

Supplementary Material

Synthesis of Spiro-tetrahydrothiopyran-oxindoles by Michael-aldol Cascade Reactions: Discovery of Potent P53-MDM2 Inhibitors with Good Antitumor Activity

Shengzheng Wang^{a,†,*}, Shuqiang Chen^{b,†}, Zhongjie Guo^{a,†}, Shipeng He^b, Fan Zhang^a, Xueying Liu^a, Weiping Chen^a, Shengyong Zhang^a and Chunquan Sheng^{b,*}

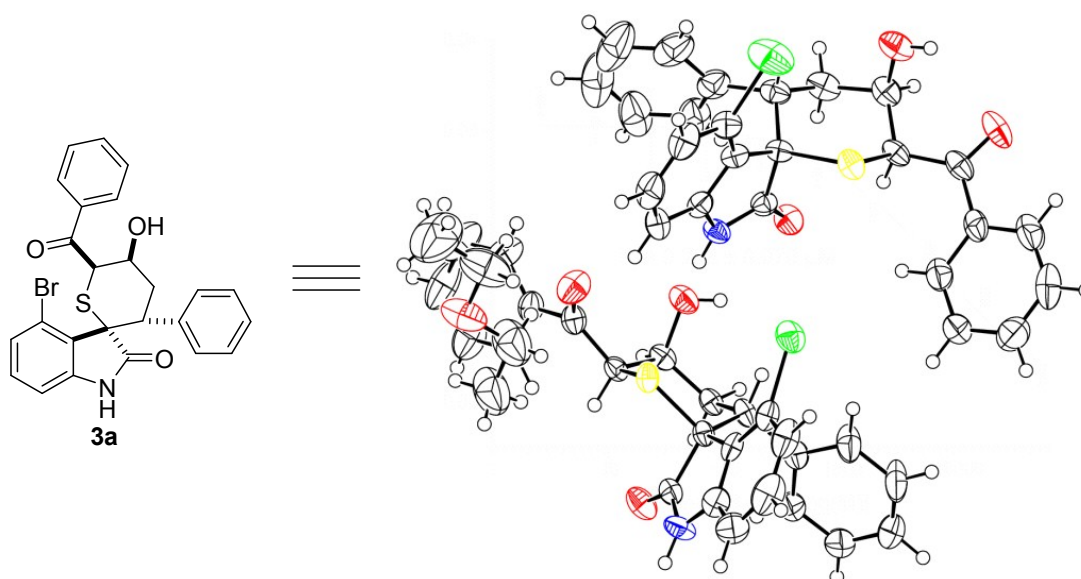
a Department of Medicinal Chemistry, School of Pharmacy, Fourth Military Medical University, 169 Changle West Road, Xi'an, 710032, P.R. China

b Department of Medicinal Chemistry, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, People's Republic of China

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X-ray structure of compound 3a



Bond precision: C-C = 0.0105 Å

Wavelength=0.71073

Cell: a=12.813 (2) b=14.490 (2) c=16.225 (4)
 alpha=108.147 (3) beta=98.120 (4) gamma=116.118 (2)
 Temperature: 243 K

	Calculated	Reported
Volume	2429.6 (8)	2429.5 (8)
Space group	P -1	P-1
Hall group	-P 1	?
Moiety formula	2(C ₂₅ H ₂₀ Br N O ₃ S), C ₄ H ₁₀ O	?
Sum formula	C ₅₄ H ₅₀ Br ₂ N ₂ O ₇ S ₂	C ₂₇ H ₂₅ Br N O _{3.50} S
Mr	1062.90	531.45
Dx, g cm ⁻³	1.453	1.453
Z	2	4
Mu (mm ⁻¹)	1.810	1.810
F ₀₀₀	1092.0	1092.0
F ₀₀₀ '	1091.77	
h, k, lmax	15, 17, 20	15, 17, 20
Nref	9634	9479
Tmin, Tmax	0.840, 0.881	0.737, 0.884
Tmin'	0.722	

Correction method= MULTI-SCAN

Data completeness= 0.984

Theta(max)= 26.100

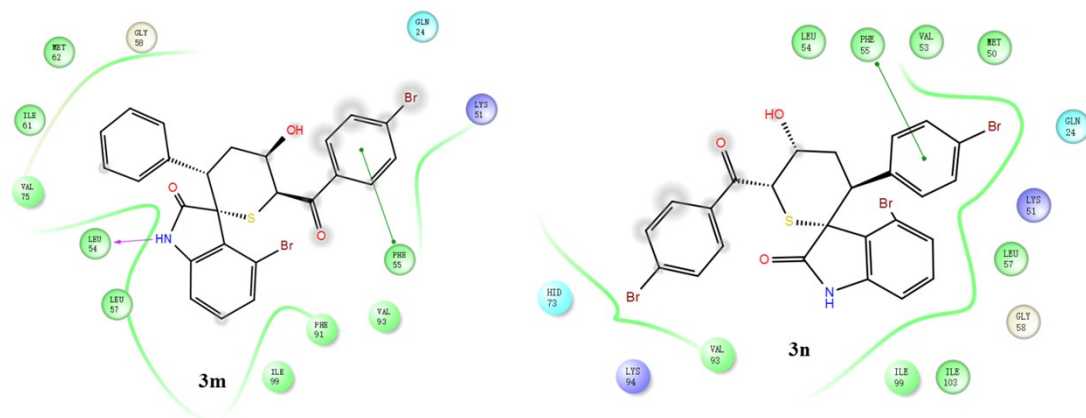
R(reflections)= 0.0572 (5961)

wR2(reflections)= 0.1788 (9479)

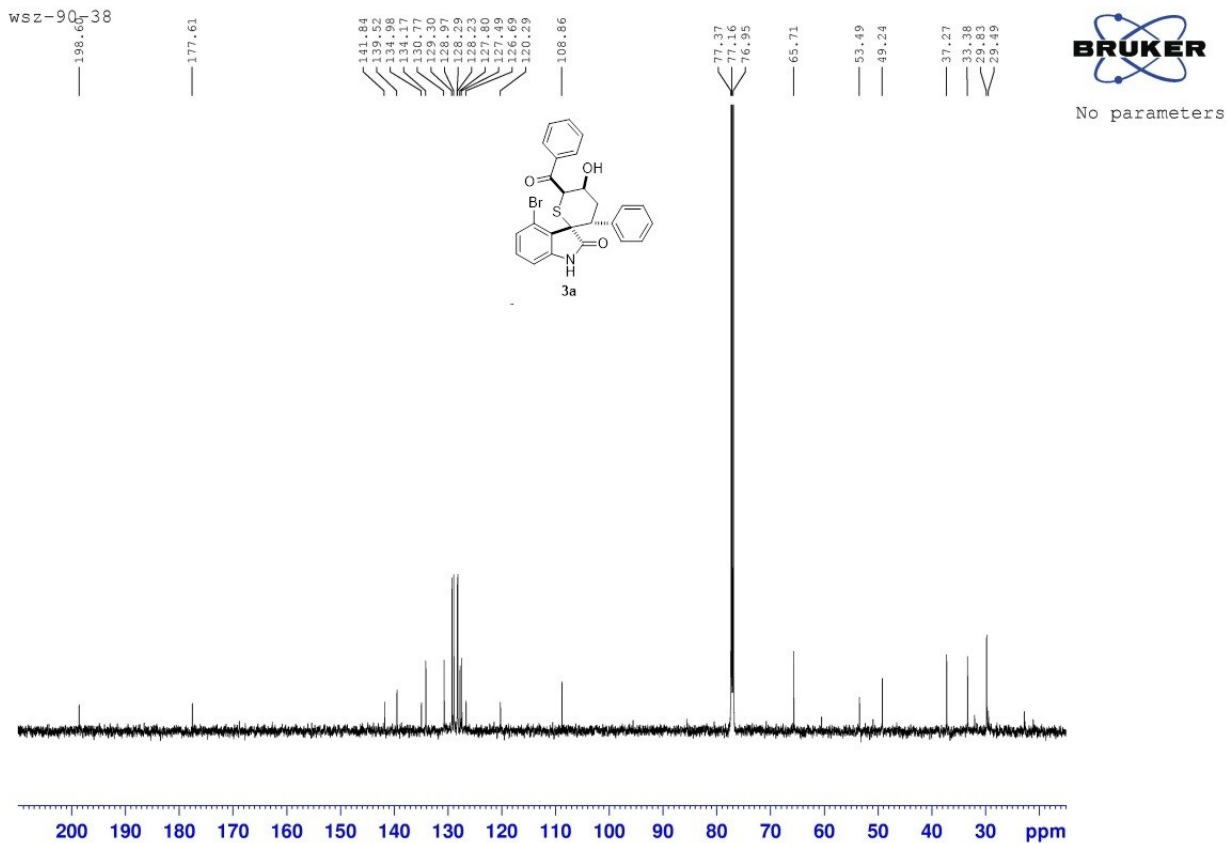
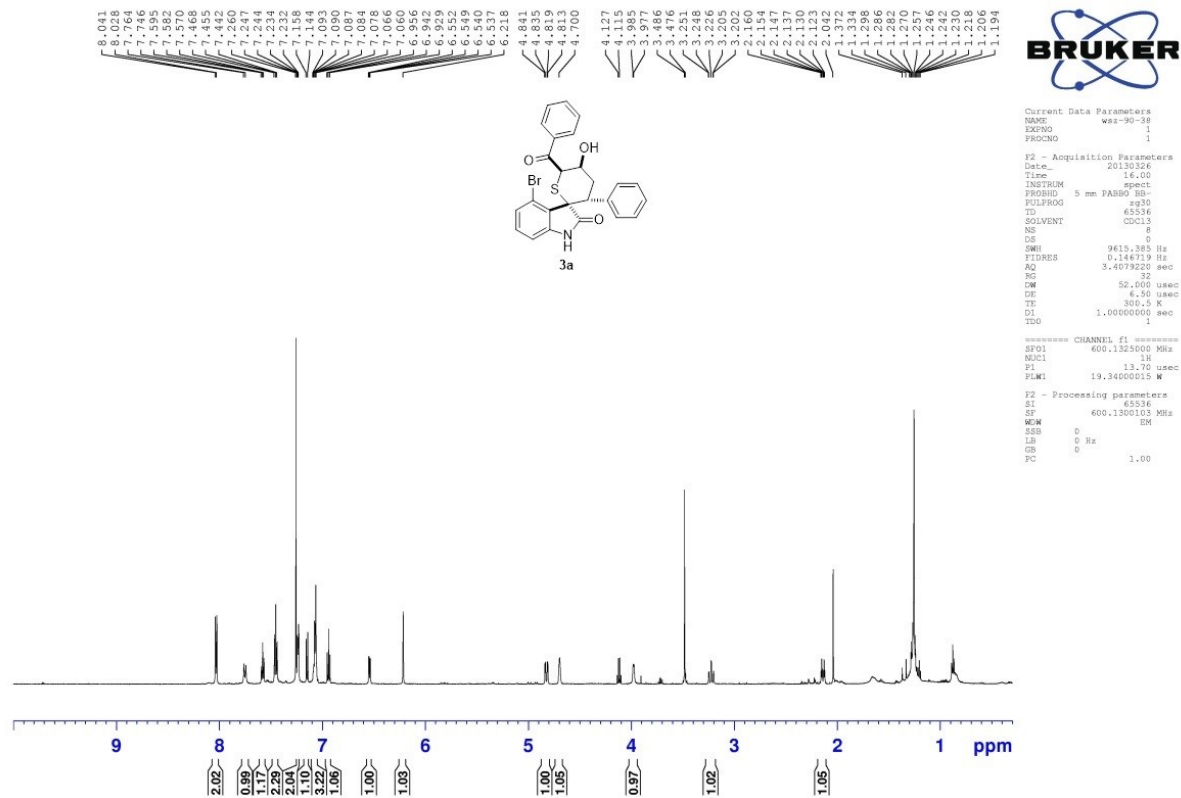
S = 1.046

Npar= 606

Schematic representation of the proposed binding mode for compounds 3m and 3n in the p53 binding domain of MDM2.

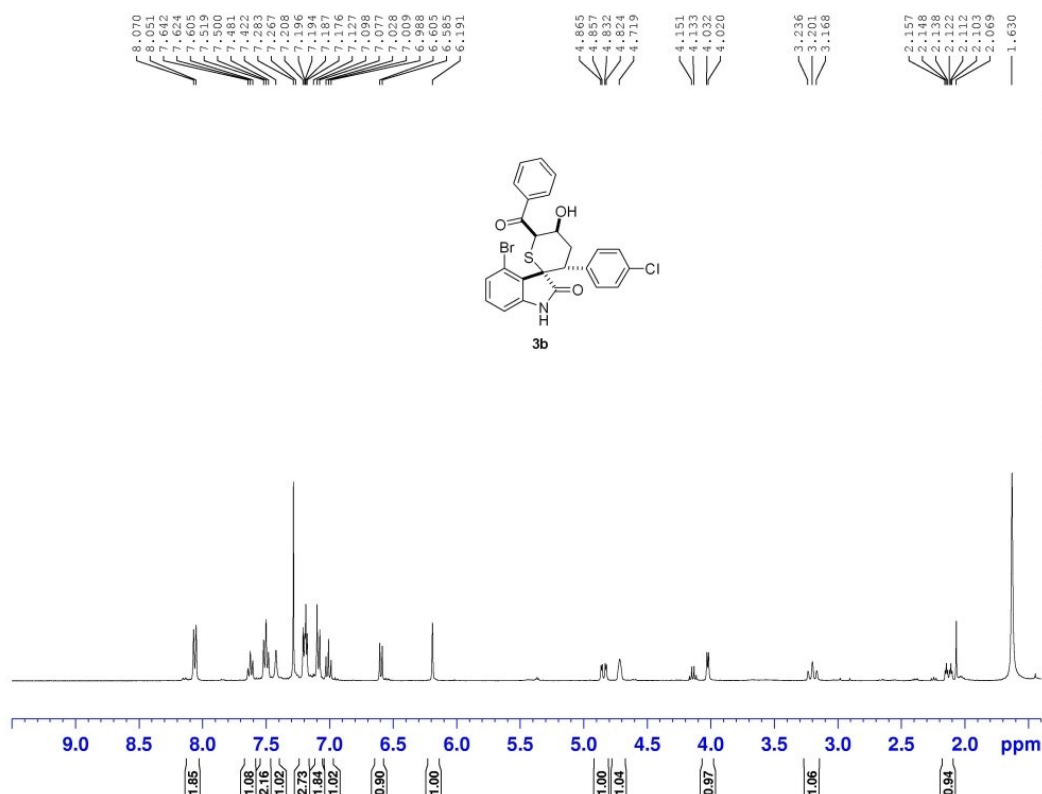


NMR Spectra
Compound 3a



Compound 3b

wsz-5-57-1



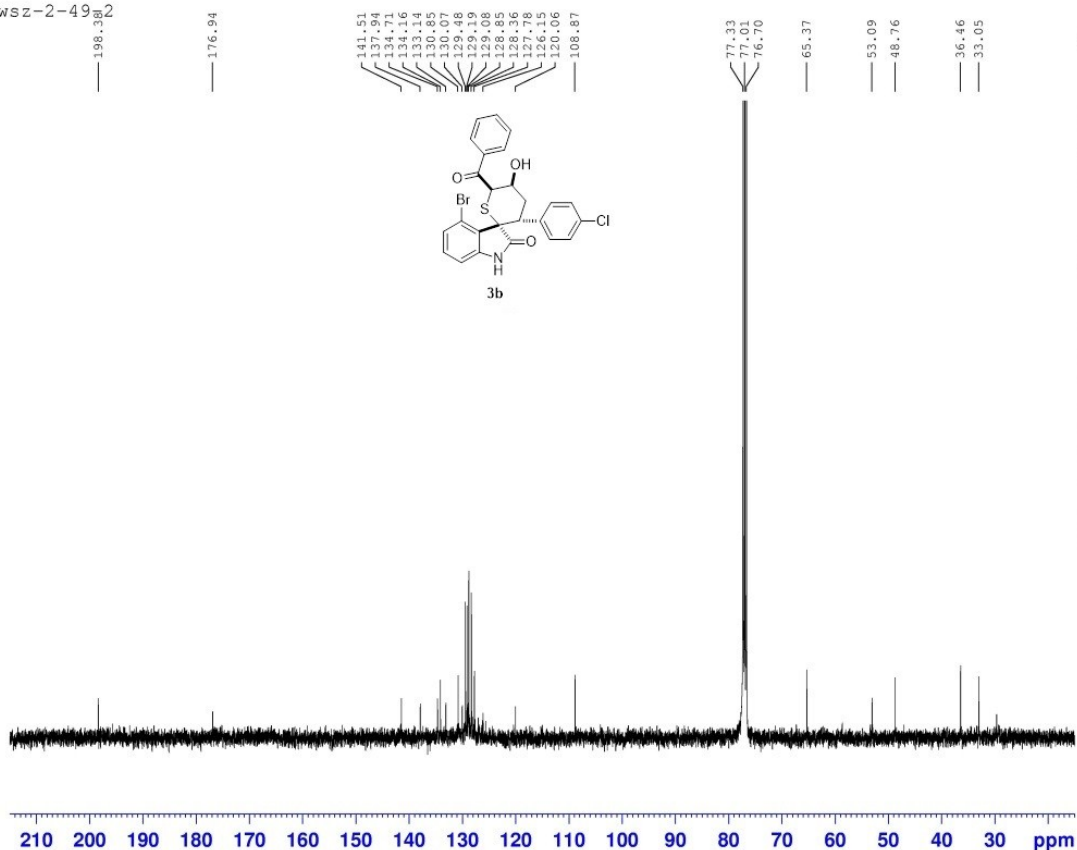
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NAME: wsz-5-57-1
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20170826
Time: 15.20
INSTRUM: spect
PROBHD: 5 mm PABBO BB/
PULPROG: zg30
TD: 65536
SOLVENT: CDCl3
NS: 16
DS: 2
SWH: 8223.685 Hz
FIDRES: 0.125493 Hz
AQ: 3.9846387 sec
RG: 107.77
DM: 60.800 usec
DE: 6.50 usec
TE: 292.0 K
D1: 1.0000000 sec
TDO: 1

===== CHANNEL f1 =====
NUC1: 1H
P1: 10.00 usec
PLW1: 17.7630095 W
SFO1: 400.1326710 MHz

F2 - Processing parameters
SI: 65536
SF: 400.1300000 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.00

wsz-2-49-2



Current Data Parameters
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EXPNO: 2
PROCNO: 1

