Synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl esters from Arylmethyl azides *via* a domino process

Jumreang Tummatorn, [†,*] Charnsak Thongsornkleeb, [†,‡] Somsak Ruchirawat, [†,‡] and Tanita Gettongsong [†]

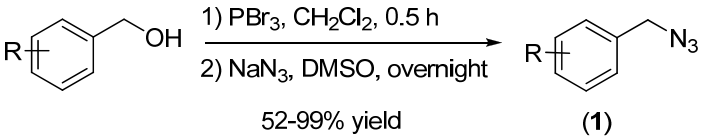
[†] *Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand*
[‡] Program on Chemical Biology, Chulabhorn Graduate Institute, Center of Excellence on Environmental Health and Toxicology, CHE, Ministry of Education, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand

Supporting Information

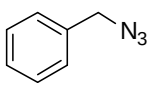
Contents: **Pages**

1. General Information. Commercial grade reagents and solvents were used as received from the supplier except where indicated otherwise. Tetrahydrofuran (THF), dichloromethane (DCM), and toluene were purified by pressure filtration through activated alumina. All glassware was oven-dried at 110 ^{o}C for two hours or more. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with 300 MHz NMR spectrometers. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) were reported in units of part per million (ppm), relative to tetramethylsilane (TMS) at δ equal to zero ppm. Coupling constants (*J*) were reported in Hertz (Hz). Infrared spectra measured using an FT-IR spectrometer and were reported in cm^{-1}. High resolution mass spectra (HRMS) was measured on a mass spectrometer.

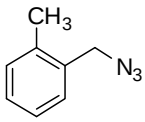
2. General procedure for the synthesis of benzylic azides (1)



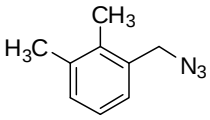
To a solution of benzyl alcohol (1.0 equiv) in DCM (2.6 mL/mmol) was added PBr_3 (0.34 equiv) at room temperature. The reaction mixture was stirred for 1 h and then the solvent was removed under reduce pressure. The residue was used for next step without further purification. The crude product was dissolved in DMSO (2.6 mL/mmol) and NaN_3 (2.5 equiv) was added at 0°C. The reaction mixture was stirred at 0°C for 0.5 h and then warmed up to room temperature. The mixture was stirred 16 h and diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to obtain the crude material which was purified on silica gel to yield the benzylic azides (**1**). (**Note:** Safety precaution should be taken seriously. DCM from the first step should be removed completely when preparing the benzylic azides using NaN_3. See: R. E. Conrow, W. D. Dean, *Org. Proc. Res. Dev*. **2008**, *12*, 1285-1286.)



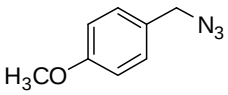
(Azidomethyl)benzene (***1a***): Yield 1.04 g (93%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 4.31 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 128.8, 128.24, 128.15, 54.7.



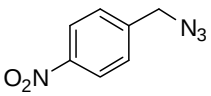
1-(Azidomethyl)-2-methylbenzene (***1b***): Yield 860 mg (84%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.17 (m, 4H), 4.29 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 133.3, 130.5, 129.2, 128.5, 126.1, 52.9, 18.8.



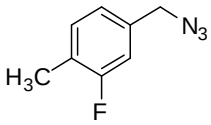
1-(Azidomethyl)-2,3-dimethylbenzene (***1c***): Yield 438 mg (75%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.09 (m, 3H), 4.33 (s, 2H), 2.30 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 135.4, 133.1, 130.3, 127.4, 125.6, 53.6, 20.4, 14.9.



1-(Azidomethyl)-4-methoxybenzene (***1d***): Yield 768 mg (85%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 2H, J = 8.4 Hz), 6.89 (d, 2H, J = 8.4 Hz), 4.24 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 129.6, 127.3, 114.0, 55.1, 54.2.

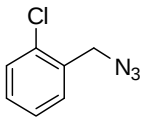


1-(Azidomethyl)-4-nitrobenzene (***1e***): Yield 500 mg (52%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.1 Hz), 4.52 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 142.7, 128.5, 123.9, 53.6.

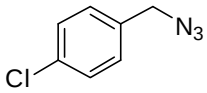


4-(Azidomethyl)-2-fluoro-1-methylbenzene (***1f***): Yield 770 mg (79%, colorless oil). IR (neat): ν_{max} 2930, 2093, 1583, 1512, 1258, 748 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, 1H, J = 7.8 Hz), 6.98 (s, 1H), 6.95 (d, 1H, J = 2.4 Hz), 4.27 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (d, J_{CF} = 244 Hz), 134.8 (d, J_{CF} = 7 Hz), 131.7 (d, J_{CF} = 5 Hz), 124.9 (d, J_{CF} = 17 Hz), 123.4 (d, J_{CF} = 3 Hz), 114.7 (d, J_{CF} = 23

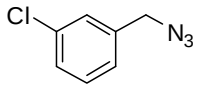
Hz), 53.9, 14.2 (d, J_{CF} = 3 Hz). HRMS (APCI) calcd for C_8H_9FN $(MH\text{-}N_2)^+$ 138.0719, found 138.0715.



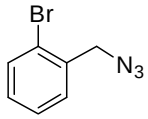
1-(Azidomethyl)-2-chlorobenzene ***(1g)***: Yield 1.32 g (73%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H), 7.30-7.27 (m, 2H), 4.48 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 133.2, 130.0, 129.7, 129.6, 127.1, 52.2.



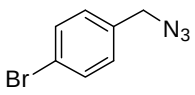
1-(Azidomethyl)-4-chlorobenzene ***(1h)***: Yield 949 mg (79%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.4 Hz), 4.30 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 133.8, 129.4, 128.9, 53.9.



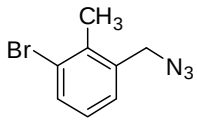
1-(Azidomethyl)-3-chlorobenzene ***(1i)***: Yield 1.07 g (83%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.30 (m, 3H), 7.20-7.17 (m, 1H), 4.31 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 134.6, 130.1, 128.4, 128.1, 126.1, 54.0.



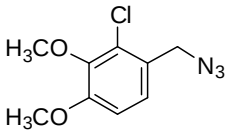
1-(Azidomethyl)-2-bromobenzene ***(1j)***: Yield 925 mg (99%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 1H, J = 8.1 Hz), 7.41-7.32 (m, 2H), 7.21 (t, 1H, J = 7.5 Hz), 4.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 133.0, 130.0, 129.8, 127.8, 123.7, 54.6.



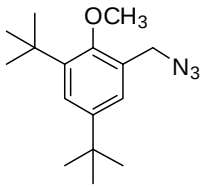
1-(Azidomethyl)-4-bromobenzene ***(1k)***: Yield 898 mg (91%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 2H, J = 8.1 Hz), 7.19 (d, 2H, J = 8.1 Hz), 4.30 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 131.9, 129.8, 122.3, 54.0.



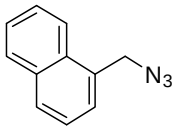
1-(Azidomethyl)-3-bromo-2-methylbenzene ***(1l)***: Yield 511 mg (97%, colorless oil). IR (neat): ν_{max} 2933, 2094, 1565, 1440, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 8.1 Hz), 7.21 (d, 1H, J = 7.5 Hz), 7.06 (t, 1H, J = 7.8 Hz), 4.37 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 135.3, 133.0, 128.5, 127.2, 126.4, 53.7, 18.9. HRMS (APCI) (Br-79) calcd for C_8H_9BrN $(MH\text{-}N_2)^+$ 197.9918, found 197.9916.



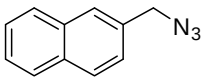
*1-(Azidomethyl)-2-chloro-3,4-dimethoxybenzene (**1m**)*: Yield 382 mg (85%, colorless oil). IR (neat): ν_{max} 2940, 2094, 1593, 1490, 1273, 1043 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, 1H, *J* = 8.4 Hz), 6.83 (d, 1H, *J* = 8.4 Hz), 4.41 (s, 2H), 3.87 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 145.7, 128.3, 126.0, 125.0, 110.2, 60.5, 55.9, 52.2. HRMS (APCI) (Cl-35) calcd for $C_9H_{11}ClNO_2$ $(MH\text{-}N_2)^+$ 200.0478, found 200.0479.



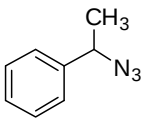
*1-(Azidomethyl)-3,5-di-tert-butyl-2-methoxybenzene (**1n**)*: Yield 632 mg (97%, white solid)); mp 41-42 °C; IR (neat): ν_{max} 2958, 2093, 1479, 1231, 1008, 861 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.18 (s, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 1.40 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 146.1, 142.3, 128.2, 125.6, 124.7, 62.5, 50.4, 35.3, 34.5, 31.4, 31.1. HRMS (APCI) calcd for $C_{16}H_{26}NO$ $(MH\text{-}N_2)^+$ 248.2014, found 248.2006.



*1-(Azidomethyl)naphthalene (**1o**)*: Yield 1.0 g (79%, colorless oil). ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, *J* = 8.1 Hz), 7.95-7.89 (m, 2H), 7.64 -7.55 (m, 2H), 7.50-7.46 (m, 2H), 4.80 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9, 131.3, 130.9, 129.4, 128.8, 127.3, 126.7, 126.1, 125.2, 123.5, 53.0.

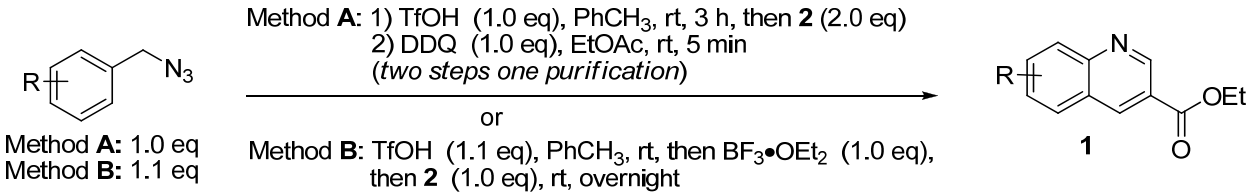


*2-(Azidomethyl)naphthalene (**1p**)*: Yield 879 mg (91%, white solid)); mp 37-38 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81-7.79 (m, 3H), 7.70 (s, 1H), 7.47 - 7.44 (m, 2H), 7.35 (d, 1H, *J* = 8.4 Hz), 4.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 133.0, 132.7, 128.6, 127.8, 127.7, 127.1, 126.4, 126.2, 125.7, 54.8.



*(1-Azidoethyl)benzene (**1q**)*: Yield 821 mg (63%, colorless oil). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 4.59 (q, 1H, *J* = 6.6 Hz), 1.51 (d, 3H, *J* = 6.6 Hz), ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 128.7, 128.0, 126.3, 61.0, 21.5.

3. General procedure for the synthesis of quinoline compounds (3)

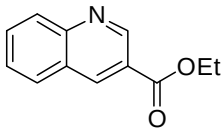


*General procedure for the representative synthesis of quinoline compounds (**3b**):*

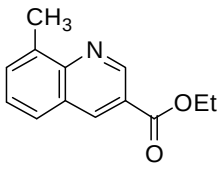
Method A: To a solution of benzylic azide **1b** (1.0 equiv, 89 mg, 0.60 mmol) in toluene (4.4 mL/mmol) was added TfOH (1.0 equiv, 58 μL, 0.60 mmol) at room temperature. The reaction mixture was stirred until the evolution of N_2 gas bubbles subsided and then ethyl 3-ethoxyacrylate (**2**) (2.0 equiv, 173 mg, 1.20 mmol) was added into the solution mixture. The reaction was stirred for 3 h and then added with sat. $NaHCO_3$ to dilute the reaction. The mixture was extracted with EtOAc (2×20 mL), and the combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was used in the next step without further purification. The crude product in EtOAc (4.4 mL/mmol) was then added with DDQ (1.0 equiv, 136 mg, 0.60 mmol) and stirred for 5 min. The solvent was removed under reduced pressure to obtain the crude material which was purified on silica gel using 10% EtOAc/hexane to yield 98 mg (76%) of quinoline product **3b** a white solid; mp 84-85 °C; IR (neat): ν_{max} 2993, 1726, 1600, 1492, 1276, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.79 (s, 1H), 7.76 (d, 1H, J = 8.1 Hz), 7.16 (d, 1H, J = 6.9 Hz), 7.49 (t, 1H, J = 7.8 Hz), 4.48 (q, 2H, J = 6.9 Hz), 2.83 (s, 3H), 1.46 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 148.9, 148.8, 138.8, 137.3, 131.9, 127.1, 127.0, 126.8, 122.9, 61.4, 18.1,14.2. HRMS (APCI) calcd for $C_{13}H_{14}NO_2$ $(M+H)^+$ 216.1019, found 216.1011.

Method B: To a solution of benzylic azide **1b** (1.1 equiv, 63 mg, 0.39 mmol) in toluene (4.6 mL/mmol) was added TfOH (1.10 equiv, 34 μL, 0.39 mmol) at room temperature. The reaction

mixture was stirred until the evolution of N_2 gas bubbles subsided. $BF_3 \bullet OEt_2$ (1.0 equiv, 89 μL, 0.35 mmol) was then added into a solution mixture followed by addition of ethyl 3-ethoxyacrylate (**2**) (1.0 equiv, 51 mg, 0.35 mmol). The reaction was stirred overnight and then added with sat. $NaHCO_3$ to dilute the reaction. The mixture was extracted with EtOAc (2×20 mL), and the combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was used in the next step, without further purification. The crude product in EtOAc (4.4 mL/mmol) was then added with DDQ (1.0 equiv, 80 mg, 0.35 mmol) and stirred for 5 min. The solvent was removed under reduced pressure to obtain the crude material which was purified on silica gel to yield the quinoline product **3**. (Note: DDQ was not required in entry 11 as the dihydroquinoline intermediate was completely oxidized to the desired quinoline product during overnight stirring.)

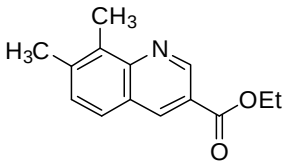


*Ethyl quinoline-3-carboxylate (**3a**)*: Yield 82 mg (79%, pale yellow solid); mp 57-58 °C; IR (neat): ν_{max} 2982, 1719, 1621, 1498, 1287, 1100, 790 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.85 (s, 1H), 8.17 (d, 1H, J = 8.4 Hz), 7.95 (d, 1H, J = 8.4 Hz), 7.84 (t, 1H, J = 7.2 Hz), 7.63 (t, 1H, J = 7.2 Hz), 4.49 (q, 2H, J = 7.2 Hz), 1.47 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 150.0, 149.8, 138.6, 131.8, 129.4, 129.1, 127.4, 126.8, 123.2, 61.5,14.3. HRMS (APCI) calcd for $C_{12}H_{12}NO_2$ $(M+H)^+$ 202.0863, found 202.0860.

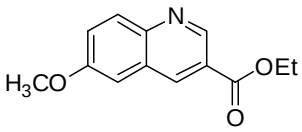


*Ethyl 8-methylquinoline-3-carboxylate (**3b**)*: Yield 98 mg (76%, white solid), mp 84-85 °C; IR (neat): ν_{max} 2993, 1726, 1600, 1492, 1276, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.79 (s, 1H), 7.76 (d, 1H, J = 8.1 Hz), 7.65 (d, 1H, J = 6.9 Hz), 7.49 (t, 1H, J = 7.8 Hz), 4.48 (q, 2H, J = 6.9 Hz), 2.83 (s, 3H), 1.46 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 148.9, 148.8, 138.8, 137.3, 131.9,

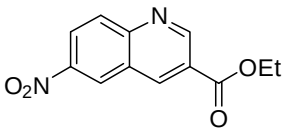
127.1, 127.0, 126.8, 122.9, 61.4, 18.1,14.2. HRMS (APCI) calcd for $C_{13}H_{14}NO_2$ $(M+H)^+$ 216.1019, found 216.1011.



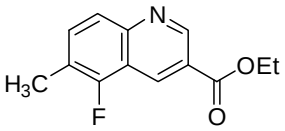
*Ethyl 7,8-dimethylquinoline-3-carboxylate (**3c**)*: Yield 76 mg (83%, white solid), mp 78-79 °C; IR (neat): ν_{max} 2921, 2852, 1725, 1614, 1464, 1269, 792 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.72 (s, 1H), 7.64 (d, 1H, *J* = 8.4 Hz), 7.40 (d, 1H, *J* = 8.1 Hz), 4.46 (q, 2H, *J* =6.9 Hz), 2.76 (s, 3H), 2.52 (s, 3H), 1.45 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 148.74, 148.68, 140.0, 138.6, 134.6, 130.2, 126.0, 125.0, 121.9, 61.2, 20.9, 14.3,13.3. HRMS (APCI) calcd for $C_{14}H_{16}NO_2$ $(M+H)^+$ 230.1176, found 230.1172.



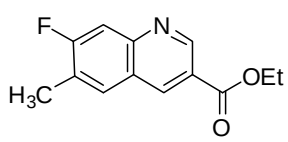
*Ethyl 6-methoxyquinoline-3-carboxylate (**3d**)*: Yield 34 mg (24%, pale yellow solid), mp 70-71 °C; IR (neat): ν_{max} 2981, 1717, 1601, 1279, 1243, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.74 (s, 1H), 8.06 (d, 1H, *J* = 9.0 Hz), 7.47 (dd, 1H, *J* = 9.0, 2.4 Hz), 7.17 (d, 1H, *J* = 1.5 Hz), 4.48 (q, 2H, *J* = 7.2 Hz), 3.96 (s, 3H), 1.46 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 158.3, 147.7, 146.1, 137.3, 130.8, 128.2, 124.7, 123.6, 106.0, 61.4,55.6, 14.3. HRMS (APCI) calcd for $C_{13}H_{14}NO_3$ $(M+H)^+$ 232.0968, found 232.0962.



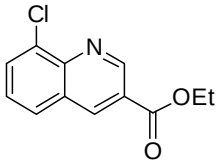
*Ethyl 6-nitroquinoline-3-carboxylate (**3e**)*: Yield 12 mg (14%, white solid), mp 186-187 °C; IR (neat): ν_{max} 2920, 1710, 1624, 1523, 1286, 849 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 9.03 (s, 1H), 8.92 (s, 1H), 8.59 (d, 1H, *J* = 9.3 Hz), 8.32 (d, 1H, *J* = 9.3 Hz), 4.53 (q, 2H, *J* = 6.9 Hz), 1.49 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 153.4, 151.6, 146.1, 140.1, 131.5, 125.9, 125.6, 125.1, 124.9, 62.1, 14.3. HRMS (APCI) calcd for $C_{12}H_{11}N_2O_4$ $(M+H)^+$ 247.0713, found 247.0715.



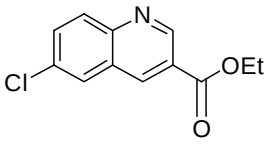
*Ethyl 5-fluoro-6-methylquinoline-3-carboxylate (**3f**)*: Yield 8 mg (10%, white solid), mp 55-56 °C; IR (neat): ν_{max} 2927, 1720, 1640, 1464, 1265, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 9.06 (s, 1H), 7.88 (d, 1H, J = 8.7 Hz), 7.74 (t, 1H, J = 8.4 Hz), 4.49 (q, 2H, J = 7.2 Hz), 2.48 (s, 3H), 1.47 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 155.6 (d, J_{CF} = 21Hz), 150.0, 148.8, 134.8 (d, J_{CF} = 6 Hz), 131.6 (d, J_{CF} = 5 Hz), 124.7 (d, J_{CF} = 4 Hz), 123.3 (d, J_{CF} = 3 Hz), 120.8 (d, J_{CF} = 16 Hz), 117.7 (d, J_{CF} = 17 Hz), 61.6, 14.3 (2xCH_3). HRMS (APCI) calcd for $C_{13}H_{13}FNO_2$ $(M+H)^+$ 234.0925, found 234.0921.



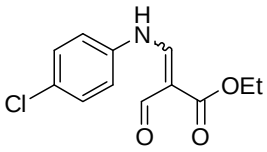
*Ethyl 7-fluoro-6-methylquinoline-3-carboxylate (**3f'**)*: Yield 25 mg (28%, white solid), mp 100-101 °C; IR (neat): ν_{max}2929, 1712, 1266, 1113, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.75 (s, 1H), 7.76 (s, 1H), 7.74 (d, 1H, J = 9.6 Hz), 4.48 (q, 2H, J = 7.2 Hz), 2.49 (s, 3H), 1.46 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 163.8 (d, J_{CF} = 253 Hz), 150.1, 137.7, 130.5 (d, J_{CF} = 6.8 Hz), 128.2 (d, J_{CF} = 21Hz), 124.0, 122.74, 122.72, 112.7 (d, J_{CF} = 22 Hz), 61.5, 15.2 (d, J_{CF} = 3.6 Hz), 14.3. HRMS (APCI) calcd for $C_{13}H_{13}FNO_2$ $(M+H)^+$ 234.0925, found 234.0922.



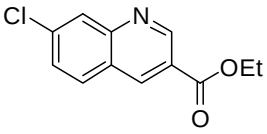
*Ethyl 8-chloroquinoline-3-carboxylate (**3g**)*: Yield 57 mg (54%, white solid), mp 95-96 °C; IR (neat): ν_{max} 2900, 1720, 1615, 1484, 1267, 781 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.86 (s, 1H), 7.96 (d, 1H, J = 7.5 Hz), 7.88 (d, 1H, J = 8.1 Hz), 7.56 (t, 1H, J = 8.1 Hz), 4.50 (q, 2H, J = 6.9 Hz), 1.47 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 150.5, 145.8, 138.9, 133.6, 131.7, 128.15, 128.11, 127.3, 124.1, 61.7,14.2. HRMS (APCI) (Cl-35) calcd for $C_{12}H_{11}ClNO_2$ $(M+H)^+$ 236.0473, found 236.0474.



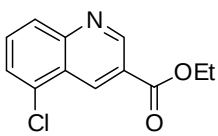
*Ethyl 6-chloroquinoline-3-carboxylate (**3h**)*: Yield 29 mg (36%, white solid), mp 107-108 °C; IR (neat): ν_{max} 2983, 1716, 1601, 1479, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.76 (s, 1H), 8.11 (d, 1H, *J* = 8.7 Hz), 7.92 (s, 1H), 7.76 (d, 1H, *J* = 9.0 Hz), 4.49 (q, 2H, *J* = 7.2 Hz), 1.47 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 150.2, 148.1, 137.6, 133.2, 132.6, 131.1, 127.52, 127.49, 124.1, 61.7, 14.3. HRMS (APCI) (Cl-35) calcd for $C_{12}H_{11}ClNO_2$ $(M+H)^+$ 236.0473, found 236.0472.



*Ethyl 3-(4-chlorophenylamino)-2-formylacrylate (**16**) (R=Cl)*: ^1H NMR (300 MHz, $CDCl_3$) δ 12.45 (br d, 1H, *J* = 12.3 Hz), 9.95 (d, 1H, *J* = 3.0 Hz), 8.35 (dd, 1H, *J* = 13.2, 3.0 Hz), 7.37 (d, 2H, *J* = 8.7 Hz), 7.16 (d, 2H, *J* = 8.4 Hz), 4.31 (q, 2H, *J* = 7.2 Hz), 1.35 (t, 3H, *J* = 7.2 Hz). HRMS (APCI) (Cl-35) calcd for $C_{12}H_{13}ClNO_3$ $(M+H)^+$ 254.0579, found 254.0574.

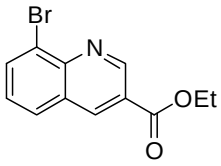


*Ethyl 7-chloroquinoline-3-carboxylate (**3i**)*: Yield 18 mg (14%, white solid), mp 85-86 °C; IR (neat): ν_{max} 2986, 1717, 1619, 1474, 1281, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.81 (s, 1H), 8.15 (s, 1H), 7.87 (d, 1H, *J* = 8.7 Hz), 7.57 (d, 1H, *J* = 8.7 Hz), 4.49 (q, 2H, *J* = 7.2 Hz), 1.47 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 151.0, 150.0, 138.3, 137.8, 130.2, 128.6, 128.5, 125.2, 123.4, 61.7, 14.2. HRMS (APCI) (Cl-35) calcd for $C_{12}H_{11}ClNO_2$ $(M+H)^+$ 236.0473, found 236.0471.

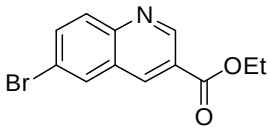


*Ethyl 5-chloroquinoline-3-carboxylate (**3i'**):* Yield 14 mg (17%, white solid), mp 97-98 °C; IR (neat): ν_{max} 2927, 1723, 1614, 1456, 1271, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 9.24 (s, 1H), 8.10 (d, 1H, *J* = 8.4 Hz), 7.78-7.69 (m, 2H), 4.51 (q, 2H, *J* = 7.2 Hz), 1.48 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0,

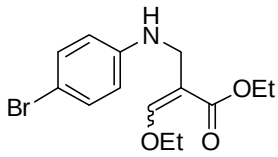
150.7, 150.4, 135.5, 132.7, 131.4, 128.6, 127.5, 125.3, 124.1, 61.8, 14.3. HRMS (APCI) (Cl-35) calcd for $C_{12}H_{11}ClNO_2$ $(M+H)^+$ 236.0473, found 236.0477.



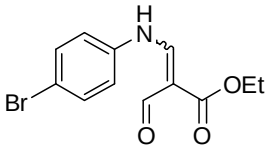
Ethyl 8-bromoquinoline-3-carboxylateb ***(3j)***: Yield 59 mg (70%, white solid), mp 100-101 °C; IR (neat): ν_{max} 2918, 1720, 1614, 1479, 1263, 777cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.84 (s, 1H), 8.17 (d, 1H, *J* = 7.5 Hz), 7.92 (d, 1H, *J* = 8.1 Hz), 7.49(t, 1H, *J* = 7.8 Hz), 4.50 (q, 2H, *J* = 7.2 Hz), 1.47 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 150.8, 146.7, 139.0, 135.3, 128.9, 128.2, 127.8, 124.8, 124.1, 61.7,14.3. HRMS (APCI) (Br-79) calcd for $C_{12}H_{11}BrNO_2$ $(M+H)^+$279.9968, found 279.9961.



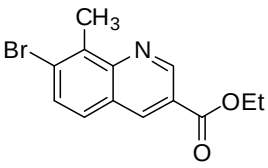
Ethyl 6-bromoquinoline-3-carboxylate ***(3k)***: Yield 42 mg (53%, white solid), mp 109-110 °C; IR (neat): ν_{max} 2923, 1717, 1600, 1445 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.74 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, *J* = 9.0 Hz), 7.88 (d, 1H, *J* = 8.7 Hz), 4.49 (q, 2H, *J* = 7.2 Hz), 1.47 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 150.4, 148.3, 137.5, 135.1, 131.1, 130.9, 128.0, 124.0, 121.3, 61.7, 14.3. HRMS (APCI) (Br-79) calcd for $C_{12}H_{11}BrNO_2$ $(M+H)^+$ 279.9968, found 279.9971.



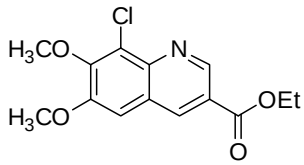
Ethyl 2-((4-bromophenylamino)methyl)-3-ethoxyacrylate ***(15)*** *(R=Br)*: light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.21 (d, 2H, *J* = 8.4 Hz), 6.55 (d, 2H, *J* = 8.7 Hz), 4.3 (br s, 1H), 4.16 (q, 2H, *J* = 7.2 Hz), 4.16 (q, 2H, *J* = 7.2 Hz), 4.10 (q, 2H, *J* = 7.2 Hz), 3.95 (s, 2H), 1.37 (t, 3H, *J* = 6.9 Hz), 1.26 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 159.1, 147.0, 131.6, 115.2, 108.9, 107.9, 70.6, 60.0, 37.5, 15.4, 14.4. HRMS (APCI) (Br-79) calcd for $C_{14}H_{19}BrNO_3$ $(M+H)^+$ 328.0543, found 328.0541.



