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SUPPORTING INFORMATION

Simple and Effective Route for Synthesis of Parvaquone, an Antiprotozoal Drug

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Experimental

A) General

Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker 400 MHz NMR spectrometer in $CDCl_3$ using Me_4Si as internal standard. Chemical shifts are reported in parts per million (ppm), coupling constants (J values) are reported in Hertz (Hz). Silica gel-G plates (Merck) were used for TLC analysis with a mixture of hexane (60–80) and ethyl acetate as eluent.

B) Experimental procedures for synthesis of intermediates and final product

Synthesis of 2-cyclohexyl-1-naphthol (4): To a chlorobenzene (40 mL) in 250 mL round bottom flask fitted with dean-stark in one neck along with condenser was added 1-naphthol (5.0 g, 34.70 mmol) followed by addition of cyclohexanol (5.55 g, 55 mmol) and *p*-toluene sulfonic acid (7.26 g, 38.17 mmol) in one lot at room temperature. The reaction mass was allowed to heat at 130 °C in a duration of one hour and then allowed to reflux for 3 h. After completion of reaction (checked by TLC using mobile phase ethyl acetate/hexane: 1/9), reaction mass was allowed to cool. Chlorobenzene was evaporated under vacuum and to the residue obtained was added dichloromethane (30 mL) and water (20 mL), organic layer was separated and washed with sodium bicarbonate solution till neutral pH. Separated organic layer was dried on sodium sulphate, evaporated under vacuum and the residue obtained on purification by column chromatography (mobile phase-ethyl acetate/ hexane: 1/9) gave 2-cyclohexyl-1-naphthol **4** as off white solid. (6.7 g, 86%); mp 96-98 °C (lit.,[12d] 98.5 °C); FT-IR ν_{max}/cm^{-1} : 3424, 2926, 2848, 1601, 1574, 1459 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4, Me_4Si) δ_H 8.01-7.27 (m, 6H, Ar-H), 4.76 (s, 1H, OH), 2.87 (m, 1H, CH), 1.85-1.49 (m, 10H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δc 147.1, 132.9, 127.6, 126.2, 125.4, 125.2, 124.6, 123.1, 121.1, 120.5, 37.7, 34.4, 33.2, 27.3, 27.0, 26.2; MS EI *m/z*: 226 (M^+), 197, 183, 170, 157 (base peak), 141, 115.

Synthesis of 2-cyclohexyl-1, 4-naphthoquinone (5): To a solution of 2-cyclohexyl-1-naphthol **4** (3.0 g, 13.25 mmol) in acetonitrile (40 mL) was dropwise added 30% hydrogen peroxide (6.76 g, 198.8 mmol and stirred for 10 min at room temperature. To this solution was slowly added hydrochloric acid (3.87 g, 106 mmol) and resulted reaction mass was allowed to stir at room temperature for 5 h. After completion of reaction the reaction mass was diluted with water (25 mL) and acetonitrile was removed under vacuum. Obtained aqueous layer was extracted with dichloromethane (30 mL), organic layer was separated washed with saturated solution of 10% $NaHCO_3$, sodium bisulfite solution, dried on sodium sulfate and evaporated under vacuum to afford crude product as residue. The crude product was purified by using column chromatography (mobile phase: ethyl acetate/hexane:1/9) afforded 2-cyclohexyl-1,4-naphthoquinone **5** as yellowish solid. (2.16 g, 68%); mp 86-88 °C (lit., [14] 87- 88 °C); FT-IR ν_{max}/cm^{-1} : 2925, 2854, 1667, 1596, 1445; ^{1}H NMR (400 MHz, CCl_4, Me_4Si) δ_H 8.55-7.92 (m, 2H, Ar-H), 7.85-7.57 (m, 2H, Ar-H), 6.63 (s, 1H, Ar-H), 3.21- 2.73 (m, 1H, CH), 1.91-1.42 (m, 10H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δc 185.6, 184.8, 156.3, 133.6, 133.5, 133.0, 132.5, 131.9, 126.7, 125.9, 36.7, 32.2, 26.4, 26.0 ; MS EI *m/z*: 240 (M^+), 206, 172 (base peak), 144, 115, 76.

