Oxidant- and Metal-Free Synthesis of 4(3*H*)-Quinazolinones from 2-Amino-*N*-methoxybenzamides and Aldehydes via Acid-Promoted Cyclocondensation and Elimination

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Supplementary Material

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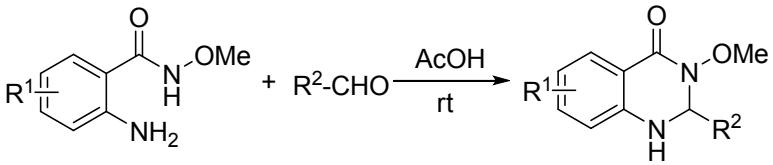
I General Information

^{1}H and ^{13}C NMR spectra were recorded on a 600 MHz instrument (150 MHz for ^{13}C NMR) at 25 °C. Chemical shifts are given in ppm and are referenced to TMS (set as 0.00 ppm) as the internal standard. The multiplicities are defined as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; and td, triplet of doublets. The coupling constants (*J*) are reported in Hertz (Hz). Reagents and solvents were purchased as reagent grade quality and were used without further purification. All reactions were performed in standard glassware (heated at 70 °C for 3 h before use). TLC plates (Silica gel GF254) were made visual by exposure to UV light. Flash column chromatography was performed over silica gel (200–300 mesh) using a mixture of petroleum ether (PE) and EtOAc as the eluent. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. Melting points were determined with a national micromelting point apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained on a Q-TOF microspectrometer.

II Preparation of Substrates

All the substrates were prepared according to our method which was lately reported.[1]

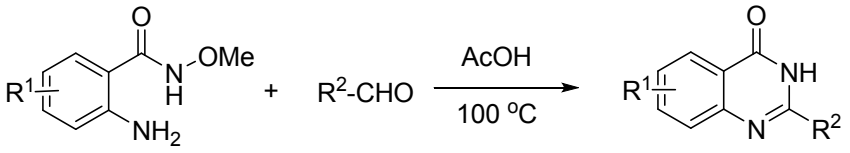
III Preparation of the 4(1*H*)-2,3-dihydroquinazolinones A



1 **2** **A**

To a solution of amide **1** (6 mmol) in AcOH (8 mL) was added aldehyde **2** (6.6 mmol). The reaction mixture was stirred at room temperature for 0.5 h. After the reaction completed, cold water (30 mL) was added. The precipitate was filtered, washed with cold EtOH. The filter cake was dried in air to give the desired intermediate **A**.

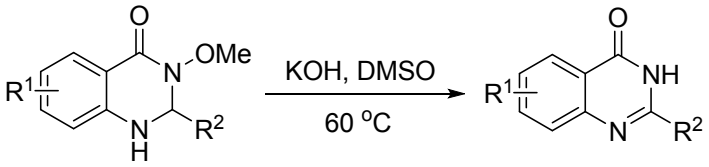
IV Preparation of the Quinazolinone Products 3



1 2 3

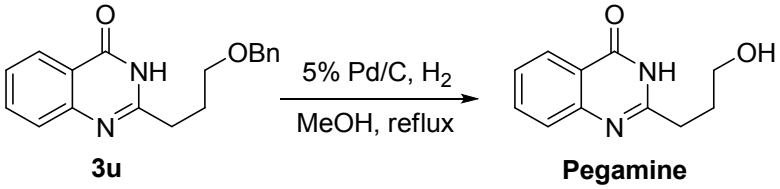
Method A[2]**:** To a solution of amide **1** (1 mmol) in AcOH (4 mL) was added aldehyde **2** (1.1 mmol).[3] The reaction mixture was heated to 100 °C for appropriate time. After the reaction completed (TLC analysis), the reaction mixture was diluted with EtOAc (20 mL), neutralized with saturated aqueous $NaHCO_3$ (20 mL), and then extracted with EtOAc (3 × 20 mL), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated by the rotary evaporator. The crude product was purified by flash column chromatography (EtOAc/PE) to give the desired compounds.

Method B[4]**:** To a solution of amide **1** (1 mmol) in AcOH (4 mL) was added aldehyde **2** (1.1 mmol). The reaction mixture was heated to 100 °C for appropriate time. After the reaction completed (TLC analysis), the reaction mixture was poured into ice water. The precipitate was filtered, washed with water and EtOAc/PE (1:5). The filter cake was dried in air to give the desired compounds.



A 3

Method C[5]**:** To a solution of 4(1*H*)-2,3-dihydroquinazolinone **A** (1 mmol) in DMSO (10 mL) was added KOH (3 mmol). The reaction mixture was heated to 60 °C for 1.5 h. After the reaction completed, the reaction mixture was poured into ice water. The precipitate was filtered, washed with water and EtOAc/PE (1:5). The filter cake was dried in air to give the desired compounds.



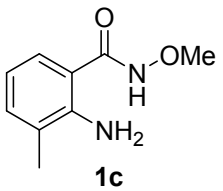
3u **Pegamine**

To a solution of **3u (**0.5 mmol) in MeOH (1.5 mL) was added 5% Pd/C (74.0 mg) under H_2 atmosphere (balloon). The reaction mixture was heated to reflux for 6 hrs.

After the reaction completed, the mixture was filtrated through celite pad, and the filtrate was concentrated in vacuo. Purification of the residue by flash silica-gel chromatography (EtOAc/PE) gave the desired compound as a white solid (88 mg, 86% yield).

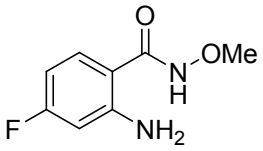
V Spectroscopic Data of the Substrates and intermediates A

The spectroscopic data and spectra of substrates 2-amino-*N*-methoxybenzamide (**1a**), 2-amino-5-bromo-*N*-methoxybenzamide (**1b**), 2-amino-*N*,4-dimethoxybenzamide (**1d**), 2-amino-6-chloro-*N*-methoxybenzamide **(1e)** and 2-amino-*N*-methoxy-4-nitrobenzamide (**1g**) have been described in our previous literature.[1]



1c

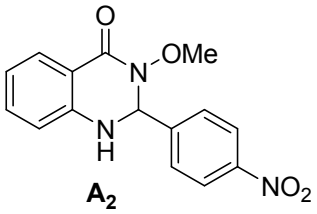
2-Amino-*N*-methoxy-3-methylbenzamide (1c). Yield: 30%, 3.30 g, white solid, mp 95-97 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 5.56 (br s, 2H), 3.85 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 147.0, 133.6, 125.3, 123.7, 116.1, 112.6, 64.3, 17.4; HRMS (ESI) m/z calcd for $C_9H_{13}N_2O_2^+$ [M + H^+] 181.0972, found 181.0975.



1f

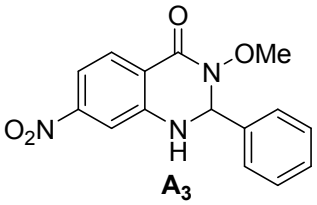
2-Amino-4-fluoro-*N*-methoxybenzamide (1f). Yield: 83%, 9.32 g, white solid, mp 137-138 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ11.42 (br s, 1H), 7.38 (t, J = 7.2, 1H), 6.63 (br s, 2H), 6.48 (dd, J = 11.9, 2.4 Hz, 1H), 6.31 (td, J = 8.6, 2.5 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.3, 164.6 (d, $J_{C\text{-}F}$ = 244.3 Hz), 152.1 (d, $J_{C\text{-}F}$ = 12.6 Hz), 130.2 (d, $J_{C\text{-}F}$ = 11.2 Hz), 108.89 (d, $J_{C\text{-}F}$ = 1.0 Hz), 101.8 (d, $J_{C\text{-}F}$ = 22.4

Hz), 101.5 (d, $J_{C\text{-}F}$ = 24.0 Hz), 63.1; HRMS (ESI) m/z calcd for $C_8H_{10}FN_2O_2^+$ [M + H^+] 185.0721, found 185.0720.



A2

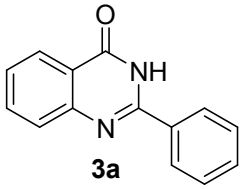
3-Methoxy-2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (A_2). Yield: 95%, 1.70 g, light yellow solid, mp 167-168 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.32 (td, *J* = 8.2, 1.5 Hz, 1H), 6.88 (t, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.86 (s, 1H), 4.70 (br s, 1H), 3.52 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 145.5, 136.8, 134.3, 131.8, 129.7, 128.8, 123.9, 119.7, 114.5, 114.3, 75.3, 63.6.; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3NaO_4^+$ [M + Na^+] 322.0798, found 322.0821.



A3

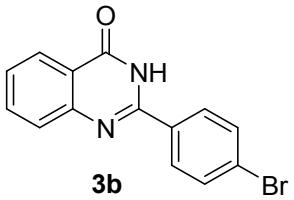
3-Methoxy-7-nitro-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (A_3). Yield: 92%, 1.65 g, yellow solid, mp 230-232 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.51 (d, *J* = 6.6 Hz, 2H), 7.48 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.43 (m, 3H), 6.28 (s, 1H), 3.62 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.1, 151.1, 146.9, 138.6, 129.2, 128.5, 127.0, 117.5, 111.3, 111.3, 108.8, 72.9, 62.4.; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3NaO_4^+$ [M + Na^+] 322.0798, found 322.0823.

VI Spectroscopic Data of Quinazolinone Products 3



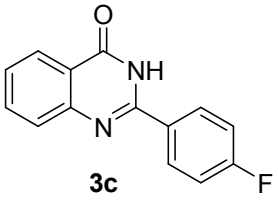
3a

2-Phenylquinazolin-4(3*H*)-one (3a).[1] Yield: 93%, 206.5 mg, white solid, mp 239-241 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.56 (br s, 1H), 8.21 (d, J = 7.9 Hz, 2H), 8.18 (dd, J = 7.9 Hz, J = 1.2 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.62-7.52 (m, 4H); HRMS (ESI) m/z calcd for $C_{14}H_{11}N_2O^+$ [M + H^+] 223.0866, found 223.0865.



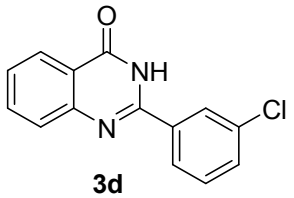
3b

2-(4-Bromophenyl)quinazolin-4(3*H*)-one (3b).[6] Yield: 95%, 286.5 mg, white solid, mp > 300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.61 (br s, 1H), 8.16 (dd, J = 7.9, 1.1 Hz, 1H), 8.13 (d, J = 8.6 Hz, 2H), 7.87-7.83 (m, 1H), 7.78-7.74 (m, 3H), 7.56-7.52 (m, 1H); HRMS (ESI) m/z calcd for $C_{14}H_{10}BrN_2O^+$ [M + H^+] 300.9971, found 300.9972.



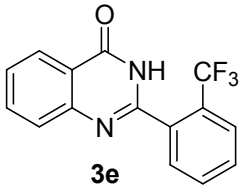
3c

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (3c).[7] Yield: 95%, 229 mg, white solid, mp 268-269 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.58 (br s, 1H), 8.31-8.23 (m, 2H), 8.16 (d, J = 7.8 Hz, 1H), 7.85 (t, J = 7.0 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 8.8 Hz, 2H); HRMS (ESI) m/z calcd for $C_{14}H_{10}FN_2O^+$ [M + H^+] 241.0772, found 241.0770.



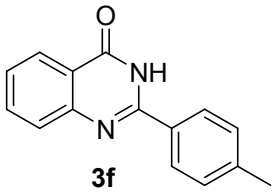
3d

2-(3-Chlorophenyl)quinazolin-4(3*H*)-one (3d).[6] Yield: 82%, 210 mg, white solid, mp 270-272 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.63 (br s, 1H), 8.25 (s, 1H), 8.16 (t, J = 6.5 Hz, 2H), 7.86 (t, J = 8.3 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H); HRMS (ESI) m/z calcd for $C_{14}H_{10}{}^{35}ClN_2O^+$ [M + H$^+$] 257.0476, found 257.0477.



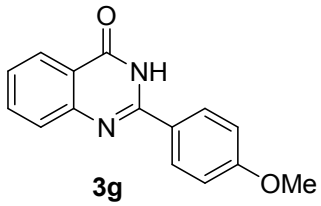
3e

2-(2-(Trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (3e). Yield: 81%, 234 mg, white solid, mp 177-179 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.48 (br s, 1H), 8.24 (d, J = 7.9 Hz, 1H), 7.88-7.78 (m, 3H), 7.77-7.67 (m, 3H), 7.54 (t, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2, 151.6, 148.7, 135.0, 132.8, 132.1, 130.58, 130.56, 128.8 (q, $J_{C\text{-}F}$ = 31.5 Hz), 127.9, 127.3, 127.0 (q, $J_{C\text{-}F}$ = 4.8 Hz), 126.3, 123.6 (q, $J_{C\text{-}F}$ = 272.1 Hz), 120.7; HRMS (ESI) m/z calcd for $C_{15}H_{10}F_3N_2O^+$ [M + H$^+$] 291.0740, found 291.0739.



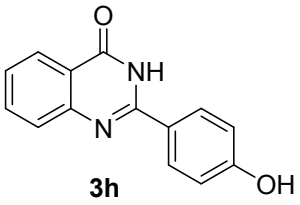
3f

2-(4-Methylphenyl)-quinazolin-4(3*H*)-one (3f).[7] Yield: 87%, 205 mg, white solid, mp 245-247 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.47 (br s, 1H), 8.15 (dd, J = 7.9, 1.1 Hz, 1H), 8.11 (d, J = 8.2 Hz, 2H), 7.83 (t, J = 8.4 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H); HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O^+$ [M + H$^+$] 237.1022, found 237.1024.



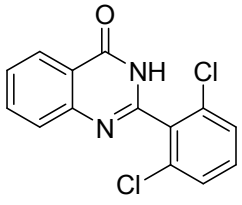
3g

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (3g).[7] Yield: 73%, 183 mg, white solid, mp 243-244 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.42 (br s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 7.6 Hz, 1H), 7.82 (t, J = 8.2 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O^+$ [M + H$^+$] 253.0972, found 253.0974.



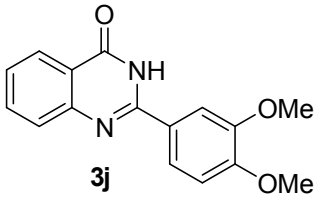
3h

2-(4-Hydroxyphenyl)quinazolin-4(3*H*)-one (3h).[8] Yield: 92%, 218 mg, light yellow solid, mp 243-244 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.29 (br s, 1H), 10.25 (br s, 1H), 8.12 (dd, J = 7.9, 1.3 Hz, 1H), 8.09 (d, J = 8.8 Hz, 2H), 7.80 (t, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H); HRMS (ESI) m/z calcd for $C_{14}H_{11}N_2O_2^+$ [M + H$^+$] 239.0815, found 239.0812.



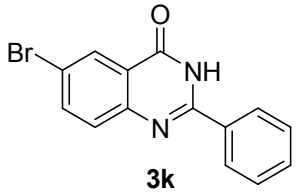
3i

2-(2,6-Dichlorophenyl)quinazolin-4(3*H*)-one (3i). Yield: 95%, 275 mg, white solid, mp 220-222 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.82 (br s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 7.9 Hz, 2H), 7.63-7.56 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.4, 149.8, 148.4, 134.8, 133.2, 132.8, 132.3, 128.3, 127.54, 127.48, 125.9, 121.4; HRMS (ESI) m/z calcd for $C_{14}H_9{}^{35}Cl_2N_2O^+$ [M + H$^+$] 291.0086, found 291.0086.



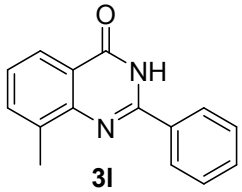
3j

2-(3,4-Dimethoxyphenyl)quinazolin-4(3*H*)-one (3j).[9] Yield: 98%, 275 mg, white solid, mp 239-240 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.44 (br s, 1H), 8.15 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.89 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.84-7.80 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{15}N_2O_3^+$ [M + H$^+$] 283.1077, found 283.1081.



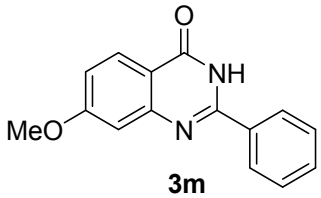
3k

6-Bromo-2-phenylquinazolin-4(3*H*)-one (3k).[10] Yield: 93%, 280 mg, white solid, mp 286-288 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.72 (br s, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.18 (d, *J* = 7.4 Hz, 2H), 7.98 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 2H); HRMS (ESI) m/z calcd for $C_{14}H_{10}BrN_2O^+$ [M + H$^+$] 300.9971, found 300.9972.



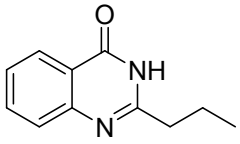
3l

8-Methyl-2-phenylquinazolin-4(3*H*)-one (3l).[10] Yield: 80%, 188 mg, white solid, mp 248-249 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.54 (br s, 1H), 8.24 (d, *J* = 6.9 Hz, 2H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.61-7.55 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 2.63 (s, 3H); HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O^+$ [M + H$^+$] 237.1022, found 237.1025.



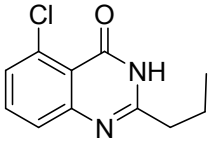
3m

7-Methoxy-2-phenylquinazolin-4(3*H*)-one (3m).[11] Yield: 98%, 248 mg, light yellow solid, mp 221-223 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.47 (br s, 1H), 8.25 (d, J = 7.6 Hz, 2H), 8.12 (d, J = 8.7 Hz, 1H), 7.68-7.60 (m, 3H), 7.26 (d, J = 1.5 Hz, 1H), 7.17 (dd, J = 8.7, 1.7 Hz, 1H), 3.99 (s, 3H); HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O_2$ [M + H$^+$] 253.0972, found 253.0976.



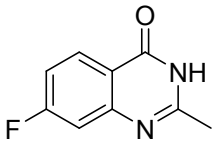
3n

2-Propylquinazolin-4(3*H*)-one (3n).[12] Yield: 79%, 148 mg, white solid, mp 181-182 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.16 (br s, 1H), 8.08 (dd, J = 7.9, 1.0 Hz, 1H), 7.77 (t, J = 8.4 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 2.58 (t, J = 7.6 Hz, 2H), 1.78-1.71 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); HRMS (ESI) m/z calcd for $C_{11}H_{13}N_2O^+$ [M + H$^+$] 189.1022, found 189.1025.



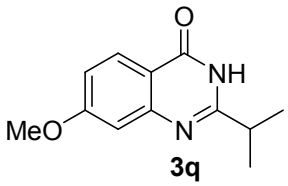
3o

5-Chloro-2-propylquinazolin-4(3*H*)-one (3o). Yield: 75%, 167 mg, white solid, mp 215-217 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.94 (br s, 1H), 7.61-7.58 (m, 2H), 7.46-7.42 (m, 1H), 2.76 (t, J = 7.7 Hz, 2H), 1.97-1.88 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 157.8, 152.0, 134.1, 134.0, 129.0, 126.5, 117.8, 37.5, 20.9, 13.8; HRMS (ESI) m/z calcd for $C_{11}H_{12}{}^{35}ClN_2O^+$ [M + H$^+$] 223.0633, found 223.0633.



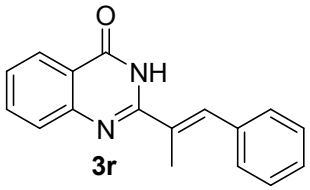
3p

7-Fluoro-2-methylquinazolin-4(3*H*)-one (3p). Yield: 95%, 169 mg, white solid, mp 255 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.29 (br s, 1H), 8.13 (t, J = 7.6 Hz, 1H), 7.35-7.29 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.6 (d, $J_{C\text{-}F}$ = 248.7 Hz), 160.9, 155.9, 151.1, 128.7 (d, $J_{C\text{-}F}$ = 10.4 Hz), 117.6 (d, $J_{C\text{-}F}$ = 22.2 Hz), 114.3, 111.5 (d, $J_{C\text{-}F}$ = 22.7 Hz), 21.4; HRMS (ESI) m/z calcd for $C_9H_8FN_2O^+$ [M + H^+] 179.0615, found 179.0616.



3q

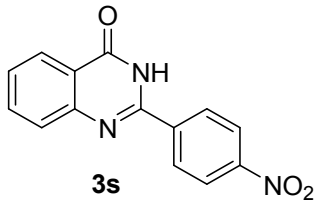
2-Isopropyl-7-methoxyquinazolin-4(3*H*)-one (3q). Yield: 80%, 175 mg, white solid, mp 197-199 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.07 (br s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), 3.93 (s, 3H), 3.10-3.02 (m, 1H), 1.45 (d, J = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 164.0, 162.0, 151.9, 127.7, 116.7, 114.2, 107.8, 55.7, 34.9, 20.4; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O_2^+$ [M + H^+] 219.1128, found 219.1130.



3r

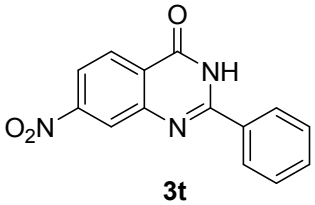
(E)-2-(1-Phenylprop-1-en-2-yl)quinazolin-4(3*H*)-one (3r). Yield: 82%, 215 mg, white solid, mp 220-222 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.22 (br s, 1H), 8.14 (dd, J = 7.9, 1.0 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.53-7.49 (m, 3H), 7.46 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 2.31 (d, J = 0.8 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.0, 154.6, 148.5, 136.1, 134.5, 134.1, 130.6, 129.4, 128.4, 127.9, 127.4, 126.5, 125.8, 121.0, 15.1; HRMS (ESI) m/z

calcd for $C_{17}H_{15}N_2O^+$ [M + H^+] 263.1179, found 263.1179.



