Electronic Supplementary Information (ESI) for Organic and Biomolecular Chemistry

Design, Synthesis, Biological Evaluation and X-ray Structural Studies of HIV-1 Protease Inhibitors Containing Substituted fused-Tetrahydropyranyl Tetrahydrofuran as P2-Ligands

Arun K. Ghosh, Cuthbert D. Martyr, Luke A. Kassekert, Prasanth R. Nyalapatla, Melinda Steffey, Johnson Agniswamy, Yuan-Fang Wang, Masayuki Amano, and Hiroaki Mitsuya

Table of contents:

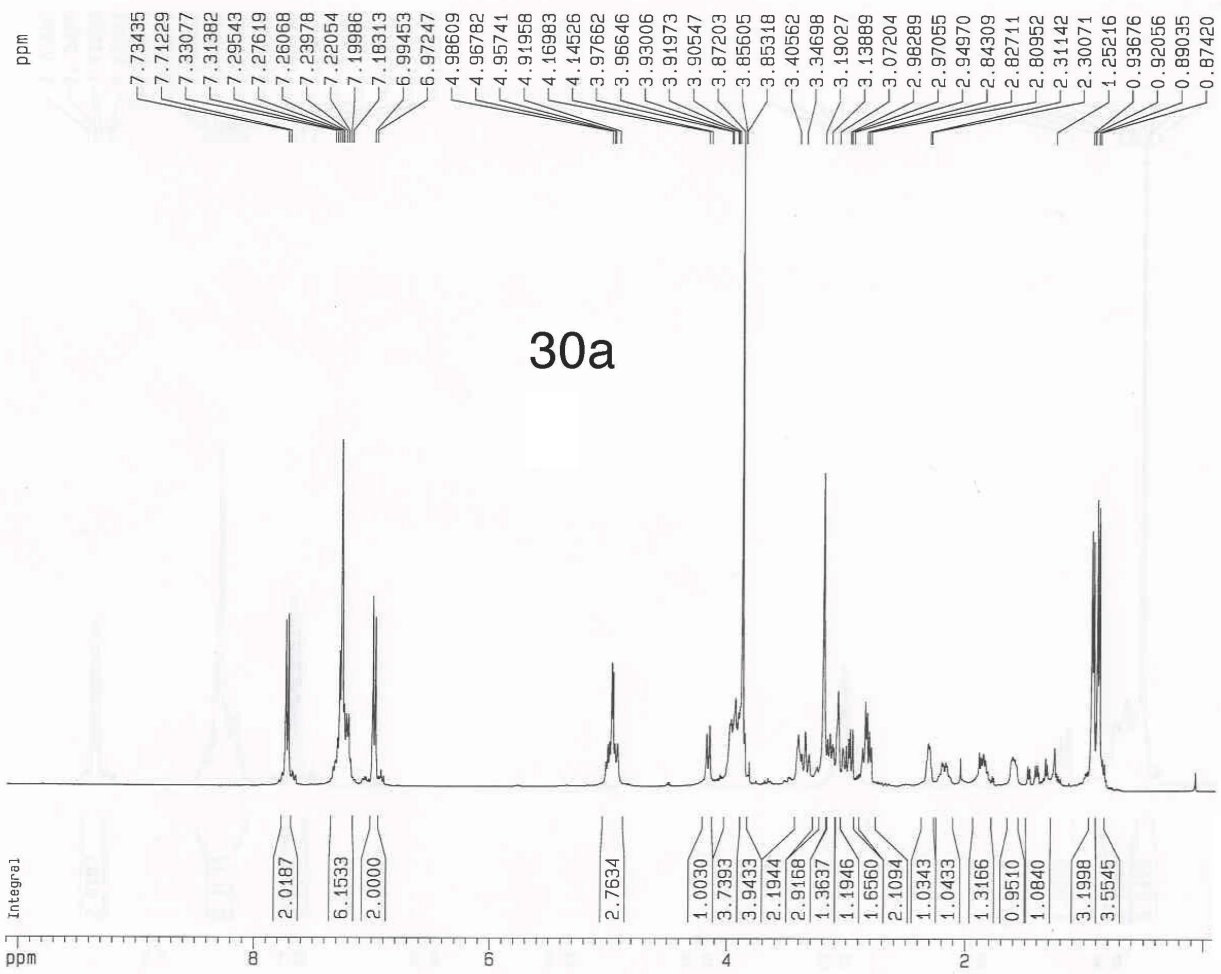
Table I. HRMS for inhibitors **30a-m**

Inhibitor	HRMS
30a	HRMS (ESI), calcd for $C_{30}H_{42}N_2O_9S$: *m/z* 629.2509 (M+Na), found *m/z* 629.2505 (M+Na).
30b	HRMS (ESI), calcd for $C_{30}H_{42}N_2O_9S$: *m/z* 629.2509 (M+Na), found *m/z* 629.2505 (M+Na)
30c	HRMS (ESI), calcd for $C_{29}H_{41}N_3O_8S$: *m/z* 614.2513 (M+Na), found *m/z* 614.2502 (M+Na).
30d	HRMS (ESI), calcd for $C_{31}H_{44}N_2O_9S$: *m/z* 643.2665 (M+Na), found *m/z* 643.2660 (M+Na)
30e	HRMS (ESI), calcd for $C_{36}H_{46}N_2O_9S$: *m/z* 705.2822 (M+Na), found *m/z* 705.2816 (M+Na).
30f	HRMS (ESI), calcd for $C_{29}H_{40}N_2O_8S$: *m/z* 593.2532 (M+H) and 615.2352 (M+Na), found *m/z* 593.2520 (M+H) and 615.2330 (M+Na)
30g	HRMS (ESI), calcd for ($C_{29}H_{39}N_5O_8S$): *m/z* 618.2598 (M+H), found *m/z* 618.2597 (M+H).
30h	HRMS (ESI), calcd for $C_{29}H_{41}N_3O_8S$: *m/z* 592.2693 (M+H), found *m/z* 592.2686 (M+H).
30i	HRMS (ESI), calcd for $C_{30}H_{43}N_3O_8S$: *m/z* 606.2849 (M+H), found *m/z* 606.2840 (M+Na)
30j	HRMS (ESI), calcd for $C_{31}H_{45}N_3O_8S$: *m/z* 620.3005 (M+Na), found *m/z* 620.3000 (M+Na)
30k	HRMS (ESI), calcd for $C_{30}H_{44}N_4O_7S$: *m/z* 605.3009 (M+H), found *m/z* 605.3005 (M+H).
30l	HRMS (ESI), calcd for $C_{32}H_{47}N_3O_8S$: *m/z* 634.3163 (M+H), found *m/z* 634.3156 (M+H).
30m	HRMS (ESI), calcd for $C_{31}H_{45}N_3O_8S$: *m/z* 620.3006 (M+H), found *m/z* 620.2998 (M+H).

Table 2. Crystallographic Data Collection and Refinement Statistics

Complex Name	PR/30b	PR/30j
Space group	$P2_12_12$	$P2_12_12$
Unit cell dimensions: (Å)		
a	58.64	58.68
b	86.33	86.06
c	45.98	46.00
Resolution range (final shell) (Å)	50-1.22 (1.26-1.22)	50-1.62 (1.68-1.62)
Unique reflections	65,344	29,447
Wilson B-factor	15.5	17.1
R_{merge} (%) overall (final shell)	6.8 (35.7)	5.7 (48.3)
I/σ(I) overall (final shell)	22.9 (2.7)	30.9 (3.9)
Completeness (%) overall (final shell)	93.1 (54.9)	96.8 (90.0)
Redundancy (final shell)	7.2 (3.2)	7.0 (6.1)
R (%)	16.1	20.3
R_{free} (%)	20.1	24.5
No. of solvent atoms (total occupancies)	195 (159)	142 (124.25)
RMS deviation from ideality		
Bonds (Å)	0.013	0.007
Angle distance (Å)	0.032	0.024
Average B-factors (Å^2)		
Main-chain atoms	15.5	16.7
Side-chain atoms	21.7	23.0
Whole chain atoms	18.5	19.8
Inhibitor	12.6	14.3
Solvent	26.5	25.7
RMS deviation to 2IEN	0.13	0.14

H1 standard parameters, CDCl3, QNP probe.



