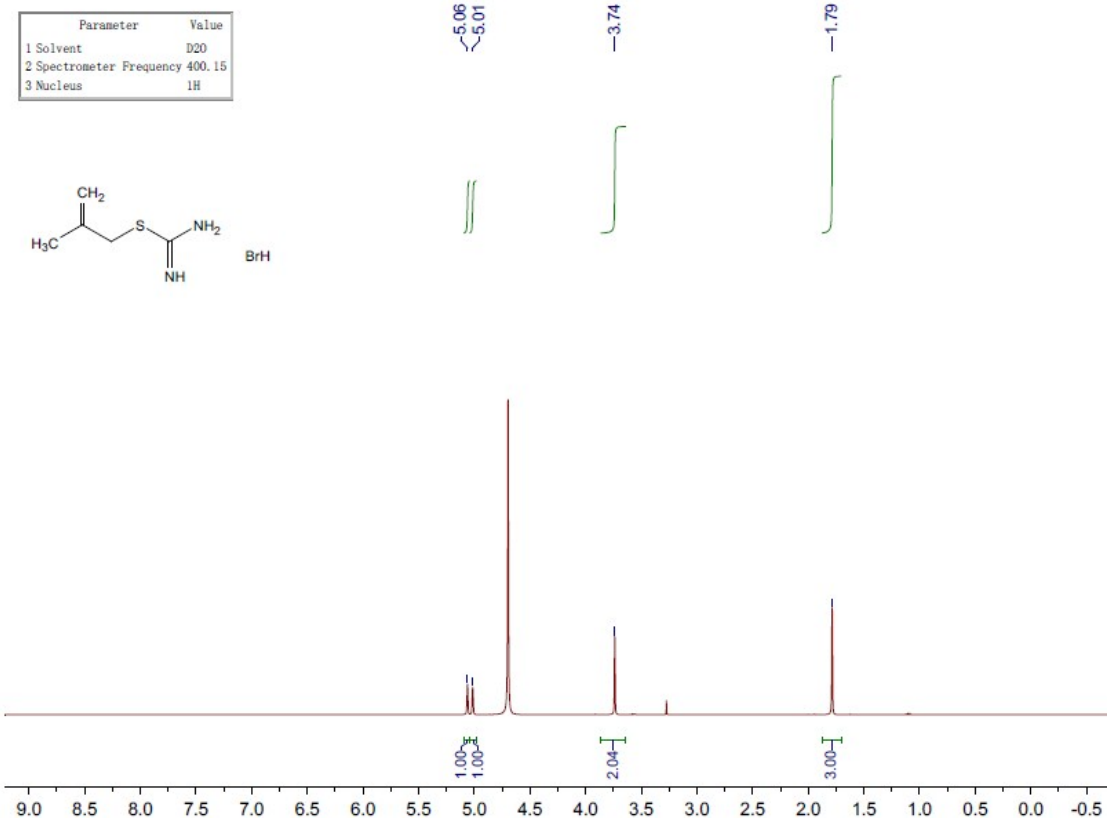
^{1}H NMR (400 MHz, D_2O) of **3f**



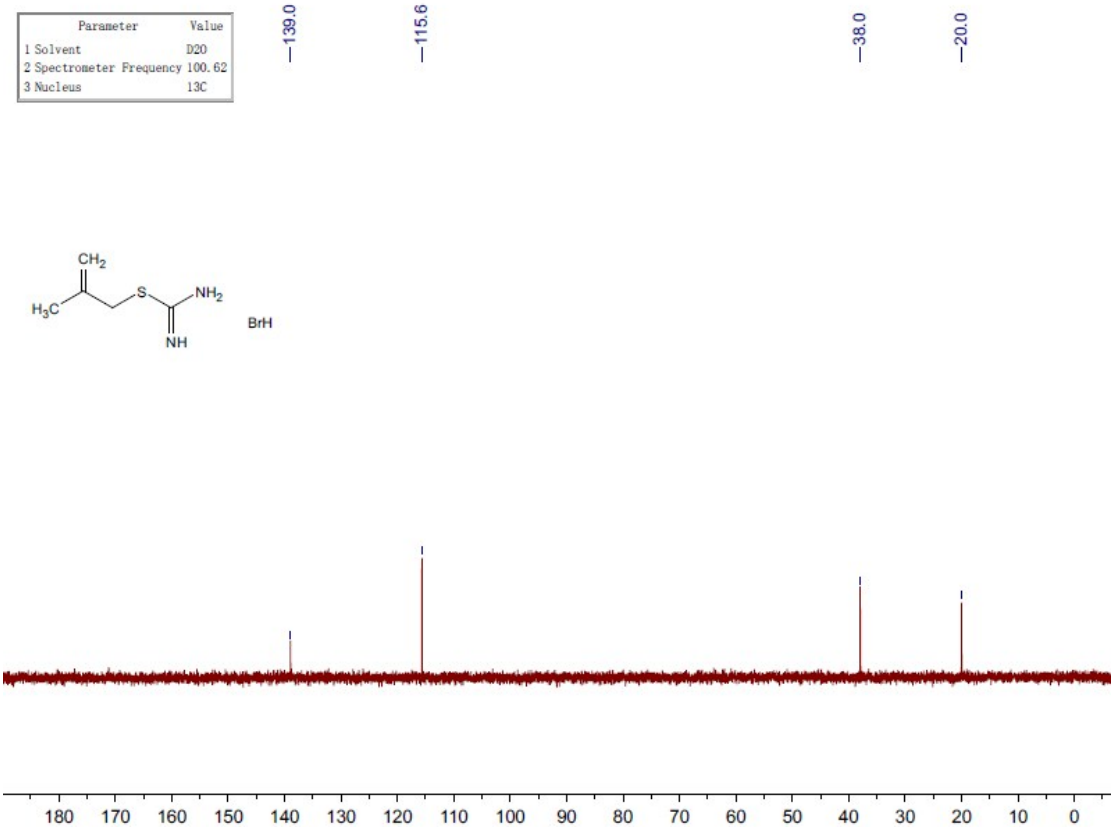
^{13}C NMR (101 MHz, D_2O) of **3f**



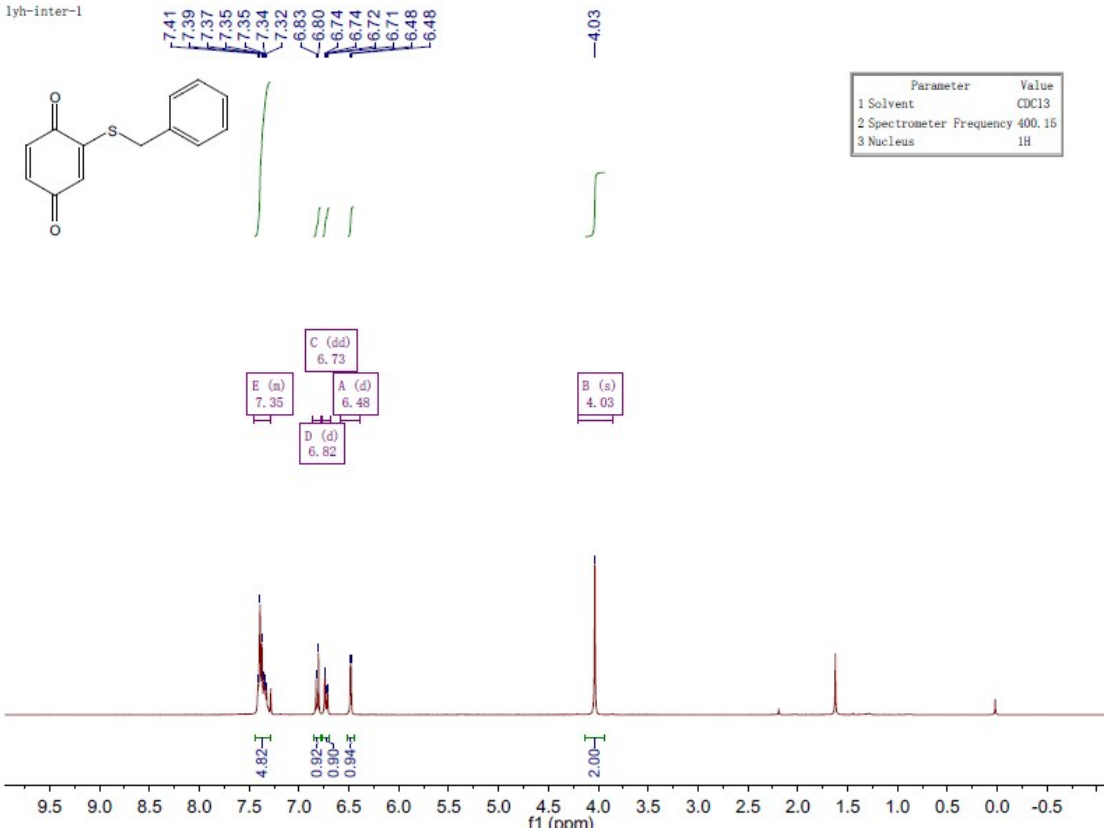
^{1}H NMR (400 MHz, D_2O) of **3g**



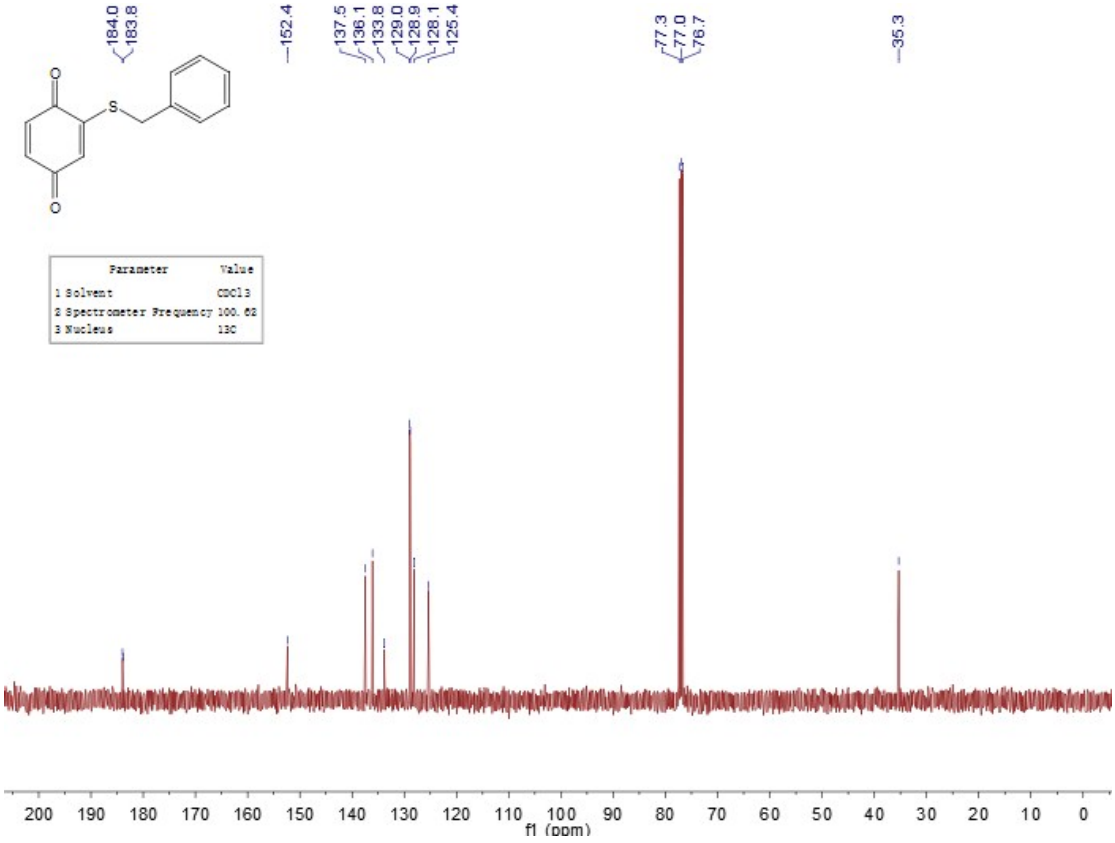
^{13}C NMR (101 MHz, D_2O) of **3g**



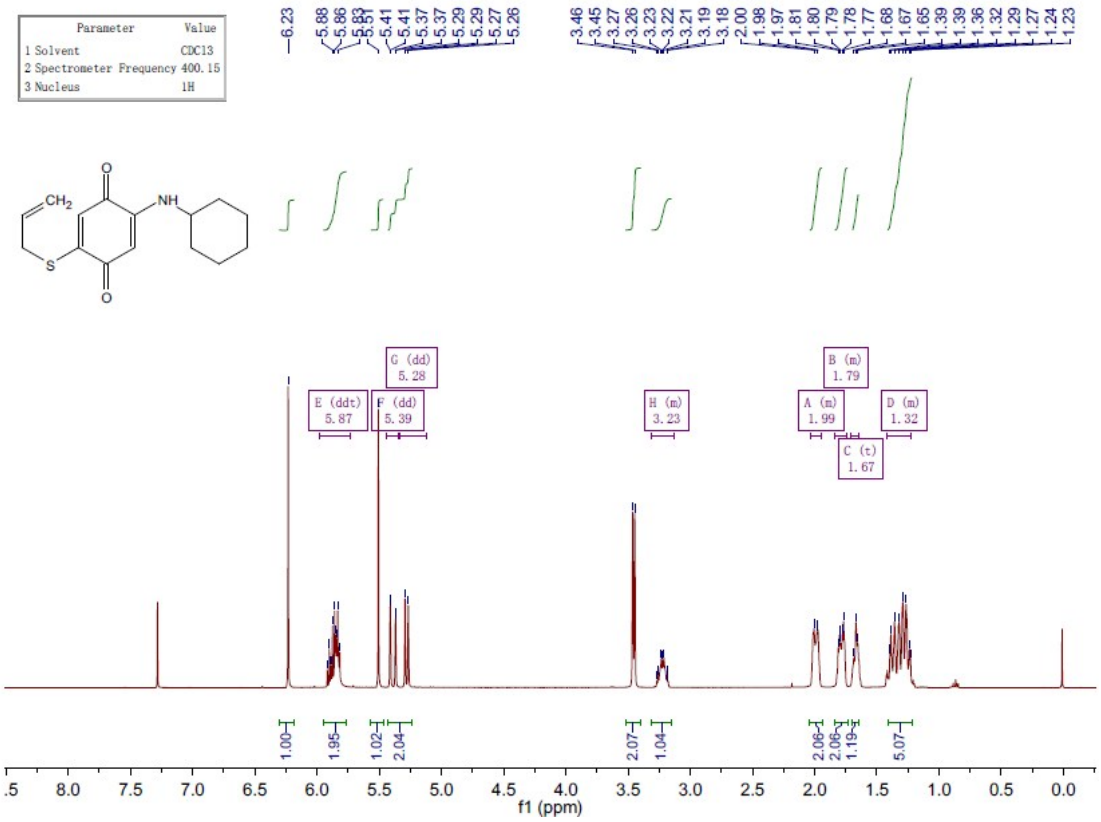
^{1}H NMR (400 MHz, $CDCl_3$) of **7c**



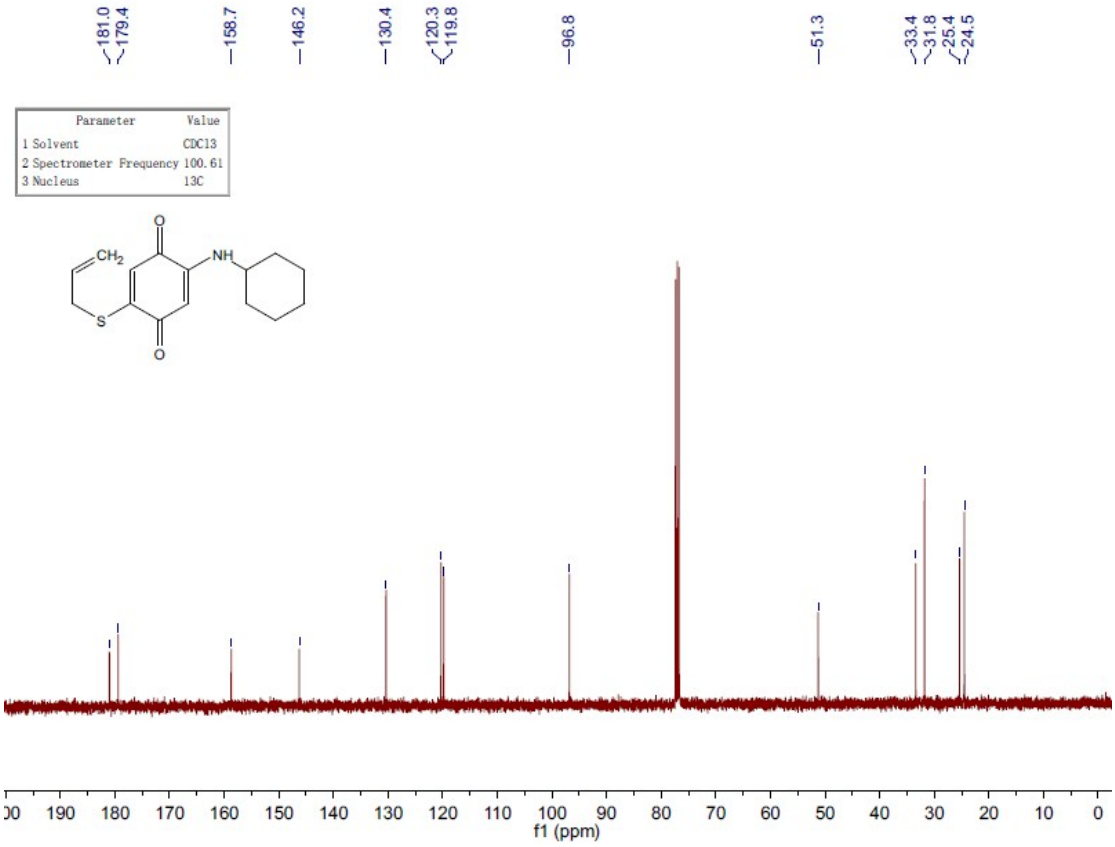
^{13}C NMR (101 MHz, $CDCl_3$) of **7c**



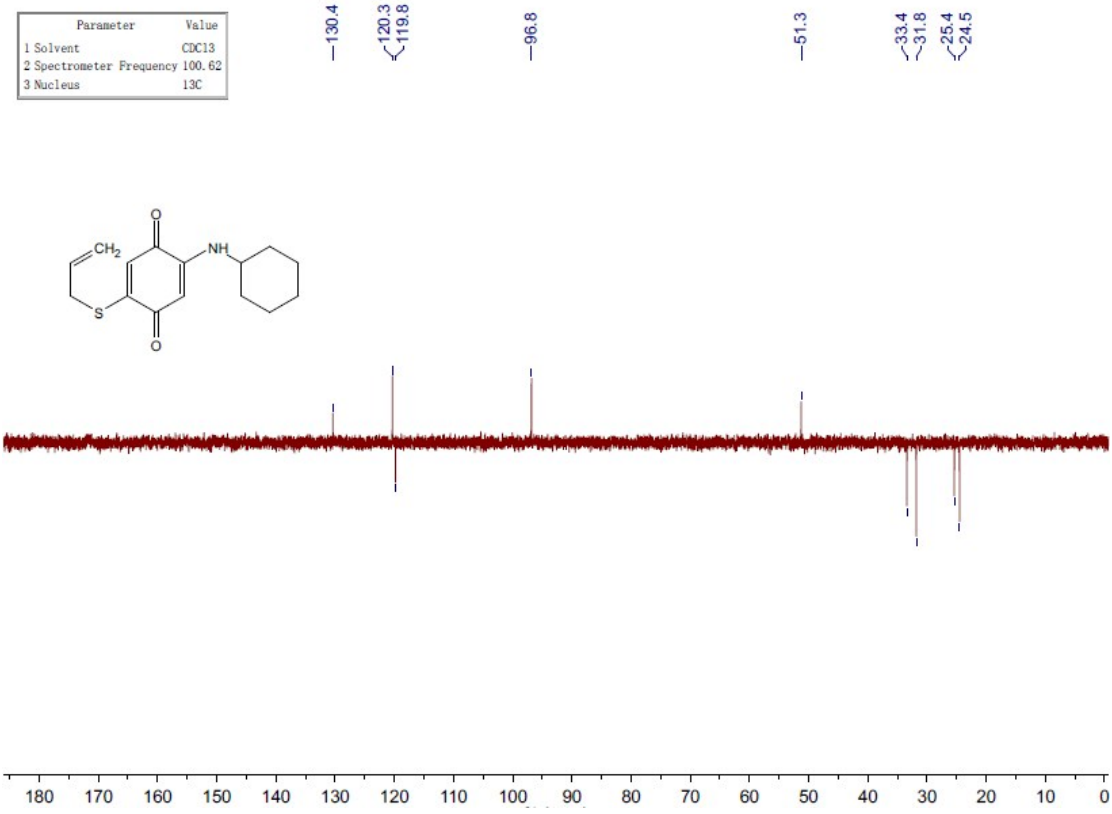
^{1}H NMR (400 MHz, $CDCl_3$) of **4aa**



