Supporting Information

Expedient Synthesis of Highly Potent Antagonists of Inhibitor of Apoptosis Protein (IAPs) with Unique Selectivity for ML-IAP

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Figure SI-1: γ-Lactone Byproduct (mentioned on Page 2 in text)

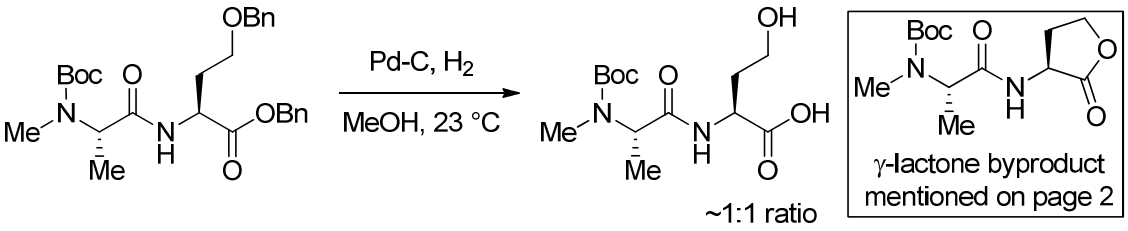


Table SI-1: Fluorescence Polarization Competition Assay Data with Error Values

	XIAP		cIAP1	cIAP2	ML-IAP
	BIR2	BIR3	BIR3	BIR3	
	K_i	K_i	K_i	K_i	K_i
Cmpd[a]	(μM)	(μM)	(μM)	(μM)	(μM)
1a	>56.0	>39.1	8.98±0.67	28.90±2.03	>25
1b	>56.0	13.3±0.4	1.18±0.16	3.31±0.38	8.337 ± 1.059
1c	>56.0	6.87±0.28	1.05±0.13	2.70±0.14	5.070 ± 3.934
1d	51.0±8.5	>39.1	5.36±0.35	9.71±0.55	>7.5
1e	>56.0	28.3±6.3	1.49±0.09	3.81±0.10	>7.5
(*S*)-**10a**	>56.0	0.44±0.02	0.061±0.001	0.149±0.013	0.344±0.137
(*S*)-**10b**	17.2±2.0	9.23±0.82	0.411±0.032	0.799±0.064	4.708±0.048
(*S*)-**10c**	>56.0	0.61±0.02	0.130±0.001	0.260±0.027	0.043±0.036
10d	>56.0	0.930±0.139	0.034±0.009	0.056±0.012	0.233±0.134
(*S*)-**10e**	9.64±0.71	0.100±0.014	0.022±0.003	0.047±0.009	0.0021±0.00019
10f	15.62±2.52	0.270±0.011	0.085±0.008	0.116±0.026	0.0046±0.0038
(*S*)-**12**	>56.0	32.64±3.17	6.97±0.80	9.72±1.60	>25
(*S*)-**15**	>56.0	0.350±0.016	<0.010	0.071±0.008	0.294±0.121
(*R*)-**15**	>56.0	>39.1	12.72±0.63	27.26±1.56	ND
GDC-0152[b]	29.8±4.6	0.258±0.015	0.102±0.012	0.144±0.014	0.041±0.006
	(0.112)	(0.028)	(0.017)	(0.043)	(0.014)

[a] Compounds **1a-1e**, **10d** and **10f** are diastereomixtures; otherwise major stereoisomer tested is indicated. [b] Measured values; reported values in parentheses, see structure above (Scheme 1A).

XIAP Fluorescence Polarization Assay Conditions

Binding of compounds to BIR1/2 of XIAP or BIR3 of XIAP was determined by fluorescence polarization. Assay buffer was 25 mM Hepes at pH 7.5/1 mM TCEP (Tris(2-carboxyethyl)phosphine hydrochloride)/0.005% Tween 20/ 20 nM AVPIAQK-rhodamine. BIR1/2 was present at 1 μM while BIR3 was present at 200 nM. Compound ranged from 100 μM to 0.0061 μM using 2 fold dilutions from the highest concentration. Assays were run in 384 well black plates read in an Analyst in fluorescence polarization mode with excitation at 530 nm, emission at 580 nm and a dichroic mirror at 565 nm. Data was fit to a nonlinear regression curve in Prism to determine the IC_{50} values of the compounds. K_i's were then calculated from the IC_{50} values.[1]

cIAP1 and cIAP2 Fluorescence Polarization Assay Conditions

Binding assays with cIAP1 BIR3 or cIAP2 BIR3 were done with Hepes at 25 mM, Tween 20 at 0.005% and AVPIAQK-rhodamine at 20 nM. cIAP1 BIR3 was at 0.095 μM while cIAP2 BIR3 was at 0.123 μM. Compound

ranged from 100 to 0.0061 μM by 2 fold dilutions. Assays were run in 384 well black plates read in an Analyst in fluorescence polarization mode with excitation at 530 nm, emission at 580 nm and a dichroic mirror at 565 nm. Data was fit to a nonlinear regression curve in Prism to determine the IC_{50} values of the compounds. *K*i's were then calculated from the IC_{50} values.

ML-IAP Fluorescence Polarization Assay Conditions

Binding of compounds to ML-IAP was determined by fluorescence polarization. Assay buffer was 25 mM Hepes at pH 7.5/1 mM TCEP (Tris(2-carboxyethyl)phosphine hydrochloride)/0.005% Tween 20/ 20 nM AVPIAQK-rhodamine. ML-IAP was present at 20 nM. Compound ranged from 200 μM to 0.00056 μM using 3 fold dilutions from the highest concentration. Assays were run in 384 well black plates read in a BMG POLARstar in fluorescence polarization mode with excitation at 544 nm and emission at 590 nm. Data was fit to a nonlinear regression curve in Prism to determine the IC_{50} values of the compounds. K_i's were then calculated from the IC_{50} values.

Caspase Derepression and Competition Fluorescence Polarization Assay Conditions

Purified recombinant human caspases 3 [0.1 nM], -7 [1 nM] or -9 [2.2 μM] were used in combination with XIAP BIR2 [1 nM] and BIR3 [2.1 μM]. During the derepression assay, caspases and the BIRs were allowed to form a complex for 30 minutes before the addition of increasing concentrations of the compound **10e**. For the competition assay, increasing concentrations of compound **10e** were added at the same time as the enzyme and inhibitor. The ratio of inhibited to uninhibited caspase activity (V_i/V_o) was obtained by monitoring the release of fluorescence from the fluorogenic substrates Ac-DEVD-afc for caspases 3 and -7 or Ac-LEHD-afc for caspase 9.

Caspase 3/7 Activity Assay

Caspase 3/7 activity assays in MDA-MB-231 cells pretreated with vehicle (0.1% DMSO) or 5 μM of **10e** or **10f** before treatment with 0 or 100 ng/mL TRAIL for 4 h. Activity is normalized to that of vehicle +TRAIL values (in the cases where TRAIL was used) or vehicle $^{-}$TRAIL (in the cases where TRAIL was not used) and all assays are carried out in triplicate as least twice. Caspase 3/7 activity was assessed utilizing CaspaseGlo® 3/7 Assay (Promega Corp., Madison, WI). Cells are seeded as for CellTiterGlo and treated as described. The assays were carried out exactly as per manufacturer's instructions before being read on a FlexStation3 plate reader utilizing SoftTek software.

TNF ELISA Assay Conditions

MDA-MB-231 and SKVO3 cells were cultured as described below before treatment with vehicle (0.1% DMSO) or 5 μM of **10e** or **10f**. 1 mL of media was removed after 6 h (6 h data not shown) and 24h and cellular debris pelleted at 16 k g for 2 min. 100 μL of supernatant was removed per sample in duplicate and TNF levels were assessed using a BD OptEIA™ Human TNF ELISA Kit II (BD Biosciences, San Jose, CA) exactly as per

manufacturer's instructions. The data was processed and graphed in excel and is expressed as averages +/- s.e.m. Error values are present, but small, thus making the error bars difficult to see.

Western Blot Analysis

Immunoblot analysis of cIAP1/2 and XIAP expression in MDA-MB-231 cells treated with vehicle (0.1% DMSO) or 5 μM of **10e** or **10f** for 24 h. Tot. Erk 1/2 and β-actin are shown as equal loading controls. Antibodies used are anti-pan-cIAP1/2 (Clone 315301, 1:1000, R&D Systems, Inc., Minneapolis, MN); anti-XIAP (#2042, 1:2000) and anti-Total Erk 1/2 (#9102, 1:5000) (both from Cell Signaling Technologies Inc. Beverly, MA); or anti-β-Actin (A5441, 1:10000, Sigma-Aldrich, St. Louis, MO).

MDA-MB-231 Cell Viability Assay Conditions

Five thousand cells per well were plated in a 96 well plate and incubated overnight at 37 ^{o}C / 5% CO_2. The following day, compounds in 2 fold dilutions were added to the plates and the plates returned to the incubator for 4 hrs. TRAIL at a final concentration of 5 ng/mL was then added to half the plate while an equivalent volume of culture media was added to the other half of the plate as a control. Twenty-three hrs later, plates were removed to the bench and 25 μL CellTiter Glo was added to each well and the plates were read for luminescence on a Luminoskan Ascent. Data was fit in Prism to a nonlinear regression curve to determine the LD_{50} of the compounds.

MDA-MB-231 Cell Viability Assay Conditions (TRAIL Dose-Response Assay)

Dose response cell viability assay of MDA-MB-231 cells cultured in the presence of vehicle (0.1% DMSO) or 5 μM of **10e** or **10f** for 4 h before addition of a dose of TRAIL for a further 20 h as described. Viability is assessed by ATP content using CellTiter Glo® (Promega Corp., Madison, WI) as per manufacturer's instructions. Values are normalized to that of vehicle/ drug alone and all experiments are carried out in at least triplicate at least three times. Error values are small and thus the error bars on the graph are difficult to discern, yet still present.

SKOV3 Cell Viability Assay Conditions

One thousand seven hundred cells per well were plated in a 384 well plate and incubated overnight at 37 °C / 5% CO_2. The following day, compounds in 10 fold dilutions were added to the plates and the plates returned to the incubator for 4 hrs. TRAIL at a final concentration of 100 ng/mL was then added to half the plate while an equivalent volume of culture media was added to the other half of the plate as a control. Twenty-three hrs later, plates were removed to the bench and 20 μL ATPlite was added to each well and the plates were read for luminescence on a BMG Labtech POLARstar. Data was fit in Prism to a nonlinear regression curve to determine the LD_{50} of the compounds.

HFF Cell Viability Assay Conditions

Normal human fibroblasts were maintained in DMEM with 10% (v/v) FBS, and penicillin/streptomycin/L-Glutamine (Omega Scientific Inc, Tarzana, CA). 5000 cells/well of a 96-well dish in 50 μL complete medium were seeded

and allowed to attach overnight. 40 μL of fresh media containing the specified drug at the concentrations described is added before re-incubation of the cells at 37 °C for 4 h. TRAIL to a final concentration of 100 ng/mL is added and the cells are again incubated at 37 °C for 20 h. Plates are removed to room temperature before addition of one half volume of freshly prepared CellTiterGlo reagent and luminescence is read on a Biotek Synergy 2 plate reader.

Molecular Modelling Specifications

The *ChemSketch* software (ACD Labs) was used to generate a 2D chemical structure of the ligand that was subsequently converted to 3D coordinate set using the Dictionary interface in the *MIFit* software (http://code.google.com/p/mifit/).

Modeling the protein:ligand complex was performed by generating a chain of low energy conformers from this starting model and overlaying selected common atoms onto the structurally related compound, (3S,6S,7R,9aS)-6-{[(2S)-2-aminobutanoyl]amino}-7-(2-aminoethyl)-N-(diphenylmethyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxamide, from the protein crystal structure of the cIAP1-BIR3 domain (entity SMK in PDB entry 3MUP).

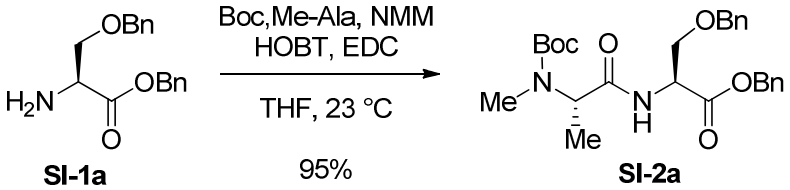
Low energy ligand conformers were generated using programs in the OpenBabel suite[2] by rotating atomic groups about randomly selected torsion angles with subsequent energy minimization. Target atoms for overlaying low energy conformers onto the docked pose of the known protein:ligand complex included the carbonyl and adjoining atoms in the central conjugated ring system. For each trial pose, the docked ligand was evaluated for the formation of acceptable non-bonded interactions with the protein binding site. Minor steric conflicts were relieved by relaxation of the conformation of the bound ligand. In parallel calculations the extent of the volume overlap with the known ligand was also assessed. All docking calculations and bound ligand evaluations were managed via the SDsearch interface.

Several docking runs of 1000 conformers each were performed in order to assess the available space in the protein binding site and the potential diversity of docking solutions. No solutions were obtained with ring puckers different from the related reference structure. When poses were scored so as to maximize volume overlap with the conformation of the known ligand the extent of the docked conformational ensemble was somewhat reduced and all of the allowed docking solutions were tightly clustered into two marginally distinct subsets.

Overall, these docking studies provided a relatively unique prediction for the protein:ligand complex in which the bound ligand adopts a low-energy conformation, makes plausible non-bonded interactions with the protein site and is consistent with previously determined cocrystal structures.

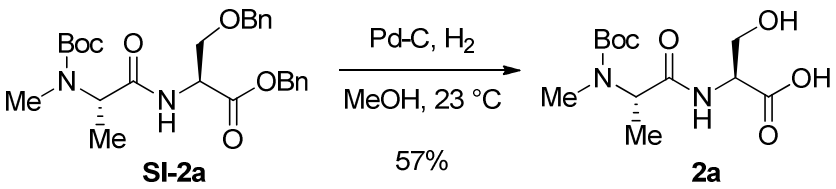
Experimental Procedures

General. All solvents were used as purchased from commercial sources or dried over 4Å molecular sieves prior to use in the case of moisture sensitive reactions. Reactions conducted under microwave irradiation were performed in a CEM Discover microwave reactor using either CEM 10 mL reaction vessels or a ChemGlass heavy wall pressure vessel (100 mL, 38 mm x 190 mm). Reaction progress was monitored by reverse-phase HPLC and/or thin-layer chromatography (TLC). High resolution mass spectrometry was performed using ESI-TOFMS, EI-MS (reference: perfluorokerosene) and APCI-MS. TLC was performed using silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed using silica gel (32-63 μm particle size) or aluminum oxide (activated, basic, ~150 mesh size). All products were purified to homogeneity by TLC analysis (single spot, unless stated otherwise), using a UV lamp and/or iodine and/or CAM or basic $KMnO_4$ for detection purposes. NMR spectra were recorded on 400 MHz and 500 MHz spectrometers at ambient temperature. ^1H and ^{13}C NMR chemical shifts are reported as δ using residual solvent as an internal standard; $CDCl_3$: 7.26, 77.16 ppm; CD_3OD: 3.31, 49.00 ppm; DMSO-d6: 2.50, 39.52 ppm, CD_3CN: 1.94 (^1H), 1.32 (^{13}C) ppm. Abbreviations used: alanine (Ala), *t*-butyloxycarbonyl (Boc), 1-hydroxybenzotriazole (HOBT), *N*-methylmorpholine (NMM), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC), palladium on carbon (Pd-C), dichloromethane (DCM), diethyl ether (Et_2O), ethyl acetate (EtOAc), 2,2,2-trifluoroethanol (TFE), methanol (MeOH), homoserine (HSer), homocysteine (HCys), triphenylmethyl or trityl (Trt), trifluoroacetic acid (TFA). Isocyanide **4e** was synthesized by the previously established route.[3]



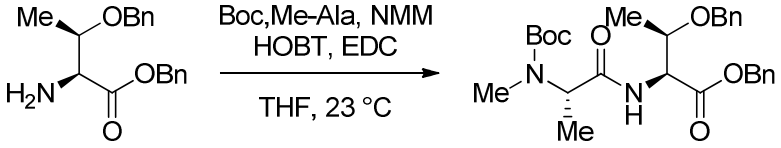
SI-1a **SI-2a**

(*S*)-Benzyl 3-(benzyloxy)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)propanoate (SI-2a). To a solution of **SI-1a** (1.74 g, 3.80 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (773 mg, 3.80 mmol, 1.0 equiv), HOBT·xH_2O (641 mg, 4.18 mmol, 1.1 equiv) and NMM (1.25 mL, 11.4 mmol, 3 equiv) in THF (45 mL) at 0 °C was added EDC·HCl (766 mg, 3.99 mmol, 1.05 equiv). After 30 min the cold bath was removed. The solution stirred for 14 h and then was quenched with saturated aqueous $NaHCO_3$ (50 mL), extracted with EtOAc (2 x 40 mL), dried over sodium sulfate and then concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (5:1→4:1→3:1 hexanes/EtOAc) to yield **SI-2a** (1.70 g, 95%). R_f = 0.20 (5:1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.27 (m, 8H), 7.19 (dd, 2H, *J* = 2.0, 8.0 Hz), 5.18 (q, 2H, *J* = 12.0 Hz), 4.79-4.74 (m, 1H), 4.45 (q, 2H, *J* = 12.0 Hz), 3.89 (dd, 1H, *J* = 3.2, 9.6 Hz), 3.66 (dd, 1H, *J* = 3.2, 9.6 Hz), 2.75 (s, 3H), 1.45 (s, 9H), 1.34 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$). δ: 171.6, 170.0, 137.5, 135.4, 128.7, 128.5, 128.5, 128.3, 127.9, 127.7, 73.4, 69.8, 67.4, 52.9, 30.0, 28.4, 13.9; HRMS calcd for $C_{26}H_{34}N_2O_6Na$: 493.23091, found 493.23211.



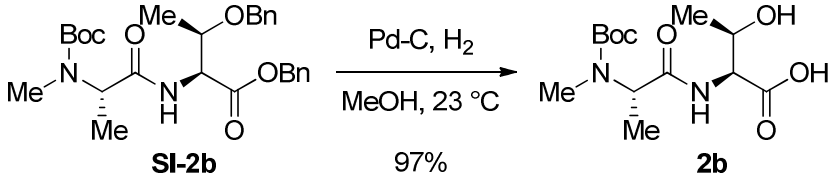
SI-2a **2a**

(*S*)-2-((*S*)-2-((*Tert*-butoxycarbonyl)(methyl)amino)propanamido)-3-hydroxypropanoic acid (2a). To a solution of **SI-2a** (1.70 g, 3.61 mmol, 1.0 equiv) in methanol (25 mL) was added 10 wt% Pd-C (100 mg). A balloon of H_2 was applied for 16 h, then the mixture was filtered through Celite with DCM and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc→100% DCM→5% MeOH/DCM) to yield **2a** (591 mg, 57%). R_f = 0.12 (7% MeOH/DCM). ^{1}H NMR (400 MHz, CD_3OD) δ: 4.41 (t, 1H, *J* = 3.6 Hz), 3.91 (dd, 1H, *J* = 4.4, 10.8 Hz), 3.83 (dd, 1H, *J* = 4.0, 11.2 Hz), 3.35-3.34 (m, 1H), 2.86 (s, 3H), 1.47 (s, 9H), 1.38 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, CD_3CN) δ: 207.9, 173.1, 172.4, 81.0, 62.6, 55.4, 30.9, 28.5. HRMS calcd for $C_{12}H_{22}N_2O_6Na$: 313.1370, found 313.1371.



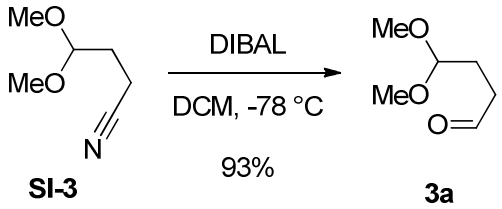
SI-1b **SI-2b**

(2*S*,3*R*)-Benzyl 3-(benzyloxy)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)butanoate (SI-2b). Same procedure as above (**SI-2a**) using **SI-1b** (4.65 g, 11.9 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (2.43 g, 11.9 mmol, 1.0 equiv), HOBT·xH_2O (2.19 g, 14.3 mmol, 1.1 equiv), NMM (3.94 mL, 35.8 mmol, 3 equiv) and EDC·HCl (2.75 g, 14.3 mmol, 1.05 equiv) in THF (100 mL). The resultant oil was purified by flash chromatography on silica gel (5:1→4:1→2:1 hexanes/EtOAc) to yield **SI-2b** (3.32 g, 57%). R_f = 0.26 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.25 (m, 8H), 7.17-7.15 (m, 2H), 5.14 (d, 1H, *J* = 6.0 Hz), 5.06 (d, 1H, *J* = 6.0 Hz), 4.67 (dd, 1H, *J* = 2.4, 9.2 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.27 (d, 1H, *J* = 12.0 Hz), 4.15 (qd, 1H, *J* = 2.0, 6.0 Hz), 2.79 (s, 3H), 1.60 (s, 1H), 1.42 (s, 9H), 1.35 (d, 3H, *J* = 7.2 Hz), 1.16 (d, 3H, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.2, 170.4, 135.5, 128.7, 128.7, 128.5, 128.5, 128.5, 128.4, 127.8, 127.8, 74.3, 70.9, 67.3, 56.8, 28.4, 16.4. HRMS calcd for $C_{27}H_{36}N_2O_6Na$: 507.2466, found 507.2468.



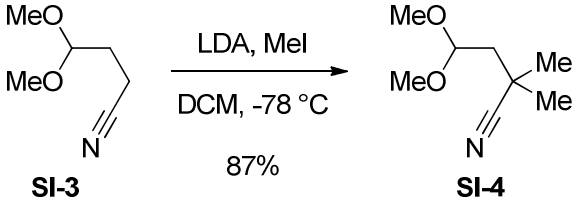
SI-2b **2b**

(2*S*,3*R*)-2-((*S*)-2-((*Tert*-butoxycarbonyl)(methyl)amino)propanamido)-3-hydroxybutanoic acid (2b). Same procedure as above (**2a**) using **SI-2b** (3.306 g, 6.82 mmol, 1.0 equiv) and 10 wt% Pd-C (150 mg) in methanol (50 mL). The resultant oil was sufficiently pure as a crude product, **2b** (2.01 g, 97%). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.44 (bs, 1H), 4.70 (bs, 1H), 4.40-4.36 (m, 1H), 4.33 (dd, 1H, *J* = 2.8, 6.4 Hz), 2.87 (s, 3H), 1.48 (s, 9H), 1.39 (d, 3H, *J* = 7.2 Hz), 1.18 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 174.7, 173.7, 157.5, 81.9, 68.2, 59.0, 55.7, 30.9, 28.6, 20.7, 14.9. HRMS calcd for $C_{13}H_{24}N_2O_6Na$: 327.15266, found 327.15236.



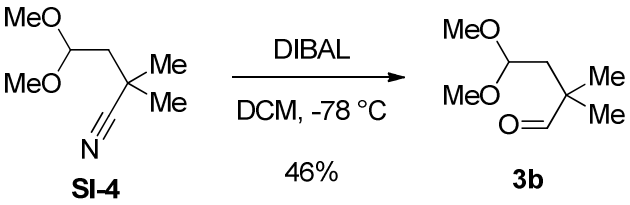
SI-3 **3a**

4,4-Dimethoxybutanal (3a). To a solution of **SI-3** (1.2 g, 9.29 mmol, 1.0 equiv) in DCM (75 mL) at -78 ºC under N_2 was added 1.1 M DIBAL in cyclohexane (23.23 mL, 10.2 mmol, 1.1 equiv). After 3 h at -78 ºC, the mixture was slowly warmed to r.t. and quenched with sat. aq. NH_4Cl (25 mL) and Rochelle salt (25 mL). Reaction progress was monitored by TLC (vanillin stain). After stirring for 1 h, the mixture was extracted with DCM (3 x 20 mL). The organics were then washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to yield a colorless, relatively volatile liquid **3a** (1.14 g, 93%) which was sufficiently pure to use without further purification. The analytical data match those previously reported.[4]



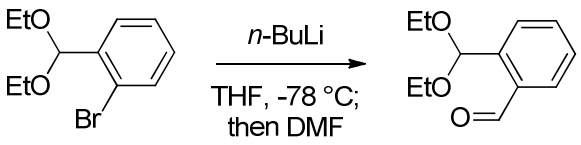
SI-3 **SI-4**

4,4-Dimethoxy-2,2-dimethylbutanenitrile (SI-4). To a solution of diisopropylamine (4.77 mL, 34.1 mmol, 2.2 equiv) in THF (50 mL) at -10 ºC under N_2 was added 1.5 M *n*-BuLi in hexanes (22.7 mL, 34.1 mmol, 2.2 equiv). After 30 min the mixture was cooled to -78 ºC and a solution of **SI-3** (2.0 g, 15.5 mmol, 1.0 equiv) in THF (10 mL) was added. After 1 h iodomethane (2.12 mL, 34.1 mmol, 2.2 equiv) was added. The mixture was slowly warmed to 0 ºC and kept there for 14 h, at which time it was quenched with sat. aq. NH_4Cl (40 mL) and extracted with EtOAc (3 x 20 mL). The organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (5:1→3:1 hexanes/EtOAc) to yield **SI-4** (2.105 g, 87%) as a yellow oil. R_f = 0.49 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.60 (t, 1H, *J* = 5.6 Hz), 3.37 (s, 6H), 1.83 (d, 2H, *J* = 4.4 Hz), 1.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 124.7, 102.4, 53.3, 43.0, 30.0, 27.5



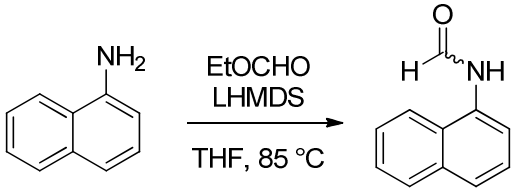
SI-4 **3b**

4,4-Dimethoxy-2,2-dimethylbutanal (3b). Same procedure as above (**3a**) using **SI-4** (500 mg, 3.18 mmol, 1.0 equiv) in DCM (25 mL) and 1.1 M DIBAL in cyclohexane (3.18 mL, 10.2 mmol, 1.1 equiv). The resultant oil was purified by flash chromatography on silica gel (DCM) to yield **3b** (232 mg, 46%) as a colorless, relatively volatile oil. Yield is highly variable and dependent upon extent of drying as the compound is fairly volatile. R_f = 0.39 (7:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.39 (s, 1H), 4.36 (t, 1H, *J* = 6.0 Hz), 3.30 (s, 6H), 1.85 (d, 2H, *J* = 5.6 Hz), 1.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.7, 102.7, 53.7, 43.9, 41.6, 21.9.



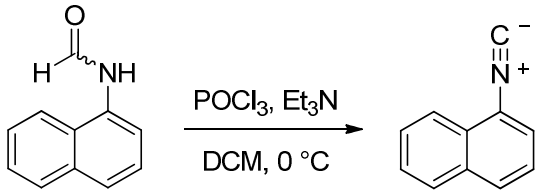
SI-5 quant. **3c**

2-(Diethoxymethyl)benzaldehyde (3c). To a solution of **SI-5** (1.94 g, 7.49 mmol, 1.0 equiv) in THF (20 mL) at -78 ºC under N_2 was added 1.5 M *n*-BuLi in hexanes (7.49 mL, 11.2 mmol, 1.5 equiv). After 30 min DMF (869 μL, 11.2 mmol, 1.5 equiv) was added. The mixture was slowly warmed to r.t. over 4 h, at which time it was quenched with sat. aq. NH_4Cl (40 mL) and extracted with EtOAc (3 x 20 mL). The organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (95:4:1 hexanes/EtOAc/Et_3N) to yield **3c** (1.34 g, quantitative) as a yellow oil. R_f = 0.46 (3:1 hexanes/EtOAc). The analytical data match those previously reported.[5]



SI-6a 64% **SI-7a**

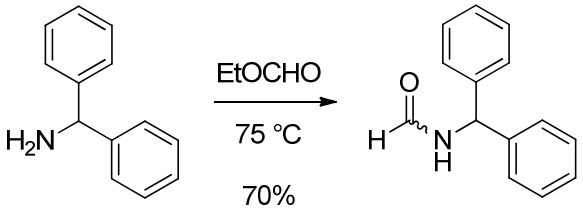
***N*-(Naphthalen-1-yl)formamide (SI-7a).** To a mixture of 1-naphthylamine (**SI-6a**, 6.0 g, 41.9 mmol, 1.0 equiv) and ethyl formate (6.74 mL, 83.8 mmol, 2 equiv) in THF (200 mL) was added 1 M LHMDS in THF (75.4 mL, 75.4 mmol, 1.8 equiv). The mixture was heated to 85 ºC for 14 h and then concentrated. The resulting solid was filtered and rinsed with hexanes to yield the first batch of **SI-7a**. The filtrate was concentrated and the filtration procedure was repeated for a second batch of product to finally yield **SI-7a** (3.05 g, 64%) as a brown solid and a 2:1 mixture of rotational isomers. R_f = 0.10 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65-8.61 (m, 2H), 8.45 (bs, 1H), 8.04-7.99 (m, 2H), 7.92-7.85 (m, 2H), 7.80 (d, 1H, *J* = 8.4 Hz), 7.73 (d, 1H, *J* = 8.0 Hz), 7.63-7.51 (m, 3H), 7.50-7.44 (m, 2H), 7.32 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 159.7, 134.4, 134.2, 132.2, 131.1, 129.0, 128.7, 127.9, 127.2, 127.2, 127.2, 127.0, 126.7, 126.4, 126.3, 125.9, 125.7, 121.4, 121.0, 120.5, 119.3. HRMS calcd for $C_{11}H_9NO$: 171.0679, found 171.0681.



SI-7a 79% **4b**

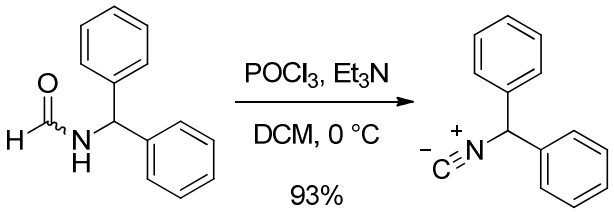
1-Isocyanonaphthalene (4b). To a solution of **SI-7a** (1.048 g, 6.12 mmol, 1.0 equiv) in DCM (20 mL) at 0 ºC was added Et_3N (4.33 mL, 31.2 mmol, 5.1 equiv) followed by phosphorus oxychloride (841 μL, 9.18 mmol, 1.5 equiv). The mixture was warmed to 23 ºC and stirred for 2 h, at which time it was poured into a mixture of saturated $NaHCO_3$ (40 mL) and 1 M NaOH (20 mL) and extracted with DCM (3 x 20 mL). The organics were dried over

Na_2SO_4, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (1:1 hexanes/DCM) to yield **4b** (740 mg, 79%) as a brown oil which was stored at 0 °C. R_f = 0.72 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, 1H, *J* = 8.4 Hz), 7.90 (d, 2H, *J* = 8.0 Hz), 7.68 (t, 1H, *J* = 7.6 Hz), 7.61 (t, 2H, *J* = 7.2 Hz), 7.45 (td, 1H, *J* = 2.4, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 133.7, 129.9, 128.5, 128.2, 128.1, 127.6, 125.1, 124.7, 123.1. HRMS calcd for $C_{11}H_8N$: 154.06513, found 154.06671.



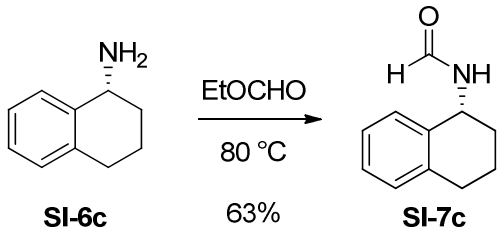
SI-6b **SI-7b**

***N*-Benzhydrylformamide (SI-7b).** A mixture of benzhydrylamine (**SI-6b**, 4.0 g, 21.8 mmol, 1.0 equiv) and ethyl formate (2.0 mL, 24.9 mmol, 1.14 equiv) was heated to 75 °C for 14 h. EtOAc was added and the mixture was triturated by sonication, then filtered and rinsed with Et_2O to yield **SI-7b** (3.24g, 70%) as a white solid. The compound exists as a mixture of rotational isomers. R_f = 0.29 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 7.34-7.19 (m, 10H), 6.69 (d, 1H, *J* = 6.0 Hz), 6.27 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 141.0, 128.8, 127.7, 127.5, 55.7. HRMS calcd for $C_{14}H_{14}NO$: 212.10699, found 212.100748.



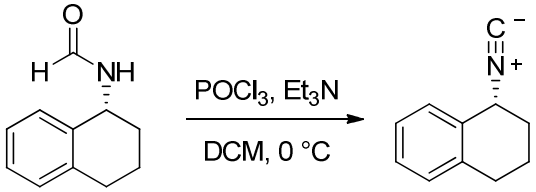
SI-7b **4c**

(Isocyanomethylene)dibenzene (4c). To a solution of **SI-7b** (1.727 g, 8.17 mmol, 1.0 equiv) in DCM (35 mL) at 0 ºC was added Et_3N (5.79 mL, 41.7 mmol, 5.1 equiv) followed by phosphorus oxychloride (1.12 mL, 12.3 mmol, 1.5 equiv). The mixture was warmed to 23 ºC and stirred for 18 h, at which time it was poured into a mixture of saturated $NaHCO_3$ (50 mL) and 1 M NaOH (20 mL) and extracted with DCM (3 x 30 mL). The organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (DCM→5:1 DCM/EtOAc) to yield **4c** (1.467 g, 93%) as an orange solid which was stored at 0 °C. R_f = 0.73 (7:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41-7.33 (m, 10H), 5.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 137.7, 129.1, 128.6, 126.7, 77.2, 62.1. HRMS calcd for $C_{14}H_{11}NNa$: 216.07837, found 216.07971.

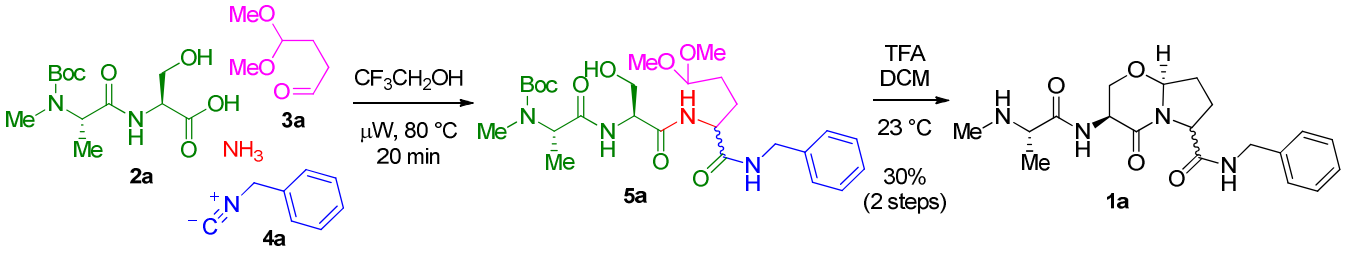


SI-6c **SI-7c**

(*R*)-*N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)formamide (SI-7c). A mixture of (*R*)-(−)-1,2,3,4-tetrahydro-1-naphthylamine (**SI-6c**, 10.0 g, 67.9 mmol, 1 equiv) and ethyl formate (6.23 mL, 77.4 mmol, 1.14 equiv) was heated to 80 °C for 14 h. Hexanes was added and the mixture was triturated by sonication, then filtered and rinsed with hexanes to yield **SI-7c** (7.44 g, 63%) as a tan solid. R_f = 0.22 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (s, 1H), 7.29-7.25 (m, 1H), 7.23-7.16 (m, 2H), 7.13-7.08 (m, 1H), 5.82 (bs, 1H), 5.28 (dd, 1H, *J* = 5.2, 14.0 Hz), 2.85-2.73 (m, 2H), 2.15-2.03 (m, 1H), 1.88-1.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 137.7, 136.1, 129.4, 128.8, 127.6, 126.5, 46.4, 30.3, 29.3, 20.0. HRMS calcd for $C_{11}H_{13}NONa$: 198.0889, found 198.0890.

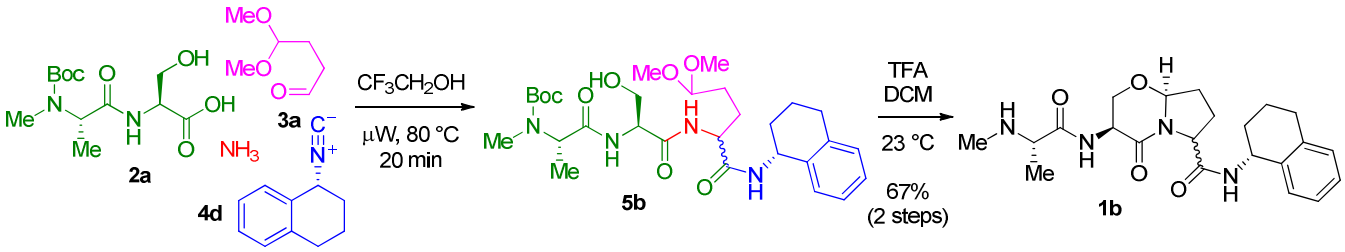


(*R*)-1-Isocyano-1,2,3,4-tetrahydronaphthalene (4d). To a solution of **SI-7c** (2.85 g, 16.3 mmol, 1.0 equiv) in DCM (40 mL) at 0 ºC was added Et_3N (11.51 mL, 82.9 mmol, 5.1 equiv) followed by phosphorus oxychloride (2.23 mL, 24.4 mmol, 1.5 equiv). The mixture was warmed to 23 ºC and stirred for 2 h, at which time it was poured into saturated $NaHCO_3$ (200 mL) and extracted with DCM (2 x 100 mL). The organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (3:1→1:1 hexanes/DCM) to yield **4d** (1.76 g, 69%) as a brown oil which was stored at 0 °C. R_f = 0.59 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.43 (m, 1H), 7.26-7.23 (m, 2H), 7.14-7.11 (m, 1H), 4.83 (app. s, 1H), 2.92-2.84 (m, 1H), 2.80-2.72 (m, 1H), 2.18-2.12 (m, 2H), 2.11-2.01 (m, 1H), 1.87-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 136.5, 132.1, 129.5, 128.6, 128.6, 126.7, 52.6, 30.7, 28.6, 19.4. HRMS calcd for $C_{11}H_{12}N$: 158.0964, found 158.0966.

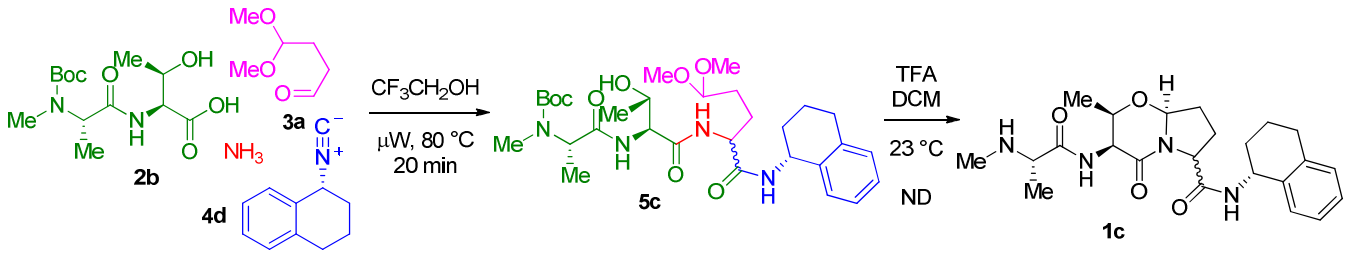


(3*S*,8a*S*)-*N*-Benzyl-3-((*S*)-2-(methylamino)propanamido)-4-oxohexahydro-2*H*-pyrrolo[2,1-b][1,3]oxazine-6-carboxamide (1a). A mixture of carboxylic acid **2a** (93 mg, 0.320 mmol, 1.0 equiv), aldehyde **3a** (44 mg, 0.336 mmol, 1.05 equiv), benzyl isocyanide (**4a**) (38 mg, 0.320 mmol, 1.0 equiv) and 7 M ammonia in MeOH (92 μL, 0.641 mmol, 2.0 equiv) in TFE (3 mL) was stirred under microwave irradiation at a set temperature of 80 ºC for 20 min. The mixture was then transferred to a round bottom flask and concentrated in vacuo, then 1 M NaOH (15 mL) was added and the mixture was extracted with DCM (3 x 7 mL). The organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant oil **5a** was combined with TFA (147 μL, 1.92 mmol, 6 equiv) in DCM (5 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and the product purified by

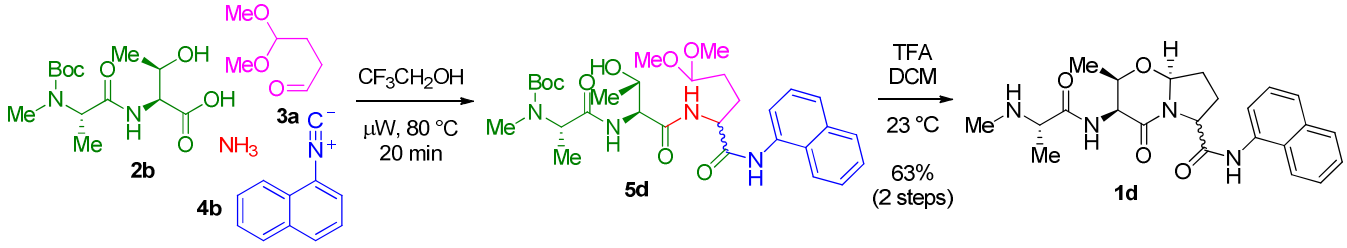
flash chromatography on basic alumina (3:1 hexanes/EtOAc→DCM→7% MeOH/DCM) to yield **1a** as a 1:1 diastereomixture of the the free base (36 mg, 30% over 2 steps). Some of the material was further purified by preparative scale HPLC for use in biological assays. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.51 (bs, 1H), 7.33-7.28 (m, 8H), 7.26-7.21 (m, 2H), 5.23 (t, 1H, *J* = 5.2 Hz), 5.16 (dd, 1H, *J* = 5.2, 8.4 Hz), 4.68 (dd, 1H, *J* = 3.2, 6.4 Hz), 4.61-4.56 (m, 2H), 4.48 (d, 1H, *J* = 15.2 Hz), 4.42-4.33 (m, 4H), 4.28 (dd, 1H, *J* = 6.4, 11.6 Hz), 4.24 (dd, 1H, *J* = 6.0, 11.6 Hz), 4.01 (dd, 1H, *J* = 3.2, 11.6 Hz), 3.92 (dd, 1H, *J* = 3.2, 11.6 Hz), 3.69 (q, 2H, *J* = 6.8 Hz), 2.61 (s, 3H), 2.60 (s, 3H), 2.41-2.29 (m, 2H), 2.26-2.16 (m, 2H), 1.94-1.82 (m, 2H), 1.49 (d, 3H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 173.6, 173.4, 167.9, 167.1, 139.7, 139.7, 129.5, 129.5, 128.4, 128.4, 128.2, 128.2, 91.1, 90.9, 71.7, 70.8, 60.7, 59.8, 58.8, 44.2, 44.0, 32.3, 32.2, 32.2, 31.2, 27.2, 26.7, 16.8, 16.7. HRMS calcd for $C_{19}H_{27}N_4O_4$: 375.2027, found 375.2028.



(3*S*,8a*S*)-3-((*S*)-2-(Methylamino)propanamido)-4-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)hexahydro-2*H*-pyrrolo[2,1-b][1,3]oxazine-6-carboxamide (1b). Same procedure as above (**1a**) with carboxylic acid **2a** (97 mg, 0.334 mmol, 1.0 equiv), aldehyde **3a** (46 mg, 0.351 mmol, 1.05 equiv), isocyanide **4d** (53 mg, 0.334 mmol, 1.0 equiv) and 7 M ammonia in MeOH (97 μL, 0.668 mmol, 2.0 equiv) in TFE (3 mL). The resultant oil **5b** was combined with TFA (177 μL, 1.55 mmol, 6 equiv) in DCM (5 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and the product purified by flash chromatography on basic alumina (3:1 hexanes/EtOAc→DCM→7% MeOH/DCM) to yield **1b** as the free base (72 mg, 67% over 2 steps). Some of the material was further purified by preparative scale HPLC for use in biological assays. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (s, 1H), 7.40-7.36 (m, 1H), 7.17-7.06 (m, 7H), 5.24 (dd, 1H, *J* = 4.8, 6.4 Hz), 5.17 (dd, 1H, *J* = 4.8, 8.0 Hz), 5.10-5.04 (m, 2H), 4.66-4.62 (m, 2H), 4.57 (t, *J* = 8.0 Hz), 4.35 (d, 1H, *J* = 7.6 Hz), 4.27 (dd, 1H, *J* = 6.4, 11.6 Hz), 4.24 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.76-3.65 (m, 2H), 2.87-2.72 (m, 4H), 2.63 (s, 3H), 2.61 (s, 3H), 2.43-2.31 (m, 2H), 2.28-2.17 (m, 2H), 2.05-1.88 (m, 7H), 1.86-1.74 (m, 5H), 1.52 (d, 3H, *J* = 7.2 Hz), 1.49 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.6, 172.9, 172.8, 171.7, 167.7, 167.0, 138.7, 138.5, 137.6, 137.6, 130.1, 129.9, 129.7, 129.3, 128.2, 128.1, 127.2, 127.2, 127.1, 91.1, 91.0, 71.6, 70.9, 60.8, 59.8, 58.9, 58.8, 58.8, 32.3, 32.3, 32.2, 31.3, 31.3, 31.2, 30.2, 30.2, 27.2, 26.8, 21.8, 21.5, 16.8, 16.7. HRMS calcd for $C_{22}H_{30}N_4O_4Na$: 437.21593, found 437.20535.

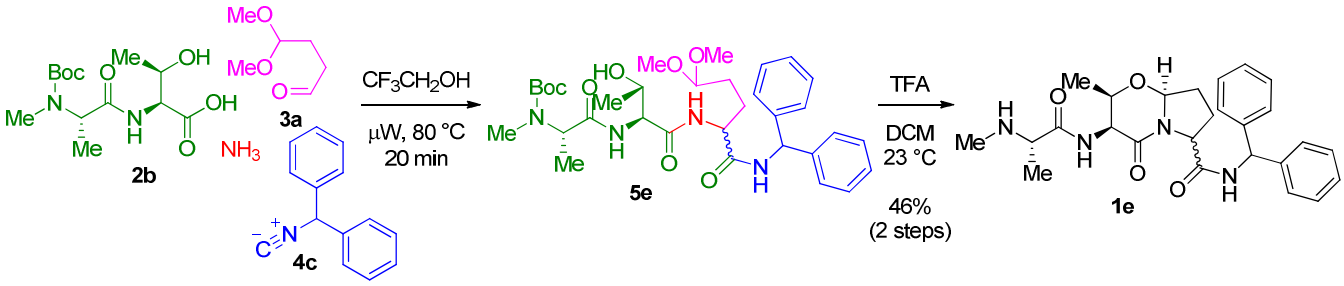


(2*R*,3*S*,8a*S*)-2-Methyl-3-((*S*)-2-(methylamino)propanamido)-4-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)hexahydro-2*H*-pyrrolo[2,1-b][1,3]oxazine-6-carboxamide (1c). Same procedure as above (**1a**) with carboxylic acid **2b** (85 mg, 0.279 mmol, 1.0 equiv), aldehyde **3a** (39 mg, 0.293 mmol, 1.05 equiv), isocyanide **4d** (44 mg, 0.279 mmol, 1.0 equiv) and 7 M ammonia in MeOH (80 μL, 0.559 mmol, 2.0 equiv) in TFE (3 mL). The resultant oil **5c** was combined with TFA (128 μL, 1.67 mmol, 6 equiv) in DCM (5 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and the product purified by flash chromatography on basic alumina (3:1 hexanes/EtOAc→DCM→7% MeOH/DCM) to yield **1c** as a slightly impure free base (94 mg, 79% semi-pure). Some of the material was further purified by preparative scale HPLC for use in biological assays and data collection. ^{1}H NMR (400 MHz, DMSO-d6) δ: 8.28 (d, 1H, *J* = 8.8 Hz), 8.26 (d, 1H, *J* = 8.8 Hz), 8.24 (s, 2H), 8.18 (d, 1H, *J* = 8.8 Hz), 8.00 (d, 1H, *J* = 8.8 Hz), 7.28 (d, 1H, *J* = 7.2 Hz), 7.16-7.06 (m, 6H), 5.25 (t, 1H, *J* = 5.6 Hz), 5.20 (dd, 1H, *J* = 5.2, 7.6 Hz), 4.99-4.92 (m, 2H), 4.60 (dd, 1H, *J* = 5.6, 8.4 Hz), 4.50 (dd, 1H, *J* = 5.2, 8.4 Hz), 4.46 (t, 1H, *J* = 7.2 Hz), 4.34-4.27 (m, 2H), 4.24 (t, 2H, *J* = 8.4 Hz), 3.13 (q, 1H, *J* = 6.8 Hz), 3.09 (q, 1H, *J* = 6.8 Hz), 2.76-2.70 (m, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.93-1.80 (m, 6H), 1.80-1.60 (m, 6H), 1.17 (d, 3H, *J* = 6.8 Hz), 1.15 (d, 3H, *J* = 6.8 Hz), 1.07 (d, 3H, *J* = 6.4 Hz), 1.00 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, DMSO-d6) δ: 174.1, 170.3, 169.9, 165.7, 165.2, 137.6, 137.4, 137.0, 136.9, 128.7, 128.5, 128.3, 127.7, 126.7, 126.6, 125.8, 125.7, 99.5, 87.7, 87.6, 73.4, 72.6, 59.2, 58.8, 58.7, 57.9, 50.5, 50.3, 46.6, 46.5, 34.0, 33.7, 30.7, 30.0, 29.9, 28.8, 28.8, 26.0, 25.7, 20.5, 18.9, 18.7, 16.5. HRMS calcd for $C_{23}H_{32}N_4O_4Na$: 451.23158, found 451.23286.

