

## **Supporting Information**

# Synthesis, Antimalarial Activity, and Structure-Activity Relationship of 7-(2-Phenoxyethoxy)-4(1*H*)-quinolones

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## I. General Information

All reagents and anhydrous solvents were obtained from Aldrich Chemical Co. and used without further purification unless otherwise noted. The identity of all title compounds was verified via  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and HPLC/HRMS. The chemical purity of the titled compounds was determined using the following conditions: an Agilent 1100 series LC/MSD with a Eclipse XDB-C18 (4.6mm x 100 mm, 5  $\mu\text{m}$ ) reversed phase column; method: 10% (v/v) of acetonitrile (+0.05% TFA) in 90% (v/v) of  $\text{H}_2\text{O}$  (+0.05% TFA), ramped to 100% acetonitrile (+0.05% TFA) over 9 min, and holding at 100% acetonitrile for 4 min with a flow rate of 0.7 mL/min, UV detector, 254 nm. The purity of each compound was  $\geq 95\%$  in this analysis. NMR spectra were recorded at ambient temperature on a 400 or 500 MHz Varian NMR spectrometer in the solvent indicated. All  $^1\text{H}$  NMR experiments are reported in  $\geq$  units, parts per million (ppm) downfield of TMS and were measured relative to the signals for chloroform (7.26 ppm) and dimethylsulfoxide (2.50 ppm). All  $^{13}\text{C}$  NMR spectra were reported in ppm relative to the signals for chloroform (77 ppm) and dimethylsulfoxide (39.5 ppm) with  $^1\text{H}$  decoupled observation. Data for  $^1\text{H}$  NMR are reported as follows: chemical shift ( $\delta$  ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant (Hz), whereas  $^{13}\text{C}$ -NMR analyses were obtained at 101 MHz and reported in terms of chemical shift. NMR data was analyzed by using MestReNova Software ver. 5.3.2-4936. High resolution mass spectra (HRMS) were performed on an Agilent LC/MSD TOF system G3250AA. Silicycle silica gel 230-400 (particle size 40-63  $\mu\text{m}$ ) mesh was used for all flash column chromatography.

## II. General Procedures

**General Procedure A: Preparation of 3-substituted 2-methylquinolin-4(1*H*)-ones.** 4(1*H*)-quinolones were prepared by using one of the standard procedures for Conrad-Limpach reaction. An oven-dry 100 ml rbf attached to a Dean-Stark trap equipped with a reflux condenser was charged with an aniline (0.025 mol), corresponded ethyl acetoacetate (0.25-0.05 mol), benzene (25 ml) and glacial acetic acid (1 ml). The mixture was heated at 100°C until no more water was separated (3-24 hours). The benzene was distilled under the reduced pressure and resulting enamine was then used in the next step without further purification. Biphenyl ether (30 ml) was stirred and heated at reflux while enamine was added rapidly through the dropping funnel. Stirring and refluxing continued for 10-15 minutes until no more ethanol separates within the Dean-Stark trap. The mixture was then allowed to cool down to room temperature while precipitation arises. The solid was filtered off and washed with hexane and acetone. Ice cold methanol washing may be necessary in some cases. The solid was typically recrystallized with DMF if necessary.

**General Procedure B: Halogenation of substituted 2-methylquinolin-4(1*H*)-one.** The halogenation was done following a similar procedure reported by Renault et al. Thus 5 eq. of iodine was added dropwise to a stirred solution or slurry of 2-methylquinolin-4(1*H*)-one in 2M solution of sodium hydroxide and MeOH (~1:1) at r.t. Stirring was continued until LCMS indicates absence of starting material (3-24 hours). In some cases more than 8 eq of iodine was needed. The mixture was then acidified with acetic acid; precipitation was collected by filtration, washed with water, and recrystallized from DMF.

**General Procedure C: Alkylation of 2-methylquinolin-4(1*H*)-one.** To a flame dried-backfilled round bottom flask is added quinolone (0.72 g, 2.8 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.37 g, 4.2 mmol). DMF (14.5 ml) is added and this slurry is allowed to stir at r.t. for 1h. Next, Iodomethane (0.88 ml, 14 mmol) is added dropwise and the reaction is left until completion is observed via HPLC analysis. The reaction is then poured onto water (20 ml) and then diluted with chloroform (20 ml). The organic layer is then washed



with water (20 ml) twice followed by brine (20 ml). The organic layer is then dried over sodium sulfate and concentrated in vacuo. The crude compound is columned via flash chromatography (Hex / EtOAc gradient).

**General Procedure D: Suzuki-Coupling of 3-iodo-2-methylquinolin-4(1*H*)-one.** An oven-dried schlenk tube is flame-dried and backfilled with argon(x3). The tube is then charged with 4(1*H*)-quinolone (100 mg, 0.4 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (14.5 mg, 0.016 mmol), SPHOS (13 mg, 0.032 mmol), boronic acid (97mg, 0.6 mmol), and anhydrous powdered K<sub>3</sub>PO<sub>4</sub> (168 mg, 0.79 mmol). The schlenk tube was fitted with a rubber septum and then evacuated and backfilled with argon (this process was repeated three times). Dry solvent (Toluene, DMF, or 2-butanol, 3mL) was added through the septum via syringe and the resulting solution was stirred for 1 min while purging with argon before replacing the rubber septum with the Teflon screwcap. The reaction was set to the oil bath until completion was observed via HPLC analysis. The reaction is cooled to room temperature and then diluted with 20 ml chloroform and 20 ml of methanol. This mixture was brought to a boil with a heat gun and then filtered over a pad of celite. The eluent was concentrated under reduced pressure and the residual oil was purified further via flash chromatography.

**General Procedure E: Suzuki-Coupling of 3-iodo-2-methylquinolin-4(1*H*)-one.** An oven-dried microwave reactor tube is flame-dried and backfilled with argon(x3). The tube is then charged with 4(1*H*)-quinolone (125 mg, 0.26 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3.5 mg, 0.004 mmol), SPHOS (3.2 mg, 0.008 mmol), boronic acid (52 mg, 0.39 mmol). The schlenk tube was fitted with a rubber septum and then evacuated and backfilled with argon (this process was repeated three times). Dry DMF 5 mL and 1M Na<sub>2</sub>CO<sub>3</sub> 1 mL was added through the septum via syringe and the resulting solution was placed in a microwave reactor for 20 minutes at 140°C. The reaction was monitored via HPLC analysis. The reaction is cooled to room temperature and then diluted with 2 ml chloroform and 2 ml of methanol. This mixture was brought to a boil with a heat gun and then filtered over a pad of celite. The eluent was concentrated under reduced pressure and the residual oil was purified further via flash chromatography.

**General Procedure F: Suzuki-Coupling of 6-butyl-4-ethoxy-3-iodo-2-methyl-7-(2-phenoxyethoxy)quinoline.** An oven-dried schlenk tube is flame-dried and backfilled with argon(x3). The tube is then charged with 6-butyl-4-ethoxy-3-iodo-2-methyl-7-(2-phenoxyethoxy)quinoline (100 mg, 0.4 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (14.5 mg, 0.016 mmol), SPHOS (13 mg, 0.032 mmol), boronic acid (97mg, 0.6 mmol), and anhydrous powdered K<sub>3</sub>PO<sub>4</sub> (168 mg, 0.79 mmol). The schlenk tube was fitted with a rubber septum and then evacuated and backfilled with argon (this process was repeated three times). Dry solvent (Toluene, DMF, or 2-butanol, 3mL) was added through the septum via syringe and the resulting solution was stirred for 1 min while purging with argon before replacing the rubber septum with the Teflon screwcap. The reaction was set to the oil bath until completion was observed via HPLC analysis. The reaction is cooled to room temperature and then diluted with 20 ml chloroform and 20 ml of methanol. This mixture was brought to a boil with a heat gun and then filtered over a pad of celite. The eluent was concentrated under reduced pressure and the residual oil was purified further via flash chromatography.

**General Procedure G: *O*-ethyl Hydrolysis.** 6-Butyl-4-methoxy-2-methyl-7-(2-phenoxyethoxy)-3-phenylquinoline (100 mg, 0.226 mmol) was dissolved in 1 mL of acetic acid and 1mL of HBr. The reaction was refluxed for 1.5h and checked via LC-MS to determine completion. Upon completion, the reaction is poured onto ice and water and filtered. The solid is then dried in an oven for 1h and recrystallized from DMF.

**General Procedure H: Alkylation of Acyl Aniline.** The mixture of phenol (700 mg, 3.78 mmol), β-bromophenetole (836 mg, 4.16 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.838 mg, 5.67 mmol) in DMF (8 mL) was stirred for overnight at 50°C. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and purified by recrystallization or flash chromatography.

**General Procedure I: Hydrolysis of Acetamide.** N-(4-Chloro-3-(methoxymethoxy)phenyl)acetamide (700 mg, 3.05 mmol) and KOH (2.39 g, 42.8 mmol) was added to a flame-dried flask and subsequently

dissolved in 10 mL of 9:1 ethanol: water solution. The mixture was refluxed over night. The ethanol was concentrated in vacuo, diluted with water (5 mL) and extracted with EA (3 X 20 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and purified by flash column chromatography to get the product (0.480 g) in 84% yield.

**J774 Cytotoxicity Assay:** Mouse macrophage cell line J774 was cultured in RPMI-1640 media with phenol-red containing L-glutamine then supplemented with 10% fetal bovine serum, penicillin (50 Units/mL) and streptomycin (50 µg/mL). For seeding into 96 well plates the J774 cells were diluted to  $5 \times 10^5$  cells/mL. Cells were dispensed into 96 well plates at a volume of 100 µL/well giving a final concentration of  $5 \times 10^4$  cells/well. Plates were incubated for 24 hours at 37°C and 5% CO<sub>2</sub> to allow the attachment of J774 to the bottom of the plate wells. Test compounds were prepared by diluting to 10 µg/mL or 20 nM followed by 1:2 serial dilutions over 11 concentrations. After 24 hours the media was removed from the wells and serially diluted test compounds were added to each well. Positive and negative control wells were included on each assay plate. Plates containing cells and test compounds were then incubated for 72 hours at 37°C and 5% CO<sub>2</sub>. After the incubation period, cell proliferation was assessed using CellTiter 96 Aqueous One Solution Cell Proliferation Assay reagent (Promega). To each well 20 µL's of reagent was added followed by incubation for 4 hours at 37°C and 5% CO<sub>2</sub>. A Spectramax M2e (Molecular Devices) plate reader was used to read absorbance at 490 nM. IC<sub>50</sub> values were determined using a custom database manager (Dataspects, Inc.). Nonlinear regression analysis was used to calculate IC<sub>50</sub>'s.

**In vitro Parasite Culturing:** *P. falciparum* clone W2/Indochina and TM90C2B/Thailand were grown in continuous culture using RPMI 1640 media containing 10% heat-inactivated type A+ human plasma, sodium bicarbonate (2.4g/L), HEPES (5.94g/L) and 4% washed human type A+ erythrocytes. Cultures were gassed with a 90% N<sub>2</sub>, 5% O<sub>2</sub> and 5%CO<sub>2</sub> mixture followed by incubation at 37°C.

**Assay Preparation:** Test compounds at 5 mg/mL in DMSO were diluted at least 1:400 and then serially diluted in duplicate over 11 concentrations. *P. falciparum* cultures with >70% ring stage parasites were

diluted to 0.5-0.7% parasitemia and 1.5% hematocrit in RPMI 1640 media. In 96-well plates a volume of 90µl/well of parasitized erythrocytes was added on top of 10µL/well of the test compound. A separate plate containing chloroquine, dihydroartemisinin and atovaquone was added to each set of assay plates as control drugs. A Beckman Coulter Biomek 3000 was used to dispense test compounds, control drugs and parasitized erythrocytes into the microtiter plates. Positive and negative controls were included in each plate. Positive controls consisted of drug-free parasitized erythrocytes and negative controls consisted of parasitized erythrocytes dosed with a high concentration of chloroquine or dihydroartemisinin that ensured 100% parasite death. Assay plates were placed into a plastic gassing chamber and equilibrated with 90% N<sub>2</sub>, 5% O<sub>2</sub> and 5%CO<sub>2</sub> mixture then incubated at 37°C for 72 hours. After 72 hours of incubation the assay plates were frozen at -80°C until later processed for parasite growth determinations.

**SYBR Green I Processing:** Assay plates were removed from -80°C and allowed to thaw at room temperature. Using the Beckman Biomek 3000 100µL was transferred from the assay plates into 96-well black assay plates. Next, 100µl of SYBR green I (Invitrogen) in 2X lysis buffer (0.2µl SYBR green I/mL of 2X lysis buffer [0.008% saponin, 0.08% Triton X-100, 20mM Tris and 5mM EDTA]) was dispensed into each well of the 96-well black assay plate using the Beckman Coulter Biomek 3000. Upon addition of SYBR green I the microtiter plates were incubated for one hour in the dark. Relative Fluorescence units (RFU) were read using a Molecular Devices Spectramax microplate reader.

**Data Analysis:** Data analysis was performed using a custom database manager (Dataspects, Inc). Non-linear regression analysis was used to calculate EC<sub>50</sub>.

### III. Compound Characterization

**Methyl 6-butyl-2-methyl-4-oxo-7-(2-phenoxyethoxy)-1,4-dihydroquinoline-3-carboxylate (5).**  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.10 (s, 1H), 8.48 (s, 1H), 7.87 (s, 1H), 7.31 (t,  $J = 8.0$  Hz, 2H), 7.05 (s, 15H), 6.98 (dd,  $J = 12.5, 7.7$  Hz, 3H), 4.40 (s, 4H), 3.72 (s, 3H), 2.61 (t,  $J = 7.5$  Hz, 2H), 1.52 (dd,  $J = 15.1, 7.9$  Hz, 2H), 1.27 – 1.21 (m, 2H), 0.84 (t,  $J = 7.3$  Hz, 3H). HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{25}\text{NO}_5$   $[\text{M}+\text{H}]^+$ : 396.1805, found 396.1800.

**3-acetamidophenyl butyrate (7).** N-(3-Hydroxyphenyl)acetamide (300 g) was stirred in pyridine (990 mL) followed by the addition of butyryl chloride (246 mL). This reaction was stirred at r.t. for 30 min until stirring stopped. The resulting crystalline suspension was left for 18h to ensure completion. The mixture was dissolved in  $\text{H}_2\text{O}$  and EA (1:1, 1000 mL), the organic layer is separated and washed with brine (3X 1000 mL). The organic layer is dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo at  $70^\circ\text{C}$  to remove pyridine. Upon cooling the oil become a very low melting solid. This solid is carefully added to a coarse 500 mL frit and dried, minimal washing with ice cold hexane was used to cake the solid. The final compound was collected to provide the title compound in 75% yield (440 g) as a light-yellow solid.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (s, 1H), 7.37 (s, 1H), 7.17 (d,  $J = 8.1$  Hz, 1H), 7.03 (d,  $J = 7.5$  Hz, 1H), 6.70 (d,  $J = 7.8$  Hz, 1H), 2.46 (t,  $J = 7.4$  Hz, 2H), 1.96 (s, 3H), 1.70 (dd,  $J = 14.7, 7.4$  Hz, 2H), 0.96 (t,  $J = 7.4$  Hz, 3H).

**N-(4-butyryl-3-hydroxyphenyl)acetamide (8).** 3-Acetamidophenyl butyrate (440 g, 1.98 mol) was added to a 2-neck 1-L round bottom flask. Finely mortared  $\text{AlCl}_3$  (560 g, 4.15 mol) was added to the flask and the two solids were heated to approximately  $150^\circ\text{C}$  at which point a glassy brittle solid forms. This process is extremely exothermic and a large amount of HCl gas is formed. This solid was removed from the reaction flask and re-mortared into a very fine orange powder. This powder was then re-heated at  $175^\circ\text{C}$  overnight. Upon cooling the solid is added to 2N  $\text{H}_2\text{SO}_4$  and ice and stirred for several hours. The solid is then filtered off and wash liberally with water. Next, 1M NaOH is used to dissolve the solid completely, followed by acidification of this solution with acetic acid. This resulting solid is filtered and

recrystallized with benzene to obtain the title compound in 75% yield (330 g).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  12.66 (s, 1H), 8.12 (s, 1H), 7.70 (d,  $J = 8.8$  Hz, 1H), 7.17 (d,  $J = 8.8$  Hz, 1H), 7.13 (s, 1H), 2.90 (t,  $J = 7.4$  Hz, 2H), 2.21 (s, 3H), 1.77 (dt,  $J = 14.8, 7.4$  Hz, 2H), 1.02 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  205.51, 169.15, 163.75, 144.90, 131.35, 115.73, 110.35, 107.37, 39.89, 24.81, 18.12, 13.85.

**N-(3-hydroxy-4-(1-hydroxybutyl)phenyl)acetamide (9).** N-(4-Butyryl-3-hydroxyphenyl)acetamide (330 g, 1.48 mol) was dissolved in 2 L of DCM and 1 L of MeOH. This solution was chilled to  $0^\circ\text{C}$  and  $\text{NaBH}_4$  (33g, 0.87 mol) was added portion-wise over 30 minutes. Upon completion by TLC the reaction is quenched by the slow addition of ice. The resulting mixture is slowly evaporated to remove the methanol. The resulting solution is taken up in 1L of EA and washed with 1M HCl. The organic layer is then washed with water (X3) and brine (X1). The organic layer is dried over  $\text{Na}_2\text{SO}_4$  concentrated in vacuo to give a brown viscous oil. This oil was exhaustively columned on a 1L column and eluted with EA:H (2:1) over the course of approximately 12 column loads to obtain the title compound in 56% yield (184 g).

**N-(4-butyl-3-hydroxyphenyl)acetamide (10).** N-(3-Hydroxy-4-(1-hydroxybutyl)phenyl)acetamide (184 g) was reduced in 20g batches by dissolving it in de-oxygenated acetic acid (210 mL) in the presence of 10% Pd/C (7g) at 60 Psi in a Parr hydrogenator for eleven hours. Upon completion the reaction was filtered over celite and diluted. The acetic acid was removed in vacuo. The resulting oil was diluted with EA and was washed with water (X3) followed by brine (X1). The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The crude compound was purified via flash chromatography with 100% EA to obtain the title compound in 70% yield (120 g) as a waxy tan solid.

**N-(4-butyl-3-(2-phenoxyethoxy)phenyl)acetamide (11).** To a flame dried flask back-filled with argon (X2) was added NaH (26.5 g, 1.1 mol) and 325 mL of anhydrous DMF. A solution of N-(4-butyl-3-hydroxyphenyl)acetamide (120 g, 0.58 mol) dissolved in 325 mL of anhydrous DMF was added via dropping funnel over 30 min at  $0^\circ\text{C}$ . The reaction was then brought to  $75^\circ\text{C}$  and held for 4h. Upon

completion the reaction was cooled to r.t. and filtered over celite. The resulting solution was diluted with EA (600 mL) and washed with ice cold water (X3) and brine (X1). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude oil was purified further via flash chromatography with Hex:EA (2:1) to obtain the title compound in 71% yield (132 g) as a light brown solid.

**4-butyl-3-(2-phenoxyethoxy)aniline (12).** N-(4-Butyl-3-(2-phenoxyethoxy)phenyl)acetamide (132 g, 0.41 mol) was dissolved in EtOH (897 mL) and H<sub>2</sub>O (104 mL). KOH (312 g, 5.57 mol) was added at 0°C and the solution was allowed to reflux for 18h. Upon completion the reaction is cooled to room temperature and diluted with 2L of water and 2L of DCM. The organic layer was washed with water (X2) and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude compound was purified further via flash chromatography with Hex:EA (1:1) to obtain the title compound in 80% yield (92 g) as a pink solid.

**4-chloro-3-methoxyaniline (13).** 900 ml of ammonia is condensed at -78°C. 1g of thinly shaven strips of sodium was added followed by 1.0g of iron (III) nitrate nonahydrate. Upon disappearance of the deep blue color 25g of thinly shaven strips of sodium was added. After 30 minutes of stirring at -78°C 50g of 2,5-dichloroanisole is added as a solution in hexane (70 ml) dropwise and the reaction is warmed to -45°C for 2h. Upon completion the ammonia is allowed to evaporate. The crude pot is then diluted in chloroform and 100g of NH<sub>4</sub>Cl is added slowly. The combines are taken up in a separatory funnel and washed with H<sub>2</sub>O (3X) followed by brine (1X). The organic layer is dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The resulting solid can be used without further purification. Yield: 99%. <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.98 (d, *J* = 8.4, 1H), 6.34 (d, *J* = 1.8, 1H), 6.16 (dd, *J* = 8.4, 1.9, 1H), 5.23 (s, 2H), 3.74 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 154.90, 149.16, 129.68, 107.02, 106.74, 98.66, 55.38. HRMS (ESI) calcd for C<sub>7</sub>H<sub>8</sub>ClNO [M+H]<sup>+</sup>: 157.0367, found: 157.0361.

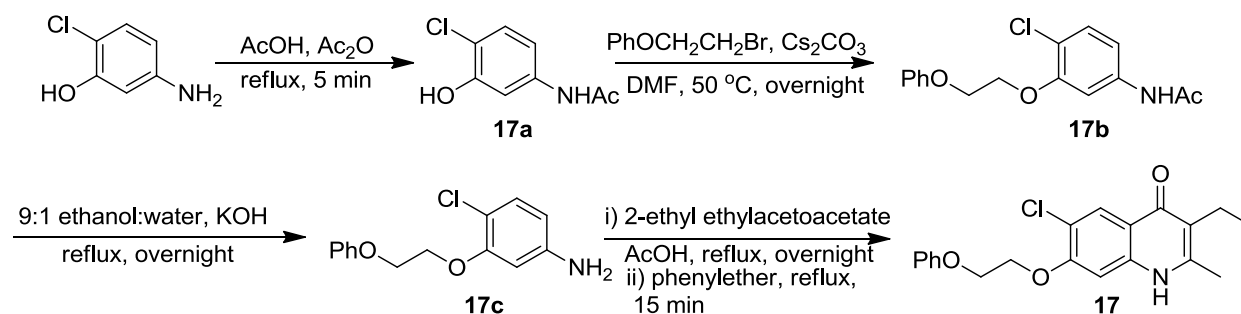
**6-butyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one (15).** <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.35 (s, 1H), 7.74 (s, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.05 – 6.87 (m, 4H), 5.79 (s, 1H), 4.38 (d, *J* = 6.7 Hz, 4H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 3H), 1.58 – 1.47 (m, 2H), 1.25 (dd, *J* = 14.6, 7.3 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 176.87, 159.75, 159.09, 149.21, 140.85, 130.18,

127.88, 125.94, 121.45, 119.12, 115.23, 108.68, 98.82, 67.50, 66.77, 32.03, 29.87, 22.51, 20.02, 14.42.

HRMS (ESI) calcd for  $C_{22}H_{25}NO_3$   $[M+H]^+$ : 352.1907, found 352.1900.

**6-butyl-3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one (16).**  $^1H$  NMR (400 MHz, DMSO)  $\delta$  11.15 (s, 1H), 7.76 (s, 1H), 7.31 (t,  $J = 7.9$  Hz, 2H), 7.02 – 6.93 (m, 3H), 6.87 (s, 1H), 4.38 (d,  $J = 9.8$  Hz, 4H), 2.58 (t,  $J = 7.4$  Hz, 2H), 2.49 – 2.43 (m, 2H), 2.34 (s, 3H), 1.51 (dd,  $J = 14.8, 7.5$  Hz, 2H), 1.25 (dd,  $J = 14.7, 7.3$  Hz, 2H), 0.98 (t,  $J = 7.3$  Hz, 3H), 0.83 (t,  $J = 7.3$  Hz, 3H).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  175.53, 159.43, 159.10, 145.05, 139.87, 130.67, 130.16, 127.57, 126.24, 121.43, 120.52, 119.25, 118.23, 115.22, 98.32, 67.42, 66.78, 32.09, 29.92, 22.50, 18.59, 17.86, 14.42.

### Synthesis of compound 17:



**N-(4-chloro-3-hydroxyphenyl) acetamide (17a).** To a solution of 4-chloro-3-hydroxy aniline (4.0 g, 28 mmol) in acetic acid (20 mL), acetic anhydride (3.0 mL, 42.0 mmol) was added and the reaction was refluxed for 5 minutes. Then the reaction mixture was cooled to room temperature and the product was solidified. It was filtered off and washed with water (10 mL) and dried to obtain the product **17a** in 93% yield (4.8 g) as a creamy white solid. There is no need for further purification.  $^1H$  NMR (400 MHz, Acetone)  $\delta$  9.26 (br s, 1H), 9.01 (s, 1H), 7.72 (d,  $J = 2.4$  Hz, 1H), 7.20 (d,  $J = 8.6$  Hz, 1H), 6.93 (dd,  $J = 8.6, 2.4$  Hz, 1H), 2.09 (s, 3H).  $^{13}C$  NMR (101 MHz, Acetone)  $\delta$  169.66, 154.05, 140.20, 130.49, 115.18, 112.16, 108.56, 24.35. HRMS (ESI) calcd for  $C_8H_8ClNO_2$   $[M+Na]^+$ : 208.0136, Found: 208.0144.

**N-[4-chloro-3-(2-phenoxy-ethoxy)-phenyl]-acetamide (17b).** The compound **17b** was synthesized starting from **17a** following the general procedure H as white powder in 82% yield.  $^1H$  NMR (400 MHz, DMSO)  $\delta$  10.08 (s, 1H), 7.56 (d,  $J = 2.0$  Hz, 1H), 7.37 – 7.25 (m, 3H), 7.16 (dd,  $J = 8.6, 2.1$  Hz, 1H), 7.00 (d,  $J = 7.9$  Hz, 2H), 6.95 (t,  $J = 7.3$  Hz, 1H), 4.38-4.28 (m, 4H), 2.05 (s, 3H).  $^{13}C$  NMR (101 MHz,

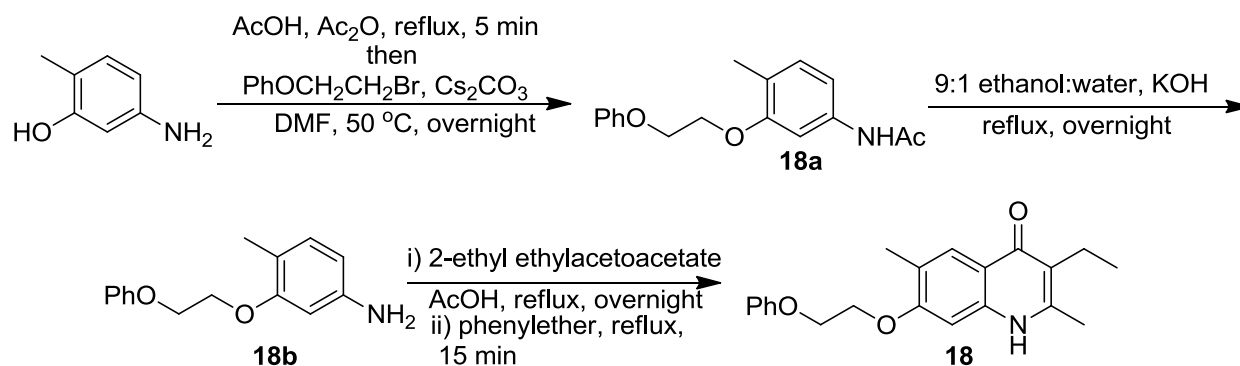


DMSO)  $\delta$  168.49, 158.27, 153.57, 139.44, 129.77, 129.51, 120.79, 114.57, 112.10, 104.83, 67.44, 66.03, 24.07. HRMS (ESI) calcd for  $C_{16}H_{16}ClNO_3$   $[M+Na]^+$ : 328.0711, Found: 328.0720.

**4-chloro-3(2-phenoxy-ethoxy)-phenylamine (17c).** The compound **17c** was prepared starting from **17b** following the general procedure I in 80% yield.  $^1H$  NMR (400 MHz, DMSO)  $\delta$  7.30 (t,  $J$  = 7.5 Hz, 2H), 7.02-6.91 (m, 4H), 6.39 (d,  $J$  = 1.1 Hz, 1H), 6.21 – 6.13 (m, 1H), 5.25 (s, 2H), 4.33-4.28 (m, 2H), 4.28 – 4.22 (m, 2H).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  158.29, 154.03, 149.10, 129.77, 129.47, 120.73, 114.56, 107.19, 99.82, 67.01, 66.14. HRMS (ESI) calcd for  $C_{14}H_{14}ClNO_2$   $[M+H]^+$ : 264.0786, Found: 264.0777.

**6-chloro-3-ethyl-2-methyl-7-(2-phenoxy-ethoxy)-1 *H*-quinolin-4-one (17).** The compound **17** was prepared according to the general procedure A in 60% yield as white crystalline compound, m.p. = 290-292°C.  $^1H$  NMR (400 MHz, DMSO)  $\delta$  11.38 (s, 1H), 7.97 (s, 1H), 7.31 (t,  $J$  = 7.9 Hz, 2H), 7.06 (s, 1H), 7.02 (d,  $J$  = 8.0 Hz, 2H), 6.96 (t,  $J$  = 7.3 Hz, 1H), 4.49-4.37 (m, 4H), 2.47 (q,  $J$  = 7.3 Hz, 2H), 2.36 (s, 3H), 0.98 (t,  $J$  = 7.3 Hz, 3H).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  173.94, 158.23, 155.36, 145.43, 139.21, 129.50, 126.02, 120.84, 120.36, 118.09, 117.64, 114.58, 100.15, 67.77, 65.92, 17.87, 17.23, 13.38. HRMS (ESI) calcd for  $C_{20}H_{20}ClNO_3$   $[M + H]^+$ : 358.1204, Found: 358.1195.

### Synthesis of Compound 18.



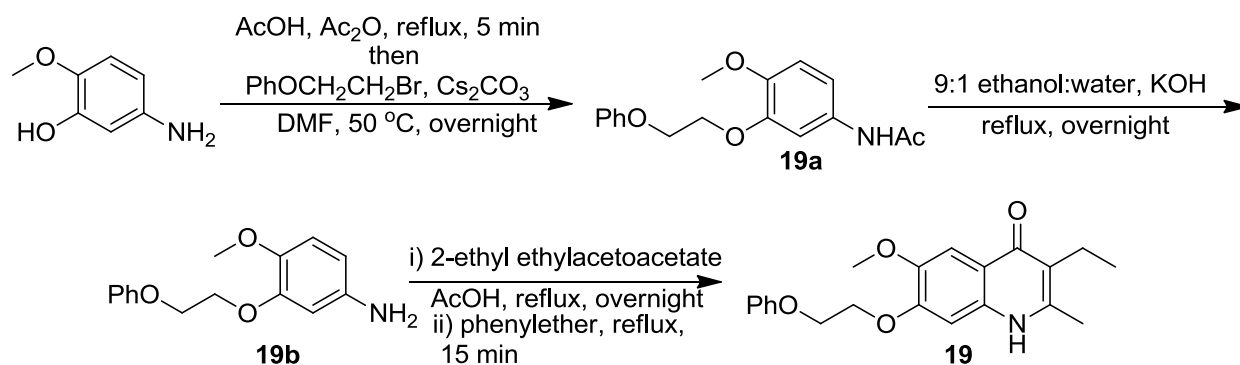
***N*-[4-methyl-3-(2-phenoxy-ethoxy)-phenyl]-acetamide (18a).** To a solution of 5-amino-2-methylphenol (1.0 g, 8.1 mmol) in acetic acid (6 mL), acetic anhydride (1.25 mL, 12.2 mmol) was added and the reaction was refluxed for 5 minutes. Then the reaction mixture was cooled to room temperature and the product was solidified. It was filtered off and washed with water (4 mL) and dried to obtain the product along with the trace amount of *O*-acylated product. The mixture was added  $\beta$ -bromophenetole

(1.33 g, 6.6 mmol) and  $\text{Cs}_2\text{CO}_3$  (2.927g, 9.0 mmol) in DMF (10 mL) was stirred for overnight at 50°C. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and recrystallized from toluene to obtain the pure product **18a** in 65% (yield over two steps) as an off-white solid.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  9.89 (s, 1H), 7.34 (s, 1H), 7.30 (t,  $J$  = 7.9 Hz, 2H), 7.08 – 6.85 (m, 5H), 4.39 – 4.28 (m, 2H), 4.26 – 4.17 (m, 2H), 2.06 (s, 3H), 2.02 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  168.08, 158.41, 156.24, 138.40, 130.20, 129.51, 120.73, 120.38, 114.57, 111.06, 103.21, 66.65, 66.21, 24.03, 15.43. HRMS (ESI) calcd for  $\text{C}_{17}\text{H}_{19}\text{NO}_3$   $[\text{M} + \text{H}]^+$ : 286.1438, Found: 286.1427.

**4-methyl-3-(2-phenoxy-ethoxy)-phenylamine (18b)**. The compound **18b** was prepared starting from **18a** according to the general procedure I in 77% yield.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.41 – 7.11 (m, 2H), 7.20 – 6.90 (m, 3H), 6.76 (d,  $J$  = 8.3 Hz, 1H), 6.26 (d,  $J$  = 2.0 Hz, 1H), 6.11 (dd,  $J$  = 7.9, 2.0 Hz, 1H), 4.86 (s, 2H), 4.29 (dd,  $J$  = 5.6, 3.5 Hz, 2H), 4.18 (dd,  $J$  = 5.6, 3.5 Hz, 2H), 1.97 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  158.45, 156.92, 147.88, 130.55, 129.49, 120.68, 114.56, 112.66, 106.22, 98.70, 66.34, 66.30, 15.17. HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_2$   $[\text{M} + \text{H}]^+$ : 244.1332, Found: 244.1326.

**3-ethyl-2,6-dimethyl-7-(2-phenoxy-ethoxy)-1H-quinolin-4-one (18)**. The compound **18** was prepared starting from **18b** (633 mg, 2.6 mmol) according to the general procedure A in 70% yield as a white powder, m.p. = 280-282°C.  $^1\text{H}$  NMR (250 MHz, DMSO)  $\delta$  11.16 (s, 1H), 7.79 (s, 1H), 7.31 (t,  $J$  = 7.8 Hz, 2H), 6.98 (m, 3H), 6.86 (s, 1H), 4.38 (m, 4H), 2.47 (q,  $J$  = 7.15 Hz, 2H), 2.34 (s, 3H), 2.18 (s, 3H), 0.97 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  175.43, 159.59, 159.07, 145.03, 139.88, 130.19, 126.97, 122.92, 121.48, 120.52, 118.22, 115.29, 98.15, 67.53, 66.77, 18.57, 17.86, 16.62, 14.25. HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{23}\text{NO}_3$   $[\text{M} + \text{H}]^+$ : 338.1751, Found: 338.1748.

## Synthesis of Compound 19.



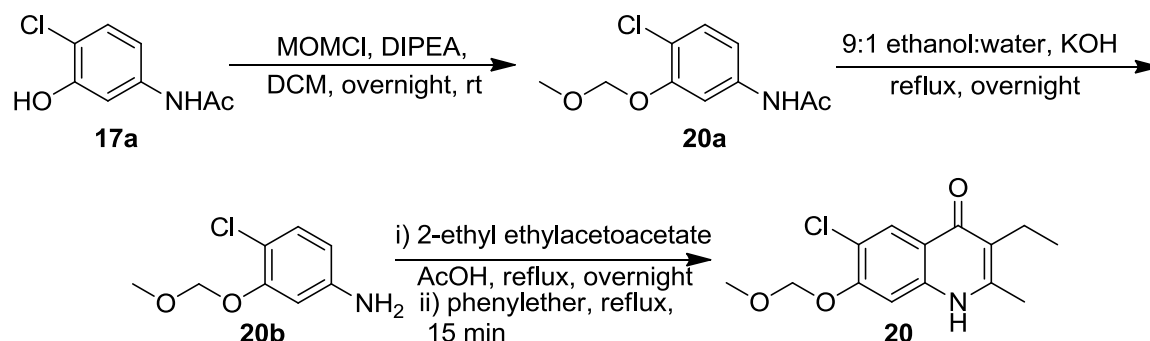
**N-[4-methoxy-3-(2-phenoxy-ethoxy)-phenyl]-acetamide (19a).** The compound **19a** was prepared starting from 5-amino-2-methoxy phenol (800 mg, 5.75 mmol) according to the procedure described for the synthesis of **18a** in 62% yield as white powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 9.80 (s, 1H), 7.35 (d, *J* = 2.2 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.10 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.99 (d, *J* = 9.08 Hz, 1H), 6.95 (t, *J* = 7.47 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 1H), 4.30 (dd, *J* = 5.5, 2.9 Hz, 2H), 4.23 (dd, *J* = 5.5, 2.9 Hz, 2H), 3.71 (s, 3H), 2.01 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 167.75, 158.26, 147.46, 144.88, 132.95, 129.49, 120.69, 114.47, 112.44, 111.57, 105.89, 67.11, 66.14, 55.72, 23.87. HRMS (ESI) calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>4</sub> [M+H]<sup>+</sup>: 302.1387, Found: 302.1377.

**4-methoxy-3-(2-phenoxy-ethoxy)-phenylamine (19b).** The compound **19b** was prepared starting from **19a** by following the general procedure I in 89% yield as dark brown solid. <sup>1</sup>H NMR (400 MHz, Acetone) δ 7.33 – 7.25 (m, 2H), 7.02 – 6.97 (m, 2H), 6.97 – 6.91 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 1H), 6.26 – 6.18 (m, 1H), 4.39 – 4.30 (m, 4H), 3.77 (s, 3H). <sup>13</sup>C NMR (101 MHz, Acetone) δ 159.99, 149.92, 146.85, 130.38, 121.66, 115.55, 114.29, 112.49, 107.67, 103.52, 68.63, 67.61, 56.79. HRMS (ESI) calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 260.1281, Found: 260.1271.

**3-ethyl-6-methoxy-2-methyl-7-(2-phenoxy-methoxy)-1H-quinolin-4-one (19).** The compound **19** was prepared starting from **19b** following the general procedure A in 79% yield as white powder, m.p. = 228-229°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.15 (s, 1H), 7.40 (s, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.05 – 6.77 (m, 4H), 4.36-4.28 (m, 4H), 3.77 (s, 3H), 2.45 (q, *J* = 7.3 Hz, 2H), 2.31 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 174.26, 158.21, 151.33, 145.95, 143.85, 134.56, 129.53, 120.79,

119.36, 117.56, 114.48, 104.73, 99.51, 67.10, 65.93, 55.35, 18.01, 17.17, 13.57. HRMS (ESI) calcd for  $C_{21}H_{23}NO_4$   $[M+H]^+$ : 354.1699, Found: 354.1700.

### Synthesis of Compound 20.

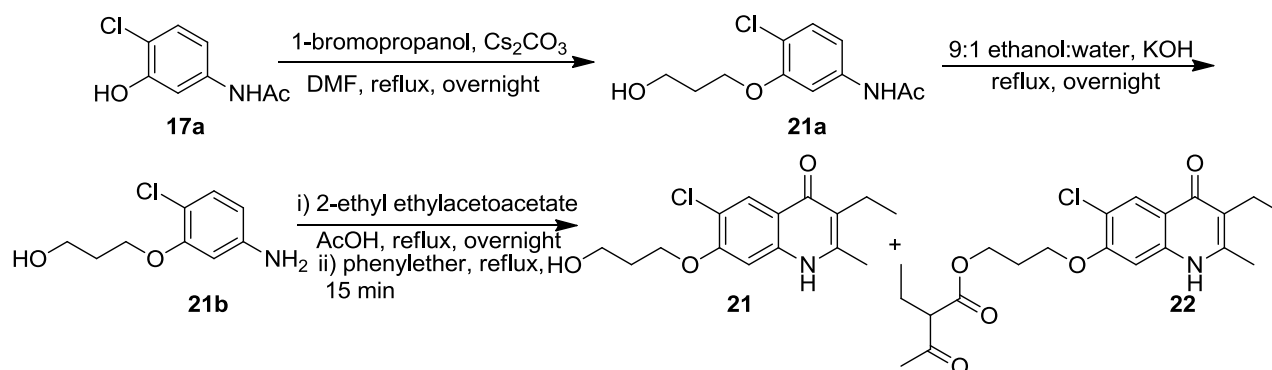


***N*-(4-chloro-3-methoxymethoxy phenyl) acetamide (20a).** To a DCM (15 mL) solution of compound **17a** (1.07 g, 5.78 mmol) was added MOMCl (0.6 mL, 7.51 mmol). DIPEA (1.8 mL, 10.4 mmol) was added at 0°C to the reaction mixture. The mixture was warmed to room temperature and stirred for overnight. Water (5 mL) was added and extracted with DCM (3 X 20 mL). The combined extracts were shaken with brine (10 mL) and dried over  $Na_2SO_4$ . The product **20a** was obtained (860 mg, 65% yield) after flash column chromatography as a white crystalline solid.  $^1H$  NMR (400 MHz, ACETONE)  $\delta$  9.25 (br s, 1H), 7.60 (d,  $J$  = 2.2 Hz, 1H), 7.32 (dd,  $J$  = 8.7, 2.2 Hz, 1H), 7.28 (d,  $J$  = 8.7 Hz, 1H), 5.23 (s, 2H), 3.46 (s, 3H), 2.07 (s, 3H).  $^{13}C$  NMR (101 MHz, ACETONE)  $\delta$  169.12, 153.80, 140.44, 130.70, 114.17, 108.43, 95.92, 56.49, 24.36. HRMS (ESI) calcd for  $C_{10}H_{12}ClNO_3$   $[M+Na]^+$ : 252.0398, Found: 252.0389.

