Palladium-catalyzed aziridination of 3,3,5,5-tetrasubstituted piperazin-2-ones.

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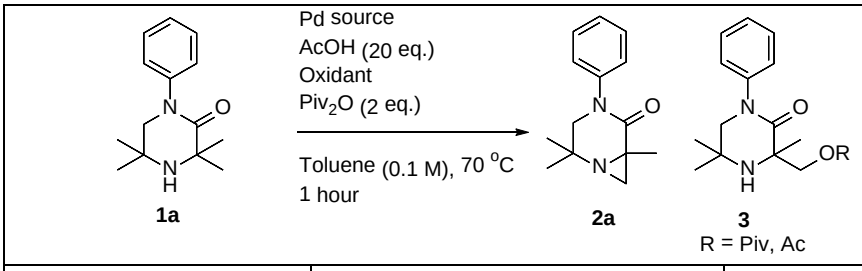
Supporting information

General method details

All reactions dealing with air- and moisture-sensitive compounds were carried out in heat-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash column chromatography was performed prep-packed Graceresolv™ silica gel cartridges on a Teledyne Isco Combiflash Rf automated chromatography system with detection at 254 nm. ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-400 (400 MHz) or AV-700 (700 MHz) NMR spectrometer. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm). Data for ^{1}H NMR were reported as: chemical shift,

integration, multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet, br = broad) and coupling constants. All ^{13}C NMR spectra were reported in ppm relative to $CDCl_3$ (77.16 ppm) or d^6-DMSO (39.50 ppm) unless otherwise stated, and were obtained with complete ^1H decoupling. All LC-MS analyses were performed on a Waters 2795 Separations Module, using a GeminiNX 5μ C18 column, with a Waters Micromass detector. IR spectra were reported on an Avatar 370 FT-IR Thermo Nicolet Spectrometer. High resolution mass spectra were obtained on a Thermo LTQ-FT/Accela/CTC/PDA instrument. Unless otherwise noted, all chemicals were commercially available and were used as received without further purification. Dry solvents were used directly from Sigma-Aldrich Sure-Seal bottles.

Additional Pd/oxidant sources screen

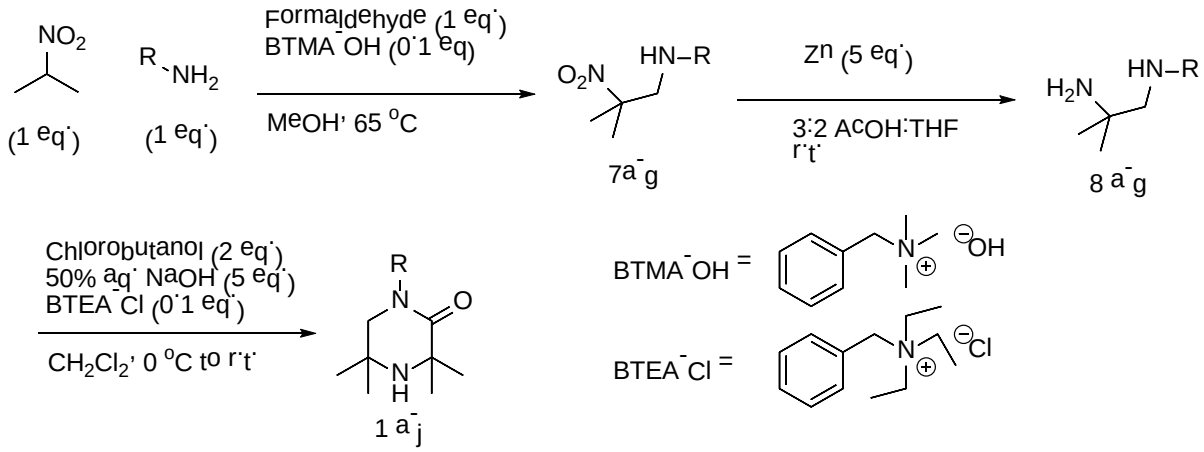


Palladium source (loading)	Oxidant (eq.)	Ratio (**2a**:**3**)
none	PIDA (1.5)	No conversion
$Pd(OAc)_2$ (5 mol%)	Air (N/A)	No conversion
$Pd(OAc)_2$ (5 mol%)	PIFA (1.5)	No conversion
$Pd(OAc)_2$ (5 mol%)	Oxone (1.5)	No conversion
$Pd(OAc)_2$ (5 mol%)	Benzoquinone (1.5)	No conversion
$Pd(OAc)_2$ (5 mol%)	Hydroxy(Tosyloxy)Iodobenzene (1.5)	No conversion
$Pd(OAc)_2$ (5 mol%)	2-iodosylbenzoic acid (1.5)	No conversion
$Pd(OAc)_2$ (5 mol%)	PIDPiv (1.5)	1:4
$Pd(OPiv)_2$ (5 mol%)	PIDPiv (1.5)	No conversion
$(allylPdCl)_2$ (3 mol%)	PIDA (1.5)	3.4:1
$Pd_2(dba)_3$ (3 mol%)	PIDA (1.5)	Trace conversion
$PdCl_2$ (5 mol%)	PIDA (1.5)	Trace conversion

PIDA = phenyliodonium diacetate; PIFA = phenyliodonium bis(trifluoroacetate); PIDPiv = phenyliodonium dipivalate; dba = dibenzylideneacetone

Synthesis of starting materials

All piperazinones were prepared using the following sequence (Scheme 1):

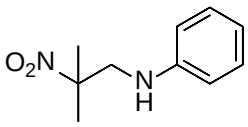


Scheme 1. Synthetic sequence to prepare the piperazinone substrates.

General procedure for the aza-Henry reaction

The Aza-Henry reaction was performed according to Johnson (method A).[1] The formaldehyde was added as a suspension in MeOH dropwise over 10-30 minutes, and the reaction was left to stir at 65 °C overnight. The reaction mixture was then evaporated to dryness, redissolved in EtOAc (20 mL) and washed with saturated NH_4Cl (20 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product, which was purified by column chromatography (0-50% EtOAc in heptane) to yield the desired nitroamine.

N-(2-methyl-2-nitropropyl)aniline (**7a**)



Yellow solid, 59%. Spectral data in agreement with literature data.[1]

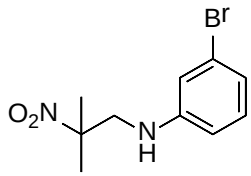
R_f = 0.57 (7:3 heptane: EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.25 - 7.10 (2H, m), 6.87 - 6.72 (1H, m), 6.70 - 6.55 (2H, m), 3.90 (1H, br s), 3.75 - 3.55 (2H, m), 1.77 - 1.59 (6H, m).

^{13}C NMR (101 MHz, $CDCl_3$): 147.7, 129.5 (2 x C), 118.4, 113.2 (2 x C), 89.1, 52.5, 24.3 (2 x C).

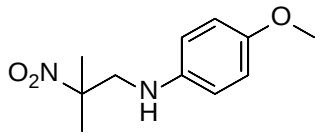
IR (neat, cm^{-1}): 3410, 1602, 1538, 1520, 1498, 1466, 1449, 1372, 1350, 1327, 1291, 1197, 1155.

3-Bromo-N-(2-methyl-2-nitropropyl)aniline (**7b**)



This material was used crude and was not isolated.

4-Methoxy-N-(2-methyl-2-nitropropyl)aniline (**7c**)



Dark yellow oil, 66%.

R_f = 0.31 (3:1 heptane: EtOAc).

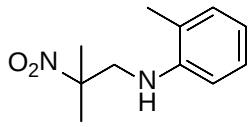
^{1}H NMR (400 MHz, $CDCl_3$): 6.86 - 6.71 (2H, m), 6.69 - 6.51 (2H, m), 3.74 (3H, s), 3.63 (1H, s), 3.55 (2H, d, *J* = 6.7 Hz), 1.65 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 153.0, 141.8, 115.2 (2 x C), 114.8 (2 x C), 89.1, 56.0, 54.0, 24.4 (2 x C).

IR (neat, cm^{-1}): 3399, 2993, 2937, 2834, 1538, 1514, 1468, 1347, 1235, 1180, 1036.

HRMS: calcd for $C_{11}H_{17}N_2O_3$ $[M+H]^+$ ESI+ 225.12337, found 225.12346.

2-Methyl-N-(2-methyl-2-nitropropyl)aniline (**7d**)



Yellow oil, 12%. This material required additional reverse-phase purification (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using 0-100% MeCN in water (containing 1% NH_3) as eluents. Data in agreement with literature data.[1]

R_f = 0.50 (7:3 heptane: EtOAc).

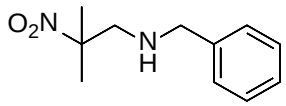
^{1}H NMR (400 MHz, $CDCl_3$): 7.11 (1H, t, J = 7.7 Hz), 7.07 (1H, d, J = 7.4 Hz), 6.70 (1H, dd, J = 1.0, 7.4 Hz), 6.64 (1H, d, J = 8.1 Hz), 3.82 (1H, s), 3.65 (2H, d), 2.14 (3H, s), 1.68 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 145.5, 130.7, 127.2, 122.7, 118.1, 110.1, 89.1, 52.2, 24.4 (2 x C), 17.5.

IR (neat, cm^{-1}): 3434, 2988, 2937, 1606, 1588, 1539, 1516, 1470, 1455, 1347, 1259.

HRMS: calcd for $C_{11}H_{17}N_2O_2$ $[M+H]^+$ ESI+ 209.12845, found 209.12846.

N-Benzyl-2-methyl-2-nitropropan-1-amine (**7e**)



Colourless oil, 49%. Data in agreement with literature data.[2]

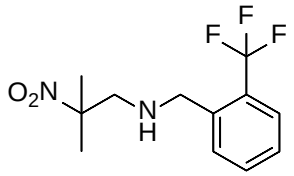
R_f = 0.46 (7:3 heptane: EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.40 - 7.15 (5H, m), 3.82 (2H, s), 2.99 (2H, s), 1.58 (6H, s). N-H signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$): 140.1, 128.6 (2 x C), 128.1(2 x C), 127.3, 88.8, 57.2, 54.3, 24.5 (2 x C).

IR (neat, cm^{-1}): 3353, 2988, 2934, 1537, 1494, 1468, 1460, 1348, 1371, 1400, 1121.

2-Methyl-2-nitro-N-(2-(trifluoromethyl)benzyl)propan-1-amine (**7f**)



Pale yellow oil, 63%.

R_f = 0.54 (7:3 heptane: EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.66 - 7.59 (2H, m), 7.53 (1H, t, *J* = 7.4 Hz), 7.35 (1H, t, *J* = 7.5 Hz), 3.98 (2H, s), 3.02 (2H, s), 1.59 (6H, s). N-H not observed.

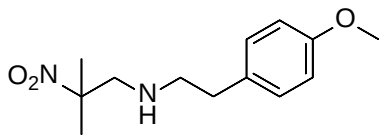
^{13}C NMR (101 MHz, $CDCl_3$): 138.7 (d, *J* = 1.4 Hz), 132.1 (d, *J* = 1.1 Hz), 130.2, 128.5 (q, *J* = 30 Hz), 127.2, 126.0 (d, *J* = 5.7), 123.3, 88.7, 57.4, 50.3, 24.4 (2 x C).

^{19}F NMR (376 MHz, $CDCl_3$): -59.53.

IR (neat, cm^{-1}): 3364, 2991, 2934, 1608, 1542, 1458, 1402, 1372, 1348, 1314, 1160, 1119, 1060, 1037.

HRMS: calcd for $C_{11}H_{14}F_3N_2O_2$ $[M+H]^+$ ESI+ 247.14166, found 247.14153.

N-(4-Methoxyphenethyl)-2-methyl-2-nitropropan-1-amine (**7g**)



Pale yellow oil, 79%. This material coeluted with some inseparable impurities but was carried through without further purification.

R_f = 0.27 (7:3 heptane: EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.12 - 7.04 (2H, m), 6.86 - 6.79 (2H, m), 3.78 (3H, s) 3.00 (2H, s), 2.85 (2H, td, *J* = 0.6, 6.8 Hz), 2.68 (2H, t, *J* = 7.1 Hz), 1.55 (6H, s), 0.78 (1H, br s).

^{13}C NMR (101 MHz, $CDCl_3$): 158.2, 131.9, 129.7 (2 x C), 114.0 (2 x C), 88.8, 57.8, 55.3, 52.0, 35.6, 24.3 (2 x C).

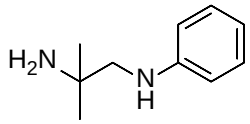
IR (neat, cm^{-1}): 2991, 2936, 2836, 1612, 1538, 1513, 1466, 1371, 1317, 1300, 1247, 1178, 1127, 1035.

HRMS: calcd for $C_{13}H_{21}N_2O_3$ $[M+H]^+$ ESI+ 253.15467, found 253.15460.

General procedure for nitro reduction

Zinc powder (5 eq.) was added portionwise to nitroamine **7a-g** (1 eq.) in 3:2 AcOH: THF (0.1-0.2 M) cooled to 0°C over a period of 10 minutes under nitrogen. The resulting suspension was stirred at 0 °C and left to warm to room temperature over 24 hours. If incomplete, further zinc powder (1 eq.) was added and the suspension was stirred at room temperature for a further 5 hours. This process was repeated until the reaction was complete. The reaction mixture was filtered through Celite© and the filtrate was evaporated to dryness to give crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% 7N methanolic ammonia in CH_2Cl_2, and pure fractions were evaporated to dryness to afford 1,2-diamine **8a-g**.

2-Methyl-N1-phenylpropane-1,2-diamine (**8a**)



Yellow/brown oil, 82%. Data in agreement with literature data.[3]

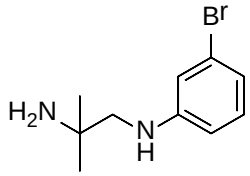
R_f = 0.53 (9:1 CH_2Cl_2: 7N NH_3/MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (2H, tt, J = 7.3, 2.1 Hz), 6.79 - 6.51 (3H, m), 4.14 (1H, s), 2.99 (2H, s), 1.59 (2H, s), 1.20 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 149.2, 129.4 (2 x C), 117.3, 113.1 (2 x C), 55.8, 50.4, 29.2 (2 x C).

IR (neat, cm^{-1}): 3346, 2962, 1603, 1506, 1470, 1317, 1256, 1182.

N1-(3-Bromophenyl)-2-methylpropane-1,2-diamine (**8b**)



Brown oil, 14% (yield over 2 steps).

R_f = 0.21 (9:1 CH_2Cl_2: 7N NH_3 in MeOH).

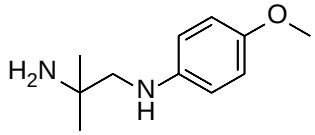
^{1}H NMR (400 MHz, $CDCl_3$): 7.07 – 6.90 (1H, m), 6.84 - 6.67 (2H, m), 6.59 - 6.48 (1H, m), 4.23 (1H, s), 2.93 (2H, s), 1.40 (2H, s), 1.19 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 150.5, 130.6, 123.5, 120.0, 115.5, 111.9, 55.3, 50.3, 29.3 (2 x C).

IR (neat, cm^{-1}): 3349, 2962, 1597, 1483, 1386, 1307, 1325, 1280, 1241, 1193, 1167, 1083, 1068.

HRMS: calcd for $C_{10}H_{16}BrN_2$ $[M+H]^+$ ESI+ 243.04914, found 243.04907.

N1-(4-Methoxyphenyl)-2-methylpropane-1,2-diamine (**8c**)



Beige solid, 96%.

R_f = 0.51 (9:1 CH_2Cl_2: 7N NH_3 in MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): 6.78 (2H, d, *J* = 9.0 Hz), 6.62 (2H, d, J = 9.0 Hz), 3.74 (3H, s), 2.93 (2H, s), 1.19 (6H, s).

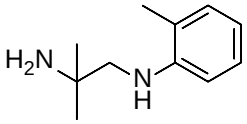
N-H signals were not observed.

^{13}C NMR (101 MHz, $CDCl_3$): 152.2, 143.6, 115.1 (2 x C), 114.3 (2 x C), 57.1, 56.0, 50.3, 29.3 (2 x C).

IR (neat, cm^{-1}): 3395, 2961, 1513, 1467, 1233, 1035.

HRMS: calcd for $C_{11}H_{19}N_2O$ $[M+H]^+$ ESI+ 195.14919, found 195.14914.

2-Methyl-N1-o-tolylpropane-1,2-diamine (**8d**)



Light brown oil, 76%. Data in agreement with literature data.[1]

R_f = 0.72 (9:1 CH_2Cl_2: 7N NH_3 in MeOH).

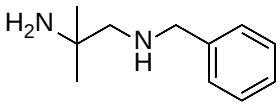
^{1}H NMR (400 MHz, $CDCl_3$): 7.15 - 7.08 (1H, m), 7.08 - 7.02 (1H, m), 6.64 (2H, td, *J* = 1.6, 8.2 Hz), 3.01 (2H, s), 2.18 (3H, s), 1.23 (6H, s). N-Hs not observed.

^{13}C NMR (101 MHz, $CDCl_3$) 147.0, 130.2, 127.2, 122.3, 116.8, 110.0, 55.6, 50.3, 29.5 (2 x C), 17.7.

IR (neat, cm^{-1}): 3342, 2964, 1608, 1583, 1546, 1459, 1371, 1314, 1160, 1120, 1059, 1037.

HRMS: calcd for $C_{11}H_{19}N_2$ $[M+H]^+$ ESI+ 179.15428, found 179.15439.

N1-Benzyl-2-methylpropane-1,2-diamine (**8e**)



Colourless oil, 93%. Data in agreement with literature data.[2]

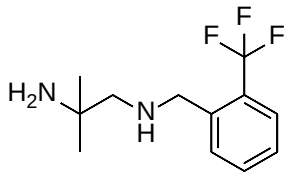
R_f = 0.33 (9:1 CH_2Cl_2: 7N NH_3 in MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): 7.39 - 7.28 (5H, m), 3.88 (1H, s), 3.83 (2H, s), 2.46 (2H, s), 1.46 (2H, br s), 1.09 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$) 141.0, 128.5 (2 x C), 128.1 (2 x C), 127.0, 61.8, 54.8, 50.0, 29.0 (2 x C).

IR (neat, cm^{-1}): 3306, 3062, 2960, 2869, 2808, 1601, 1585, 1495, 1454, 1382, 1119, 1028.

2-Methyl-N1-(2-(trifluoromethyl)benzyl)propane-1,2-diamine (**8f**)



Pale yellow oil, 60%.

R_f = 0.56 (9:1 CH_2Cl_2: 7N NH_3 in MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): 7.68 (1H, d, *J* = 7.7 Hz), 7.63 (1H, d, *J* = 7.8 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.34 (1H, t, *J* = 7.6 Hz), 3.99 (2H, s), 2.50 (2H, s), 2.23 (3H, s), 1.12 (6H, s).

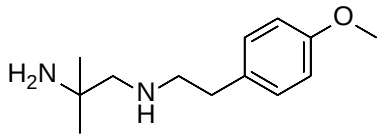
^{13}C NMR (101 MHz, $CDCl_3$): 139.7 – 139.1 (m), 132.2 – 131.6 (m), 130.1, 128.8 – 128.7 (m), 126.8, 125.9 (q, *J* = 5.8 Hz), 123.3, 61.4, 50.6 (q, *J* = 2.1 Hz), 50.2, 28.4 (2 x C).

^{19}F NMR (376 MHz, $CDCl_3$): -59.61.

IR (neat, cm^{-1}): 3360, 2990, 2940, 1608, 1541, 1456, 1314, 1160, 1118, 1037.

HRMS: calcd for $C_{11}H_{16}F_3N_2$ $[M+H]^+$ ESI+ 247.14166, found 247.14153.

N1-(4-methoxyphenethyl)-2-methylpropane-1,2-diamine (**8g**)



Colourless oil, 68%. This material coeluted with some inseparable impurities but was carried through without further purification.

R_f = 0.73 (9:1 CH_2Cl_2: 7N NH_3 in MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): 7.18 - 7.05 (2H, m), 6.88 - 6.77 (2H, m), 3.79 (3H, s), 2.94 - 2.79 (2H, m), 2.75 (2H, d, *J* = 7.0 Hz), 2.46 (2H, s), 1.07 (6H, s).

N-H signals appeared under the water signal.

^{13}C NMR (101 MHz, $CDCl_3$) 158.2, 132.5 (2 x C), 129.8 (2 x C), 114.1, 62.3, 55.4, 52.6, 50.0, 35.8, 29.0 (2 x C).

IR (neat, cm^{-1}): 3346, 2958, 2834, 1612, 1513, 1464, 1308, 1246, 1179, 1121, 1036.

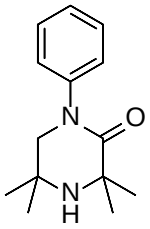
HRMS: calcd for $C_{13}H_{23}N_2O$ $[M+H]^+$ ESI+ 223.18049, found 223.18037.

General synthesis procedure of piperazinones

Piperazin-2-ones **1a-j** were prepared according to Lai.[4] For compounds **1a-g** commercially available chlorobutanol (2 eq.) was used, whilst for **1h** and **1j** the respective ketone (2 eq.), chloroform (1.5 eq.) and acetone cyanohydrin (0.1 eq.) were used.

50% aqueous sodium hydroxide (5 eq.) was added dropwise to 1,1,1-trichloro-2-methylpropan-2-ol (chlorobutanol, 2 eq.), diamine **8a-g** (1 eq.) and N-benzyl-N,N-diethylethanaminium chloride (BTEAC, 0.1 eq.) in CH_2Cl_2 (0.1 M) cooled to 0°C. The resulting mixture was stirred at 0 °C and left to warm to room temperature over 20 hours. The reaction mixture was treated with water until any solid had dissolved. The organic layer was separated, and the aqueous layer was was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product which was purified by flash silica chromatography (0-100% EtOAc in heptane).

3,3,5,5-Tetramethyl-1-phenylpiperazin-2-one (**1a**)



Off-white solid, 50%. Spectral data in agreement with literature data.[4]

R_f = 0.11 (EtOAc).

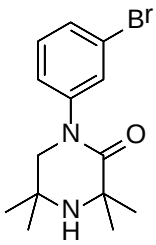
^{1}H NMR (400 MHz, $CDCl_3$): 7.47 - 7.31 (2H, m), 7.28 - 7.13 (3H, m), 3.58 (2H, s), 1.45 (6H, s), 1.28 (6H, s).

N-H signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$): 174.0, 143.6, 129.2 (2 x C), 126.6, 125.8 (2 x C), 62.8, 56.0, 49.6, 30.6 (2 x C), 27.9 (2 x C).

IR (neat, cm^{-1}): 3311, 3075, 2955, 2924, 2866, 1635, 1600, 1489, 1307.

1-(3-Bromophenyl)-3,3,5,5-tetramethylpiperazin-2-one (**1b**)



R_f = 0.15 (EtOAc).

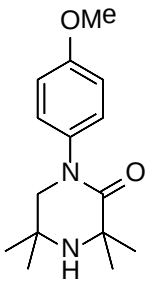
^{1}H NMR (400 MHz, $CDCl_3$): 7.49 - 7.42 (1H, m), 7.37 (1H, ddd, J = 1.9, 2.7, 6.6 Hz), 7.28 - 7.21 (2H, m), 3.59 (2H, s), 1.51 (1H, s), 1.46 (6H, s), 1.29 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 174.1, 144.7, 130.4, 129.7, 128.9, 124.5, 122.5, 62.6, 56.1, 49.6, 30.6 (2 x C), 27.9 (2 x C).

IR (neat, cm^{-1}): 3389, 2927, 2858, 1720, 1658, 1587, 1543, 1477, 1379, 1317.

HRMS: calcd for $C_{14}H_{20}BrN_2O$ $[M+H]^+$ ESI+ 311.07535, found 311.07559.

1-(4-Methoxyphenyl)-3,3,5,5-tetramethylpiperazin-2-one (**1c**)



White solid, 47%.

R_f = 0.11 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.21 - 7.10 (2H, m), 6.96 - 6.84 (2H, m), 3.80 (3H, s), 3.56 (2H, s), 1.46 (7H, s), 1.29 (6H, s).

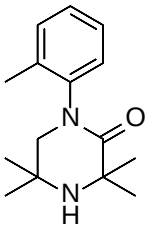
N-H appears under the CH_3 signal.

^{13}C NMR (101 MHz, $CDCl_3$): 174.1, 158.2, 136.6, 127.0 (2 x C), 114.5 (2 x C), 63.2, 56.0, 55.7, 49.5, 30.7 (2 x C), 27.9 (2 x C).

IR (neat, cm^{-1}): 3426, 3301, 2972, 1658, 1639, 1608, 1512.

HRMS: calcd for $C_{15}H_{23}N_2O_2$ $[M+H]^+$ ESI+ 263.17540, found 263.17538.

3,3,5,5-Tetramethyl-1-o-tolylpiperazin-2-one (**1d**)



White solid, 34%.

R_f = 0.20 (EtOAc).

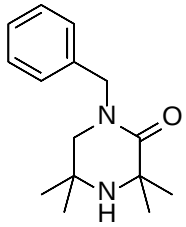
^{1}H NMR (400 MHz, $CDCl_3$): 7.25 - 7.17 (3H, m), 7.09 (1H, dd, *J* = 1.9, 7.6 Hz), 3.55 (1H, d, *J* = 12.1 Hz), 3.43 (1H, d, *J* = 12.1 Hz), 2.24 (3H, s), 1.49 (4H, s), 1.47 (3H, s), 1.38 (3H, s), 1.28 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 173.3, 142.2, 135.6, 131.1, 127.7, 127.4, 126.8, 63.2, 56.0, 49.4, 31.1, 30.4, 28.5, 27.5, 18.0.

IR (neat, cm^{-1}): 3312, 3022, 2960, 2923, 1626.

HRMS: calcd for $C_{15}H_{23}N_2O$ $[M+H]^+$ ESI+ 247.18049, found 247.18039.

1-Benzyl-3,3,5,5-tetramethylpiperazin-2-one (**1e**)



Yellow gum, 59%.

$\mathbf{R_f}$ = 0.12 (EtOAc).

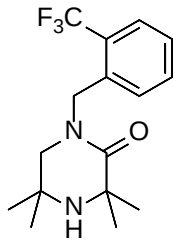
^{1}H NMR (400 MHz, $CDCl_3$): 7.45 - 7.11 (5H, m), 4.60 (2H, s), 3.09 (2H, s), 1.55 (1H, s), 1.42 (6H, s), 1.09 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 174.1, 137.3, 128.7 (2 x C), 128.5 (2 x C), 127.7, 59.0, 55.6, 51.1, 48.8, 30.7 (2 x C), 27.8 (2 x C).

IR (neat, cm^{-1}): 3502, 3312, 3036, 2971, 2927, 1634, 1495, 1454, 1432, 1371, 1381, 1336, 1305, 1233, 1196, 1164, 1080, 1030, 1013.

HRMS: calcd for $C_{15}H_{23}N_2O$ $[M+H]^+$ ESI+ 247.18049, found 247.18060.

3,3,5,5-tetramethyl-1-(2-(trifluoromethyl)benzyl)piperazin-2-one (**1f**)



White solid, 16%. This material required additional reverse-phase purification (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using 0-100% MeCN in water (containing 1% NH_3) as eluents.

$\mathbf{R_f}$ = 0.25 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.65 (1H, d, *J* = 7.8 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.43 (1H, d, *J* = 7.8 Hz), 7.36 (1H, t, *J* = 7.6 Hz), 4.83 (2H, s), 3.09 (2H, s), 1.45 (6H, s), 1.13 (6H, s).

N-H signal not observed.

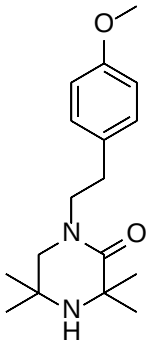
^{13}C NMR (101 MHz, $CDCl_3$): 174.7, 136.2, 132.3, 129.3, 128.8 (q, *J* = 30.2 Hz), 127.4, 126.0 (q, *J* = 5.8 Hz), 123.1, 59.5, 55.7, 48.8, 47.0, 30.8, 27.9.

^{19}F NMR (376 MHz, $CDCl_3$): -58.97.

IR (neat, cm^{-1}): 3501, 3316, 2973, 1642, 1494, 1450, 1440, 1370, 1314, 1163, 1117, 1061, 1039.

HRMS: calcd for $C_{15}H_{20}F_3N_2O$ $[M+H]^+$ ESI+ 315.16787, found 315.16821.

1-(4-Methoxyphenethyl)-3,3,5,5-tetramethylpiperazin-2-one (**1g**)



Colourless oil, 58%.

R_f = 0.15 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.21 - 7.07 (2H, m), 6.89 - 6.74 (2H, m), 3.78 (3H, s), 3.63 - 3.53 (2H, m), 3.11 (2H, s), 2.89 - 2.71 (2H, m), 1.33 (6H, s), 1.14 (6H, s).

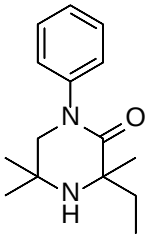
N-H signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$): 173.9, 158.4, 131.0, 129.9, 114.1, 60.5, 55.5, 55.4, 50.1, 49.0, 32.8, 30.5 (2 x C), 27.8 (2 x C).

IR (neat, cm^{-1}): 3476, 3311, 2969, 2932, 2853, 2836, 1635, 1584, 1513, 1490, 1464, 1442, 1427, 1370, 1302, 1247, 1168, 1036.

HRMS: calcd for $C_{17}H_{27}N_2O_2$ $[M+H]^+$ ESI+ 291.20670, found 291.20679.

3-Ethyl-3,5,5-trimethyl-1-phenylpiperazin-2-one (**1h**)



Colourless gum, isolated as a racemic mixture, 10%. This material required additional reverse-phase purification (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using 0-100% MeCN in water (containing 1% NH_3) as eluents, followed by HPLC (Waters SunFire column, 5µ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid).

R_f = 0.13 (1:1 heptane: EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.42 - 7.35 (2H, m), 7.29 - 7.23 (3H, m), 3.76 (1H, d, *J* = 12.3 Hz), 3.45 (1H, d, *J* = 12.3 Hz), 2.02 – 1.86 (1H, m), 1.75 - 1.61 (1H, m), 1.51 (3H, s), 1.44 (3H, s), 1.31 (3H, s), 1.03 (3H, t, *J* = 7.4 Hz).

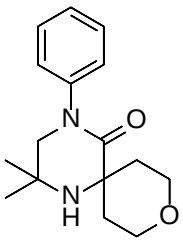
N-H signal not observed. Sample contains 0.91 eq. ammonium formate.

^{13}C NMR (101 MHz, $CDCl_3$): 164.7, 143.2, 129.4 (2 x C), 127.1, 125.9 (2 x C), 62.1, 60.0, 50.9, 50.3, 35.7, 28.2, 28.0, 26.1, 8.5.

IR (neat, cm^{-1}): 3406, 2925, 2854, 1643, 1595, 1547, 1462, 1351, 1314.

HRMS: calcd for $C_{15}H_{23}N_2O$ $[M+H]^+$ ESI+ 247.18049, found 247.18060.

2,2-Dimethyl-4-phenyl-9-oxa-1,4-diazaspiro[5.5]undecan-5-one (**1j**)



Pale yellow solid, 21%

R_f = 0.31 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) 7.47 - 7.31 (2H, m), 7.27 - 7.22 (3H, m), 3.88 (2H, dt, *J* = 4.2, 11.4 Hz), 3.79 (2H, td, *J* = 2.6, 11.2 Hz), 3.58 (2H, s), 2.33 (2H, ddd, *J* = 4.6, 10.8, 14.7 Hz), 1.55 (2H, d, *J* = 12.7 Hz), 1.29 (6H, s).

N-H signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$) 173.0, 143.5, 129.3 (2 x C), 126.8, 125.8 (2 x C), 63.2 (2 x C), 61.9, 55.4, 49.9, 37.1 (2 x C), 28.3 (2 x C).

IR (neat, cm^{-1}): 3399, 3308, 2964, 2864, 1646, 1642, 1594, 1494, 1475, 1381, 1315.

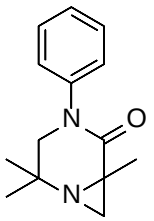
HRMS: calcd for $C_{16}H_{23}N_2O_2$ $[M+H]^+$ ESI+ 275.17540, found 275.17551.

Aziridination procedure

Pivalic anhydride (2 eq.) was added to starting piperazin-2-one (1 eq.), $Pd(OAc)_2$ (0.05 eq.) and PIDA (1.5 eq.) in 1,2-DCE (0.1 M) at 70°C under air. The resulting mixture was stirred at 70 °C for 1 hour or until LC-MS showed full conversion of starting material (as judged by disappearance from the $[M+H]^+$ mass ion for the starting material by MS). The reaction mixture was then left to cool to room temperature and filtered through a pad of Celite and the filter cake was washed with CH_2Cl_2 (2 x 5 mL). The solvent was removed under reduced pressure to give a residue which was suspended in CH_2Cl_2 and was purified by flash silica chromatography (0-100% EtOAc in heptane).

All compounds were isolated as racemic mixtures.

2,2,6-Trimethyl-4-phenyl-1,4-diazabicyclo[4.1.0]heptan-5-one (**2a**)



Brown gum, 73%.

R_f = 0.09 (EtOAc).

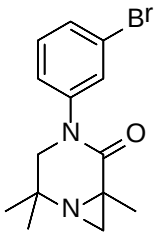
^{1}H NMR (400 MHz, $CDCl_3$): 7.42 - 7.32 (2H, m), 7.27 - 7.17 (3H, m), 3.54 (1H, d, *J* = 13.3 Hz), 3.16 (1H, d, *J* = 13.3 Hz), 2.41 (1H, s), 1.91 (1H, s), 1.52 (3H, s), 1.41 (3H, s), 1.24 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 169. 9, 143.0, 129.3 (2 x C), 126.9, 125.9 (2 x C), 55.7, 51.1, 37.9, 32.9, 26.5, 26.1, 20.7.

IR (neat, cm^{-1}): 3057, 2967, 2925, 1738, 1651, 1594, 1494, 1453, 1427, 1377, 1322, 1261, 1188, 1112, 1096, 1071, 1044.

HRMS: calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ ESI+ 231.14919, found 231.14899.

4-(3-Bromophenyl)-2,2,6-trimethyl-1,4-diazabicyclo[4.1.0]heptan-5-one (**2b**)



Pale orange solid, 52%.

R_f = 0.26 (EtOAc)

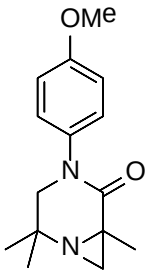
^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (1H, t, *J* = 1.8 Hz), 7.41 - 7.37 (1H, m), 7.30 - 7.23 (1H, m), 7.20 (1H, ddd, *J* = 1.2, 1.9, 8.0 Hz), 3.55 (1H, d, *J* = 13.3 Hz), 3.15 (1H, d, *J* = 13.2 Hz), 2.42 (1H, s), 1.95 (1H, s), 1.53 (3H, s), 1.41 (3H, s), 1.27 (3H, s),

^{13}C NMR (101 MHz, $CDCl_3$): 169.9, 144.0, 130.4, 129.9, 129.0, 124.5, 122.5, 55.3, 51.1, 37.8, 32.9, 26.4, 26.0, 20.6.

IR (neat, cm^{-1}): 2973, 1737, 1657, 1650, 1587, 1477, 1414, 1383, 1323, 1558, 1160.

HRMS: calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ ESI+ 309.0966, found 309.0959.

4-(4-Methoxyphenyl)-2,2,6-trimethyl-1,4-diazabicyclo[4.1.0]heptan-5-one (**2c**)



Pale yellow solid, 72%.

R_f = 0.13 (EtOAc).

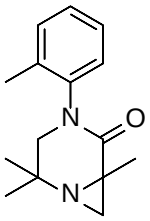
^{1}H NMR (400 MHz, $CDCl_3$): 7.18 - 7.01 (2H, m), 6.96 - 6.78 (2H, m), 3.80 (3H, s), 3.51 (1H, d, *J* = 13.4 Hz), 3.11 (1H, d, *J* = 13.3 Hz), 2.39 (1H, s), 1.90 (1H, s), 1.51 (3H, s), 1.40 (3H, s), 1.23 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 170.0, 158.3, 136.0, 127.1 (2 x C), 114.8 (2 x C), 56.1, 55.6, 51.1, 37.8, 32.9, 26.5, 26.2, 20.7.

IR (neat, cm^{-1}): 2974, 2939, 1645, 1607, 1513, 1463, 1426, 1337, 1330, 1249, 1186, 1104, 1020.

HRMS: calcd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$ ESI+ 261.15975, found 261.15942.

2,2,6-Trimethyl-4-o-tolyl-1,4-diazabicyclo[4.1.0]heptan-5-one (**2d**)



Yellow gum, 53%, 2:1 mixture of conformers. This material required additional reverse-phase purification (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using 0-100% MeCN in water (containing 1% NH_3) as eluents.

R_f = 0.34 (EtOAc).

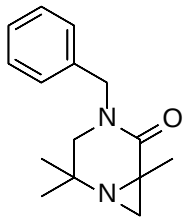
^{1}H NMR (700 MHz, $CDCl_3$): 7.24 – 7.14 (3H, m), 7.03 – 6.96 (1H, m), 3.46 (1H, d, *J* = 13.6 Hz), 3.05 – 2.91 (1H, m), 2.43 – 2.33 (1H, m), 2.25 (1H, s), 2.16 (2H, s), 1.93 – 1.85 (1H, m), 1.52 – 1.48 (3H, m), 1.47 – 1.44 (3H, m), 1.21 (3H, s).

^{13}C NMR (176 MHz, $CDCl_3$): 169.3, 141.8, 141.2, 135.9, 135.1, 131.2 131.0, 127.8, 127.5, 127.0, 126.7, 126.4, 56.0, 55.2, 50.9, 50.8, 37.7, 37.5, 33.0, 32.8, 27.4, 26.7, 26.3, 25.9, 20.3, 18.1, 17.6.

IR (neat, cm^{-1}): 2971, 2931, 1650, 1495, 1469, 1426, 1378, 1326, 1260, 1187, 1133, 1096, 1045.

HRMS: calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ ESI+ 245.1654, found 245.1659.

4-Benzyl-2,2,6-trimethyl-1,4-diazabicyclo[4.1.0]heptan-5-one (**2e**)



Colourless gum, 18%. This material required additional reverse-phase purification (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using 0-100% MeCN in water (containing 1% NH_3) as eluents.

R_f = 0.13 (EtOAc).

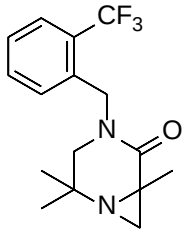
^{1}H NMR (700 MHz, $CDCl_3$): 7.34 - 7.28 (2H, m), 7.28 - 7.24 (1H, m), 7.22 (2H, d, *J* = 7.2 Hz), 4.56 (1H, d, *J* = 14.5 Hz), 4.52 (1H, d, *J* = 14.4 Hz), 2.95 (1H, d, *J* = 13.3 Hz), 2.72 (1H, d, *J* = 13.3 Hz), 2.14 (1H, s), 1.80 (1H, s), 1.49 (3H, s), 1.11 (3H, s), 1.10 (3H, s).

^{13}C NMR (176 MHz, $CDCl_3$): 170.1, 136.8, 128.8 (2 x C), 128.5 (2 x C), 127.8, 51.7, 50.8, 50.5, 37.3, 32.9, 26.5, 26.2, 20.6.

IR (neat, cm^{-1}): 2967, 2927, 2855, 1642, 1496, 1454, 1388, 1322, 1244, 1178.

HRMS: calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ ESI+ 245.16484, found 245.16501.

2,2,6-Trimethyl-4-(2-(trifluoromethyl)benzyl)-1,4-diazabicyclo[4.1.0]heptan-5-one (**2f**)



Colourless oil, 56%. This material required additional reverse-phase purification (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using 0-100% MeCN in water (containing 1% NH_3) as eluents.

R_f = 0.42 (EtOAc).

^{1}H NMR (700 MHz, $CDCl_3$): 7.61 (1H, d, *J* = 7.8 Hz), 7.50 (1H, t, *J* = 7.5 Hz), 7.40 - 7.28 (2H, m), 4.80 (1H, d, *J* = 15.7 Hz), 4.69 (1H, d, *J* = 15.7 Hz), 2.99 (1H, d, *J* = 13.4 Hz), 2.65 (1H, d, *J* = 13.3 Hz), 2.20 (1H, s), 1.84 (1H, s), 1.49 (3H, s), 1.15 (3H, s), 1.10 (3H, s).

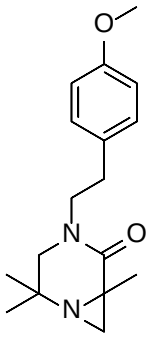
^{13}C NMR (176 MHz, $CDCl_3$): 170.9, 135.9, 132.5, 129.4, 128.8 (d, *J* = 30.3 Hz), 127.7, 126.1 (d, J = 5.6 Hz), 124.5 (q, *J* = 273.8 Hz), 52.3, 50.7, 46.8, 37.5, 33.2, 26.8, 26.3, 20.7.

^{19}F NMR (471 MHz, $CDCl_3$): -58.91.

IR (neat, cm^{-1}): 2972, 2933, 1650, 1610, 1500, 1459, 1369, 1314, 1272, 1246, 1168, 1177, 1061, 1039.

HRMS: calcd for $C_{16}H_{20}F_3N_2O$ $[M+H]^+$ ESI+ 313.15222, found 313.15250.

4-(4-Methoxyphenethyl)-2,2,6-trimethyl-1,4-diazabicyclo[4.1.0]heptan-5-one (**2g**)



Yellow gum (62%).

R_f = 0.13 (EtOAc).

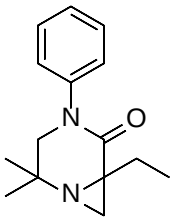
^{1}H NMR (400 MHz, $CDCl_3$): 7.17 - 7.06 (2H, m), 6.87 - 6.74 (2H, m), 3.77 (3H, s), 3.68 (1H, ddd, J = 5.9, 9.1, 13.4 Hz), 3.34 (1H, ddd, *J* = 6.5, 8.9, 13.4 Hz), 2.93 (1H, d, *J* = 13.2 Hz), 2.83 (1H, ddd, *J* = 6.5, 9.0, 13.6 Hz), 2.77 - 2.64 (2H, m), 2.04 (1H, s), 1.74 (1H, s), 1.43 (3H, s), 1.17 (3H, s), 1.12 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 169.7, 158.3, 130.8, 129.7, 114.0, 55.3, 53.4, 50.5, 50.1, 37.2, 32.8, 32.7, 26.5, 26.1, 20.3.

IR (neat, cm^{-1}): 2970, 2932, 2868, 2836, 1640, 1513, 1498, 1466, 1423, 1399, 1370, 1323, 1246, 1176, 1036.

HRMS: calcd for $C_{19}H_{29}N_2O_3$ $[M+H]^+$ ESI+ 289.19105, found 289.19125.

6-Ethyl-2,2-dimethyl-4-phenyl-1,4-diazabicyclo[4.1.0]heptan-5-one (**2h**)



White solid, 68%.

R_f = 0.28 (EtOAc).

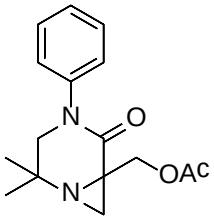
^{1}H NMR (400 MHz, $CDCl_3$): 7.43 - 7.30 (2H, m), 7.25 - 7.18 (3H, m), 3.52 (1H, d, *J* = 13.3 Hz), 3.16 (1H, d, *J* = 13.2 Hz), 2.52 - 2.39 (1H, m), 2.37 (1H, s), 1.92 (1H, s), 1.41 (3H, s), 1.26 (3H, s), 1.19 - 1.04 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): 169.0, 143.1, 129.2, 126.8, 125.9, 55.5, 50.6, 42.6, 32.5, 27.7, 26.7, 26.2, 10.9.

IR (neat, cm^{-1}): 2963, 2920, 1645, 1584, 1491, 1463, 1440, 1260., 1185, 1094.

HRMS: calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ ESI+ 245.16484, found 245.1647.

(2,2-Dimethyl-5-oxo-4-phenyl-1,4-diazabicyclo[4.1.0]heptan-6-yl)methyl acetate (**2i**)



Yellow solid, 51%.

R_f = 0.38 (EtOAc).

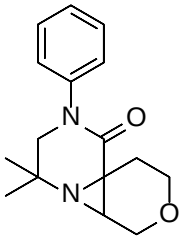
^{1}H NMR (400 MHz, $CDCl_3$): 7.46 - 7.31 (2H, m), 7.31 - 7.16 (3H, m), 4.93 (1H, d, *J* = 11.3 Hz), 3.81 (1H, d, *J* = 11.3 Hz), 3.56 (1H, d, *J* = 13.4 Hz), 3.21 (1H, d, *J* = 13.4 Hz), 2.48 (1H, s), 2.12 (1H, s), 2.09 (3H, s), 1.44 (3H, s), 1.28 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 170.8, 167.0, 142.4, 129.3 (2 x C), 127.0, 125.7 (2 x C), 66.3, 55.2, 51.0, 39.9, 30.4, 26.0, 21.1.

IR (neat, cm^{-1}): 2970, 2932, 2873, 1738, 1658, 1595, 1498, 1470, 1453, 1428, 1384, 1368, 1330, 1313, 1248, 1181, 1037.

HRMS: calcd for $C_{16}H_{21}N_2O_3$ $[M+H]^+$ ESI+ 289.15467, found 289.15448.

4,4-Dimethyl-2-phenylhexahydropyrano[4',3':2,3]azireno[1,2-a]pyrazin-1(2H)-one (**2j**)



Yellow solid, 45%.

$\mathbf{R_f}$ = 0.35 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.43 - 7.34 (2H, m), 7.27 - 7.18 (3H, m), 4.00 (1H, d, *J* = 12.1 Hz), 3.86 (1H, dd, *J* = 3.0, 12.1 Hz), 3.78 - 3.68 (1H, m), 3.57 (1H, d, *J* = 13.4 Hz), 3.32 (1H, ddd, *J* = 4.8, 9.3, 11.5 Hz), 3.19 (1H, d, *J* = 13.3 Hz), 2.92 (1H, dt, *J* = 4.6, 14.4 Hz), 2.68 (1H, d, *J* = 2.8 Hz), 1.80 (1H, ddd, *J* = 5.6, 9.2, 14.6 Hz), 1.43 (3H, s), 1.26 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 168.2, 143.1, 129.4 (2 x C), 127.0, 125.9 (2 x C), 65.1, 63.2, 55.9, 50.9, 39.2, 35.2, 26.2, 25.8, 24.3.

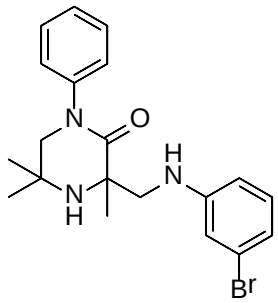
IR (neat, cm^{-1}): 2967, 2931, 2871, 1736, 1651, 1594, 1494, 1427, 1384, 1321, 1248, 1125.

HRMS: calcd for $C_{16}H_{21}N_2O_2$ $[M+H]^+$ ESI+ 273.15975, found 273.15982.

Transformation of aziridine products

Conditions A: The nucleophile (1.1 eq.) was added to **2a** (1 eq.) and tris(perfluorophenyl)borane (0.1 eq.) in MeCN (0.1 M) at room temperature under N_2. The resulting solution was stirred at 65 °C for 18 hours. The solvent was removed under reduced pressure and the residue was directly purified by flash silica chromatography to give the product.

3-((3-Bromophenylamino)methyl)-3,5,5-trimethyl-1-phenylpiperazin-2-one (**5a**)



Brown gum, 48%. This material required additional reverse-phase purification (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using 0-100% MeCN in water (containing 1% NH_3) as eluents.

