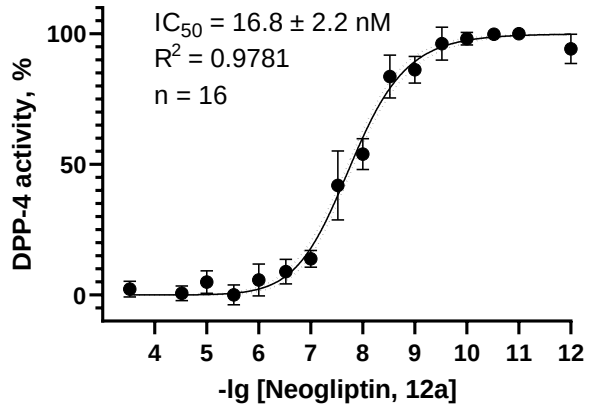
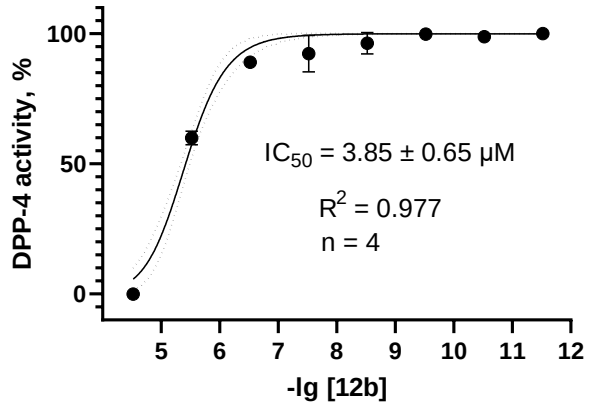
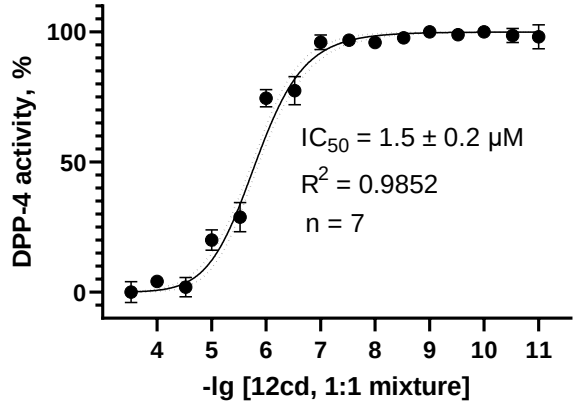
Supplementary material 1

Design, synthesis and biological evaluation of Neogliptin, a novel 2-azabicyclo[2.2.1]hepnane-based inhibitor of dipeptidyl peptidase-4 (DPP-4)

Concentration-response curves of the synthesized compounds **12a** (neogliptin), **12b** and **12c**+**12d** (1:1 mixture of diastereomers).

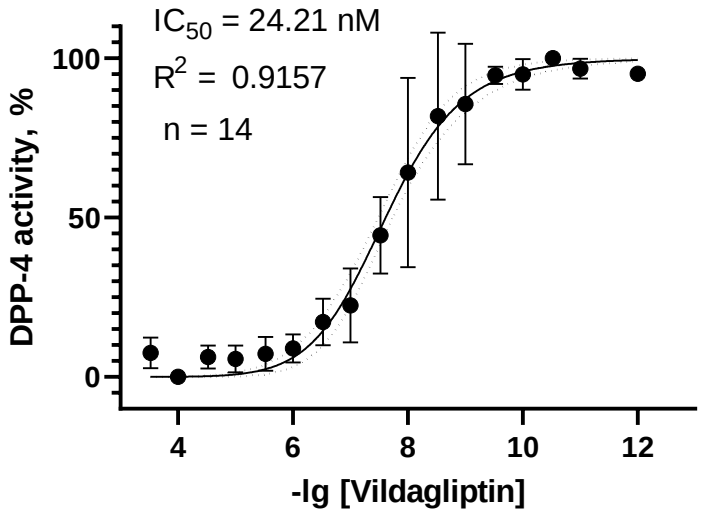


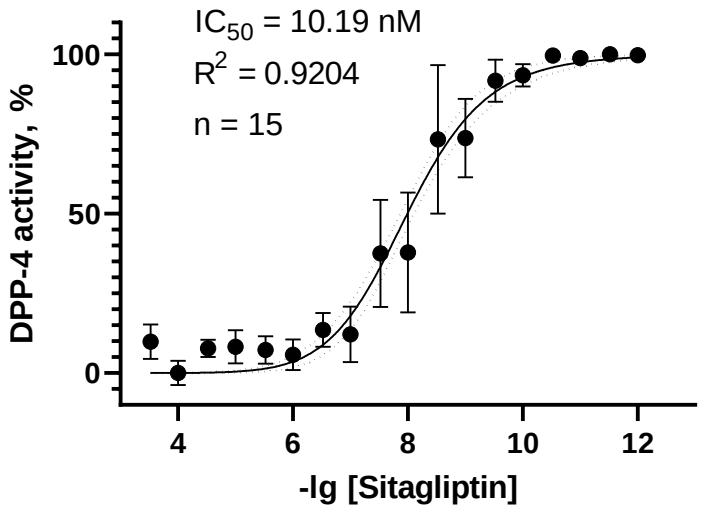


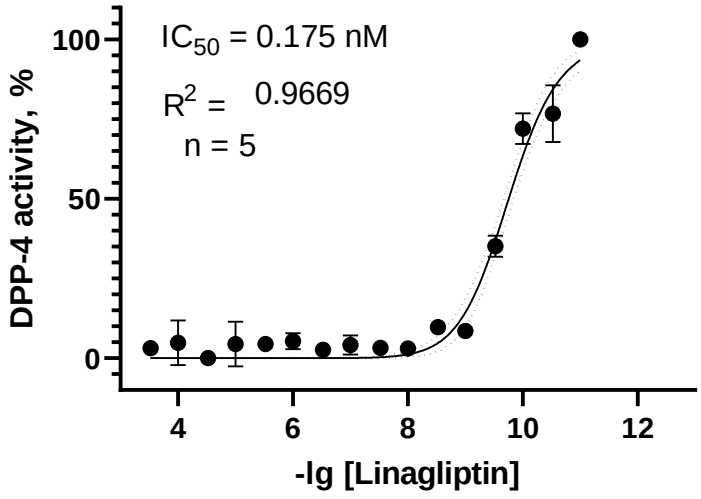


Supplementary material 1

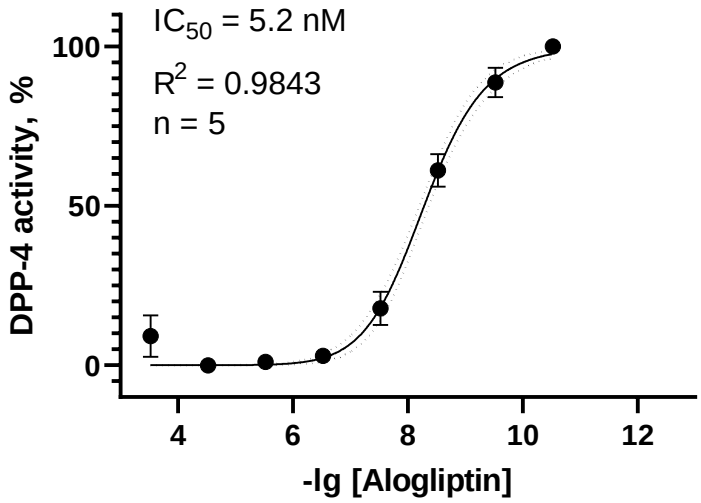
Concentration-response curves of the four marketed DPP4 inhibitors (data was obtained using the same assay conditions).







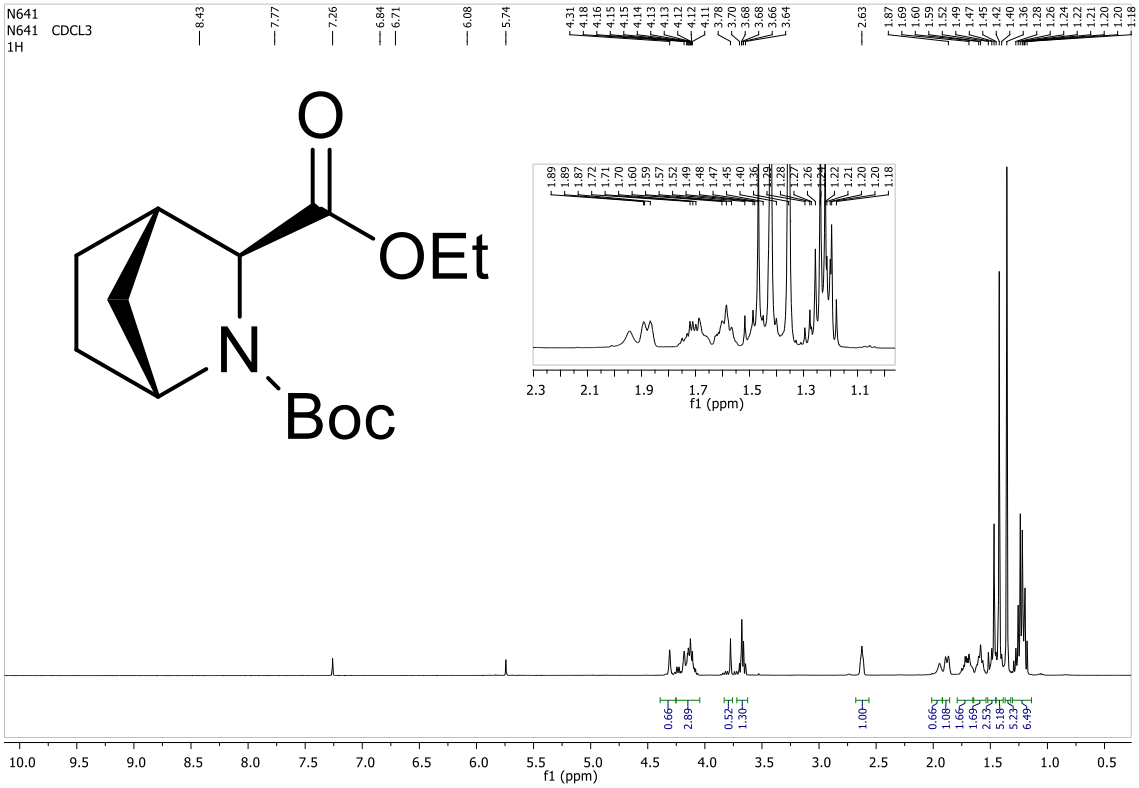
Supplementary material 1



NMR-spectra of the key intermediates and target compounds.

