Supporting Information

Metal-Free Transannulation Reaction of Indoles with Nitrostyrenes: A Simple Practical Synthesis of 3-Substituted 2-Quinolones

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General information

Reagents, solvents and catalysts were purchased from commercial sources (Acros Organics or Sigma-Aldrich) and used as received. The reaction vessels were washed and oven-dried without special precautions. The materials were handled and reactions were performed in vessels open to the atmosphere. The reaction progress was monitored by thin layer chromatography using pre-coated glass-supported TLC plates Silica gel 60 F254 (250 μm) (EMD Chemicals Inc.), visualized with UV light. Filtration of reaction mixtures was performed using a short pad of Silica gel (32-63 μm, 60 Å pore size). ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400 and Bruker DRX-500 spectrometers. Chemical shifts (δ) are reported in ppm relative to the TMS internal standard. Multiplet types are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). IR spectra were recorded on Specord 75 IR in KBr. Nitroalkenes **2c**, **2d**, **2f**, **2l** compounds were synthesized using standard procedure.[1] Elemental analyses (EA) were performed on CHN-1 analyzer (KOVO).

Synthesis of 2-Quinolones from Indoles

General procedure: The mixture of indole (1.0 mmol), 2-nitrostyrene (1.2 mmol) and 80% PPA (2-3 g) was stirred at 80-85 ^{o}C for 30 min. Indole consumption was monitored by TLC. After indole reacted completely, the temperature was increased to 95-100 ^{o}C and the reaction mixture was stirred for 3 h. Then, the mixture was cooled down to room temperature, poured in water (50 mL) and neutralized by aqueous ammonia solution to pH~8. Aqueous phase was extracted twice with chloroform and combined organic layers were filtered through a short pad of Silica gel. The filtrate was concentrated in vacuum, and the residue was purified by recrystallization.

3-Phenylquinolin-2(1*H*)-one (5aa): Colorless solid, mp 234-235°C (dichloromethane/ethanol), (lit. mp 235 °C).[2] The NMR spectral data are consistent with published results.[3] IR: 3456, 1647 cm^{-1}.

3-(4-Methoxy-phenyl)quinolin-2(1*H*)-one (5ab): Colorless solid, mp 259-261°C (dichloromethane/ethanol). The NMR spectral data are consistent with published results.[4] IR: 3480, 1661 cm^{-1}.

(1) (a) Worral, D.E. *J. Am. Chem. Soc*., **1938**, *60*, 2841. (b) Rosenmund, K. W. *Ber*., **1909**, *42*, 4778. (c) Eltsov, A. B. *Russ. J. Gen. Chem.*, **1962**, *32*, 1525. (c) Schmidt, E.; Rutz, G. *Ber*. **1928**, *61*, 2142.
(2) Katsuhiko, H. *Chem. Pharm. Bull.*, **1987**, *35*, 2819.
(3) Pailer, M. *Monatsh. Chem*., **1965**, *96,* 1695.
(4) Manley, P.J.; Bilodeau, M.T. *Org. Lett.,* **2004**, *6*, 2433.

3-(4-*i*-Propylphenyl)quinolin-2(1*H*)-one (5ac): Colorless solid, mp 220-221 °C (dichloromethane/ethanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ, ppm: 11.46 (br. s, 1H), 7.92 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.50 (ddd, *J* = 7.8, 7.7, 1.1 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.21 (dd, *J* = 8.7, 7.8 Hz, 1H), 3.02-2.94 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 162.5, 148.5, 137.4, 137.3,133.0, 131.9, 129.6, 128.3, 127.2, 125.9, 122.1, 119.9, 114.9, 33.5, 23.4 (2C); IR: 3445, 1652 cm^{-1}; EA: Calcd for $C_{18}H_{17}NO$: C 82.10, H 6.51, N 5.32. Found: C 82.21, H 6.46, N 5.27.

3-(3,4-Dimethyl)quinolin-2(1*H*)-one (5ad): Colorless solid, mp 252-253 °C (dichloromethane/ ethanol). ^{1}H NMR (500 MHZ, $CDCl_3$) δ, ppm: 11.71 (br. s, 1H), 7.87 (s, 1H), 7.59-7.58 (m, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.46 (dd, *J* = 7.7, 7.6 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 8.2, 7.7 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 163.3, 138.0, 137.9, 136.9, 136.5, 133.9, 132.8, 130.2, 130.1, 129.7, 127.8, 126.5, 122.6, 120.8, 115.6, 20.6, 19.8. IR: 3442, 1656 cm^{-1}; EA: Calcd for $C_{17}H_{15}NO$: C 81.90, H 6.06, N 5.62; Found: C 82.04, H 6.01, N 5.56.

3-(3,4-dimethoxy)quinolin-2(1*H*)-one (5ae): Colorless solid, mp 209-210°C (dichloromethane/ethanol), (lit. mp 211°C).[3] The NMR spectral data are consistent with published results.[8] IR: 3462, 1651 cm^{-1}.

3-(4-Ethoxy-phenyl) quinolin-2(1*H*)-one (5af): Colorless solid, mp 215-217 °C (dichloromethane/ethanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ, ppm: 11.37 (br. s, 1H), 7.87 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H) 7.47 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.21 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 163.2, 159.3, 137.8, 137.3, 132.2, 130.2, 130.0, 128.5, 127.8, 122.7, 120.7, 115.4, 114.5, 63.6, 15.0. IR: 3455, 1648 cm^{-1}. EA: Calcd for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28. Found: C 77.19, H 5.61, N 5.23.

3-(2-Fluoro-phenyl)quinolin-2(1*H*)-one (5ag): Colorless solid, mp 233-235°C (dichloromethane/ethanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ, ppm: 11.50 (br. s, 1H), 7.92 (s, 1H), 7.63 (ddd, *J* = 9.3, 7.5, 1.7 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.50 (ddd, *J* = 7.8, 7.7, 1.3 Hz, 1H), 7.42-7.37 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.28-7.18 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 162.5, 160.5 (d, $^{1}J_{CF}$ = 248 Hz), 140.9 (d, J_{CF} = 2.5 Hz), 138.4, 131.9 (d, J_{CF} = 2.5 Hz), 130.8, 130.1, 128.1 (2C), 127.8, 124.1 (d, J_{CF} = 3.8 Hz), 122.9, 120.0, 116.0 (d, J_{CF} = 22.5 Hz), 115.8; IR: 3502, 1650 cm^{-1}. EA: Calcd for $C_{15}H_{10}NFO$: C 75.30, H 4.21, N 5.85. Found: C 75.48, H 4.16, N 5.78.

3-(3-Fluoro-phenyl)quinolin-2(1*H*)-one (5ah): Colorless solid, mp 220-221 °C (dichloromethane/ethanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ, ppm: 12.22 (br. s, 1H), 7.95 (s, 1H), 7.65-7.57 (m, 3H), 7.52 (dt, *J* = 7.7, 0.8 Hz, 1H), 7.48-7.39 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.12 (ddd, *J* = 8.4, 8.3, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 163.1,

162.8 (d, $^{1}J_{CF}$ = 240 Hz), 139.1, 138.3, 131.1 130.9, 129.8 (d, J_{CF} = 8.8 Hz), 128.1, 124.6 (d, J_{CF} = 2.5 Hz), 123.0, 120.3, 116.2 (d, J_{CF} = 22.5 Hz), 115.8, 115.3, 115.1; IR: 3495, 1648 cm^{-1}; EA: Calcd for $C_{15}H_{10}NFO$: C 75.30, H 4.21, N 5.85. Found: C 75.46, H 4.17, N, 5.74.

