Practical Synthesis of a p38 MAP Kinase Inhibitor

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Supporting information

General Methods

Commercial reagents were used without purification and solvents were used without drying. All reactions were conducted under nitrogen unless otherwise specified. ^{1}H and ^{13}C NMR spectra were obtained on 300, 400 or 600 MHz spectrometers in $CDCl_3$ or d_6-DMSO as solvent. The chemical shifts were reported in δ ppm relative to TMS. IR spectra were recorded using a universal ATR sampling unit. Melting points determined by differential scanning calorimetry experiments using DCS Q2000 instrument.

Experimental Procedures

2-*tert*-Butyl-6-chloro-1-hydroxy-3-oxoisoindoline-4-carbaldehyde (17a). An analytically pure sample of the title compound was isolated by preparative HPLC from a batch of crude 2-*tert*-butyl-5-chloro-3-hydroxyisoindolin-1-one (**16**): mp 153-154 °C. HRMS (*m/z*): [M+H$^+$] calcd for $[C_{13}H_{15}ClNO_3]^+$: 268.07350; Found 268.07379. IR 3337, 2979, 2918, 1692, 1664, 1598, 1473, 1447, 1392, 1375, 1366, 1319, 1258, 1234, 1214, 1197, 1150, 1127, 1086, 1065, 1027, 970, 933, 911, 897, 878, 814, 799, 787, 764, 696, 658 cm^{-1}. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 11.00 (s, 1H), 7.91 (s, 1H), 7.80 (s, 1H), 6.83 (bs, 1H), 6.13 (s, 1H), 1.54 (s, 9H) ppm. ^{13}C NMR (d_6-DMSO, 101 MHz): δ 189.4, 165.9, 148.6, 137.4, 131.6, 125.8, 81.6, 28.1 ppm.

2-*tert*-Butyl-5-chloro-3-hydroxy-1-oxoisoindoline-4-carbaldehyde (17b). 2-*tert*-Butyl-5-chloro-3-hydroxyisoindolin-1-one (**16**) (0.39 g, 1.6 mmol) was dissolved in THF (46 ppm water by KF) (5.0 mL). The resulting light colored solution was cooled to ca. 0 °C under nitrogen. MeLi in diethoxymethane (3.0M) (1.1 mL, 3.3 mmol, 2.1 equiv.) was added dropwise between -4 °C and 0 °C to briefly afford an orange solution that

gradually turned into a thick, dark bluish slurry. The reaction mixture was stirred between -9 °C and 3 °C for 80 min. at which point the reaction mixture was rapidly quenched with DMF (560 ppm water by KF) (0.30 mL, 2.5 equiv.) (internal temperature reached 12 °C). The resulting dark fluid mixture was then quenched with brine (ca. 5 mL). The major product in the organic layer had MS 268, but different retention time than **17a**. The organic layer was stripped to afford an orange oil which after chromatographic purification afforded the title compound **17b** as a yellow waxy solid (85 mg). mp 109 °C. HRMS (*m/z*): [M+H$^+$] calcd for [$C_{13}H_{15}ClNO_3$]$^+$: 268.07350; Found 268.07337. IR 3218, 2972, 2869, 1695, 1673, 1662, 1590, 1484, 1446, 1390, 1364, 1311, 1269, 1254, 1218, 1198, 1184, 1161, 1129, 1055, 1024, 990, 978, 927, 901, 856, 821, 772, 733, 714 cm^{-1}. ^{1}H NMR (*d*$_6$-DMSO, 400 MHz): δ 10.47 (s, 1H), 7.77 (AB, 2H), 6.48 (AB, 2H), 1.53 (s, 9H) ppm. ^{13}C NMR (*d*$_6$-DMSO, 101 MHz): δ 189.2, 164.5, 146.8, 137.5, 132.3, 132.0, 127.7, 80.1, 53.7, 27.7 ppm.

***N*'-((7-Chloro-4-hydroxyphthalazin-5-yl)methylene)acetohydrazide (23a).** An analytically pure sample of the title compound was isolated by preparative HPLC from a batch of crude 6-chlorophthalazin-1-ol (**24**): mp 349-351 °C. HRMS (*m/z*): [M+Na$^+$] calcd for [$C_{11}H_9ClN_4NaO_2$]$^+$: 287.03062; Found 287.03048. IR 3168, 2935, 1668, 1608, 1588, 1560, 1389, 1341, 1319, 1294, 1265, 1168, 1150, 1111, 1076, 1019, 959, 932, 896, 888, 868, 843, 784, 676 cm^{-1}. *Note:* two species **23a$_a$** and **23a$_b$** (ca. 6:4 ratio) exist at 25 °C in ^{1}H and ^{13}C NMR timescales. ^{1}H NMR (*d*$_6$-DMSO, 400 MHz): δ 12.83 (s$_b$, 0.4H), 12.78 (s$_a$, 0.6H), 11.85 (s$_b$, 0.4H), 11.60 (s$_a$, 0.6H), 9.58 (s$_b$, 0.4H), 9.43 (s$_a$, 0.6H), 8.32 (s, 1H), 8.19 (s, 1H), 8.10 (s, 1H), 2.23 (s, 1.8H), 1.98 (s, 1.2H) ppm. ^{13}C NMR (*d*$_6$-

DMSO, 101 MHz): δ 172.7 (C_a), 166.4 (C_b), 160.1, 143.2 (C_b), 140.8 (C_a), 137.8 (2C), 128.5, 127.5, 22.2 (C_b), 21.2 (C_a) ppm.

***N-tert*-Butyl-8-chlorophthalazine-5-carboxamide (23b).** Aliquot of a crude **17b** (*vide supra*) (43 mg) was dissolved in AcOH (1.0 mL). Aqueous hydrazine (80 wt%) (49 mg) was added and the resulting orange solution was stirred at 90 °C for 0.5 hour. The major product detected by LC/MS analysis had MS 264 (**23b**). HRMS (*m/z*): [M+H$^+$] calcd for $[C_{13}H_{15}ClN_3O]^+$: 264.08981; Found 264.08974.

Lithium 3-iodo-4-methylbenzoate (26).

A 22 L rotary evaporator flask was charged with 3-iodo-4-methylbenzoic acid (**8**) (2.41 kg, 9.19 mol), lithium hydroxide (0.220 kg, 9.19 mol), and ethanol (9.6 L). The mixture was heated to 59 °C with stirring to form a solution. After approximately 15 min. the lithium carboxylate salt precipitated out to form a slurry. The slurry was concentrated to a powder under vacuum with a jacket temperature of 59 °C. The solids were transferred to drying trays and dried under vacuum at 96 °C for approximately 16 hours until constant weight was achieved to afford anhydrous lithium 3-iodo-4-methylbenzoate (**26**) (2.44 kg, 0.38 wt% water by Karl Fischer titration, 99.5% yield).

3-Borono-4-methylbenzoic acid (27) (organolithium process).

A 22 L reactor fitted with overhead stirring, nitrogen gas inlet, condenser, gas outlet trap, thermowell, and transfer assembly was thoroughly inerted with nitrogen. Anhydrous THF (4.8 L) was added and cooled to less than -70 °C. 1.7 M *tert*-butyllithium in pentane (2.9 L, 4.9 mol) was slowly added while keeping the internal temperature below -70 °C. This solution continued to stir below -70 °C to form a thick bright yellow slurry. A 12 L

reactor fitted with overhead stirring, nitrogen gas inlet, gas outlet trap, and thermowell was inerted with nitrogen, charged with anhydrous THF (6.9 L) and cooled to approximately 5 °C. Lithium 3-iodo-4-methylbenzoate (**26**) (613 g, 2.29 mol) was added slowly in portions (exothermed to 9 °C). The resulting clear orange solution of lithium carboxylate was cooled to -70 °C and slowly transferred into the 22 L reactor containing *tert*-butyllithium at less than -67 °C and allowed to stir for over 2 hours forming a clear red solution. Trimethylborate (400 mL, 3.52 mol) was added when metalation was complete. A green slurry that developed was allowed to warm to approximately -5 °C. The reaction mixture was quenched with DI water (3.7 L) added rapidly. The reaction mixture exothermed to approximately 15 °C. Agitation was stopped and the resulting clear upper organic layer was discarded. The lower aqueous layer, which contained the dissolved product as a lithium salt, was filtered to remove insoluble boric acid salts using DI water (0.40 L) to rinse the filter. The combined bright yellow aqueous layers from two identical runs were transferred into a 50 L reactor fitted with overhead stirrer and extracted with dichloromethane (4.0 L). The lower organic layer was removed and discarded. A 10% HCl aq. was added at ≤10 °C to achieve a pH of 2.4. The product was collected by filtration, washed with DI water (1.4 L), and held on the filter for approximately 30 minutes to remove excess moisture. The crude product was recrystallized by charging the wet solids from the filter to a 50 L reactor and dissolving in THF (3.5 L) resulting in a clear orange-yellow solution. The clear solution was treated with *n*-hexane (1.3 L) over at least 15 minutes to generate seed material. The resulting suspension was treated with an additional *n*-hexane (12.3 L). The resulting slurry was aged with stirring for at least 30 minutes, then filtered. The filtercake was washed with

n-hexane (1 L) and air-dried. The solids were transferred to drying trays and dried under vacuum at ≤30 °C to a constant weight to afford 3-borono-4-methylbenzoic acid (**27**) (68.2-92.1 wt% potency) as a hydrate[1] (96.2-99.7% LC purity, 58.8-84.8% assay corrected yield).

3-(1-Hydroxyphthalazin-6-yl)-4-methylbenzoic acid (28).

A 5 L jacketed reactor equipped with mechanical stirrer, reflux condenser, nitrogen blanket, and temperature probe was charged with 6-chlorophthalazin-1-ol (**24**) (101 g, 560 mmol), 3-borono-4-methylbenzoic acid (**27**) hydrate (116 g on a dry-basis, 644 mmol), $Pd_2(dba)_3$ (2.56 g, 2.80 mmol), 2'-methyl(dicyclohexylphosphino)biphenyl (2.55 g, 7.00 mmol) and inerted with nitrogen. Deoxygenated *n*-butanol (0.56 L) and deoxygenated deionized water (0.14 L) were added and efficient agitation was established. To the resulting uniform slurry was added deoxygenated dicyclohexylamine (446 mL, 2.24 mol) in one portion (adiabatic temperature change 18 °C to 34 °C). The reaction mixture was heated to 85 °C overnight (stirout was reached after 165 min.). Conversion check (by HPLC) after 17 h showed >99% LC conversion of heteroaryl chloride and 5% LC boronic acid remaining. After 20 h at 85 °C reaction mixture was adjusted to 60 °C and 6 N NaOH aq. (0.67 L, 4.0 mol) was added slowly. Stirring was continued at 60 °C until all the solids dissolved (approx. 30 min.). Reaction mixture was cooled to 25 °C and layers were allowed to separate. Lower viscous aqueous layer was retained, upper organic layer was discarded. The aqueous layer was washed with dichloromethane (1.0 L; *note:* layer separation was slow) to afford a crude aqueous solution (1.2 L) of the sodium salt of the product. The solution was diluted with deionized water (0.5 L) and 5 M HCl aq. (0.3 L, 1.5 mol) was added slowly with efficient

agitation to effect precipitation of a voluminous material (supernatant at pH 10; contained approx. 5% assay yield of title compound). The precipitate was collected by vacuum filtration (*note:* filtration was slow due to small particle size and foaming), wetcake was transferred into a vacuum oven and dried at 65 °C to a constant weight (0.20 kg). This material was slurried in deionized water (1.0 L) to afford a suspension (pH 10) which was then adjusted to pH 6-7 with 5 M HCl aq. (125 mL, 0.63 mol). The suspension was passed through a fine filter (*note:* filtration was slow). The resulting pasty wetcake was vacuum-dried at 80 °C to afford **28** as a grayish powder (91.5 wt%, 147 g, 85.8% yield). A sample of this material was reslurried in refluxing *iso*propanol to afford 3-(1-hydroxyphthalazin-6-yl)-4-methylbenzoic acid (**28**) as an off-white crystals: mp 297-298 °C. HRMS (*m/z*): [M+H$^+$] calcd for $[C_{16}H_{13}N_2O_3]^+$: 281.09207; Found 281.09213. IR 3168, 2902, 2549, 1666, 1619, 1609, 1566, 1436, 1367, 1313, 1261, 1164, 1037, 938, 907, 891, 843, 821, 787, 763, 688 cm^{-1}. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 13.00 (bs, 1 H), 12.71 (s, 1 H), 8.42 (s, 1 H), 8.29 (d, J = 8.0 Hz, 1 H), 7.98 (s, 1 H), 7.93 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.85 (s, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (d_6-DMSO, 101 MHz): δ 166.9, 159.4, 145.4, 140.2, 139.8, 138.2, 132.5, 130.9, 130.3, 130.0, 128.9, 126.9, 126.4, 125.5, 20.2 ppm. Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.39; H, 4.13; N, 10.13.

***N*-Cyclopropyl-3-(1-hydroxyphthalazin-6-yl)-4-methylbenzamide (34).** 3-(1-Hydroxyphthalazin-6-yl)-4-methylbenzoic acid (**28**) (1.40 g, 5.00 mmol) was suspended in THF (10 mL). CDI (1.25 g, 7.71 mmol) was added followed by THF (5 mL). The resulting suspension was stirred at reflux. Briefly became a cloudy solution within 5 min. at reflux, then voluminous precipitate started to appear. After 1.5 hour at reflux the

reaction mixture was cooled to room temperature. The precipitate was collected by filtration, rinsed thoroughly with THF, and air-dried on a filter to afford the acyl imidazolide[2] as an off-white flakes. Aliquot of this material (0.33 g, 1.0 mmol) was suspended in 1,2-dichloroethane (5.0 mL) and allowed to react with excess cyclopropylamine (1.0 mL, 14 mmol) at room temperature. After 18 hours complete conversion of the acyl imidazolide to the cyclopropylamide was determined by HPLC. The reaction mixture was evaporated to dryness. The solid residue was triturated with deionized water at room temperature and filtered to afford the title compound **34** as a fine white powder (0.27 g, 83% yield): mp 284-285 °C. HRMS (*m/z*): [M+H$^+$] calcd for $[C_{19}H_{18}N_3O_2]^+$: 320.13935; Found 320.13862. IR 3290, 3165, 2871, 2109, 1655, 1634, 1545, 1502, 1452, 1361, 1321, 1250, 1155, 1129, 1048, 1027, 965, 908, 845, 867, 791, 755, 720, 703, 687 cm^{-1}. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 12.75 (s, 1 H), 8.50 (d, J = 3.5 Hz, 1 H), 8.43 (s, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 7.99 (s, 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 7.85 (d, J = 8.5 Hz, 1 H), 7.82 (s, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 2.93-2.83 (m, 1 H), 2.32 (s, 3 H), 0.75-0.65 (m, 2 H), 0.62-0.54 (m, 2 H) ppm. ^{13}C NMR (d_6-DMSO, 101 MHz): δ 166.8, 159.5, 145.8, 139.4, 138.2, 132.7, 132.2, 130.6, 130.0, 128.2, 127.09, 126.9, 126.3, 125.5, 23.1, 20.0, 5.7 ppm. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 70.98; H, 5.54; N, 13.00.

***N*-Benzyl-4-methyl-3-(1-morpholinophthalazin-6-yl)benzamide (39).**

A 250 mL round bottom flask was charged with 4-methyl-3-(1-morpholinophthalazin-6-yl)benzoic acid (**33**) (5.00 g, 14.3 mmol), imidazole (0.97 g, 14.3 mmol) and THF (25 ml). *N,N*-Carbonyldiimidazole (3.48 g, 21.5 mmol) was added at rt and the mixture was stirred for 1h at rt. Benzylamine (6.25 ml, 57.2 mmol) was added in one portion and the

mixture was stirred for 15 h at rt. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 1 N HCl (3 x 30 mL). After removal of the excess amines from the organic phase the product precipitated and was isolated by vacuum filtration. The crude product was suspended in *iso*propanol, stirred for 2 h and isolated by filtration. Drying in the vacuum oven at 60 °C afforded *N*-benzyl-4-methyl-3-(1-morpholinophthalazin-6-yl)benzamide (**39**) as a white solid. mp 268-284 °C. HRMS (*m/z*): [M+H$^+$] calcd for $[C_{27}H_{27}N_4O_2]^+$: 439.21285; Found 439.21212. IR 3273, 3044, 2961, 2603, 2033, 1658, 1623, 1596, 1562, 1526, 1497, 1443, 1420, 1385, 1362, 1347, 1331, 1297, 1273, 1258, 1211, 1144, 1115, 1069, 1003, 934, 913, 895, 860, 823, 782, 763, 734, 715, 704, 695, 675 cm^{-1}. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 9.41 (s, 1 H), 8.41 (d, J = 8.7 Hz, 1 H), 8.32 (s, 1 H), 8.15 (dd, J = 8.6 Hz, 1.7 Hz, 1 H), 7.89 (dd, J = 9.3 Hz, 1.7 Hz, 1 H), 7.86 (s, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.31-7.27 (m, 4H), 7.25-7.20 (m, 1H), 3.90-3.86 (m, 4 H), 3.65-3.55 (m, 4 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (d_6-DMSO, 101 MHz): δ 166.3, 158.3, 146.9, 146.0, 139.8, 139.3, 139.2, 135.9, 132.6, 131.5, 129.5, 129.2, 129.0, 128.8, 127.9, 127.7, 127.3, 126.8, 121.4, 62.1, 51.6, 43.0, 20.4 ppm. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 66.56; H, 5.48; N, 11.43.

Table 1. *Ortho*-formylation of **12c**.

Entry	Alkyllithium (equiv.)	Addition / reaction temp.[a]	Time (hours)[b]	Conv. (%)[c]	17a (mol%)[c]	Scale[d]
1	^{t}BuLi (2.5)	-70 ºC / -78 ºC	1.0	100	4	1 g
2	^{t}BuLi (2.5)	-50 ºC / -78 ºC	1.0	100	9	10 g
3	^{n}BuLi (2.5)	-22 ºC / -10 ºC	1.0	99.6	1.4	1 g
4	^{n}BuLi (2.2)	-11 ºC / -10 ºC	2.5	99.3	19.6	0.2 kg
5	^{n}BuLi (2.2)	-10 ºC / -10 ºC	2.0	96.6	7.2	20 g
6	^{n}BuLi (2.0)	-11 ºC / -10 ºC	2.0	98.3	6.3	0.2 kg
7	MeLi (2.5)	-17 ºC / -18 ºC	1.5	92.3	0.6	1 g
8	MeLi (2.5) / TMEDA (2.0)	-19 ºC / -18 ºC	1.5	94.1	1.1	1 g
9	MeLi (2.5) / TMEDA (2.0)	-22 ºC / -22 ºC	0.5	77.1	0.2	1 g
10	MeLi (2.5)	-17 ºC / -8 ºC	2.0	97.7	0.0	1 g
11	MeLi (2.5) / TMEDA (2.0)	-17 ºC / -8 ºC	2.0	98.4	0.0	1 g
12	MeLi (2.1)	-20 ºC / -8 ºC	3.0	99.2	0.0	10 g
13	MeLi (2.1)	-17 ºC / -8 ºC	3.0	98.3-98.4	1.5-2.3	0.3 kg
14	MeLi (2.0)	-12 ºC / -9 ºC	3.5	95.2	1.5	0.3 kg
15	MeLi (2.05)	-15 ºC / -8 ºC	5.0	93.5	2.5	0.3 kg
16	MeLi (2.05)	-17 ºC / -8 ºC	4.0	94.3-95.5	0.7-0.9	2 kg
17	MeLi (1.8)	-45 ºC / -17 ºC	3.0	87.8	0.0	5 g
18	MeLi (1.8)	9 ºC / 3 ºC	2.0	90.0	0.0	5 g
19	MeLi (3.0)	-16 ºC / -5 ºC	3.5	98.2	5.0	5 g
20	MeLi (3.0) / HMPT (2.0)	4 ºC / -2 ºC	2.5	98.6	11.6	3 g

[a] Highest temperature during addition of alkyllithium / temperature during the lithiation period.

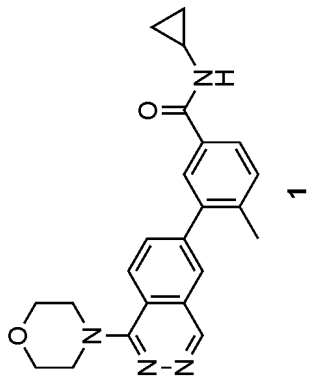
[b] Reaction time with alkyllithium including the addition time (prior addition of DMF).

[c] LC peak area% (at 215 nm) of **12c** remaining in quenched mixture (only **12c**, **16**, and **17a** are integrated).

[d] Amount of **12c** used in reaction.

[1] The analysis of actual water content was not conclusive by methods tested to date (coulometric, volumetric, or evaporative KF, GC-TCD). Water content by coulometric or volumetric Karl Fischer may both include titration of the boronic acid hydroxyls. Temperature of the evaporative KF and GC-TCD methods may cause dehydration of the boronic acid to the borinic acid.

[2] Acyl imidazolide confirmed by ^{1}H NMR.



