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Palladium-Catalyzed Domino Heck / Intermolecular Cross-Coupling: Efficient Synthesis of 4-Alkylated Isoquinoline Derivatives

Tuanli Yao,*, Tao Liu and Changhui Zhang

College of Chemistry and Chemical Engineering, Shaanxi University of Science and Technology, 6 Xuefu Road, Weiyang District, Xi'an, Shaanxi, 710021, China

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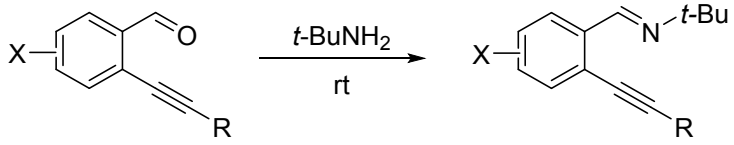
General Information:

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer (operatingat 400 and 101 MHz respectively) in $CDCl_3$ (residual internal standard $CHCl_3$= δ 7.26), DMSO-d6 (residual internal standard CD_3SOCD_2H = δ 2.50). HPLC/MS analysis was carried out with gradient elution (5% CH_3CN to 100% CH_3CN) on an Agilent 1200 RRLC with a photodiode array UV detector and an Agilent 6224 TOF mass spectrometer (also used to produce high resolution mass spectra). Melting points were determined on a Stanford

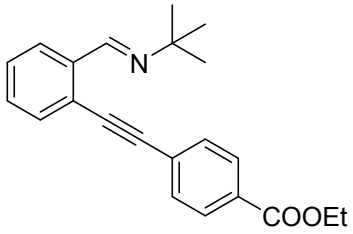
Research Systems OptiMelt apparatus. The infrared (IR) spectra were acquired as thin films using a universal ATR sampling accessory on a Bruker Vertex 80 FT-IR spectrometer and the absorption frequencies are reported in cm^{-1}. Flash chromatography separations were carried out using silica gel columns. The new compounds were characterized by ^{1}H NMR,^{13}C NMR, HRMS and IR. The structure of known compounds were further confirmed by comparing their ^{1}H NMR and ^{13}C NMR data with those of literature. All reagents and solvents were used as received from commercial sources without further purification. Compounds **1a**,[1] **1o**,[2] **1p**,[1] **1q**, [2] **1r**,[3] **1s**,[1] **1t**,[1] **1u**,[4] **1v**,[1] **1w**,[5] **1x**,[4] **2a**,[6] **2b**,[7] **2c**,[6] **2d**,[7] **2e**,[8] **2f**,[8] **2g**,[6] **2h**,[6] **2i**,[8] **2j**,[8] **2k**,[7] **2l**,[8] **2m**,[9] **2n**[6] were prepared by following literature procedure.

Experimental Procedures

General Procedure for Preparation of Imine 1.[8]

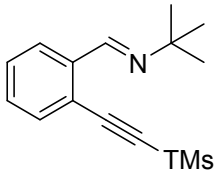


A mixture of the aldehyde (0.6 mmol) and *t*-$BuNH_2$ (20 equiv) was stirred at room temperature for 20 h. The progress of the reaction was monitored by NMR. The completed reaction was diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure afforded desired imine, which was used without further purification.



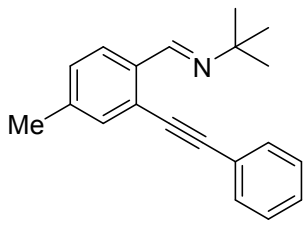
1e

Ethyl (E)-4-((2-((*tert*-butylimino)methyl)phenyl)ethynyl)benzoate (1e). This product was obtained as yellow oil (0.1778 g, 89%). ^{1}H NMR (400 MHz, DMSO) δ 8.84 (s, 1H), 8.05 – 7.96 (m, 3H), 7.75 – 7.68 (m, 2H), 7.68 – 7.63 (m, 1H), 7.55 – 7.47 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 165.1, 152.7, 137.2, 132.5, 131.6, 130.4, 129.9, 129.5, 126.6, 125.8, 122.3, 93.9, 89.2, 61.0, 57.7, 29.5, 14.1 (one carbon missing due to overlap); IR (neat) 1647, 1524, 1369, 1319 cm^{-1} ; HRMS calcd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1802, found 334.1809.



1i

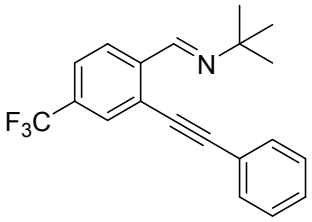
(*E*)-*N*-*tert*-Butyl-1-(2-((trimethylsilyl)ethynyl)phenyl)methanimine (1i). This product was obtained as a brown oil (0.1266 g, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.06 – 7.98 (m, 1H), 7.45 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.36-7.25 (m, 2H), 1.29 (s, 9H), 0.25 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 138.4, 132.5, 129.8, 129.0, 126.0, 123.9, 102.4, 100.3, 58.0, 29.9, 0.2; IR (neat) 1592,1387, 1351cm^{-1} ; HRMS calcd for $C_{16}H_{24}NSi$ $[M+H]^+$: 258.1673, found 258.1675.



1j

(E)-*N*-*tert*-Butyl-1-(4-methyl-2-(phenylethynyl)phenyl)methanimine (1j). This product was obtained as a yellow solid (0.1454 g, 88%): mp 59-60 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.80 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.52

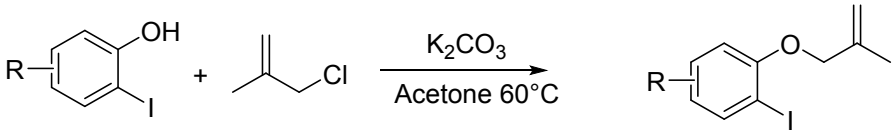
(m, 2H), 7.52 – 7.38 (m, 4H), 7.27 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H), 1.26 (d, *J* = 1.2 Hz, 9H); ^{13}C NMR (101 MHz, DMSO) δ 152.6, 140.2, 134.5, 132.4, 131.2, 129.9, 129.1, 128.9, 125.6, 122.9, 122.1, 94.5, 86.5, 57.5, 29.5, 20.7; IR (neat) 1649,1545, 1370, 1329 cm^{-1} ; HRMS calcd for $C_{20}H_{22}N$ $[M+H]^+$: 276.1747, found 276.1754.



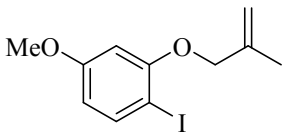
1l

(*E*)-*N*-*tert*-Butyl-1-(2-(phenylethynyl)-4-(trifluoromethyl)phenyl)methanimine (1l). This product was obtained as a yellow solid (0.1798 g, 91%): mp 65-66 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.86 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.66-7.55 (m, 2H), 7.54 – 7.43 (m, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 152.0, 140.3, 131.5, 130.5 (q, *J* = 32.3 Hz), 129.6, 129.0, 126.9, 125.5, 125.2(q, *J* = 4.0 Hz), 123.8, 122.3, 121.4, 96.4, 84.9, 58.2, 29.3; IR (neat) 1639, 1368, 1337, 1170, 1131cm^{-1} ; HRMS calcd for $C_{20}H_{19}F_3N$ $[M+H]^+$: 330.1464, found 330.1469.

General Procedure for Preparation of compound 2[2]

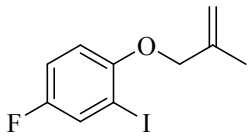


To a solution of 2-iodophenol (1.8 mmol) and oven-dried K_2CO_3 (3.0 equiv) in acetone (18 mL), 3-chloro-2-methylprop-1-ene (2.0 equiv) were added. The resulting mixture was stirred at 60 ℃ overnight. The reaction was concentrated in vacuo, diluted with brine and extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purification by column chromatography (Silica Gel, petroleum ether / EtOAc) to afford compound **2**.



2o

1-Iodo-4-methoxy-2-((2-methylallyl)oxy)benzene (2o). This product was obtained as a colorless oil (0.3936 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 1H), 6.39 (d, *J* = 2.7 Hz, 1H), 6.30 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.18 (dd, *J* = 1.4, 0.8 Hz, 1H), 5.05 – 4.97 (m, 1H), 4.43 (s, 2H), 3.76 (s, 3H), 1.85 (d, *J* = 0.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 158.0 140.3, 139.3, 113.2, 107.4, 100.5, 75.5, 72.6, 55.7, 19.7; IR (neat) 1590, 1480, 1353, 1200, 1167 cm^{-1}; HRMS calcd for $C_{11}H_{14}IO_2$ $[M+H]^+$: 305.0033, found 305.0029.

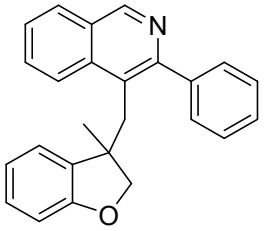


2q

4-Fluoro-2-iodo-1-((2-methylallyl)oxy)benzene (2q). This product was obtained as a yellow oil (0.2471 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.6, 3.0 Hz, 1H), 6.98 (ddd, *J* = 9.0, 7.8, 3.0 Hz, 1H), 6.71 (dd, *J* = 9.0, 4.6 Hz, 1H), 5.16 (s, 1H), 5.03 – 4.97 (m, 1H), 4.42 (s, 2H), 1.84 (d, *J* = 0.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (d, *J* = 244.4 Hz), 154.0 (d, *J* = 3.0 Hz), 140.3, 126.3 (d, *J* = 25.3 Hz), 115.7 (d, *J* = 22.2 Hz), 113.3, 112.6 (d, *J* = 8.1 Hz), 86.1 (d, *J* = 8.1 Hz), 73.5, 19.7; IR (neat) 1591, 1483, 1351, 1190 cm^{-1} ; HRMS calcd for $C_{10}H_{11}FIO$ $[M+H]^+$: 292.9833, found 292.9831.

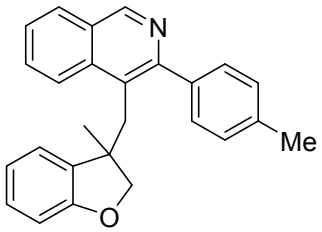
General procedure for the Synthesis of 4-Alkylated Isoquinoline Derivatives:

To a solution of aryl halides (0.2 mmol), $Pd(PPh_3)_4$ (0.05 equiv), and oven-dried K_2CO_3 (3.0 equiv) in DMF (5mL), imine (1.2 equiv) was added. The resulting reaction mixture was heated at 100 °C under argon for 6h. The reaction were monitored by TLC to establish completion. After cooling to room temperature, the reaction was diluted with ethyl acetate (35mL), washed with water (3×15mL) and brine (15mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (Silica Gel, petroleum ether / EtOAc) to afford product **3**.



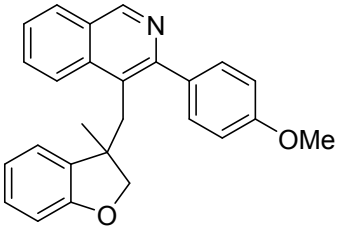
3a

4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3a). This product was obtained as a yellow solid (0.0461 g, 71%): mp 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.01 – 7.89 (m, 1H), 7.63 (s, 1H), 7.56-7.42 (m, 6H), 7.39 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.52 (s, 1H), 6.32 (s, 1H), 4.22 (d, *J* = 8.7 Hz, 1H), 3.82 (d, *J* = 8.6 Hz, 1H), 3.74-3.62 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 153.9, 150.6, 141.8, 137.1, 134.7, 130.4, 130.1, 128.6, 128.3, 128.1, 127.9, 127.3, 126.7, 125.0, 124.3, 123.5, 120.6, 109.9, 83.2, 48.0, 36.3, 24.2; IR (neat) 1677, 1592, 1478, 1351, 973, 752, 704 cm^{-1} ; HRMS calcd for $C_{25}H_{22}NO$ $[M+H]^+$: 352.1696, 352.1701.



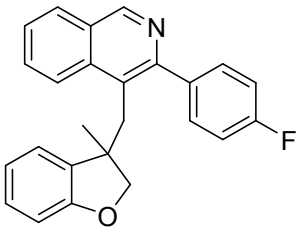
3b

4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-(p-tolyl)isoquinoline (3b). This product was obtained as a white solid (0.0562 g, 77%): mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.97 – 7.87 (m, 1H), 7.60 (s, 1H), 7.53 – 7.37 (m, 4H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.99 (td, *J* = 7.9, 1.2 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 6.33 (d, *J* = 5.6 Hz, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 3.82 (d, *J* = 8.6 Hz, 1H), 3.74-3.63 (m, 2H), 2.42 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 153.7, 150.4, 138.6, 137.7, 137.3, 134.8, 130.24, 130.17, 129.4, 128.3, 128.2, 127.2, 126.7, 125.1, 124.3, 123.6, 120.6, 109.9, 83.3, 48.0, 36.3, 24.2, 21.5 ; IR (neat) 1592, 1385, 1350, 764 cm^{-1} ; HRMS calcd for $C_{26}H_{24}NO$ $[M+H]^+$: 366.1852, found 366.1862.



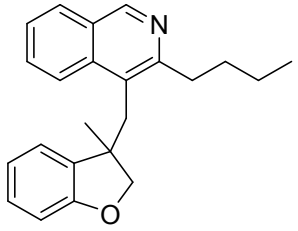
3c

3-(4-Methoxyphenyl)-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3c). This product was obtained as a white solid (0.0534 g, 70%): mp 123-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.96 – 7.82 (m, 1H), 7.63 (s, 1H), 7.54-7.31 (m, 4H), 7.05-6.85 (m, 3H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.53 (s, 1H), 6.35 (s, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 3.86 (s, 3H), 3.81 (d, *J* = 8.6 Hz, 1H), 3.71 (d, *J* = 14.1 Hz, 1H), 3.68-3.58 (m, 1H), 0.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 159.3, 153.8, 150.5, 137.2, 134.8, 134.5, 131.6, 129.9, 128.3, 128.0, 127.2, 126.5, 124.8, 124.2, 123.5, 120.5, 114.0, 109.8, 83.1, 55.5, 48.0, 36.3, 24.3 ; IR (neat) 1650, 1613, 1513, 1476, 1371, 1327, 751 cm^{-1} ; HRMS calcd for $C_{26}H_{24}NO_2$ $[M+H]^+$: 382.1802, found 382.1808.



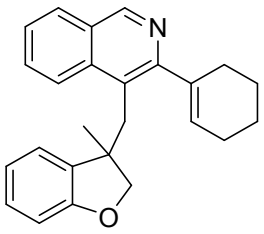
3d

3-(4-Fluorophenyl)-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3d). This product was obtained as a yellow solid (0.0456 g, 62%): mp 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.94 (d, *J* = 7.3 Hz, 1H), 7.65 (s, 1H), 7.58-7.38 (m, 4H), 7.20-7.06 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.52 (s, 1H), 6.27 (s, 1H), 4.22 (d, *J* = 8.5 Hz, 1H), 3.83 (d, *J* = 8.3 Hz, 1H), 3.70-3.58 (m, 2H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6(d, *J* = 248.5 Hz), 159.6, 152.7, 150.5, 137.6, 137.3, 134.4, 132.1(d, *J* = 8.1 Hz), 130.4, 128.5, 128.3, 127.4, 127.0, 125.3, 124.4, 123.5, 120.7, 115.6(d, *J* = 22.2 Hz), 110.0, 83.2, 48.1, 36.5, 24.4; IR (neat) 166, 1563, 1510, 1477, 1371, 1331, 749 cm^{-1} ; HRMS calcd for $C_{25}H_{21}FNO$ $[M+H]^+$: 370.1602, found 370.1607.



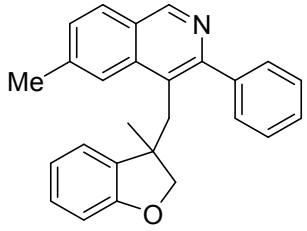
3g

3-Butyl-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3g). This product was obtained as a yellow oil (0.0654 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.89 – 7.83 (m, 1H), 7.68 (dd, *J* = 7.0, 4.3 Hz, 1H), 7.55-7.38 (m, 2H), 7.09 (td, *J* = 8.0, 1.2 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.65 (t, *J* = 6.6 Hz, 1H), 6.49 (d, *J* = 7.2 Hz, 1H), 4.51 (d, *J* = 8.7 Hz, 1H), 4.06 (d, *J* = 8.7 Hz, 1H), 3.45-3.35 (m, 2H), 2.63 (s, 2H), 1.55 (dt, *J* = 9.3, 7.0 Hz, 2H), 1.38 (s, 3H), 1.27 (dt, *J* = 14.9, 7.4 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.4, 150.8, 136.9, 134.6, 129.9, 128.6, 128.2, 127.0, 125.9, 123.9, 123.80, 123.78, 120.7, 110.0, 83.3, 47.7, 36.3, 35.0, 32.4, 24.4, 23.0, 14.1; IR (neat) 1592, 1476, 1379, 1350, 974, 751 cm^{-1} ; HRMS calcd for $C_{23}H_{26}NO$ $[M+H]^+$: 332.2009, found 332.2022.



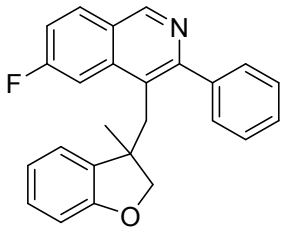
3h

3-(Cyclohex-1-en-1-yl)-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3h). This product was obtained as a brown oil (0.0286 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.85 (dd, *J* = 5.2, 4.1 Hz, 1H), 7.58 (s, 1H), 7.50-7.36 (m, 2H), 7.12 – 6.98 (m, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.70 – 6.48 (m, 2H), 5.74 (s, 1H), 4.43 (d, *J* = 8.7 Hz, 1H), 3.98 (d, *J* = 8.6 Hz, 1H), 3.64 (s, 2H), 2.48 (s, 1H), 2.39 (s, 1H), 2.25 – 2.15 (m, 2H), 1.81 (dt, *J* = 5.7, 5.0 Hz, 2H), 1.72 (dt, *J* = 10.7, 4.6 Hz, 2H), 1.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 156.7, 150.5, 138.9, 137.2, 135.4, 129.68, 129.65, 128.3, 128.0, 127.1, 126.1, 124.4, 123.7, 123.6, 120.7, 110.0, 83.3, 47.3, 36.7, 29.4, 25.7, 25.2, 23.2, 22.2; IR (neat) 2929, 1588, 1479, 1384, 1349, 974, 750 cm^{-1} ; HRMS calcd for $C_{25}H_{26}NO$ $[M+H]^+$: 356.2009, found 356.2016.



3j

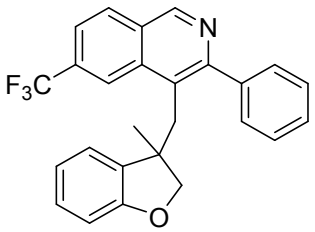
6-Methyl-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3j). This product was obtained as a yellow solid (0.0498 g, 68%): mp 128-131°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.62-7.52 (m, 2H), 7.52-7.45 (m, 2H), 7.43 (ddd, *J* = 7.2, 3.6, 1.3 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.30-7.10 (m, 1H), 6.96 (td, *J* = 8.0, 1.2 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.44 (s, 1H), 6.18 (s, 1H), 4.25 (d, *J* = 8.7 Hz, 1H), 3.87 (d, *J* = 8.4 Hz, 1H), 3.72-3.59 (m, 2H), 2.33 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 151.1, 148.7, 142.5, 139.3, 138.1, 134.1, 130.5, 129.9, 128.9, 128.6, 128.4, 126.2, 125.3, 123.9, 123.7, 120.5, 109.8, 83.6, 47.9, 36.5, 23.8, 22.7(one carbon missing due to overlap); IR (neat) 1662, 1569, 1478, 1454, 1371, 1331, 749, 702 cm^{-1} ; HRMS calcd for $C_{26}H_{24}NO$ $[M+H]^+$: 366.1852, found 366.1860.



3k

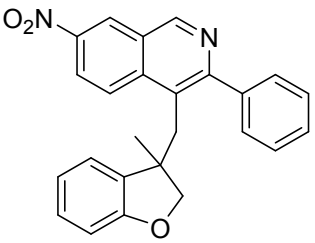
6-Fluoro-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3k). This product was obtained as a yellow solid (0.0487 g, 66%): mp 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.94 (dd, *J* = 8.9, 5.8 Hz, 1H), 7.53 (d, *J* = 7.1 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.26 (dt, *J* = 8.6, 2.2 Hz, 1H), 7.09 (d, *J* = 6.3 Hz, 1H), 6.99 (td, *J* = 8.0, 1.2 Hz, 1H), 6.67 (d, *J* = 7.4 Hz, 1H), 6.49 (s, 1H), 6.25 (s, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 3.85 (d, *J* = 8.6 Hz, 1H), 3.60 (s, 2H), 0.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8(d, *J* = 253.5 Hz), 159.6, 153.6, 149.7, 140.6, 139.3(d, *J* = 10.1 Hz), 134.0, 131.2(d, *J* = 10.1 Hz), 130.3, 128.8, 128.7, 128.4, 125.4(d, *J* = 5.1 Hz), 124.3, 123.5, 120.5, 117.7(d, *J* = 26.3 Hz), 110.0, 108.6(d, *J* = 23.3 Hz), 83.3, 47.9, 36.8, 23.8; IR (neat) 1669, 1580,

1478, 1348, 751, 701 cm^{-1} ; HRMS calcd for $C_{25}H_{21}FNO$ $[M+H]^+$: 370.1602, found 370.1605.



3l

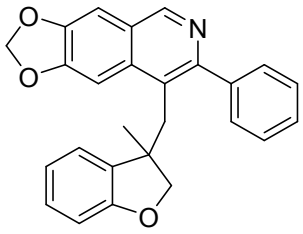
4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenyl-6-(trifluoromethyl)isoquinoline (3l). This product was obtained as a yellow solid (0.0441 g, 53%): mp 136-138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.77 – 7.53 (m, 4H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.45 – 7.38 (m, 1H), 6.93 (td, *J* = 8.0, 1.2 Hz, 1H), 6.62 (s, 1H), 6.52-5.75 (m, 2H), 4.26 (d, *J* = 8.7 Hz, 1H), 3.88 (d, *J* = 8.1 Hz, 1H), 3.70 (q, *J* = 13.9 Hz, 2H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.6, 150.6, 141.7, 136.3, 133.4, 131.2 (q. *J* = 32.3 Hz), 130.4, 129.0, 128.8, 128.2, 127.9, 125.8, 125.3, 123.7, 122.5, 122.3 (q, *J* = 3.0 Hz), 122.2 (q, *J* = 4.5 Hz), 120.4, 110.1, 48.0, 36.8, 23.8 (one carbon missing due to overlap); IR (neat) 1592, 1384, 1351, 764 cm^{-1} ; HRMS calcd for $C_{26}H_{21}F_3NO$ $[M+H]^+$: 420.1570, found 420.1579.



3m

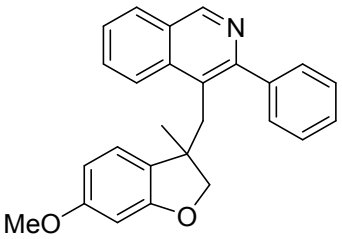
4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-7-nitro-3-phenylisoquinoline (3m). This product was obtained as a yellow solid (0.0413 g, 53%): mp 161-163 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.82 (d, *J* = 2.2 Hz, 1H), 8.01 (s, 1H), 7.65 – 7.37 (m, 6H), 7.01 – 6.93 (m, 1H), 6.62 (s, 1H), 6.55-5.55 (m, 2H), 4.24 (d, *J* = 8.7 Hz, 1H), 3.87 (d, *J* = 6.8 Hz, 1H), 3.80-3.52 (m, 2H), 0.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 157.2, 151.9, 145.5, 140.6, 139.9, 133.5, 130.3, 128.9, 128.8, 128.7, 126.4, 125.8, 124.5, 123.7, 122.6, 120.6, 110.1, 83.5, 48.0, 36.8, 23.5 (one carbon

missing due to overlap); IR (neat) 1655, 1621, 1562, 1527, 1480, 1342, 749, 700 cm^{-1}; HRMS calcd for $C_{25}H_{21}N_2O_3$ $[M+H]^+$: 397.1547, found 397.1555.



3n

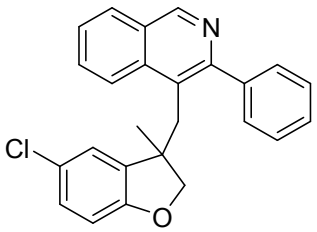
8-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-7-phenyl-[1,3]dioxolo[4,5-g]isoquinoline (3n). This product was obtained as a yellow solid (0.0540 g, 68%): mp 220-221°C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.13 (s, 1H), 7.06 – 6.97 (m, 1H), 6.86 (s, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.56 (s, 1H), 6.33 (s, 1H), 6.02 (d, *J* = 5.3 Hz, 2H), 4.18 (d, *J* = 8.7 Hz, 1H), 3.82 (d, *J* = 8.6 Hz, 1H), 3.66-3.40 (m, 2H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 152.8, 151.5, 148.0, 141.4, 136.0, 134.6, 130.3, 128.6, 128.4, 127.9, 124.9, 124.8, 123.5, 120.5, 109.9, 103.3, 101.9, 101.1, 83.2, 47.9, 37.0, 24.1(one carbon missing due to overlap); IR (neat) 1650, 1528, 1457, 1371, 1325, 1039, 793 cm^{-1} ; HRMS calcd for $C_{26}H_{22}NO_3$ $[M+H]^+$: 396.1594, found 396.1601.



3o

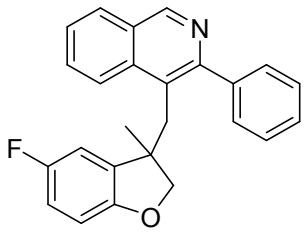
4-((6-Methoxy-3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3o). This product was obtained as a yellow oil (0.0463 g, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.02 – 7.92 (m, 1H), 7.63 (s, 1H), 7.57 – 7.48 (m, 4H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 6.23 (s, 1H), 6.17-5.83 (m, 2H), 4.21 (d, *J* = 8.7 Hz, 1H), 3.84 (d, *J* = 8.4 Hz, 1H), 3.79 – 3.55 (m, 5H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 160.7, 152.8, 150.0, 140.7, 137.5, 130.6, 130.4, 128.7, 128.3, 128.1, 127.1, 127.0, 126.5, 125.9, 124.5, 123.6, 106.2, 96.5, 55.7, 47.5, 36.5, 24.3(one carbon

missing due to overlap); IR (neat) 1593, 1495, 1385, 1349, 765 cm^{-1} ; HRMS calcd for $C_{26}H_{24}NO_2$ $[M+H]^+$: 382.1802, found 382.1811.



3p

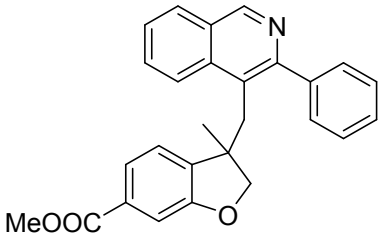
4-((5-Chloro-3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3p). This product was obtained as a yellow solid (0.0403 g, 52%): mp 155-157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.00 – 7.93 (m, 1H), 7.80-7.53 (m, 3H), 7.53-7.49 (m, 2H), 7.49 – 7.43 (m, 2H), 7.43 – 7.36 (m, 1H), 6.92 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.16 (s, 1H), 4.22 (d, *J* = 8.8 Hz, 1H), 3.85 (d, *J* = 8.6 Hz, 1H), 3.75-3.54 (m, 2H), 0.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 153.1, 150.3, 140.6, 137.3, 136.3, 130.7, 130.4, 128.8, 128.5, 128.3, 127.24, 127.18, 125.5, 125.1, 124.1, 110.8, 83.6, 48.2, 36.3, 24.2(two carbon missing due to overlap); IR (neat) 1597, 1470, 1359, 1086, 762, 703 cm^{-1} ; HRMS calcd for $C_{25}H_{21}ClNO$ $[M+H]^+$: 386.1306, found 386.1318.



3q

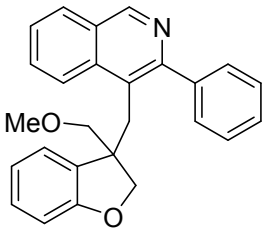
4-((5-Fluoro-3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3q). This product was obtained as a yellow solid (0.0480 g, 65%): mp 115-117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.95 (dd, *J* = 5.2, 4.2 Hz, 1H), 7.63 (d, *J* = 5.5 Hz, 1H), 7.56 – 7.47 (m, 4H), 7.47 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 6.66 (td, *J* = 8.8, 2.7 Hz, 1H), 6.54 (dd, *J* = 8.6, 4.1 Hz, 1H), 5.96 (dd, *J* = 8.6, 3.9 Hz, 1H), 4.21 (d, *J* = 8.8 Hz, 1H), 3.84 (d, *J* = 8.7 Hz, 1H), 3.78-3.55 (m, 2H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7(d, *J* = 238.4 Hz), 155.3(d, *J* = 1.0 Hz), 154.0, 150.8, 141.6, 137.1, 136.1, 130.3, 130.2, 128.6, 128.3, 127.9, 127.3, 126.8, 124.5,

124.0, 114.4 (d, *J* = 24.2 Hz), 110.9(d, *J* = 25.3 Hz), 110.0(d, *J* = 8.0 Hz), 83.6, 48.2 (d, *J* = 2 Hz), 36.1, 24.2; IR (neat) 1591, 1385, 1350, 767 cm^{-1} ; HRMS calcd for $C_{25}H_{21}FNO$ $[M+H]^+$: 370.1602, found 370.1610.



