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Archivio della ricerca – postprint

Supporting Information

Efficient Biginelli synthesis of 2-aminodihydropyrimidines under microwave irradiation

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Table of contents

1. General experimental methods.

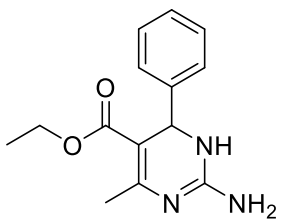
MW mediated reactions were run in a CEM Discovery instrument. NMR spectra were recorded on a Varian 500 MHz spectrometer in DMSO-d_6, unless otherwise stated, at 500 MHz (^{1}H) and 125.68 MHz (^{13}C) or on a Varian 400 at 400 MHz (^{1}H) and 100 MHz (^{13}C); chemical shifts are in ppm (δ) in the specified solvents. Coupling constants *J* are given in Hertz. ^{1}H and ^{13}C NMR resonances were assigned using a combination of DEPT, COSY, HSQC spectra. Infrared (IR) spectra were recorded as Nujol mull on NaCl plates on a Nicolet Avatar FT-IR spectrometer. Melting points are uncorrected. Electrospray (ESI) mass spectra were obtained on a Bruker Daltonics Esquire 4000 spectrometer. High Resolution Mass Spectra were obtained on a Bruker micrOTOF-Q. Yields refer to spectroscopically (^{1}H NMR) homogeneous materials. Commercial reagents and solvents were purchased from Sigma-Aldrich. β-Ketoamides 1-(piperidin1-yl)-1,3-butanedione and 1-N-propyl-1,3-butanedione were prepared by the literature.[1]

2. General procedures for the synthesis of 2-amino-3,4-diihydropyrimidines 1-26.

To a 0.5 M alcohol solution of the appropriate aldehyde (1 mmol), the 1,3-dicarbonyl compound (1.1mmol), guanidine hydrochloride (2.0 mmol), and sodium hydrogen carbonate (4 mmol) were added. The mixture was irradiated for 10 minutes in a microwave oven at 120°C unless otherwise stated. After cooling the reaction mixture, cold water was added until dissolution of $NaHCO_3$ and the mixture left in the fridge for 30min until complete precipitation of the product. The solid formed was filtered, washed with cold water and dried *under vacuo*, and purified by trituration with diisopropyl ether.

3. Characterization data of compounds 1-26.

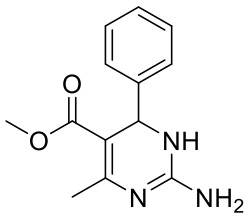
Ethyl 2-amino-6-methyl-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (1).[2]



Was prepared by reacting benzaldehyde, guanidine hydrochloride and ethylacetoacetate; 70% yield; white solid, m.p. 175-178°C; IR: 3285, 3500-250 (broad), 1713, 1665, 1612, cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.05 (t, 3H, J = 7.3 Hz, CH_3CH$_2$O), 2.17 (s, 3H, C(6)CH$_3$), 3.89 (q, 2H, J = 7.3 Hz, CH$_3$CH_2O), 5.17 (s, 1H, H-4), 6.16 (br, 2H, NH$_2$), 7.15-7.30 (m, 5H, Ph), 7.39 (s, 1H,

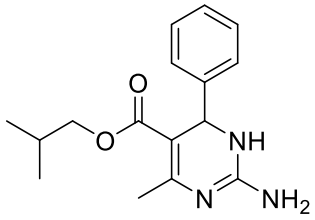
NH) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 14.78, 23.92, 53.19, 58.65, 97.86, 126.92, 127.57, 128.85, 147.38, 155.92, 161.26, 166.90 ppm; ESI-MS, *m/z*: 260.4 $[M+H]^+$.

Methyl 2-amino-6-methyl-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (2).



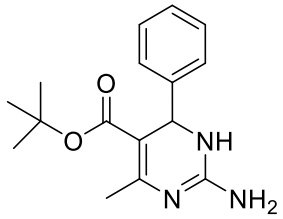
Was prepared using benzaldehyde, guanidine hydrochloride and methylacetoacetate; 75% yield; yellow solid, mp 112-118°C; IR: 3030, 3500-2500 (broad), 1697, 1626, 1557 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 3.46 (s, 3H, CH_3O), 5.19 (s, 1H, H-4), 6.21 (br, 2H, NH_2), 7.21-7.30 (m, 5H, Ph), 7.41 (s, 1H, NH) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 23.77, 49.93, 52.41, 96.73, 126.14, 126.89, 128.20, 146.50, 155.45, 161.43, 166.58 ppm; HRMS-ESI, *m/z*: 246.1237 $[M+H]^+$; calcd for: $[C_{13}H_{16}N_3O_2]^+$: 246.1237; 268.1051 $[M+Na]^+$; calcd for: $[C_{13}H_{15}N_3NaO_2]^+$: 268.1056.

Isobutyl 2-amino-6-methyl-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (3).



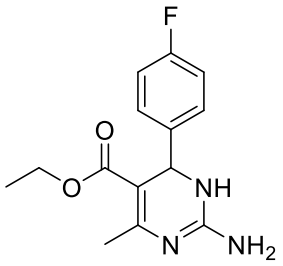
Was prepared by reacting benzaldehyde, guanidine hydrochloride and isobutylacetoacetate in isobutanol. The upper alcohol phase was separated, concentrated until formation of a solid material, that was filtered and triturated with diethyl ether; 71% yield; yellow solid, mp 115-117 °C; IR: 3316, 3500 – 2500 (broad), 1692, 1626, 1598 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.72, 0.74 (2d, J = 3.5 Hz each, 6H, $(CH_3)_2CH$), 1.71 (m, 1H, $CH(CH_3)_2$), 2.20 (*s*, 3H, C(6)CH_3), 3.64 (dd, J = 10.6, 6.3 Hz, 2H, CH_2O), 5.18 (s, 1H, H-4), 6.13 (s, 2H, NH_2), 7.16 - 7.29 (*m*, 6H, NH and Ph) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 19.46, 19.49, 24.25, 27.86, 53.09, 68.90, 97.21, 126.69, 127.36, 128.63, 146.94, 155.74, 161.87, 166.60 ppm; HRMS-ESI, *m/z*: 288.1705 $[M+H]^+$; calcd for: $[C_{16}H_{22}N_3O_2]^+$: 288.1706.

t-Butyl 2-amino-6-methyl-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (4).



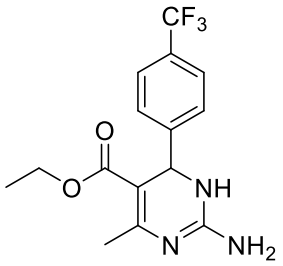
Was prepared using benzaldehyde, guanidine hydrochloride and t-butyl acetoacetate in ^{t}BuOH; 81 % yield; white solid, mp 108-110°C; IR: 3400-2800 (broad), 1705, 1538, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 9H, ^{t}BuO), 2.18 (s, 3H, C(6)-CH_3), 5.15 (s, 1H, H-4), 6.11 – 6.69 (br, 2H, NH_2), 7.21 (m, 2H, ArH), 7.29 (m, 3H, PhH), 7.17 - 7.33 (br, 1H, NH) ppm; ^{13}C NMR (125.68 MHz, $CDCl_3$): δ 22.85, 28.08, 53.03, 78.02, 99.69, 126.37, 127.11, 128.25, 146.09, 154.16, 156.60, 165.60 ppm; HRMS-ESI, *m/z*: 288.1714 $[M+H]^+$; calcd for: $[C_{16}H_{22}N_3O_2]^+$: 288.1706.

Ethyl 2-amino-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (5).



Was prepared using 4-fluorobenzaldehyde, guanidine hydrochloride and ethylacetoacetate; 45% yield; yellow solid, mp 113-115°C; IR: 3305, 3500-2500 (broad), 1710, 1664, 1608 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.07 (t, 3H, J = 7.3 Hz, CH_3CH$_2$O), 2.20 (s, 3H, C(6)CH$_3$), 3.91 (q, 2H, J = 7.3 Hz CH$_3$CH_2O), 5.20 (s, 1H, H-4), 6.29 (br, 2H, NH_2), 7.05-7.30 (*m*, 5H, Ph + NH) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 14.32, 23.47, 52.02, 58.11, 97.14, 114.74 (d, ^{2}J = 21.3 Hz), 128.13 (d, ^{3}J = 8.8 Hz), 142.96 (d, ^{4}J = 2.5 Hz), 155.07, 160.19 (d, ^{1}J = 236.0 Hz), 166.06 ppm; HRMS-ESI, *m/z*: 278.1305 $[M+H]^+$; calcd for: $[C_{14}H_{17}FN_3O_2]^+$ 278.1299.

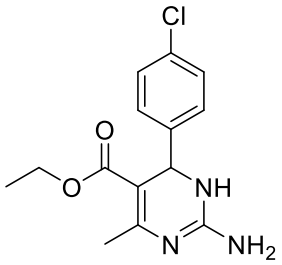
Ethyl 2-amino-4-(4-trifluorophenyl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (6).



Was prepared reacting 4-(trifluoromethyl)benzaldehyde, guanidine hydrochloride and ethylacetoacetate; 91% yield; white solid, mp 110-112°C; IR: 3300, 3500-2600 (broad), 1713, 1667, 1617 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.07 (t, 3H, J = 7.3 Hz, CH_3CH$_2$O), 2.20 (s, 3H, C(6)CH$_3$), 3.92 (q, 2H, J = 7.3 Hz CH$_3$CH_2O), 5.29 (s, 1H, H-4), 6.28 (br, 2H, NH_2), 7.43 (d,

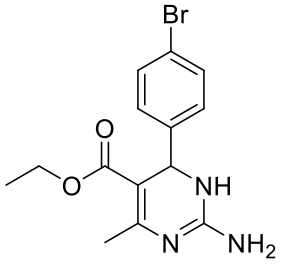
2H, ArH), 7.56-7.75 (broad, 1H, NH), 7.67 (d, 2H, ArH), ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.77, 23.80, 52.86, 58.73, 97.15, 124.8 (q, ^1J = 275.0 Hz, CF_3), 125.70 (d, ^4J = 3.0 Hz), 127.47 (d, ^3J = 8.0 Hz), 128.00 (q, ^2J = 34.0 Hz), 151.38, 155.40, 160.75, 166.36; HRMS-ESI, *m/z:* 328.1270 $[M+H]^+$; calcd. for $[C_{15}H_{17}F_3N_3O_2]^+$: 328.1267.

Ethyl 2-amino-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (7).[3]



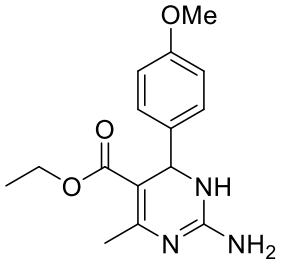
Was prepared by reacting 4-chlorobenzaldehyde, guanidine hydrochloride and ethylacetoacetate; 75% yield, yellow solid, mp 188-9°C; lit.[3] 188°C; IR: 3310, 3500-2600 (broad), 1706, 1684, 1655 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.05 (t, 3H, J = 7.3 Hz, CH_3CH$_2$O), 2.17 (s, 3H, C(6)CH$_3$), 3.90 (q, 2H, J = 7.3 Hz CH$_3$CH_2O), 5.17 (s, 1H, C(4)H), 6.20 (br, 2H, NH$_2$), 7.21 (d, 2H, ArH), 7.34-7.37 (br and d, 3H, ArH and NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.76, 23.74, 52.54, 58.65, 97.42, 128.58, 128.60, 129.24, 131.84, 145.91, 155.39, 160.76, 166.40 ppm; HRMS-ESI, *m/z:* 294.1011 $[M+H]^+$; calcd. for $[C_{14}H_{17}ClN_3O_2]^+$: 294.1004.

Ethyl 2-amino-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (8).



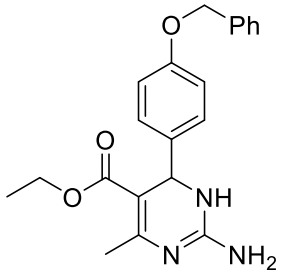
Was prepared by reacting 4-bromobenzaldehyde, guanidine hydrochloride and ethylacetoacetate; 72% yield, yellow solid, mp 130-2 °C; IR: 3310, 3500-2600 (broad), 1703, 1664, 1605 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.05 (t, 3H, J = 7.3 Hz, CH_3CH$_2$O), 2.17 (s, 3H, C(6)CH$_3$), 3.90 (q, 2H, J = 7.3 Hz CH$_3$CH_2O), 5.16 (s, 1H, H-4), 6.22 (br, 2H, NH$_2$), 7.15 (d, 2H, ArH), 7.34 (br, 1H, NH) 7.47 (d, 2H, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.55, 23.85, 52.61, 58.63, 97.26,120.45, 128.96, 131.51, 146.39, 152.85, 155.56, 166.33 ppm; HRMS-ESI, *m/z*: 338.0498 $[M+H]^+$; calcd for: $[C_{14}H_{17}BrN_3O_2]^+$ 338.0499.

Ethyl 2-amino-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (9).[4]



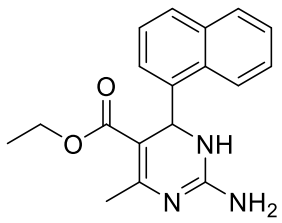
Was prepared reacting 4-methoxybenzaldehyde, guanidine hydrochloride and ethylacetoacetate; 64% yield, white solid, mp 133-135 °C; IR: 3323, 3500-2500 (broad), 1671, 1628, cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.06 (t, 3H, J = 7.3 Hz, CH_3CH$_2$O), 2.16 (s, 3H, C(6)CH$_3$), 3.69 (s, 3H, MeO), 3.89 (q, 2H, J = 7.3 Hz CH$_3$CH_2O), 5.11 (s, 1H, H-4), 6.10 (br, 2H, NH$_2$), 6.82 (d, 2H, ArH), 7.11 (d, 2H, ArH), 7.25 (br, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.78, 23.71, 52.47, 58.54, 98.00, 113.94, 127.81, 139.27, 155.35, 158.69.76, 166.55 ppm; HRMS-ESI, *m/z*: 290.1499 $[M+H]^+$; calcd. for $[C_{15}H_{20}N_3O_3]^+$: 290.1499.

Ethyl 2-amino-4-(4-benzyloxyphenyl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (10).



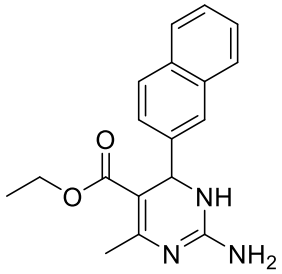
Was prepared by reacting 4-(benzyloxy)benzaldehyde, guanidine hydrochloride and ethylacetoacetate; 82% yield, mp 160-2°C; IR: 3282, 3500-2500 (broad), 1725, 1708, 1667, 1610, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (t, 3H, J = 7.5 Hz, CH_3CH$_2$O), 2.15 (s, 3H, CH$_3$C(6)), 3.86 (m, 2H, J = 7.5 Hz, CH$_3$CH_2O), 5.03 (s, 2H, PhCH_2O), 5.10 (s, 1H, H-4), 6.09 (bs, 2H, NH$_2$), 6.88 (d, 2H, ArH), 7.09 (d, 2H, ArH), 7.27-7.43 (m, 6H, Ph and NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.82, 24.18, 52.41, 58.46, 69.57, 114.84, 127.80, 128.04, 128.19, 128.85, 137.63, 139.70, 155.70, 157.74, 161.29, 166.62 ppm; HRMS-ESI, *m/z*: 366.1812 $[M+H]^+$, calcd for $[C_{21}H_{24}N_3O_3]^+$ 366.1812.

Ethyl 2-amino-6-methyl-4-(naphthalen-1-yl)-3,4-dihydropyrimidine-5-carboxylate (11).



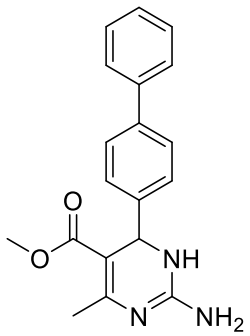
Was prepared by reacting 1-naphtaldehyde, guanidine HCl and ethylacetoacetate; 80% yield, pale yellow solid, mp 222-23 °C; IR: 3380, 3187, 1652, 1585 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.82 (t, 3H, J = 7.4 Hz, CH_3CH$_2$O), 2.32 (s, 3H, C(6)CH$_3$), 3.77 (m, 2H, J = 7.4 Hz, CH$_3$CH_2O), 5.99 (bs, 1H, NH$_2$), 6.08 (s, 1H, H-4), 7.24 (bs, 1H, NH), 7.35 (bd, 1H, J = 6.2 Hz, NH), 7.45 (t, 1H, J = 7.9 Hz, ArH), 7.52 (t, 1H, J = 7.1 Hz, ArH), 7.59 (t, 1H, J = 7.5 Hz, ArH), 7.81 (d, 1H, J = 7.9 Hz, ArH), 7.93 (d, 1H, J = 7.1 Hz, ArH), 8.35 (d, 1H, J = 7.5 Hz, ArH) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 14.14, 23.41, 48.50, 58.09, 96.41, 123.49, 124.40, 125.54, 125.79, 126.18, 127.53, 128.58, 133.62, 141.32, 154.73, 160.87, 166.19 ppm; HRMS-ESI, *m/z*: 310.1560 $[M+H]^+$; calcd for: $[C_{18}H_{20}N_3O_2]^+$ 310.1550.

Ethyl 2-amino-6-methyl-4-(naphthalen-2-yl)-3,4-dihydropyrimidine-5-carboxylate (12).



Was prepared by reacting 2-naphtaldehyde, guanidine HCl and ethylacetoacetate; 68% yield; light brown solid, mp 165–167 °C; IR: 3350, 3500-2700 (broad), 1703, 1661, 1602 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.06 (t, 3H, J = 7.4 Hz, CH_3CH$_2$O), 2.24 (s, 3H, C(6)CH$_3$), 3.92 (q, 2H, J = 7.4 Hz, CH$_3$CH_2O), 5.38 (s, 1H, H-4), 6.24 (s, 2H, NH$_2$), 7.43-7.51 (m, 4H, ArH), 7.64 (s, 1H, ArH), 7.85 (m, 3H, ArH and NH) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 14.77, 23.64, 53.43, 58.68, 97.76, 124.73, 125.62, 126.11, 126.58, 127.88, 128.21, 128.57, 132.72, 133.13, 144.13, 155.35, 160.26, 166.51 ppm; HRMS-ESI, *m/z:* 310.1558 $[M+H]^+$; calcd for: $[C_{18}H_{20}N_3O_2]^+$ 310.1550.

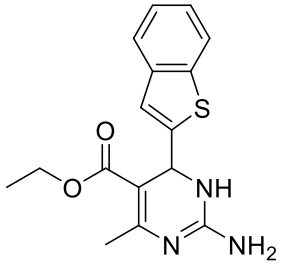
Methyl 2-amino-4-([1,1'-biphenyl]-4-yl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (13).



Was prepared by reacting biphenyl-4-carboxaldehyde, guanidine HCl and methylacetoacetate; 51% yield, orange solid, mp 152-157 °C; IR: 3289, 3500-2500 (broad), 1698, 1651, 1598 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, C(6)CH$_3$), 3.50 (s, 3H, CH$_3$O), 5.27 (s, 1H, H-4), 7.29-7.63 (br + 3m, 12H, 9 ArH + 3 NH) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 22.88, 50.76,

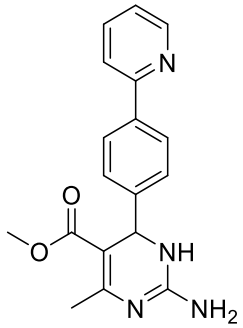
52.59, 79.61, 98.27, 127.07, 127.22, 127.27, 127.78, 129.33, 129.38, 139.61, 145.20, 154.96, 166.77 ppm; HRMS-ESI, *m/z*: 322.1560 $[M+H]^+$; calcd for $[C_{19}H_{20}N_3O_2]^+$ 322.1550.

Ethyl 2-amino-4-(benzo[b]thiophen-2-yl)-6-methyl-3,4-dihydropyrimidine-5-carboxylate (14).



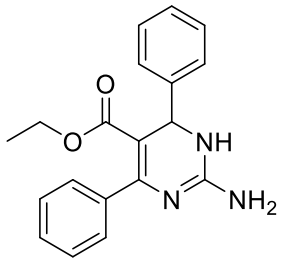
Was prepared by reacting benzo[b]thiophene-2-carboxaldehyde, guanidine HCl and ethylacetoacetate; 50% yield, light brown solid, mp 132-5 °C; IR: 3340, 3200-2600 (broad), 1710, 1610, 1559, cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.15 (t, 2H, J = 7.2 Hz, CH_3CH_2O), 2.16 (s, 3H, C(6)CH_3), 4.00 (q, 3H, J = 7.2 Hz, CH_3CH_2O), 5.55 (s, 1H, H-4), 6.45 (bs, 2H, NH_2), 7.10 (s, 1H, CH=C), 7.25, 7.29 (dt, 1H, ArH), 7.72 (bs, 1H, NH), 7.73 (d, J = 7.8 Hz, 1H, ArH), 7.83 (d, J = 7.8 Hz,1H, ArH) ppm; ^{13}C NMR (125.68 MHz, DMSO-d_6): δ 14.47, 23.64, 48.86, 58.32, 96.96, 118.92, 122.46, 123.22, 123.86, 124.21, 138.76, 139.11, 151.38, 155.54, 160.82, 165.74 ppm; HRMS-ESI, *m/z*: 316.1116 $[M+H]^+$; calcd. for $[C_{16}H_{18}N_3O_2S]^+$ 316.1114.

Methyl 2-amino-4-[4-(2-pyridinyl)phenyl]-6-methyl-3,4-dihydropyrimidine-5-carboxylate (15).



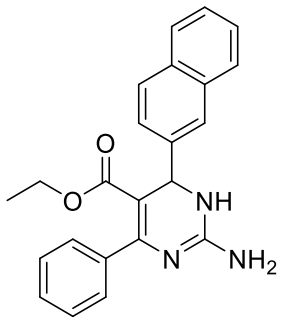
Was prepared by reacting 4-(2-pyridinyl)benzaldehyde, guanidine HCl and methylacetoacetate; 74% yield, light-orange solid, mp 137-142 °C; IR: 3288, 3500-2550 (broad) 1710, 1668, 1595 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): δ 2.22 (s, 3H, C(6)CH_3), 3.48 (s, 3H, CH_3O), 5.25 (s, 1H, C(4)H), 6.23 (bs, 2H, NH_2), 7.31 (m, 1H, H-5'), 7.33 (d, 2H, J = 8.5 Hz, ArH), 7.46 (bs, 1H, NH), 7.85 (dt, J = 2.0 and 7.9 Hz, 1H, H-3'), 7.89 (t, J = 7.9 Hz, 1H, H-4'), 7.99 (d, 2H, J = 8.5 Hz, ArH), 8.64 (d, J = 3.9 Hz, 1H, H-6') ppm; ^{13}CNMR (125.68 MHz, DMSO-d_6): δ 23.25, 50.12, 52.36, 97.04, 120.19, 122.47, 126.60, 126.63, 137.20, 137.60, 147.00, 155.02, 155.93, 166.53 ppm; HRMS-ESI, *m/z*: 323.1512 $[M+H]^+$; calcd for $[C_{18}H_{19}N_4O_2]^+$ 323.1503.

Ethyl 2-amino-4,6-diphenyl-3,4-dihydropyrimidine-5-carboxylate (16).[5]



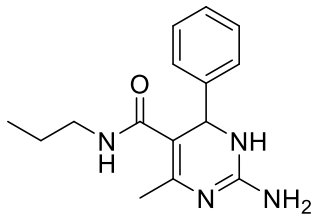
Was prepared by reacting benzoylacetoacetate, guanidine hydrochloride and benzaldehyde; 71% yield; mp 225-7°C, light brown solid, mp 225-7°C; IR: 3393, 3500-2500 (broad), 1652, 1570 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.74 (t, 3H, J = 7.5 Hz, CH_3CH$_2$O), 3.67 (m, 2H, J = 7.5 Hz, CH$_3$CH_2O), 5.30 (s, 1H, H-4), 6.31 (bs, 2H, NH$_2$), 7.30 (m, 11H, 2 x Ph and NH) ppm; ^{13}C-NMR (125.68 MHz, DMSO-d_6): δ 14.09, 53.32, 58.54, 98.00, 126.73, 127.28, 127.48, 127.52, 128.53, 128.75, 142.86, 146.63, 155.70, 161.23, 166.63. ppm; ESI-MS, *m/z*: 322.3 $[M+H]^+$.

Ethyl 2-amino-4-(naphthalen-2-yl)-6-phenyl-3,4-dihydropyrimidine-5-carboxylate (17).



Was prepared using benzoylacetoacetate, guanidine hydrochloride and 2-naphthylaldehyde; 79% yield; 69%, light brown solid, mp 230°C (dec); IR: 3393, 3500-2500 (broad), 1651, 1621, 1568 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.71 (t, 3H, J = 7.5 Hz, CH_3CH$_2$O), 3.75 (m, 2H, J = 7.5 Hz, CH$_3$CH_2O), 5.46 (s, 1H, H-4), 6.31 (bs, 2H, NH$_2$), 7.25 (s, 5H, Ph), 7.47 (m, 2H, ArH), 7.58 (m, 1H, ArH), 7.76 (s, 1H, ArH), 7.86 (m, 3H, ArH), 7.40 – 7.64 (broad, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.10, 53.62, 58.56, 97.74, 124.73, 125.62, 126.17, 126.61,127.30, 127.52, 127.90, 128.27, 128.57, 128.69, 132.79, 133.18, 143.12, 144.06, 155.75, 161.75, 166.67 ppm; HRMS-ESI, *m/z*: 372.1708; $[M+H]^+$; calcd for $[C_{23}H_{22}N_3O_2]^+$ 372.1707.

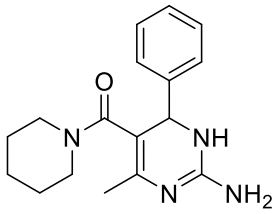
2-Amino-6-methyl-4-phenyl-5-(aminopropyl-1-carbonyl)-3,4-dihydropyrimidine (18).



Was prepared using benzaldehyde, guanidine hydrochloride and 1-N-propyl-1,3-butanedione;[1] for 8 min at 100°C: 73% yield; white solid, m.p. 160°C (dec.); IR 3283, 3500-2500, 1713, 1673, 1616

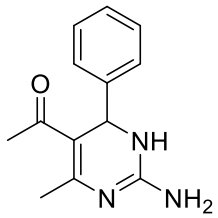
cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.71 (t, 3H, CH_3CH$_2$CH$_2$), 1.25 (m, 2H, CH$_3$CH_2CH$_2$), 1.96 (s, 3H, C(6)CH$_3$), 2.84-3.04 (m, 2H, CH$_3$CH$_2$CH_2), 5.23 (s, 1H, H-4), 7.08 (br, 2H, NH$_2$), 7.13-7.38 (m, 7H, Ph + NH) ppm ; ^1H NMR (400 MHz, MeOD-d_6): 0.75 (t, 3H, CH_3CH$_2$CH$_2$), 1.37 (m, 2H, CH$_3$CH_2CH$_2$), 2.02 (s, 3H, C(6)CH$_3$), 3.05 (m, 2H, CH$_3$CH$_2$CH_2), 5.31 (s, 1H, H-4), 7.19-7.31 (2m, 5H, Ph) ppm; ^{13}C NMR (100 MHz, MeOD): δ 10.13, 18.88, 21.95, 40.78, 55.16, 106.00, 126.37, 127.24, 128.20, 143.57, 144.63, 153.66, 158.52, 170.12; HRMS-ESI, *m/z*: 273.1715 $[M+H]^+$; calcd for: $[C_{15}H_{21}N_4O]^+$ 273.1710.

2-Amino-6-methyl-4-phenyl-5-(piperidin-1-carbonyl)-3,4-dihydropyrimidine (19).



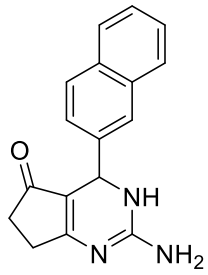
Was prepared using benzaldehyde, guanidine hydrochloride and 1-(piperidin1-yl)-1,3-butanedione;[1] 62% yield after trituration with hot ethyl acetate; white solid, m.p. 257 °C (dec.); IR 3500-2500 (broad), 1662, 1593 cm^{-1}; ^1H NMR (400 MHz, MeOD): δ 1.04–1.58 (broad, 6H, piperidine CH$_2$), 1.72 (s, 3H, C(6)CH$_3$), 2.76 - 3.30 (broad, 4H, CH_2N piperidine), 5.11 (s, 1H, H-4), 7.23-7.36 (m, 5H) ppm; ^{13}C NMR (125.68 MHz, MeOD): δ 18.15, 23.78, 25.25, 42.19, 56.69, 104.38, 126.16, 127.44, 128.40, 137.51, 144.77,153.89, 169.98 ppm; HRMS-ESI, *m/z*: 299.1868 $[M+H]^+$; calcd for: $[C_{17}H_{23}N\,O]^+$ 299.1866.

5-Acetyl-2-amino-6-methyl-4-phenyl-3,4-dihydropyrimidine (20).[3]



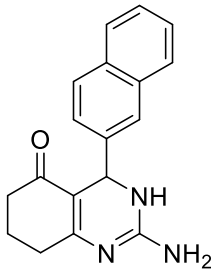
Was prepared by reacting benzaldehyde, guanidine hydrochloride and acetylacetone; 85% yield; mp 210-2°C; IR 3284, 3500-2500, 1669, 1558 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.04 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 5.27 (s, 1H, H-4), 6.25 (br, 2H, NH$_2$), 7.13-7.38 (m, 6H, Ph + NH) ppm ; ^{13}C NMR (DMSO-d_6): δ 25.18, 30.54, 53.00, 109.42, 126.82, 127.39, 128.71, 146.26, 155.48, 160.63, 192.62; MS-ESI, *m/z*: 230.1 $[M+H]^+$.

2-Amino-4-(naphtalen-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one (21).



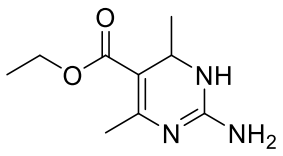
Was prepared by reacting 2-naphthylaldehyde, guanidine hydrochloride and 1,3-cyclopentanedione at 140°C for 40 min; 76% yield; white solid, mp > 240°C; IR 3284, 3500-2500, 1652, 1611, 1584 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.34 (m, 4H, 2 x CH_2), 5.17 (s, 1H, H-4), 6.91 (br, 2H, NH_2), 7.24 (dd, 1H, naphtyl), 7.31-7.45 (m, 3H, naphthyl + NH), 7.49 (s, 1H, naphtyl), 7.65-7.79 (m, 3H, naphtyl) ppm ; ^{13}C NMR (DMSO-d_6): δ 29.72 (CH), 30.33 (CH_2), 117.25, 124.35, 125.11, 125.88, 126.94, 127.36, 127.45, 127.62, 131.55, 133.01, 138.39, 141.44, 158.11, 198.00; HRMS-ESI, *m/z*: 292.1293 $[M+H]^+$; calcd for: $[C_{18}H_{18}N_3O]^+$ 278.1293.

2-Amino-4-(naphtalen-2-yl)-4,6,7,8-tetrahydro-5(*3H*)-quinazolinone (22).



Was prepared by reacting 2-naphthylaldehyde, guanidine hydrochloride and 1,3-cyclohexanedione at 140°C for 20 min; 85% yield; yellow solid, mp > 240°C; IR 3270, 3500-2500, 1684, 1654 (broad) cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6): δ 1.76,1.80 (2m, 1H each, ring CH_2), 2.12 (m, 2H, CH_2C=), 2.35 (m, 2H, CH_2CO), 5.43 (s, 1H, H-4), 6.49 (br, 2H, NH_2), 7.36 (brs, 1H, NH), 7.41 - 7.48 (m, 3H, naphtyl), 7.63 (s, 1H, naphtyl), 7.81-7.85 (m, 3H, naphtyl) ppm ; ^{13}C-NMR (DMSO-d_6): δ 21.11, 29.95, 36.65, 50.57, 108.52, 124.61, 125.26, 125.97, 126.36, 127.62, 128.00, 128.39, 132.48, 132.87, 142,86, 155.30, 163.04, 192.90; HRMS-ESI, *m/z*: 292.1444 $[M+H]^+$; calcd for: $[C_{18}H_{18}N_3O]^+$ 292.1444.

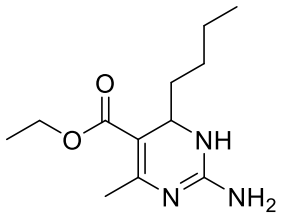
Ethyl 2-amino-4,6-dimethyl-3,4-dihydropyrimidine-5-carboxylate (23).[5]



Was prepared by reacting ethanal, guanidine hydrochloride and ethylacetoacetate; 36% yield, white solid, mp 195-197°C; IR: 3392, 3200-2600 (broad), 1683, 1587, cm^{-1}; ^1H-NMR (500 MHz,

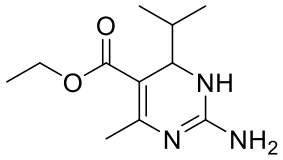
DMSO-d_6): δ 0.97 (d, 3H, J = 6.0 Hz, CH(4)CH_3), 1.16 (t, 3H, J = 7.0 Hz CH_3CH$_2$O), 2.10 (s, 3H, C(6)CH_3), 3.99 (m, 2H, CH_3CH_2O) 4.18 (q, 1H, J = 6.0 Hz, H-4), 6.05 (b*s*, 2H, NH_2), 6.81 (s, 1H, NH) ppm; ^{13}C-NMR (125.68 MHz, DMSO-d_6): δ 14.97, 23.81, 23.87, 45.43, 58.39, 98.71, 155.81, 160.63, 166.45 ppm; HRMS-ESI, *m/z*: 198.1240 $[M+H]^+$; calcd for $[C_9H_{16}N_3O_2]^+$: 198.1237.

Ethyl 2-amino-4-butyl-6-methyl-3,4-dihydropyrimidine-5-carboxylate (24).



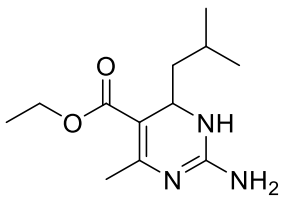
Was prepared by reacting pentanal, guanidine hydrochloride and ethylacetoacetate; 48% yield; light yellow solid, mp 113-115°C; IR: 3300, 1710, 1670, 1616, 1458, 1376, 1257, 1094 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (t, 3H, J = 7.2 Hz, CH_3(CH$_2$)$_3$), 1.16 (t, 3H, J = 7.2 Hz, CH_3CH$_2$O), 1.17 - 1.35 (m, 6H, CH_3(CH_2)$_3$), 2.10 (s, 3H, C(6)CH_3), 3.90-4.05 (m, 2H, CH_3CH_2O), 4.09 (d, 1H, J = 6.5 Hz, H-4), 6.01 (bs, 2H, NH_2), 6.90 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.99, 14.49, 21.96, 23.40, 25.78, 36.46, 48.82, 57.92, 97.29, 155.56, 165.06, 166.09 ppm. HRMS-ESI, *m/z*: 240.1707 $[M+H]^+$; calcd for $[C_{12}H_{22}N_3O_2]^+$ 240.1707.

Ethyl 2-amino-4-isopropyl-6-methyl-3,4-dihydropyrimidine-5-carboxylate (25). [5]



Was prepared using 2-methylpropanal, guanidine HCl and ethylacetoacetate; 51% yield, white solid, mp 171-2°C; IR: 3405, 3200-2500 (broad), 1715, 1608 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.70, 0.78 (2d, J = 6.1 Hz, 6H, CH(CH_3)$_2$), 1.14 (t, J = 7.0 Hz, 3H, CH_3CH$_2$O), 1.59 (m, 1H, CH(CH$_3$)$_2$), 2.11 (s, 3H, CH_3C(6)), 3.96 (m, 1H, H-4) 4.00 (m, 2H, CH_3CH$_2$O), 6.40 (br, 2H, NH_2) ^{13}C-NMR (125 MHz, DMSO-d_6): δ 14.90, 16.34, 18.58, 23.78, 35.05, 54.83, 58.43, 96.40, 156.53, 161.00, 166.91. HRMS-ESI, *m/z*: 226.1546 $[M+H]^+$; calcd. for $[C_{11}H_{20}N_3O_2]^+$ 226.1550.

Ethyl 2-amino-4-isobutyl-6-methyl-3,4-dihydropyrimidine-5-carboxylate (26).



Was prepared by reacting 3-methylbutanal, guanidine hydrochloride and ethylacetoacetate: 43% yield, white solid, mp 110-112 °C; IR: 3386, 3150-2500, 1713, 1612 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85, 0.86 (2d, J = 6.9 Hz, 6H, CH(CH_3)$_2$), 0.99 (m, 1H, CH_2 isobutyl), 1.16 (t, J =

7.0 Hz, 3H, C*H*$_3$CH$_2$O), 1.31 (m, 1H, CH$_2$ isobutyl) 1.67 (m, 1H, C*H*(CH$_3$)$_2$), 2.10 (s, 3H, CH$_3$C(6)), 3.98 (m, 2H, C*H*$_3$CH$_2$O), 4.13 (dd, J = 3.5 Hz and 9.5 Hz, 1H, H-4), 6.25 – 6.75 (br, 2H, NH$_2$) ppm; ^{13}CNMR (125 MHz, DMSO-d_6): δ 14.84, 21.72, 22.88, 23.36, 24.28, 46.25, 47.35, 58.22, 99.01, 155.80, 159.89, 166.07. HRMS-ESI, *m/z*: 240.1716 $[M + H]^+$; HRMS-ESI: Calcd. for $[C_{12}H_{22}N_3O_2]^+$ 240.1707.

