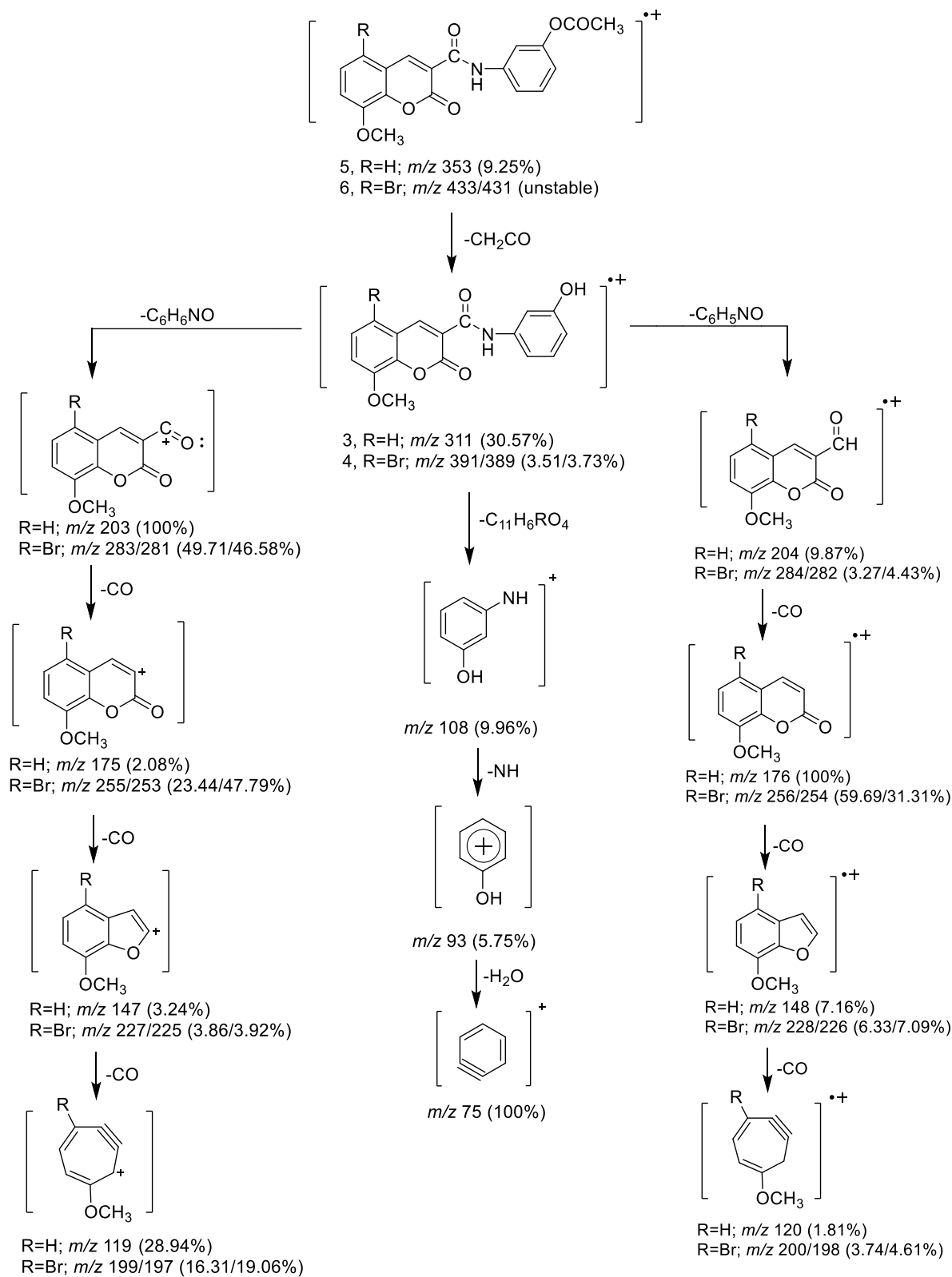


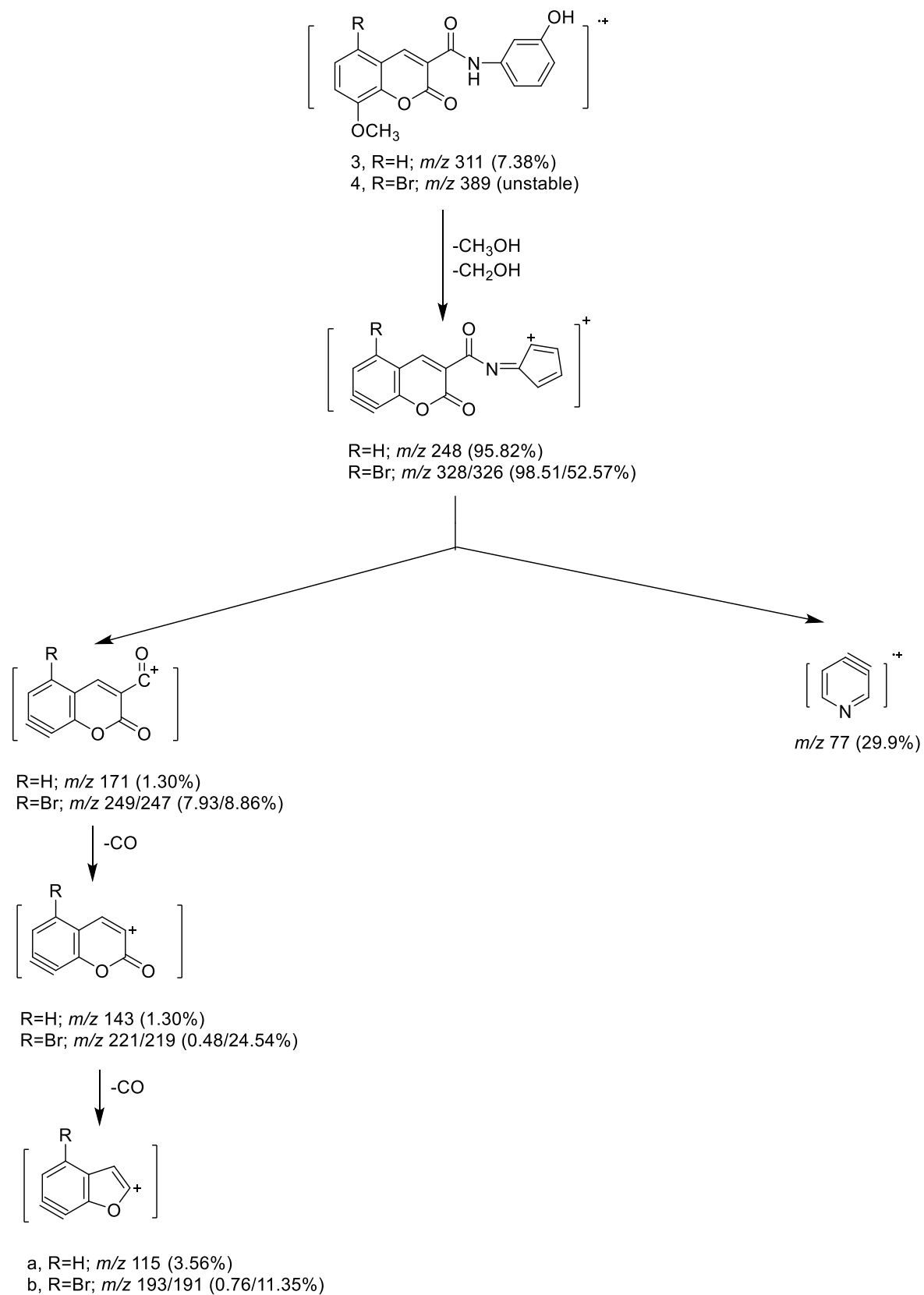
Supplementary Materials

Unveiling the Antitumor Potential of Novel *N*-(Substituted-Phenyl)-8-Methoxycoumarin-3-Carboxamides as Dual Inhibitors of VEGFR2 Kinase and Cytochrome P450 for Targeted Treatment of Hepatocellular Carcinoma