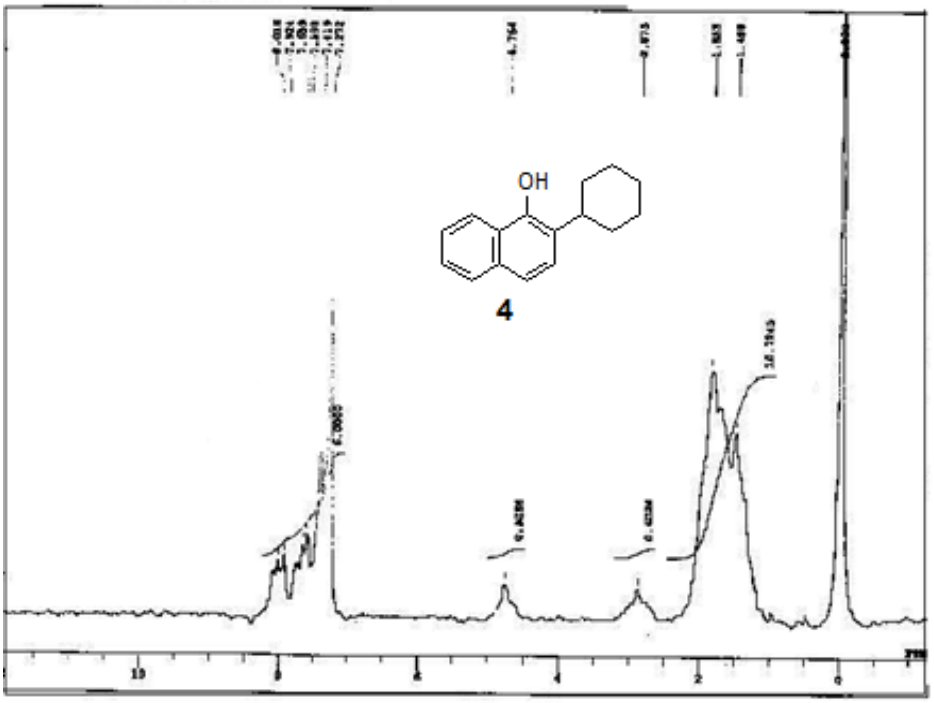
Synthesis of 2-cyclohexyl-(2,3)-oxirane-1, 4-naphthoquinone (6): To a solution of **5** (0.5 g, 2.08 mmol) in ethanol (20 mL) was added 30% hydrogen peroxide (2.4 mL, 79.1 mmol) at 5-10 °C. To this resulting solution, was added a cold aq. solution of sodium carbonate (0.11 g in 1 mL of water) and reaction mixture was allowed to stir until the yellow color disappeared. Reaction progress was monitored by TLC at regular intervals. After completion of reaction, water was added causing precipitation of white solid. Obtained white solid was filtered and washed with cool water (10 mL)

followed by drying to give crude 2-cyclohexyl-(2, 3)-oxirane-1, 4-naphthoquinone which was further purified by column chromatography afforded **6** as off white solid. (0.4 g, 76%); mp 77-79 °C (lit., [14] 79-80 °C); FT-IR ν_{max}/cm^{-1} : 3052, 2927, 2854, 1695, 1590, 1292 ; ^{1}H NMR (400 MHz, CCl_4, Me_4Si) δ_H 8.03-7.48 (m, 4H, Ar-H), 4.25 (s, 1H, CH), 2.55-2.40 (m, 1H, CH), 1.78-1.60 (m, 10H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δc 192.3, 191.5, 134.5, 134.2, 133.0, 131.6, 127.5, 126.6, 66.6, 58.1, 34.7, 29.1, 26.5, 26.1, 26.0, 25.9; MS EI *m/z*: 256 (M^+), 173, 149, 122, 105 (base peak), 77.