Current Data Parameters

NAME	CMD-F-080b
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20100901
Time	11.38
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	64
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	1024
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1694000 MHz
NUCLEUS	1H

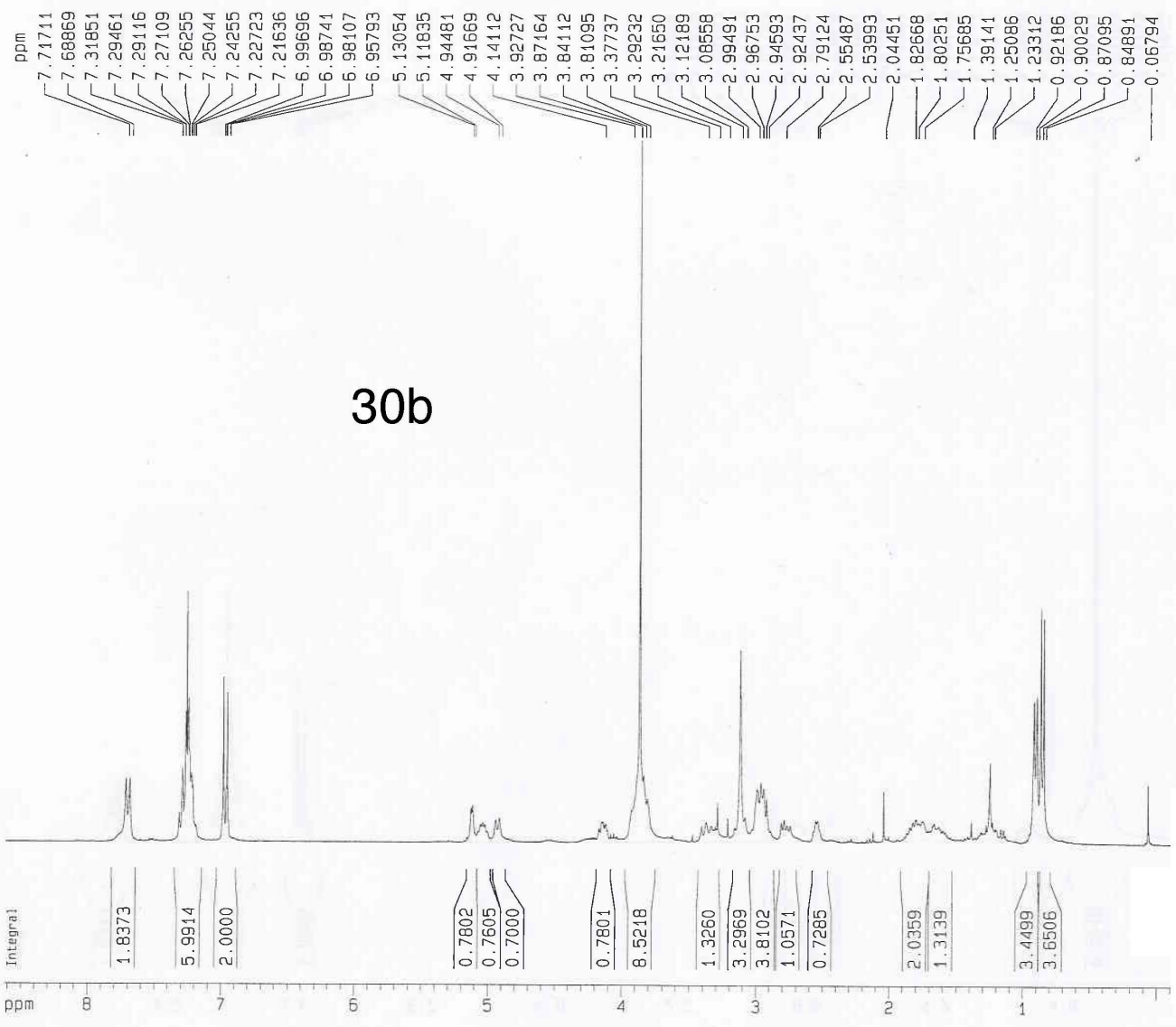
F2 - Processing parameters

SI	8192
SF	400.1669660 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.100 ppm
F1	4041.69 Hz
F2P	-0.100 ppm
F2	-40.02 Hz
PPMCM	0.51000 ppm/cm
HZCM	204.08516 Hz/cm

1H standard parameters, CDCl3, QNP probe.



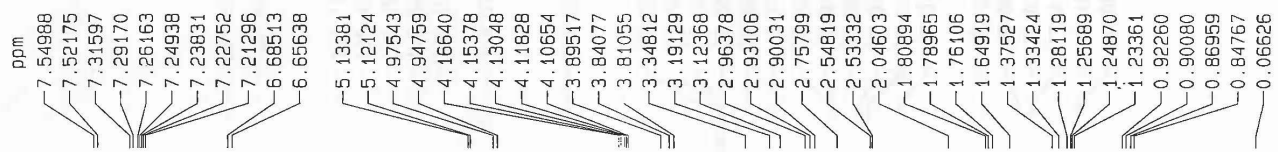

```
Current Data Parameters
NAME                  COM-F-183
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_              20110114
Time                      10.59
INSTRUM                   spect
PROBHD     5 mm QNP  1H
PULPROG                   zg30
TD                       16384
SOLVENT                   CDCl3
NS                           32
DS                            2
SWH                4237.288 Hz
FIDRES             0.258624 Hz
AQ                 1.9333620 sec
RG                         2048
DW                      118.000 usec
DE                       158.57 usec
TE                       300.0 K
D1                 2.00000000 sec
P1                      11.25 usec
SFO1               300.1350100 MHz
NUCLEUS                     1H

F2 - Processing parameters
SI                         8192
SF                 300.1333670 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00

1D NMR plot parameters
CX                       20.00 cm
F1P                      8.620 ppm
F1                     2587.08 Hz
F2P                     -0.108 ppm
F2                      -32.41 Hz
PPMCM                 0.43639 ppm/cm
HZCM                130.97476 Hz/cm
```

1H standard parameters, CDCl3, QNP probe.



Current Data Parameters

NAME	CDM-6-130
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20110524
Time	20.41
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	43
DS	2
SWH	4237.288 Hz
FIDRES	0.258624 Hz
AQ	1.9333620 sec
RG	2850
DW	118.000 usec
DE	168.57 usec
TE	300.0 K
D1	2.00000000 sec
P1	11.25 usec
SFO1	300.1350100 MHz
NUCLEUS	1H

