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General Information

All manipulations were carried out under nitrogen atmosphere inside a static dissipative acrylic isolation glovebox with iris ports provided by Abbvie for installation (TDI #60245DGSDRPIP 1/4'"). DMA (*N*,*N*-dimethylacetamide anhydrous, 99.8%, Catalog #271012, Millipore Sigma) was purchased and used directly. Methanol solution (MeOH/DMSO 1:1 (v/v), Catalog number 650188, Millipore Sigma) was purchased and used directly for UPLC-MS plate solution. $NiCl_2$ (Millipore Sigma), NaI (Millipore Sigma), Zn flake (-325 mesh, Alfa Aesar), di-*O*-octylphthalate, 4,4´-di-*tert*-butyl-2,2´-biphenyl (dtbbpy), pyridine-2,6-*bis*(*N*-cyanocaroxamidine) ($PyBCam^{CN}$), and TFA (trifluoroacetic acid, *ReagentPlus*®, 99%, catalog number T6508, Millipore Sigma) were used as received. In addition, all alkyl bromides and aryl bromides used were either commercially acquired and directly used or were procured through our internal inventory and used without any further purification.

ChemBeads were loaded according to our published procedures using glass beads (Millipore Sigma acid-washed, 212-300 µm, 50-70 U.S. sieve, catalog number G1277), in plastic 20 mL scintillation vials (Fisher part number 03-337-23A). For milling solids down to fine powders, 3 mm yttria stabilized zirconia milling balls (MSE Supplies, product number MSE-MM-YSZ-3) were used. To sieve the milled powders a 3" Sonic Sifter Separator (VWR, part number L3S50 300µm) was used. In addition, for HTE screens we used 1.8 mL glass vials (12 × 32mm, 9-425 thread, VWR, product number 46610-724) with caps from Agilent (12mm cap blue with PTFE red rubber septa, 9-425 thread, product number 5182-0717). For analysis of the screens, filtration was conducted using a 350 µL GHP 96-well filter plate (Pall Laboratories) into an LCMS plate (200 µL volume, V-bottom 96-well plate, Corning, part number 29444-102).

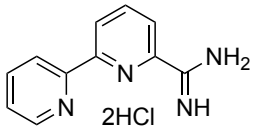
Additionally, zinc-coated ChemBeads were also prepared with a vortex mixer using the following method. To a 20-mL scintillation vial in a nitrogen filled glove box was weighed 7.954 g of glass ChemBeads, followed by 1.280 g of acid-washed Zn powder, then another 11.037 g glass ChemBeads for a total mass of 20.271 g (1.280 g, 0.0196 mmol Zn and 18.991 g glass ChemBeads). The vial was sealed using a plastic screw cap and electrical tape, then removed from the glove box. The vial was then placed on a conical vortex mixer to activate agitation for 15 min. The coating process appeared complete within a few minutes (no loose solid reagent visible), but in order to ensure an even coating of the solid reagent, agitation was continued for 15 min. Comparison of the masses of identical volumes of uncoated ChemBeads and Zn coated ChemBeads consistently indicated an increase in density corresponding to a loading of 4.8% Mn by mass.

Library and HTE analytical crude reaction monitoring and final product purity checks were performed on a Waters Acquity UPLC system equipped with an in-line photodiode array detector (PDA) and an SQD mass spectrometer, running MassLynx 4.1 and Openlynx 4.1 software (Waters Corporation, Milford, MA, USA). The SQD mass spectrometer was operated under positive ESI ionization conditions. The column used was a Waters BEH C8, 1.7 µm (2.1 mm × 30 mm) at a temperature of 55 °C. The following ammonium acetate analytical method was used: a gradient of 10-100% acetonitrile (A) and 10 mM ammonium acetate in water (B) was used, at a flow rate of 1.0 mL/min (0-0.1 min 10% A, 0.1-1.1 min 10-

100% A, 1.1-1.3 min 100% A, 1.3-1.4 min 100-10% A). Isolation of products from reaction mixtures was accomplished by preparative-scale reverse-phase HPLC on 2-coupled C8 5 µm 100 Å columns (30 mm × 75 mm each). When possible, an ammonium acetate purification method was used: a gradient of acetonitrile (A) and 10 mM ammonium acetate in water (B) was used, at a flow rate of 50 mL/min (0-0.5 min 5% A, 0.5-8.5 min linear gradient 05-100% A, 8.7-10.7 min 100% A, 10.7-11 min linear gradient 100-05% A). The following TFA purification method was used for samples which were not compatible with the analytical ammonium acetate method: a gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/min (0-0.5 min 5% A, 0.5-8.5 min linear gradient 05-100% A, 8.7-10.7 min 100% A, 10.7-11 min linear gradient 100-05% A). Samples were injected in 2 mL DMSO:MeOH (1:1). An Agilent 1100 Series Purification system was used, consisting of the following modules: Agilent 1100 Series LC/MSD SL mass spectrometer with API-electrospray source; two Agilent 1100 Series preparative pumps; Agilent 1100 Series isocratic pump; Agilent 1100 Series diode array detector with preparative (0.3mm) flow cell; Agilent active-splitter, IFC-PAL fraction collector / autosampler. The make-up pump for the mass spectrometer used 3:1 methanol:water with 0.1% formic acid at a flow rate of 1 mL/min. Fraction collection was automatically triggered when the extracted ion chromatogram (EIC) for the target mass exceeded the threshold specified in the method. The system was controlled using Agilent Chemstation (Rev B.10.03), Agilent A2Prep, and Leap FractPal software, with custom Chemstation macros for data export.

NMR spectra were acquired on a Bruker Avance 500 MHz spectrometer with a DCH cryoprobe and a 600 MHz spectrometer, both equipped with sample changers. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane and referenced to solvent (e.g. DMSO-d_6). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, etc.), coupling constant, and integration. Coupling constants (*J*) are given in Hertz (Hz). High-resolution mass spectrometry characterization was acquired using a Thermo ScientificTM Q ExactiveTM Hybrid Quadrupole-Orbitrap high-resolution, accurate-mass (HRAM) Mass Spectrometer.

Preparation of BpyCAM•2HCl[1,2] (L13)



Note: although this compound has been reported in the literature as a mono-HCl salt, based upon EA and HRMS analysis, this ligand is a mixture of mono- and bis-HCl salts.

In a round bottomed flask, 6-cyano-2,2´-bipyridine (1 equiv) and NaOMe (2 equiv) were dissolved in MeOH and set to reflux overnight. The reaction was cooled to rt, NH_4Cl (1 equiv) was added, and the reaction was heated back up to reflux and allowed to stir overnight. The reaction was cooled to rt, treated with activated carbon, and filtered. Solvent was evaporated in vacuo and the resulting powder was

recrystallized from isopropanol to give 2,2´-bipyridine-6-carboxamidine bishydrochloride (BpyCAM•2HCl). ^{1}H NMR (500 MHz, DMSO) δ 8.84 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.76 – 8.74 (m, 1H), 8.72 (d, *J* = 7.9 Hz, 1H), 8.43 – 8.40 (m, 1H), 8.30 (t, *J* = 7.9 Hz, 1H), 8.03 (td, *J* = 7.8, 1.8 Hz, 1H), 7.55 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H); ^{1}H NMR (500 MHz, MeOD) δ 8.75 – 8.69 (m, 2H), 8.61 (d, *J* = 8.0 Hz, 1H), 8.29 – 8.19 (m, 2H), 8.01 (td, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 162.2, 156.1, 154.1, 149.9, 144.1, 140.0, 138.0, 125.6, 125.2, 123.8, 122.3; ^{13}C NMR (126 MHz, MeOD) δ 156.5, 154.0, 149.2, 139.3, 137.6, 125.4, 124.9, 122.5, 121.9; HRMS (ESI): *m/*z calcd for $C_{11}H_{12}N_4^{2+}$ $[M+2H]^{2+}$: 100.0531; found: 100.0461; elemental analysis calcd (%) for $C_{11}H_{12}N_4Cl_2$: C 48.73, H 4.46, N 20.66; found: C 47.09, H 4.51, N 22.16.

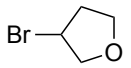
Preparation and Assembly of HTE Screening Plates

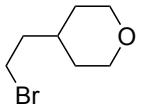
The common reagents used for the catalytic reactions were coated on glass beads with different loadings using the Resodyn LabRAM Acoustic Mixer. The coating process took approximately 20-30 minutes at 70 times the acceleration of gravity (70G = 70% on our mixer) inside a plastic vial for $NiCl_2$(glyme) and ligands; 60% for 30 minutes for Zn, and 50% with 5-minute intervals for NaI. The Resodyn PharmaRAM II Acoustic Mixer was also used to make ChemBeads of reagents: 10 min at 70G for $NiCl_2$ glyme, ligands, and Zn; 10 min at 50G for NaI. To be successful, the ligands and NaI needed to first be milled down to a fine powder for the coating process. Milling can be done with the LabRAM instrument and the process took approximately 20-30 minutes at 40-45G inside a plastic vial. The milled material was sieved to load onto the glass beads. The loadings for each reagent are as follow: **$NiCl_2$(glyme)** (3% loading w/w), **NaI** (3% loading w/w), **Zn flake** (10% loading w/w), **Ligand 1** ($PyBCam^{CN}$, 3% loading w/w), **Ligand 10** (dtbbpy, 3% loading w/w), **Ligand 13** (*[2,2'-bipyridine]-6-carboximidamide hydrochloride*, BpyCam•HCl, 3% loading w/w).

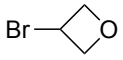
All screening plates were prepared using the Chemspeed SWAVE that was modified internally to dispense ChemBeads to 1.8 mL glass vials. The program used to do the dispensing is also an internally modified version of the Chemspeed software.

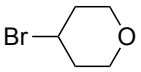
Using the Chemspeed SWAVE under nitrogen atmosphere, a 48-well metal block with 37 1.8 mL vials was charged with $NiCl_2$(glyme) ChemBeads, **Ligand 1** ChemBeads, Zn ChemBeads, and NaI ChemBeads. Two more sets were made using **Ligand 10** ChemBeads and **Ligand 13** ChemBeads in place of **Ligand 1** ChemBeads, keeping the other variables the same. In total 27 sets were made. The plates were stored in a glovebox under nitrogen atmosphere prior to use.

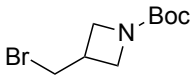
Alkyl halide monomers

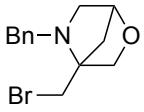
A1 

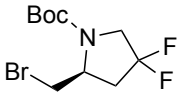
A2 

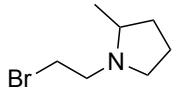
A3 

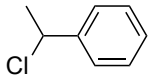
A4 

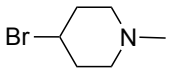
A5 

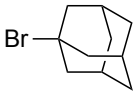
A6 

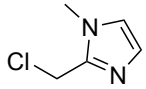
A7 

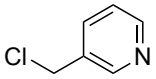
A8 

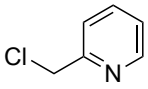
A9 

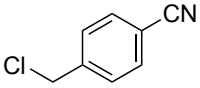
A10 

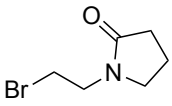
A11 

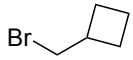
A12 

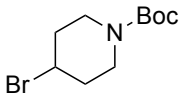
A13 

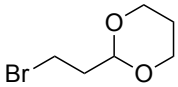
A14 

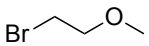
A15 

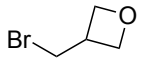
A16 

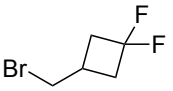
A17 

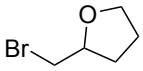
A18 

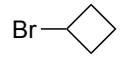
A19 

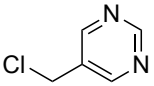
A20 

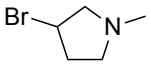
A21 

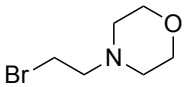
A22 

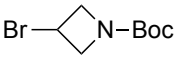
A23 

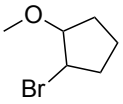
A24 

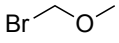
A25 

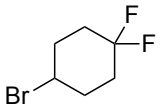
A26 

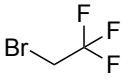
A27 

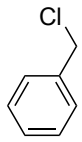
A28 

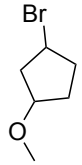
A29 

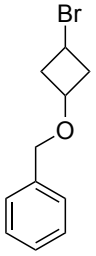
A30 

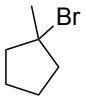
A31 

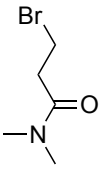
A32 

A33 

A34 

A35 

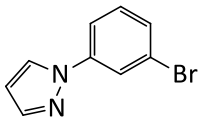
A36 

A37 

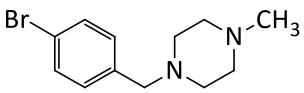
Alkyl Bromide Monomer Stock Solutions

There were 37 alkyl bromide monomers used to screen each of the 6 aryl bromides in a high throughput experimentation manner. For each alkyl bromide, 1.0 mmol was weighed out and placed in a 4 mL vial with septa cap. The headspace was purged inside the glovebox before anhydrous DMA (1 mL) was added and the mixture stirred until complete dissolution.

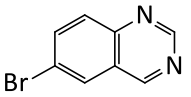
Aryl Bromide Stock Solutions



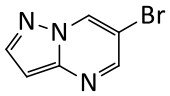
Core 1



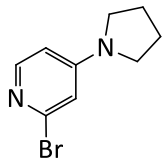
Core 2



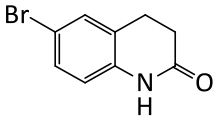
Core 3



Core 4



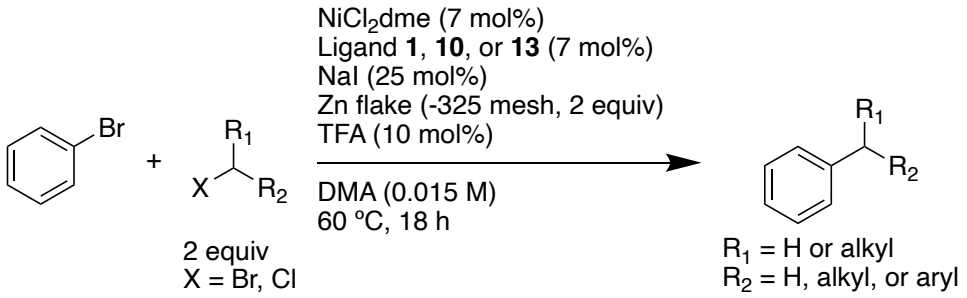
Core 5



Core 6

Six aryl bromides were used for the high throughput experimentation. In each case, aryl bromide (0.6 mmol) was placed in a 4 mL vial and the vial was moved into the inert-atmosphere glovebox. The aryl bromides were diluted with anhydrous DMA (3.33 mL).

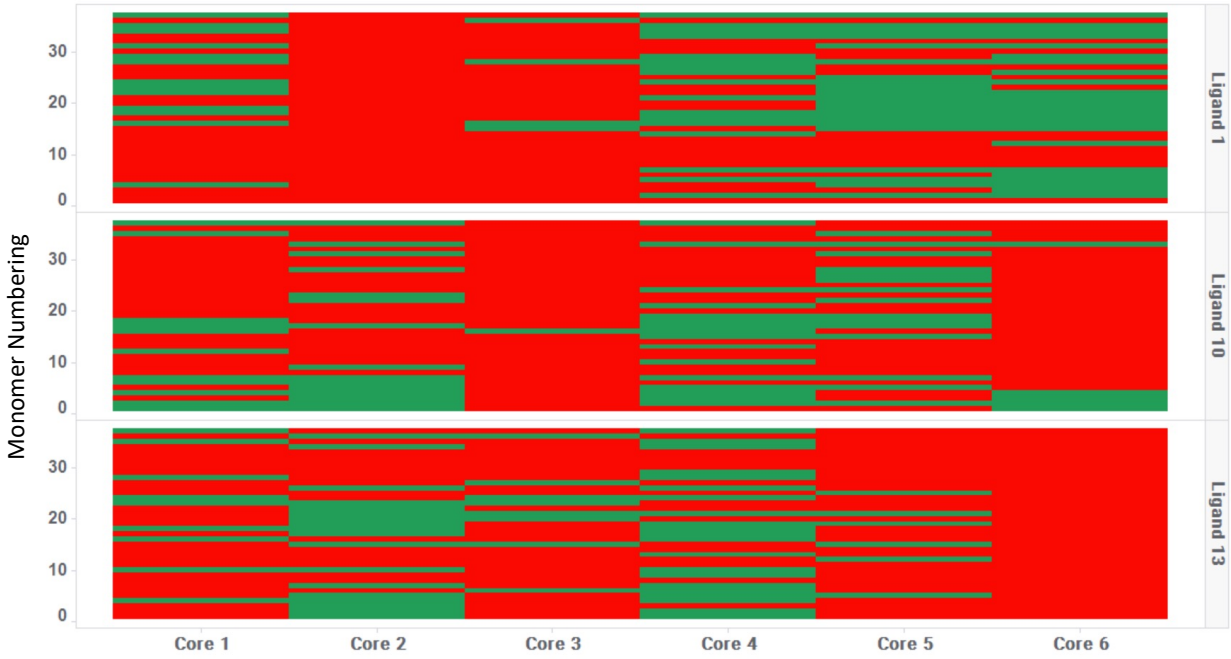
HTE Screening General Procedure



Pre-plated set: 37 × 1.8 mL glass vials were charged with $NiCl_2$(glyme), NaI, Zn, and ligand (**Ligand 1**, **Ligand 10**, or **Ligand 13**) on ChemBeads using a Chemspeed SWAVE system.

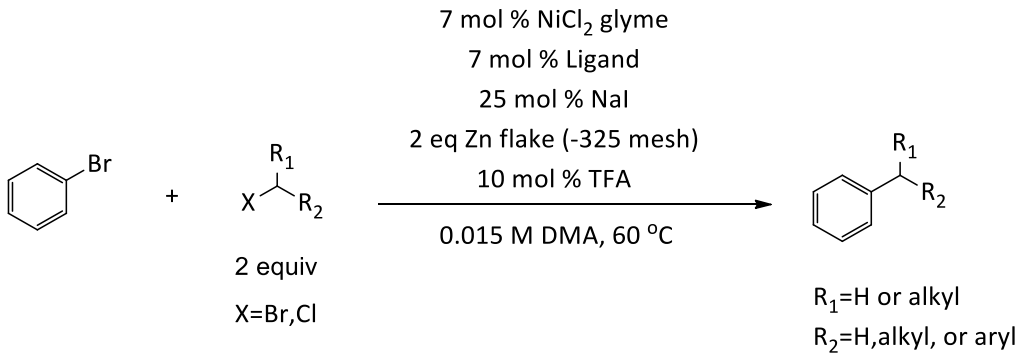
Using the purge box, to the screening plate vials, 10 µL of the pre-weighed 4 mL vial of the alkyl bromide stock solution in DMA (anhydrous, 0.02 mmol, 2 equiv) was added to their corresponding vial in sequence followed by 30 µL of the aryl bromide core stock solution (0.01 mmol, 1 equiv, 0.18 M). To each vial was added 10 µL of a 0.1 M solution of trifluoroacetic acid (5.4 µmol, 10 mol%) in DMA. The vials were capped and placed on the heater/shaker (Torrey Pines Echotherm) at 60°C on setting 7 to heat/shake overnight. Upon completion, the vials on the metal block were placed on a Tecan EVO instrument to assemble the UPLC analysis plate. To each vial a calculated amount of internal standard, di-*N*-octyl phthalate (0.003 mmol, 0.5 equiv), in a 0.01 M solution in methanol was added. This was diluted with DMSO/MeOH (1:1 v/v) to achieve 500 µL as a total volume. To a 350µL GHP 96-well filter plate with a 200 µL volume V-bottom 96-well plate, 75 µL of the solution is added with an additional 75 µL of DMSO/MeOH (1:1 v/v). The filter plate and 96-well regular plate were centrifuged together in a speed vac for 5 min. The resulting sample plate was placed in the UPLC for analysis using a either the AA method or the TFA method depending on the substrate.

Heat-Map of HTE Results by Ligand and Core



Red denotes no product ion detected, green denotes product ion detected.

Scale-Up General Procedure 1 for C(sp^2)-C(sp^3) Coupling on 0.1 mmol Scale



A 4 mL scintillation vial was charged with a stir bar, $NiCl_2$•glyme (0.007 mmol, 7 mol%), NaI (0.25 mmol, 25 mol%), Ligand (**1**, **10**, or **13**) (0.007 mmol, 7 mol%), and Zn flake (0.2 mmol, 2 equiv). The vial was moved into a nitrogen atmosphere dry box and 100 µL of a 2 M stock solution of alkyl halide in DMA (0.2 mmol, 2 equiv). To this, 300 µL of a 0.333 M DMA stock solution of the aryl bromide core (0.1 mmol, 1 equiv) was added followed by the addition of trifluoroacetic acid (0.01 mmol, 10 mol%). The vial was capped using a septa cap (National Scientific, catalog number C4015-75A) and placed to heat at 60 °C for 18 h using a 4 mL deep well plate on the heater/shaker (Torrey Pines Echotherm) at setting 7. Upon completion the reaction was passed through a syringe filter using a 3 mL syringe with a Whatman 20-micron PTFE filter disc and washed with 1 mL of DMA, then dried under N_2 line. The crude mixture was dissolved in 1.8 mL of DMSO and purified using reverse phase HPLC to afford the final product.

It is important to note that the ChemBeads version of the reagents used were also employed in the scale ups. There was no difference in reactivity between ChemBeads reagents versus non ChemBeads reagents. The ChemBeads loadings for the scale up reactions are the same as the screens with the only difference being in NaI where the loading was 20% w/w loading rather than 3% w/w loading.

Note that 27 of the products were isolated and fully characterized (vide infra).

Products isolated in >95% purity

Alkyl #	Core #	Ligand	Product	MW	Isolated Yield (%)	Purity	RT (min) EIC	LCMS (M+H)
1	Core 1	Ligand 10	**1**	214.2631	11	>95%	0.6263	215.1
2	Core 1	Ligand 10	**2**	256.3428	27	>95%	0.7379	257.2
4	Core 1	Ligand 1	**4**	228.2896	4	>95%	0.47	229.1
4	Core 1	Ligand 13	**4**	228.2896	12	>95%	0.6927	229.1
7	Core 1	Ligand 10	**7**	363.4016	13	>95%	0.8276	364.2
10	Core 1	Ligand 13	**10**	241.3315	3	>95%	0.5034	242.2
16	Core 1	Ligand 1	**16**	255.315	2	>95%	0.62	256.2
16	Core 1	Ligand 10	**16**	255.315	15	>95%	0.5877	256.1
16	Core 1	Ligand 13	**16**	255.315	3	>95%	0.6113	256.2
17	Core 1	Ligand 10	**17**	212.2902	25	>95%	0.8238	213.1
18	Core 1	Ligand 1	**18**	327.4207	2	>95%	0.88	328.4
18	Core 1	Ligand 10	**18**	327.4207	12	>95%	0.8327	328.3
19	Core 1	Ligand 1	**19**	258.3156	8	>95%	0.72	259.2
19	Core 1	Ligand 13	**19**	258.3156	9	>95%	0.71	259.2
23	Core 1	Ligand 1	**23**	228.2896	9	>95%	0.715	229.2
23	Core 1	Ligand 13	**23**	228.2896	27	>95%	0.7172	229.2
24	Core 1	Ligand 1	**24**	198.2637	15	>95%	0.85	199.1
24	Core 1	Ligand 13	**24**	198.2637	28	>95%	0.8027	199.2
31	Core 1	Ligand 1	**31**	262.2978	8	>95%	0.8483	262.9
35	Core 1	Ligand 13	**35**	304.3856	6	>95%	0.8906	305.2
37	Core 1	Ligand 13	**37**	243.3043	3	>95%	0.611	244.2
1	Core 2	Ligand 10	**38**	260.3746	14	>95%	0.4077	261.3
2	Core 2	Ligand 10	**39**	302.4543	5	>95%	0.4894	303.3
3	Core 2	Ligand 13	**40**	246.348	17	>95%	0.3723	247.3
4	Core 2	Ligand 13	**41**	274.4011	26	>95%	0.5322	275.3
5	Core 2	Ligand 10	**42**	359.5056	10	>95%	0.5533	360.3
7	Core 2	Ligand 10	**44**	409.5131	6	>95%	0.6008	410.3
16	Core 2	Ligand 10	**53**	301.4265	6	>95%	0.4898	302.3
17	Core 2	Ligand 10	**54**	258.4017	14	>95%	0.4549	259.2
17	Core 2	Ligand 13	**54**	258.4017	11	>95%	0.5606	259.3
18	Core 2	Ligand 13	**55**	373.5322	6	>95%	0.5646	374.4
20	Core 2	Ligand 13	**57**	248.3639	26	>95%	0.4063	248.5
21	Core 2	Ligand 13	**58**	260.3746	14	>95%	0.401	261.3
22	Core 2	Ligand 10	**59**	294.3827	13	>95%	0.5236	295.2
22	Core 2	Ligand 13	**59**	294.3827	18	>95%	0.5006	295
23	Core 2	Ligand 13	**60**	274.4011	19	>95%	0.5692	247.3
24	Core 2	Ligand 10	**61**	244.3752	25	>95%	0.6748	244.9
28	Core 2	Ligand 10	**65**	345.479	13	>95%	0.5236	346.2
31	Core 2	Ligand 10	**68**	308.4093	8	>95%	0.5236	309.2
33	Core 2	Ligand 1	**70**	280.4073	2	>95%	0.472	281.3

Alkyl #	Core #	Ligand	Product	MW	Isolated Yield (%)	Purity	RT (min) EIC	LCMS (M+H)
15	Core 3	Ligand 1	**89**	245.2786	8	>95%	0.66	246.3
16	Core 3	Ligand 1	**90**	241.2884	9	>95%	0.413	242.1
16	Core 3	Ligand 10	**90**	241.2884	23	>95%	0.4302	242.1
20	Core 3	Ligand 13	**94**	188.2258	9	>95%	0.5185	189.1
21	Core 3	Ligand 13	**95**	200.2365	9	>95%	0.5013	201.2
24	Core 3	Ligand 13	**98**	184.2371	28	>95%	0.6827	185.2
1	Core 4	Ligand 13	**112**	189.2138	23	>95%	0.474	190.1
2	Core 4	Ligand 10	**113**	231.2936	10	>95%	0.5687	232.2
2	Core 4	Ligand 13	**113**	231.2936	34	>95%	0.5686	232.1
4	Core 4	Ligand 13	**115**	203.2404	5	>95%	0.487	204.1
5	Core 4	Ligand 1	**116**	288.3449	1	>95%	0.6592	289.2
5	Core 4	Ligand 10	**116**	288.3449	7	>95%	0.6591	289.1
5	Core 4	Ligand 13	**116**	288.3449	12	>95%	0.4652	289.2
7	Core 4	Ligand 10	**118**	338.3524	7	>95%	0.6974	319.1
7	Core 4	Ligand 13	**118**	338.3524	25	>95%	0.6978	339.2
9	Core 4	Ligand 13	**120**	223.2731	17	>95%	0.6849	224.2
16	Core 4	Ligand 1	**127**	230.2658	9	>95%	0.4436	231.1
17	Core 4	Ligand 1	**128**	187.241	20	>95%	0.4426	188.1
17	Core 4	Ligand 13	**128**	187.241	10	>95%	0.6503	188.1
18	Core 4	Ligand 1	**129**	302.3715	6	>95%	0.7021	303.3
18	Core 4	Ligand 10	**129**	302.3715	15	>95%	0.7022	303.1
18	Core 4	Ligand 13	**129**	302.3715	5	>95%	0.7024	303.1
19	Core 4	Ligand 10	**130**	233.2664	32	>95%	0.5127	234.2
19	Core 4	Ligand 13	**130**	233.2664	13	>95%	0.5128	234.2
21	Core 4	Ligand 1	**132**	189.2138	5	>95%	0.4264	190.1
21	Core 4	Ligand 13	**132**	189.2138	4	>95%	0.1289	190.1
24	Core 4	Ligand 10	**135**	173.2144	17	>95%	0.5857	174.1
28	Core 4	Ligand 1	**139**	274.3183	3	>95%	0.6285	275.4
29	Core 4	Ligand 1	**140**	217.267	15	>95%	0.5902	218.1
33	Core 4	Ligand 10	**144**	209.2465	9	>95%	0.6331	210.1
34	Core 4	Ligand 1	**145**	217.267	7	>95%	0.5601	218.2
34	Core 4	Ligand 13	**145**	217.267	5	>95%	0.5772	218.2
35	Core 4	Ligand 1	**146**	279.3364	8	>95%	0.698	280.2
37	Core 4	Ligand 1	**148**	218.2551	8	>95%	0.448	219.2
37	Core 4	Ligand 10	**148**	218.2551	1	>95%	0.4512	219.2
37	Core 4	Ligand 13	**148**	218.2551	30	>95%	0.448	219.1
4	Core 5	Ligand 1	**152**	232.3214	12	>95%	0.472	233.2
5	Core 5	Ligand 1	**153**	317.4259	4	>95%	0.631	318.2
5	Core 5	Ligand 10	**153**	317.4259	49	>95%	0.5923	318.3
5	Core 5	Ligand 13	**153**	317.4259	11	>95%	0.6352	318.3

Alkyl #	Core #	Ligand	Product	MW	Isolated Yield (%)	Purity	RT (min) EIC	LCMS (M+H)
7	Core 5	Ligand 1	**155**	367.4334	12	>95%	0.6995	368.3
7	Core 5	Ligand 10	**155**	367.4334	22	>95%	0.648	368.3
15	Core 5	Ligand 10	**163**	263.337	11	>95%	0.5451	264.2
16	Core 5	Ligand 1	**164**	259.3467	9	>95%	0.4078	260.2
17	Core 5	Ligand 10	**165**	216.322	45	>95%	0.588	217.2
18	Core 5	Ligand 1	**166**	331.4525	9	>95%	0.6694	332.3
19	Core 5	Ligand 1	**167**	262.3474	36	>95%	0.515	263.2
19	Core 5	Ligand 10	**167**	262.3474	44	>95%	0.502	263.2
19	Core 5	Ligand 13	**167**	262.3474	18	>95%	0.5107	263.1
22	Core 5	Ligand 10	**170**	252.3029	29	>95%	0.5535	253.2
23	Core 5	Ligand 1	**171**	232.3214	23	>95%	0.4979	233.2
24	Core 5	Ligand 1	**172**	202.2954	24	>95%	0.5493	202.9
24	Core 5	Ligand 10	**172**	202.2954	12	>95%	0.5322	203.2
28	Core 5	Ligand 1	**176**	303.3993	12	>95%	0.6525	304.2
28	Core 5	Ligand 10	**176**	303.3993	29	>95%		
31	Core 5	Ligand 10	**179**	266.3295	6	>95%	0.5709	267.2
33	Core 5	Ligand 1	**181**	238.3275	4	>95%	0.5408	247.2
33	Core 5	Ligand 10	**181**	238.3275	25	>95%	0.575	239.1
35	Core 5	Ligand 1	**183**	308.4174	22	>95%	0.6653	309.6
35	Core 5	Ligand 10	**183**	308.4174	18	>95%	0.6266	309.2
29	Core 6	Ligand 1	**214**	245.3169	13	>95%	0.6278	246.1
31	Core 6	Ligand 1	**216**	265.2984	8	>95%	0.6875	266.1
33	Core 6	Ligand 1	**218**	237.2964	2	>95%	0.692	238.2
35	Core 6	Ligand 1	**220**	307.3862	27	>95%	0.7351	308.2
37	Core 6	Ligand 1	**222**	246.3049	2	>95%	0.486	247.2

Products isolated in <95% purity

Alkyl #	Core #	Ligand	Product	MW	Isolated Yield-Scale up (after cleanup)	Estimated Purity
18	Core 1	Ligand 13	**18**	327.4207	5	~50%
34	Core 1	Ligand 1	**34**	242.3162	5.6	~25%
35	Core 1	Ligand 1	**35**	304.3856	25	~50%
1	Core 2	Ligand 13	**38**	260.3746	35	~80%
4	Core 2	Ligand 10	**41**	274.4011	10	~78%
9	Core 2	Ligand 10	**46**	294.4338	9	~85%
19	Core 2	Ligand 13	**56**	304.4271	29	85%
23	Core 2	Ligand 10	**60**	274.4011	49	~85%
33	Core 2	Ligand 10	**70**	280.4073	12	~47%
36	Core 2	Ligand 13	**73**	272.4283	12	~50%
37	Core 2	Ligand 10	**74**	289.4158	11	~70%
23	Core 3	Ligand 13	**97**	214.2631	41.6	~25%
36	Core 3	Ligand 1	**110**	212.2902	20	~50%
4	Core 4	Ligand 10	**115**	203.2404	8	~70%
15	Core 4	Ligand 10	**126**	234.256	8.3	~70%
16	Core 4	Ligand 10	**127**	230.2658	11.2	~70%
16	Core 4	Ligand 13	**127**	230.2658	8.8	~75%
17	Core 4	Ligand 10	**128**	187.241	13.6	75%
21	Core 4	Ligand 10	**132**	189.2138	10.4	~50%
28	Core 4	Ligand 13	**139**	274.3183	13.6	60%/40%
29	Core 4	Ligand 13	**140**	217.267	12.8	~50%
17	Core 5	Ligand 1	**165**	216.322	22.4	~70%
18	Core 5	Ligand 10	**166**	331.4525	6.2	~60%
20	Core 5	Ligand 1	**168**	206.2841	9.8	~80%
21	Core 5	Ligand 1	**169**	218.2948	7.2	~80%
21	Core 5	Ligand 13	**169**	218.2948	20	~40%
25	Core 5	Ligand 13	**173**	240.3036	5.5	~40%
31	Core 5	Ligand 1	**179**	266.3295	1.6	~50%
37	Core 5	Ligand 1	**185**	247.336	6.2	~70%
34	Core 6	Ligand 1	**219**	245.3169	34	~40%

Products that could not be isolated

Alkyl #	Core #	Ligand	Product	MW
5	Core 1	Ligand 1	5	313.3941
17	Core 1	Ligand 1	17	212.2902
20	Core 1	Ligand 1	20	202.2524
26	Core 1	Ligand 1	26	227.3049
26	Core 1	Ligand 10	26	227.3049
28	Core 1	Ligand 10	28	299.3675
2	Core 1	Ligand 13	2	256.3428
5	Core 1	Ligand 13	5	313.3941
7	Core 1	Ligand 13	7	363.4016
12	Core 1	Ligand 13	12	238.2878
17	Core 1	Ligand 13	17	212.2902
20	Core 1	Ligand 13	20	202.2524
22	Core 1	Ligand 13	22	248.2712
26	Core 1	Ligand 13	26	227.3049
33	Core 1	Ligand 13	33	234.2958
7	Core 2	Ligand 1	44	409.5131
11	Core 2	Ligand 13	48	324.5029
13	Core 2	Ligand 13	50	281.3953
14	Core 2	Ligand 13	51	281.3953
16	Core 2	Ligand 13	53	301.4265
24	Core 2	Ligand 13	61	244.3752
31	Core 2	Ligand 13	68	308.4093
35	Core 2	Ligand 13	72	350.4971
37	Core 2	Ligand 13	74	289.4158
12	Core 5	Ligand 1	160	242.3195
33	Core 5	Ligand 13	181	238.3275
23	Core 6	Ligand 1	208	231.2903
5	Core 6	Ligand 10	190	316.3948
16	Core 6	Ligand 10	201	258.3156

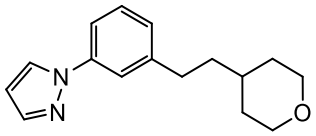
Scale-Up General Procedure 2 for C(sp2)-C(sp3) Coupling at 0.5 mmol Scale

In a N_2 filled glove box, a catalyst stock solution was made by charging an oven dried 1-dram vial with $NiCl_2$•glyme (38.5 mg, 0.175 mmol), **Ligand 13** (41.0 mg, 0.151 mmol), a PTFE-coated stir bar, and DMA (4 mL). The vial was stirred at rt for 15 min.

Into a separate 1-dram vial was added the aryl bromide core and the alkyl halide (0.50 mmol each), NaI (*if necessary*, 18.7 mg, 0.125 mmol, 25 mol %), and Zn flake (65.4 mg, 1.0 mmol, 2 equiv). To this was added 800 µL (0.030 mmol, 0.06 equiv, 6 mol%) of the catalyst stock solution. The vial was capped using a PTFE septa cap and stir at 40 °C for 18 h. After the 18 h, the reaction mixture was diluted with $NaOH_{aq}$ (2 M, 20 mL) and extracted into DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography.

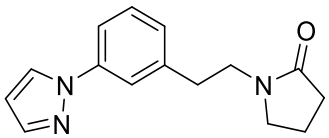
Characterization Data

1-(3-(2-(tetrahydro-2H-pyran-4-yl)ethyl)phenyl)-1H-pyrazole (2)



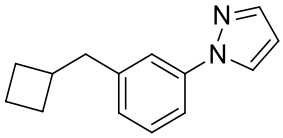
General procedure 1 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 22.31 mg, 0.10 mmol) as the aryl halide, 4-(2-bromoethyl)tetrahydro-2H-pyran (**A2**, 38.62 mg, 0.20 mmol) as the alkyl reagent, and **Ligand 10** (1.88 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**2**) (6.9 mg, 27% yield, >90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 8.33 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.64 (t, J = 2.0 Hz, 1H), 7.58 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.13 (dt, J = 7.8, 1.3 Hz, 1H), 6.48 (dd, J = 2.5, 1.7 Hz, 1H), 3.82 (ddd, J = 11.1, 4.3, 2.1 Hz, 2H), 3.27 (td, J = 11.6, 2.2 Hz, 2H), 2.71 – 2.65 (m, 2H), 1.67 – 1.61 (m, 2H), 1.61 – 1.56 (m, 2H), 1.56 – 1.48 (m, 1H), 1.28 – 1.17 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 144.5, 141.2, 140.2, 129.8, 128.1, 126.6, 118.7, 116.3, 108.2, 67.5, 38.6, 34.5, 33.1, 32.4. HRMS (ESI+): *m/z* calcd for $C_{16}H_{21}N_2O^+$: 257.1648 $[M+H]^+$; found: 257.1652.

