

Synthesis, molecular modeling and anti-inflammatory activity of new benzo[a]pyrano[2,3-c]phenazine compounds

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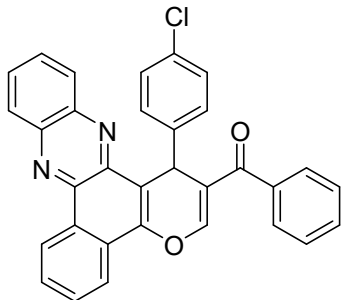
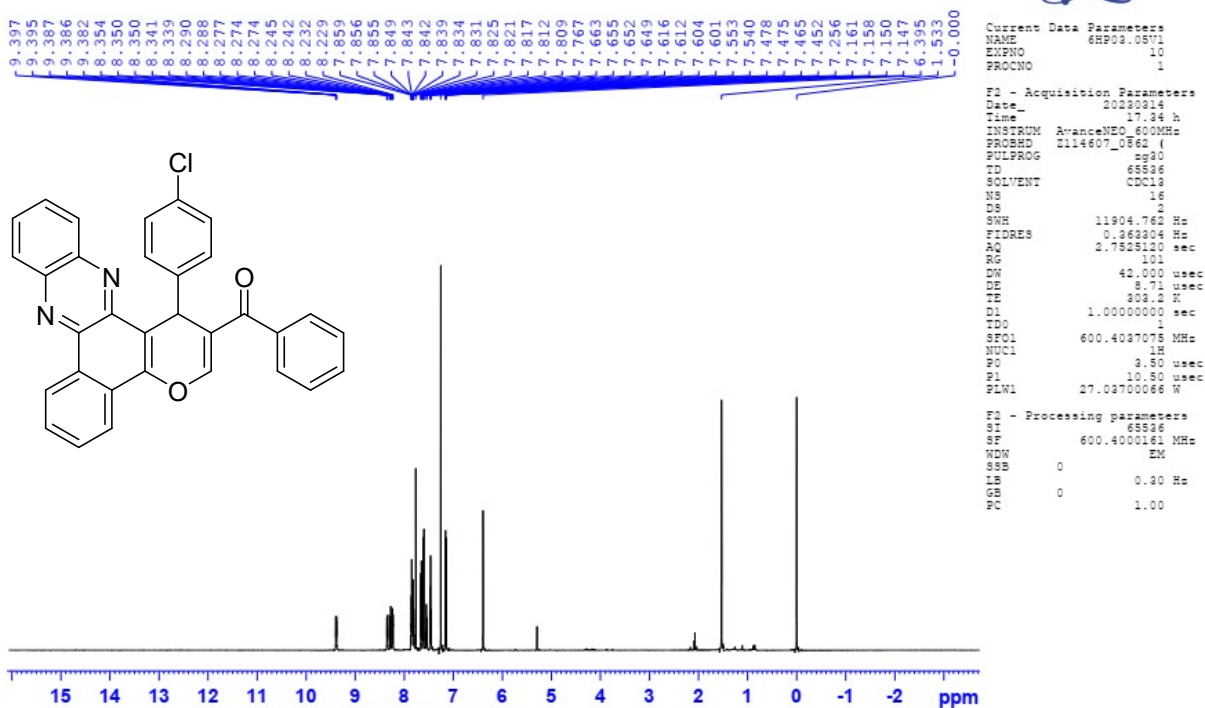
^eNovalix, Chau. du Vexin, 27100 Val-de-Reuil, France