**4-chloro-3-methoxymethoxy-phenylamine (20b).** To the compound **20b** was prepared according to the general procedure I starting from **20a** (700 mg, 3.05 mmol) in 84% yield as dark brown solid.  $^1H$  NMR (400 MHz, DMSO)  $\delta$  6.99 (d,  $J$  = 8.5 Hz, 1H), 6.44 (d,  $J$  = 2.5 Hz, 1H), 6.20 (dd,  $J$  = 8.5, 2.5 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 3.39 (s, 3H).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  152.64, 149.00, 129.73, 108.32, 108.03, 101.96, 94.34, 55.70. HRMS (ESI) calcd for  $C_8H_{10}ClNO_2$   $[M+H]^+$ : 188.0473, Found: 188.0476.

**6-chloro-3-ethyl-7-methoxymethoxy-2-methyl-1*H*-quinoline-4-one (20).** The compound **20** was synthesized by following the general procedure A, starting from aniline **20b** in 17% yield as light brown powder, m.p. = 217-219°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.99 (s, 1H), 7.22 (s, 1H), 5.37 (s, 2H), 3.45 (d, *J* = 1.2 Hz, 3H), 2.46 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 173.91, 153.88, 145.66, 138.97, 125.98, 120.31, 118.67, 118.11, 102.52, 94.83, 56.02, 17.87, 17.19, 13.36. HRMS (ESI) calcd for C<sub>14</sub>H<sub>16</sub>ClNO<sub>3</sub> [M+H]<sup>+</sup>: 282.0892, Found: 282.0889.

### Synthesis of compound 21 and 22.



**N-[4-chloro-3-(3-hydroxy-propoxy)-phenyl]-acetamide (21a).** The compound **21a** was prepared starting from **17a** by following the general procedure H in 60% yield as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 10.04 (s, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.12 (dd, *J* = 8.6, 2.1 Hz, 1H), 4.58 (t, *J* = 5.1 Hz, 1H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.58 (dd, *J* = 11.3, 5.9 Hz, 2H), 2.03 (s, 3H), 1.94 – 1.81 (m, 2H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 168.43, 153.78, 139.41, 129.56, 114.83, 111.57, 104.47, 65.47, 57.11, 31.91, 24.04. HRMS (ESI) calcd for C<sub>11</sub>H<sub>14</sub>ClNO<sub>3</sub> [M+H]<sup>+</sup>: 244.0735, Found: 244.0734.

**3-(5-amino-2-chloro-phenoxy)-propan-1-ol (21b).** The compound **21b** was prepared starting from **21a** following the general procedure I in 67% yield as a light brown solid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.95 (d, *J* = 8.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.12 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.20 (s, 2H), 4.53 (t, *J* = 5.1 Hz, 1H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.60 - 3.53 (m, 2H), 1.85 (t, *J* = 6.3 Hz, 2H). <sup>13</sup>C NMR (101

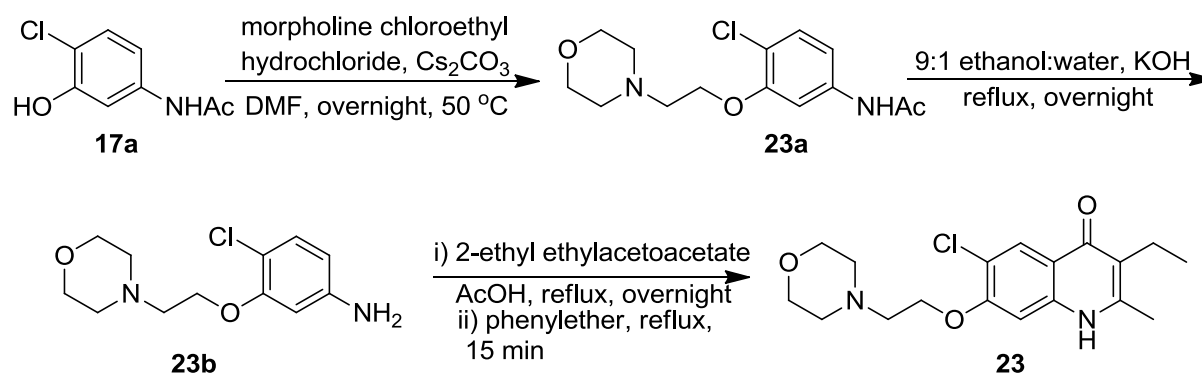
MHz, DMSO)  $\delta$  154.25, 149.06, 129.56, 106.68, 99.54, 95.81, 65.02, 57.21, 32.04. HRMS (ESI) calcd for  $C_9H_{12}ClNO_2$   $[M+Na]^+$ : 224.0449, Found: 224.0455.

**Compound 21 and 22.** The above mixture of the compounds was prepared starting from **21b** following the general procedure A in 21% yield (over the mixture of the regular product **21** and a transesterification product **22**). The mixture was separated by preparative HPLC by dissolving in minimal amount of methanol.

**6-chloro-3-ethyl-7-(3-hydroxy-propoxy)-2-methyl-1H-quinolin-4-one (21).**  $^1H$  NMR (400 MHz, DMSO)  $\delta$  11.31 (br s, 1H), 7.94 (s, 1H), 6.98 (s, 1H), 4.60 (br s, 1H), 4.15 (t,  $J$  = 6.2 Hz, 2H), 3.59 (d,  $J$  = 5.0 Hz, 2H), 2.45 (q,  $J$  = 7.4 Hz, 2H), 2.33 (s, 3H), 1.97 – 1.88 (m, 2H), 0.96 (t,  $J$  = 7.4 Hz, 3H).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  173.97, 155.60, 145.34, 139.31, 125.85, 120.27, 117.82, 117.73, 99.75, 65.82, 57.01, 31.68, 17.87, 17.25, 13.40. HRMS (ESI) calcd for  $C_{15}H_{18}ClNO_3$   $[M+H]^+$ : 296.1048, Found: 296.1046.

**2-ethyl-3-oxo-butyricacid-3-(6-chloro-3-ethyl-2-methyl-4-oxo-1,4-dihydro-quinolin-7-yloxy)-propyl ester (22).**  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  9.46 (s, 1H), 8.31 (s, 1H), 6.68 (s, 1H), 4.36 (dt,  $J$  = 11.1, 5.5 Hz, 1H), 4.25 (dt,  $J$  = 11.3, 5.6 Hz, 1H), 4.15 (t,  $J$  = 6.6 Hz, 2H), 3.45 (t,  $J$  = 7.4 Hz, 1H), 2.62 (q,  $J$  = 7.83 Hz, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 2.21 – 2.09 (m, 2H), 2.01 – 1.83 (m, 2H), 1.09 (t,  $J$  = 7.3 Hz, 3H), 0.95 (t,  $J$  = 7.4 Hz, 3H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  175.90, 168.89, 156.24, 144.63, 139.00, 127.74, 122.08, 119.77, 118.87, 98.85, 65.33, 61.67, 61.52, 29.41, 27.98, 21.82, 18.68, 18.25, 13.45, 11.97. HRMS (ESI) calcd for  $C_{21}H_{26}ClNO_5$   $[M+Na]^+$ : 430.1392, Found: 430.1391.

### Synthesis of Compound 23.

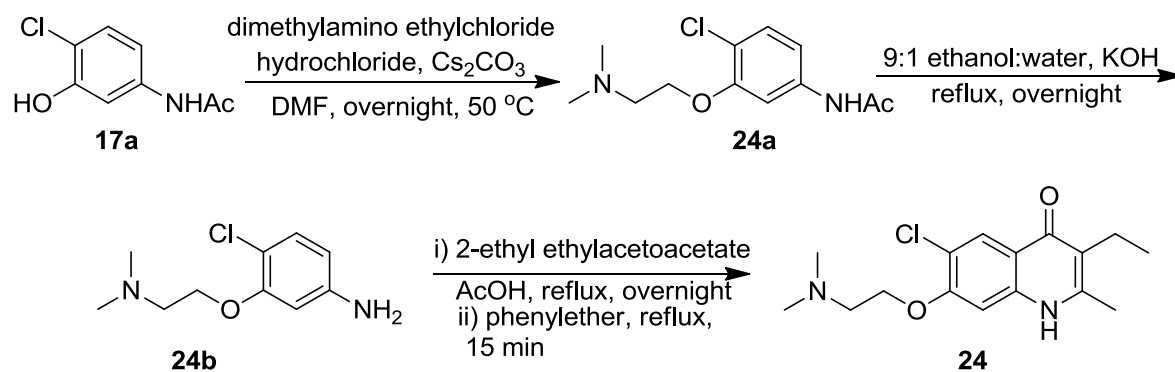


***N*-[4-chloro-3-(2-morpholin-4-yl-ethoxy)-phenyl]-acetamide (23a).** The compound **23a** was prepared by using the general procedure H in 69% yield starting from **17a**, with 2.5 eq of Cs<sub>2</sub>CO<sub>3</sub> and 1.1 eq of 4-(2-chloroethyl) morpholine hydrochloride. <sup>1</sup>H NMR (400 MHz, DMSO) δ 9.97 (s, 1H), 7.43 (s, 1H), 7.22 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 4.02 (t, *J* = 5.4 Hz, 2H), 3.59 – 3.41 (m, 4H), 2.65 (t, *J* = 5.3 Hz, 2H), 2.48-2.38 (m, 4H), 1.96 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 168.48, 153.63, 139.44, 129.65, 114.89, 111.81, 104.61, 66.81, 66.23, 56.61, 53.74, 24.08. HRMS (ESI) calcd for C<sub>14</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>3</sub> [M+Na]<sup>+</sup>: 321.0976, Found: 321.0971.

**4-chloro-3-(2-morpholin-4-yl-ethoxy)-phenylamine (23b).** The compound **23b** was prepared starting from **23a** according to the general procedure I in 87% yield. <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.93 (d, *J* = 8.5 Hz, 1H), 6.30 (d, *J* = 2.2 Hz, 1H), 6.10 (dd, *J* = 8.5, 2.2 Hz, 1H), 5.17 (s, 2H), 3.99 (t, *J* = 5.8 Hz, 2H), 3.56 – 3.51 (m, 4H), 2.66 (t, *J* = 5.8 Hz, 2H), 2.47 (d, *J* = 3.9 Hz, 4H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 154.09, 149.05, 129.63, 107.24, 106.91, 99.65, 66.45, 66.19, 56.73, 53.71. HRMS (ESI) calcd for C<sub>12</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 257.10513, Found: 257.10397.

**6-chloro-3ethyl-2-methyl-7-(2-morpholin-4-yl-ethoxy)-1 *H*-quinolin-4-one (23).** The compound **23** was synthesized starting from aniline **23b** by following the general procedure A in 12% yield as beige powder, m.p. = 270-271 °C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.29 (s, 1H), 7.93 (s, 1H), 6.95 (s, 1H), 4.18 (t, *J* = 5.4 Hz, 2H), 3.65 – 3.47 (m, 4H), 2.76 (t, *J* = 5.2 Hz, 2H), 2.60 – 2.37 (m, 6H), 2.32 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 174.65, 156.10, 146.08, 139.93, 126.60, 121.01, 118.63, 118.37, 100.60, 67.96, 66.88, 57.04, 54.40, 18.55, 17.92, 14.08. HRMS (ESI) calcd for C<sub>18</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 351.1470, Found: 351.1463.

## Synthesis of Compound 24.



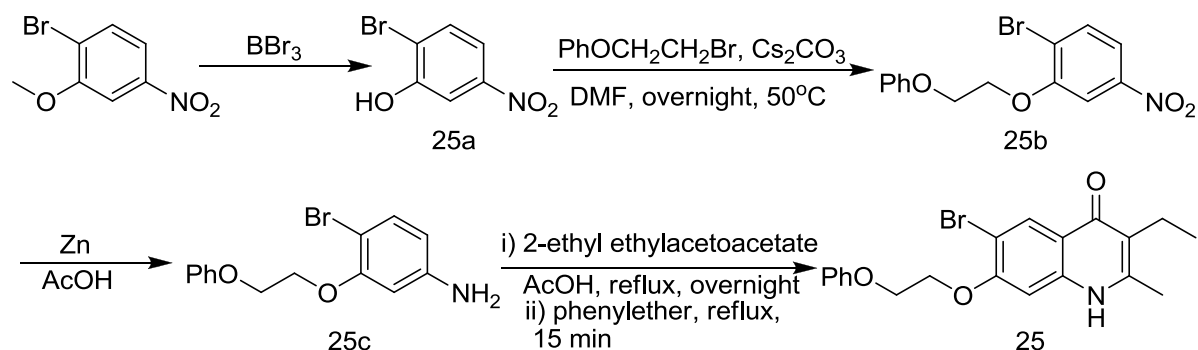
**N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-acetamide (24a).** The compound **24a** was prepared starting from **17a** and 2-dimethylamino ethyl chloride hydrochloride, following the general procedure H in 80% yield.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  10.04 (s, 1H), 7.49 (d,  $J = 2.1$  Hz, 1H), 7.30 (d,  $J = 8.6$  Hz, 1H), 7.13 (dd,  $J = 8.6, 2.2$  Hz, 1H), 4.06 (t,  $J = 5.8$  Hz, 2H), 2.68 (t,  $J = 5.7$  Hz, 2H), 2.25 (s, 6H), 2.04 (s, 3H). HRMS (ESI) calcd for  $\text{C}_{12}\text{H}_{17}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 257.1051, Found: 257.1042.

**4-chloro-3-(2-dimethylamino-ethoxy)-phenylamine (24b).** The compound **24b** was prepared starting from **24a** according to the general procedure I in 81% yield.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  6.96 (d,  $J = 8.5$  Hz, 1H), 6.33 (d,  $J = 2.4$  Hz, 1H), 6.13 (dd,  $J = 8.5, 2.4$  Hz, 1H), 5.21 (s, 2H), 4.00 (t,  $J = 5.8$  Hz, 2H), 2.67 (t,  $J = 5.8$  Hz, 2H), 2.26 (s, 6H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  154.09, 149.07, 129.65, 107.19, 106.87, 99.55, 66.54, 57.35, 45.57. HRMS (ESI) calcd for  $\text{C}_{10}\text{H}_{15}\text{ClN}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 215.0946, Found: 215.0937.

**6-chloro-7-(2-dimethylamino-ethoxy)-3-ethyl-2-methyl-1H-quinolin-4-one (24).** The compound **24** was prepared starting from **24b** according to the general procedure A in 53% yield as a light brown solid, m.p. =  $227\text{--}230^\circ\text{C}$ .  $^1\text{H}$  NMR (250 MHz, DMSO)  $\delta$  11.34 (s, 1H), 7.92 (s, 1H), 6.96 (s, 1H), 4.15 (t,  $J = 5.7$  Hz, 2H), 2.71 (t,  $J = 5.7$  Hz, 2H), 2.43 (q,  $J = 7.54$  Hz, 2H), 2.32 (s, 3H), 2.24 (s, 6H), 0.94 (t,  $J = 7.54$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  173.93, 155.39, 145.41, 139.28, 125.87, 120.26, 117.90, 117.65, 99.82, 67.45, 57.05, 45.66, 17.87, 17.18, 13.39. HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{21}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 309.1364, Found: 309.1364.



## Synthesis of Compound 25.



**2-bromo-5-nitro-phenol (25a).** To the DCM (10 mL) solution of 1-bromo-2-methoxy-4-nitrobenzene (1.0 gr, 4.3 mmol) was added  $\text{BBr}_3$  (8.58 mL of 1.0 M solution, 8.6 mmol) at  $0^\circ\text{C}$ . The reaction mixture warmed to room temperature and stirred for overnight. The mixture was quenched with water and extracted with ethyl acetate (3 X 20 mL). The combined extracts were dried and the crude was purified by flash column chromatography to get the desired compound as pale brown powder in 65% yield (600 mg).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (s, 1H), 7.79-7.59 (m, 2H), 5.92 (br s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  152.97, 148.49, 132.62, 117.44, 116.43, 111.20.

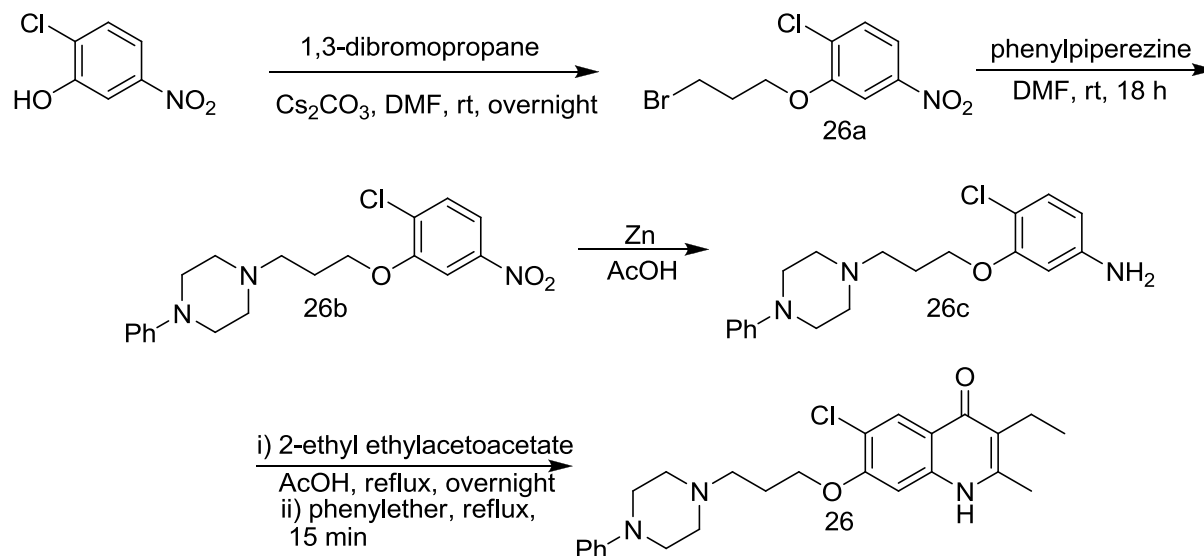
**1-bromo-4-nitro-2-(2-phenoxy-ethoxy)-benzene (25b).** The compound **25b** was prepared by using the general procedure H, starting from compound **25a** as pale yellow solid in 80% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (d,  $J = 2.3$  Hz, 1H), 7.77 – 7.66 (m, 2H), 7.33-7.26 (m, 2H), 7.00-6.93 (m, 3H), 4.49 (dd,  $J = 5.6, 3.5$  Hz, 2H), 4.41 (dd,  $J = 6.0, 3.5$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.37, 133.68, 129.55, 121.38, 120.28, 116.91, 114.73, 108.08, 68.58, 66.18. HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{12}\text{BrNO}_4$   $[\text{M}+\text{Na}]^+$ : 359.9842, Found: 359.9855.

**4-bromo-3-(2-phenoxy-ethoxy)-phenylamine (25c).** To the mixture of **25b** (600 mg, 1.8 mmol) and zinc dust (1.157 g, 18.0 mmol) in ethanol (10 mL) was added acetic acid (1.068 mL, 18 mmol) at  $0^\circ\text{C}$ . The reaction mixture was warmed to room temperature and stirred for 4 hours. Then the mixture was filtered, the solvent was distilled off under reduced pressure and the crude was purified by flash column chromatography to obtain the aniline **25c** in 84% yield.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.33 – 7.26 (m, 2H), 7.11 (d,  $J = 8.5$  Hz, 1H), 7.02 – 6.98 (m, 2H), 6.97 - 6.92 (m, 1H), 6.37 (d,  $J = 2.4$  Hz, 1H), 6.13

(dd,  $J = 8.5, 2.4$  Hz, 1H), 5.28 (s, 2H), 4.31 (dd,  $J = 5.3, 3.0$  Hz, 2H), 4.24 (dd,  $J = 5.8, 2.8$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  158.77, 155.38, 150.21, 133.10, 129.94, 121.20, 115.06, 108.45, 100.28, 67.56, 66.64. HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{14}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$ : 308.0281, Found: 308.0268.

**6-bromo-3-ethyl-2-methyl-7-(2-phenoxy-ethoxy)-1H-quinolin-4-one (25).** The compound **25** was prepared starting from **25c** according to the general procedure A in 15% yield as the mixture of two isomers. The required isomer **25** was separated by preparative HPLC by dissolving the mixture in minimal amount of methanol.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  11.32 (s, 1H), 8.11 (s, 1H), 7.27 (t,  $J = 7.8$  Hz, 2H), 7.11 – 6.78 (m, 4H), 4.39 (m, 4H), 2.43 (q,  $J = 7.3$  Hz, 2H), 2.32 (s, 3H), 0.94 (t,  $J = 7.3$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  173.93, 158.36, 156.01, 145.72, 139.90, 129.48, 120.88, 120.49, 118.80, 114.55, 106.78, 99.92, 67.90, 66.08, 17.88, 17.24, 13.40. HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{20}\text{BrNO}_3$   $[\text{M}+\text{Na}]^+$ : 424.0519, Found: 424.0517.

### Synthesis of Compound 26.



**2-(3-bromo-propoxy)-1-chloro-4-nitro benzene (26a).** To the DMF (18 mL) solution of 2-chloro-5-nitro phenol (2.0 g, 11.5 mmol) was added 1,3-dibromo propane (1.3 mL, 12.65 mmol) and  $\text{Cs}_2\text{CO}_3$  (4.1 g, 12.65 mmol) and stirred overnight at room temperature. Water (20 mL) was added to the mixture, extracted with DCM (3 X 25 mL) and combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuo. The crude product was purified by flash column chromatography to get the title compound

**26a** in 64% (2.176 g) yield as colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 – 7.74 (m, 2H), 7.49 (d,  $J$  = 9.0 Hz, 1H), 4.26 (t,  $J$  = 5.7 Hz, 2H), 3.64 (t,  $J$  = 6.3 Hz, 2H), 2.45 – 2.34 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.50, 147.22, 130.41, 130.31, 116.46, 107.79, 66.95, 31.82, 29.37.

**1-[3-(2-chloro-5-nitro-phenoxy)-propyl]-4-phenyl-piperazine (26b).** To the compound **26a** (2.1 g, 7.1 mmol) in DMF (9 mL), was added N-phenyl piperazine (1.16 g, 7.1 mmol) and  $\text{K}_2\text{CO}_3$  (1.28 g, 9.23 mmol). The mixture was stirred for 18 hours at room temperature. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3 X 20 mL). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by flash column chromatography to get the title compound **26b** in 78% yield as yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.80 -7.73 (m, 2H), 7.49 (dd,  $J$  = 8.1, 0.8 Hz, 1H), 7.29 – 7.21 (m, 2H), 6.95 – 6.89 (m, 2H), 6.88 – 6.80 (m, 1H), 4.21 (t,  $J$  = 6.3 Hz, 2H), 3.27 – 3.13 (m, 4H), 2.70 – 2.53 (m, 6H), 2.17 – 2.05 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.84, 151.22, 147.18, 130.28, 130.20, 129.03, 119.61, 116.06, 115.97, 107.68, 67.86, 54.64, 53.24, 49.08, 26.26. HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{22}\text{ClN}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 376.1423, Found: 376.1411.

**4-chloro-3-[3-(4-phenyl-piperzin-1-yl)-propoxy]-phenylamine (26c).** The compound **26c** was prepared starting from **26b** following the procedure described for the synthesis of **25c** in 76% yield as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.15 (t,  $J$  = 7.9 Hz, 2H), 6.92 (d,  $J$  = 8.5 Hz, 1H), 6.86 (d,  $J$  = 8.1 Hz, 2H), 6.71 (t,  $J$  = 7.2 Hz, 1H), 6.28 (d,  $J$  = 1.9 Hz, 1H), 6.08 (dd,  $J$  = 8.5, 2.0 Hz, 1H), 5.16 (s, 2H), 3.92 (t,  $J$  = 6.3 Hz, 2H), 3.11 - 3.03 (m, 4H), 2.51 – 2.40 (m, 6H), 1.95 – 1.76 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  154.24, 150.99, 149.07, 129.60, 128.84, 118.67, 115.26, 107.32, 106.78, 99.65, 66.32, 54.30, 52.76, 48.16, 26.11. HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{24}\text{ClN}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 346.1681, Found: 346.1669.

**6-chloro-3-ethyl-2-methyl-7-[3-(4-phenyl-piperazin-1-yl)-propoxy]-1*H*-quinolin-4-one (26).** The compound 26 was prepared starting from aniline **26c** (306 mg, 0.886 mmol) following the general procedure A to get the title compound **26** in 22% yield as white crystalline, m.p. = 253-255°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.29 (s, 1H), 7.94 (s, 1H), 7.18 (t, *J* = 7.9 Hz, 2H), 6.98 (s, 1H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.75 (d, *J* = 7.2 Hz, 1H), 4.14 (t, *J* = 6.2 Hz, 2H), 3.15 – 3.05 (m, 4H), 2.63 – 2.36 (m, 8H), 2.32 (s, 3H), 2.06 – 1.94 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 173.98, 155.57, 150.99, 145.34, 139.29, 128.87, 125.88, 120.29, 118.73, 117.86, 117.73, 115.30, 99.84, 67.22, 54.20, 52.75, 48.19, 25.78, 19.77, 17.87, 17.26, 13.41. HRMS (ESI) calcd for C<sub>25</sub>H<sub>30</sub>ClN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 440.2099, Found: 440.2098.

**3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one (27).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.20 (s, 1H), 8.03 – 7.88 (m, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 6.97 (dd, *J* = 20.1, 7.7 Hz, 3H), 6.89 (d, *J* = 6.9 Hz, 2H), 4.36 (s, 4H), 2.47 (d, *J* = 7.5 Hz, 2H), 2.35 (s, 3H), 0.98 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 175.01, 160.32, 158.23, 144.95, 140.72, 129.53, 127.01, 120.79, 120.00, 118.06, 114.60, 114.48, 112.45, 99.07, 66.57, 66.01, 17.87, 17.21, 13.53.

**6-butyl-3-iodo-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one (28).** Following general procedure B the title compound was prepared from **15** in 89% yield as a light yellow powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.78 (s, 1H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.02 – 6.92 (m, 4H), 4.40 (s, 4H), 2.61 (d, *J* = 10.1 Hz, 5H), 1.57 – 1.49 (m, 2H), 1.26 (dt, *J* = 14.6, 7.3 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

**6-butyl-4-ethoxy-3-iodo-2-methyl-7-(2-phenoxyethoxy)quinolone (30).** Following general procedure C the title compound was prepared in 77% yield as a beige solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.68 (s, 1H), 7.35 – 7.24 (m, 3H), 6.95 (t, *J* = 7.1 Hz, 3H), 4.40 (dd, *J* = 17.5, 5.0 Hz, 4H), 4.16 (q, *J* = 7.0 Hz, 2H), 2.89 (s, 3H), 2.77 – 2.71 (m, 2H), 1.62 (dt, *J* = 14.0, 7.3 Hz, 5H), 1.34 (dt, *J* = 14.5, 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 162.58, 160.66, 158.99, 158.66, 149.45, 133.56, 129.48, 121.57, 121.09, 117.57, 114.71, 106.65, 87.05, 70.66, 66.76, 66.22, 31.64, 30.44, 30.38, 22.46, 15.81, 13.95.

**6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-phenylquinolin-4(1H)-one (31).** Following general procedure E the title compound was prepared in 49% yield. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.44 (s, 1H), 7.80 (s, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.33 – 7.25 (m, 3H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.02 – 6.93 (m, 4H), 4.40 (d, *J* = 4.9 Hz, 4H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.17 (s, 3H), 1.57 – 1.49 (m, 2H), 1.25 (dd, *J* = 14.6, 7.3 Hz, 2H), 0.83 (dd, *J* = 7.8, 6.7 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 174.34, 159.14, 158.42, 145.43, 139.42, 136.46, 131.02, 129.51, 127.66, 127.36, 126.27, 125.86, 120.78, 120.46, 118.35, 114.54, 97.88, 66.84, 66.09, 31.41, 29.26, 21.81, 18.76, 13.74. HRMS (ESI) calcd for C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 428.2220, found 428.2225.

**6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(pyridin-4-yl)quinolin-4(1H)-one (32).** Following general procedure E the title compound was prepared in 41% yield. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.62 (s, 1H), 8.56 (d, *J* = 4.2 Hz, 2H), 7.80 (s, 1H), 7.30 (dd, *J* = 13.1, 5.8 Hz, 4H), 7.04 – 6.90 (m, 4H), 4.40 (s, 4H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.57 – 1.48 (m, 2H), 1.24 (dt, *J* = 14.4, 7.4 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 173.70, 159.38, 158.42, 148.96, 145.97, 144.53, 139.43, 129.52, 127.81, 126.35, 125.79, 120.80, 118.25, 117.87, 114.55, 98.04, 66.91, 66.09, 31.35, 29.25, 21.81, 18.71, 13.74. HRMS (ESI) calcd for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 429.2173, found 429.2179.

**6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(pyridin-3-yl)quinolin-4(1H)-one (33).** Following general procedure E the title compound was prepared in 36% yield. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.59 (s, 1H), 8.46 (d, *J* = 11.9 Hz, 2H), 7.81 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 6.98 (dd, *J* = 21.4, 9.4 Hz, 4H), 4.41 (s, 4H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.53 (dt, *J* = 15.1, 7.6 Hz, 2H), 1.25 (dd, *J* = 14.6, 7.4 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 174.69, 159.76, 158.85, 151.91, 147.70, 146.62, 139.93, 138.94, 132.54, 129.95, 128.14, 126.23, 123.35, 121.22, 118.61, 117.33, 114.98, 98.44, 67.32, 66.52, 31.80, 29.69, 22.25, 19.20, 14.18. HRMS (ESI) calcd for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 429.2173, found 429.2172.

**6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(4-(trifluoromethyl)phenyl)quinolin-4(1H)-one (34).** Following general procedure D the title compound was prepared in 60% yield. <sup>1</sup>H NMR (400 MHz,

DMSO)  $\delta$  11.56 (s, 1H), 7.80 (s, 1H), 7.72 (d,  $J$  = 8.1 Hz, 2H), 7.48 (d,  $J$  = 8.0 Hz, 2H), 7.31 (t,  $J$  = 7.9 Hz, 2H), 7.03 – 6.94 (m, 4H), 4.41 (s, 4H), 2.61 (t,  $J$  = 7.4 Hz, 2H), 2.21 (s, 3H), 1.58 – 1.49 (m, 2H), 1.24 (dt,  $J$  = 14.6, 7.3 Hz, 2H), 0.83 (t,  $J$  = 7.3 Hz, 3H).  $^{19}\text{F}$  NMR (376 MHz, DMSO)  $\delta$  -61.19.  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  174.69, 160.01, 159.10, 146.52, 141.69, 140.13, 132.60, 130.20, 128.37, 127.55 (q,  $J$  = 31.31 Hz), 126.50, 125.13, 123.84, 121.47, 119.72, 118.95, 115.22, 98.67, 67.56, 66.76, 32.06, 29.94, 22.49, 19.42, 14.42. HRMS (ESI) calcd for  $\text{C}_{29}\text{H}_{28}\text{F}_3\text{NO}_3$   $[\text{M}+\text{H}]^+$ : 496.2094, found 496.2097.

**6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(4-(trifluoromethoxy)phenyl)quinolin-4(1H)-one (35).**

Following general procedure E the title compound was prepared in 37% yield.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  11.53 (s, 1H), 7.80 (s, 1H), 7.37 – 7.29 (m, 6H), 7.02 – 6.94 (m, 4H), 4.40 (d,  $J$  = 2.7 Hz, 4H), 2.63 – 2.57 (m, 2H), 2.19 (s, 3H), 1.54 (dd,  $J$  = 14.9, 7.3 Hz, 2H), 1.25 (dd,  $J$  = 14.8, 7.4 Hz, 2H), 0.83 (t,  $J$  = 7.3 Hz, 3H).  $^{19}\text{F}$  NMR (376 MHz, DMSO)  $\delta$  -56.62.  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  174.18, 159.28, 158.43, 146.84, 145.77, 139.45, 135.79, 132.93, 129.53, 127.59, 125.82, 121.46, 120.80, 120.27, 119.00, 118.92, 118.25, 114.54, 97.94, 66.88, 66.09, 31.41, 29.29, 21.83, 18.79, 13.76. HRMS (ESI) calcd for  $\text{C}_{29}\text{H}_{28}\text{F}_3\text{NO}_4$   $[\text{M}+\text{H}]^+$ : 512.2043, found 512.2046.

**6-butyl-3-(3-(4-fluorophenoxy)phenyl)-2-methyl-7-(2phenoxyethoxy)quinolin-4(1H)-one (36).**

Following general procedure E the title compound was prepared in 71% yield.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  11.48 (s, 1H), 7.79 (s, 1H), 7.38 (t,  $J$  = 7.9 Hz, 1H), 7.30 (dd,  $J$  = 11.9, 4.1 Hz, 2H), 7.22 (t,  $J$  = 8.8 Hz, 2H), 7.11 – 7.06 (m, 2H), 7.01 – 6.86 (m, 7H), 4.39 (d,  $J$  = 5.4 Hz, 4H), 2.59 (t,  $J$  = 7.5 Hz, 2H), 2.20 (s, 3H), 1.52 (dt,  $J$  = 14.8, 7.4 Hz, 2H), 1.24 (dd,  $J$  = 14.7, 7.4 Hz, 2H), 0.83 (t,  $J$  = 7.3 Hz, 3H).  $^{19}\text{F}$  NMR (376 MHz, DMSO)  $\delta$  -120.09.  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  174.10, 159.18, 158.05 (d,  $J$  = 240.4 Hz), 158.40, 156.46, 152.72 (d,  $J$  = 2.02 Hz), 145.59, 139.37, 138.40, 129.48, 129.15, 127.46, 126.20, 125.80, 120.89, 120.76, 120.41 (d,  $J$  = 7.07 Hz), 119.66, 118.29, 116.81 (d,  $J$  = 23.23 Hz), 116.15, 114.53, 97.89, 66.84, 66.08, 31.36, 29.21, 21.78, 18.76, 13.70. HRMS (ESI) calcd for  $\text{C}_{34}\text{H}_{32}\text{FNO}_4$   $[\text{M}+\text{H}]^+$ : 538.2388, found 538.2386.

**6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(4-((4-(trifluoromethoxy)phenoxy)methyl)phenyl)quinolin-4(1H)-one (37).**

Following general procedure E the title compound was prepared in 69% yield. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.41 (s, 1H), 7.76 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.25 (m, 4H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.01 – 6.87 (m, 5H), 5.11 (s, 2H), 4.37 (d, *J* = 3.4 Hz, 4H), 2.59 – 2.54 (m, 2H), 2.16 (s, 3H), 1.54 – 1.47 (m, 2H), 1.24 – 1.17 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H). <sup>19</sup>F NMR (376 MHz, DMSO) δ -57.31. <sup>13</sup>C NMR (101 MHz, DMSO) δ 174.61, 159.63, 158.84, 157.76, 146.22, 146.00, 142.25, 139.84, 136.60, 134.97, 131.56, 129.96, 127.90, 127.74, 126.29, 122.95, 121.23, 120.50, 118.73, 116.37, 114.97, 98.33, 70.19, 67.30, 66.53, 31.83, 29.70, 22.24, 19.22, 14.17. HRMS (ESI) calcd for C<sub>36</sub>H<sub>34</sub>F<sub>3</sub>NO<sub>5</sub> [M+H]<sup>+</sup>: 618.2462, found 618.2461.

**6-butyl-2-methyl-3-(2-methyl-4-(4-(trifluoromethoxy)phenoxy)phenyl)-7-(2-phenoxyethoxy)quinolin-4(1H)-one (38).**

Following general procedure F the title compound was prepared in 49% yield. Note: This reaction was performed in a microwave reactor at a temperature of 110°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.44 (s, 1H), 7.75 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.02 – 6.91 (m, 6H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.37 (s, 4H), 2.59 – 2.54 (m, 2H), 2.03 (s, 3H), 1.98 (s, 3H), 1.54 – 1.47 (m, 2H), 1.22 (dd, *J* = 14.7, 7.5 Hz, 2H), 0.80 (t, *J* = 7.2 Hz, 3H). <sup>19</sup>F NMR (376 MHz, DMSO) δ -57.31. <sup>13</sup>C NMR (101 MHz, DMSO) δ 170.34, 159.91, 158.35, 155.68, 155.55, 149.41, 143.58, 139.93, 139.59, 132.55, 130.11, 130.04, 129.47, 124.82, 122.80, 121.35, 120.78, 120.09, 119.70, 118.79, 118.52, 116.20, 114.45, 98.20, 67.16, 65.98, 31.24, 29.42, 21.84, 19.36, 18.67, 13.67. HRMS (ESI) calcd for C<sub>36</sub>H<sub>34</sub>F<sub>3</sub>NO<sub>5</sub> [M+H]<sup>+</sup>: 618.2462, found 618.2450.

**6-butyl-2-methyl-3-(2-methyl-4-(trifluoromethyl)phenyl)-7-(2-phenoxyethoxy)quinolin-4(1H)-one (39).**

Following general procedure E the title compound was prepared in 13% yield. <sup>1</sup>H NMR (400 MHz, DMSO) δ 11.57 (s, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.03 – 6.94 (m, 4H), 4.41 (s, 4H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.12 (s, 3H), 2.04 (s, 3H), 1.57 – 1.49 (m, 2H), 1.26 (dd, *J* = 14.6, 7.3 Hz, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). <sup>19</sup>F NMR (376 MHz, DMSO) δ -57.51. <sup>13</sup>C NMR (101 MHz, DMSO) δ 174.29, 159.77, 158.81, 146.33, 141.56, 140.02, 139.65, 132.33,

129.97, 128.30, 128.19, 127.88, 126.38, 126.34, 126.27, 126.13, 123.56, 122.64, 122.60, 121.26, 119.26, 118.45, 114.96, 98.45, 67.37, 66.51, 31.86, 29.71, 22.28, 19.63, 18.69, 14.14. HRMS (ESI) calcd for  $C_{30}H_{30}F_3NO_3$   $[M+H]^+$ : 510.2250, found 510.2246.

**6-butyl-3-(2,4-dimethylphenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one (40).** Following general procedure F the title compound was prepared in 64% yield. Note: This reaction was performed in a microwave reactor at a temperature of 110°C.  $^1H$  NMR (400 MHz, DMSO)  $\delta$  11.56 (s, 1H), 7.81 (s, 1H), 7.35 – 7.27 (m, 3H), 7.22 (d,  $J$  = 8.3 Hz, 1H), 7.05 – 6.93 (m, 5H), 4.38 (d,  $J$  = 5.9 Hz, 4H), 2.60 (t,  $J$  = 7.3 Hz, 2H), 2.03 (s, 6H), 1.52 (dd,  $J$  = 14.8, 7.6 Hz, 2H), 1.27 – 1.21 (m, 2H), 0.82 (t,  $J$  = 7.3 Hz, 3H).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  173.96, 159.21, 158.41, 145.82, 140.19, 139.59, 135.53, 132.69, 131.32, 129.49, 129.09, 127.61, 125.75, 125.34, 120.78, 118.81, 118.12, 114.53, 97.98, 66.86, 66.07, 31.46, 29.28, 21.88, 19.18, 18.29, 13.74. HRMS (ESI) calcd for  $C_{30}H_{33}NO_3$   $[M+H]^+$ : 456.2533, found 456.2541.

**6-butyl-3-(2-fluoro-4-(trifluoromethyl)phenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one (41).** Following general procedure F the title compound was prepared in 48% yield.  $^1H$  NMR (400 MHz, DMSO)  $\delta$  12.38 (s, 1H), 7.90 (s, 1H), 7.71 (d,  $J$  = 9.3 Hz, 1H), 7.66 – 7.46 (m, 2H), 7.31 (t,  $J$  = 7.8 Hz, 2H), 7.11 (s, 1H), 7.05 – 6.79 (m, 3H), 4.43 (s, 4H), 2.74 – 2.52 (m, 2H), 2.23 (s, 3H), 1.53 (dd,  $J$  = 14.6, 7.5 Hz, 2H), 1.28 – 1.19 (m, 2H), 0.82 (t,  $J$  = 7.3 Hz, 3H).  $^{19}F$  NMR (376 MHz, DMSO)  $\delta$  -61.11, -110.84.  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  172.39, 160.41 (d,  $J$  = 247.45 Hz), 160.31, 158.83, 148.67, 140.11, 135.08, 130.16, 129.92, 129.69, 128.20 (d,  $J$  = 16.16), 125.70, 123.90 (q,  $J$  = 273.71 Hz), 121.38, 121.23, 117.38, 114.98, 113.41, 113.22, 98.69, 67.52, 66.47, 31.69, 29.76, 22.25, 18.92, 14.13. HRMS (ESI) calcd for  $C_{29}H_{27}F_4NO_3$   $[M+H]^+$ : 514.1999, found 514.2000.

