

Supplementary Information

Design, Synthesis, and Biological Evaluation of Procaine-Based Triazole-Isoxazoline Hybrids as Selective PI3K/mTOR Inhibitors for Esophageal Cancer Therapy: An *in-vitro*, and *in-vivo* study

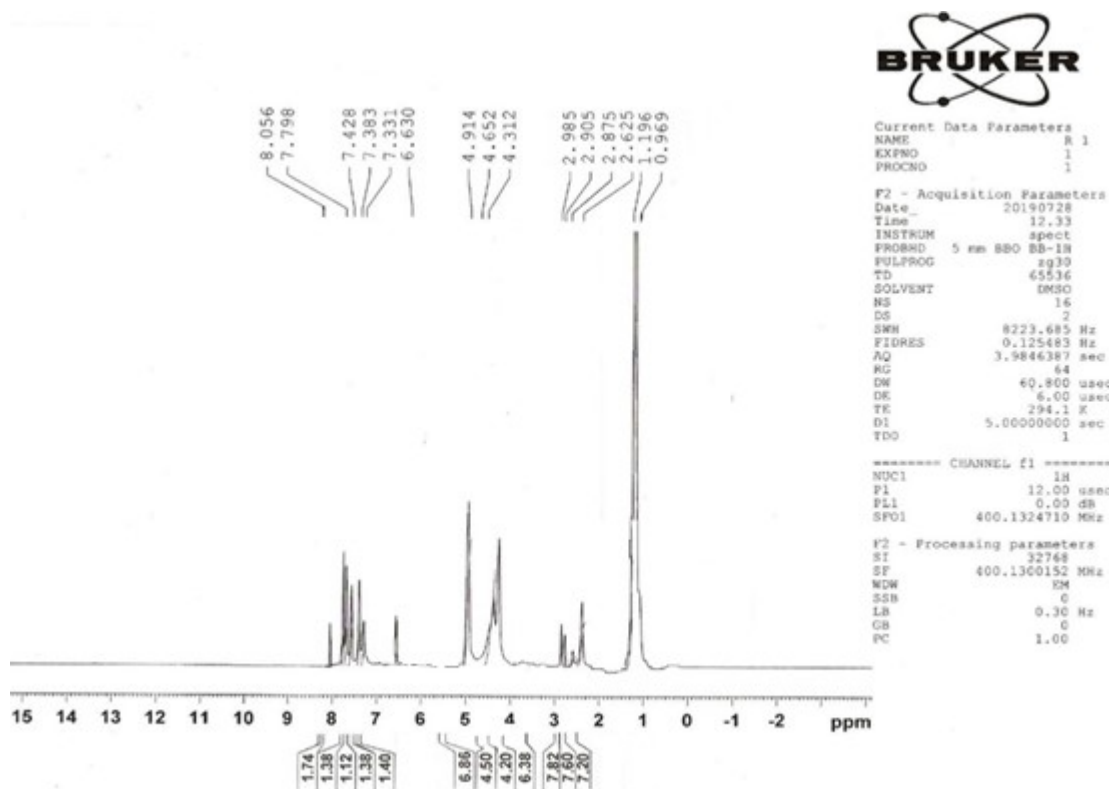
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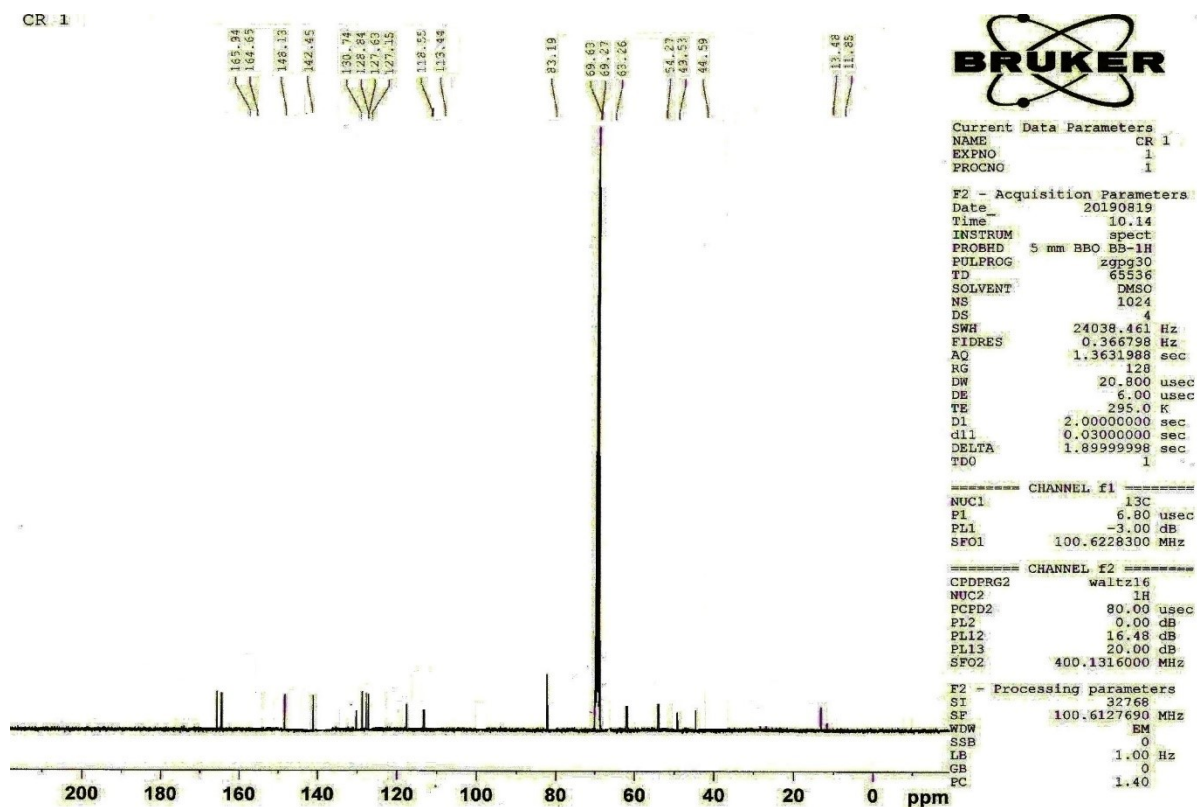
Corresponding author