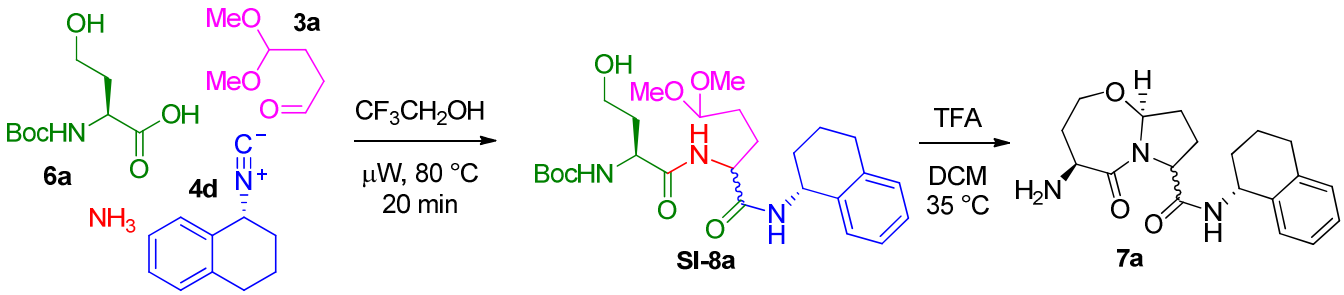


(2*R*,3*S*,8a*S*)-2-Methyl-3-((*S*)-2-(methylamino)propanamido)-*N*-(naphthalen-1-yl)-4-oxohexahydro-2*H*-pyrrolo[2,1-b][1,3]oxazine-6-carboxamide (1d). Same procedure as above (**1a**) with carboxylic acid **2b** (100 mg, 0.328 mmol, 1.0 equiv), aldehyde **3a** (46 mg, 0.344 mmol, 1.05 equiv), isocyanide **4b** (50 mg, 0.328 mmol, 1.0 equiv) and 7 M ammonia in MeOH (94 μL, 0.657 mmol, 2.0 equiv) in TFE (3 mL). The resultant oil **5d** was combined with TFA (151 μL, 1.97 mmol, 6 equiv) in DCM (5 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and the product purified by flash chromatography on basic alumina (1:1 hexanes/EtOAc→DCM→7% MeOH/DCM) to yield **1d** as the free base (88 mg, 63% over 2 steps). Some of the material was further purified by preparative scale HPLC for use in biological assays. ^{1}H NMR (400 MHz, CD_3OD)

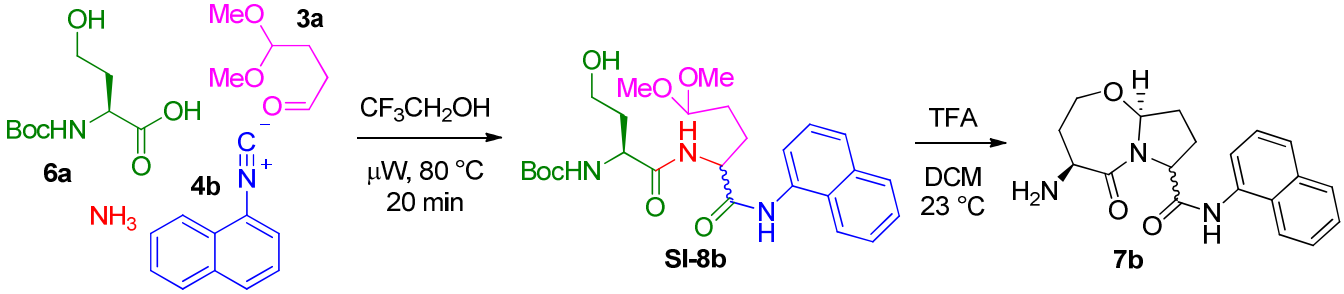
δ: 8.53 (bs, 1H), 8.13-8.09 (m, 1H), 8.05 (d, 1H, *J* = 6.8 Hz), 7.92-7.87 (m, 2H), 7.81 (t, 2H, *J* = 6.4 Hz), 7.56-7.46 (m, 8H), 5.29 (dd, 1H, *J* = 5.2, 8.0 Hz), 5.21 (dd, 1H, *J* = 4.8, 8.4 Hz), 4.83 (t, 1H, *J* = 8.4 Hz), 4.71-4.67 (m, 2H), 4.62 (d, 1H, *J* = 4.0 Hz), 4.36-4.24 (m, 2H), 3.70 (q, 1H, *J* = 6.8 Hz), 3.65 (q, 1H, *J* = 6.8 Hz), 2.59 (s, 3H), 2.52 (s, 3H), 2.42-2.32 (m, 2H), 2.31-2.18 (m, 2H), 2.16-2.02 (m, 2H), 1.96-1.85 (m, 1H), 1.50 (d, 3H, *J* = 6.8 Hz), 1.38 (d, 3H, *J* = 7.2 Hz), 1.24 (t, 6H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 173.3, 173.2, 172.7, 172.4, 168.3, 167.5, 135.7, 135.7, 134.0, 133.7, 130.6, 130.6, 129.3, 129.2, 128.2, 128.1, 127.5, 127.4, 127.3, 127.2, 126.4, 126.4, 124.6, 124.3, 124.1, 123.8, 91.0, 90.9, 76.3, 75.7, 60.6, 59.5, 59.1, 58.9, 52.8, 52.5, 32.6, 32.4, 32.2, 31.2, 26.7, 26.2, 17.3, 17.2, 16.7. HRMS calcd for $C_{23}H_{29}N_4O_4$: 425.2183, found 425.2181.



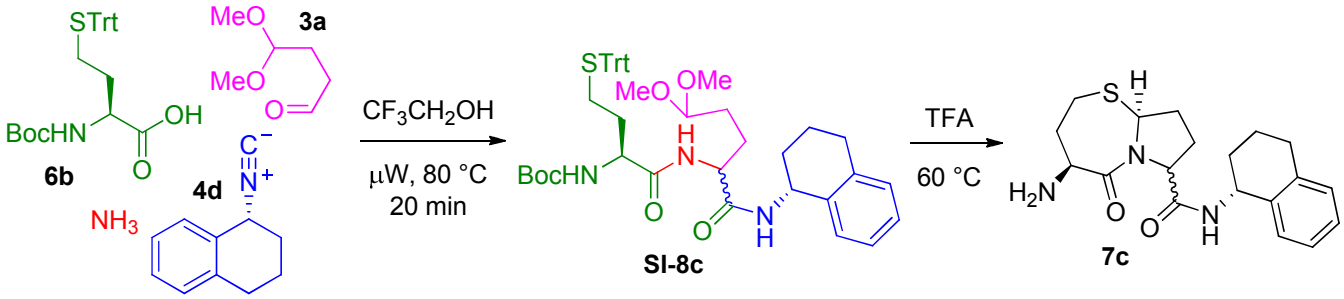
(2*R*,3*S*,8a*S*)-*N*-Benzhydryl-2-methyl-3-((*S*)-2-(methylamino)propanamido)-4-oxohexahydro-2*H*-pyrrolo[2,1-b][1,3]oxazine-6-carboxamide (1e). Same procedure as above (**1a**) with carboxylic acid **2b** (105 mg, 0.345 mmol, 1.0 equiv), aldehyde **3a** (47 mg, 0.362 mmol, 1.05 equiv), isocyanide **4c** (67 mg, 0.345 mmol, 1.0 equiv) and 7 M ammonia in MeOH (99 μL, 0.690 mmol, 2.0 equiv) in TFE (3 mL). The resultant oil **5e** was combined with TFA (159 μL, 2.07 mmol, 6 equiv) in DCM (5 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and the product purified by flash chromatography on basic alumina (1:1 hexanes/EtOAc→DCM→7% MeOH/DCM) to yield **1e** as the free base (73 mg, 46% over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.38-7.18 (m, 20H), 6.17 (s, 1H), 6.15 (s, 1H), 5.21 (dd, 1H, *J* = 5.2, 8.0 Hz), 5.13 (dd, 1H, *J* = 4.8, 8.8 Hz), 4.66 (t, 1H, *J* = 7.6 Hz), 4.62 (d, 1H, *J* = 4.4 Hz), 4.56 (d, 1H, *J* = 4.4 Hz), 4.47 (d, 1H, *J* = 8.4 Hz), 4.28 (dd, 1H, *J* = 4.4, 6.4 Hz), 4.22 (dd, 1H, *J* = 4.4, 6.4 Hz), 3.25 (q, 1H, *J* = 6.8 Hz), 3.21 (q, 1H, *J* = 6.8 Hz), 2.36 (s, 3H), 2.30 (s, 3H), 2.39-2.25 (m, 2H), 2.19-2.12 (m, 2H), 2.06-1.86 (m, 4H), 1.85-1.79 (m, 2H), 1.31 (d, 3H, *J* = 6.8 Hz), 1.26 (d, 3H, *J* = 7.2 Hz), 1.20 (d, 3H, *J* = 6.4 Hz), 1.18 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 176.8, 176.6, 173.0, 172.7, 168.0, 167.6, 143.0, 142.8, 142.6, 142.6, 129.7, 129.6, 129.5, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.3, 128.1, 90.7, 90.6, 76.3, 75.5, 60.4, 60.3, 60.0, 59.2, 58.5, 58.4, 52.5, 52.2, 34.2, 34.1, 32.1, 31.1, 29.5, 26.7, 26.1, 19.2, 19.1, 16.8, 16.7. HRMS calcd for $C_{26}H_{32}N_4O_4Na$: 487.23158, found 487.23308.



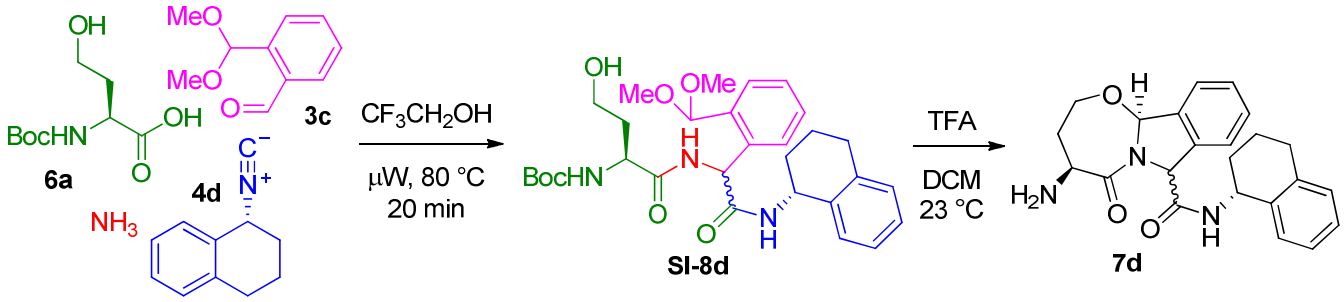
(4*S*,9a*S*)-4-Amino-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (7a). A mixture of Boc-*N*-HSer-OH (**6a**) (318 mg, 1.45 mmol, 1.0 equiv), aldehyde **3a** (201 mg, 1.52 mmol, 1.05 equiv), isocyanide **4d** (228 mg, 1.45 mmol, 1.0 equiv) and 7 M ammonia in MeOH (414 μL, 2.90 mmol, 2.0 equiv) in TFE (5 mL) was stirred under microwave irradiation at a set temperature of 80 ºC for 20 min. The mixture was then transferred to a round bottom flask and concentrated in vacuo, then 1 M NaOH (15 mL) was added and the mixture was extracted with DCM (3 x 7 mL). The organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant oil **SI-8a** was combined with TFA (834 μL, 10.9 mmol, 8 equiv) in DCM (5 mL) and stirred at 35 ºC for 14 h. The mixture was concentrated in vacuo and **7a** used without further purification in the next step.



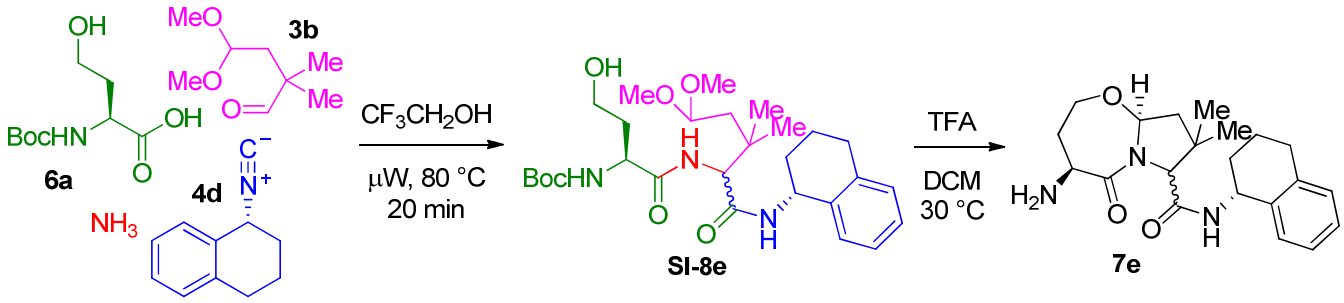
(4*S*,9a*S*)-4-Amino-*N*-(naphthalen-1-yl)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (7b). Same procedure as above (**7a**) with Boc-*N*-HSer-OH (**6a**) (150 mg, 0.684 mmol, 1.0 equiv), aldehyde **3a** (95 mg, 0.718 mmol, 1.05 equiv), isocyanide **4b** (105 mg, 0.684 mmol, 1.0 equiv) and 7 M ammonia in MeOH (195 μL, 1.37 mmol, 2.0 equiv) in TFE (4 mL). The resultant oil **SI-8b** was combined with TFA (314 μL, 4.10 mmol, 6 equiv) in DCM (5 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and **7b** used without further purification in the next step.



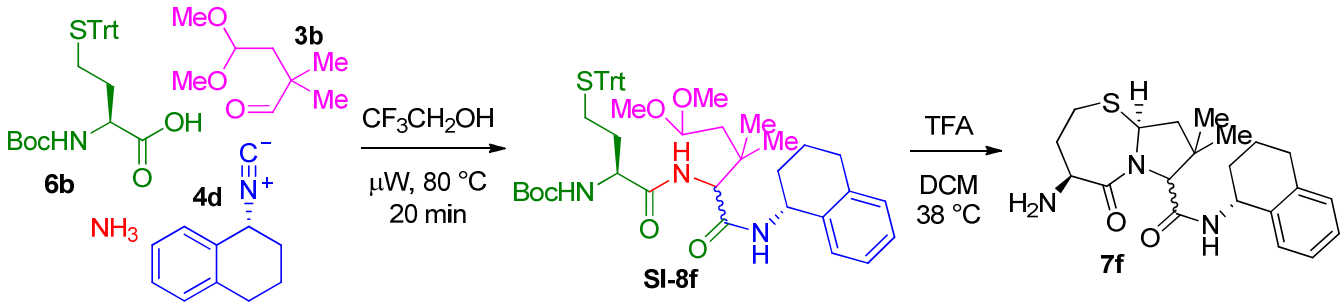
(4*S*,7*S*,9a*S*)-4-Amino-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]thiazepine-7-carboxamide (7c). Same procedure as above (**7a**) with Boc-*N*-HCys(Trt)-OH (**6b**) (665 mg, 1.39 mmol, 1.0 equiv), aldehyde **3a** (193 mg, 1.46 mmol, 1.05 equiv), isocyanide **4d** (219 mg, 1.39 mmol, 1.0 equiv) and 7 M ammonia in MeOH (398 μL, 2.78 mmol, 2.0 equiv) in TFE (5 mL). The resultant oil **SI-8c** was combined with TFA (1.07 mL, 13.9 mmol, 10 equiv) in DCM (5 mL) and stirred at 60 ºC for 6 h. The mixture was concentrated in vacuo, then partially purified (trityl byproduct removed and more polar product(s) collected) by flash chromatography on basic alumina (3:1 hexanes/EtOAc→DCM→7% MeOH/DCM) to yield semi-pure **7c**.



(4*S*,11b*S*)-4-Amino-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)-2,3,4,5,7,11b-hexahydro-[1,3]oxazepino[2,3-a]isoindole-7-carboxamide (7d). Same procedure as above (**7a**) with Boc-*N*-HSer-OH (**6a**) (175 mg, 0.800 mmol, 1.0 equiv), aldehyde **3c** (144 mg, 0.800 mmol, 1.0 equiv), isocyanide **4d** (126 mg, 0.800 mmol, 1.0 equiv) and 7 M ammonia in MeOH (229 μL, 1.60 mmol, 2.0 equiv) in TFE (4 mL). The resultant oil **SI-8d** was combined with TFA (490 μL, 6.40 mmol, 8 equiv) in DCM (3 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and **7d** used without further purification in the next step.

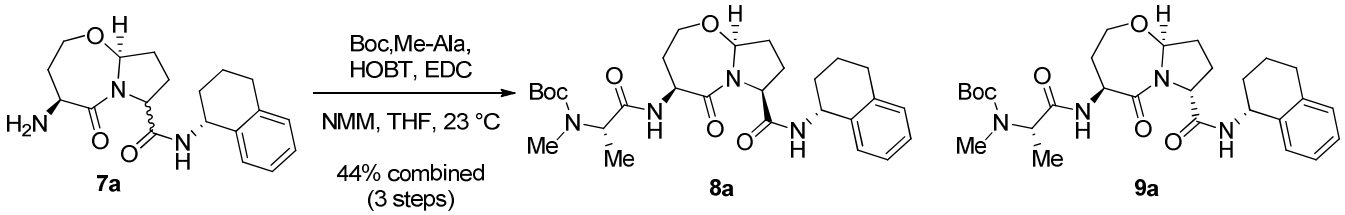


(4*S*,9a*S*)-4-Amino-8,8-dimethyl-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (7e). Same procedure as above (**7a**) with Boc-*N*-HSer-OH (**6a**) (157 mg, 0.718 mmol, 1.0 equiv), aldehyde **3b** (144 mg, 0.718 mmol, 1.0 equiv), isocyanide **4d** (113 mg, 0.718 mmol, 1.0 equiv) and 7 M ammonia in MeOH (205 μL, 1.44 mmol, 2.0 equiv) in TFE (4 mL). The resultant oil **SI-8e** was combined with TFA (473 μL, 7.18 mmol, 10 equiv) in DCM (4 mL) and stirred at 30 ºC for 14 h. The mixture was concentrated in vacuo and **7e** used without further purification in the next step.



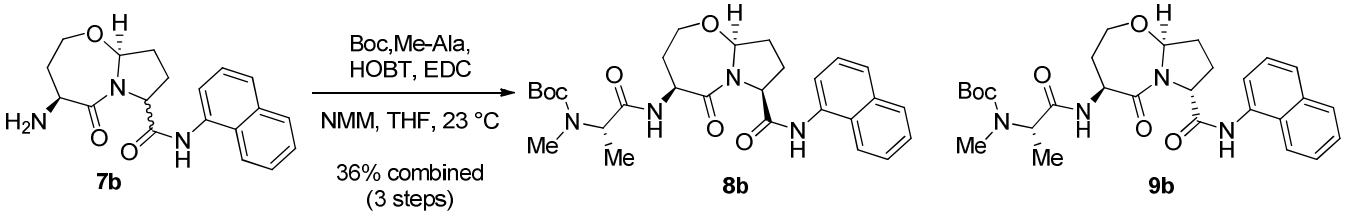
(4*S*,7*S*,9a*S*)-4-Amino-8,8-dimethyl-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]thiazepine-7-carboxamide (7f). Same procedure as above (**7a**) with Boc-*N*-HCys(Trt)-OH (**6b**) (500 mg, 1.05 mmol, 1.0 equiv), aldehyde **3b** (176 mg, 1.10 mmol, 1.05 equiv), isocyanide **4d** (165 mg, 1.05 mmol, 1.0 equiv) and 7 M ammonia in MeOH (299 μL, 2.09 mmol, 2.0 equiv) in TFE (5 mL). The resultant oil **SI-8f** was

combined with TFA (804 μL, 10.5 mmol, 10 equiv) in DCM (5 mL) and stirred at 38 ºC for 14 h. The mixture was concentrated in vacuo, then partially purified (trityl byproduct removed and more polar product(s) collected) by flash chromatography on basic alumina (3:1 hexanes/EtOAc→DCM→7% MeOH/DCM) to yield semi-pure **7f**.



7a **8a** **9a**

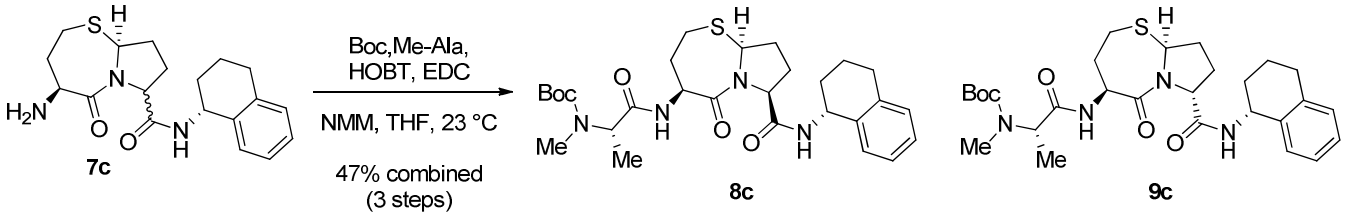
***tert*-Butyl methyl((2*S*)-1-oxo-1-(((4*S*,9a*S*)-5-oxo-7-(((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)octahydropyrrolo[2,1-b][1,3]oxazepin-4-yl)amino)propan-2-yl)carbamate (8a) and (9a).** To a solution of crude **7a**•TFA (622 mg, 1.36 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (276 mg, 1.36 mmol, 1.0 equiv), HOBT·xH_2O (229 mg, 1.50 mmol, 1.1 equiv) and NMM (598 μL, 5.44 mmol, 4 equiv) in THF (15 mL) at 0 °C was added EDC·HCl (274 mg, 1.43 mmol, 1.05 equiv). After 30 min the cold bath was removed. The solution stirred for 14 h and then was quenched with saturated aqueous $NaHCO_3$ (25 mL), extracted with EtOAc (2 x 20 mL), dried over sodium sulfate and then concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (2:1→1:1→1:3 hexanes/EtOAc) to yield, after 3 steps, partially separated diastereomers **8a** (30 mg, 4%, ~3:1 d.r.) and **9a** (40 mg, 5%, ~3:1 d.r.), along with unseparated **8a**+**9a** (267 mg, 35%). Data for **8a:** R_f = 0.40 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23-7.05 (m, 4H), 6.84 (d, 1H, *J* = 8.0 Hz), 5.22 (t, 1H, *J* = 6.4 Hz), 5.18-5.08 (m, 1H), 4.69 (dd, 1H, *J* = 5.6, 10.8 Hz), 4.62 (d, 1H, *J* = 7.6 Hz), 4.13-4.03 (m, 1H), 3.95 (q, 1H, *J* = 12.8 Hz), 2.75 (s, 3H), 2.80-2.74 (m, 1H), 2.47-2.37 (m, 1H), 2.17-1.89 (m, 4H), 1.88-1.69 (m, 5H), 1.43 (s, 9H), 1.32 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 169.9, 169.8, 137.6, 137.3, 136.9, 136.7, 129.3, 129.2, 128.6, 128.3, 27.4, 127.3, 126.4, 126.2, 90.3, 90.0, 70.7, 70.6, 61.1, 60.6, 53.1, 52.6, 47.7, 47.7, 33.3, 32.7, 32.5, 30.2, 30.1, 29.8, 29.3, 29.3, 28.4, 28.4, 25.9, 20.5, 20.1. Data for **9a**: R_f = 0.55 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24-7.11 (m, 4H), 7.11-7.05 (m, 1H), 6.69 (bs, 1H), 5.21 (d, 1H, *J* = 5.6 Hz), 5.10 (q, 1H, *J* = 6.8 Hz), 4.75 (dd, 1H, *J* = 7.6, 11.6 Hz), 4.55 (d, 1H, *J* = 8.0 Hz), 4.47 (t, 1H, *J* = 8.8 Hz), 4.01 (d, 1H, *J* = 12.8 Hz), 3.97 (t, 1H, *J* = 12.4 Hz), 2.82-2.75 (m, 2H), 2.77 (s, 3H), 2.45-2.33 (m, 1H), 2.32-2.24 (m, 1H), 2.24-2.13 (m, 2H), 2.06-1.93 (m, 3H), 1.84-1.76 (m, 2H), 1.74-1.64 (m, 5H), 1.45 (s, 9H), 1.34 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 171.0, 169.8, 137.6, 136.7, 129.3, 128.6, 127.4, 126.4, 90.0, 70.6, 66.0, 61.2, 53.2, 47.8, 33.3, 32.7, 30.2, 29.3, 28.5, 25.8, 20.2, 14.0. HRMS calcd for $C_{28}H_{40}N_4O_6$: 551.2840, found 551.2838.



7b **8b** **9b**

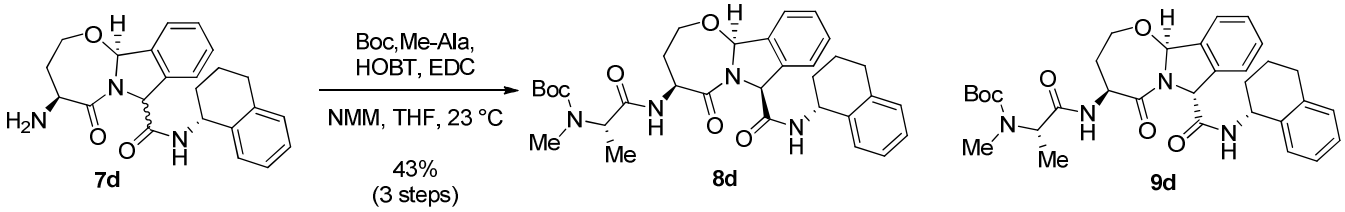
***tert*-Butyl methyl((2*S*)-1-(((4*S*,9a*S*)-7-(naphthalen-1-ylcarbamoyl)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepin-4-yl)amino)-1-oxopropan-2-yl)carbamate (8b) and (9b).** Same procedure as above (**8a**) using

crude **7b**•TFA (209 mg, 0.615 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (125 mg, 0.615 mmol, 1.0 equiv), HOBT·xH_2O (104 mg, 0.677 mmol, 1.1 equiv), NMM (338 μL, 3.08 mmol, 5 equiv [to soak up xs TFA]) and EDC·HCl (124 mg, 0.646 mmol, 1.05 equiv) in THF (10 mL). The resultant oil was purified by flash chromatography on silica gel (2:1→1:1→1:3 hexanes/EtOAc) to yield, after 3 steps, separated diastereomers **8b** (43 mg, 12%, ~6:1 d.r.) and **9b** (37 mg, 10%, ~6:1 d.r.), along with unseparated **8b**+**9b** (49 mg, 14%). Data for **8b**: R_f = 0.33 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.10 (d, 1H, *J* = 7.6 Hz), 7.98 (d, 1H, *J* = 8.8 Hz), 7.86 (d, 1H, *J* = 8.0 Hz), 7.67 (d, 1H, *J* = 8.4 Hz), 7.56-7.44 (m, 3H), 7.32 (s, 1H), 5.33 (t, 1H, *J* = 6.4 Hz), 4.90 (d, 1H, *J* = 6.4 Hz), 4.81 (dd, 1H, *J* = 5.2, 10.4 Hz), 4.19 (dt, 1H, *J* = 2.8, 12.8 Hz), 4.07-3.98 (m, 1H), 2.78 (s, 3H), 2.59-2.46 (m, 2H), 2.32-2.21 (m, 1H), 2.01-1.91 (m, 3H), 1.85-1.74 (m, 1H), 1.44 (s, 9H), 1.36 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 171.4, 169.1, 168.5, 134.1, 132.7, 128.9, 126.6, 126.5, 126.0, 125.9, 125.5, 120.7, 119.8, 90.7, 70.8, 61.2, 52.8, 32.8, 32.6, 30.2, 28.5, 28.4, 25.6. Data for **9b**: R_f = 0.42 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.47 (s, 1H), 8.03 (d, 1H, *J* = 7.2 Hz), 7.94 (d, 1H, *J* = 7.6 Hz), 7.82 (d, 1H, *J* = 7.6 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.55 (s, 1H), 7.50-7.40 (m, 2H), 7.31 (s, 1H), 5.21 (s, 1H), 4.96 (d, 1H, *J* = 7.6 Hz), 4.85-4.78 (m, 1H), 4.43 (t, 1H, *J* = 8.8 Hz), 4.14 (d, 1H, *J* = 12.8 Hz), 3.99 (t, 1H, *J* = 12.0 Hz), 2.79 (s, 3H), 2.61-2.53 (m, 1H), 2.26-2.14 (m, 1H), 2.11-1.97 (m, 2H), 1.90-1.78 (m, 1H), 1.46 (s, 9H), 1.34 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 173.3, 172.4, 168.5, 134.1, 132.8, 128.7, 126.5, 126.1, 125.8, 125.4, 121.0, 119.5, 90.3, 70.6, 65.9, 61.6, 53.2, 49.2, 33.6, 32.5, 30.3, 30.3, 28.5, 28.5, 28.4, 24.6. HRMS calcd for $C_{28}H_{36}N_4O_6Na$: 547.25271, found 547.25362.



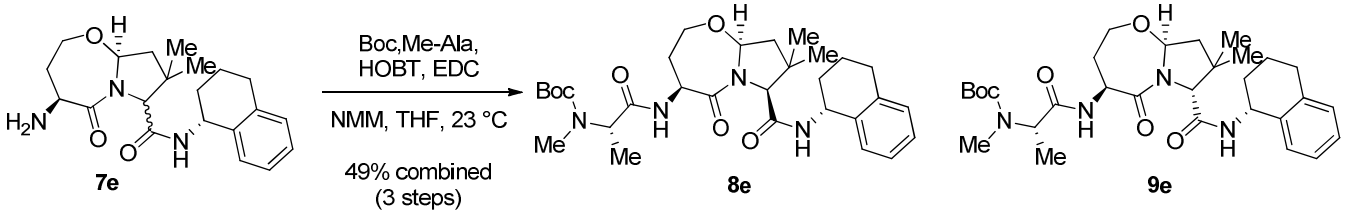
***tert*-Butyl methyl((2*S*)-1-oxo-1-(((4*S*,9a*S*)-5-oxo-7-(((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)octahydropyrrolo[2,1-b][1,3]thiazepin-4-yl)amino)propan-2-yl)carbamate (8c) and (9c).** Same procedure as above (**8a**) using crude **7c**•TFA (658 mg, 1.39 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (282 mg, 1.39 mmol, 1.0 equiv), HOBT·xH_2O (234 mg, 1.39 mmol, 1.1 equiv), NMM (917 μL, 8.34 mmol, 6 equiv [to soak up xs TFA]) and EDC·HCl (280 mg, 1.46 mmol, 1.05 equiv) in THF (18 mL). The resultant oil was purified by flash chromatography on silica gel (1:1→1:2→1:3 hexanes/EtOAc) to yield, after 3 steps, separated diastereomers **8c** (121 mg, 16%, ~3:1 d.r.) and **9c** (100 mg, 13%, ~3:1 d.r.) along with unseparated **8c**+**9c** (136 mg, 18%). Data for **8c**: R_f = 0.27 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, 1H, *J* = 7.6 Hz), 7.25-7.21 (m, 1H), 7.16-7.04 (m, 4H), 5.17 (q, 1H, *J* = 7.2 Hz), 5.08 (t, 1H, *J* = 7.2 Hz), 4.74 (d, 1H, *J* = 8.0 Hz), 4.53 (dd, 1H, *J* = 6.0, 10.8 Hz), 3.35-3.22 (m, 1H), 2.76 (s, 3H), 2.63-2.46 (m, 1H), 2.20 (d, 1H, *J* = 12.8 Hz), 2.12-1.98 (m, 2H), 1.92-1.71 (m, 5H), 1.59 (q, 1H, *J* = 12.4 Hz), 1.43 (s, 9H), 1.31 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 169.6, 169.3, 137.3, 129.2, 129.1, 128.8, 127.2, 126.1, 62.3, 61.8, 52.8, 47.6, 33.0, 32.1, 30.4, 30.2, 29.3, 28.4, 28.4, 26.5, 20.5. Data for **9c**: R_f = 0.44 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22-7.12 (m, 4H), 7.09-7.04 (m, 1H), 6.62 (bs, 1H), 5.28 (d, 1H, *J* = 7.6 Hz), 5.09 (d, 1H, *J* = 6.4 Hz), 4.66-4.56 (m, 2H), 3.32 (t,

1H, *J* = 12.0 Hz), 2.87-2.68 (m, 3H), 2.75 (s, 3H), 2.35-2.19 (m, 3H), 2.08-1.96 (m, 2H), 1.85-1.69 (m, 5H), 1.45 (s, 9H), 1.29 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 169.6, 137.6, 136.6, 129.3, 128.6, 127.4, 126.3, 63.8, 61.3, 53.5, 47.7, 33.7, 31.7, 30.1, 29.3, 28.5, 28.4, 20.1. HRMS calcd for $C_{28}H_{40}N_4O_5SNa$: 567.26116, found 567.26151.



7d **8d** **9d**

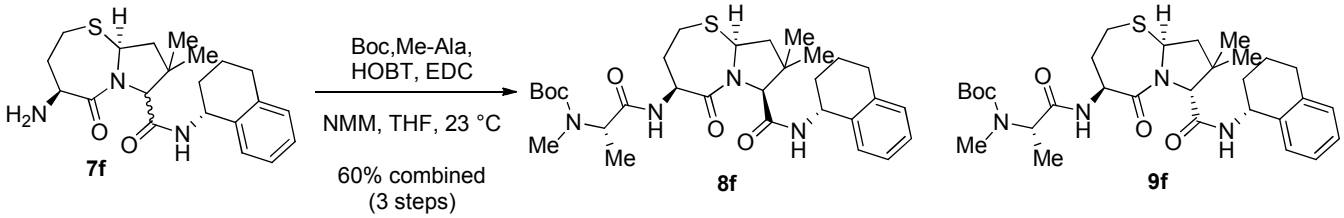
***tert*-Butyl methyl((2*S*)-1-oxo-1-(((4*S*,11b*S*)-5-oxo-7-(((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)-2,3,4,5,7,11b-hexahydro-[1,3]oxazepino[2,3-a]isoindol-4-yl)amino)propan-2-yl)carbamate (8d) and (9d).** Same procedure as above (**8a**) using crude **7d**•TFA (323 mg, 0.640 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (130 mg, 0.640 mmol, 1.0 equiv), HOBT·xH_2O (108 mg, 0.704 mmol, 1.1 equiv), NMM (281 μL, 2.56 mmol, 4 equiv) and EDC·HCl (129 mg, 0.672 mmol, 1.05 equiv) in THF (12 mL). The resultant oil was purified by flash chromatography on silica gel (3:1→1:1→1:2 hexanes/EtOAc) to yield, after 3 steps, the unseparated diastereomixture **8d**+**9d** (200 mg, 43%). By NMR, one of the diastereomers seems to exist as a pair of rotational isomers. R_f = 0.18 (1:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, 1H, *J* = 7.6 Hz), 7.47 (q, 1H, *J* = 4.4 Hz), 7.44-7.39 (m, 5H), 7.38-7.34 (m, 1H), 7.32-7.27 (m, 1H), 7.18-7.14 (m, 3H), 7.10-7.06 (m, 1H), 7.03 (d, 1H, *J* = 7.2 Hz), 6.90 (d, 1H, *J* = 7.2 Hz), 6.74 (d, 1H, *J* = 7.6 Hz), 6.44-6.36 (m, 3H), 6.21 (s, 1H), 5.50 (bs, 2H), 5.17-5.10 (m, 1H), 5.03 (dd, 1H, *J* = 8.0, 14.4 Hz), 4.88-4.80 (m, 2H), 4.72-4.66 (m, 1H), 4.44 (td, 2H, *J* = 8.8 Hz), 4.31-4.15 (m, 5H), 2.80 (s, 3H), 2.79 (s, 3H), 2.77 (s, 3H), 2.71 (t, 4H, *J* = 6.4 Hz), 2.22-2.08 (m, 3H), 2.06-1.98 (m, 2H), 1.86-1.73 (m, 5H), 1.71-1.61 (m, 2H), 1.48 (s, 9H), 1.46 (s, 9H), 1.35 (d, 3H, *J* = 7.2 Hz), 1.34 (d, 3H, *J* = 7.2 Hz), 1.33 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 172.4, 170.5, 168.3, 168.1, 137.7, 137.2, 136.8, 136.5, 136.5, 135.9, 135.7, 135.7, 135.2, 130.7, 130.5, 129.4, 129.3, 129.0, 128.7, 127.8, 127.4, 127.2, 126.4, 126.2, 125.0, 125.0, 122.9, 122.3, 122.3, 92.0, 91.5, 71.4, 71.4, 66.7, 66.5, 65.9, 53.3, 52.8, 49.2, 47.9, 47.7, 30.3, 29.3, 29.2, 28.5, 28.4, 28.4, 20.4, 20.2. HRMS calcd for $C_{32}H_{41}N_4O_6Na$: 599.28401, found 599.28561.



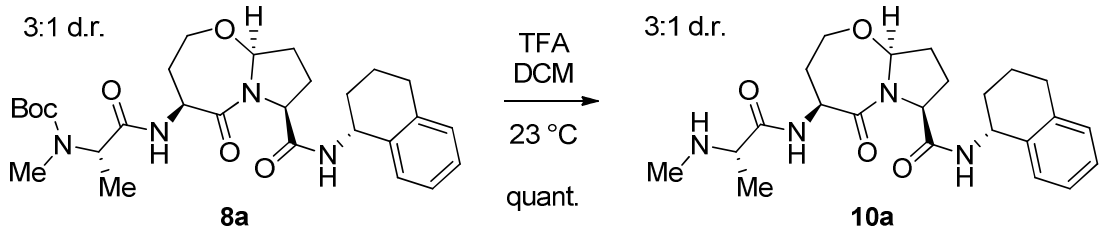
7e **8e** **9e**

***tert*-Butyl ((*S*)-1-(((4*S*,7*S*,9a*S*)-8,8-dimethyl-5-oxo-7-(((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)octahydropyrrolo[2,1-b][1,3]oxazepin-4-yl)amino)-1-oxopropan-2-yl)(methyl)carbamate (8e) and (9e).** Same procedure as above (**8a**) using crude **7e**•TFA (270 mg, 0.555 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (113 mg, 0.555 mmol, 1.0 equiv), HOBT·xH_2O (93 mg, 0.610 mmol, 1.1 equiv), NMM (366 μL, 3.33 mmol, 6 equiv [to soak up xs TFA]) and EDC·HCl (112 mg, 0.582 mmol, 1.05 equiv) in THF (10 mL). The resultant oil was purified by flash chromatography on silica gel (3:1→1:1→1:3 hexanes/EtOAc) to yield, after 3 steps, separated

diastereomer **8e** (29 mg, 7%, >10:1 d.r.) along with unseparated **8e**+**9e** (168 mg, 42%). Data for **8e**: R_f = 0.30 (1:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29-7.25 (m, 2H), 7.17-7.12 (m, 2H), 7.09-7.05 (m, 1H), 6.72 (d, 1H, *J* = 8.0 Hz), 5.24 (t, 1H, *J* = 5.6 Hz), 5.16 (dd, 1H, *J* = 5.6, 6.8 Hz), 4.70 (dd, 1H, *J* = 5.6, 11.2 Hz), 4.16 (s, 1H), 4.05-3.98 (m, 1H), 3.93 (q, 1H, *J* = 12.4 Hz), 2.79 (s, 3H), 2.78-2.73 (m, 2H), 2.19 (dd, 1H, *J* = 6.8, 14.0 Hz), 2.06-1.96 (m, 2H), 1.88 (dd, 1H, *J* = 6.0, 14.0 Hz), 1.87-1.69 (m, 5H), 1.66-1.60 (m, 1H), 1.47 (s, 9H), 1.34 (d, 3H, *J* = 7.2 Hz), 1.18 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 168.8, 137.3, 136.7, 136.6, 129.2, 128.9, 127.4, 126.4, 89.3, 89.2, 70.9, 70.7, 52.6, 47.5, 46.1, 39.6, 30.2, 29.7, 29.2, 28.5, 28.4, 23.8, 21.2, 19.9, 14.3, 14.0. Data for **9e**: R_f = 0.39 (1:3 hexanes/EtOAc). HRMS calcd for $C_{30}H_{44}N_4O_6Na$: 579.3153, found 579.3155.

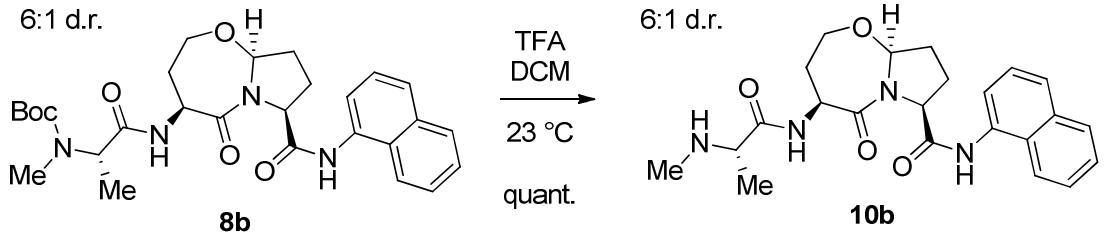


***tert*-Butyl ((2*S*)-1-(((4*S*,9a*S*)-8,8-dimethyl-5-oxo-7-(((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)octahydropyrrolo[2,1-b][1,3]thiazepin-4-yl)amino)-1-oxopropan-2-yl)(methyl)carbamate (8f) and (9f).** Same procedure as above (**8a**) using crude **7f**•TFA (387 mg, 0.998 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (202 mg, 0.998 mmol, 1.0 equiv), HOBT·xH_2O (168 mg, 1.10 mmol, 1.1 equiv), NMM (329 μL, 2.99 mmol, 3 equiv) and EDC·HCl (201 mg, 1.05 mmol, 1.05 equiv) in THF (10 mL). The resultant oil was purified by flash chromatography on silica gel (3:1→1:1→1:3 hexanes/EtOAc) to yield, after 3 steps, separated diastereomer **8f** (12 mg, 2%) and **9f** (47 mg, 8%), along with unseparated **8f**+**9f** (300 mg, 50%) and unreacted Boc-**7f** (59 mg, 12%) left over from the previous reaction. Data for diastereomixture: ^{1}H NMR (400 MHz, CD_3OD) δ: 7.32-7.28 (m, 1H), 7.18-7.11 (m, 6H), 7.10-7.06 (m, 2H), 5.49 (d, 1H, *J* = 9.2 Hz), 5.41 (q, 1H, *J* = 8.0 Hz), 5.09 (t, 1H, *J* = 6.0 Hz), 5.03 (t, 1H, *J* = 6.0 Hz), 5.03 (t, 1H, *J* = 12.0 Hz), 4.69-4.57 (m, 4H), 4.24 (d, 1H, *J* = 12.4 Hz), 4.19-4.16 (m, 1H), 3.31 (d, 2H, *J* = 2.0 Hz), 3.29-3.21 (m, 2H), 2.86 (s, 6H), 2.81 (s, 3H), 2.80-2.75 (m, 2H), 2.68-2.56 (m, 1H), 2.31-2.20 (m, 3H), 2.02-1.75 (m, 13H), 1.48 (s, 18H), 1.37 (d, 3H, *J* = 7.6 Hz), 1.32 (d, 3H, *J* = 7.2 Hz), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 172.7, 171.8, 171.4, 138.8, 138.5, 137.4, 137.4, 130.2, 130.1, 130.0, 130.0, 129.8, 129.8, 128.5, 128.3, 128.2, 127.2, 73.3, 73.3, 63.9, 61.9, 61.7, 54.8, 54.2, 54.1, 47.6, 47.2, 40.9, 40.9, 40.8, 33.8, 33.2, 32.2, 31.3, 31.2, 31.1, 30.8, 30.2, 30.1, 28.7, 28.7, 28.7, 25.3, 23.9, 21.3, 21.0. Data for **8f**: R_f = 0.24 (1:1 hexanes/EtOAc). Data for **9f**: R_f = 0.38 (1:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.29 (m, 1H), 7.20-7.12 (m, 3H), 7.08 (d, 1H, *J* = 7.2 Hz), 6.00 (d, 1H, *J* = 8.8 Hz), 5.33 (d, 1H, *J* = 8.8 Hz), 5.14-5.07 (m, 1H), 4.57-4.47 (m, 1H), 4.06-4.02 (m, 1H), 3.28 (t, 1H, *J* = 12.8 Hz), 2.85-2.79 (m, 2H), 2.76 (s, 3H), 2.34-2.26 (m, 1H), 2.01-1.90 (m, 2H), 1.87-1.73 (m, 6H), 1.47 (s, 9H), 1.35 (s, 3H), 1.30 (d, 3H, *J* = 7.2 Hz), 1.25-1.20 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 170.6, 170.6, 169.3, 137.9, 136.3, 129.4, 129.1, 129.0, 127.5, 126.3, 73.0, 62.8, 53.9, 47.8, 46.5, 39.9, 39.8, 33.3, 32.7, 30.6, 30.1, 29.3, 28.5, 28.5, 24.6, 19.8. HRMS calcd for $C_{30}H_{44}N_4O_5S$: 595.2925, found 595.2922.



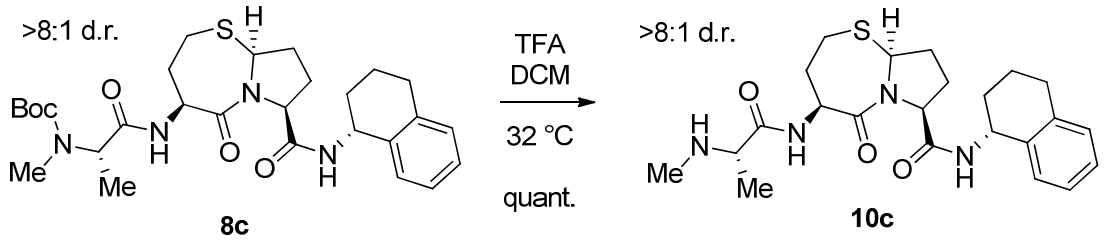
8a **10a**

(4*S*,7*S*,9a*S*)-4-((*S*)-2-(Methylamino)propanamido)-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (10a). To a solution of **8a** (30 mg, 0.057 mmol, 1 equiv, ~3:1 d.r.) in DCM (2 mL) was added TFA (35 μL, 0.454 mmol, 8 equiv). After stirring for 20 h at 23 °C, the solution was concentrated. The product was eluted through a short plug (~400 mg) of Silicyle® TMA-chloride ion exchange resin with MeOH to yield **10a**•HCl (26 mg, quantitative) as the major diastereomer (~3:1). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.38-7.35 (m, 1H), 7.15-7.06 (m, 3H), 5.41-5.38 (m, 1H), 5.09-5.03 (m, 1H), 4.42 (t, 1H, *J* = 6.4 Hz), 4.15 (dt, 1H, *J* = 2.8, 12.8 Hz), 4.04-3.96 (m, 1H), 3.95-3.89 (m, 1H), 2.86-2.71 (m, 2H), 2.67 (s, 3H), 2.32-2.25 (m, 1H), 2.12 (q, 2H, *J* = 7.2 Hz), 2.06-1.96 (m, 2H), 1.94-1.85 (m, 1H), 1.85-1.74 (m, 2H), 1.58 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 173.4, 172.7, 172.7, 172.2, 169.6, 169.3, 138.6, 138.5, 137.8, 137.7, 130.0, 130.0, 129.6, 129.2, 128.2, 128.1, 127.1, 91.0, 71.3, 71.2, 62.4, 62.4, 58.4, 58.3, 54.4, 54.2, 34.0, 33.6, 33.3, 33.2, 31.8, 31.3, 31.2, 30.2, 30.2, 28.2, 28.0, 21.7, 21.6, 16.4, 16.4. HRMS calcd for $C_{23}H_{33}N_4O_4$: 429.2496, found 429.2495.



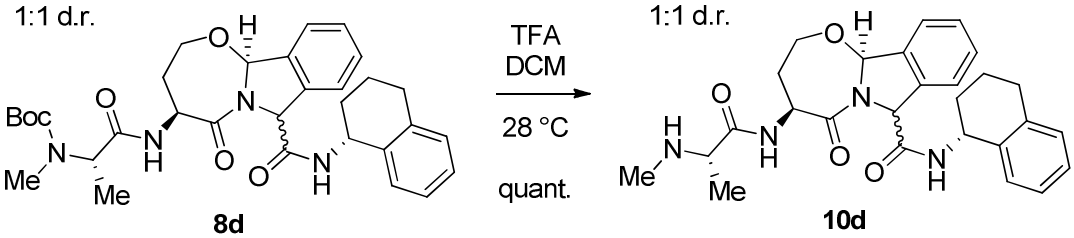
8b **10b**

(4*S*,7*S*,9a*S*)-4-((*S*)-2-(Methylamino)propanamido)-*N*-(naphthalen-1-yl)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (10b). To a solution of **8b** (12 mg, 0.023 mmol, 1 equiv, ~6:1 d.r.) in DCM (1 mL) was added TFA (14 μL, 0.183 mmol, 8 equiv). After stirring for 20 h at 23 °C, the solution was concentrated to yield **10b**•TFA (12 mg, quantitative) as the major diastereomer (~6:1). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.12-8.08 (m, 1H), 7.92-7.88 (m, 1H), 7.79 (d, 1H, *J* = 8.4 Hz), 7.67 (dd, 1H, *J* = 1.2, 7.2 Hz), 7.56-7.45 (m, 3H), 5.48 (q, 1H, *J* = 2.8 Hz), 4.99 (d, 1H, *J* = 12.0 Hz), 4.75 (t, 2H, *J* = 6.8 Hz), 4.21 (dt, 1H, *J* = 2.8, 12.4 Hz), 4.10-4.00 (m, 1H), 3.96-3.87 (m, 1H), 2.68 (s, 3H), 2.44-2.29 (m, 2H), 2.22-2.07 (m, 2H), 1.83 (dd, 1H, *J* = 2.0, 14.4 Hz), 1.60 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 172.9, 172.5, , 169.7, 135.7, 134.0, 129.9, 127.3, 127.2, 126.5, 123.5, 91.1, 71.4, 62.8, 58.4, 54.3, 49.0, 33.8, 33.4, 31.8, 28.1, 16.4. HRMS calcd for $C_{23}H_{28}N_4O_4Na$: 447.20028, found 447.20189.



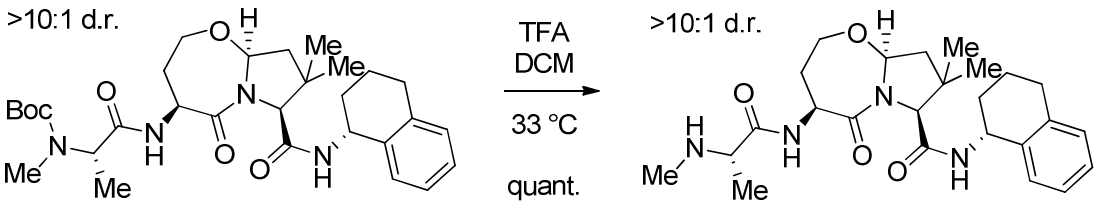
8c **10c**

(4*S*,7*S*,9a*S*)-4-((*S*)-2-(Methylamino)propanamido)-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]thiazepine-7-carboxamide (10c). Same procedure as above (**10a**) using **8c** (90 mg, 0.165 mmol, 1 equiv, >8:1 d.r.) and TFA (126 μL, 1.65 mmol, 10 equiv) in DCM (4 mL). After stirring for 20 h at 32 °C, the solution was concentrated. The product was eluted through a short plug (~500 mg) of Silicyle® TMA-chloride ion exchange resin with MeOH to yield **10c**•HCl (79 mg, quantitative) as the major diastereomer (>8:1 d.r.). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.39-7.34 (m, 1H), 7.17-7.05 (m, 4H), 5.46-5.39 (m, 1H), 5.07 (t, 1H, *J* = 6.8 Hz), 4.77 (dd, 1H, *J* = 2.0, 11.2 Hz), 4.57 (dd, 1H, *J* = 5.2, 7.6 Hz), 3.94-3.87 (m, 1H), 3.29-3.21 (m, 1H), 3.02 (ddd, 1H, *J* = 2.8, 6.0, 14.4 Hz), 2.82-2.75 (m, 2H), 2.66 (s, 3H), 2.60-2.49 (m, 1H), 2.25-2.17 (m, 2H), 2.15-2.09 (m, 1H), 2.05-1.95 (m, 2H), 1.95-1.74 (m, 4H), 1.53 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 172.3, 171.9, 169.5, 138.7, 138.5, 137.6, 137.3, 130.2, 130.0, 129.9, 129.5, 128.4, 128.3, 127.2, 127.1, 63.9, 63.4, 63.1, 58.4, 58.3, 55.1, 54.2, 54.1, 34.1, 33.3, 31.8, 31.8, 31.3, 31.0, 30.1, 30.1, 28.8, 28.5, 21.5, 21.1, 16.4, 16.3. HRMS calcd for $C_{23}H_{33}N_4O_3S$: 445.2268, found 445.2267.