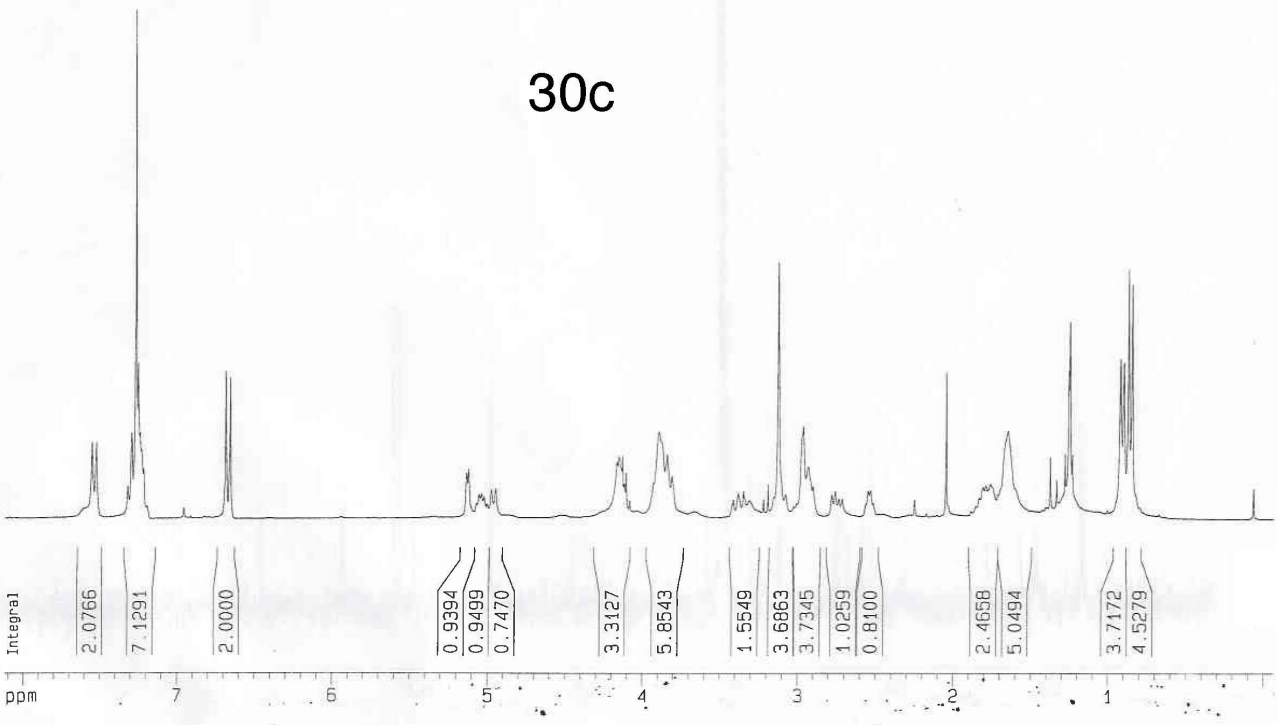
F2 - Processing parameters

SI	8192
SF	300.1333670 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

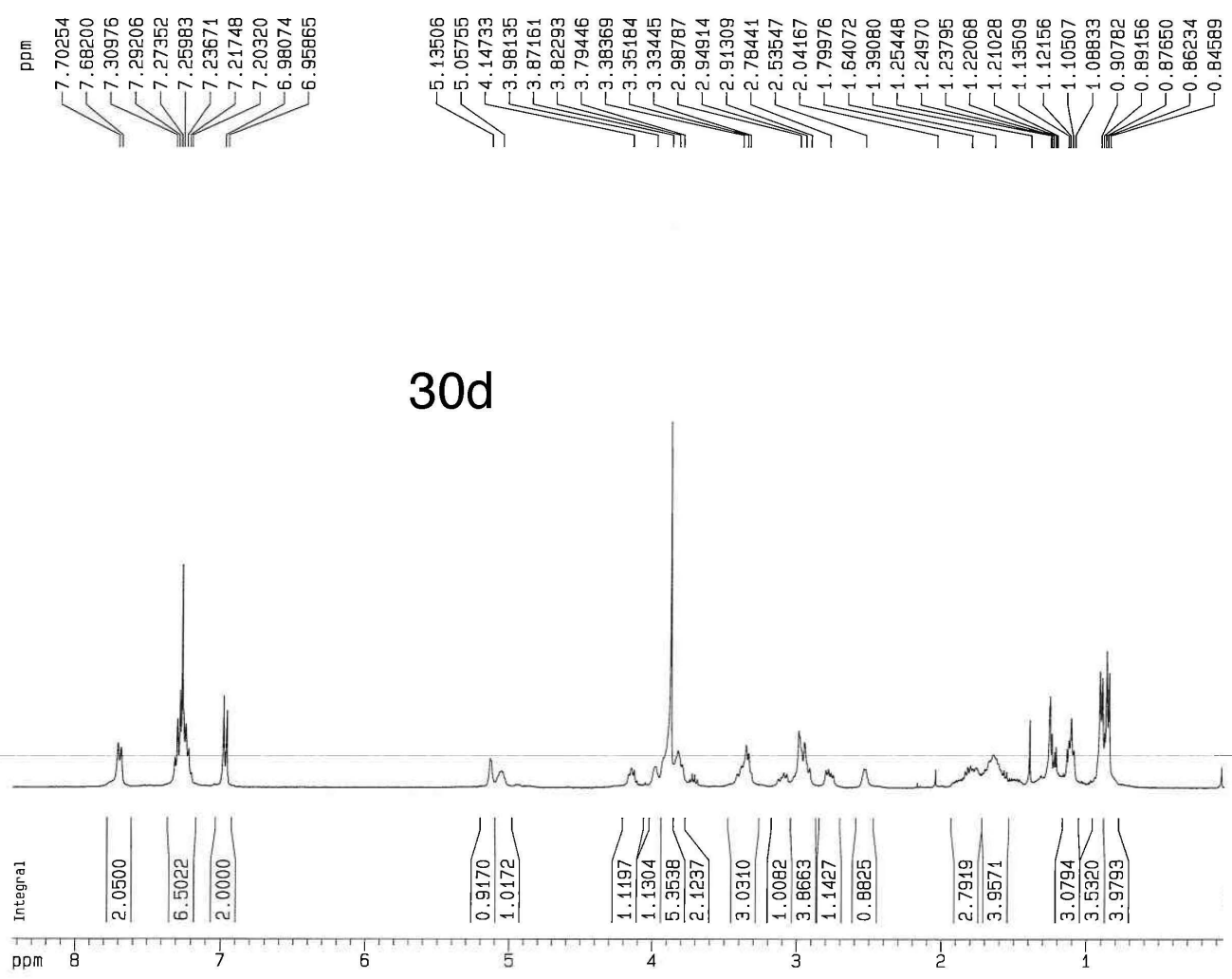
1D NMR plot parameters

CX	20.00 cm
F1P	9.118 ppm
F1	2436.36 Hz
F2P	-0.064 ppm
F2	-19.12 Hz
PPMCM	0.40907 ppm/cm
HZCM	122.77499 Hz/cm

30c



H1 standard parameters, CDCl3, QNP probe.



Current Data Parameters

NAME	CDM-G-063-b
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20111007
Time	15.39
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	40
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	128
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1694000 MHz
NUCLEUS	1H