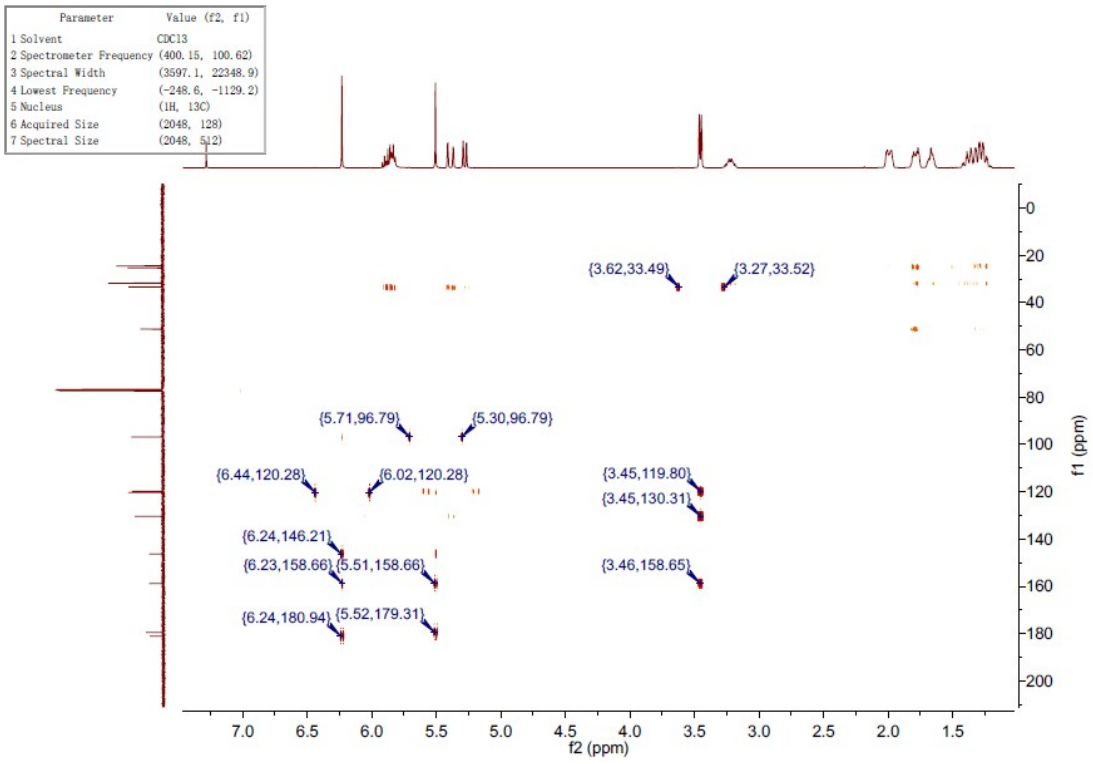
^{13}C NMR (101 MHz, $CDCl_3$) of **4aa**



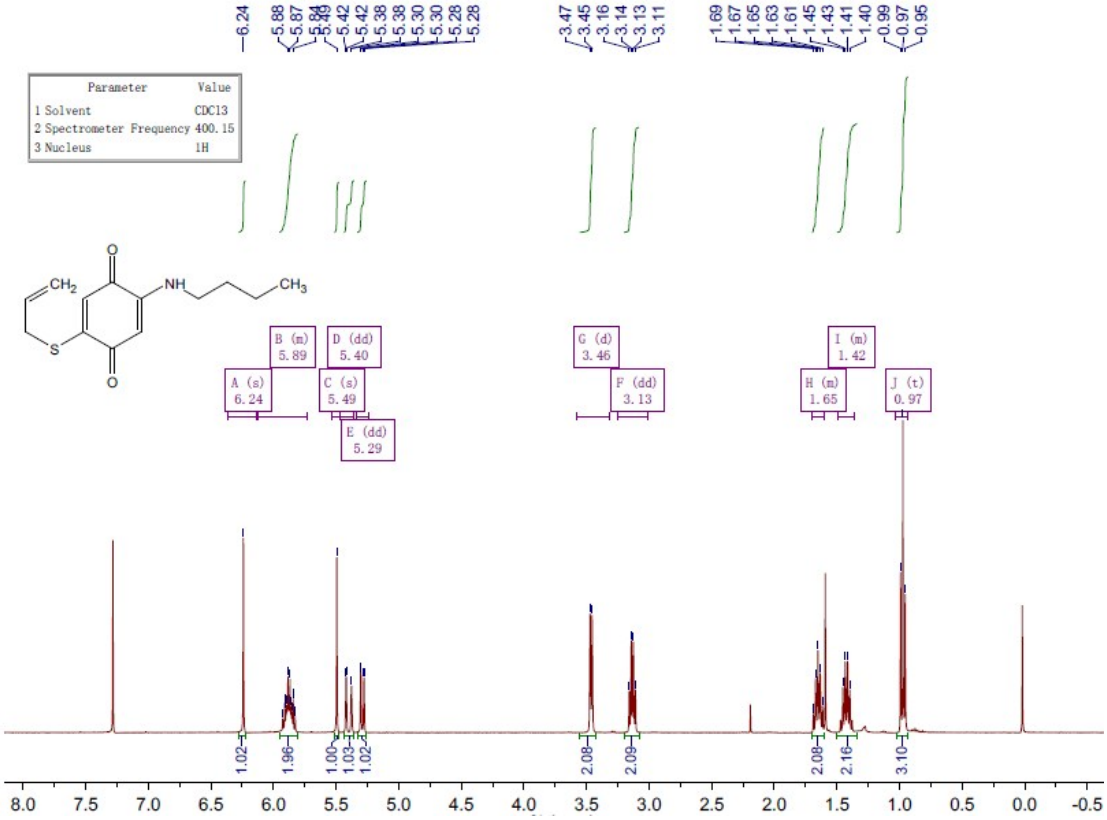
DEPT 135 of **4aa**



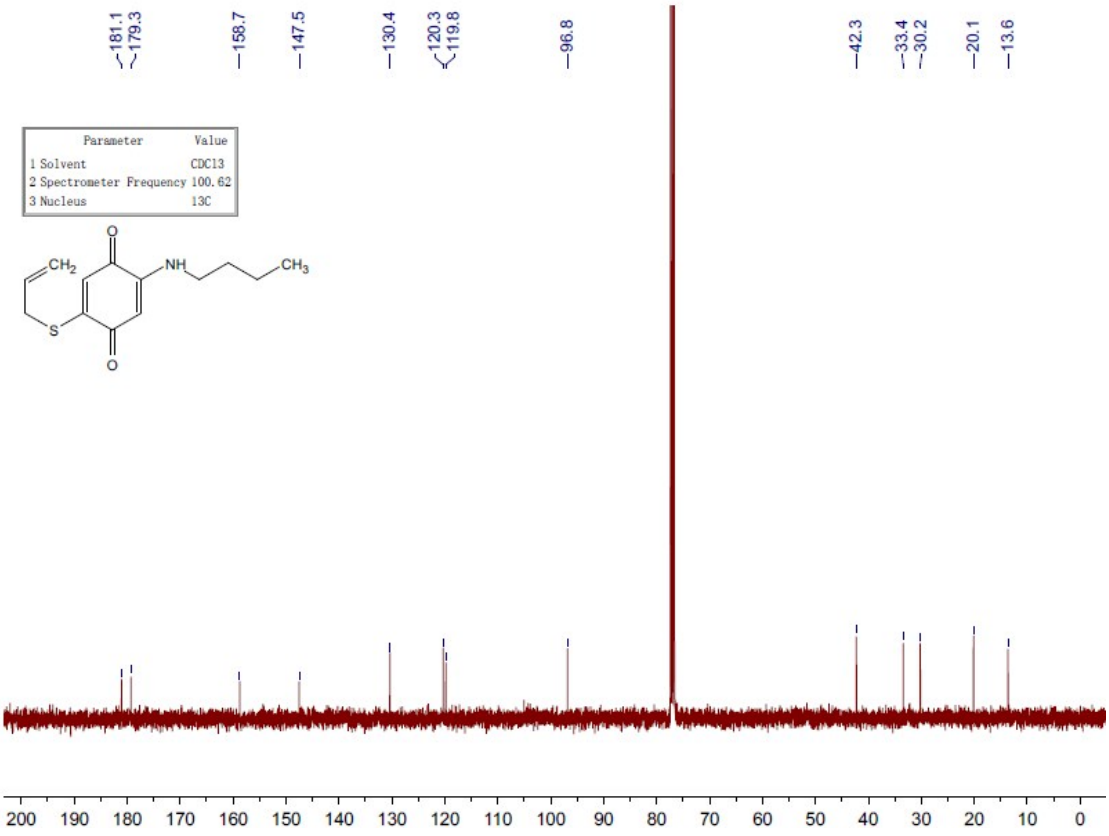
HMBC of **4aa**



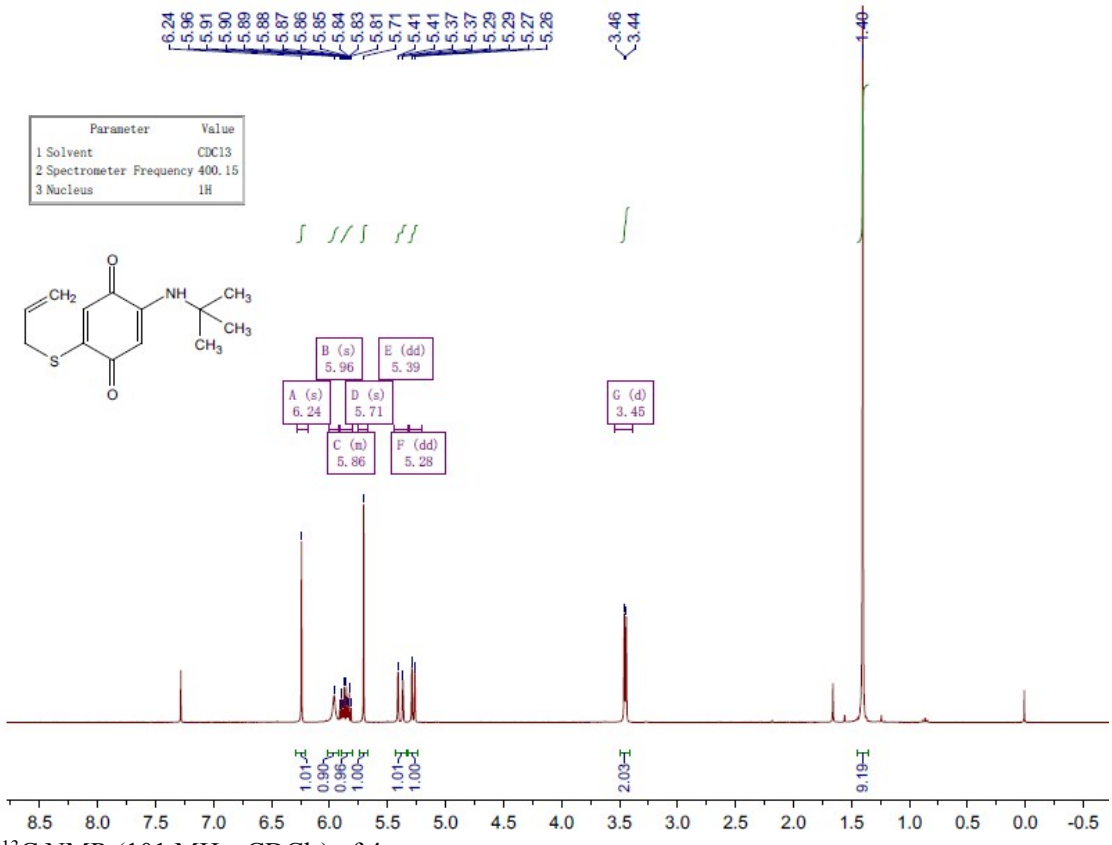
^{1}H NMR (400 MHz, $CDCl_3$) of **4ab**



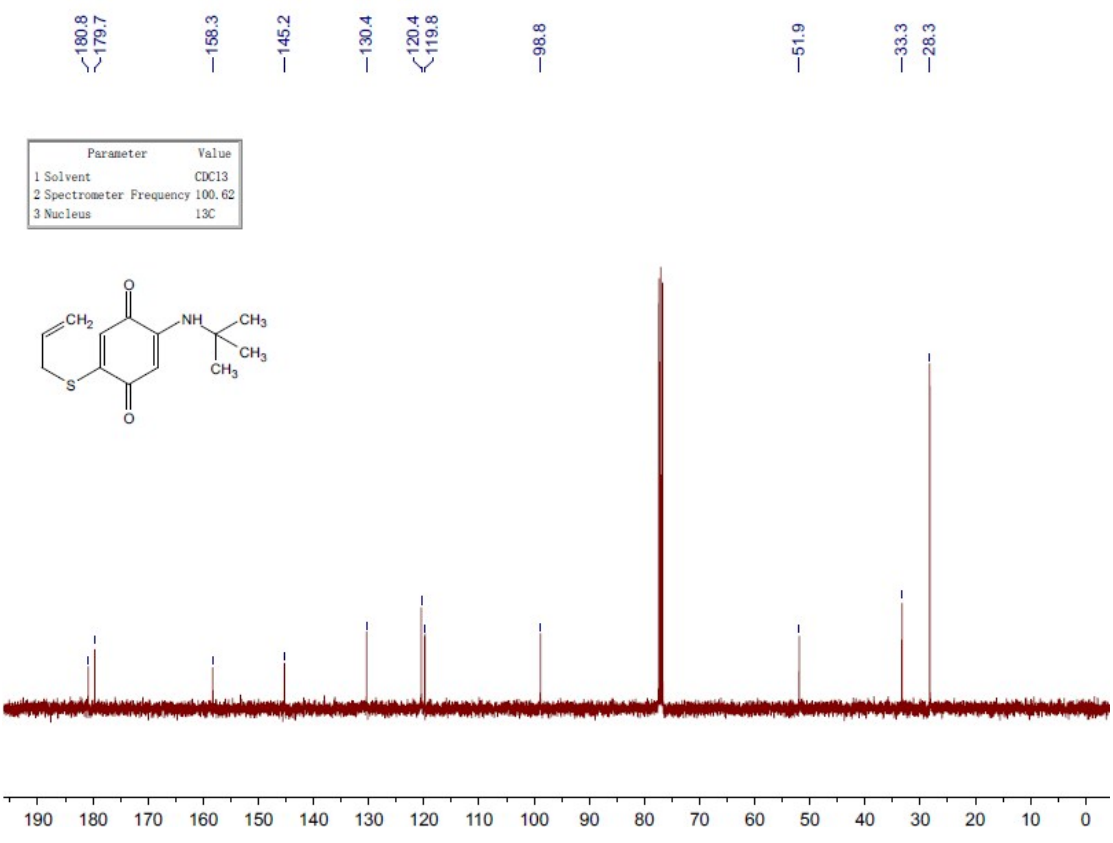
^{13}C NMR (101 MHz, $CDCl_3$) of **4ab**



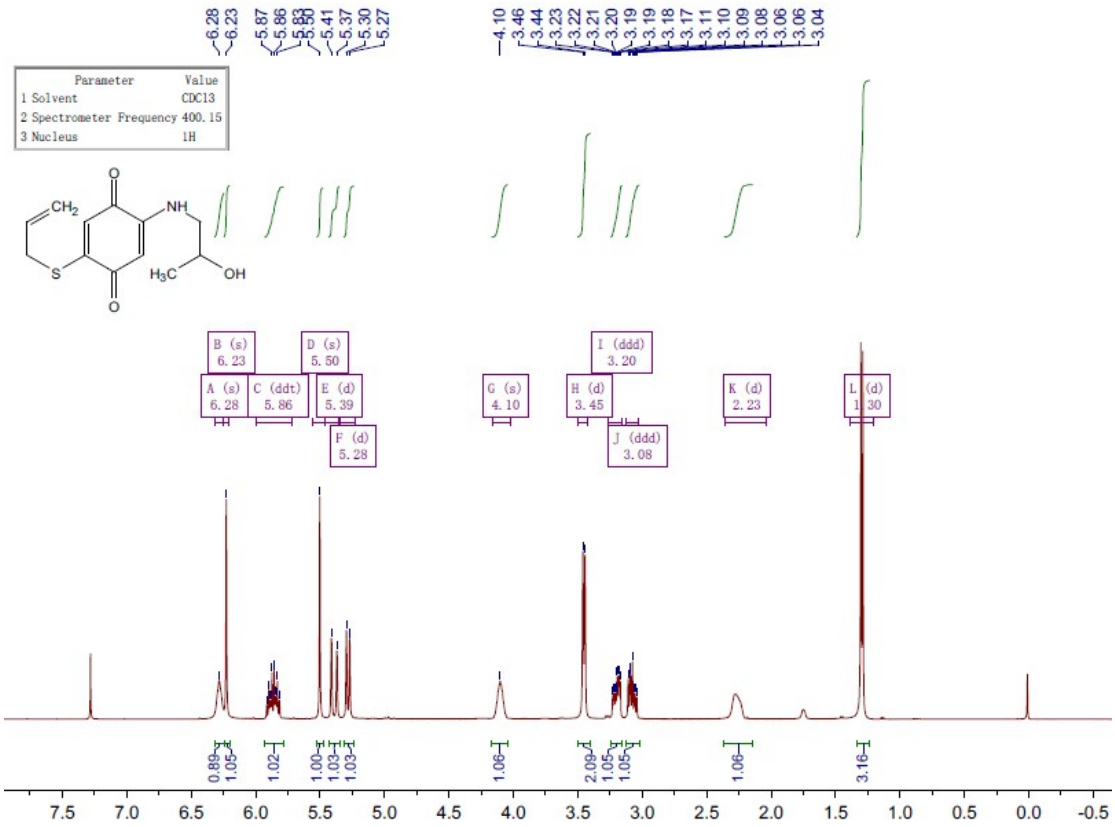
^{1}H NMR (400 MHz, $CDCl_3$) of **4ac**



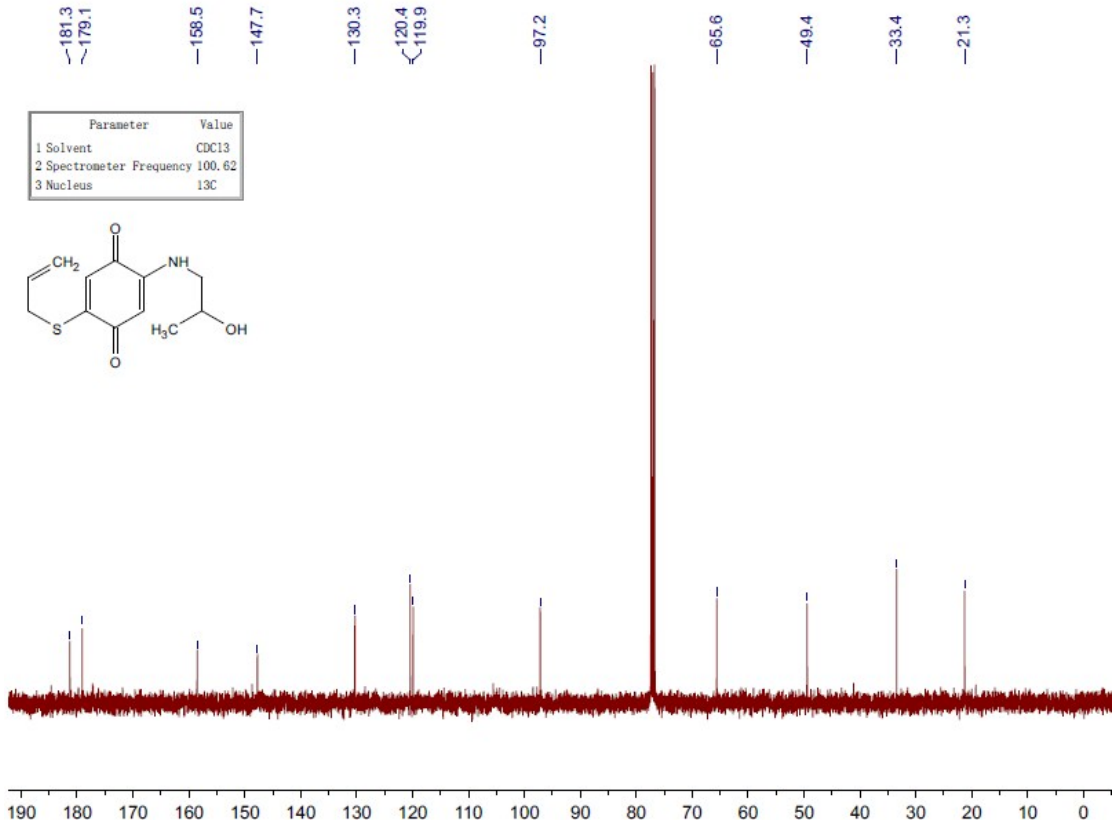
^{13}C NMR (101 MHz, $CDCl_3$) of **4ac**



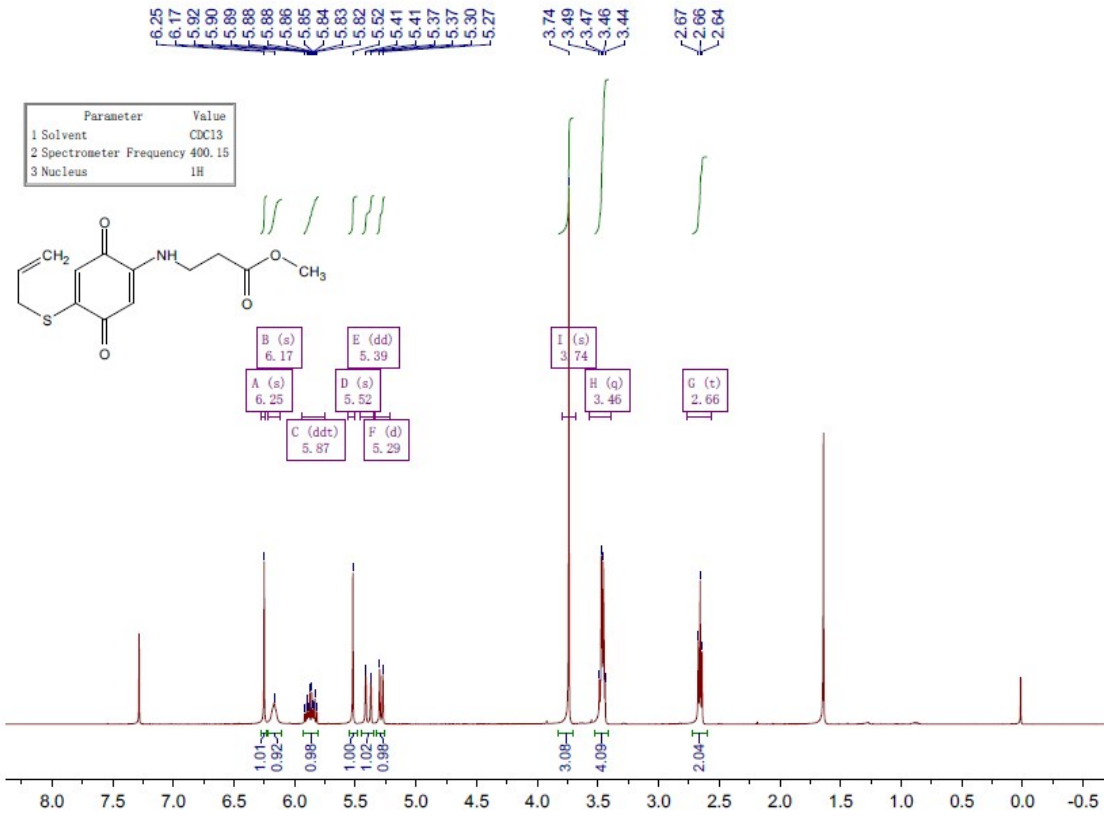
^{1}H NMR (400 MHz, $CDCl_3$) of **4ad**