3-(4-Fluoro-phenyl)quinolin-2(1*H*)-one (5ai): Colorless solid, mp 246-248 °C (dichloromethane/ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 11.97 (br. s, 1H), 8.11 (s, 1H), 7.85-7.81 (m, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.50 (dd, J = 7.7 and 7.6 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.28-7.17 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ, ppm: 161.9 (d, $^{1}J_{CF}$ = 244 Hz), 161.0, 138.4, 137.6, 132.6 (d, J_{CF} = 3.0 Hz), 130.8 (d, J_{CF} = 8.0 Hz), 130.4 (2C), 130.3, 128.3, 122.0, 119.5, 114.8 (d, J_{CF} = 22.0 Hz, 2C), 114.7; IR: 3588, 1651 cm^{-1}; EA: Calcd for $C_{15}H_{10}NFO$: C 75.30, H 4.21, N 5.85. Found: C 75.42, H 4.17, N 5.73.

3-(3,4-dichloro-phenyl)quinolin-2(1*H*)-one (5aj): Colorless solid, mp 298-299 °C (dichloromethane/ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 12.06 (bs, 1H), 8.27 (s, 1H), 8.11 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 8.4, 2.0 Hz, 1H), 7.74 (d, J = 7.8, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 7.7, 7.6 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.21 (dd, J = 8.2, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ, ppm: 160.7, 138.7, 138.6, 136.8, 130.8, 130.6, 130.4, 130.3, 130.1, 128.8, 128.5, 128.4, 122.1, 119.3 114.8; IR: 3495, 1648 cm^{-1}; EA: Calcd for $C_{15}H_9Cl_2NO$: C 62.09, H 3.13, N 4.83. Found: C 62.28, H 3.07, N 4.72.

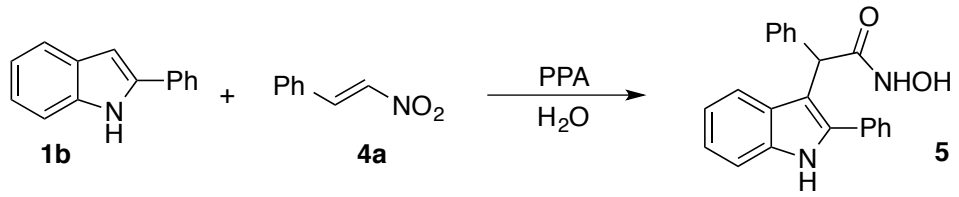
3-(3-Bromo-phenyl)quinolin-2(1*H*)-one (5ak): Colorless solid, mp 211-212 °C (dichloromethane/ethanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ, ppm: 11.35 (bs, 1H), 7.96 (bs, 1 H), 7.92 (s, 1H), 7.75 (d, J = 7.71 Hz, 1H), 7.62 (d, J = 7.79 Hz, 1H), 7.55-7.51 (m, 2H), 7.36-7.33 (m, 2H), 7.24 (t, J = 7.71 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 162.6, 139.0, 138.3, 138.2, 131.9, 131.3, 131.1, 130.9, 129.9, 128.2, 127.7, 123.0, 122.5, 120.3 115.6. IR: 3485, 1648 cm^{-1}. EA: Calcd for $C_{15}H_{10}BrNO$: C 60.02, H 3.36, N 4.67. Found: C 60.16, H 3.29, N, 4.59.

3-*n*-Propilquinolin-2(1*H*)-one (5al): Colorless solid, mp 142-143 °C (hexane/ethyl acetate) (lit. mp. 142-143 °C).[5] NMR spectral data are consistent with published results.[5] IR: 3455, 1655 cm^{-1}.

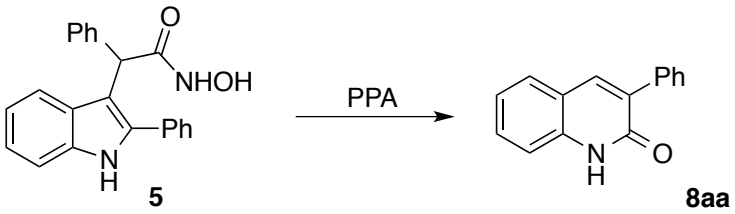
1-Methyl-3-phenylquinolin-2(1H)-one (5ca): Colorless solid, mp 140-142°C (ligroin) (lit. mp 140-142 °C)[14]. The NMR and IR spectral data are consistent with published results.[5,6,7]

(5) Park, K. K.; Jung, J. Y. *Heterocycles*, **2005**, *65(9),* 2095.
(6) Kaslow, C.E. *J. Org. Chem*. **1958**, *23*, 271.
(7) Ahlbrecht, H.; Vonderheid, C. *Ber*. **1975**, *108*, 2300.

Experiments on Isolation of Intermediate Hydroxamic Acid and its Further Conversion into 2-Quinolone

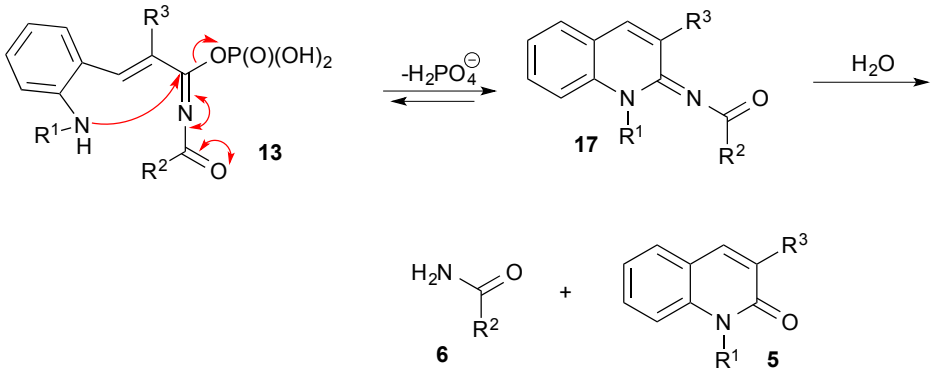


***N*-Hydroxy-2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)acetamide** (**3**): Mixture of 2-phenylindole (**1b**) (1.0 mmol, 193 mg), β-nitrostyrene (**2a**) (1.2 mmol, 179 mg) and PPA (4 g) was stirred at 70-75° for 30 min. The reaction mixture was cooled down to room tempereature, poored into water (50 ml), and neutralized by aqueous ammonia to pH~8. Formed precipitate was filtered off and recrystallized from benzene/petroleum ether mixture to afford pale yellow crystals, mp 220-221 °C. Yield 328 mg (0.96 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ, ppm: 11.30 (br. s, 1H), 10.75 (br. s, 1H), 8.81 (br. s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.54-7.48 (m, 4H), 7.41 (dd, *J* = 7.2, 7.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.27-7.16 (m, 5H), 7.06 (dd, *J* = 7.6, 7.4 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 5.10 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 168.6, 140.7, 136.2, 132.5, 128.6, 128.5, 128.0, 127.9, 127.7, 127.6, 126.1, 122.3, 121.1, 118.5, 110.9, 109.2, 46.0; EA: Calcd for $C_{22}H_{18}N_2O_2$: C 77.17, H 5.30, N 8.18. Found: C 77.33, H 5.22, N 8.11.



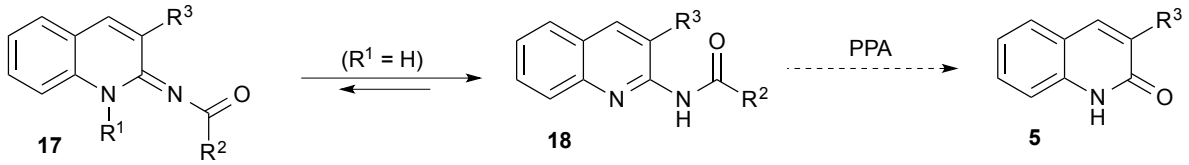
Hydroxamic acid **5** obtained as described above (239 mg, 0.7 mmol) was stirred in PPA at 95-100 ^{0}C for 5 h. The mixture was cooled down, poured into water (50 ml), and neutralized with aqueous ammonia to pH~8. The aqueous mixture was extracted with chloroform (2 x 50 mL) and combined organic phases were filtered through a short pad of Silica gel (32-63 μm, 60 Å pore size). Filtrate was concentrated in vacuum to afford a sample of quinolone **8aa** identical to the material described above. Yield 141 mg (0.64 mmol, 91%).