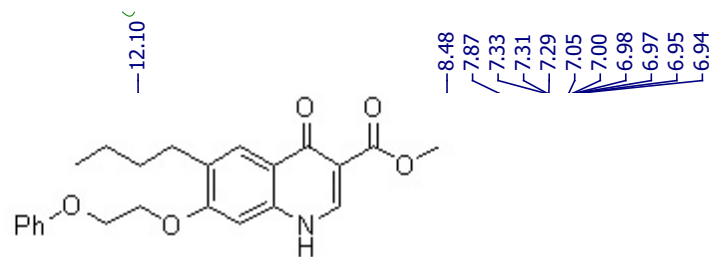
**6-butyl-3-(4-chloro-2-methylphenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one (42).** Following general procedure F the title compound was prepared in 52% yield.  $^1H$  NMR (400 MHz, DMSO)  $\delta$  11.44 (s, 1H), 7.79 (s, 1H), 7.31 (t,  $J$  = 7.6 Hz, 2H), 7.01 (dd,  $J$  = 23.2, 14.6 Hz, 5H), 6.88 (d,  $J$  = 7.8 Hz, 2H), 4.39 (d,  $J$  = 6.0 Hz, 4H), 2.64 – 2.55 (m, 2H), 2.29 (s, 3H), 2.00 (d,  $J$  = 14.3 Hz, 6H),



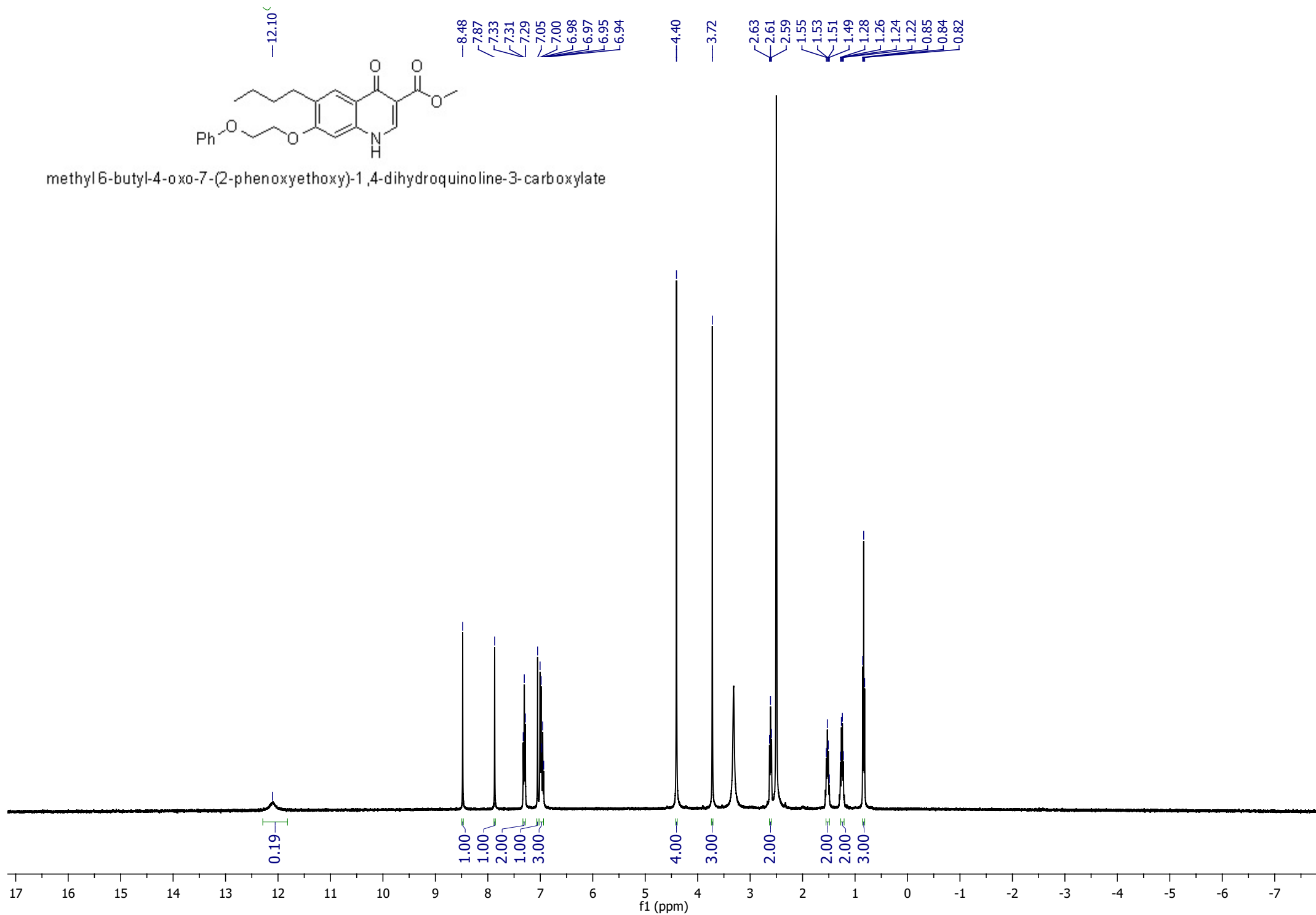
1.53 (dt,  $J = 14.8, 7.5$  Hz, 2H), 1.25 (dd,  $J = 14.8, 7.3$  Hz, 2H), 0.83 (t,  $J = 7.3$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  174.65, 159.50, 158.85, 146.04, 139.97, 137.59, 136.15, 133.93, 131.21, 130.61, 129.94, 127.77, 126.48, 126.25, 121.22, 120.41, 118.60, 114.98, 98.34, 67.28, 66.52, 31.93, 29.72, 22.31, 21.15, 19.76, 18.78, 14.18. HRMS (ESI) calcd for  $\text{C}_{29}\text{H}_{30}\text{ClNO}_3$   $[\text{M}+\text{H}]^+$ : 476.1987, found 476.1984.

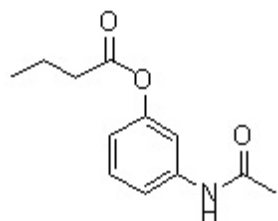
**6-butyl-3-(3,5-dimethylisoxazol-4-yl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one (43).**

Following general procedure F the title compound was prepared in 10% yield. Note: This reaction was performed in a microwave reactor at a temperature of 110°C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  11.70 (s, 1H), 7.79 (s, 1H), 7.30 (dd,  $J = 8.4, 7.5$  Hz, 2H), 7.01 – 6.92 (m, 4H), 4.39 (d,  $J = 2.3$  Hz, 4H), 2.63 – 2.57 (m, 2H), 2.16 (d,  $J = 2.8$  Hz, 6H), 1.98 (s, 3H), 1.55 – 1.50 (m, 2H), 1.24 (d,  $J = 7.5$  Hz, 2H), 0.84 (d,  $J = 7.3$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  174.30, 165.72, 160.26, 159.35, 158.41, 147.95, 139.57, 129.50, 127.91, 125.68, 120.79, 117.75, 114.55, 110.87, 107.78, 98.12, 66.94, 66.08, 31.41, 29.24, 21.85, 18.21, 13.73, 11.24, 10.23. HRMS (ESI) calcd for  $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 447.2278, found 447.2289.

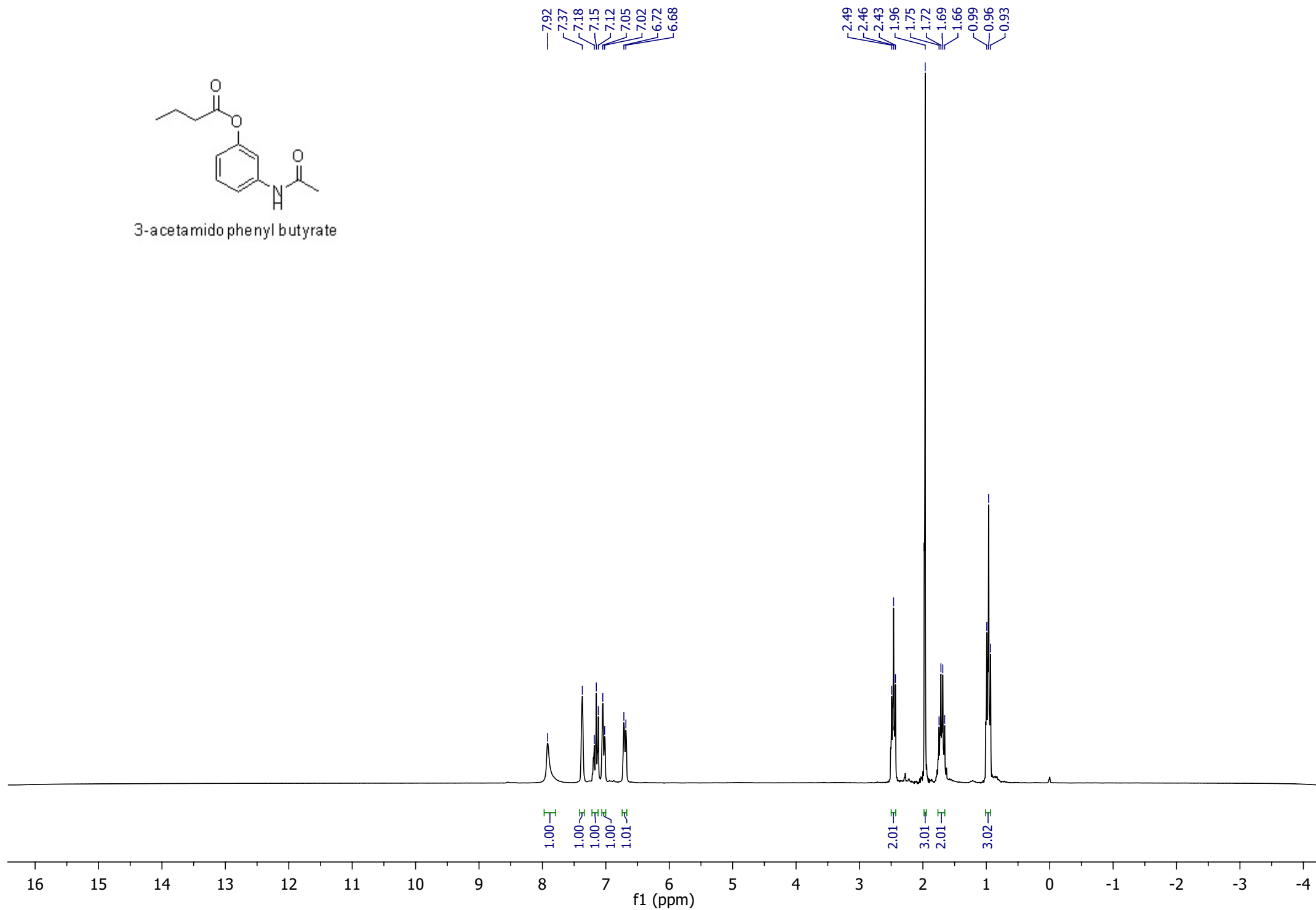


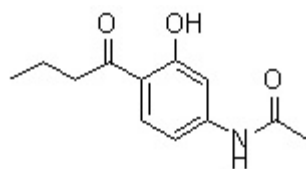
methyl 6-butyl-4-oxo-7-(2-phenoxyethoxy)-1,4-dihydroquinoline-3-carboxylate



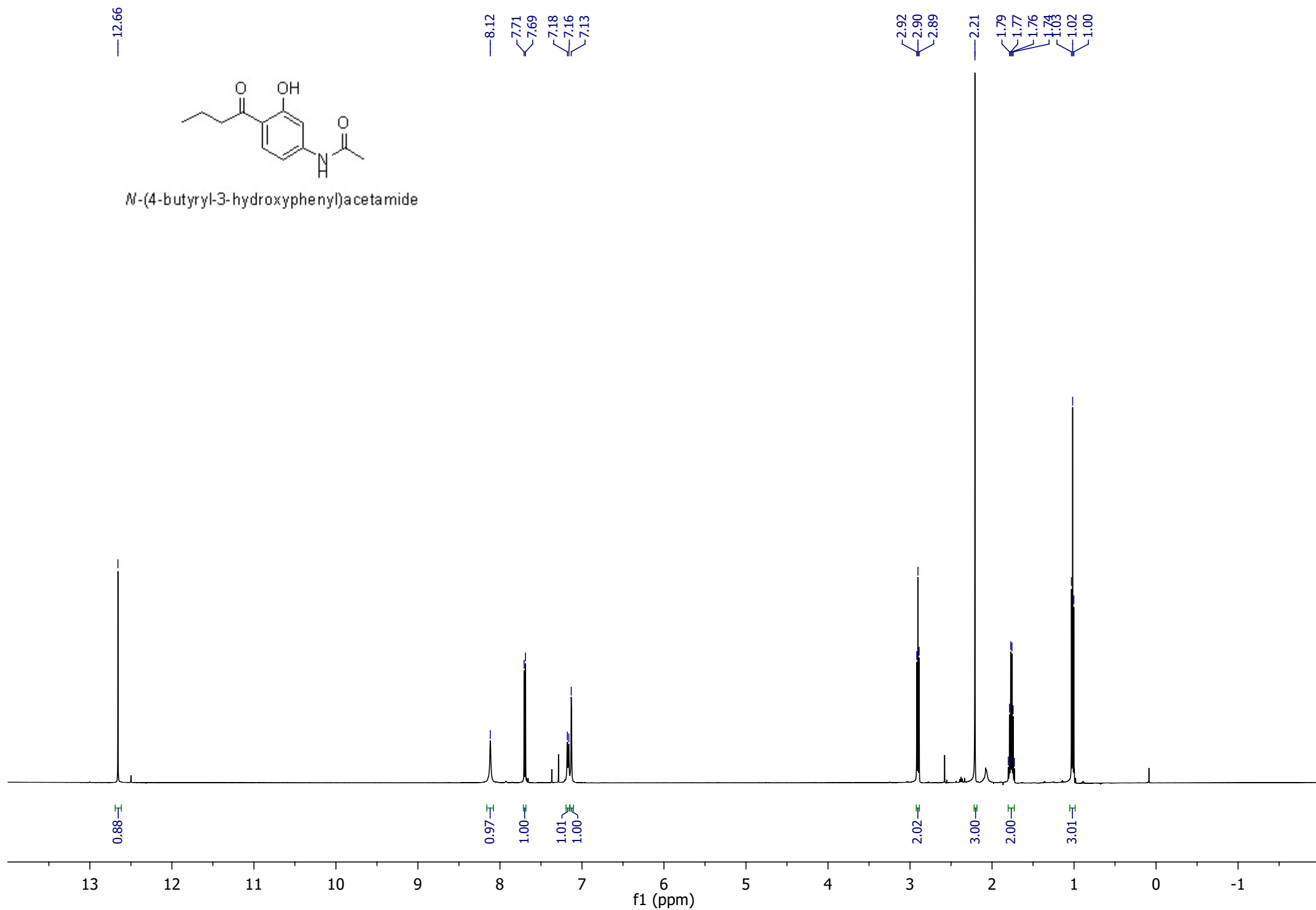


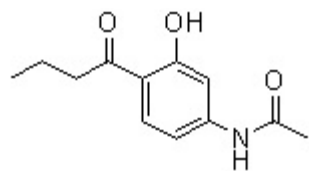
3-acetamido phenyl butyrate



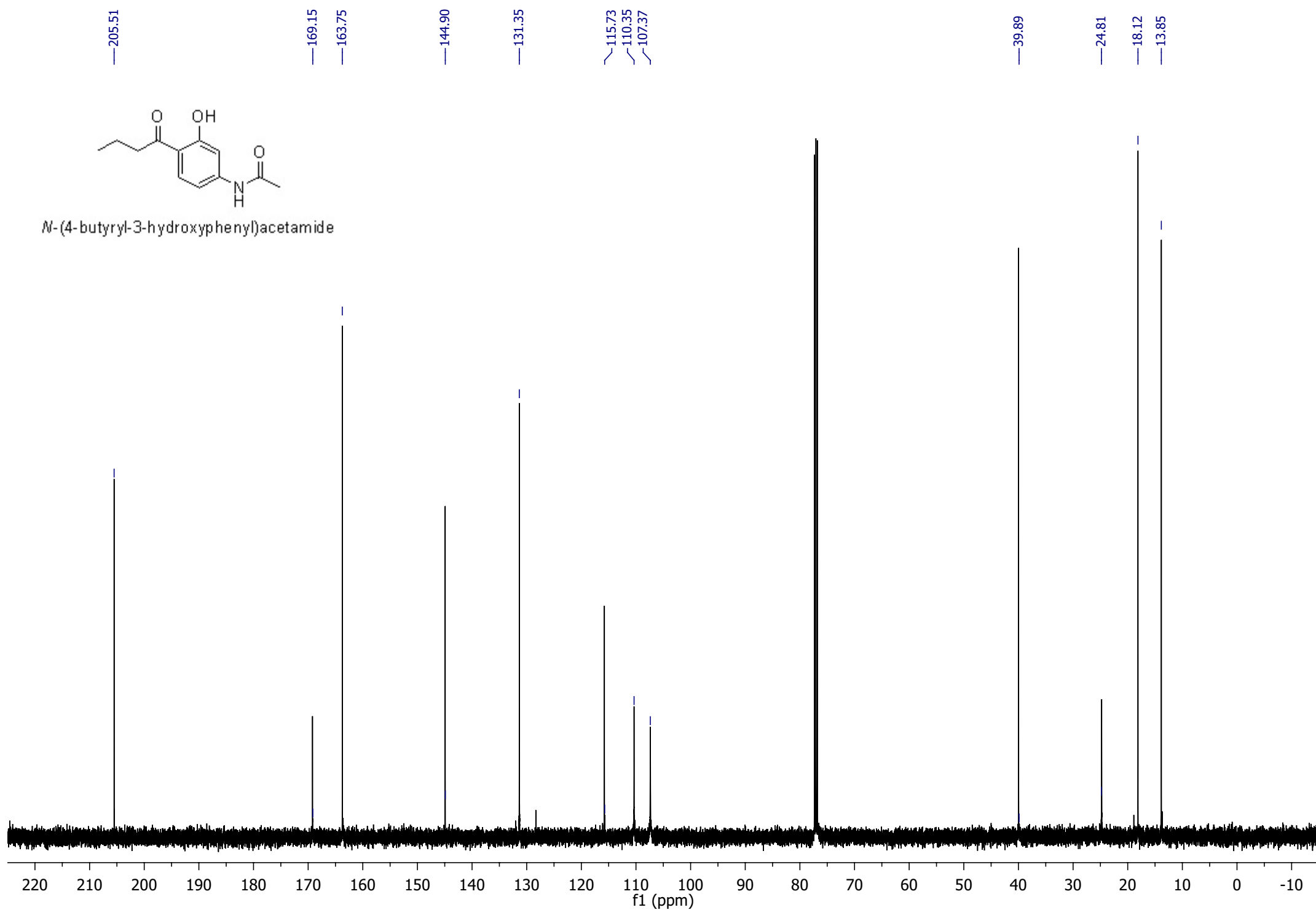


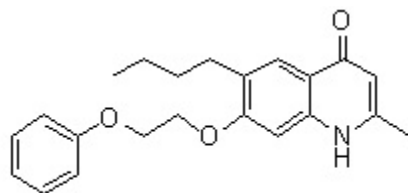
*N*-(4-butyl-3-hydroxyphenyl)acetamide



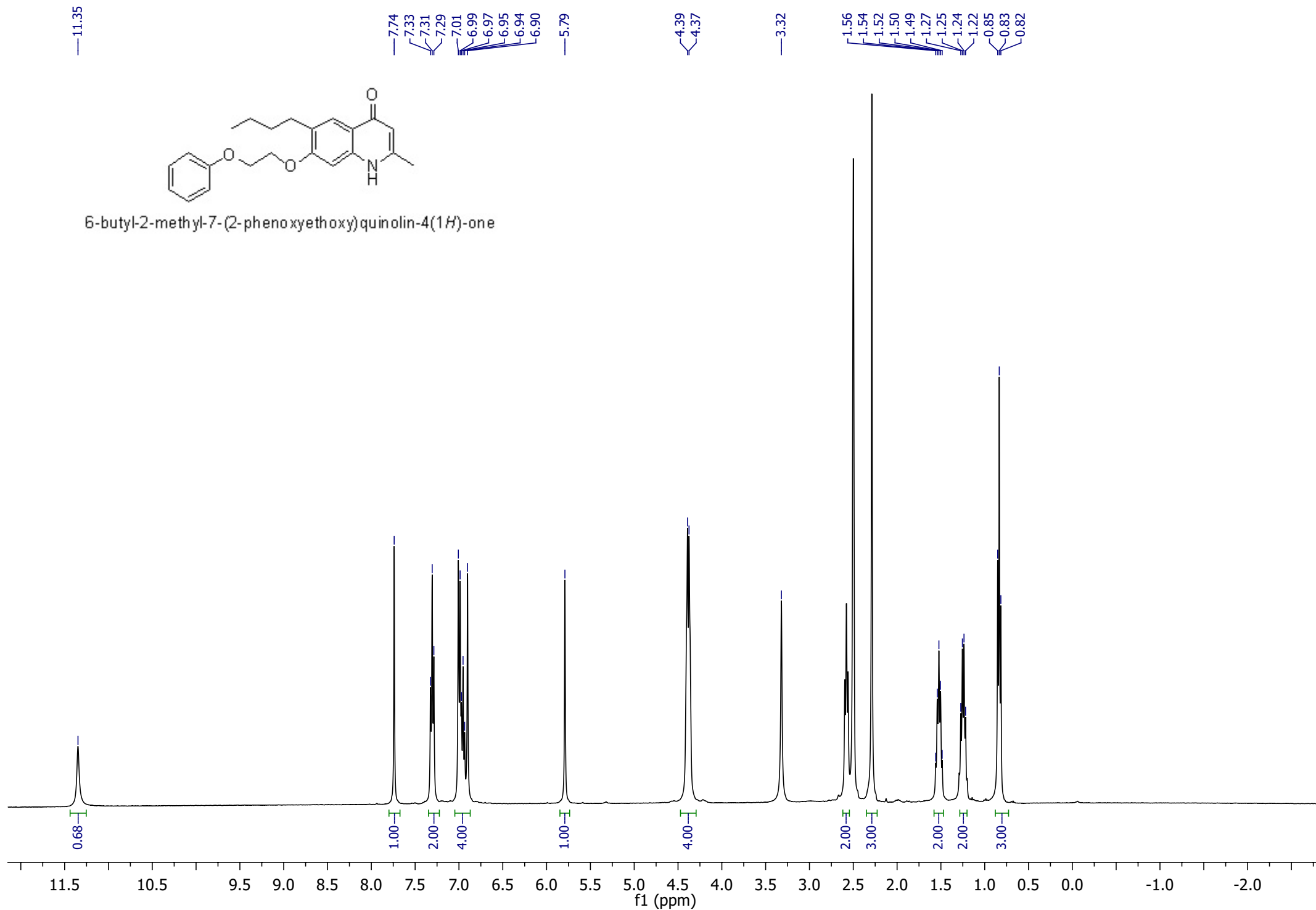


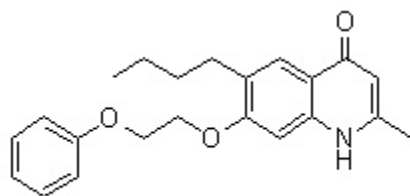
*N*-(4-butyryl-3-hydroxyphenyl)acetamide



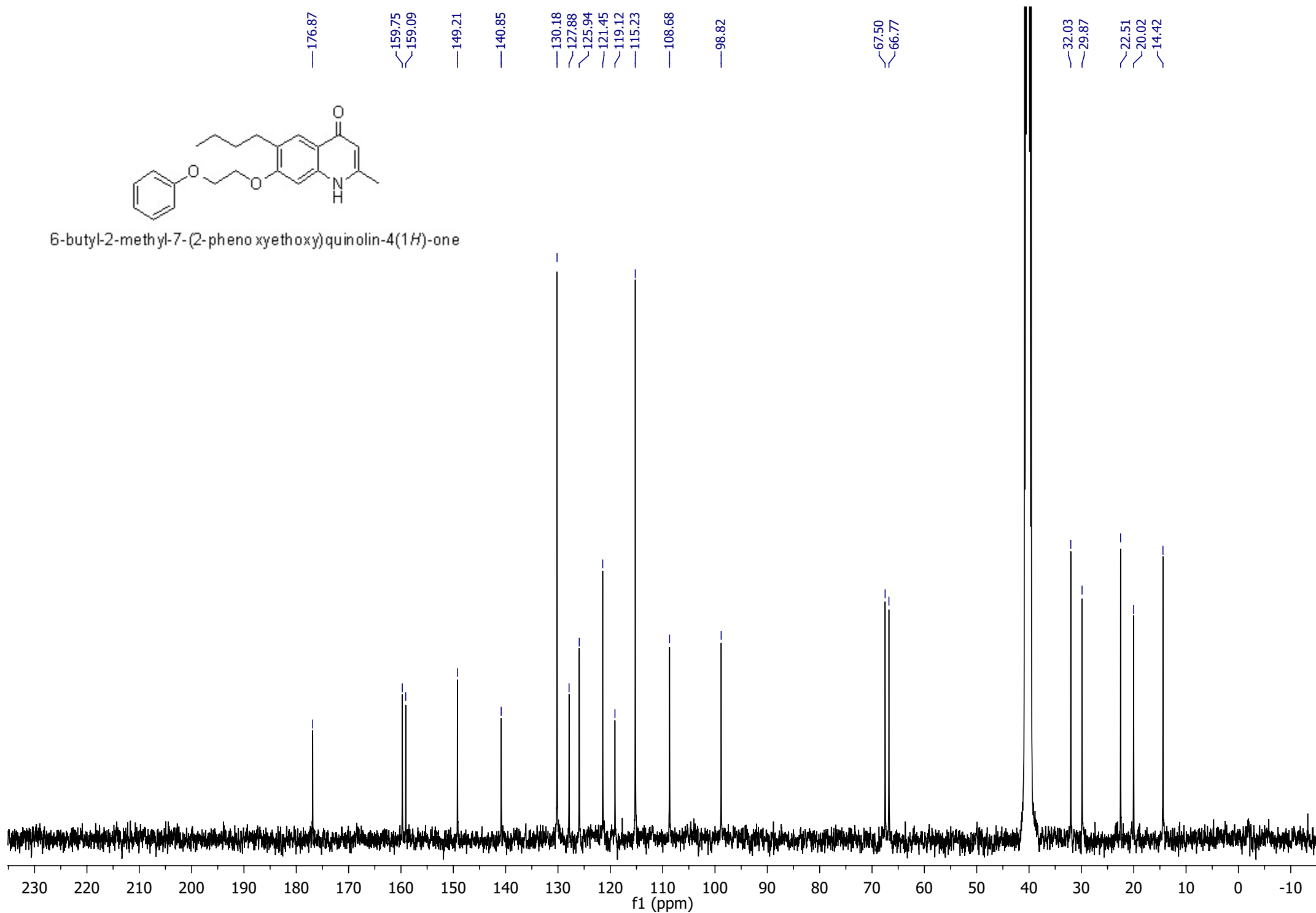


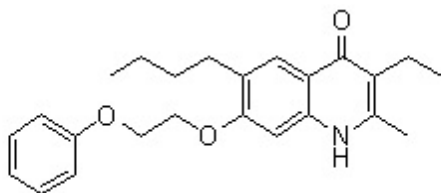
6-butyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one



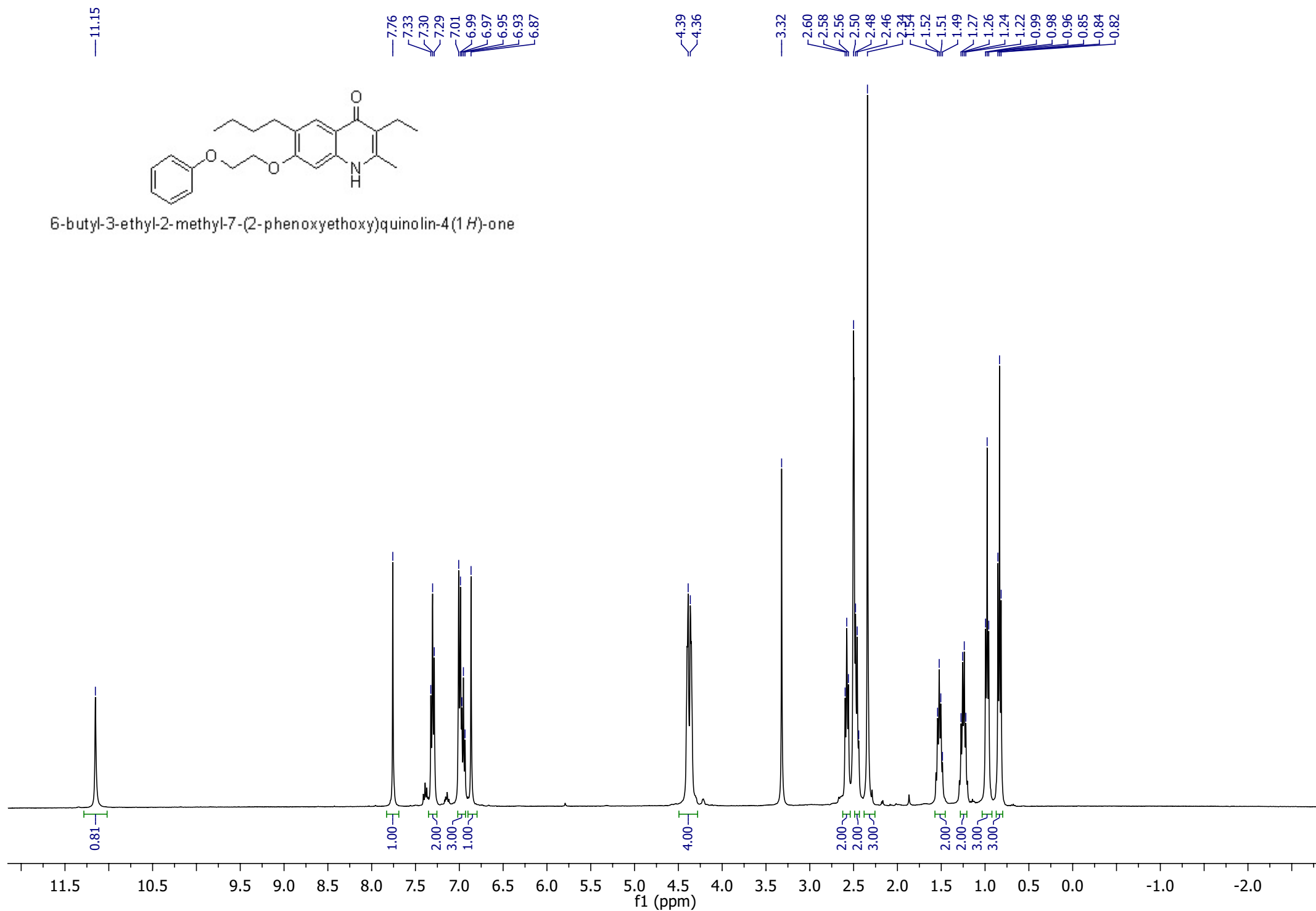


6-butyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one

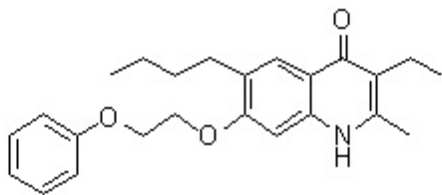




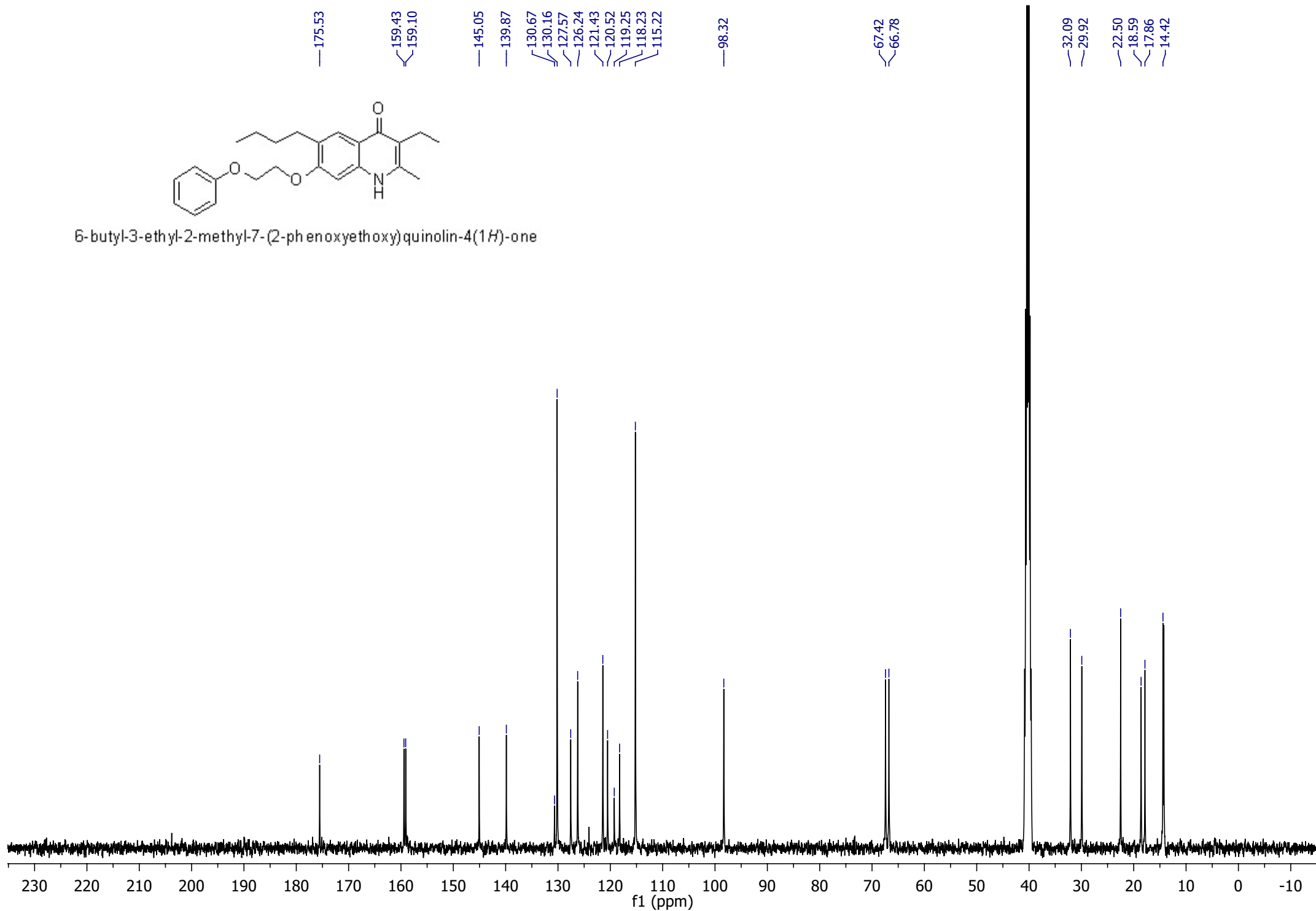
6-butyl-3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one

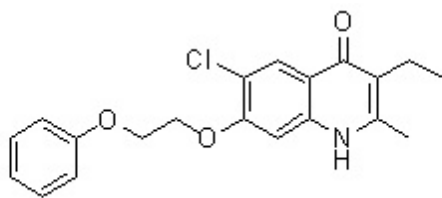




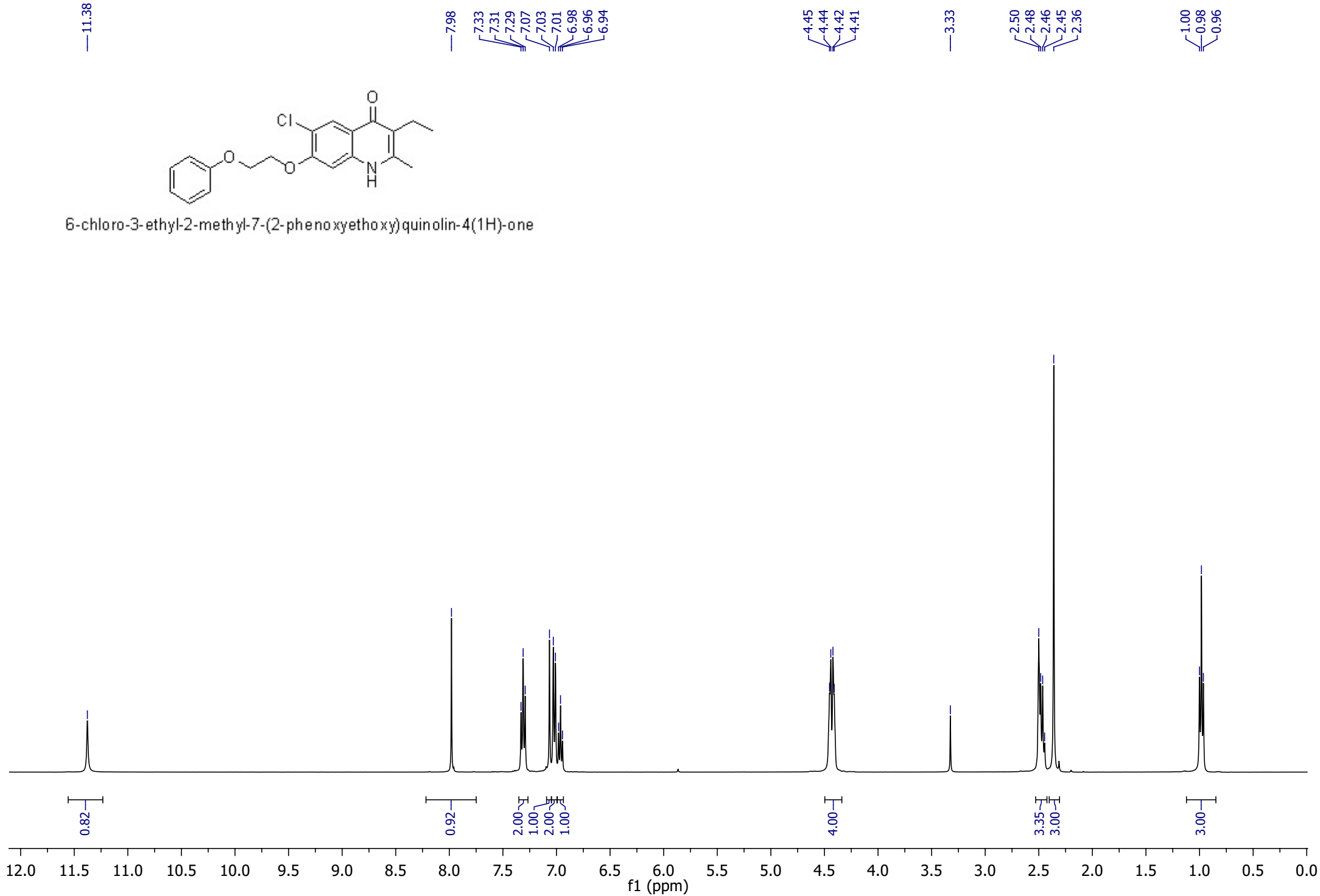


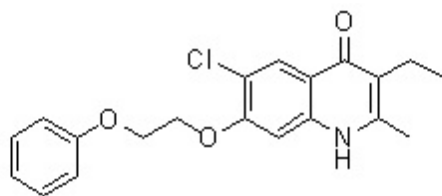
6-butyl-3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one





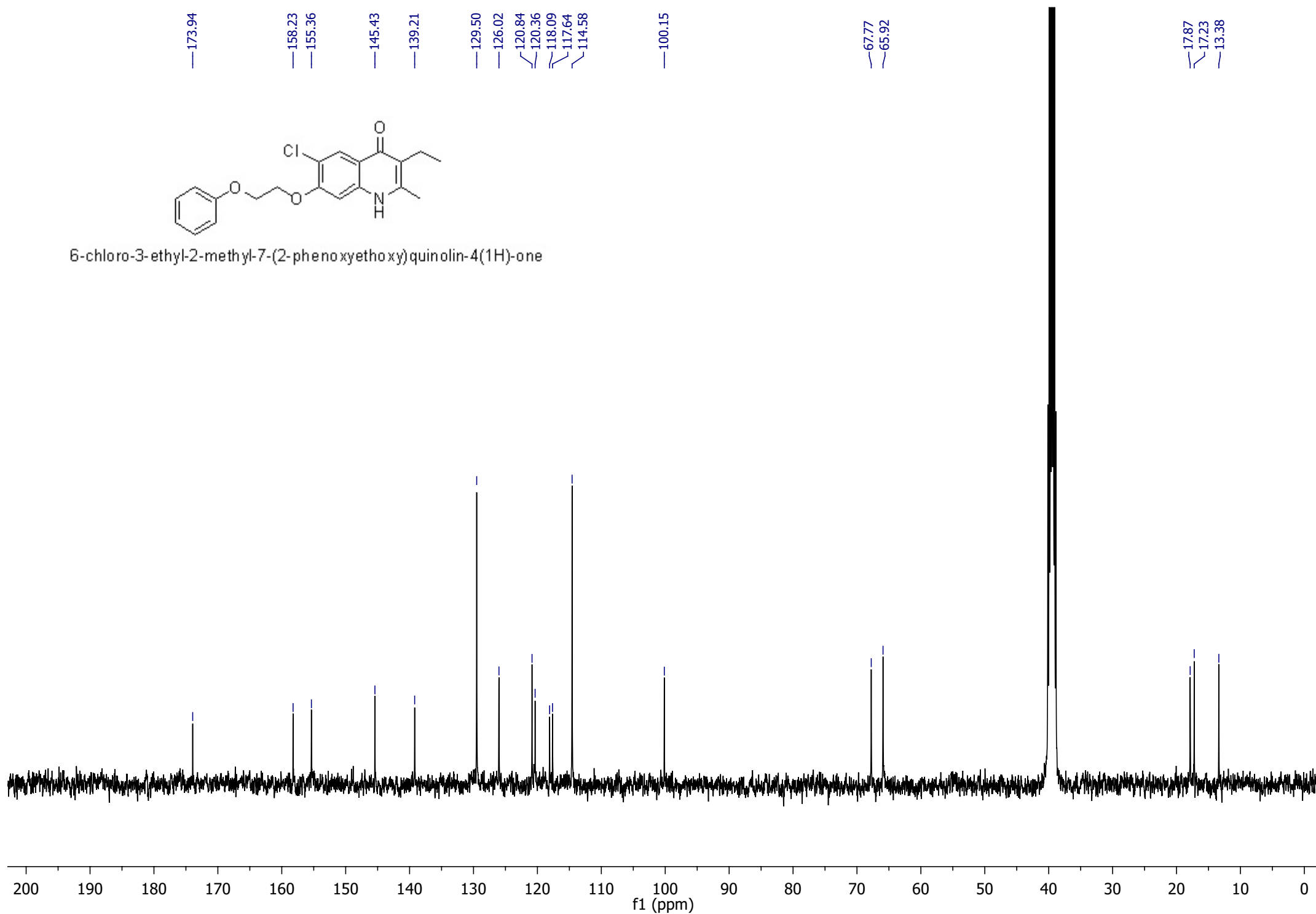
6-chloro-3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one