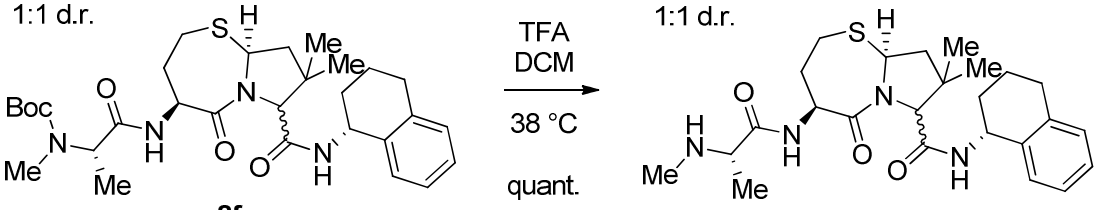
8d **10d**

(4*S*,11b*S*)-4-((*S*)-2-(Methylamino)propanamido)-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)-2,3,4,5,7,11b-hexahydro-[1,3]oxazepino[2,3-a]isoindole-7-carboxamide (10d). Same procedure as above (**10b**) using **8d** (38 mg, 0.066 mmol, 1 equiv, 1:1 d.r.) and TFA (40 μL, 0.527 mmol, 8 equiv) in DCM (2 mL). After stirring for 20 h at 28 °C, the solution was concentrated to yield **10d**•TFA (38 mg, quantitative) as a 1:1 diastereomixture. Data for the 1:1 diastereomixture: ^{1}H NMR (400 MHz, CD_3OD) δ: 7.53-7.45 (m, 7H), 7.39-7.35 (m, 1H), 7.26 (d, 1H, *J* = 7.2 Hz), 7.16-7.07 (d, 2H, *J* = 2.0 Hz), 6.53 (d, 1H, *J* = 1.6 Hz), 6.47 (s, 1H), 5.57 (d, 1H, *J* = 1.6 Hz), 5.47 (s, 1H), 5.11-5.03 (m, 3H), 4.66 (dd, 1H, *J* = 9.2, 11.2Hz), 4.46 (td, 1H, *J* = 2.0, 9.2 Hz), 4.35-4.27 (m, 4H), 3.97 (q, 1H, *J* = 6.8 Hz), 3.88 (q, 1H, *J* = 7.2 Hz), 2.89-2.74 (m, 3H), 2.70 (s, 3H), 2.69 (s, 3H), 2.62-2.54 (m, 1H), 2.33 (tt, 1H, *J* = 1.6, 10.8 Hz), 2.02-1.92 (m, 6H), 1.85-1.76 (m, 3H), 1.62 (d, 3H, *J* = 7.2 Hz), 1.55 (d, 3H, *J* = 7.2 Hz), 1.54 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ:176.8, 172.2, 172.0, 171.0, 170.5, 170.4, 169.7, 169.2, 162.8, 162.4, 138.7, 138.6, 138.5, 138.4, 137.7, 137.5, 136.9, 136.6, 131.3, 131.3, 130.3, 130.2, 130.1, 130.0, 129.7, 129.5, 128.2, 128.2, 127.1, 126.3, 123.2, 123.2, 101.3, 93.2, 92.4, 72.1, 72.0, 67.3, 67.2, 66.9, 58.4, 58.4, 58.2, 54.6, 54.4, 50.2, 34.2, 33.5, 31.8, 31.8, 31.4, 31.0, 30.2, 30.2, 29.2, 21.6, 21.4, 16.4, 16.4, 16.2. HRMS calcd for $C_{27}H_{33}N_4O_4$: 477.2496, found 477.2493.



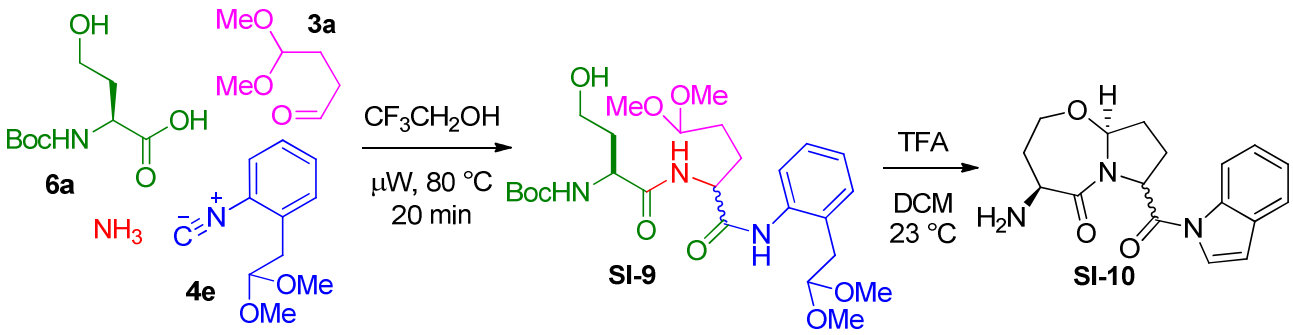
8e **10e**

(4*S*,7*S*,9a*S*)-8,8-Dimethyl-4-((*S*)-2-(methylamino)propanamido)-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (10e). Same procedure as above (**10b**) using **8e** (25 mg, 0.045 mmol, 1 equiv, 10:1 d.r.) and TFA (35 μL, 0.449 mmol, 10 equiv) in DCM (1 mL). After stirring for 20 h at 33 °C, the solution was concentrated to yield **10e**•TFA (25 mg, quantitative) as the major diastereomer (10:1 d.r.). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.15 (d, 1H, *J* = 8.4 Hz), 7.32 (d, 1H, *J* = 6.4 Hz), 7.17-7.07 (m, 3H), 5.44 (t, 1H, *J* = 6.4 Hz), 5.10 (q, 1H, *J* = 6.8 Hz), 4.14 (dt, 1H, *J* = 3.2, 12.0 Hz), 4.08 (s, 1H), 3.99-3.91 (m, 2H), 2.80 (p, 2H, *J* = 6.0 Hz), 2.68 (s, 3H), 2.20 (dd, 1H, *J* = 6.4, 13.2 Hz), 2.08-1.96 (m, 3H), 1.89-1.77 (m, 4H), 1.58 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 172.2, 171.5, 169.6, 138.5, 137.6, 130.1, 129.7, 128.3, 127.1, 117.5, 114.6, 90.5, 71.7, 71.3, 58.4, 54.2, 47.0, 40.1, 33.2, 31.8, 31.4, 30.1, 29.3, 24.2, 21.4, 16.3. HRMS calcd for $C_{25}H_3N_4O_4$: 457.2809, found 457.2811.

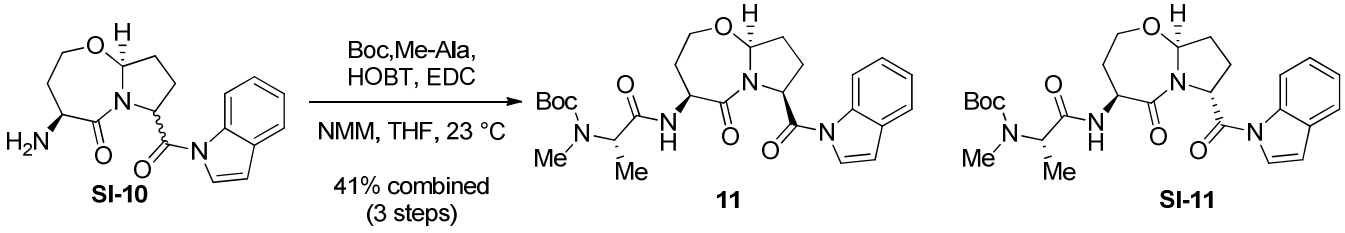


8f **10f**

(4*S*,9a*S*)-8,8-Dimethyl-4-((*S*)-2-(methylamino)propanamido)-5-oxo-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)octahydropyrrolo[2,1-b][1,3]thiazepine-7-carboxamide (10f). Same procedure as above (**10a**) using **8f** (62 mg, 0.108 mmol, 1 equiv, 1:1 d.r.) and TFA (66 μL, 0.866 mmol, 8 equiv) in DCM (3 mL). After stirring for 20 h at 38 °C, the solution was concentrated. The product was eluted through a short plug (~500 mg) of Silicyle® TMA-chloride ion exchange resin with MeOH to yield **10f**•HCl (54 mg, quantitative) as a 1:1 diastereomixture. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.34-7.27 (m, 2H), 7.18-7.06 (m, 7H), 5.54-5.45 (m, 1H), 5.41 (t, 1H, *J* = 8.0 Hz), 5.11-5.06 (m, 1H), 5.06-5.01 (m, 1H), 4.77-4.71 (m, 2H), 4.23 (s, 1H), 4.16 (s, 1H), 3.97-3.89 (m, 2H) 3.29-3.19 (m, 2H), 2.93-2.84 (m, 2H), 2.78 (dd, 4H, *J* = 6.4, 12.8 Hz), 2.68 (s, 6H), 2.32-2.21 (m, 3H), 2.01-1.75 (m, 12H), 1.55 (d, 3H, *J* = 7.2 Hz), 1.54-1.50 (m, 2H), 1.47 (d, 3H, *J* = 6.8 Hz), 1.40-1.37 (m, 2H), 1.16 (s, 6H), 1.14 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 172.4, 172.3, 171.8, 171.4, 169.3, 168.9, 138.8, 138.5, 137.4, 137.4, 130.1, 130.1, 129.8, 128.3, 127.1, 127.0, 73.4, 63.8, 61.8, 58.3, 55.1, 54.4, 40.9, 40.9, 40.7, 33.6, 32.1, 31.8, 31.7, 31.3, 31.1, 30.9, 30.2, 30.1, 28.7, 23.9, 21.3, 21.0, 16.3, 16.2. HRMS calcd for $C_{25}H_{37}N_4O_3S$: 473.2581, found 473.2579.

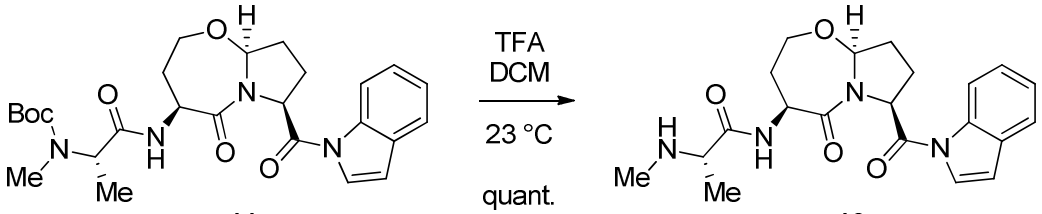


(4*S*,9a*S*)-4-Amino-7-(1*H*-indole-1-carbonyl)hexahydropyrrolo[2,1-b][1,3]oxazepin-5(2*H*)-one (SI-10). Same procedure as above (**7a**) with Boc-*N*-HSer-OH (**6a**) (313 mg, 1.43 mmol, 1.0 equiv), aldehyde **3a** (198 mg, 1.50 mmol, 1.05 equiv), isocyanide **4e** (273 mg, 1.43 mmol, 1.0 equiv) and 7 M ammonia in MeOH (408 μL, 2.85 mmol, 2.0 equiv) in TFE (5 mL). The resultant oil **SI-9** was combined with TFA (1.09 mL, 14.3 mmol, 10 equiv) in DCM (5 mL) and stirred at 23 ºC for 14 h. The mixture was concentrated in vacuo and **SI-10** used without further purification in the next step.



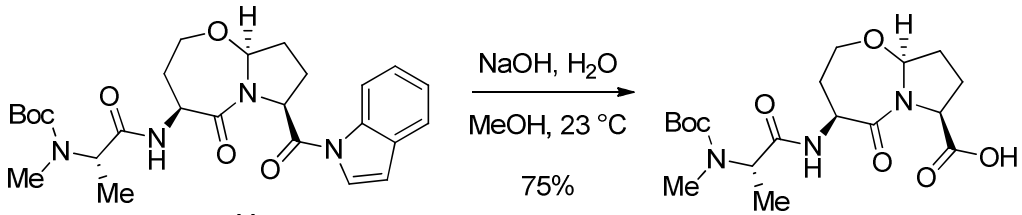
***tert*-Butyl ((2*S*)-1-(((4*S*,9a*S*)-7-(1*H*-indole-1-carbonyl)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepin-4-yl)amino)-1-oxopropan-2-yl)(methyl)carbamate (11) and (SI-11).** Same procedure as above (**8a**) using crude **SI-10**•TFA (611 mg, 1.43 mmol, 1.0 equiv), Boc-*N*-Me-Ala-OH (291 mg, 1.43 mmol, 1.0 equiv), HOBT·xH_2O (241 mg, 1.57 mmol, 1.1 equiv), NMM (786 μL, 7.15 mmol, 5 equiv [to soak up xs TFA]) and EDC·HCl (288 mg, 1.50 mmol, 1.05 equiv) in THF (15 mL). The resultant oil was purified by flash chromatography on silica gel (2:1→1:1→1:4 hexanes/EtOAc) to yield, after 3 steps, separated diastereomers **11** (150 mg, 21%) and **SI-11** (144 mg, 20%). Data for **11**: R_f = 0.27 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, 1H, *J* = 8.4 Hz), 7.57 (d, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 4.0 Hz), 7.35 (t, 1H, *J* = 8.4 Hz), 7.28 (t, 1H, *J* = 7.6 Hz), 7.16 (s, 1H), 6.69 (d, 1H, *J* = 3.6 Hz), 5.35 (dd, 1H, *J* = 3.6, 6.4 Hz), 5.28 (dd, 1H, *J* = 4.8, 8.0 Hz), 4.80 (dd, 1H, *J* = 6.0, 10.8 Hz), 4.75-4.65 (m, 1H), 4.31 (dt, 1H, *J* = 3.2, 12.8 Hz), 4.12 (q, 1H, *J* = 7.2 Hz), 4.05 (t, 1H, *J* = 13.2 Hz), 2.76 (s, 3H), 2.44-2.31 (m, 2H), 2.30-2.19 (m, 2H), 2.05-1.98 (m, 2H), 1.42 (s, 9H), 1.34 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1, 170.8, 168.8, 135.9, 130.2, 125.3, 124.0, 124.0, 120.8, 117.0, 110.0, 89.7, 80.6, 80.6, 77.2, 70.8, 64.3, 60.4, 59.7, 53.0, 32.6, 30.3, 28.3, 28.3, 28.3, 27.2, 21.0. Data for **SI-11**: R_f = 0.50 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (s, 1H), 7.57 (d, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 4.0 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 7.28 (d, 1H, *J* = 7.6 Hz), 7.18 (s, 1H), 6.71 (d, 1H, *J* = 3.6 Hz), 5.44-5.39 (m, 2H), 4.88 (dd, 1H, *J* = 5.6, 11.2 Hz), 4.75-4.69 (m, 1H), 4.47 (t, 2H, *J* = 8.8 Hz), 4.31-4.24 (m, 1H), 4.17 (dt, 1H, *J* = 3.2, 12.8 Hz), 4.13-4.04 (m, 1H), 3.72-3.66 (m, 1H), 3.56-3.48 (m, 1H), 2.79 (s, 3H), 2.66-2.54 (m, 1H), 2.37 (sept, 1H, *J* = 6.8 Hz), 2.21-2.06 (m, 4H), 1.81 (qd, 1H, *J* = 3.6, 14.0 Hz), 1.67-1.58 (m, 1H), 1.43 (s, 9H), 1.33 (d, 3H, *J* =

7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 171.1, 168.7, 135.8, 130.2, 125.4, 124.1, 123.8, 121.0, 116.7, 110.3, 89.6, 70.7, 65.8, 60.0, 53.0, 49.1, 33.1, 32.2, 30.4, 28.4, 28.4, 28.4, 26.9. Also included below are 1D-NOESY and DEPT-135 spectra for **11** and the HSQC spectra for both **11** and **SI-11**. HRMS calcd for $C_{26}H_{34}N_4O_6Na$: 521.2371, found 521.2372.



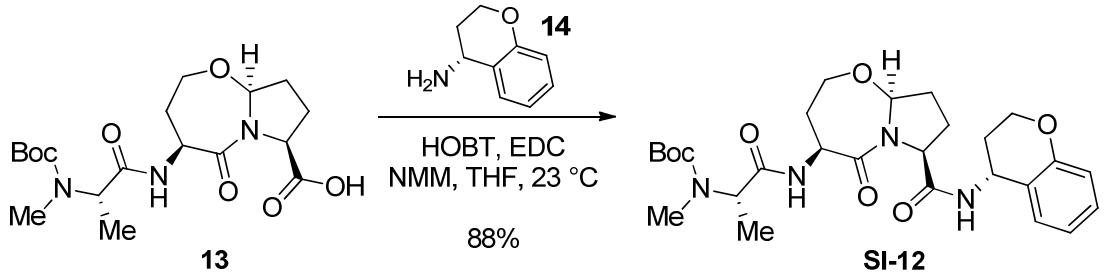
11 **12**

(*S*)-*N*-((4*S*,7*S*,9a*S*)-7-(1*H*-Indole-1-carbonyl)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepin-4-yl)-2-(methylamino)propanamide (12). Same procedure as above (**10b**) using **11** (52 mg, 0.104 mmol, 1 equiv) and TFA (64 μL, 0.834 mmol, 8 equiv) in DCM (2 mL). After stirring for 20 h at 23 °C, the solution was concentrated to yield **12**•TFA (53 mg, quantitative) as a single diastereomer. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.39 (d, 1H, *J* = 8.0 Hz), 7.84 (d, 1H, *J* = 4.0 Hz), 7.58 (d, 1H, *J* = 7.2 Hz), 7.33-7.24 (m, 2H), 6.73 (d, 1H, *J* = 4.0 Hz), 5.50-5.46 (m, 1H), 5.34 (t, 1H, *J* = 6.8 Hz), 4.26 (dt, 1H, *J* = 3.2, 12.4 Hz), 4.10-4.02 (m, 1H), 3.92-3.84 (m, 2H), 2.65 (s, 3H), 2.28 (qd, 1H, *J* = 3.6, 12.4 Hz), 2.19-2.05 (m, 2H), 1.86 (d, 1H, *J* = 14.0 Hz), 1.55 (dd, 2H, *J* = 4.0, 7.2 Hz), 1.50 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 172.2, 171.0, 169.6, 137.2, 131.9, 126.0, 126.0, 125.0, 122.0, 117.4, 110.7, 90.9, 71.4, 61.5, 58.3, 54.4, 49.0, 33.7, 33.2, 31.7, 28.3, 16.3. HRMS calcd for $C_{21}H_{26}N_4O_4Na$: 421.18463, found 421.18593.

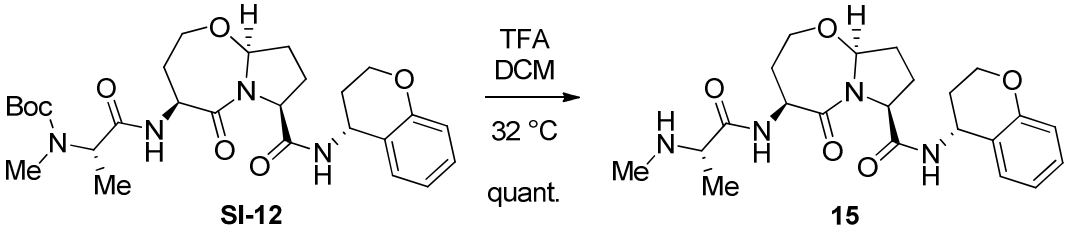


11 **13**

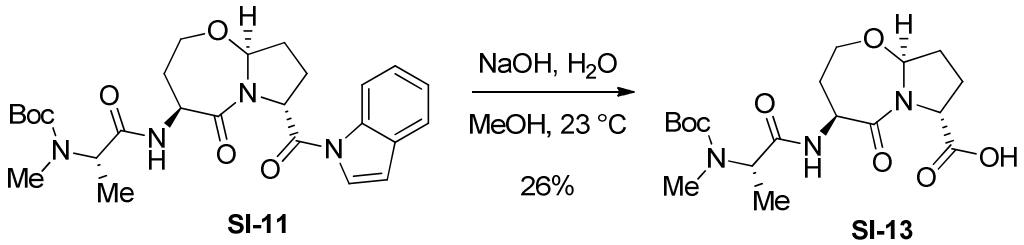
(4*S*,7*S*,9a*S*)-4-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)propanamido)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxylic acid (13). To a solution of **11** (142 mg, 0.285 mmol, 1.0 equiv) in MeOH (6 mL) was added 1M NaOH (1 mL). After stirring for 3 h, the methanol was removed in vacuo. Then EtOAc (10 mL) and 1 M NaOH (8 mL) were added and an extraction was performed, with the organic layer being discarded. The aqueous layer was acidified with 3M HCl to pH ≤ 2 and then extracted with DCM (3 x 5 mL). The organics were dried over sodium sulfate, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc→DCM→5% MeOH/DCM) to yield **13** as a colorless oil (85 mg, 75%) as a single diastereomer. R_f = 0.17 (7% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (bs, 1H), 5.22 (m, 1H), 4.77 (t, 1H, *J* = 8.0 Hz), 4.52-4.46 (m, 1H), 4.14 (d, 1H, *J* = 12.8 Hz), 3.95 (t, 1H, *J* = 12.0 Hz), 2.78 (s, 3H), 2.32-2.18 (m, 2H), 2.13-2.02 (m, 2H), 2.00-1.85 (m, 2H), 1.44 (s, 9H), 1.33 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 171.5, 156.2, 156.1, 89.8, 80.8, 80.7, 70.7, 59.7, 52.9, 32.7, 30.4, 30.4, 28.4, 28.4, 26.5, 26.5, 14.2. HRMS calcd for $C_{18}H_{29}N_3O_7Na$: 422.18977, found 422.19015.



***tert*-Butyl ((*S*)-1-(((4*S*,7*S*,9a*S*)-7-((*R*)-chroman-4-ylcarbamoyl)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepin-4-yl)amino)-1-oxopropan-2-yl)(methyl)carbamate (SI-12).** To a solution of **13** (50 mg, 0.125 mmol, 1.0 equiv), (*R*)-chroman-4-ylamine•HCl (**14**, 23 mg, 0.125 mmol, 1.0 equiv), HOBT·xH_2O (21 mg, 0.138 mmol, 1.1 equiv) and NMM (41 μL, 0.376 mmol, 3 equiv) in THF (5 mL) at 0 °C was added EDC·HCl (25 mg, 0.131 mmol, 1.05 equiv). After 30 min the cold bath was removed. The solution stirred for 14 h and then was quenched with saturated aqueous $NaHCO_3$ (15 mL), extracted with EtOAc (2 x 10 mL), dried over sodium sulfate and then concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc) to yield **SI-12** (58 mg, 88%) as a single diastereomer. R_f = 0.11 (1:2 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16-7.10 (m, 3H), 6.91 (d, 1H, *J* = 7.2 Hz), 6.86-6.77 (m, 2H), 5.22 (t, 1H, *J* = 6.0 Hz), 5.12 (q, 1H, *J* = 6.8 Hz), 4.68 (dd, 1H, *J* = 6.0, 11.2 Hz), 4.59 (d, 1H, *J* = 7.2 Hz), 4.22 (td, 1H, *J* = 2.8, 7.2 Hz), 4.15-4.08 (m, 1H), 4.06-4.01 (m, 1H), 3.92 (t, 1H, *J* = 12.4 Hz), 2.74 (s, 3H), 2.41-2.37 (m, 2H), 2.25-2.17 (m, 1H), 2.16-2.07 (m, 1H), 2.02 (pd, 1H, *J* = 2.8, 7.2 Hz), 1.95-1.84 (m, 2H), 1.61-1.45 (m, 1H), 1.42 (s, 9H), 1.31 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 170.1, 155.0, 129.3, 128.9, 122.3, 120.7, 117.2, 90.2, 77.2, 70.6, 63.6, 60.5, 52.6, 43.8, 32.7, 32.5, 30.2, 29.0, 28.4, 25.9. HRMS calcd for $C_{27}H_{38}N_4O_7Na$: 553.26327, found 553.26399.

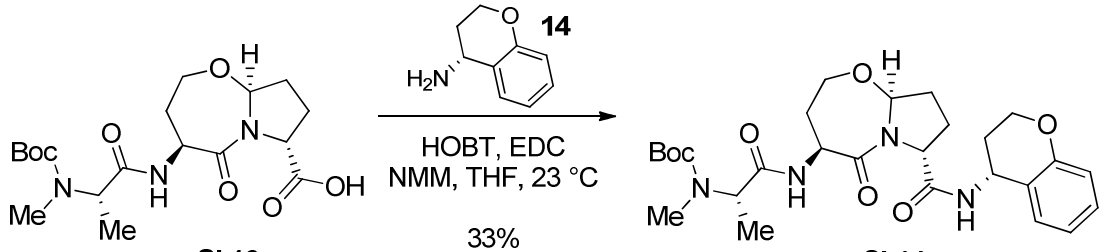


(4*S*,7*S*,9a*S*)-*N*-((*R*)-Chroman-4-yl)-4-((*S*)-2-(methylamino)propanamido)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (15). To a solution of **SI-12** (58 mg, 0.109 mmol, 1 equiv) in DCM (2 mL) was added TFA (83 μL, 1.09 mmol, 10 equiv). After stirring for 20 h at 32 °C, the solution was concentrated. The product was eluted through a short plug (~500 mg) of Silicyle® TMA-chloride ion exchange resin with MeOH to yield **15**•HCl (51 mg, quantitative) as a single diastereomer. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.33 (d, 1H, *J* = 7.6 Hz), 7.13 (t, 1H, *J* = 8.4 Hz), 6.86 (t, 1H, *J* = 7.2 Hz), 6.76 (d, 1H, *J* = 8.0 Hz), 5.39 (dd, 1H, *J* = 3.6, 6.8 Hz), 5.08 (t, 1H, *J* = 6.0 Hz), 4.40 (d, 1H, *J* = 6.8 Hz), 4.26-4.12 (m, 3H), 4.03-3.89 (m, 2H), 2.67 (s, 3H), 2.33-2.24 (m, 1H), 2.14-1.97 (m, 6H), 1.81 (dd, 1H, *J* = 2.0, 14.0 Hz), 1.58 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 172.9, 172.2, 169.6, 156.4, 130.5, 130.0, 123.5, 121.6, 117.8, 91.0, 71.3, 64.6, 62.3, 58.4, 54.2, 49.0, 44.9, 33.6, 33.3, 31.8, 30.2, 28.0, 16.4. HRMS calcd for $C_{22}H_{31}N_4O_5$: 431.2289, found 431.2286.



SI-11 **SI-13**

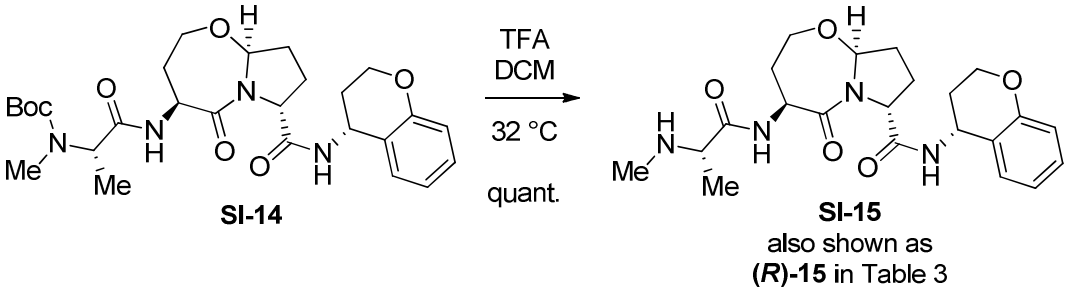
(4*S*,7*R*,9a*S*)-4-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxylic acid (SI-13). To a solution of **SI-11** (105 mg,-0.211 mmol, 1.0 equiv) in MeOH (4 mL) was added 1M NaOH (1 mL). After stirring for 3 h, the methanol was removed in vacuo. HPLC analysis of the crude reaction mixture revealed that diastereomer **SI-11** didn't react as cleanly as **11**. Then DCM (10 mL) and 1 M NaOH (8 mL) were added and an extraction was performed, with the organic layer being discarded. The aqueous layer was acidified with 3M HCl to pH ≤ 2 and then extracted with DCM (3 x 5 mL). The organics were dried over sodium sulfate, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc→DCM→5% MeOH/DCM) to yield **SI-13** as a colorless oil (22 mg, 26%) as a single diastereomer. R_f = 0.14 (7% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.25 (d, 1H, *J* = 6.8 Hz), 4.83 (dd, 1H, *J* = 5.6, 9.6 Hz), 4.65 (d, 1H, *J* = 8.8 Hz), 4.14-4.09 (m, 1H), 4.0 (t, 1H, *J* = 12.0 Hz), 2.79 (s, 3H), 2.41-2.31 (m, 1H), 2.27-2.11 (m, 2H), 2.06-1.96 (m, 1H), 1.78 (qd, 1H, *J* = 3.6, 12.0 Hz), 1.46 (s, 9H), 1.33 (d, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 172.0, 171.3, 89.6, 80.9, 70.7, 60.6, 59.8, 53.1, 33.0, 32.5, 30.5, 28.5, 26.1, 21.2, 14.3, 14.1. HRMS calcd for $C_{18}H_{29}N_3O_7Na$: 422.18977, found 422.19015.



SI-13 **SI-14**

***tert*-Butyl ((*S*)-1-(((4*S*,7*R*,9a*S*)-7-((*R*)-chroman-4-ylcarbamoyl)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepin-4-yl)amino)-1-oxopropan-2-yl)(methyl)carbamate (SI-14).** To a solution of **SI-13** (21 mg, 0.0053 mmol, 1.0 equiv), (*R*)-chroman-4-ylamine•HCl (**14**, 10 mg, 0.0053 mmol, 1.0 equiv), HOBT·xH_2O (9 mg, 0.0058 mmol, 1.1 equiv) and NMM (17 μL, 0.0158 mmol, 3 equiv) in THF (3 mL) at 0 °C was added EDC·HCl (11 mg, 0.0055 mmol, 1.05 equiv). After 30 min the cold bath was removed. The solution stirred for 14 h and then was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with EtOAc (2 x 10 mL), dried over sodium sulfate and then concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (1:1→1:3 hexanes/EtOAc) to yield **SI-14** (9 mg, 33%) as a single diastereomer. R_f = 0.51 (1:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20-7.12 (m, 3H), 6.89 (t, 1H, *J* = 7.6 Hz), 6.82 (d, 1H, *J* = 8.4 Hz), 5.23-5.19 (m, 1H), 5.12-5.05 (m, 1H), 4.79-4.71 (m, 1H), 4.55 (d, 1H, *J* = 8.0 Hz), 4.26-4.19 (m, 1H), 4.15-4.06 (m, 2H), 3.97 (t, 1H, *J* = 12.0 Hz), 2.77 (s, 3H), 2.39-2.26 (m, 1H), 2.24-2.13 (m, 2H), 2.07-2.00 (m, 1H), 1.99-1.91 (m, 2H), 1.80-1.70 (m, 2H), 1.44 (s, 9H), 1.34 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 171.1, 169.9, 155.2, 129.4,

129.3, 122.0, 120.9, 117.3, 90.1, 70.6, 63.4, 61.1, 53.1, 43.8, 33.4, 32.7, 32.1, 29.8, 29.1, 28.5, 25.6, 22.8, 14.3. HRMS calcd for $C_{27}H_{38}N_4O_7Na$: 553.26327, found 553.26399.



SI-14 **SI-15**
also shown as
(***R***)**-15** in Table 3

(4*S*,7*R*,9a*S*)-*N*-((*R*)-chroman-4-yl)-4-((*S*)-2-(methylamino)propanamido)-5-oxooctahydropyrrolo[2,1-b][1,3]oxazepine-7-carboxamide (SI-15). To a solution of **SI-14** (58 mg, 0.109 mmol, 1 equiv) in DCM (2 mL) was added TFA (83 μL, 1.09 mmol, 10 equiv). After stirring for 20 h at 32 °C, the solution was concentrated to yield **SI-15**•TFA (51 mg, quantitative) as a single diastereomer. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.43 (d, 1H, *J* = 8.0 Hz), 7.15-7.09 (m, 2H), 6.85 (t, 1H, *J* = 8.0 Hz), 6.78-6.73 (m, 1H), 5.40 (d, 2H, *J* = 5.6 Hz), 5.10-5.04 (m, 1H), 4.99 (dd, 1H, *J* = 2.4, 11.2 Hz), 4.53 (d, 1H, *J* = 9.2 Hz), 4.21 (t, 2H, *J* = 5.2 Hz), 4.14 (dt, 1H, *J* = 3.2, 13.2 Hz), 4.05-3.96 (m, 1H), 3.91 (q, 1H, *J* = 7.2 Hz), 2.67 (s, 3H), 2.44-2.31 (m, 1H), 2.30-2.18 (m, 1H), 2.16-2.07 (m, 1H), 2.04-1.95 (m, 3H), 1.93-1.81 (m, 2H), 1.52 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 173.5, 172.7, 169.3, 156.5, 130.2, 129.9, 123.5, 121.6, 117.9, 91.1, 71.2, 64.6, 62.3, 58.3, 54.4, 44.9, 34.0, 33.3, 31.8, 30.1, 28.2, 16.4. HRMS calcd for $C_{22}H_{30}N_4O_5Na$: 453.21084, found 453.21280.

References

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(2) O'Boyle, N.; Banck, M.; James, C.; Morley, C.; Vandermeersch, T.; Hutchison, G. *Journal of Cheminformatics* **2011**, *3*, 33.

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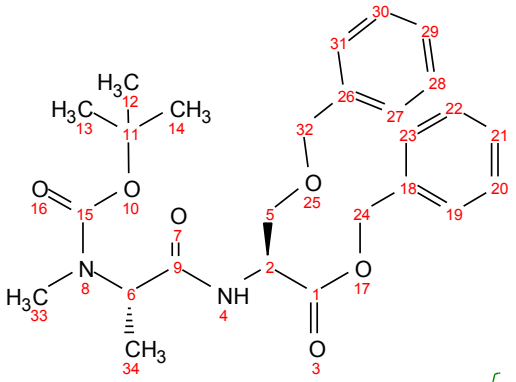
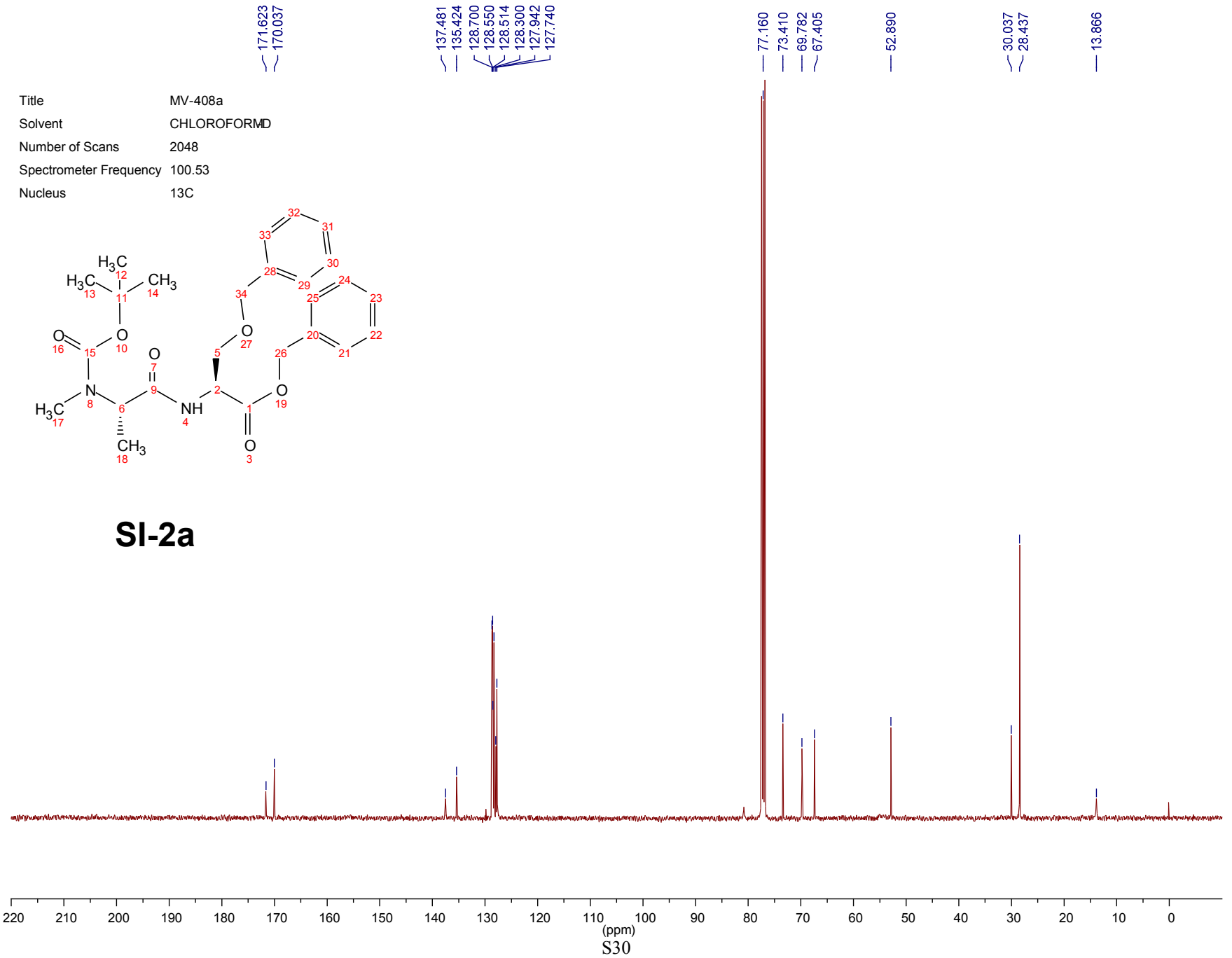
(5) Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata., O. *J. Org. Chem.* **2010**, *75*, 914.

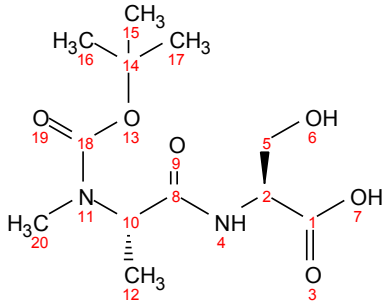
Title	MV-408a
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



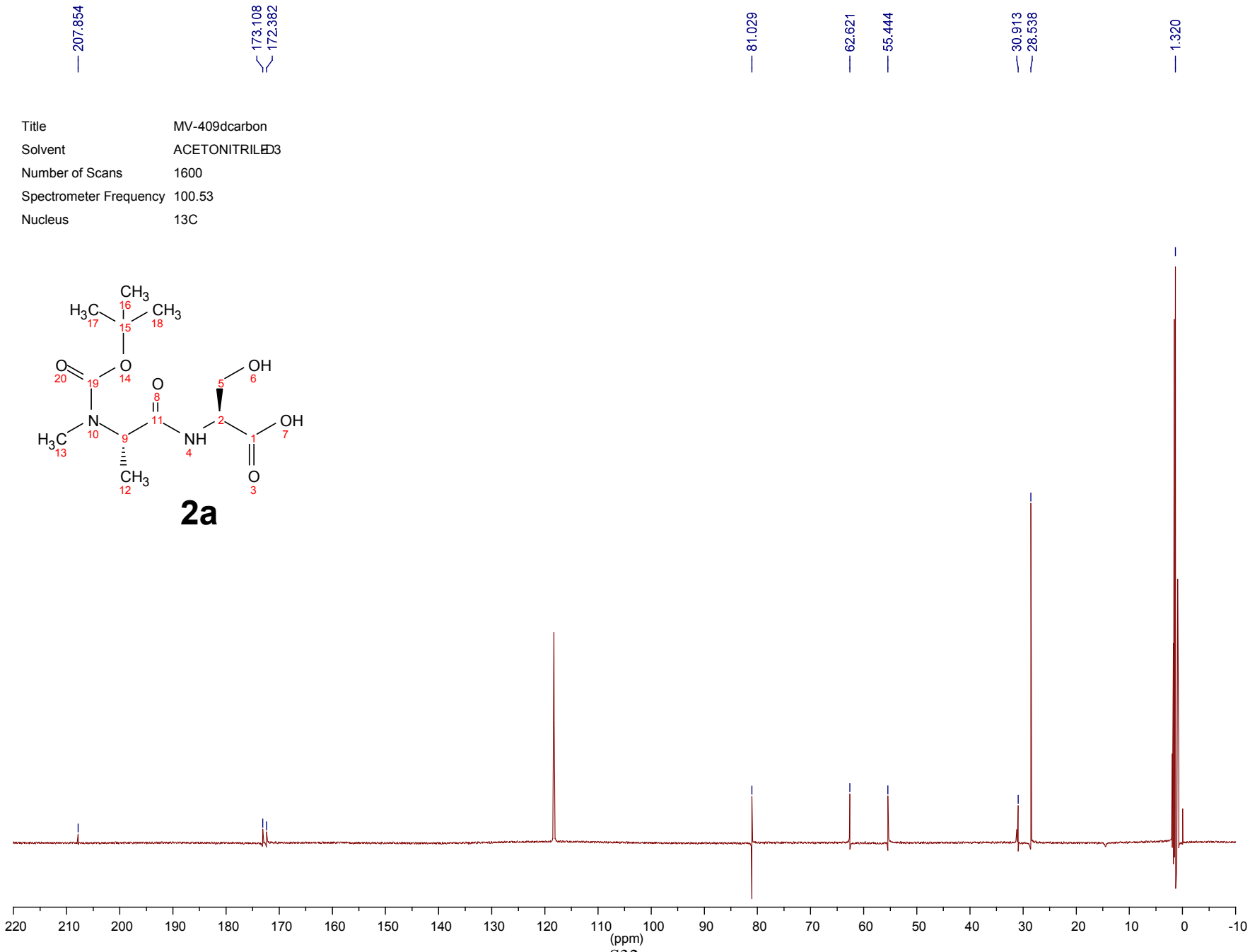
SI-2a


171.623
170.037
137.481
135.424
128.700
128.550
128.514
128.300
127.942
127.740
77.160
73.410
69.782
67.405
52.890
30.037
28.437
13.866
Title MV-408a
Solvent CHLOROFORM-D
Number of Scans 2048
Spectrometer Frequency 100.53
Nucleus 13C
SI-2a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

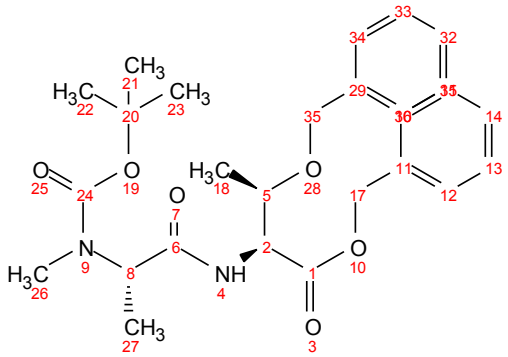
Title	MV-325
Solvent	METHANOL-D4
Number of Scans	24
Spectrometer Frequency	399.78
Nucleus	1H



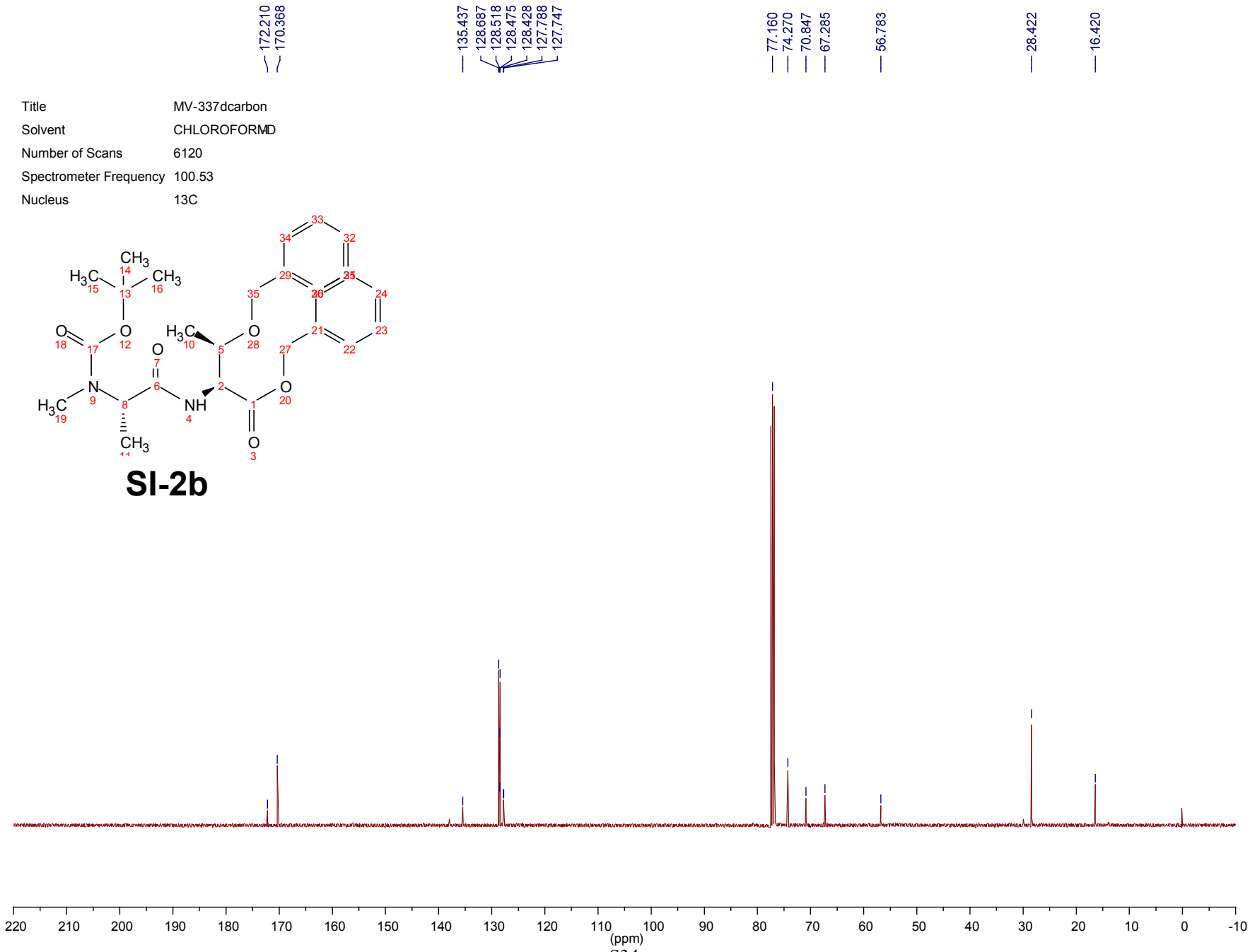
2a


207.854
173.108
172.382
81.029
62.621
55.444
30.913
28.538
1.320
Title MV-409dcarbon
Solvent ACETONITRILE-D3
Number of Scans 1600
Spectrometer Frequency 100.53
Nucleus 13C
2a
(ppm)

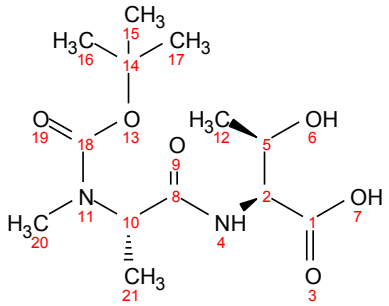
Title	MV-337d
Solvent	CHLOROFORM-D
Number of Scans	24
Spectrometer Frequency	399.78
Nucleus	1H



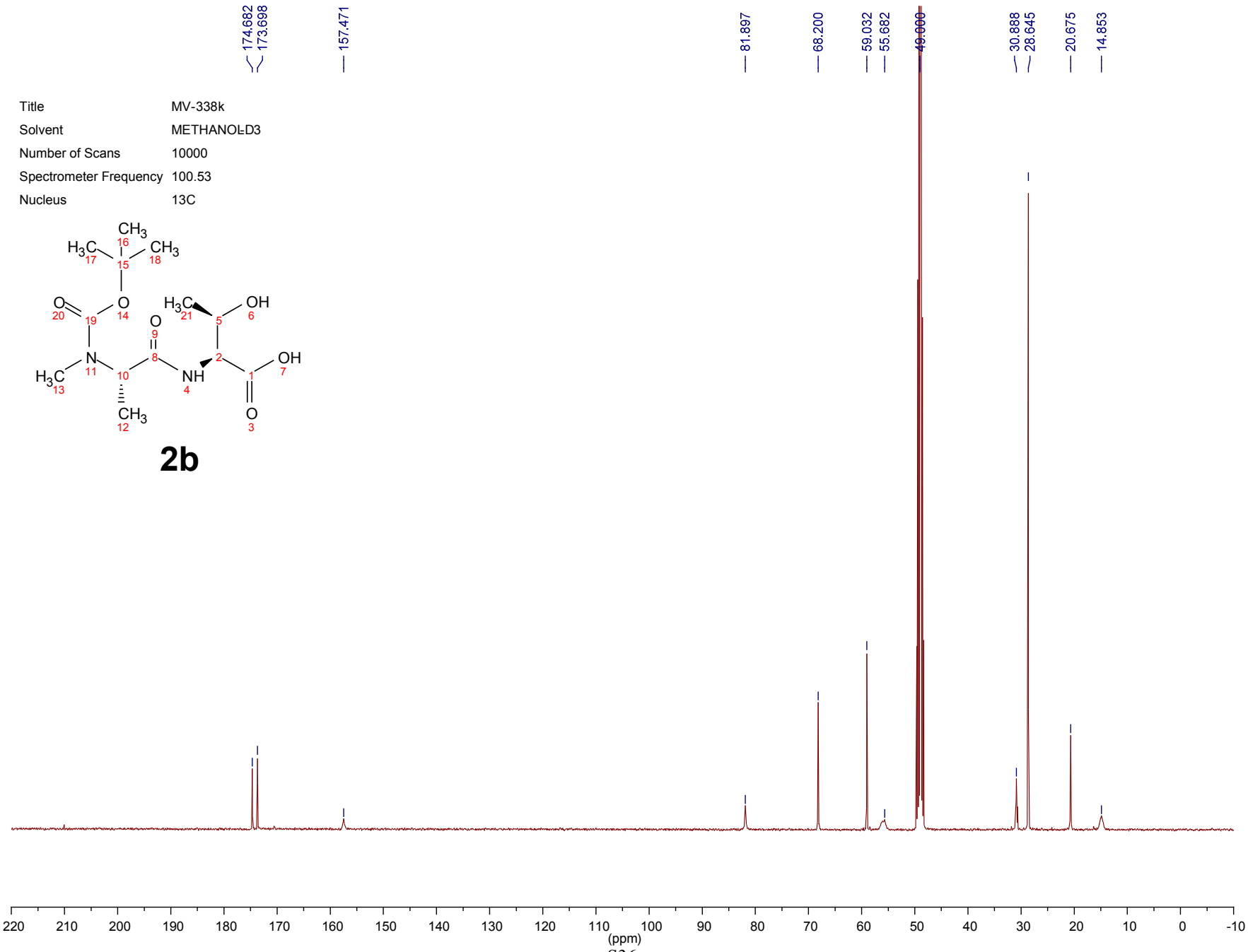
SI-2b

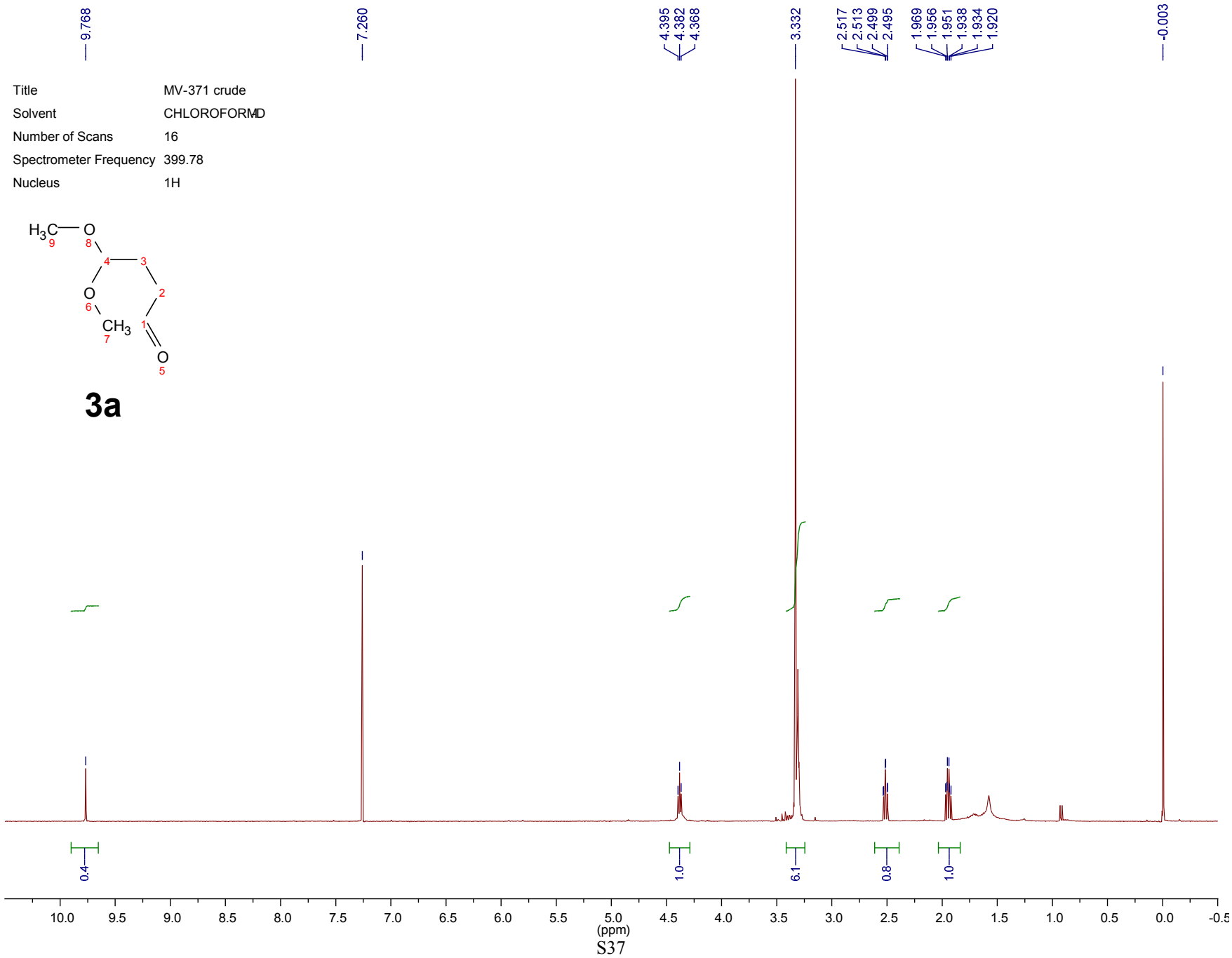

172.210
170.368
135.437
128.687
128.518
128.475
128.428
127.788
127.747
77.160
74.270
70.847
67.285
56.783
28.422
16.420
Title MV-337dcarbon
Solvent CHLOROFORM-D
Number of Scans 6120
Spectrometer Frequency 100.53
Nucleus 13C
SI-2b
(ppm)