Ruling out an Alternative End-Game in the Mechanistic Rationale



Scheme 1

An alternative mechanistic end-game could be envisioned involving intramolecular nucleophilic attack by aniline moiety to iminium sp^2-carbon followed by displacement of phosphate leaving group. This would lead to the formation of acyliminium intermediate **17**, which upon aqueous quench would afford target structure **5** and amide byproduct **6** (Scheme 1). However, if this mechanism is operating compound **17** possessing R^1 = H would quickly undergo aromatization into thermodynamically more stable acylamino-quinoline **18** (Scheme 2). To afford the final 2-quinolone product in this case PPA assisted hydrolysis of **18** should be carried out under typical reaction and post-reaction work up conditions.



Scheme 2

In order to evaluate this possibility the following experiments were performed.

1) A mixture of 2-acetaminoquinoline (186 mg, 1 mmol) was heated at 110 ^oC in 80% PPA (3 mL) for 6 hr, then cooled down to room temperature, poured into water (25 mL) and neutralized with aqueous ammonia. The mixture was extracted with dichloromethane (3 x 25 mL), combined organic phases were concentrated to recover starting 2-acetaminoquinoline in quantitative yield.

2) A mixture of 2-acetaminoquinoline (186 mg, 1 mmol), 2-methylindole **1a** (131 mg, 1 mmol) and β-nitrostyrene **2a** (179 mg, 1.2 mmol) was heated at 110 ^{o}C in 80% PPA (3 mL) for 6 hr, then cooled down to room temperature, poured into water (25 mL) and neutralized with aqueous ammonia. The mixture was extracted with dichloromethane (3 x 25 mL), combined organic phases were concentrated to afford crude oily residue. 2-acetaminoquinoline in quantitative yield. LC/MS analysis of this material demonstrated two major components: 2-quinolone **5aa** (formed from 2-methylindole and β-nitrostyrene) and unreacted 2-.

These experiments demonstrated that direct conversion of acetaminoquinolines into 2-quinolones is impossible under our reaction conditions, which ruled out the discussed above mechanistic hypothesis, involving 2-acylaminoquinolines as end-game intermediates.

Three-Component Coupling en route to 2-Quinolones

General procedure: The mixture of arylhydrozone (1.0 mmol), acetophenone (1.0 mmol), and 2-3 g of PPA was stirred at 100-110 ^{o}C for 40 min. Consumption of starting arylhydrozine was monitored by TLC. Then the temperature was decreased to 80-85^{o}C and 1.2 mmol of corresponded 2-nitrostyrol was added. The mixture was heated during 30 min. The disappearing of intermediate indole was monitored by TLC. After indole reacted completely, the temperature was increased to 95-100 ^{o}C and the reaction mixture was heated for 3 h. The mixture was cooled to room temperature, poured in water (50 mL) and neutralized by ammonia solution. Organic part was extracted two times by chloroform and filtrated through silica gel. The solvent was removed. The compound was purified by recrystallization.

6-Methyl-3-phenylquinolin-2(1H)-one (5da)

White solid, mp 218-219 °C (ethanol) (lit. mp 218-219 °C)[8]. NMR spectral data are consistent with published results.[8] IR: 3450, 1660 cm^{-1}.

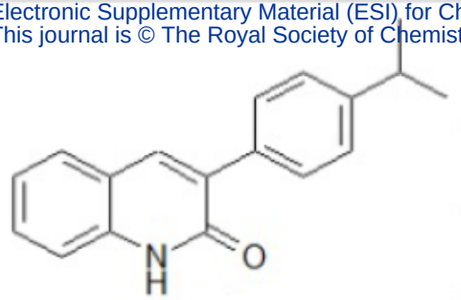
6-Methoxy-3-phenyl(1H)quinolin-2(1H)-one (5ea)

Pale yellow solid, mp 248-249 °C (chloroform/ethyl acetate) (lit. mp 248-249 °C)[9]. NMR spectral data are consistent with published results.[4] IR: 3445, 1642 cm^{-1}.

6-Chloro-3-phenylquinolin-2(1H)-one (5fa)

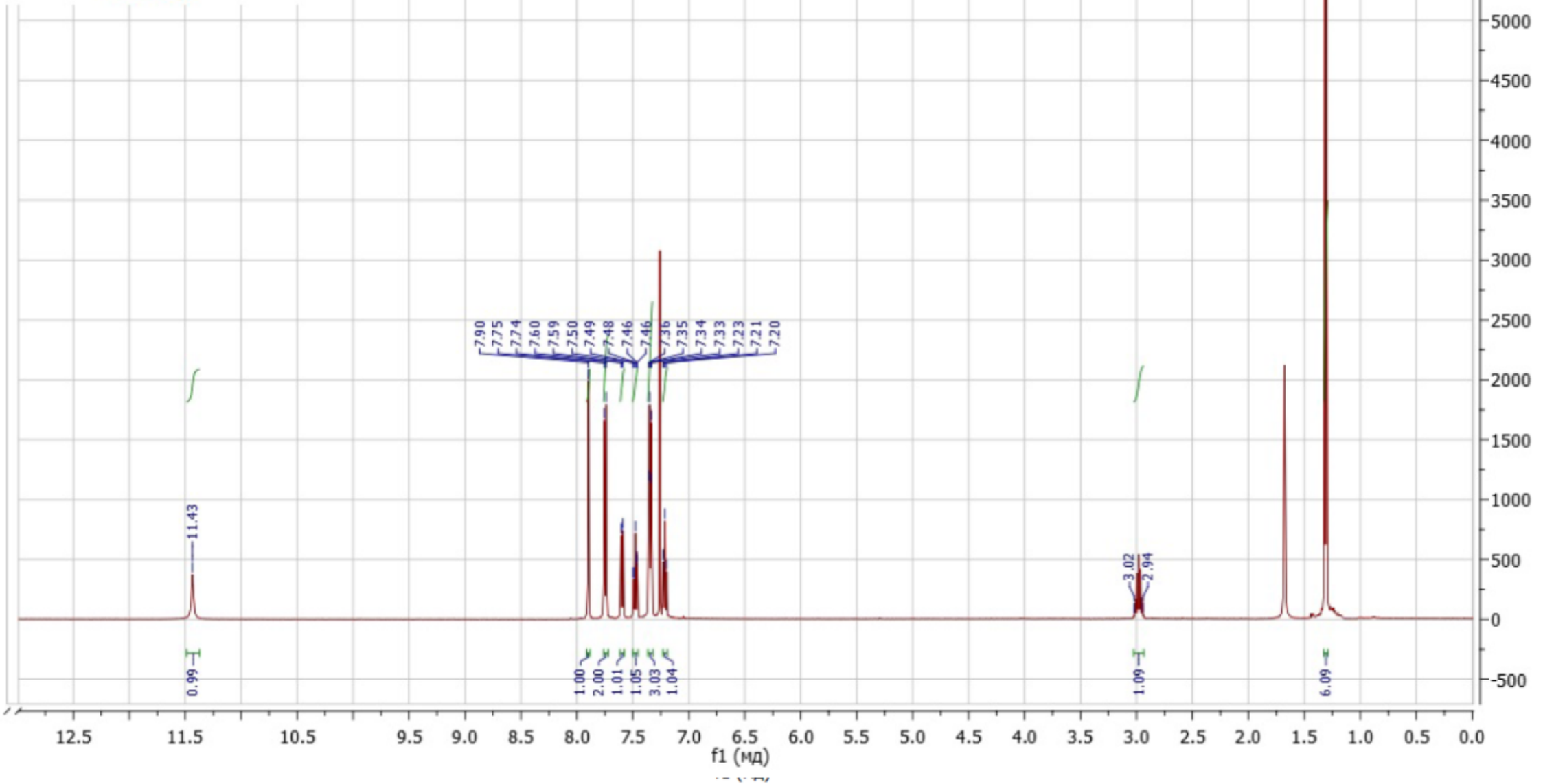
Colorless solid, mp 249-250 °C (hexane/ethyl acetate) (lit. mp 249-250 °C)[5]. NMR spectral data are consistent with published results.[5] IR: 3455, 1650 cm^{-1}.