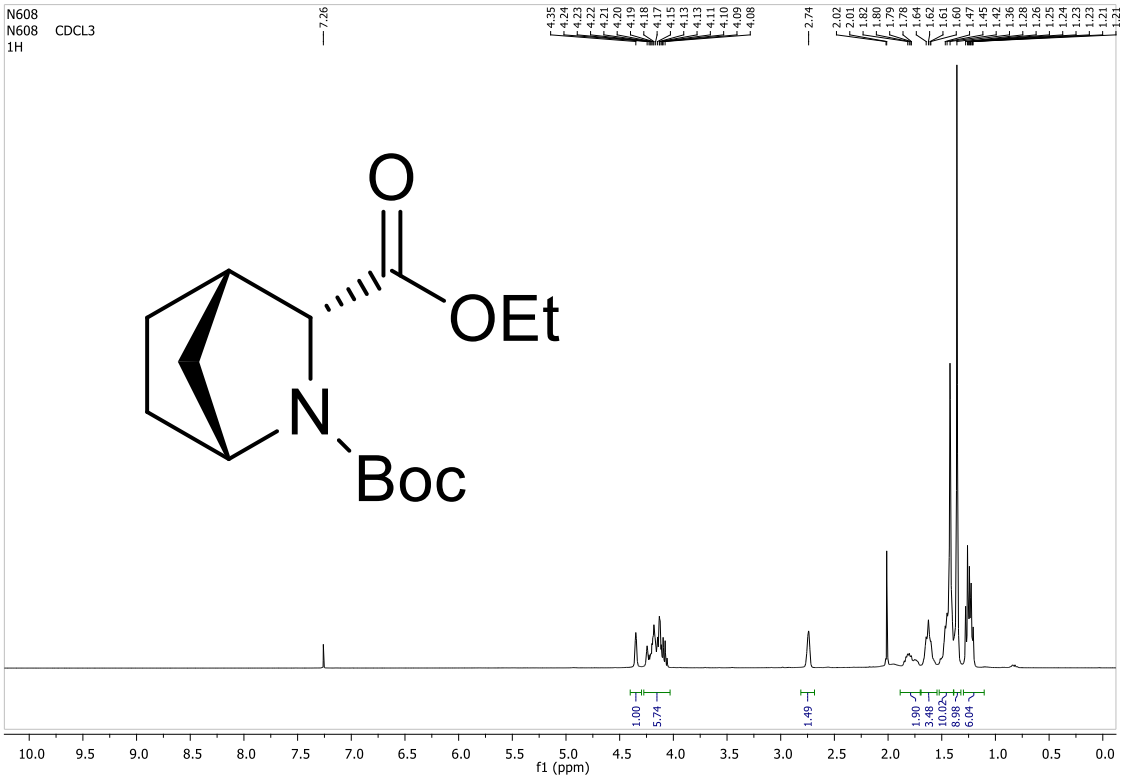
5a,b

^{1}H NMR



5c,d

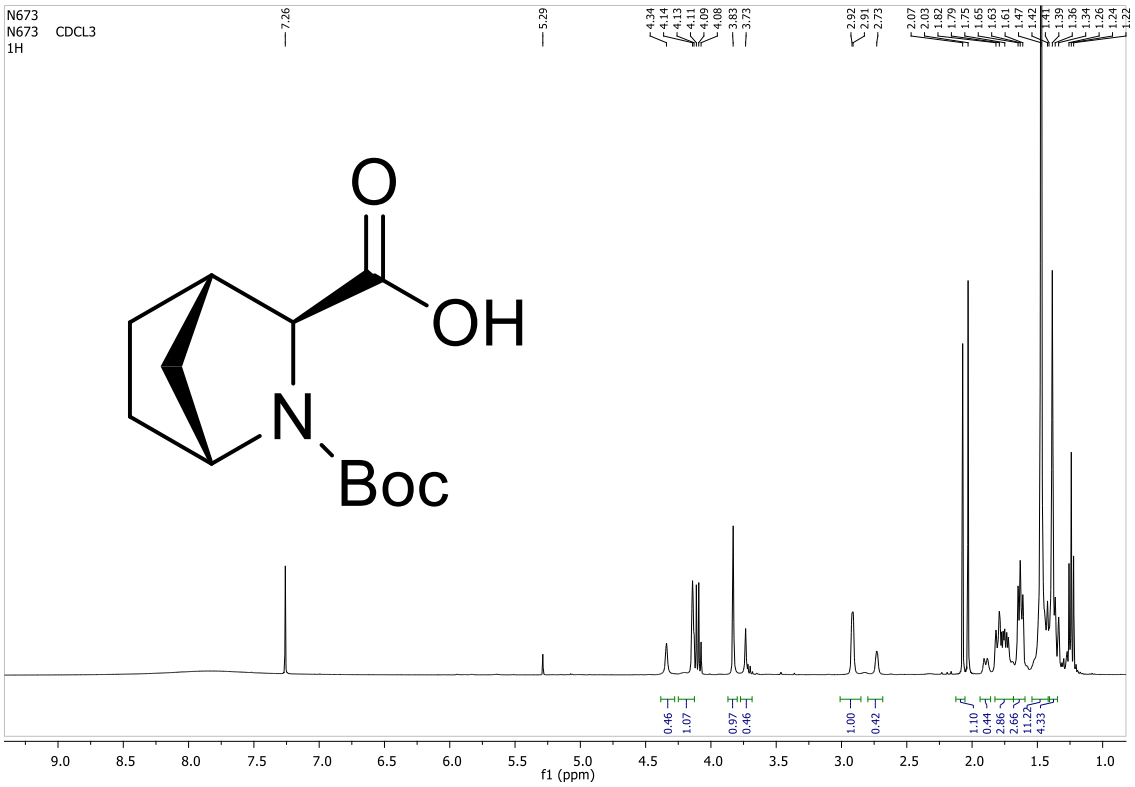
^{1}H NMR



6a,b

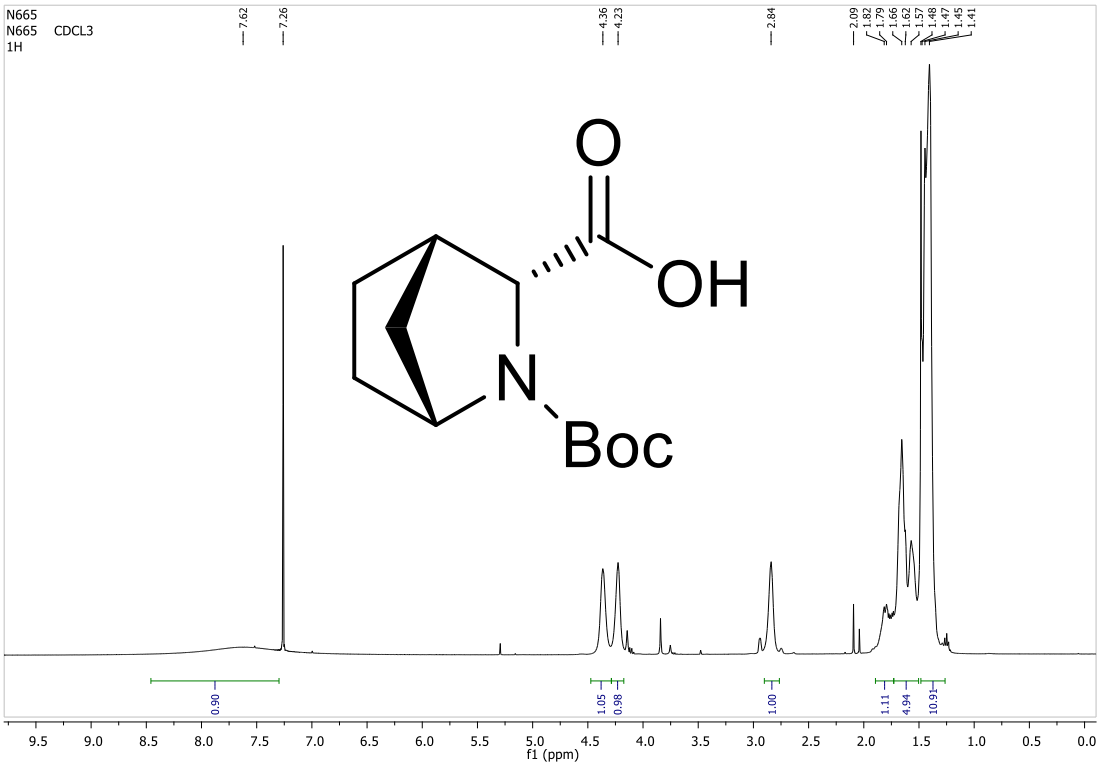
^{1}H NMR

Supplementary material 1



6c,d

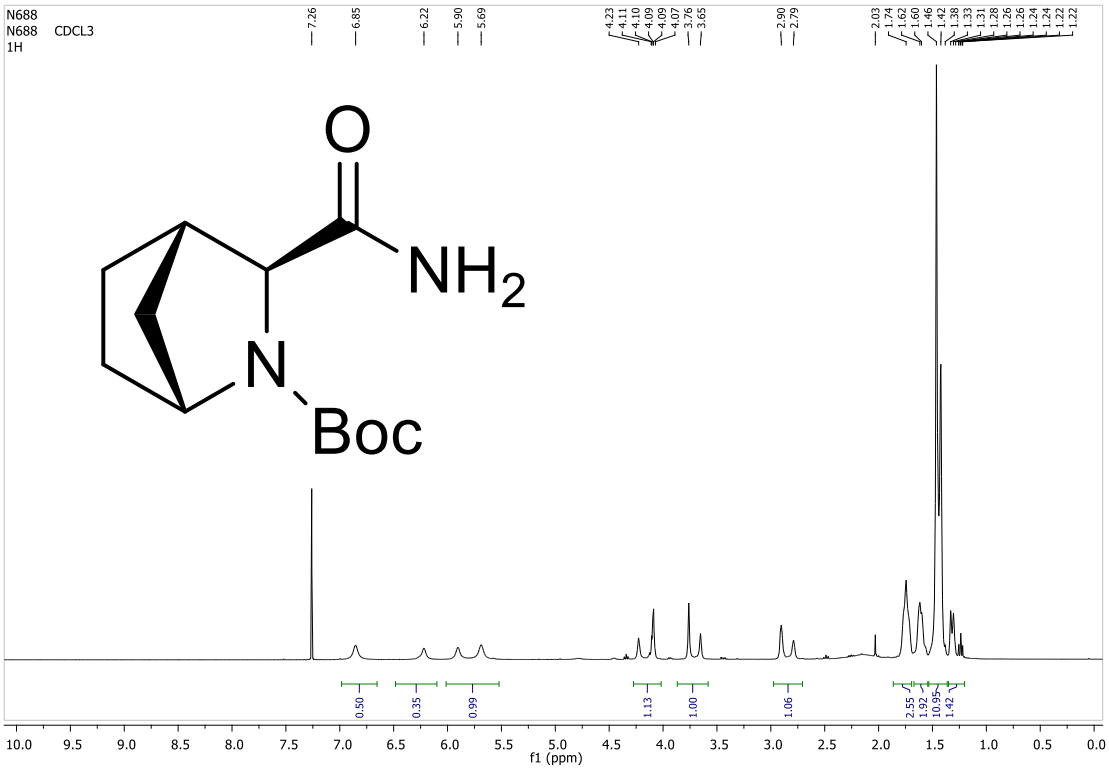
^{1}H NMR



7a,b

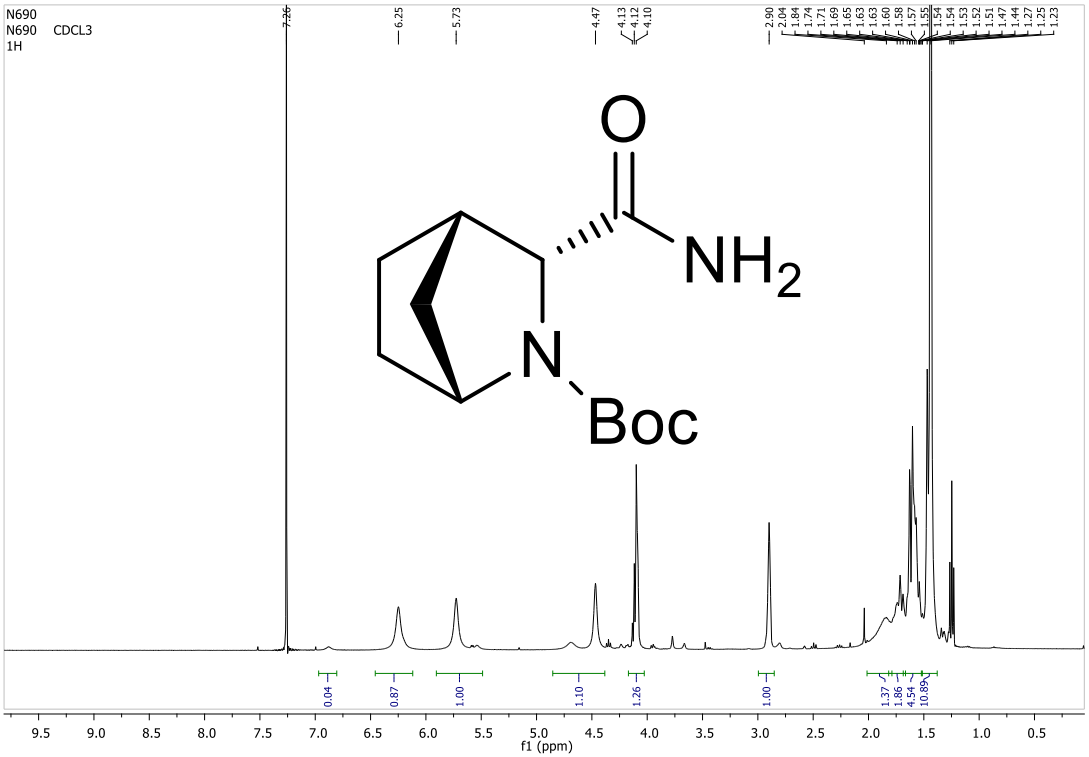
^{1}H NMR

Supplementary material 1



7c,d

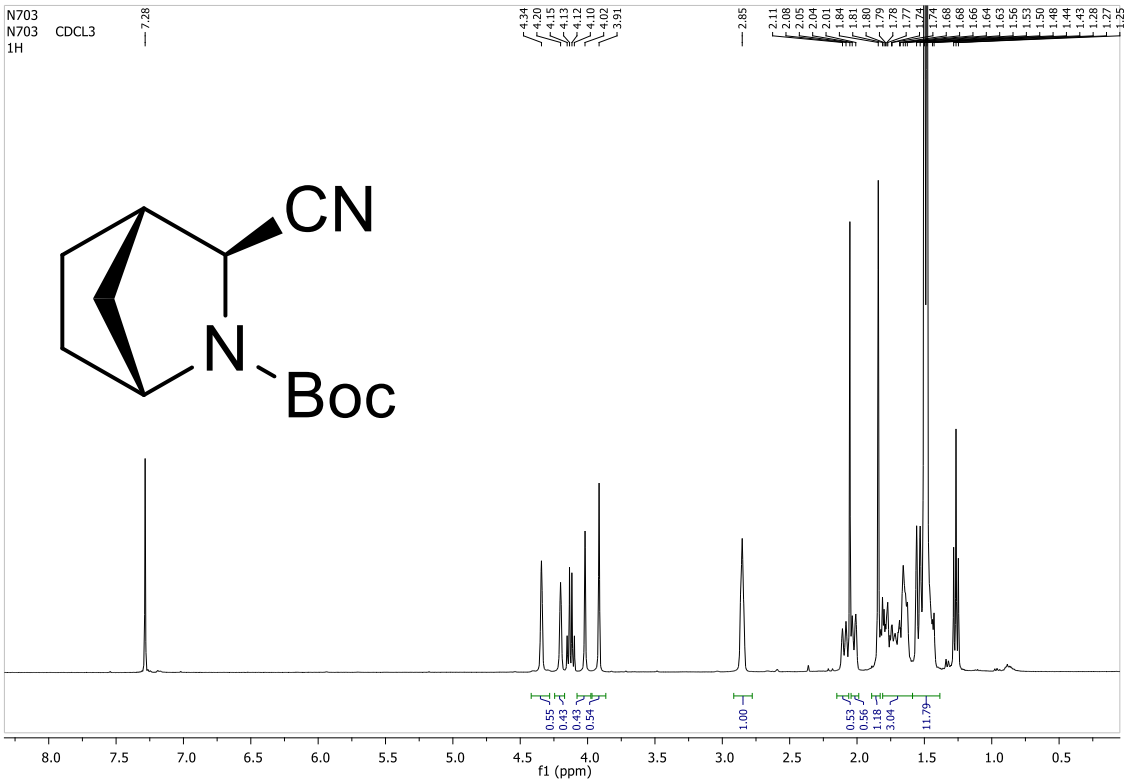
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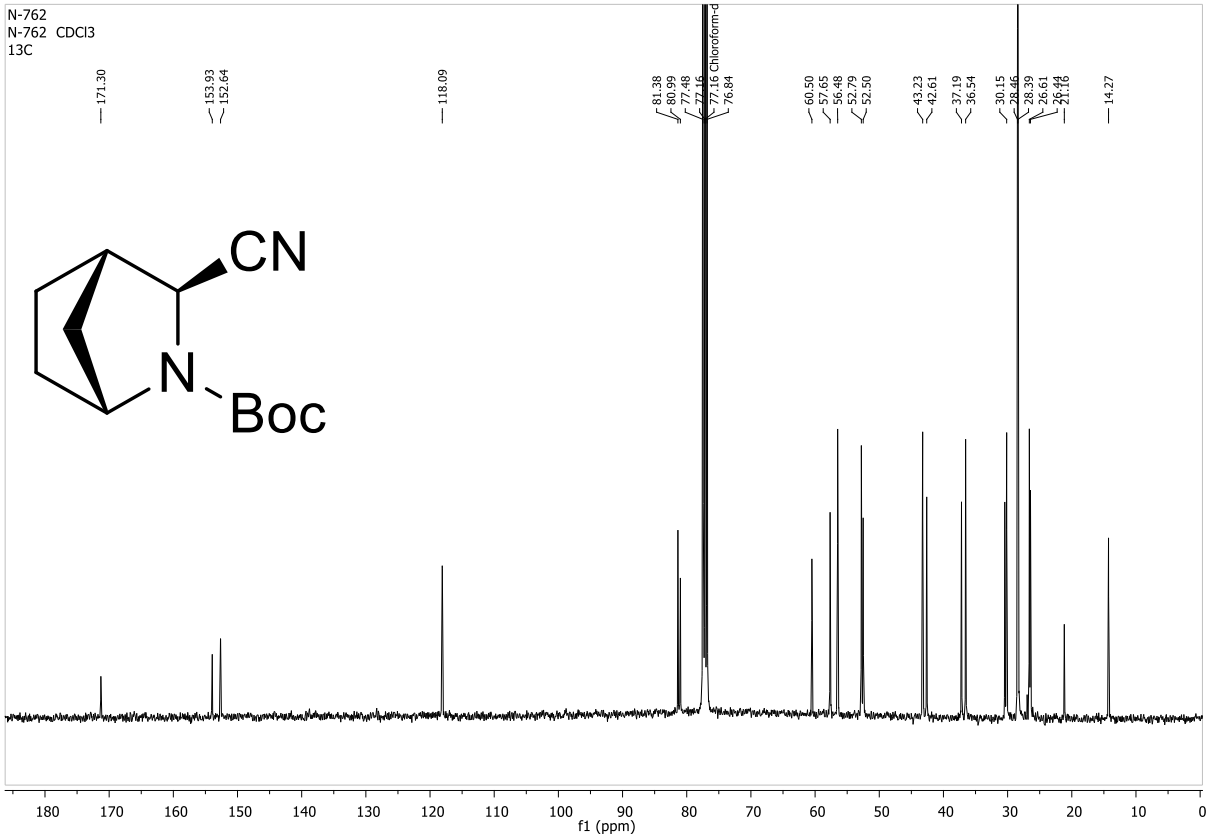
8a,b