Title	MV-338k
Solvent	METHANOL-D3
Number of Scans	48
Spectrometer Frequency	399.78
Nucleus	1H

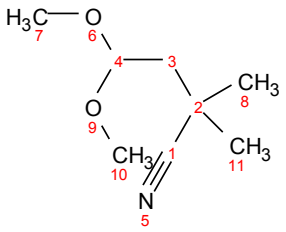


2b


174.682
173.698
157.471
81.897
68.200
59.032
55.682
40.000
30.888
28.645
20.675
14.853
Title MV-338k
Solvent METHANOL-D3
Number of Scans 10000
Spectrometer Frequency 100.53
Nucleus 13C
2b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

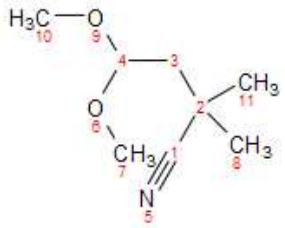

9.768
7.260
4.395
4.382
4.368
3.332
2.517
2.513
2.499
2.495
1.969
1.956
1.951
1.938
1.934
1.920
-0.003
Title MV-371 crude
Solvent CHLOROFORM-D
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
3a
0.4
1.0
6.1
0.8
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

Title	MV-427 crude
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H

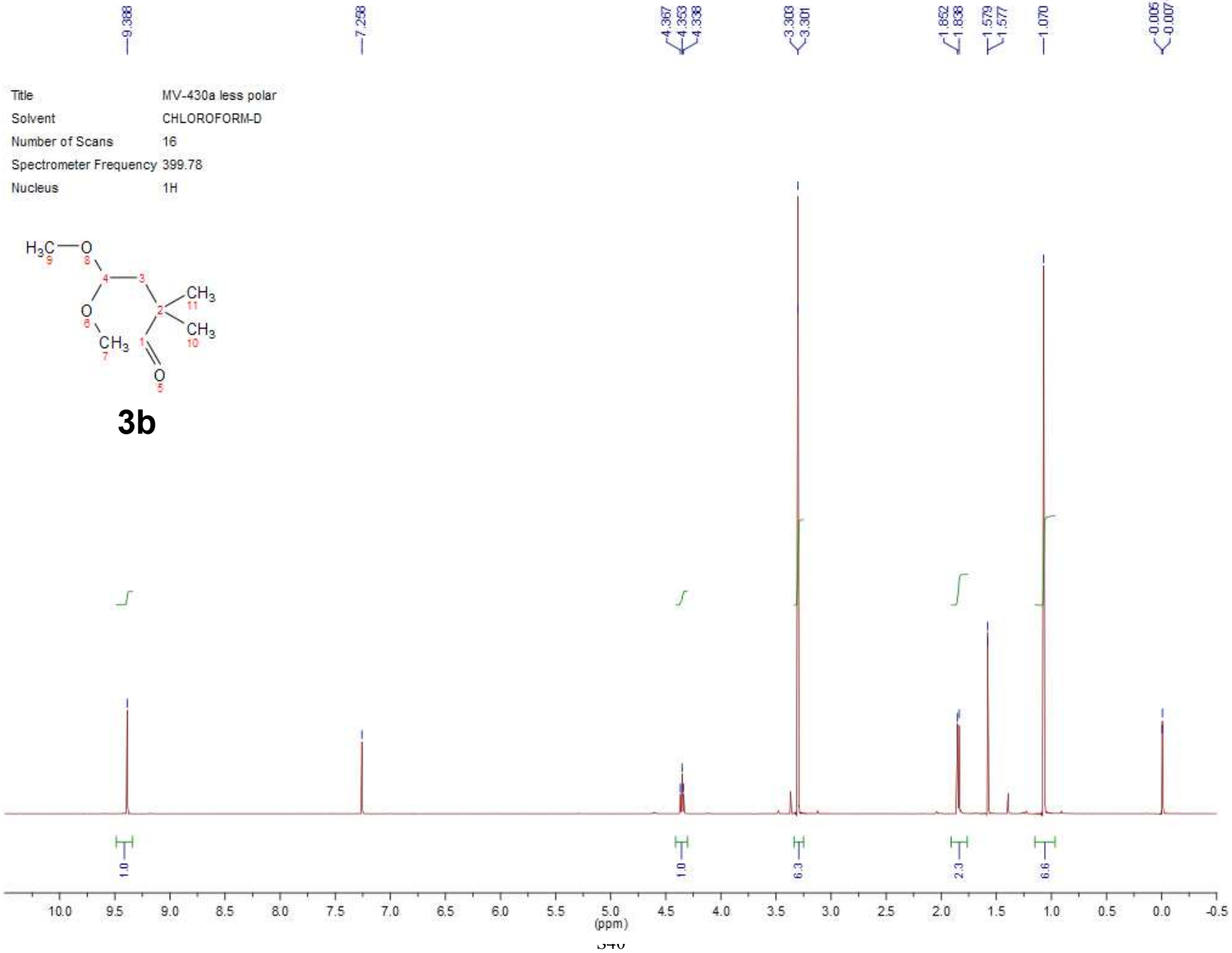


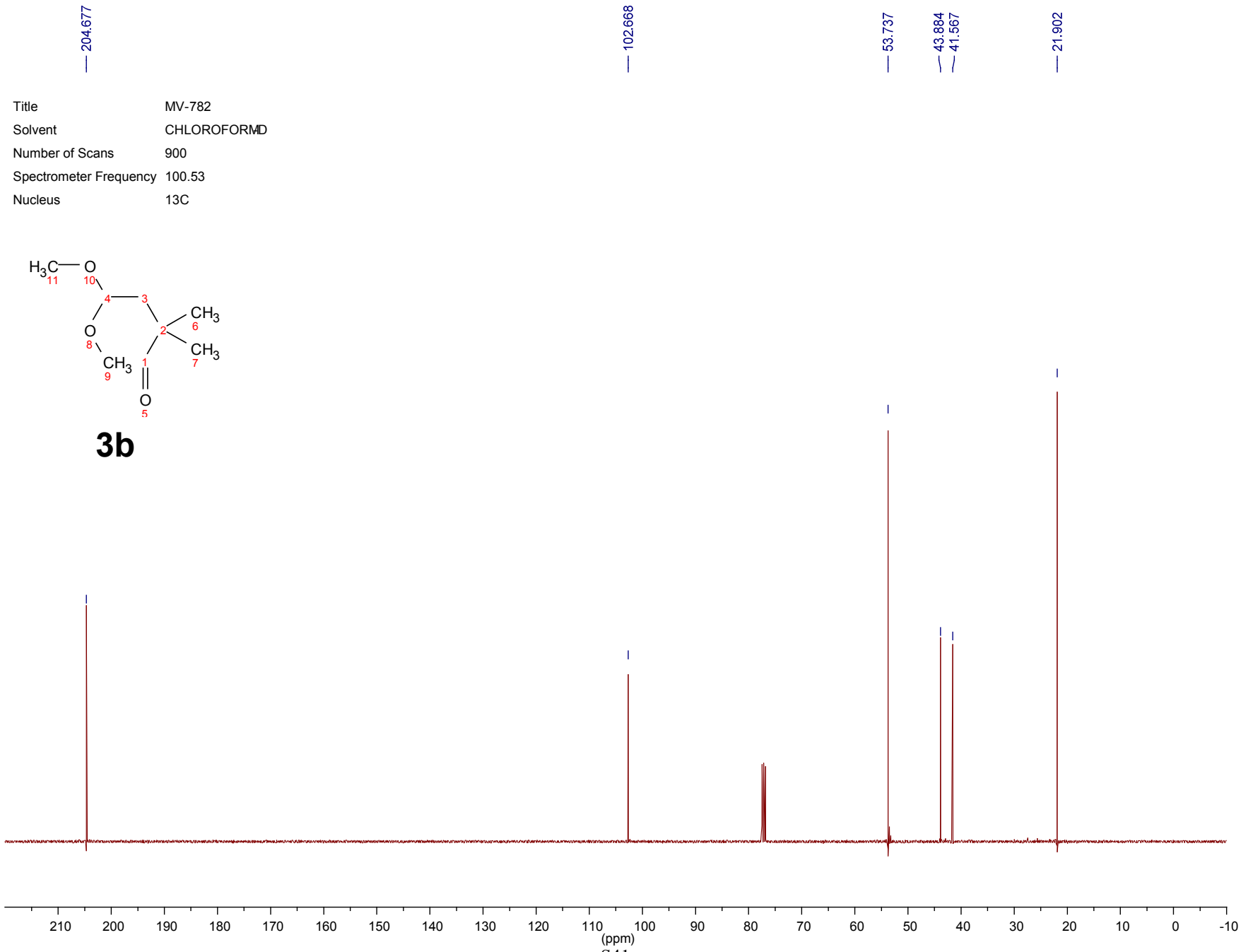
SI-4

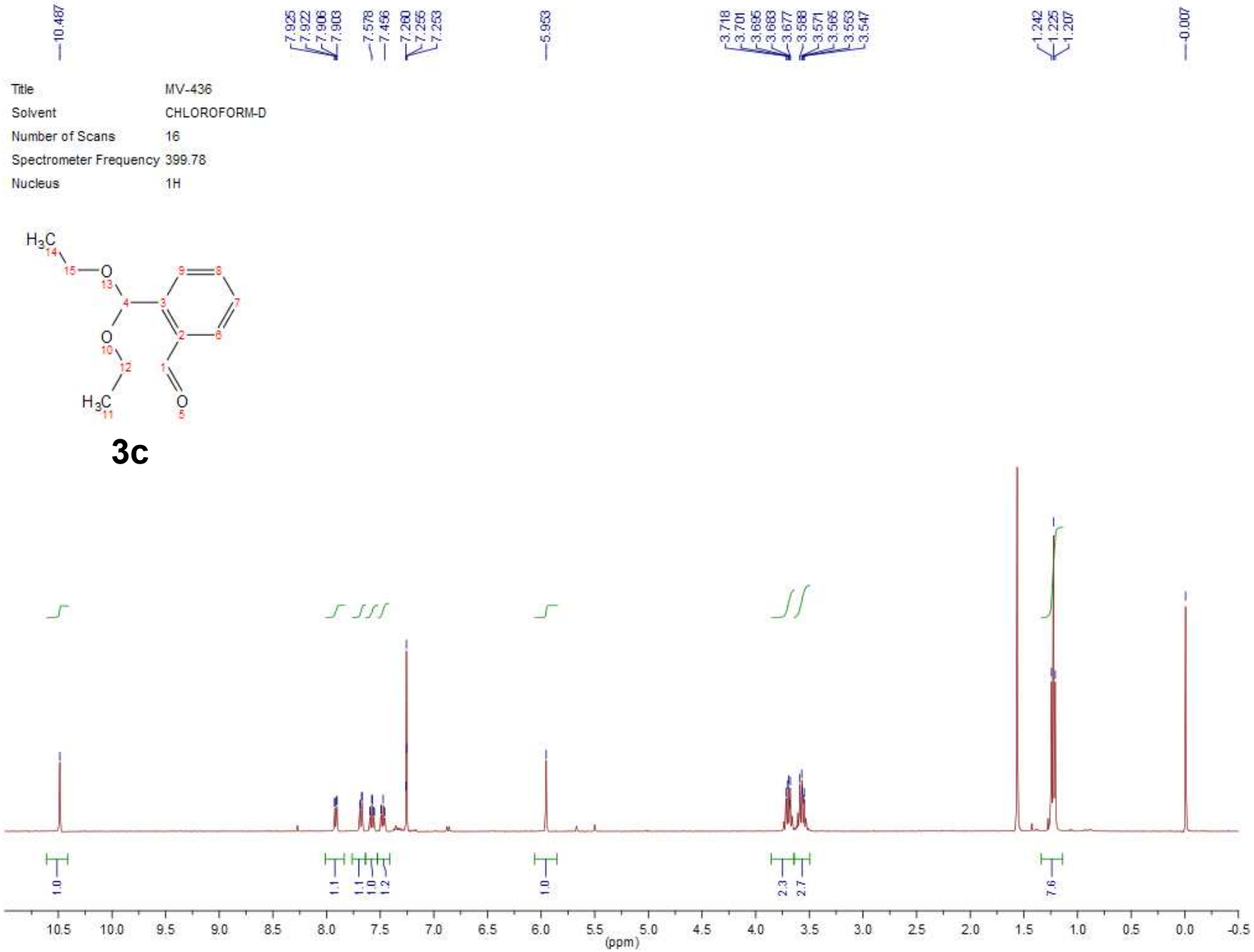
Title	MV-427
Solvent	CHLOROFORM-D
Number of Scans	1024
Spectrometer Frequency	100.53
Nucleus	13C



SI-4

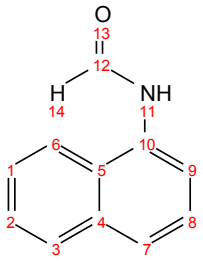

9.388
7.258
4.367
4.353
4.338
3.303
3.301
1.852
1.838
1.579
1.577
1.070
0.005
0.007
Title MV-430a less polar
Solvent CHLOROFORM-D
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
3b
1.0
1.0
6.3
2.3
6.6
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


204.677
102.668
53.737
43.884
41.567
21.902
Title MV-782
Solvent CHLOROFORM-D
Number of Scans 900
Spectrometer Frequency 100.53
Nucleus 13C
3b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

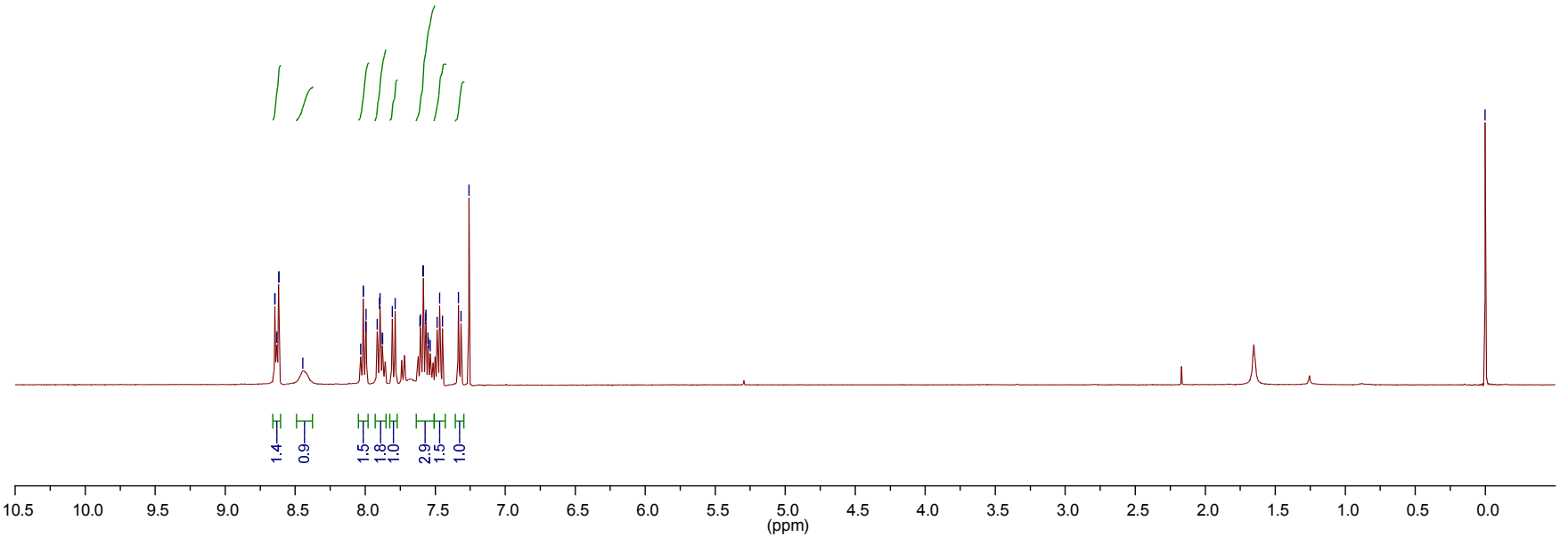

10.487
7.925
7.922
7.906
7.903
7.578
7.456
7.260
7.255
7.253
5.953
3.718
3.701
3.695
3.683
3.677
3.588
3.571
3.565
3.553
3.547
1.242
1.225
1.207
0.007
Title MV-436
Solvent CHLOROFORM-D
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
1.0
1.1
1.1
1.0
1.2
1.0
2.3
2.7
7.6
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

3c

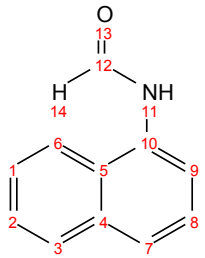
Title	MV-341d
Solvent	CHLOROFORM-D
Number of Scans	24
Spectrometer Frequency	399.78
Nucleus	1H



SI-7a

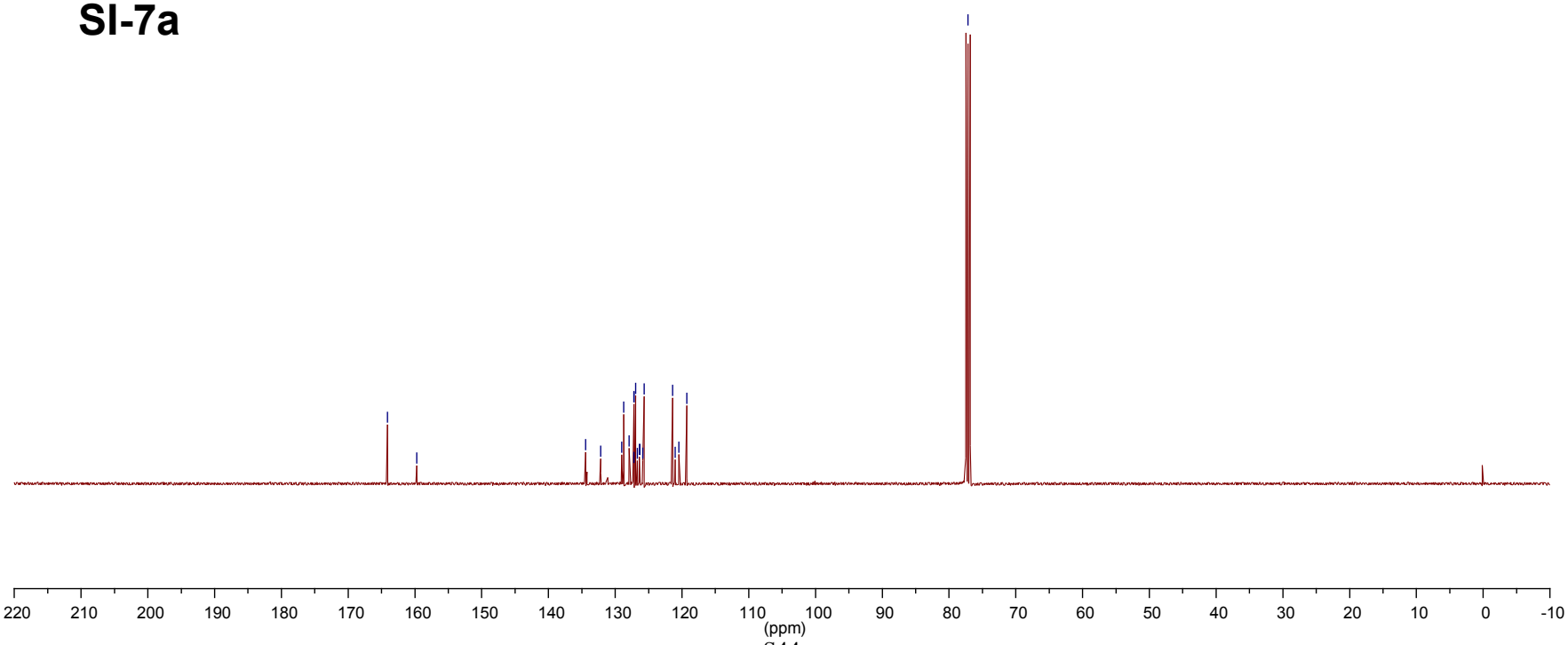


Title	MV-341d
Solvent	CHLOROFORM-D
Number of Scans	12000
Spectrometer Frequency	100.53
Nucleus	13C



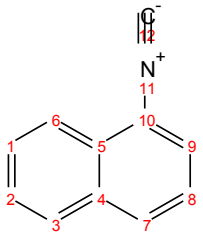
mix of geometrical isomers
(rotamers)

SI-7a

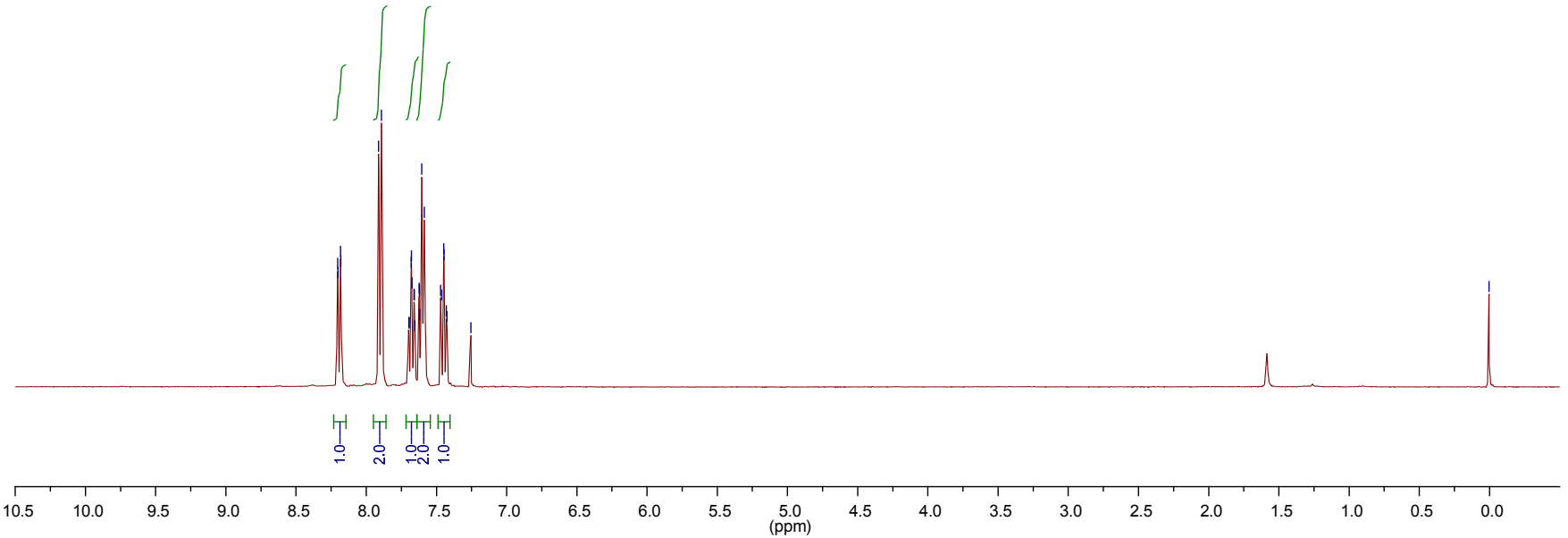


8.204
8.202
8.183
8.181
7.893
7.622
7.587
7.254
0.003

Title	MV-342
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H

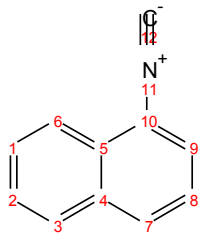


4b

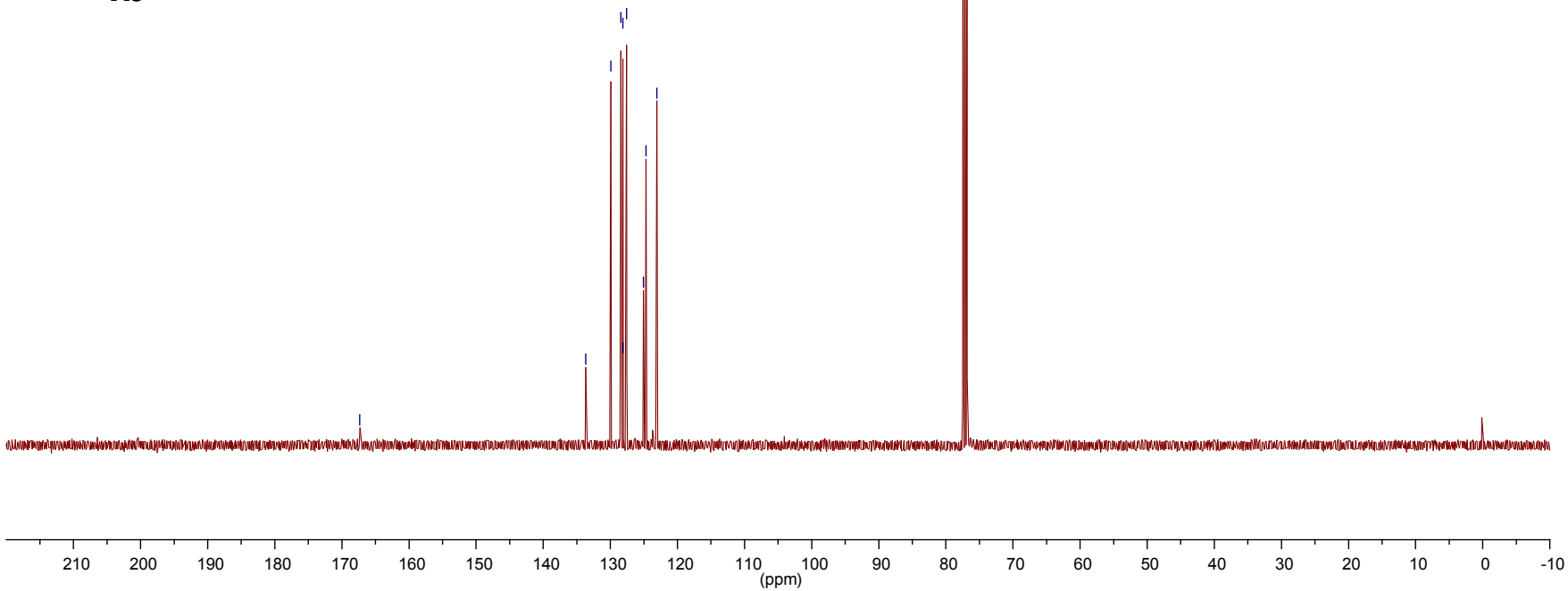


Title	MV-342
Solvent	CHLOROFORM-D
Number of Scans	2000
Spectrometer Frequency	100.53
Nucleus	13C

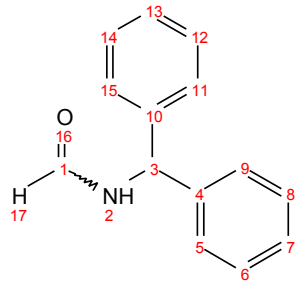
167.325
133.676
129.918
128.447
128.147
128.119
127.557
125.060
124.685
123.077
77.160



4b



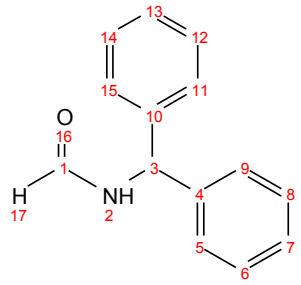
Title	MV-352c
Solvent	CHLOROFORM-D
Spectrometer Frequency	399.78
Nucleus	1H



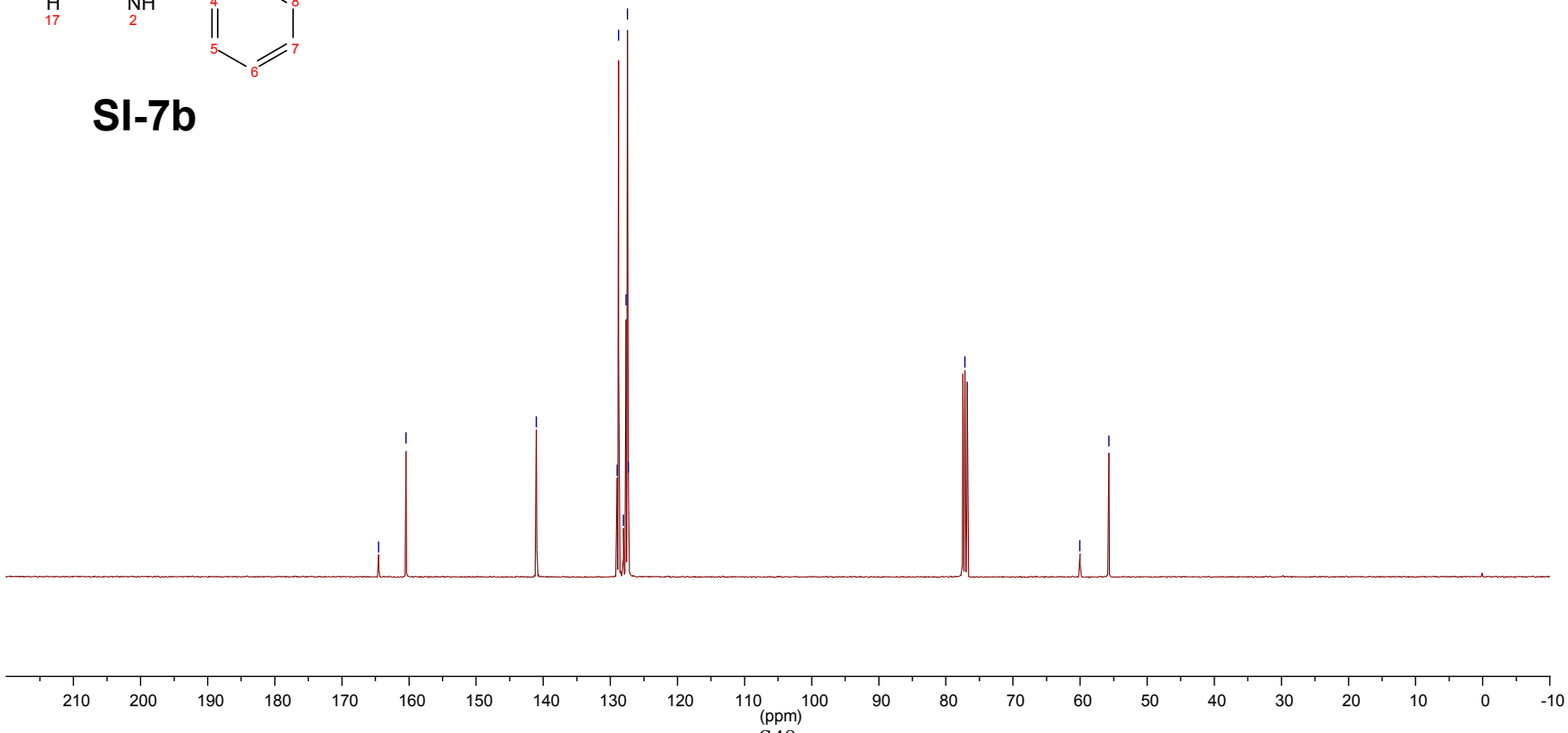
SI-7b

Title	MV-352c
Solvent	CHLOROFORM-D
Spectrometer Frequency	100.53
Nucleus	13C

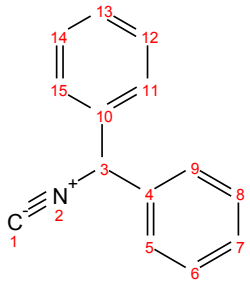
164.519
160.450
141.034
128.992
128.769
128.049
127.661
127.464
127.311
77.160
60.029
55.714



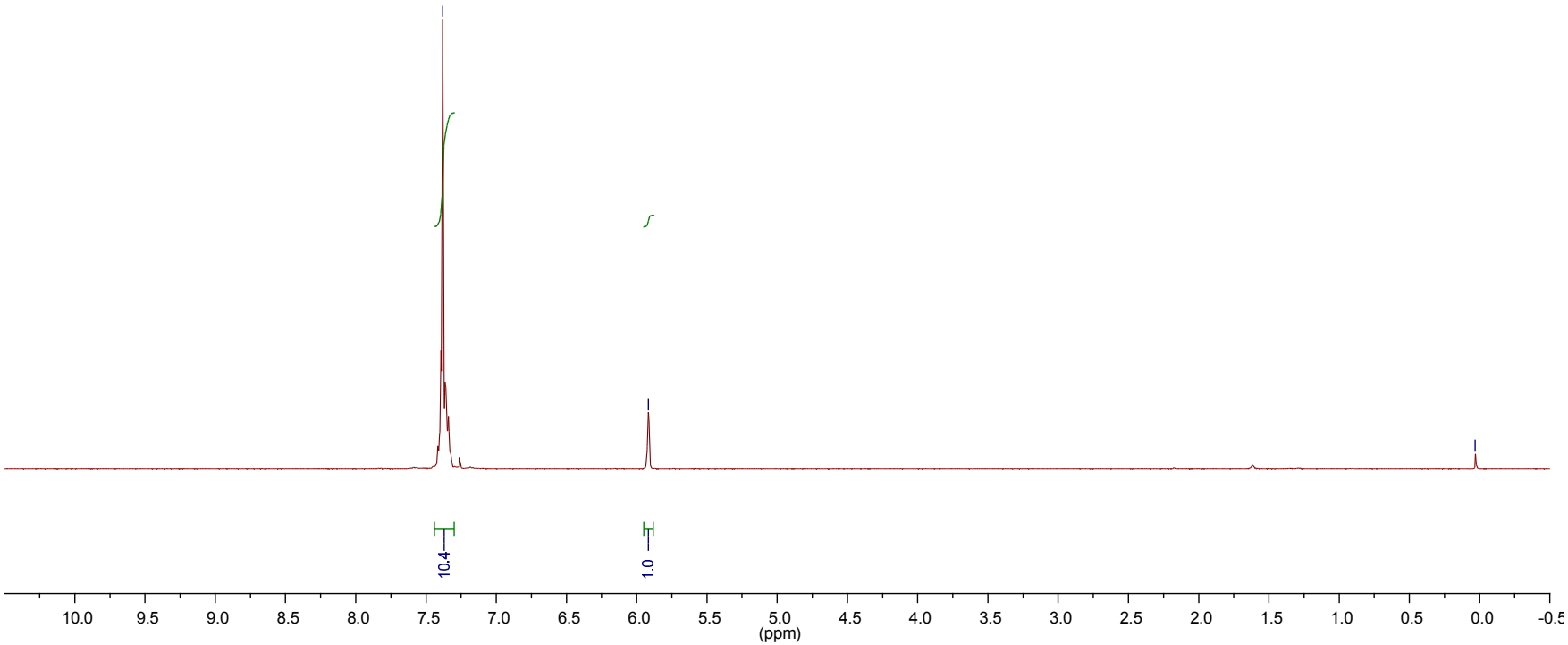
SI-7b



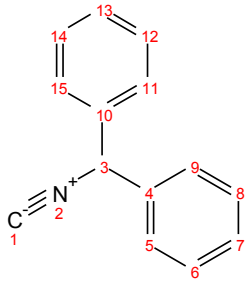
Title	MV-354
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



4c

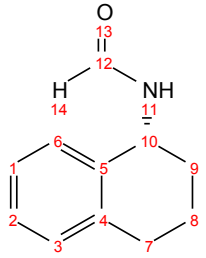


Title	MV-354
Solvent	CHLOROFORM-D
Number of Scans	2000
Spectrometer Frequency	100.53
Nucleus	13C

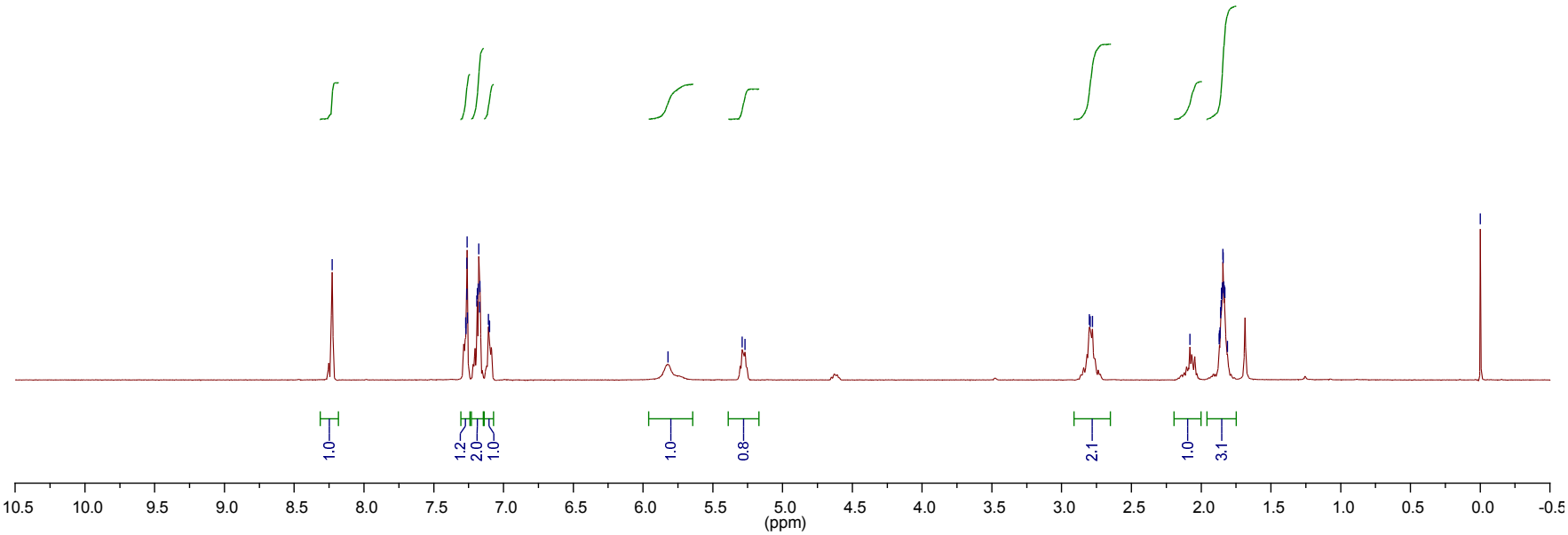


4c

Title	MV-328a
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H

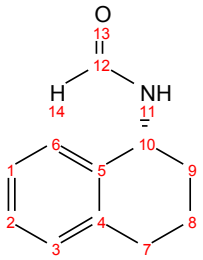


SI-7c

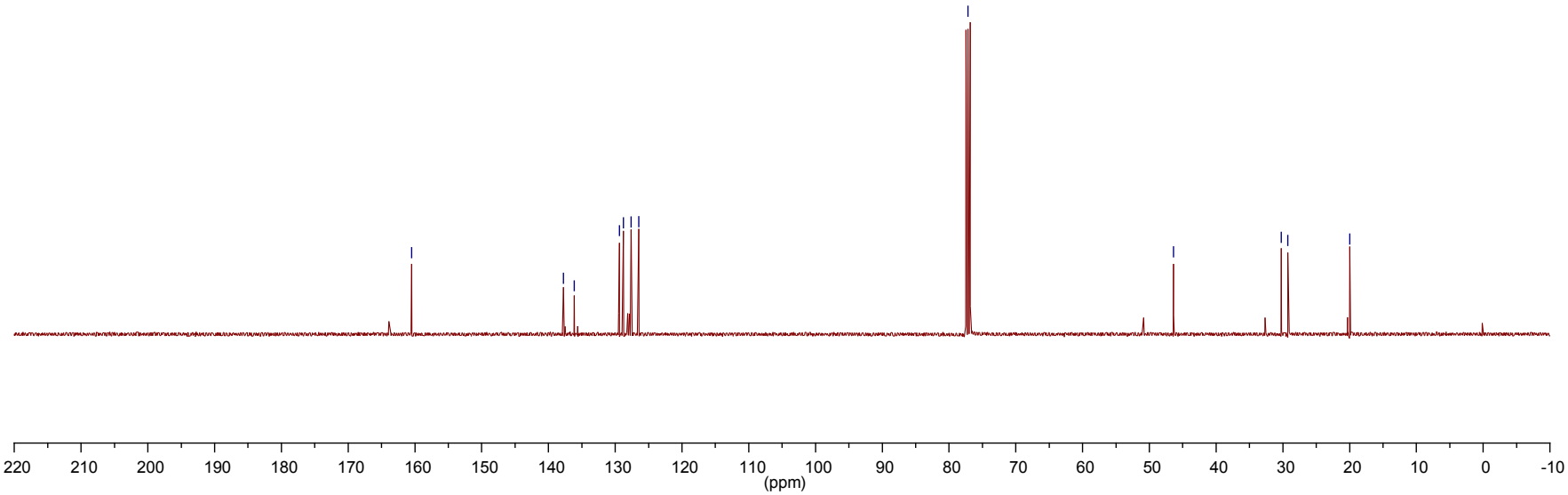


Title	MV-328a
Solvent	CHLOROFORM-D
Number of Scans	3200
Spectrometer Frequency	100.53
Nucleus	13C

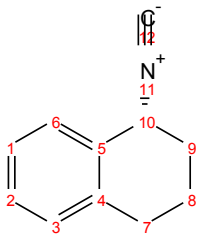
160.493
137.738
136.127
129.376
128.773
127.606
126.471
77.160
46.378
30.260
29.263
19.992



SI-7c

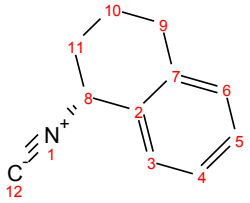


Title	MV-329z on 6/29/11
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H

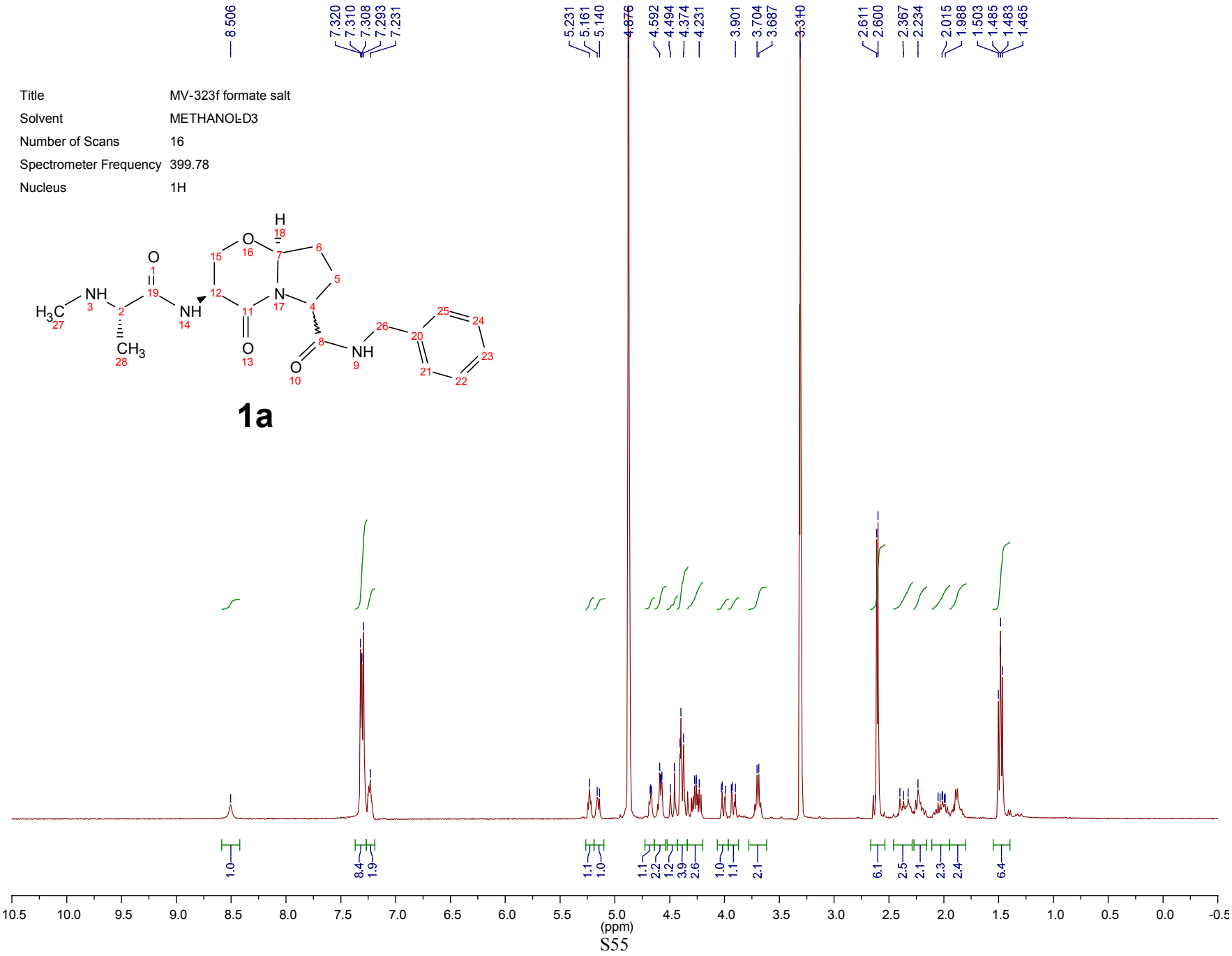


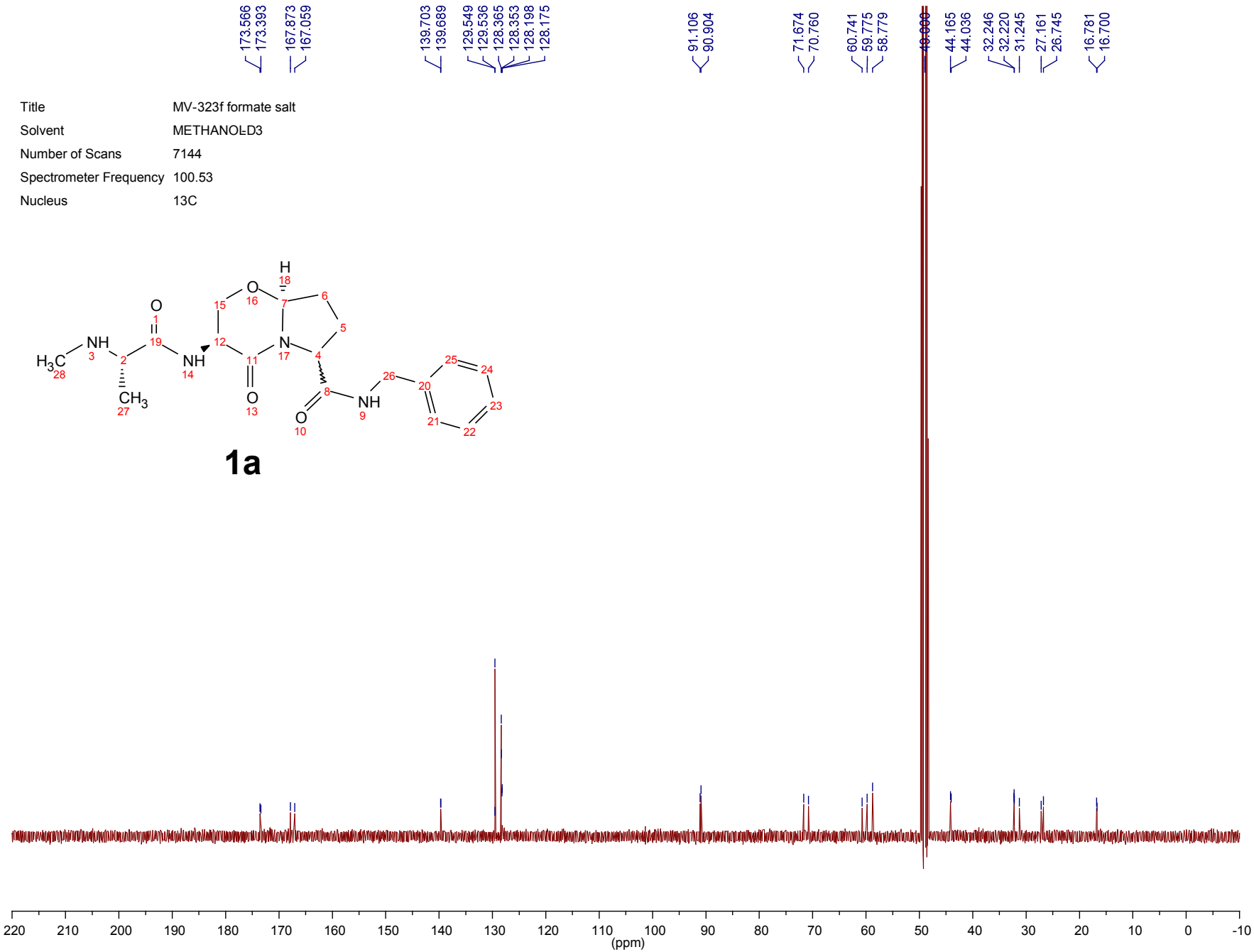
4d

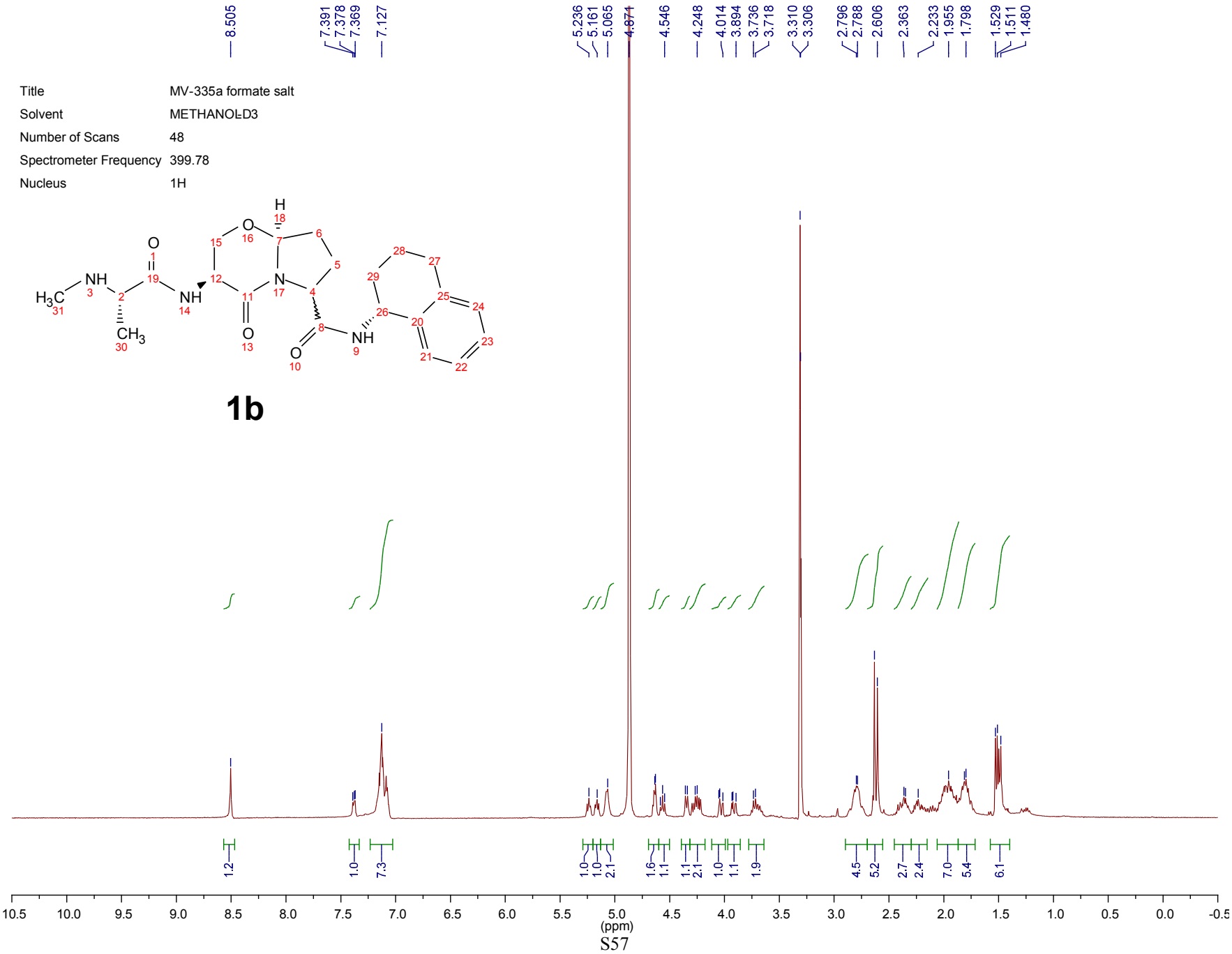
Title	MV-329
Solvent	CHLOROFORM-D
Number of Scans	3000
Spectrometer Frequency	100.53
Nucleus	13C