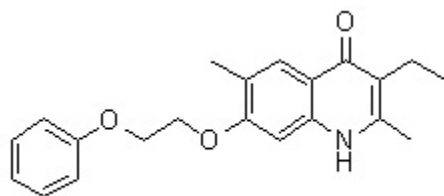




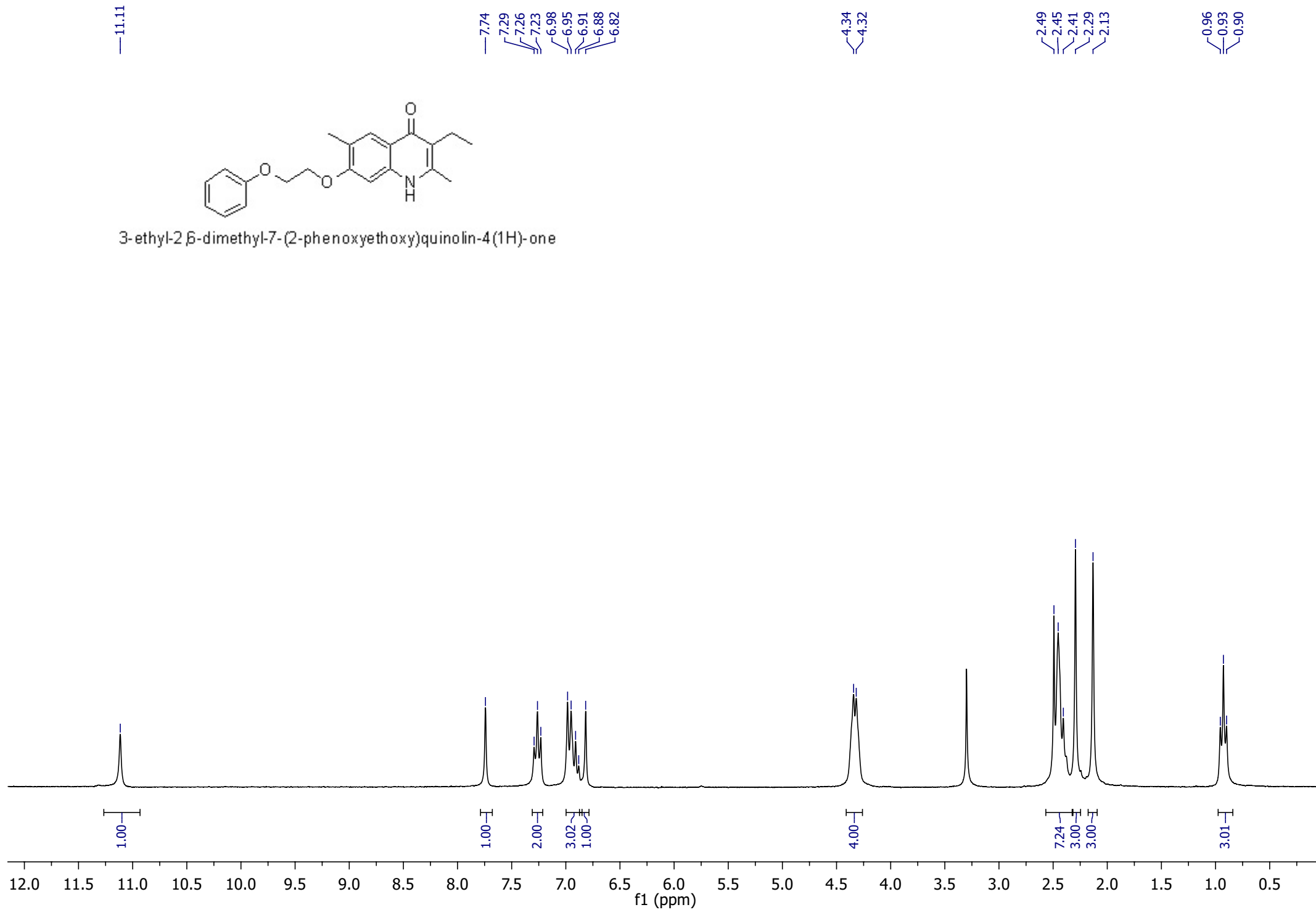
6-chloro-3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one

—173.94  
 —158.23  
 —155.36  
 —145.43  
 —139.21  
 —129.50  
 —126.02  
 120.84  
 120.36  
 118.09  
 117.64  
 114.58  
 —100.15  
 67.77  
 65.92  
 17.87  
 17.23  
 13.38





3-ethyl-2,6-dimethyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one



—175.43

159.59  
159.07

—145.03

—139.88

—130.19

—126.97

—122.92

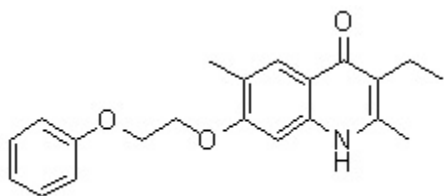
—121.48

—120.52

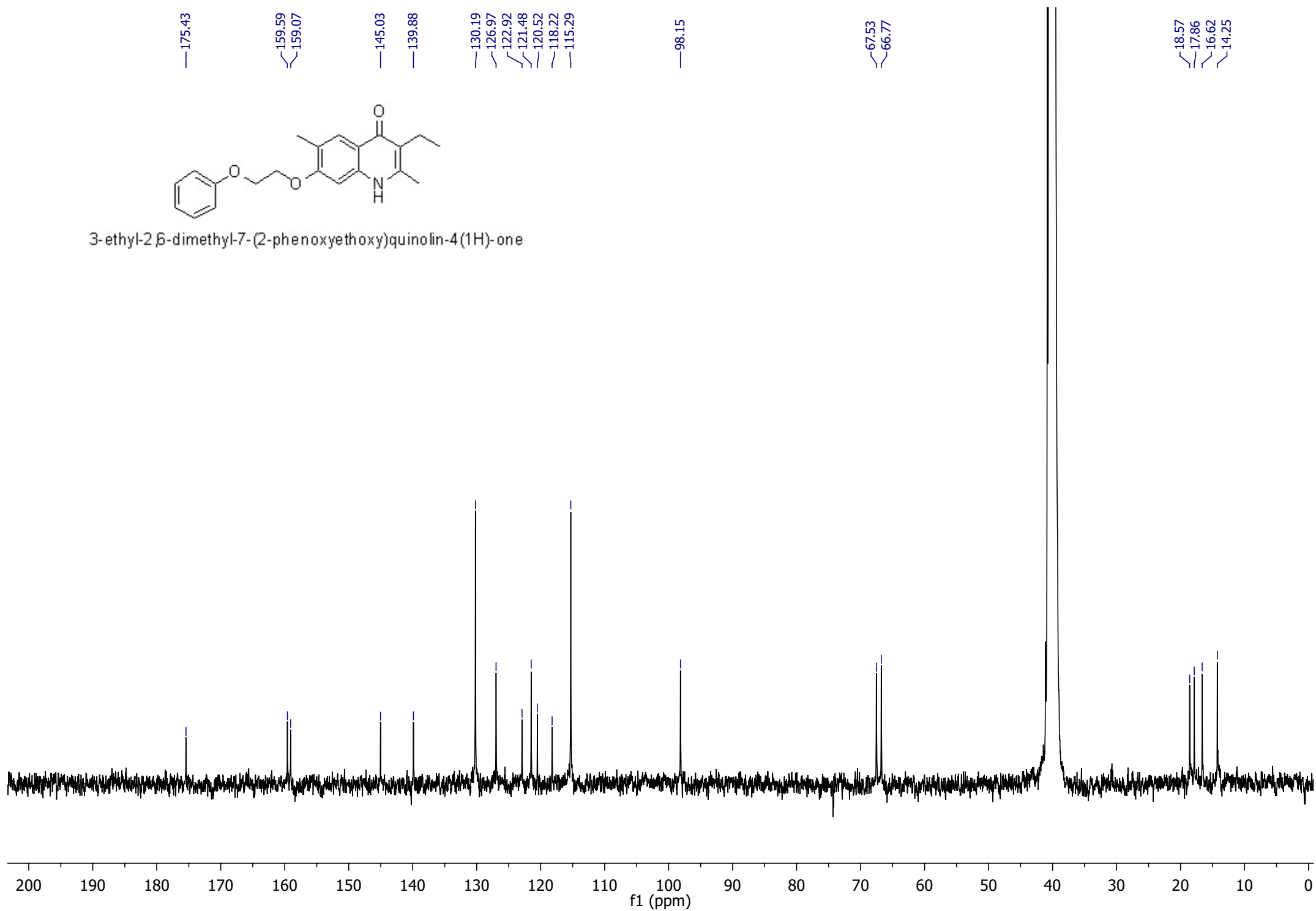
—118.22

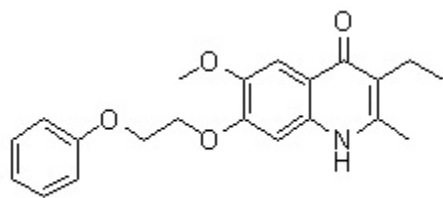
—115.29

—98.15

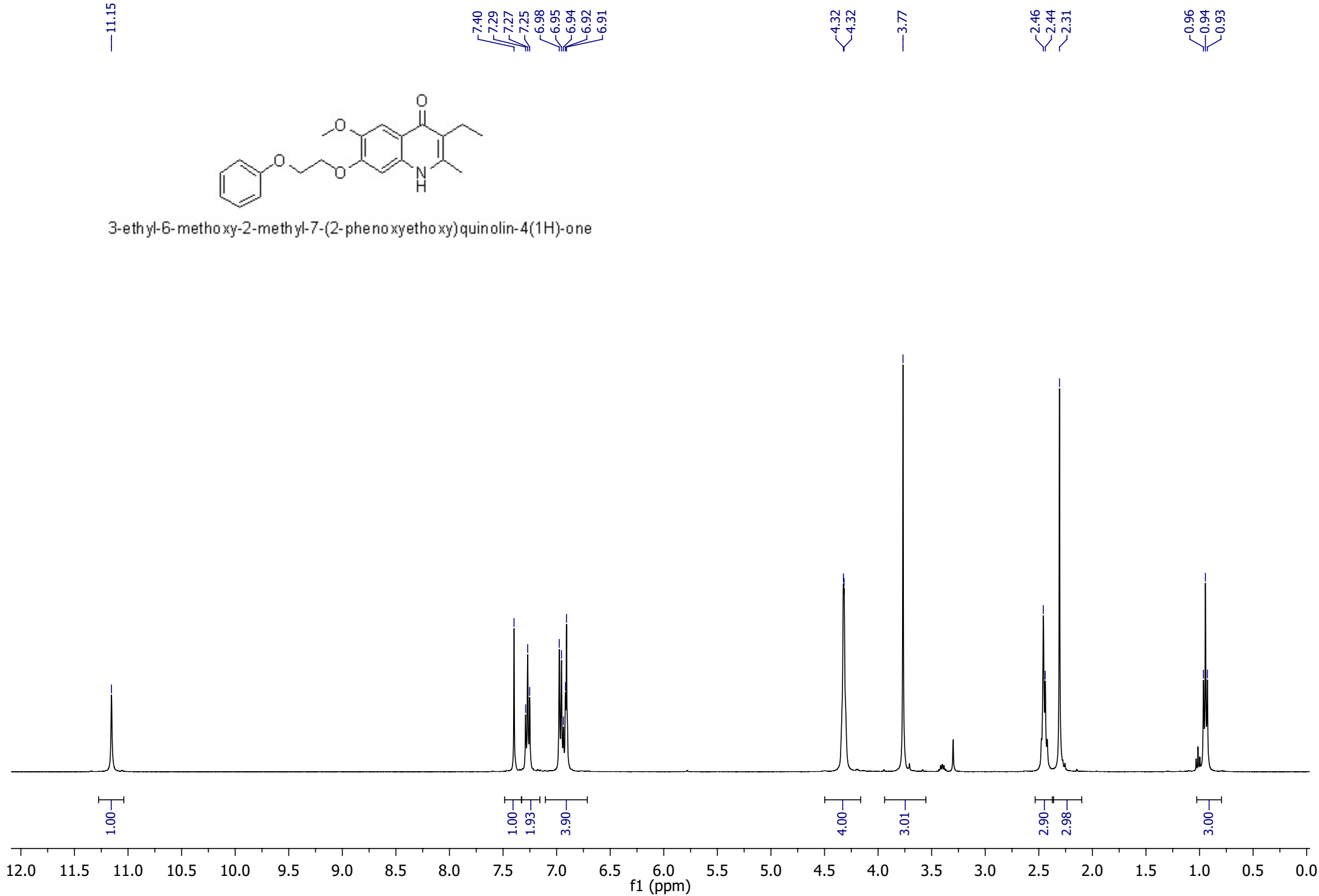
67.53  
66.7718.57  
17.86  
16.62  
14.25

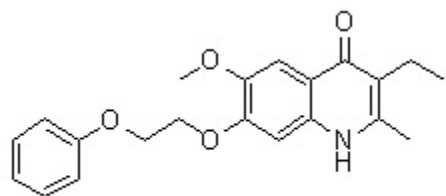
3-ethyl-2,6-dimethyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one





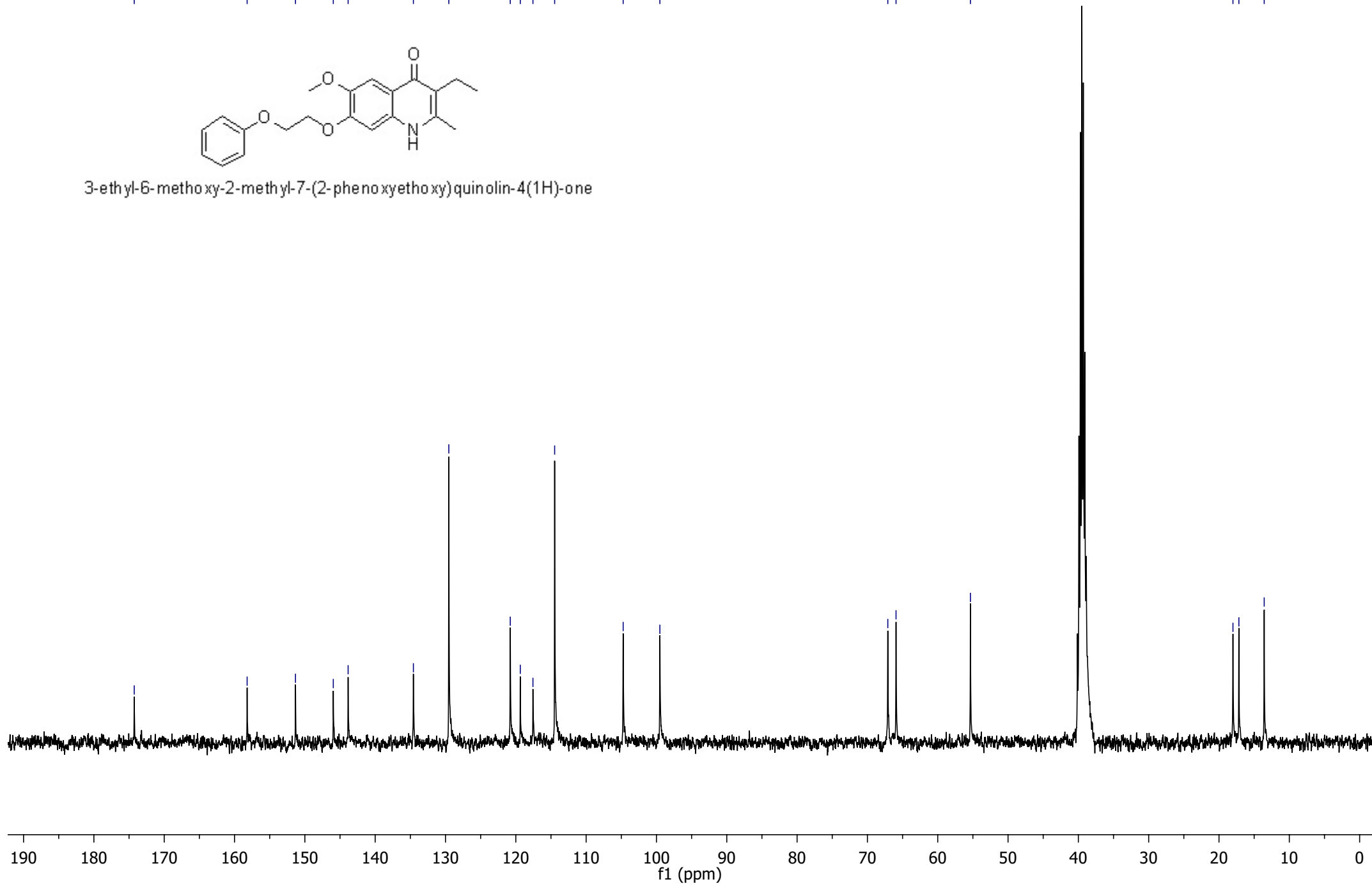
3-ethyl-6-methoxy-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one

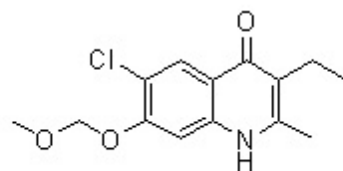




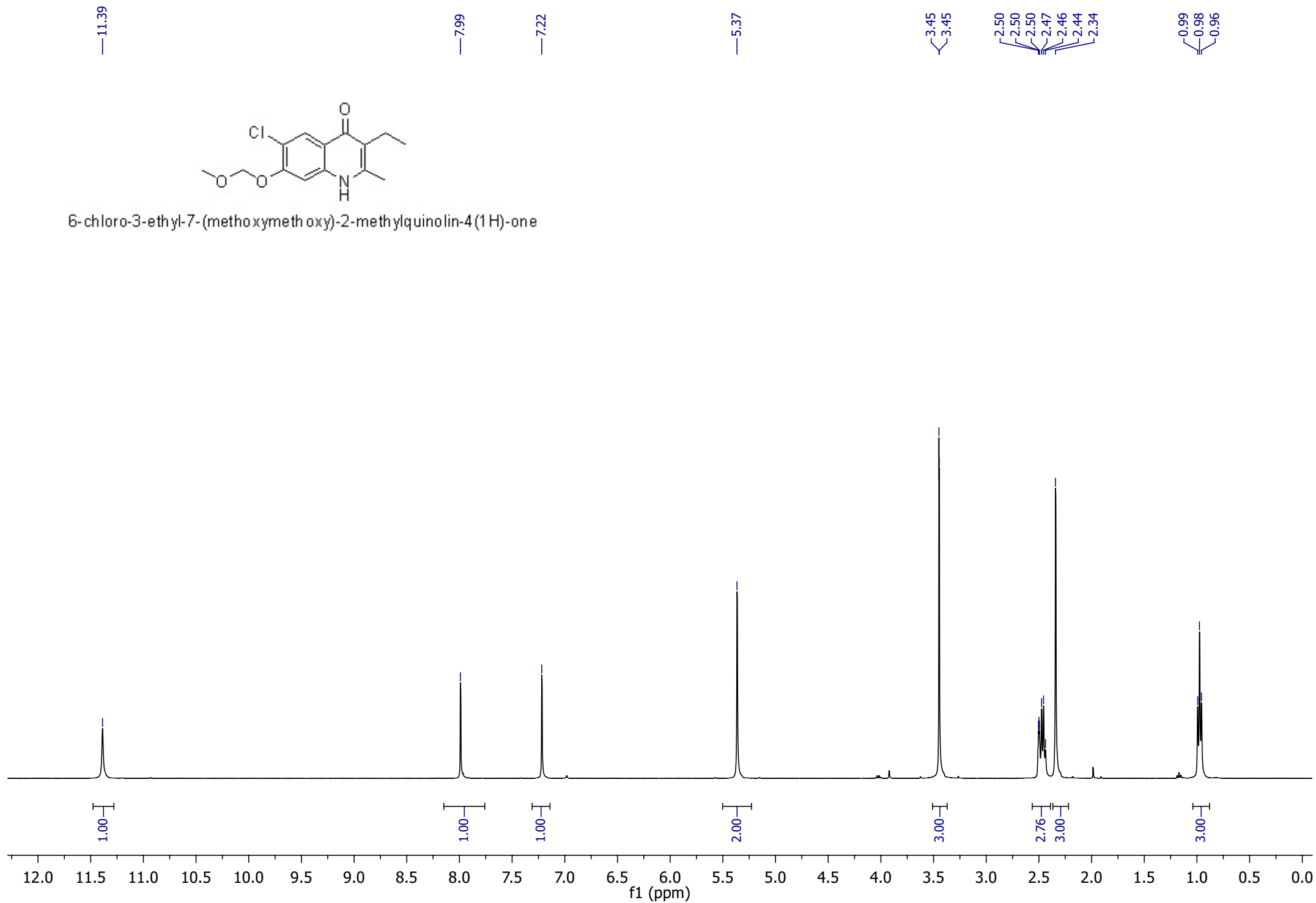
3-ethyl-6-methoxy-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one

—174.26  
 —158.21  
 —151.33  
 —145.95  
 —143.85  
 —134.56  
 —129.53  
 —120.79  
 —119.36  
 —117.56  
 —114.48  
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 —67.10  
 —65.93  
 —55.35  
 —18.01  
 —17.17  
 —13.57

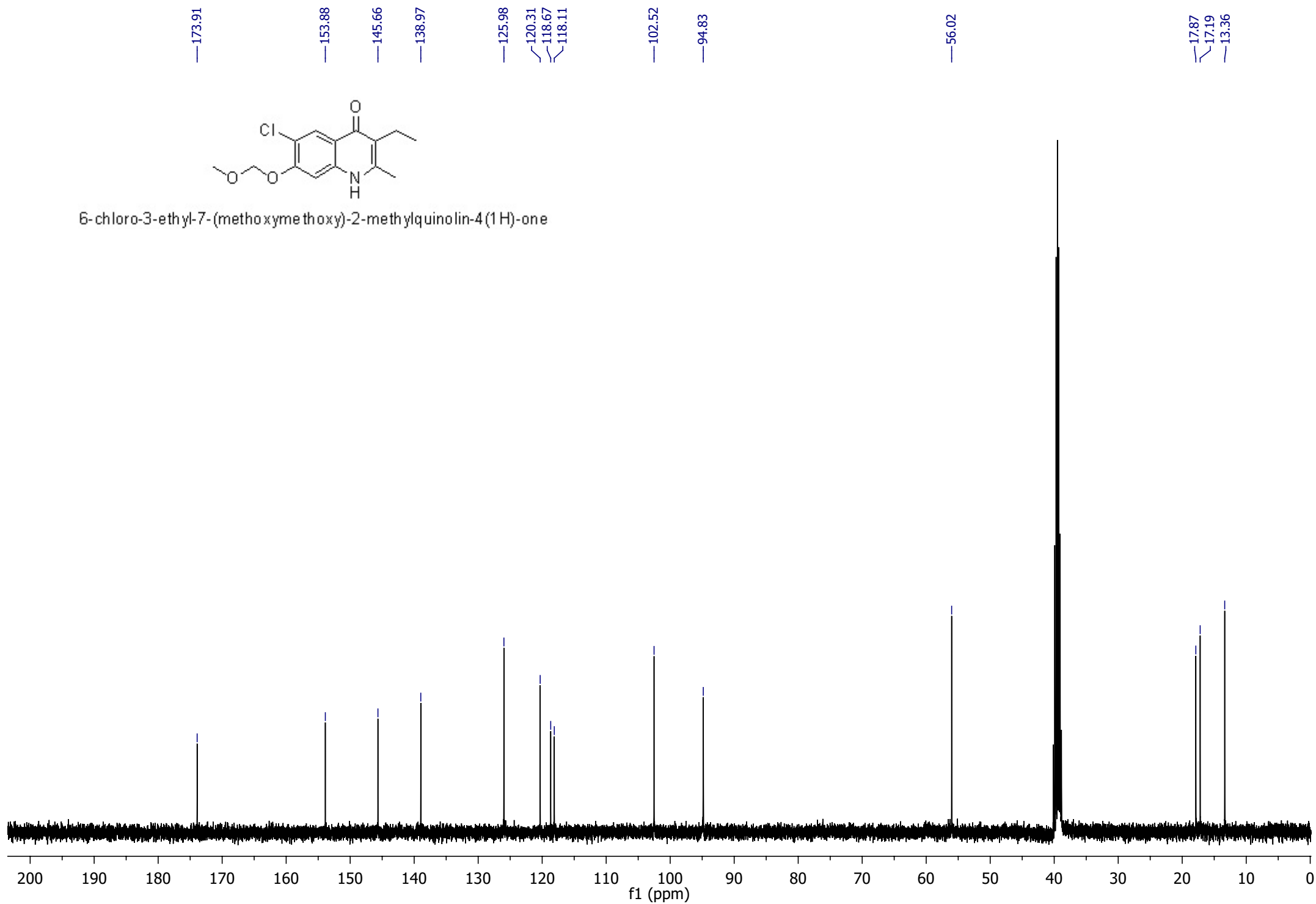
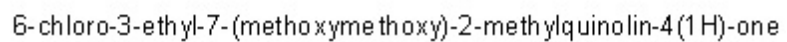


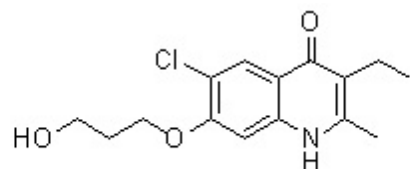


6-chloro-3-ethyl-7-(methoxymethoxy)-2-methylquinolin-4(1H)-one

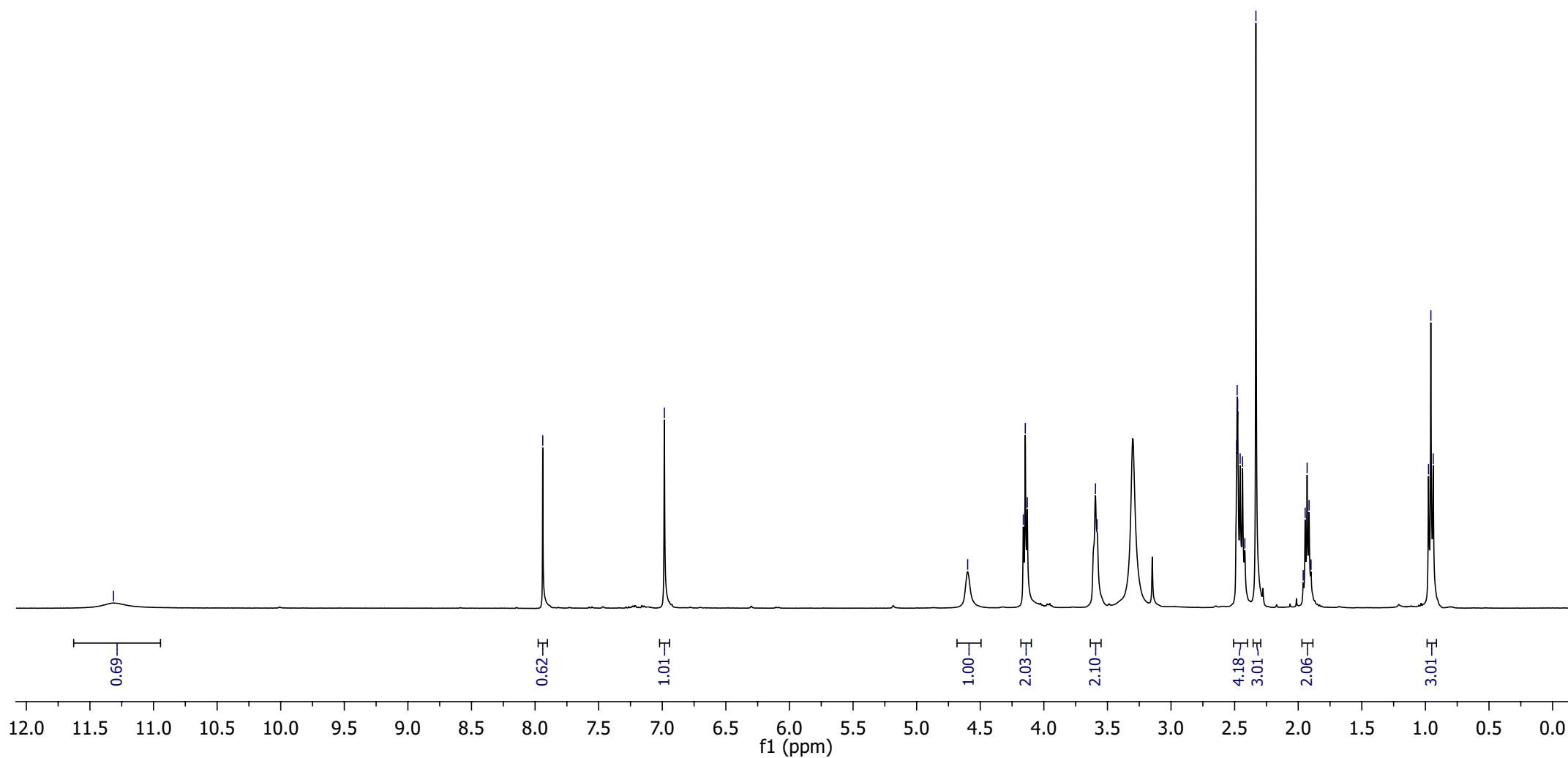


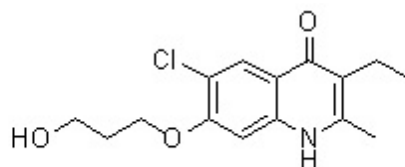




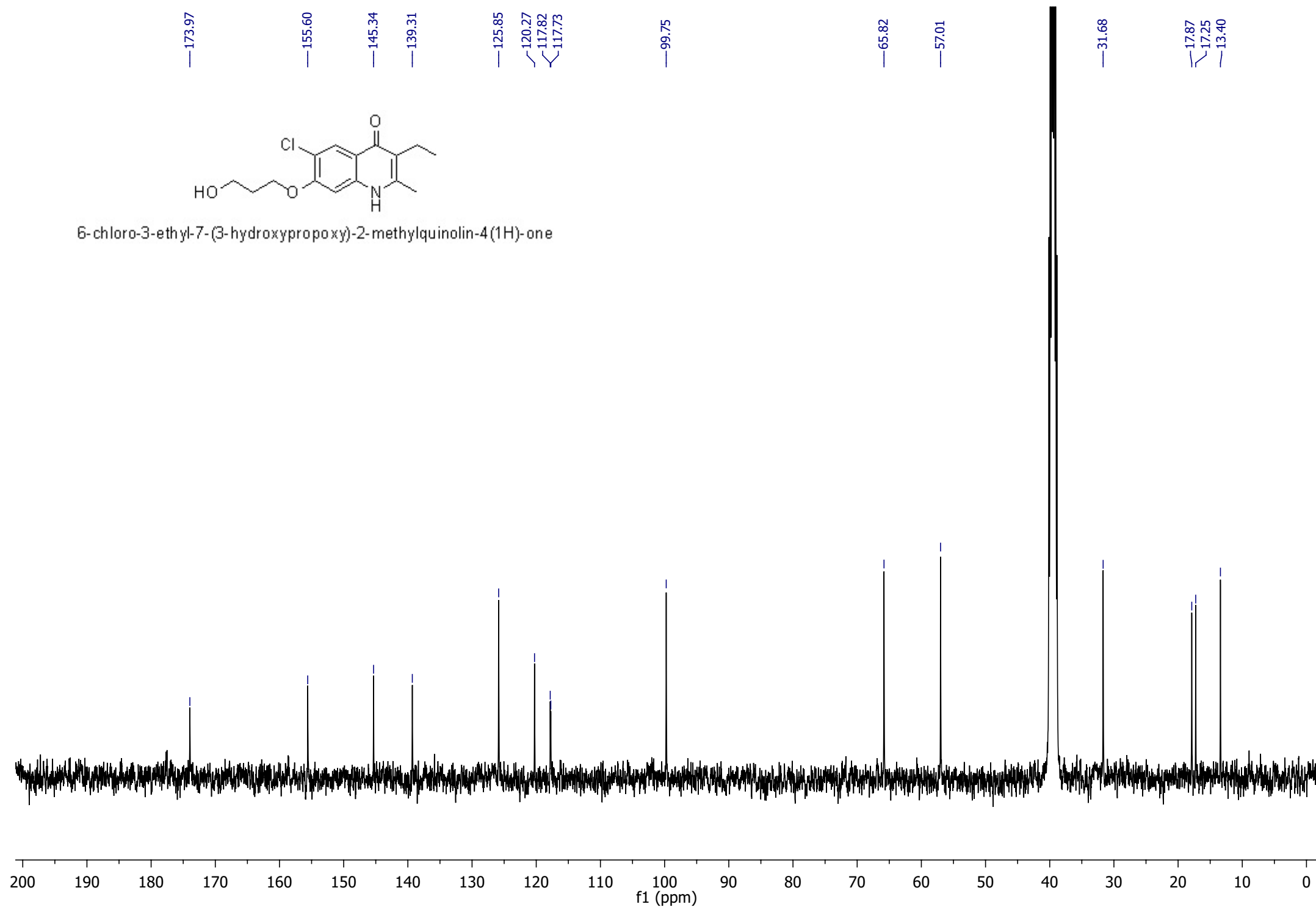


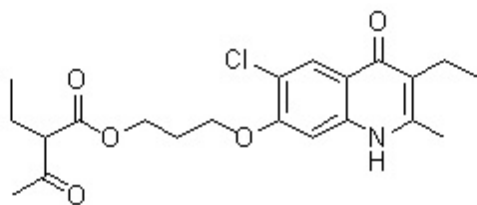
6-chloro-3-ethyl-7-(3-hydroxypropoxy)-2-methylquinolin-4(1H)-one



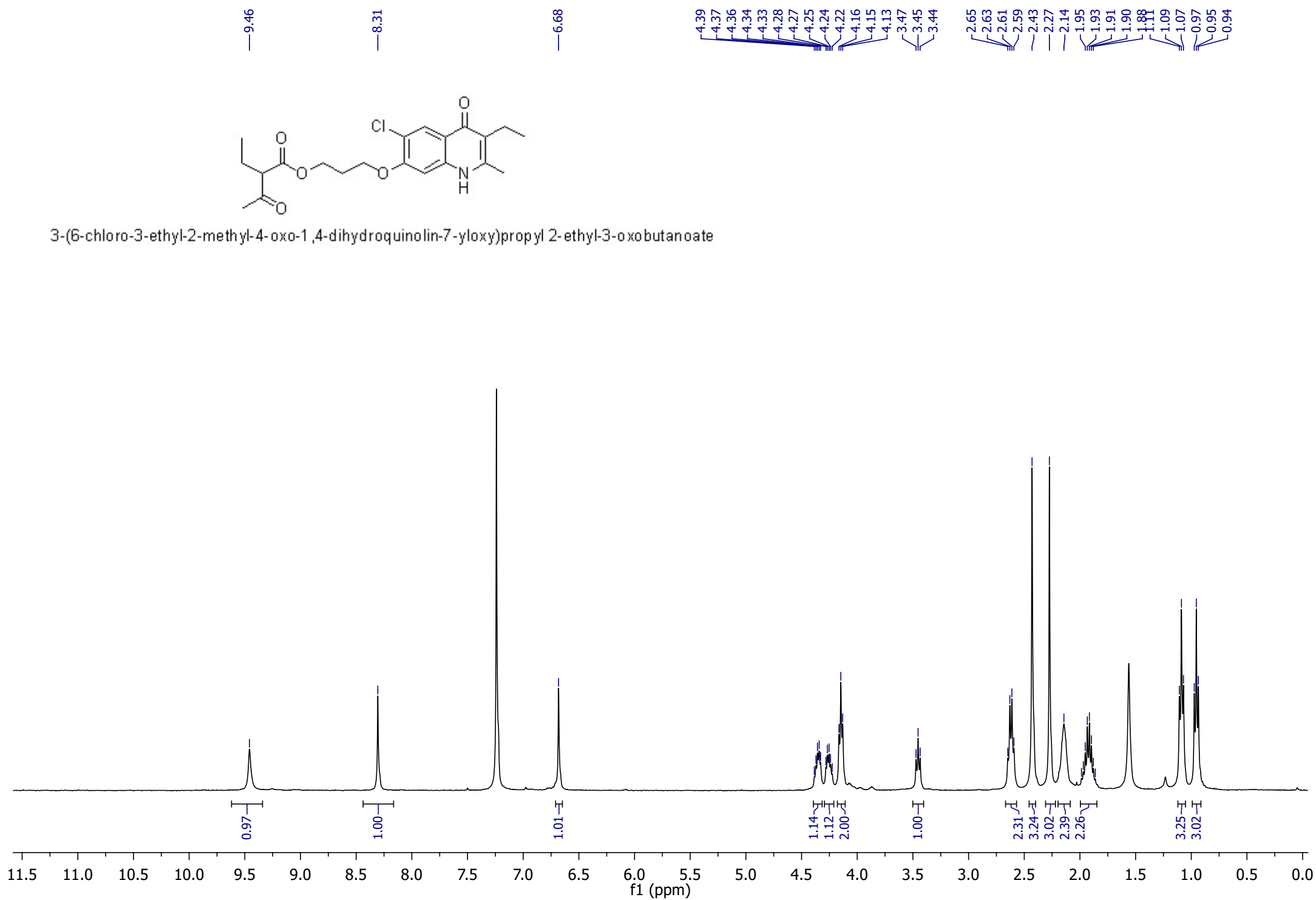


6-chloro-3-ethyl-7-(3-hydroxypropoxy)-2-methylquinolin-4(1H)-one

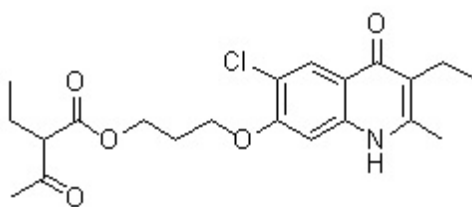




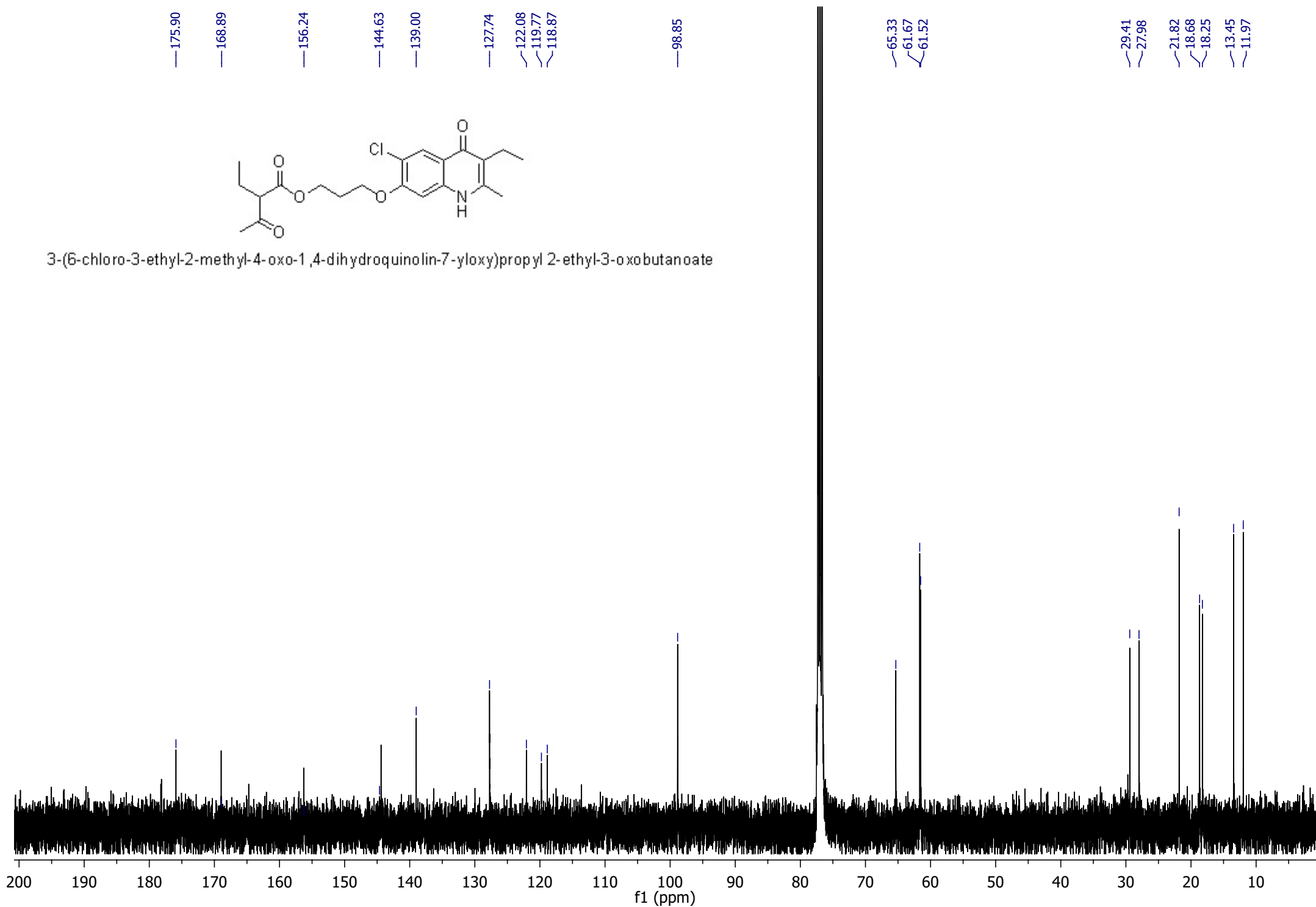
3-(6-chloro-3-ethyl-2-methyl-4-oxo-1,4-dihydroquinolin-7-yloxy)propyl 2-ethyl-3-oxobutanoate