^{1}H NMR

Supplementary material 1



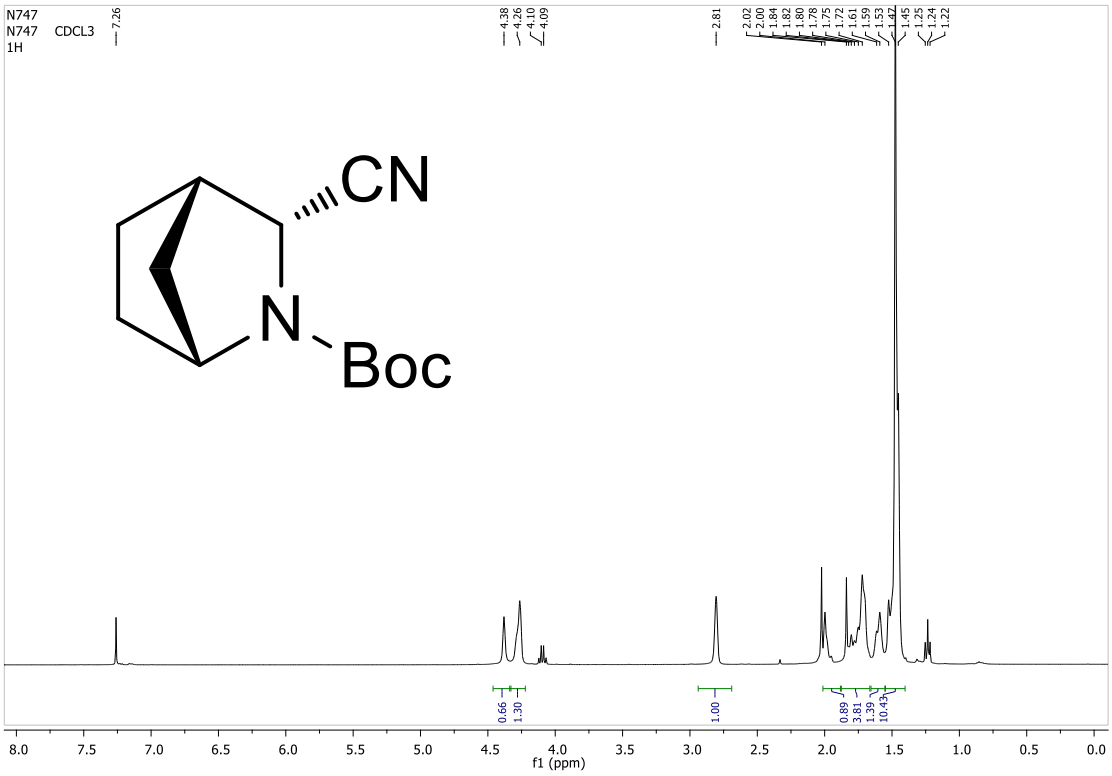
$^{13}C\{^{1}H\}$ NMR



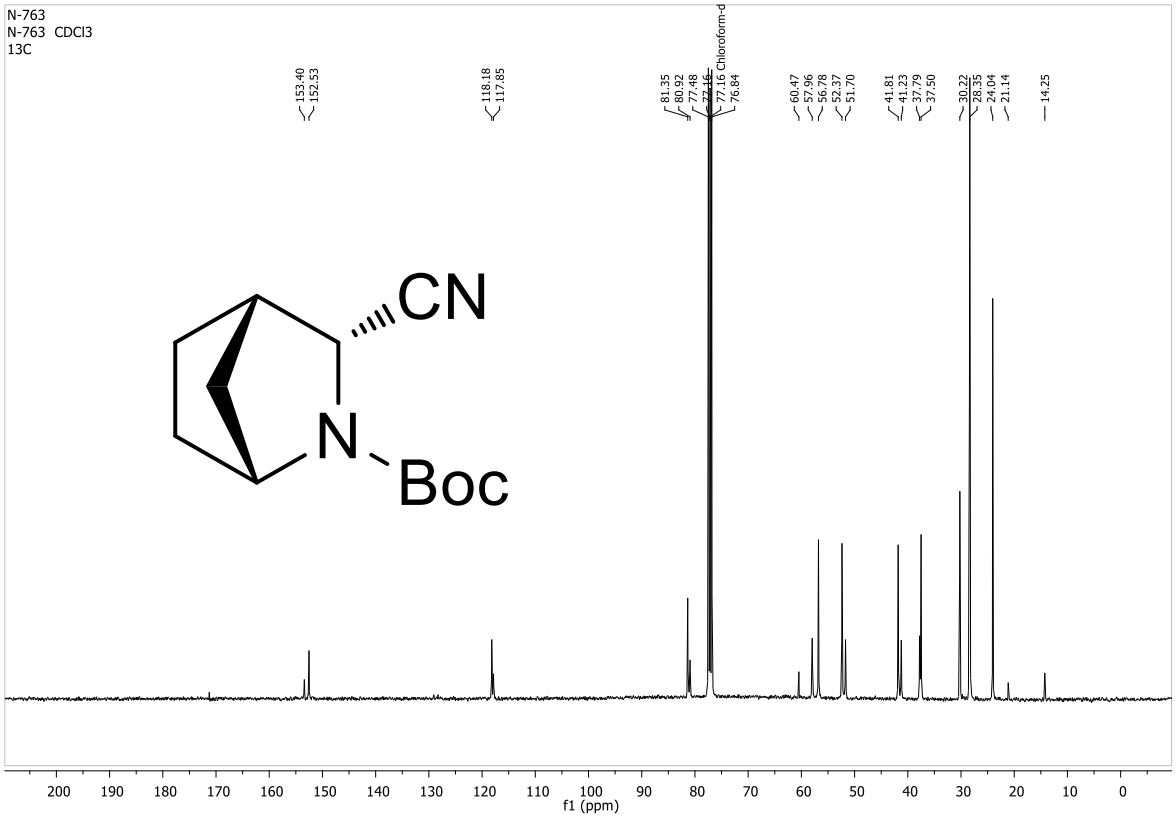
8c,d

^{1}H NMR

Supplementary material 1



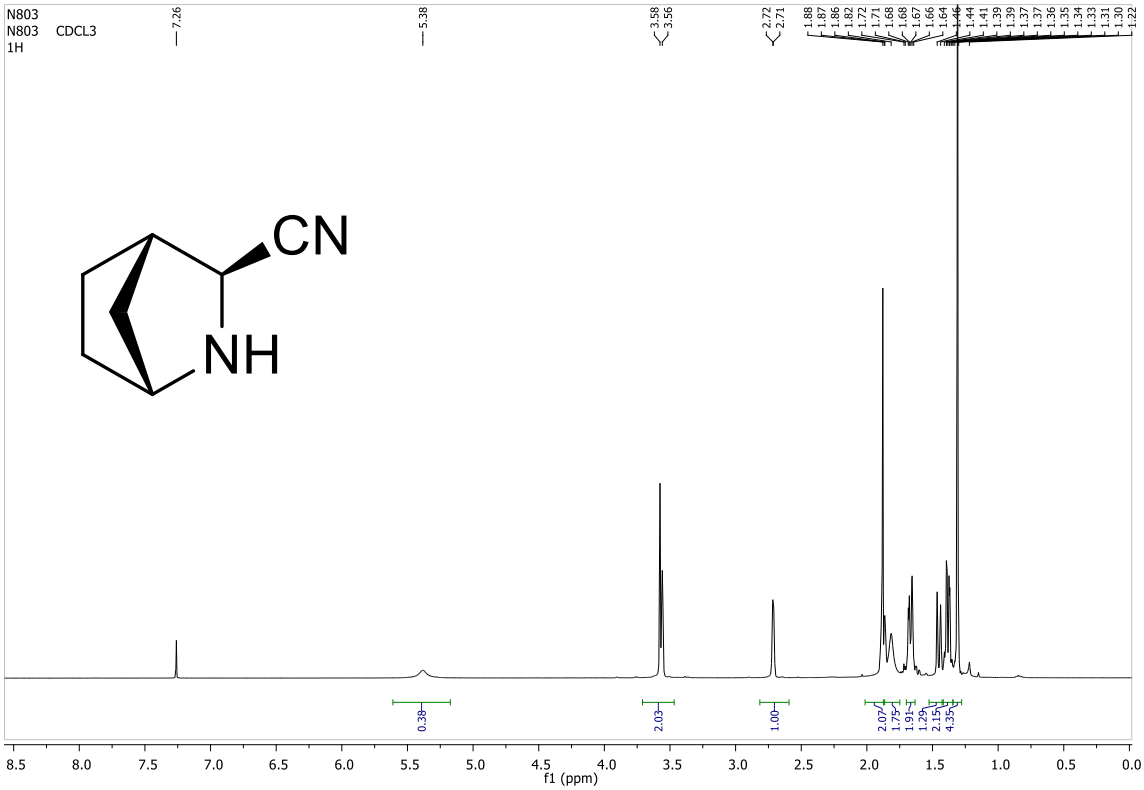
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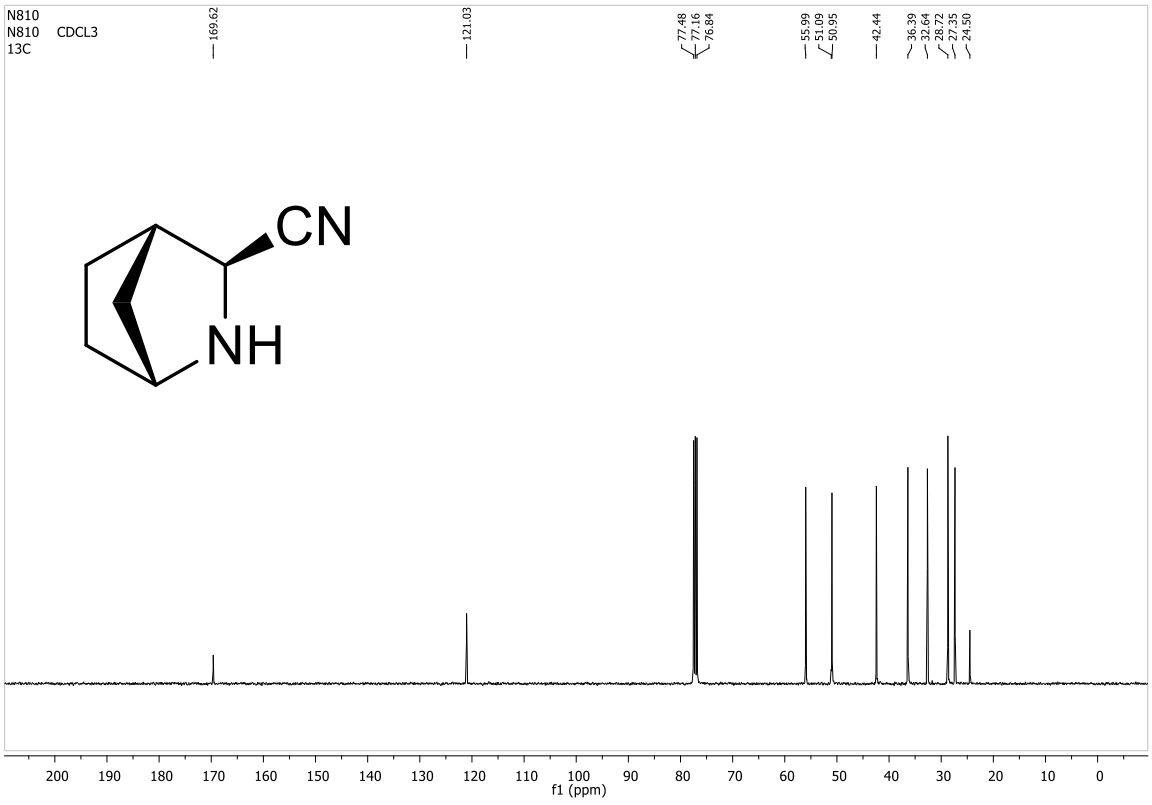
9a,b