R_f = 0.14 (1:1 heptane: EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.41 - 7.34 (2H, m), 7.28 - 7.21 (1H, m), 7.18 (2H, dd, *J* = 1.2, 8.5 Hz), 6.99 (1H, t, *J* = 8.0 Hz), 6.84 (1H, t, *J* = 2.0 Hz), 6.79 (1H, ddd, *J* = 0.8, 1.8, 7.8 Hz), 6.59 (1H, ddd, *J* = 0.7, 2.3, 8.2 Hz), 4.67 (1H, t, *J* = 5.9 Hz), 3.61 (1H, d, *J* = 12.1 Hz), 3.51 (1H, d, *J* = 12.1 Hz), 3.43 (1H, dd, *J* = 6.5, 12.2 Hz), 3.14 (1H, dd, *J* = 5.8, 12.2 Hz), 1.51 (3H, s), 1.36 (3H, s), 1.27 (3H, s).

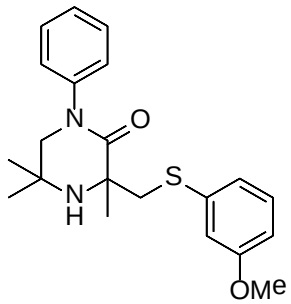
N-H signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$): 172.4, 150.1, 143.1, 130.6, 129.3, 127.0, 125.8, 123.4, 120.3, 116.3, 112.3, 62.3, 59.2, 53.7, 49.7, 28.0, 27.9, 27.3.

IR (neat, cm^{-1}): 2970, 1656, 1643, 1595, 1492, 1453, 1423, 1394, 1381, 1316, 1264, 1172.

HRMS: calcd for $C_{20}H_{25}BrN_3O$ $[M+H]^+$ ESI+ 402.11755, found 402.11783.

3-((3-Methoxyphenylthio)methyl)-3,5,5-trimethyl-1-phenylpiperazin-2-one (**5b**)



Yellow gum, 99%.

R_f = 0.31 (1:1 heptane: EtOAc).

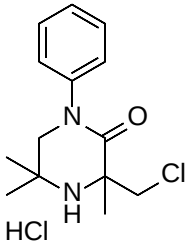
^{1}H NMR (400 MHz, $CDCl_3$): 7.40 - 7.33 (2H, m), 7.27 - 7.18 (3H, m), 7.16 (1H, d, *J* = 8.1 Hz), 7.02 (1H, dt, *J* = 1.2, 7.7 Hz), 7.01 - 6.98 (1H, m), 6.72 (1H, ddd, *J* = 0.8, 2.5, 8.3 Hz), 3.80 - 3.72 (4H, m), 3.61 (1H, d, *J* = 12.9 Hz), 3.41 (1H, d, *J* = 11.8 Hz), 3.19 (1H, d, *J* = 12.9 Hz), 1.84 (1H, br s),1.57 (3H, s), 1.37 (3H, s), 1.17 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 171.8, 160.1, 143.4, 138.0, 129.9 (2 x C), 129.2, 126.9, 126.0 (2 x C), 122.1, 115.2, 112.5, 62.8, 60.0, 55.4, 49.2, 47.7, 29.5, 28.4, 26.8.

IR (neat, cm^{-1}): 3316, 3062, 2968, 2933, 2835, 1651, 1590, 1478, 1422, 1380, 1366, 1316, 1283, 1247, 1230, 1178, 1097, 1074, 1041.

HRMS: calcd for $C_{21}H_{27}N_2O_2S$ $[M+H]^+$ ESI+ 371.17878, found 371.17911.

3-(Chloromethyl)-3,5,5-trimethyl-1-phenylpiperazin-2-one hydrochloride (**5c**)



4M HCl in 1,4-dioxane (10 eq.) was added dropwise to **2a** (1 eq.) in CH_2Cl_2 (0.1 M) at room temperature. The resulting solution was stirred at room temperature for 2 days over the weekend. The solvent was removed under a stream of N_2 to give a sticky orange gum which was redissolved in MeOH and re-evaporated to give a yellow solid, which was suspended in Et_2O and collected by filtration to give the title compound as a yellow/ochre solid (60% as an HCl salt).

^{1}H NMR (400 MHz, d^6-DMSO): 10.37 (1H, br s), 9.82 (1H, br s), 7.48 - 7.42 (2H, m), 7.33 (3H, td, *J* = 1.3, 7.6 Hz), 4.45 (1H, d, *J* = 11.8 Hz), 4.18 (1H, d, *J* = 13.2 Hz), 3.95 (1H, d, *J* = 11.7 Hz), 3.68 (1H, d, *J* = 13.3 Hz), 1.77 (3H, s), 1.59 (3H, s), 1.56 (3H, s).

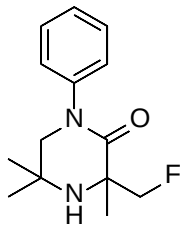
^{13}C NMR (101 MHz, d^6-DMSO): 164.9, 141.7, 129.0 (2 x C), 127.3, 125.8 (2 x C), 61.6, 56.8, 54.7, 51.0, 23.4, 23.0, 21.8.

IR (neat, cm^{-1}): 3419, 1659, 1642, 1494, 1440, 1384, 1332.

HRMS: calcd for $C_{14}H_{20}ClN_2O$ $[M+H]^+$ ESI+ 267.12587, found 267.12576.

Conditions B

3-(Fluoromethyl)-3,5,5-trimethyl-1-phenylpiperazin-2-one (**5d**)



Triethylamine trihydrofluoride (4 eq.) was added dropwise to **2a** (1 eq.) in MeCN (0.1 M) at room temperature in a small thick-walled teflon vessel with a screw cap with a small stirred bar. The vessel was sealed and was stirred at 75 °C 4 days. Additional triethylamine trihydrofluoride (1 eq.) was added daily. The reaction was directly purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in heptane. Pure fractions were evaporated to dryness to afford the title compound as a white foam (84%).

$\mathbf{R_f}$ = 0.49 (EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$): 7.49 - 7.30 (2H, m), 7.32 - 7.11 (3H, m), 4.69 (1H, dd, *J* = 8.6, 47.0 Hz), 4.20 (1H, dd, *J* = 8.6, 48.0 Hz), 3.66 (1H, d, *J* = 12.0 Hz), 3.50 (1H, d, *J* = 12.0 Hz), 1.73 (1H, br s), 1.40 (3H, d, J = 2.5 Hz), 1.37 (3H, s), 1.26 (3H, s).

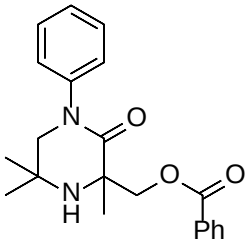
^{13}C NMR (101 MHz, $CDCl_3$): 170.6, 143.1, 129.3, 127.0, 125.8, 89.3 (d, *J* = 175.6 Hz), 62.7, 59.6 (d, *J* = 17.8 Hz), 49.5, 28.3, 26.9, 24.7 (d, *J* = 5.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): -100.01.

IR (neat, cm^{-1}): 3326, 2968, 1646, 1595, 1454, 1443, 1382, 1368, 1321, 1195, 1024.

HRMS: calcd for $C_{14}H_{20}FN_2O$ $[M+H]^+$ ESI+ 255.15542, found 255.15543.

(2,6,6-Trimethyl-3-oxo-4-phenylpiperazin-2-yl)methyl benzoate (**5e**)



benzoic acid (1.1 eq.) was added to **2a** (1 eq.) in MeCN (0.1 M) at 75°C and stirred at 75 °C for 3 days. LC-MS shows the reaction stalls at 90% conversion, despite addition of more acid. The solvent was removed under a stream of N_2 gas and the residue was purified by flash silica chromatography, elution gradient 0 to 70% EtOAc in heptane. Pure fractions were evaporated to dryness to afford the title compound as a colourless oil (63%).

R_f = 0.67 (EtOAc).

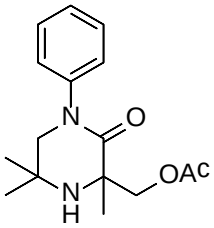
^{1}H NMR (400 MHz, $CDCl_3$): 8.11 - 8.03 (2H, m), 7.60 - 7.54 (1H, m), 7.49 - 7.42 (2H, m), 7.38 (2H, td, *J* = 1.9, 7.2 Hz), 7.30 - 7.21 (3H, m), 4.50 (1H, d, *J* = 10.7 Hz), 4.42 (1H, d, *J* = 10.7 Hz), 3.68 (1H, d, *J* = 11.9 Hz), 3.49 (1H, d, *J* = 11.9 Hz), 1.73 (1H, s), 1.55 (3H, s), 1.38 (3H, s), 1.22 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 170.8, 166.4, 143.2, 133.1, 130.2, 129.6, 129.2, 128.5, 126.8, 125.6, 71.8, 62.6, 59.2, 49.4, 28.5, 26.8, 26.2.

IR (neat, cm^{-1}): 3325, 2970, 2932, 2807, 1721, 1657, 1595, 1489, 1475, 1452, 1381, 1317, 1272, 1219, 1176, 1113, 1098, 1071, 1027.

HRMS: calcd for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ ESI+ 353.18597, found 353.18597.

(2,6,6-Trimethyl-3-oxo-4-phenylpiperazin-2-yl)methyl acetate (**3**)



2a (1 eq.) in acetic acid (0.1 M) was stirred at 70 °C for 18 hours. The solvent was removed under a stream of N_2 gas and the residue was purified by flash silica chromatography, elution gradient 0 to 70% EtOAc in heptane. Pure fractions were evaporated to dryness to afford the title compound as a colourless oil (71%).

R_f = 0.34 (EtOAc).

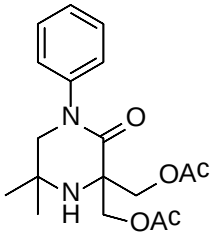
^{1}H NMR (400 MHz, $CDCl_3$): 7.43 - 7.35 (2H, m), 7.30 - 7.20 (3H, m), 4.28 (1H, d, *J* = 10.6 Hz), 4.11 (1H, d, *J* = 10.7 Hz), 3.66 (1H, d, *J* = 12.0 Hz), 3.50 (1H, d, *J* = 12.0 Hz), 2.11 (3H, s), 1.53 (1H, br s), 1.46 (3H, s), 1.36 (3H, s), 1.25 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 170.9, 143.2, 129.3 (2 x C), 126.9, 125.8 (2 x C), 71.5, 62.5, 58.8, 49.5, 28.4, 27.2, 26.2, 21.2.

IR (neat, cm^{-1}): 3326, 2971, 2934, 1740, 1657, 1595, 1494, 1474, 1454, 1422, 1380, 1370, 1319, 1233, 1190, 1044.

HRMS: calcd for $C_{16}H_{23}N_2O_3$ $[M+H]^+$ ESI+ 291.1709, found 291.1712.

(6,6-Dimethyl-3-oxo-4-phenylpiperazine-2,2-diyl)bis(methylene) diacetate (**4**)



Pivalic anhydride (2 eq.) was added to **2a** (1 eq.), $Pd(OAc)_2$ (0.05 eq.) and PIDA (3 eq.) in acetic acid (0.1 M) at 70°C under air. The resulting mixture was stirred at 70 °C for 18 hours. The reaction mixture was filtered through Celite and the filter cake was washed with CH_2Cl_2 (2 x 5 mL). The solvent was removed under reduced pressure and the orange residue obtained was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford the title compound as an orange gum (38%). **3** (37%) was also recovered.

R_f = 0.47 (EtOAc).

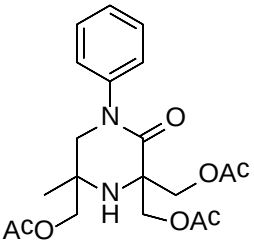
^{1}H NMR (400 MHz, $CDCl_3$): 7.48 - 7.33 (2H, m), 7.28 - 7.21 (3H, m), 4.39 (1H, d, *J* = 11.1 Hz), 4.30 (1H, d, *J* = 11.1 Hz), 3.57 (2H, s), 2.12 (6H, s), 1.66 (1H, br s), 1.30 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): 170.8 (2 x C), 142.9, 129.4 (2 x C), 127.1, 125.7 (2 x C), 67.9, 61.7, 61.3, 49.6, 28.0 (2 x C), 21.1 (2 x C).

IR (neat, cm^{-1}): 3339, 1743, 1661, 1657, 1494, 1378, 1321, 1227, 1043.

HRMS: calcd for $C_{18}H_{25}N_2O_5$ $[M+H]^+$ ESI+ 349.17580, found 349.17554.

(6-Methyl-3-oxo-4-phenylpiperazine-2,2,6-triyl)tris(methylene) triacetate (**6**)



Pivalic anhydride (2 eq.) was added to **1a** (1 eq.), PIDA (3 eq.) and $Pd(OAc)_2$ (0.05 eq.) in acetic acid (0.1 M) at 70°C under air. The resulting solution was stirred at 70 °C for 18 hours. Further PIDA (3 eq.) was added and the mixture was stirred at 70 °C for a further 24 hours. The solvent was removed under reduced pressure and the residue was directly purified by flash silica chromatography, elution gradient 0 to 75% EtOAc in heptane. Pure fractions were evaporated to dryness to afford a yellow gum. This material contains traces of inseparable tetra- and pentaacetates, but the major component is the triacetate (combined yield 45%).

$\mathbf{R_f}$ = 0.51 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): 7.43 - 7.37 (2H, m), 7.30 - 7.20 (3H, m), 4.36 (2H, dd, *J* = 6.7, 11.1 Hz), 4.27 (2H, d, *J* = 11.1 Hz), 4.20 (1H, dd, *J* = 2.6, 11.2 Hz), 3.94 (1H, d, *J* = 11.1 Hz), 3.82 - 3.70 (1H, m), 3.67 - 3.55 (1H, m), 2.12 (3H, s), 2.12 (3H, s), 2.05 (3H, s), 1.27 (3H, s).

N-H signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$): 170.7, 170.6, 170.5, 167.6, 142.4, 129.3 (2 x C), 127.2, 125.6 (2 x C), 68.5, 67.6, 67.4, 61.2, 56.7, 51.6, 23.9, 20.9, 20.9, 20.8.

IR (neat, cm^{-1}): 3348, 2972, 1743, 1661, 1595, 1494, 1475, 1427, 1377, 1230, 1042.

HRMS: calcd for $C_{20}H_{27}N_2O_7$ $[M+H]^+$ ESI+ 407.18128, found 407.18106.

References

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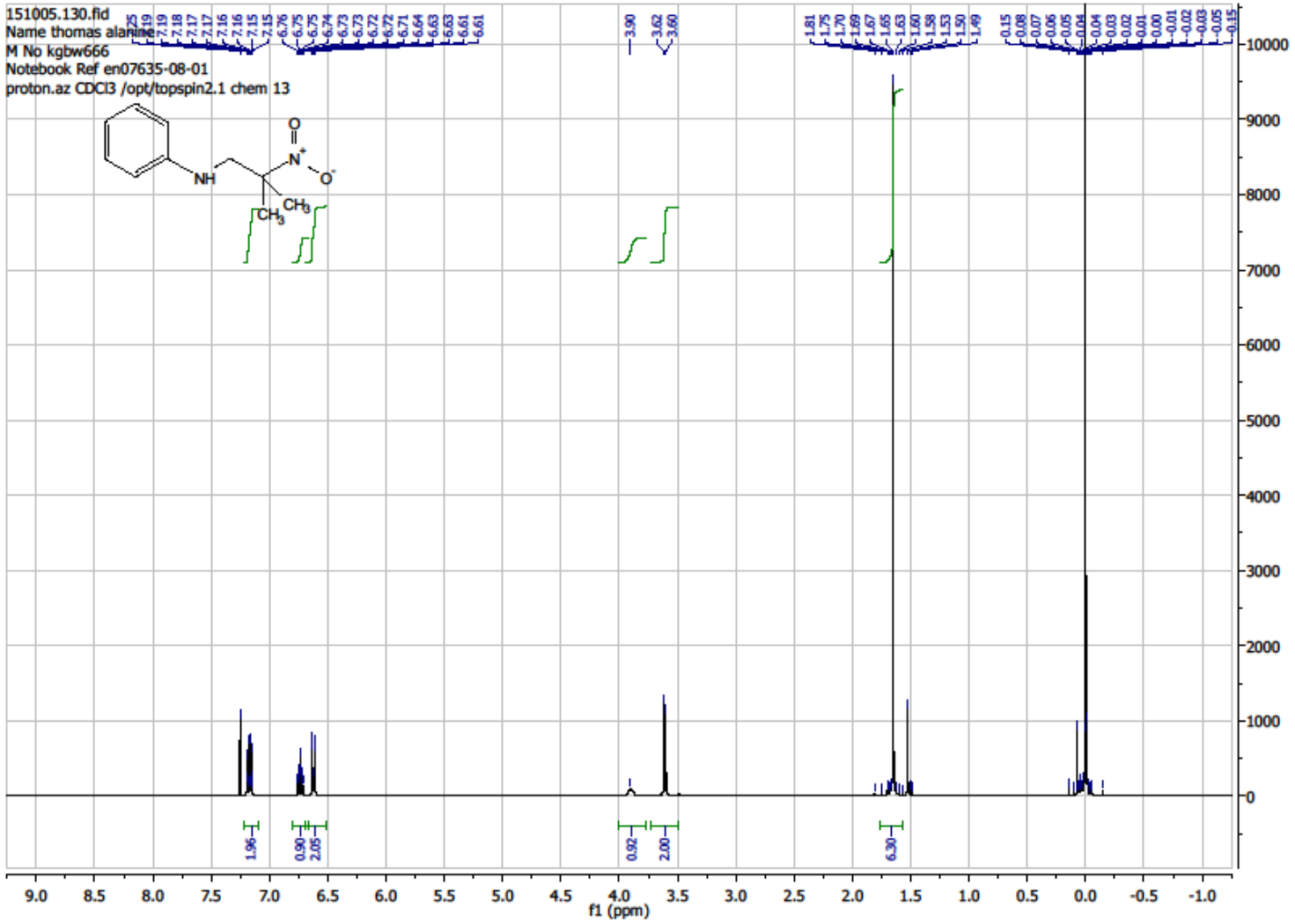
(3) Agrawal, S.; Lenormand, M.; Martin-Matute, B., *Org. Lett.*, **2012,** *14*, 1456-1459.

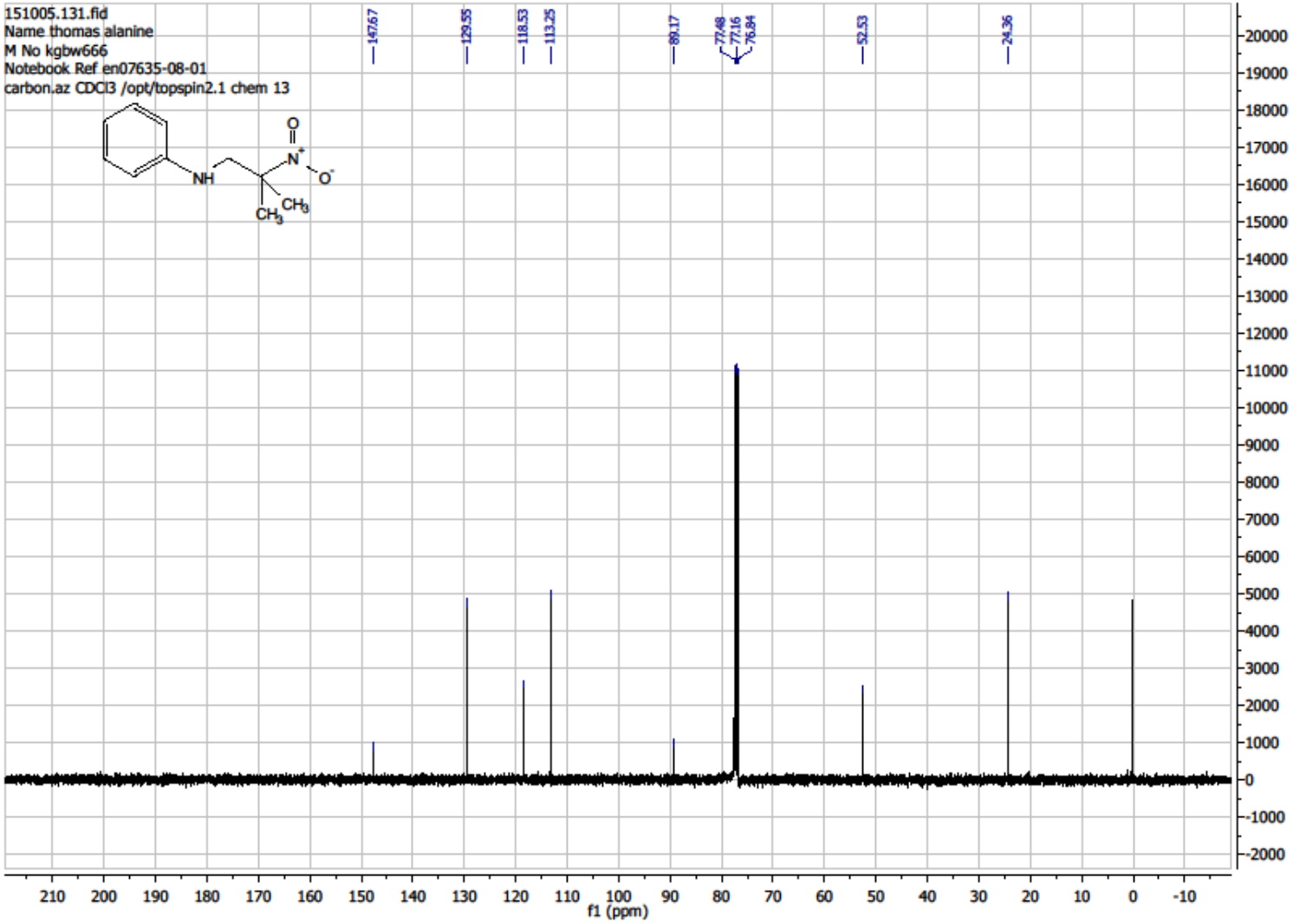
(4) Lai, J. T., *J. Org. Chem.*, **1980,** *45*, 754-755.

NMR spectra

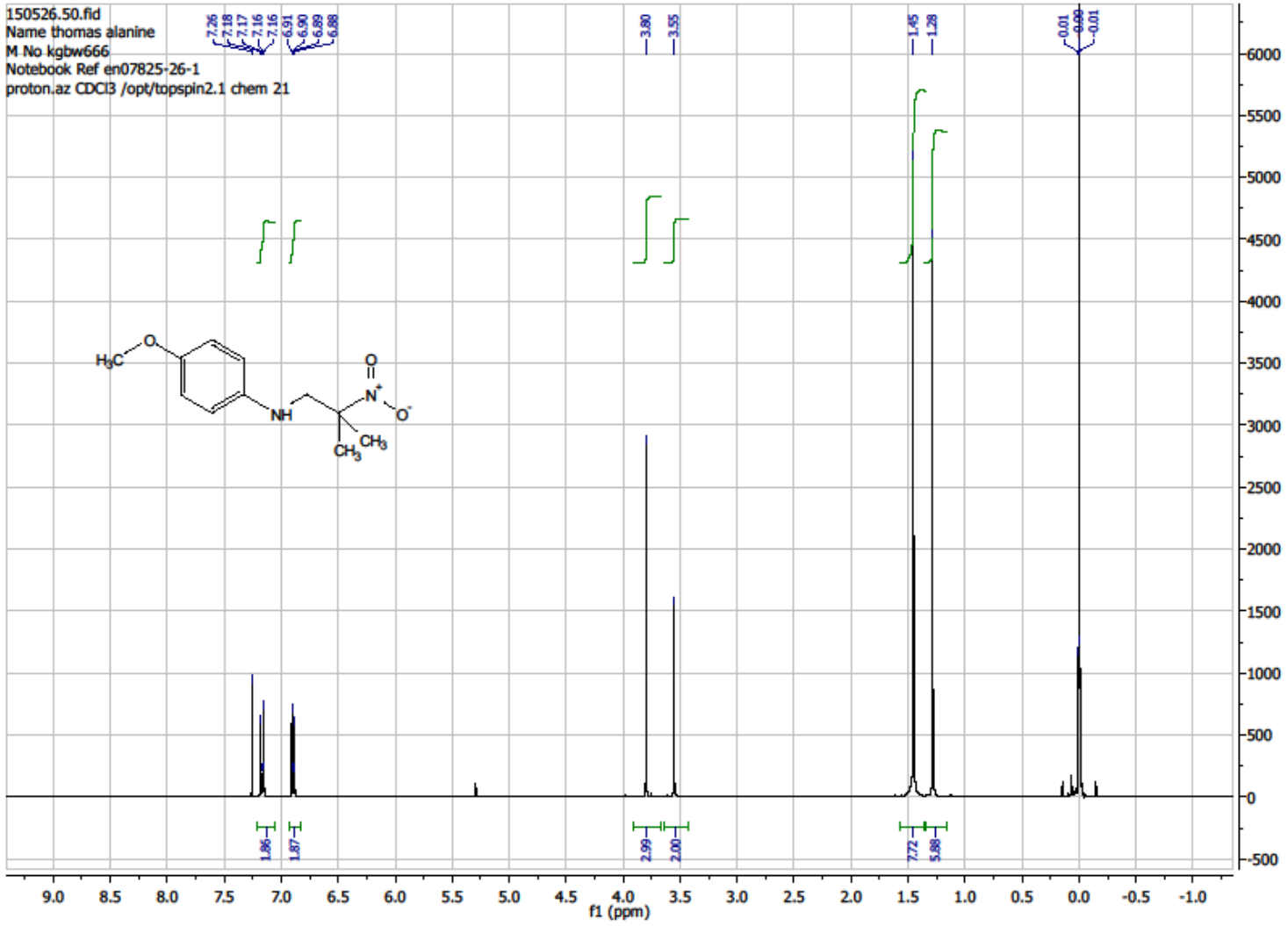
7a ^{1}H NMR 400 MHz



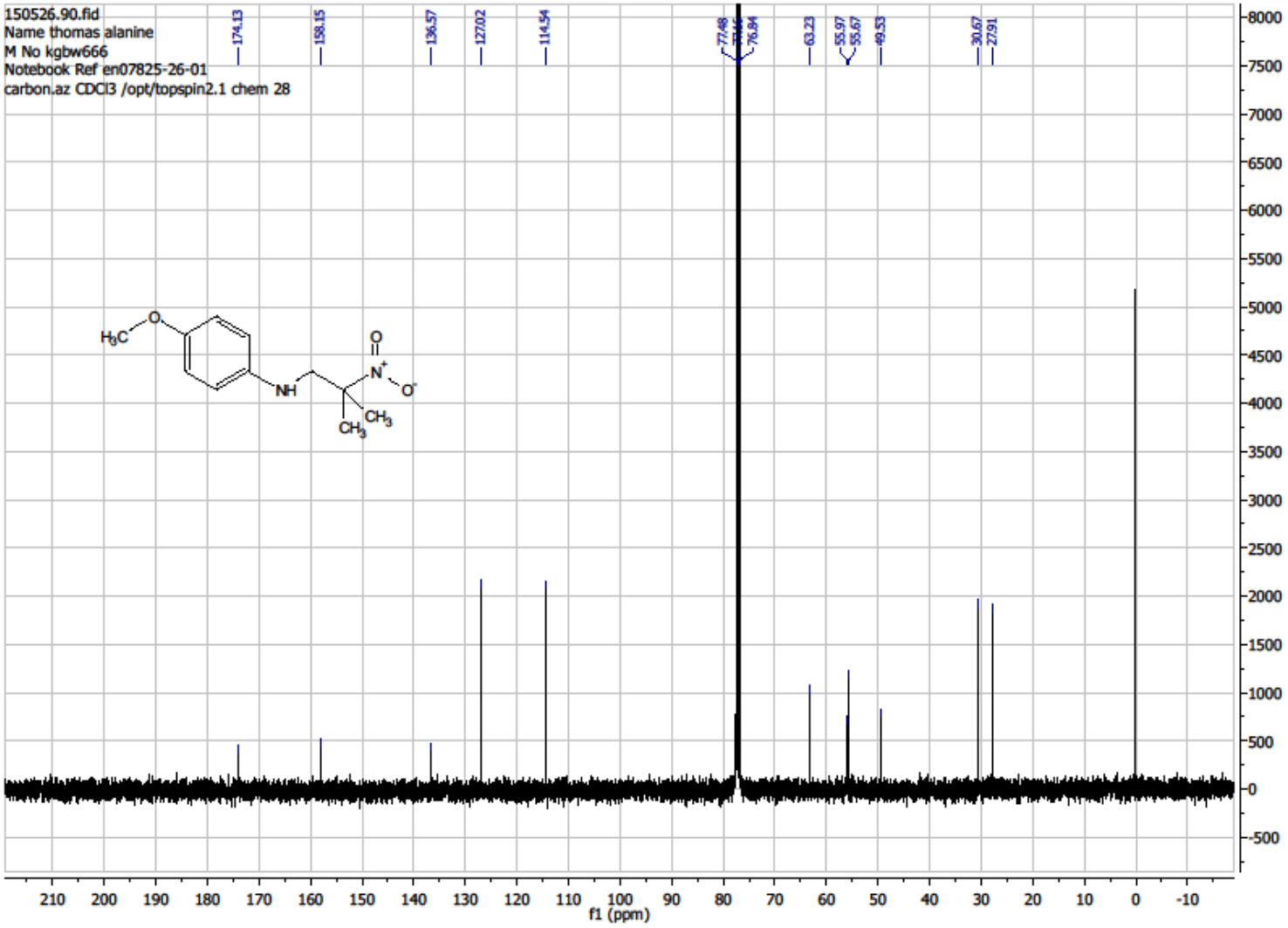
7a ^{13}C NMR 101 MHz



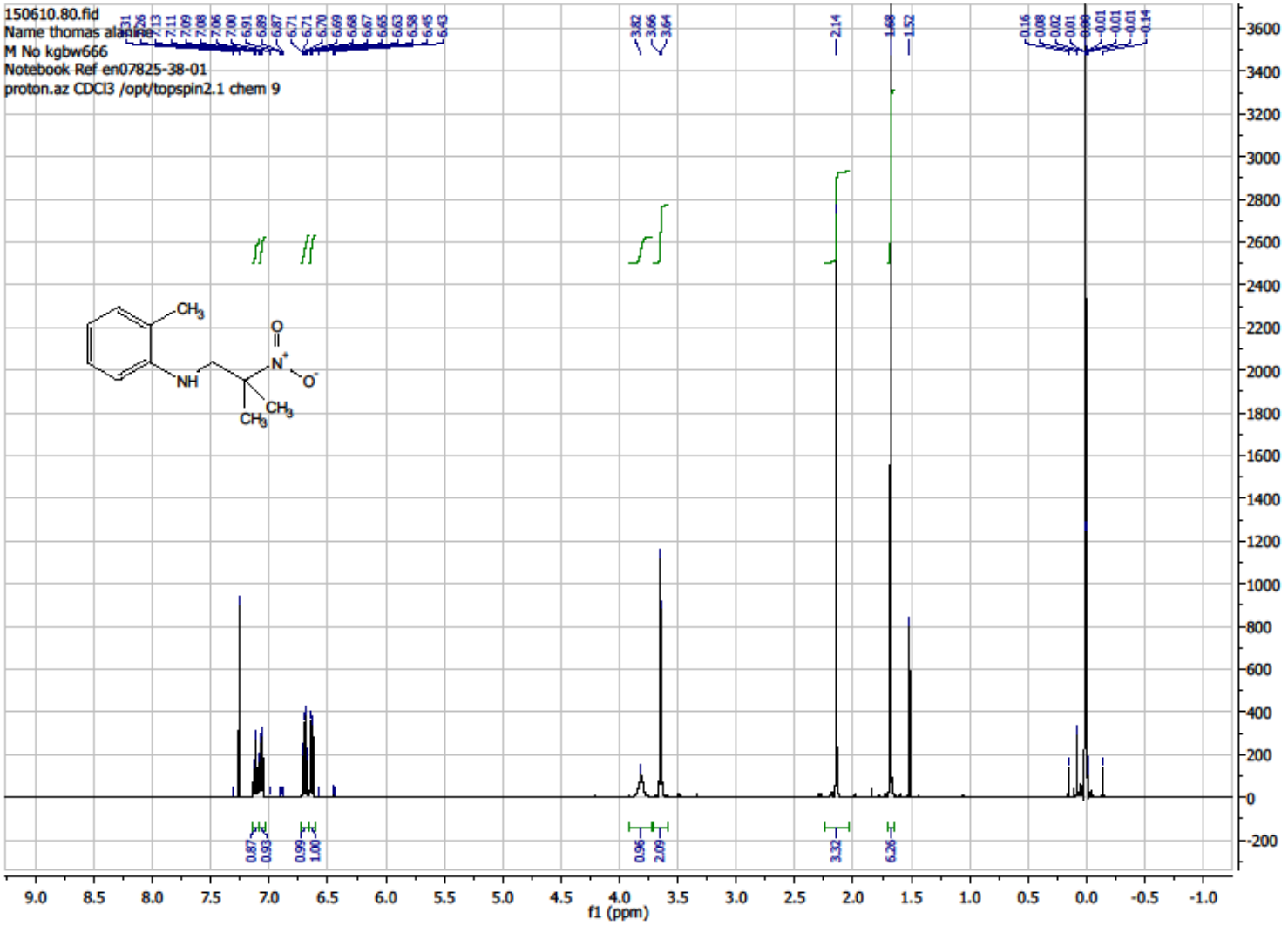
7c ^{1}H NMR 400 MHz



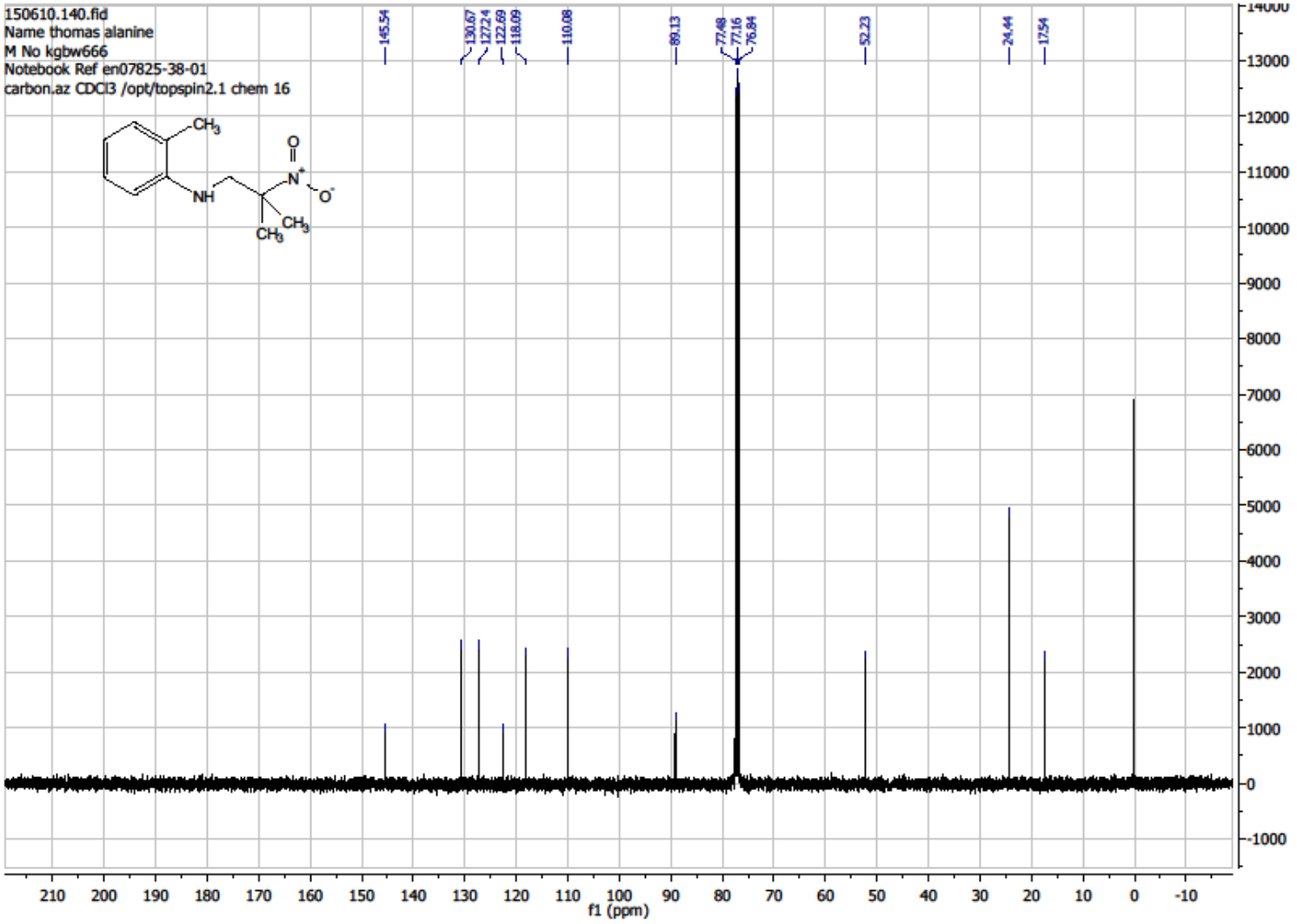
7c ^{13}C NMR 101 MHz



7d ^{1}H NMR 400 MHz



7d ^{13}C NMR 101 MHz



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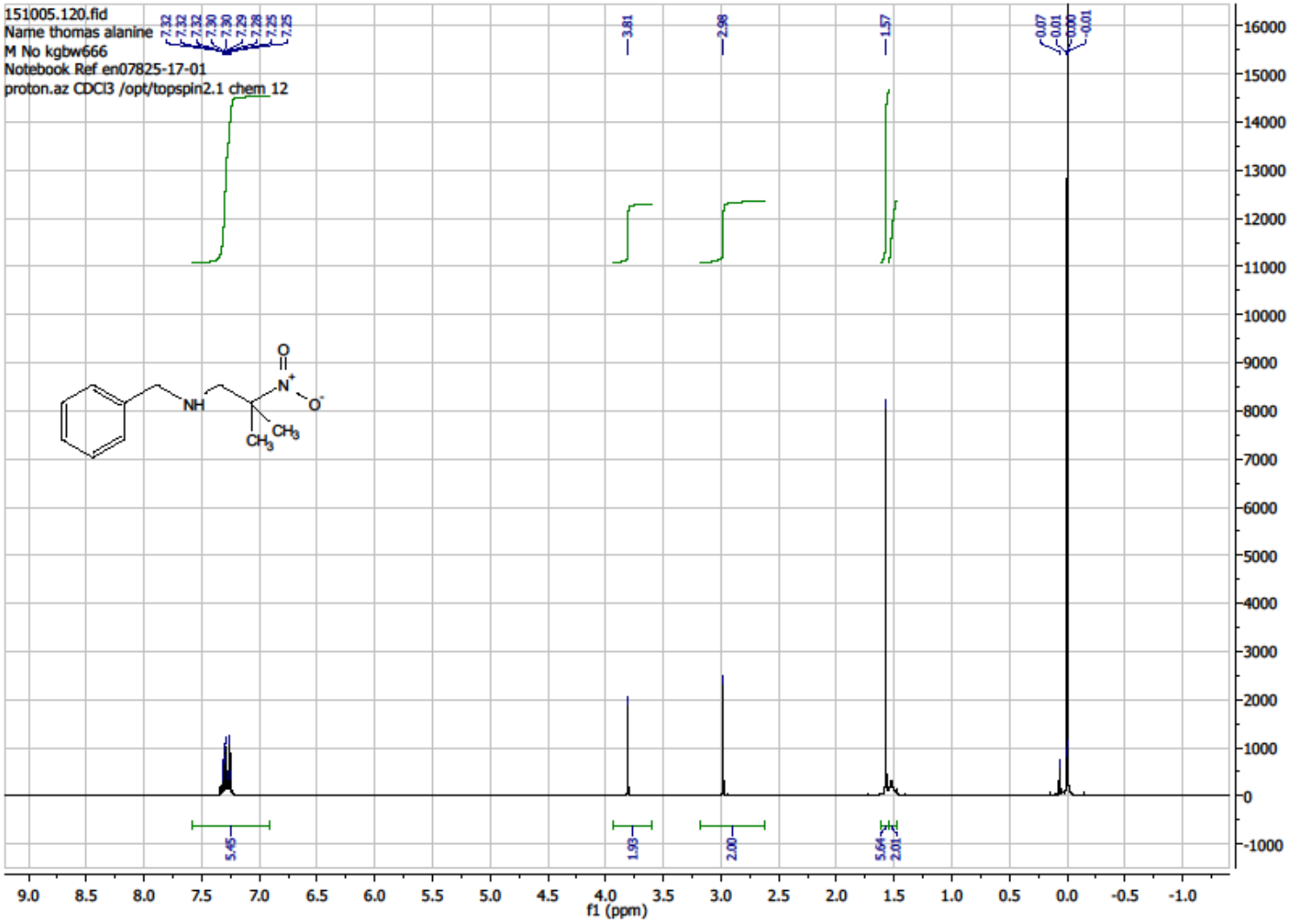
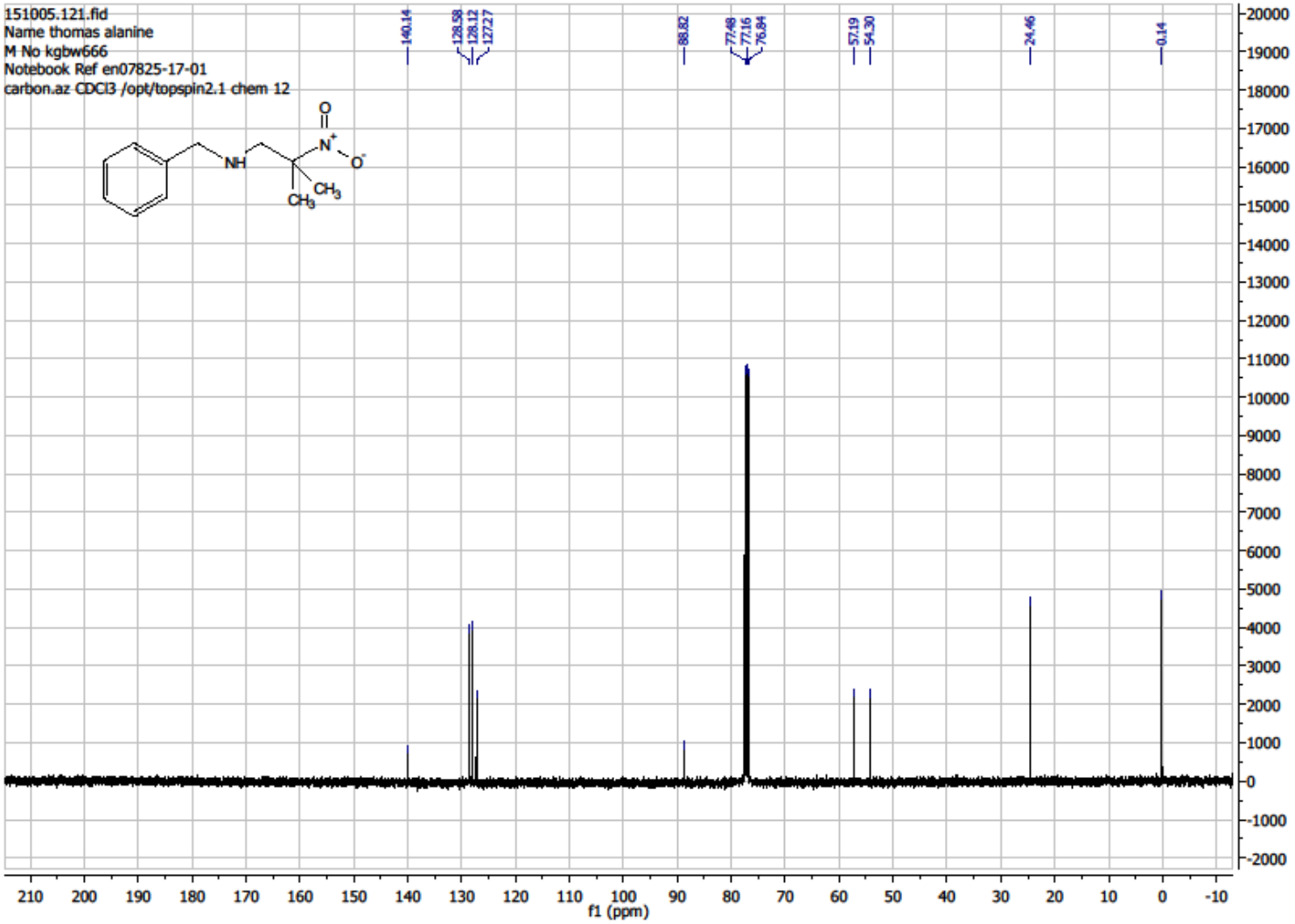
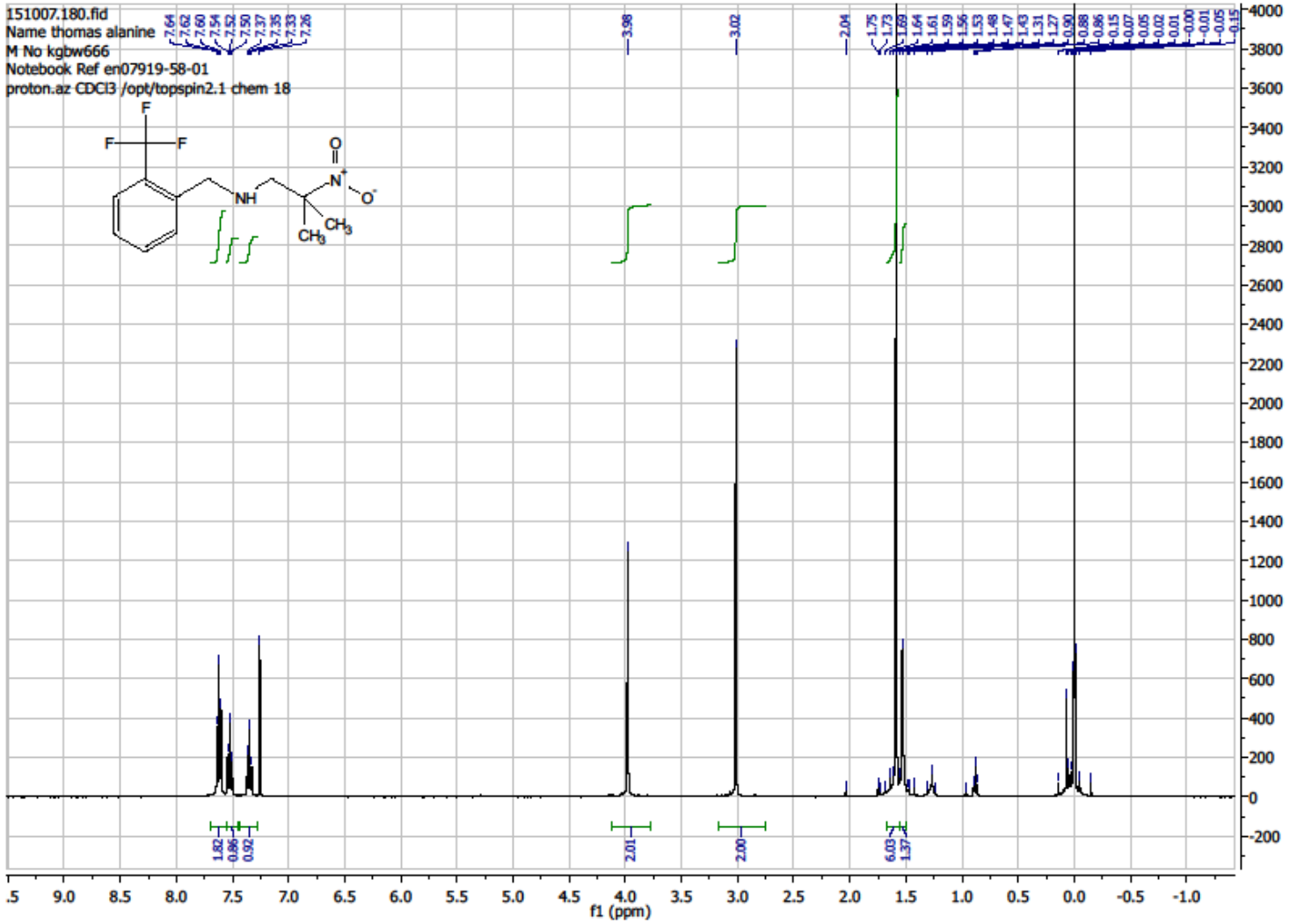