References

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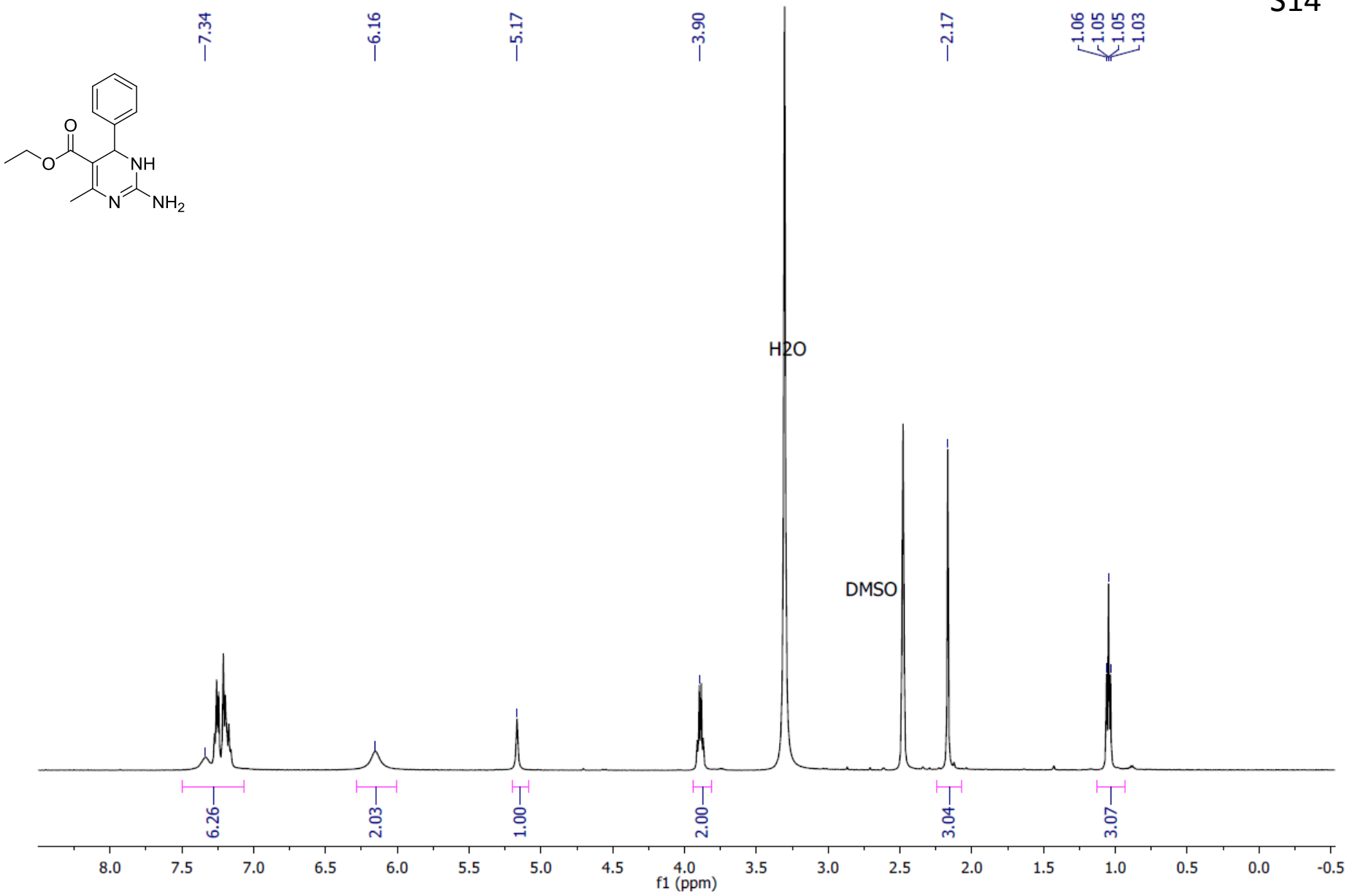
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1.06
1.05
1.05
1.03
H2O
DMSO
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2.03
1.00
2.00
3.04
3.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
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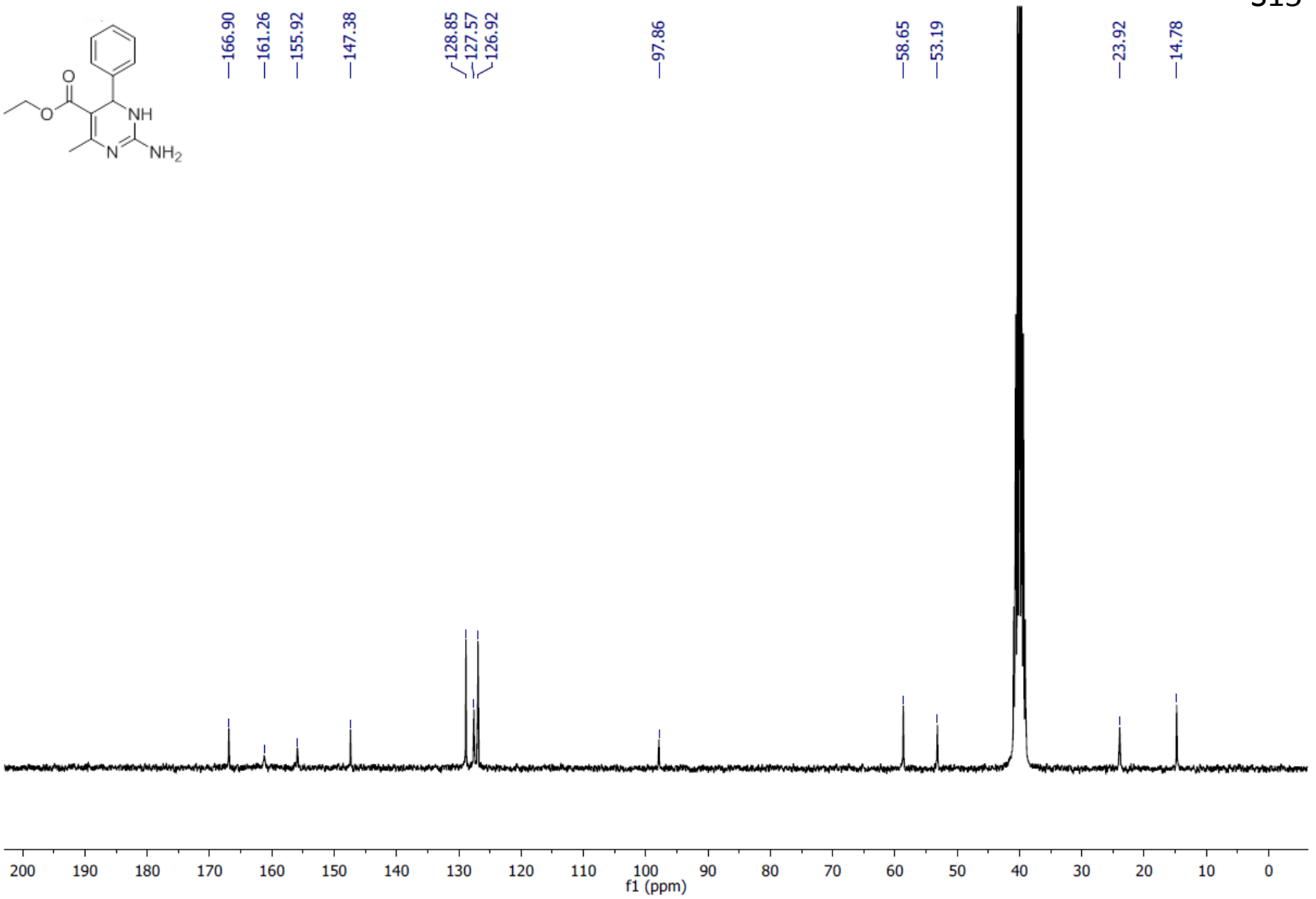
O
NH
N
NH2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N
NH2
200
190
180
170
160
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130
120
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100
90
80
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50
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10
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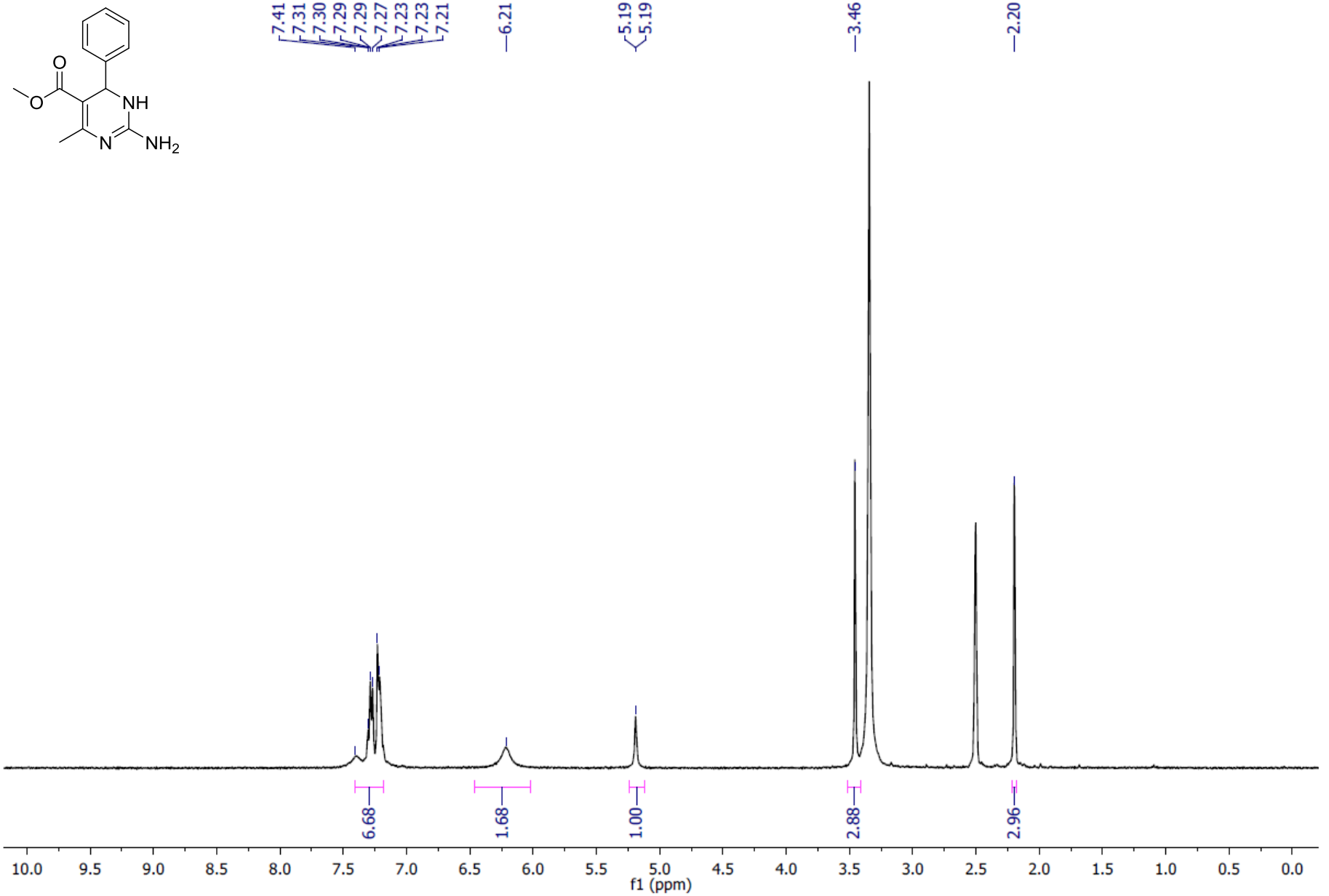
f1 (ppm)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O
O
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N
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8.5
8.0
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1.0
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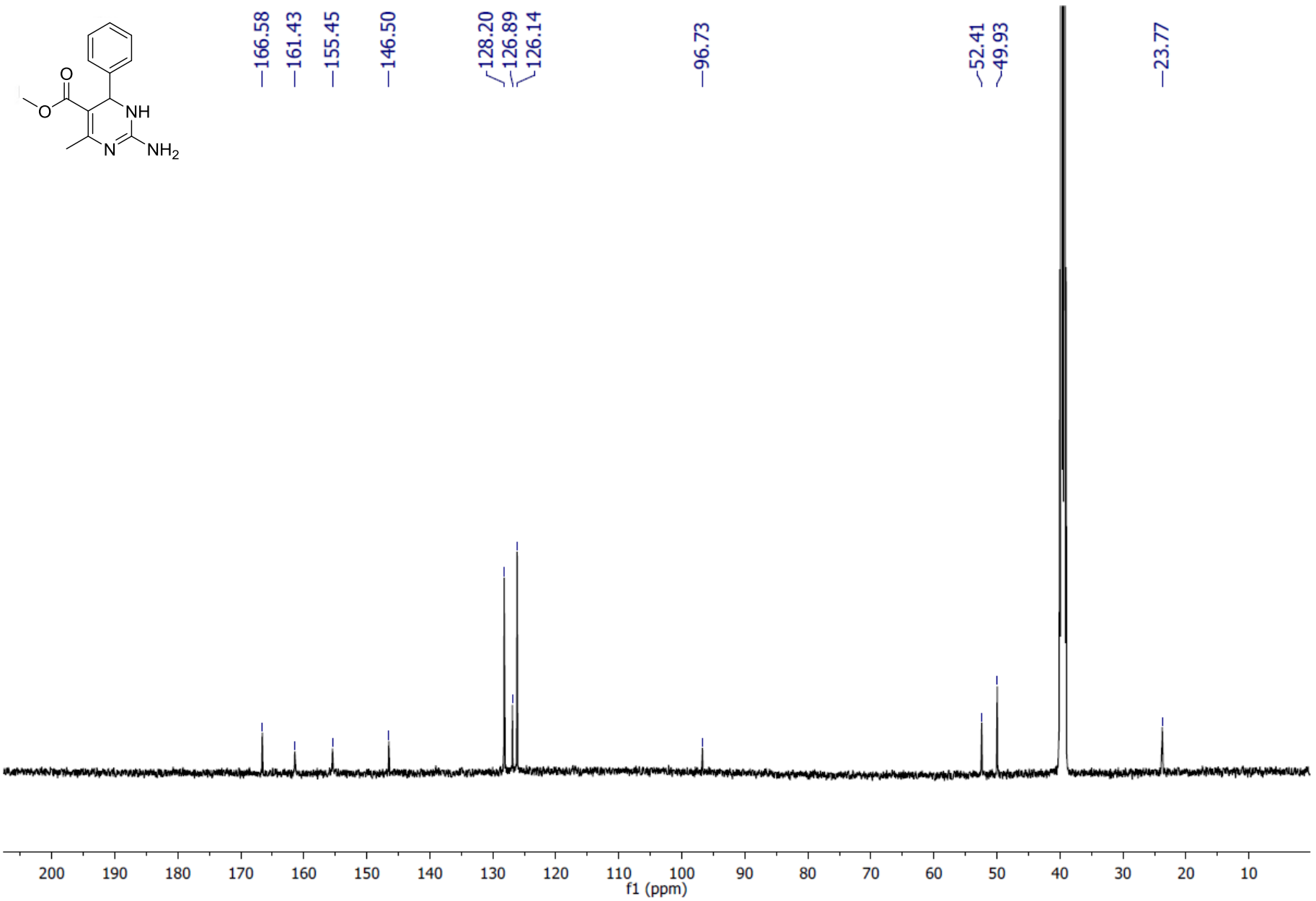
f1 (ppm)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23.77
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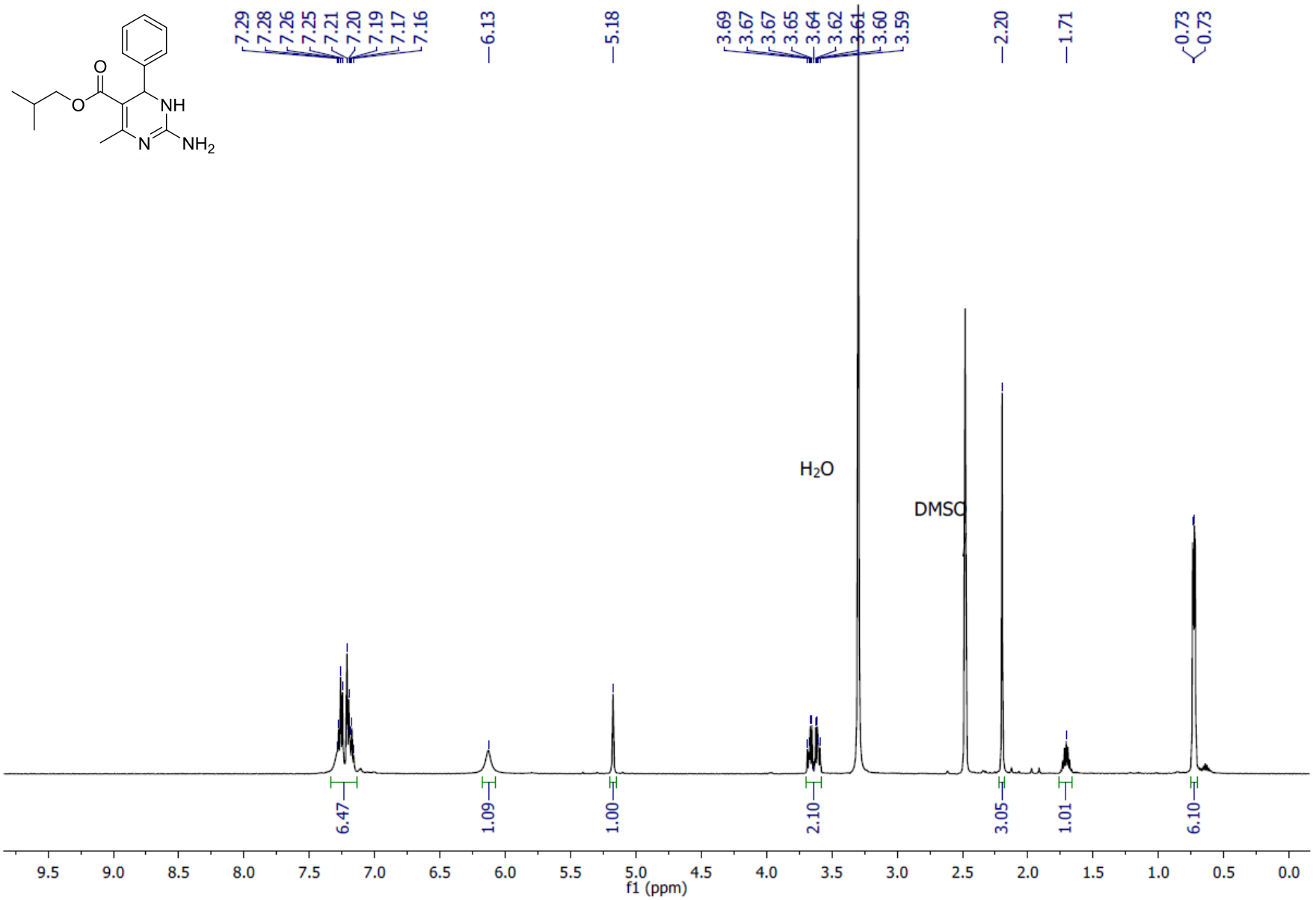
O
NH
N
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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3.67
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3.62
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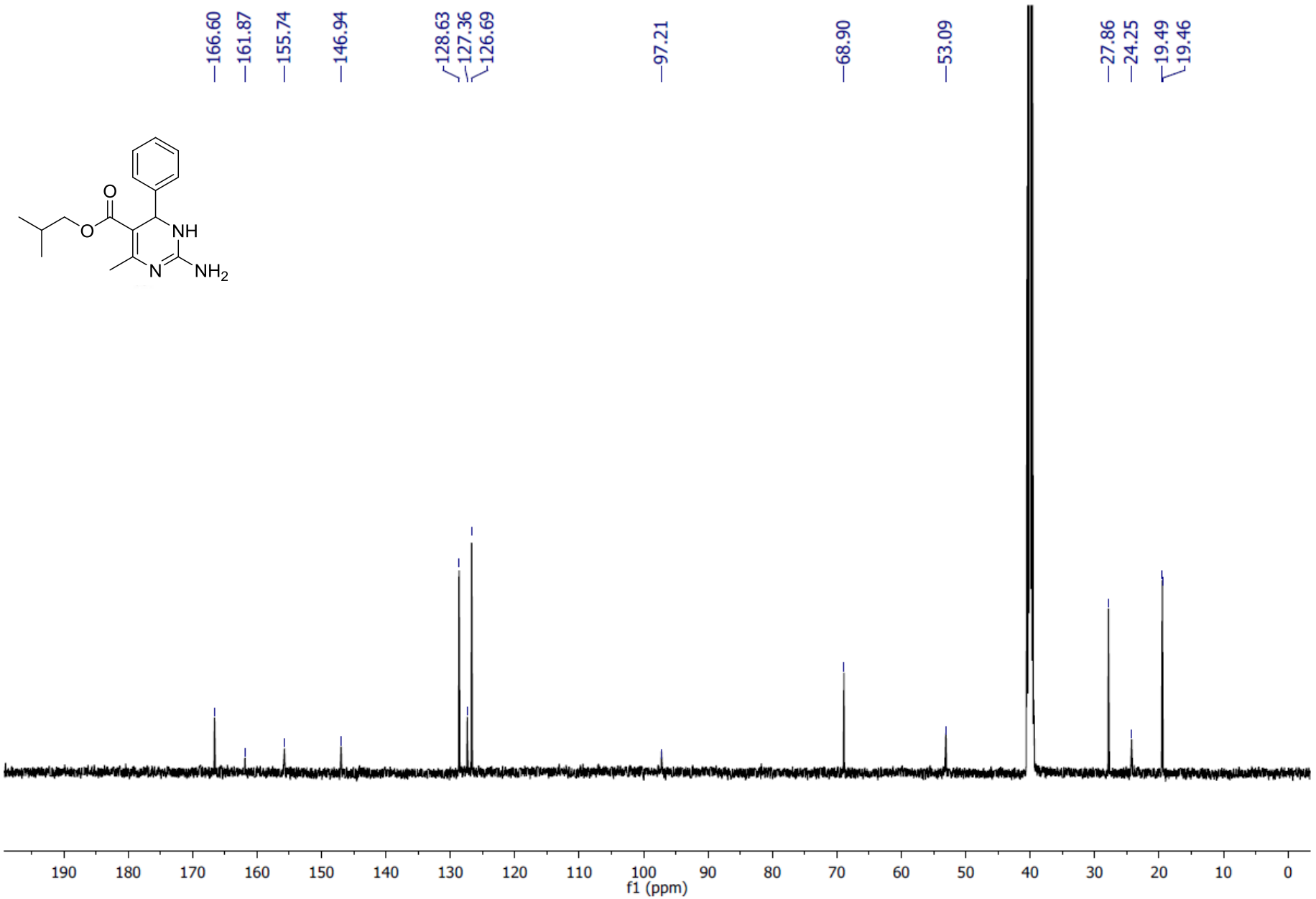
f1 (ppm)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NH2
190
180
170
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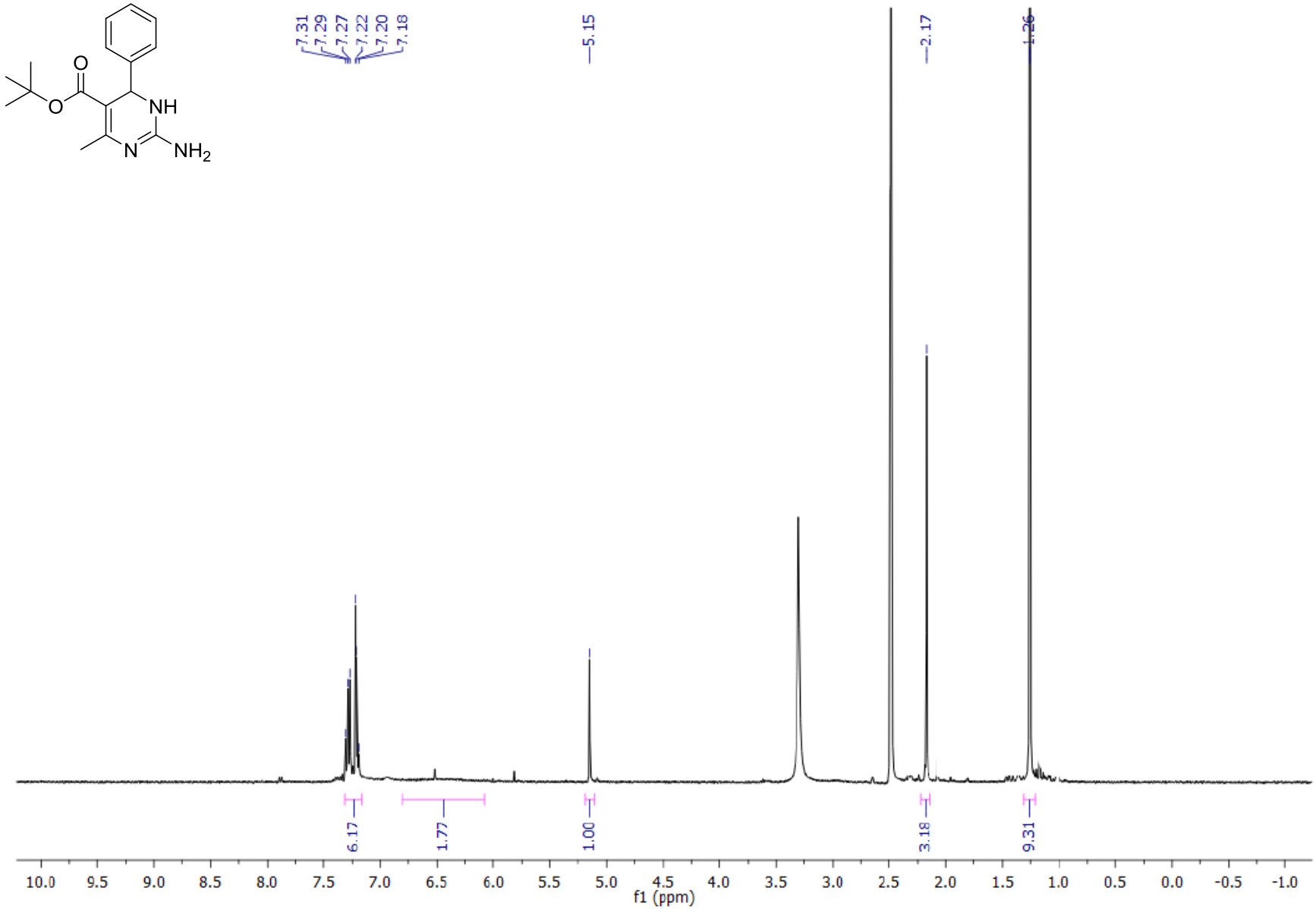
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
NH
N
NH2
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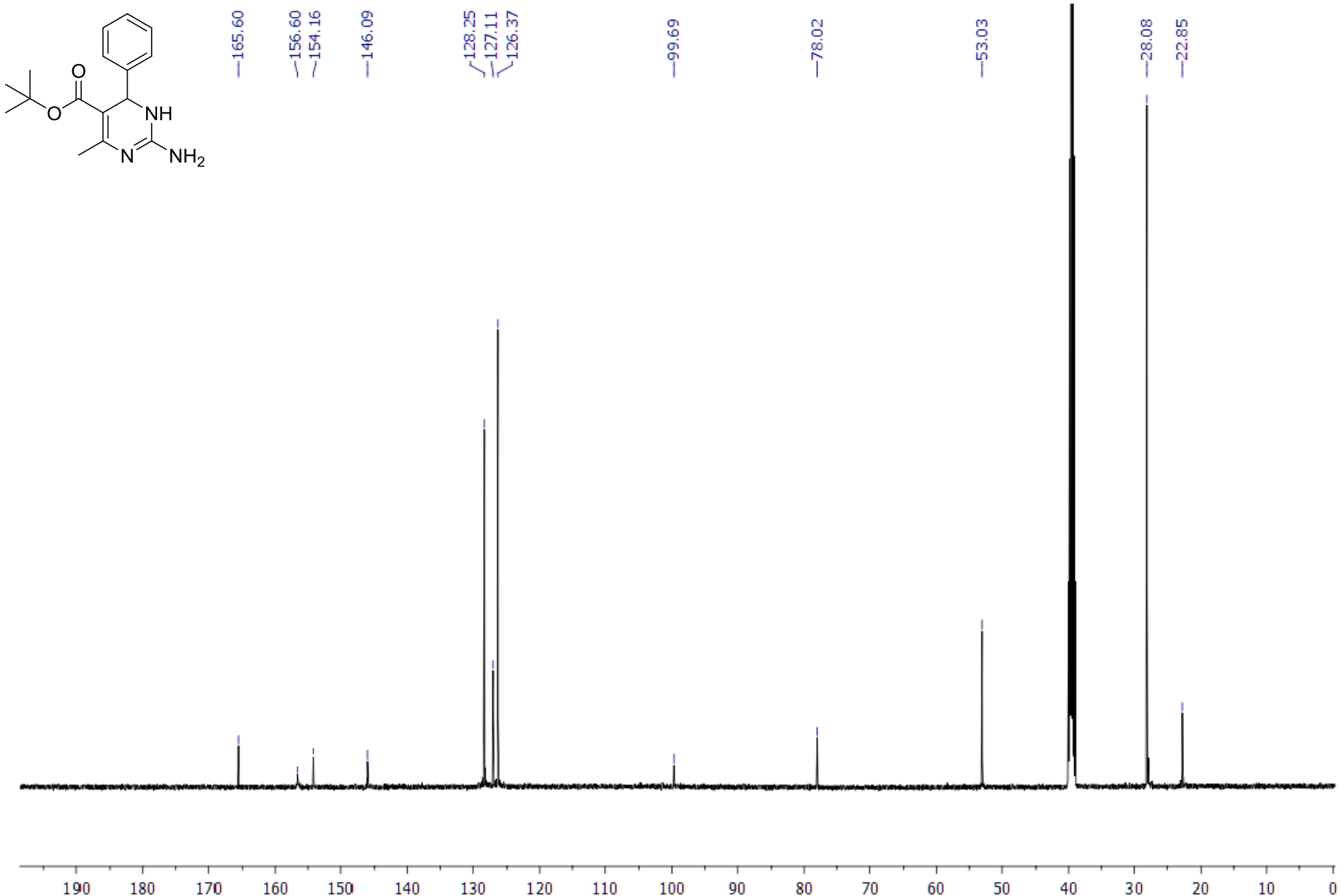
7.27
7.22
7.20
7.18
5.15
2.17
1.26
6.17
1.77
1.00
3.18
9.31
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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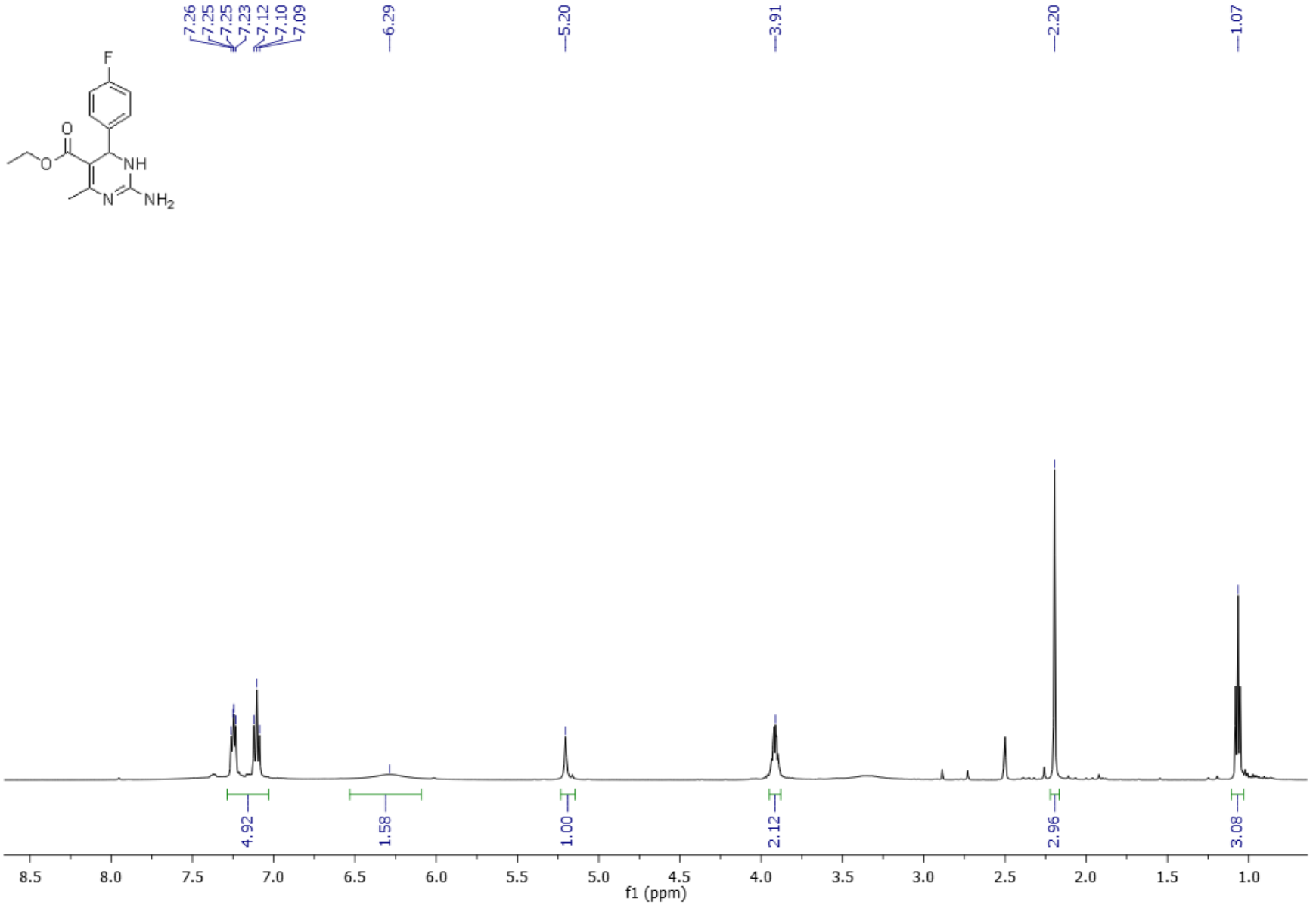
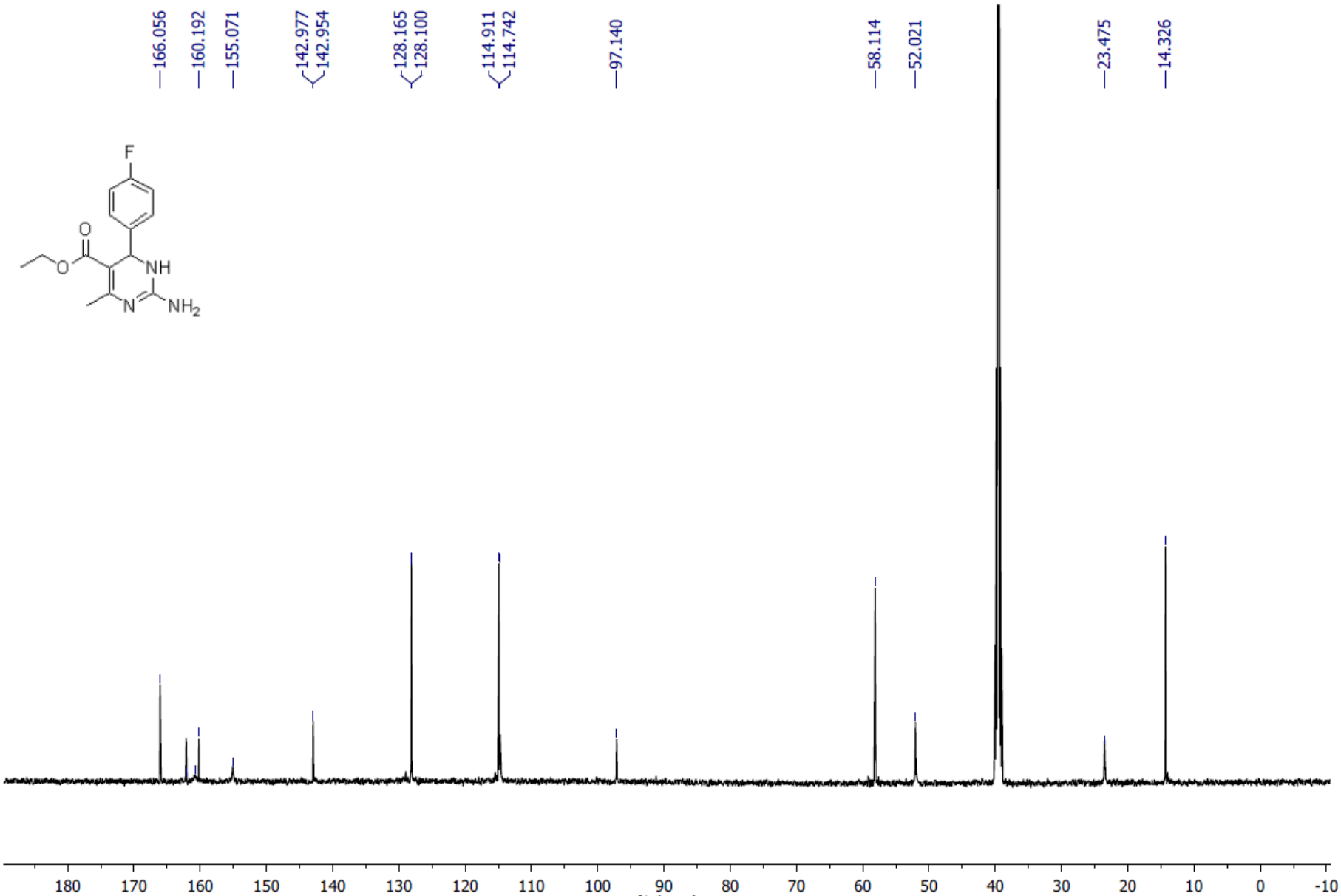
O
NH
N
NH2
165.60
156.60
154.16
146.09
128.25
127.11
126.37
99.69
78.02
53.03
28.08
22.85
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.26
7.25
7.25
7.23
7.12
7.10
7.09
6.29
5.20
3.91
2.20
1.07
F
O
O
NH
N
NH2
4.92
1.58
1.00
2.12
2.96
3.08
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
f1 (ppm)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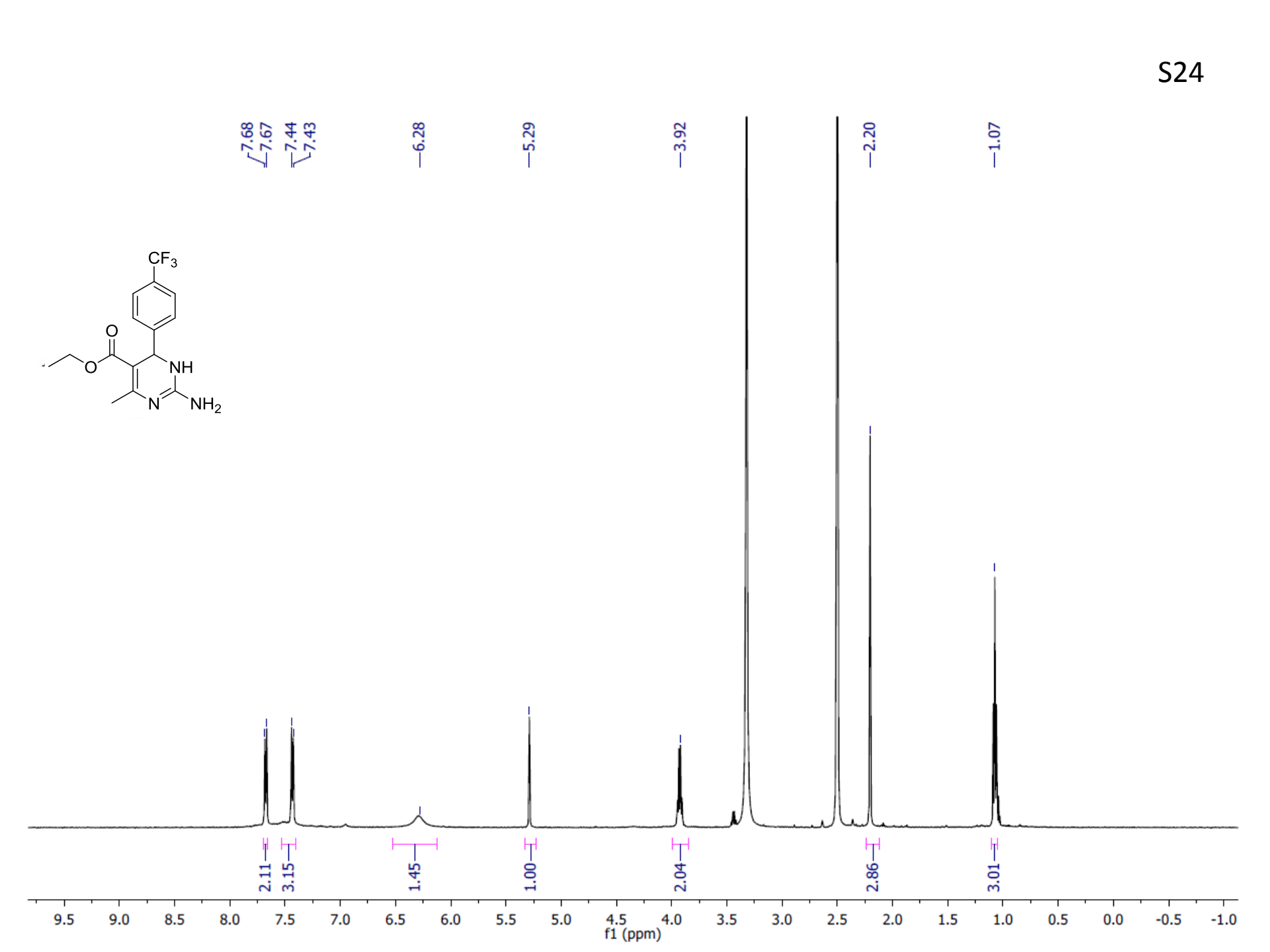
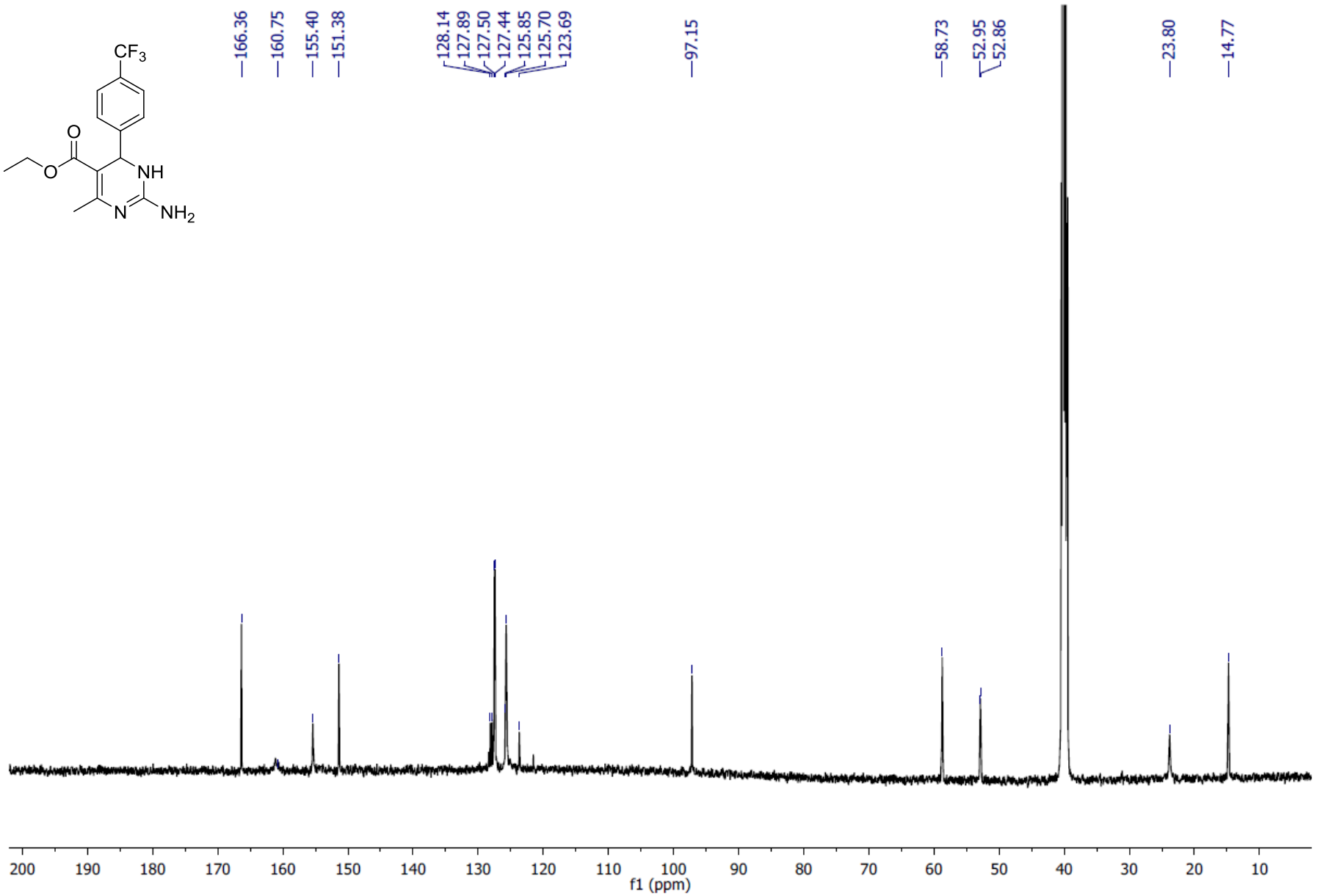
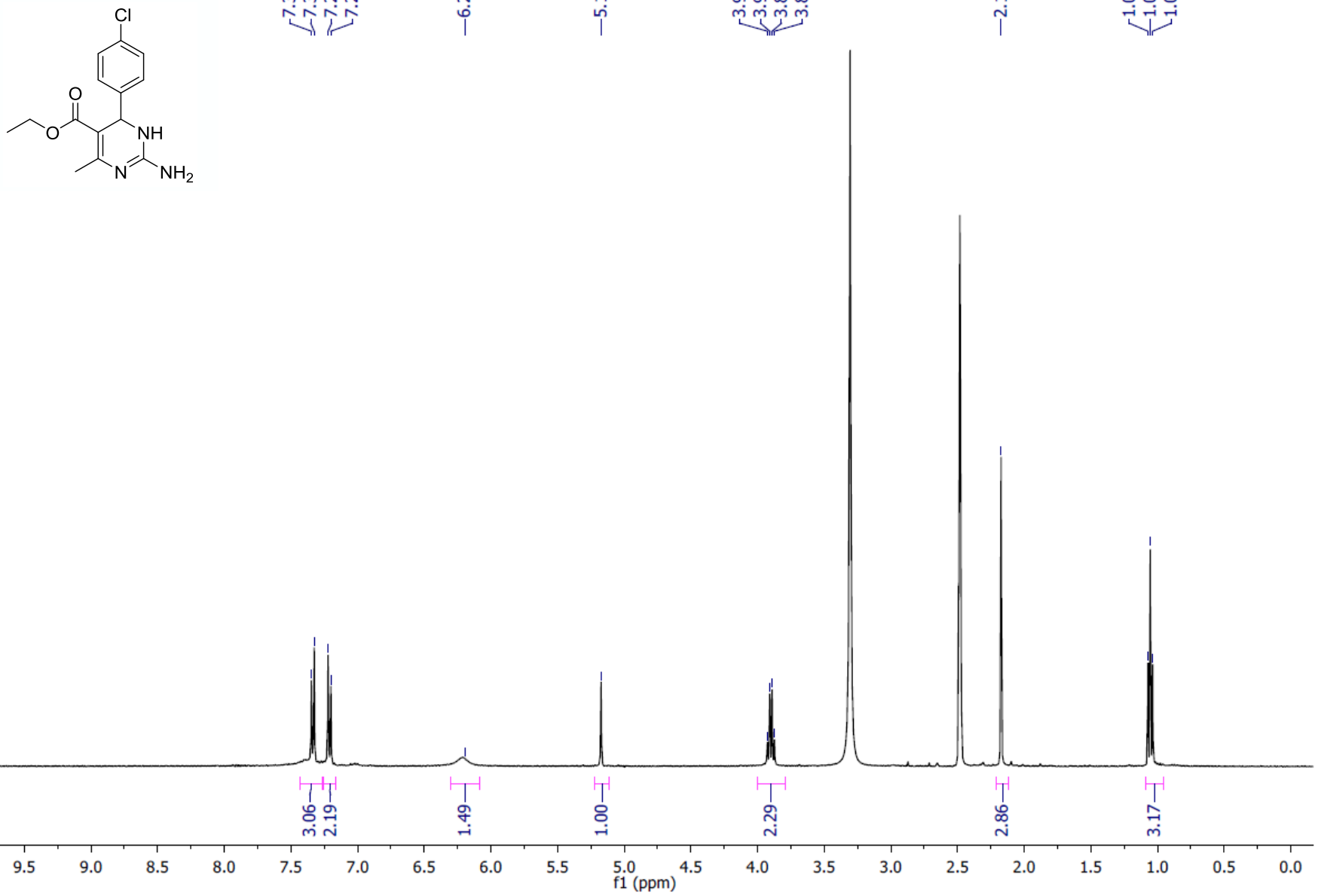
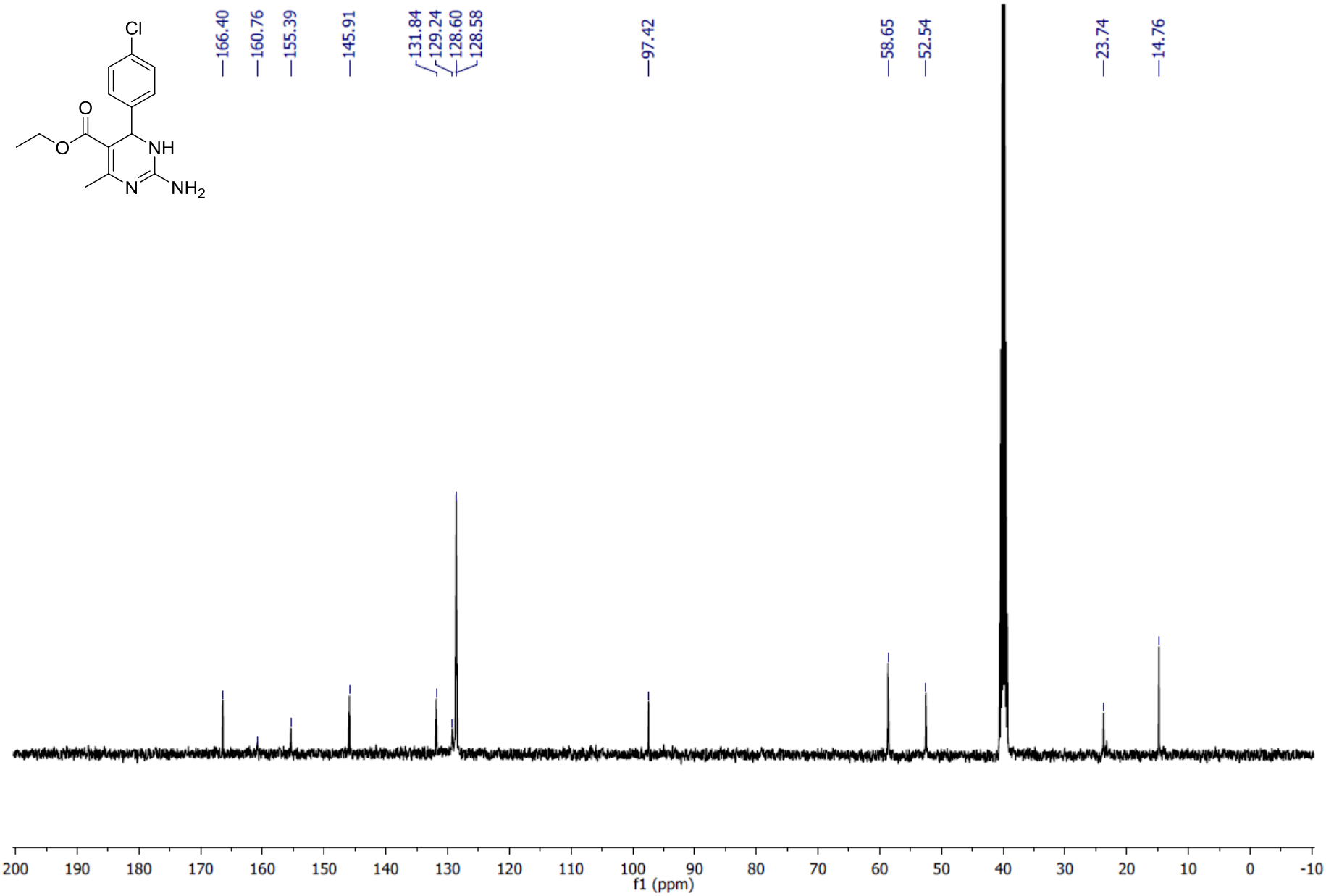
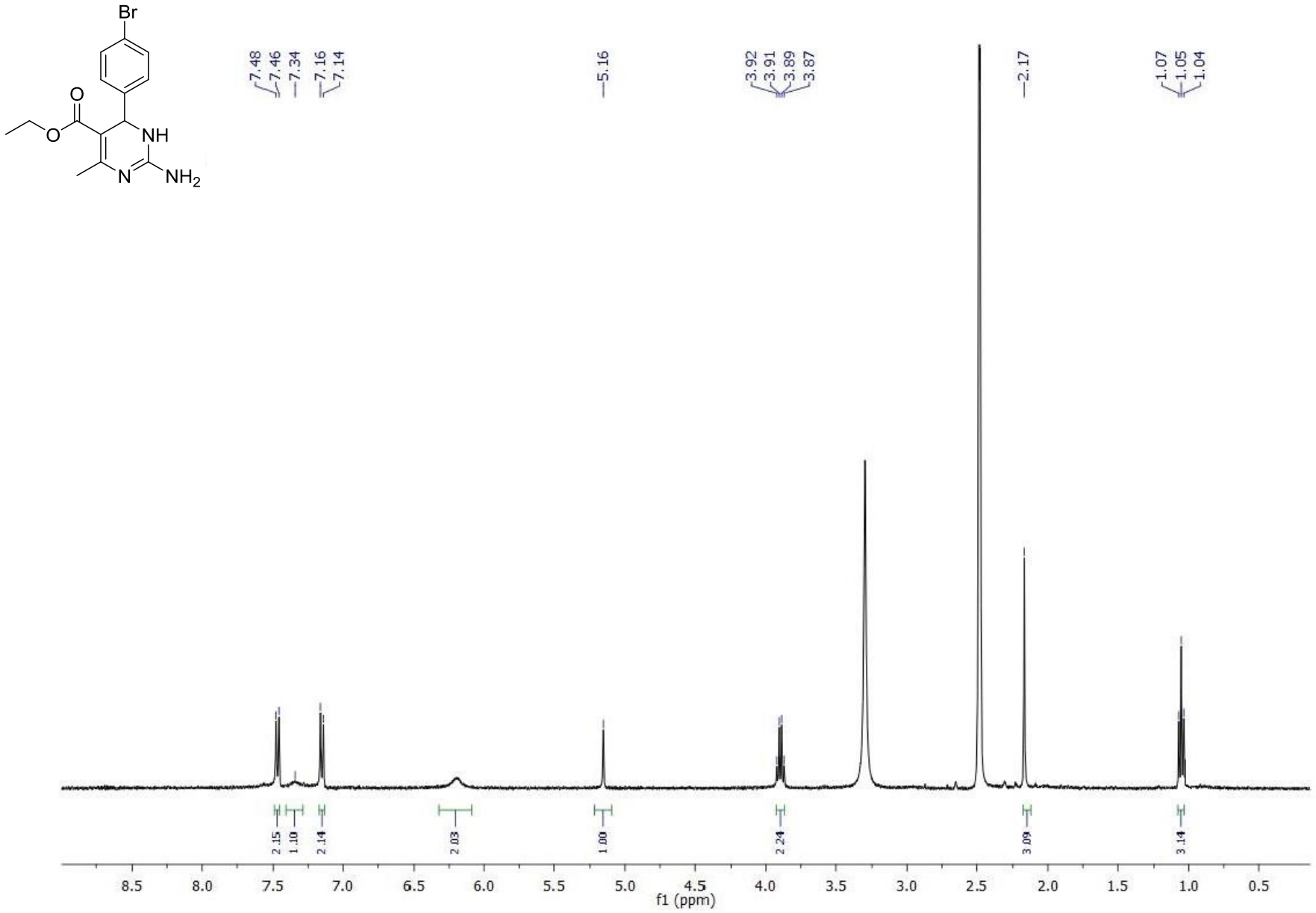
160.192
155.071
142.977
142.954
128.165
128.100
114.911
114.742
97.140
58.114
52.021
23.475
14.326
F
O
O
NH
N
NH2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