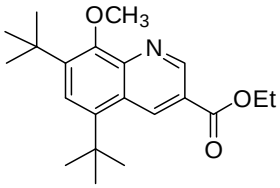
Ethyl 3-(4-bromophenylamino)-2-formylacrylate ***(16)*** *(R=Br)*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.44 (br d, 1H, *J* = 11.1 Hz), 9.95 (d, 1H, *J* = 3.6 Hz), 8.36 (dd, 1H, *J* = 13.2, 3.6 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 7.10 (d, 2H, *J* = 8.7 Hz), 4.30 (q, 2H, *J* = 7.2 Hz), 1.34 (t, 3H, *J* = 7.2 Hz).



Ethyl 7-bromo-8-methylquinoline-3-carboxylate ***(3l)***: Yield 94 mg (77%, white solid), mp 107-108 °C; IR (neat): ν_{max} 2987, 1729, 1612, 1479, 1261, 785 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.73 (s, 1H), 7.72 (d, 1H, *J* = 8.7 Hz), 7.60 (d, 1H, *J* = 8.7 Hz), 4.48 (q, 2H, *J* = 7.2 Hz), 2.92 (s, 3H), 1.46 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 149.6, 149.0, 138.7, 137.5, 131.6, 128.4, 127.3, 125.7, 123.0, 61.5, 17.6, 14.3. HRMS (APCI) (Br-79) calcd for $C_{13}H_{13}BrNO_2$ $(M+H)^+$ 294.0124, found 294.0119.

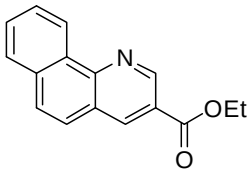


Ethyl 8-chloro-6,7-dimethoxyquinoline-3-carboxylate ***(3m)***: Yield 40 mg (53%, white solid), mp 112-113 °C; IR (neat): ν_{max} 2987, 1717, 1605, 1478, 1264, 1002 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.72 (s, 1H), 7.15 (s, 1H), 4.48 (q, 2H, *J* = 6.9 Hz), 4.06 (s, 3H), 4.04 (s, 3H), 1.46 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 153.6, 151.0, 148.4, 142.9, 137.2, 126.2, 125.0, 123.4, 105.5, 61.5, 61.1, 56.2, 14.3. HRMS (APCI) (Cl-35) calcd for $C_{14}H_{15}ClNO_4$ $(M+H)^+$ 296.0684, found 296.0679.

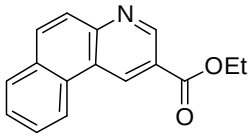


Ethyl 5,7-di-tert-butyl-8-methoxyquinoline-3-carboxylate ***(3n)***: Yield 70 mg (70%, pale yellow solid), mp 101-102 °C; IR (neat): ν_{max} 2961, 1723, 1605, 1466, 1238, 1092 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 9.40 (s, 1H), 7.64 (s, 1H), 4.49 (q, 2H, *J* = 7.2 Hz), 4.16 (s, 3H), 1.62 (s, 9H), 1.52 (s, 9H), 1.47 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 153.2, 147.0, 146.0, 142.5, 141.7,

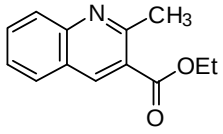
137.2, 124.9, 124.1, 120.7, 62.4, 61.3, 36.2, 35.8, 32.2, 30.5, 14.3. HRMS (APCI) calcd for $C_{21}H_{30}NO_3$ $(M+H)^+$ 344.2220, found 344.2211.



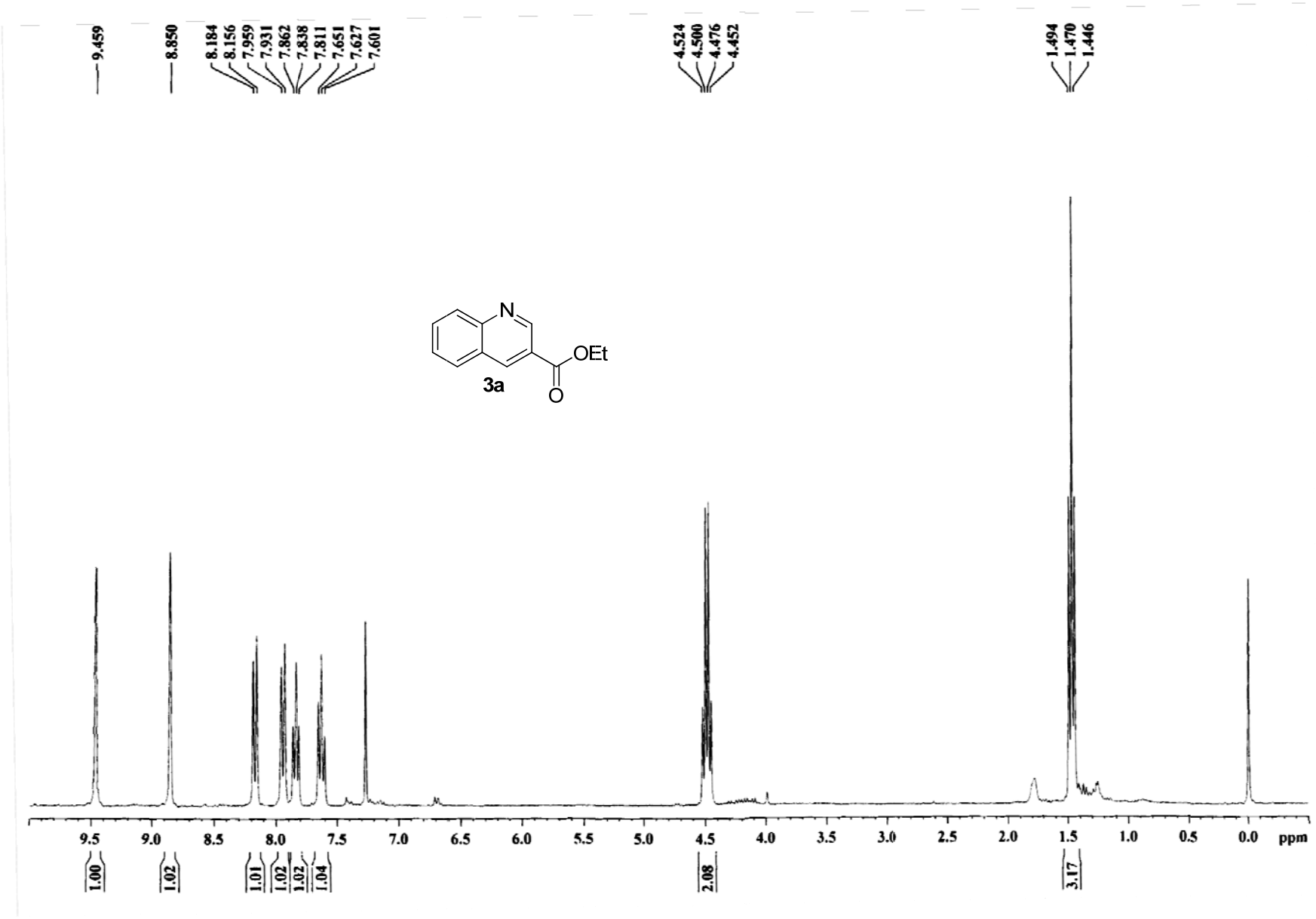
*Ethyl benzo[h]quinoline-3-carboxylate (**3o**)*: Yield 32 mg (56%, white solid), mp 101-102 °C; IR (neat): ν_{max} 2983, 1716, 1598, 1314, 1260, 1212, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 9.34-9.31 (m, 1H), 8.81 (s, 1H), 7.95-7.86 (m, 2H), 7.78-7.75 (m, 3H), 4.50 (q, 2H, *J* = 7.2 Hz), 1.48 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 149.0, 148.9, 137.7, 134.5, 131.0, 129.2, 128.6, 127.9, 127.4, 125.5, 125.2, 125.1, 123.9, 61.4, 14.3. HRMS (APCI) calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1019, found 252.1020.

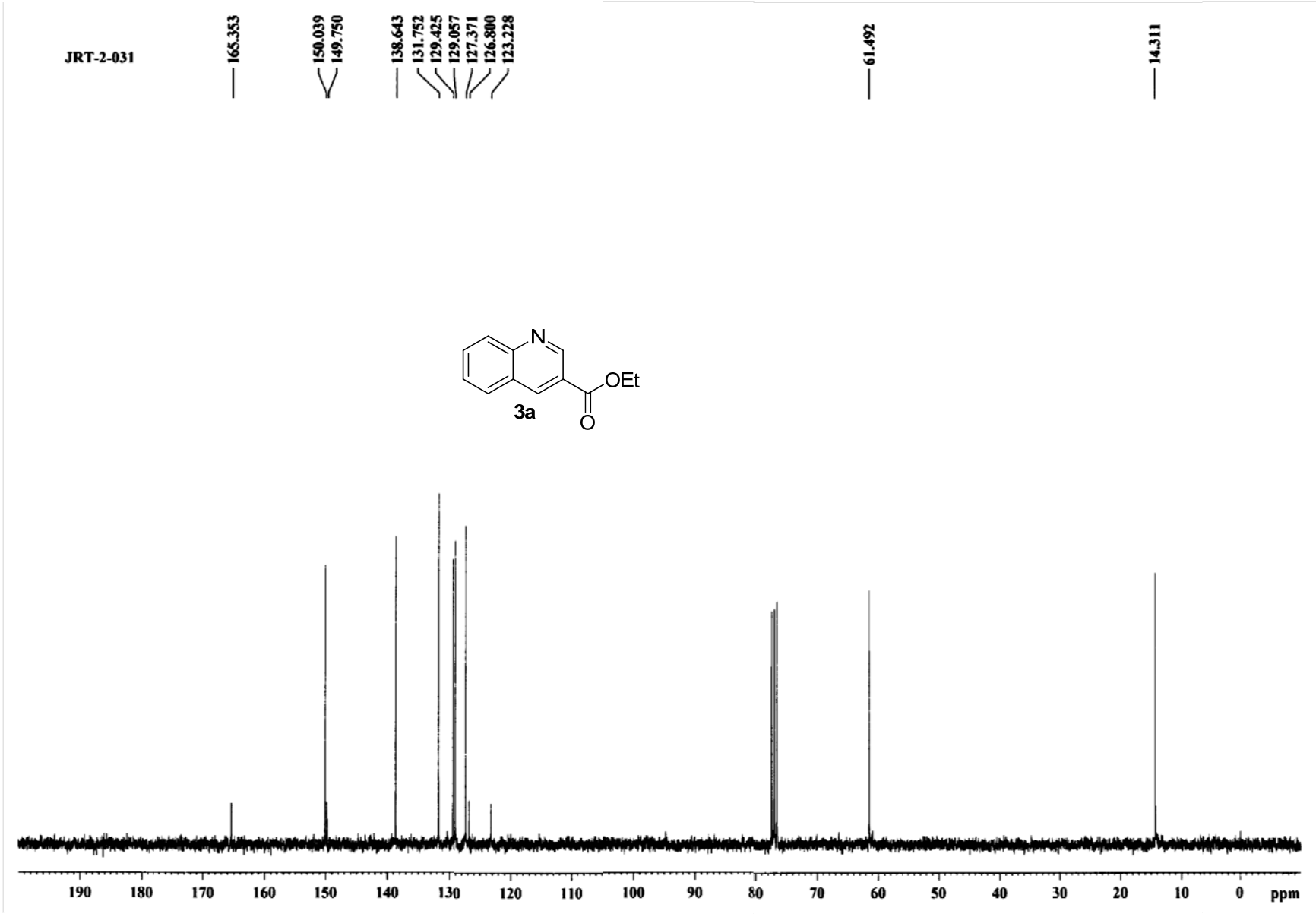


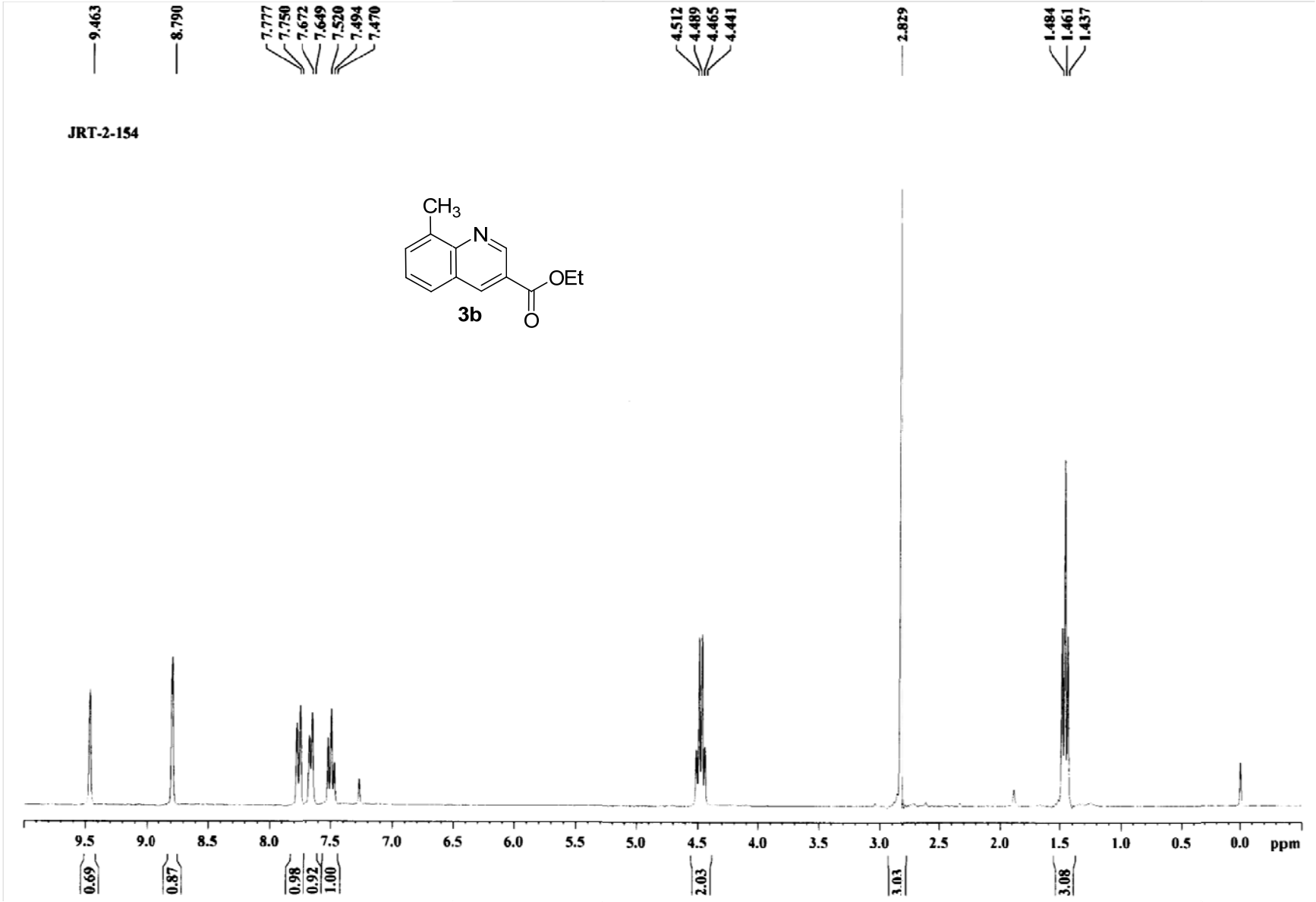
*Ethyl benzo[f]quinoline-2-carboxylate (**3p**)*: Yield 49 mg (64%, white solid), mp 106-107 °C; IR (neat): ν_{max} 2922, 1717, 1604, 1465, 1278, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 9.49 (s, 1H), 8.69 (d, 1H, *J* = 7.8 Hz), 8.06 (d, 1H, *J* = 9.0 Hz), 8.00 (d, 1H, *J* = 9.3 Hz), 7.94 (d, 1H, *J* = 7.5 Hz), 7.77-7.66 (m, 2H), 4.52 (q, 2H, *J* = 6.9 Hz), 1.50 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 150.3, 149.7, 133.3, 132.7, 131.7, 129.7, 128.8, 127.8, 127.70, 127.66, 124.4, 123.3, 122.8, 61.6, 14.4. HRMS (APCI) calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1019, found 252.1013.

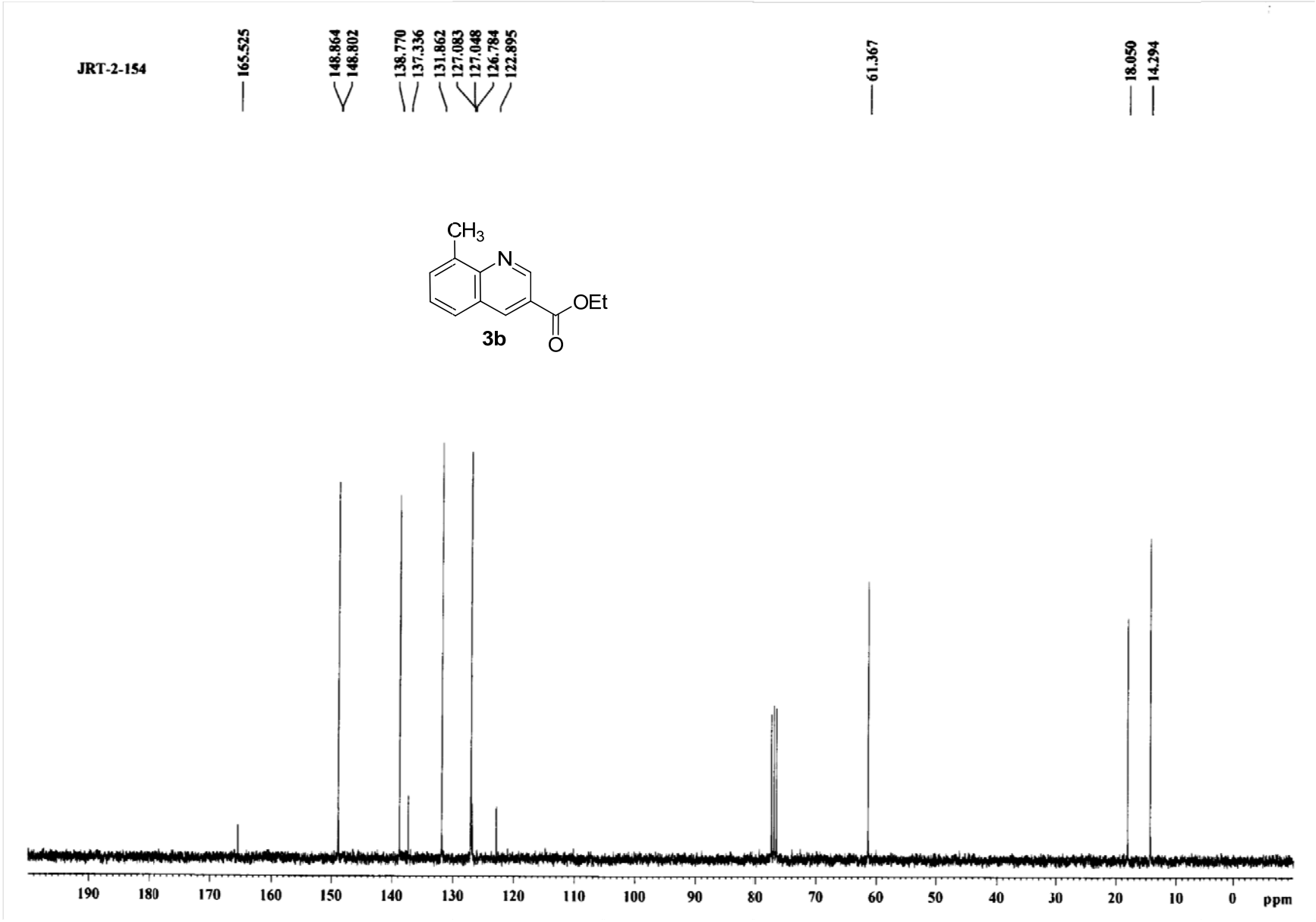


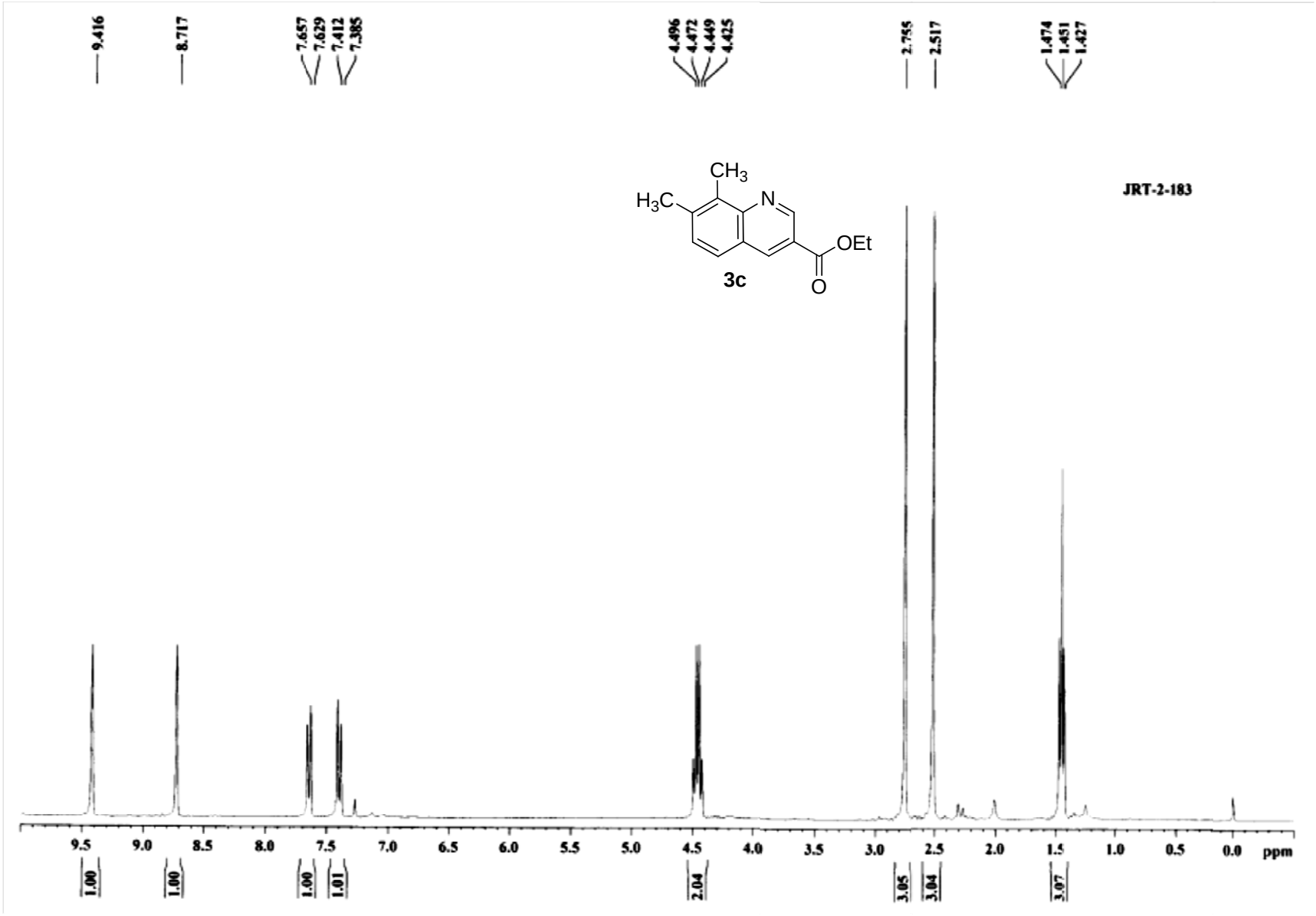
*Ethyl 2-methylquinoline-3-carboxylate (**3q**)*: ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.06 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 7.8 Hz), 7.80 (t, 1H, *J* = 8.1 Hz), 7.56 (t, 1H, *J* = 7.5 Hz), 4.46 (q, 2H, *J* = 7.2 Hz), 3.01 (s, 3H), 1.48 (t, 3H, *J* = 7.2 Hz).); (Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menendez, J. C. *J. Org. Chem.*, **2009**, *74*, 5715–5718.)