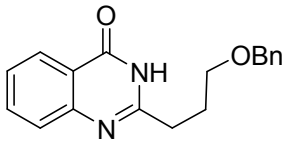
3s

2-(4-nitrophenyl)quinazolin-4(3*H*)-one (3s).[6] Yield: 81%, 216 mg, yellow solid, mp > 300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.83 (br s, 1H), 8.45-8.37 (m, 4H), 8.17 (d, J = 7.2 Hz, 1H), 7.85 (t, J = 6.0 Hz, 1H), 7.78 (d, J = 7.0 Hz, 1H), 7.56 (t, J = 6.5 Hz, 1H).; HRMS (ESI) m/z calcd for $C_{14}H_9N_3O_3^+$ [M + Na^+] 290.0536, found 290.0542.



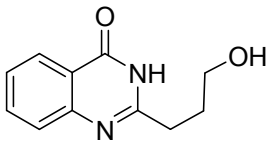
3t

7-nitro-2-phenylquinazolin-4(3*H*)-one (3t).[13] Yield: 74%, 198 mg, yellow solid, mp > 300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.90 (br s, 1H), 8.42 (d, J = 1.8 Hz, 1H), 8.36 (d, J = 8.7 Hz, 1H), 8.24-8.19 (m, 3H), 7.64 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.5 Hz, 2H).; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3O_3^+$ [M + Na^+] 268.0717, found 268.0757.



3u

2-(3-(Benzyloxy)propyl)quinazolin-4(3*H*)-one (3u). Yield: 86%, 253 mg, white solid, mp 123-124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.71 (br s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 7.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.35-7.28 (m, 4H), 7.27-7.24 (m, 1H), 4.56 (s, 2H), 3.65 (t, J = 6.0 Hz, 2H), 2.92 (t, J = 7.3 Hz, 2H), 2.22-2.17 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.8, 156.5, 152.5, 138.1, 134.7, 128.4, 127.7, 127.7, 127.2, 126.4, 126.3, 120.7, 73.0, 69.3, 32.9, 27.1; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_2^+$ [M + H^+] 295.1441, found 295.1441.



Pegamine[14] Yield: 86%, 88 mg, white solid, mp 150-151 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.19 (br s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 4.59 (br s, 1H), 3.50-3.46 (m, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.92-1.85 (m, 2H); HRMS (ESI) m/z calcd for $C_{11}H_{13}FN_2O_2^+$ [M + H^+] 205.0972, found 205.0976.

VII References

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2 Products **3a-c**, **3e**, **3f-j**, **3m-p** and **3u** were prepared according to method A.

3 3 Equiv of acetaldehyde was used when preparing product **3p**.

4 Products **3d**, **3k-l**, **3q** and **3r** were prepared according to method B.

5 Products **3s** and **3t** were prepared according to method C.

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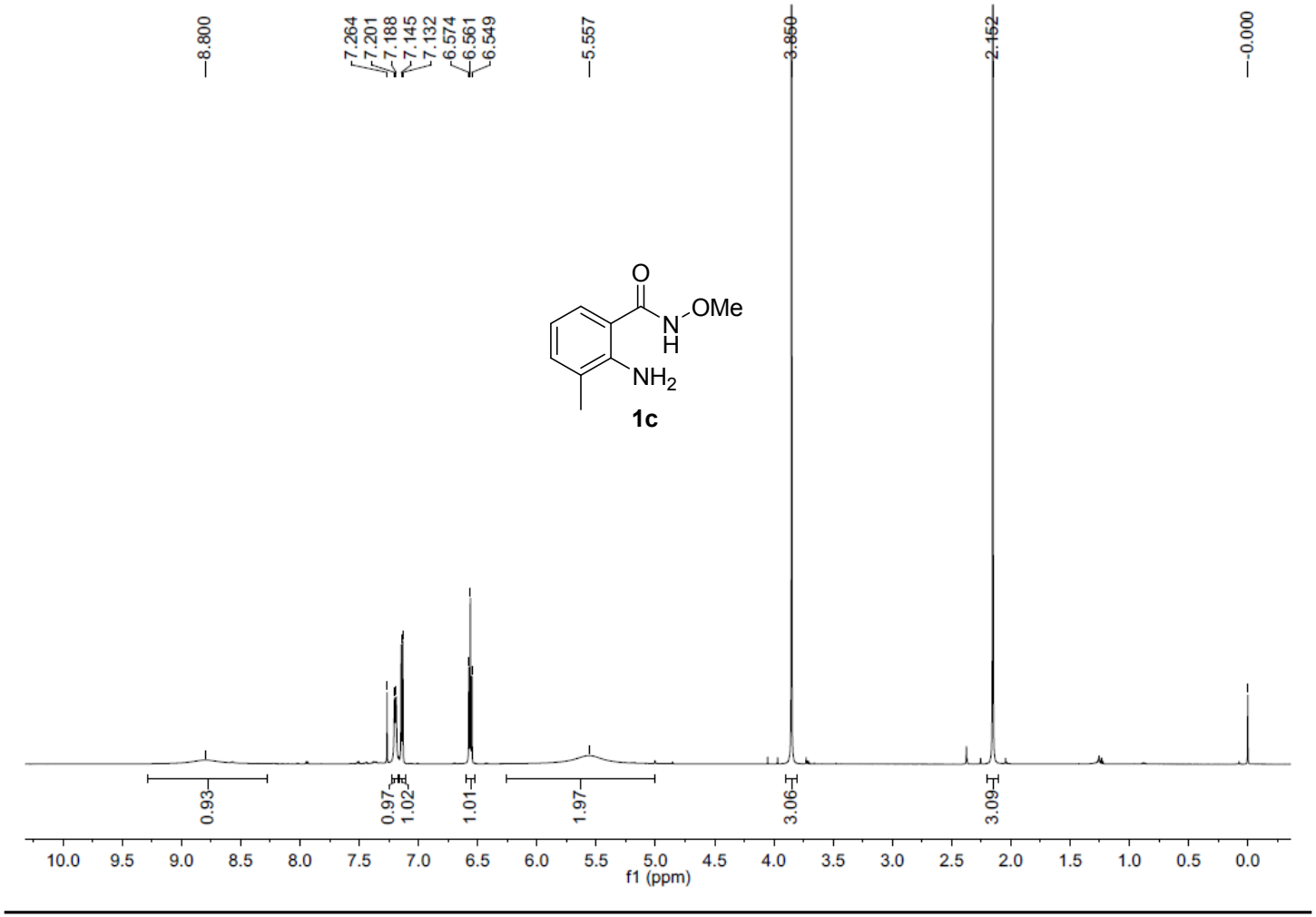
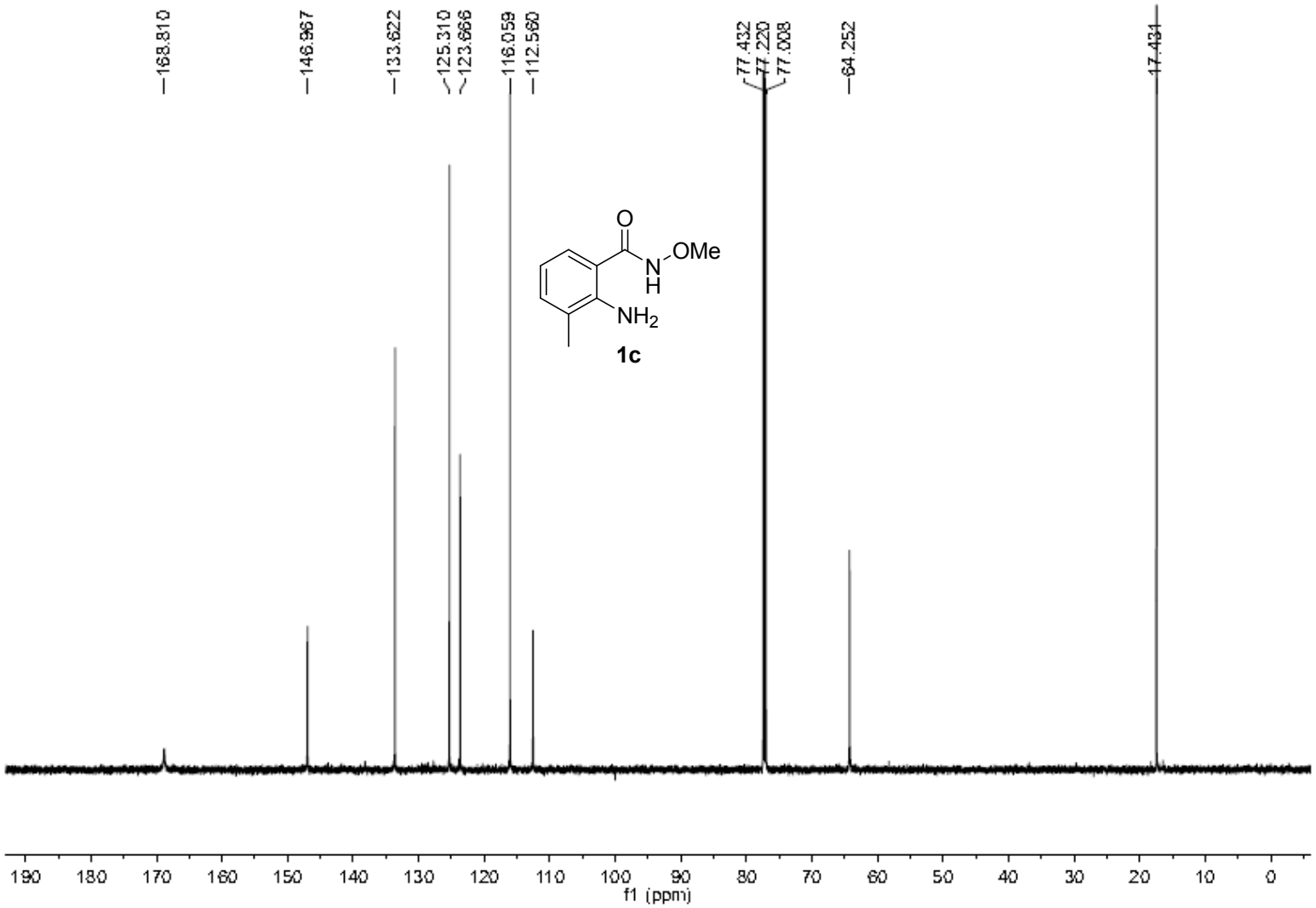
VIII ^{1}H and ^{13}C NMR Spectra of the Substrates and Products

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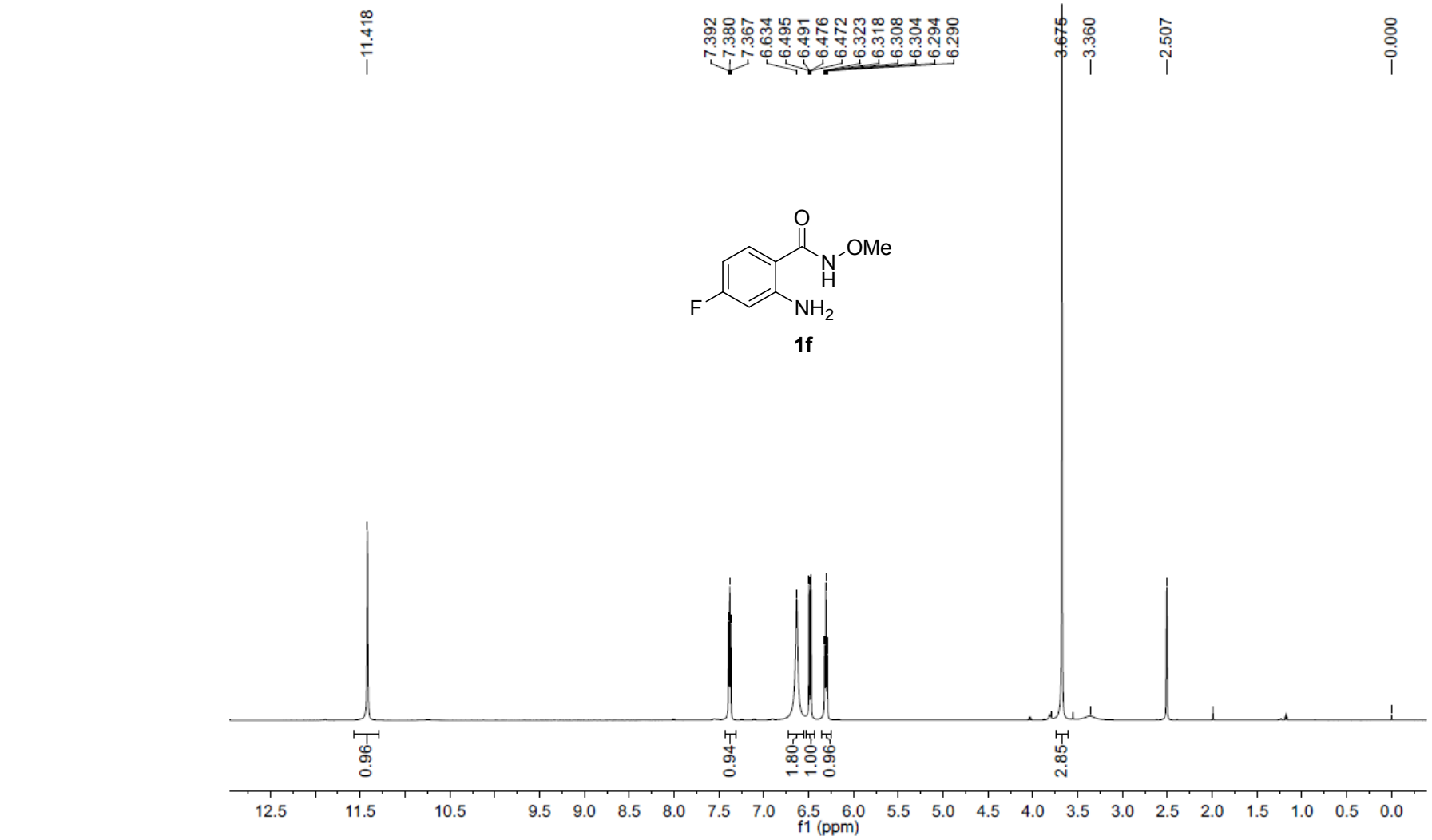
133.622
125.310
123.666
116.059
112.560
77.432
77.220
77.008
64.252
17.431
O
N
H
OMe
NH2
1c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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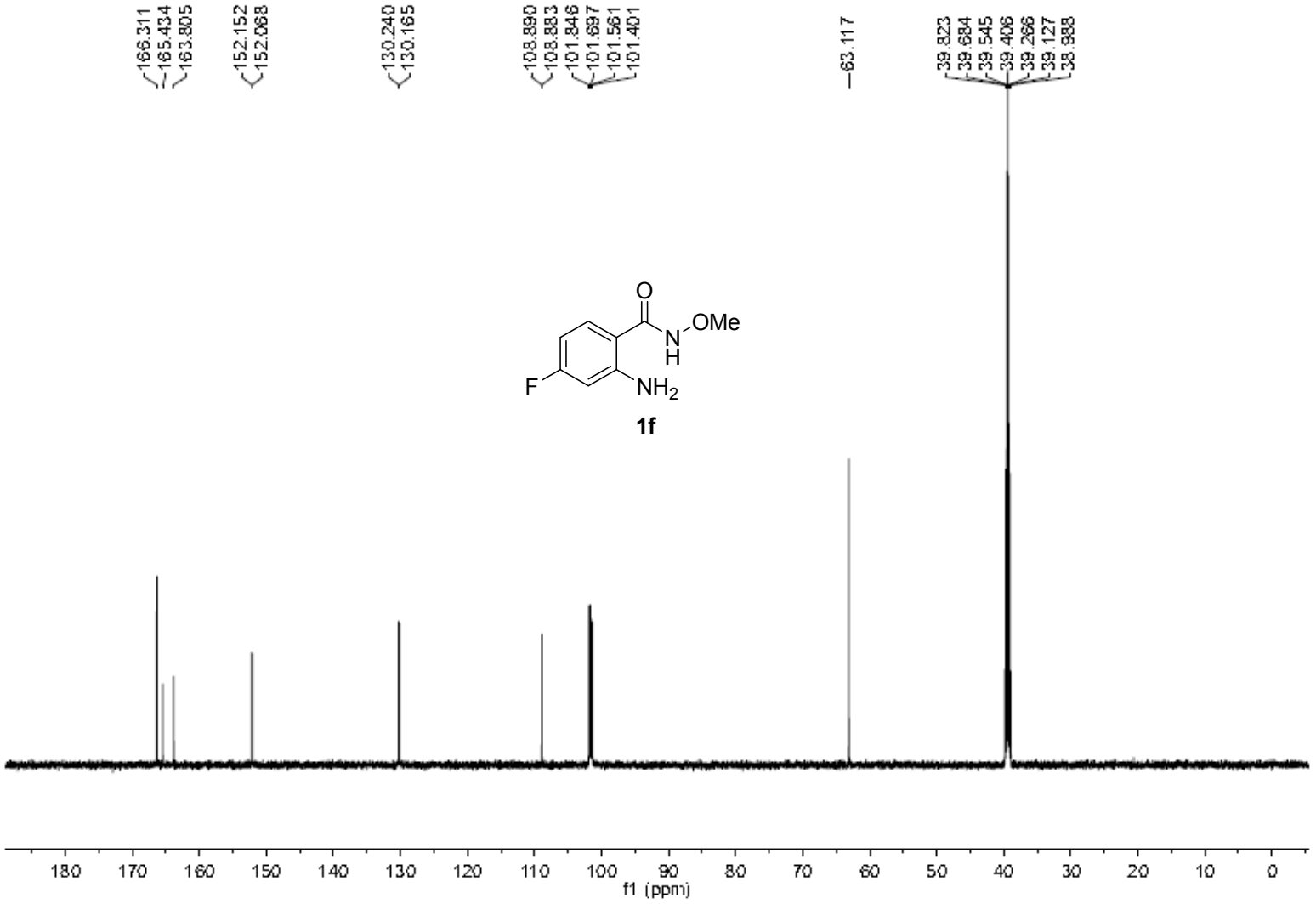
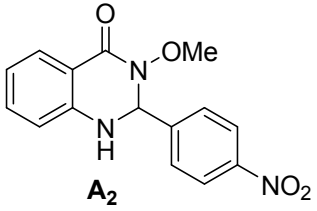
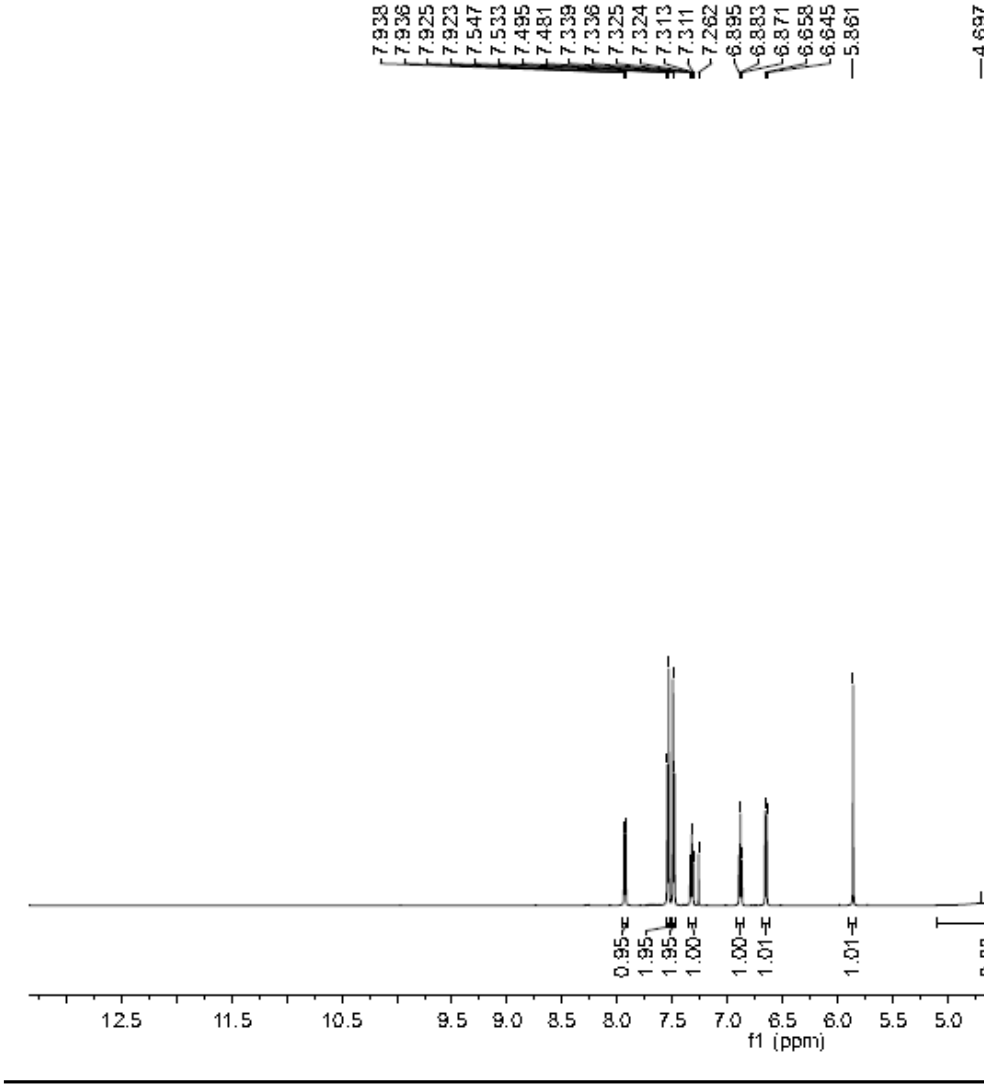
7.392
7.380
7.367
6.634
6.495
6.491
6.476
6.472
6.323
6.318
6.308
6.304
6.294
6.290
3.675
3.360
2.507
0.000
O
N
H
OMe
F
NH2
1f
0.96
0.94
1.80
1.00
0.96
2.85
12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


166.311
165.434
163.805
152.152
152.068
130.240
130.165
108.890
108.883
101.846
101.697
101.561
101.401
63.117
39.823
39.684
39.545
39.406
39.266
39.127
38.988
O
N
H
OMe
F
NH2
1f
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
OMe
N
H
NO2