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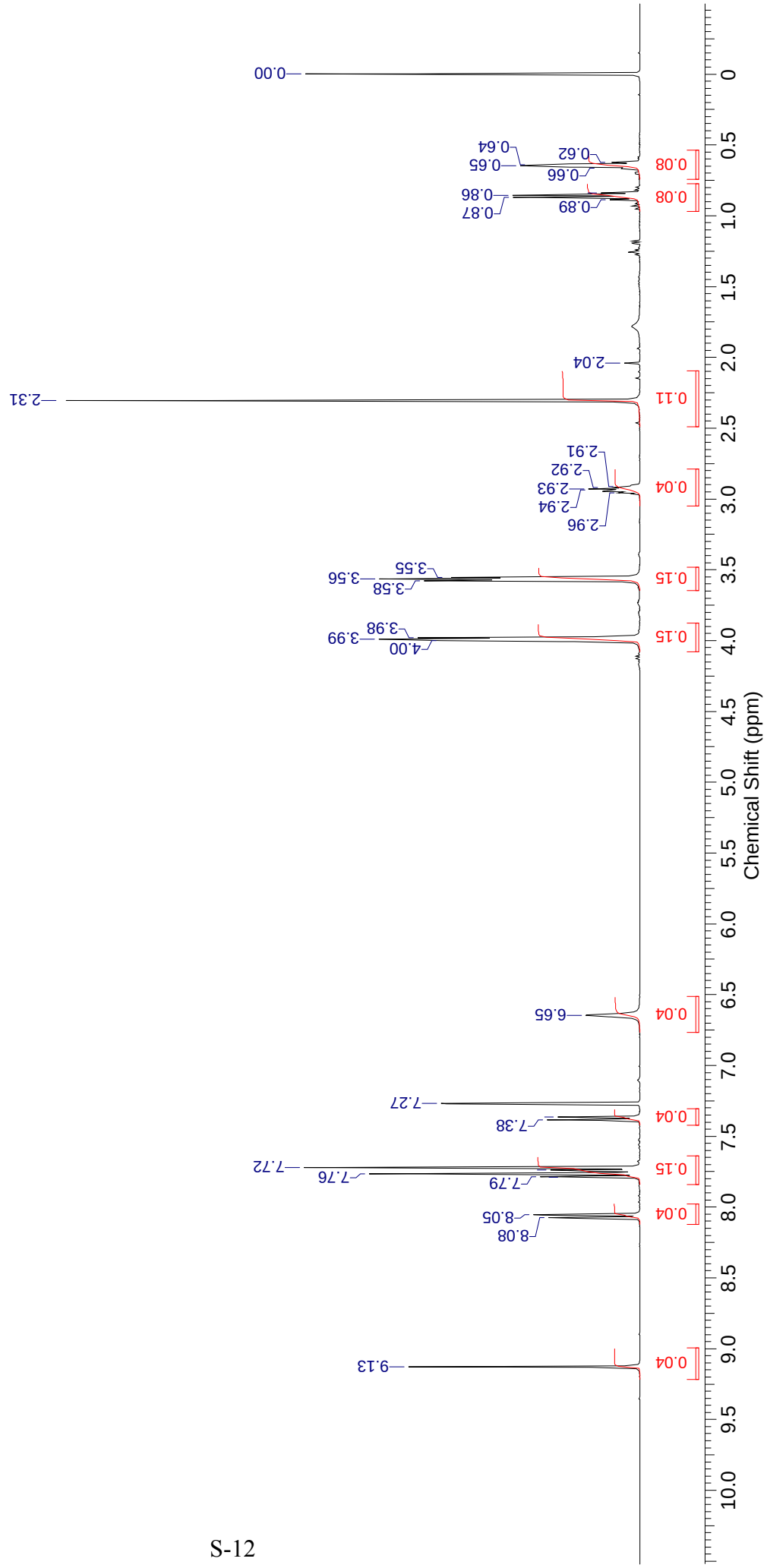

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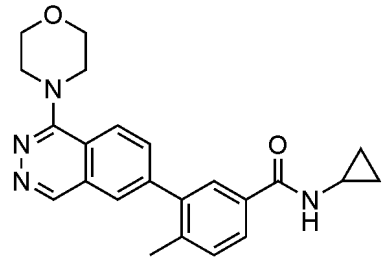

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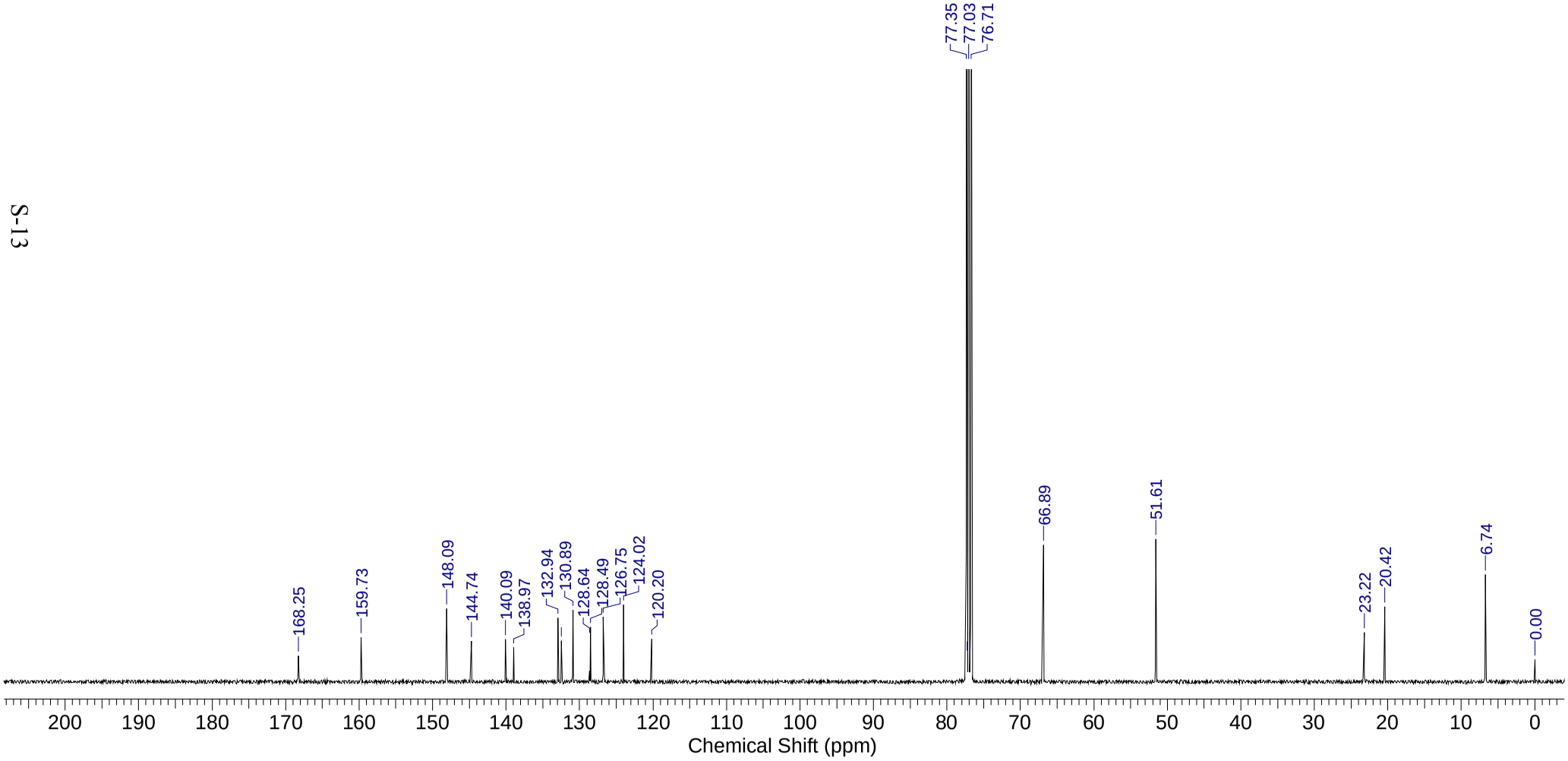

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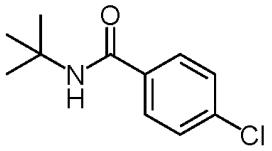
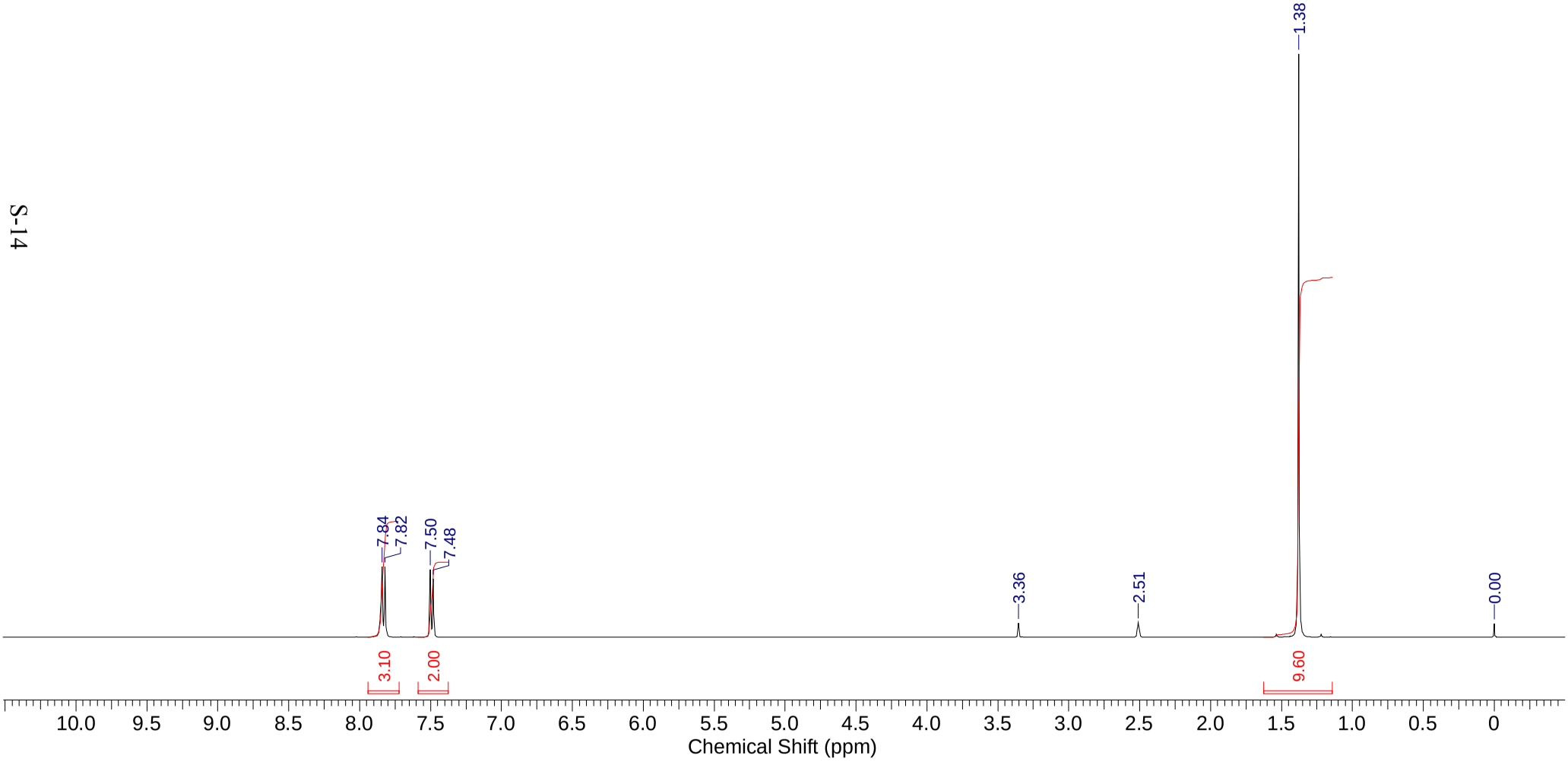
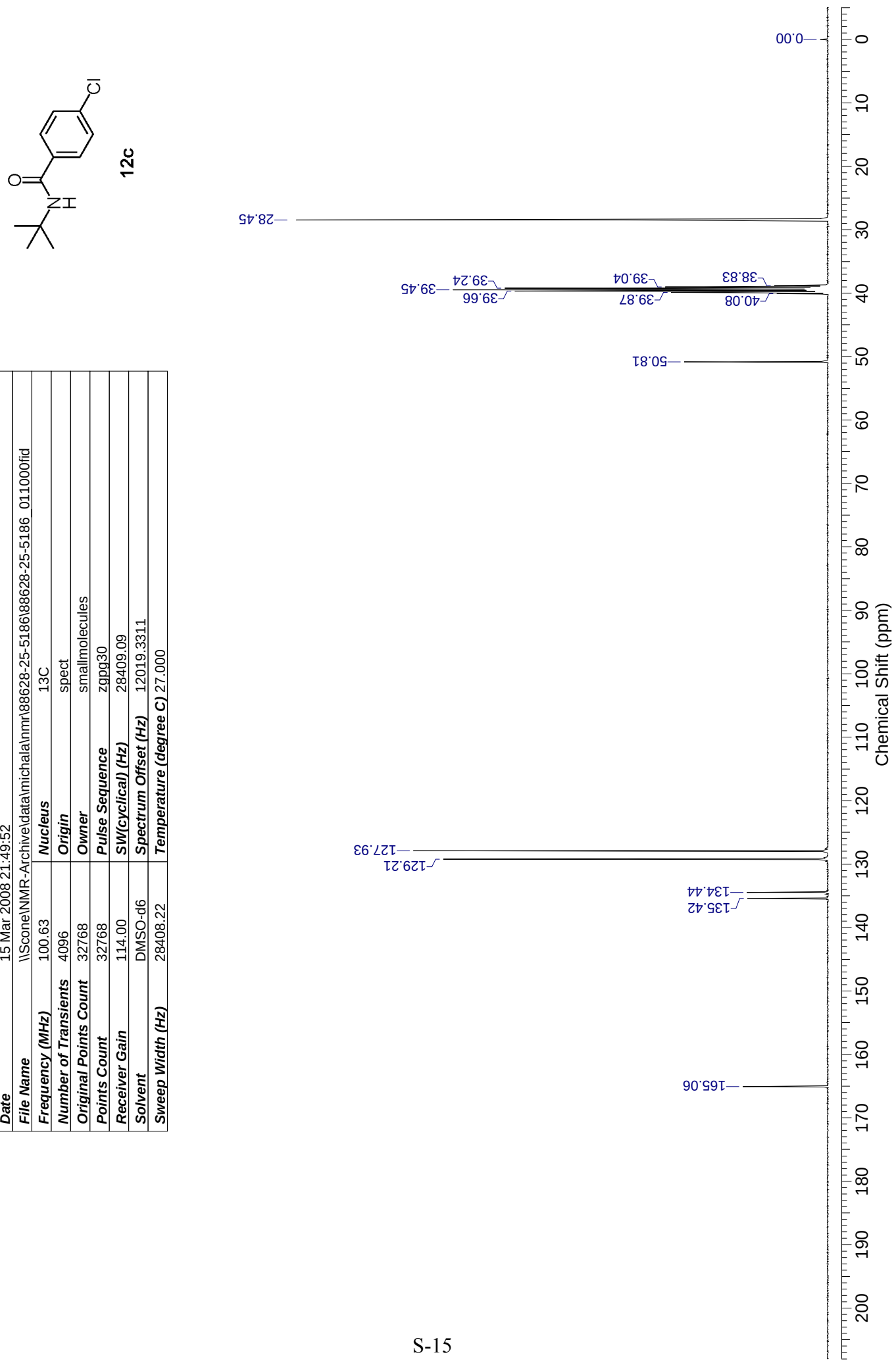


12c





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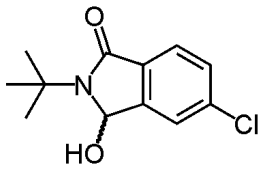
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	27.000

Acquisition Time (sec)	1.9924	***Comment***	michala
Date	15 Mar 2008 01:31:44		
File Name	\\Scone\NMR-Archive\data\michala\nmr\88628-25-5187\88628-25-5187_010000fid		
Frequency (MHz)	400.16	***Nucleus***	1H
Number of Transients	16	***Origin***	spect
Original Points Count	16384	***Owner***	smallmolecules
Points Count	16384	***Pulse Sequence***	zg30
Receiver Gain	128.00	***SW(cyclical) (Hz)***	8223.68
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2470.2676
Sweep Width (Hz)	8223.18	***Temperature (degree C)***	27.000



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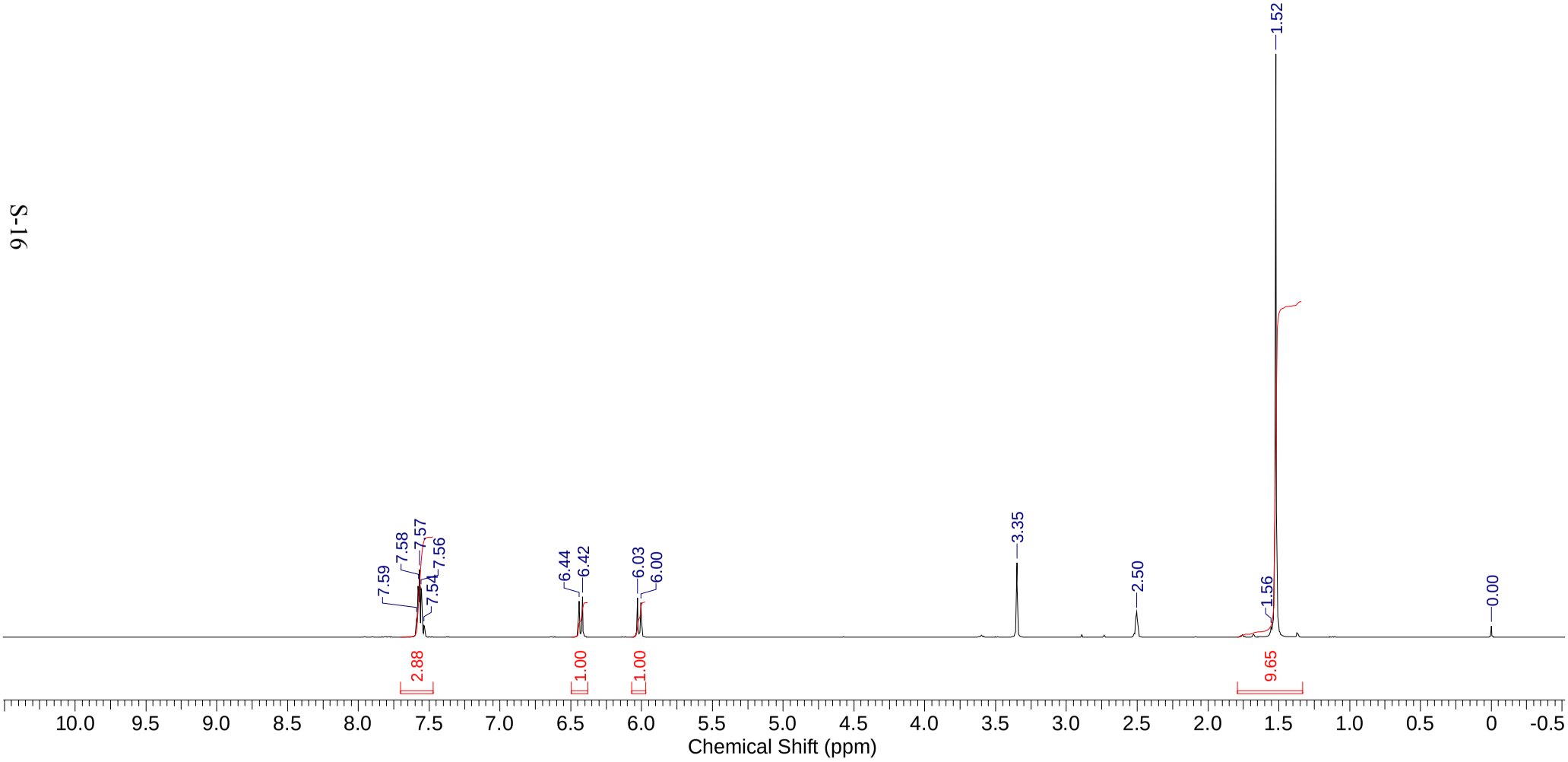
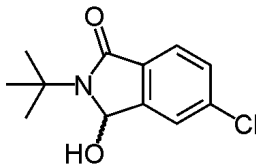
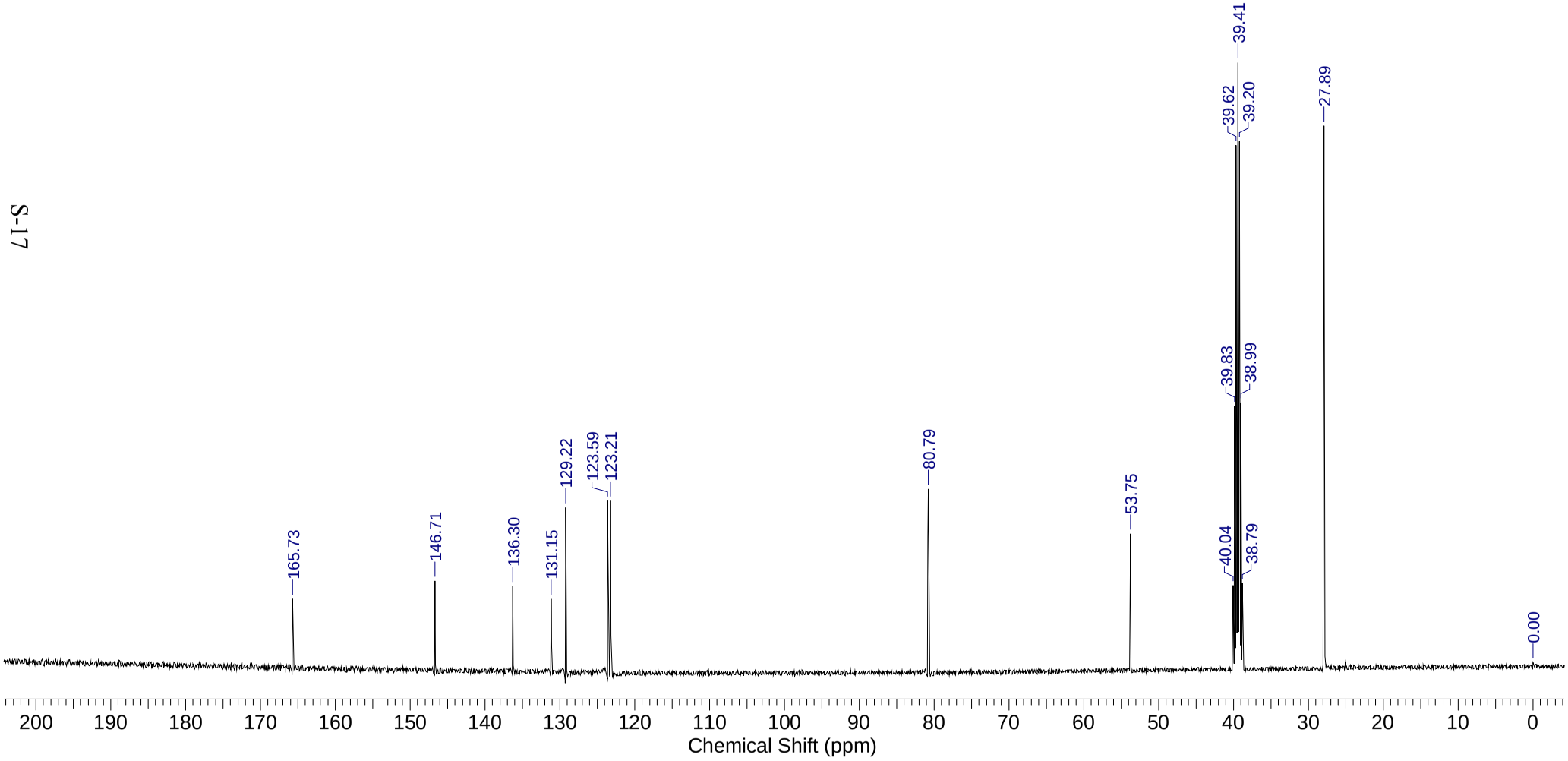
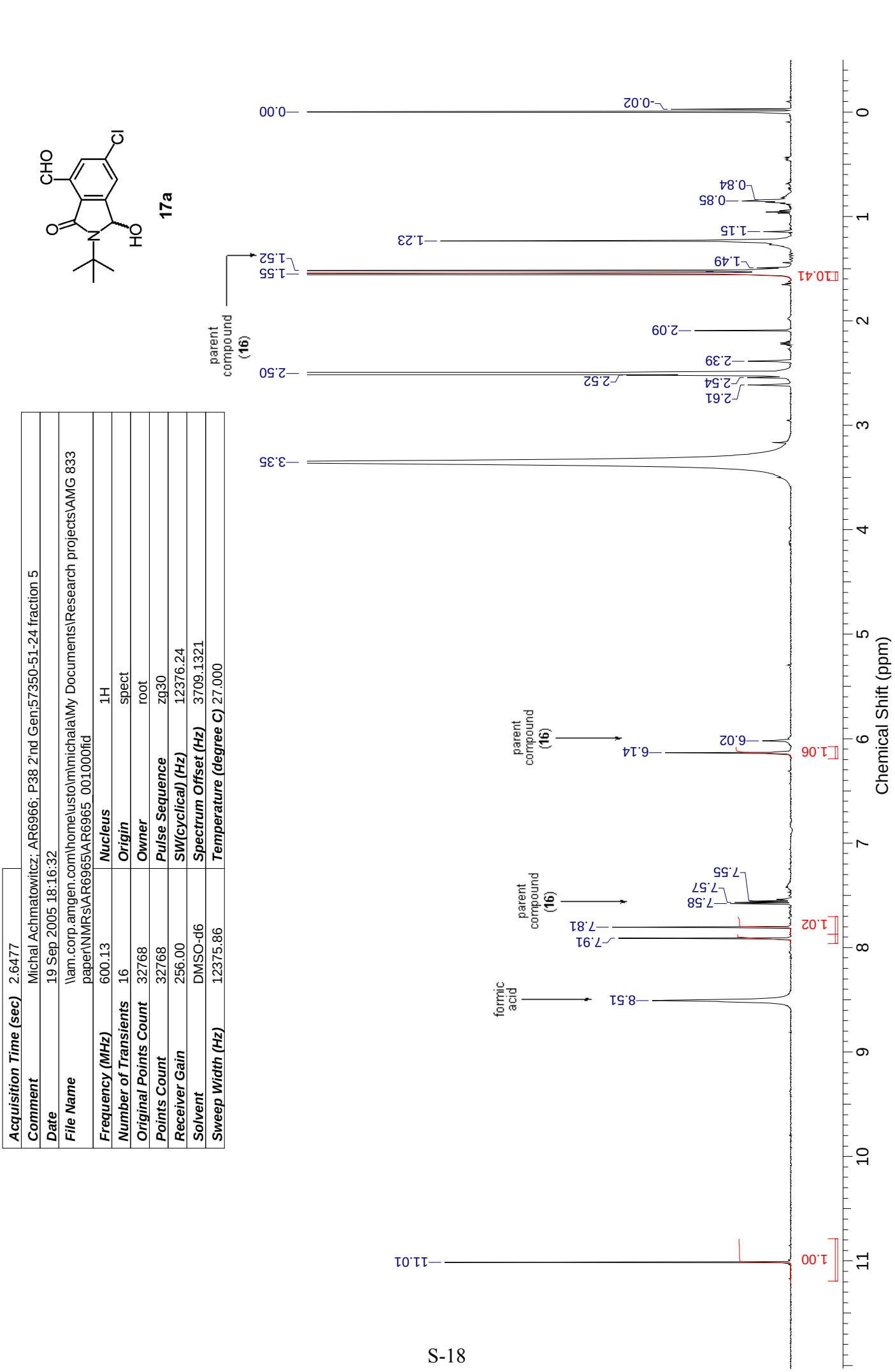


