Synthesis and biological evaluation of highly functionalized dispiro heterocycles

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Experimental

The melting points of all compounds were determined on a Toshniwal apparatus. The purity of compounds was checked on thin layers of silica Gel-G coated glass plates and n-hexane: ethyl acetate (8:2) as eluent. IR spectra were recorded on a Shimadzu FT IR–8400S spectrophotometer using KBr pellets. ^{1}H, and ^{13}C spectra were recorded in DMSO-d_6 using TMS as an internal standard on a Bruker Avance II 400 spectrophotometer at 400 and 100 MHz respectively. Mass spectrums of representative compounds were recorded on JEOL-AccuTOF JMS-T100LC Mass spectrometer at 70 eV. Elemental microanalyses were carried out on a Carlo-Erba 1108 CHN analyzer. Single crystal X-ray diffraction was performed on a Bruker Kappa Apex II instrument.

General procedure for the Synthesis of dispiro [3*H*-indole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione derivatives (4a-k)

A dry 50 mL flask was charged with substituted isatin **1** (2.0 mmol), sarcosine **2** (2.0 mmol), and 1-methyl-3,5-bis[(*E*)-arylidene]piperidin-4-one **3** (2.0 mmol), in methanol (10 mL). The reaction mixture was stirred at refluxing temperature for appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was cooled at room temperature. The solid precipitate was filtered, washed with methanol, dried and recrystallized from ethanol to furnish pure dispiro[3*H*-indole-3,2′-pyrrolidine-3′,3″-piperidine]-2(1*H*),4″-dione derivatives with absolute chemo and regioselectivity.

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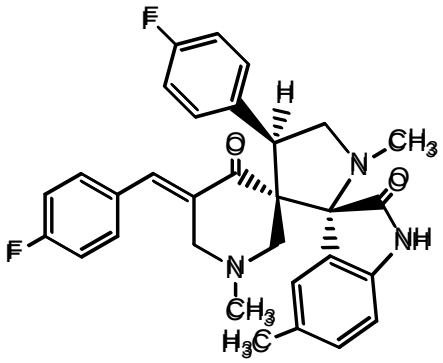
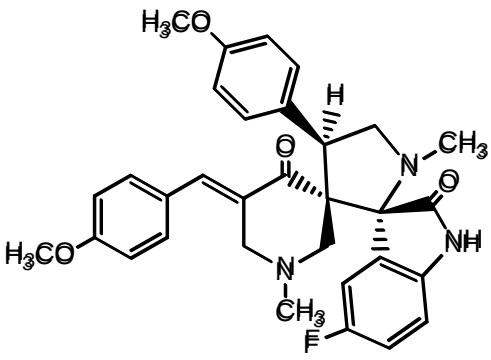
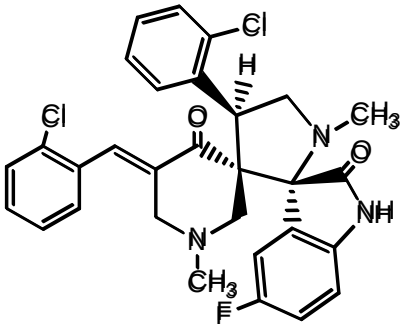
Spectral data of compounds 4



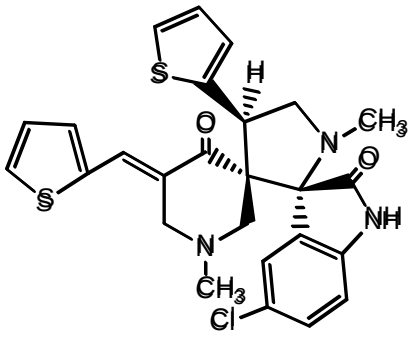
1',1''-Dimethyl-4'-(4-fluorophenyl)-5''-[(4-fluorophenyl)methylene]-dispiro[5-(3*H*)-methylindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4a). White solid; M.p: 230-232 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1680, 1708, 3248; ^{1}H NMR (400 MHz, DMSO-d_6): 1.59 (d, 1H, J=12.6 Hz, 2"-CH_2), 1.97 (s, 6H, 1'-N-CH_3 and 1"-N-CH_3), 2.24 (s, 3H, CH_3), 3.02 (dd, 1H, J=2.5, Hz, 6"-CH_2), 3.12-3.22 (m, 3H, 2"-CH_2, 6"-CH_2 and 5'-CH_2), 3.73-3.77 (m, 1H, 5'-CH_2), 4.60-4.64 (dd, 1H, J=7.20 Hz, 7.20 Hz, 4'-CH), 6.45–7.34 (m, 11H, Ar-H), 6.68 (s, 1H, C═CH), 10.22 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.76, 34.10. 44.17, 44.56, 56.16, 56.69, 57.11, 64.56, 74.91, 108.35, 115.41, 115.62, 126.89, 127.54, 128.63, 129.22, 130.72, 130.79, 131.00, 131.03, 132.10, 132.18, 133.31, 134.50, 134.52, 135.07, 140.86, 159.84, 160.79, 176.46, 197.83; MS m/z: 514.0 [M+H]$^{+}$; Anal. calcd for $C_{31}H_{29}F_2N_3O_2$: C, 72.50; H, 5.69; N, 8.18. Found: C, 72.57; H, 5.62; N, 8.14.



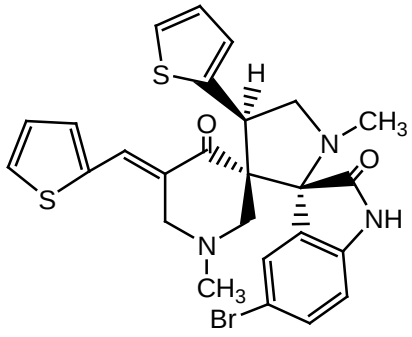
1',1''-Dimethyl-4'-(4-methoxyphenyl)-5''-[(4-methoxyphenyl)methylene]-dispiro[5-(3*H*)-fluoroindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4b). Yellow solid; M.p: 260-262 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1676, 1706, 3251; ^{1}H NMR (400 MHz, DMSO-d_6): 1.58 (d, 1H, J=12.4 Hz, 2''-CH_2), 1.98 (s, 3H, 1'-N-CH_3), 2.00 (s, 3H, 1''-N-CH_3), 3.02 (dd, 1H, J=2.4 Hz, 6''-CH_2), 3.12-3.17 (m, 2H, 2''-CH_2 and 6''-CH_2), 3.71 (d, 1H, 5'-CH_2), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.77-3.81 (m, 1H, 5'-CH_2), 4.57 (dd, 1H, J=7.2 Hz, 4'-CH), 6.54–7.56 (m, 11H, Ar-H), 6.83 (s, 1H, C═CH), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 34.12, 44.12, 44.62, 55.22, 55.27, 56.20, 56.54, 56.87, 64.94, 75.23, 108.61, 113.64, 113.98, 114.11, 114.28, 114.52, 126.86, 127.22, 129.01, 129.82, 129.93, 130.99, 131.62, 131.97, 132.37, 134.22, 136.74, 139.55, 158.01, 159.96, 176.57, 197.62; MS m/z: 542.0 [M+H]$^{+}$; Analysis calcd for $C_{32}H_{32}FN_3O_4$: C, 70.96; H, 5.96; N, 7.76. Found: C, 70.84; H, 5.90; N, 7.74.



4'-(2-chlorophenyl)-5''-[(2-chlorophenyl)methylene]-1',1''-dimethyldispiro[5-(3*H*)-fluoroindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4c). White solid; M.p: 227-229 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1682, 1705, 3246; ^{1}H NMR (300 MHz, DMSO-d_6): 1.59 (d, 1H, J=12.3 Hz, 2''-CH_2), 1.99 (s, 6H, 1'-N-CH_3, 1''-N-CH_3), 3.01-3.26 (m, 5H, 2''-CH_2, 6''-CH_2, 5'-CH_2), 3.71-3.77 (m, 1H, 5'-CH_2), 4.59 (t, 1H, J=6.9 Hz, 4'-CH), 6.55–7.60 (m, 11H, Ar-H), 6.92 (s, 1H, C═CH), 10.51 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 34.63, 44.46, 44.98, 56.63, 57.02, 57.43, 65.60, 75.27, 111.22, 113.00, 115.42, 115.70, 127.24, 127.95, 129.93, 131.13, 131.24, 131.66, 132.66, 132.77, 133.59, 134.60, 136.22, 143.11, 159.99, 161.01, 176.49, 198.20; MS m/z: 551.1 [M+H]$^{+}$; Anal. calcd for $C_{30}H_{26}Cl_2FN_3O_2$: C, 65.46; H, 4.76; N, 7.63. Found: C, 65.55; H, 4.69; N, 7.60.

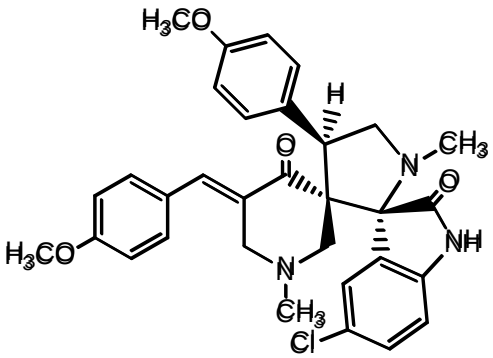


1',1''-Dimethyl-4'-(2-thienyl)-5''-[(2-thienyl)methylene]-dispiro[5-(3*H*)-chloroindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4d). White solid; M.p. 240-242 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1680, 1709, 3249; ^{1}H NMR (300 MHz, DMSO-d_6): 1.82 (d, 1H, J=12.3 Hz, 2''-CH_2), 1.98 (s, 3H, 1'-N-CH_3), 2.07 (s, 3H, 1''-N-CH_3), 2.98 (d, 1H, J=15.3Hz, 6''-CH_2), 3.21-3.30 (m, 3H, 2''-CH_2, 6''-CH, 5'-CH_2), 3.69-3.75 (m, 1H, 5'-CH_2), 4.83-4.89 (m, 1H, 4'-CH), 6.61–7.84 (m, 9H, Ar-H), 6.75 (s, 1H, C═CH), 10.53 (s,1H, NH),. MS m/z: 511.2 [M+H]$^{+}$; Anal. calcd for $C_{26}H_{24}ClN_3O_2S_2$: C, 61.22; H, 4.74; N, 8.24. Found: C, 61.09; H, 4.78; N, 8.26.

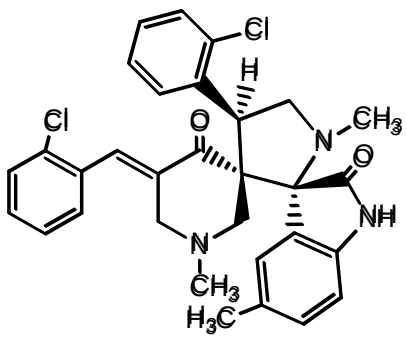


1',1''-Dimethyl-4'-(2-thienyl)-5''-[(2-thienyl)methylene]-dispiro[5-(3*H*)-bromoindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4e). White solid;

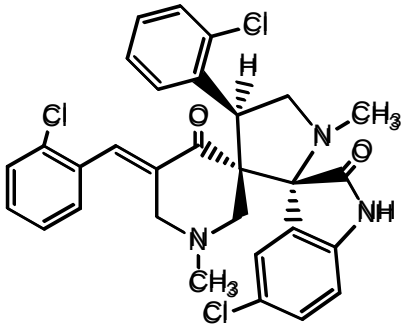
M.p: 238-240 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1676, 1706, 3246; ^{1}H NMR (300 MHz, DMSO-d_6): 1.65 (d, 1H, J=12.1 Hz, 2"-CH_2), 2.01 (s, 3H, 1'-N-CH_3), 2.08 (s, 3H, 1"-N-CH_3), 3.12 (d, 1H, J=7.4 Hz, 6"-CH_2), 3.20-3.32 (m, 3H, 2"-CH_2, 6"-CH_2, 5'-CH_2), 3.67-3.74 (m, 1H, 5'-CH_2), 4.81-4.87 (m, 1H, 4'-CH), 6.58-7.79 (m, 9H, Ar), 6.72 (1H, s, C=CH), 10.43 (s, 1H, NH); MS m/z: 554.52 [M+H]$^{+}$; Anal. calcd for $C_{26}H_{24}BrN_3O_2S_2$: C, 56.31; H, 4.36; N, 7.58.Found: C, 56.40; H, 4.28; N, 7.55.