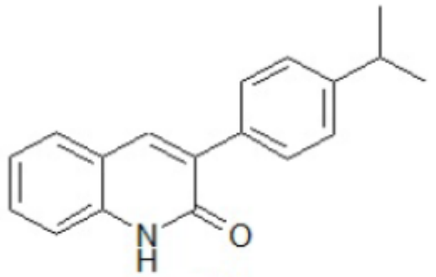
(8) Eicher, T.; Schneider, V. *Synthesis*, **1989**, 372.
(9) Fu, L. *Synthesis*, **2011**, 1547.



5ac

^{1}H NMR - $CDCl_3$
500 MHz

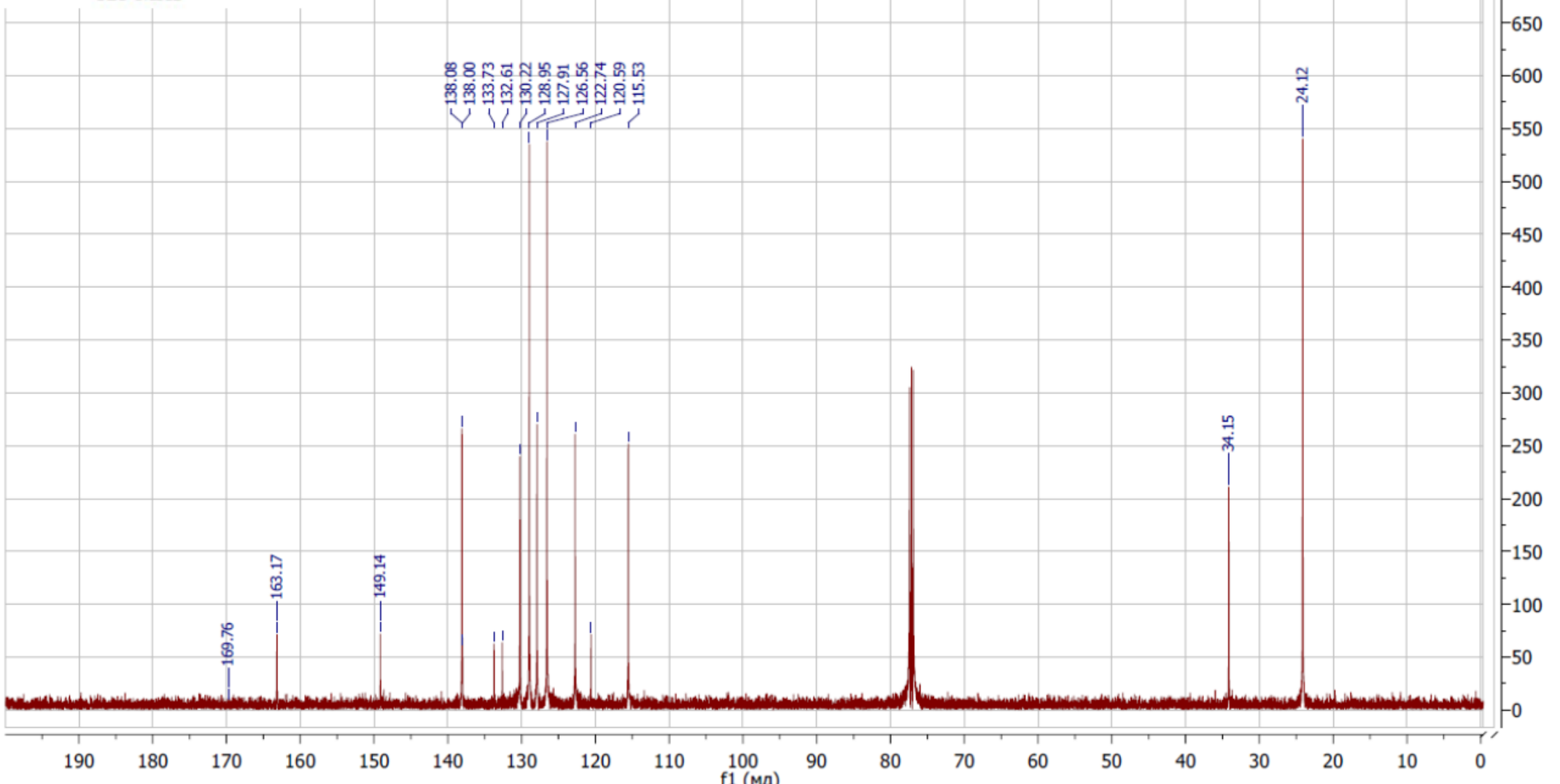


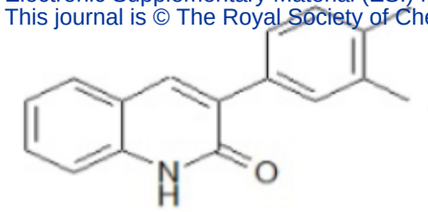


5ac

^{13}C NMR - $CDCl_3$

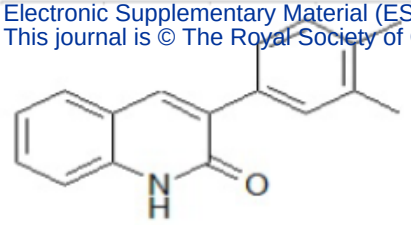