Acquisition Time (sec)	1.1535	***Comment***	michala
Date	15 Mar 2008 02:25:04		
File Name	\\Scone\NMR-Archive\data\michala\nmr\88628-25-5187\88628-25-5187_011000fid		
Frequency (MHz)	100.63	***Nucleus***	13C
Number of Transients	512	***Origin***	spect
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***Pulse Sequence***	zgpg30
Receiver Gain	80.60	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12016.7305
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	27.000

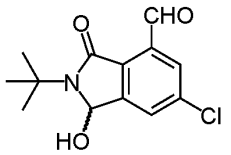


16



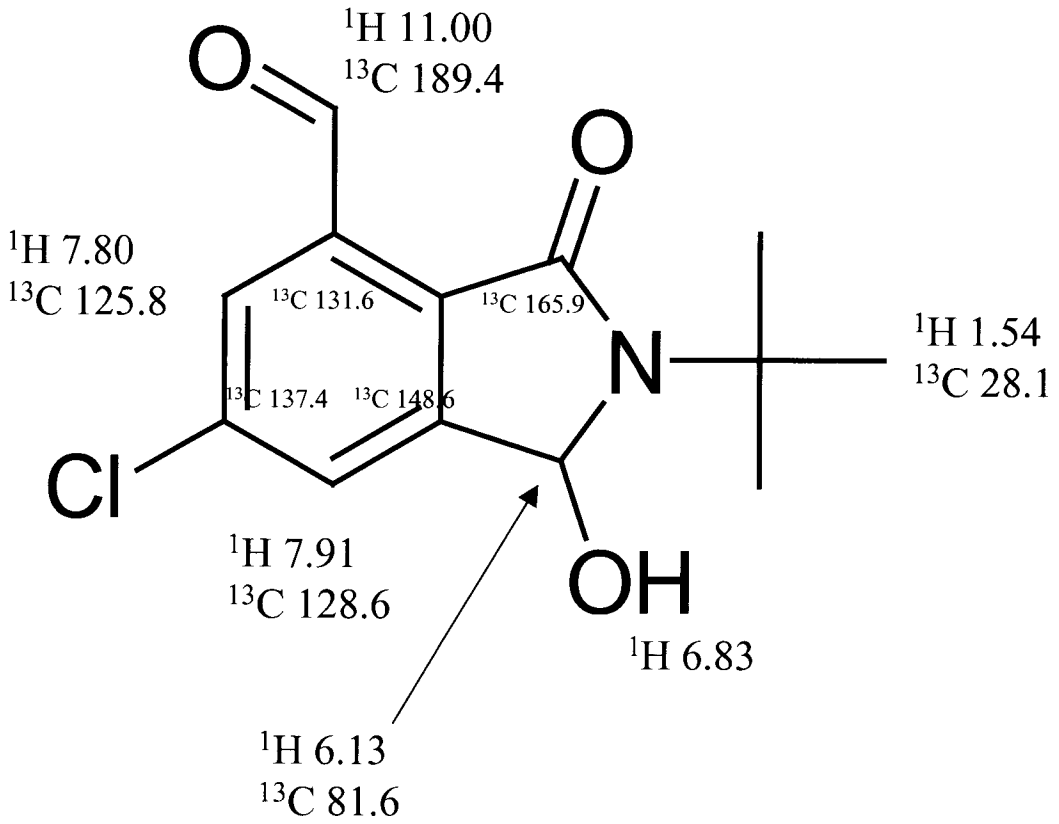

17a
CHO
Cl
O
N
HO
Acquisition Time (sec) 2.6477
Comment Michal Achmatowitcz; AR6966; P38 2'nd Gen;57350-51-24 fraction 5
Date 19 Sep 2005 18:16:32
File Name \\am.corp.amgen.com\home\usto\m\michala\My Documents\Research projects\AMG 833 paper\NMRs\AR6965\AR6965_001000fid
Frequency (MHz) 600.13
Nucleus 1H
Number of Transients 16
Origin spect
Original Points Count 32768
Owner root
Points Count 32768
Pulse Sequence zg30
Receiver Gain 256.00
SW(cyclical) (Hz) 12376.24
Solvent DMSO-d6
Spectrum Offset (Hz) 3709.1321
Sweep Width (Hz) 12375.86
Temperature (degree C) 27.000
parent compound (16)
formic acid
11.01
8.51
7.91
7.81
7.58
7.57
7.55
6.14
6.02
3.35
2.61
2.54
2.52
2.50
2.39
2.09
1.55
1.52
1.49
1.23
1.15
0.85
0.84
0.00
-0.02
1.00
1.02
1.06
10.41
Chemical Shift (ppm)

Michal Achmatowitcz; AR6966; P38 2'nd Gen; 57350-51-24
Fraction 5

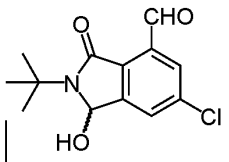


17a

Measured mass: 267.07



Michal Achmatowitcz; AR6966; P38 2'nd Gen;57350-51-24
fraction 5



17a

BRUKER

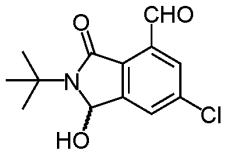
Current Data Parameters
NAME AR6965
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050919
Time 11.16
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6477449 sec
RG 256
DW 40.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 3.80 dB
SFO1 600.1337060 MHz

F2 - Processing parameters
SI 32768
SF 600.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Michal Achmatowitcz; AR6966; P38 2'nd Gen;57350-51-24
fraction 5



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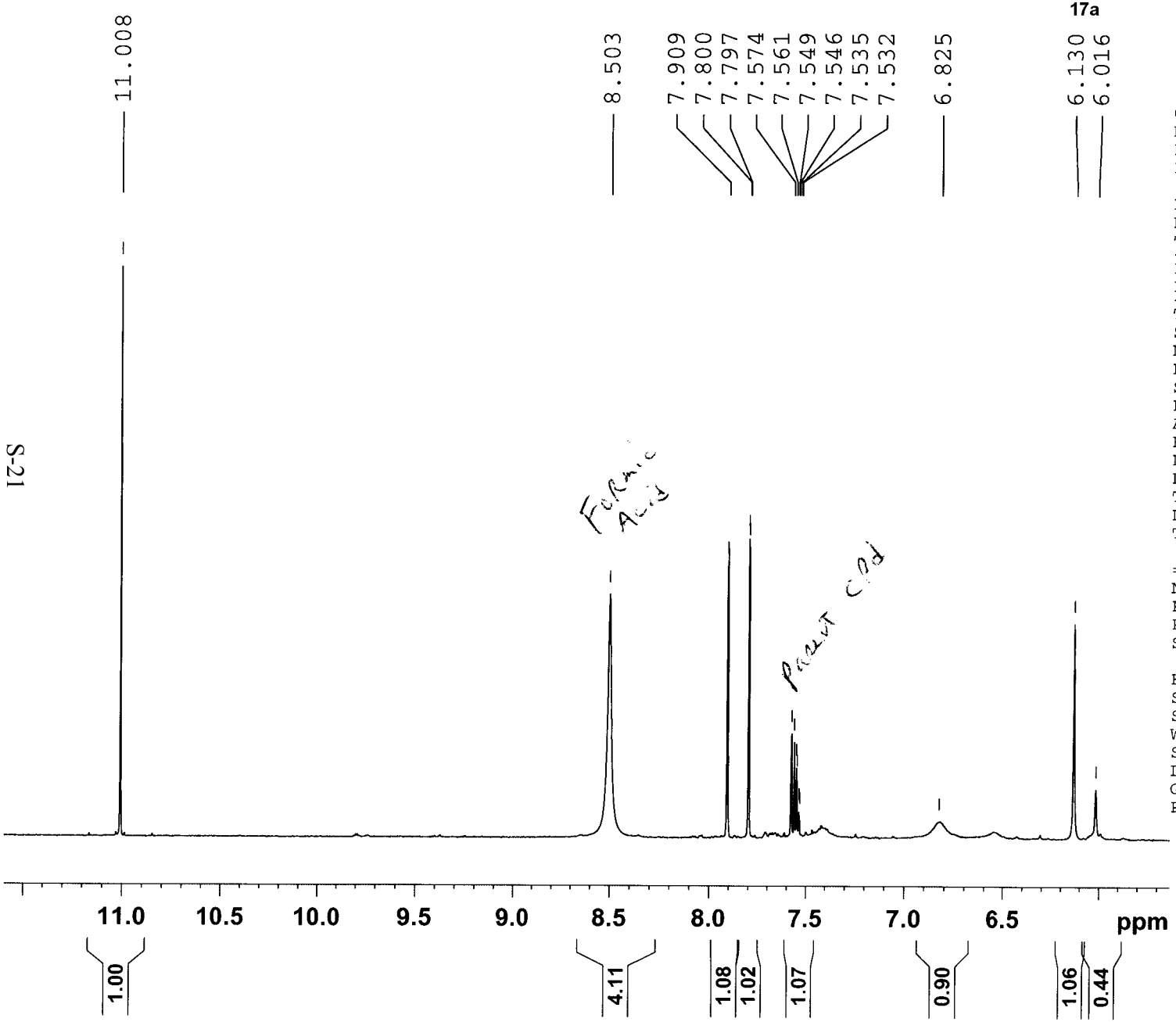


S-21

BRUKER

Current Data Parameters
NAME AR6965
EXPNO 1
PROCNO 1

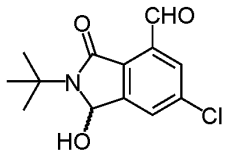
F2 - Acquisition Parameters
Date_ 20050919
Time 11.16
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6477449 sec
RG 256
DW 40.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 3.80 dB
SFO1 600.1337060 MHz

F2 - Processing parameters
SI 32768
SF 600.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SFS

Michal Achmatowitcz; AR6966; P38 2'nd Gen;57350-51-24
fraction 5



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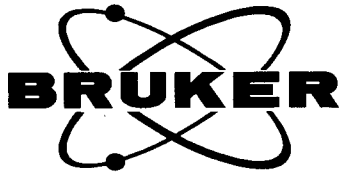
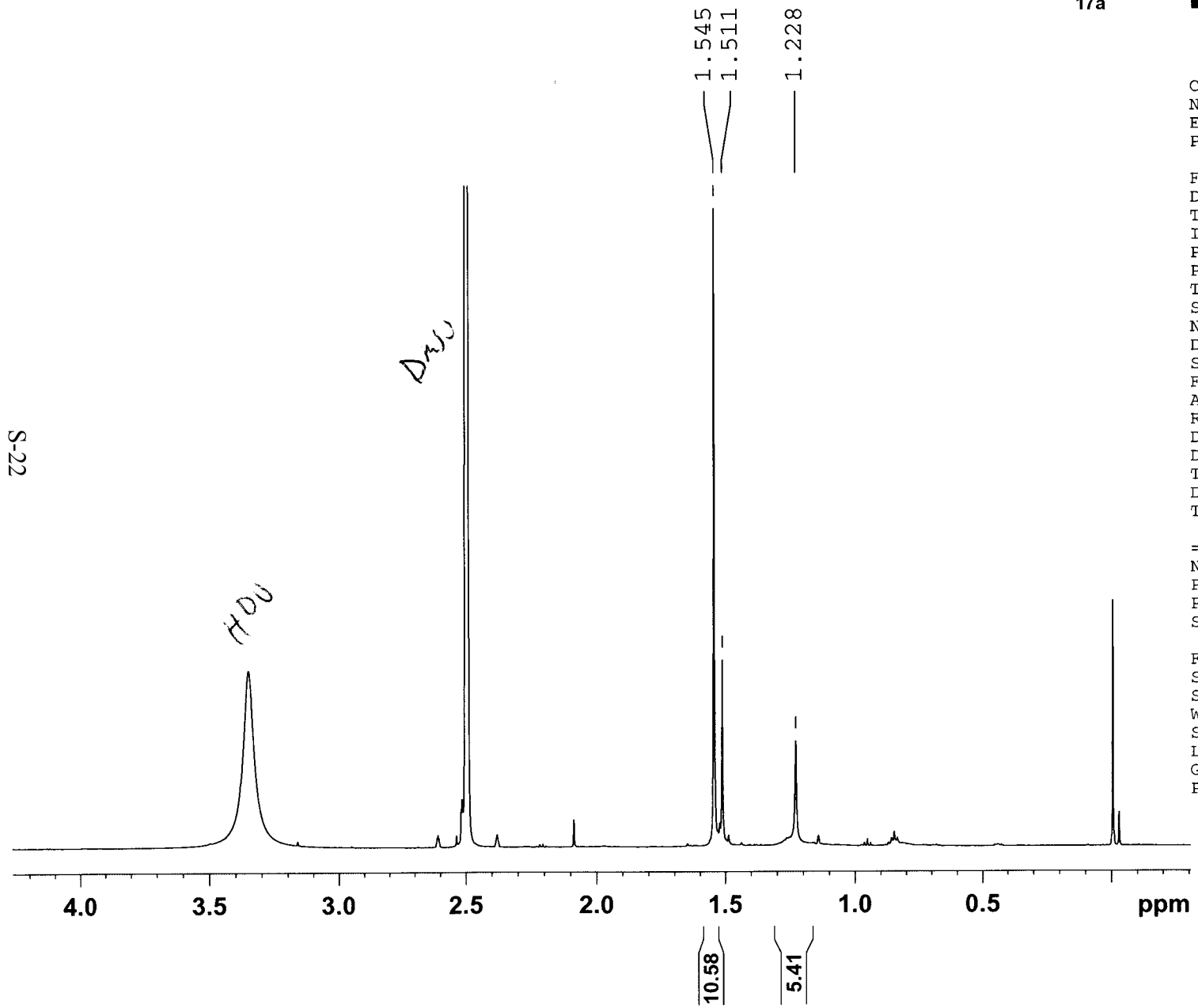




S-22

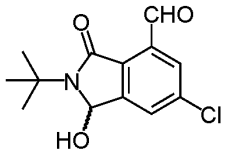
Current Data Parameters
NAME AR6965
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050919
Time 11.16
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6477449 sec
RG 256
DW 40.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 3.80 dB
SFO1 600.1337060 MHz

F2 - Processing parameters
SI 32768
SF 600.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Michal Achmatowitcz; AR6965; P38 2'nd Gen;57350-34-8
fraction 5



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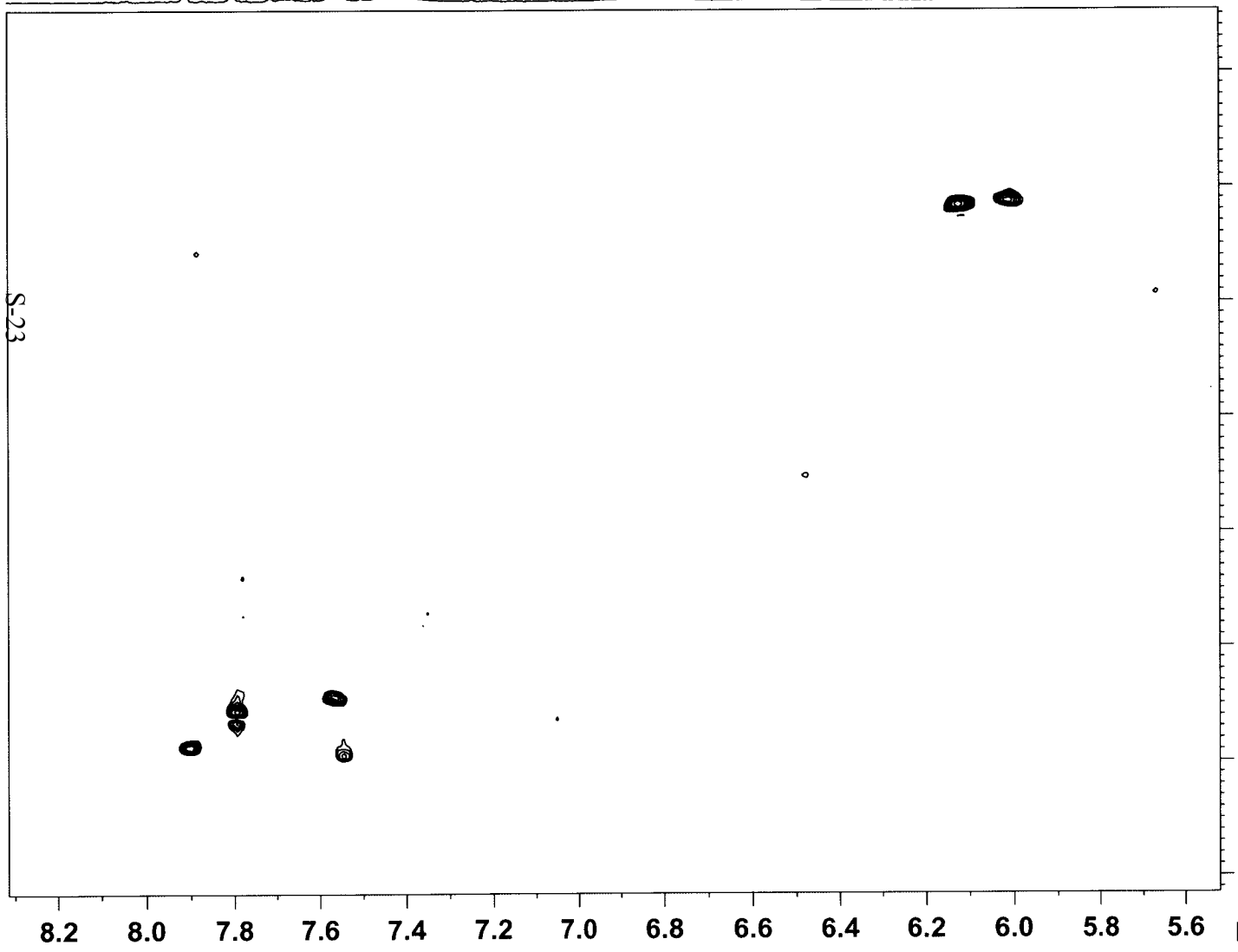
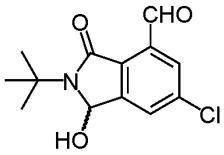