Eman M. Radwan ¹, Eman Abo-Elabass ², Atef E. Abd El-Baky ³, Hussah Abdullah Alshwyeh ^{4,5}, Riyadh A. Almaimani ⁶, Ghassan Almaimani ⁷, Ibrahim Abdel Aziz Ibrahim ⁸, Abdulaziz Albogami ⁹, Mariusz Jaremko ^{10,*}, Samar Z. Alshawwa ¹¹, Essa M. Saied ^{12,13,*}



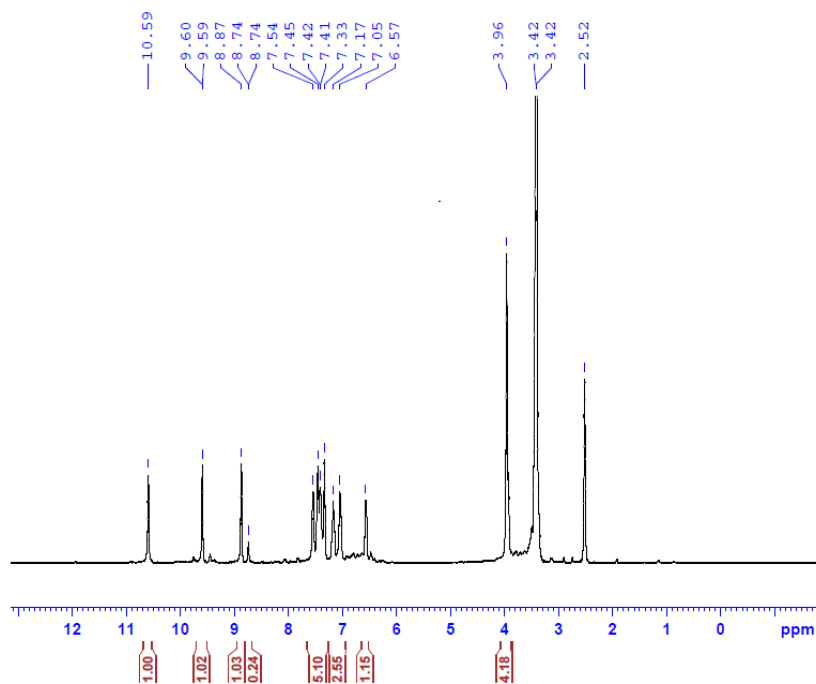
Scheme S1. The fragmentation pathways of compounds **3-6**.



Scheme S2. The fragmentation pathways of compounds **3-4**.

Ibrahim Mohey - COI -110 - Hnmr - T

COMP. 03



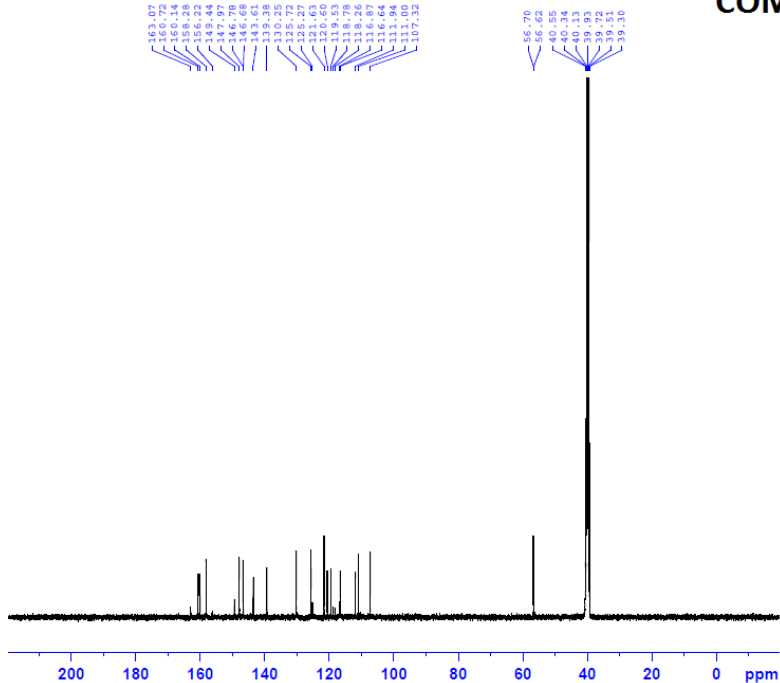
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NAME Ibrahim Mohey - COI -110 - Hnmr - T
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220120
Time_ 11:48 h
INSTRUM spect
PROBHD 1H0618_0945 (1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 4
DS 4
SWH 8012.820 Hz
FIDRES 0.264023 Hz
AQ 4.089465 sec
RG 197.77
DM 20.800 usec
DE 6.50 usec
TE 294.2 K
D1 2.0000000 sec
D11 0.0300000 sec
TDO 1
SFO1 100.624712 MHz
NUC1 13C
P1 10.00 usec
PL1 0.0000000 W
SFO2 400.2024712 MHz
NUC2 1H
PC 1.00

F2 - Processing parameters
SI 32768
SF 100.6203700 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
```

Ibrahim Mohey - COI-110 - Hnmr - T

COMP 03



```
Current Data Parameters
NAME Ibrahim Mohey - COI-110 - Hnmr - T
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220204
Time_ 19:24 h
INSTRUM spect
PROBHD 1H0618_0945 (1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2200
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.363148 sec
RG 197.77
DM 20.800 usec
DE 6.50 usec
TE 294.2 K
D1 2.0000000 sec
D11 0.0300000 sec
TDO 1
SFO1 100.624712 MHz
NUC1 13C
P1 10.00 usec
PL1 0.0000000 W
SFO2 400.201608 MHz
NUC2 1H
CPDPRG2 wait16
PCPD2 90.00 usec
PLM2 13.0000000 W
PLM12 0.29249999 W
PLM13 0.14713000 W

