Supporting Information

Practical Synthesis of Sultams via Sulfonamide Dianion Alkylation: Application in the synthesis of Chiral Sultams

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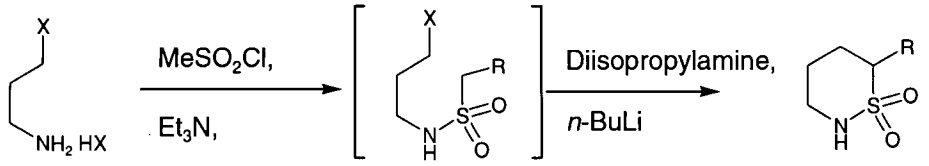
General Experimental Information

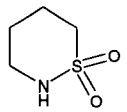
All reactions were carried out under nitrogen. Flash chromatography was carried out with EM science Silica gel 60 (neutral, 230-400 mesh). Thin-layer chromatography (TLC) was performed on EM science Silica gel (0.25mm, precoated on glass).
Visualization of compounds on TLC was accomplished by UV illumination or by staining with a solution prepared from 25g of ammonium molybdate and 1 g of ceric sulfate in 500 mL of 10% aq. sulfuric acid, followed by heating.
^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz with chemical shifts reported in ppm relative to the residual deuterated solvent. Optical rotations were measured using a Perkin-Elmer 241 Polarimeter at 23 °C using sodium lamp (D line). HPLC analysis was performed on a Hewlett Packard 1100 MSD instrument.

General procedures for the conversion of ω-halo alkylamine to sultam:



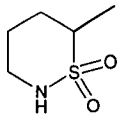
To a stirred slurry of haloalkylamine-HX salt (108 mmol) either in THF (X=Br, 300 mL) or acetonitrile (X=Cl) were added triethylamine (220mmol) and methanesulfonyl chloride (108 mmol) simultaneously via dropping funnels over 30 min (keeping the internal temp 5~10 °C). After 1 h at this temperature, the reaction was warmed to room temperature and stirred for an additional 1.5 h.
The triethylamine-HX salt was removed by filtration and the cake was washed with THF (40 mL). The THF solution of crude bromosulfonamide was used for next step without further purification.

The solution of halosulfonamide (106 mmol) in THF (340 mL) was placed in a 3-neck flask and cooled to -30°C. After addition of diisopropylamine (26.5 mmol) and 1,10-phenanthroline (30 mg), a solution *n*-BuLi in hexane (240 mmol, 1.6 M) was slowly added via a dropping funnel over period of 30 min maintaining the internal temperature range of -30 °C to -10 °C. During this time, a brown color appeared which indicated that 1.25 equiv of n-BuLi had been added. Then, the resulting solution was slowly warmed to 0 °C over 2 h. After 2h at 0 °C, the reaction was quenched by addition of 2N HCl (pH adjusted to ~5). After addition of 20% brine (75 mL), the phases were separated and the aq. layer was back-extracted with 100 mL of ethyl acetate. Concentration of the combined organic layers followed by crystallization gave the desired product.



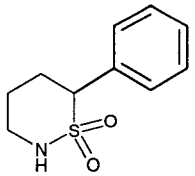
1,2-thiazinane 1,1-dioxide (1)

Conditions: 3-bromopropylamine-HBr (23.6g, 108 mmol), methanesulfonyl chloride (8.4 ml, 108 mmol), triethylamine (30.8 mL, 220 mmol) in THF (300mL); diisopropylamine (3.7 mL, 26.5 mmol), *n*-BuLi in hexane (163 mL, 240 mmol, 1.6 M). reaction temperature ;~ -30 °C to -10 °C ; then 0 °C for 2h. Crystallization (ethyl acetate-heptane , 1:1) of the crude reaction mixture afforded the desired product, **1** (9.4g, 72%) as a slightly yellow solid, mp 112~113 °C (lit.[1] 113 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.62 (br s, 1H), 3.41~3.37 (m, 1H), 3.10~3.07 (m, 2H), 2.22~2.16 (m, 2H), 1.64~1.58 (m, 2H);); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.2, 45.4, 24.1, 23.7 ppm.



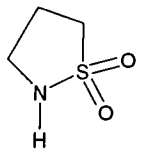
6-methyl-1,2-thiazinane 1,1-dioxide (6)

Conditions: *3-Chloropropylamine-HCl* (6.3g, 49 mmol), ethanesulfonyl chloride (5.12 ml, 53.9 mmol), triethylamine (15.0 mL, 107 mmol) in acetonitrile (80 mL); diisopropylamine (1.55 mL, 11 mmol), *n*-BuLi in hexane (63 mL, 100.8 mmol, 1.6 M). THF (130 mL) reaction temperature ;~ -30 °C to -10 °C ; then 0 °C for 2h. Filtration of the crude reaction mixture over small plug of silica gel (ethyl acetate-hexane-methylene chloride , 3:6:1) afforded the desired product, **6** (5.4g, 72%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (br s, 1H), 3.40~3.33 (m, 2H), 3.08~3.02 (m, 2H), 2.08~2.14 (m, 1H), 1.88~1.98 (m, 1H), 1.72~1.77 (m, 1H), 1.57~1.60 (m, 1H), 1.39 (d, J = 6.75Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.1, 45.4, 31.6, 25.2, 14.0 ppm.



6-phenyl-1,2-thiazinane 1,1-dioxide (8)

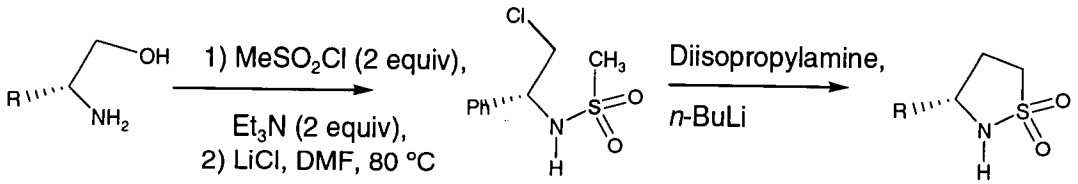
Conditions: 3-Bromopropylamine-HBr (6.1g, 27.8mmol), α-toluenesulfonyl chloride (5.5 g, 29 mmol), triethylamine (8.2 mL, 58.38 mmol) in THF (100 mL); diisopropylamine (0.97 mL, 6.9 mmol), *n*-BuLi in hexane (63 mL, 39.2 mmol, 1.6 M). THF (130 mL) reaction temperature ;~ -40 °C to -10 °C ; then 0 °C for 2h. Filtration of the crude reaction mixture over small plug of silica gel (ethyl acetate-hexane-methylene chloride, 3:6:1) afforded the desired product **8** as a yellow solid (4.4g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.35 (m, 5H), 4.36 (br s, 1H), 4.11 (dd, 1H, J = 12.8, 3.4Hz), 3.65~3.55 (m, 1H), 3.45~3.38 (m, 1H), 2.68~2.57 (m, 1H), 2.33~2.27 (m, 1H), 1.98~1.91 (m, 1H), 1.82~1.70; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 129.3, 128.9, 128.1, 67.1, 45.4, 30.5, 26.8 ppm



isothiazolidine 1,1-dioxide (11)

Conditions: 2-Chloroethylamine-HCl (12.2g, 106 mmol), methanesulfonyl chloride (8.6, 111 mmol), triethylamine (31.2 mL, 223 mmol) in acetonitrile (150 mL); diisopropylamine (3.5 mL, 25 mmol), *n*-BuLi in hexane (135 mL, 216 mmol, 1.6 M). THF (330 mL), reaction temperature; ~ -60 °C to -50 °C; then warmed to 0 °C over a period of 2h. Filtration of the crude reaction mixture over small plug of silica gel (ethyl acetate-hexane-methylene chloride, 3:6:1) afforded the desired product **11** (7.6g, 60%) as an oil.[2]
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (br s, 1H), 3.43 (m, 2H), 3.09 (t, 2H, J = 7.54 Hz), 2.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.5, 42.2, 23.9 ppm.

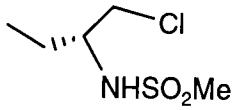
General procedures for the conversion of β-amino alcohol to 1,3-sultam:



Typical procedure; To a stirred solution of the amino alcohol (36.6 mmol) and triethylamine (75 mmol) in THF were added methanesulfonyl chloride (75 mmol) at 0°C. After aging for 4h at room temperature, 30 ml of MTBE was added. After filtration of the triethylamine-HCl salt, the filtrate was concentrated to afford bis-mesylate.

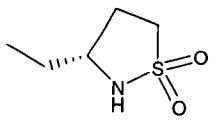
The resulting presumed bis-mesylate was treated with NaCl (55 mmol) in DMF (45 mL) and warmed to 80 °C. After aging for 16h at this temperature, the reaction was cooled to room temperature and diluted with water (30 mL) and EtOAc-hexanes (50 mL, 2:1). After phase separation, the organic layer was washed sequentially with 0.5N HCl and brine. The solution was dried over Na_2SO_4, filtered and concentrates under reduced pressure. The crude material was eluted through a small plug of silica gel (hex/EtOAc, 2:1) to afford the chloromethane-sulfonate.

The solution of chlorosulfonamide (34 mmol) in THF (100 mL) was placed in 500 mL RBF and cooled to -60°C under nitrogen atmosphere. After addition of diisopropylamine (8.3 mmol) and 1,10-phenanthroline (15 mg), a solution *n*-BuLi in hexane (73 mmol, 1.6 M) was slowly added via a dropping funnel maintaining the internal temperature below -50 °C over a period of 30 min. Then, the resulting solution was slowly warmed to 0 °C over 4 h. After 2h at 0 °C, the reaction was quenched by addition of 2N HCl (pH adjusted to ~5). After addition of 20% brine (30 mL), the phases were separated. The aq. layer was back-extracted with ethyl acetate (40 mL). Concentration of the combined organic layers followed by flash or filtering silica gel chromatography gave the desired product.



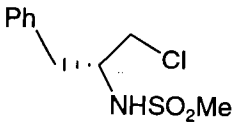
N-[(1*R*)-1-(chloromethyl)propyl]methanesulfonamide (16)

$[\alpha]_D^{23}$ +16.8° (c 0.037, EtOH); NMR ($CDCl_3$, 400 MHz) δ 4.50 (br s, 1H), 3.74 (dd, 1H, *J* = 11.20, 4.04), 3.66~3.58 (m, 2H), 3.04 (s, 3H), 1.68 (m, 2H), 1.01 (t, 3H, *J* = 7.40 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.1, 48.1, 42.1, 26.1, 10.3 ppm.



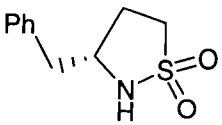
(3*R*)-3-ethylisothiazolidine 1,1-dioxide (17)

$[\alpha]_D^{23}$ +13.3° (c 0.037, EtOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.30 (br s, 1H), 3.54~3.50 (m, 1H), 3.24~3.14 (m, 1H), 3.04~3.04 (m, 1H), 2.54~2.46 (m, 1H), 2.12~2.02 (m, 1H), 1.70~1.57 (m, 2H), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.6, 48.1, 29.4, 28.9, 10.4 ppm.



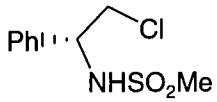
N-[(1*R*)-1-benzyl-2-chloroethyl]methanesulfonamide (19)

$[\alpha]_D^{23}$ -33.9° (c 0.038, EtOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.25 (m, 5H), 4.84 (br d, *J* =8.8 Hz, 1H), 3.88 (m, 1H), 3.70 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.63 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.02 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.86 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.8, 129.6, 129.0, 127.4, 56.4, 48.1, 42.4, 39.2 ppm.



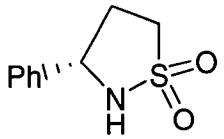
(3*R*)-3-benzylisothiazolidine 1,1-dioxide (20)

$[\alpha]_D^{23}$ -22.3° (c 0.031, EtOH)[3]; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.15 (m, 5H), 4.62 (br s, 1H), 3.90~3.80 (m, 1H), 3.26~3.20 (m, 1H), 3.16~3.06 (m, 1H), 3.00~2.84 (m, 2H), 2.53~2.45 (m, 1H), 2.21~2.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 129.1, 128.9, 128.7, 127.2, 56.11, 47.9, 42.2, 28.9 ppm.



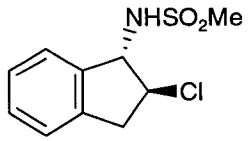
N-[(1*R*)-2-chloro-1-phenylethyl]methanesulfonamide (22)

$[\alpha]_D^{23}$ -49.2° (c 0.031, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.34 (m, 5H), 5.30 (br d, *J* = 6.8Hz, 1H), 4.81 (m, 1H), 3.88 (dd, *J* = 11.4, 7.2 Hz, 1H), 3.77 (m, *J* = 11.4, 7.2 Hz, 1H), 2.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.8, 129.1, 128.8, 126.9, 58.7, 48.3, 42.0 ppm.