Chunyang Zhang

Email: zcy198200@outlook.com



¹³C NMR of 8a

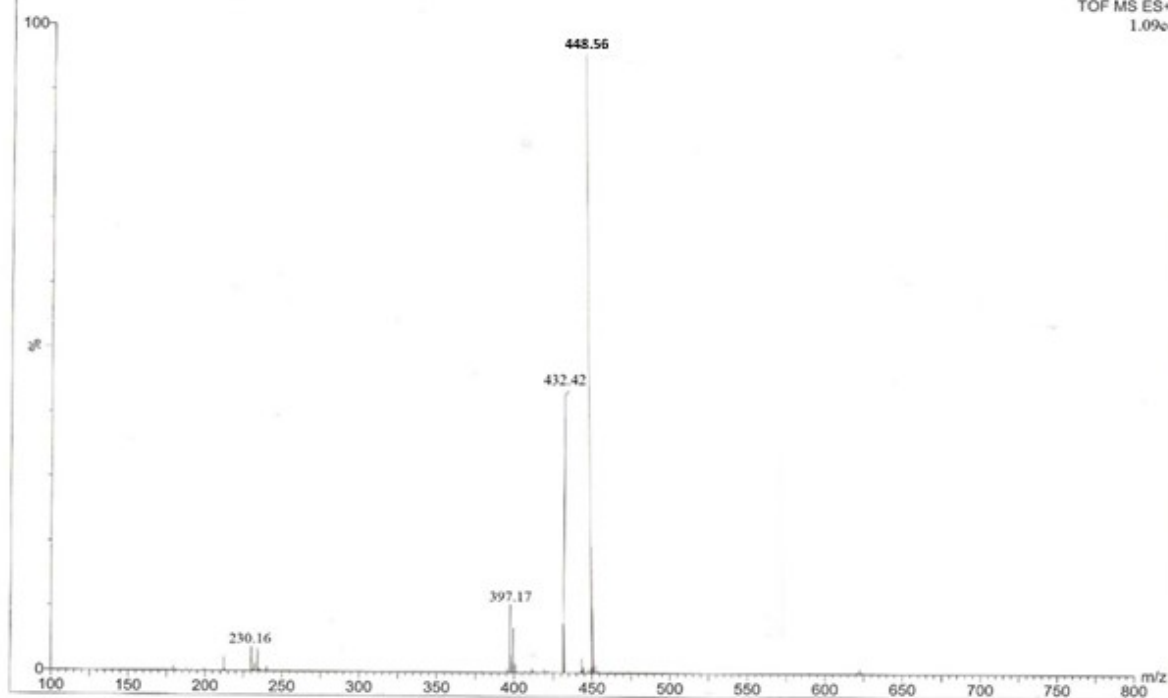


Mass of 8a

28-Oct-2019 10:23:04 CR 1

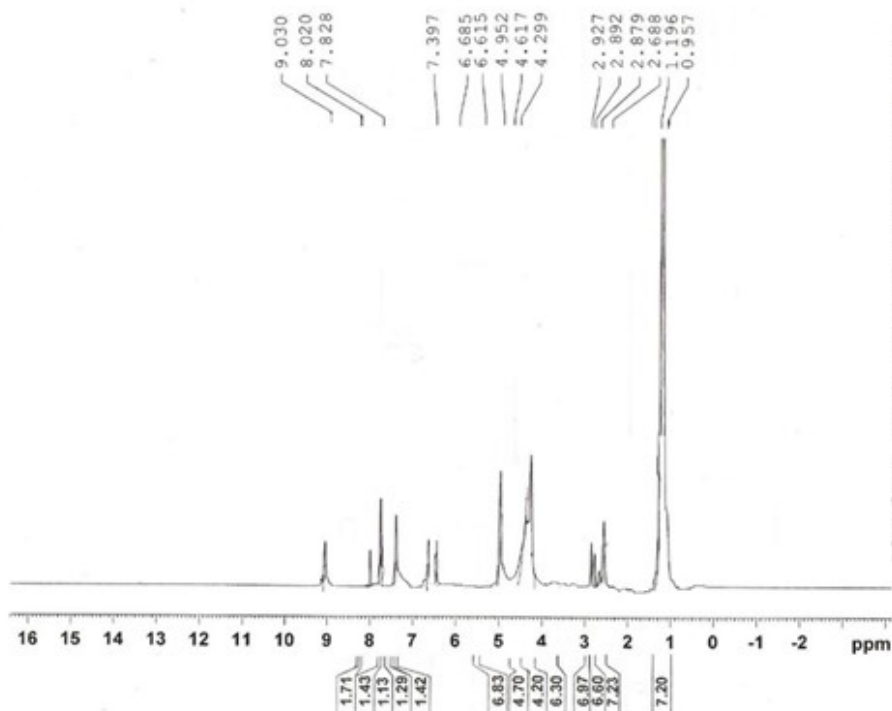
PD6 5 (0.093) Sm (Min, 1x3.00); Sb (1.80.00); Cm (2.12)

TOF MS ES+
1.09e4



^1H NMR of 8b

R 6



Current Data Parameters
NAME R 6
EXPNO 1
PROCNO 1

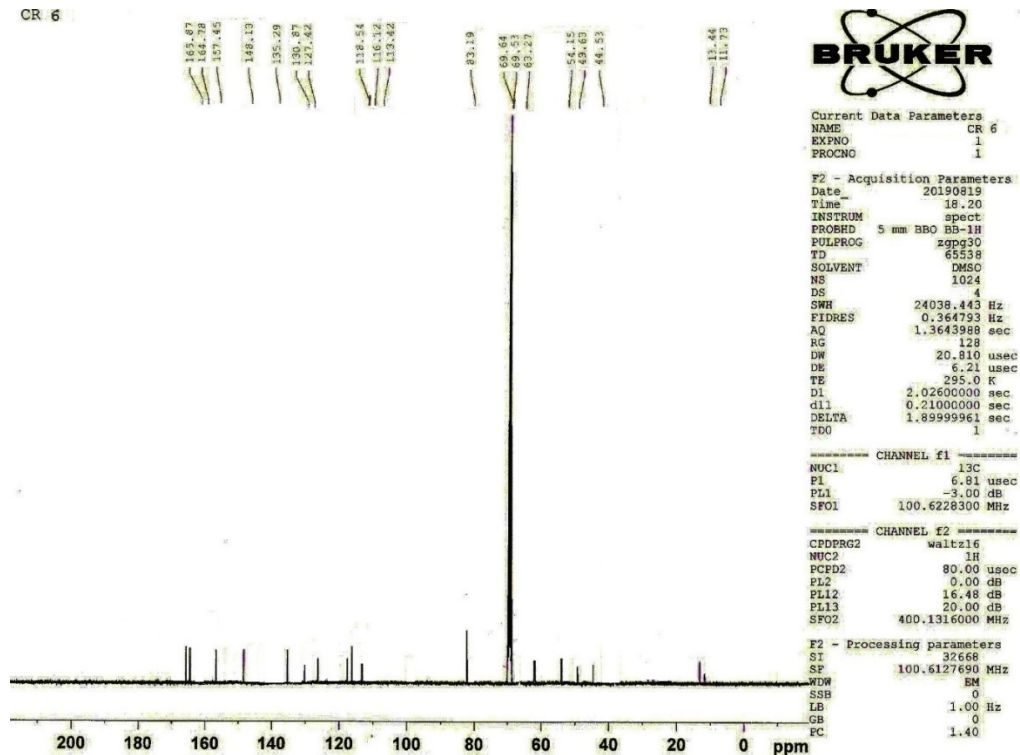
F2 - Acquisition Parameters
Date 20190729
Time 12.29
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65235
SOLVENT DMSO
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9826547 sec
RG 64
DW 60.840 usec
DE 6.00 usec
TE 294.1 K
D1 5.04000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1360152 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

 ^{13}C NMR of 8b

CR 6



Current Data Parameters
NAME CR 6
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20190819
Time 18.20
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65538
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.443 Hz
FIDRES 0.364793 Hz
AQ 1.3643988 sec
RG 128
DW 20.810 usec
DE 6.21 usec
TE 295.0 K
D1 2.02600000 sec
d11 0.21000000 sec
DELTA 1.89999961 sec
TD0 1

===== CHANNEL f1 =====
NUC1 13C
P1 6.81 usec
PL1 -3.00 dB
SFO1 100.6228300 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 16.48 dB
PL13 20.00 dB
SFO2 400.1316000 MHz

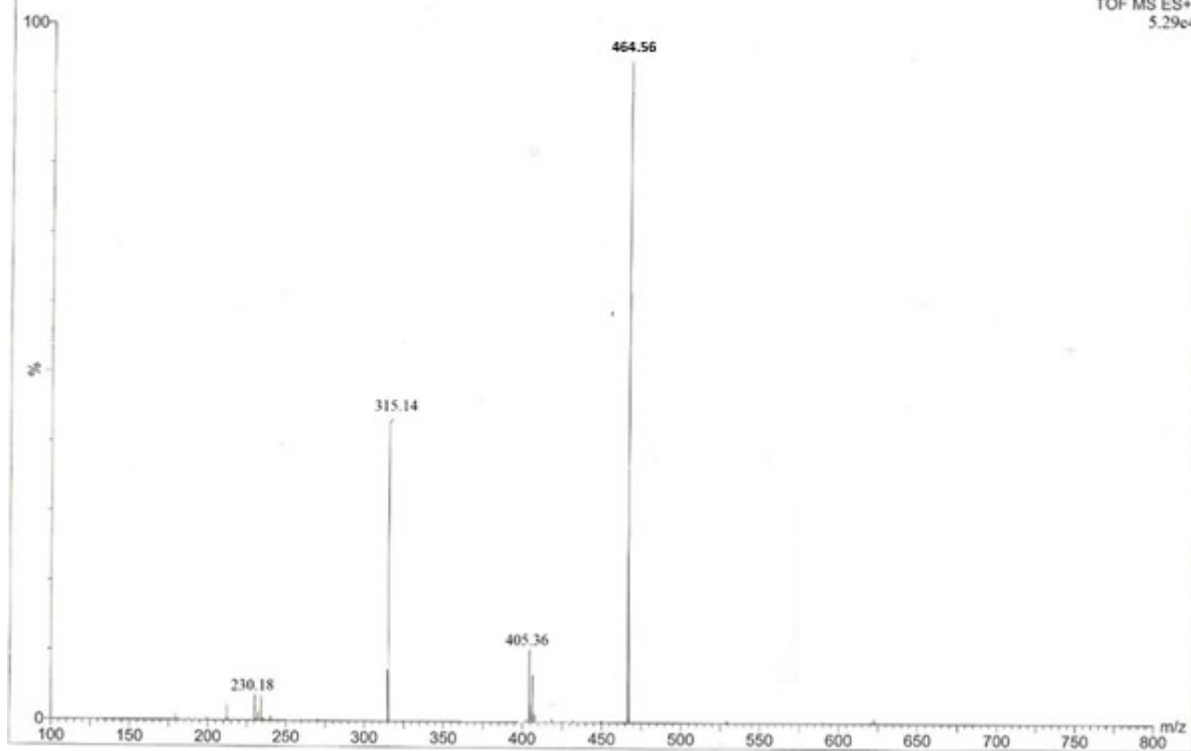
F2 - Processing parameters
SI 32668
SP 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Mass of 8b