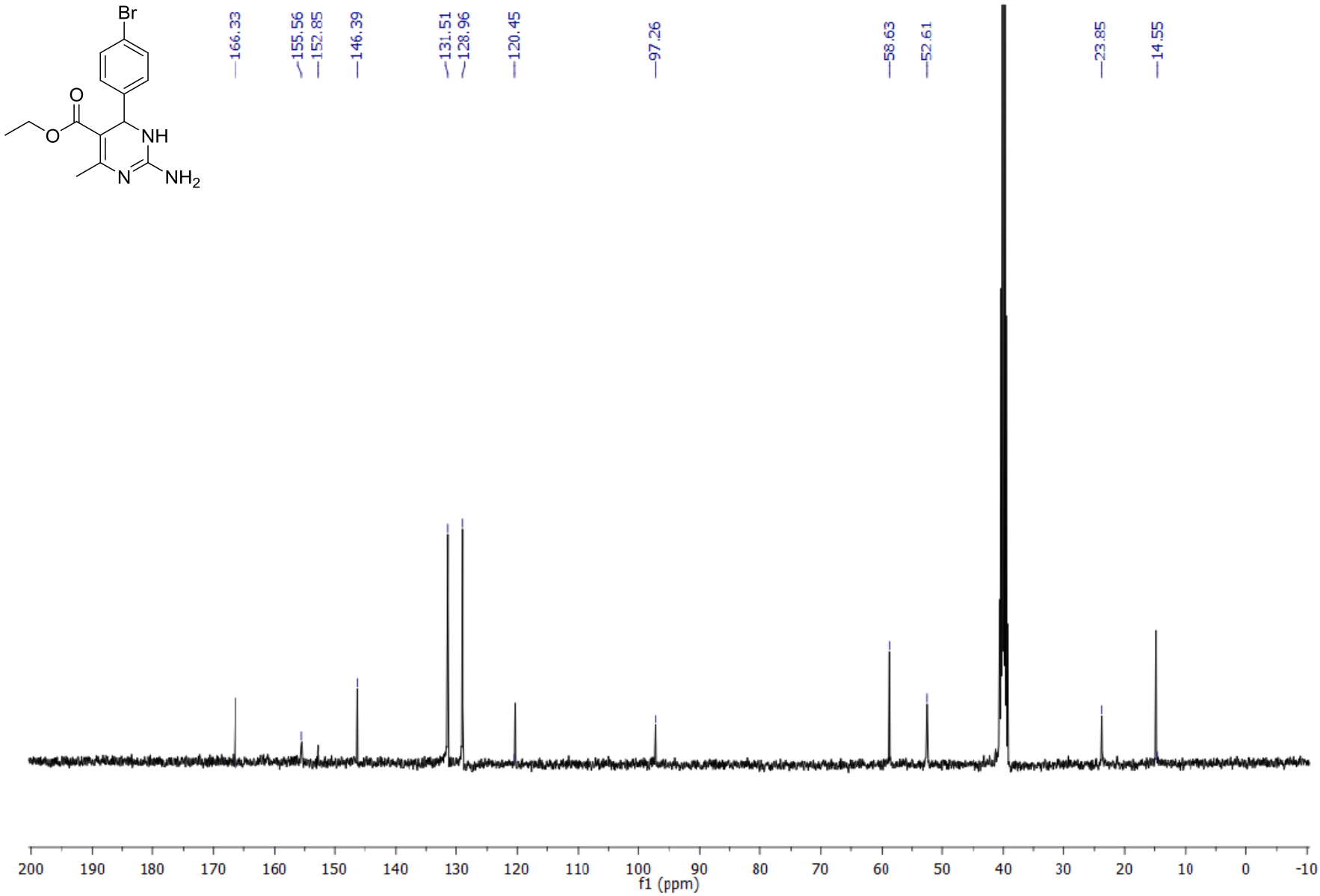

7.68
7.67
7.44
7.43
6.28
5.29
3.92
2.20
1.07
CF3
O
O
NH
N
NH2
2.11
3.15
1.45
1.00
2.04
2.86
3.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

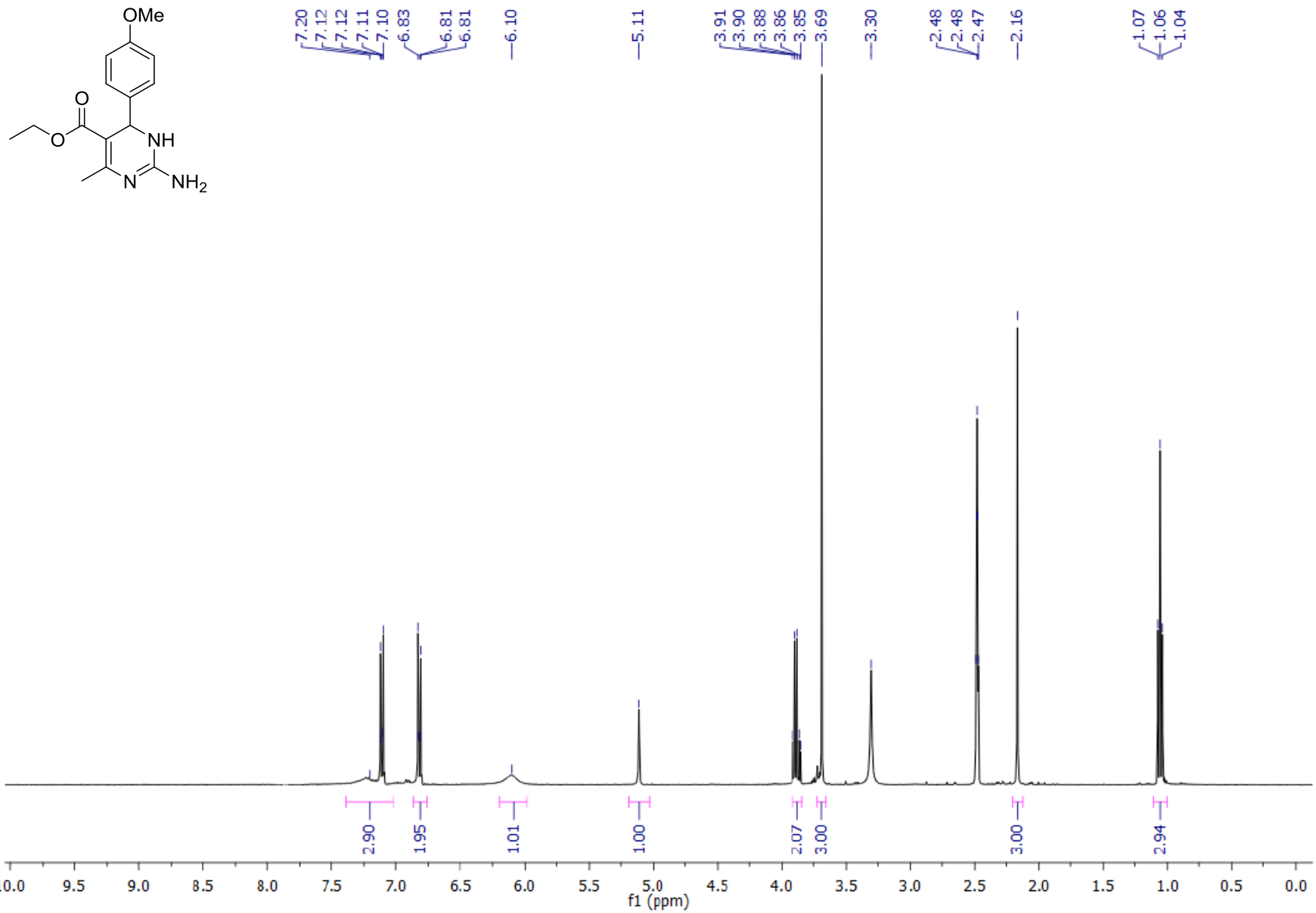

CF3
O
O
NH
N
NH2
166.36
160.75
155.40
151.38
128.14
127.89
127.50
127.44
125.85
125.70
123.69
97.15
58.73
52.95
52.86
23.80
14.77
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

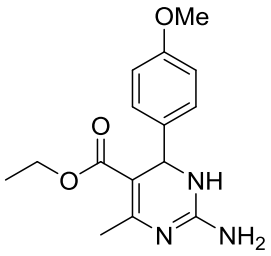

Cl
O
O
NH
N
NH2
7.35
7.32
7.22
7.20
6.20
5.17
3.92
3.91
3.89
3.87
2.17
1.07
1.05
1.04
3.06
2.19
1.49
1.00
2.29
2.86
3.17
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Cl
O
O
NH
N
NH2
166.40
160.76
155.39
145.91
131.84
129.24
128.60
128.58
97.42
58.65
52.54
23.74
14.76
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

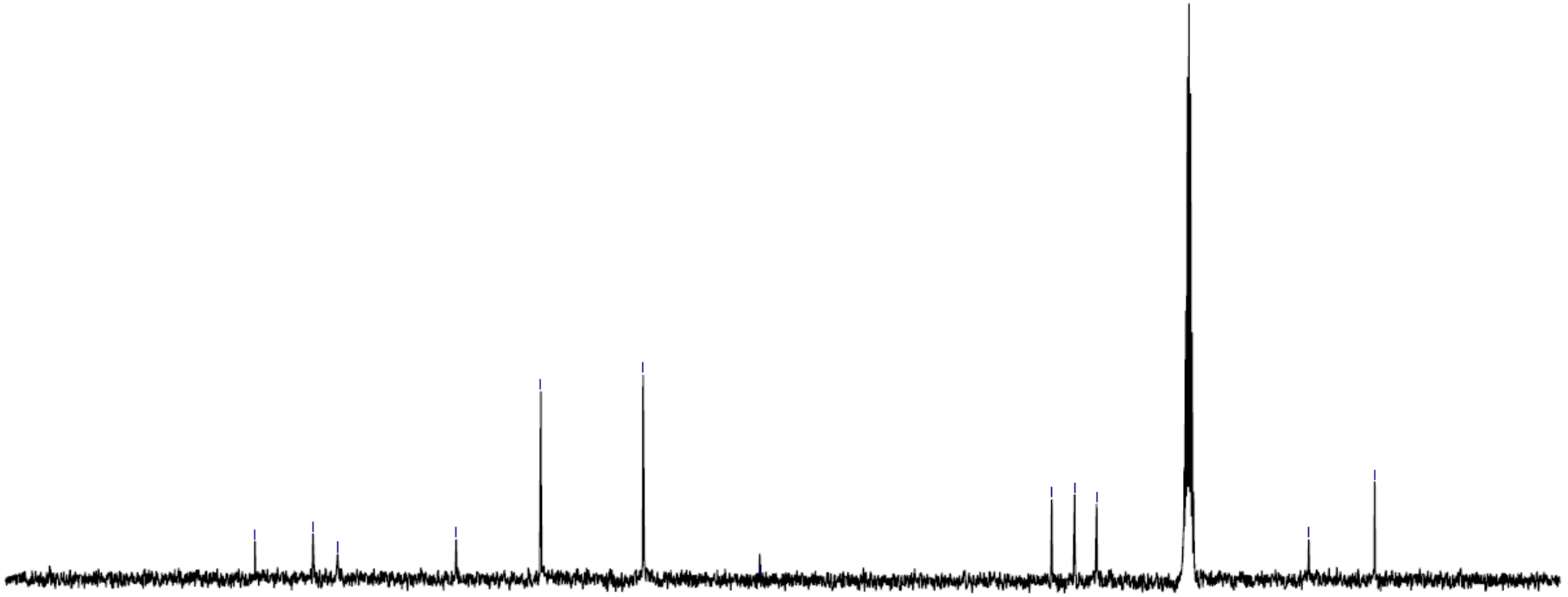

Br
O
O
NH
N
NH2
7.48
7.46
7.34
7.16
7.14
5.16
3.92
3.91
3.89
3.87
2.17
1.07
1.05
1.04
2.15
1.10
2.14
2.03
1.00
2.24
3.09
3.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Br
O
O
NH
N
NH2
166.33
155.56
152.85
146.39
131.51
128.96
120.45
97.26
58.63
52.61
23.85
14.55
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

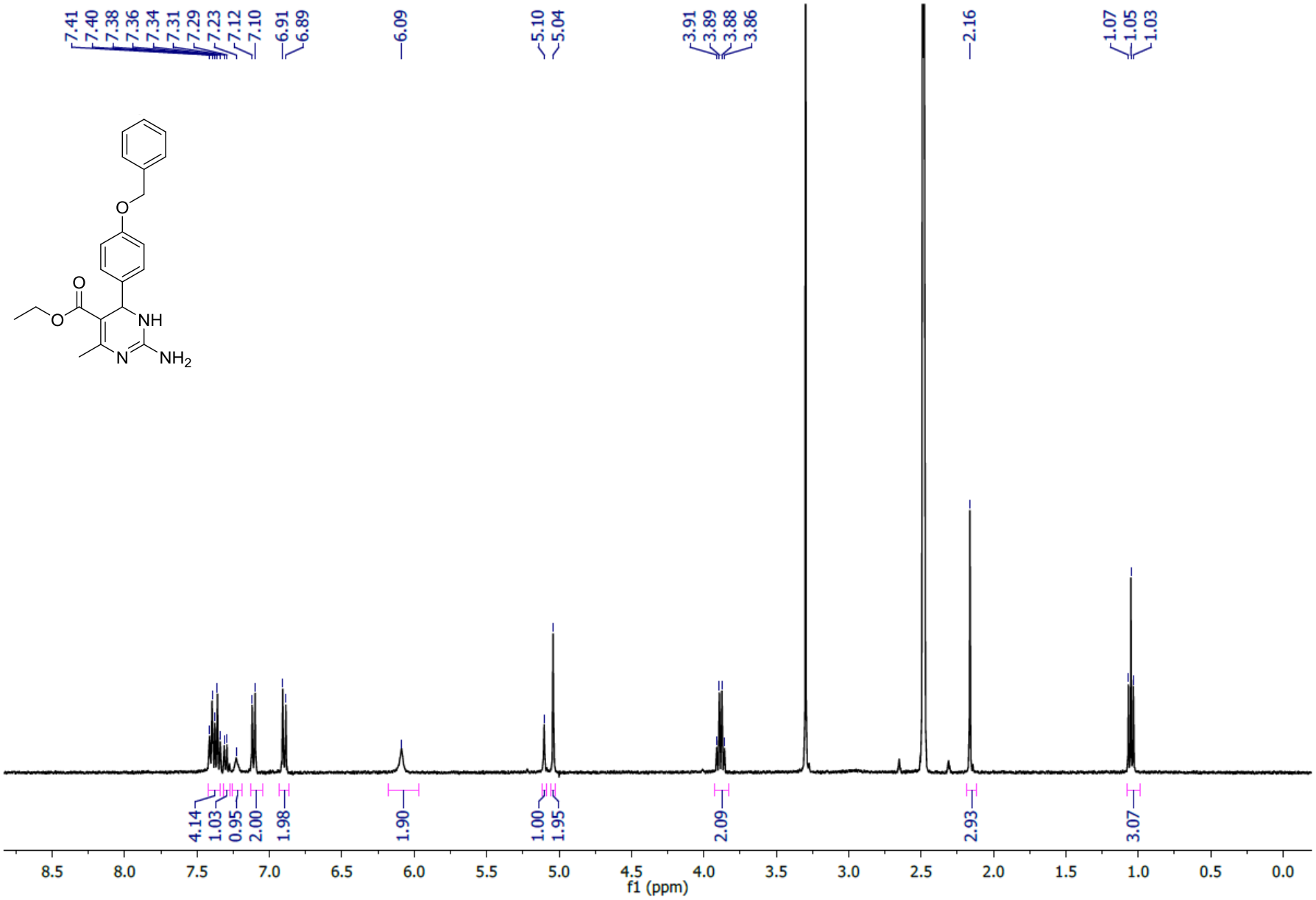

OMe
O
O
NH
N
NH2
7.20
7.12
7.12
7.11
7.10
6.83
6.81
6.81
6.10
5.11
3.91
3.90
3.88
3.86
3.85
3.69
3.30
2.48
2.48
2.47
2.16
1.07
1.06
1.04
2.90
1.95
1.01
1.00
2.07
3.00
3.00
2.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

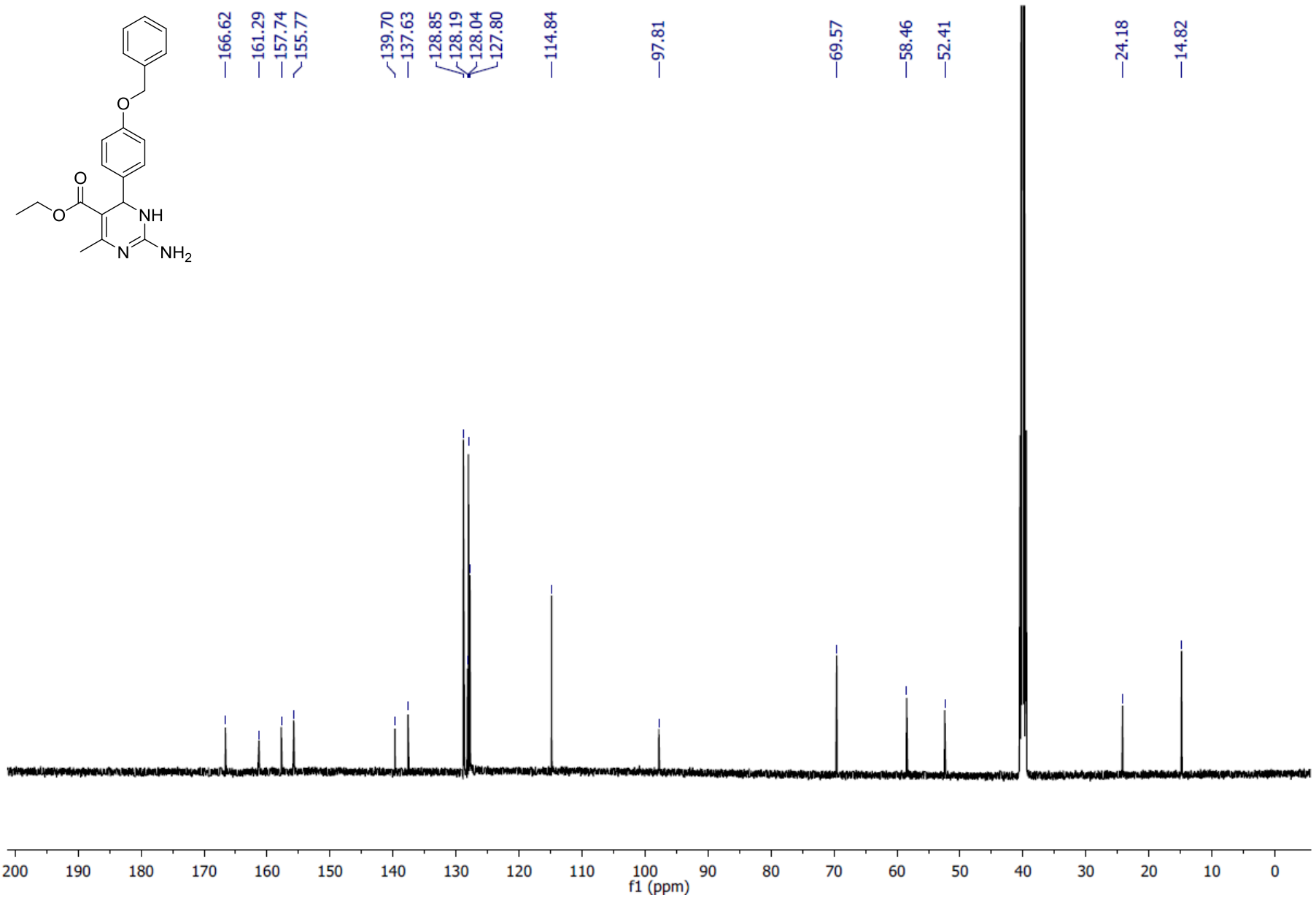


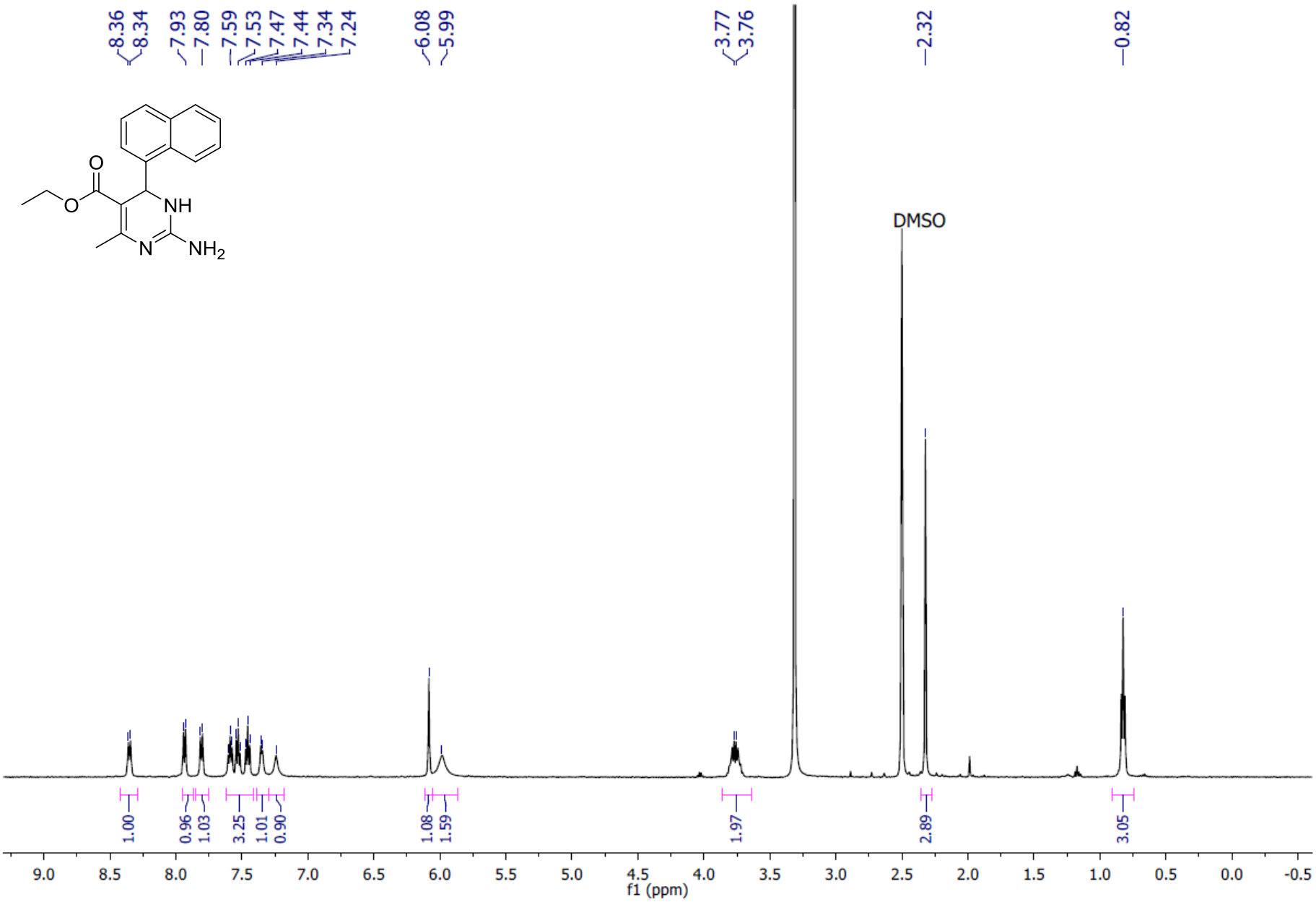
166.55
158.69
155.35
139.27
127.81
113.94
98.00
58.54
55.45
52.47
23.71
14.78

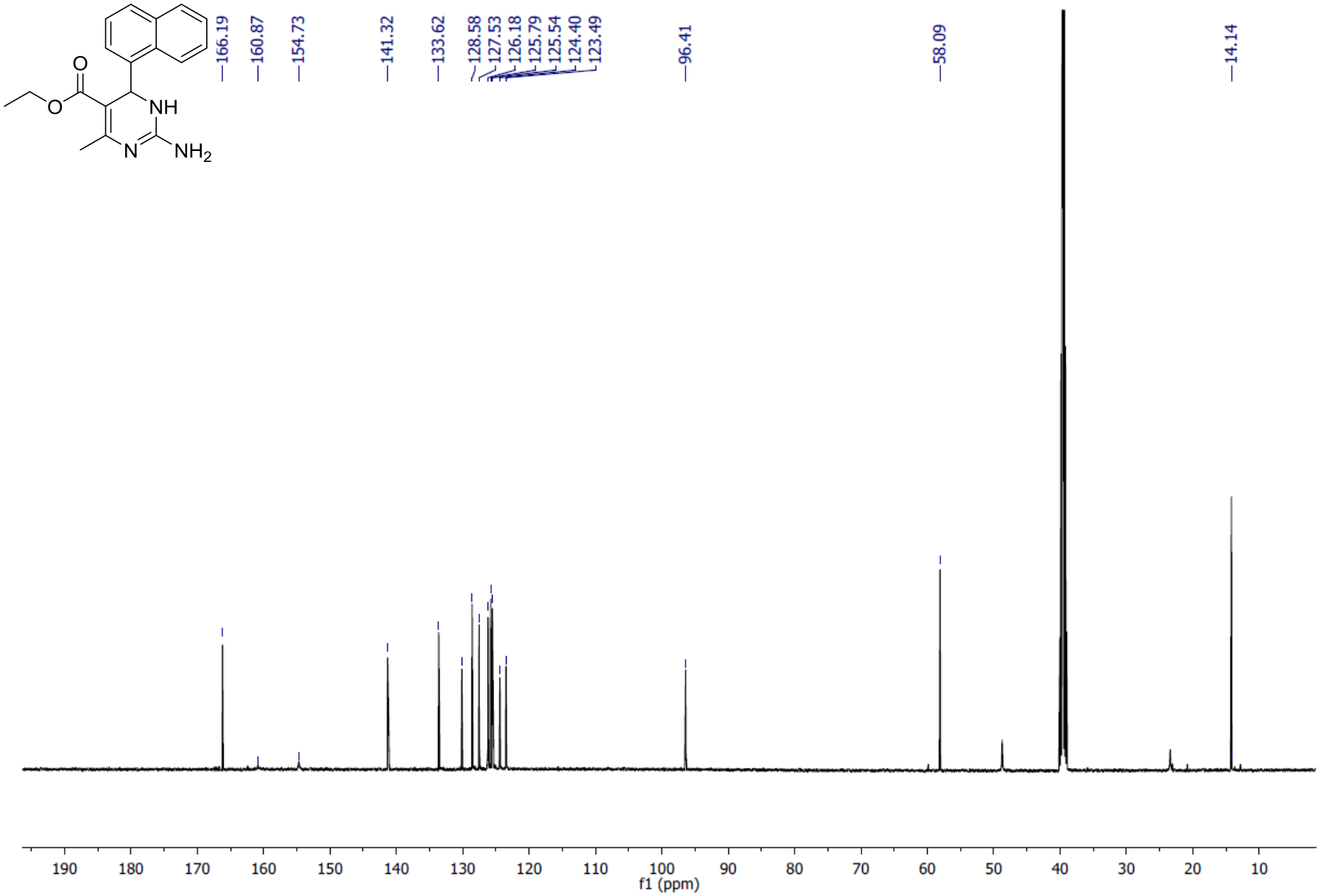


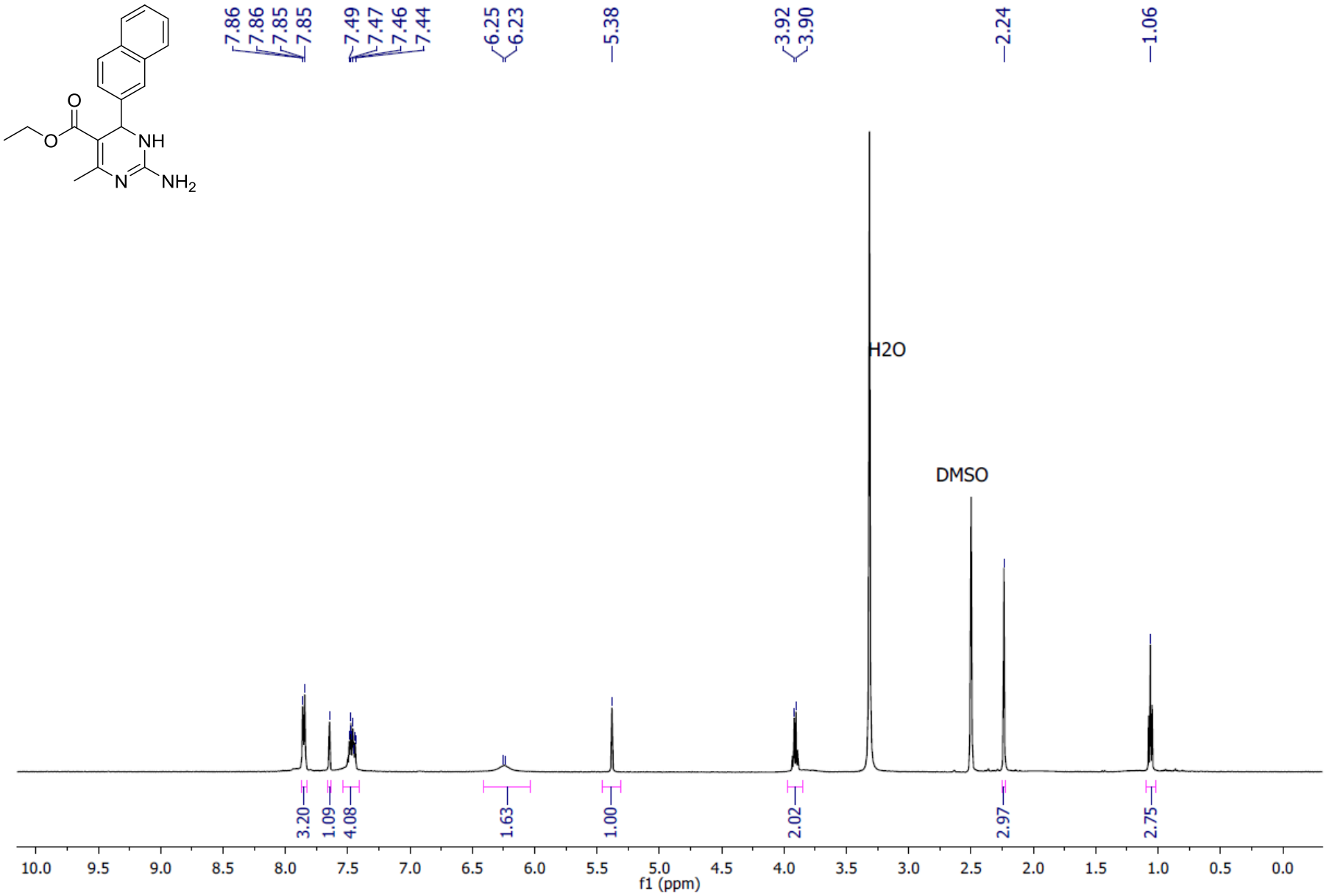
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