3r

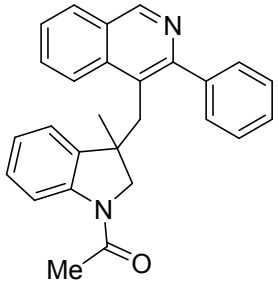
Methyl 3-methyl-3-((3-phenylisoquinolin-4-yl)methyl)-2,3-dihydrobenzo furan-6-carboxylate (3r). This product was obtained as a yellow oil (0.0464 g, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.58 – 7.34 (m, 7H), 7.28 – 7.09 (m, 1H), 6.60-5.10 (m, 2H), 4.24 (d, *J* = 8.9 Hz, 1H), 3.92 – 3.78 (m, 4H), 3.78-3.61 (m, 2H), 0.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 159.6, 152.3, 150.0, 139.9, 139.8, 137.4, 131.1, 130.7, 130.3, 128.8, 128.7, 128.4, 127.4, 127.1, 125.5, 124.2, 123.3, 122.7, 110.8, 83.5, 52.3, 48.0, 36.1, 24.1; IR (neat) 1718, 1591, 1384, 1350, 766, 704 cm^{-1} ; HRMS calcd for $C_{27}H_{24}NO_3$ $[M+H]^+$: 410.1751, found 410.1762.



3s

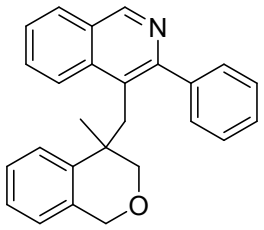
4-((3-(Methoxymethyl)-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3s). This product was obtained as a yellow oil (0.0402 g, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.12 – 7.83 (m, 2H), 7.64 – 7.45 (m, 3H), 7.45-7.25 (m, 5H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 6.42 (s, 1H), 5.97 (d, *J* = 6.9 Hz, 1H), 4.19 (d, *J* = 9.1 Hz, 1H), 4.12 (d, *J* = 9.1 Hz, 1H), 3.94 (d, *J* = 15.8 Hz, 1H), 3.75 (d, *J* = 14.2 Hz, 1H), 3.27 (d, *J* = 9.0 Hz, 1H), 3.21 – 2.99 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 150.8, 141.7, 137.3, 130.2, 130.1, 129.9, 128.7, 128.4, 128.0, 127.5, 127.2, 126.7, 124.7, 124.2, 120.3, 109.7, 80.5, 76.7, 59.0, 52.1, 31.5(two carbon missing

due to overlap); IR (neat) 1633, 1567, 1389, 1355, 770 cm^{-1} ; HRMS calcd for $C_{26}H_{24}NO_2$ $[M+H]^+$: 382.1802, found 382.1815.



3t

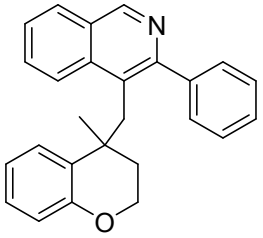
1-(3-Methyl-3-((3-phenylisoquinolin-4-yl)methyl)indolin-1-yl)ethan-1-one (3t). This product was obtained as a yellow solid (0.0550 g, 70%): mp 135-137 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 6.6 Hz, 2H), 7.50-7.42 (m, 3H), 7.42 – 7.36 (m, 1H), 7.32 (s, 1H), 7.09 (dd, *J* = 18.6, 10.9 Hz, 1H), 6.75 (s, 1H), 6.67-6.28 (m, 1H), 3.80 – 3.46 (m, 3H), 3.30 (d, *J* = 10.6 Hz, 1H), 1.89 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 154.1, 151.0, 142.1, 142.0, 138.8, 137.1, 130.4, 130.3, 130.1, 128.7, 128.3, 128.2, 127.9, 127.3, 126.8, 124.4, 123.9, 122.8, 117.1, 61.3, 46.1, 37.4, 25.4, 24.1; IR (neat) 1594, 1353, 765 cm^{-1} ; HRMS calcd for $C_{27}H_{25}N_2O$ $[M+H]^+$:393.1961, found 393.1964.



3u

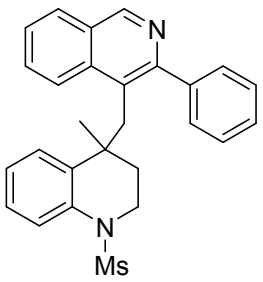
4-((4-Methylisochroman-4-yl)methyl)-3-phenylisoquinoline (3u). This product was obtained as a yellow solid (0.0310 g, 42%): mp 206-209 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.54 – 7.29 (m, 9H), 7.18-6.74 (m, 3H), 6.39 (dd, *J* = 19.4, 7.7 Hz, 1H), 4.70 (broad, 2H), 3.98 (d, *J* = 14.1 Hz, 1H), 3.67-3.61 (m, 2H), 3.23 (s, 1H), 0.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 150.0, 141.4, 137.6, 133.8, 130.5, 130.4, 128.5, 128.1, 127.8, 127.3, 126.9, 126.4, 126.2, 125.1, 124.1, 69.0, 39.7, 36.4, 22.6 (four carbon missing due to overlap); IR (neat) 1582, 1386, 1352, 1096, 763,701 cm^{-1} ; HRMS

calcd for $C_{26}H_{24}NO$ [M+H]$^+$: 366.1852, found 366.1863.



3v

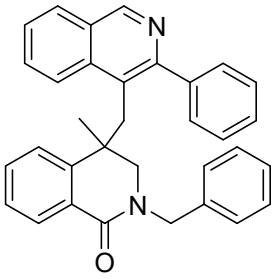
4-((4-Methylchroman-4-yl)methyl)-3-phenylisoquinoline (3v). This product was obtained as a yellow solid (0.0904 g, 82%): mp 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.11-7.89 (m, 2H), 7.69-7.53 (m, 2H), 7.53 – 7.25 (m, 5H), 6.98 (t, *J* = 8.3 Hz, 1H), 6.76 – 6.37 (m, 3H), 3.85-3.74 (m, 2H), 3.64 (s, 1H), 3.45 (td, *J* = 11.4, 1.8 Hz, 1H), 1.72 (d, *J* = 14.1 Hz, 1H), 1.67 – 1.48 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 150.2, 141.4, 137.6, 130.3, 129.5, 128.7, 128.4, 128.0, 127.6, 127.4, 126.9, 125.9, 124.9, 120.1, 117.2, 62.2, 38.2, 37.1, 36.0, 29.2(three carbon missing due to overlap); IR (neat) 1641, 1564, 1396, 1367, 1221, 751 cm^{-1} ; HRMS calcd for $C_{26}H_{24}NO$ [M+H]$^+$: 366.1852, found 366.1859.



3w

4-Methyl-1-(methylsulfonyl)-4-((3-phenylisoquinolin-4-yl)methyl)-1,2,3,4-tetrahydroquinoline (3w). This product was obtained as a yellow oil (0.0709 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.03-7.87 (m, 2H), 7.64-7.48 (m, 3H), 7.46 – 7.27 (m, 5H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 6.3 Hz, 2H), 3.75 (d, *J* = 14.0 Hz, 1H), 3.68 – 3.41 (m, 2H), 3.07 (t, *J* = 10.9 Hz, 1H), 2.54 (s, 3H), 1.78 – 1.63 (m, 1H), 1.45 – 1.31 (m, 1H), 0.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 150.6, 142.0, 137.1, 136.0, 135.8, 130.2, 130.0, 128.5, 128.4, 128.1, 127.7, 127.3, 126.9, 126.7, 124.8, 124.6, 124.4, 122.4, 42.3, 39.2, 38.91, 38.1, 35.0, 30.1; IR (neat) 1650, 1575, 1489, 1446, 1340, 1156, 963, 767 cm^{-1} ; HRMS calcd for $C_{27}H_{27}N_2O_2S$ [M+H]$^+$: 443.1788, found

443,1792.



3x

2-Benzyl-4-methyl-4-((3-phenylisoquinolin-4-yl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (3x). This product was obtained as a yellow oil (0.0882 g, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.10 (s, 1H), 7.96 (s, 1H), 7.71 – 7.26 (m, 12H), 7.22-7.15 (m, 1H), 7.11-6.69 (m, 2H), 6.06 (s, 1H), 4.88 (d, *J* = 13.7 Hz, 1H), 4.54 (d, *J* = 14.2 Hz, 1H), 3.69 (s, 1H), 3.39 (d, *J* = 12.4 Hz, 1H), 3.20 (d, *J* = 14.3 Hz, 1H), 2.94 (d, *J* = 12.2 Hz, 1H), 0.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 148.2, 143.0, 138.3, 137.0, 132.4, 131.7, 130.5, 129.3, 129.1, 128.9, 128.7, 128.2, 128.1, 127.5, 126.4, 125.4, 124.4, 57.9, 50.6, 39.9, 35.4, 22.5 (six carbon missing); IR (neat) 1646, 1593, 1384, 1351, 762, 701 cm^{-1} ; HRMS calcd for $C_{33}H_{30}N_2O$ $[M+H]^+$: 469.2274, found 469.2280.

Procedure for Palladium catalyzed domino Heck / annulation of 2-alkynyl aldehyde with *tert*-butylamine:

A solution of **1a** (0.0822 g, 0.3 mmol), 2-(phenylethynyl)benzaldehyde (**5**, 0.0928 g, 0.45 mmol, 1.5 equiv) and *tert*-butyl amine (0.0494 g, 0.68 mmol, 2.25 equiv) in DMF (5 mL) was stirred under argon at room temperature for 30 min, before $Pd(PPh_3)_4$ (0.0173 g, 0.015 mmol, 0.05 equiv) and oven-dried K_2CO_3 (0.1244 g, 0.9 mmol, 3.0 equiv) were added. The resulting reaction mixture was heated at 100 °C under argon for 7h. The reaction was monitored by TLC to establish completion. After cooling to room temperature, the reaction was diluted with ethyl acetate (35mL), washed with water (3×15mL) and brine (15mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (Silica Gel, petroleum ether / EtOAc) to afford product **3a** (0.0295 g, 28%).

References

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Single Crystallographic Data of 3a

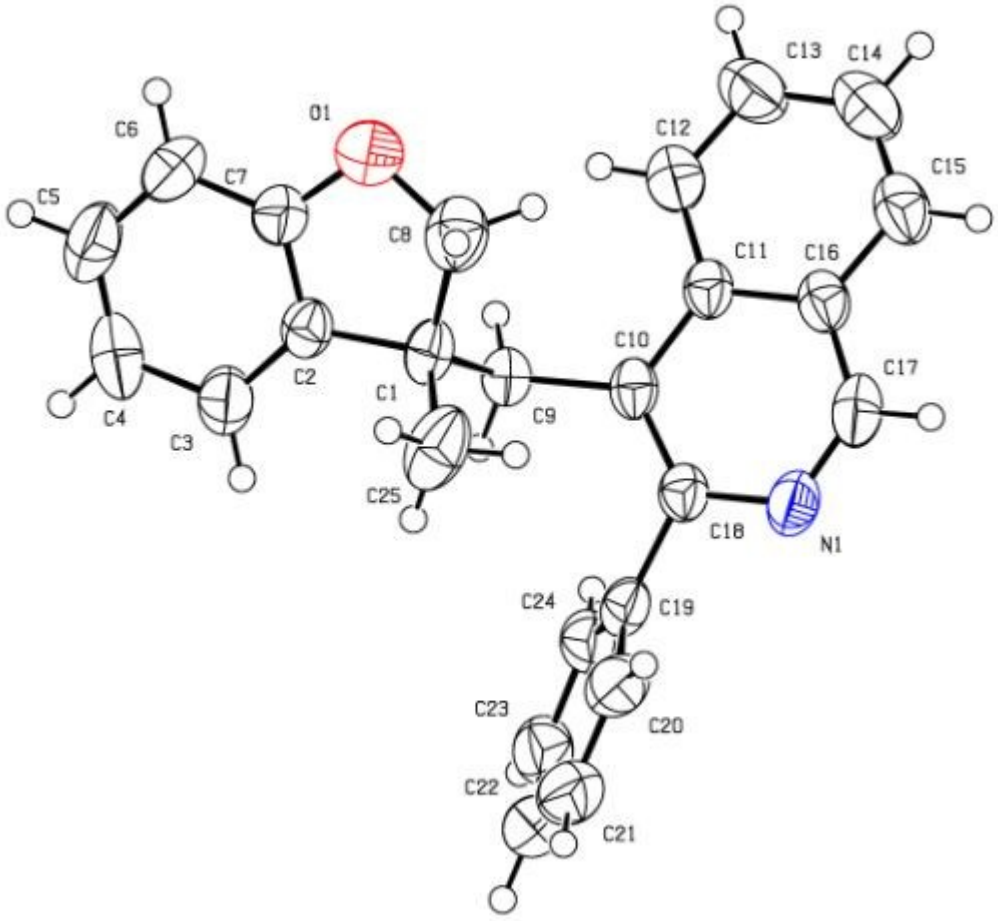
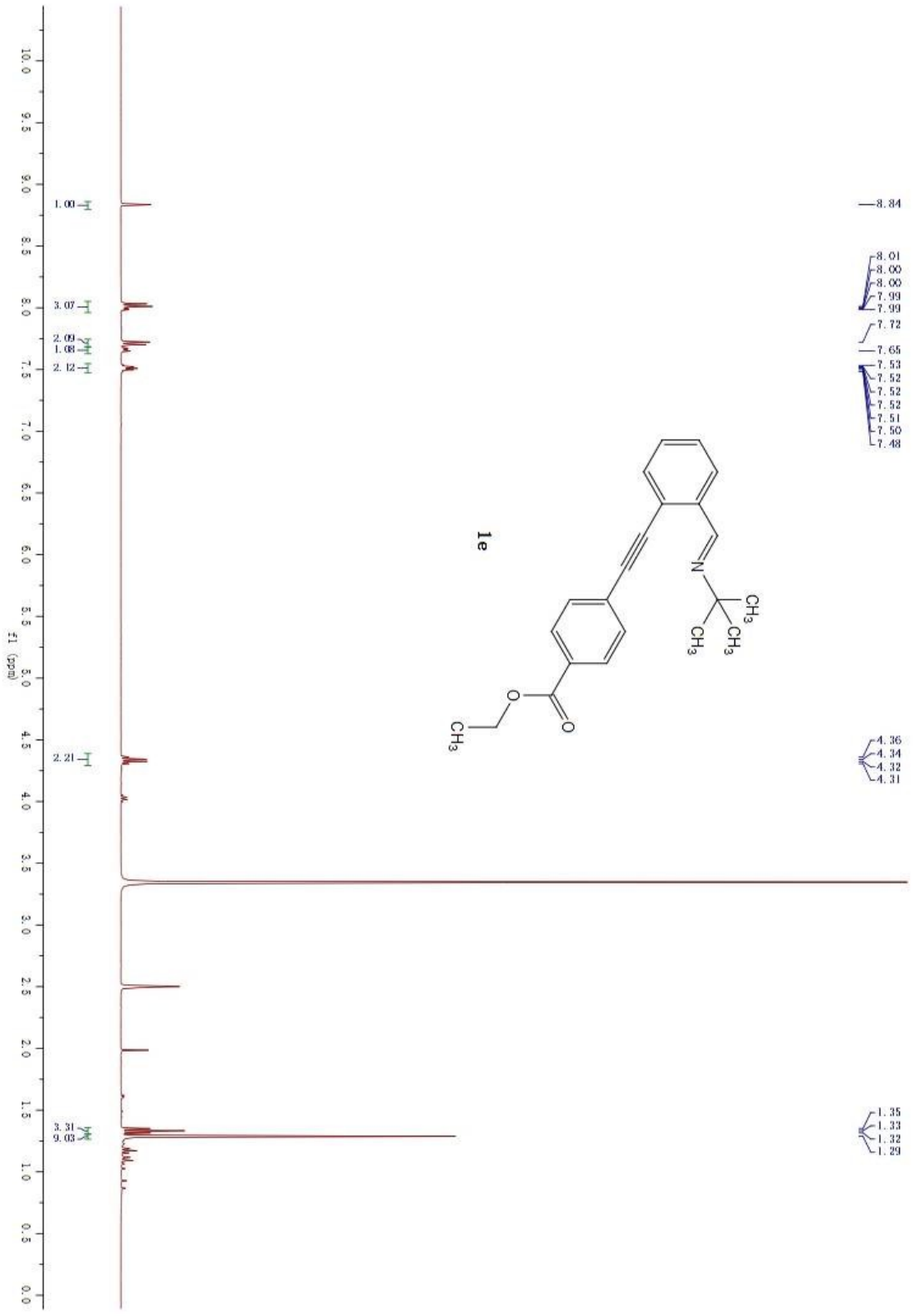


Table 1. Crystal data and structure refinement for **3a**.

Identification code	1	
Empirical formula	C25 H21 N O	
Formula weight	351.43	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.1675(4) Å	α= 90°.
	b = 13.1365(8) Å	β= 101.0748(19)°.
	c = 10.0074(6) Å	γ = 90°.
Volume	924.71(9) $Å^3$	
Z	2	
Density (calculated)	1.262 Mg/m^3	