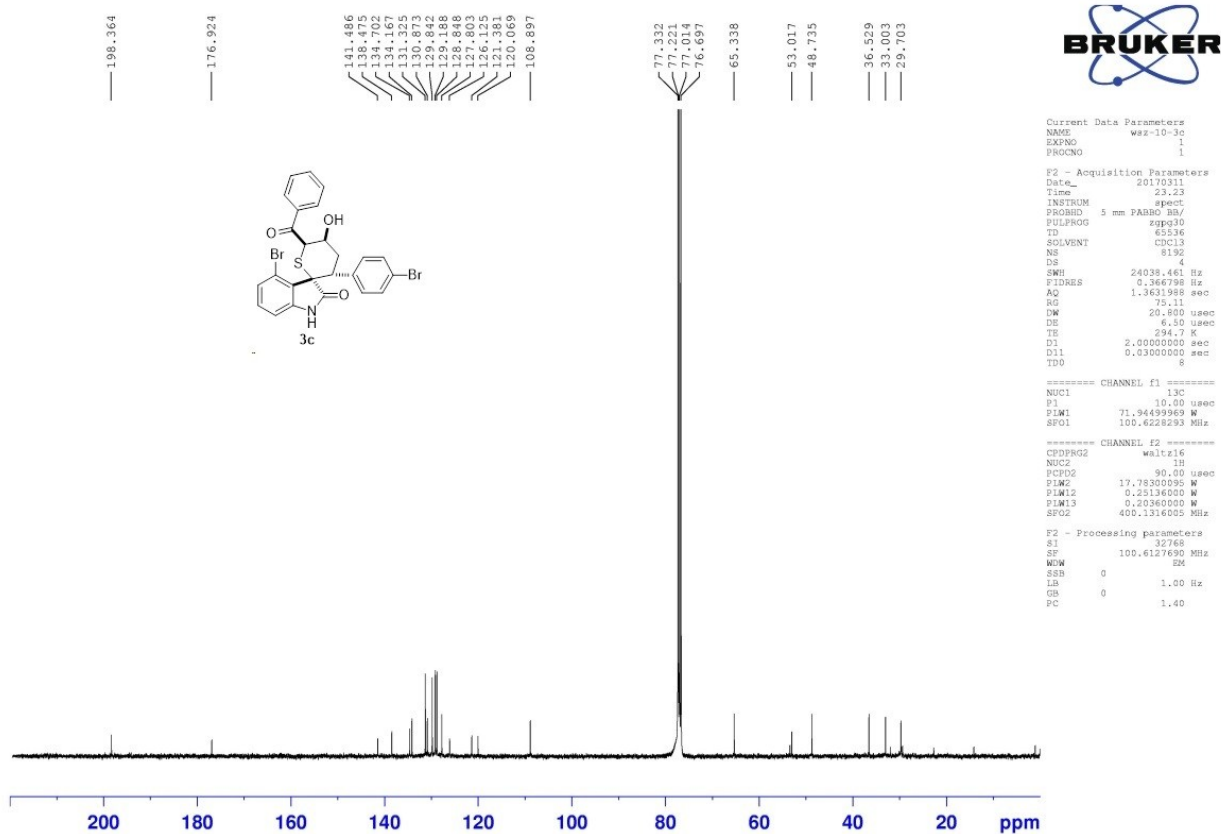
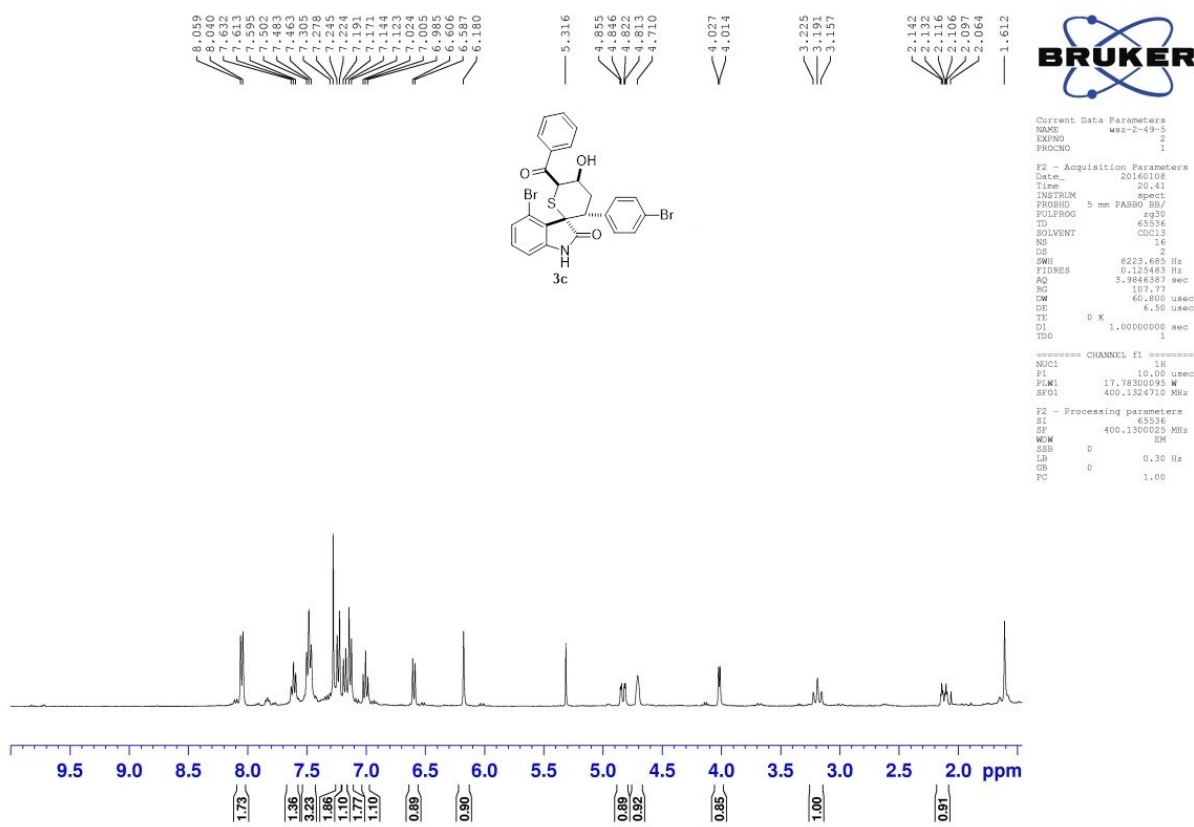
F2 - Acquisition Parameters
Date_: 20161009
Time: 12.07
INSTRUM: spect
PROBHD: 5 mm PABBO BB/
PULPROG: zgpg30
TD: 65536
SOLVENT: CDCl3
NS: 2048
DS: 4
SWH: 24038.461 Hz
FIDRES: 9.360790 Hz
AQ: 1.3631988 sec
RG: 107.77
DM: 20.800 usec
DE: 6.50 usec
TE: 0 K
D1: 2.0000000 sec
D11: 0.0300000 sec
TDO: 2

===== CHANNEL f1 =====
NUC1: 13C
P1: 10.00 usec
PLW1: 71.3449983 W
SFO1: 100.6229293 MHz

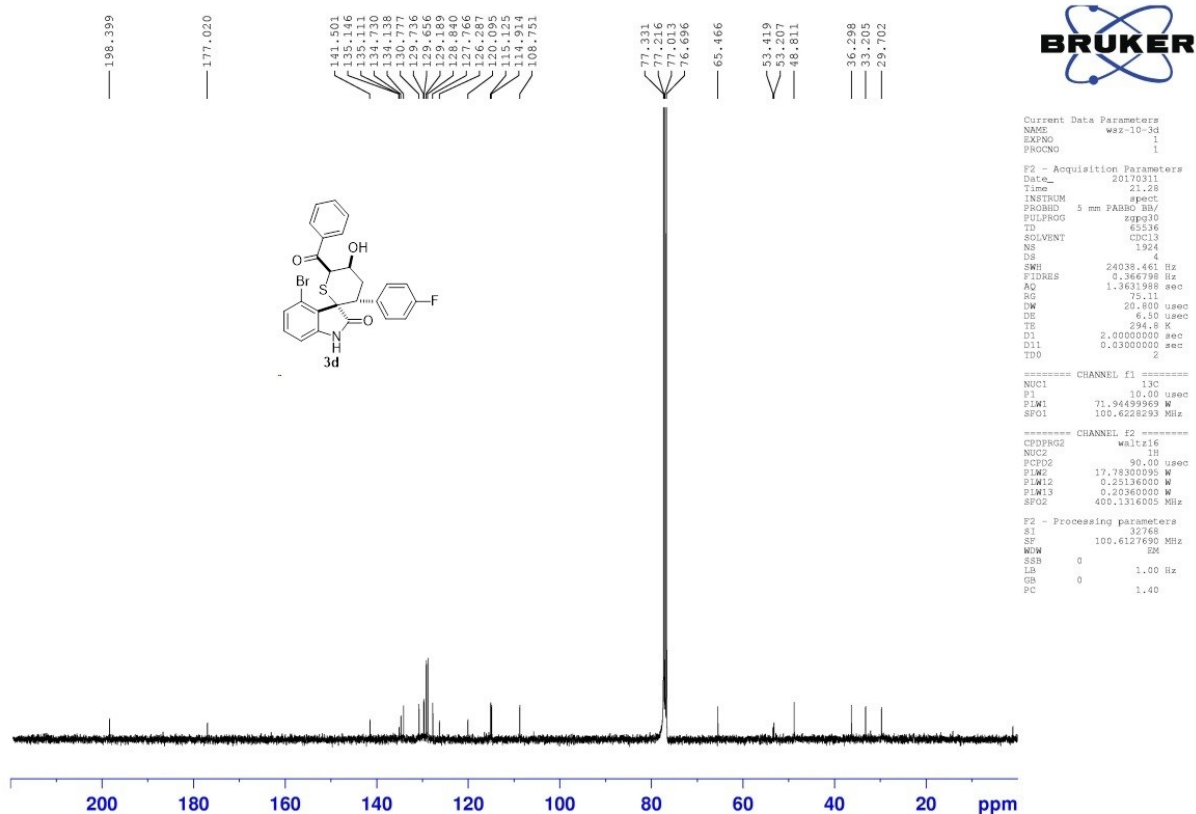
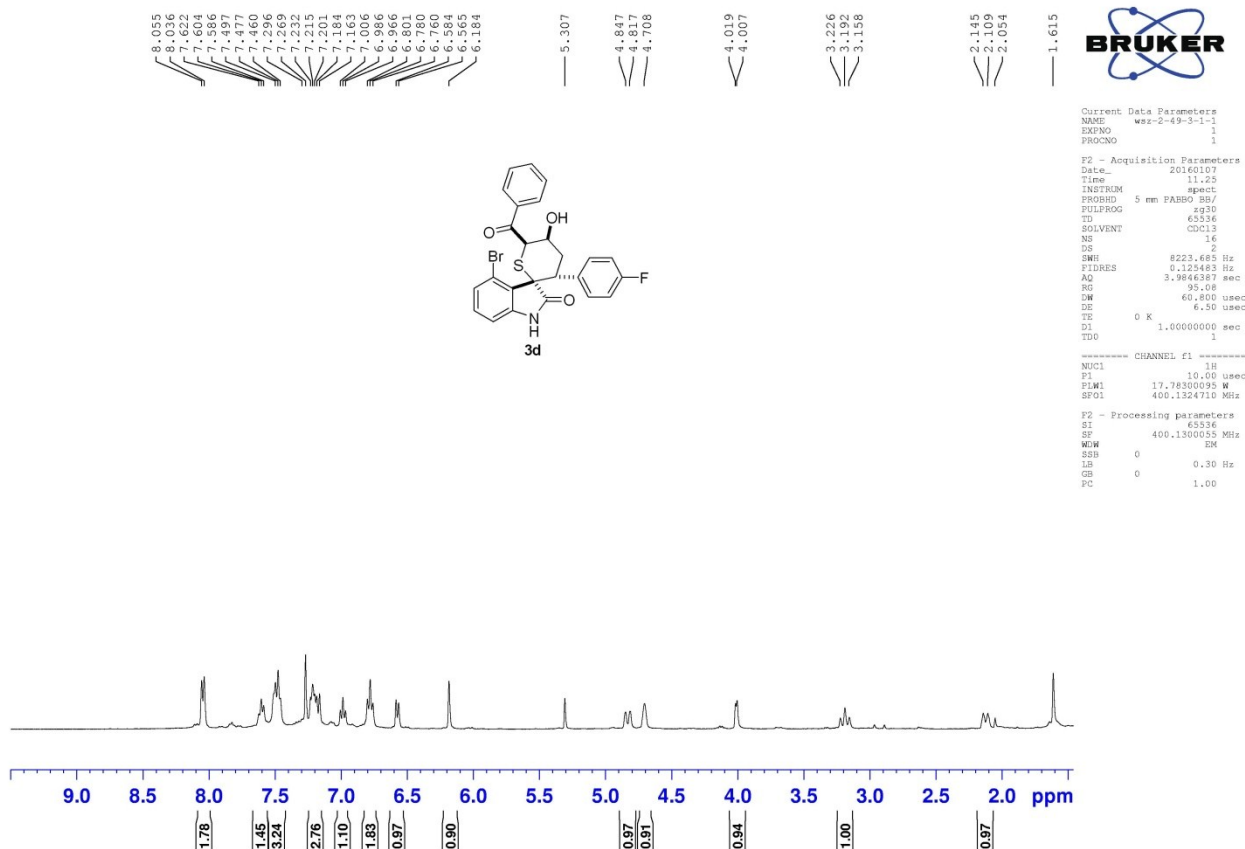
===== CHANNEL f2 =====
CPDPRG2: waltz16
NUC2: 1H
PCPD2: 90.00 usec
PLW2: 17.7630095 W
PLW3: 0.25134000 W
PLW3: 0.20366000 W
SFO2: 400.1314600 MHz

F2 - Processing parameters
SI: 32768
SF: 100.6127490 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40

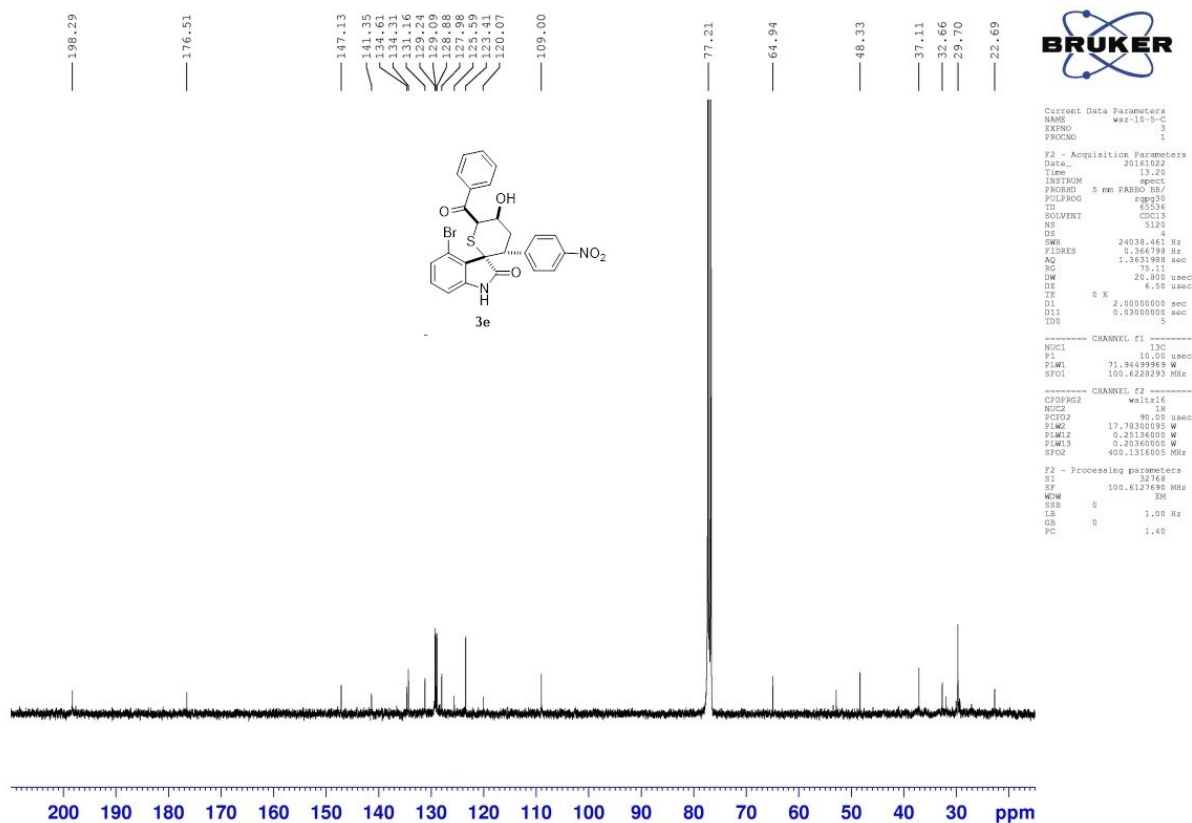
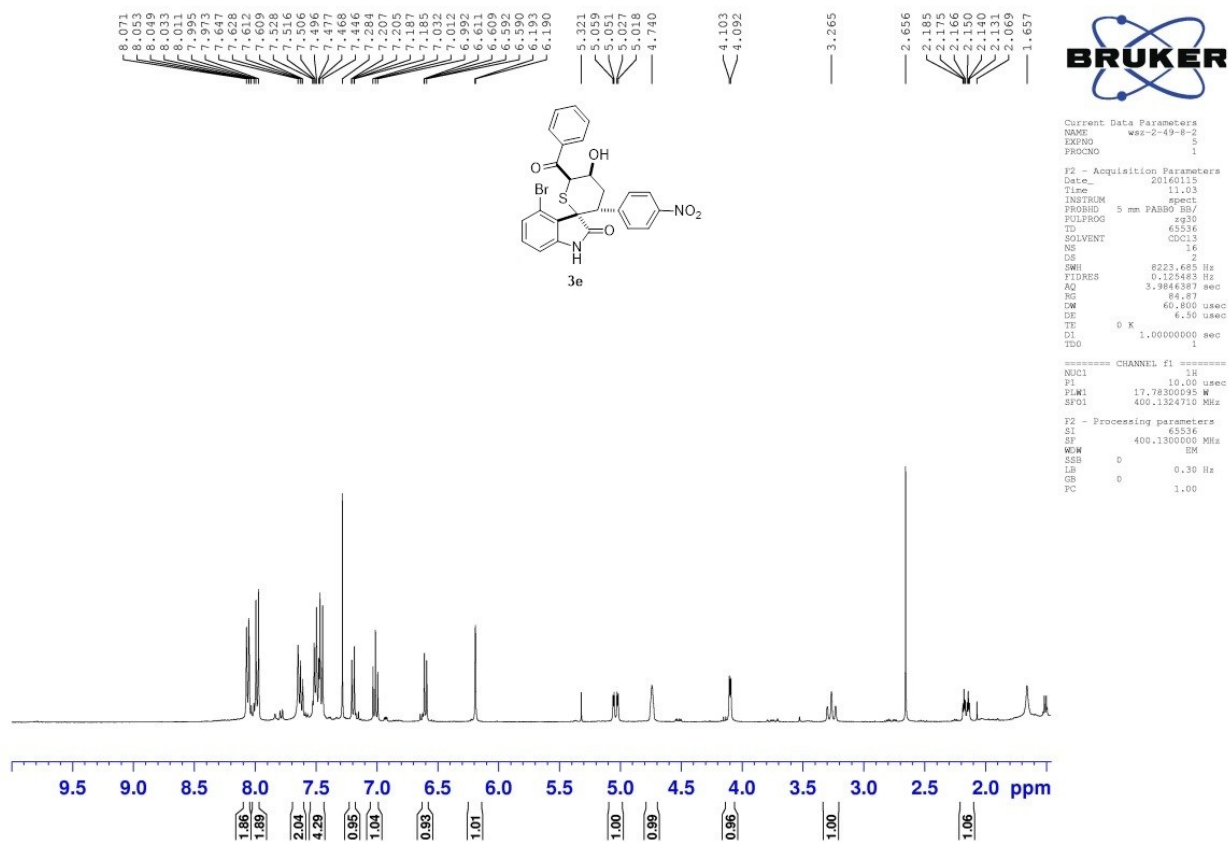
Compound 3c