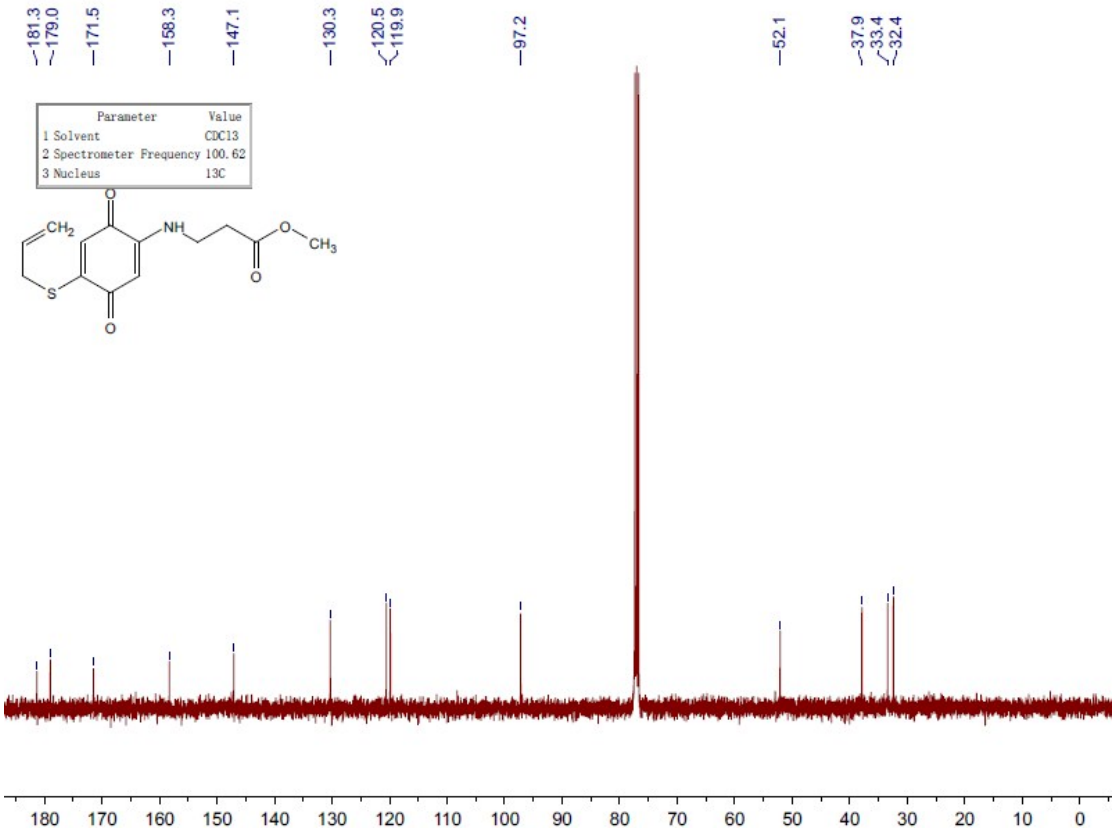
^{13}C NMR (101 MHz, $CDCl_3$) of **4ad**



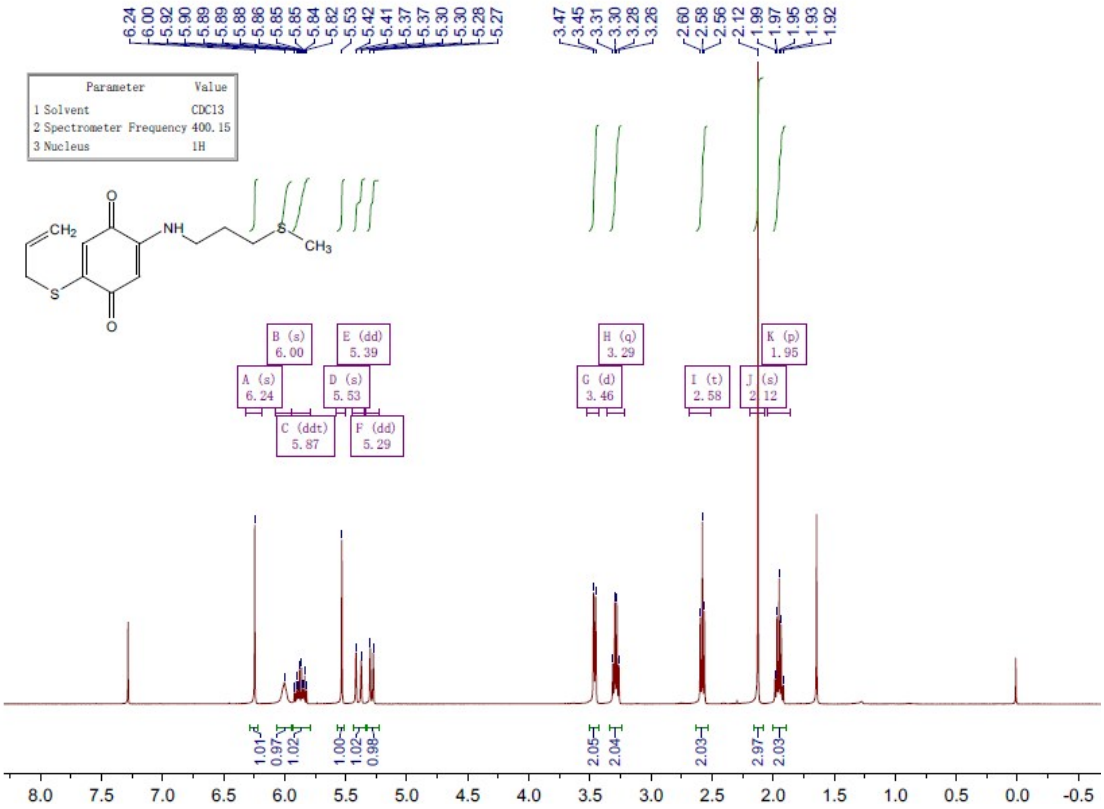
^{1}H NMR (400 MHz, $CDCl_3$) of **4ae**



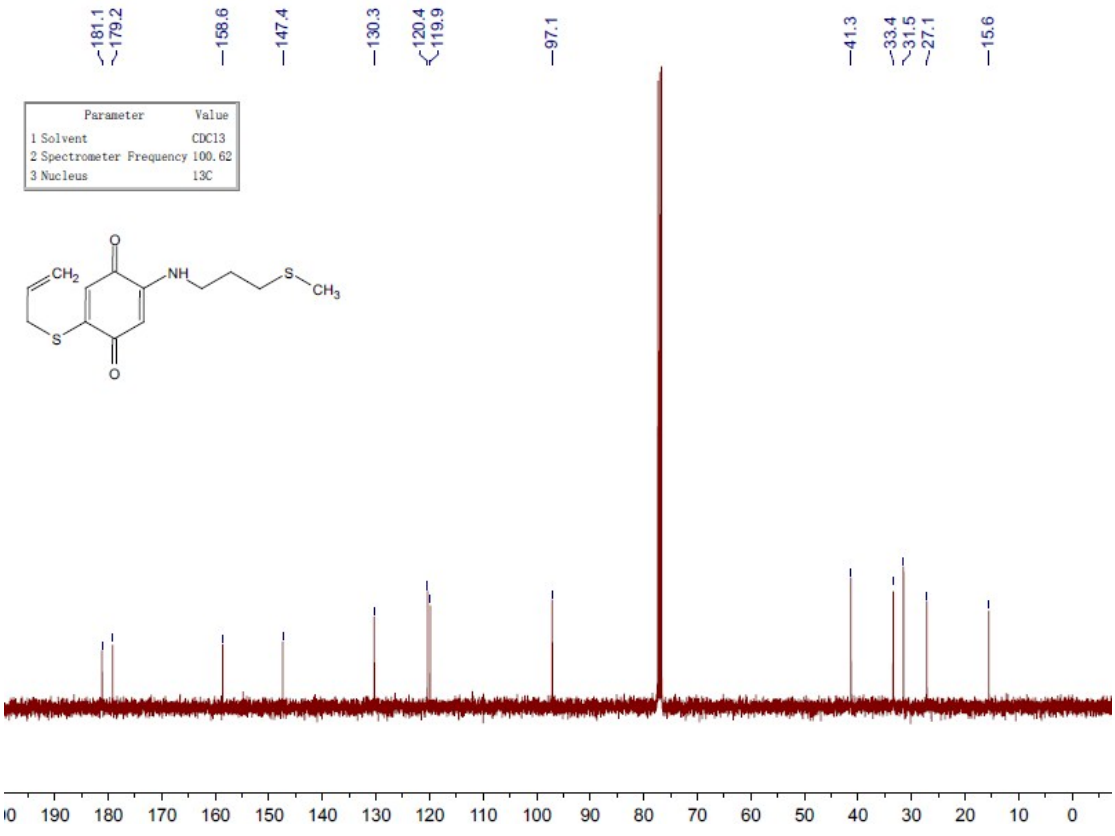
^{13}C NMR (101 MHz, $CDCl_3$) of **4ae**



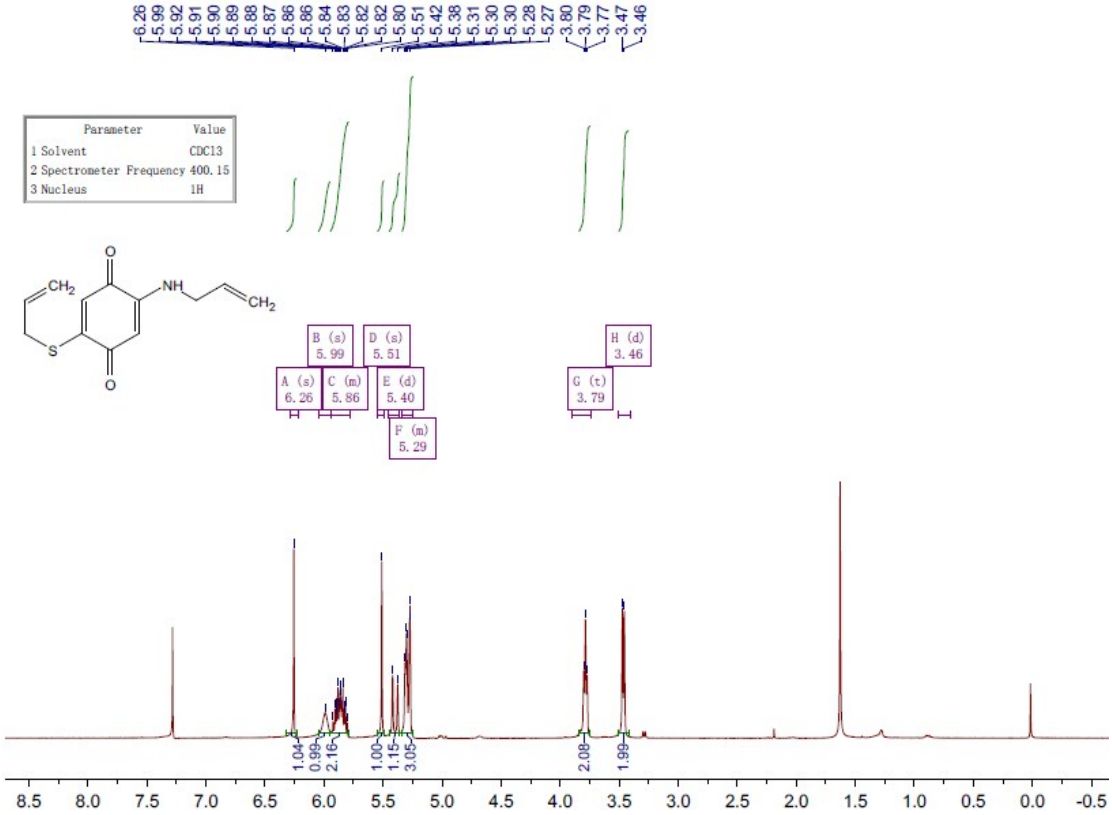
^{1}H NMR (400 MHz, $CDCl_3$) of **4af**



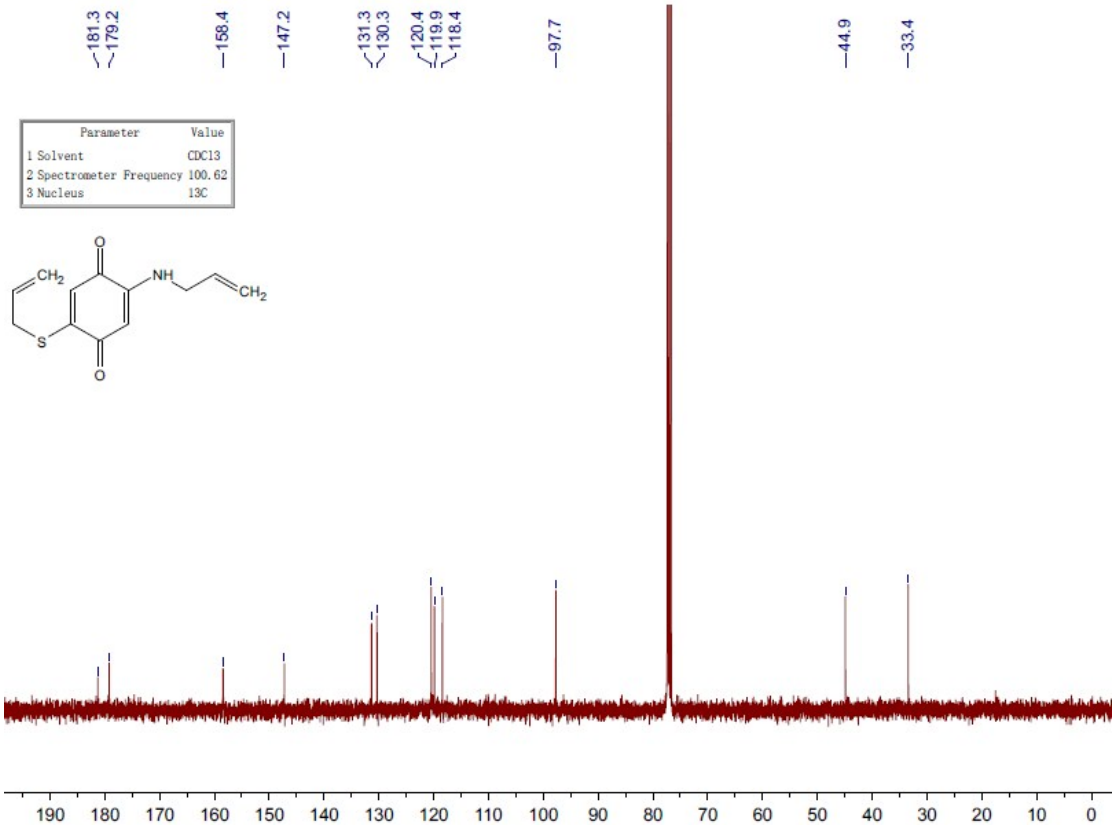
^{13}C NMR (101 MHz, $CDCl_3$) of **4af**



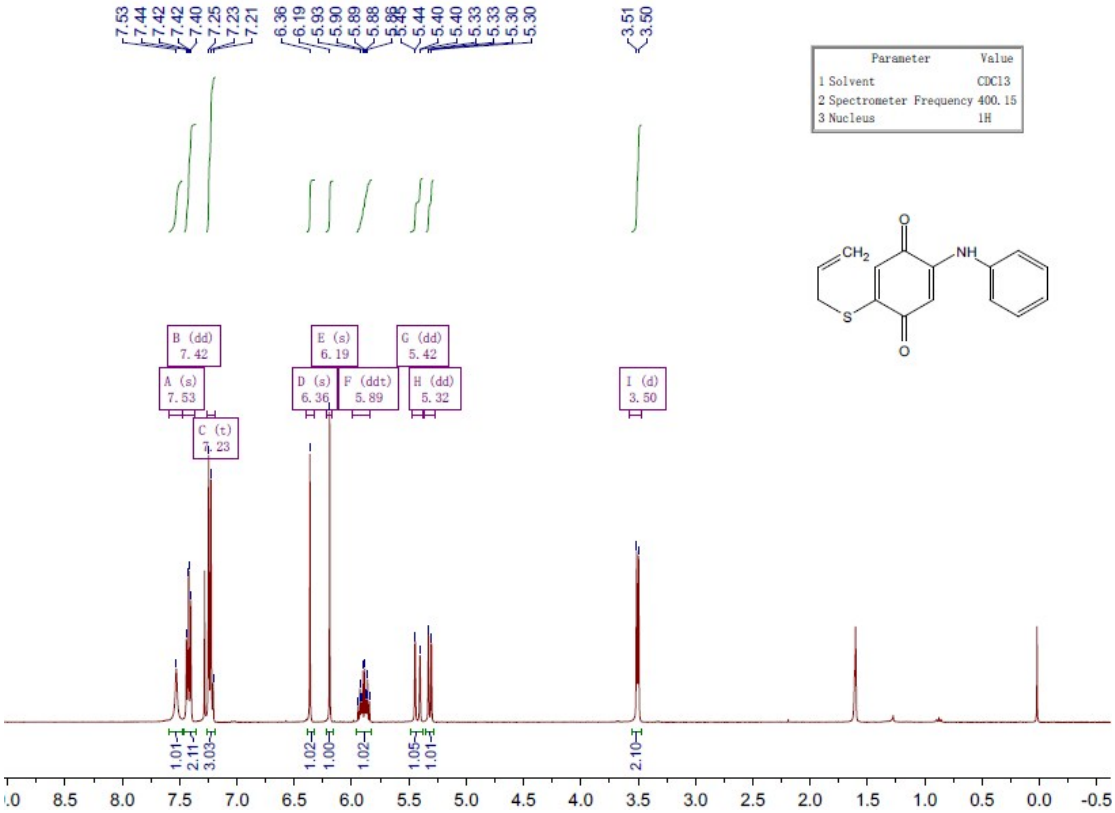
^{1}H NMR (400 MHz, $CDCl_3$) of **4ag**



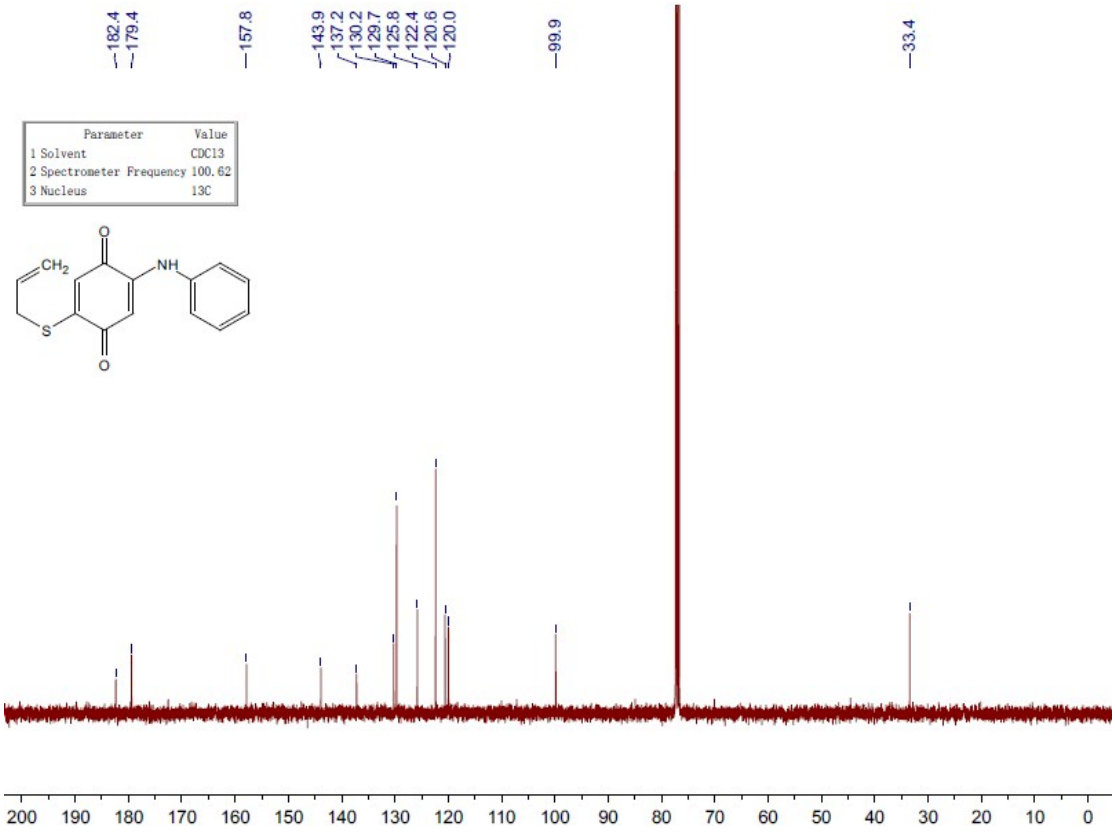
^{13}C NMR (101 MHz, $CDCl_3$) of **4ag**