Absorption coefficient	0.076 mm^{-1}
F(000)	372
Crystal size	0.221 x 0.207 x 0.113 mm^3
Theta range for data collection	3.101 to 27.604°.
Index ranges	-9<=h<=9, -17<=k<=17, -12<=l<=13
Reflections collected	14464
Independent reflections	4285 [R(int) = 0.0657]
Completeness to theta = 25.242°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.991 and 0.983
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4285 / 1 / 245
Goodness-of-fit on F^2	1.072
Final R indices [I>2sigma(I)]	R1 = 0.0618, wR2 = 0.1104
R indices (all data)	R1 = 0.1326, wR2 = 0.1316
Absolute structure parameter	0.9(10)
Extinction coefficient	n/a
Largest diff. peak and hole	0.210 and -0.172 $e.Å^{-3}$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7.52
7.51
7.50
7.48
4.36
4.34
4.32
4.31
1.35
1.33
1.32
1.29
1.00
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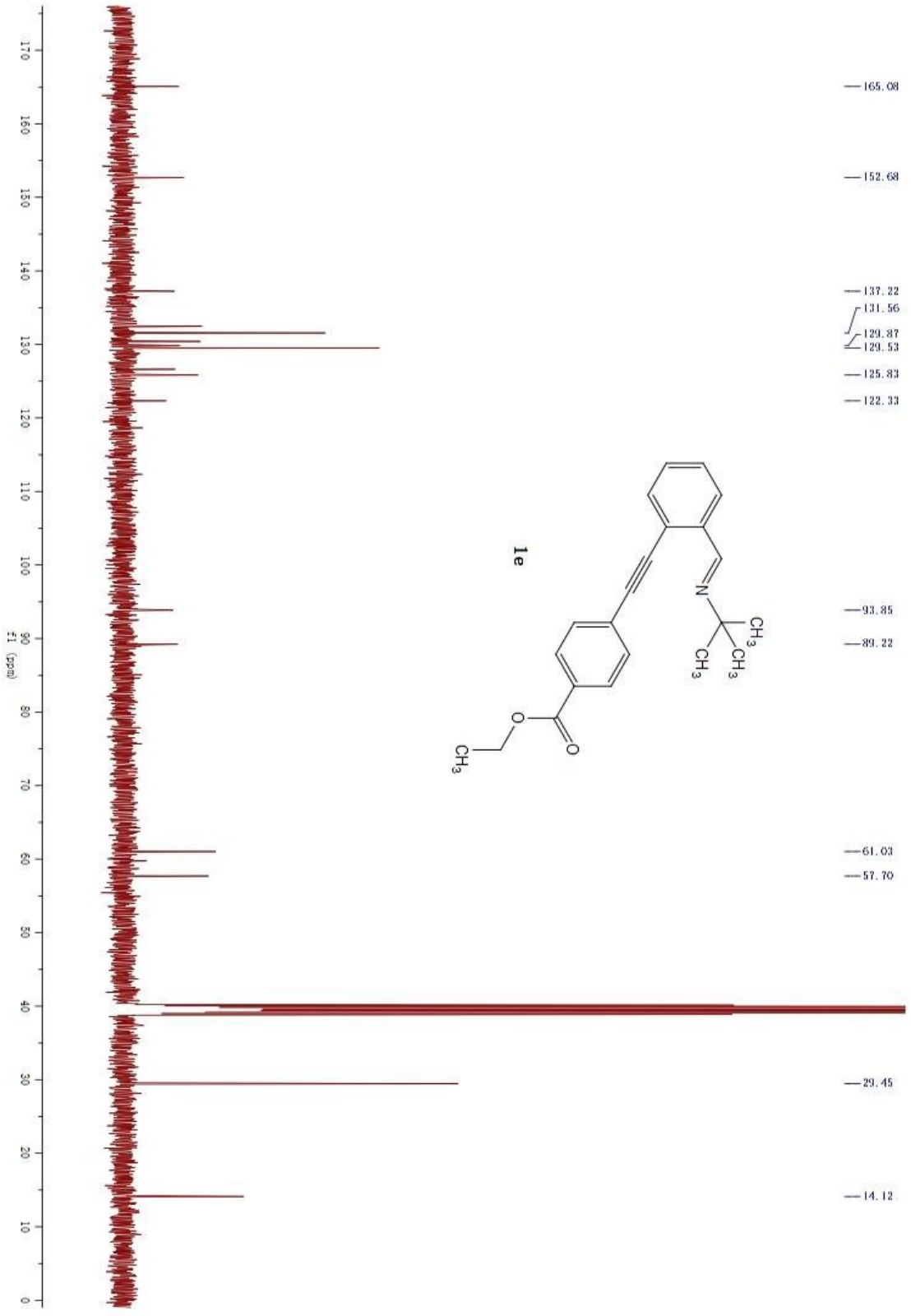
2.09
1.08
2.12
2.21
3.31
9.03
f1 (ppm)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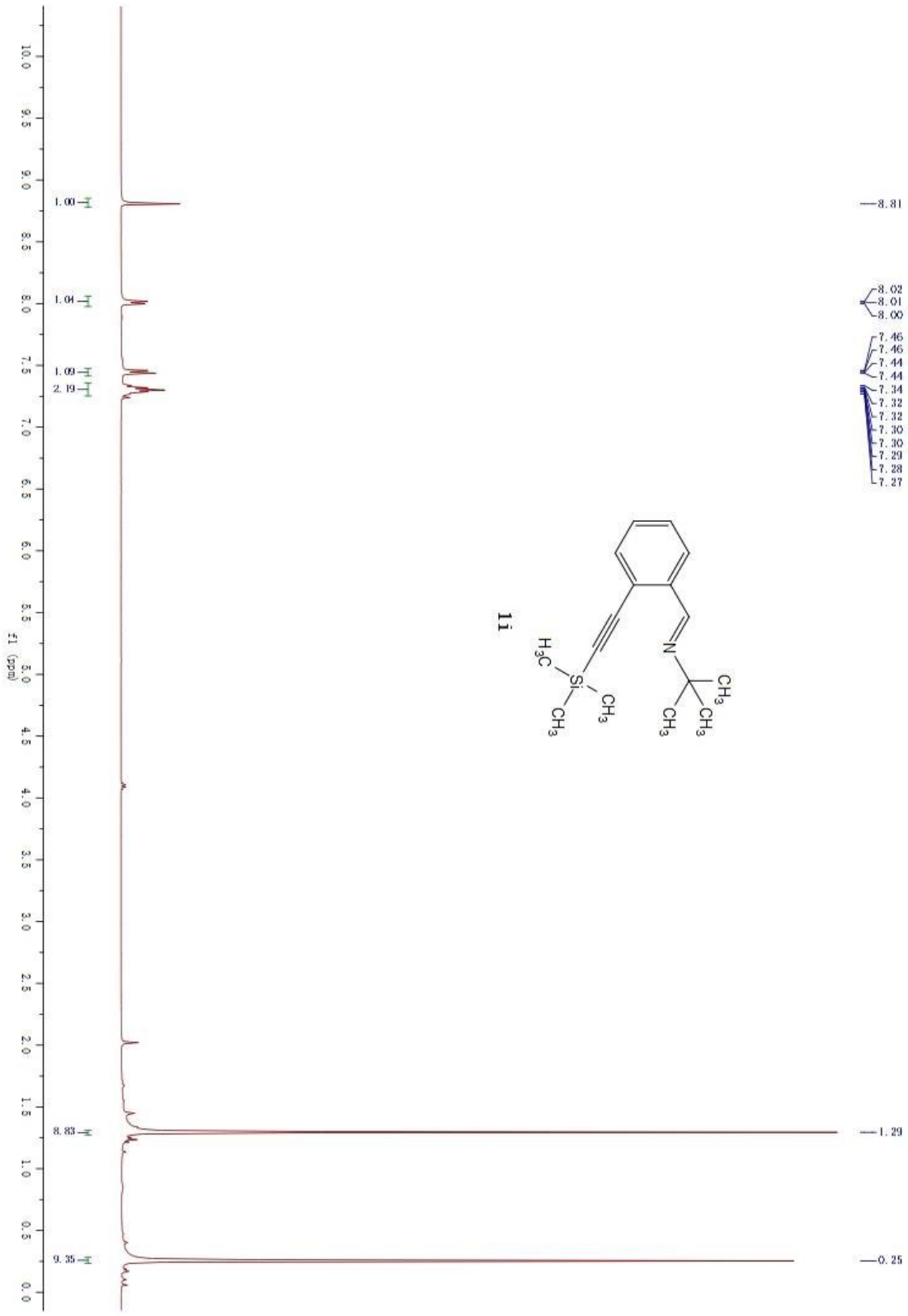
CH3
CH3
O
O
CH3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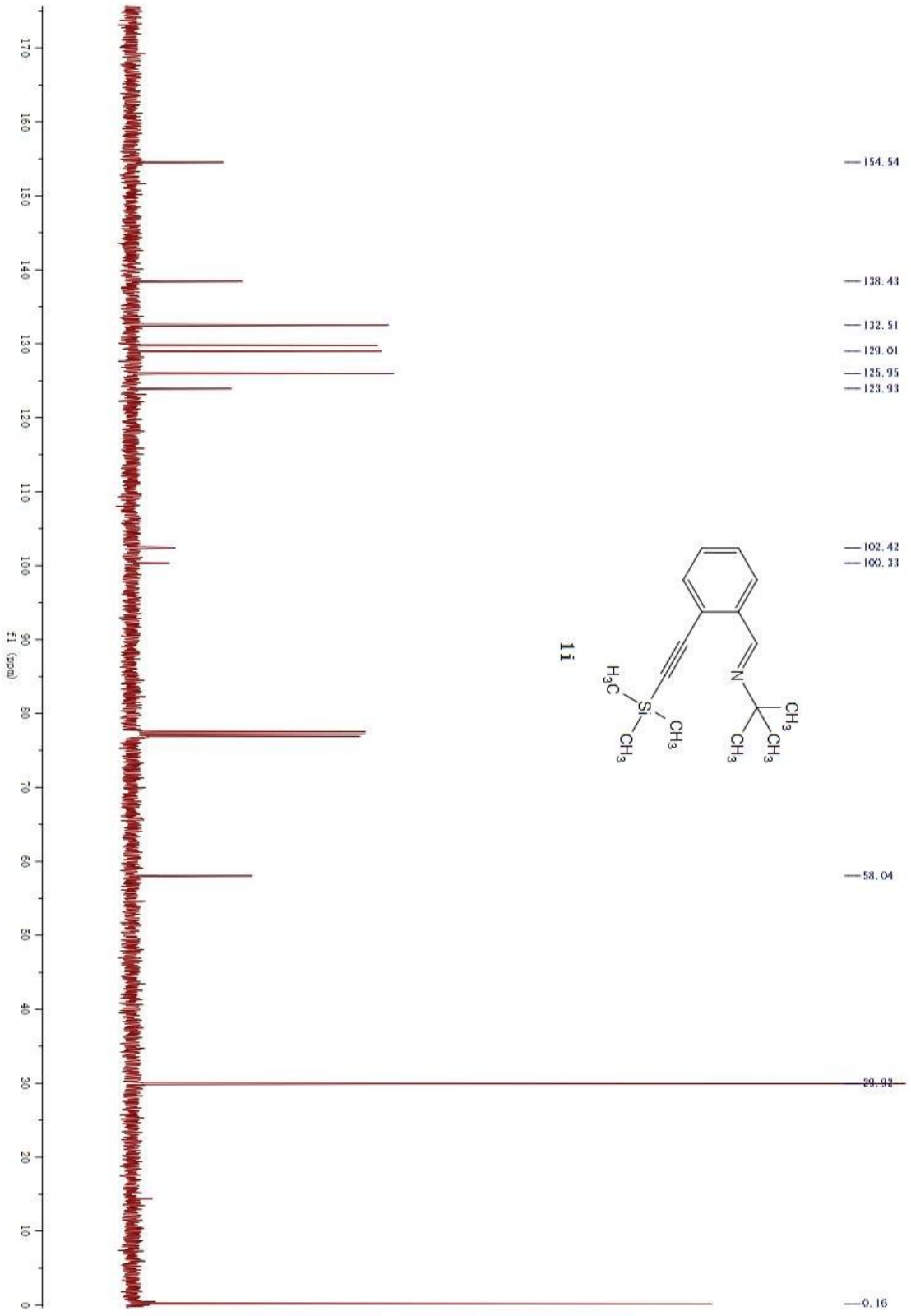
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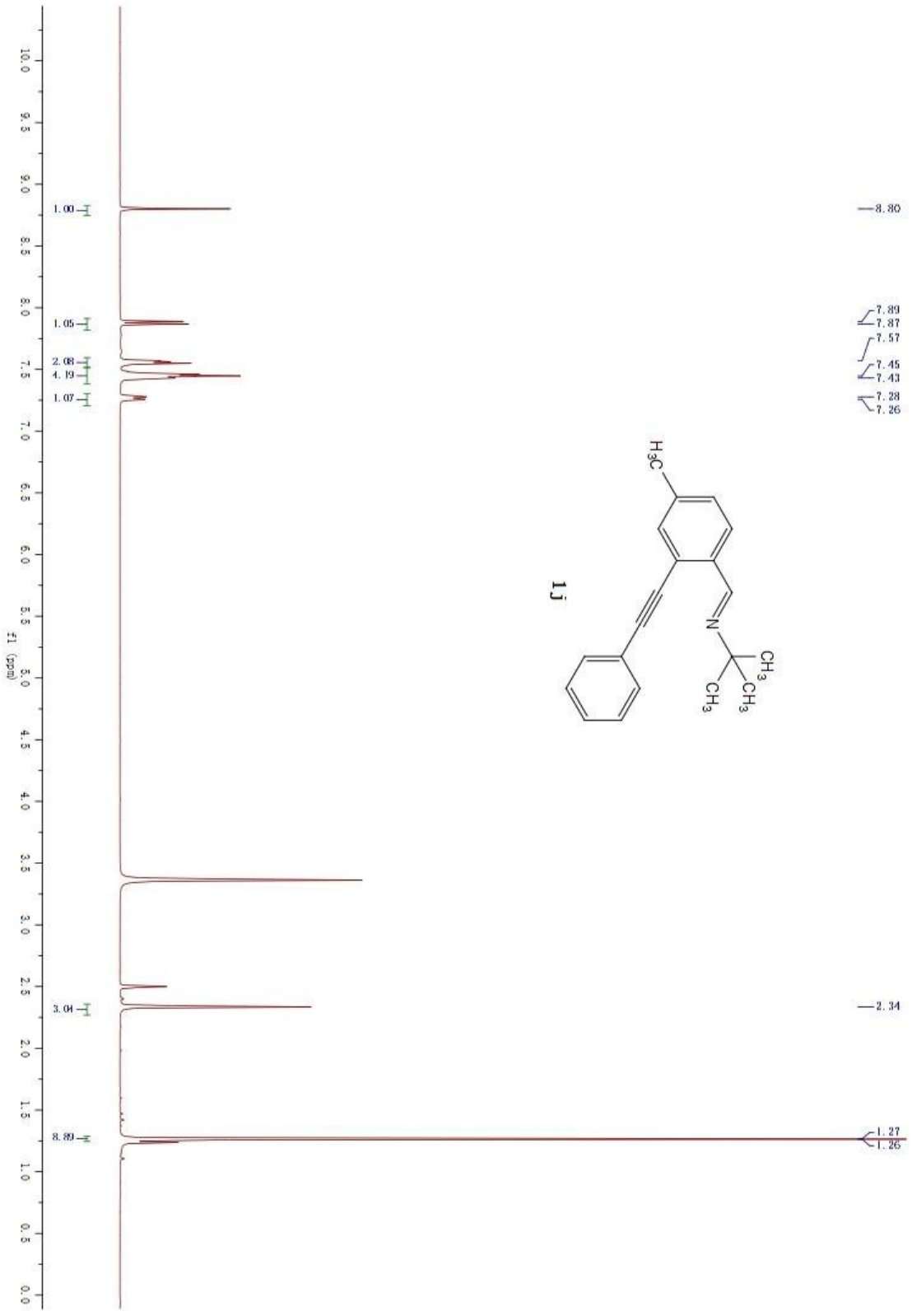
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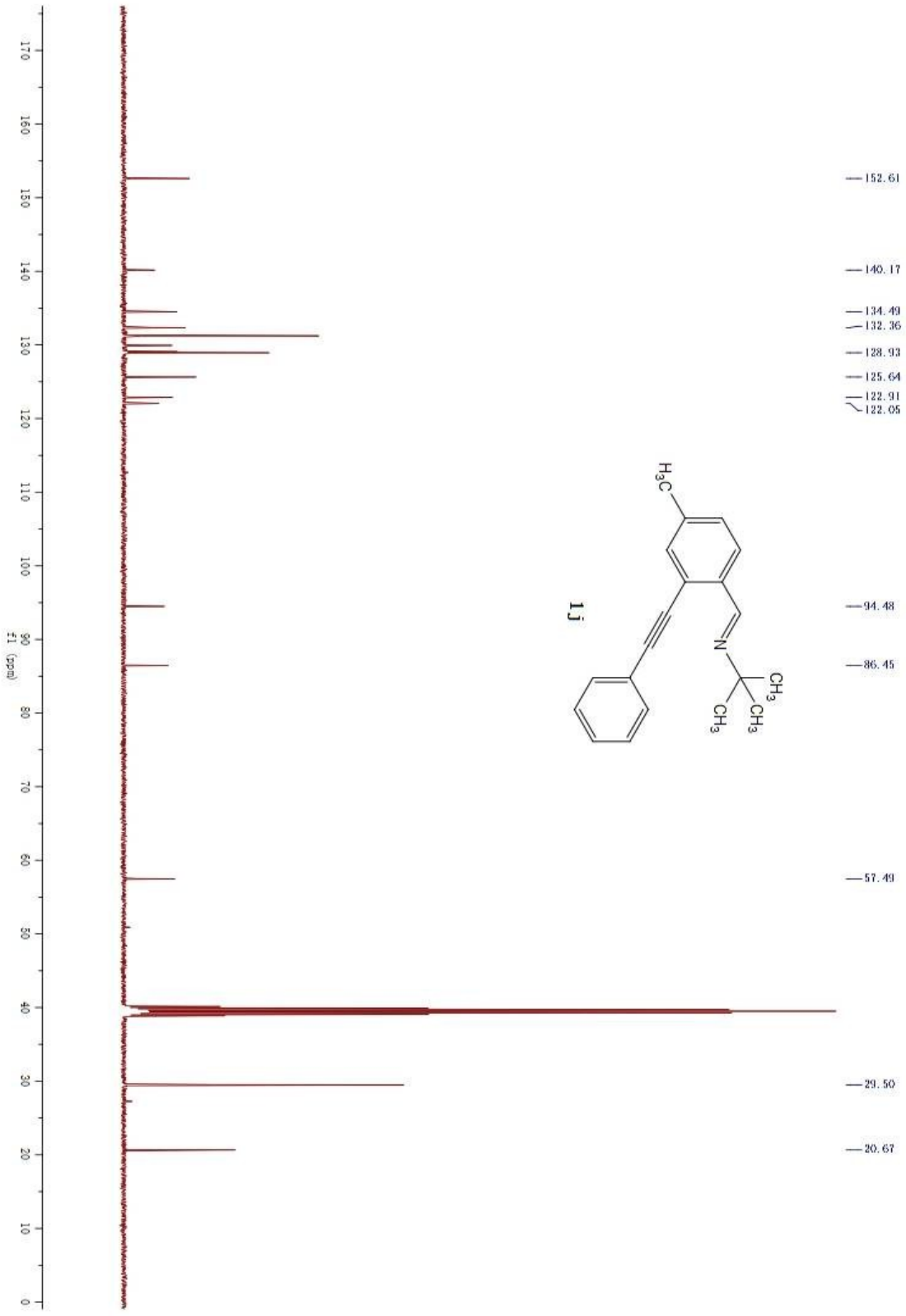
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N
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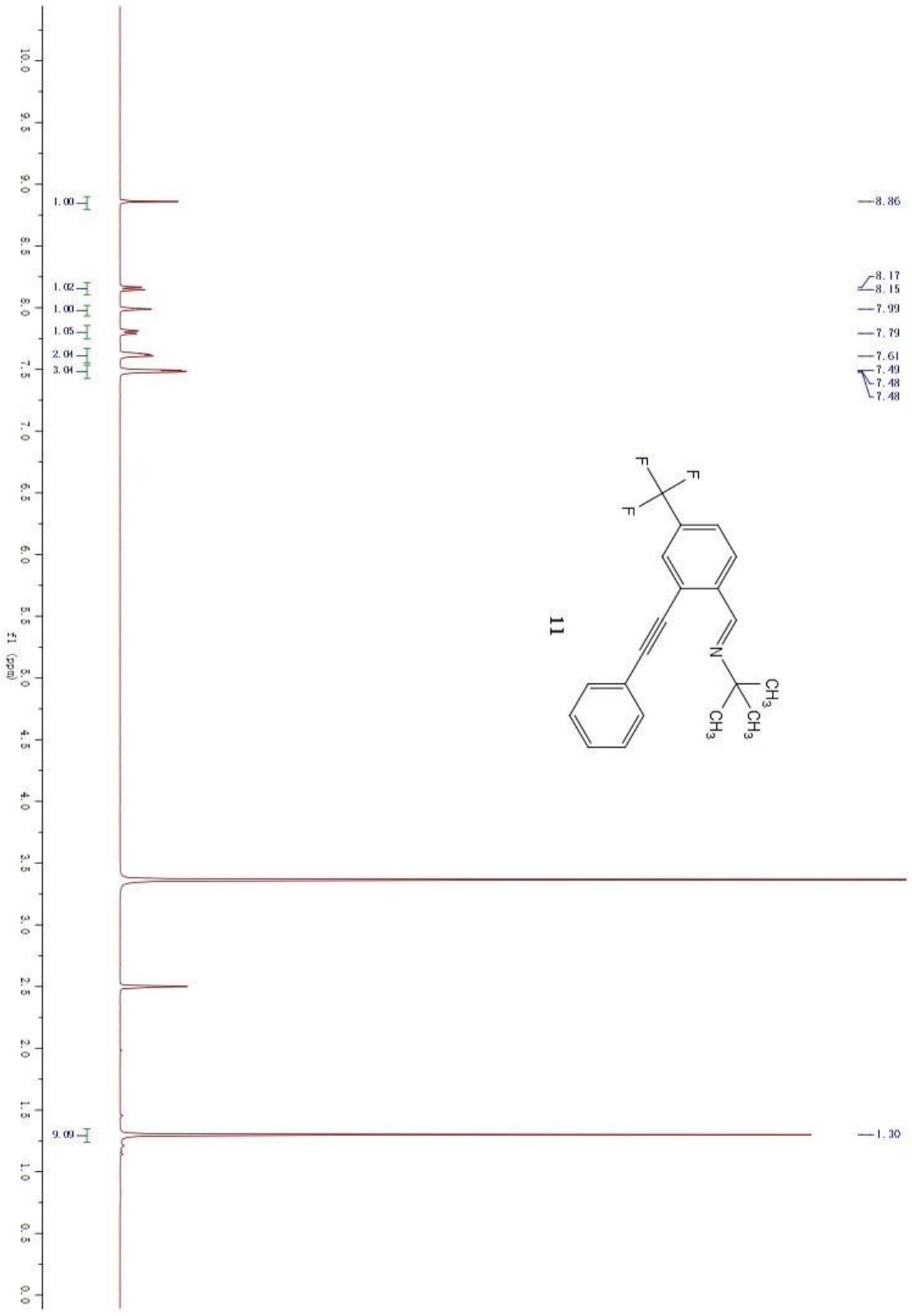
CH3
CH3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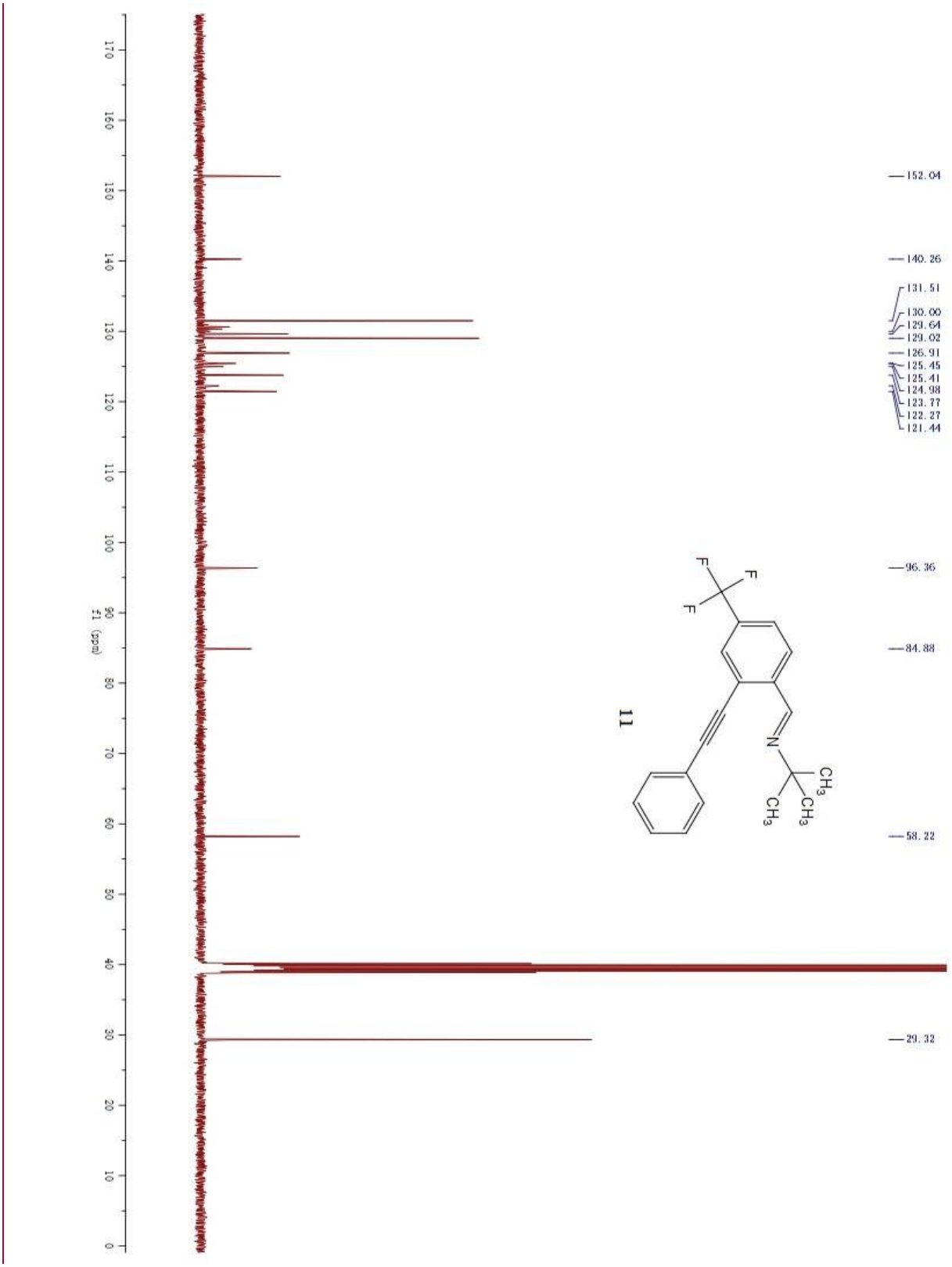
F
F
N
CH3
CH3
CH3

11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F
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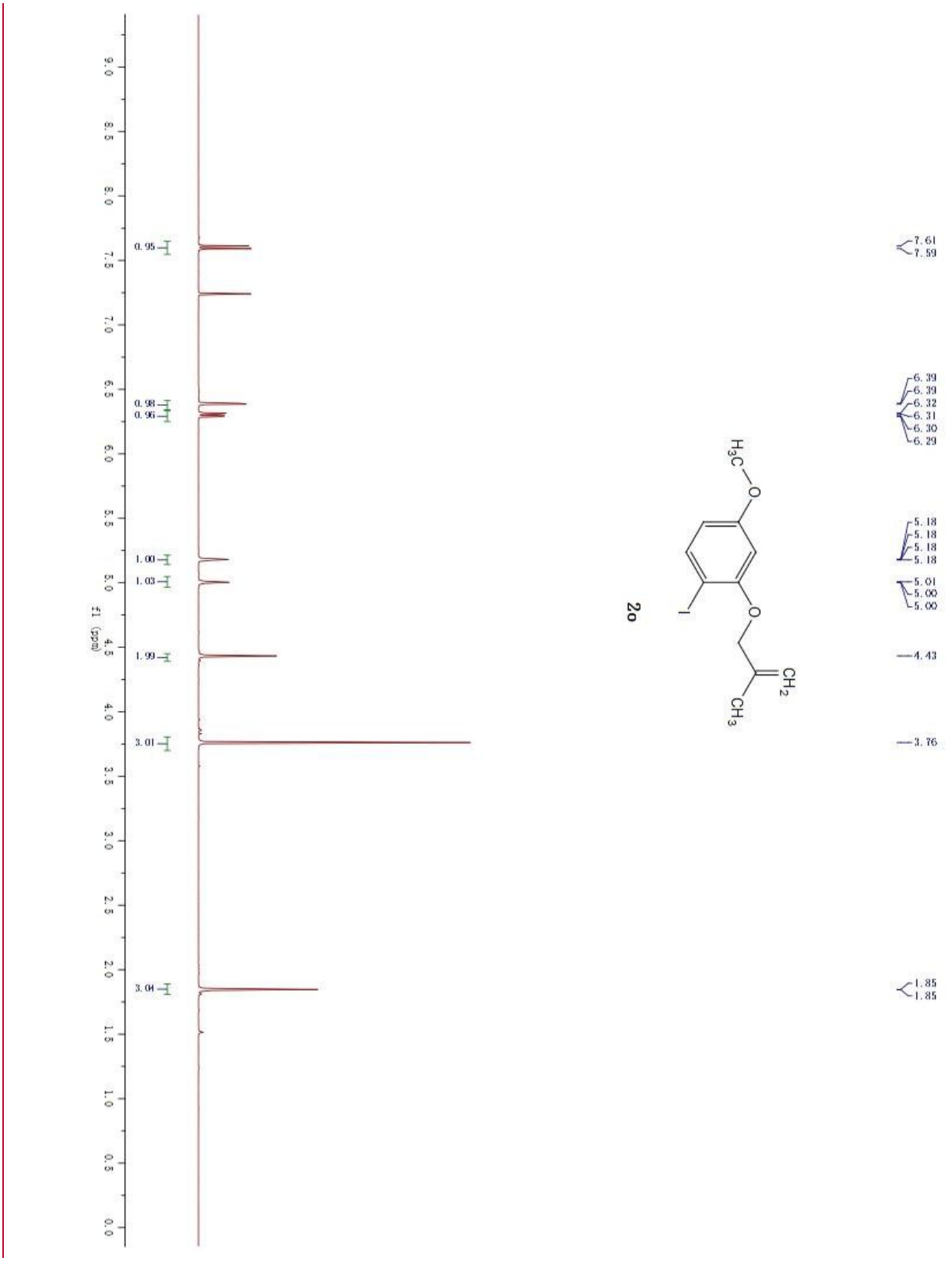
CH3
CH3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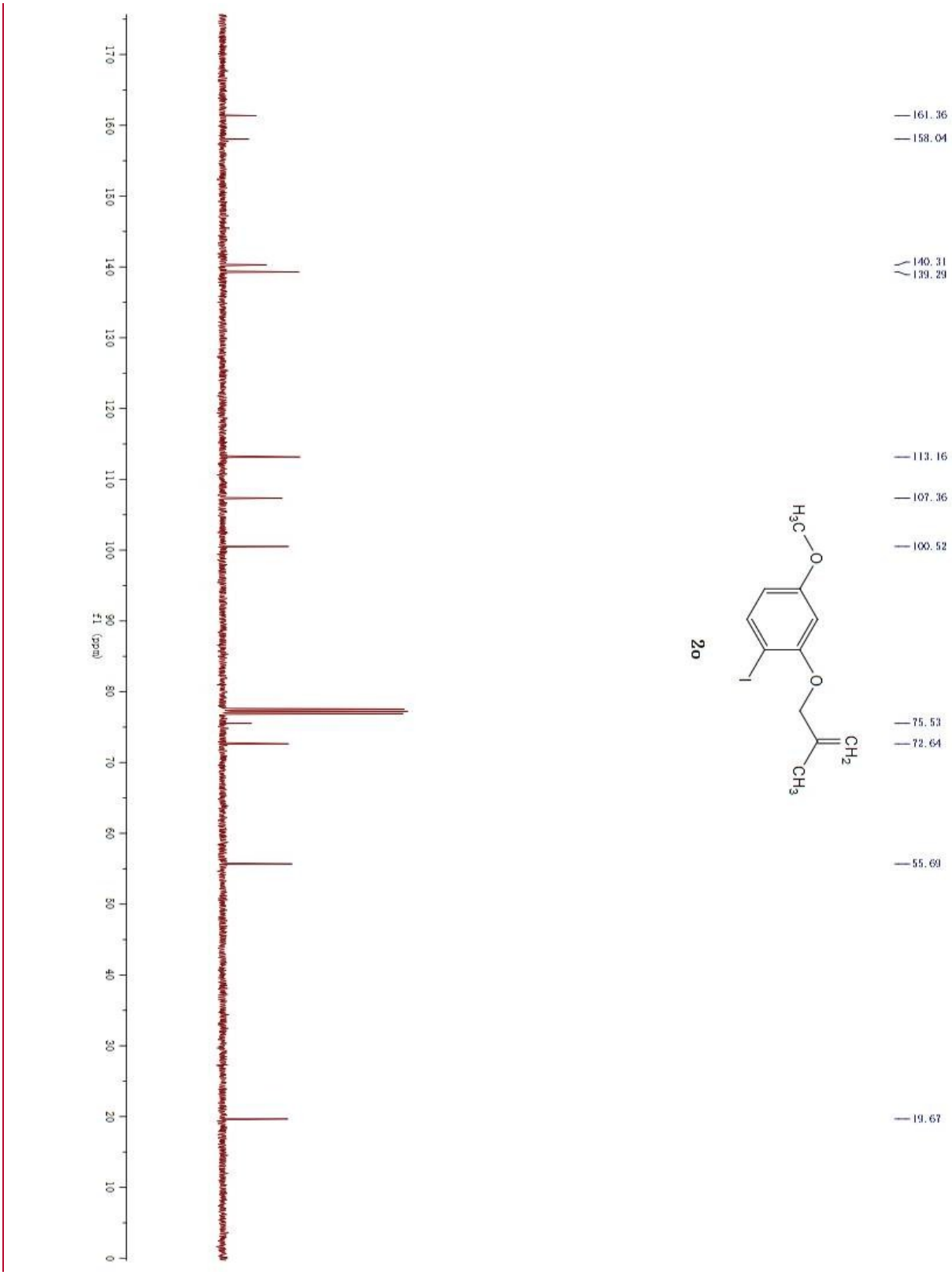
f1 (ppm)
2o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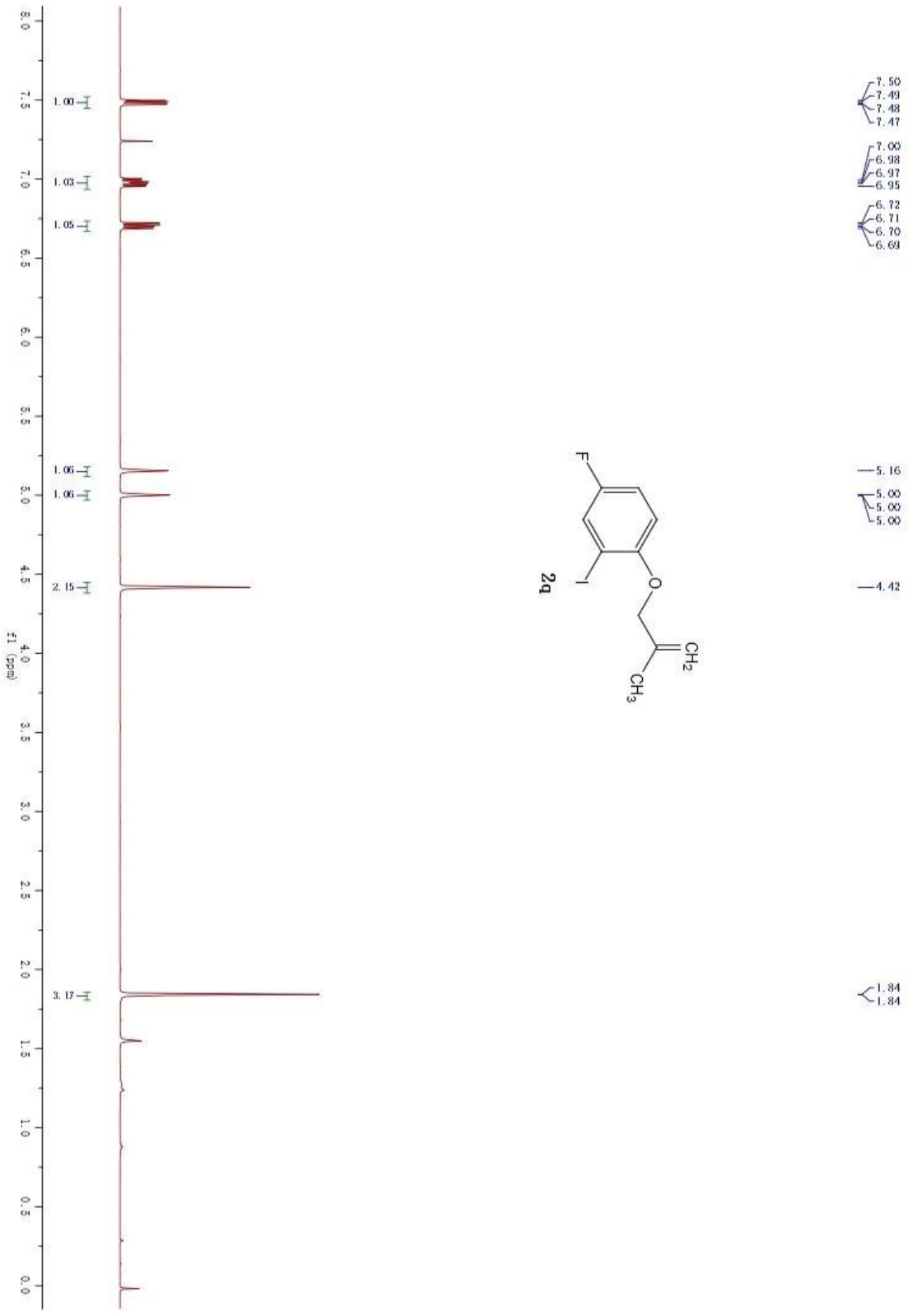
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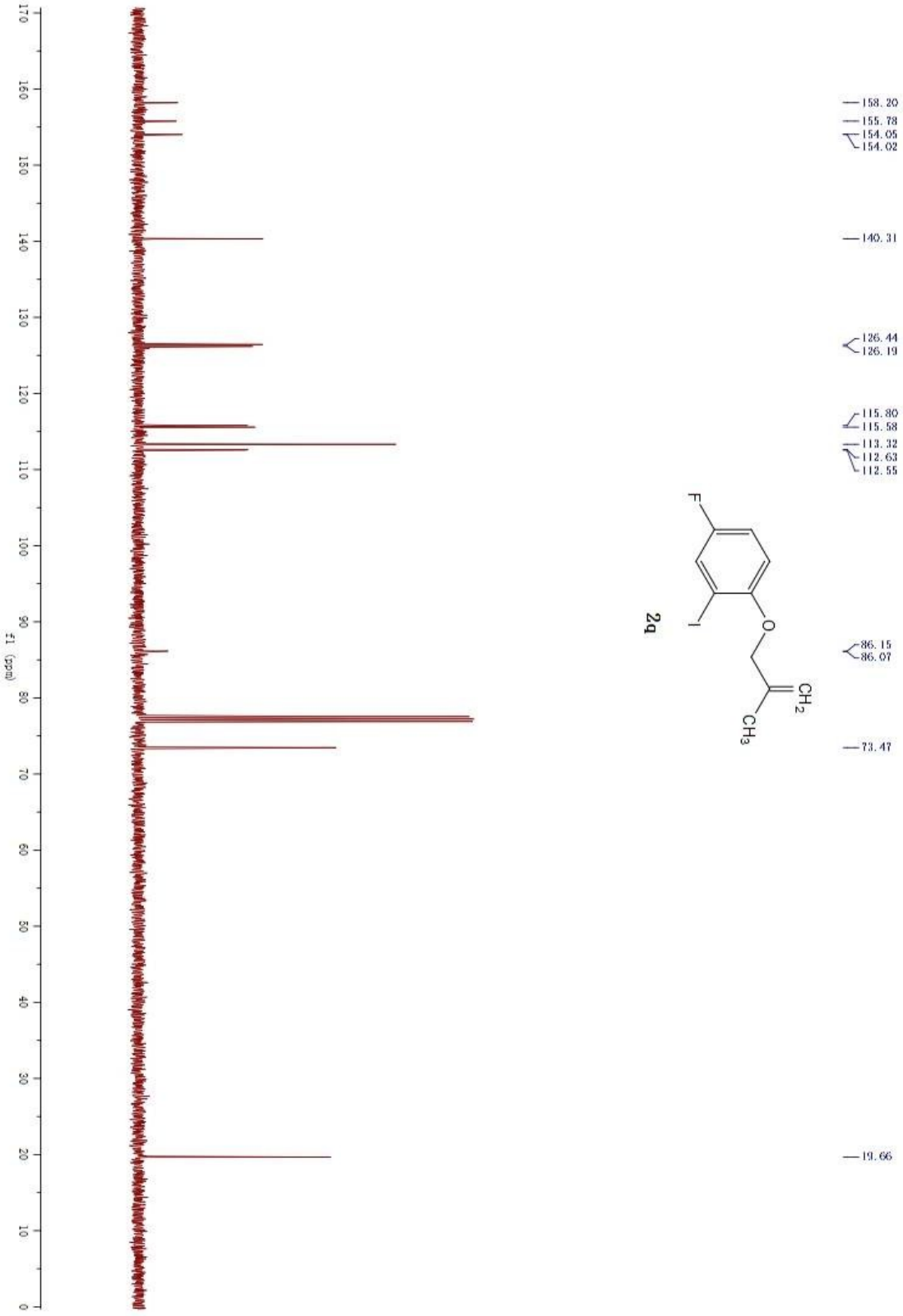
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O
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CH3
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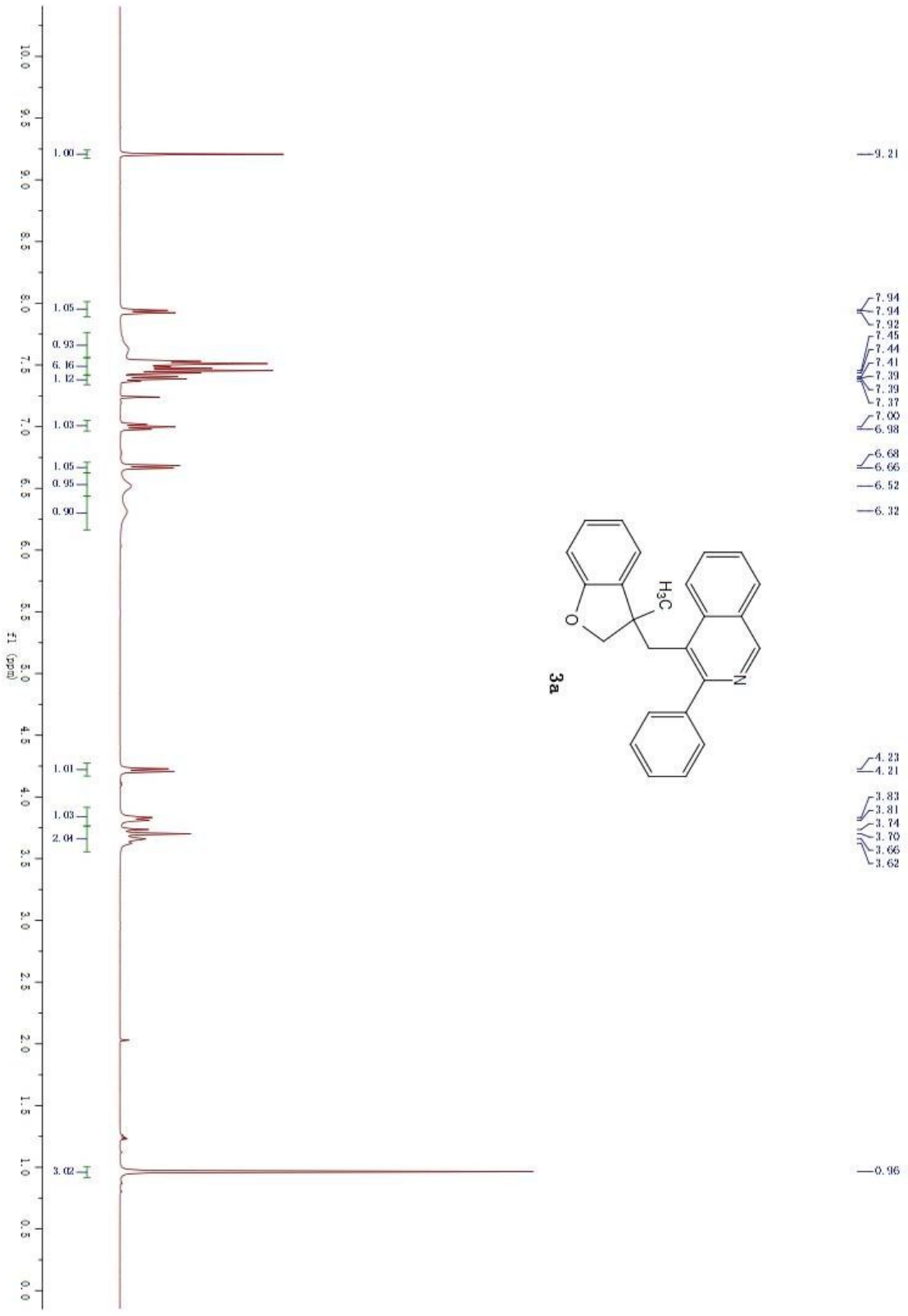
f1 (ppm)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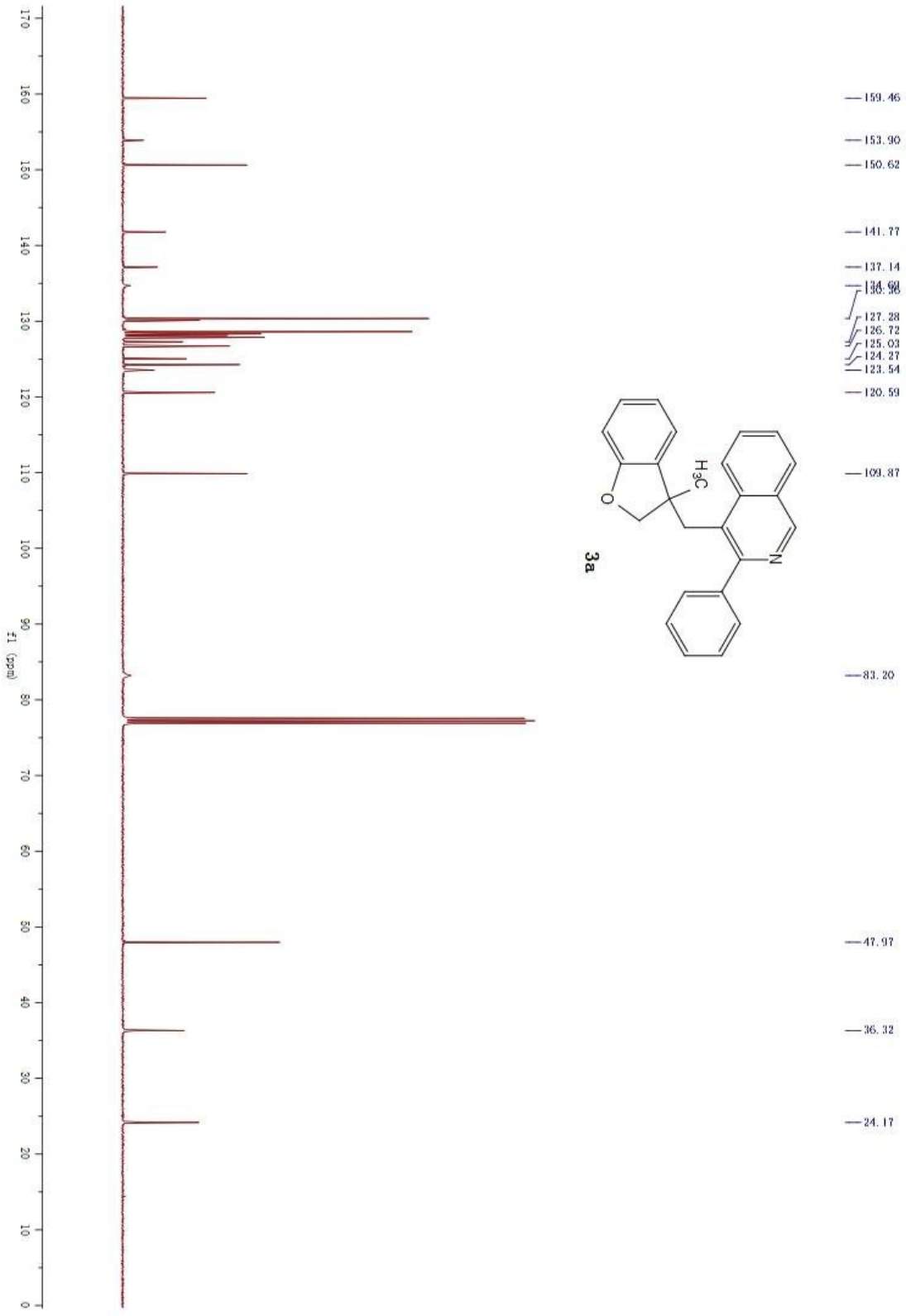
O
N