S-23

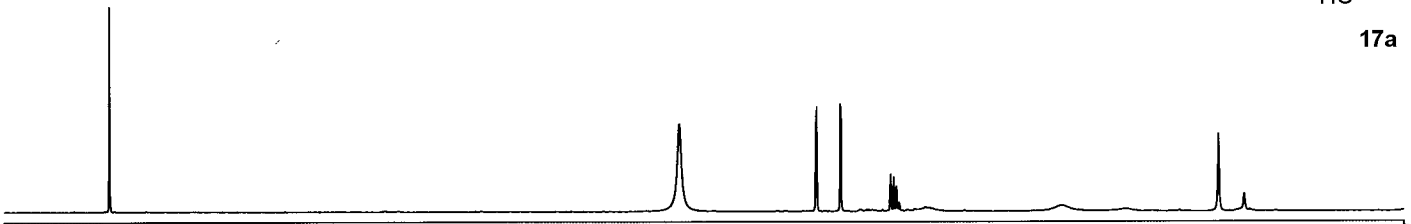
```
Current Data Parameters
NAME                  AR6965
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20050919
Time                  11.29
INSTRUM                spect
PROBHD    5 mm CPTCI 1H-
PULPROG        hsqcedetgp
TD                     1024
SOLVENT                DMSO
NS                        4
DS                       16
SWH                8012.820 Hz
FIDRES             7.825020 Hz
AQ                 0.0640100 sec
RG                     16384
DW                    62.400 usec
DE                     6.00 usec
TE                    300.0 K
CNST2            145.0000000
d0                 0.00000300 sec
D1                 1.50000000 sec
d4                 0.00172414 sec
d11                0.03000000 sec
d13                0.00000400 sec
D16                0.00020000 sec
D21                0.00345000 sec
DELTA              0.00222800 sec
DELTA1             0.00071614 sec
IN0                0.00002000 sec
ST1CNT                   128
ZGOPTNS

======== CHANNEL f1 ========
NUC1                      1H
P1                     8.00 usec
p2                    16.00 usec
P28                   50.00 usec
PL1                    3.80 dB
SFO1            600.1336080 MHz

======== CHANNEL f2 ========
CPDPRG2                garp
NUC2                    13C
P3                    15.00 usec
p4                    30.00 usec
PCPD2                 55.00 usec
PL2                   -2.00 dB
PL12                   9.00 dB
SFO2            150.9140640 MHz

====== GRADIENT CHANNEL =====
GPNAM1             SINE.100
GPNAM2             SINE.100
GPZ1                  80.00 %
GPZ2                  20.10 %
P16                 1000.00 usec

F1 - Acquisition parameters
ND0                        2
TD                       200
SFO1               150.9141 MHz
FIDRES          125.000000 Hz
SW                 165.657 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                      1024
SF              600.1300000 MHz
WDW                    QSINE
SSB                        2
LB                      0.00 Hz
GB                         0
PC                      1.00

F1 - Processing parameters
SI                      1024
MC2          echo-antiecho
SF              150.9028090 MHz
WDW                    QSINE
SSB                        2
LB                      0.00 Hz
GB                         0
```

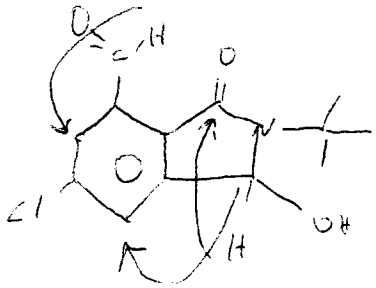
Michal Achmatowitcz; AR6966; P38 2nd Gen; 57350-51-24; fraction 5

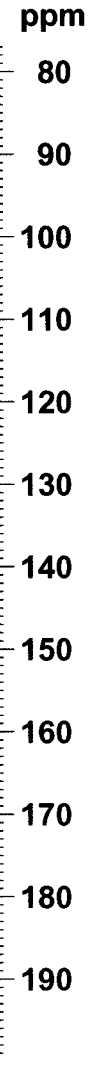


17a

BRUKER

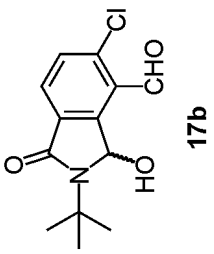






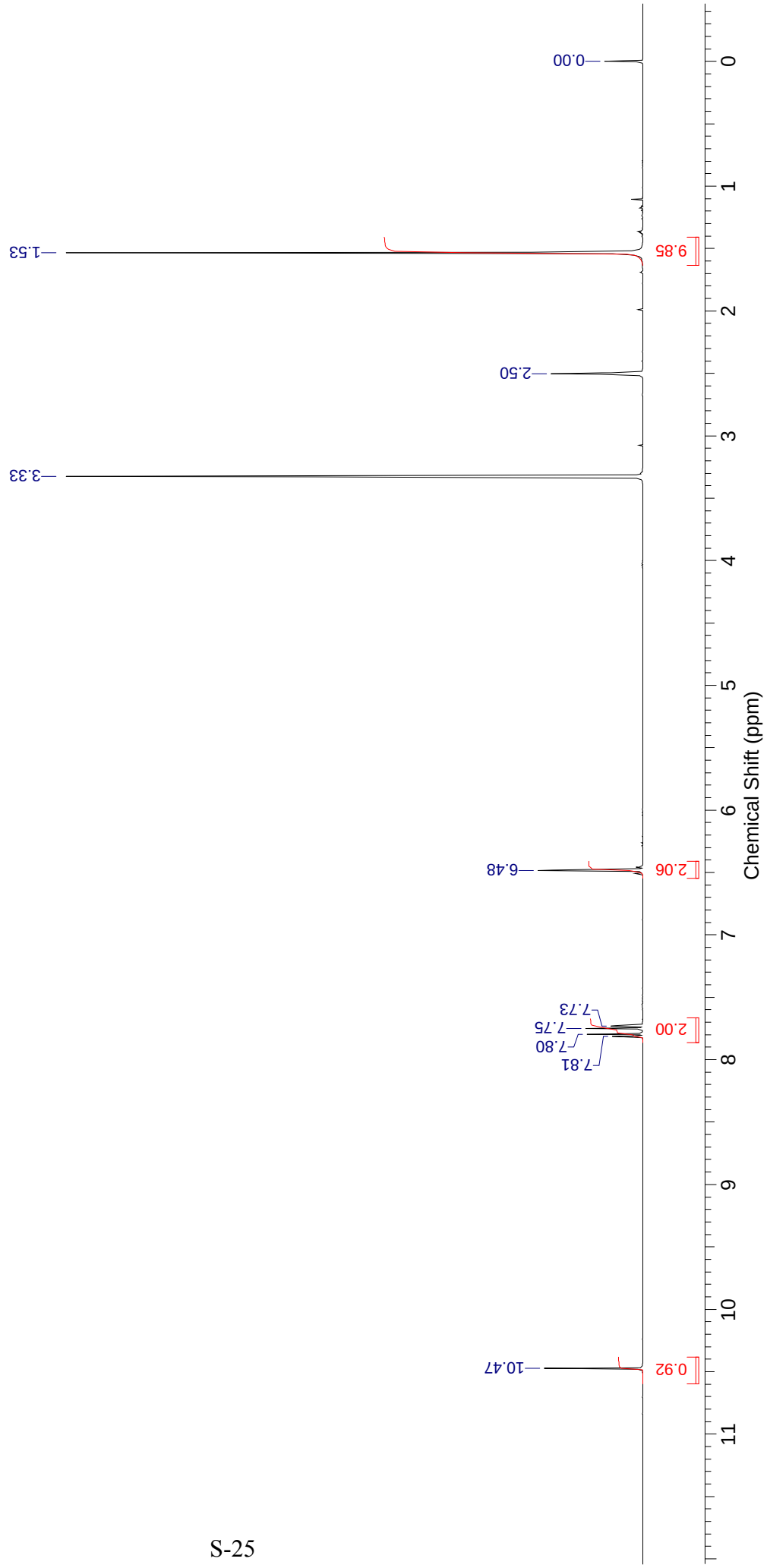

```
Current Data Parameters
NAME                  AR6965
EXPNO                      3
PROCNO                     1

F2 - Acquisition Parameters
Date_              20050919
Time                  11.51
INSTRUM               spect
PROBHD   5 mm CPTCI 1H-
PULPROG          hmbcgpndqf
TD                      4096
SOLVENT                 DMSO
NS                        32
DS                        16
SWH                 8012.820 Hz
FIDRES              1.956255 Hz
AQ                  0.2557028 sec
RG                      16384
DW                     62.400 usec
DE                      6.00 usec
TE                     300.0 K
CNST13              8.0000000
d0                  0.00000300 sec
D1                  1.20000005 sec
d6                  0.06250000 sec
D16                 0.00020000 sec
IN0                 0.00001490 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                      8.00 usec
p2                     16.00 usec
PL1                     3.80 dB
SFO1            600.1336080 MHz

======== CHANNEL f2 ========
NUC2                     13C
P3                     15.00 usec
PL2                    -2.00 dB
SFO2            150.9178750 MHz

====== GRADIENT CHANNEL =====
GPNAM1               SINE.100
GPNAM2               SINE.100
GPNAM3               SINE.100
GPZ1                   50.00 %
GPZ2                   30.00 %
GPZ3                   40.10 %
P16                  1000.00 usec

F1 - Acquisition parameters
ND0                        2
TD                       214
SFO1            150.9179 MHz
FIDRES          156.808624 Hz
SW                 222.353 ppm
FnMODE                    QF

F2 - Processing parameters
SI                      1024
SF            600.1300000 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2                       QF
SF            150.9028090 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
```

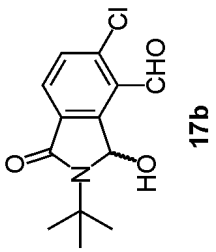
SFJ



17b

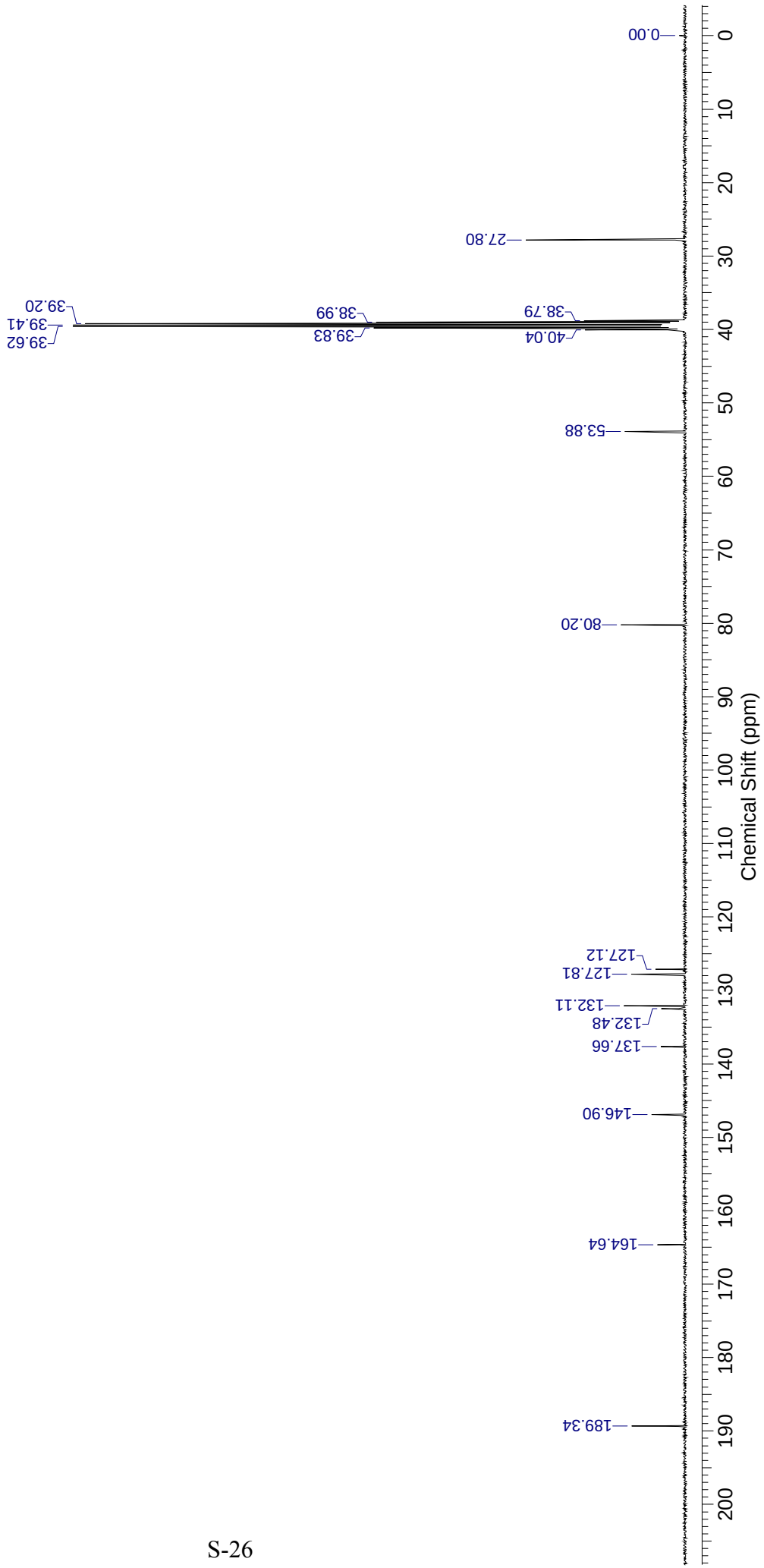
Acquisition Time (sec)	1.9924	***Comment***	michala
Date	13 Aug 2008 00:06:24		
File Name	\\Scone\NMR-Archive\data\michala\nmr\88628-41-75\88628-41-75_010000fid		
Frequency (MHz)	400.16	***Nucleus***	1H
Number of Transients	64	***Origin***	spect
Original Points Count	16384	***Owner***	smallmolecules
Points Count	16384	***Pulse Sequence***	zg30
Receiver Gain	322.00	***SW(cyclical) (Hz)***	8223.68
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2470.2676
Sweep Width (Hz)	8223.18	***Temperature (degree C)***	27.000



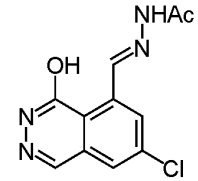


17b

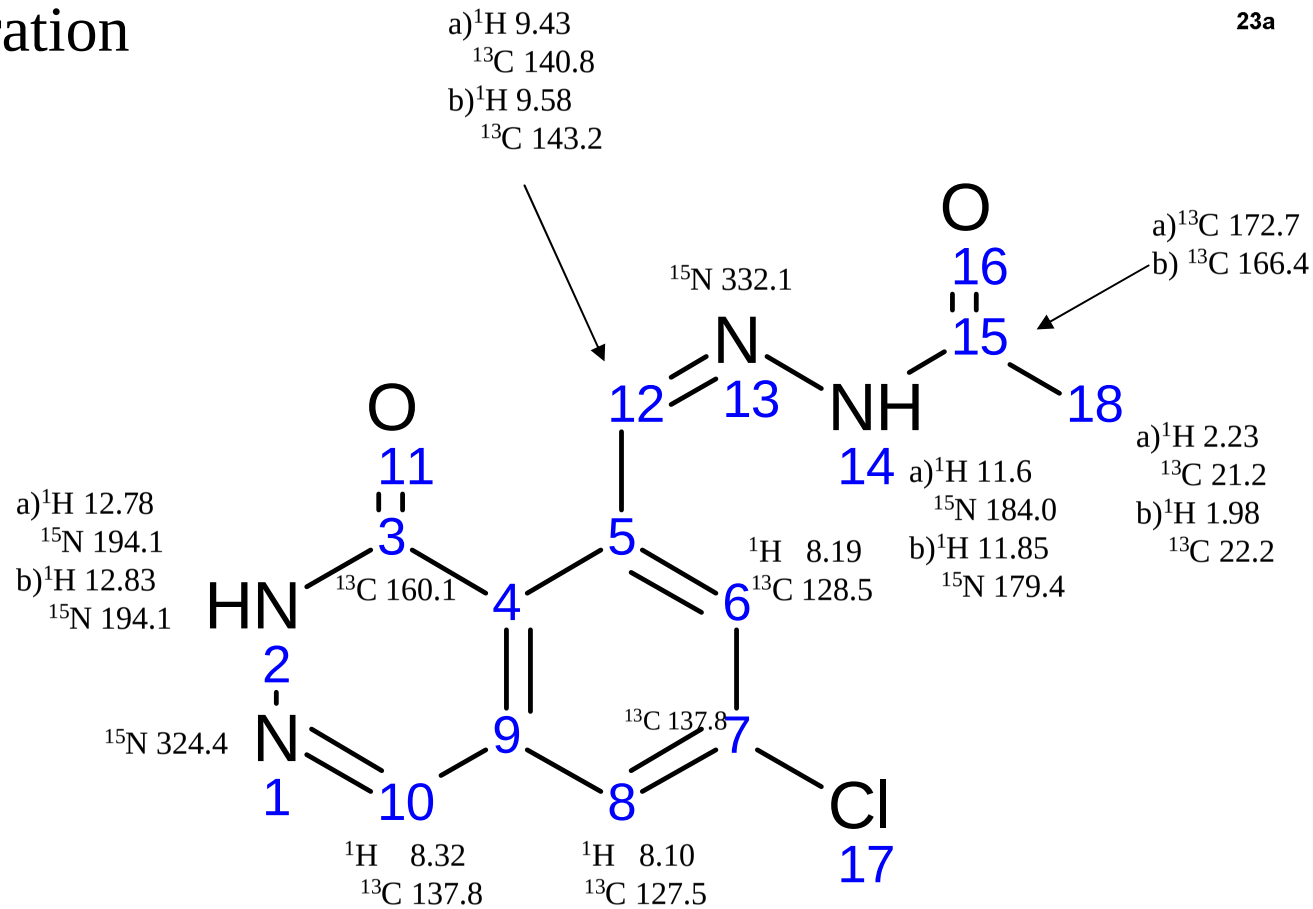
Acquisition Time (sec)	1.1535	***Comment***	michala
Date	13 Aug 2008 07:20:02		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-41-75_11.dx		
Frequency (MHz)	100.63	***Nucleus***	13C
Number of Transients	4096	***Origin***	Bruker BioSpin GmbH
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12016.7305
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	24.900



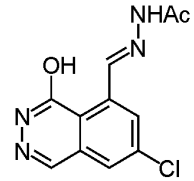
AR6965
Michal Achmatowicz
P38 2'nd Generation
57350-34-8
DMSO



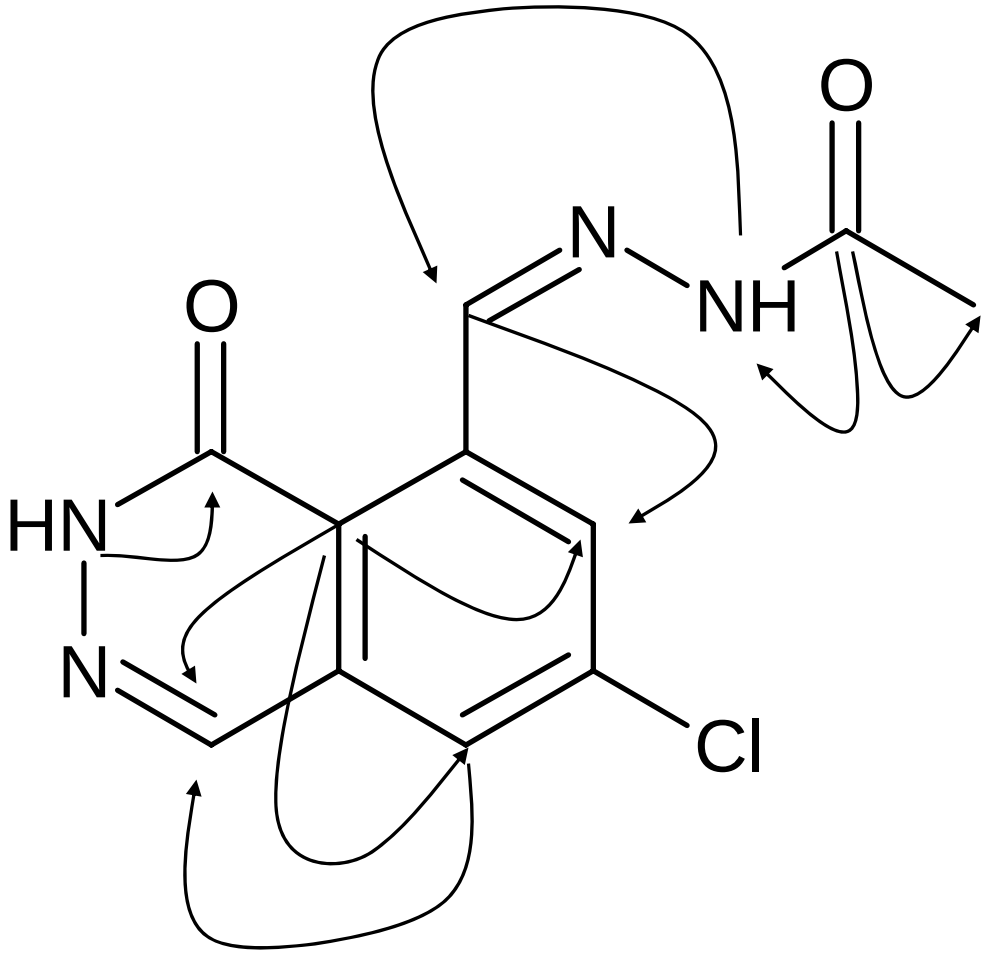
23a



*note-two rotamers exist at 25 C. The assignments of each rotamer are designated a and b respectively.