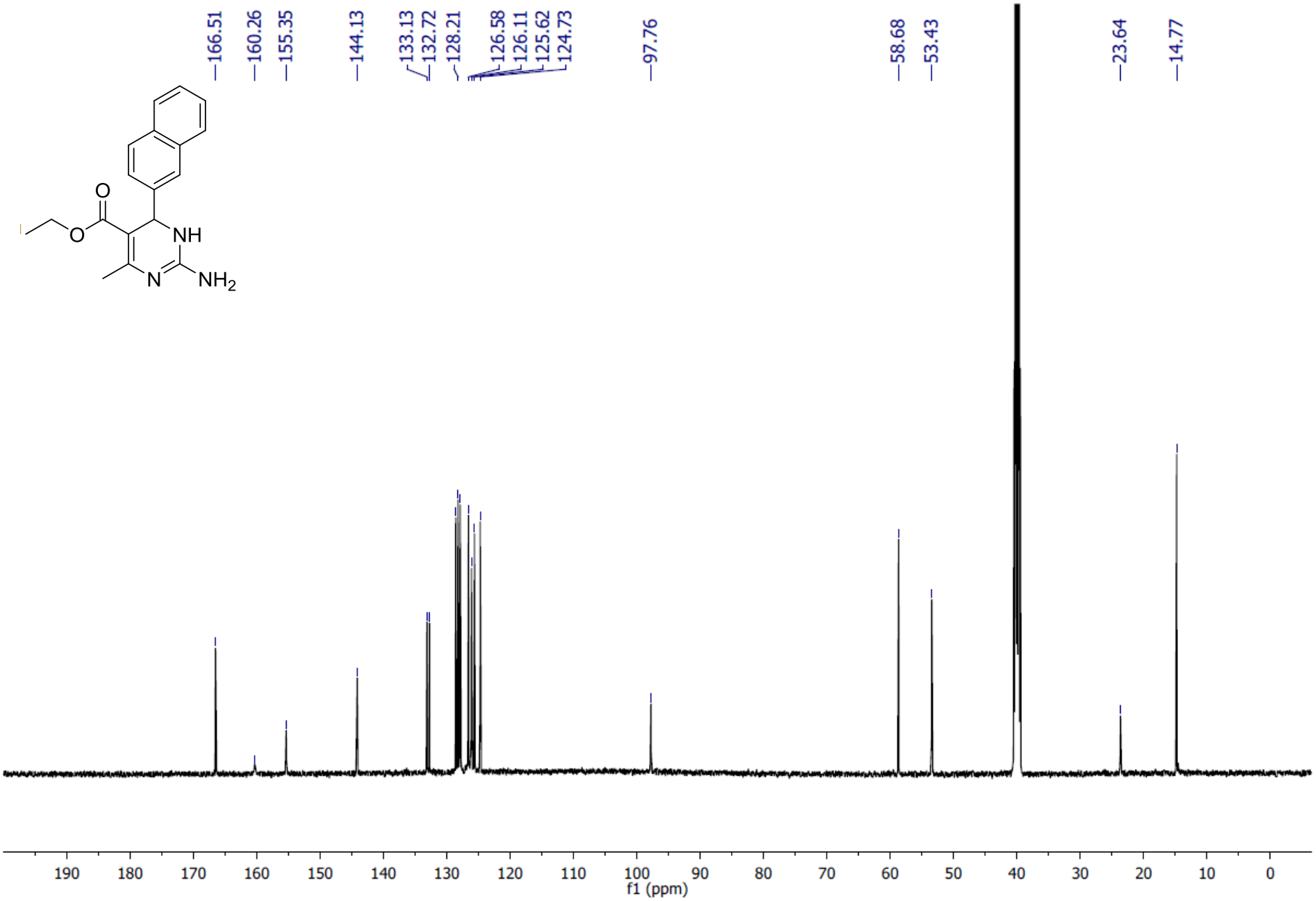

7.41
7.40
7.38
7.36
7.34
7.31
7.29
7.23
7.12
7.10
6.91
6.89
6.09
5.10
5.04
3.91
3.89
3.88
3.86
2.16
1.07
1.05
1.03
O
O
O
NH
N
NH2
4.14
1.03
0.95
2.00
1.98
1.90
1.00
1.95
2.09
2.93
3.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

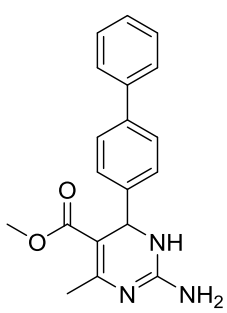

166.62
161.29
157.74
155.77
139.70
137.63
128.85
128.19
128.04
127.80
114.84
97.81
69.57
58.46
52.41
24.18
14.82
O
O
O
NH
N
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

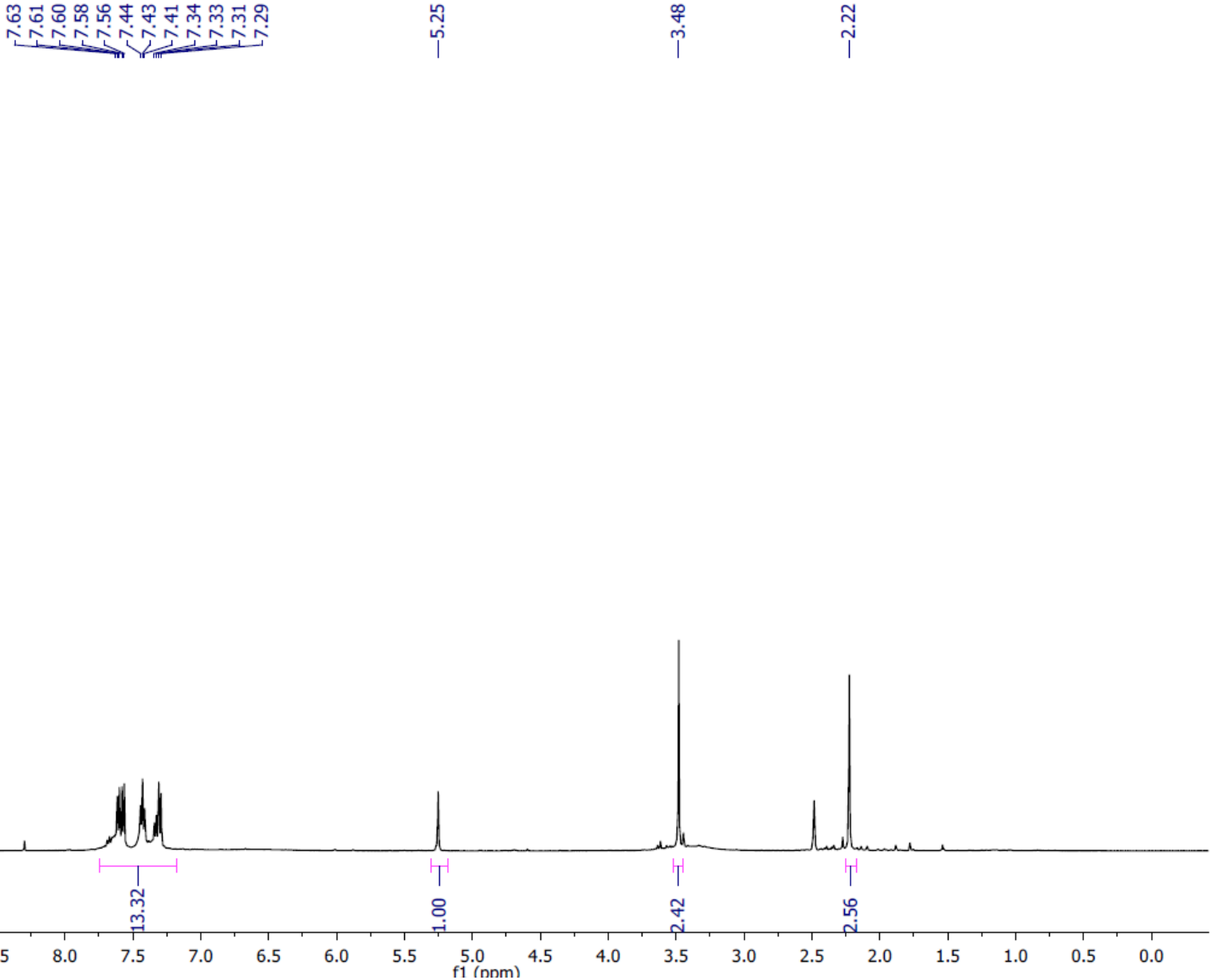

8.36
8.34
7.93
7.80
7.59
7.53
7.47
7.44
7.34
7.24
6.08
5.99
3.77
3.76
2.32
0.82
DMSO
O
O
NH
N
NH2
1.00
0.96
1.03
3.25
1.01
0.90
1.08
1.59
1.97
2.89
3.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


O
O
NH
N
NH2
166.19
160.87
154.73
141.32
133.62
128.58
127.53
126.18
125.79
125.54
124.40
123.49
96.41
58.09
14.14
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

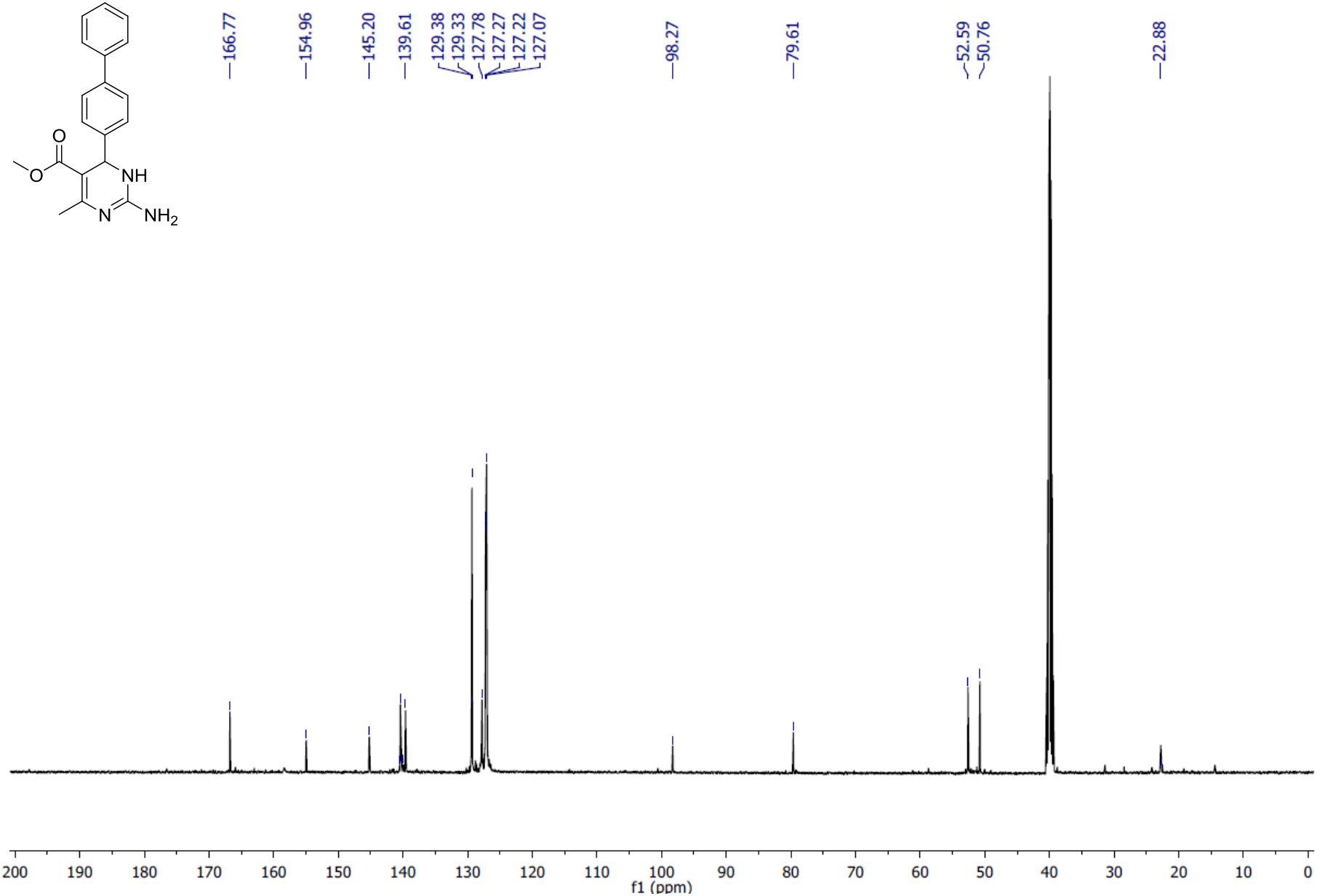

7.86
7.86
7.85
7.85
7.49
7.47
7.46
7.44
6.25
6.23
5.38
3.92
3.90
2.24
1.06
H2O
DMSO
3.20
1.09
4.08
1.63
1.00
2.02
2.97
2.75
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
O
O
NH
N
NH2

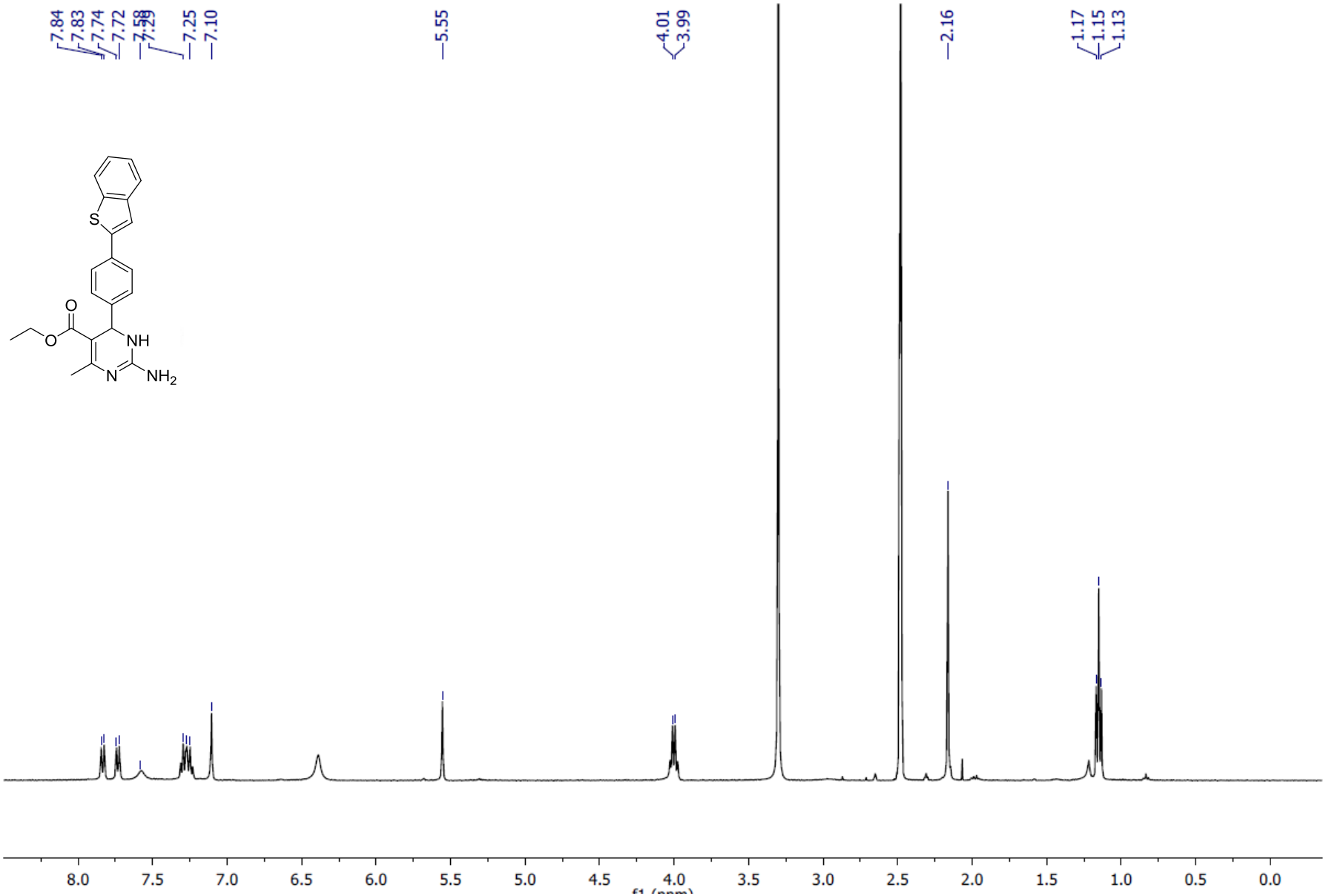

166.51
160.26
155.35
144.13
133.13
132.72
128.21
126.58
126.11
125.62
124.73
97.76
58.68
53.43
23.64
14.77
O
O
NH
N
NH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

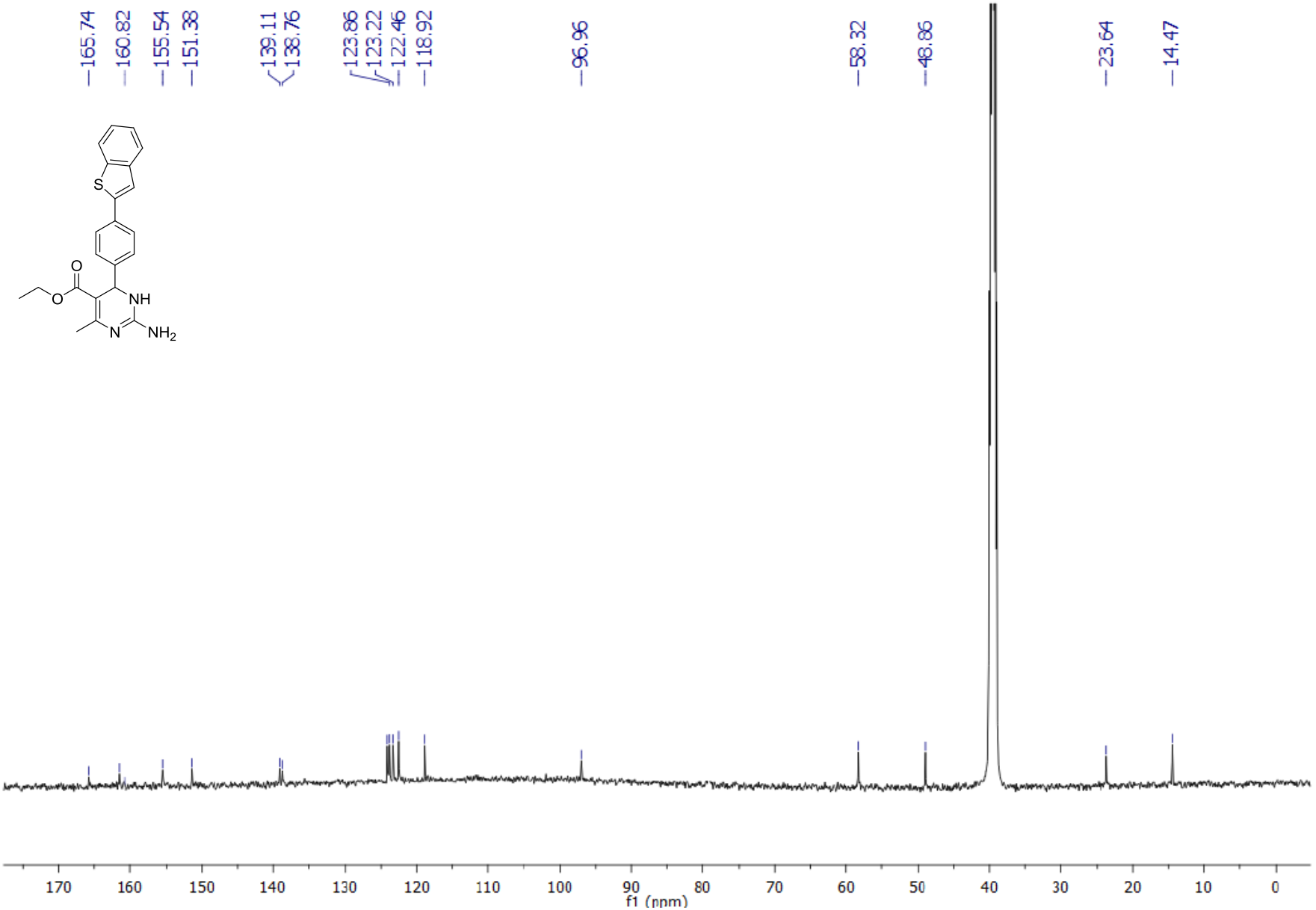

O
O
NH
N
NH2


7.63
7.61
7.60
7.58
7.56
7.44
7.43
7.41
7.34
7.33
7.31
7.29
5.25
3.48
2.22
13.32
1.00
2.42
2.56
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)

O
O
NH
N
NH2


166.77
154.96
145.20
139.61
129.38
129.33
127.78
127.27
127.22
127.07
98.27
79.61
52.59
50.76
22.88
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.84
7.83
7.74
7.72
7.58
7.25
7.10
5.55
4.01
3.99
2.16
1.17
1.15
1.13
S
O
O
NH
N
NH2
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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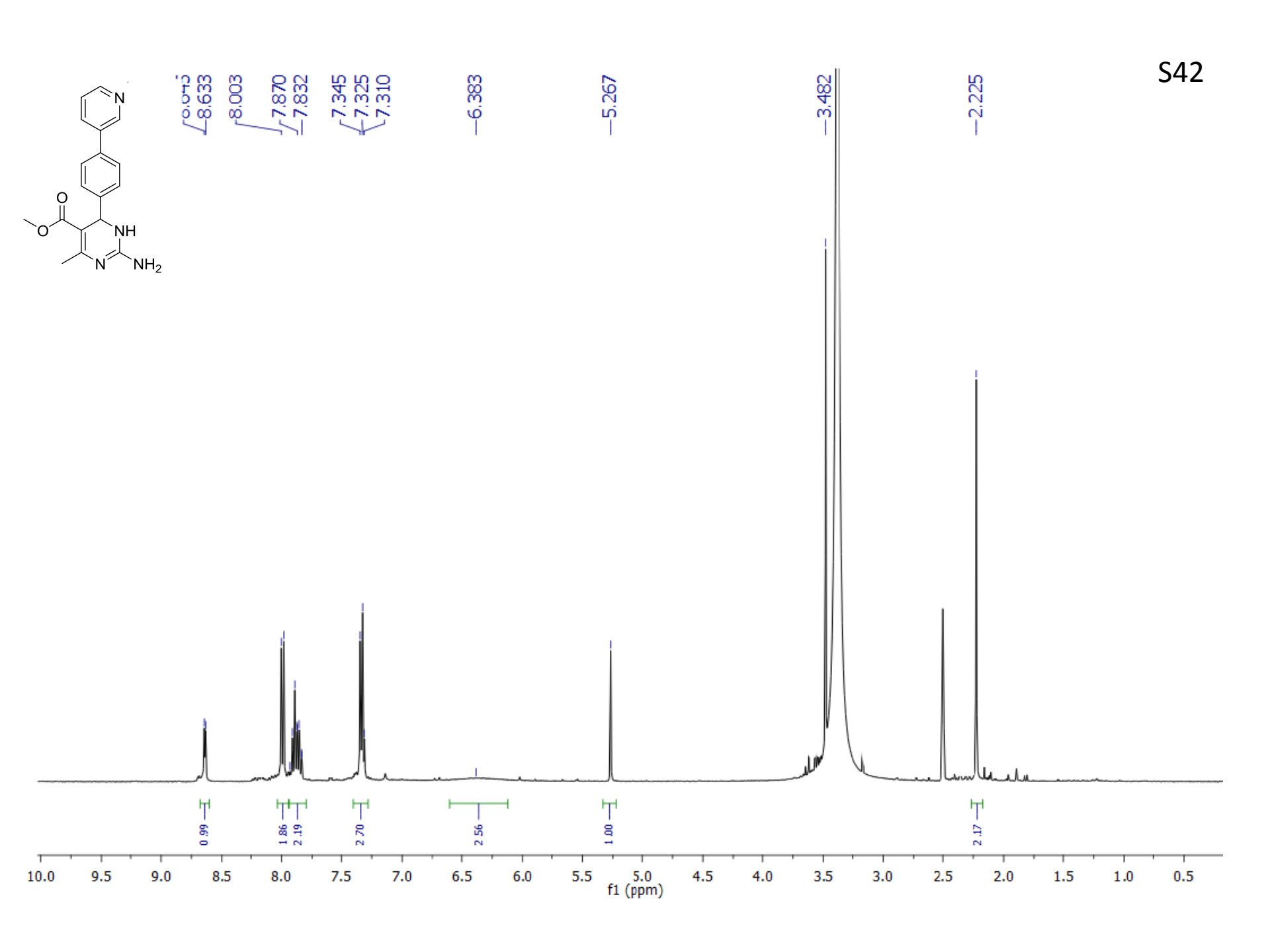
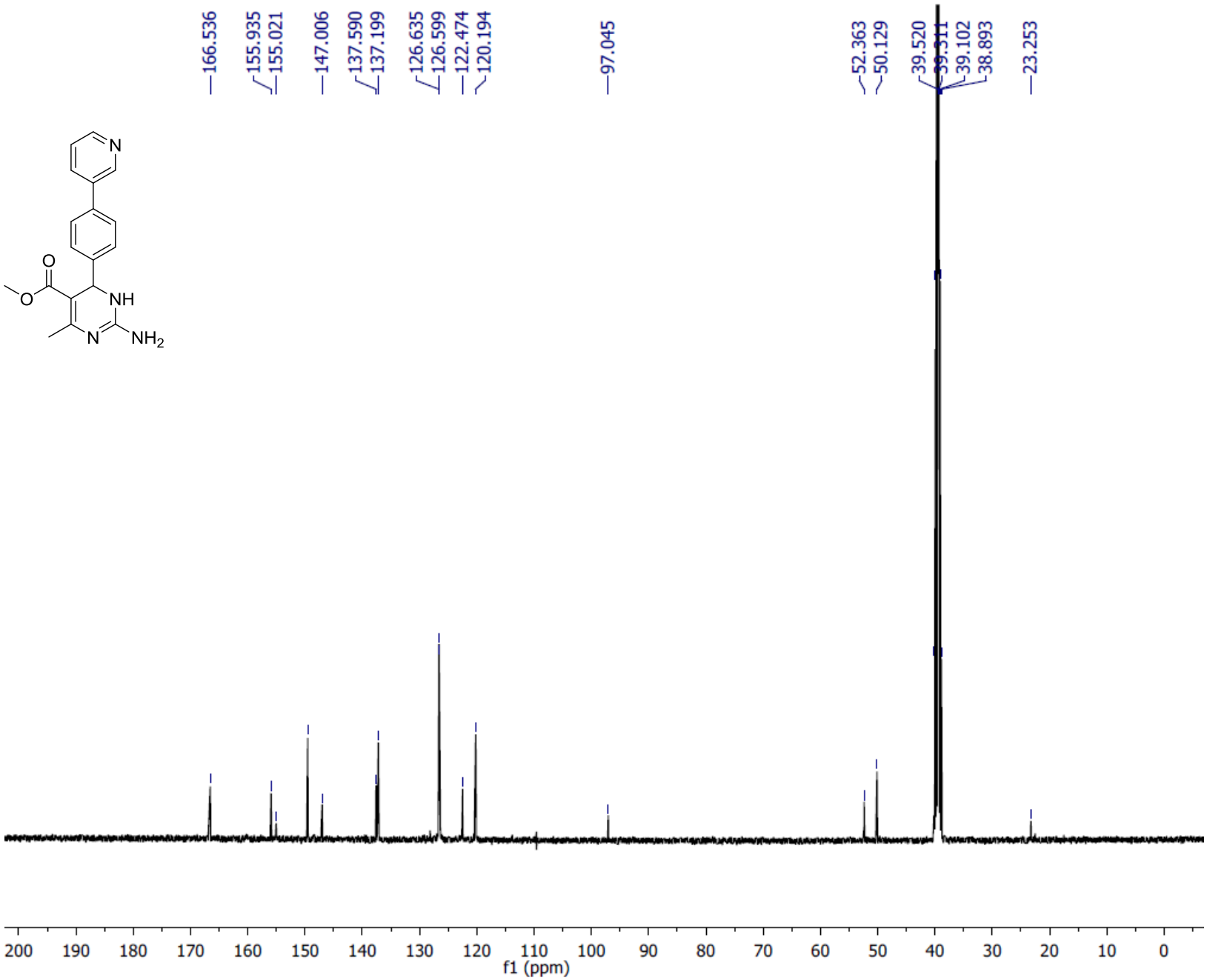
155.54
151.38
139.11
138.76
123.86
123.22
122.46
118.92
96.96
58.32
48.86
23.64
14.47
S
O
O
NH
N
NH2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.633
8.003
7.870
7.832
7.345
7.325
7.310
6.383
5.267
3.482
2.225
0.99
1.86
2.19
2.70
2.56
1.00
2.17
f1 (ppm)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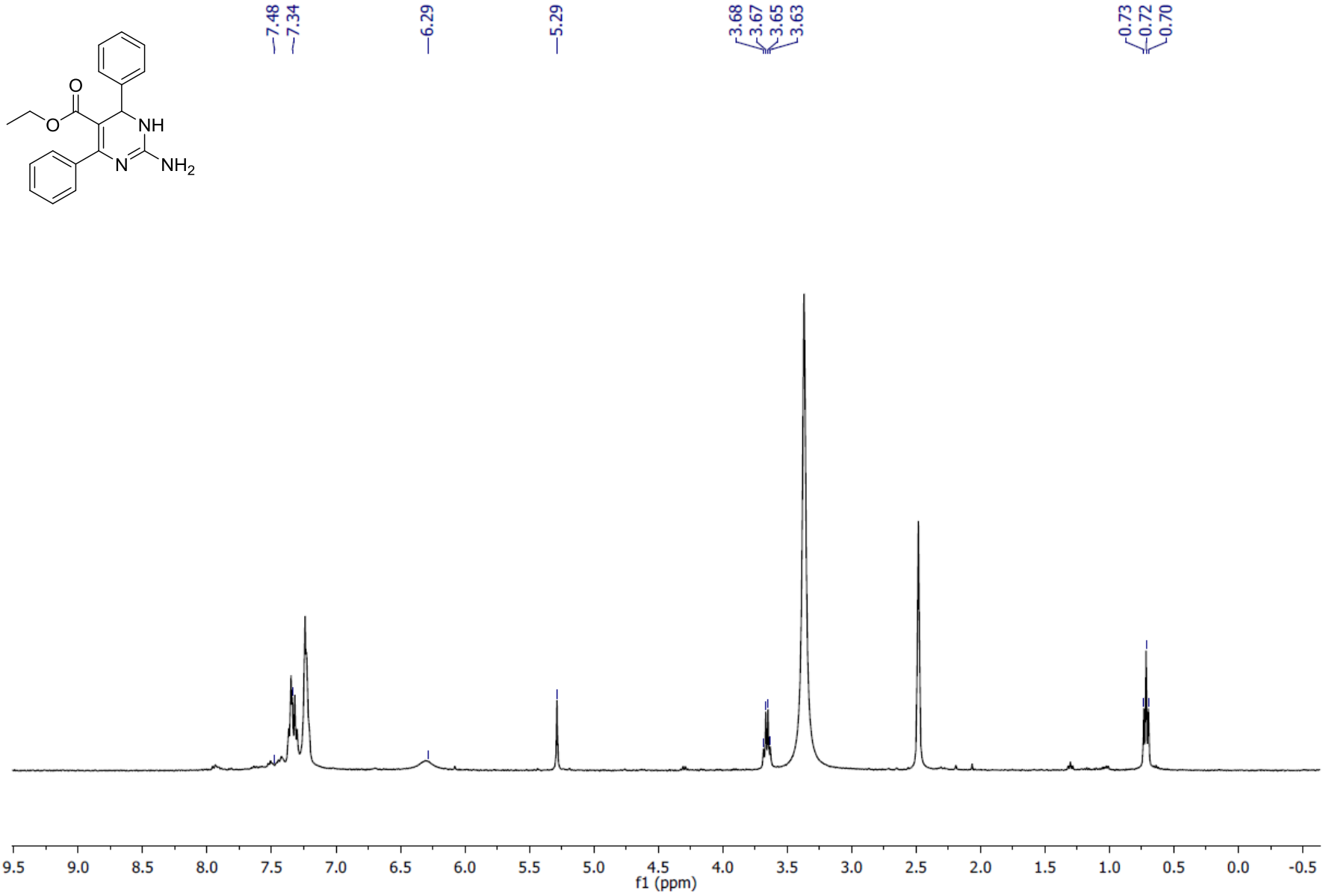
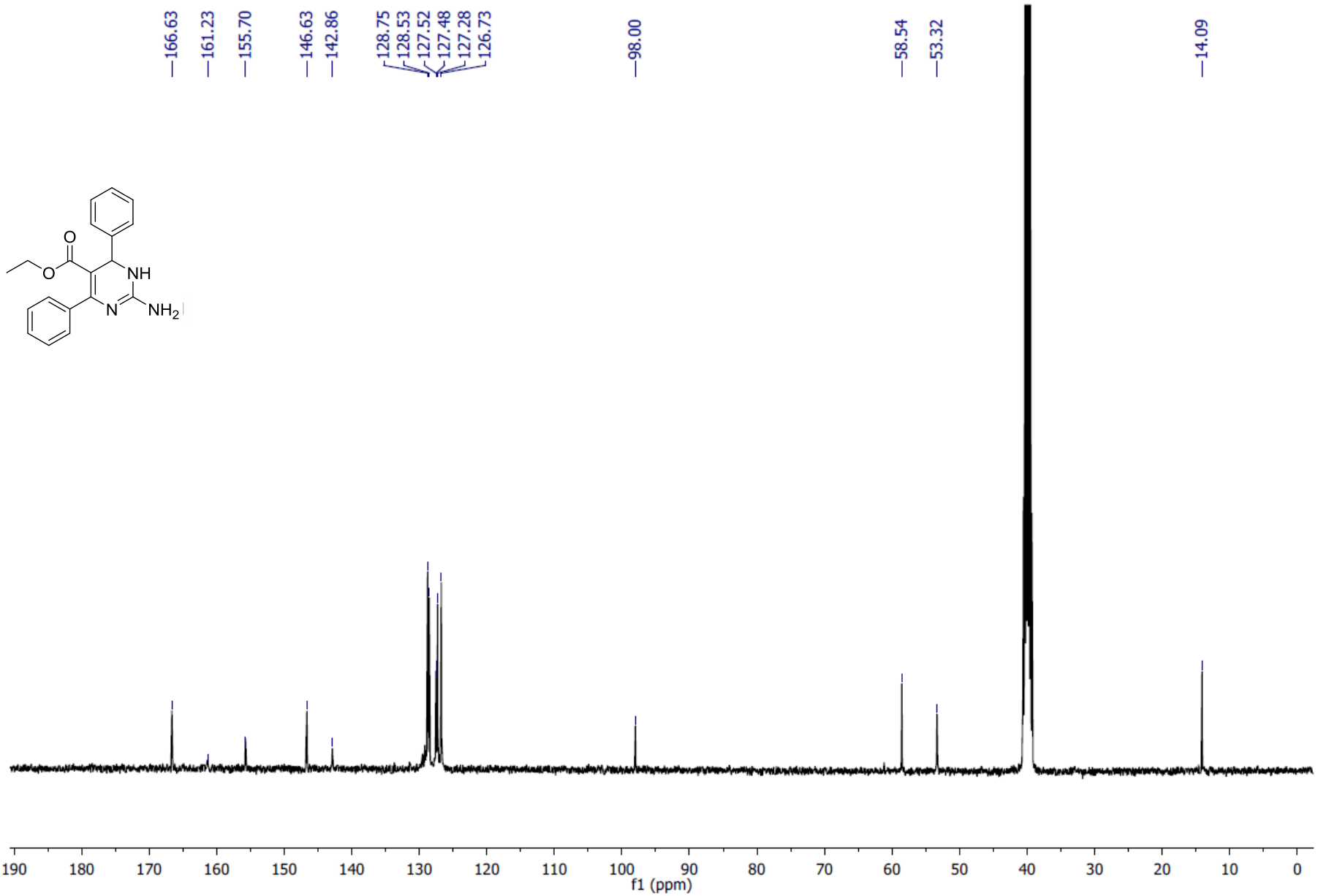
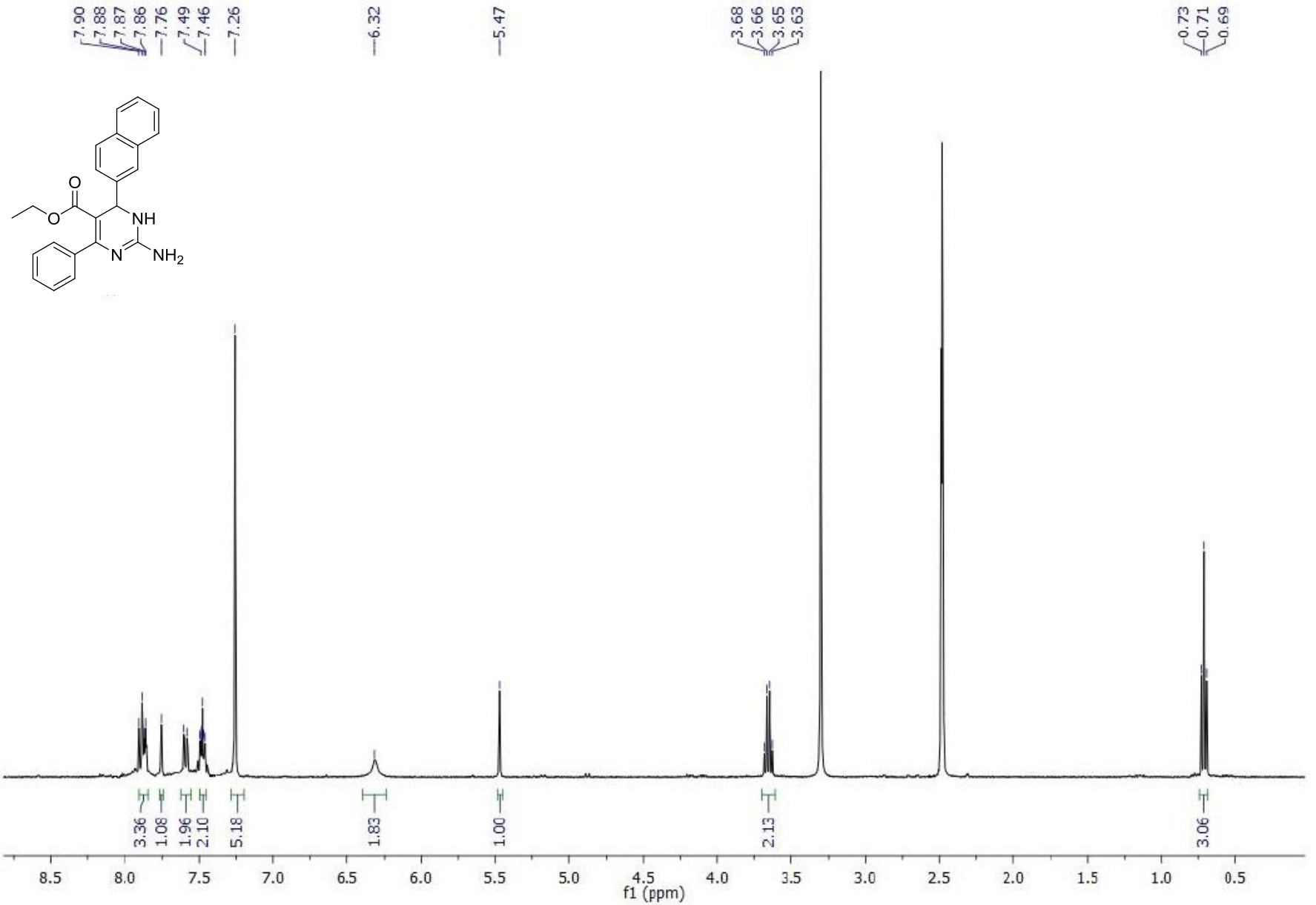
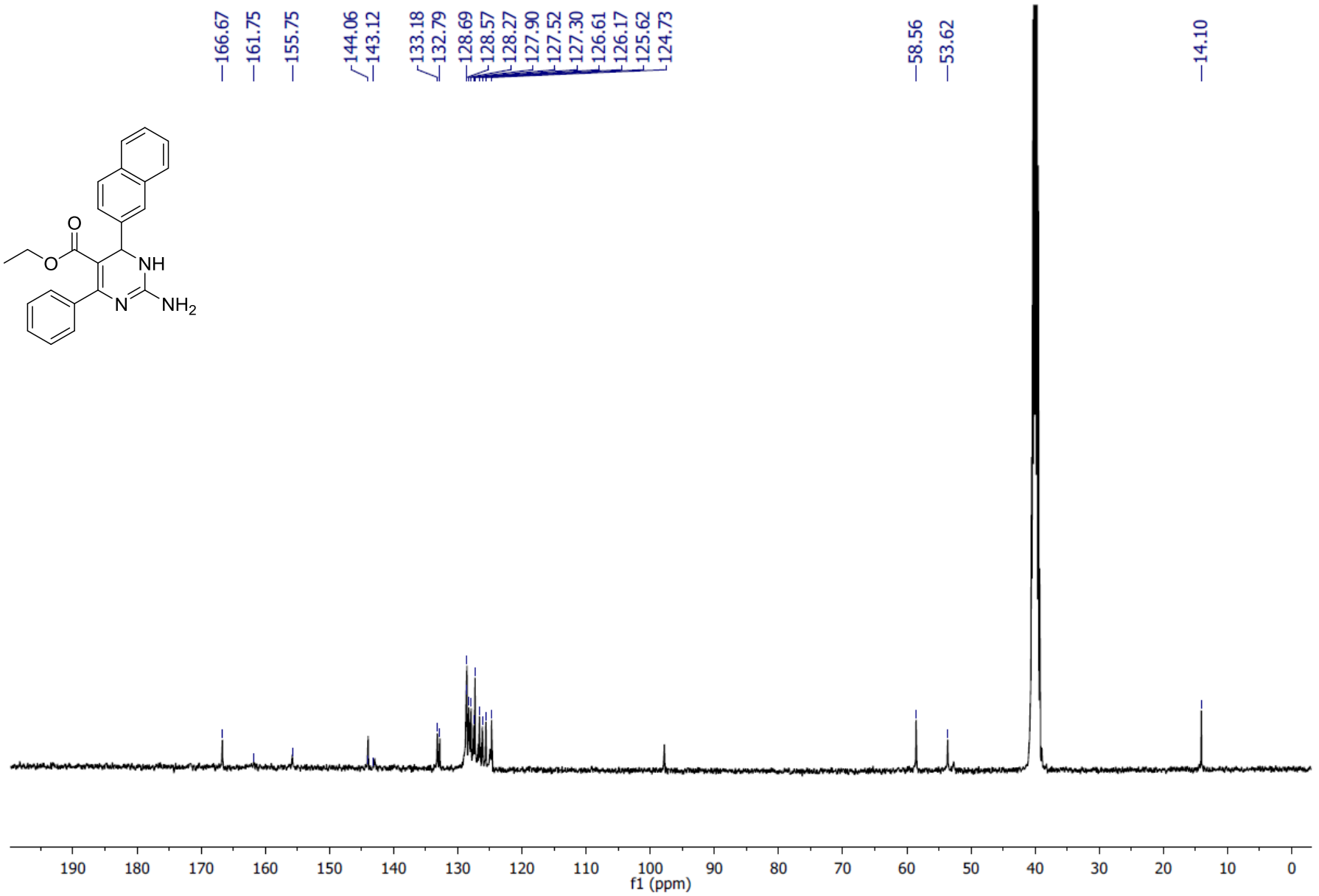
155.935
155.021
147.006
137.590
137.199
126.635
126.599
122.474
120.194
97.045
52.363
50.129
39.520
39.311
39.102
38.893
23.253
N
O
O
NH
N
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