3a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O
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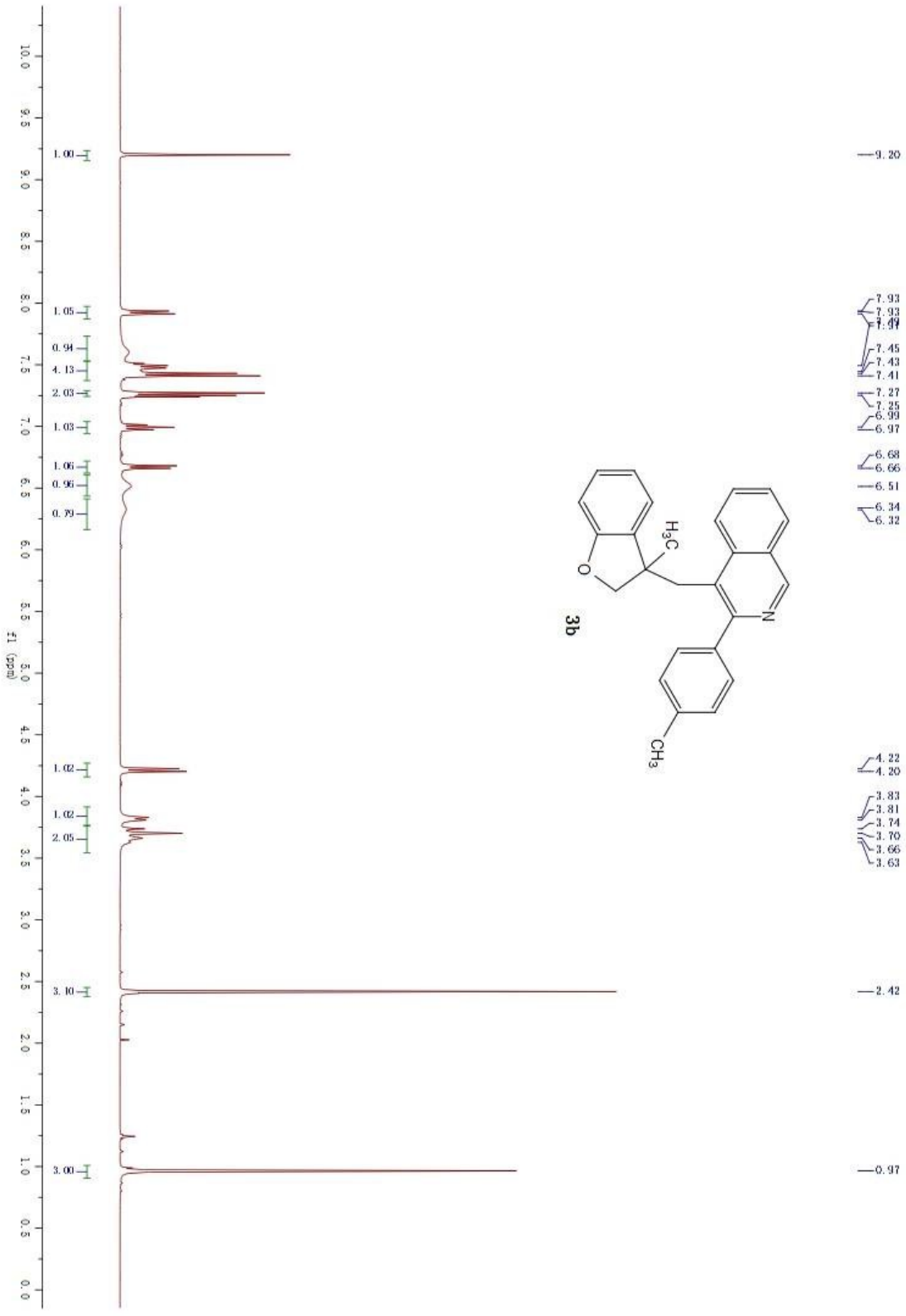
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O
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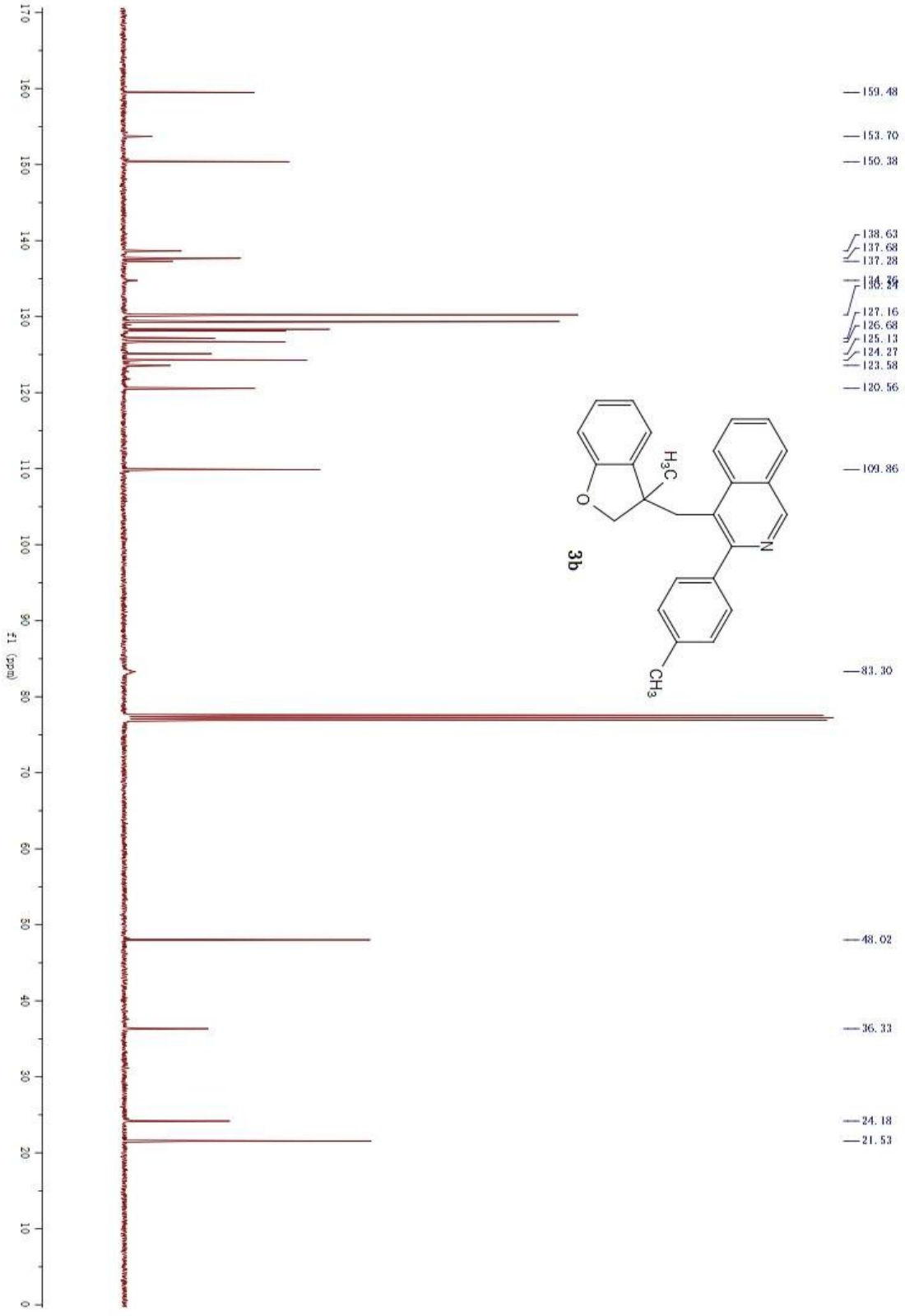
3b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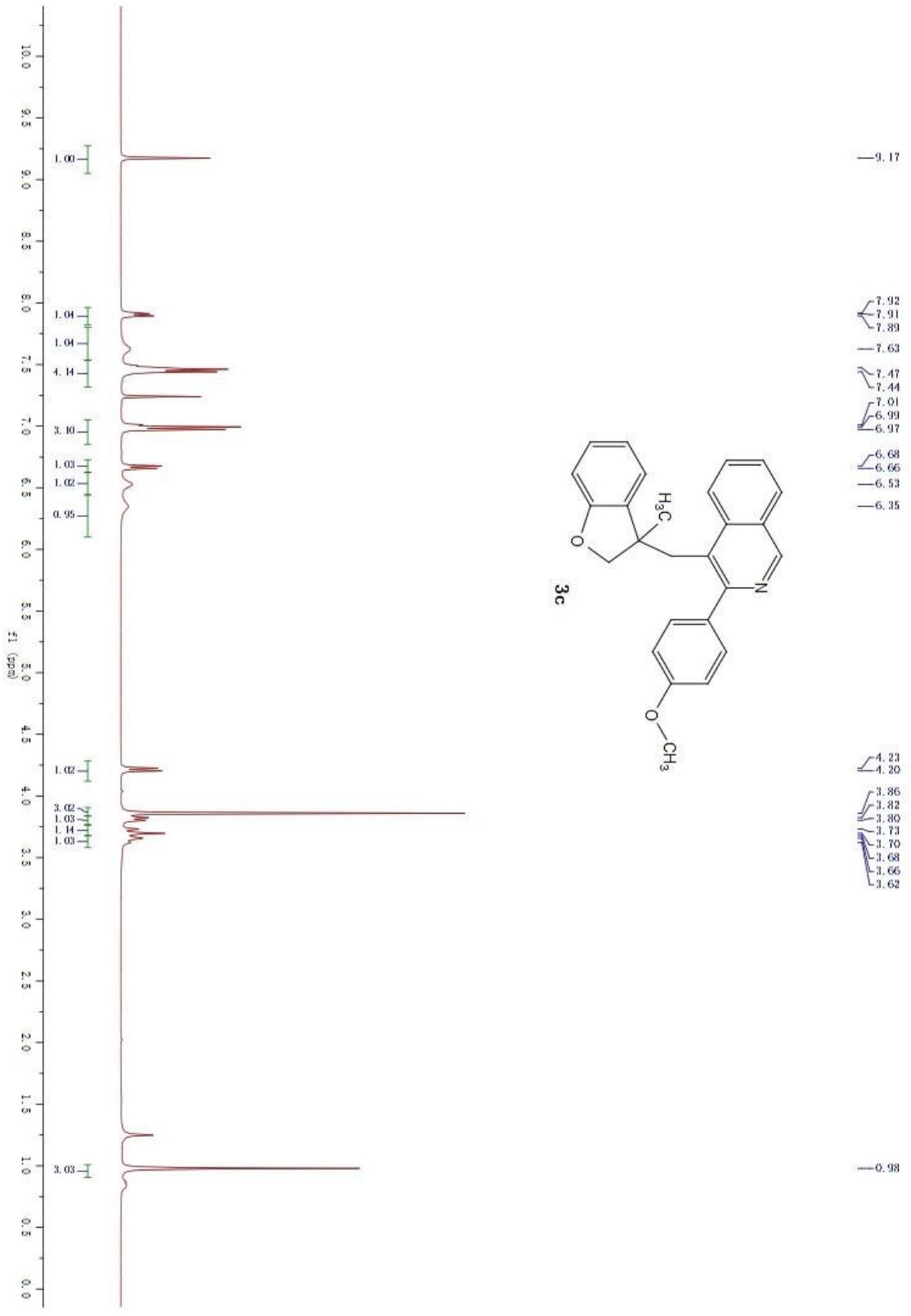
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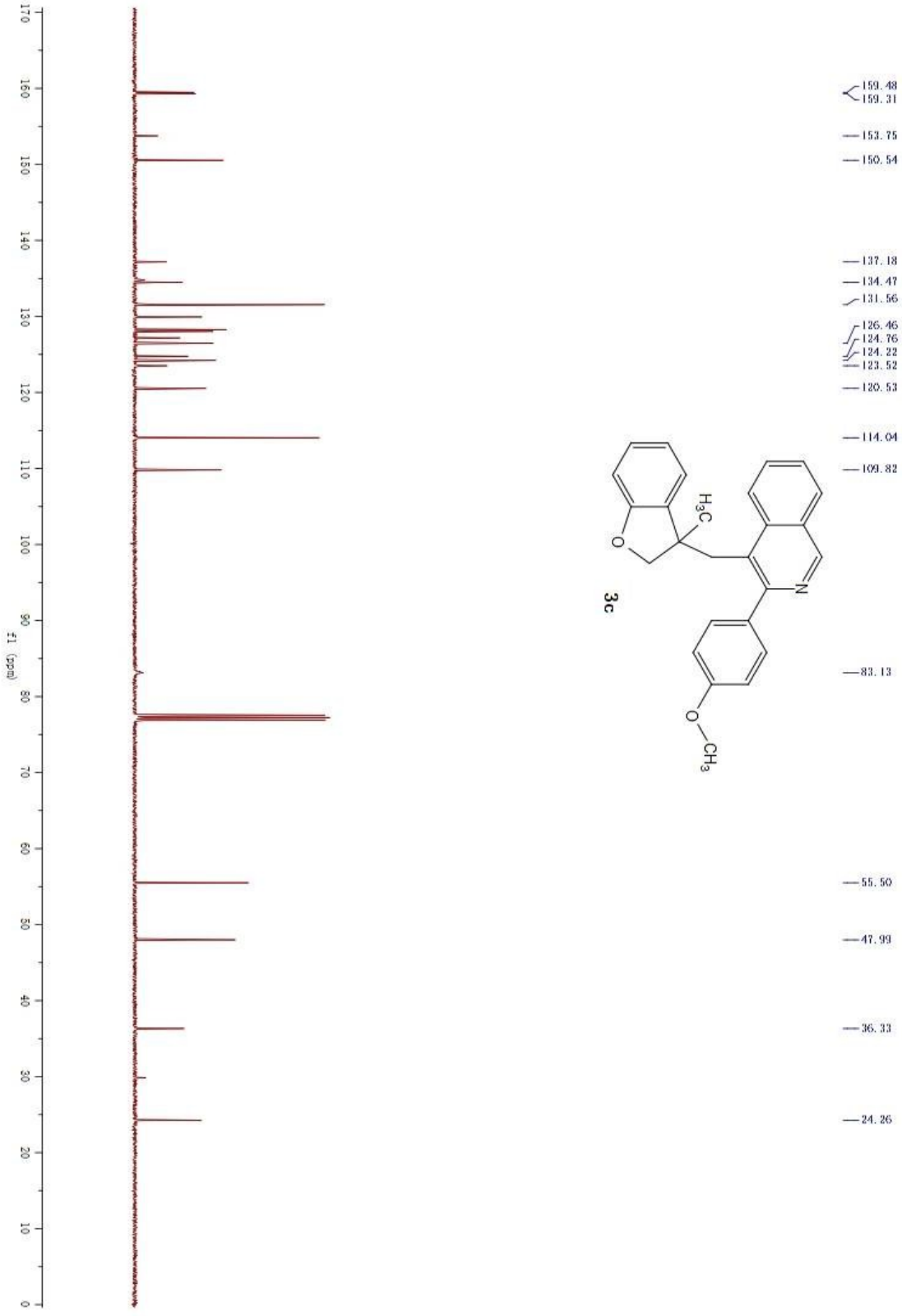
f1 (ppm)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114.04
109.82
83.13
55.50
47.99
36.33
24.26
H3C
O
N
O
CH3
3c
f1 (ppm)