A_2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7.925
7.923
7.547
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7.324
7.313
7.311
7.262
6.895
6.883
6.871
6.658
6.645
5.861
0.95
1.95
1.95
1.00
1.00
1.01
1.01
12.5
11.5
10.5
9.5
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7.0
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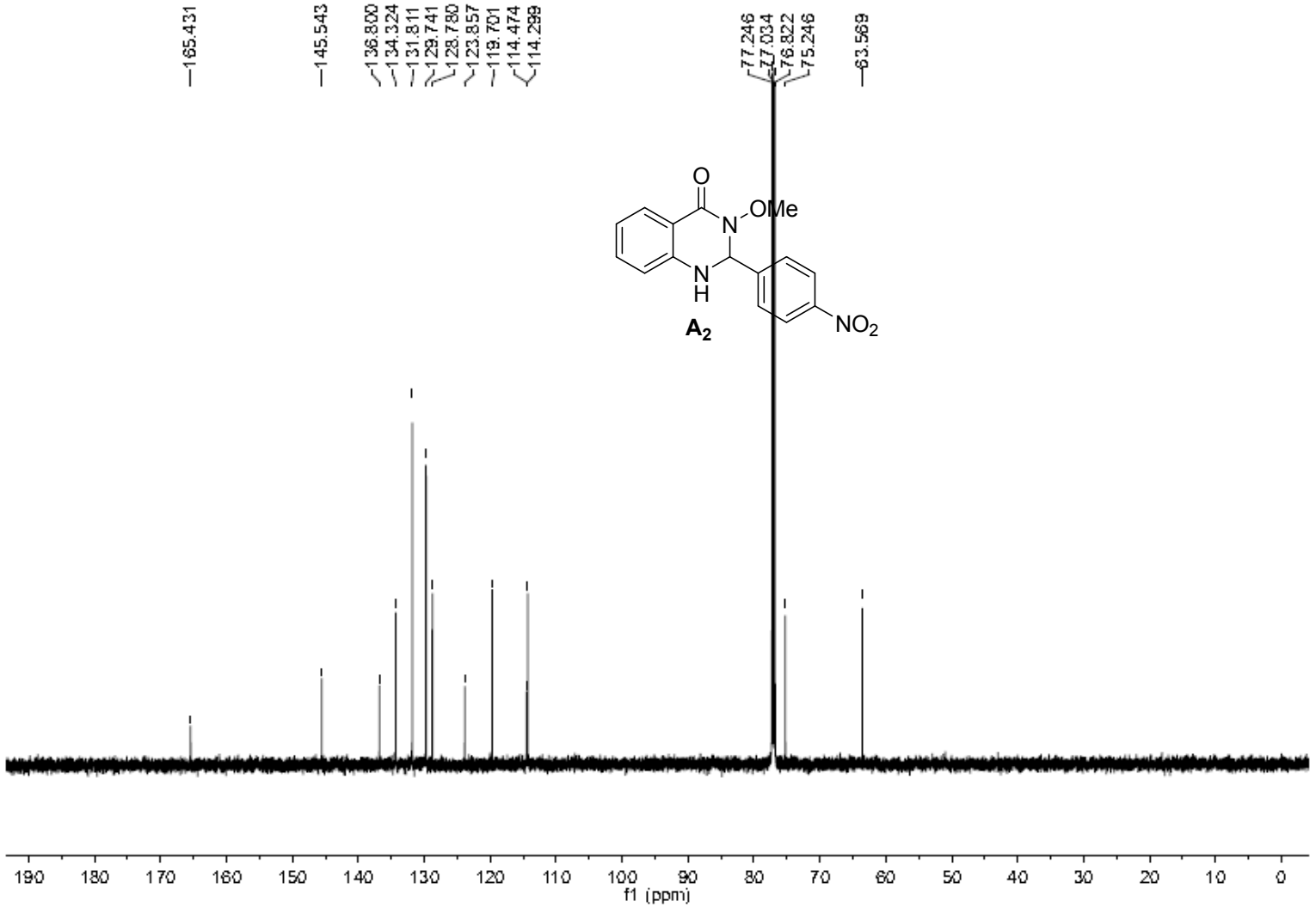
6.0
5.5
5.0
f1 (ppm)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136.800
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77.246
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76.822
75.246
63.569
O
N
OMe
N
H
NO2
A2
190
180
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150
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130
120
110
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90
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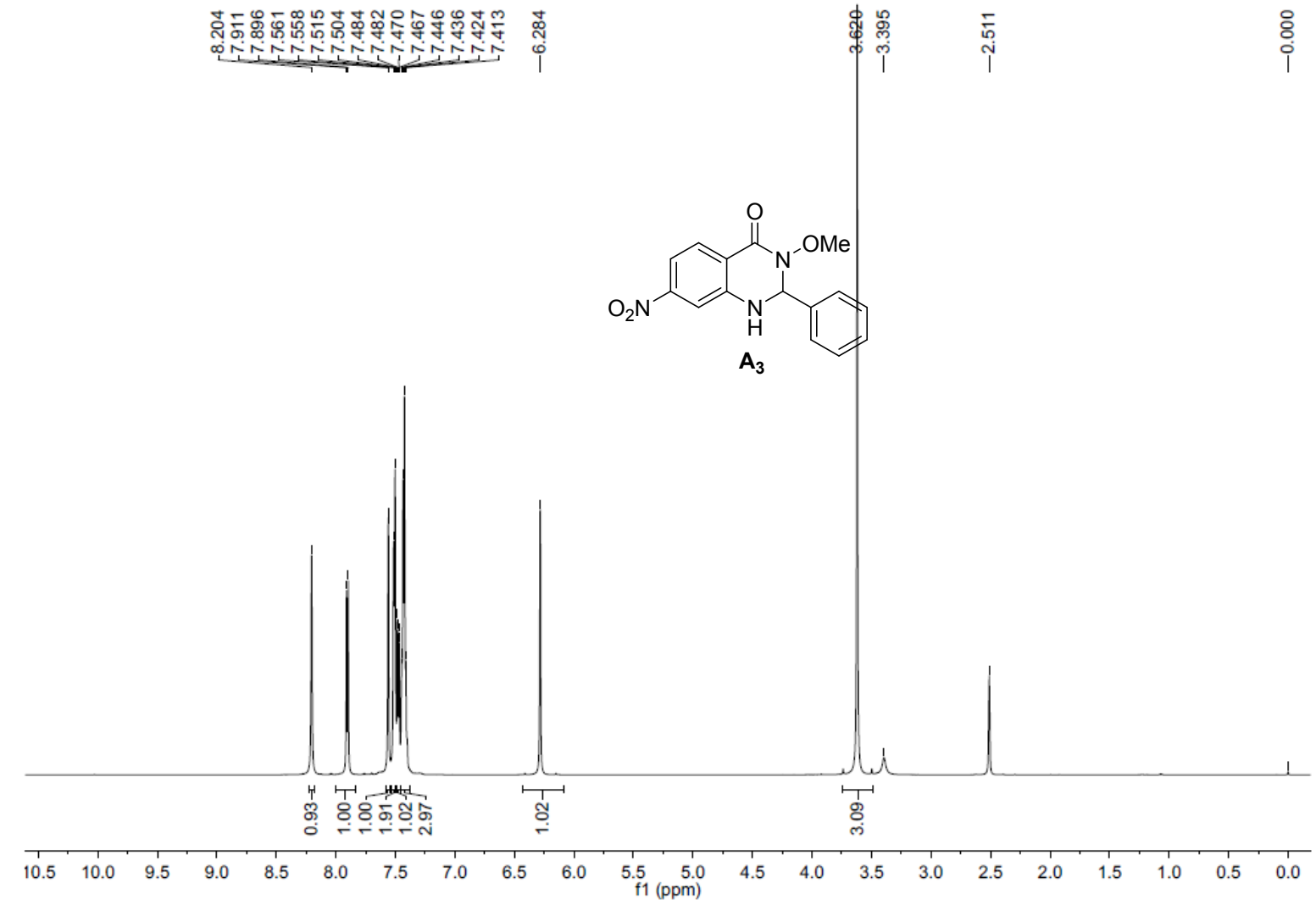
50
40
30
20
10
0
f1 (ppm)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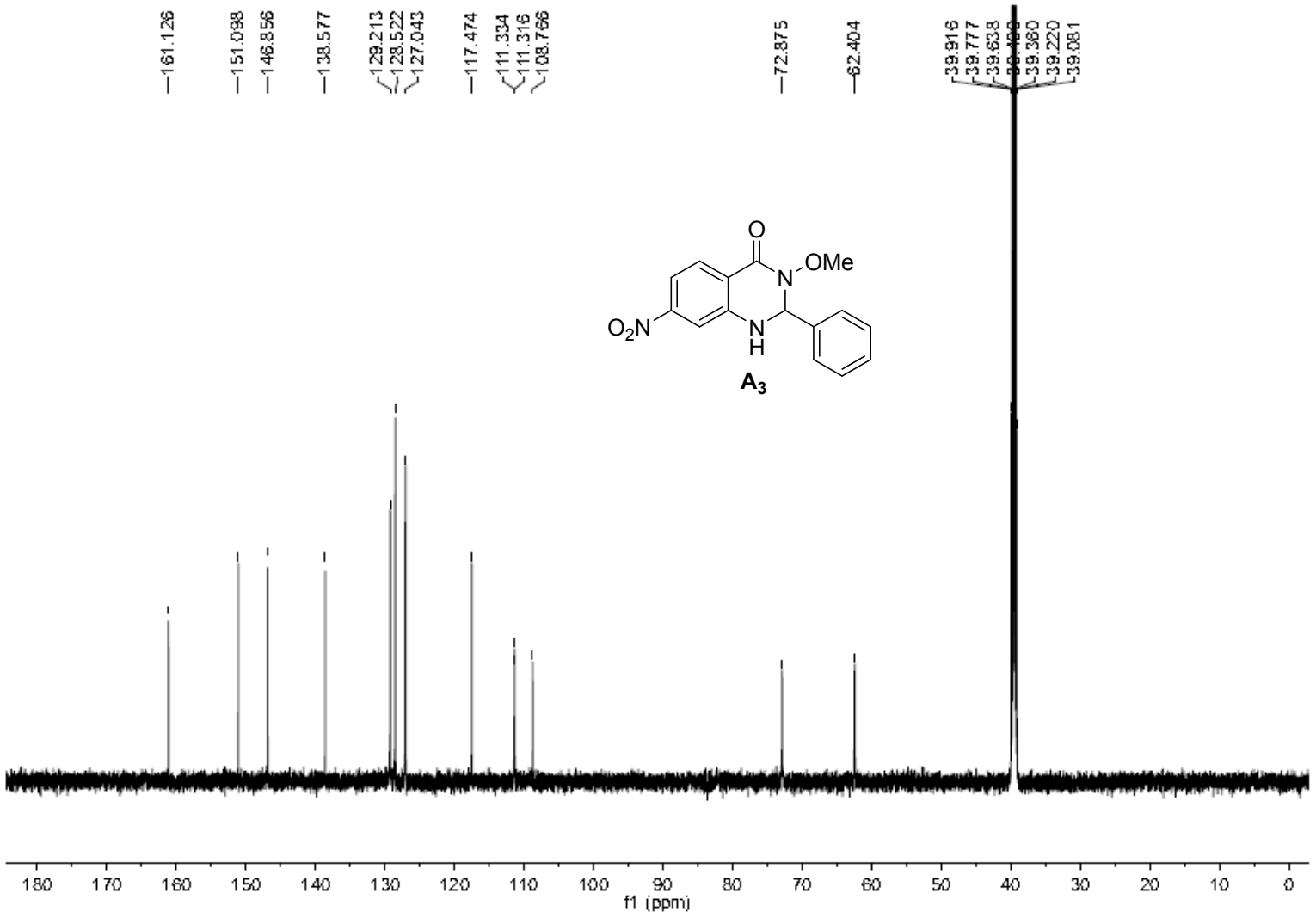
7.896
7.561
7.558
7.515
7.504
7.484
7.482
7.470
7.467
7.446
7.436
7.424
7.413
6.284
3.620
3.395
2.511
0.000
O
N
OMe
O2N
N
H
A3
0.93
1.00
1.00
1.91
1.02
2.97
1.02
3.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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151.088
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138.577
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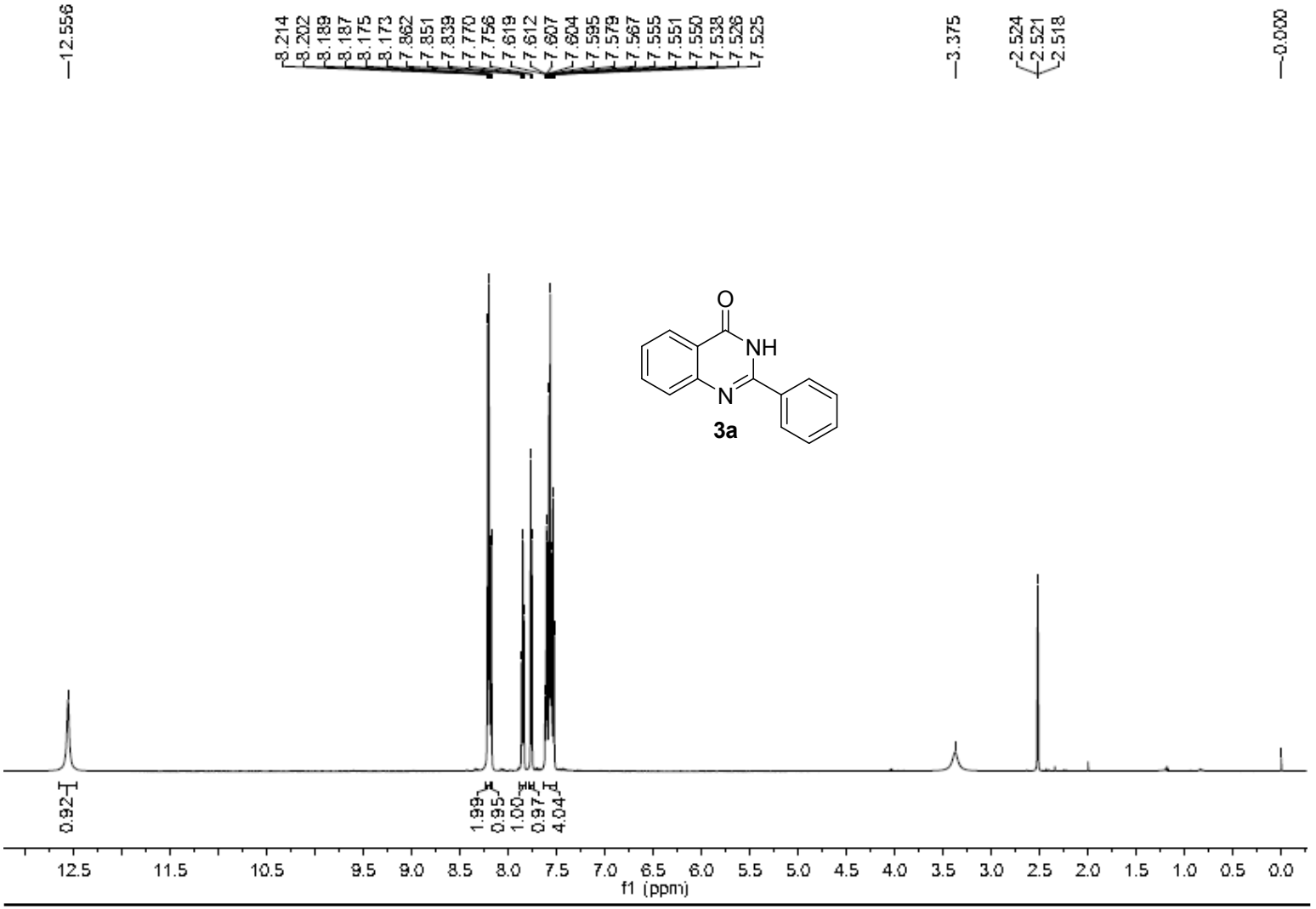
62.404
39.916
39.777
39.638
39.360
39.220
39.081
O
N
OMe
O2N
N
H
A3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.612
7.607
7.604
7.595
7.579
7.567
7.555
7.551
7.550
7.538
7.526
7.525
3.375
2.524
2.521
2.518
0.000
O
NH
N
3a
0.92
1.99
0.95
1.00
0.97
4.04
12.5
11.5
10.5
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
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2.5
2.0
1.5
1.0
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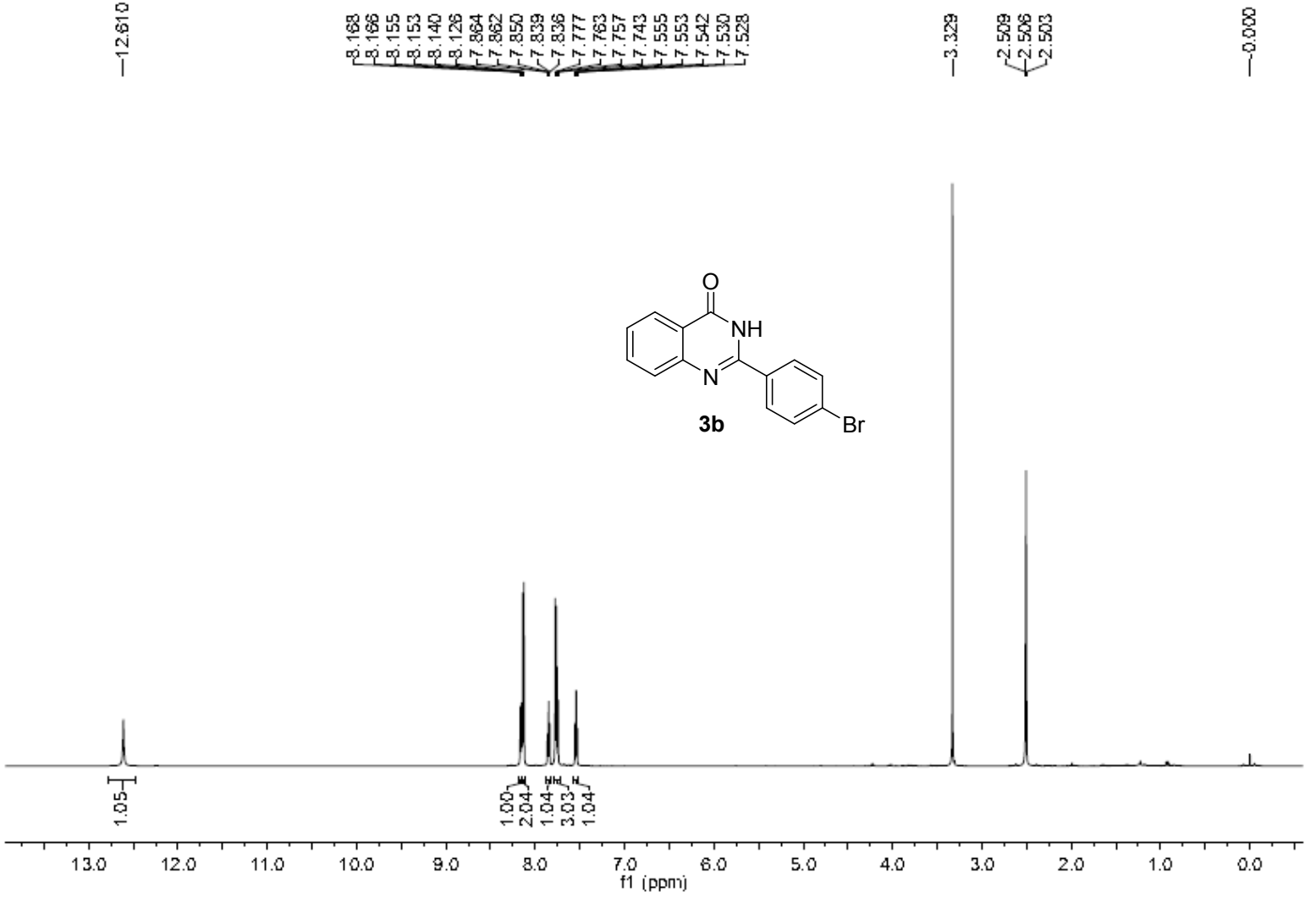
0.0
f1 (ppm)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7.763
7.757
7.743
7.555
7.553
7.542
7.530
7.528
3.329
2.509