1-(3-(1H-pyrazol-1-yl)phenethyl)pyrrolidin-2-one (16)



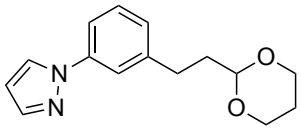
General procedure 1 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 55.8 mg, 0.25 mmol) as the aryl halide, 1-(2-bromoethyl)pyrrolidin-2-one (**A16**, 96.0 mg, 0.5 mmol) as the alkyl reagent, and **Ligand 13** (4.10 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**16**) (11 mg, 17 % yield, >90% pure by ^{1}H NMR) ^{1}H NMR (400 MHz, DMSO) δ 8.34 (d, *J* = 2.5 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.63 (ddd, *J* = 8.1, 2.3, 1.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.15 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.49 (dd, *J* = 2.5, 1.7 Hz, 1H), 3.47 (dd, *J* = 7.8, 6.7 Hz, 2H), 3.34 – 3.26 (m, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.16 (t, *J* = 8.1 Hz, 2H), 1.94 – 1.82 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.2, 141.2, 141.3, 140.2, 129.9, 128.1, 126.9, 119.0, 116.7, 108.2, 46.9, 43.4, 33.3, 30.9, 18.0. HRMS (ESI+): *m/z* calcd for $C_{15}H_{18}N_3O^+$: 257.1444 $[M+H]^+$; found: 256.1451.

1-(3-(cyclobutylmethyl)phenyl)-1H-pyrazole (17)



General procedure 1 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 55.8 mg, 0.25 mmol) as the aryl halide, 1-(2-bromoethyl)pyrrolidin-2-one (**A17**, 74.5 mg, 0.50 mmol) as the alkyl reagent, and **Ligand 10** (4.72 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound (**17**) (5.8 mg, 11 % yield, 97% pure by ^{1}H NMR). ^{1}H NMR (600 MHz, DMSO) δ 8.47 (dd, *J* = 2.5, 0.6 Hz, 1H), 7.72 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.37 (td, *J* = 7.7, 0.7 Hz, 1H), 7.14 – 7.07 (m, 1H), 6.52 (dd, *J* = 2.5, 1.7 Hz, 1H), 2.74 (d, *J* = 7.6 Hz, 2H), 2.59 (hept, *J* = 7.8 Hz, 1H), 2.03 – 1.93 (m, 2H), 1.86 – 1.78 (m, 2H), 1.76 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 142.8, 141.2, 140.2, 129.7, 128.1, 126.7, 118.8, 116.3, 108.4, 108.4, 108.1, 42.5, 37.1, 36.9, 36.8, 36.7, 27.9, 18.4, 18.3, 18.1. HRMS (ESI+): *m/z* calcd for $C_{14}H_{17}N_2^+$: 213.17 $[M+H]^+$; found: 213.139.

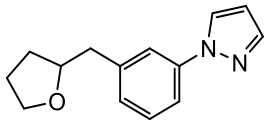
1-(3-(2-(1,3-dioxan-2-yl)ethyl)phenyl)-1*H*-pyrazole (19)



General procedure 2 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 111.5 mg, 0.50 mmol) as the aryl halide, 2-(2-bromoethyl)-1,3-dioxane (**A19**, 97.53 mg, 0.50 mmol) as the alkyl reagent, 25 mol % NaI (18.7 mg, 0.125 mmol), and **Ligand 13** (8.2 mg, 0.030 mmol, 6 mol %). After the reaction was complete, the reaction mixture was diluted with aqueous NaOH (2M, 20 mL) and extracted into DCM. The combined organic layers were dried over Na_2SO_4 concentrated in vacuo to produce an orange oil. The

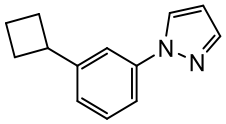
crude residue was purified by flash column chromatography on silica (10-20% EtOAc in cyclohexane) affording product **19** as a clear colorless oil in 59% yield (76.7 mg, 0.297 mmol) that was inseparable from the homodimer of the alkyl halide, 1,4-di(1,3-dioxan-2-yl)butane (9.0 mg, 0.037 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.56 (t, *J* = 2.0 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.13 (dt, *J* = 7.6, 1.3 Hz, 1H), 6.46 (t, *J* = 2.2 Hz, 1H), 4.53 (t, *J* = 5.2 Hz, 1H), 4.12 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.75 (td, *J* = 12.4, 2.3 Hz, 2H), 2.83 – 2.75 (m, 2H), 2.16 – 2.04 (m, 1H), 1.99 – 1.91 (m, 2H), 1.63 – 1.60 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 140.9, 140.3, 129.4, 126.8, 126.6, 119.4, 116.8, 107.5, 102.3, 101.3, 66.9, 36.5, 35.2, 30.1, 25.9, 25.8, 23.9; HRMS (ESI): *m/z* calcd for $C_{15}H_{19}N_2O_2^+$: 259.1441 [*M*+H]$^+$; found: 259.1437.

1-(3-((tetrahydrofuran-2-yl)methyl)phenyl)-1H-pyrazole (23)



General procedure 1 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 22.3mg, 0.10 mmol) as the aryl halide, 4-(2-bromoethyl)tetrahydro-2H-pyran (**A23**, 38.62 mg, 0.20 mmol) as the alkyl reagent, and **Ligand 13** (1.88 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under N_2 stream. The crude residue was dissolved in DMA and filtered through celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**23**) (6.9 mg, 27% yield).^{1}H NMR (400 MHz, DMSO) δ 8.32 (d, *J* = 2.4 Hz, 1H), 7.68 (t, *J* = 2.1 Hz, 2H), 7.61 (ddd, *J* = 8.1, 2.3, 1.0 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.16 (dt, *J* = 7.6, 1.4 Hz, 1H), 6.48 (dd, *J* = 2.5, 1.8 Hz, 1H), 4.10 – 3.99 (m, 1H), 3.79 (ddd, *J* = 8.2, 7.2, 6.1 Hz, 1H), 3.62 (td, *J* = 7.9, 6.3 Hz, 1H), 2.83 (qd, *J* = 13.7, 6.3 Hz, 2H), 1.97 – 1.72 (m, 3H), 1.53 (ddt, *J* = 11.4, 8.3, 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 141.2, 140.0, 129.6, 128.1, 127.5, 119.6, 116.5, 108.1, 79.5, 67.5, 67.4, 41.5, 31.0, 25.5. HRMS (ESI+): *m/z* calcd for $C_{14}H_{17}N_2O^+$: 229.1341 [M+H]$^+$; found: 229.1347.

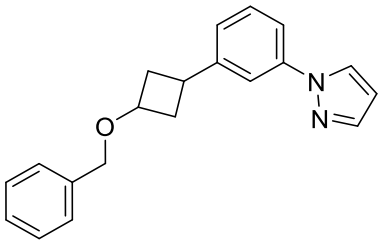
1-(3-cyclobutylphenyl)-1H-pyrazole (24)



General procedure 1 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 55.8 mg, 0.25 mmol) as the aryl halide, cyclobutyl bromide (**A24**, 67.5 mg, 0.50 mmol) as the alkyl reagent, and Ligand **13** (4.10 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**24**) (14 mg, 28% yield) ^{1}H NMR (400 MHz, DMSO) δ 8.35 (dd, *J* = 2.6, 0.6 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.58 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.15 (ddt, *J* = 7.6, 1.8, 0.9 Hz, 1H), 6.48 (dd, *J* = 2.5, 1.8 Hz, 1H), 3.60 (p, *J* = 8.6 Hz, 1H), 2.41 – 2.32 (m, 2H), 2.21 – 2.09 (m, 2H), 2.07 – 1.95 (m,

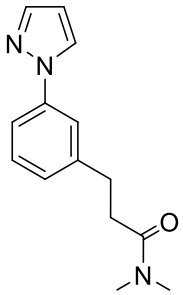
1H), 1.92 – 1.82 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 147.7, 141.2, 140.1, 129.8, 128.2, 124.5, 116.7, 116.3, 108.1, 37.5, 29.7, 18.2. HRMS (ESI+): *m/z* calcd $C_{13}H_{15}N_2^+$: 199.1230 $[M+H]^+$;found: 199.1231.

1-(3-(3-(benzyloxy)cyclobutyl)phenyl)-1H-pyrazole (35)



General procedure 1 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 55.8 mg, 0.25 mmol) as the aryl halide, ((3-bromocyclobutoxy)methyl)benzene (**A35**, 121 mg, 0.50 mmol) as the alkyl reagent, and **Ligand 13** (4.11 mg, 0.50 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**35**) (20 mg, 27% yield, apparent ~2:1 mixture of cis and trans isomers). ^{1}H NMR (600 MHz, DMSO) δ 8.51 (ddd, *J* = 3.1, 2.5, 0.6 Hz, 1H), 7.74 – 7.72 (m, 1H), 7.71 – 7.69 (m, 1H), 7.65 (ddt, *J* = 8.1, 2.3, 1.3 Hz, 1H), 7.42 (q, *J* = 7.6 Hz, 1H), 7.39 – 7.33 (m, 4H), 7.31 – 7.27 (m, 1H), 7.23 – 7.16 (m, 1H), 6.53 (ddd, *J* = 3.3, 2.5, 1.7 Hz, 1H), 4.43 (d, *J* = 2.9 Hz, 2H), 4.04 (tt, *J* = 7.9, 6.5 Hz, 1H), 3.08 (tt, *J* = 10.3, 7.6 Hz, 1H), 2.71 – 2.65 (m, 1H), 2.49 – 2.44 (m, 1H), 2.43 – 2.38 (m, 1H), 2.04 – 1.97 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 147.5, 146.7, 141.3, 140.3, 140.2, 138.93, 138.86, 129.93, 129.86, 128.6, 128.20, 128.19, 128.12, 128.08, 127.83, 127.80, 124.8, 117.04, 117.00, 116.5, 116.4, 108.1, 71.7, 69.61, 69.54, 68.8, 38.1, 36.3, 33.7, 30.5. HRMS (ESI+): *m/z* calcd $C_{20}H_{21}N_2O^+$: 305.1648 $[M+H]^+$;found: 305.1655.

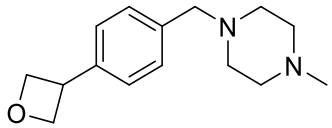
3-(3-(1H-pyrazol-1-yl)phenyl)-N,N-dimethylpropanamide (37)



General procedure 1 was followed using 1-(3-bromophenyl)-1H-pyrazole (**Core 1**, 55.8 mg, 0.25 mmol) as the aryl halide, 3-bromo-*N,N*-dimethylpropanamide (**A37**, 67.5 mg, 0.5 mmol) as the alkyl reagent, and **Ligand 13** (4.10 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**37**) (14 mg, 22% yield) ^{1}H NMR (400 MHz, DMSO) δ 8.33 (d, *J* = 2.4 Hz, 1H), 7.70 –

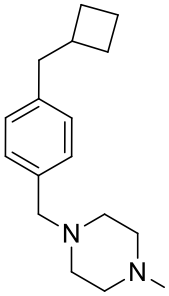
7.65 (m, 2H), 7.59 (ddd, *J* = 8.1, 2.3, 1.0 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.16 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.48 (dd, *J* = 2.5, 1.7 Hz, 1H), 2.91 (t, *J* = 7.6 Hz, 6H), 2.65 (dd, *J* = 8.3, 6.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 171.6, 143.7, 141.3, 140.2, 129.8, 128.1, 126.7, 118.9, 116.5, 108.2, 37.1, 35.3, 34.4, 31.1. HRMS (ESI+): *m/z* calcd $C_{14}H_{18}N_3O^+$: 244.1444 $[M+H]^+$;found: 244.1447.

1-methyl-4-(4-(oxetan-3-yl)benzyl)piperazine (40)



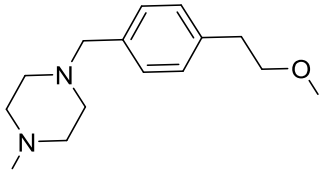
General procedure 1 was followed using 1-(4-bromobenzyl)-4-methylpiperazine (**Core 2**, 67.3 mg, 0.25 mmol) as the aryl halide, 3-bromooxetane (**A3**, 68.5 mg, 0.50 mmol) as the alkyl reagent and **Ligand 13** (4.10 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**40**) (23 mg, 37% yield, 90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 1H), 4.96 – 4.88 (m, 2H), 4.63 – 4.57 (m, 2H), 4.27 – 4.17 (m, 1H), 3.42 (s, 2H), 2.33 (m, 8H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 140.7, 137.3, 129.5, 127.0, 78.0, 62.2, 55.2, 53.0, 46.2, 39.4. HRMS (ESI+): *m/z* calcd $C_{15}H_{23}N_2O^+$: 247.1805 $[M+H]^+$;found: 247.1808.

1-(4-(cyclobutylmethyl)benzyl)-4-methylpiperazine (54)



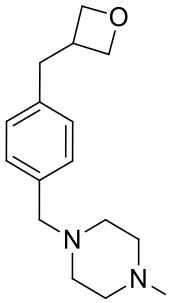
General procedure 1 was followed using 1-(4-bromobenzyl)-4-methylpiperazine (**Core 2**, 67.3 mg, 0.25 mmol) as the aryl halide, (bromomethyl)cyclobutene (**A17**, 74.5 mg, 0.5 mmol) as alkyl reagent, and **Ligand 13** (5.27 mg, 0.50 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**54**) (9.2 mg, 14% yield, >90% pure by ^{1}H NMR) ^{1}H NMR (500 MHz, PYRIDINE) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 7H), 3.47 (s, 2H), 3.06 (s, 3H), 2.71 (s, 3H), 2.66 (s, 3H), 2.64 (s, 1H), 2.51 (p, *J* = 7.8 Hz, 1H), 1.96 (dddd, *J* = 11.5, 8.1, 5.6, 1.6 Hz, 2H), 1.82 – 1.72 (m, 2H), 1.72 – 1.62 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 139.8, 135.9, 129.2, 128.6, 62.3, 55.1, 52.9, 46.1, 42.3, 37.1, 28.0, 18.3. HRMS (ESI+): *m/z* calcd $C_{17}H_{27}N_2^+$: 259.2169 $[M+H]^+$;found: 259.2171.

1-(4-(2-methoxyethyl)benzyl)-4-methylpiperazine (57)



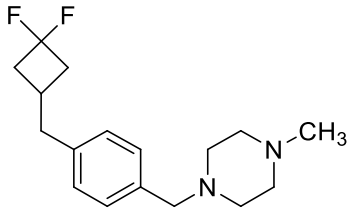
General procedure 1 was followed using 1-(4-bromobenzyl)-4-methylpiperazine (**Core 2**, 67.3mg, 0.25 mmol) as the aryl halide, 1-bromo-2-methoxyethane (**A20**, 69.5 mg, 0.50 mmol) as the alkyl reagent, and **Ligand 13** (5.27 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**57**) (38 mg, 32% yield, >90% pure by ^{1}H NMR) ^{1}H NMR (500 MHz, PYRIDINE) δ 7.29 (s, 4H), 3.61 (s, 3H), 3.57 (t, *J* = 6.8 Hz, 2H), 3.45 (s, 2H), 3.25 (s, 2H), 3.10 (s, 2H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.73 – 2.70 (m, 2H), 2.69 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 159.0, 139.8, 130.3, 129.4, 73.0, 60.0, 58.2, 51.8, 49.0, 42.6, 35.4. HRMS (ESI+): *m/z* calcd $C_{15}H_{25}N_2O^+$: 249.1961 $[M+H]^+$;found: 249.1965.

1-methyl-4-(4-(oxetan-3-ylmethyl)benzyl)piperazine (58)



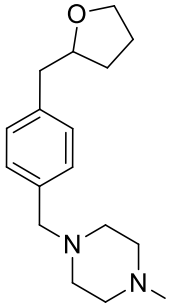
General procedure 1 was followed using 1-(4-bromobenzyl)-4-methylpiperazine (**Core 2**, 67.3 mg, 0.25 mmol) as the aryl halide, 3-(bromomethyl)oxetane (**A21**, 75.5 mg, 0.5 mmol) as the alkyl reagent , and **Ligand 13** (5.27 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**58**) (7.5 mg, 12% yield, 96% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.62 (dd, *J* = 7.7, 5.8 Hz, 2H), 4.32 (t, *J* = 6.1 Hz, 2H), 3.38 (s, 3H), 3.29 (s, 3H), 3.28 – 3.17 (m, 1H), 2.92 (d, *J* = 7.8 Hz, 2H), 2.40 – 2.21 (m, 7H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 138.5, 136.5, 129.4, 128.5, 76.3, 62.3, 55.2, 52.9, 46.2, 38.9, 35.9. HRMS (ESI+): *m/z* calcd $C_{16}H_{25}N_2O^+$: 261.1961 $[M+H]^+$;found: 261.1964.

1-(4-((3,3-difluorocyclobutyl)methyl)benzyl)-4-methylpiperazine (59)



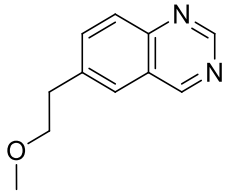
General procedure 1 was followed using 1-(4-bromobenzyl)-4-methylpiperazine (**Core 2**, 67.3 mg, 0.25 mmol) as the aryl halide, 3-(bromomethyl)-1,1-difluorocyclobutane (**A22**, 92.5mg, 0.50 mmol) as the alkyl reagent, and **Ligand 13** (5.27 mg, 0.02mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound (**59**) as the *bis*-trifluoroacetic acid salt (27 mg, 21% yield) ^{1}H NMR (500 MHz, pyridine-d_5) δ 7.33 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 3.61 (s, 5H), 3.48 (s, 2H), 3.06 (s, 2H), 2.70 (d, *J* = 7.6 Hz, 5H), 2.66 (s, 3H), 2.58 (ddt, *J* = 14.2, 11.6, 7.7 Hz, 2H), 2.37 – 2.31 (m, 1H), 2.30 – 2.21 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 140.3, 130.4, 129.1, 60.2, 52.0, 49.1, 42.7, 40.7, 40.2 (t, *J* = 20.6 Hz, 2C), 24.3 (t, *J* = 6.2 Hz). Note: due to the small amount of material and the presence of trifluoroacetate, we were unable to fully resolve the difluoromethane CF_2 carbon in the ^{13}C NMR spectrum, although a small peak near the expected 121 ppm was observed. HRMS (ESI+): *m/z* calcd $C_{17}H_{25}F_2N_2^+$: 295.1980 $[M+H]^+$;found: 295.1981.

1-methyl-4-(4-((tetrahydrofuran-2-yl)methyl)benzyl)piperazine (60)



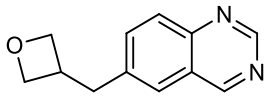
General procedure 1 was followed using 1-(4-bromobenzyl)-4-methylpiperazine (**Core 2**, 67.3 mg, 0.25 mmol) as the aryl halide, 2-(bromomethyl)tetrahydrofuran (**A23**, 82.5 mg, 0.50 mmol) as alkyl reagent , and **Ligand 13** (5.27mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**60**) (11 mg, 15% yield, 92% pure by ^{1}H NMR). ^{1}H NMR (500 MHz, DMSO) δ 7.22 – 7.13 (m, 4H), 3.94 (p, *J* = 6.6 Hz, 1H), 3.76 (ddd, *J* = 8.3, 7.2, 6.0 Hz, 1H), 3.58 (td, *J* = 7.8, 6.2 Hz, 2H), 3.39 (s, 2H), 2.79 – 2.63 (m, 2H), 2.40 – 2.22 (m, 6H), 2.13 (s, 3H), 1.90 (s, 2H), 1.87 – 1.73 (m, 3H), 1.52 – 1.42 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 138.0, 136.3, 129.4, 129.0, 79.7, 67.3, 62.3, 55.2, 53.0, 46.2, 41.3, 31.0, 25.5. HRMS (ESI+): *m/z* calcd $C_{17}H_{27}N_2O^+$: 275.2118 $[M+H]^+$;found: 275.2122.

6-(2-methoxyethyl)quinazoline (94)



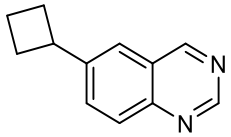
General procedure 1 was followed using 6-bromoquinazoline (**Core 3**, 52.3 mg, 0.25 mmol) as the aryl halide, 1-bromo-2-methoxyethane (**A20**, 69.5 mg, 0.5 mmol) as the alkyl reagent, and **Ligand 13** (4.10 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**94**) (15mg, 32% yield, >95% pure by ^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 9.21 (s, 1H), 7.94 (dq, *J* = 1.7, 0.9 Hz, 1H), 7.93 – 7.90 (m, 2H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.28 (s, 3H), 3.06 (td, *J* = 6.6, 0.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 160.5, 155.0, 148.7, 140.1, 136.7, 127.9, 127.0, 125.1, 72.6, 58.4, 35.7. HRMS (ESI+): *m/z* calcd $C_{11}H_{13}N_2O^+$: 189.1022 $[M+H]^+$;found: 189.1024.

6-(oxetan-3-ylmethyl)quinazoline (95)



General procedure 1 was followed using 6-bromoquinazoline (**Core 3**, 20.90 mg, 0.10 mmol) as the aryl halide, 3-(bromomethyl)oxetane (**A21**, 30.20 mg, 0.20 mmol) as the alkyl reagent, and **Ligand 13** (1.64 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**95**) (2 mg, 9% yield, >90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 9.22 (s, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.87 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.85 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.69 (dd, *J* = 7.6, 5.8 Hz, 2H), 4.40 (t, *J* = 6.0 Hz, 2H), 3.48 – 3.34 (m, 1H), 3.21 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 160.5, 155.0, 148.6, 140.2, 136.3, 128.2, 126.2, 125.1, 76.1, 38.9, 35.5. HRMS (ESI+): *m/z* calcd $C_{12}H_{13}N_2O^+$: 201.1022 $[M+H]^+$; found: 201.1026.

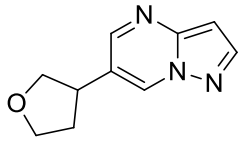
6-cyclobutylquinazoline (98)



General procedure 1 was followed using 6-bromoquinazoline (**Core 3**, 20.90 mg, 0.10 mmol) as the aryl halide, bromocyclobutane (**A24**, 27.00 mg, 0.20 mmol) as the alkyl reagent, and **Ligand 13** (1.64 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The

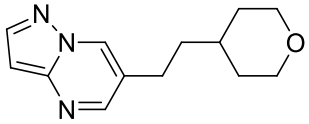
crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**98**) (5.1 mg, 28% yield, >90% pure by ^{1}H NMR). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 9.24 (s, 1H), 7.99 – 7.92 (m, 3H), 3.78 (p, *J* = 9.0 Hz, 1H), 2.41 (qt, *J* = 8.1, 2.6 Hz, 2H), 2.27 – 2.16 (m, 2H), 2.12 – 2.01 (m, 1H), 1.93 – 1.84 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 160.6, 154.9, 148.5, 146.1, 134.6, 128.0, 125.1, 124.0, 29.5, 18.2. Note: we estimate that the tertiary benzylic cyclobutane carbon would appear underneath the DMSO residual solvent peak and could not locate it.[3] HRMS (ESI+): *m/z* calcd $C_{12}H_{13}N_{12}^{+}$: 185.1073 $[M+H]^{+}$; found: 185.1076.

6-(tetrahydrofuran-3-yl)pyrazolo[1,5-a]pyrimidine (112)



General procedure 1 was followed using 6-bromopyrazolo[1,5-a]pyrimidine(**Core 4**, 49.51 mg, 0.25 mmol) as the aryl halide, 3-bromotetrahydrofuran (**A1**, 75.5 mg, 0.50 mmol) as the alkyl reagent, and **Ligand 13** (4.10 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**112**) (5.4 mg, 11% yield, 90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 9.00 (dd, *J* = 2.1, 1.0 Hz, 1H), 8.56 (d, *J* = 2.2 Hz, 1H), 8.17 (d, *J* = 2.3 Hz, 1H), 6.69 (dd, *J* = 2.3, 0.9 Hz, 1H), 4.05 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.99 (td, *J* = 8.4, 4.7 Hz, 1H), 3.82 (dt, *J* = 8.4, 7.5 Hz, 1H), 3.67 (dd, *J* = 8.4, 7.1 Hz, 1H), 3.50 (p, *J* = 7.5 Hz, 1H), 2.42 – 2.32 (m, 1H), 2.06 (dq, *J* = 12.4, 7.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 151.0, 147.4, 144.9, 133.1, 123.4, 96.2, 73.4, 67.9, 39.5, 33.2. HRMS (ESI+): *m/z* calcd $C_{10}H_{12}N_{3}O^{+}$: 190.0975 $[M+H]^{+}$; found: 190.0978.

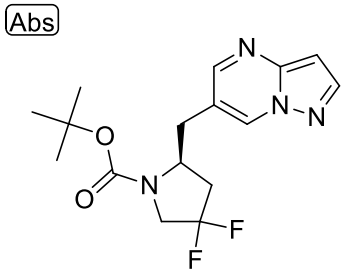
6-(2-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazolo[1,5-a]pyrimidine (113)



General procedure 1 was followed using 6-bromopyrazolo[1,5-a]pyrimidine(**Core 4**, 19.8 mg, 0.10 mmol) as the aryl halide, 2-(2-bromoethyl)-1,3-dioxane (**A2**, 39.0mg, 0.20 mmol) as the alkyl reagent, and **Ligand 13** (1.64 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**113**) (7.8 mg, 34% yield, >90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 8.84 (dd, *J* = 2.1, 1.0 Hz, 1H), 8.45 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 2.3, 1.0 Hz, 1H), 3.83 (ddd, *J* = 11.3, 4.3, 2.1 Hz, 2H), 3.30 (dd, *J* = 11.6, 2.2 Hz, 2H), 2.71 – 2.66 (m, 2H), 1.68 – 1.58 (m, 4H), 1.53 (ddt,

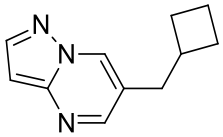
J = 13.3, 6.7, 3.4 Hz, 1H), 1.29 – 1.17 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 152.0, 147.4, 144.6, 133.6, 122.8, 96.1, 67.5, 37.8, 34.2, 33.0, 26.2. HRMS (ESI+): *m/z* calcd $C_{13}H_{18}N_3O^+$: 232.1444 $[M+H]^+$; found: 232.1447.

(S)-tert-butyl-4,4-difluoro-2-(pyrazolo[1,5-a]pyrimidin-6-ylmethyl)pyrrolidine-1-carboxylate (118)



General procedure 1 was followed using 6-bromopyrazolo[1,5-a]pyrimidine(**Core 4**, 19.8 mg, 0.10 mmol) as the aryl halide, (*R*)-*tert*-butyl 2-(bromomethyl)-4,4-difluoropyrrolidine-1-carboxylate (**A7**, 60.0 mg, 0.20 mmol) as the alkyl reagent, and **Ligand 13** (1.64 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**118**) (8.6 mg, 25% yield, >90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 8.80 (dt, *J* = 2.1, 1.0 Hz, 1H), 8.42 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 2.3, 0.9 Hz, 1H), 4.59 (t, *J* = 4.9 Hz, 1H), 4.00 (ddt, *J* = 10.3, 5.1, 1.5 Hz, 2H), 3.75 – 3.67 (m, 2H), 2.74 (ddd, *J* = 8.9, 6.5, 1.0 Hz, 2H), 1.96 – 1.83 (m, 3H), 1.34 (dtt, *J* = 13.3, 2.8, 1.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 153.5, 152.2, 147.4, 144.9, 134.8, 128.8 (t, J_{CF} = 230.7 Hz), 119.0, 96.2, 80.0, 57.1, 52.6, 34.4, 33.7, 28.0. Note: many of the carbon peaks were broadened, presumably due to E/Z isomers in the *N*-Boc group, which prevented us from identifing J_{CF} for any carbons except for the CF_2. HRMS (ESI+): *m/z* calcd $C_{16}H_{21}F_2N_4O_2^+$: 339.1627 $[M+H]^+$; found: 339.1632.

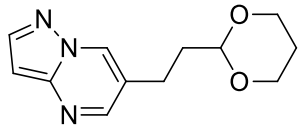
6-(cyclobutylmethyl)pyrazolo[1,5-a]pyrimidine (128)



General procedure 1 was followed using 6-bromopyrazolo[1,5-a]pyrimidine (**Core 4**, 49.51mg, 0.25 mmol) as the aryl halide, (bromomethyl)cyclobutene (**A17**, 74.5mg, 0.50 mmol) as the alkyl reagent, and **Ligand 13** (1.64 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**128**) (4 mg, 8% yield, 90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 8.93 (dq, *J* = 1.9, 0.9 Hz, 1H), 8.46 (d, *J* = 2.1 Hz, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 6.66 (dd, *J* = 2.3, 0.9 Hz, 1H), 2.74 (d, *J* = 7.6 Hz, 2H), 2.60 (dt, *J* = 15.4, 7.8 Hz, 1H), 1.99 (tdd, *J* = 8.2, 6.8, 3.0 Hz, 2H), 1.88 – 1.78 (m, 2H), 1.78 – 1.68 (m,

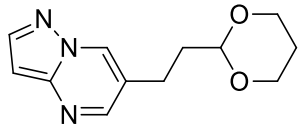
2H). ^{13}C NMR (101 MHz, DMSO) δ 152.0, 147.3, 144.6, 133.6, 121.2, 96.1, 36.2, 35.9, 27.5, 18.0. HRMS (ESI+): *m/z* calcd $C_{11}H_{14}N_3^+$: 188.1182 $[M+H]^+$; found: 188.1185.

6-(2-(1,3-dioxan-2-yl)ethyl)pyrazolo[1,5-a]pyrimidine (130)



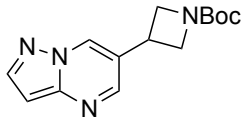
General procedure 1 was followed using 6-bromopyrazolo[1,5-a]pyrimidine (**Core 4**, 19.8 mg, 0.10 mmol) as the aryl halide, 2-(2-bromoethyl)-1,3-dioxane (**A19**, 39.0mg, 0.20 mmol) as the alkyl reagent, and **Ligand 13** (1.64 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**130**) (4.8 mg, 21% yield, >90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 8.80 (dt, *J* = 2.1, 1.0 Hz, 1H), 8.42 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 2.3, 0.9 Hz, 1H), 4.59 (t, *J* = 4.9 Hz, 1H), 4.00 (ddt, *J* = 10.3, 5.1, 1.5 Hz, 2H), 3.75 – 3.67 (m, 2H), 2.74 (ddd, *J* = 8.9, 6.5, 1.0 Hz, 2H), 1.96 – 1.83 (m, 3H), 1.34 (dtt, *J* = 13.3, 2.8, 1.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 152.1, 147.4, 144.6, 133.7, 122.2, 100.9, 96.1, 66.5, 35.8, 25.9, 24.0. HRMS (ESI+): *m/z* calcd $C_{12}H_{16}N_3O_2^+$: 234.1237 $[M+H]^+$; found: 234.1239.

6-(2-(1,3-dioxan-2-yl)ethyl)pyrazolo[1,5-*α*]pyrimidine (130)



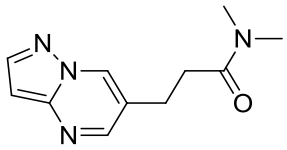
General procedure 2 was followed using 6-bromopyrazolo[1,5-a]pyrimidine (**Core 4**, 99.01 mg, 0.50 mmol) as the aryl halide, 2-(2-bromoethyl)-1,3-dioxane (**A19**, 97.53 mg, 0.50 mmol) as the alkyl reagent, and **Ligand 13** (8.2 mg, 0.030 mmol, 6 mol %). After the reaction was complete, the reaction mixture was diluted with aqueous NaOH (2M, 20 mL) and extracted into DCM. The combined organic layers were dried over Na_2SO_4 concentrated in vacuo to produce an orange oil. The crude residue was purified by flash column chromatography on silica (20% EtOH, 20% Et_3N in cyclohexane) affording product **130** as yellow crystals in 19% yield (23 mg, 0.097 mmol) that was inseparable from the homodimer of the alkyl halide, 1,4-di(1,3-dioxan-2-yl)butane (11.2 mg, 0.049 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 2.2, 1.0 Hz, 1H), 8.39 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 2.4, 1.0 Hz, 1H), 4.58 (t, *J* = 5.0 Hz, 1H), 3.81 – 3.70 (m, 4H), 2.84 – 2.77 (m, 4H), 2.00 – 1.94 (m, 2H), 1.42 – 1.37 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 147.6, 144.5, 132.9, 121.6, 102.3, 100.6, 96.6, 66.9, 35.7, 35.2, 26.0, 25.7, 24.1, 23.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{16}N_3O_2^+$: 234.1237 [*M*+H]$^+$; found: 234.1234.

***tert*-butyl 3-(pyrazolo[1,5-*a*]pyrimidin-6-yl)azetidine-1-carboxylate (139)**



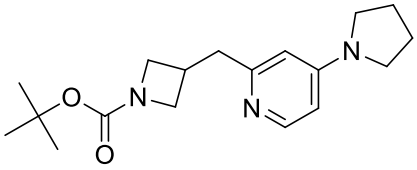
General procedure 2 was followed using 6-bromopyrazolo[1,5-a]pyrimidine (**Core 4**, 99.01 mg, 0.50 mmol) as the aryl halide, 1-Boc-3-bromoazetidine (**A28**, 118.1 mg, 0.50 mmol) as the alkyl reagent, 25 mol % NaI (18.7 mg, 0.125 mmol), and **Ligand 13** (8.2 mg, 0.030 mmol, 6 mol %). After the reaction was complete, the reaction mixture was diluted with aqueous NaOH (2M, 20 mL) and extracted into DCM. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to produce an orange oil. The crude residue was purified by flash column chromatography on silica (20% EtOH, 20% Et_3N in cyclohexane) affording product **139** as white crystals in 15% yield (21 mg, 0.075 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.2 Hz, 1H), 8.46 (d, *J* = 2.3 Hz, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 6.64 (dd, *J* = 2.4, 0.9 Hz, 1H), 4.36 (t, *J* = 8.8 Hz, 2H), 3.95 (dd, *J* = 8.8, 5.7 Hz, 2H), 3.72 (tt, *J* = 8.6, 5.7 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 149.2, 147.8, 145.2, 132.3, 122.3, 97.1, 80.2, 55.9, 29.0, 28.4; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_4O_2^+$: 275.1503 [*M*+H]$^+$; found: 275.1498.

N,N-dimethyl-3-(pyrazolo[1,5-a]pyrimidin-6-yl)propenamide (148)



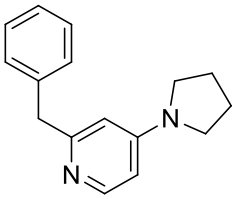
General procedure was followed using 6-bromopyrazolo[1,5-a]pyrimidine (**Core 4**, 19.8 mg, 0.10 mmol) as the aryl halide, 3-bromo-N,N-dimethylpropanamide (**A37**, 36.0 mg, 0.20 mmol) as the alkyl reagent, and **Ligand 13** (1.64 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound (**148**) (6.6 mg, 30% yield, >90% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 8.85 (dd, *J* = 2.2, 1.1 Hz, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 6.60 (dd, *J* = 2.4, 0.9 Hz, 1H), 2.98 – 2.94 (m, 1H), 2.91 (dd, *J* = 8.5, 6.0 Hz, 4H), 2.89-2.81 (m, 3H), 2.72 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 171.3, 152.4, 147.4, 144.6, 134.0, 122.3, 96.0, 37.0, 35.3, 33.6, 24.9. HRMS (ESI+): *m/z* calcd $C_{11}H_{15}N_4O^+$: 219.1240 [M+H]$^+$; found: 219.1244.

tert-butyl 3-((4-(pyrrolidin-1-yl)pyridin-2-yl)methyl)azetidine-1-carboxylate (153)



General procedure was followed using 2-bromo-4-(pyrrolidin-1-yl)pyridine (**Core 5**, 56.78 mg, 0.25 mmol) as the aryl halide, tert-butyl 3-(bromomethyl)azetidine-1-carboxylate (**A28**, 125.07 mg, 0.50 mmol) as the alkyl reagent, and **Ligand 10** (4.8 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound (**153**) (35 mg, 33% yield, 96% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 13.28 (s, 1H), 8.12 (dd, *J* = 7.0, 3.6 Hz, 1H), 6.77 – 6.71 (m, 2H), 3.95 – 3.87 (m, 2H), 3.64(s, 2H), 3.50 – 3.45 (m, 4H), 3.02 (d, *J* = 7.8 Hz, 2H), 2.97 – 2.87 (m, 1H), 2.03 – 1.98 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 156.0, 154.9, 151.3, 139.6, 107.1, 106.7, 79.0, 50.3, 48.6, 36.7, 28.5, 28.0, 25.1. HRMS (ESI+): *m/z* calcd $C_{18}H_{28}N_3O_2^+$: 318.2172 $[M+H]^+$; found: 318.2182.

2-benzyl-4-(pyrrolidin-1-yl)pyridine (181)



General procedure was followed using 2-bromo-4-(pyrrolidin-1-yl)pyridine (**Core 5**, 56.78 mg, 0.25 mmol) as the aryl halide, benzyl chloride (**A33**, 63.3 mg, 0.50 mmol) as the alkyl reagent, and **Ligand 10** (4.8 mg, 0.02 mmol). After the reaction was complete, the reaction was concentrated under a stream of dinitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound (**181**) (30 mg, 34% yield, 92% pure by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO) δ 13.39 (s, 1H), 8.12 (d, *J* = 7.1 Hz, 1H), 7.35 (d, *J* = 4.4 Hz, 4H), 7.31 – 7.25 (m, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.74 (dd, *J* = 7.2, 2.7 Hz, 1H), 4.10 (s, 2H), 3.47 (dt, *J* = 8.8, 6.5 Hz, 4H), 2.00 (q, *J* = 3.4 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 154.9, 152.5, 139.5, 137.3, 129.2, 129.1, 127.5, 107.4, 106.7, 48.6, 38.58, 25.0. HRMS (ESI+): *m/z* calcd $C_{16}H_{19}N_2^+$: 239.1543 $[M+H]^+$; found: 239.1547.