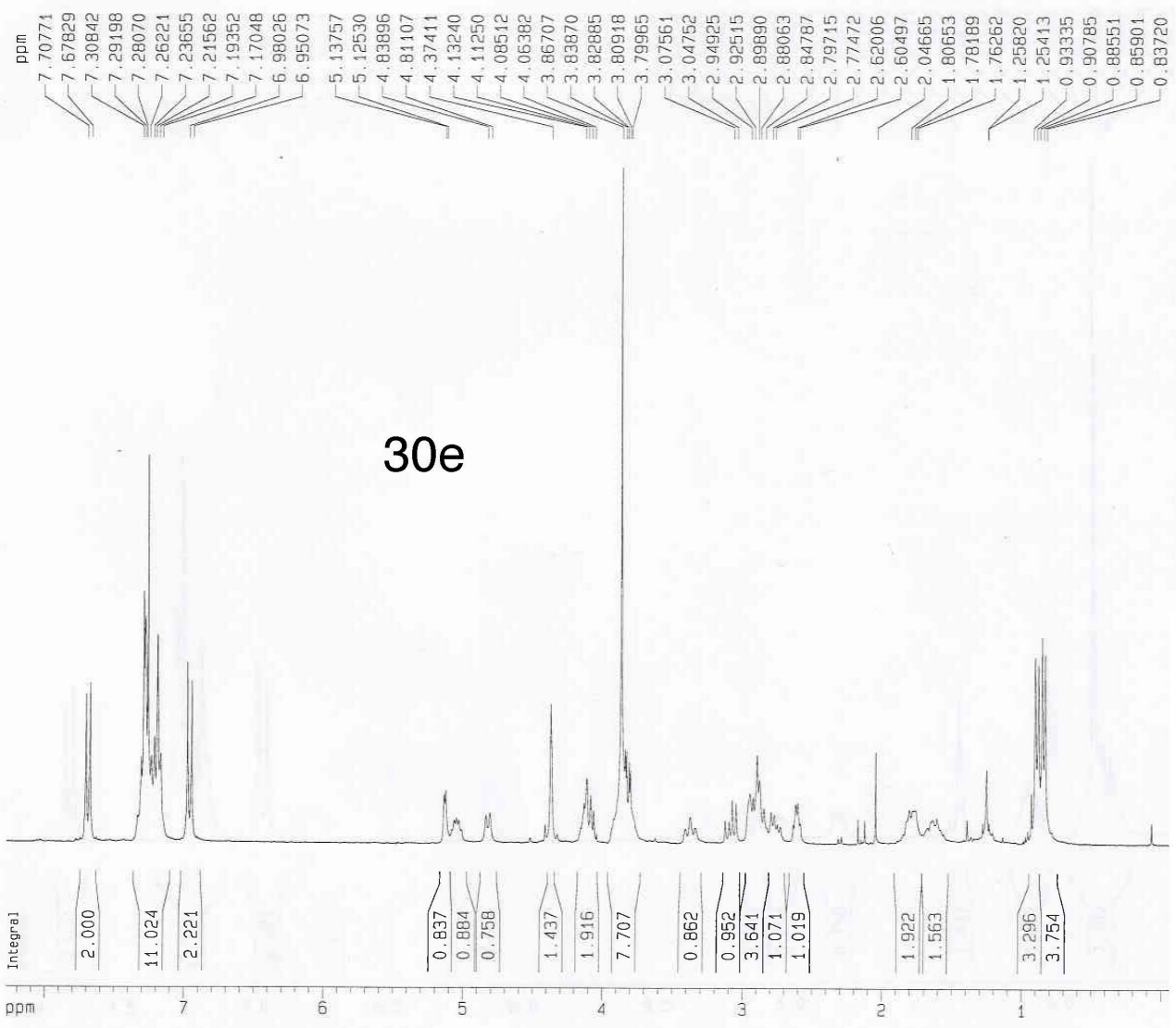
F2 - Processing parameters

SI	8192
SF	400.1669660 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.432 ppm
F1	3374.25 Hz
F2P	0.047 ppm
F2	18.74 Hz
PPMCM	0.41926 ppm/cm
HZCM	167.77536 Hz/cm

1H standard parameters, CDCl3, QNP probe.



Current Data Parameters

NAME	CDM-F-182
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20110114
Time	10.51
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	32
DS	2
SWH	4237.288 Hz
FIDRES	0.258624 Hz
AQ	1.9333620 sec
RG	128
DW	118.000 usec
DE	158.57 usec
TE	300.0 K
D1	2.00000000 sec
P1	11.25 usec
SFO1	300.1350100 MHz
NUCLEUS	1H

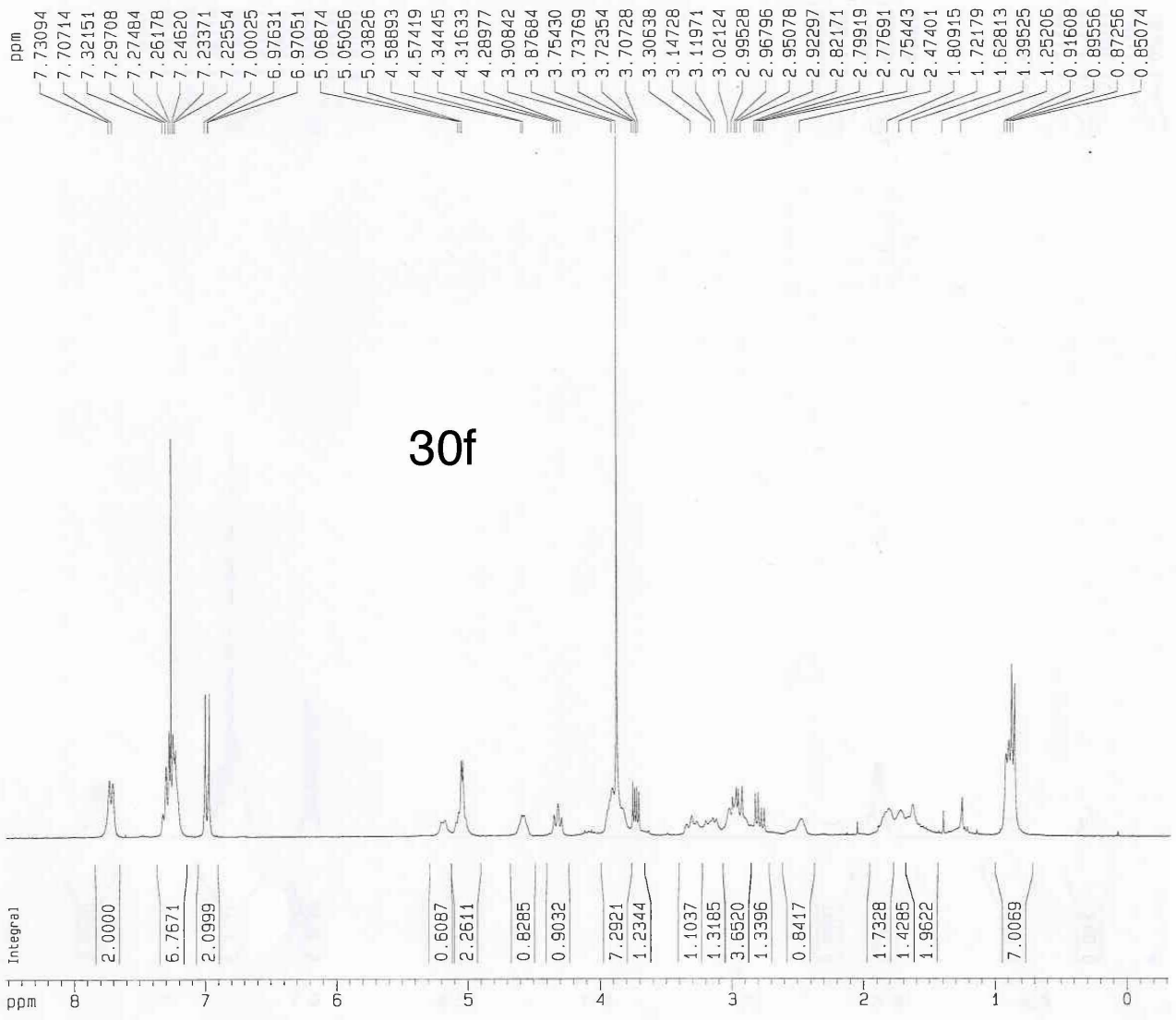
F2 - Processing parameters

SI	8192
SF	300.1333670 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.280 ppm
F1	2485.14 Hz
F2P	-0.093 ppm
F2	-27.98 Hz
PPMCM	0.41867 ppm/cm
HZCM	125.65598 Hz/cm

1H standard parameters, CDCl3, QNP probe.