F2 - Processing parameters
SI 32768
SF 100.6203700 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
```

Figure S1. ¹H NMR and ¹³C NMR spectra of compound 3.

hamed-COI110 #574 RT: 1.98 AV: 1 NL: 1.07E5
: (0,0) + c EI Full ms [50.00-500.00]

COMP 03

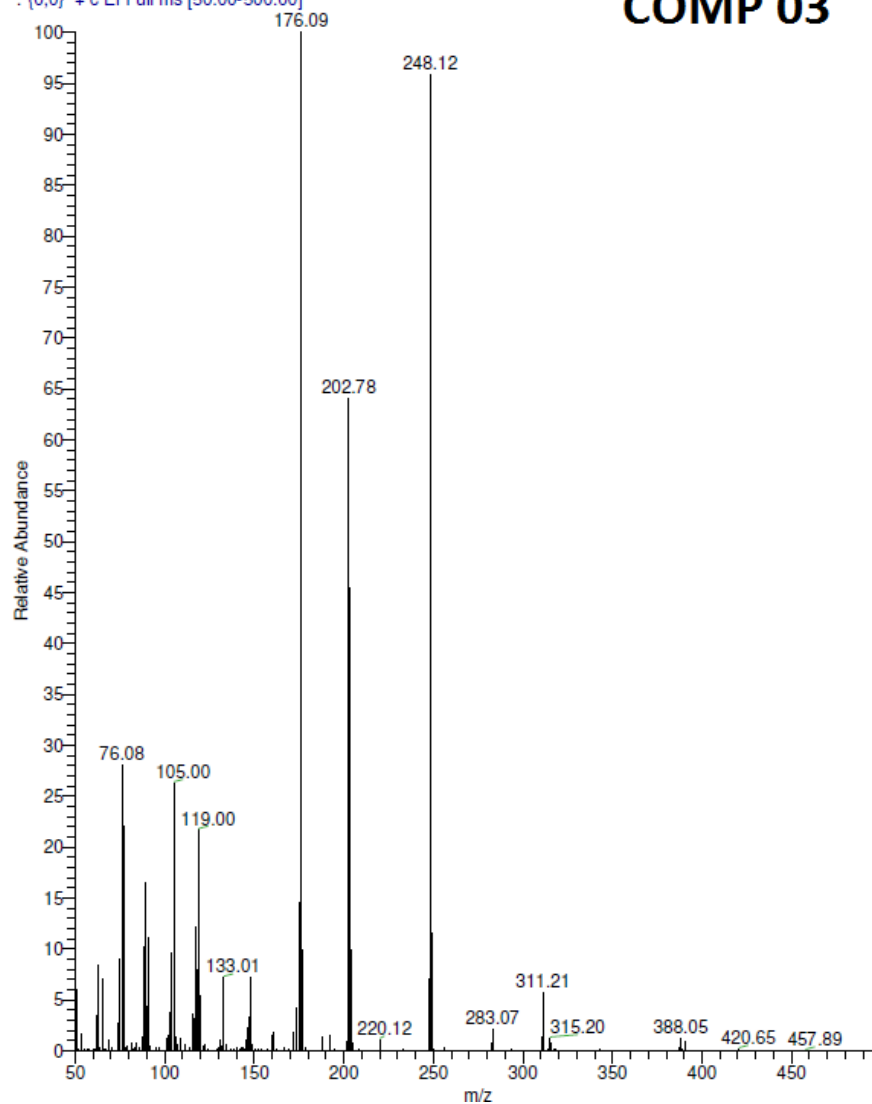


Figure S1b. Mass spectrum of compound 3.

hamed-COI112 #6 RT: 0.05 AV: 1 NL: 5.14E4
Γ: {0,0} + c EI Full ms [50.00-500.00]

COMP 04

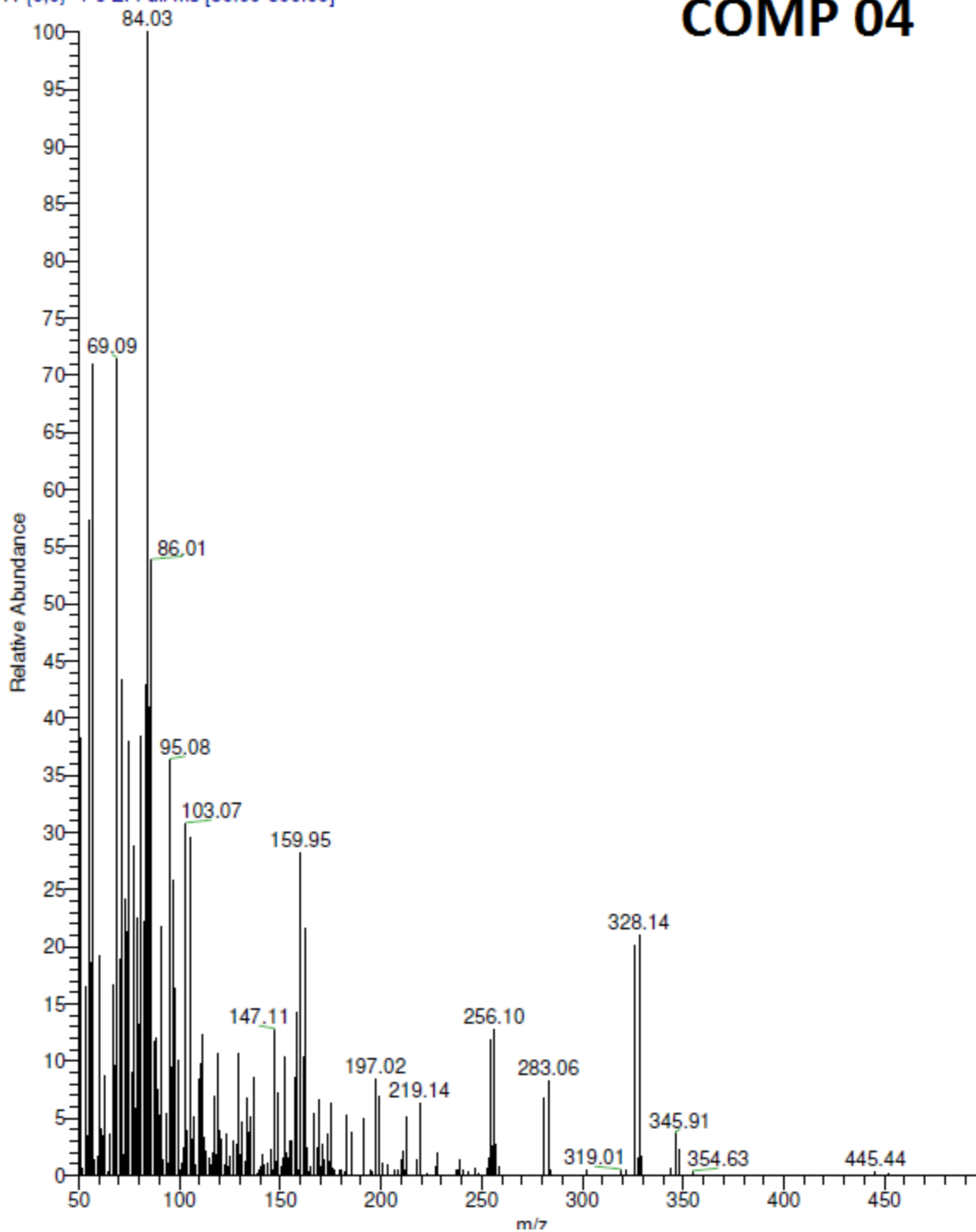
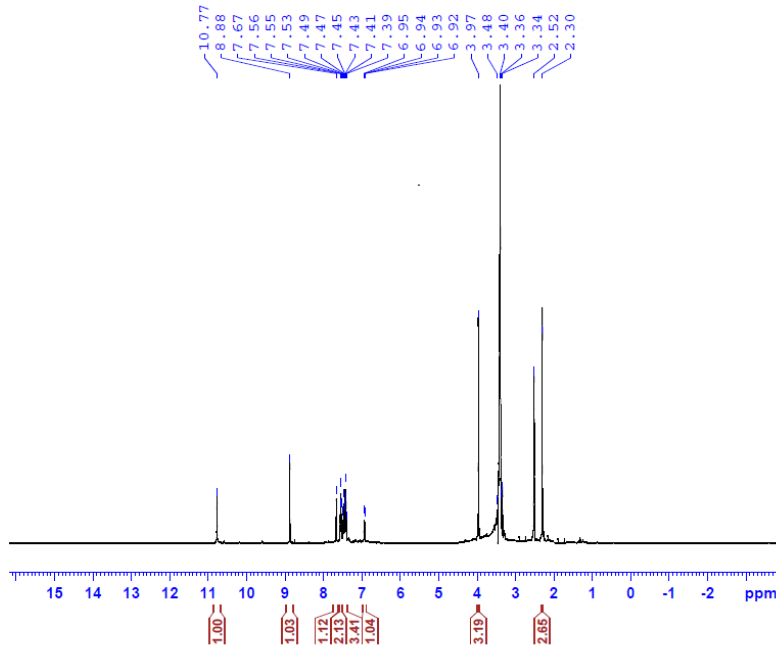


Figure S2. Mass spectrum of compound 4.

COMP 05

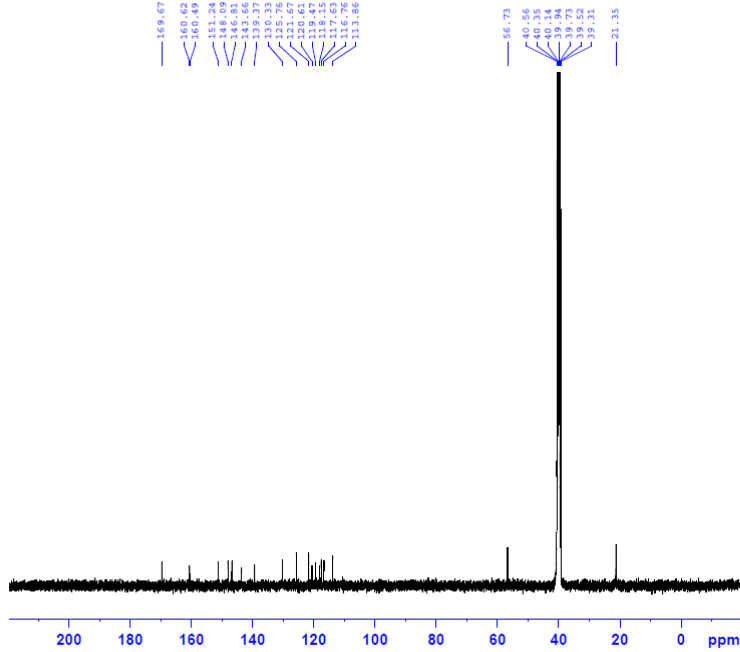
Ibrahim Mohey - COI -111 - Hnmr - T



Current Data Parameters
NAME Ibrahim Mohey - COI -111 - Hnmr - T
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220129
Time 21:09 h
INSTRUM spect
PROBHD Z106618.0946 (1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2
DS 4
SWH 8012.820 Hz
FIDRES 0.266372 Hz
AQ 4.092465 sec
RG 320
SFO 400.1460000 MHz