1',1''-Dimethyl-4'-(4-methoxyphenyl)-5''-[(4-methoxyphenyl)methylene]-dispiro[5-(3*H*)-chloroindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4f). Yellow solid; M.p: 240-242 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1682, 1710, 3253; ^{1}H NMR (300 MHz, DMSO-d_6): 1.58 (d, 1H, J=12.3 Hz, 2"-CH_2), 1.99 (s, 6H, 1'-N-CH_3, 1"-N-CH_3), 299 (d, 1H, J=14.7 Hz, 6"-CH_2), 3.13 (d, 1H, J=8.7 Hz, 2"-CH_2), 3.25 (d, 1H, J=14.7 Hz, 6"-CH_2), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.80-3.83 (m, 2H, 5'-CH_2), 4.58 (t, 1H, J=6.3 Hz, 4'-CH), 6.57-7.56 (m, 11H, Ar-H), 6.80 (s, 1H, C=CH), 10.45 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 34.23, 44.02, 44.67, 54.97, 55.28, 56.62, 56.95, 57.06, 65.10, 75.05, 110.06, 124.83, 126.79, 126.92, 127.29, 128.25, 129.37, 129.91, 131.19, 131.66, 131.98, 132.45, 134.32, 136.98, 142.26, 158.09, 160.02, 176.33, 197.74; MS m/z: 559.3 [M+H]$^{+}$; Anal. calcd for $C_{32}H_{32}ClN_3O_4$: C, 68.87; H, 5.78; N, 7.53. Found: C, 68.73; H, 5.82; N, 7.56.

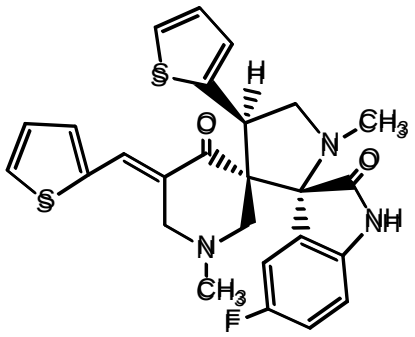


4'-(2-Chlorophenyl)-5''-[(2-chlorophenyl)methylene]-1',1''-dimethyldispiro[5-(3*H*)-methylindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4g). White solid; M.p: 258-260 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1685, 1705, 3243; ^{1}H NMR (300 MHz, DMSO-d_6): 1.70 (d, 1H, J=12.3 Hz, 2''-CH_2), 1.85 (3H, s, CH_3), 1.93 (s, 3H, 1'-N-CH_3), 2.17 (s, 3H, 1''-N-CH_3), 2.91 (d, 1H, J=12.3 Hz, 6''-CH_2), 2.97-3.16 (m, 2H, 2''-CH_2, 5'-CH_2), 3.28 (d, 1H, J=7.8 Hz, 6''-CH_2), 3.79 (t, 1H, J=8.7 Hz, 5'-CH_2), 4.85-4.91 (m 1H, 4'-CH), 6.55-7.94 (m, 11H, Ar-H), 6.69 (s, 1H, C=CH), 10.40 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 21.11, 34.16, 42.07, 45.08, 56.82, 57.21, 57.79, 62.76, 76.18, 108.74, 126.34, 127.02, 127.23, 127.80, 128.46, 128.81, 129.14, 129.69, 130.19, 130.60, 130.78, 132.04, 132.62, 133.69, 134.41, 134.79, 136.75, 141.13, 176.56, 196.60; MS m/z: 547.0 [M+H]$^{+}$; Anal. calcd for $C_{31}H_{29}Cl_2N_3O_2$: C, 68.13; H, 5.35; N, 7.69. Found: C, 67.96; H, 5.42; N, 7.71.

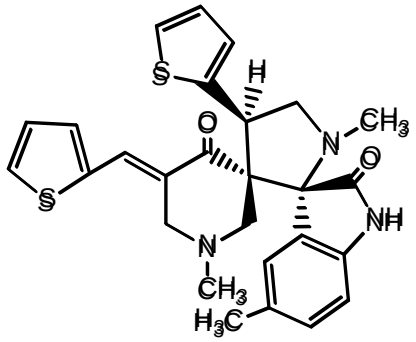


4'-(2-Chlorophenyl)-5''-[(2-chlorophenyl)methylene]-1',1''-dimethyldispiro[5-(3*H*)-chloroindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4h). White solid; M.p: 244-246 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1683, 1708, 3247; ^{1}H NMR 300 MHz, DMSO-d_6): 1.70 (d, 1H, J=12.3 Hz, 2''-CH_2), 1.89 (s, 3H, 1'-N-CH_3), 1.97 (s, 3H, 1''-N-CH_3), 2.95 (d, 2H, J=12.3 Hz, 2''-CH_2), 3.05-3.15 (m, 2H, 6''-CH_2, 5'-CH_2), 3.32 (d, 1H, J=7.8 Hz, 6''-CH_2), 3.77-3.83 (m, 1H, 5'-CH_2), 4.85-4.90 (m, 1H, 4'-CH), 6.69-7.90 (m, 11H, Ar-H), 6.84 (s, 1H, C=CH), 10.70 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 34.59, 42.41, 45.40, 57.06, 57.60, 58.12, 63.74, 76.46, 110.91, 125.96, 127.40, 127.54, 128.93, 128.99, 129.65, 130.03, 130.61, 131.00, 131.09, 133.02, 133.45, 134.18, 134.49, 135.13,

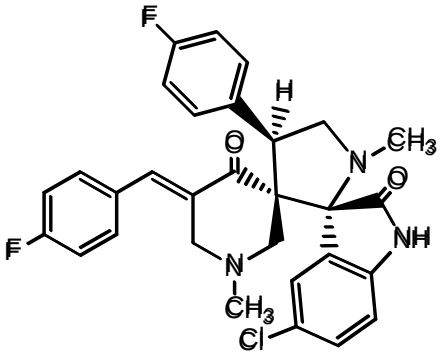
136.86, 142.86, 176.73, 196.91; MS m/z: 567.2 $[M+H]^+$; Anal. calcd for $C_{30}H_{26}Cl_3N_3O_2$: C, 63.56; H, 4.62; N, 7.41. Found: C, 63.64; H, 4.53; N, 7.37.



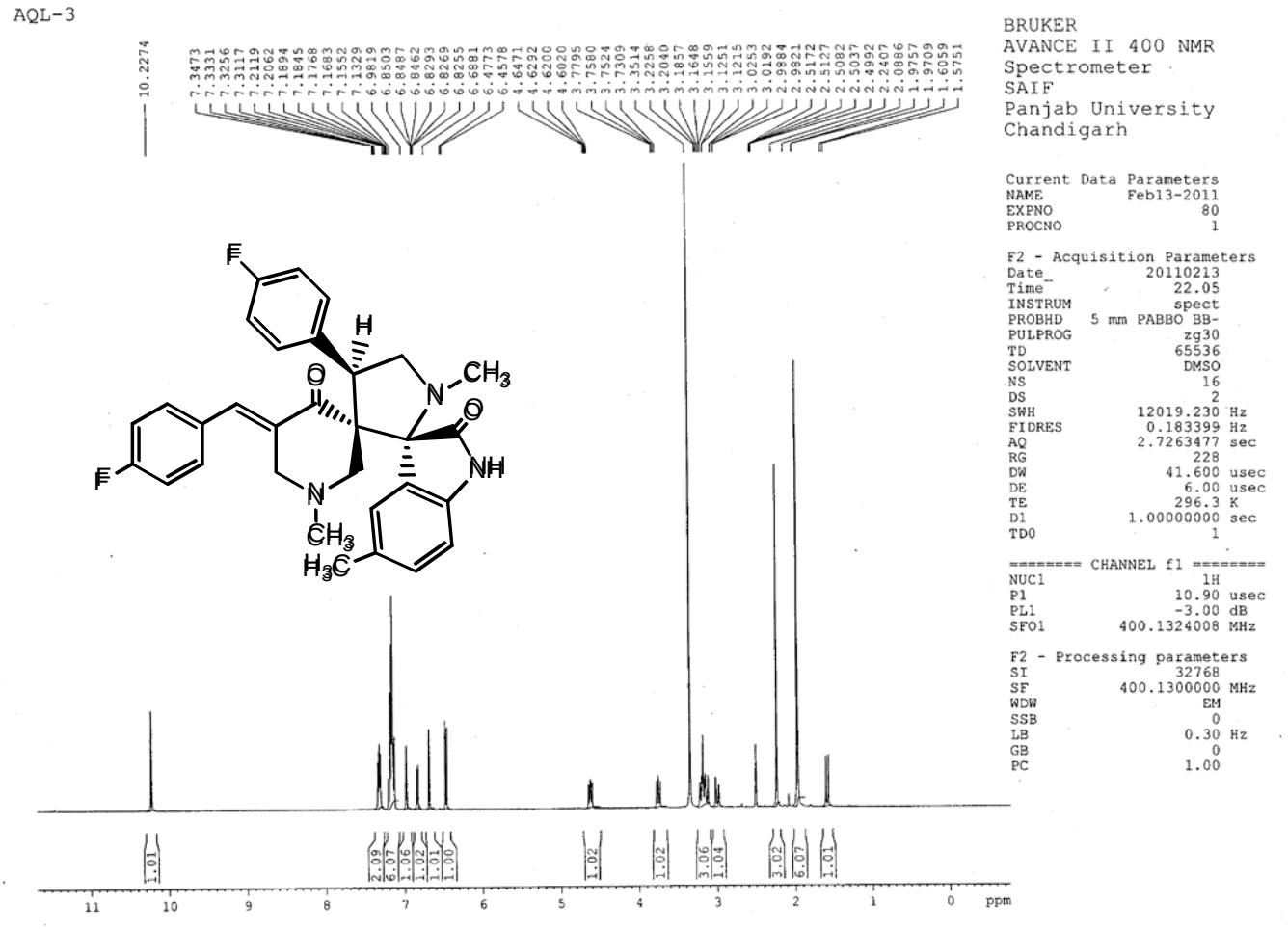
1',1''-Dimethyl-4'-(2-thienyl)-5''-[(2-thienyl)methylene]-dispiro[5-(3*H*)-fluoroindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4i). White solid; M.p: 260-262 ^oC; IR (KBr) (ν_{max}, cm^{-1}): 1679, 1711, 3251; ^1H NMR (300 MHz, DMSO-d_6): 1.82 (d, 1H, J=12.3 Hz, 2''-CH_2), 1.97 (s, 3H, 1'-N-CH_3), 2.08 (s, 3H, 1''-N-CH_3), 2.98 (d, 1H, J=15.6 Hz, 6''-CH_2), 3.23-3.28 (m, 2H, 2''-CH_2, 6''-CH_2), 3.37 (d, 1H, J=15.6 Hz, 5'-CH_2), 3.70-3.77 (m, 1H, 5'-CH_2), 4.80-4.86 (m, 1H, 4'-CH), 6.55-7.84 (m, 9H, Ar), 6.54 (s, 1H, C=CH), 10.43 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 33.86, 44.54, 51.30, 55.38, 56.44, 57.25, 64.50, 75.16, 109.34, 124.51, 125.88, 126.97, 128.41, 128.56, 128.67, 129.46, 132.43, 134.12, 137.35, 139.69, 140.60, 155.79, 158.91, 176.34, 196.09; MS m/z: 494.1 $[M+H]^+$; Anal. calcd for $C_{26}H_{24}FN_3O_2S_2$: C, 63.26; H, 4.90; N, 8.51. Found: C, 63.15; H, 4.84; N, 8.49.