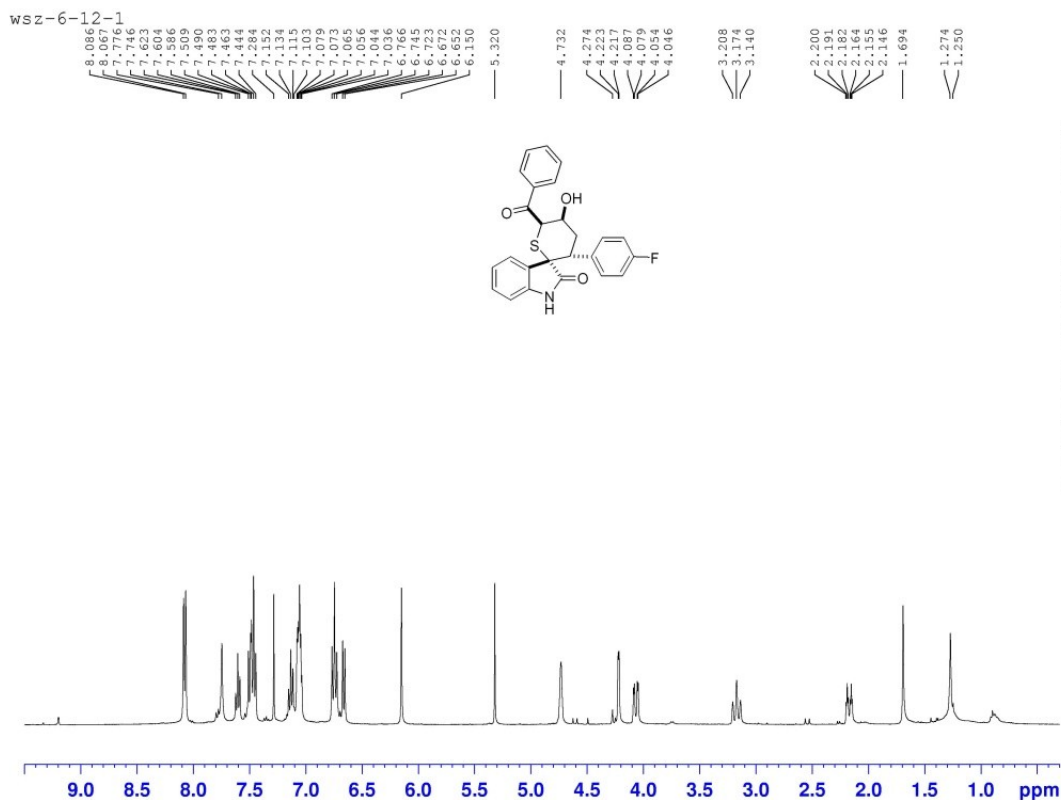
Compound 3d



Compound 3e



Compound 3f

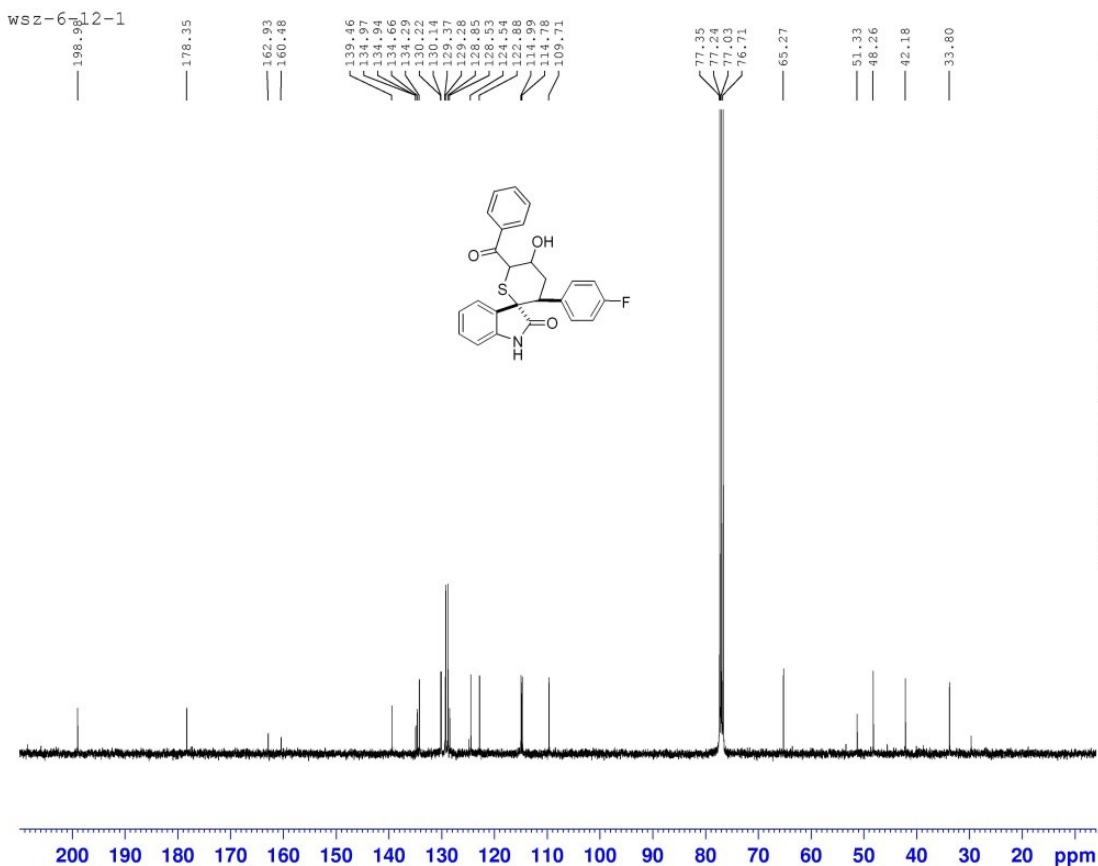


Current Data Parameters
NAME wsz-6-12-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20171012
Time 16.00
INSTRUM spect
PROBHD 5 mm F4BBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.984387 sec
RG 84.87
DM 60.800 usec
DE 6.50 usec
TE 292.0 K
D1 1.00000000 sec
TDO 1

===== CHANNEL f1 =====
NUC1 1H
P1 10.00 usec
PLW1 17.78300095 W
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME wsz-6-12-1
EXPNO 3
PROCNO 1

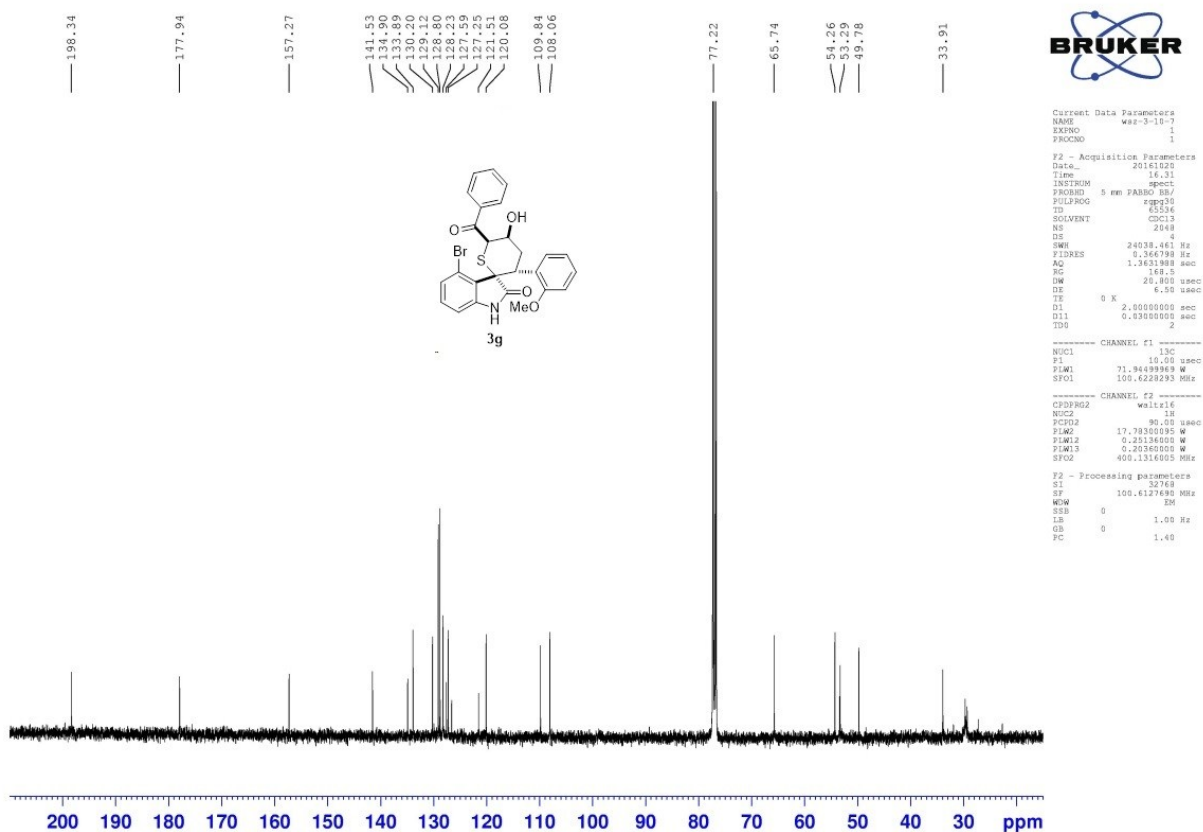
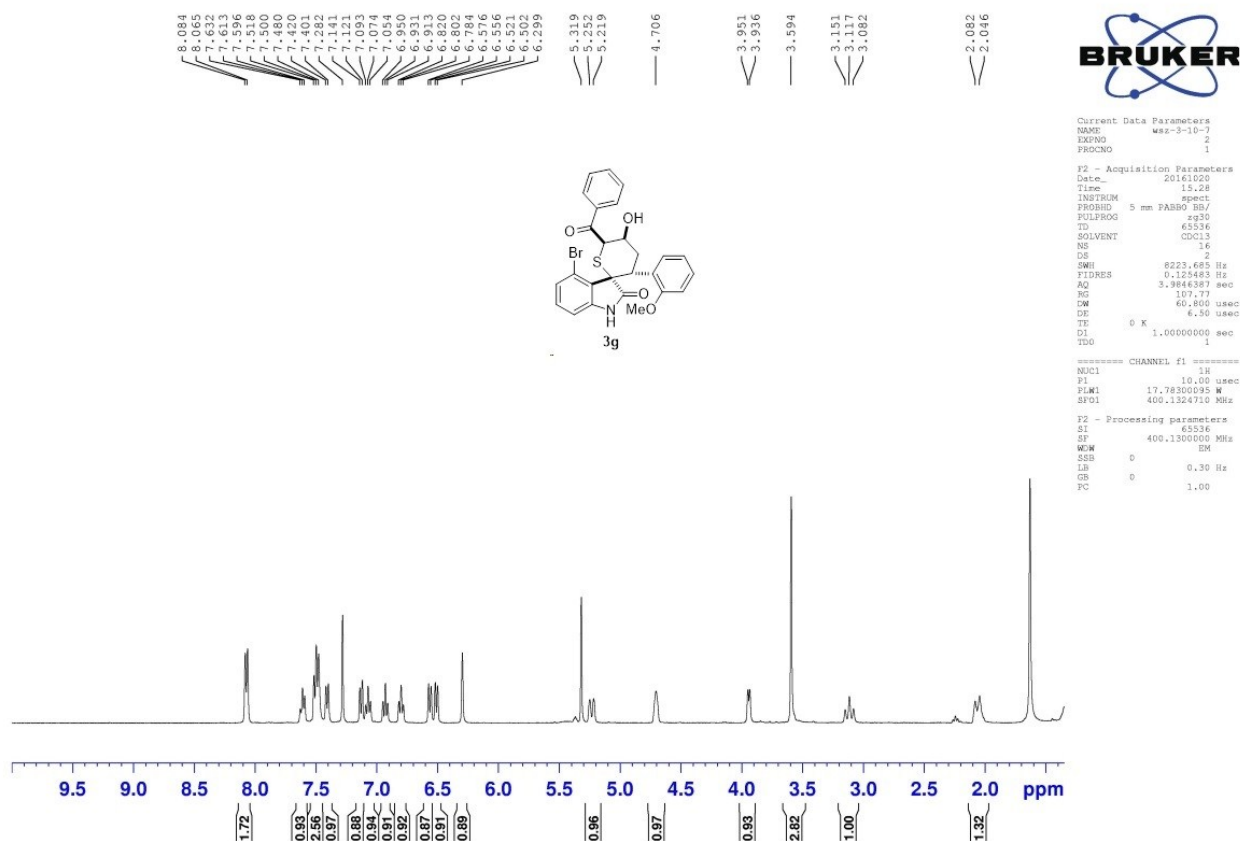
F2 - Acquisition Parameters
Date_ 20171012
Time 16.48
INSTRUM spect
PROBHD 5 mm F4BBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1032
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.361986 sec
RG 75.11
DM 20.800 usec
DE 6.50 usec
TE 293.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 6

===== CHANNEL f1 =====
NUC1 13C
P1 10.00 usec
PLW1 71.34499969 W
SFO1 100.6228293 MHz

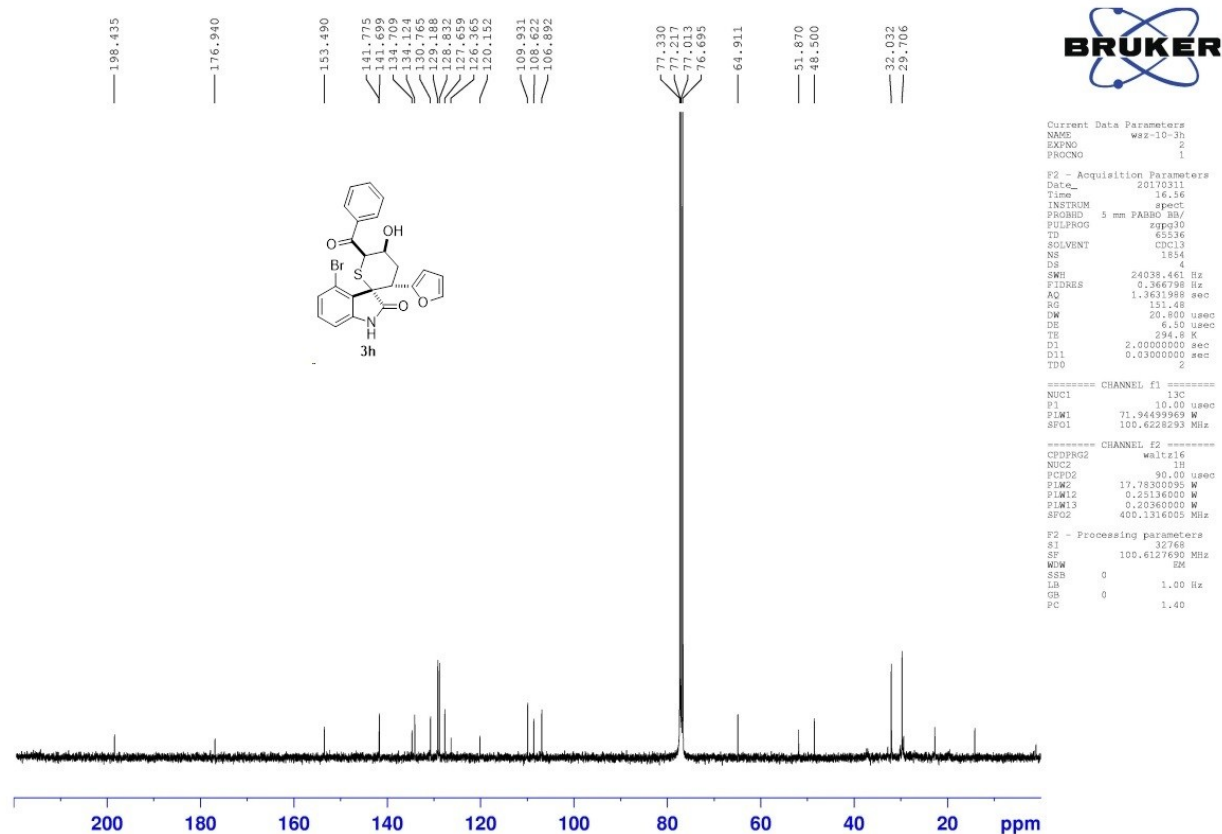
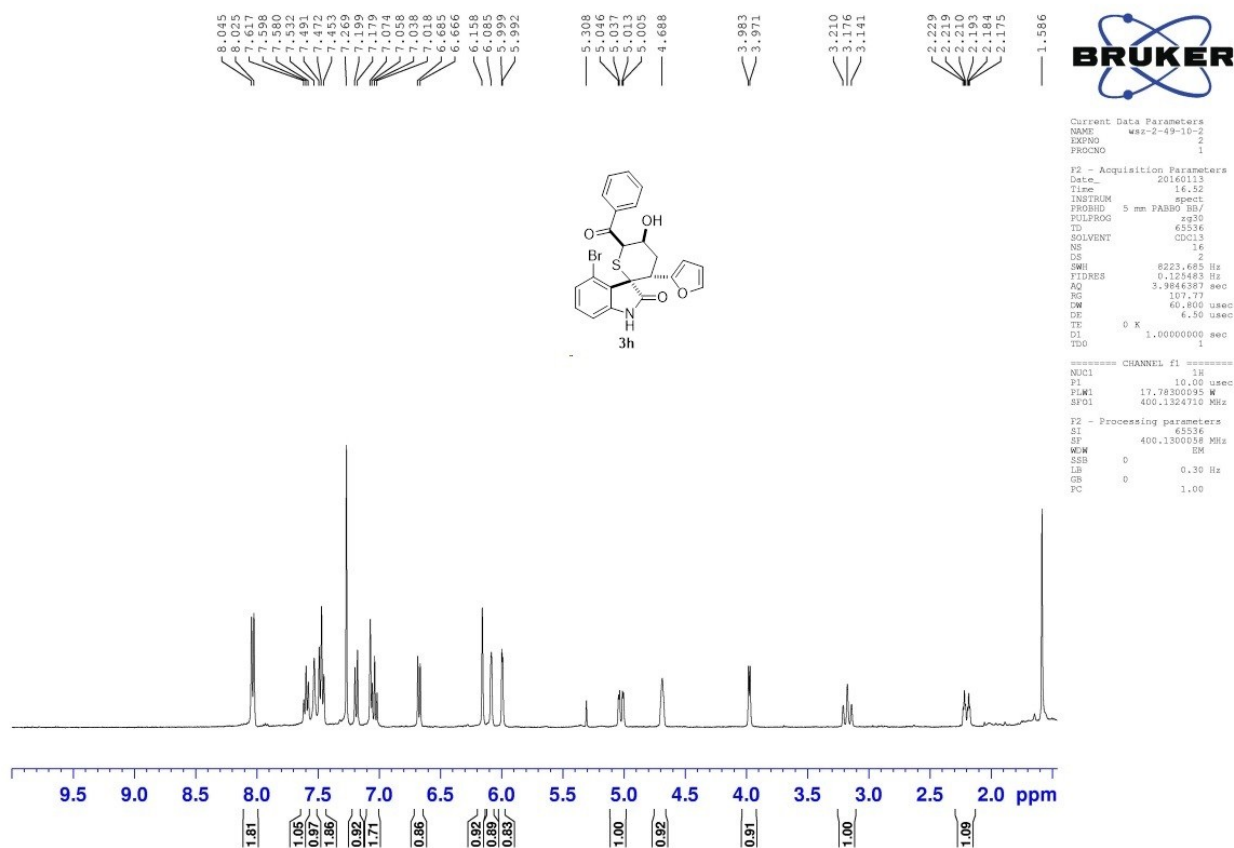
===== CHANNEL f2 =====
CPDPRG2 Maltz16
NUC2 1H
PCPDZ 80.00 usec
PLW2 17.78300095 W
PLW12 0.25136000 W
PLW13 0.20360000 W
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