28-Oct-2019 18:45:09 CR 6

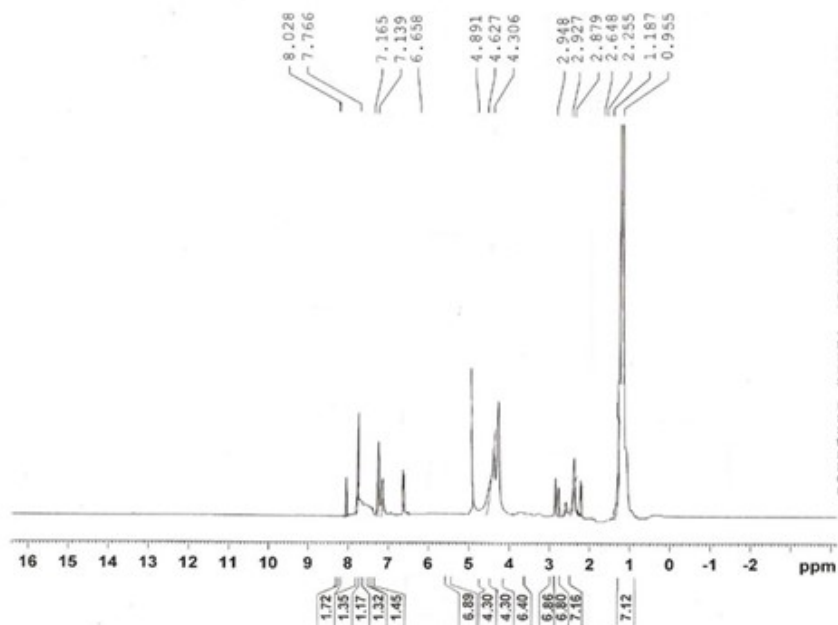
PD7 3 (0.086) Sm (Mn, 1x3.26); Sb (1.92.21); Cm (2.14)

TOF MS ES+
5.29e4



^1H NMR of 8c

R 2



Current Data Parameters
NAME R 2
EXPNO 1
PROCNO 1

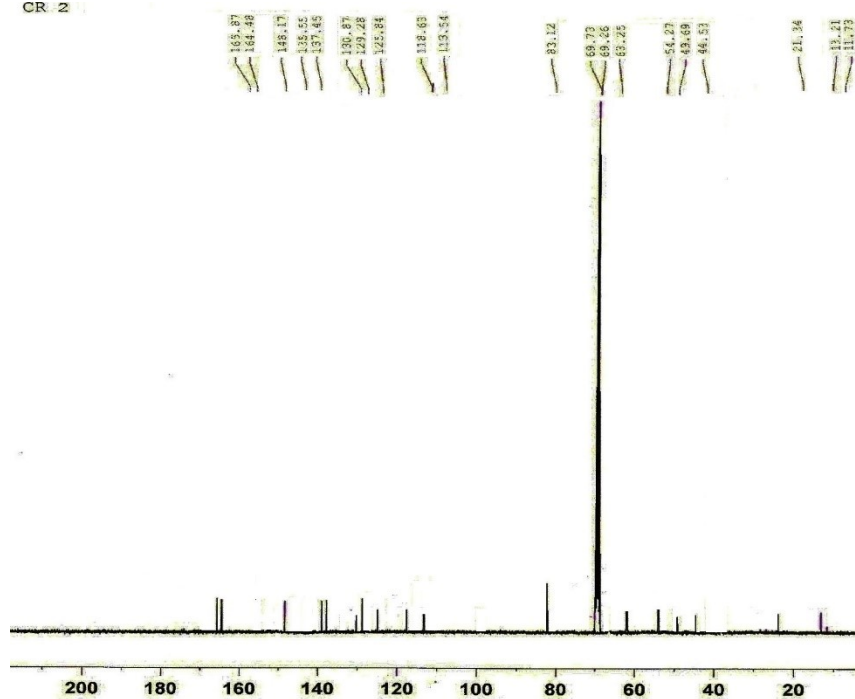
F2 - Acquisition Parameters
Date_ 20190728
Time_ 13.48
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8223.682 Hz
FIDRES 0.125483 Hz
AQ 3.9846327 sec
RG 64
DW 60.800 usec
DE 6.00 usec
TE 294.1 K
D1 5.0000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300132 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

¹³C NMR of 8c

CR 2



Current Data Parameters
NAME CR 2
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20190819
Time_ 12.08
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.462 Hz
FIDRES 0.362798 Hz
AQ 1.3632982 sec
RG 128
DW 20.800 usec
DE 6.00 usec
TE 295.0 K
D1 2.02000000 sec
d11 0.23000000 sec
DELTA 1.89999928 sec
TD0 1

===== CHANNEL f1 =====
NUC1 13C
P1 6.90 usec
PL1 -3.00 dB
SFO1 100.6228300 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 16.48 dB
PL13 20.00 dB
SFO2 400.1316000 MHz

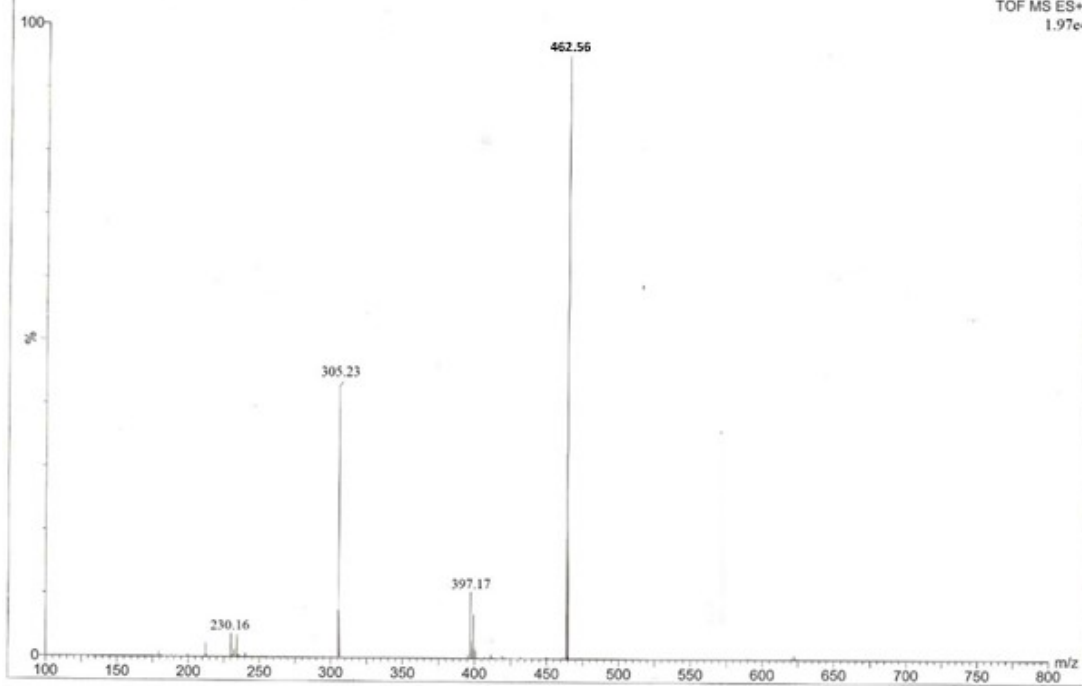
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Mass of 8c