9.20
7.95
7.93
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F
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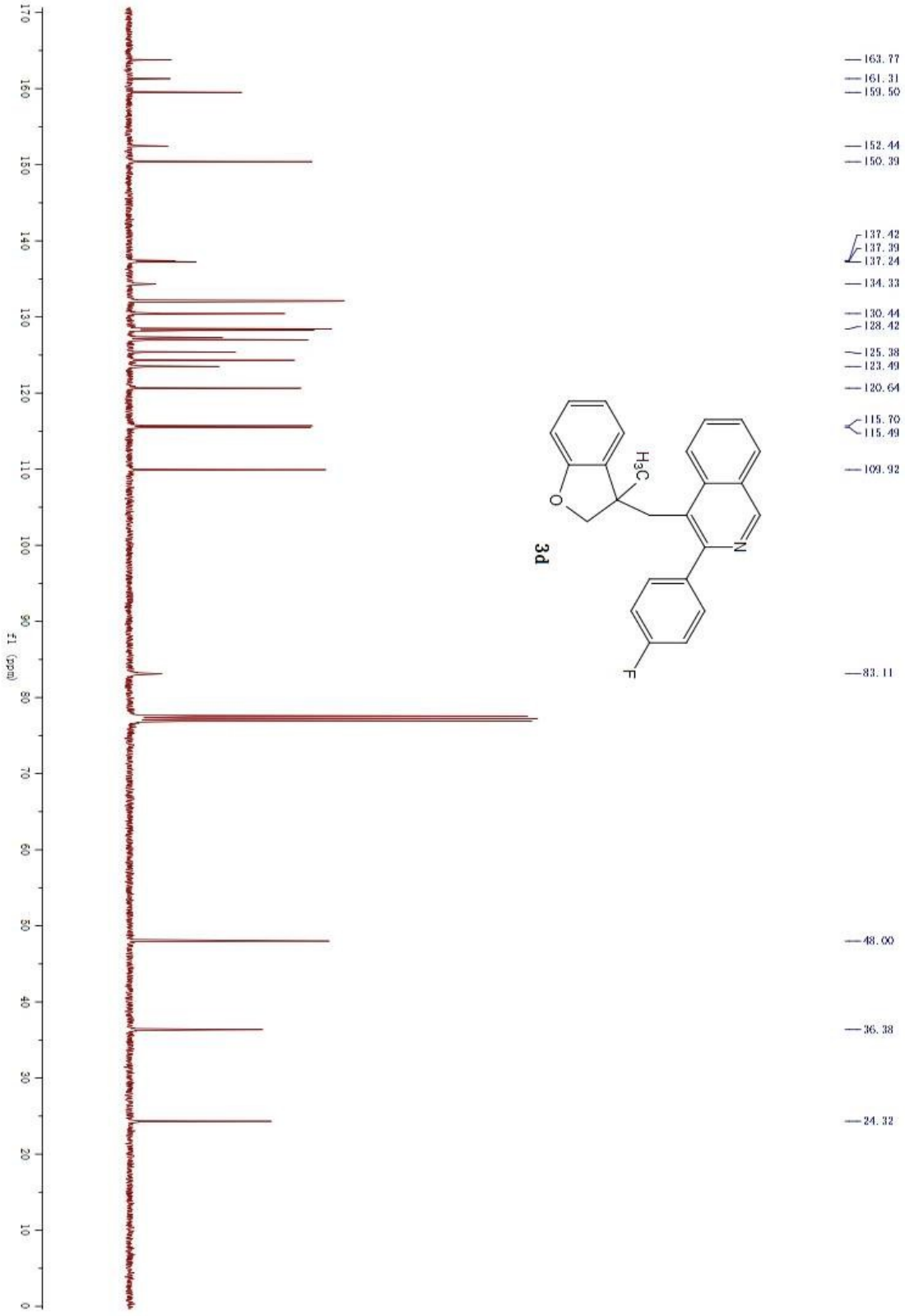
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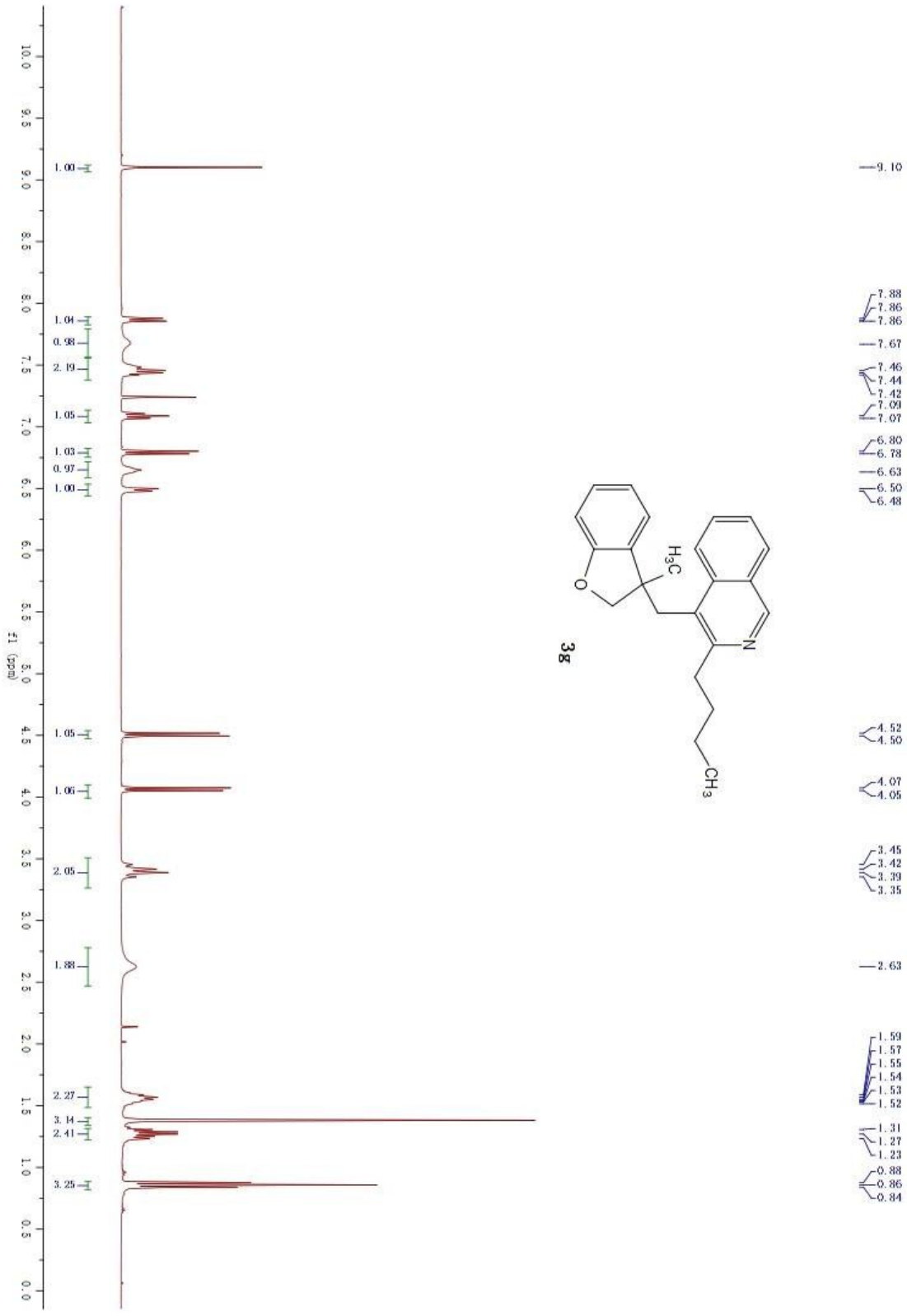
O
N
F
3d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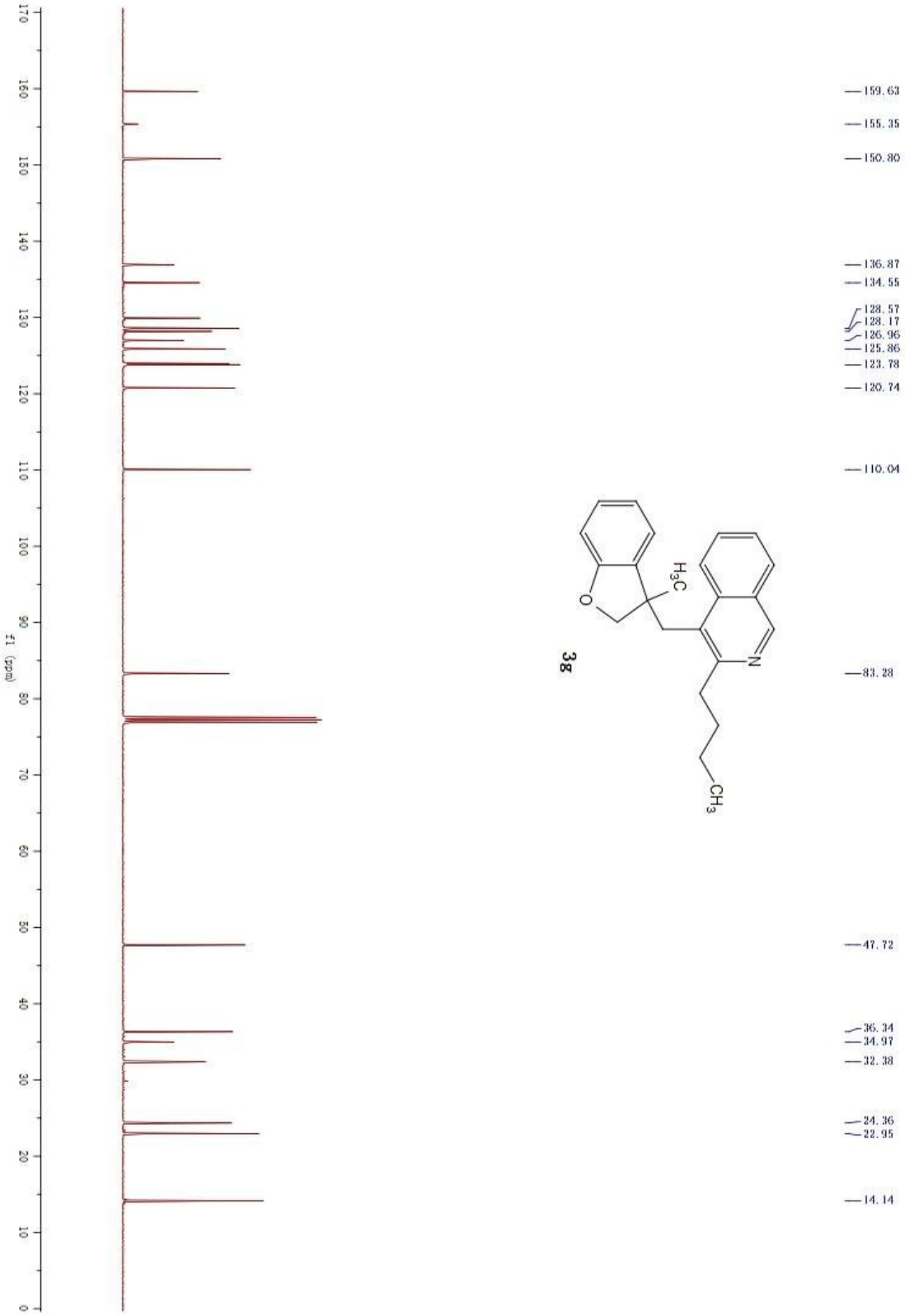
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123.78
120.74
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83.28
47.72
36.34
34.97
32.38
24.36
22.95
14.14
f1 (ppm)
3g
H3C
O
N
CH3

9.08
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7.86
7.85
7.84
7.58
7.43
7.41
7.05
7.03
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1.68
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1.08
2.18
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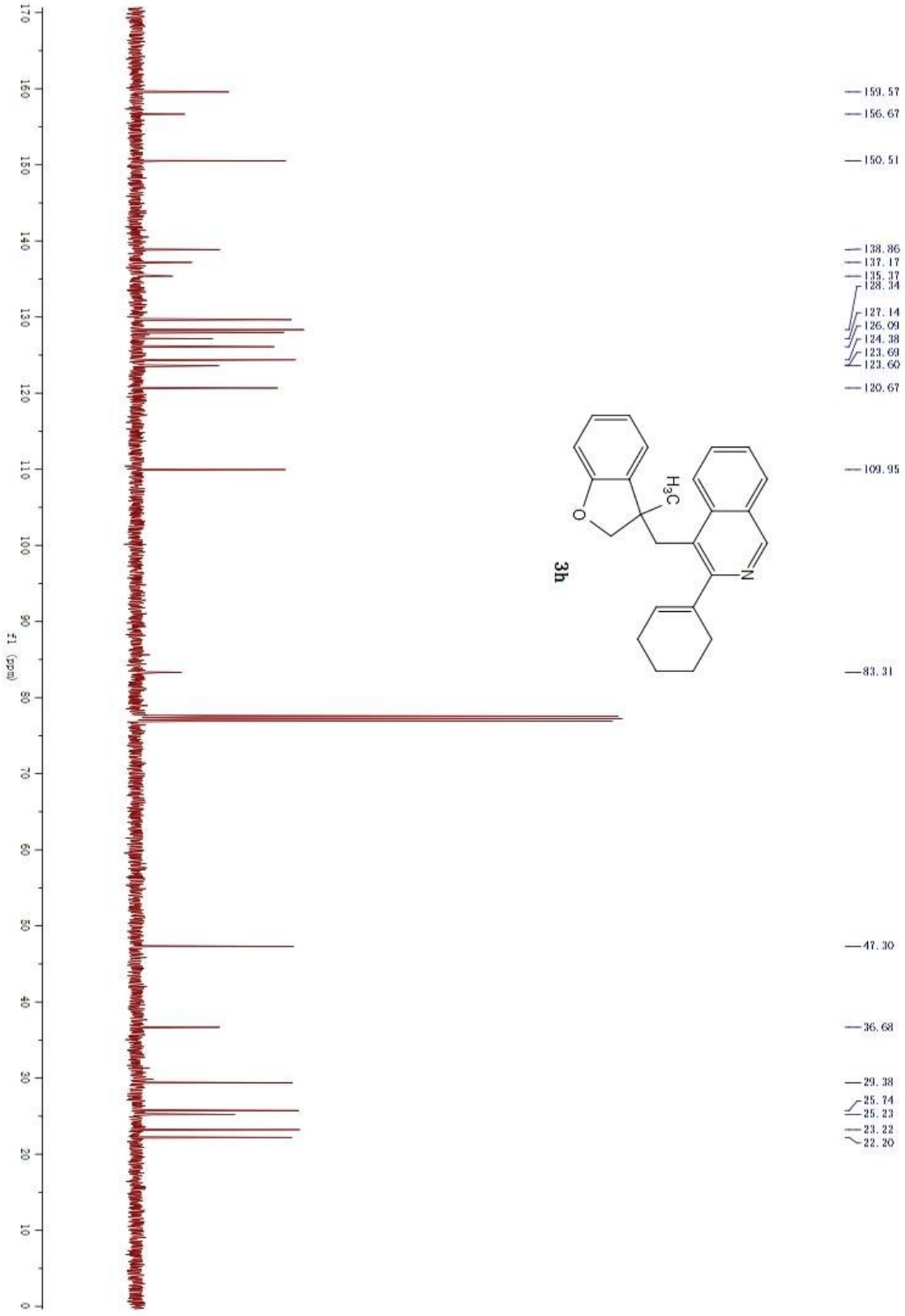
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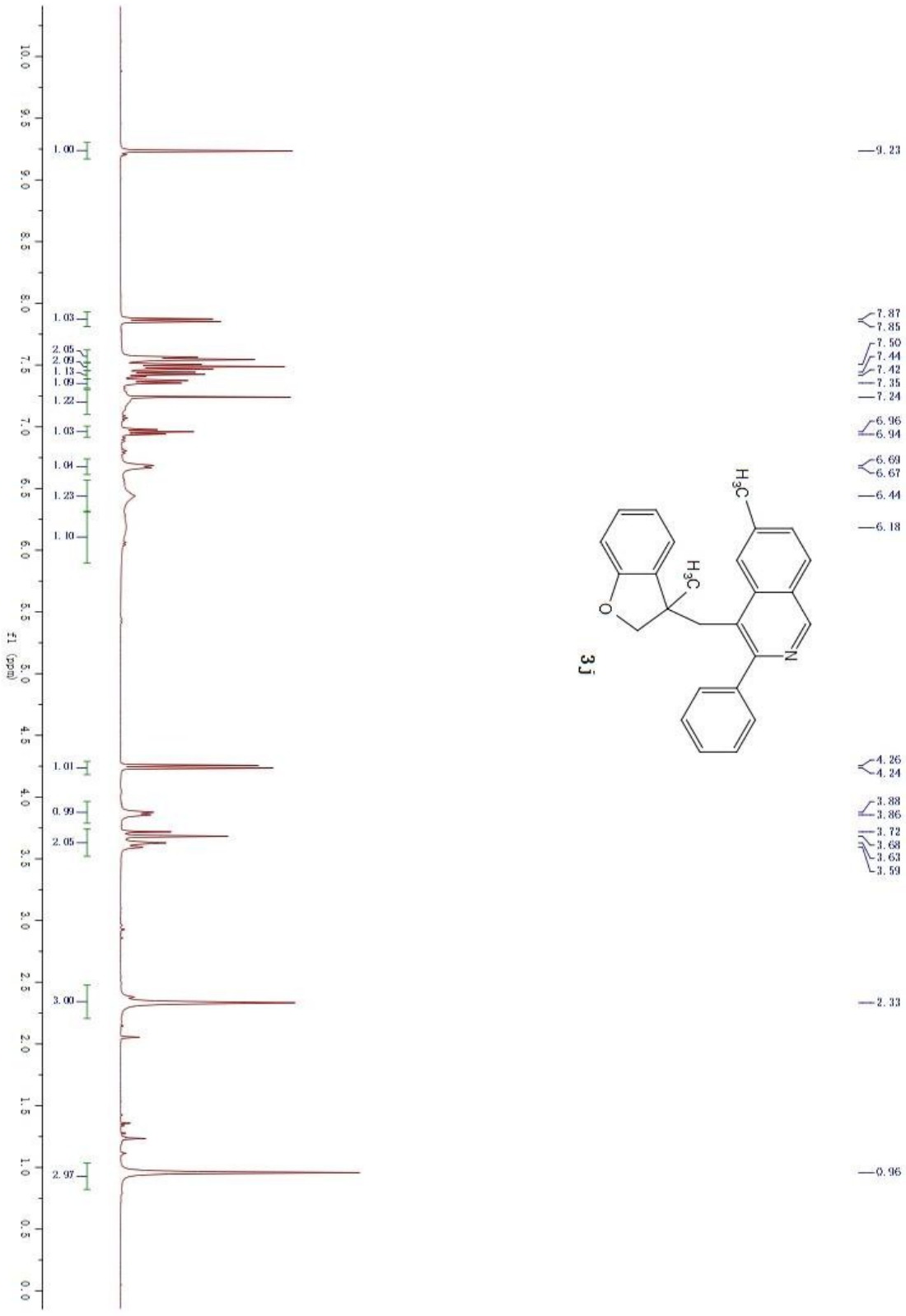
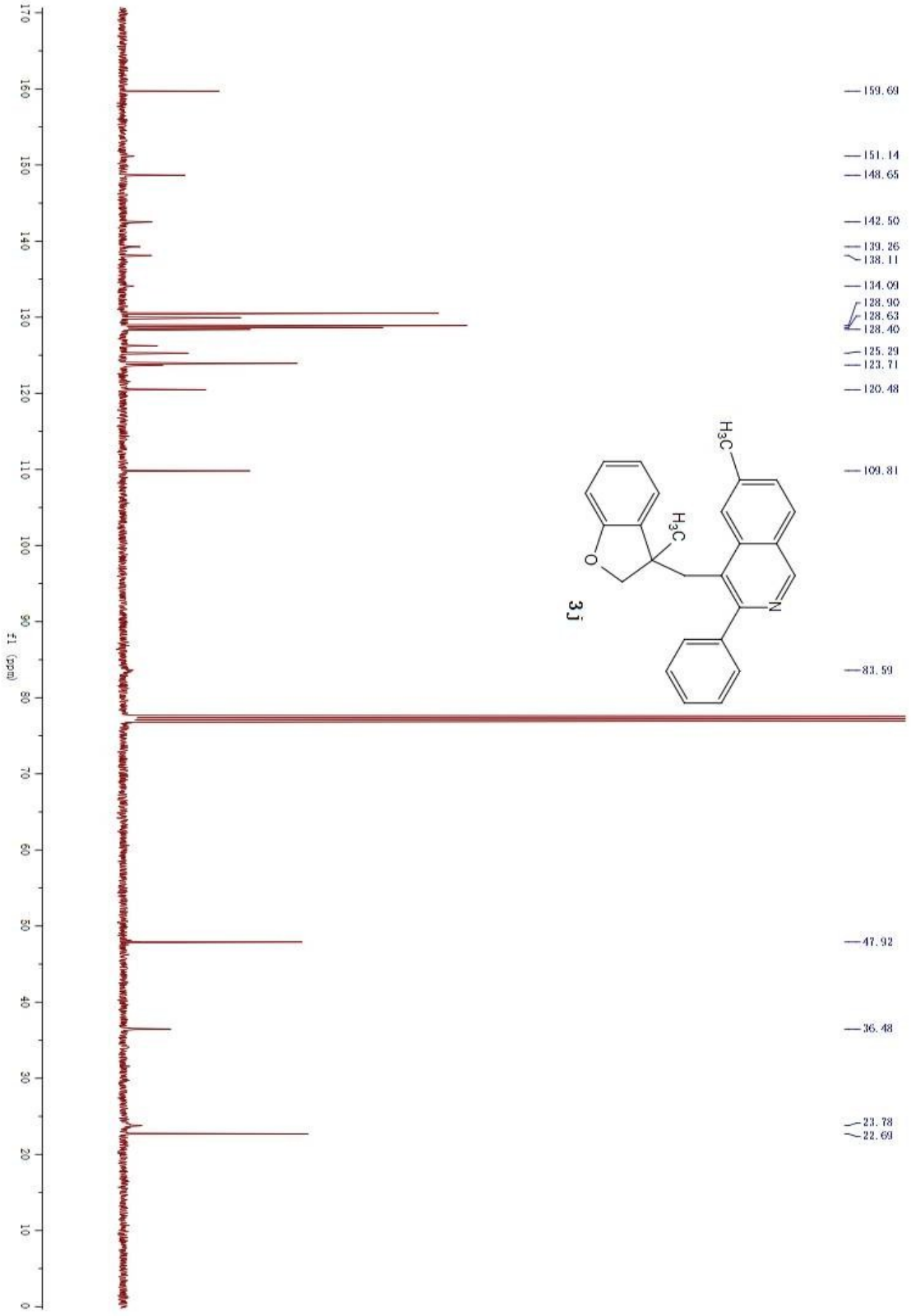
123.69
123.60
120.67
109.95
83.31
47.30
36.68
29.38
25.74
25.23
23.22
22.20
f1 (ppm)
H3C
O
N
3h


9.23
7.87
7.85
7.50
7.44
7.42
7.35
7.24
6.96
6.94
6.69
6.67
6.44
6.18
4.26
4.24
3.88
3.86
3.72
3.68
3.63
3.59
2.33
0.96
H3C
H3C
O
N
3j
f1 (ppm)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151.14
148.65
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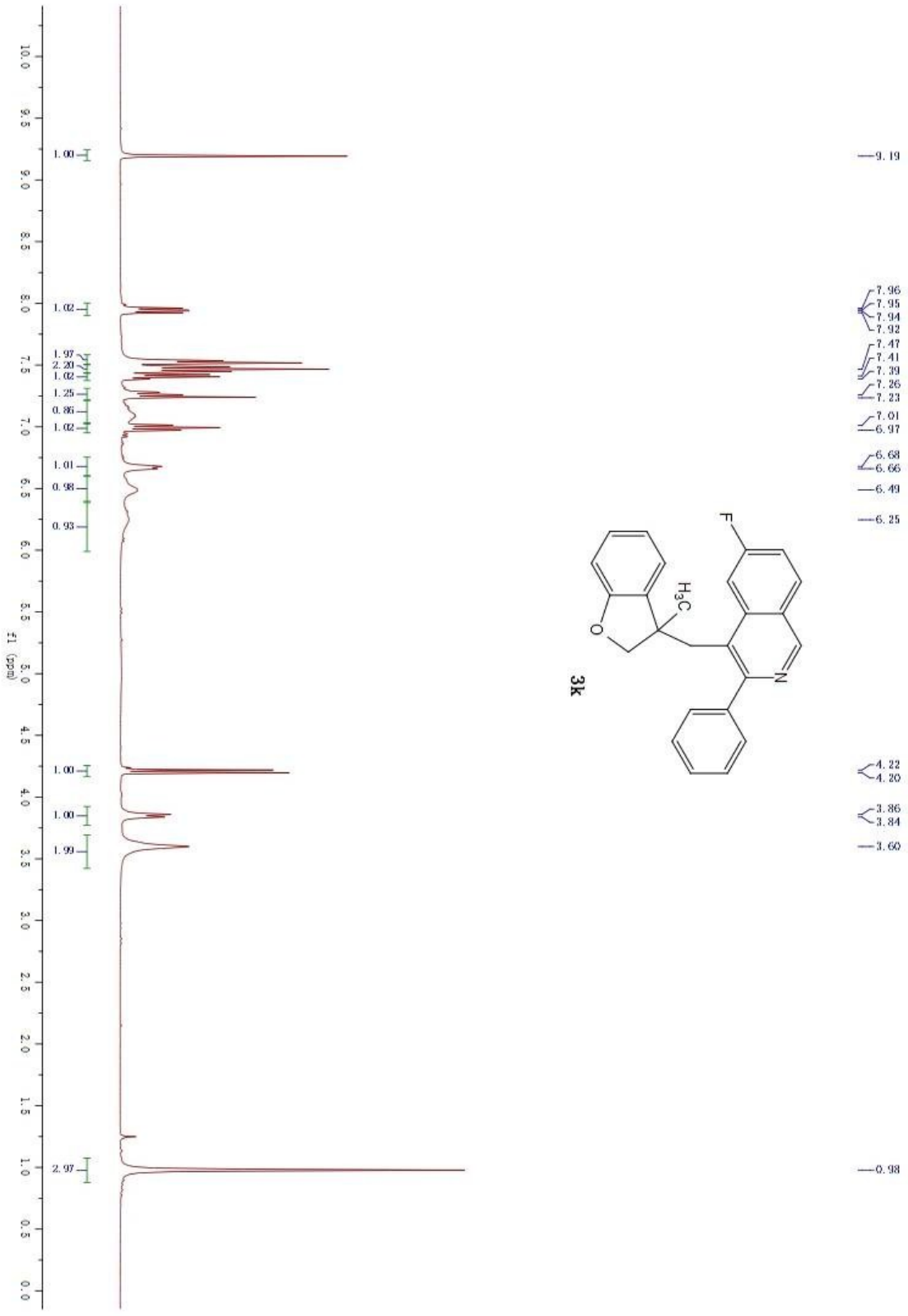
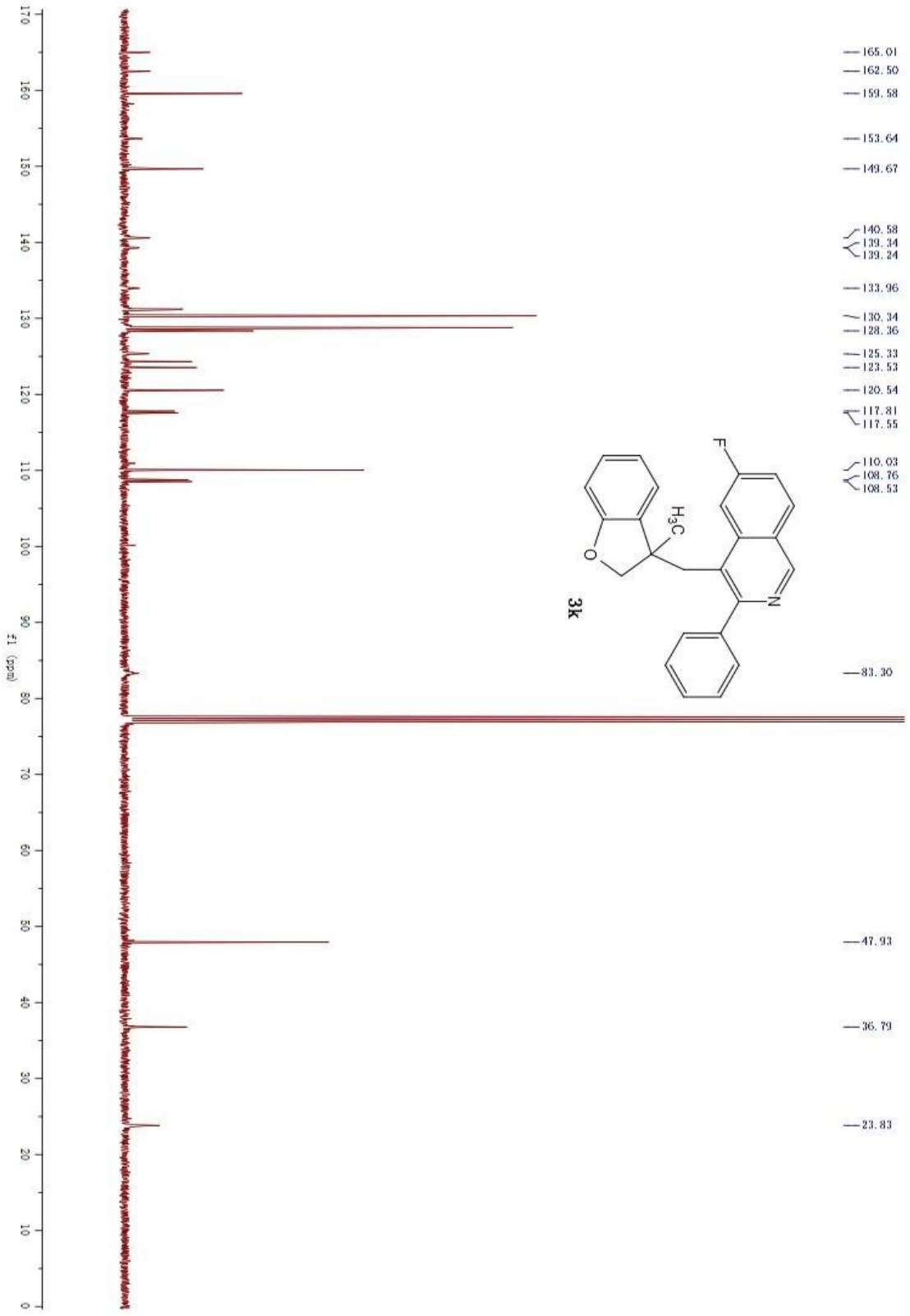
139.26
138.11
134.09
128.90
128.63
128.40
125.29
123.71
120.48
109.81
83.59
47.92
36.48
23.78
22.69
f1 (ppm)
H3C
H3C
O
N
3j