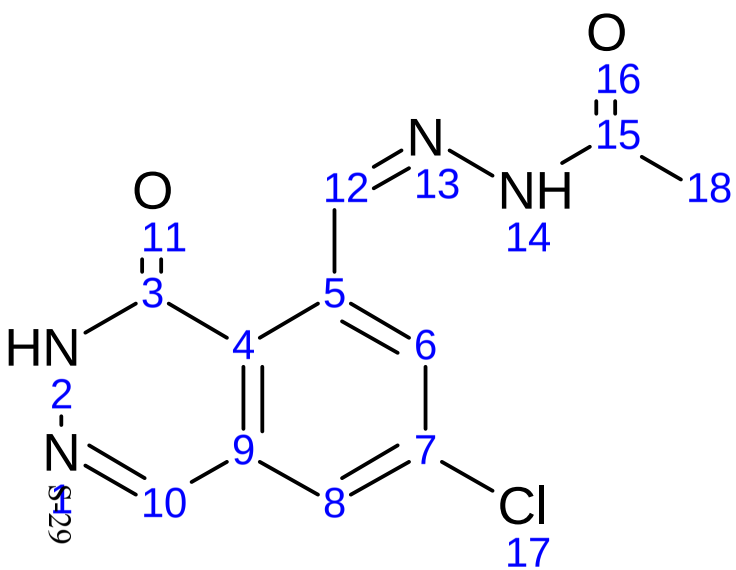


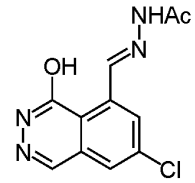
23a



HMBC (^{1}H-^{13}C 2 and 3 bond correlations)

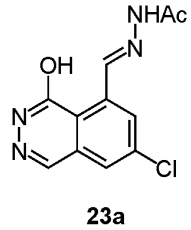
^{1}H spectrum 25 C



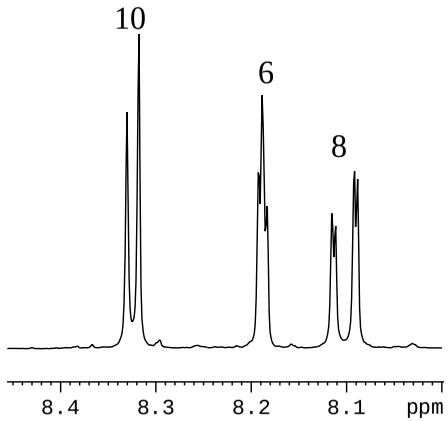


23a

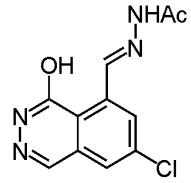
^{1}H spectrum 25 C



23a



^{1}H spectrum 25 C



23a

18 a

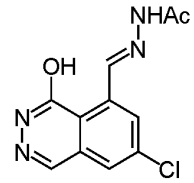
18 b

4.0 3.5 3.0 2.5 2.0 1.5 ppm

3.23

0.51

^{1}H spectrum 25 C and 77 C



23a

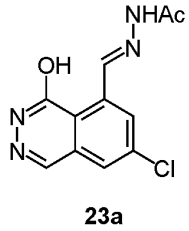
77 C

25 C

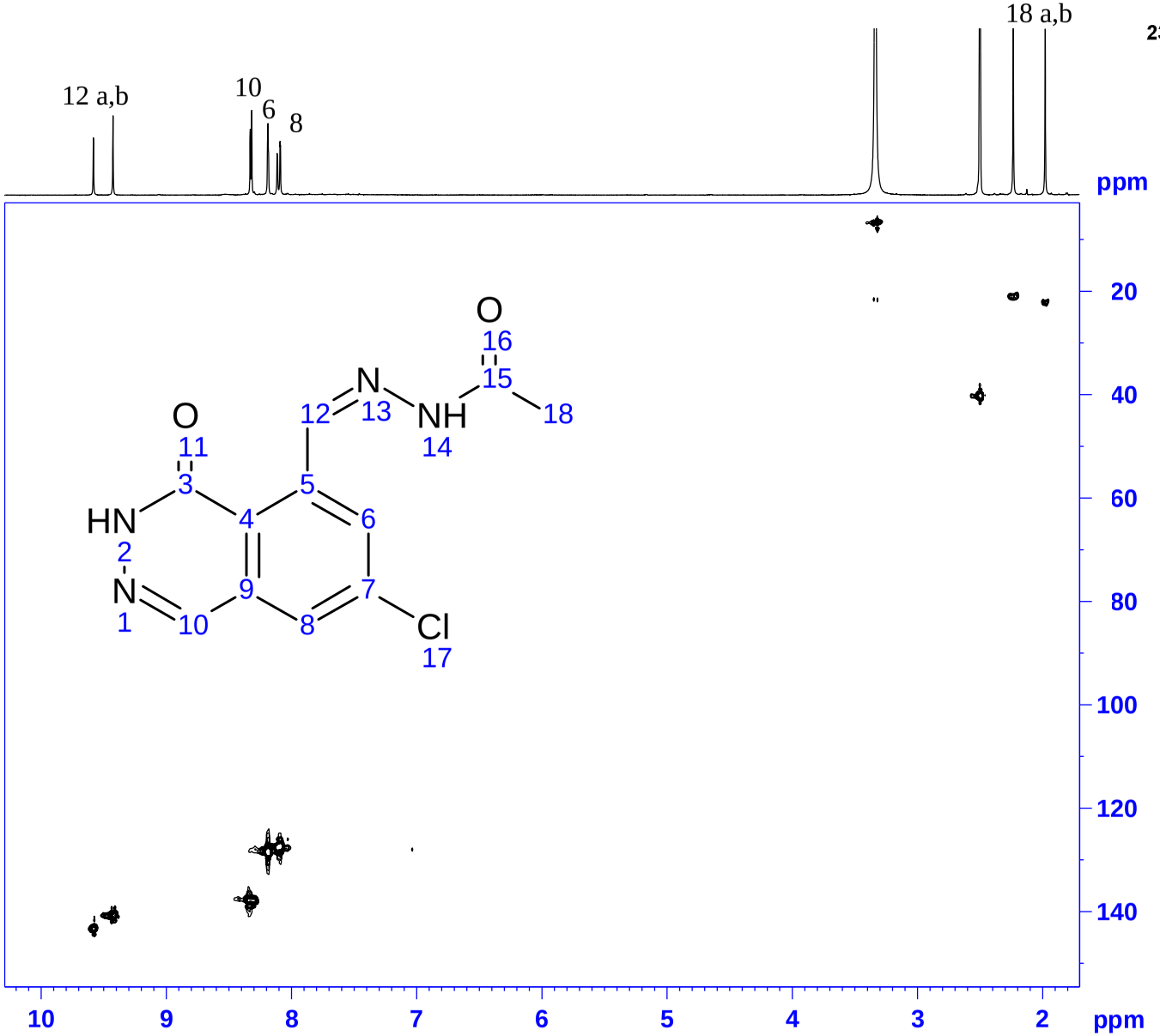
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 ppm

1.00 0.95 0.98 1.08 1.03 1.07

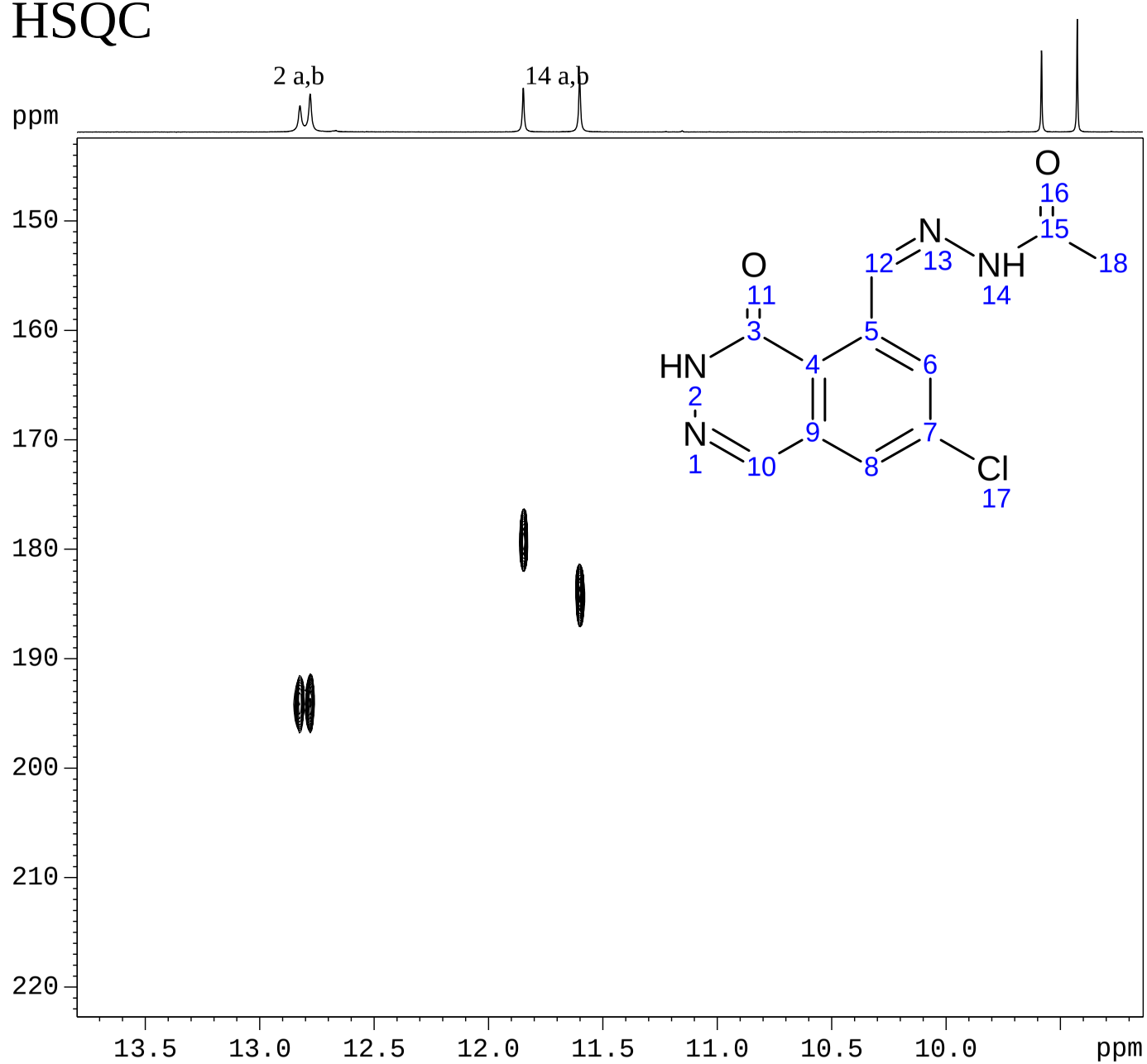
^{1}H-^{13}C HSQC

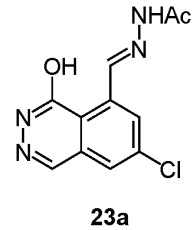


23a



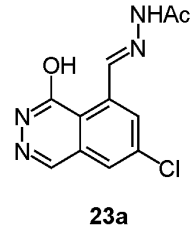
^{1}H-^{15}N HSQC





23a

^{1}H-^{13}C HMBC



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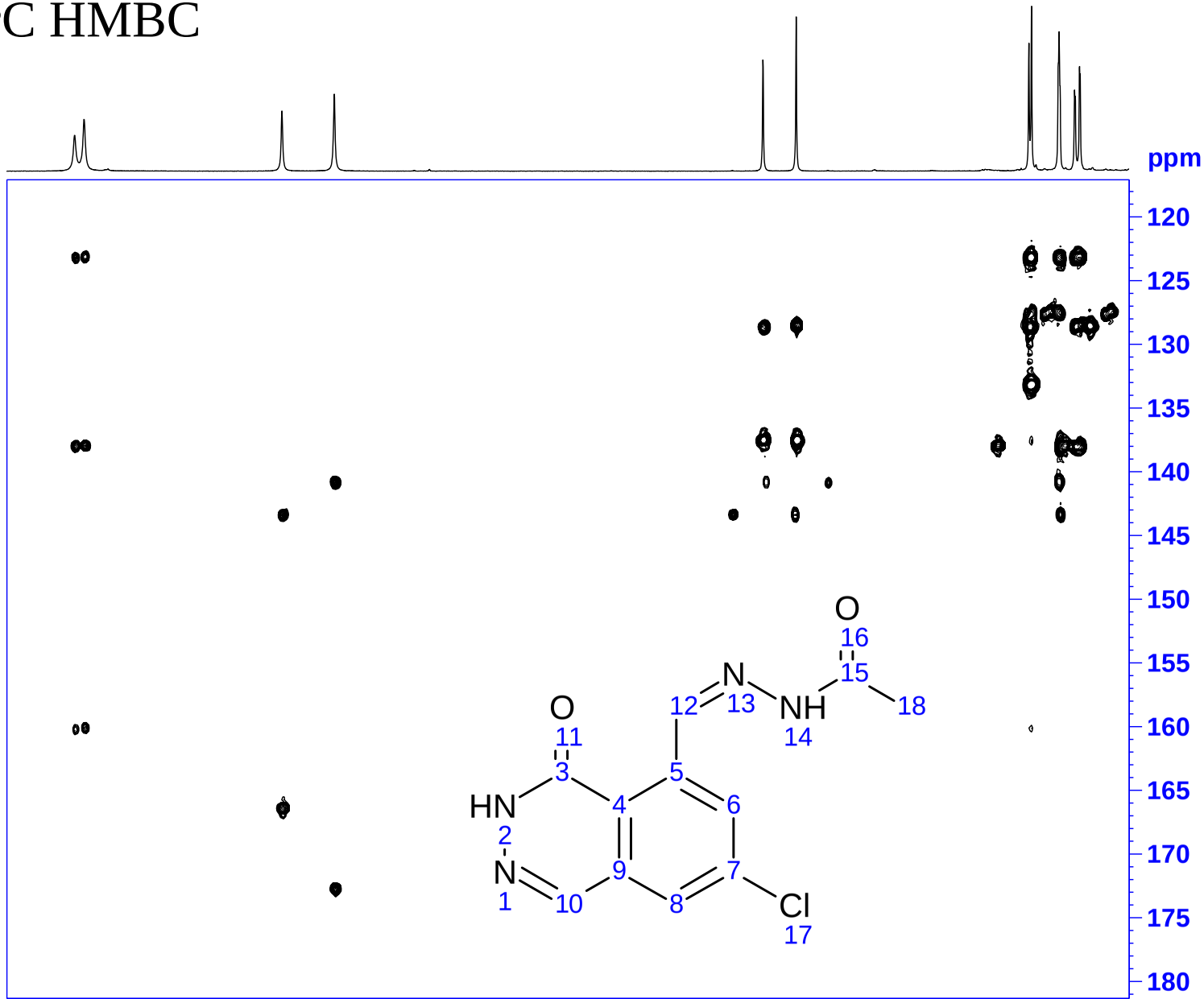
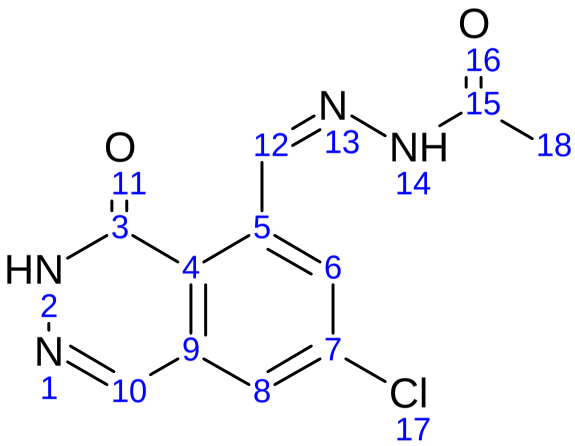
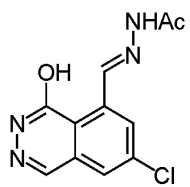


^{1}H-^{1}H NOESY



-Red crosspeaks are due to chemical exchange whereas black crosspeaks are due to protons that are spatially close (NOES)



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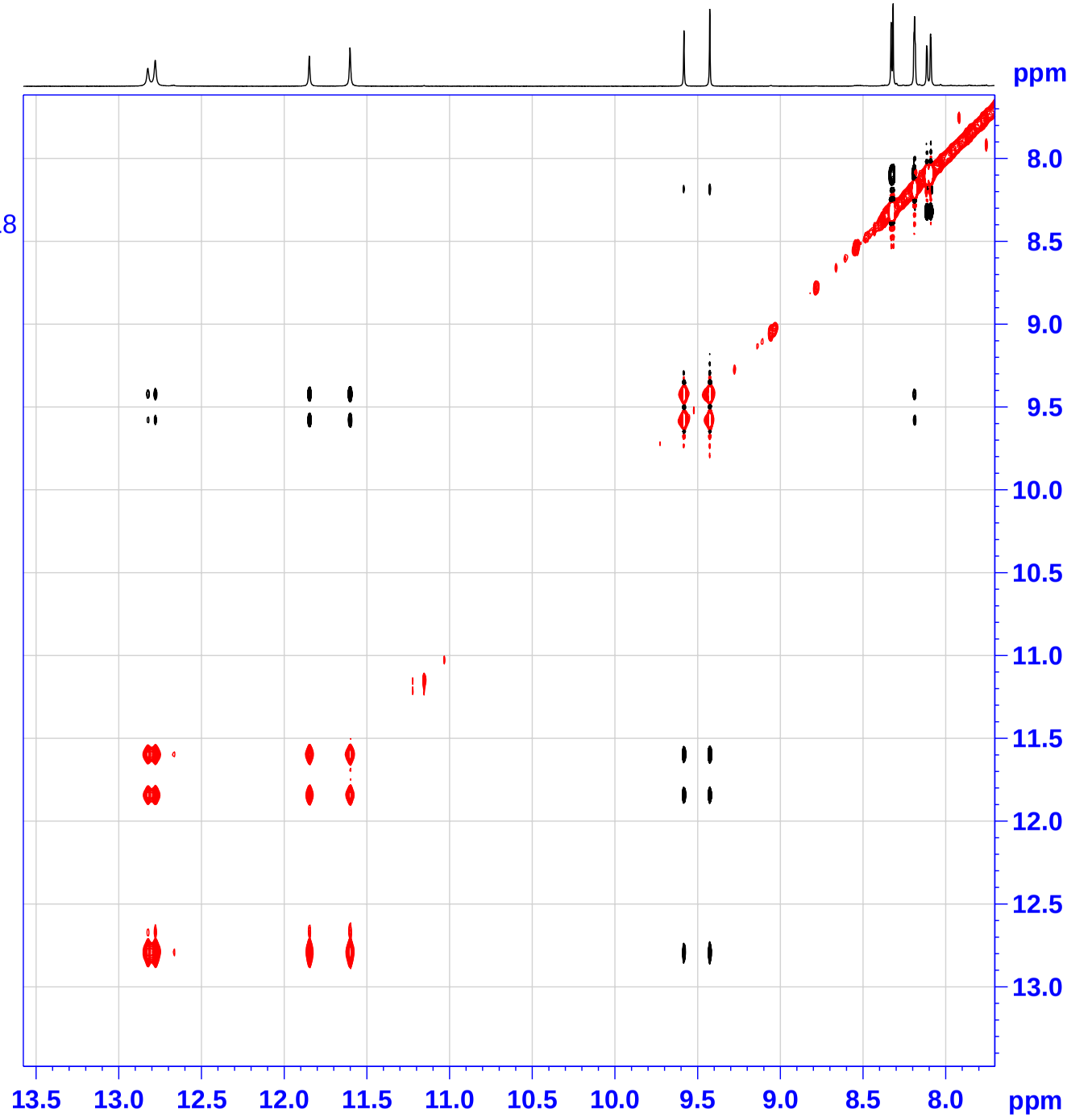
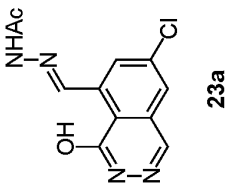
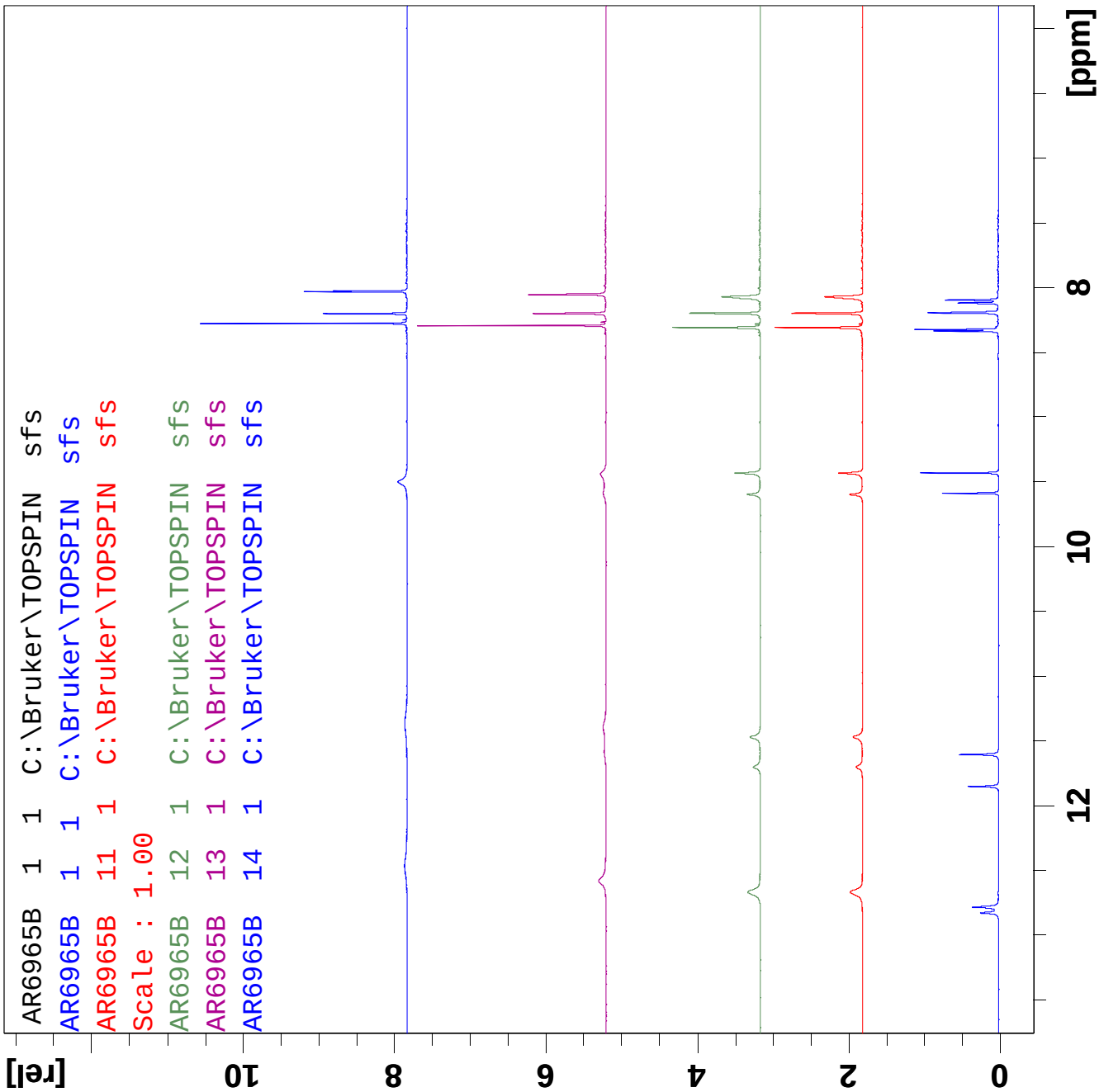