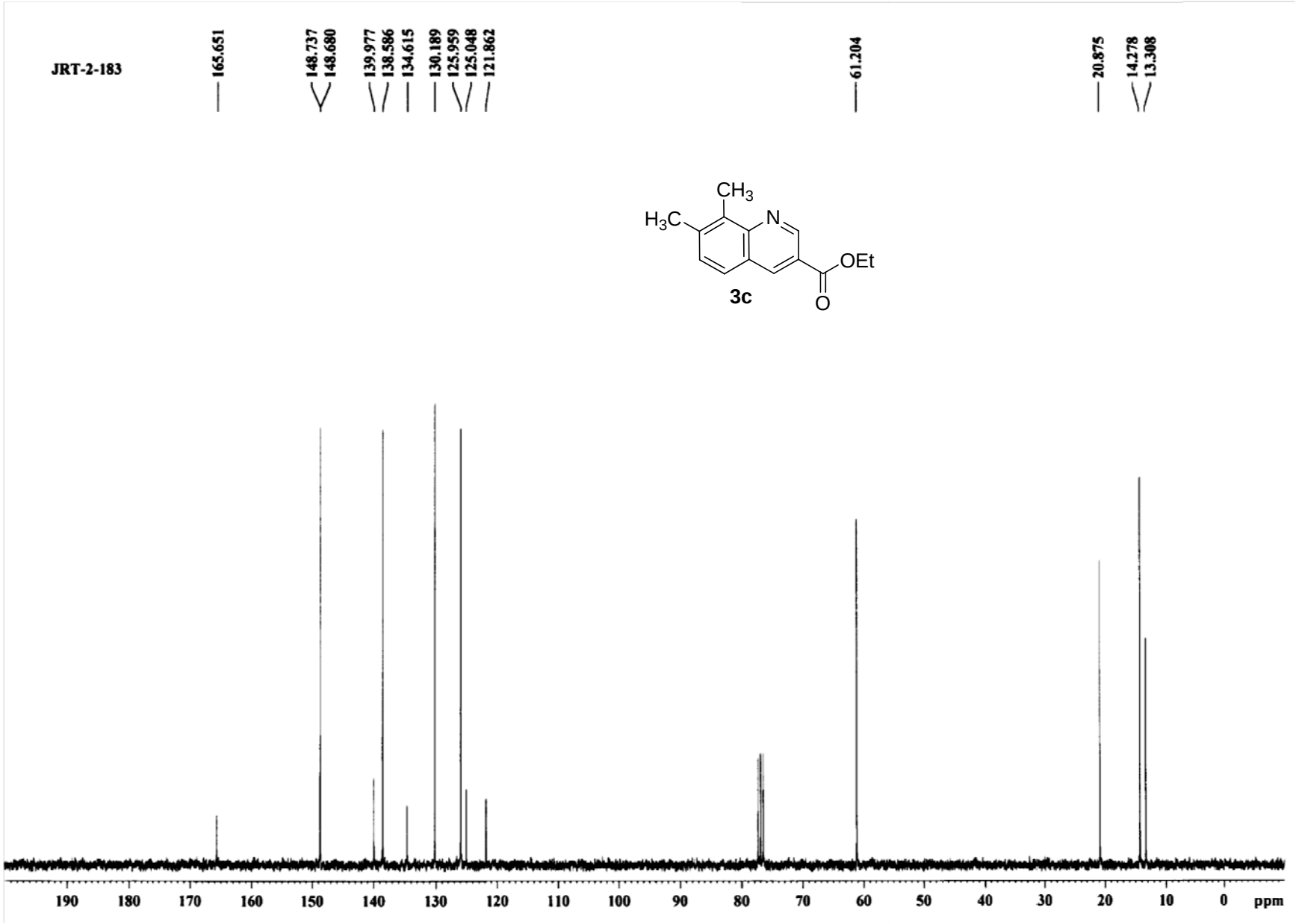


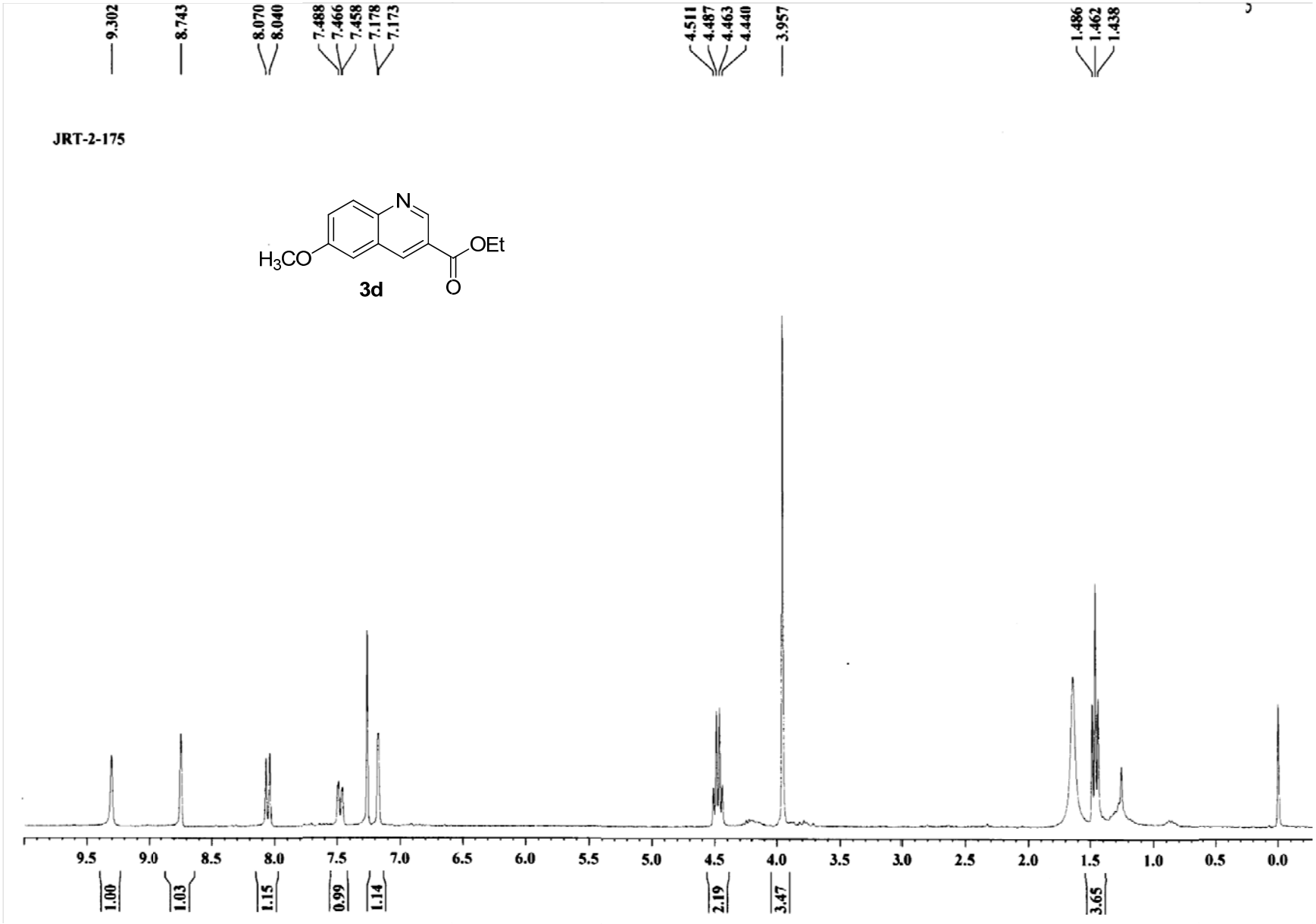


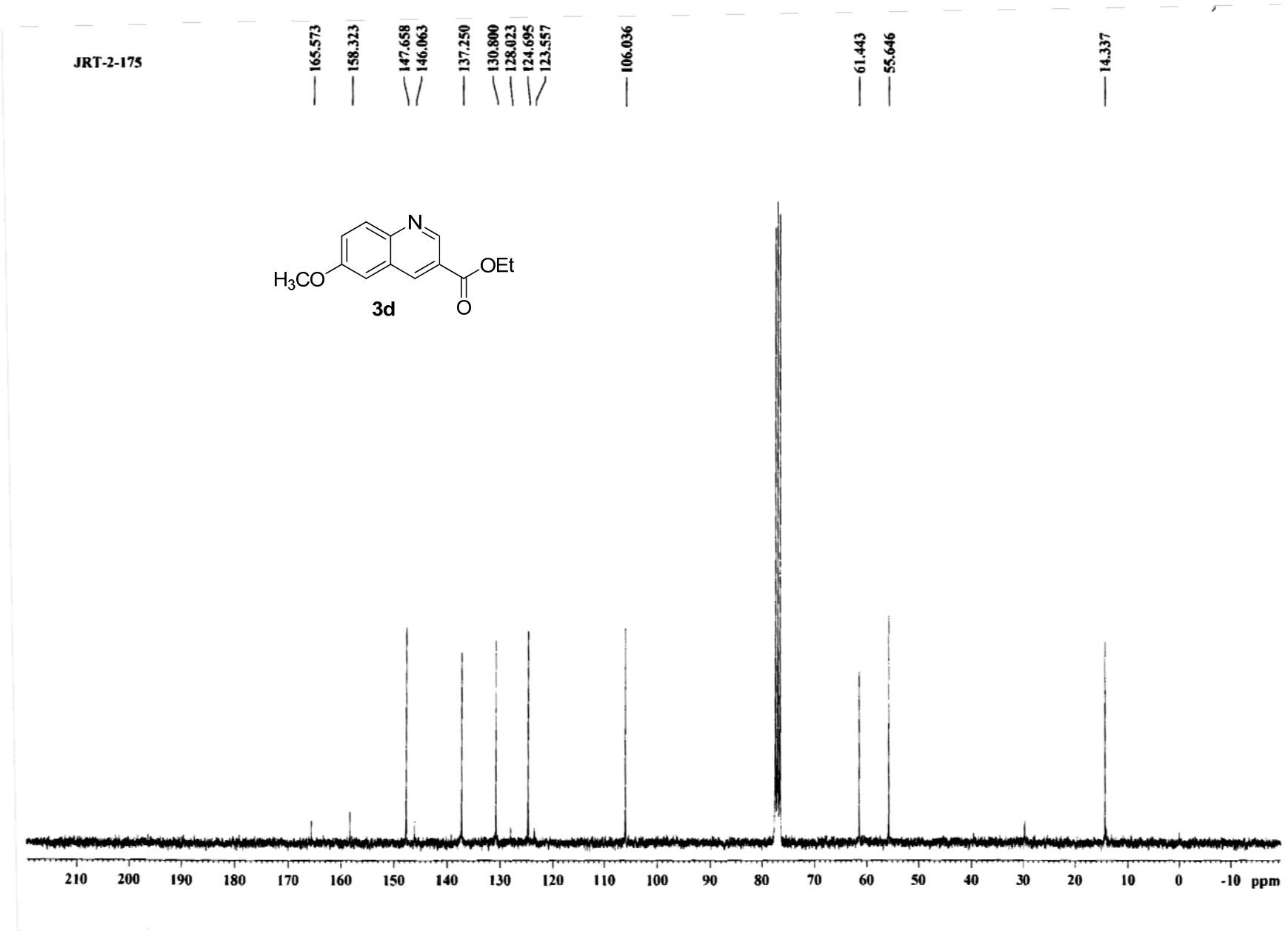


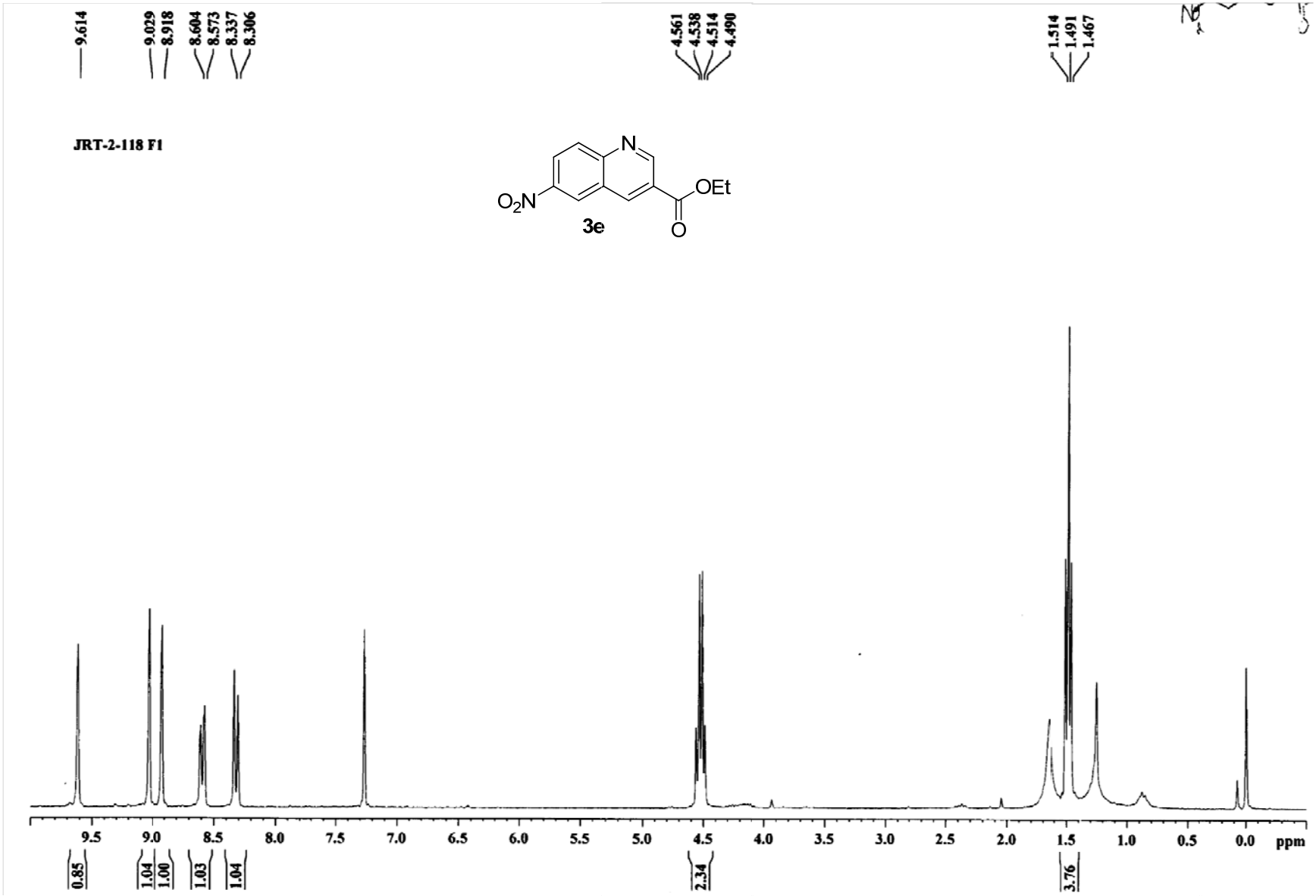


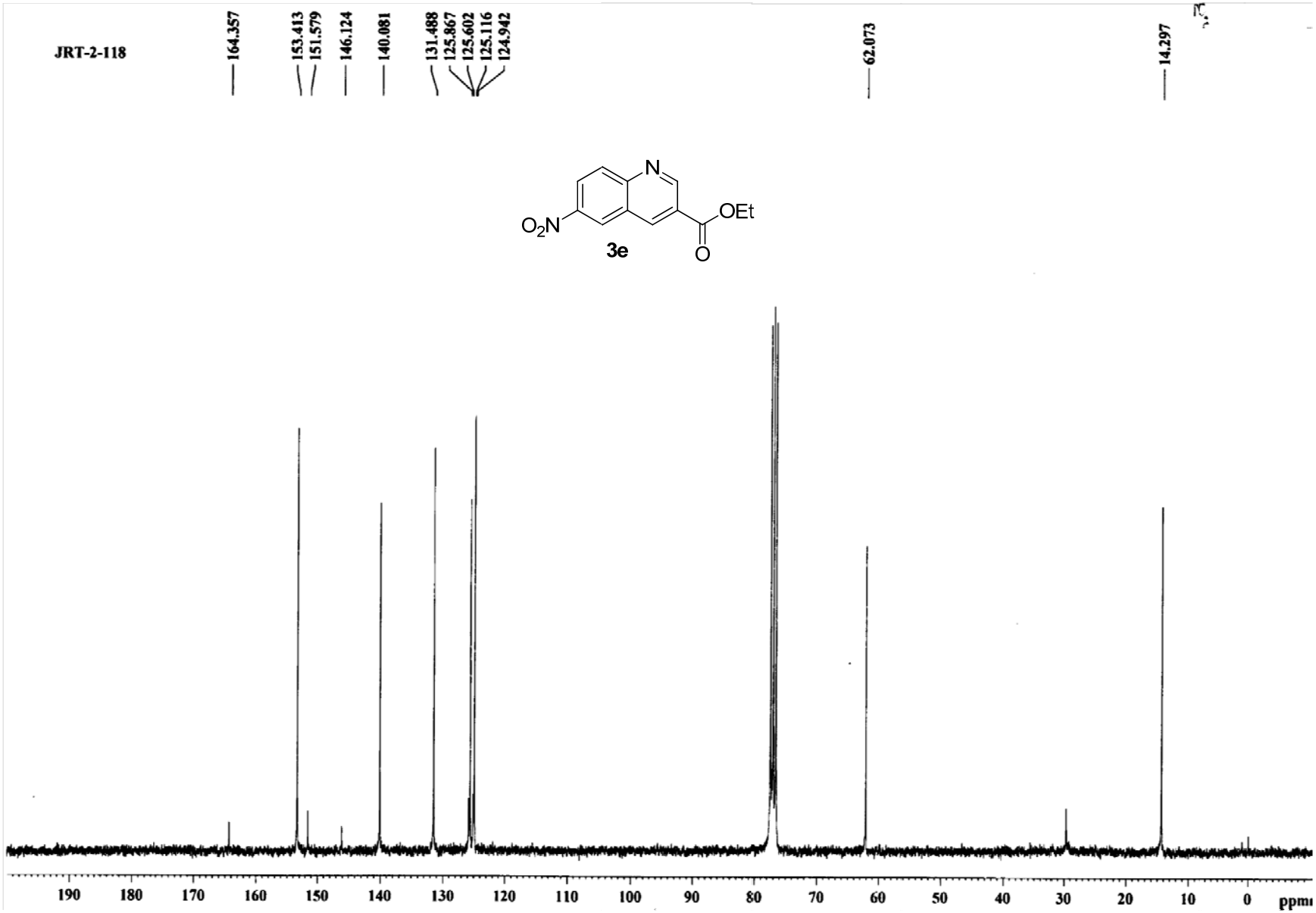


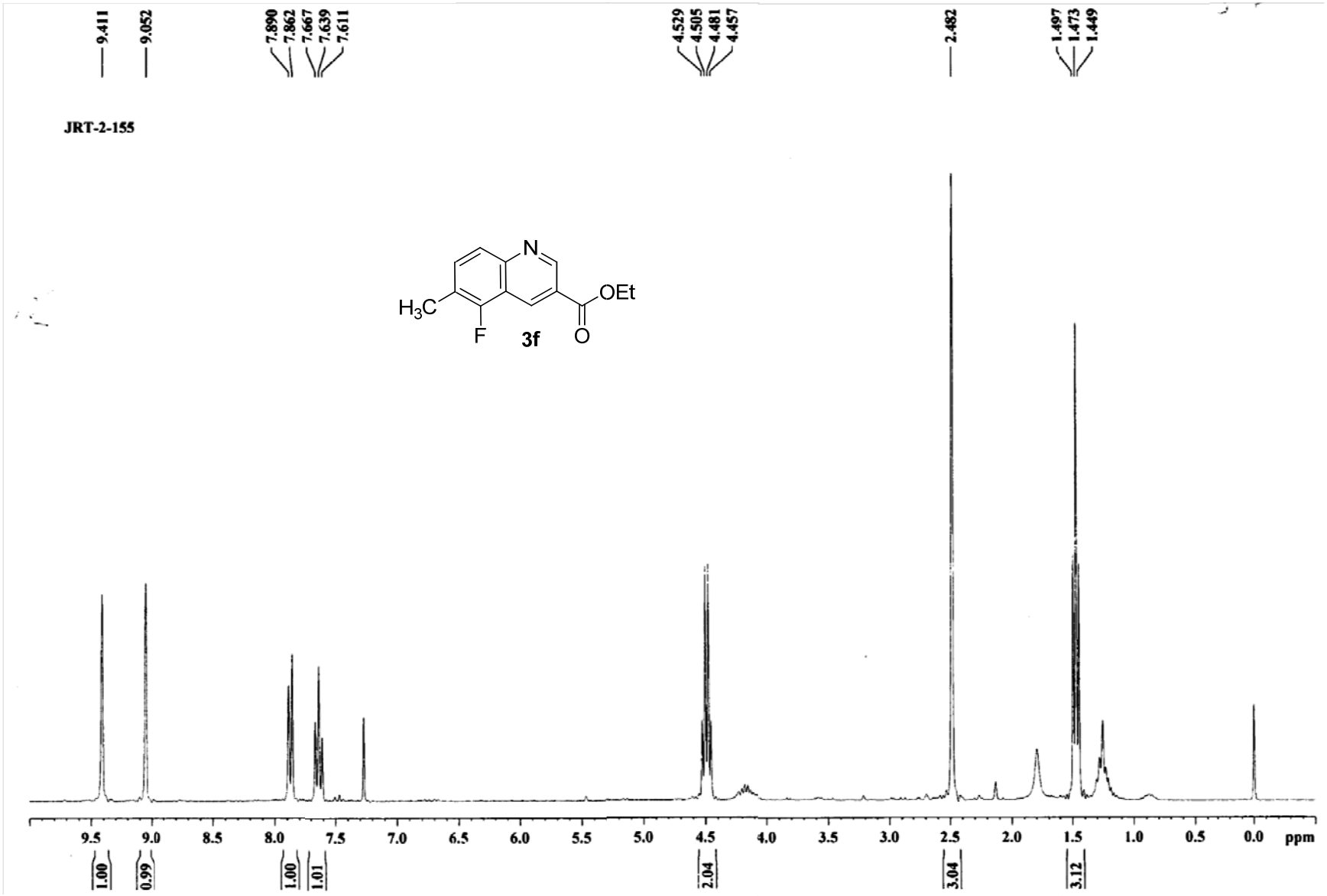


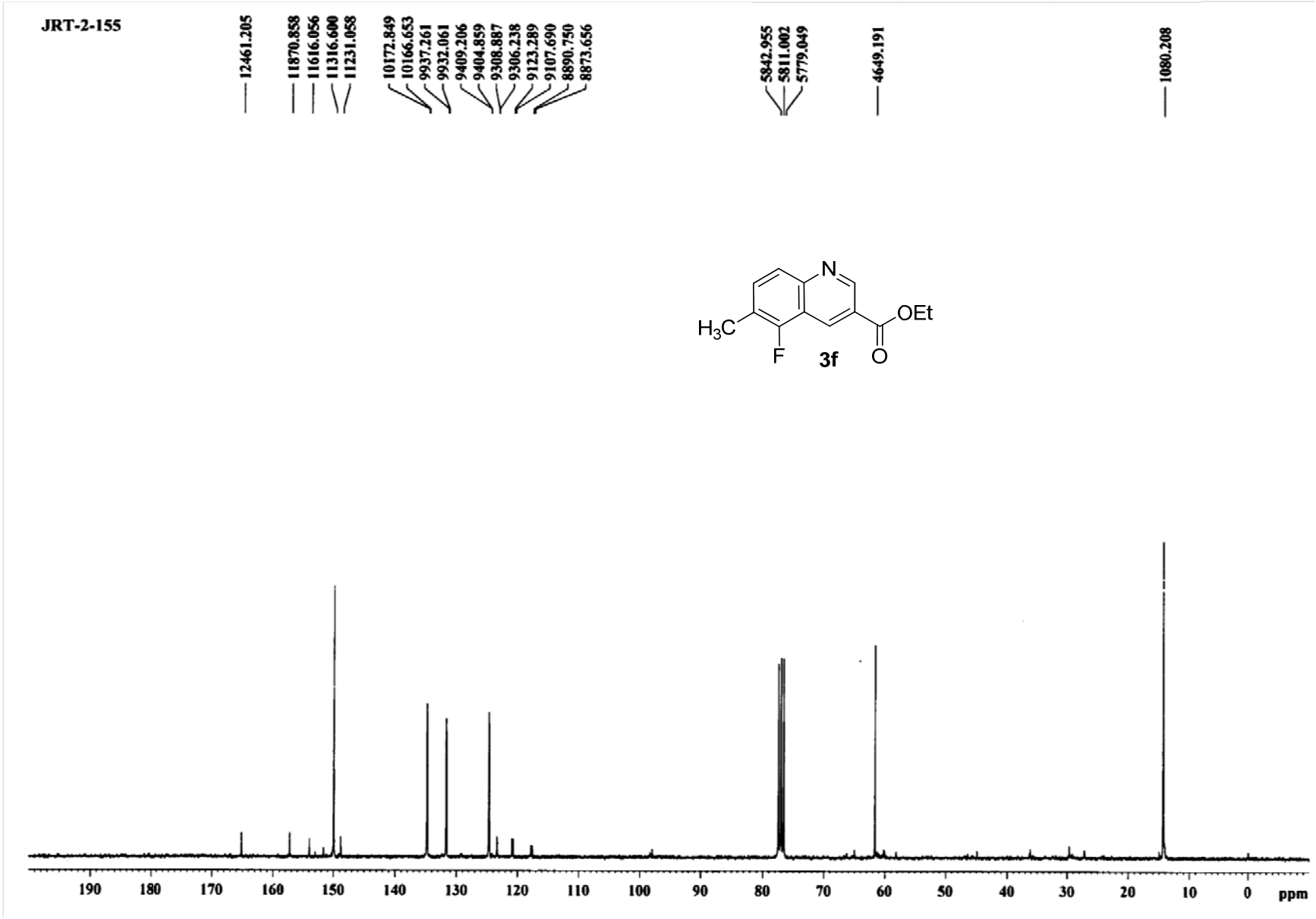


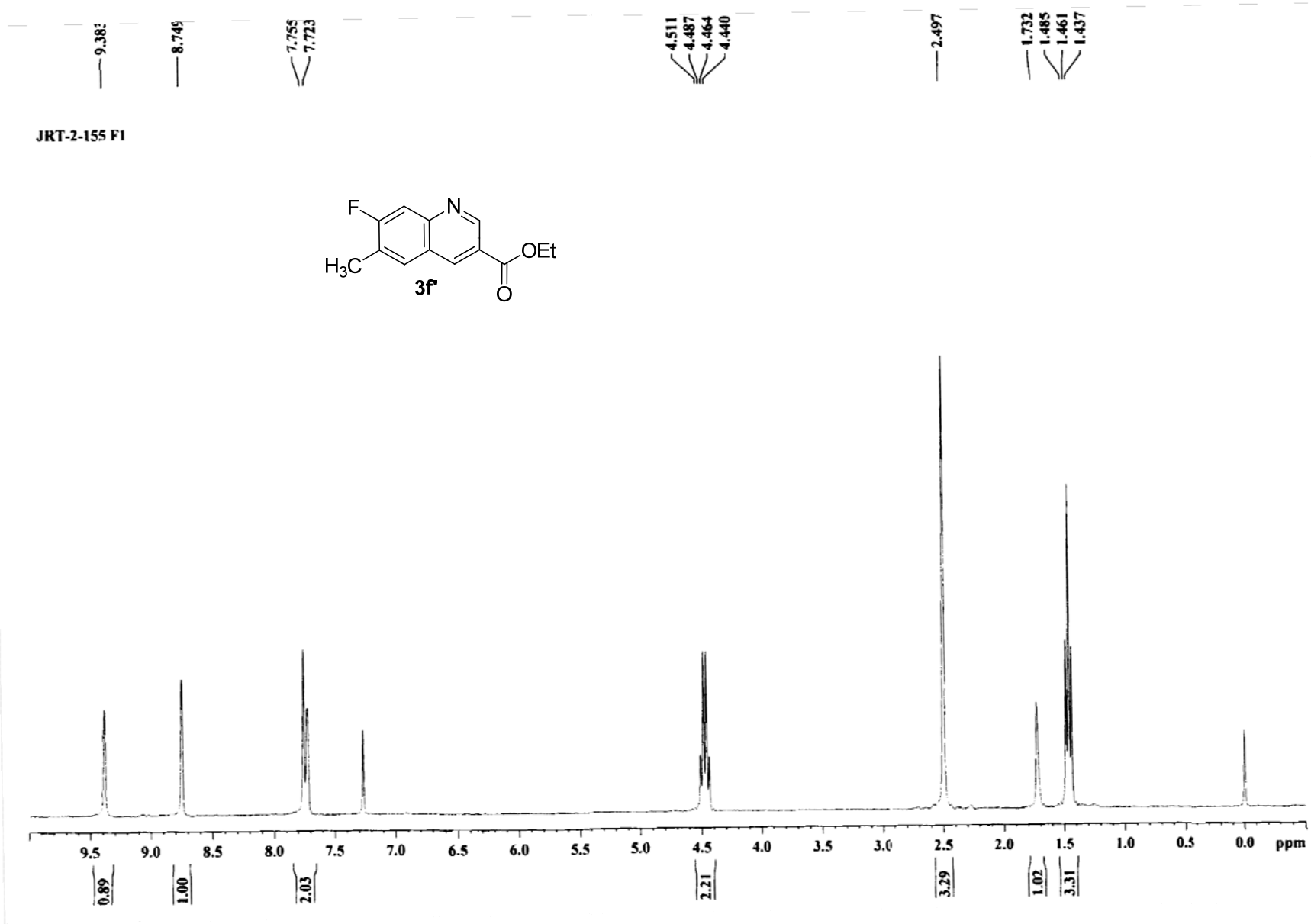


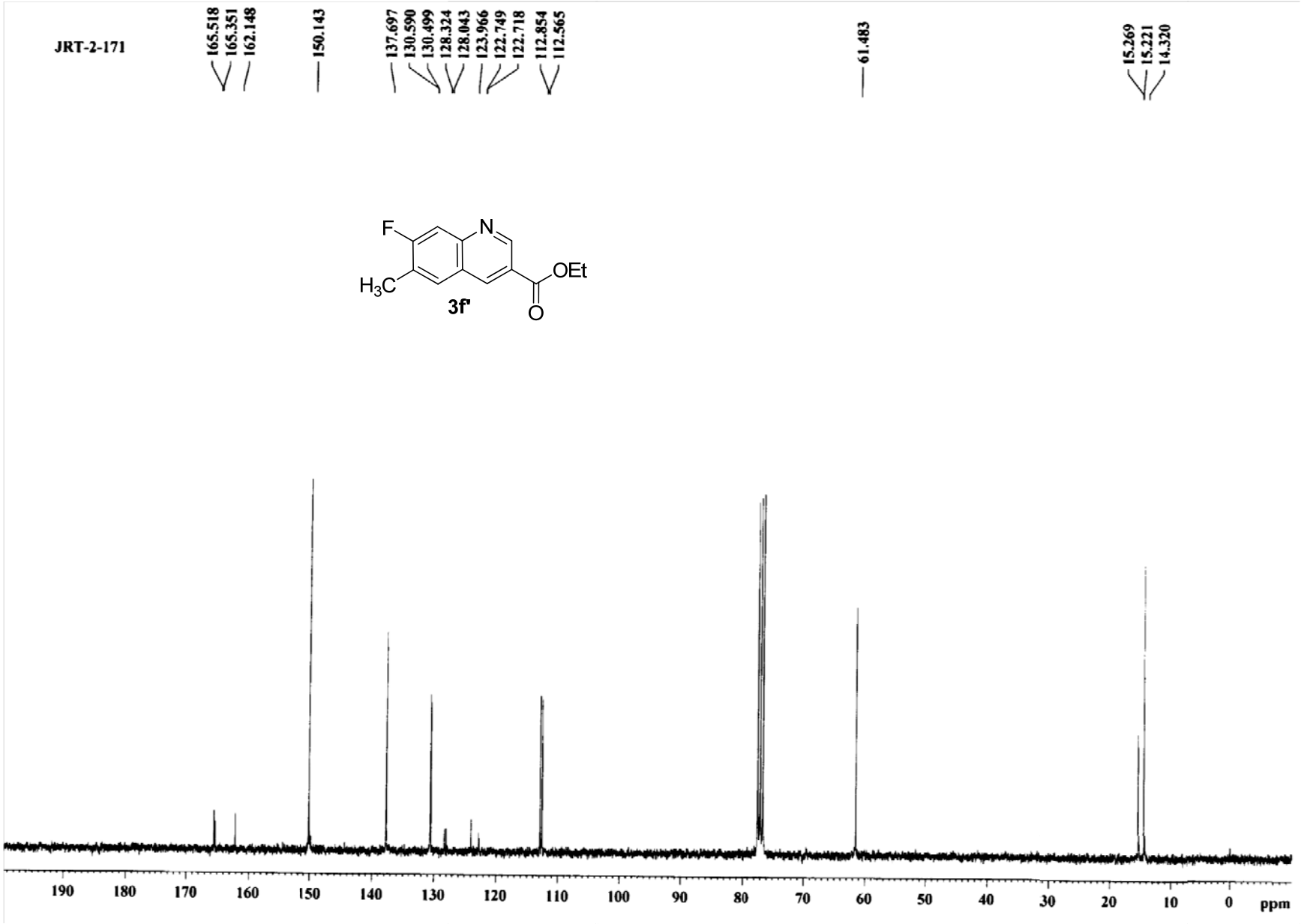