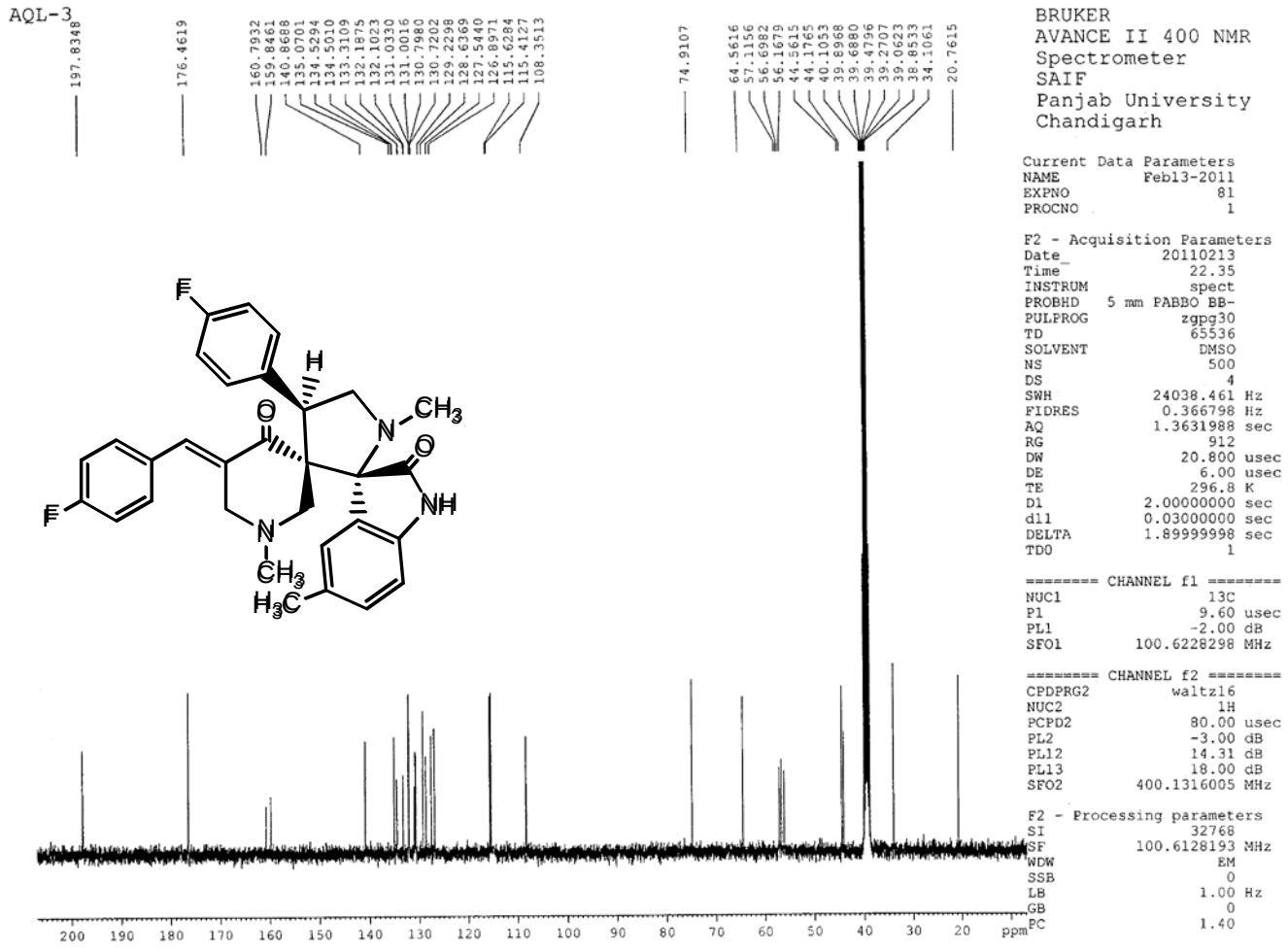
1',1''-Dimethyl-4'-(2-thienyl)-5''-[(2-thienyl)methylene]-dispiro[5-(3*H*)-methylindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4j). White solid; M.p: 245-247 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1677, 1706, 3245; ^{1}H NMR (300 MHz, DMSO-d_6): 1.83 (d, 1H, J=12.0 Hz, 2''-CH_2), 1.96 (3H, s, CH_3), 2.06 (s, 3H, 1'-N-CH_3), 2.11 (s, 3H, 1''-N-CH_3), 2.95 (d, 1H, J=15.3 Hz, 6''-CH_2), 3.22-3.37 (m, 3H, 2''-CH_2, 6''-CH_2, 5'-CH_2), 3.75 (t, 1H, J=9.3 Hz, 5'-CH_2), 4.87 (t, 1H, J=8.4 Hz, 4'-CH), 6.47-7.81 (m, 10H, Ar), 6.64 (s, 1H, C=CH), 10.26 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 20.57, 34.42, 42.34, 44.64, 55.81, 56.64, 57.32, 64.03, 75.04, 108.25, 124.44, 125.91, 126.64, 126.94, 127.57, 128.36, 128.67, 128.85, 129.15, 129.48, 131.08, 131.84, 133.36, 138.09, 140.99, 176.33, 196.38; MS m/z: 490.1 [M+H]$^{+}$; Anal. calcd for $C_{27}H_{27}N_3O_2S_2$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.16; H, 5.51; N, 8.61.



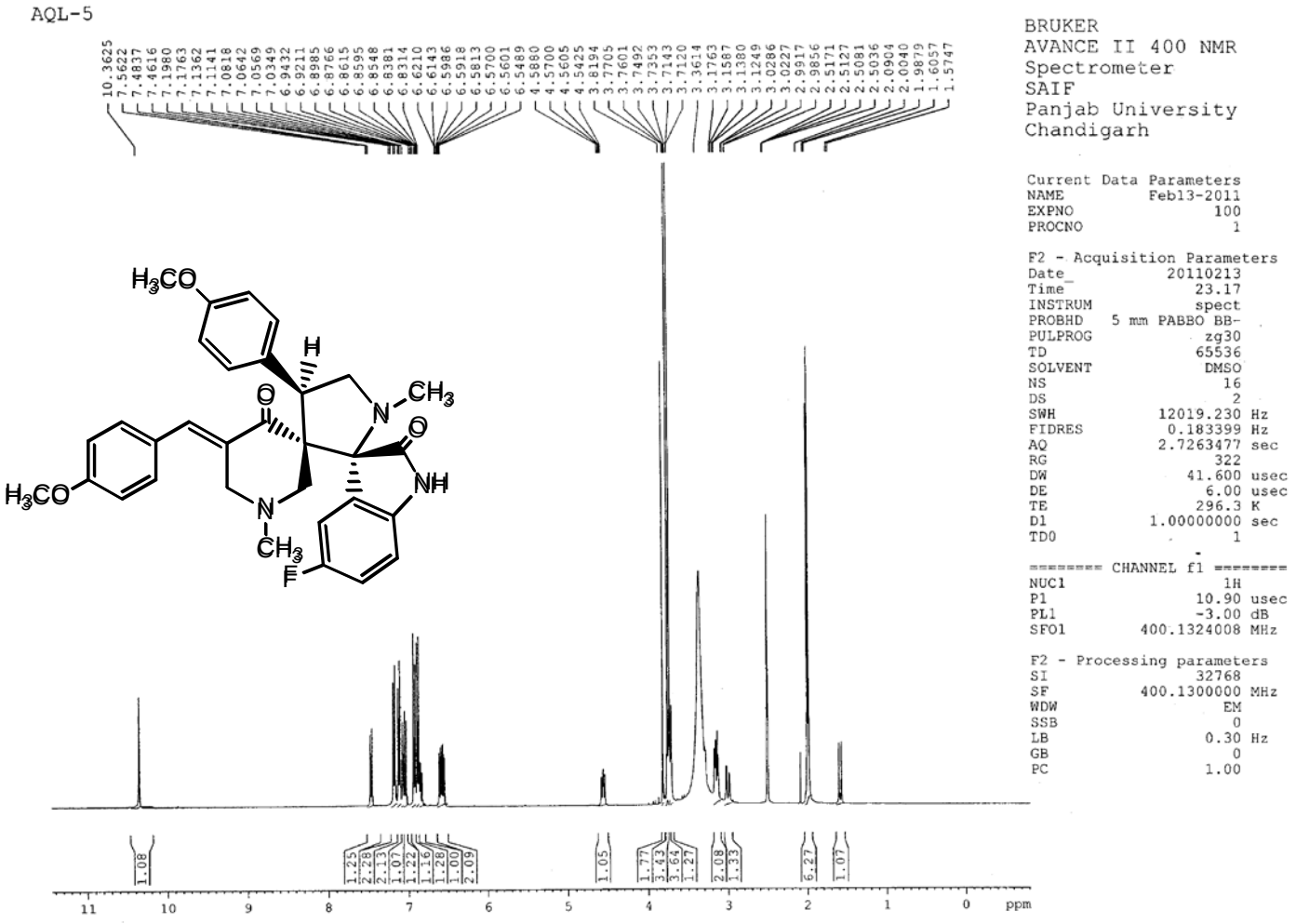
1',1''-Dimethyl-4'-(4-fluorophenyl)-5''-[(4-fluorophenyl)methylene]-dispiro[5-(3*H*)-chloroindole-3,2'-pyrrolidine-3',3''-piperidine]-2(1*H*),4''-dione (4k). White solid; M.p: 228-230 ^{o}C; IR (KBr) (ν_{max}, cm^{-1}): 1683, 1709, 3252; ^{1}H NMR (300 MHz, DMSO-d_6): 1.59 (d, 1H, J=12.3 Hz, 2''-CH_2), 2.00 (s, 6H, 1'-N-CH_3, 1''-N-CH_3), 3.02-3.21 (m, 4H, 6''-CH_2, 2''-CH_2, 5'-CH_2), 3.72-3.78 (m, 1H, 5'-CH_2), 4.65 (t, 1H, J=6.6 Hz, 4'-CH), 6.59-7.32 (m, 11H, Ar), 6.80 (s, 1H, C=CH), 10.53 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 34.63, 44.49, 44.99, 56.68, 57.02, 57.44, 65.56, 75.38, 110.66, 115.41, 115.69, 115.96, 116.25, 125.31, 127.20, 128.85, 129.51, 131.15, 131.25, 132.62, 132.74, 133.61, 134.66, 136.22, 142.74, 160.0, 161.01, 176.65, 198.19; MS m/z: 535.2 [M+H]$^{+}$; Anal. calcd for $C_{30}H_{26}ClF_2N_3O_2$: C, 67.48; H, 4.91; N, 7.87. Found: C, 67.61; H, 4.99; N, 7.84.