DE 42.400 usec
TE 293.2 K
D1 1.00000000 sec
TDS
SFO1 400.2024112 MHz
NUC1 13C
P1 13.00000000 usec
PL1 13.00000000 W
F2 - Processing parameters
SI 65536
SF 400.2000000 MHz
WDW EM
SSB 0
LB 0.35 Hz
GB 0
PC 1.00

COMP 05

Ibrahim Mohey - COI-111 - Hnmr - T



Current Data Parameters
NAME Ibrahim Mohey - COI-111 - Hnmr - T
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220204
Time 21:33 h
INSTRUM spect
PROBHD Z106618.0946 (1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2200
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 197.77
SFO 100.6261260 MHz
DE 20.800 usec
TE 294.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TDS
SFO1 100.6404331 MHz
NUC1 13C
P1 10.00000000 usec
PL1 47.00000000 W
SFO2 400.2016008 MHz
NUC2 1H
CPDPRG12 waltz16
PCPD2 80.00 usec
PLM2 13.00000000 W
PLM12 0.29249999 W
PLM13 0.14713000 W
F2 - Processing parameters
SI 65536
SF 100.6303700 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S3. ¹H NMR and ¹³C NMR spectra of compound 5.

named-COI111 #912 RT: 3.13 AV: 1 NL: 9.40E4
: (0,0) + c EI Full ms [50.00-500.00]

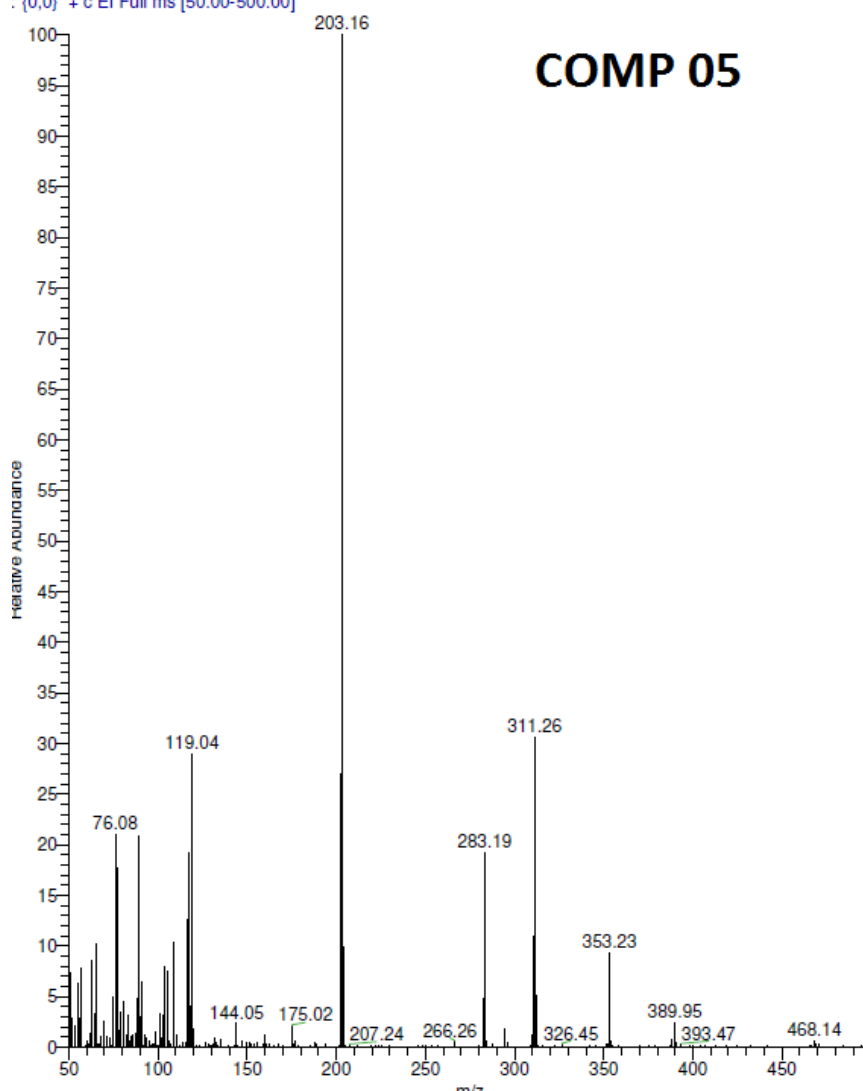
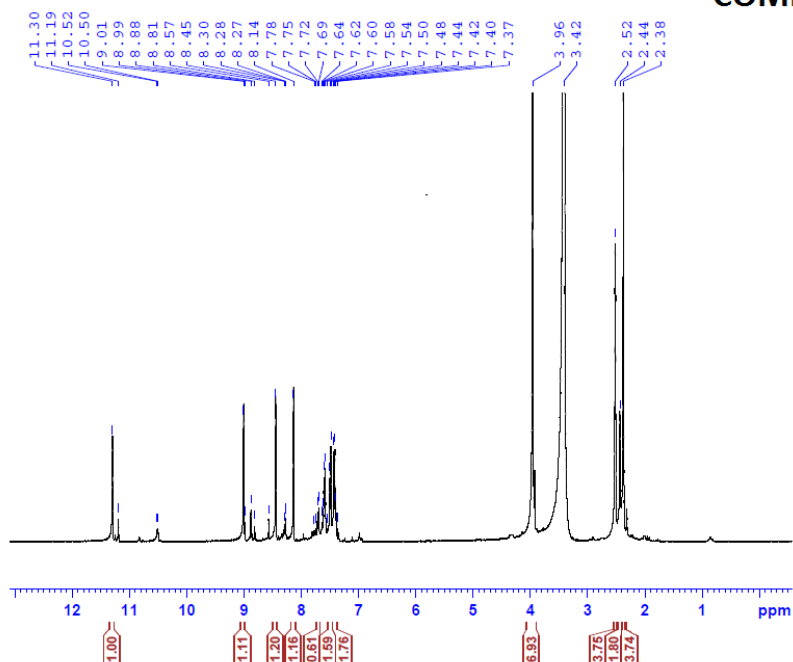


Figure S3b. Mass spectrum of compound **5**.

Ibrahim Mohey - COI-113 - Hnmr - T



COMP 06

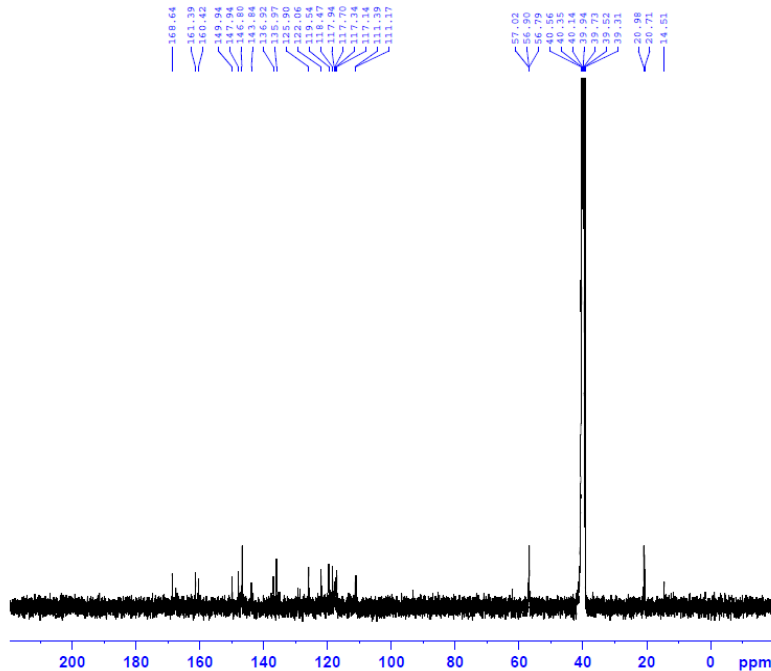


Current Data Parameters
NAME Ibrahim Mohey - COI-113 - Hnmr - T
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220229
Time 11:58 h
INSTRUM spect
PROBHD 5108618_098 (1
PULPROG zgpg30
TD 65536
SOLVENT DMF0
NS 15
DS 4
SWH 8011.800 Hz
FIDRES 0.244532 Hz
AQ 4.088465 sec
RG 112.56
RW 65.450 usec
DE 6.50 usec
TE 295.2 K
D1 1.00000000 sec
TDS 400.200470 MHz
SFO1 13
P1 13.00 usec
PLM1 13.0000000 W

F2 - Processing parameters
SI 65536
SF 400.200000 MHz
WDW EM
SSB 0
LB 0 0.30 Hz
GB 0
PC 1.00

Ibrahim Mohey - COI-113 - Hnmr - T



COMP 06



Current Data Parameters
NAME Ibrahim Mohey - COI-113 - Hnmr - T