28-Oct-2019 11:38:12 CR 2

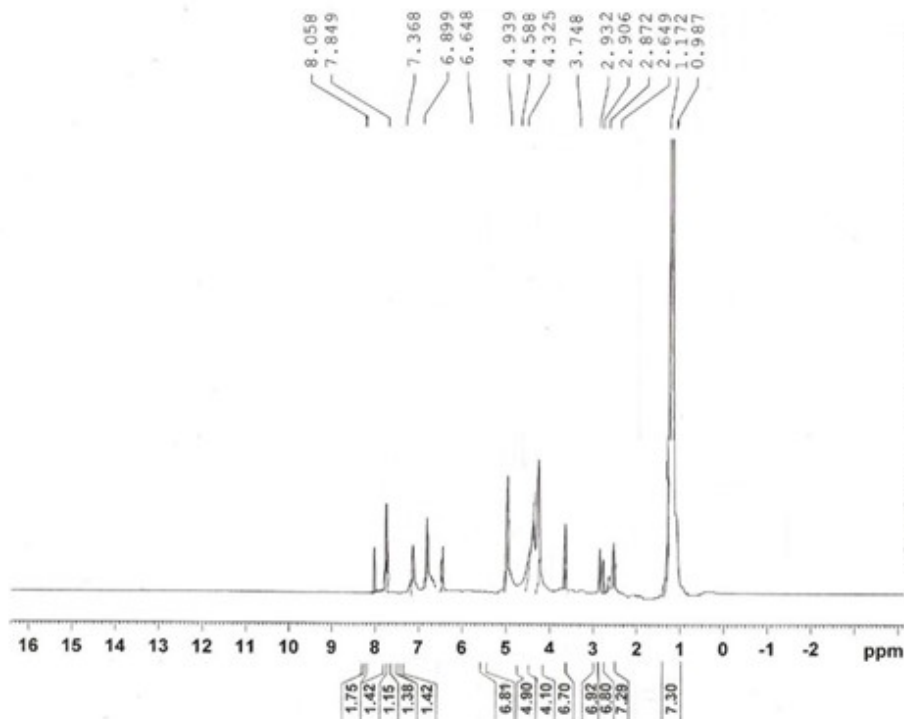
PD2 4 (0.091) Sm (Mn, 1x3.02); Sb (1.82.01); Cm (2.25)

TOF MS ES+
1.97e4



^1H NMR of 8d

R 7



Current Data Parameters
 NAME R 7
 EXPNO 1
 PROCNO 1

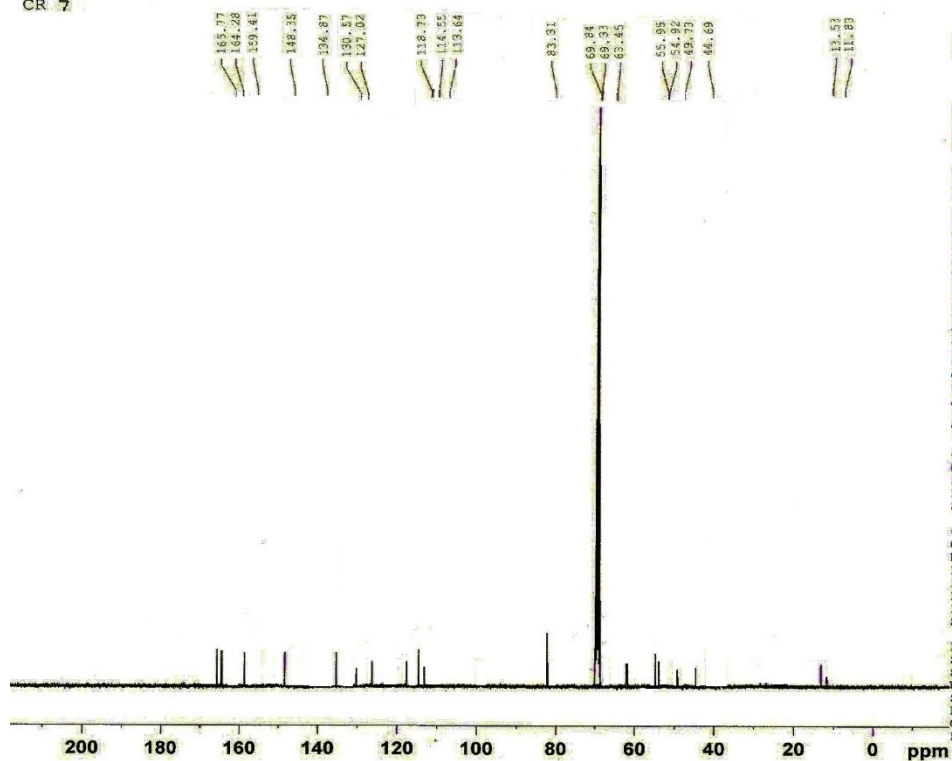
F2 - Acquisition Parameters
 Date 20190729
 Time 14.20
 INSTRUM spect
 PROBHD 5 mm BBO BB-1H
 PULPROG zg30
 TD 65735
 SOLVENT DMSO
 NS 16
 DS 2
 SWH 8223.785 Hz
 FIDRES 0.125483 Hz
 AQ 3.9876598 sec
 RG 64
 DW 60.840 usec
 DE 6.00 usec
 TE 294.1 K
 D1 5.04000000 sec
 TDO 1

===== CHANNEL f1 =====
 NUC1 1H
 P1 12.00 usec
 PL1 0.00 dB
 SFO1 400.1324710 MHz

F2 - Processing parameters
 SI 32768
 SF 400.1360152 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

¹³C NMR of 8d

CR 7



Current Data Parameters
 NAME CR 7
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date 20190819
 Time 19.38
 INSTRUM spect
 PROBHD 5 mm BBO BB-1H
 PULPROG zgpg30
 TD 65535
 SOLVENT DMSO
 NS 1024
 DS 4
 SWH 24038.445 Hz
 FIDRES 0.364793 Hz
 AQ 1.3643965 sec
 RG 128
 DW 20.960 usec
 DE 6.25 usec
 TE 295.0 K
 D1 2.02500000 sec
 d11 0.26000000 sec
 DELTA 1.89999565 sec
 TDO 1

===== CHANNEL f1 =====
 NUC1 13C
 P1 6.95 usec
 PL1 -3.00 dB
 SFO1 100.6228300 MHz

===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 80.00 usec
 PL2 0.00 dB
 PL12 16.48 dB
 PL13 20.00 dB
 SFO2 400.1316000 MHz

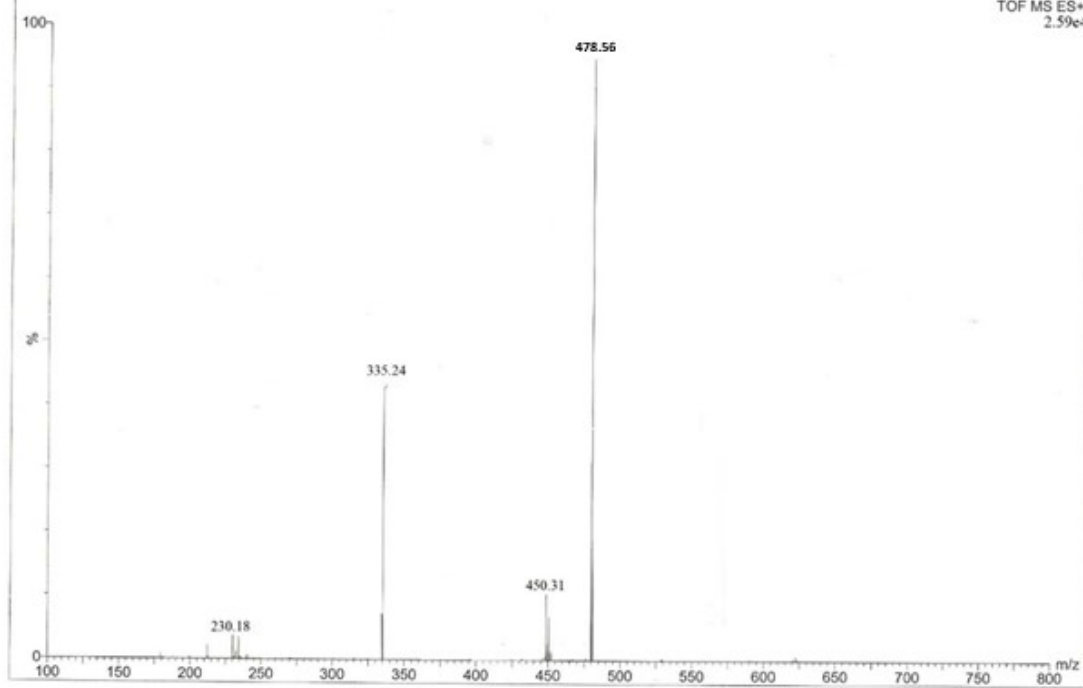
F2 - Processing parameters
 SI 32768
 SF 100.6127690 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