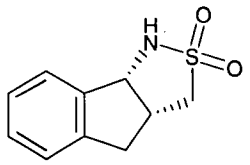
(3*S*)-3-phenylisothiazolidine 1,1-dioxide (23)

$[\alpha]_D^{23}$ -50.5° (c 0.033, EtOH)[4]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.30 (m, 5H), 4.76~4.71 (m, 1H), 4.62 (br s, 1H), 3.40~3.33 (m, 1H), 3.26~3.18 (m, 1H), 2.82~2.79 (m, 1H), 2.46~2.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.2, 129.0, 128.5, 126.0, 58.2, 48.2, 32.2 ppm.



N-[(1S, 2*S*)-2-chloro-2,3-dihydro-1*H*-inden-1-yl]methanesulfonamide (25)

$[\alpha]_D^{23}$ +91.3° (c 0.016, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (m, 1H), 7.32 (m, 2H), 7.31 (m, 1H), 5.03 (t, *J* = 8.4 Hz, 1H), 4.80 (br d, 1H), 4.29 (dd, *J* = 15.5, 7.6 Hz, 1H), 3.49 (dd, *J* = 15.9, 7.6 Hz, 1H,), 3.20 (s, 3H), 3.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.5, 138.7, 129.3, 128.1, 124.7, 124.3, 67.0, 63.2, 42.67, 40.1 ppm.

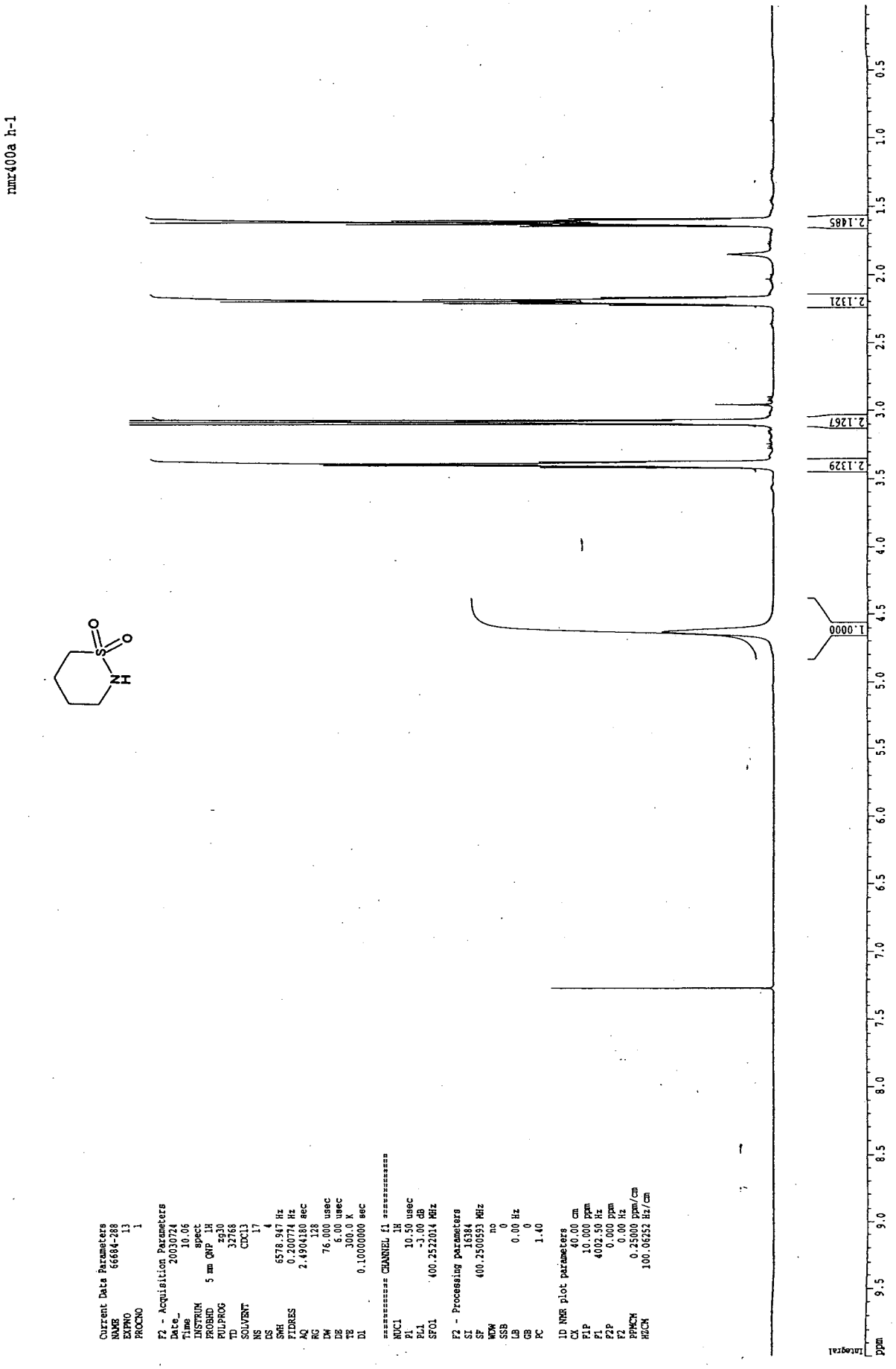


(3a*R*, 8b*R*)-3,3a,4,8b-tetrahydro-1*H*-indeno[1,2-*c*]isothiazole 2,2-dioxide (26)

$[\alpha]_D^{23}$ -101.2° (c 0.023, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.27 (m, 4H), 5.05 (d, *J* = 7.3 Hz, 1H), 3.63~3.56 (m, 1H), 3.40~3.50 (m, 2H), 3.03 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.89 (dd, 1H, *J* = 12.7, 7.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.3, 139.9, 129.5, 127.9, 125.4, 125.1, 63.0, 52.9, 39.8, 37.5 ppm.

References

1. White, E. H.; Lim, H. M. *J. Org. Chem.* **1987**, *52*, 2162.
2. Bliss, A. D.; Cline, W. K.; Hamilton, C. E.; Sweeting, O. *J. Org. Chem.* **1963**, *28*, 3537.
3. The antipode of sultam **20** has been reported in literature. However, no optical rotation value was given, see; Spaltenstein, A., Almond, M. R., Bock, W. J., Cleary, D. G., Furfine, E. S., Hazen, R. J., Kazmierski, W. M., Salituro, F. G., Tung, R. D., Wright. L, L. *Bioorganic. Med. Chem. Lett.* **2000**, *10*, 1159.
4. For the racemic *N*-methyl sultam **23** synthesis, see; Togo, H.; Harada, Y.; Yokoyama, M. *J. Org. Chem.* **2000**, *65*, 926.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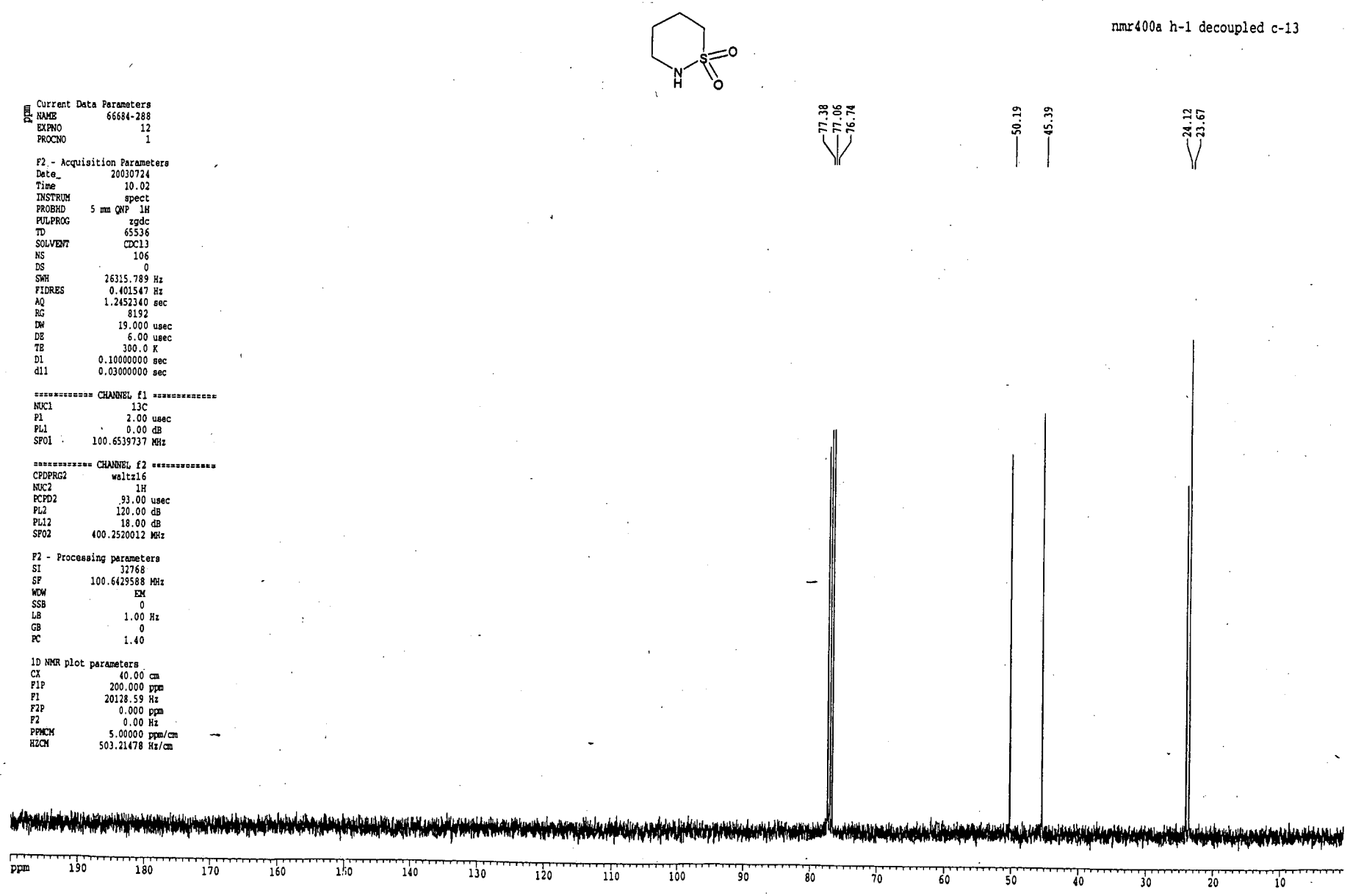