7e ^{13}C NMR 101 MHz



7f ^{1}H NMR 400 MHz



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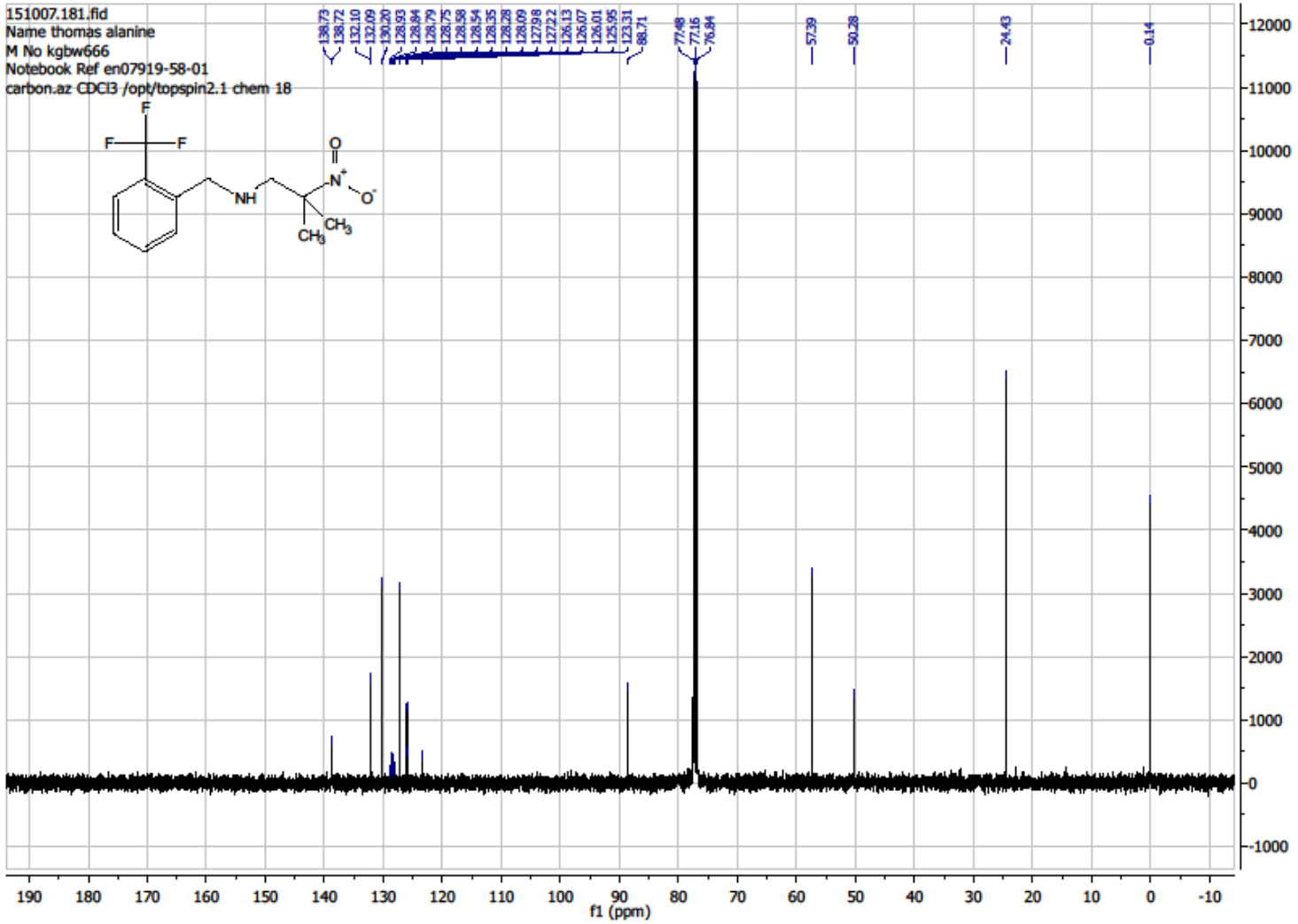
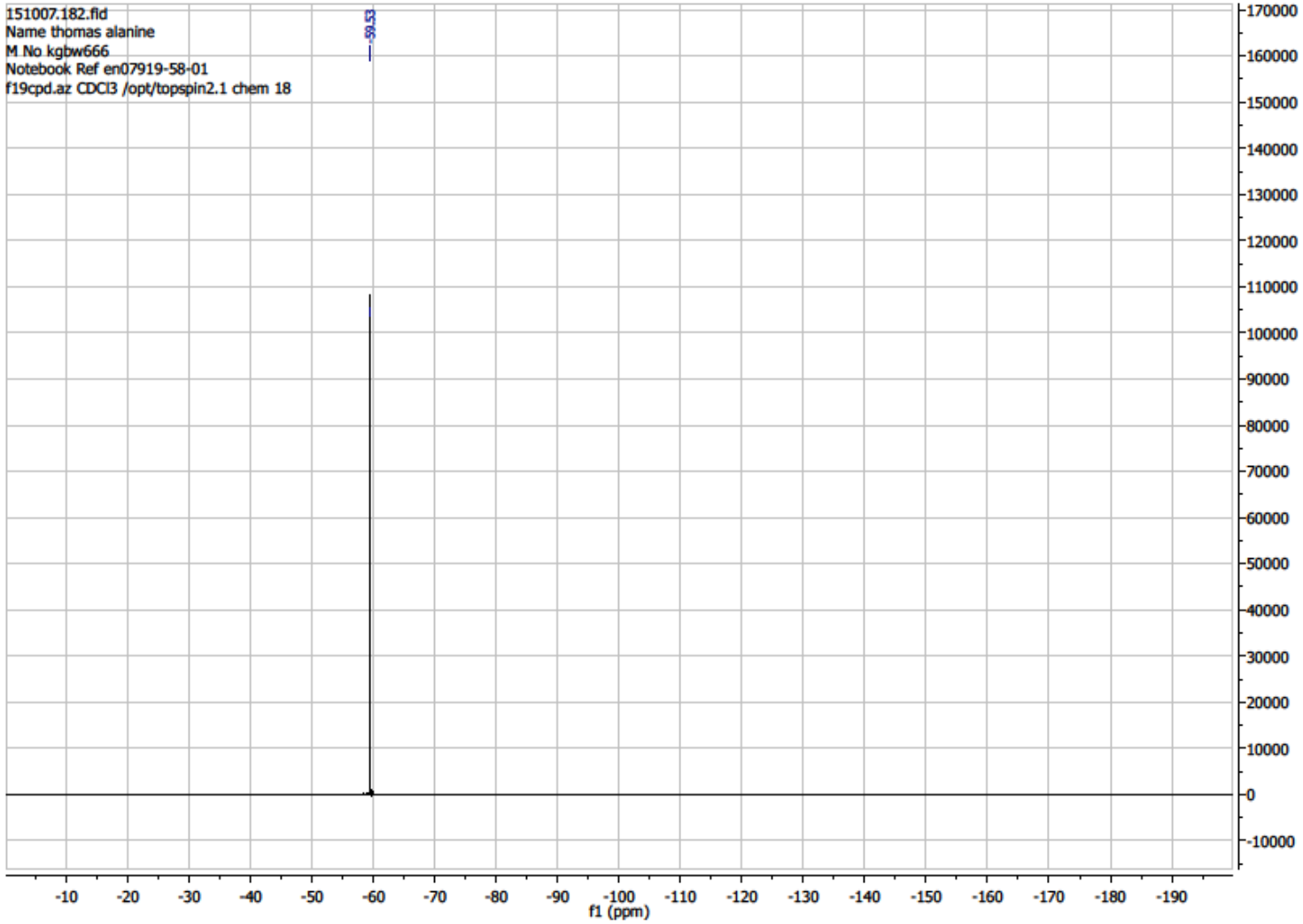
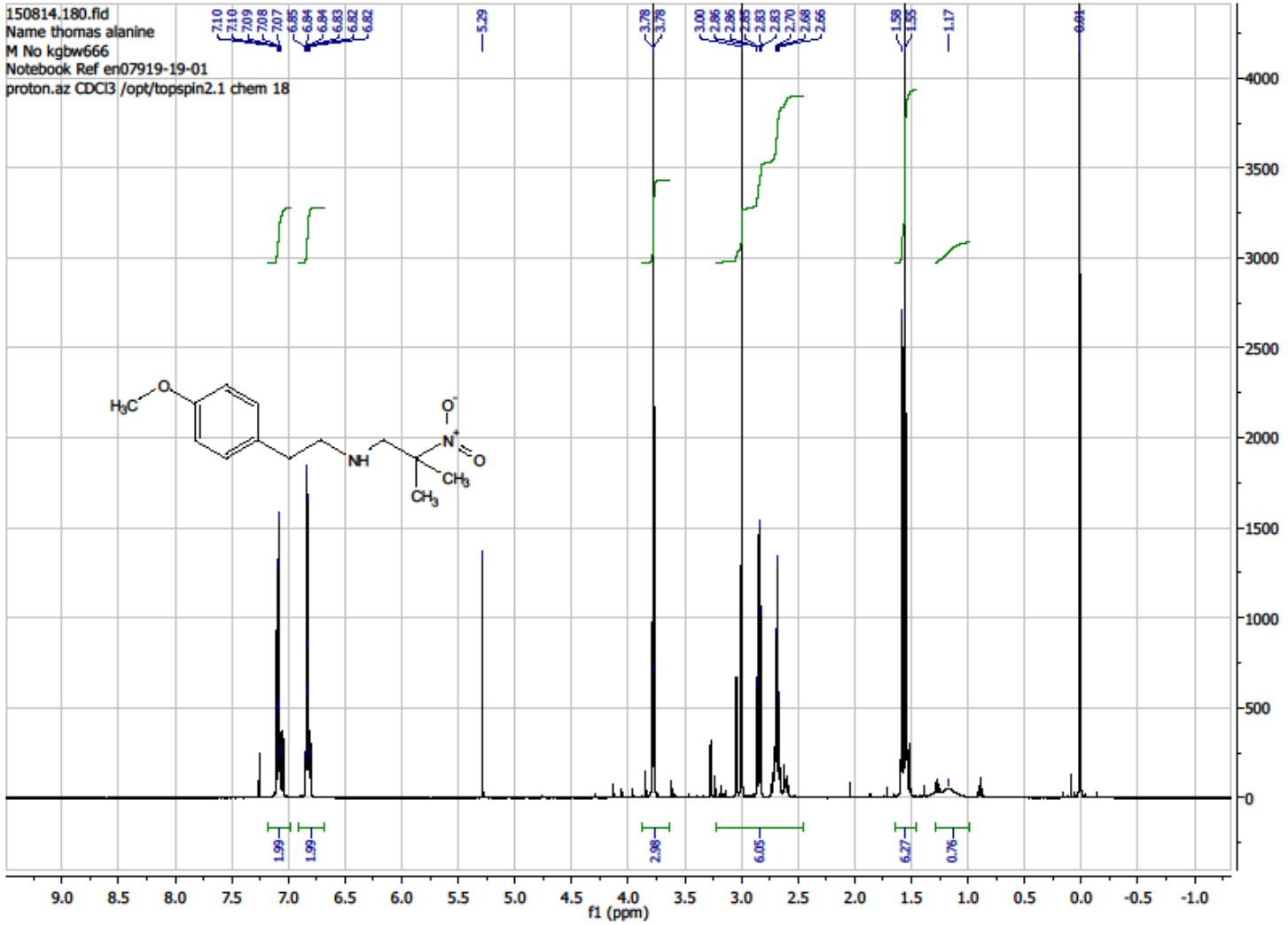