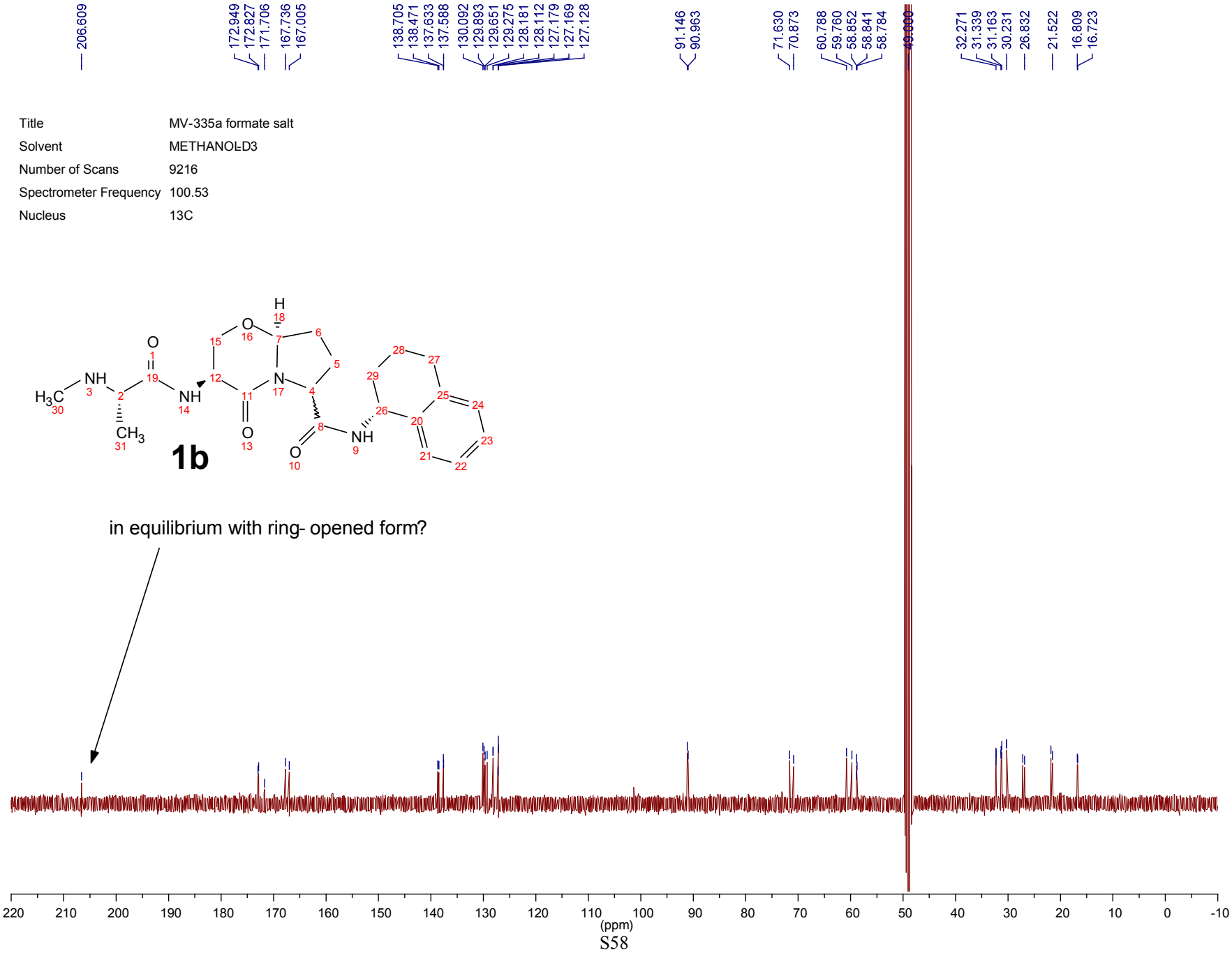


4d

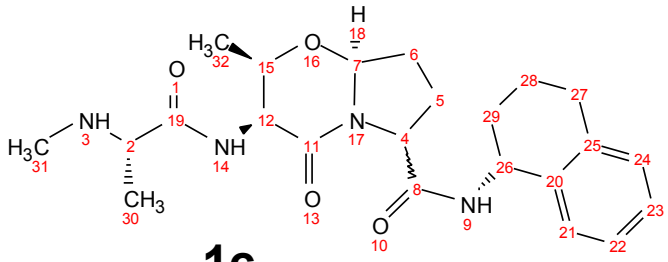

8.506
7.320
7.310
7.308
7.293
7.231
5.231
5.161
5.140
4.876
4.592
4.494
4.374
4.231
3.901
3.704
3.687
3.340
2.611
2.600
2.367
2.234
2.015
1.988
1.503
1.485
1.483
1.465
Title MV-323f formate salt
Solvent METHANOL-D3
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
1a
1.0
8.4
1.9
1.1
1.0
1.1
2.2
1.2
3.9
2.6
1.0
1.1
2.1
6.1
2.5
2.1
2.3
2.4
6.4
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


173.566
173.393
167.873
167.059
139.703
139.689
129.549
129.536
128.365
128.353
128.198
128.175
91.106
90.904
71.674
70.760
60.741
59.775
58.779
49.000
44.165
44.036
32.246
32.220
31.245
27.161
26.745
16.781
16.700
Title MV-323f formate salt
Solvent METHANOL-D3
Number of Scans 7144
Spectrometer Frequency 100.53
Nucleus 13C
1a
(ppm)

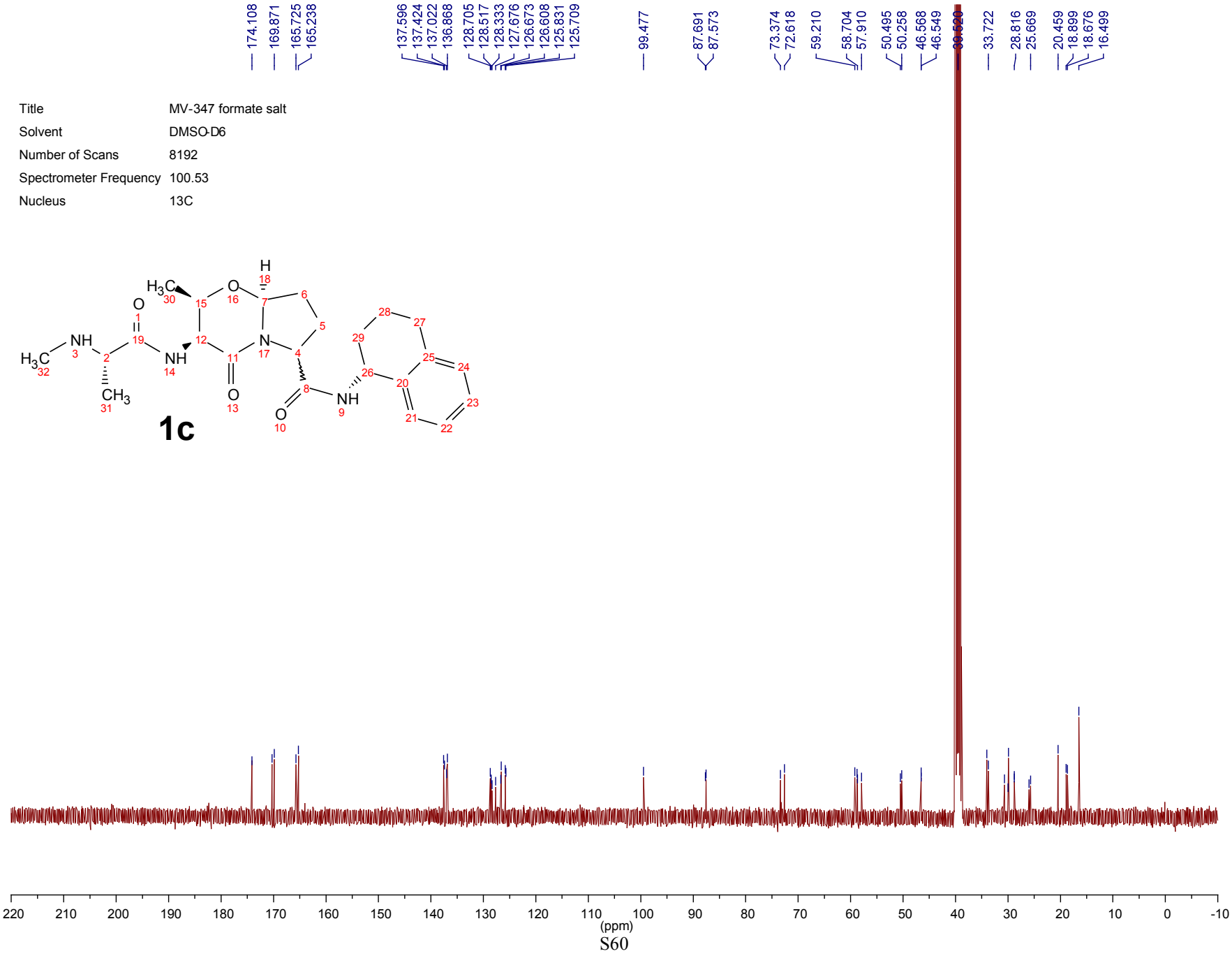

8.505
7.391
7.378
7.369
7.127
5.236
5.161
5.065
4.874
4.546
4.248
4.014
3.894
3.736
3.718
3.310
3.306
2.796
2.788
2.606
2.363
2.233
1.955
1.798
1.529
1.511
1.480
Title MV-335a formate salt
Solvent METHANOL-D3
Number of Scans 48
Spectrometer Frequency 399.78
Nucleus 1H
1b
1.2
1.0
7.3
1.0
1.0
2.1
1.6
1.1
1.1
2.1
1.0
1.1
1.9
4.5
5.2
2.7
2.4
7.0
5.4
6.1
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

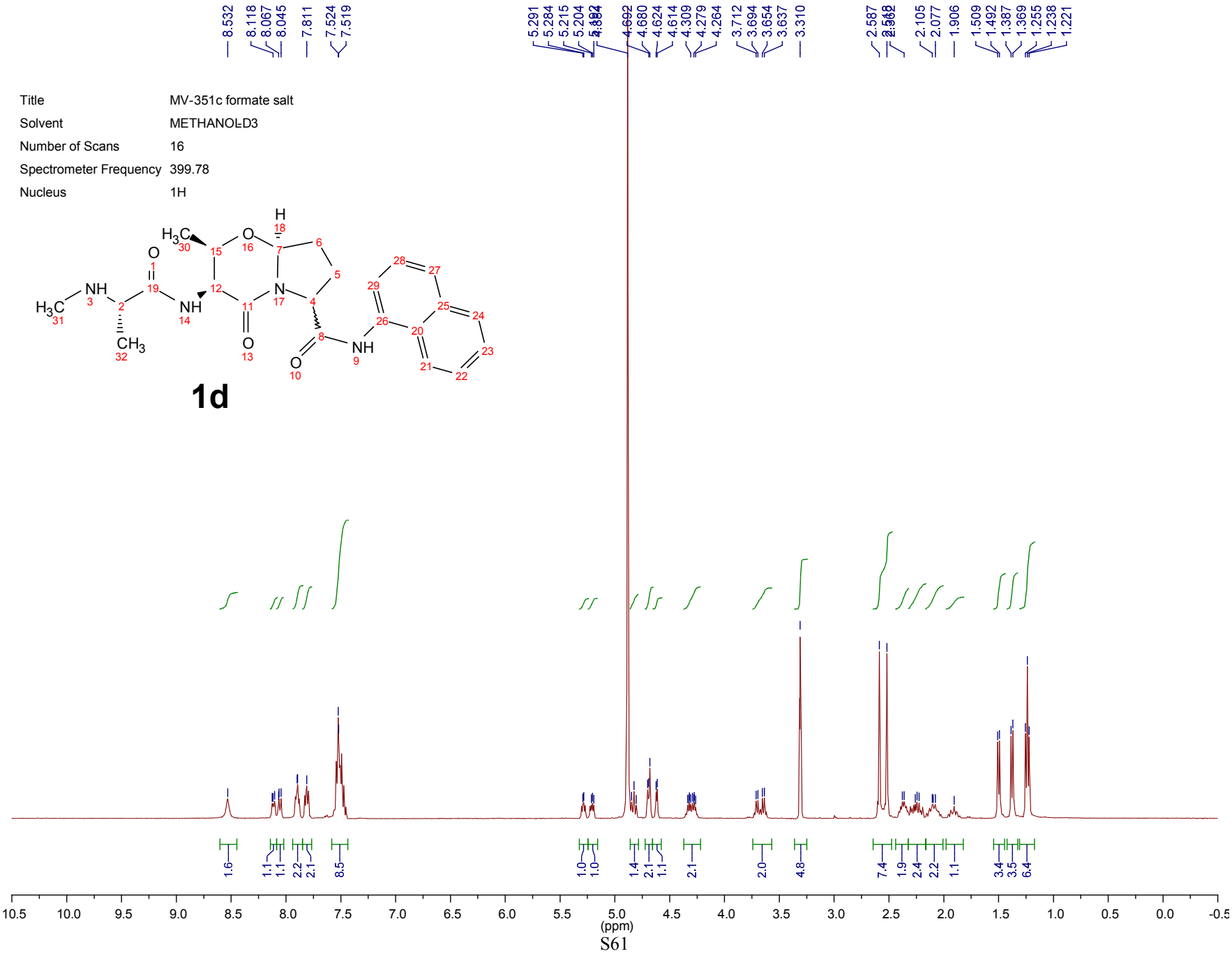

206.609
172.949
172.827
171.706
167.736
167.005
138.705
138.471
137.633
137.588
130.092
129.893
129.651
129.275
128.181
128.112
127.179
127.169
127.128
91.146
90.963
71.630
70.873
60.788
59.760
58.852
58.841
58.784
49.000
32.271
31.339
31.163
30.231
26.832
21.522
16.809
16.723
Title MV-335a formate salt
Solvent METHANOL-D3
Number of Scans 9216
Spectrometer Frequency 100.53
Nucleus 13C
1b
in equilibrium with ring- opened form?
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

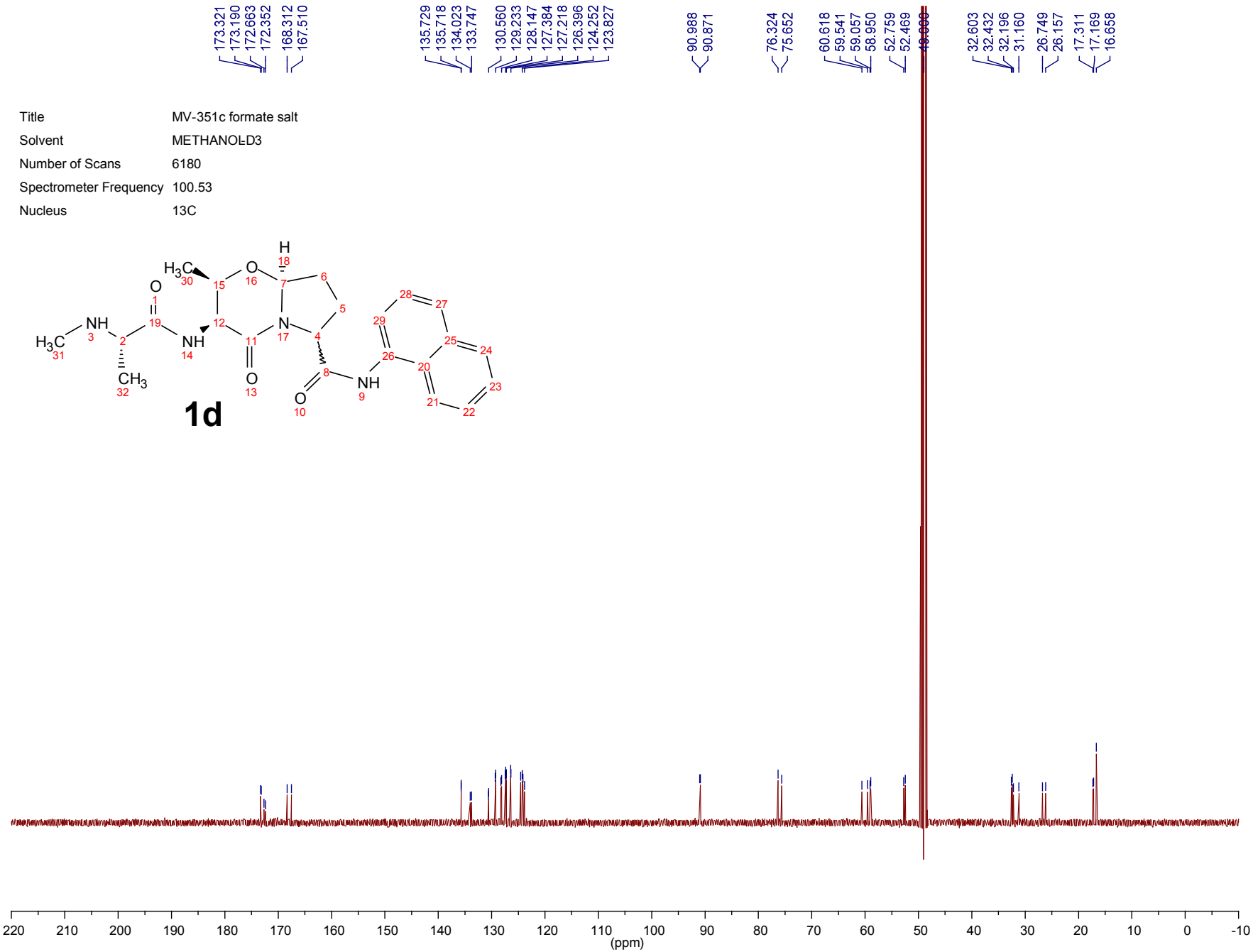
Title	MV-347a formate salt
Solvent	DMSO-D6
Number of Scans	24
Spectrometer Frequency	399.78
Nucleus	1H



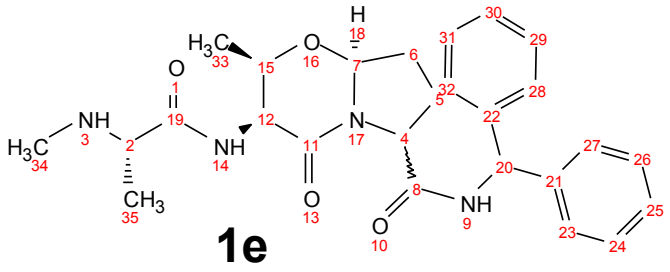
1c


174.108
169.871
165.725
165.238
137.596
137.424
137.022
136.868
128.705
128.517
128.333
127.676
126.673
126.608
125.831
125.709
99.477
87.691
87.573
73.374
72.618
59.210
58.704
57.910
50.495
50.258
46.568
46.549
33.722
28.816
25.669
20.459
18.899
18.676
16.499
Title MV-347 formate salt
Solvent DMSO-D6
Number of Scans 8192
Spectrometer Frequency 100.53
Nucleus 13C
1c
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

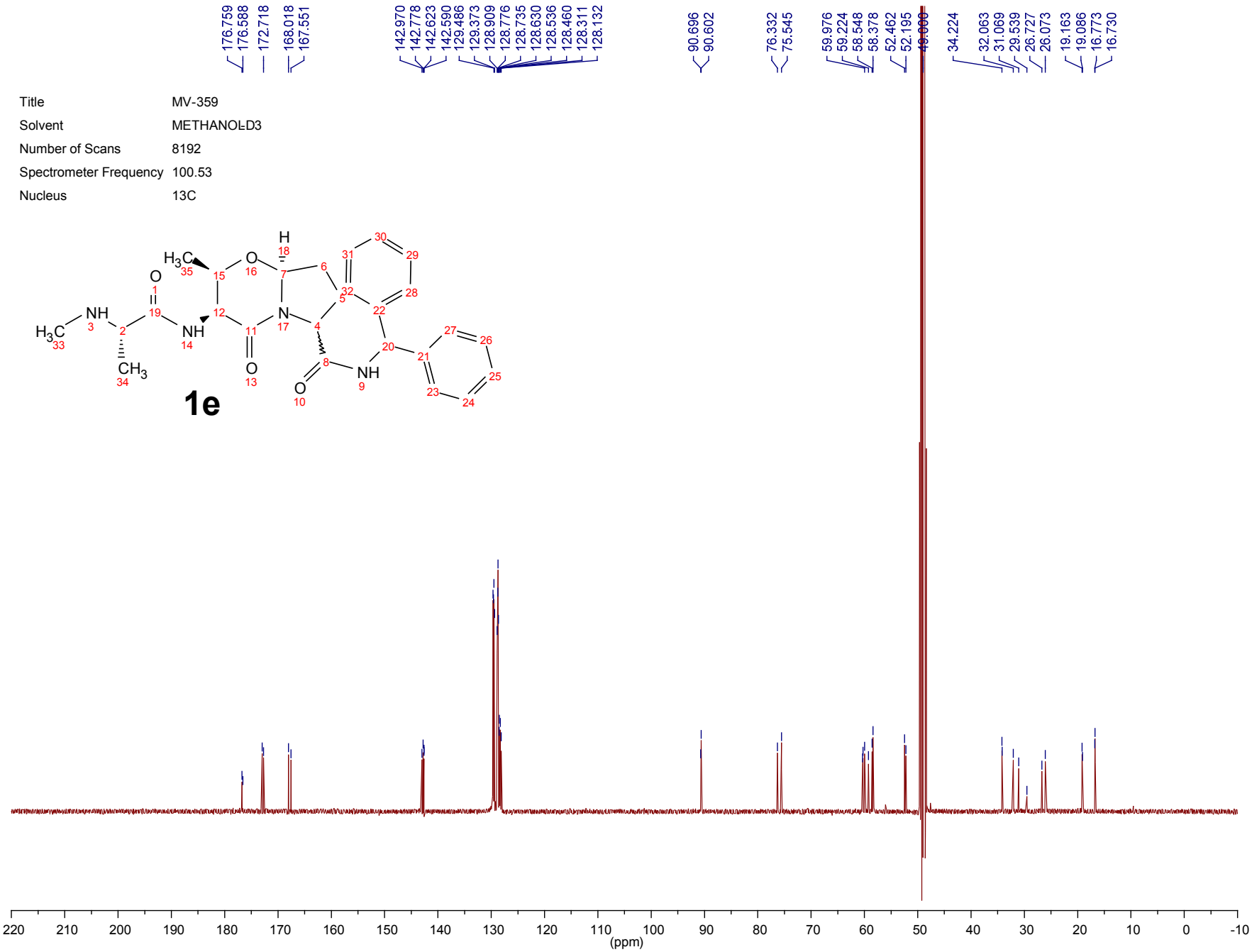

Title MV-351c formate salt
Solvent METHANOL-D3
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
1d
(ppm)


173.321
173.190
172.663
172.352
168.312
167.510
135.729
135.718
134.023
133.747
130.560
129.233
128.147
127.384
127.218
126.396
124.252
123.827
90.988
90.871
76.324
75.652
60.618
59.541
59.057
58.950
52.759
52.469
49.000
32.603
32.432
32.196
31.160
26.749
26.157
17.311
17.169
16.658
Title MV-351c formate salt
Solvent METHANOL-D3
Number of Scans 6180
Spectrometer Frequency 100.53
Nucleus 13C
1d
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

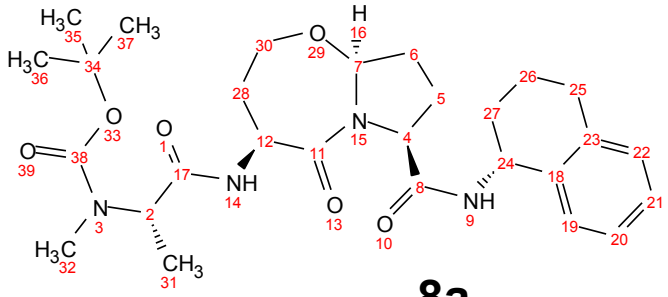
Title	MV-359a
Solvent	METHANOL-D3
Number of Scans	24
Spectrometer Frequency	399.78
Nucleus	1H



1e

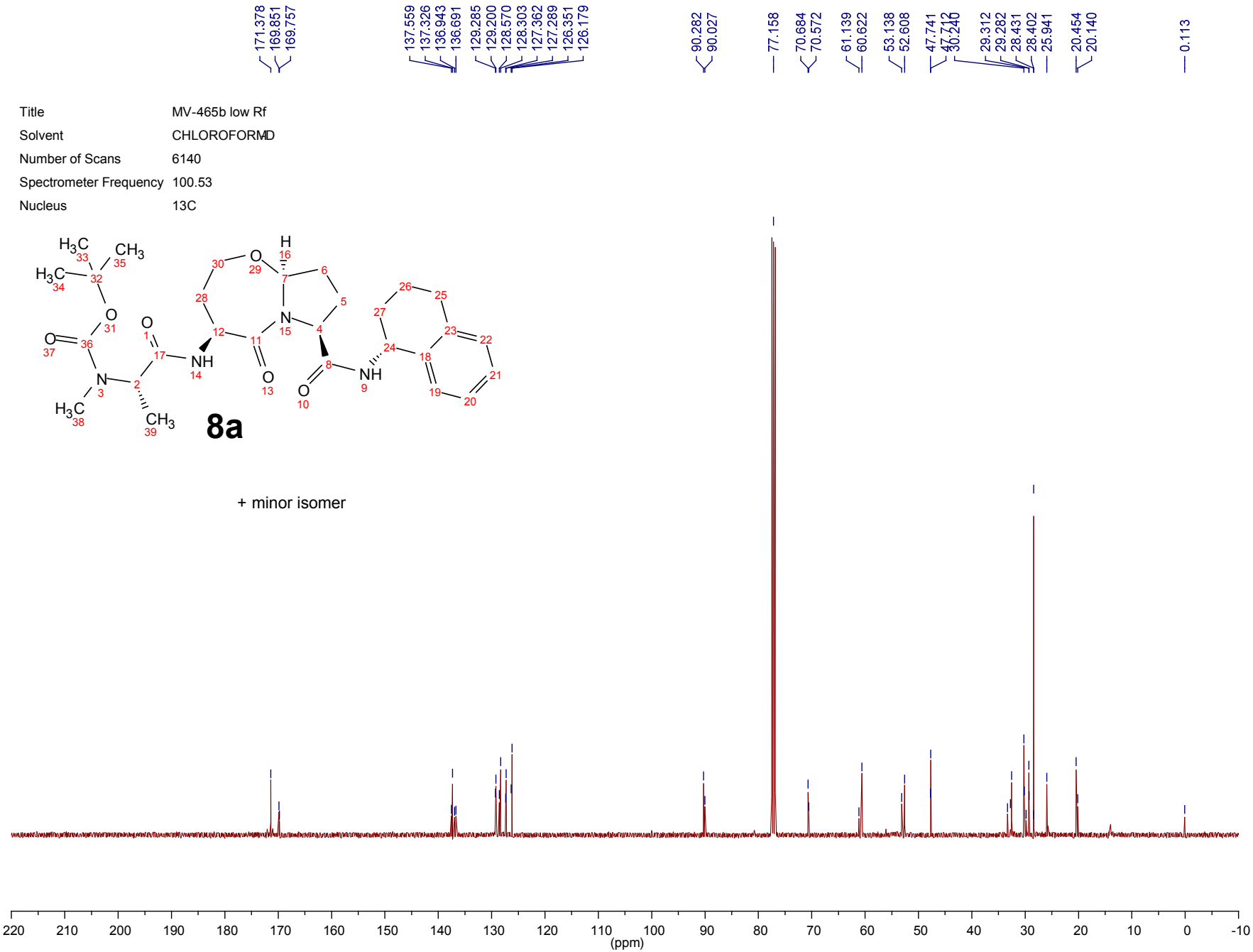

176.759
176.588
172.718
168.018
167.551
142.970
142.778
142.623
142.590
129.486
129.373
128.909
128.776
128.735
128.630
128.536
128.460
128.311
128.132
90.696
90.602
76.332
75.545
59.976
59.224
58.548
58.378
52.462
52.195
49.000
34.224
32.063
31.069
29.539
26.727
26.073
19.163
19.086
16.773
16.730
Title MV-359
Solvent METHANOL-D3
Number of Scans 8192
Spectrometer Frequency 100.53
Nucleus 13C
1e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

Title	MV-465b low Rf
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H

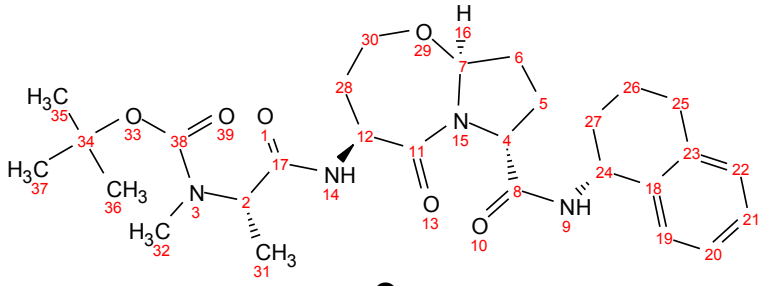


8a

+ minor isomer

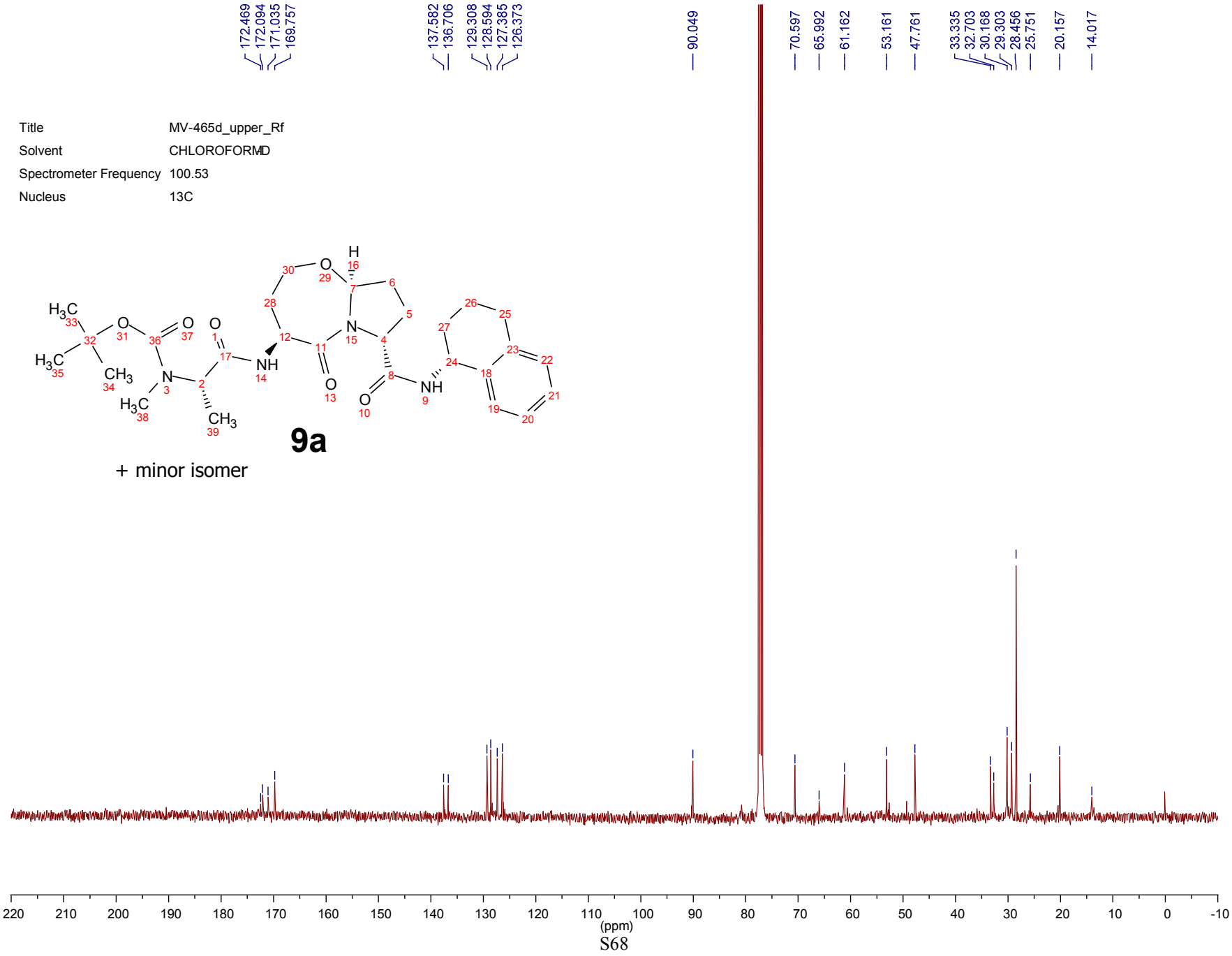

171.378
169.851
169.757
137.559
137.326
136.943
136.691
129.285
129.200
128.570
128.303
127.362
127.289
126.351
126.179
90.282
90.027
77.158
70.684
70.572
61.139
60.622
53.138
52.608
47.741
47.712
30.240
29.312
29.282
28.431
28.402
25.941
20.454
20.140
0.113
Title MV-465b low Rf
Solvent CHLOROFORM-D
Number of Scans 6140
Spectrometer Frequency 100.53
Nucleus 13C
8a
+ minor isomer
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

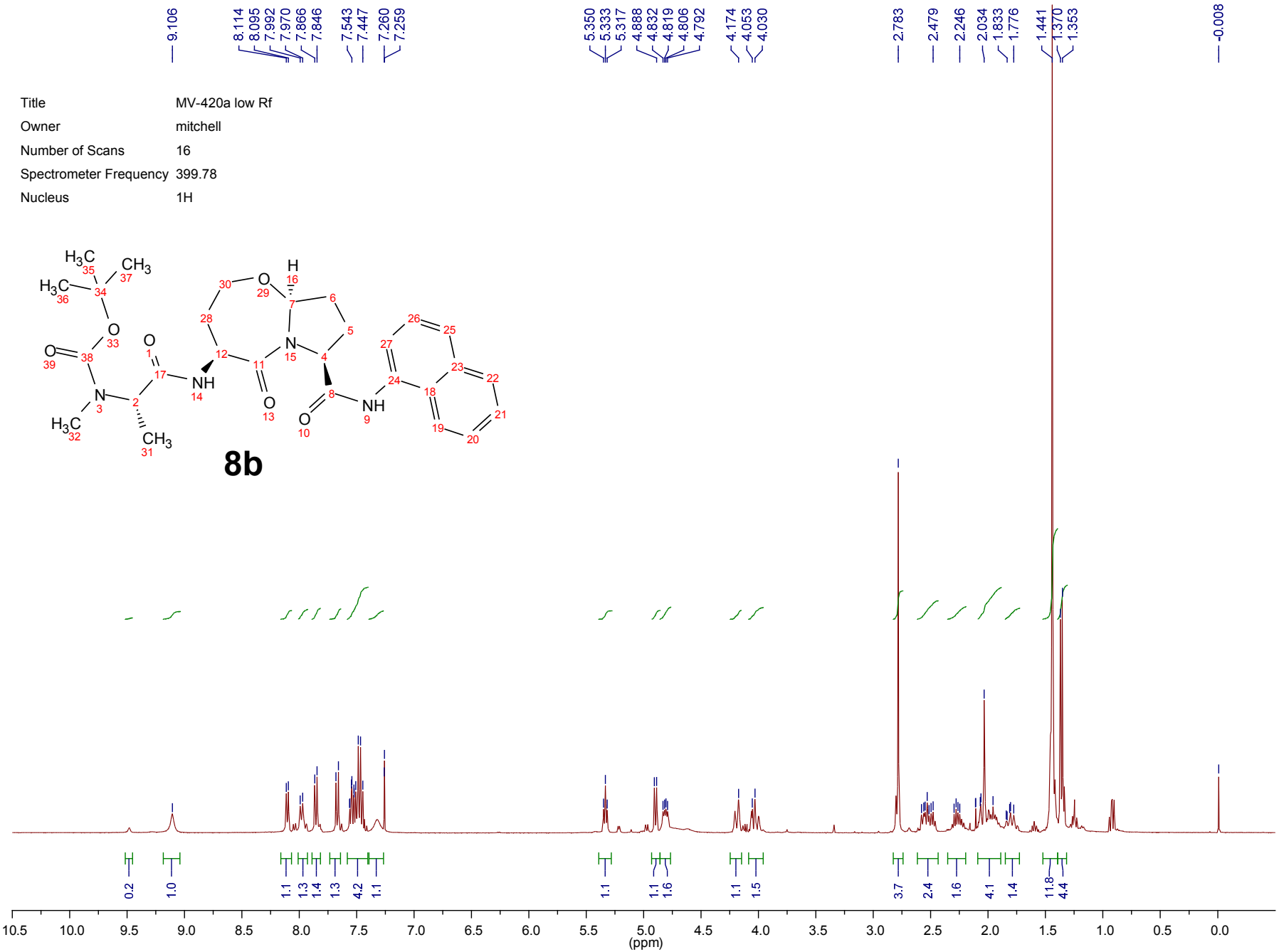
Title	MV-465d_upper_Rf
Solvent	CHLOROFORM-D
Number of Scans	24
Spectrometer Frequency	399.78
Nucleus	1H



9a

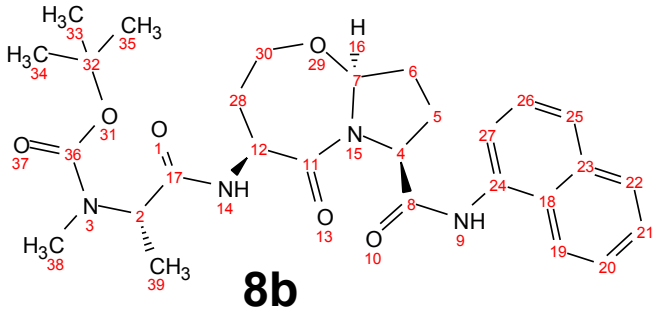
+ minor isomer


172.469
172.094
171.035
169.757
137.582
136.706
129.308
128.594
127.385
126.373
90.049
70.597
65.992
61.162
53.161
47.761
33.335
32.703
30.168
29.303
28.456
25.751
20.157
14.017
Title MV-465d_upper_Rf
Solvent CHLOROFORM-D
Spectrometer Frequency 100.53
Nucleus 13C
9a
+ minor isomer
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


9.106
8.114
8.095
7.992
7.970
7.866
7.846
7.543
7.447
7.260
7.259
5.350
5.333
5.317
4.888
4.832
4.819
4.806
4.792
4.174
4.053
4.030
2.783
2.479
2.246
2.034
1.833
1.776
1.441
1.370
1.353
-0.008
Title MV-420a low Rf
Owner mitchell
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
8b
0.2
1.0
1.1
1.3
1.4
1.3
4.2
1.1
1.1
1.1
1.6
1.1
1.5
3.7
2.4
1.6
4.1
1.4
11.8
4.4
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

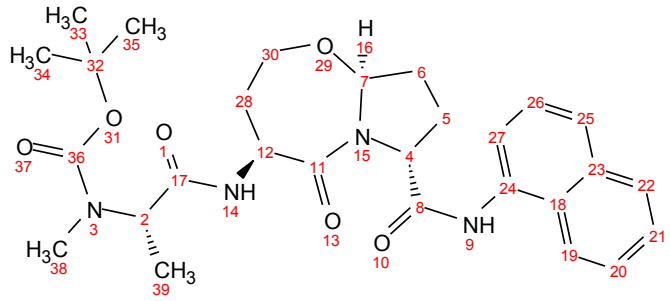
172.051
171.387
171.363
171.355
169.062
168.508
134.132
132.662
126.483
125.475
120.689
119.754
90.703
77.160
70.795
61.241
52.796
32.799
32.617
30.214
28.461
28.440
28.419
28.408
25.616

Title	MV-420a low Rf
Solvent	CHLOROFORM-D
Number of Scans	2048
Spectrometer Frequency	100.53
Nucleus	13C



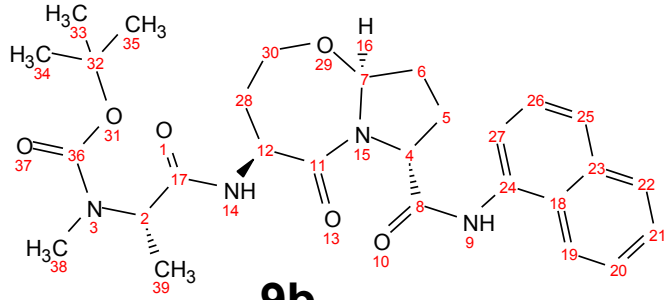
8b

Title	MV-420 upper Rf
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



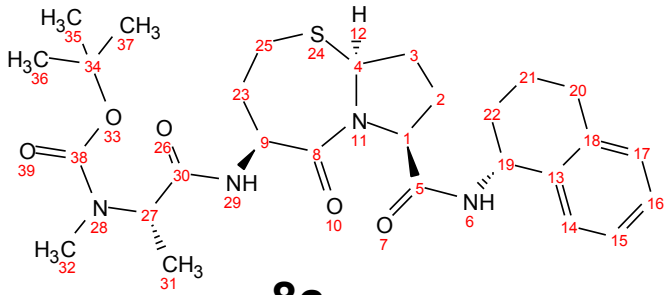
9b

Title	MV-420 upper Rf
Solvent	CHLOROFORM-D
Number of Scans	2048
Spectrometer Frequency	100.53
Nucleus	13C

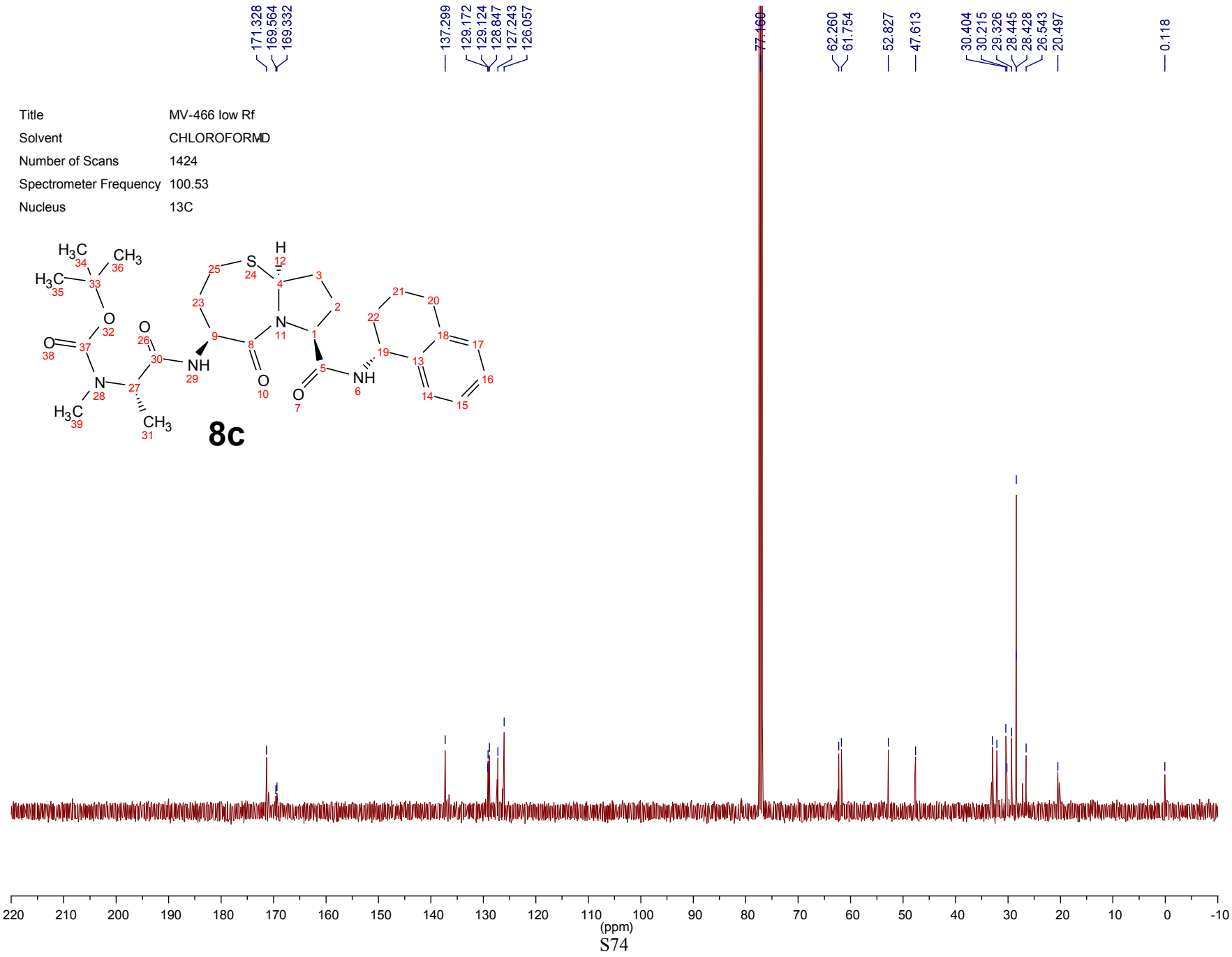


9b

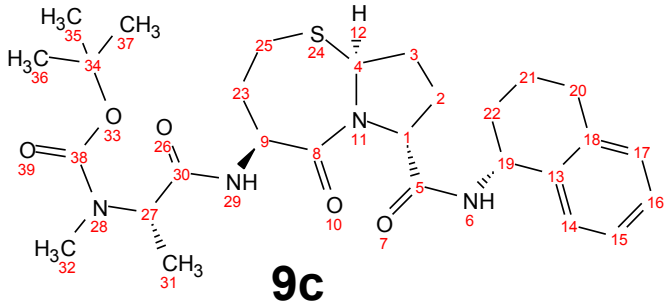
Title	MV-466 low Rf
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