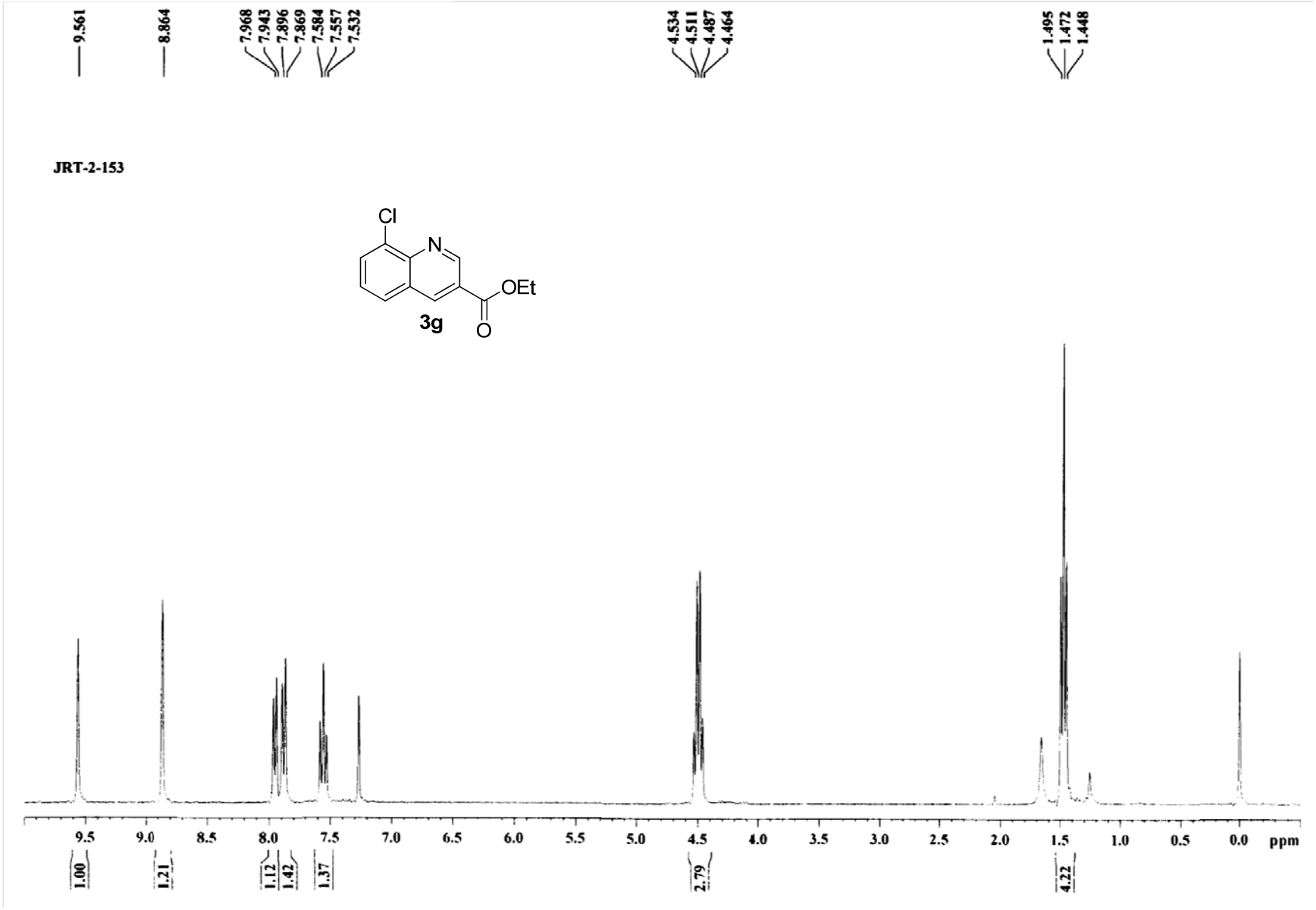


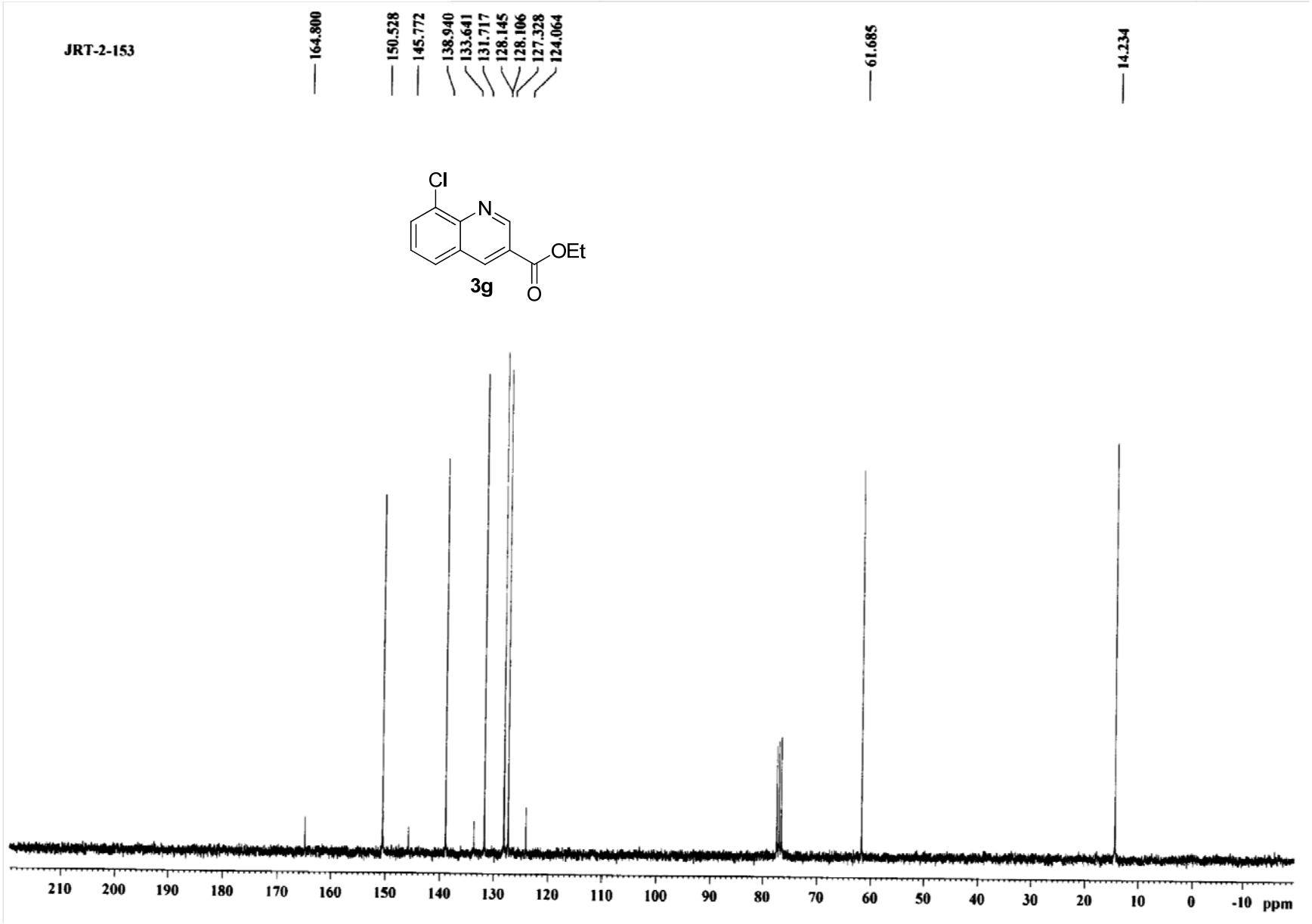


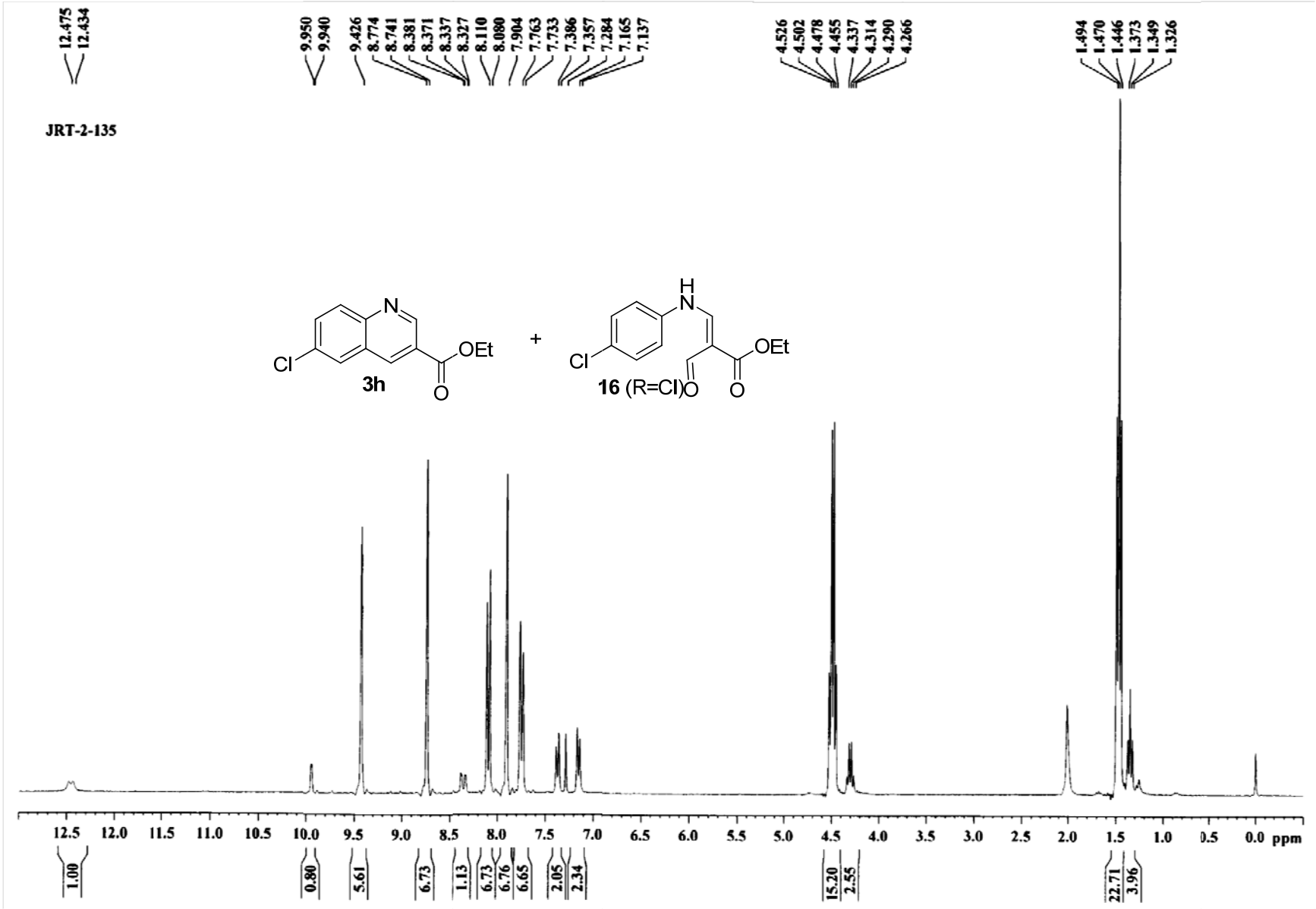


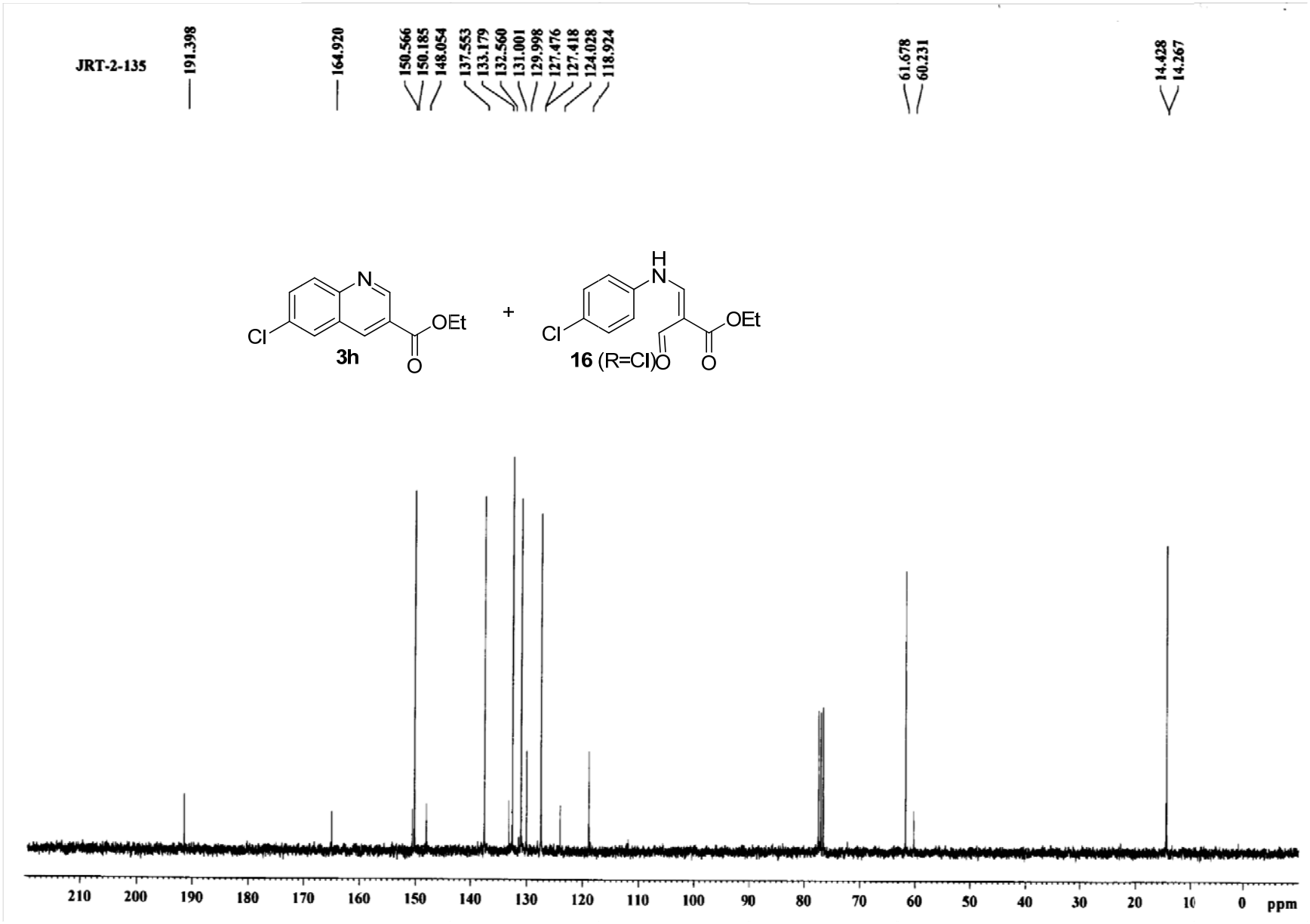

9.38
8.74
7.75
7.72
4.51
4.48
4.46
4.44
2.49
1.73
1.48
1.46
1.43
JRT-2-155 F1
F
N
OEt
H3C
O
3f'
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.89
1.00
2.03
2.21
3.29
1.02
3.31