NHAc
N
Cl
OH
N
N

23a


AR6965B 1 1 C:\Bruker\TOPSPIN sfs
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Scale : 1.00
AR6965B 12 1 C:\Bruker\TOPSPIN sfs
AR6965B 13 1 C:\Bruker\TOPSPIN sfs
AR6965B 14 1 C:\Bruker\TOPSPIN sfs
[rel]
10
8
6
4
2
0
12
10
8
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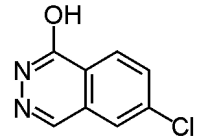
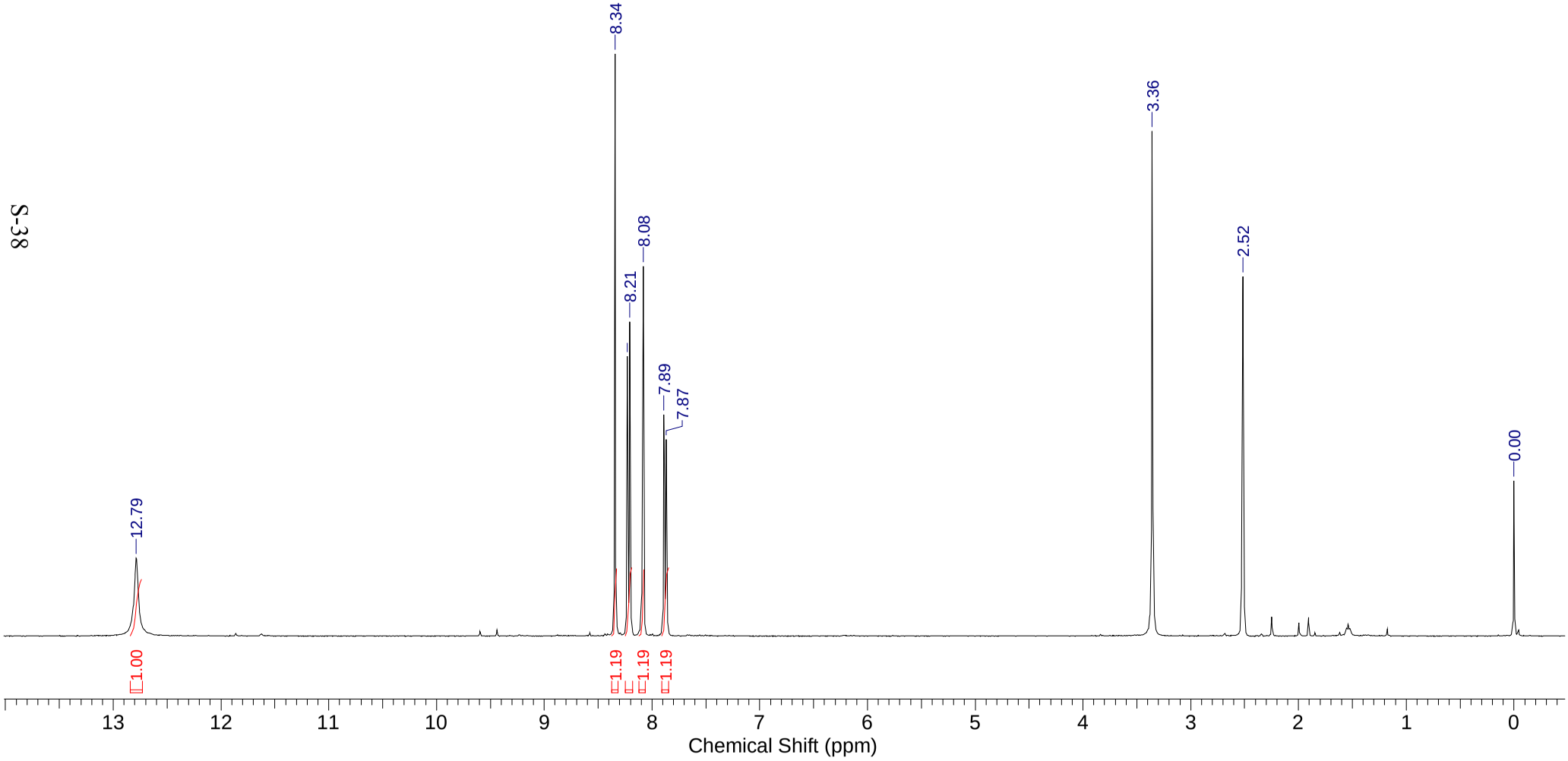
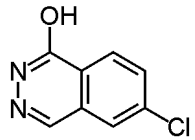
Acquisition Time (sec)	1.9924	***Comment***	michala
Date	15 Mar 2008 01:22:57		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-5188_10.dx		
Frequency (MHz)	400.16	***Nucleus***	1H
Number of Transients	16	***Origin***	Bruker BioSpin GmbH
Original Points Count	16384	***Owner***	smallmolecules
Points Count	16384	***SW(cyclical) (Hz)***	8223.68
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2475.6719
Sweep Width (Hz)	8223.18	***Temperature (degree C)***	27.000



24



Acquisition Time (sec)	1.1535	***Comment***	michala
Date	15 Mar 2008 01:58:02		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-5188_11.dx		
Frequency (MHz)	100.63	***Nucleus***	13C
Number of Transients	512	***Origin***	Bruker BioSpin GmbH
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12018.4639
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	23.900



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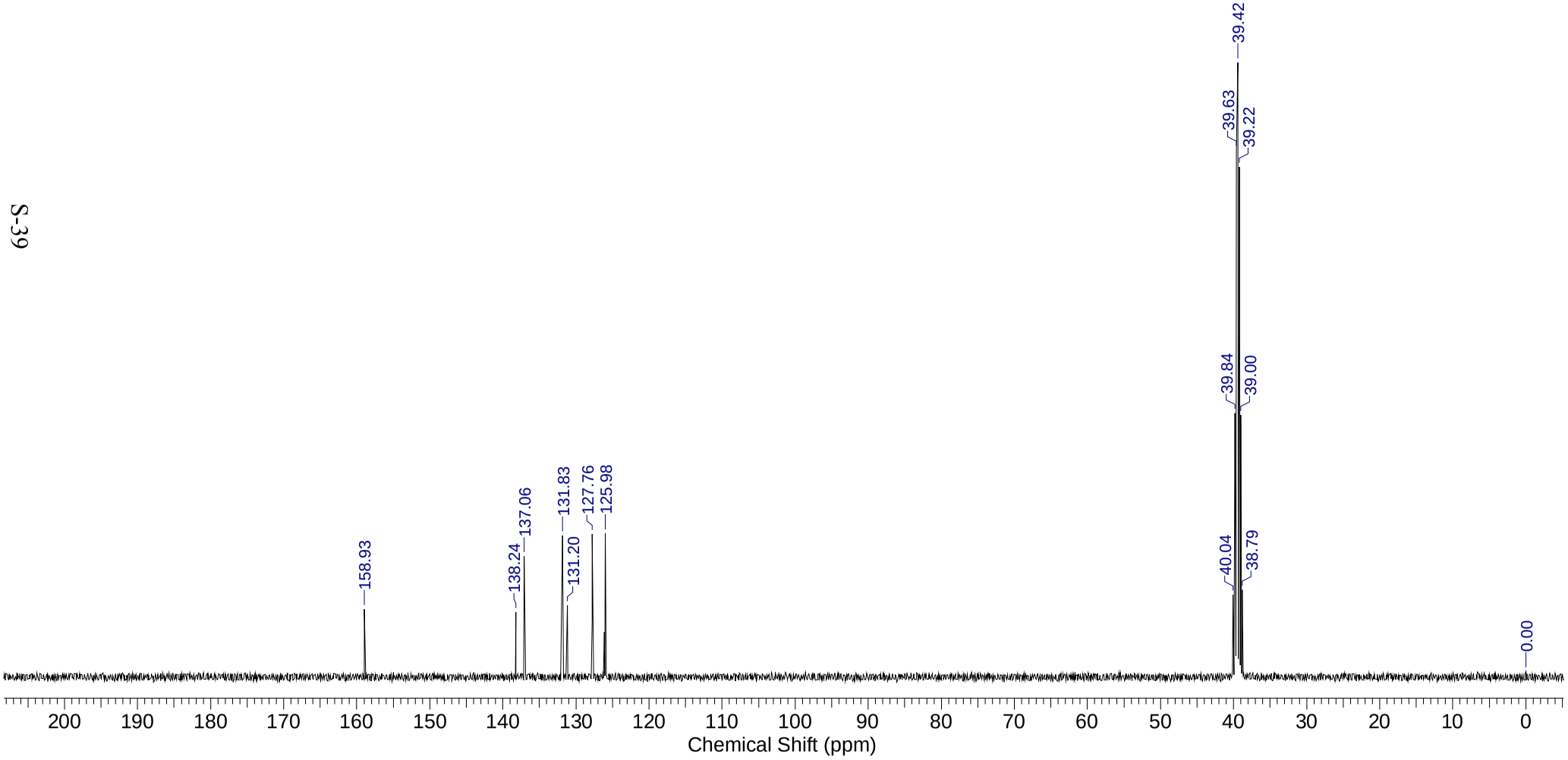

Acquisition Time (sec)	5.1120	***Comment***	othiel
Date	15 Aug 2008 23:42:56		
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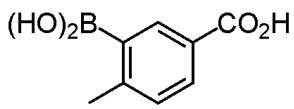
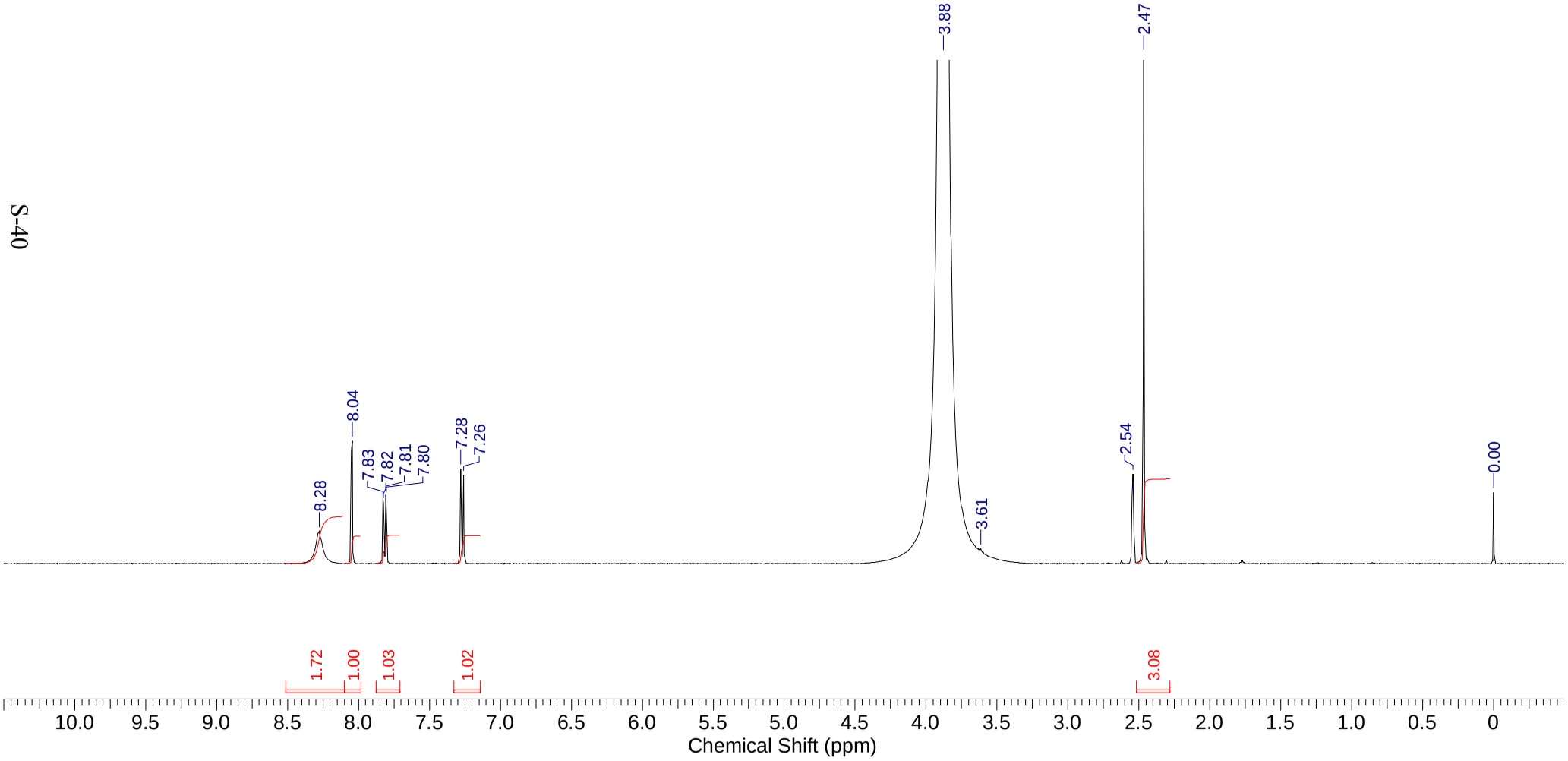
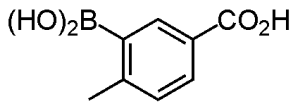
Frequency (MHz)	400.23	***Nucleus***	1H
Number of Transients	32	***Origin***	spect
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***Pulse Sequence***	zg30
Receiver Gain	16.00	***SW(cyclical) (Hz)***	6410.26
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2419.1577
Sweep Width (Hz)	6410.06	***Temperature (degree C)***	27.000



27



Acquisition Time (sec)	1.1535	***Comment***	othiel
Date	16 Aug 2008 06:04:48		
File Name	\\Scone\NMR-Archive\data\othiel\nmr\63529-52-02\63529-52-02_012000fid		
Frequency (MHz)	100.65	***Nucleus***	13C
Number of Transients	4096	***Origin***	spect
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***Pulse Sequence***	zgpg30
Receiver Gain	1290.00	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12025.4004
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	27.000



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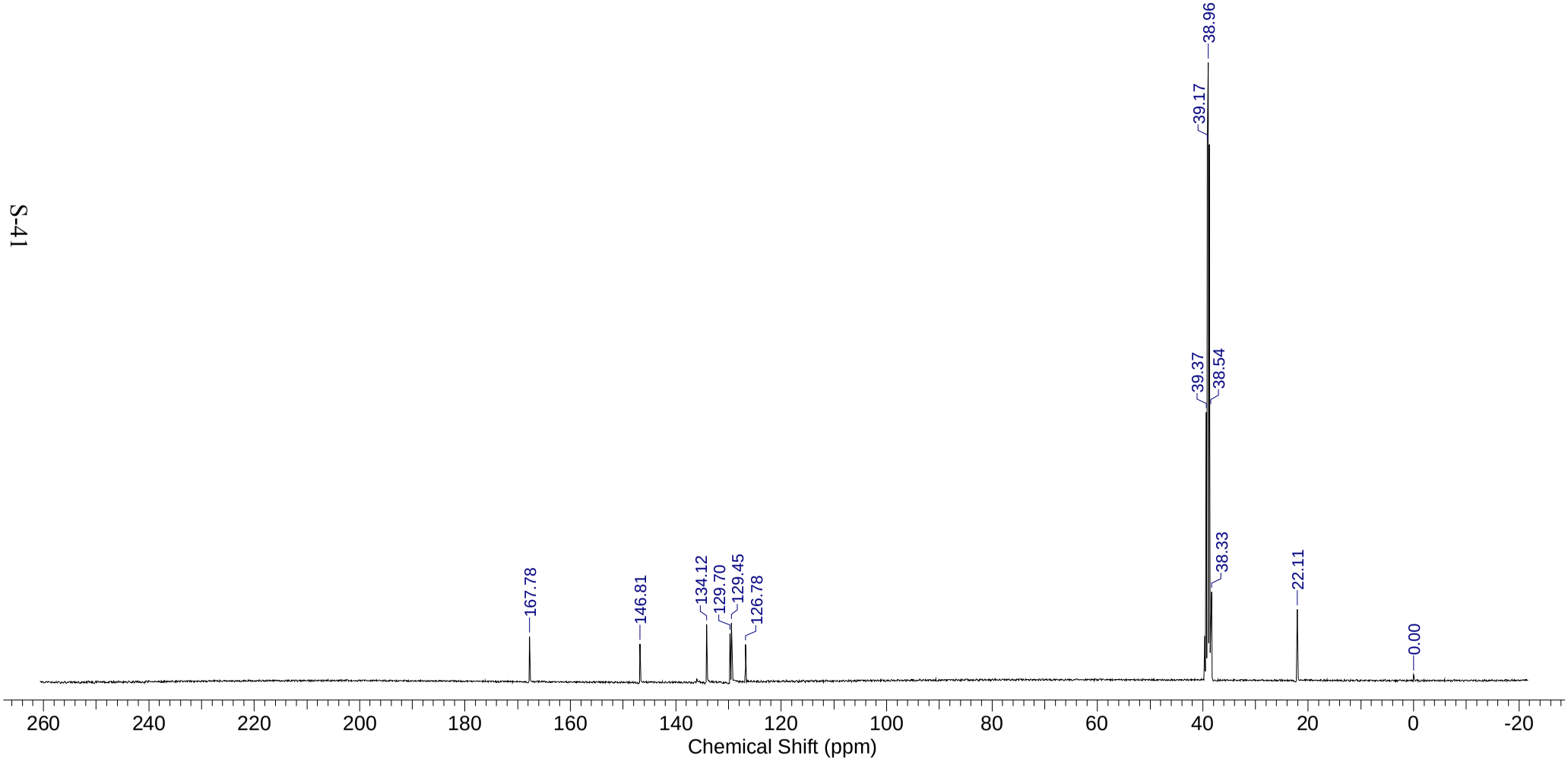
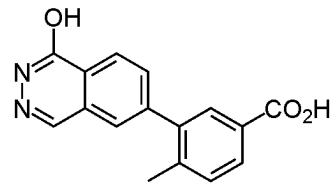


Acquisition Time (sec)	1.9924	***Comment***	michala
Date	12 Jun 2008 17:23:26		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-2_10.dx		
Frequency (MHz)	400.16	***Nucleus***	1H
Number of Transients	64	***Origin***	Bruker BioSpin GmbH
Original Points Count	16384	***Owner***	smallmolecules
Points Count	16384	***SW(cyclical) (Hz)***	8223.68
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2472.9878
Sweep Width (Hz)	8223.18	***Temperature (degree C)***	27.000