9.19
7.96
7.95
7.94
7.92
7.47
7.41
7.39
7.26
7.23
7.01
6.97
6.68
6.66
6.49
6.25
4.22
4.20
3.86
3.84
3.60
0.98
F
H3C
O
N
3k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162.50
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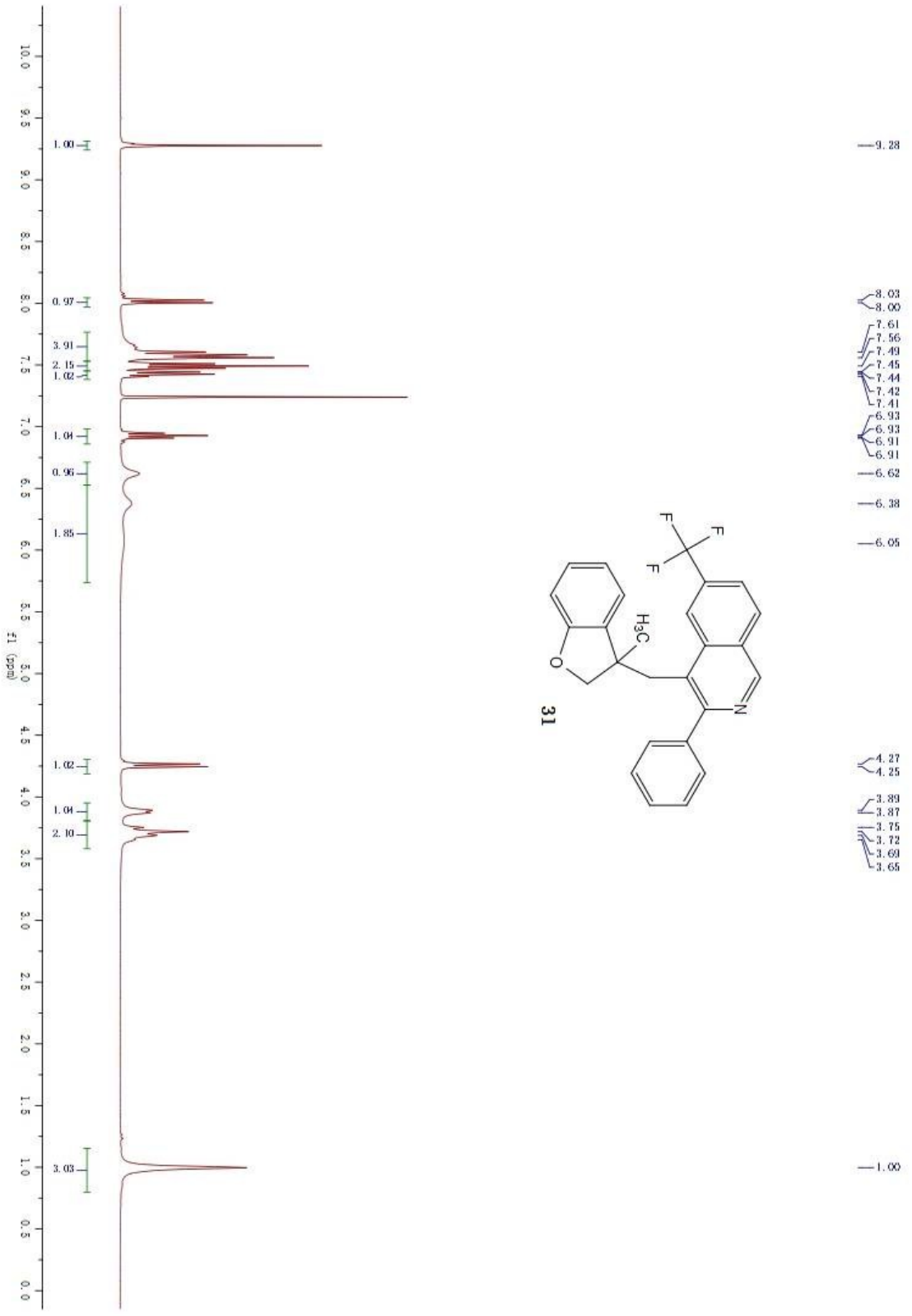
140.58
139.34
139.24
133.96
130.34
128.36
125.33
123.53
120.54
117.81
117.55
110.03
108.76
108.53
83.30
47.93
36.79
23.83
F
H3C
O
N
3k
f1 (ppm)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8.03
8.00
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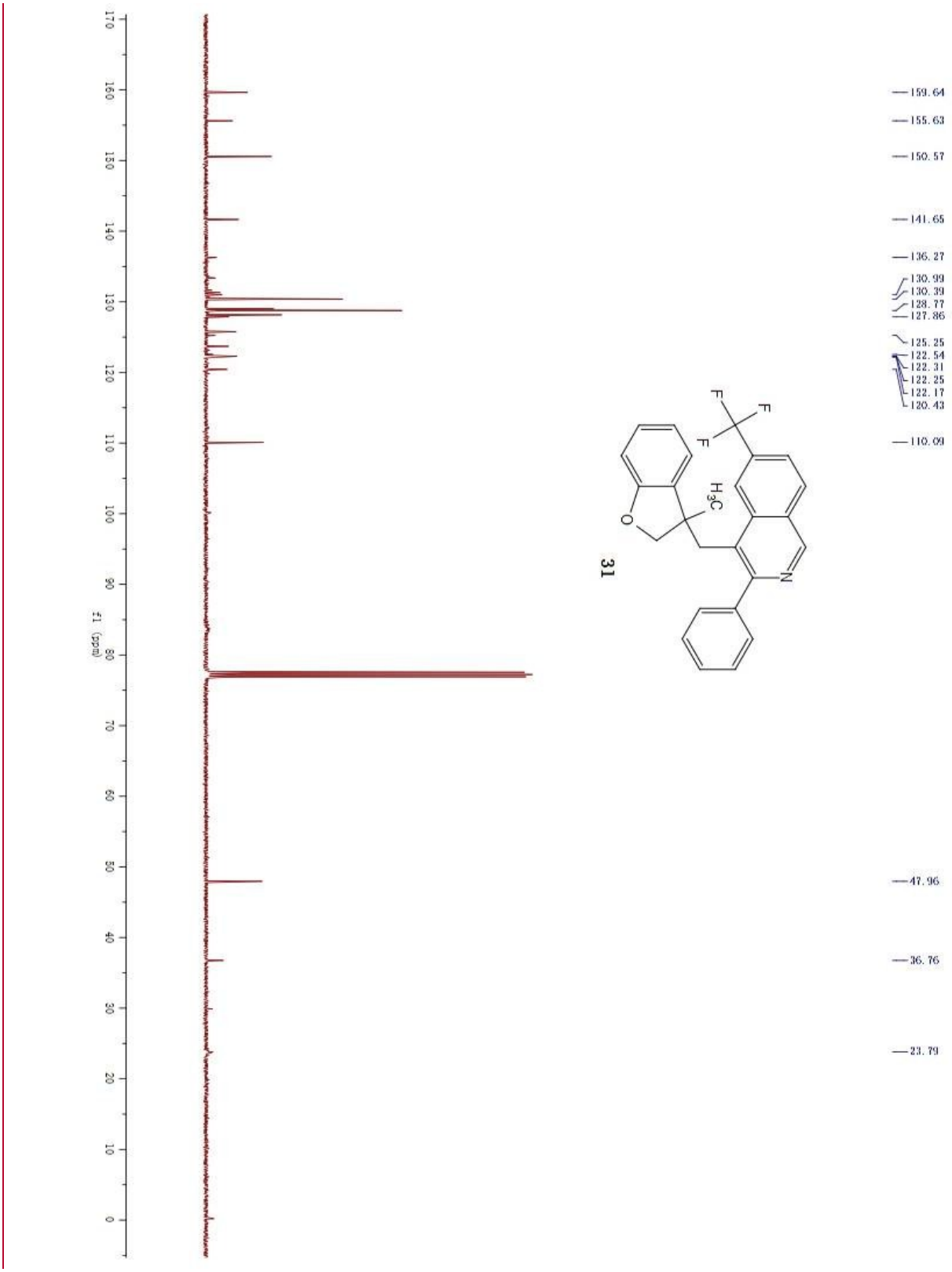
7.45
7.44
7.42
7.41
6.93
6.93
6.91
6.91
6.62
6.38
6.05
4.27
4.25
3.89
3.87
3.75
3.72
3.69
3.65
1.00
1.00
0.97
3.91
2.15
1.02
1.04
0.96
1.85
1.02
1.04
2.10
3.03
f1 (ppm)
F
F
F
H3C
O
N
31


159.64
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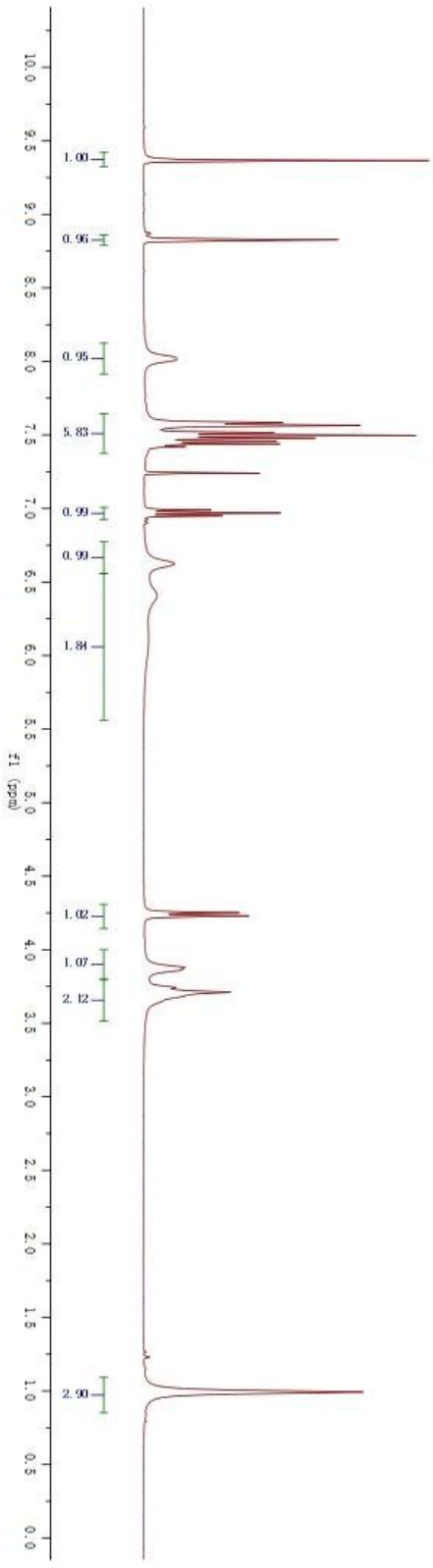
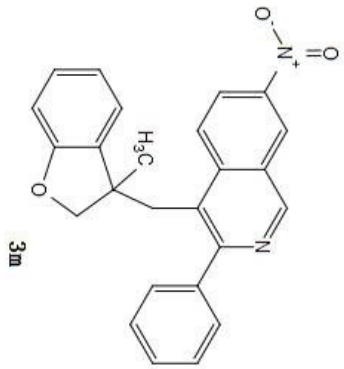
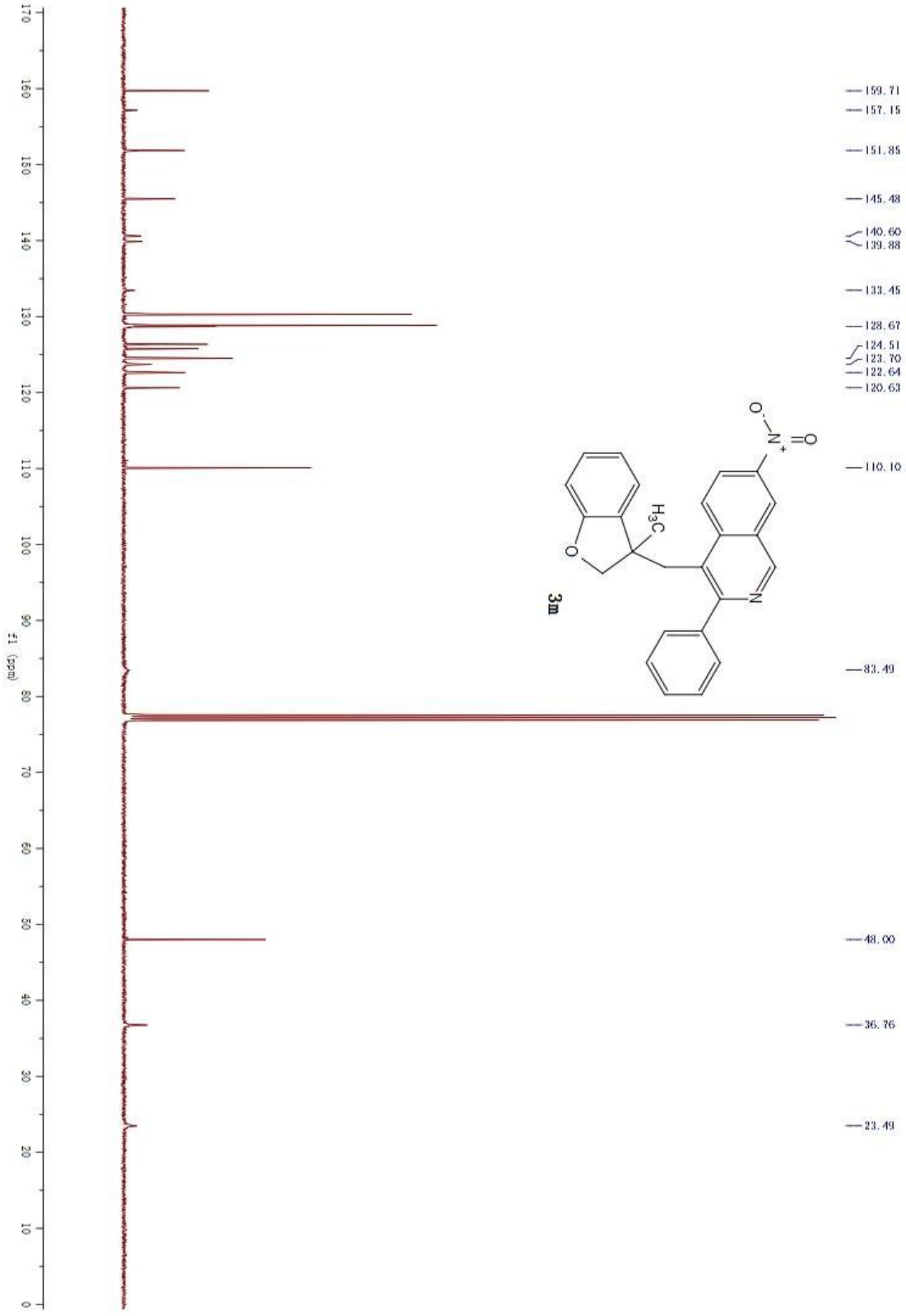
141.65
136.27
130.99
130.39
128.77
127.86
125.25
122.54
122.31
122.25
122.17
120.43
110.09
47.96
36.76
23.79
f1 (ppm)
F
F
F
H3C
O
N
31

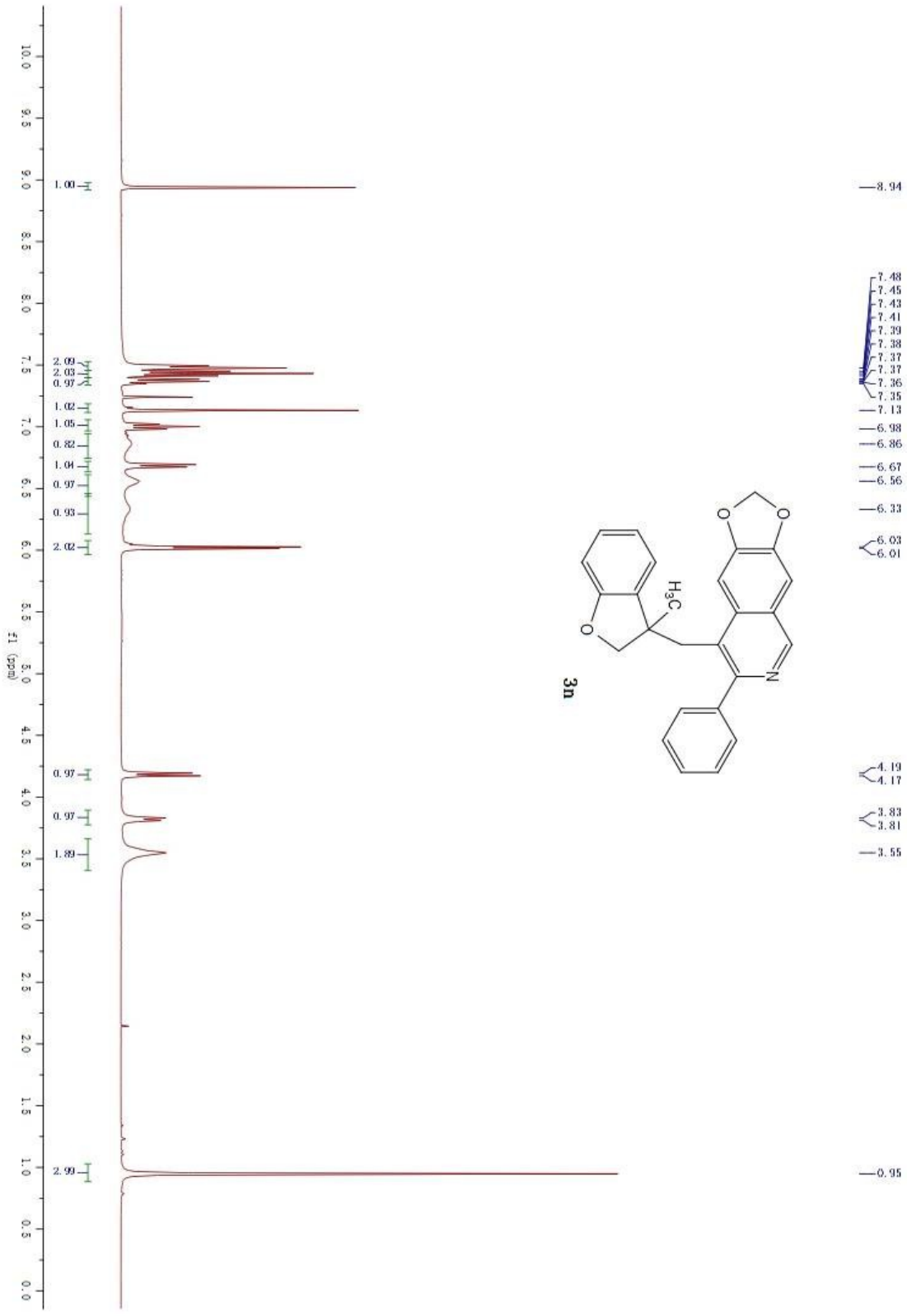


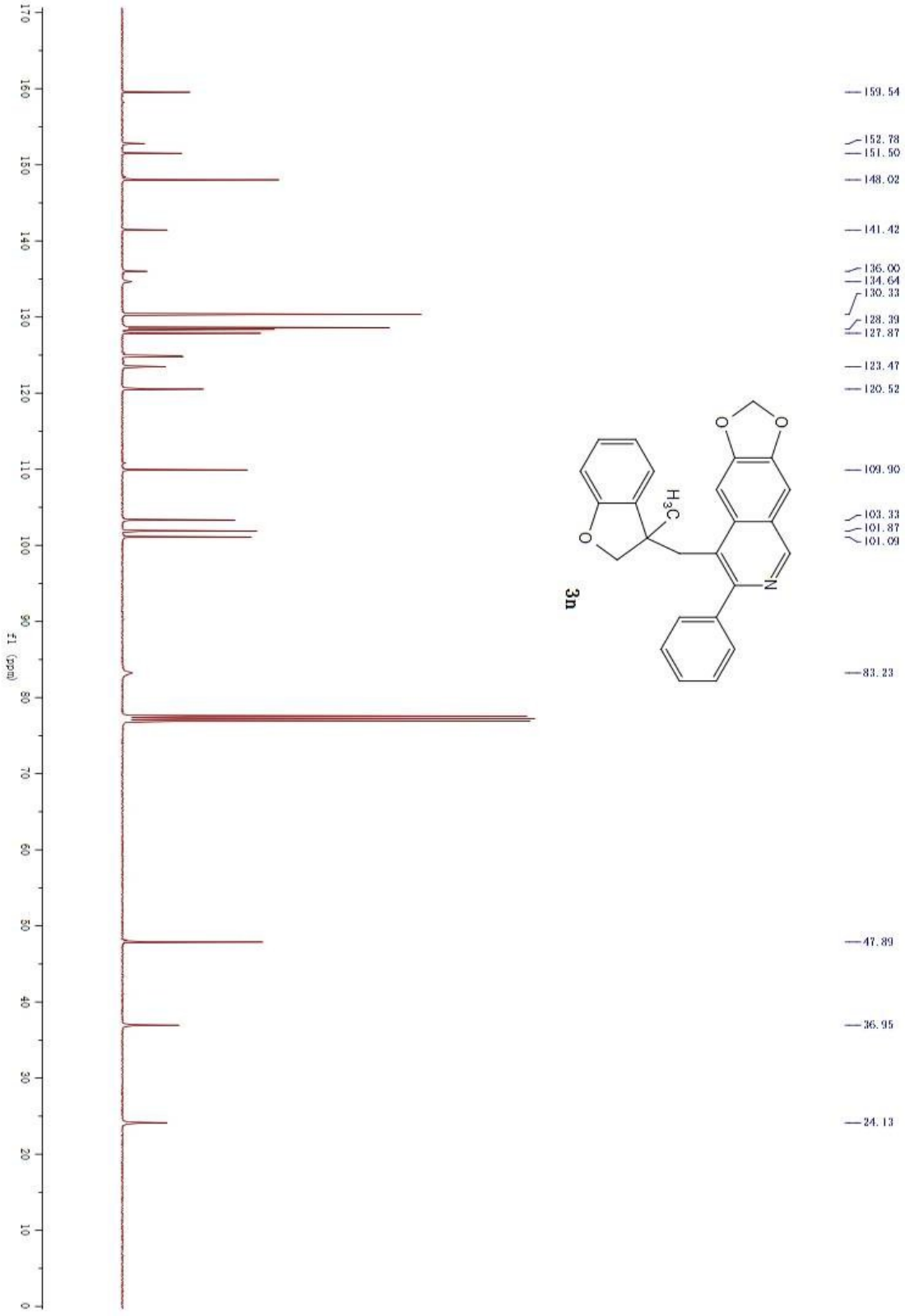


3m

9.37
8.83
8.82
8.01
6.97
6.95
6.95
6.62
6.41
6.12
4.25
4.23
3.88
3.86
3.74
3.71
0.99


159.71
157.15
151.85
145.48
140.60
139.88
133.45
128.67
124.51
123.70
122.64
120.63
110.10
83.49
48.00
36.76
23.49
f1 (ppm)
3m