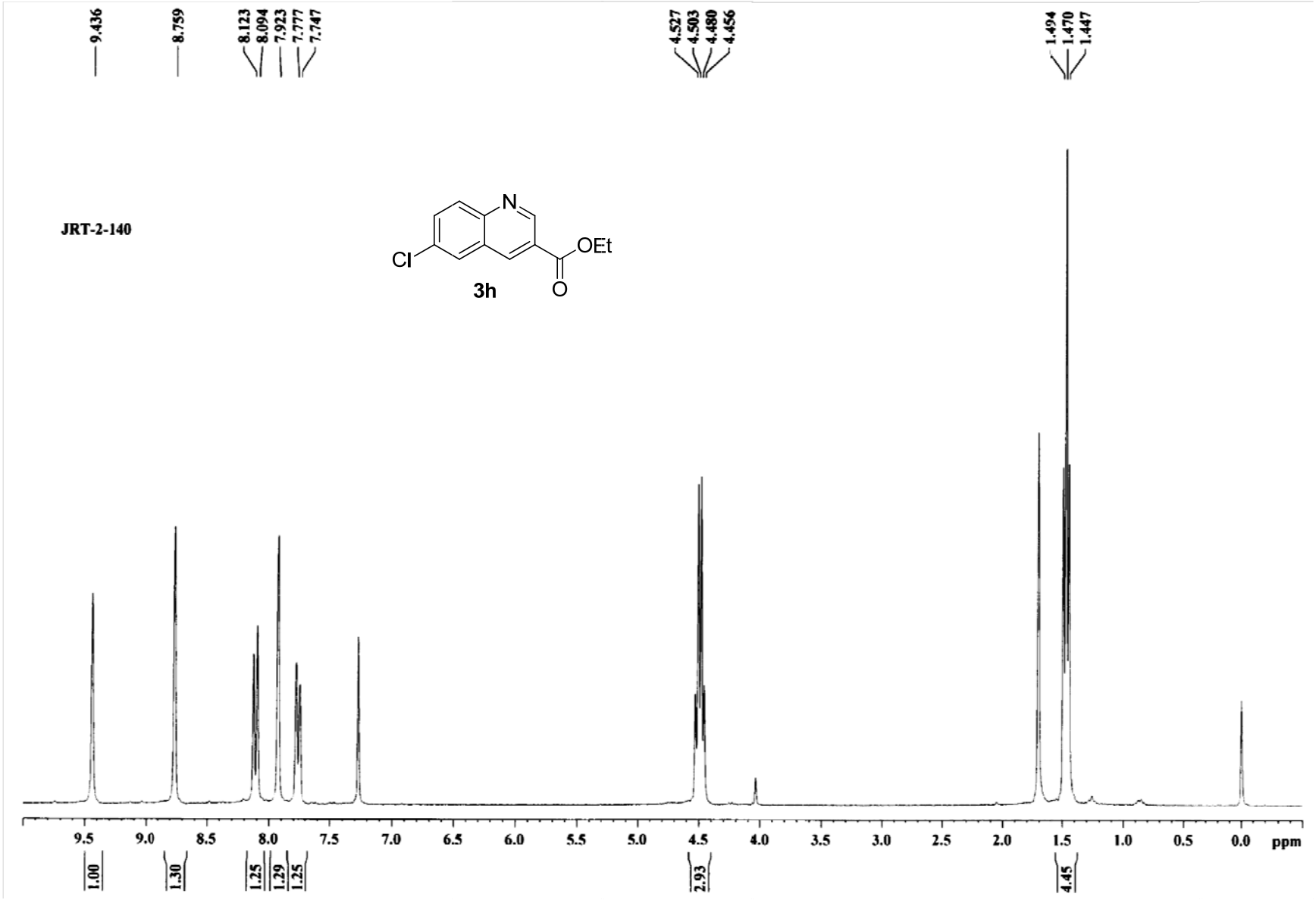


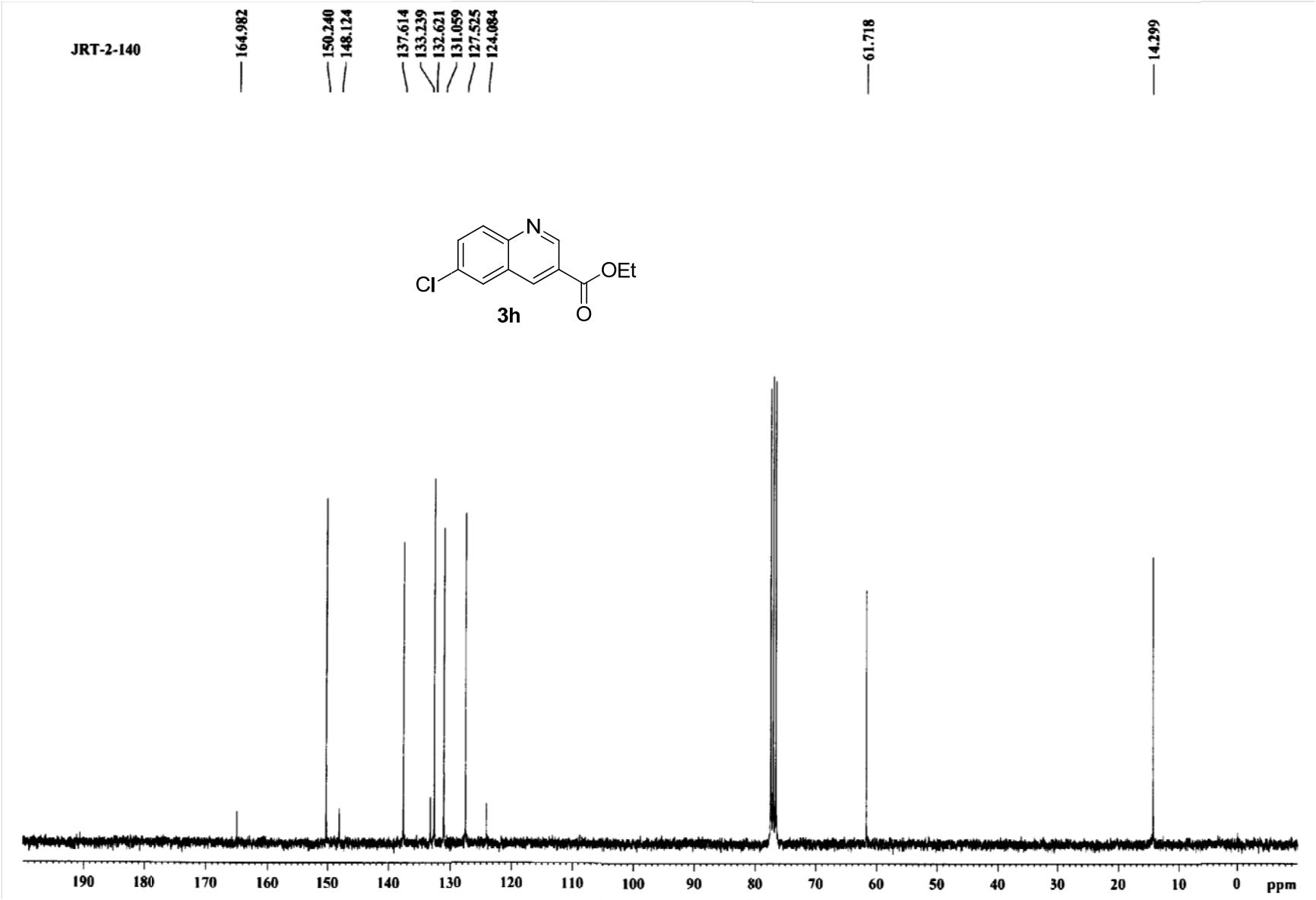


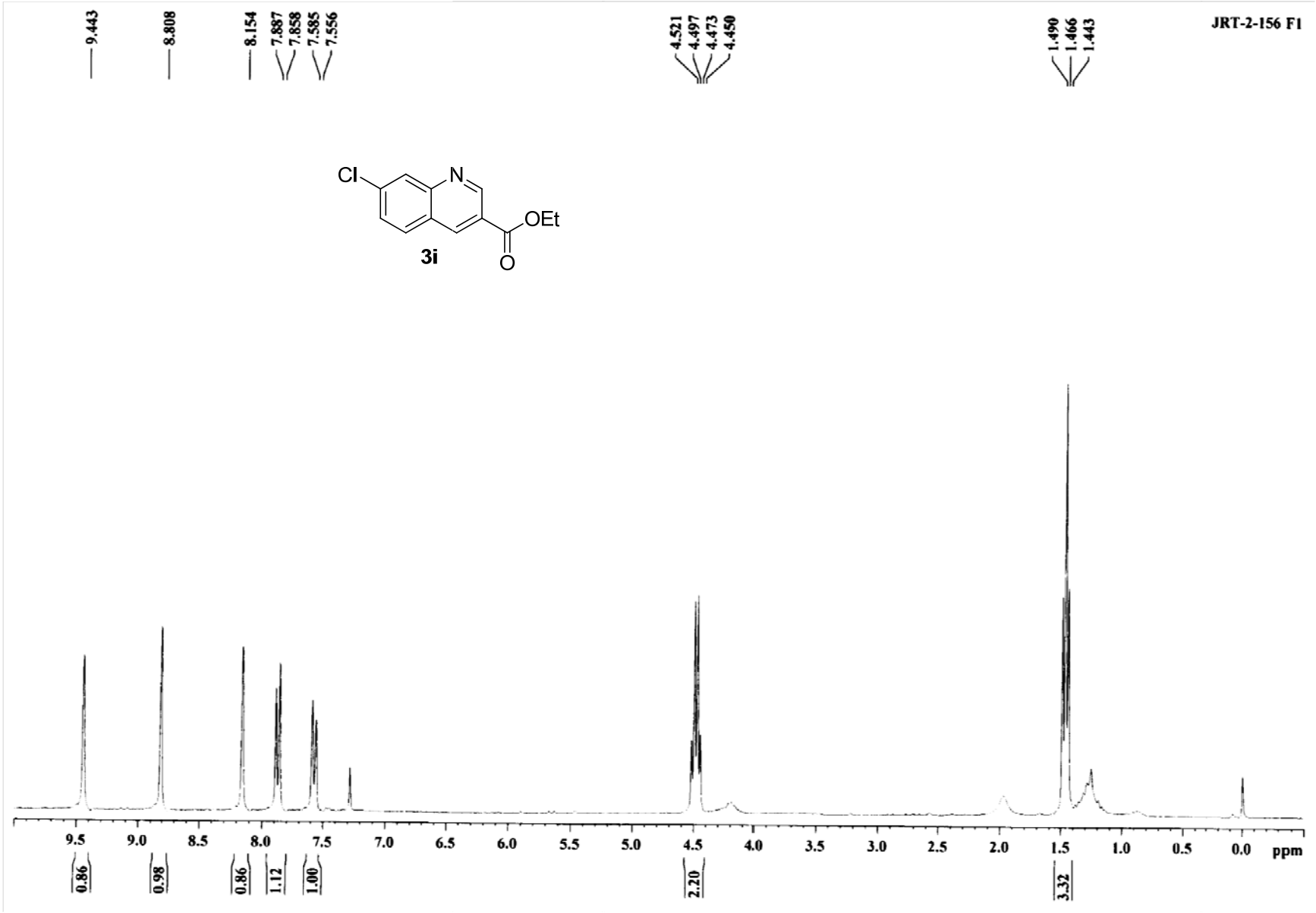


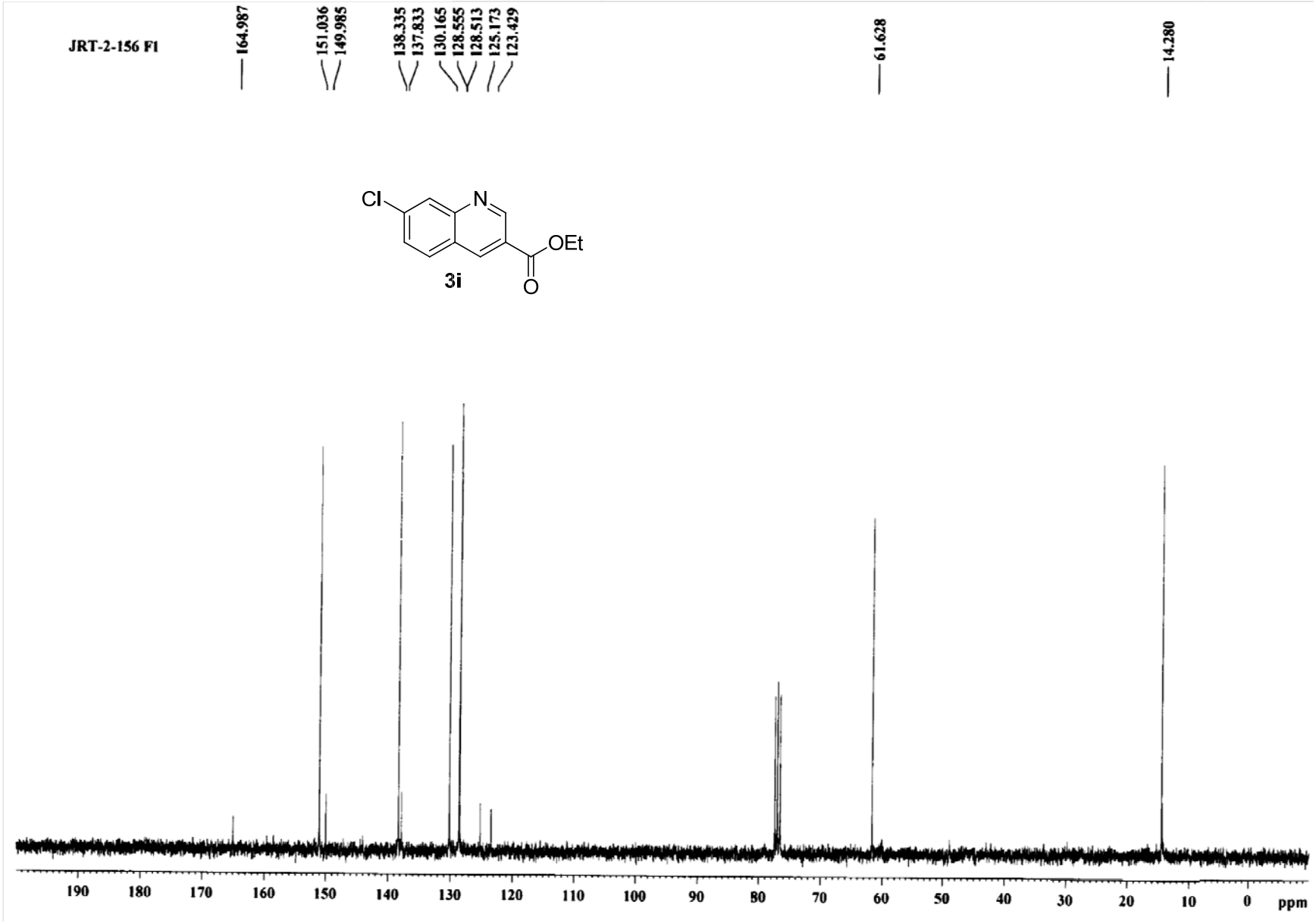


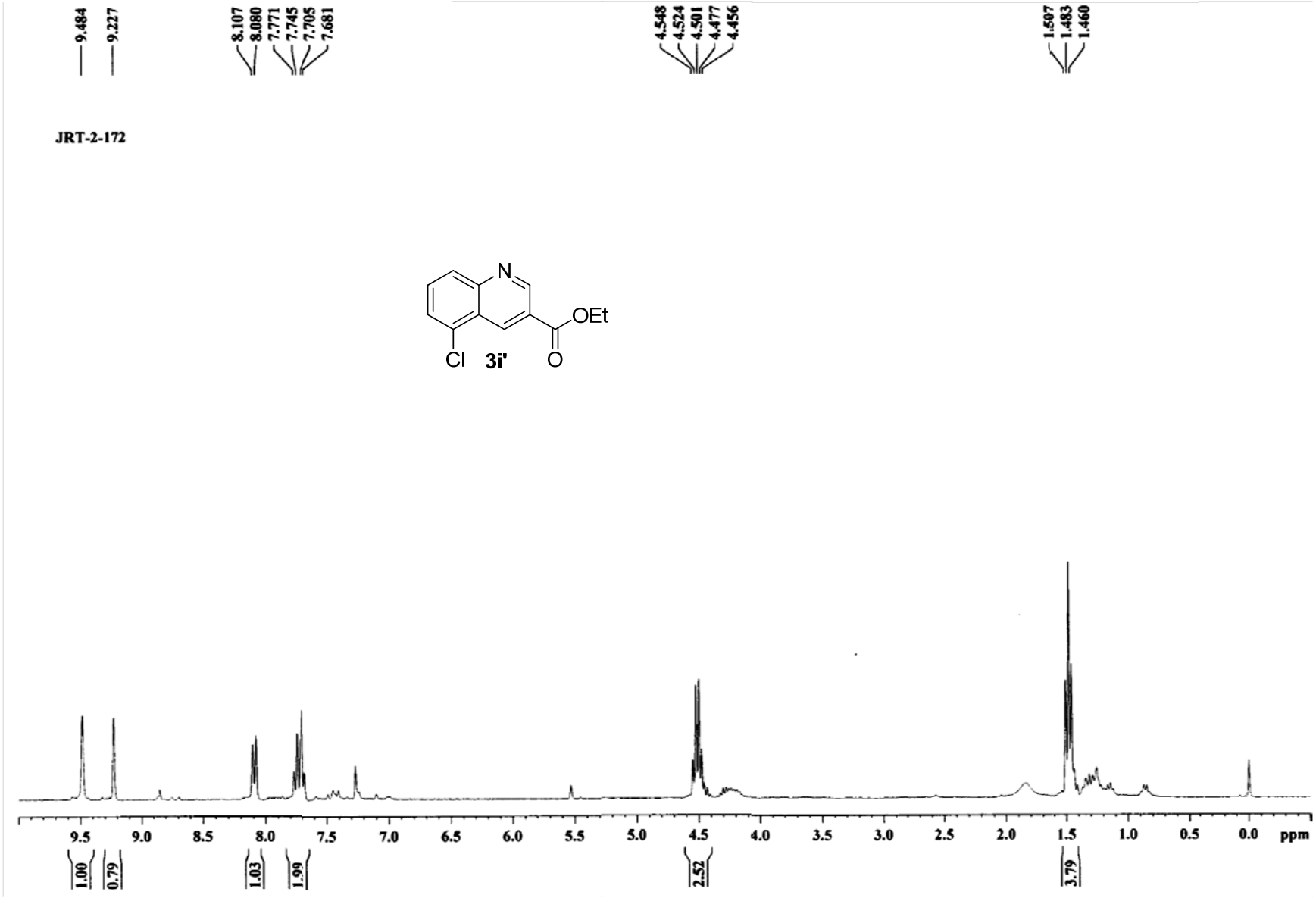


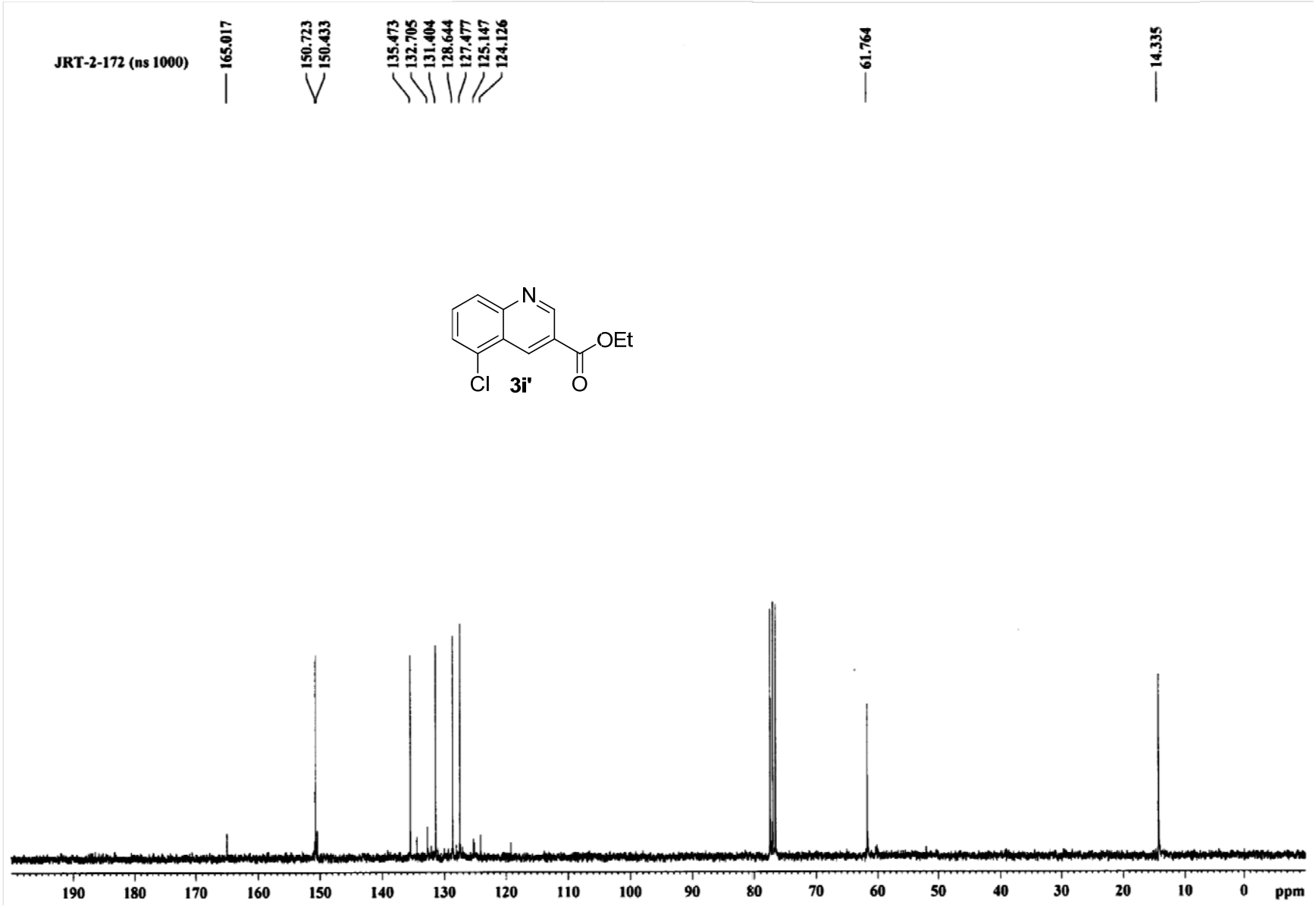


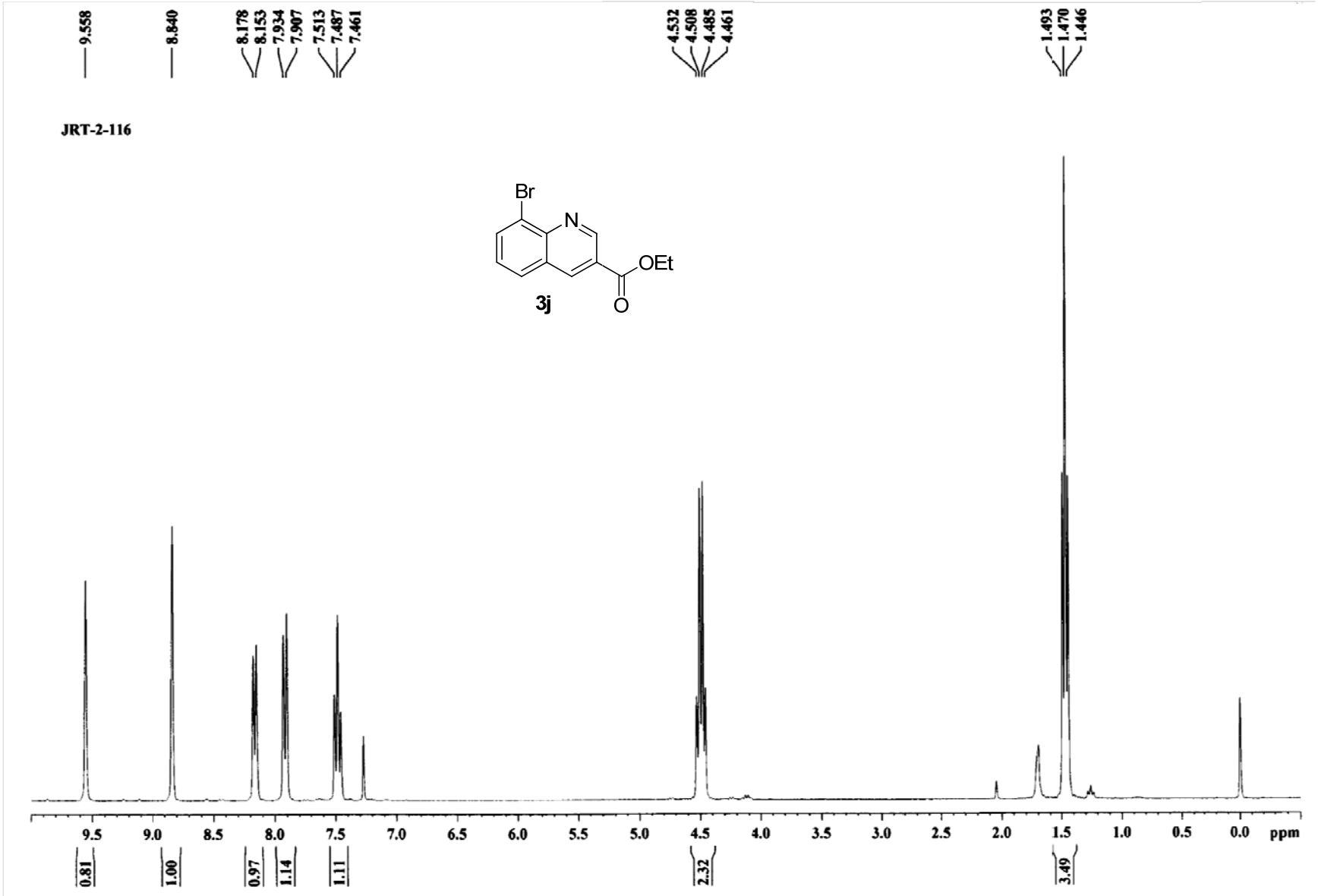


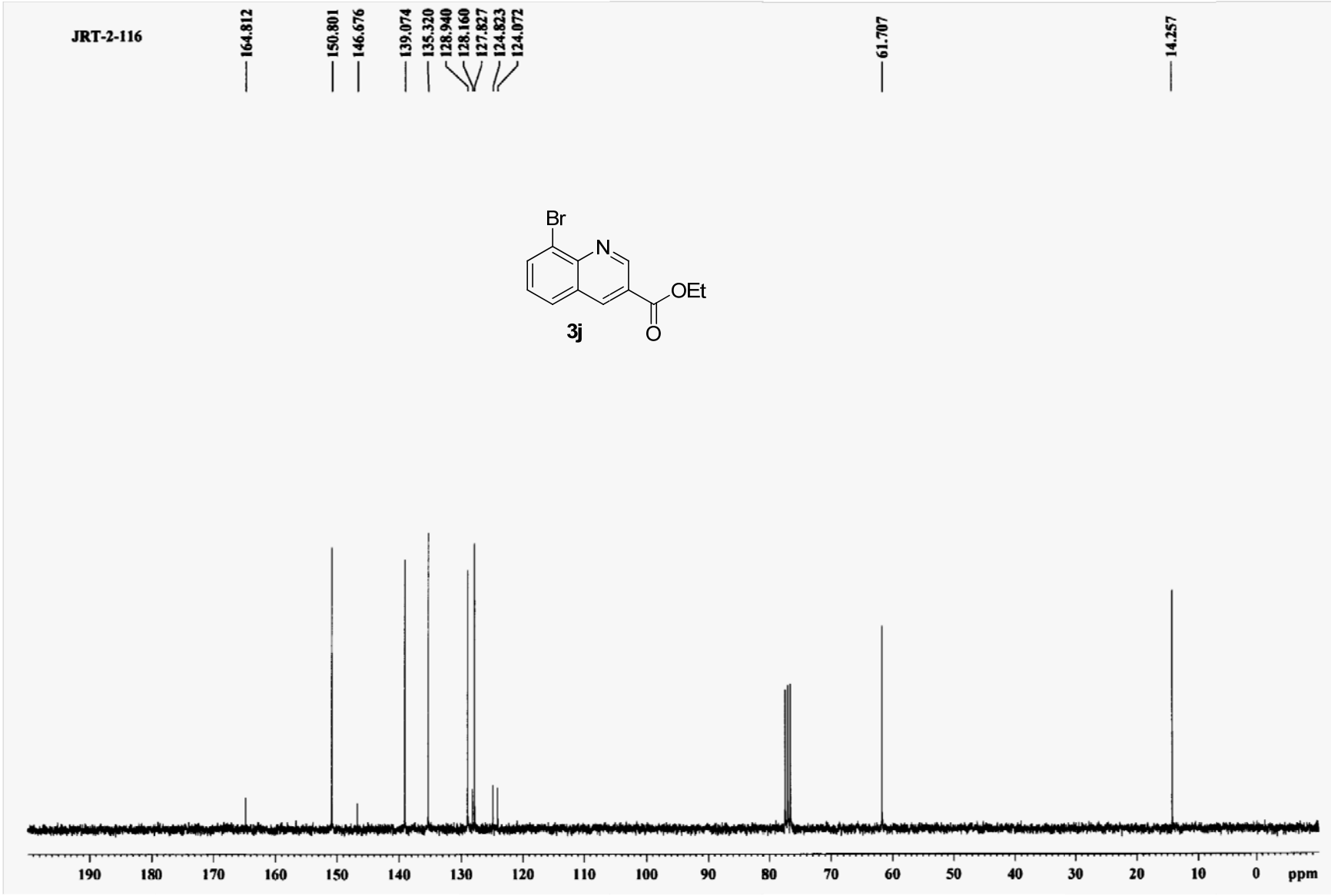


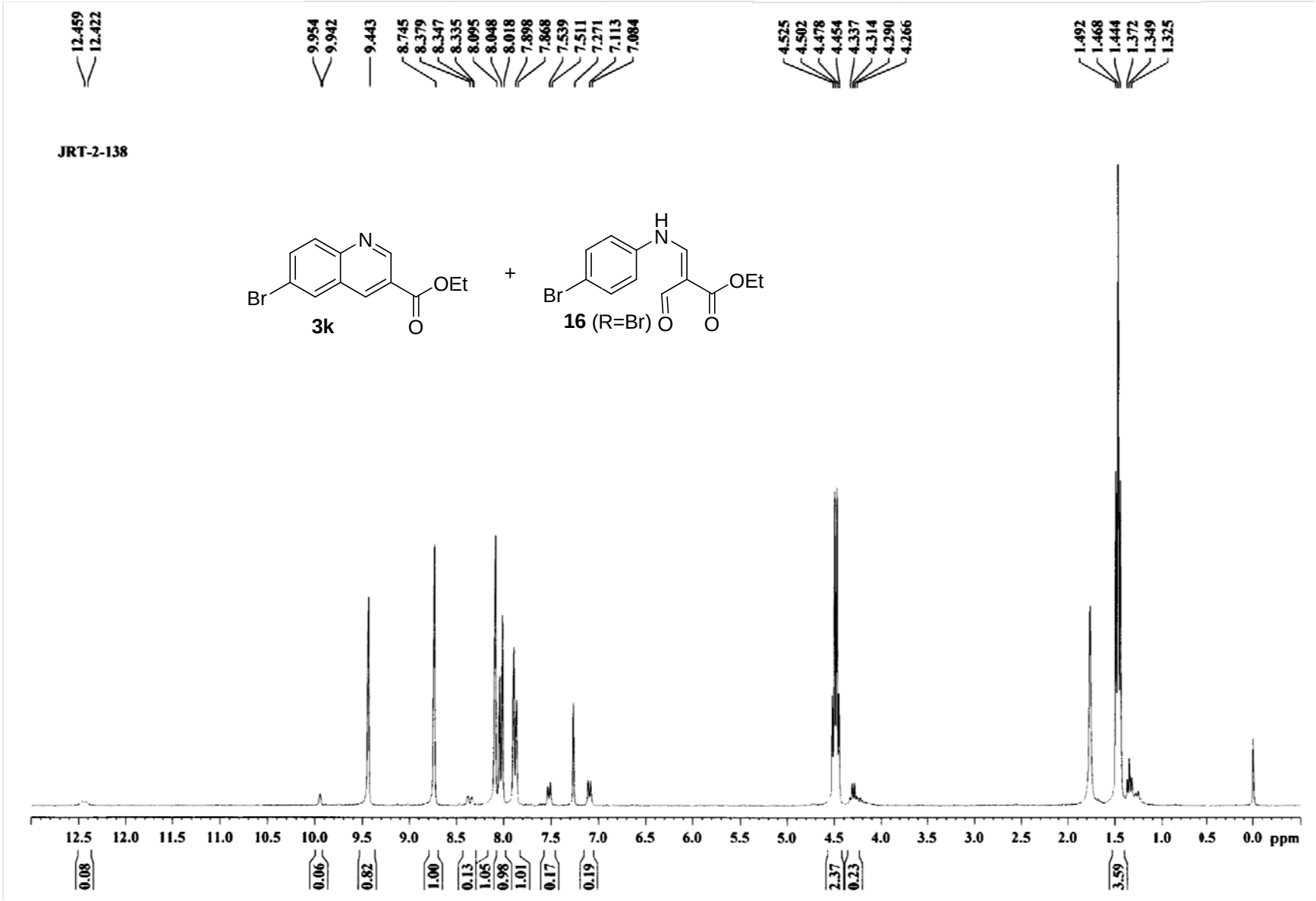