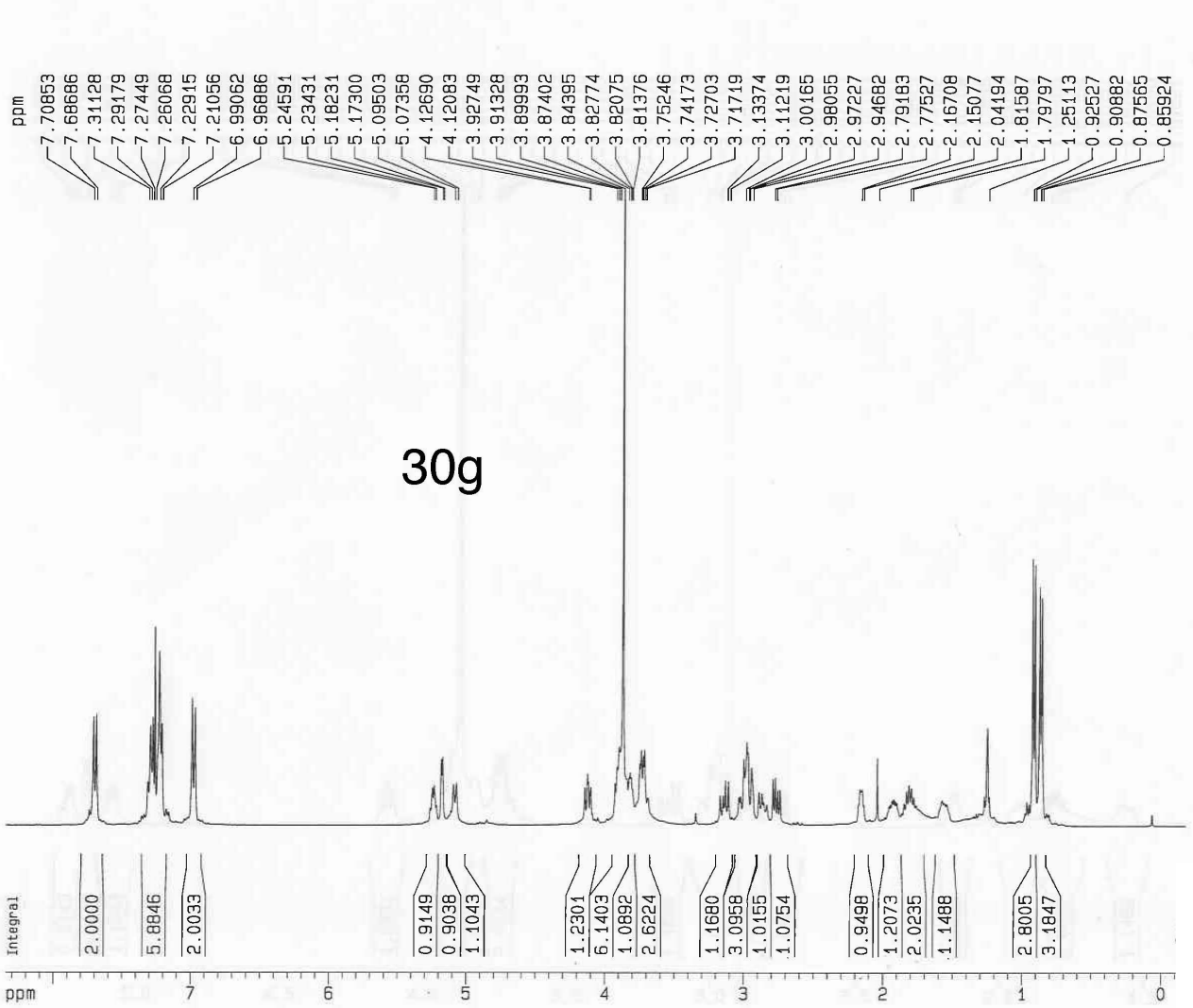
Current Data Parameters
NAME CDN-G-004c
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110121
Time 11.17
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 28
DS 2
SWH 4237.288 Hz
FIDRES 0.258624 Hz
AQ 1.9333620 sec
RG 4096
DW 118.000 usec
DE 168.57 usec
TE 300.0 K
D1 2.00000000 sec
P1 11.25 usec
SFO1 300.1330100 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 8192
SF 300.1333670 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 8.515 ppm
F1 2556.06 Hz
F2P -0.330 ppm
F2 -98.90 Hz
PPMCM 0.44230 ppm/cm
HZCM 132.74768 Hz/cm

H1 standard parameters, CDCl3, QNP probe.



Current Data Parameters

NAME	CDM-H-026
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20110902
Time	12.20
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	24
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	1430
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1694000 MHz
NUCLEUS	1H

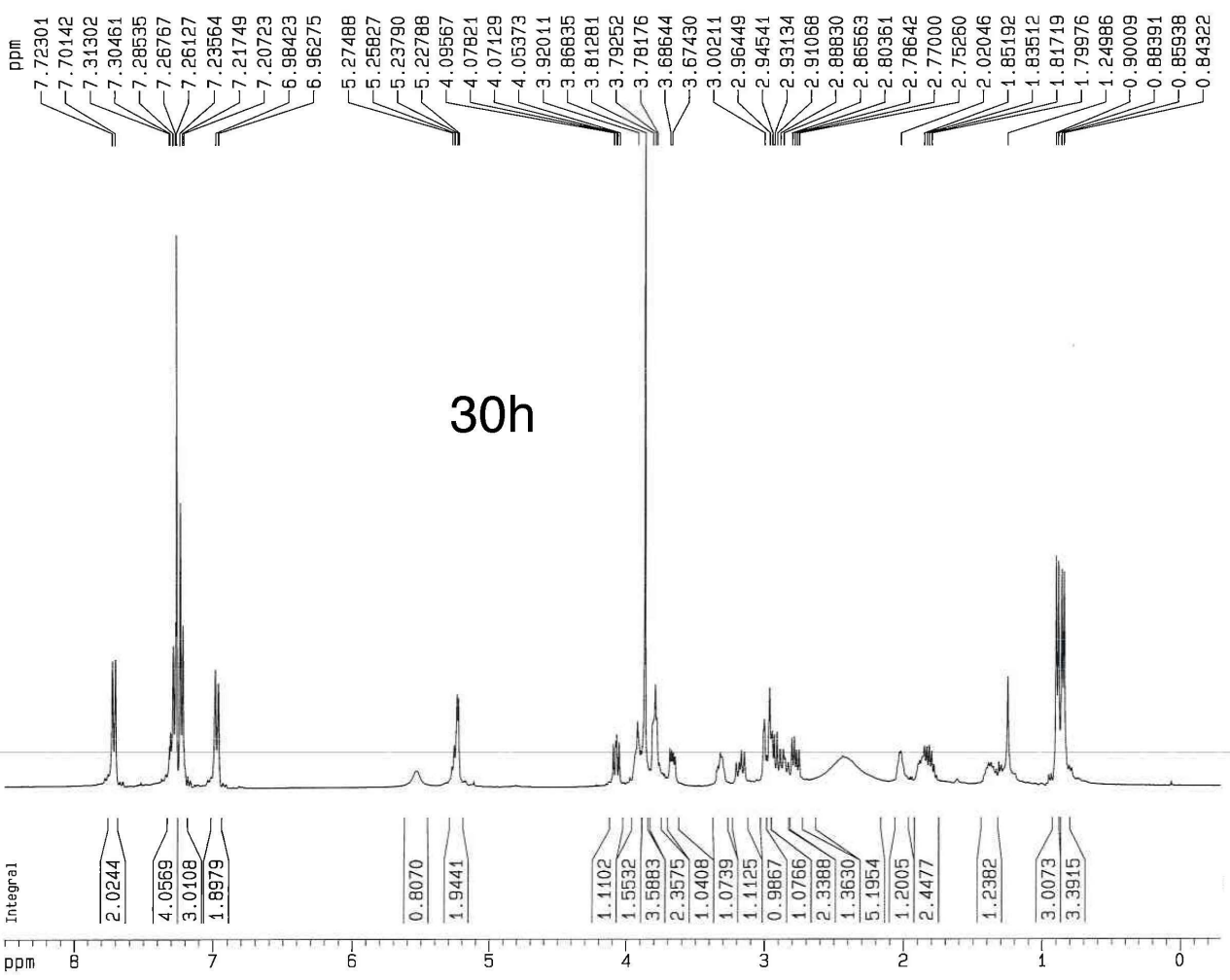
F2 - Processing parameters

SI	8192
SF	400.1669660 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.344 ppm
F1	3338.99 Hz
F2P	-0.173 ppm
F2	-69.41 Hz
PPMCM	0.42587 ppm/cm
HZCM	170.41983 Hz/cm

H1 standard parameters, CDCl3, QNP probe.