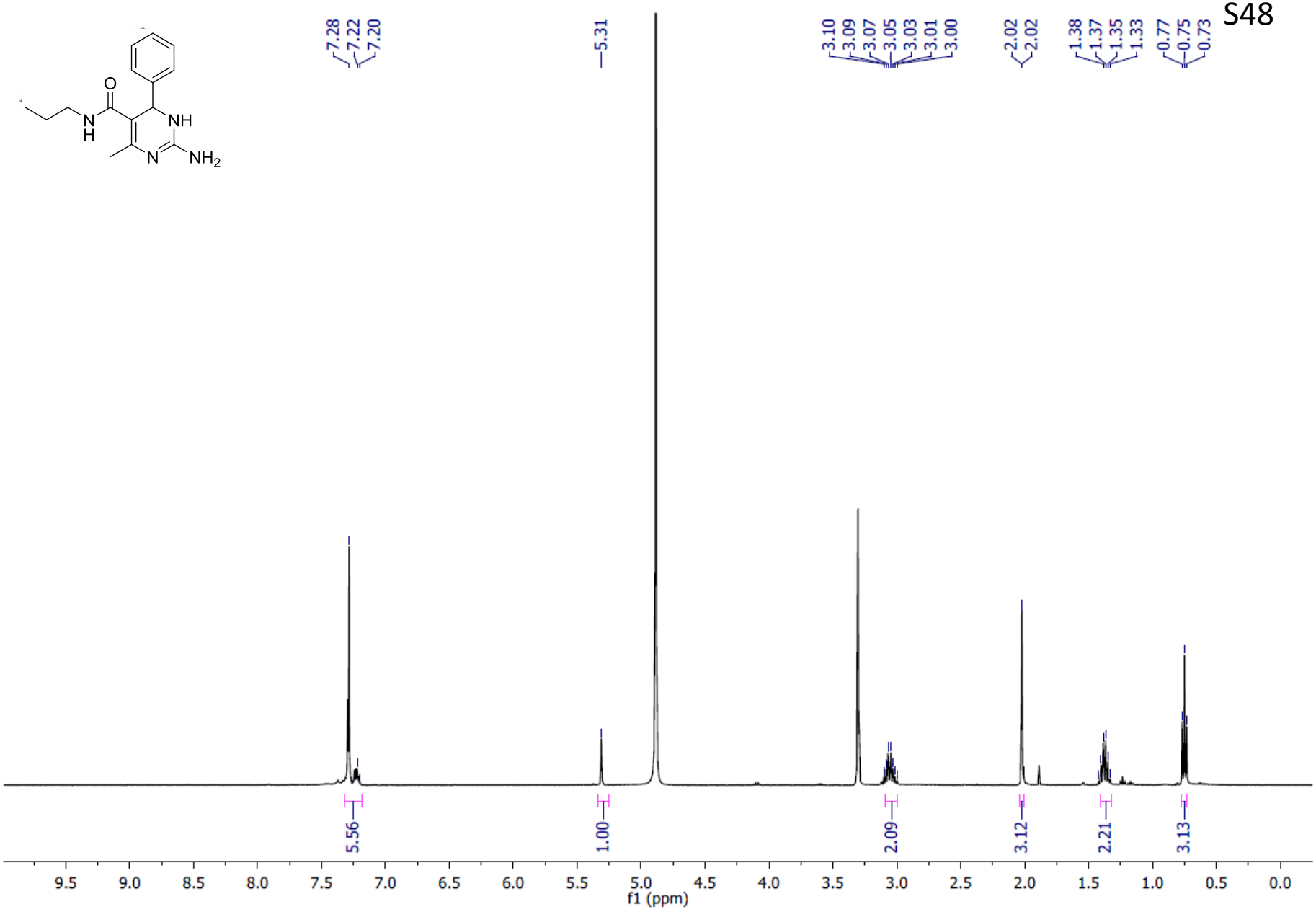

7.48
7.34
6.29
5.29
3.68
3.67
3.65
3.63
0.73
0.72
0.70
O
O
NH
N
NH2
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

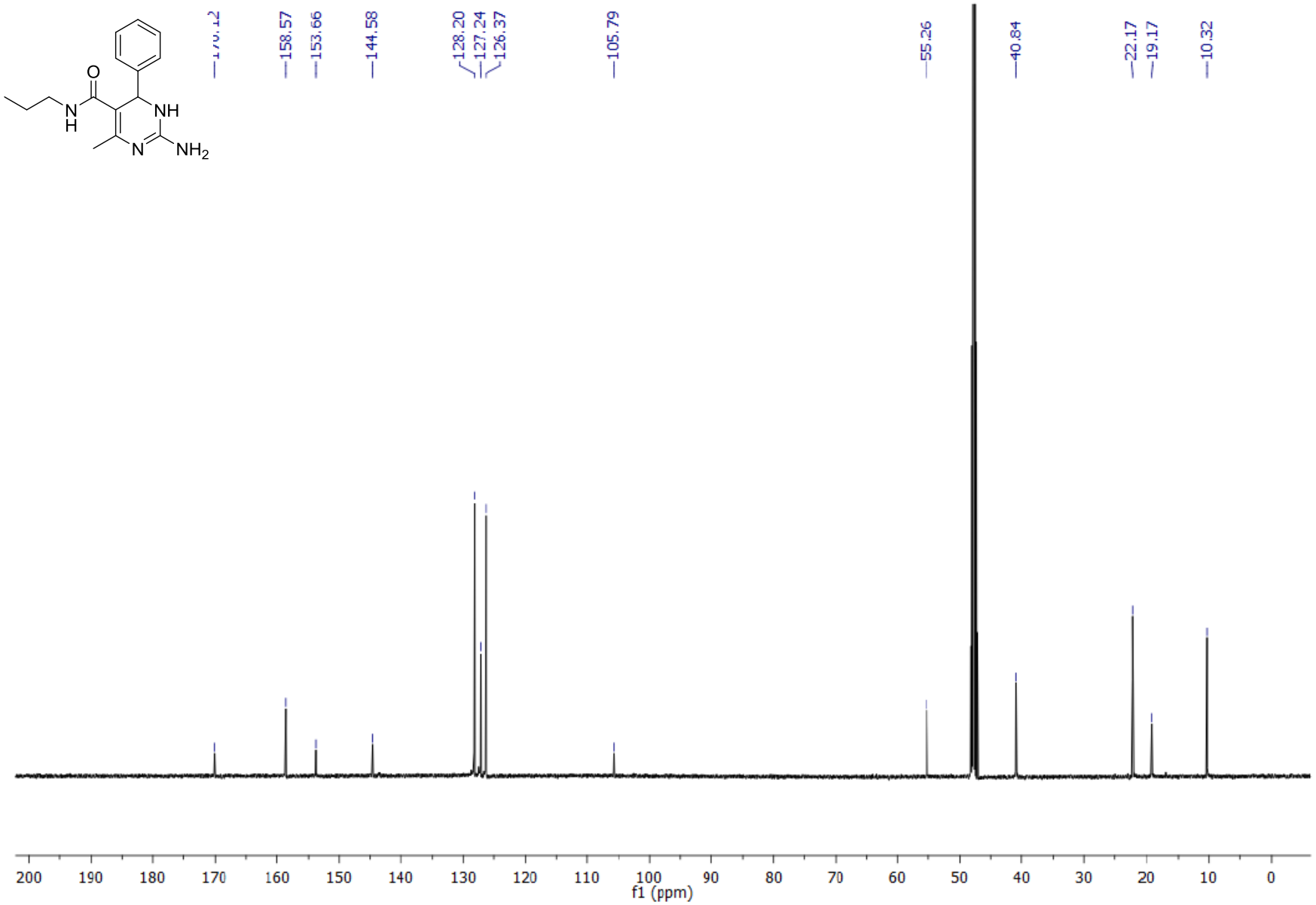

166.63
161.23
155.70
146.63
142.86
128.75
128.53
127.52
127.48
127.28
126.73
98.00
58.54
53.32
14.09
O
O
NH
N
NH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

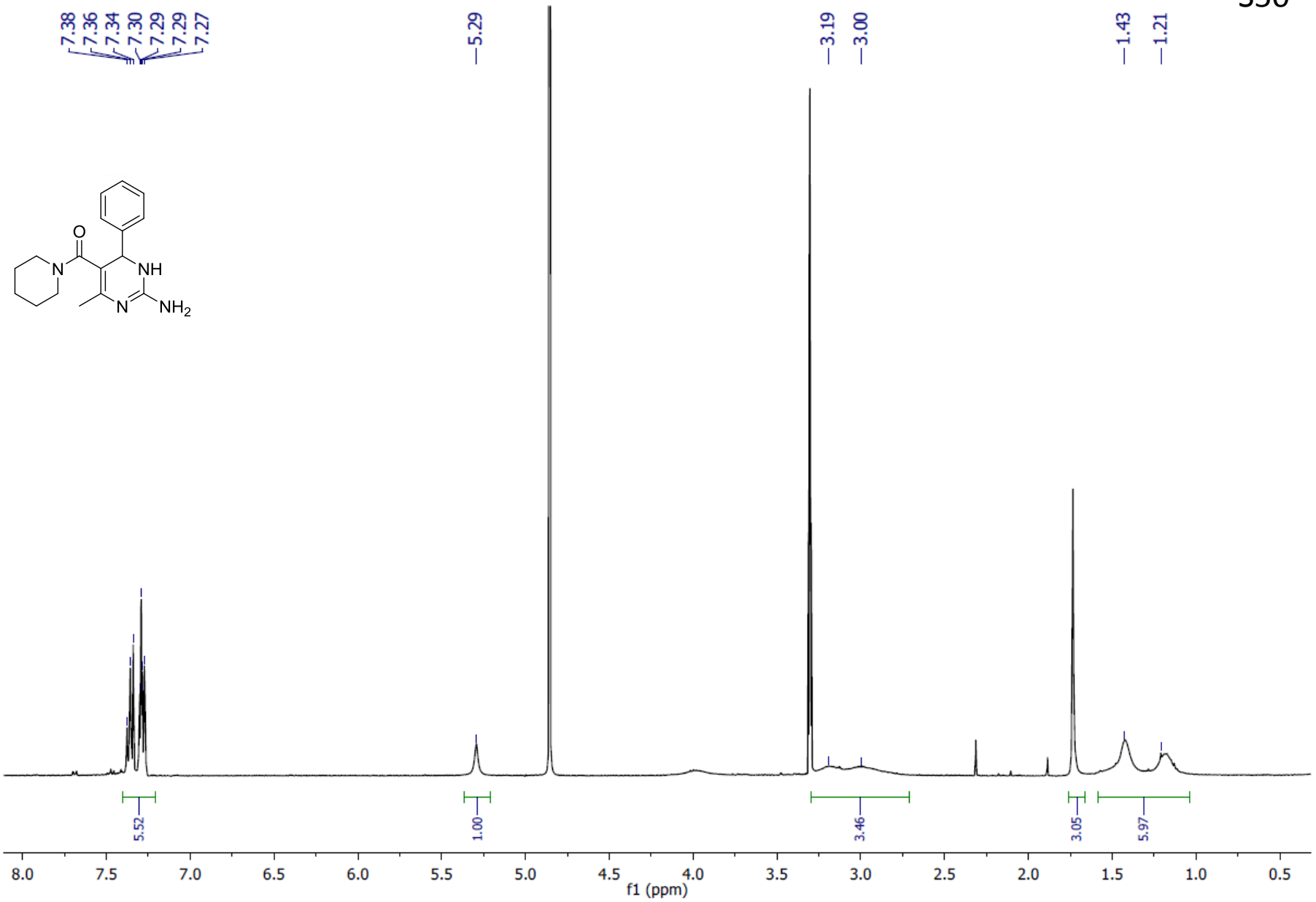

7.90
7.88
7.87
7.86
7.76
7.49
7.46
7.26
6.32
5.47
3.68
3.66
3.65
3.63
0.73
0.71
0.69
O
O
NH
N
NH2
3.36
1.08
1.96
2.10
5.18
1.83
1.00
2.13
3.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

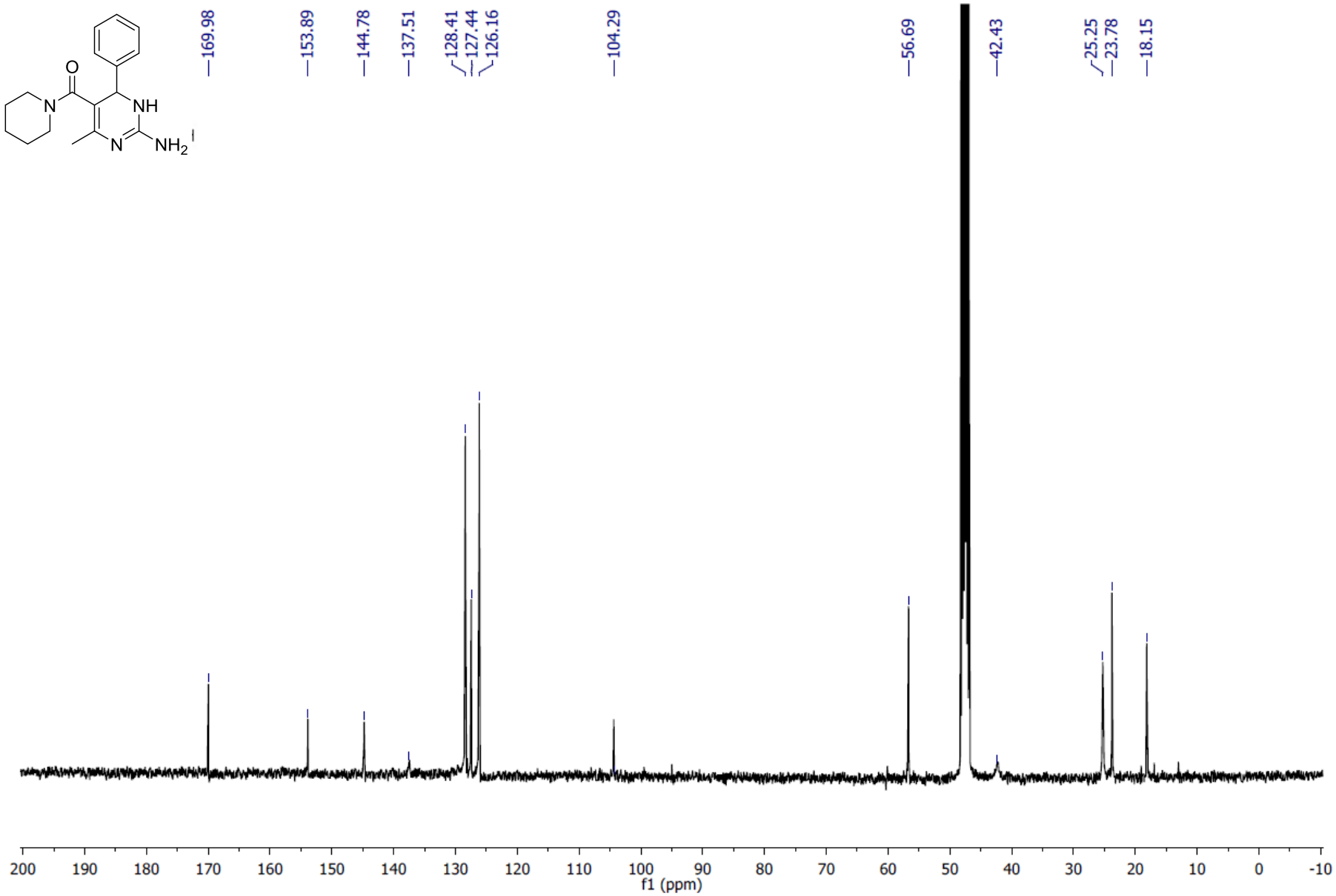

166.67
161.75
155.75
144.06
143.12
133.18
132.79
128.69
128.57
128.27
127.90
127.52
127.30
126.61
126.17
125.62
124.73
58.56
53.62
14.10
O
O
NH
N
NH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

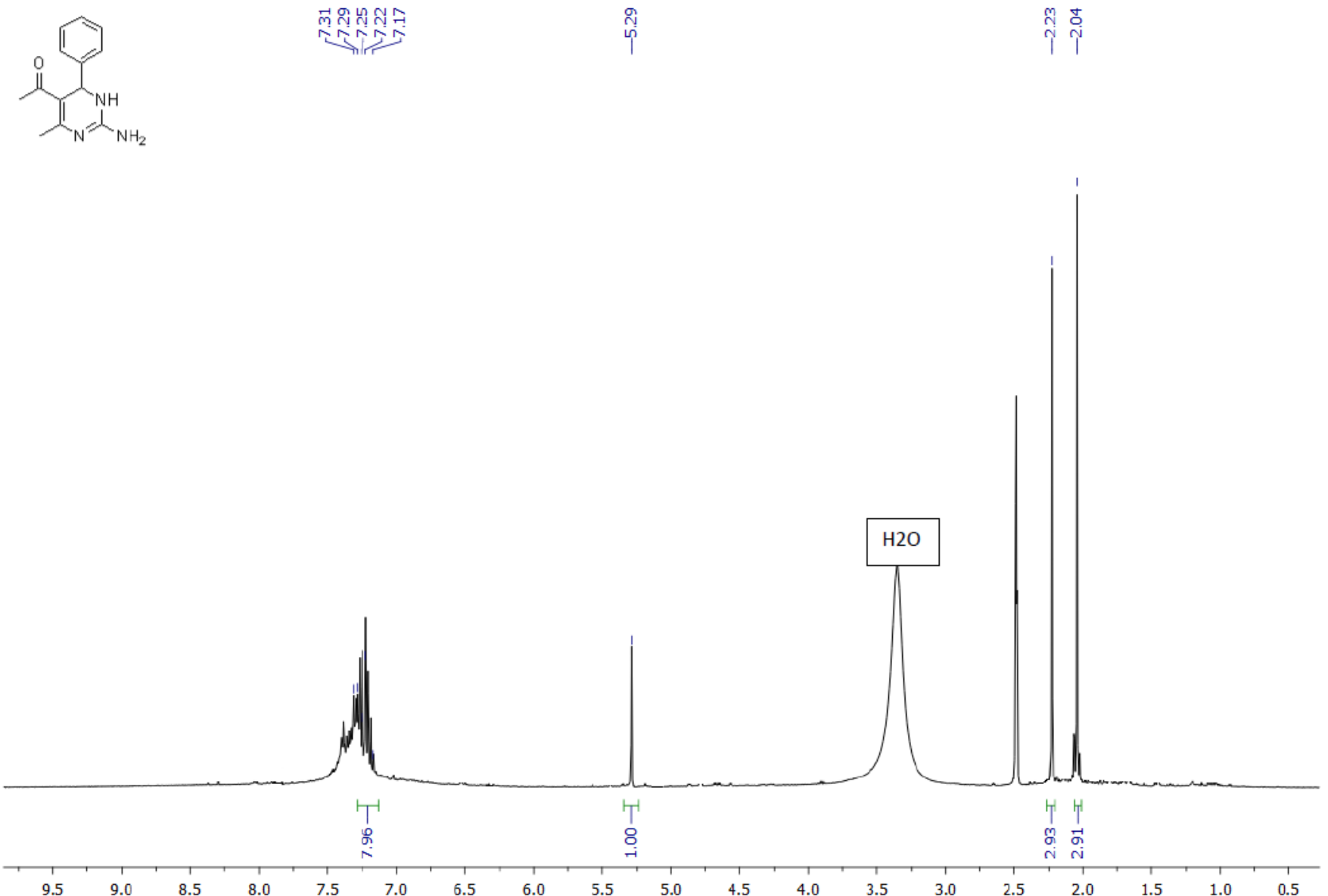
O
N
H
NH
N
NH2

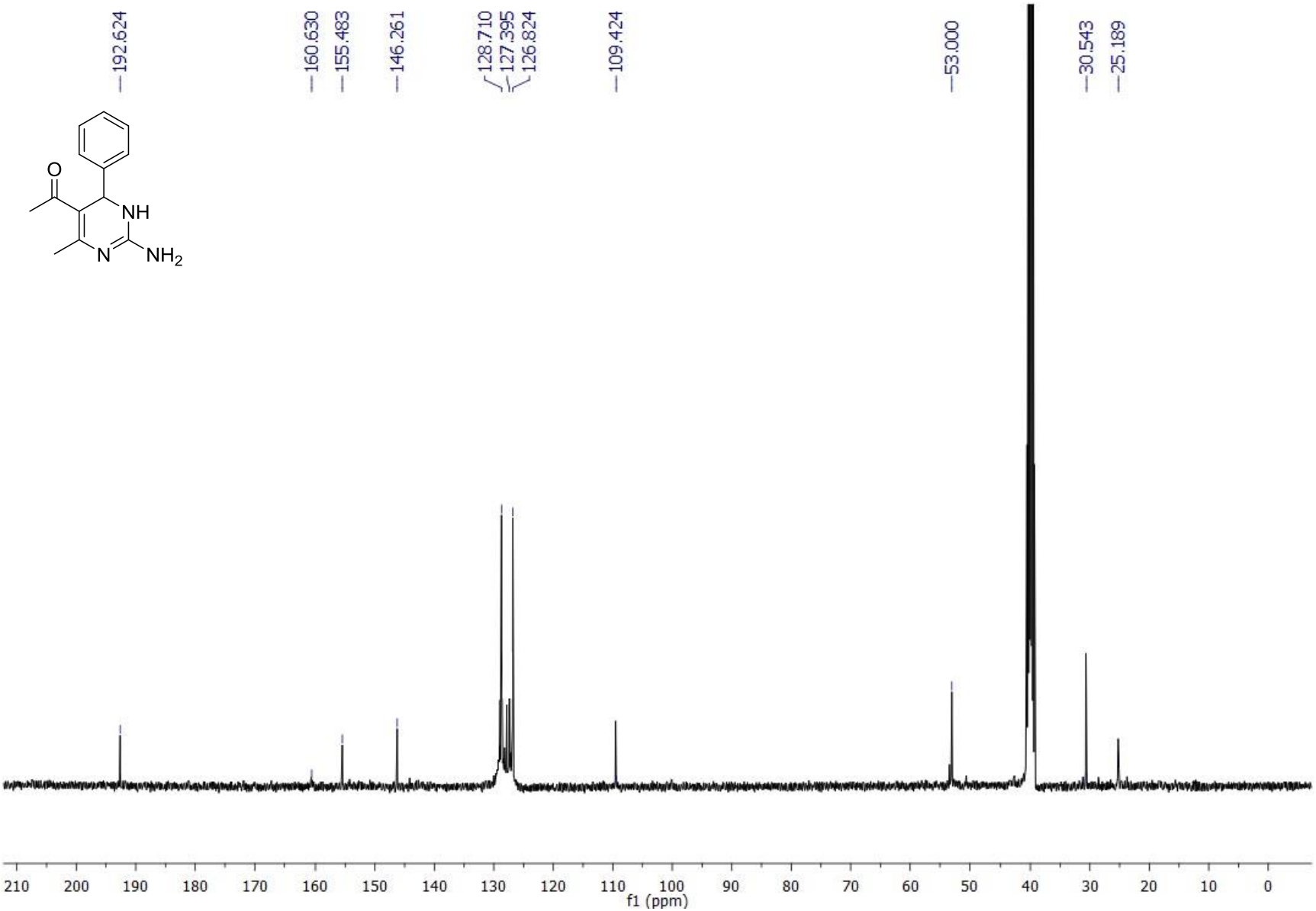

7.28
7.22
7.20
5.31
3.10
3.09
3.07
3.05
3.03
3.01
3.00
2.02
2.02
1.38
1.37
1.35
1.33
0.77
0.75
0.73
5.56
1.00
2.09
3.12
2.21
3.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

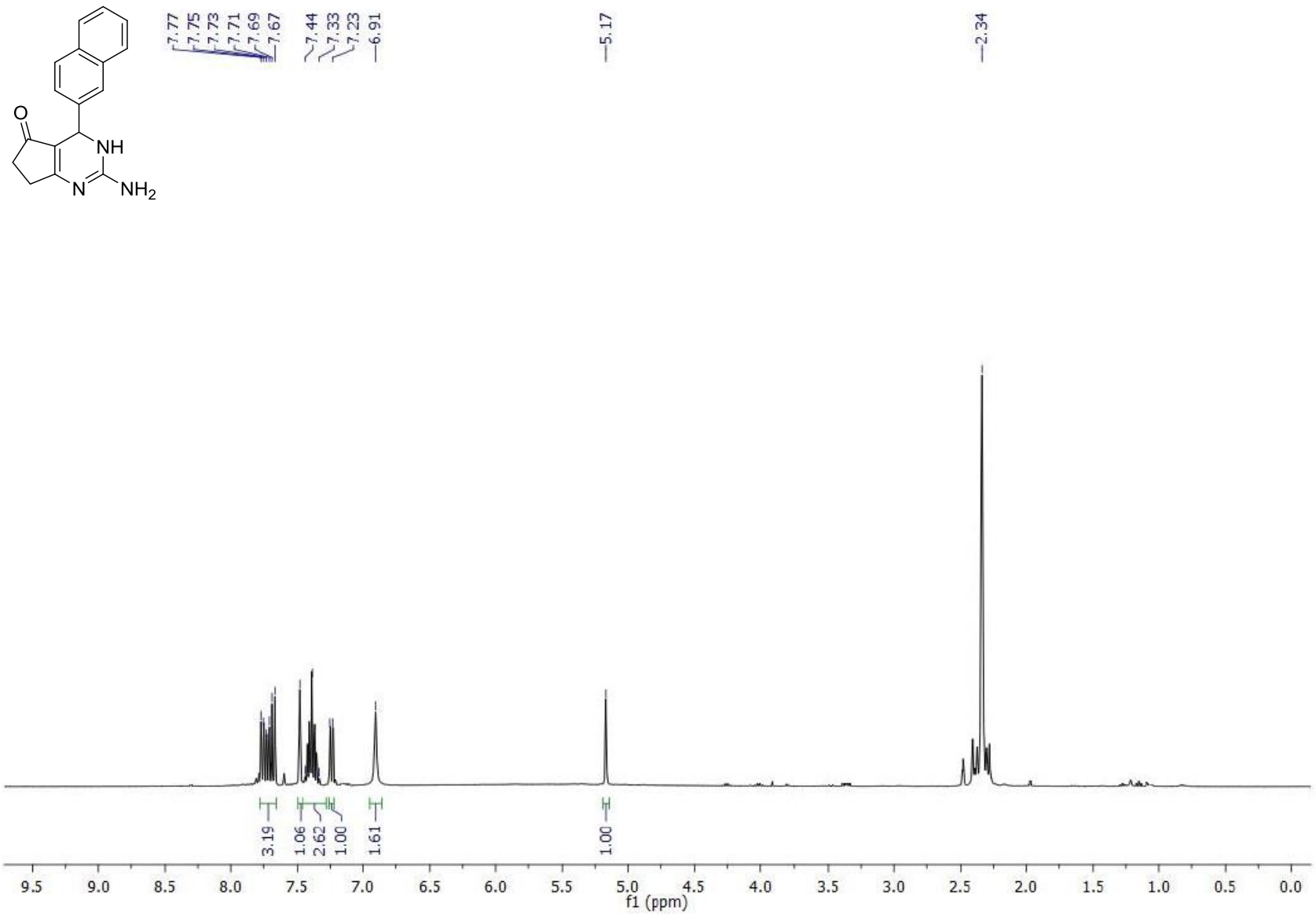

158.57
153.66
144.58
128.20
127.24
126.37
105.79
55.26
40.84
22.17
19.17
10.32
O
N
H
NH
N
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

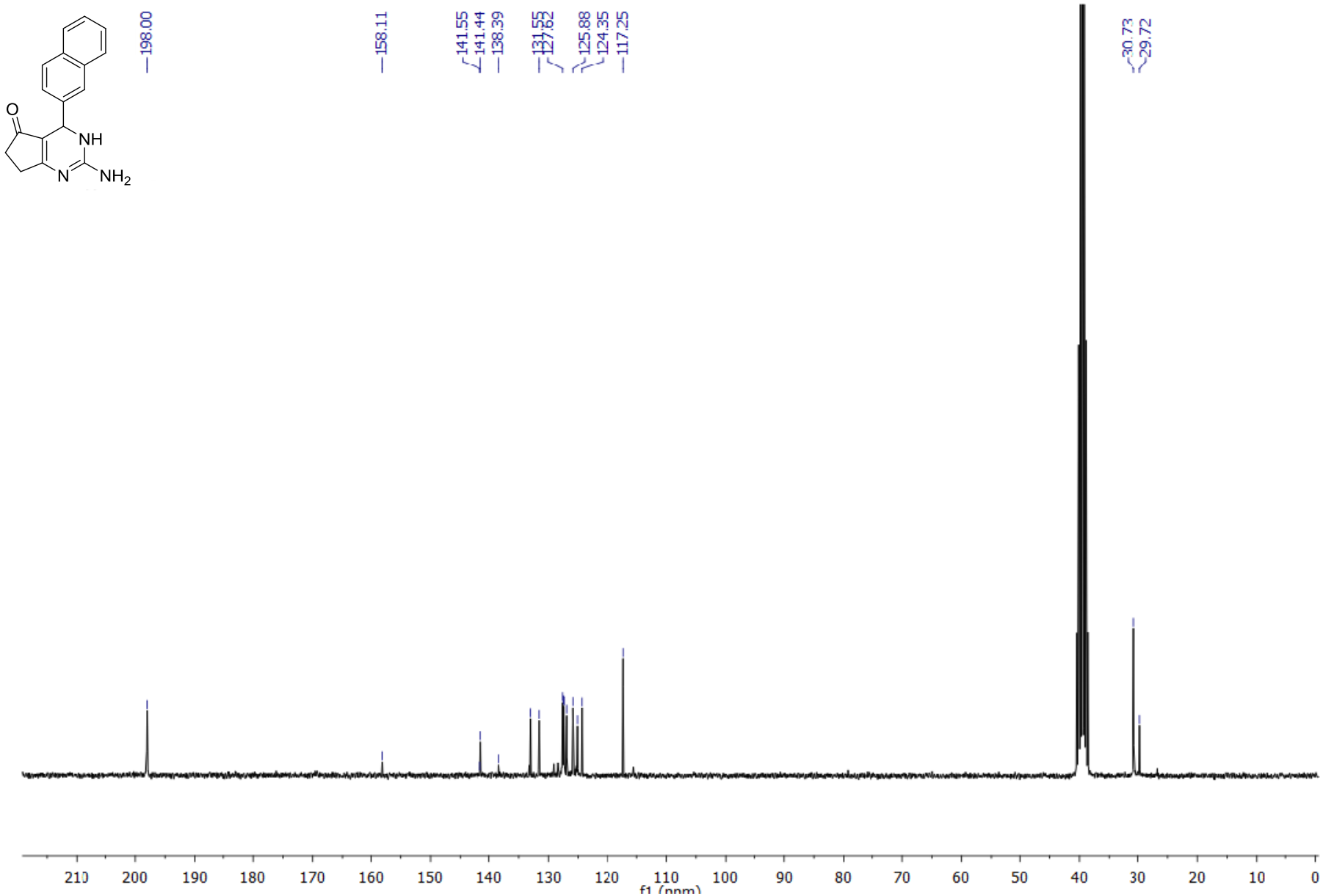

7.38
7.36
7.34
7.30
7.29
7.29
7.27
5.29
3.19
3.00
1.43
1.21
O
N
NH
N
NH2
5.52
1.00
3.46
3.05
5.97
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

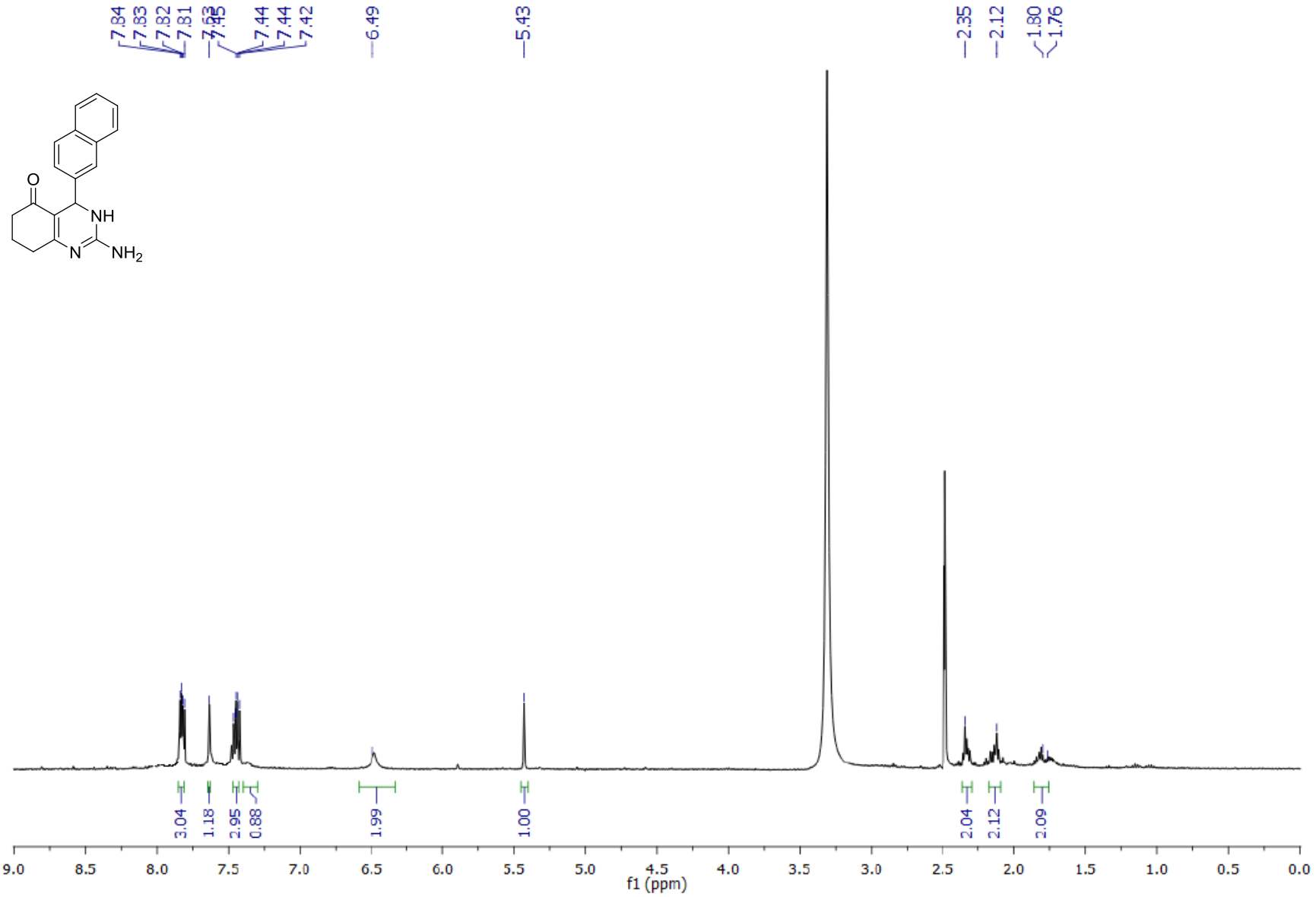

169.98
153.89
144.78
137.51
128.41
127.44
126.16
104.29
56.69
42.43
25.25
23.78
18.15
O
N
NH
N
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