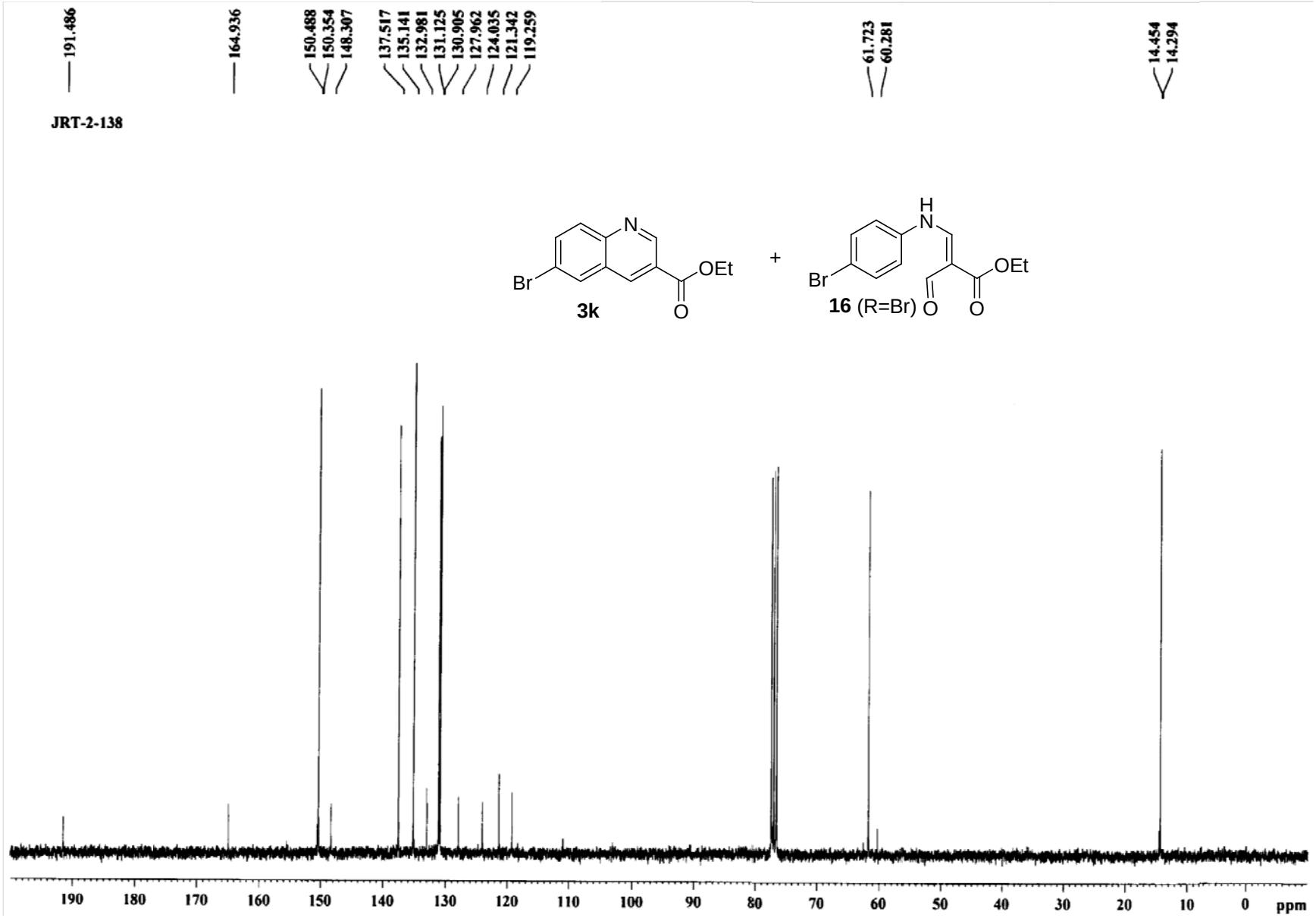


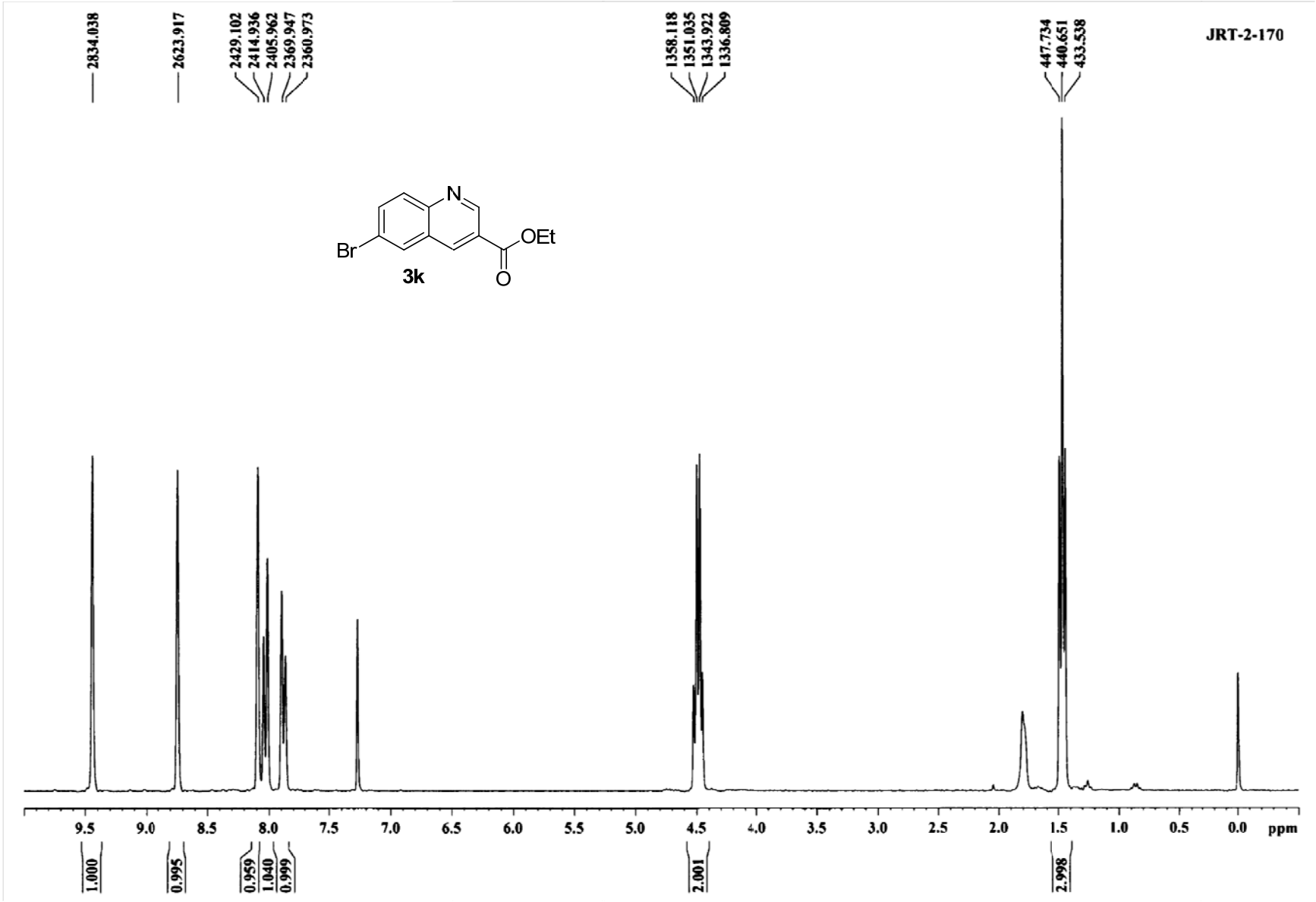


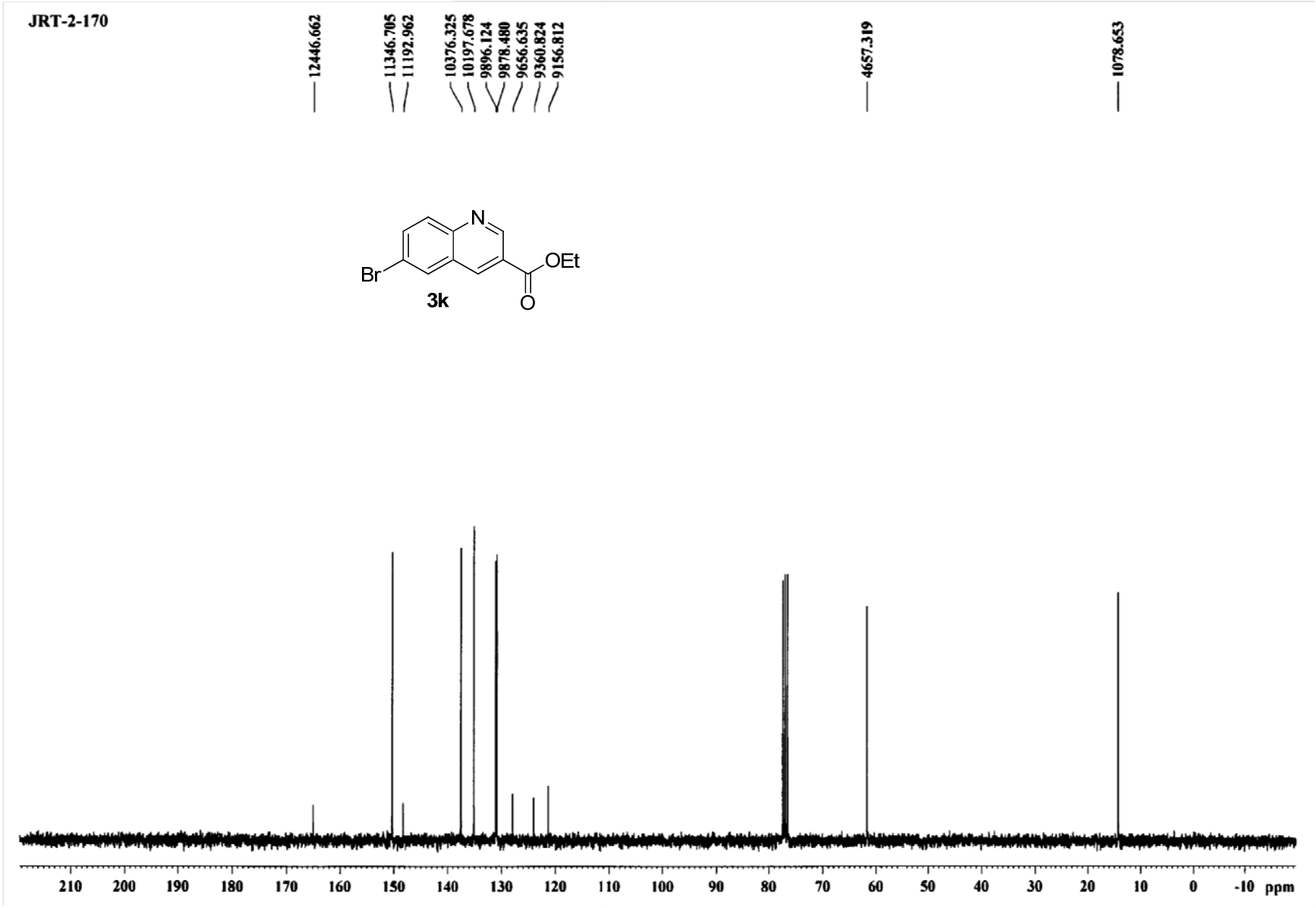


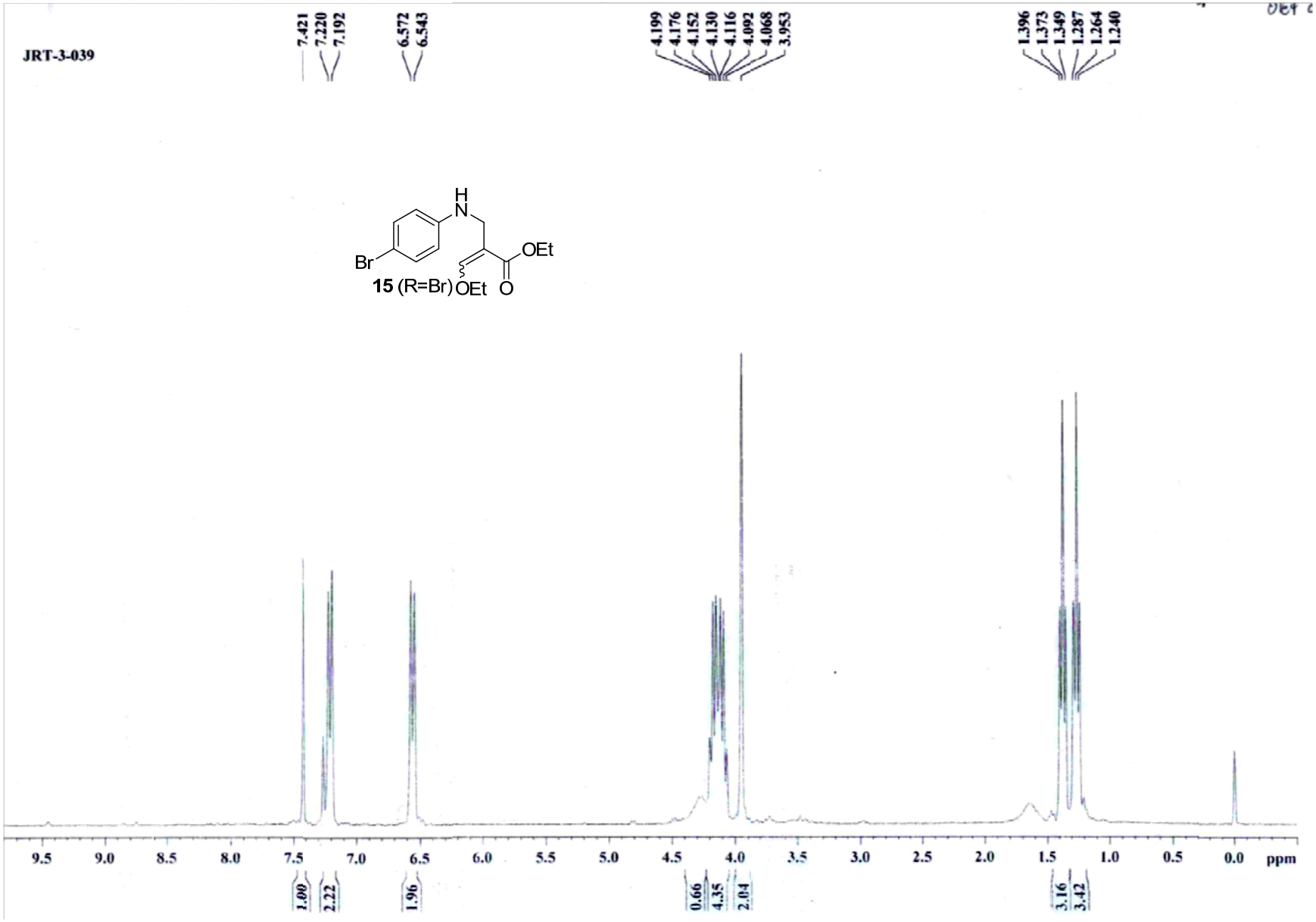


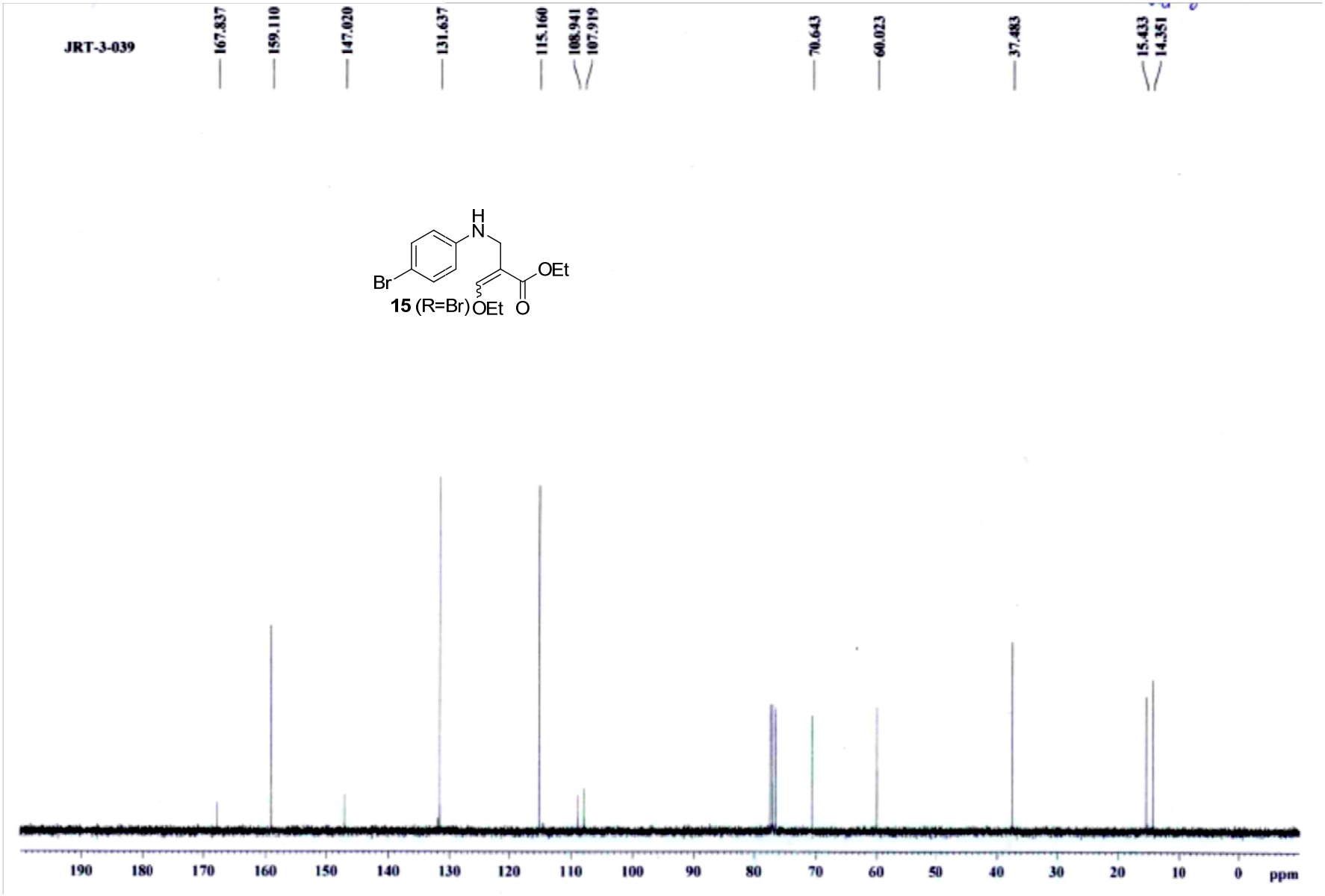


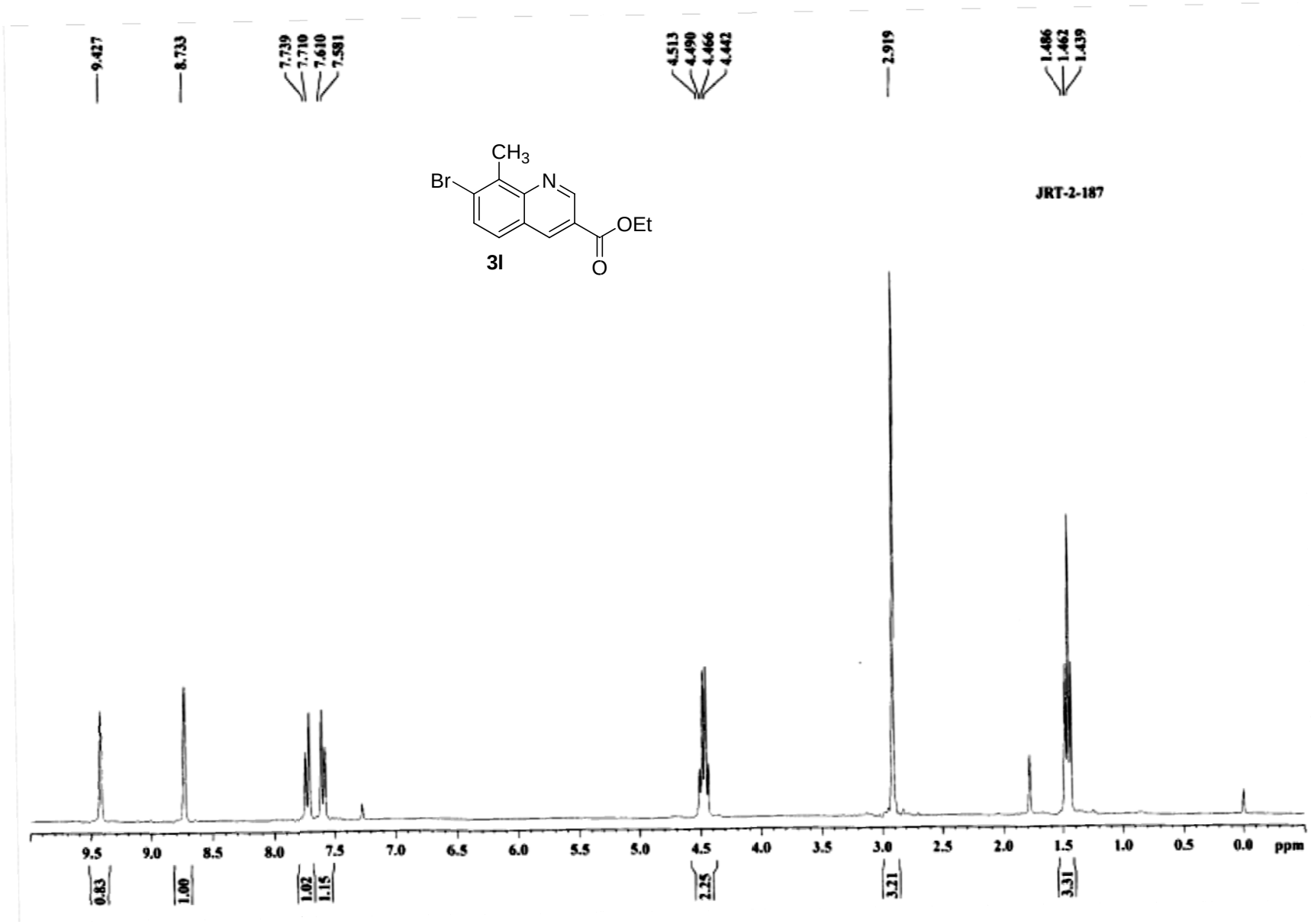


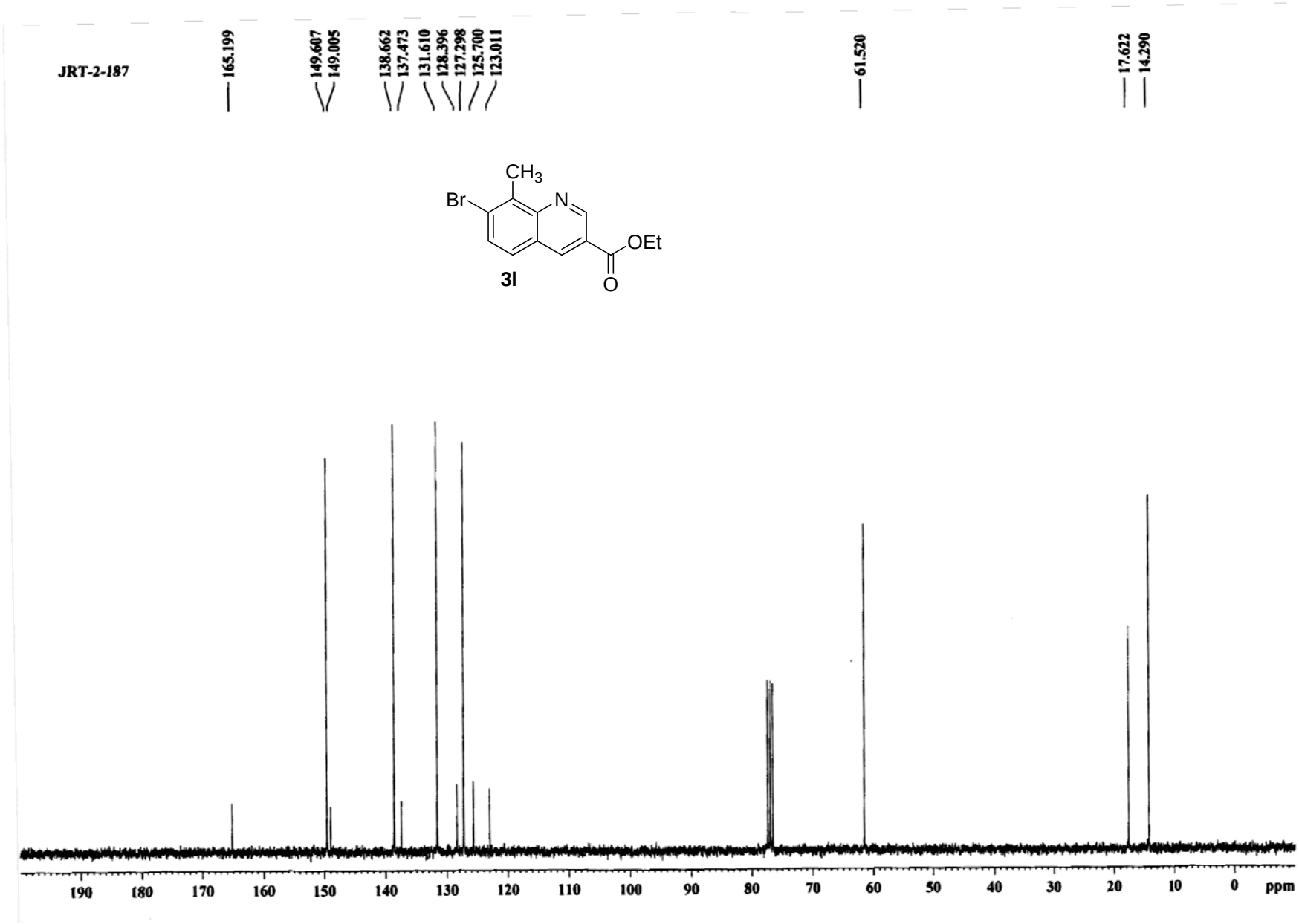


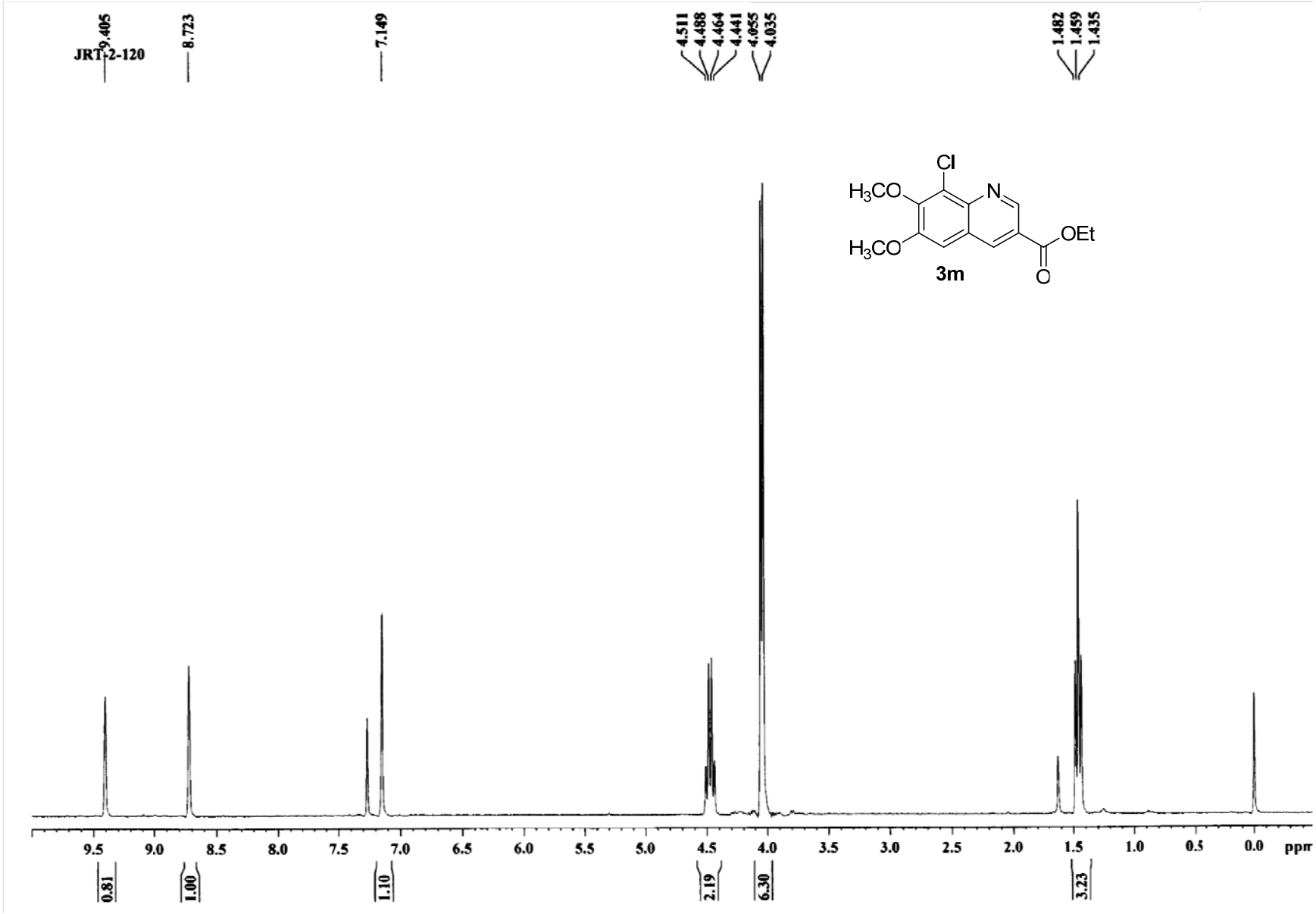


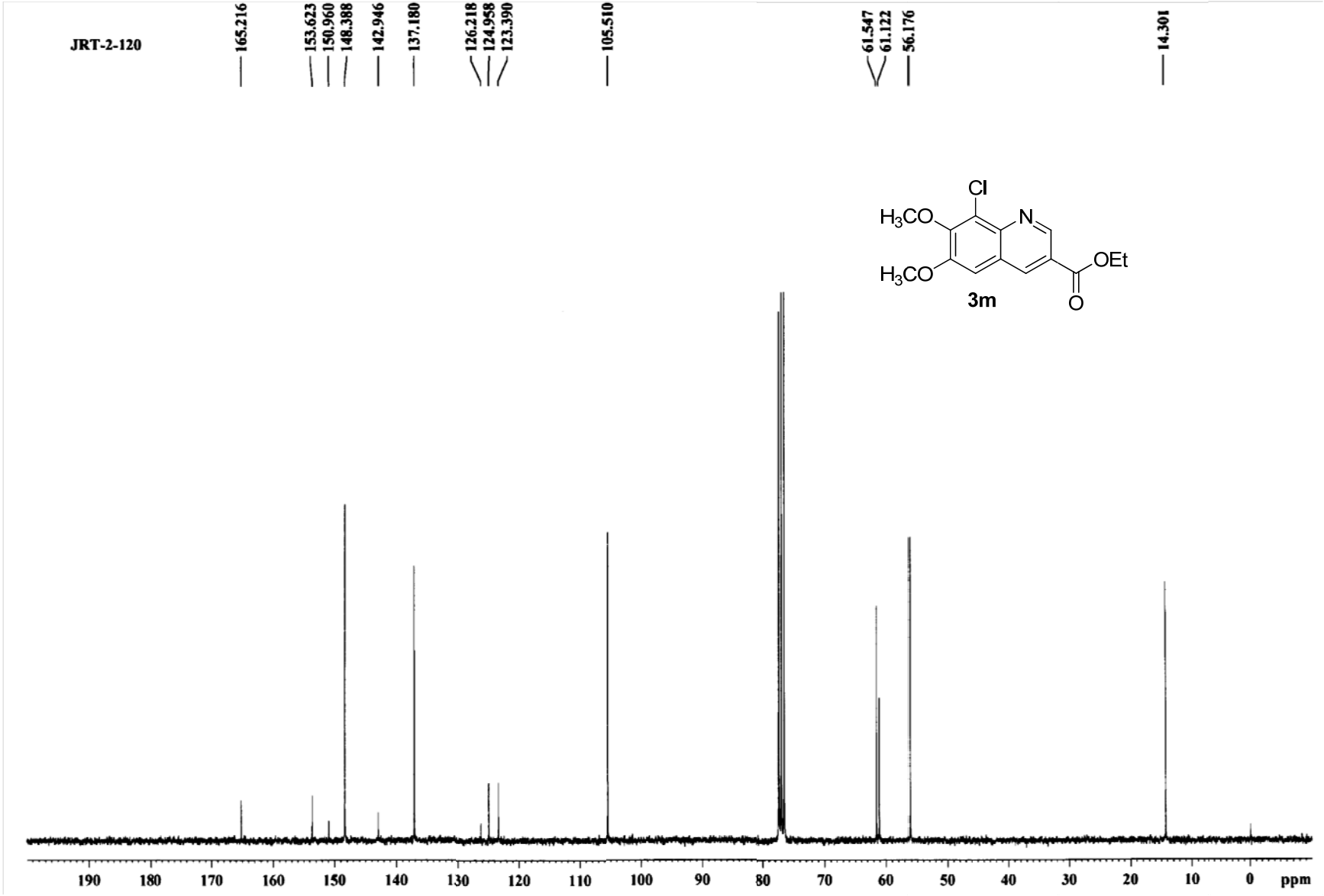


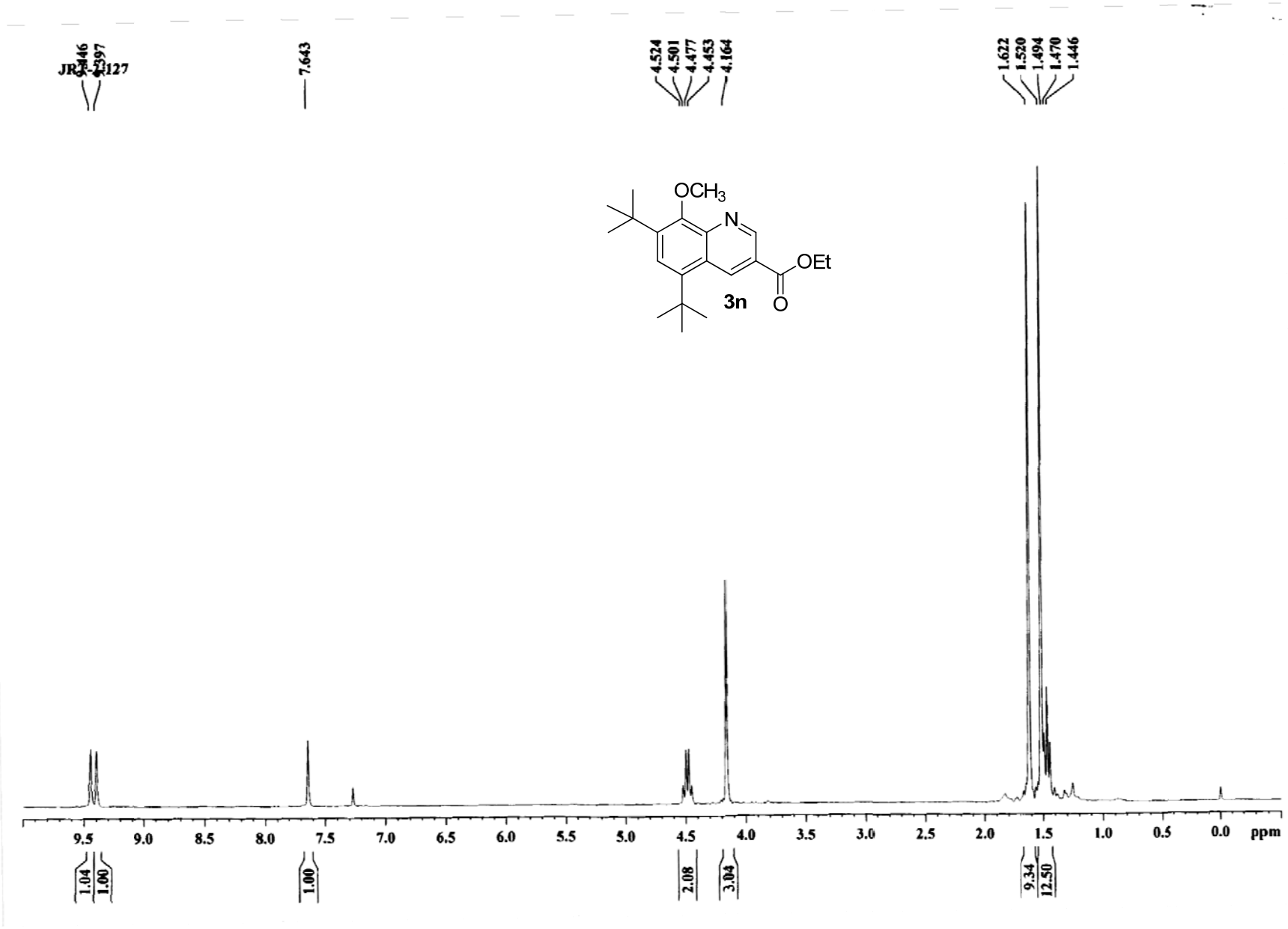