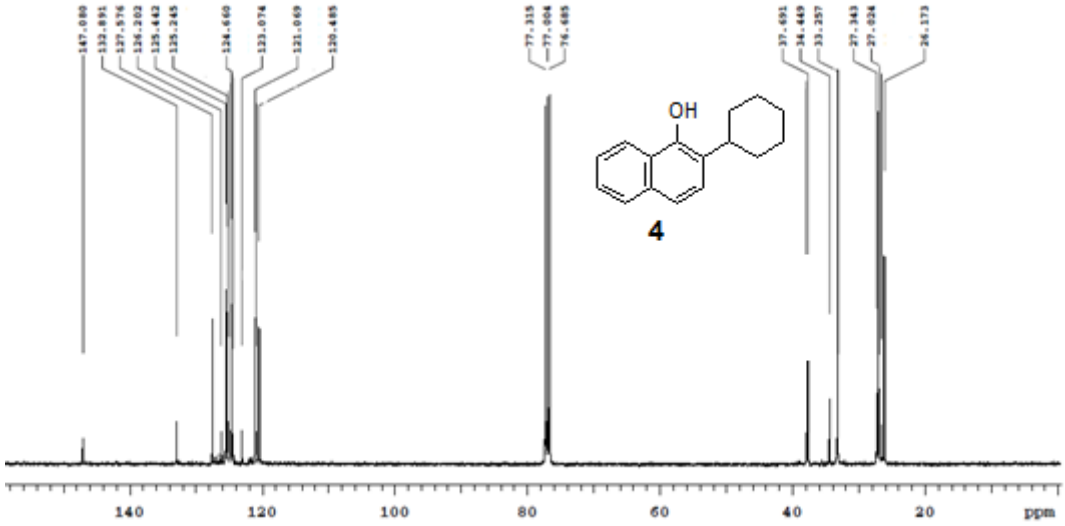
Synthesis of 2-cyclohexyl-3-hydroxy-1, 4-naphthoquinone (Parvaquone, 1): Sulfuric acid (7.30 mL) was added into the flask containing 2-cyclohexyl-(2, 3)-oxirane-1, 4-naphthoquinone (0.5 g, 1.95 mmol) and resulted bright red solution was stirred at room temperature for 15 min. The reaction mass was slowly added to chilled water and the mixture was extracted repeatedly with dichloromethane (3 x 20 mL). Organic layers were combined, dried on sodium sulfate and evaporated to give brown oil. The brown oil after column chromatography gave **1** as yellowish solid. (0.38 g; 76%); mp 136-138 °C (lit.,[14] 135-136 °C); FT-IR ν_{max}/cm^{-1} : 3354, 2926, 2843, 1656, 1594, 1446; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ_H 8.17-7.96 (m, 2H, Ar-H), 7.82-7.59 (m, 2H, Ar-H), 7.34 (s, 1H, OH), 3.22-2.85 (m, 1H, CH), 1.85-1.12 (m, 10H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δc 184.6, 181.9, 152.8, 135.4, 134.9, 132.7, 129.2, 127.8, 126.9, 125.9, 35.1, 29.2, 26.7, 25.9 ; MS EI *m/z*: 256 (M^+, base peak), 213, 188, 161, 115, 105.

$^{1}H/^{13}C$ NMR and Mass spectra of intermediates and final product

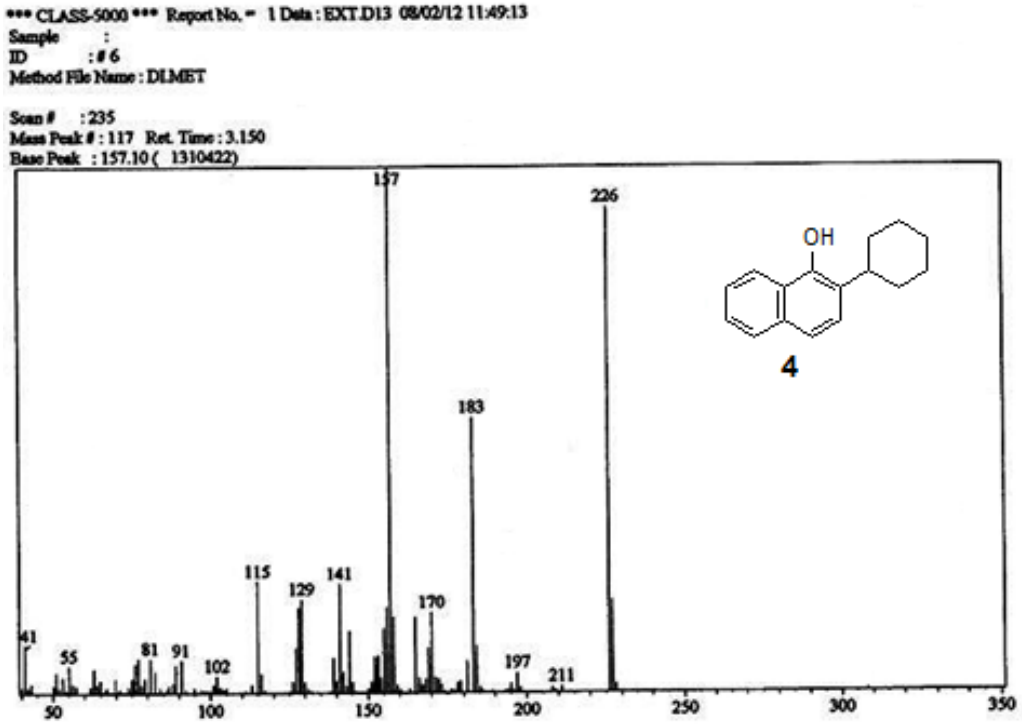
^{1}H NMR spectrum: 2-Cyclohexyl-1-naphthol (4)