2.506
2.503
0.000
O
NH
N
Br
3b
1.05
1.00
2.04
1.04
3.03
1.04
13.0
12.0
11.0
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7.0
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3.0
2.0
1.0
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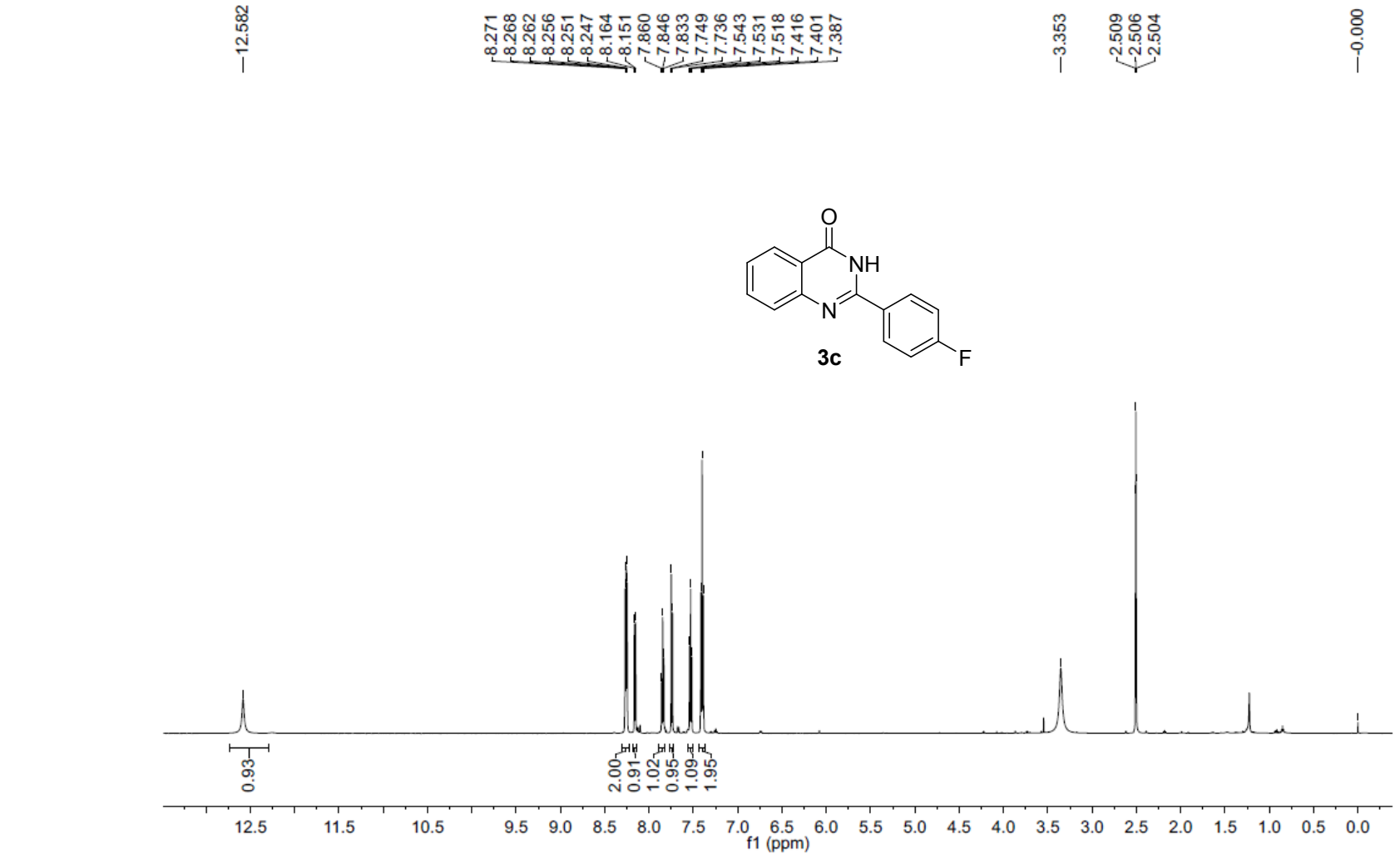
f1 (ppm)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7.736
7.543
7.531
7.518
7.416
7.401
7.387
3.353
2.509
2.506
2.504
0.000
O
NH
N
F
3c
0.93
2.00
0.91
1.02
0.95
1.09
1.95
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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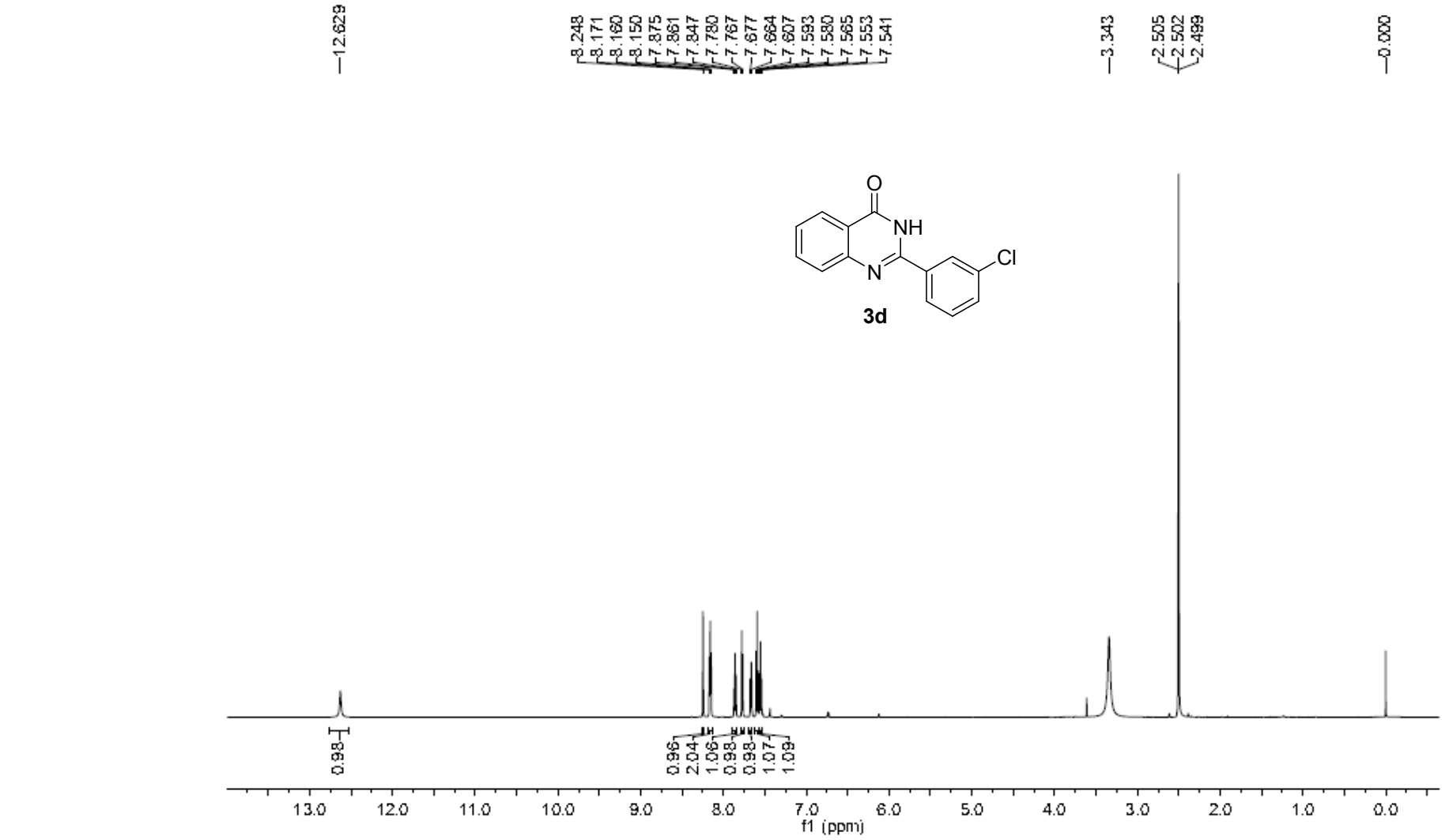
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7.847
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7.767
7.677
7.664
7.607
7.593
7.580
7.565
7.553
7.541
3.343
2.505
2.502
2.499
0.000
O
NH
N
Cl
3d
0.98
0.96
2.04
1.06
0.98
0.98
1.07
1.09
13.0
12.0
11.0
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9.0
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7.0
6.0
5.0
4.0
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2.0
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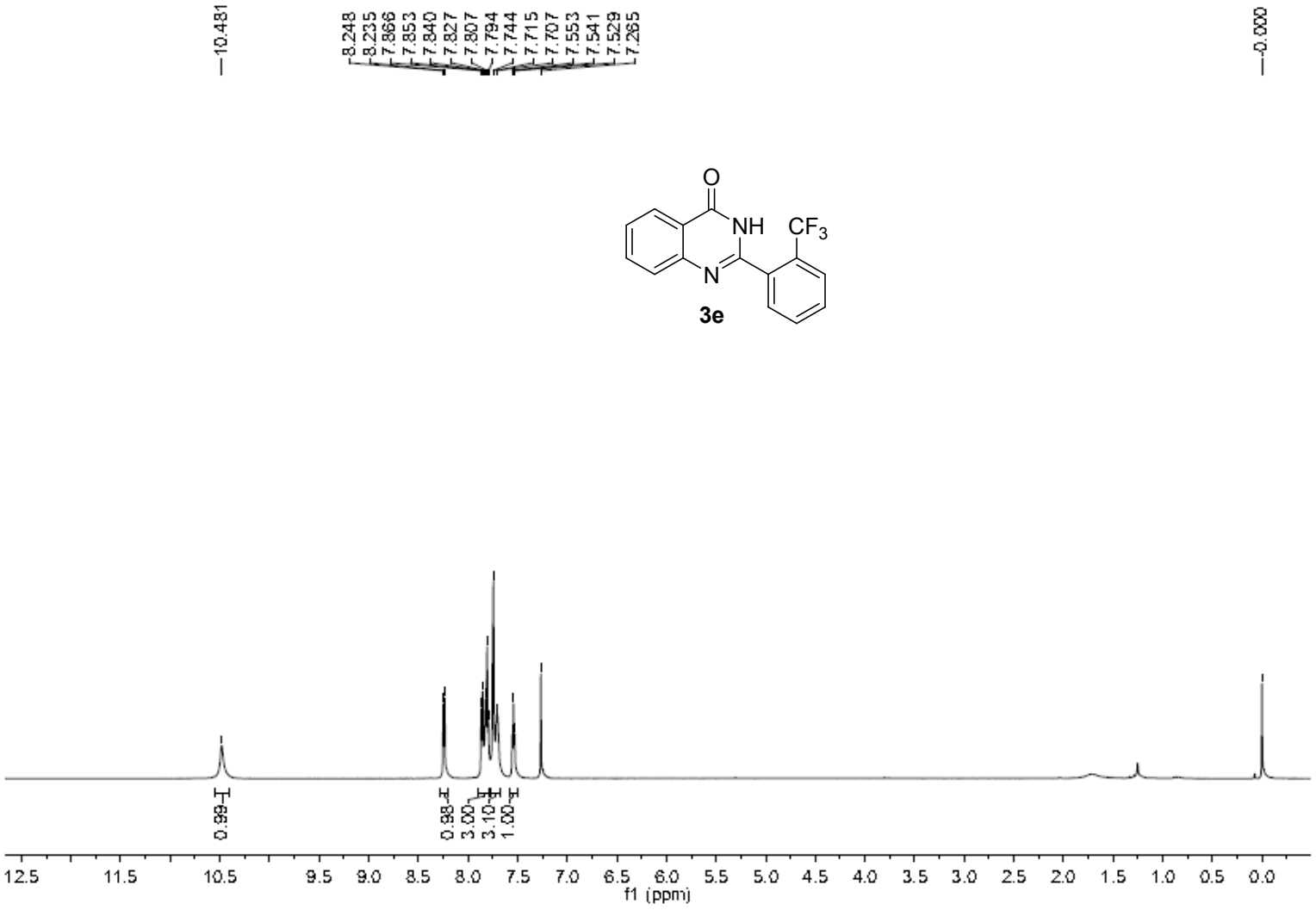
0.0
f1 (ppm)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7.807
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7.744
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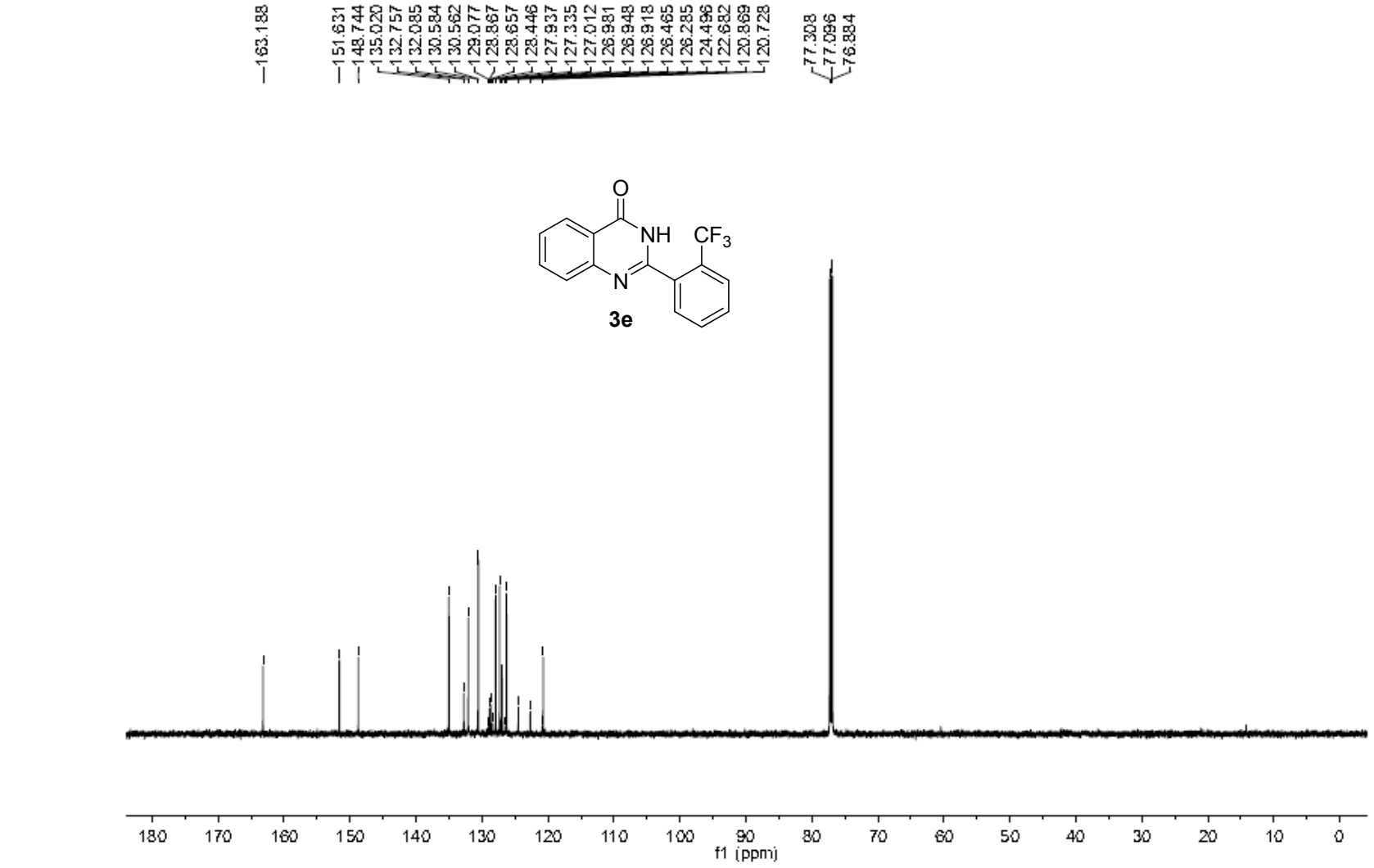
7.707
7.553
7.541
7.529
7.265
0.000
O
NH
CF3
N
3e
0.99
0.98
3.00
3.10
1.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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135.020
132.757
132.085
130.584
130.562
129.077
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128.657
128.446
127.937
127.335
127.012
126.981
126.948
126.918
126.465
126.285
124.496
122.682
120.869
120.728
77.308
77.096
76.884
O
NH
CF3
N
3e
180
170
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130
120
110
100
90
80
70
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50
40
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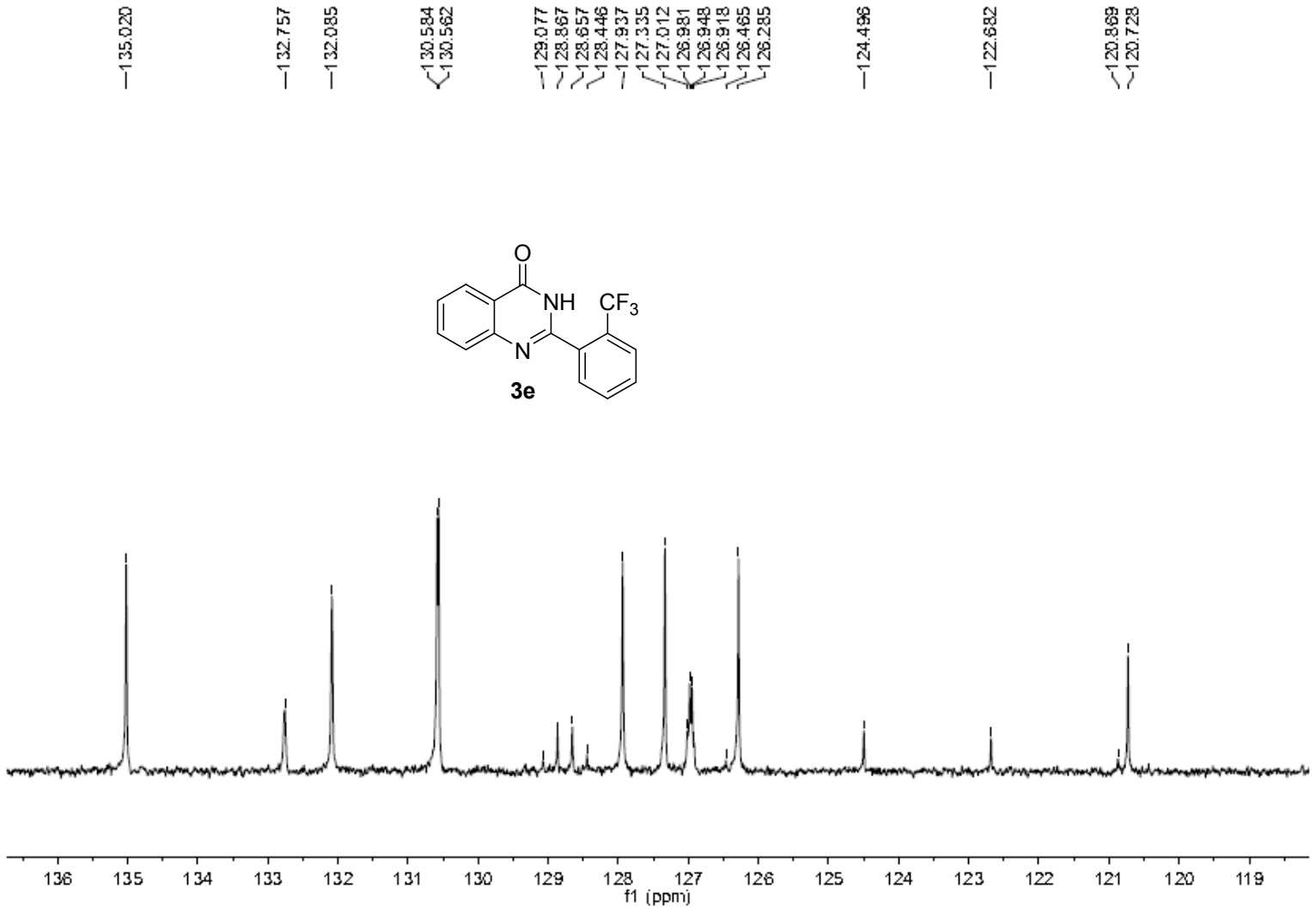
10
0