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220204
Time 23:43 h
INSTRUM spect
PROBHD 5108618_0945 (1
PULPROG zgpg30
TD 65536
SOLVENT DMF0
NS 2200
DS 4
SWH 24038.461 Hz
FIDRES 0.732596 Hz
AQ 1.3631488 sec
RG 197.77
RW 20.800 usec
DE 6.50 usec
TE 295.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TDS 100.6404331 MHz
SFO1 13
P1 10.00 usec
PLM1 47.0000000 W
SFO2 400.2016008 MHz
EPO2 1H
MUC2 1H
CPCPG2 waltz16
PCPD2 90.00 usec
PLM2 13.0000000 W
PLM12 0.29249999 W
PLM13 0.14713000 W

F2 - Processing parameters
SI 32768
SF 100.6303700 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S4. ¹H NMR and ¹³C NMR spectra of compound 6.

hamed-CO1113 #628 RT: 2.17 AV: 1 NL: 1.26E5
: (0,0) + c EI Full ms [50.00-500.00]

COMP 06

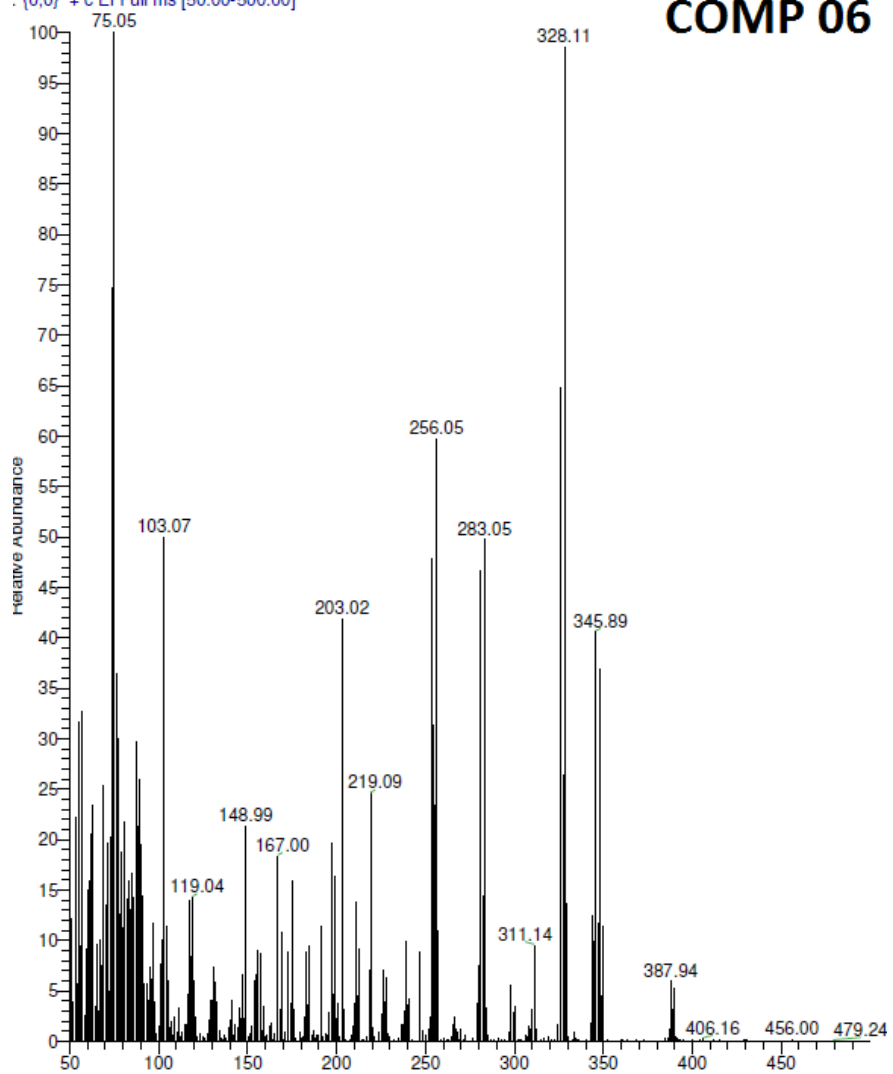
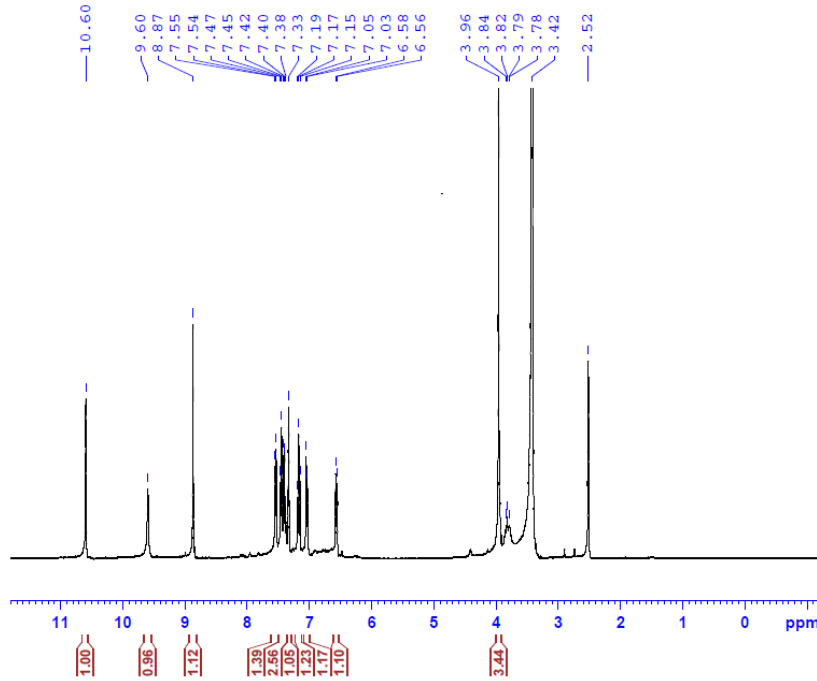


Figure S4b. Mass spectrum of compound 6.

COMP 07

Ibrahim Mohey - COI -114 - Hnmr - T

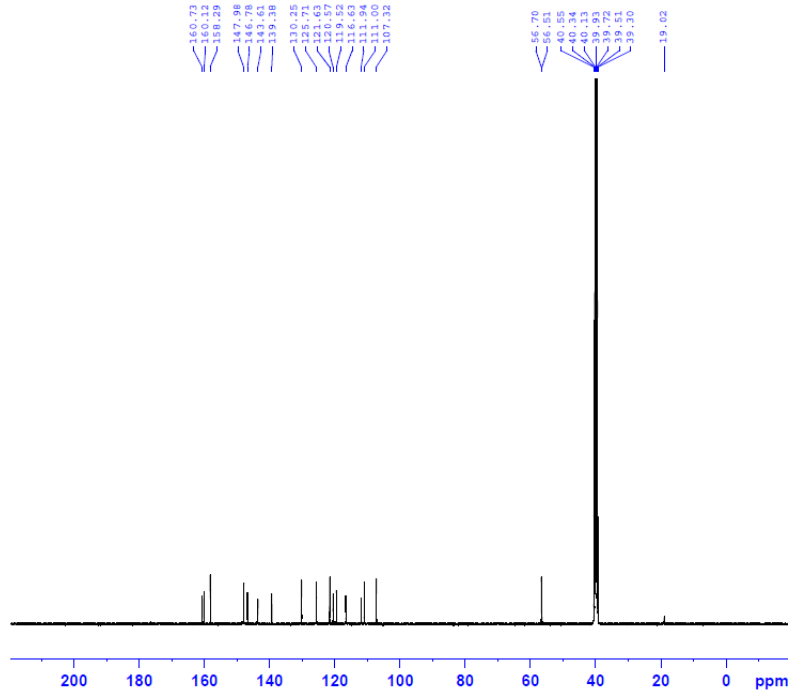