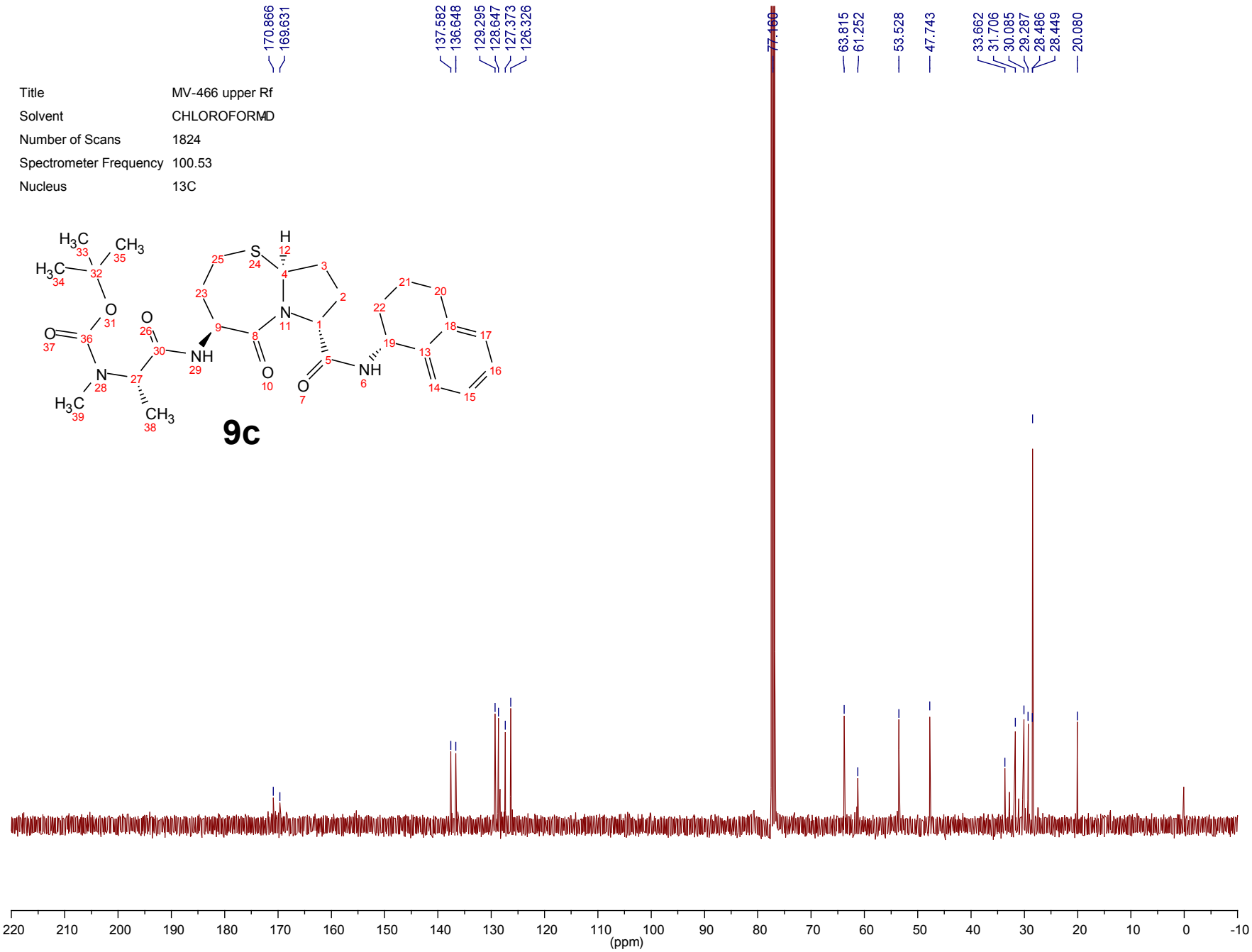
8c

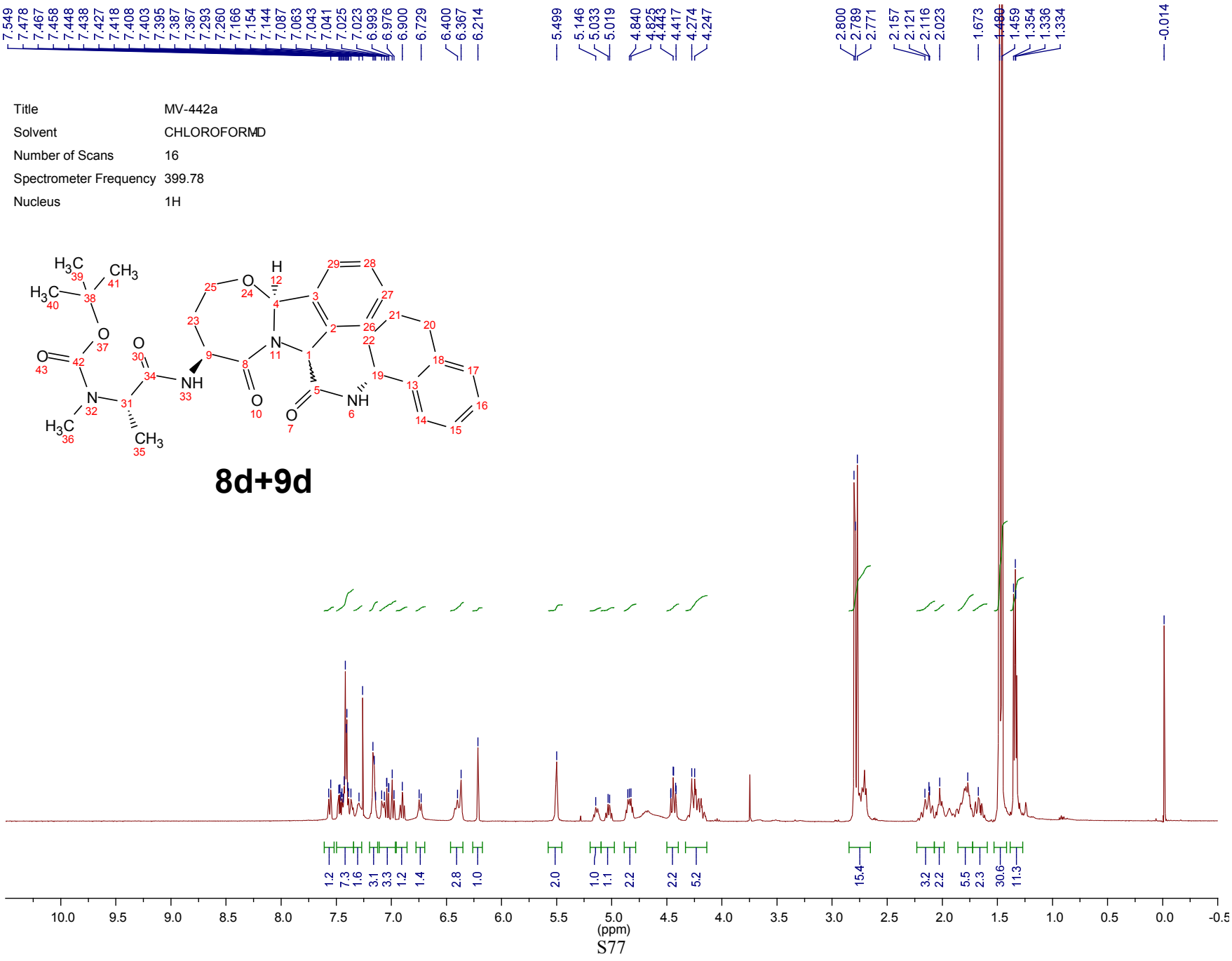

171.328
169.564
169.332
137.299
129.172
129.124
128.847
127.243
126.057
77.160
62.260
61.754
52.827
47.613
30.404
30.215
29.326
28.445
28.428
26.543
20.497
0.118
Title MV-466 low Rf
Solvent CHLOROFORM-D
Number of Scans 1424
Spectrometer Frequency 100.53
Nucleus 13C
8c
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

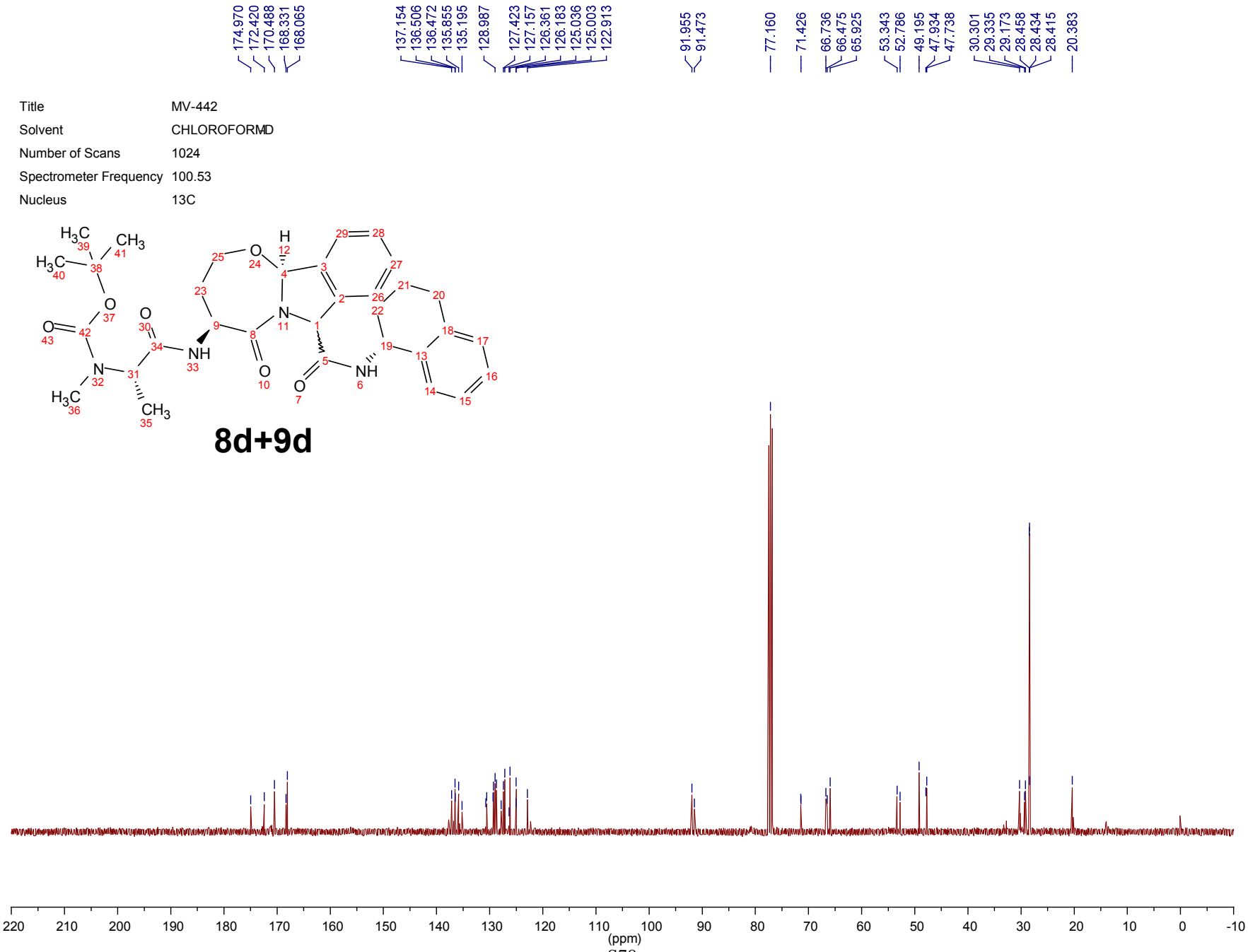
Title	MV-466d upper Rf
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



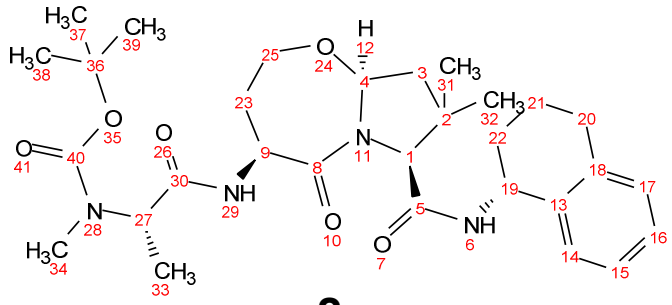
9c


170.866
169.631
137.582
136.648
129.295
128.647
127.373
126.326
77.160
63.815
61.252
53.528
47.743
33.662
31.706
30.085
29.287
28.486
28.449
20.080
Title MV-466 upper Rf
Solvent CHLOROFORM-D
Number of Scans 1824
Spectrometer Frequency 100.53
Nucleus 13C
9c
(ppm)


7.549 7.478 7.467 7.458 7.448 7.438 7.427 7.418 7.408 7.403 7.395 7.387 7.367 7.293 7.260 7.166 7.154 7.144 7.087 7.063 7.043 7.041 7.025 7.023 6.993 6.976 6.900 6.729 6.400 6.367 6.214
5.499 5.146 5.033 5.019 4.840 4.825 4.443 4.417 4.274 4.247
2.800 2.789 2.771 2.157 2.121 2.116 2.023 1.673 1.480 1.459 1.354 1.336 1.334 -0.014
Title MV-442a
Solvent CHLOROFORM-D
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
8d+9d
1.2 7.3 1.6 3.1 3.3 1.2 1.4 2.8 1.0 2.0 1.0 1.1 2.2 2.2 5.2 15.4 3.2 2.2 5.5 2.3 30.6 11.3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


174.970
172.420
170.488
168.331
168.065
137.154
136.506
136.472
135.855
135.195
128.987
127.423
127.157
126.361
126.183
125.036
125.003
122.913
91.955
91.473
77.160
71.426
66.736
66.475
65.925
53.343
52.786
49.195
47.934
47.738
30.301
29.335
29.173
28.458
28.434
28.415
20.383
Title MV-442
Solvent CHLOROFORM-D
Number of Scans 1024
Spectrometer Frequency 100.53
Nucleus 13C
8d+9d
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

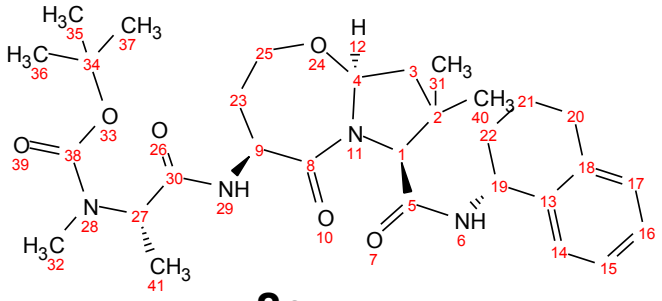
Title	MV-435 low Rf
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



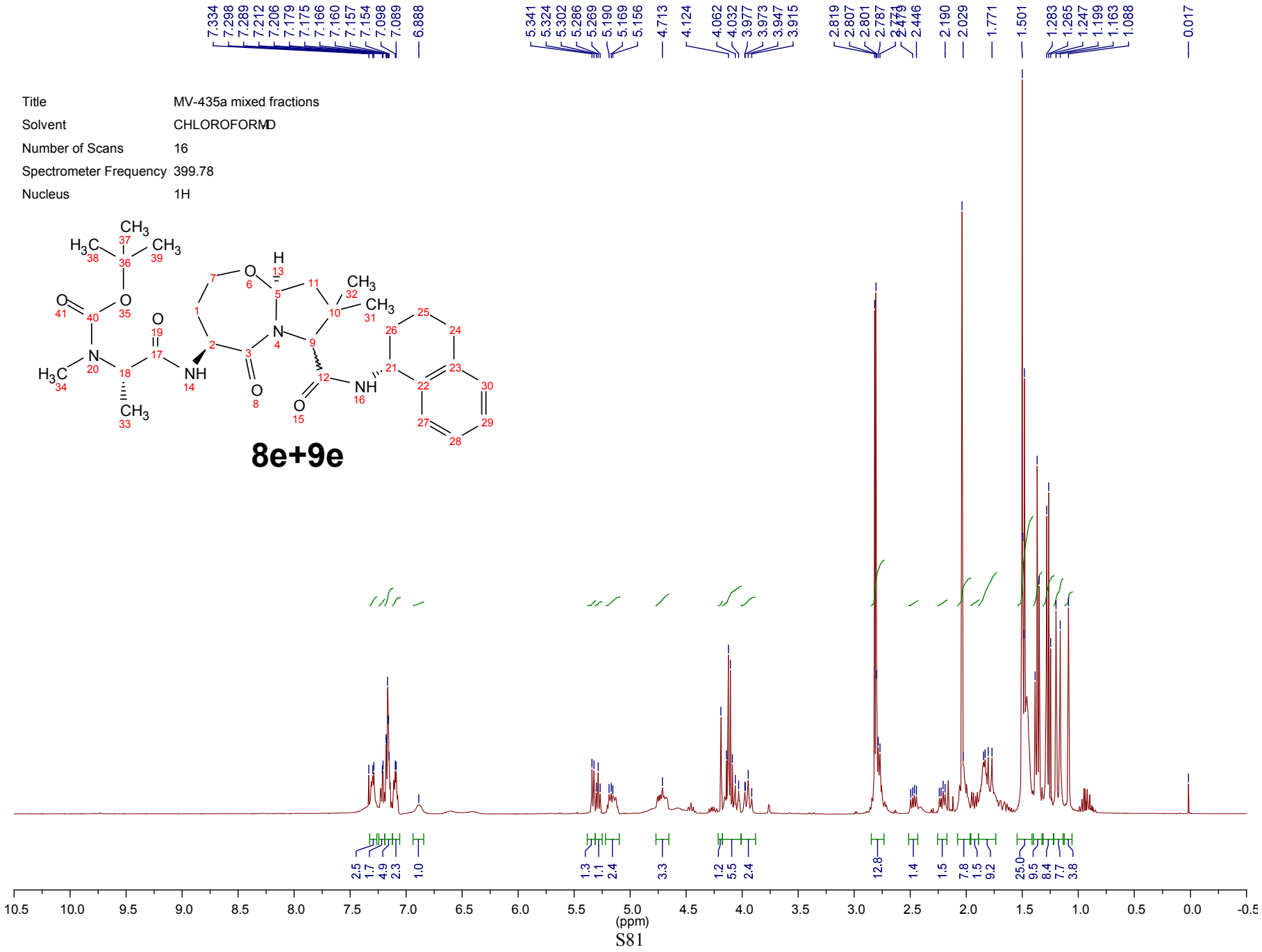
8e

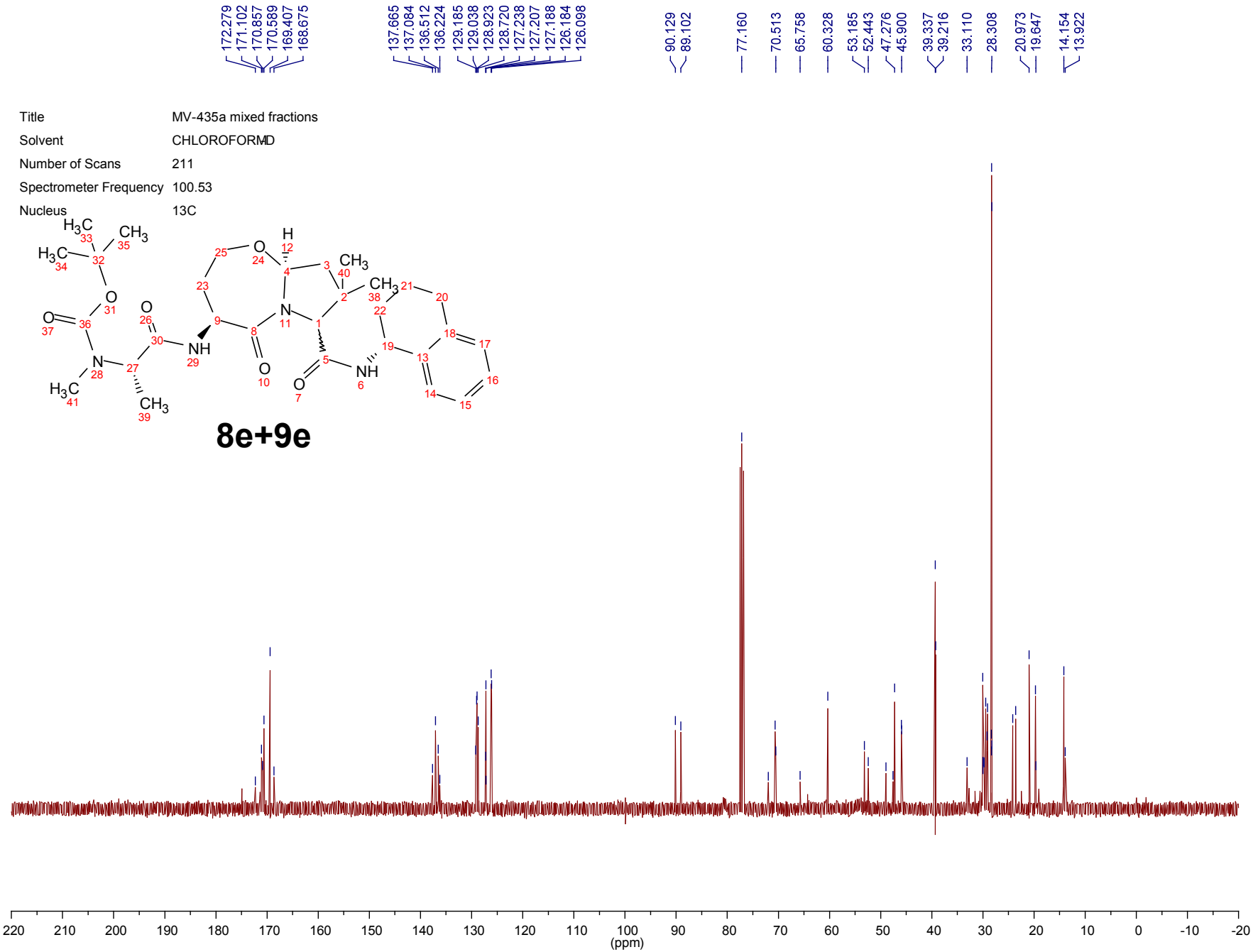
170.720
168.785
137.265
136.663
136.646
129.226
128.852
127.377
126.359
89.277
89.248
77.160
70.899
70.713
52.572
47.455
46.111
39.552
29.234
28.478
28.450
23.777
19.891
14.317
14.025

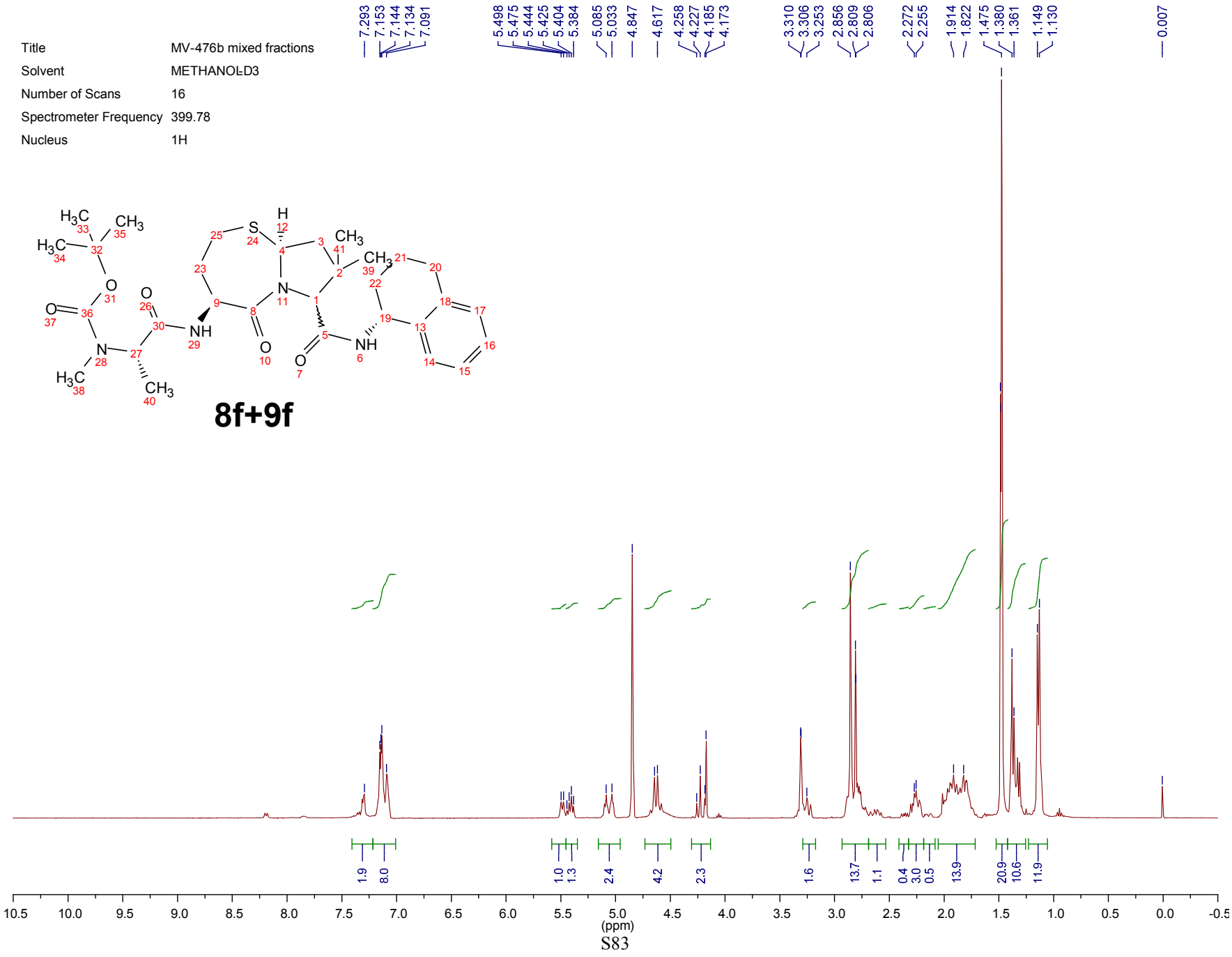
Title	MV-435 low Rf
Solvent	CHLOROFORM-D
Number of Scans	528
Spectrometer Frequency	100.53
Nucleus	13C

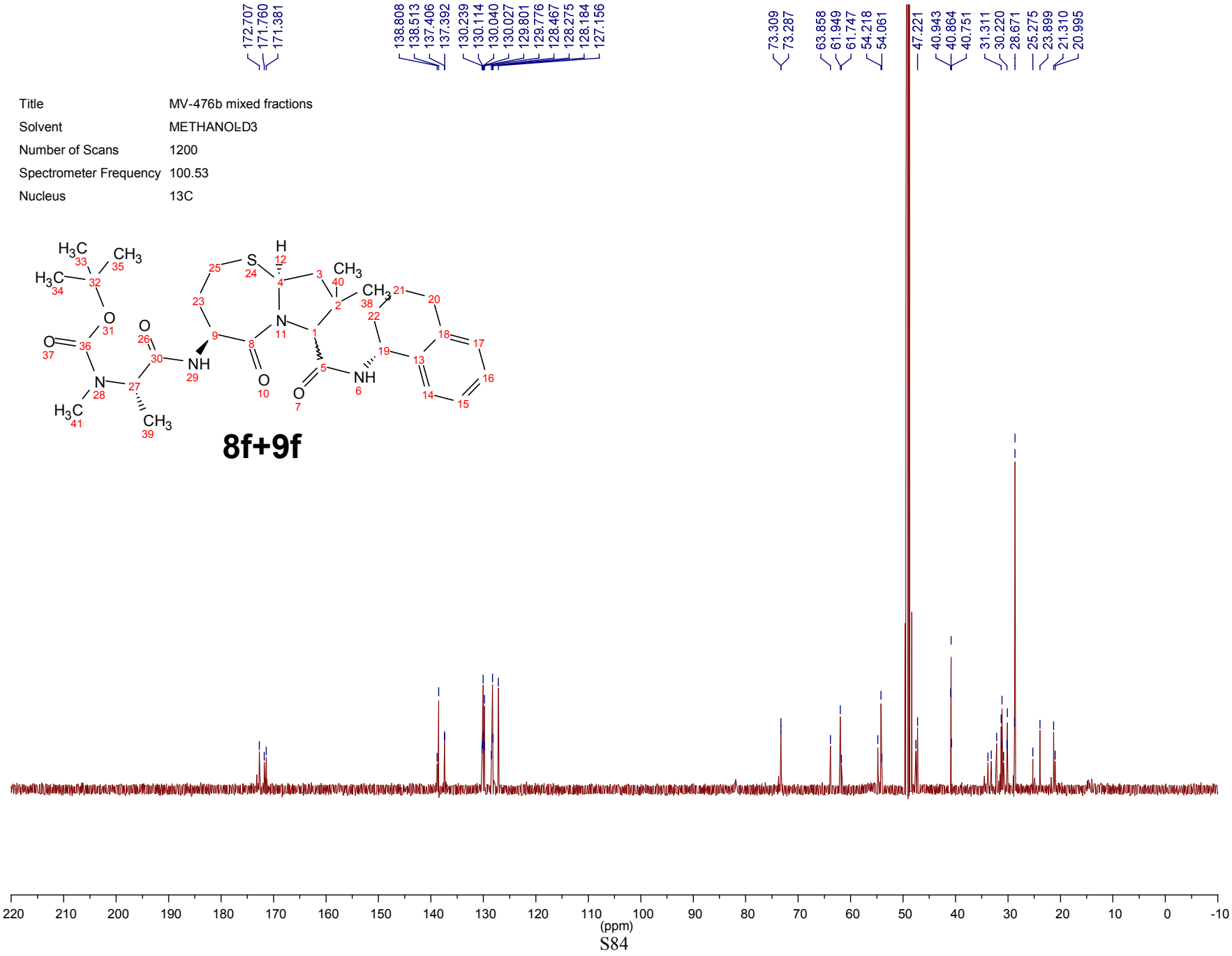


8e

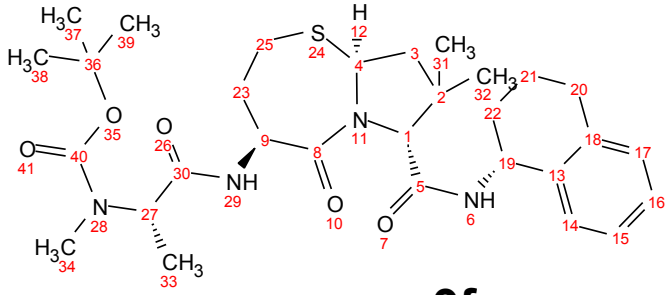

Title MV-435a mixed fractions
Solvent CHLOROFORM-D
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
8e+9e
(ppm)


172.279
171.102
170.857
170.589
169.407
168.675
137.665
137.084
136.512
136.224
129.185
129.038
128.923
128.720
127.238
127.207
127.188
126.184
126.098
90.129
89.102
77.160
70.513
65.758
60.328
53.185
52.443
47.276
45.900
39.337
39.216
33.110
28.308
20.973
19.647
14.154
13.922
Title MV-435a mixed fractions
Solvent CHLOROFORM-D
Number of Scans 211
Spectrometer Frequency 100.53
Nucleus 13C
8e+9e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)


Title MV-476b mixed fractions
Solvent METHANOL-D3
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
7.293
7.153
7.144
7.134
7.091
5.498
5.475
5.444
5.425
5.404
5.384
5.085
5.033
4.847
4.617
4.258
4.227
4.185
4.173
3.310
3.306
3.253
2.856
2.809
2.806
2.272
2.255
1.914
1.822
1.475
1.380
1.361
1.149
1.130
0.007
8f+9f
1.9
8.0
1.0
1.3
2.4
4.2
2.3
1.6
13.7
1.1
0.4
3.0
0.5
13.9
20.9
10.6
11.9
(ppm)

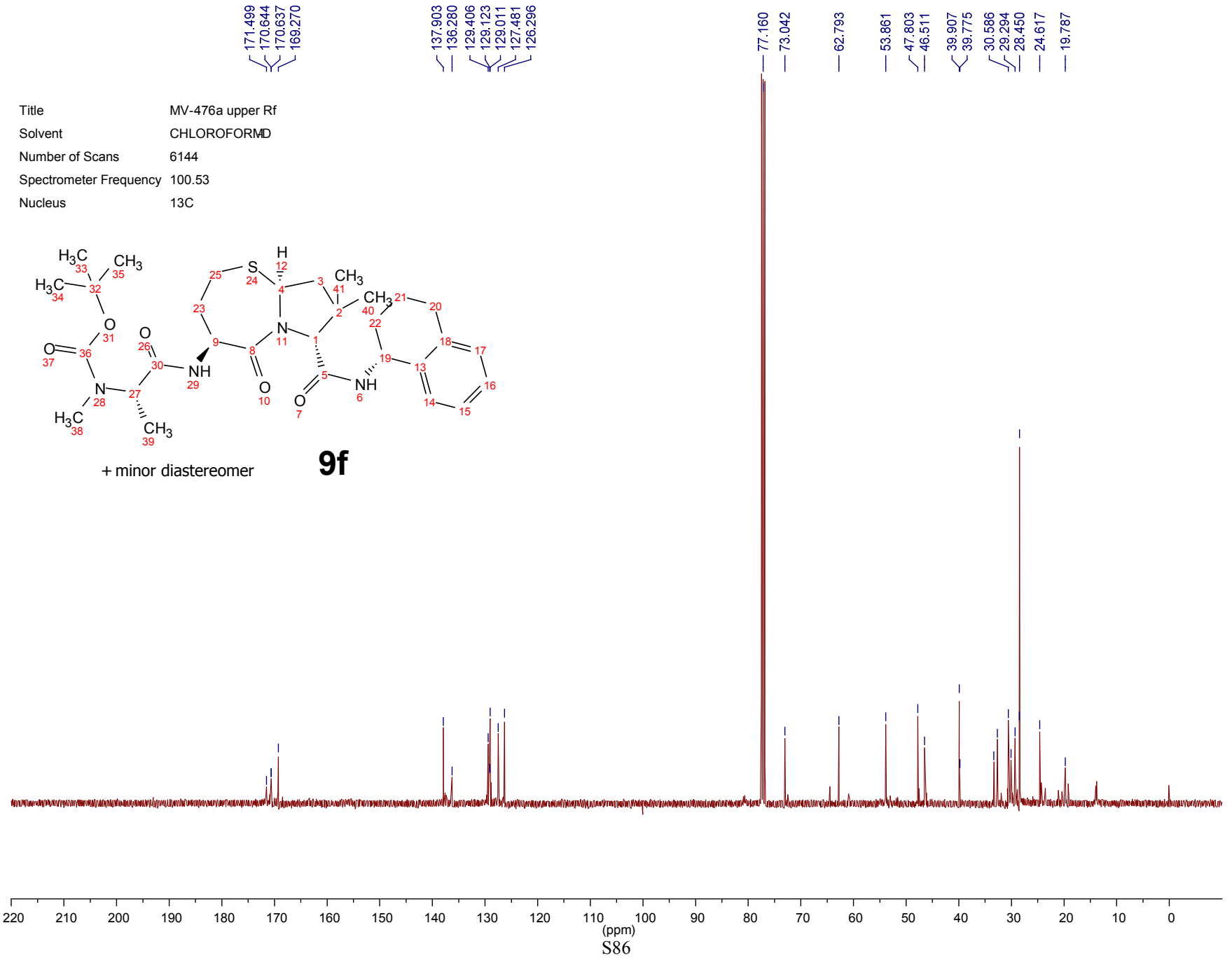

172.707
171.760
171.381
138.808
138.513
137.406
137.392
130.239
130.114
130.040
130.027
129.801
129.776
128.467
128.275
128.184
127.156
73.309
73.287
63.858
61.949
61.747
54.218
54.061
47.221
40.943
40.864
40.751
31.311
30.220
28.671
25.275
23.899
21.310
20.995
Title MV-476b mixed fractions
Solvent METHANOL-D3
Number of Scans 1200
Spectrometer Frequency 100.53
Nucleus 13C
8f+9f
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

Title	MV-476a upper Rf
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H

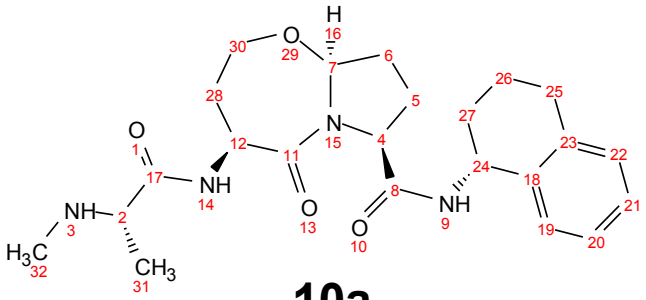


9f

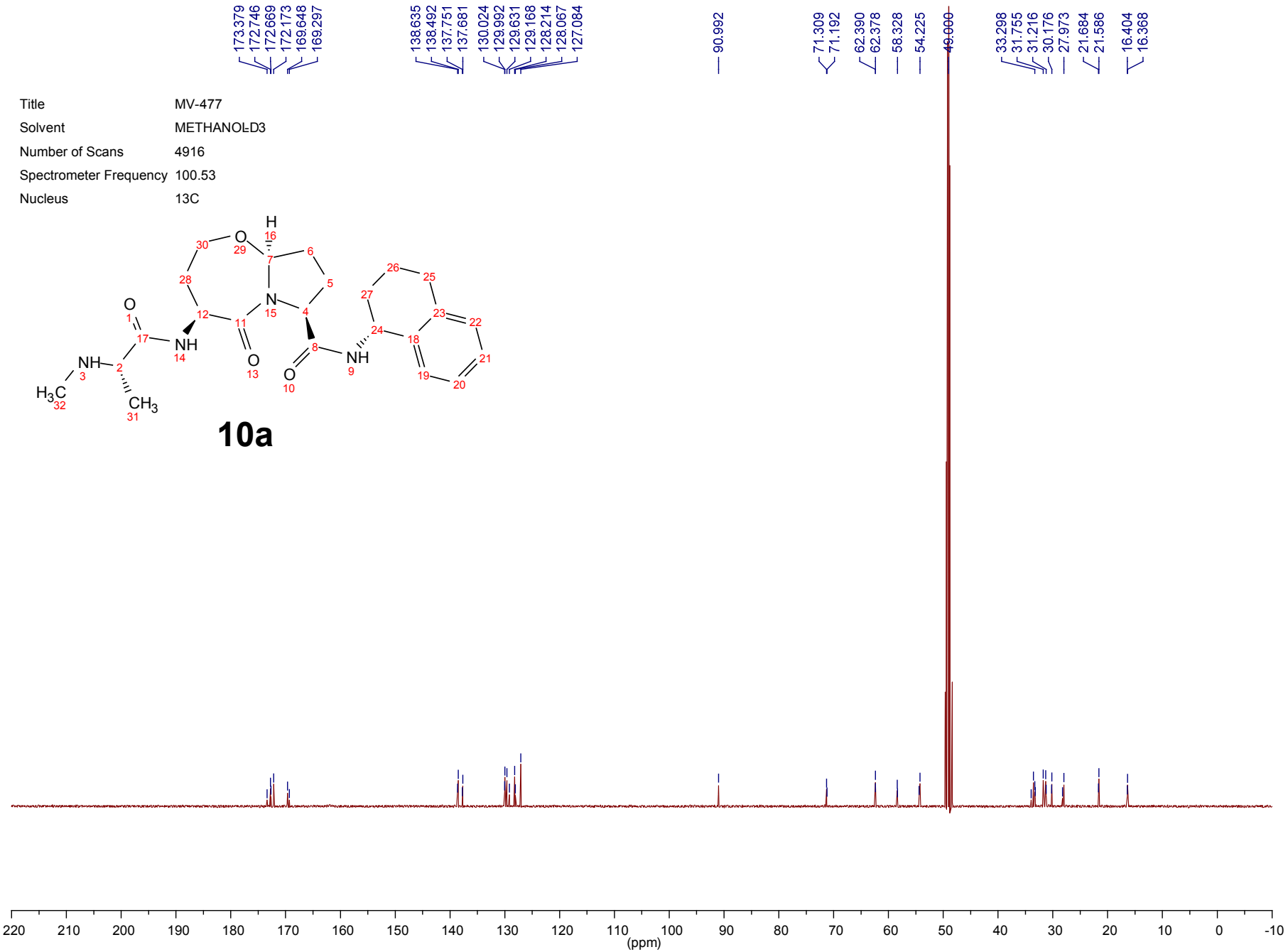
+ minor diastereomer

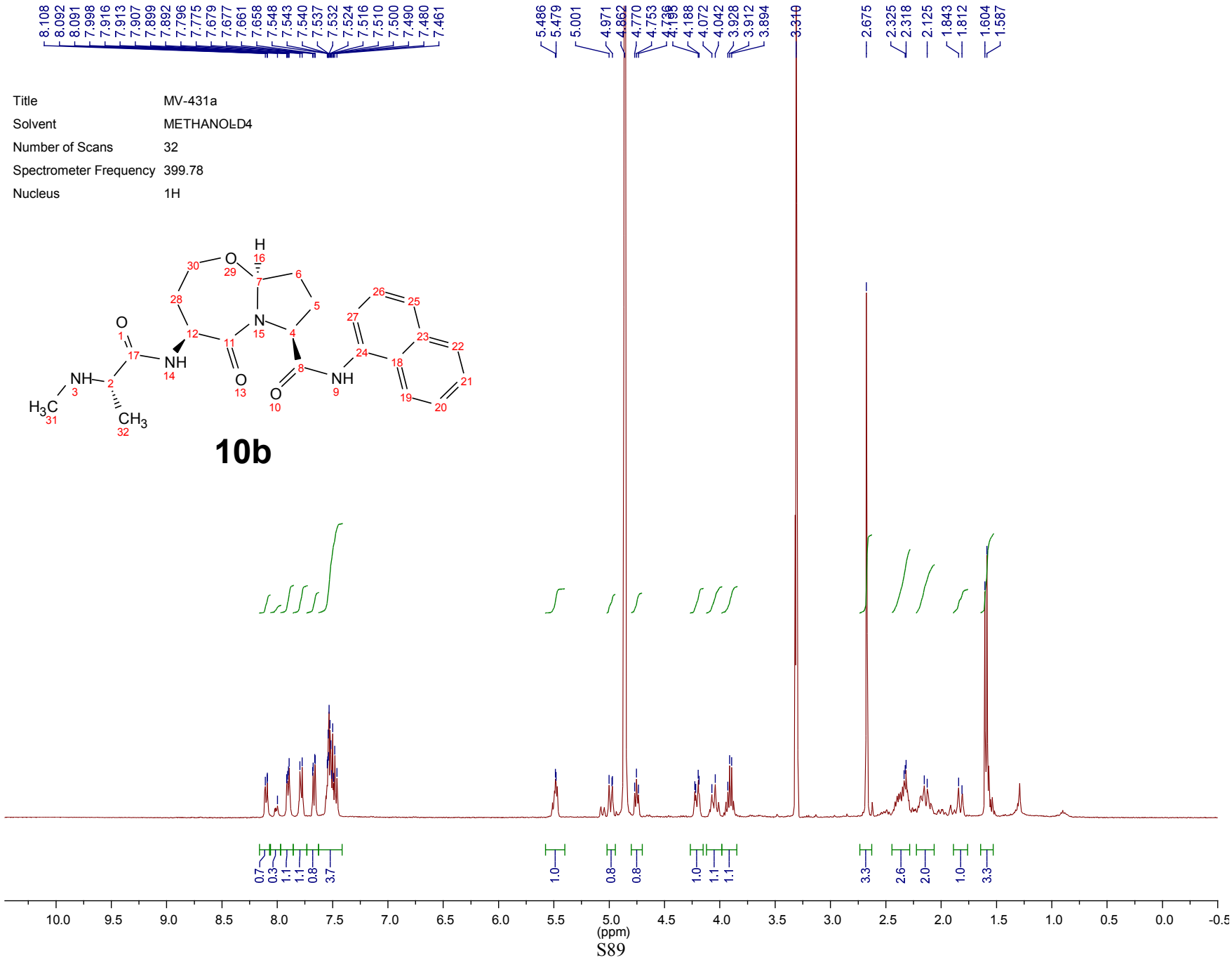

171.499
170.644
170.637
169.270
137.903
136.280
129.406
129.123
129.011
127.481
126.296
77.160
73.042
62.793
53.861
47.803
46.511
39.907
39.775
30.586
29.294
28.450
24.617
19.787
Title MV-476a upper Rf
Solvent CHLOROFORM-D
Number of Scans 6144
Spectrometer Frequency 100.53
Nucleus 13C
+ minor diastereomer
9f
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

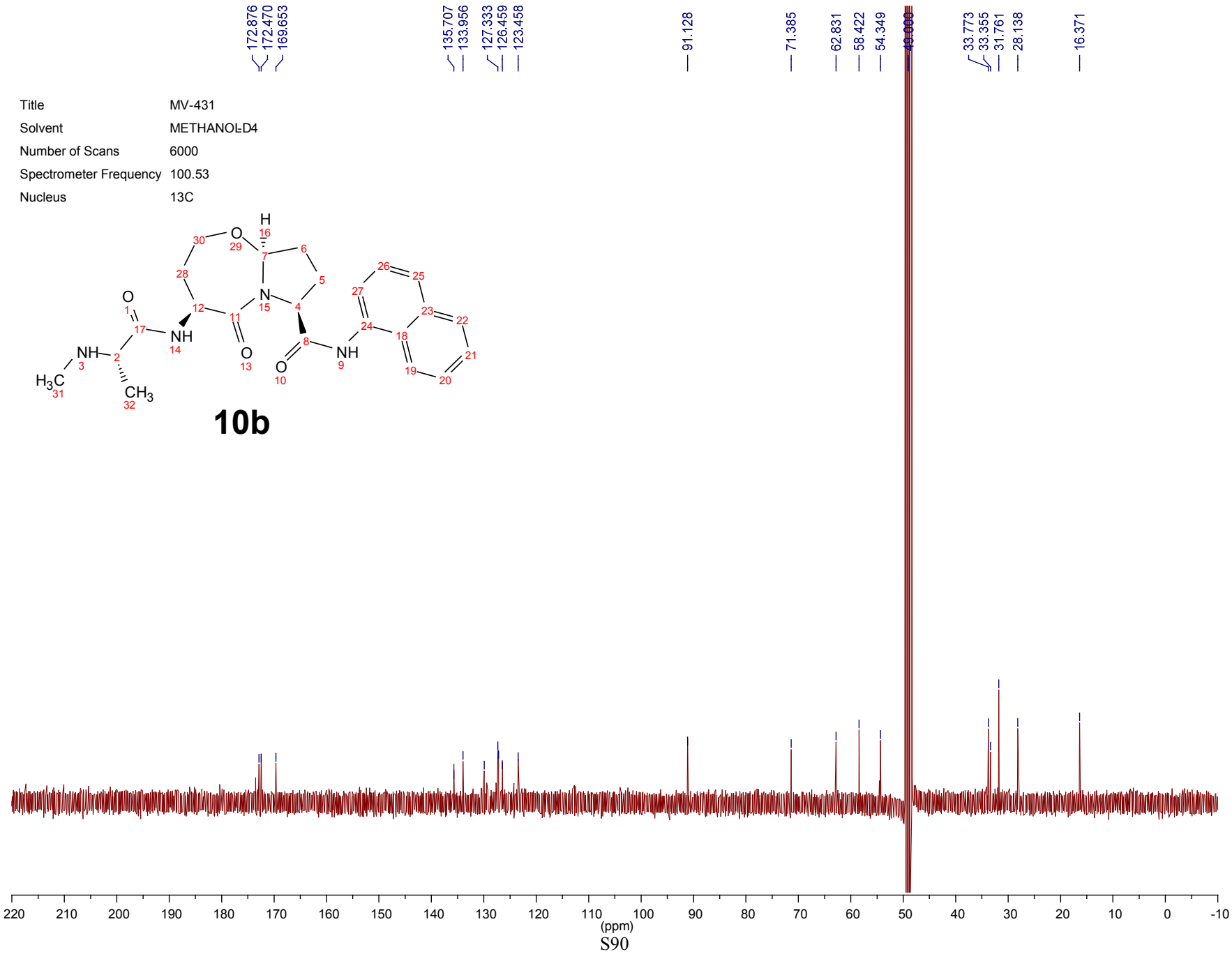
Title	MV-477
Solvent	METHANOL-D3
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



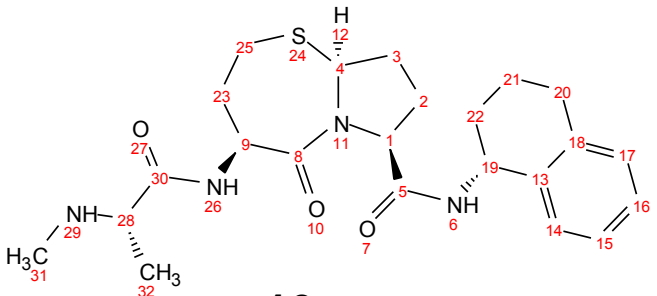
10a


173.379
172.746
172.669
172.173
169.648
169.297
138.635
138.492
137.751
137.681
130.024
129.992
129.631
129.168
128.214
128.067
127.084
90.992
71.309
71.192
62.390
62.378
58.328
54.225
49.000
33.298
31.755
31.216
30.176
27.973
21.684
21.586
16.404
16.368
Title MV-477
Solvent METHANOL-D3
Number of Scans 4916
Spectrometer Frequency 100.53
Nucleus 13C
10a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

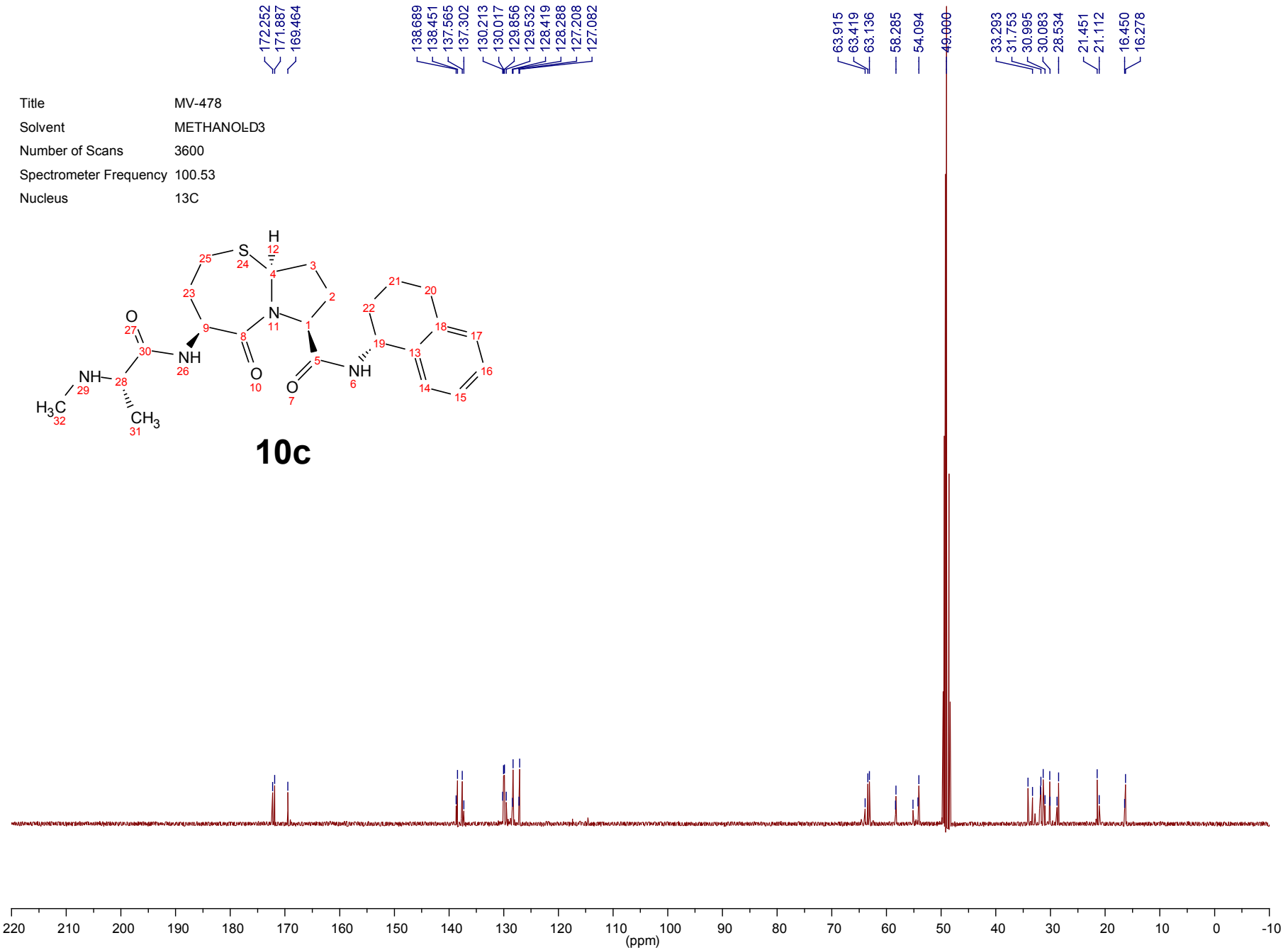

8.108
8.092
8.091
7.998
7.916
7.913
7.907
7.899
7.892
7.796
7.775
7.679
7.677
7.661
7.658
7.548
7.543
7.540
7.537
7.532
7.524
7.516
7.510
7.500
7.490
7.480
7.461
5.486
5.479
5.001
4.971
4.862
4.770
4.753
4.188
4.072
4.042
3.928
3.912
3.894
3.310
2.675
2.325
2.318
2.125
1.843
1.812
1.604
1.587
Title MV-431a
Solvent METHANOL-D4
Number of Scans 32
Spectrometer Frequency 399.78
Nucleus 1H
10b
0.7
0.3
1.1
1.1
0.8
3.7
1.0
0.8
0.8
1.0
1.1
1.1
3.3
2.6
2.0
1.0
3.3
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