f1 (ppm)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132.757
132.085
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128.657
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126.981
126.948
126.918
126.465
126.285
124.496
122.682
120.869
120.728
O
NH
CF3
N
3e
136
135
134
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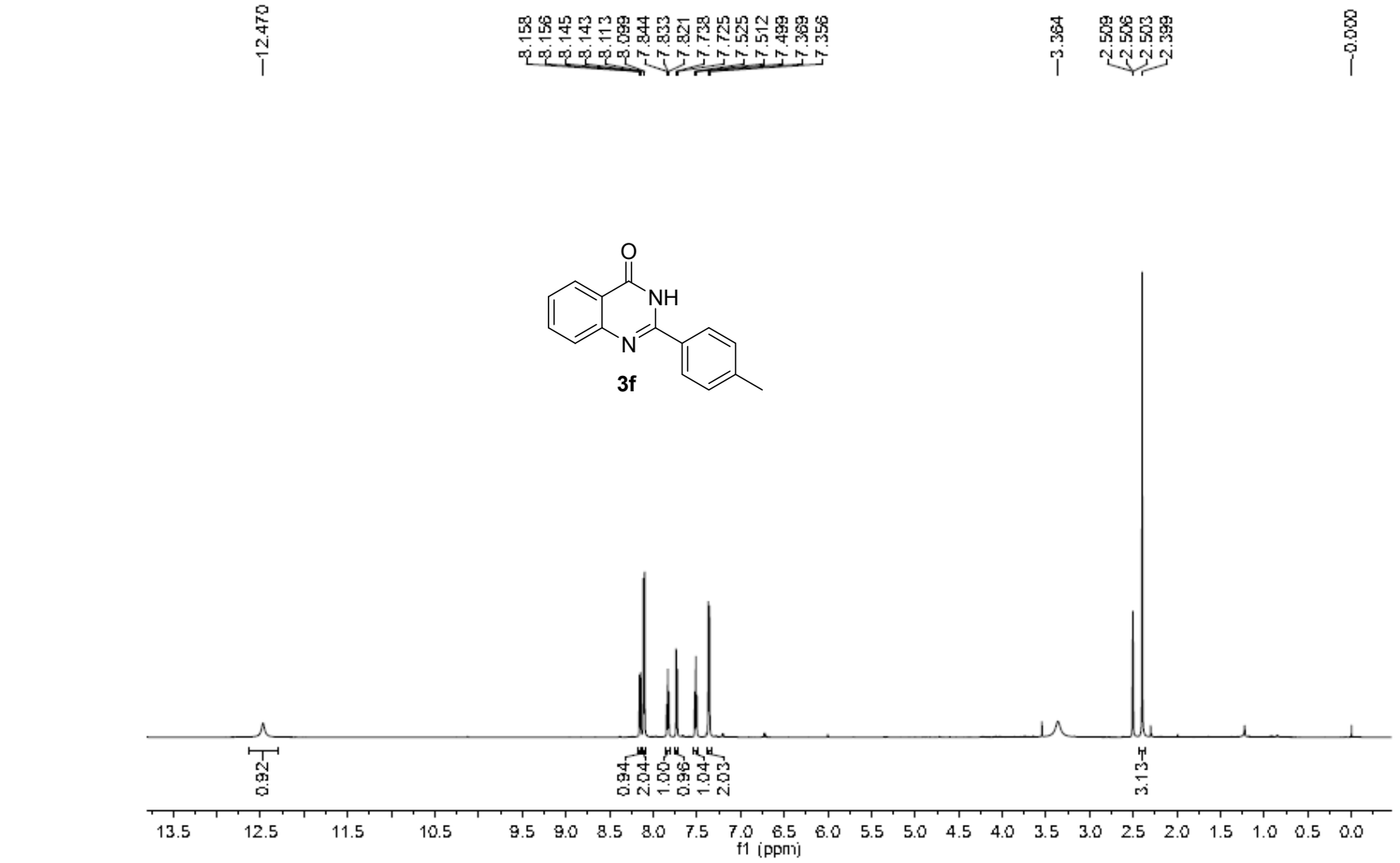
132
131
130
129
128
127
126
125
124
123
122
121
120
119
f1 (ppm)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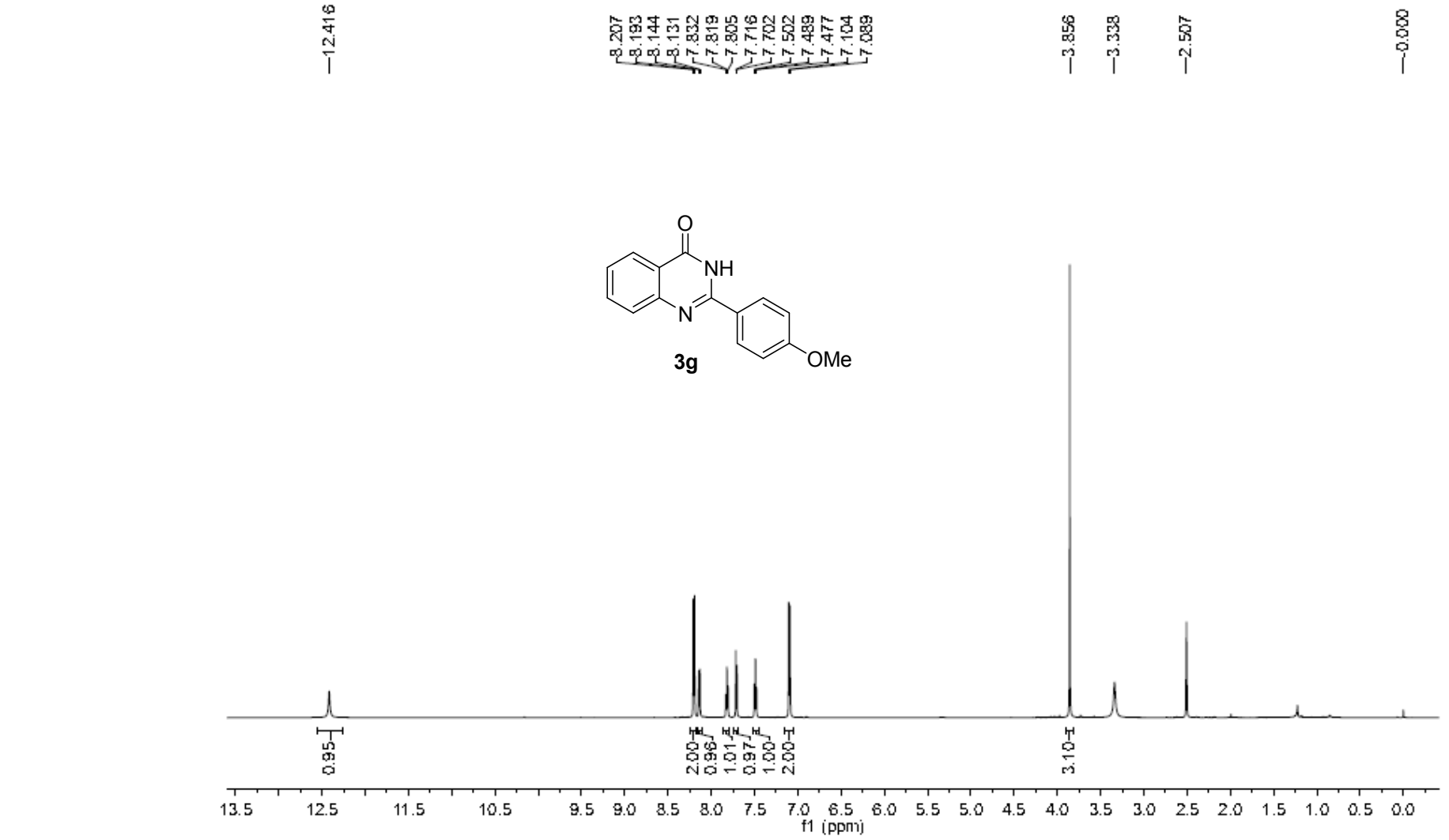
7.844
7.833
7.821
7.738
7.725
7.525
7.512
7.499
7.369
7.356
3.364
2.509
2.506
2.503
2.399
0.000
O
NH
N
3f
0.92
0.94
2.04
1.00
0.96
1.04
2.03
3.13
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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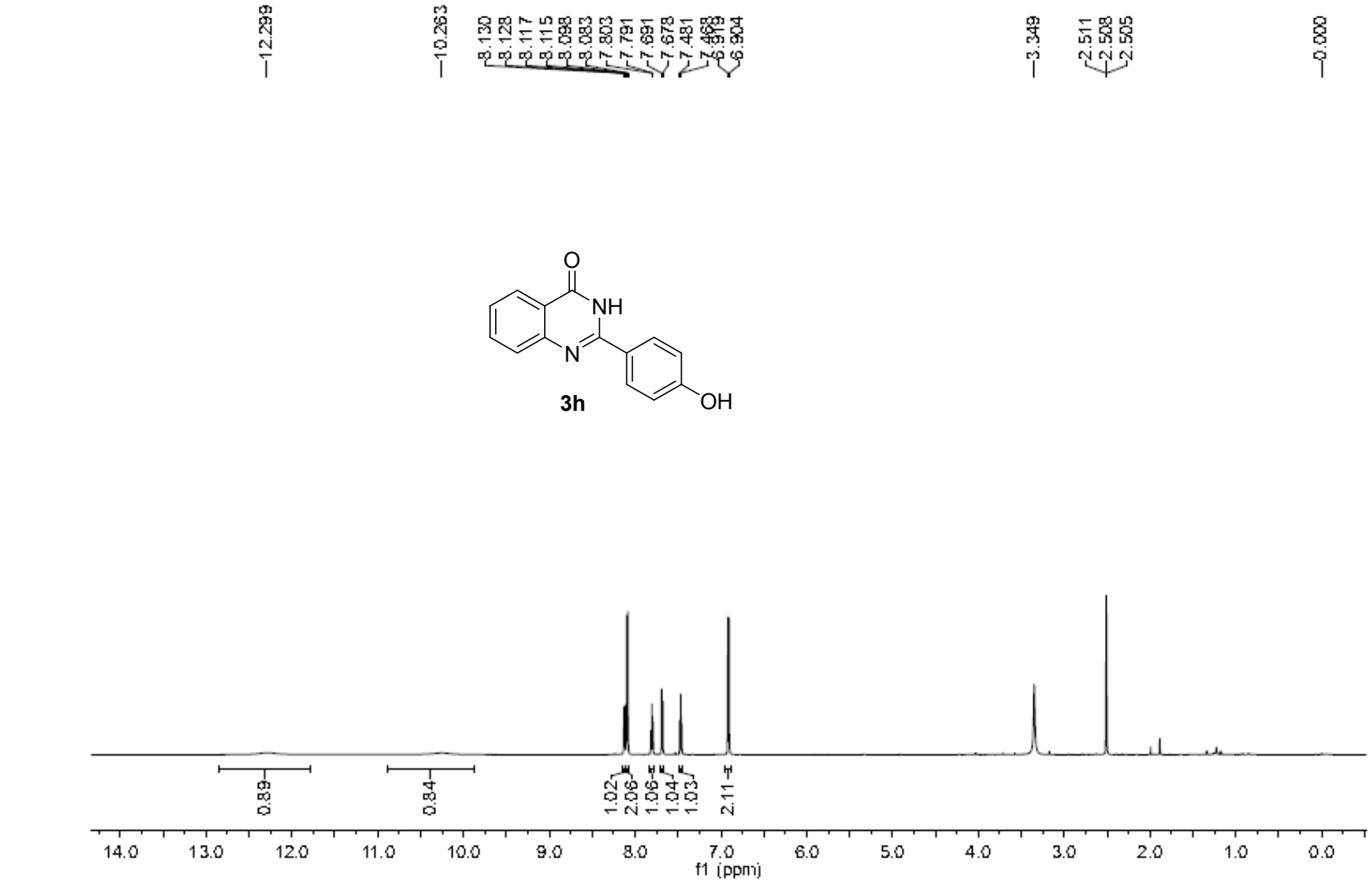
8.193
8.144
8.131
7.832
7.819
7.805
7.716
7.702
7.502
7.489
7.477
7.104
7.089
3.856
3.338
2.507
0.000
O
NH
N
OMe
3g
0.95
2.00
0.96
1.01
0.97
1.00
2.00
3.10
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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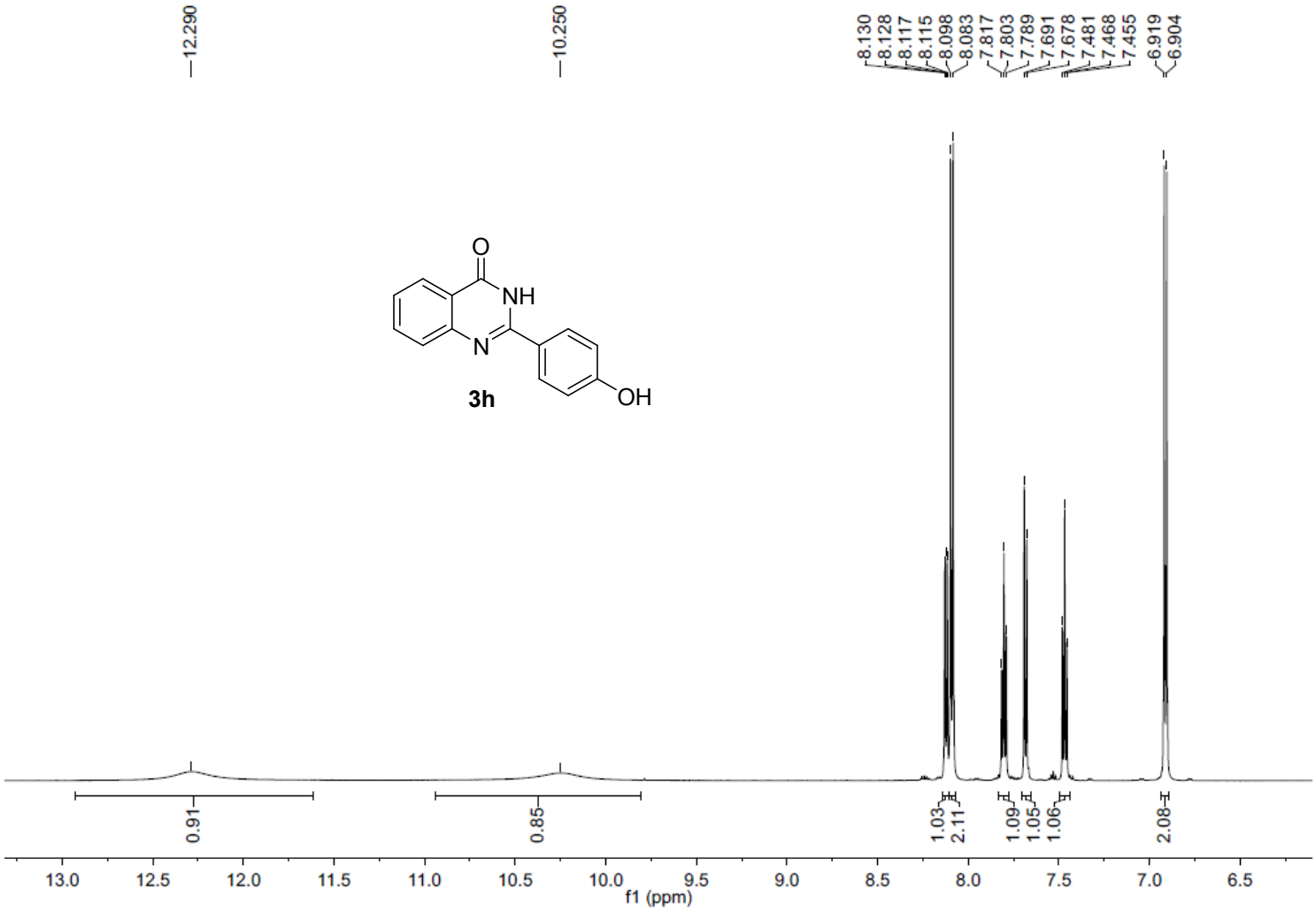
10.263
8.130
8.123
8.117
8.115
8.098
8.083
7.803
7.791
7.691
7.678
7.481
7.468
6.919
6.904
3.349
2.511
2.508
2.505
0.000
O
NH
N
OH
3h
0.89
0.84
1.02
2.06
1.06
1.04
1.03
2.11
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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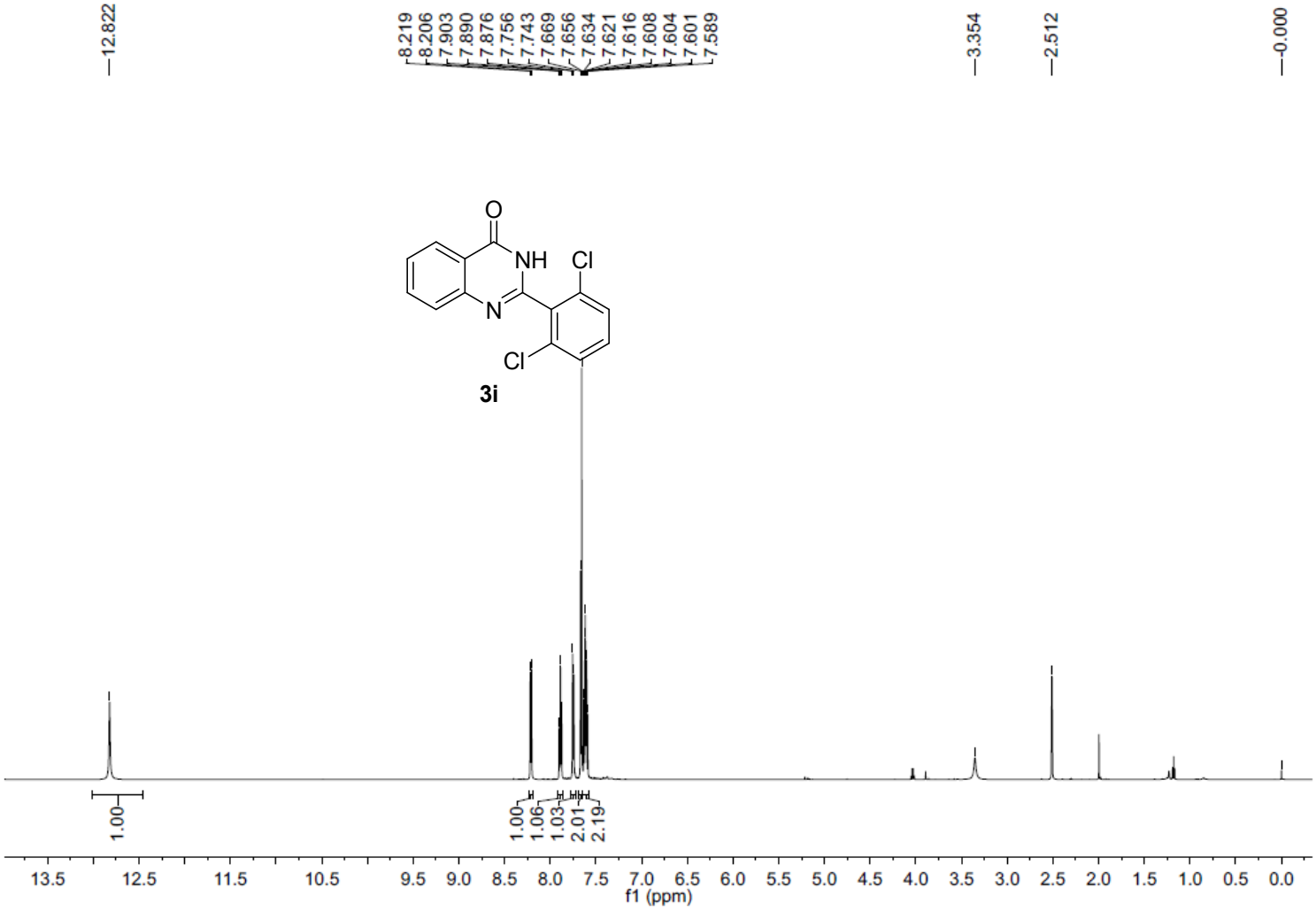
10.250
8.130
8.128
8.117
8.115
8.098
8.083
7.817
7.803
7.789
7.691
7.678
7.481
7.468
7.455
6.919
6.904
O
NH
N
OH
3h
0.91
0.85
1.03
2.11
1.09
1.05
1.06
2.08
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)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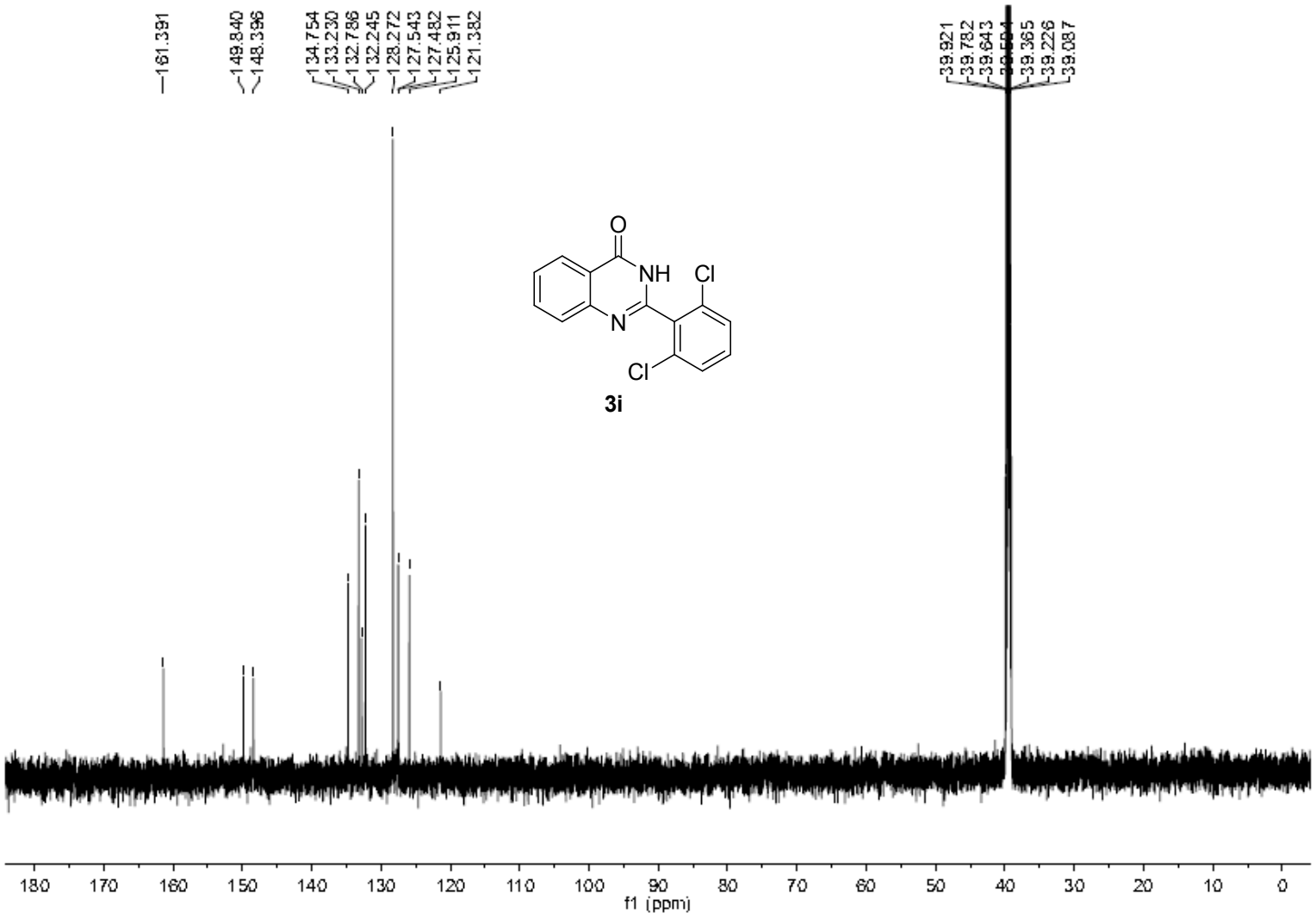
8.219
8.206
7.903
7.890
7.876
7.756
7.743
7.669
7.656
7.634
7.621
7.616
7.608
7.604
7.601
7.589
3.354
2.512
0.000
O
NH
Cl
N
Cl
3i
1.00
1.00
1.06
1.03
2.01
2.19
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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149.840
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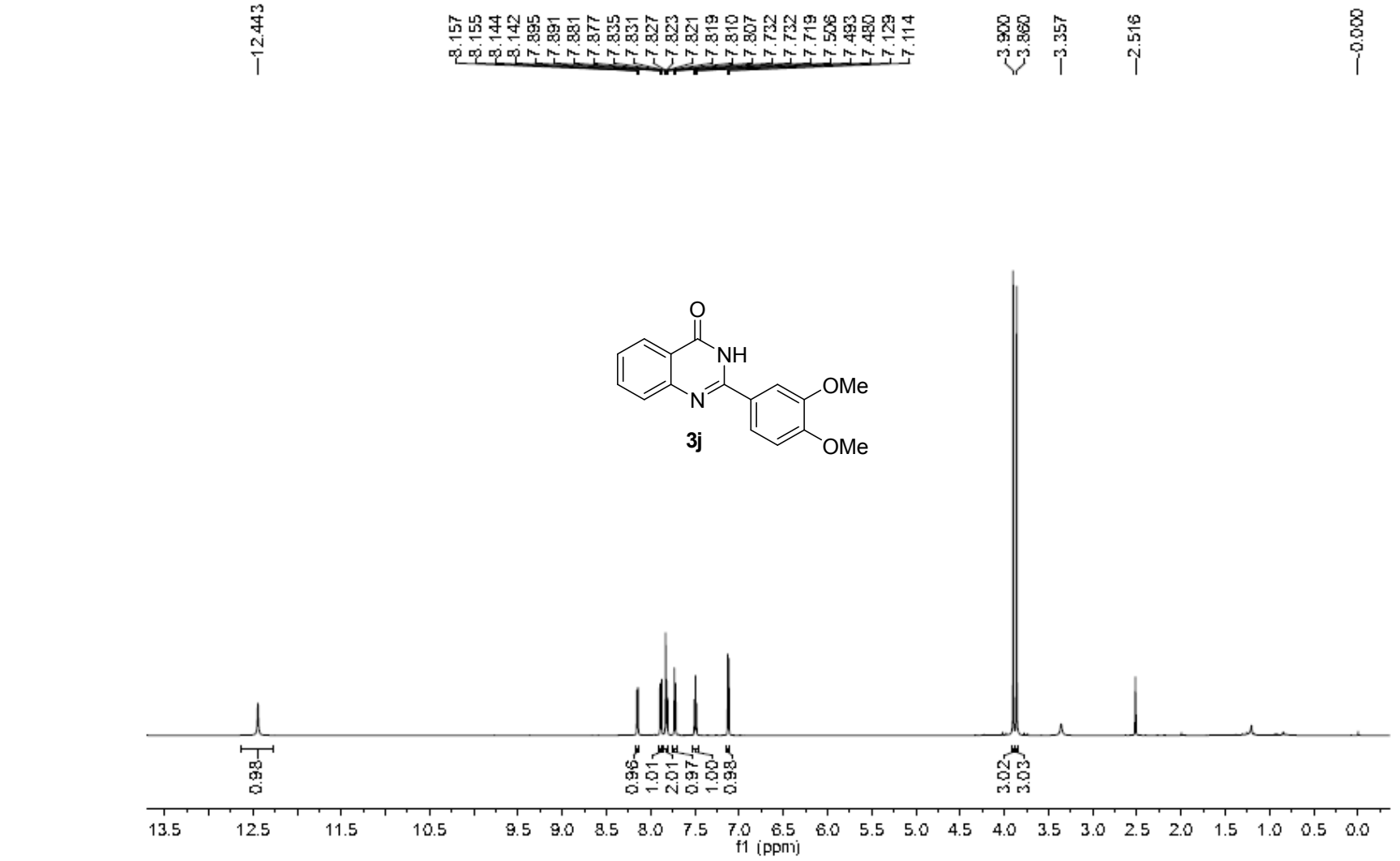