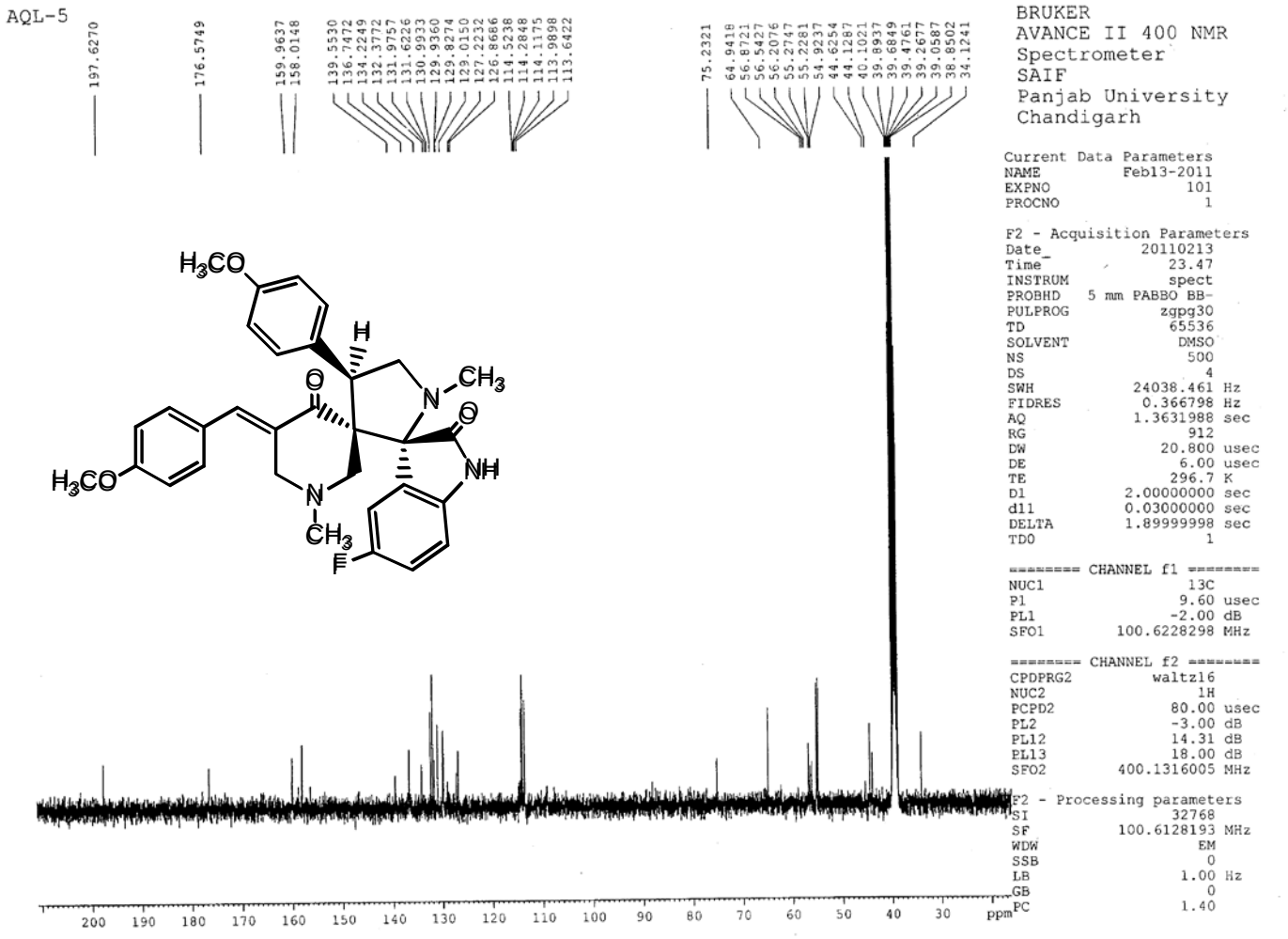
^{1}H spectrum of **4a**



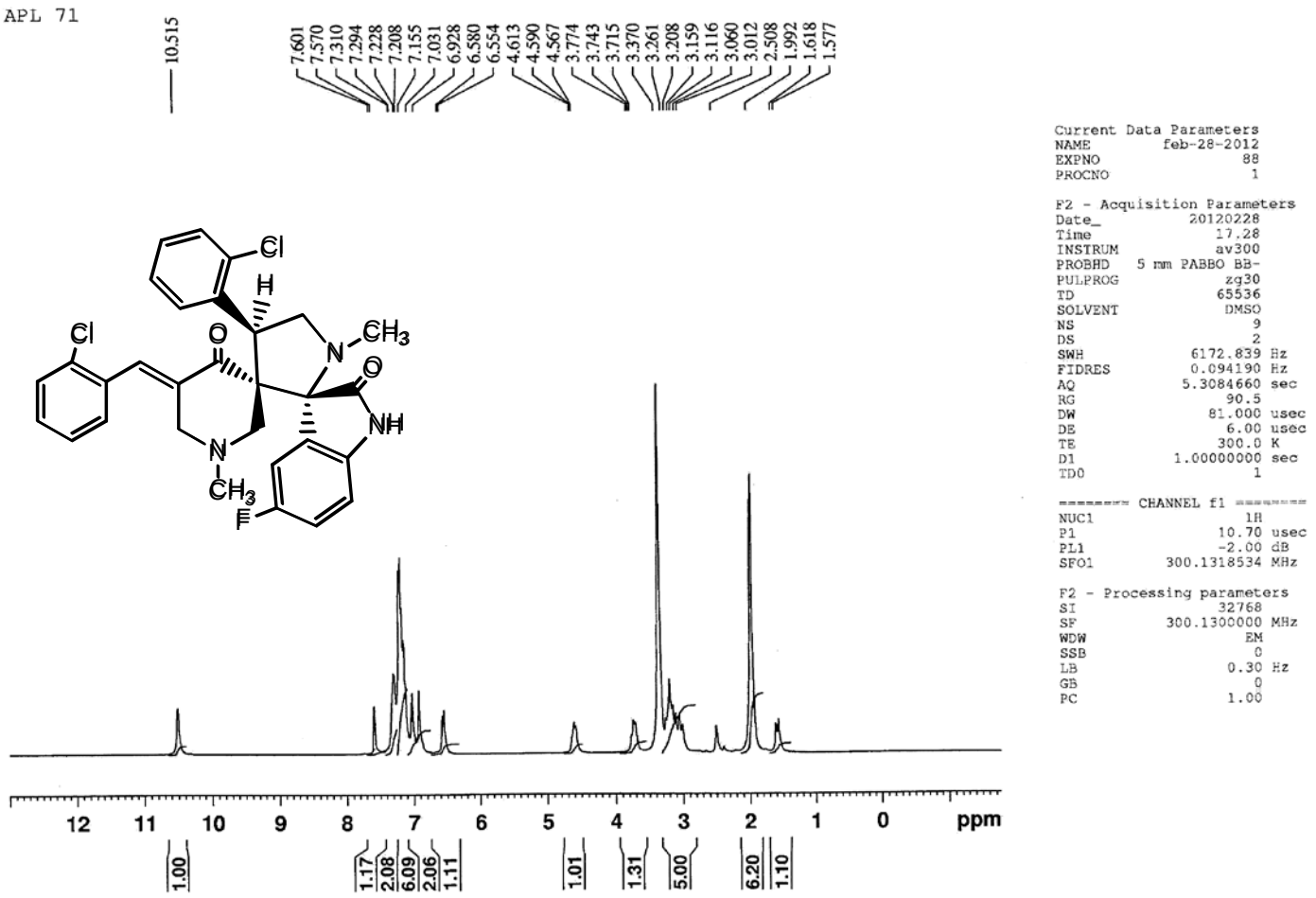
^{13}C spectrum of **4a**



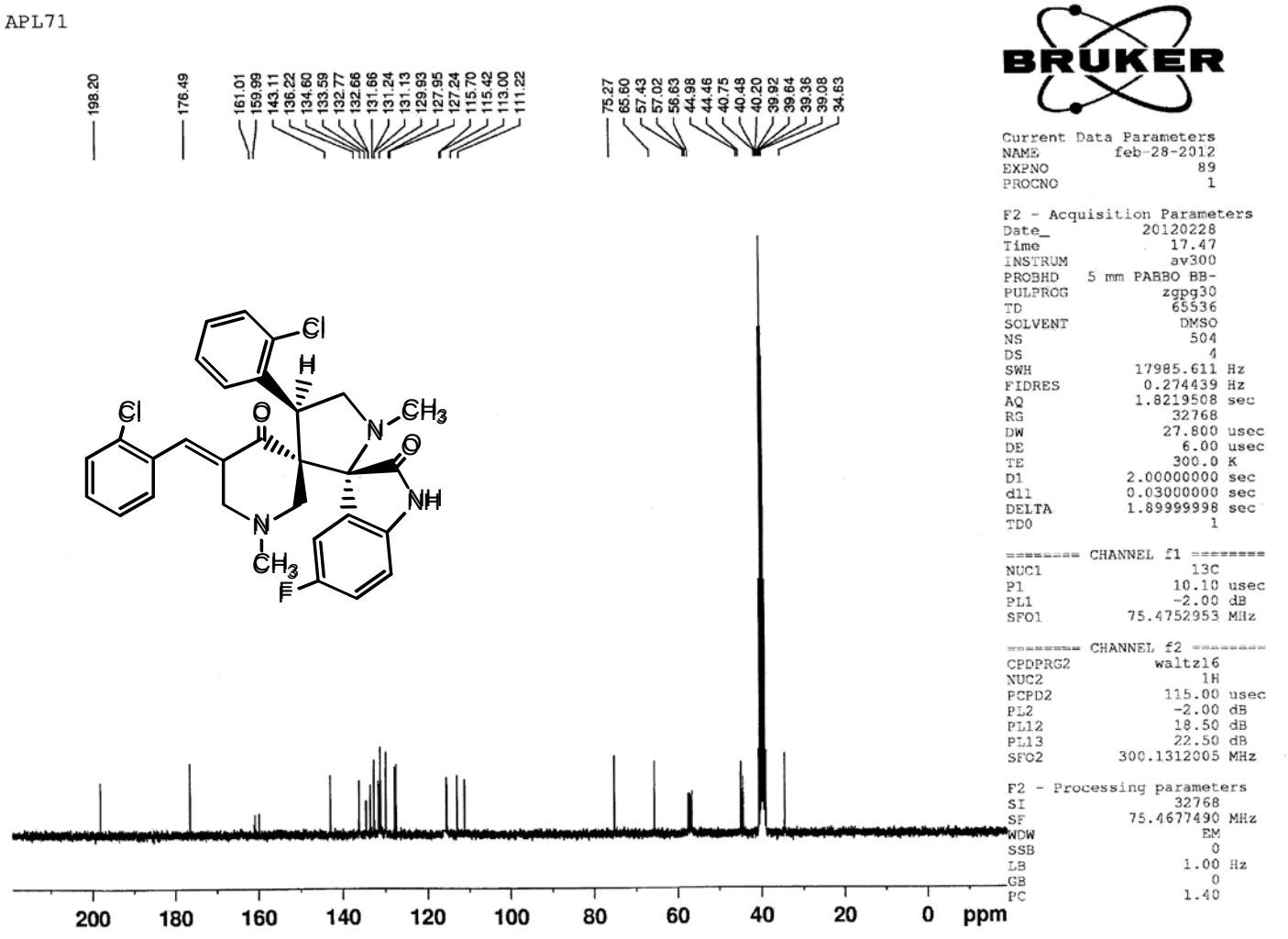
^{1}H spectrum of **4b**



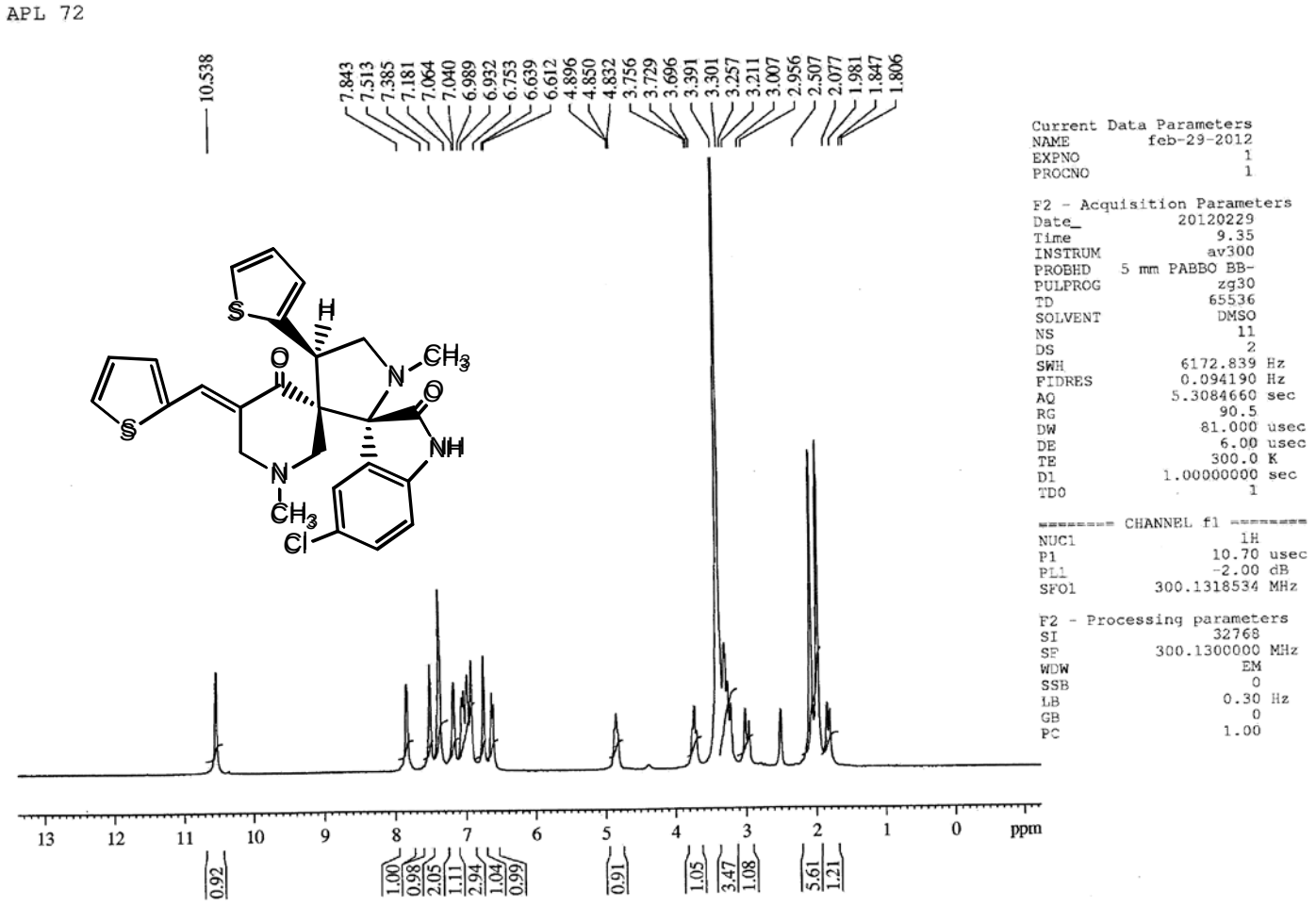
^{13}C spectrum of **4b**



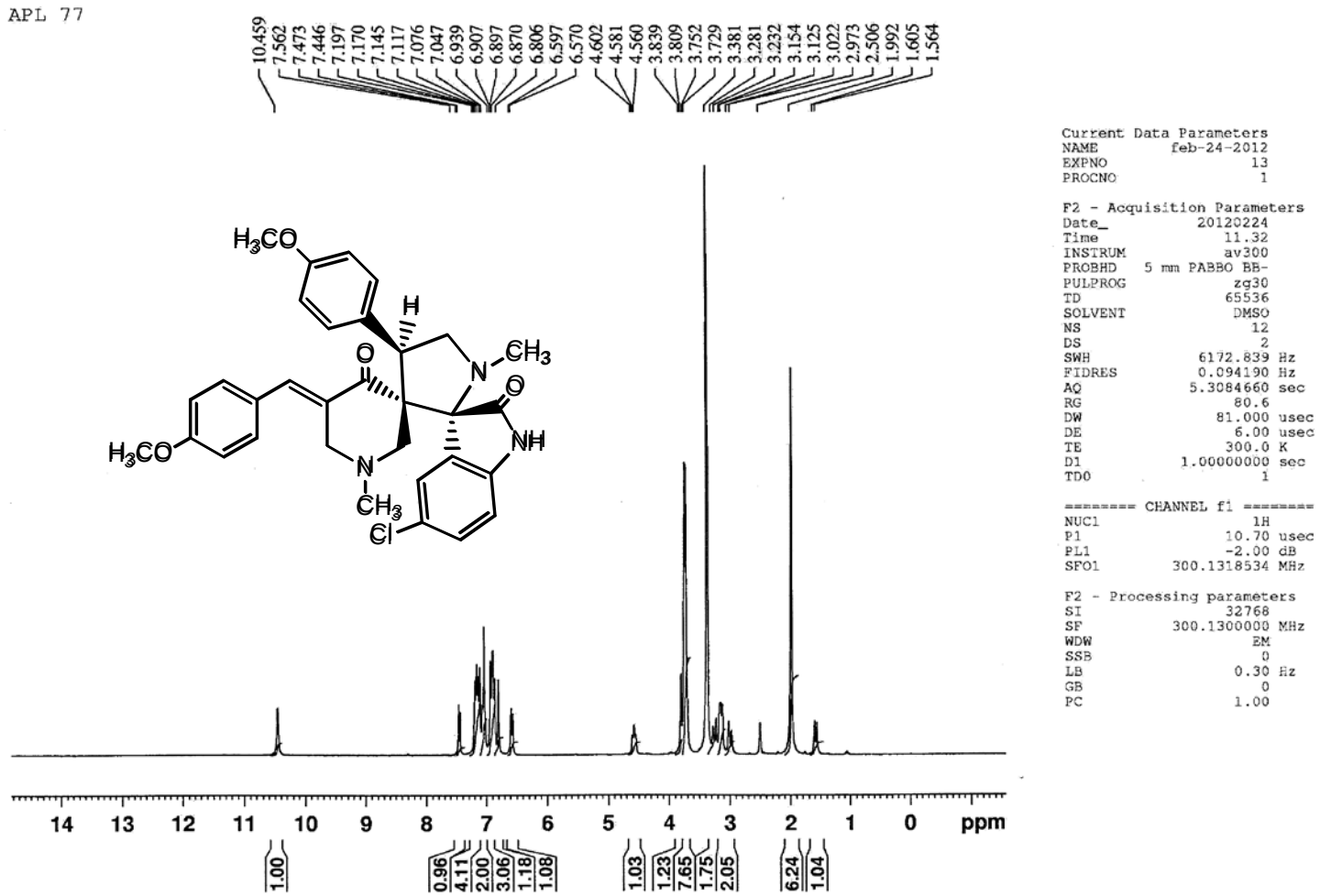
^{1}H spectrum of **4c**



^{13}C spectrum of **4c**

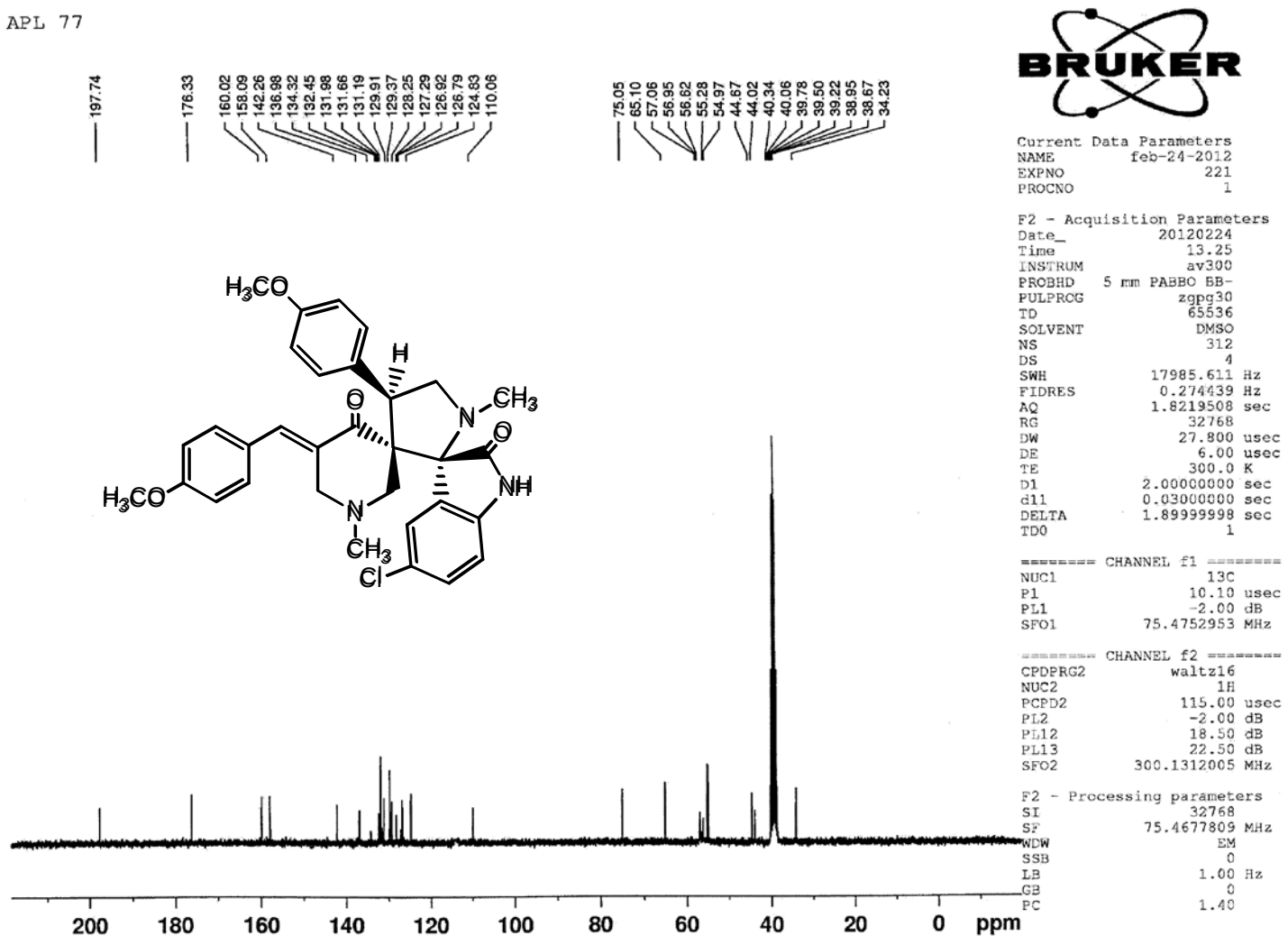


^{1}H spectrum of 4d

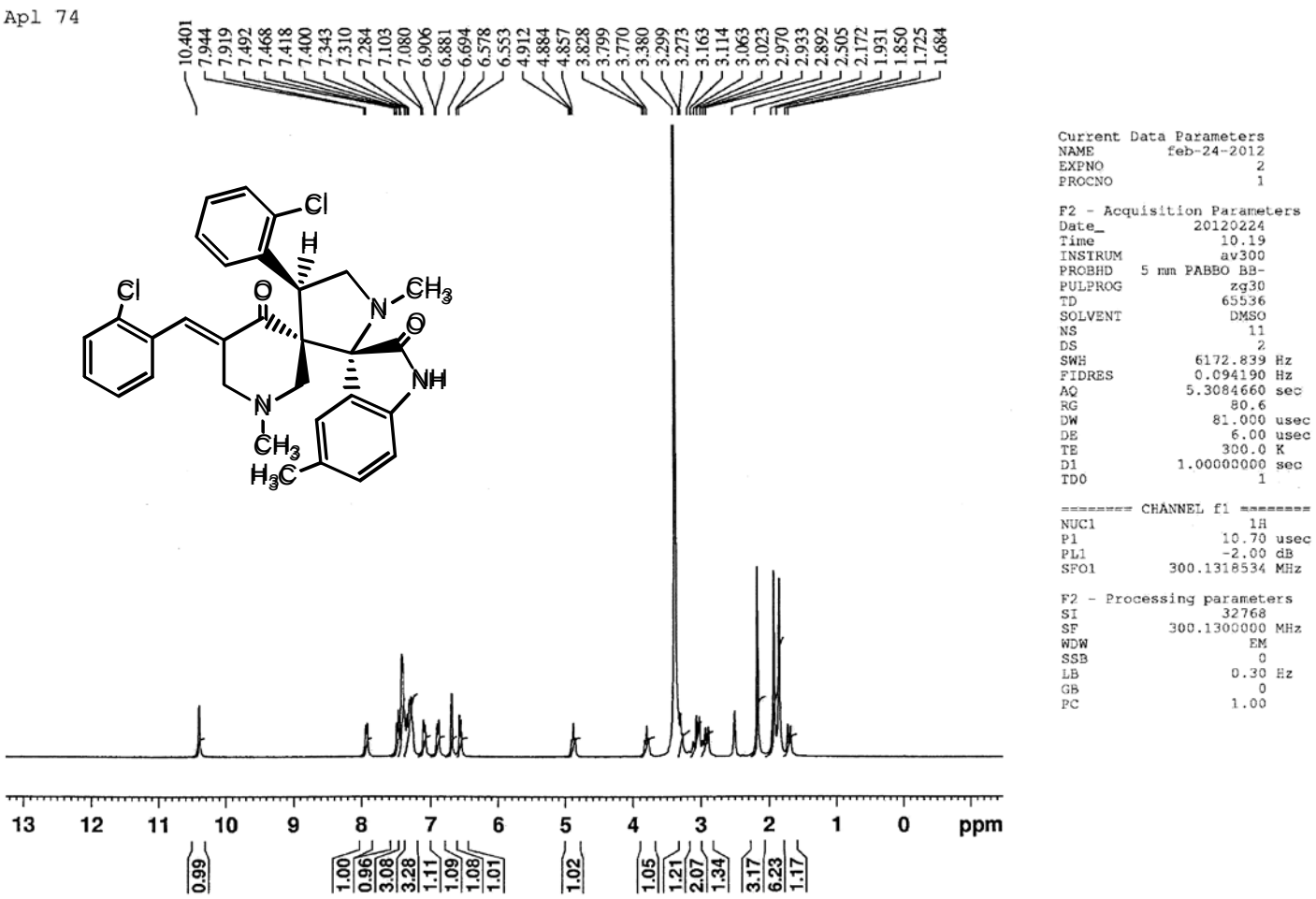



```
Current Data Parameters
NAME                  feb-24-2012
EXPNO                          13
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20120224
Time                        11.32
INSTRUM                      av300
PROBHD    5 mm PABBO BB-
PULPROG                      zg30
TD                          65536
SOLVENT                      DMSO
NS                             12
DS                              2
SWH                     6172.839 Hz
FIDRES                  0.094190 Hz
AQ                      5.3084660 sec
RG                           80.6
DW                         81.000 usec
DE                           6.00 usec
TE                          300.0 K
D1                     1.00000000 sec
TD0                             1

======== CHANNEL f1 ========
NUC1                           1H
P1                          10.70 usec
PL1                         -2.00 dB
SFO1                300.1318534 MHz

F2 - Processing parameters
SI                          32768
SF                300.1300000 MHz
WDW                            EM
SSB                             0
LB                           0.30 Hz
GB                              0
PC                           1.00
```