125 MHz





5ad

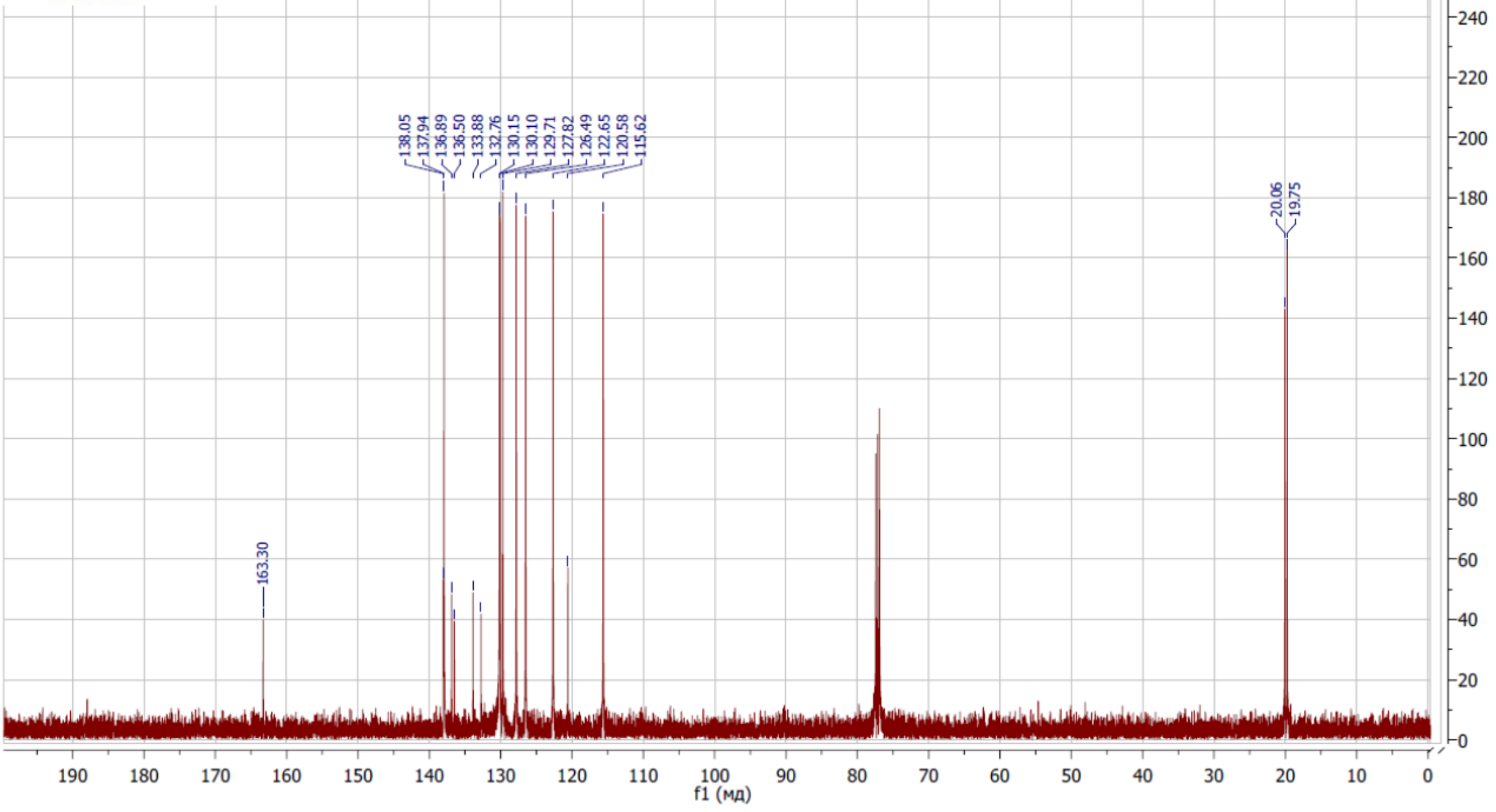
^{1}H NMR - $CDCl_3$
500 MHz



5ad

^{13}C NMR - $CDCl_3$

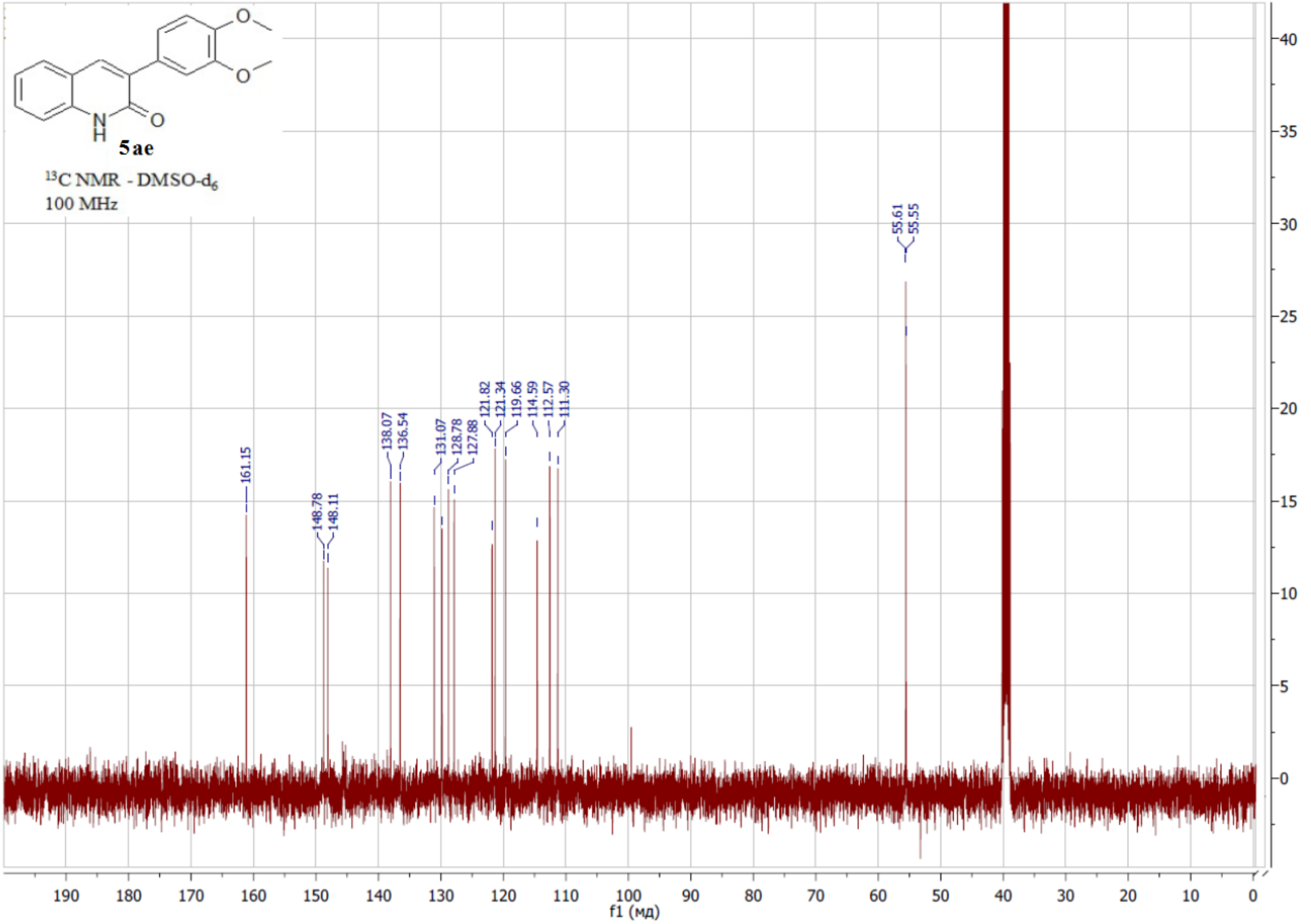
125 MHz

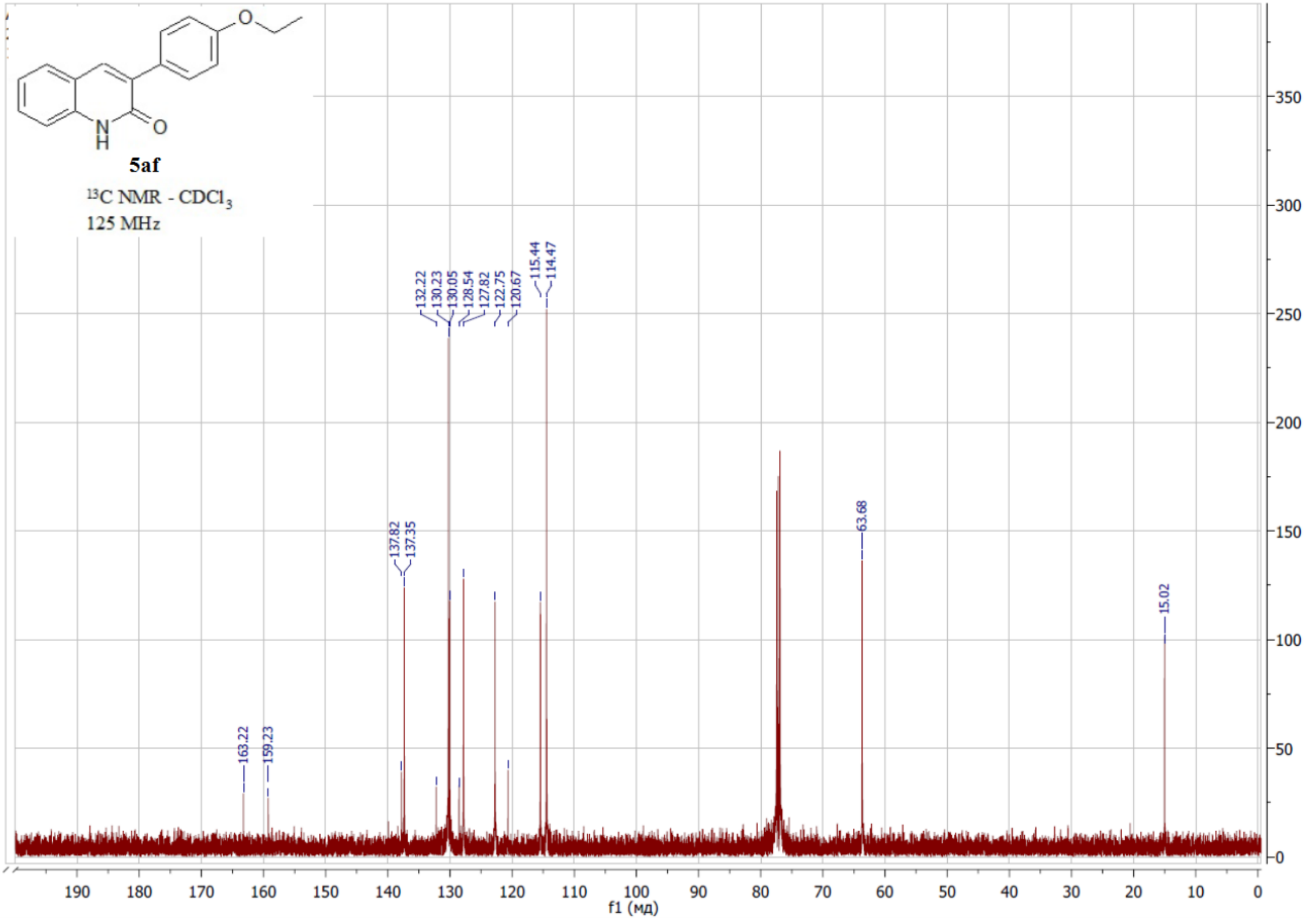


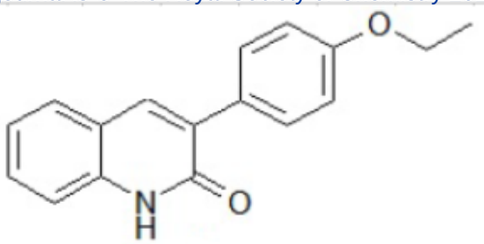
8ae

^{1}H NMR - DMSO-d_6

400 MHz