Current Data Parameters

NAME	CDM-H-031
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20110905
Time	17.34
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	32
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	2860
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1694000 MHz
NUCLEUS	1H

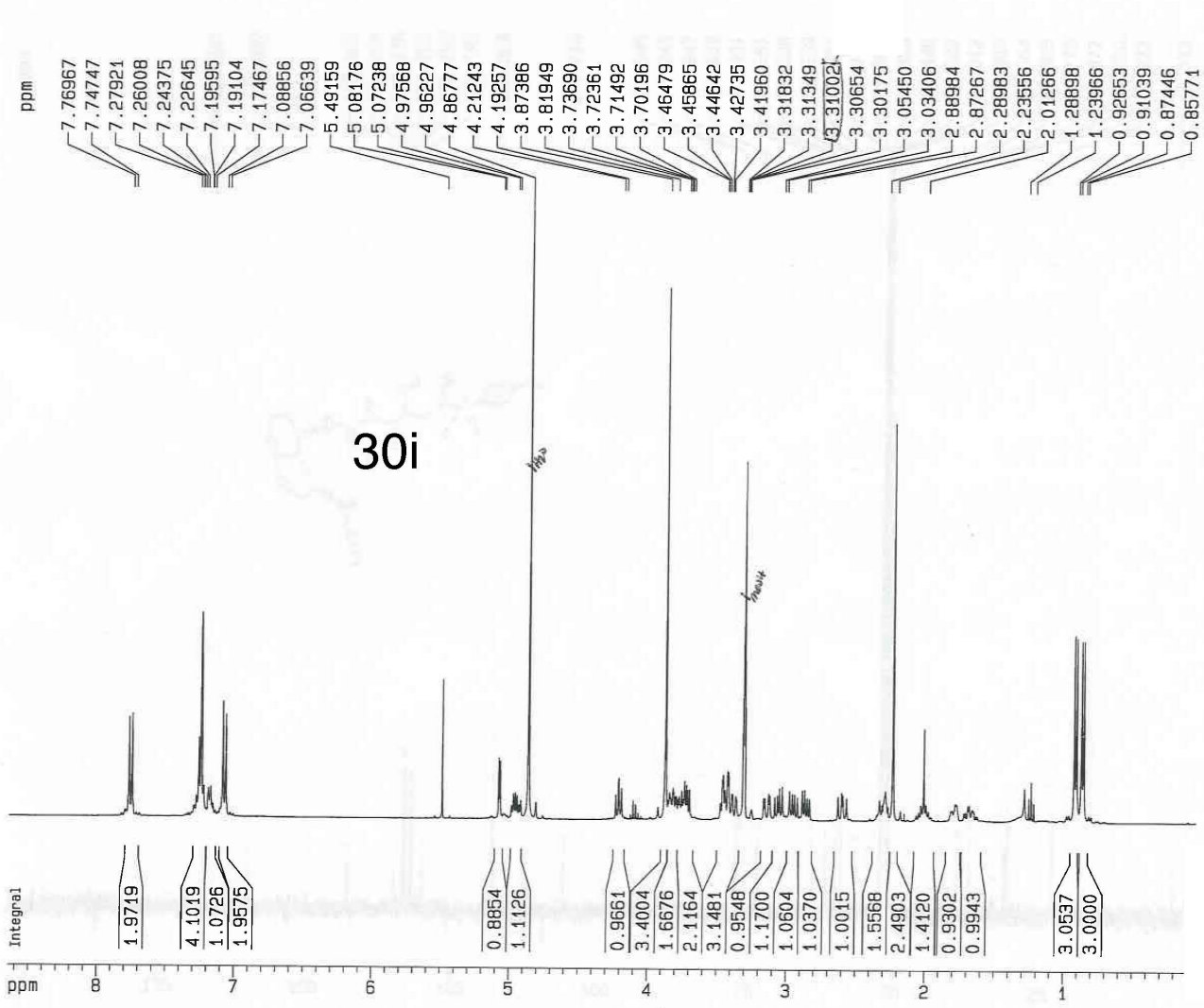
F2 - Processing parameters

SI	8192
SF	400.1669660 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.506 ppm
F1	3403.63 Hz
F2P	-0.291 ppm
F2	-116.42 Hz
PPMCM	0.43982 ppm/cm
HZCM	176.00255 Hz/cm

H1 standard parameters, CD3OD, QNP probe.



Current Data Parameters

NAME	CDM-H-102
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20111111
Time	14.11
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	MeOH
NS	32
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	1430
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1709450 MHz
NUCLEUS	1H