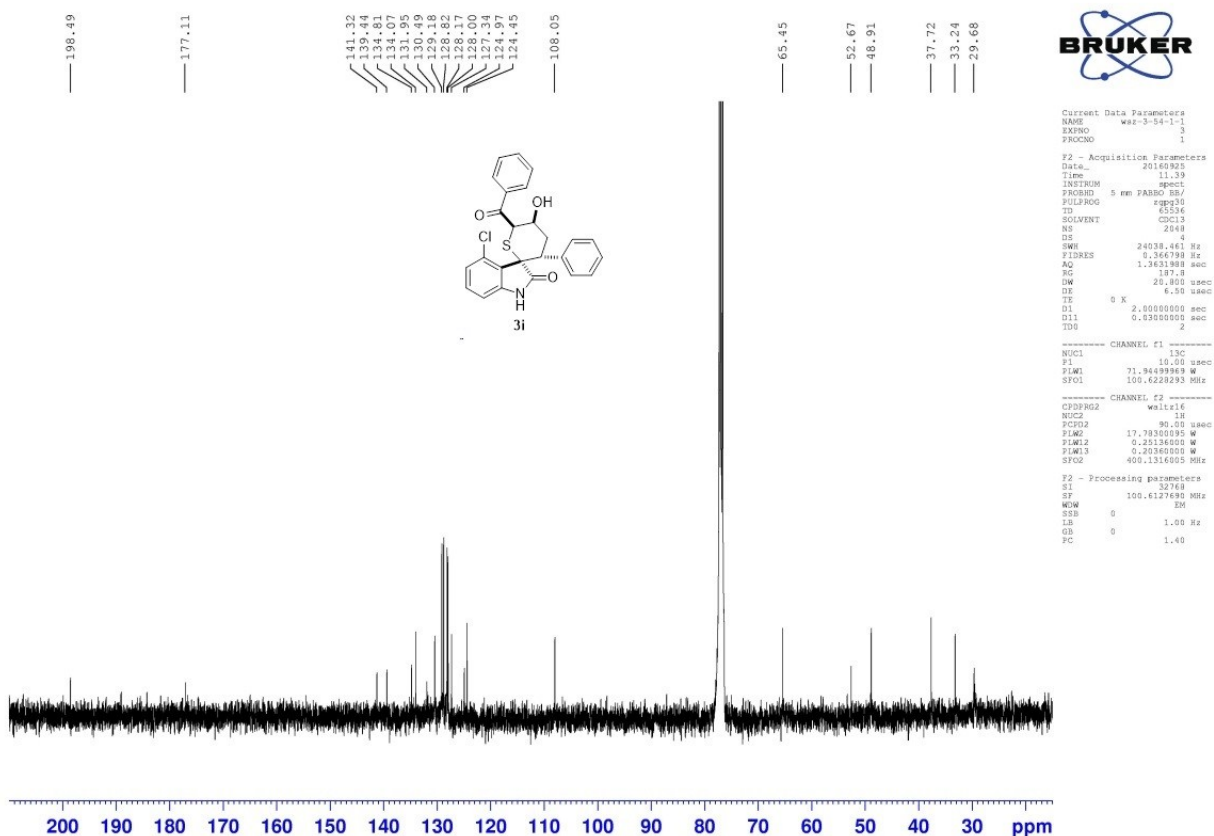
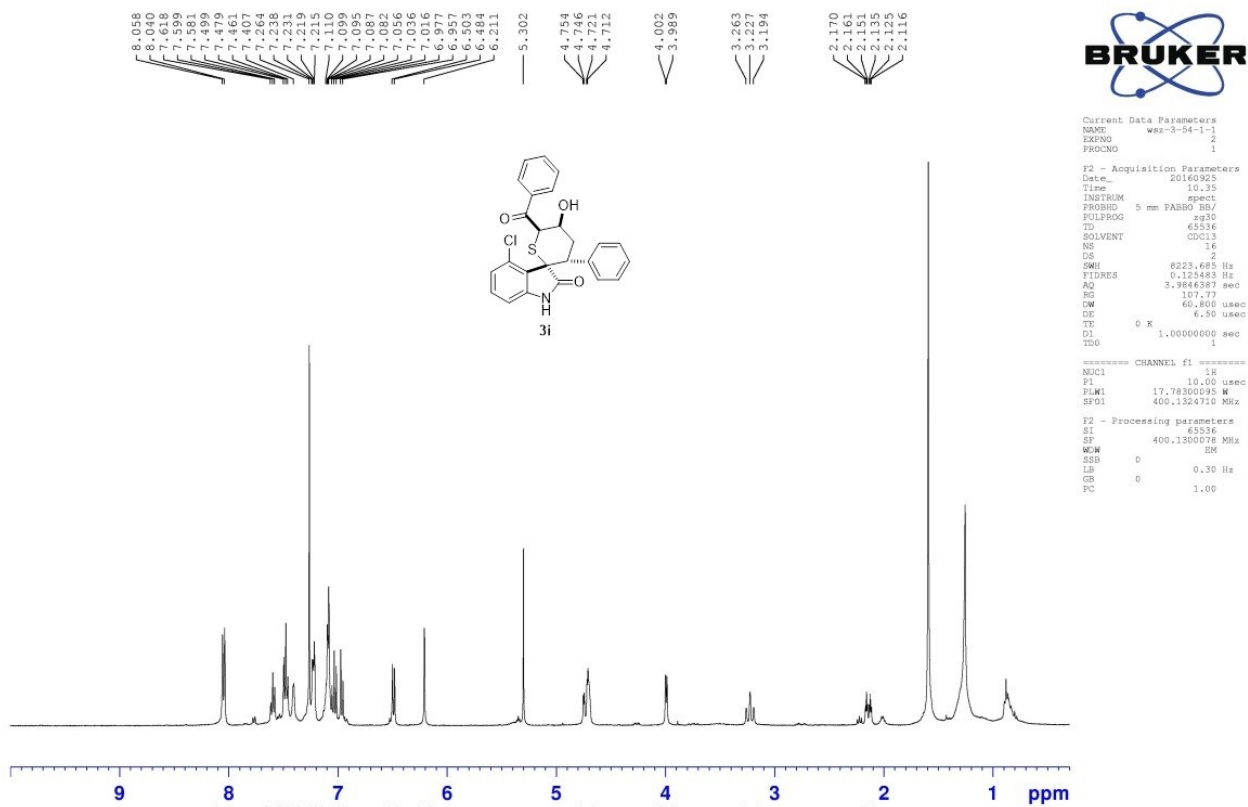
Compound 3g



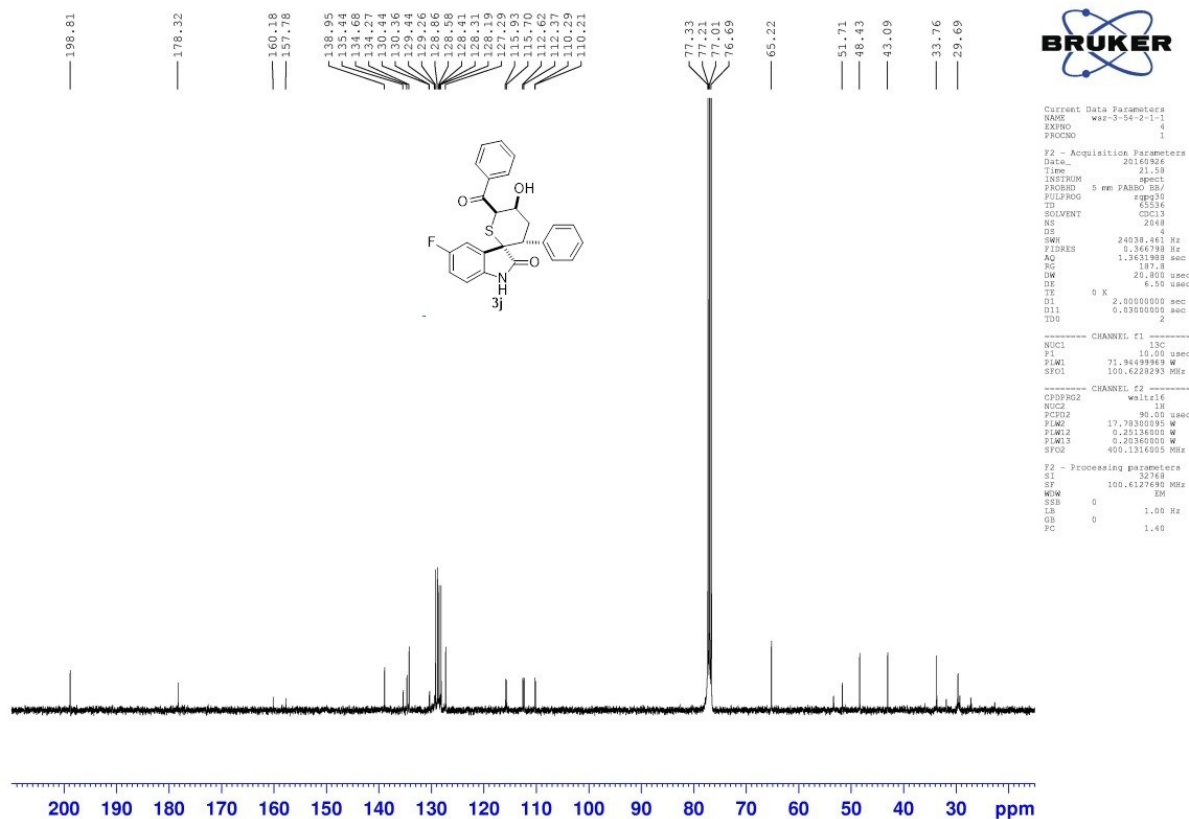
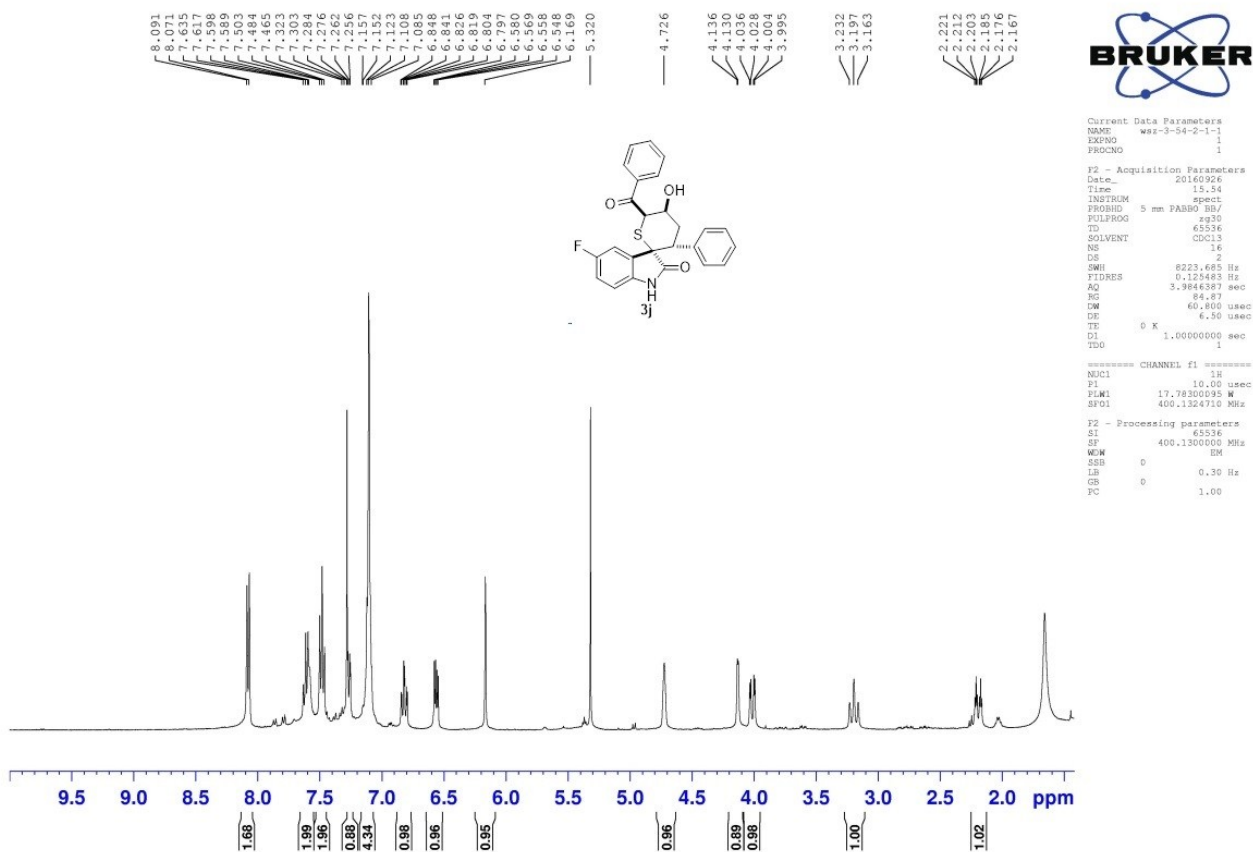
Compound 3h



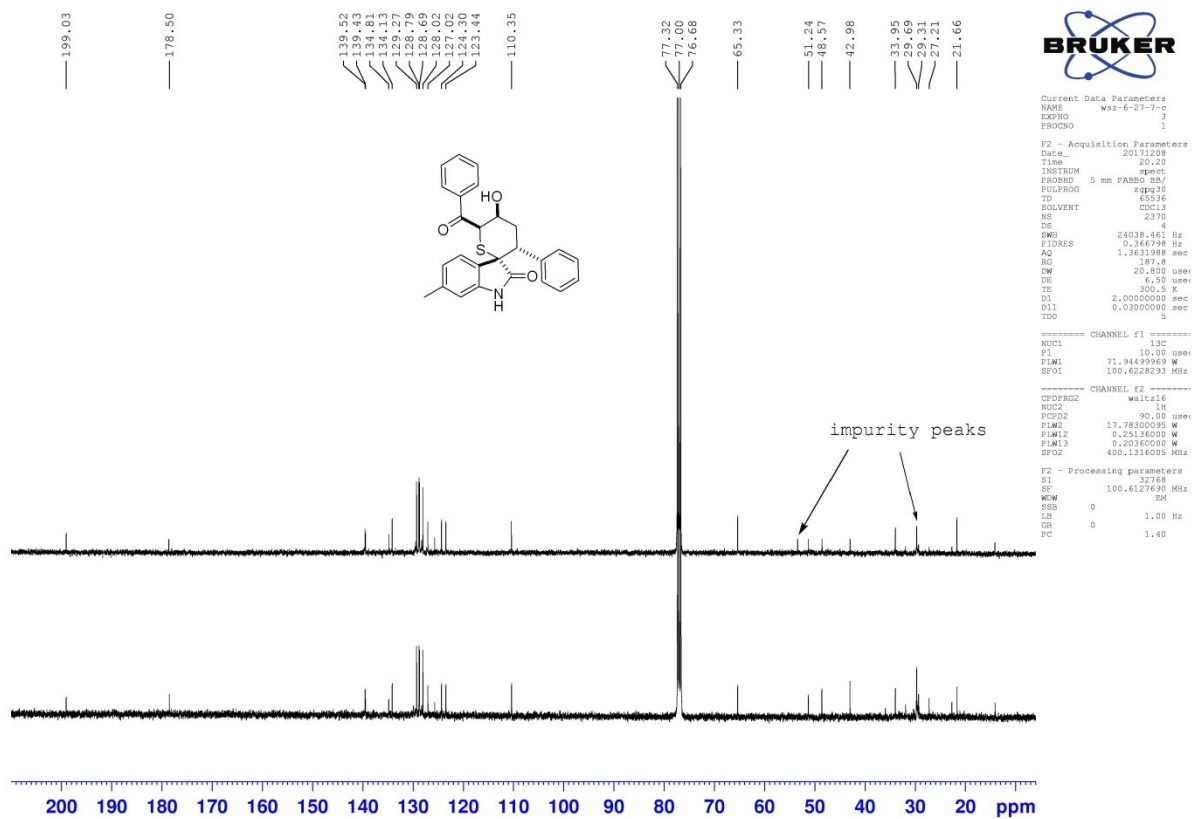
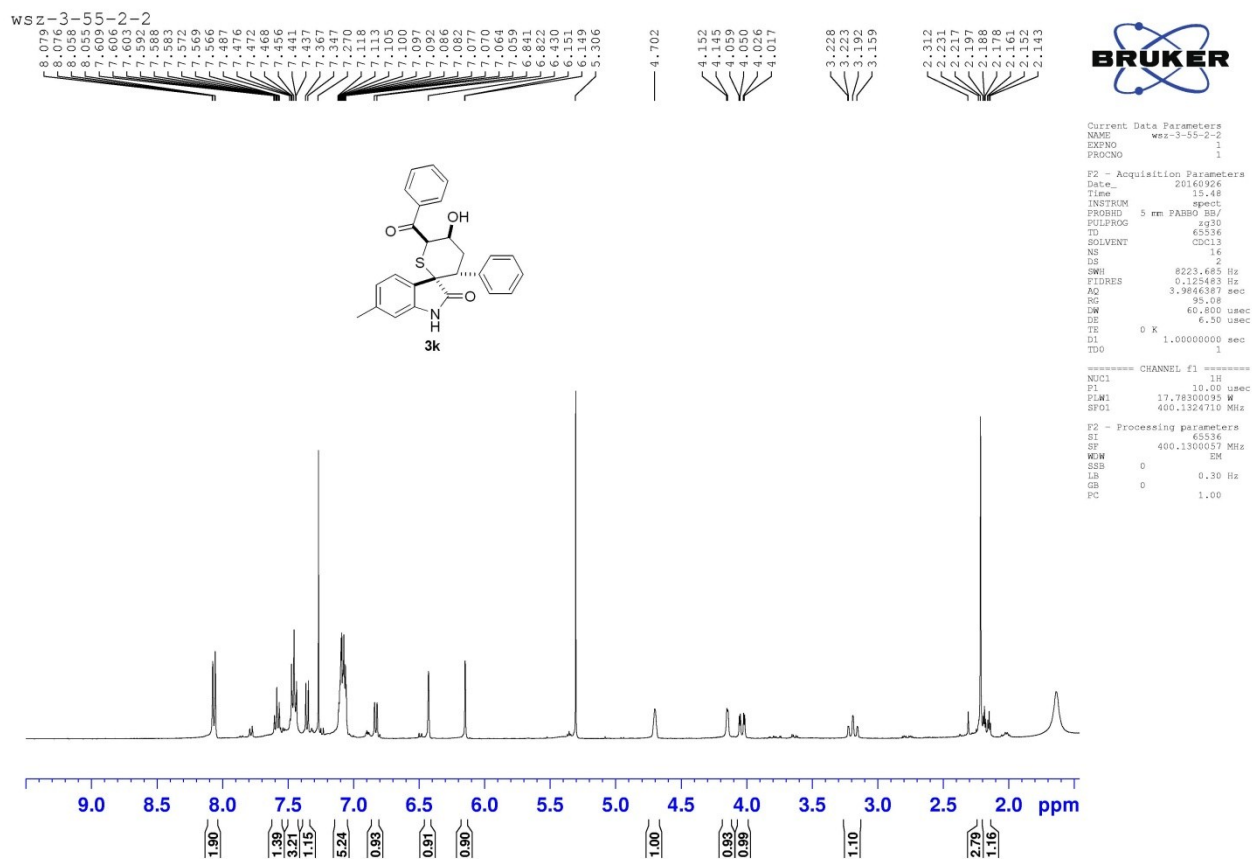
Compound 3i