132.786
132.245
128.272
127.543
127.482
125.911
121.382
39.921
39.782
39.643
39.365
39.226
39.087
O
NH
Cl
N
Cl
3i
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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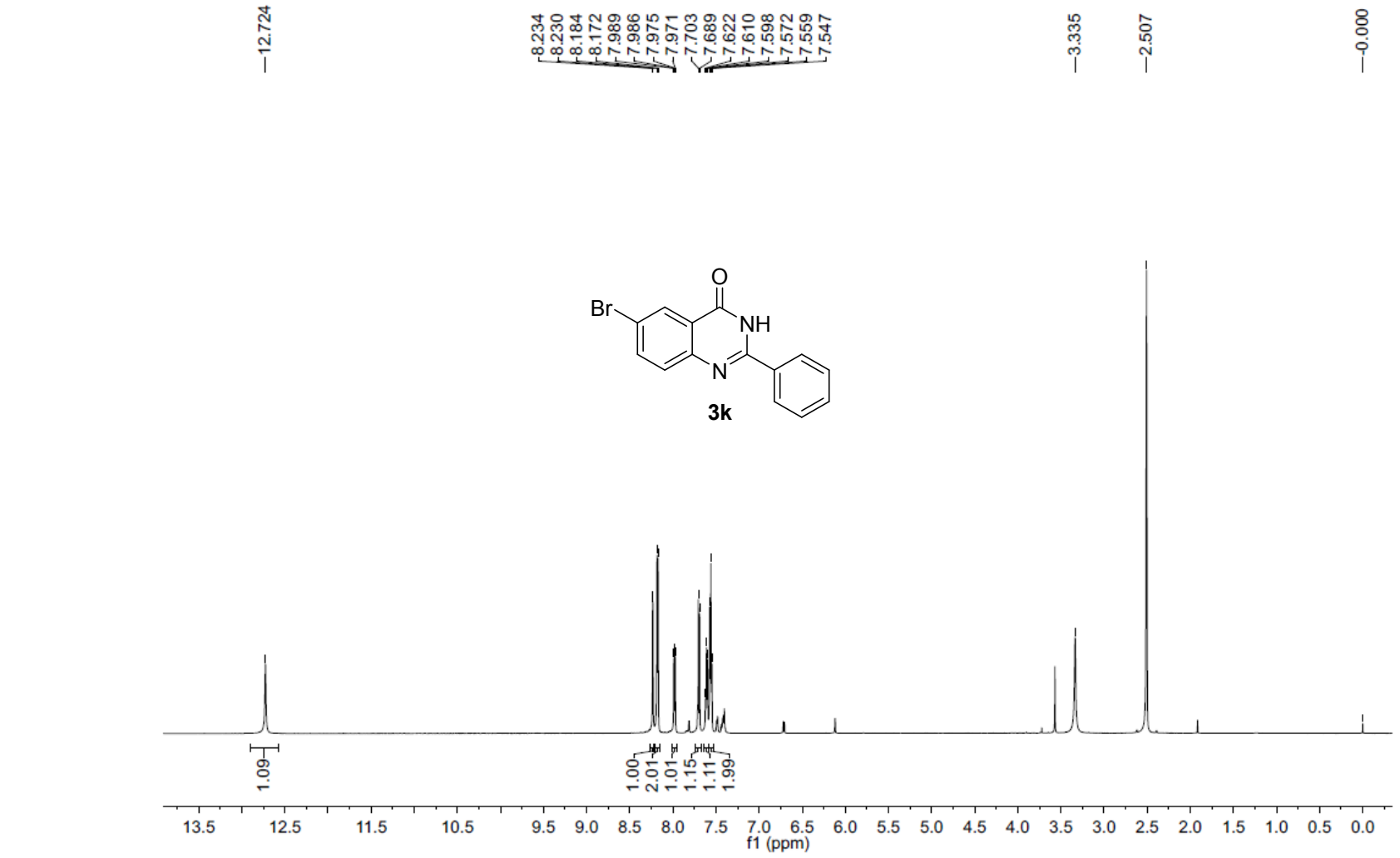
8.155
8.144
8.142
7.895
7.891
7.881
7.877
7.835
7.831
7.827
7.823
7.821
7.819
7.810
7.807
7.732
7.732
7.719
7.506
7.493
7.480
7.129
7.114
3.900
3.860
3.357
2.516
0.000
O
NH
N
OMe
OMe
3j
0.98
0.96
1.01
2.01
0.97
1.00
0.98
3.02
3.03
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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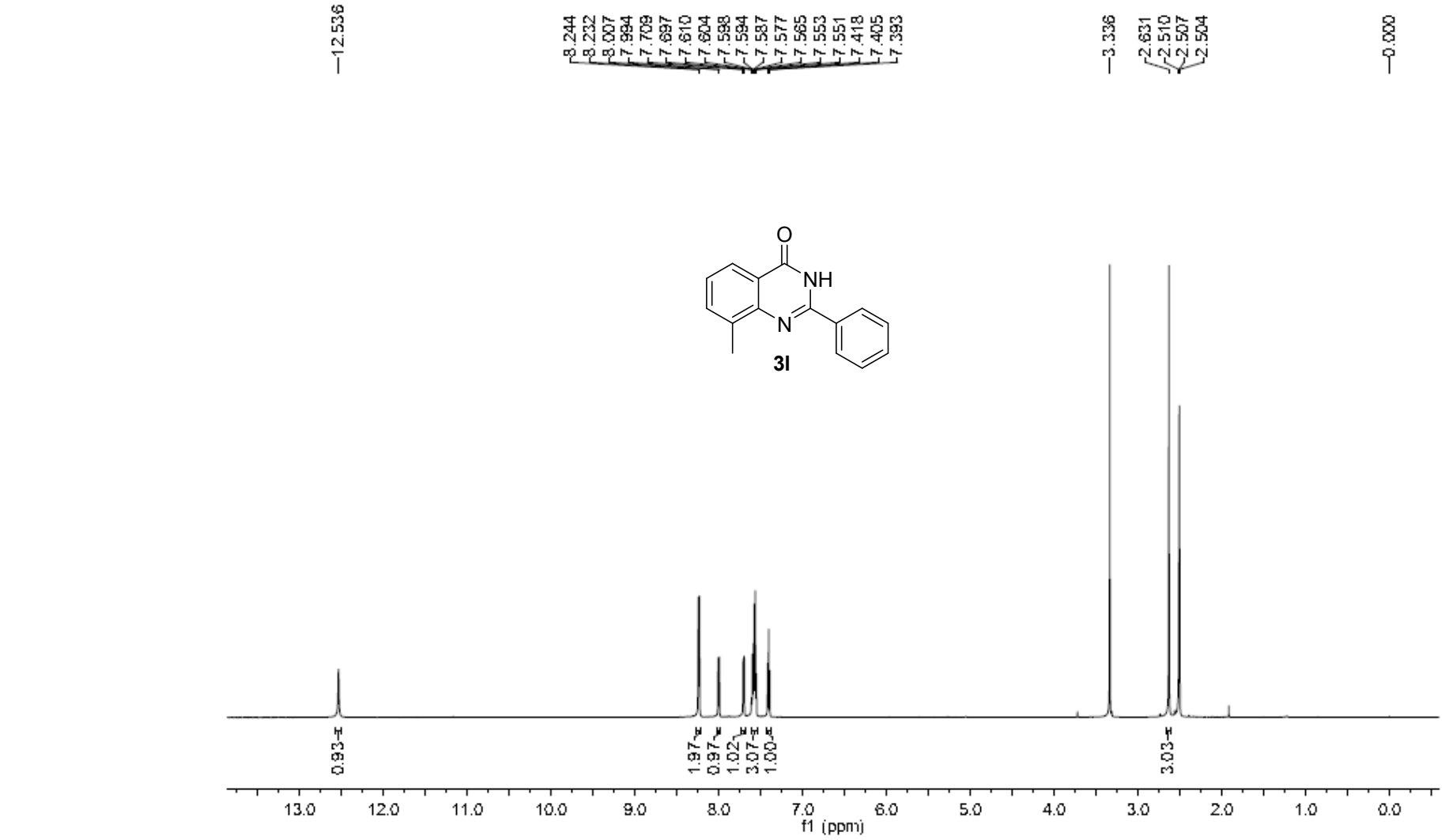
7.975
7.971
7.703
7.689
7.622
7.610
7.598
7.572
7.559
7.547
3.335
2.507
0.000
Br
O
NH
N
3k
1.09
1.00
2.01
1.01
1.15
1.11
1.99
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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7.697
7.610
7.604
7.598
7.594
7.587
7.577
7.565
7.553
7.551
7.418
7.405
7.393
3.336
2.631
2.510
2.507
2.504
0.000
O
NH
N
3l
0.93
1.97
0.97
1.02
3.07
1.00
3.03
13.0
12.0
11.0
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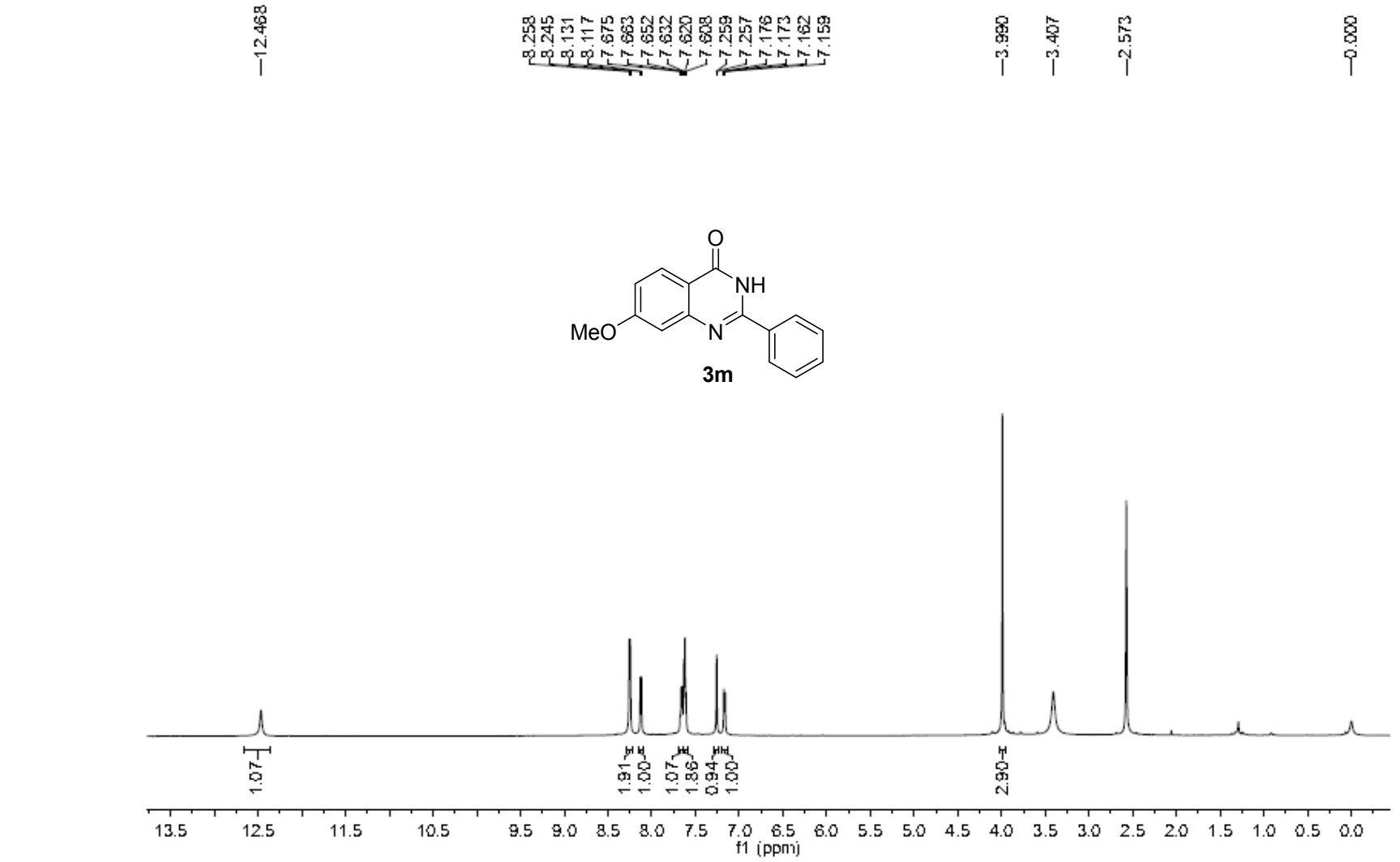
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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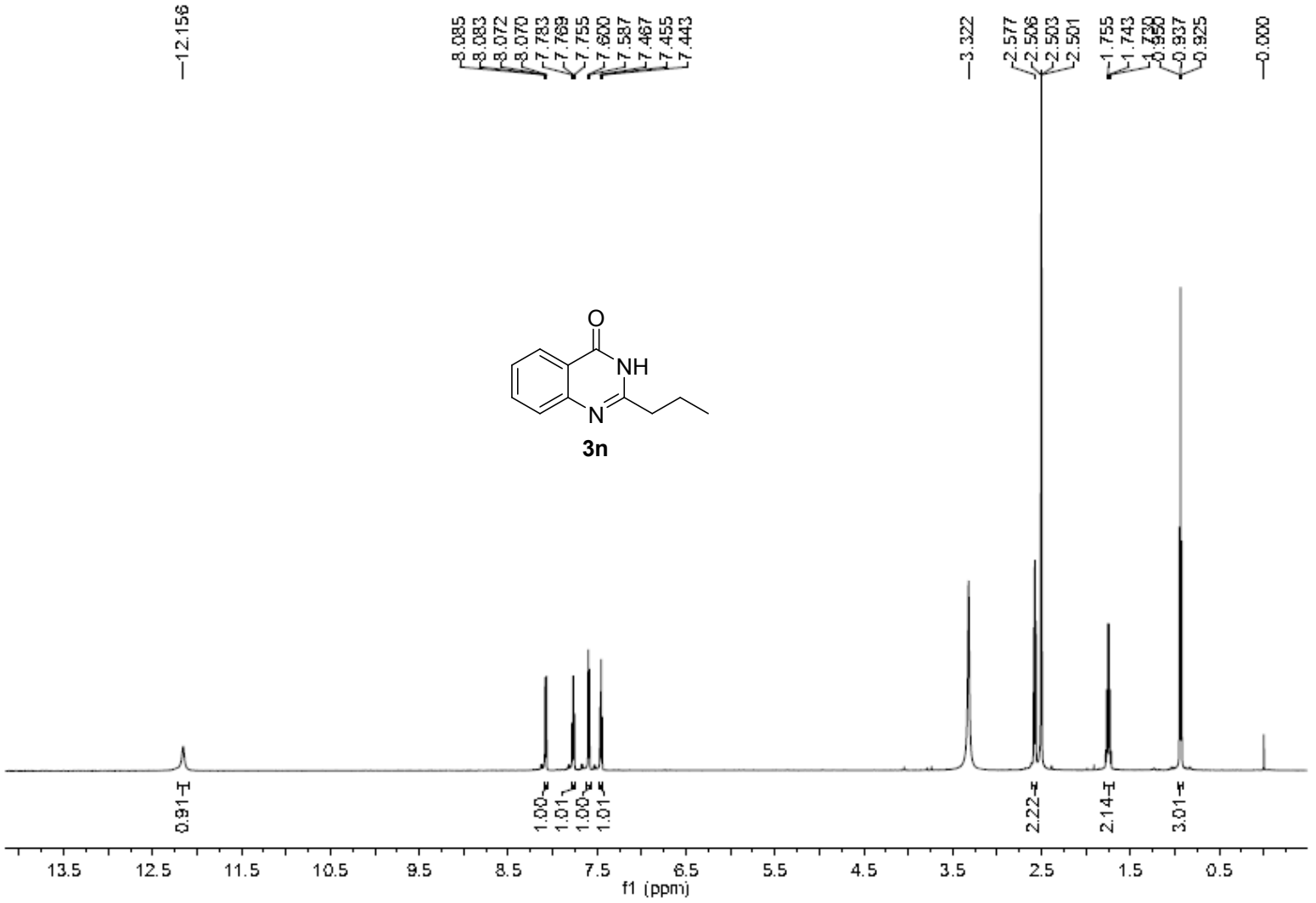
7.663
7.652
7.632
7.620
7.608
7.259
7.257
7.176
7.173
7.162
7.159
3.990
3.407
2.573
0.000
O
NH
N
MeO
3m
1.07
1.91
1.00
1.07
1.86
0.94
1.00
2.90
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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8.070
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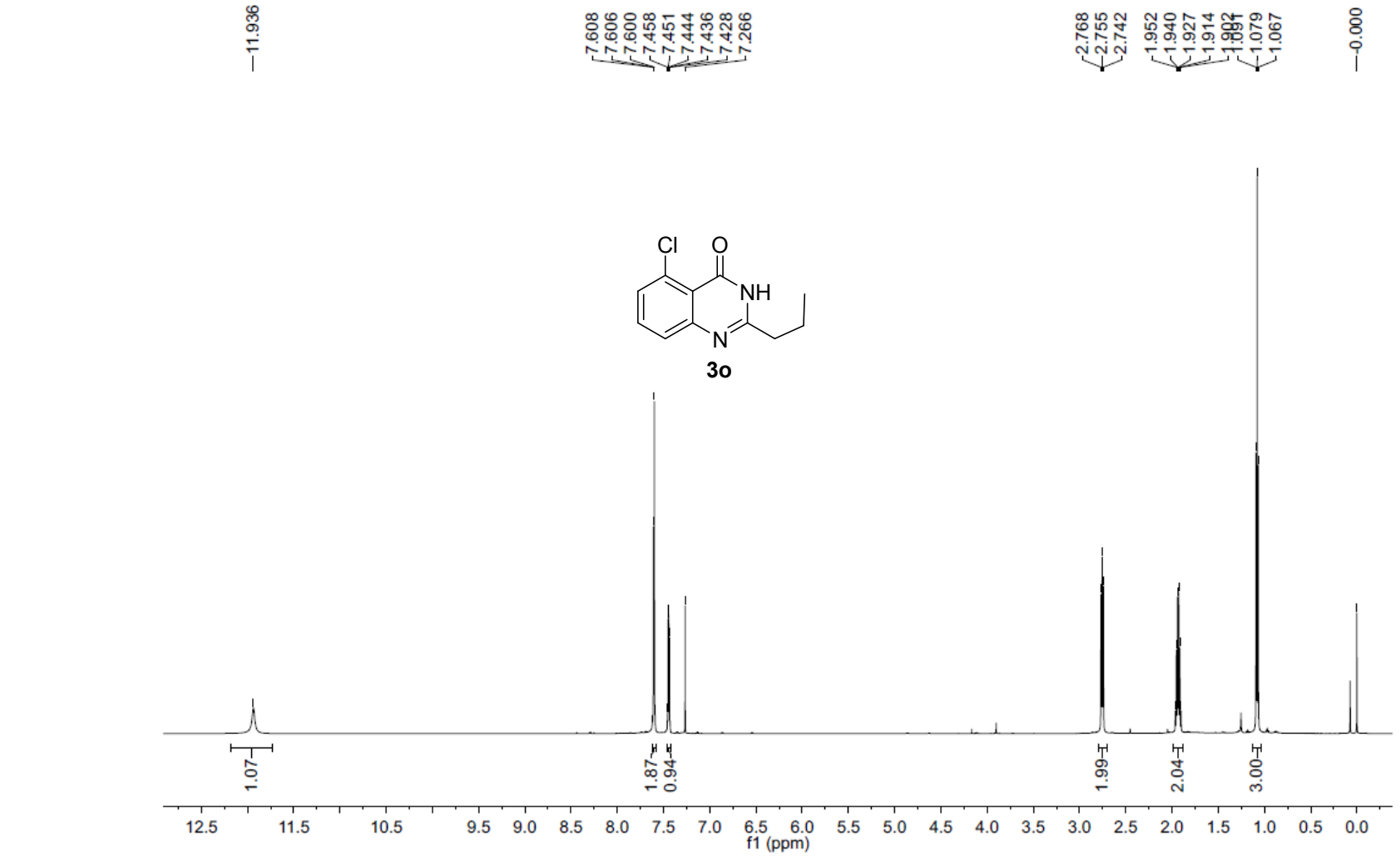
7.755
7.600
7.587
7.467
7.455
7.443
3.322
2.577
2.506
2.503
2.501
1.755
1.743
0.937
0.925
0.000
O
NH
N
3n
0.91
1.00
1.01
1.00
1.01
2.22
2.14
3.01
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)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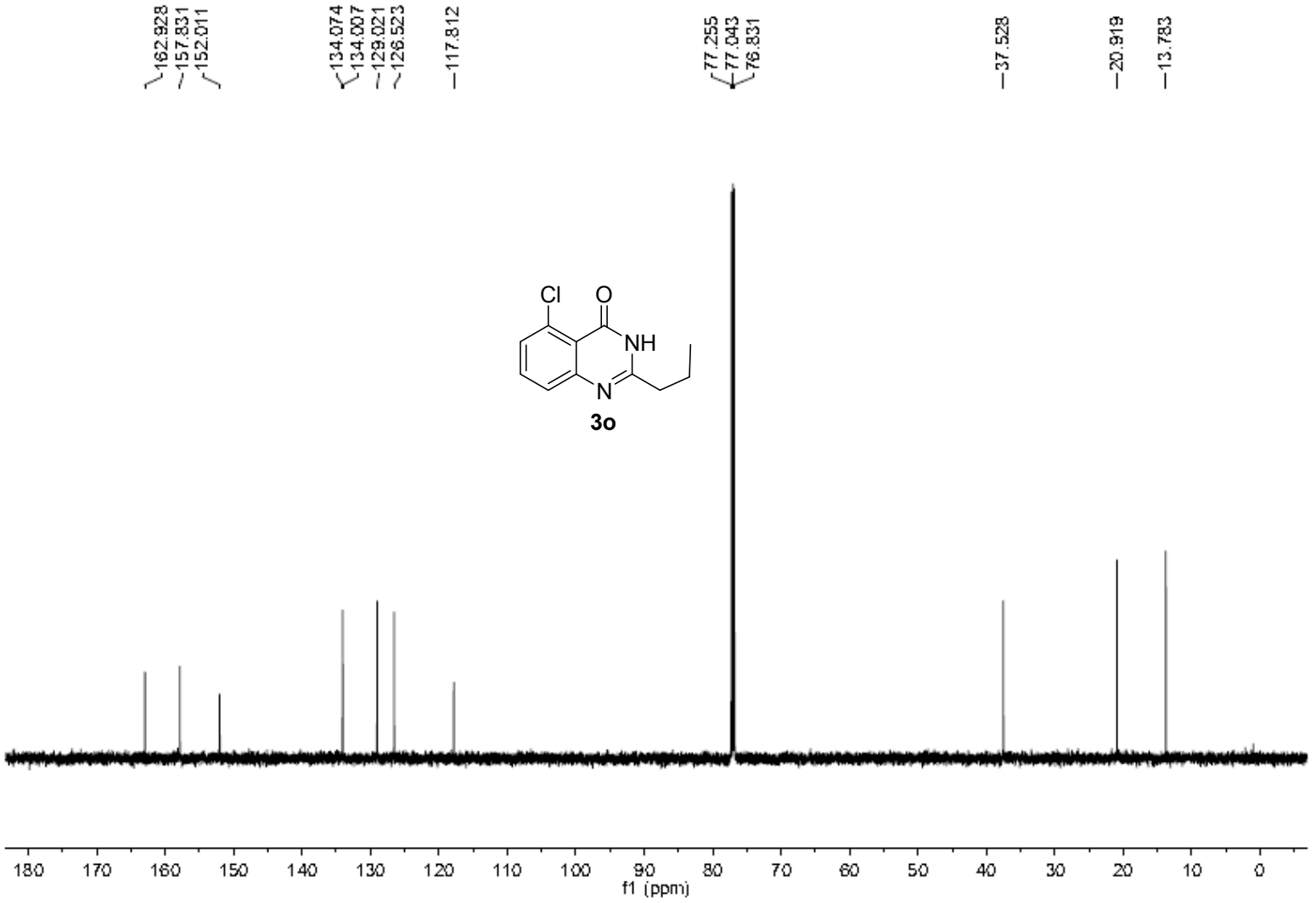
7.451
7.444
7.436
7.428
7.266
2.768
2.755
2.742
1.952
1.940
1.927
1.914
1.079
1.067
0.000
Cl
O
NH
N
3o
1.07