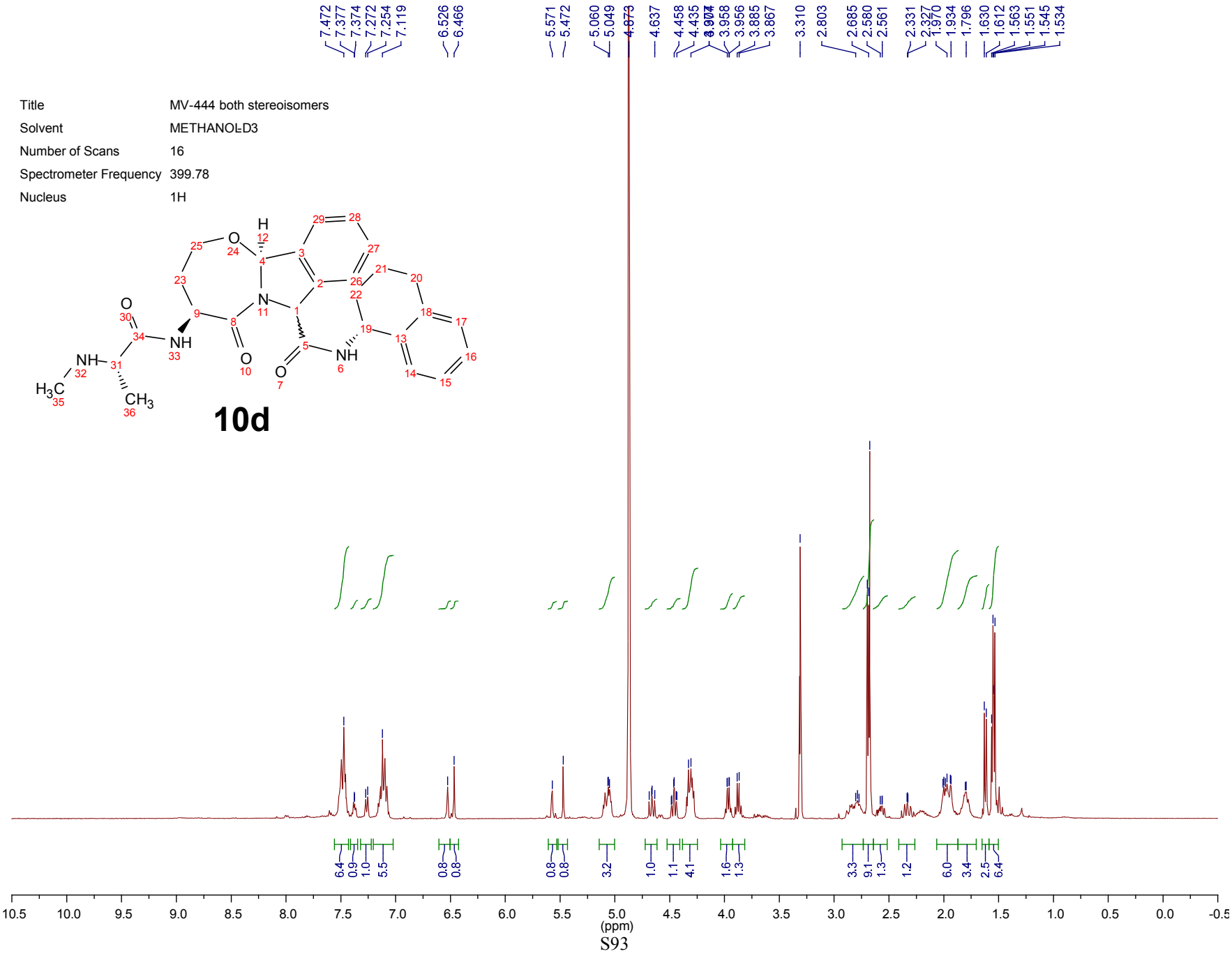

172.876
172.470
169.653
135.707
133.956
127.333
126.459
123.458
91.128
71.385
62.831
58.422
54.349
49.000
33.773
33.355
31.761
28.138
16.371
Title MV-431
Solvent METHANOL-D4
Number of Scans 6000
Spectrometer Frequency 100.53
Nucleus 13C
10b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

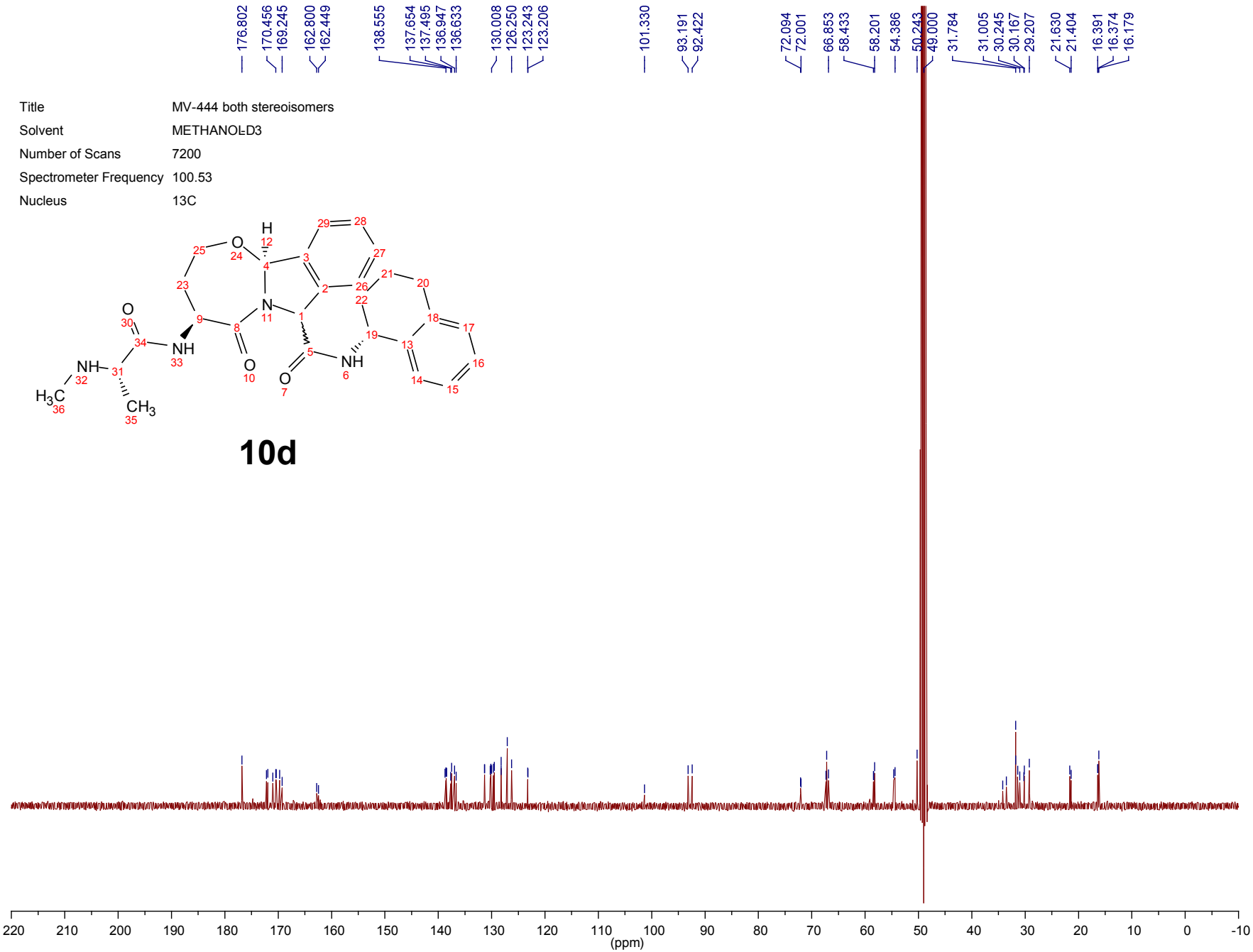
Title	MV-478
Solvent	METHANOL-D3
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H

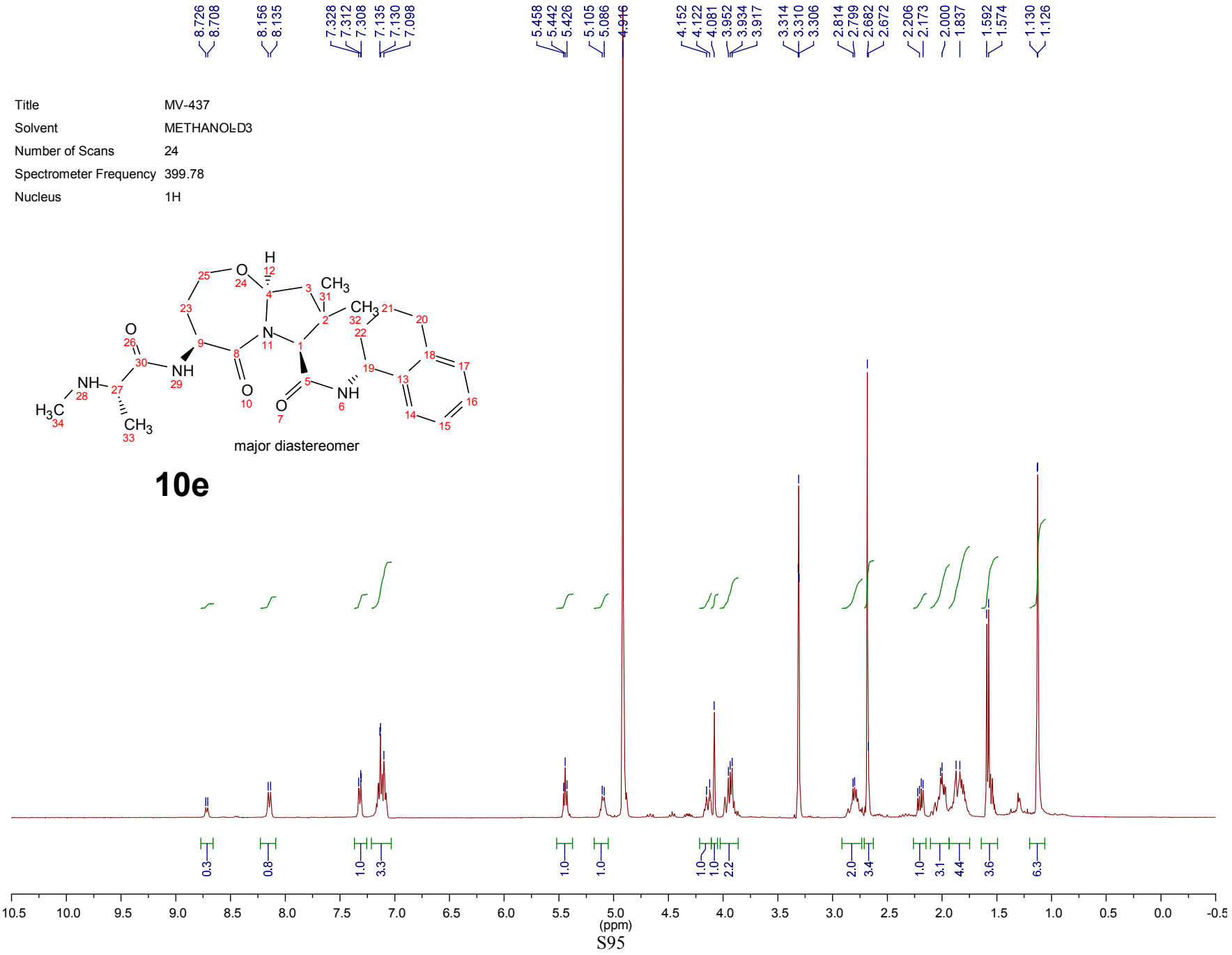


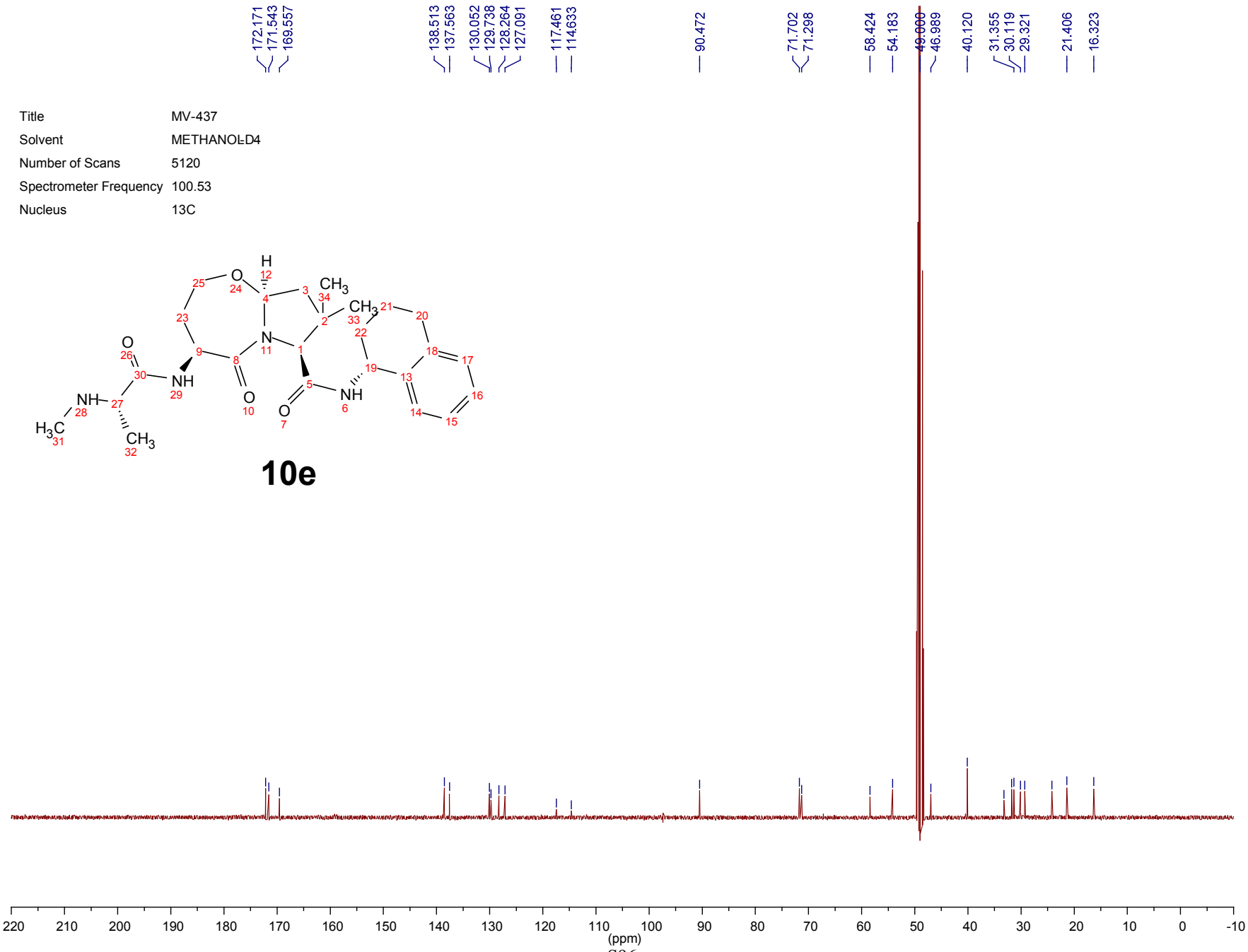
10c


172.252
171.887
169.464
138.689
138.451
137.565
137.302
130.213
130.017
129.856
129.532
128.419
128.288
127.208
127.082
63.915
63.419
63.136
58.285
54.094
49.000
33.293
31.753
30.995
30.083
28.534
21.451
21.112
16.450
16.278
Title MV-478
Solvent METHANOL-D3
Number of Scans 3600
Spectrometer Frequency 100.53
Nucleus 13C
10c
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

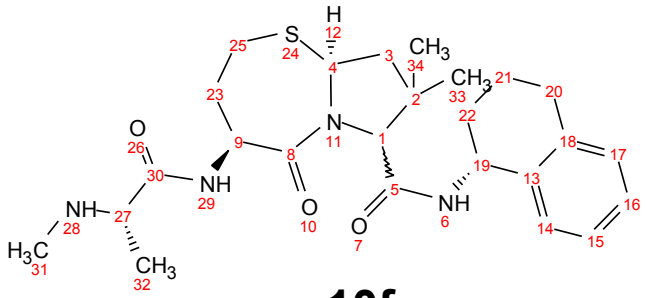

Title MV-444 both stereoisomers
Solvent METHANOL-D3
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
10d
7.472
7.377
7.374
7.272
7.254
7.119
6.526
6.466
5.571
5.472
5.060
5.049
4.873
4.637
4.458
4.435
3.958
3.956
3.885
3.867
3.310
2.803
2.685
2.580
2.561
2.331
2.327
1.970
1.934
1.796
1.630
1.612
1.563
1.551
1.545
1.534
6.4
0.9
1.0
5.5
0.8
0.8
0.8
0.8
3.2
1.0
1.1
4.1
1.6
1.3
3.3
9.1
1.3
1.2
6.0
3.4
2.5
6.4
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


176.802
170.456
169.245
162.800
162.449
138.555
137.654
137.495
136.947
136.633
130.008
126.250
123.243
123.206
101.330
93.191
92.422
72.094
72.001
66.853
58.433
58.201
54.386
50.243
49.000
31.784
31.005
30.245
30.167
29.207
21.630
21.404
16.391
16.374
16.179
Title MV-444 both stereoisomers
Solvent METHANOL-D3
Number of Scans 7200
Spectrometer Frequency 100.53
Nucleus 13C
10d
(ppm)

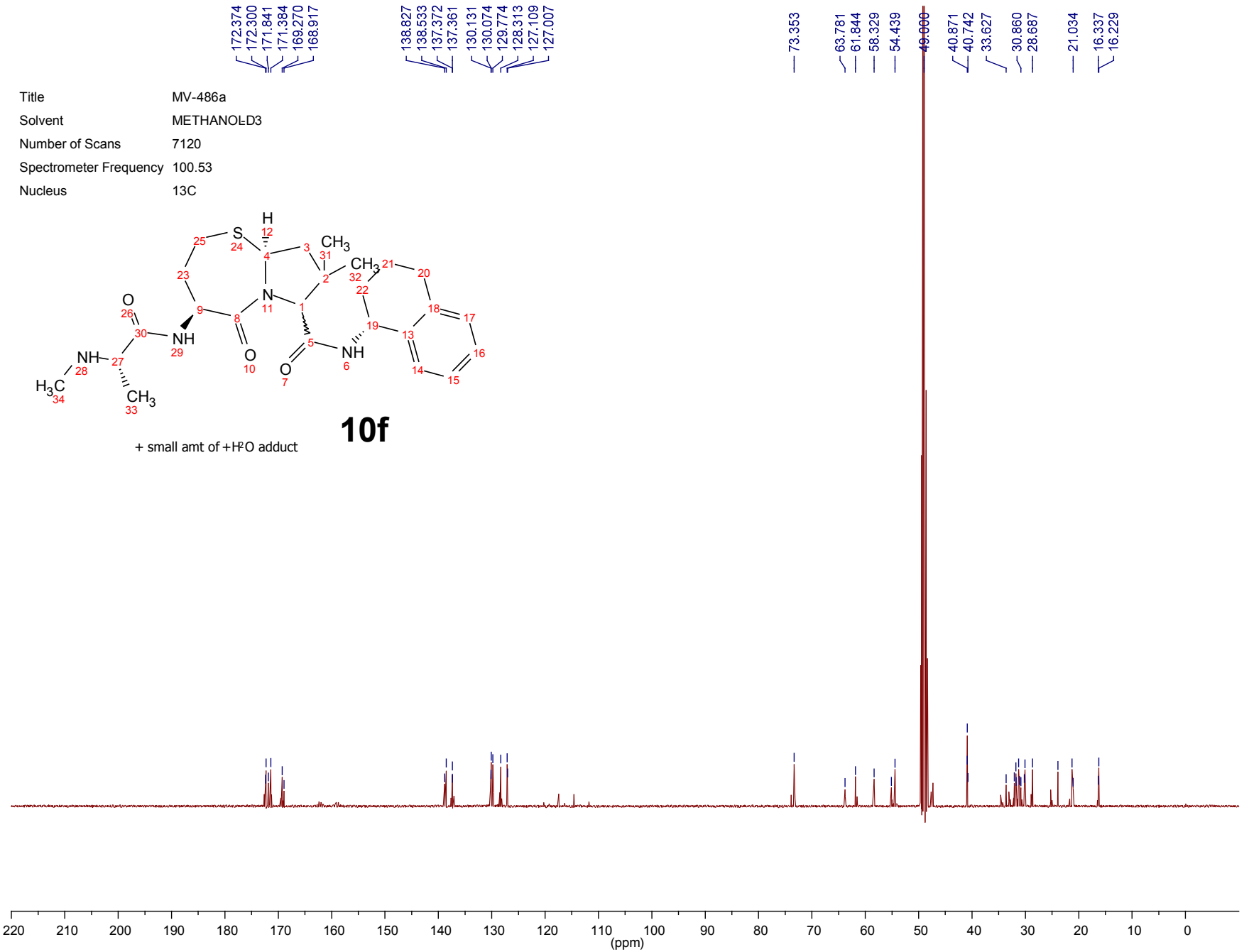

8.726
8.708
8.156
8.135
7.328
7.312
7.308
7.135
7.130
7.098
5.458
5.442
5.426
5.105
5.086
4.916
4.152
4.122
4.081
3.952
3.934
3.917
3.314
3.310
3.306
2.814
2.799
2.682
2.672
2.206
2.173
2.000
1.837
1.592
1.574
1.130
1.126
Title MV-437
Solvent METHANOL-D3
Number of Scans 24
Spectrometer Frequency 399.78
Nucleus 1H
major diastereomer
10e
0.3
0.8
1.0
3.3
1.0
1.0
1.0
1.0
2.2
2.0
3.4
1.0
3.1
4.4
3.6
6.3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

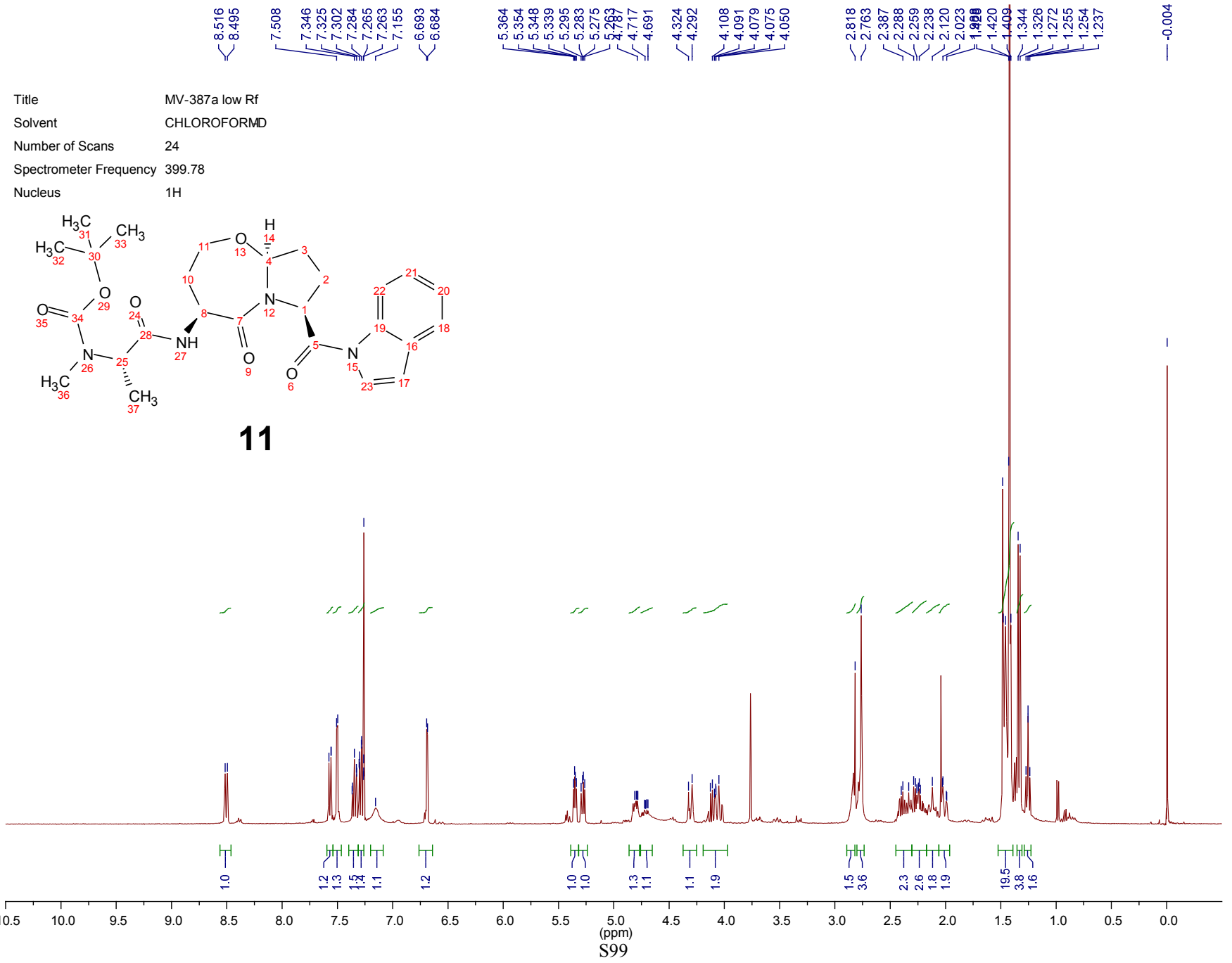

172.171
171.543
169.557
138.513
137.563
130.052
129.738
128.264
127.091
117.461
114.633
90.472
71.702
71.298
58.424
54.183
49.000
46.989
40.120
31.355
30.119
29.321
21.406
16.323
Title MV-437
Solvent METHANOL-D4
Number of Scans 5120
Spectrometer Frequency 100.53
Nucleus 13C
10e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

Title	MV-486a
Solvent	METHANOL-D3
Number of Scans	24
Spectrometer Frequency	399.78
Nucleus	1H



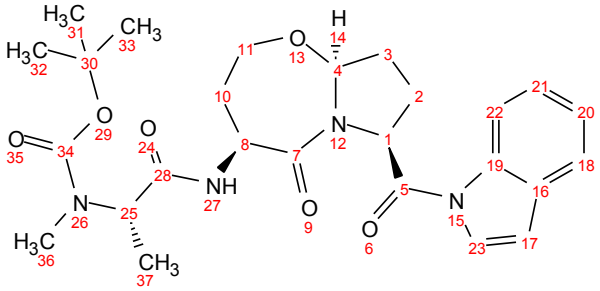
10f


172.374
172.300
171.841
171.384
169.270
168.917
138.827
138.533
137.372
137.361
130.131
130.074
129.774
128.313
127.109
127.007
73.353
63.781
61.844
58.329
54.439
49.000
40.871
40.742
33.627
30.860
28.687
21.034
16.337
16.229
Title MV-486a
Solvent METHANOL-D3
Number of Scans 7120
Spectrometer Frequency 100.53
Nucleus 13C
10f
+ small amt of +H2O adduct
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

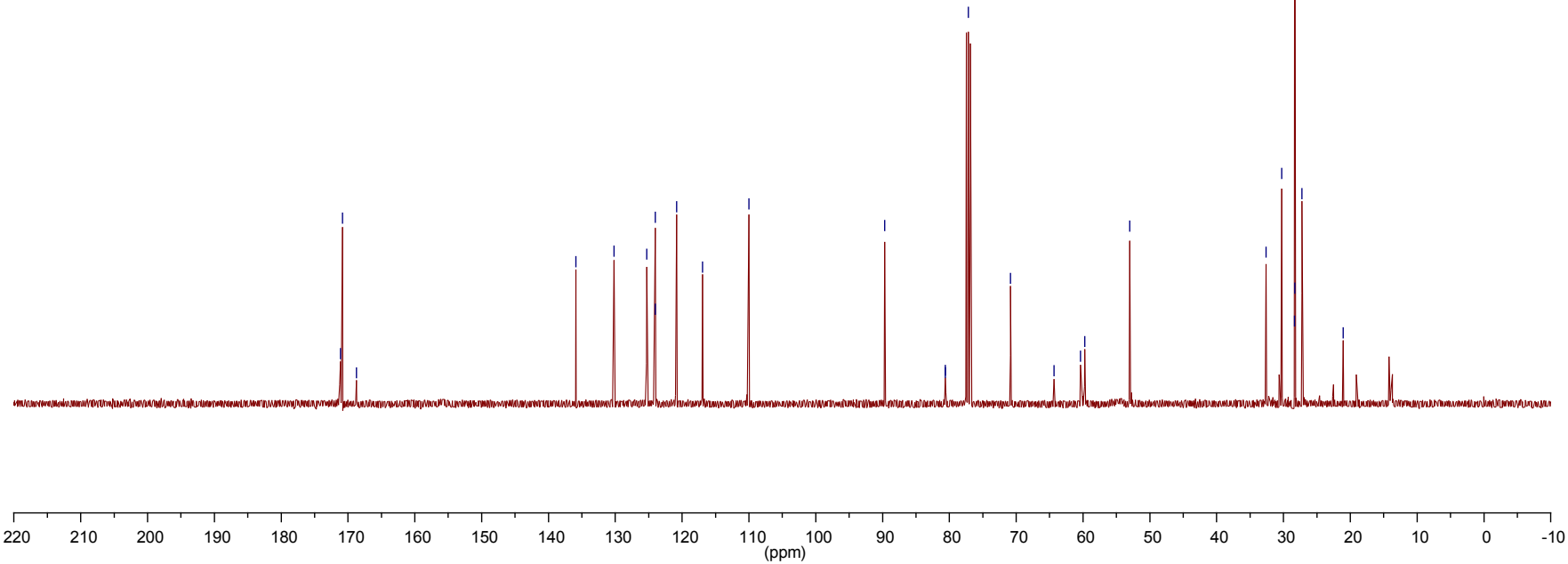

Title MV-387a low Rf
Solvent CHLOROFORM-D
Number of Scans 24
Spectrometer Frequency 399.78
Nucleus 1H
11
(ppm)

171.133
170.817
168.754
135.897
130.196
124.001
120.837
116.952
109.990
89.665
80.600
80.590
77.160
70.841
64.338
60.376
59.742
53.000
32.614
30.284
28.346
28.325
28.314
27.230
21.047

Title	MV-419a low Rf
Solvent	CHLOROFORM-D
Number of Scans	868
Spectrometer Frequency	100.53
Nucleus	13C



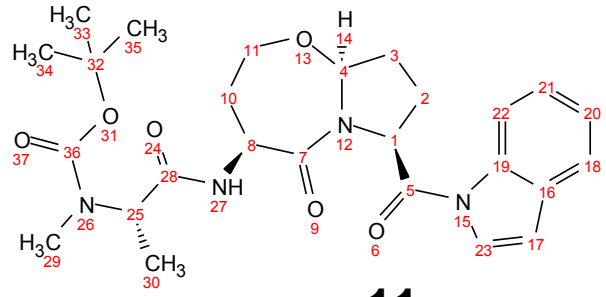
11



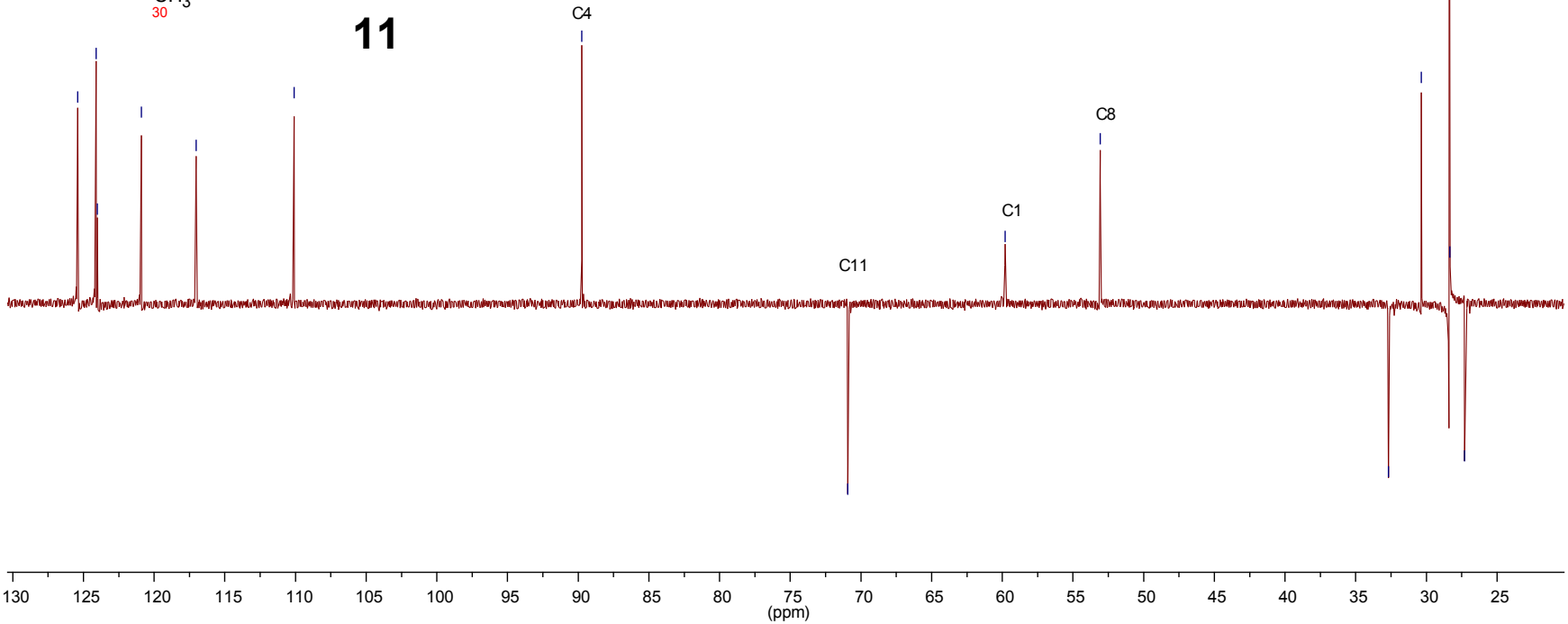
125.399
124.111
124.010
120.900
117.035
110.097
89.739
70.930
59.800
53.076
32.688
30.353
28.387
28.340
27.306

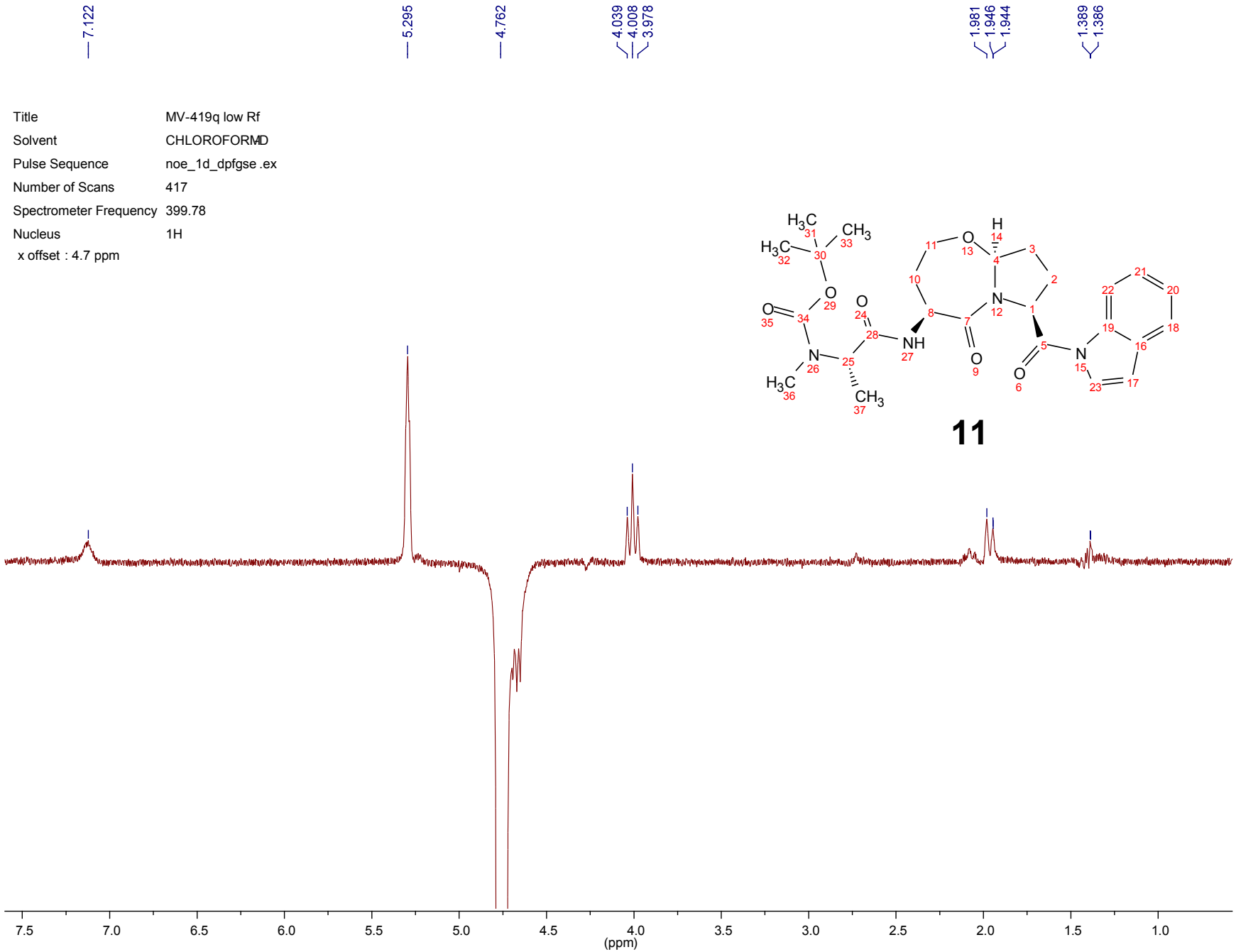
Title	MV-419k low Rf
Solvent	CHLOROFORM-D
Pulse Sequence	dept.ex2
Number of Scans	453
Spectrometer Frequency	100.53
Nucleus	13C

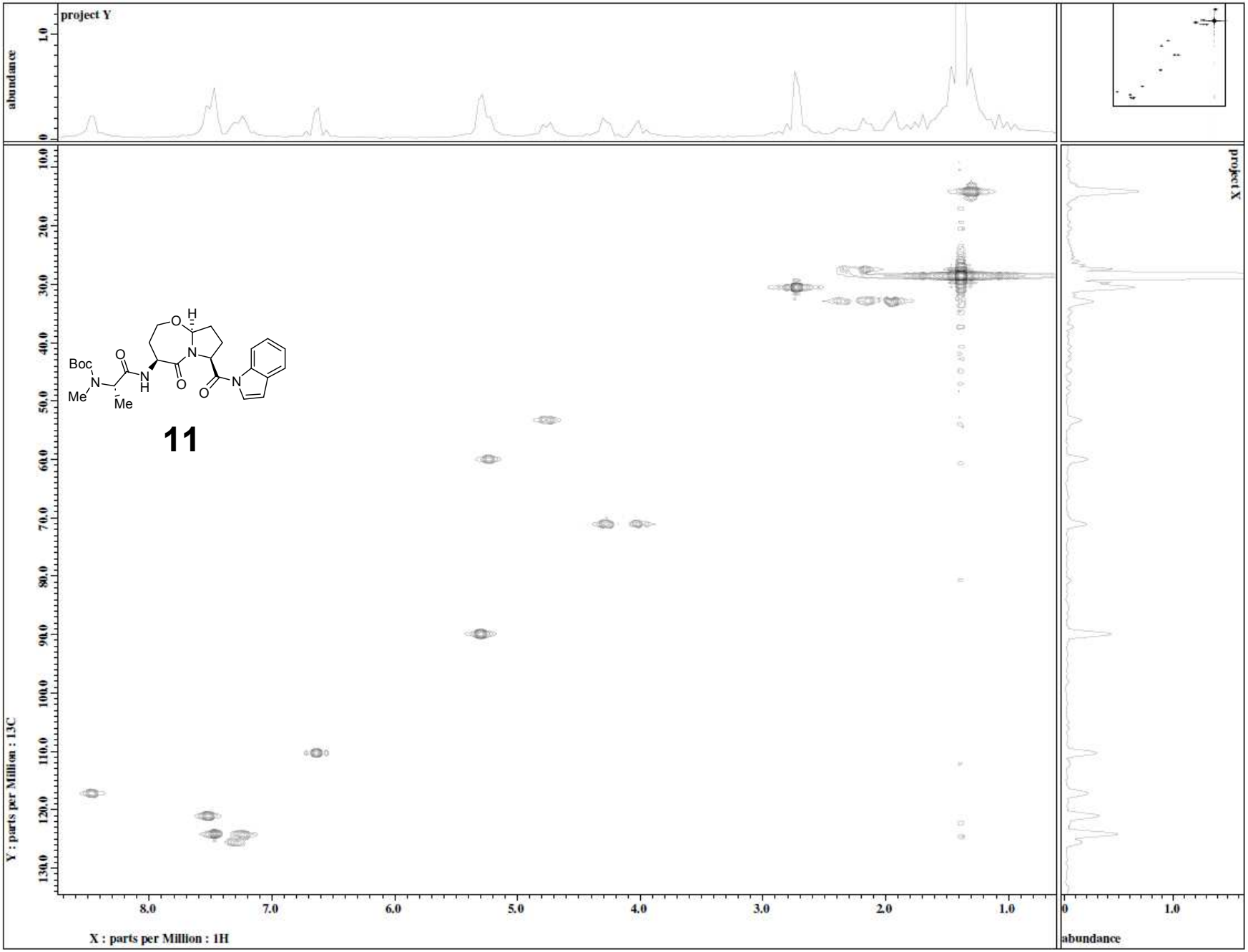
DEPT-135

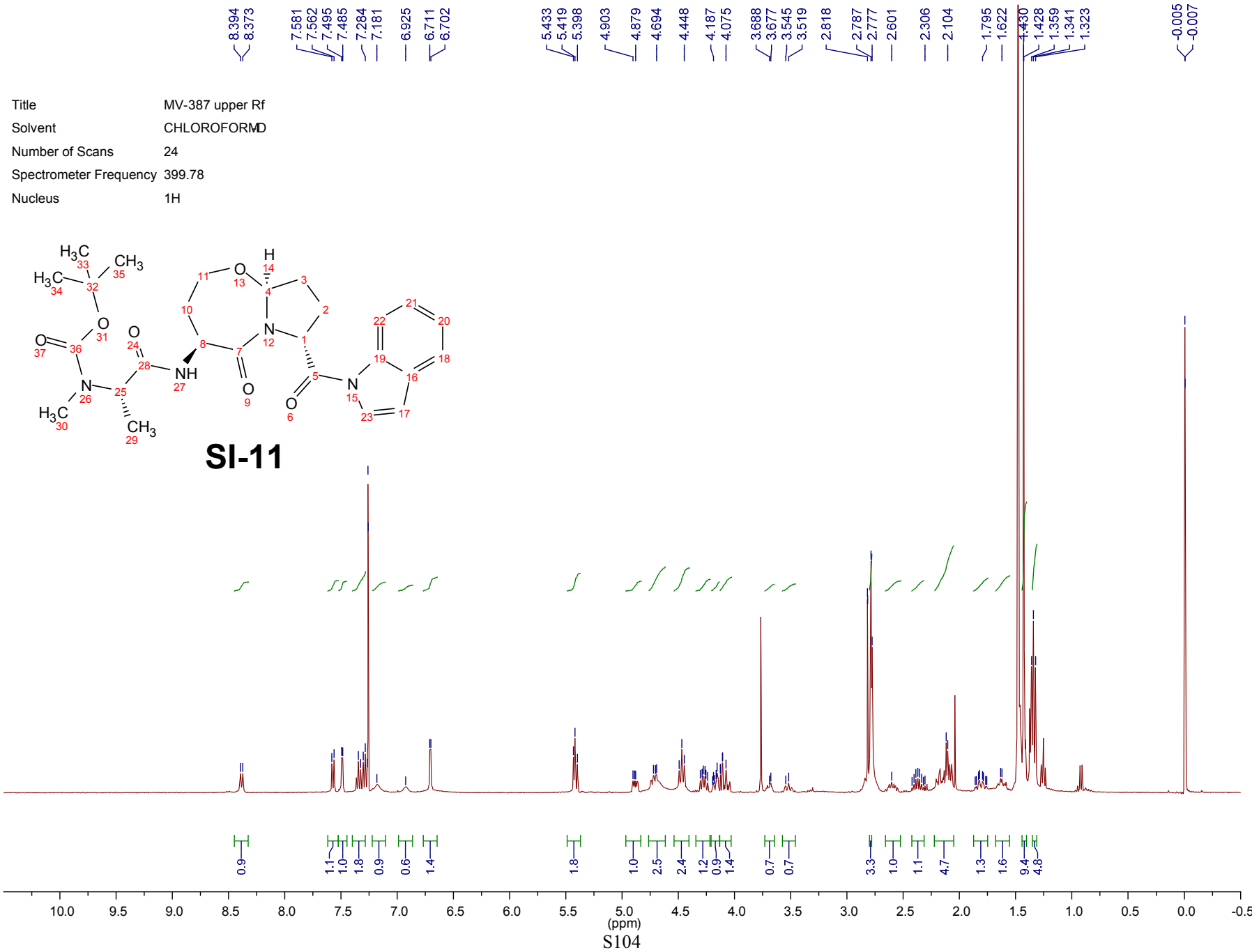


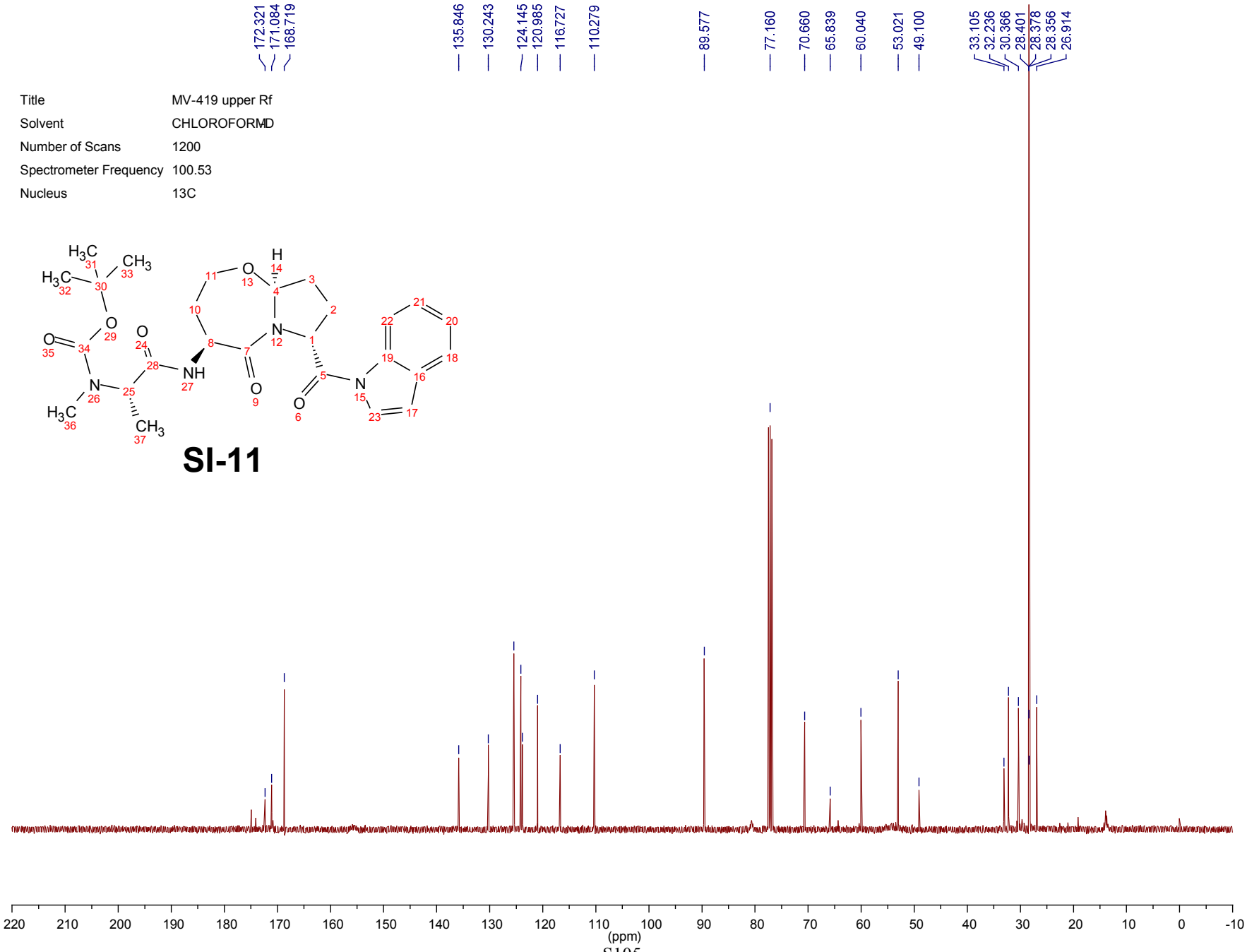
11



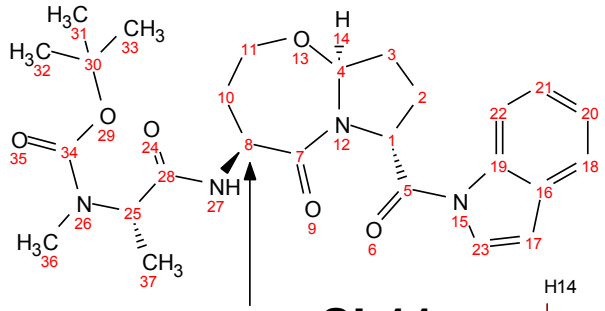

7.122
5.295
4.762
4.039
4.008
3.978
1.981
1.946
1.944
1.389
1.386
Title MV-419q low Rf
Solvent CHLOROFORM-D
Pulse Sequence noe_1d_dpfgse .ex
Number of Scans 417
Spectrometer Frequency 399.78
Nucleus 1H
x offset : 4.7 ppm
11
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)


project Y
abundance
project X
Y : parts per Million : 13C
X : parts per Million : 1H
abundance
Boc
Me
Me
11

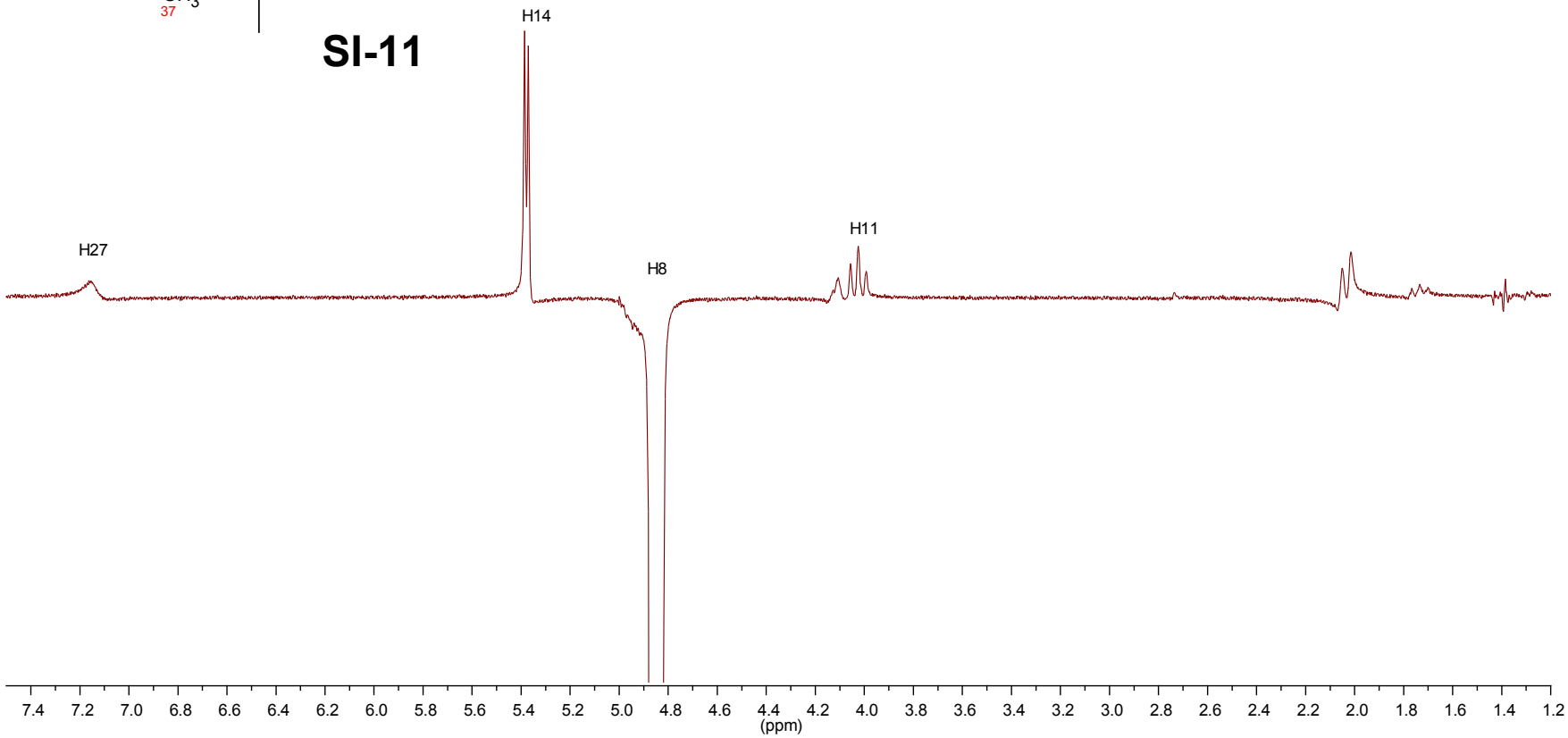

8.394
8.373
7.581
7.562
7.495
7.485
7.284
7.181
6.925
6.711
6.702
5.433
5.419
5.398
4.903
4.879
4.694
4.448
4.187
4.075
3.688
3.677
3.545
3.519
2.818
2.787
2.777
2.601
2.306
2.104
1.795
1.622
1.430
1.428
1.359
1.341
1.323
-0.005
-0.007
Title MV-387 upper Rf
Solvent CHLOROFORM-D
Number of Scans 24
Spectrometer Frequency 399.78
Nucleus 1H
SI-11
0.9
1.1
1.0
1.8
0.9
0.6
1.4
1.8
1.0
2.5
2.4
1.2
0.9
1.4
0.7
0.7
3.3
1.0
1.1
4.7
1.3
1.6
9.4
4.8
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