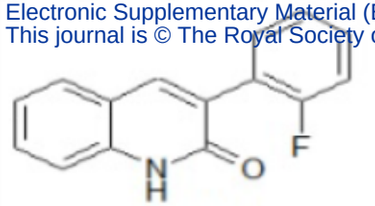




5af

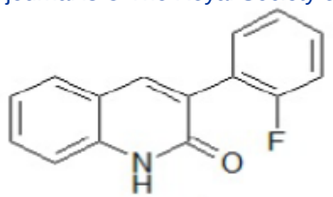
^{1}H NMR - $CDCl_3$

500 MHz



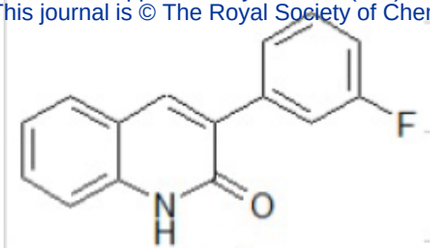
5ag

^{1}H NMR - $CDCl_3$
500 MHz



5ag

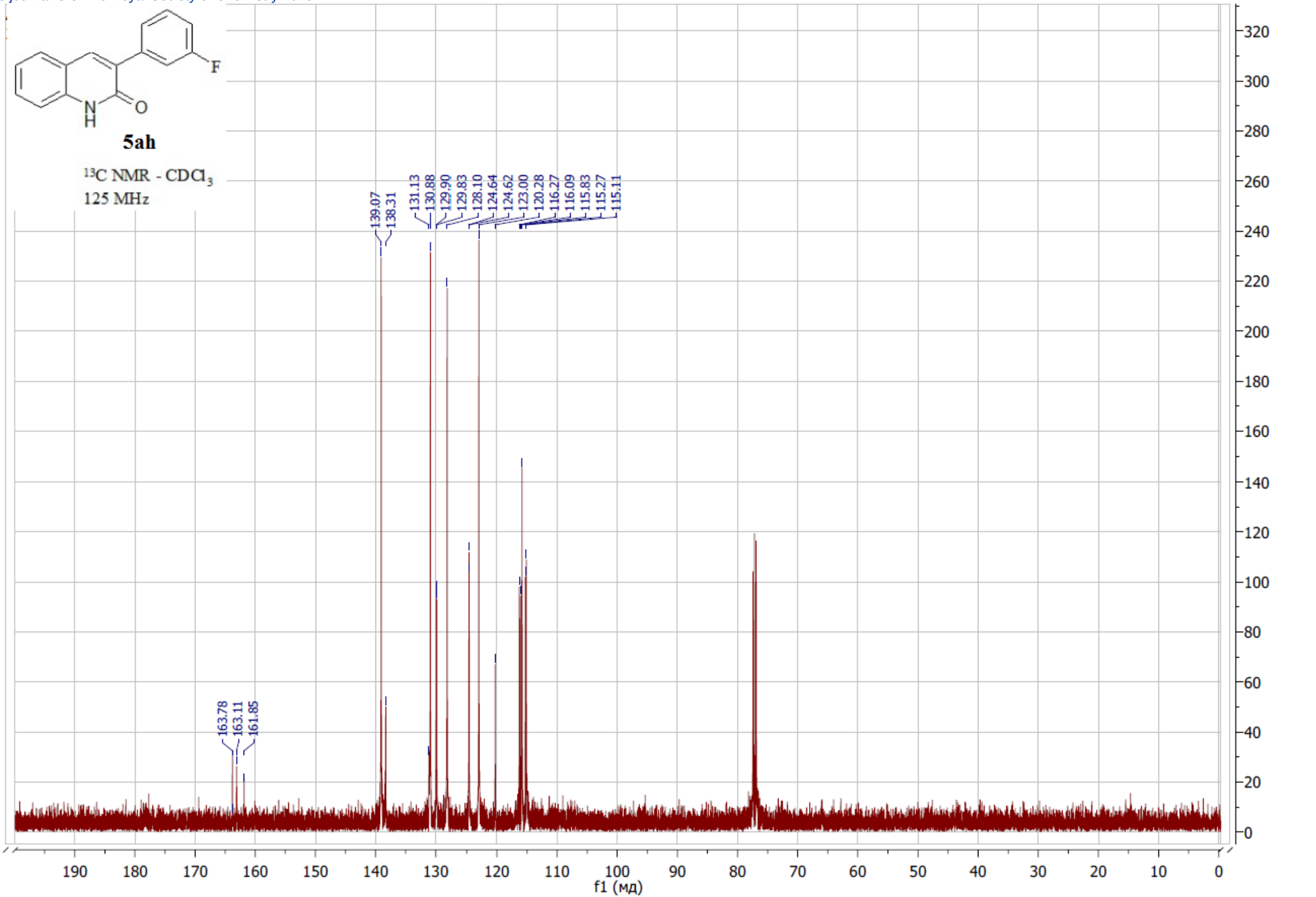
^{13}C NMR - $CDCl_3$
125 MHz

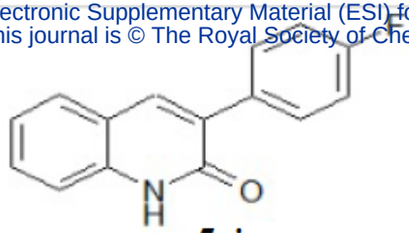


5ah