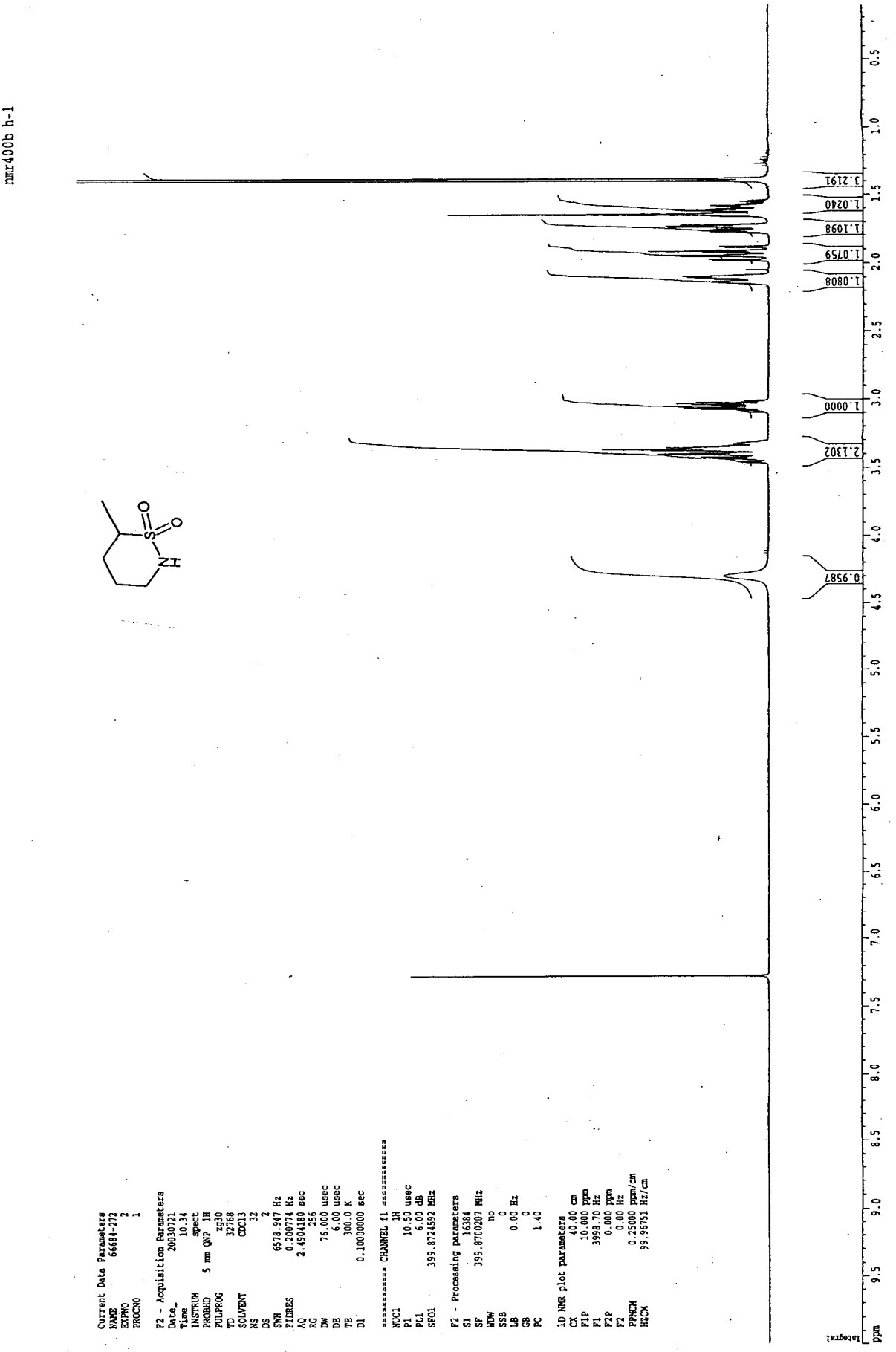

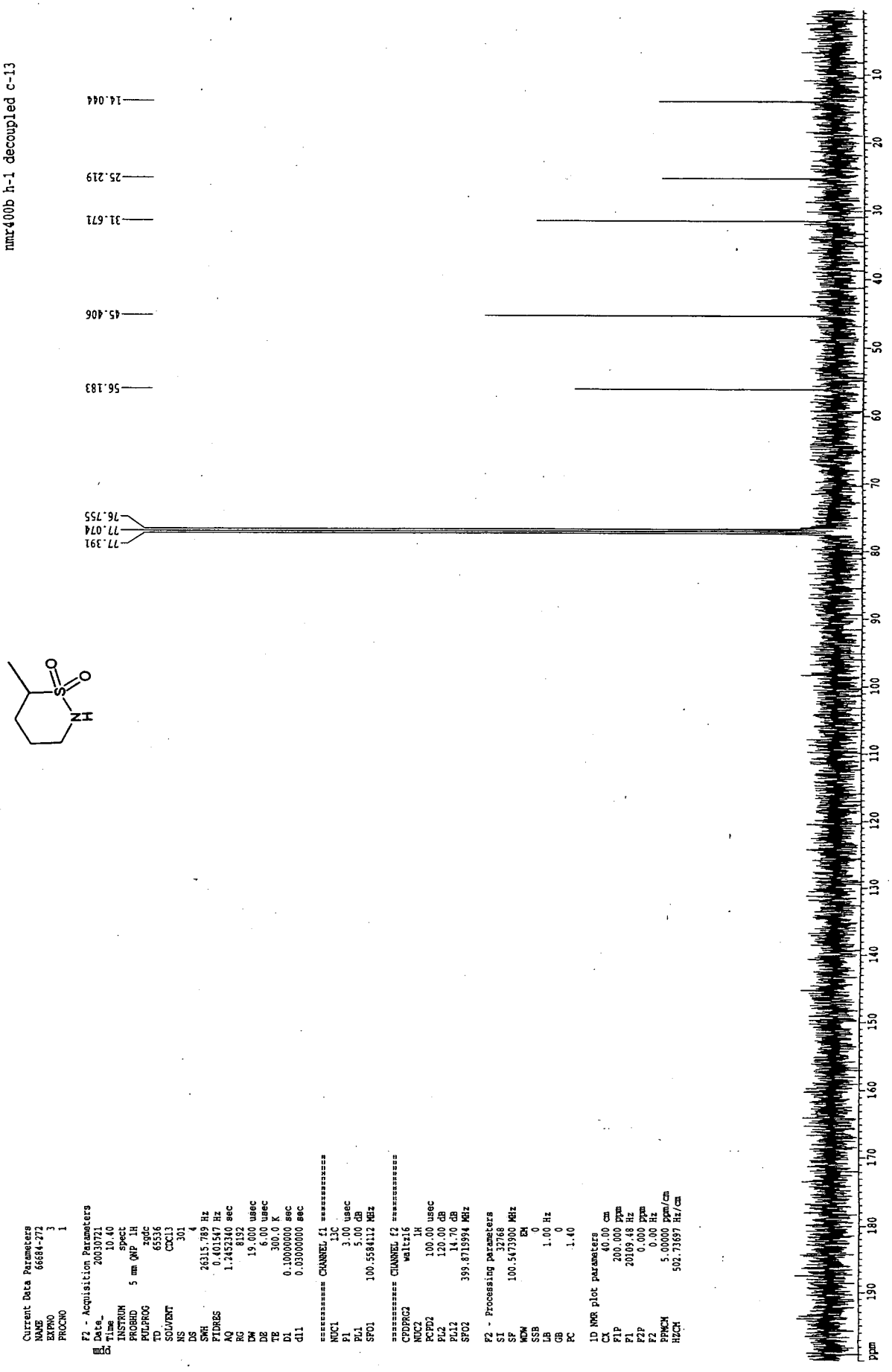

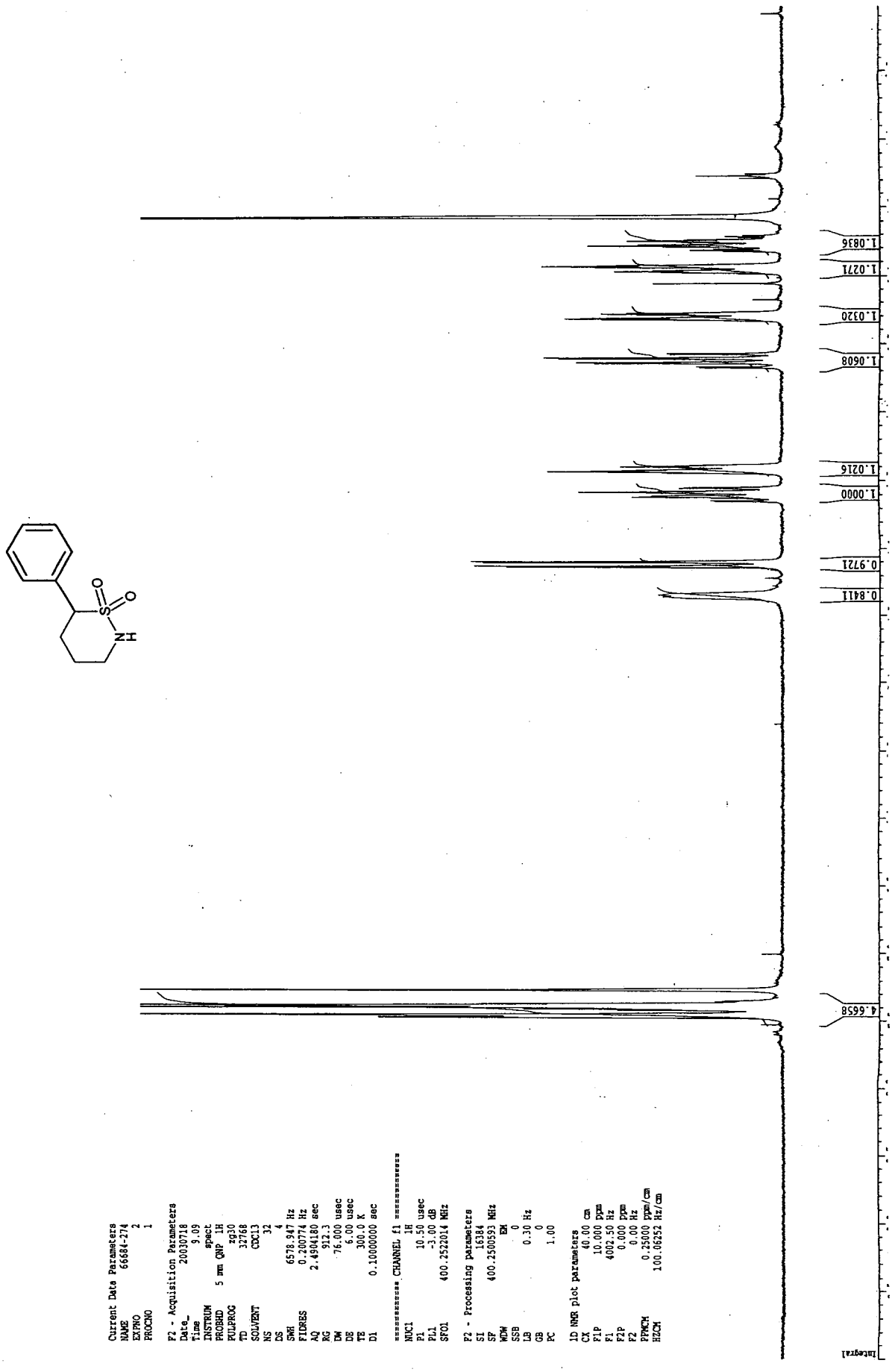


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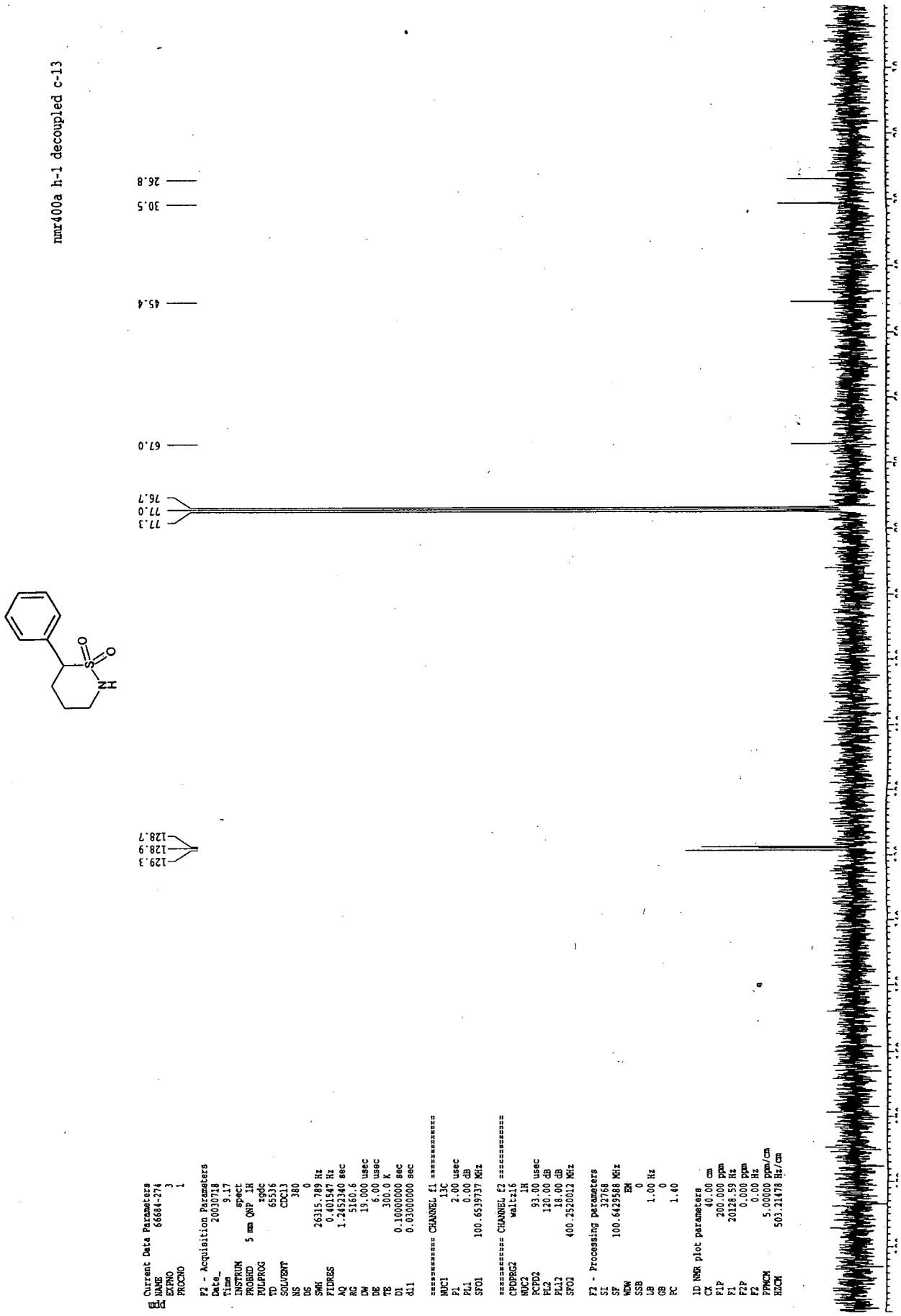