```

Current Data Parameters
NAME Ibrahim Mohey - COI -114 - Hnmr - T
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220129
Time 13:03 h
INSTRUM spect
PROBHD Z108618 0945 (
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1
DS 4
SWH 8012.820 Hz
FIDRES 0.244652 Hz
AQ 4.089465 sec
RG 58.52
DM 62.400 usec
DE 6.00 usec
TE 293.2 K
D1 1.0000000 sec
D11 1.0000000 sec
SFO1 400.2024713 MHz
NUC1 13
P1 13.10 usec
PL1 13.0000000 W
F2 - Processing parameters
SI 65536
SF 400.2024713 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
    
```

COMP 07

Ibrahim Mohey - COI-114 - Hnmr - T



```

Current Data Parameters
NAME Ibrahim Mohey - COI-114 - Hnmr - T
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220205
Time 1:52 h
INSTRUM spect
PROBHD Z108618 0945 (
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 4
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 197.77
DM 20.800 usec
DE 6.50 usec
TE 294.8 K
D1 2.0000000 sec
D11 0.0300000 sec
TD0 1
SFO1 100.6404311 MHz
NUC1 13C
P1 10.00 usec
PLM1 47.0000000 W
SFO2 400.2016008 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 90.00 usec
PLM2 13.0000000 W
PLM12 0.29249999 W
PLM13 0.14713000 W
F2 - Processing parameters
SI 32768
SF 100.6303700 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
    
```

Figure S5. ¹H NMR and ¹³C NMR spectra of compound 7.

hamed-CO1114 #1019 H1: 3.50 AV: 1 NL: 4./3E5
: [0.0] + c EI Full ms [50.00-500.00]

COMP 07

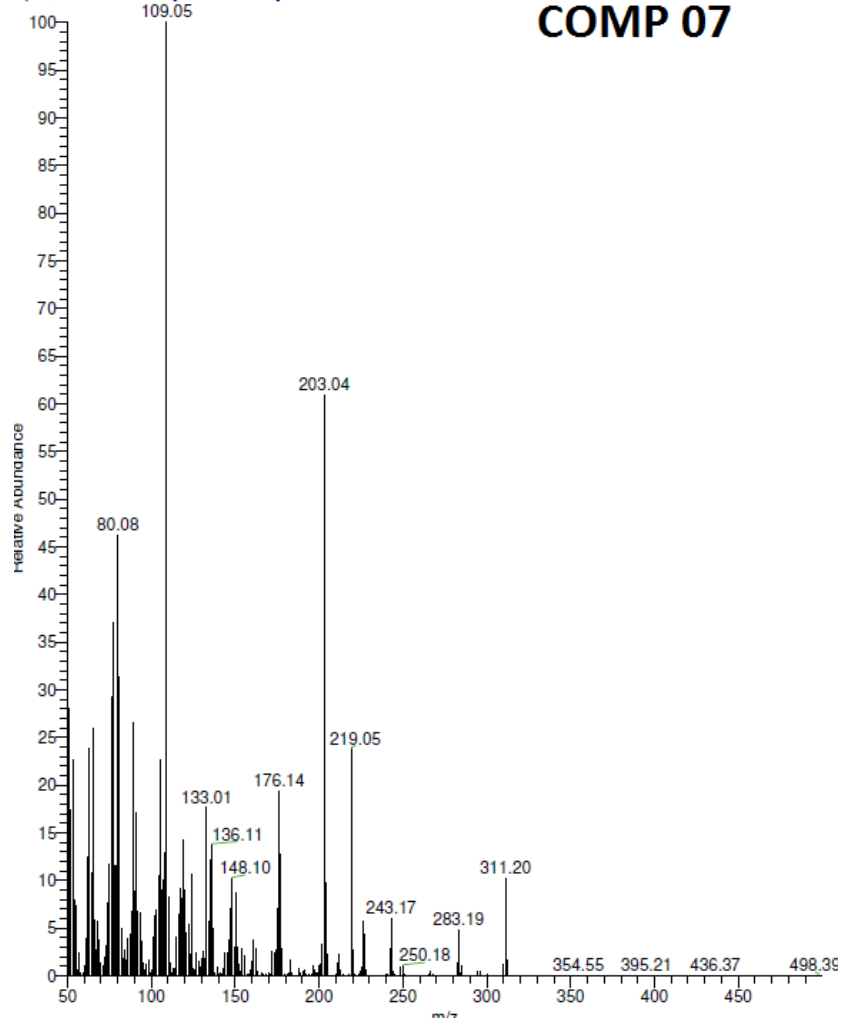
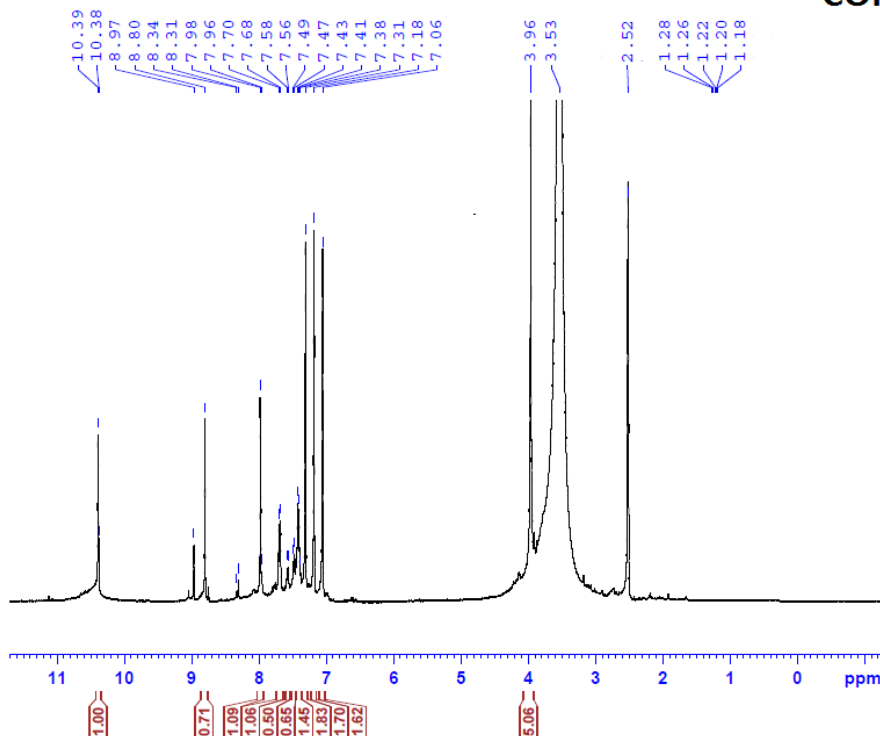


Figure S5. Mass spectrum of compound 7.

Ibrahim Mohey - COI -115 - Hnmr - T



COMP 08



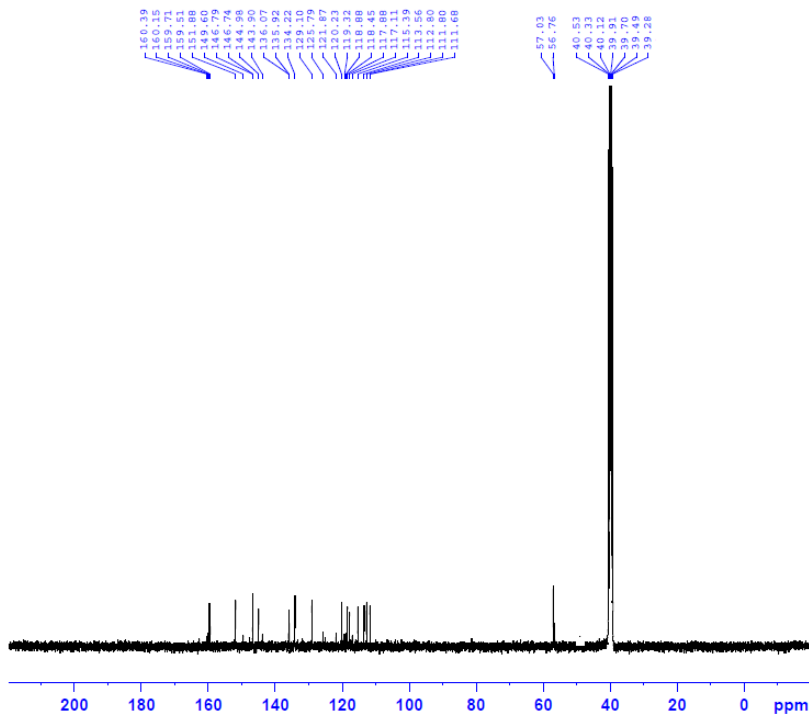
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Current Data Parameters
NAME Ibrahim Mohey - COI -115 - Hnmr - T
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220125
Time 12.07 h
INSTRUM spect
PROBHD Z108618_0945
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2
DS 4
SWH 8013.823 Hz
FIDRES 0.244532 Hz
AQ 4.089445 sec
RG 58.93
DE 62.450 usec
TE 295.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TDO 0
SFO1 400.2024712 MHz
NUC1 13
F1 13.50 usec
F2 13.00000000 W

F2 - Processing parameters
SI 65536
SF 400.2024712 MHz
WDW EM
SSB 0
GB 0
PC 1.00
    
```