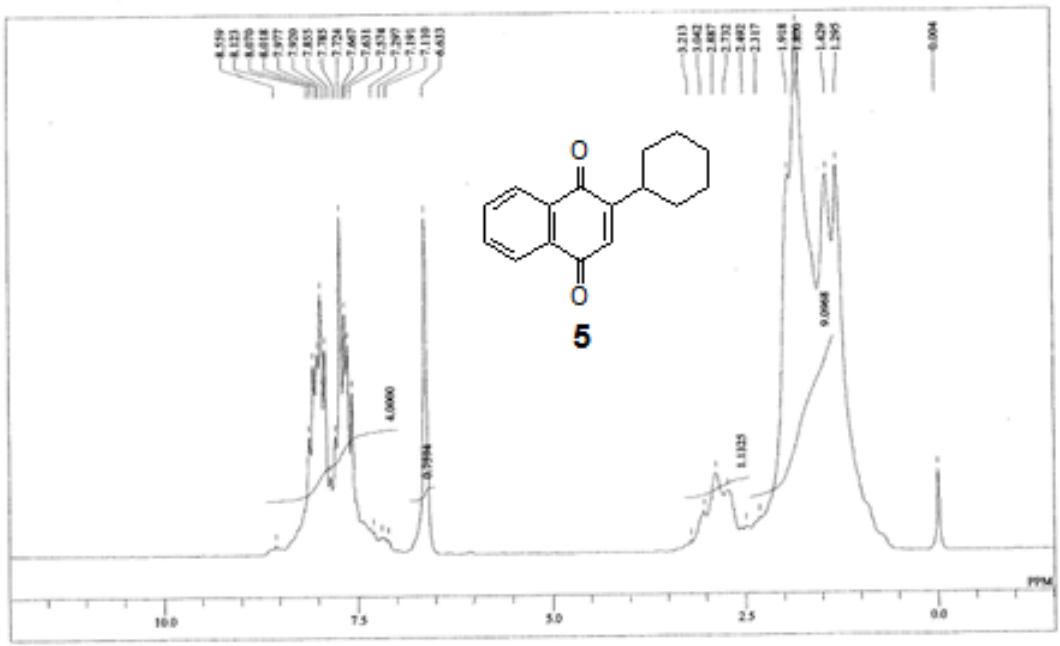
^{13}C NMR spectrum: 2-Cyclohexyl-1-naphthol (4)