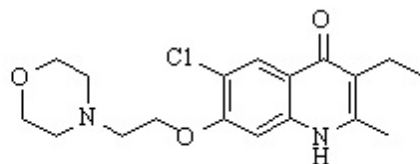


—175.90  
 —168.89  
 —156.24  
 —144.63  
 —139.00  
 —127.74  
 —122.08  
 —119.77  
 —118.87  
 —98.85  
 —65.33  
 —61.67  
 —61.52  
 —29.41  
 —27.98  
 —21.82  
 —18.68  
 —18.25  
 —13.45  
 —11.97

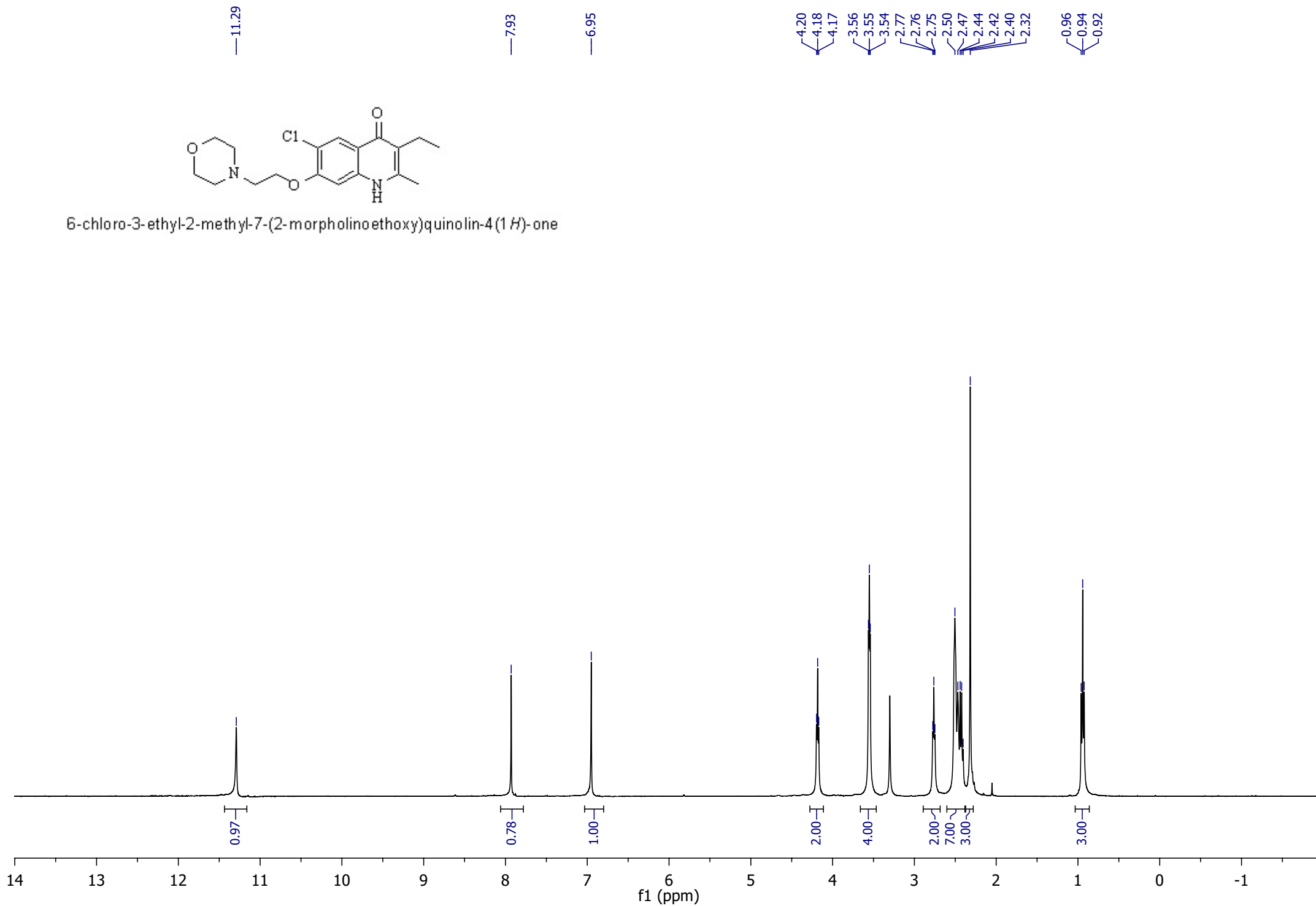


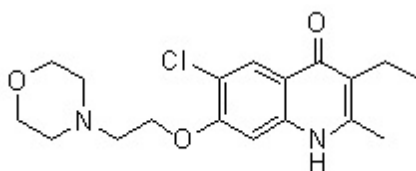
3-(6-chloro-3-ethyl-2-methyl-4-oxo-1,4-dihydroquinolin-7-yloxy)propyl 2-ethyl-3-oxobutanoate





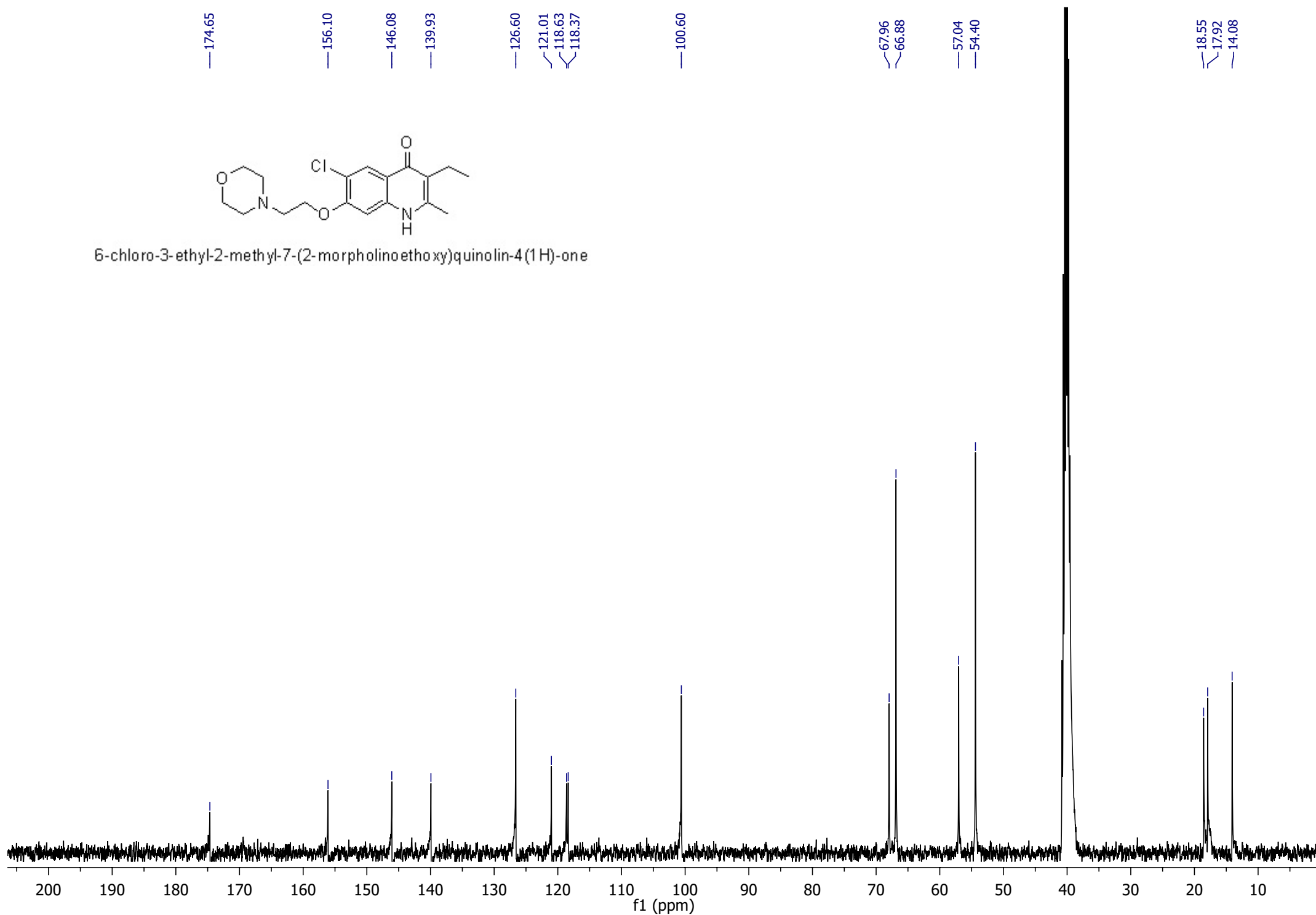
6-chloro-3-ethyl-2-methyl-7-(2-morpholinoethoxy)quinolin-4(1*H*)-one

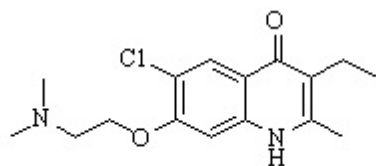




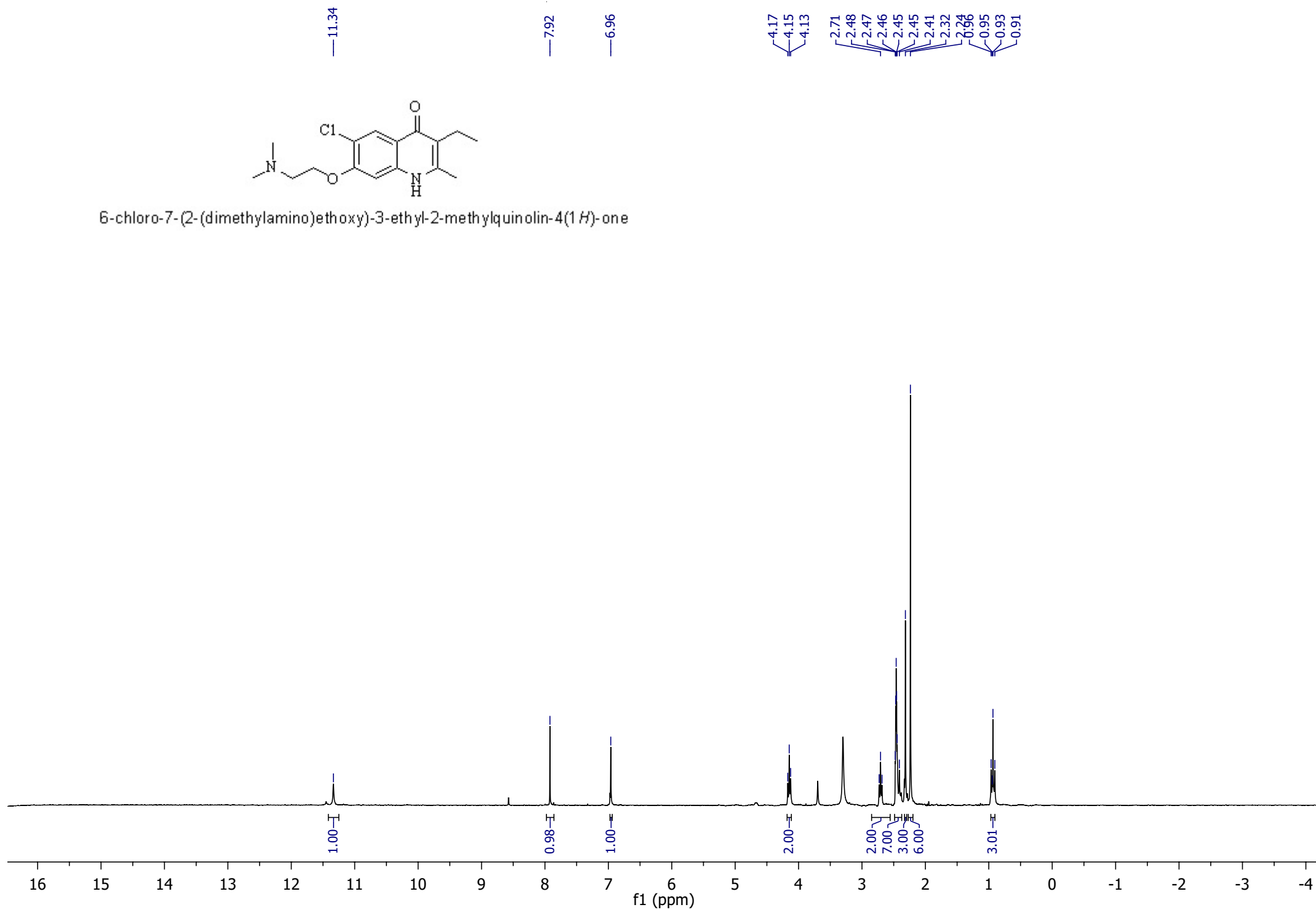
6-chloro-3-ethyl-2-methyl-7-(2-morpholinoethoxy)quinolin-4(1H)-one

—174.65  
 —156.10  
 —146.08  
 —139.93  
 —126.60  
 —121.01  
 —118.63  
 —118.37  
 —100.60  
 —67.96  
 —66.88  
 —57.04  
 —54.40  
 —18.55  
 —17.92  
 —14.08

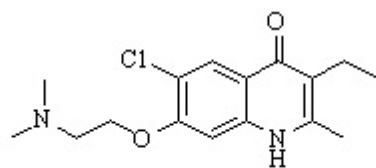




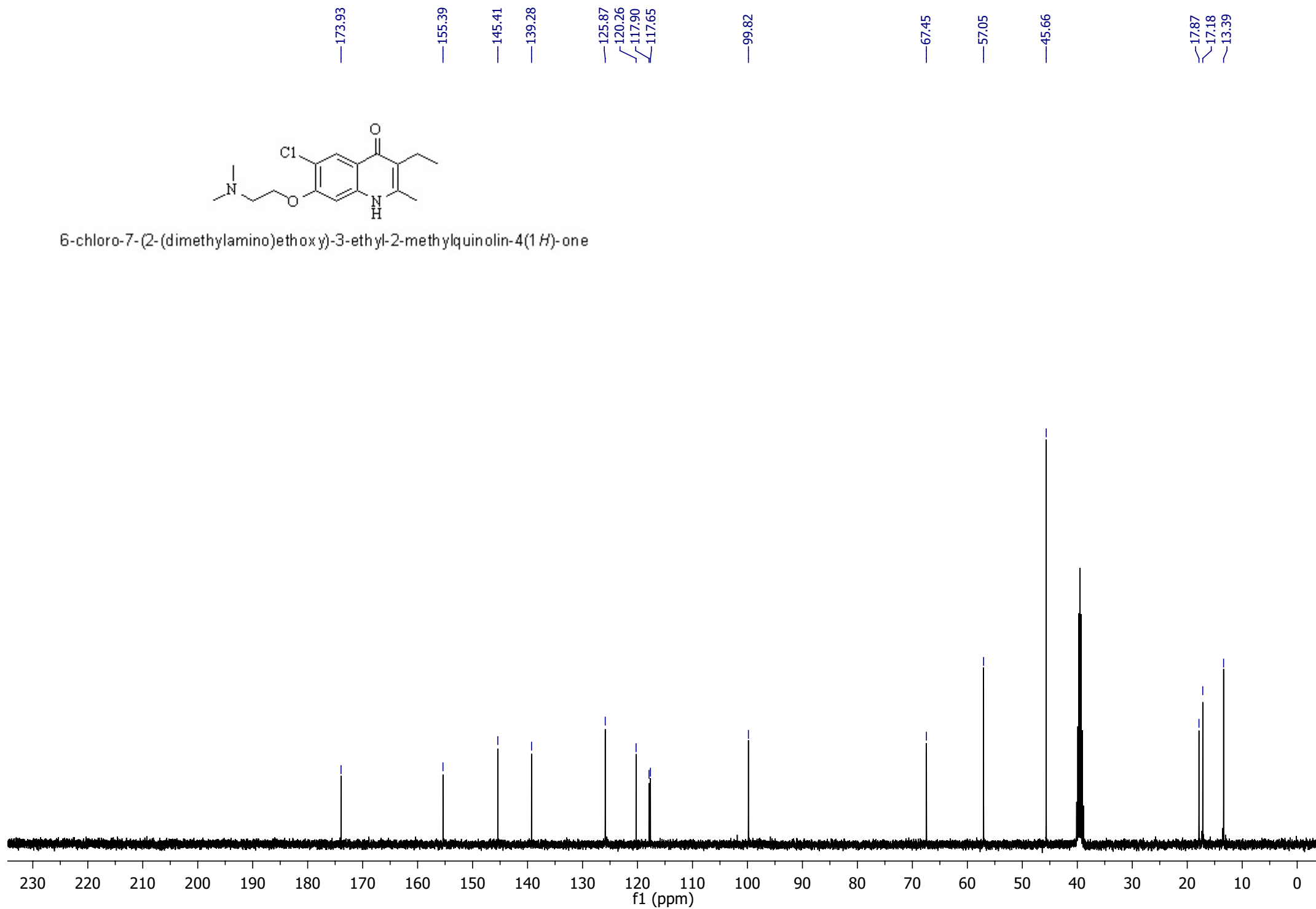
6-chloro-7-(2-(dimethylamino)ethoxy)-3-ethyl-2-methylquinolin-4(1 *H*)-one







6-chloro-7-(2-(dimethylamino)ethoxy)-3-ethyl-2-methylquinolin-4(1*H*)-one



—11.35

—8.13

7.32

7.30

7.28

7.02

7.00

6.97

6.93

4.42

4.41

2.49

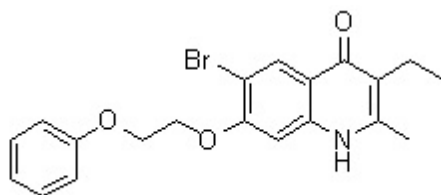
2.45

2.35

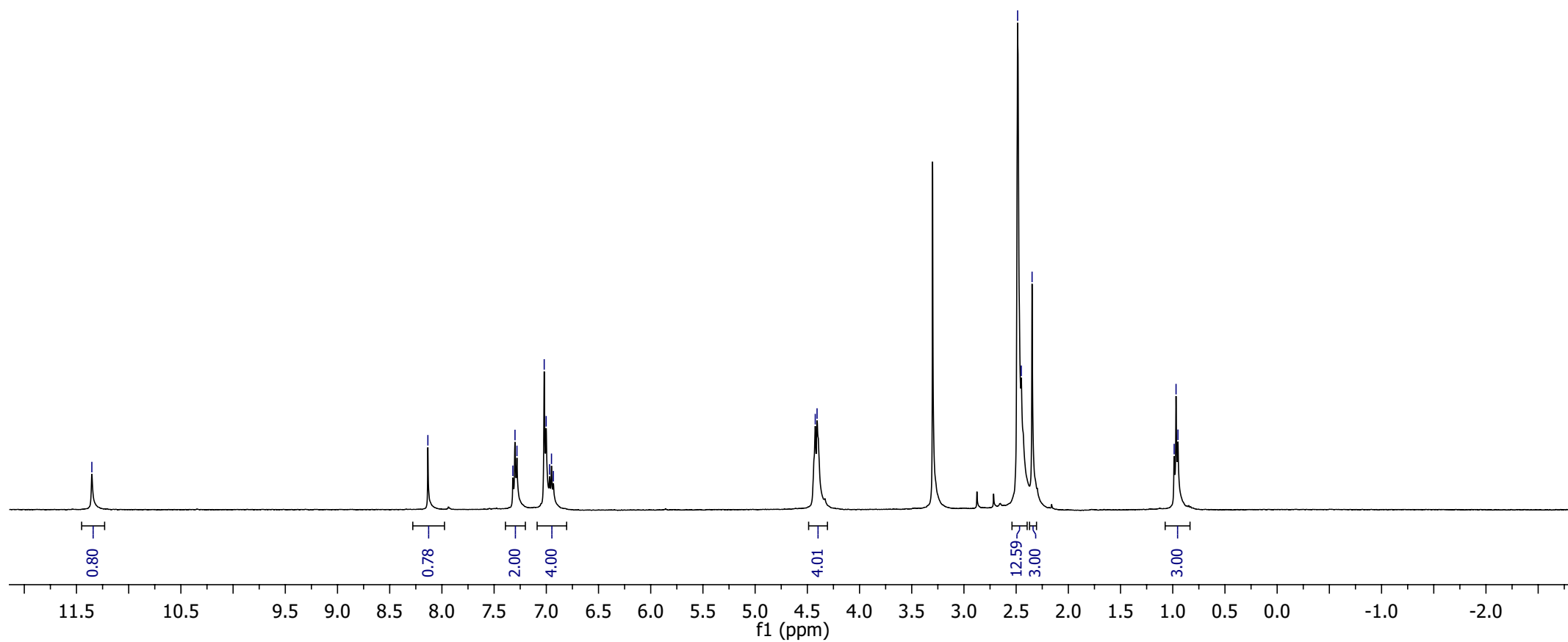
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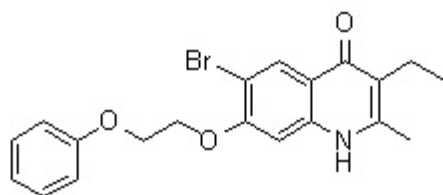
0.97

0.95

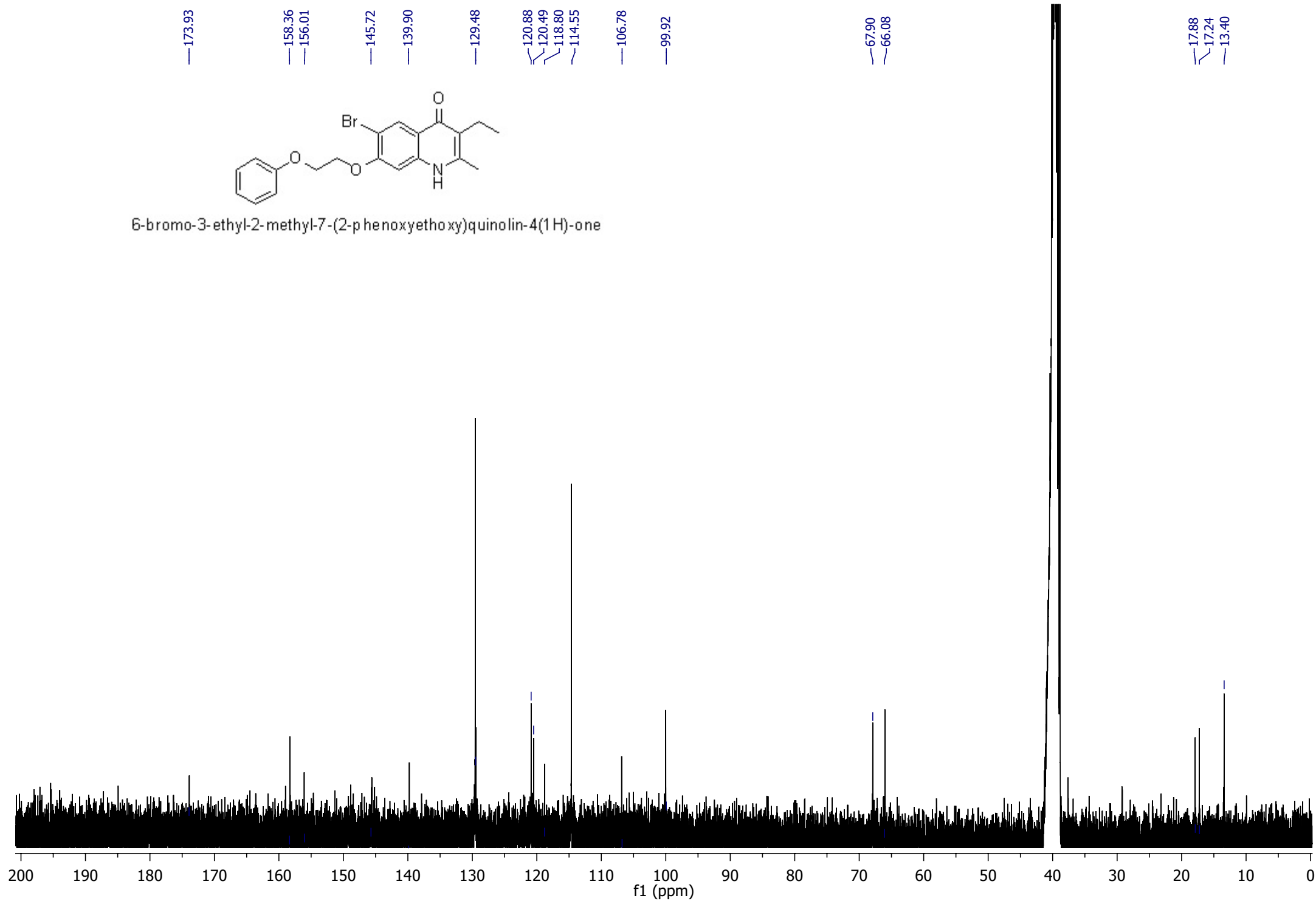


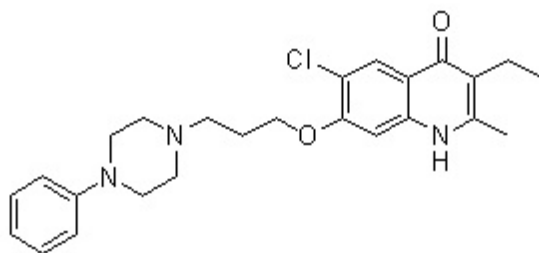
6-bromo-3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one



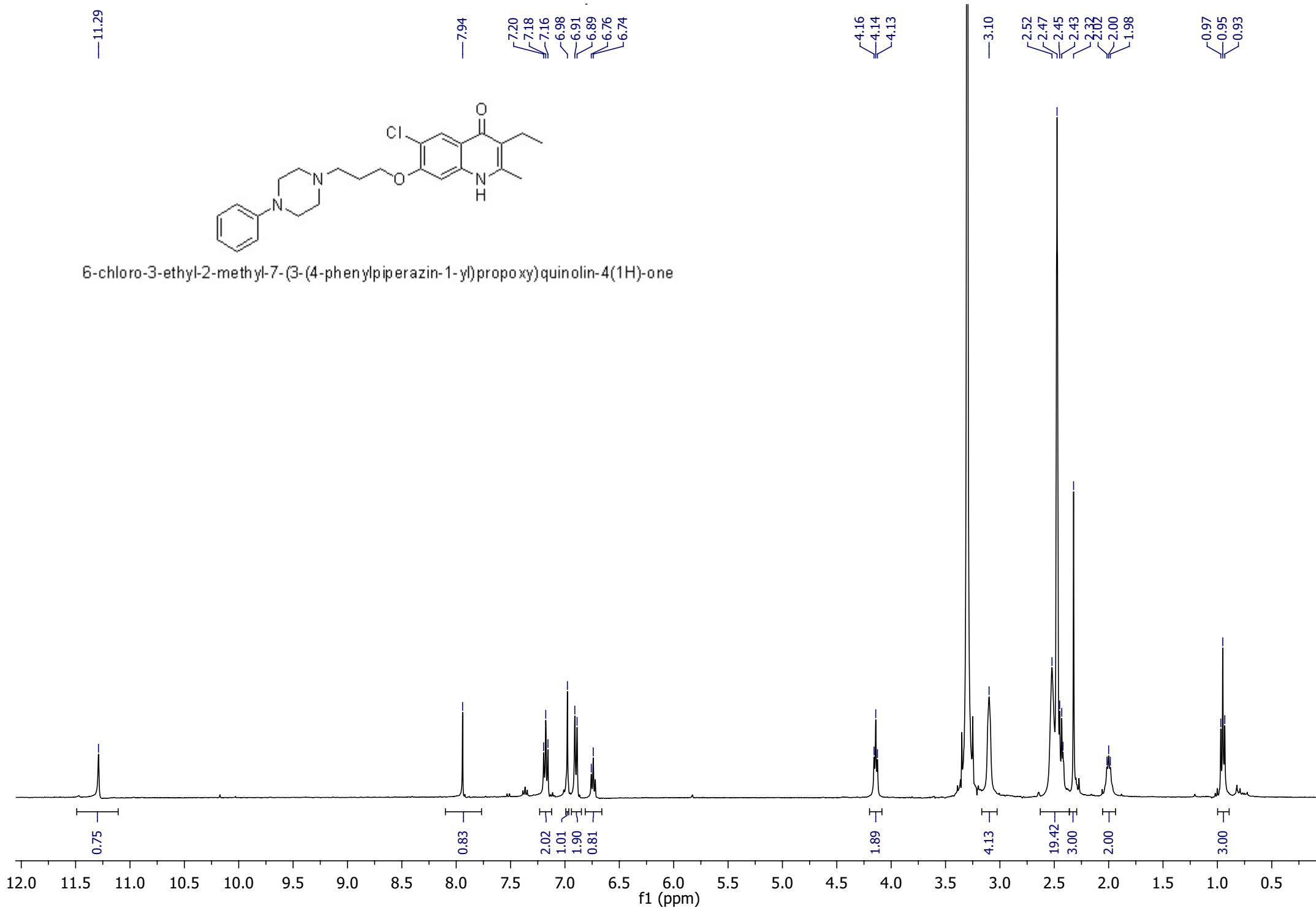


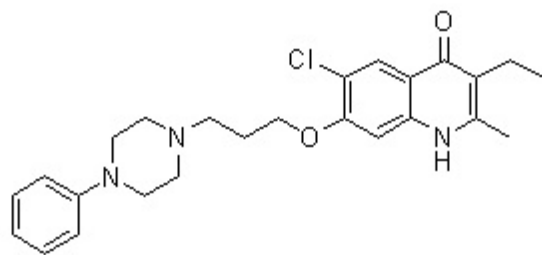
6-bromo-3-ethyl-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1H)-one



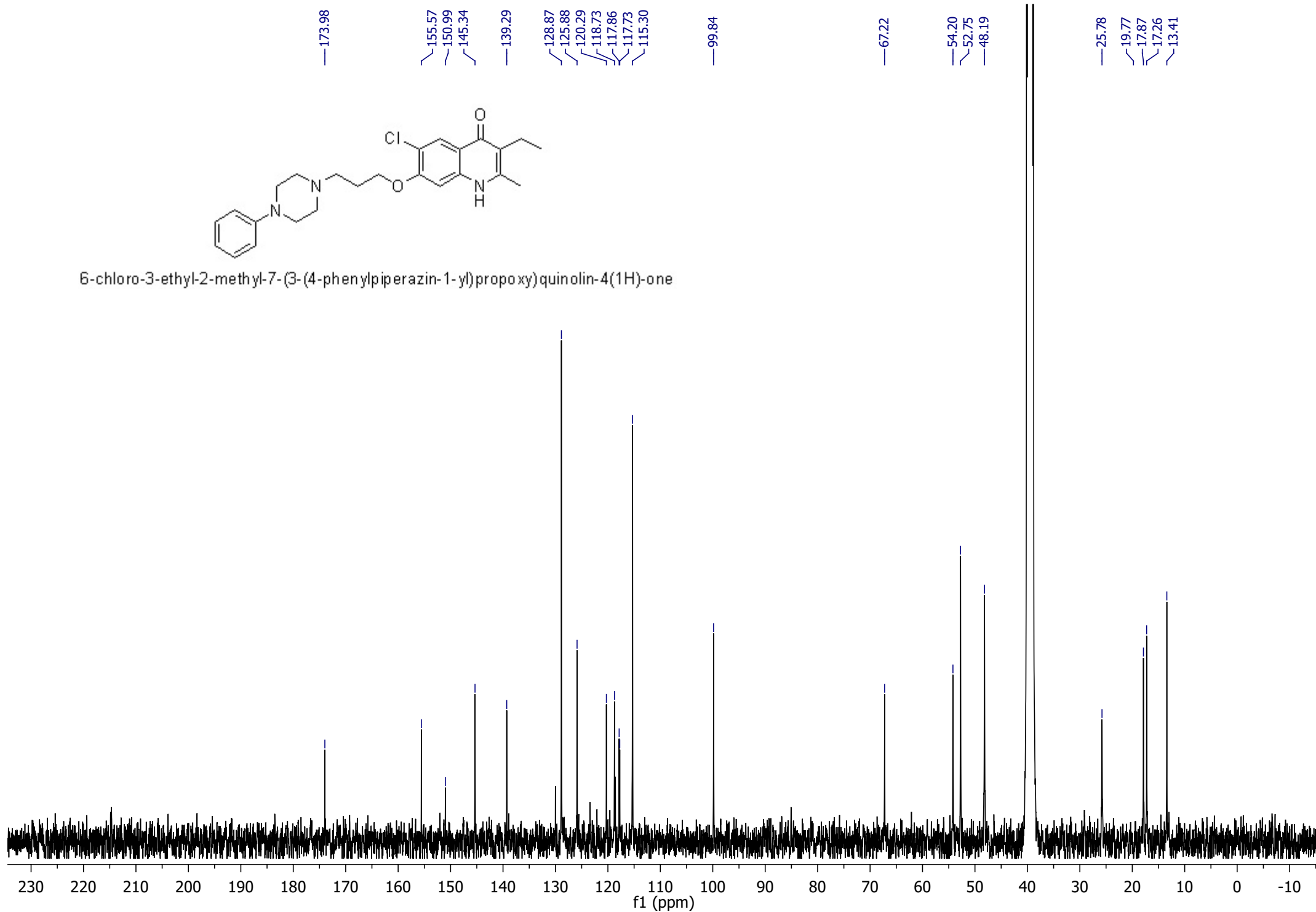


6-chloro-3-ethyl-2-methyl-7-(3-(4-phenylpiperazin-1-yl)propoxy)quinolin-4(1H)-one

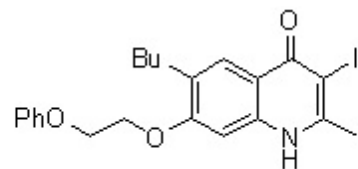




6-chloro-3-ethyl-2-methyl-7-(3-(4-phenylpiperazin-1-yl)propoxy)quinolin-4(1H)-one



—11.95

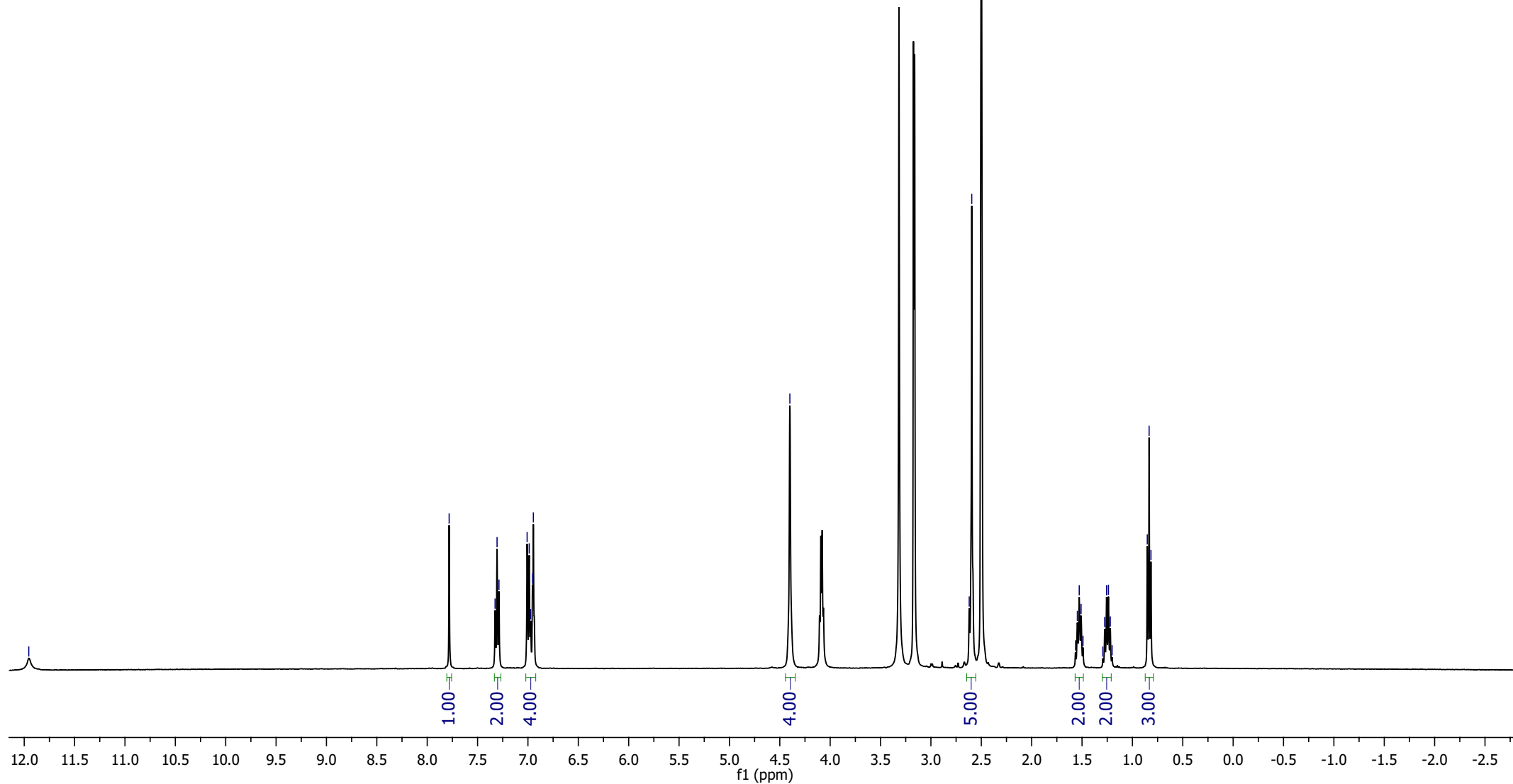


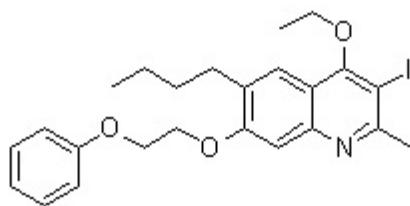
6-butyl-3-iodo-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one

7.78  
7.33  
7.31  
7.29  
7.01  
6.99  
6.97  
6.95

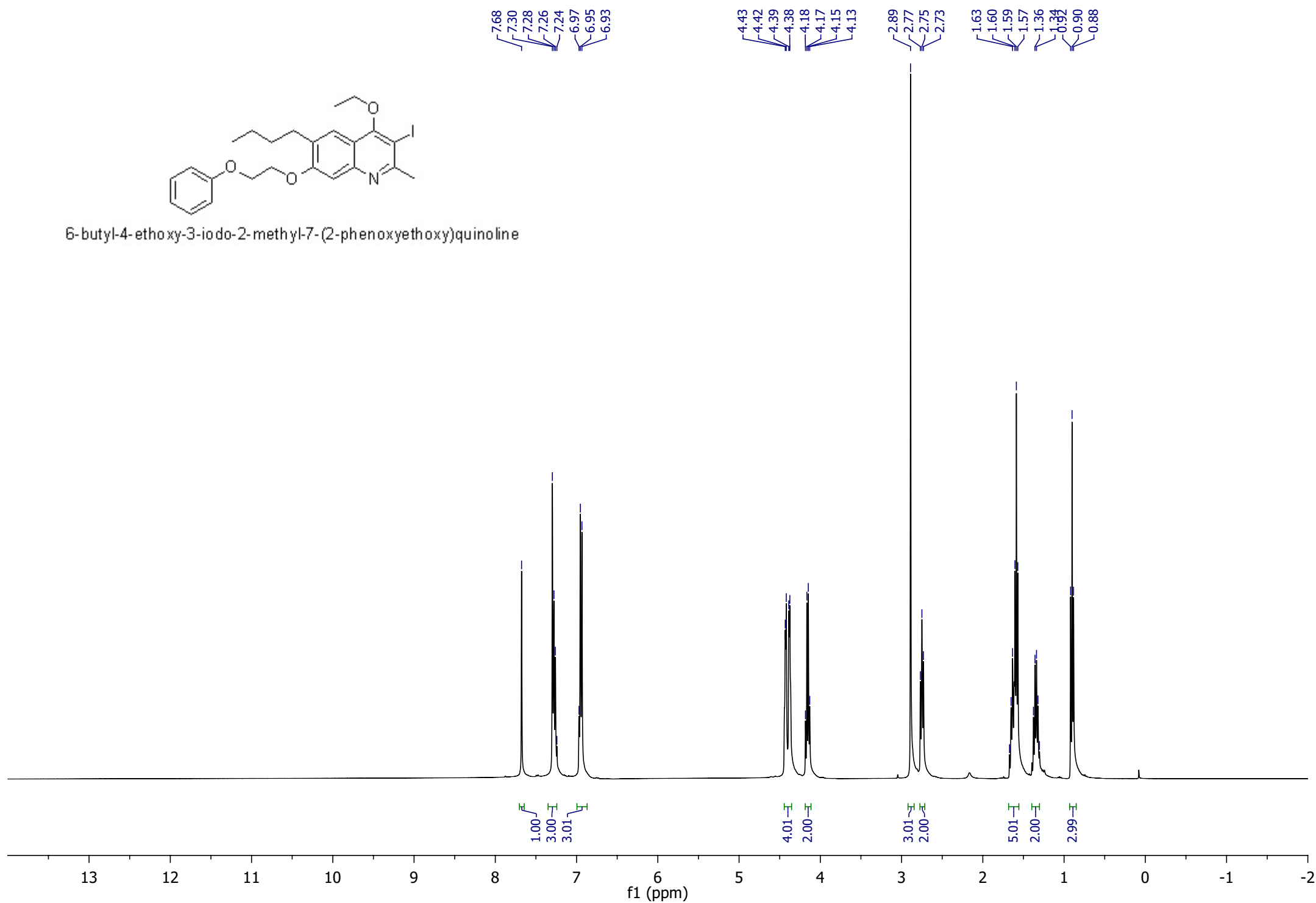
—4.40

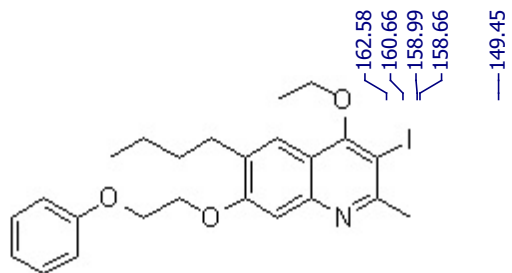
2.62  
2.59  
1.56  
1.55  
1.53  
1.51  
1.49  
1.29  
1.27  
1.26  
1.24  
1.22  
1.20  
0.85  
0.83  
0.82