Mass of 8d

28-Oct-2019 20:15:46 CR 7

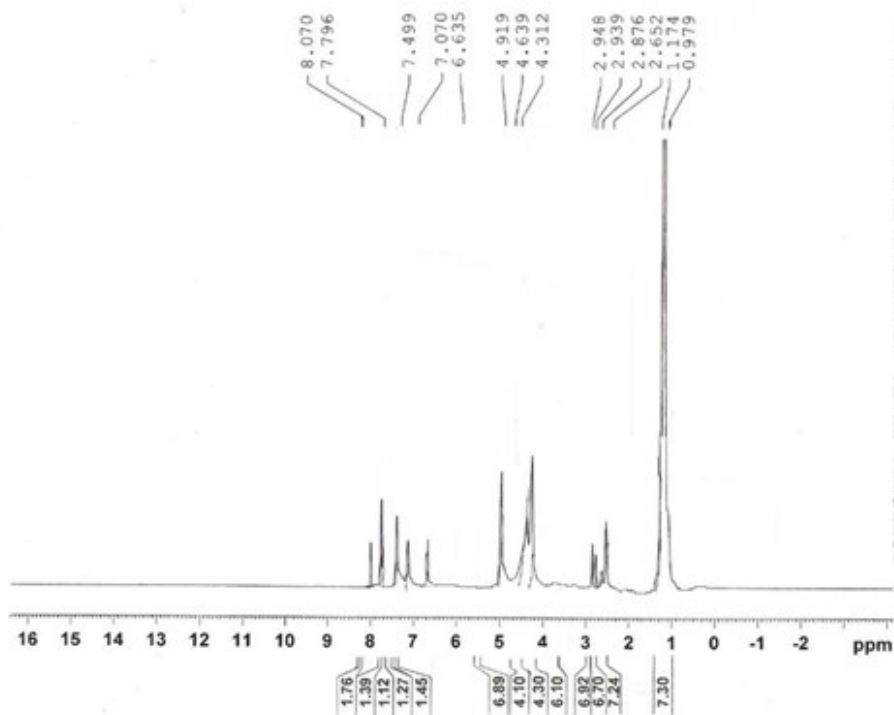
PD2 4(0.091) Sm (Mn, 1x3.18); Sb (1.94,28); Cm (2.18)

TOF MS ES+
2.59e4



^1H NMR of 8e

R 5



Current Data Parameters
 NAME R 5
 EXPNO 1
 PROCNO 1

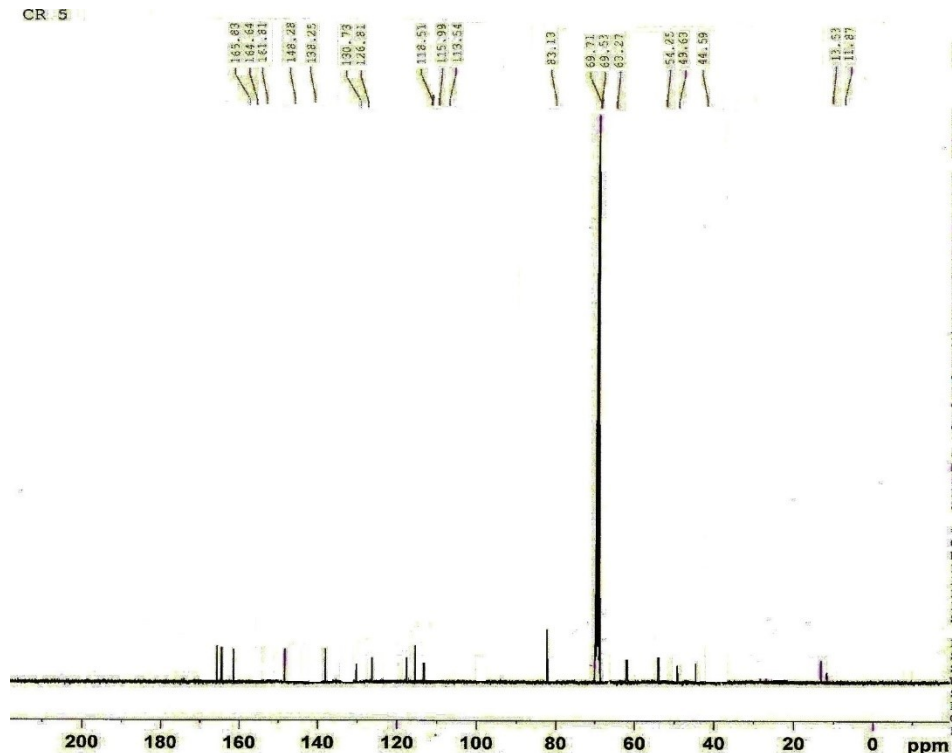
F2 - Acquisition Parameters
 Date 20190729
 Time 10.35
 INSTRUM spect
 PROBHD 5 mm BBO BB-1H
 PULPROG zg30
 TD 65535
 SOLVENT DMSO
 NS 16
 DS 2
 SWH 8223.685 Hz
 FIDRES 0.125483 Hz
 AQ 3.9856587 sec
 RG 64
 DW 60.850 usec
 DE 8.00 usec
 TE 294.1 K
 D1 5.05000000 sec
 TDO 1

===== CHANNEL f1 =====
 NUC1 1H
 P1 12.00 usec
 PL1 0.00 dB
 SFO1 400.1324710 MHz

F2 - Processing parameters
 SI 32768
 SF 400.1360152 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

 ^{13}C NMR of 8e

CR 5



Current Data Parameters
 NAME CR 5
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date 20190819
 Time 16.36
 INSTRUM spect
 PROBHD 5 mm BBO BB-1H
 PULPROG zgpg30
 TD 65535
 SOLVENT DMSO
 NS 1024
 DS 4
 SWH 24038.443 Hz
 FIDRES 0.364793 Hz
 AQ 1.3643998 sec
 RG 128
 DW 20.820 usec
 DE 6.20 usec
 TE 295.0 K
 D1 2.02100000 sec
 d11 0.26000000 sec
 DELTA 1.89999968 sec
 TDO 1

===== CHANNEL f1 =====
 NUC1 13C
 P1 6.86 usec
 PL1 -3.00 dB
 SFO1 100.6228300 MHz

===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 80.00 usec
 PL2 0.00 dB
 PL12 16.48 dB
 PL13 20.00 dB
 SFO2 400.1316000 MHz

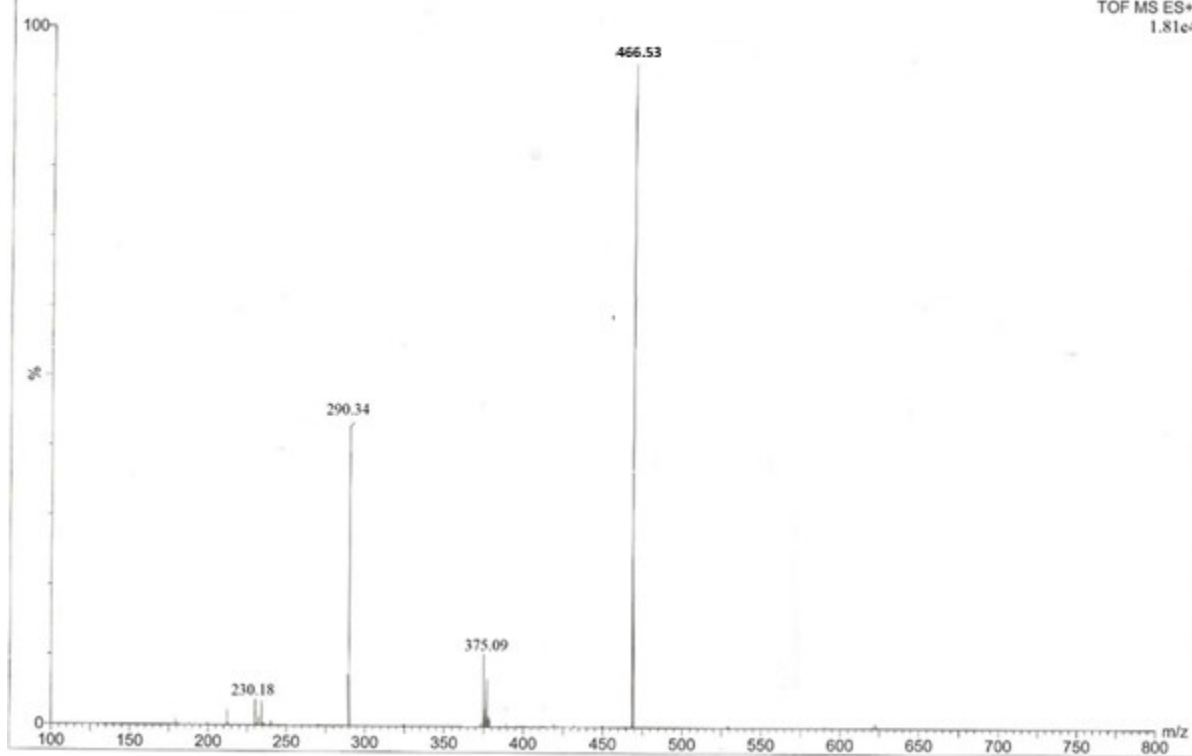
F2 - Processing parameters
 SI 32668
 SF 100.6127690 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