References

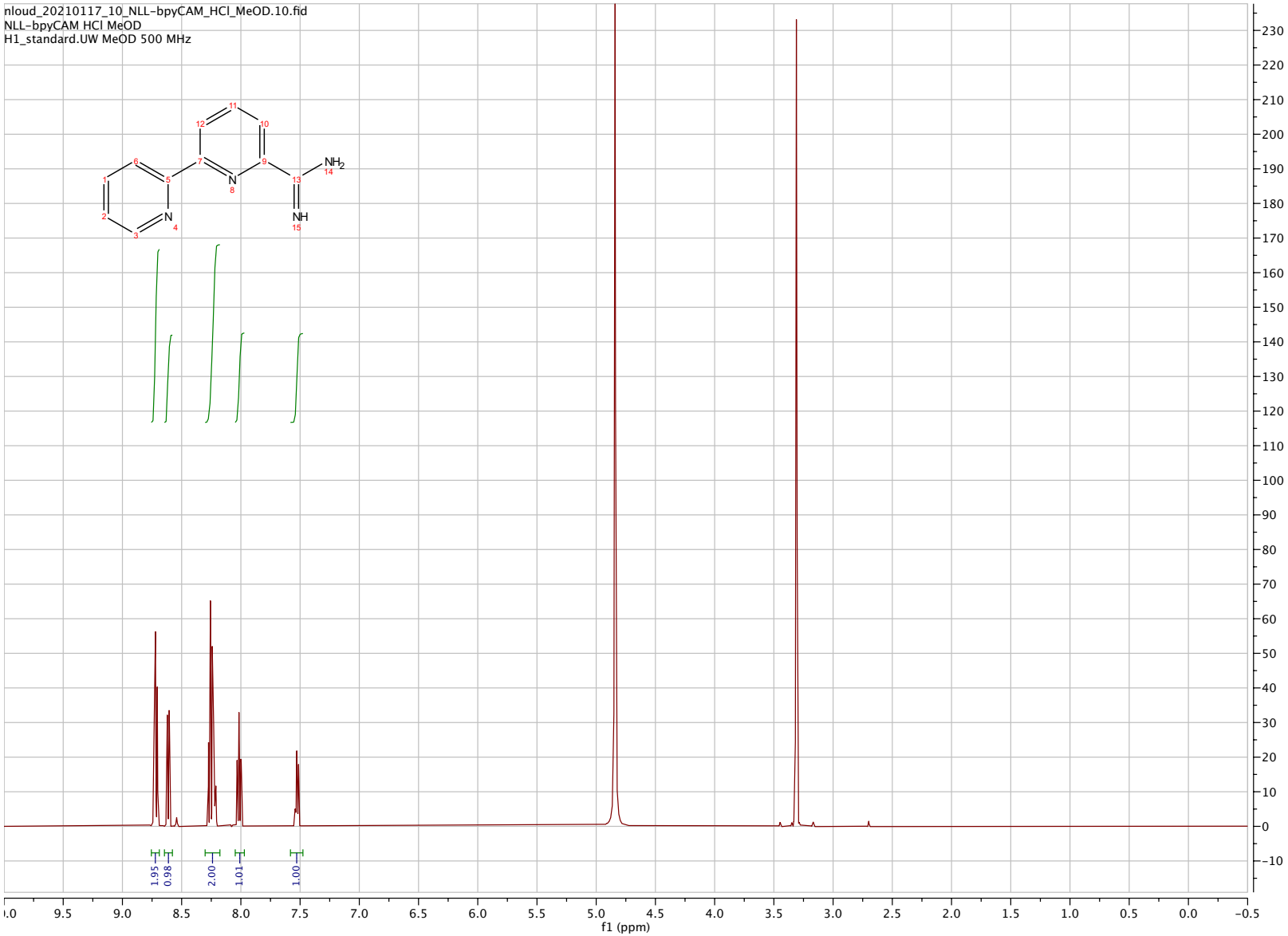
[1] F. C. Schaefer, G. A. Peters, *J. Org. Chem.* **1961**, *26*, 412-418.

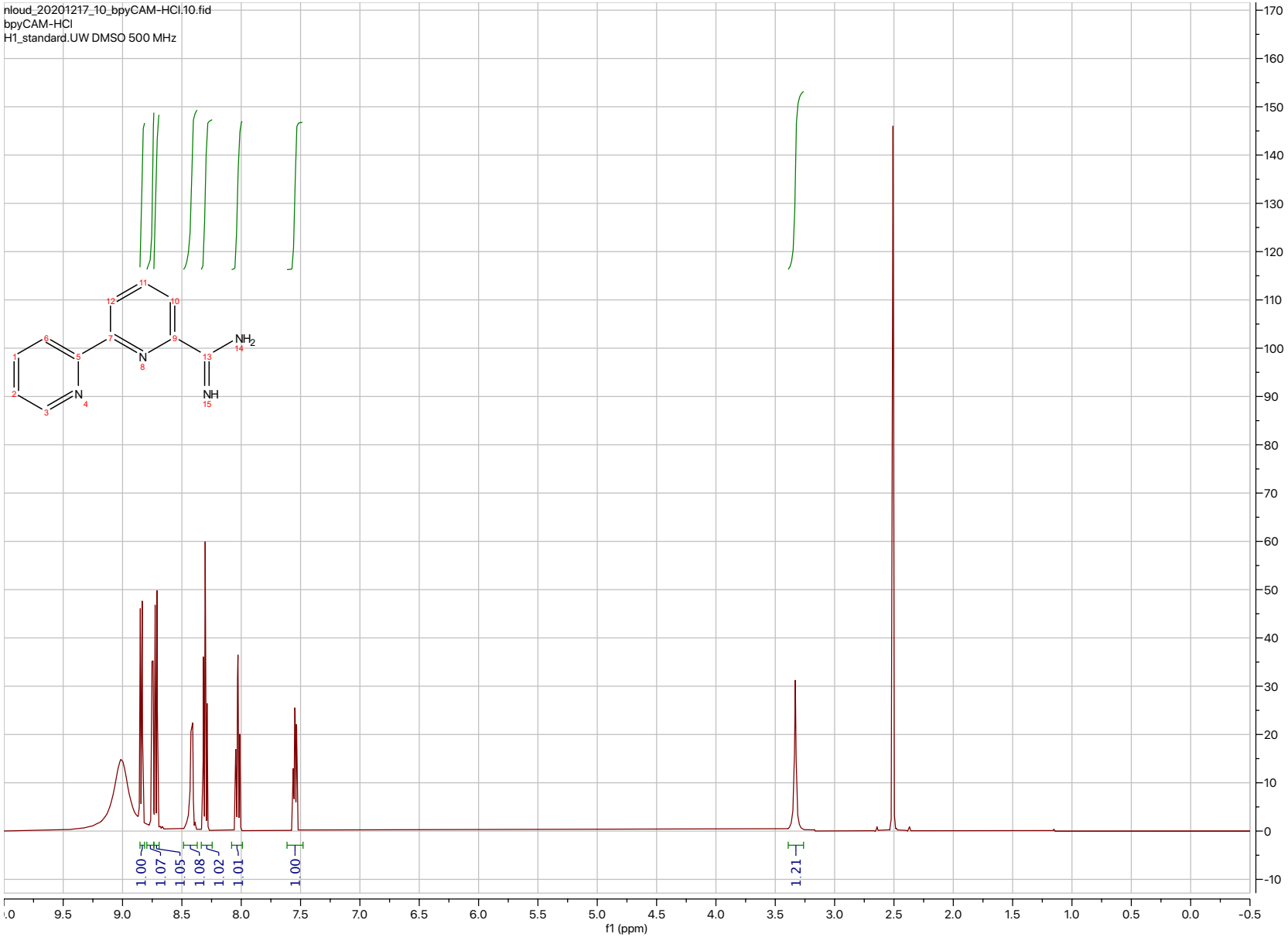
[2] E. Bejan, H. Aït-Haddou, J.-C. Daran, G. G. A. Balavoine, *Eur. J. Org. Chem.* **1998**, 2907-2912.

[3] A. Maercker, K. S. Oeffner, U. Girreser, *Tetrahedron* **2004**, *60*, 8245-8256.

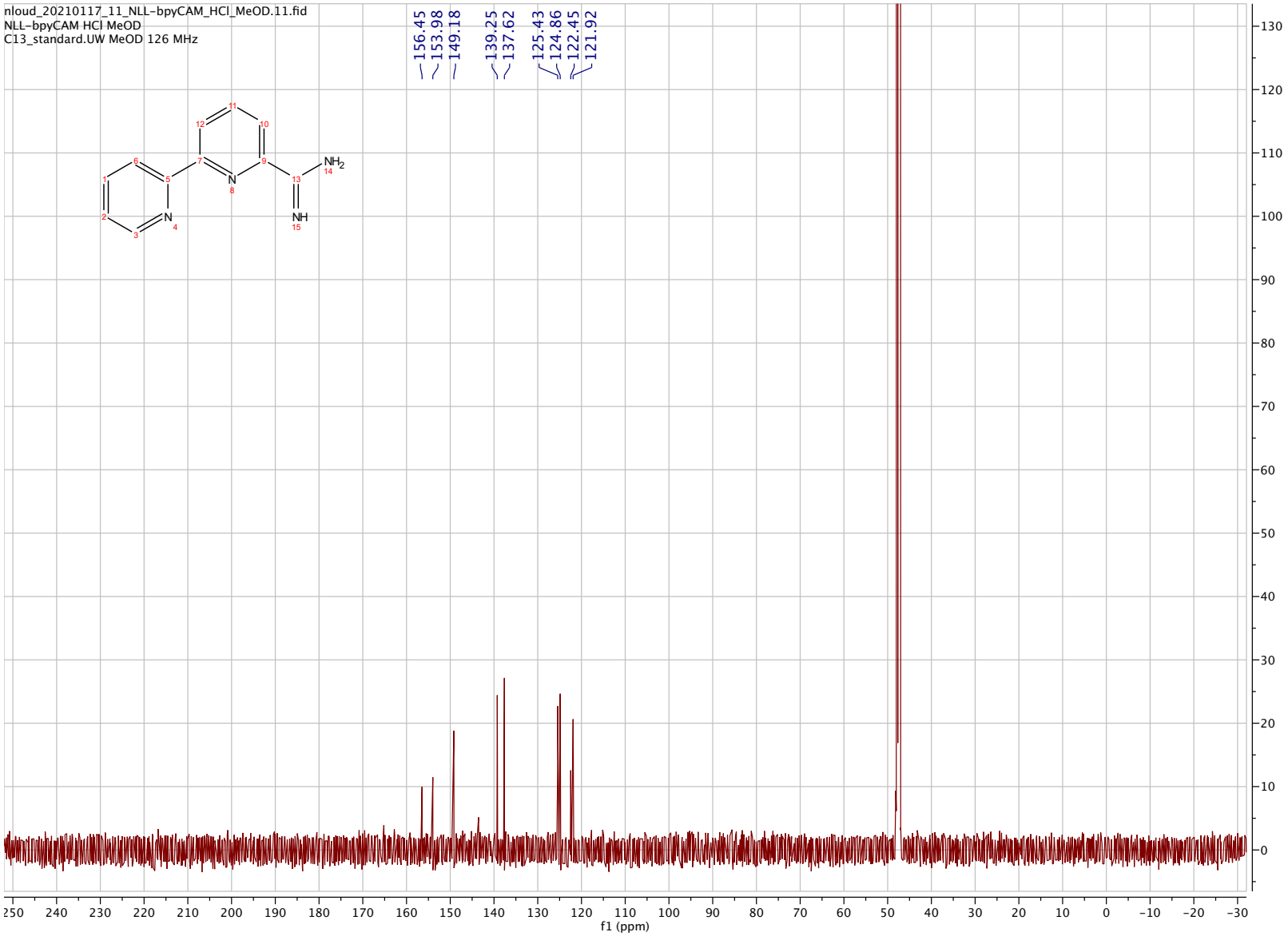
NMR Spectra

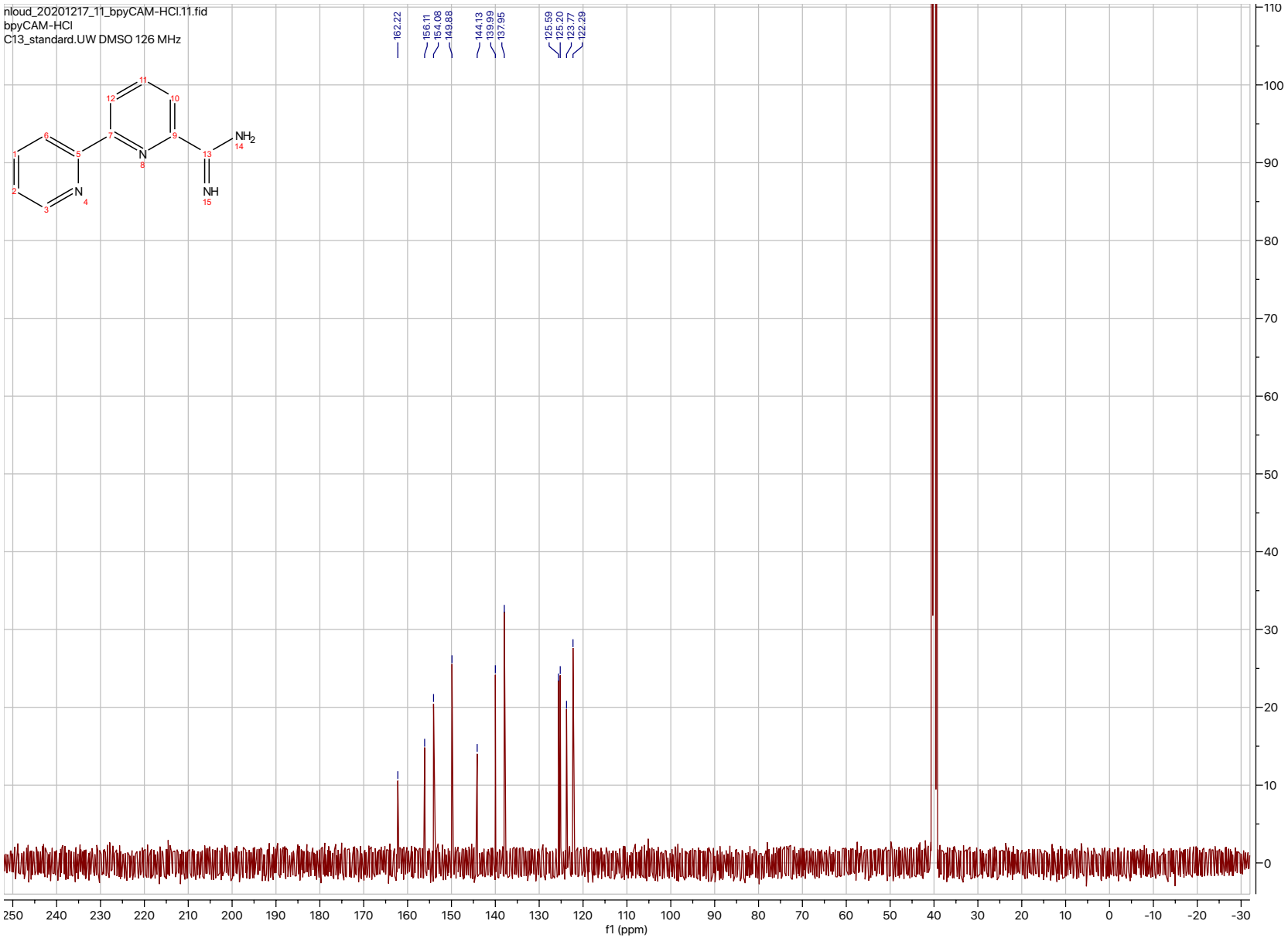
Ligand 13 ^{1}H NMR



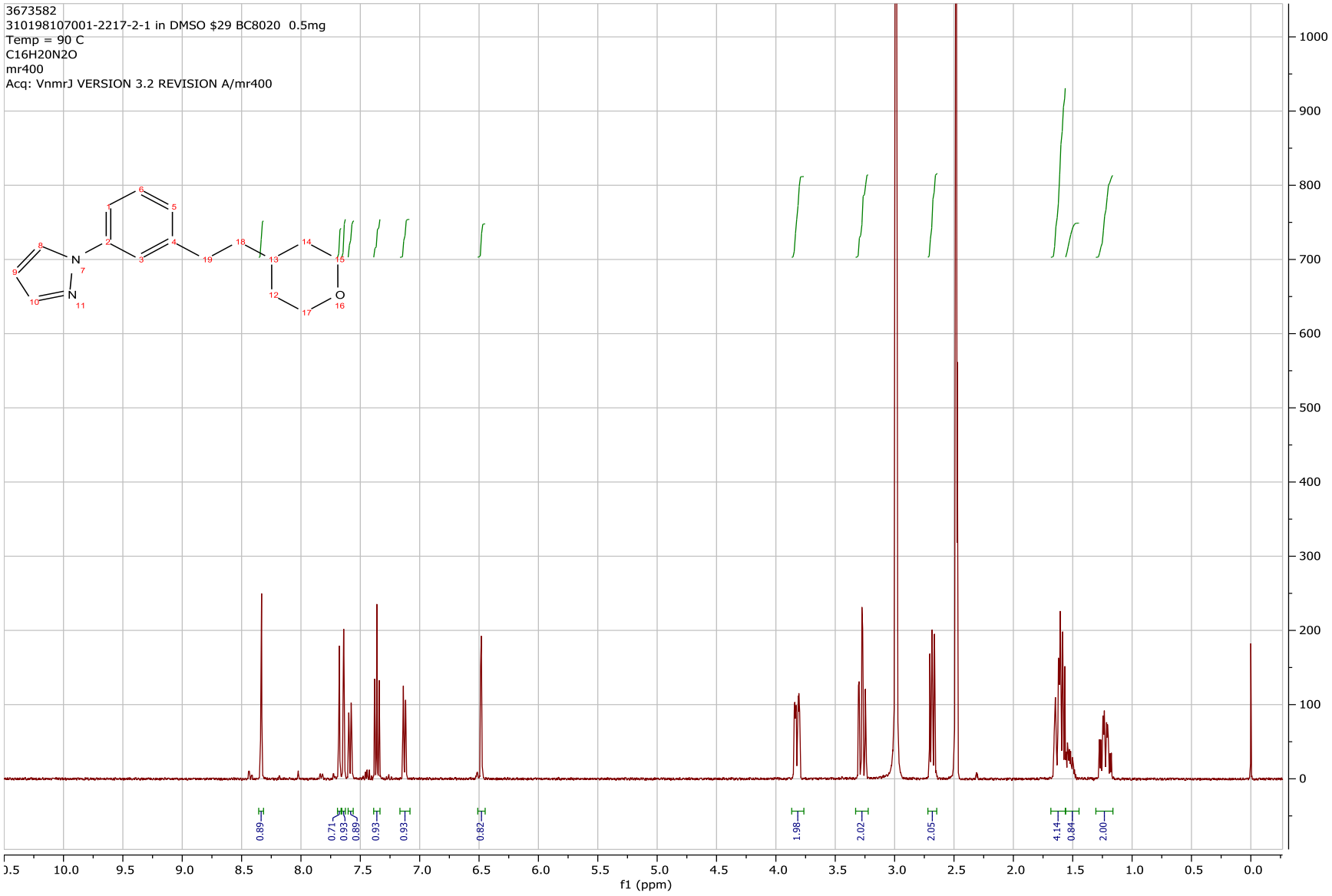

nloud_20201217_10_bpyCAM-HCl.10.fid
bpyCAM-HCl
H1_standard.UW DMSO 500 MHz
NH2
NH
1.00
1.07
1.05
1.08
1.02
1.01
1.00
1.21
f1 (ppm)

Ligand 13 ^{13}C NMR

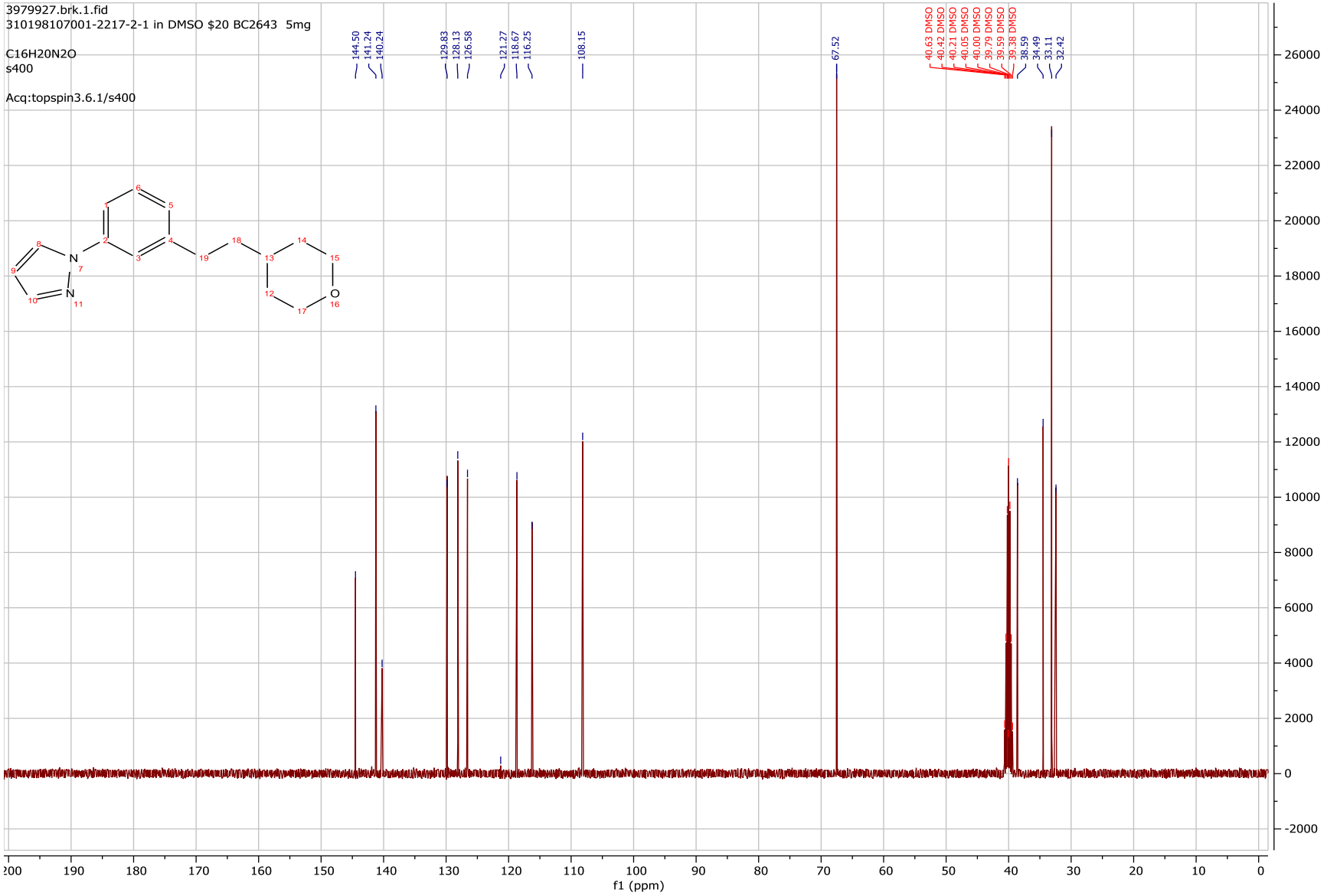



nloud_20201217_11_bpyCAM-HCl.11.fid
bpyCAM-HCl
C13_standard.UW DMSO 126 MHz
162.22
156.11
154.08
149.88
144.13
139.99
137.95
125.59
125.20
123.77
122.29
NH2
NH
f1 (ppm)