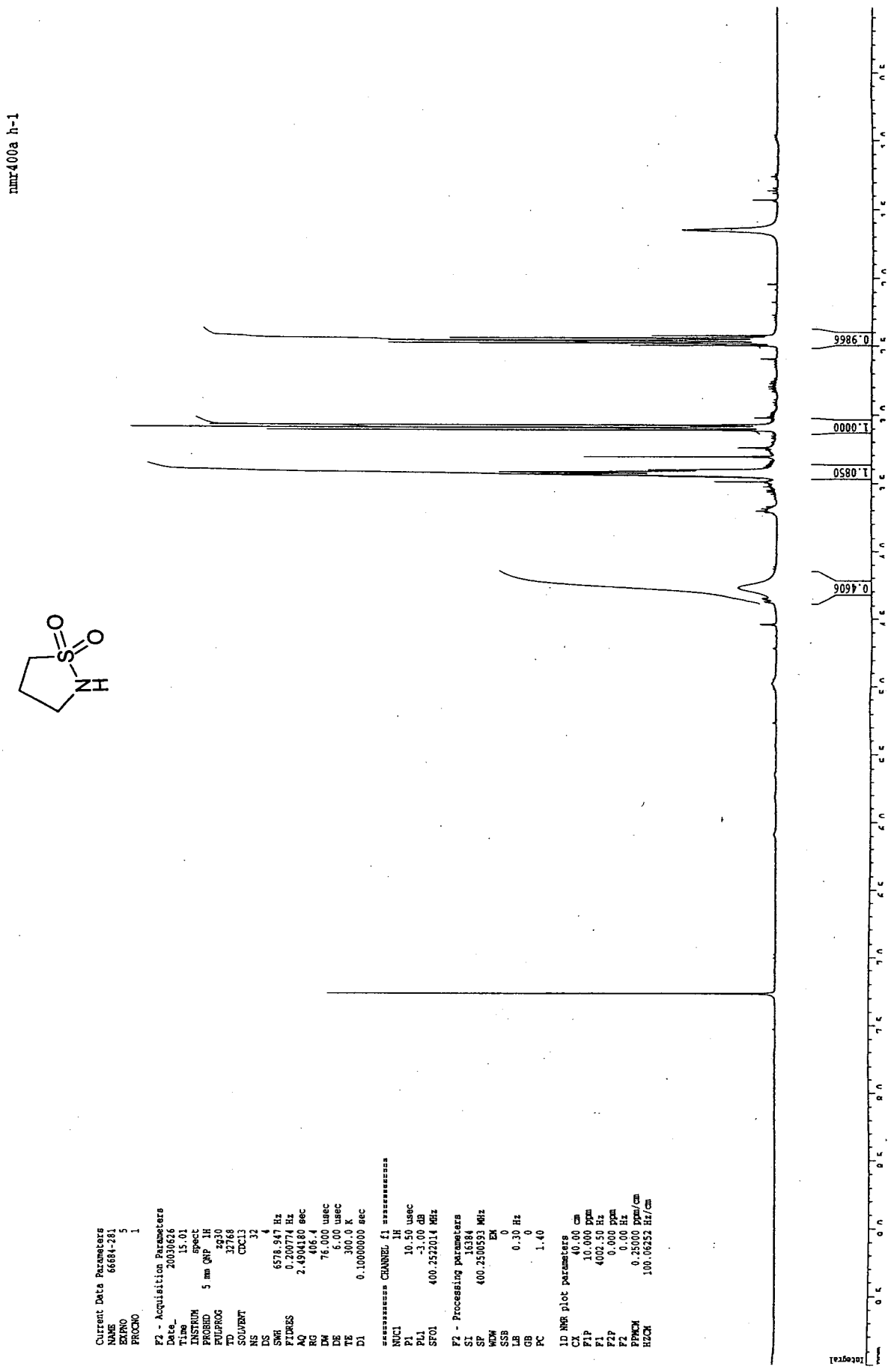

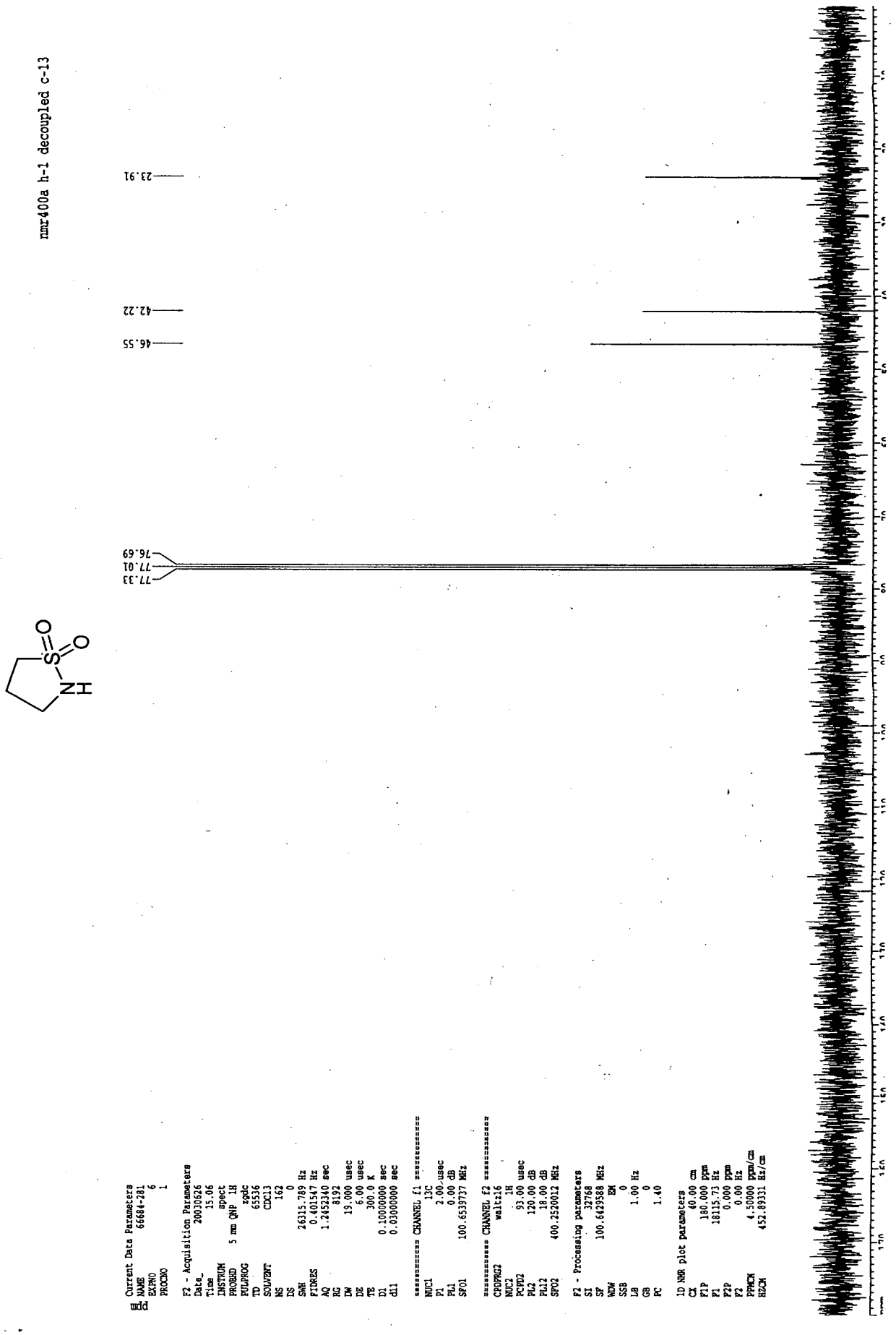

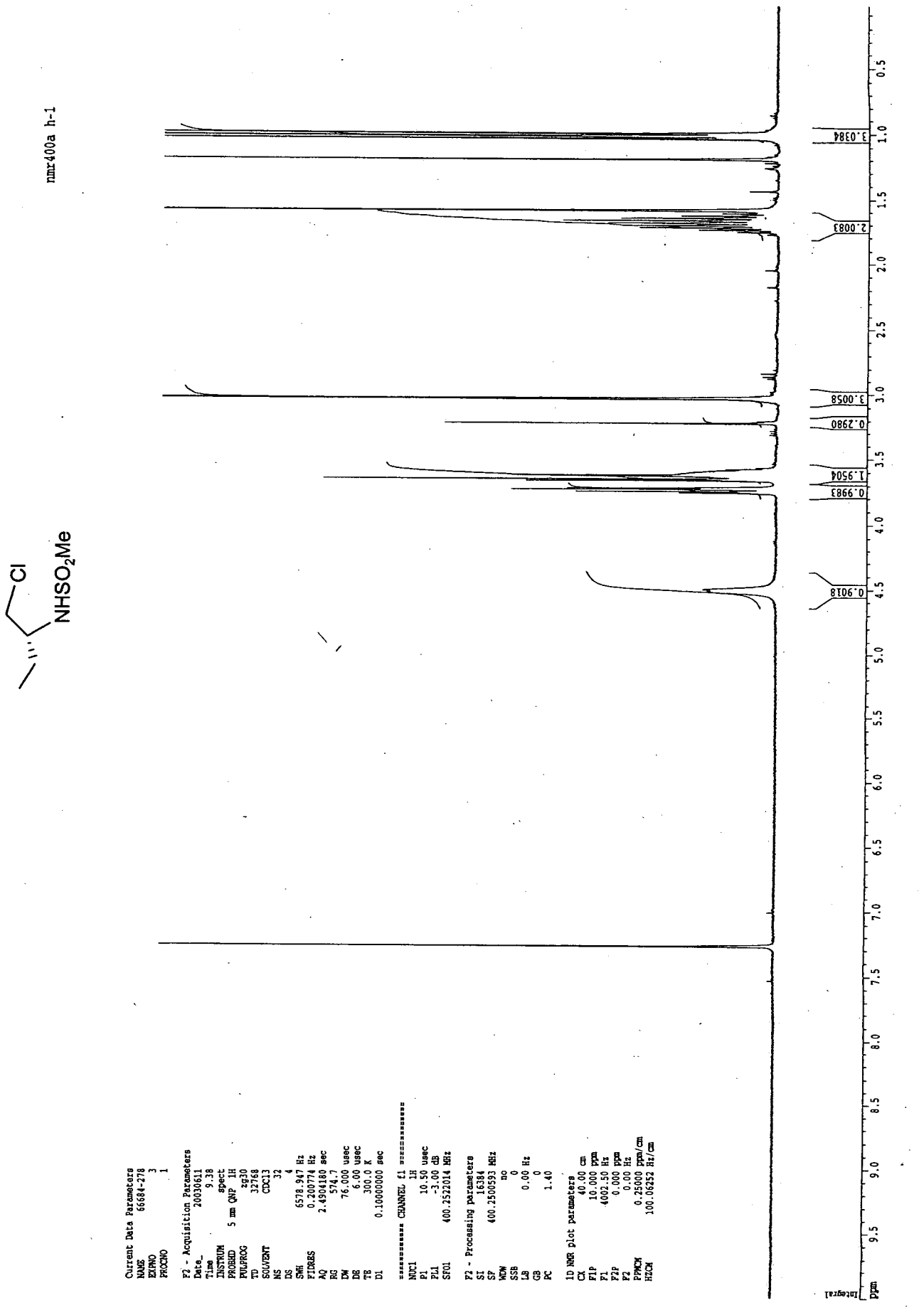

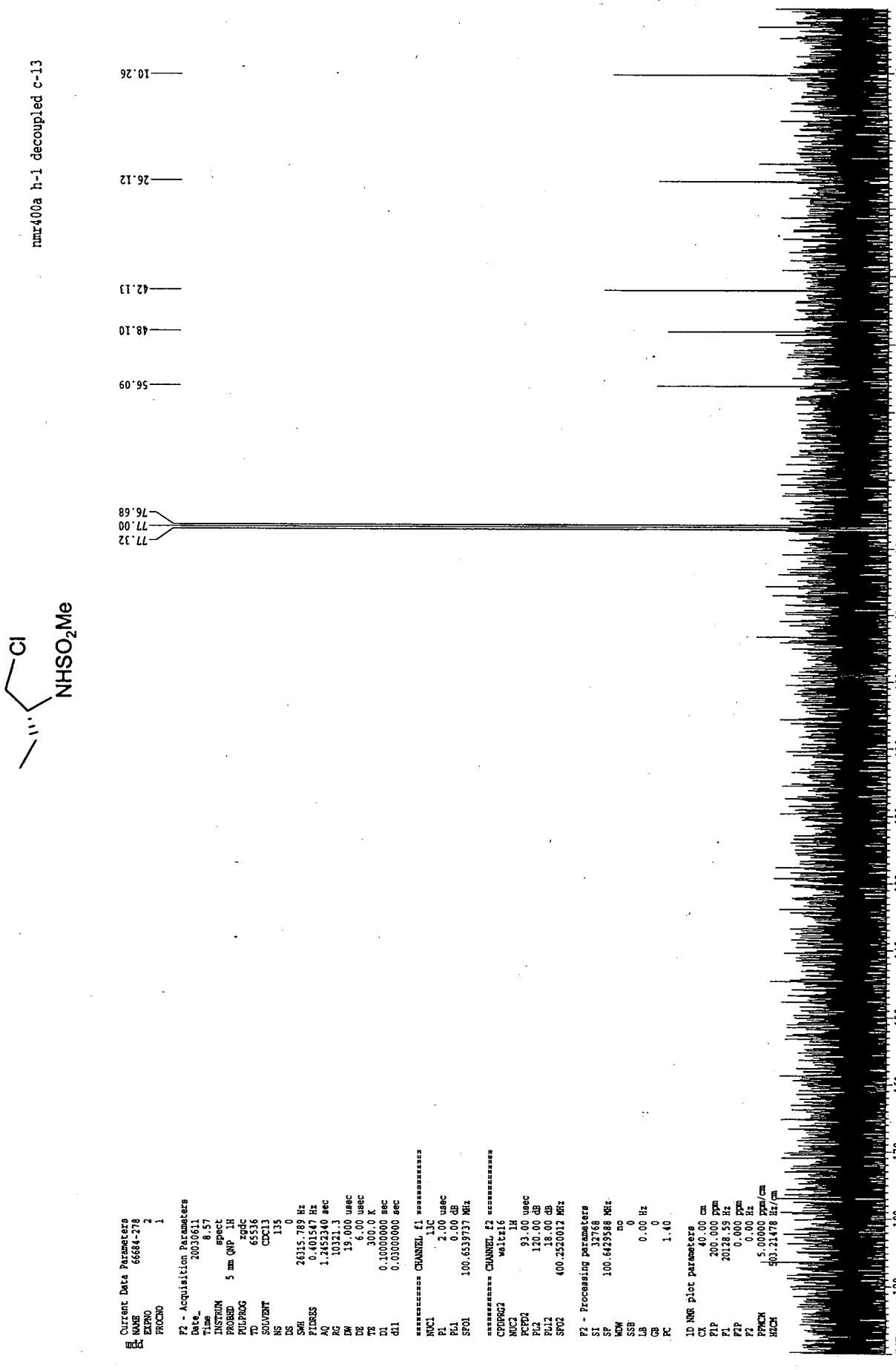

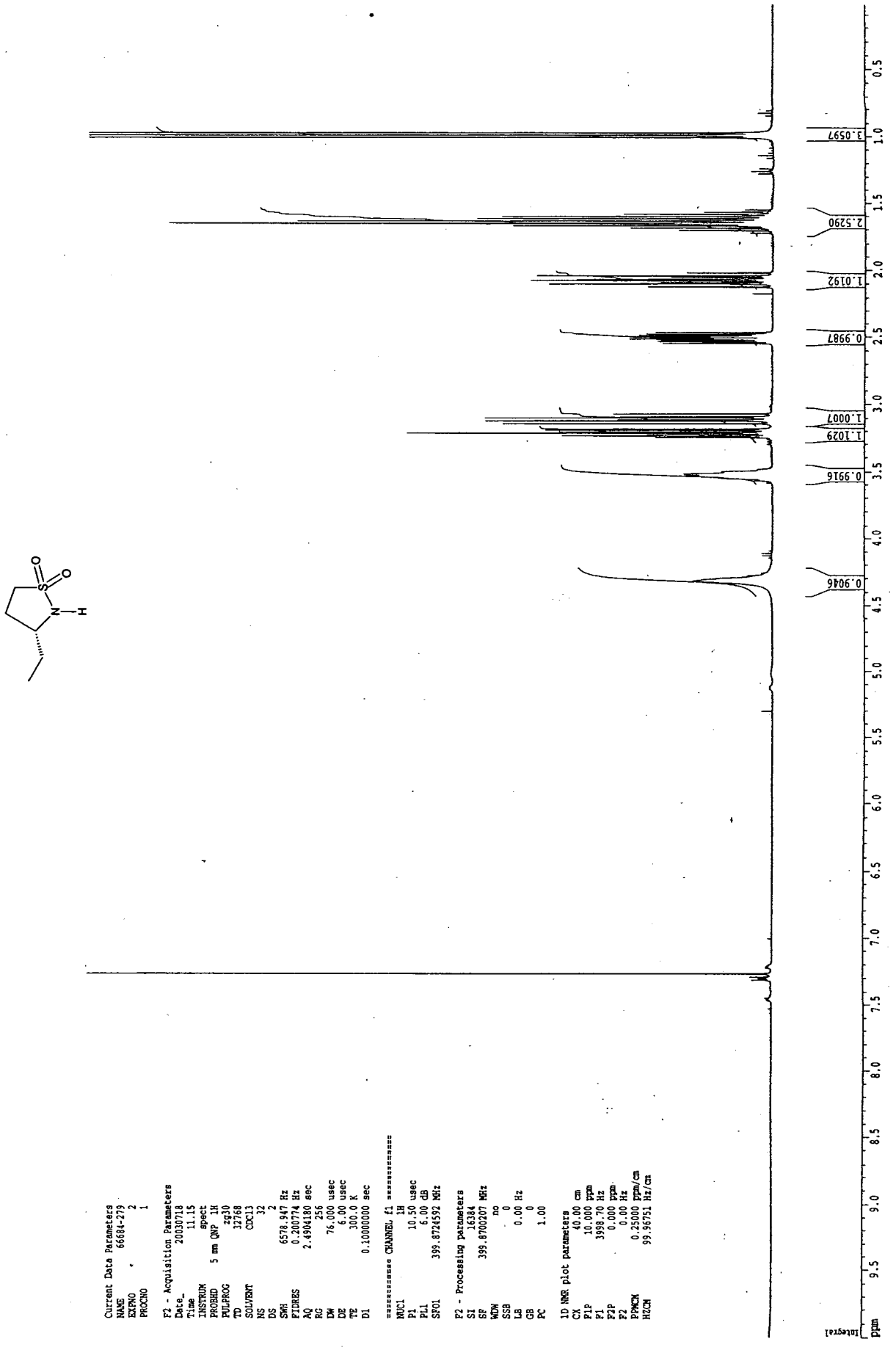

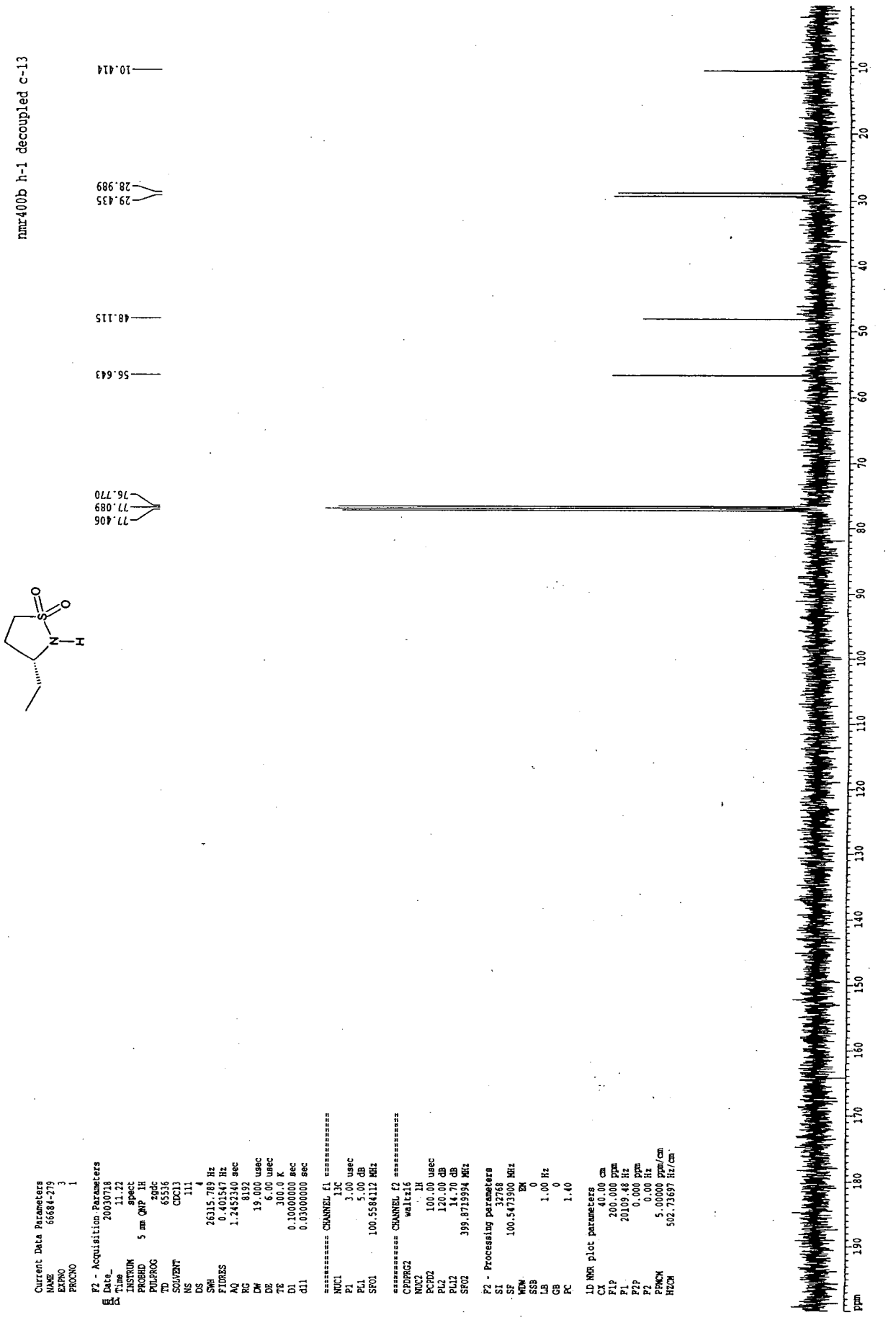

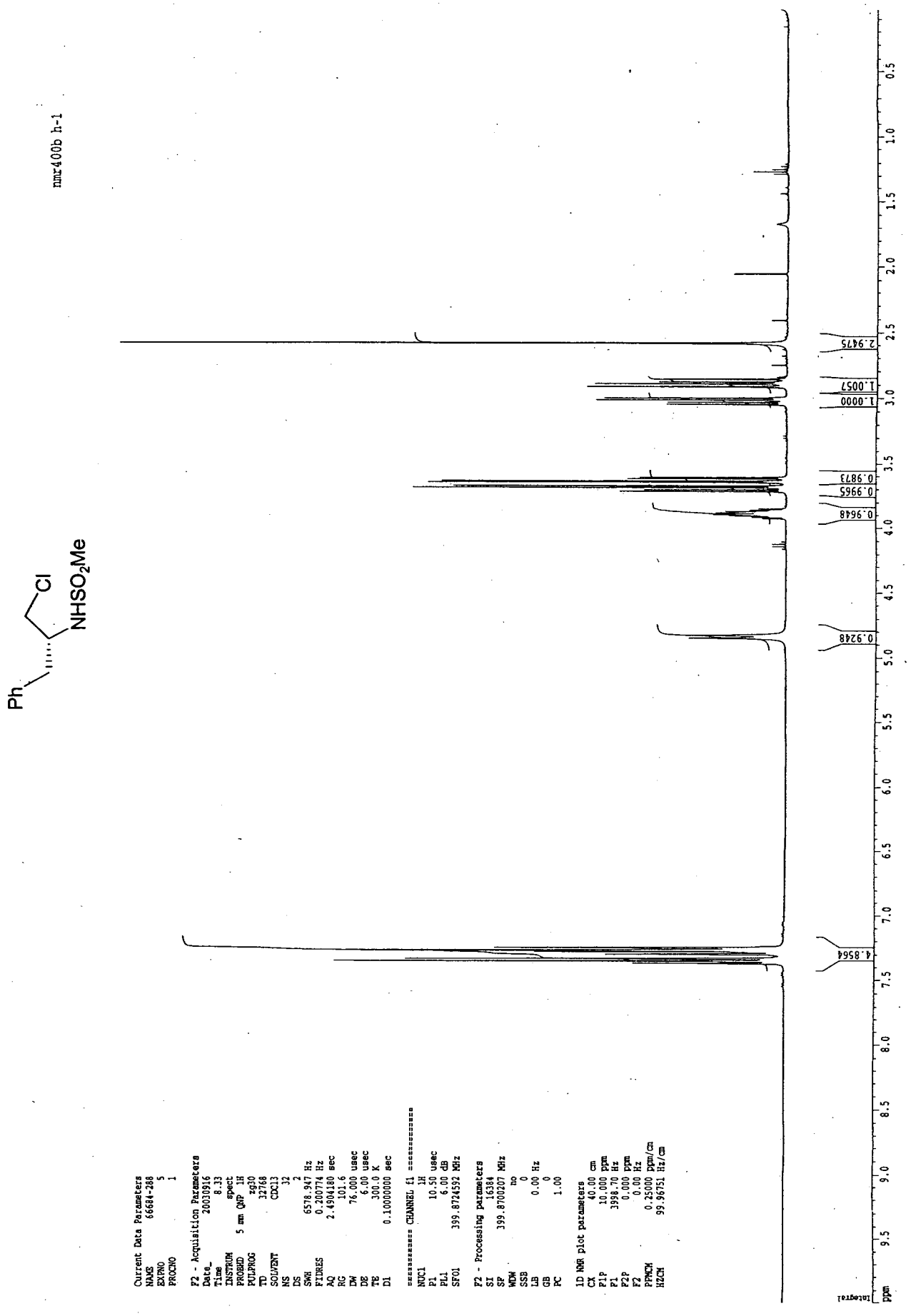

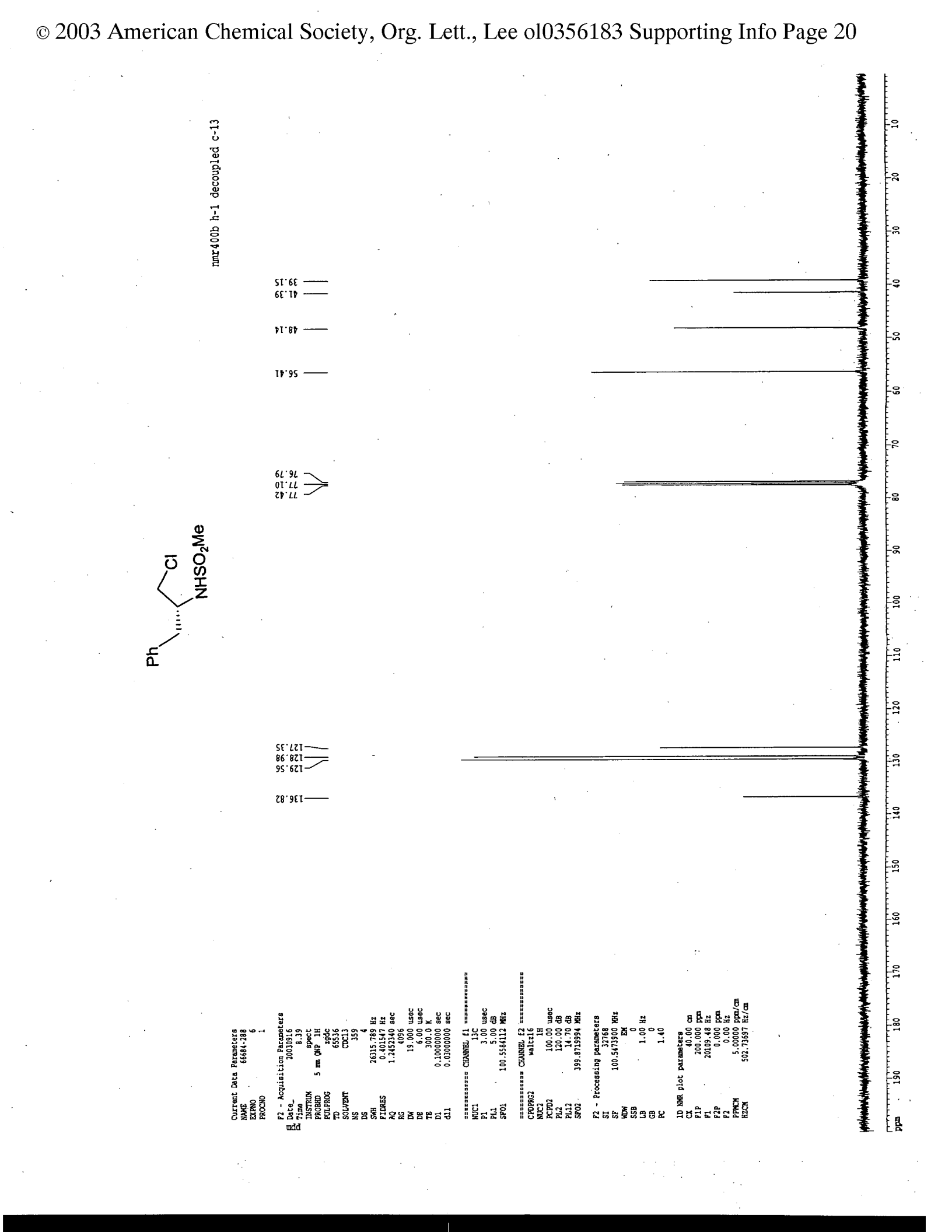

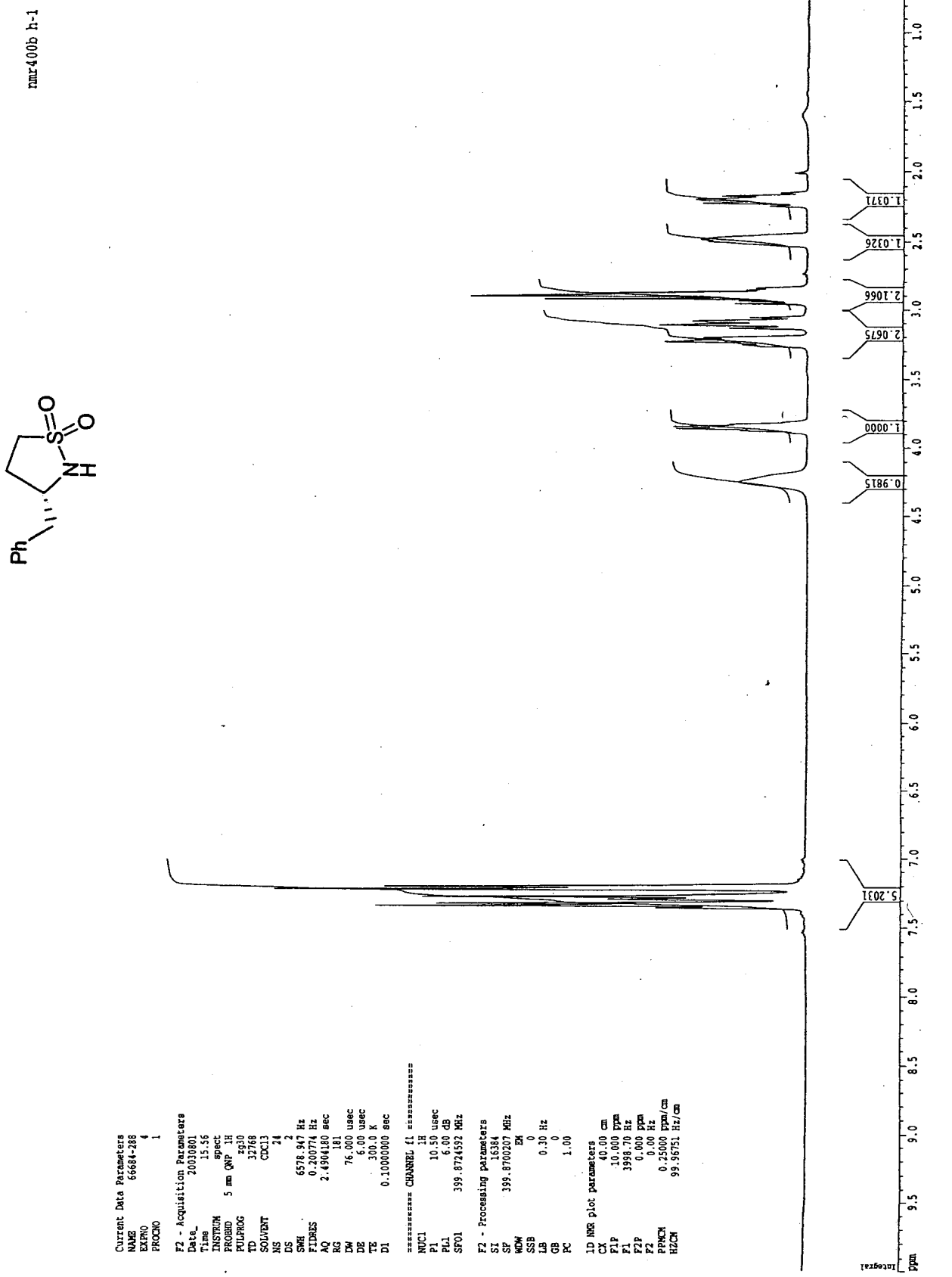


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Current Data Parameters
NAME        66684-288
EXPNO               4