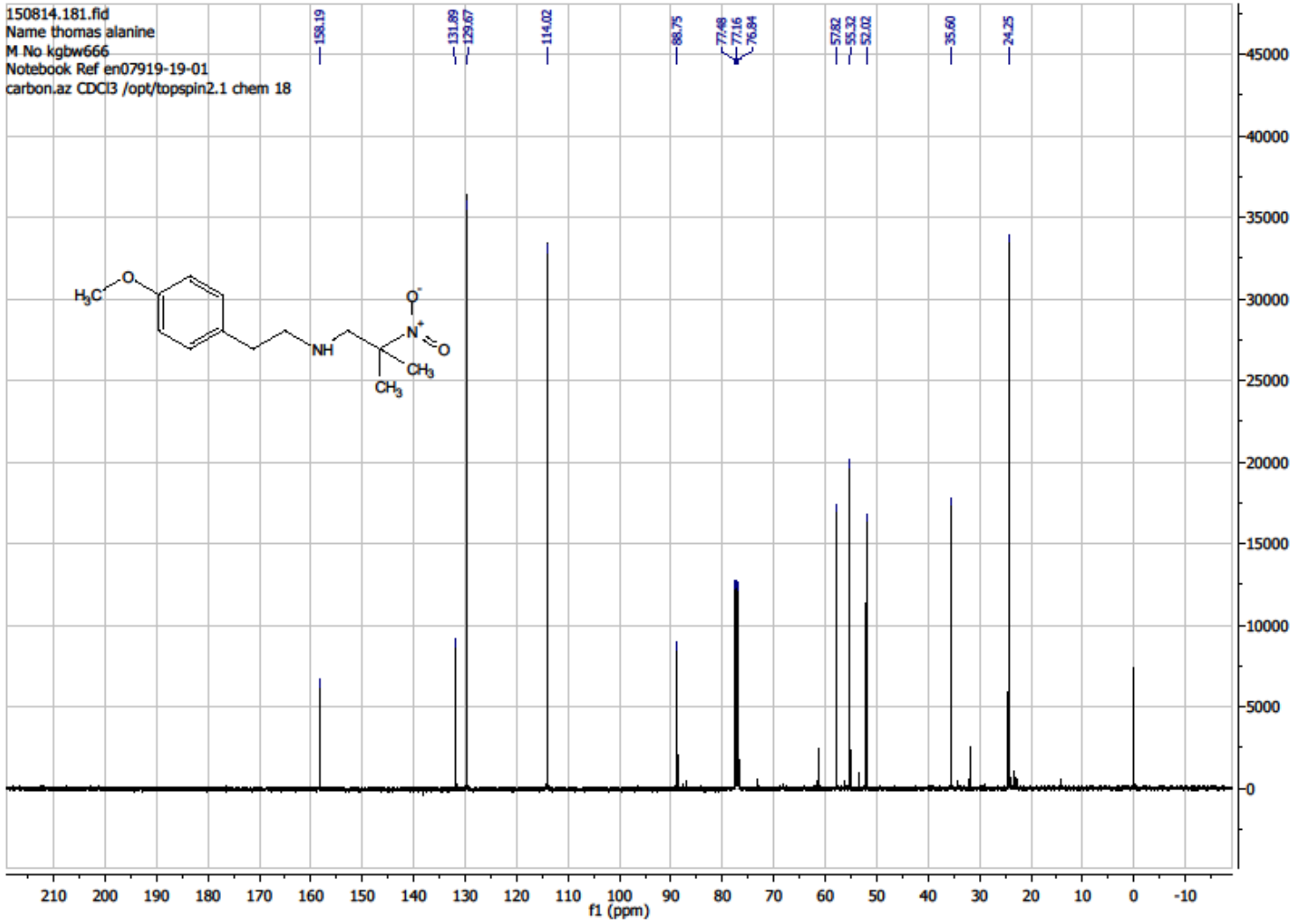
7f ^{19}F NMR 376 MHz



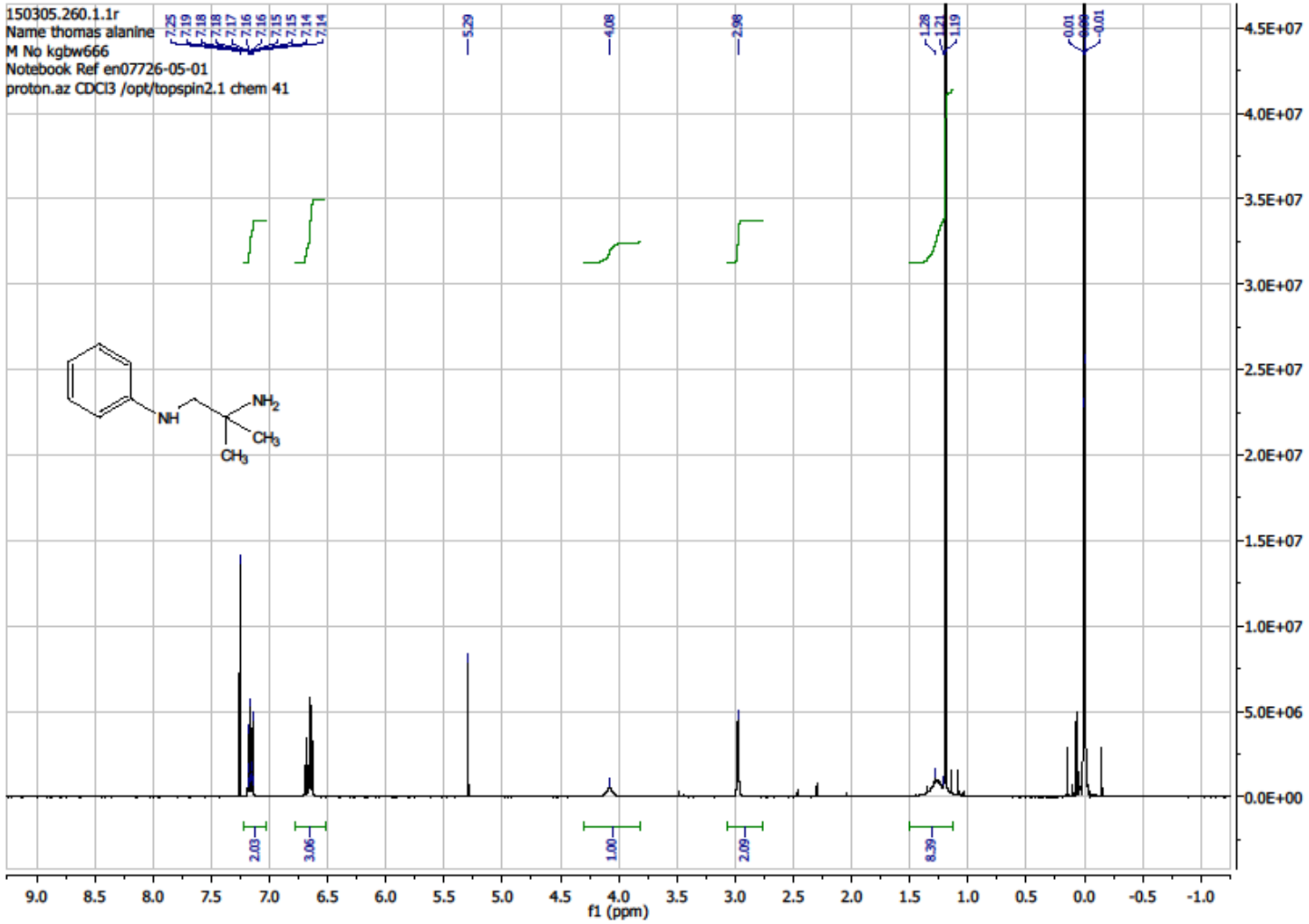
7g ^{1}H NMR 400 MHz



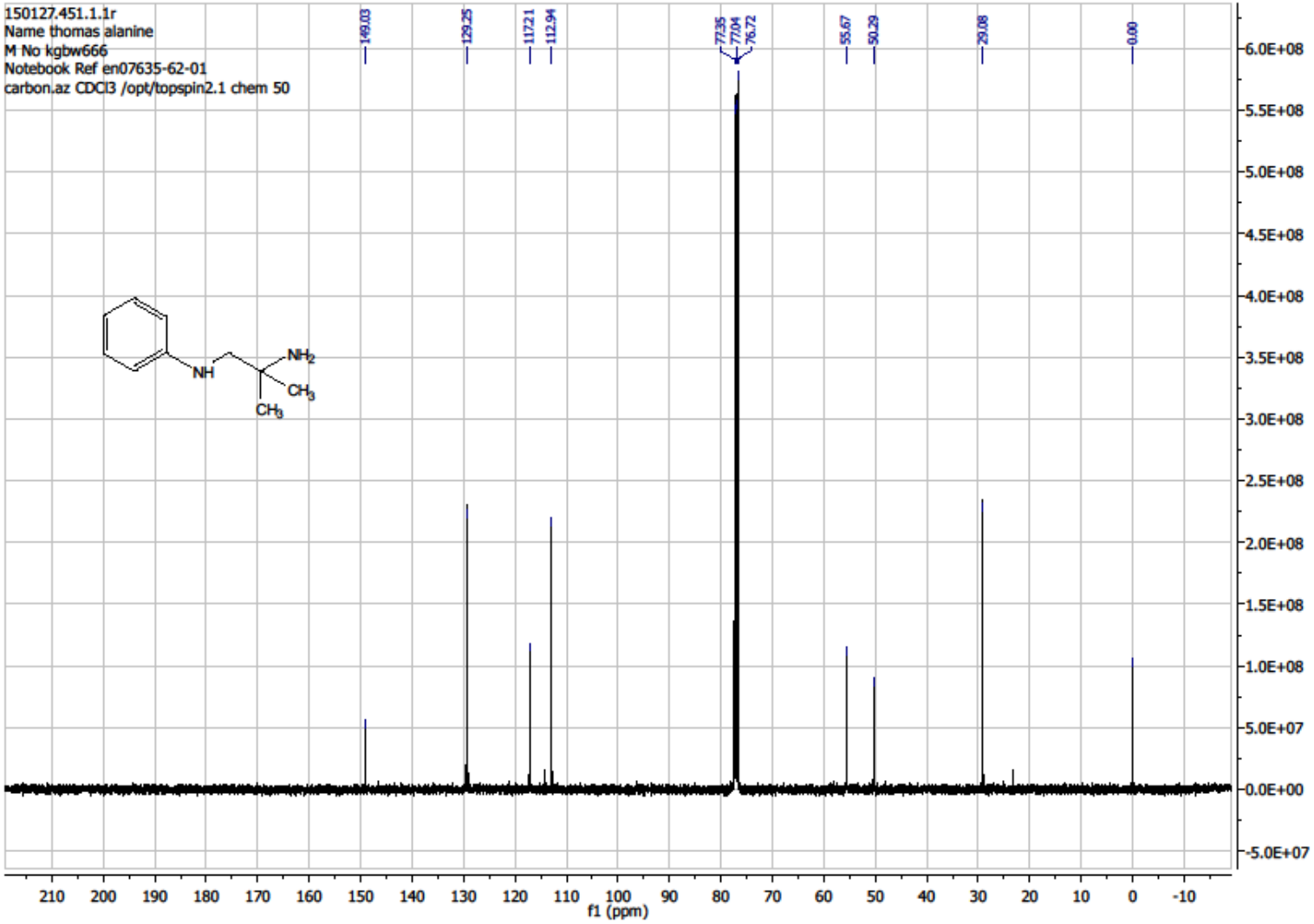
7g ^{13}C NMR 101 MHz



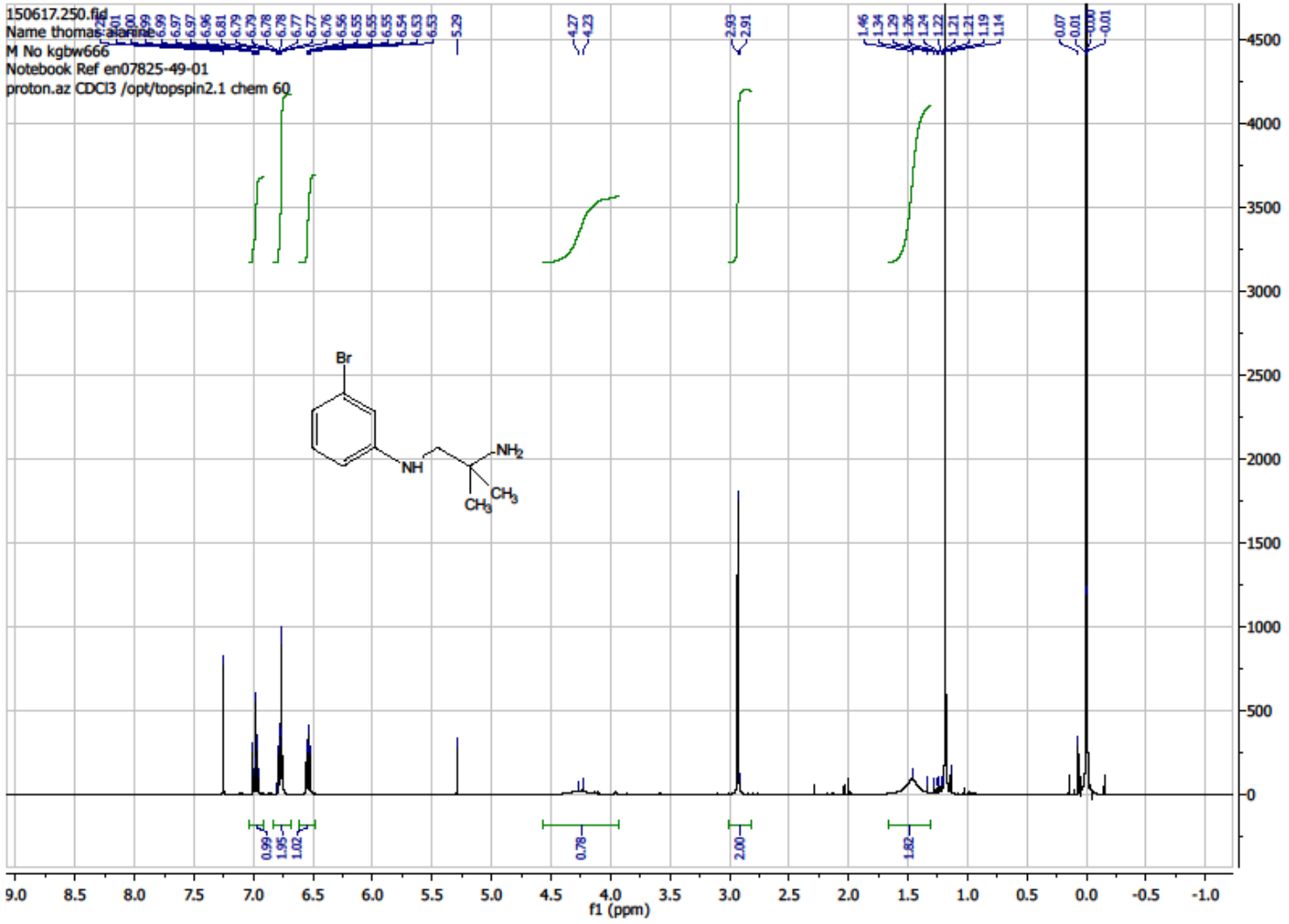
8a ^{1}H NMR 400 MHz



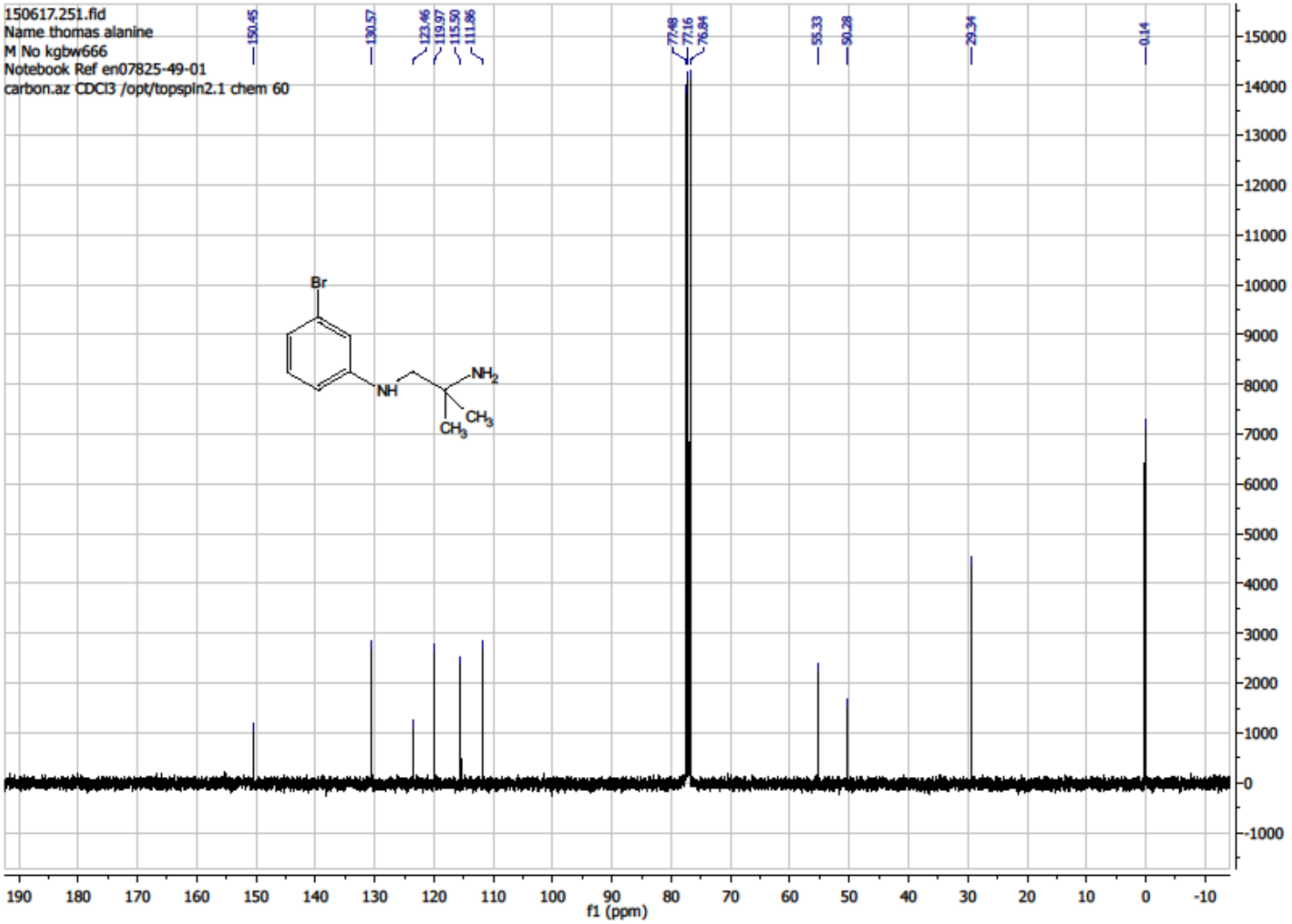
8a ^{13}C NMR 101 MHz



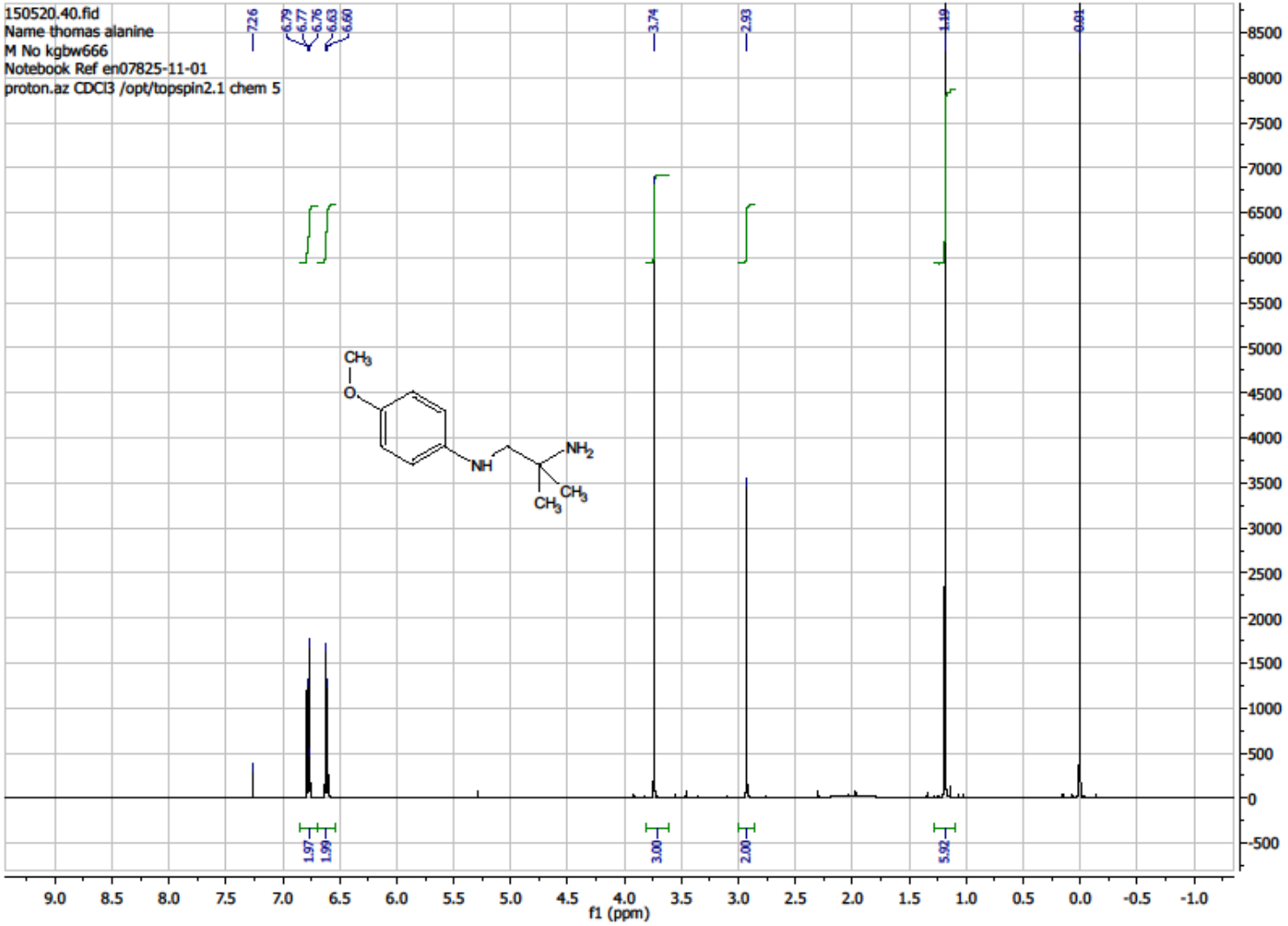
8b ^{1}H NMR 400 MHz



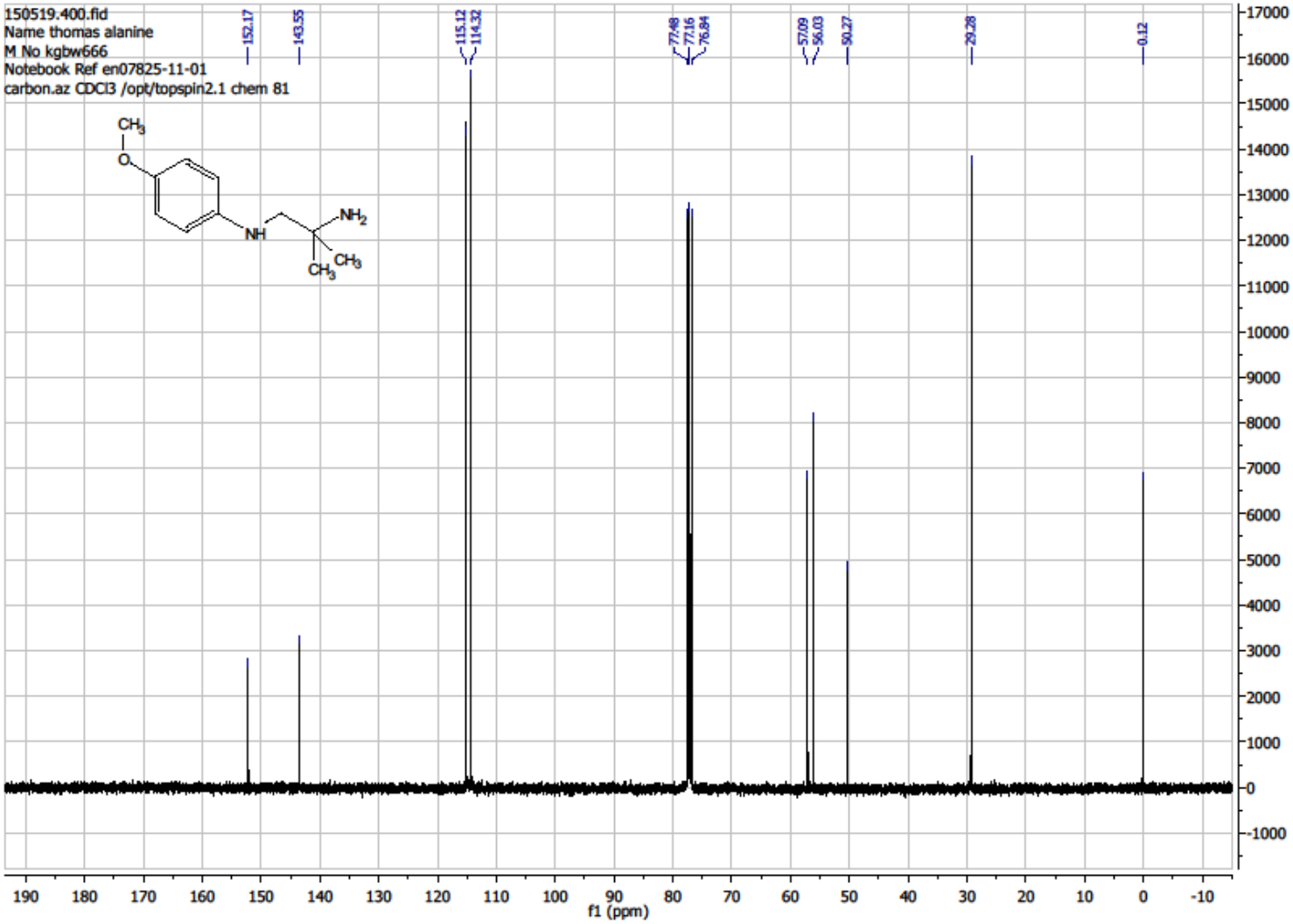
8b ^{13}C NMR 101 MHz



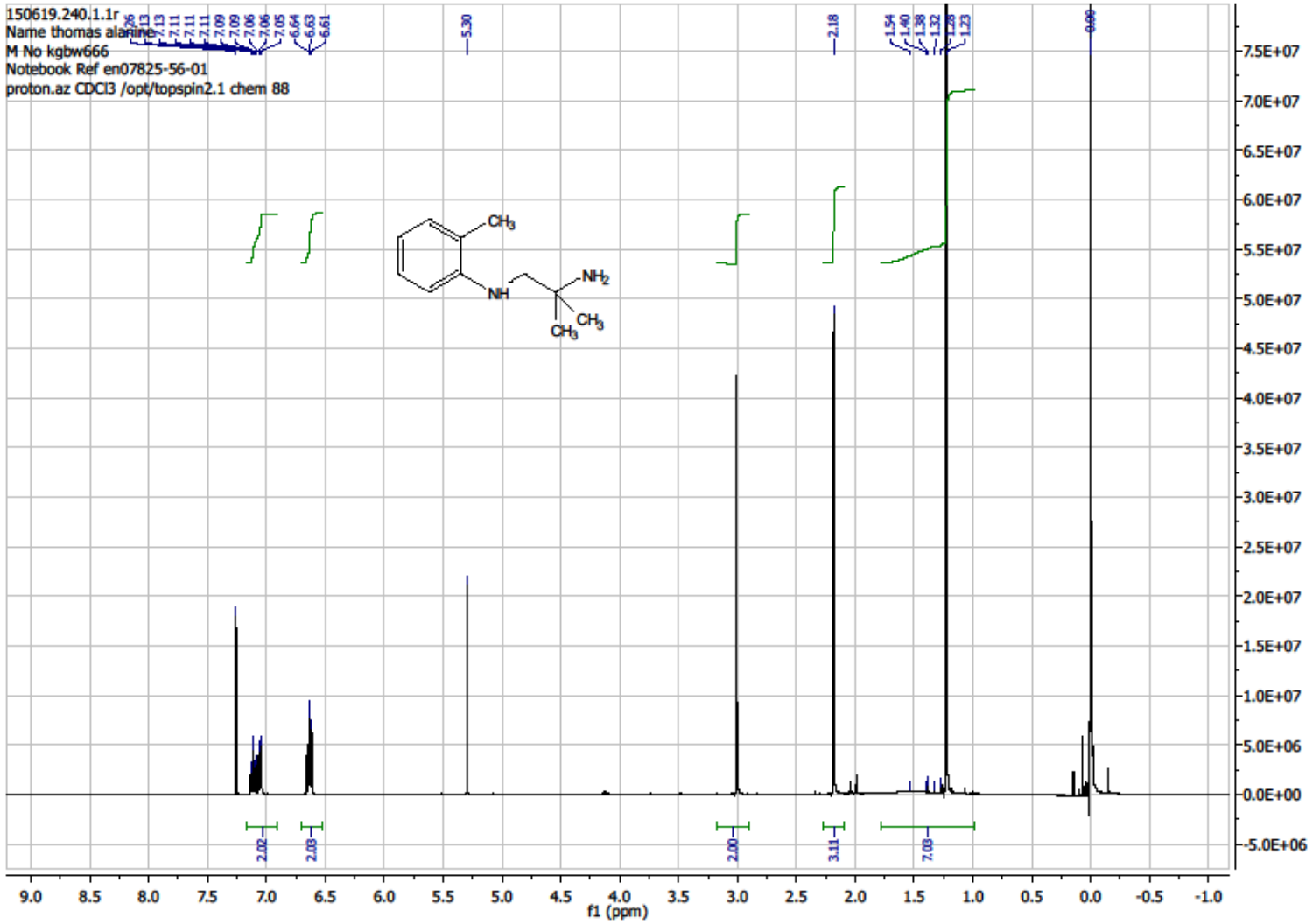
8c ^{1}H NMR 400 MHz



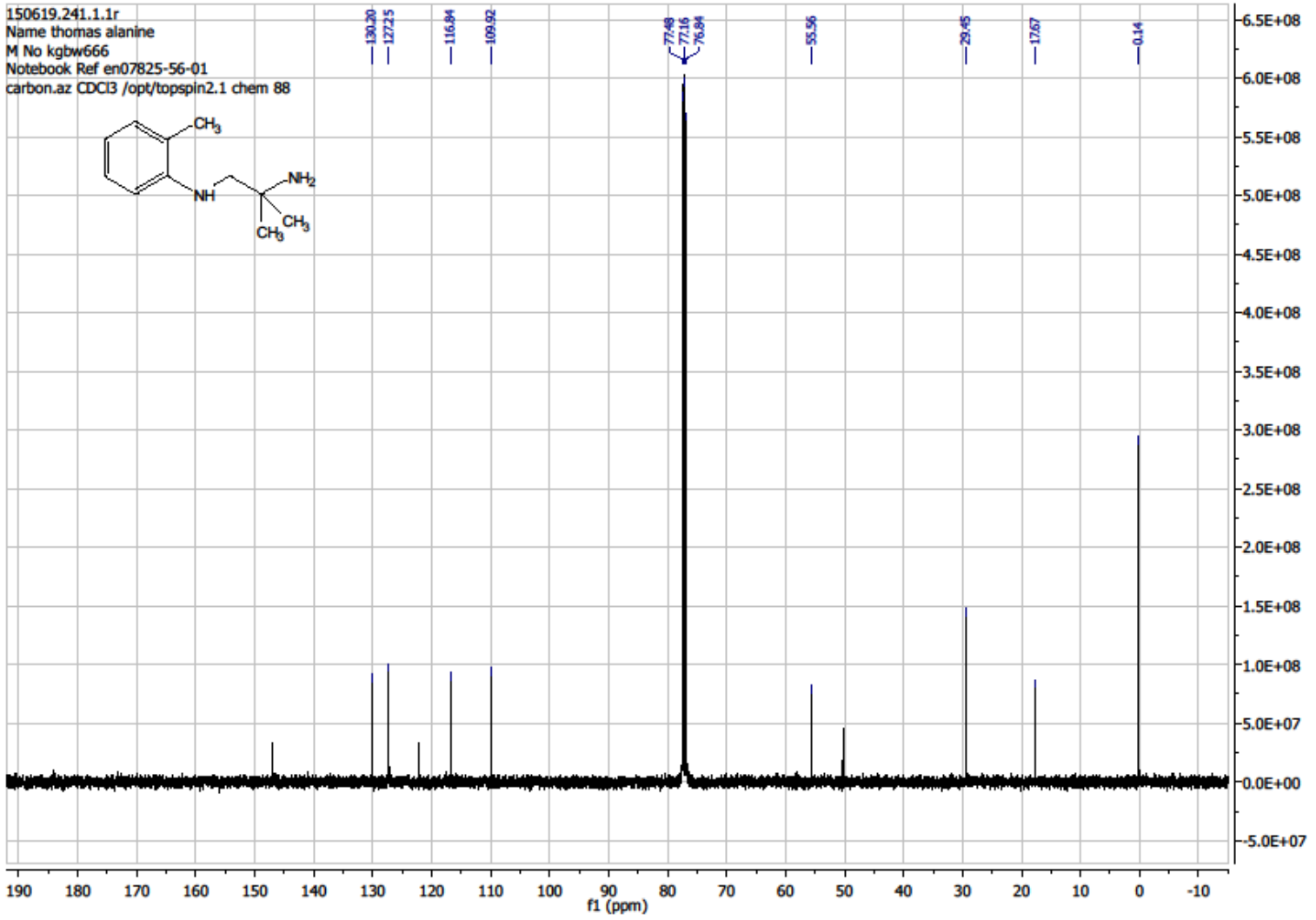
8c ^{13}C NMR 101 MHz



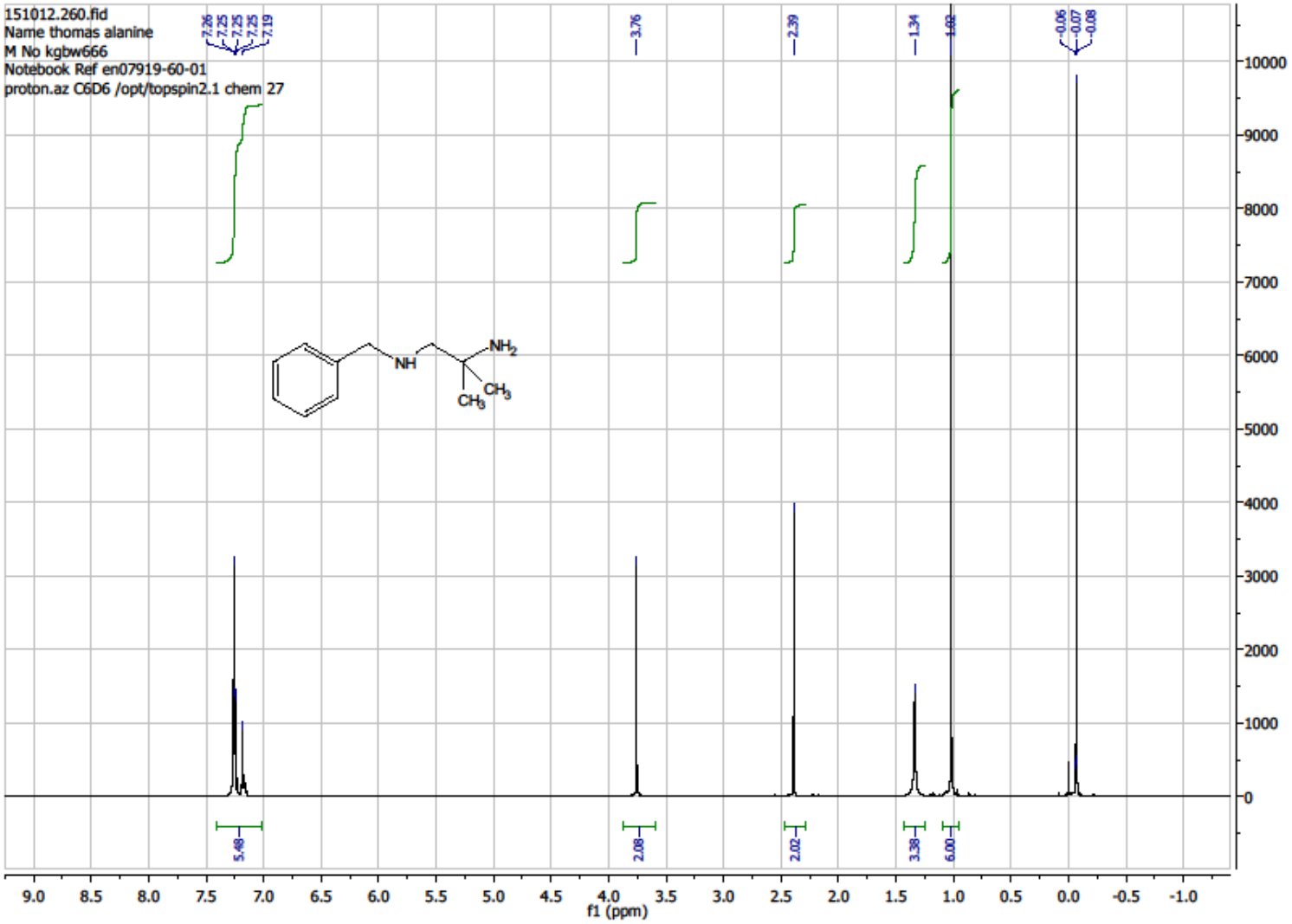
8d ^{1}H NMR 400 MHz



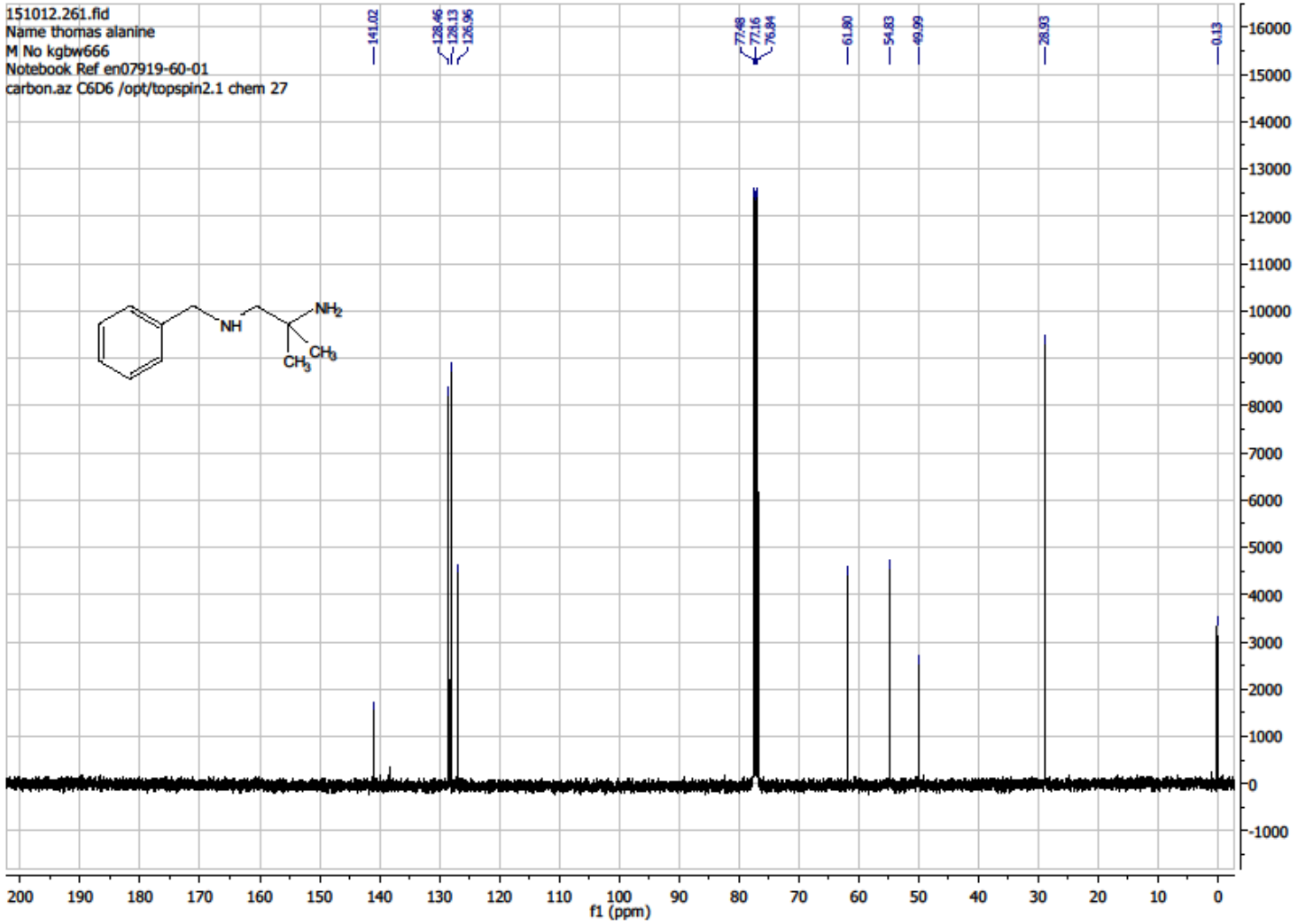
8d ^{13}C NMR 101 MHz



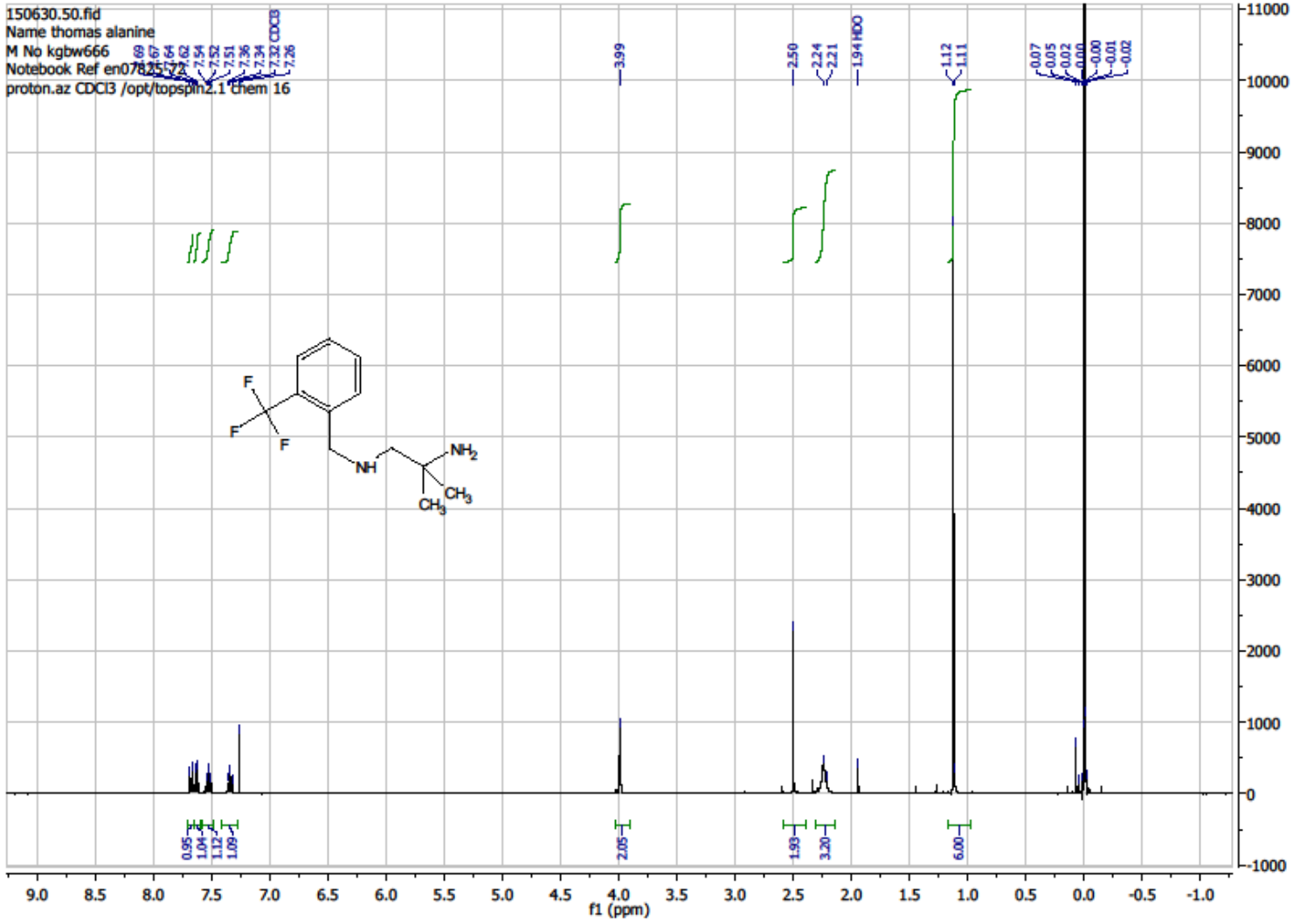
8e ^{1}H NMR 400 MHz



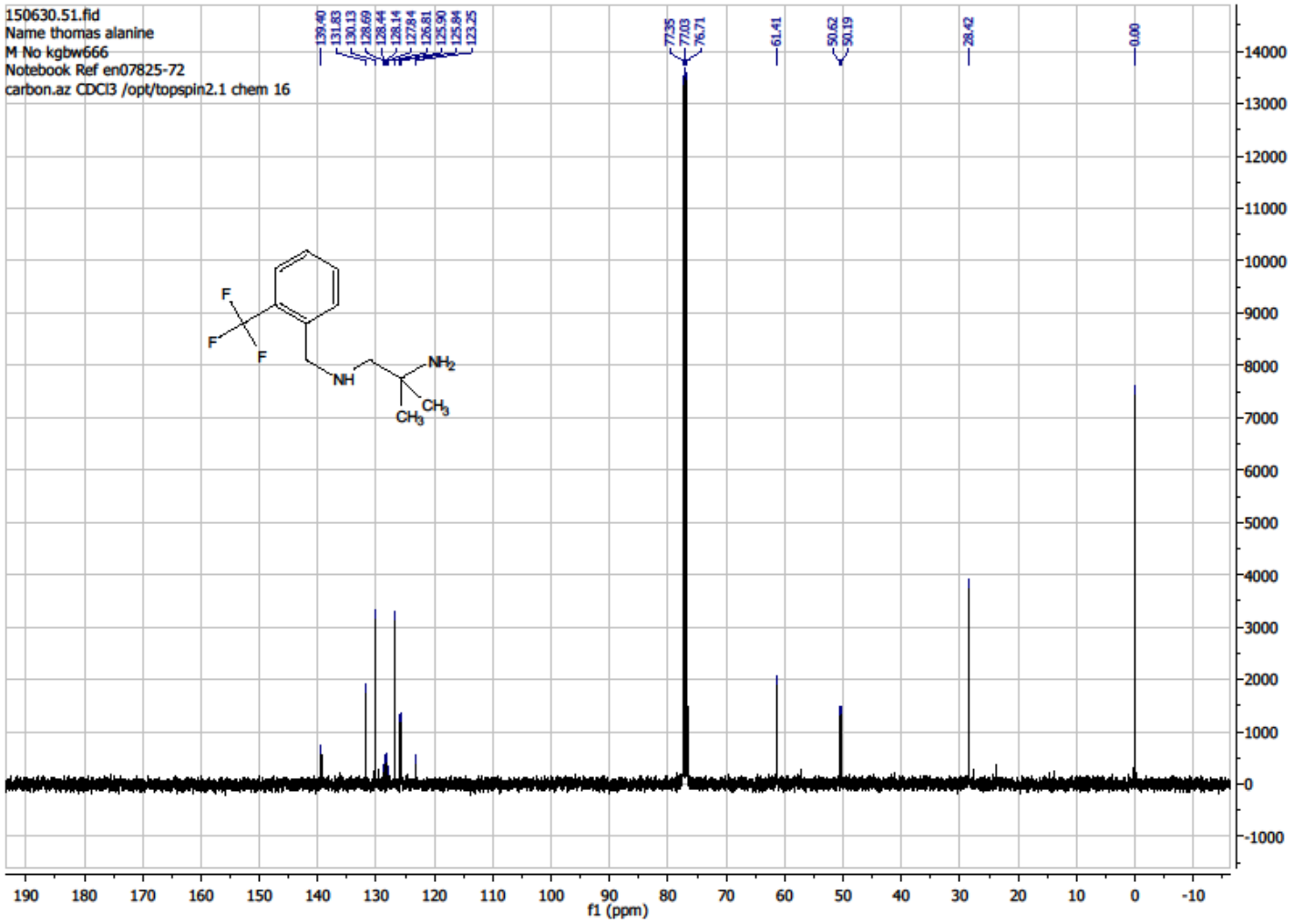
8e ^{13}C NMR 101 MHz



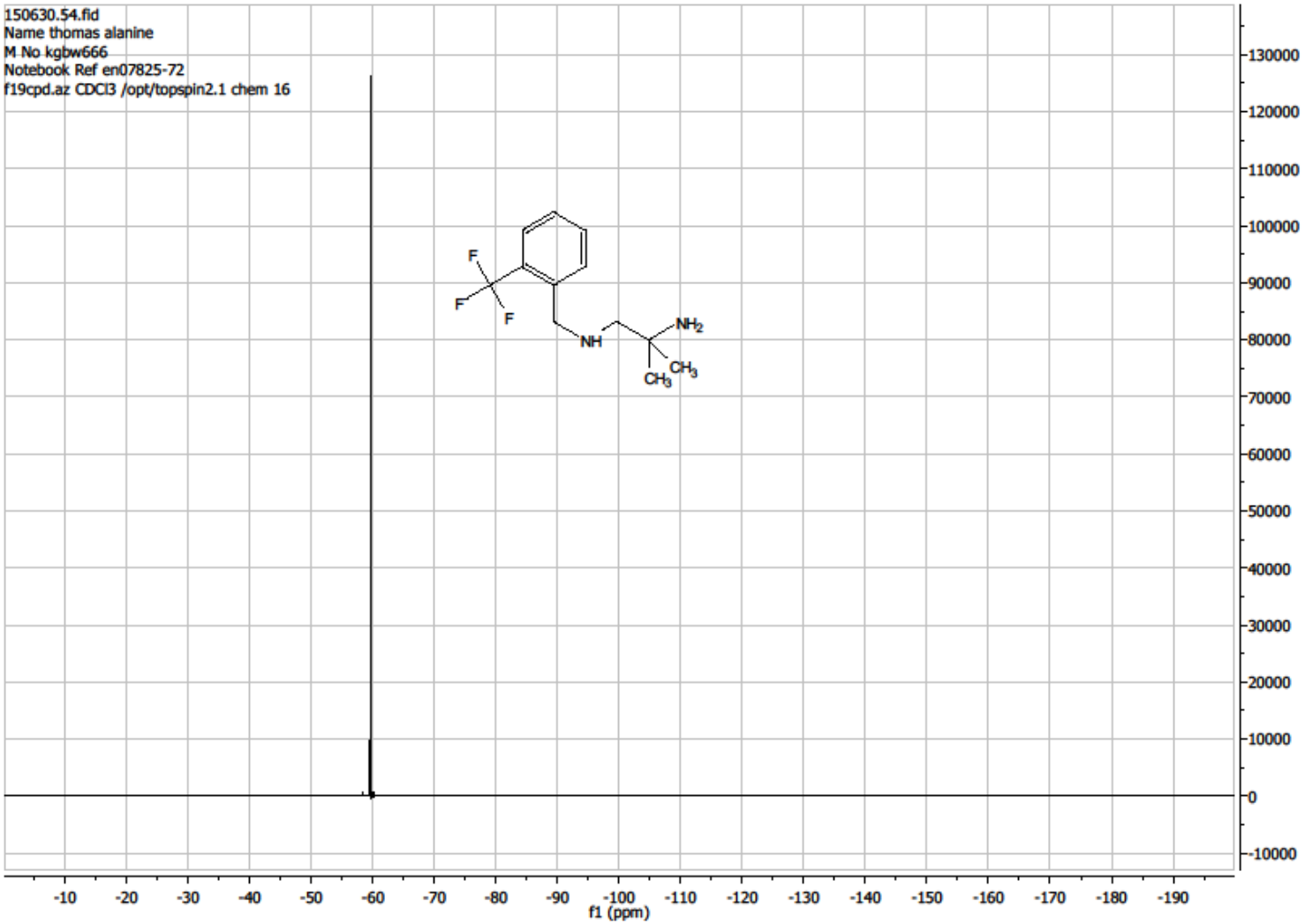
8f ^{1}H NMR 400 MHz



8f ^{13}C NMR 101 MHz



8f ^{19}F NMR 376 MHz



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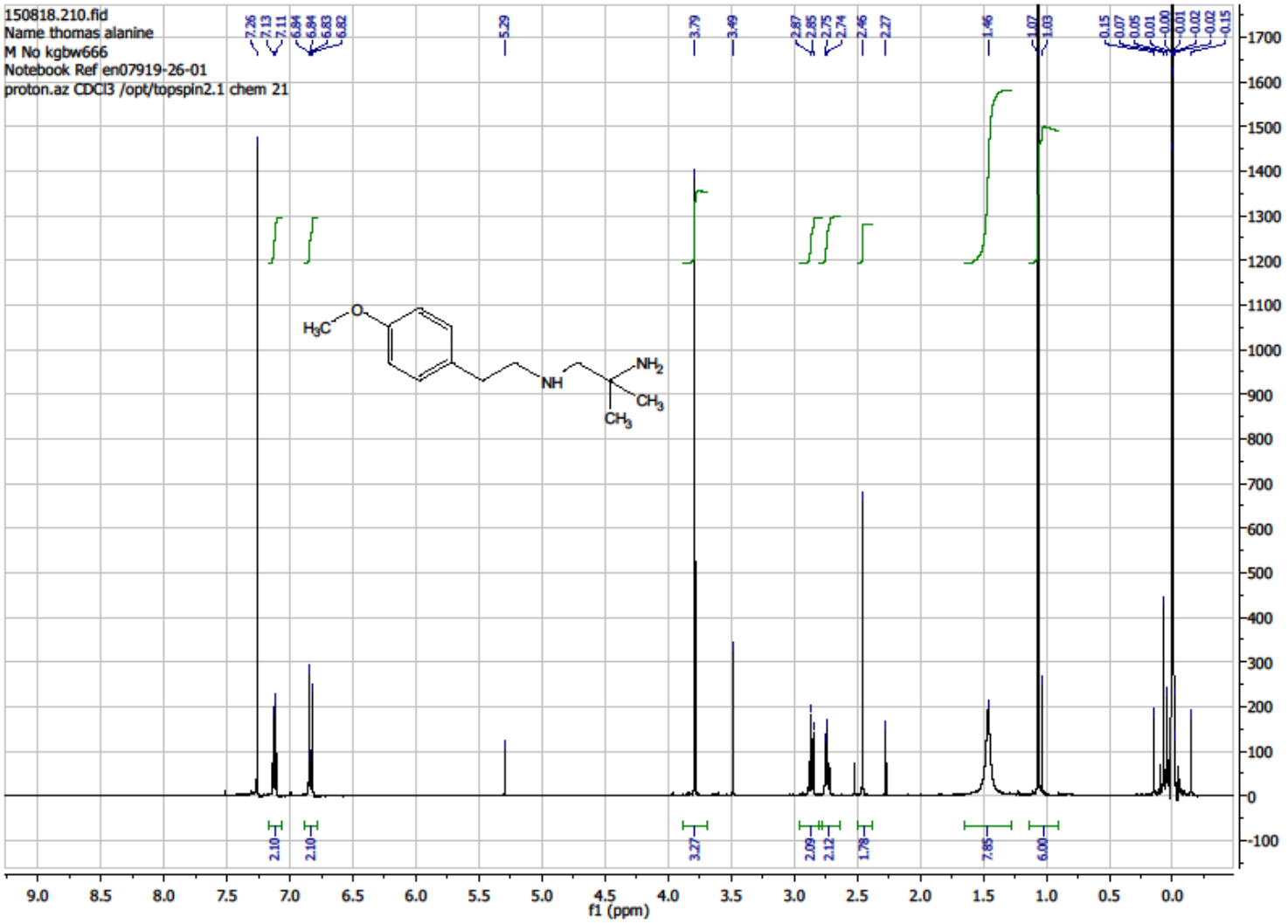
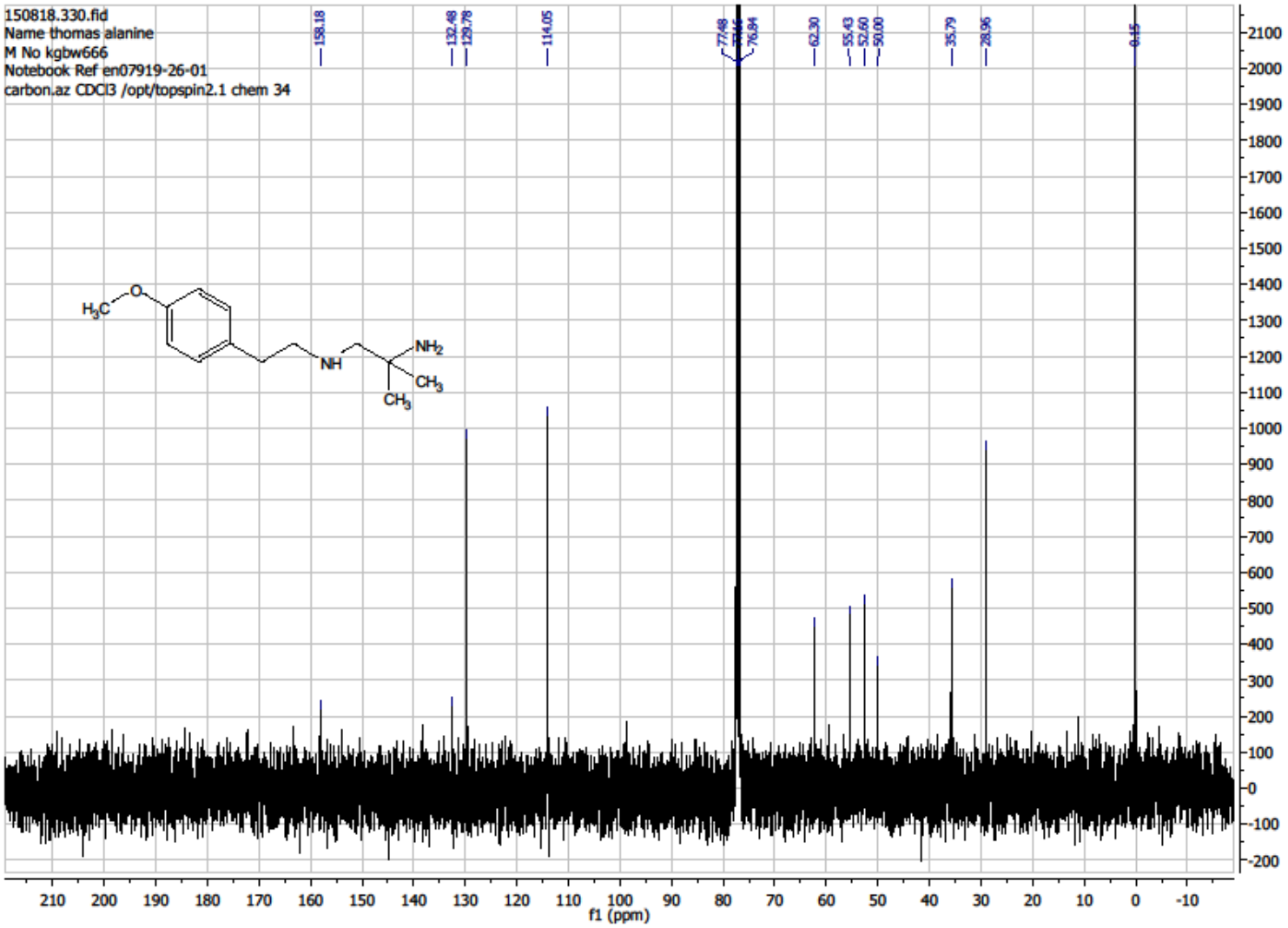
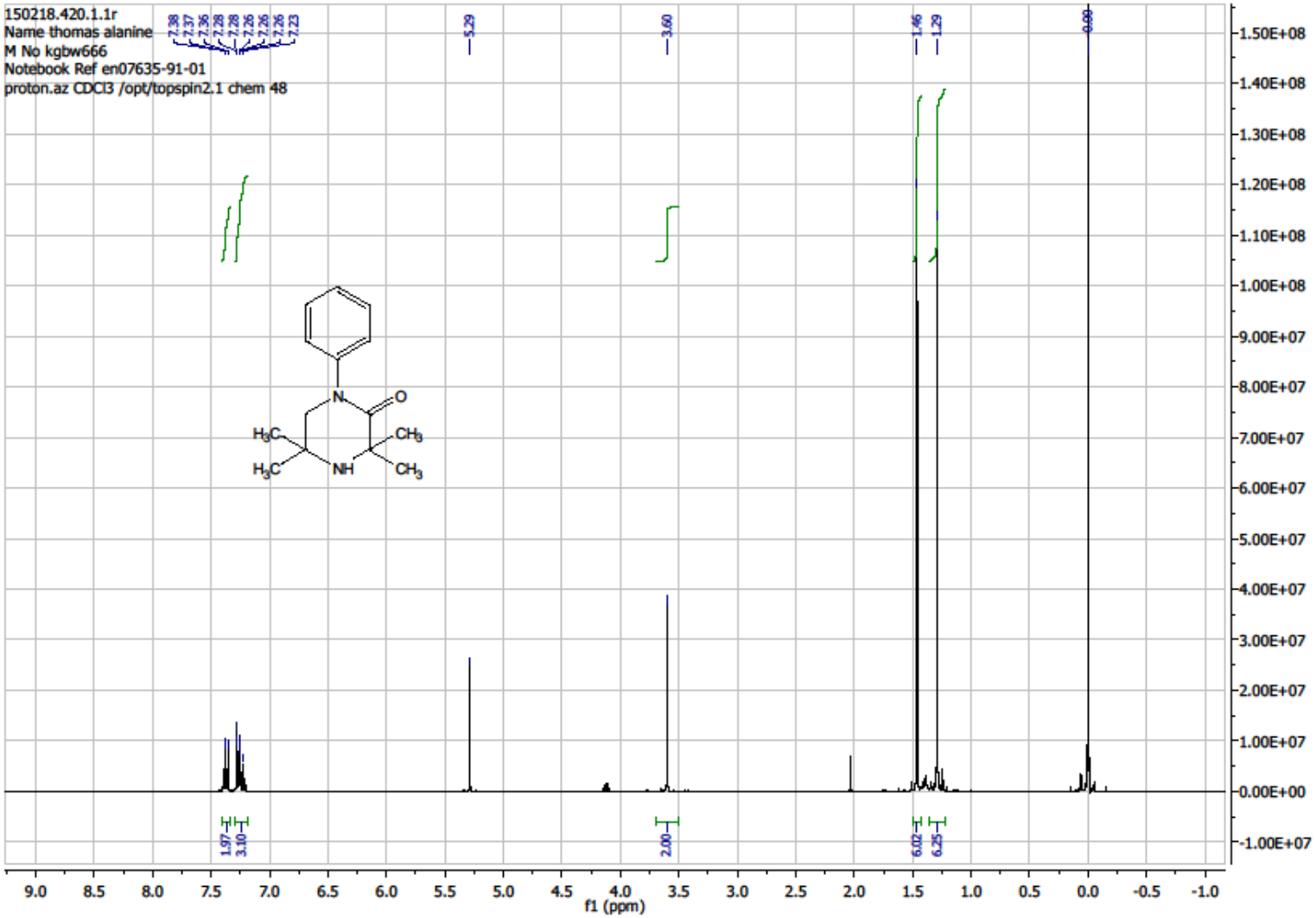
8g ^{1}H NMR 400 MHz