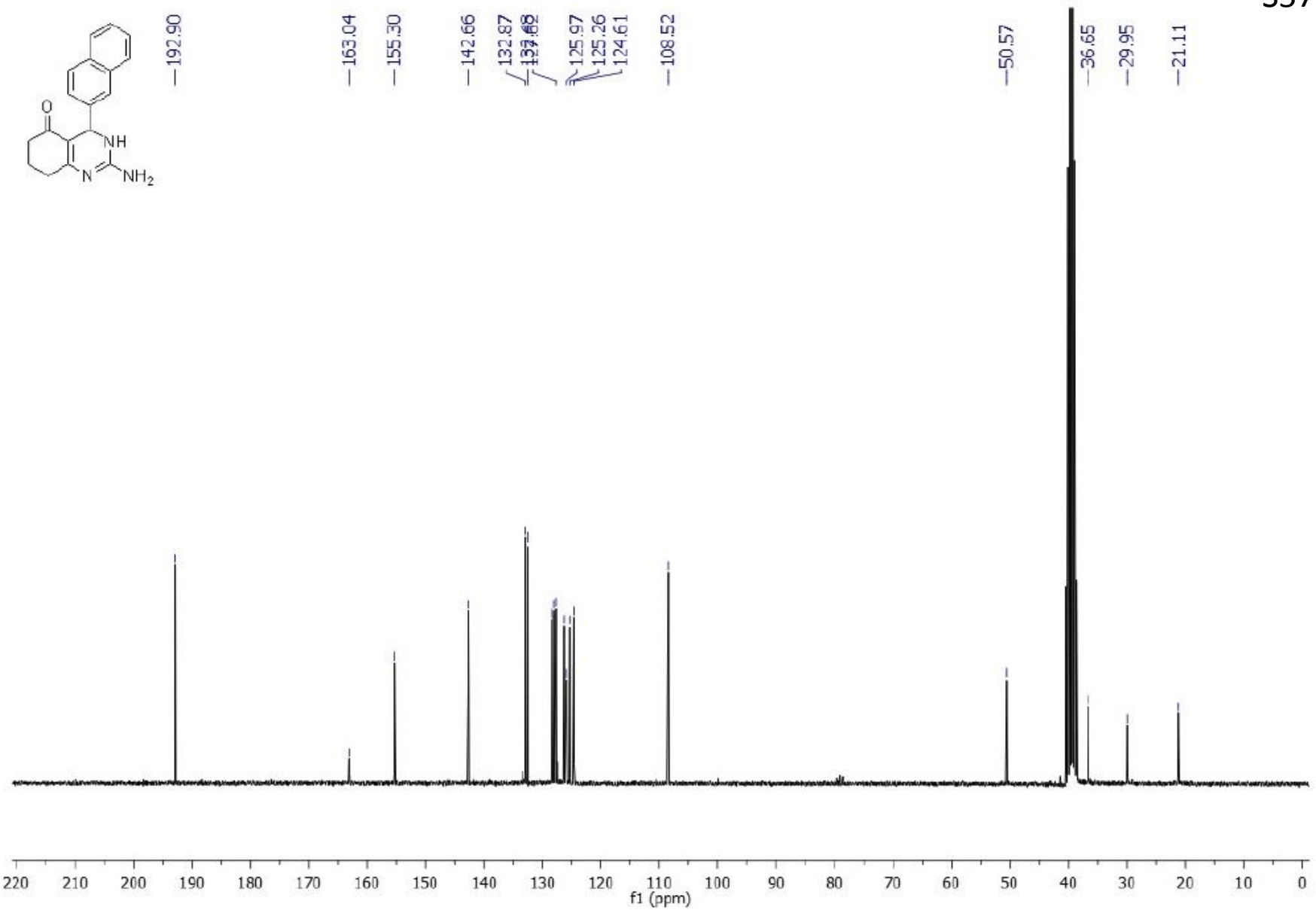

O
NH
N
NH2
7.31
7.29
7.25
7.22
7.17
5.29
2.23
2.04
H2O
7.96
1.00
2.93
2.91
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


192.624
160.630
155.483
146.261
128.710
127.395
126.824
109.424
53.000
30.543
25.189
O
NH
N
NH2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

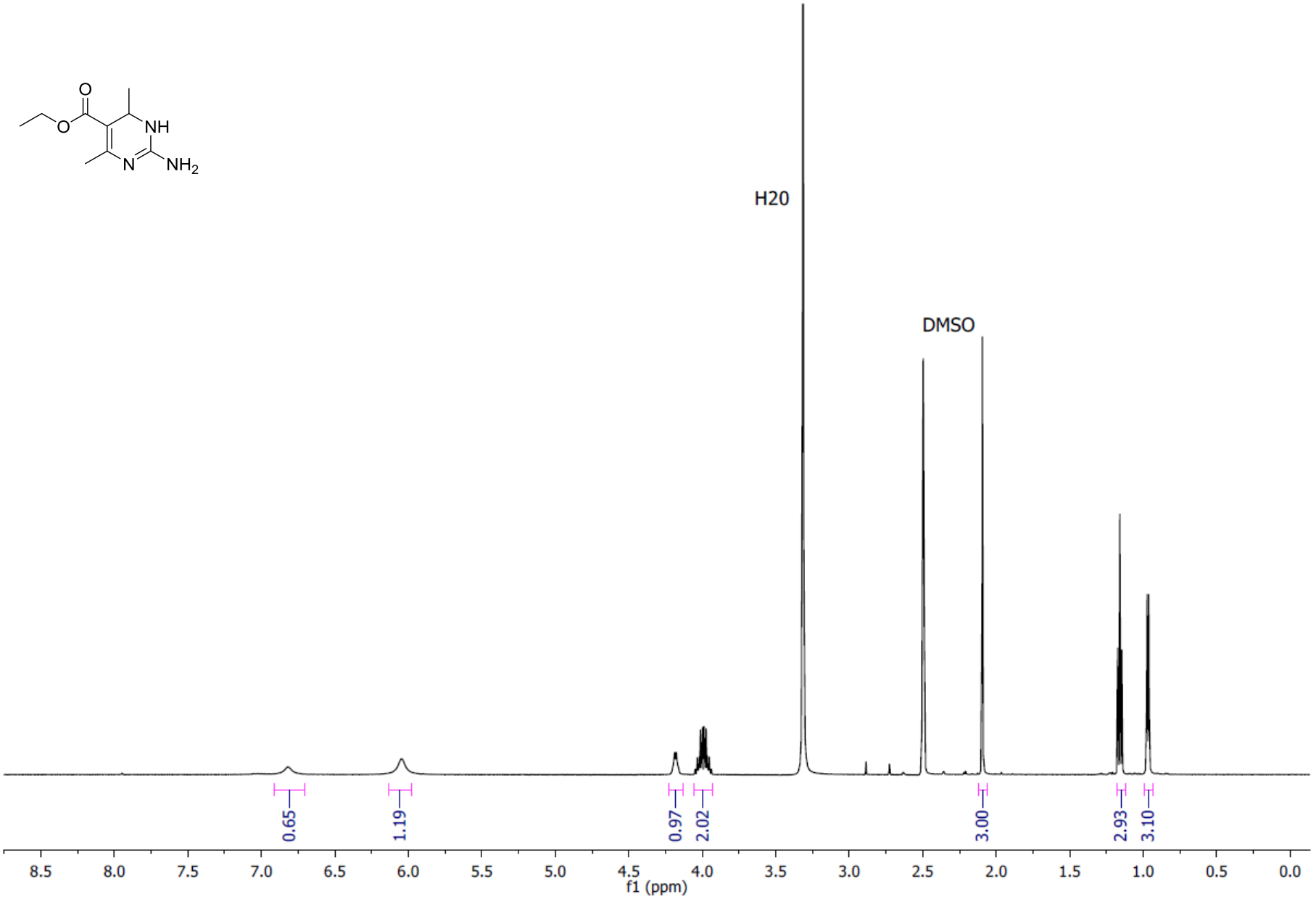

7.77
7.75
7.73
7.71
7.69
7.67
7.44
7.33
7.23
6.91
5.17
2.34
O
NH
N
NH2
3.19
1.06
2.62
1.00
1.61
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

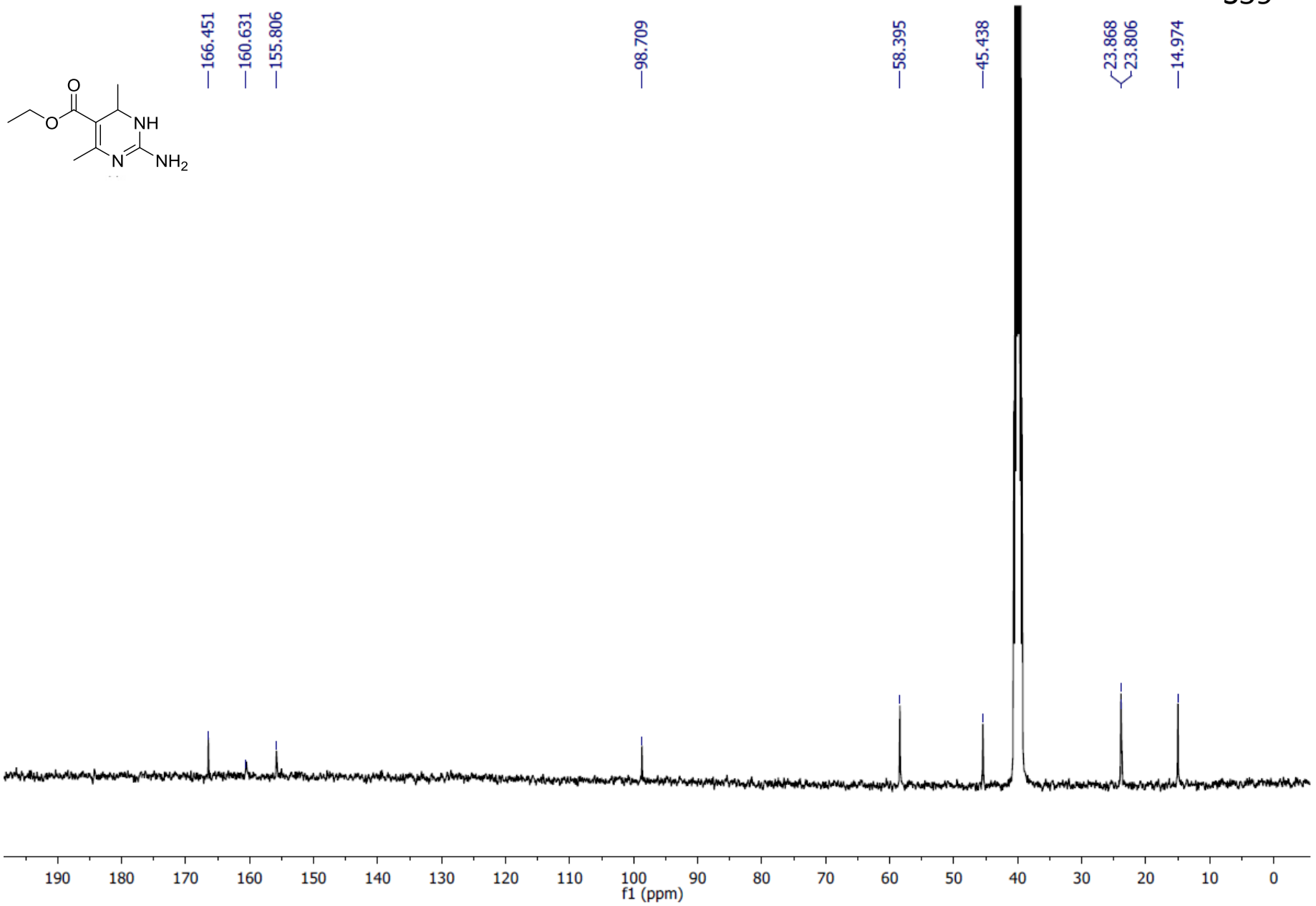

198.00
158.11
141.55
141.44
138.39
131.55
127.82
125.88
124.35
117.25
30.73
29.72
O
NH
N
NH2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

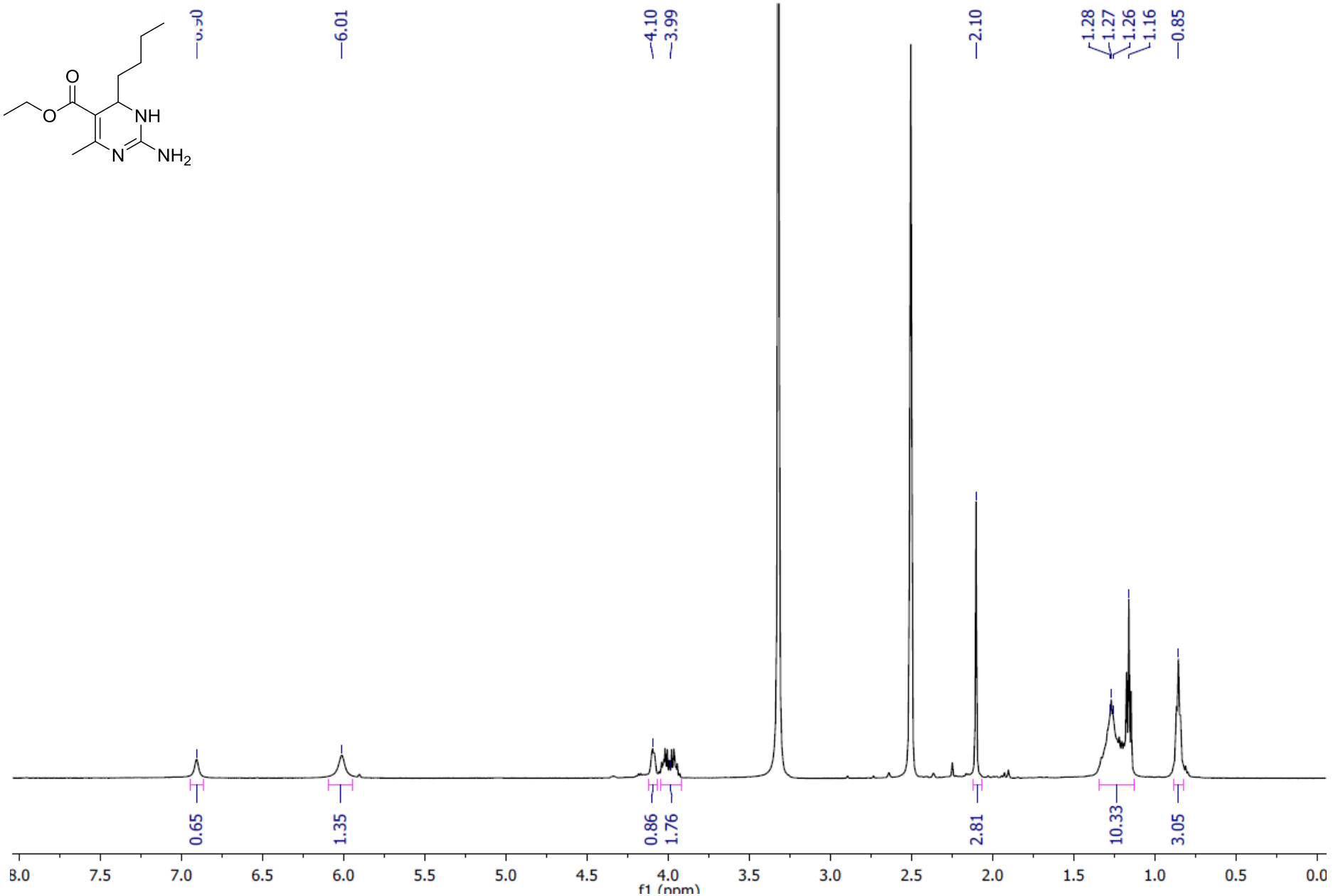

7.84
7.83
7.82
7.81
7.63
7.45
7.44
7.44
7.42
6.49
5.43
2.35
2.12
1.80
1.76
O
NH
N
NH2
3.04
1.18
2.95
0.88
1.99
1.00
2.04
2.12
2.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

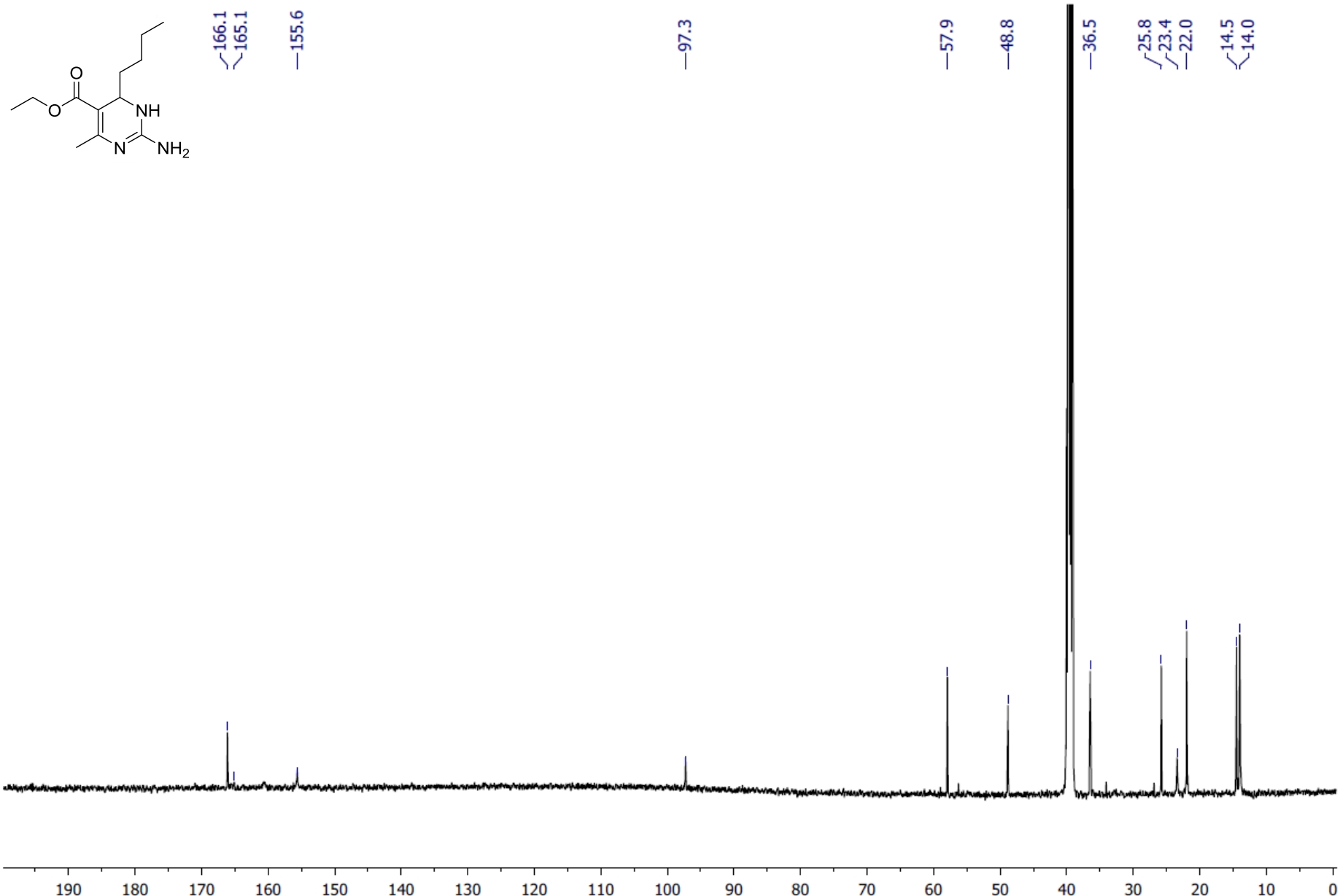

192.90
163.04
155.30
142.66
132.87
125.97
125.26
124.61
108.52
50.57
36.65
29.95
21.11
O
NH
N
NH2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

O
O
NH
N
NH2

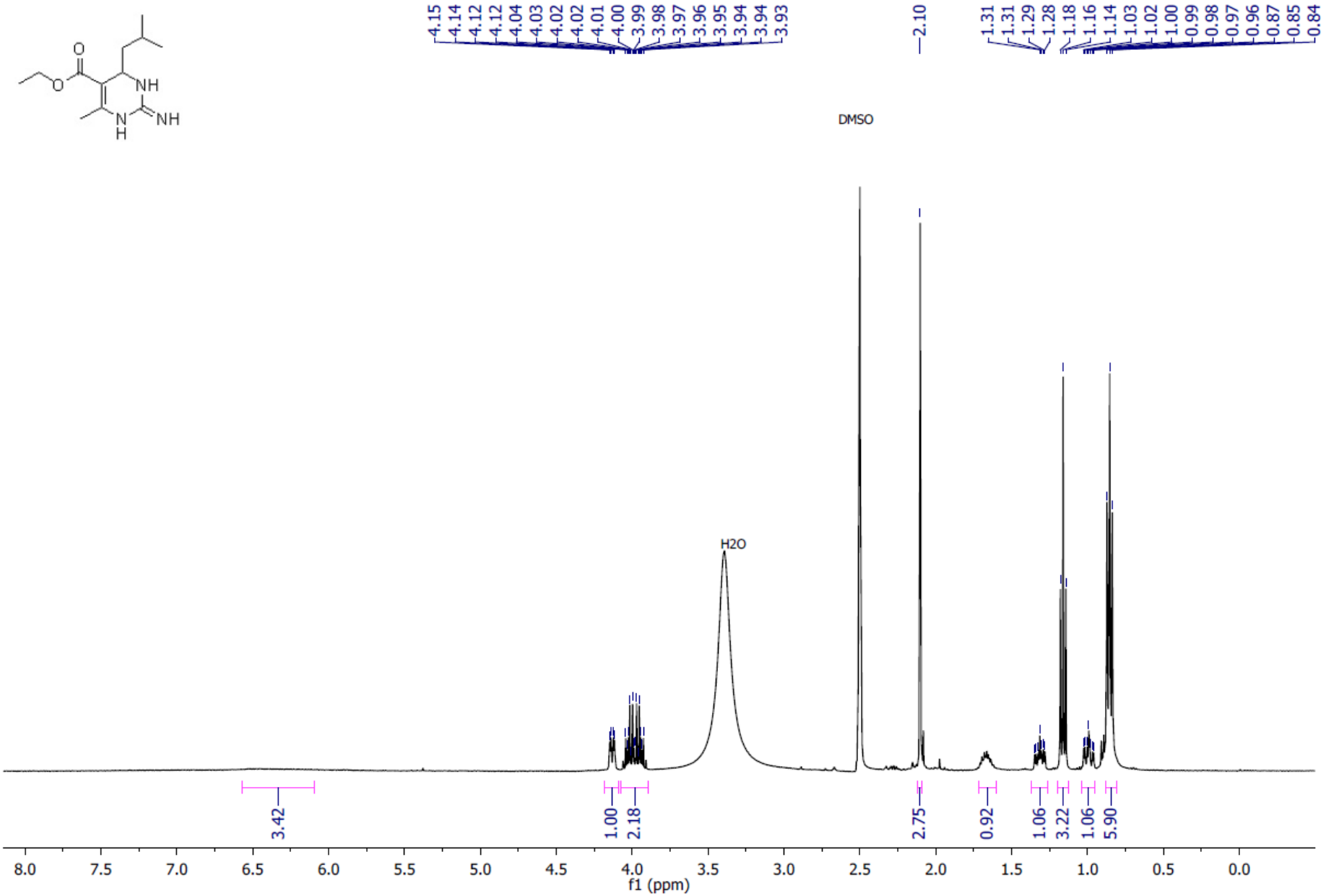

H20
DMSO
0.65
1.19
0.97
2.02
3.00
2.93
3.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

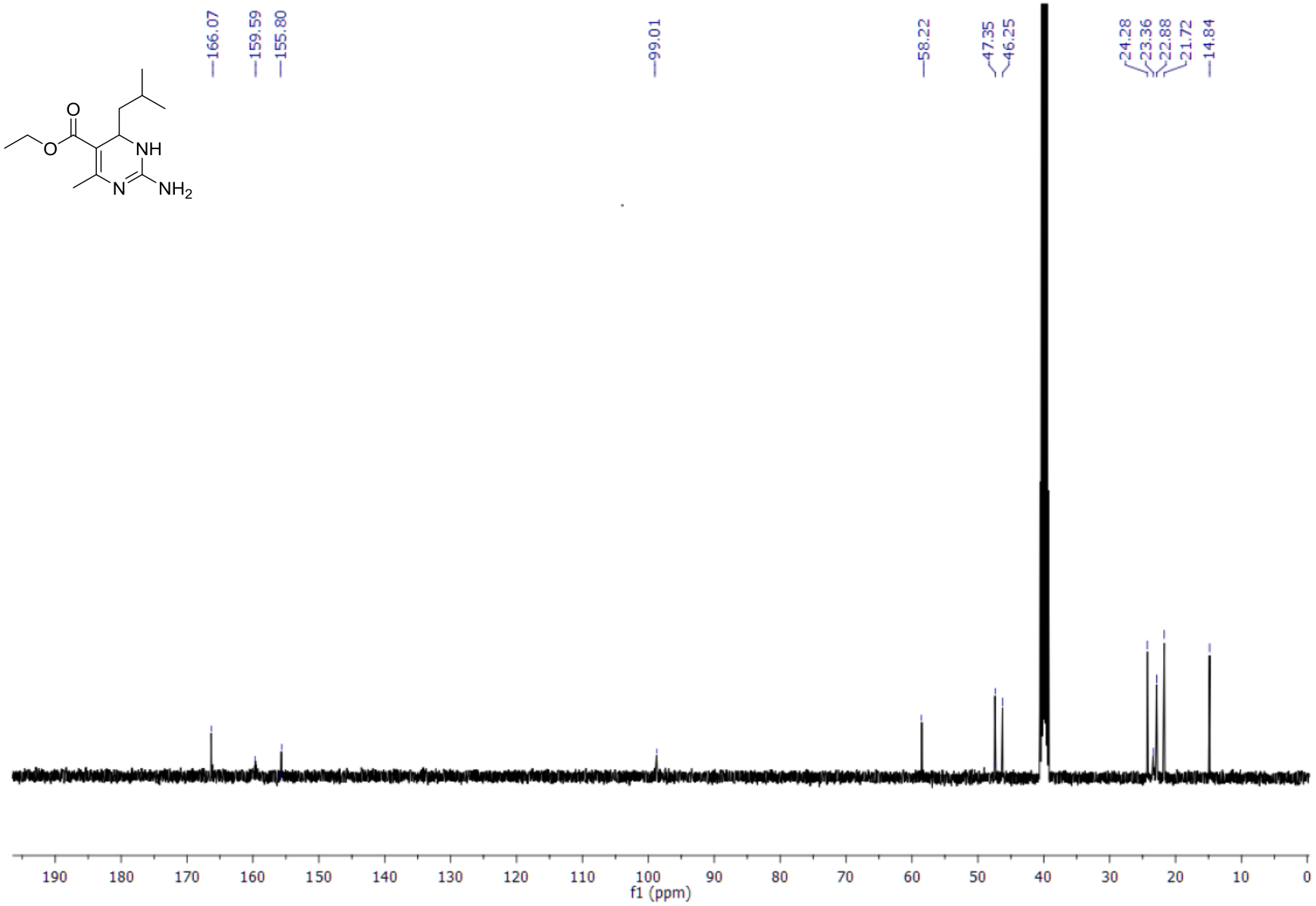

166.451
160.631
155.806
98.709
58.395
45.438
23.868
23.806
14.974
O
O
NH
N
NH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

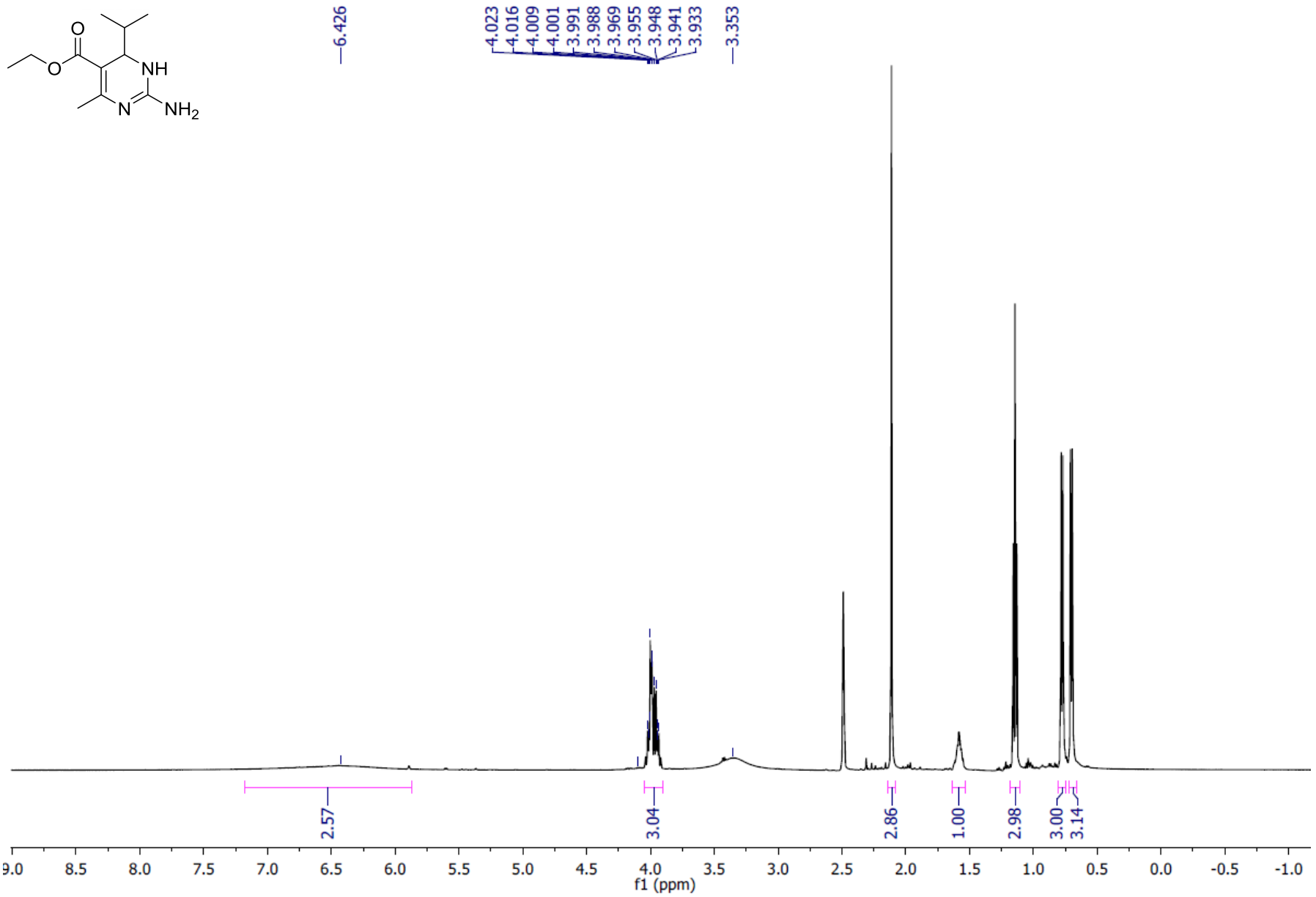

6.01
4.10
3.99
2.10
1.28
1.27
1.26
1.16
0.85
0.65
1.35
0.86
1.76
2.81
10.33
3.05
f1 (ppm)

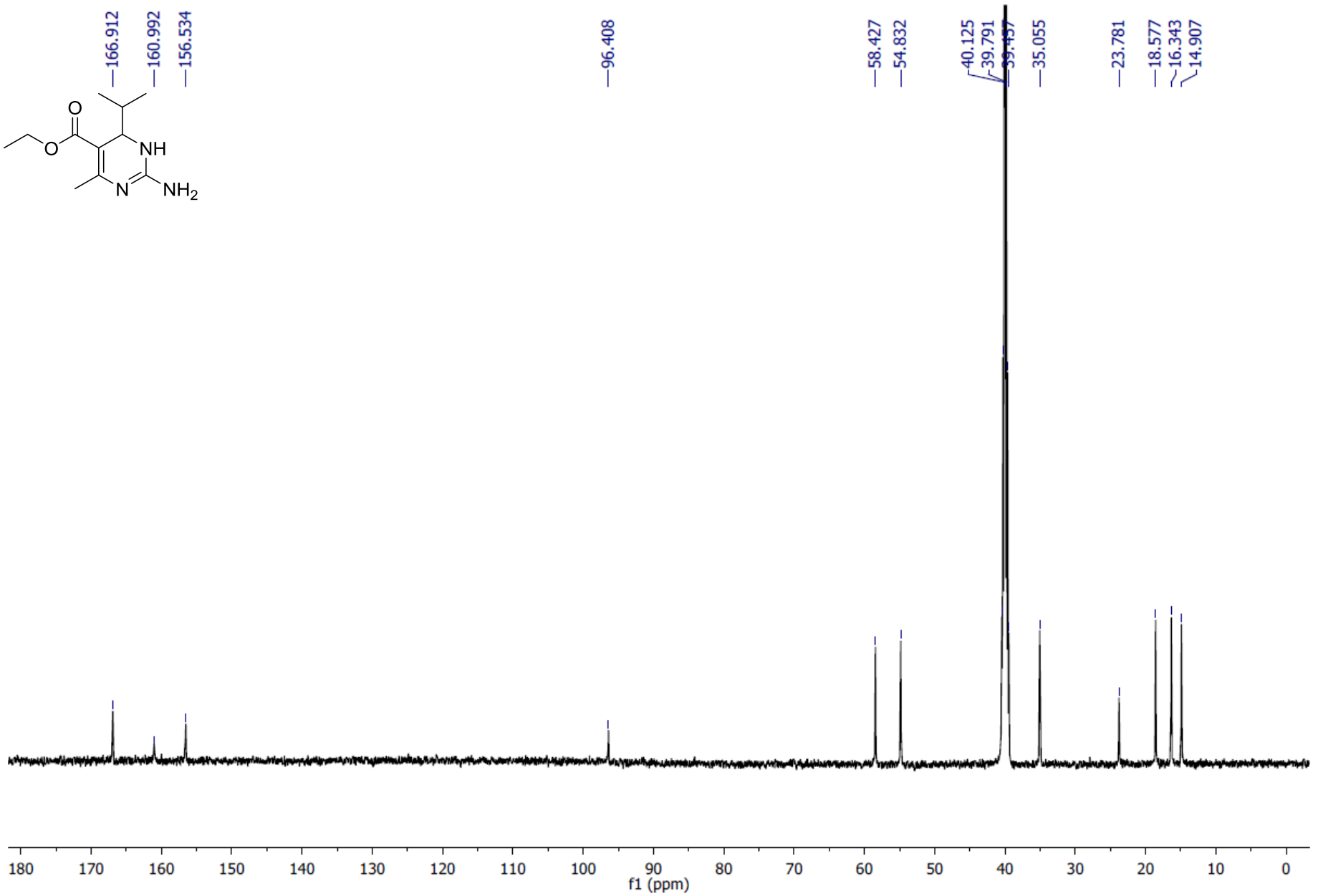

166.1
165.1
155.6
97.3
57.9
48.8
36.5
25.8
23.4
22.0
14.5
14.0
O
O
NH
N
NH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

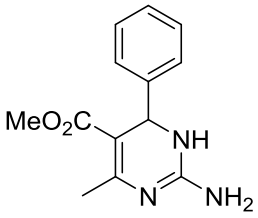
O
O
NH
N
H
NH

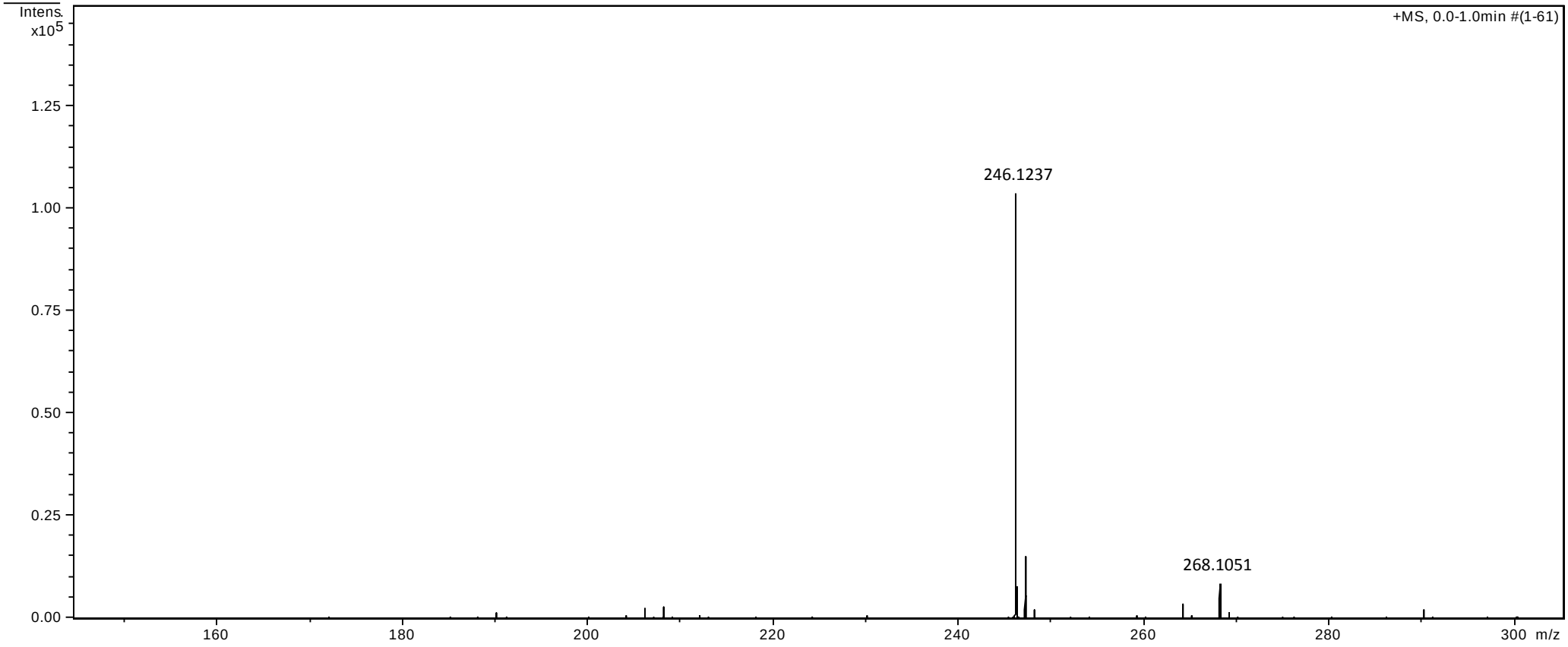

4.15
4.14
4.12
4.12
4.04
4.03
4.02
4.02
4.01
4.00
3.99
3.98
3.97
3.96
3.95
3.94
3.94
3.93
2.10
1.31
1.31
1.29
1.28
1.18
1.16
1.14
1.03
1.02
1.00
0.99
0.98
0.97
0.96
0.87
0.85
0.84
DMSO
H2O
3.42
1.00
2.18
2.75
0.92
1.06
3.22
1.06
5.90
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

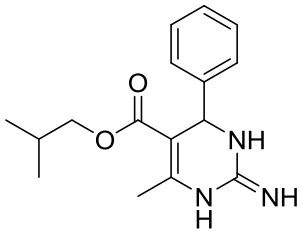

166.07
159.59
155.80
99.01
58.22
47.35
46.25
24.28
23.36
22.88
21.72
14.84
O
O
NH
N
NH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

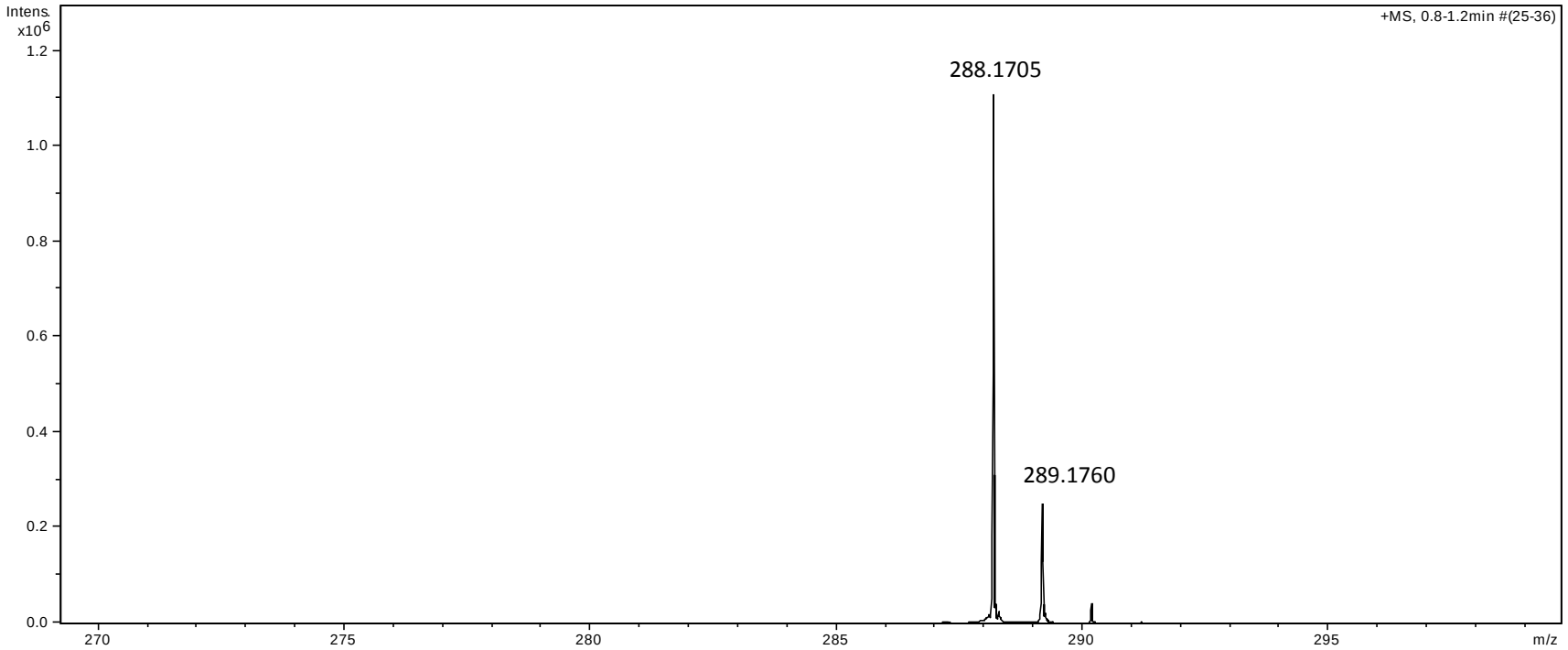

6.426
4.023
4.016
4.009
4.001
3.991
3.988
3.969
3.955
3.948
3.941
3.933
3.353
2.57
3.04
2.86
1.00
2.98
3.00
3.14
f1 (ppm)