^{1}H spectrum of **4f**

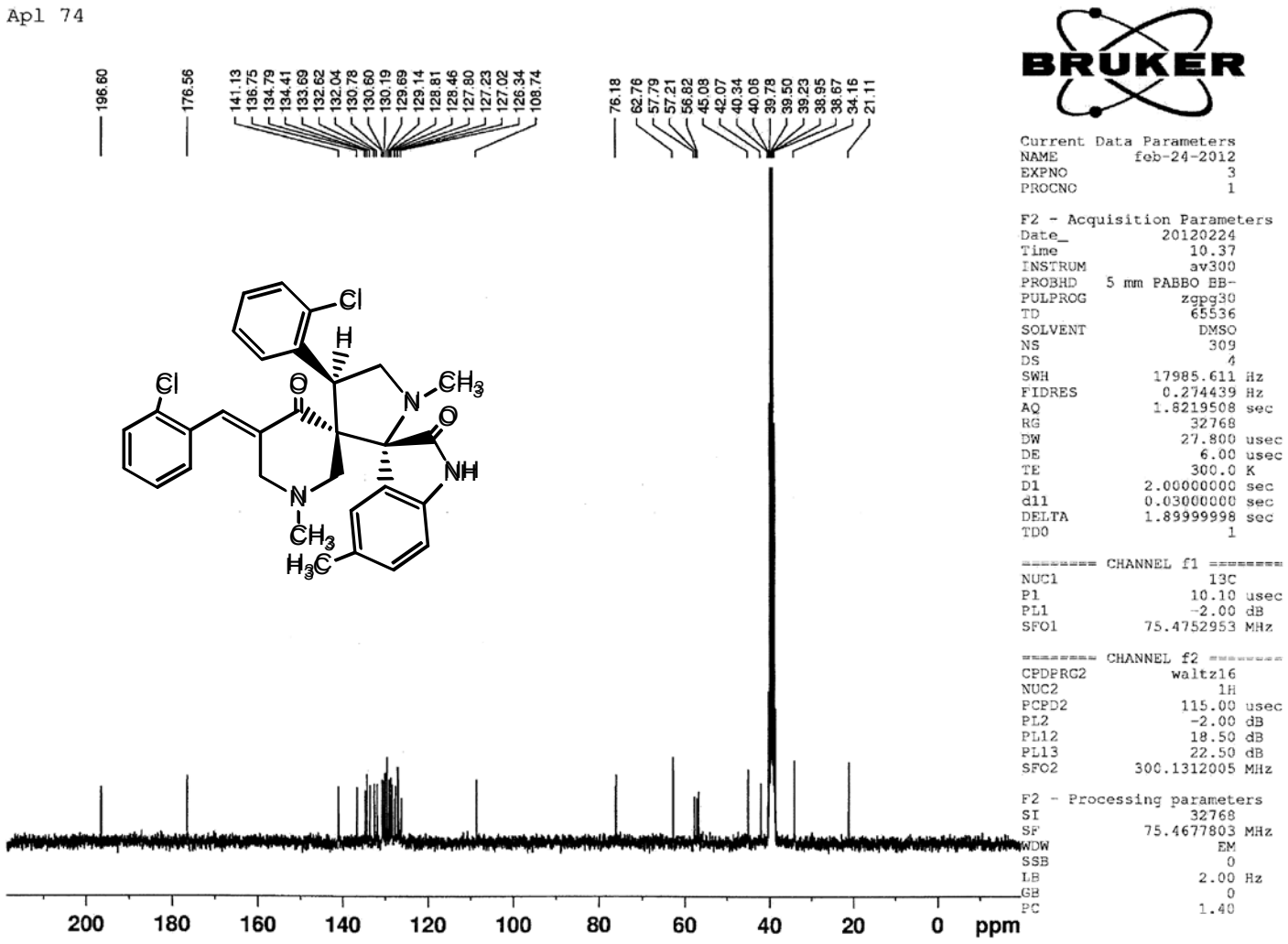


^{13}C spectrum of **4f**

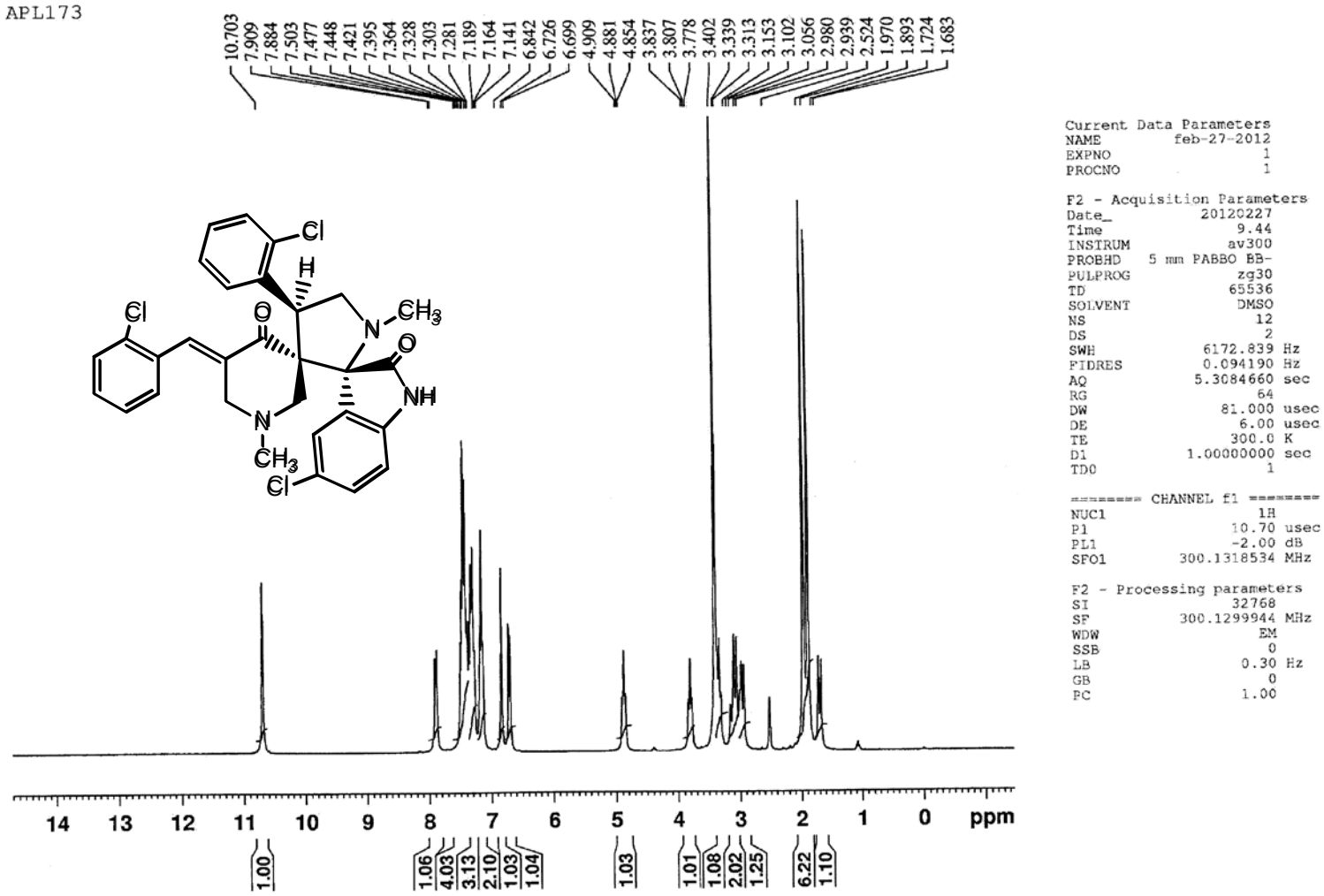



```
Current Data Parameters
NAME                  feb-24-2012
EXPNO                           2
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20120224
Time                        10.19
INSTRUM                     av300
PROBHD    5 mm PABBO BB-
PULPROG                      zg30
TD                          65536
SOLVENT                      DMSO
NS                             11
DS                              2
SWH                     6172.839 Hz
FIDRES                  0.094190 Hz
AQ                      5.3084660 sec
RG                           80.6
DW                         81.000 usec
DE                           6.00 usec
TE                          300.0 K
D1                     1.00000000 sec
TD0                             1

======== CHANNEL f1 ========
NUC1                           1H
P1                          10.70 usec
PL1                         -2.00 dB
SFO1                300.1318534 MHz

F2 - Processing parameters
SI                          32768
SF                  300.1300000 MHz
WDW                            EM
SSB                             0
LB                           0.30 Hz
GB                              0
PC                           1.00
```