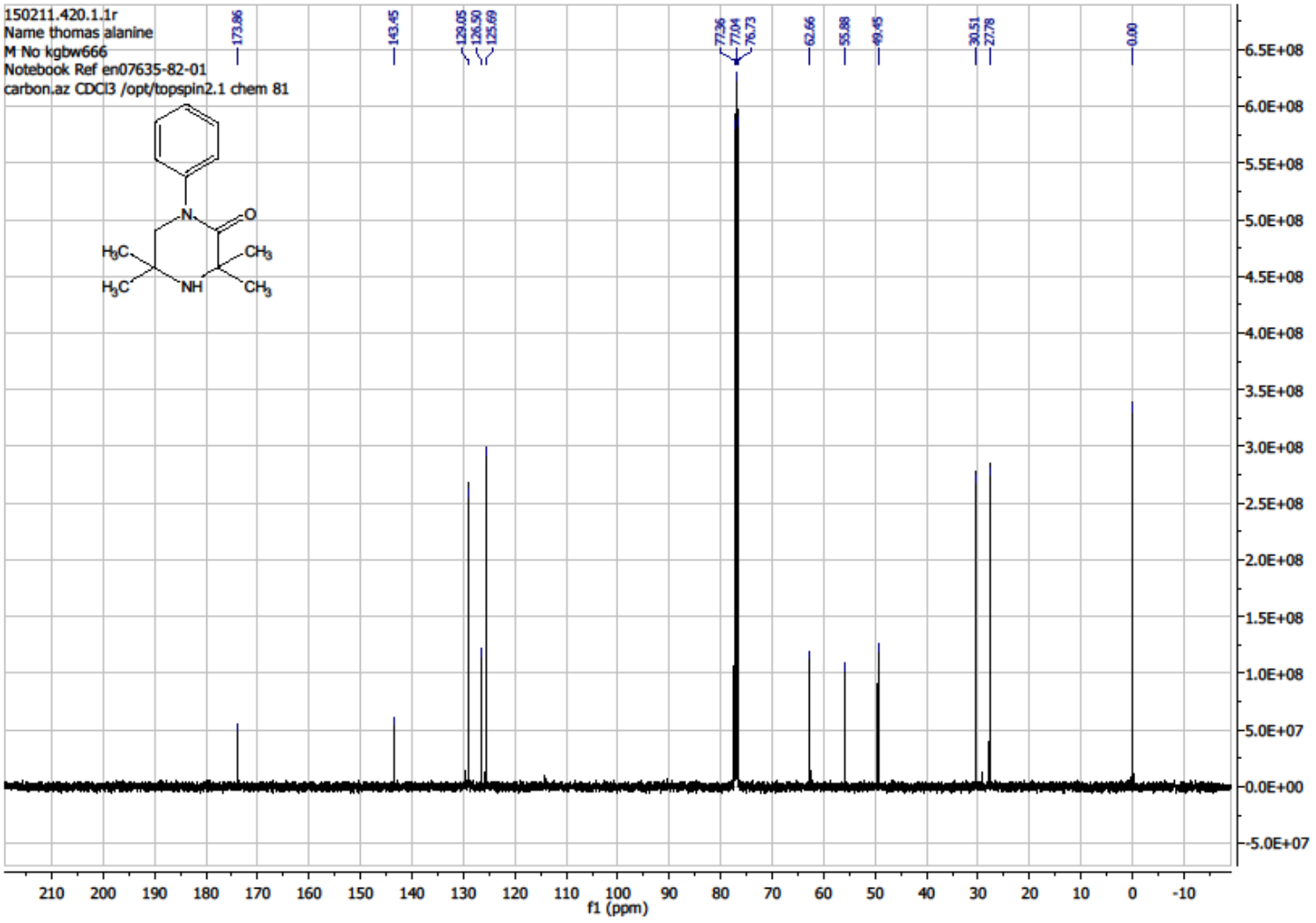
8g ^{13}C NMR 101 MHz



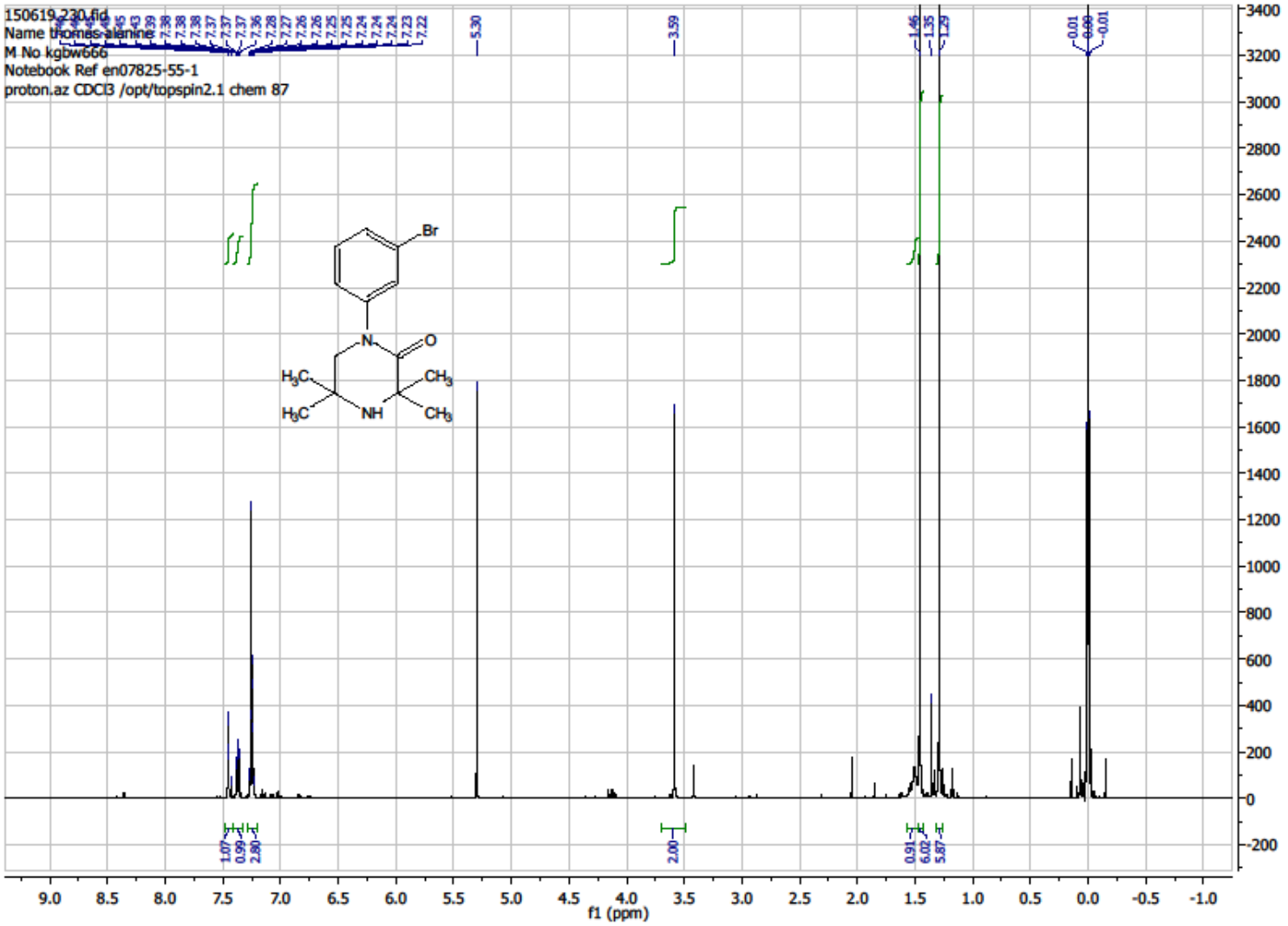
1a ^{1}H NMR 400 MHz



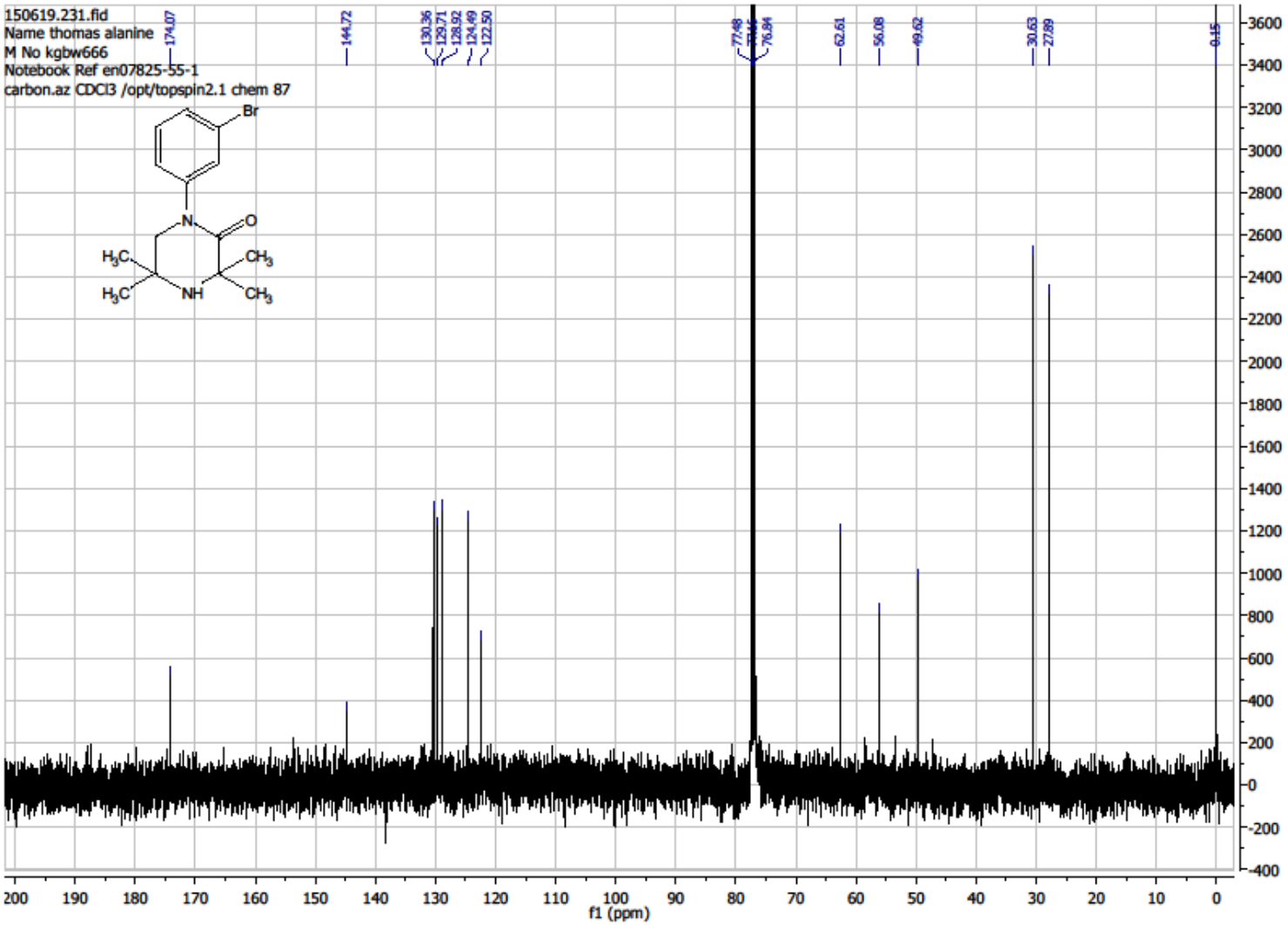
1a ^{13}C NMR 101 MHz



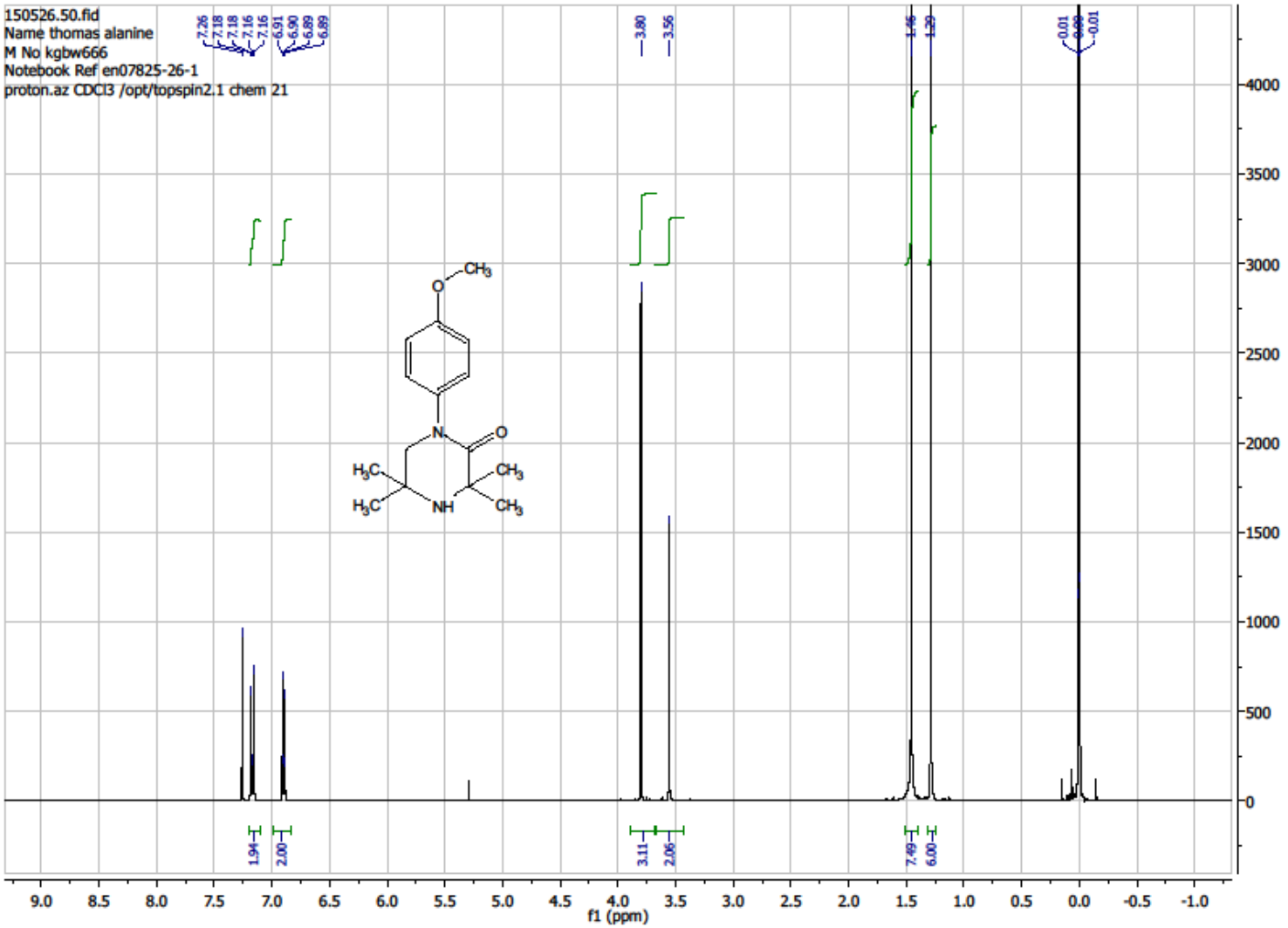
1b ^{1}H NMR 400 MHz



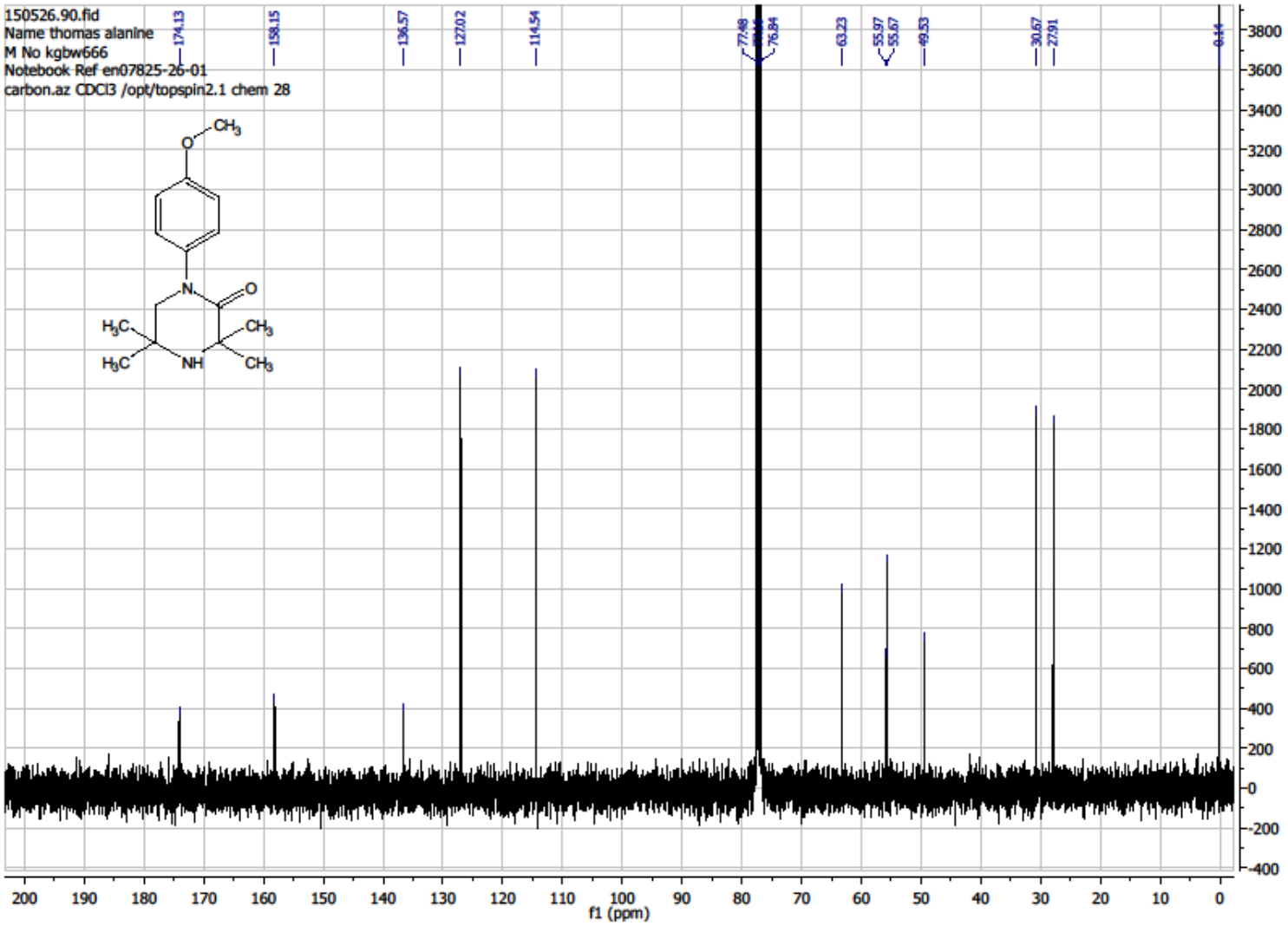
1b ^{13}C NMR 101 MHz



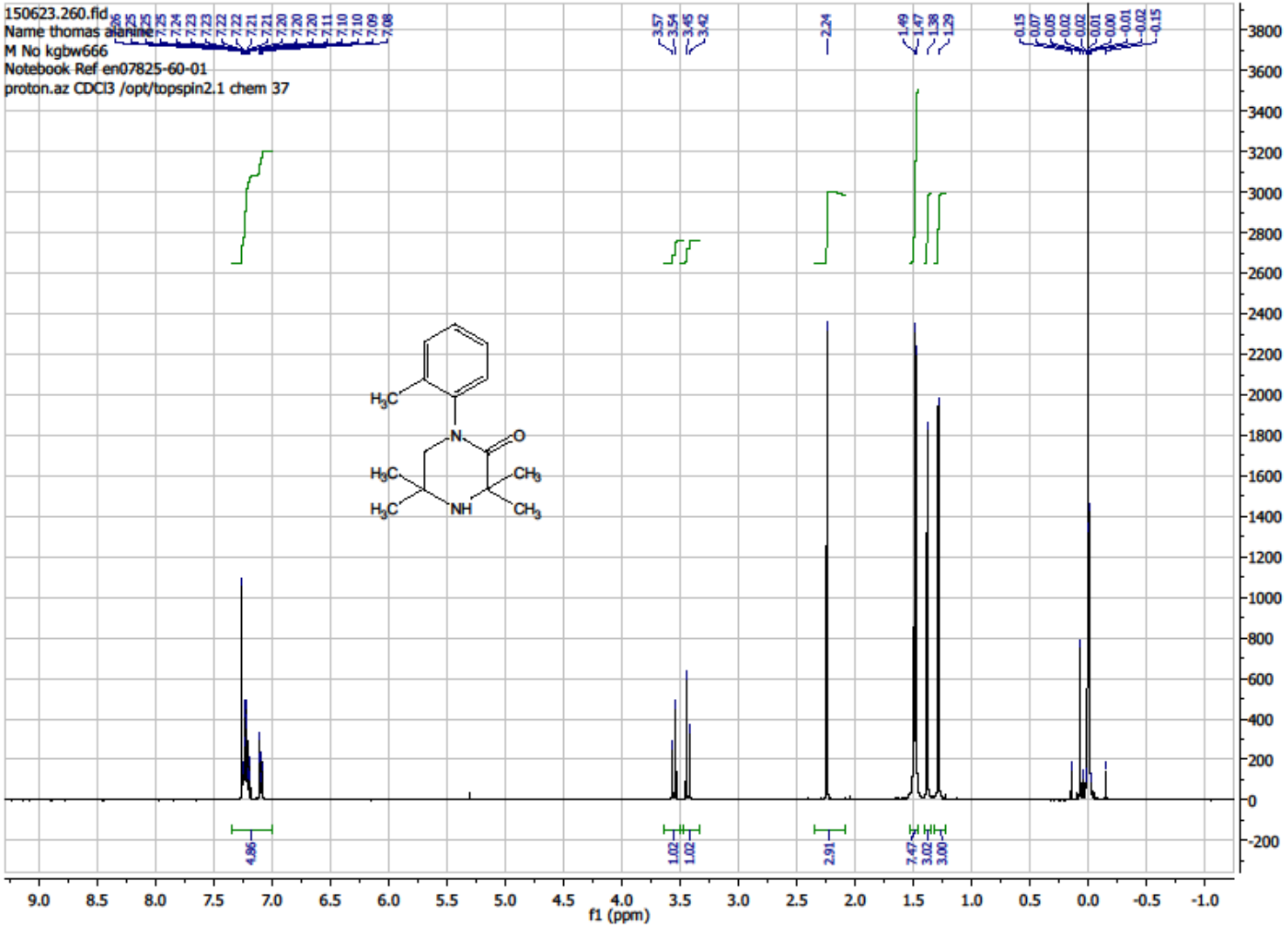
1c ^{1}H NMR 400 MHz



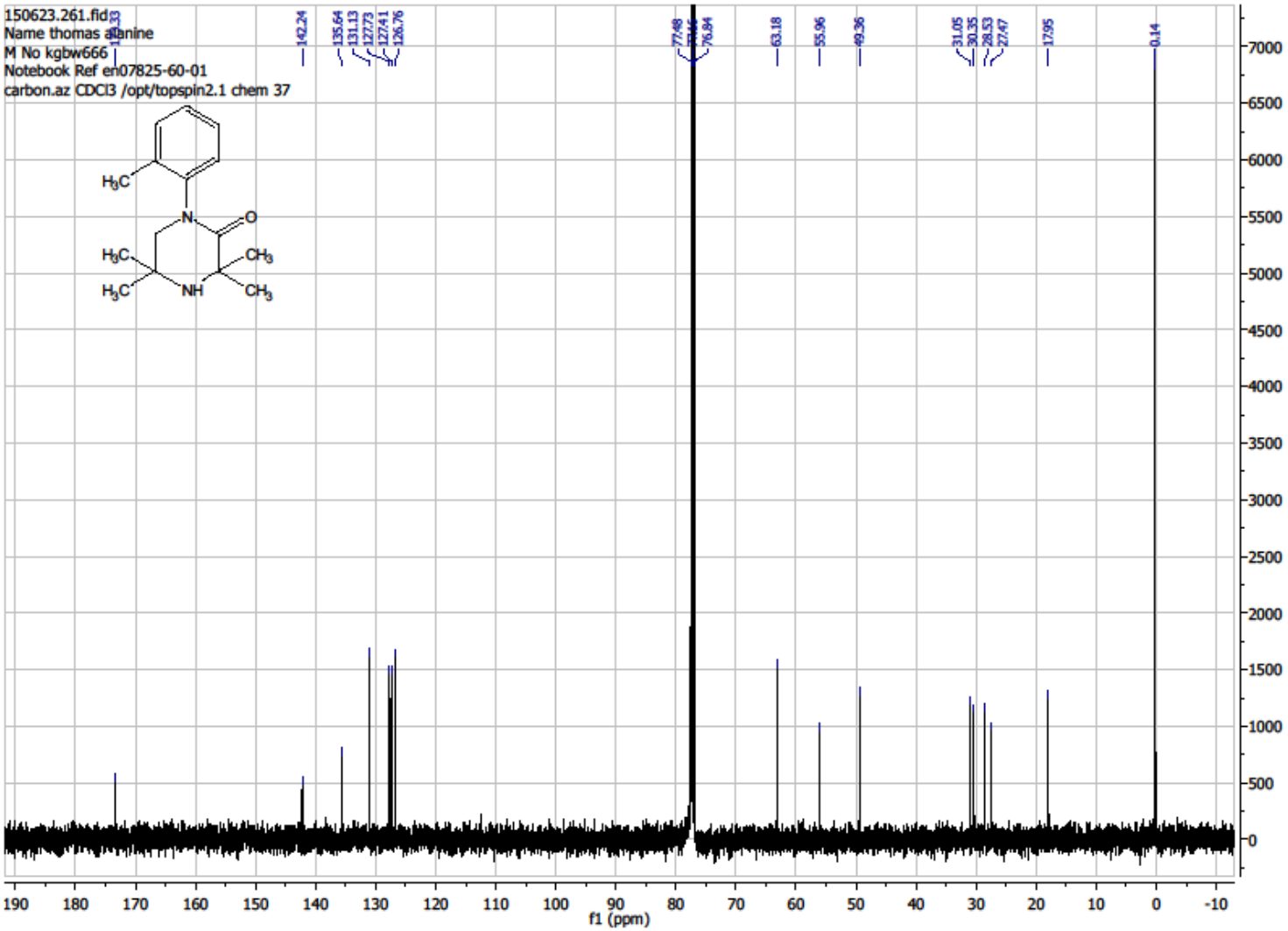
1c ^{13}C NMR 101 MHz



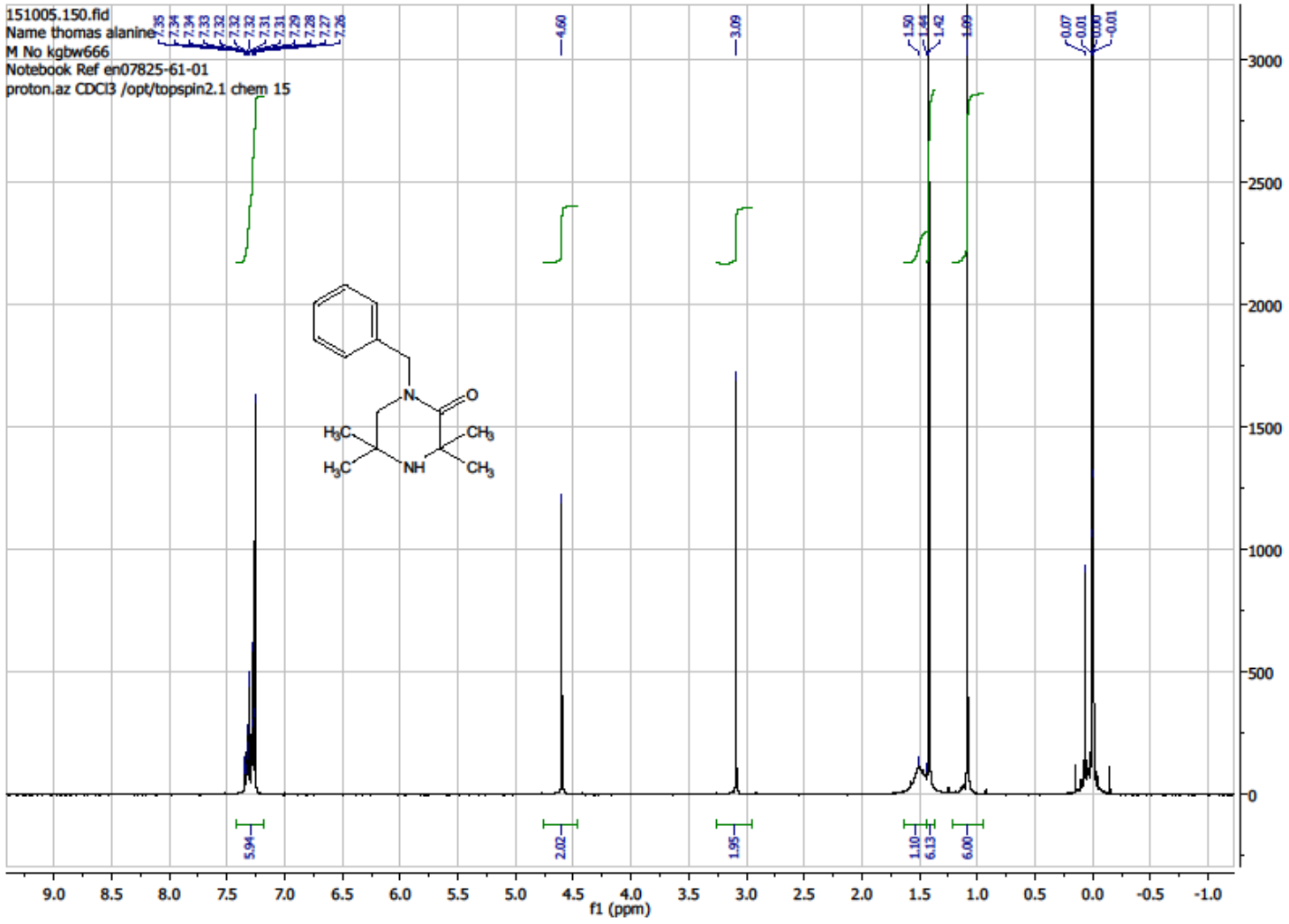
1d ^{1}H NMR 400 MHz



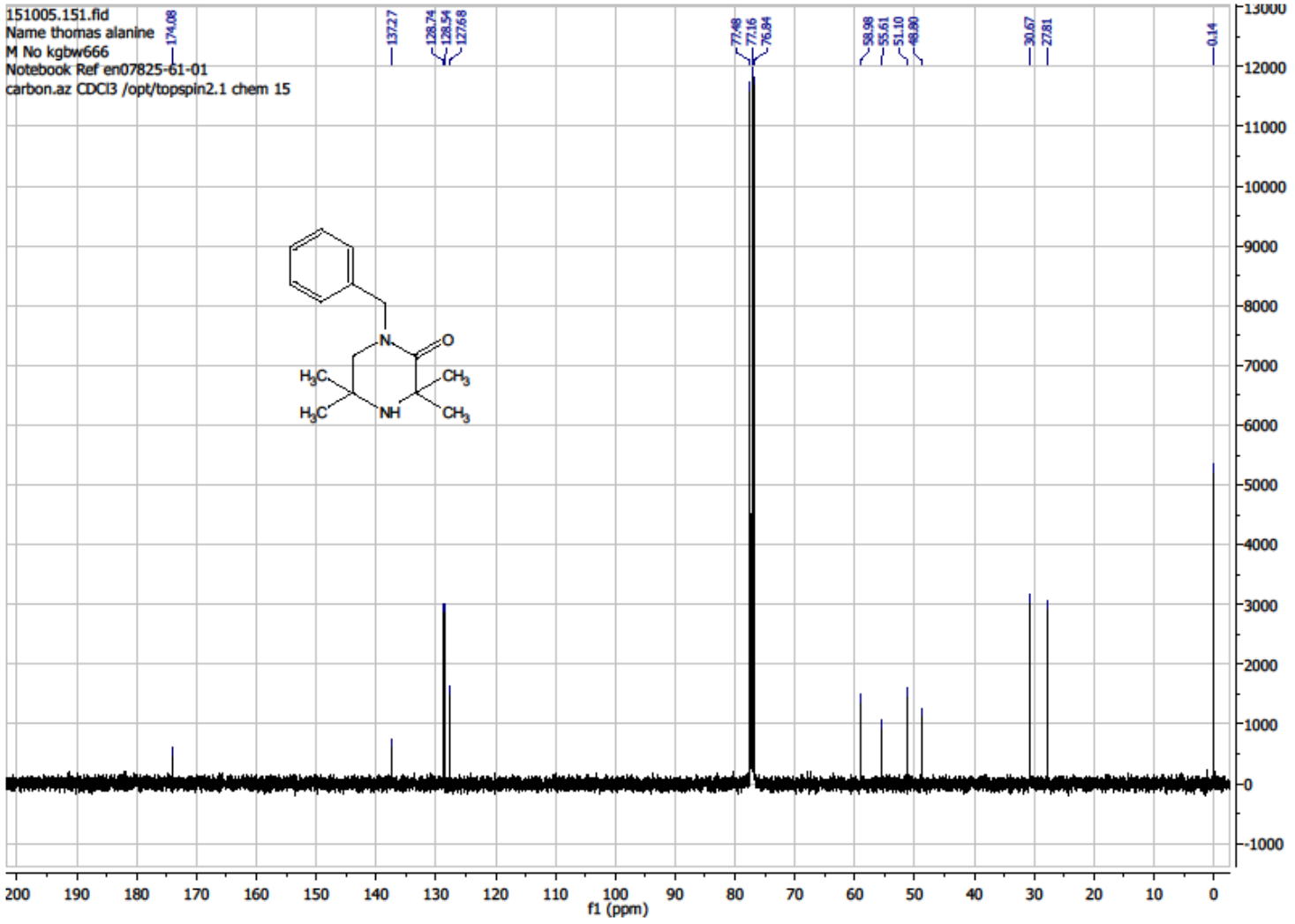
1d ^{13}C NMR 101 MHz



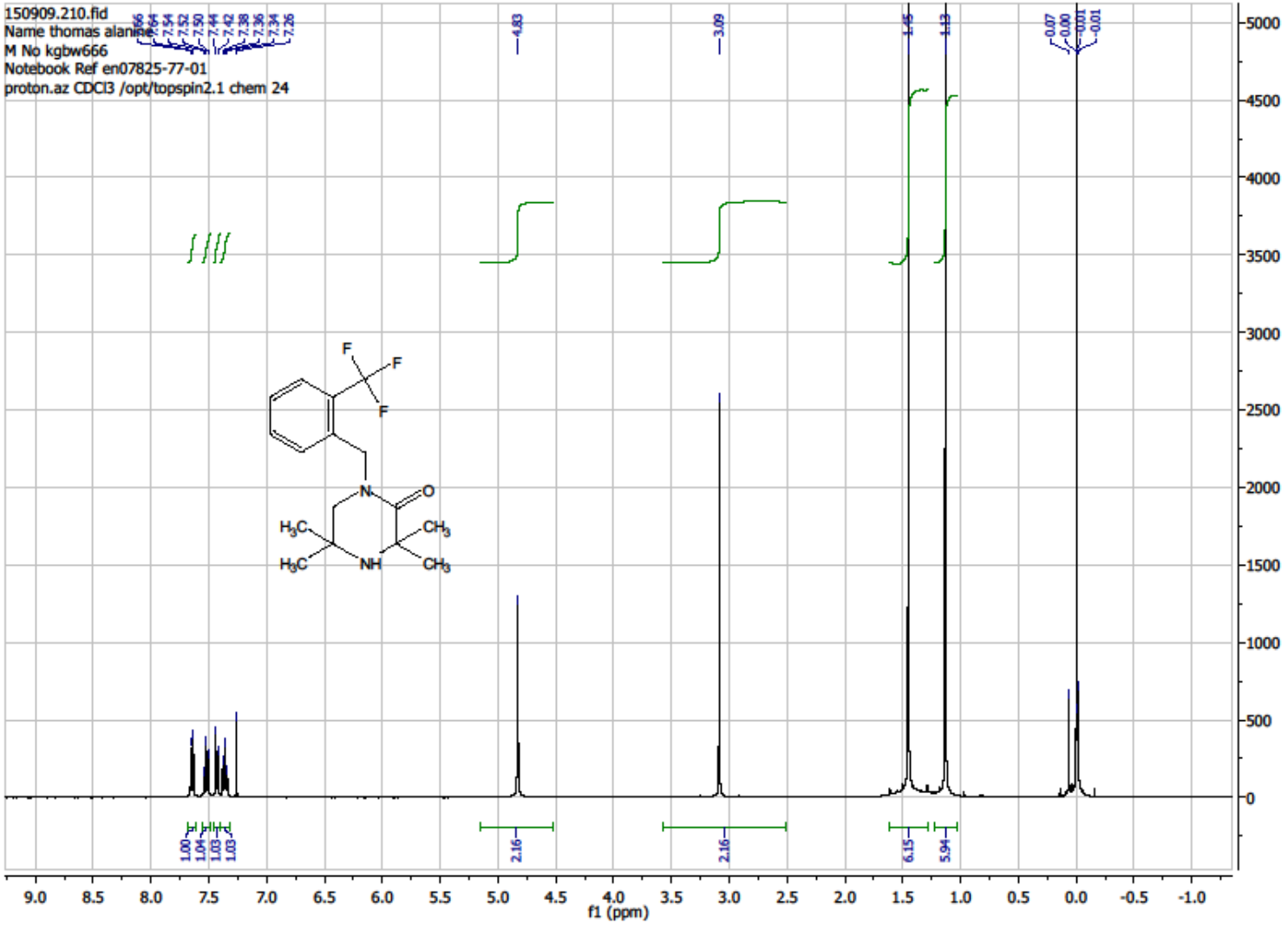
1e ^{1}H NMR 400 MHz



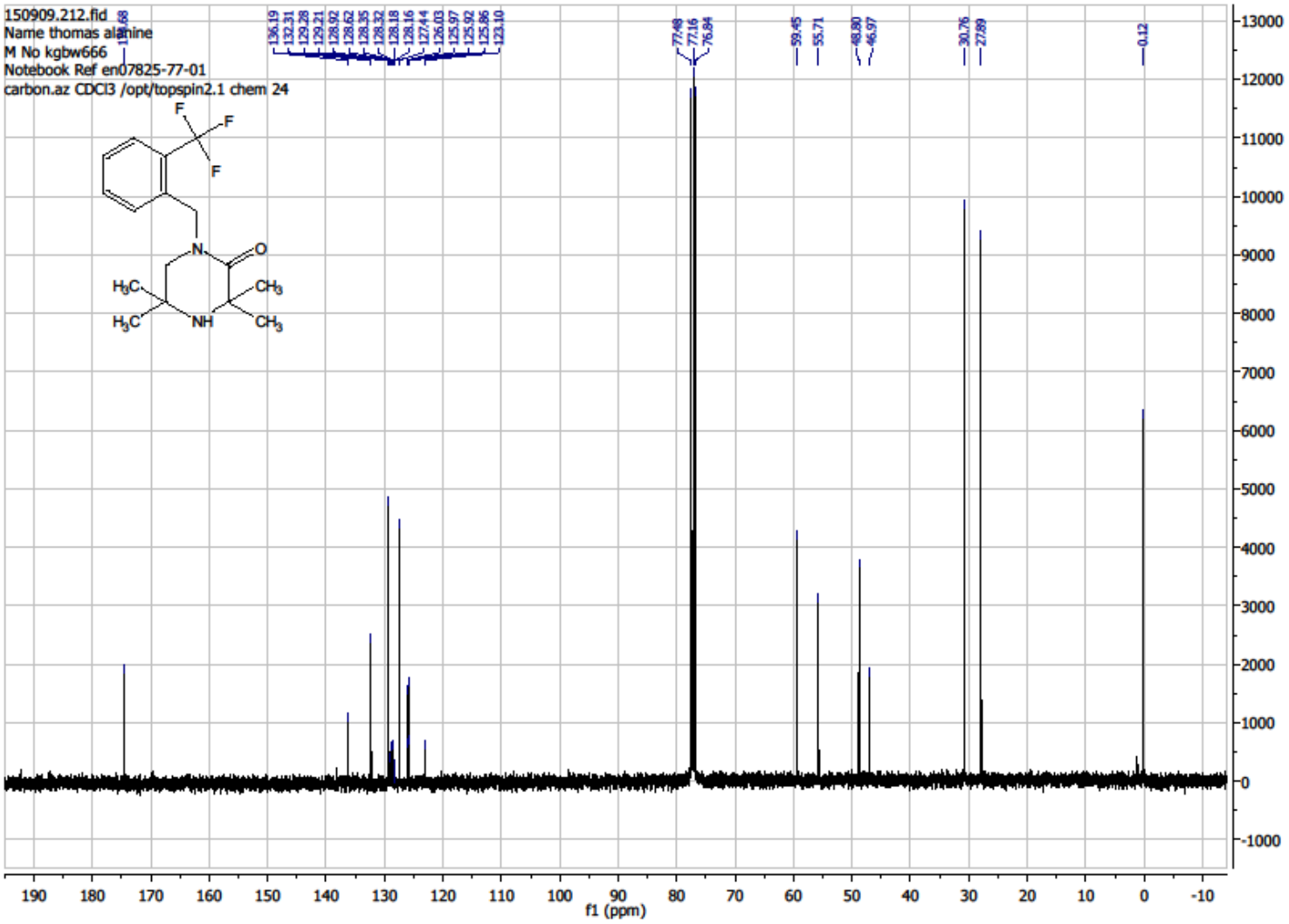
1e ^{13}C NMR 101 MHz



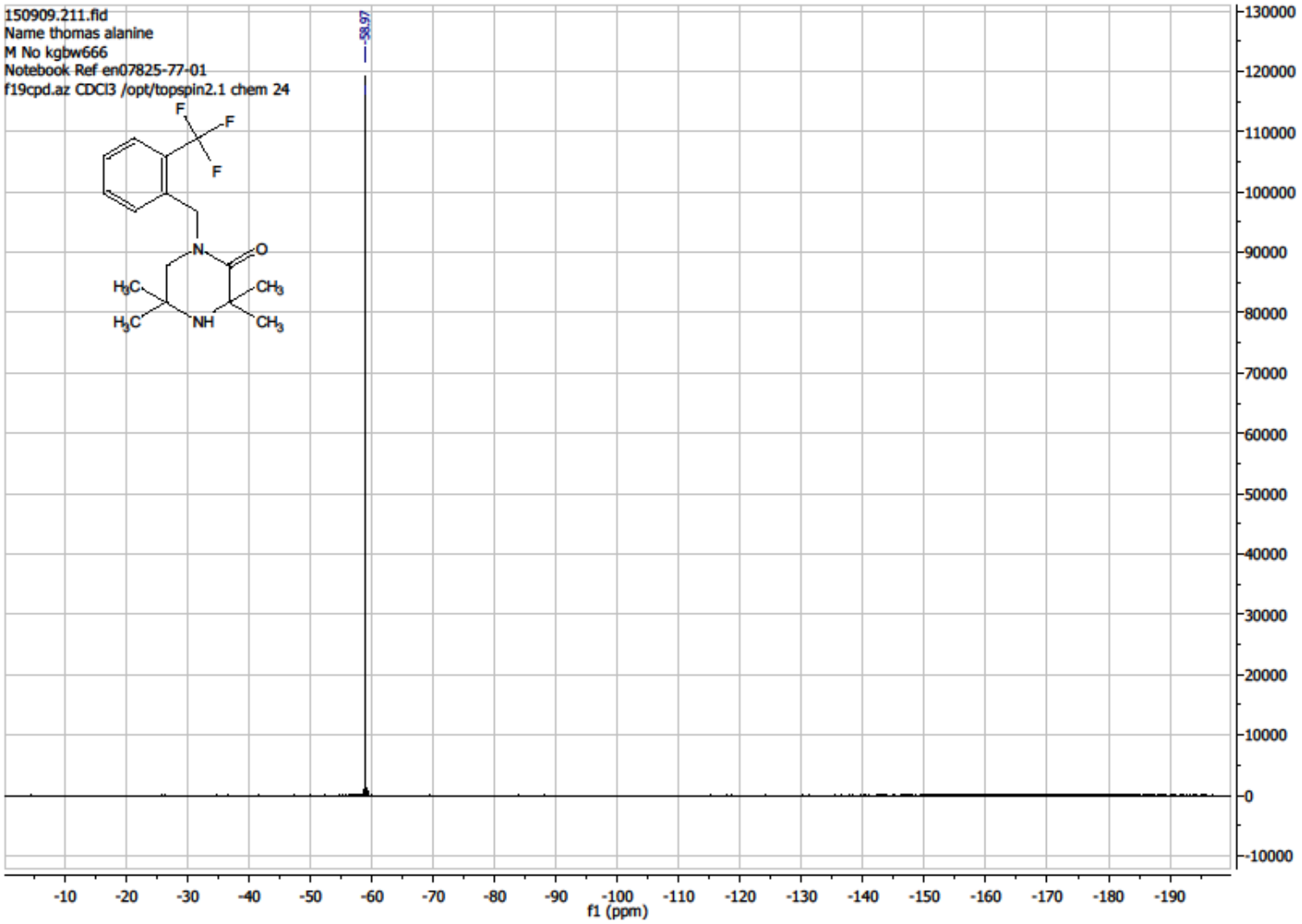
1f ^{1}H NMR 400 MHz



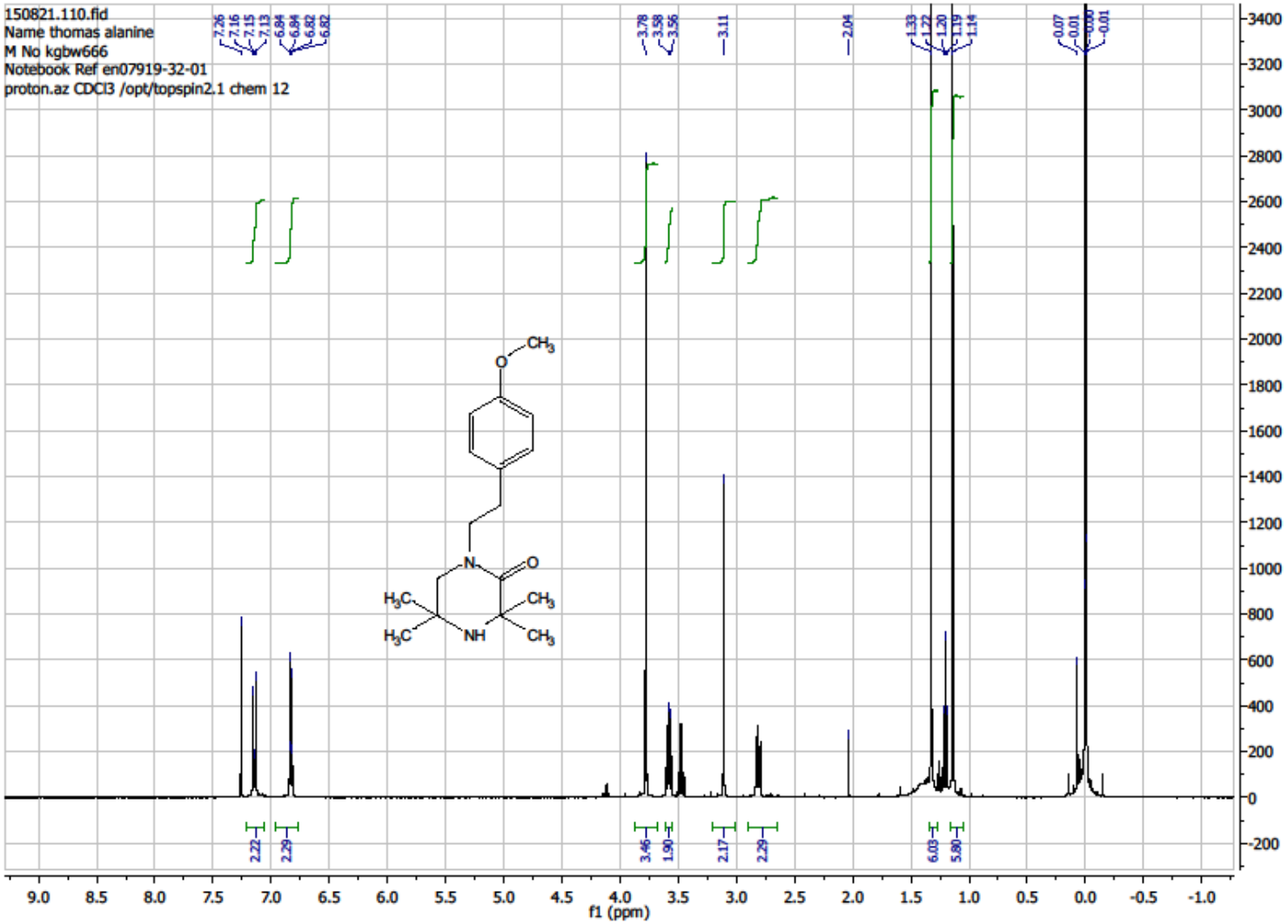
1f ^{13}C NMR 101 MHz