^{1}H NMR

Supplementary material 1



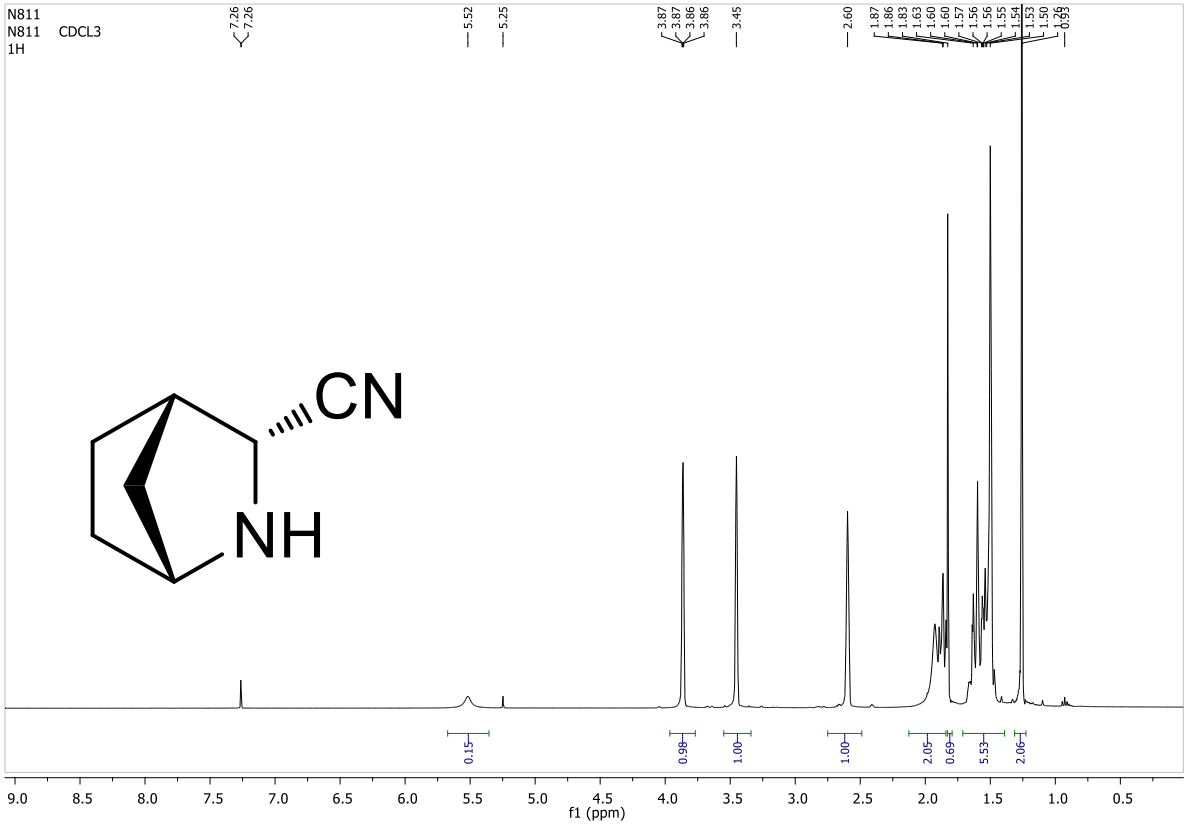
$^{13}C\{^{1}H\}$ NMR



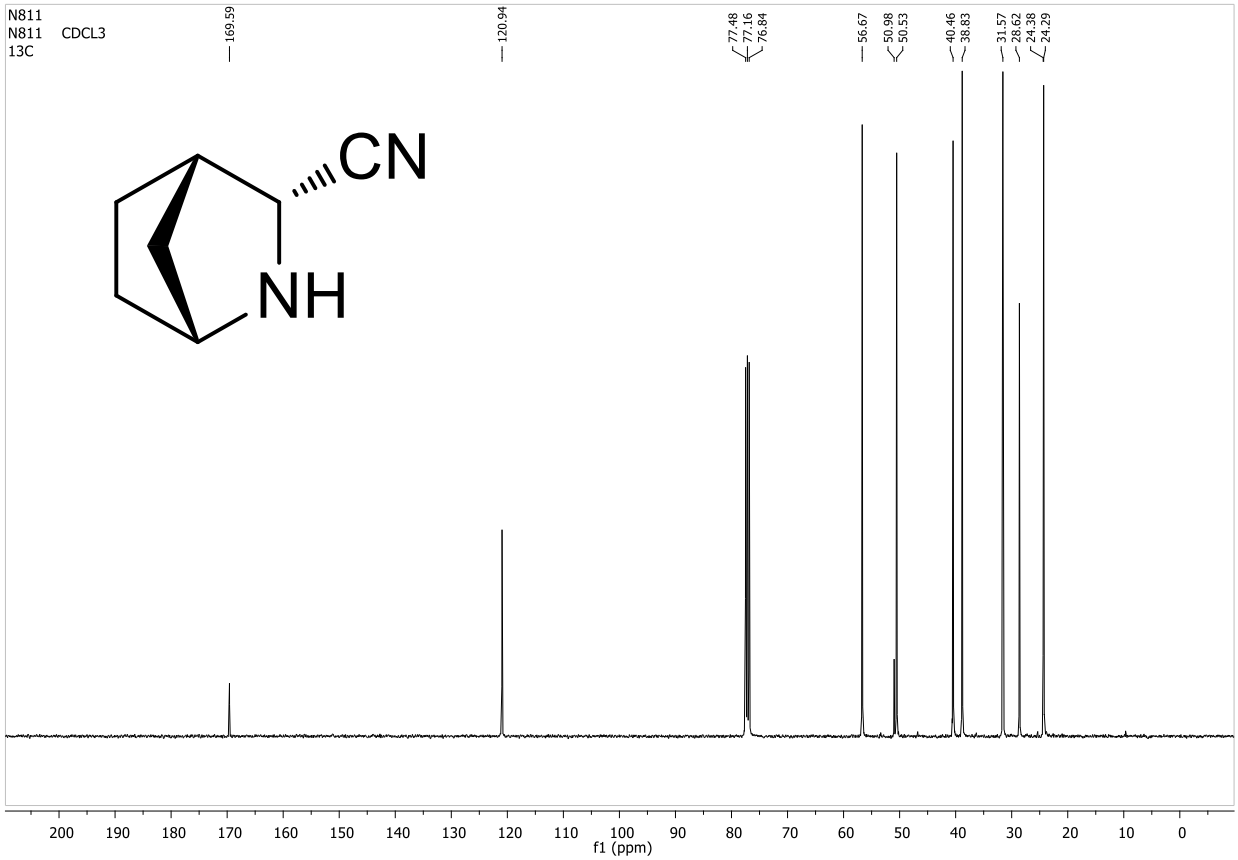
9c,d

^{1}H NMR

Supplementary material 1



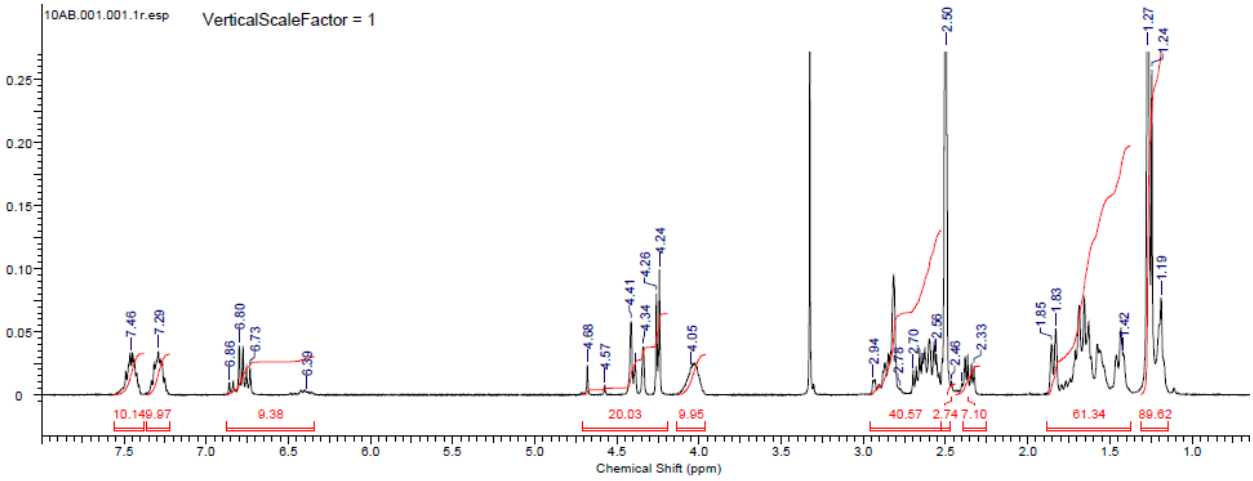
$^{13}C\{^{1}H\}$ NMR



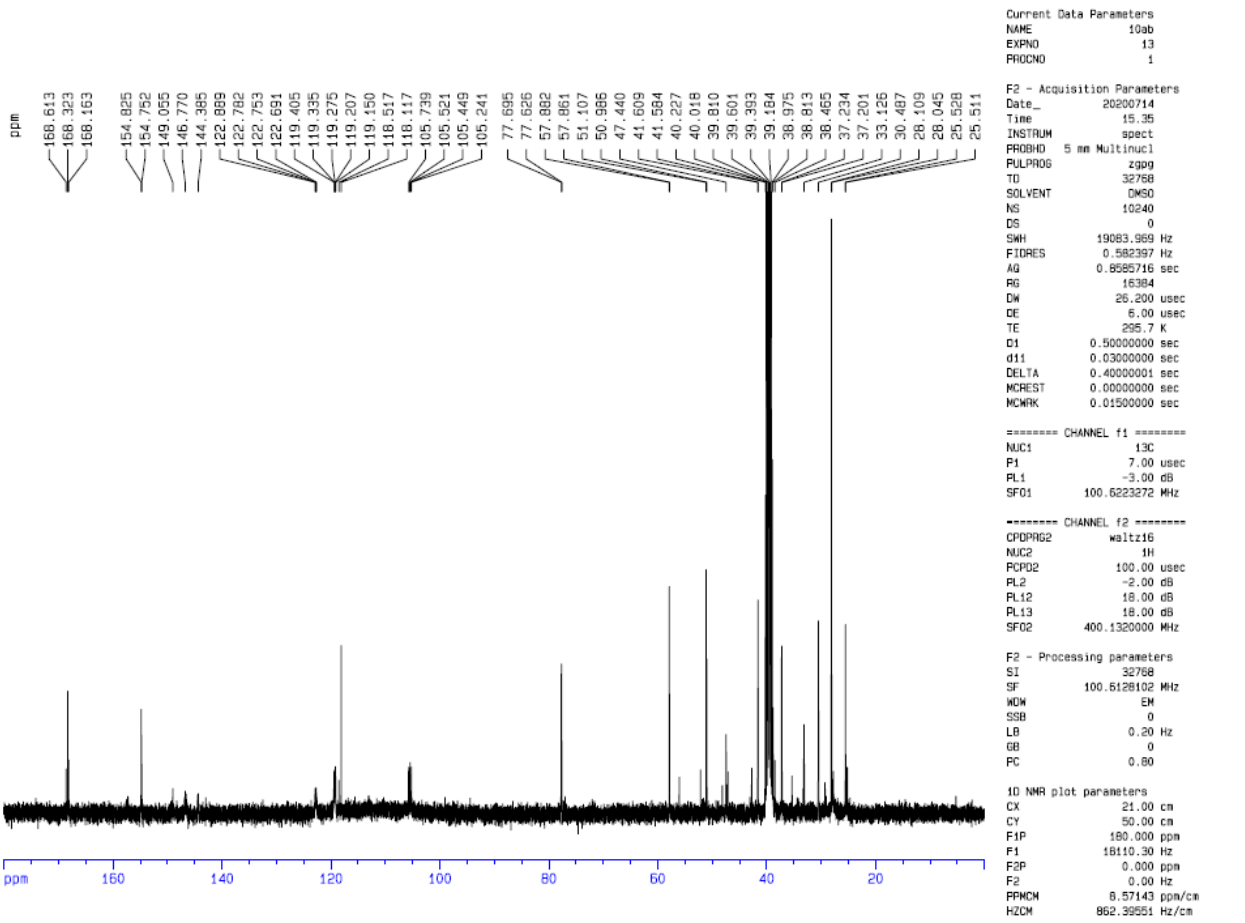
Supplementary material 1

11a,b

^{1}H NMR

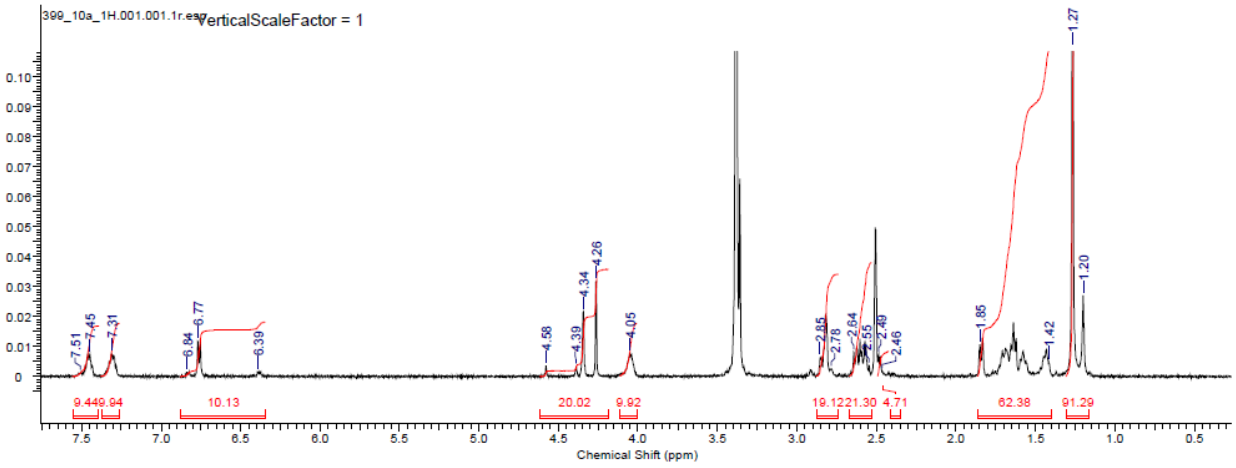


^{13}C{^{1}H} NMR



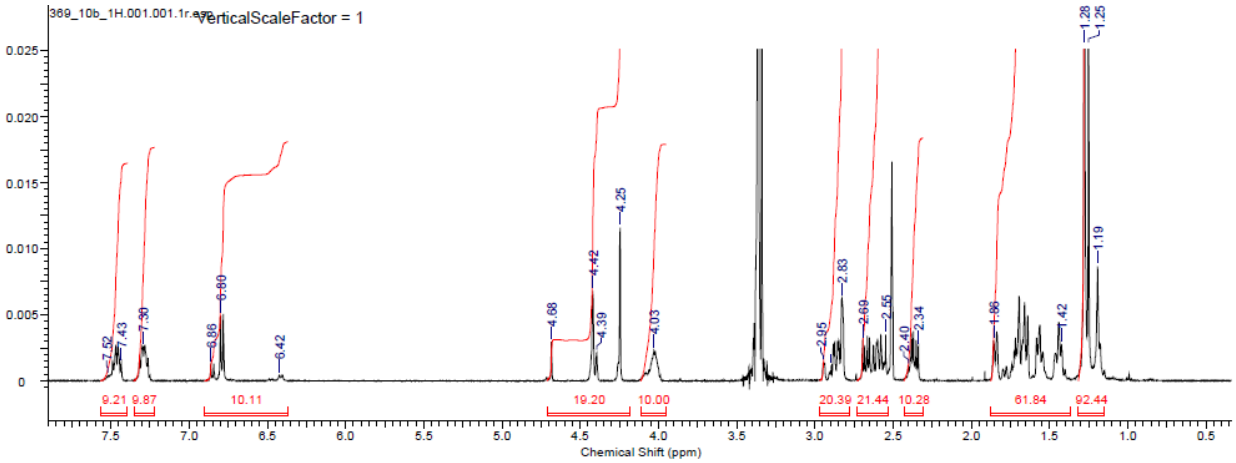
11a

^{1}H NMR



11b

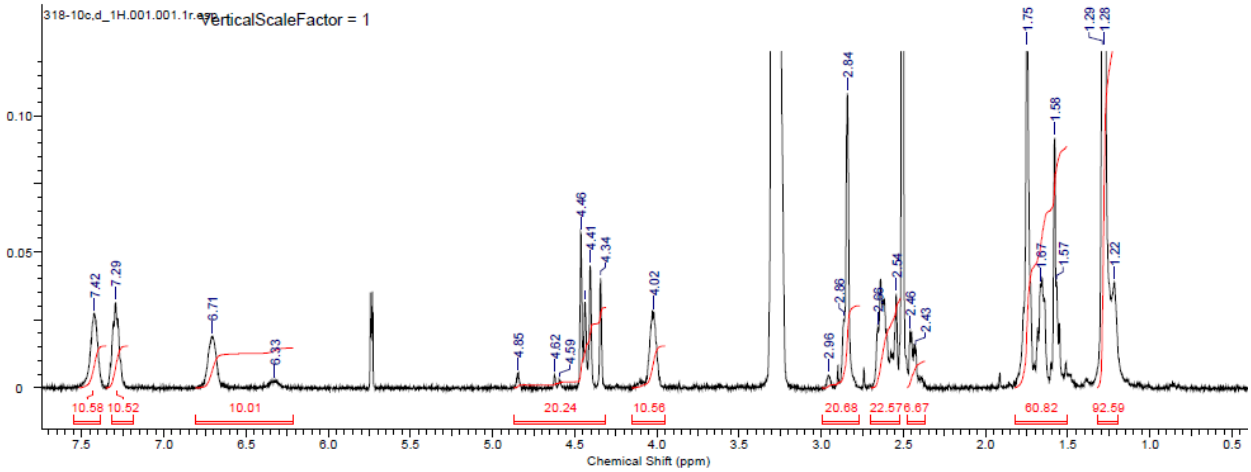
^{1}H NMR



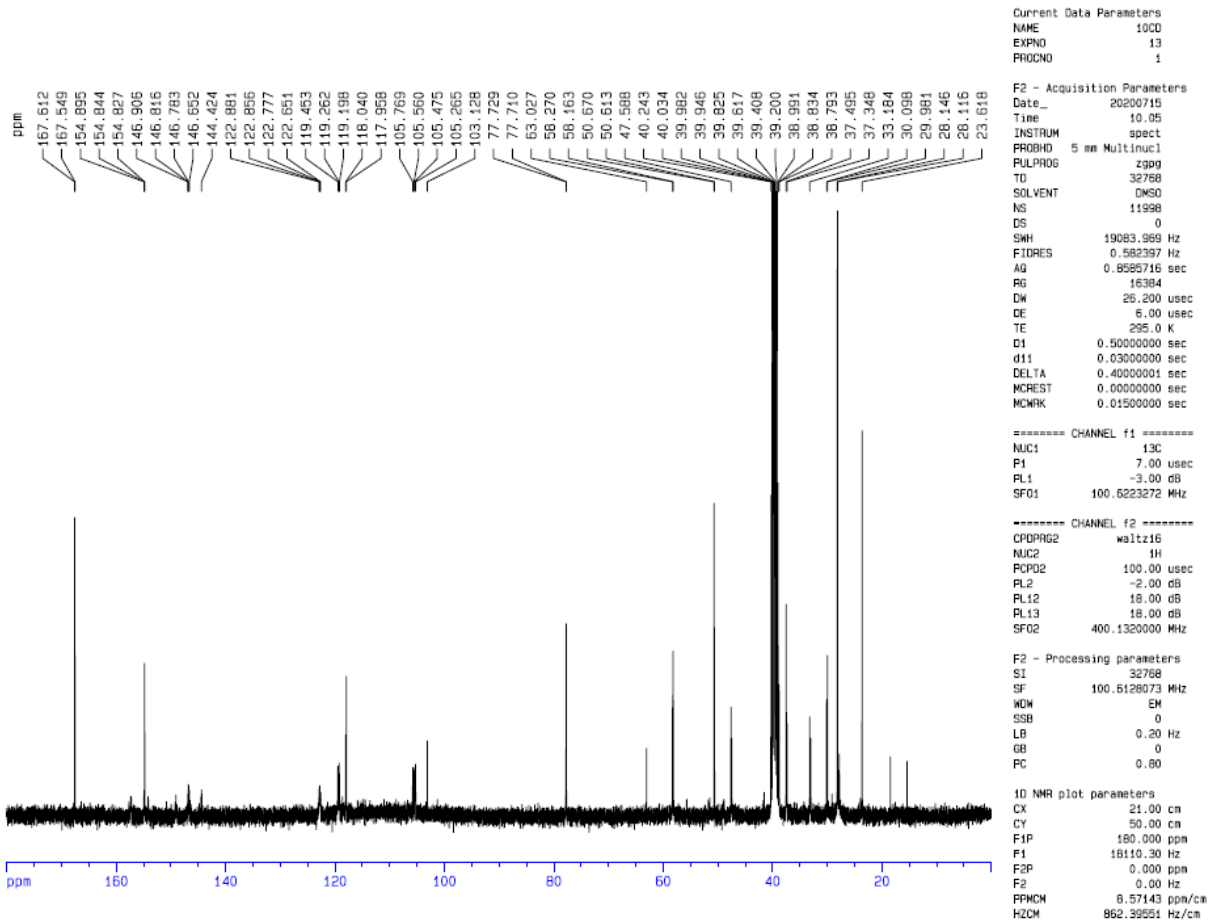
11c,d

^{1}H NMR

Supplementary material 1



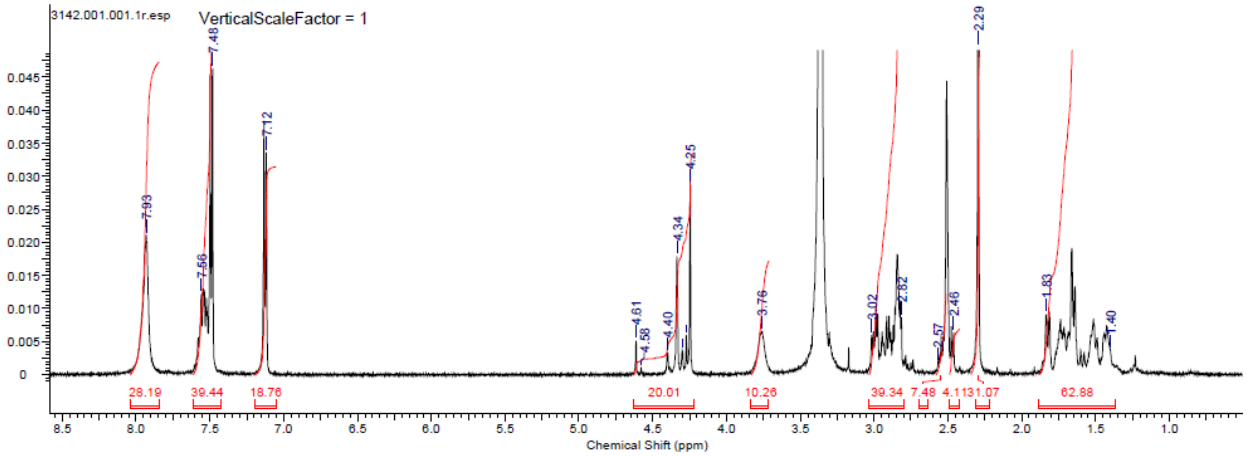
$^{13}C\{^{1}H\}$ NMR



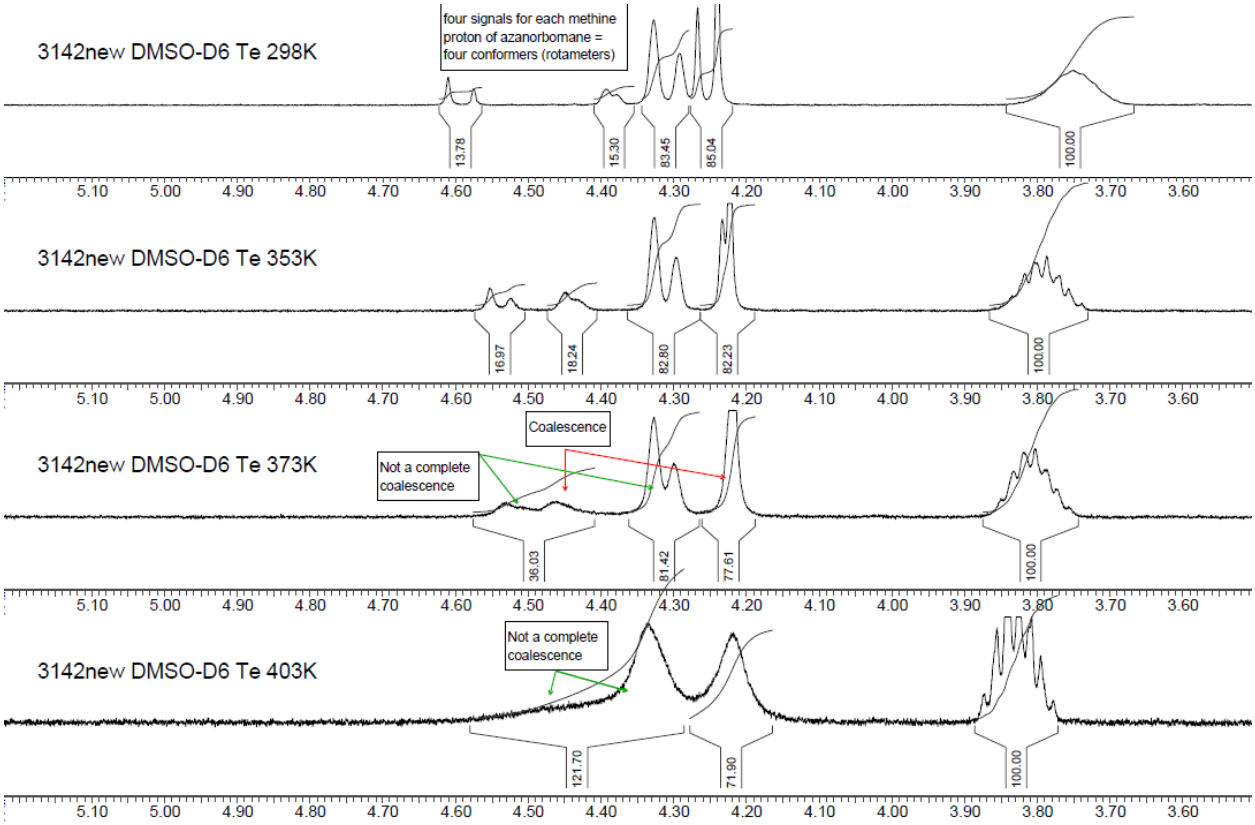
Supplementary material 1

12a,b

^{1}H NMR at RT

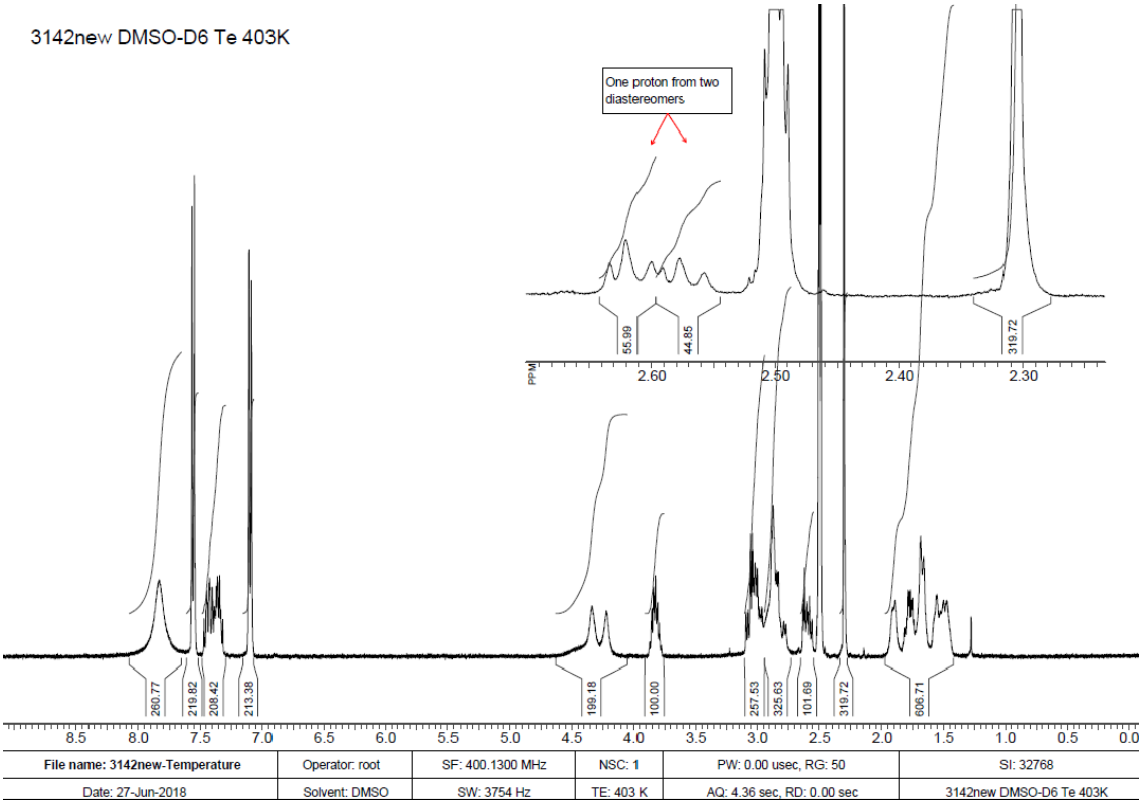


^{1}H NMR registered at different temperatures

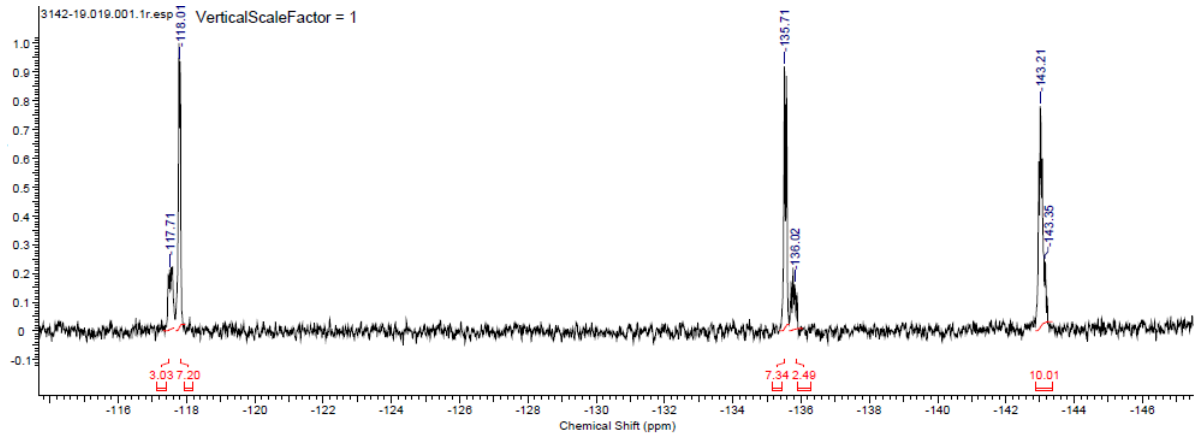


Supplementary material 1