Mass of 8e

28-Oct-2019 16:12:52 CR 5

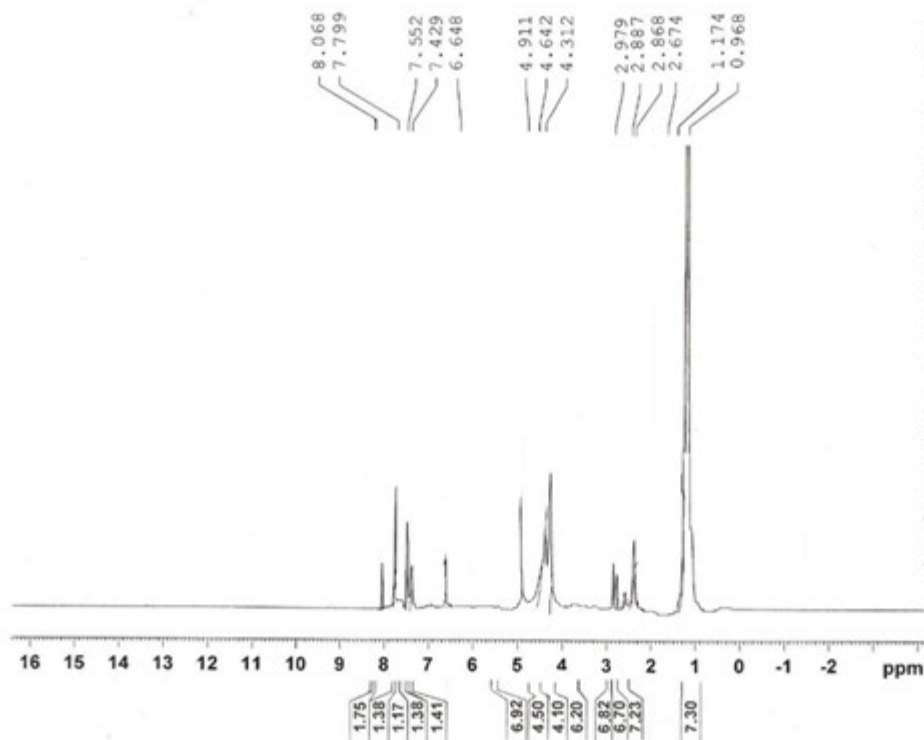
PD5 6 (0.092) Sm (Mn, 1x3.12); Sb (1.87.18); Cm (2.09)

TOF MS ES+
1.81e4



^1H NMR of 8f

R 3



Current Data Parameters
NAME R 1
EXPNO 1
PROCNO 1

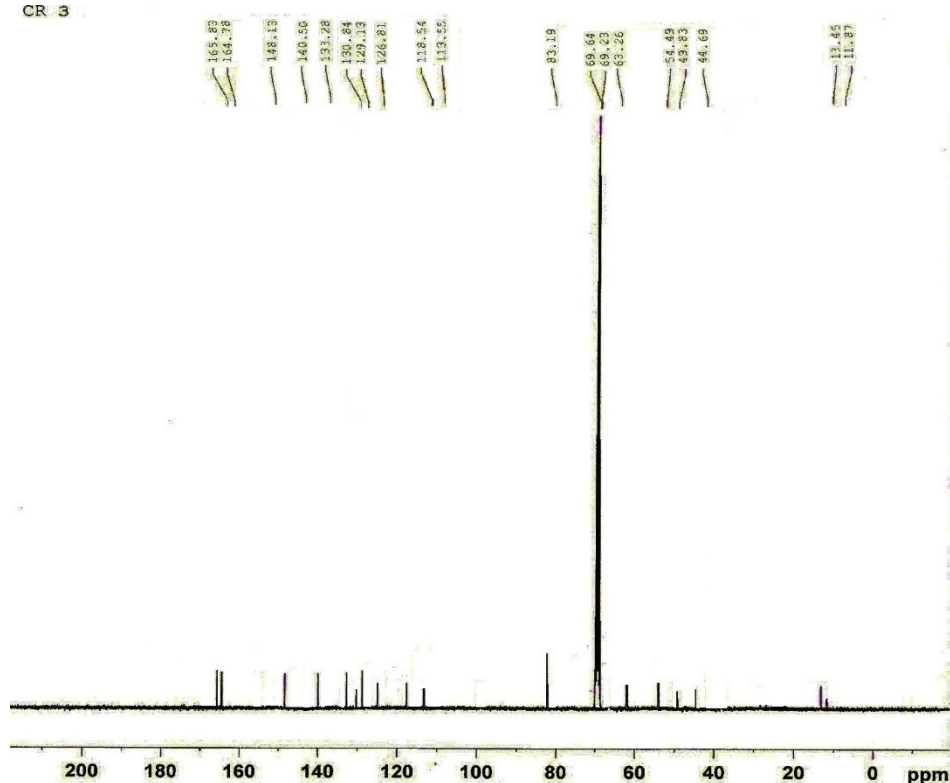
F2 - Acquisition Parameters
Date_ 20190728
Time 14.53
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8223.682 M
FIDRES 0.125483 M
AQ 3.9846537 s
RG 64
DW 60.800 u
DE 6.00 u
TE 294.1 K
D1 5.00000000 s
TD0 1

----- CHANNEL f1 -----
NUC1 1H
P1 12.00 u
PL1 0.00 dB
SFO1 400.1324710 M

F2 - Processing parameter
SI 32768
SF 400.1300152 M
WDW EM
SSB 0
LB 0.30 H
GB 0
PC 1.00

 ^{13}C NMR of 8f

CR 3



Current Data Parameters
NAME CR 3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20190819
Time 13.38
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.463 Hz
FIDRES 0.363798 Hz
AQ 1.3633983 sec
RG 128
DW 20.800 usec
DE 6.00 usec
TE 295.0 K
D1 2.03000000 sec
d11 0.21000000 sec
DELTA 1.89999918 sec
TD0 1

----- CHANNEL f1 -----
NUC1 13C
P1 6.81 usec
PL1 -3.00 dB
SFO1 100.6228300 MHz

----- CHANNEL f2 -----
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 16.48 dB
PL13 20.00 dB
SFO2 400.1316000 MHz