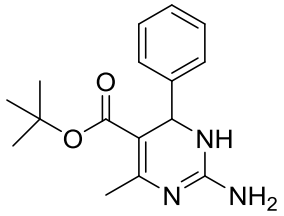

166.912
160.992
156.534
96.408
58.427
54.832
40.125
39.791
39.457
35.055
23.781
18.577
16.343
14.907
O
O
NH
N
NH2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

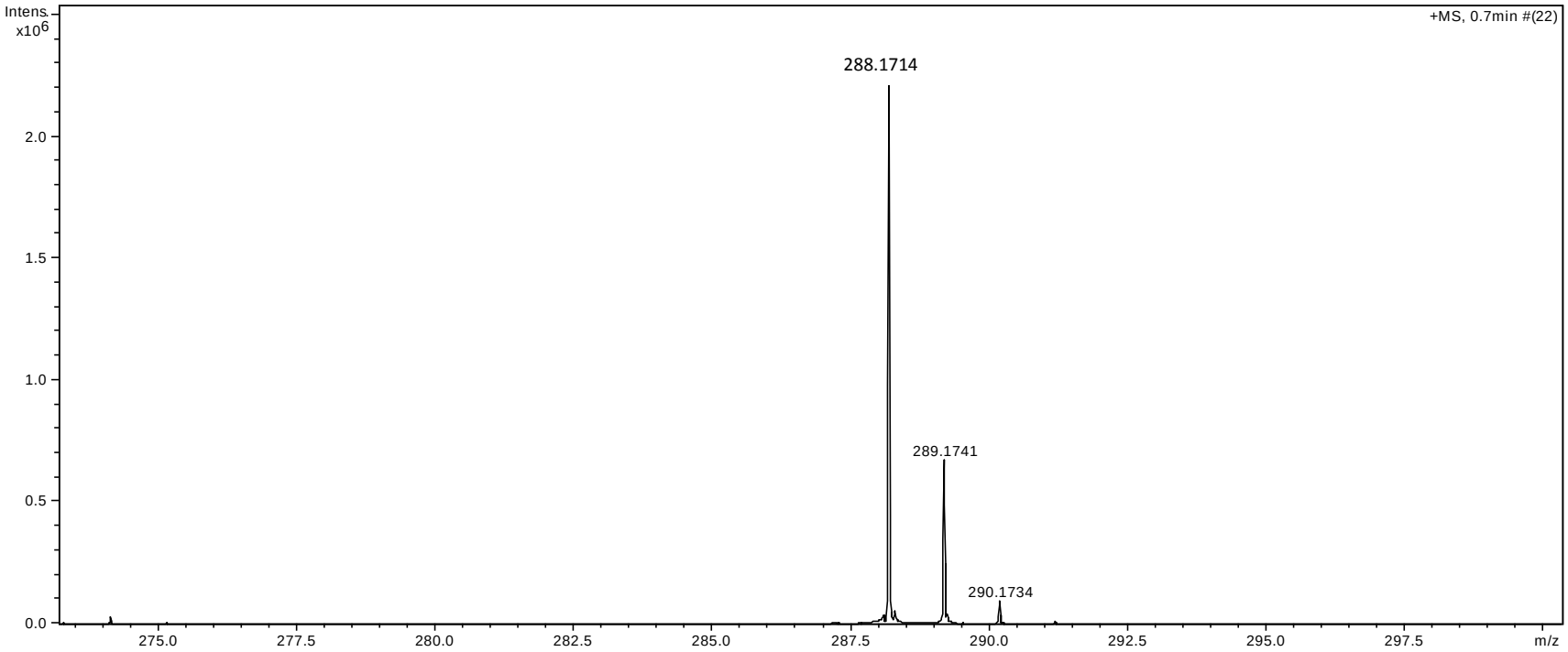

MeO2C
NH
N
NH2

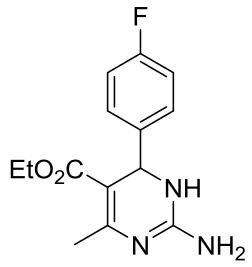

Intens.
x10^5
1.25
1.00
0.75
0.50
0.25
0.00
+MS, 0.0-1.0min #(1-61)
246.1237
268.1051
160
180
200
220
240
260
280
300
m/z

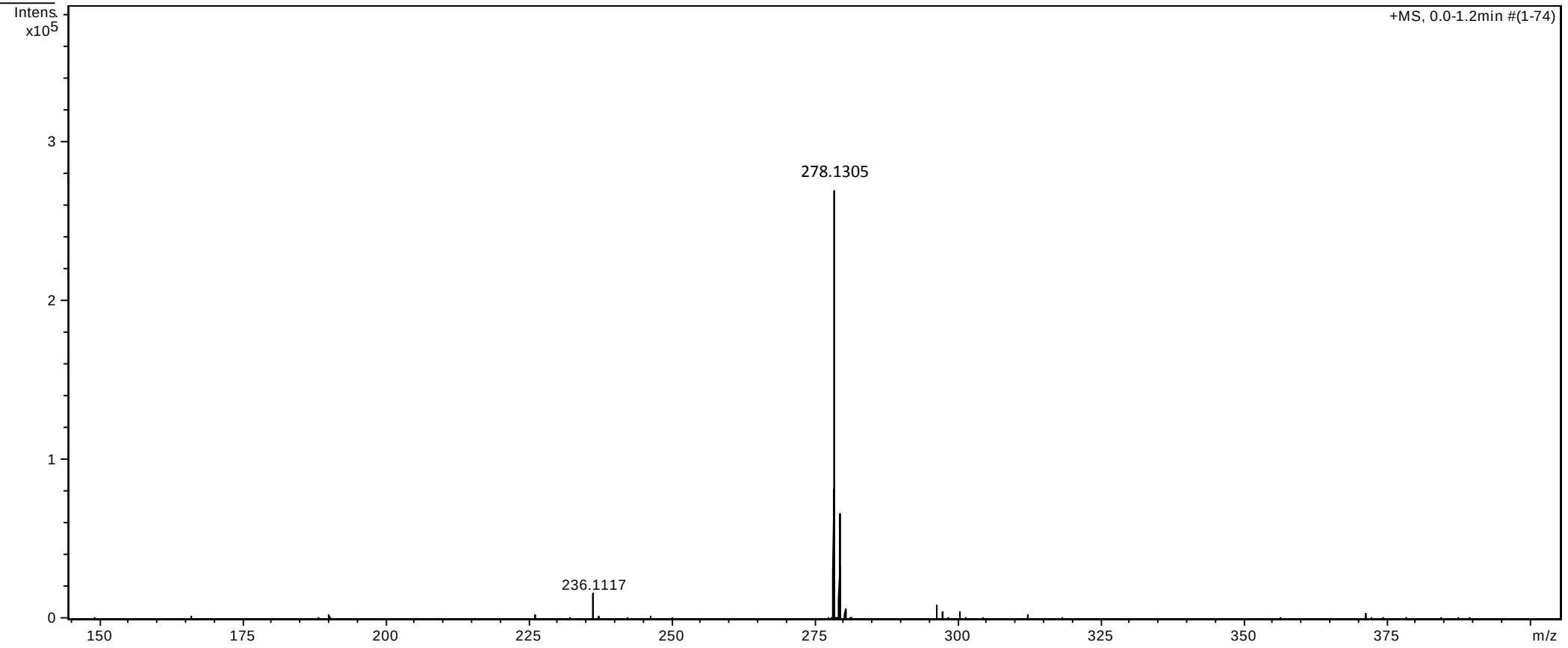

O
O
NH
N
H
NH

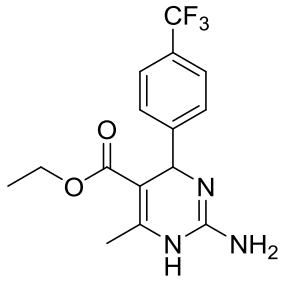

Intens.
x10^6
1.2
1.0
0.8
0.6
0.4
0.2
0.0
+MS, 0.8-1.2min #(25-36)
288.1705
289.1760
270
275
280
285
290
295
m/z

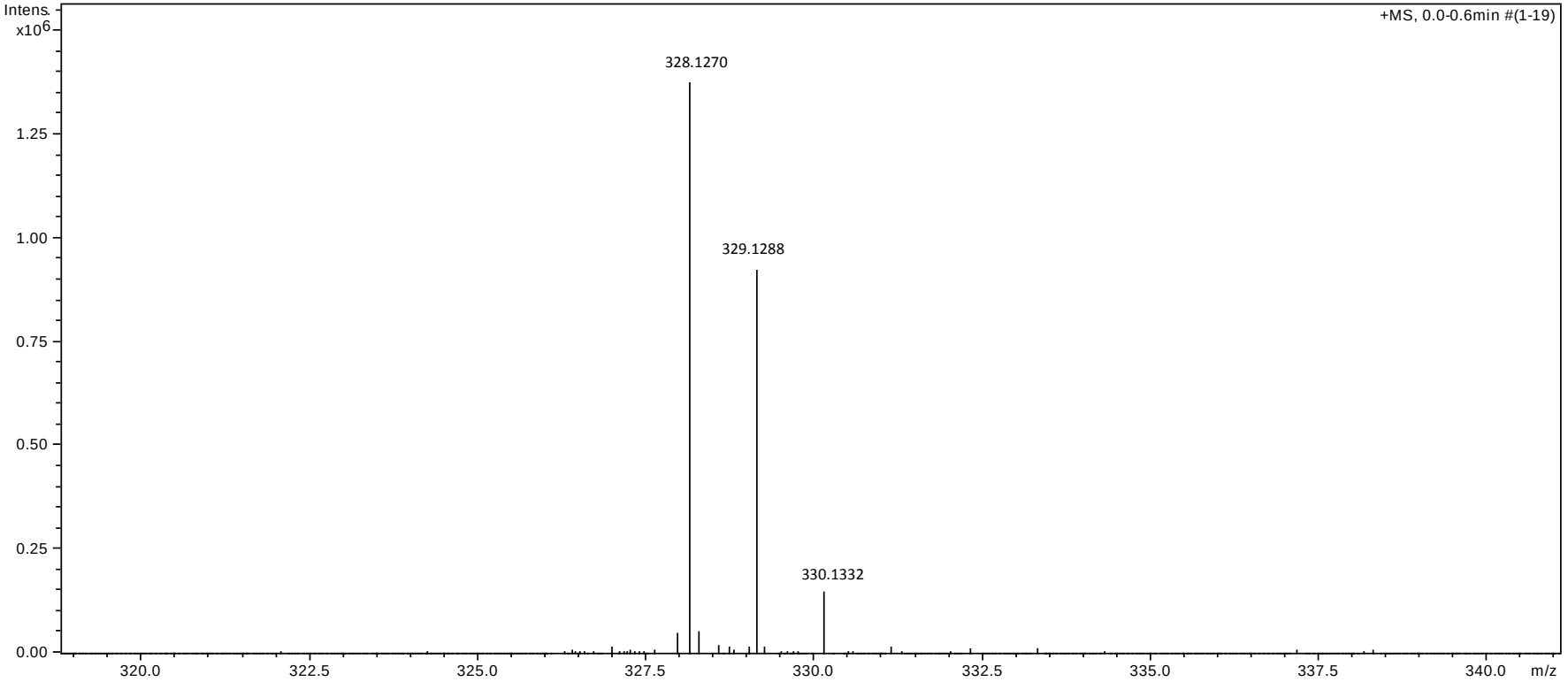

O
O
NH
N
NH2

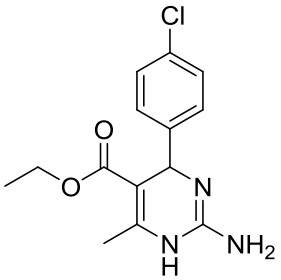

Intens.
x10^6
+MS, 0.7min #(22)
288.1714
289.1741
290.1734
2.0
1.5
1.0
0.5
0.0
275.0
277.5
280.0
282.5
285.0
287.5
290.0
292.5
295.0
297.5
m/z

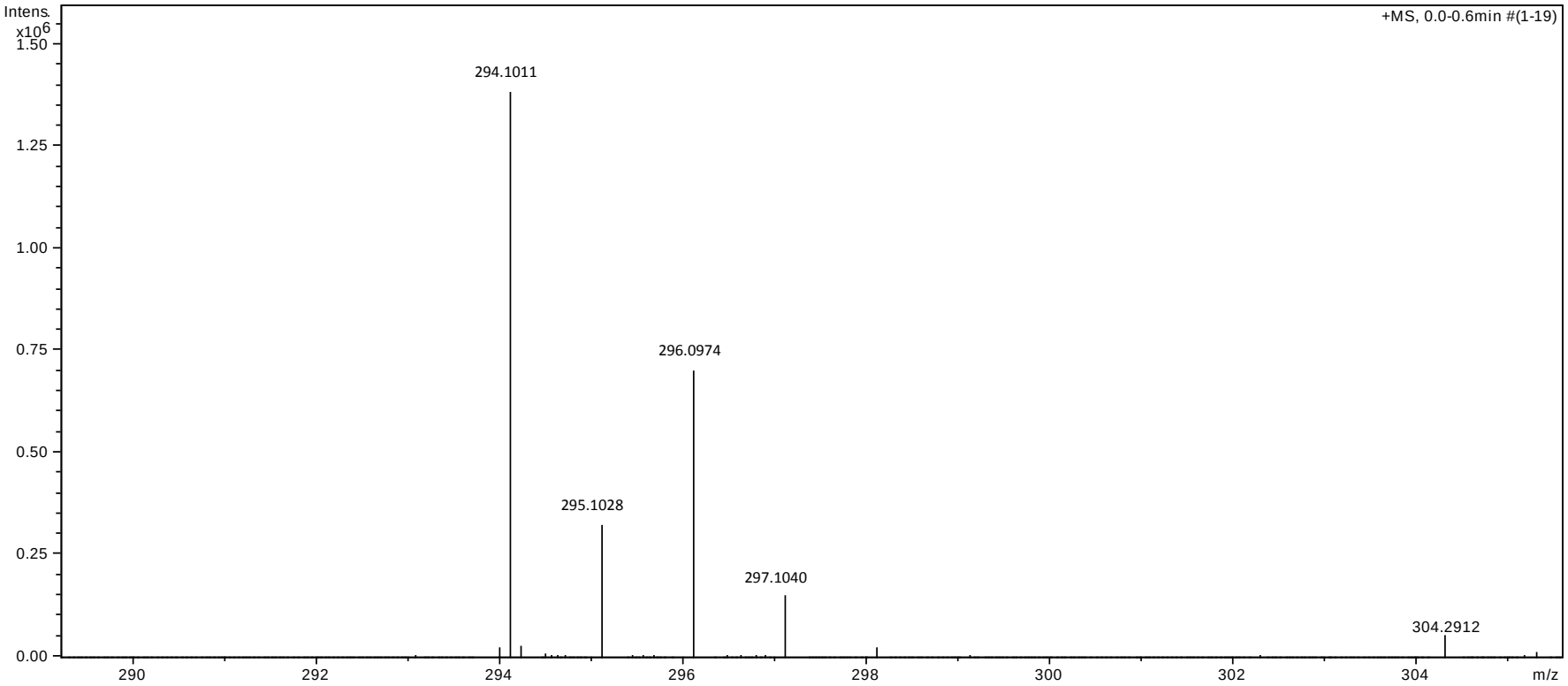

F
EtO2C
NH
N
NH2

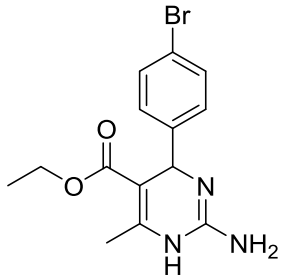

Intens.
x10^5
+MS, 0.0-1.2min #(1-74)
278.1305
236.1117
0
1
2
3
150
175
200
225
250
275
300
325
350
375
m/z

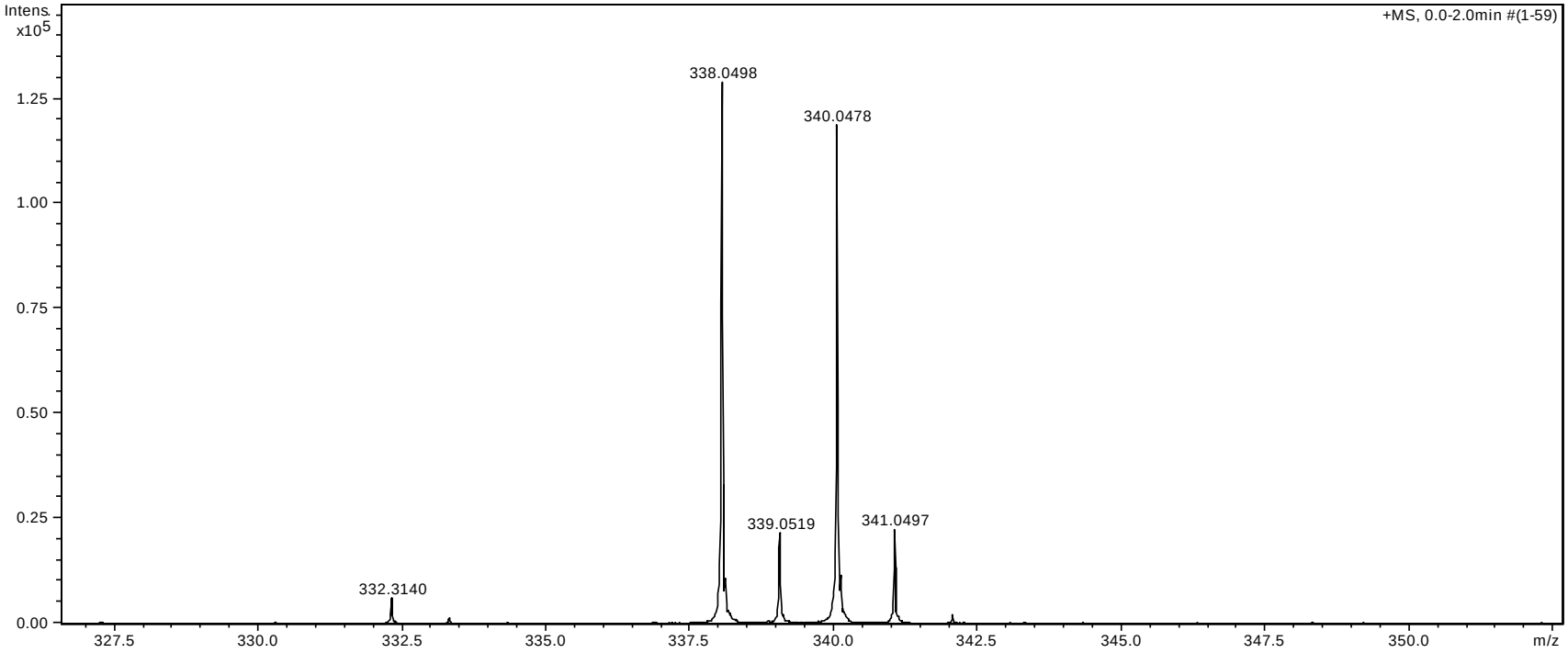

CF3
O
O
N
N
H
NH2

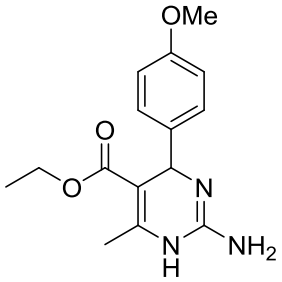

Intens.
x10^6
+MS, 0.0-0.6min #(1-19)
328.1270
329.1288
330.1332
1.25
1.00
0.75
0.50
0.25
0.00
320.0
322.5
325.0
327.5
330.0
332.5
335.0
337.5
340.0
m/z

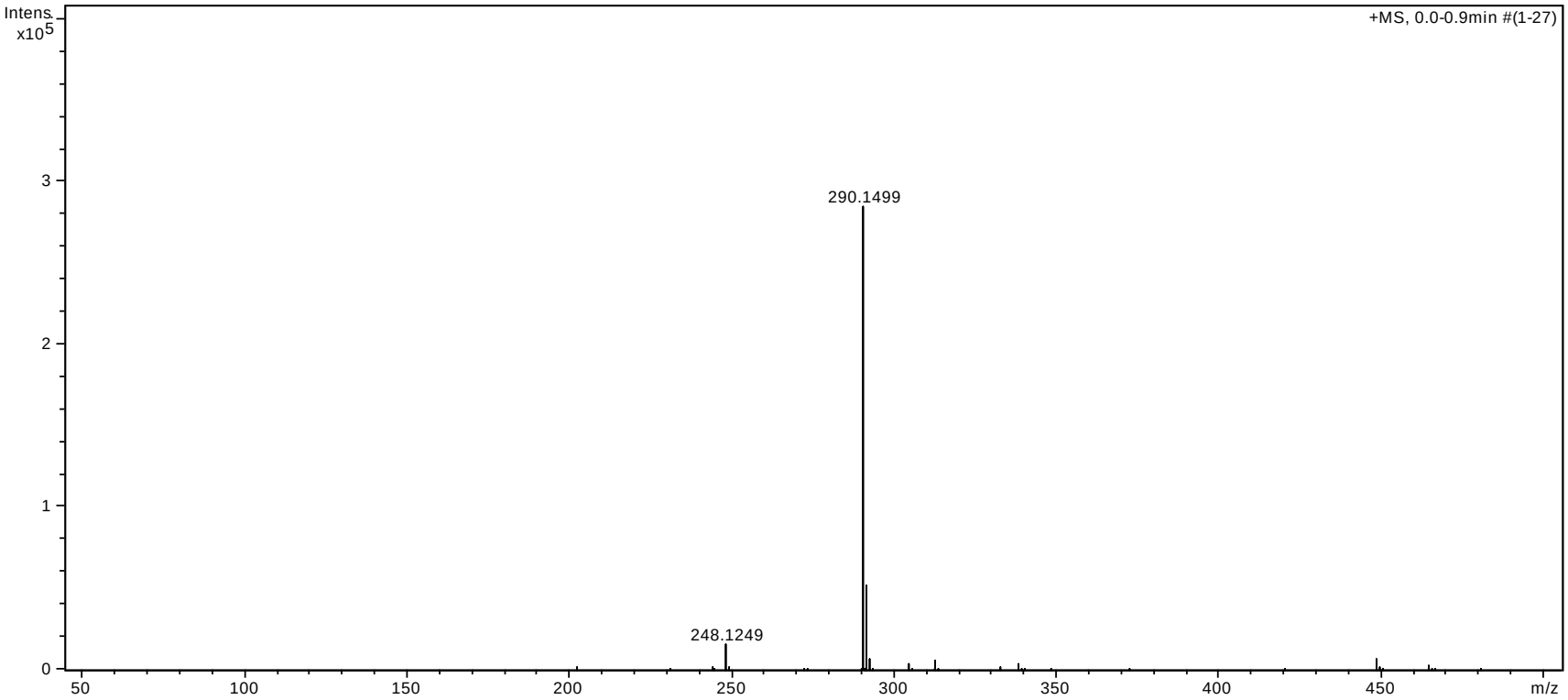

Cl
O
O
N
N
H
NH2

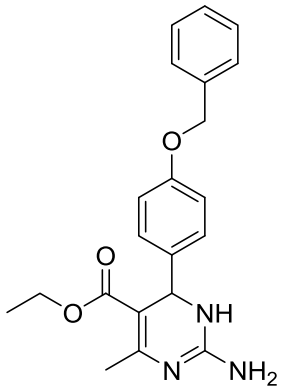

Intens.
x10^6
1.50
1.25
1.00
0.75
0.50
0.25
0.00
+MS, 0.0-0.6min #(1-19)
294.1011
296.0974
295.1028
297.1040
304.2912
290
292
294
296
298
300
302
304
m/z

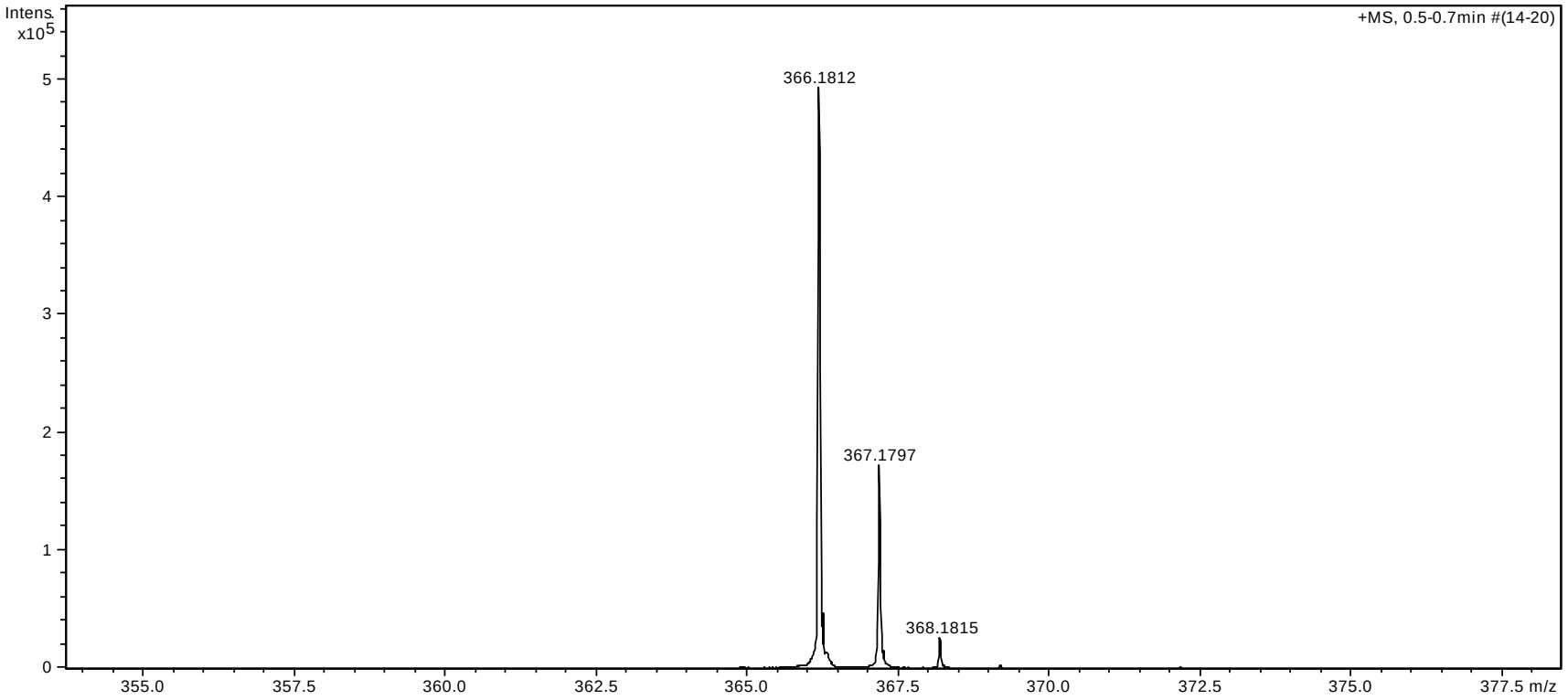

Br
O
O
N
N
H
NH2

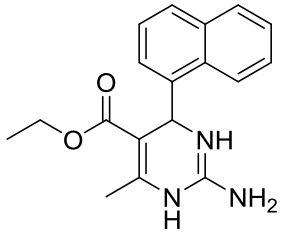

Intens.
x10^5
+MS, 0.0-2.0min #(1-59)
338.0498
340.0478
339.0519
341.0497
332.3140
1.25
1.00
0.75
0.50
0.25
0.00
327.5
330.0
332.5
335.0
337.5
340.0
342.5
345.0
347.5
350.0
m/z

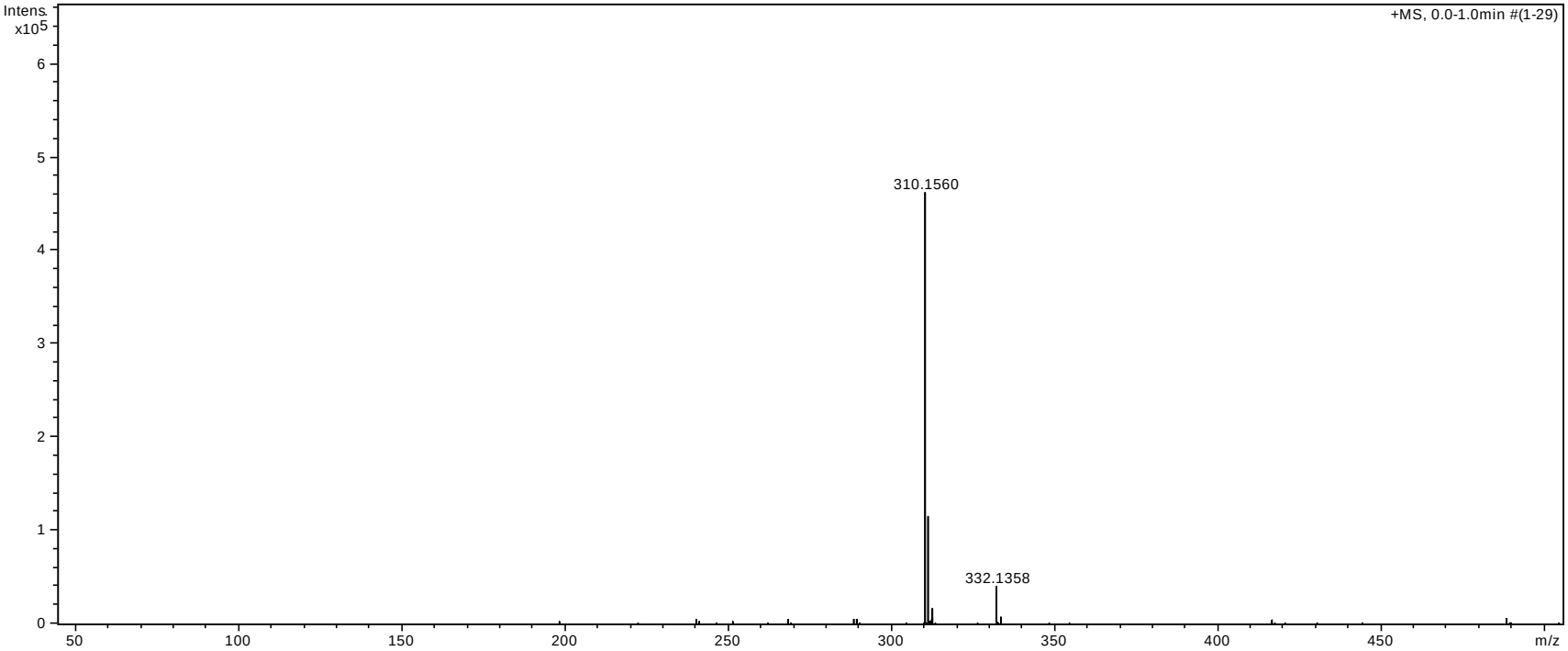

OMe
O
O
N
N
H
NH2

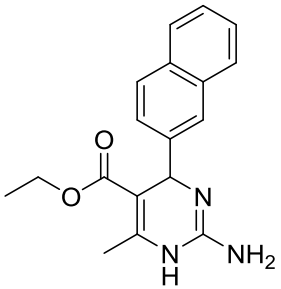

Intens.
x10^5
+MS, 0.0-0.9min #(1-27)
3
2
1
0
290.1499
248.1249
50
100
150
200
250
300
350
400
450
m/z

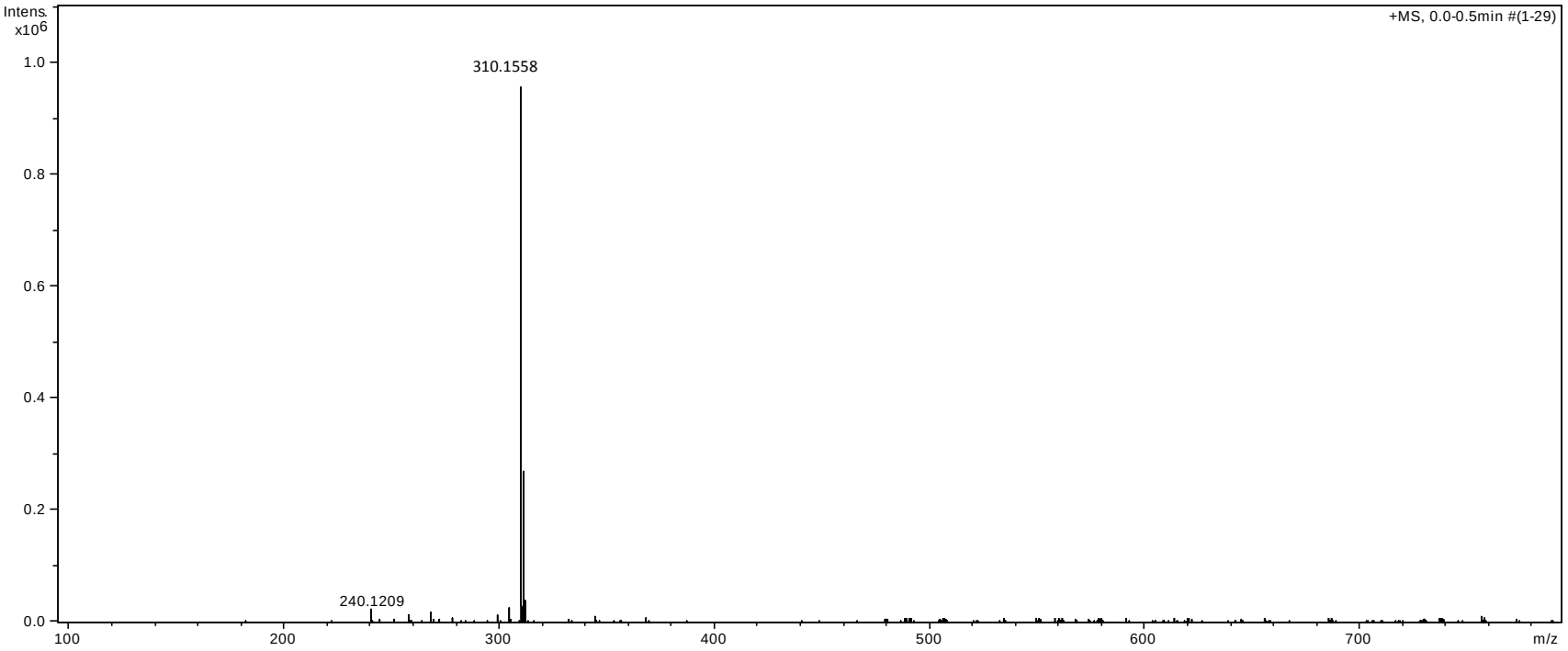

O
O
O
NH
N
NH2

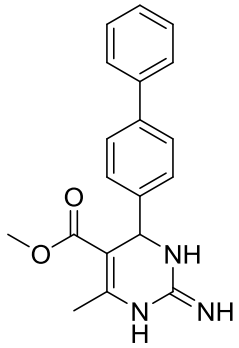

Intens.
x10^5
+MS, 0.5-0.7min #(14-20)
366.1812
367.1797
368.1815
0
1
2
3
4
5
355.0
357.5
360.0
362.5
365.0
367.5
370.0
372.5
375.0
377.5 m/z

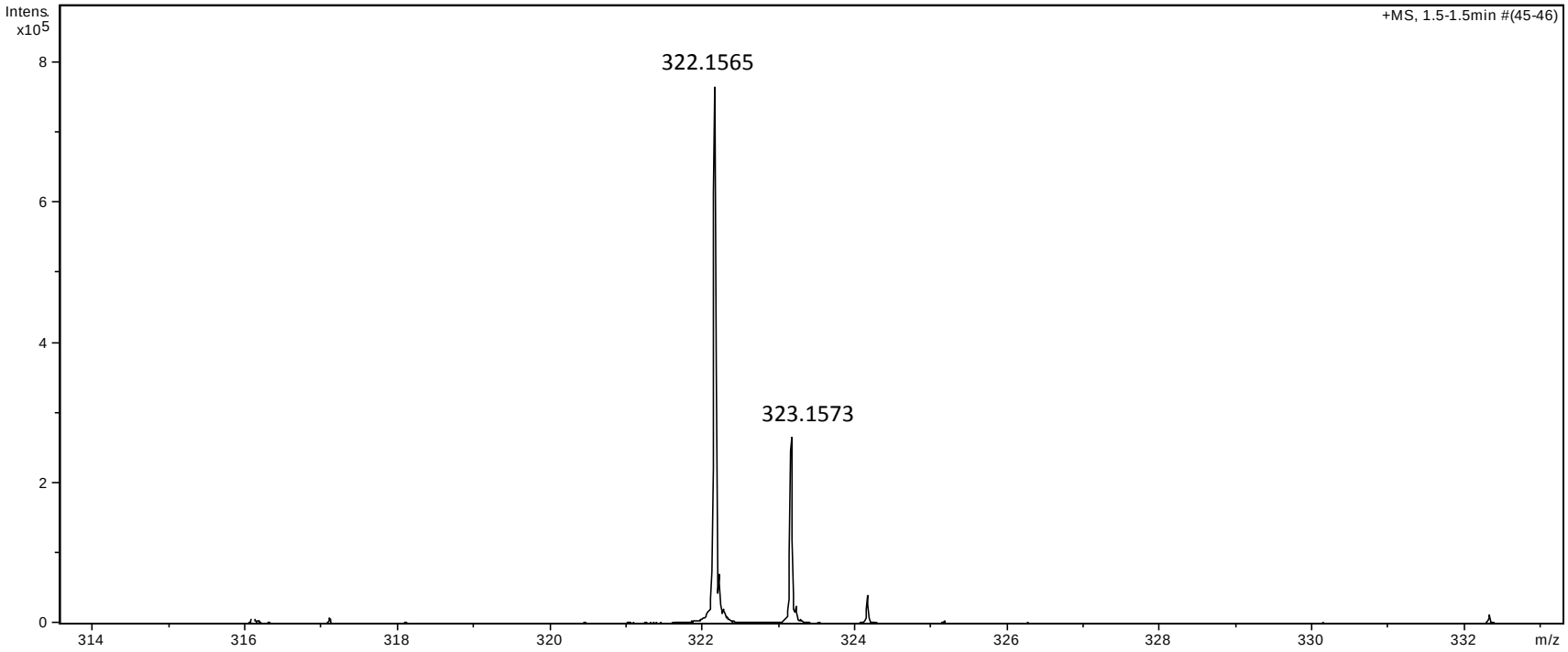

O
O
NH
N
H
NH2

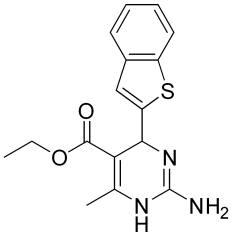

Intens.
x10^5
+MS, 0.0-1.0min #(1-29)
6
5
4
3
2
1
0
310.1560
332.1358
50
100
150
200
250
300
350
400
450
m/z