1.87
0.94
1.99
2.04
3.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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152.011
134.074
134.007
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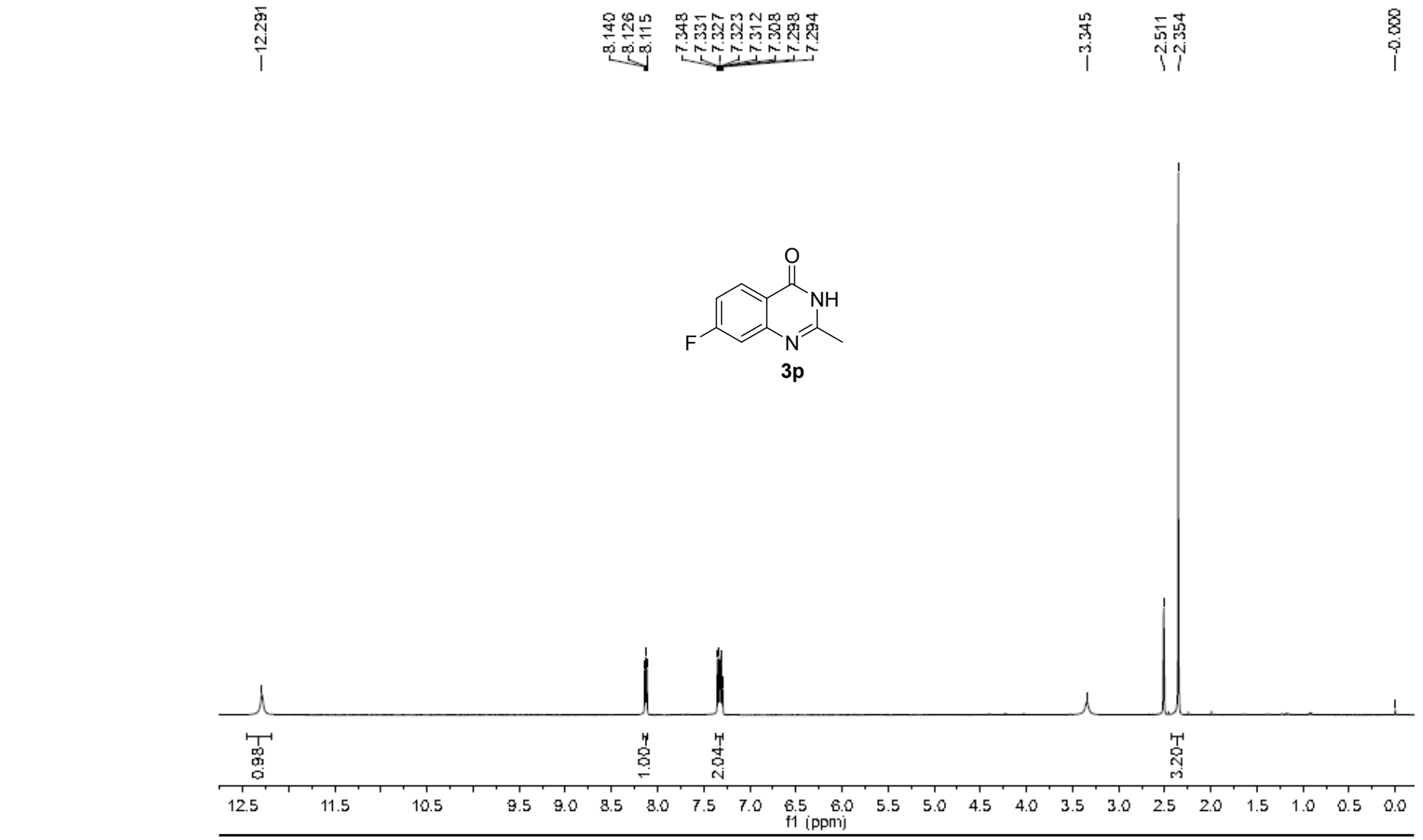
126.523
117.812
77.255
77.043
76.831
37.528
20.919
13.783
Cl
O
NH
N
3o
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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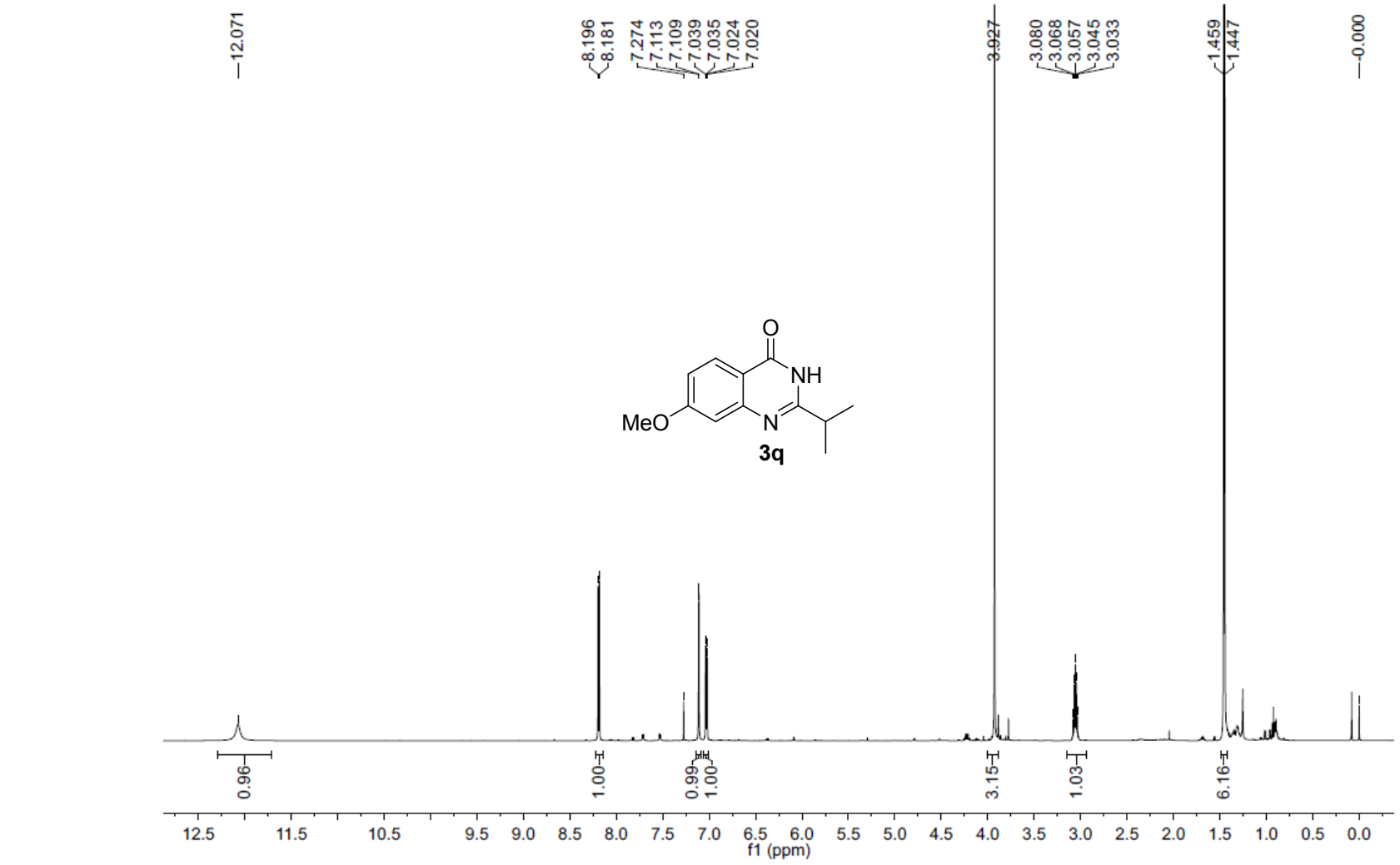
7.331
7.327
7.323
7.312
7.308
7.298
7.294
3.345
2.511
2.354
0.000
O
NH
N
F
3p
0.98
1.00
2.04
3.20
12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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7.109
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7.035
7.024
7.020
3.927
3.080
3.068
3.057
3.045
3.033
1.459
1.447
0.000
O
NH
MeO
N
3q
0.96
1.00
0.99
1.00
3.15
1.03
6.16
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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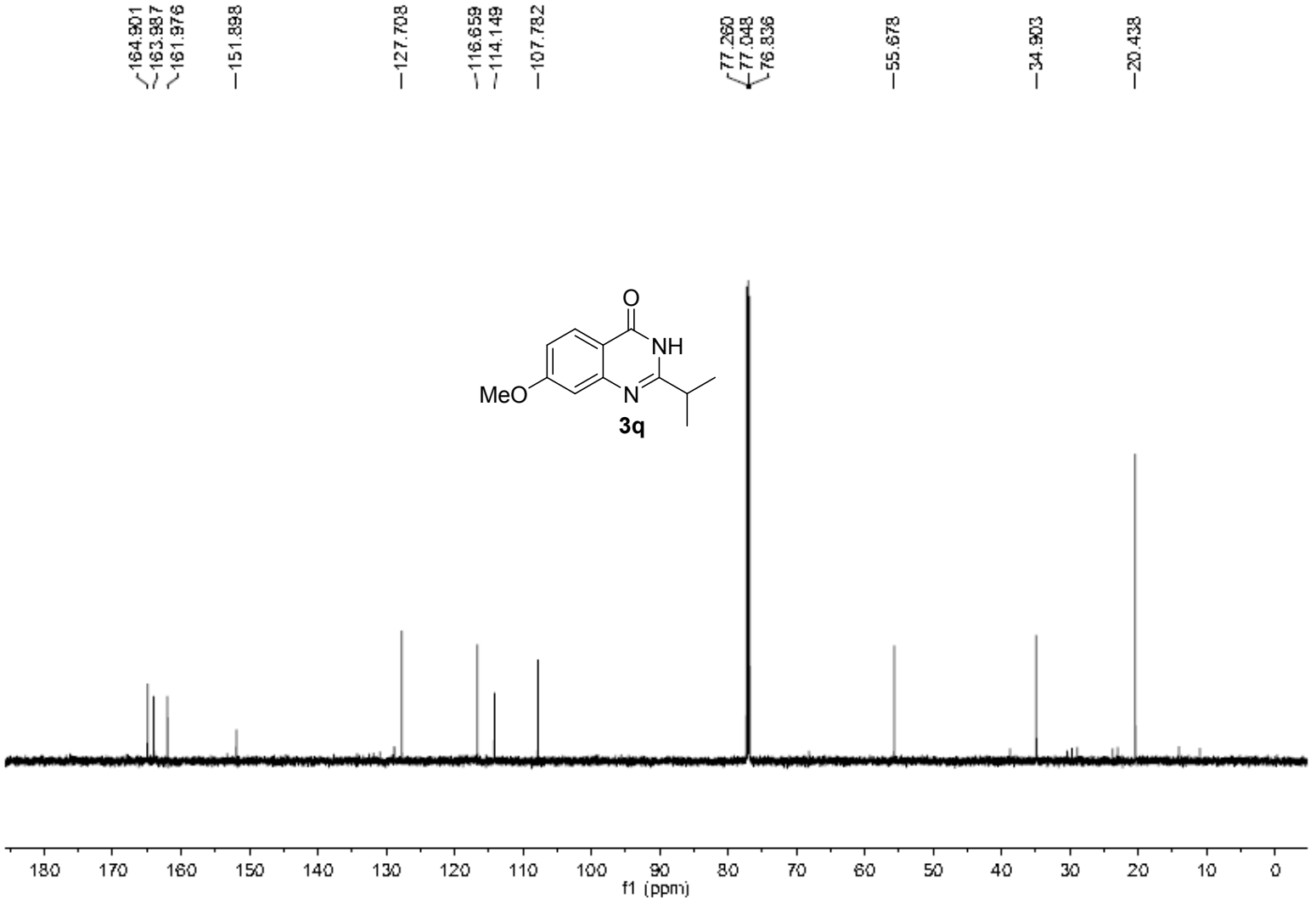
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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151.898
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116.659
114.149
107.782
77.260
77.048
76.836
55.678
34.903
20.438
O
NH
MeO
N
3q
180
170
160
150
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130
120
110
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90
80
70
60
50
40
30
20
10
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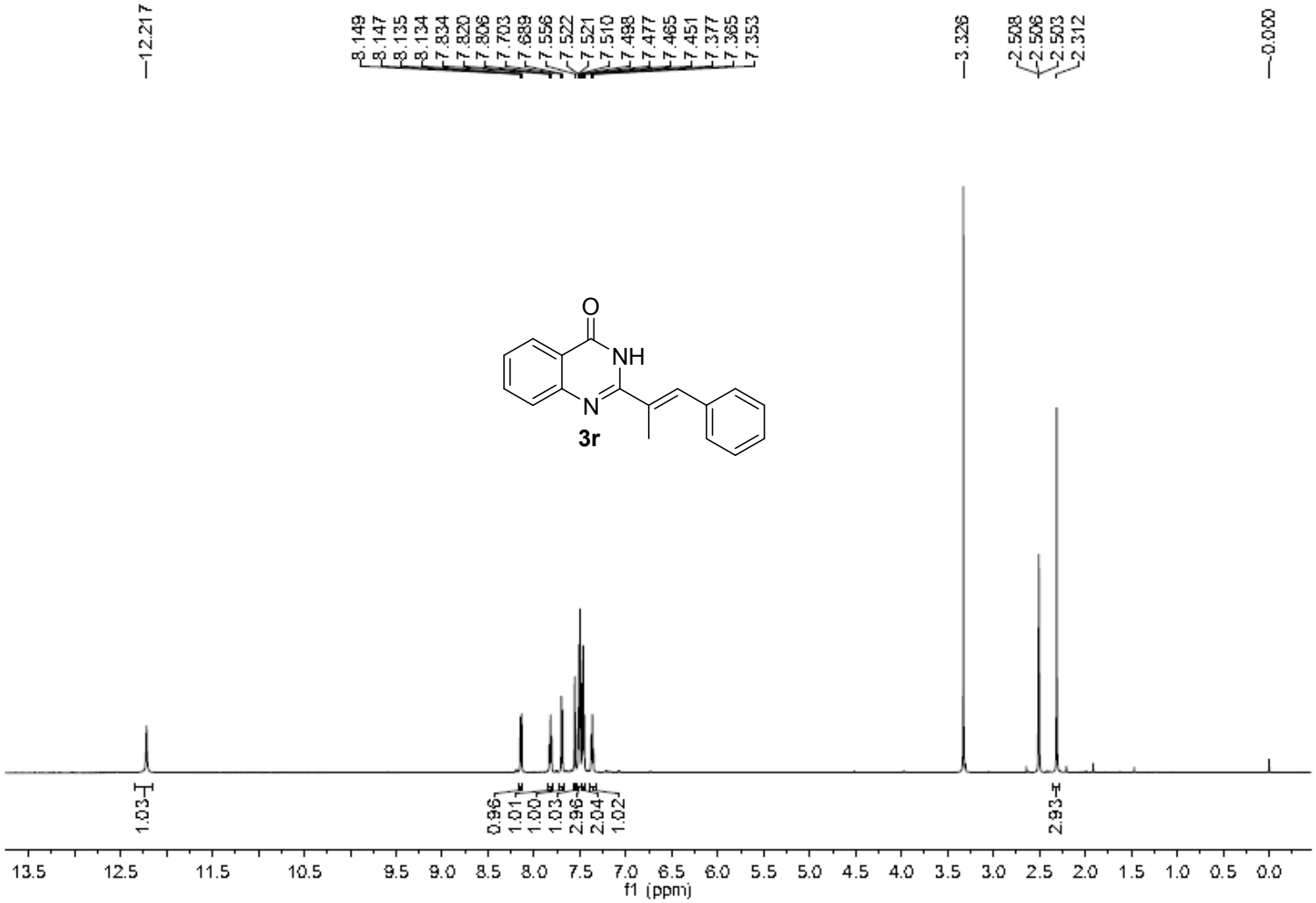
f1 (ppm)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7.556
7.522
7.521
7.510
7.498
7.477
7.465
7.451
7.377
7.365
7.353
3.326
2.508
2.506
2.503
2.312
0.000
O
NH
N
3r
1.03
0.96
1.01
1.00
1.03
2.96
2.04
1.02
2.93
13.5
12.5
11.5
10.5
9.5
9.0
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6.5
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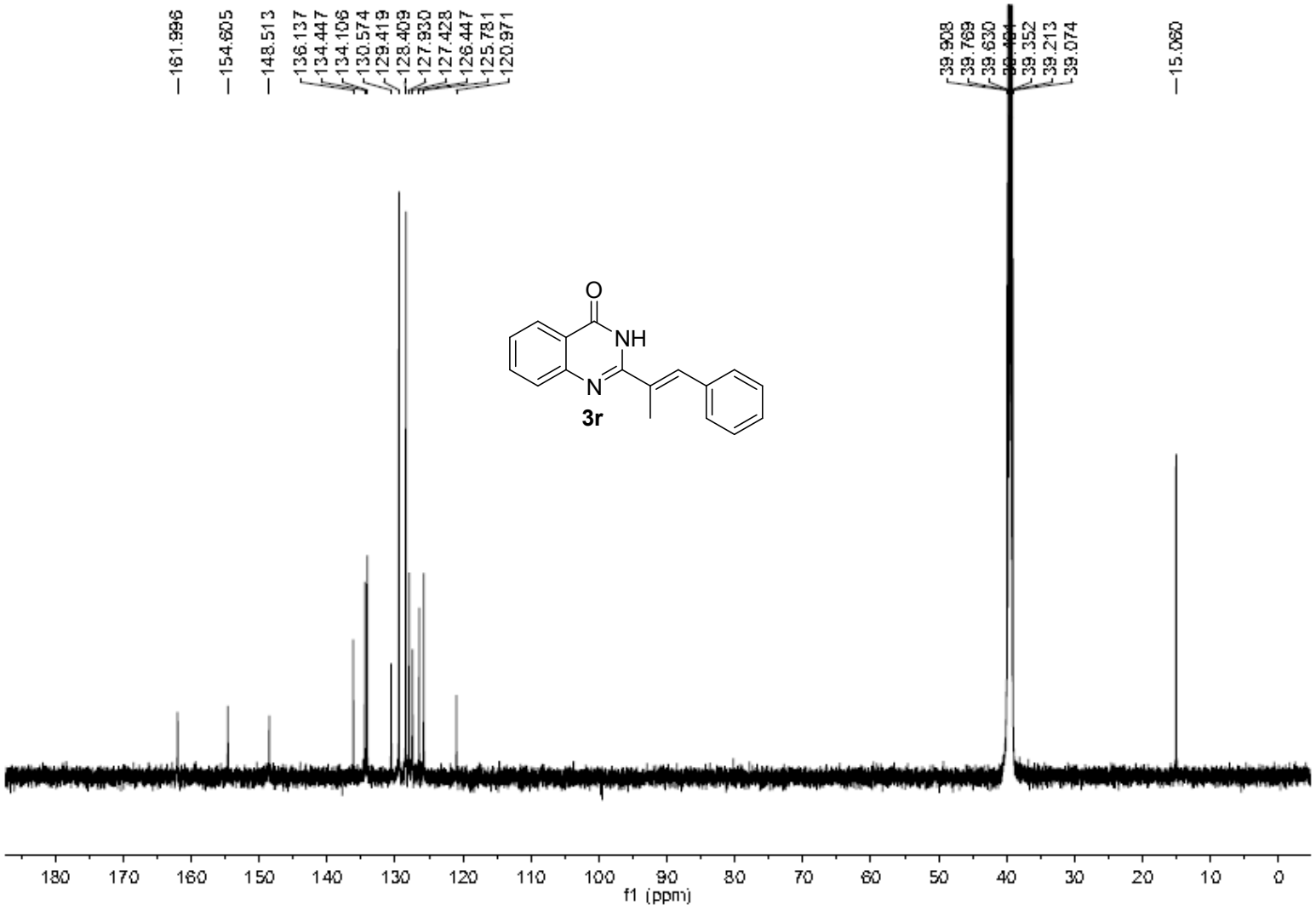
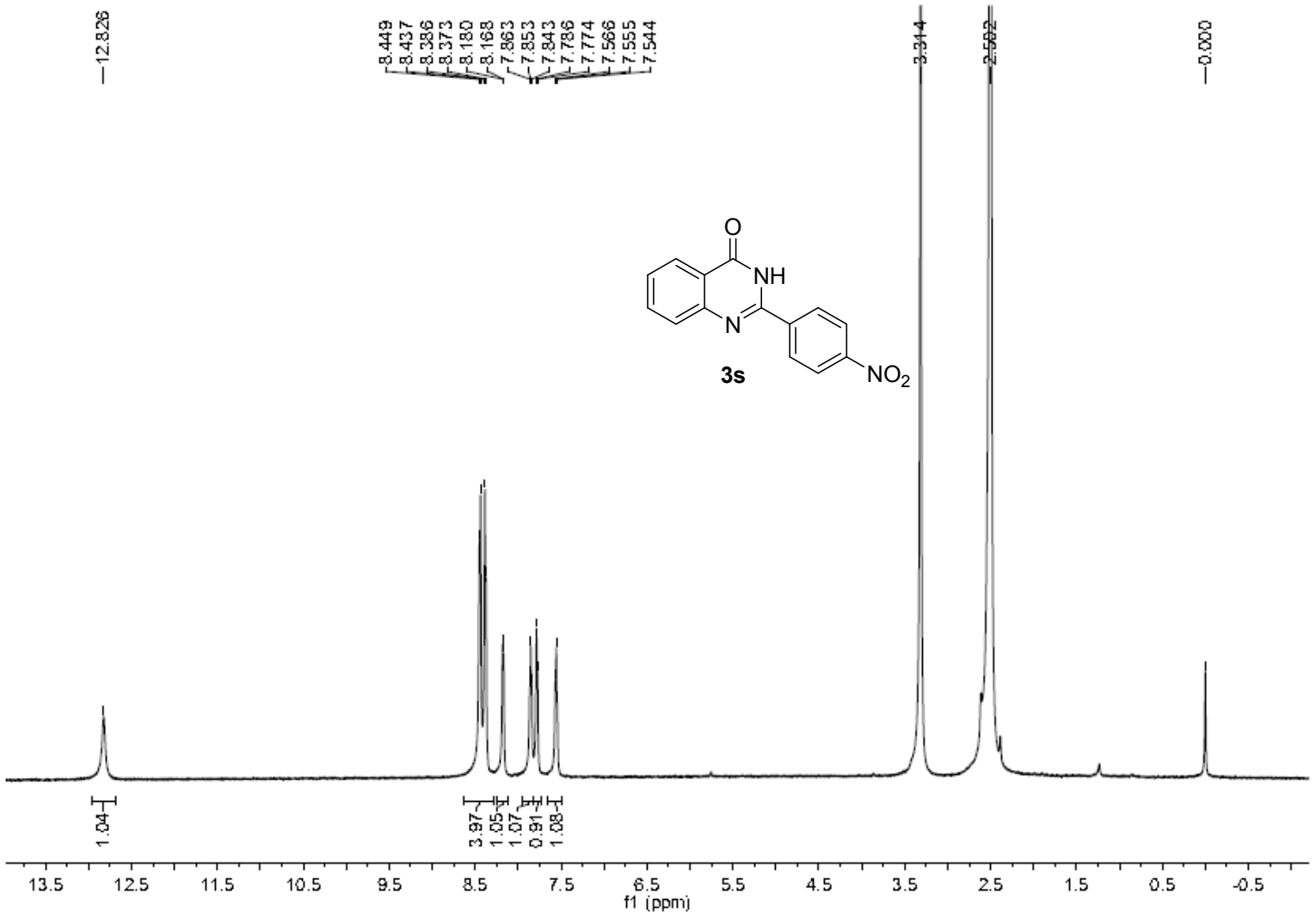
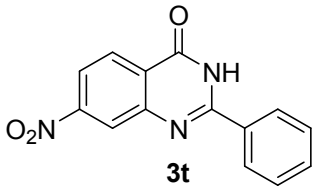
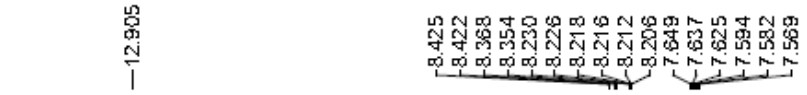
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