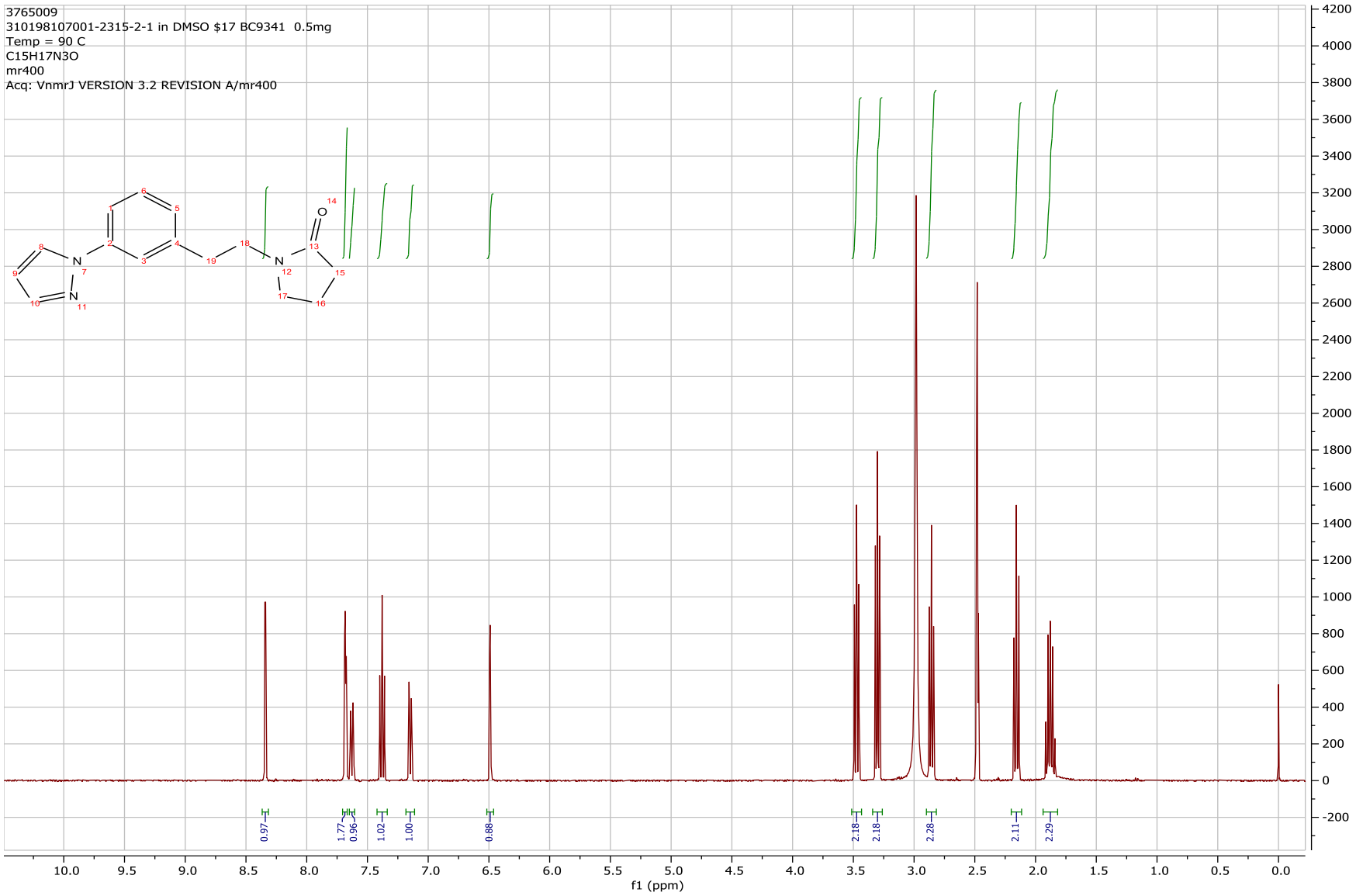
Compound 2 ^{1}HNMR



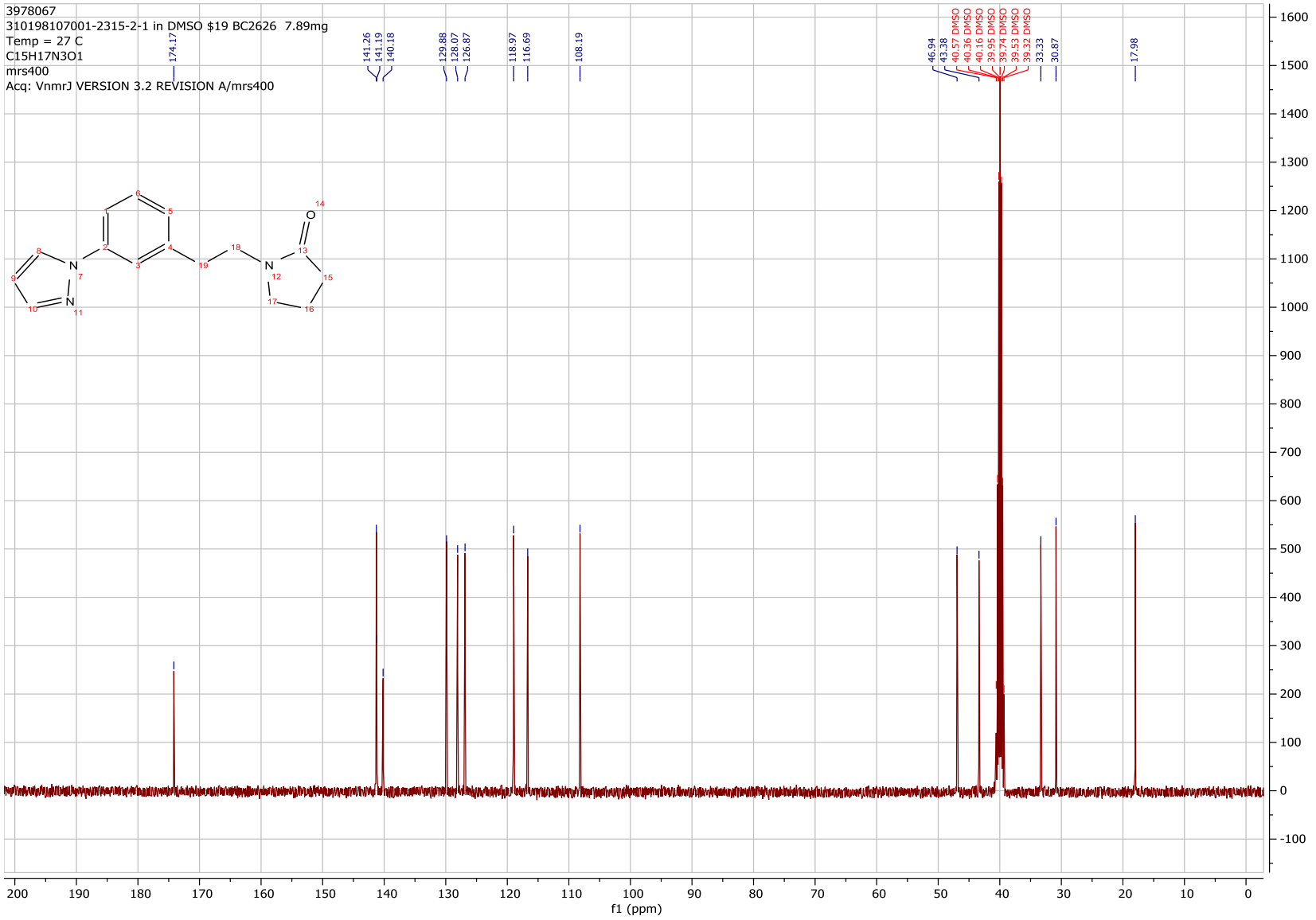
Compound 2 ^{13}C NMR



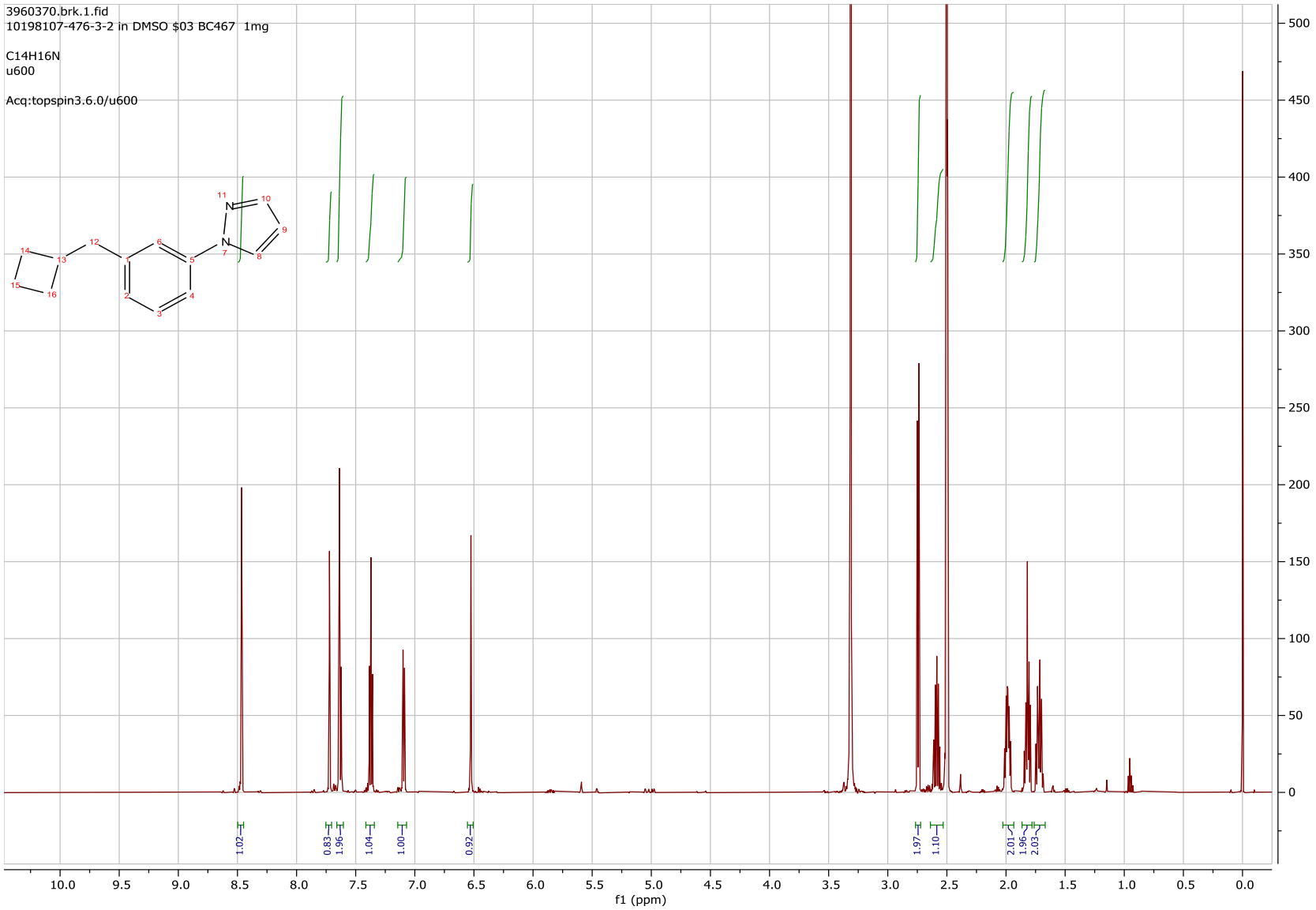
Compound 16 ^{1}HNMR



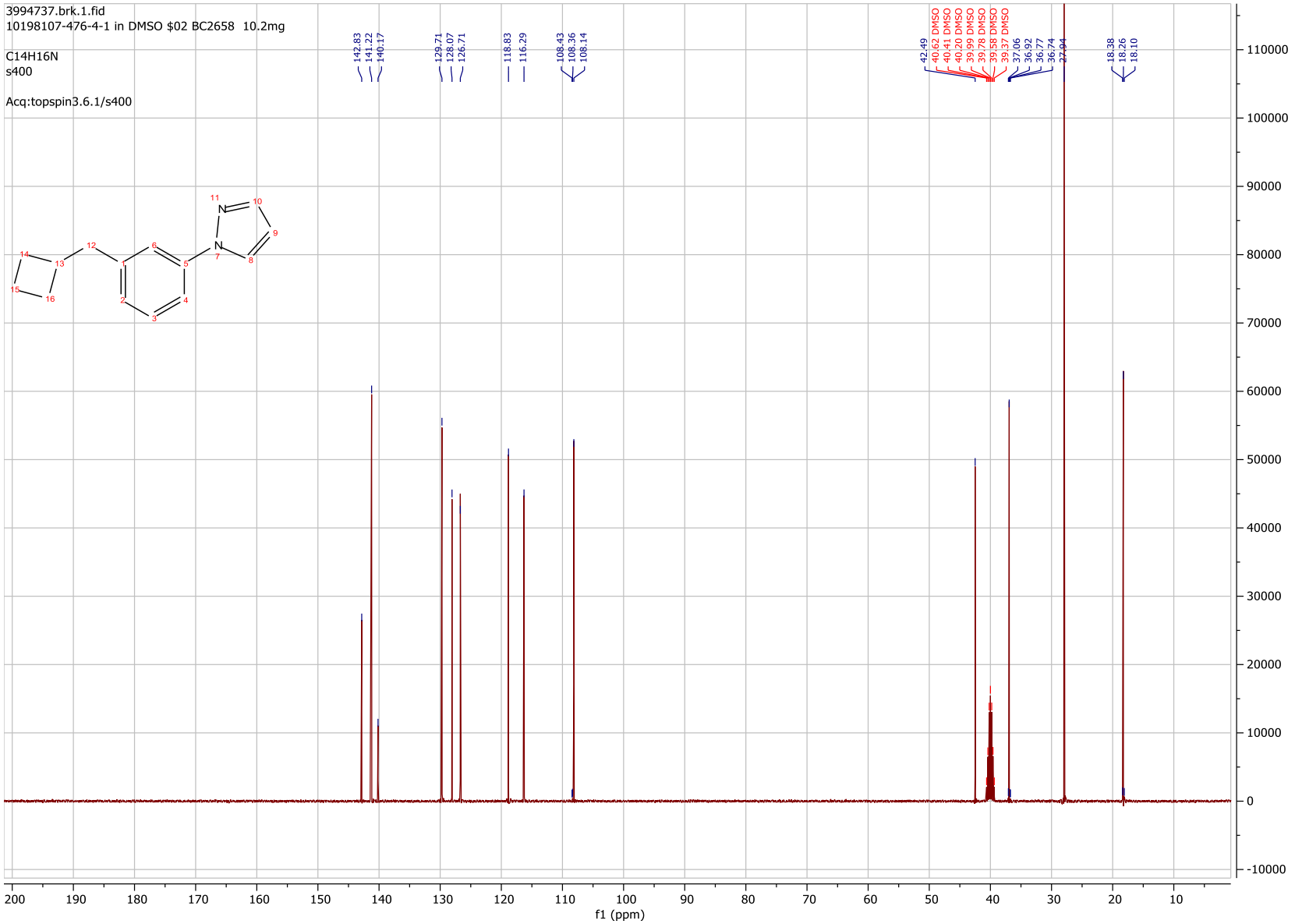
Compound 16 ^{13}C NMR



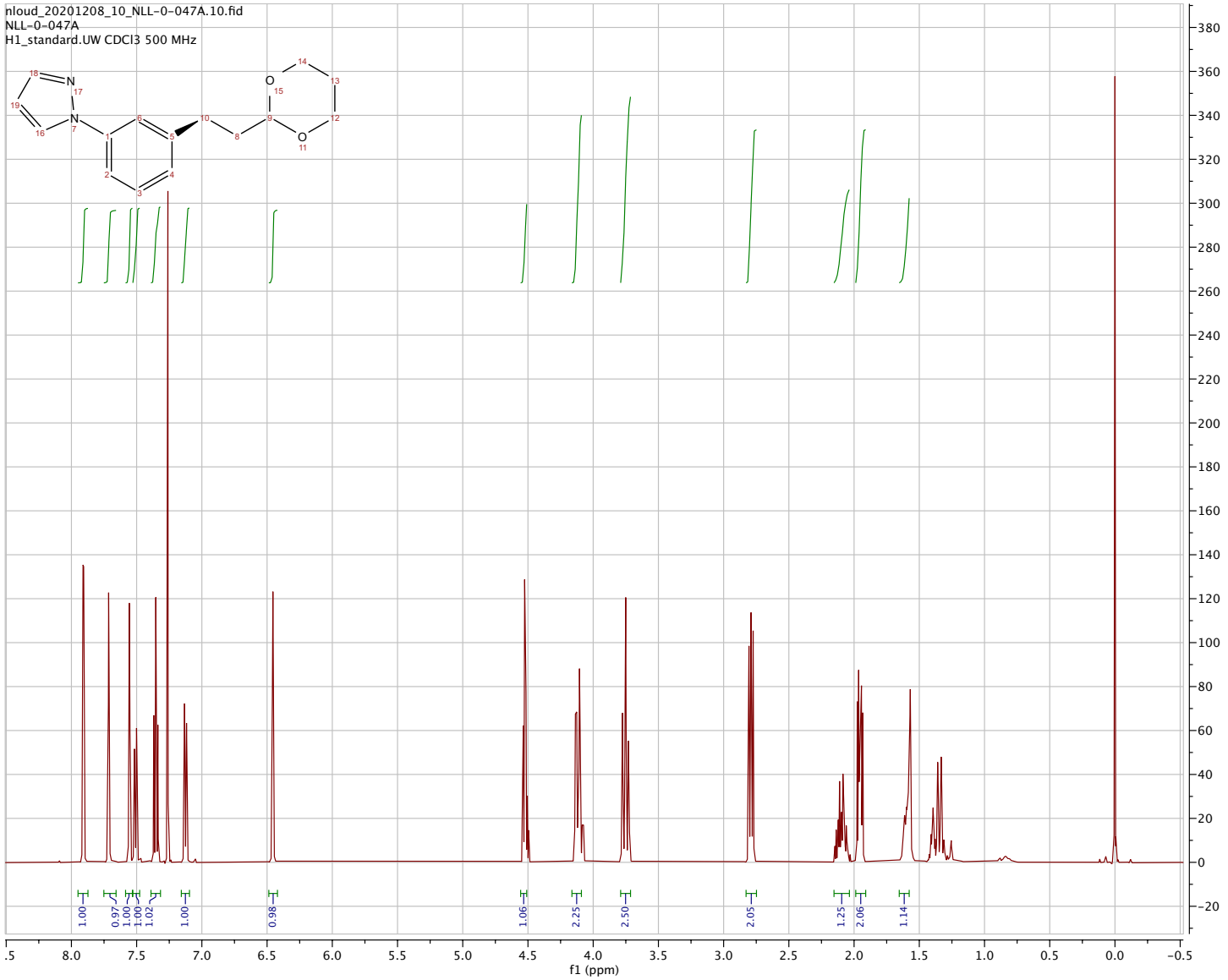
Compound 17 ^{1}HNMR



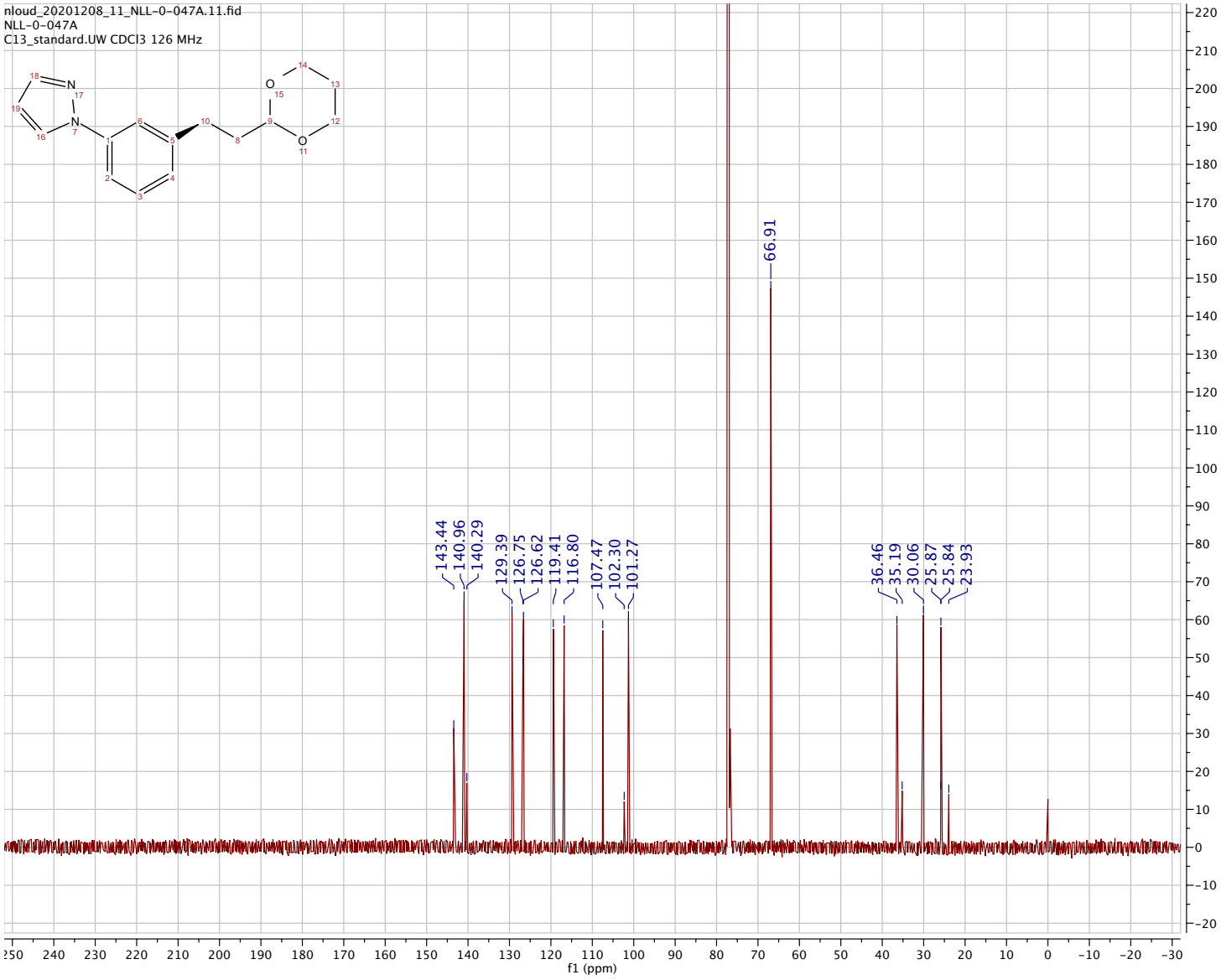
Compound 17 ^{13}C NMR



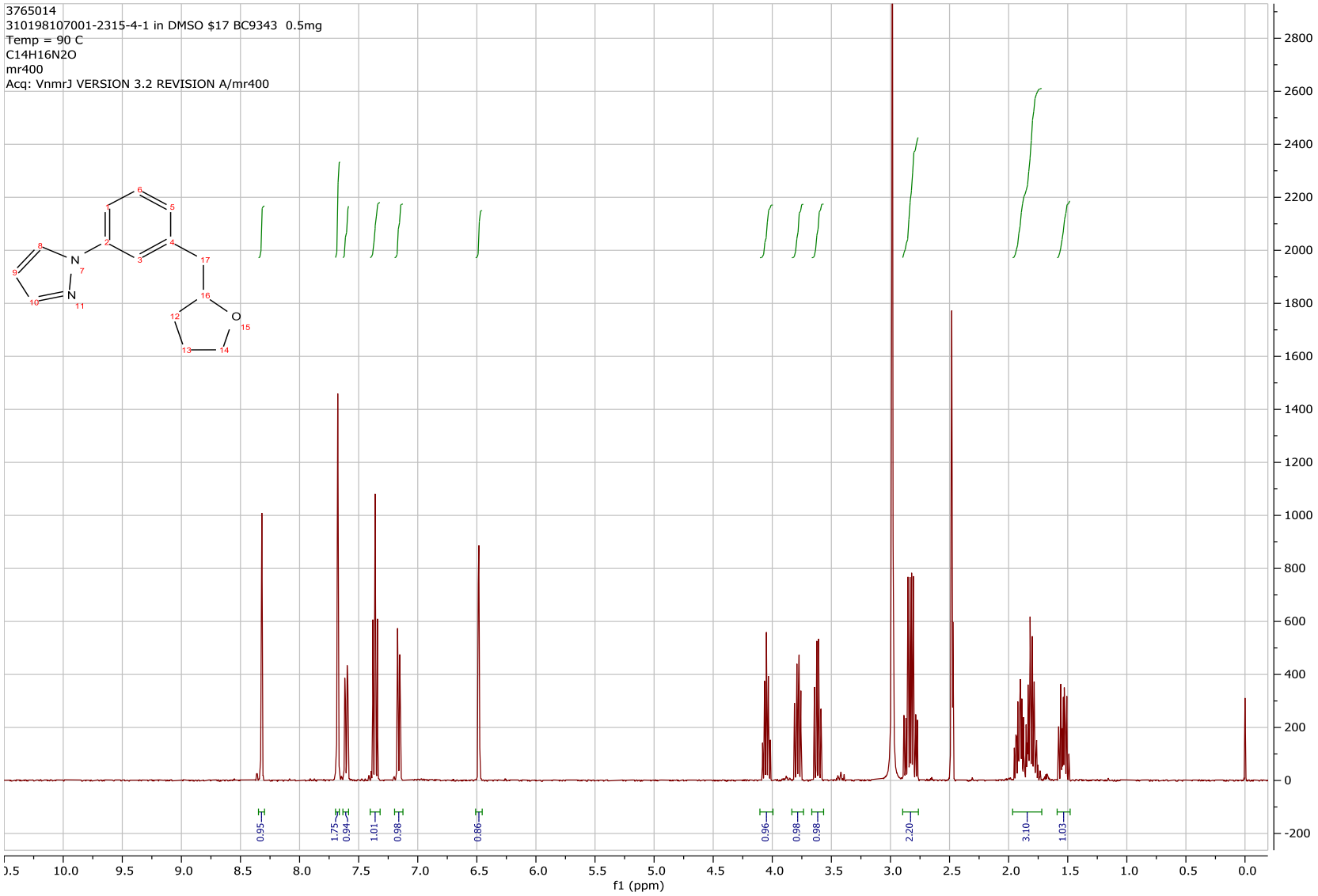
Compound 19 ^{1}HNMR



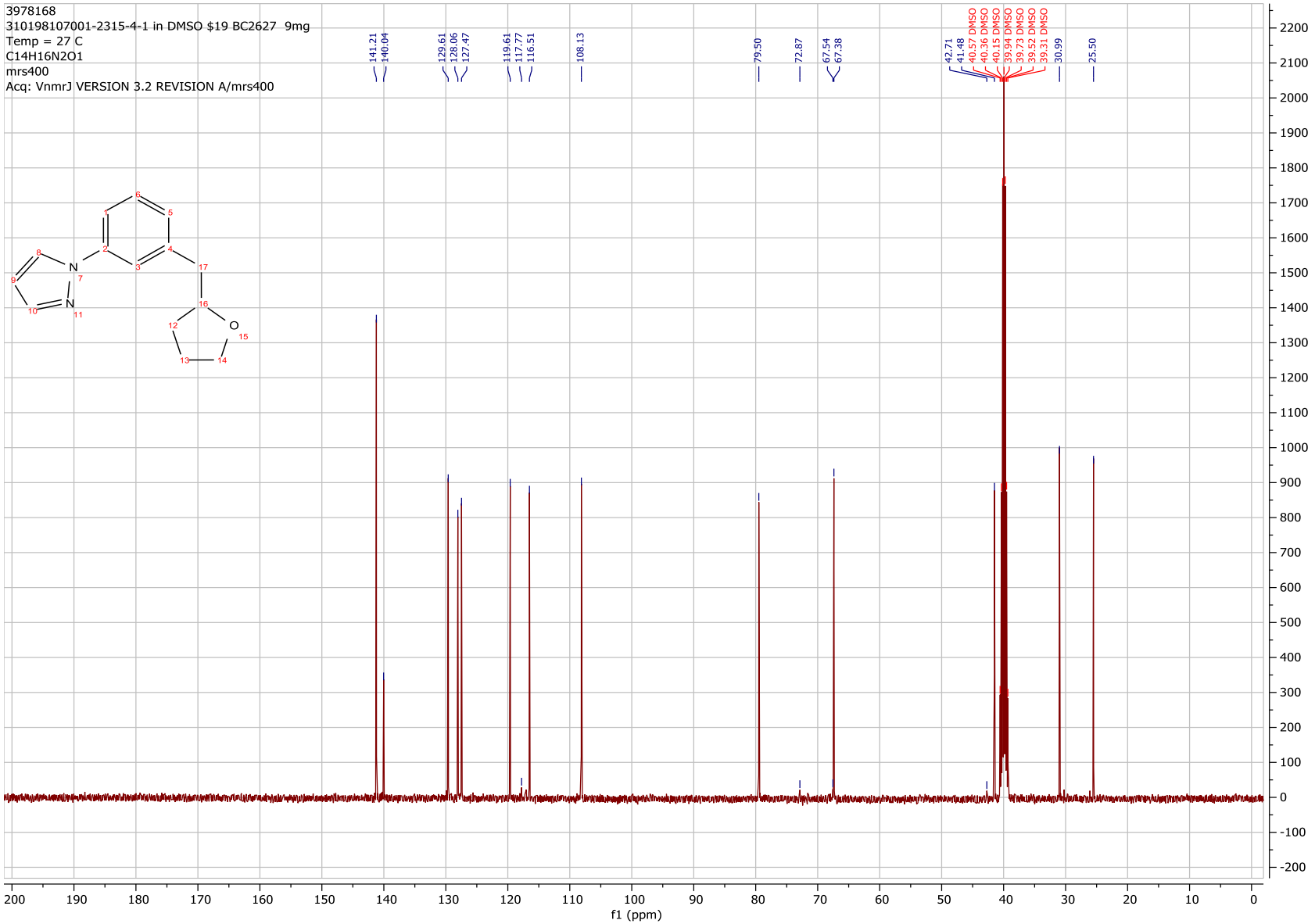
Compound 19 ^{13}C NMR



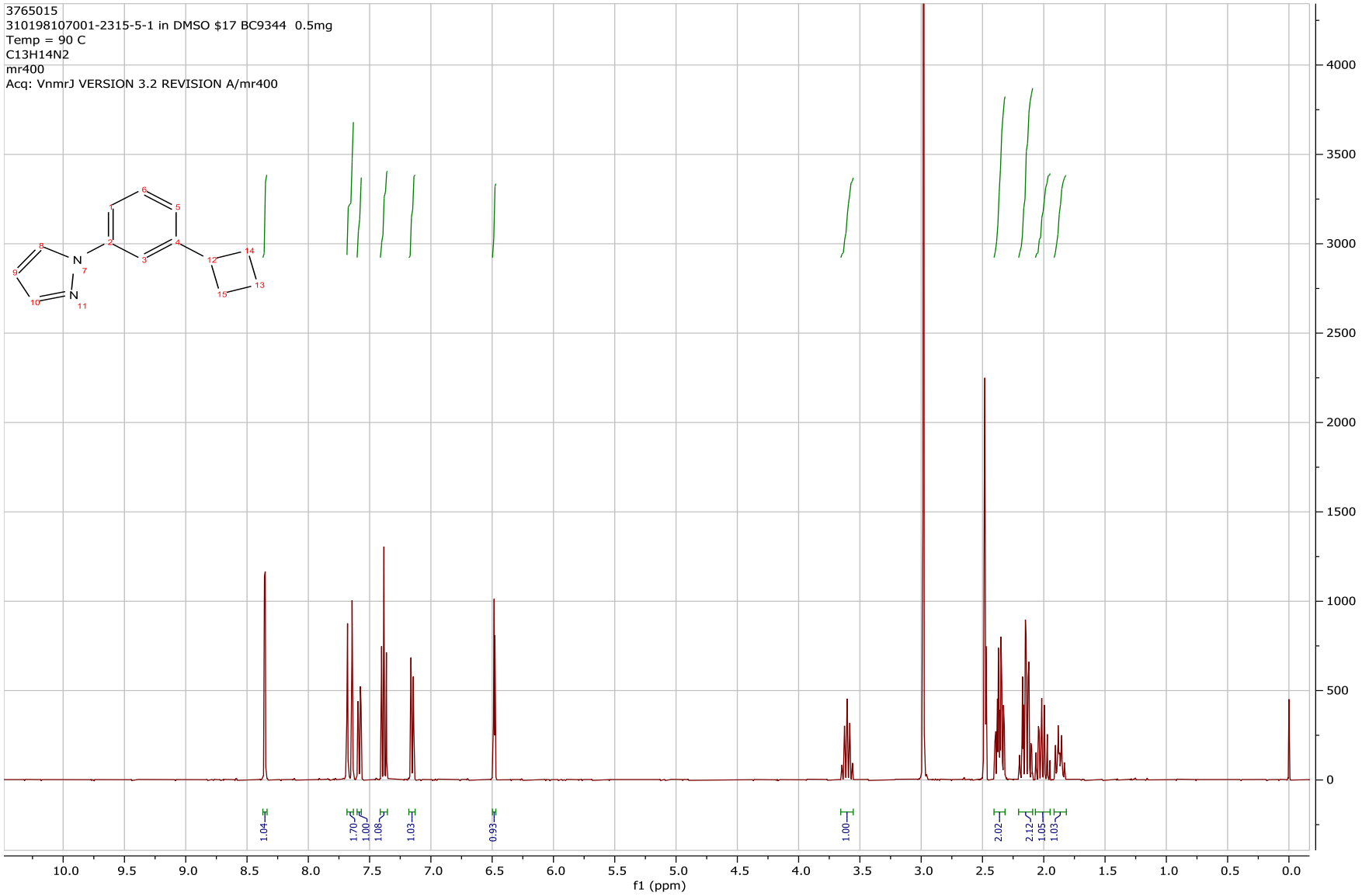
Compound 23 ^{1}H NMR



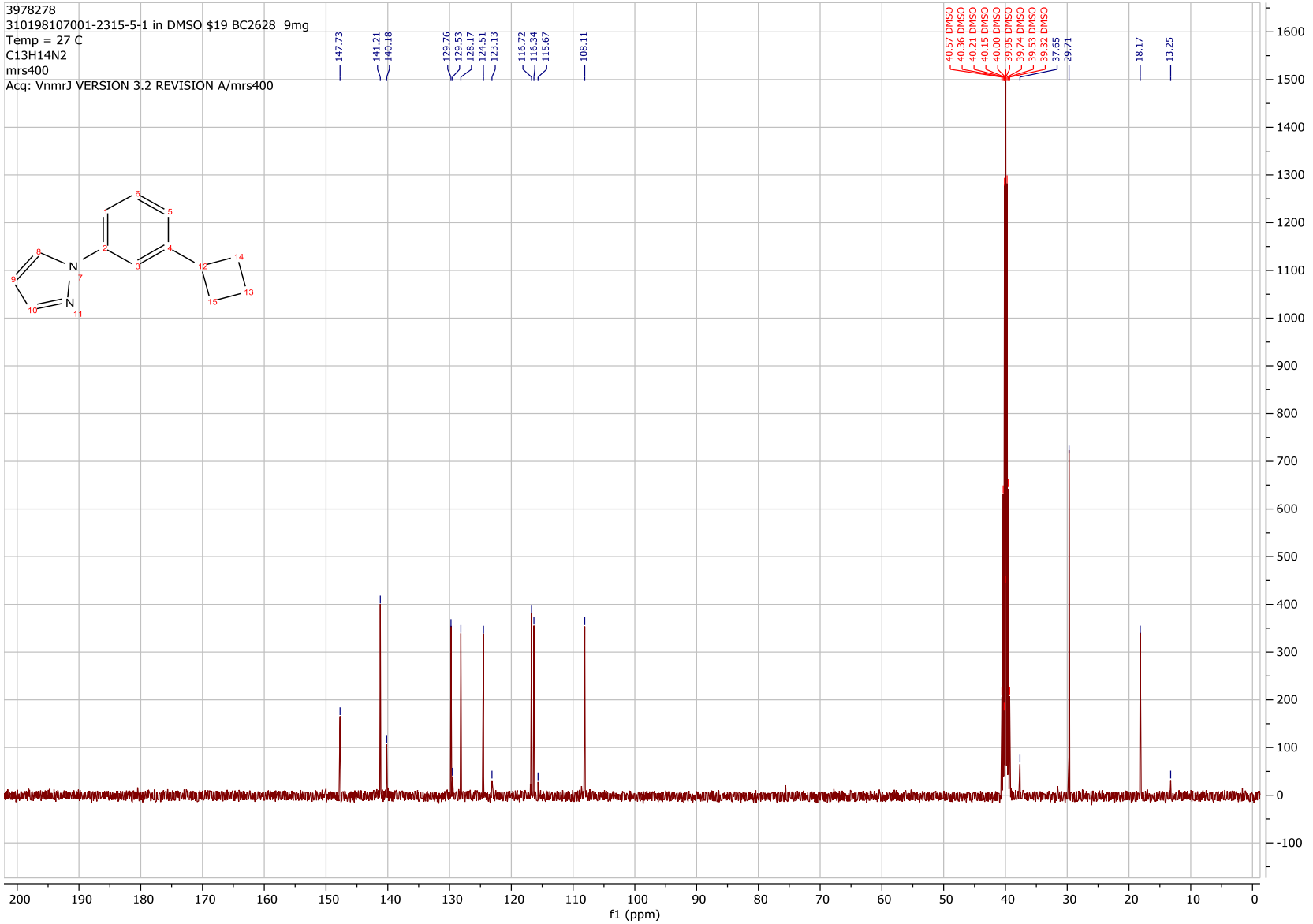
Compound 23 ^{13}C NMR



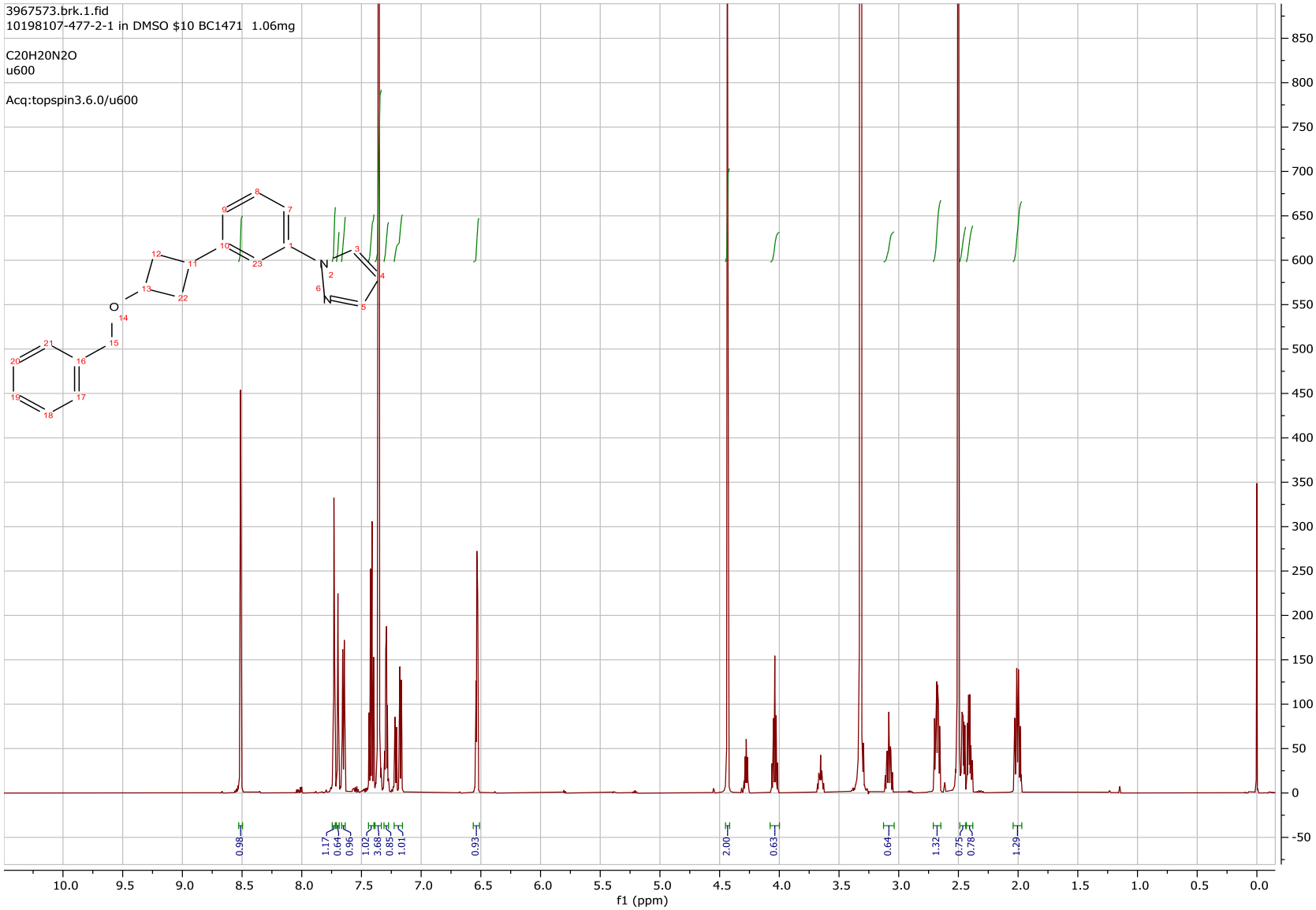
Compound 24 ^{1}HNMR



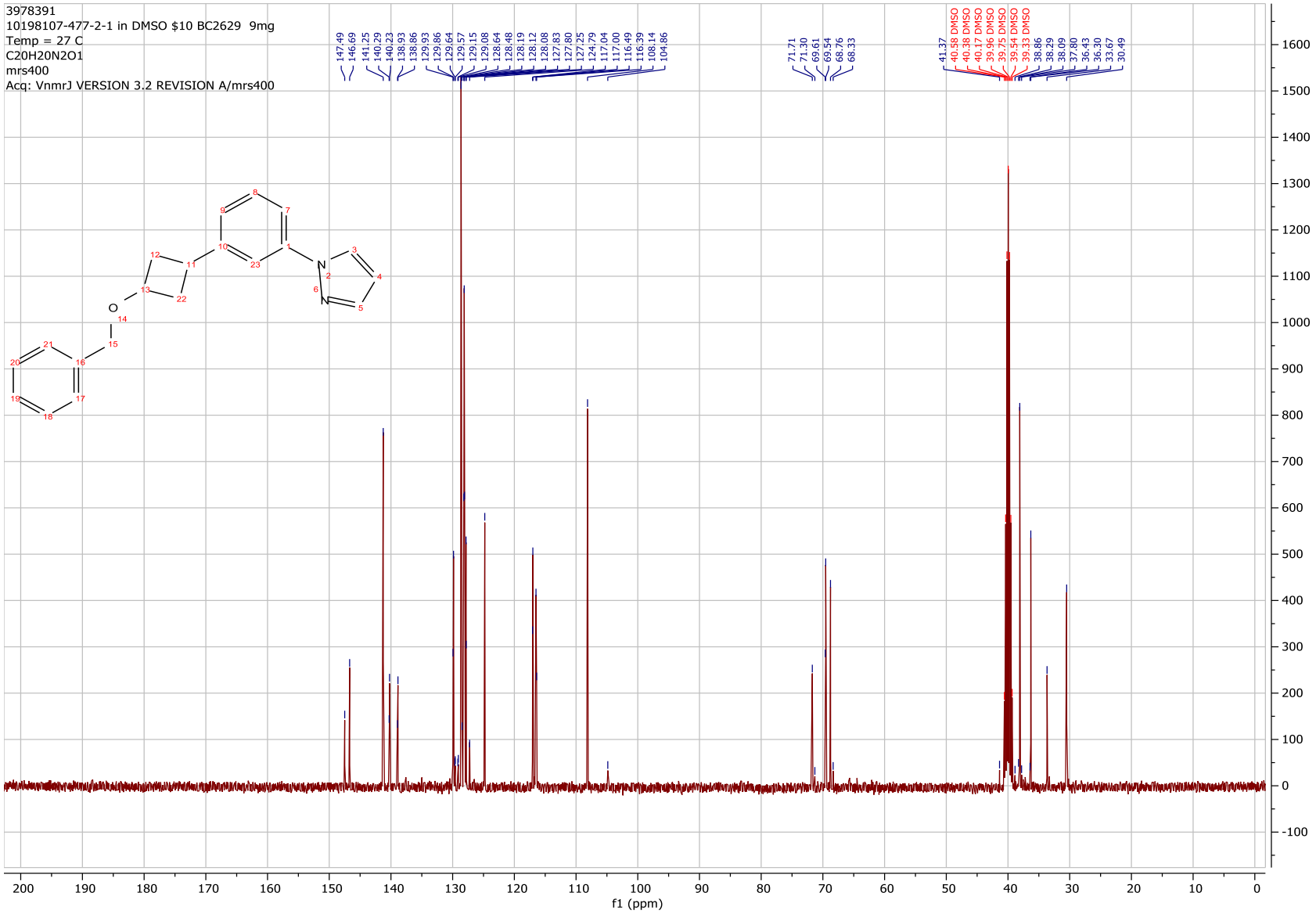
Compound 24 ^{13}C NMR



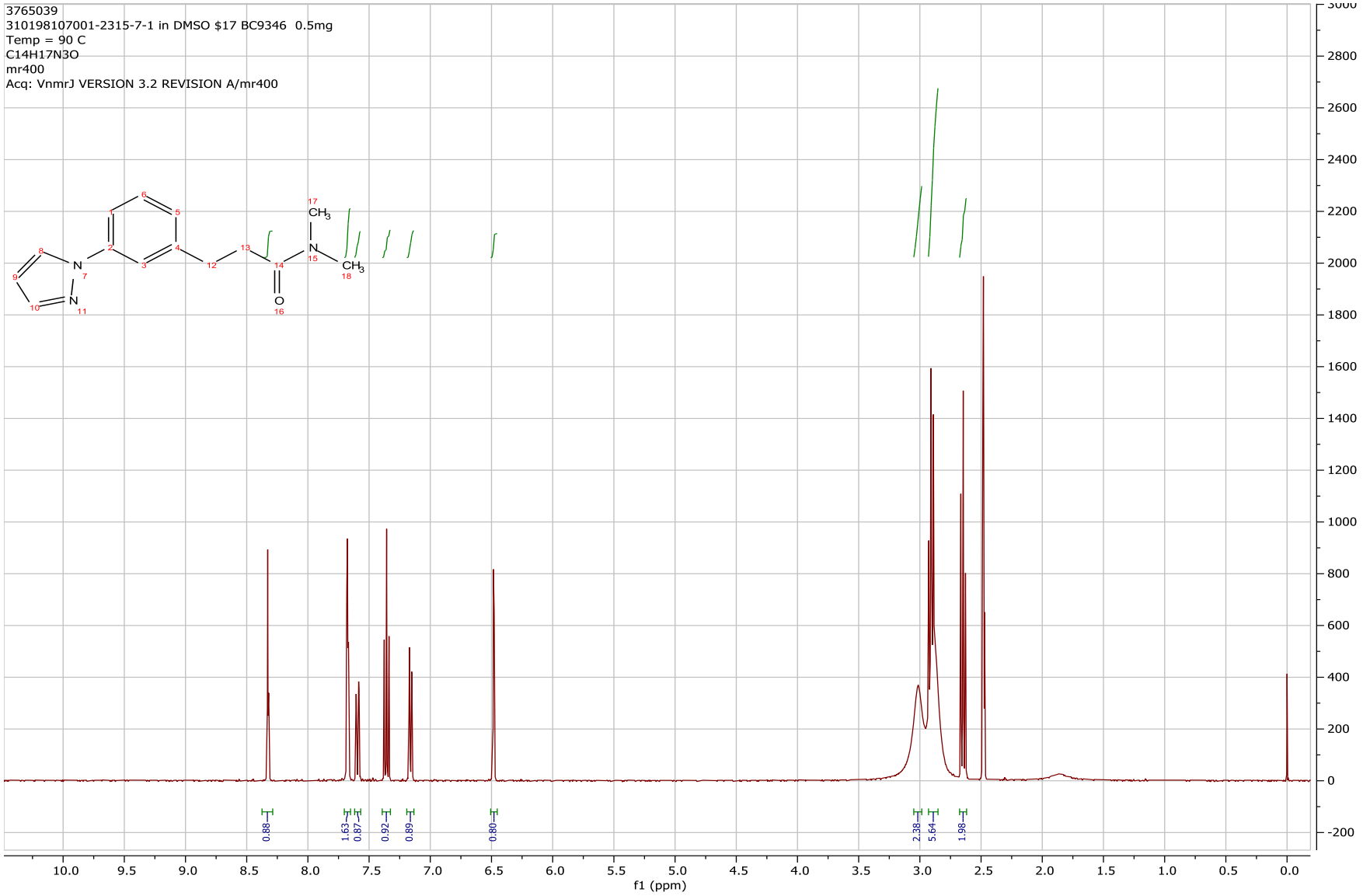
Compound 35 ^{1}HNMR



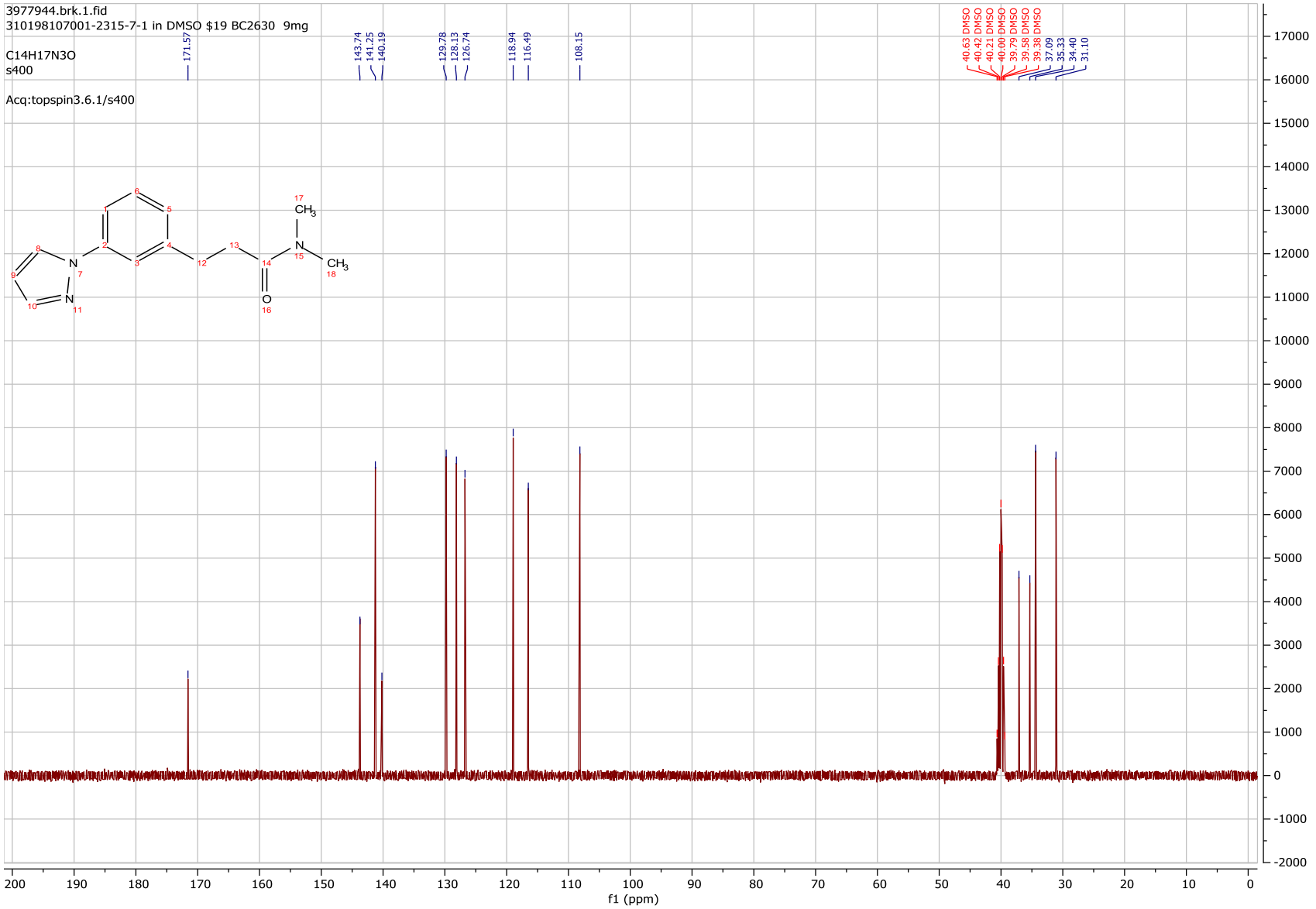