^{1}H NMR registered at temperature 403 K

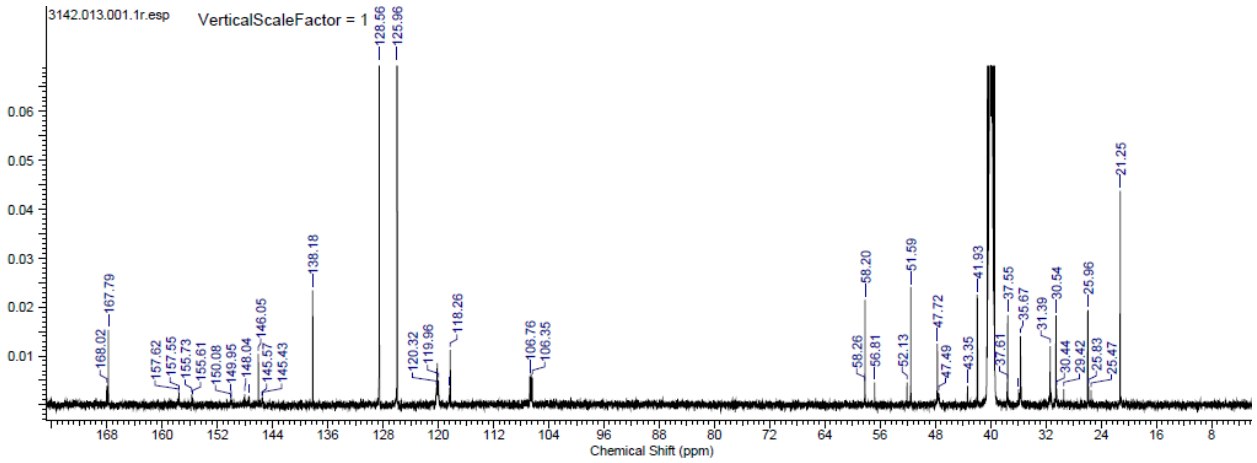


^{19}F NMR

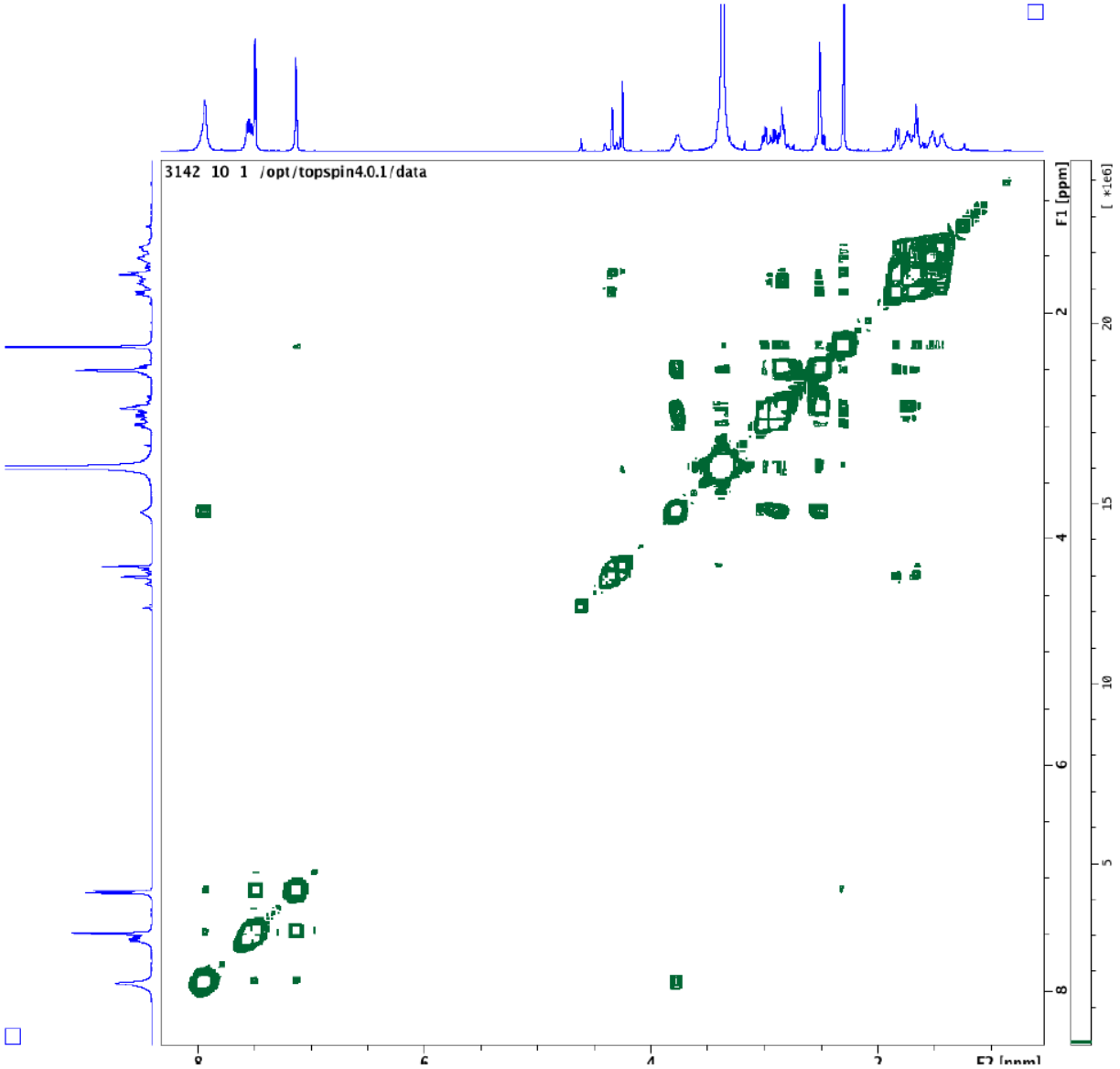


^{13}C{^{1}H} NMR

Supplementary material 1

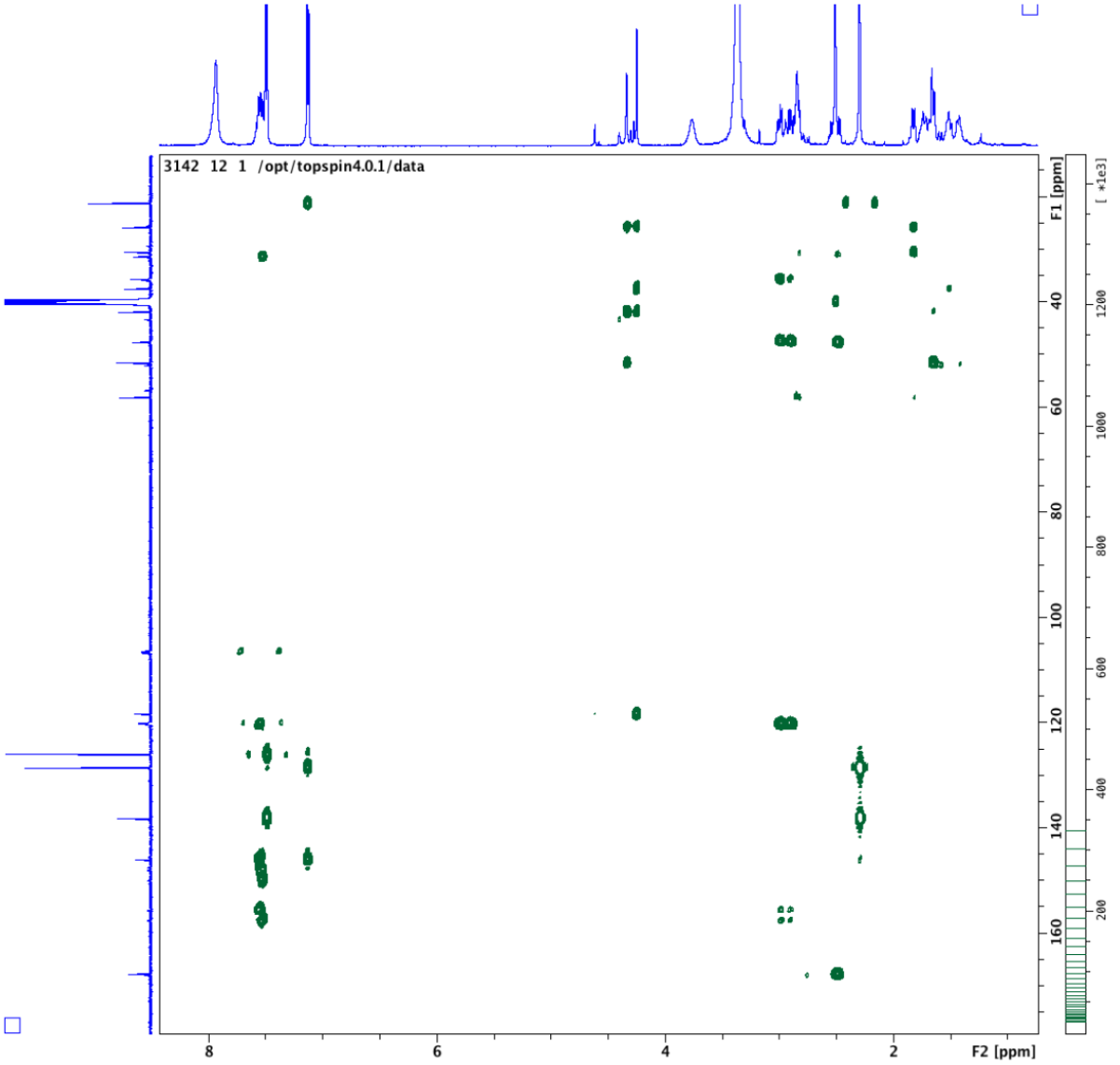


COSY



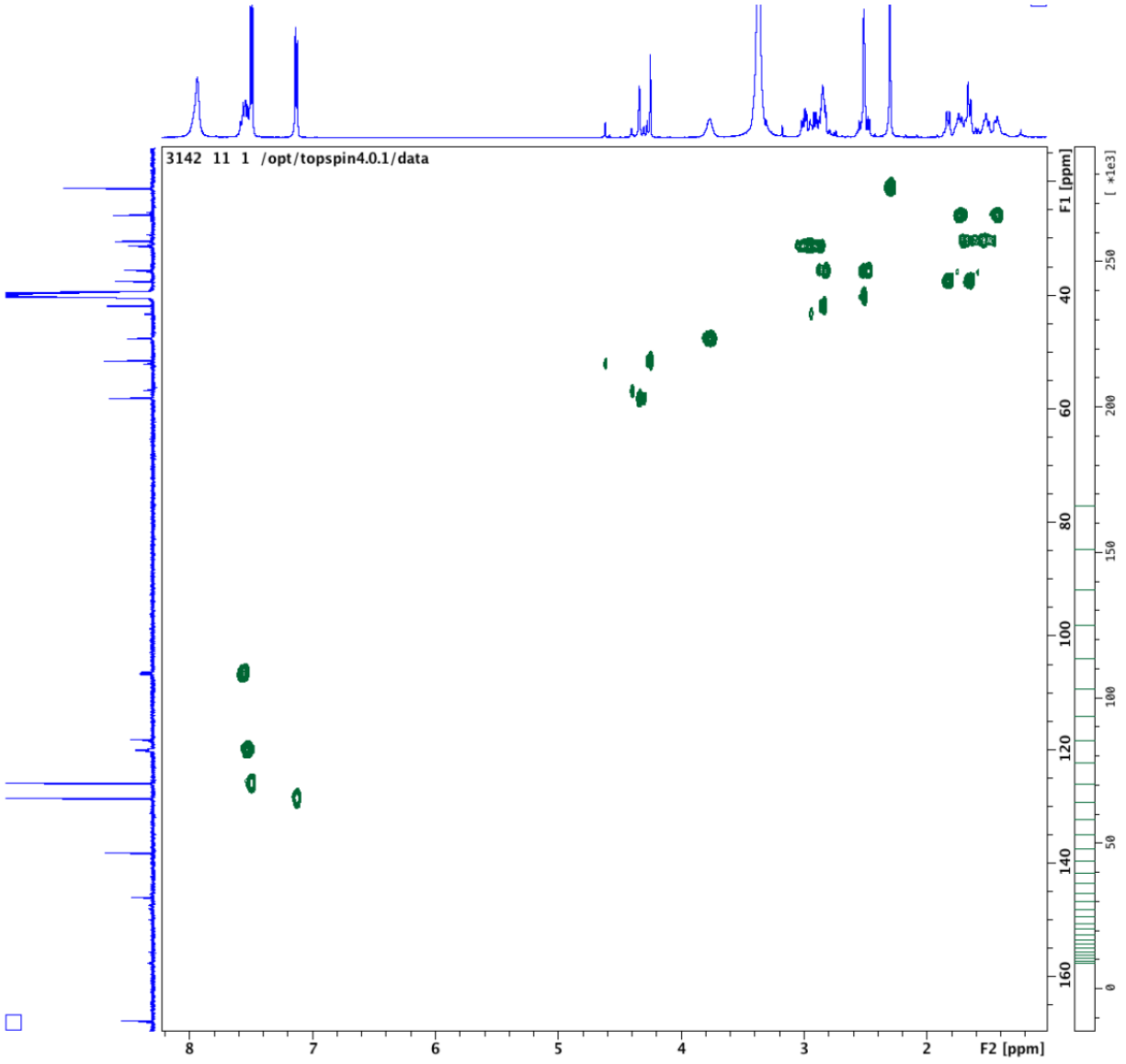
Supplementary material 1

HMBC



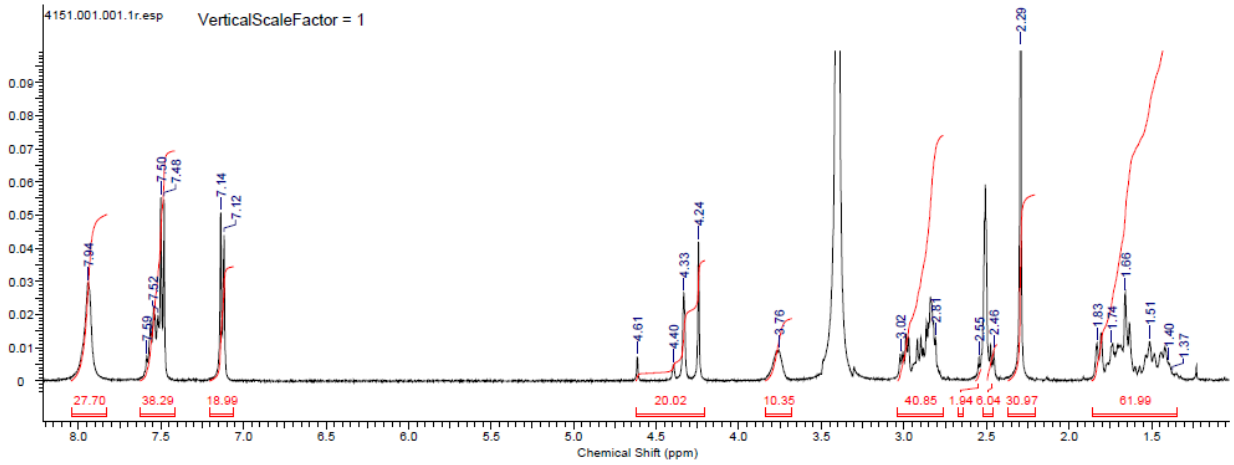
Supplementary material 1

HSQC

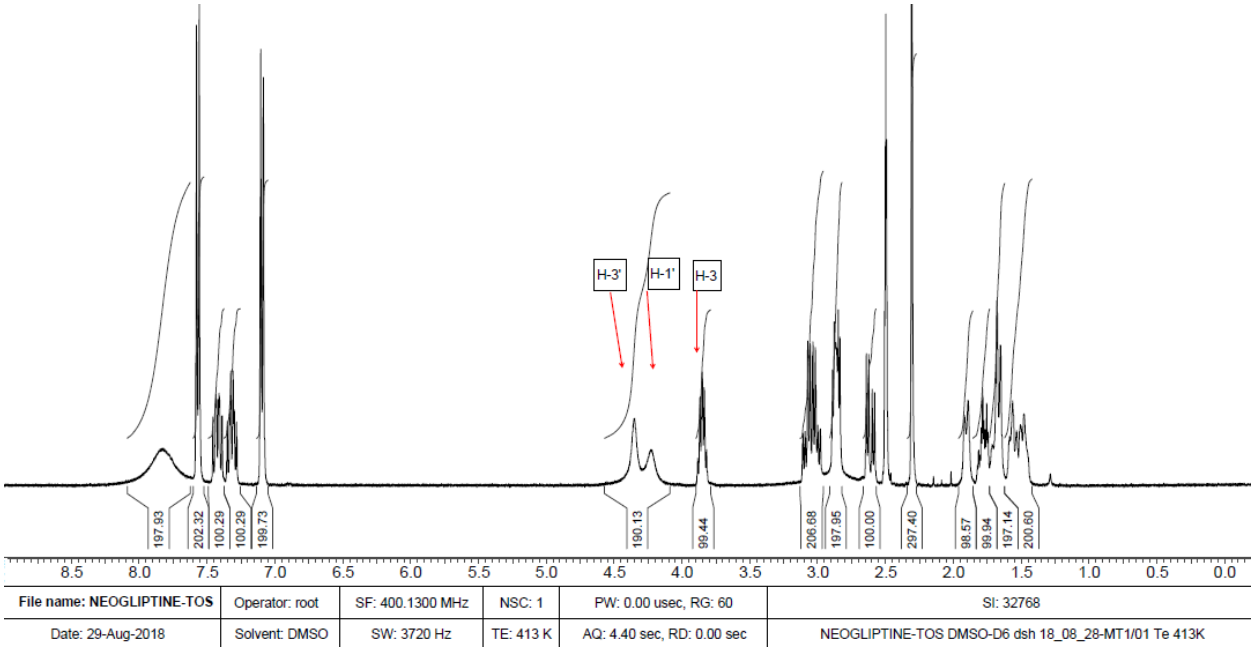


12a

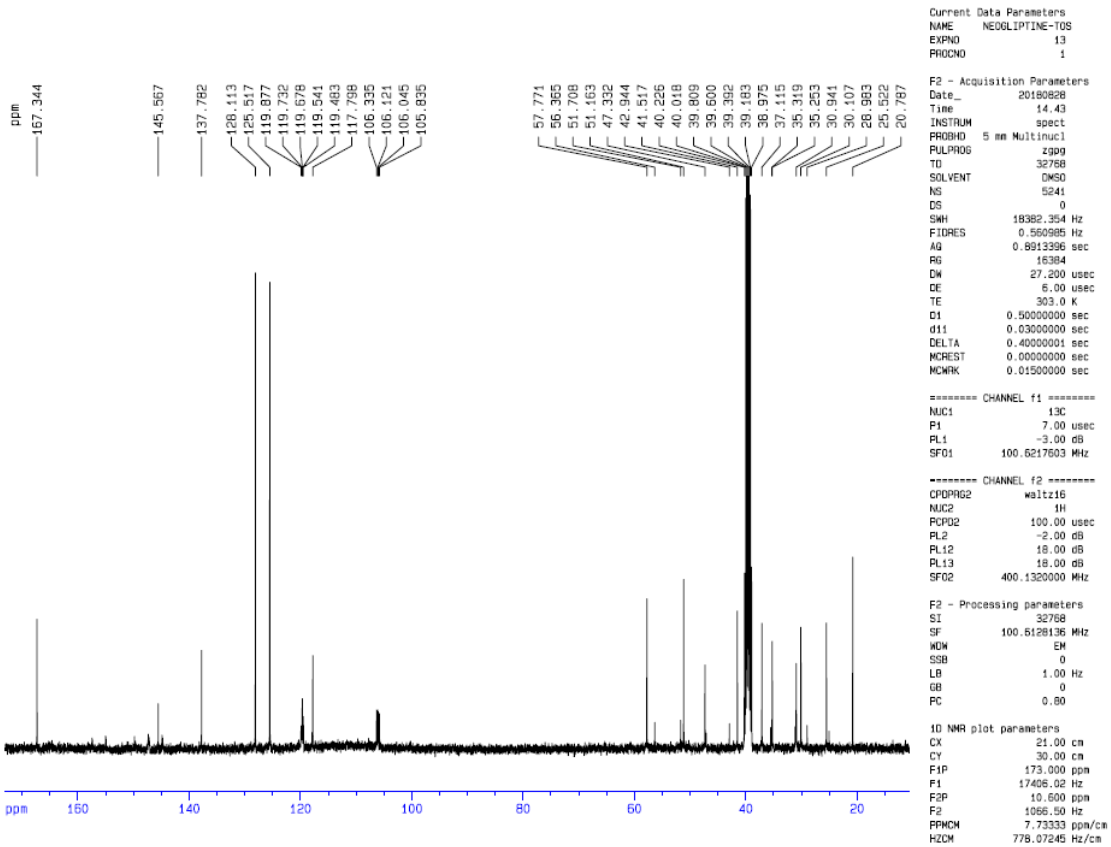
^{1}H NMR at RT



^{1}H NMR at temperature 413 K

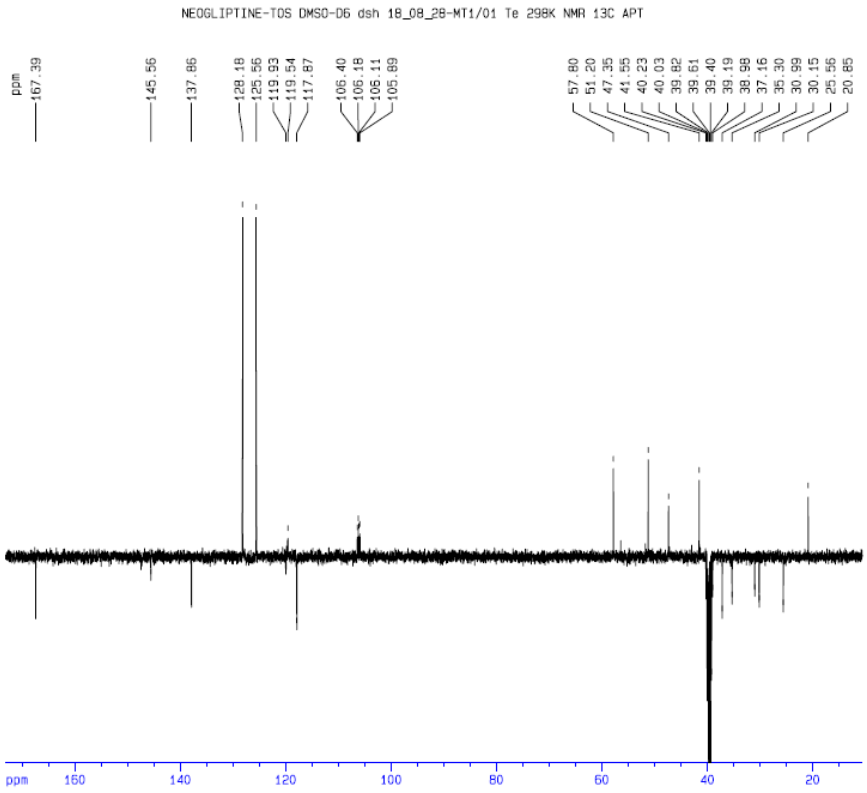


$^{13}C\{^{1}H\}$ NMR



^{13}C apt NMR

Supplementary material 1




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PROCNO                  1

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FIDRES         0.548877 Hz
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DE                 6.00 usec
TE                298.0 K