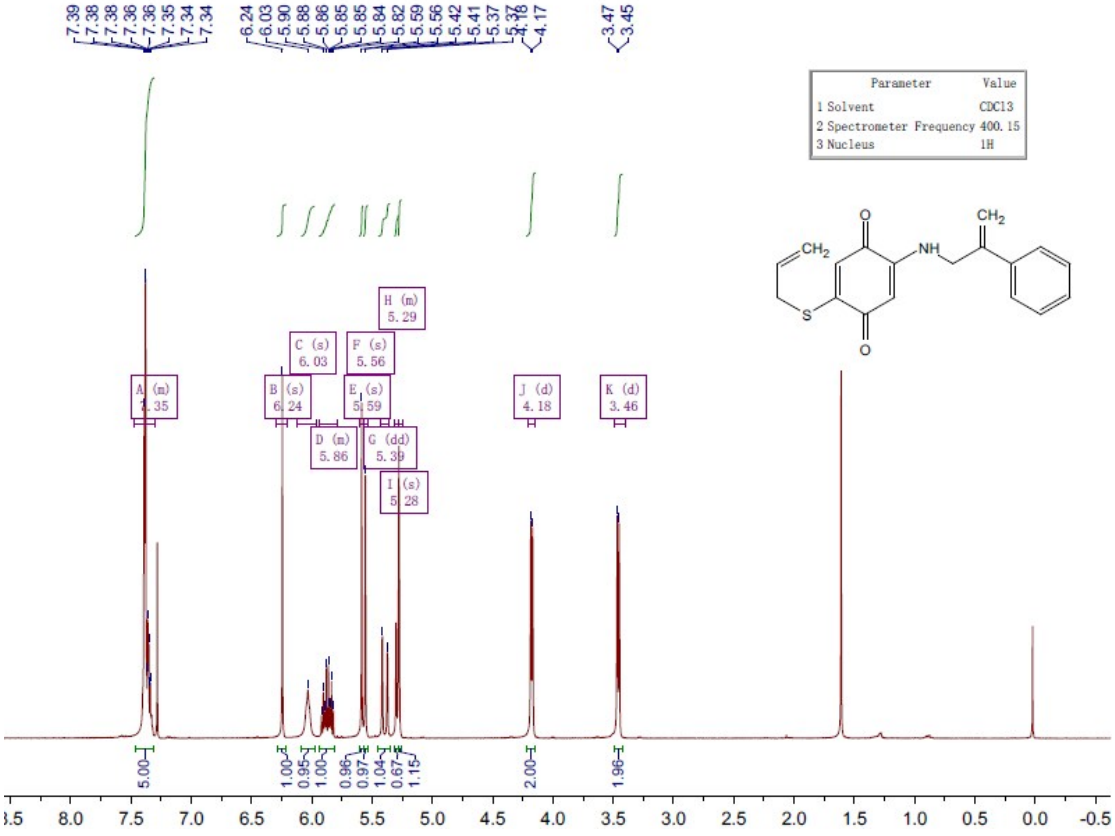
^{1}H NMR (400 MHz, $CDCl_3$) of **4ah**



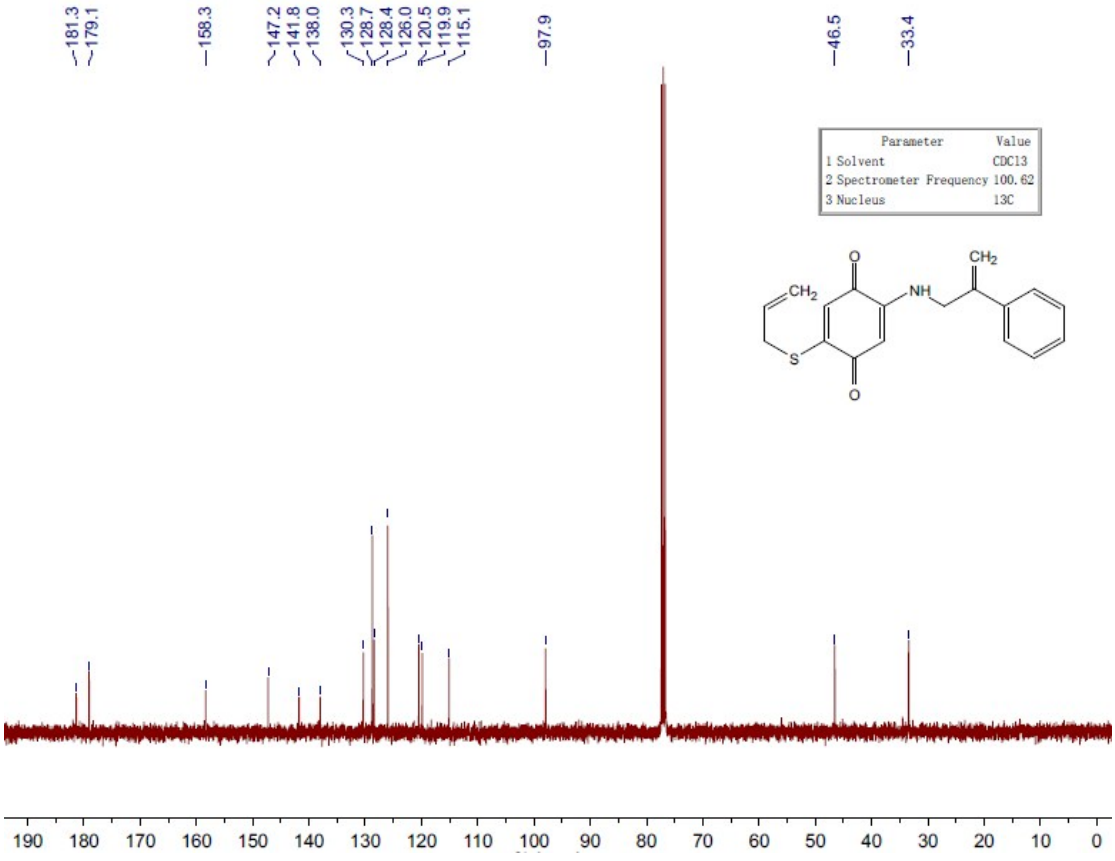
^{13}C NMR (101 MHz, $CDCl_3$) of **4ah**



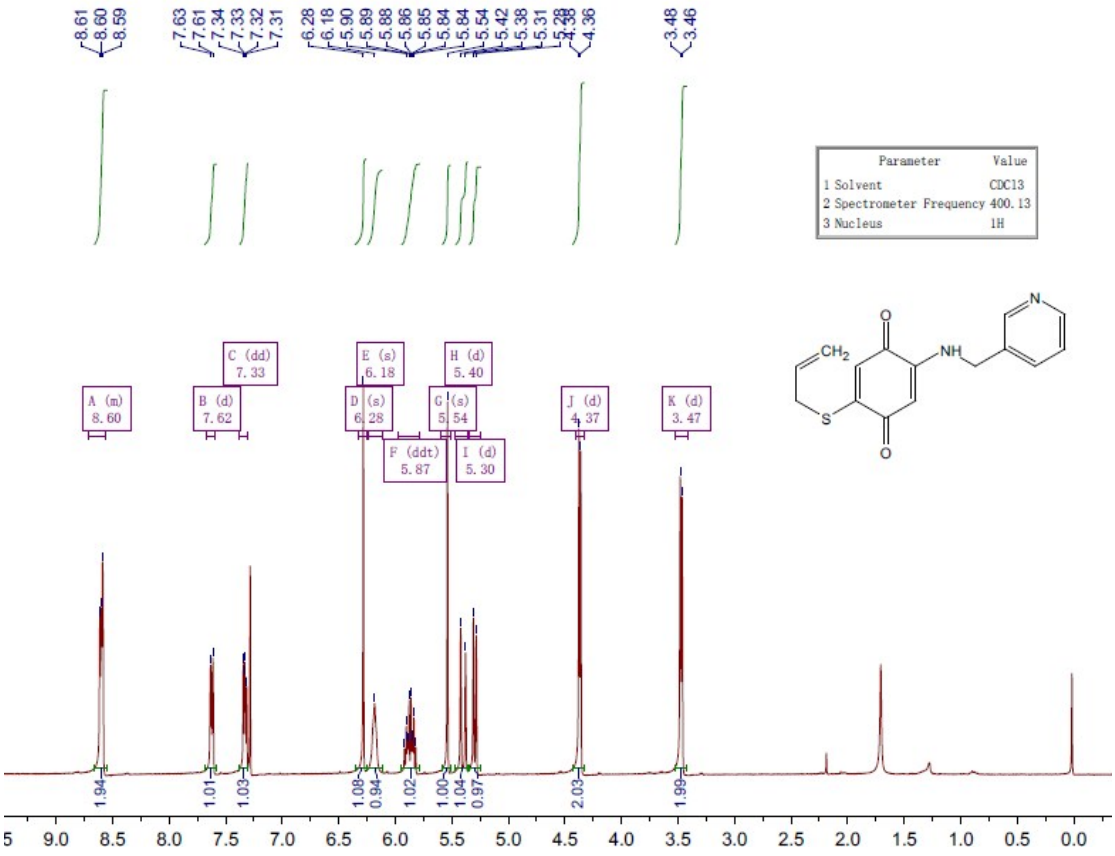
^{1}H NMR (400 MHz, $CDCl_3$) of **4ai**



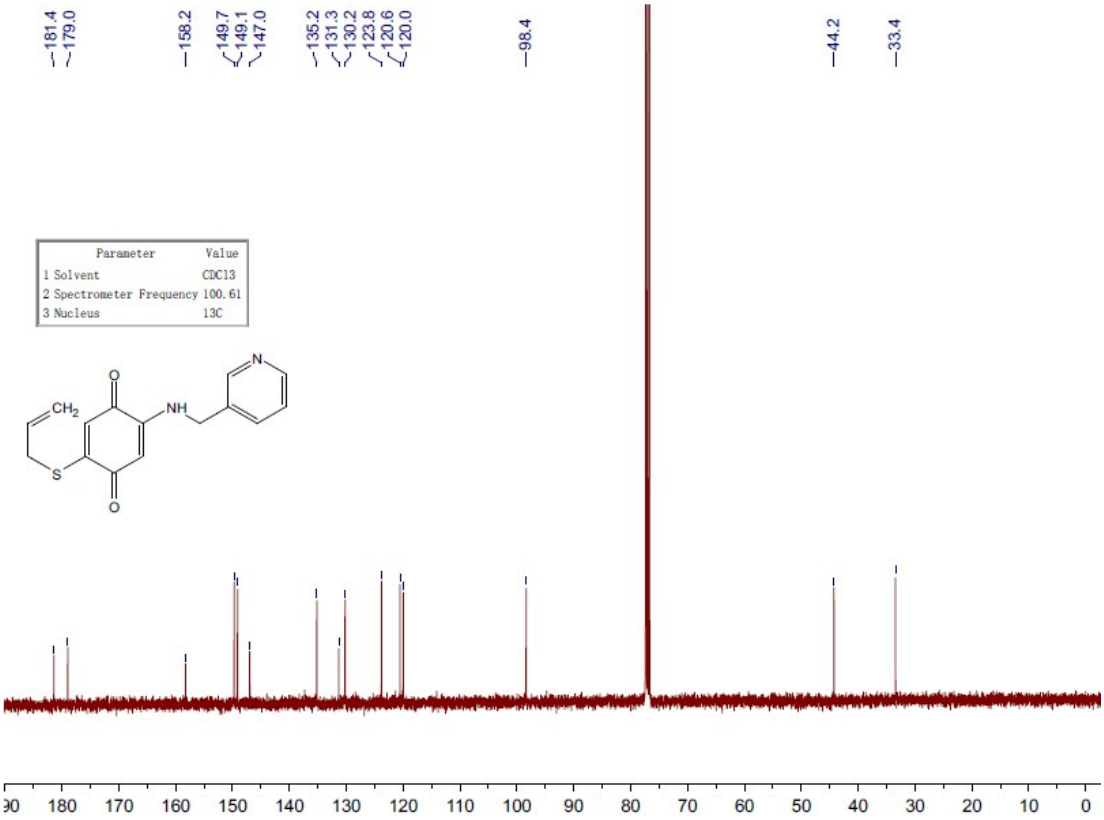
^{13}C NMR (101 MHz, $CDCl_3$) of **4ai**



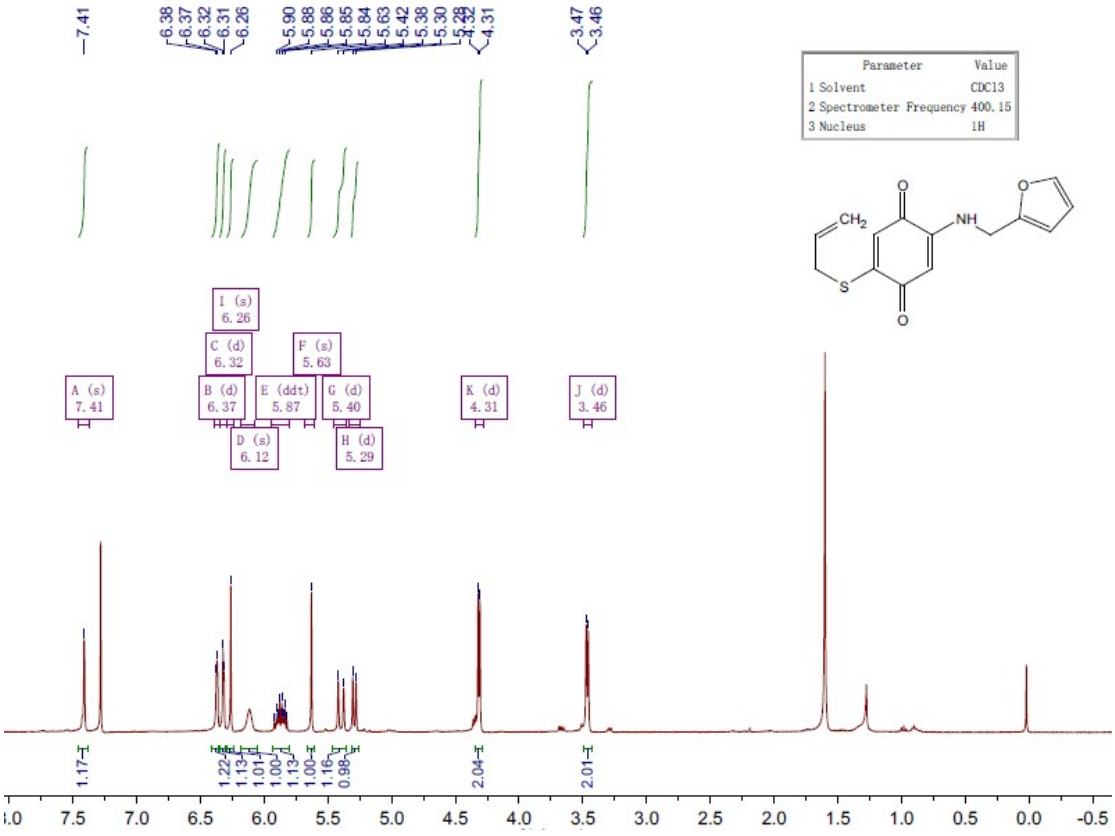
^{1}H NMR (400 MHz, $CDCl_3$) of **4aj**



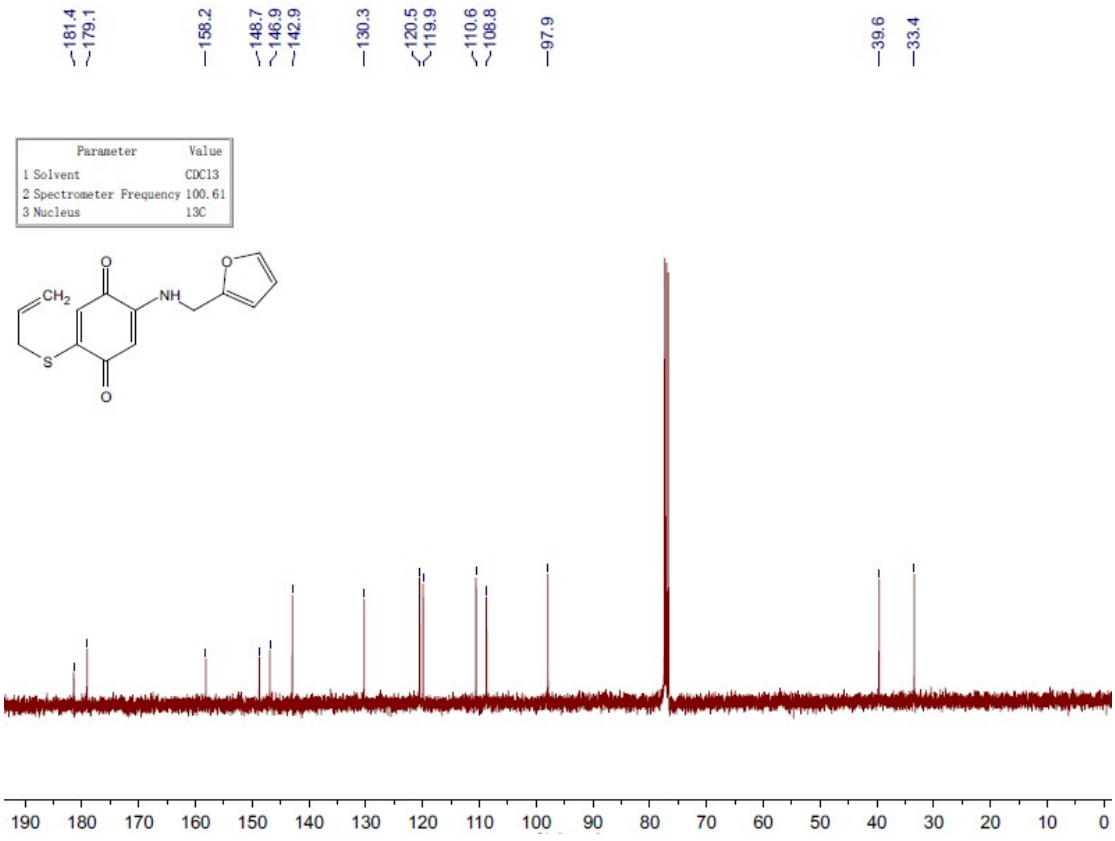
^{13}C NMR (101 MHz, $CDCl_3$) of **4aj**



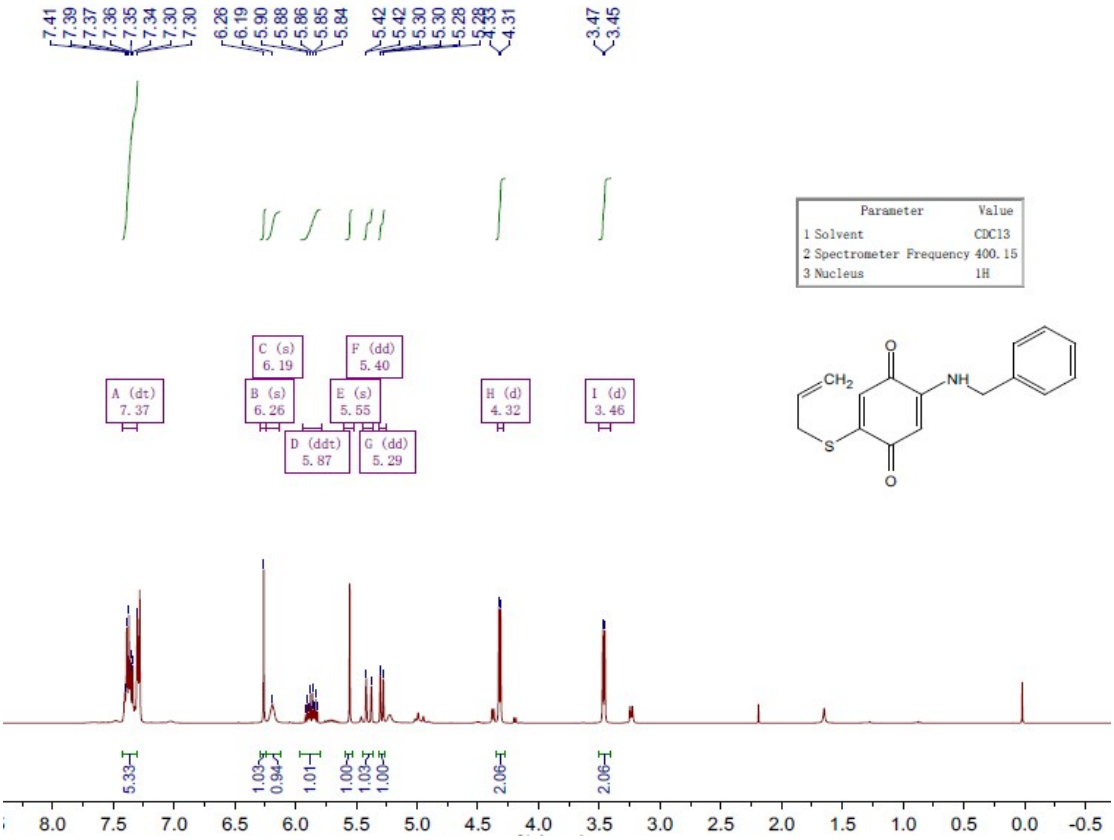
^{1}H NMR (400 MHz, $CDCl_3$) of **4ak**