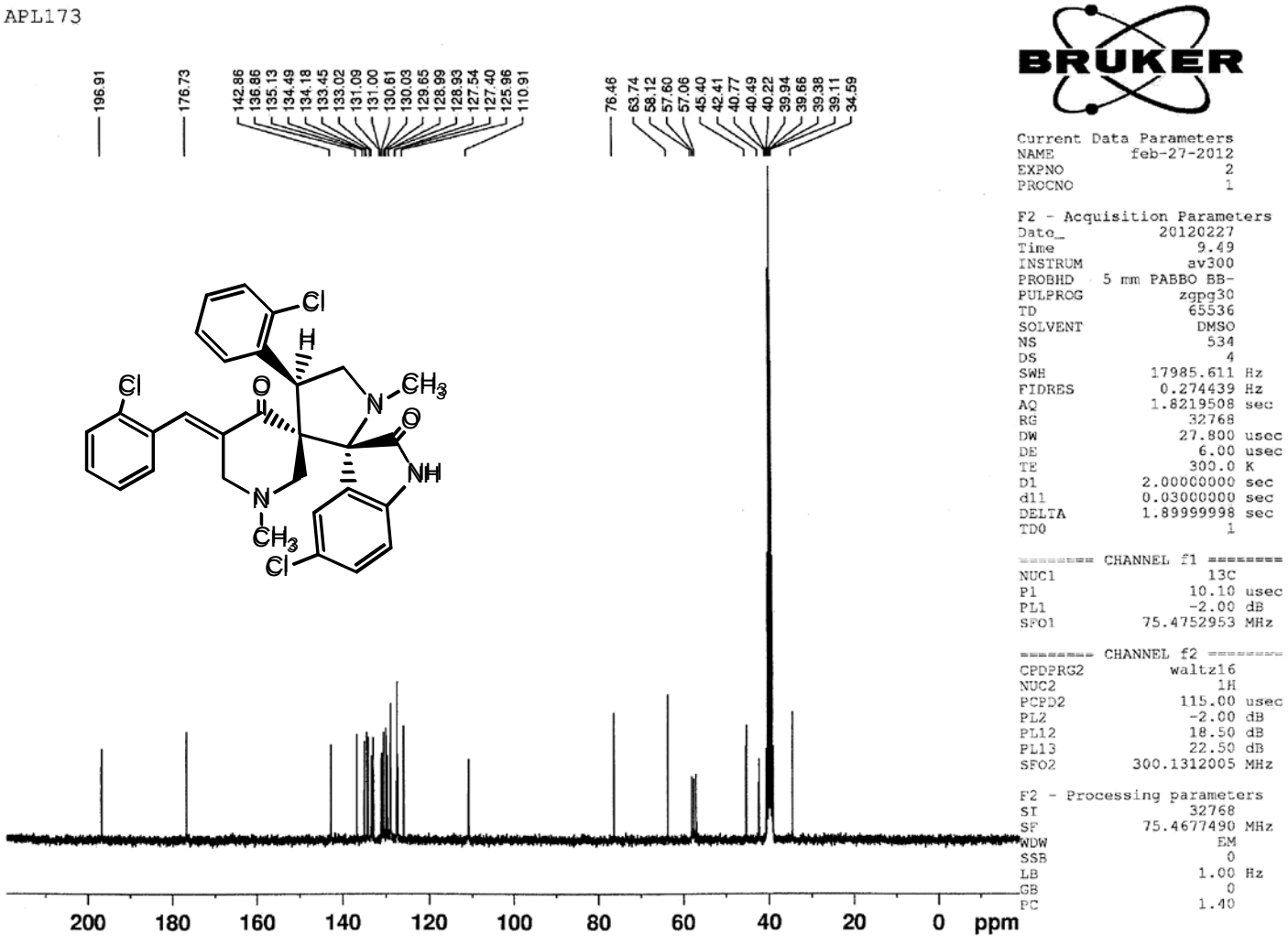
^{1}H spectrum of **4g**



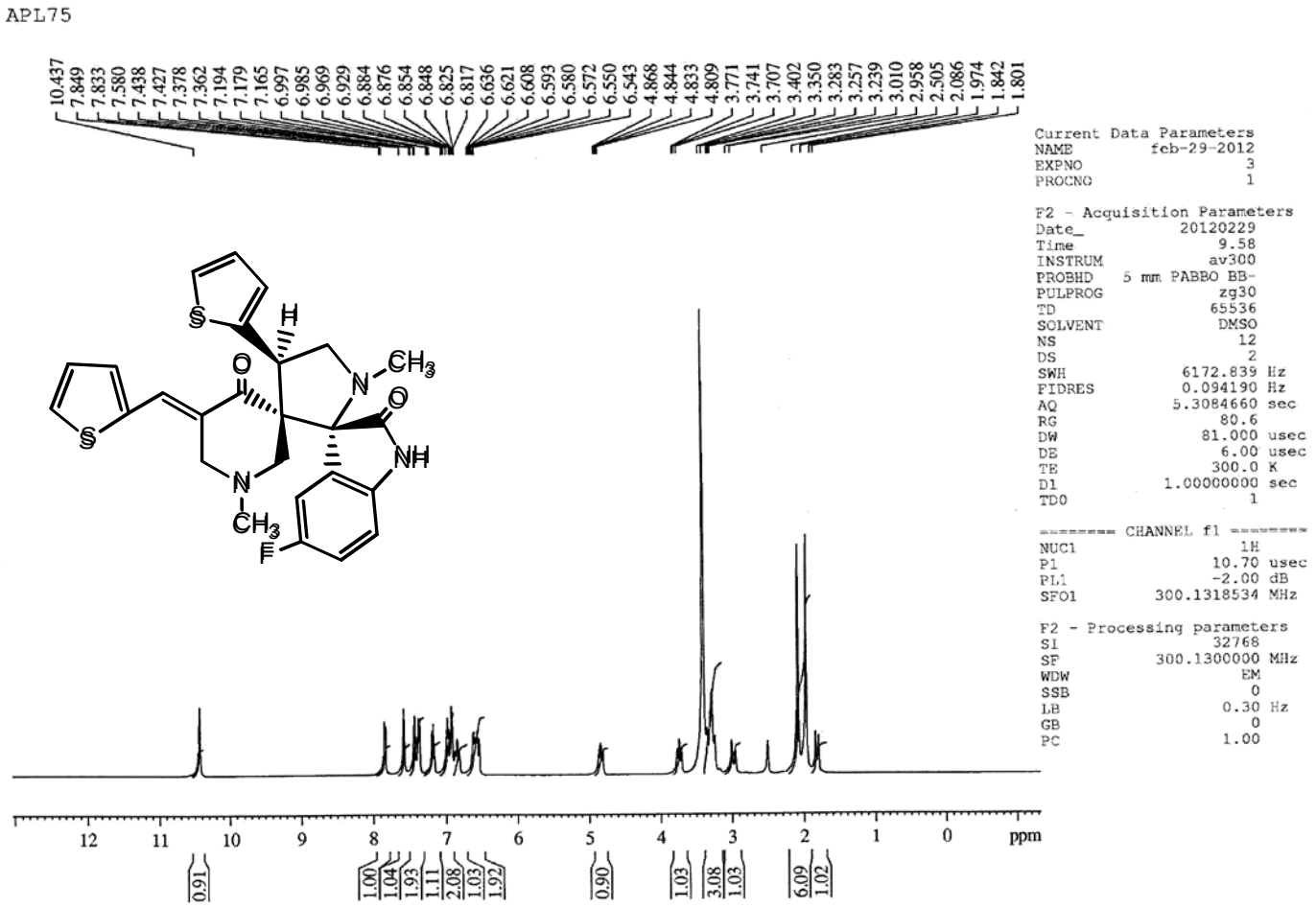
^{13}C spectrum of **4g**



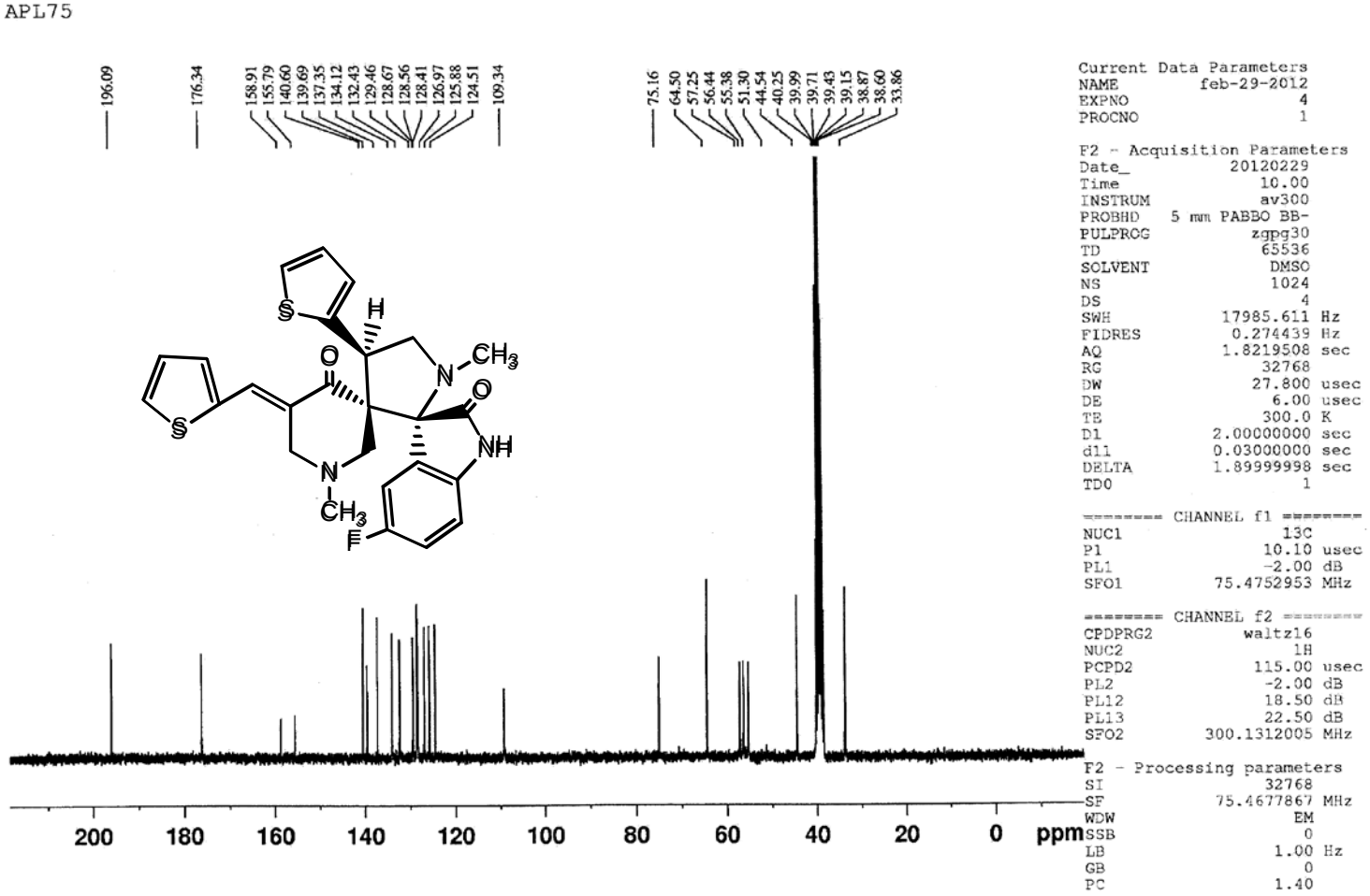
^{1}H spectrum of **4h**



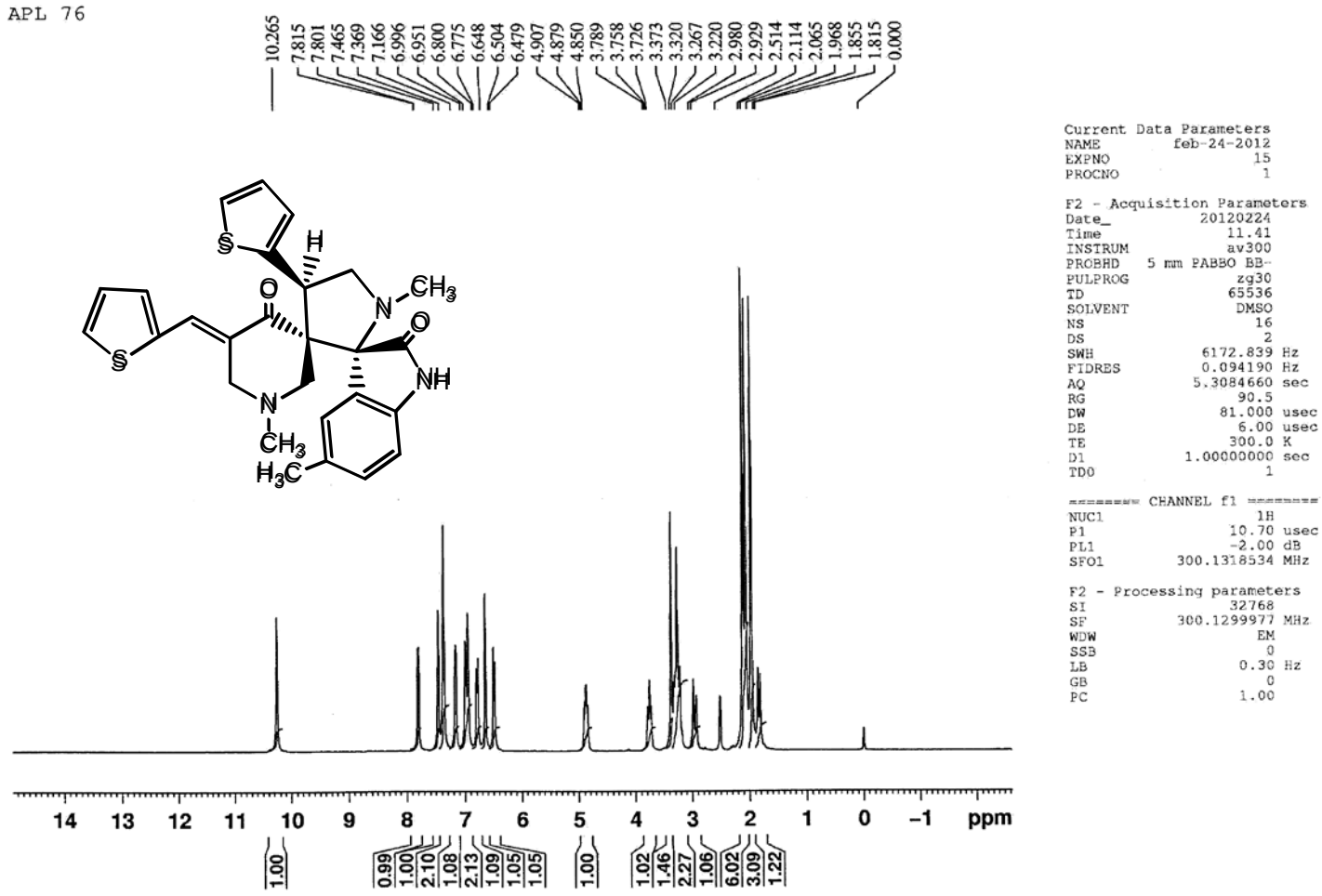
^{13}C spectrum of **4h**



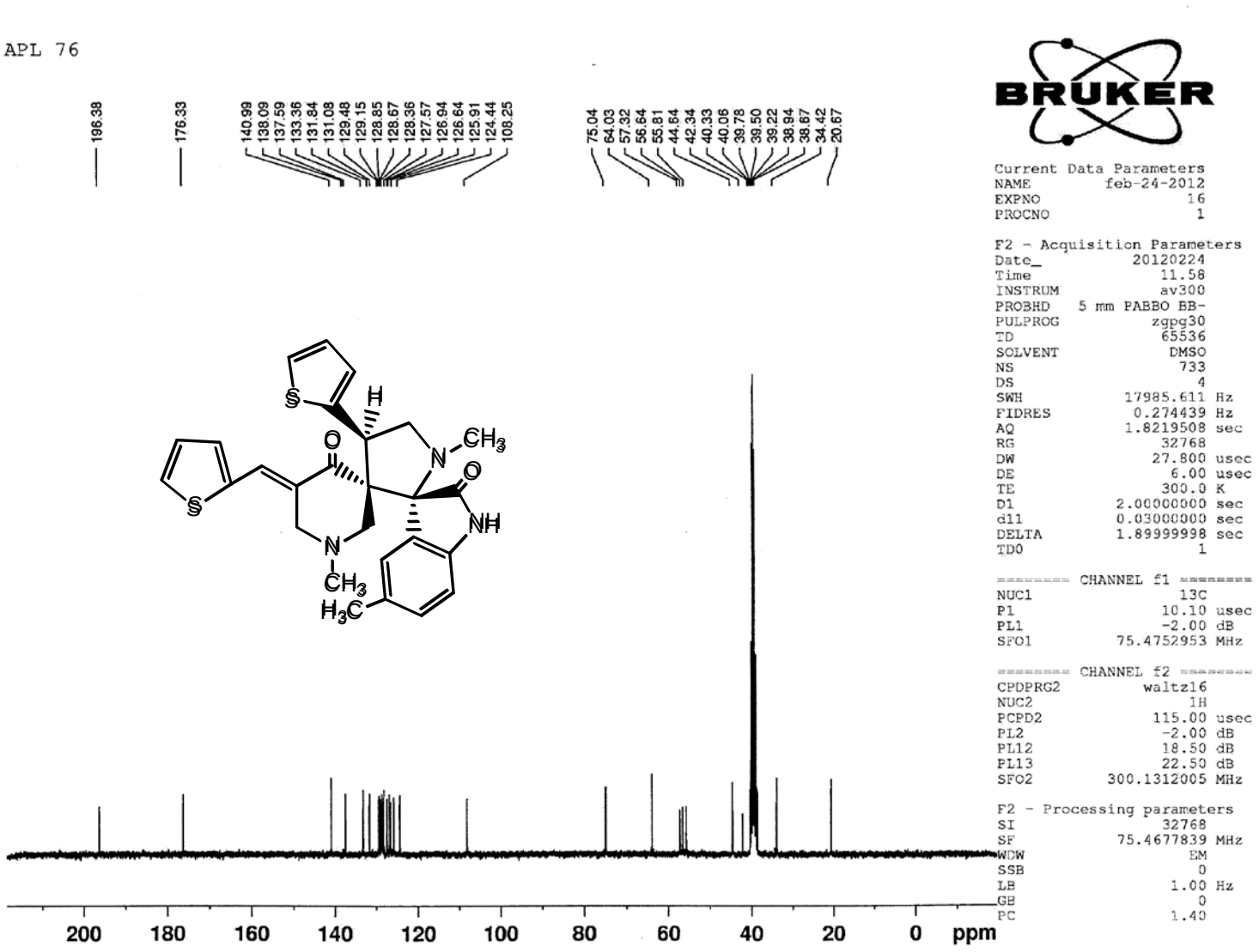
^{1}H spectrum of **4i**