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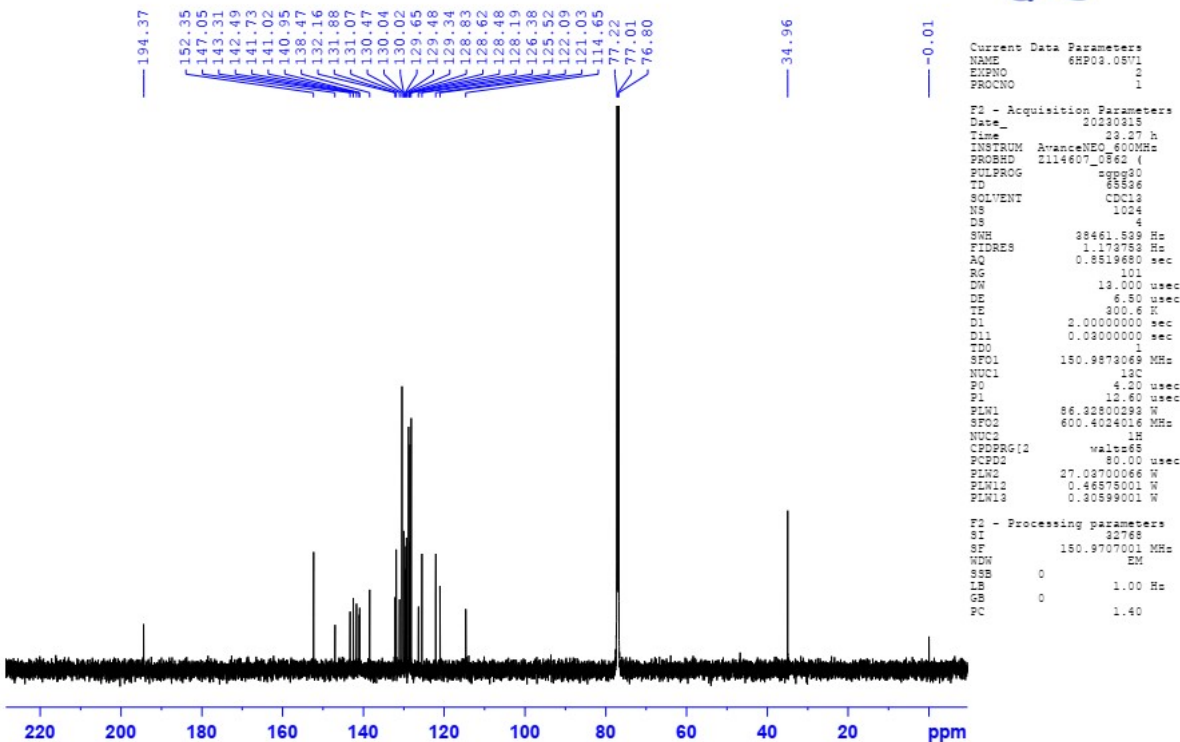
(1-(4-Chlorophenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)(phenyl)methanone (7a).	2
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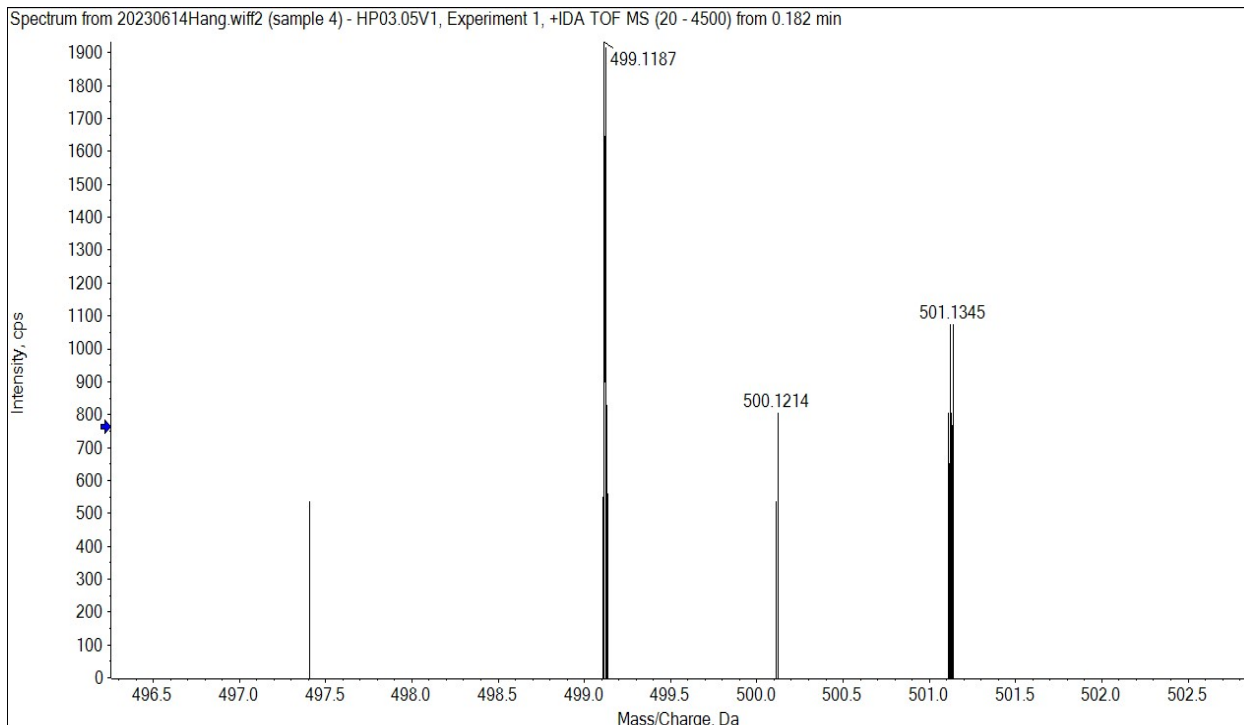
(1-(4-Chlorophenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)(phenyl)methanone (7a).