Compound 35 ^{13}C NMR



Compound 37 ^{1}HNMR



Compound 37 ^{13}C NMR



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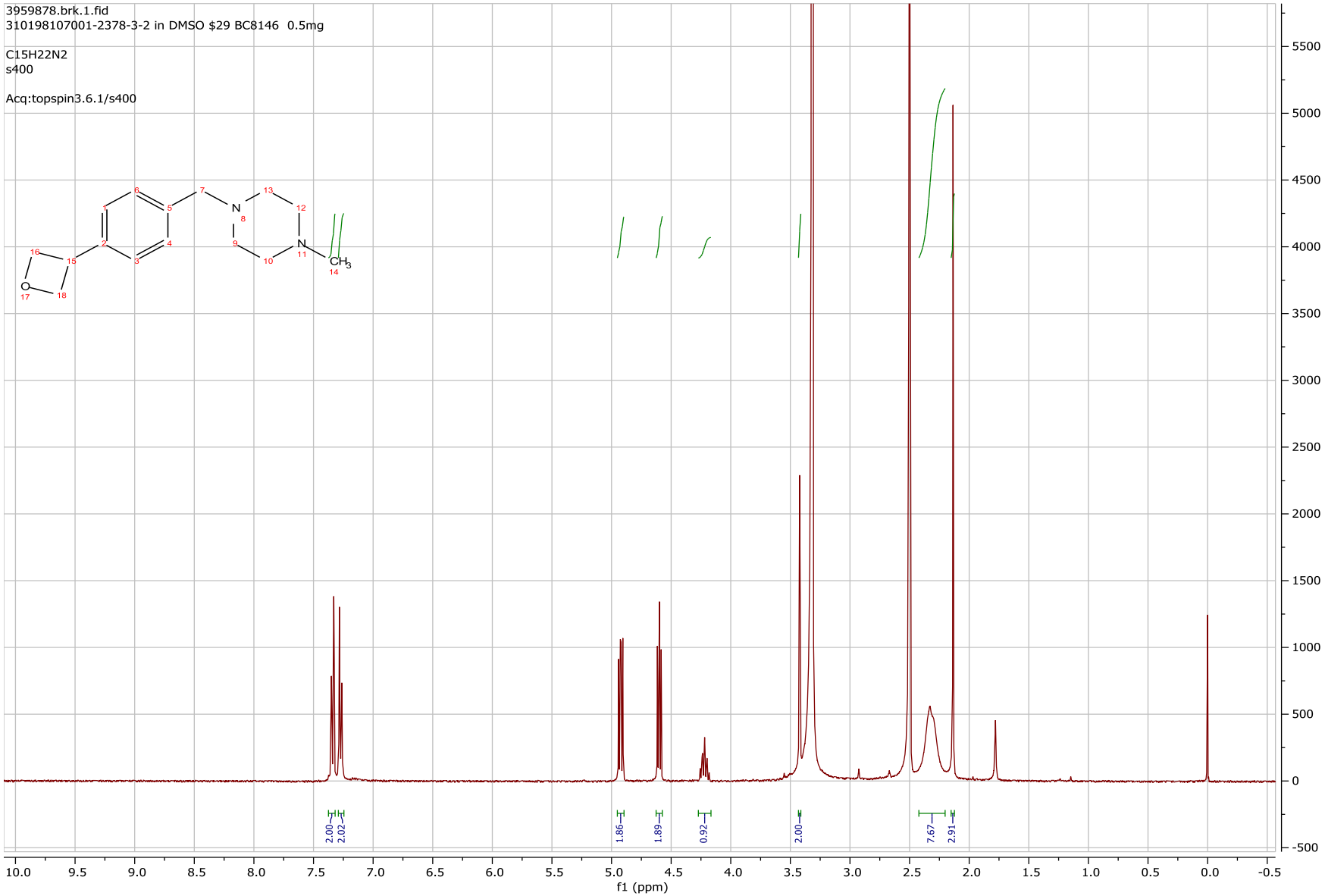
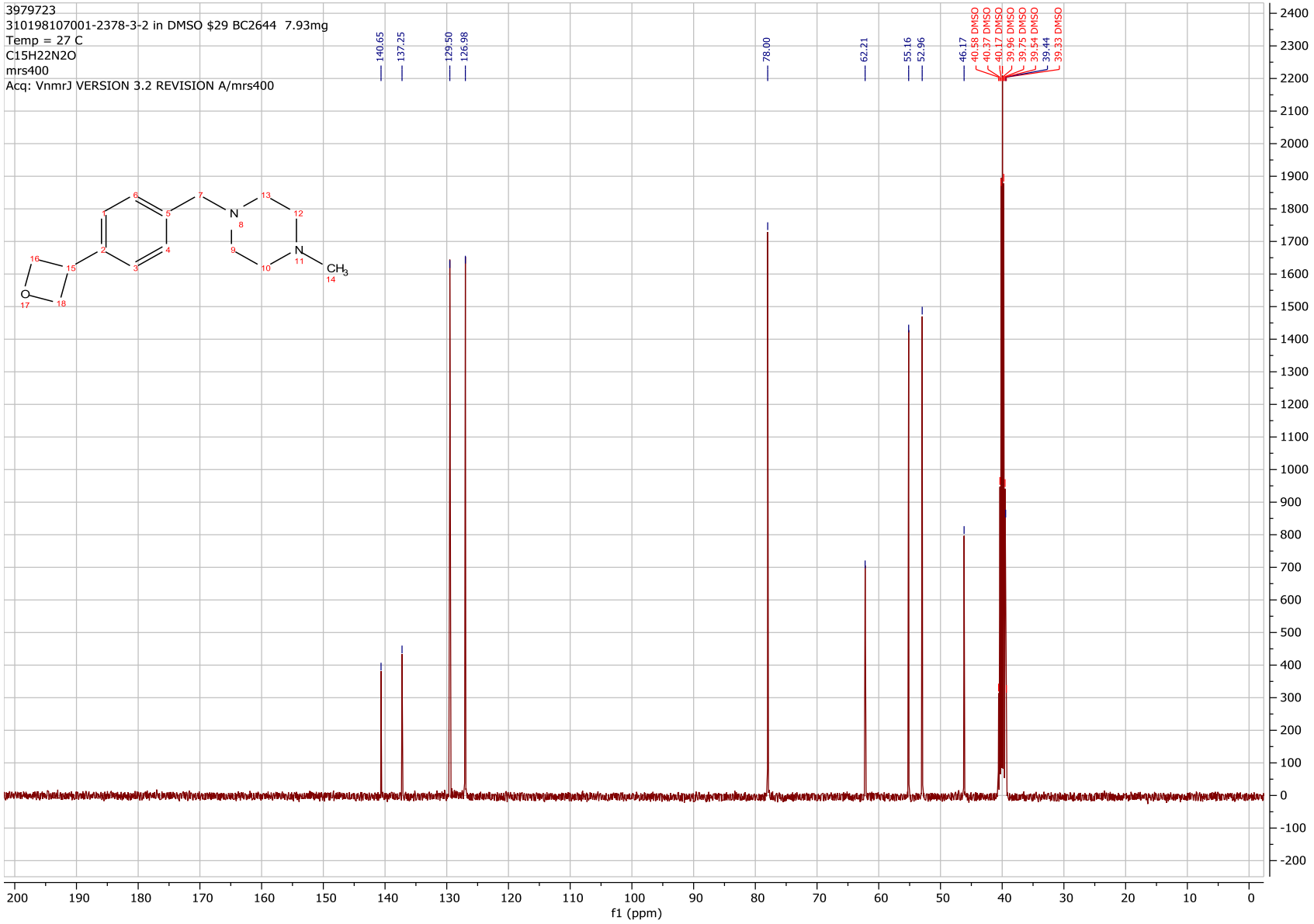
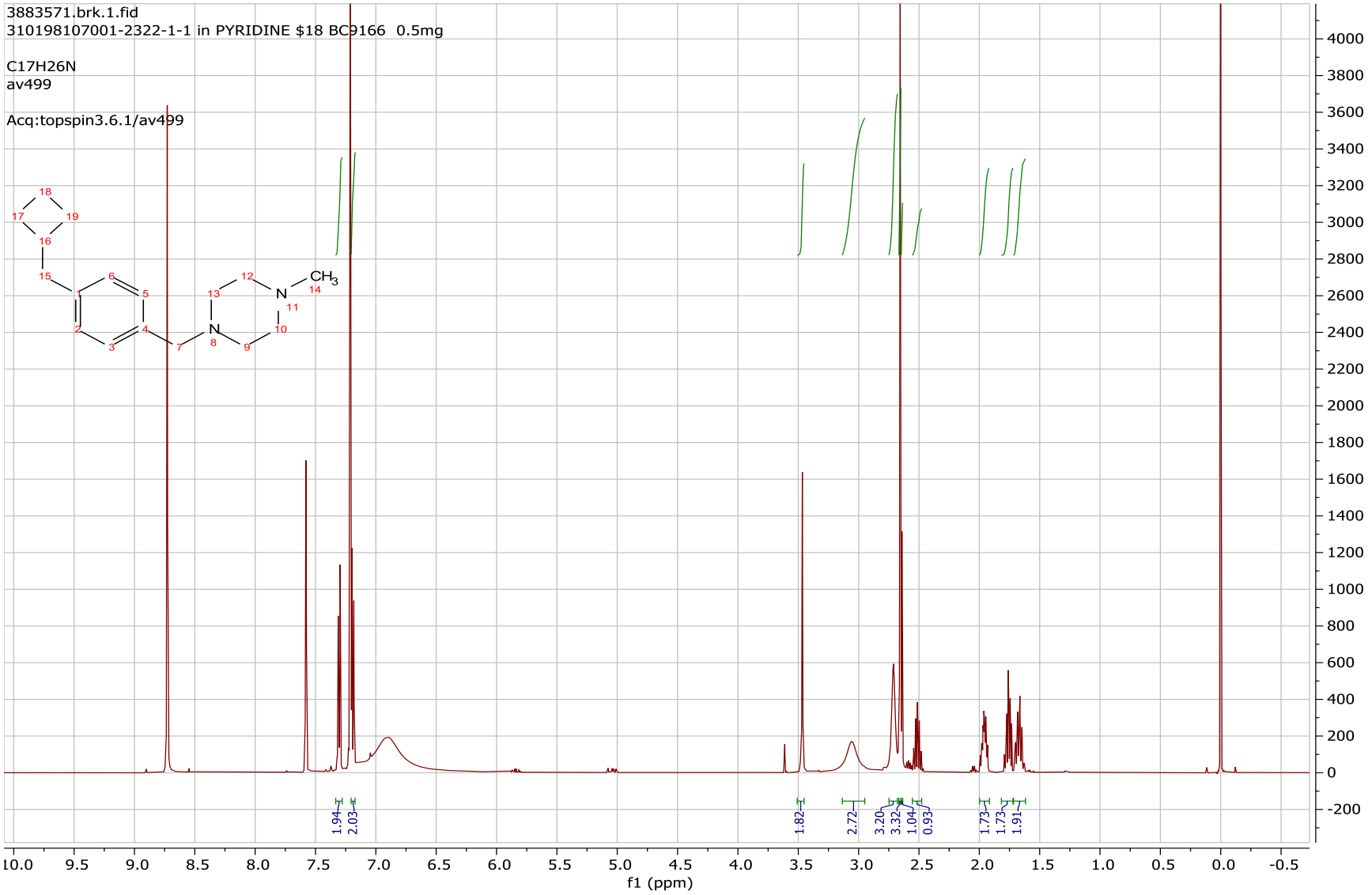


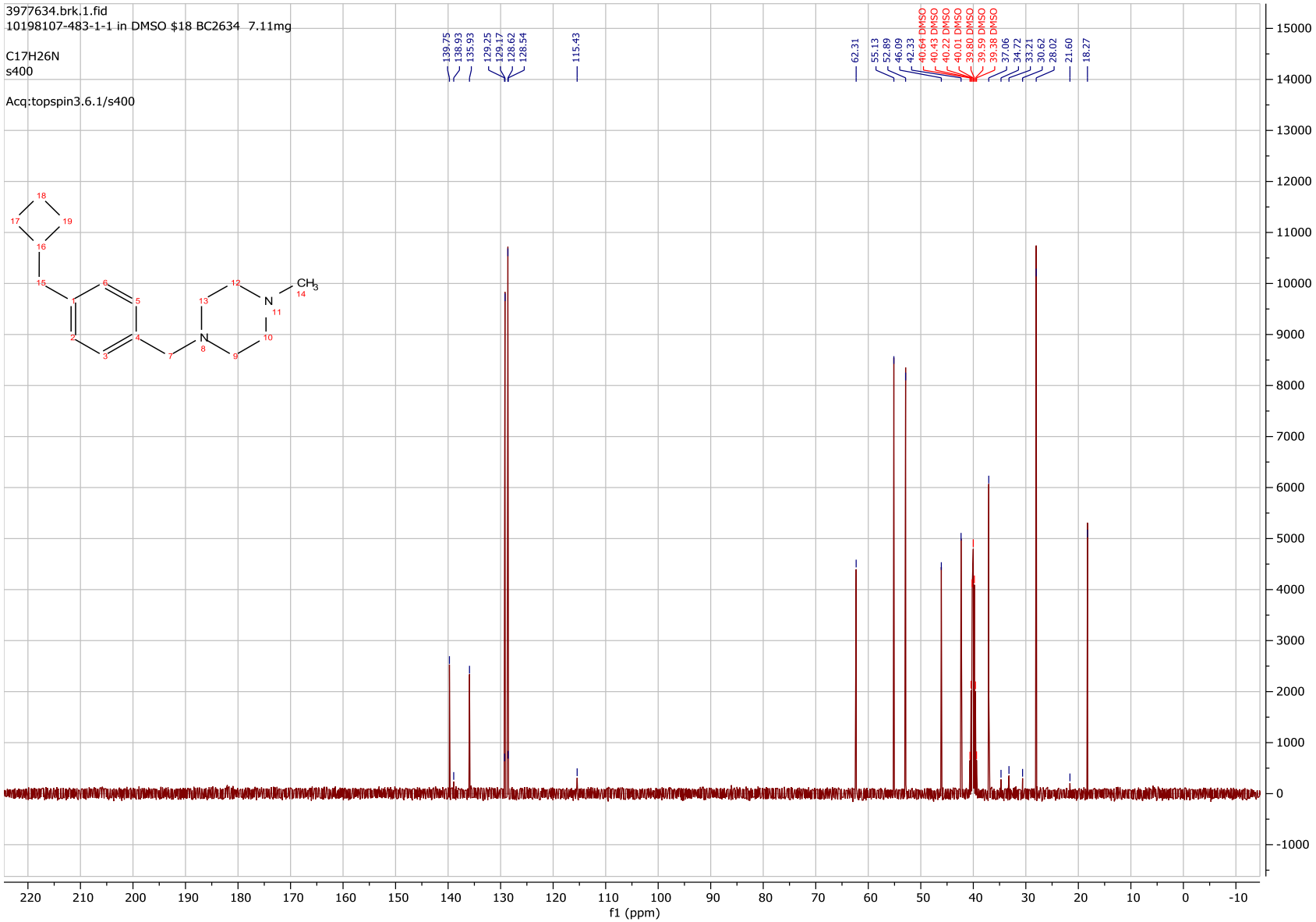
Compound 40 ^{13}C NMR



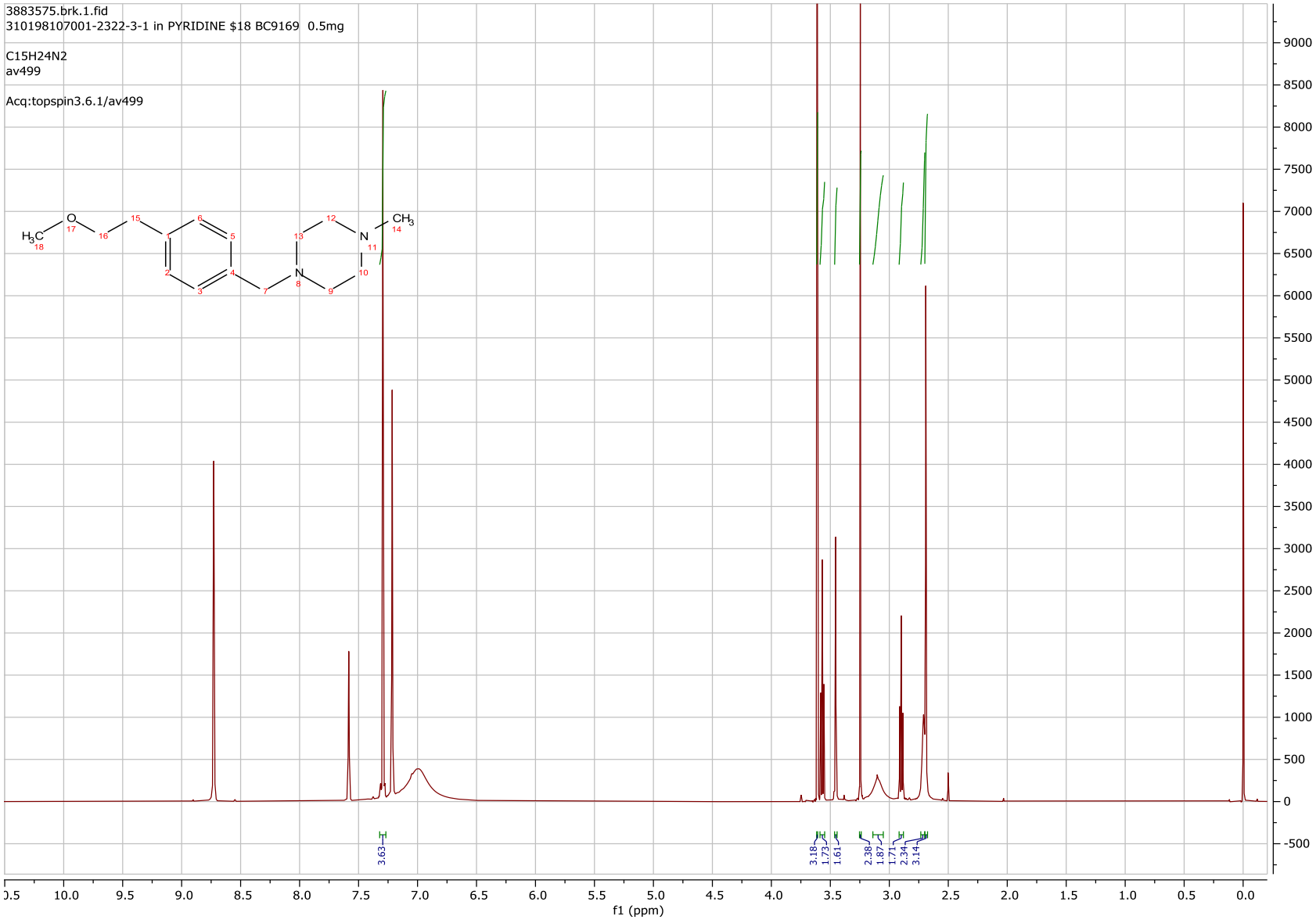
Compound 54 ^{1}HNMR



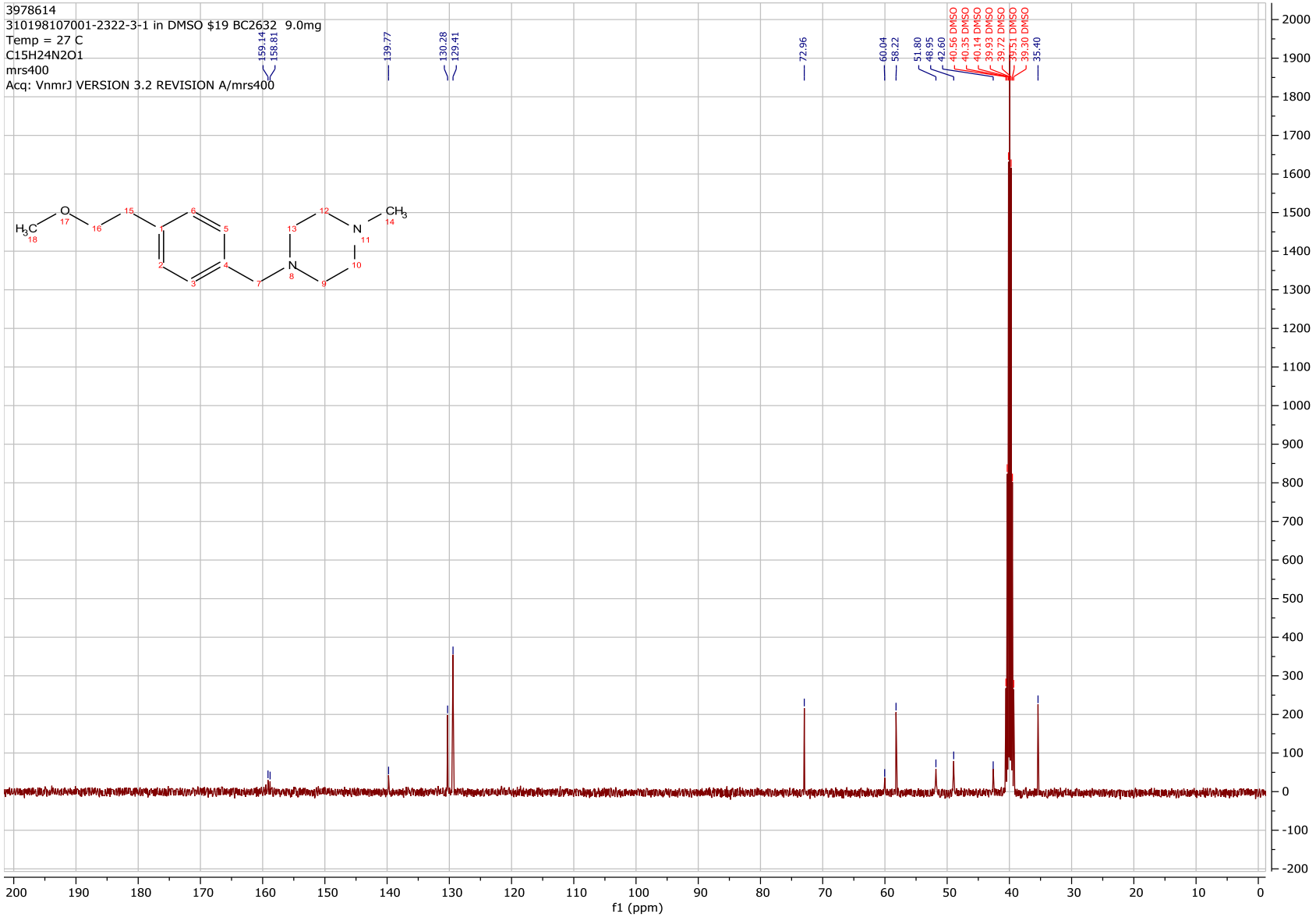
Compound 54 ^{13}C NMR



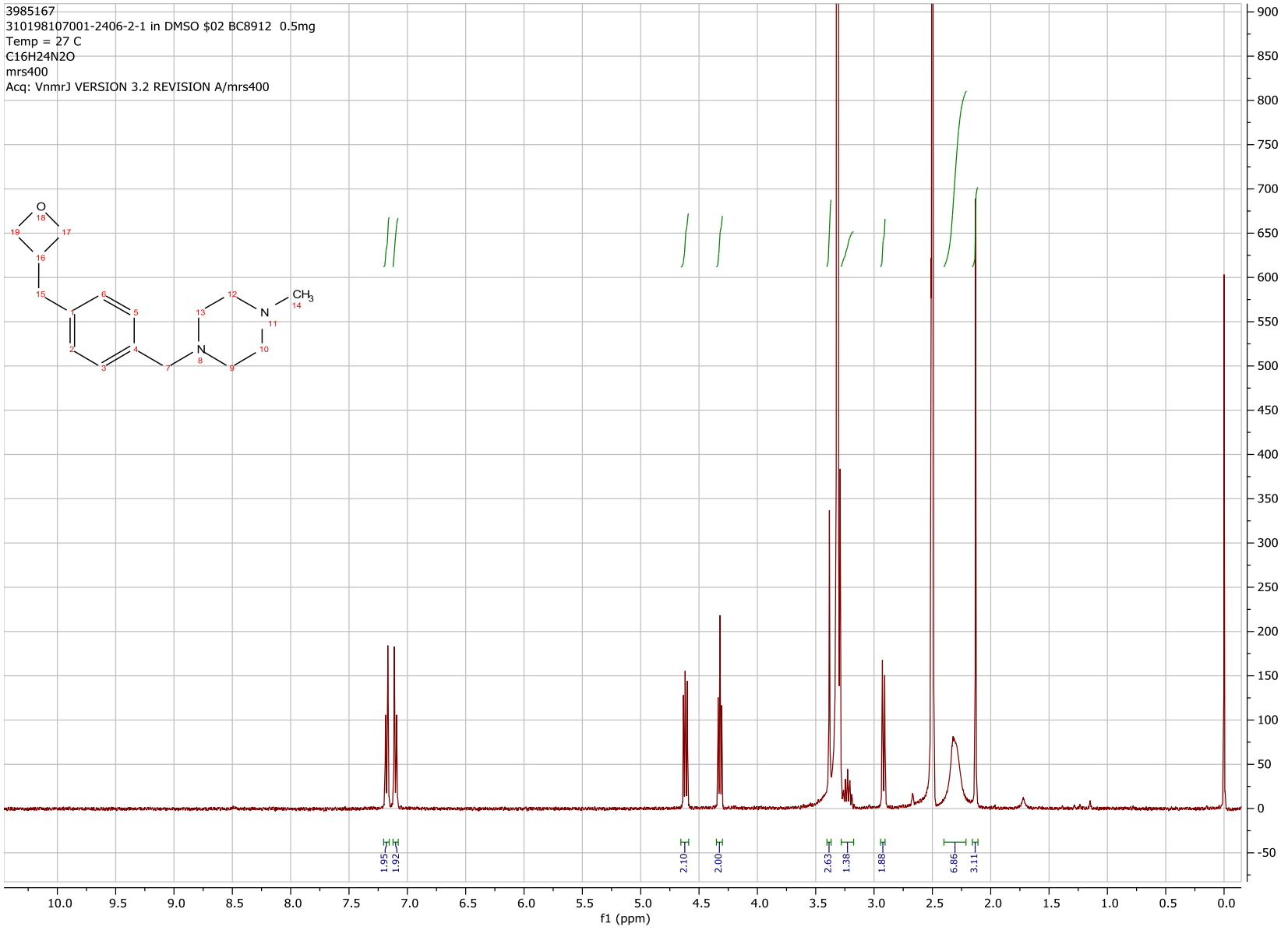
Compound 57 ^{1}HNMR



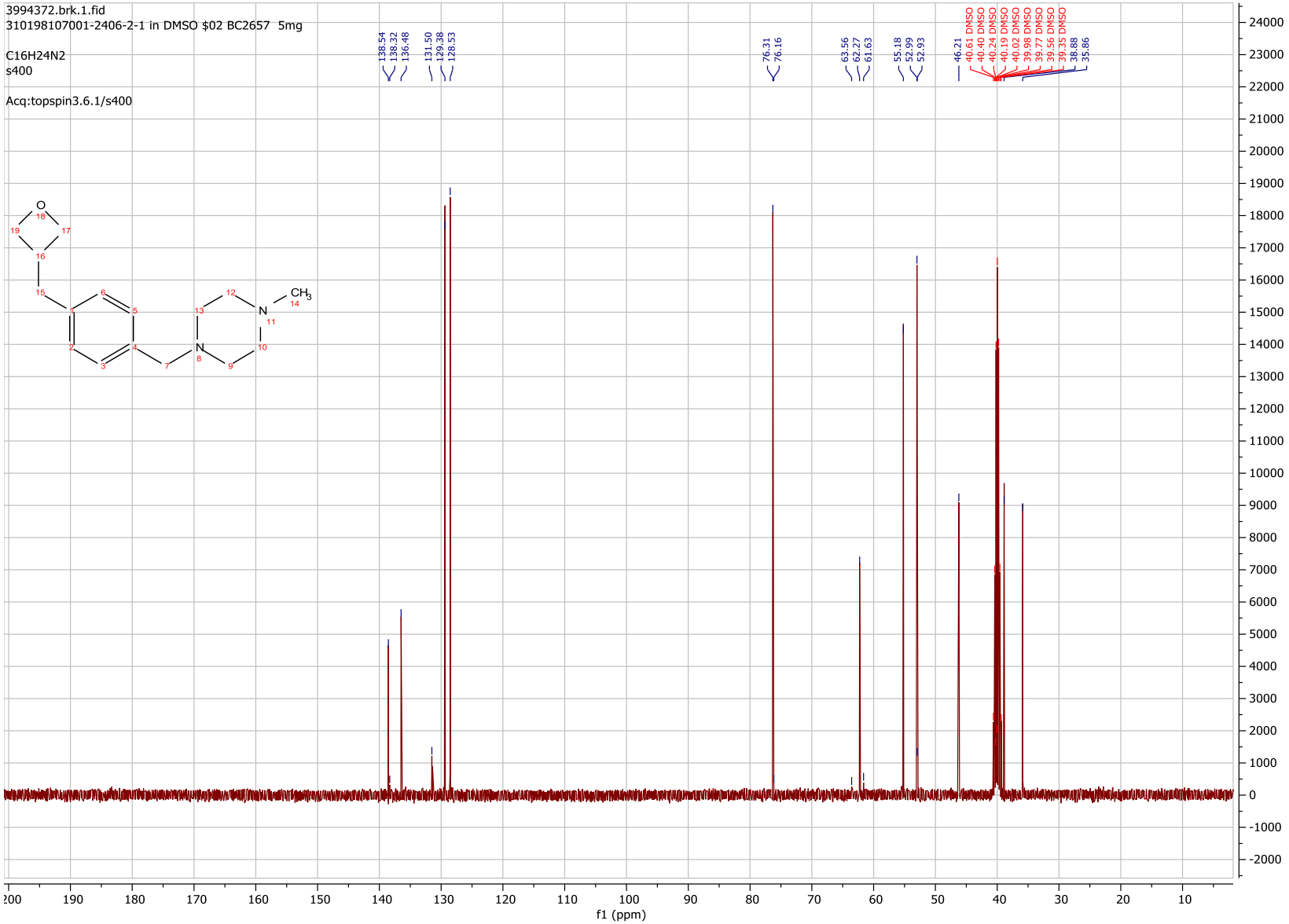
Compound 57 ^{13}C NMR



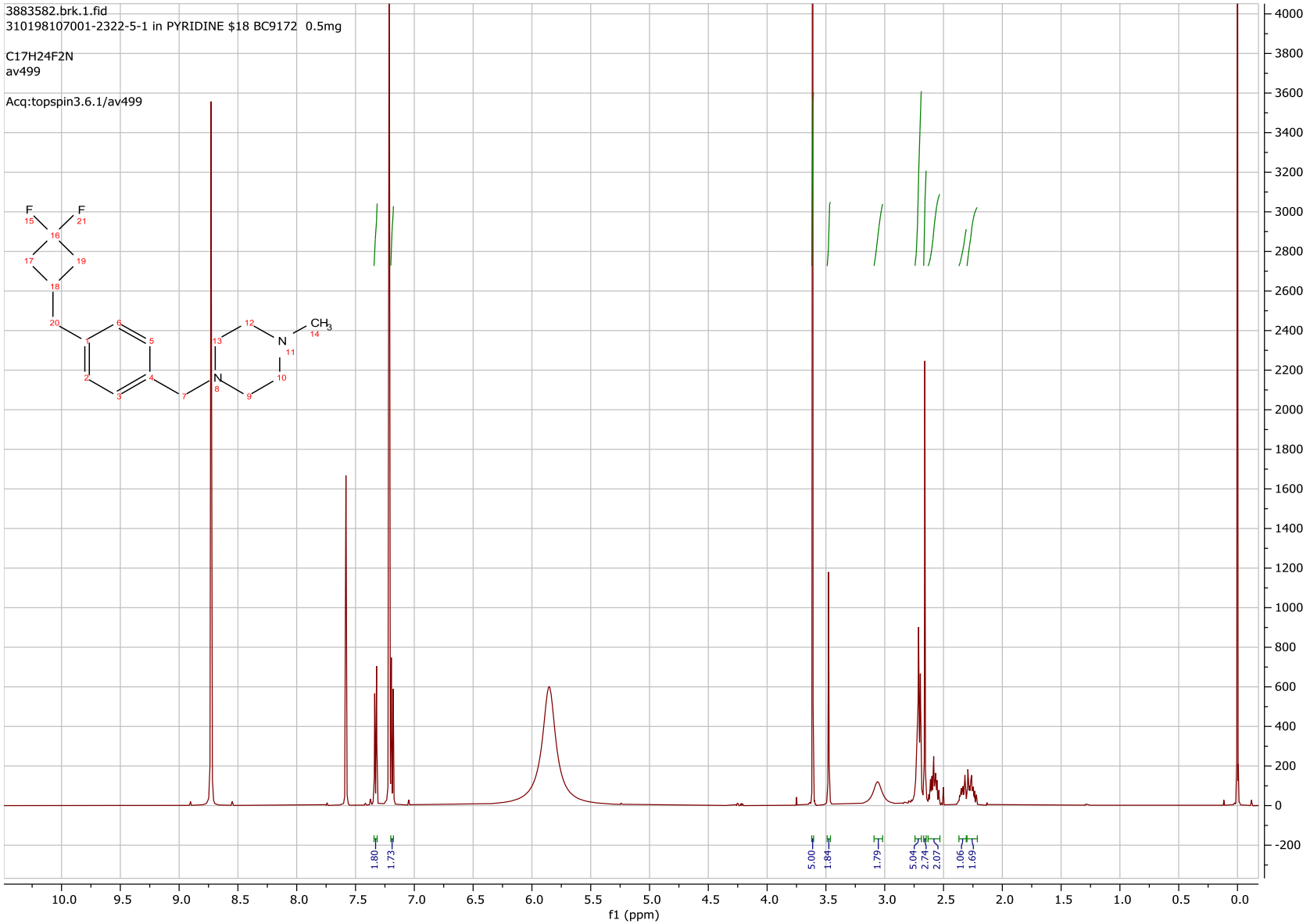
Compound 58 ^{1}HNMR



Compound 58 ^{13}C NMR



Compound 59 ^{1}HNMR



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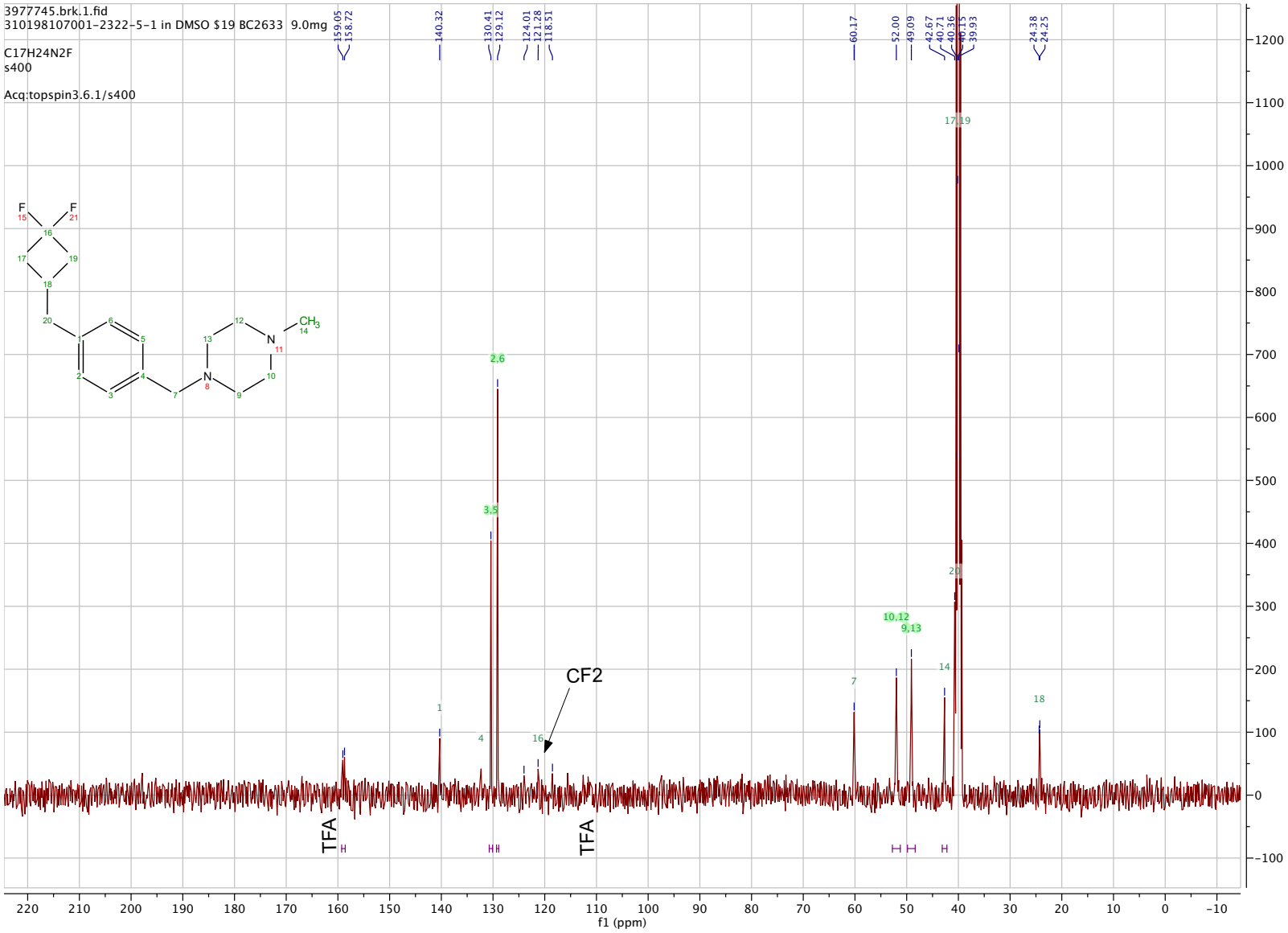
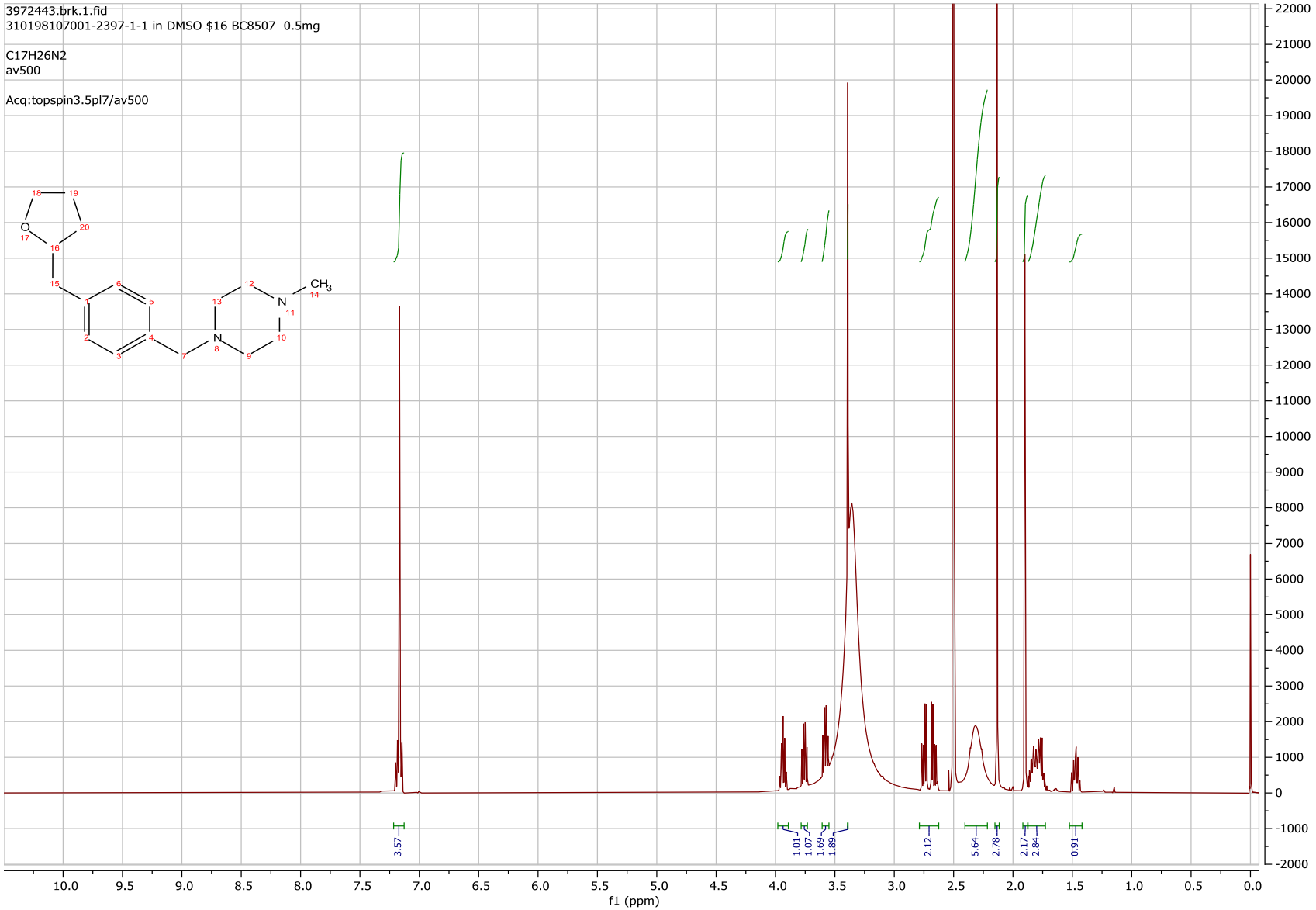
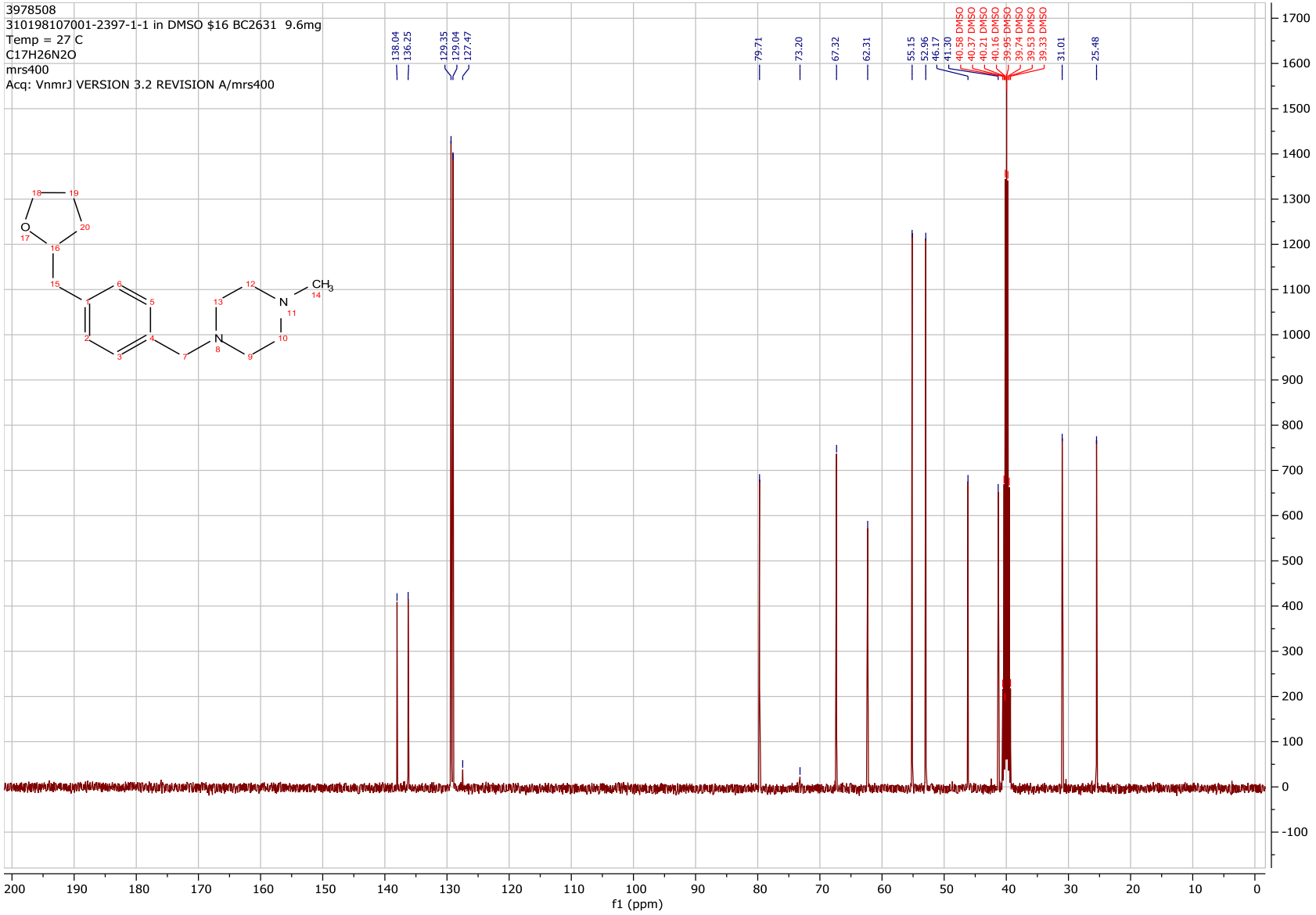