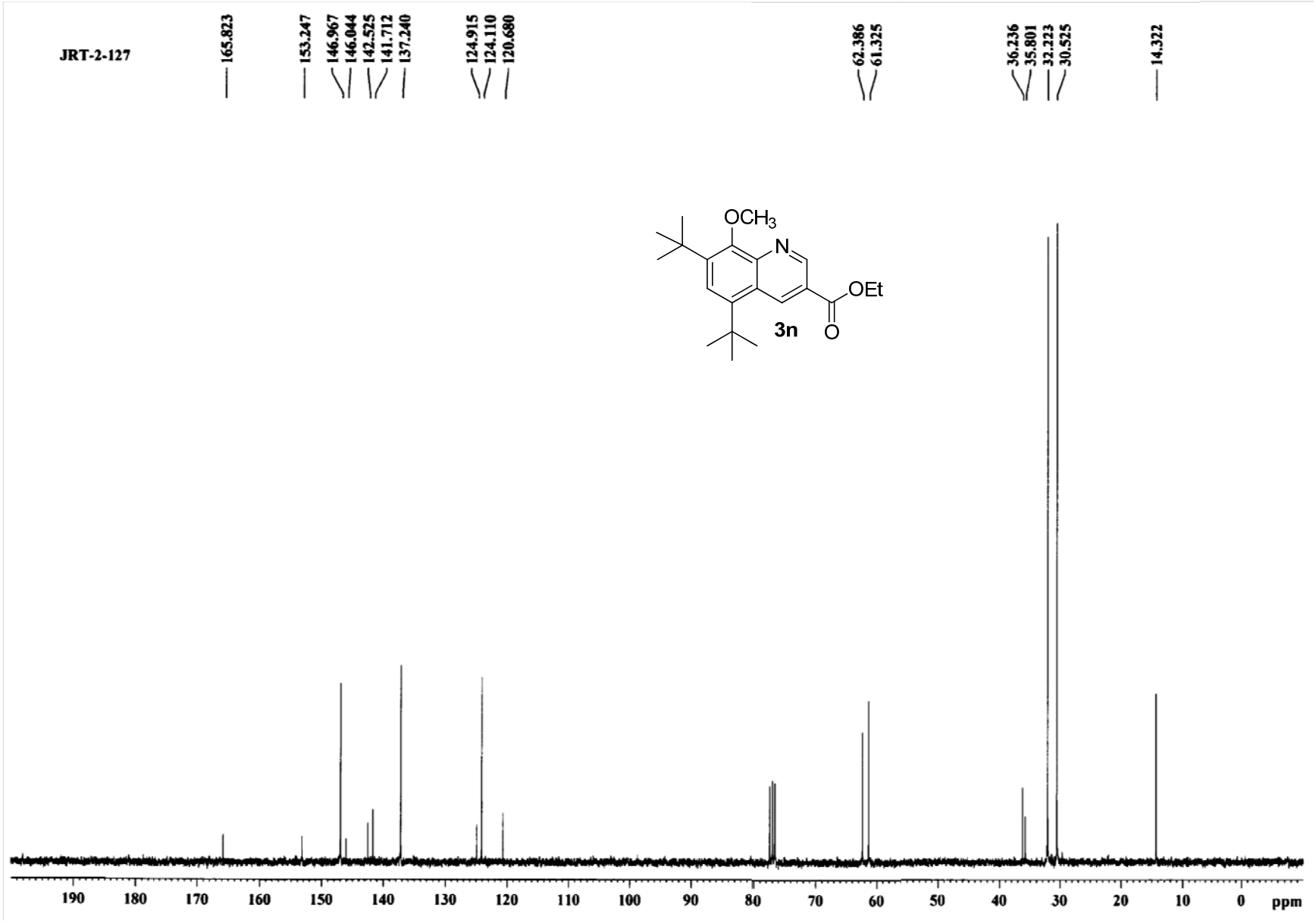


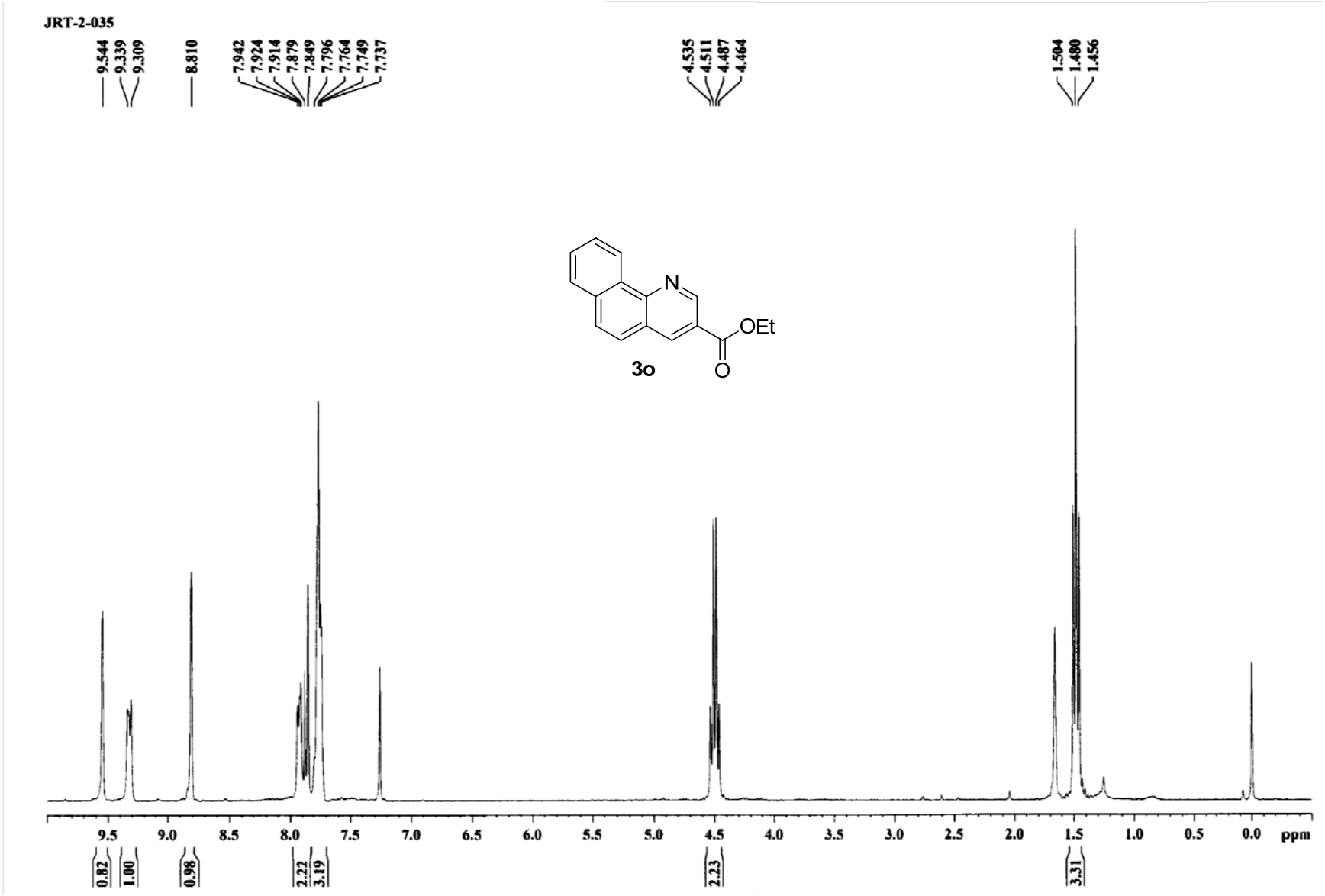


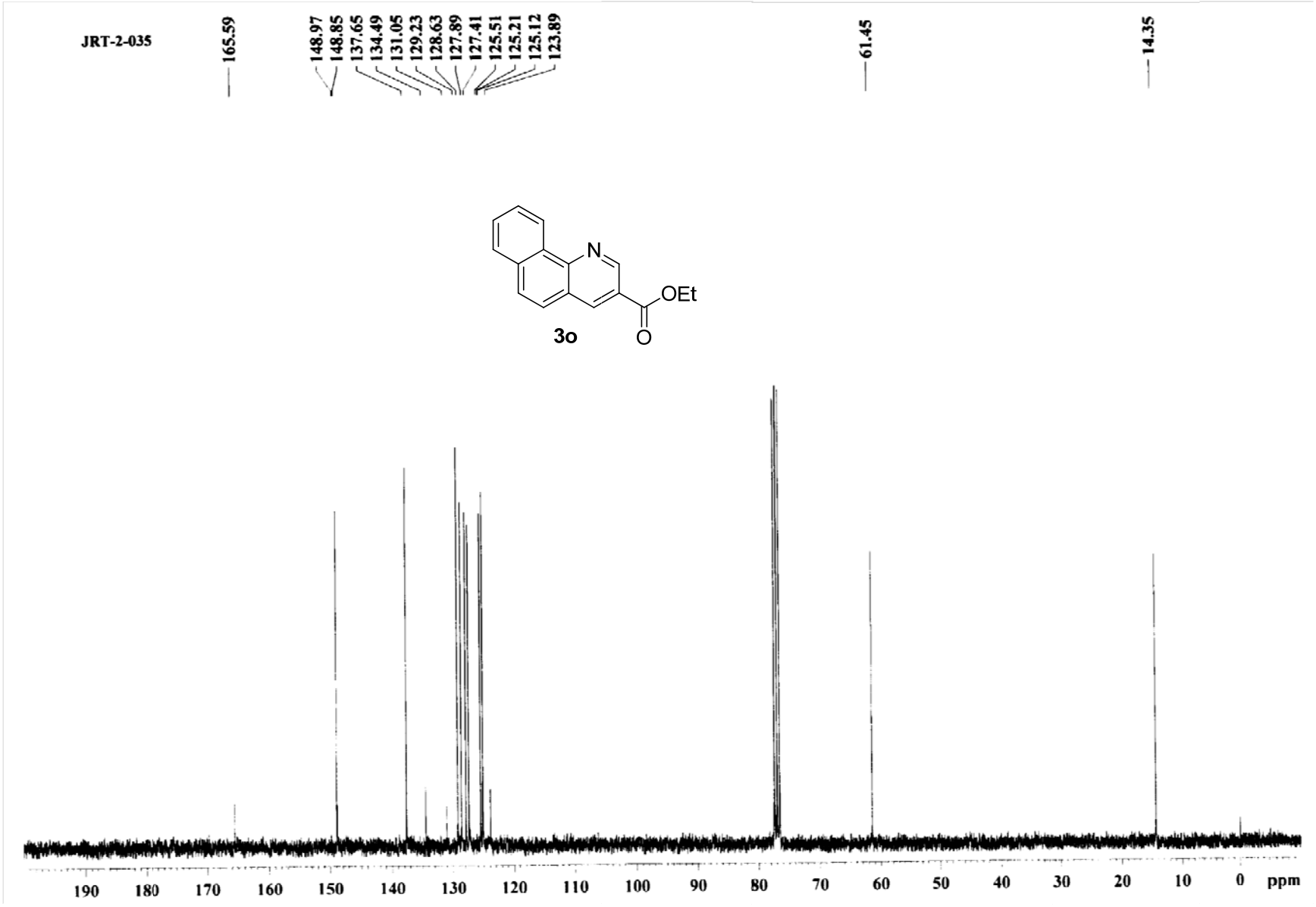


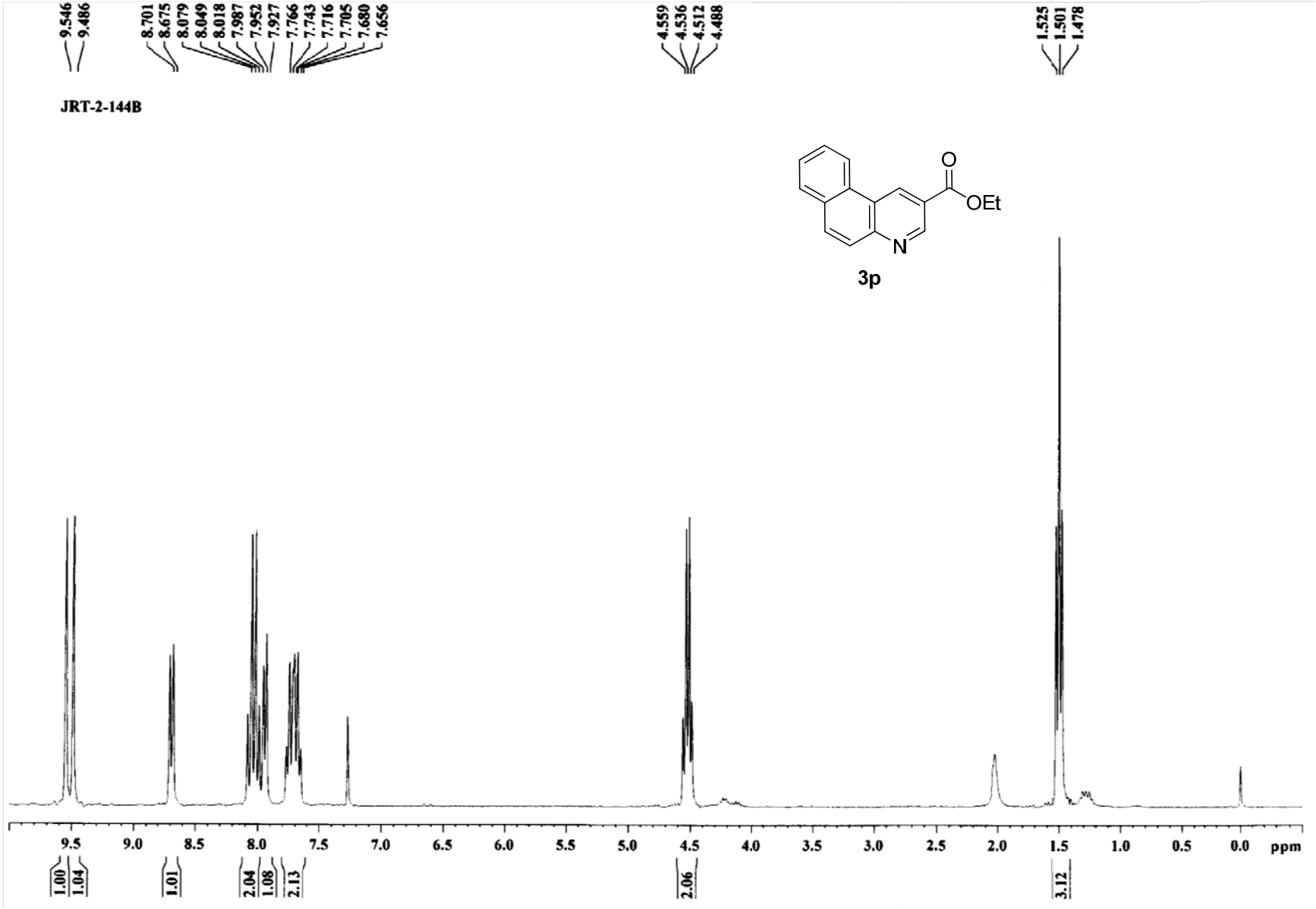


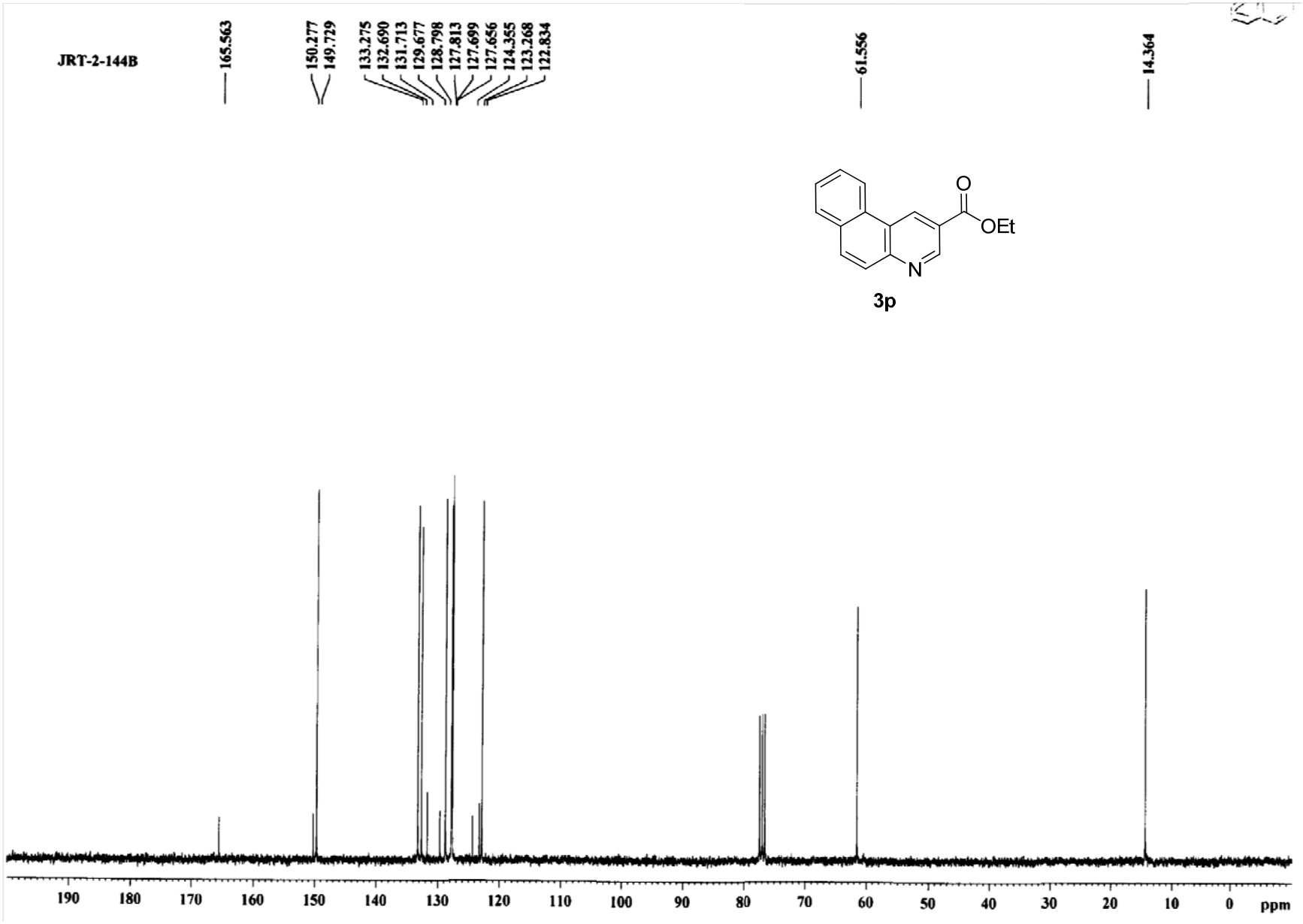

7.643
4.524
4.501
4.477
4.453
4.164
1.622
1.520
1.494
1.470
1.446
OCH3
N
OEt
O
3n
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.04
1.00
1.00
2.08
3.04
9.34
12.50