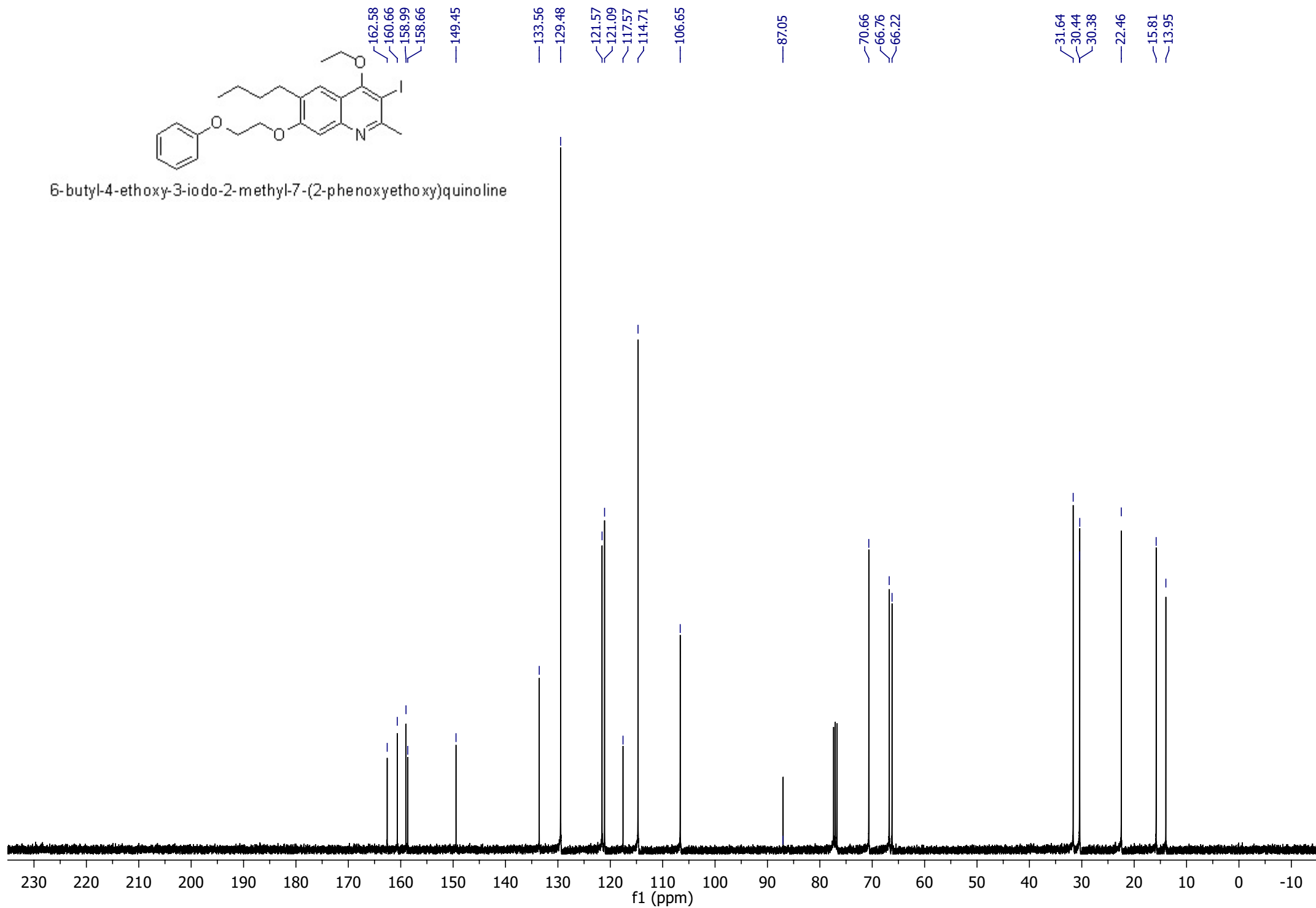


6-butyl-4-ethoxy-3-iodo-2-methyl-7-(2-phenoxyethoxy)quinoline

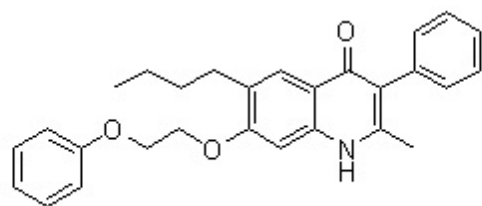




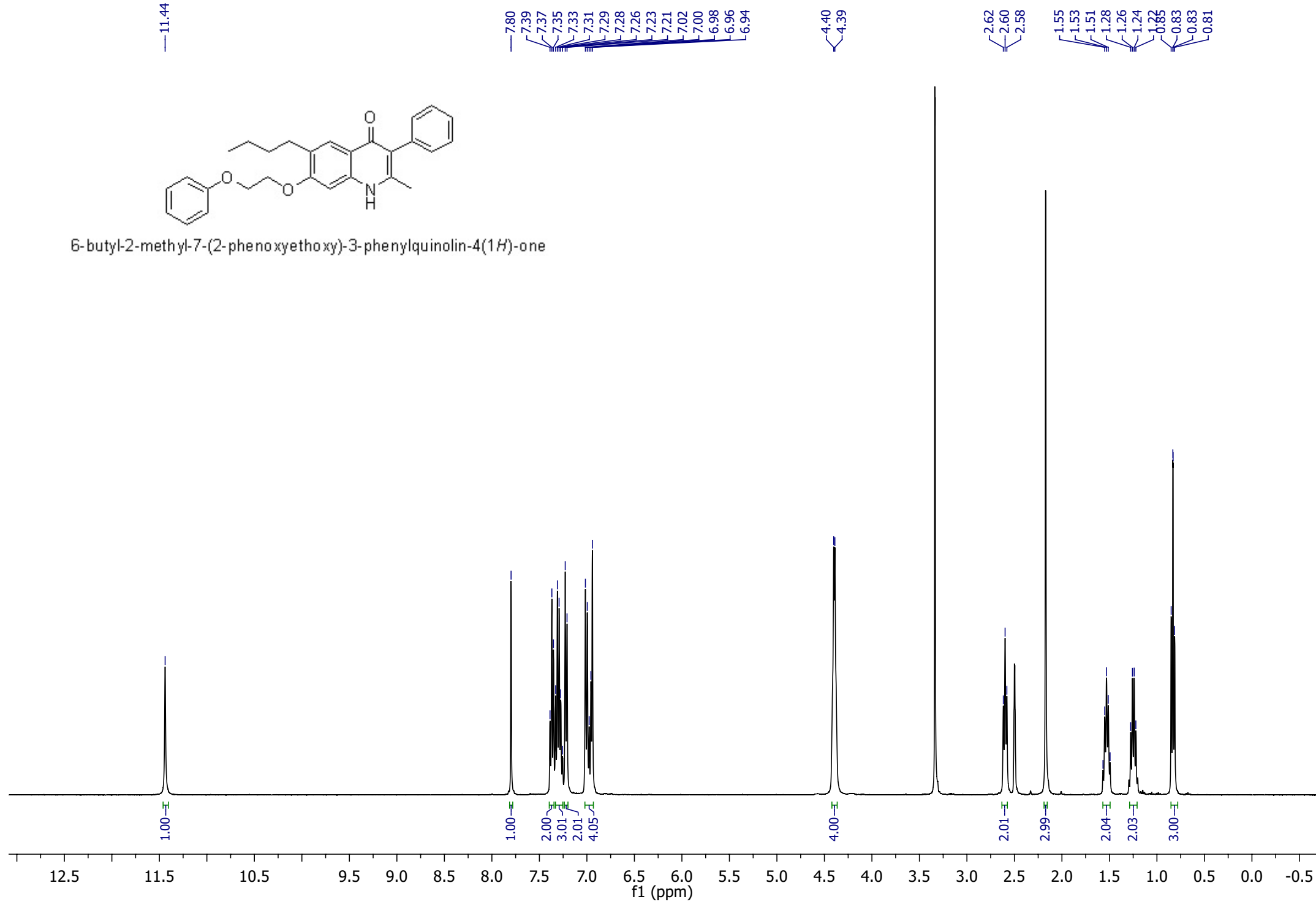
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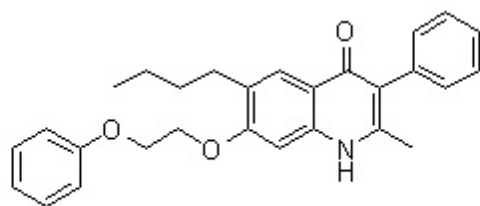




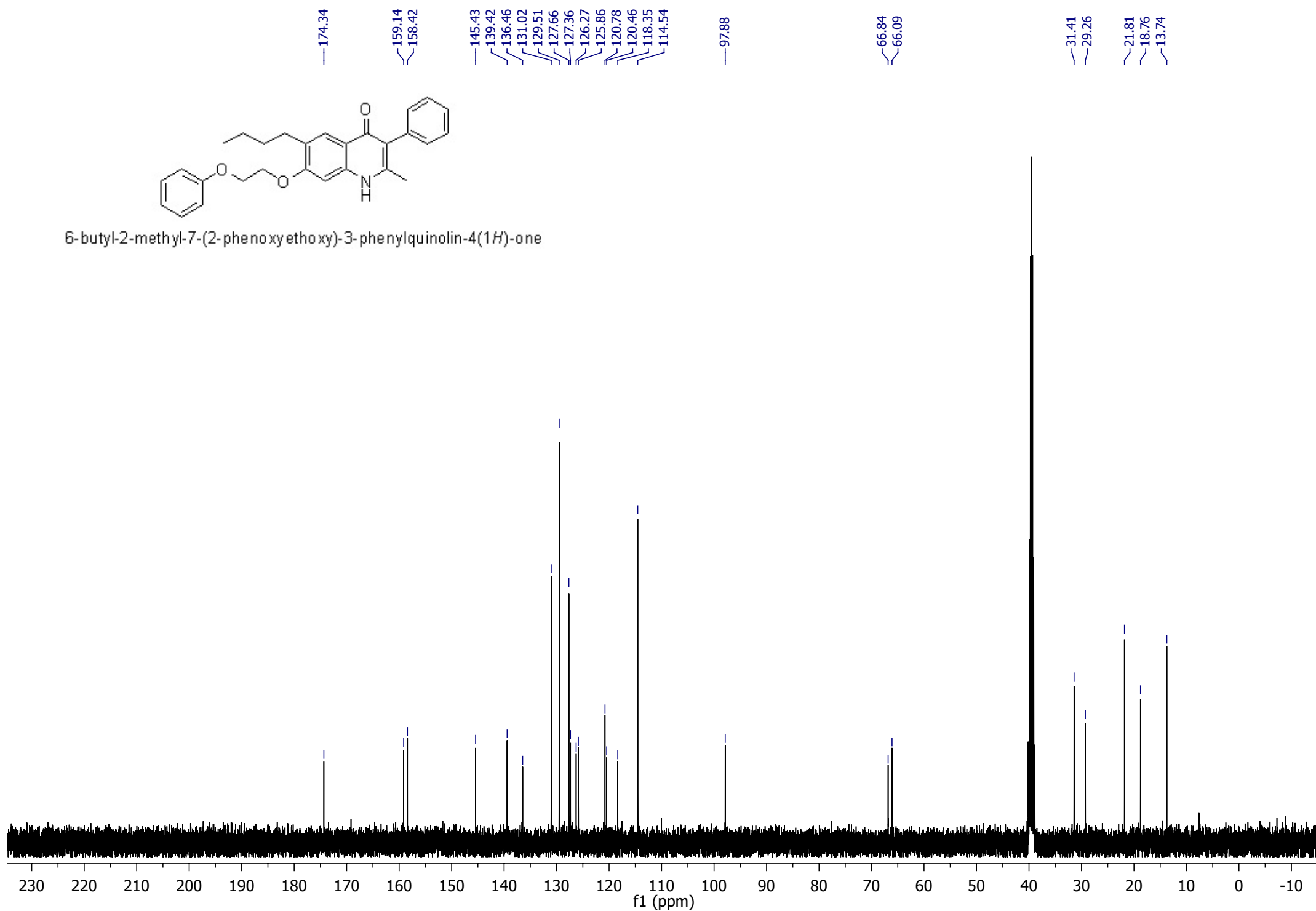


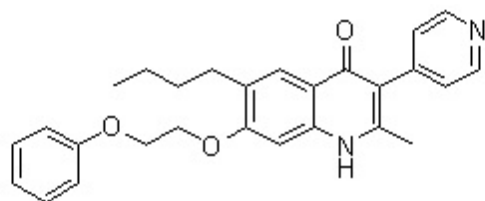
6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-phenylquinolin-4(1*H*)-one



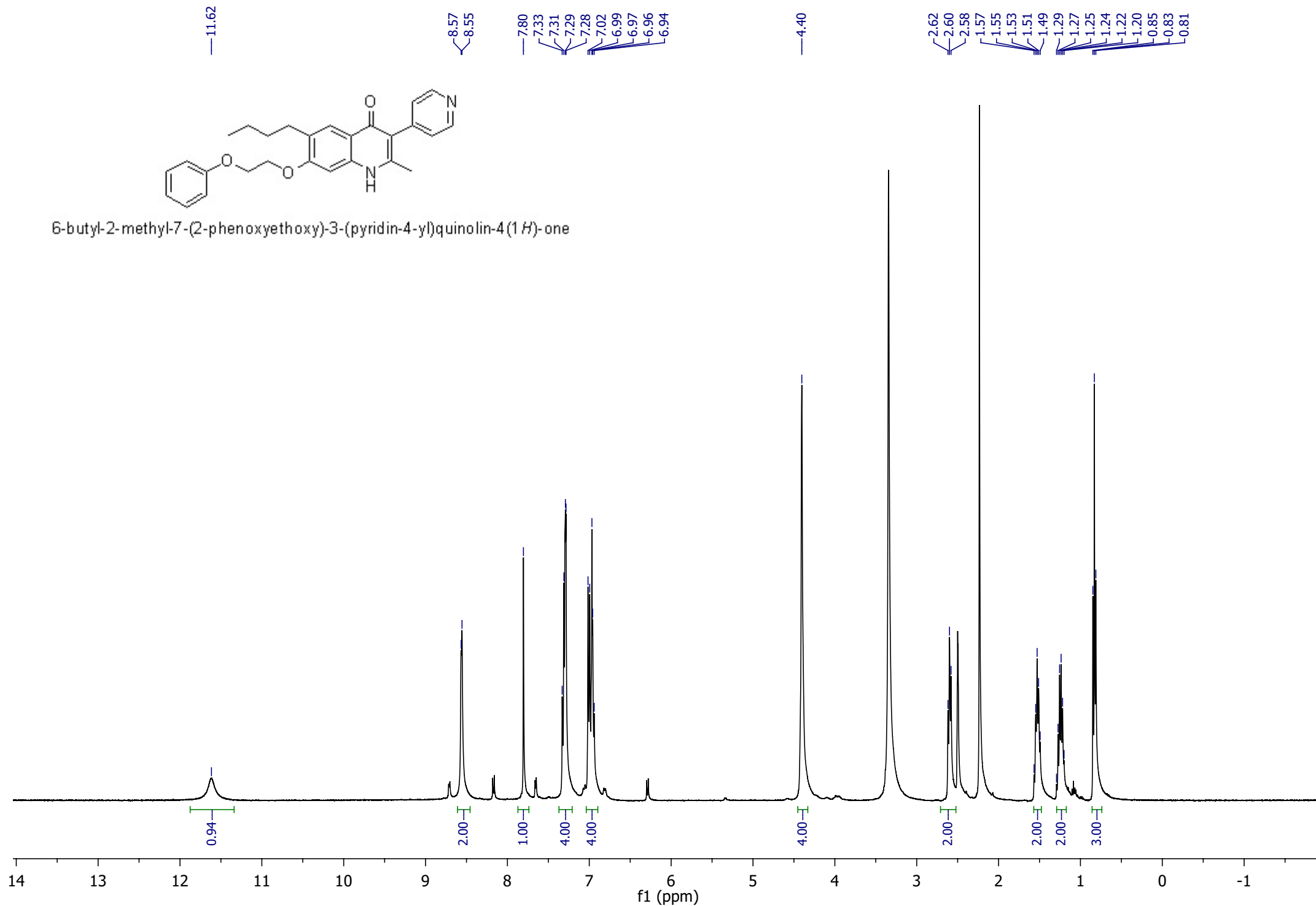


6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-phenylquinolin-4(1*H*)-one

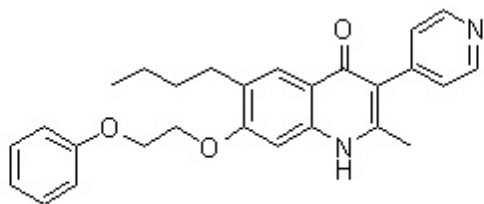




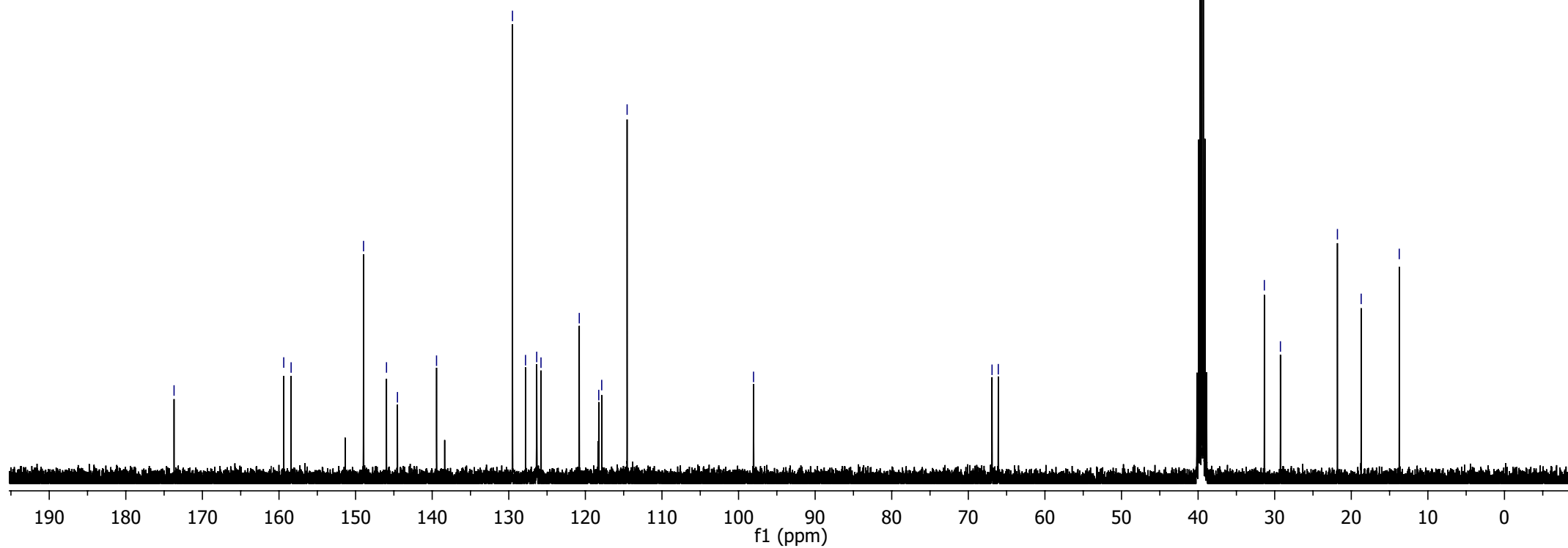
6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(pyridin-4-yl)quinolin-4(1*H*)-one

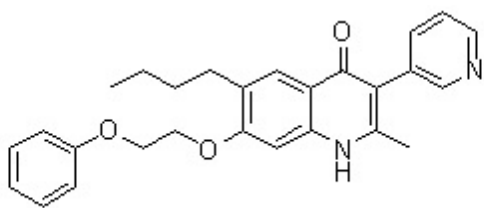


—173.70  
 —159.38  
 —158.42  
 —148.96  
 —145.97  
 —144.53  
 —139.43  
 —129.52  
 —127.81  
 —126.35  
 —125.79  
 —120.80  
 —118.25  
 —117.87  
 —114.55  
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 —66.09  
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 —13.74

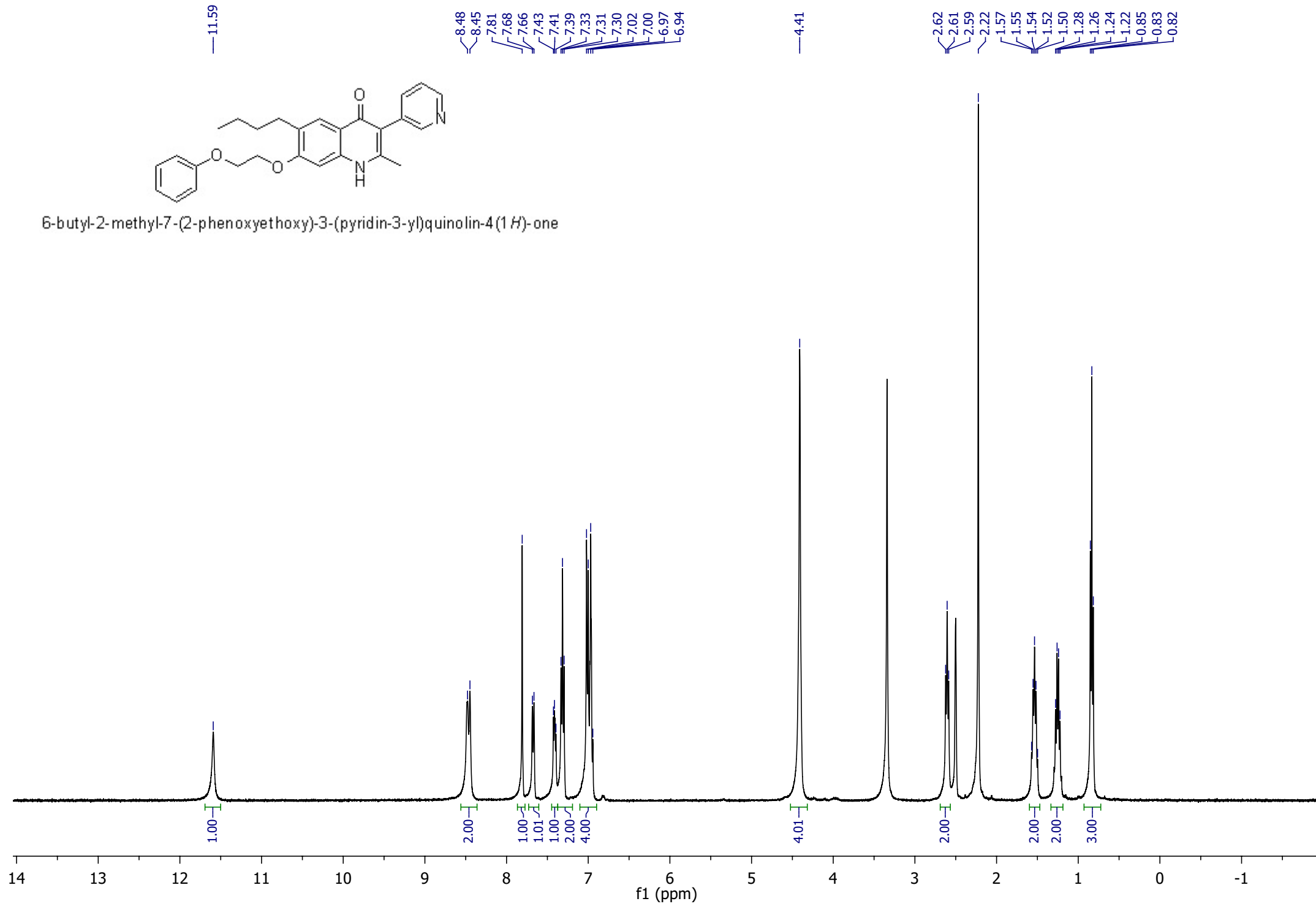


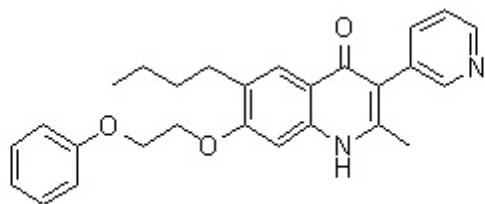
6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(pyridin-4-yl)quinolin-4(1*H*)-one



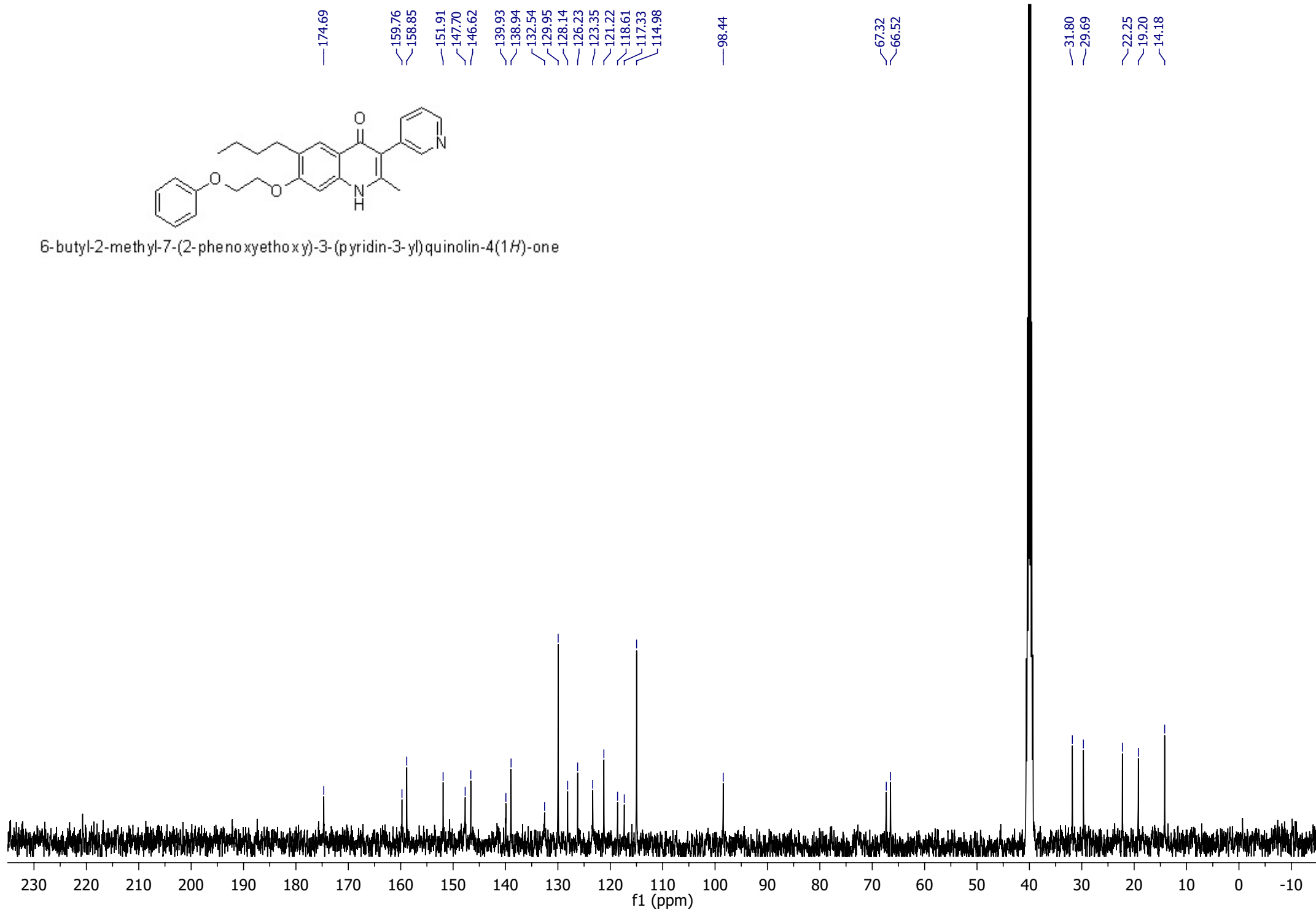


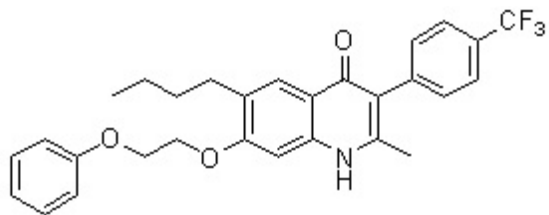
6-butyl-2-methyl-7-(2-phenoxyethoxy)-3-(pyridin-3-yl)quinolin-4(1*H*)-one



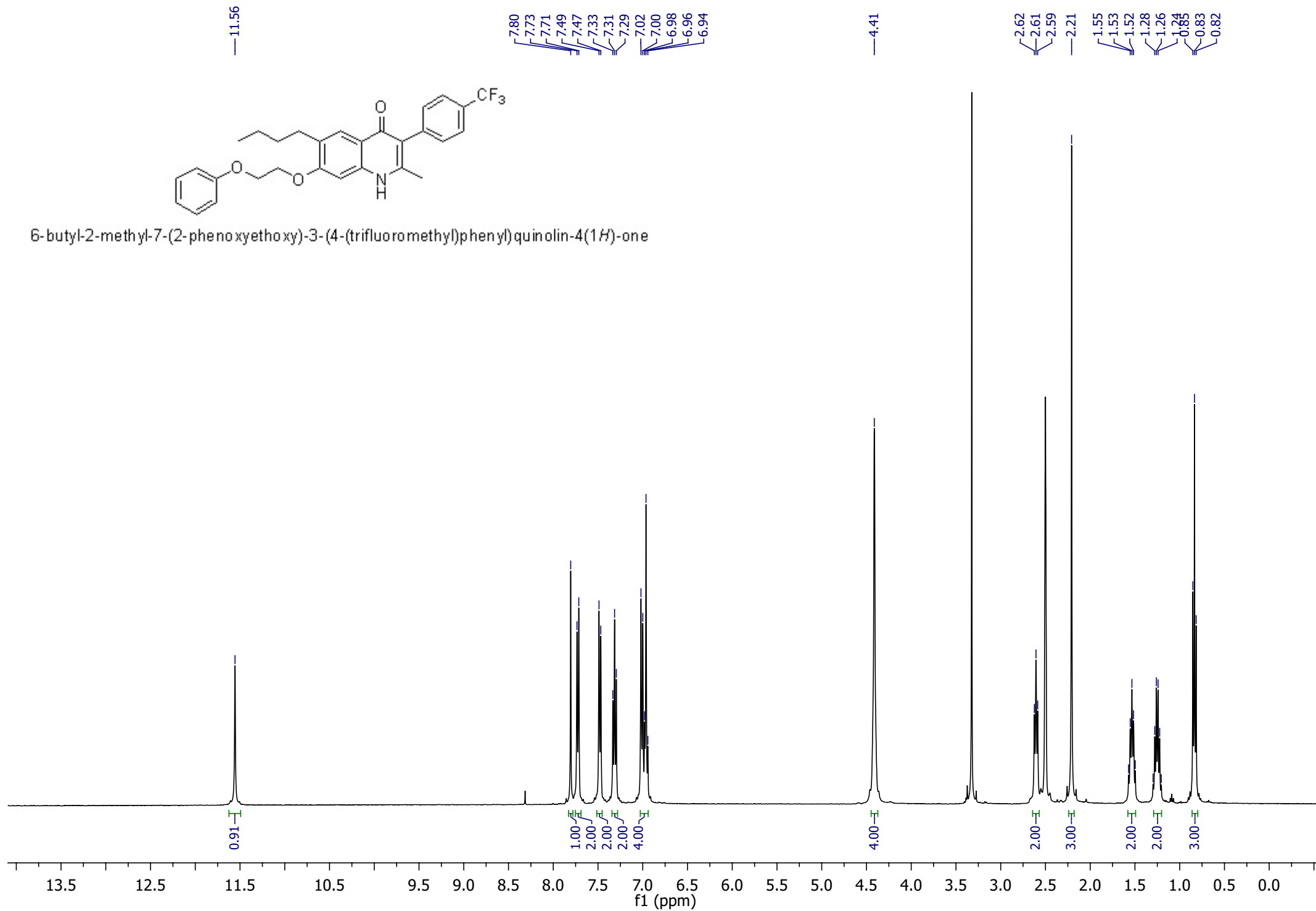


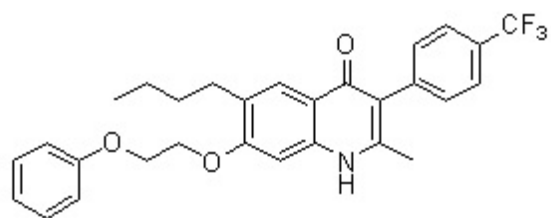
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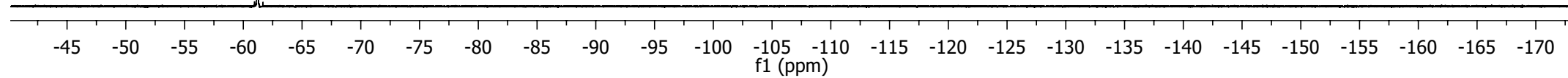
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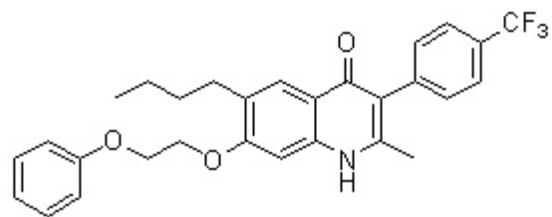


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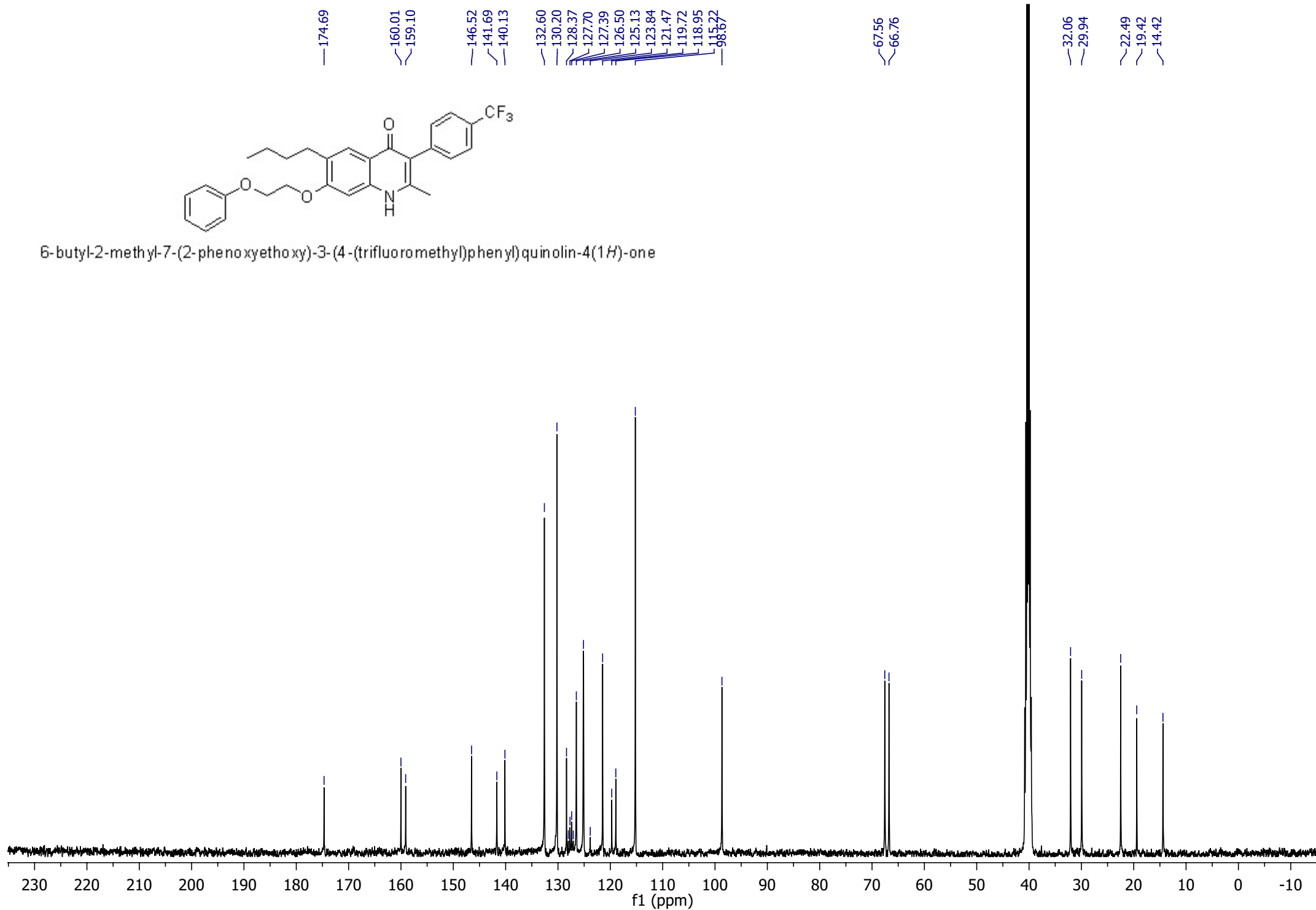
61.19