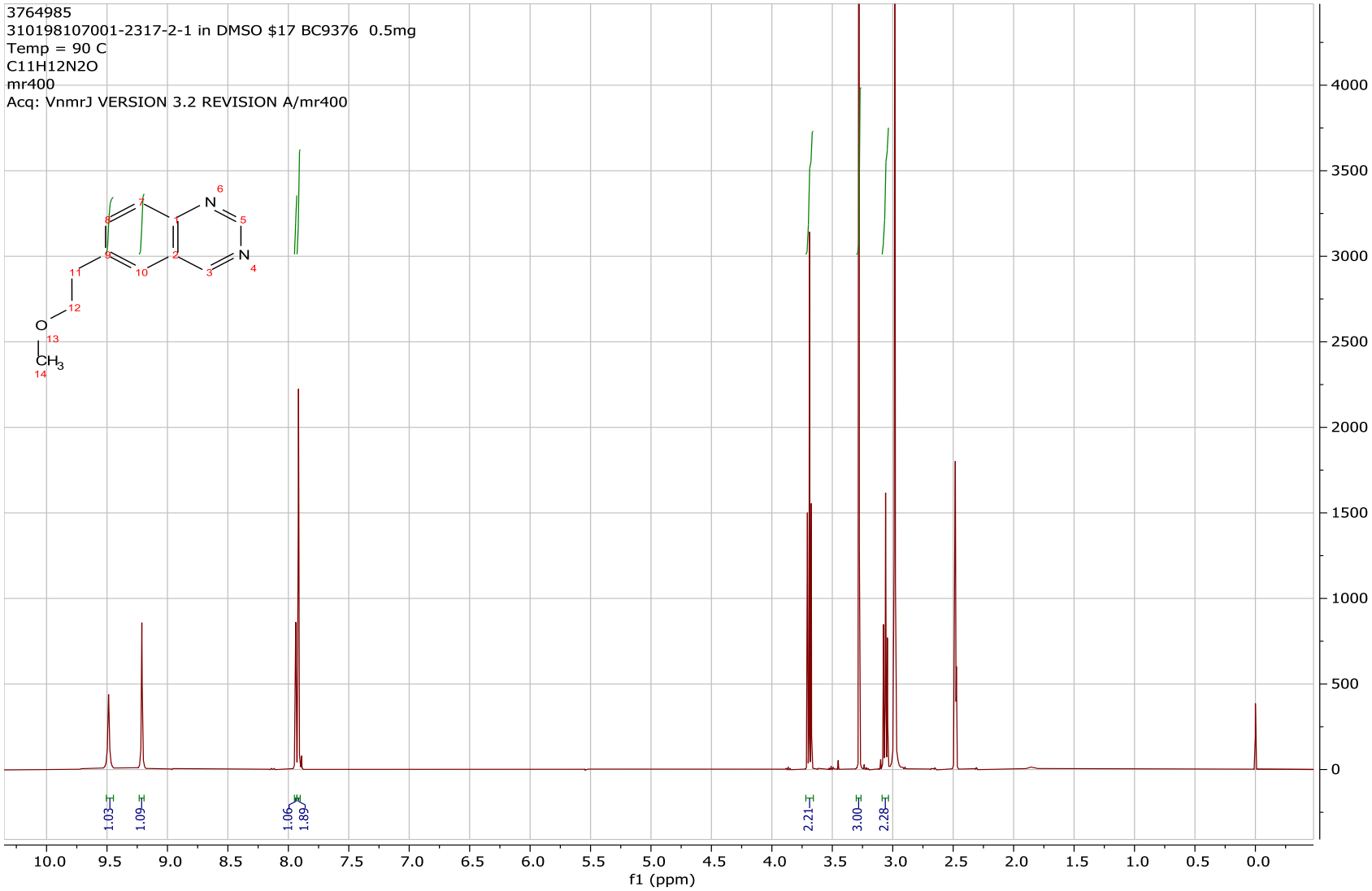
Compound 60 ^{1}HNMR



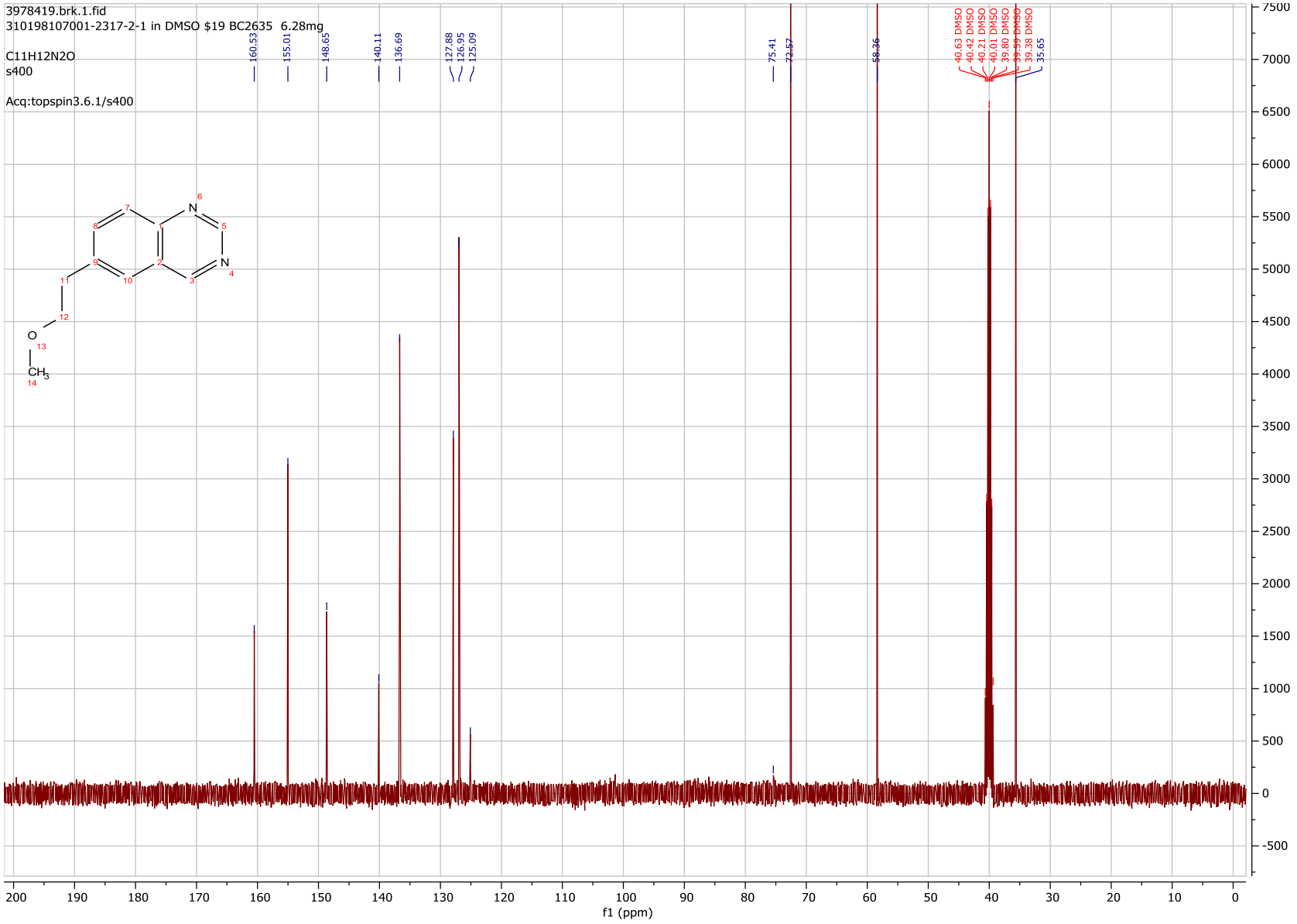
Compound 60 ^{13}C NMR



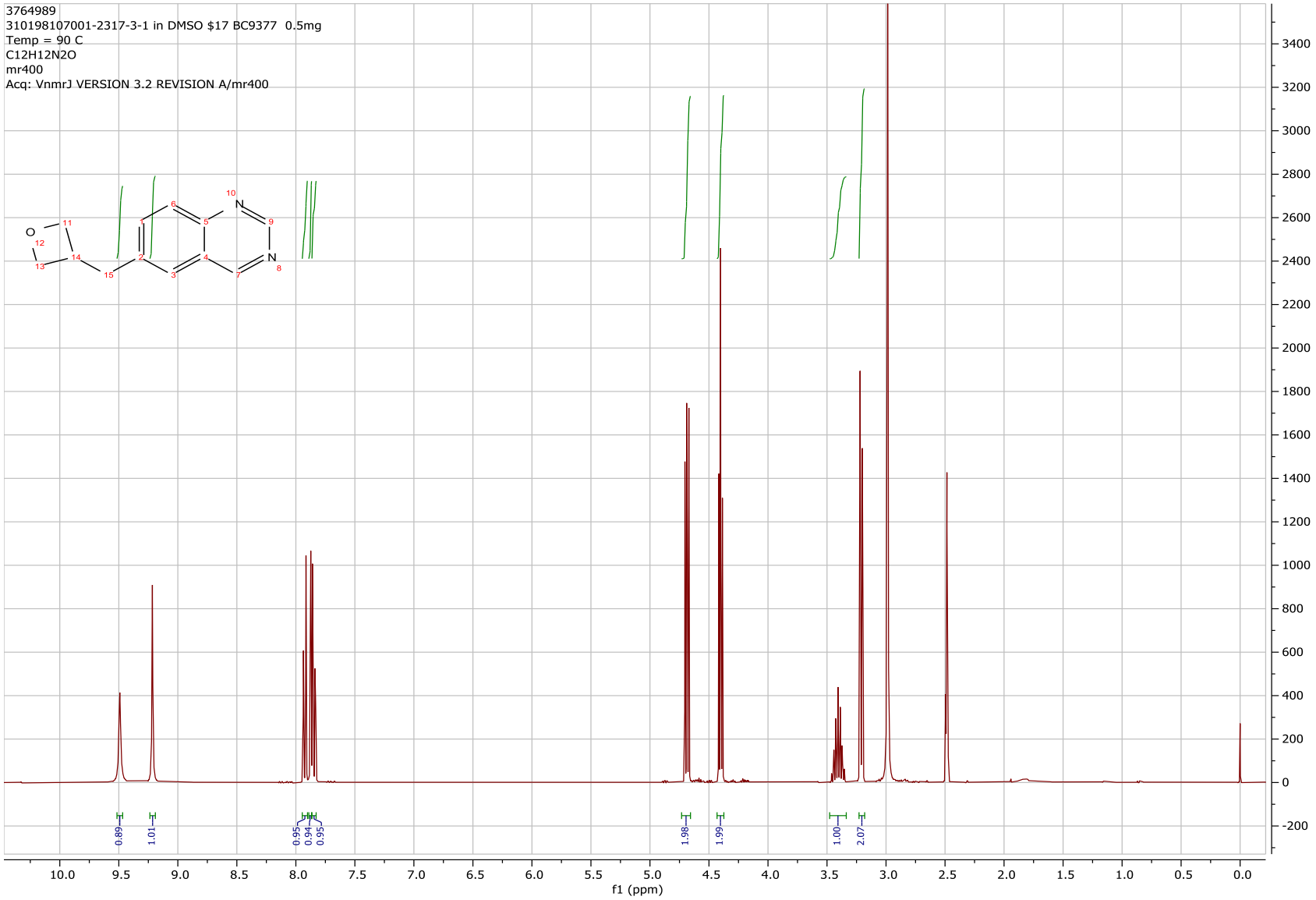
Compound 94 ^{1}HNMR



Compound 94 ^{13}C NMR



Compound 95 ^{1}HNMR



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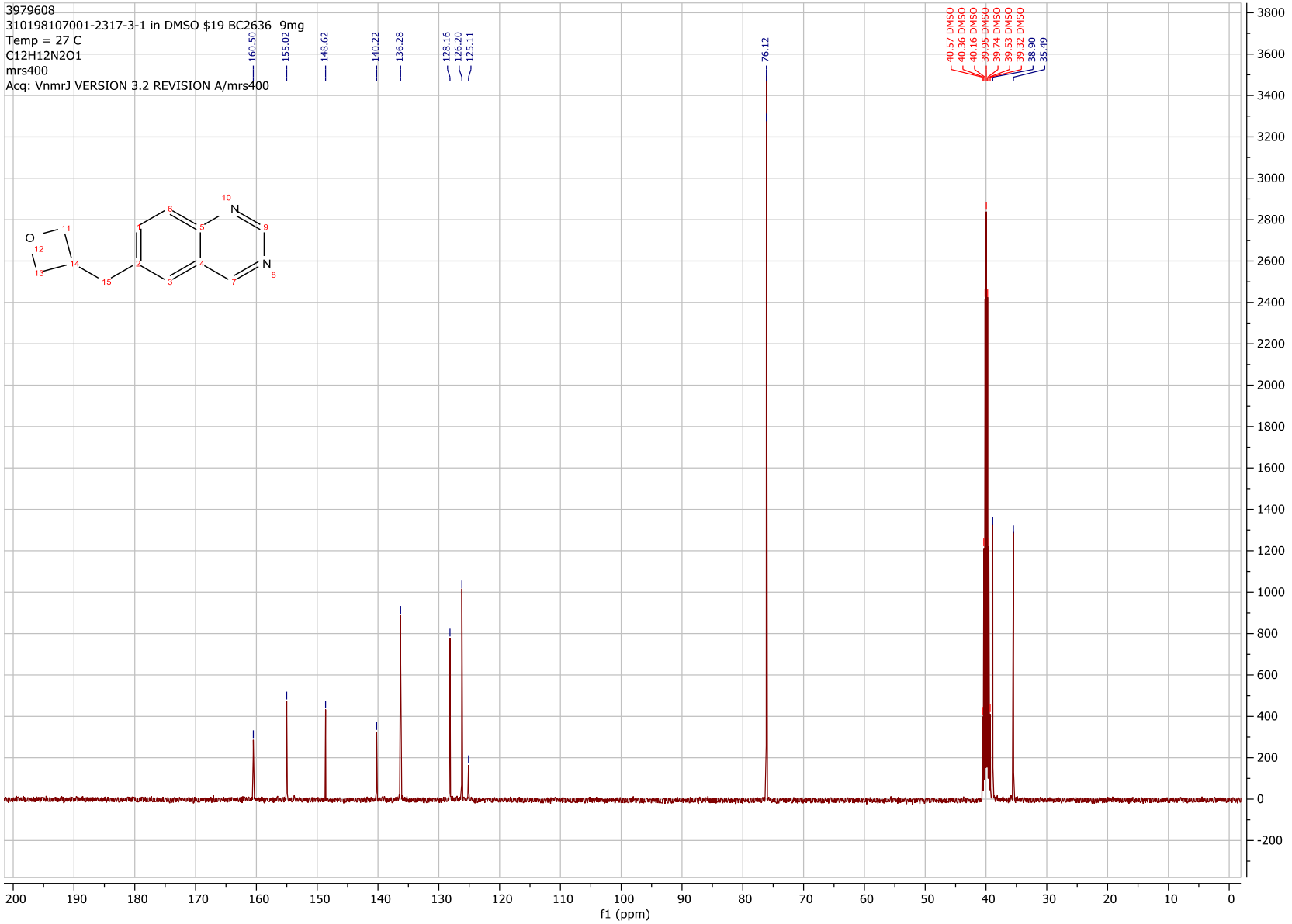
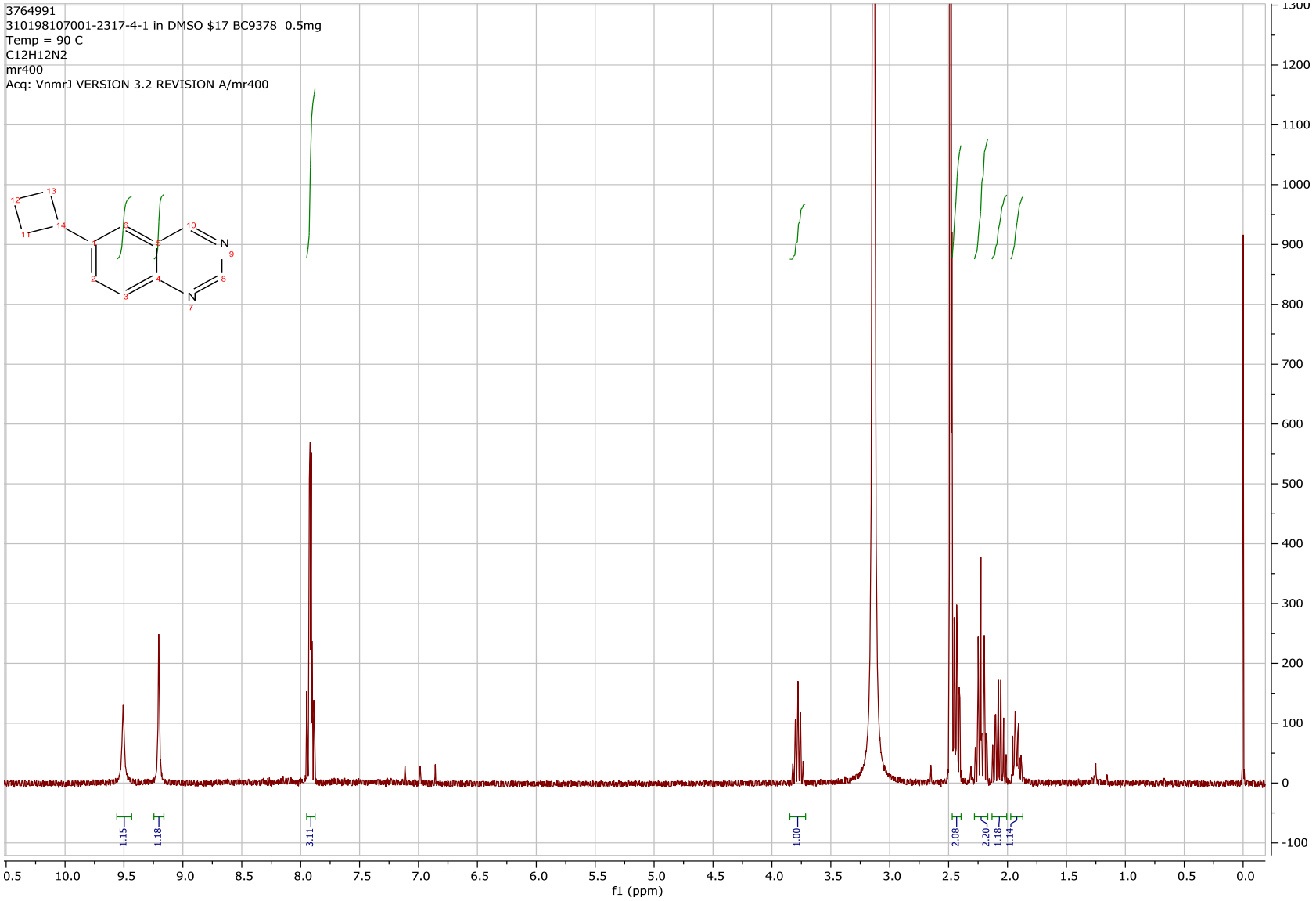


Compound 98 ^{1}HNMR



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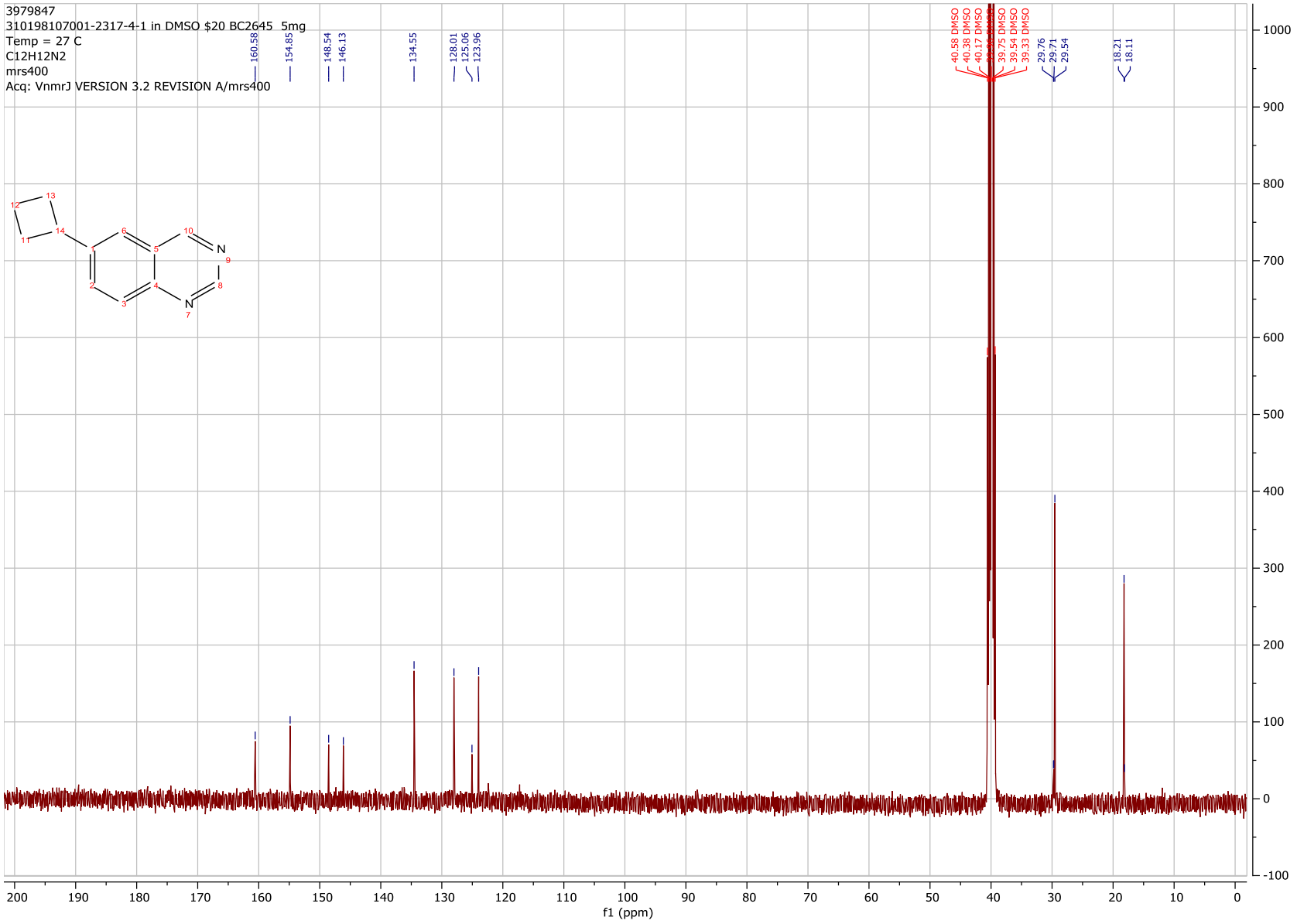
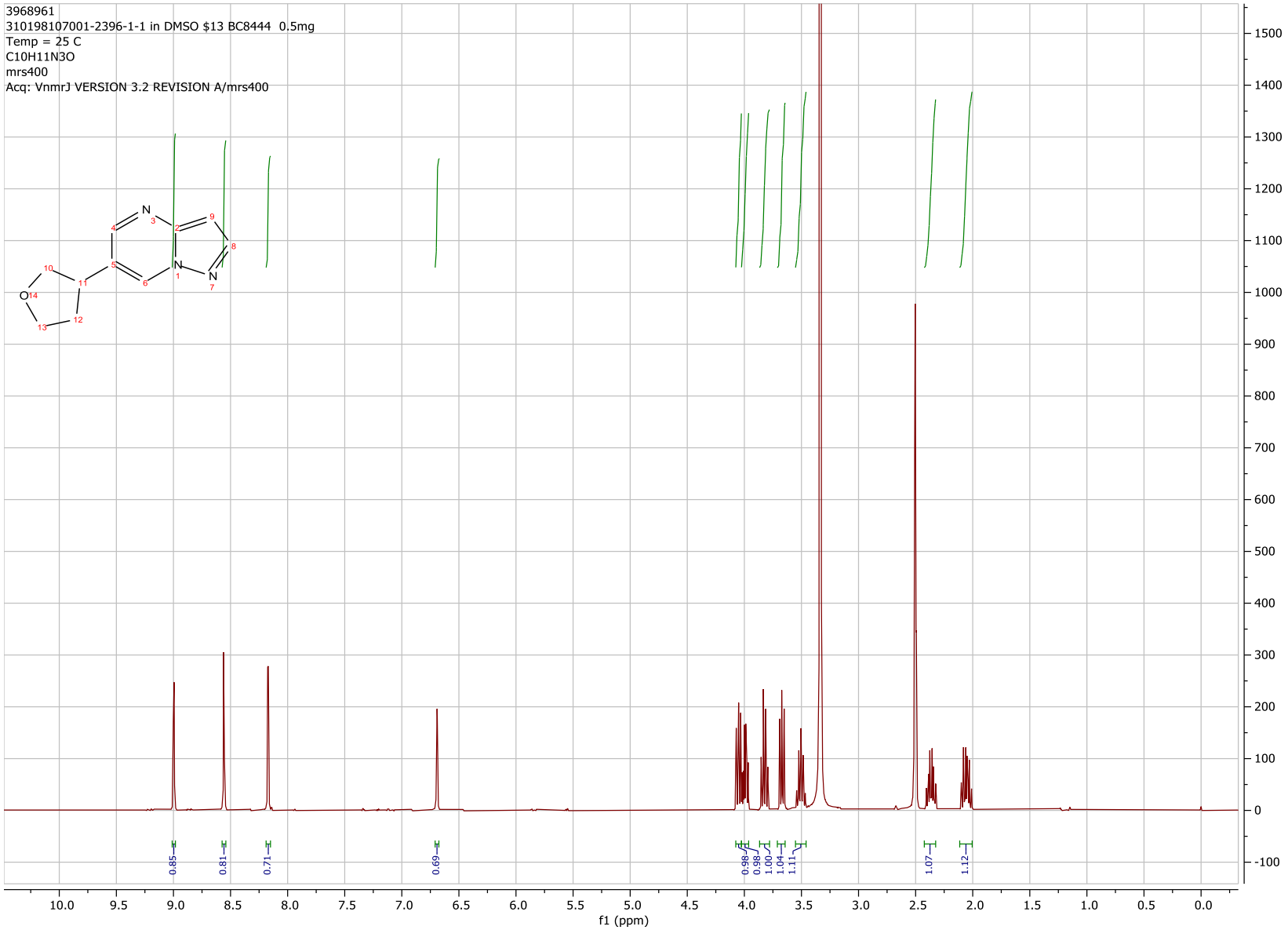
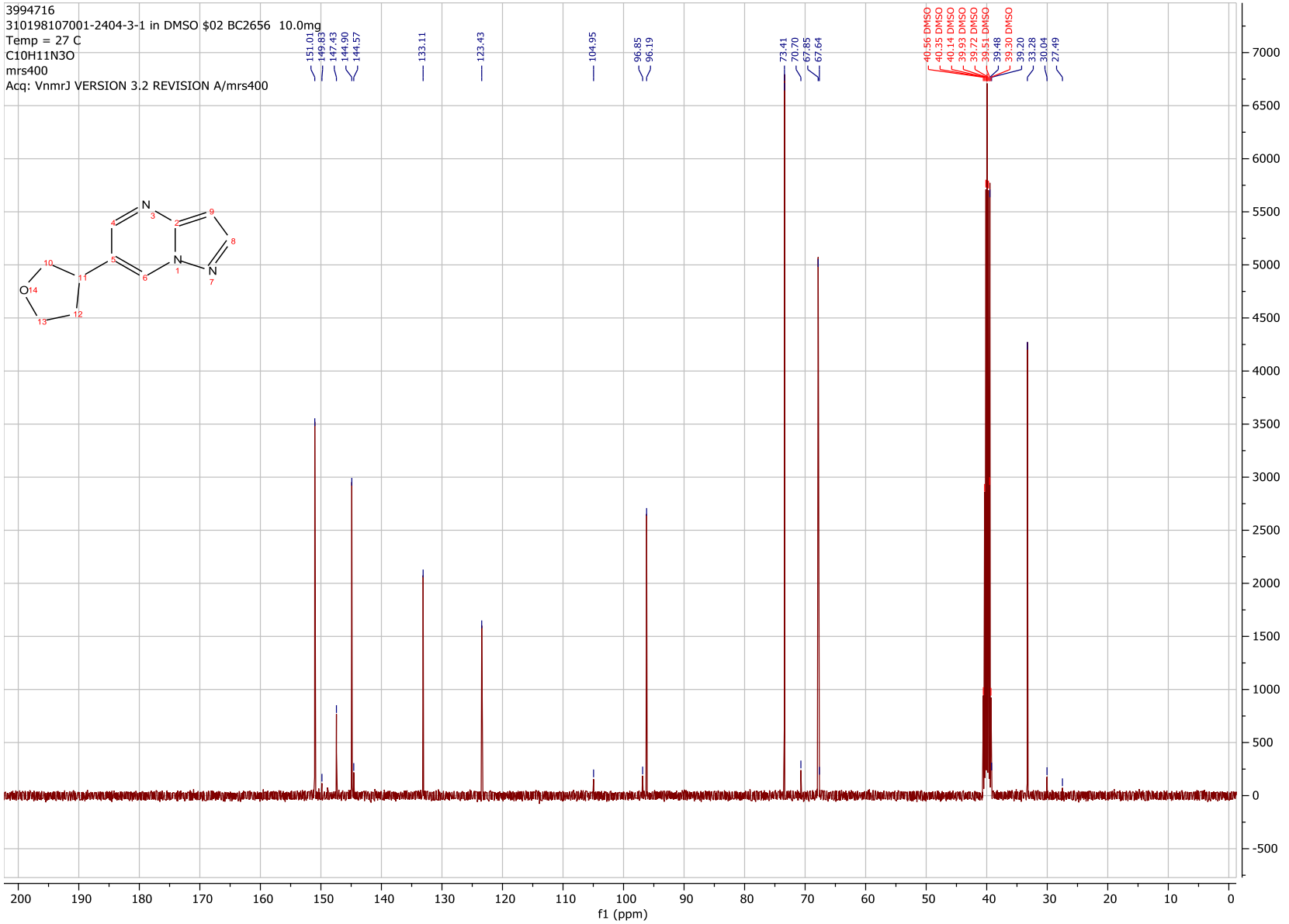


Compound 112 ^{1}HNMR



Compound 112 ^{13}C NMR



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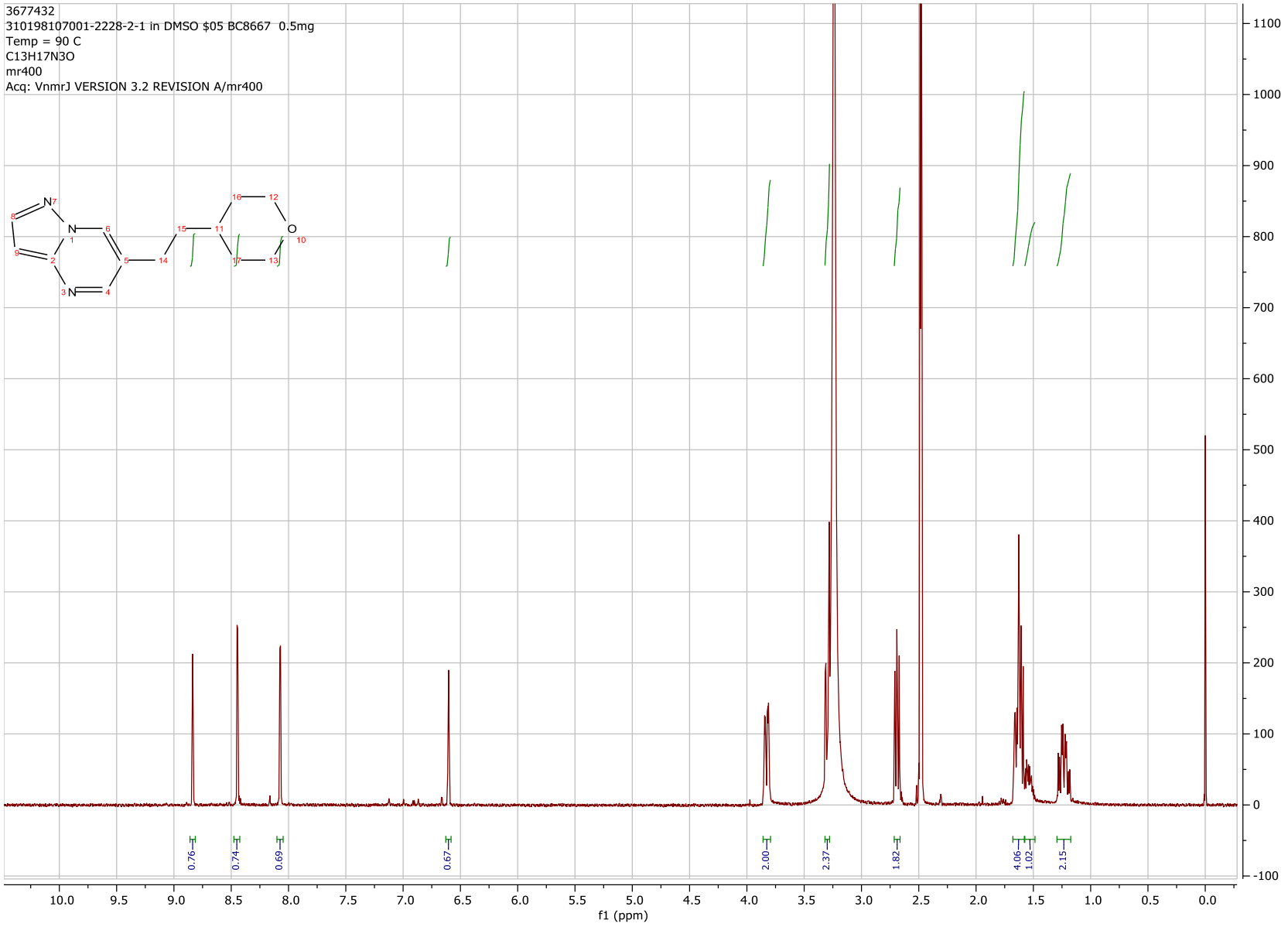