f1 (ppm)
10.0
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
1.00
2.09
2.03
0.97
1.02
1.05
0.82
1.04
0.97
0.93
2.02
0.97
0.97
1.89
2.99
8.94
7.48
7.45
7.43
7.41
7.39
7.38
7.37
7.37
7.36
7.35
7.13
6.98
6.86
6.67
6.56
6.33
6.03
6.01
4.19
4.17
3.83
3.81
3.55
0.95
H3C
O
O
O
N
3n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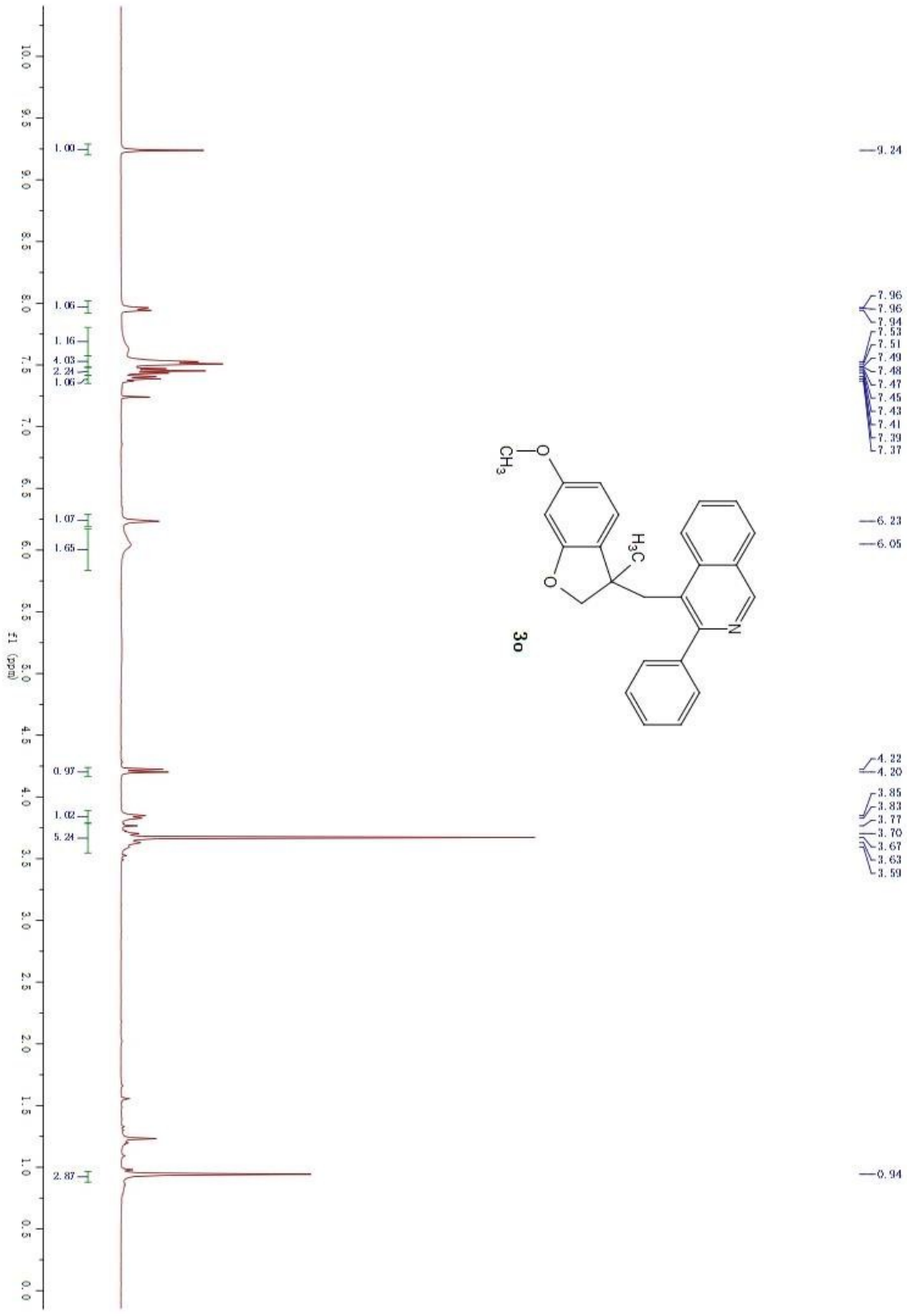
151.50
148.02
141.42
136.00
134.64
130.33
128.39
127.87
123.47
120.52
109.90
103.33
101.87
101.09
83.23
47.89
36.95
24.13
H3C
O
O
O
N
3n
f1 (ppm)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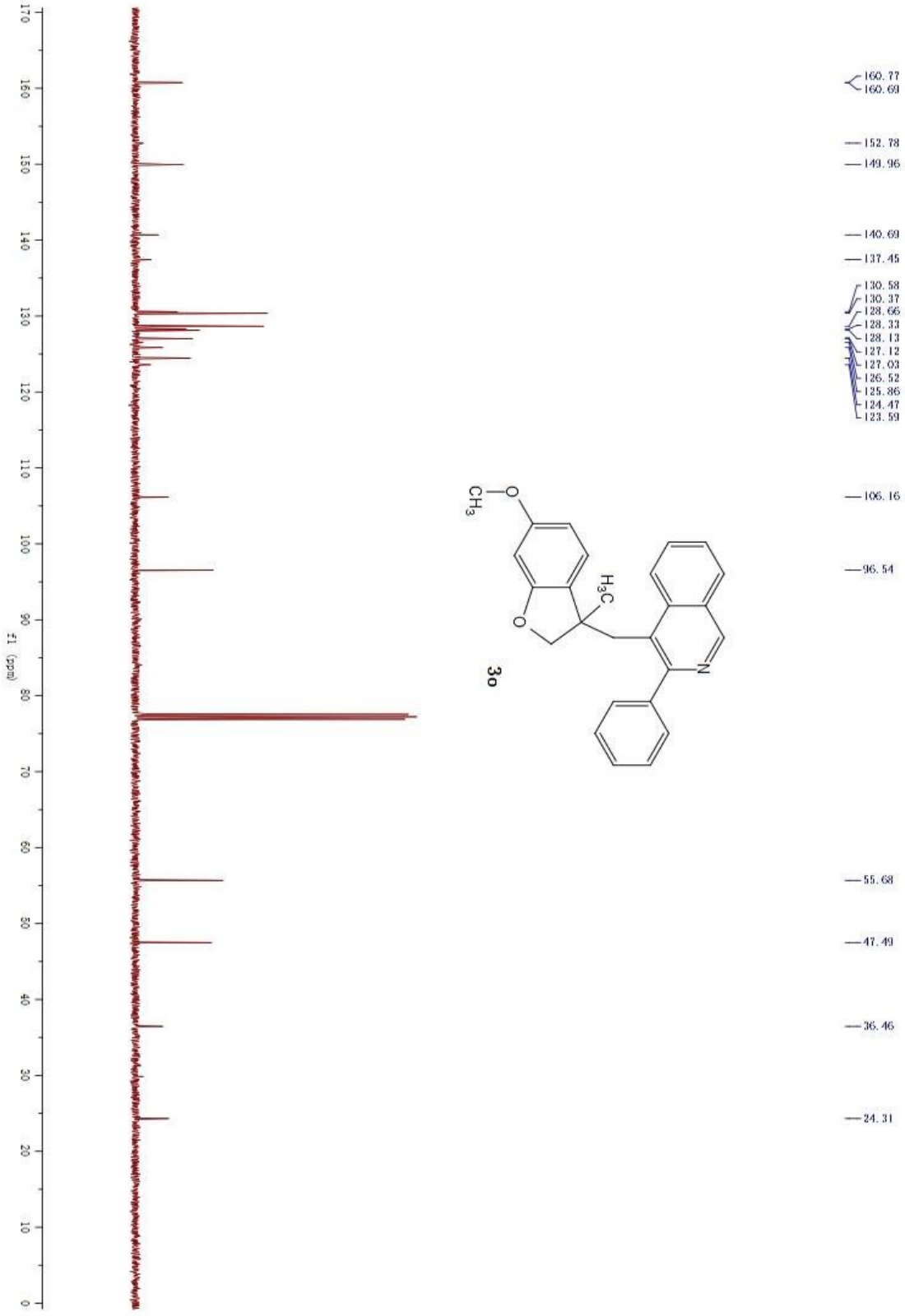
7.96
7.96
7.94
7.53
7.51
7.49
7.48
7.47
7.45
7.43
7.41
7.39
7.37
6.23
6.05
4.22
4.20
3.85
3.83
3.77
3.70
3.67
3.63
3.59
0.94
1.00
1.06
1.16
4.03
2.24
1.06
1.07
1.65
0.97
1.02
5.24
2.87
f1 (ppm)
O
CH3
H3C
O
N
3o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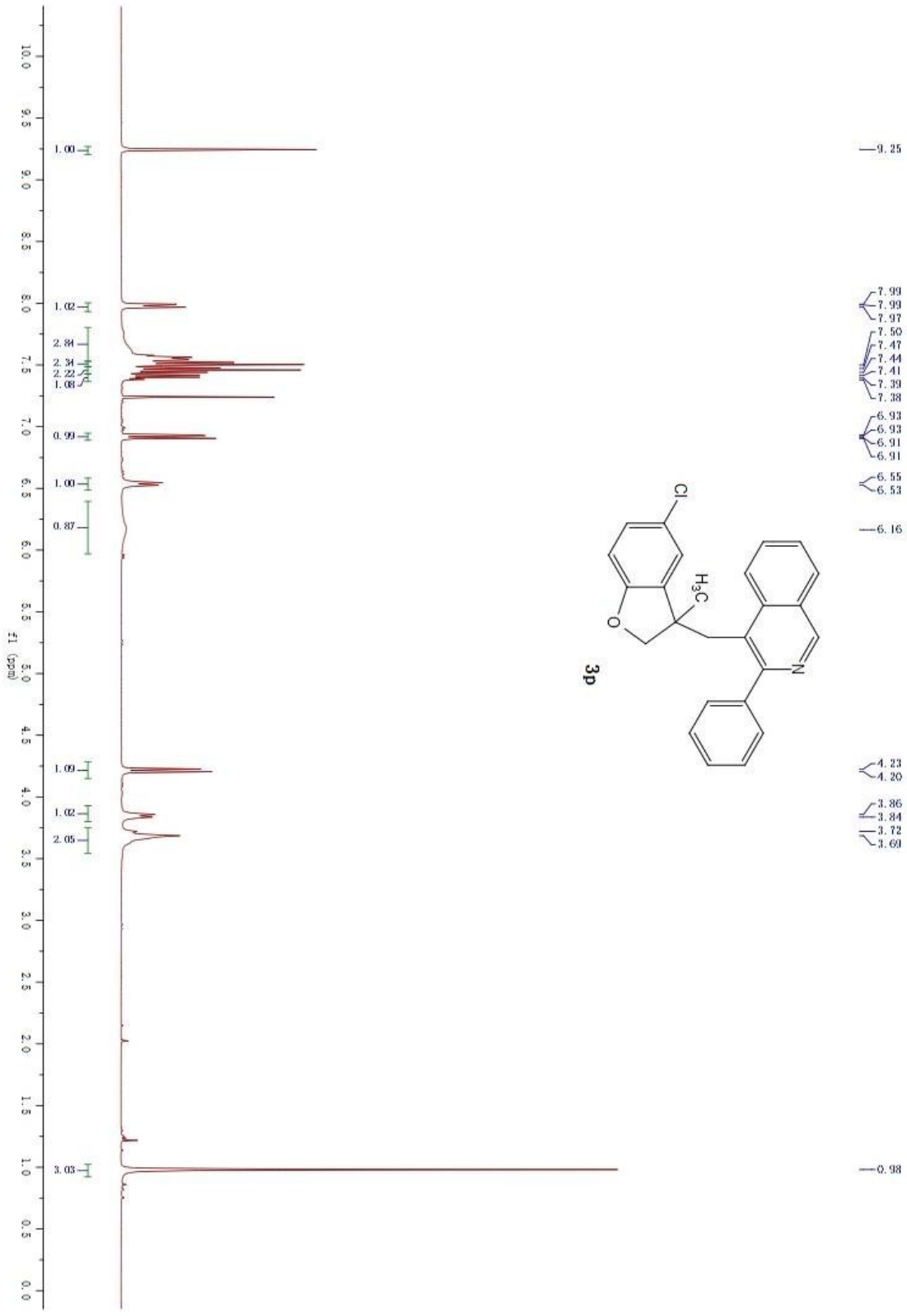
140.69
137.45
130.58
130.37
128.66
128.33
128.13
127.12
127.03
126.52
125.86
124.47
123.59
106.16
96.54
55.68
47.49
36.46
24.31
f1 (ppm)
O
CH3
H3C
O
N
3o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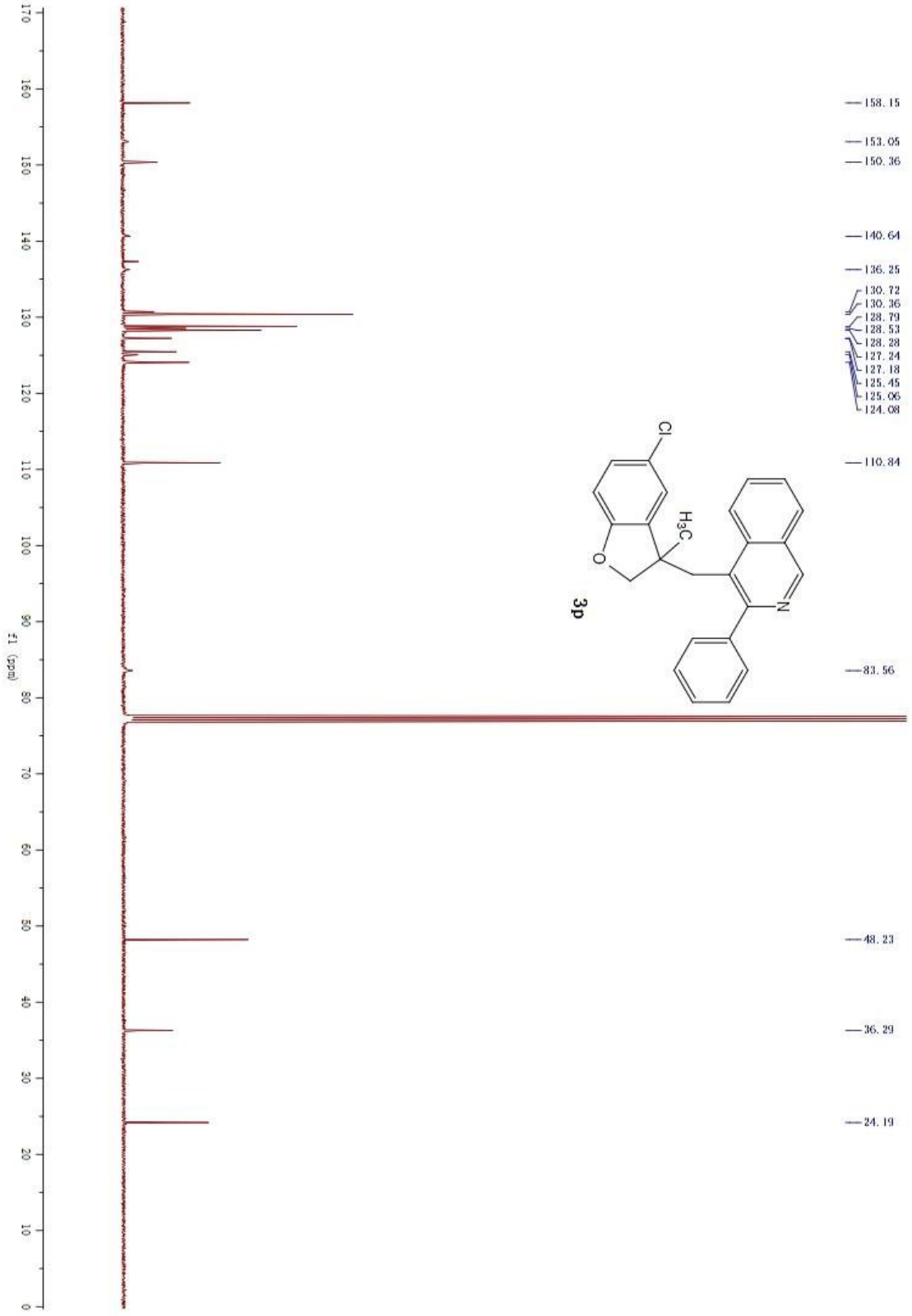
7.99
7.99
7.97
7.50
7.47
7.44
7.41
7.39
7.38
6.93
6.93
6.91
6.91
6.55
6.53
6.16
4.23
4.20
3.86
3.84
3.72
3.69
0.98
1.00
1.02
2.84
2.34
2.22
1.08
0.99
1.00
0.87
1.09
1.02
2.05
3.03
f1 (ppm)
Cl
O
H3C
N
3p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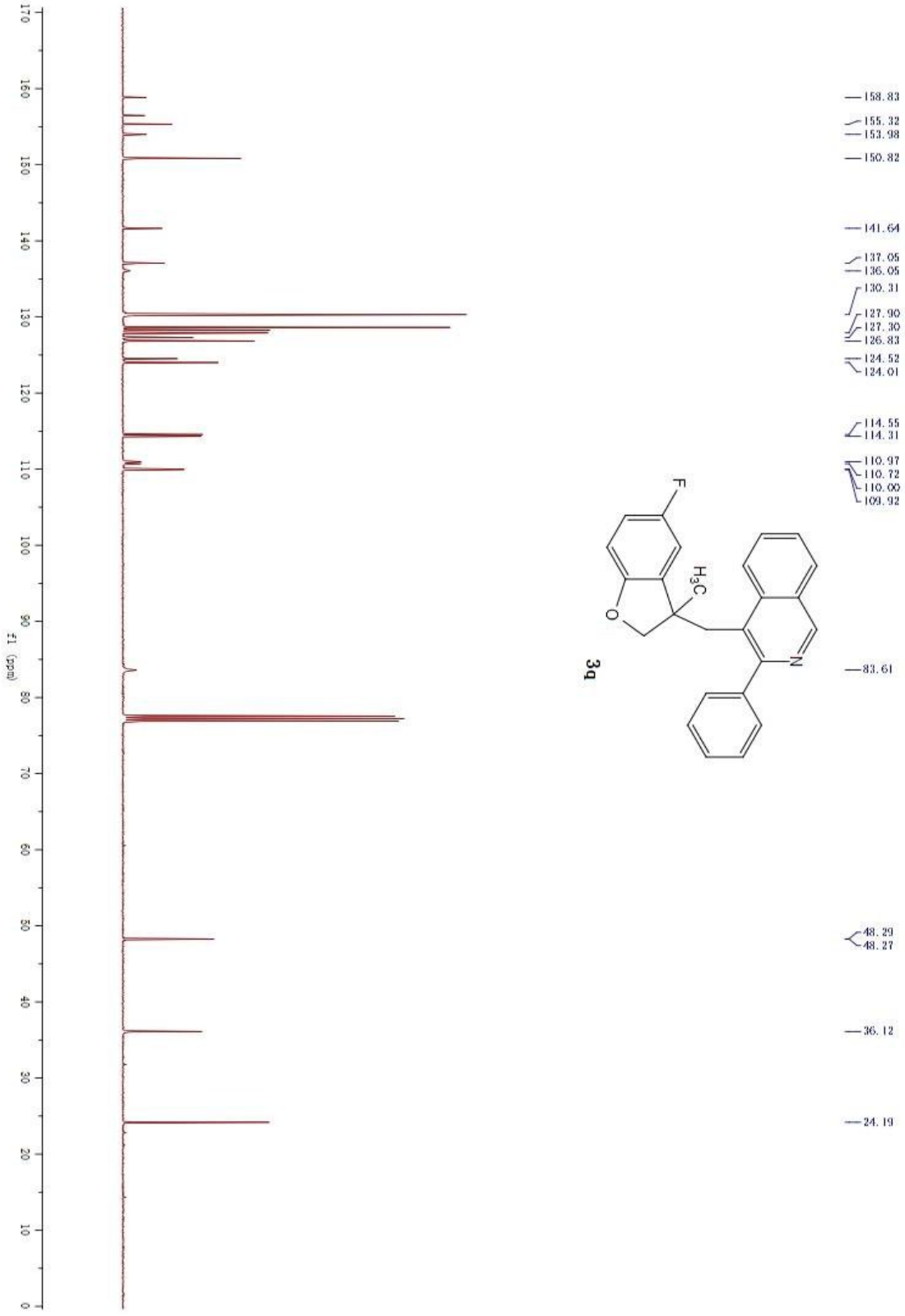
140.64
136.25
130.72
130.36
128.79
128.53
128.28
127.24
127.18
125.45
125.06
124.08
110.84
83.56
48.23
36.29
24.19
Cl
H3C
O
N
3p
f1 (ppm)

9.21
7.96
7.95
7.93
7.46
7.44
7.40
7.40
7.38
7.37
7.36
6.65
6.64
6.63
6.56
6.55
6.53
6.52
5.97
5.96
5.95
5.94
4.22
4.20
3.85
3.83
3.72
3.69
3.67
3.63
0.97
1.00
1.01
0.87
4.12
2.17
1.06
1.02
0.99
0.83
1.03
1.07
2.19
3.12
f1 (ppm)
F
H3C
O
N
3q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155.32
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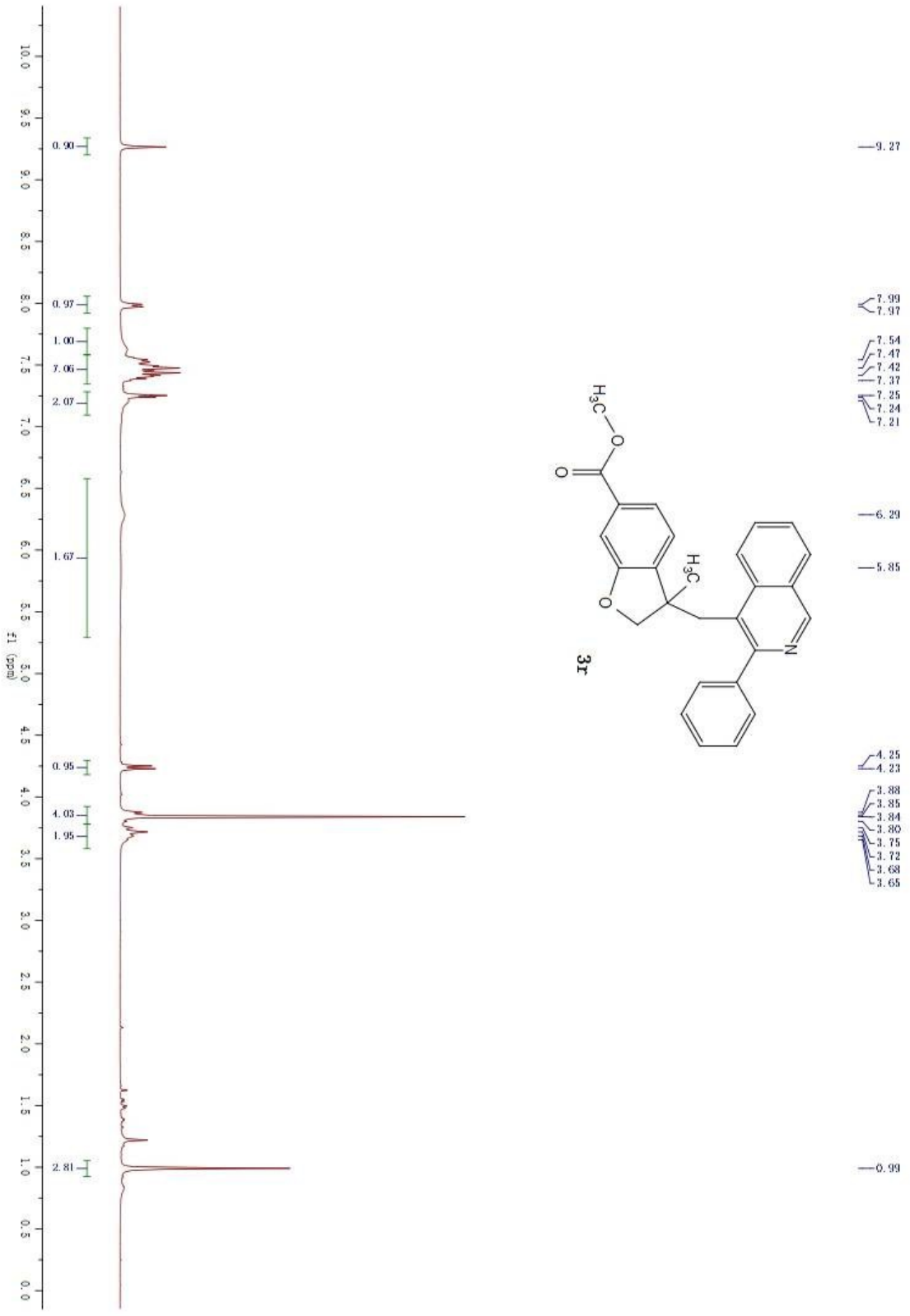
141.64
137.05
136.05
130.31
127.90
127.30
126.83
124.52
124.01
114.55
114.31
110.97
110.72
110.00
109.92
83.61
48.29
48.27
36.12
24.19
F
H3C
O
N
3q
f1 (ppm)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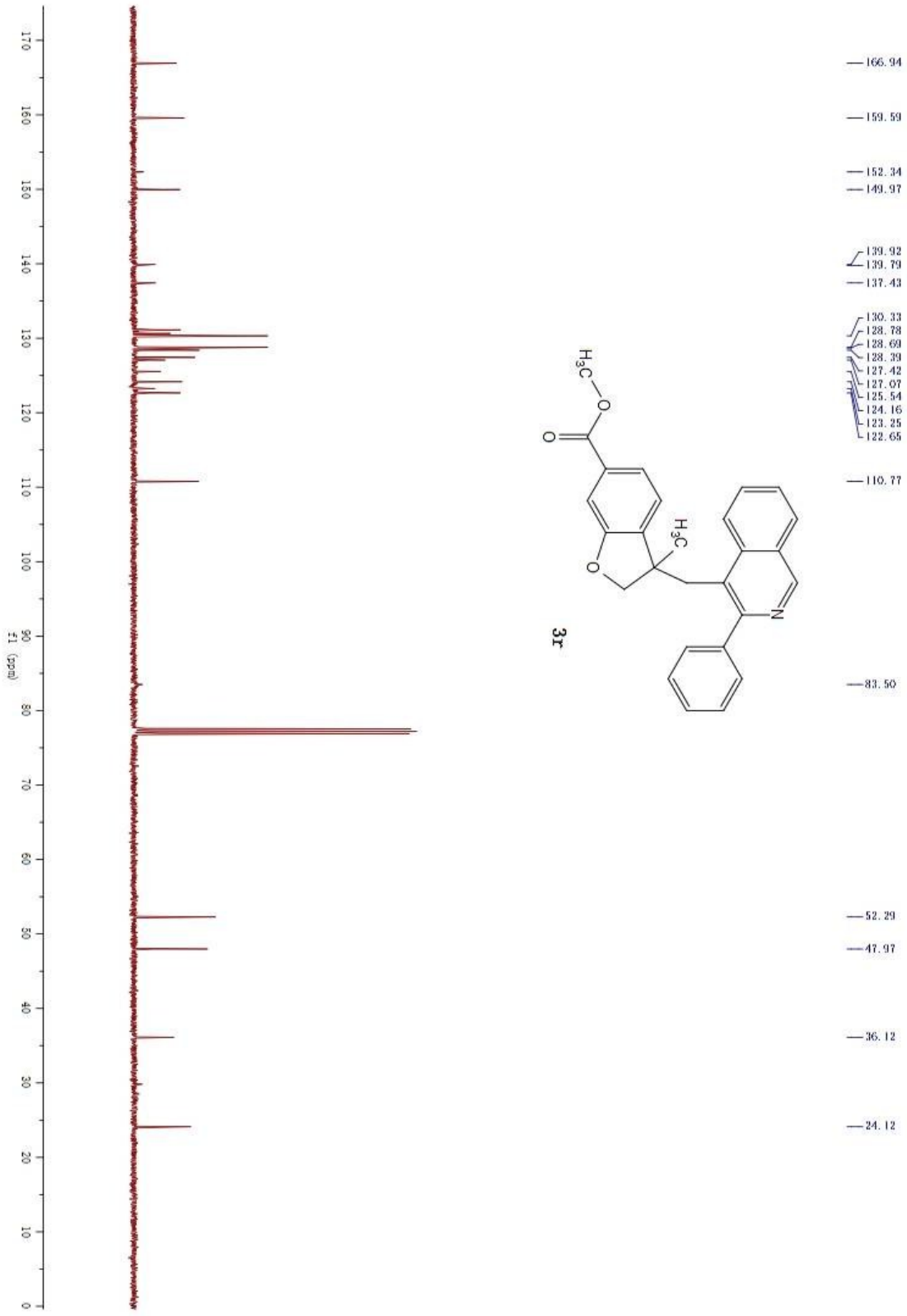
7.99
7.97
7.54
7.47
7.42
7.37
7.25
7.24
7.21
6.29
5.85
4.25
4.23
3.88
3.85
3.84
3.80
3.75
3.72
3.68
3.65
0.99
0.90
0.97
1.00
7.06
2.07
1.67
0.95
4.03
1.95
2.81
f1 (ppm)
H3C
O
O
H3C
O
N
3r


166.94
159.59
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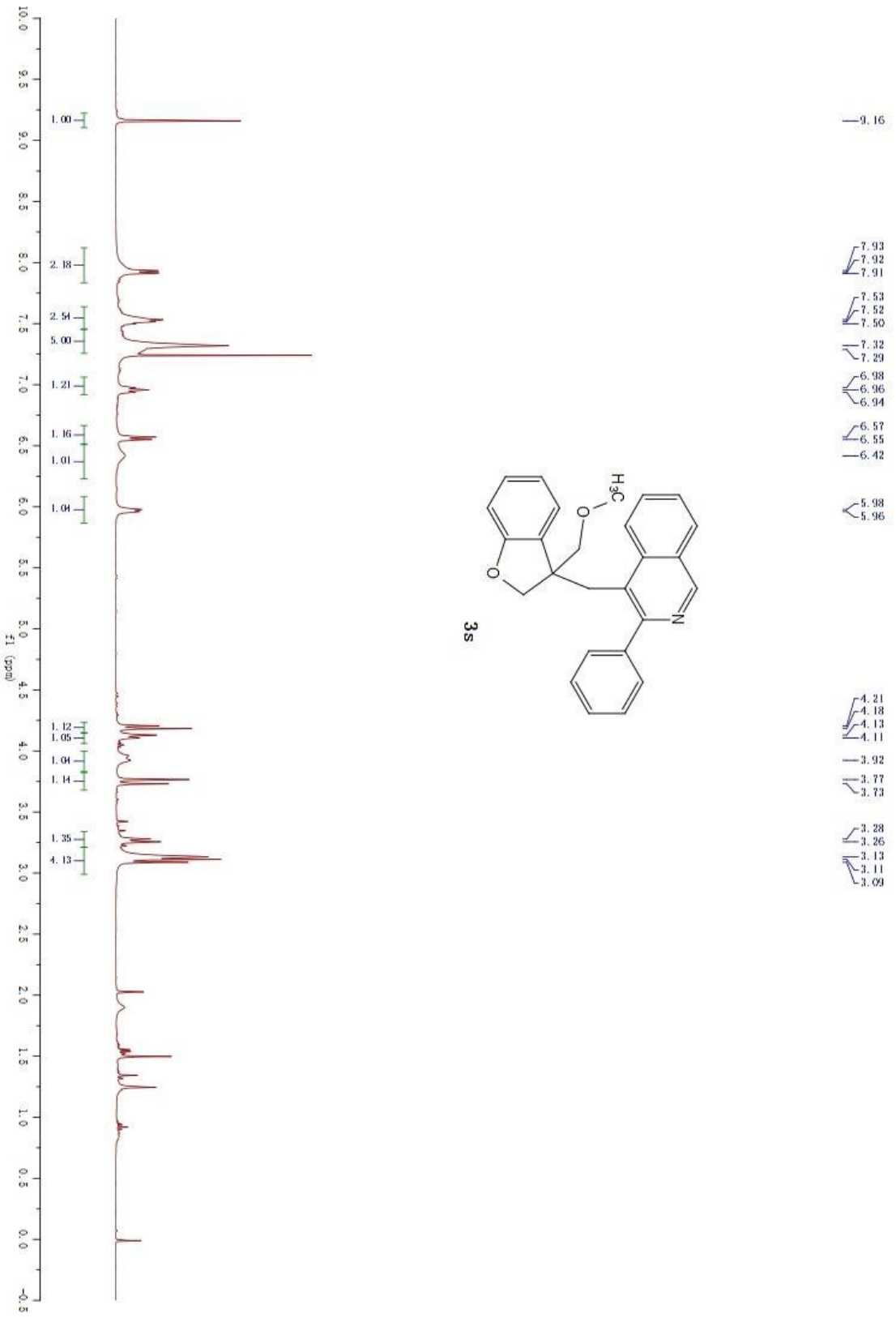
149.97
139.92
139.79
137.43
130.33
128.78
128.69
128.39
127.42
127.07
125.54
124.16
123.25
122.65
110.77
83.50
52.29
47.97
36.12
24.12
f1 (ppm)
3r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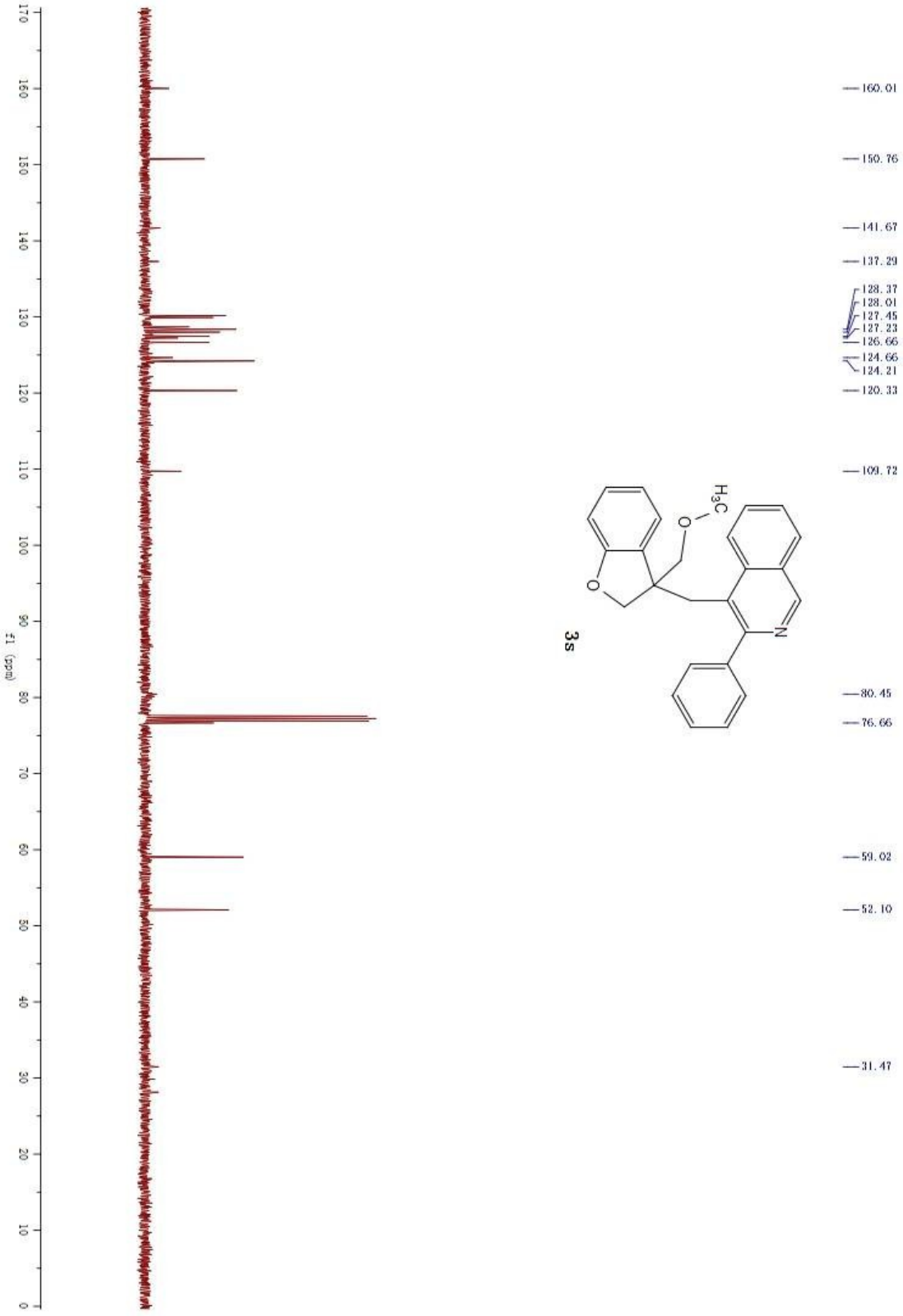
7.92
7.91
7.53
7.52
7.50
7.32
7.29
6.98
6.96
6.94
6.57
6.55
6.42
5.98
5.96
4.21
4.18
4.13
4.11
3.92
3.77
3.73
3.28
3.26
3.13
3.11
3.09
1.00
2.18
2.54
5.00
1.21
1.16
1.01
1.04
1.12
1.05
1.04
1.14
1.35
4.13
f1 (ppm)
H3C
O
O
N
3s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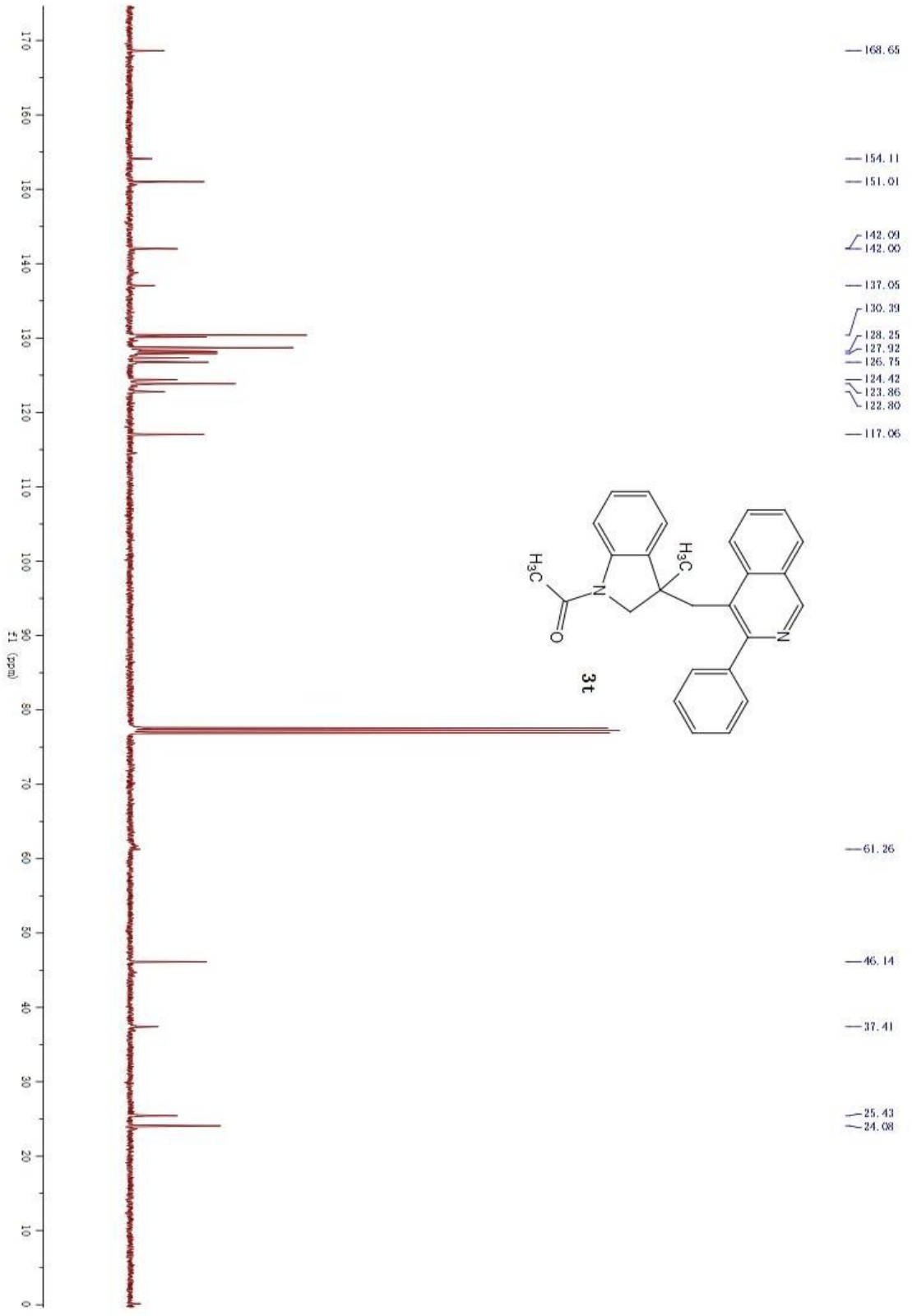
128.37
128.01
127.45
127.23
126.66
124.66
124.21
120.33
109.72
80.45
76.66
59.02
52.10
31.47
f1 (ppm)
3s