172.321
171.084
168.719
135.846
130.243
124.145
120.985
116.727
110.279
89.577
77.160
70.660
65.839
60.040
53.021
49.100
33.105
32.236
30.366
28.401
28.378
28.356
26.914
Title MV-419 upper Rf
Solvent CHLOROFORM-D
Number of Scans 1200
Spectrometer Frequency 100.53
Nucleus 13C
SI-11
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

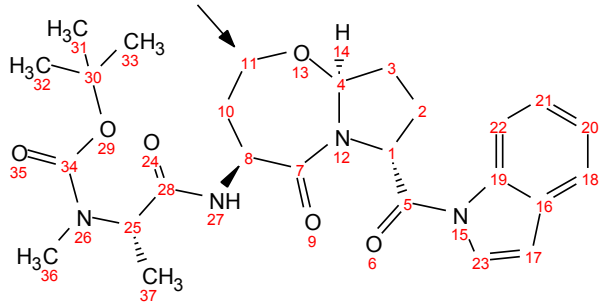
Title	MV-419 upper Rf
Solvent	CHLOROFORM-D
Pulse Sequence	noe_1d_dpfgse .ex
Number of Scans	480
Spectrometer Frequency	399.78
Nucleus	1H



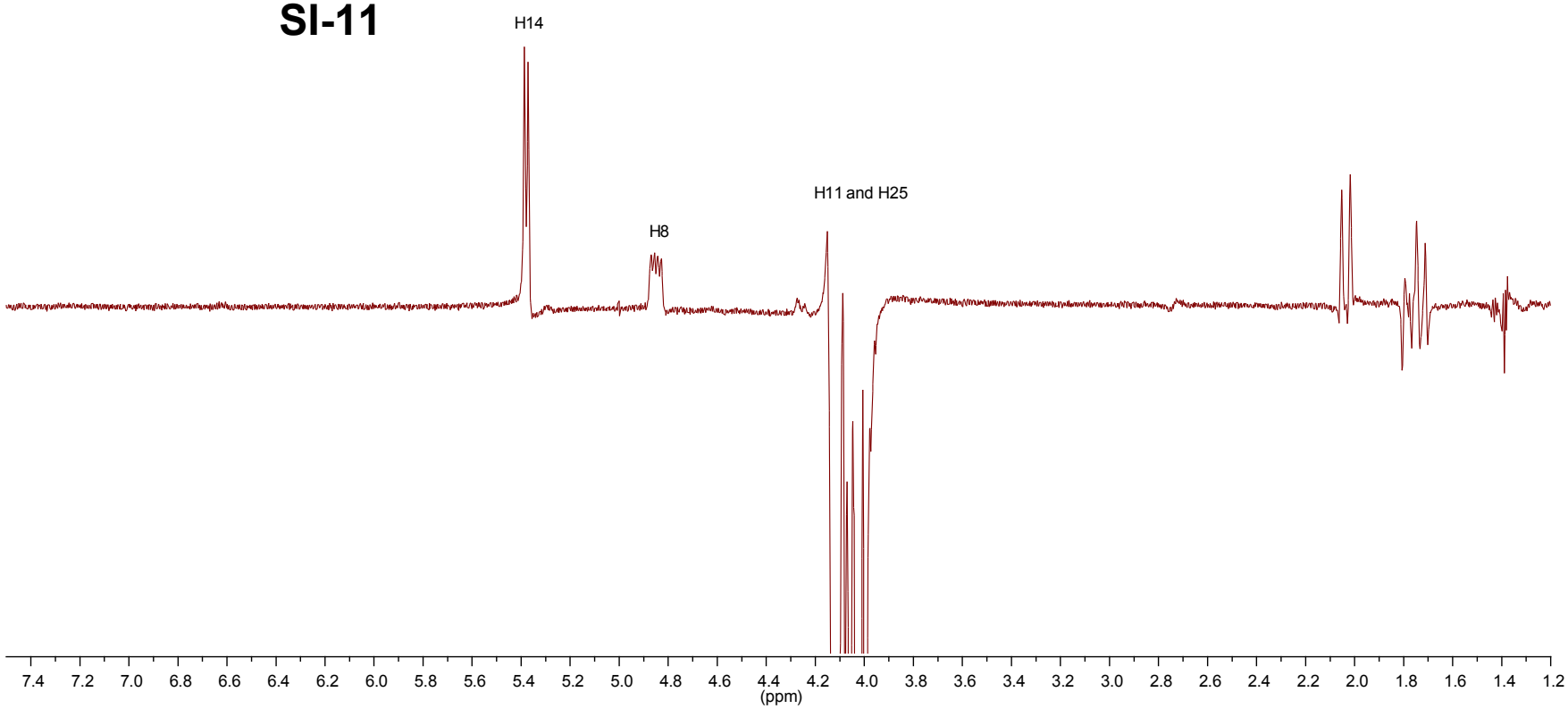
SI-11

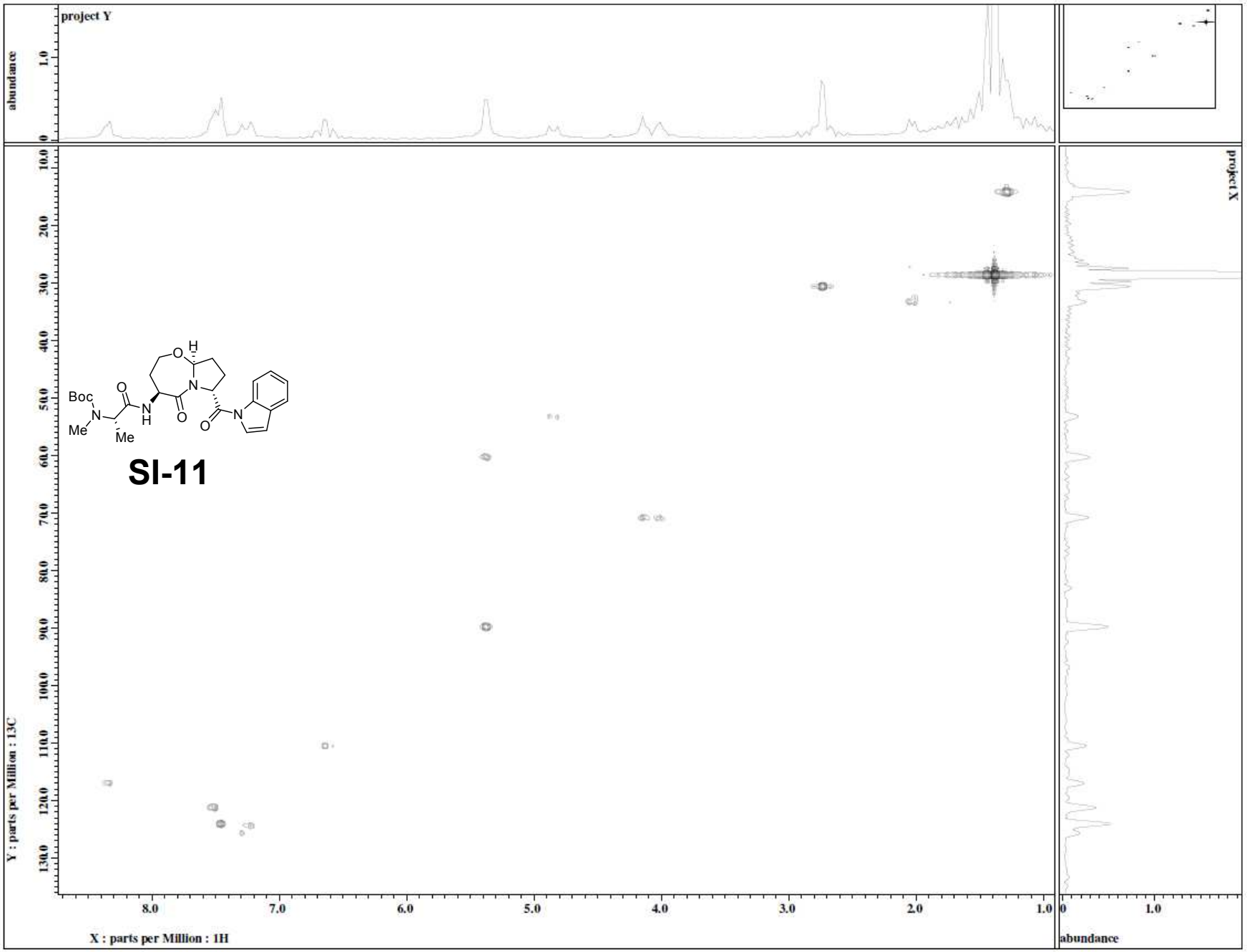


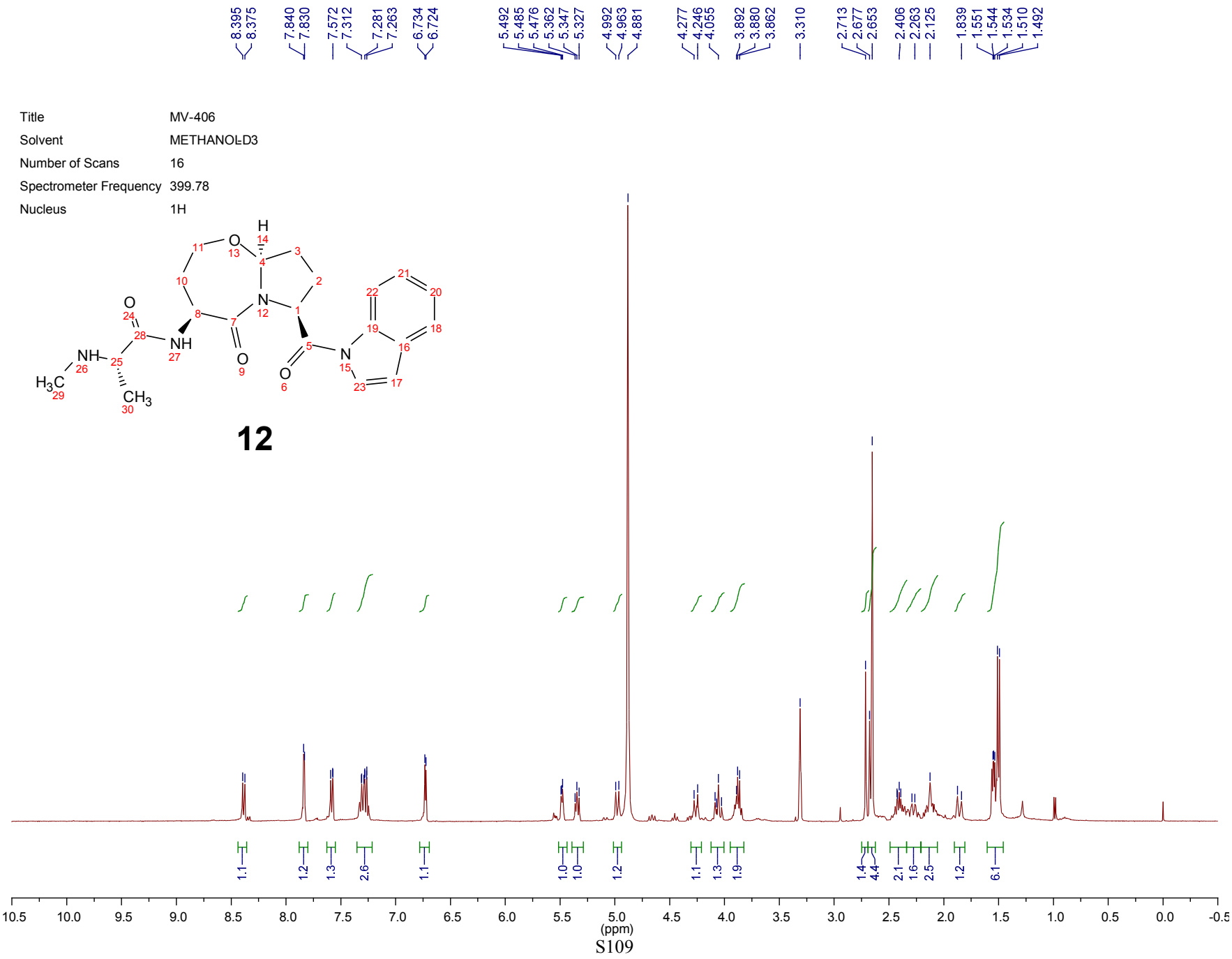
Title	MV-419c upper Rf
Solvent	CHLOROFORM-D
Pulse Sequence	noe_1d_dpfgse .ex
Number of Scans	700
Spectrometer Frequency	399.78
Nucleus	1H

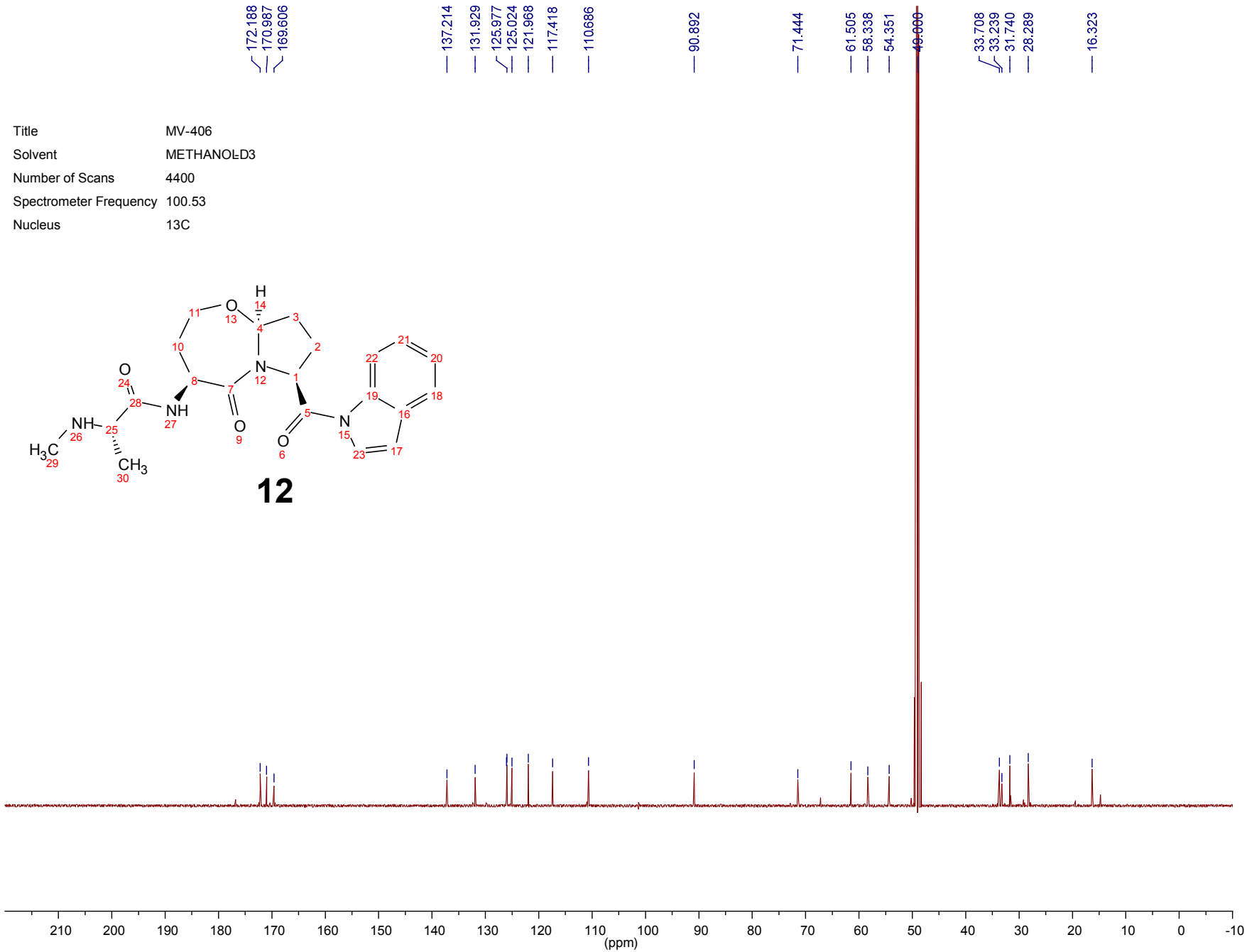


SI-11

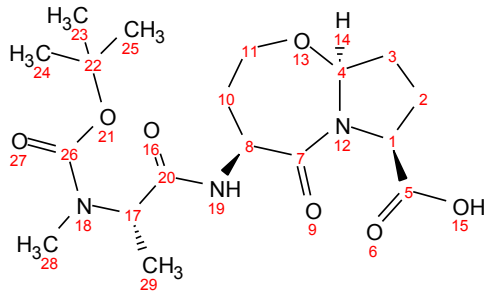



project Y
abundance
project X
Y : parts per Million : 13C
X : parts per Million : 1H
abundance
Boc
Me
Me
SI-11

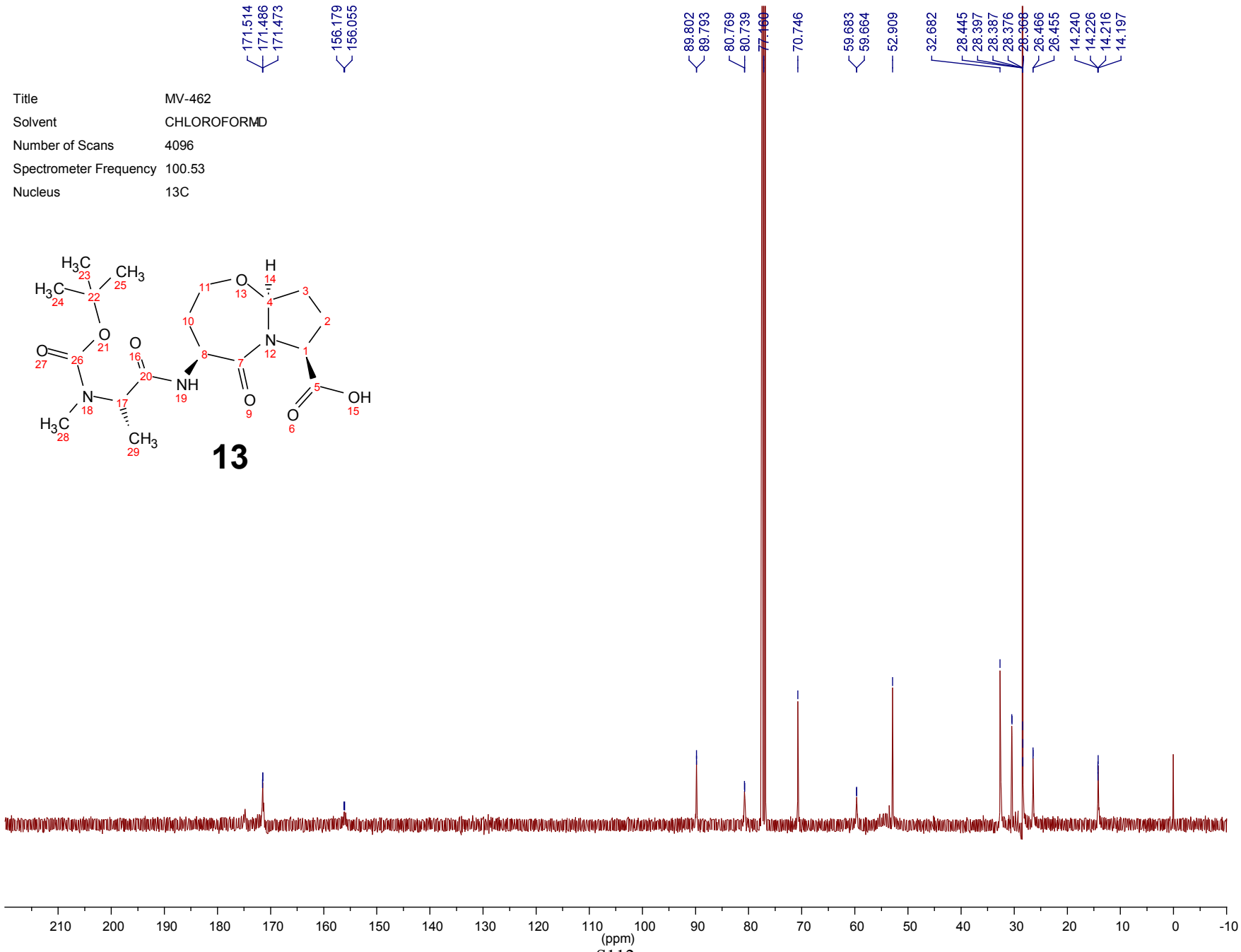

8.395
8.375
7.840
7.830
7.572
7.312
7.281
7.263
6.734
6.724
5.492
5.485
5.476
5.362
5.347
5.327
4.992
4.963
4.881
4.277
4.246
4.055
3.892
3.880
3.862
3.310
2.713
2.677
2.653
2.406
2.263
2.125
1.839
1.551
1.544
1.534
1.510
1.492
Title MV-406
Solvent METHANOL-D3
Number of Scans 16
Spectrometer Frequency 399.78
Nucleus 1H
12
1.1
1.2
1.3
2.6
1.1
1.0
1.0
1.2
1.1
1.3
1.9
1.4
4.4
2.1
1.6
2.5
1.2
6.1
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


172.188
170.987
169.606
137.214
131.929
125.977
125.024
121.968
117.418
110.686
90.892
71.444
61.505
58.338
54.351
40.000
33.708
33.239
31.740
28.289
16.323
Title MV-406
Solvent METHANOL-D3
Number of Scans 4400
Spectrometer Frequency 100.53
Nucleus 13C
12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

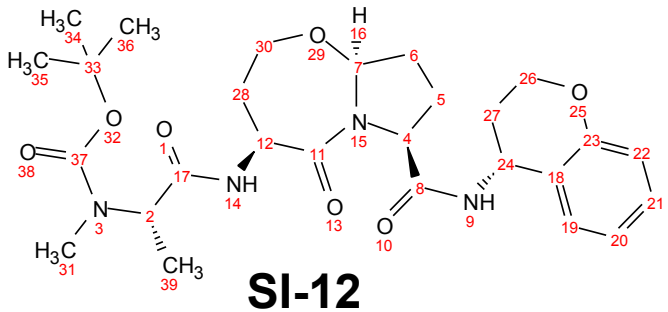
Title	MV-462a
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



13


171.514
171.486
171.473
156.179
156.055
89.802
89.793
80.769
80.739
77.160
70.746
59.683
59.664
52.909
32.682
28.445
28.397
28.387
28.376
28.366
26.466
26.455
14.240
14.226
14.216
14.197
Title MV-462
Solvent CHLOROFORM-D
Number of Scans 4096
Spectrometer Frequency 100.53
Nucleus 13C
13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

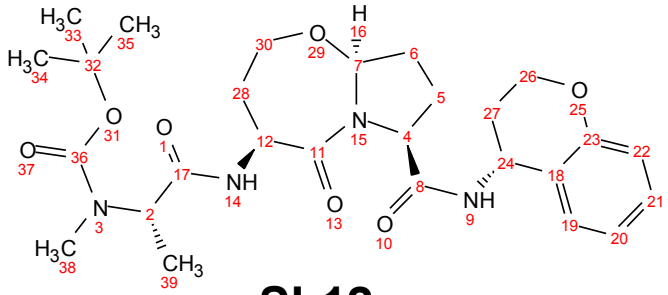
Title	MV-470
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



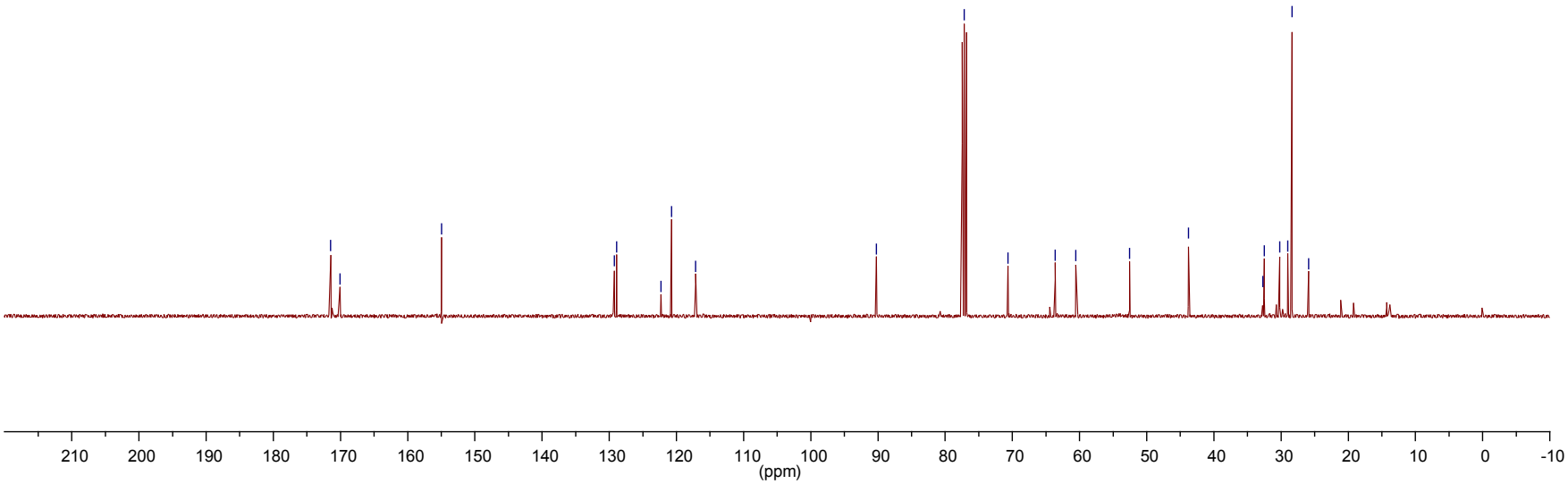
SI-12

171.455
170.082
154.968
129.251
128.905
122.315
120.724
117.154
90.223
77.160
70.649
63.640
60.540
52.555
43.801
32.722
32.514
30.210
29.010
28.392
25.911

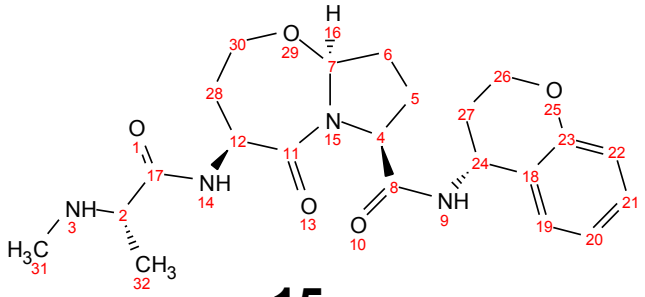
Title	MV-470
Solvent	CHLOROFORM-D
Number of Scans	2800
Spectrometer Frequency	100.53
Nucleus	13C



SI-12



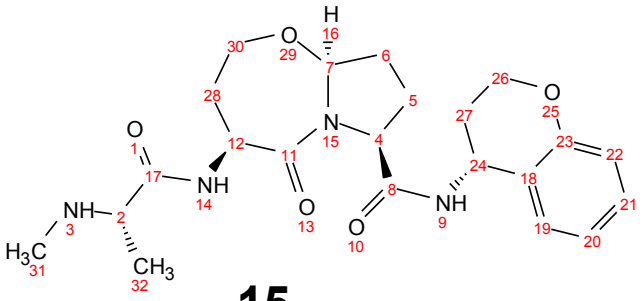
Title	MV-479
Solvent	METHANOL-D3
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



15

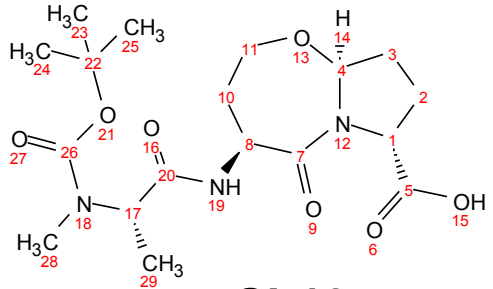
172.891
172.159
169.647
156.388
130.495
129.986
123.549
121.579
117.808
90.953
71.298
64.632
62.311
58.364
54.229
49.000
44.910
33.568
33.263
31.752
30.179
28.000
16.370

Title	MV-479
Solvent	METHANOL-D3
Number of Scans	3568
Spectrometer Frequency	100.53
Nucleus	13C

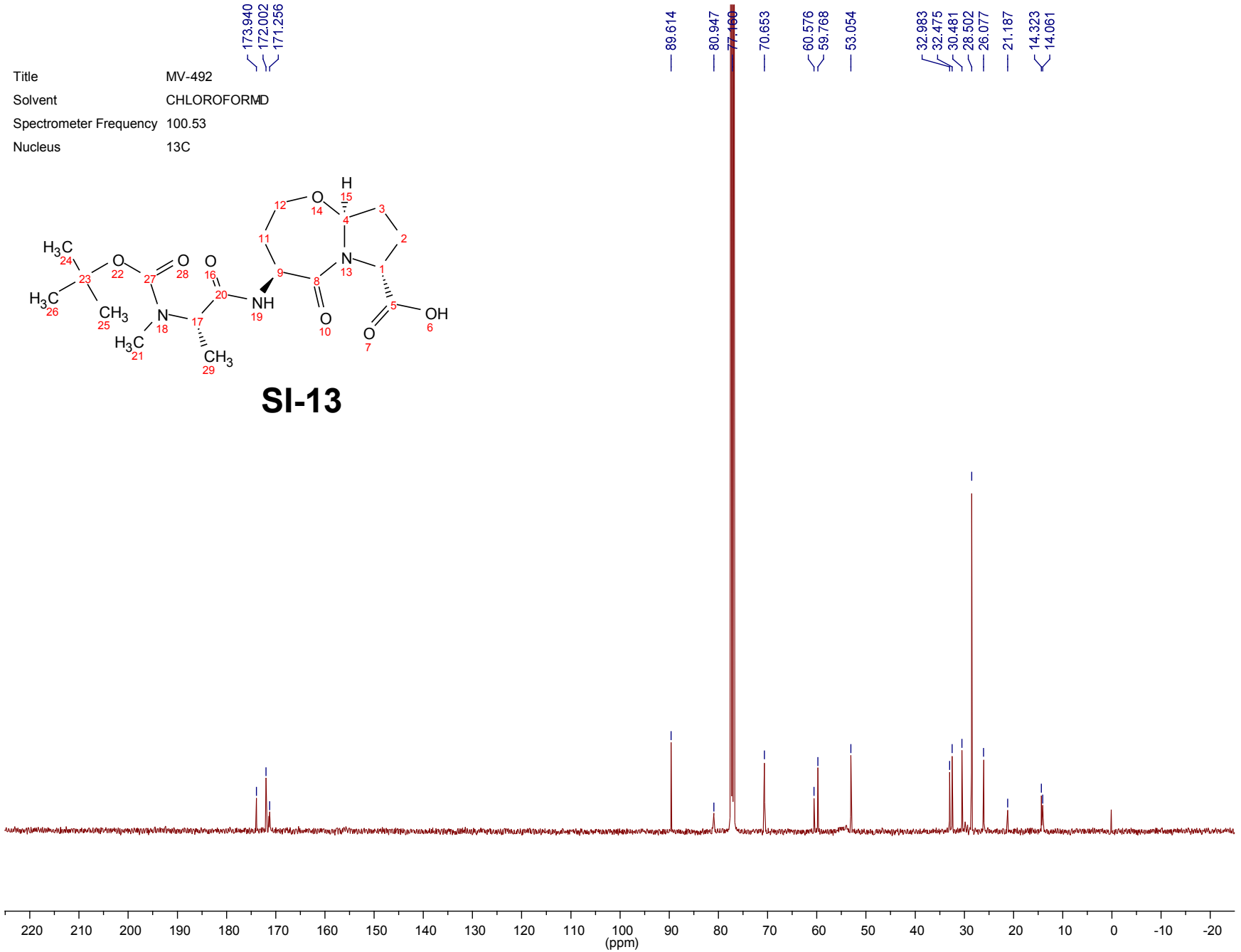


15

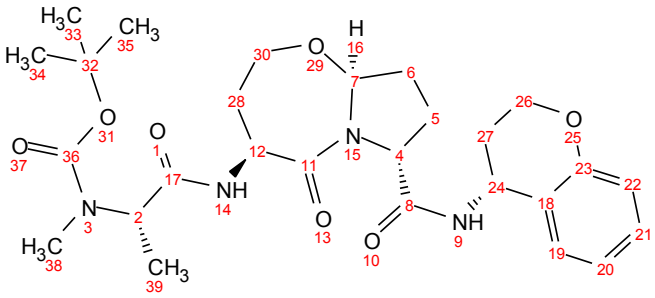
Title	MV-492
Solvent	CHLOROFORM-D
Number of Scans	32
Spectrometer Frequency	399.78
Nucleus	1H



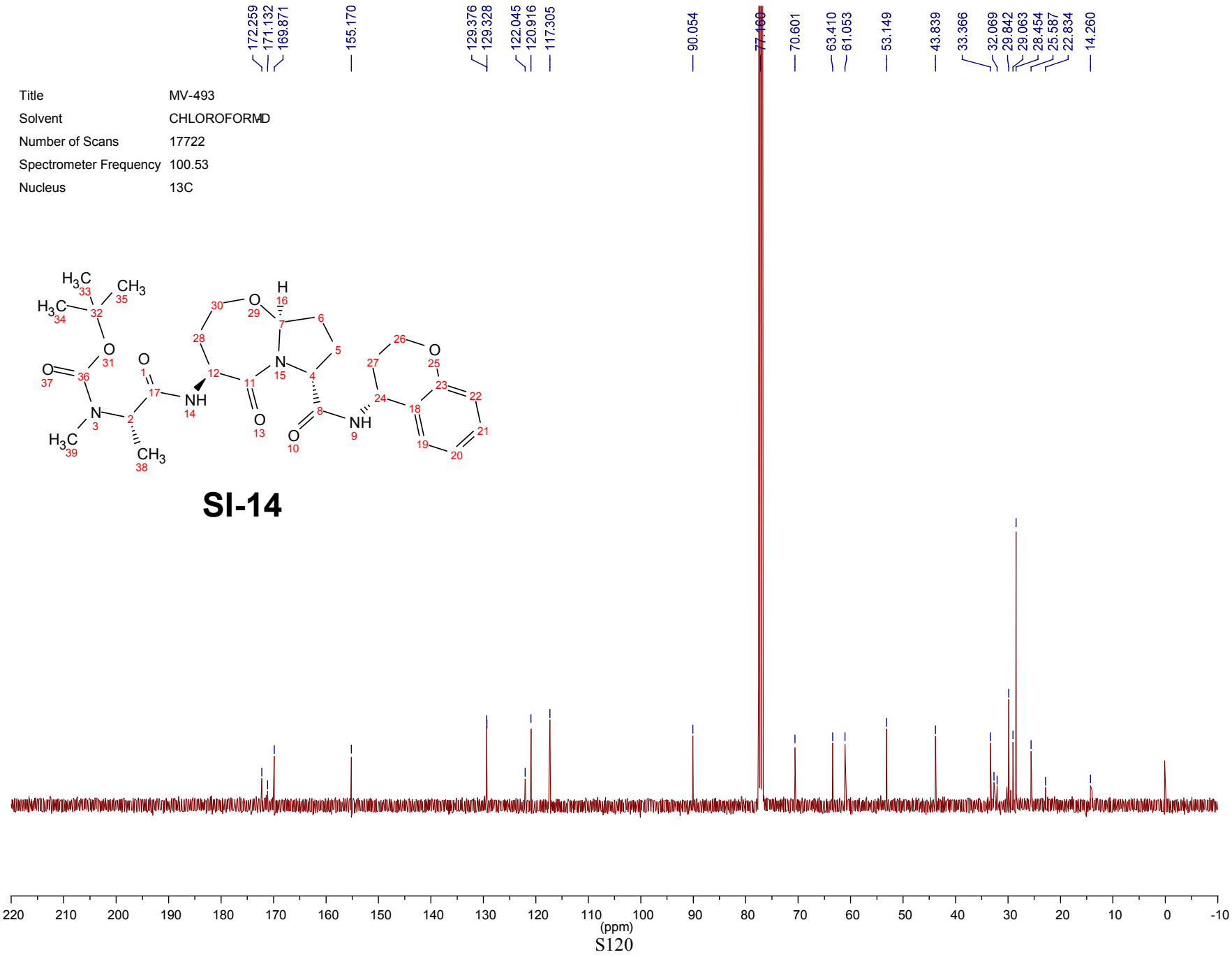
SI-13

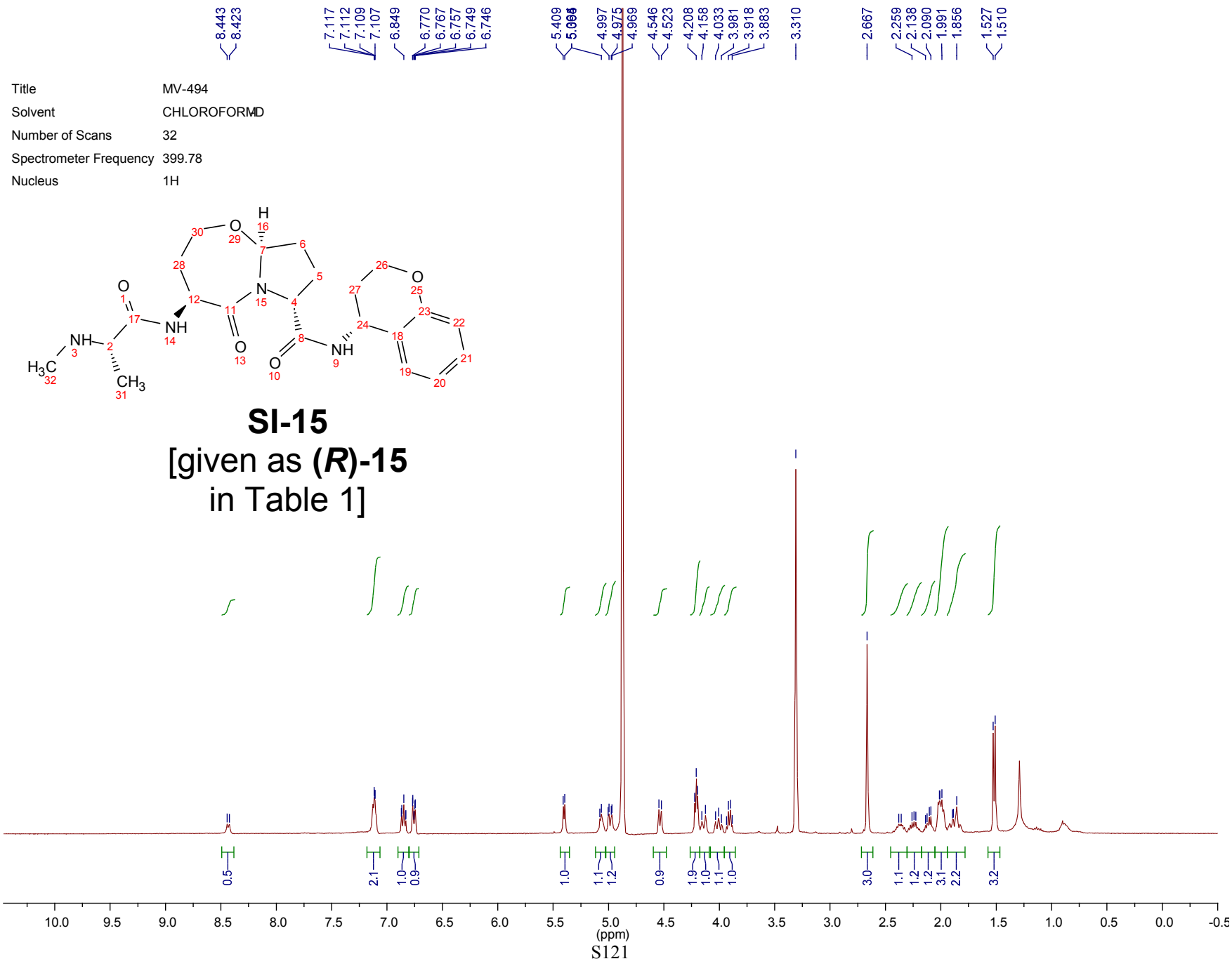

173.940
172.002
171.256
89.614
80.947
77.100
70.653
60.576
59.768
53.054
32.983
32.475
30.481
28.502
26.077
21.187
14.323
14.061
Title MV-492
Solvent CHLOROFORM-D
Spectrometer Frequency 100.53
Nucleus 13C
SI-13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
(ppm)

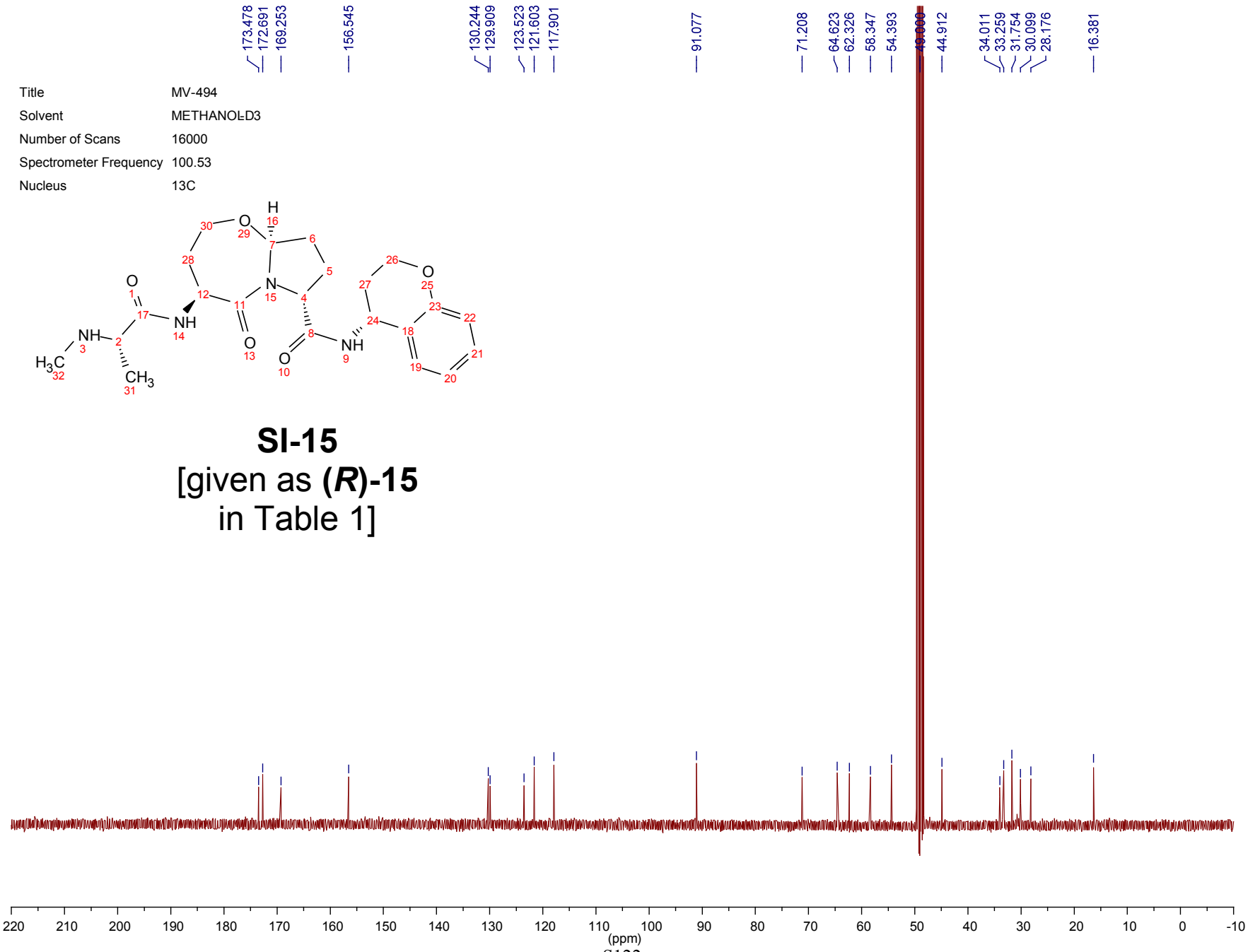
Title	MV-493
Solvent	CHLOROFORM-D
Number of Scans	32
Spectrometer Frequency	399.78
Nucleus	1H



SI-14

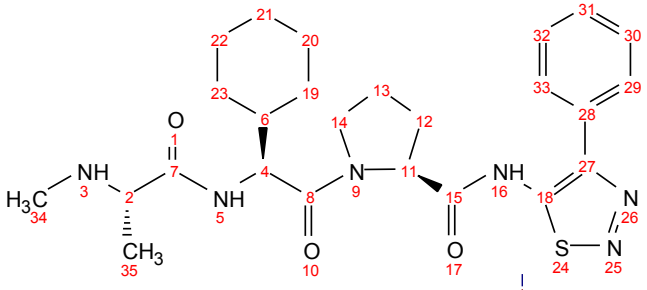

172.259
171.132
169.871
155.170
129.376
129.328
122.045
120.916
117.305
90.054
77.160
70.601
63.410
61.053
53.149
43.839
33.366
32.069
29.842
29.063
28.454
25.587
22.834
14.260
Title MV-493
Solvent CHLOROFORM-D
Number of Scans 17722
Spectrometer Frequency 100.53
Nucleus 13C
SI-14
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


8.443
8.423
7.117
7.112
7.109
7.107
6.849
6.770
6.767
6.757
6.749
6.746
5.409
4.997
4.975
4.969
4.546
4.523
4.208
4.158
4.033
3.981
3.918
3.883
3.310
2.667
2.259
2.138
2.090
1.991
1.856
1.527
1.510
Title MV-494
Solvent CHLOROFORM-D
Number of Scans 32
Spectrometer Frequency 399.78
Nucleus 1H
SI-15
[given as (R)-15
in Table 1]
0.5
2.1
1.0
0.9
1.0
1.1
1.2
0.9
1.9
1.0
1.1
1.0
3.0
1.1
1.2
1.2
3.1
2.2
3.2
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

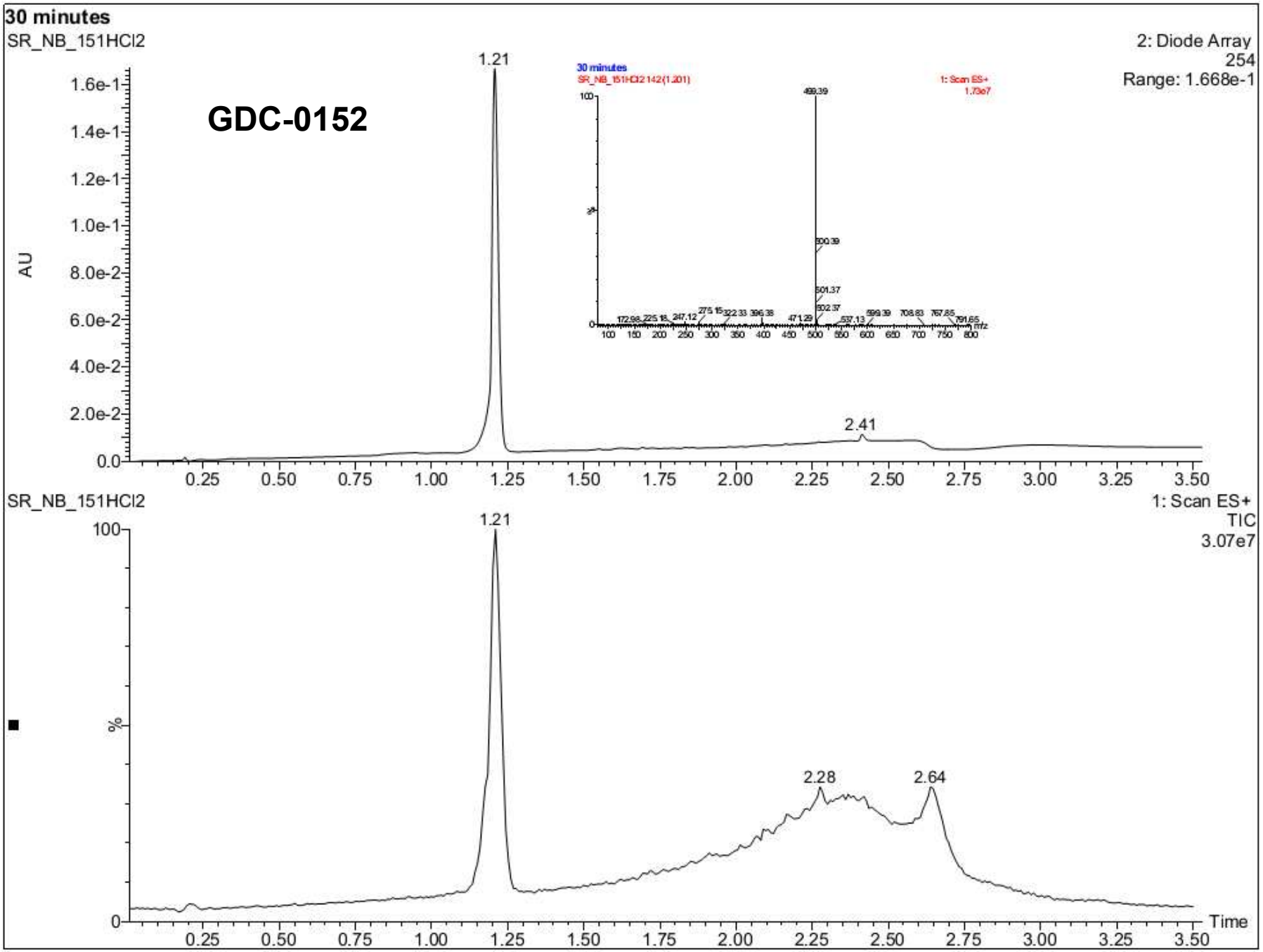


SI-15
[given as (***R***)-**15** in Table 1]

Title	GDC-0152
Solvent	CHLOROFORM-D
Number of Scans	16
Spectrometer Frequency	399.78
Nucleus	1H



GDC-0152


30 minutes
SR_NB_151HCl2
2: Diode Array
254
Range: 1.668e-1
GDC-0152
1.21
2.41
AU
30 minutes
SR_NB_151HCl2 142(1.201)
1: Scan ES+
1.73e7
499.39
500.39
501.37
502.37
SR_NB_151HCl2
1: Scan ES+
TIC
3.07e7
1.21
2.28
2.64
%
Time