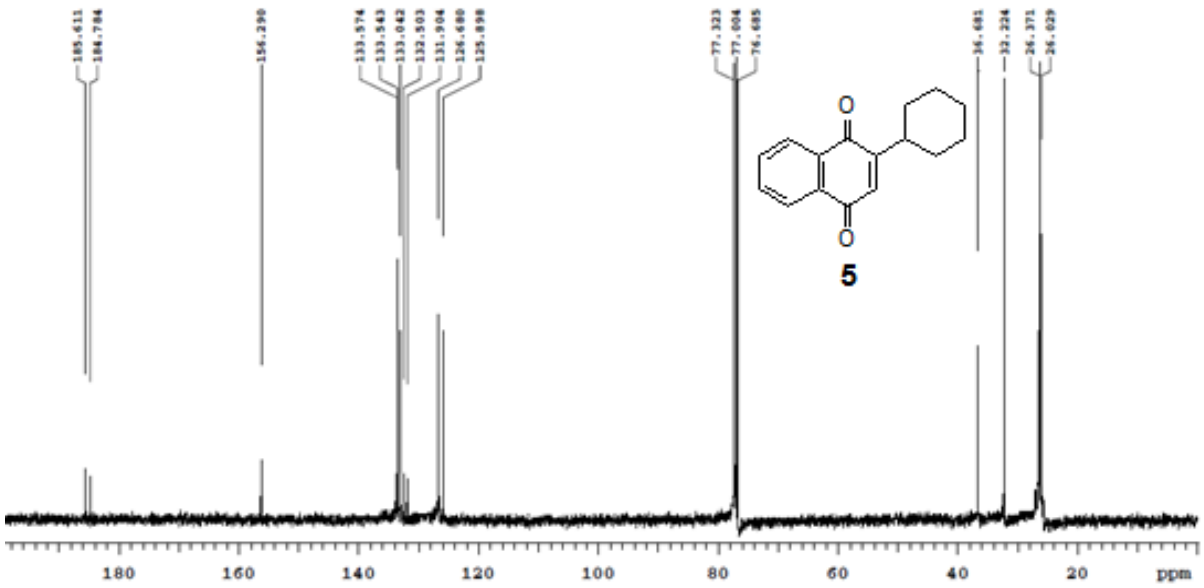
Mass Spectrum of 2-cyclohexyl-1-naphthol (4)



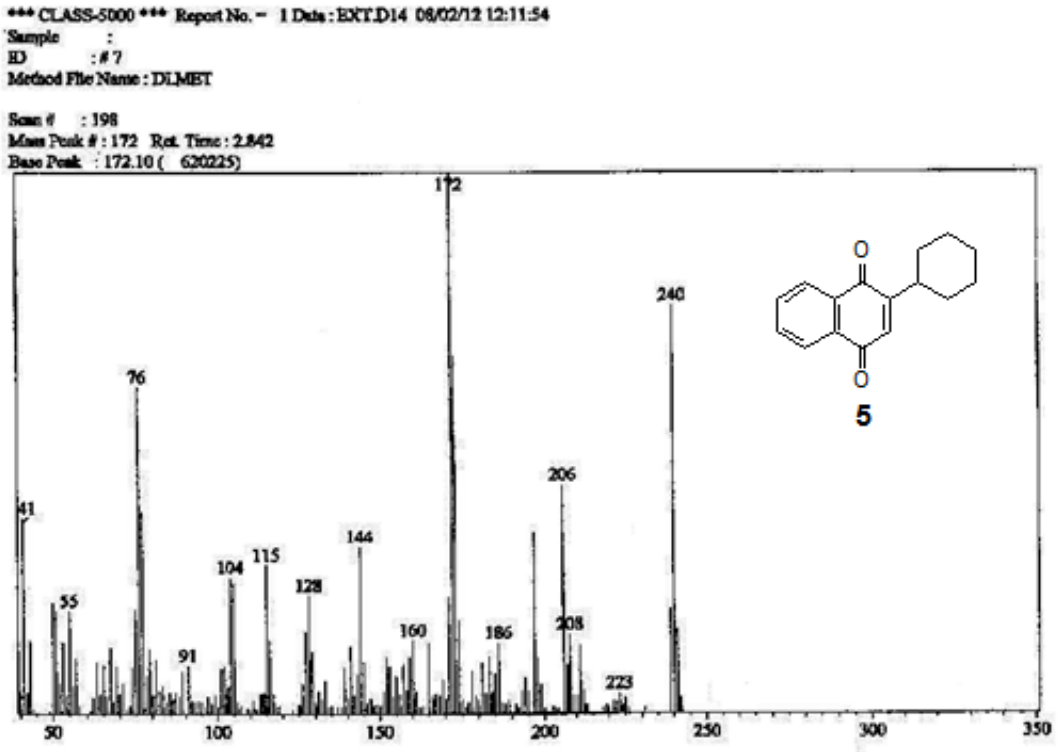
^{1}H NMR spectrum: 2-cyclohexyl-1, 4-naphthoquinone (5)