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D21             0.00000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
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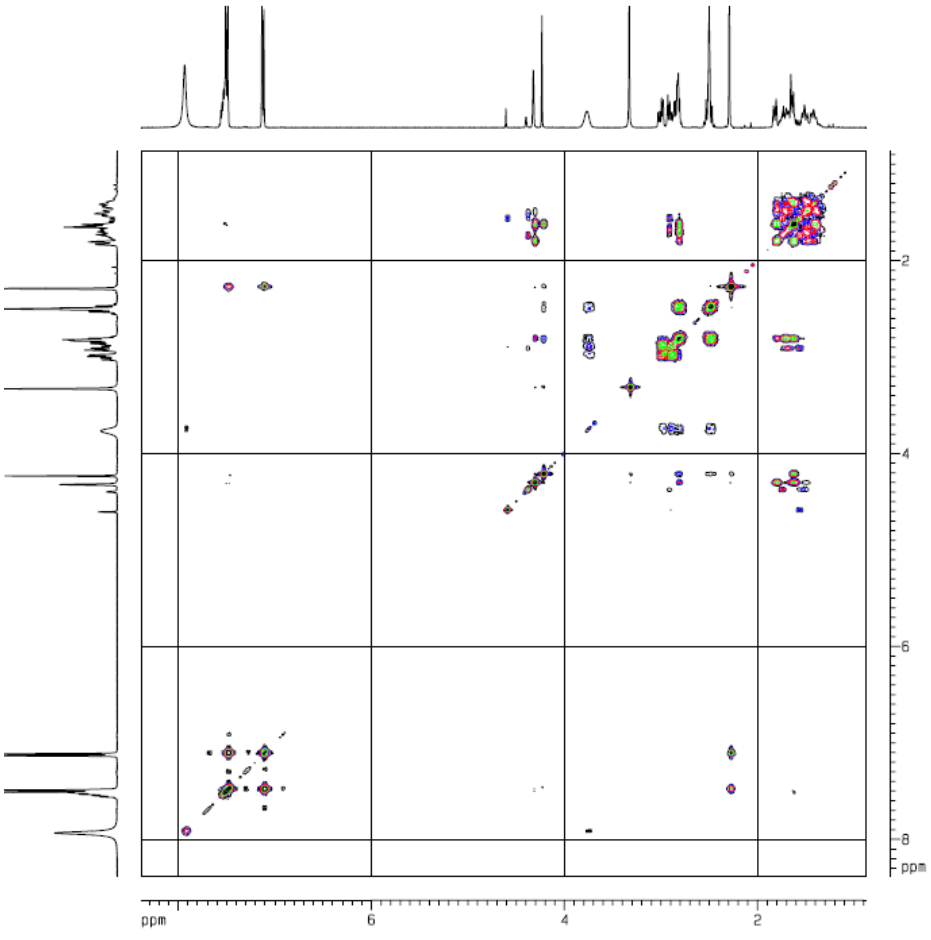
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F2 - Processing parameters
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1D NMR plot parameters
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Supplementary material 1

COSY



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MCWRK 1.00000000 sec

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GPX2 0.00 %
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GPY2 0.00 %
GPZ1 20.00 %
GPZ2 20.00 %
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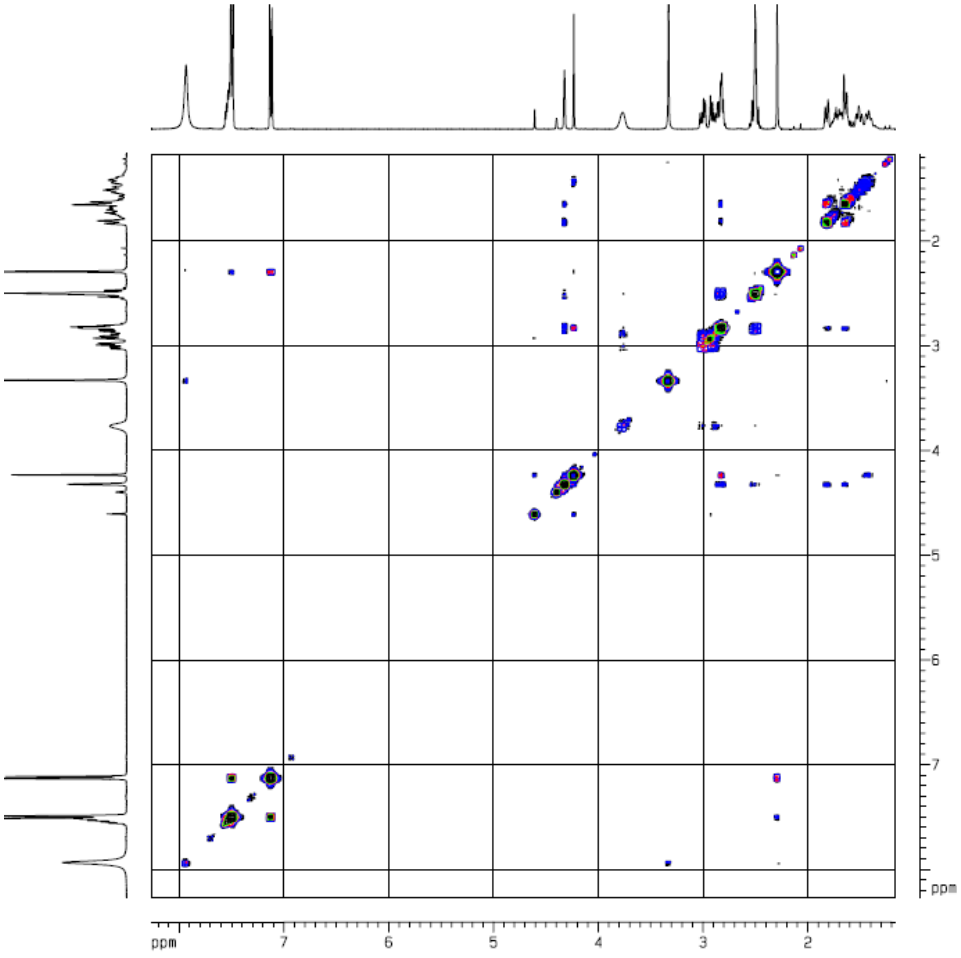
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Supplementary material 1

NOESY



Current Data Parameters
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EXPNO 70
PROCNO 1