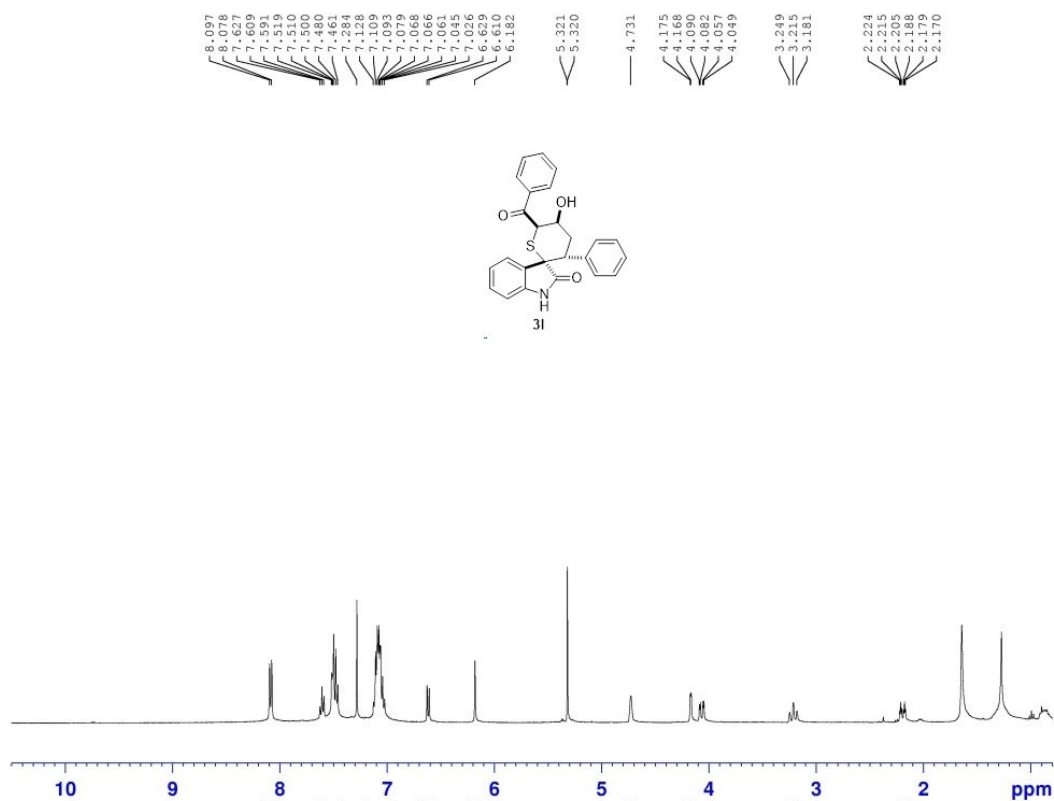
Compound 3j



Compound 3k



Compound 3l

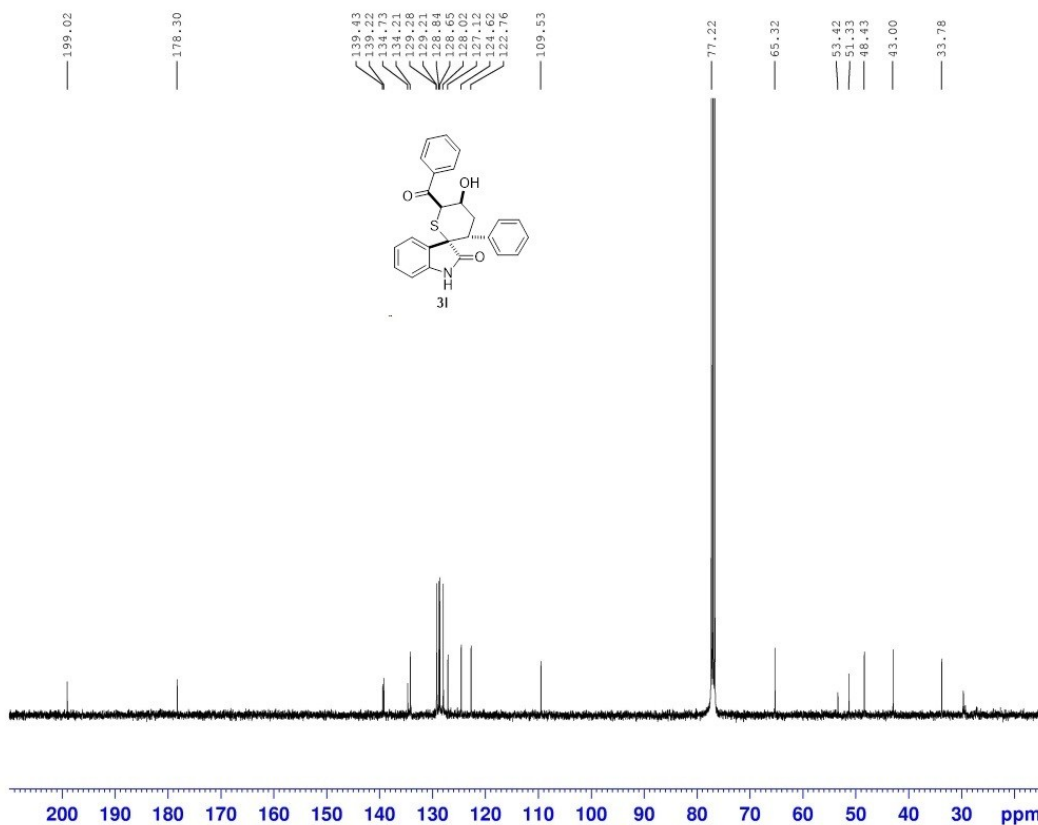


Current Data Parameters
NAME wsr-3-55-6-1
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161010
Time 20.38
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 35.08
CW 60.800 usec
DE 4.30 usec
TE 0 K
DT 1.00000000 sec
TDO 1

===== CHANNEL f1 =====
NUC1 1H
P1 10.00 usec
PLM1 17.78300095 W
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WEW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME wsr-3-55-6-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161011
Time 10.07
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2560
DS 24038.461 Hz
SWH 8.364798 Hz
FIDRES 1.2631908 sec
AQ 107.77
RG 28.800 usec
CW 6.50 usec
TE 0 K
DT 2.00000000 sec
D11 0.03000000 sec
TDO 0

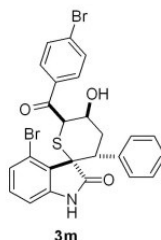
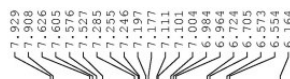
===== CHANNEL f1 =====
NUC1 13C
P1 10.00 usec
PLM1 71.94499969 W
SFO1 100.6228293 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLM2 17.78300095 W
PLM3 0.20360000 W
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WEW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Compound 3m

wsz-27-6-1

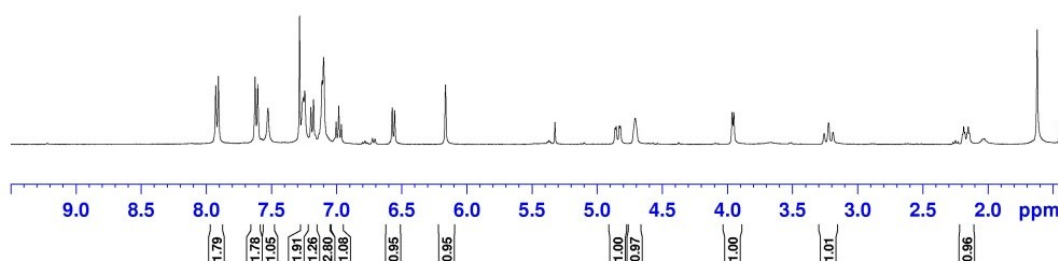


Current Data Parameters
NAME wsz-27-6-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20171120
Time 17.29
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9646387 sec
RG 95.08
DM 60.800 usec
DE 6.50 usec
TE 292.4 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 1H
P1 10.00 usec
PLW1 17.78300095 W
SFO1 400.1324710 MHz

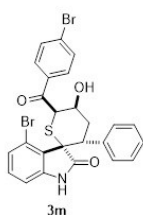
F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDM 0
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



197.479

177.323

141.520
139.288
138.284
132.191
130.720
130.638
129.439
128.179
127.759
127.408
126.370
120.163
108.702



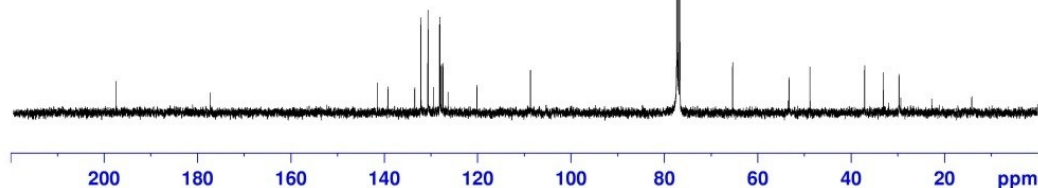
Current Data Parameters
NAME wsz-10-3m
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170311
Time 12.23
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 107.77
DM 29.800 usec
DE 6.50 usec
TE 294.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

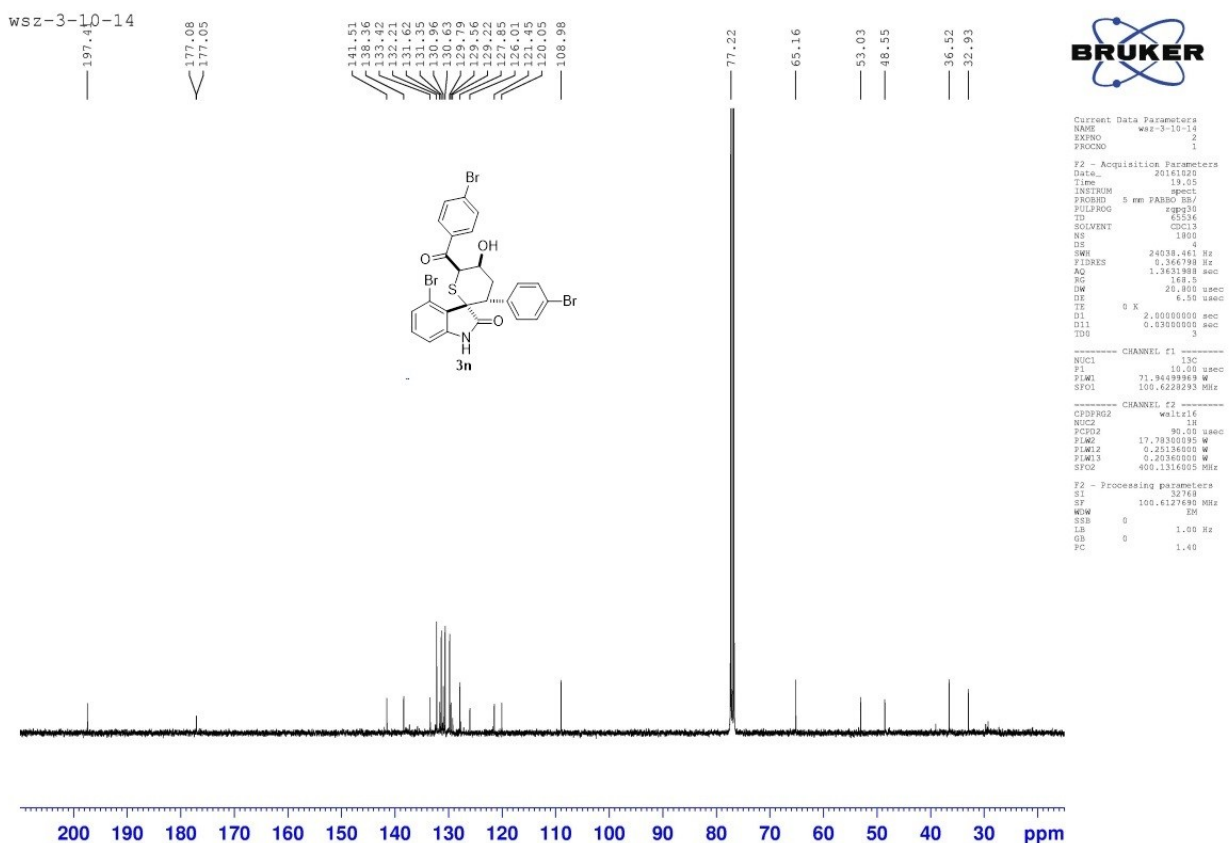
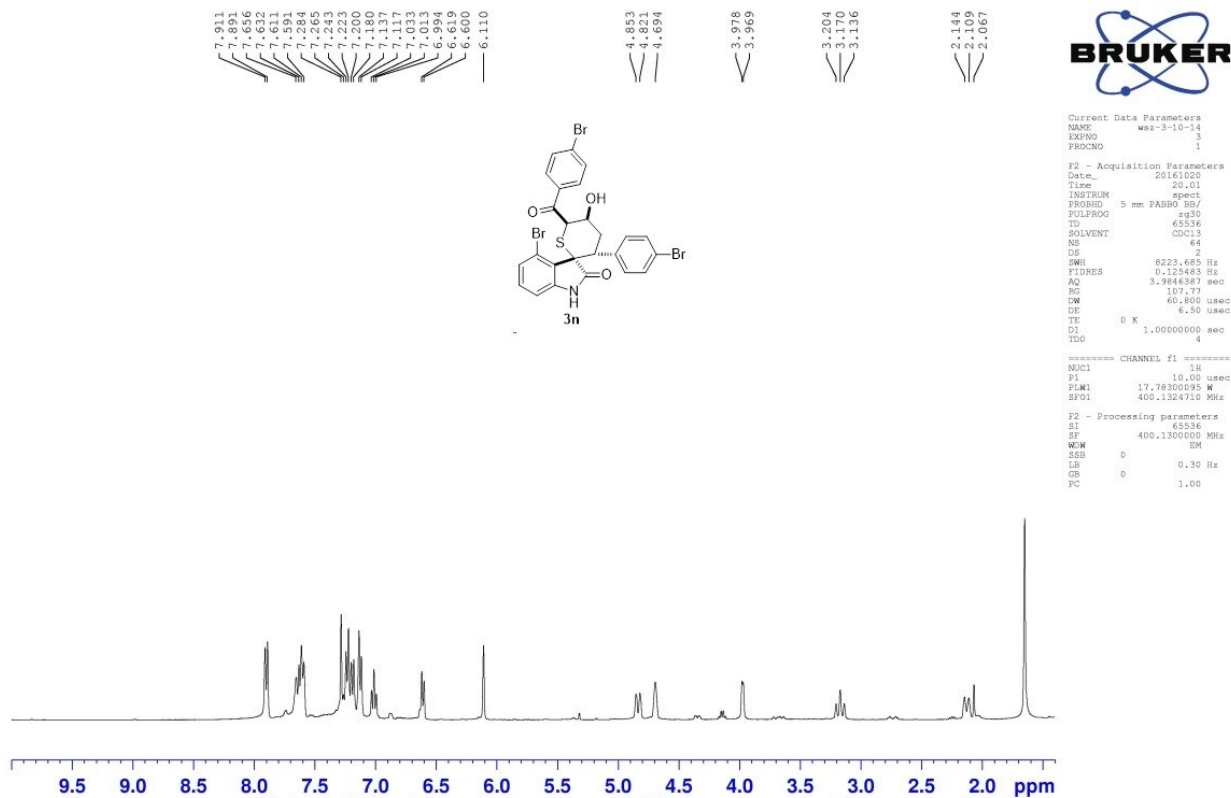
===== CHANNEL f1 =====
NUC1 13C
P1 10.00 usec
PLW1 71.34499969 W
SFO1 100.6288293 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 17.78300095 W
PLW12 0.25136000 W
PLW13 0.20360000 W
SFO2 400.1316005 MHz

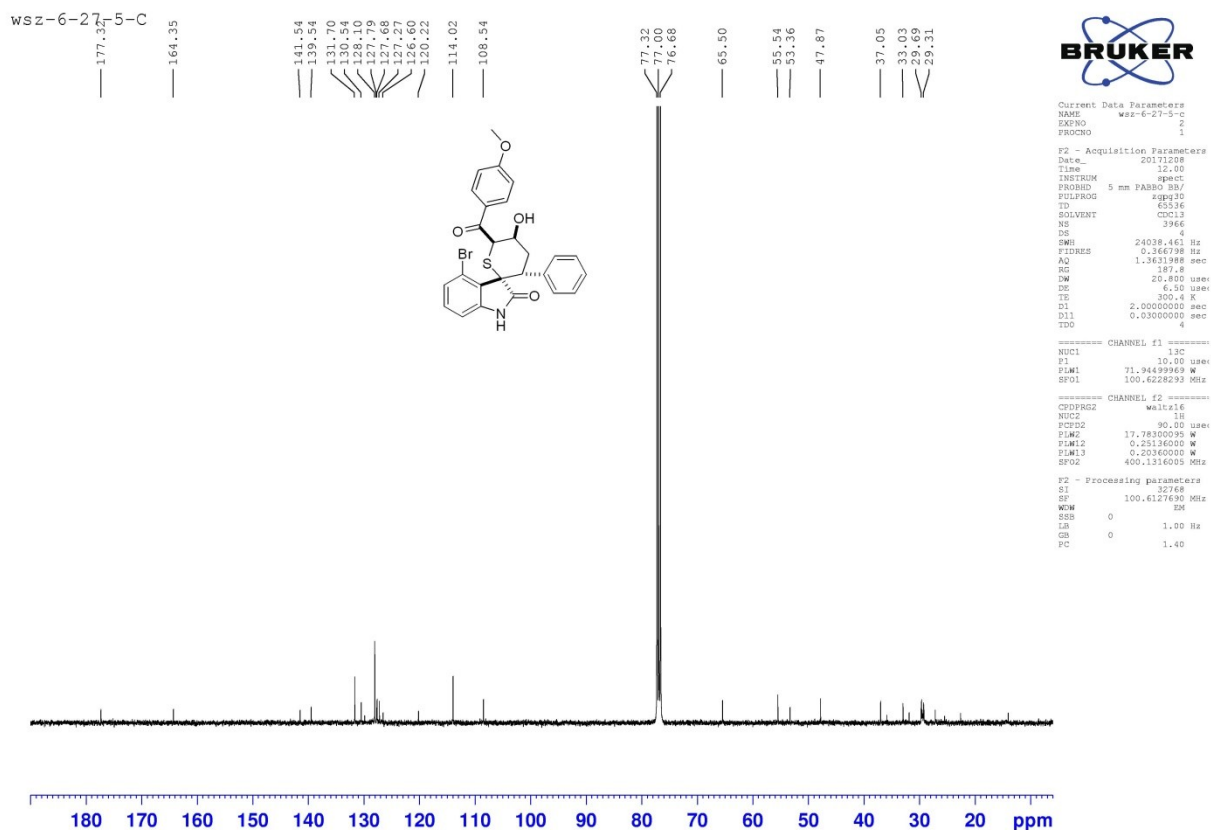
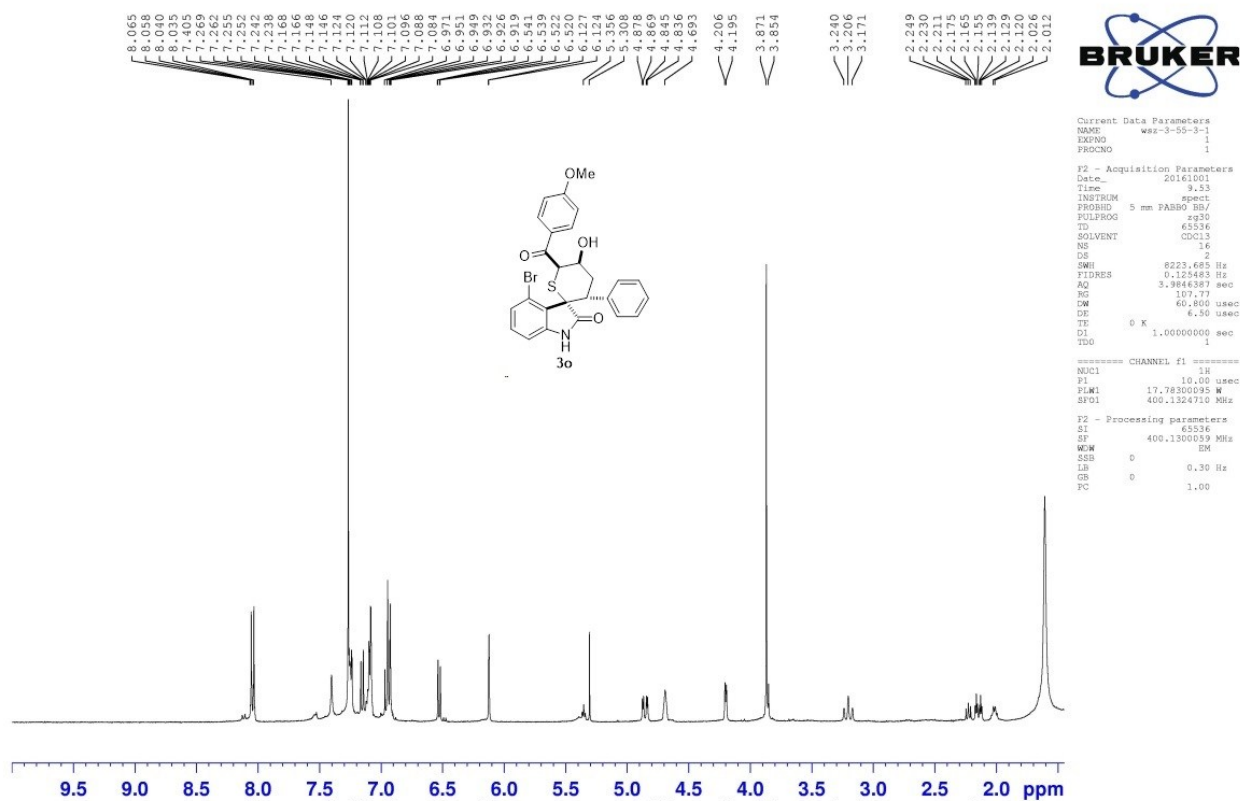
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDM 0
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