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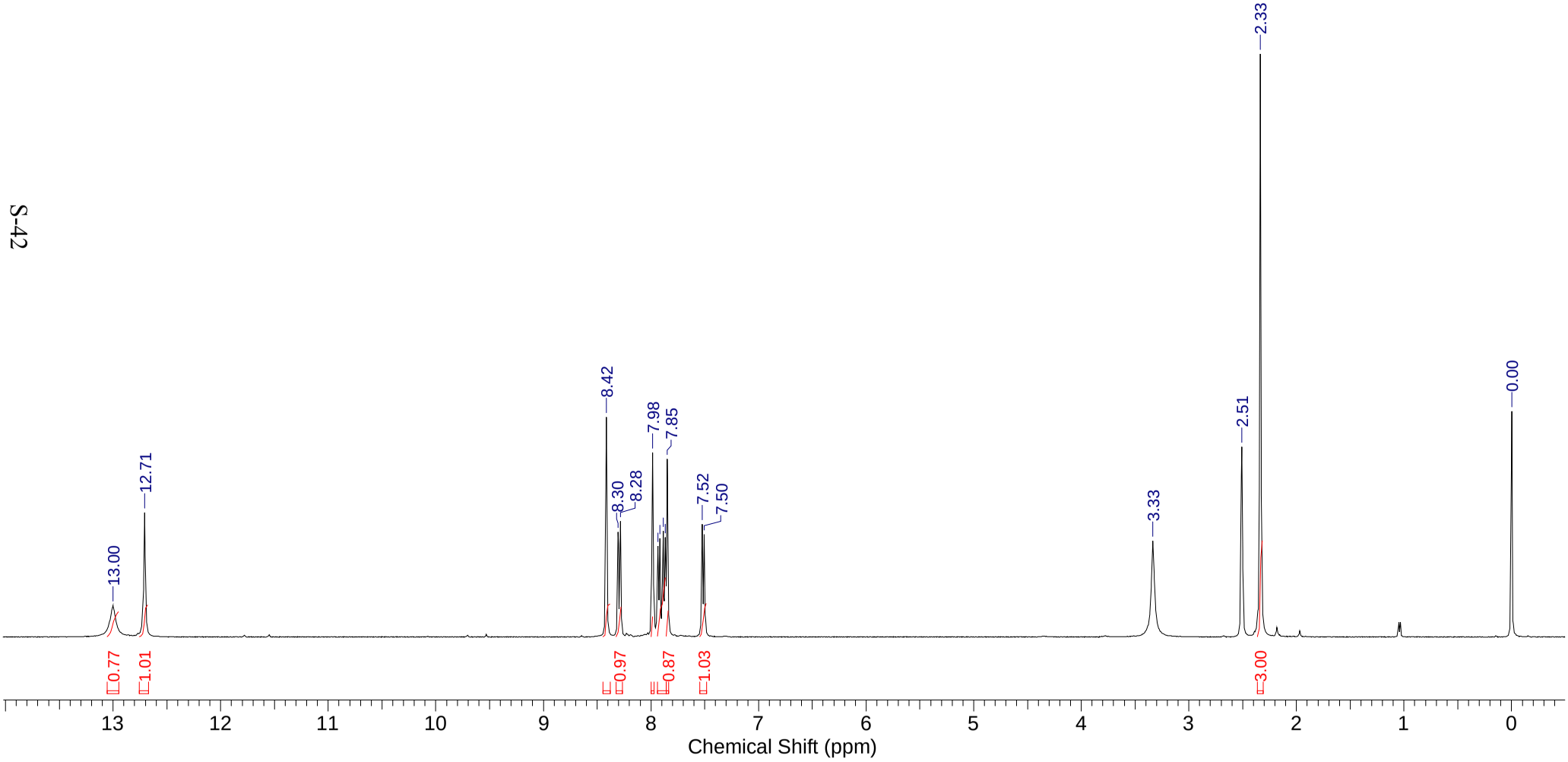
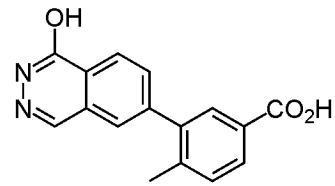


Acquisition Time (sec)	1.1535	***Comment***	michala
Date	15 Mar 2008 19:09:41		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-9238_11.dx		
Frequency (MHz)	100.63	***Nucleus***	13C
Number of Transients	4096	***Origin***	Bruker BioSpin GmbH
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12017.5967
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	23.500



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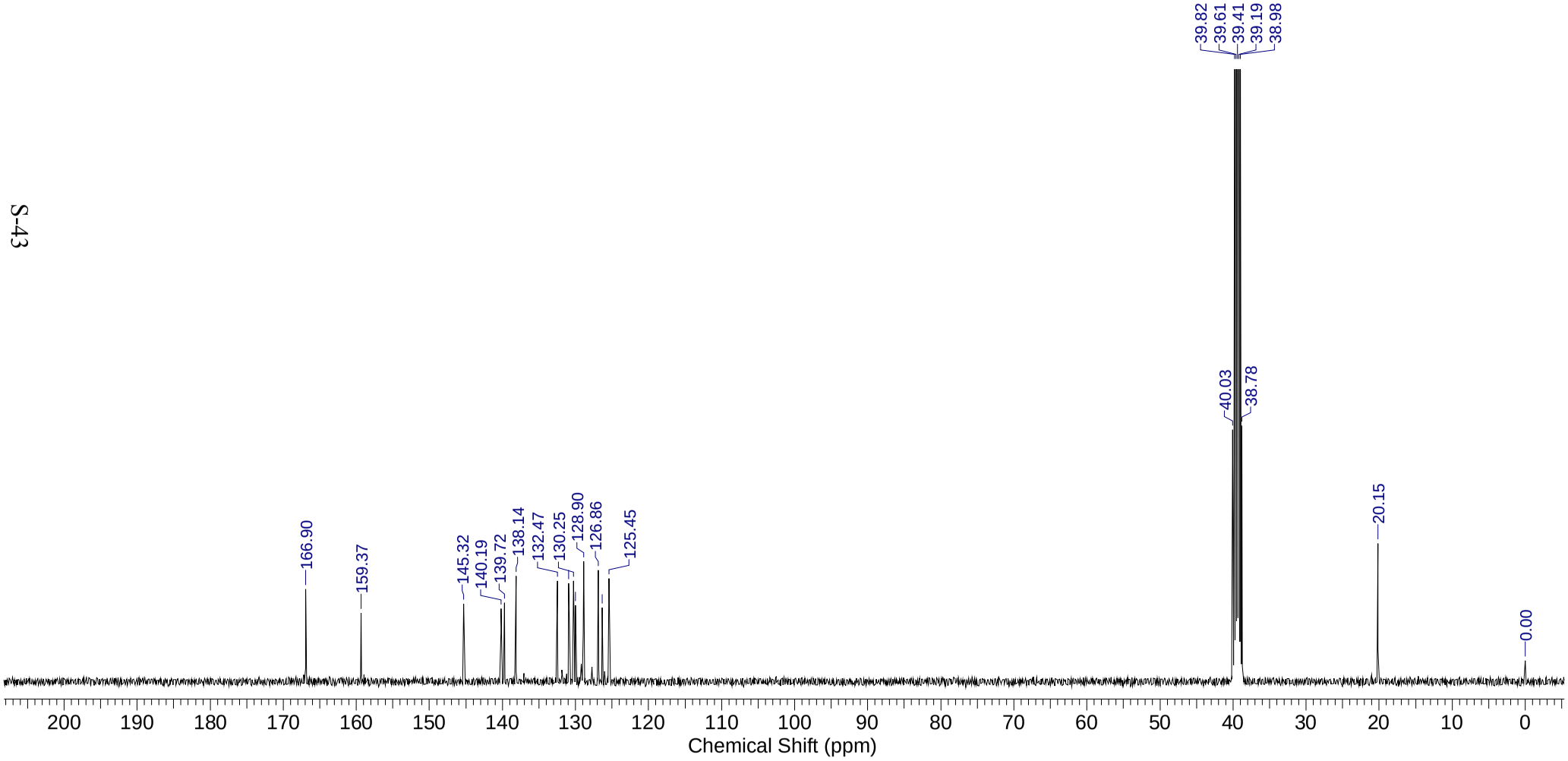
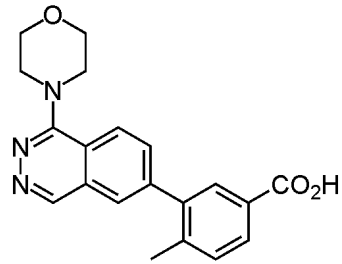


Acquisition Time (sec)	1.9924	***Comment***	michala
Date	15 Mar 2008 03:07:51		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-5154_10.dx		
Frequency (MHz)	400.16	***Nucleus***	1H
Number of Transients	16	***Origin***	Bruker BioSpin GmbH
Original Points Count	16384	***Owner***	smallmolecules
Points Count	16384	***SW(cyclical) (Hz)***	8223.68
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2478.4214
Sweep Width (Hz)	8223.18	***Temperature (degree C)***	27.000



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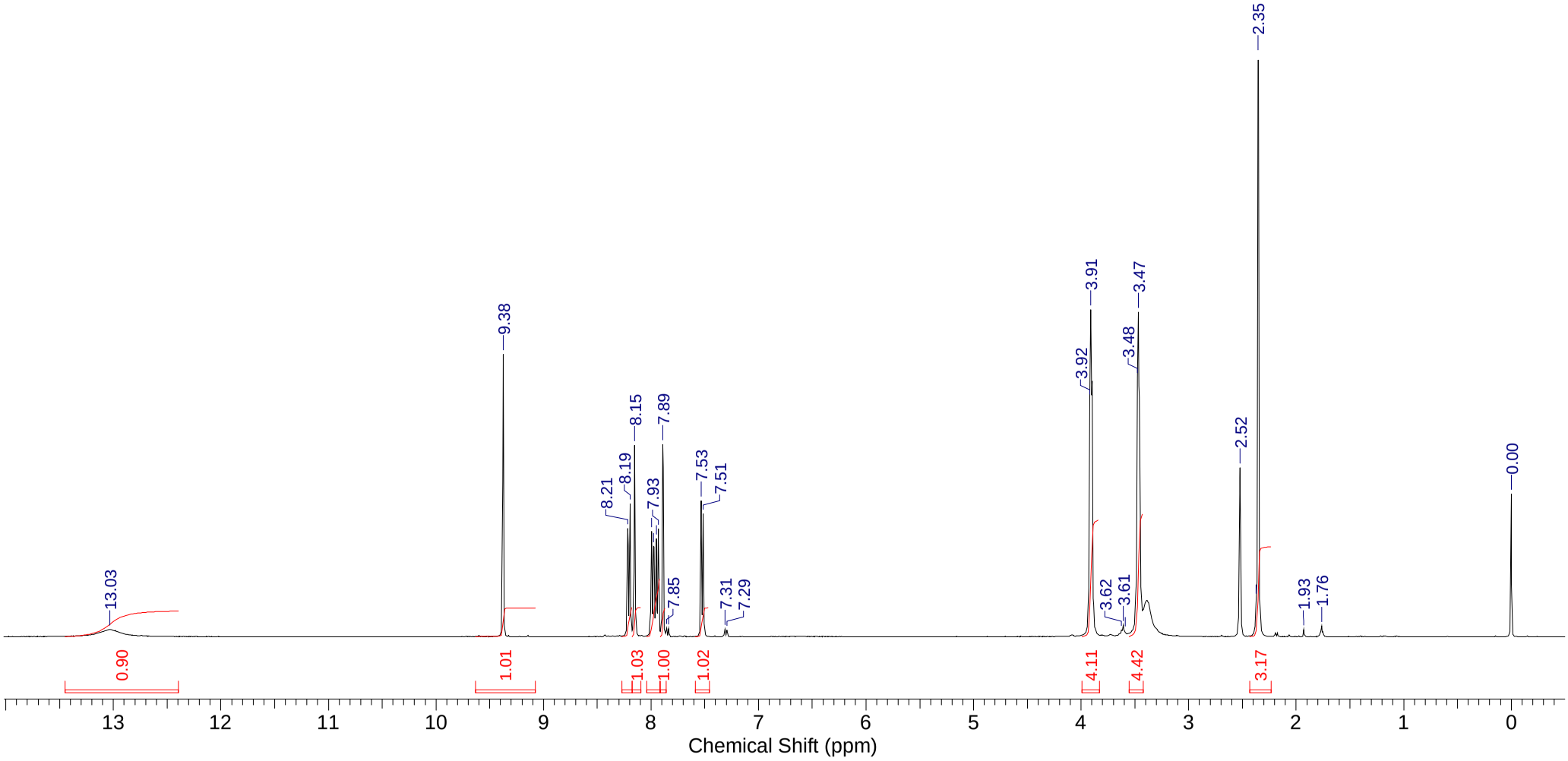
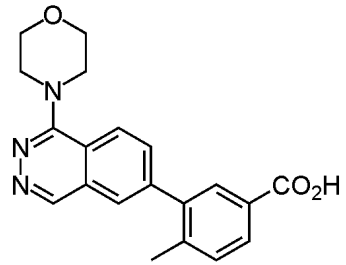


Acquisition Time (sec)	1.1535	***Comment***	michala
Date	15 Mar 2008 03:34:28		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-5154_11.dx		
Frequency (MHz)	100.63	***Nucleus***	13C
Number of Transients	512	***Origin***	Bruker BioSpin GmbH
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12020.1982
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	27.000



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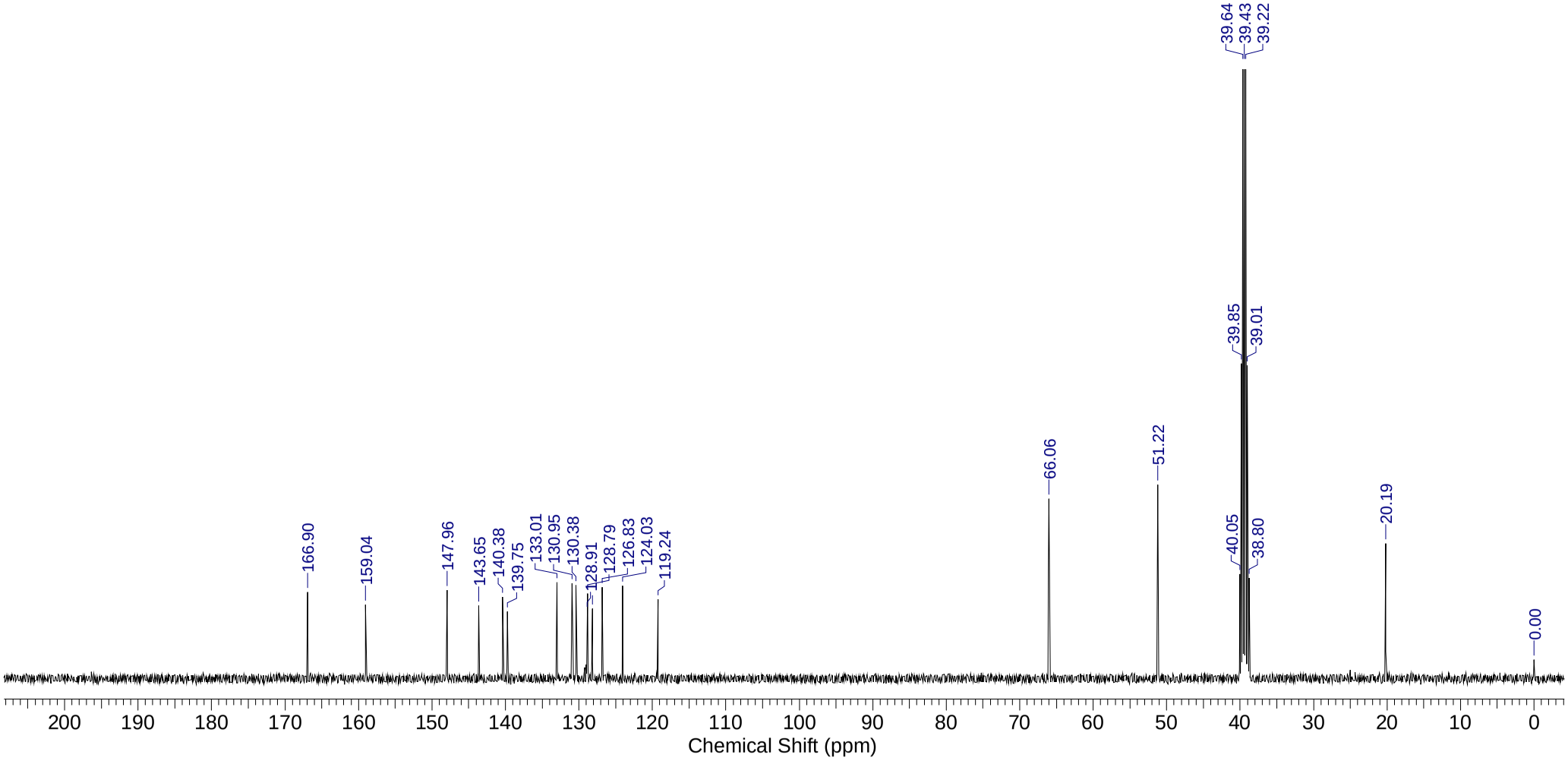
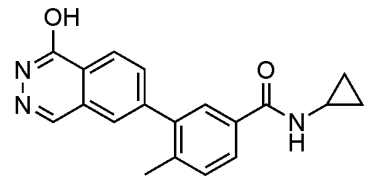


Acquisition Time (sec)	1.9924	***Comment***	michala
Date	15 Mar 2008 04:51:38		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-4368_10.dx		
Frequency (MHz)	400.16	***Nucleus***	1H
Number of Transients	16	***Origin***	Bruker BioSpin GmbH
Original Points Count	16384	***Owner***	smallmolecules
Points Count	16384	***SW(cyclical) (Hz)***	8223.68
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2480.4346
Sweep Width (Hz)	8223.18	***Temperature (degree C)***	27.000



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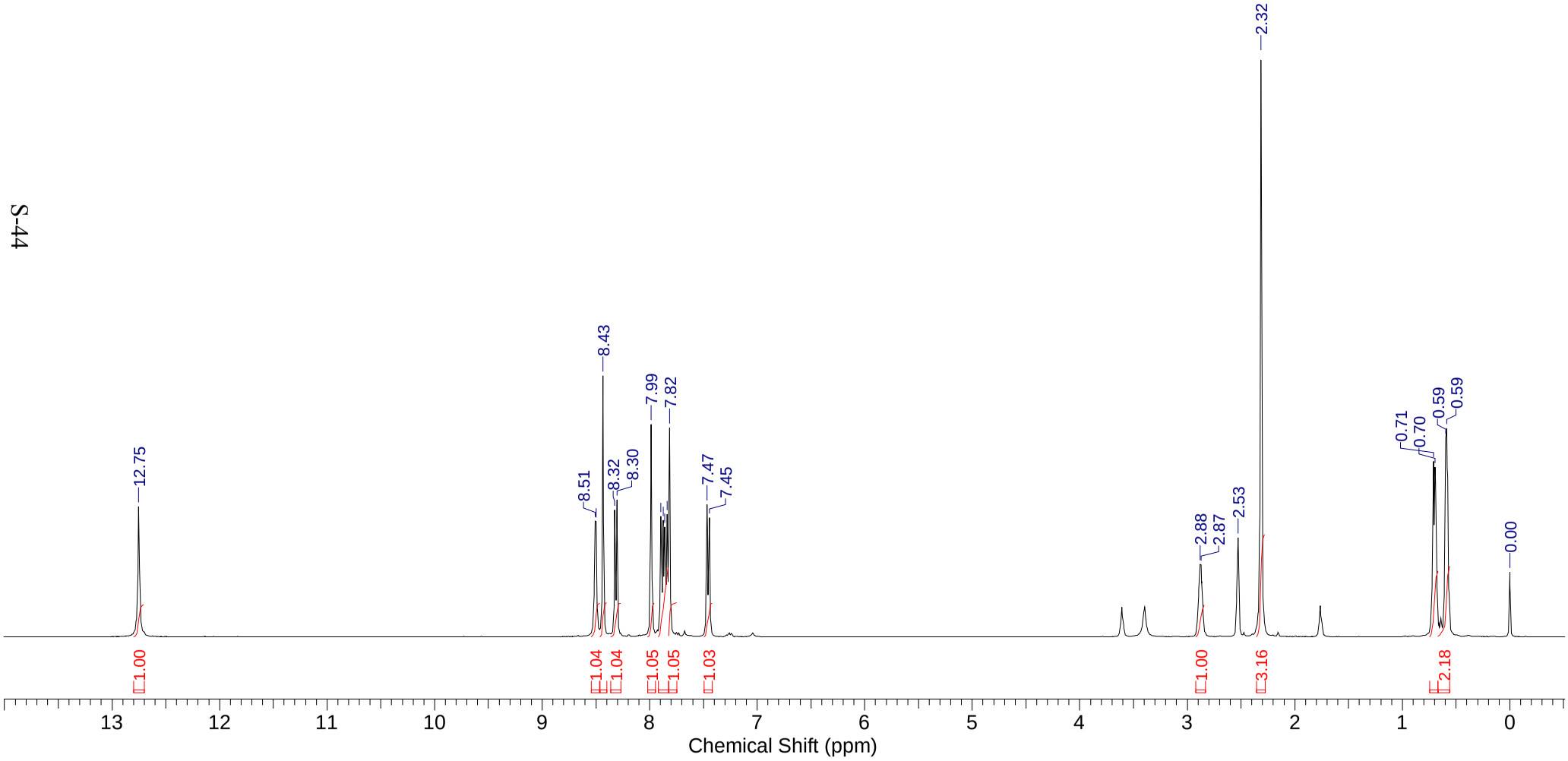
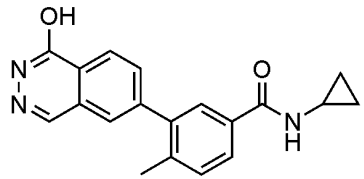


Acquisition Time (sec)	1.1535	***Comment***	michala
Date	15 Mar 2008 05:17:33		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-4368_11.dx		
Frequency (MHz)	100.63	***Nucleus***	13C
Number of Transients	512	***Origin***	Bruker BioSpin GmbH
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12021.0654
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	27.000