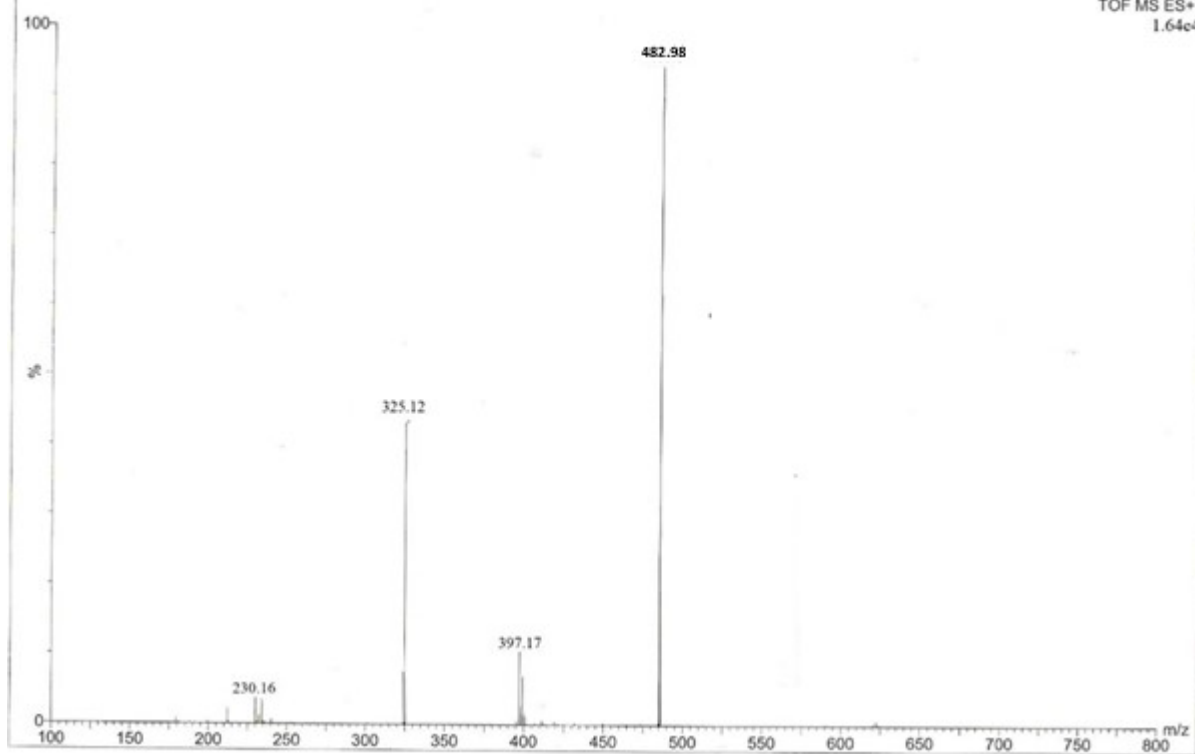
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW BM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Mass of 8f

28-Oct-2019 13:18:52 CR 3

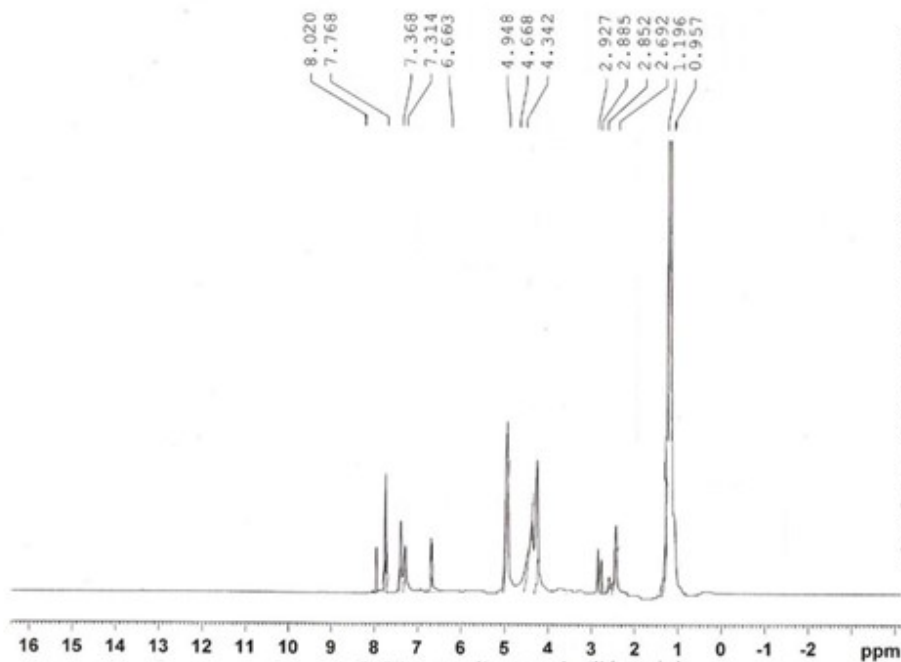
PD3 5 (0.095) Sm (Mn, 1x3.08); Sb (1.89.06); Cm (2.45)

TOF MS ES+
1.64e4



^1H NMR of 8g

R 4



Current Data Parameters
NAME R 4
EXPNO 1
PROCNO 1

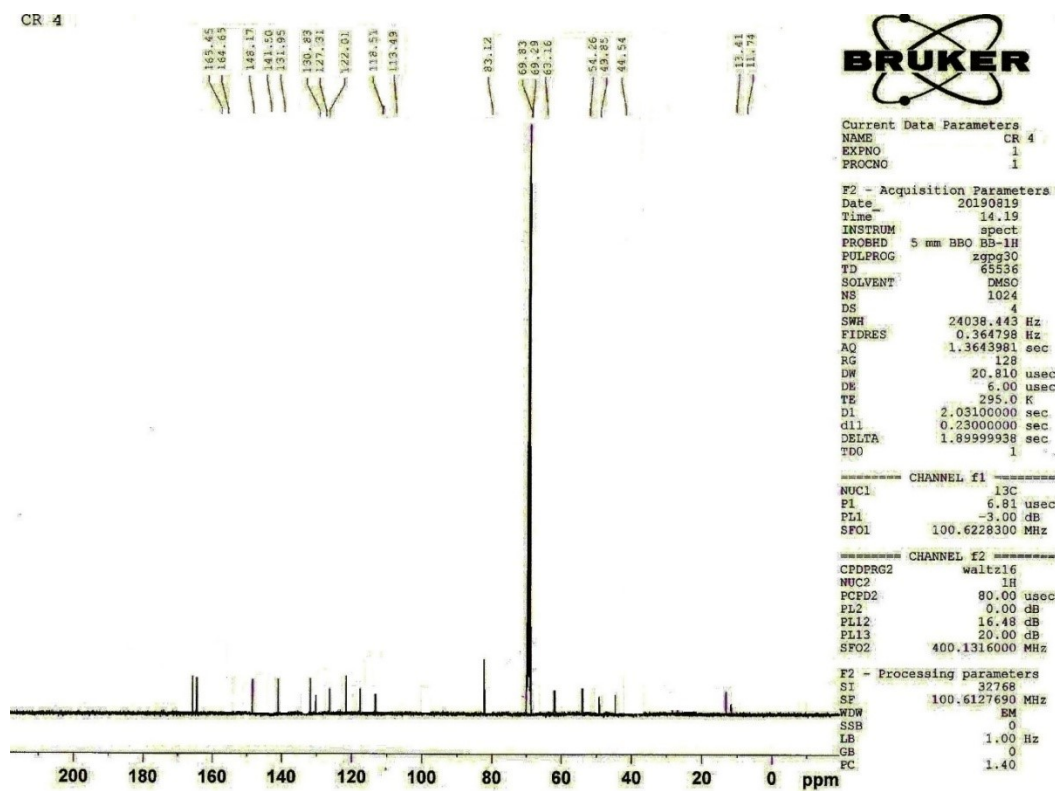
F2 - Acquisition Parameters
Date 20190728
Time 16.37
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846487 sec
RG 64
DW 60.820 usec
DE 6.00 usec
TE 294.1 K
D1 5.02000000 sec
TDO 1

===== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1360152 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

 ^{13}C NMR of 8g

CR 4



Current Data Parameters
NAME CR 4
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20190819
Time 14.19
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.443 Hz
FIDRES 0.364798 Hz
AQ 1.3643981 sec
RG 128
DW 20.810 usec
DE 6.00 usec
TE 295.0 K
D1 2.03100000 sec
d11 0.23000000 sec
DELTA 1.89999938 sec
TDO 1

===== CHANNEL f1 =====
NUC1 ^{13}C
P1 6.81 usec
PL1 -3.00 dB
SFO1 100.6228300 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 16.48 dB
PL13 20.00 dB
SFO2 400.1316000 MHz