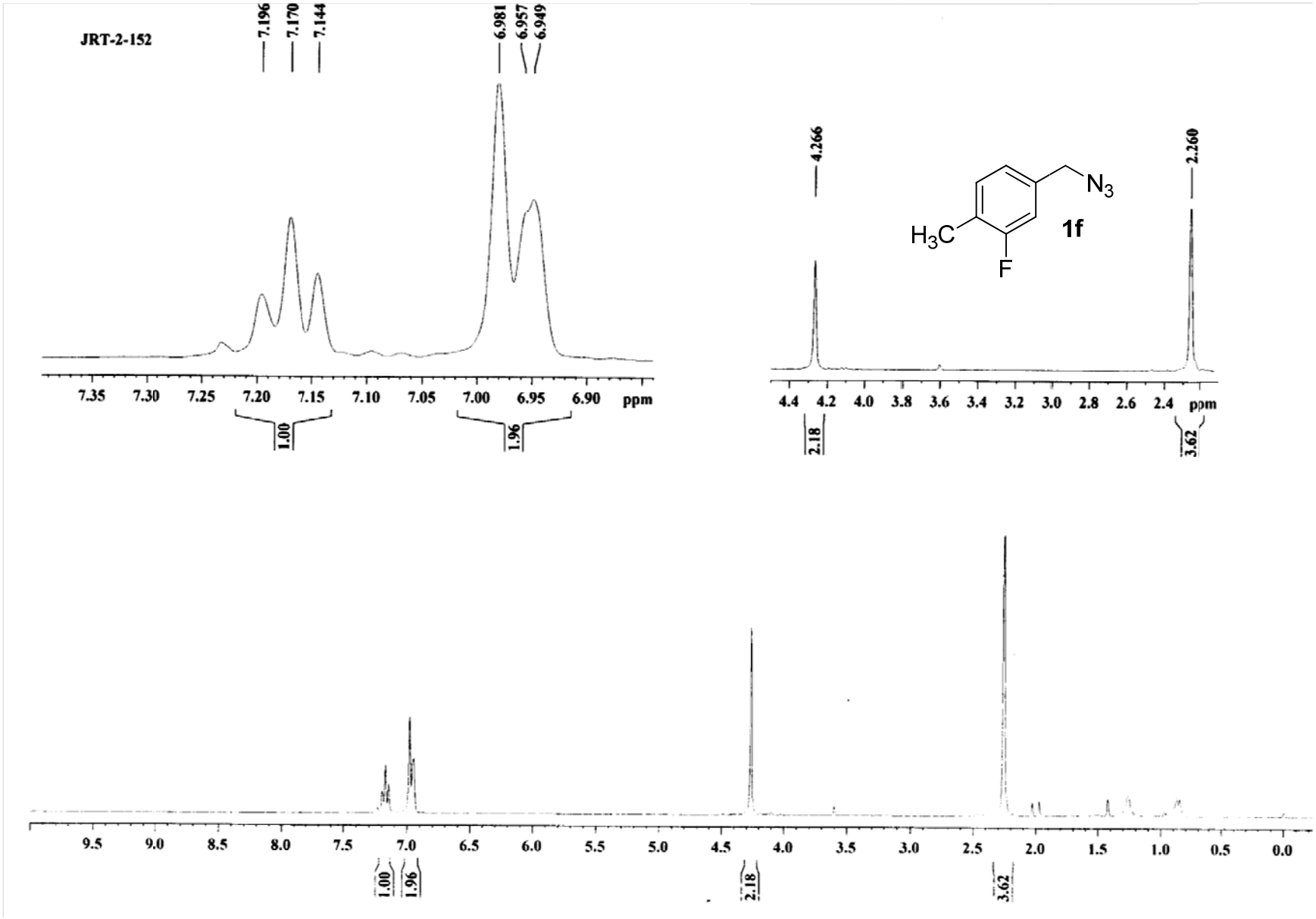


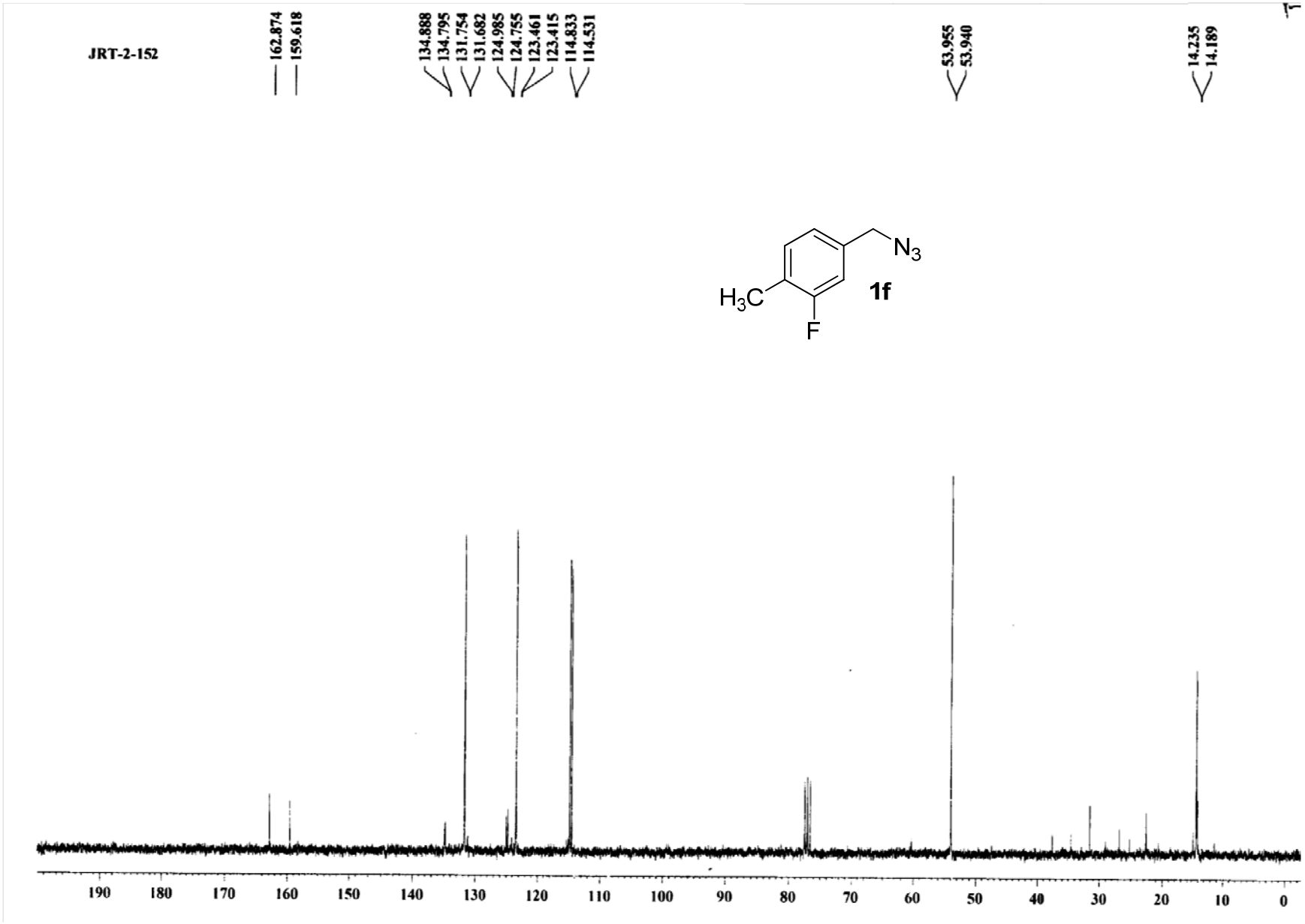


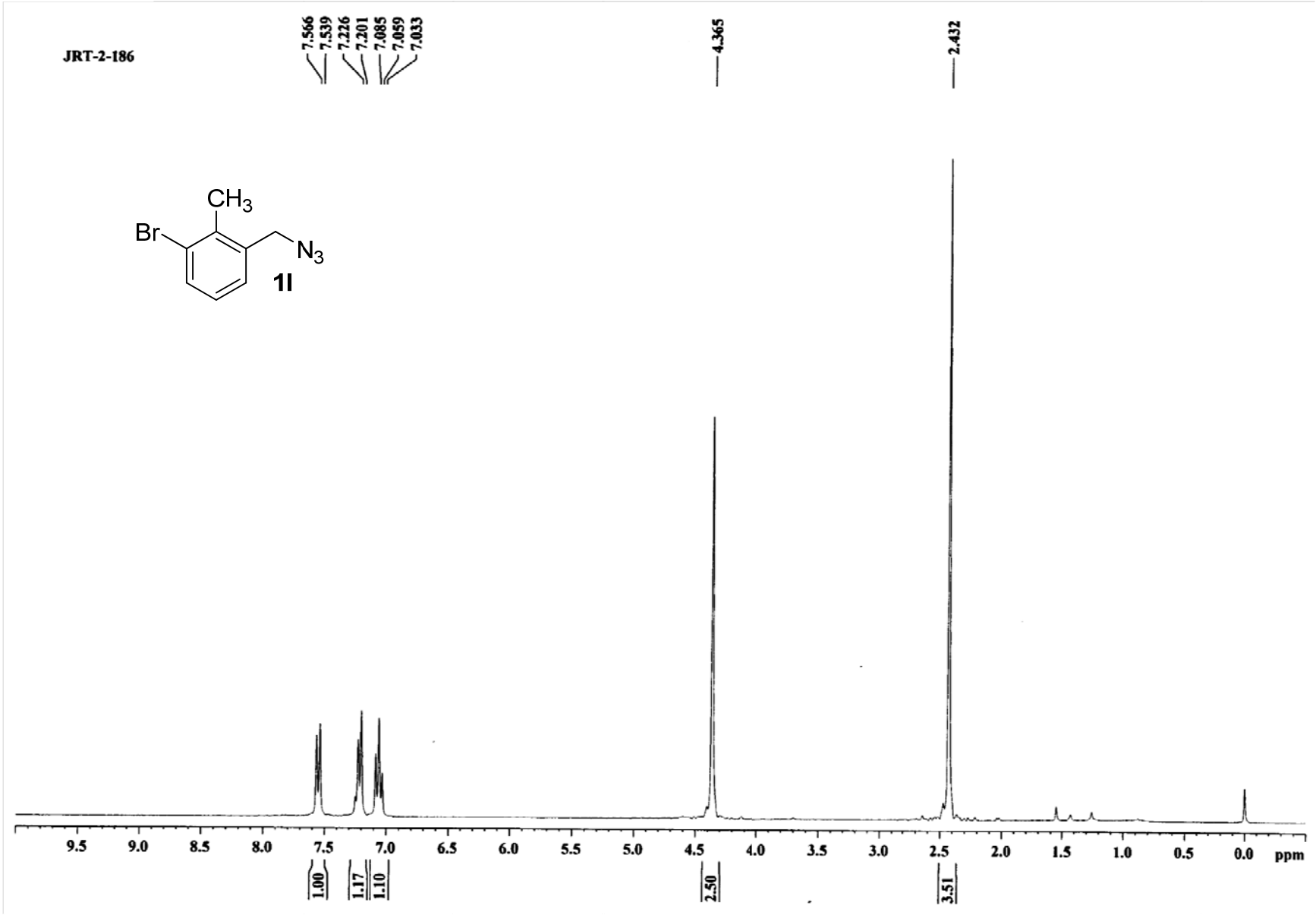


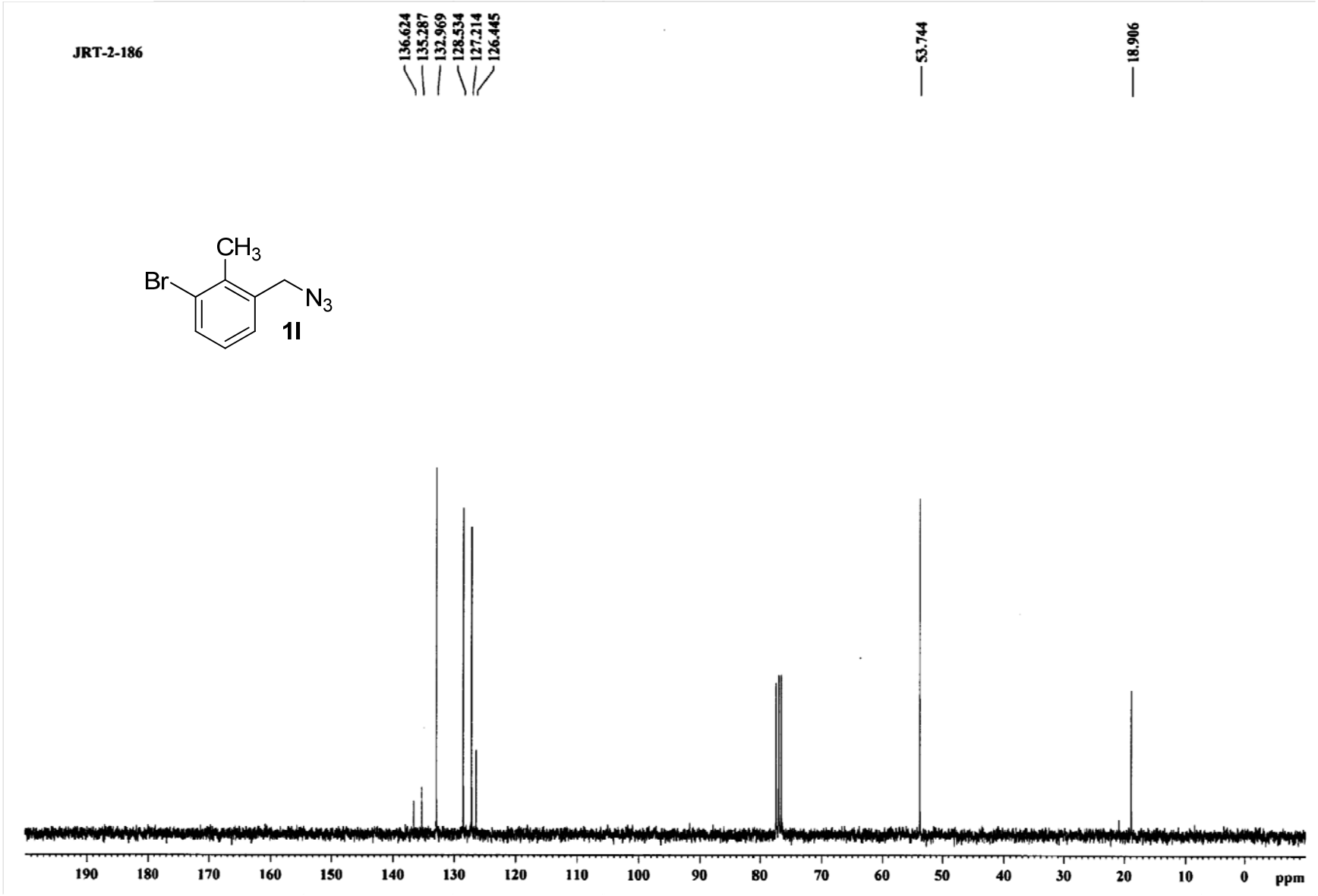


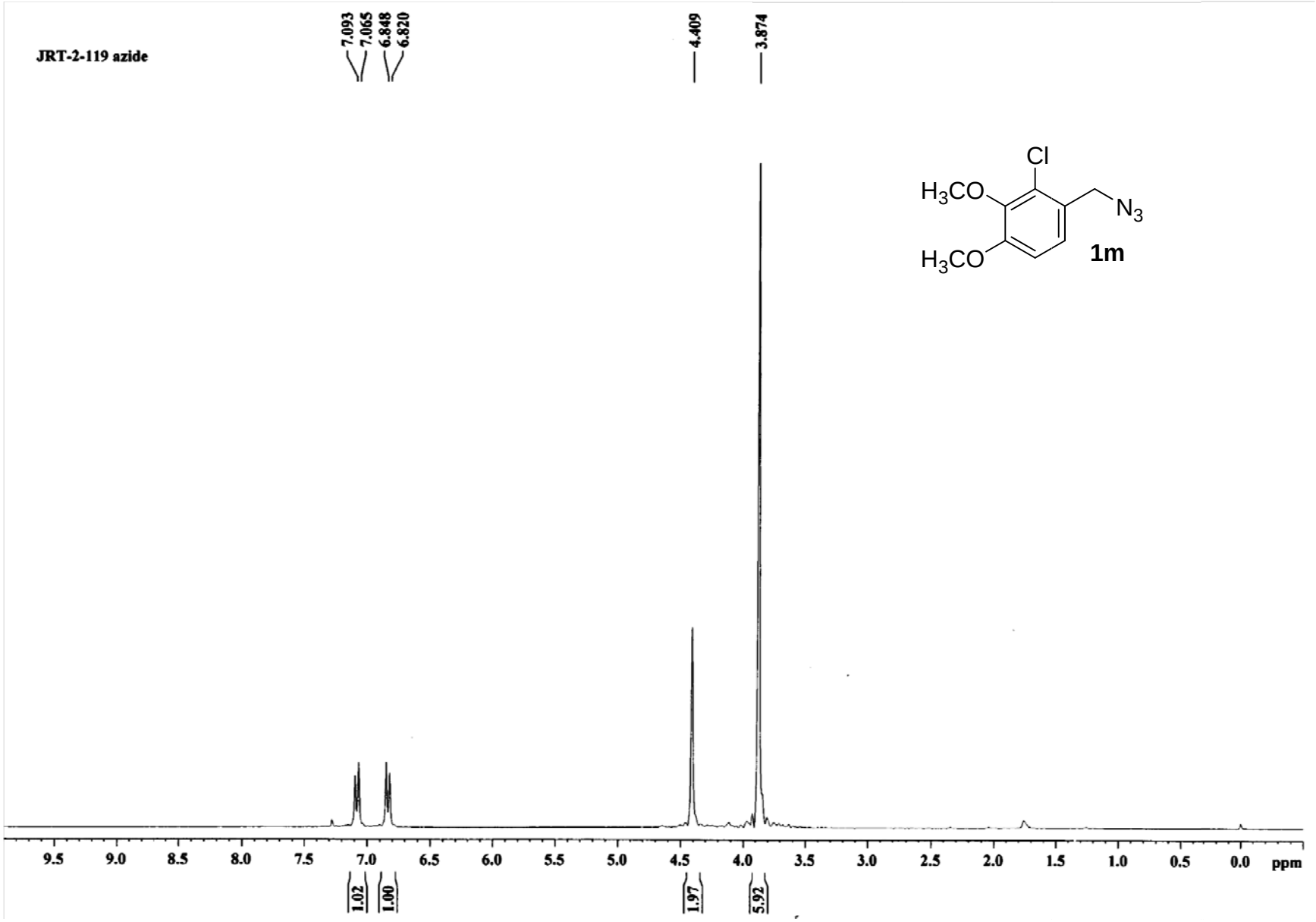


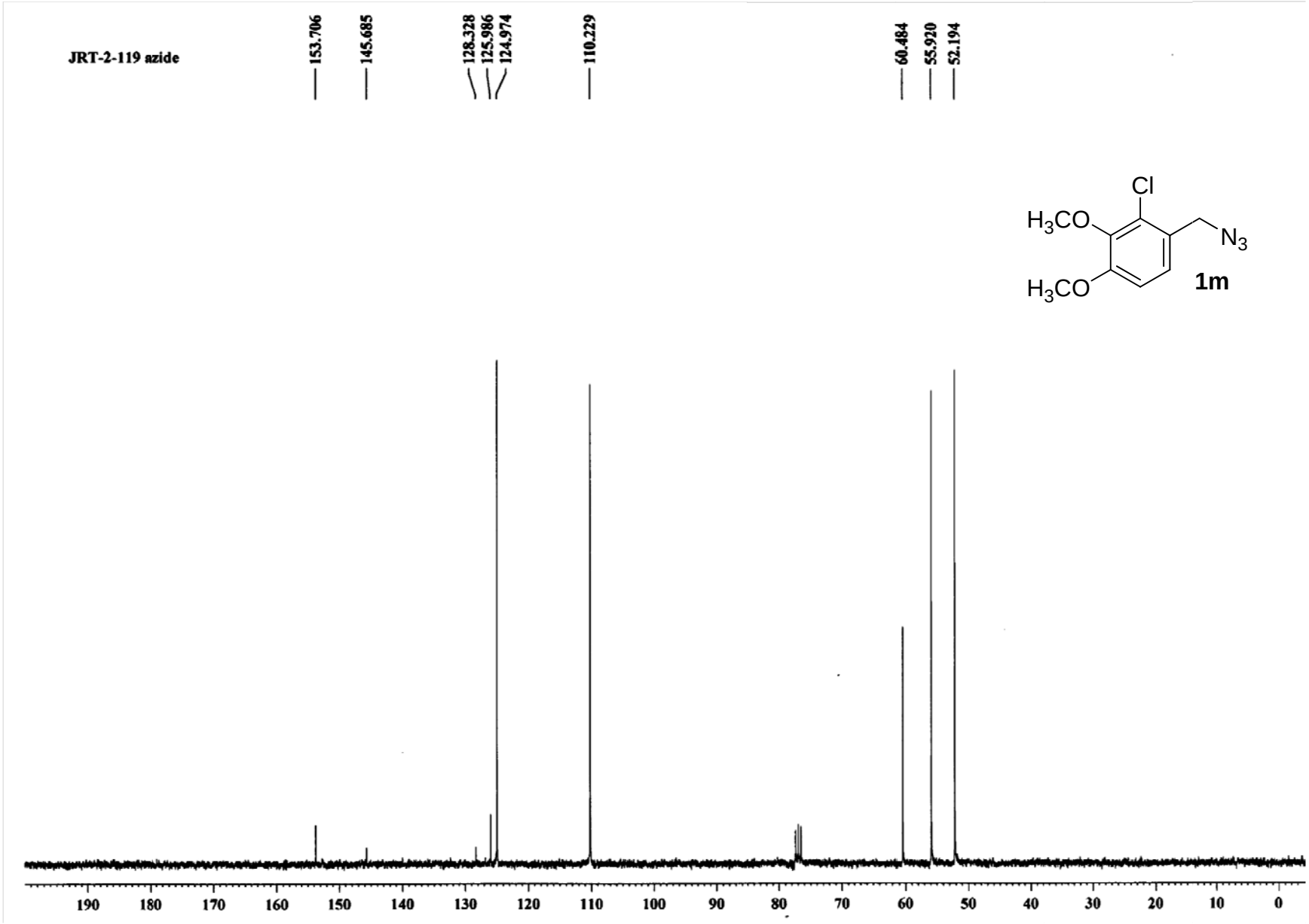


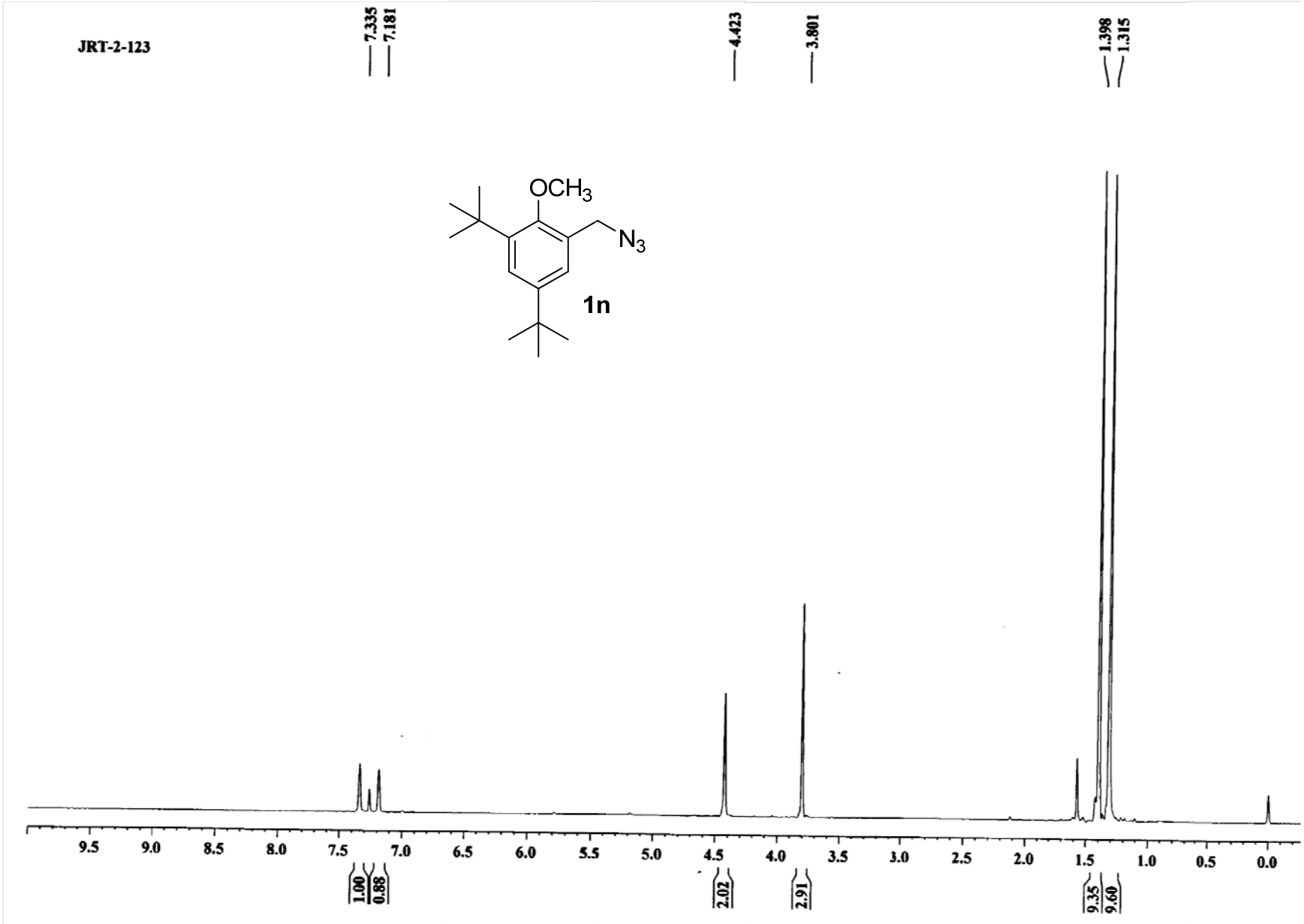


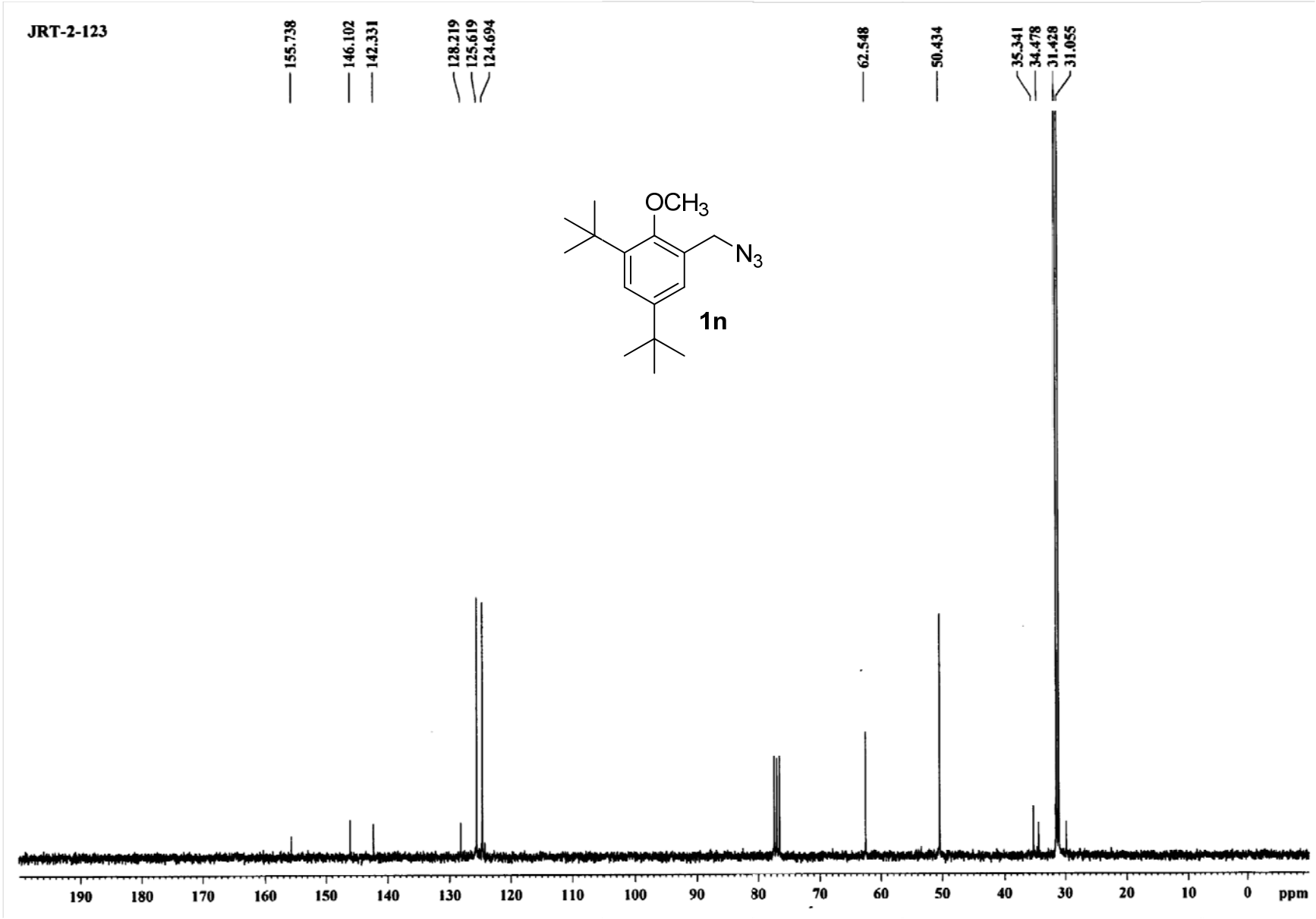






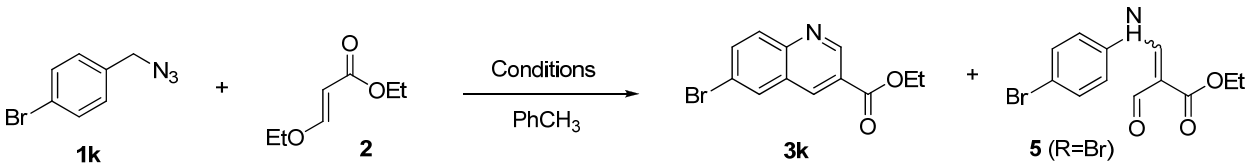






Optimizing for Method B

In optimizing for Method B, we used *p*-bromobenzyl azide as the substrate and varied several reaction variables to determine the ratio between the desired quinoline product and uncyclized by-product. In some cases, we obtained isolated yields of the desired quinoline as summarized in the table below.



entry	Equivalent of **1k**	Equivalent of **2**	Conditions	Note
1	1.0	2.0	1) TfOH (1.0 eq), rt 2) 50°C, MW, 1h 3) DDQ	Ratio (**3k**:**5**); 3:1
2	1.0	2.0	1) TfOH (1.0 eq), rt 2)))), 1h 3) DDQ	Ratio (**3k**:**5**); 3:1
3	1.0	2.0	1) TfOH (2.5 eq), 3 h, rt 2) DDQ	Ratio (**3k**:**5**); 2.3:1
4	1.0	2.0	1) TfOH (1.0 eq), rt 2) 90°C, MW, 1h 3) DDQ	Ratio (**3k**:**5**); 3.6:1
5	1.0	2.0	1) TfOH (1.0 eq), rt 2) $TiCl_4$ (1.0 eq), overnight 3) DDQ (1.0 eq)	Complex mixture
6	1.0	2.0	1) TfOH (1.0 eq), rt 2) $SnCl_4$ (1.0 eq), overnight 3) DDQ (1.0 eq)	Ratio (**3k**:**5**); 1:3
7	1.0	2.0	1) TfOH (1.0 eq), rt 2) BF_3•OEt_3 (2.0 eq), overnight	Only compound **3k** was obtained in 41%

8	1.1	1.0	1) TfOH (1.1 eq), rt, overnight 2) DDQ (1.0 eq)	Only compound **3k** was obtained in 14%
8	1.1	1.0	1) TfOH (1.1 eq), rt 2) BF_3•OEt_3 (1.0 eq), overnight	Only compound **3k** was obtained in 56%
9	1.1	1.0	1) TfOH (1.0 eq), rt 2) mixture of BF_3•OEt_3 (1.0 eq) and **2** (1.0 eq) in $PhCH_3$, overnight	Complex mixture
10	1.1	1.0	1) TfOH (1.0 eq), rt 2) mixture of BF_3•OEt_3 (1.0 eq) and **2** (1.0 eq) in $PhCH_3$, 3 h	Complex mixture
11	1.1	1.0	1) TfOH (1.1 eq), rt 2) BF_3•OEt_3 (1.0 eq), overnight 3x dilution compared to entry 8	Complex mixture