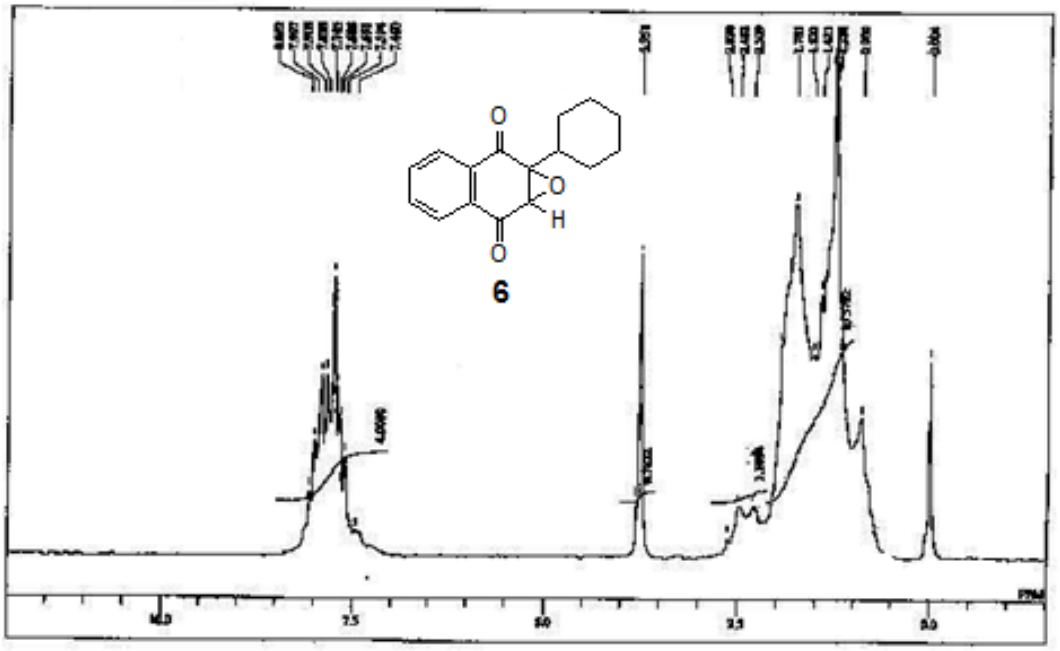
^{13}C NMR spectrum: 2-cyclohexyl-1, 4-naphthoquinone (5)



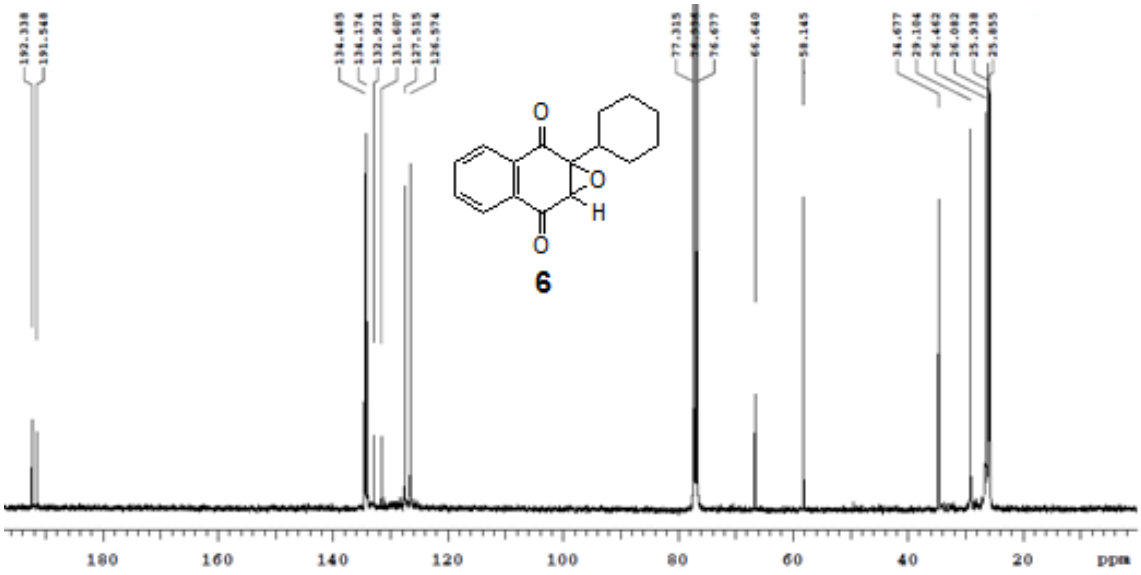
Mass spectrum: 2-cyclohexyl-1, 4-naphthoquinone (5)