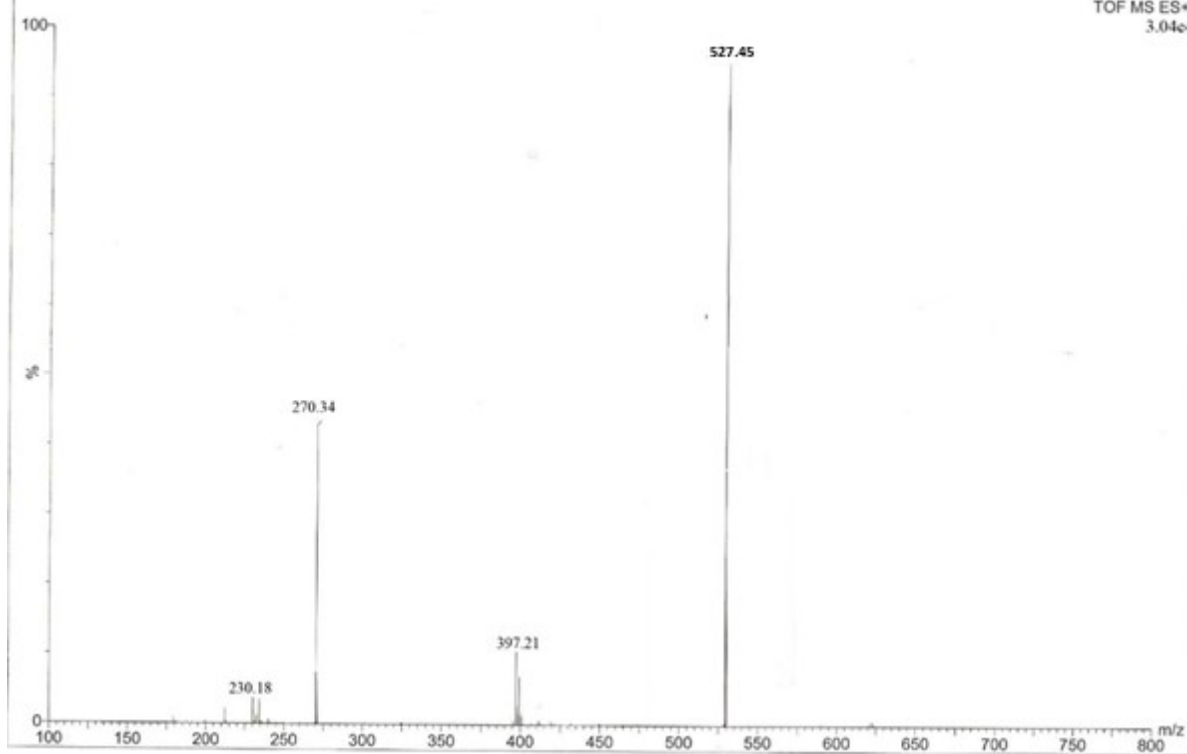
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Mass of 8g

28-Oct-2019 14:56:02 CR 4

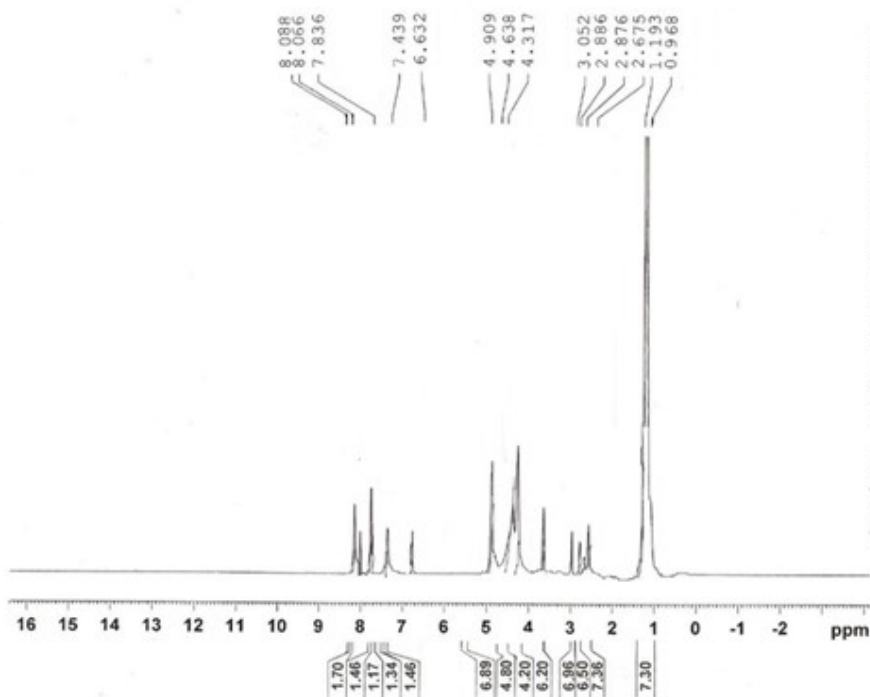
PD4 1 (0.089) Sm (Mn, 1x3.04); Sb (1,82.07); Cm (2.03)

TOF MS ES+
3.04e4



^1H NMR of 8h

R 8



Current Data Parameters
NAME R 8
EXPNO 1
PROCNO 1

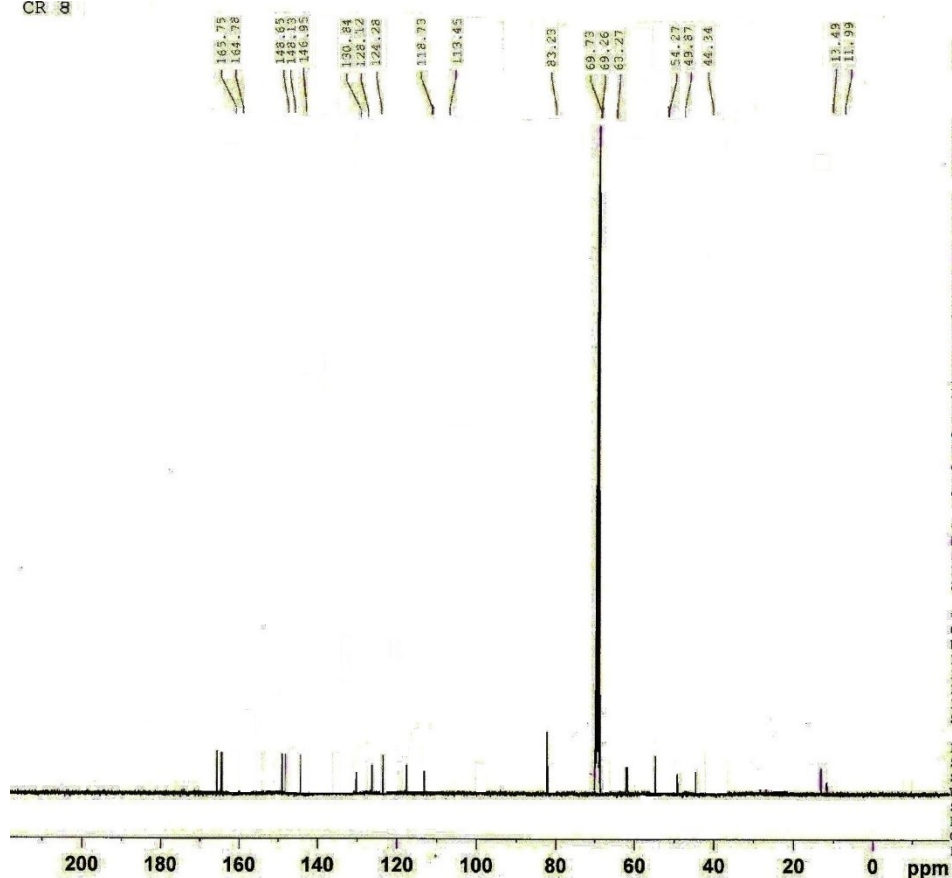
F2 - Acquisition Parameters
Date_ 20190729
Time_ 16.28
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65635
SOLVENT DMSO
NS 16
DS 2
SWH 8223.786 Hz
FIDRES 0.125463 Hz
AQ 3.9676698 sec
RG 64
DW 60.846 usec
DE 6.00 usec
TE 294.1 K
D1 5.04600000 sec
TDO 1

----- CHANNEL f1 -----
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1360152 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

¹³ C NMR of 8h

CR 8



Current Data Parameters
NAME CR 8
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20190819
Time_ 22.35
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.445 Hz
FIDRES 0.364793 Hz
AQ 1.3643663 sec
RG 128
DW 20.863 usec
DE 6.35 usec
TE 295.0 K
D1 2.02800000 sec
d11 0.35000000 sec
DELTA 1.89999535 sec
TDO 1

----- CHANNEL f1 -----
NUC1 13C
P1 6.86 usec
PL1 -3.00 dB
SFO1 100.6228600 MHz

----- CHANNEL f2 -----
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 16.46 dB
PL13 20.00 dB
SFO2 400.1316000 MHz

F2 - Processing parameters
SI 32669
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Mass of 8h

28-Oct-2019 22:38:59 CR 8

PD1 7(0.082) Sm (Mn, 1x3.23); Sb (1.82.12); Cm (2.23)

TOF MS ES+
2.12e4