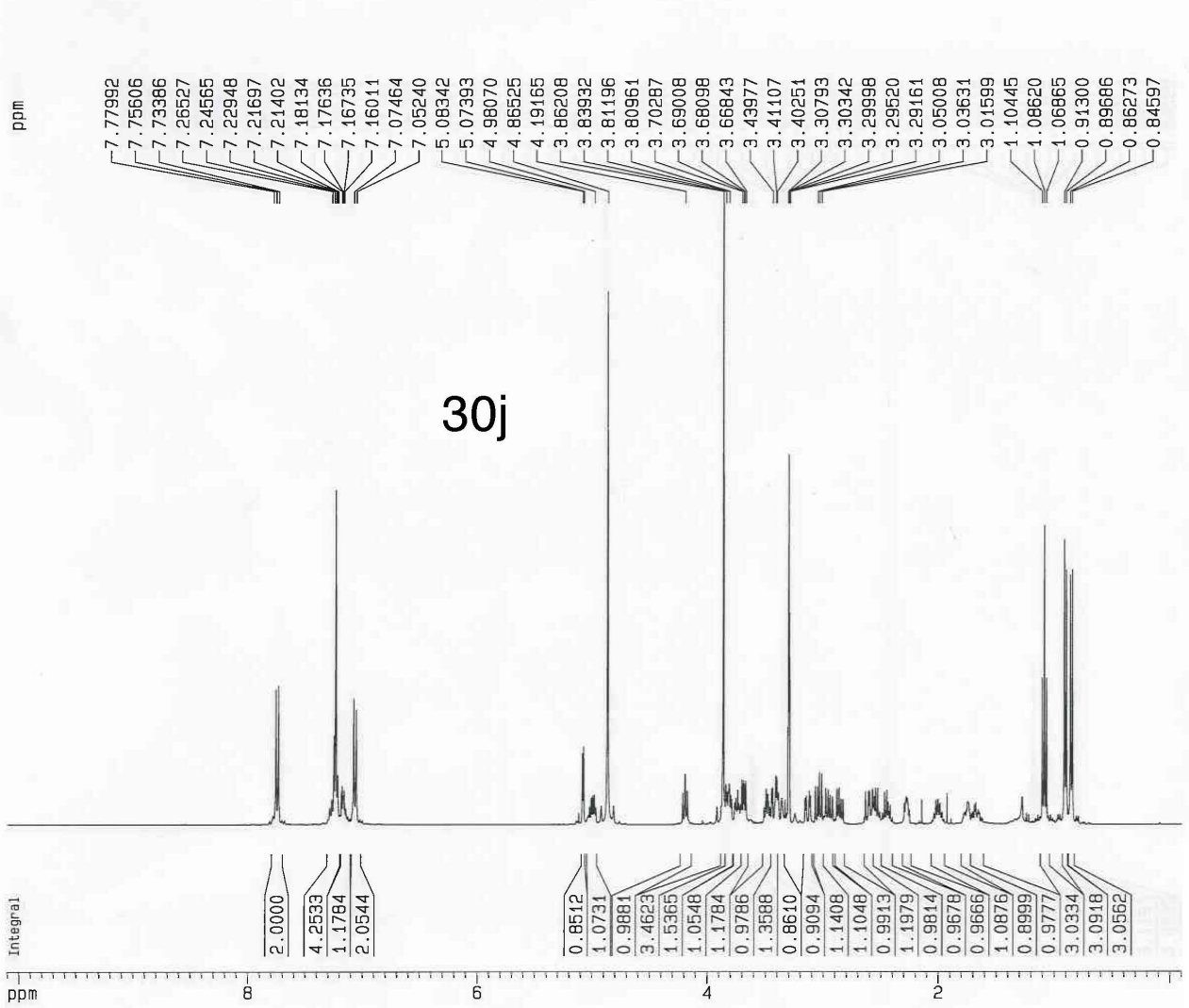
F2 - Processing parameters

SI	8192
SF	400.1685410 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.643 ppm
F1	3458.81 Hz
F2P	0.044 ppm
F2	17.71 Hz
PPMCM	0.42996 ppm/cm
HZCM	172.05466 Hz/cm

H1 standard parameters, CD3OD, QNP probe.



Current Data Parameters

NAME	CDM-H-069b
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20111012
Time	14.02
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	MeOH
NS	40
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	1024
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1709450 MHz
NUCLEUS	1H

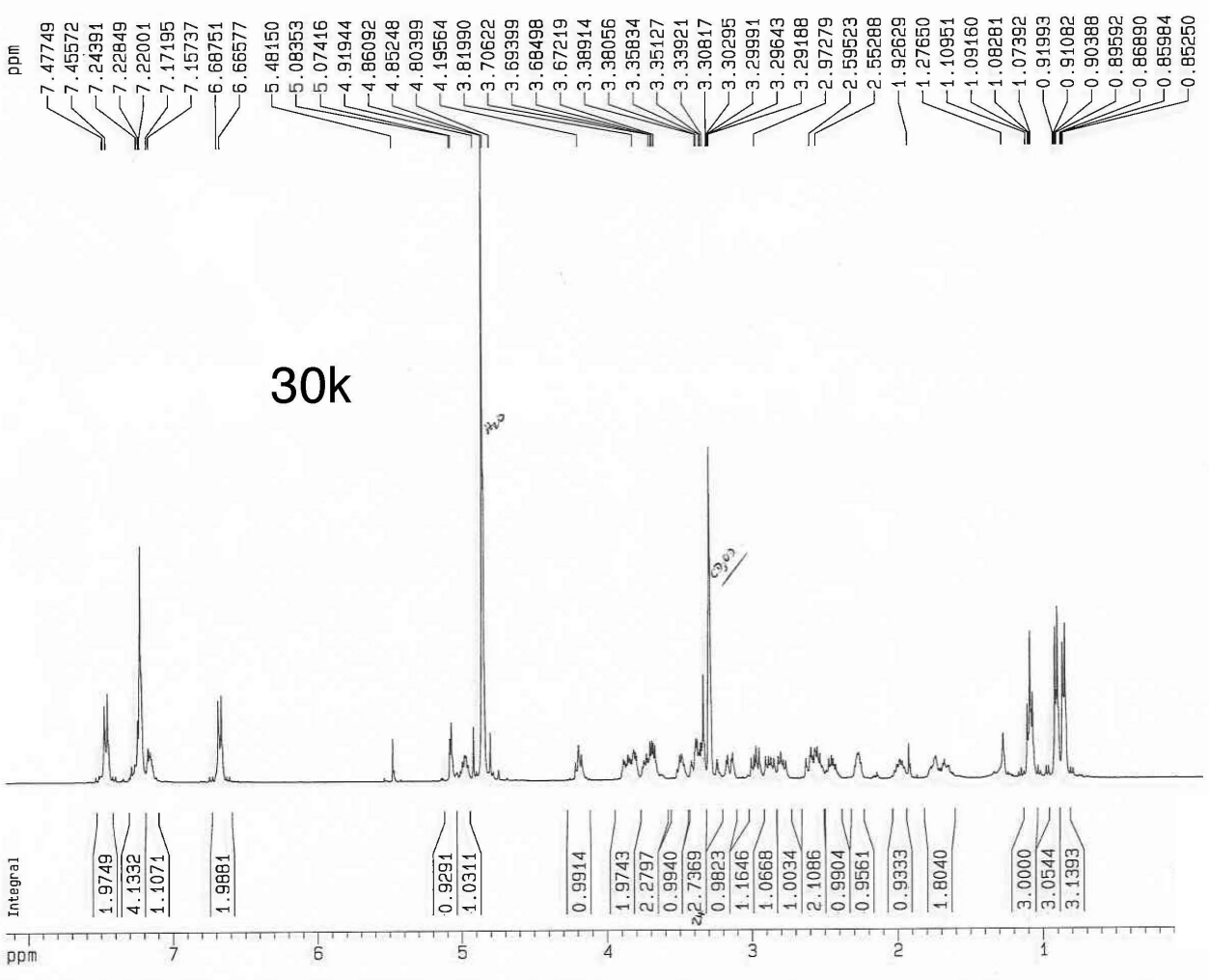
F2 - Processing parameters

SI	8192
SF	400.1685450 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.100 ppm
F1	4041.70 Hz
F2P	-0.100 ppm
F2	-40.02 Hz
PPMCM	0.51000 ppm/cm
HZCM	204.08597 Hz/cm

H1 standard parameters, CD3OD, QNP probe.



Current Data Parameters

NAME	~~CDM H-128~~ CDM-H-178
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20120221
Time	20.41
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	MeOH
NS	32
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	1024
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1709450 MHz
NUCLEUS	1H