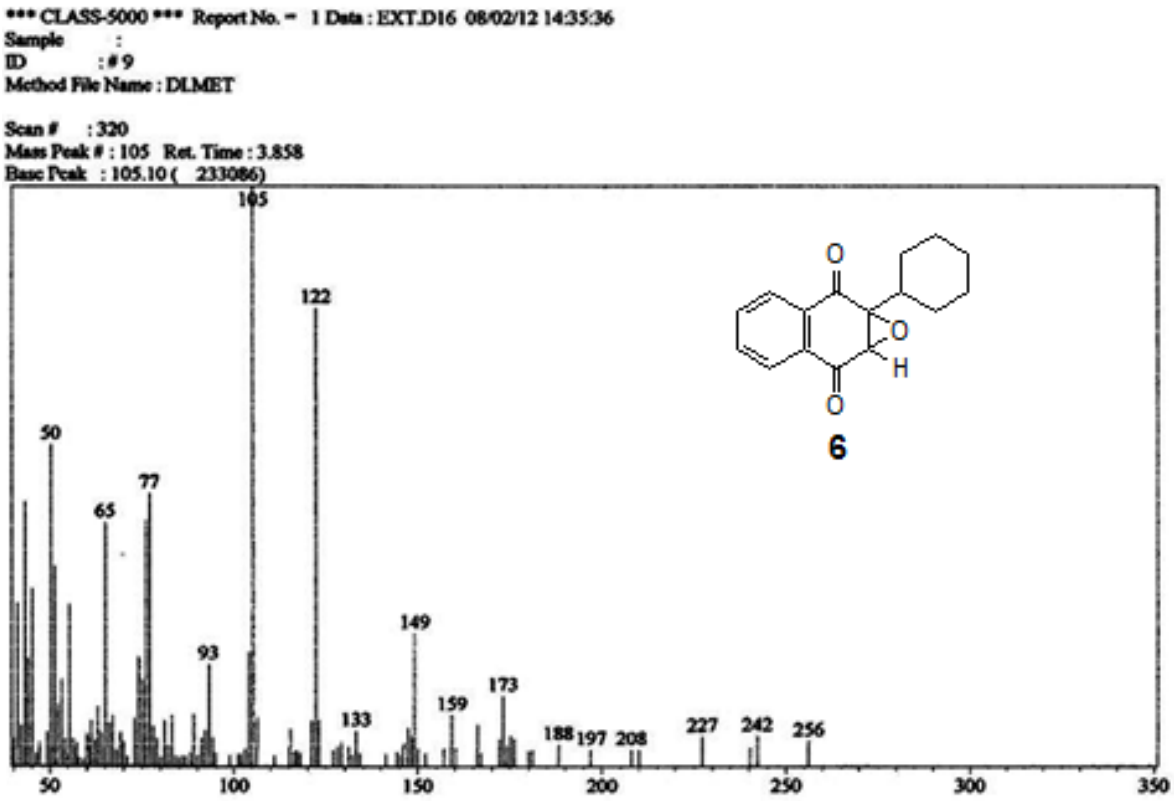
^{1}H NMR spectrum: 2-cyclohexyl-(2, 3)-oxirane-1, 4-naphthoquinone (6)