Ibrahim Mohey - COI-115 - Hnmr - T



COMP 08



```

Current Data Parameters
NAME Ibrahim Mohey - COI-115 - Hnmr - T
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220205
Time 4.01 h
INSTRUM spect
PROBHD Z108618_0945
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2
DS 4
SWH 24038.461 Hz
FIDRES 0.731596 Hz
AQ 1.3631488 sec
RG 197.77
DE 20.800 usec
TE 295.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 0
SFO1 100.6404331 MHz
NUC1 13
F1 10.00 usec
F2 47.00000000 W
SFO2 400.2016008 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 90.00 usec
FLM2 13.00000000 W
FLM12 0.23249999 W
FLM13 0.14713000 W

F2 - Processing parameters
SI 32768
SF 100.6303700 MHz
WDW EM
SSB 0
GB 0
PC 1.40
    
```

Figure S6. ¹H NMR and ¹³C NMR spectra of compound 8.

amed-COI115 #60 RT: 0.23 AV: 1 NL: 5.53E4
{0,0} + c EI Full ms [50.00-500.00]

COMP 08

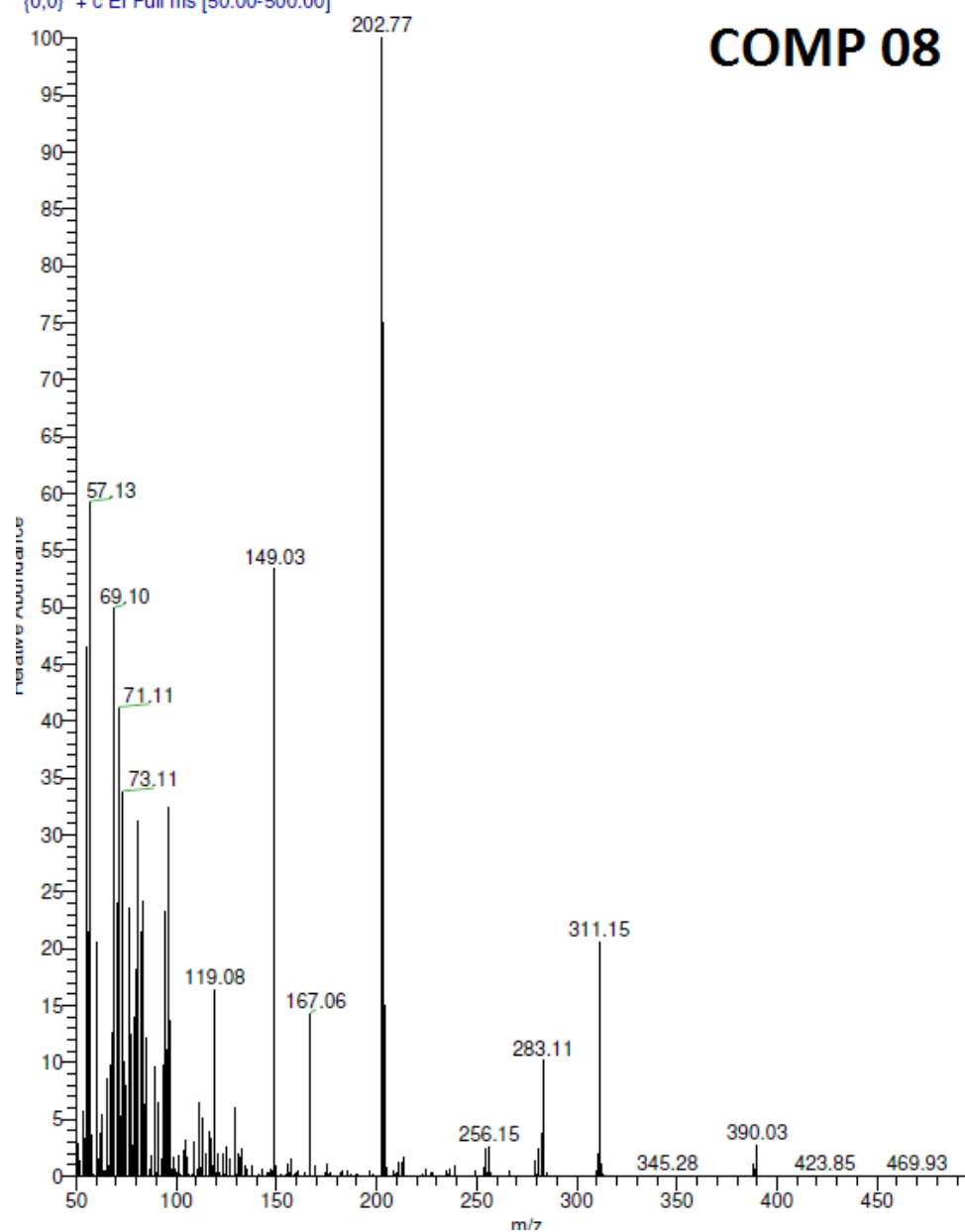


Figure S6b. Mass spectrum of compound 8.