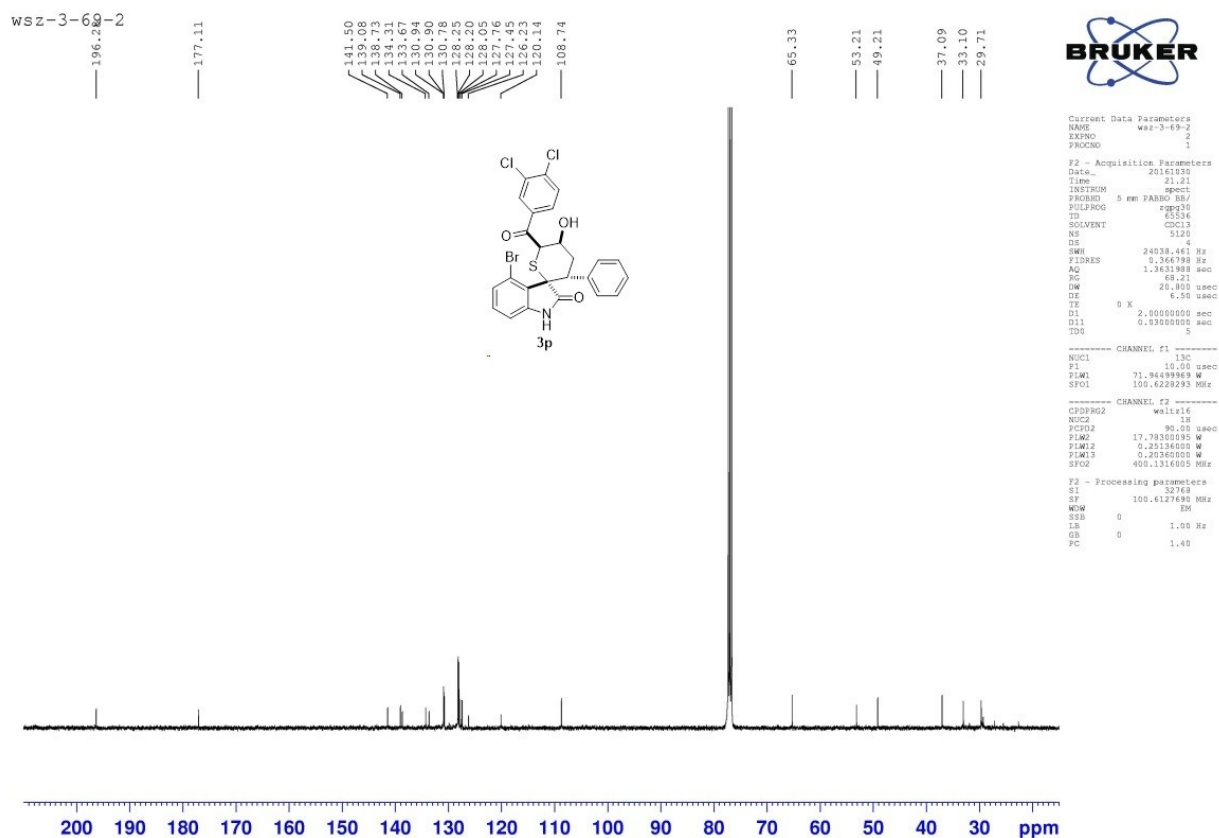
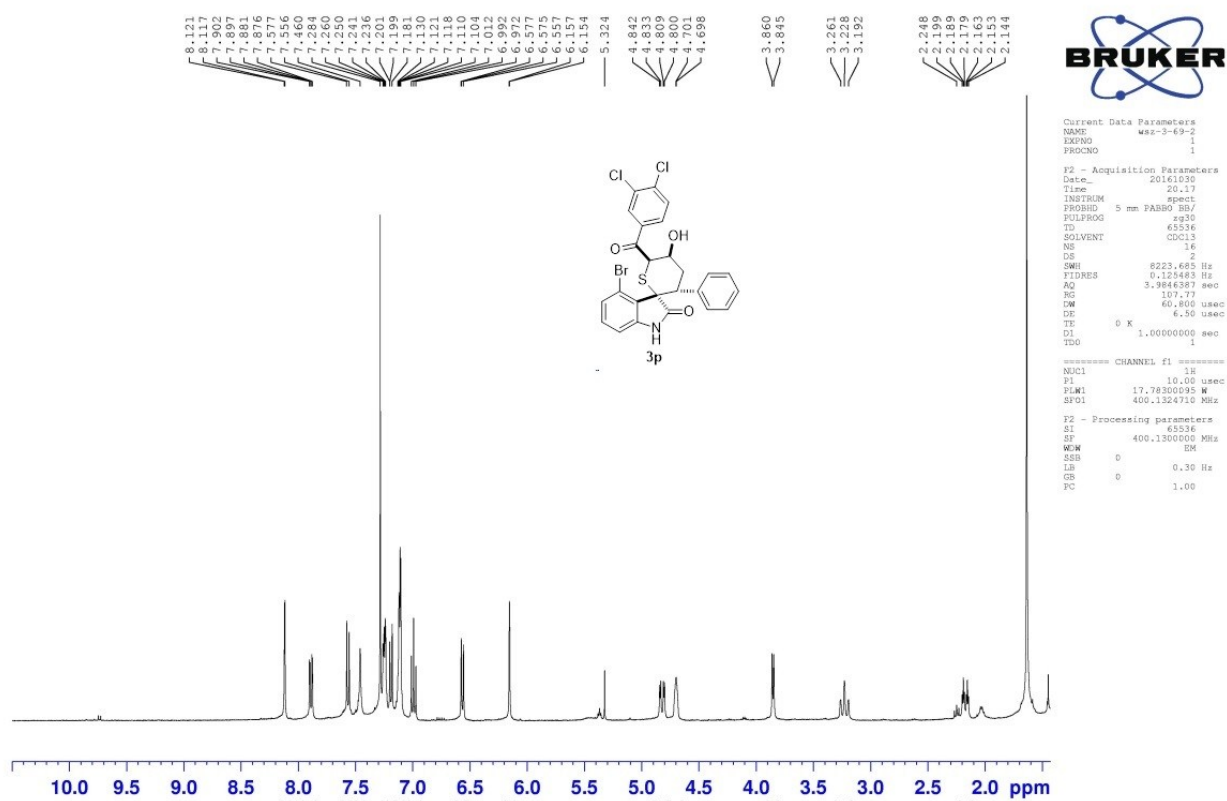
Compound 3n



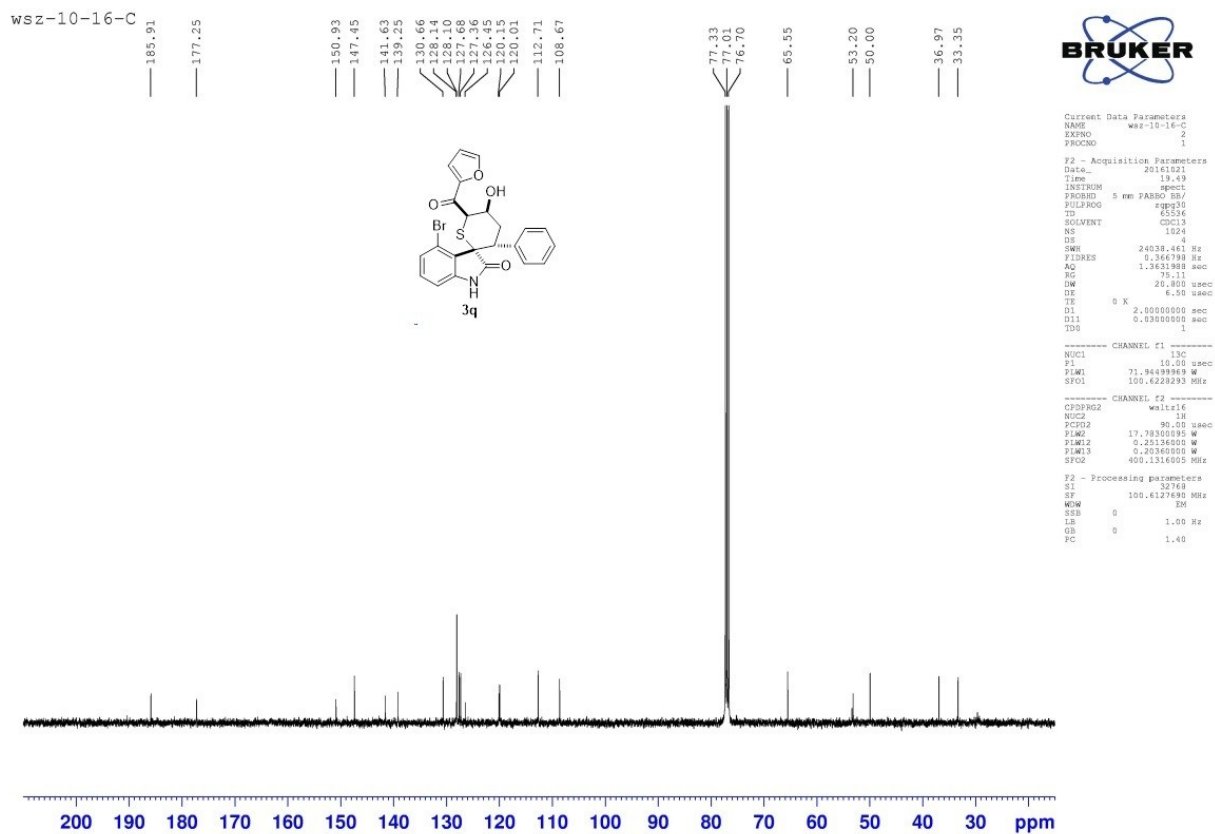
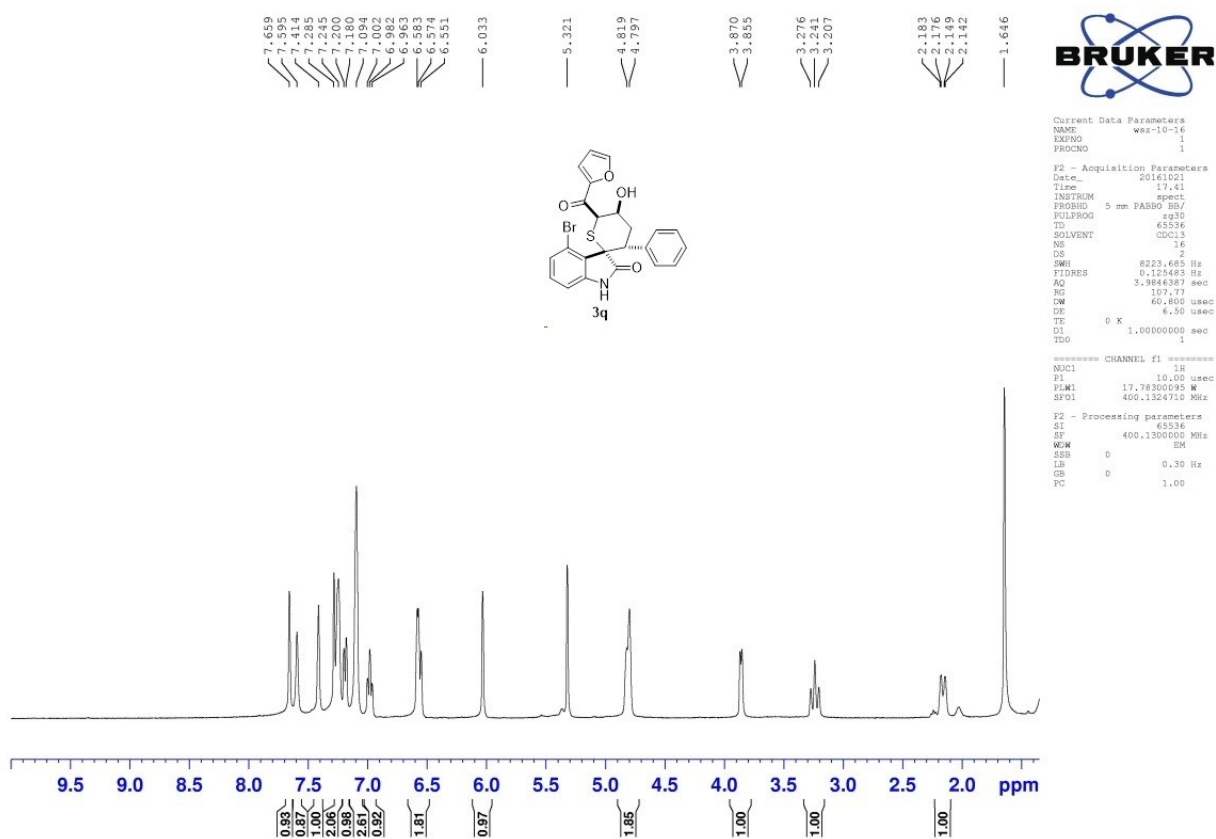
Compound 3o



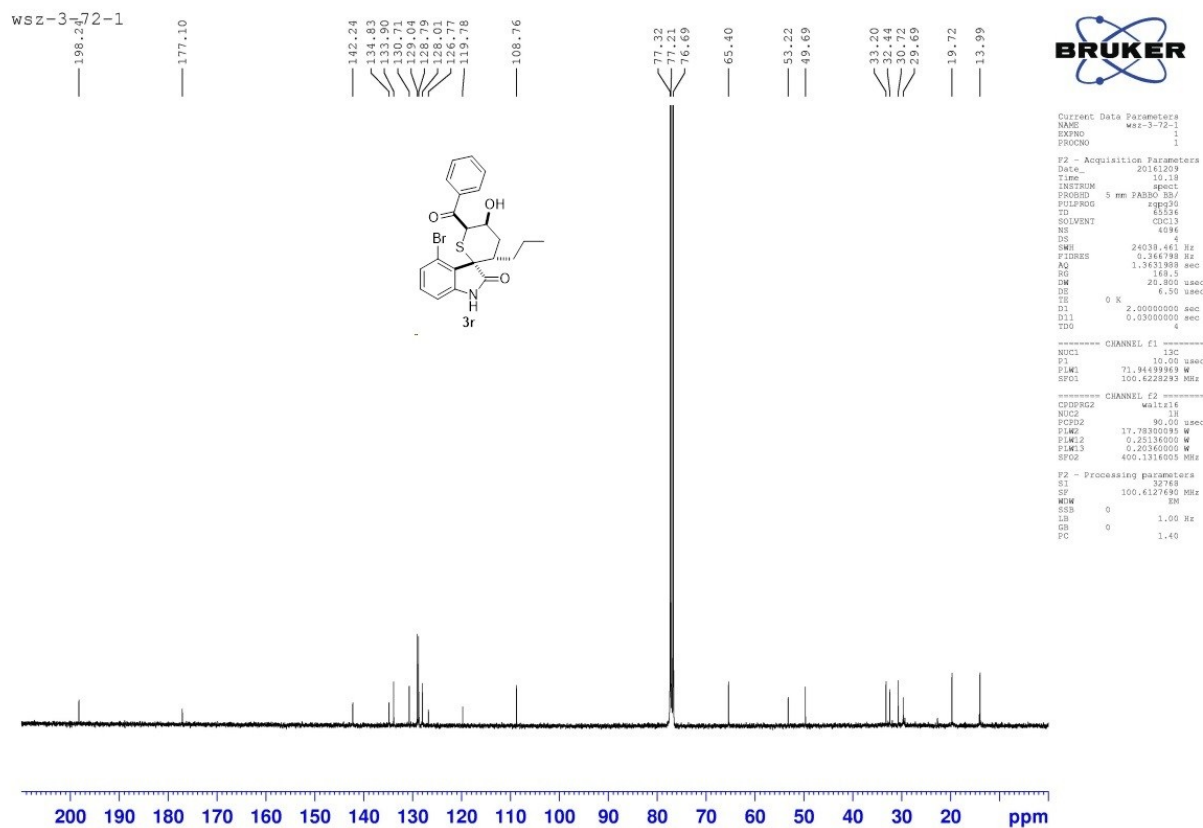
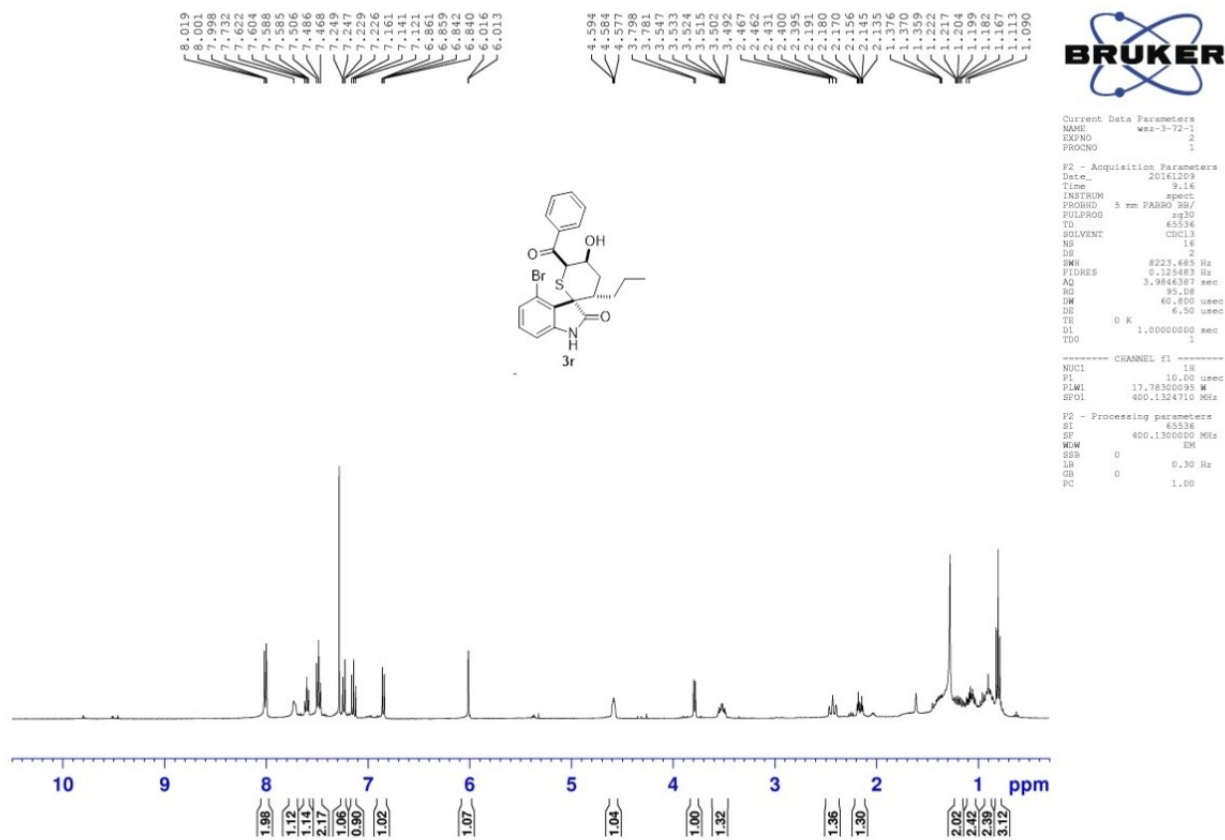
Compound 3p