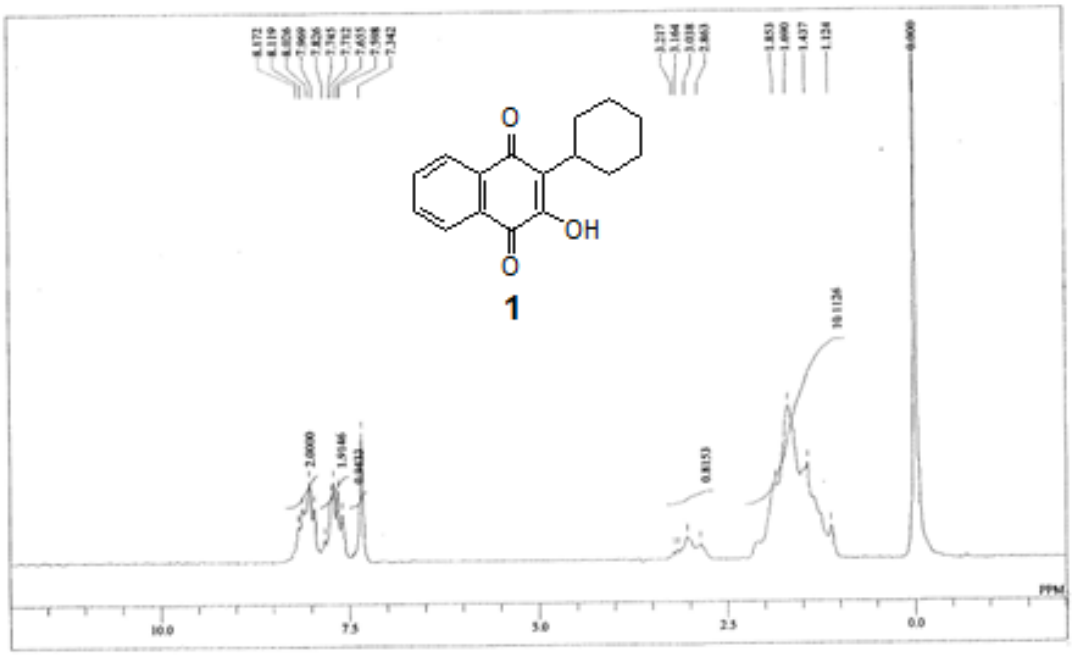
^{13}C NMR spectrum: 2-cyclohexyl-(2, 3)-oxirane-1, 4-naphthoquinone (6)



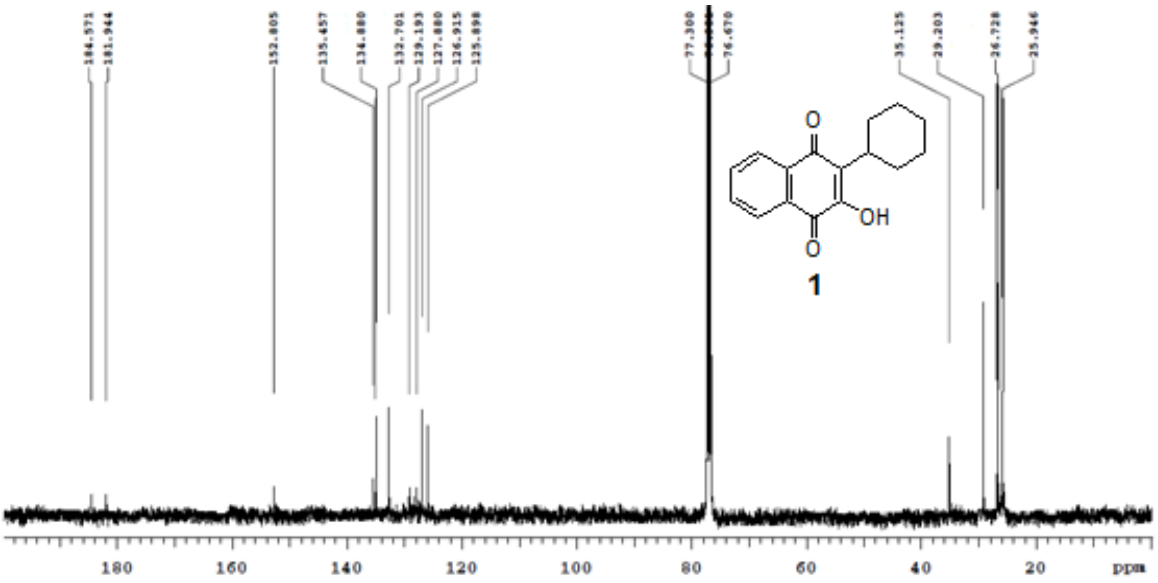
Mass spectrum: 2-cyclohexyl-(2, 3)-oxirane-1, 4-naphthoquinone (6)



^{1}H NMR Spectrum: 2-cyclohexyl-3-hydroxy-1, 4-naphthoquinone (1)



^{13}C NMR Spectrum: 2-cyclohexyl-3-hydroxy-1, 4-naphthoquinone (1)



Mass Spectrum of 2-cyclohexyl-3-hydroxy-1, 4-naphthoquinone (1)