9.19
8.04
8.02
7.47
7.43
7.38
7.32
7.10
7.08
7.05
6.75
6.57
6.35
3.68
3.66
3.65
3.32
3.29
1.89
0.99
3t
f1 (ppm)


168.65
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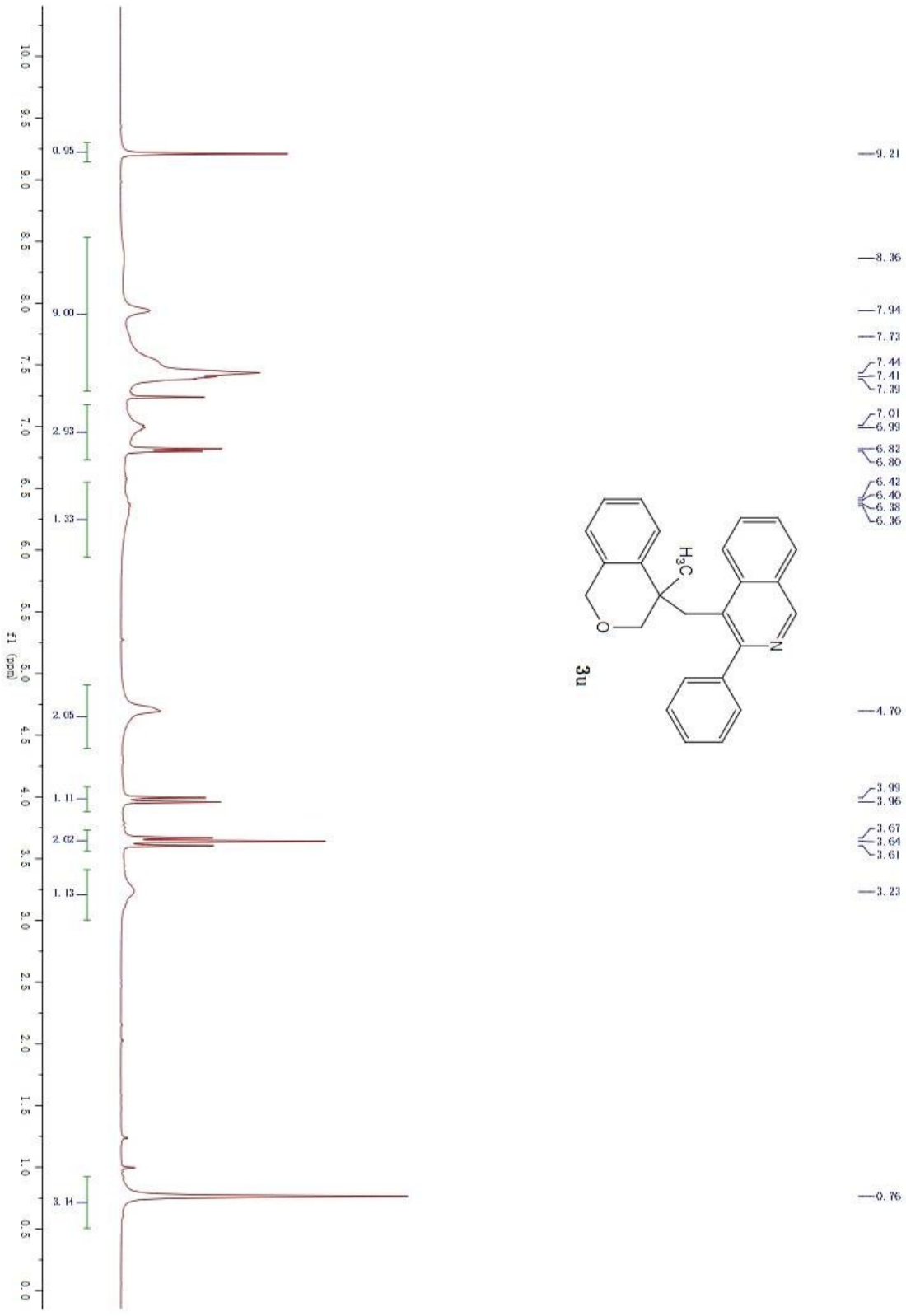
142.09
142.00
137.05
130.39
128.25
127.92
126.75
124.42
123.86
122.80
117.06
61.26
46.14
37.41
25.43
24.08
f1 (ppm)
3t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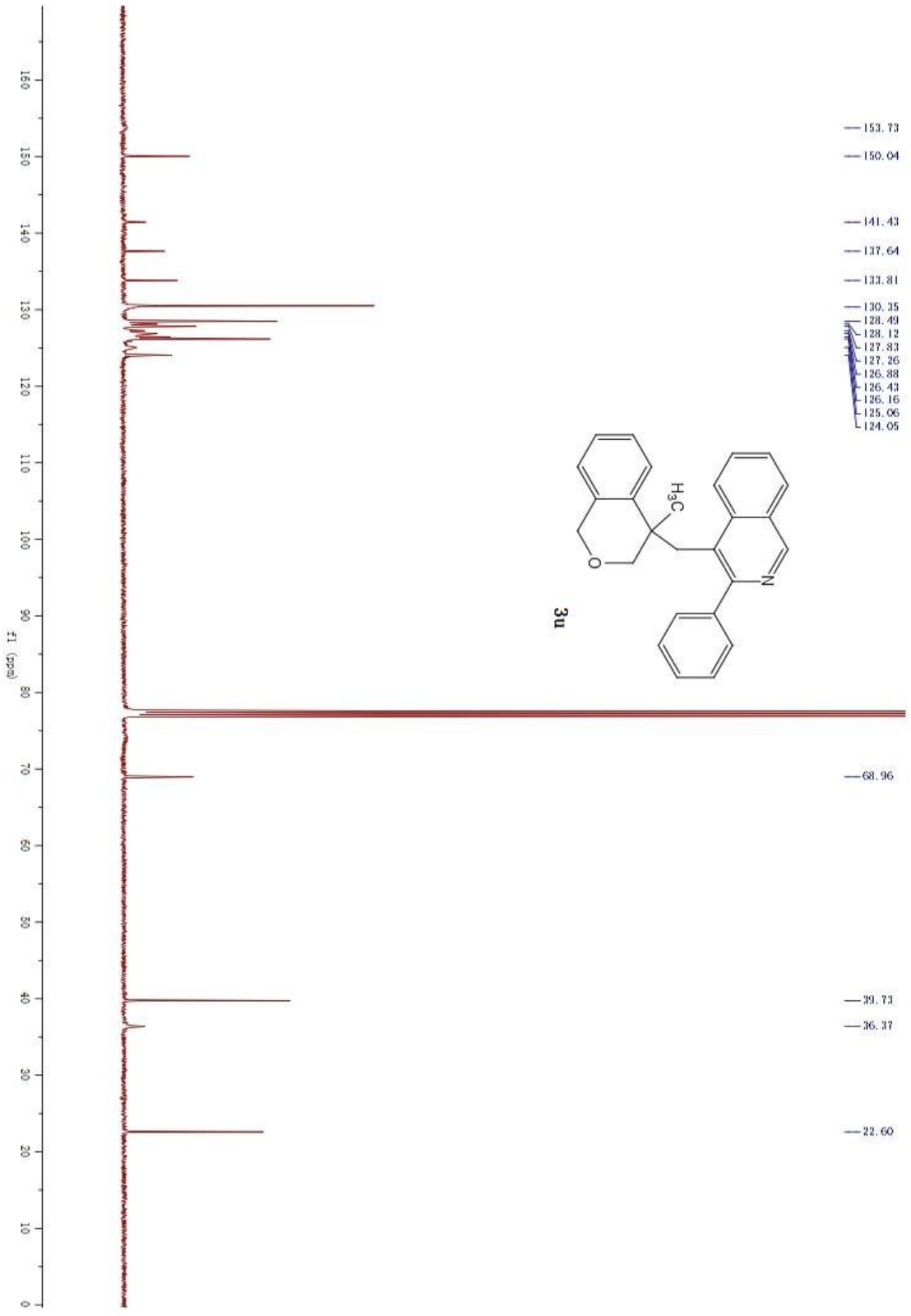
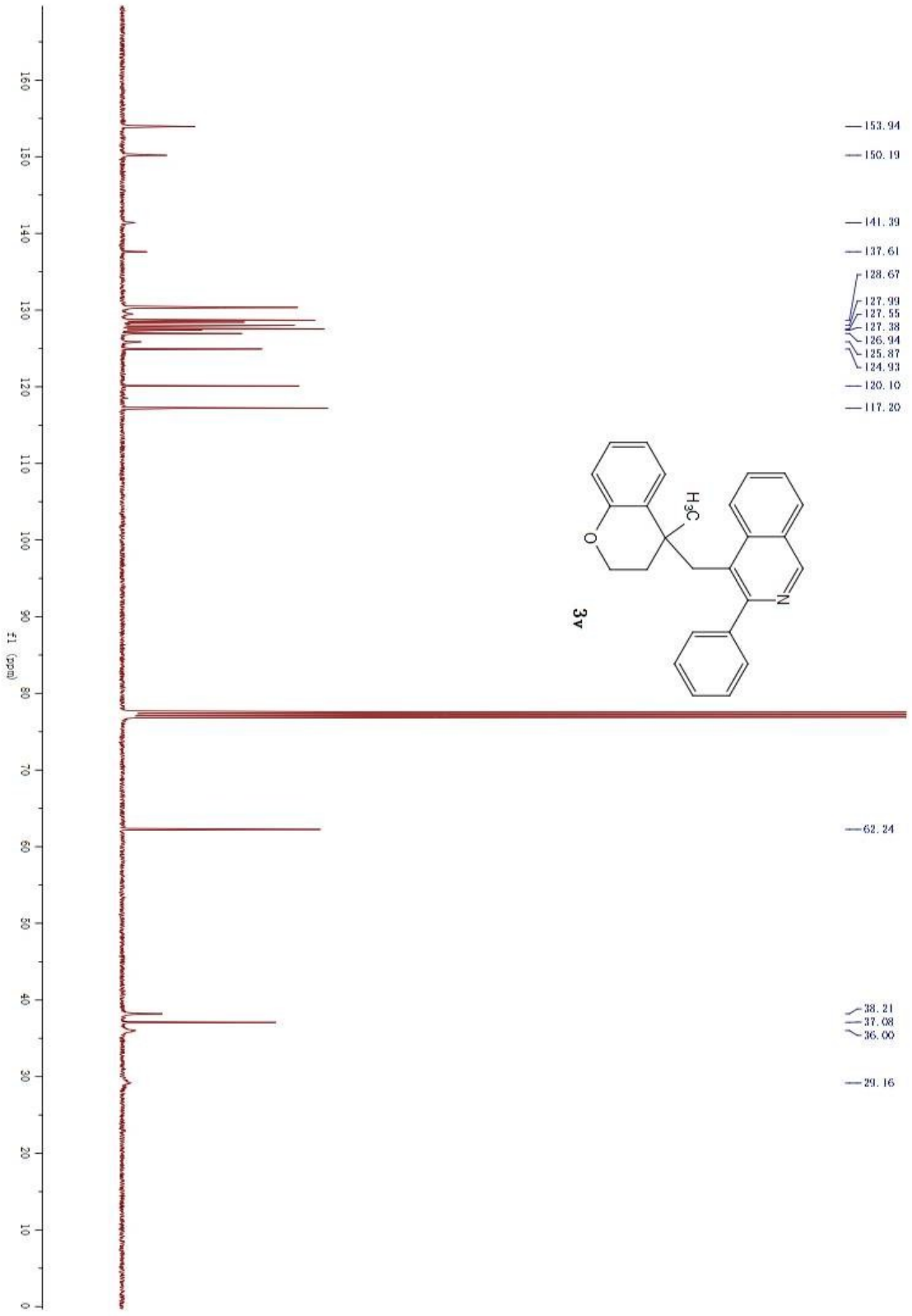
7.73
7.44
7.41
7.39
7.01
6.99
6.82
6.80
6.42
6.40
6.38
6.36
4.70
3.99
3.96
3.67
3.64
3.61
3.23
0.76
0.95
9.00
2.93
1.33
2.05
1.11
2.02
1.13
3.14
f1 (ppm)
H3C
O
N
3u


153.73
150.04
141.43
137.64
133.81
130.35
128.49
128.12
127.83
127.26
126.88
126.43
126.16
125.06
124.05
68.96
39.73
36.37
22.60
H3C
O
N
3u
f1 (ppm)

9.22
8.04
8.02
8.00
7.98
7.63
7.59
7.55
7.36
7.00
6.98
6.96
6.67
6.65
6.60
6.58
6.56
3.85
3.82
3.77
3.74
3.64
3.48
3.48
3.45
3.45
3.42
3.42
1.74
1.71
1.61
1.60
1.58
1.57
1.55
1.54
0.97
1.05
2.12
2.26
4.89
1.03
2.85
2.10
1.02
1.14
1.06
1.12
3.22
f1 (ppm)
H3C
O
N

3v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150.19
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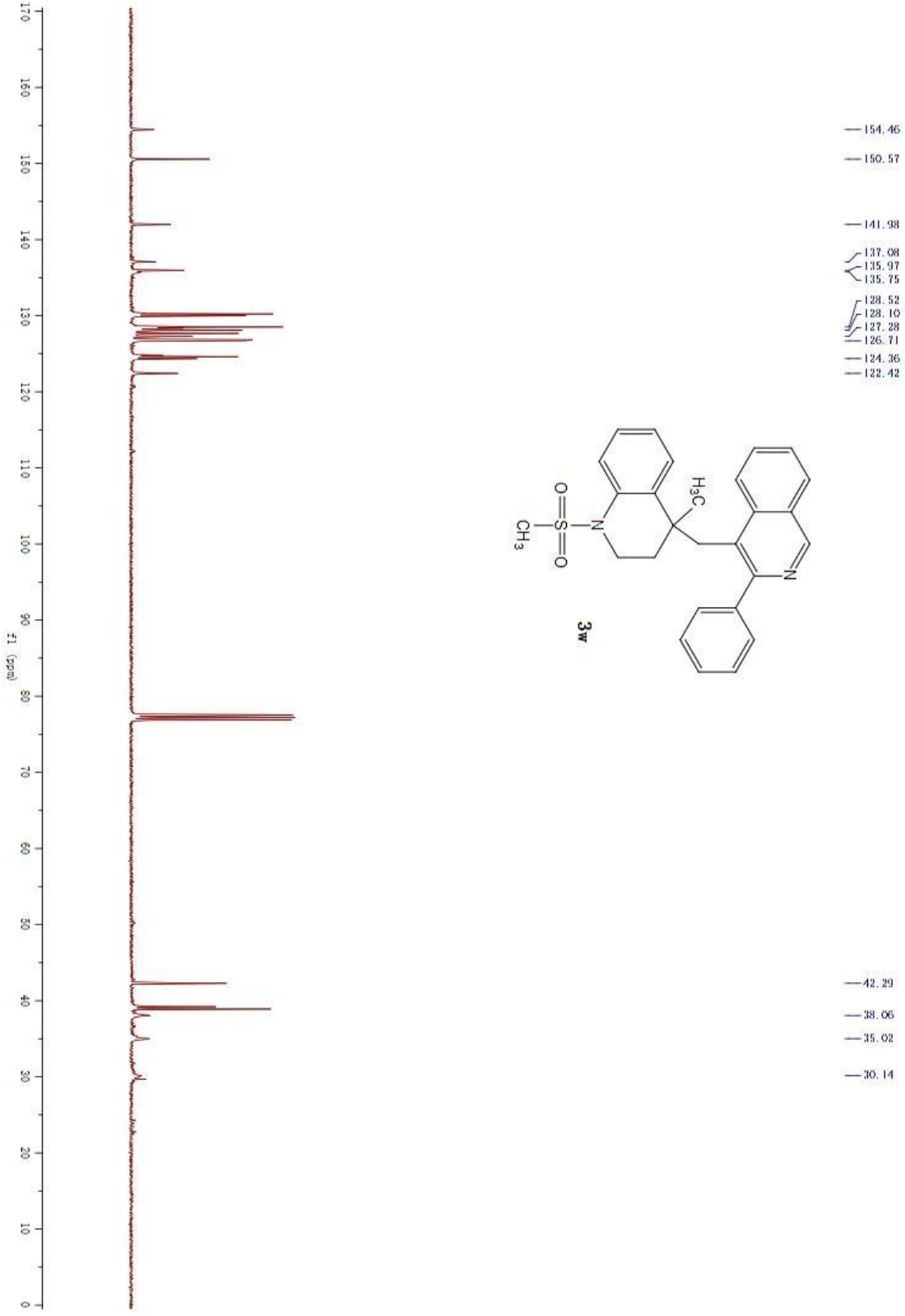
137.61
128.67
127.99
127.55
127.38
126.94
125.87
124.93
120.10
117.20
62.24
38.21
37.08
36.00
29.16
H3C
O
N
3v
f1 (ppm)

9.17
7.98
7.95
7.94
7.59
7.55
7.51
7.38
7.06
7.04
6.88
6.86
3.76
3.73
3.64
3.61
3.52
3.10
3.07
3.04
2.54
1.74
1.72
1.67
1.41
1.39
1.36
0.99
1.00
2.10
3.63
5.67
1.45
2.21
1.08
2.35
1.27
3.27
1.34
1.21
3.40
f1 (ppm)
3w


154.46
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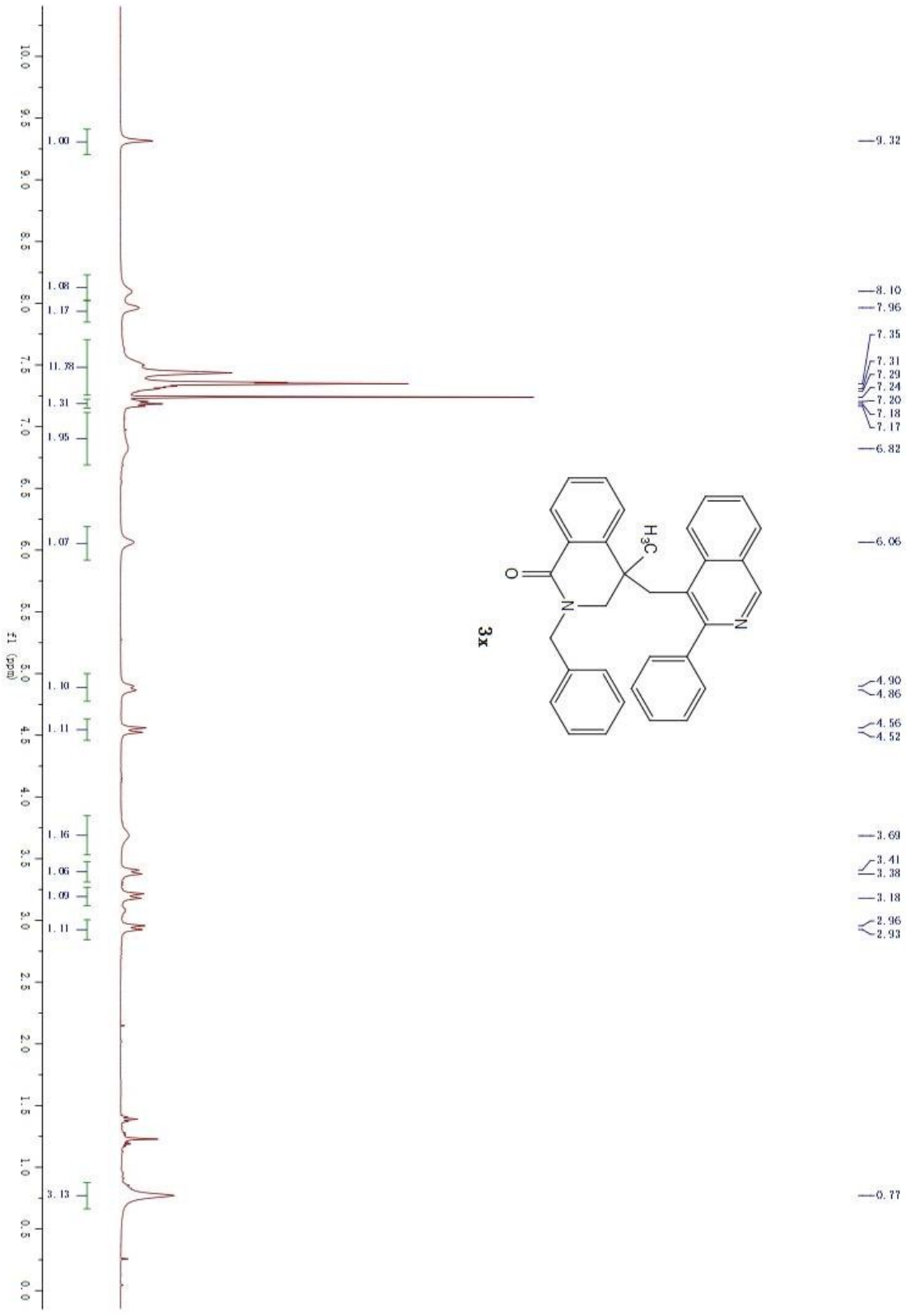
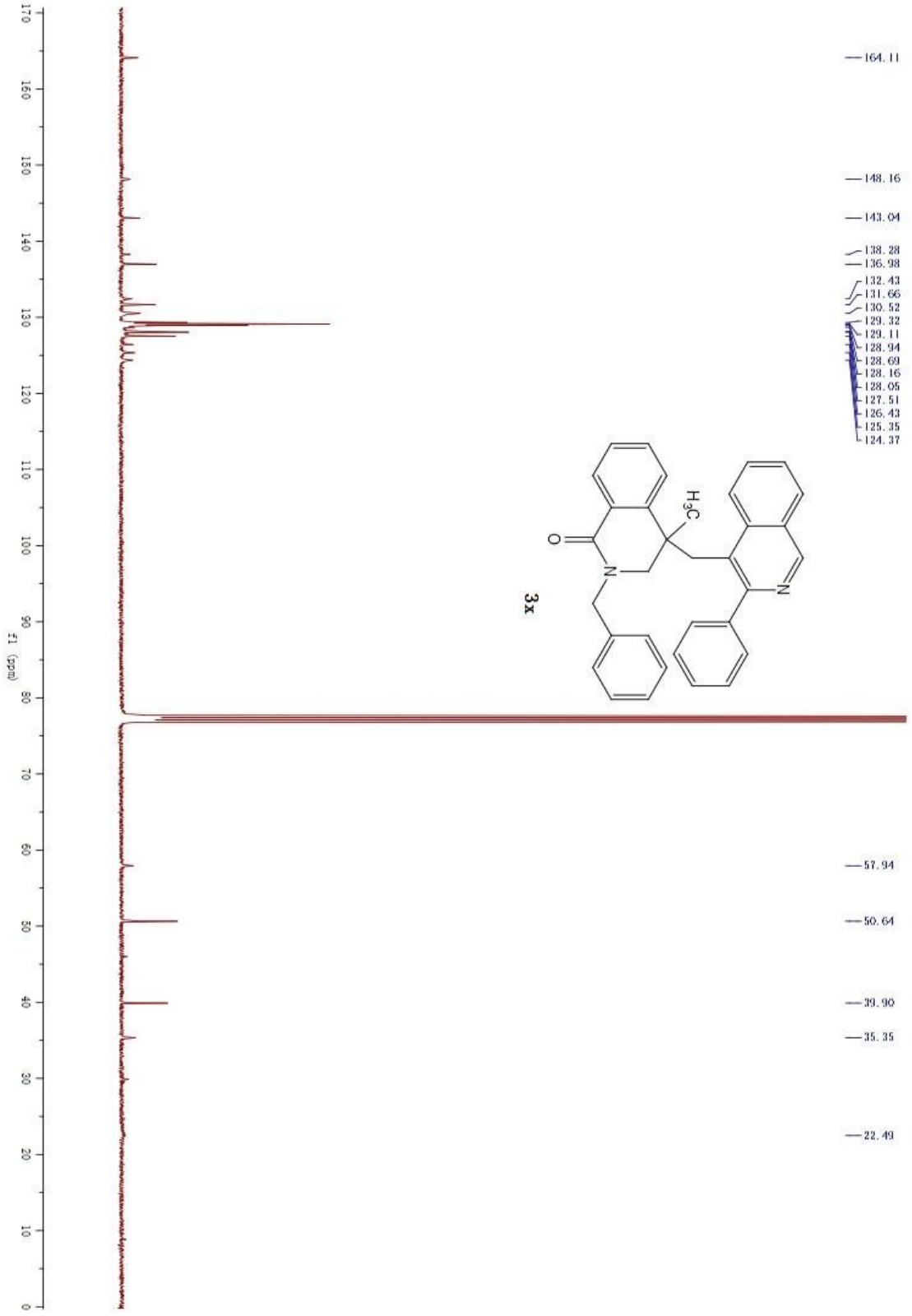
137.08
135.97
135.75
128.52
128.10
127.28
126.71
124.36
122.42
42.29
38.06
35.02
30.14
f1 (ppm)
3w


9.32
8.10
7.96
7.35
7.31
7.29
7.24
7.20
7.18
7.17
6.82
6.06
4.90
4.86
4.56
4.52
3.69
3.41
3.38
3.18
2.96
2.93
0.77
1.00
1.08
1.17
11.78
1.31
1.95
1.07
1.10
1.11
1.16
1.06
1.09
1.11
3.13
f1 (ppm)
H3C
O
N
N
3x


164.11
148.16
143.04
138.28
136.98
132.43
131.66
130.52
129.32
129.11
128.94
128.69
128.16
128.05
127.51
126.43
125.35
124.37
57.94
50.64
39.90
35.35
22.49
f1 (ppm)
3x