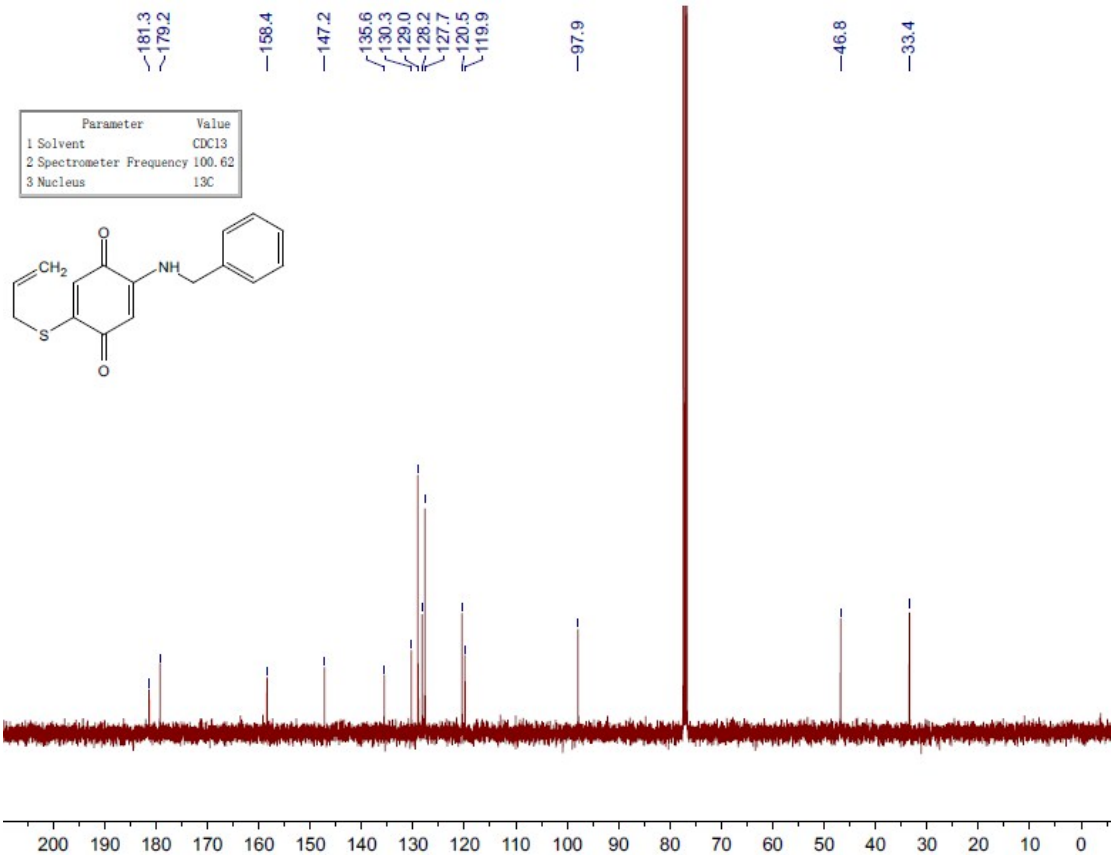
^{13}C NMR (101 MHz, $CDCl_3$) of **4ak**



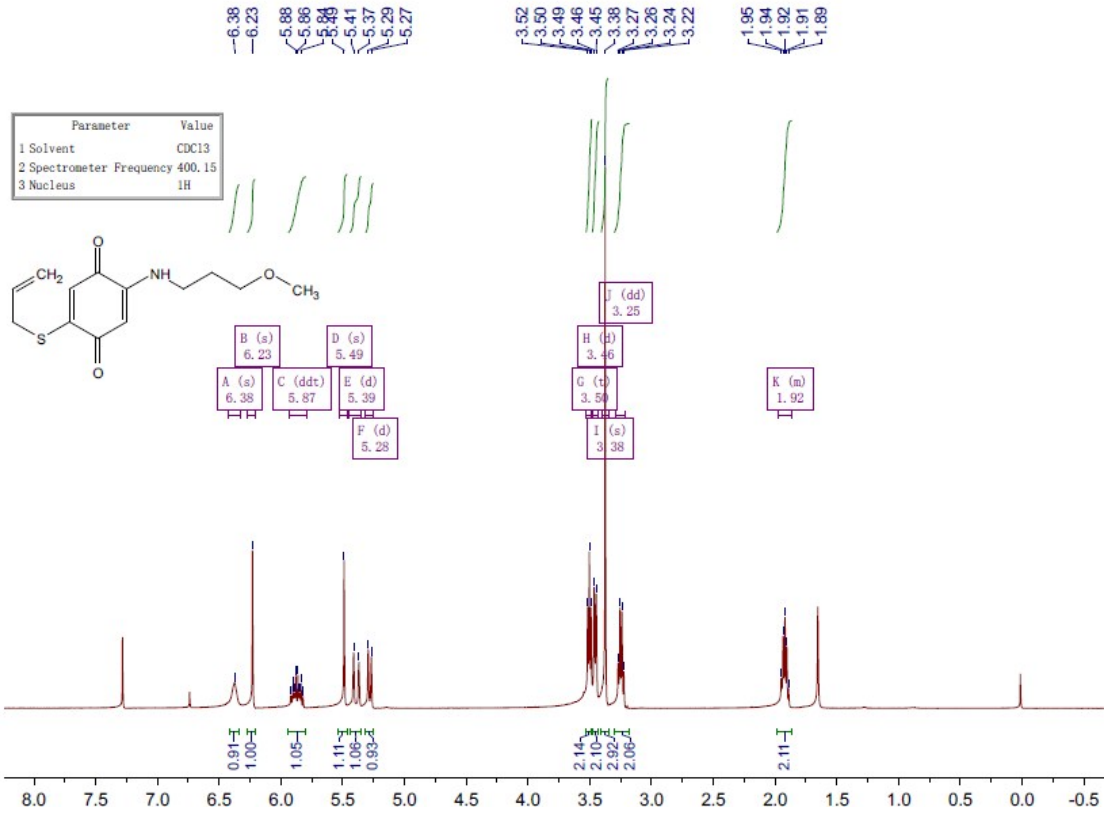
^{1}H NMR (400 MHz, $CDCl_3$) of **4al**



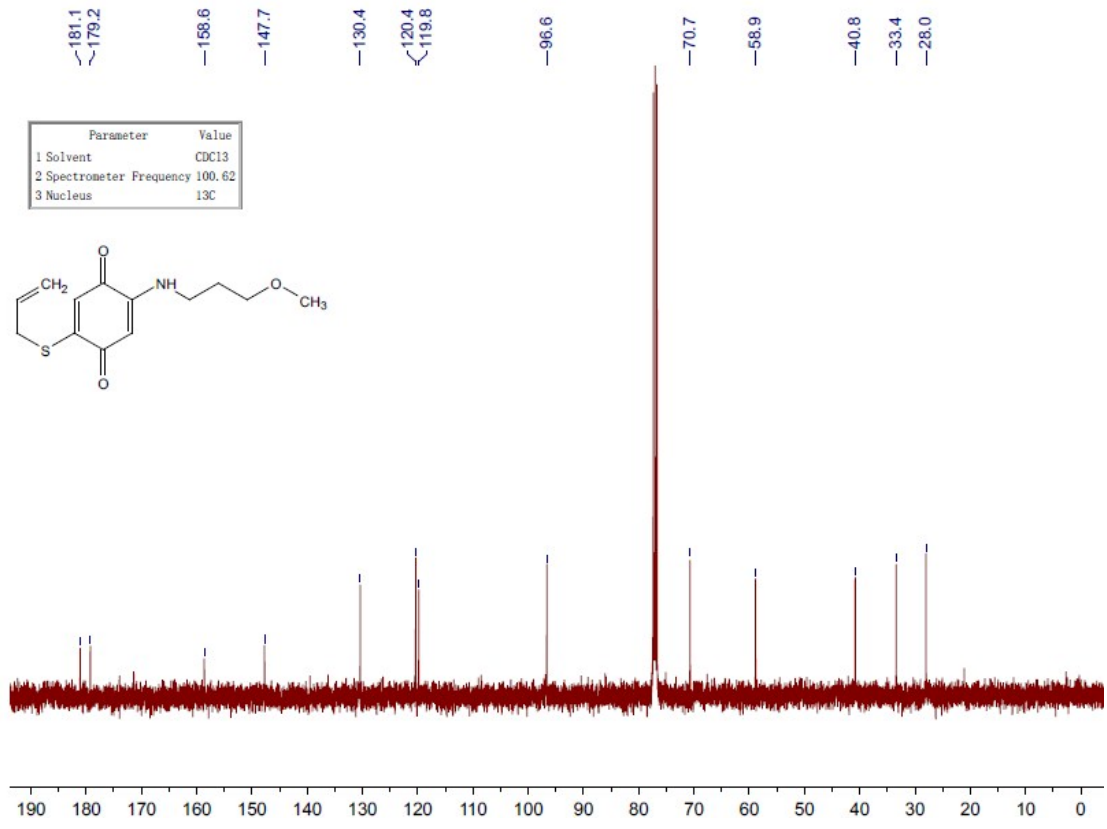
^{13}C NMR (101 MHz, $CDCl_3$) of **4al**



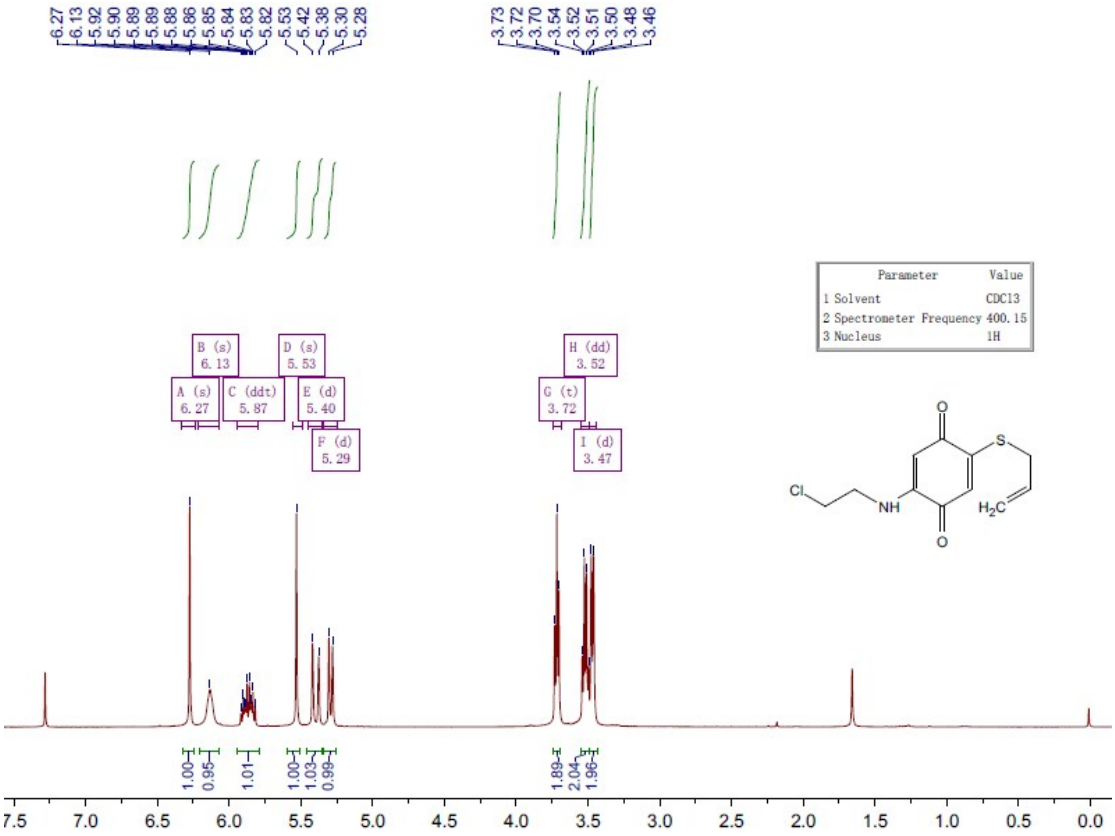
^{1}H NMR (400 MHz, $CDCl_3$) of **4am**



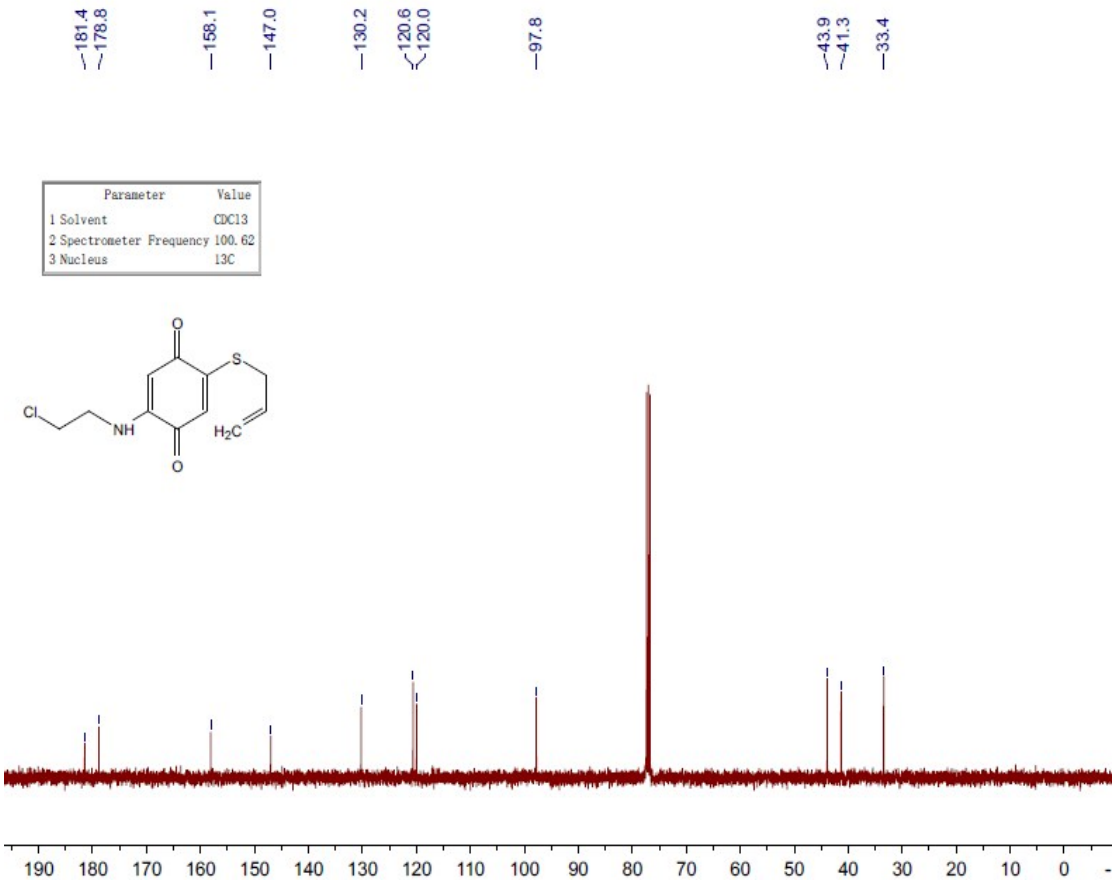
^{13}C NMR (101 MHz, $CDCl_3$) of **4am**



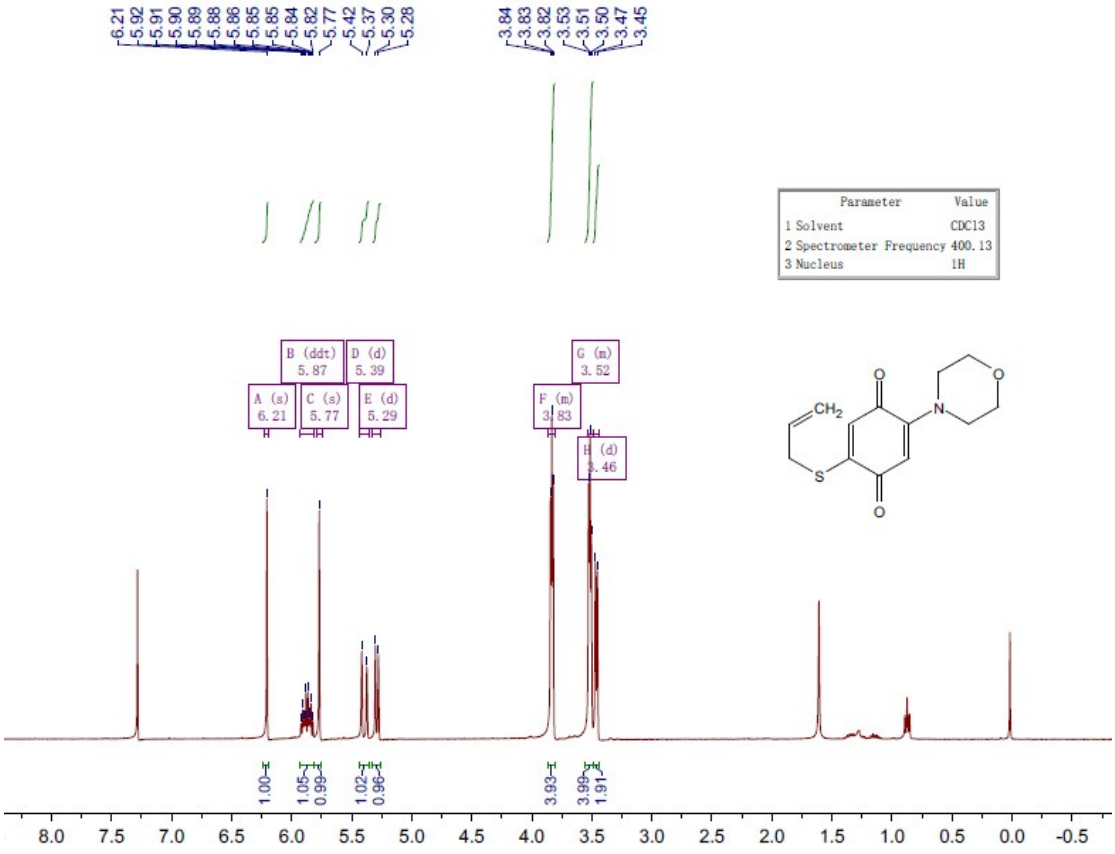
^{1}H NMR (400 MHz, $CDCl_3$) of **4an**



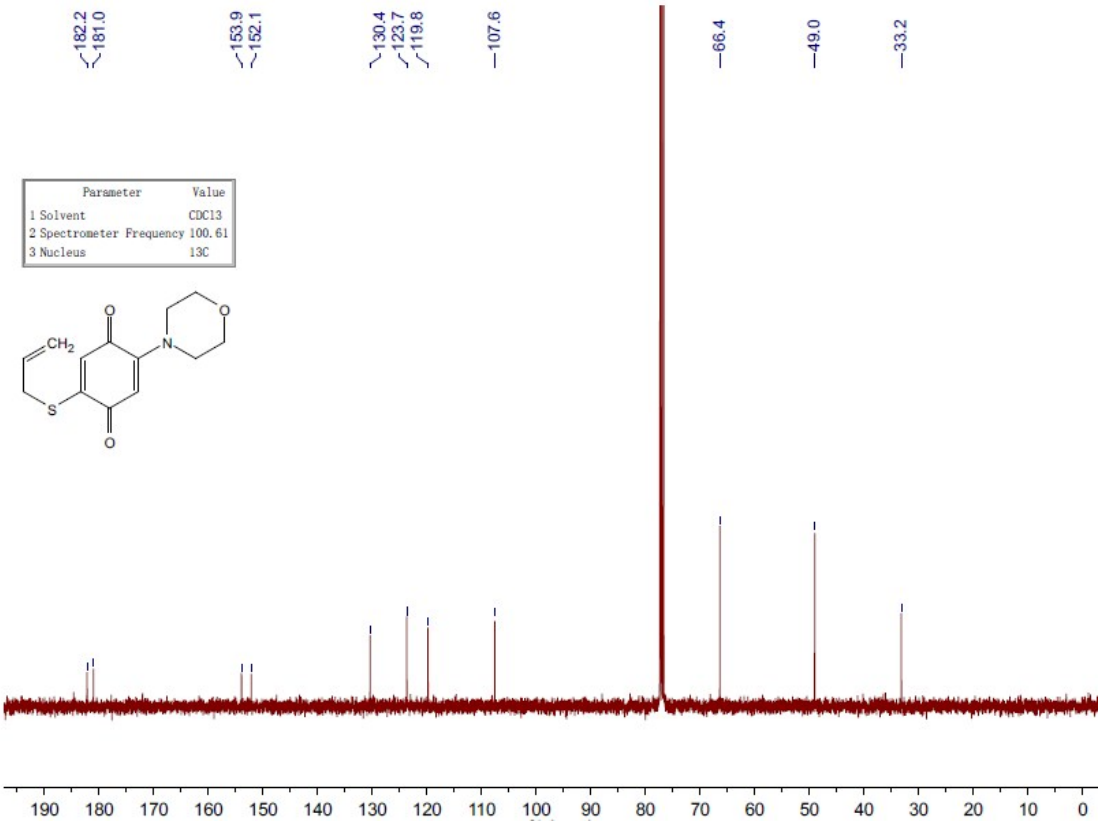
^{13}C NMR (101 MHz, $CDCl_3$) of **4an**