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TAU 0.24800000 sec

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====== GRADIENT CHANNEL =====
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GPZ2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 40.00 %
GPZ2 -40.00 %
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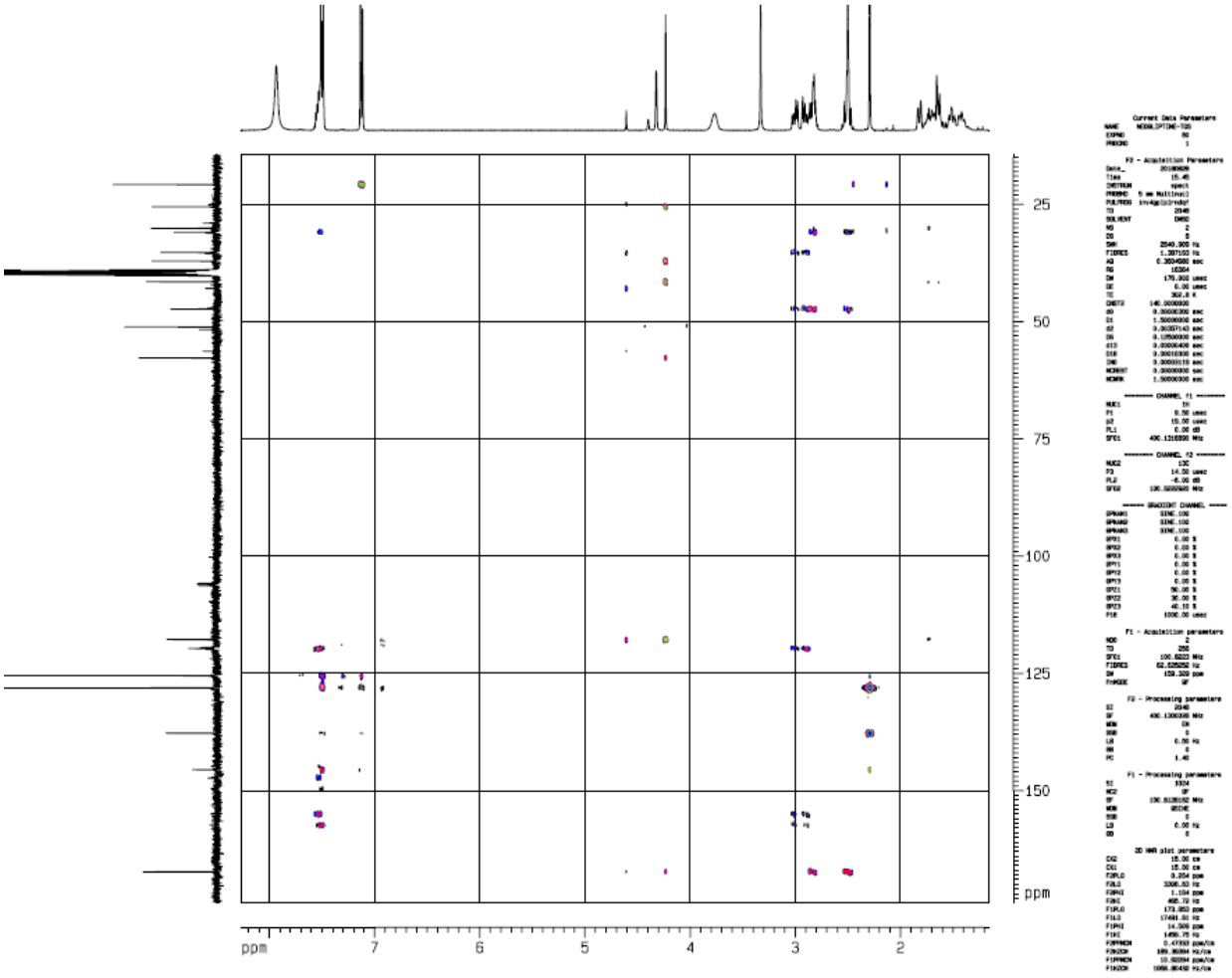
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SSB 0
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2D NMR plot parameters
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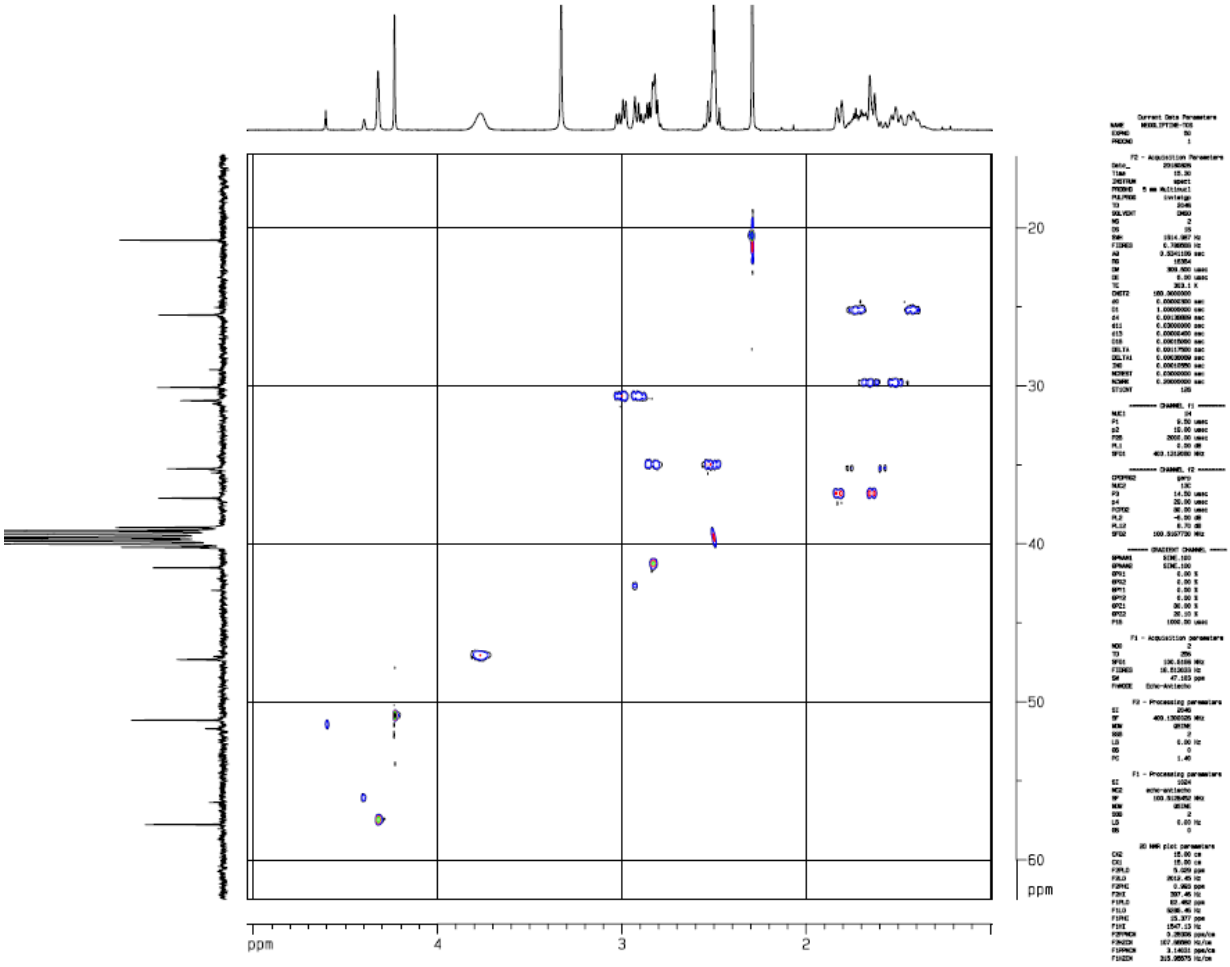
Supplementary material 1