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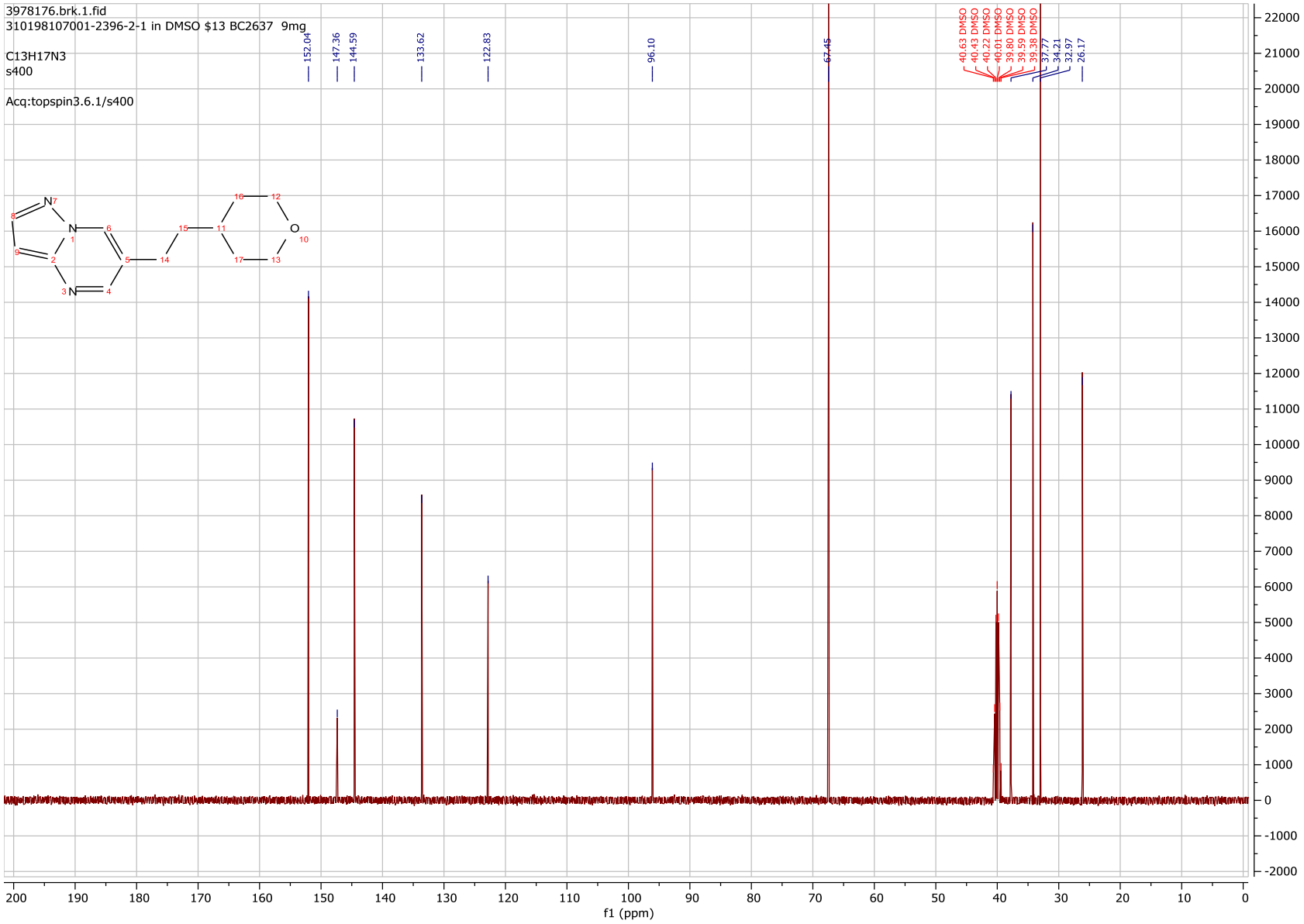
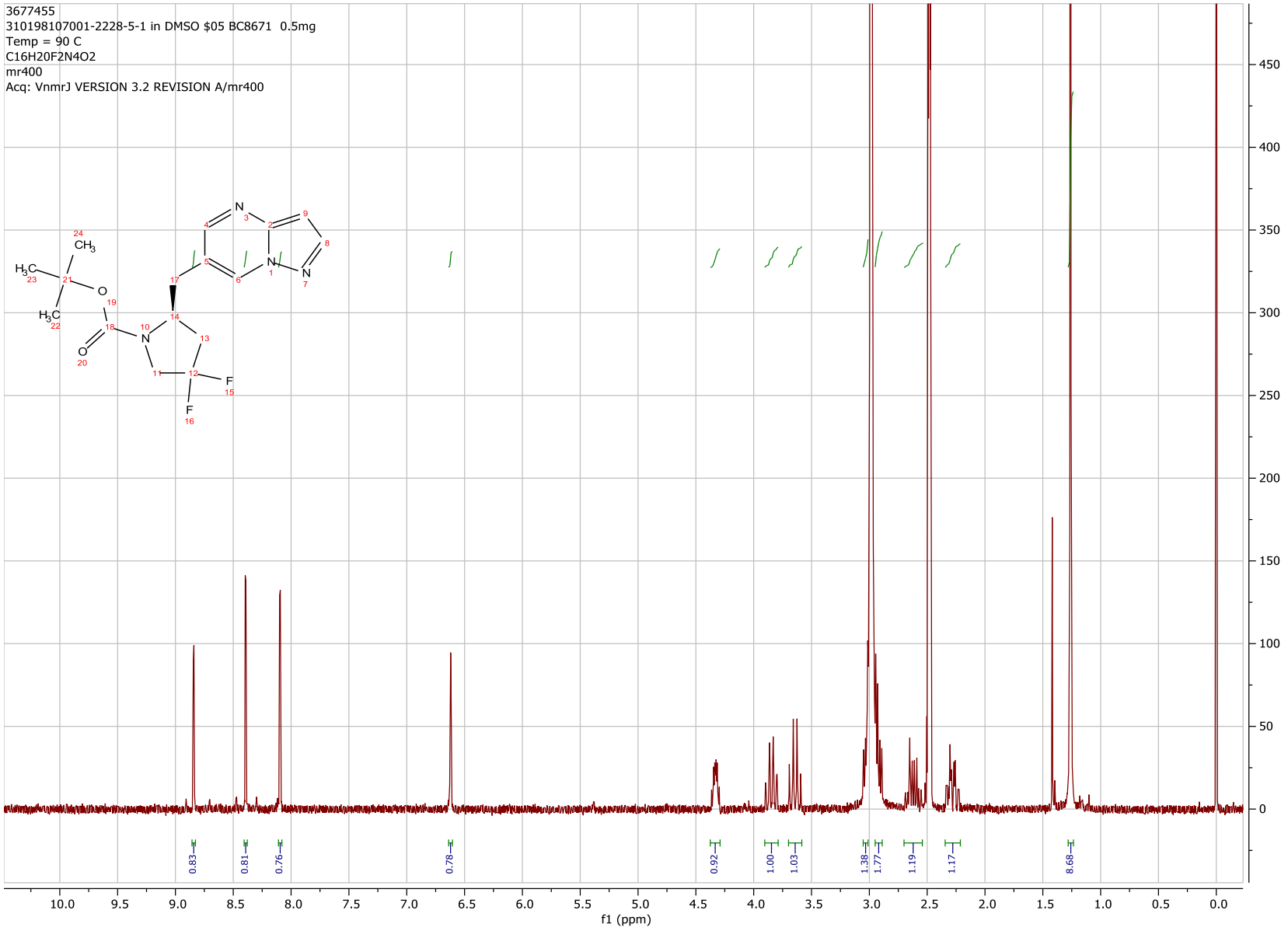
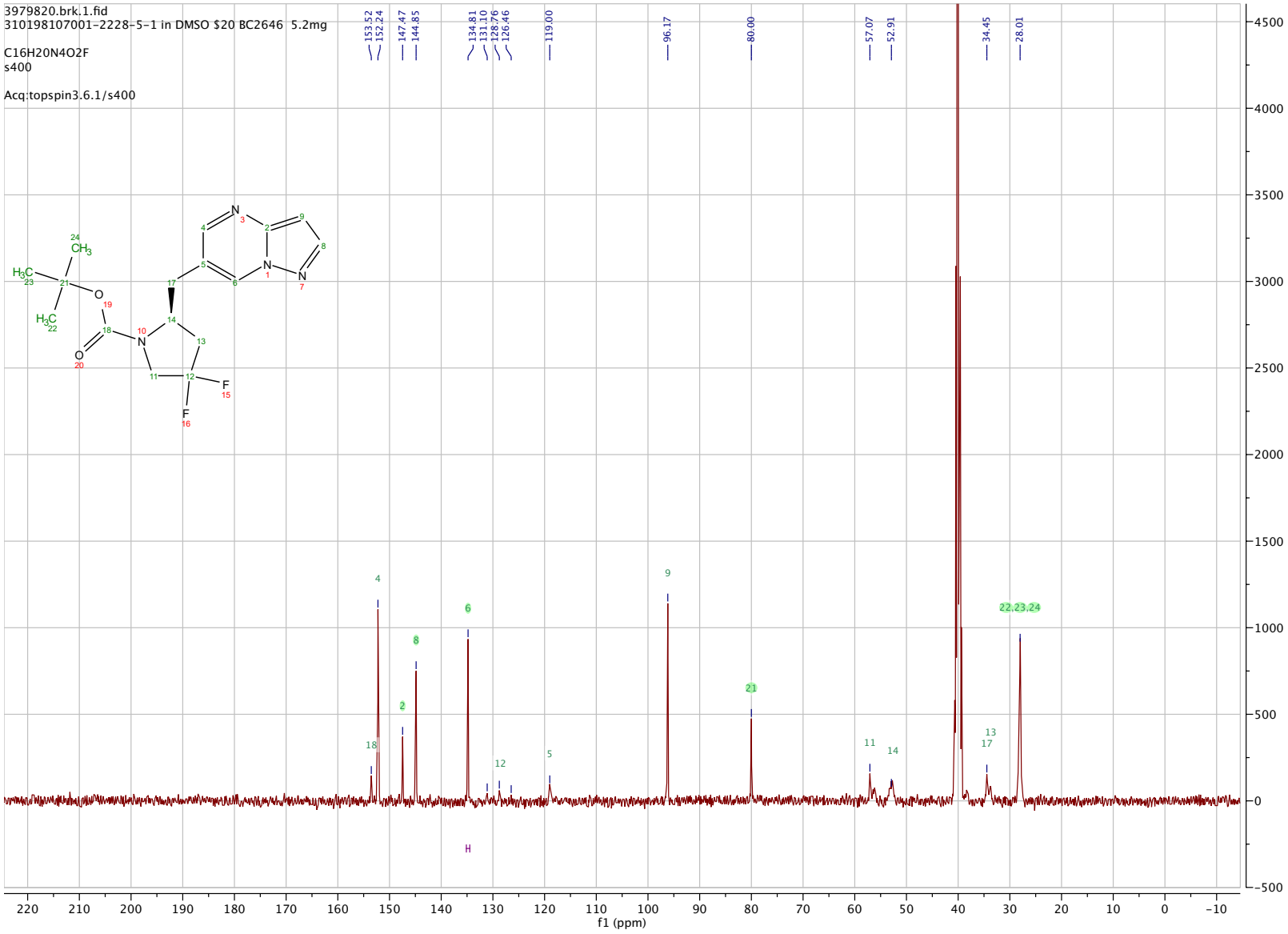