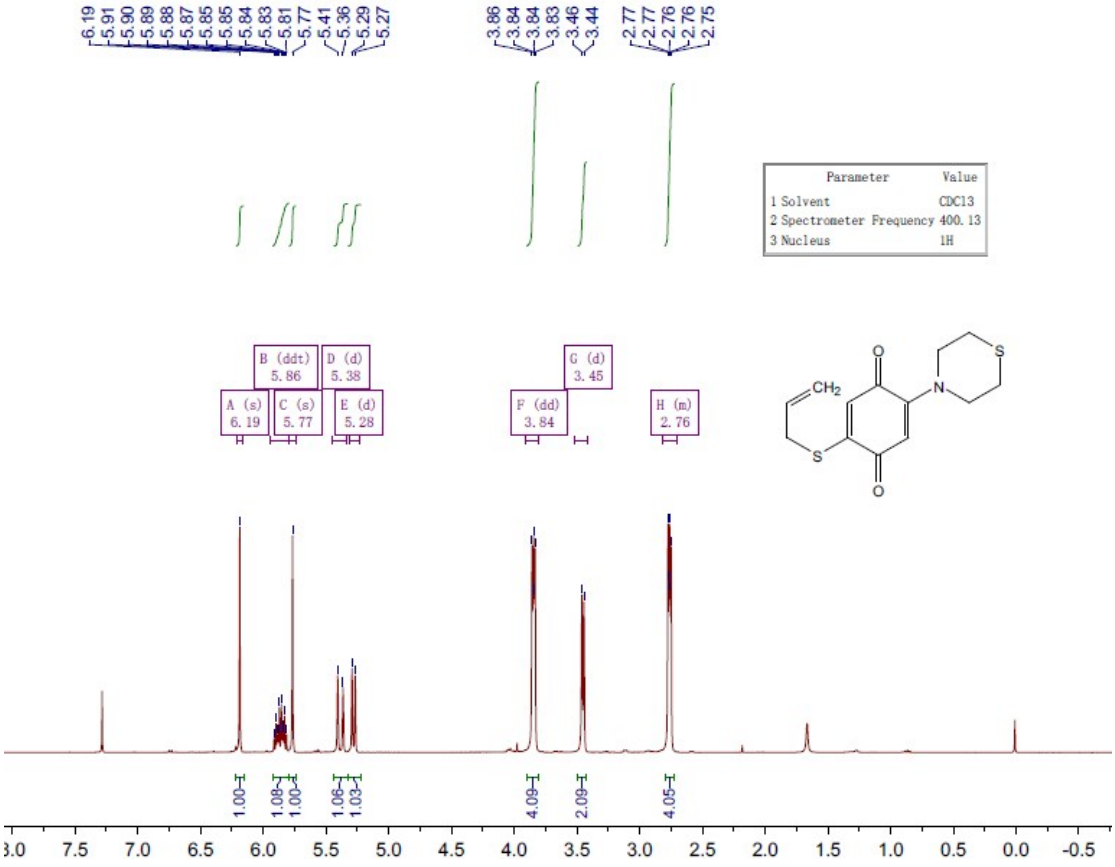
^{1}H NMR (400 MHz, $CDCl_3$) of **4ao**



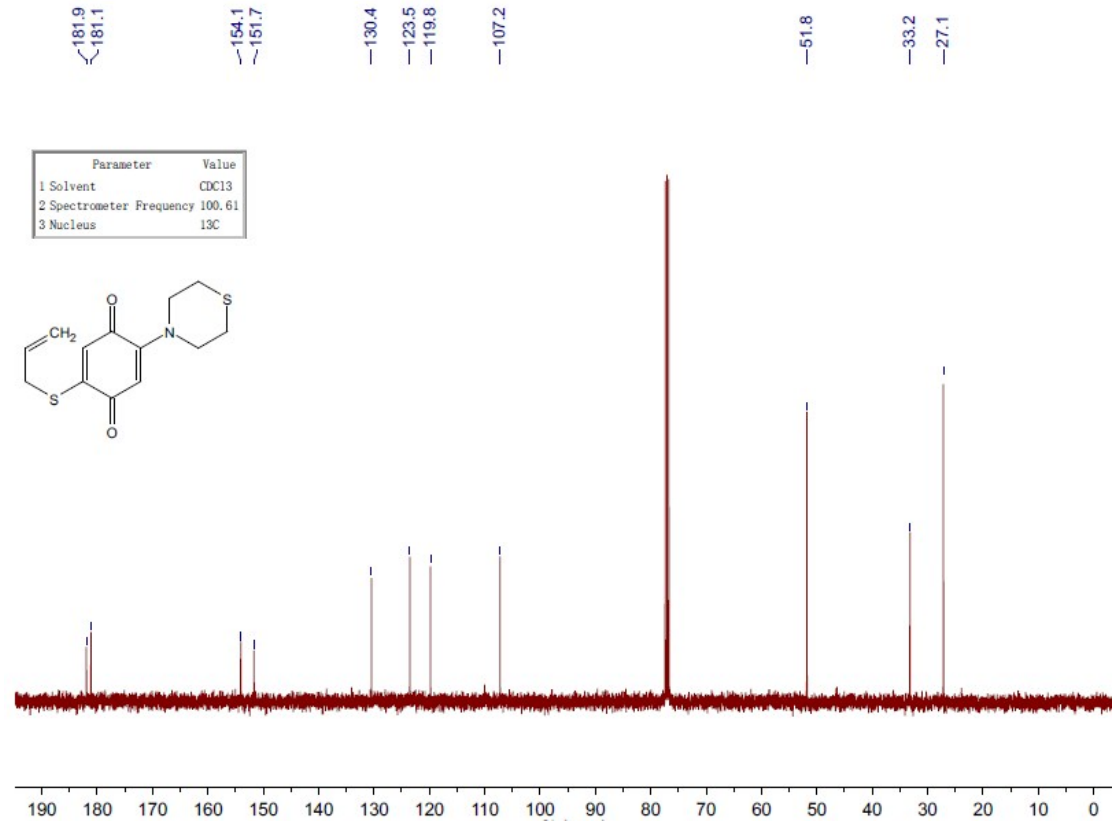
^{13}C NMR (101 MHz, $CDCl_3$) of **4ao**



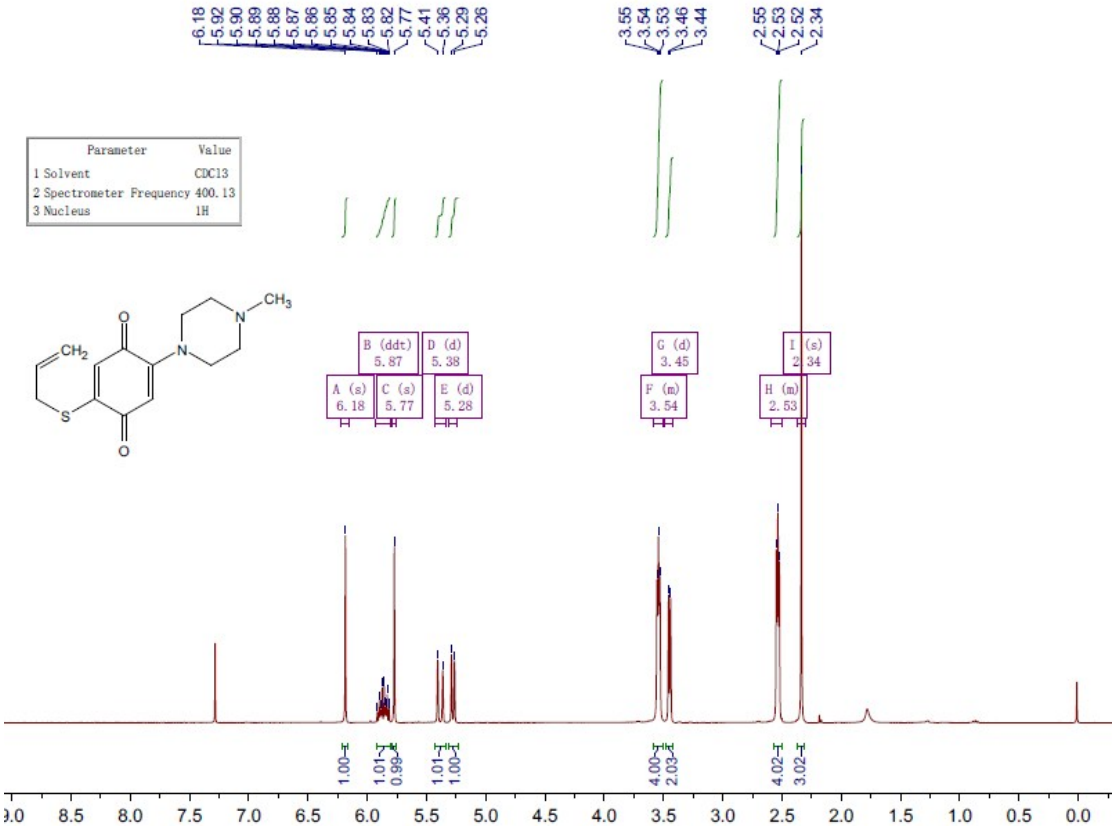
^{1}H NMR (400 MHz, $CDCl_3$) of **4ap**



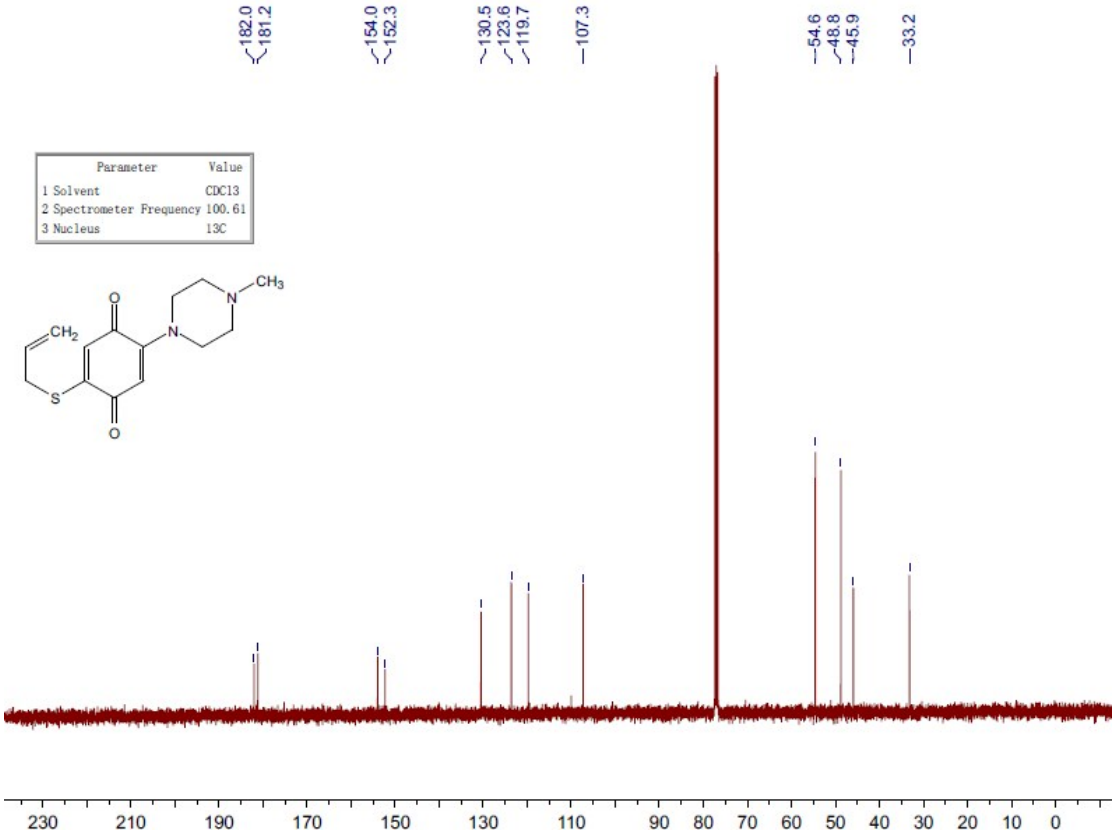
^{13}C NMR (101 MHz, $CDCl_3$) of **4ap**



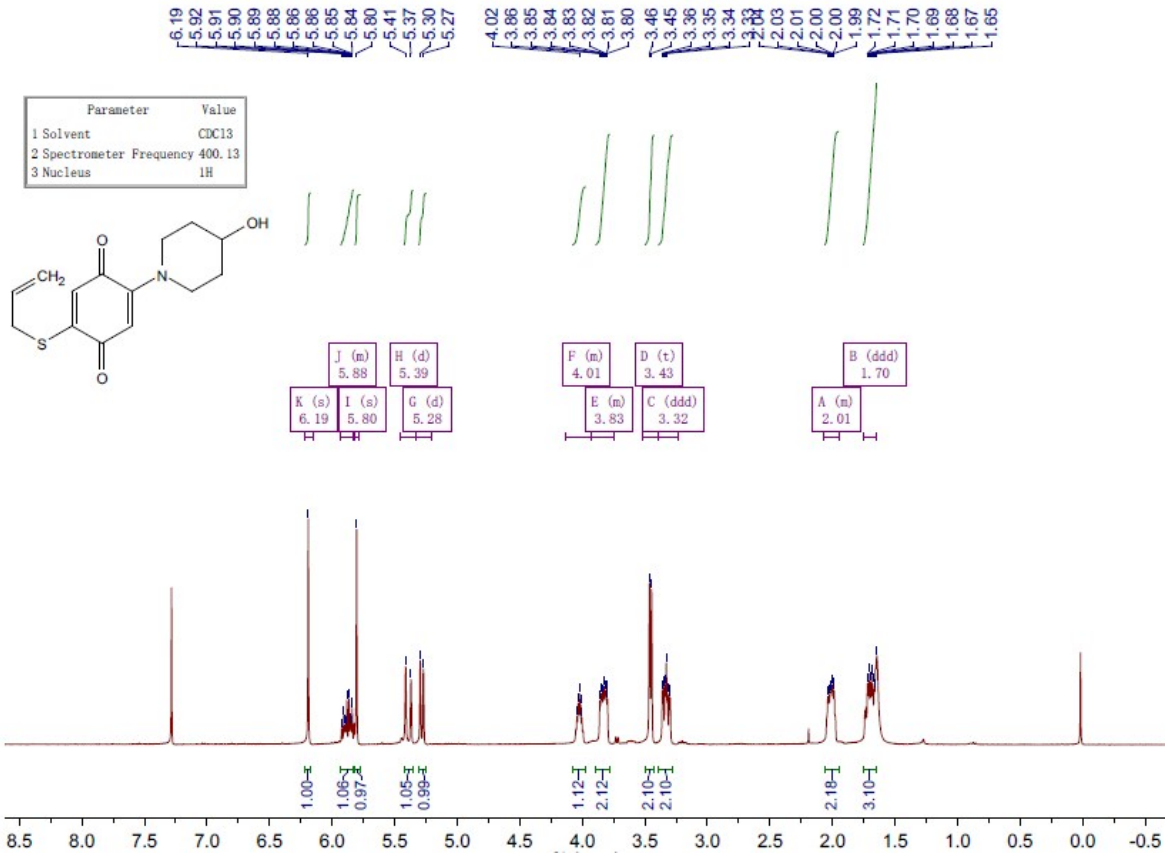
^{1}H NMR (400 MHz, $CDCl_3$) of **4aq**



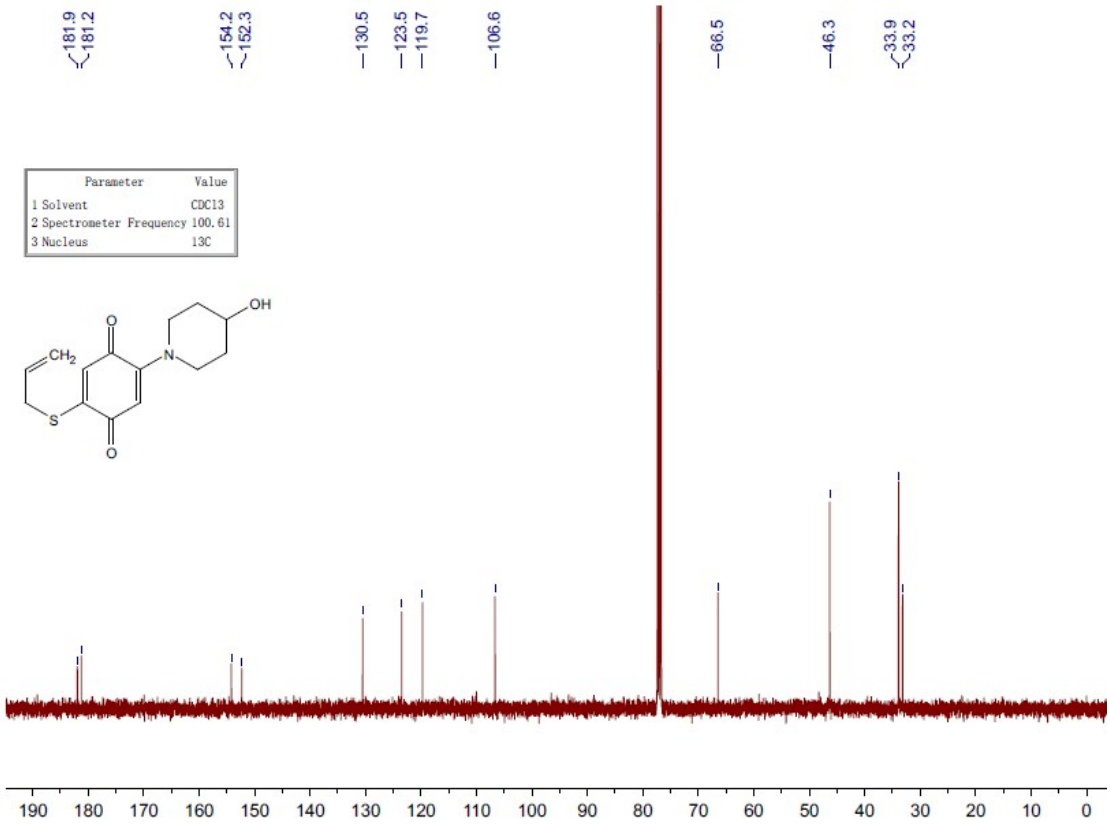
^{13}C NMR (101 MHz, $CDCl_3$) of **4aq**



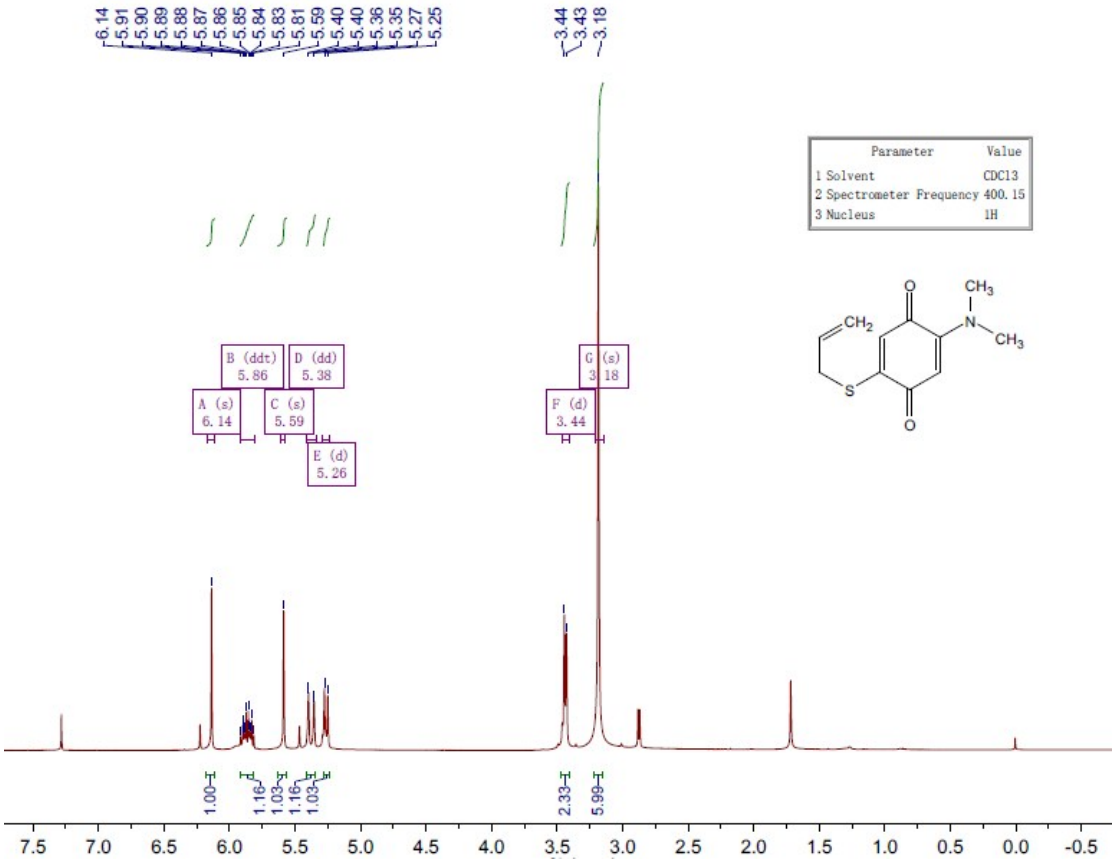
^{1}H NMR (400 MHz, $CDCl_3$) of **4ar**



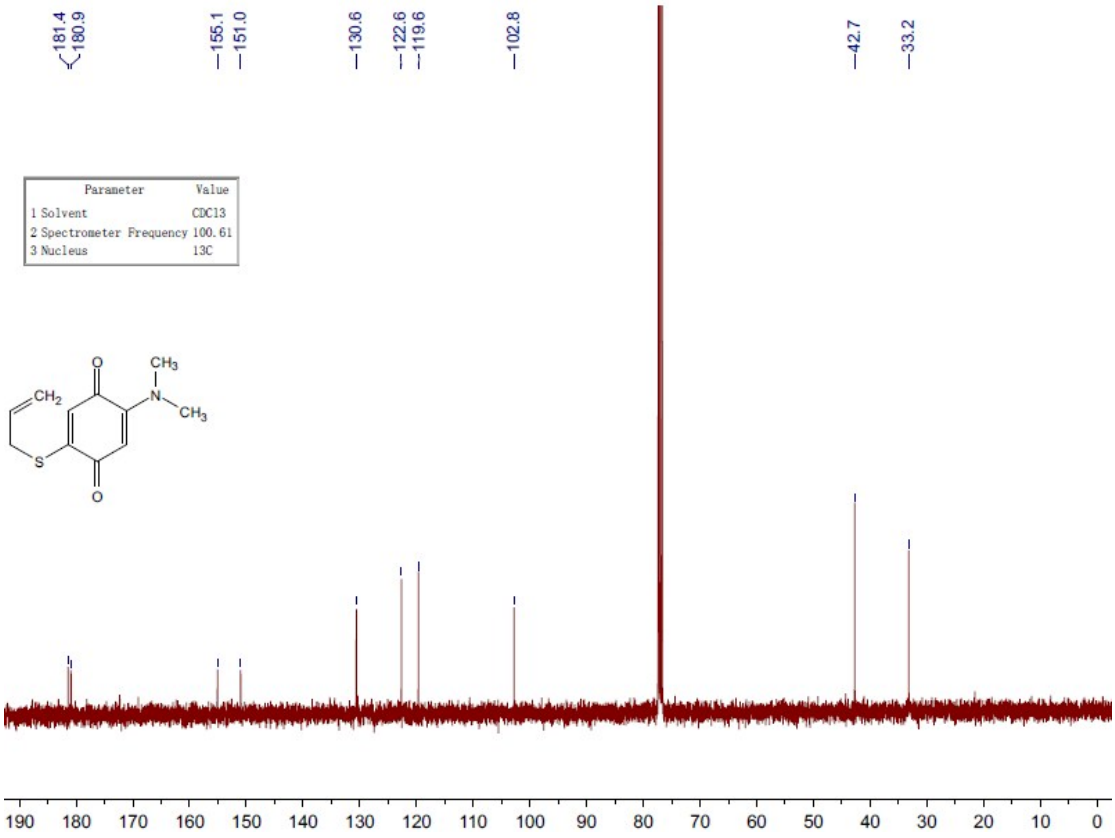
^{13}C NMR (101 MHz, $CDCl_3$) of **4ar**