PROCNO              1

F2 - Acquisition Parameters
Date_          20030801
Time               15.56
INSTRUM             spect
PROBHD   5 mm QNP 1H
PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   24
DS                    2
SWH           6578.947 Hz
FIDRES        0.200774 Hz
AQ            2.4904180 sec
RG                  181
DW               76.000 usec
DE                6.00 usec
TE                300.0 K
D1            0.10000000 sec

========== CHANNEL f1 ==========
NUC1                1H
P1               10.50 usec
PL1               6.00 dB
SFO1        399.8724592 MHz

F2 - Processing parameters
SI                 16384
SF          399.8700207 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                40.00 cm
F1P               10.000 ppm
F1             3998.70 Hz
F2P               0.000 ppm
F2                0.00 Hz
PPMCM          0.25000 ppm/cm
HZCM          99.96751 Hz/cm
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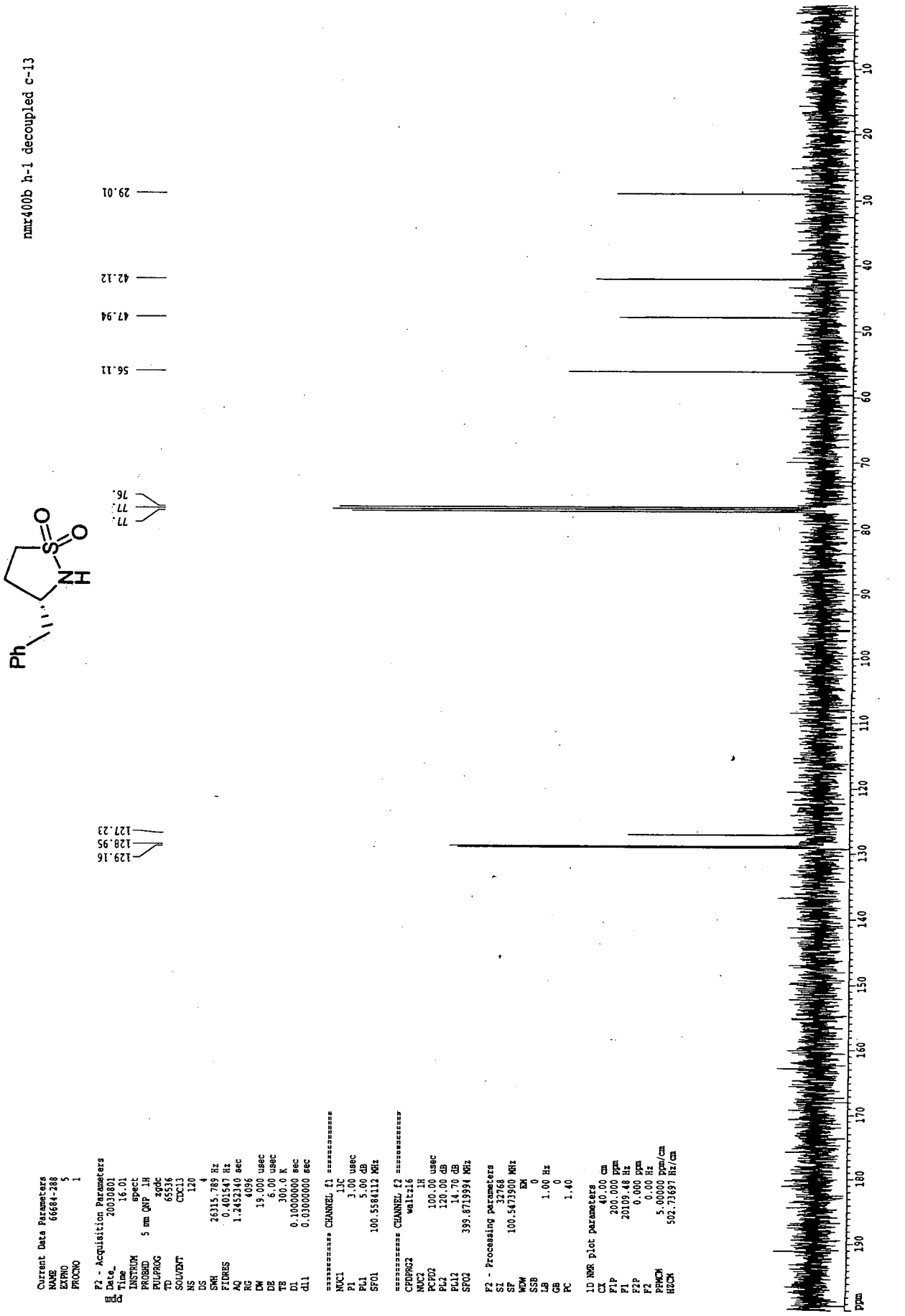