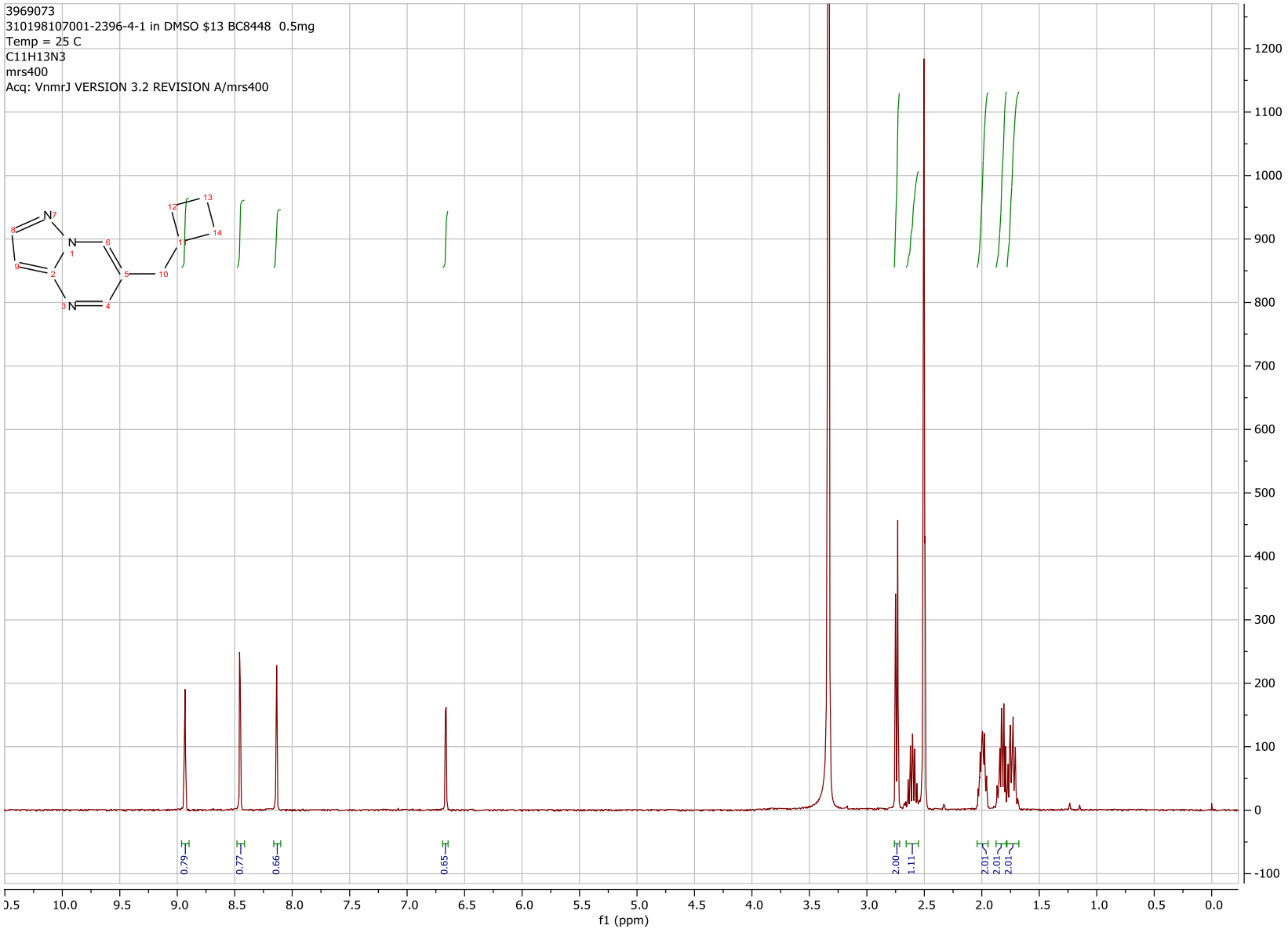
Compound 118 ^{1}HNMR



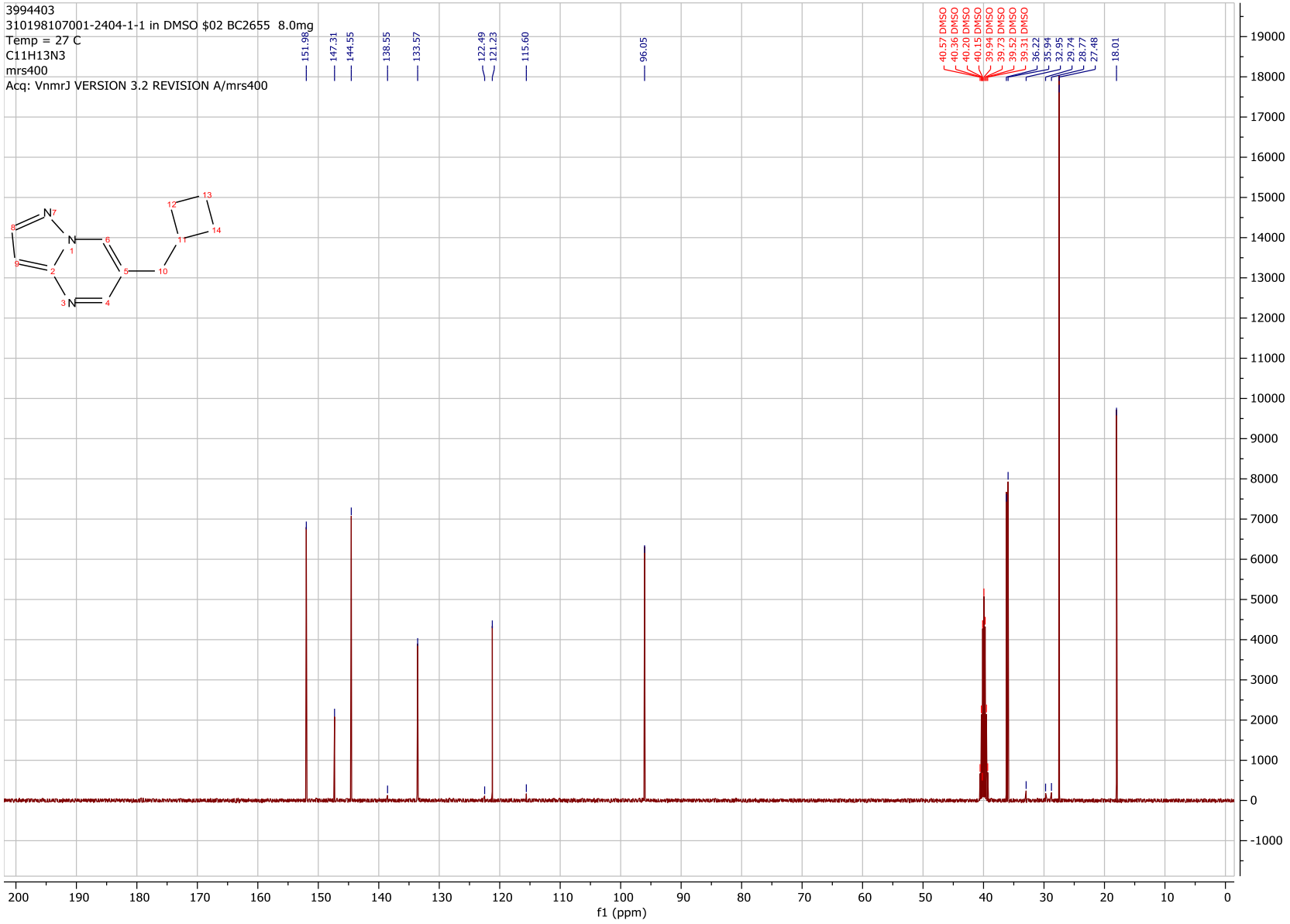
Compound 118 ^{13}C NMR



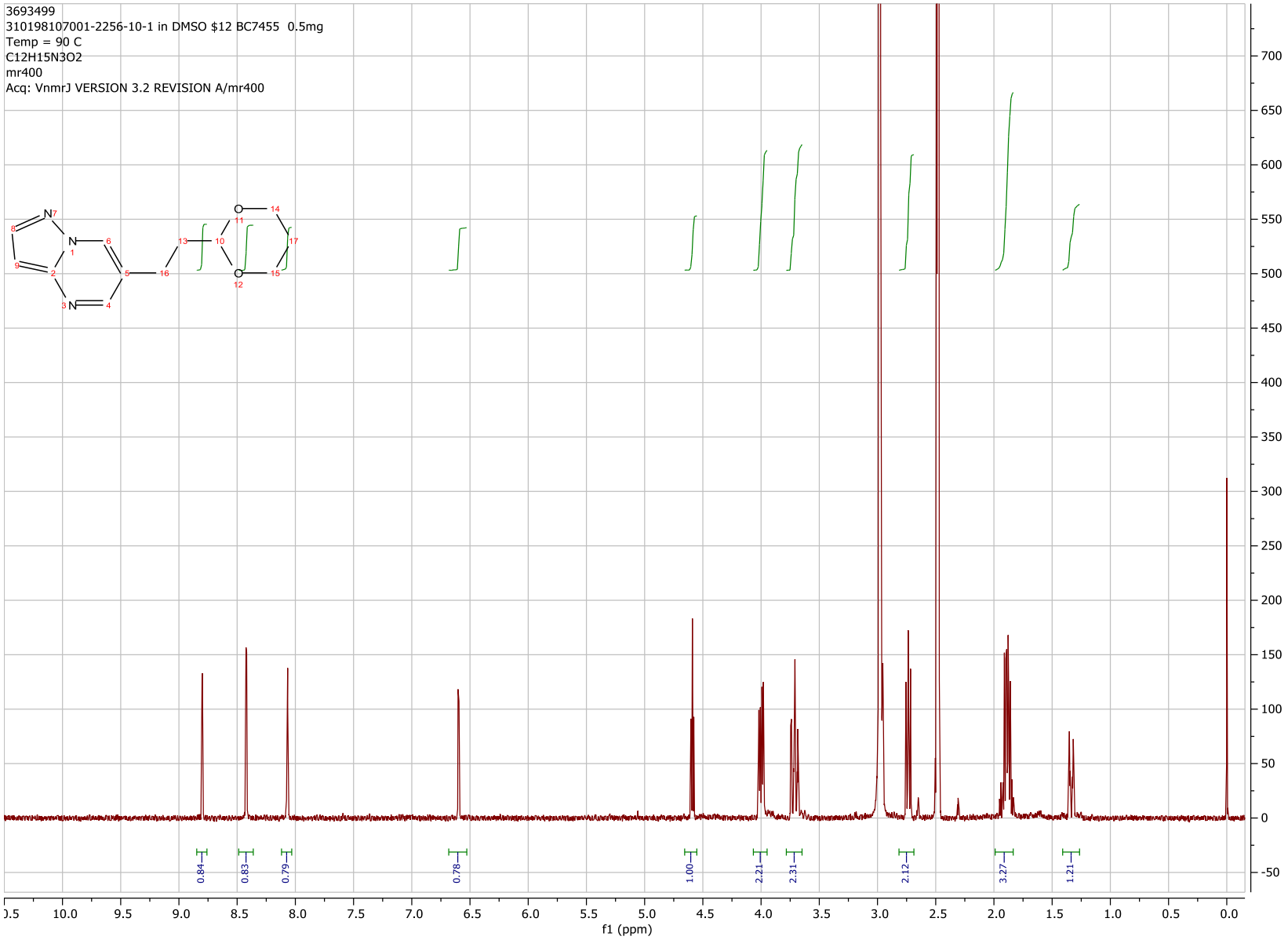
Compound 128 ^{1}HNMR



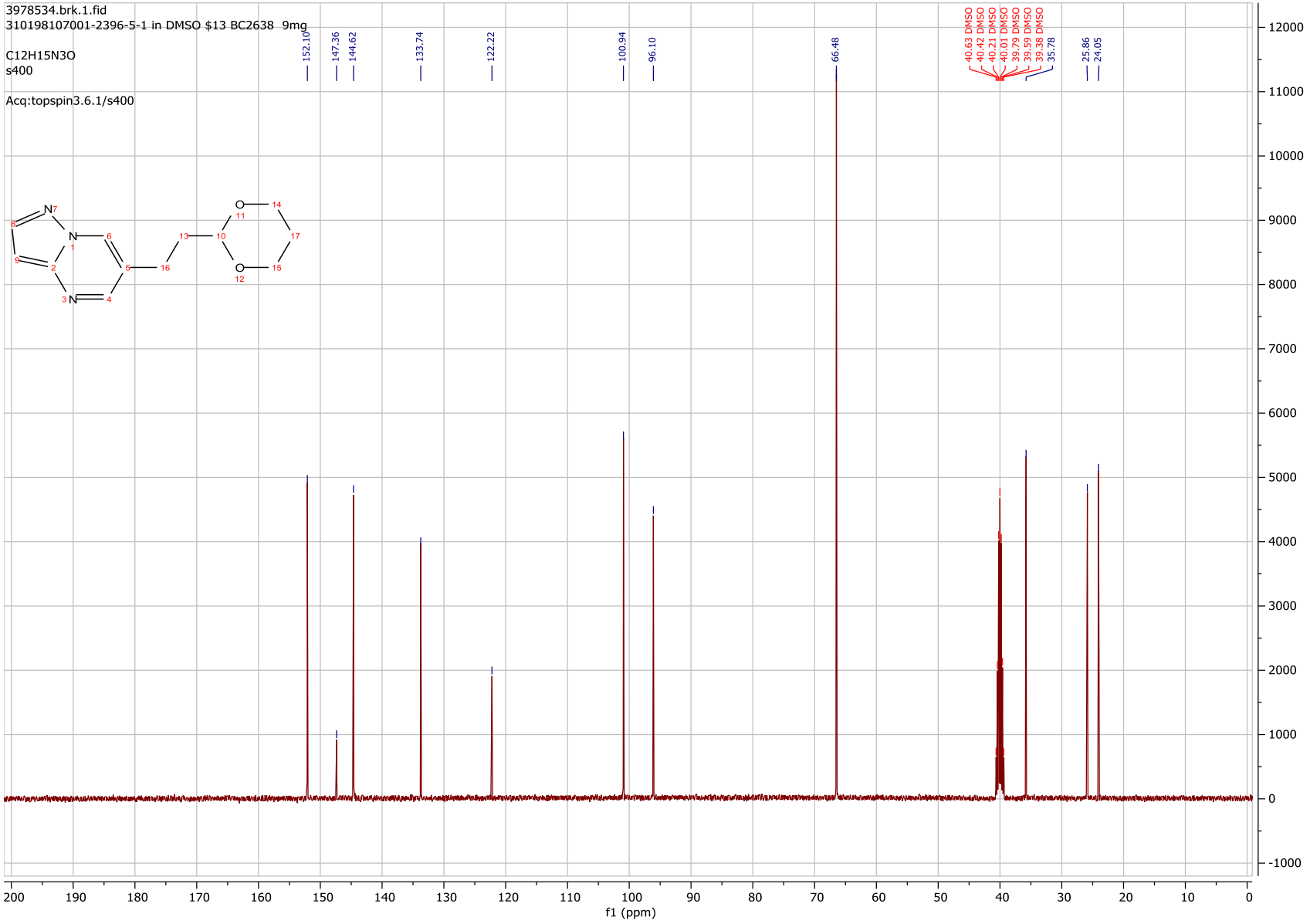
Compound 128 ^{13}C NMR



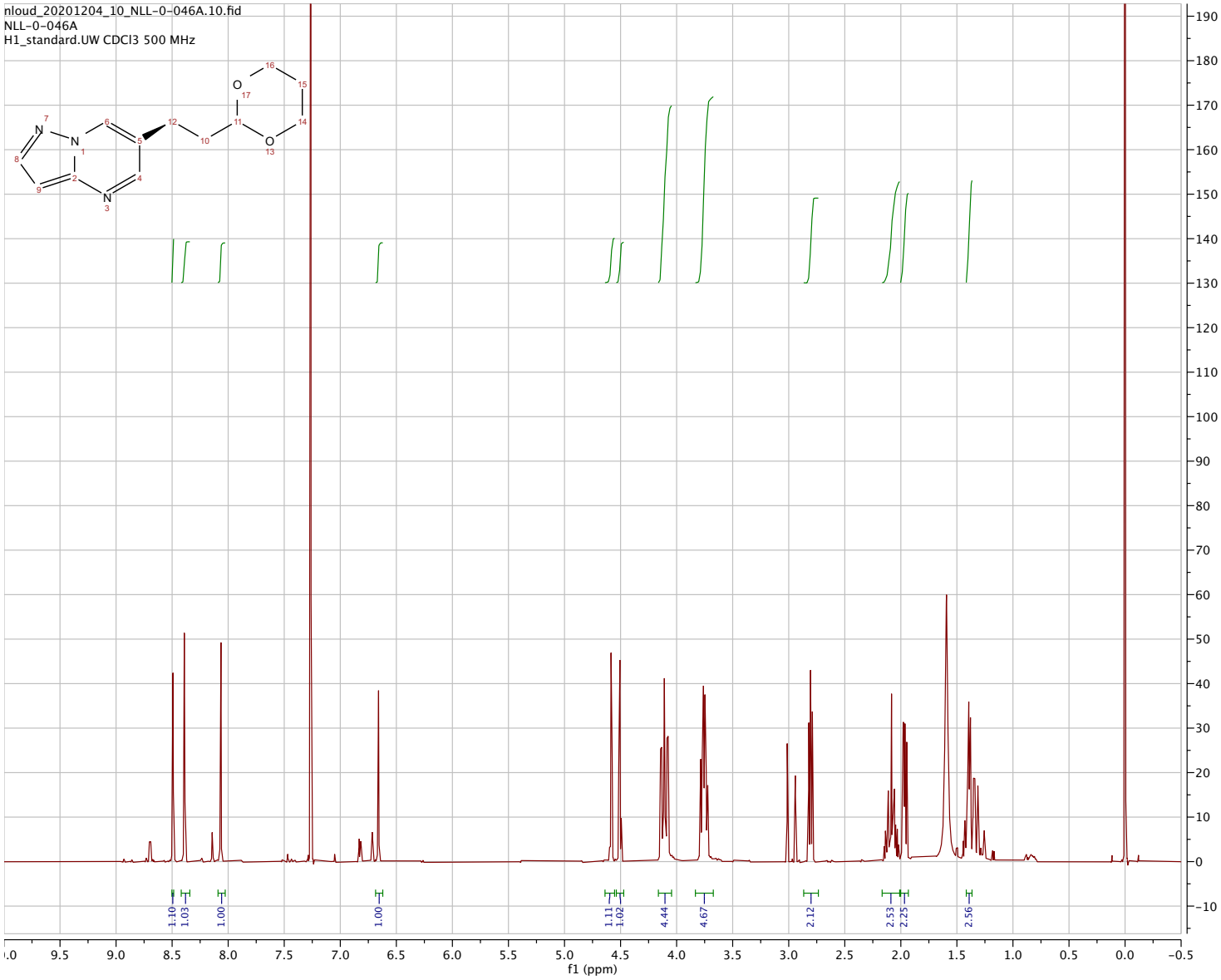
Compound 130 ^{1}H NMR



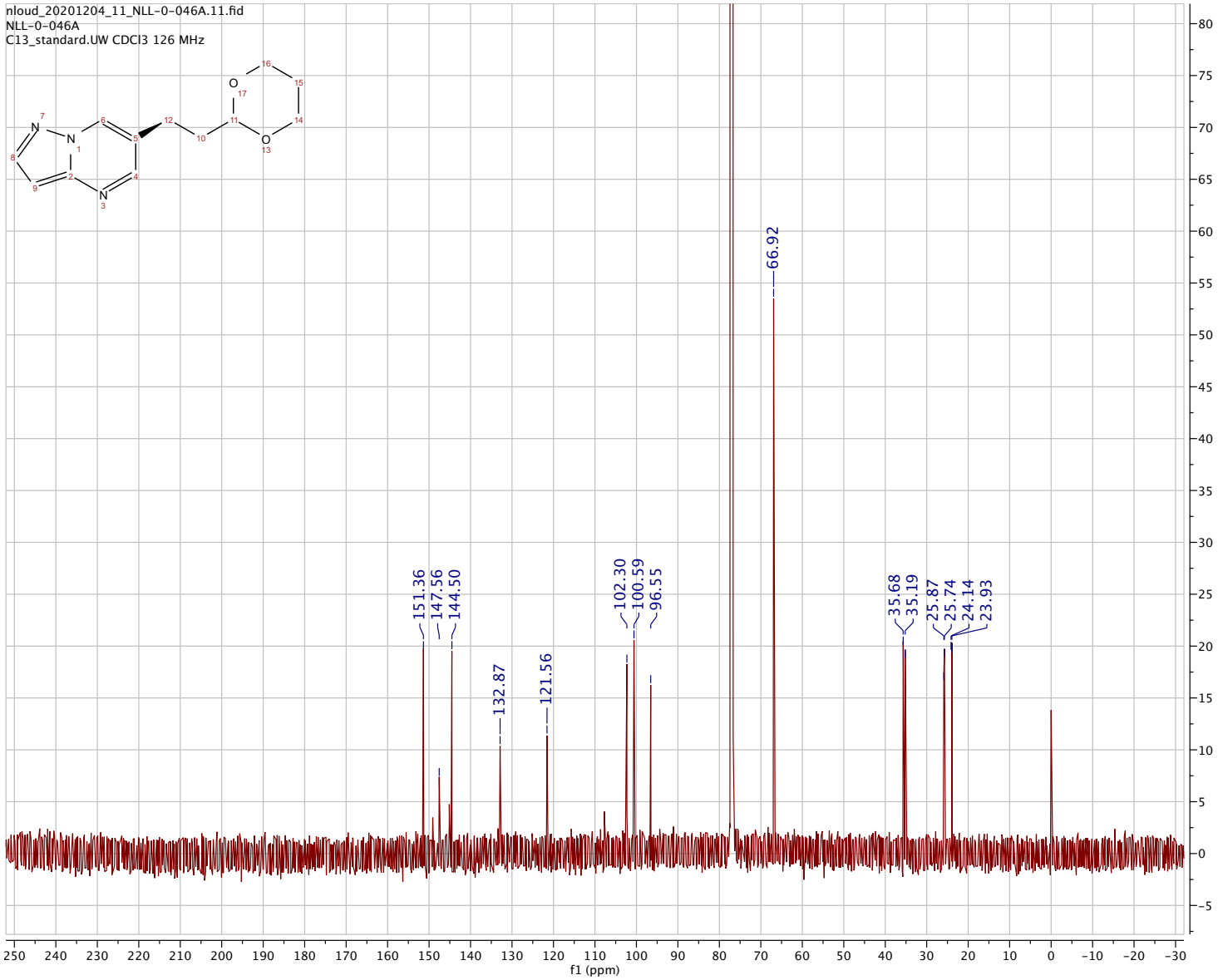
Compound 130 ^{13}C NMR



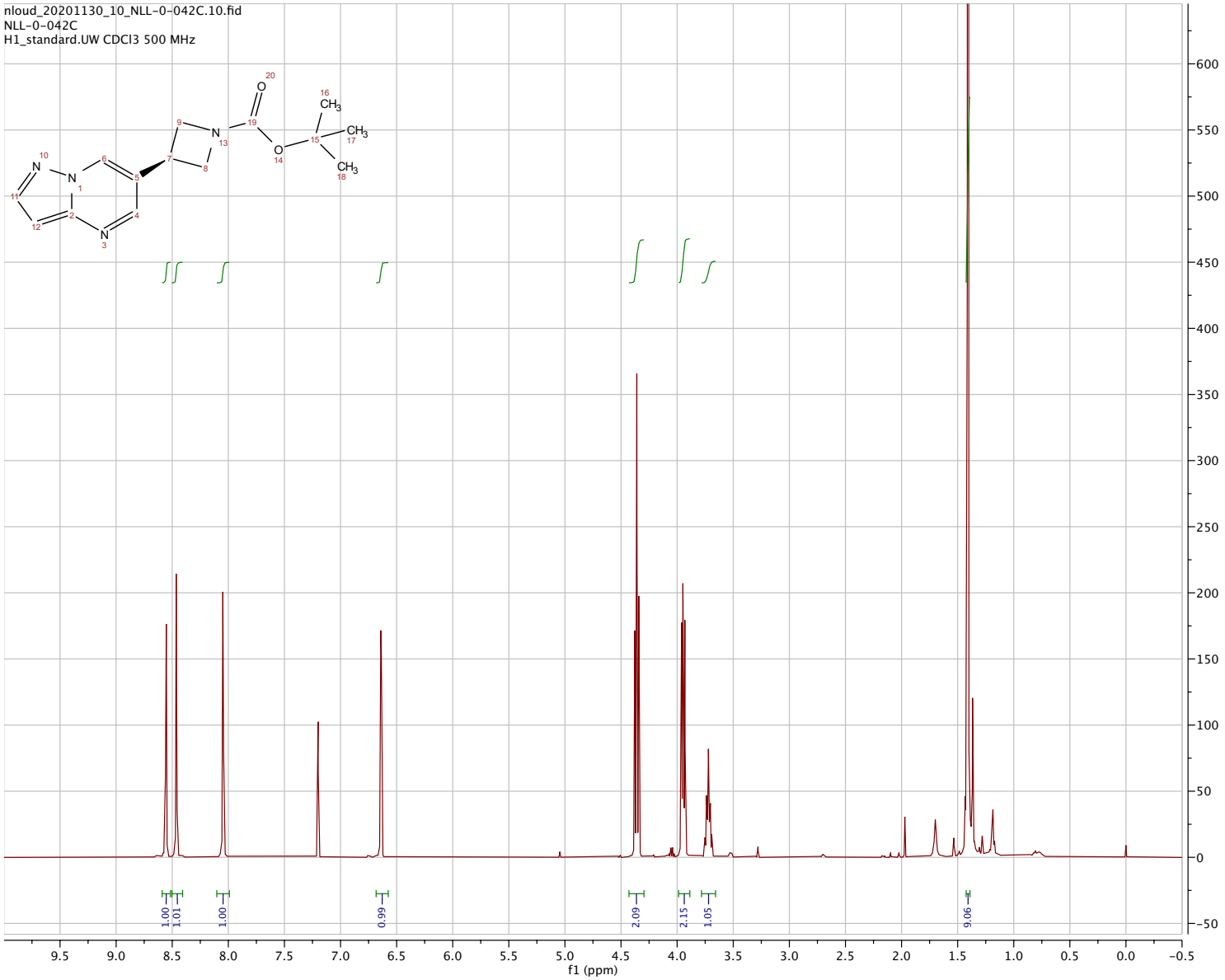
Compound 130 ^{1}H NMR



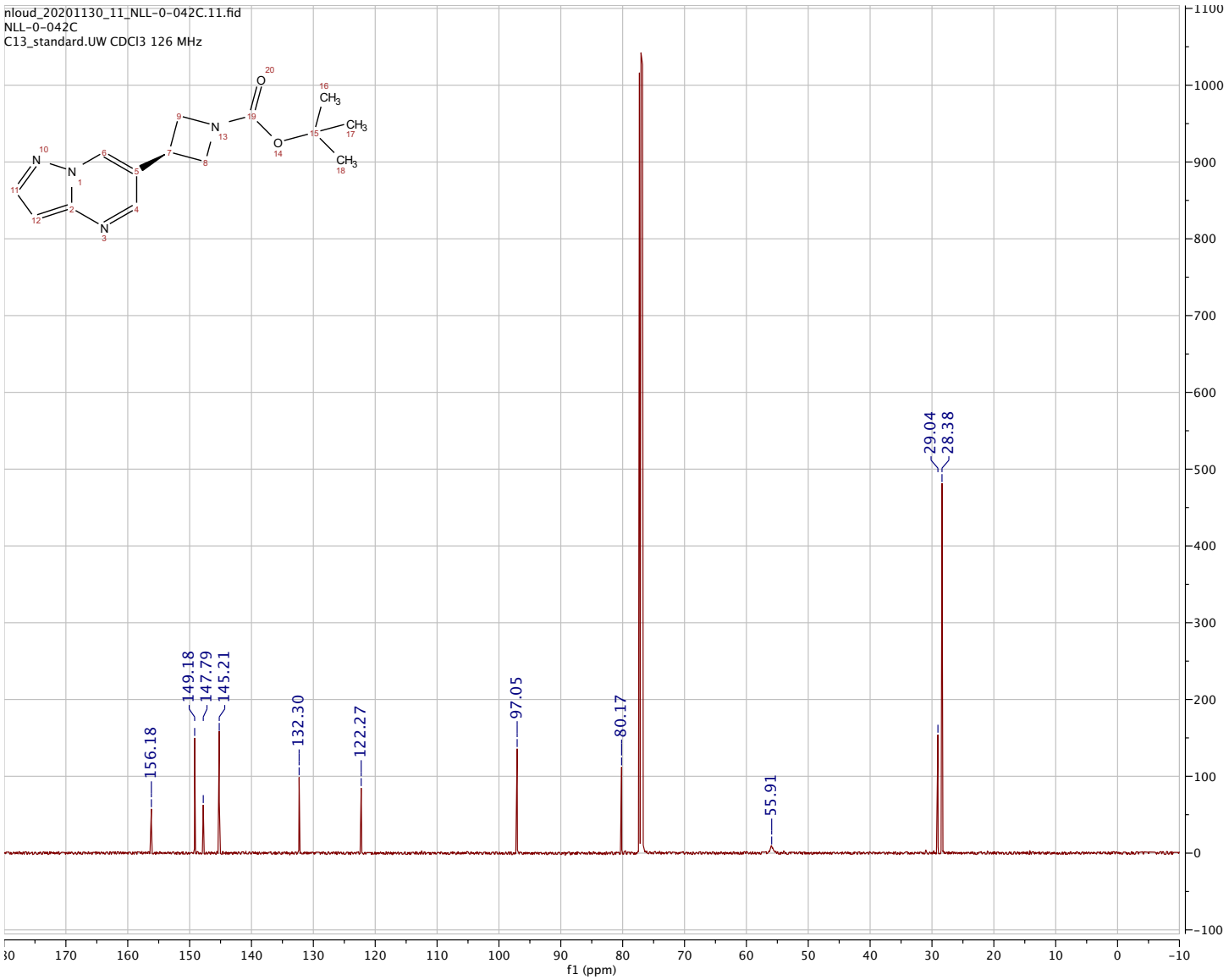
Compound 130 ^{13}C NMR



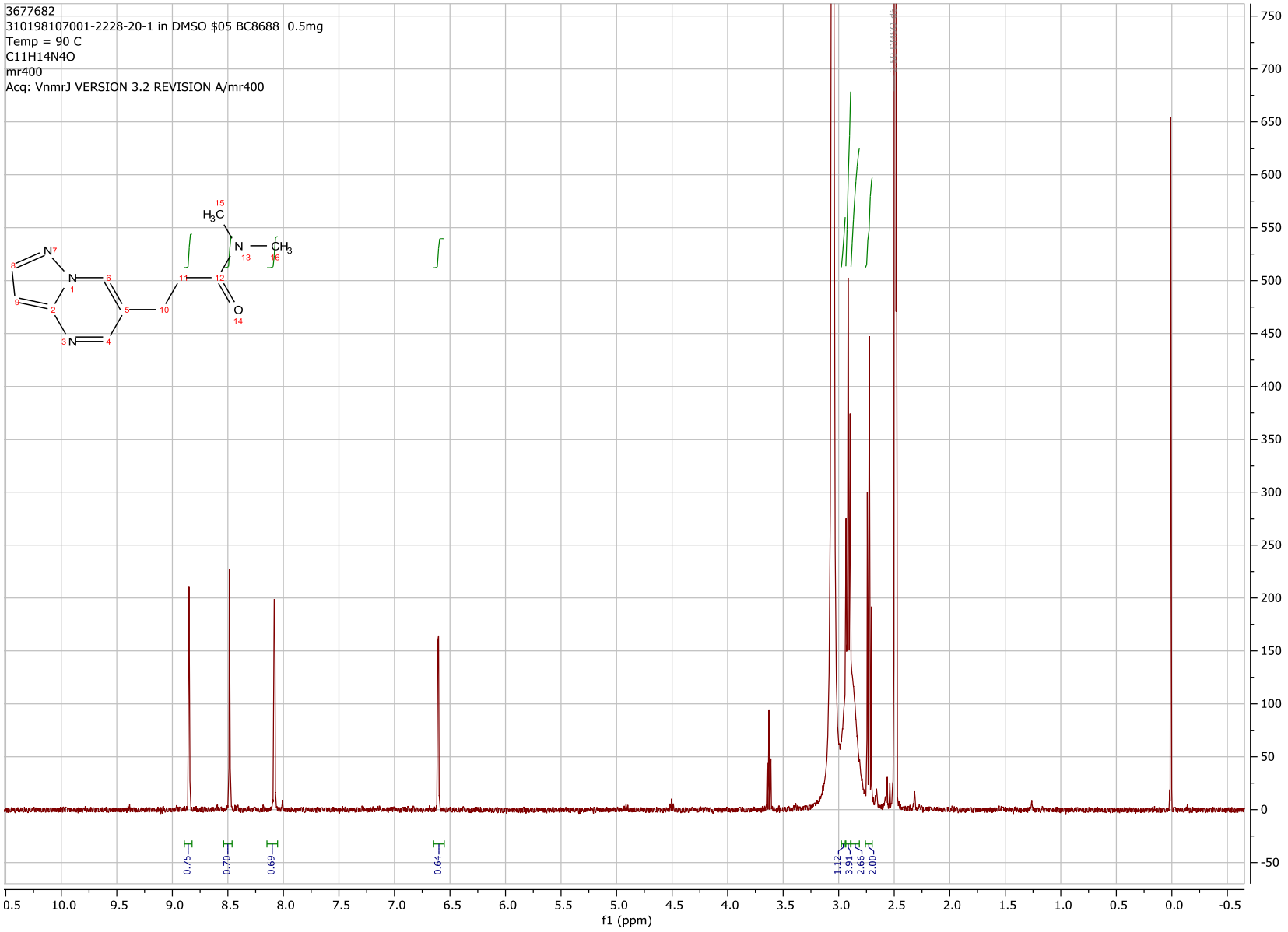
Compound 139 ^{1}H NMR



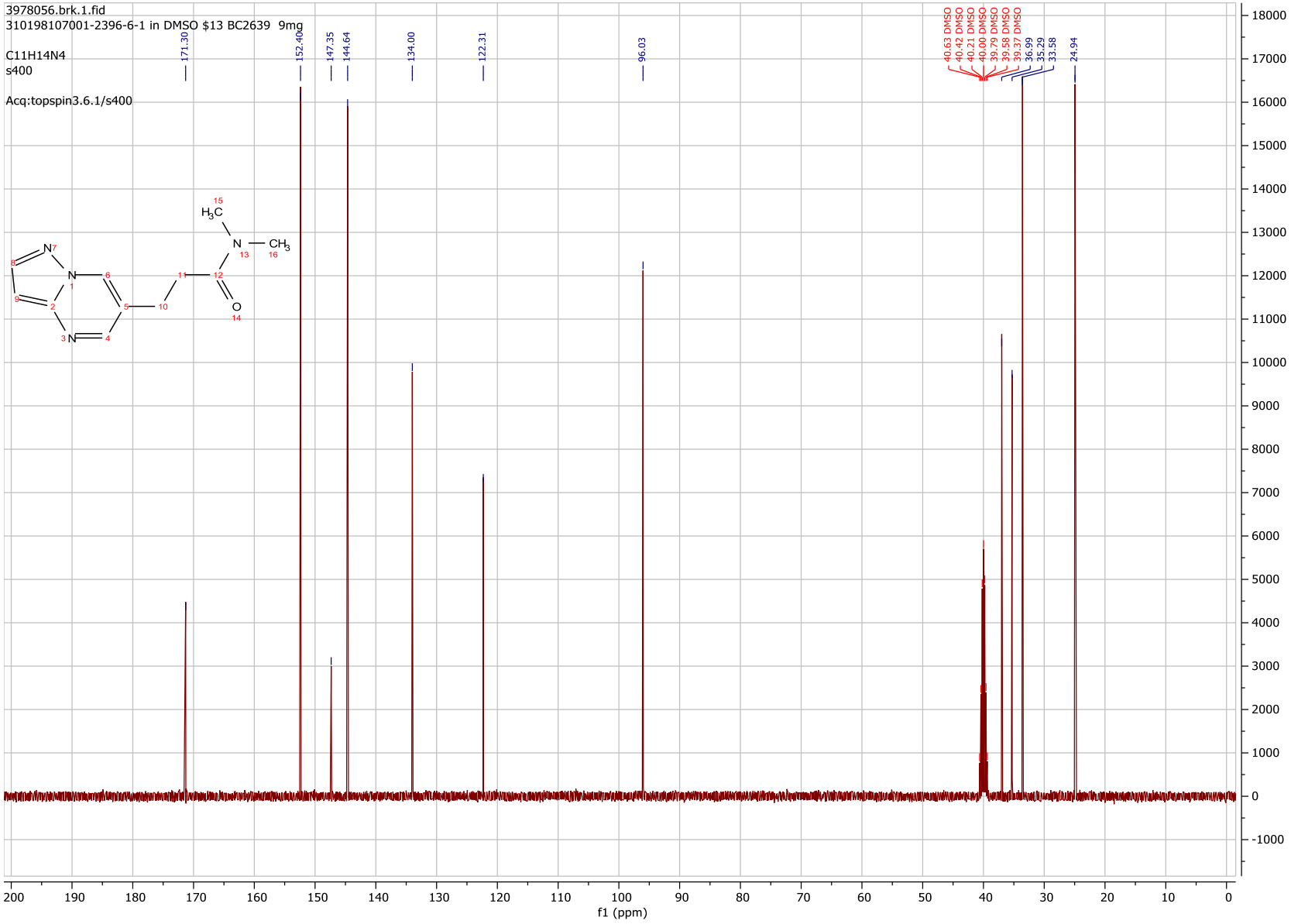
Compound 139 ^{13}C NMR



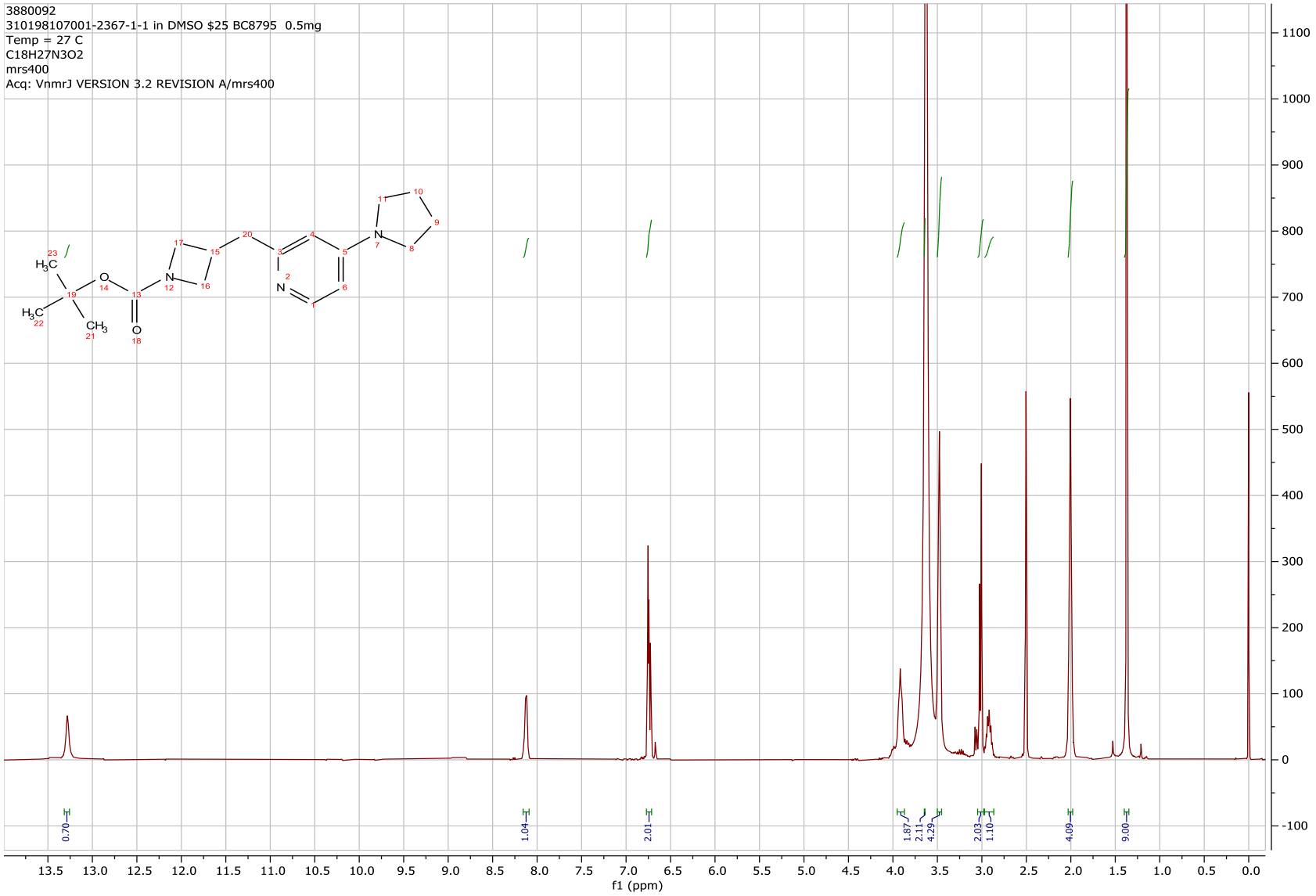
Compound 148 ^{1}H NMR



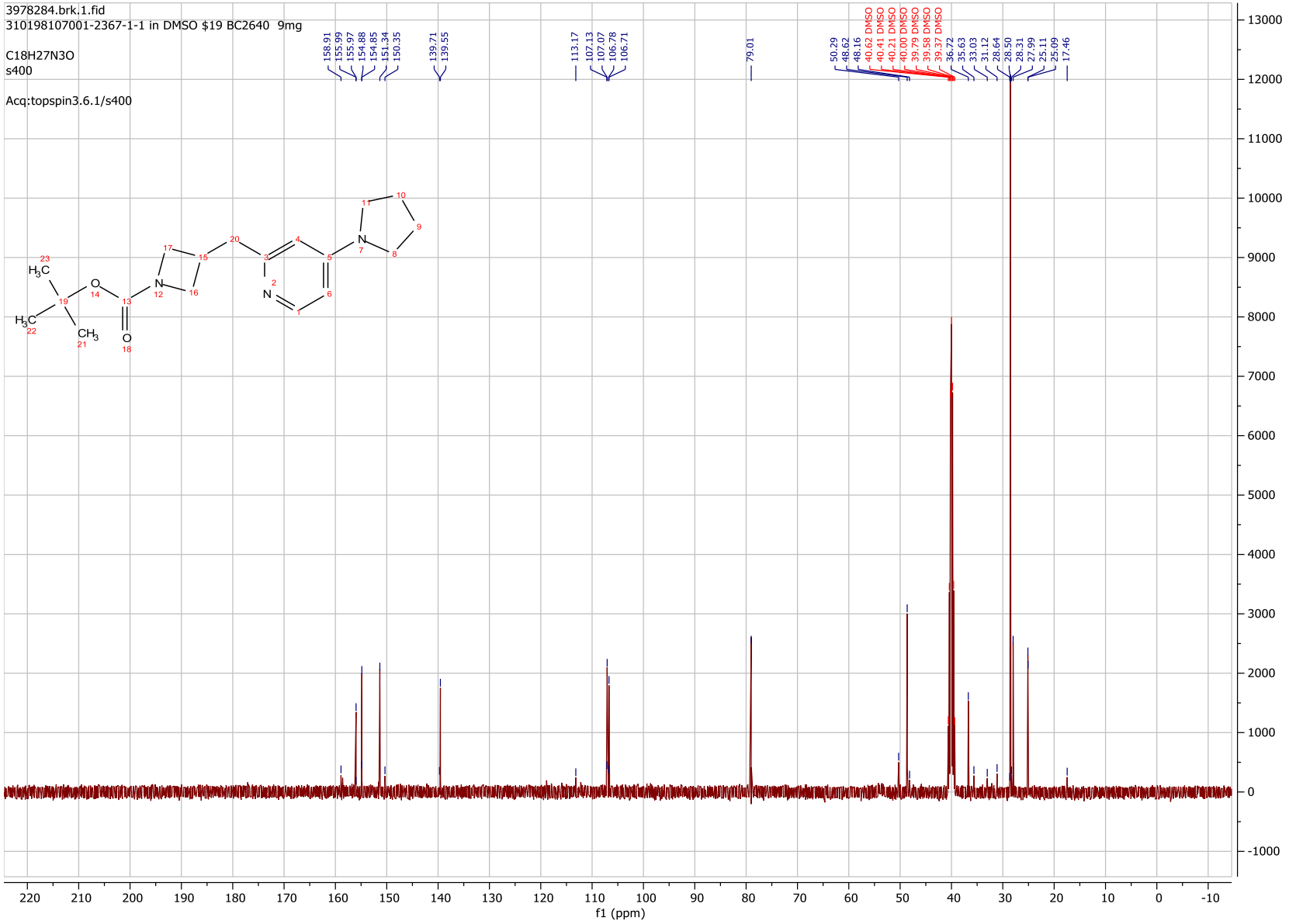
Compound 148 ^{13}C NMR



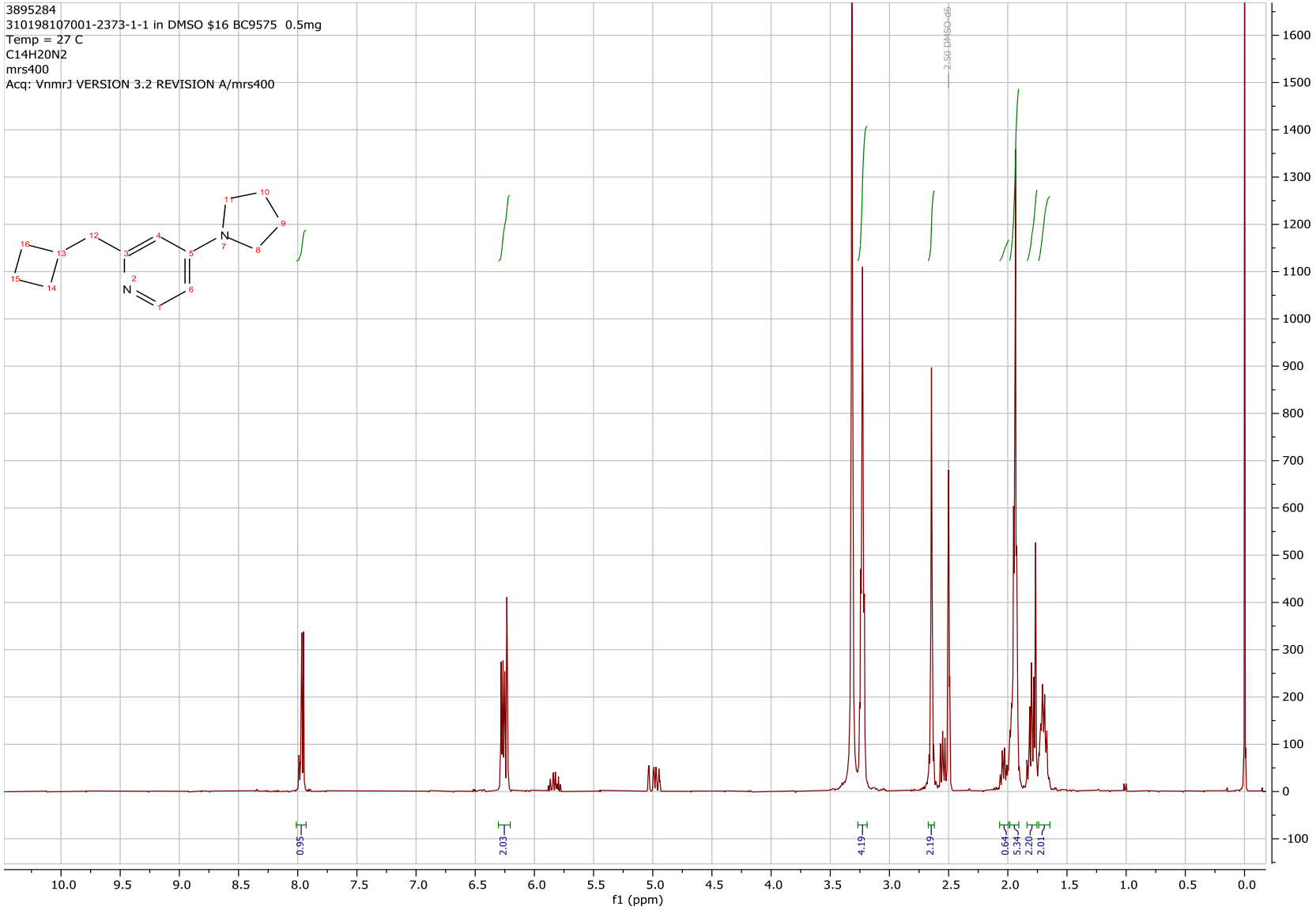
Compound 153 ^{1}HNMR



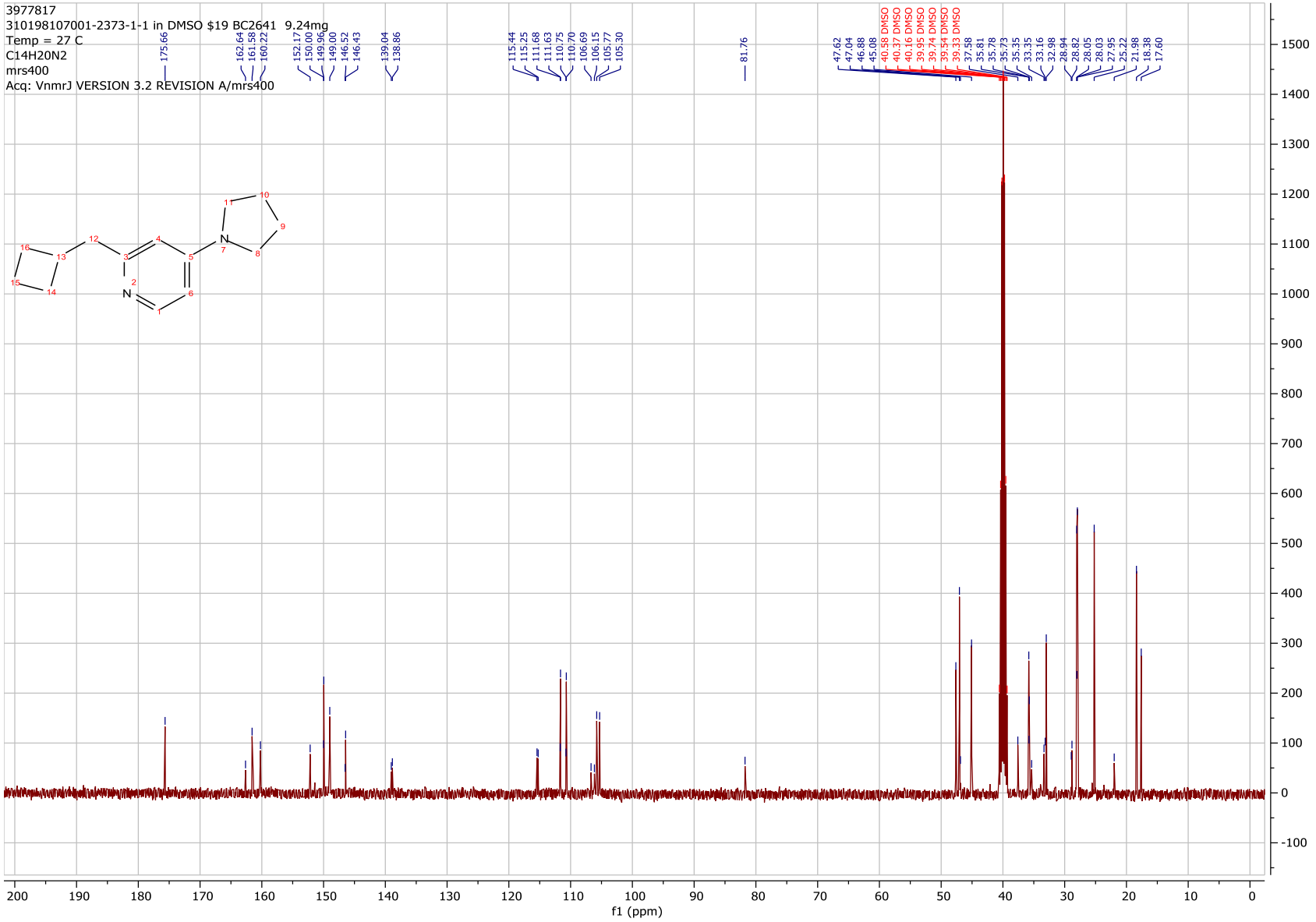
Compound 153 ^{13}C NMR



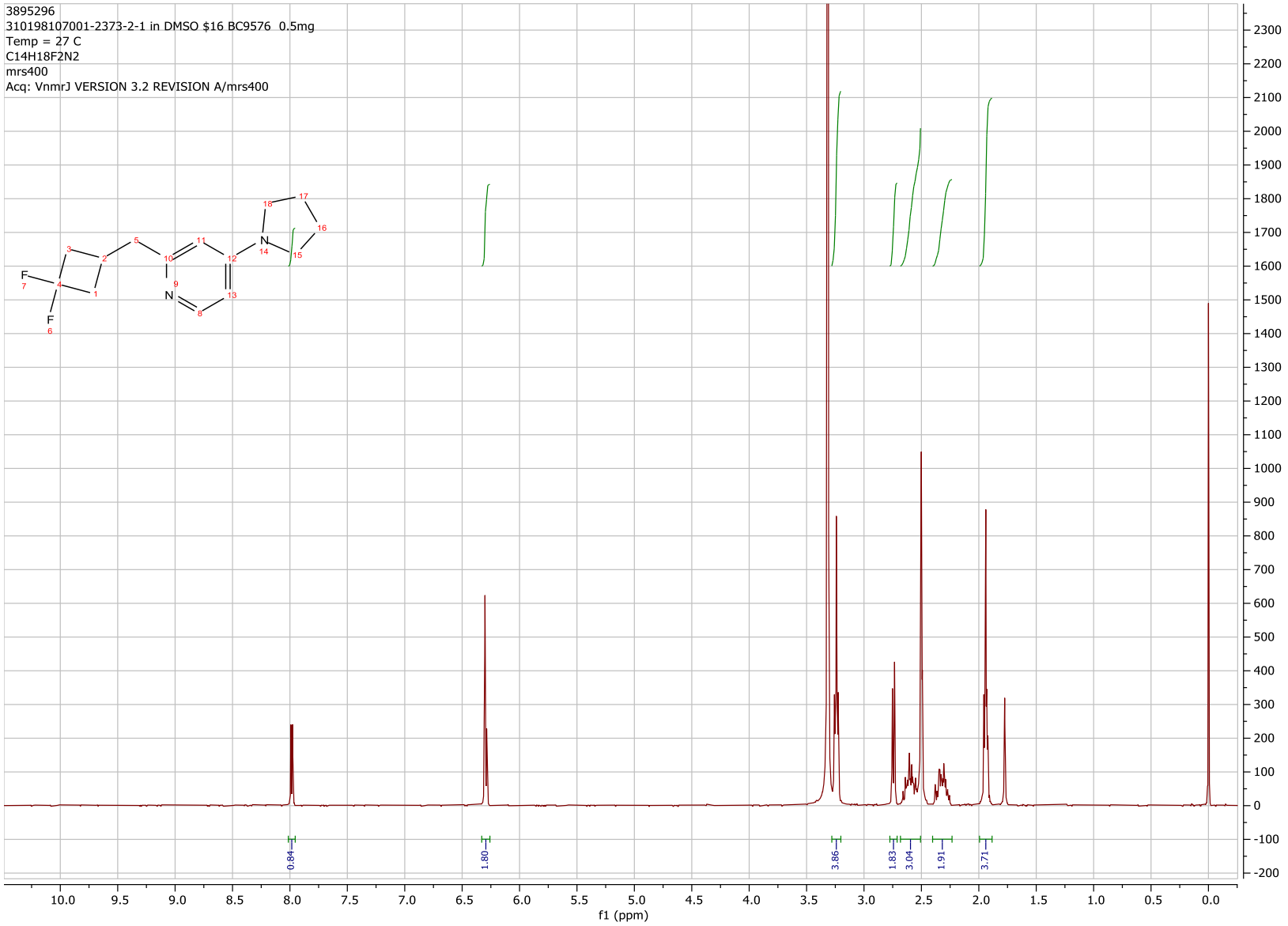
Compound 165 ^{1}HNMR



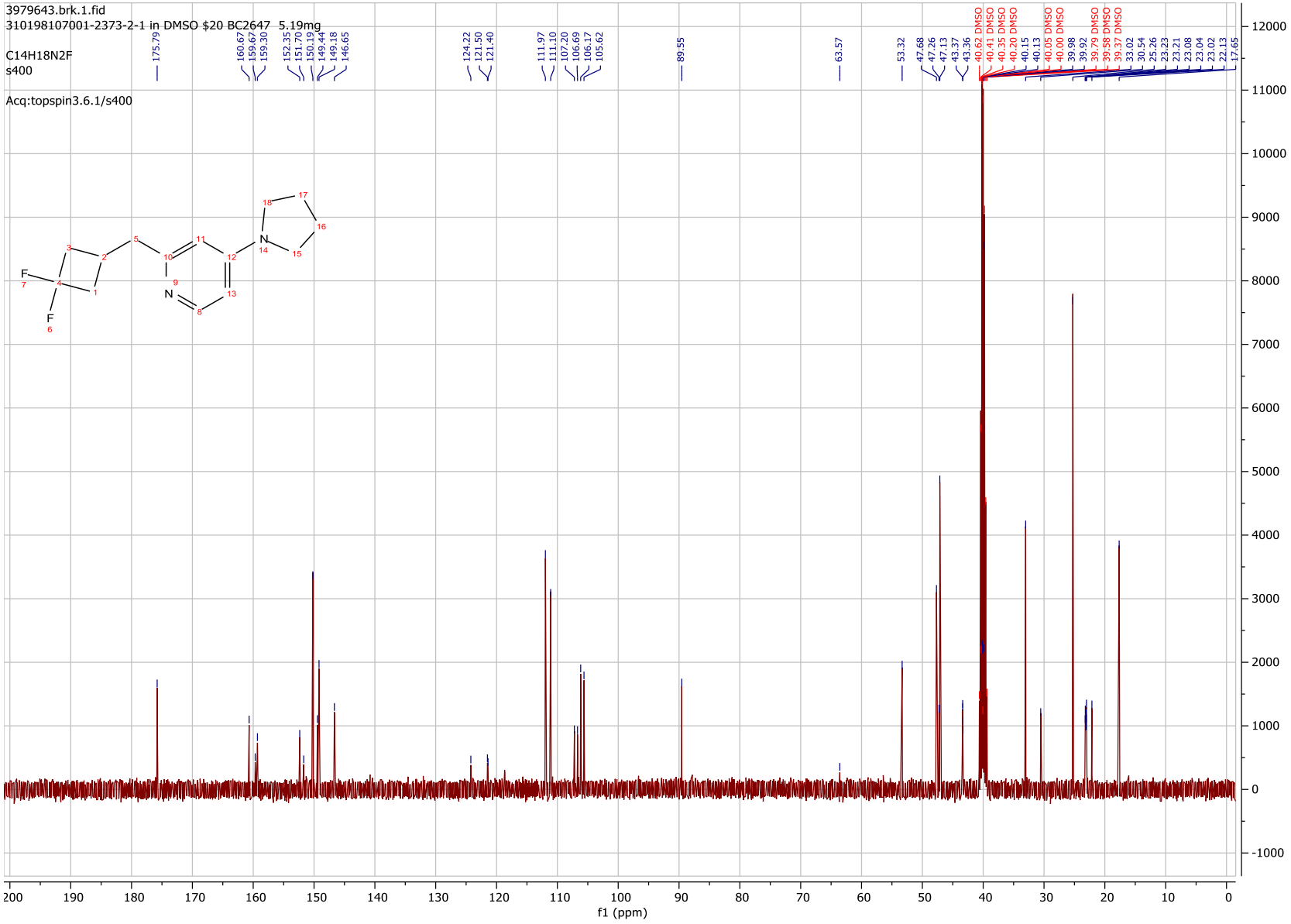
Compound 165 ^{13}C NMR



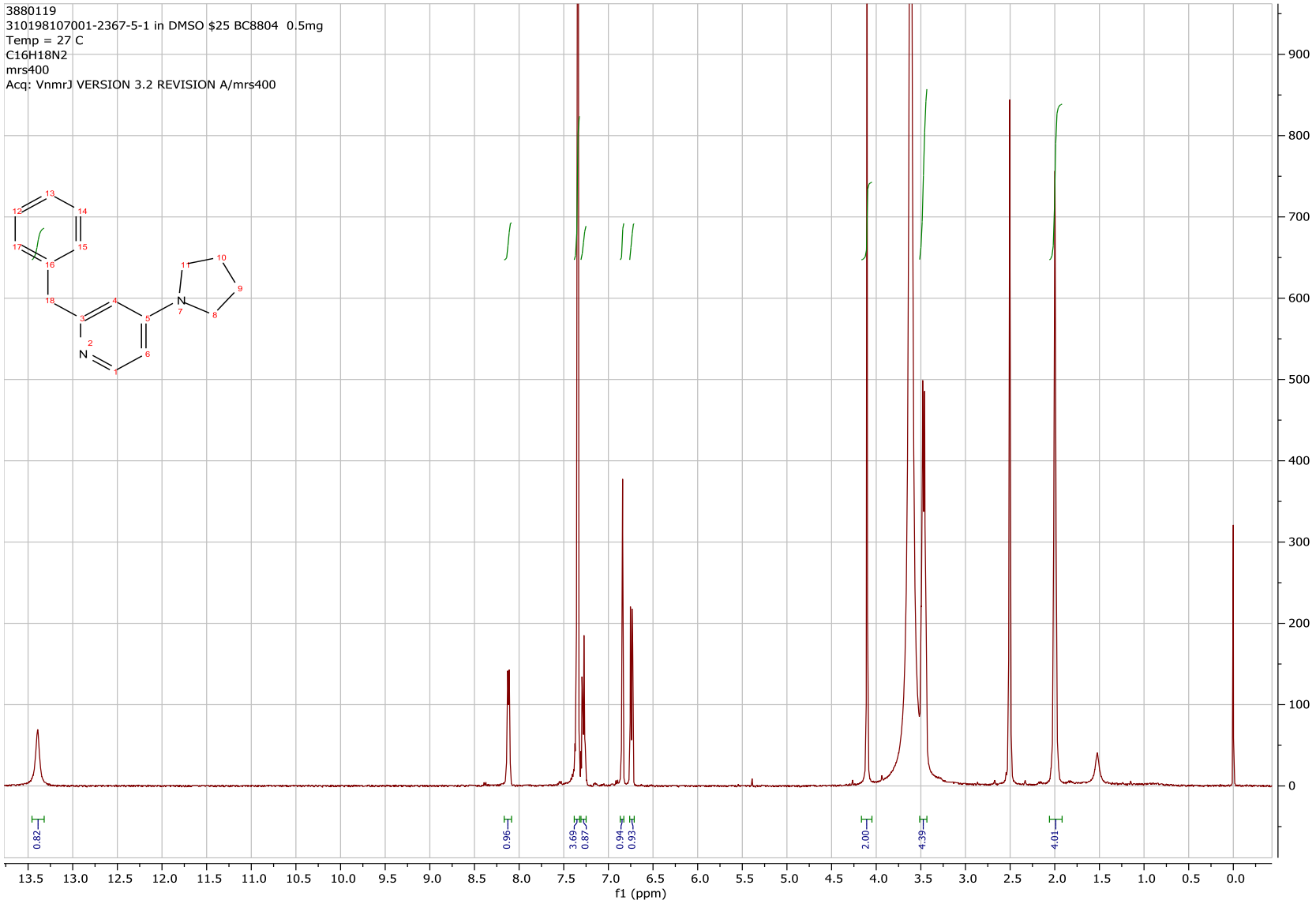
Compound 170 ^{1}HNMR



Compound 170 ^{13}C NMR



Compound 181 ^{1}HNMR



Compound 181 ^{13}C NMR