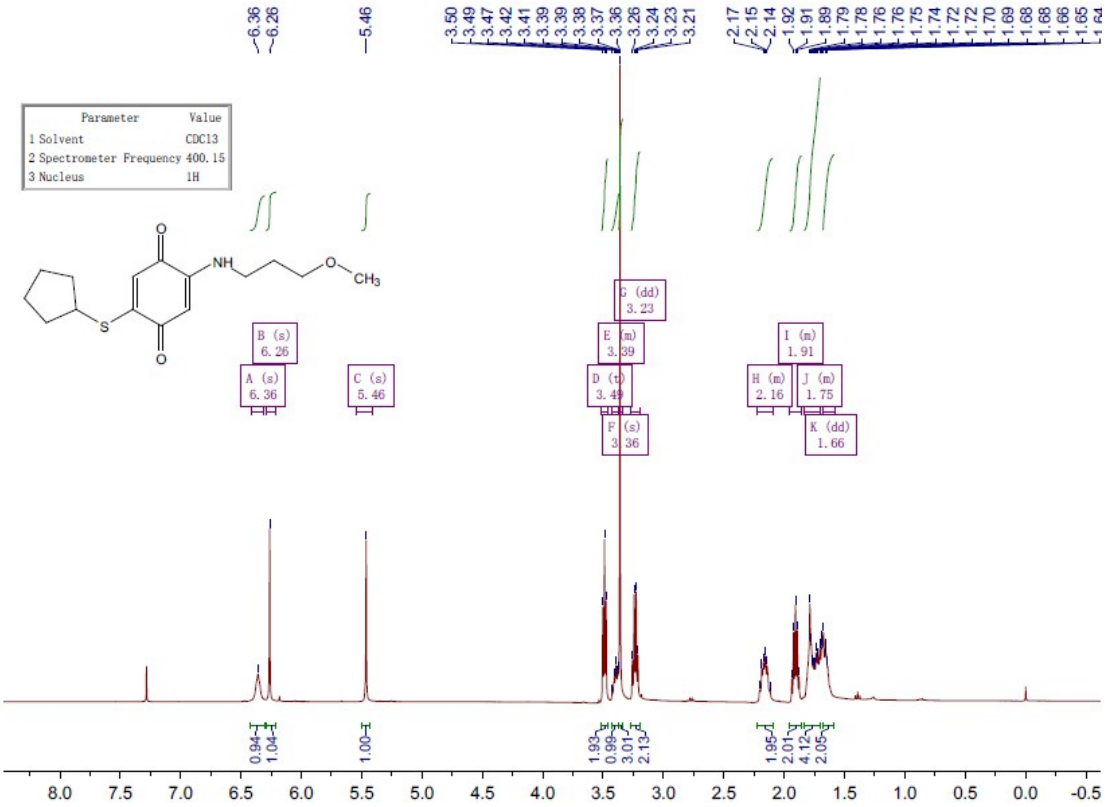
^{1}H NMR (400 MHz, $CDCl_3$) of **4as**



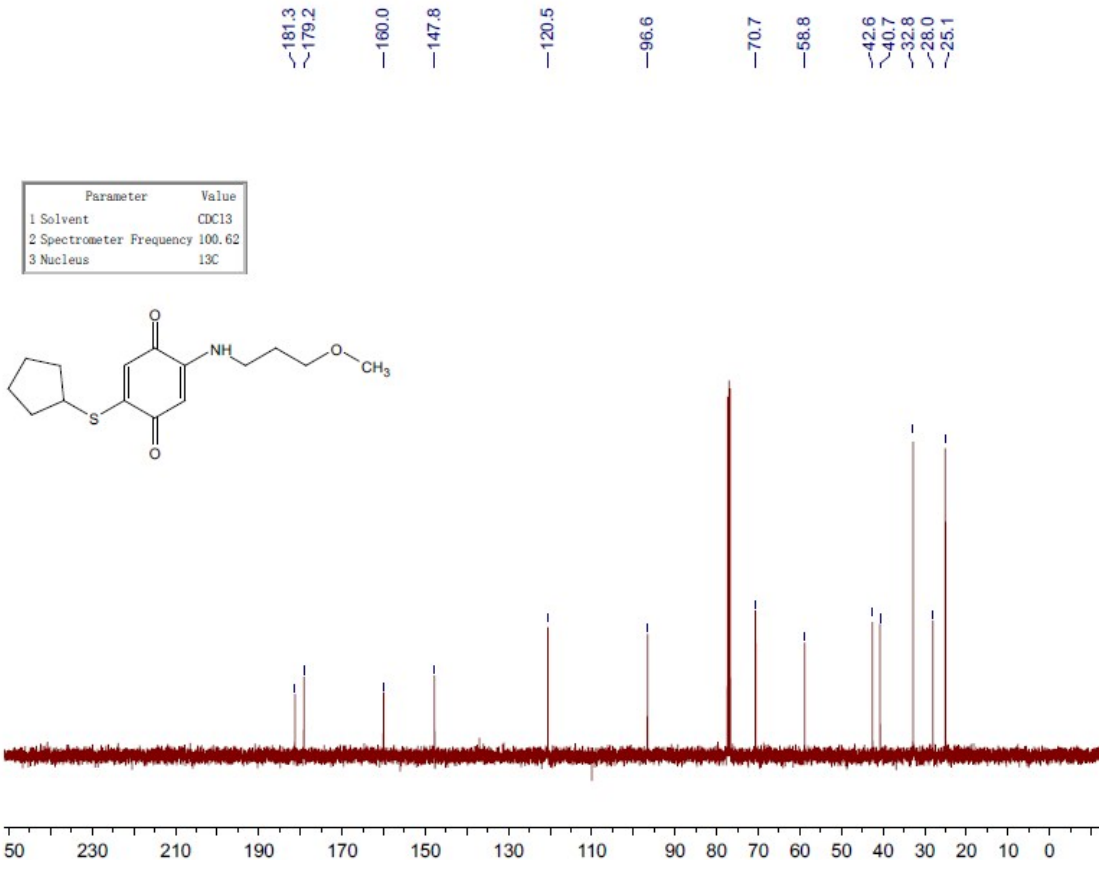
^{13}C NMR (101 MHz, $CDCl_3$) of **4as**



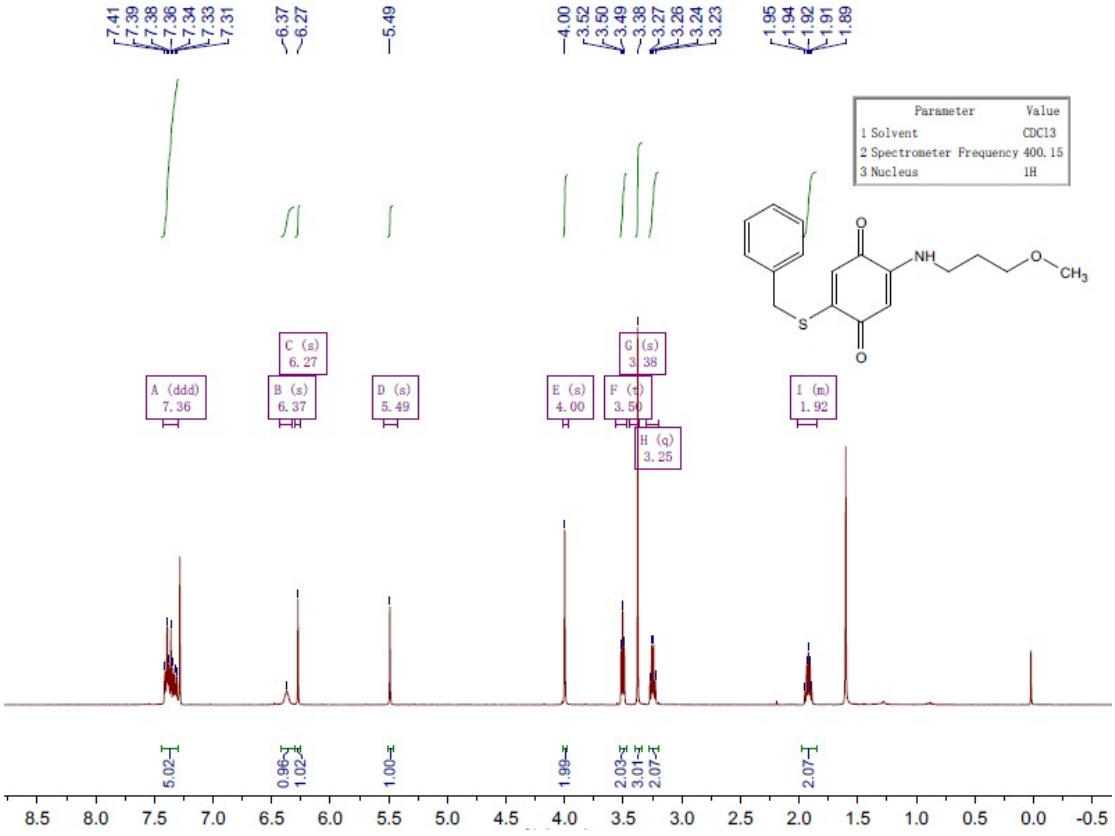
^{1}H NMR (400 MHz, $CDCl_3$) of **4mb**



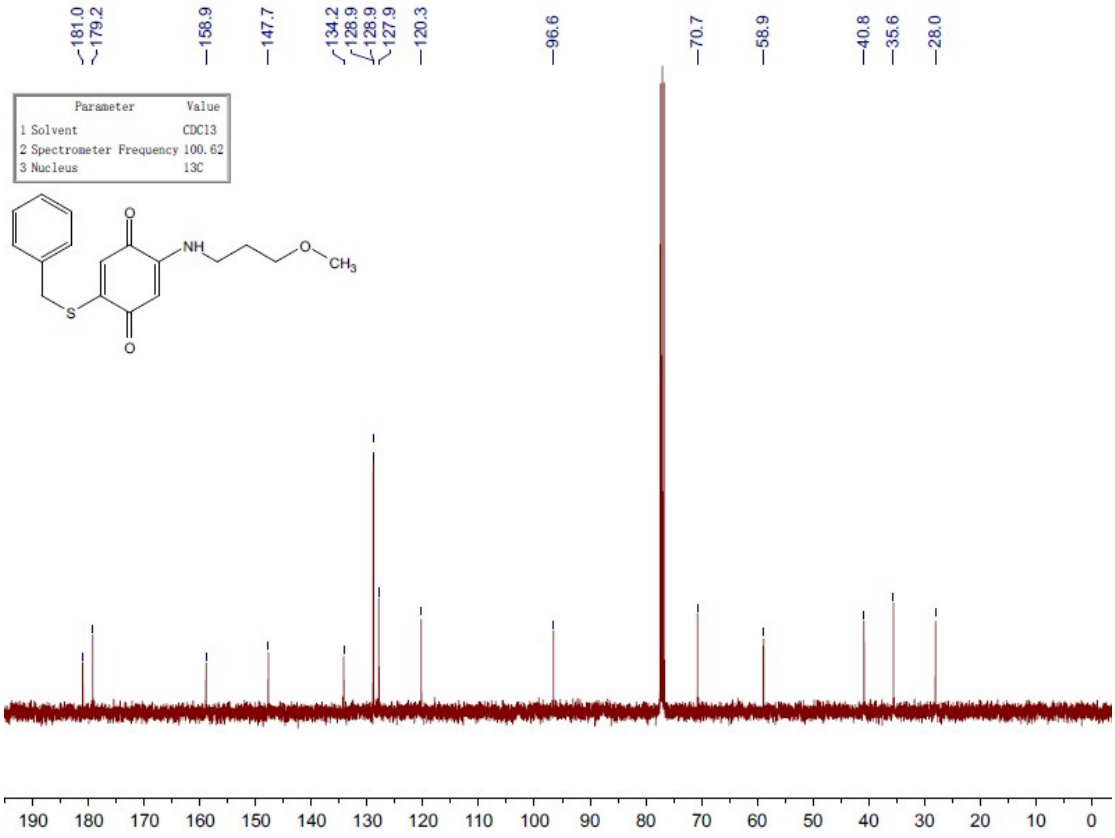
^{13}C NMR (101 MHz, $CDCl_3$) of **4mb**



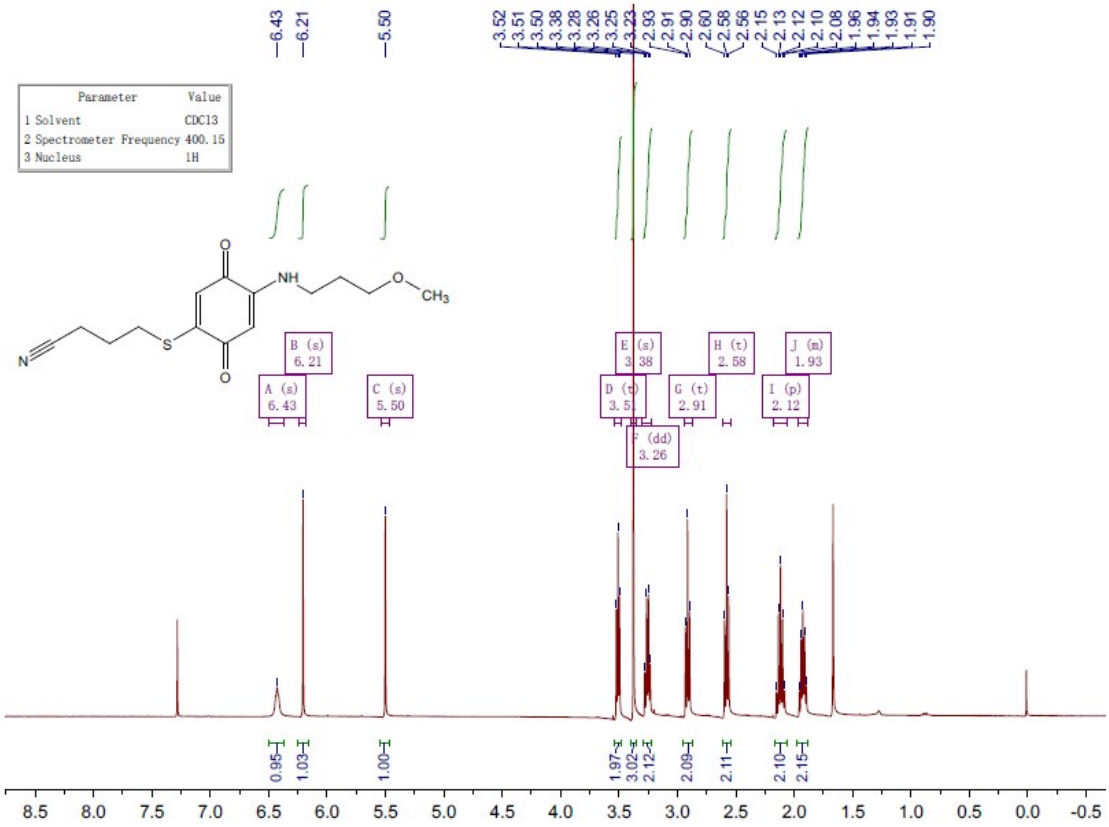
^{1}H NMR (400 MHz, $CDCl_3$) of **4mc**



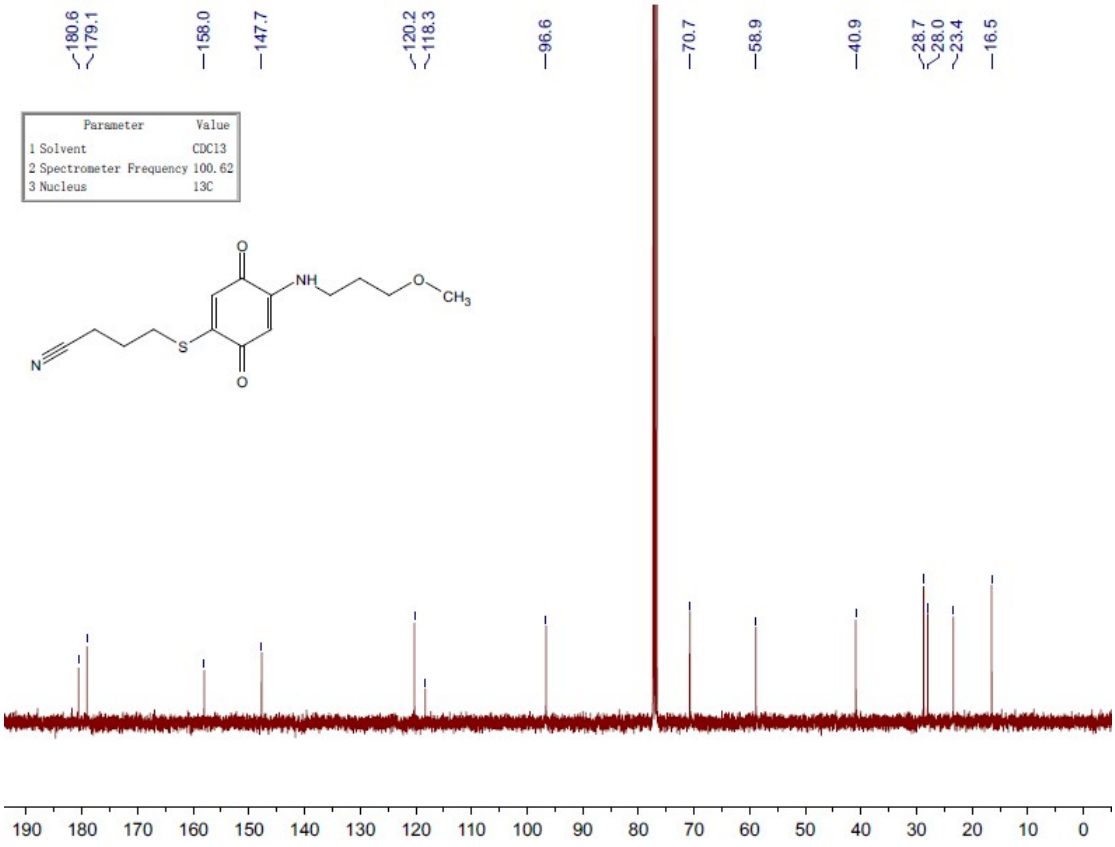
^{13}C NMR (101 MHz, $CDCl_3$) of **4mc**



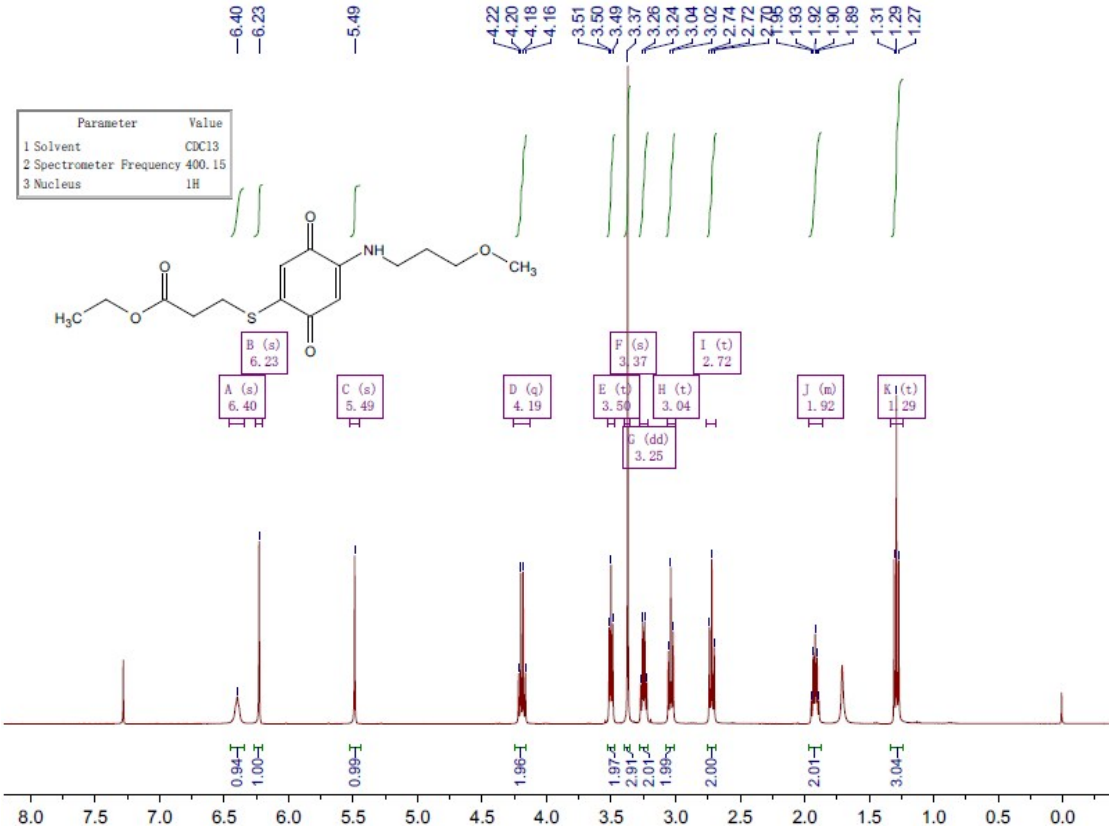
^{1}H NMR (400 MHz, $CDCl_3$) of **4md**