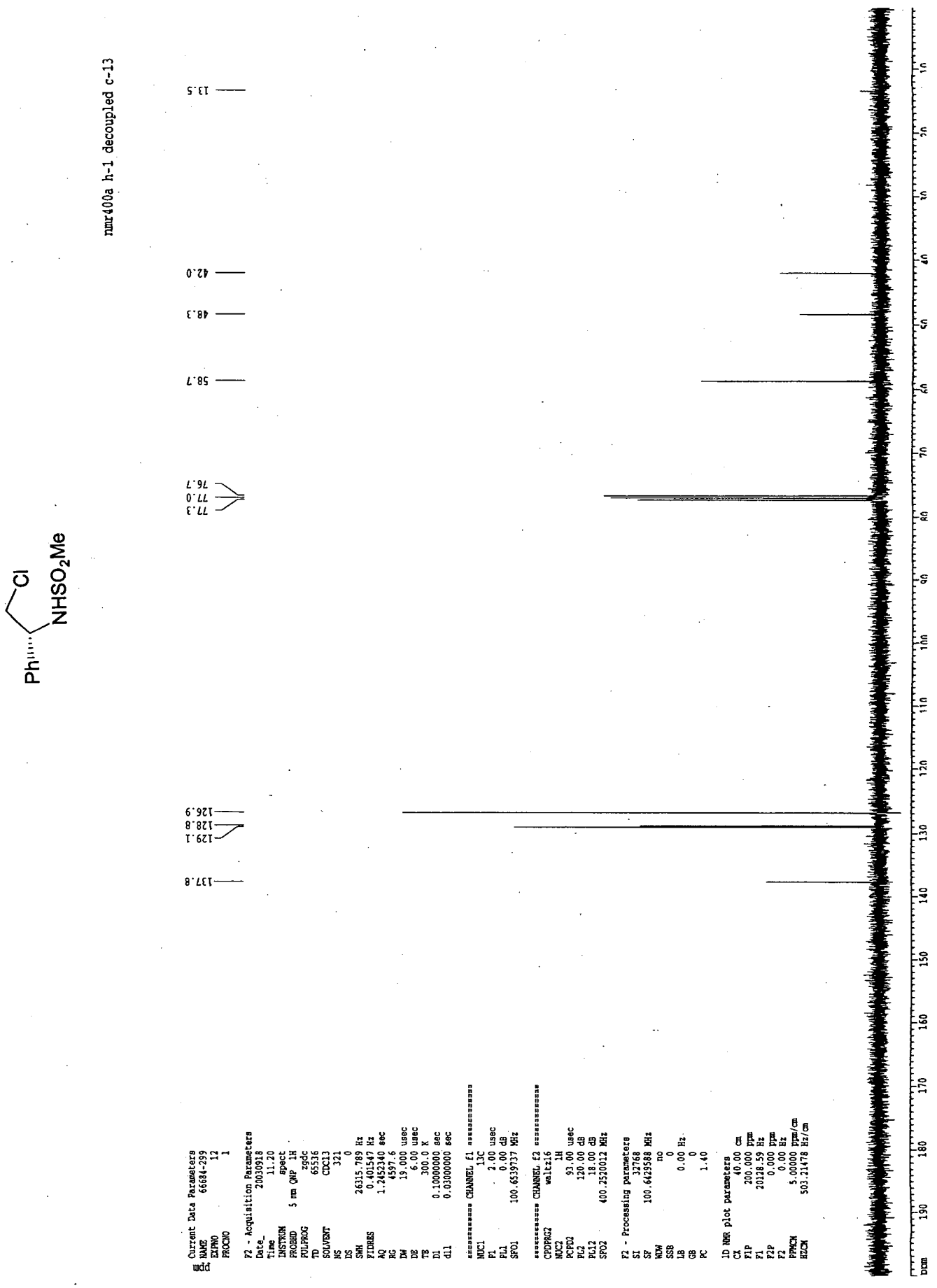

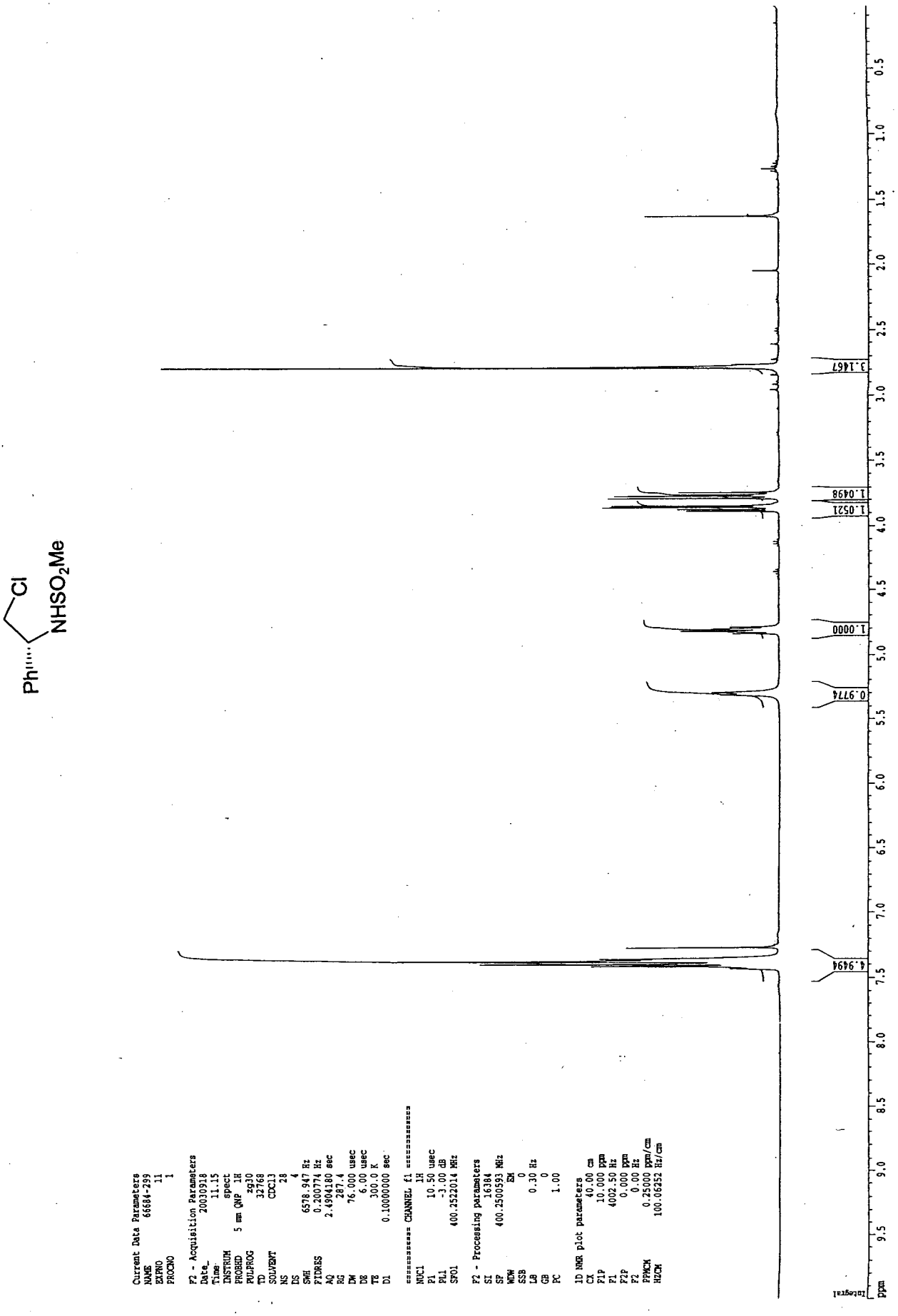


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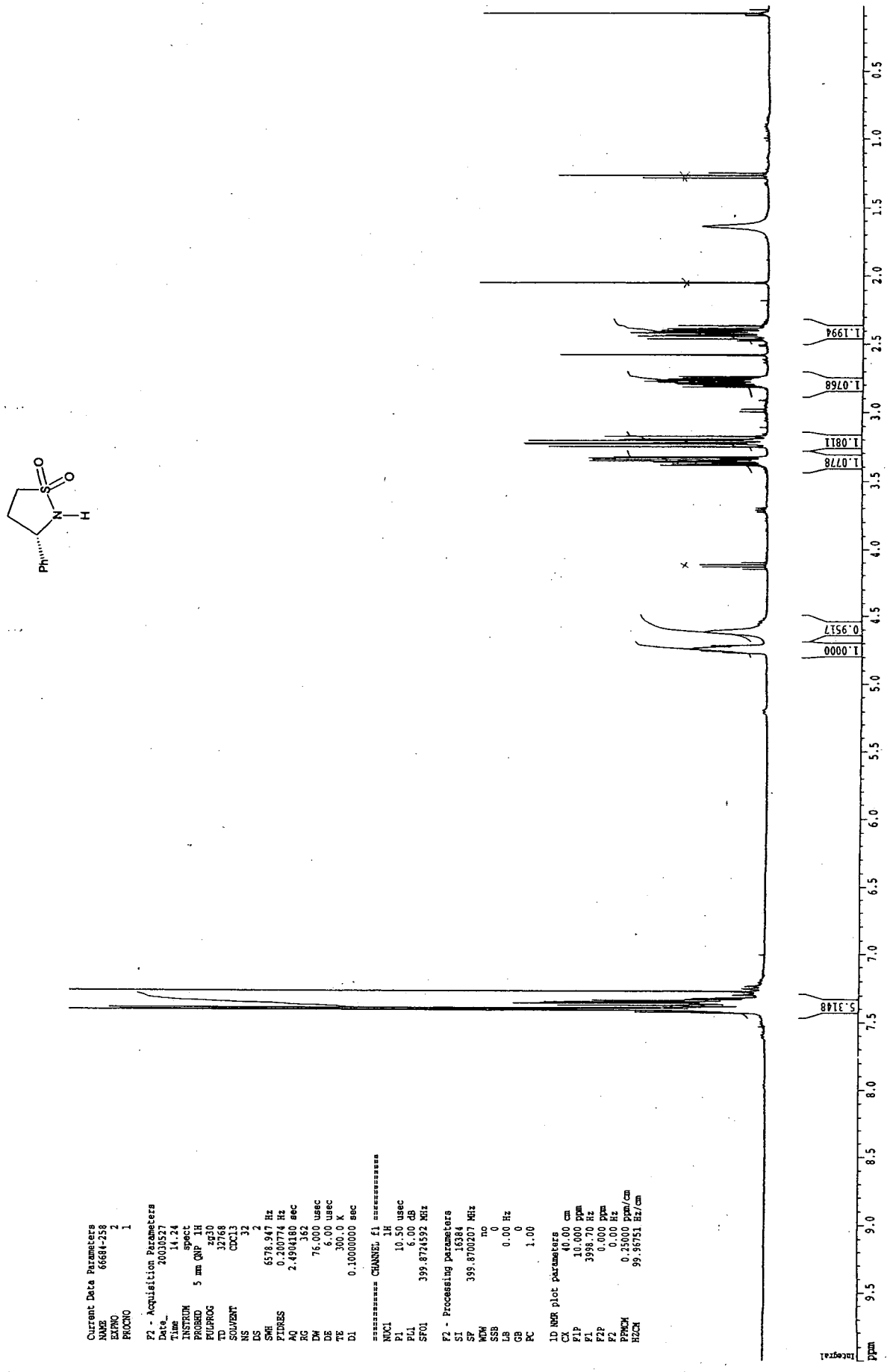
Current Data Parameters
NAME          66684-299
EXPNO             11
PROCNO             1

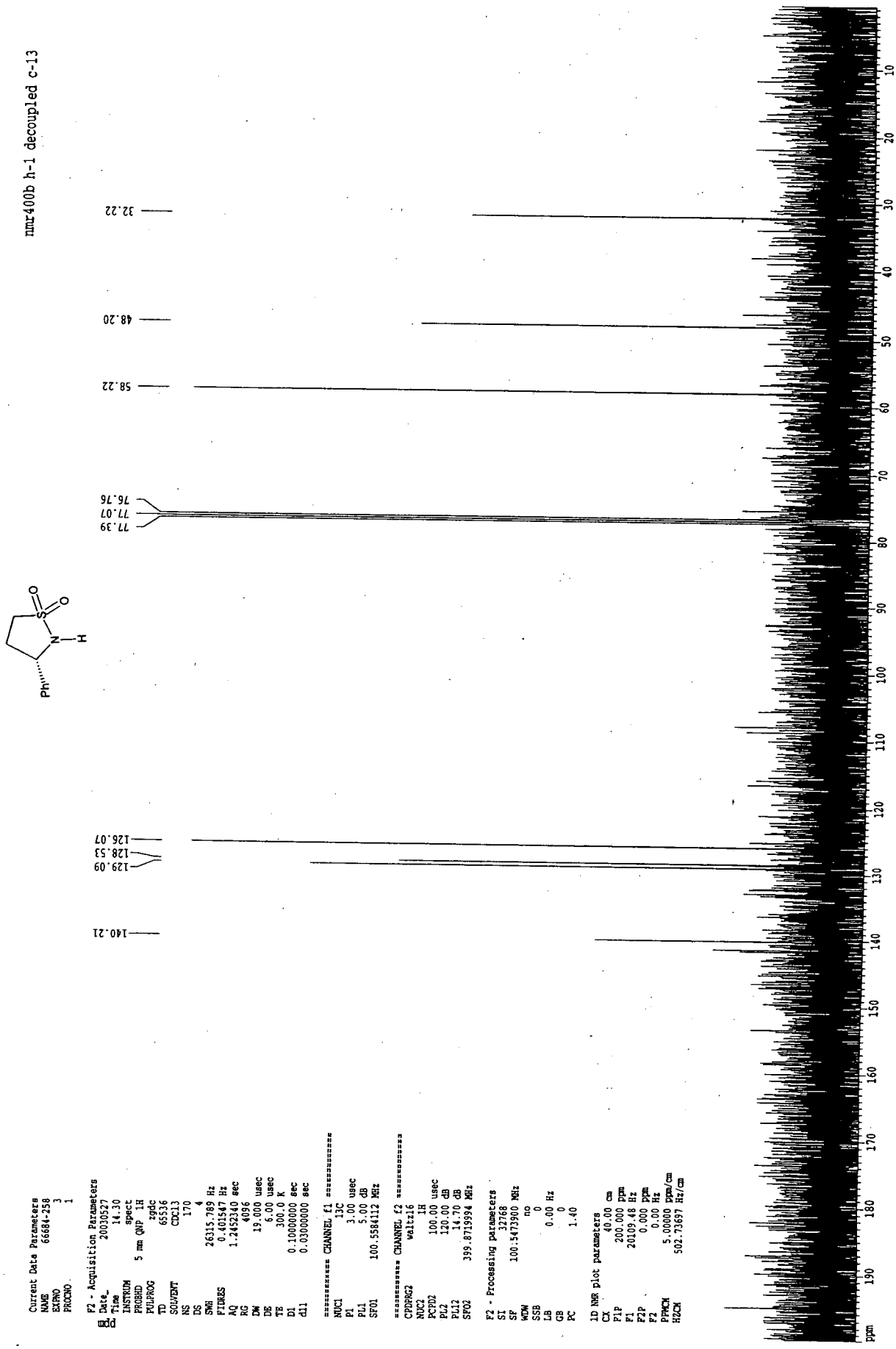
F2 - Acquisition Parameters
Date_          20030918
Time              11.15
INSTRUM           spect
PROBHD   5 mm QNP 1H
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                  28
DS                   4
SWH           6578.947 Hz
FIDRES        0.200774 Hz
AQ            2.4904180 sec
RG                287.4
DW               76.000 usec
DE                6.00 usec
TE                300.0 K
D1            0.10000000 sec