^{1}H NMR - $CDCl_3$

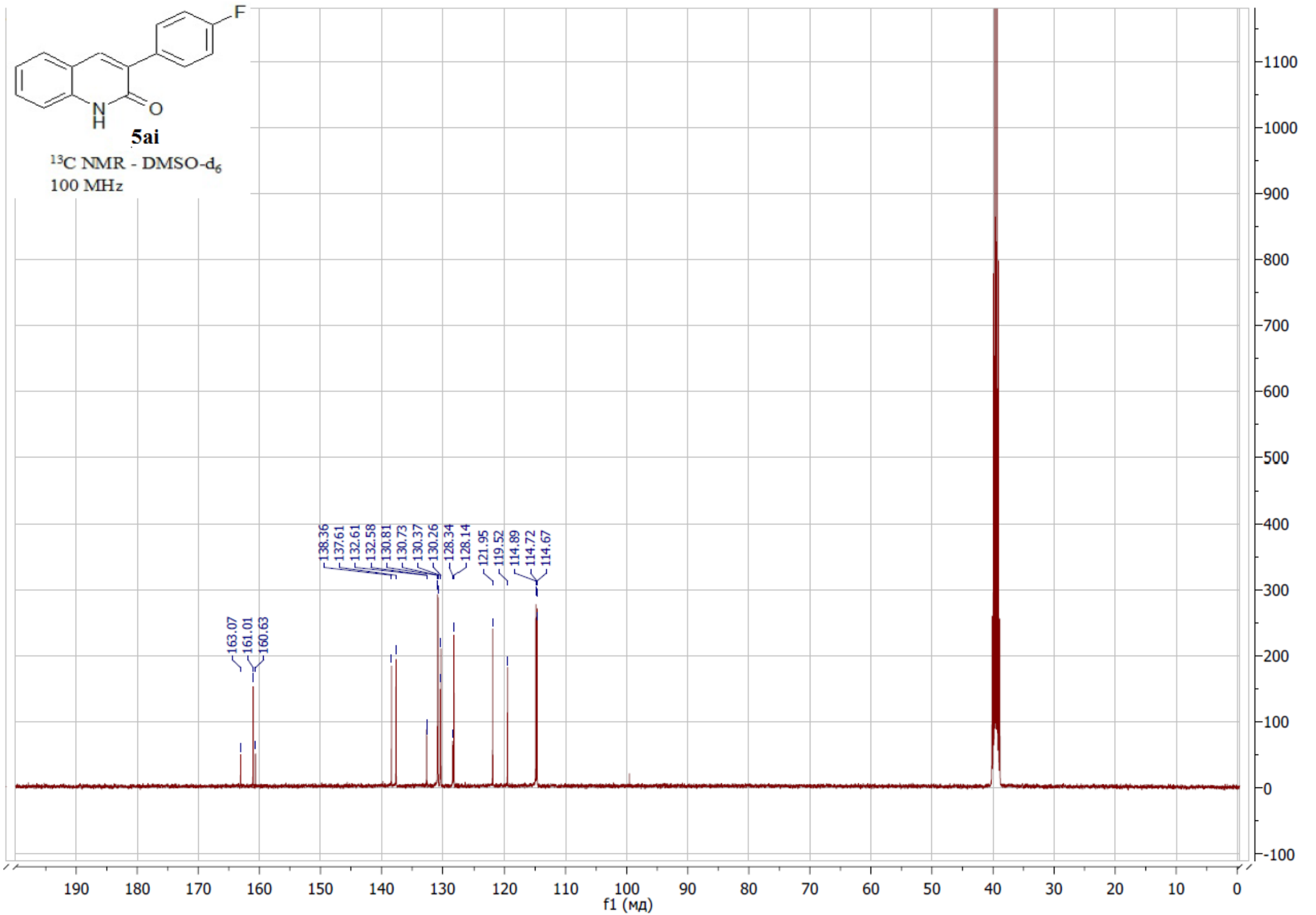
500 MHz

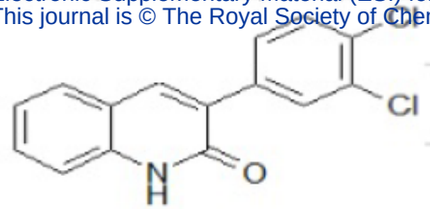




5ai

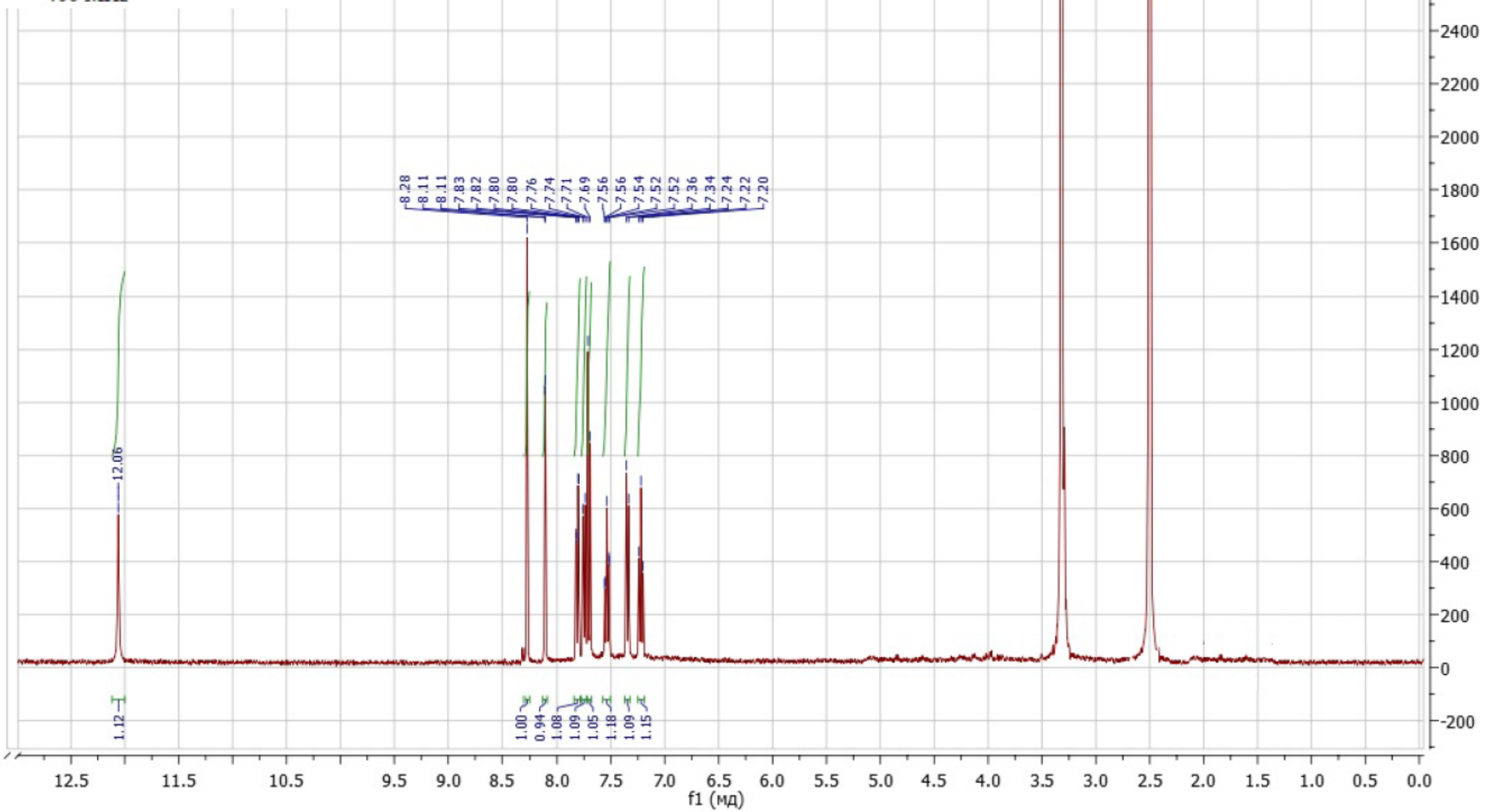
^{1}H NMR - DMSO-d_6
400 MHz

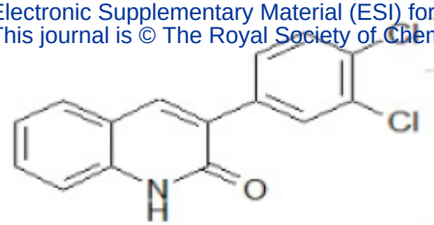




5aj

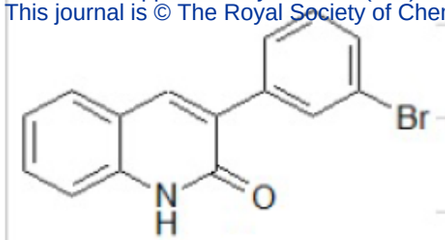
^{1}H NMR - DMSO-d_6
400 MHz