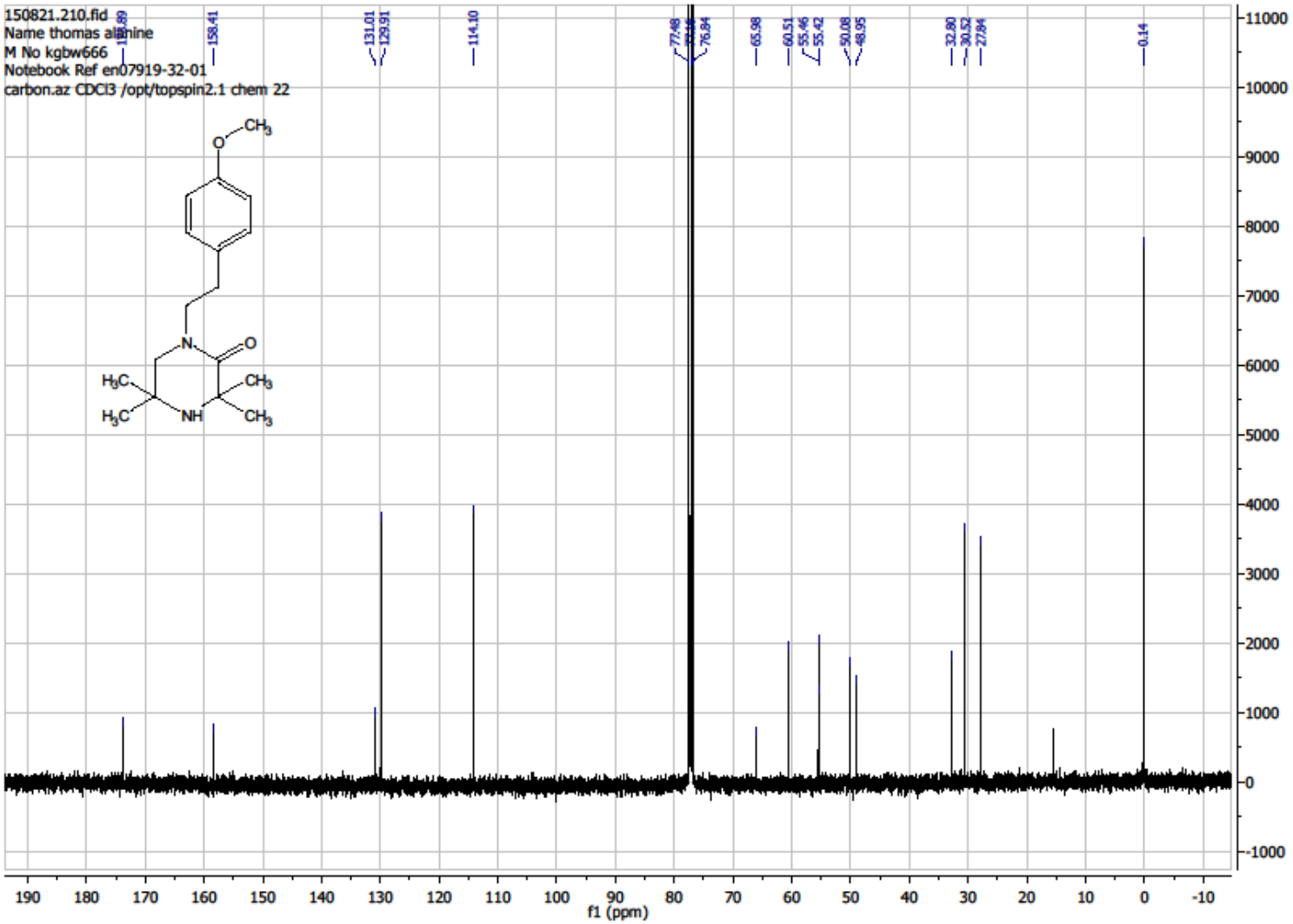
1f ^{19}F NMR 376 MHz



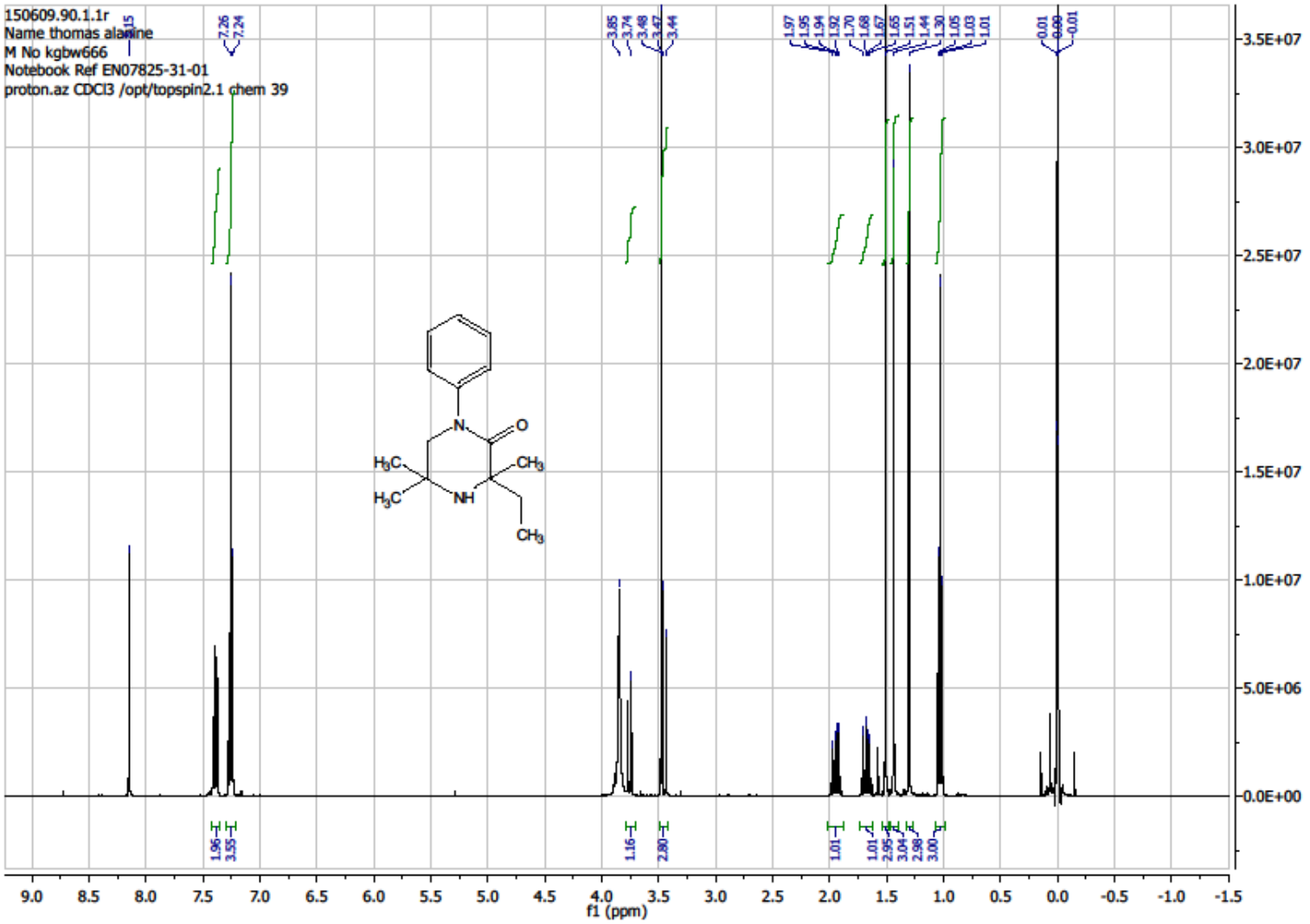
1g ^{1}H NMR 400 MHz



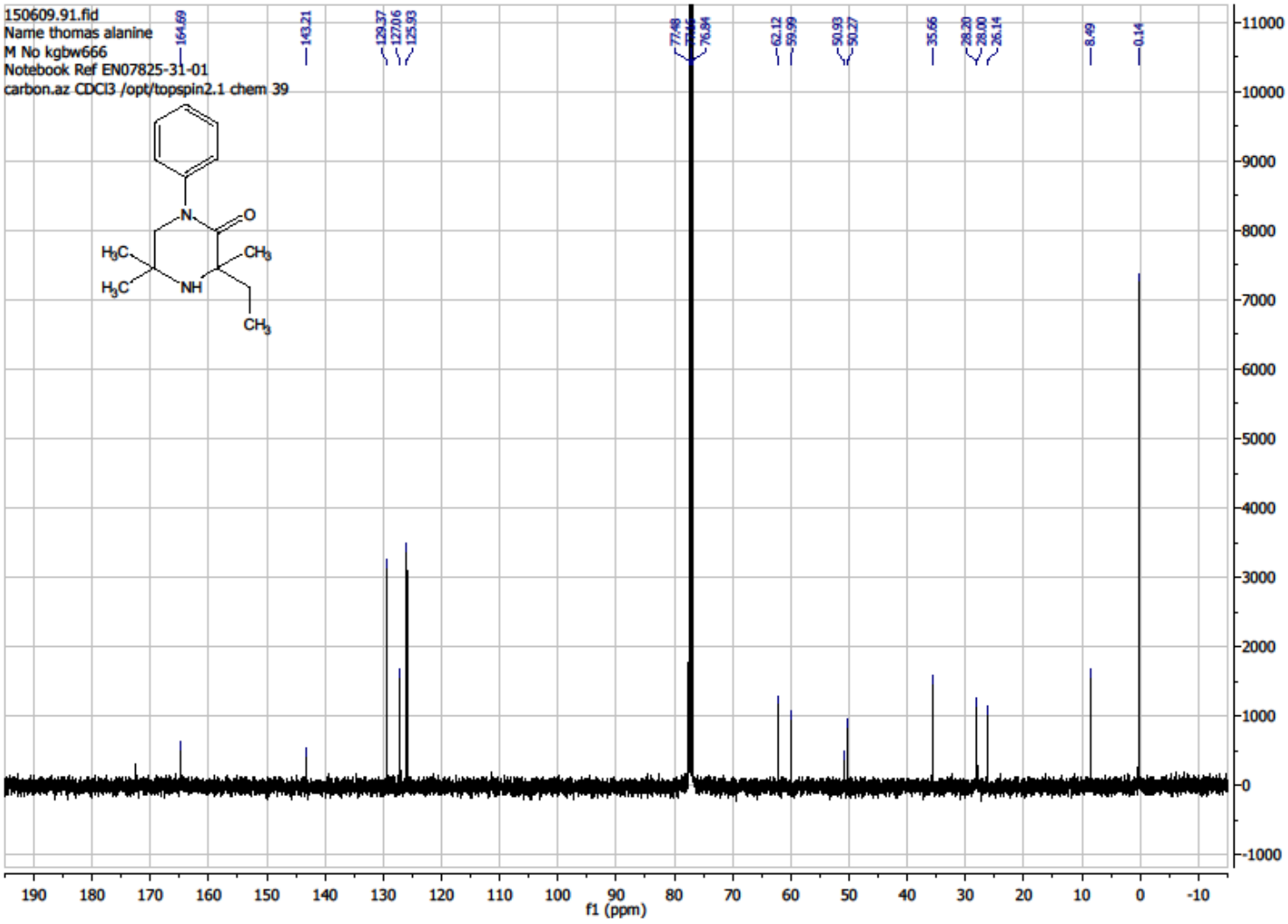
1g ^{13}C NMR 101 MHz



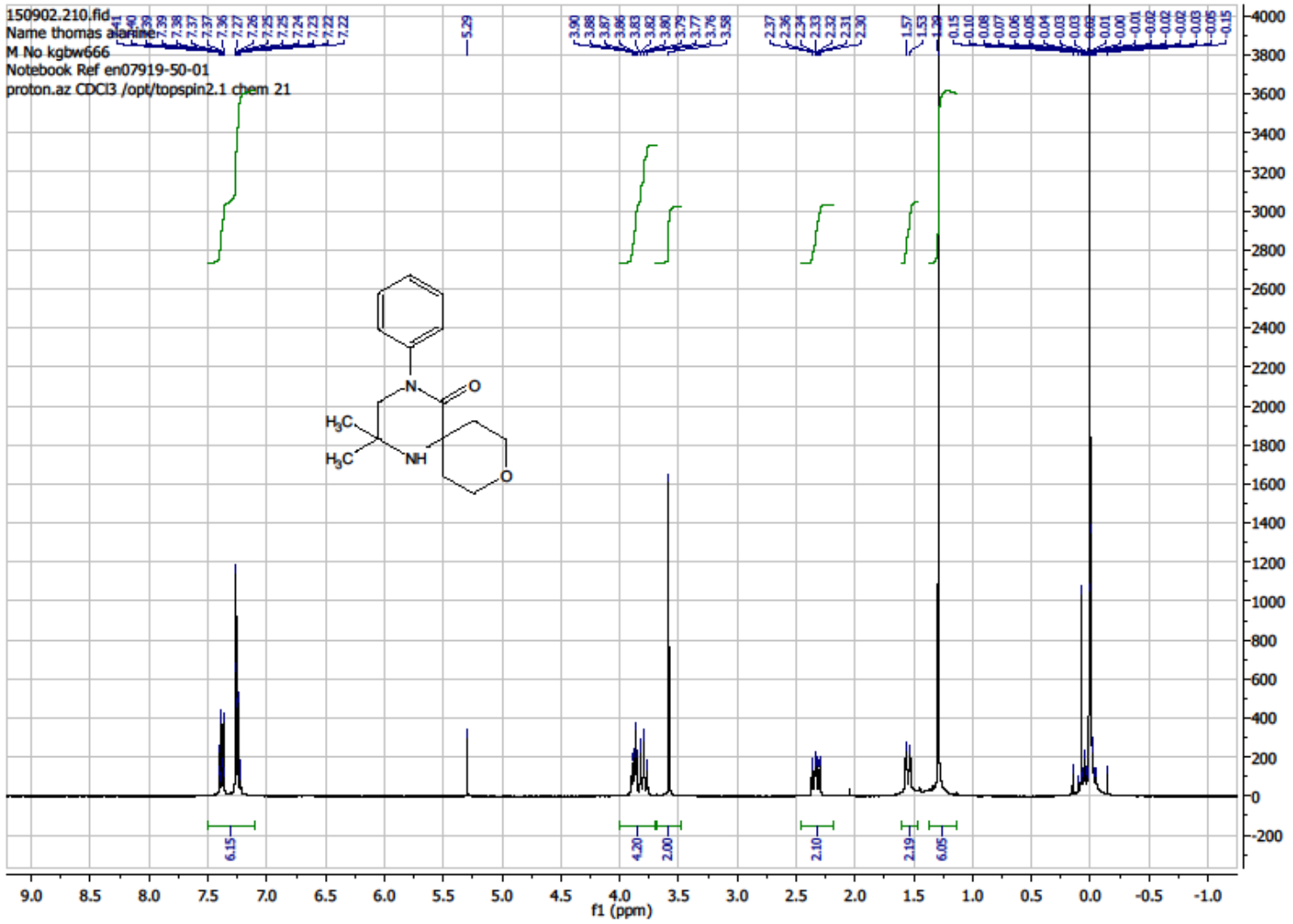
1h ^{1}H NMR 400 MHz



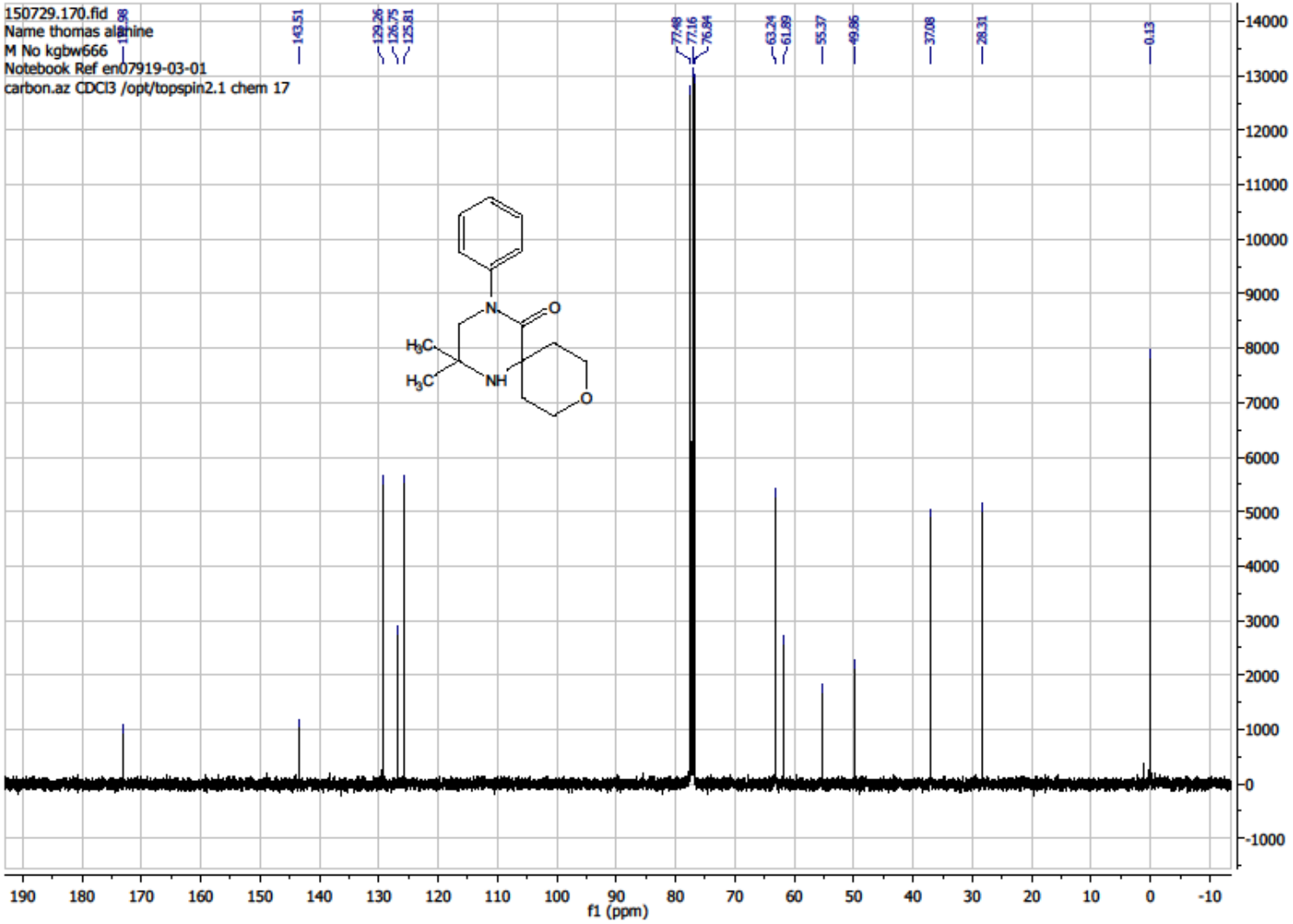
1h ^{13}C NMR 101 MHz



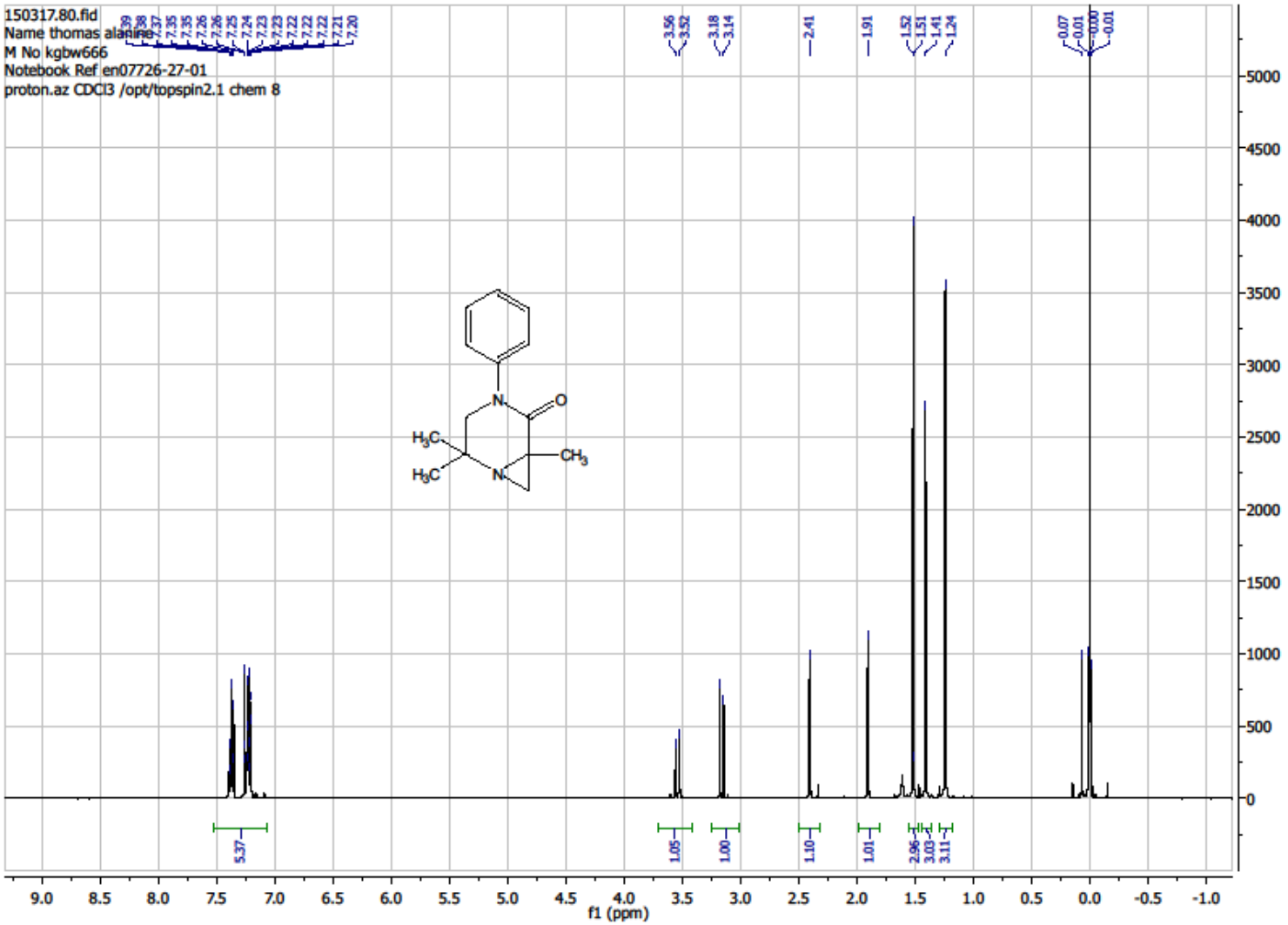
1j ^{1}H NMR 400 MHz



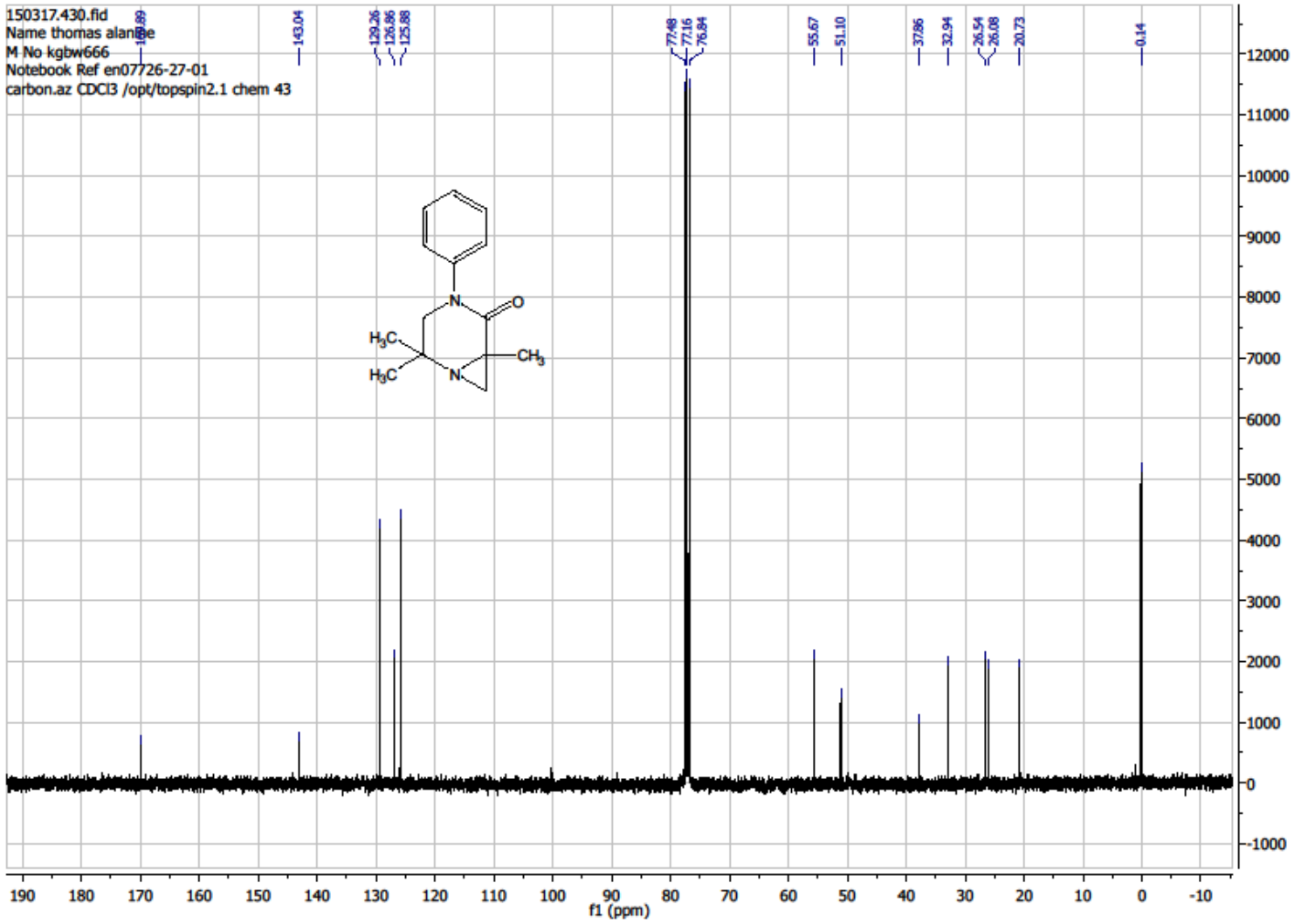
1j ^{13}C NMR 101 MHz



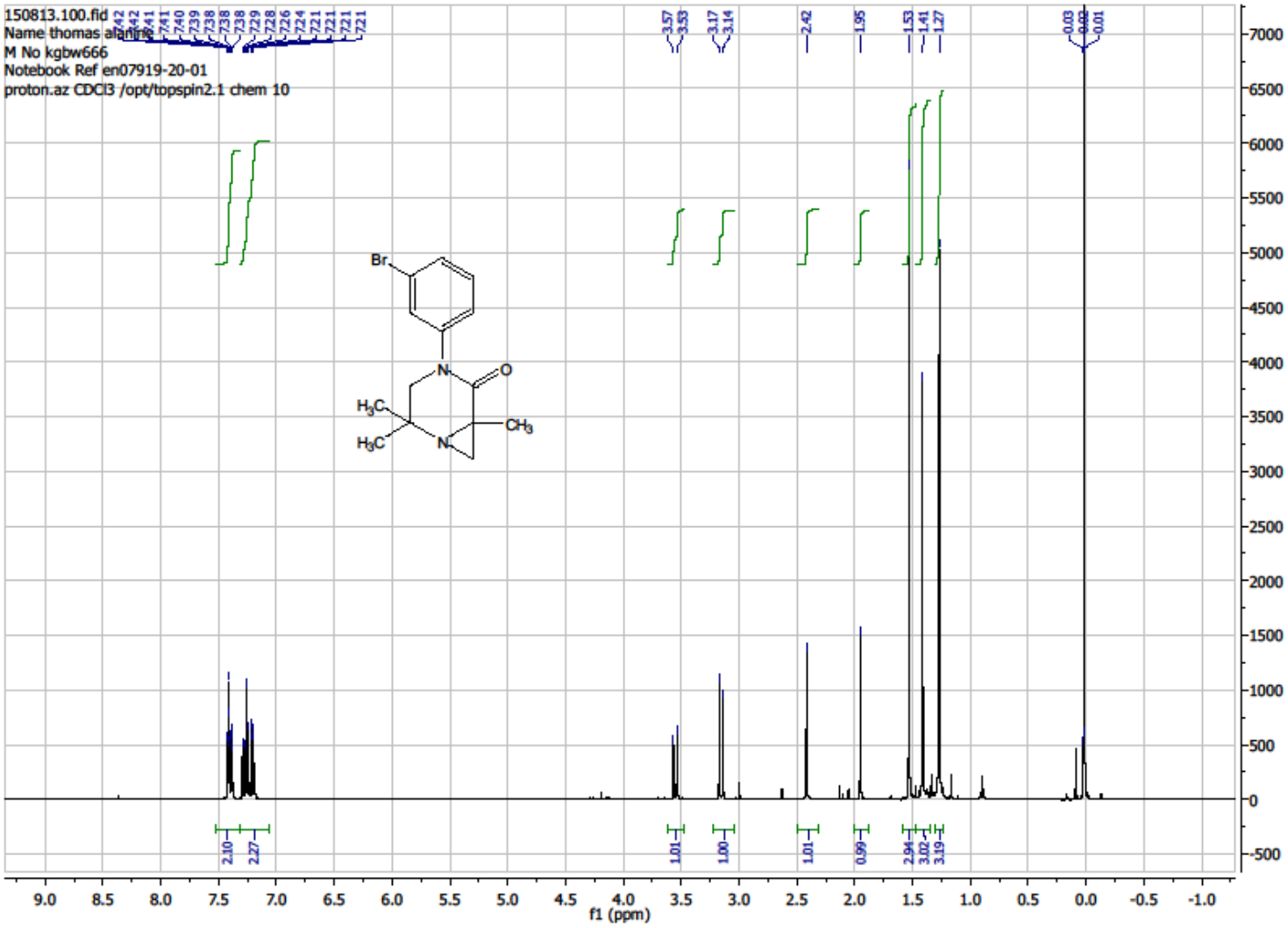
2a ^{1}H NMR 400 MHz



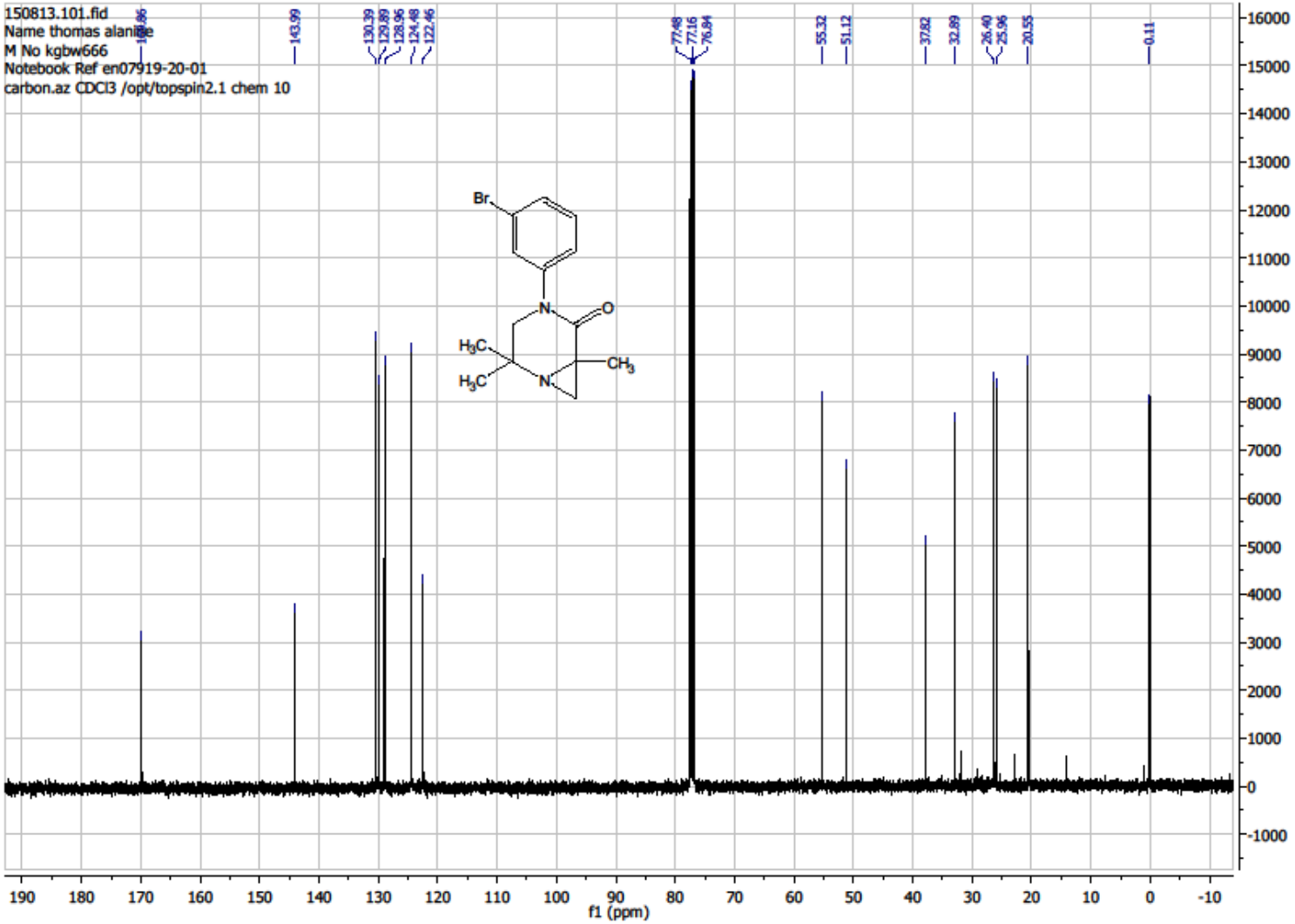
2a ^{13}C NMR 101 MHz



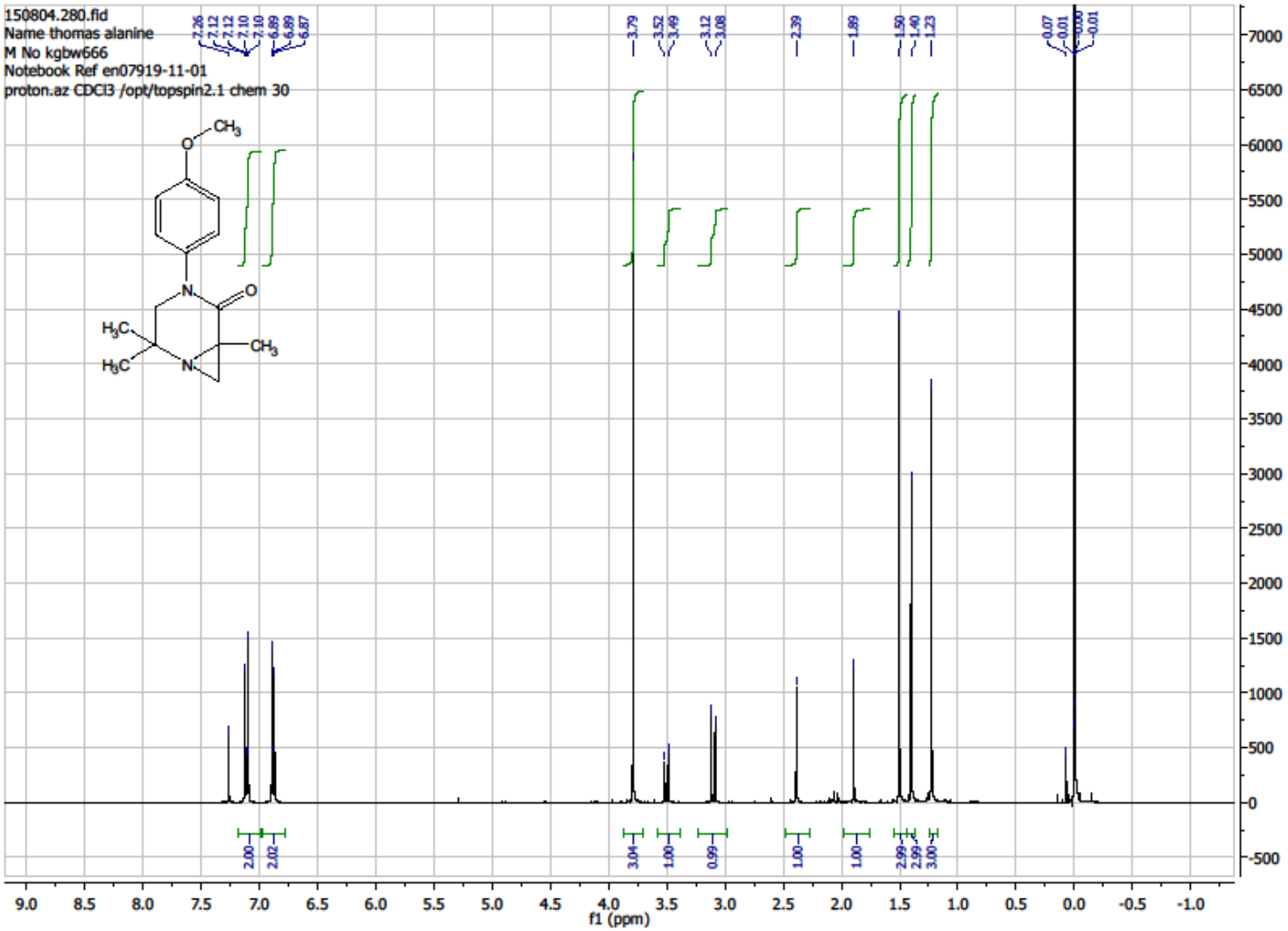
2b ^{1}H NMR 400 MHz



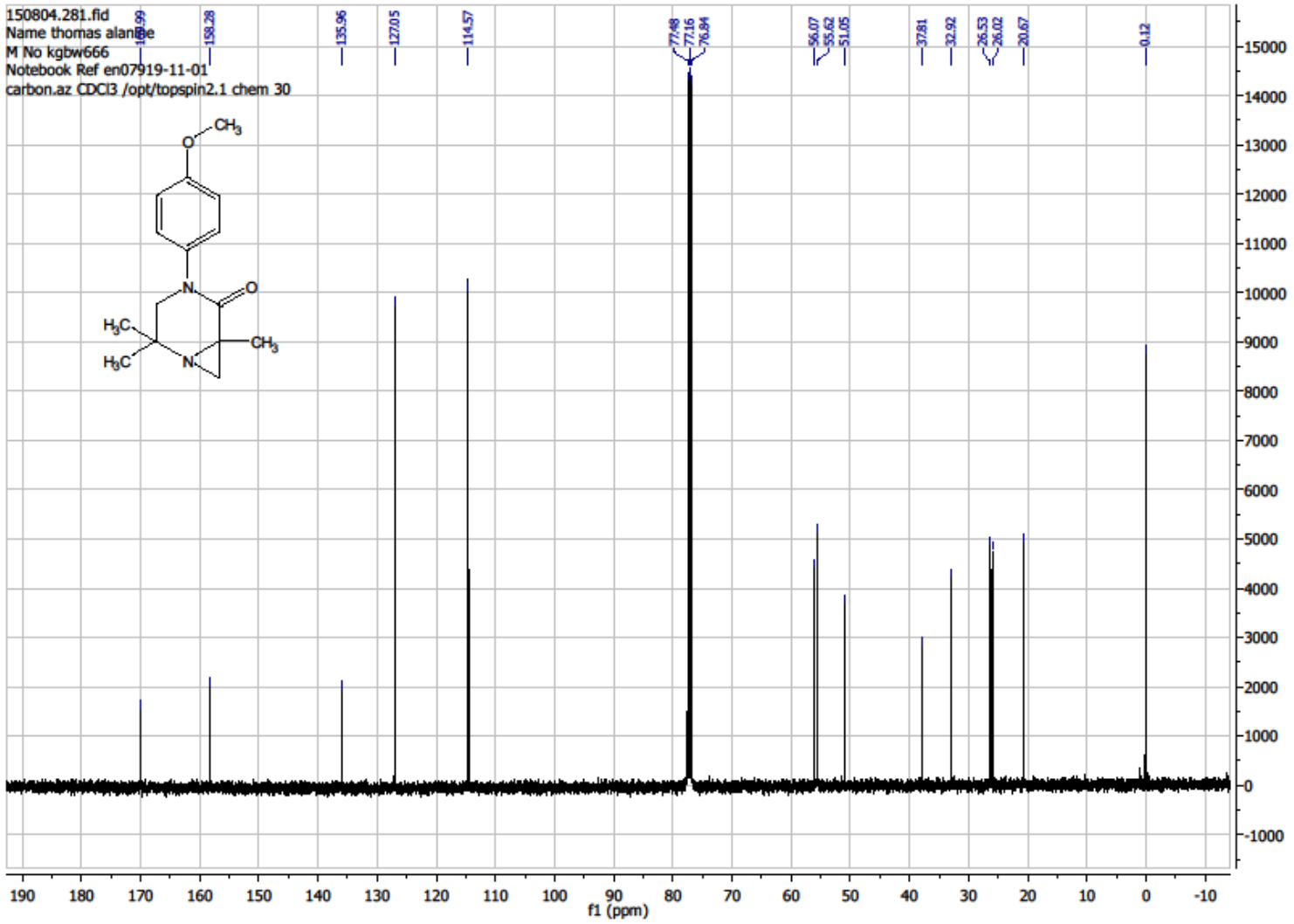
2b ^{13}C NMR 101 MHz



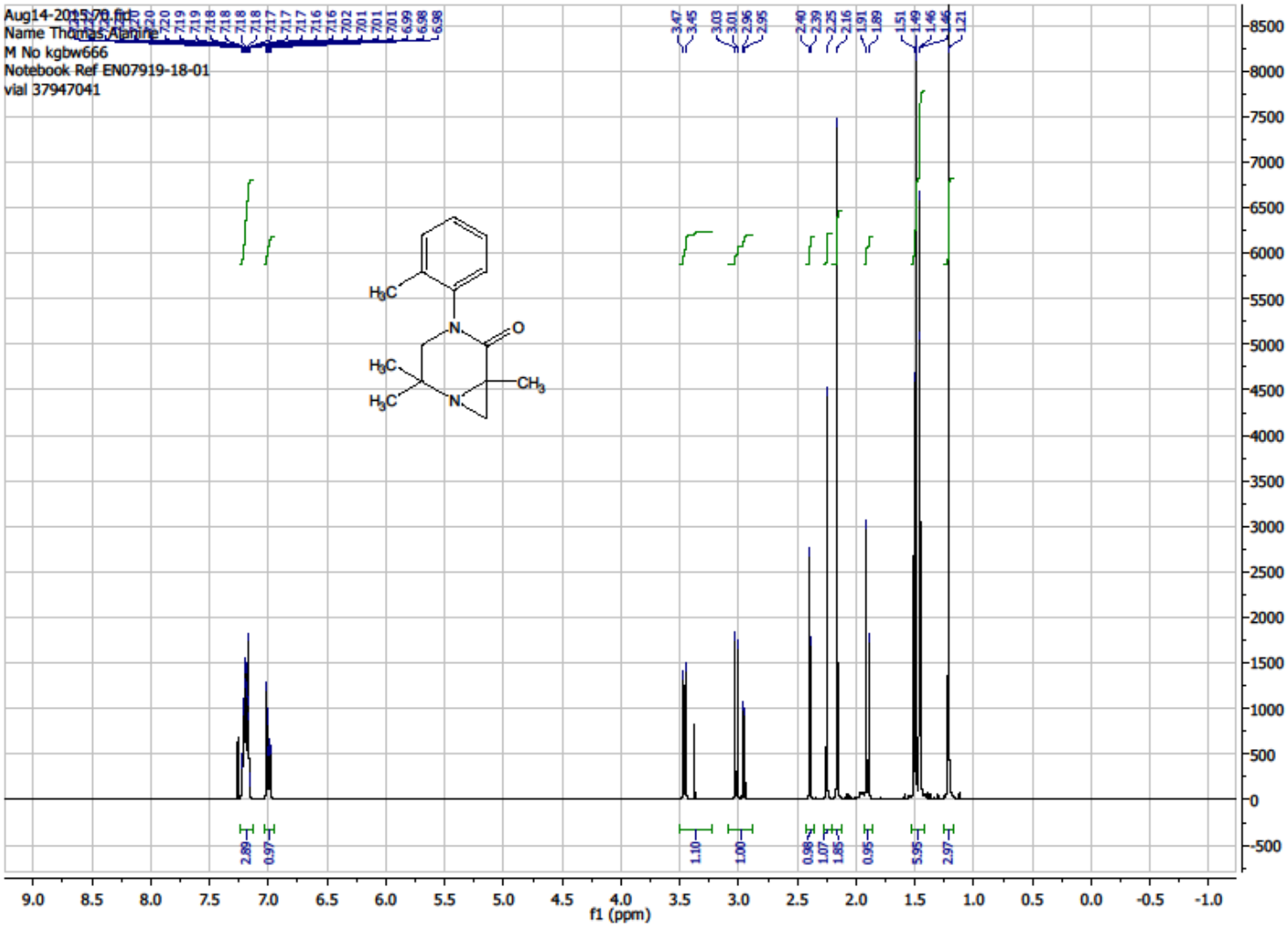
2c ^{1}H NMR 400 MHz



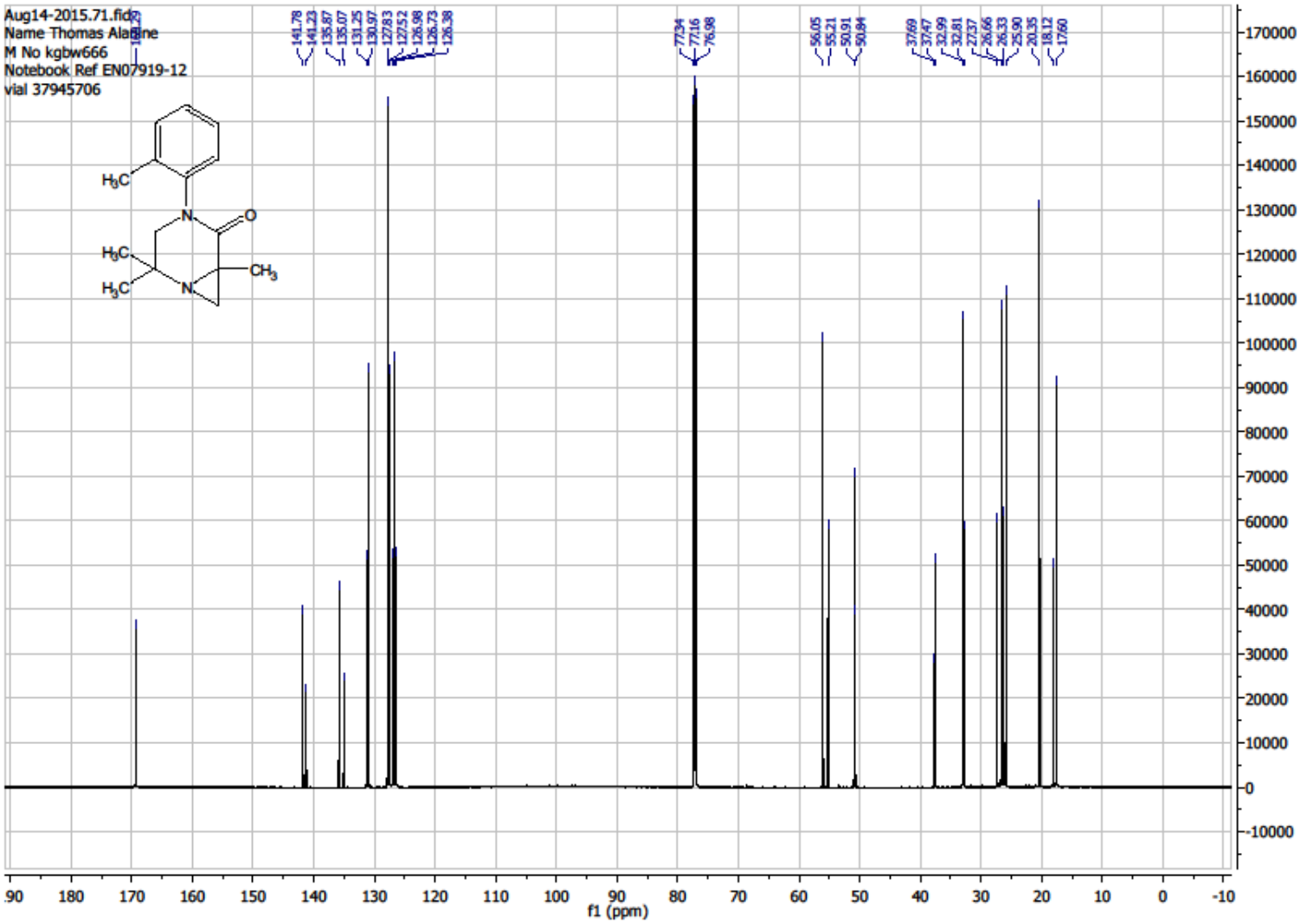
2c ^{13}C NMR 101 MHz