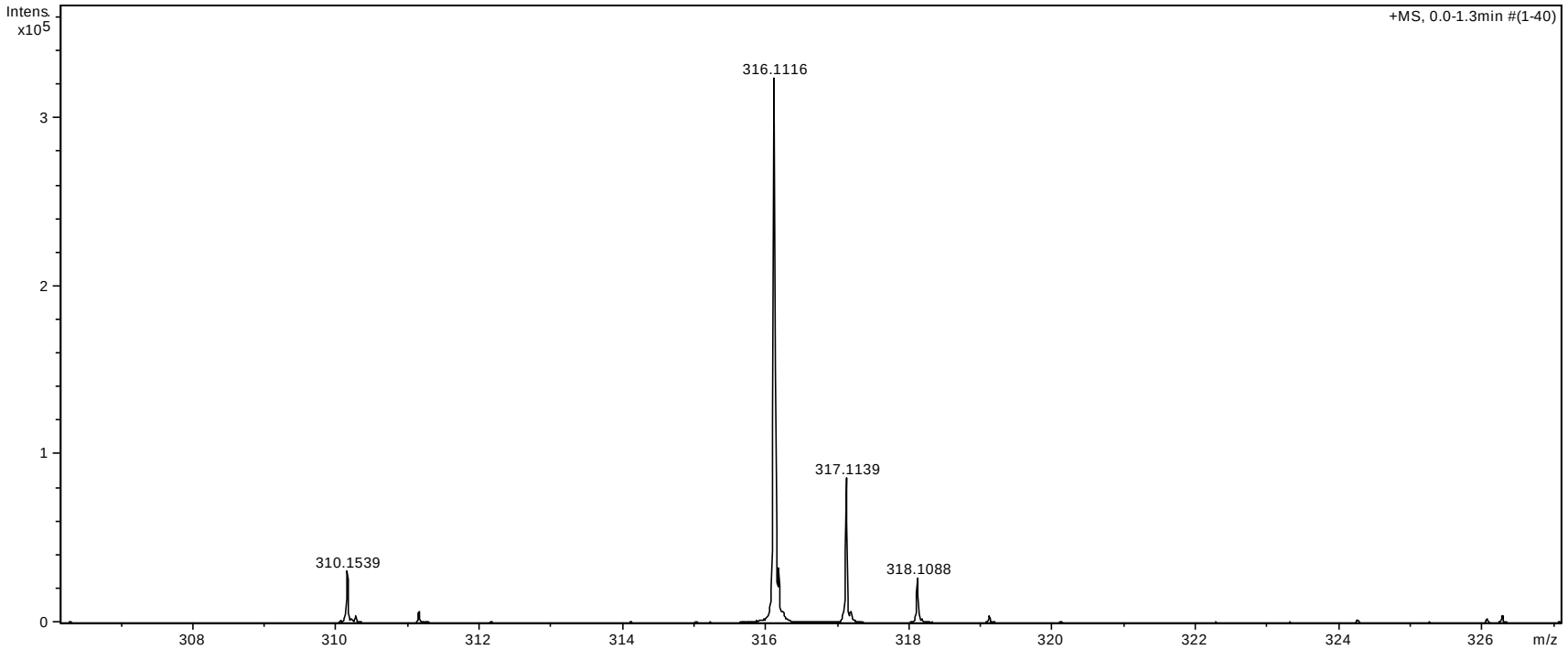

O
O
N
N
H
NH2

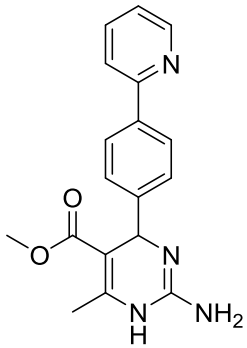

Intens.
x10^6
+MS, 0.0-0.5min #(1-29)
310.1558
240.1209
1.0
0.8
0.6
0.4
0.2
0.0
100
200
300
400
500
600
700
m/z

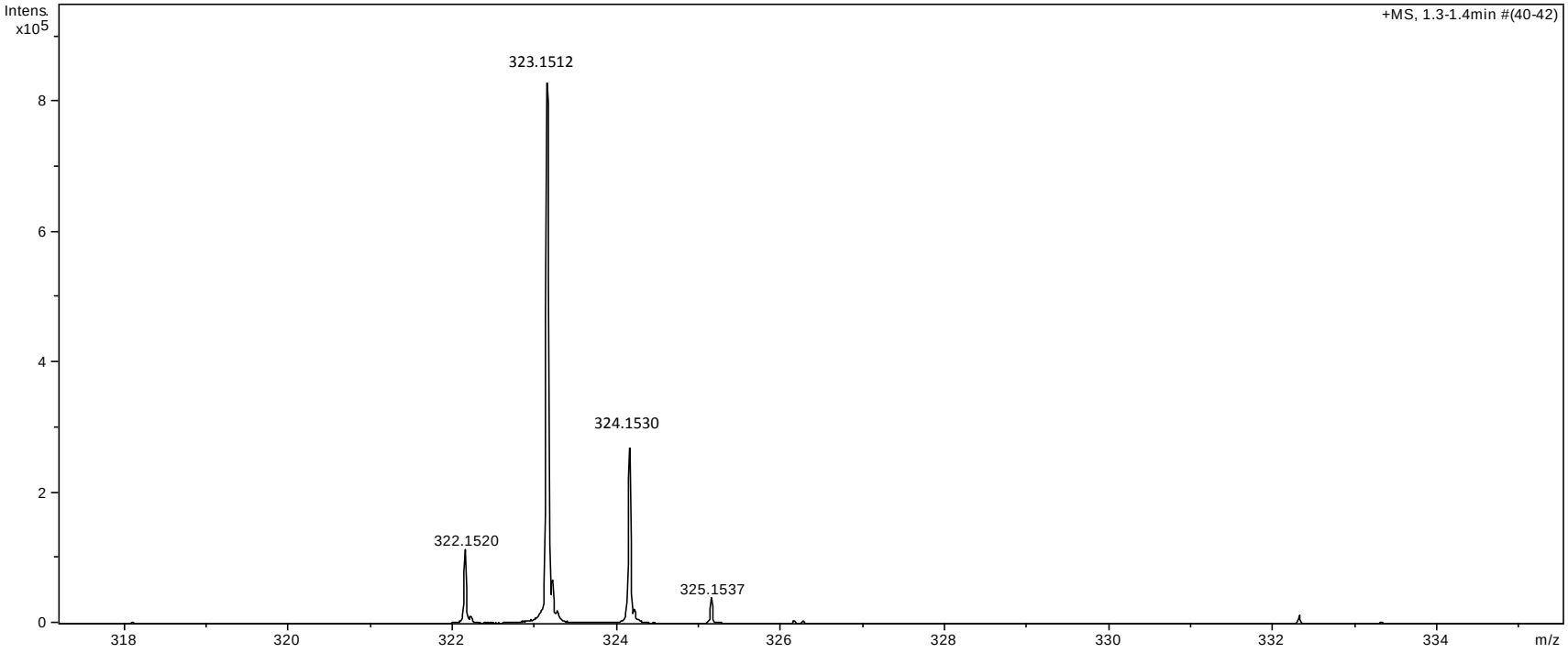

O
O
NH
N
H
NH

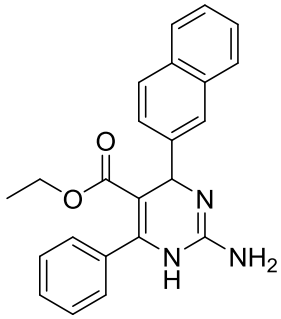

Intens.
x10^5
+MS, 1.5-1.5min #(45-46)
322.1565
323.1573
8
6
4
2
0
314
316
318
320
322
324
326
328
330
332
m/z

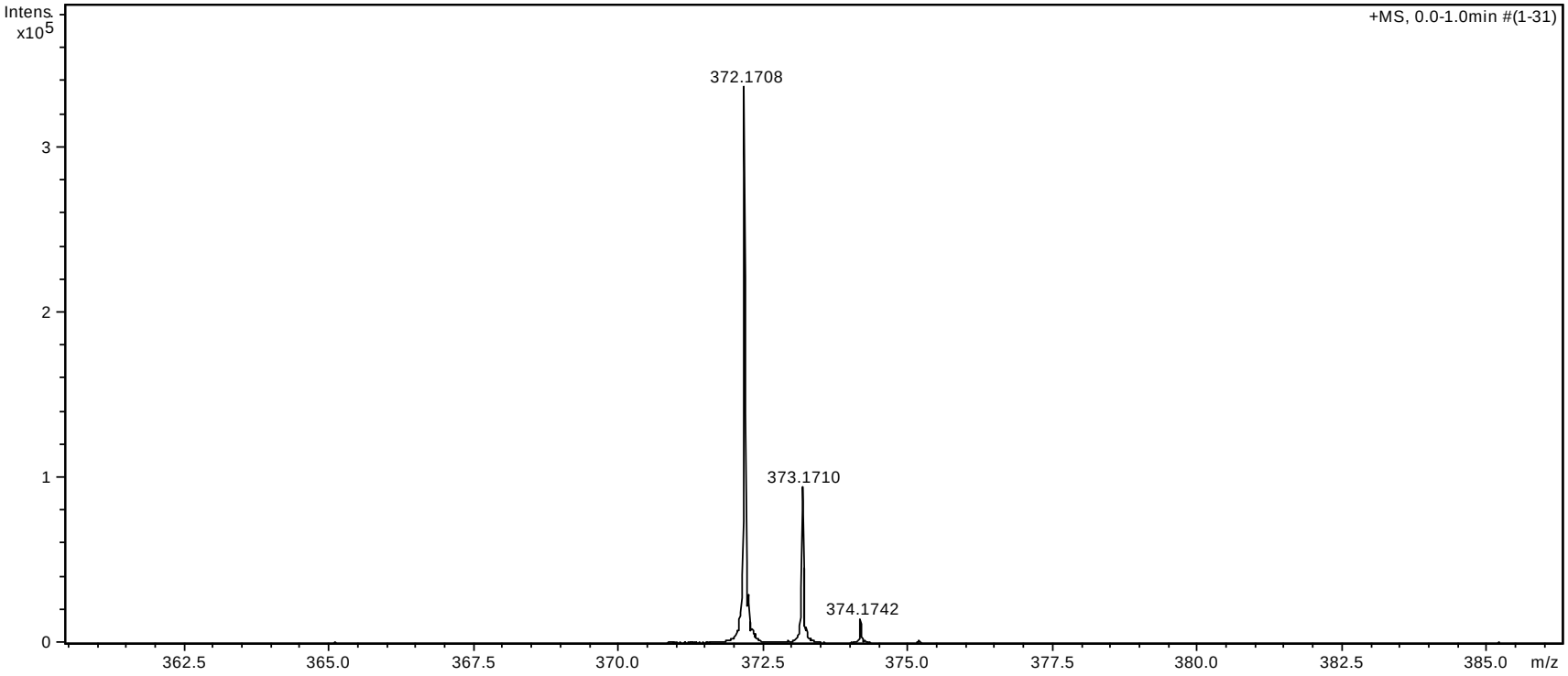

O
O
S
N
N
H
NH2

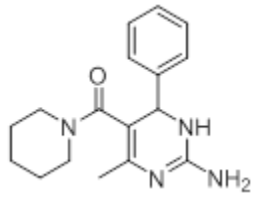

Intens.
x10^5
+MS, 0.0-1.3min #(1-40)
316.1116
317.1139
310.1539
318.1088
0
1
2
3
308
310
312
314
316
318
320
322
324
326
m/z

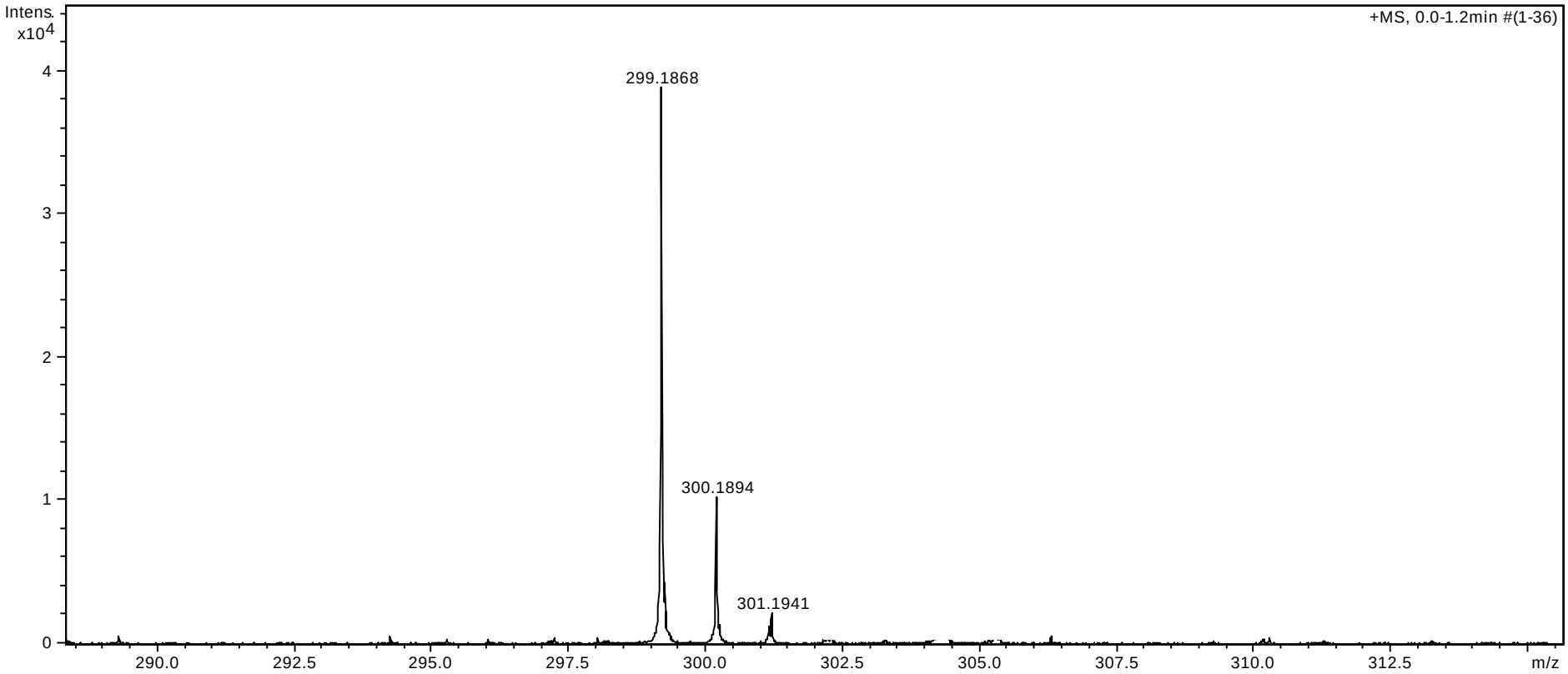

N
O
O
N
N
H
NH2

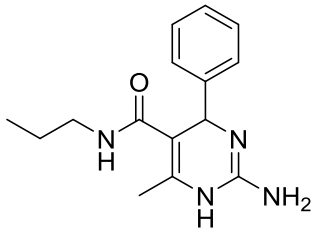

Intens.
x10^5
+MS, 1.3-1.4min #(40-42)
323.1512
324.1530
322.1520
325.1537
0
2
4
6
8
318
320
322
324
326
328
330
332
334
m/z

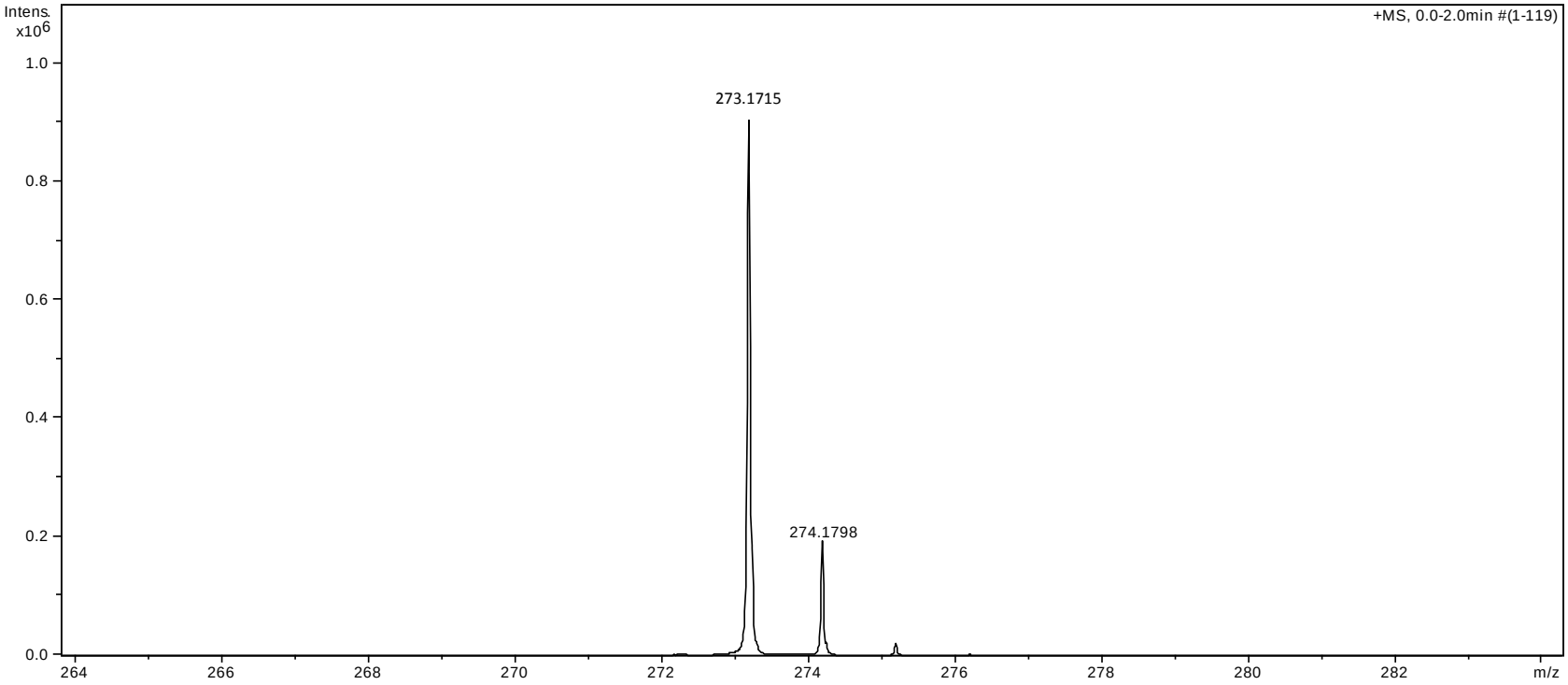

O
O
N
N
H
NH2

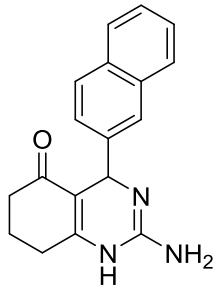

Intens.
x10^5
+MS, 0.0-1.0min #(1-31)
372.1708
373.1710
374.1742
3
2
1
0
362.5
365.0
367.5
370.0
372.5
375.0
377.5
380.0
382.5
385.0
m/z

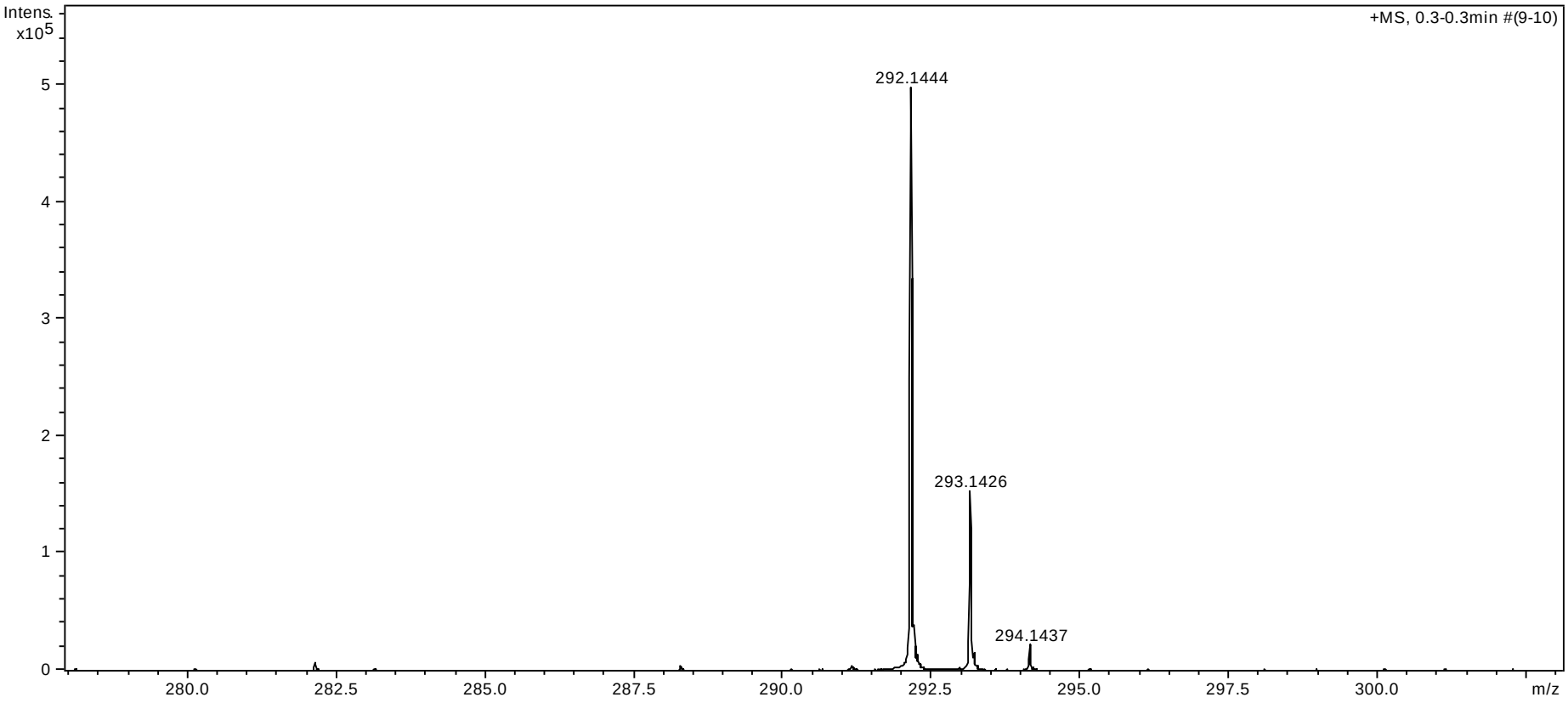

O
N
NH
N
NH2

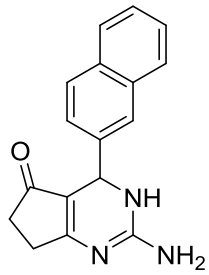

Intens.
x10^4
+MS, 0.0-1.2min #(1-36)
4
3
2
1
0
299.1868
300.1894
301.1941
290.0
292.5
295.0
297.5
300.0
302.5
305.0
307.5
310.0
312.5
m/z

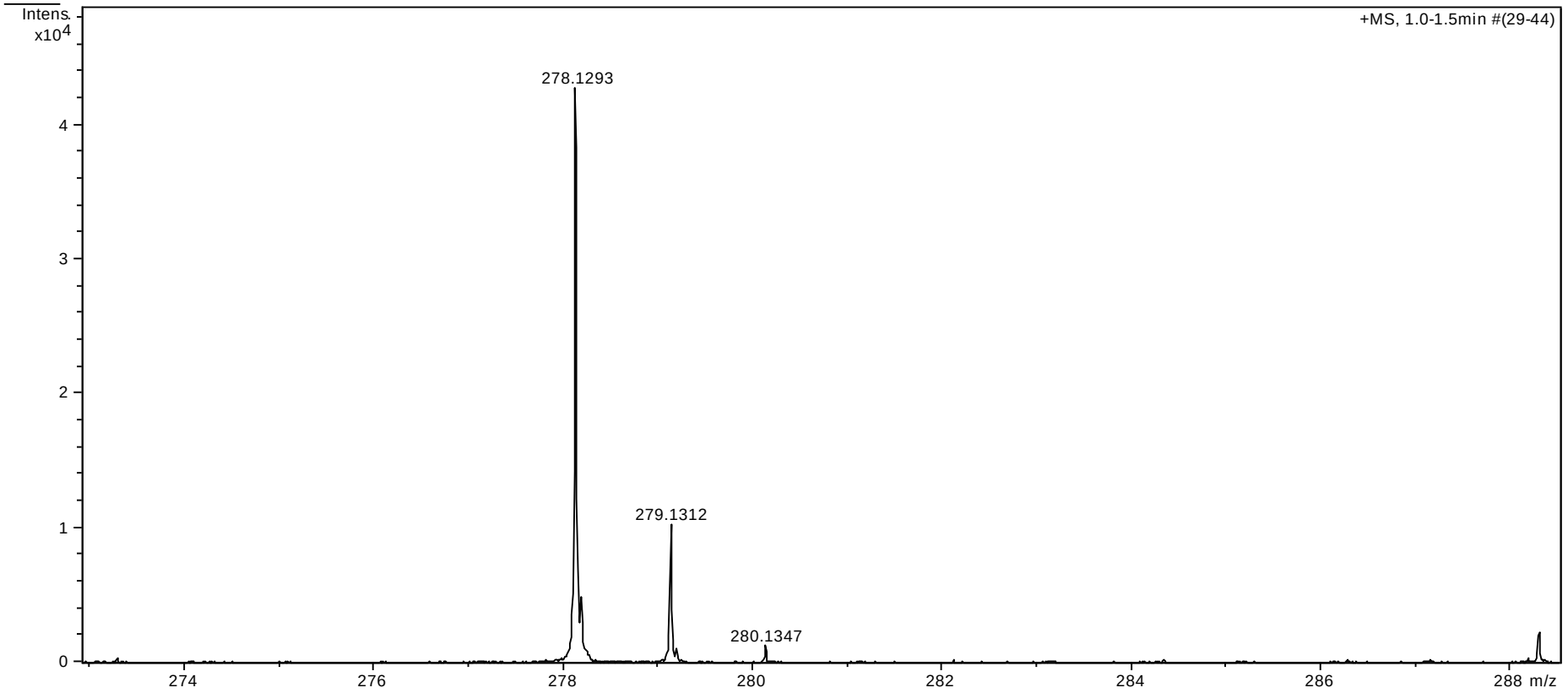

O
N
H
N
N
H
NH2

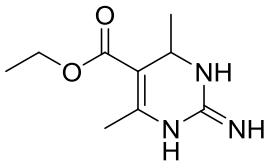

Intens.
x10^6
+MS, 0.0-2.0min #(1-119)
1.0
0.8
0.6
0.4
0.2
0.0
273.1715
274.1798
264
266
268
270
272
274
276
278
280
282
m/z

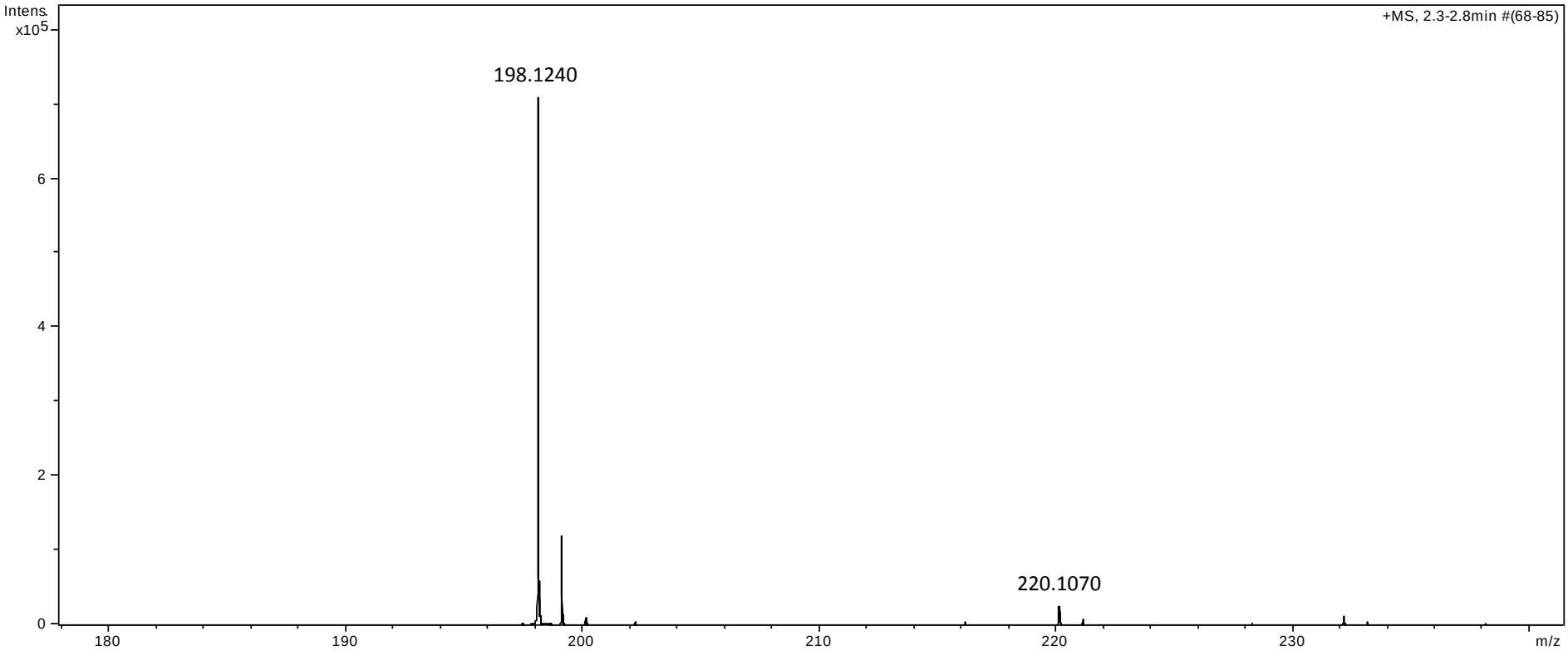

O
N
N
H
NH2

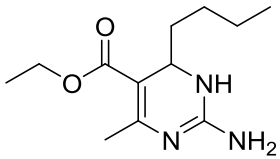

Intens.
x10^5
+MS, 0.3-0.3min #(9-10)
292.1444
293.1426
294.1437
0
1
2
3
4
5
280.0
282.5
285.0
287.5
290.0
292.5
295.0
297.5
300.0
m/z

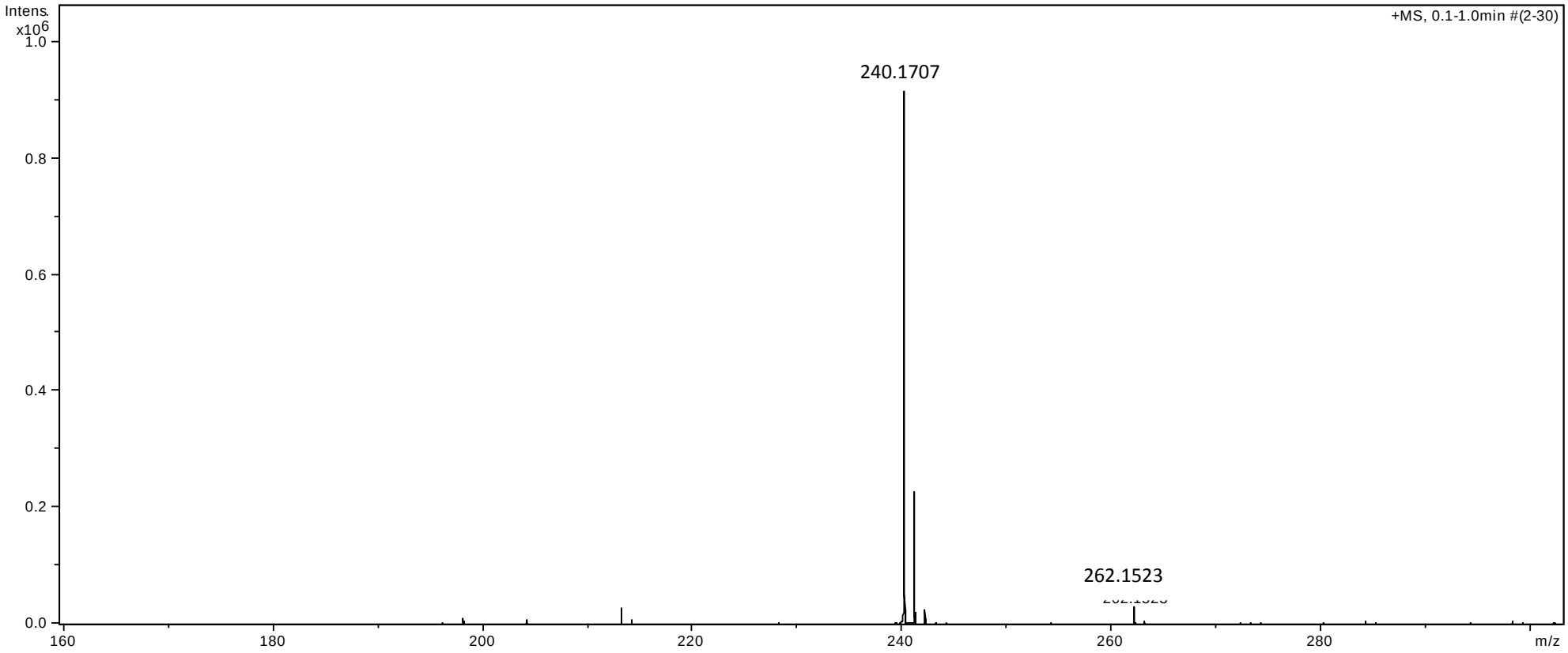

O
NH
N
NH2

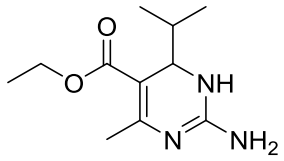

Intens.
x10^4
+MS, 1.0-1.5min #(29-44)
278.1293
279.1312
280.1347
0
1
2
3
4
274
276
278
280
282
284
286
288 m/z

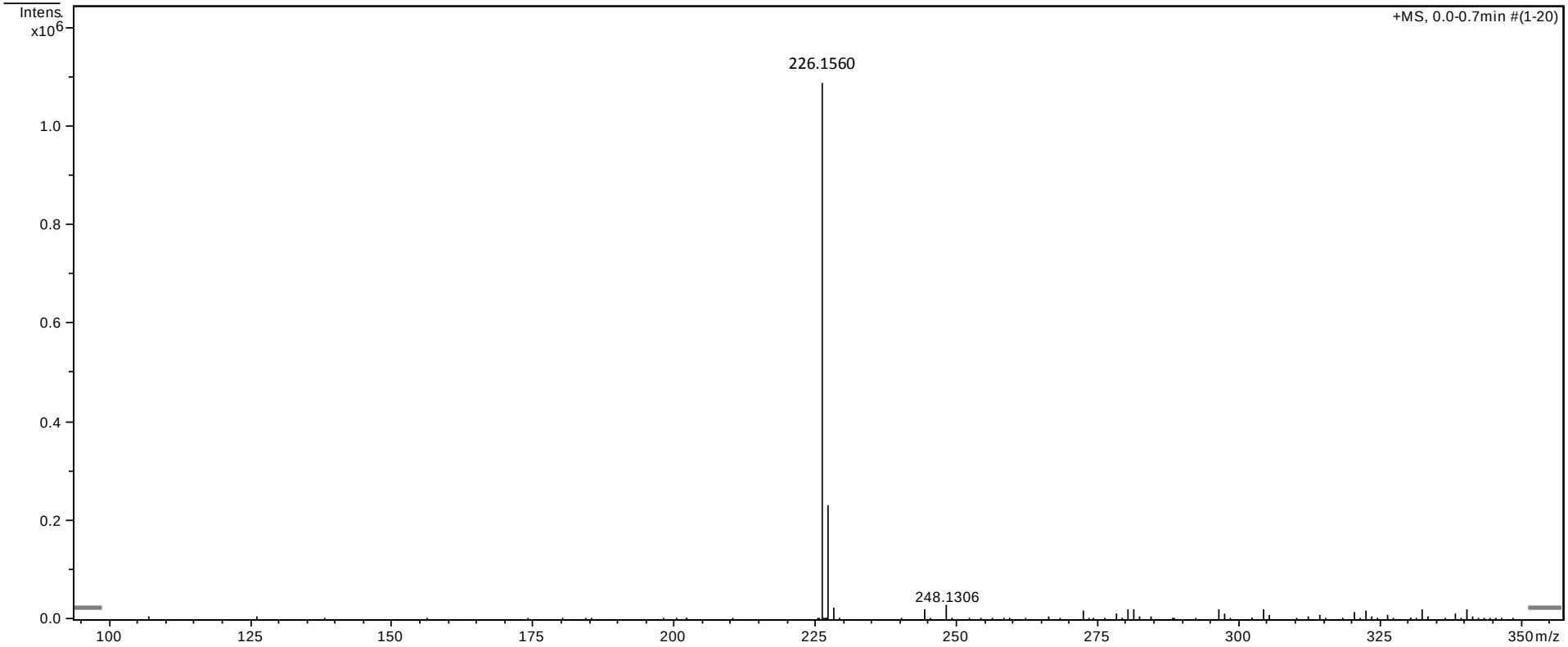

O
O
NH
N
H
NH

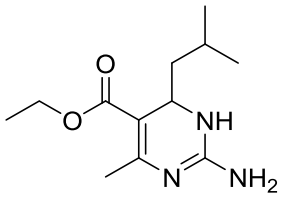

Intens.
x10^5
+MS, 2.3-2.8min #(68-85)
198.1240
220.1070
6
4
2
0
180
190
200
210
220
230
m/z

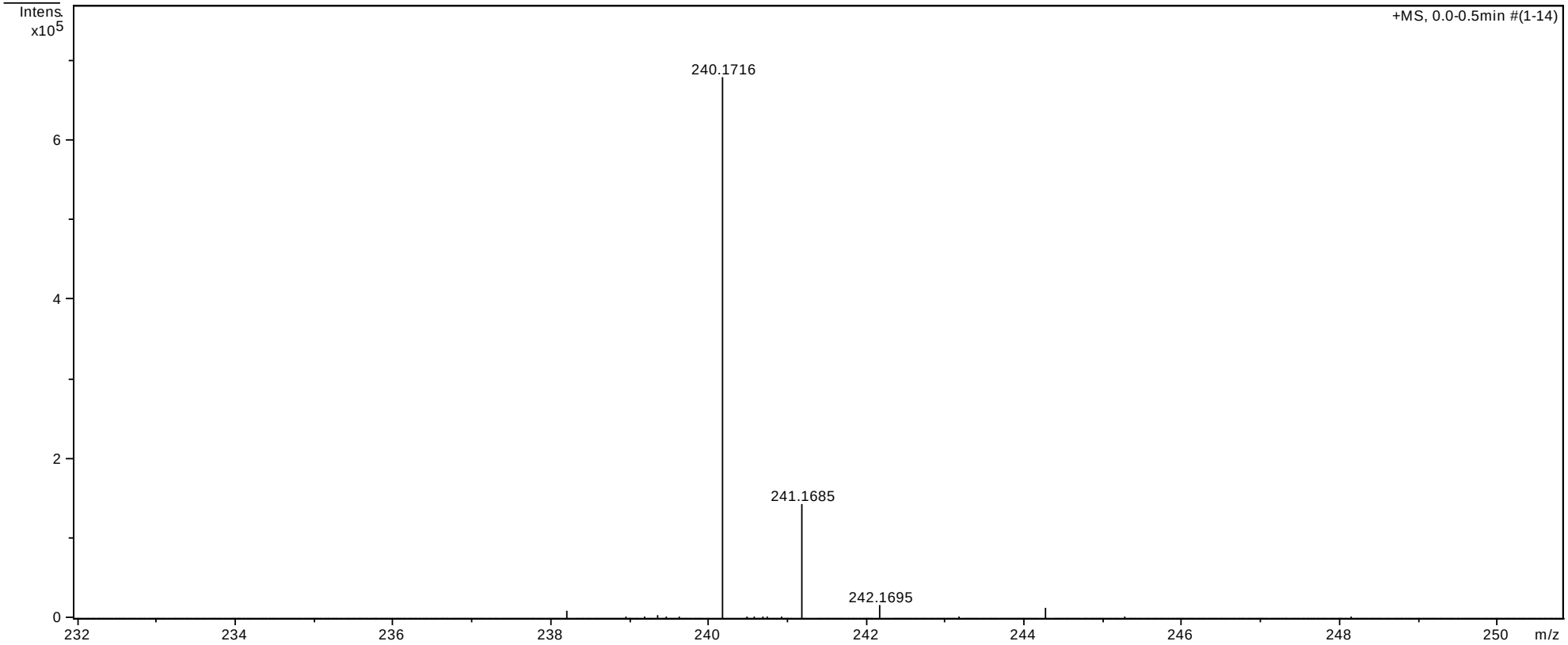

O
O
NH
N
NH2


Intens.
x10^6
1.0
0.8
0.6
0.4
0.2
0.0
+MS, 0.1-1.0min #(2-30)
240.1707
262.1523
160
180
200
220
240
260
280
m/z


O
O
NH
N
NH2


Intens.
x10^6
+MS, 0.0-0.7min #(1-20)
226.1560
248.1306
1.0
0.8
0.6
0.4
0.2
0.0
100
125
150
175
200
225
250
275
300
325
350
m/z


O
O
NH
N
NH2


Intens.
x10^5
+MS, 0.0-0.5min #(1-14)
240.1716
241.1685
242.1695
6
4
2
0
232
234
236
238
240
242
244
246
248
250
m/z