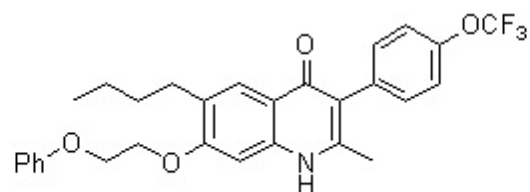




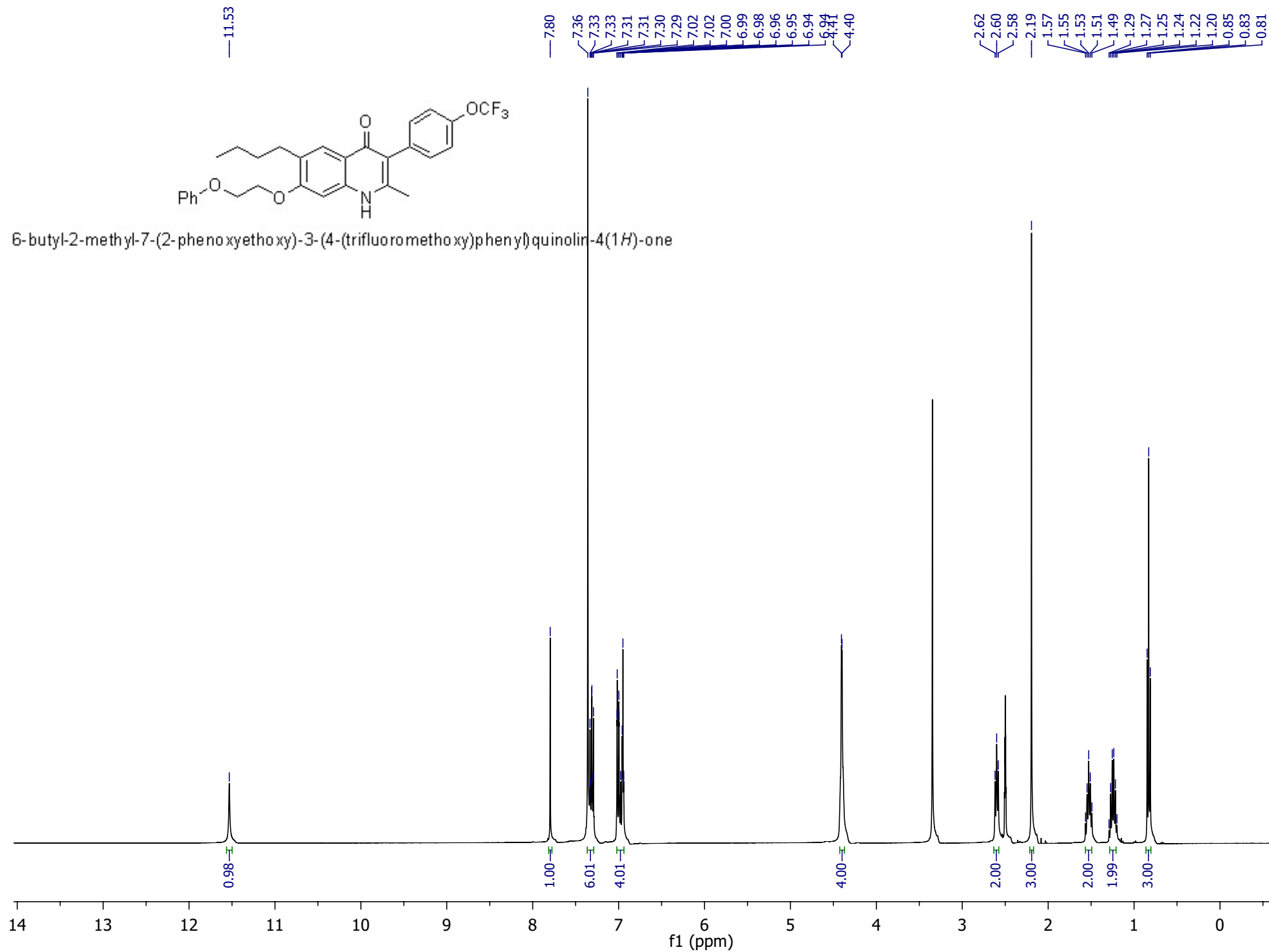


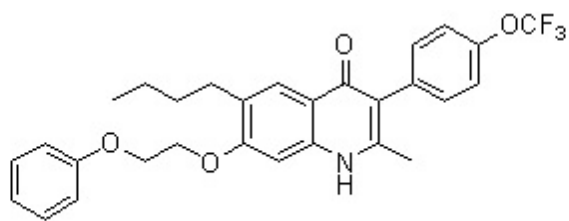
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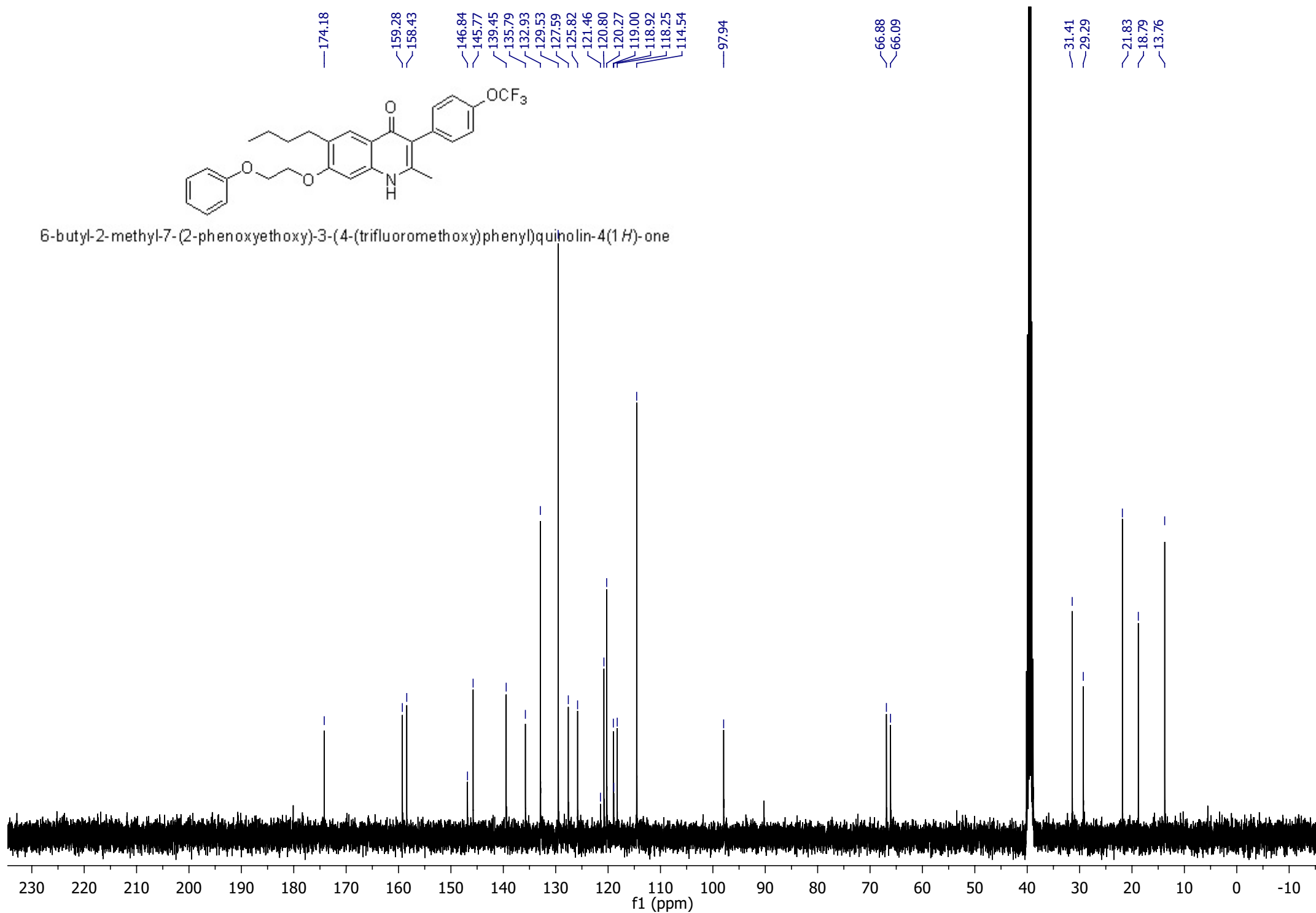


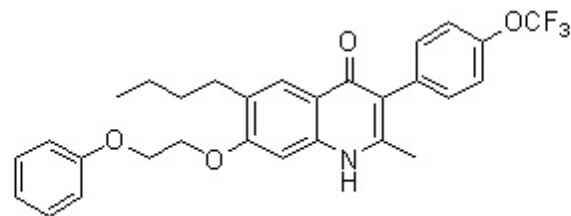
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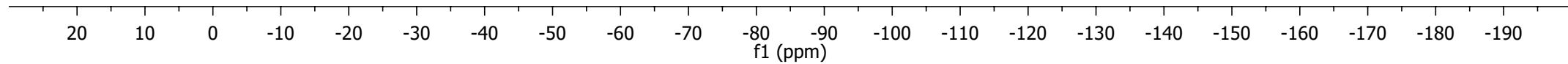
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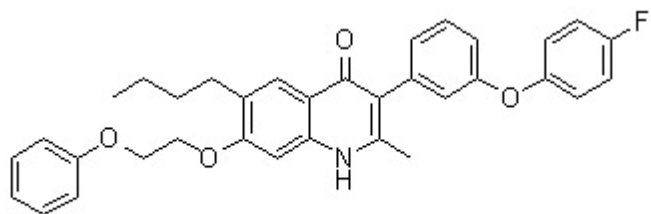




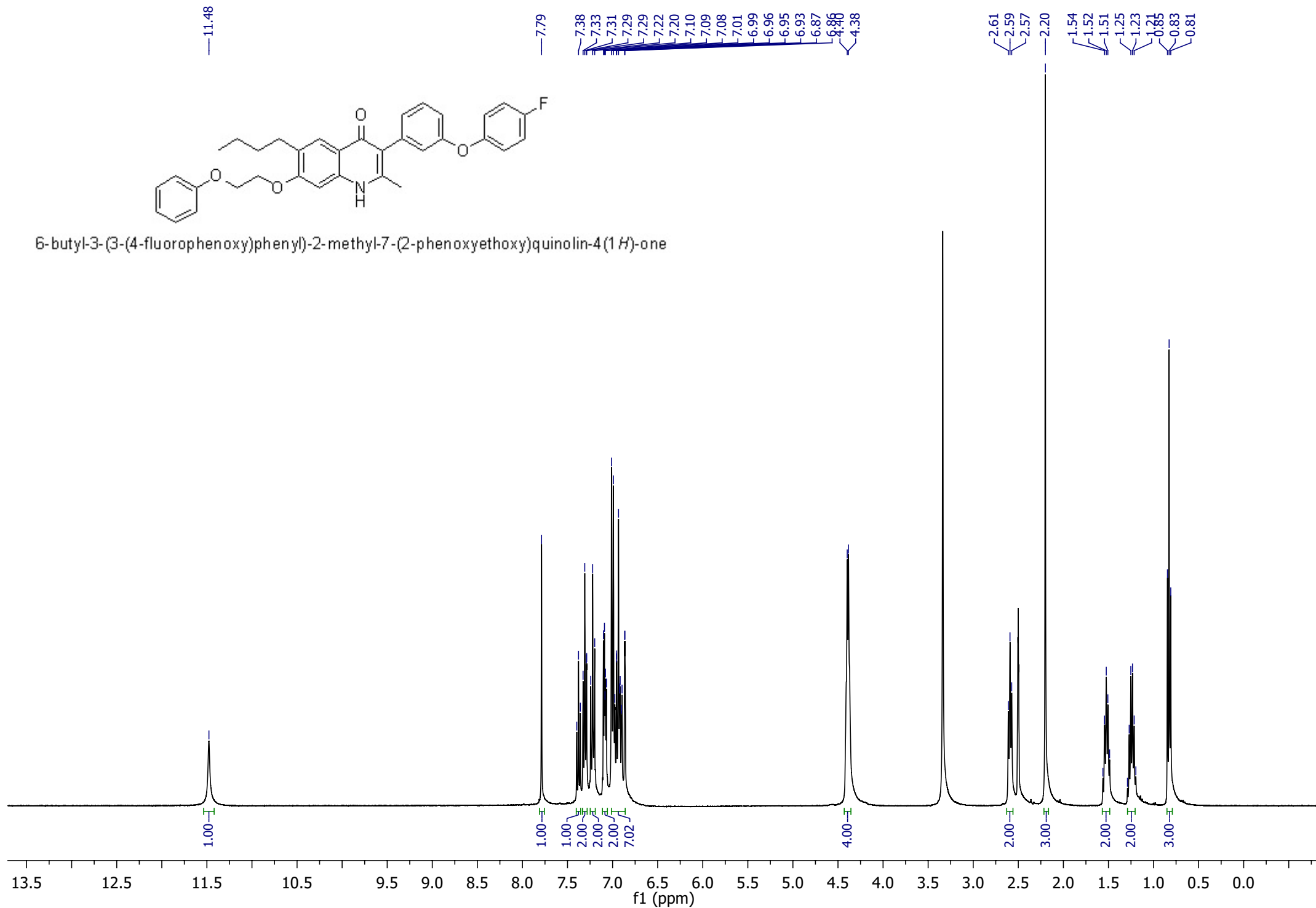
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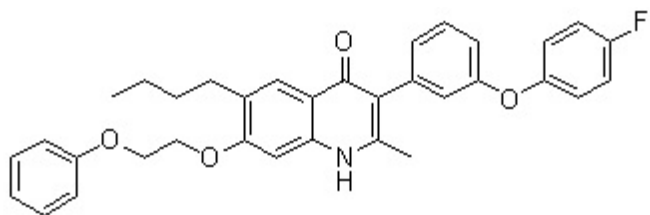
—56.62



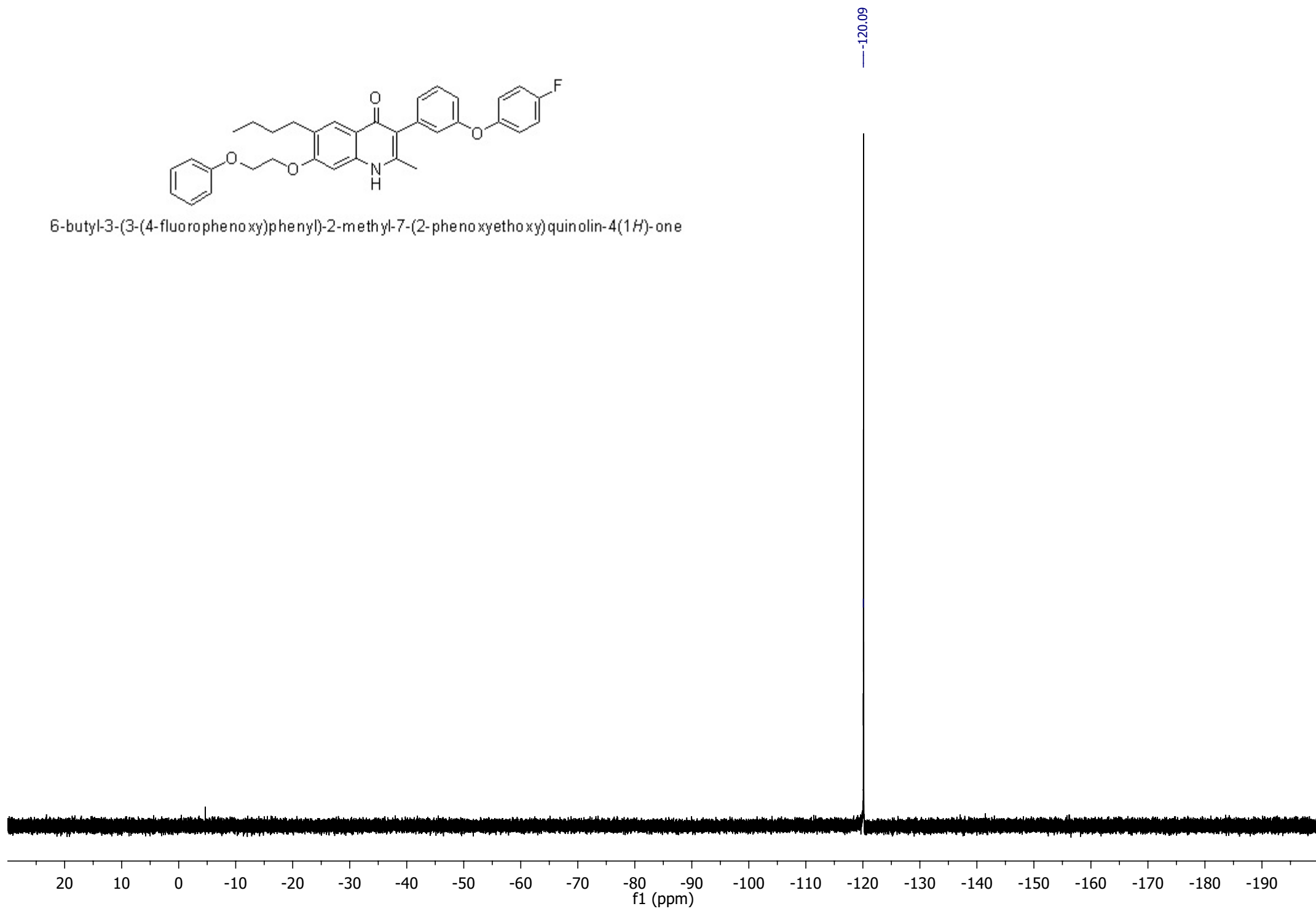


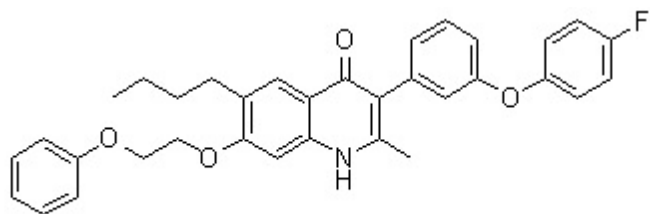
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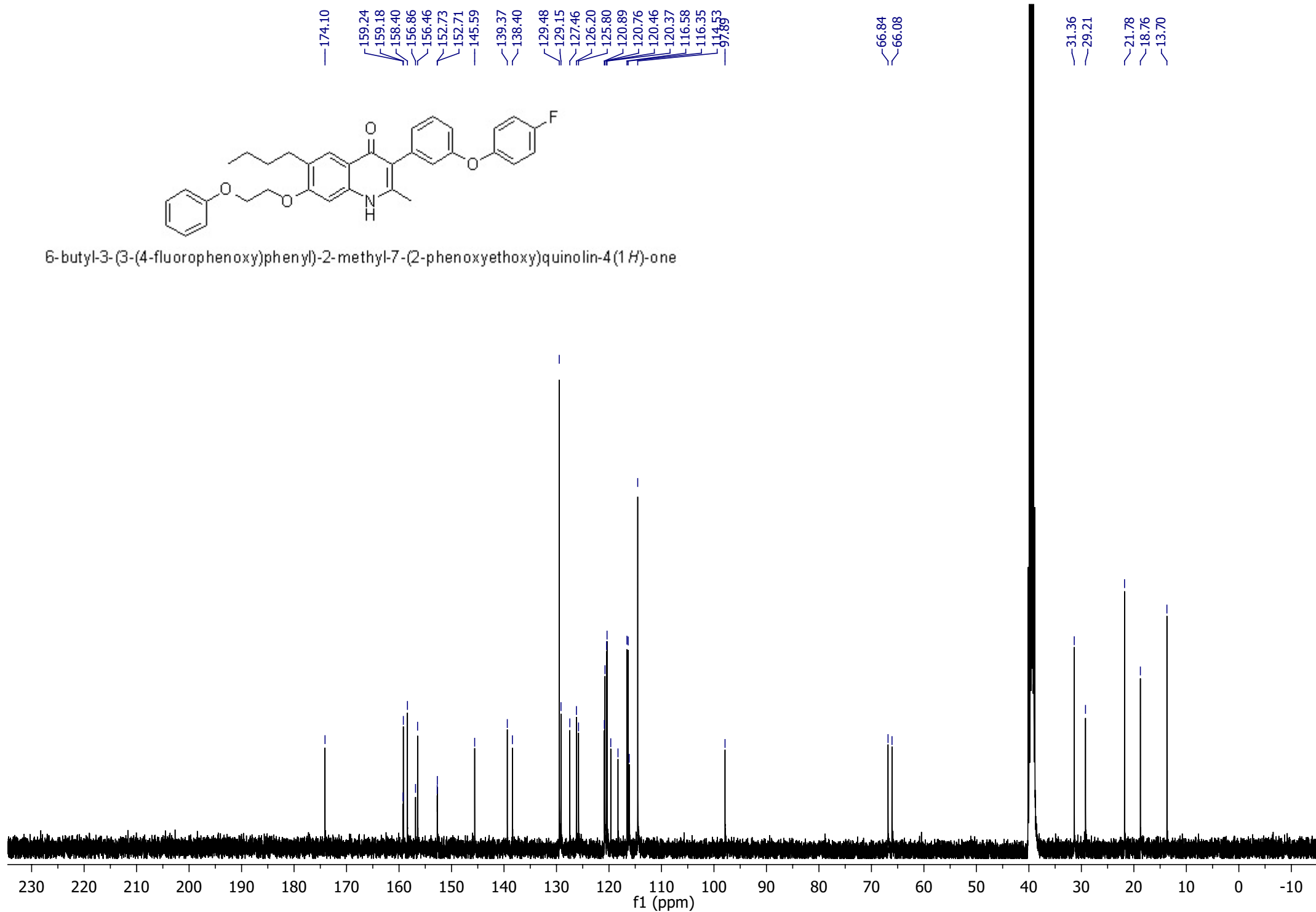


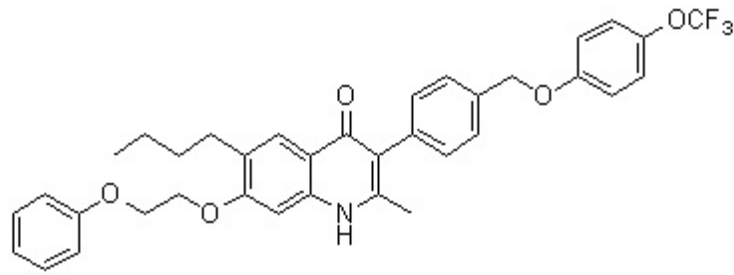
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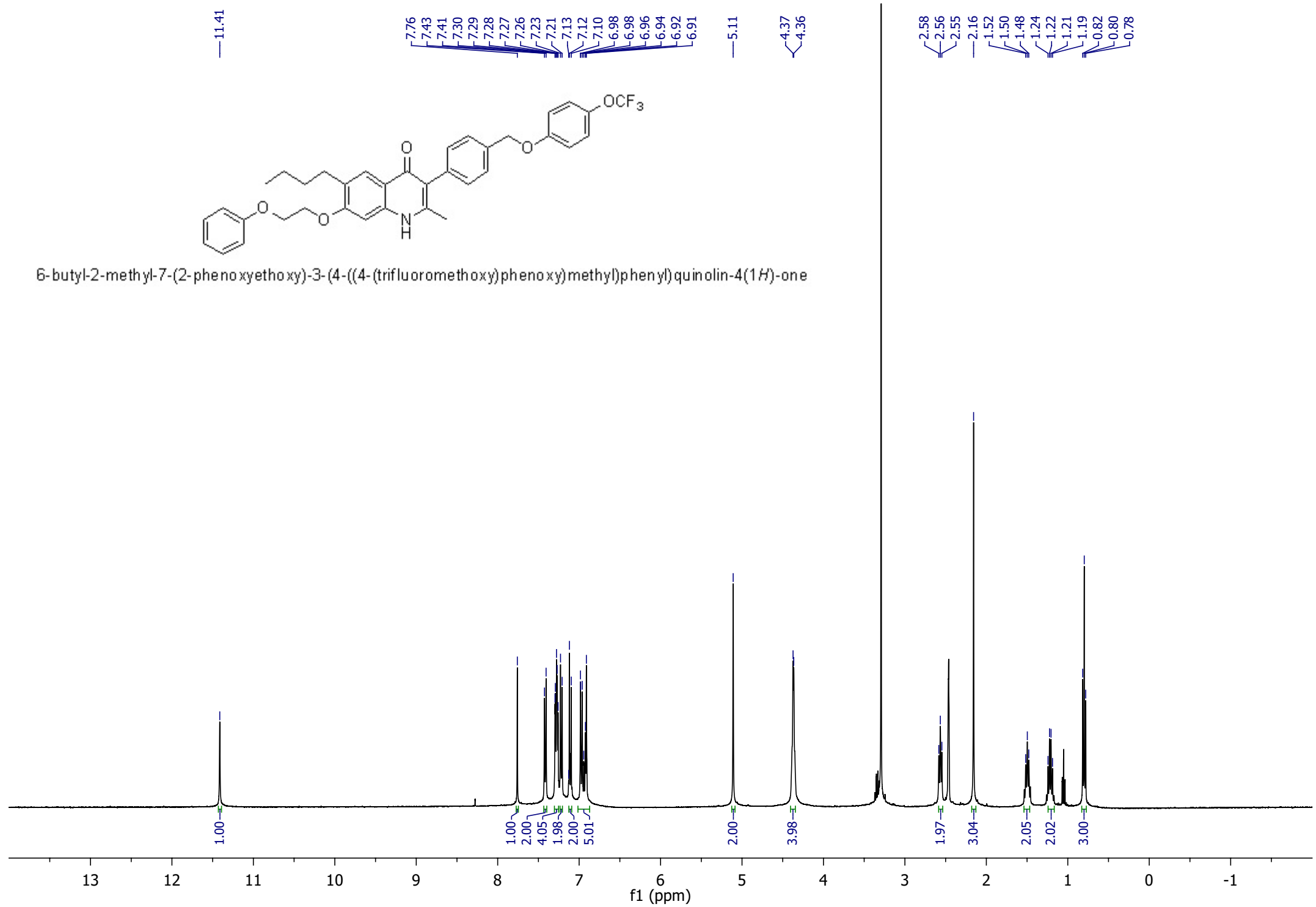


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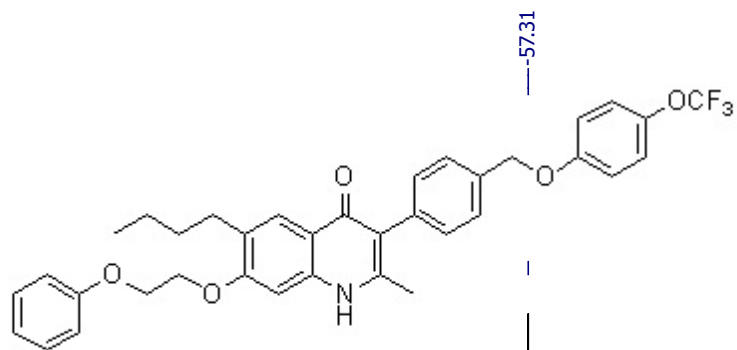




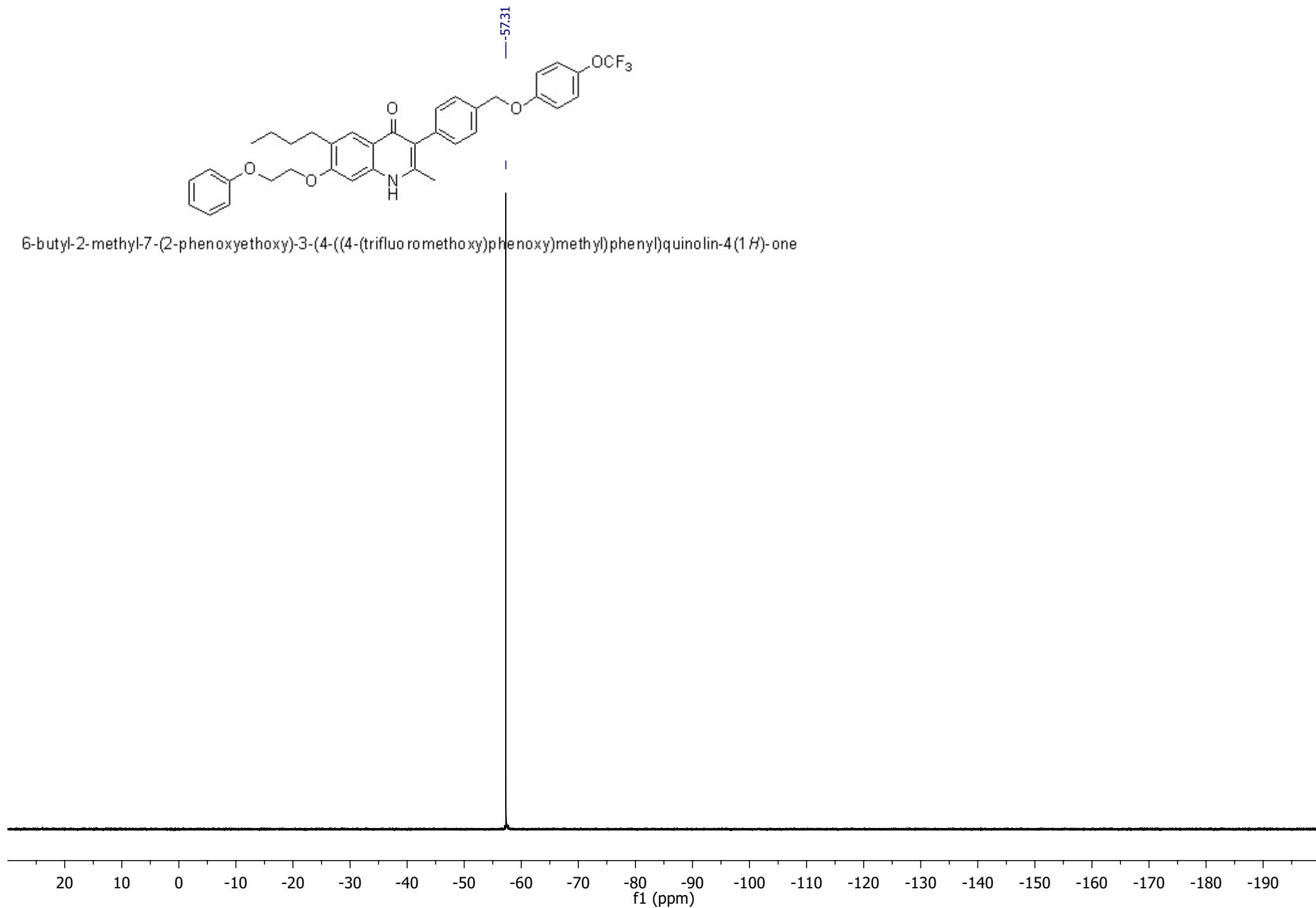
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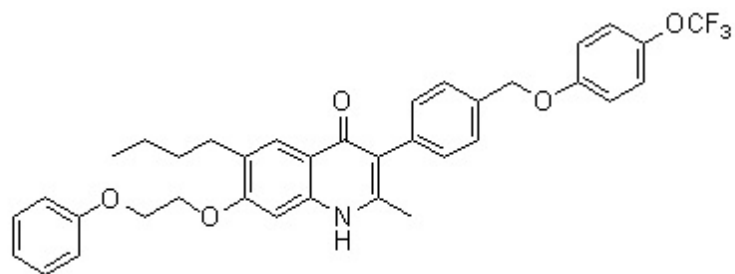




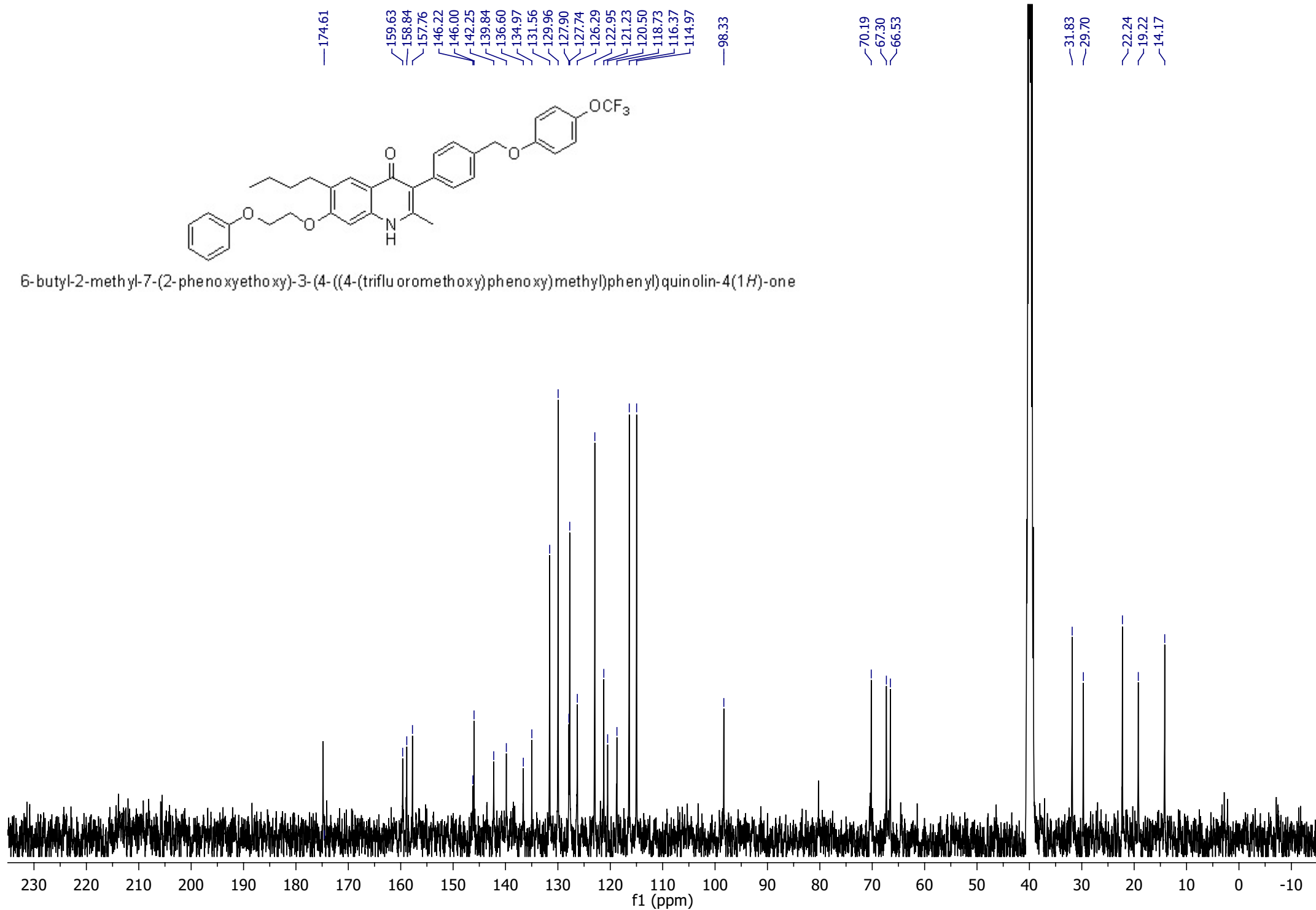


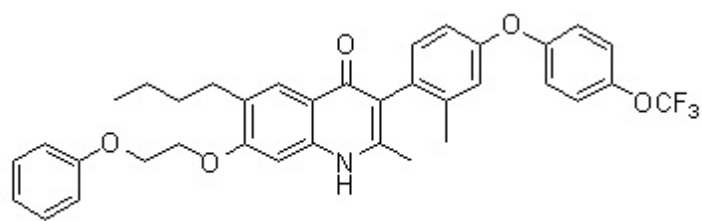
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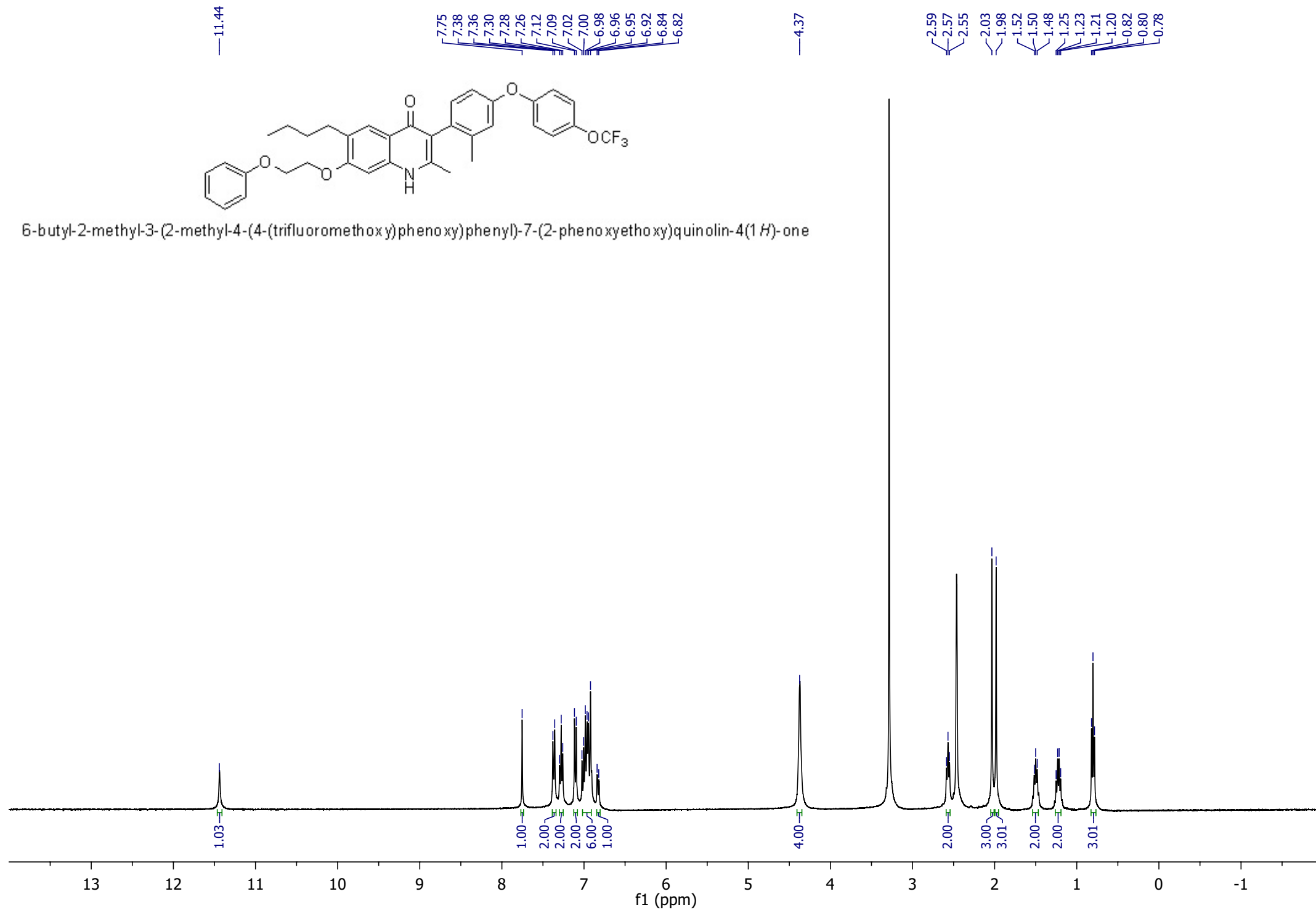


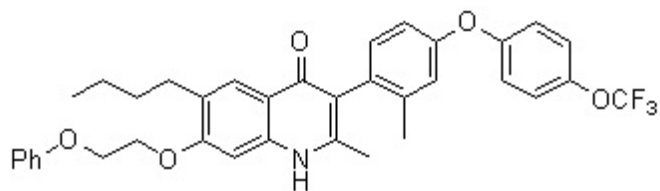
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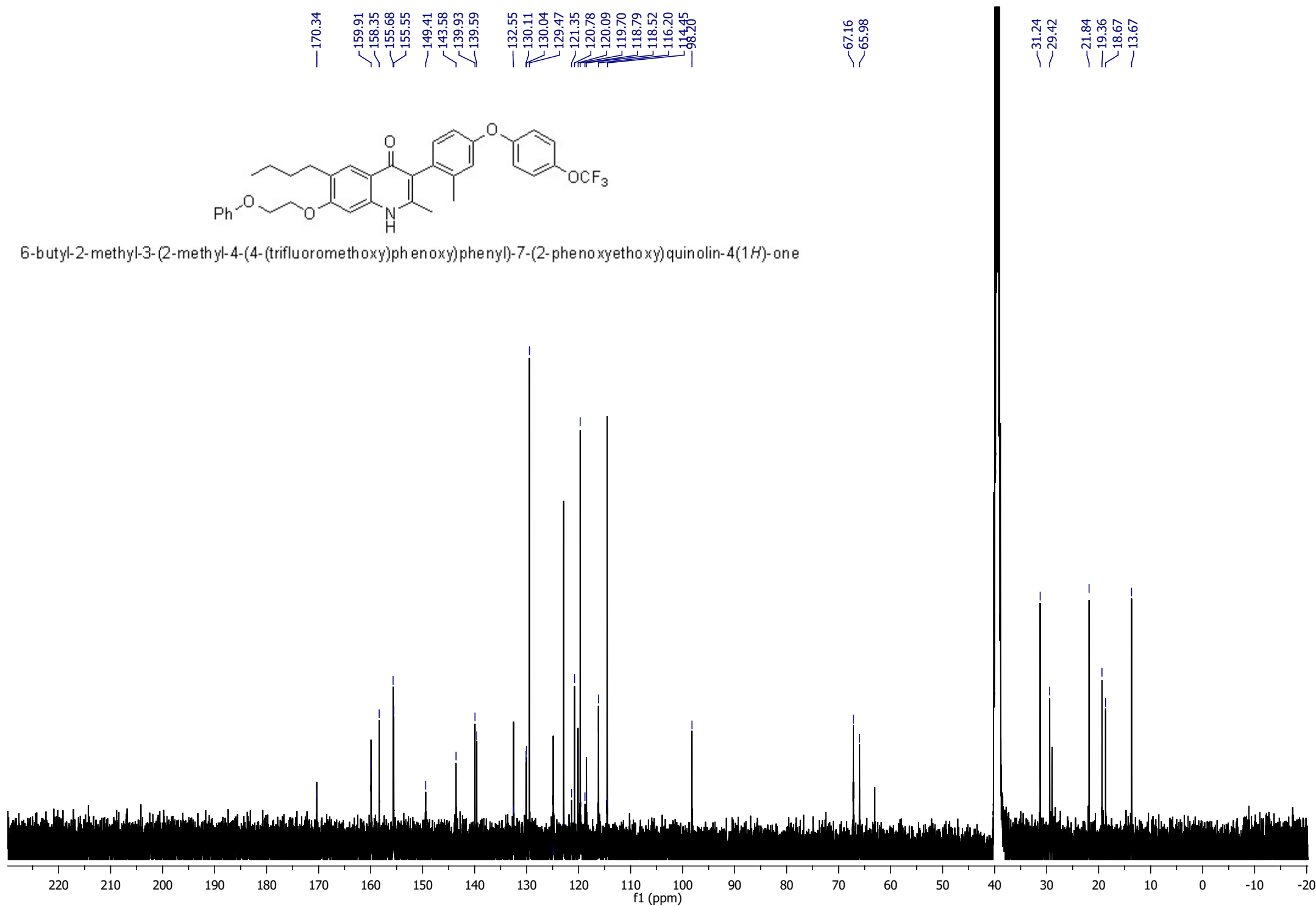