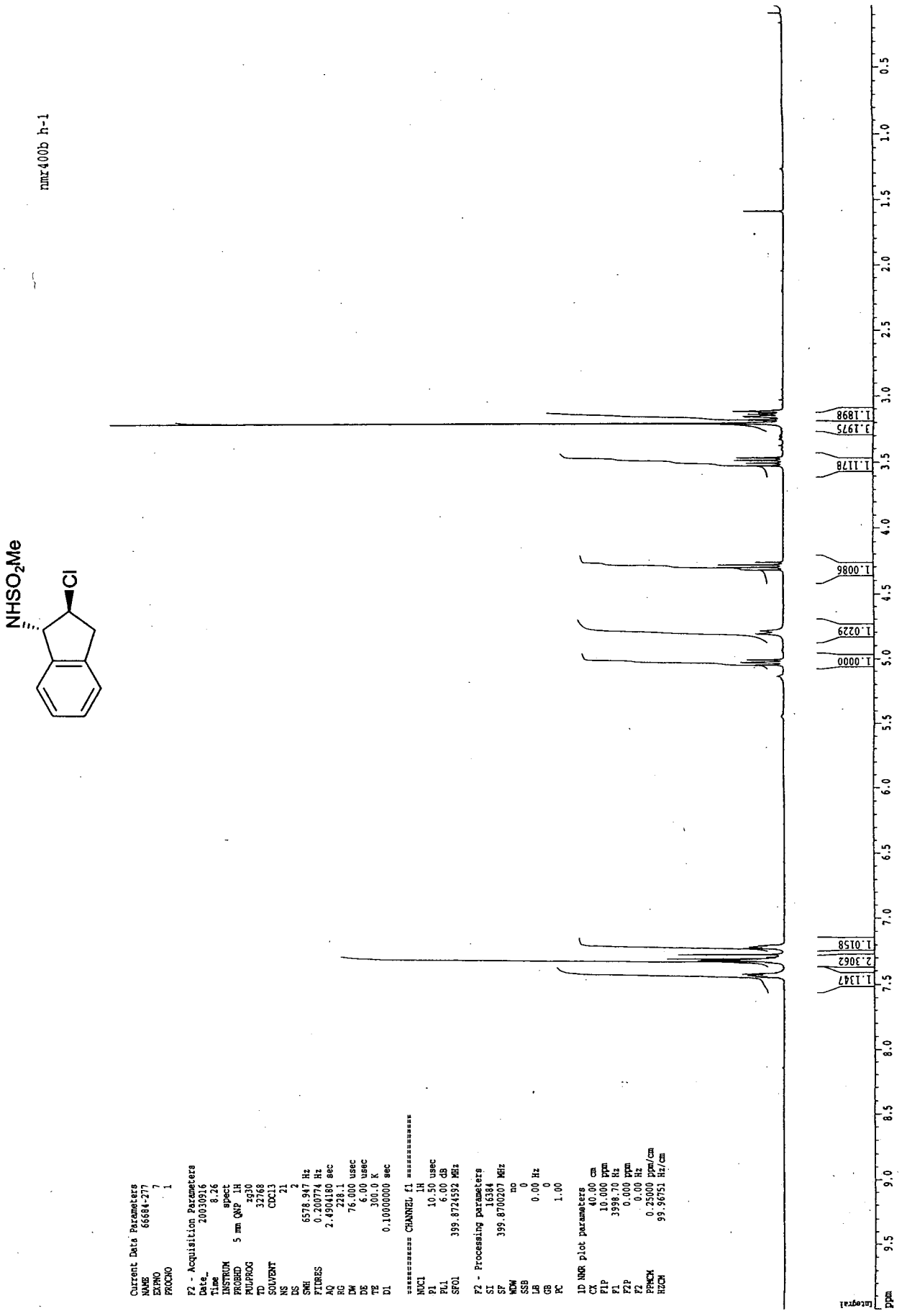
========== CHANNEL f1 ==========
NUC1                1H
P1                10.50 usec
PL1               -3.00 dB
SFO1         400.2522014 MHz

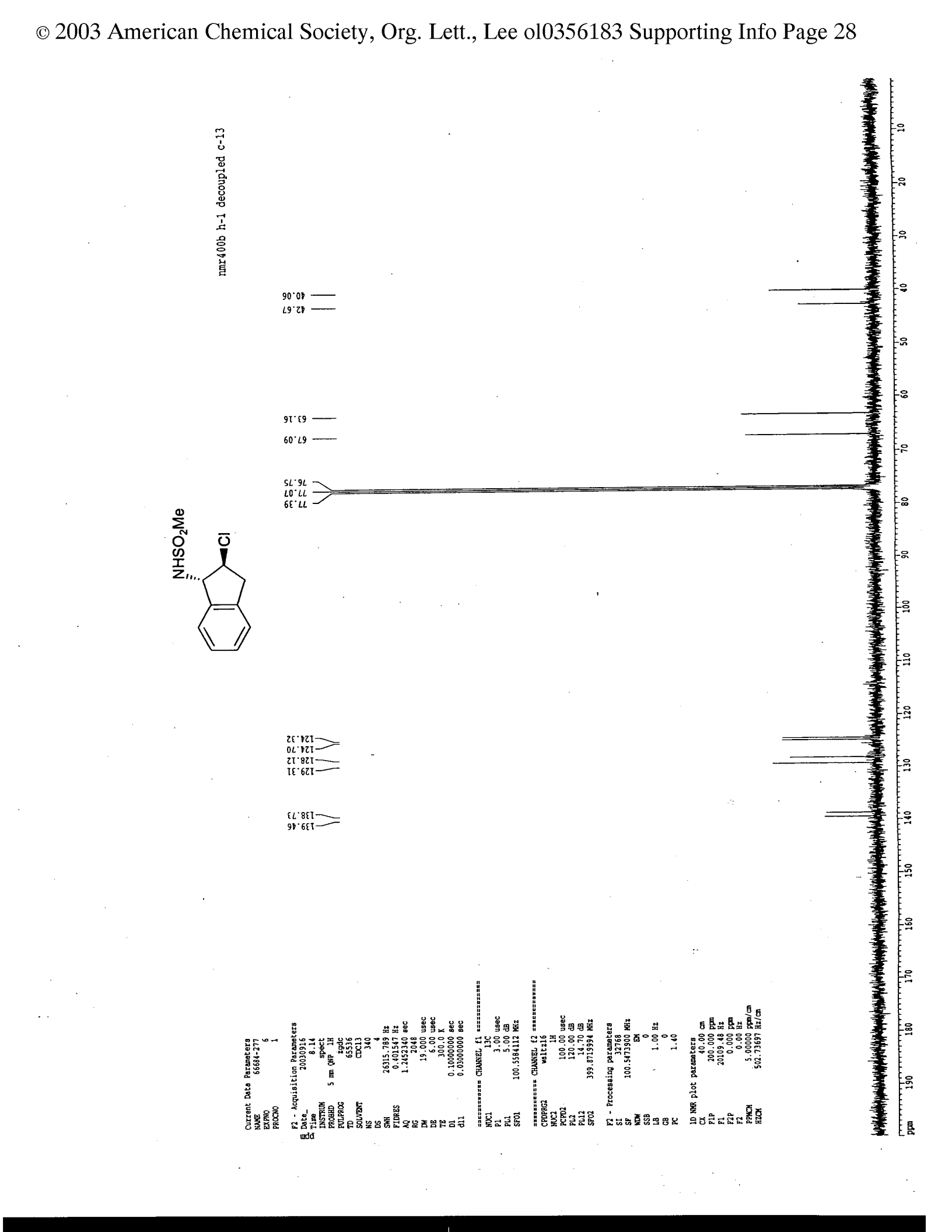
F2 - Processing parameters
SI                16384
SF           400.2500593 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

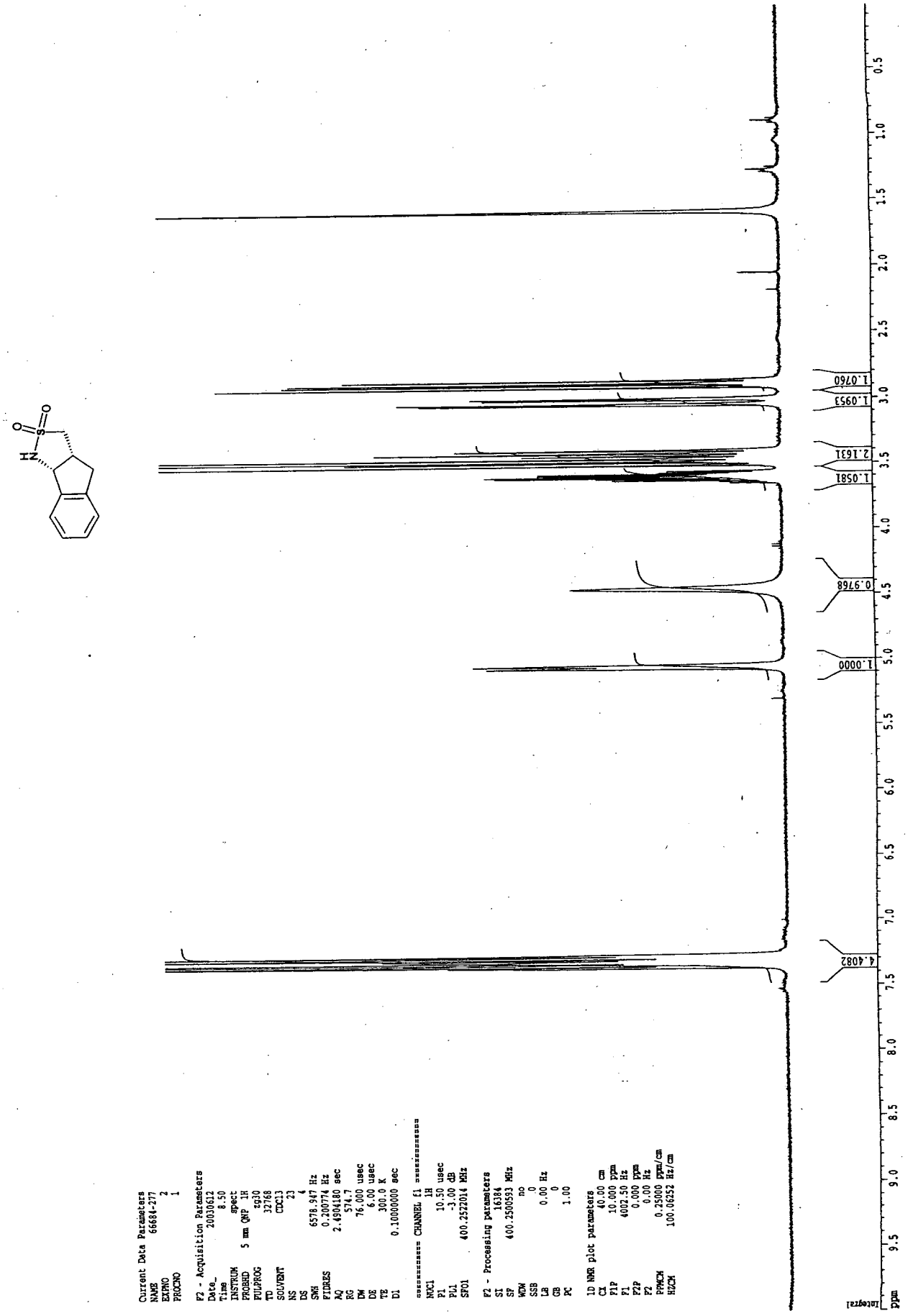
1D NMR plot parameters
CX                40.00 cm
F1P               10.000 ppm
F1              4002.50 Hz
F2P               0.000 ppm
F2                0.00 Hz
PPMCM          0.25000 ppm/cm
HZCM         100.06252 Hz/cm
```









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Current Data Parameters
NAME          66684-277
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20030612
Time               8.50
INSTRUM            spect
PROBHD     5 mm QNP 1H
PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   23
DS                    4
SWH           6578.947 Hz
FIDRES        0.200774 Hz
AQ            2.4904180 sec
RG                574.7
DW               76.000 usec
DE                6.00 usec
TE                300.0 K
D1            0.10000000 sec

========== CHANNEL f1 ==========
NUC1                1H
P1                10.50 usec
PL1               -3.00 dB
SFO1       400.2522014 MHz

F2 - Processing parameters
SI                 16384
SF         400.2500593 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 40.00 cm
F1P               10.000 ppm
F1              4002.50 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          0.25000 ppm/cm
HZCM          100.06252 Hz/cm
```