HMBC



Supplementary material 1

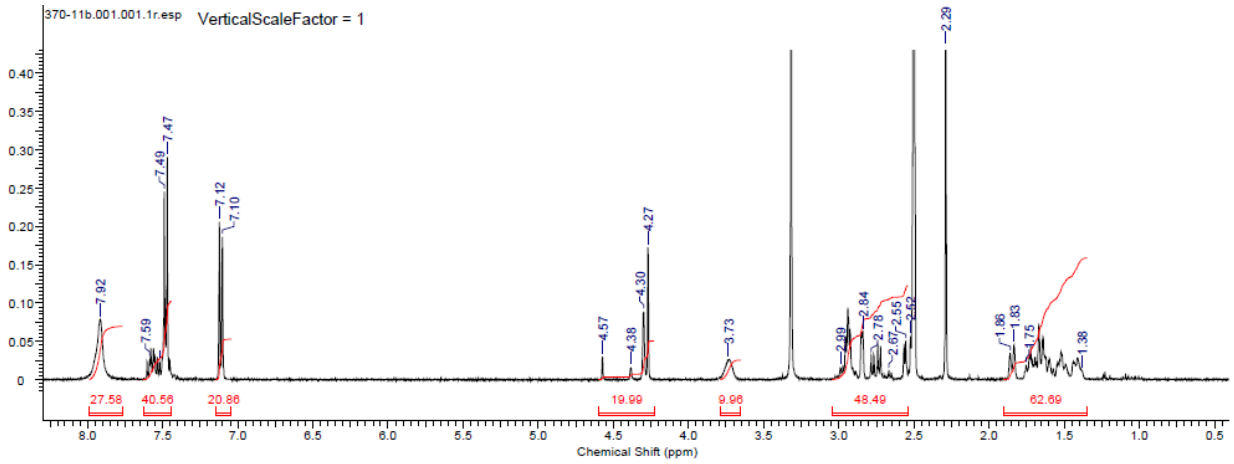
HSCQ



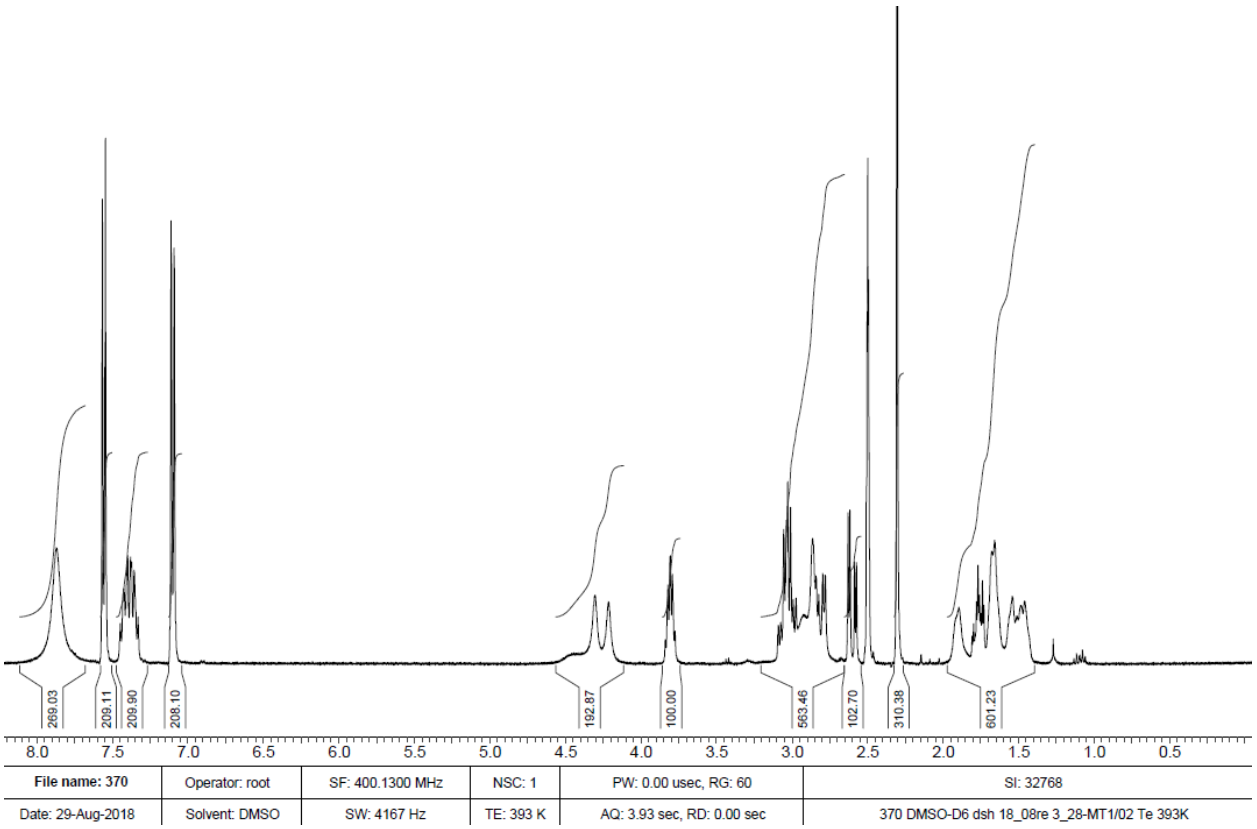
Supplementary material 1

12b

^{1}H NMR at RT

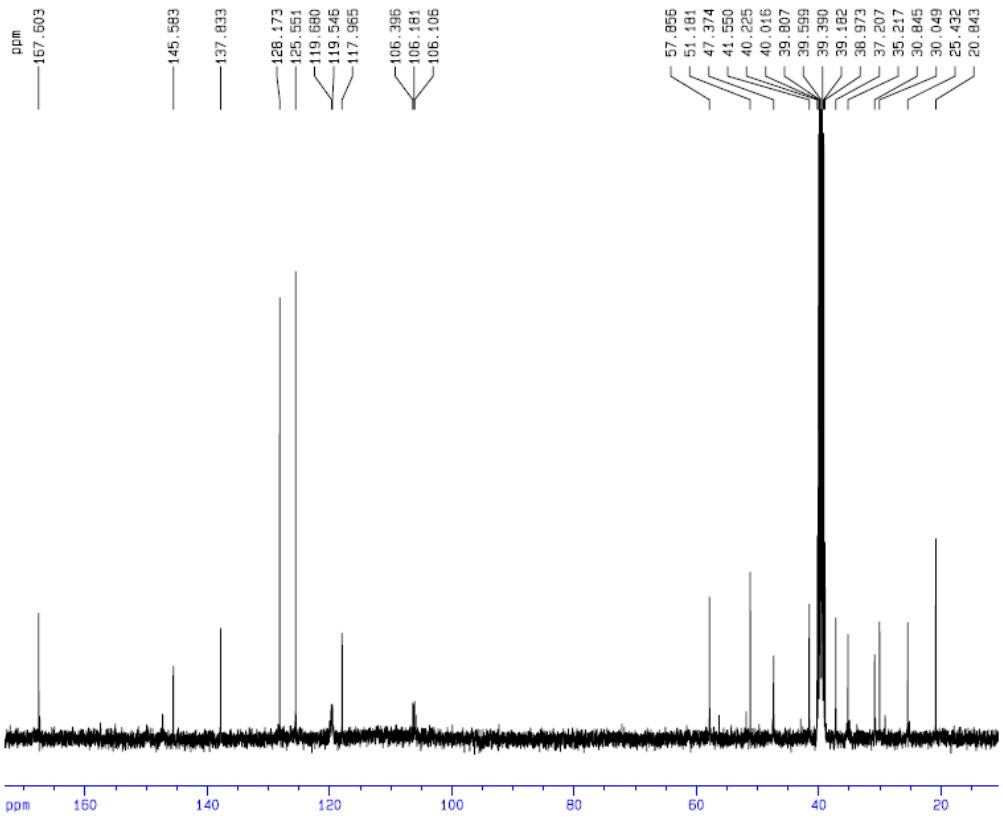


^{1}H NMR at temperature 393 K



Supplementary material 1

$^{13}C\{^{1}H\}$ NMR




```
Current Data Parameters
NAME                  370
EXPNO                  13
PROCNO                  1

F2 - Acquisition Parameters
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Time                11.54
INSTRUM             spect
PROBHD   5 mm Multinucl
PULPROG             zgpg
TD                 32768
SOLVENT             DMSO
NS                  2048
DS                     0
SWH           18382.354 Hz
FIDRES        0.560985 Hz
AQ            0.8913396 sec
RG                 16384
DW               27.200 usec
DE                6.00 usec
TE                298.0 K
D1            0.50000000 sec
d11           0.03000000 sec
DELTA         0.40000001 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                   7.00 usec
PL1                 -3.00 dB
SFO1         100.6217603 MHz

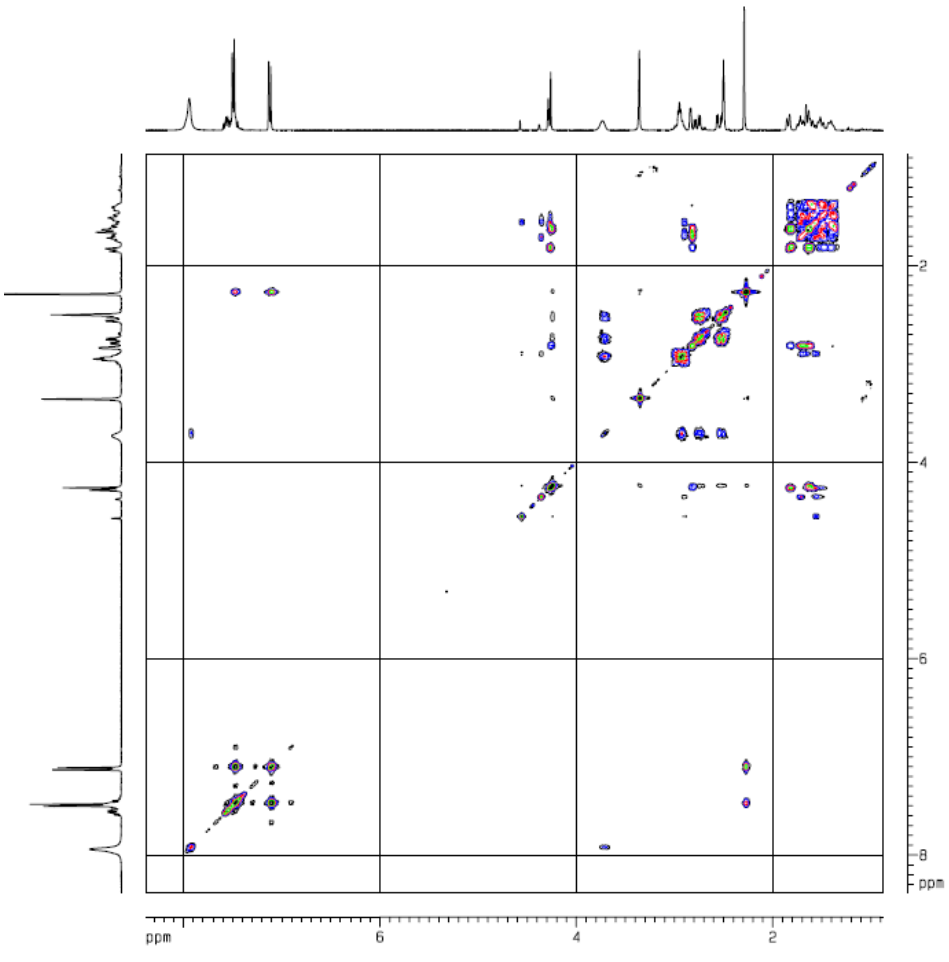
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CPDPRG2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                 -2.00 dB
PL12                18.00 dB
PL13                18.00 dB
SFO2         400.1320000 MHz

F2 - Processing parameters
SI                 32768
SF           100.6128091 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  0.80

1D NMR plot parameters
CX                 21.00 cm
CY                 30.00 cm
F1P               173.000 ppm
F1              17406.02 Hz
F2P                10.600 ppm
F2              1066.50 Hz
PPMCM              7.73333 ppm/cm
HZCM            778.07239 Hz/cm
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Supplementary material 1

COSY



Current Data Parameters
NAME 370
EXPNO 30
PROCNO 1

F2 - Acquisition Parameters
Date_ 20190829
Time 12.45
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG cosygpqf
TD 1024
SOLVENT DMSO
NS 1
DS 16
SWH 3004.808 Hz
FIDRES 2.934382 Hz
AQ 0.1704436 sec
RG 60
DW 166.400 usec
DE 6.00 usec
TE 296.0 K
d0 0.00000300 sec
D1 1.00000000 sec
d13 0.00000400 sec
D16 0.00010000 sec
IN0 0.00033278 sec
MCREST 0.00000000 sec
MCWRK 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P0 10.00 usec
P1 10.00 usec
PL1 0.00 dB
SFO1 400.1318630 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 20.00 %
GPZ2 20.00 %
P16 1600.00 usec

F1 - Acquisition parameters
ND0 1
TD 512
SFO1 400.1319 MHz
FIDRES 5.865205 Hz
SW 7.510 ppm
FnMODE QF

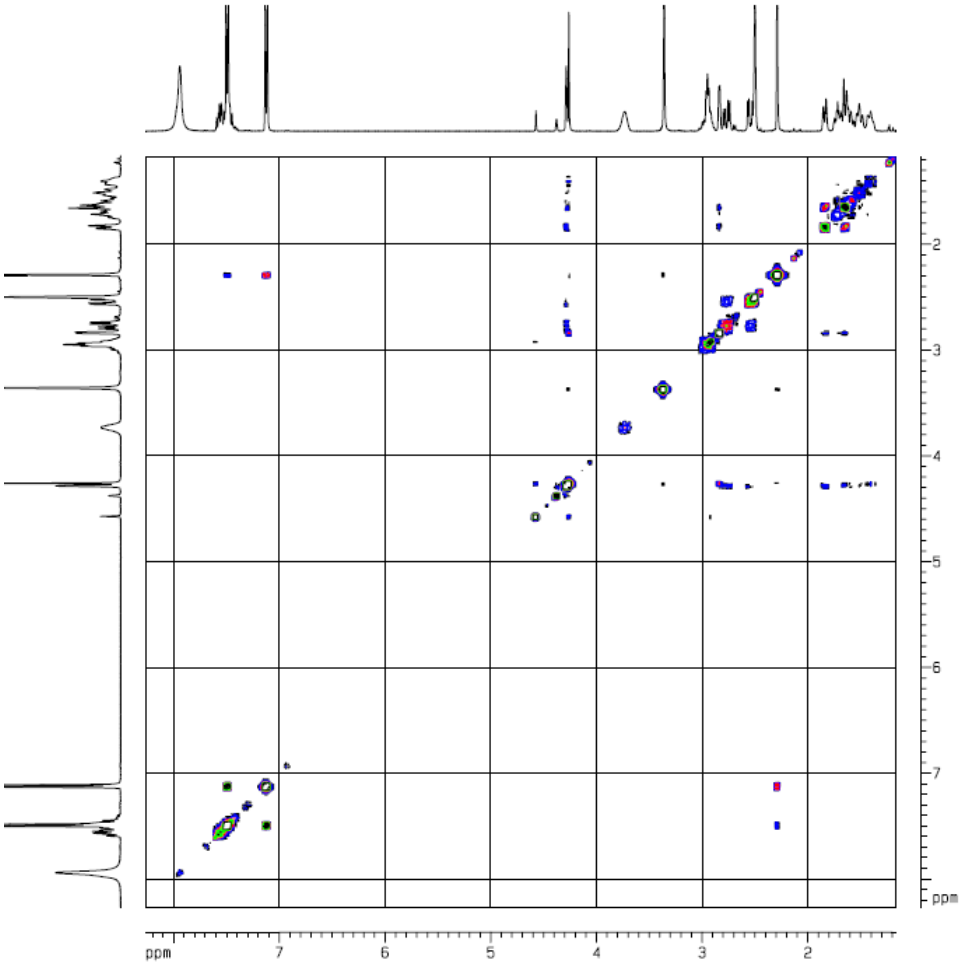
F2 - Processing parameters
SI 1024
SF 400.1300108 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 0.60

F1 - Processing parameters
SI 1024
WDW QF
SF 400.1300120 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0

2D NMR plot parameters
CX2 15.00 cm
CX1 15.00 cm
F2PLO 8.384 ppm
F2LO 3354.62 Hz
F2PHI 0.574 ppm
F2HI 349.81 Hz
F1PLO 8.381 ppm
F1LO 3353.55 Hz
F1PHI 0.571 ppm
F1HI 348.52 Hz
F2PPMCM 0.50064 ppm/cm
F2HZCM 200.32051 Hz/cm
F1PPMCM 0.50068 ppm/cm
F1HZCM 200.33656 Hz/cm

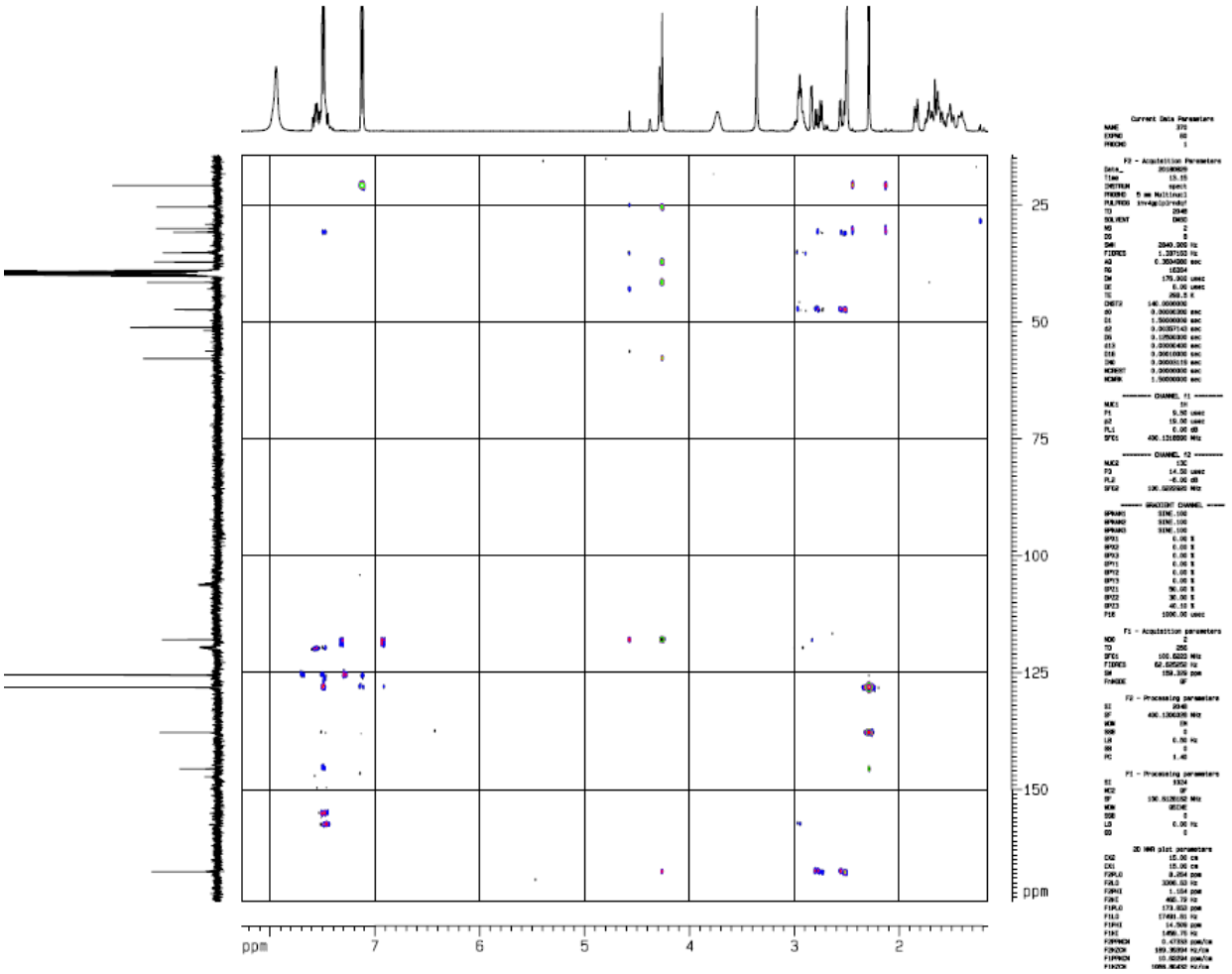
Supplementary material 1

NOESY



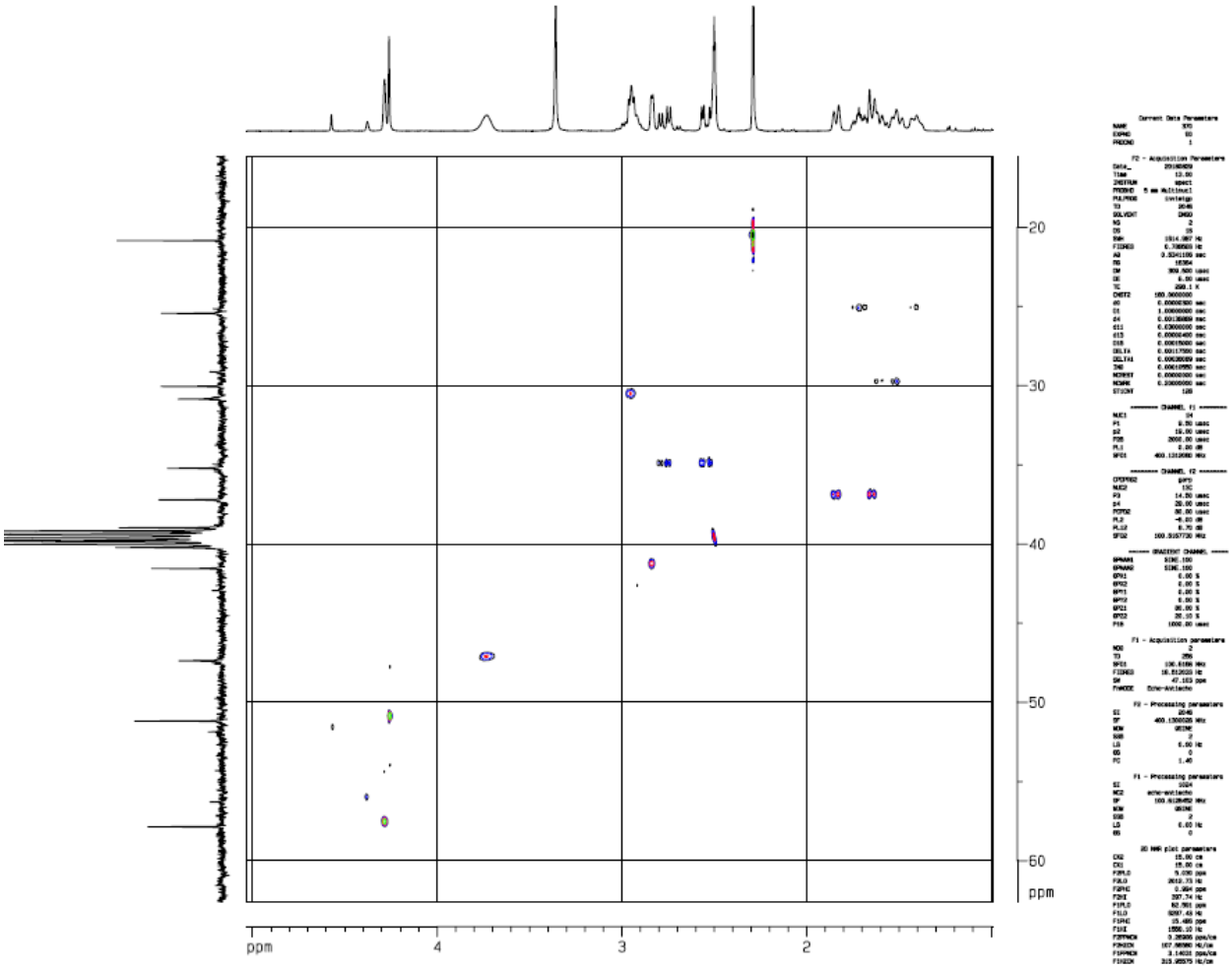
Supplementary material 1

HMBC



Supplementary material 1

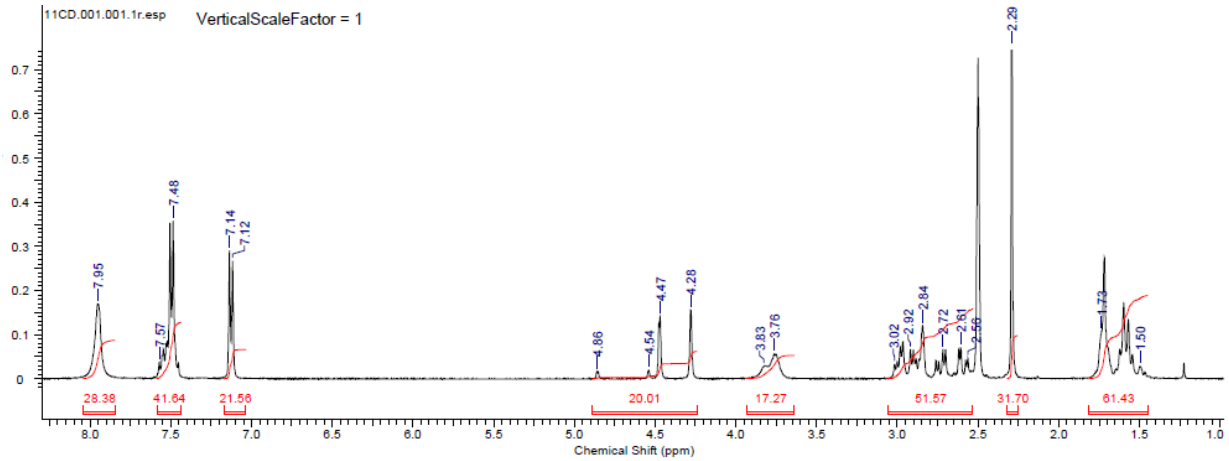
HSQC



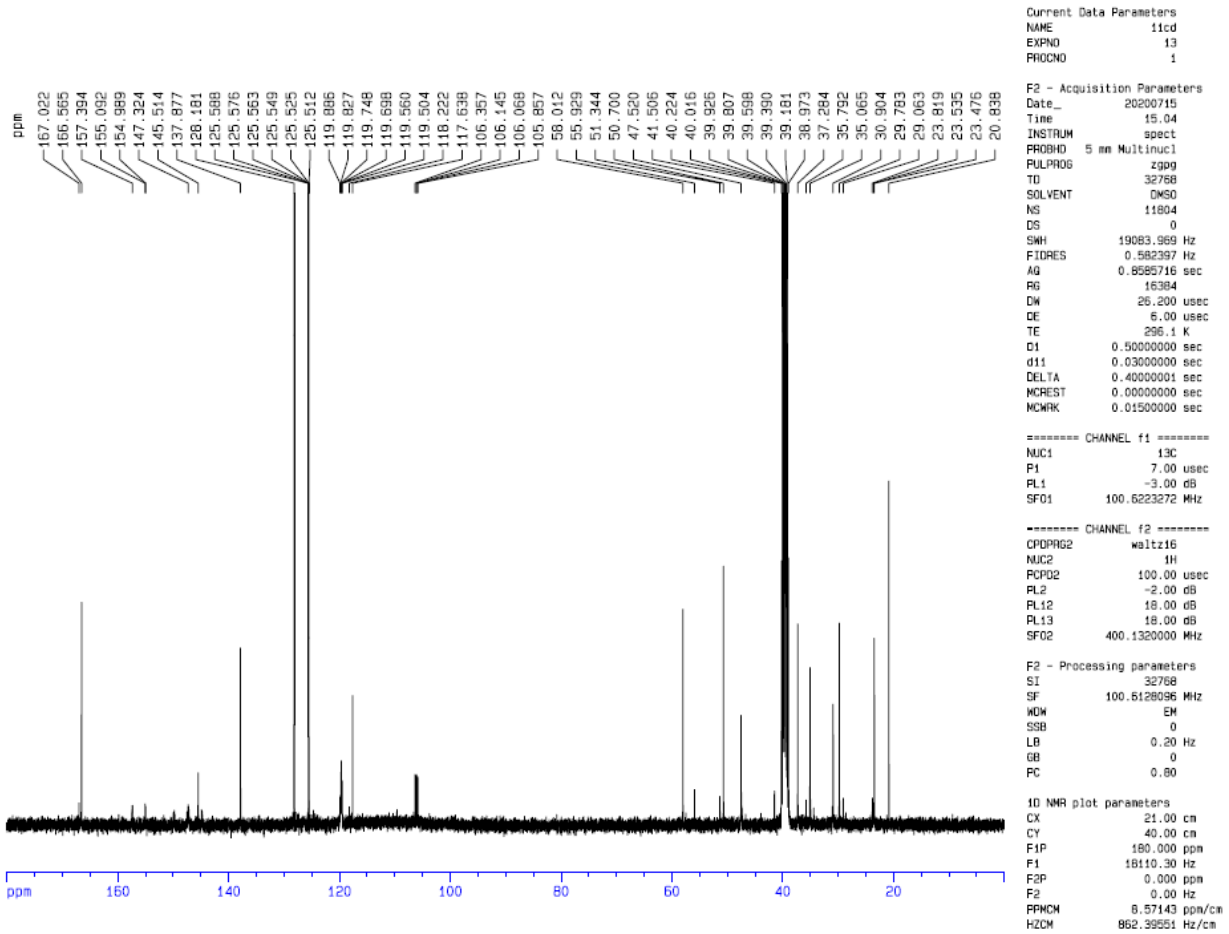
Supplementary material 1

12c,d

^{1}H NMR



^{13}C{^{1}H} NMR




```
Current Data Parameters
NAME                  11cd
EXPNO                   13
PROCNO                   1

F2 - Acquisition Parameters
Date_              20200715
Time                  15.04
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PROBHD   5 mm Multinucl
PULPROG               zgpg
TD                   32768
SOLVENT               DMSO
NS                   11804
DS                       0
SWH               19083.969 Hz
FIDRES            0.582397 Hz
AQ                0.8585716 sec
RG                   16384
DW                  26.200 usec
DE                   6.00 usec
TE                  296.1 K
D1                0.50000000 sec
d11               0.03000000 sec
DELTA             0.40000001 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                    7.00 usec
PL1                  -3.00 dB
SFO1           100.6223272 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                    1H
PCPD2                100.00 usec
PL2                  -2.00 dB
PL12                 18.00 dB
PL13                 18.00 dB
SFO2           400.1320000 MHz

F2 - Processing parameters
SI                   32768
SF             100.6128096 MHz
WDW                     EM
SSB                      0
LB                    0.20 Hz
GB                       0
PC                    0.80

1D NMR plot parameters
CX                   21.00 cm
CY                   40.00 cm
F1P                180.000 ppm
F1                 18110.30 Hz
F2P                  0.000 ppm
F2                    0.00 Hz
PPMCM              8.57143 ppm/cm
HZCM             862.39551 Hz/cm
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