5aj

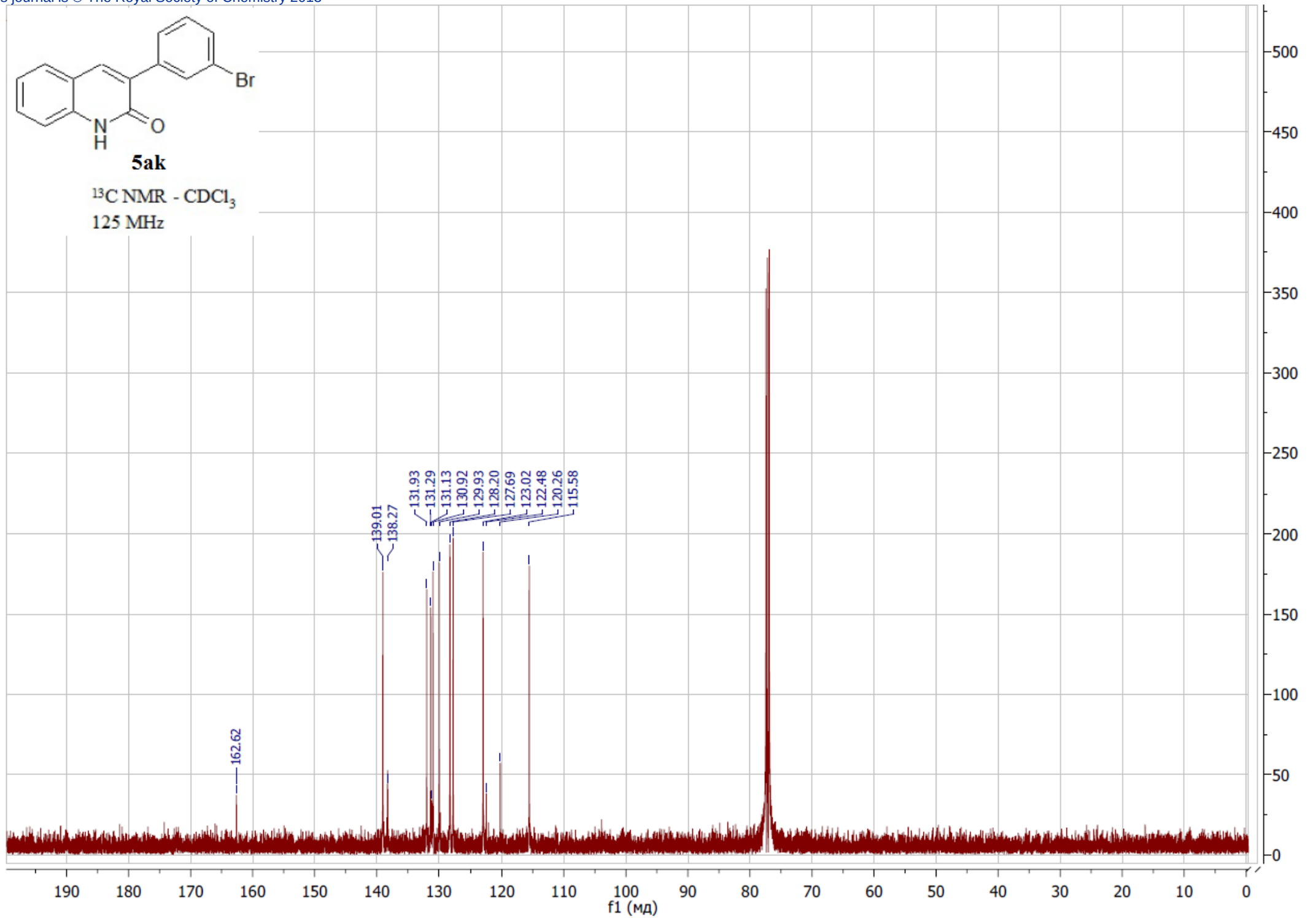
^{13}C NMR - DMSO-d_6
100 MHz

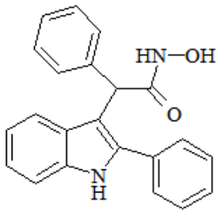


8ak

^{1}H NMR - $CDCl_3$

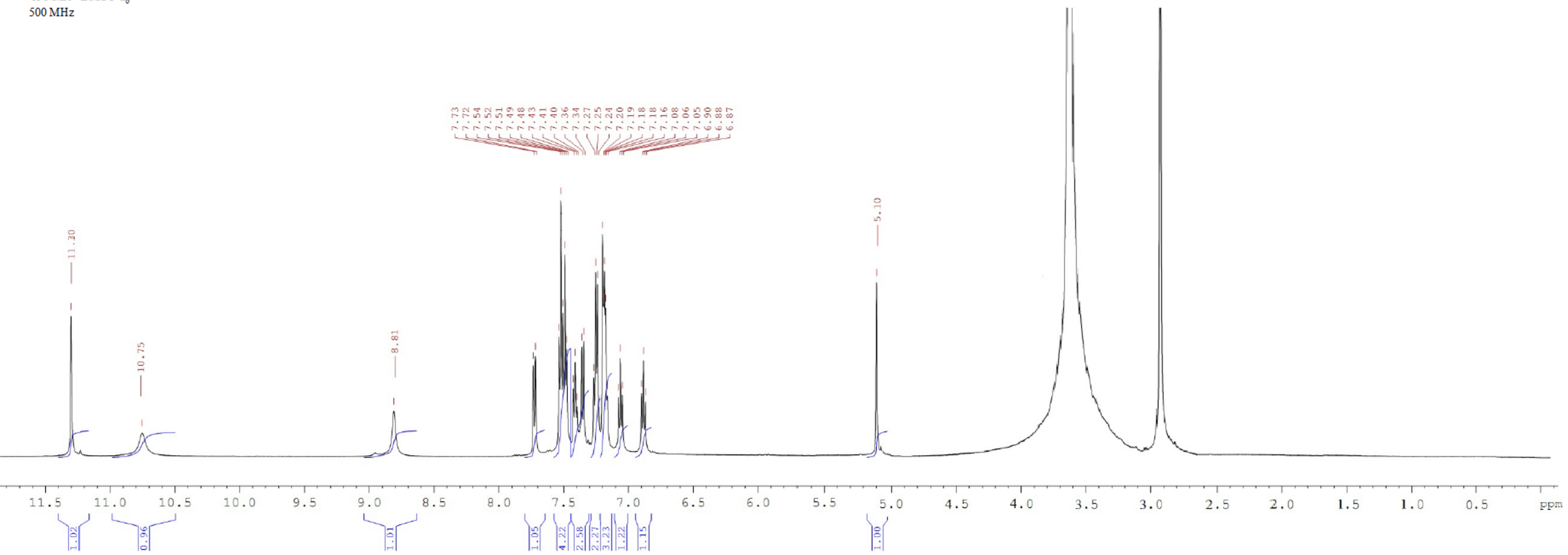
500 MHz

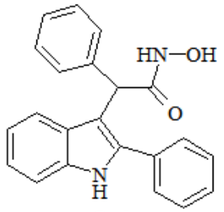




3ab

^{1}H NMR - DMSO-d_6
500 MHz





3ab

^{13}C NMR - DMSO-d_6
125 MHz