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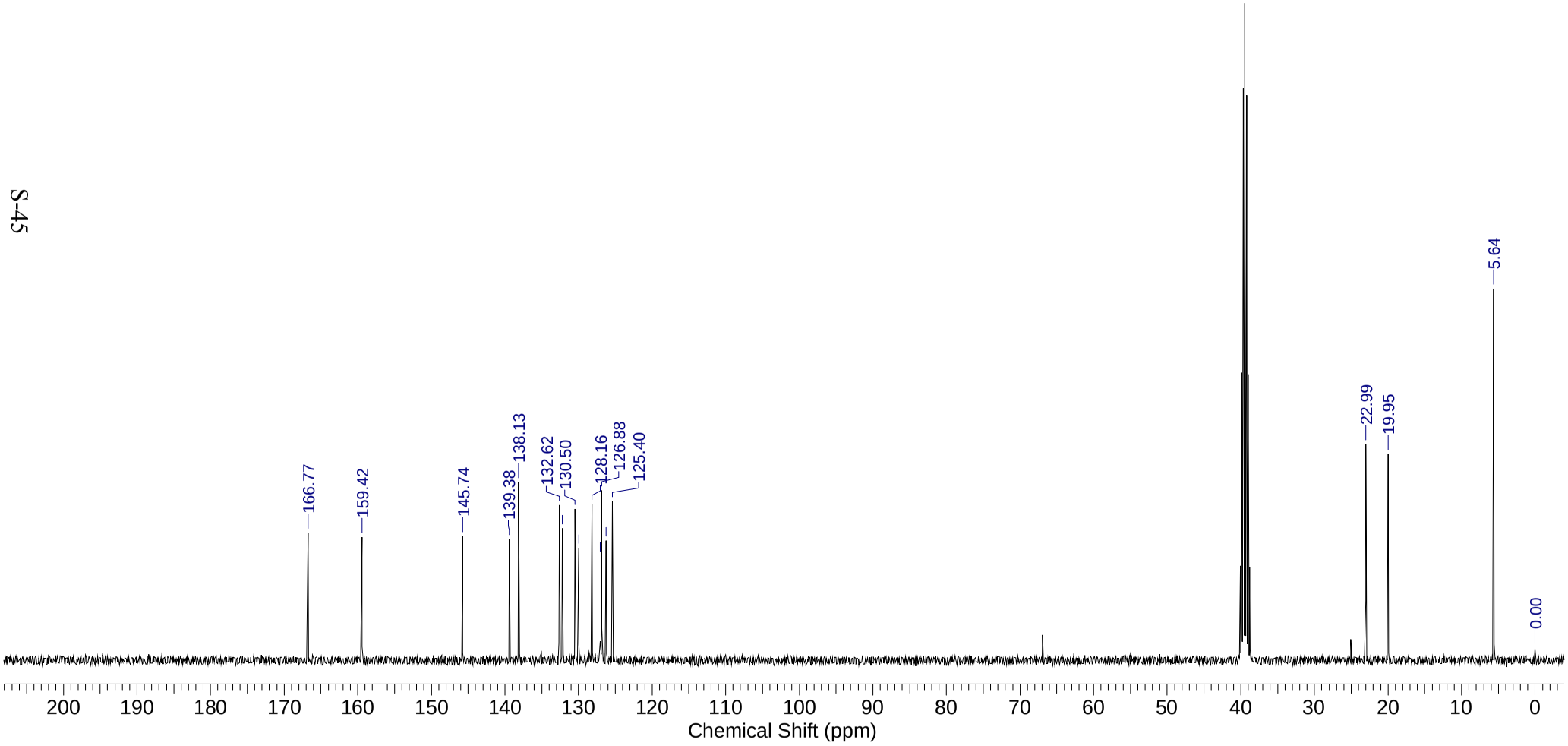
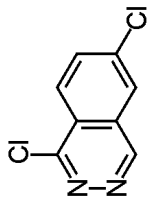
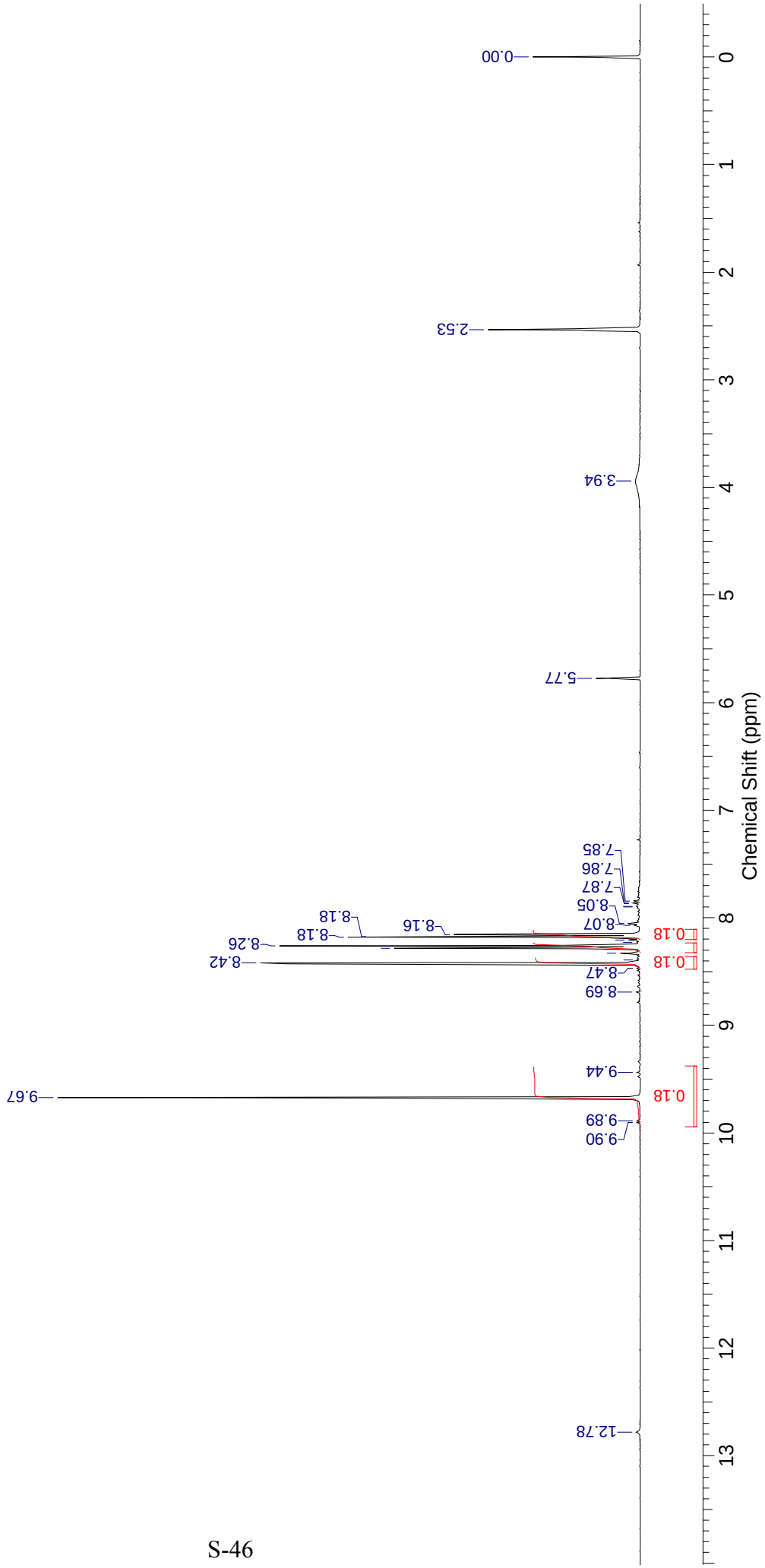
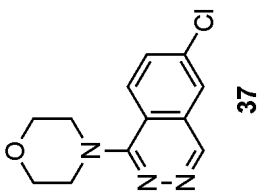




35

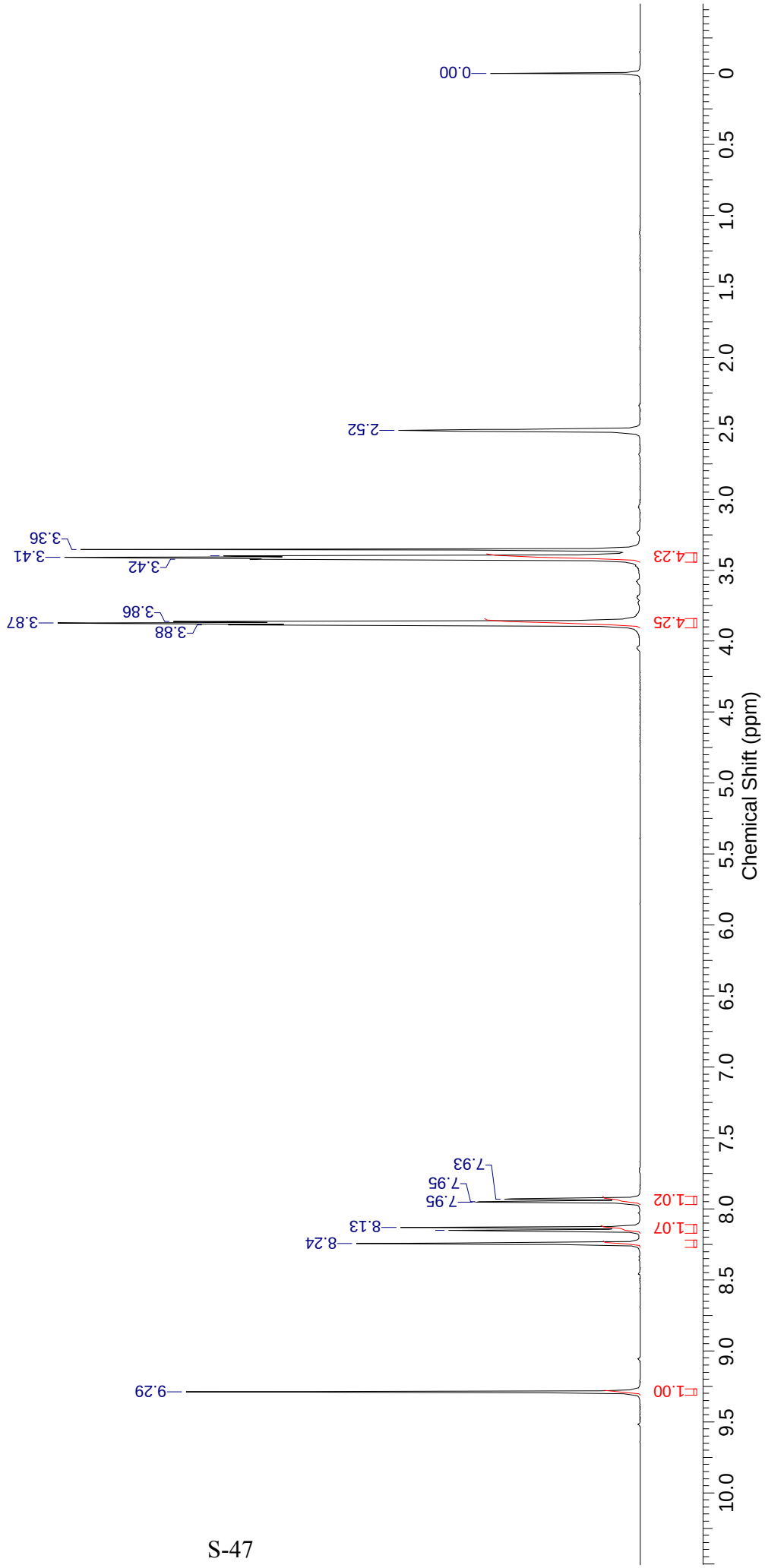
Acquisition Time (sec)	1.9924	Comment	michala
Date	31 Jul 2008 20:35:27		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-1086_15.dx		
Frequency (MHz)	400.16	Nucleus	1H
Number of Transients	16	Origin	Bruker BioSpin GmbH
Original Points Count	16384	Owner	smallmolecules
Points Count	16384	SW(cyclical) (Hz)	8223.68
Solvent	DMSO-d6	Spectrum Offset (Hz)	2482.4155
Sweep Width (Hz)	8223.18	Temperature (degree C)	27.000



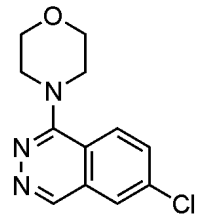


37

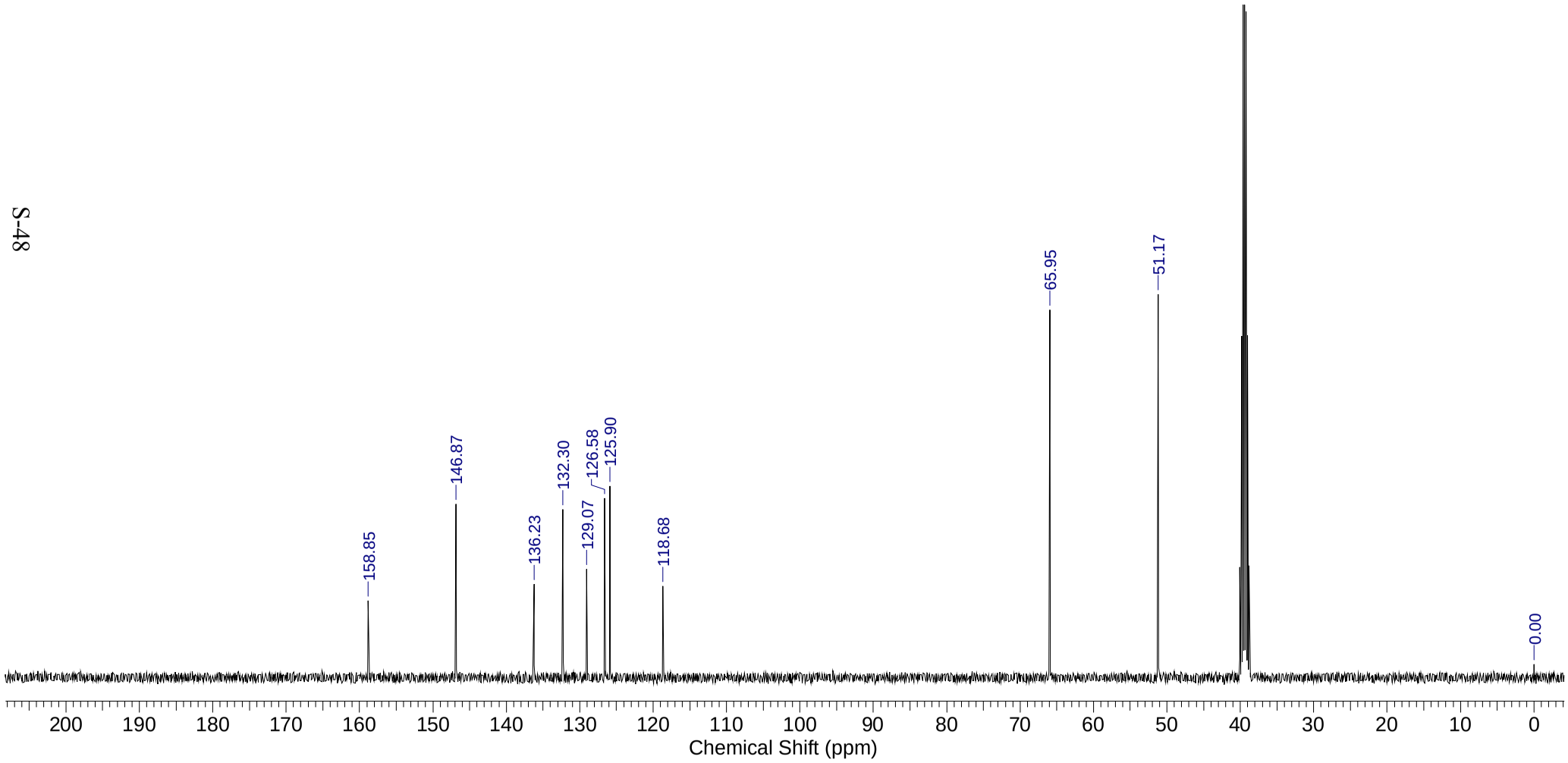
Acquisition Time (sec)	1.9924
Comment	michala
Date	18 Mar 2008 20:07:11
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-9660_10.dx
Frequency (MHz)	400.16
Nucleus	1H
Number of Transients	64
Origin	Bruker BioSpin GmbH
Original Points Count	16384
Owner	smallmolecules
Points Count	16384
SW(cyclical) (Hz)	8223.68
Solvent	DMSO-d6
Spectrum Offset (Hz)	2475.2598
Sweep Width (Hz)	8223.18
Temperature (degree C)	27.000



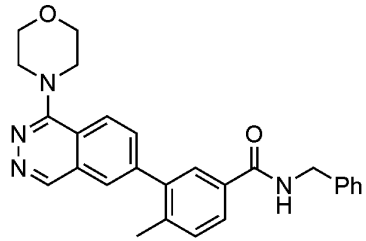
Acquisition Time (sec)	1.1535	***Comment***	michala
Date	18 Mar 2008 21:19:23		
File Name	\\Scone\NMR-Archive\jcamp\michala\2008\88628-25-9660_11.dx		
Frequency (MHz)	100.63	***Nucleus***	13C
Number of Transients	512	***Origin***	Bruker BioSpin GmbH
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***SW(cyclical) (Hz)***	28409.09
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	12018.4639
Sweep Width (Hz)	28408.22	***Temperature (degree C)***	27.000



37



Acquisition Time (sec)	5.1120	***Comment***	othiel
Date	19 Aug 2008 00:34:08		
File Name	\\Scone\NMR-Archive\data\othiel\nmr\62529-55-03\62529-55-03_010000fid		
Frequency (MHz)	400.35	***Nucleus***	1H
Number of Transients	32	***Origin***	spect
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***Pulse Sequence***	zg30
Receiver Gain	90.50	***SW(cyclical) (Hz)***	6410.26
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	2408.5413
Sweep Width (Hz)	6410.06	***Temperature (degree C)***	27.000



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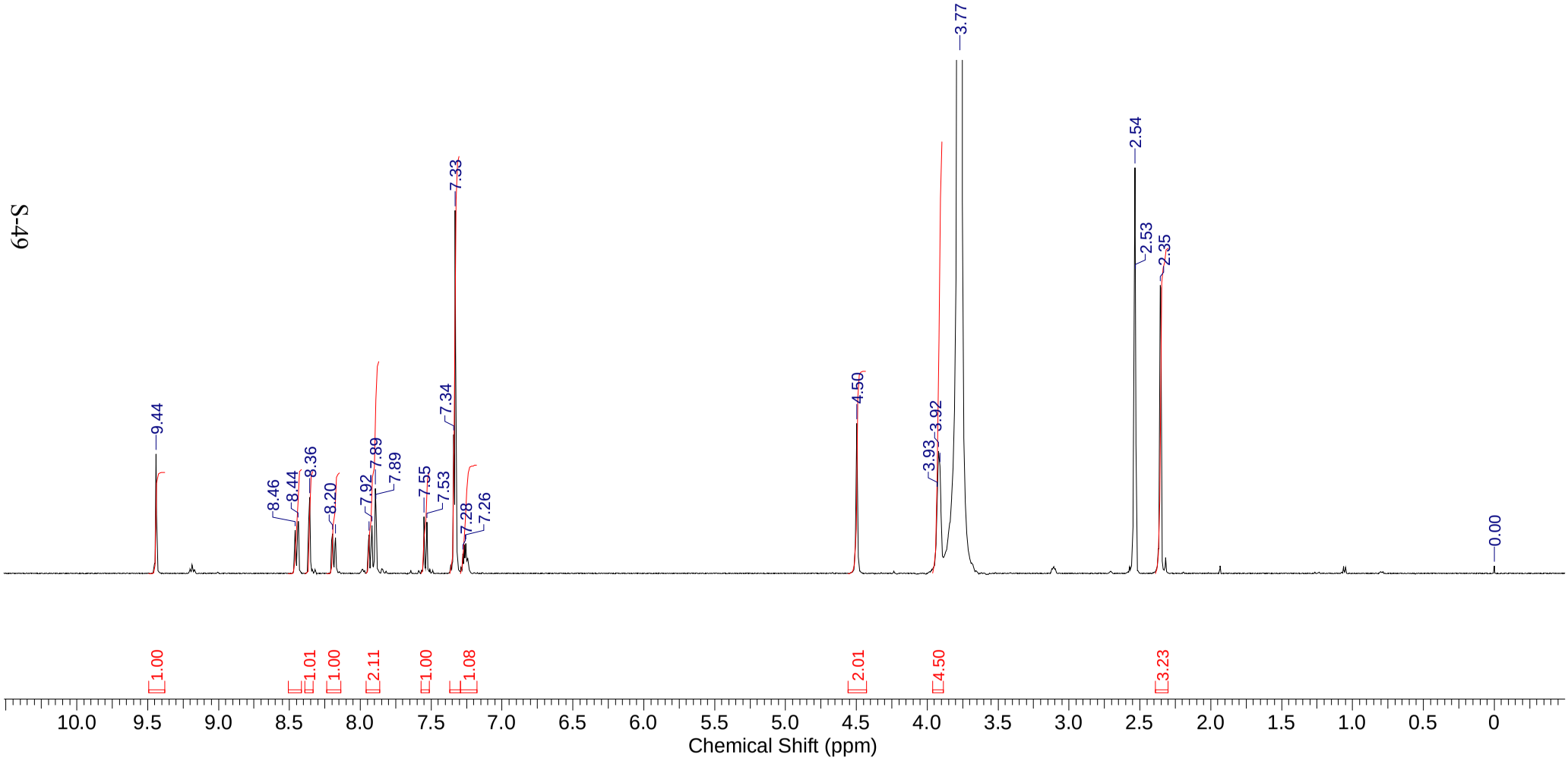

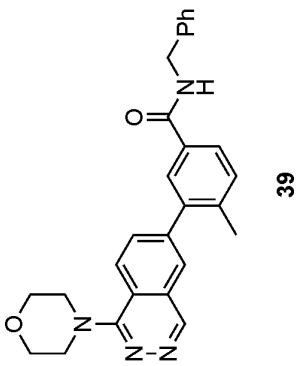

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Acquisition Time (sec)	1.4157	***Comment***	othiel
Date	19 Aug 2008 04:54:39		
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Frequency (MHz)	100.68	***Nucleus***	13C
Number of Transients	4096	***Origin***	Bruker BioSpin GmbH
Original Points Count	32768	***Owner***	smallmolecules
Points Count	32768	***SW(cyclical) (Hz)***	23147.44
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	10063.8154
Sweep Width (Hz)	23146.73	***Temperature (degree C)***	27.000