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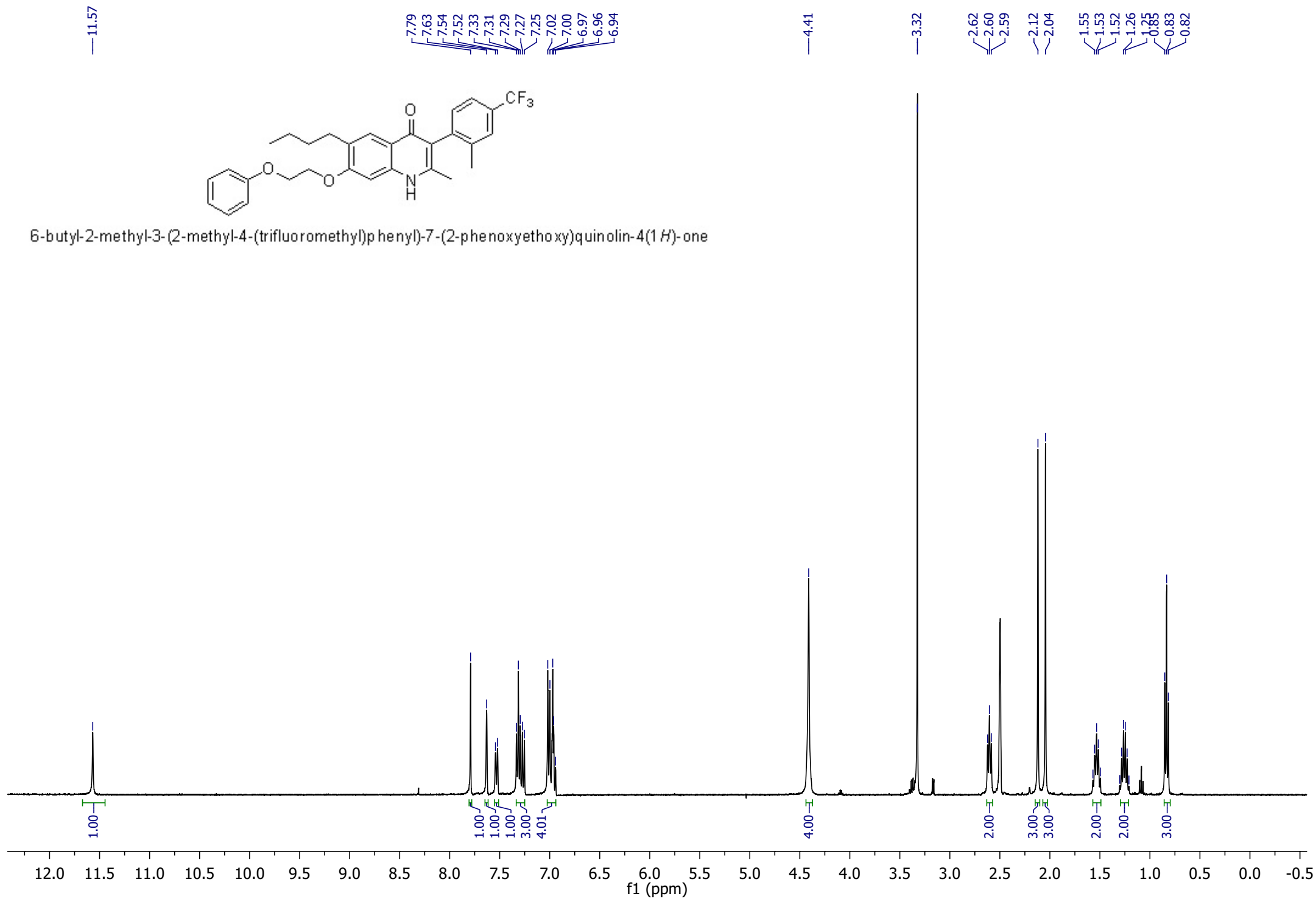
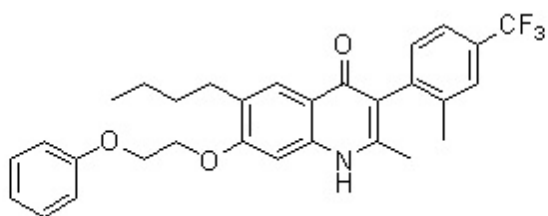


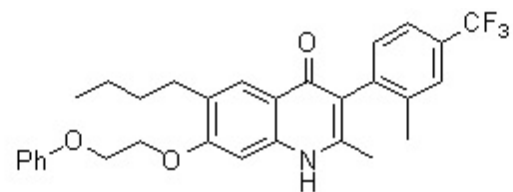


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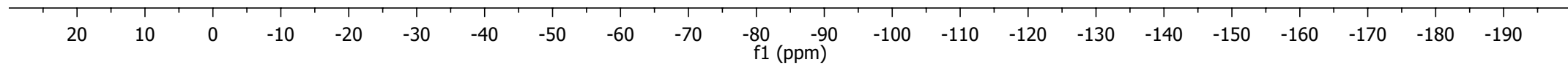
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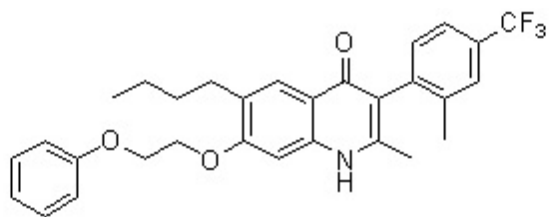




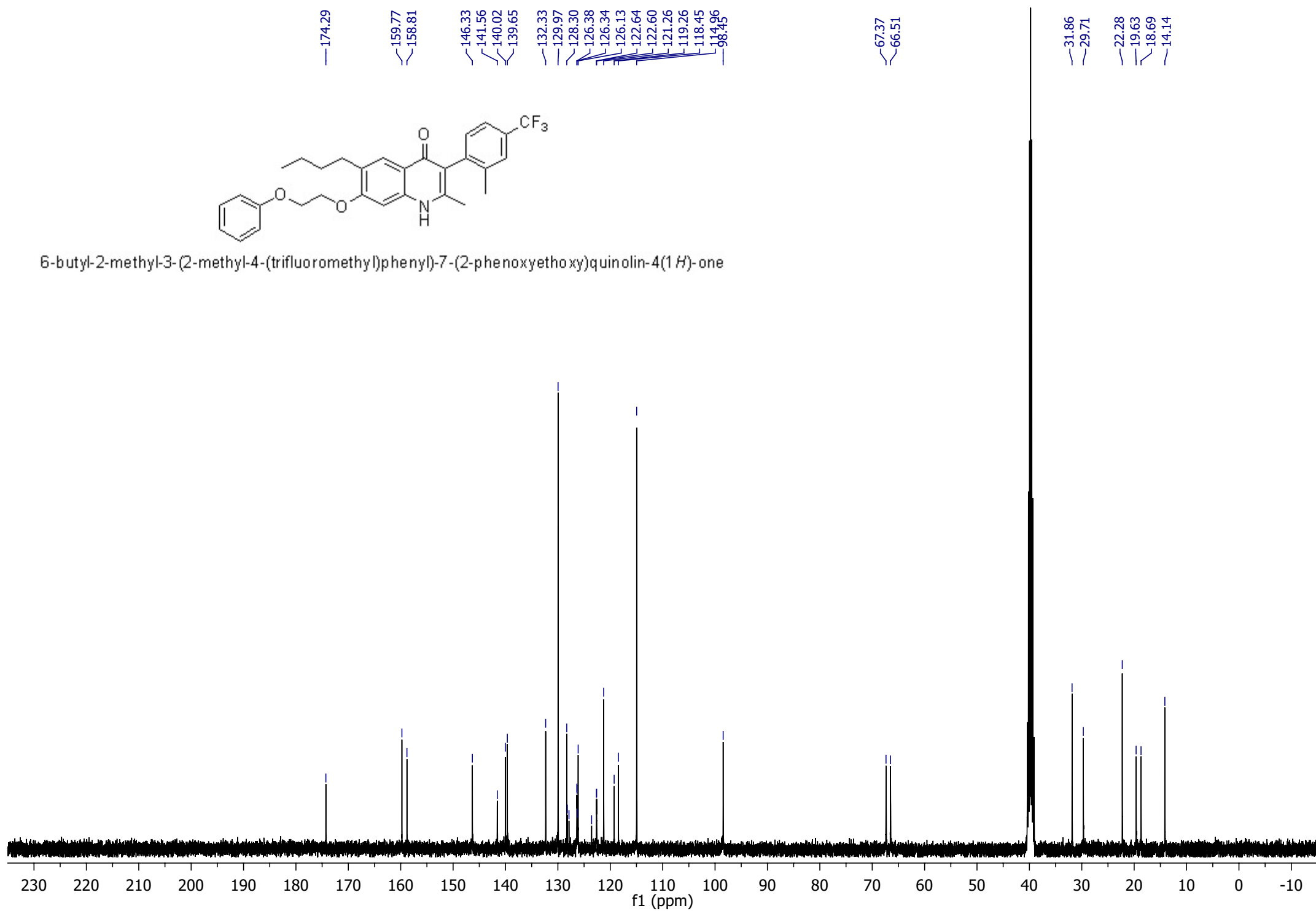
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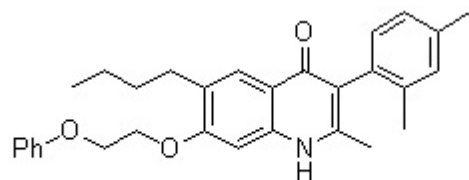
57.51



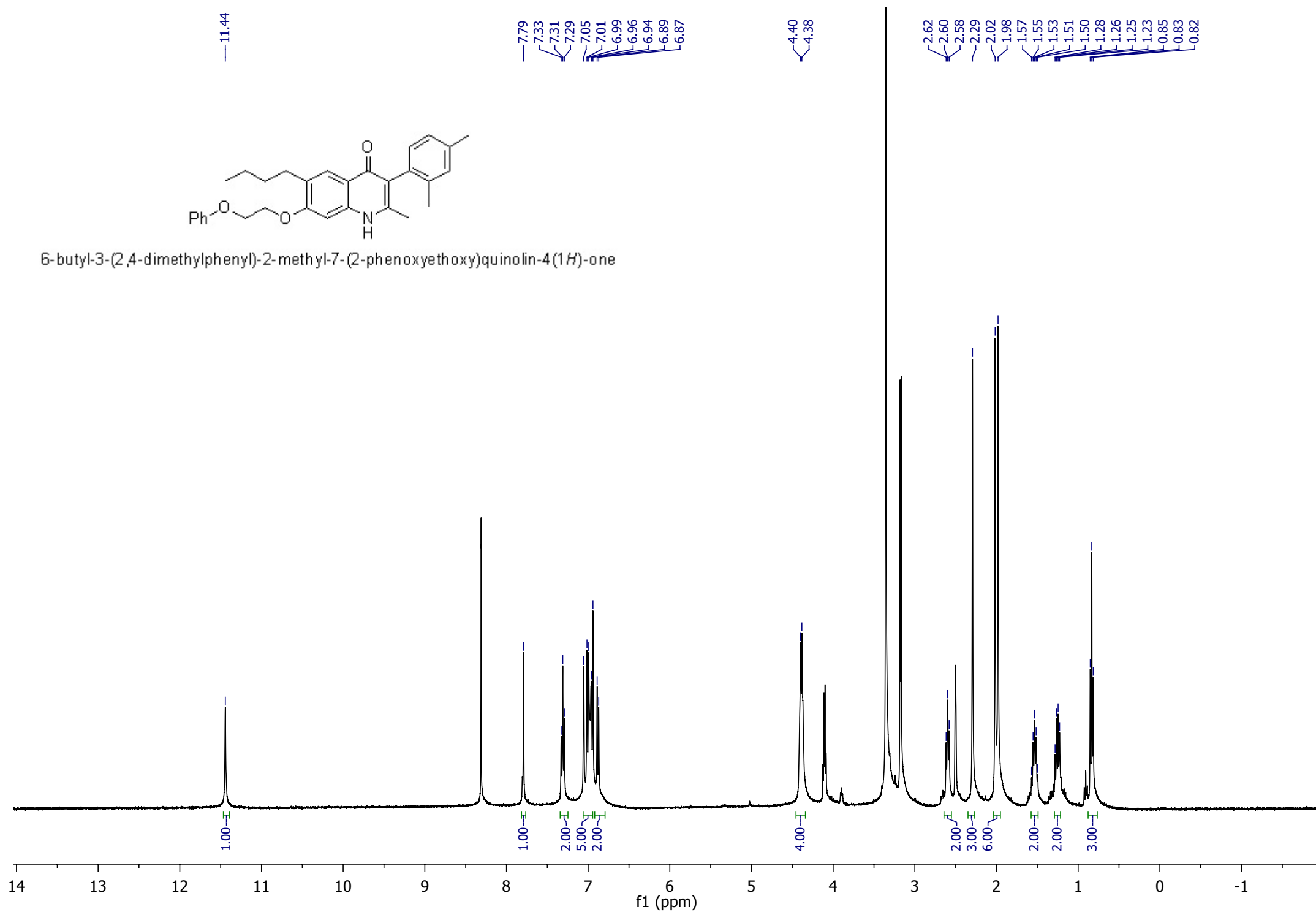


6-butyl-2-methyl-3-(2-methyl-4-(trifluoromethyl)phenyl)-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one

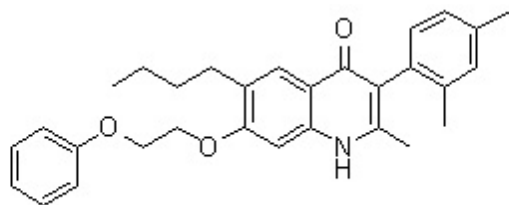




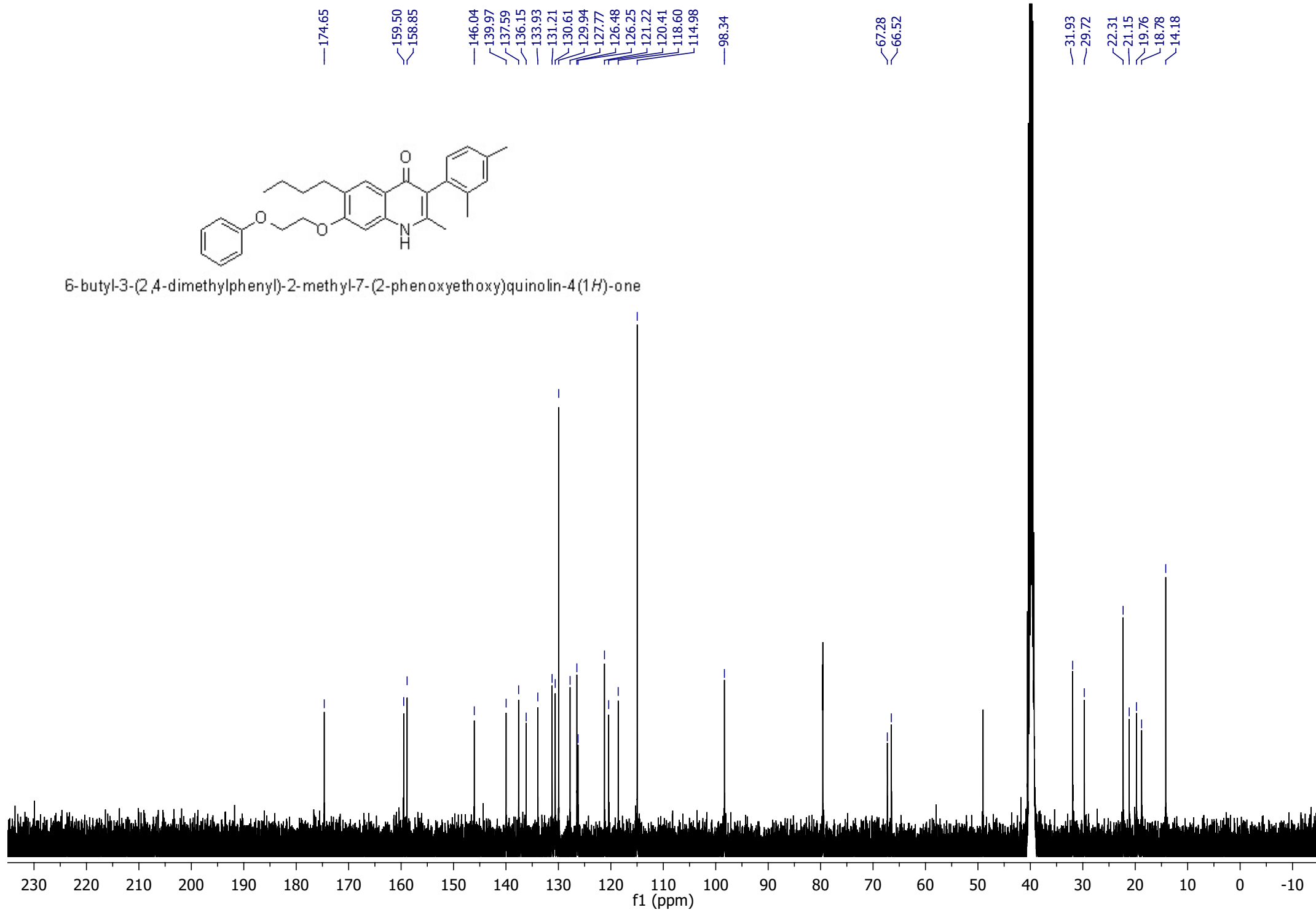
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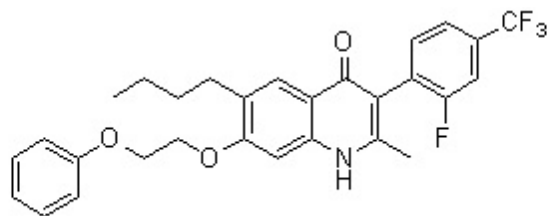




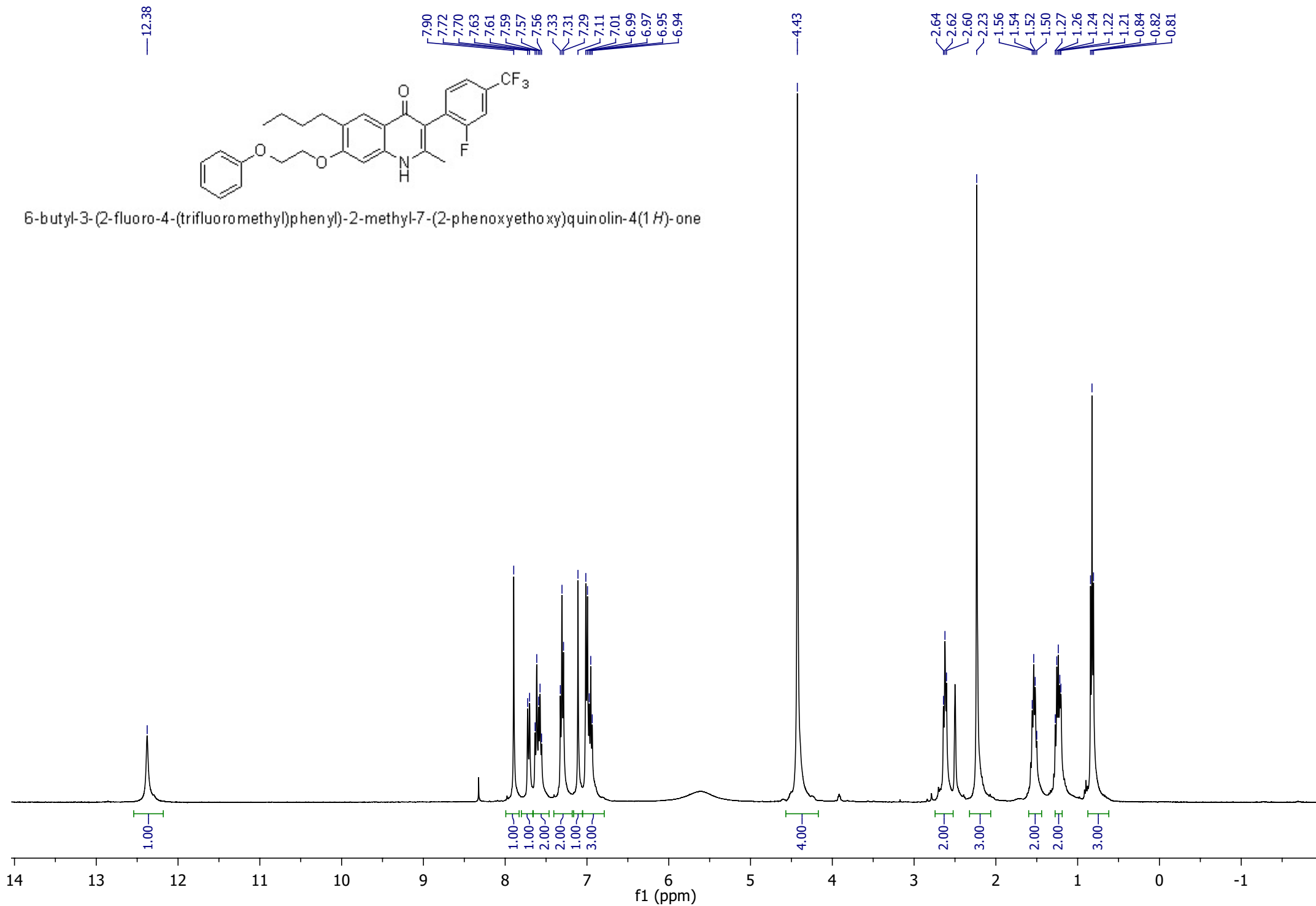


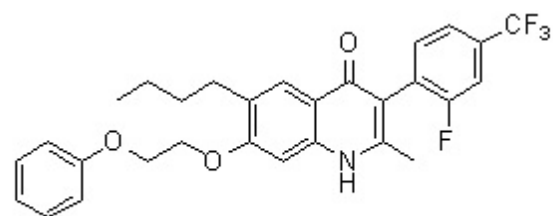
6-butyl-3-(2,4-dimethylphenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one



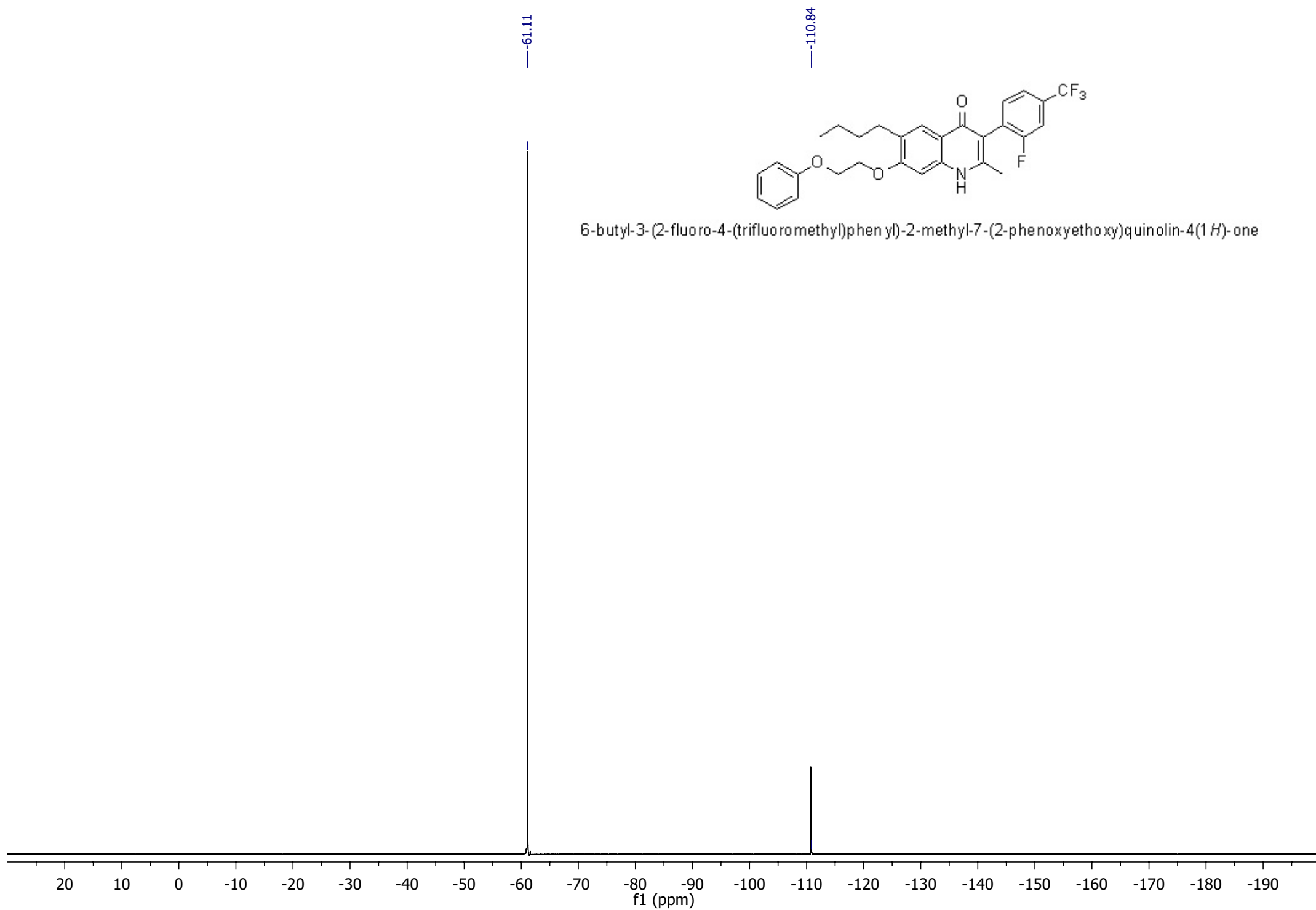


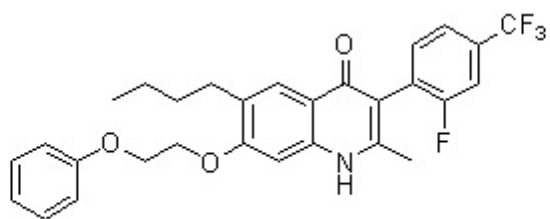
6-butyl-3-(2-fluoro-4-(trifluoromethyl)phenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one



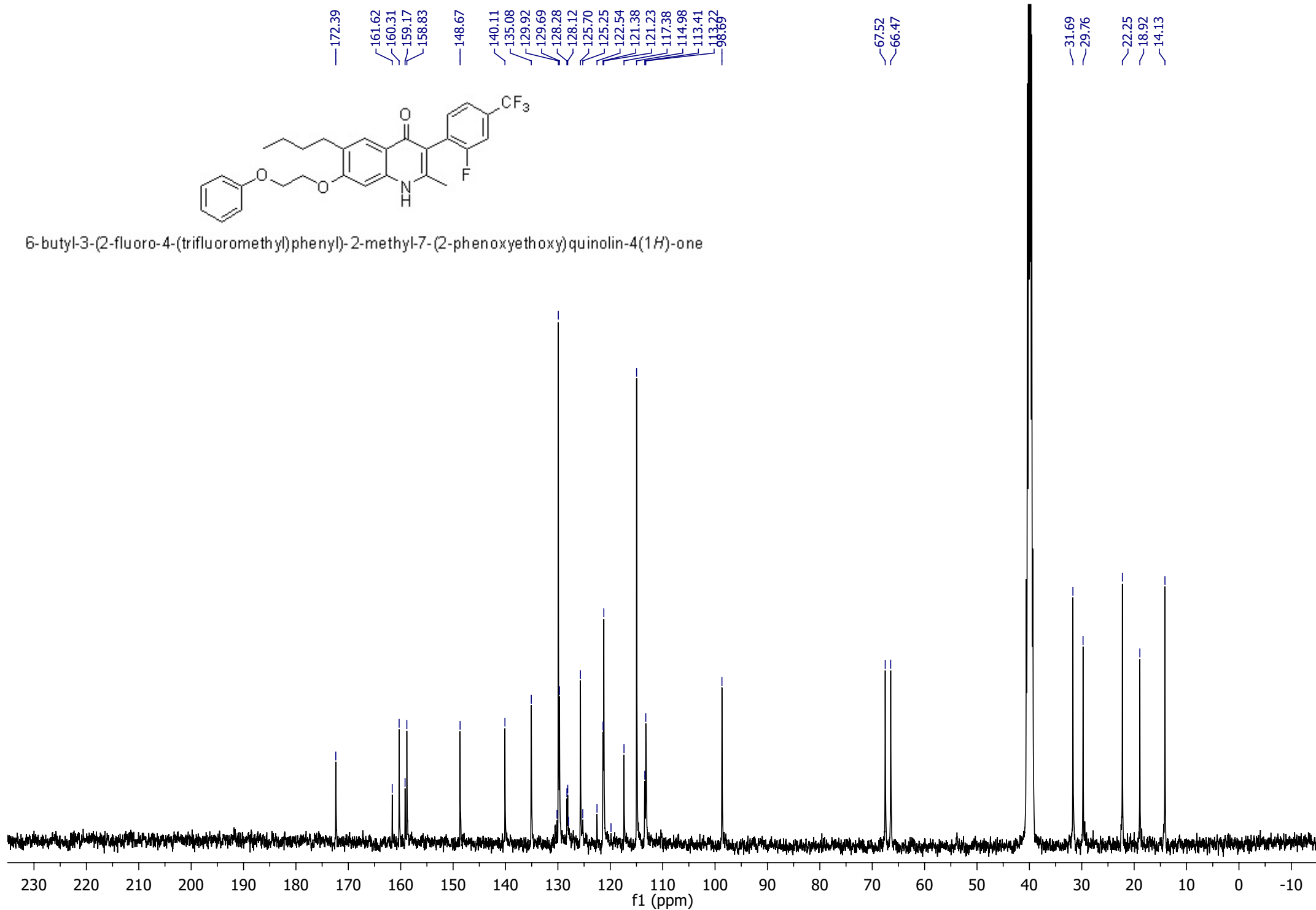


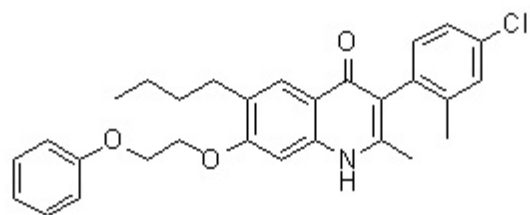
6-butyl-3-(2-fluoro-4-(trifluoromethyl)phenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one



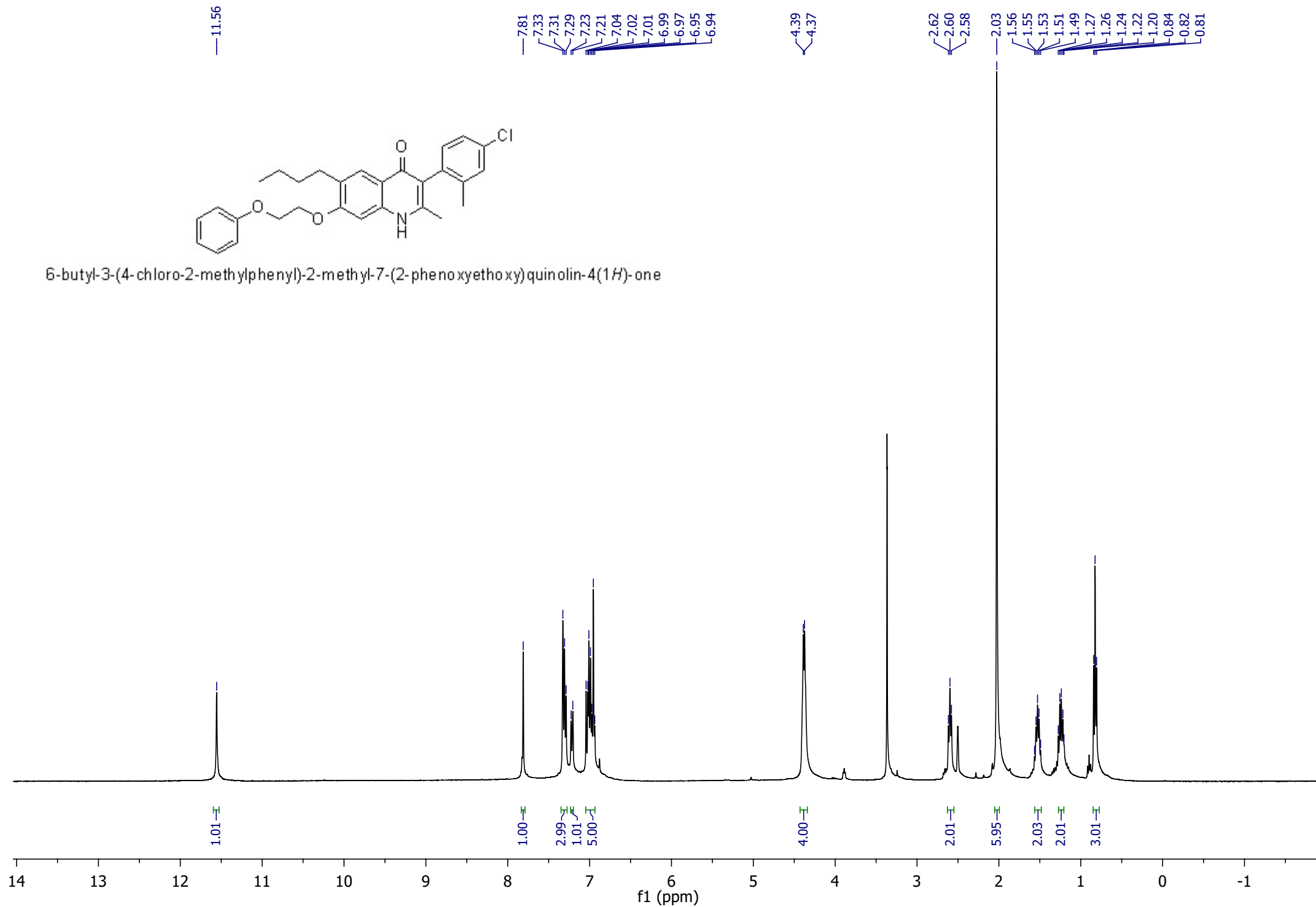


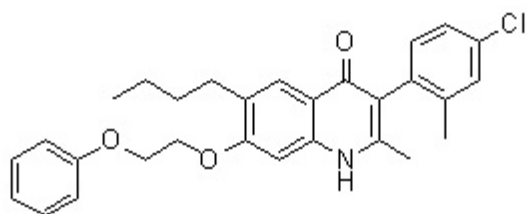
6-butyl-3-(2-fluoro-4-(trifluoromethyl)phenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one



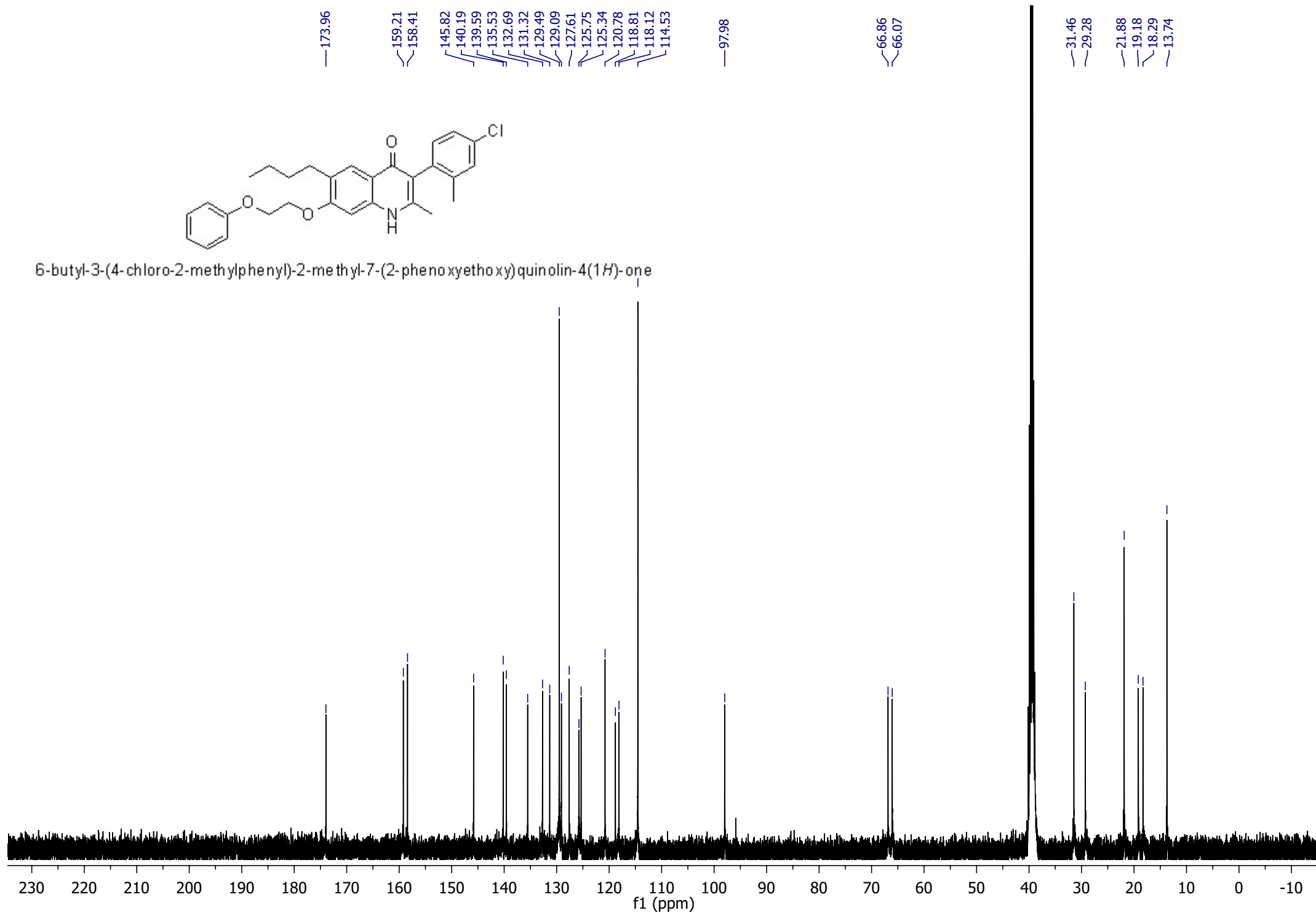


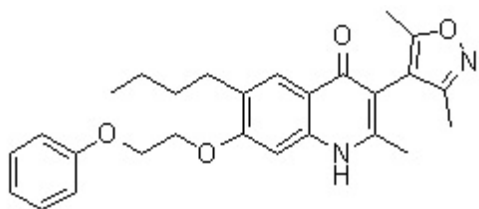
6-butyl-3-(4-chloro-2-methylphenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one



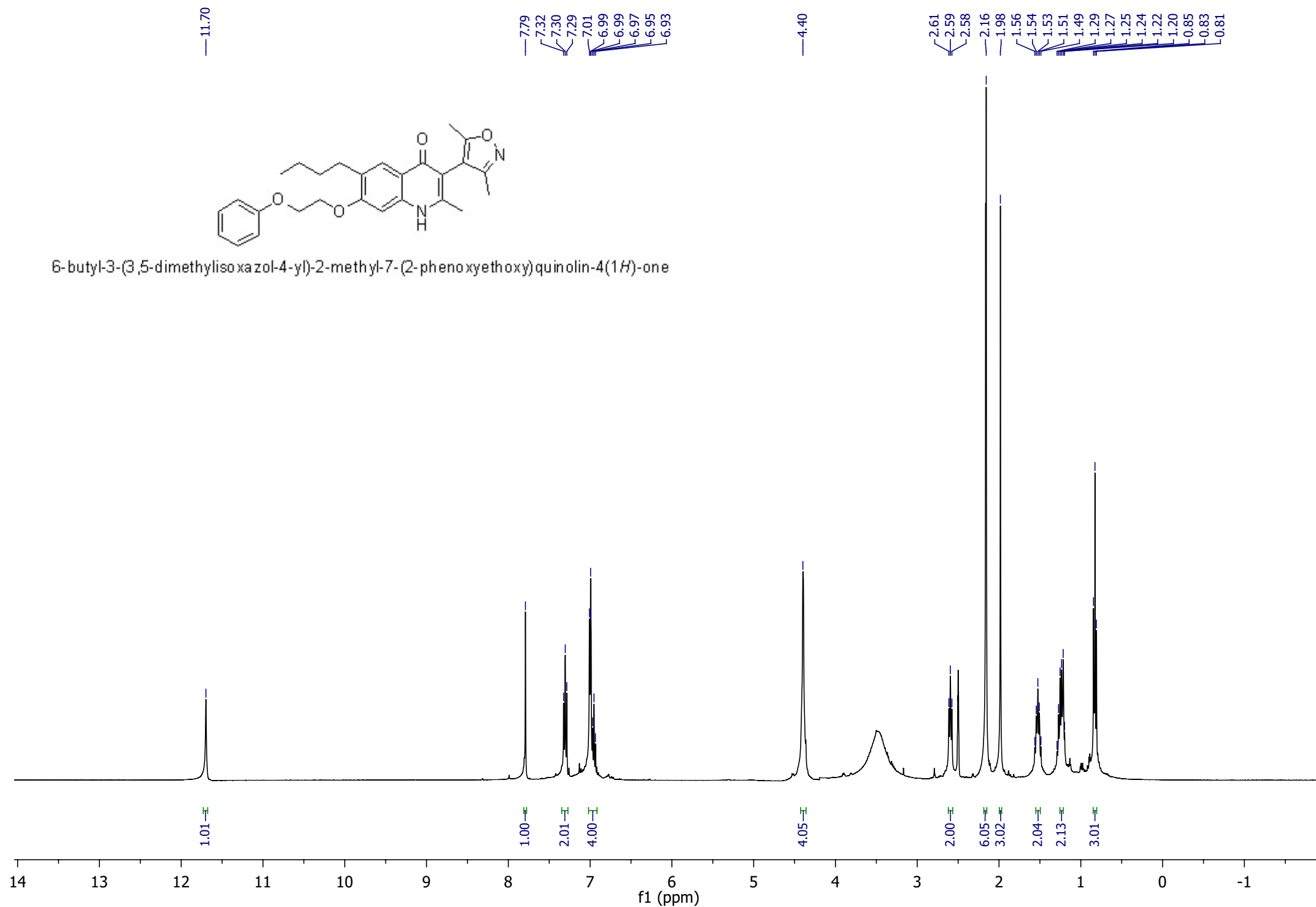


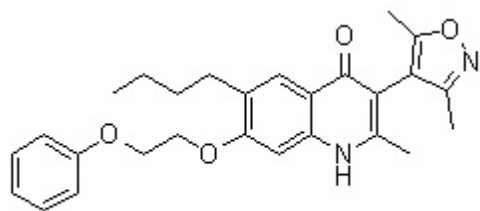
6-butyl-3-(4-chloro-2-methylphenyl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one





6-butyl-3-(3,5-dimethylisoxazol-4-yl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one





6-butyl-3-(3,5-dimethylisoxazol-4-yl)-2-methyl-7-(2-phenoxyethoxy)quinolin-4(1*H*)-one