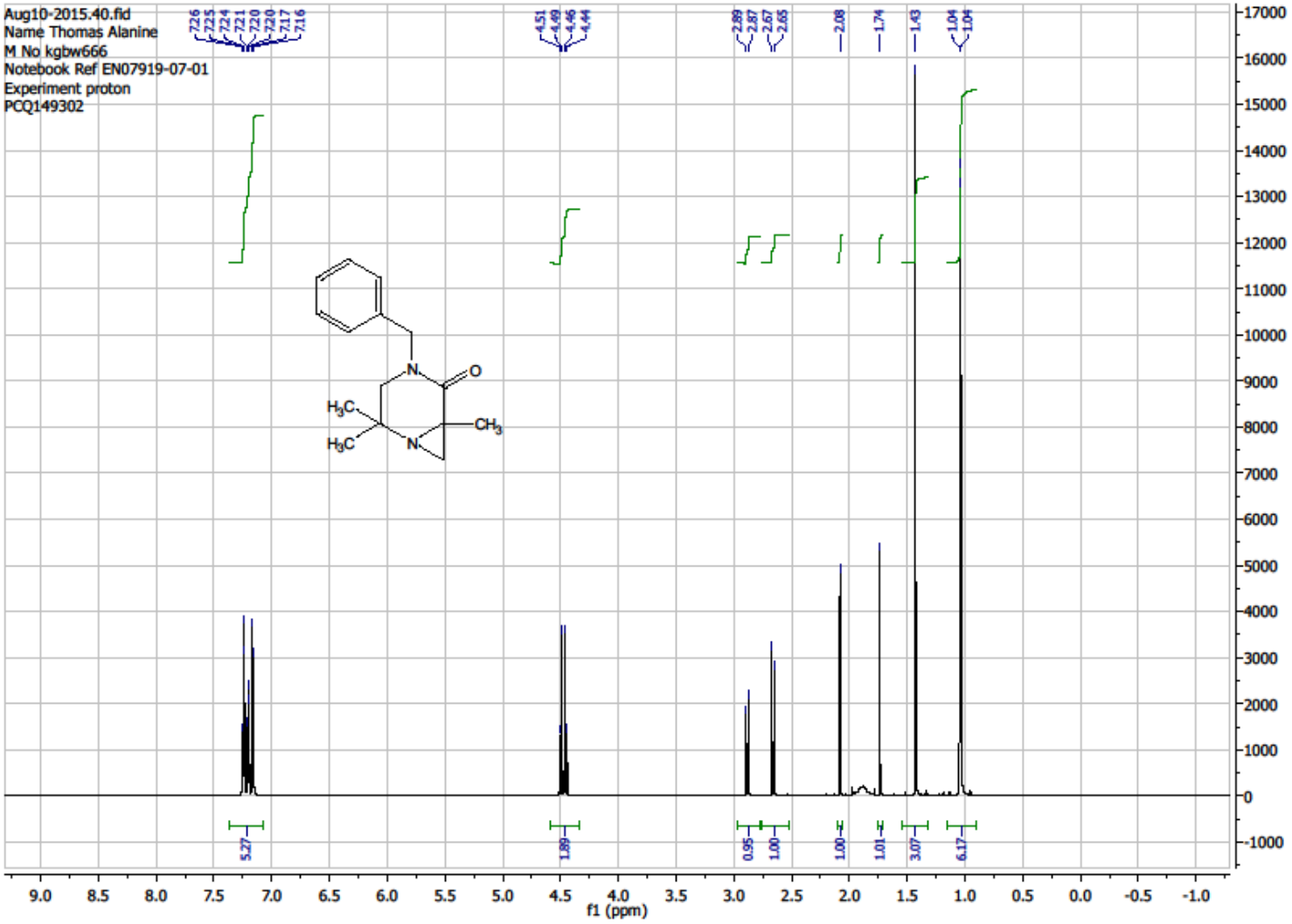
2d ^{1}H NMR 700 MHz



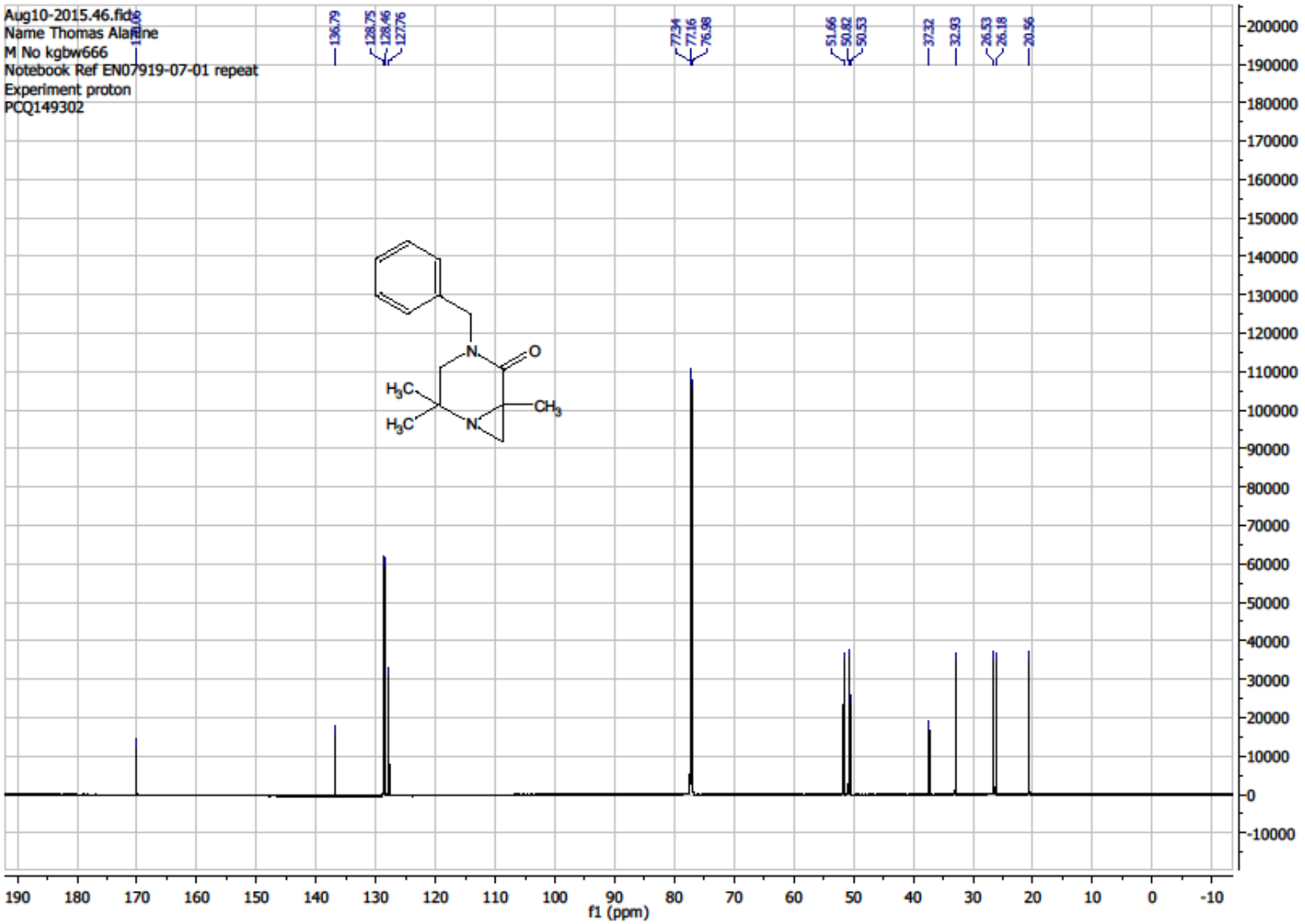
2d ^{13}C NMR 176 MHz



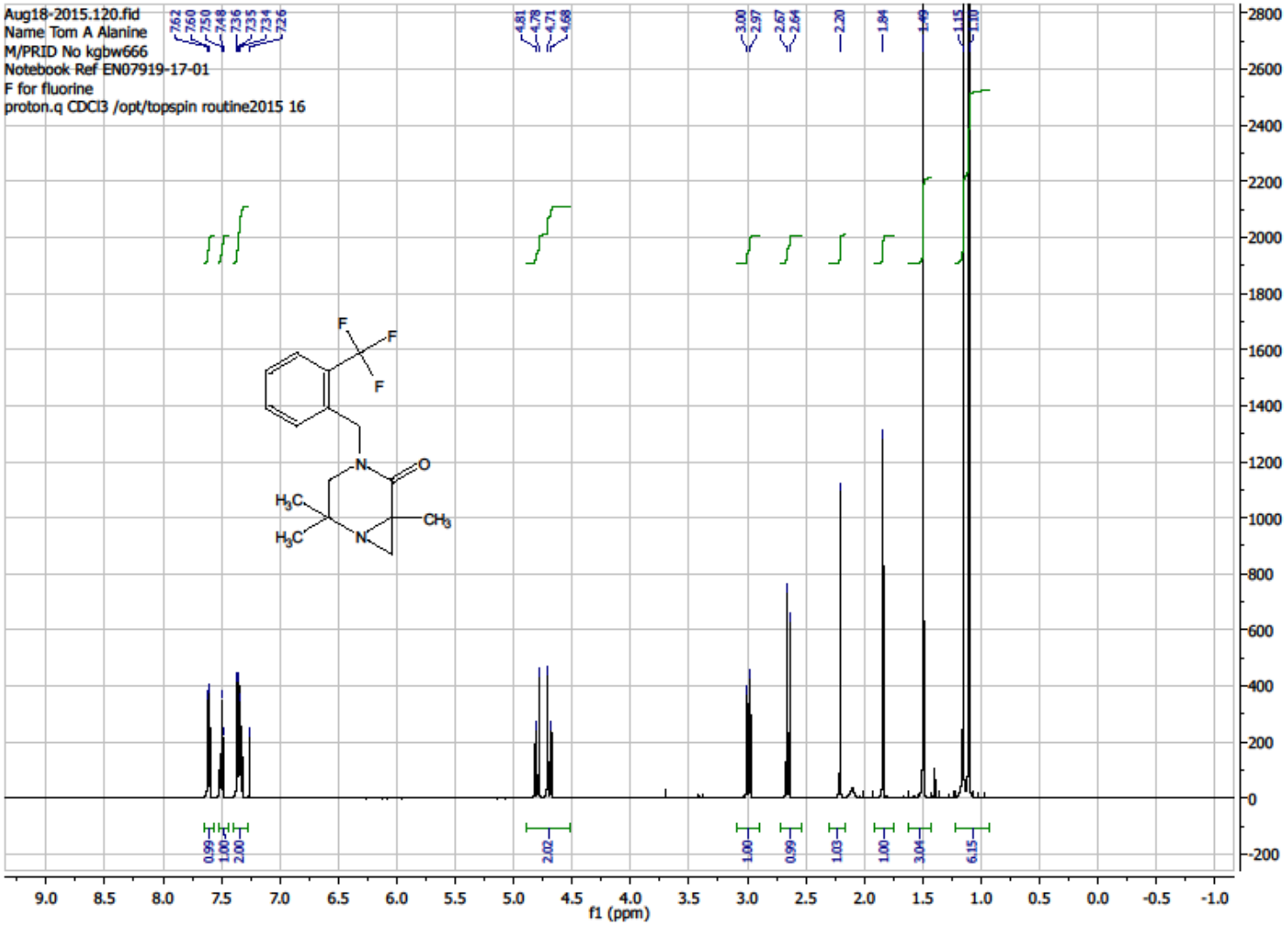
2e ^{1}H NMR 700 MHz



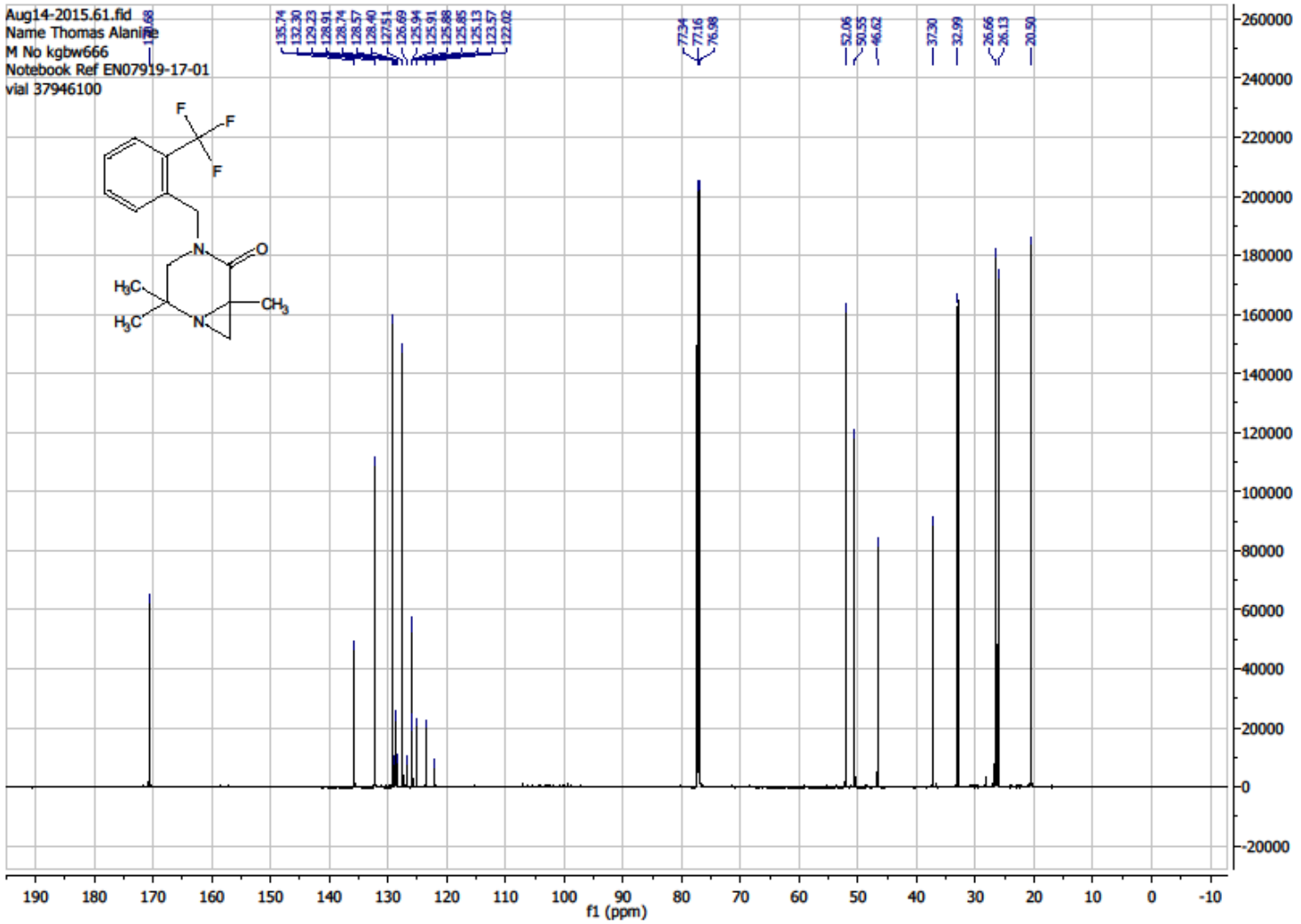
2e ^{13}C NMR 176 MHz



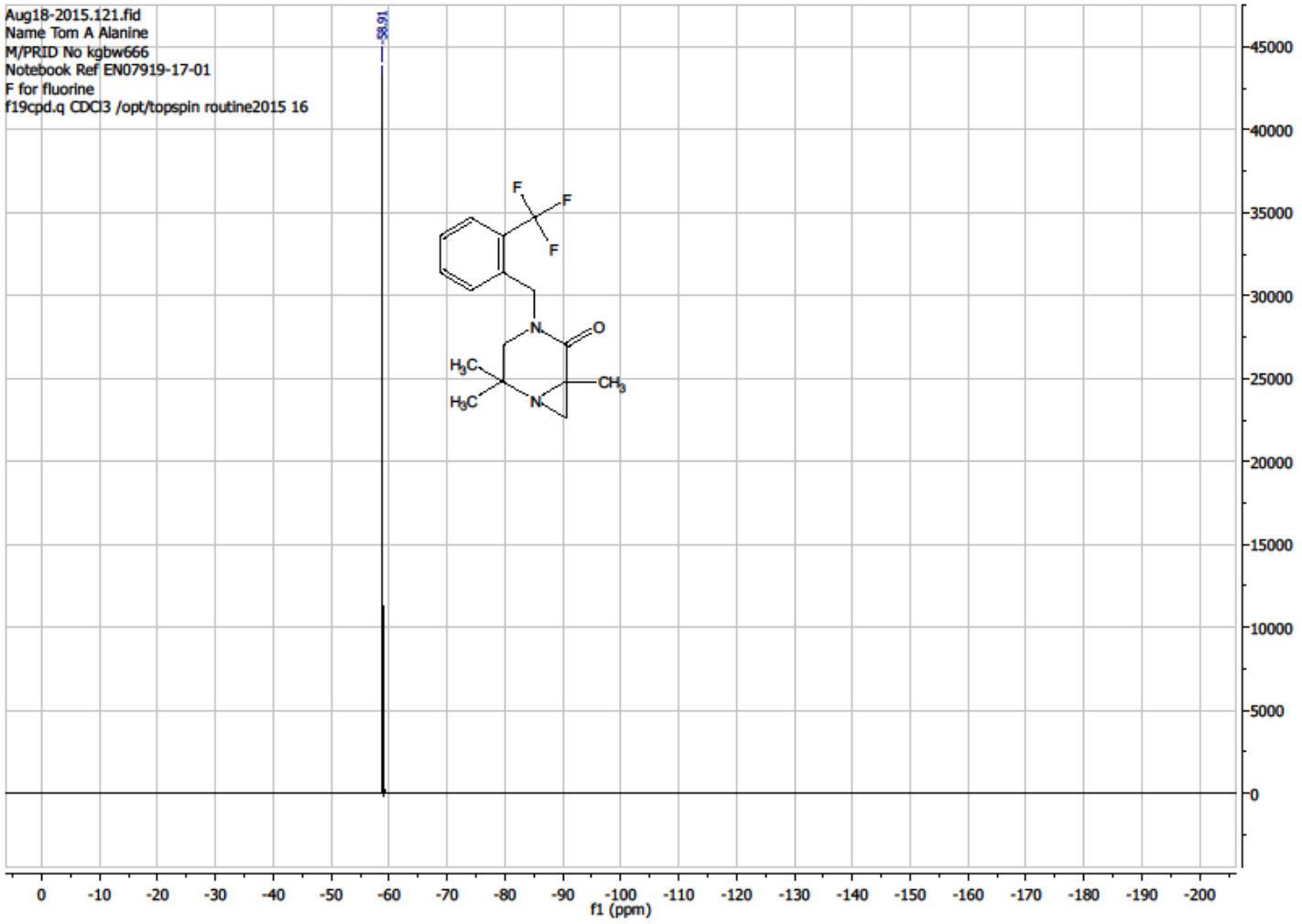
2f ^{1}H NMR 700 MHz



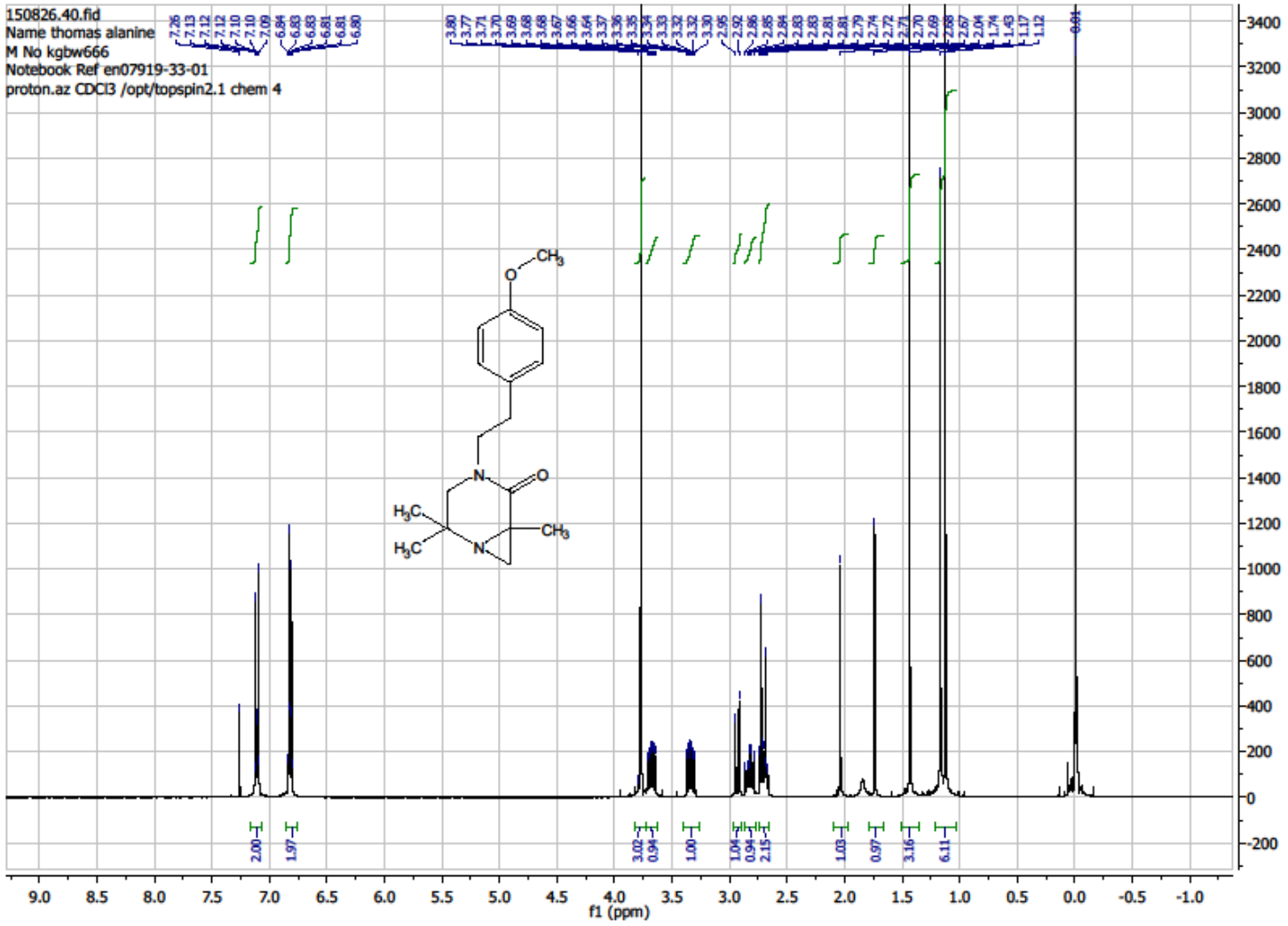
2f ^{13}C NMR 176 MHz



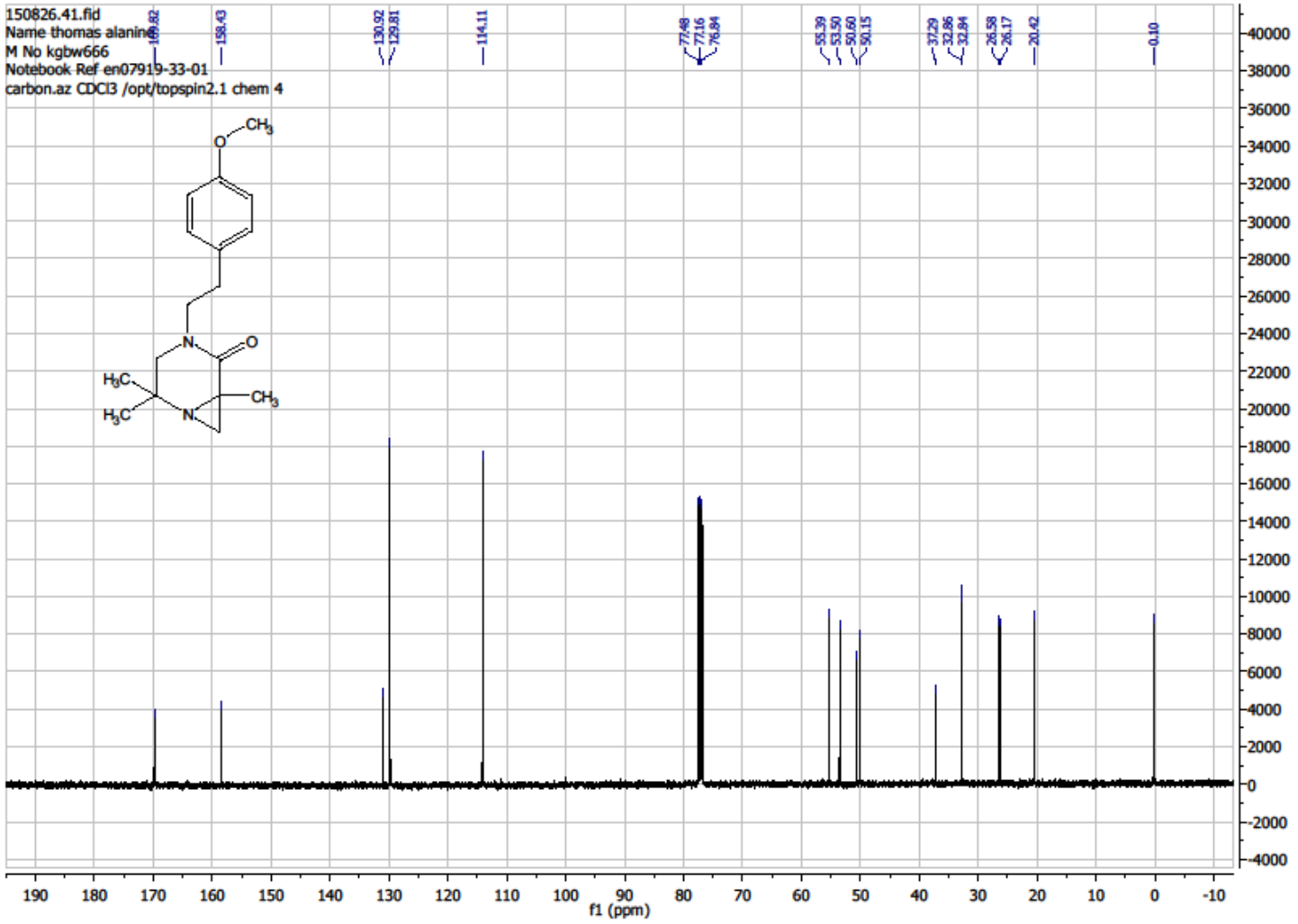
2f ^{19}F NMR 476 MHz



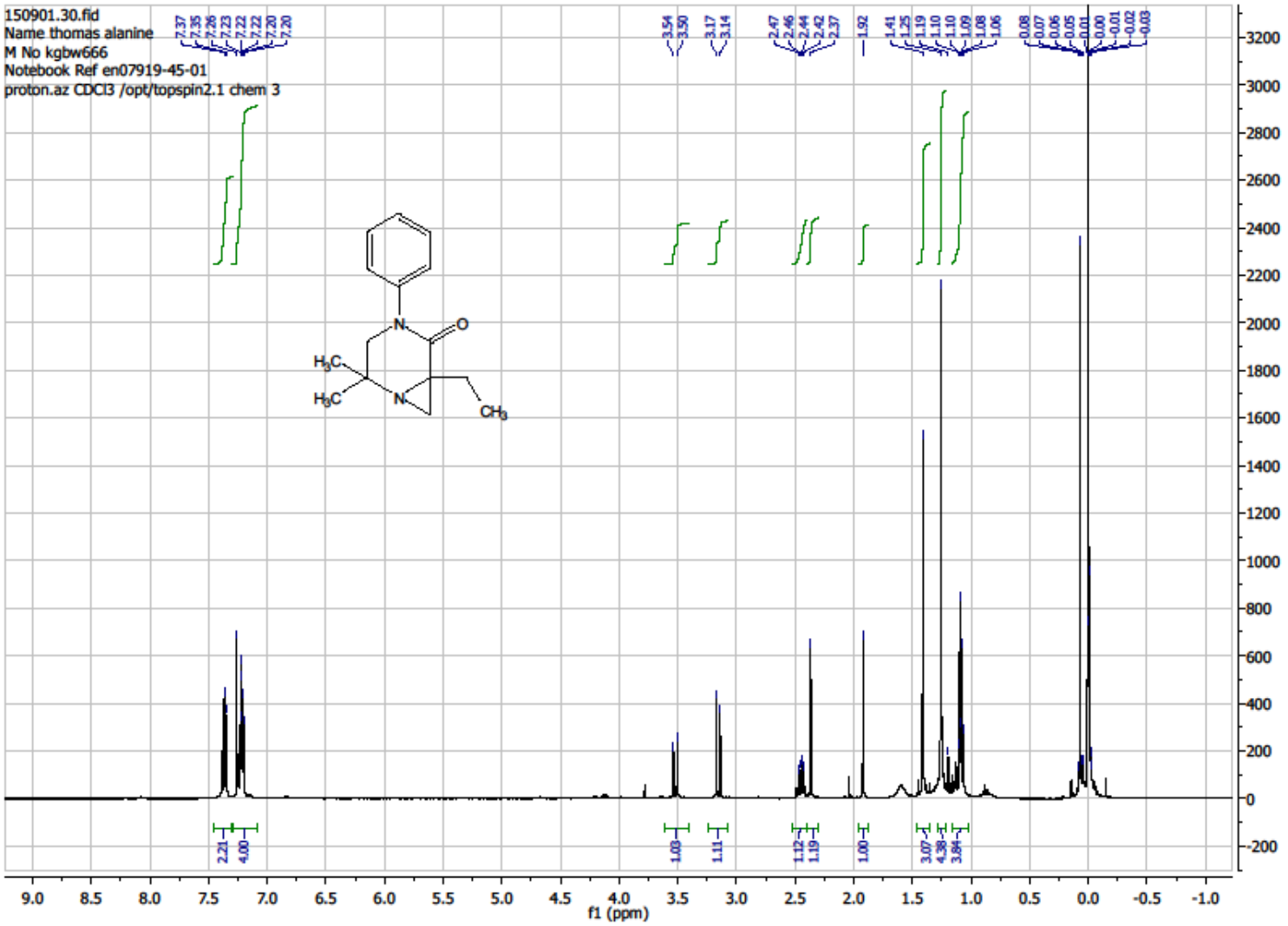
2g ^{1}H NMR 400 MHz



2g ^{13}C NMR 101 MHz



2h ^{1}H NMR 400 MHz



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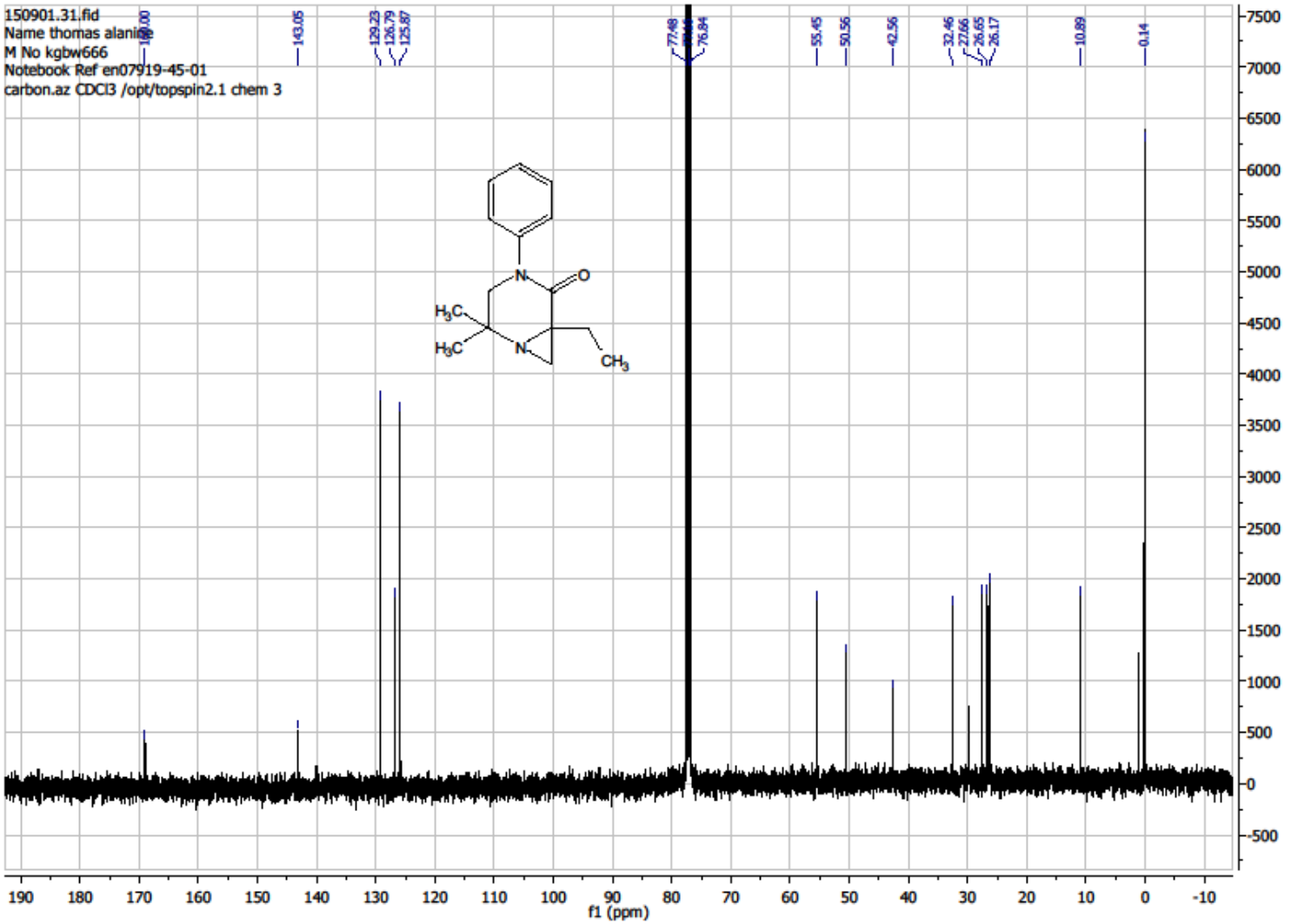

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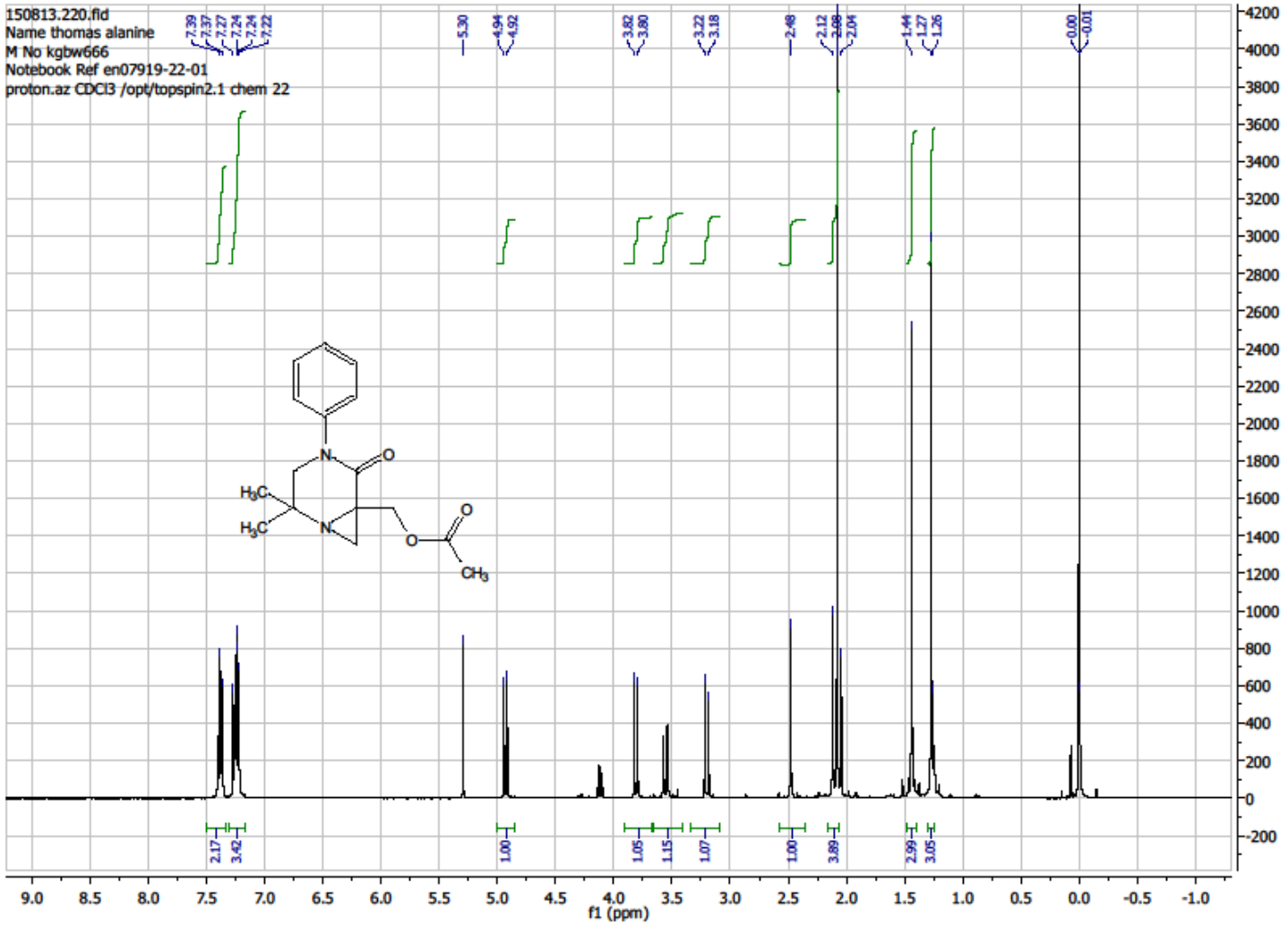
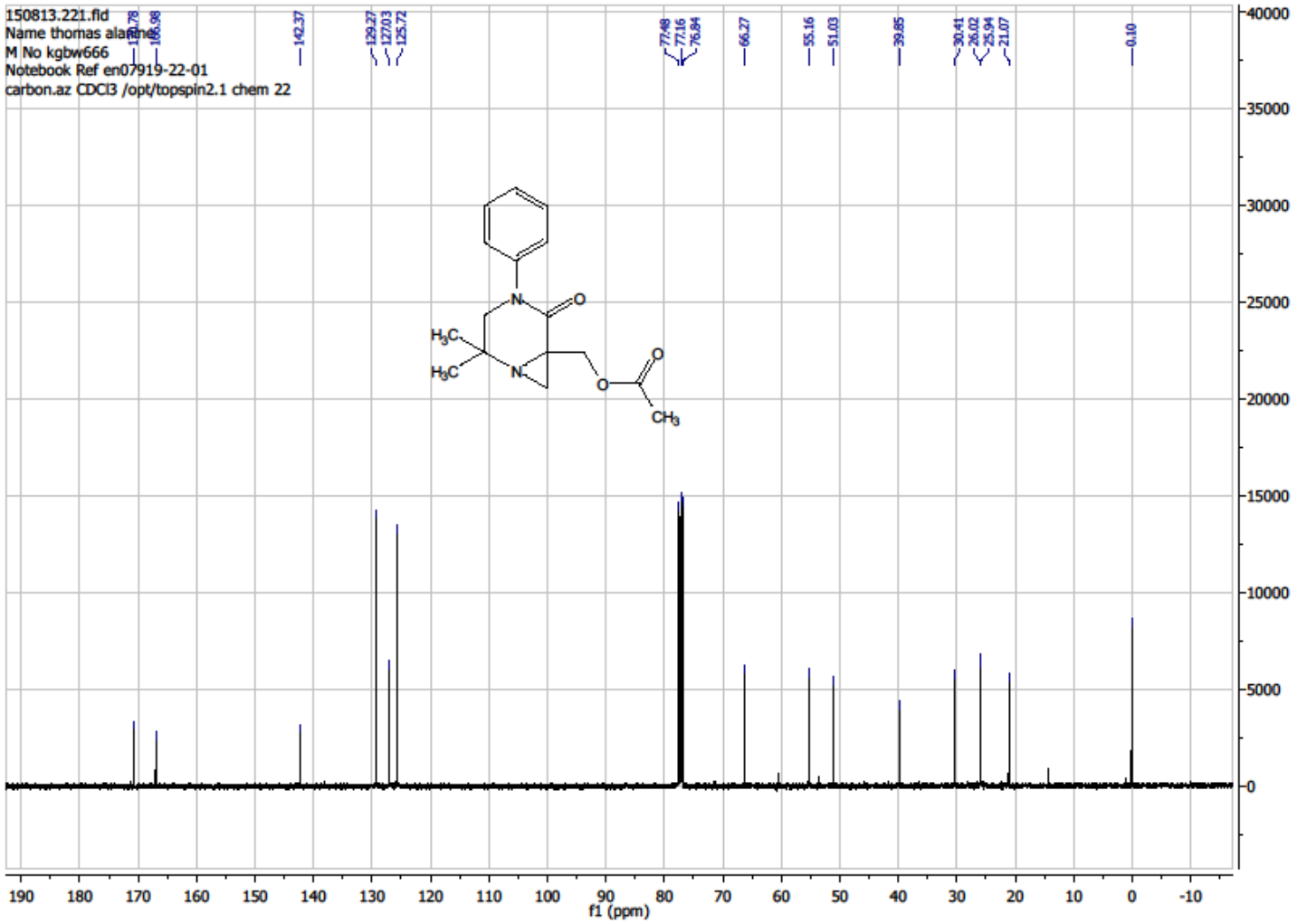
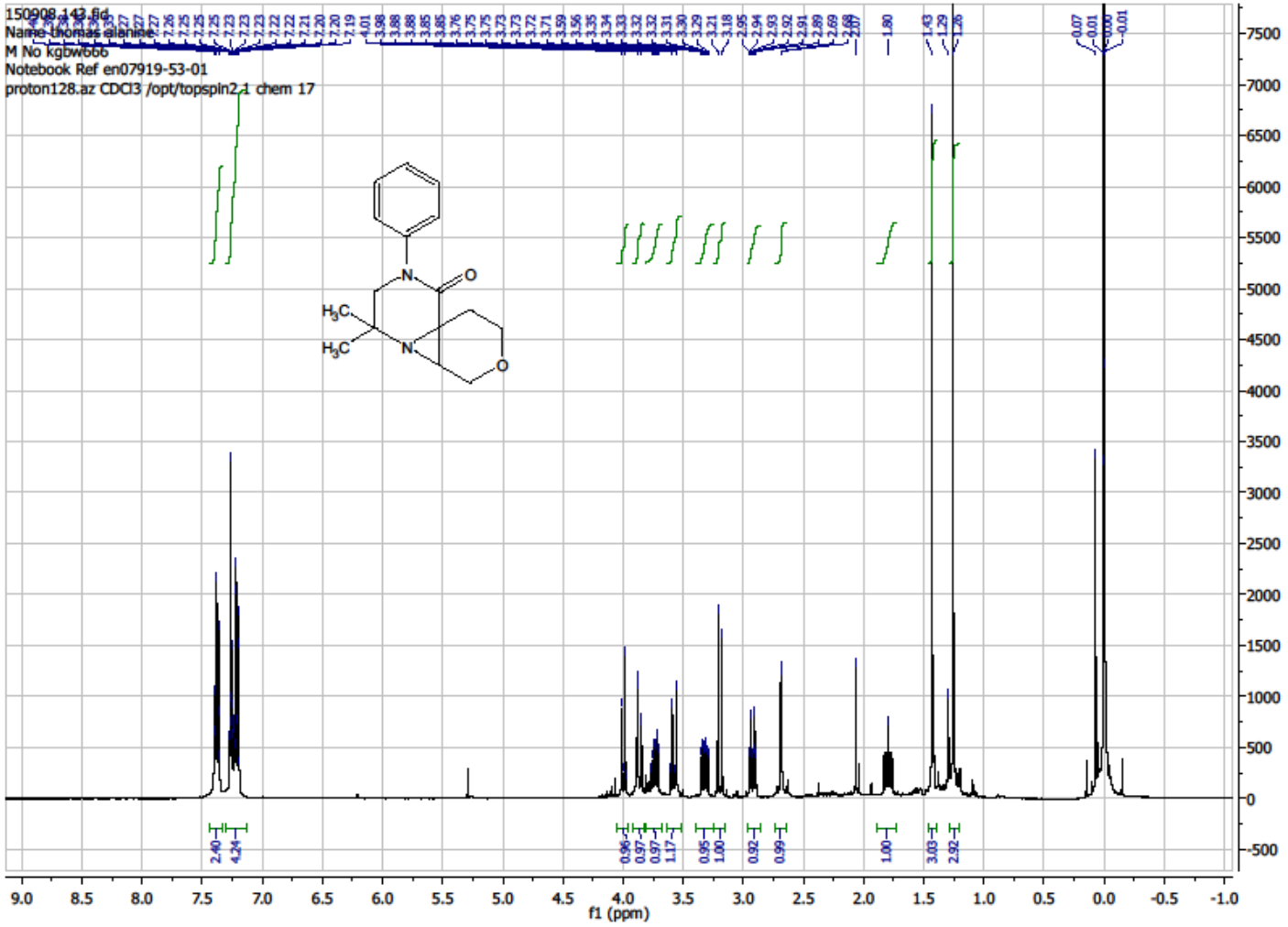