Compound 3q

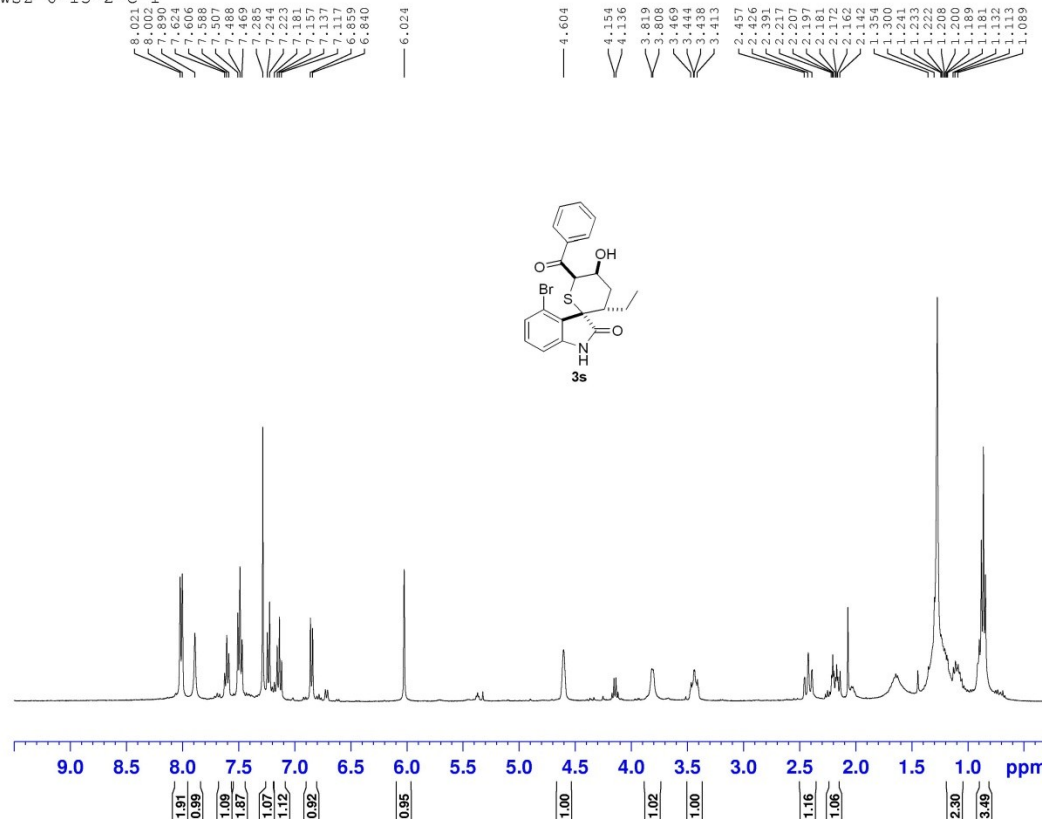


Compound 3r



Compound 3s

wsz-6-13-2-c-1

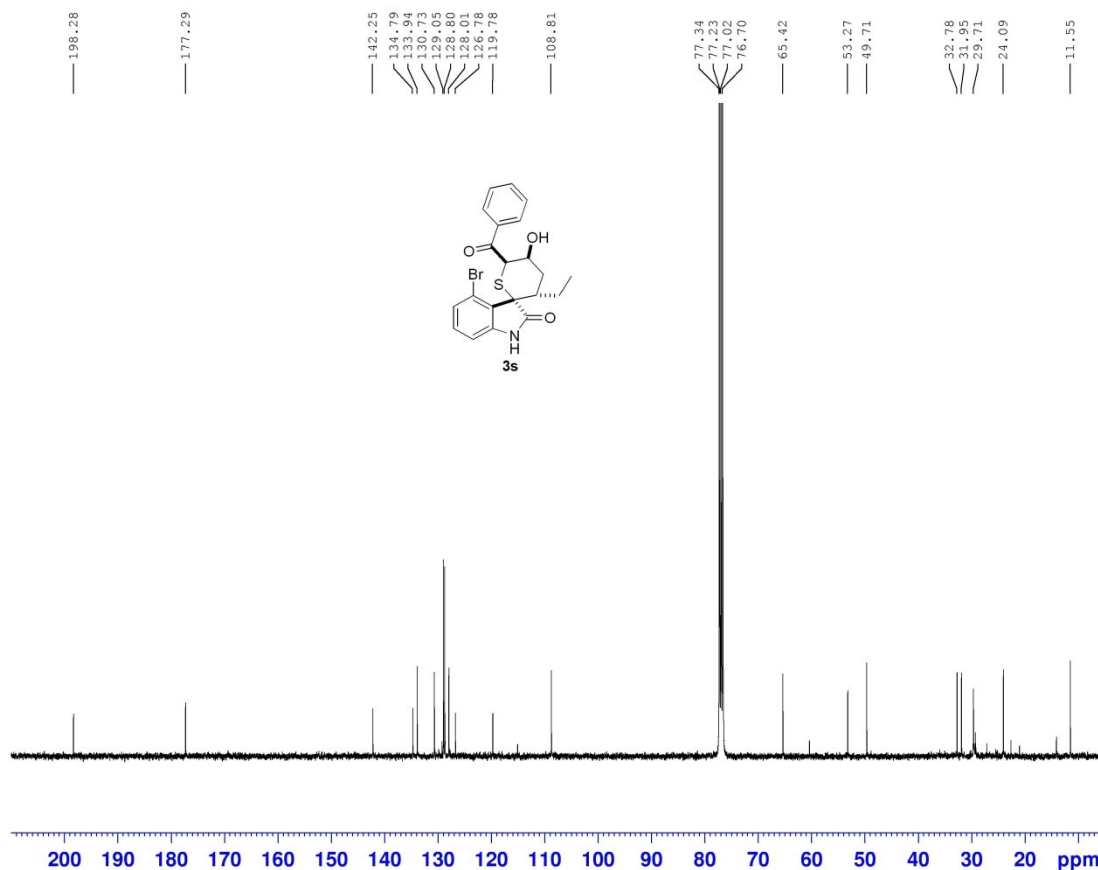


Current Data Parameters
NAME: wsz-6-13-2-c-1
EXNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20171204
Time: 20.23
INSTRUM: spect
PROBHD: 5 mm PABBO BB/
PULPROG: zg30
TD: 65536
SOLVENT: CDCl3
NS: 16
DS: 2
SWH: 8223.685 Hz
FIDRES: 0.125483 Hz
AQ: 3.9846387 sec
RG: 95.08
DM: 60.800 usec
DE: 6.30 usec
TE: 293.3 K
D1: 1.0000000 sec
TD0: 1

===== CHANNEL f1 =====
NUC1: 1H
P1: 10.00 usec
PLM1: 17.78300095 W
SF01: 400.1304710 MHz

F2 - Processing parameters
SI: 65536
SF: 400.1300000 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.00



Current Data Parameters
NAME: wsz-6-13-2-c-1
EXNO: 2
PROCNO: 1

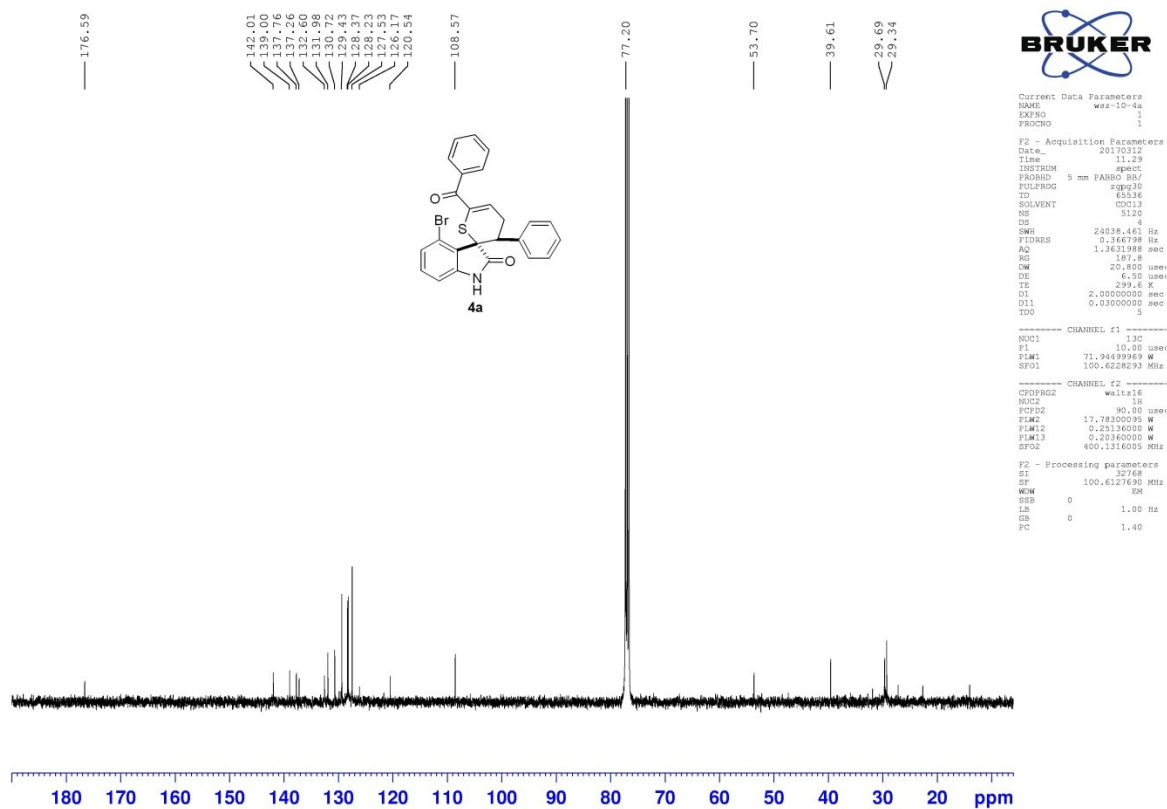
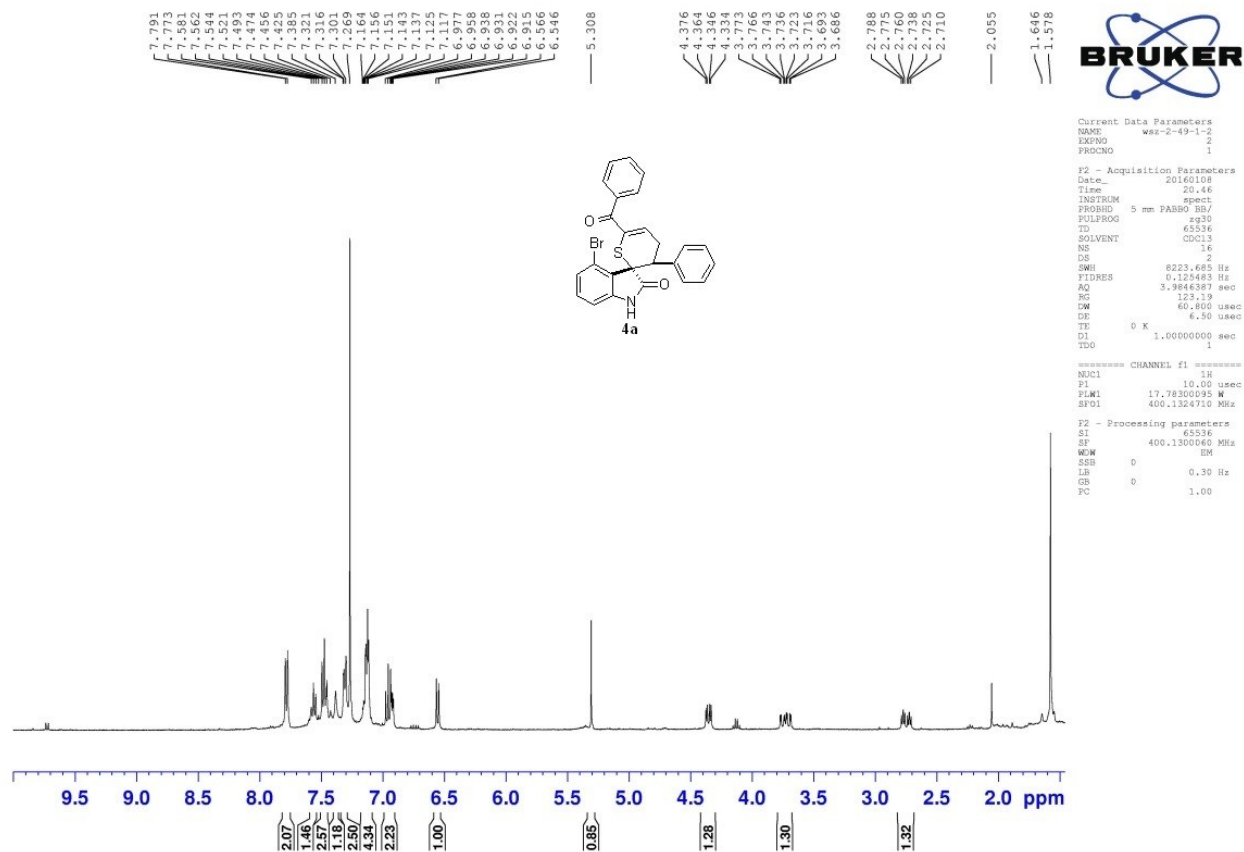
F2 - Acquisition Parameters
Date_: 20171204
Time: 23.46
INSTRUM: spect
PROBHD: 5 mm PABBO BB/
PULPROG: zgpg30
TD: 65536
SOLVENT: CDCl3
NS: 8192
DS: 4
SWH: 24038.461 Hz
FIDRES: 0.366798 Hz
AQ: 1.263398 sec
RG: 151.48
DM: 20.800 usec
DE: 6.50 usec
TE: 303.7 K
D1: 2.0000000 sec
D11: 0.0300000 sec
TD0: 8

===== CHANNEL f1 =====
NUC1: 13C
P1: 10.00 usec
PLM1: 71.9449999 W
SF01: 100.6228293 MHz

===== CHANNEL f2 =====
CPDPRG2: waltz16
NUC2: 1H
PCPD2: 90.00 usec
PLM2: 17.78300095 W
PLM12: 0.25136000 W
PLM13: 0.20360000 W
SF02: 400.1316005 MHz

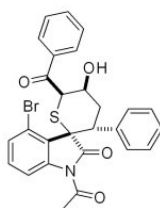
F2 - Processing parameters
SI: 32768
SF: 100.6127690 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40

Compound 4a



Compound 3aa

wsz-4-7

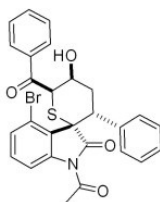
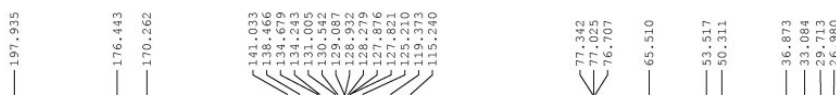
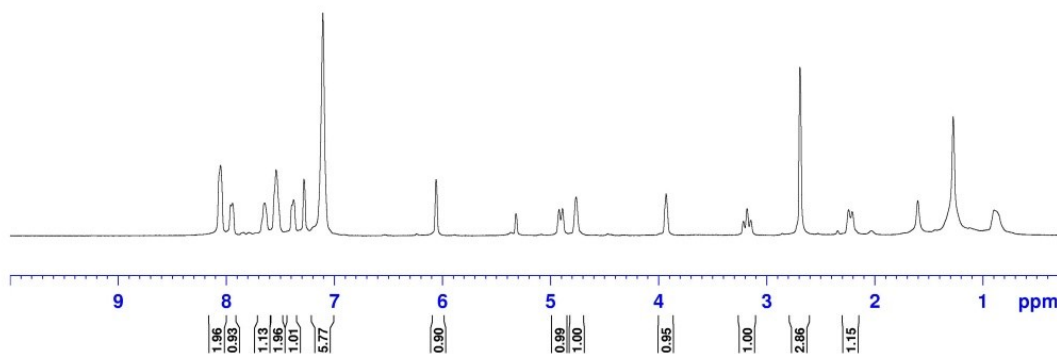


Current Data Parameters
NAME wsz-4-7
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170505
Time 16.45
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 s
RG 95.08
DW 60.800 u
DE 6.50 u
TE 291.8 K
D1 1.00000000 s
TD0 1

CHANNEL f1
NUC1 1H
P1 10.00 u
PLW1 17.78300095 W
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



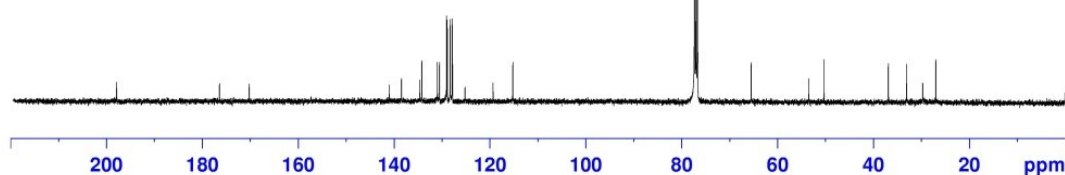
Current Data Parameters
NAME wsz-4-7-C
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170507
Time 20.15
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2048
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 168.5
DW 20.800 usec
DE 6.50 usec
TE 292.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 2

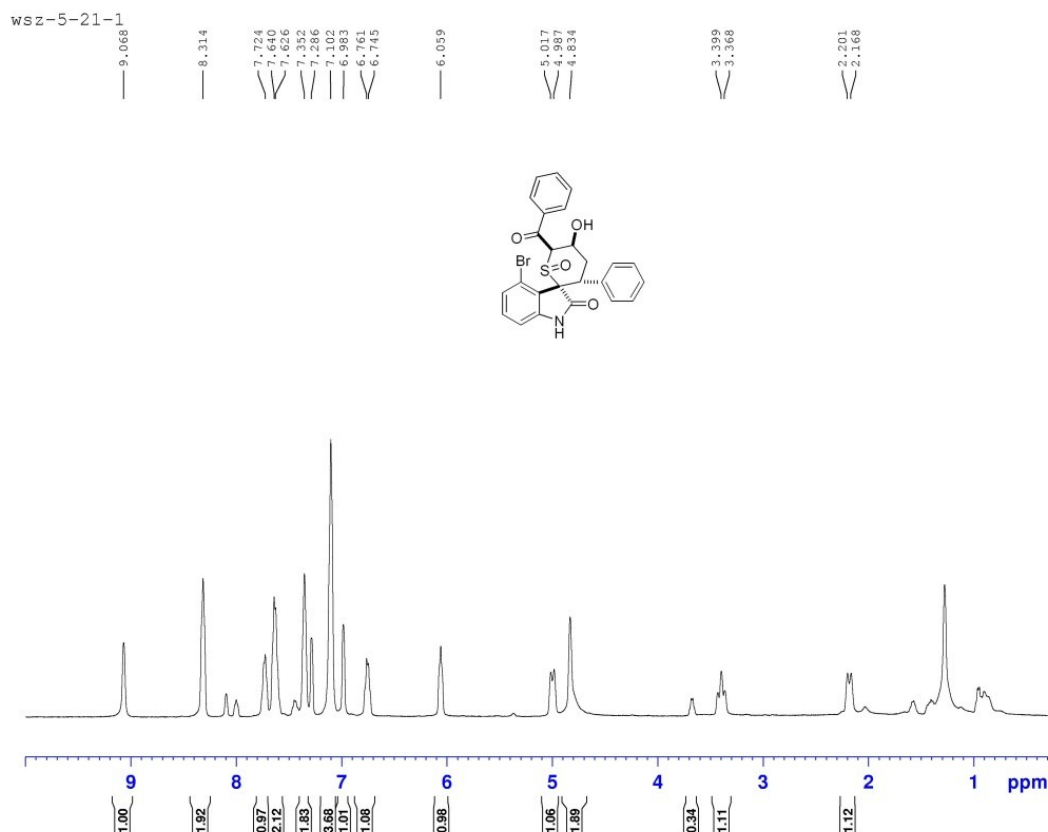
CHANNEL f1
NUC1 13C
P1 10.00 usec
PLW1 71.94499969 W
SFO1 100.6228293 MHz

CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 17.78300095 W
PLW12 0.25136000 W
PLW13 0.20360000 W
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Compound 3ab

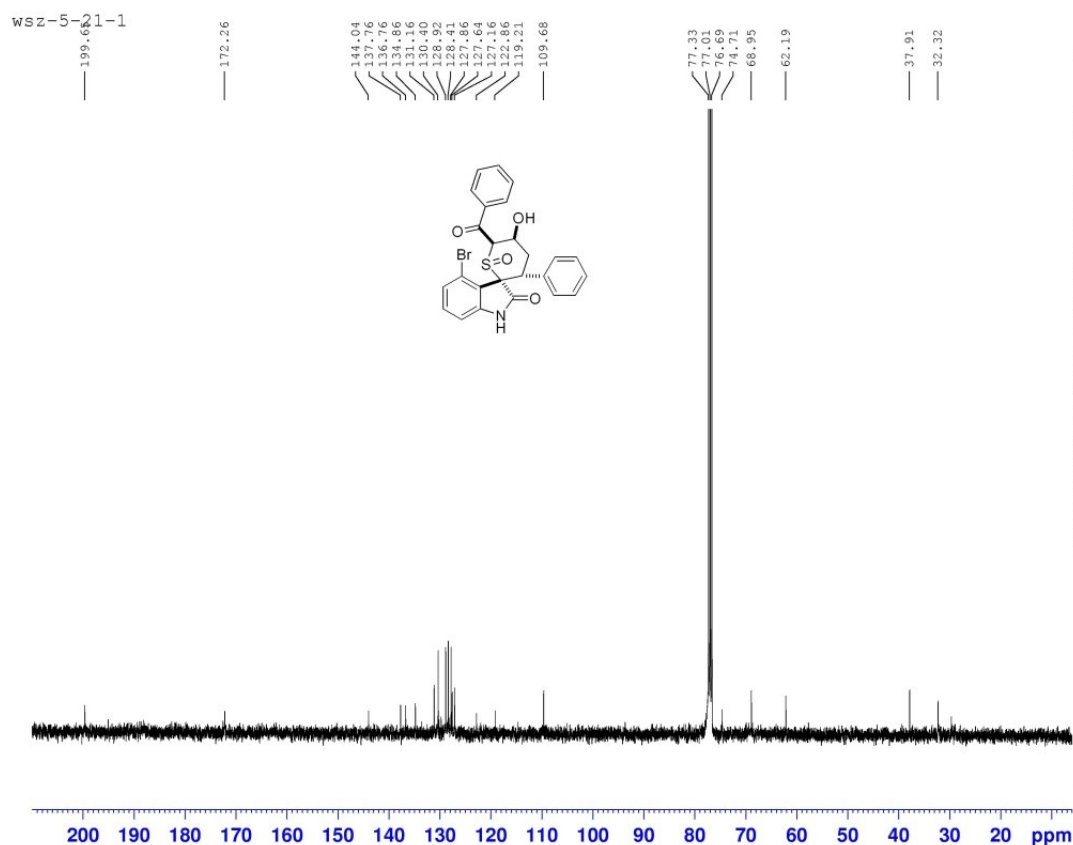


Current Data Parameters
NAME wsz-5-21-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170619
Time 9.10
INSTRUM spect
PROBHD 5 mm FARGO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 107.77
DM 60.800 usec
DE 6.50 usec
TE 299.6 K
D1 1.00000000 sec
TDO 1

===== CHANNEL f1 =====
NUC1 1H
P1 10.00 usec
PLW1 17.78300095 M
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME wsz-5-21-1
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170620
Time 12.02
INSTRUM spect
PROBHD 5 mm FARGO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 502
DS 4
SWH 24038.46 Hz
FIDRES 0.366798 Hz
AQ 1.361988 sec
RG 187.8
DM 20.800 usec
DE 6.50 usec
TE 297.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 3

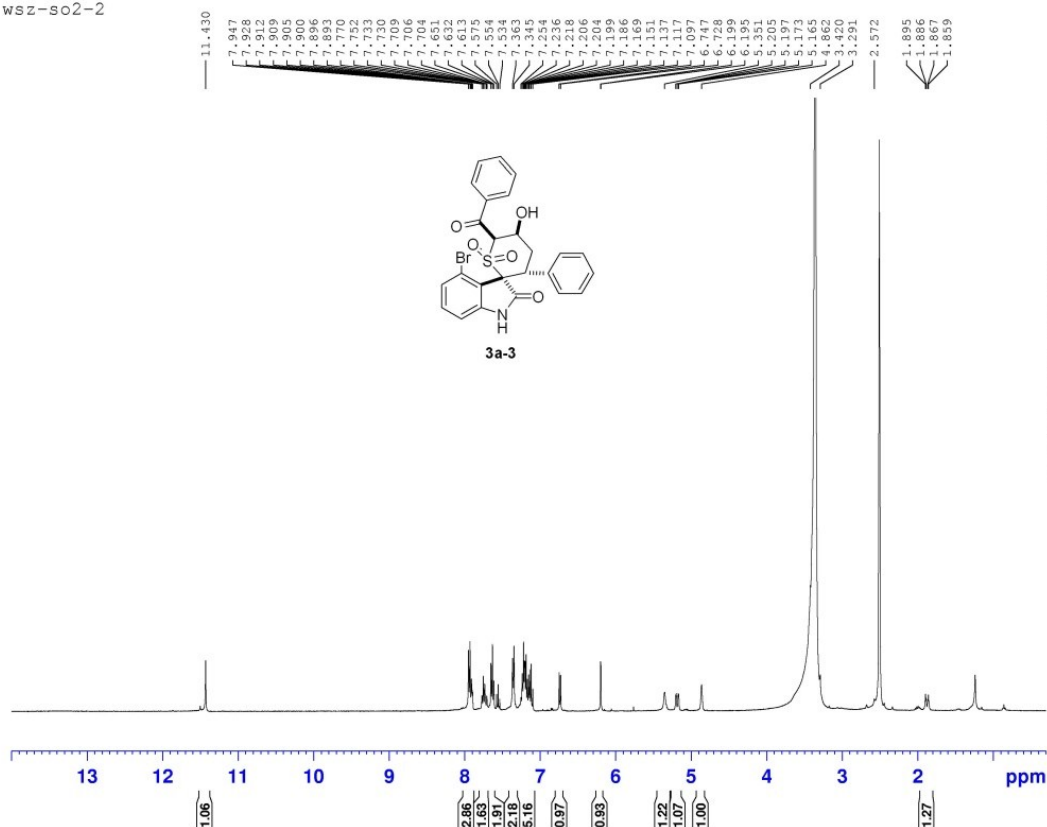
===== CHANNEL f1 =====
NUC1 13C
P1 10.00 usec
PLW1 17.78300095 M
SFO1 100.6228293 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 17.78300095 M
PLW12 0.23136000 M
PLW13 0.20360000 M
SFO2 400.1316003 MHz

F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Compound 3ac

wsz-so2-2



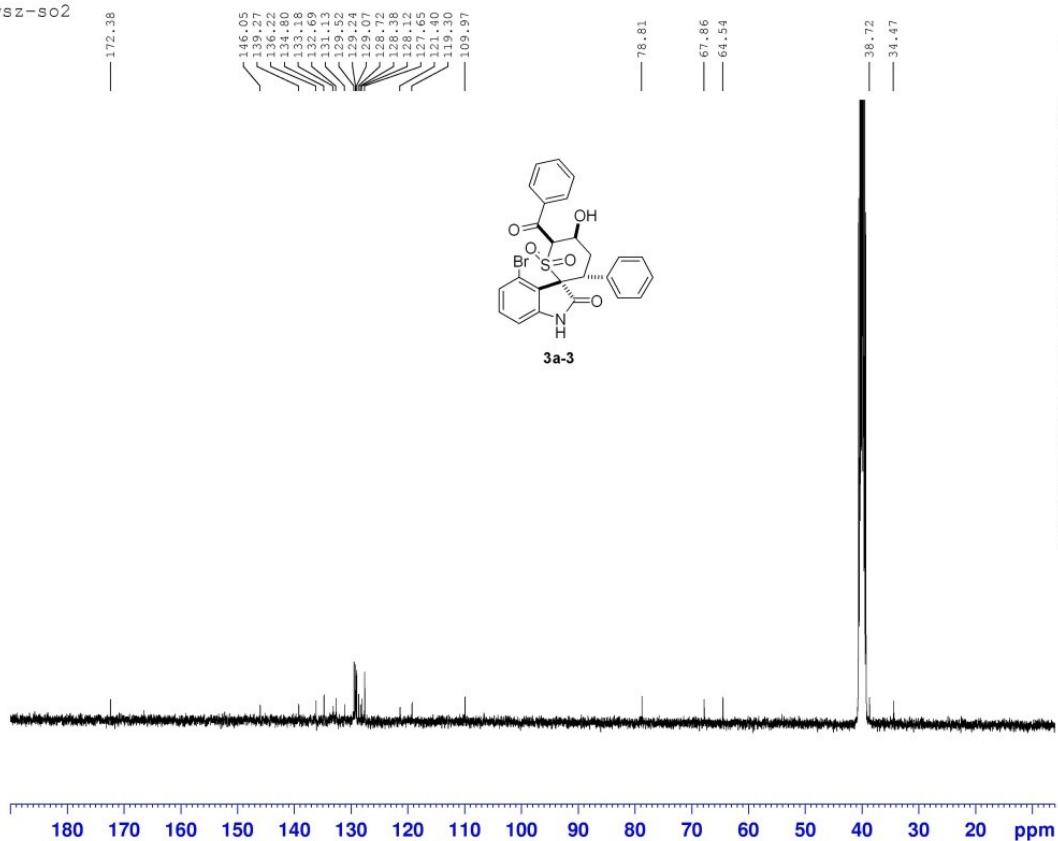
Current Data Parameters
NAME: wsz-so2-2
EXPNO: 2
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20170701
Time: 15:11
INSTRUM: spect
PROBHD: 5 mm FANBO BB/
PULPROG: zg30
TD: 65536
SOLVENT: DMSO
NS: 16
DS: 2
SWH: 8223.685 Hz
FIDRES: 0.125493 Hz
AQ: 3.9846387 sec
RG: 95.08
DM: 60.800 usec
DE: 6.50 usec
TE: 296.5 K
D1: 1.0000000 sec
TDO: 1

===== CHANNEL f1 =====
NUC1: 1H
P1: 10.00 usec
PLM1: 17.78300095 W
SFO1: 400.1324710 MHz

F2 - Processing parameters
SI: 65536
SF: 400.1300000 MHz
MCH: SM
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.00

wsz-so2



Current Data Parameters
NAME: wsz-so2
EXPNO: 3
PROCNO: 1

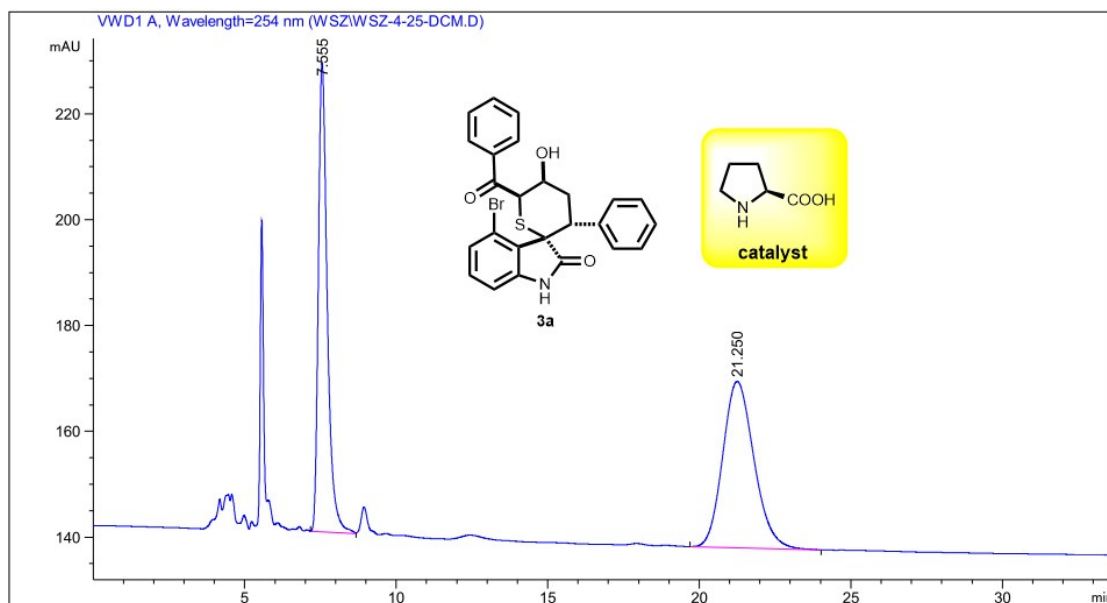
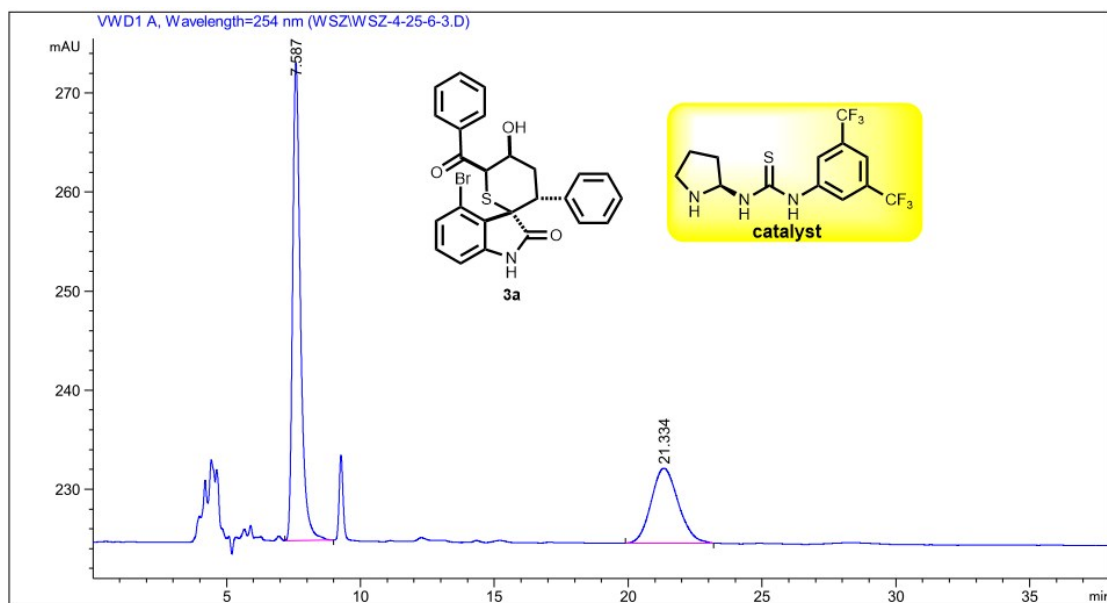
F2 - Acquisition Parameters
Date_: 20170630
Time: 13:21
INSTRUM: spect
PROBHD: 5 mm FANBO BB/
PULPROG: zgpg30
TD: 65536
SOLVENT: DMSO
NS: 4096
DS: 4
SWH: 24038.461 Hz
FIDRES: 0.366738 Hz
AQ: 1.3631388 sec
RG: 187.8
DM: 20.800 usec
DE: 6.50 usec
TE: 297.6 K
D1: 2.0000000 sec
D11: 0.0300000 sec
TDO: 4

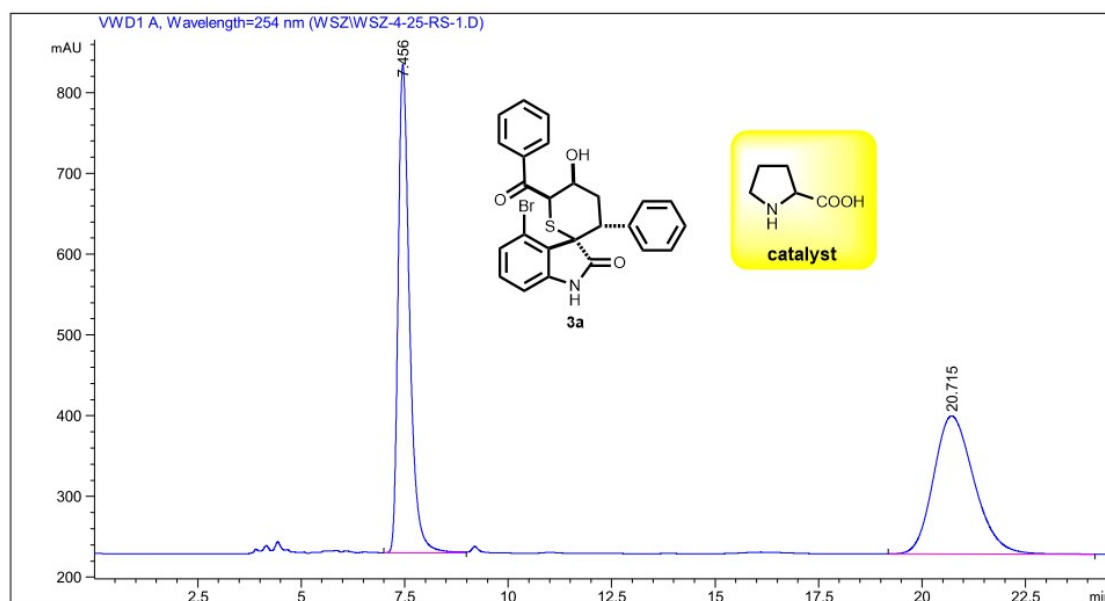
===== CHANNEL f1 =====
NUC1: 13C
P1: 10.00 usec
PLM1: 71.84499869 W
SFO1: 100.6228293 MHz

===== CHANNEL f2 =====
CPDPRG2: waltz16
NUC2: 1H
PCPD2: 90.00 usec
PLM2: 17.78300095 W
PLM12: 0.23136000 M
PLM13: 0.20360000 M
SFO2: 400.1316005 MHz

F2 - Processing parameters
SI: 32768
SF: 100.6127690 MHz
MCH: DM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40

HPLC Profile for compound **3a**





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.456	BV	0.2908	1.16092e4	605.19696	50.0317
2	20.715	BB	1.0537	1.15945e4	170.86116	49.9683

- [1] S. Wang, Z. Guo, S. Chen, Y. Jiang, F. Zhang, X. Liu, W. Chen, C. Sheng, *Chem.-Eur. J.*, **2017**, 23, <https://doi.org/10.1002/chem.201703837>.
- [2] H. Huang, Q. Chen, X. Ku, L. Meng, L. Lin, X. Wang, C. Zhu, Y. Wang, Z. Chen, M. Li, H. Jiang, K. Chen, J. Ding, H. Liu, *J. Med. Chem.* **2010**, 53, 3048-3064.