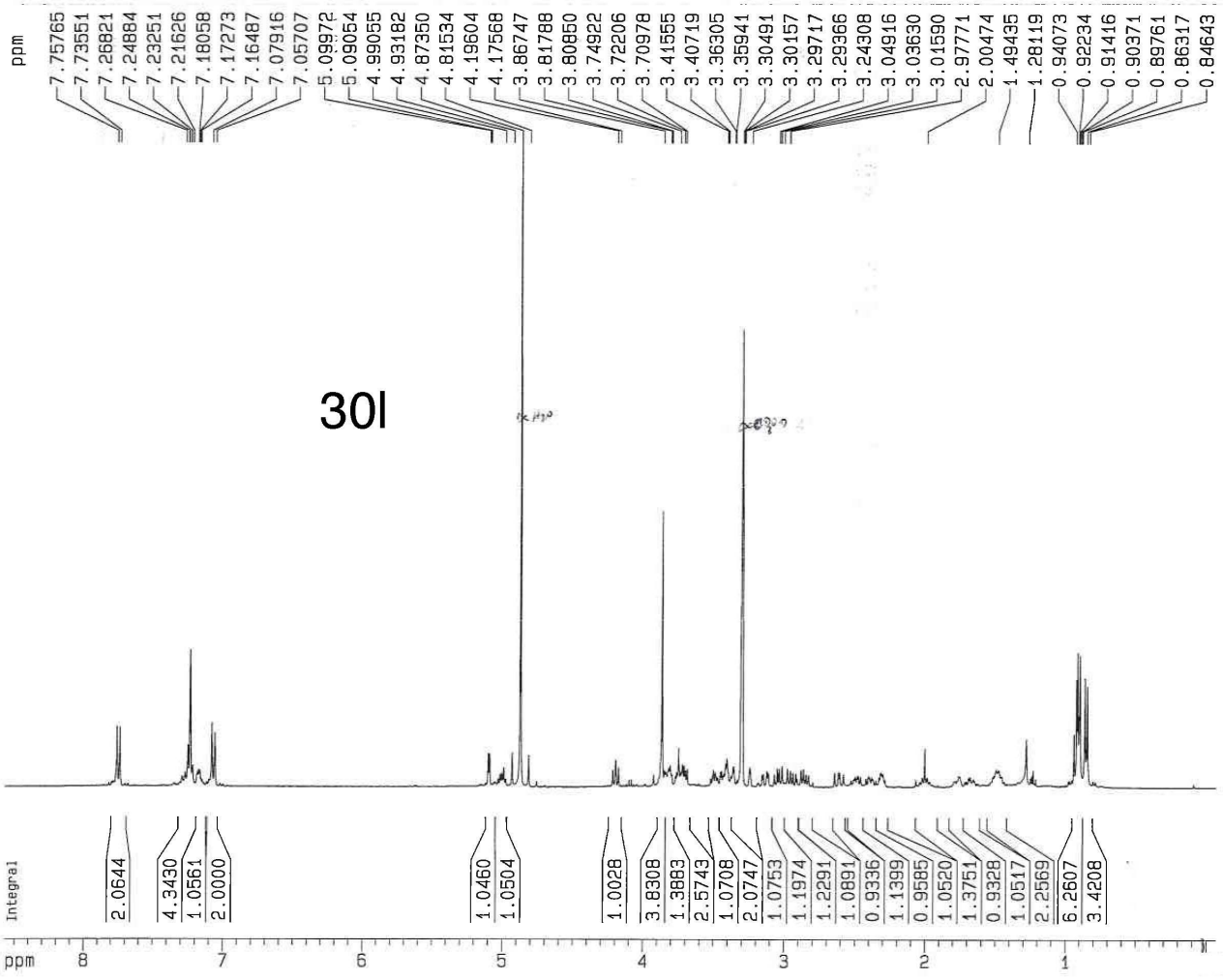
F2 - Processing parameters

SI	8192
SF	400.1685450 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.156 ppm
F1	3263.61 Hz
F2P	-0.098 ppm
F2	-39.30 Hz
PPMCM	0.41269 ppm/cm
HZCM	165.14552 Hz/cm

H1 standard parameters, CD3OD, QNP probe.



Current Data Parameters

NAME	CDM-H-191
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20120305
Time	11.36
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	MeOH
NS	32
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	2860
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1709450 MHz
NUCLEUS	1H

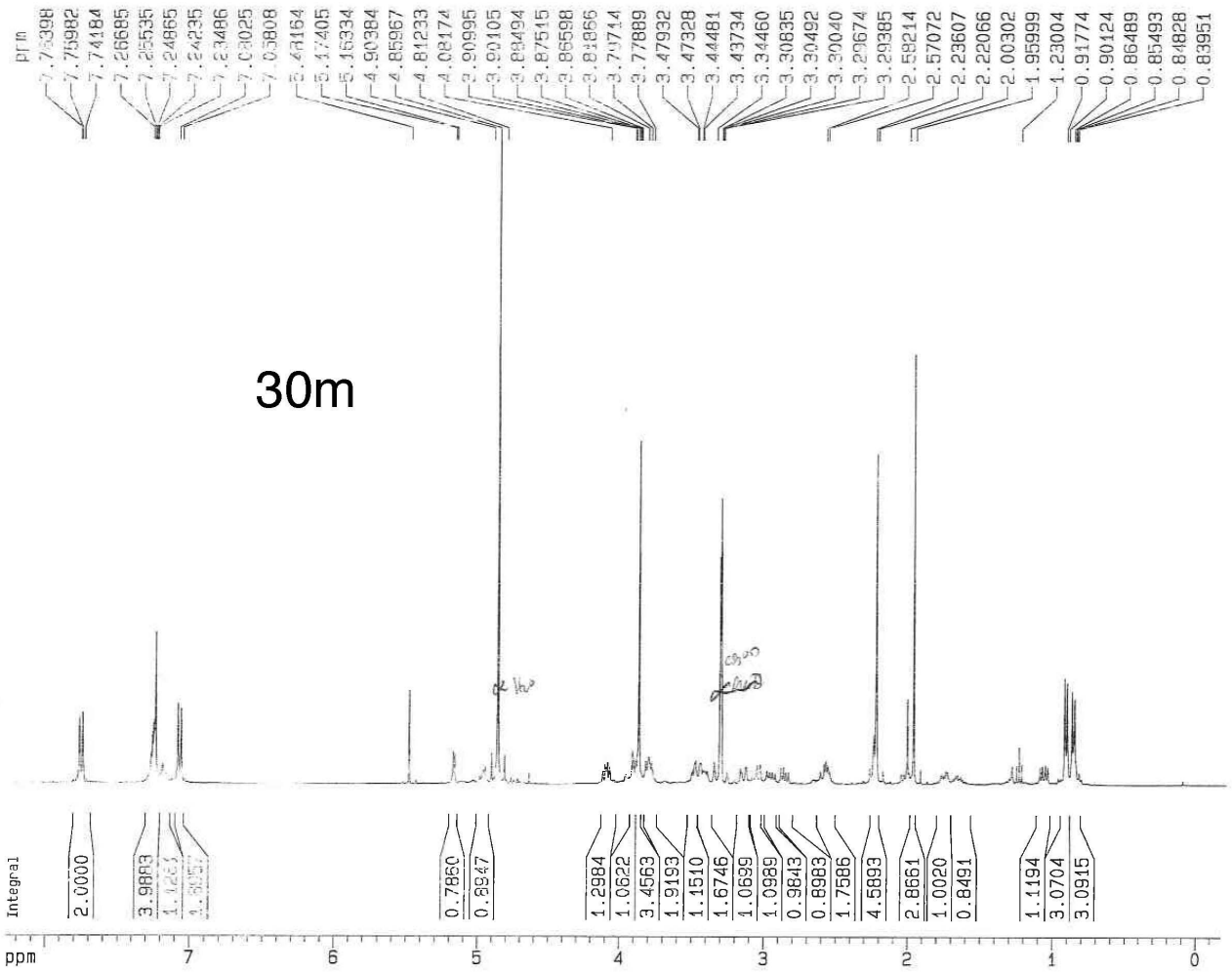
F2 - Processing parameters

SI	8192
SF	400.1685450 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.567 ppm
F1	3428.40 Hz
F2P	-0.068 ppm
F2	-27.01 Hz
PPMCM	0.43174 ppm/cm
HZCM	172.77045 Hz/cm

H1 standard parameters, CD3OD, QNP probe.



Current Data Parameters

NAME	CDM-H-106
EXPNO	1
PROCNO	2

F2 - Acquisition Parameters

Date_	20111121
Time	13.57
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	MeOH
NS	40
DS	2
SWH	5617.978 Hz
FIDRES	0.342894 Hz
AQ	1.4582260 sec
RG	2048
DW	89.000 usec
DE	127.14 usec
TE	300.0 K
D1	2.00000000 sec
P1	9.50 usec
SFO1	400.1709450 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	8192
SF	400.1685450 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.274 ppm
F1	3310.87 Hz
F2P	-0.214 ppm
F2	-85.78 Hz
PPMCM	0.42440 ppm/cm
HZCM	169.83218 Hz/cm