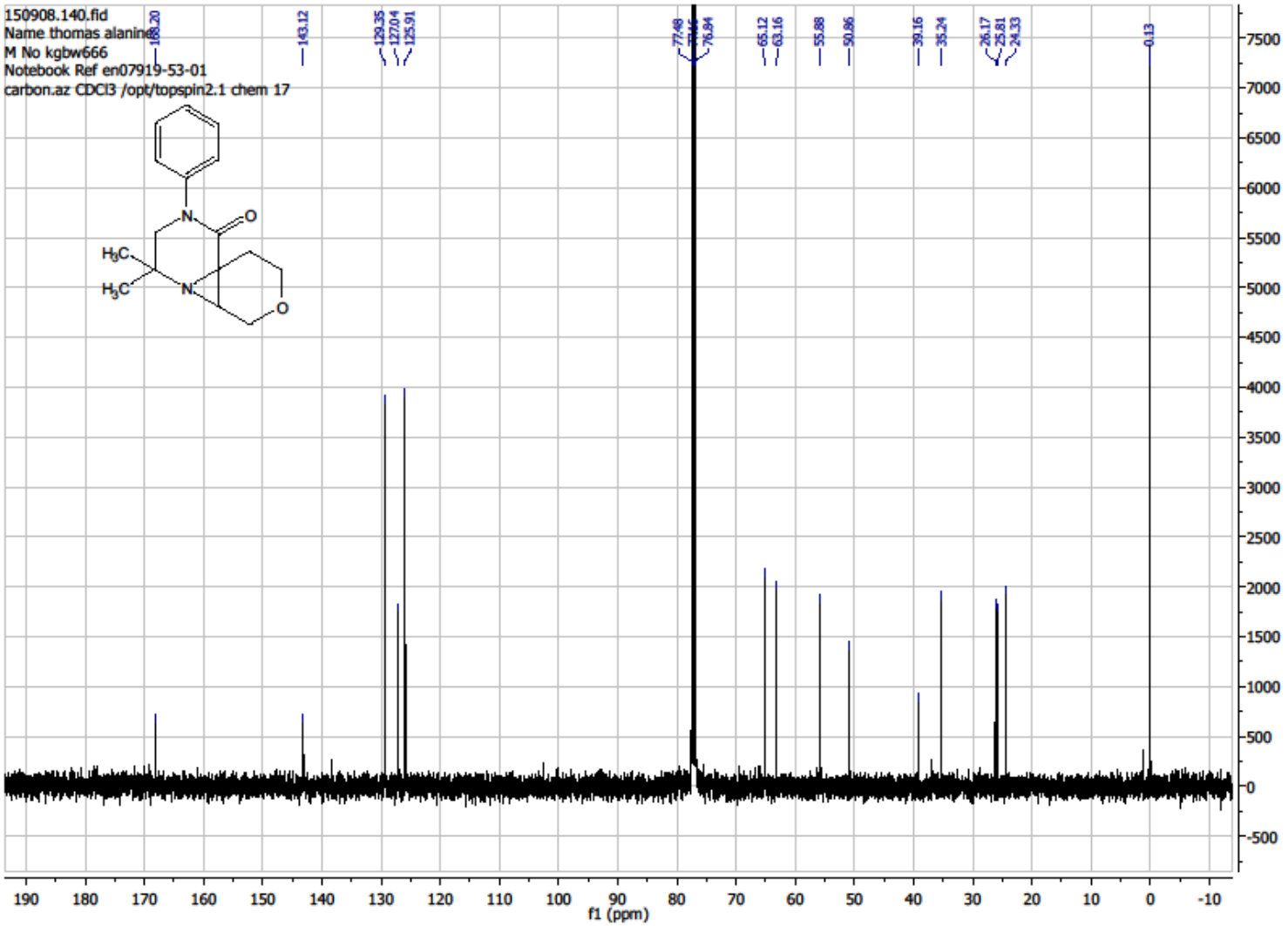
2i ^{13}C NMR 101 MHz



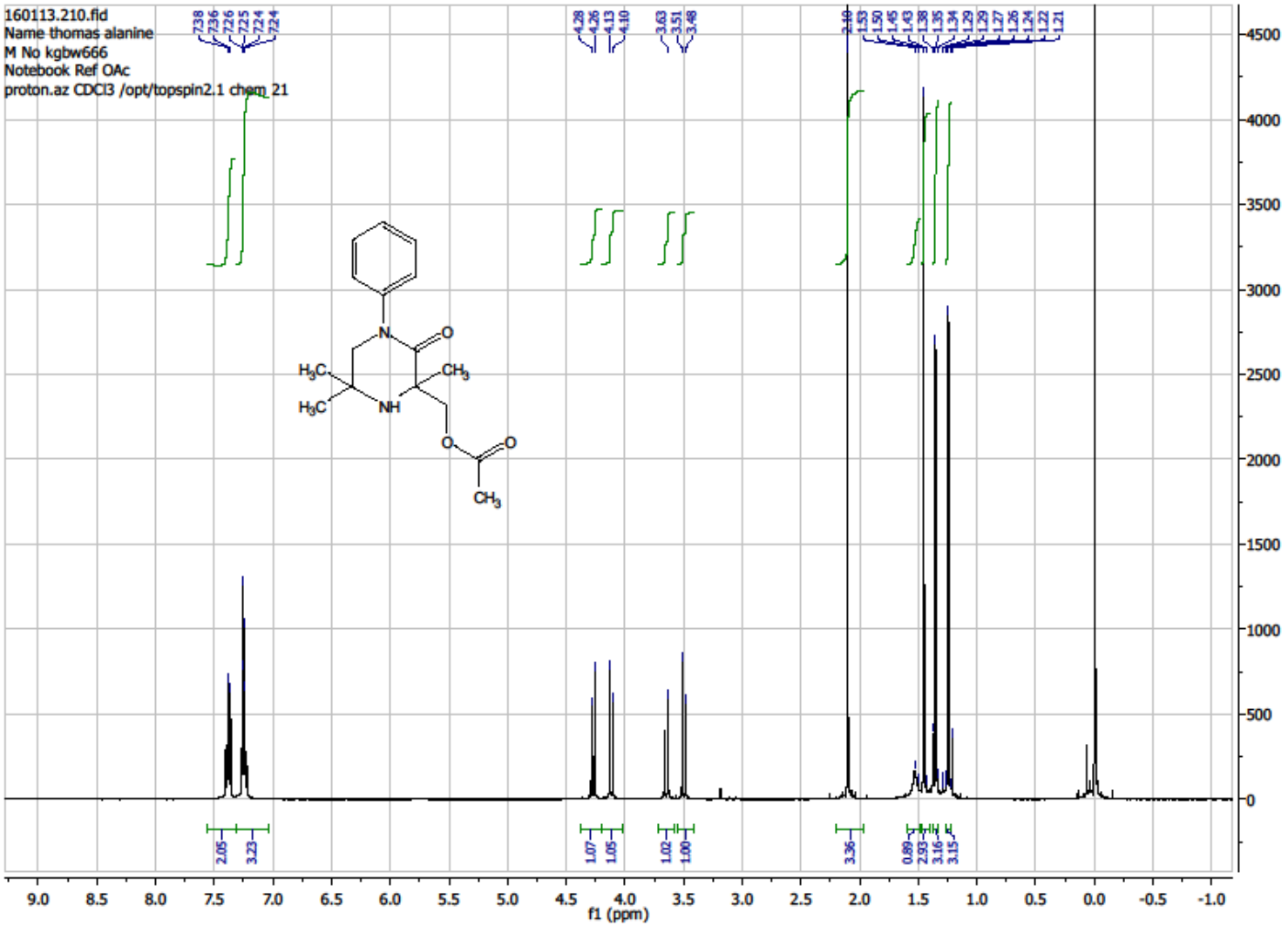
2j ^{1}H NMR 400 MHz



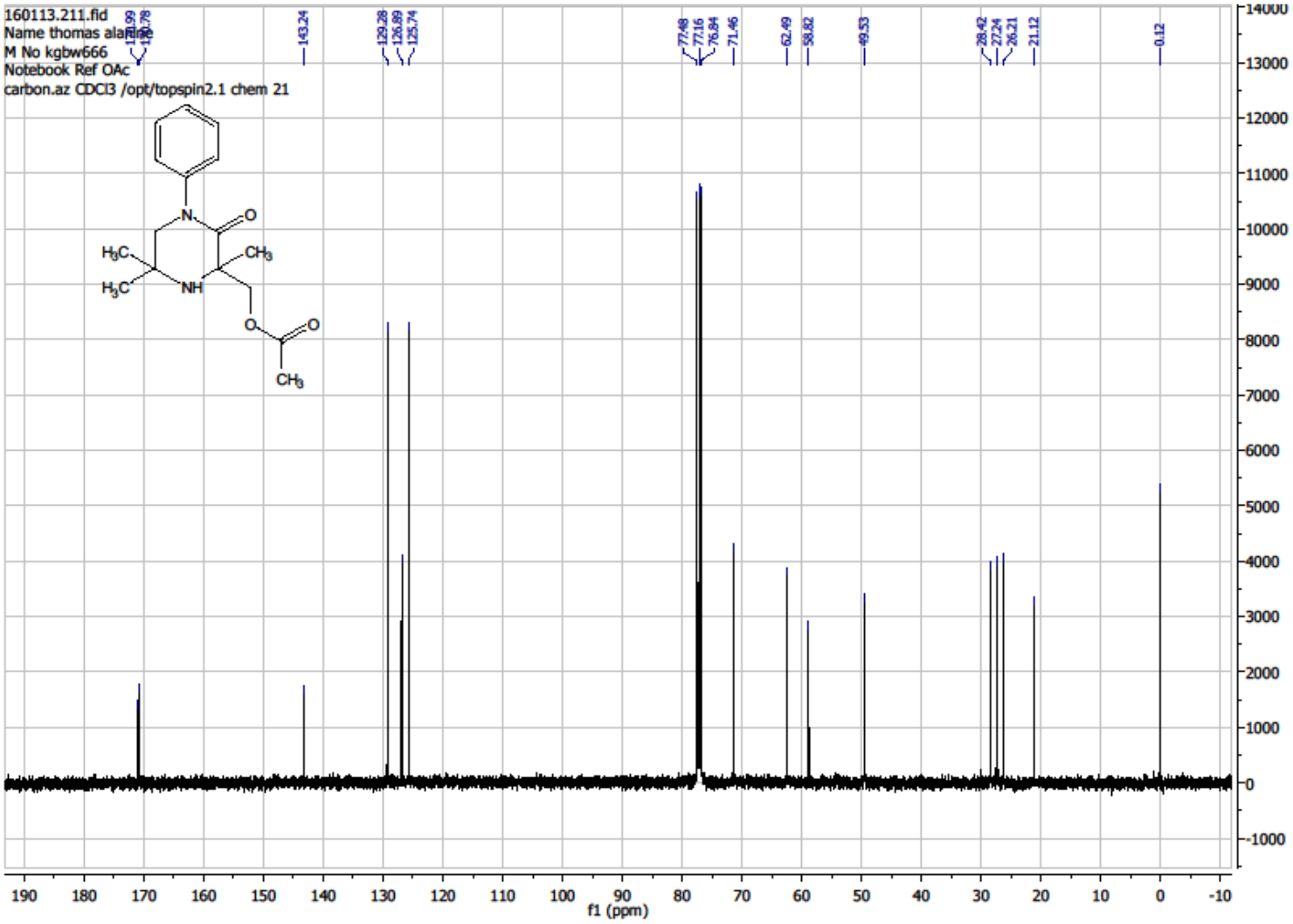
2j ^{13}C NMR 101 MHz



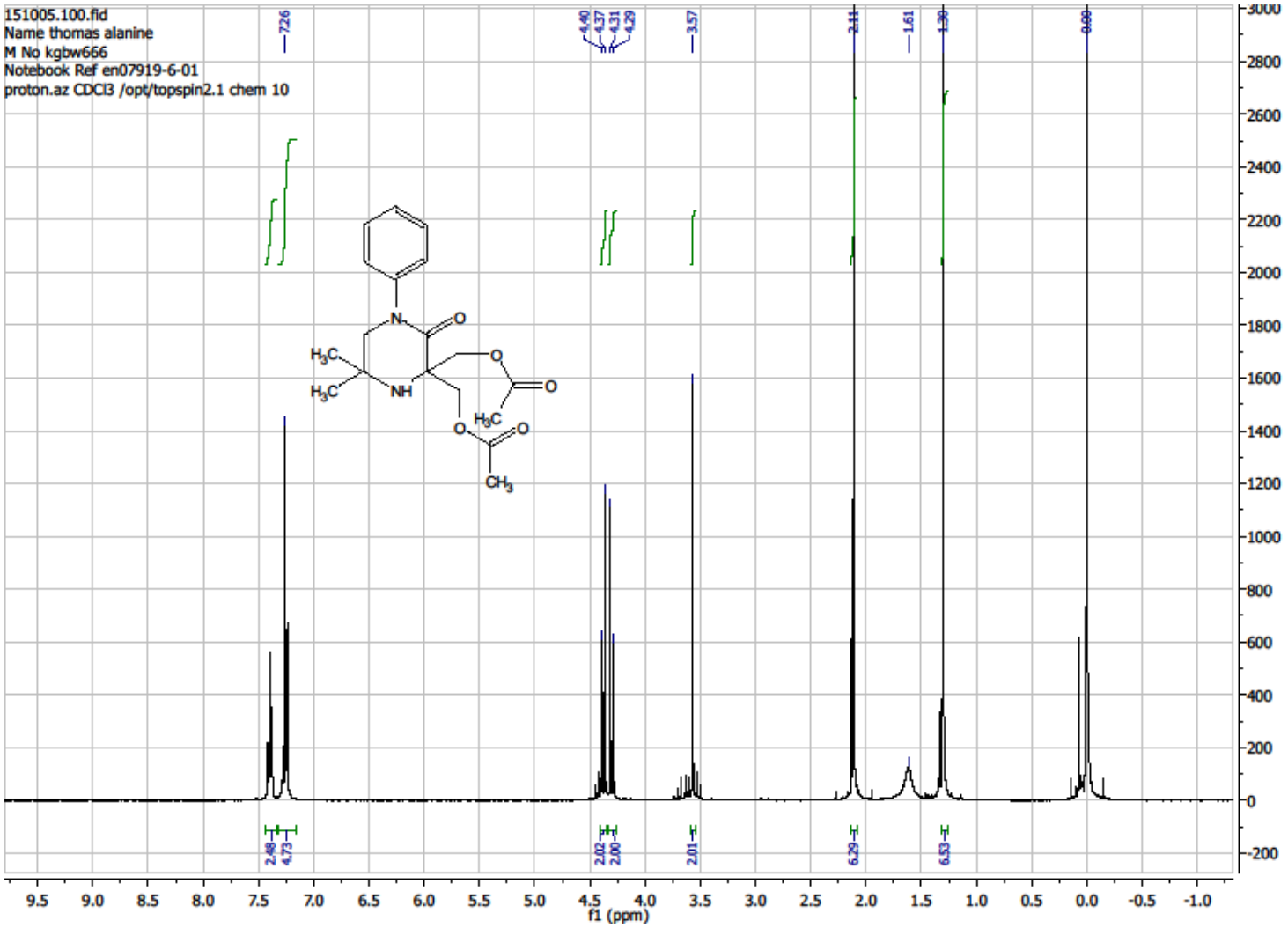
3 ^{1}H NMR 400 MHz



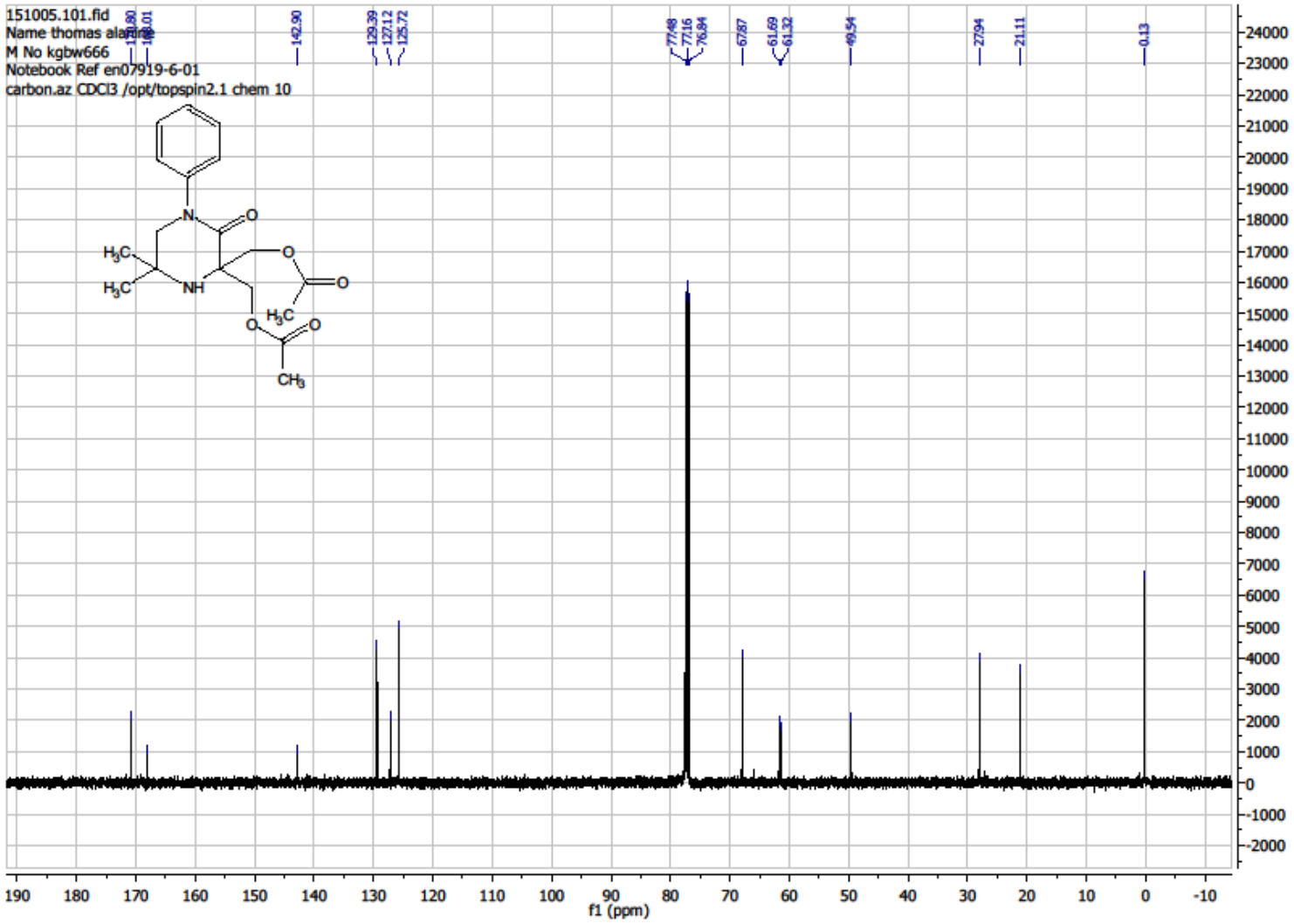
3 ^{13}C NMR 101 MHz



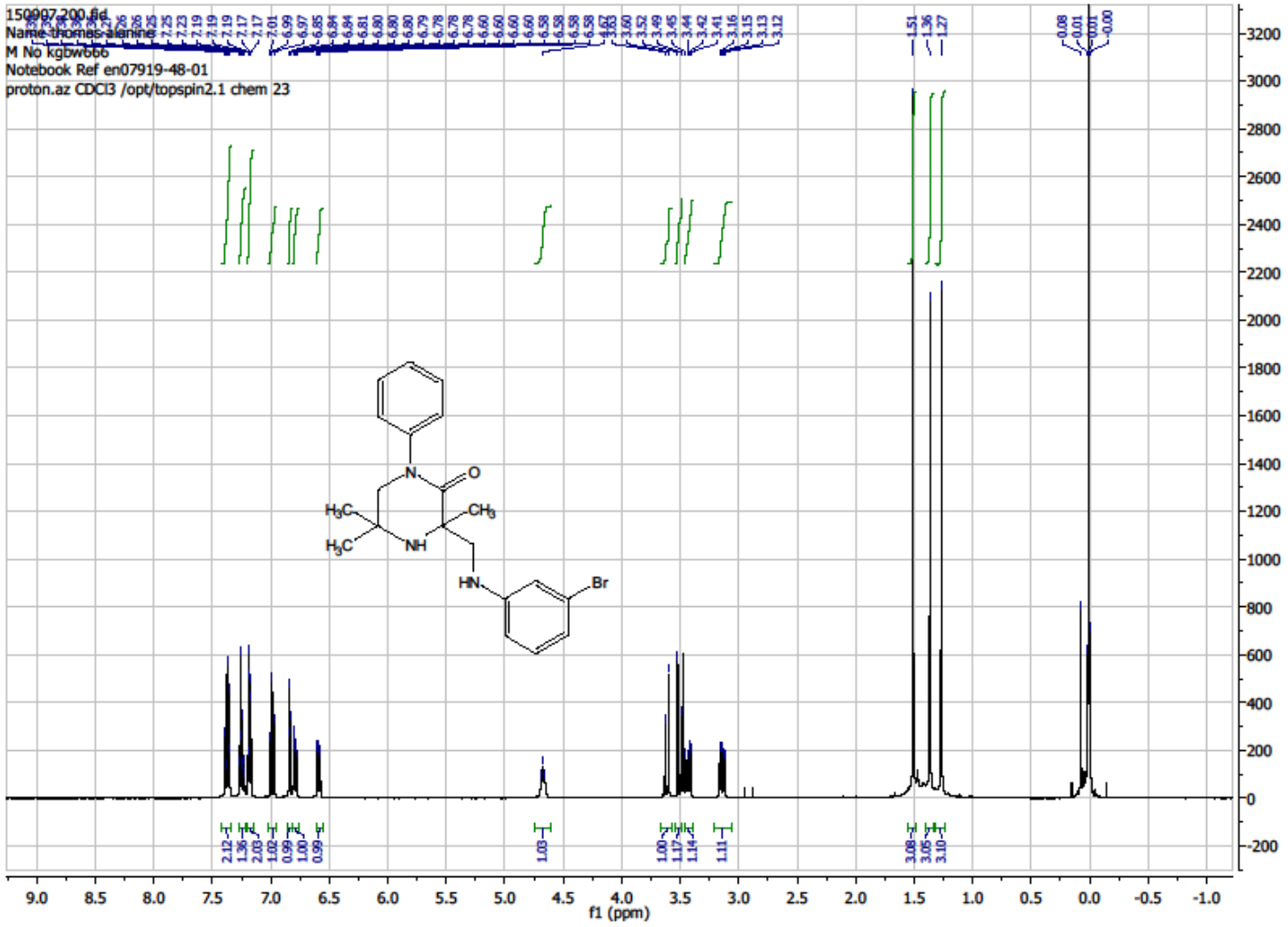
4 ^{1}H NMR 400 MHz



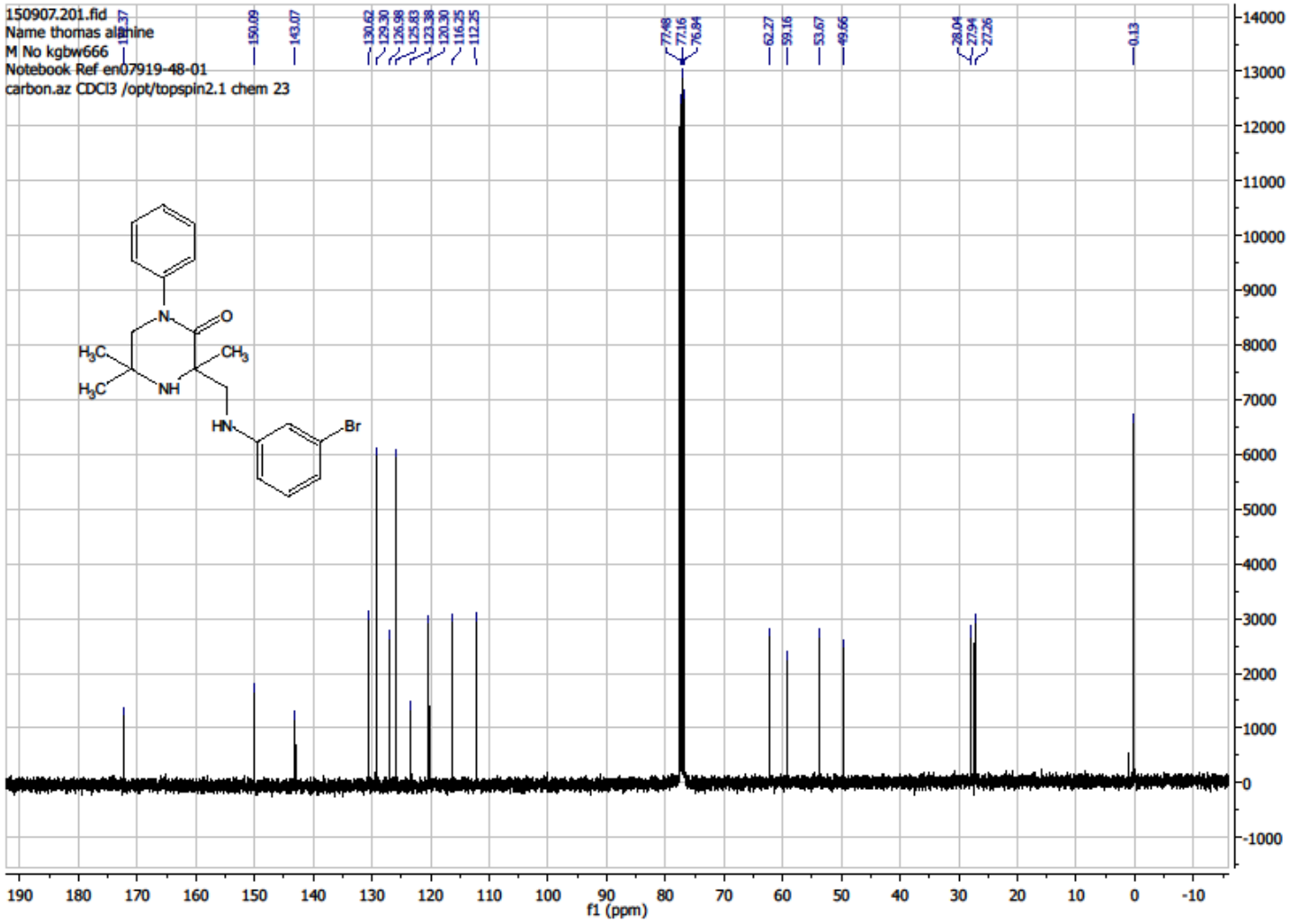
4 ^{13}C NMR 101 MHz



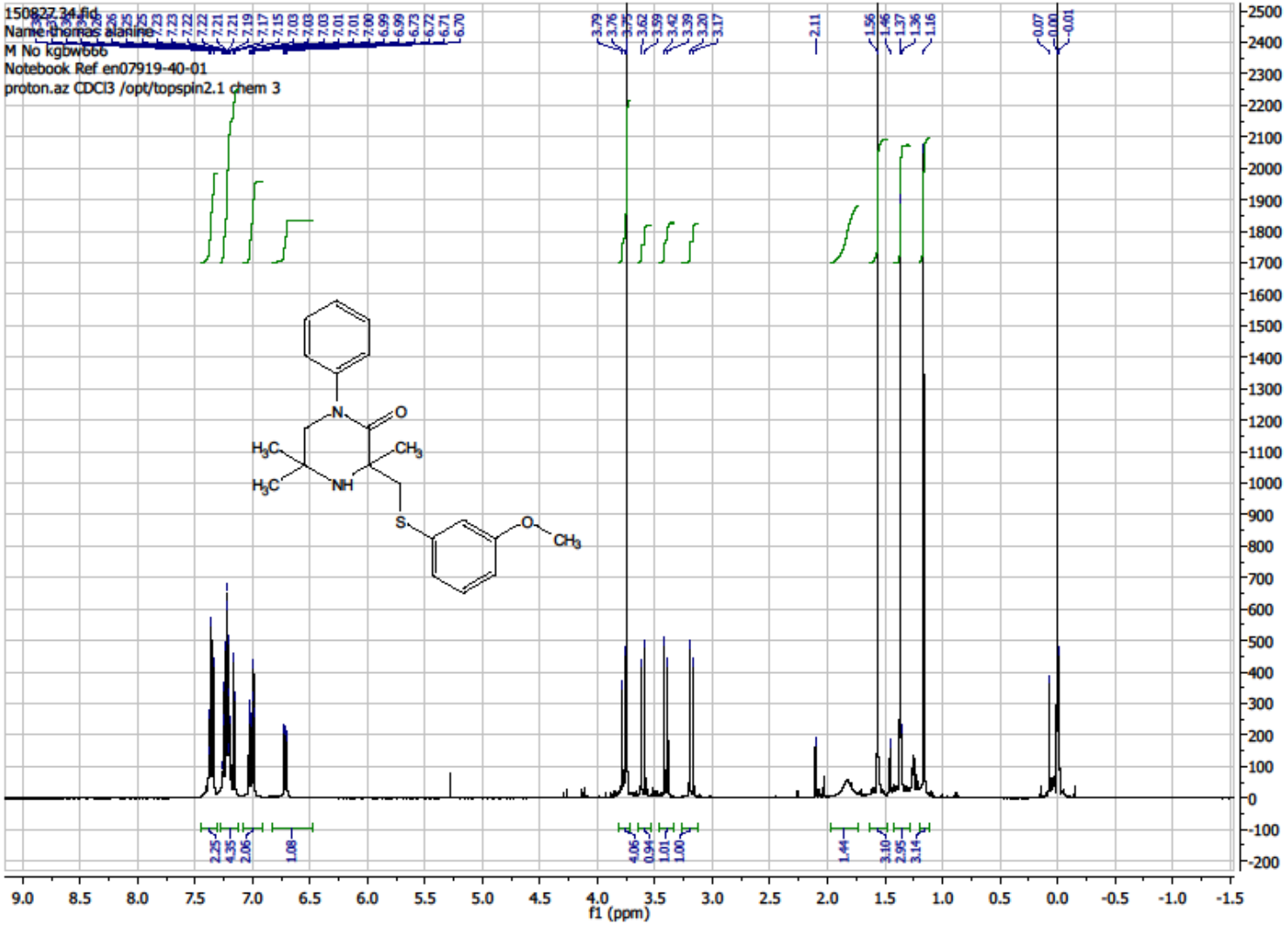
5a ^{1}H NMR 400 MHz



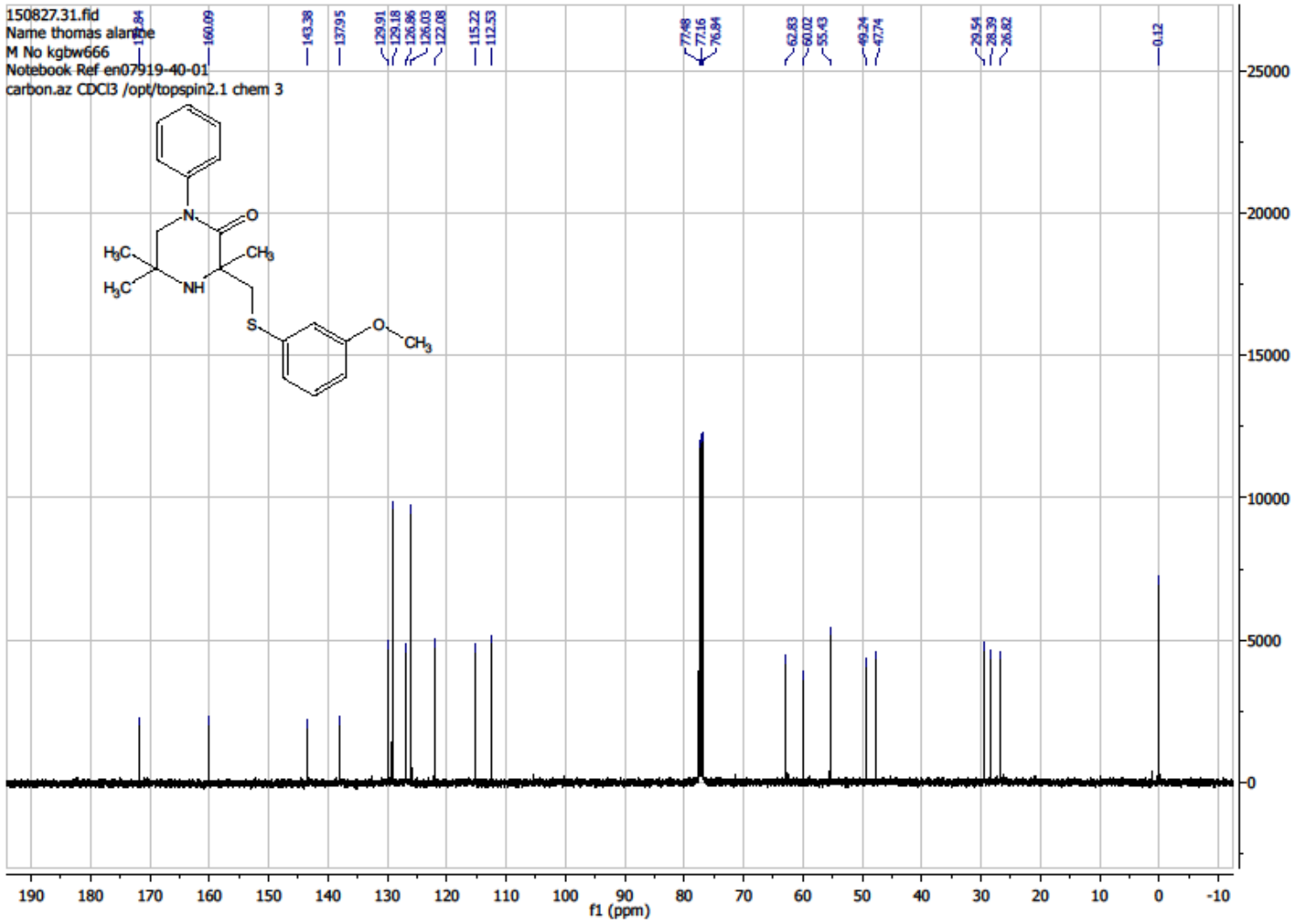
5a ^{13}C NMR 101 MHz



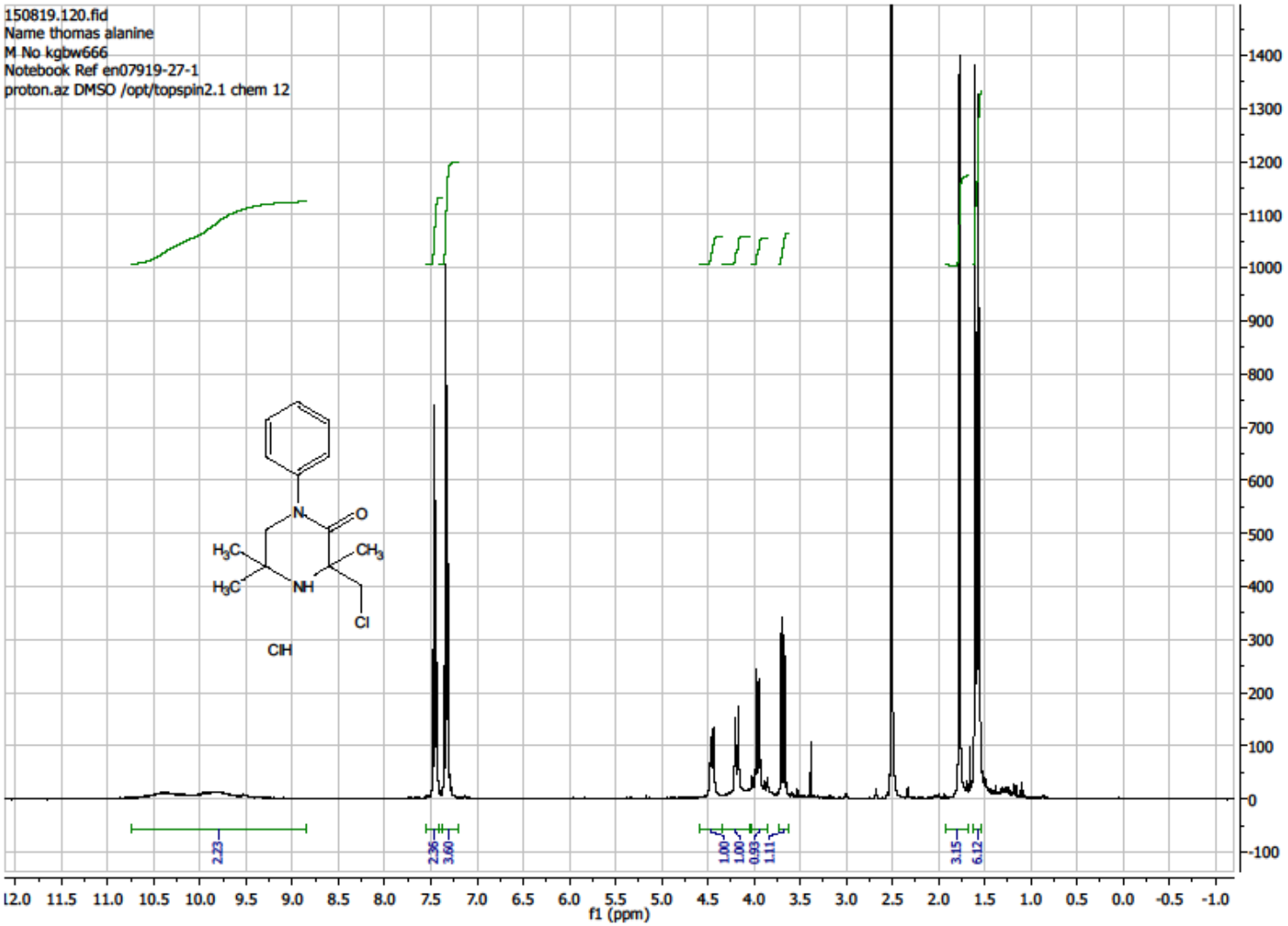
5b ^{1}H NMR 400 MHz



5b ^{13}C NMR 101 MHz



5c ^{1}H NMR 400 MHz



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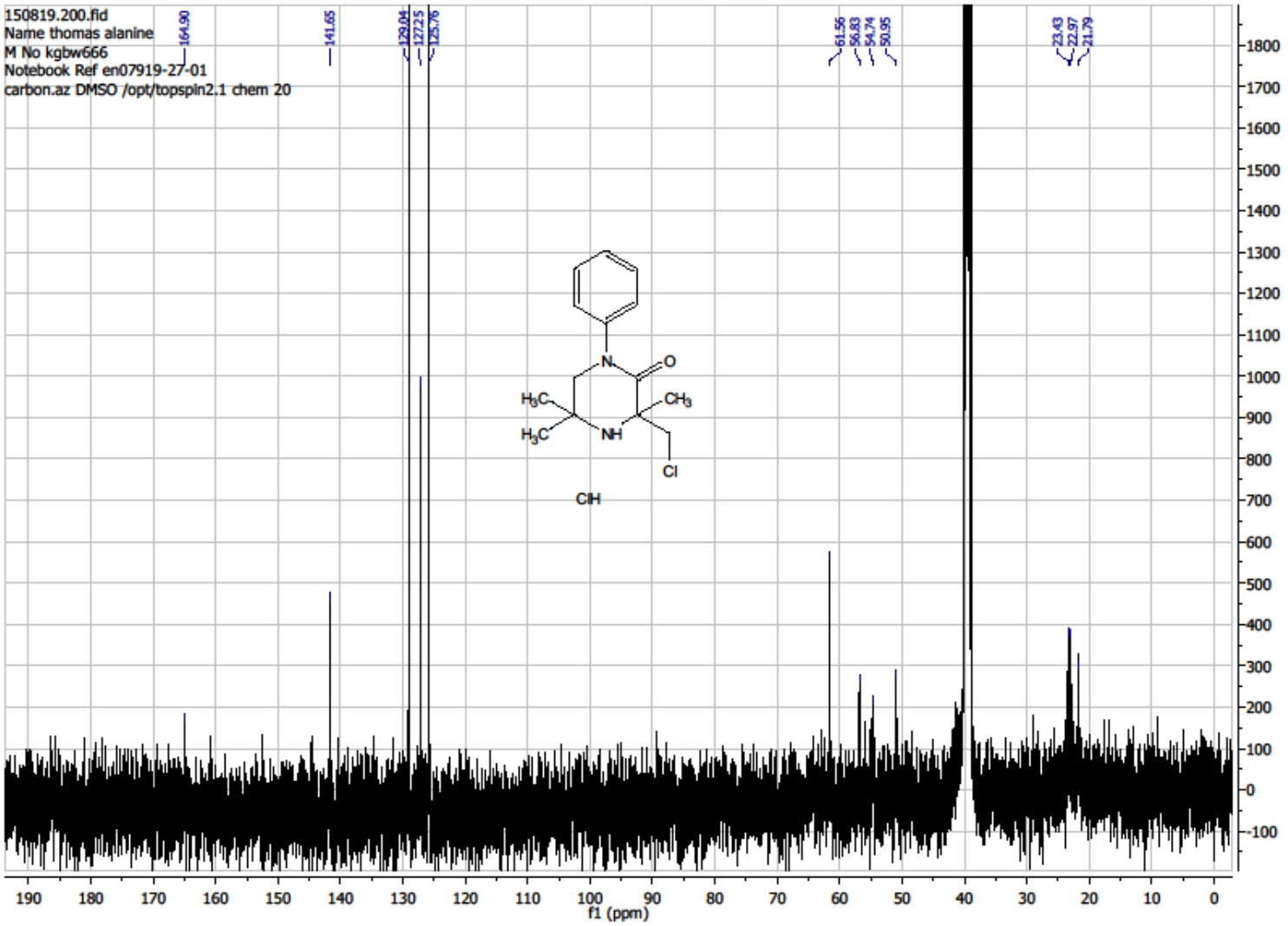
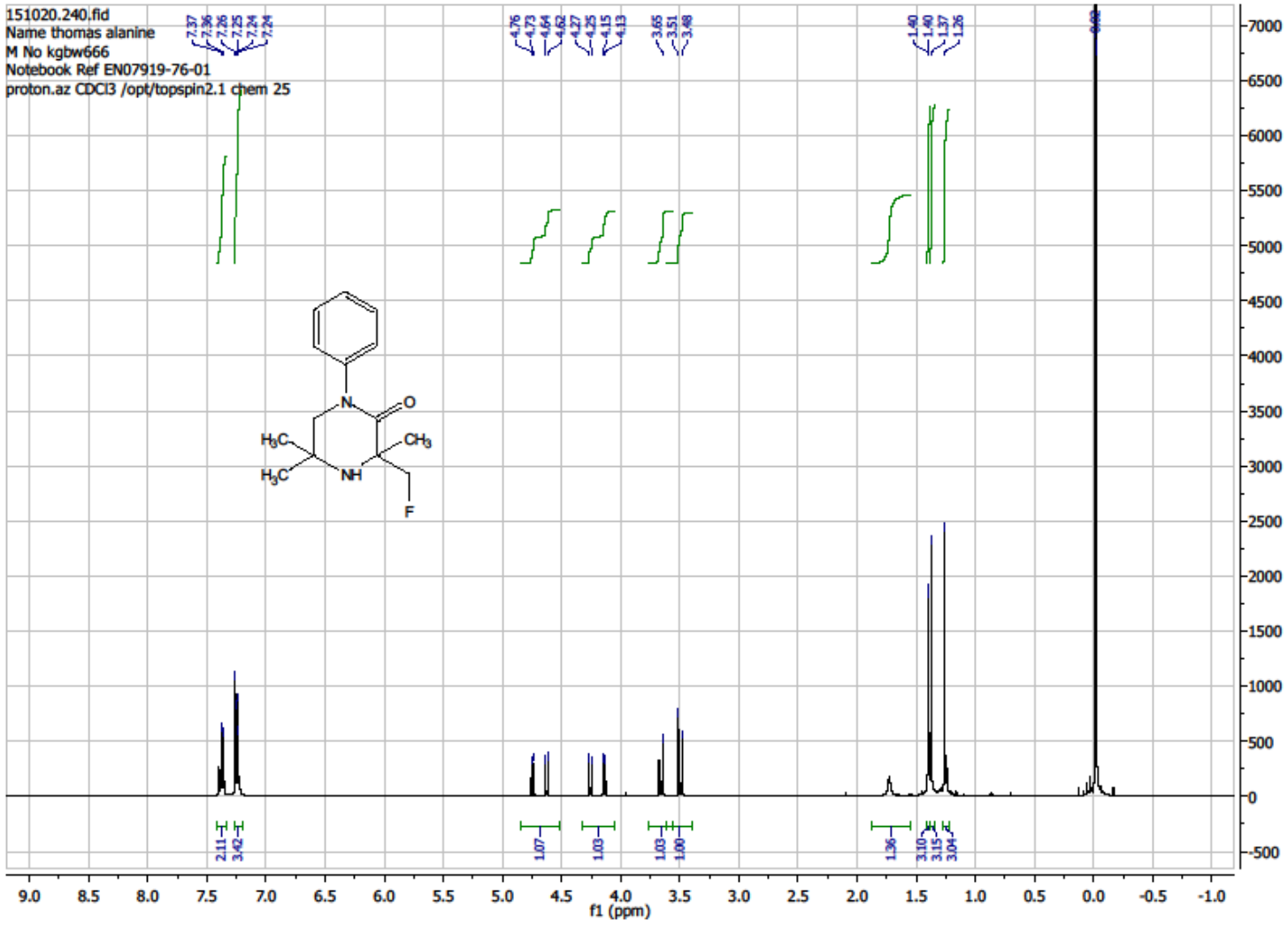
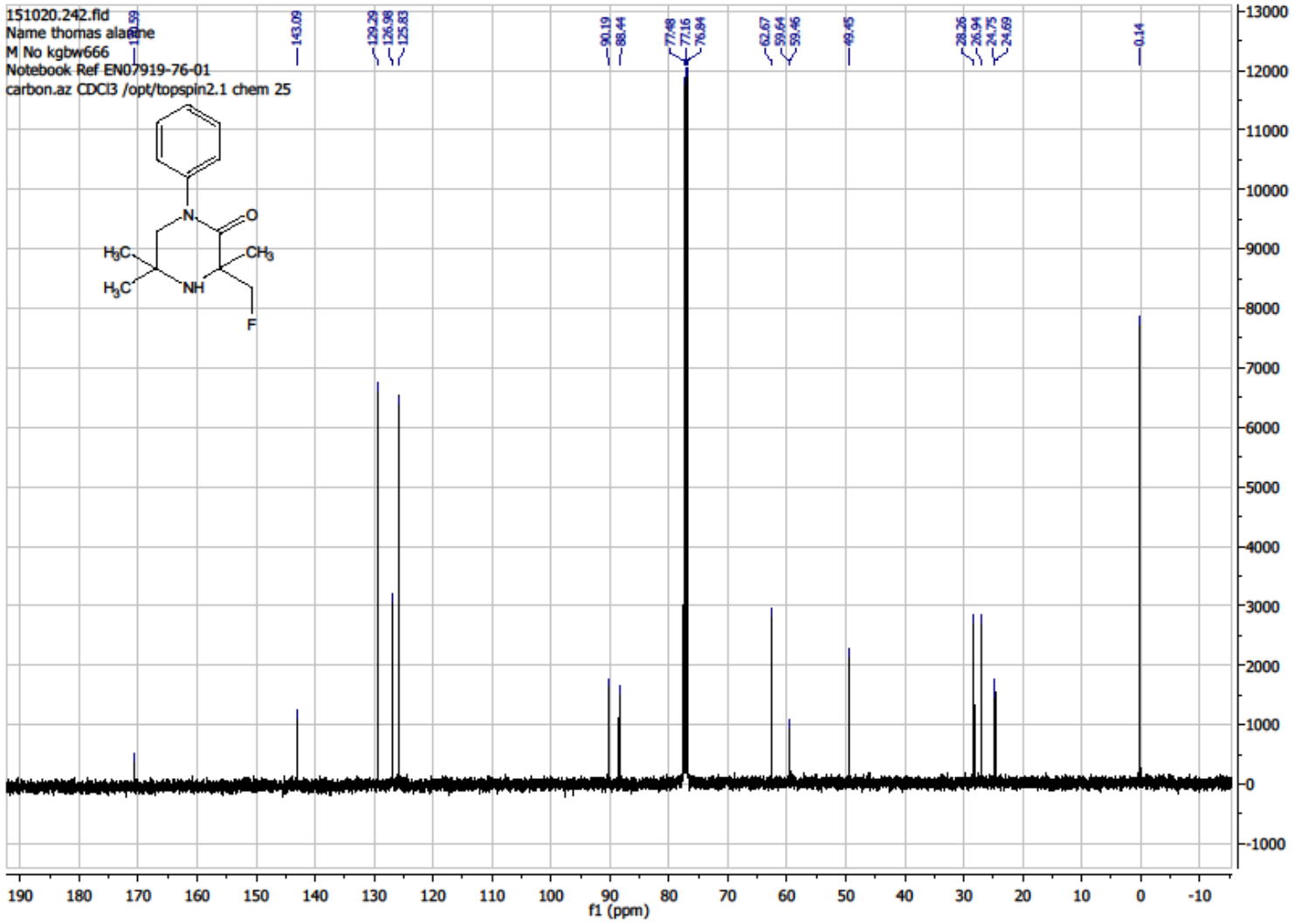


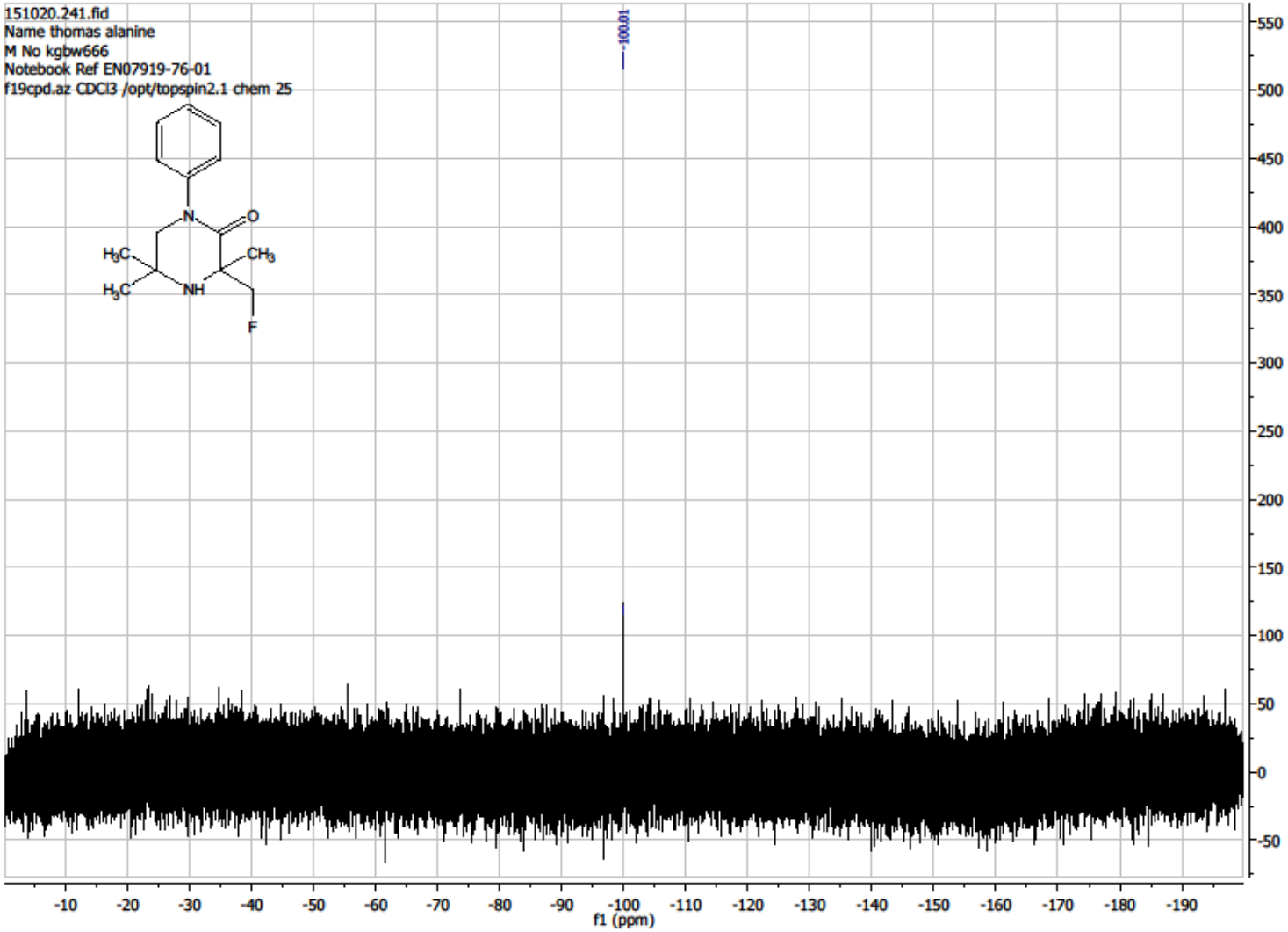
5d ^{1}H NMR 400 MHz



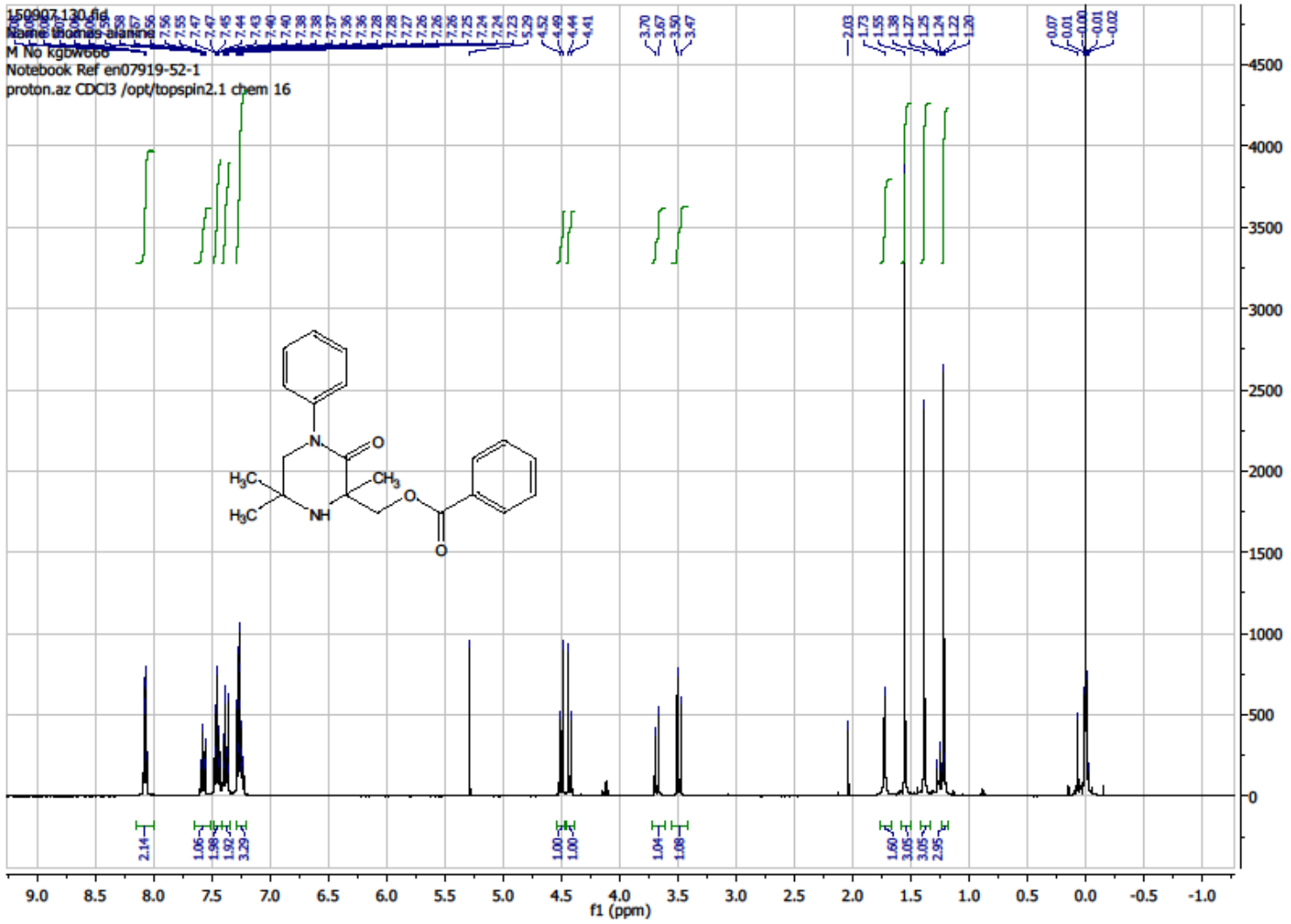
5d ^{13}C NMR 101 MHz



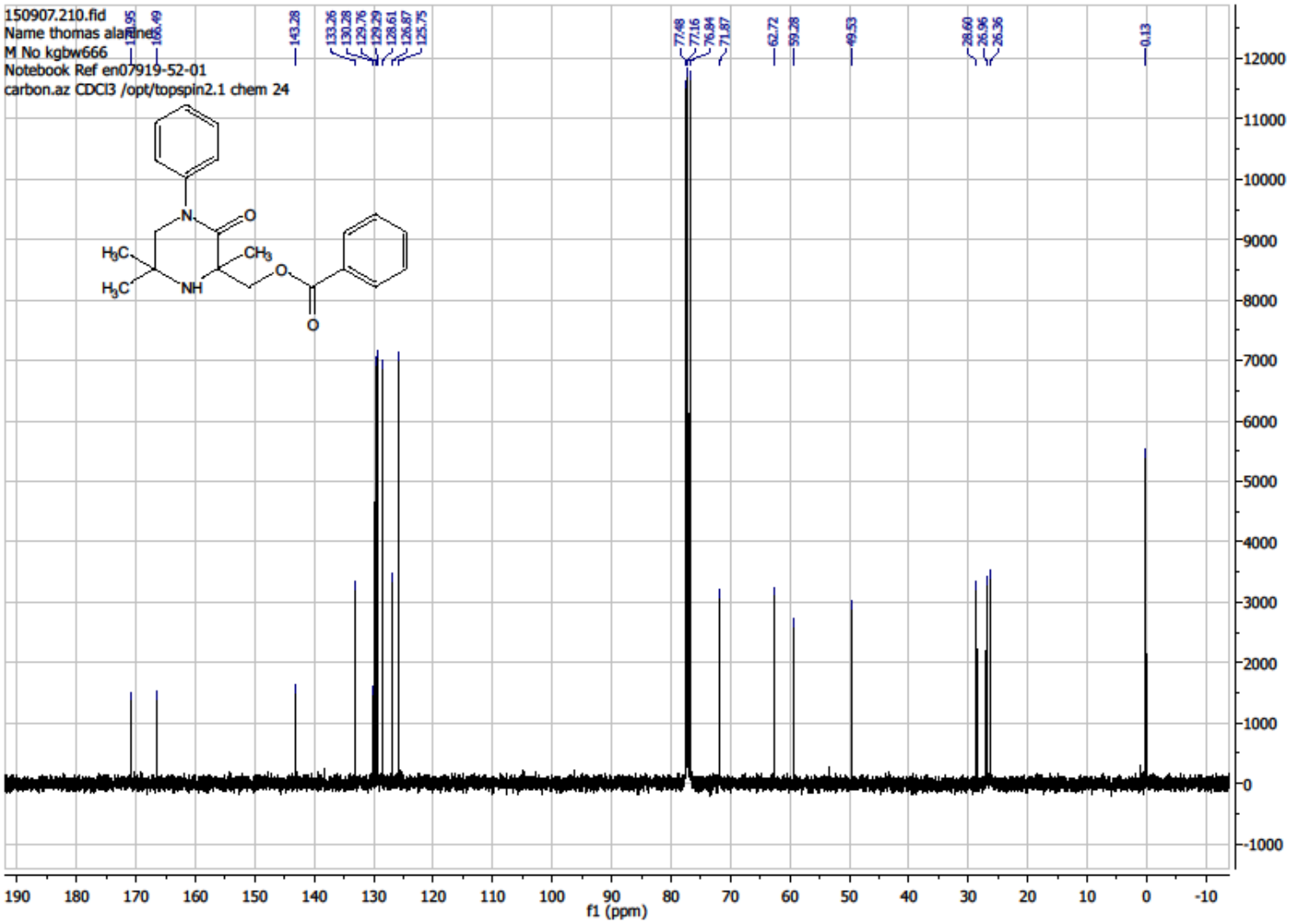
5d ^{19}F NMR 176 MHz



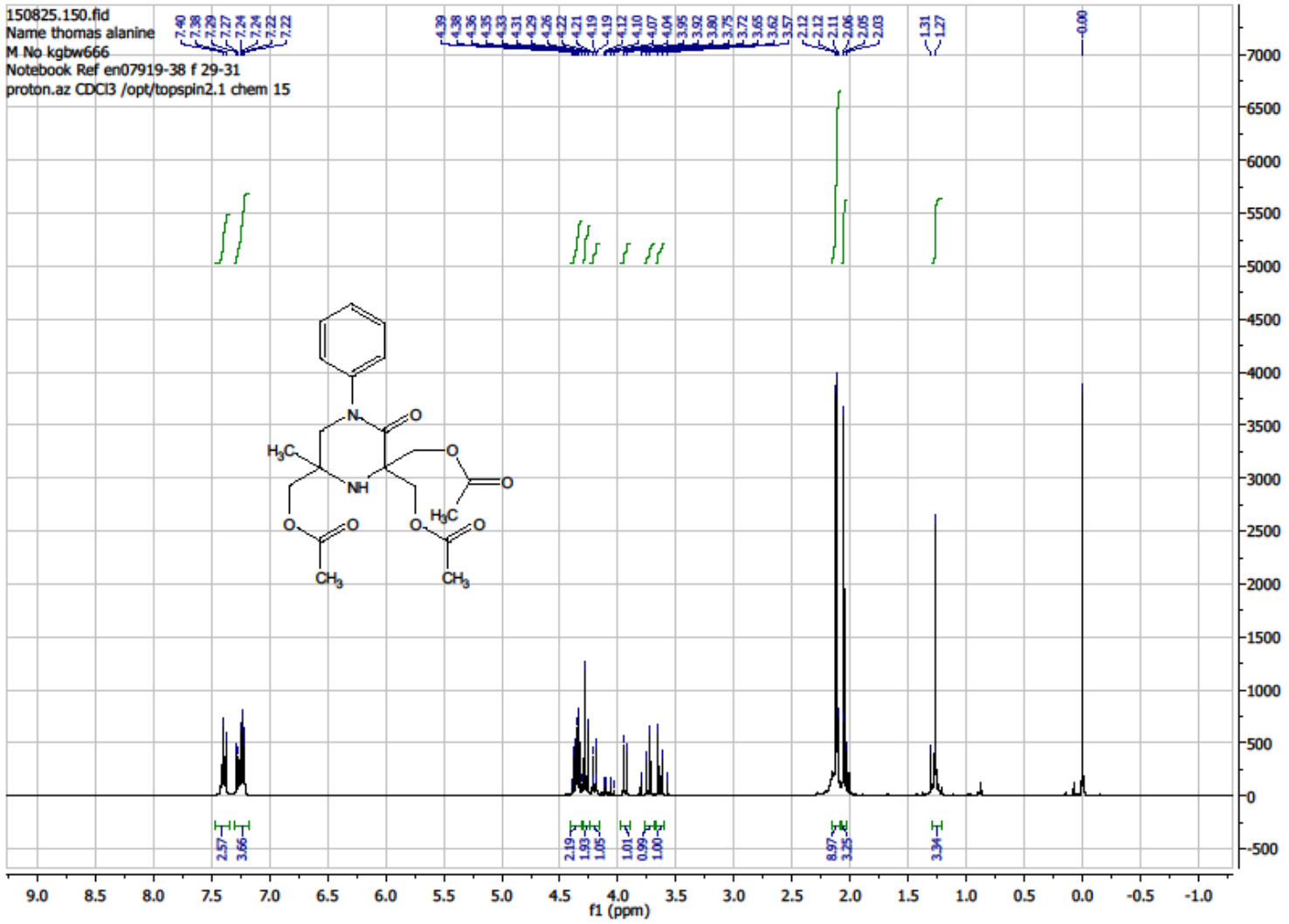
5e ^{1}H NMR 400 MHz



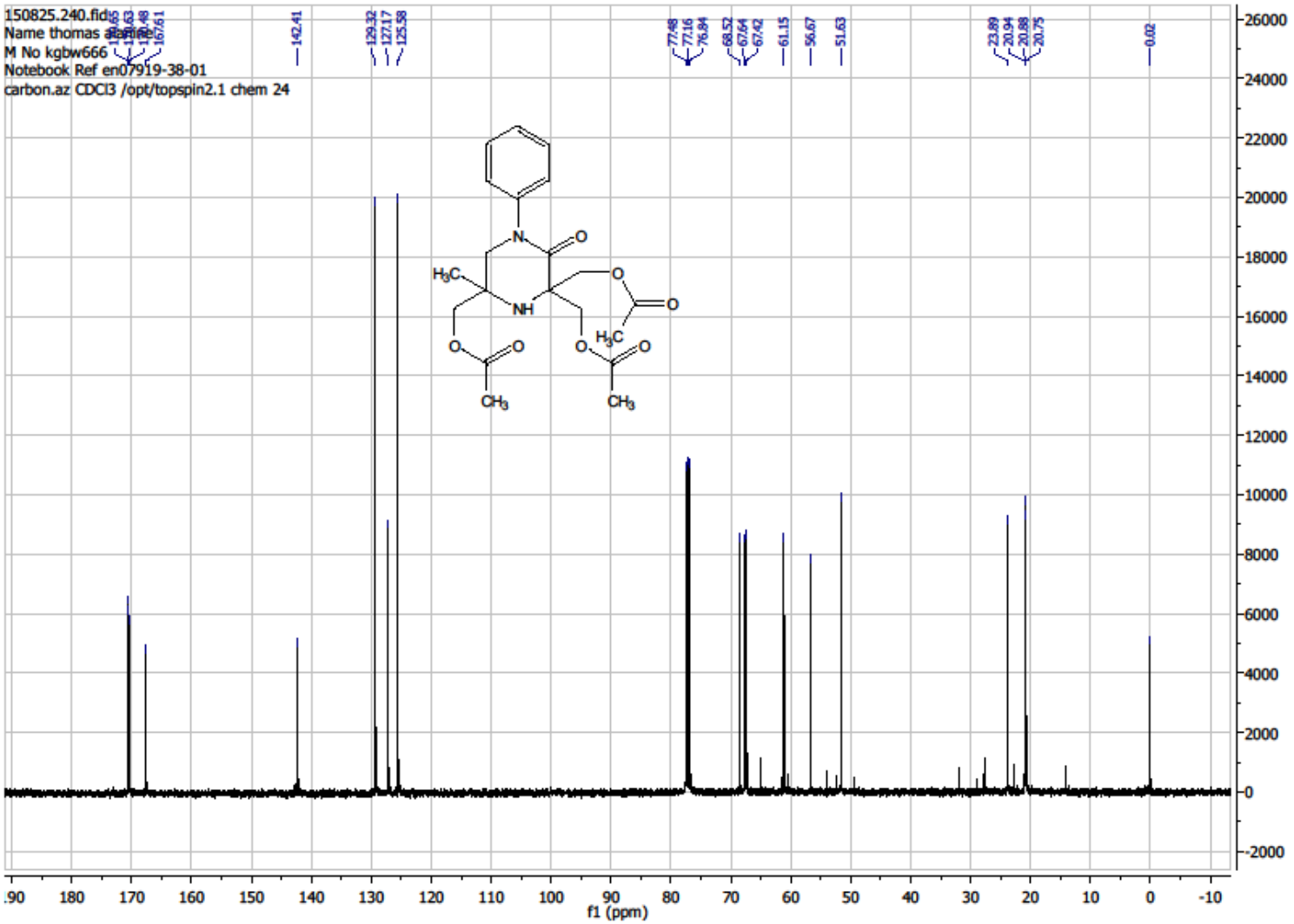
5e ^{13}C NMR 101 MHz



6 ^{1}H NMR 400 MHz



6 ^{13}C NMR 101 MHz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Name thomas
M No kgbw666
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