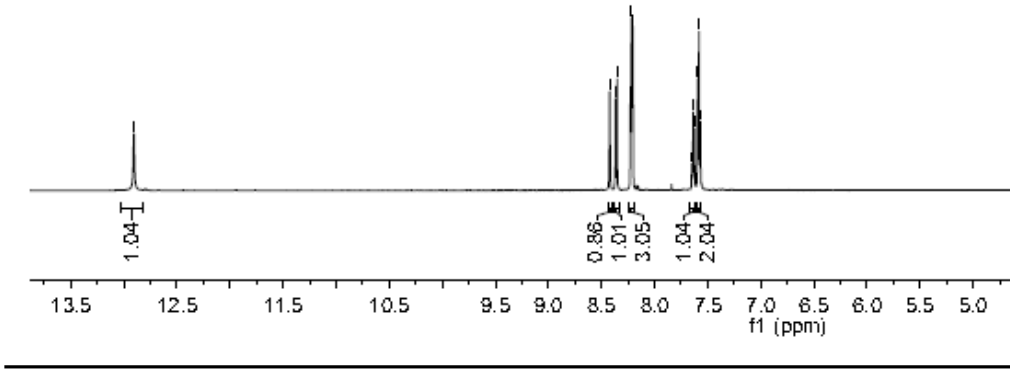

161.996
154.605
148.513
136.137
134.447
134.106
130.574
129.419
128.409
127.930
127.428
126.447
125.781
120.971
39.908
39.769
39.630
39.352
39.213
39.074
15.060
O
NH
N
3r
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

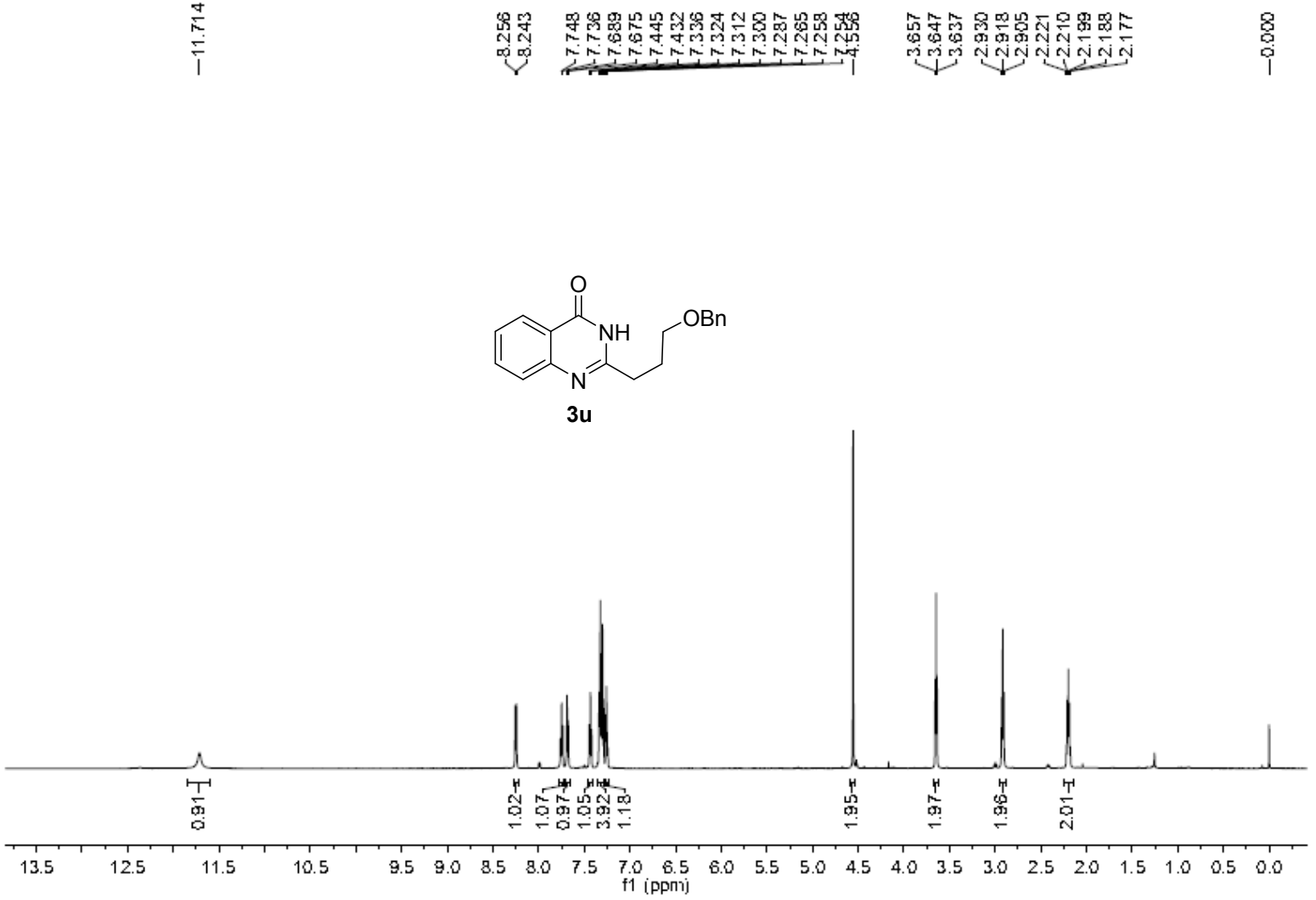

12.826
8.449
8.437
8.386
8.373
8.180
8.168
7.863
7.853
7.843
7.786
7.774
7.566
7.555
7.544
3.314
2.562
0.000
O
NH
N
NO2
3s
1.04
3.97
1.05
1.07
0.91
1.08
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

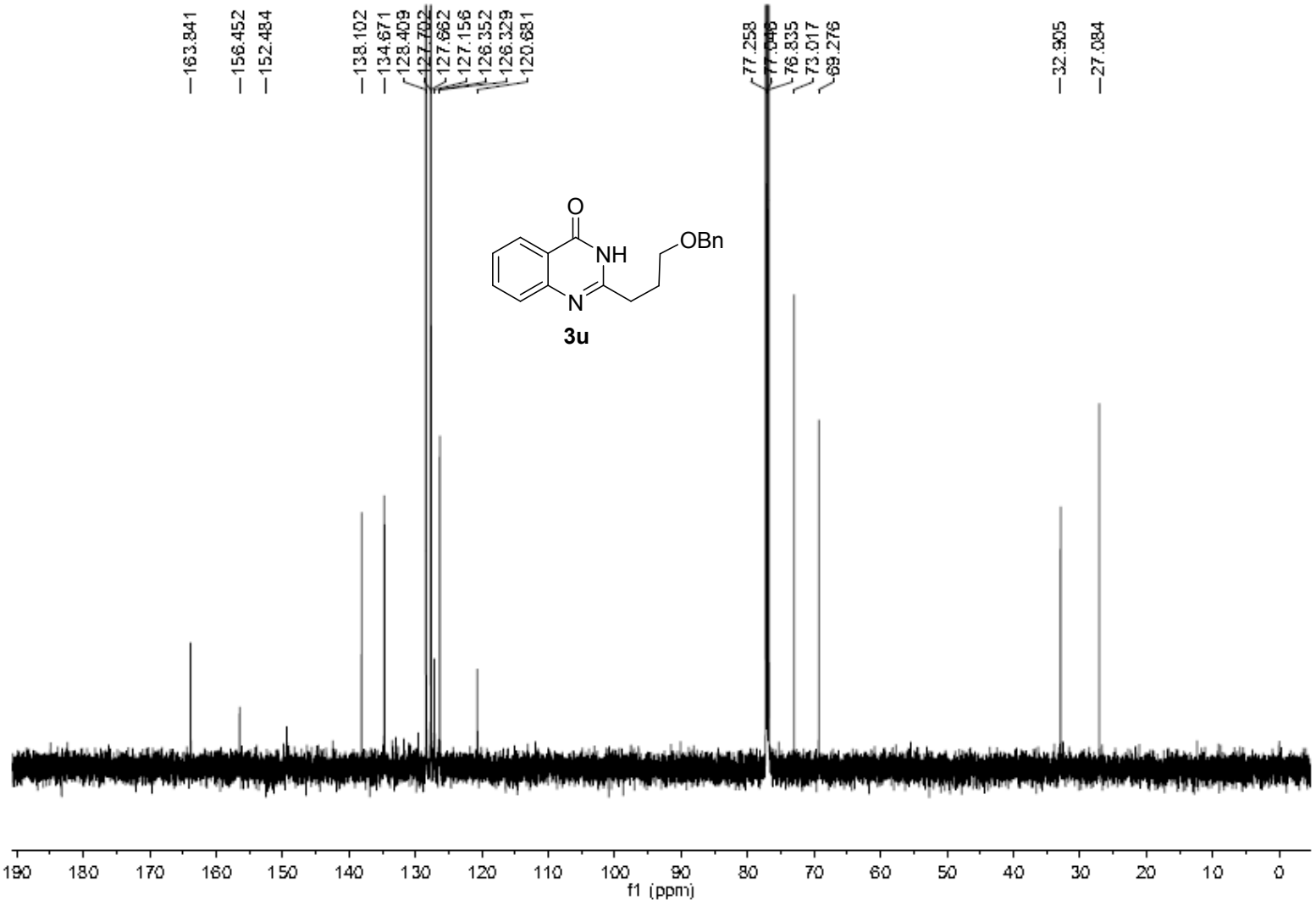

O
NH
O_2N
N

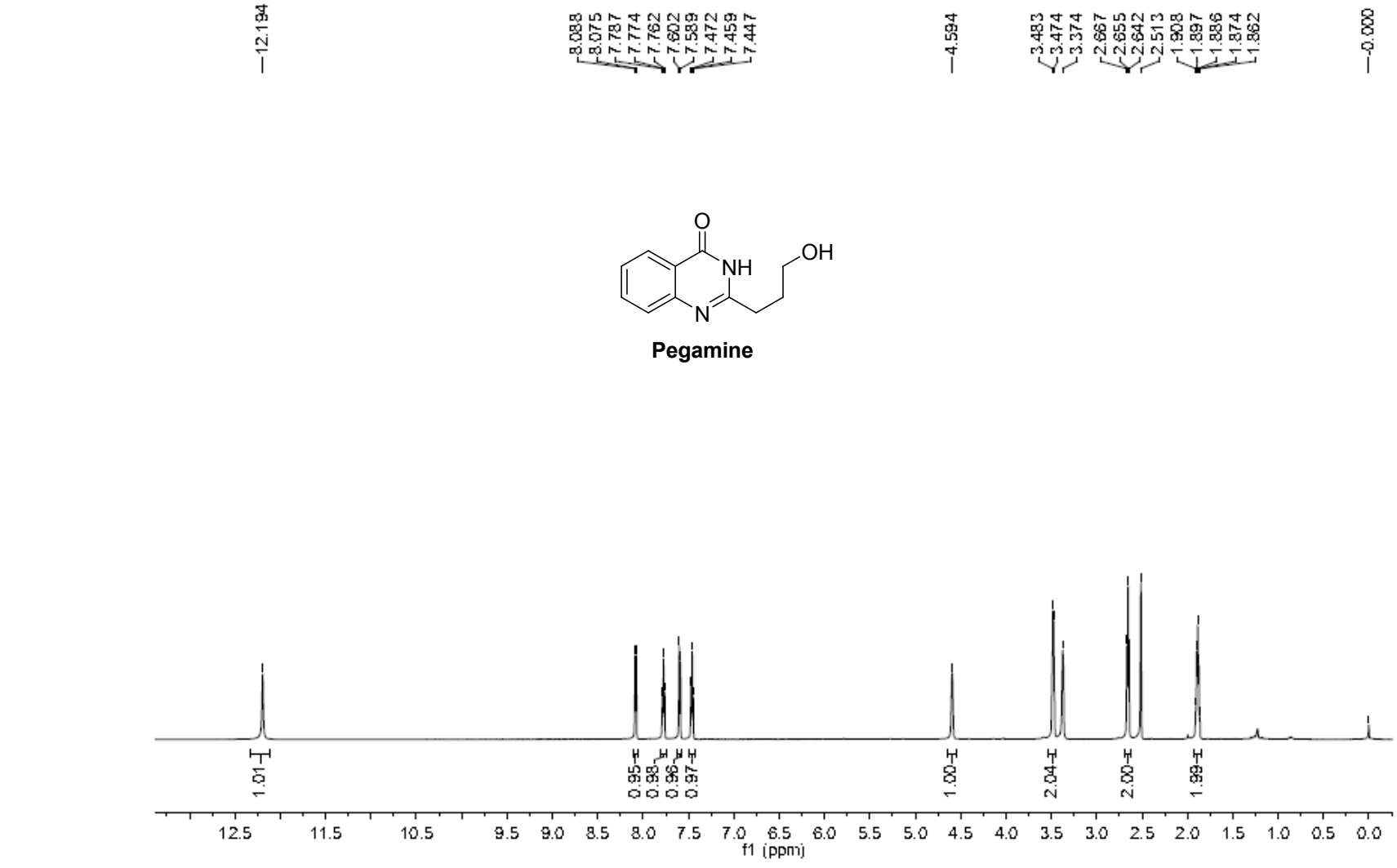
3t


12.905
8.425
8.422
8.368
8.354
8.230
8.226
8.218
8.216
8.212
8.206
7.649
7.637
7.625
7.594
7.582
7.569


1.04
0.86
1.01
3.05
1.04
2.04
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)


11.714
8.256
8.243
7.748
7.736
7.689
7.675
7.445
7.432
7.336
7.324
7.312
7.300
7.287
7.265
7.258
7.254
4.556
3.657
3.647
3.637
2.930
2.918
2.905
2.221
2.210
2.199
2.188
2.177
0.000
O
NH
N
OBn
3u
0.91
1.02
1.07
0.97
1.05
3.92
1.18
1.95
1.97
1.96
2.01
13.5 12.5 11.5 10.5 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
f1 (ppm)


163.841
156.452
152.484
138.102
134.671
128.409
127.792
127.662
127.156
126.352
126.329
120.681
77.258
76.835
73.017
69.276
32.905
27.084
O
NH
N
OBn
3u
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


12.194
8.088
8.075
7.787
7.774
7.762
7.602
7.589
7.472
7.459
7.447
4.594
3.483
3.474
3.374
2.667
2.655
2.642
2.513
1.908
1.897
1.886
1.874
1.862
0.000
O
NH
N
OH
1.01
0.95
0.98
0.96
0.97
1.00
2.04
2.00
1.99
f1 (ppm)

Pegamine