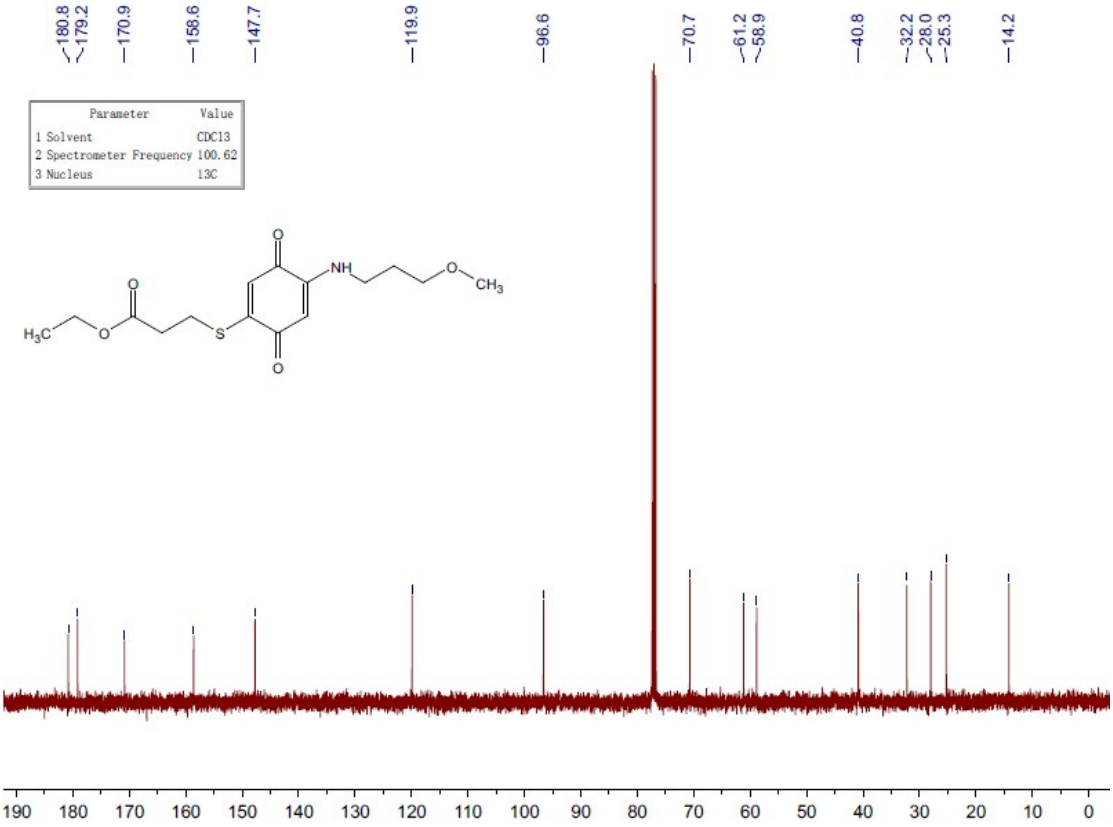
^{13}C NMR (101 MHz, $CDCl_3$) of **4md**



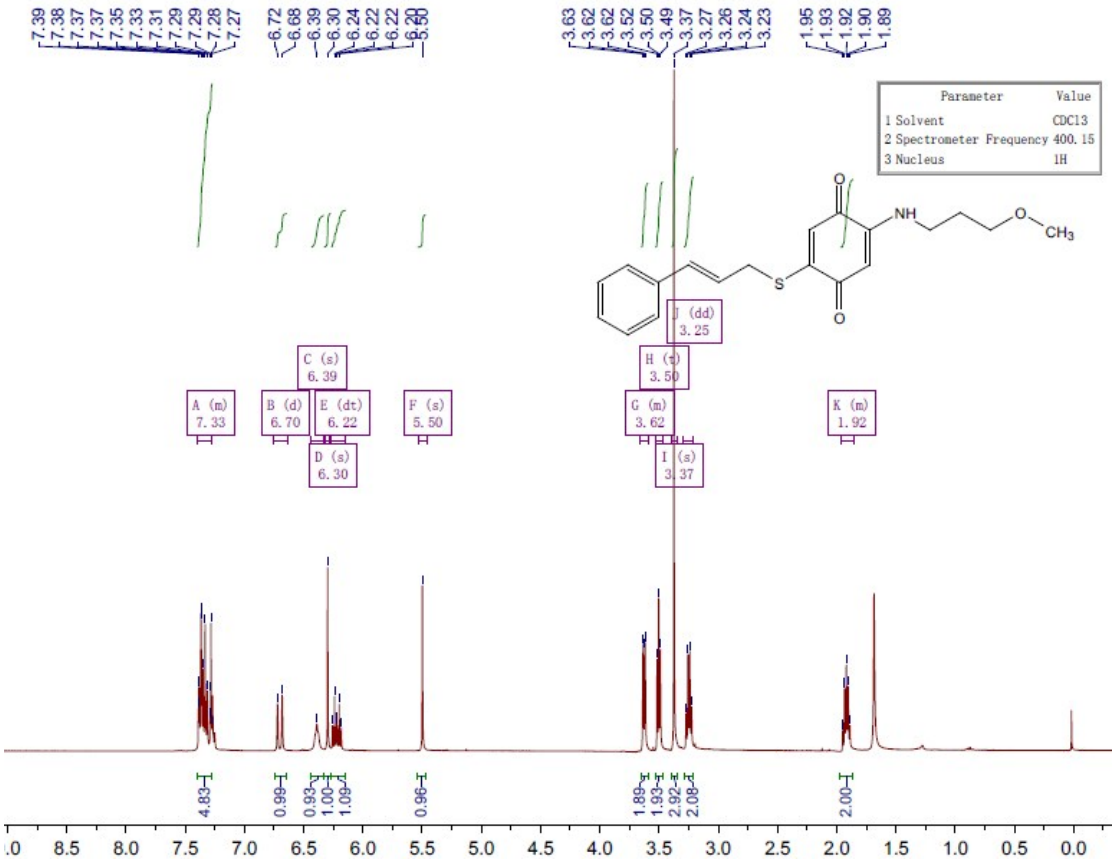
^{1}H NMR (400 MHz, $CDCl_3$) of **4me**



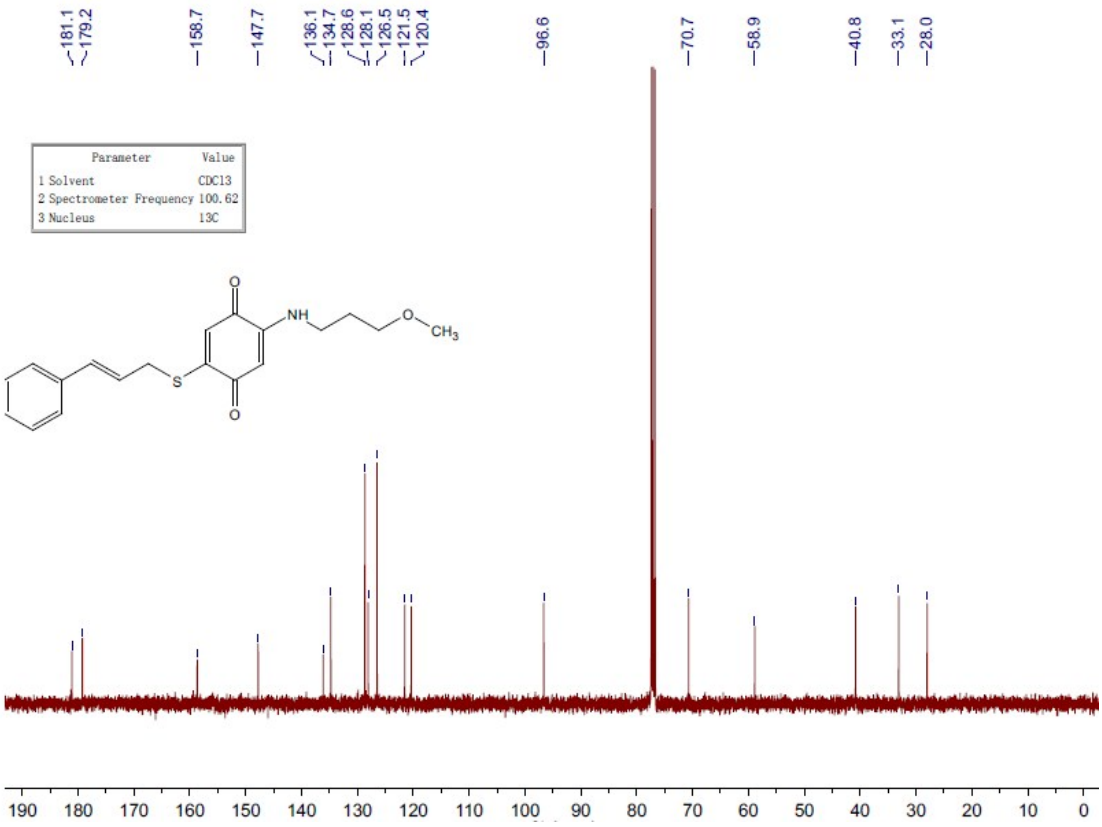
^{13}C NMR (101 MHz, $CDCl_3$) of **4me**



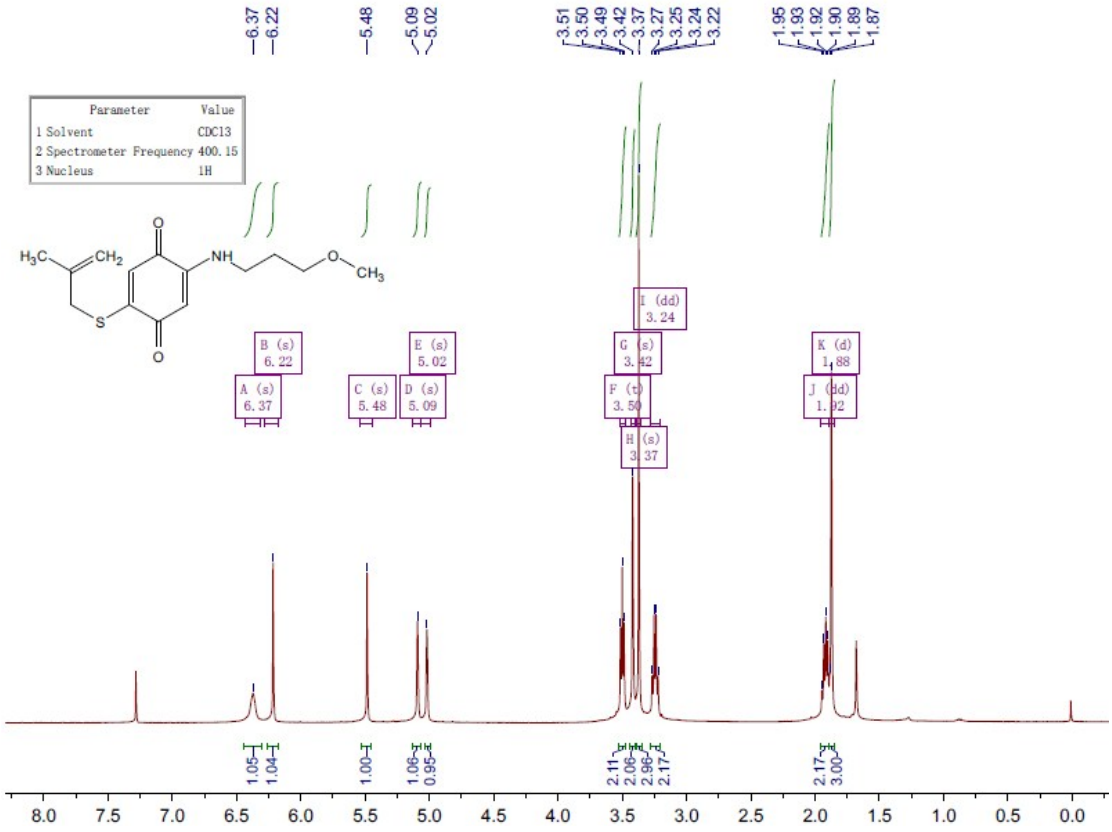
^{1}H NMR (400 MHz, $CDCl_3$) of **4mf**



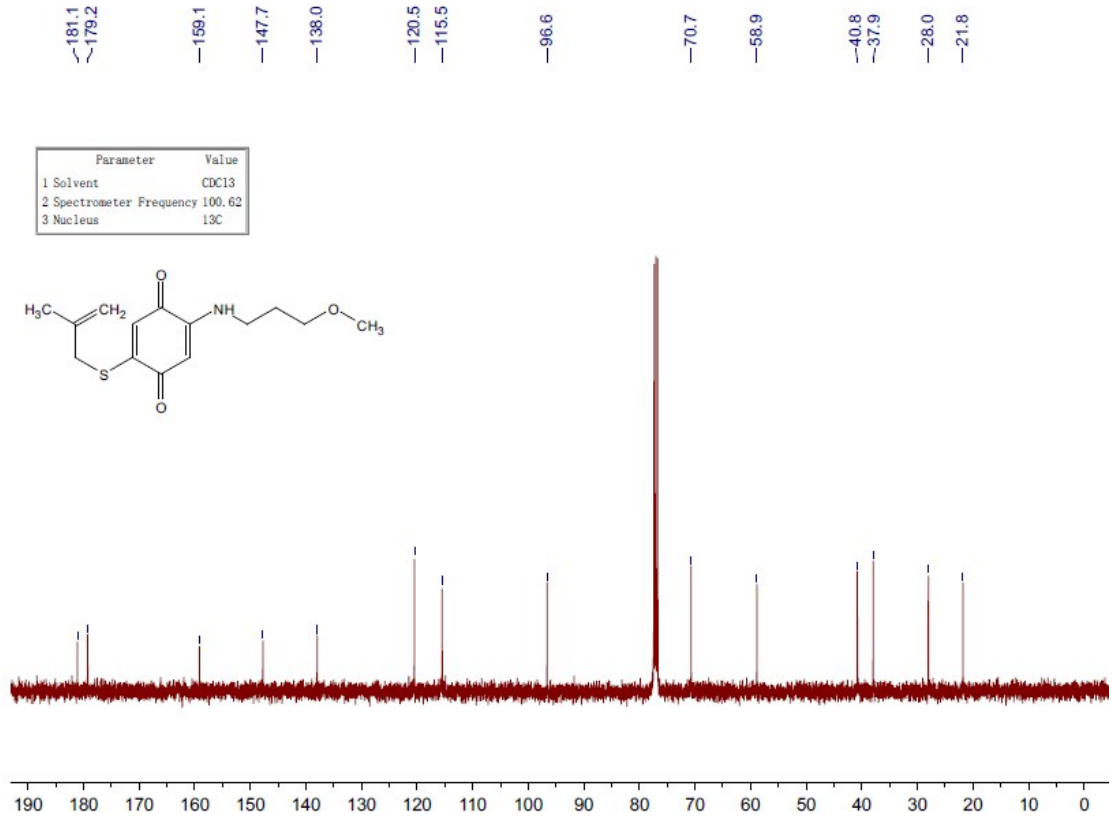
^{13}C NMR (101 MHz, $CDCl_3$) of **4mf**



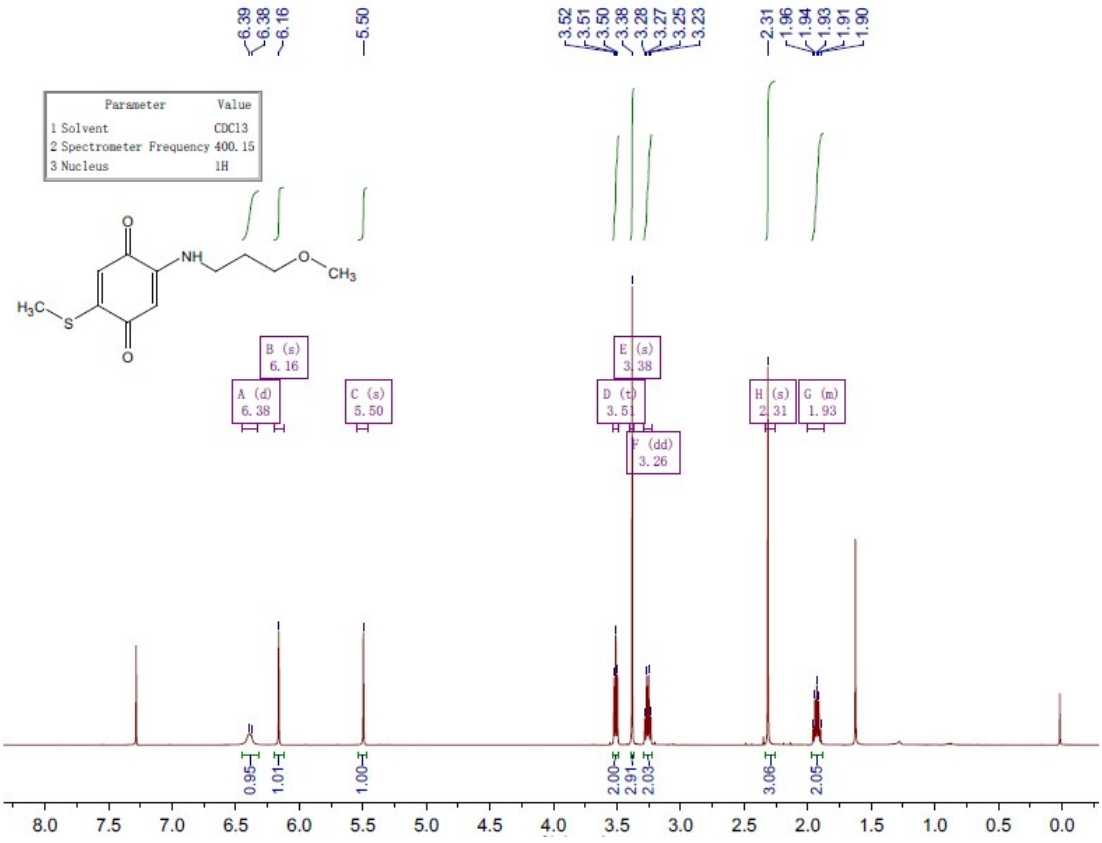
^{1}H NMR (400 MHz, $CDCl_3$) of **4mg**



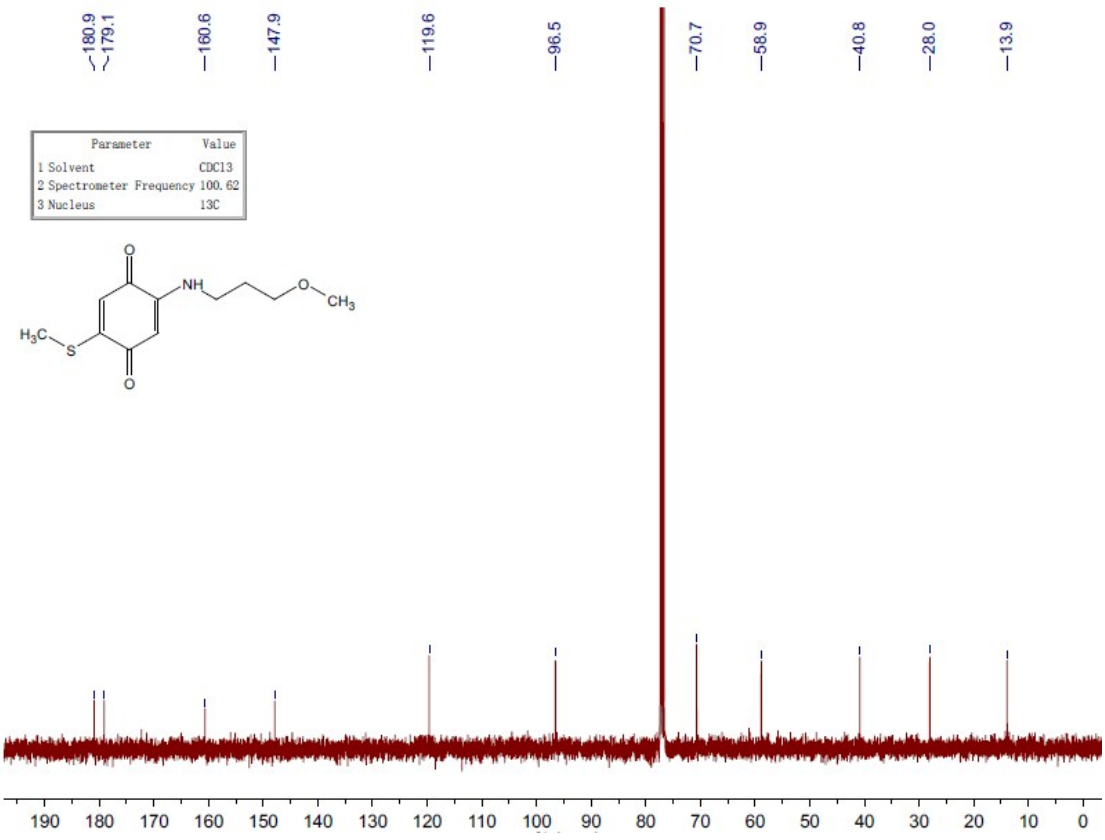
^{13}C NMR (101 MHz, $CDCl_3$) of **4mg**



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



^{13}C NMR (101 MHz, $CDCl_3$) of **4mh**



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