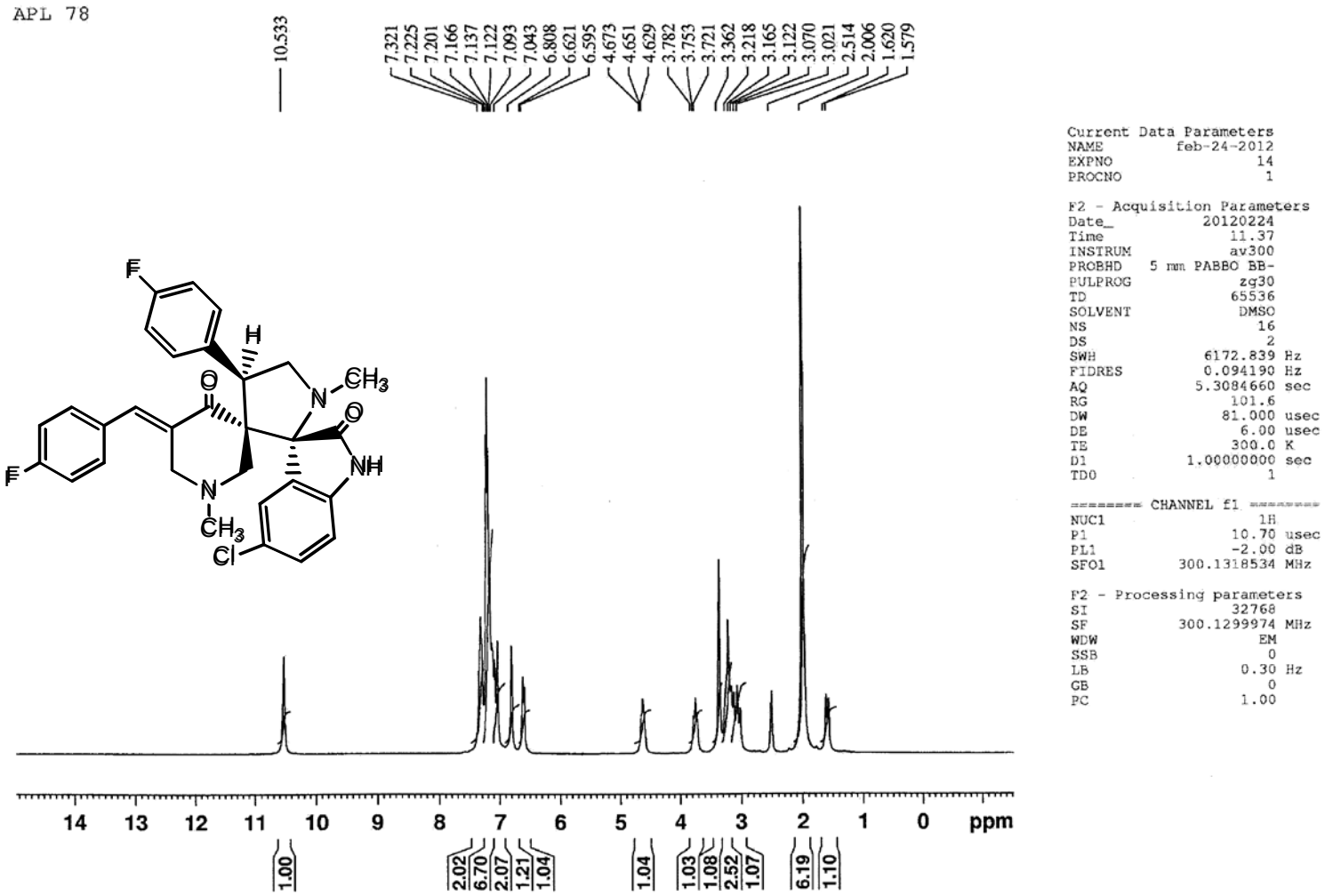
^{13}C spectrum of **4i**



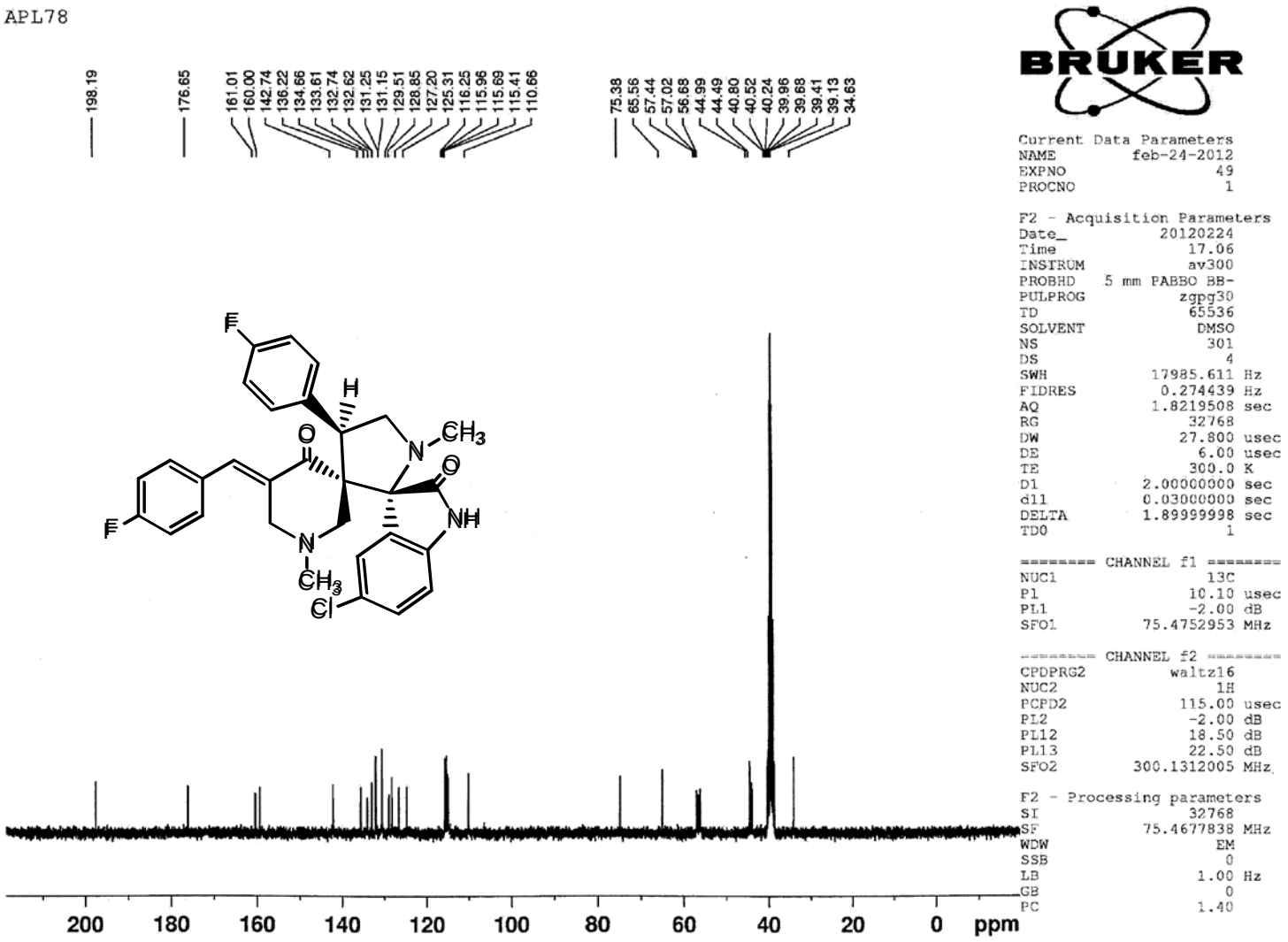
^{1}H spectrum of **4j**



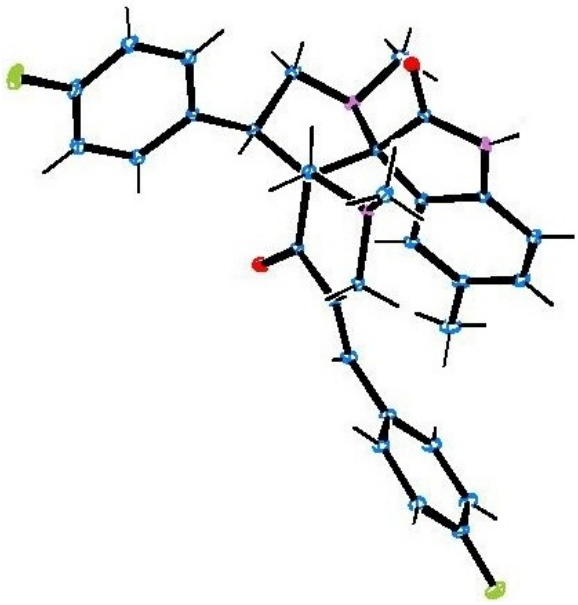
^{13}C spectrum of **4j**

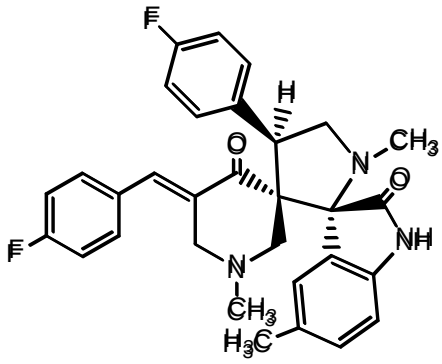


^{1}H spectrum of **4k**



^{13}C spectrum of **4k**





ORTEP diagram of compounds **4a (**(CCDC 883122)