HP03.05V1-CDC13-1H



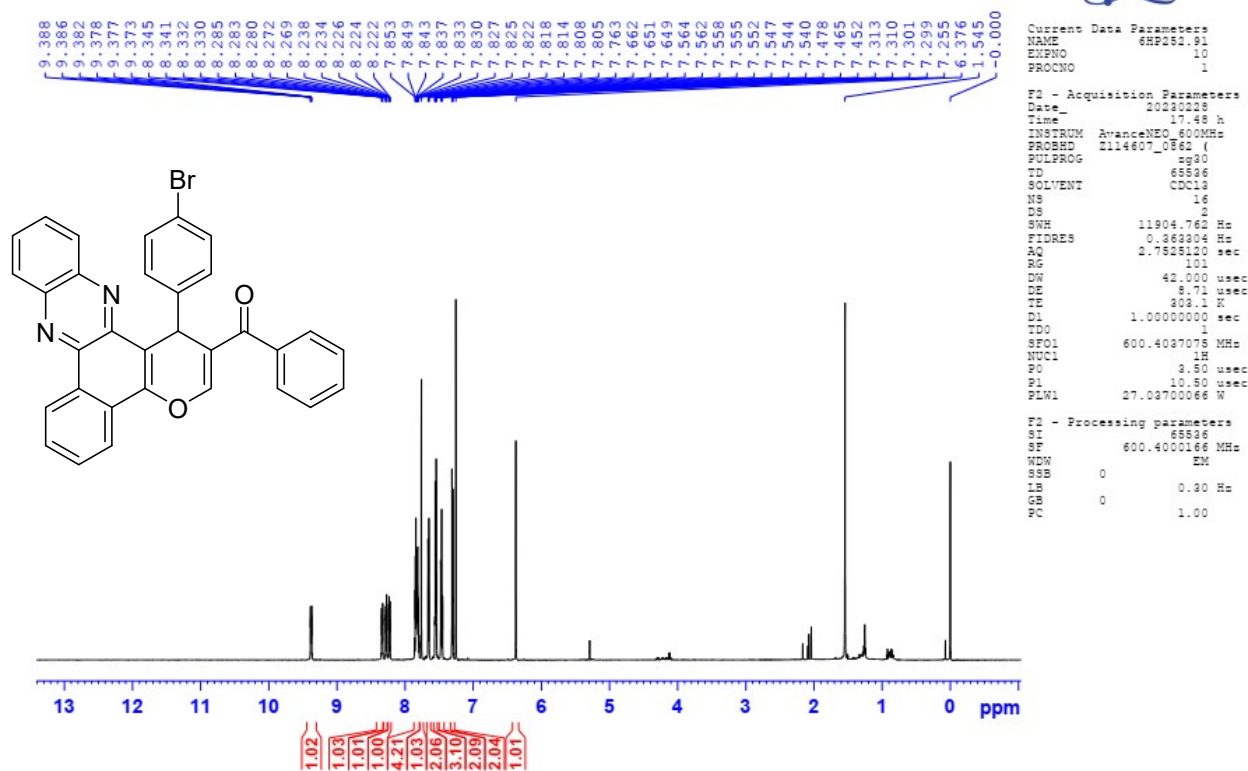
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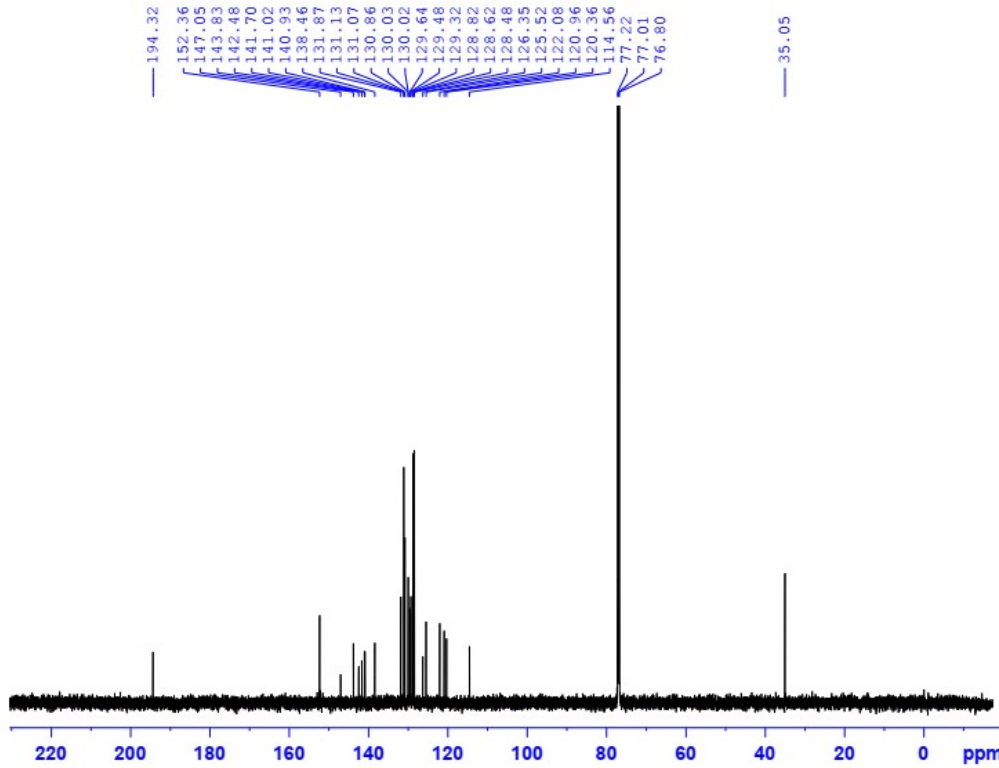


(1-(4-Bromophenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)(phenyl)methanone (7b).

HP252.91-CDC13-1H



HP252.91-CDC13-C13CPD



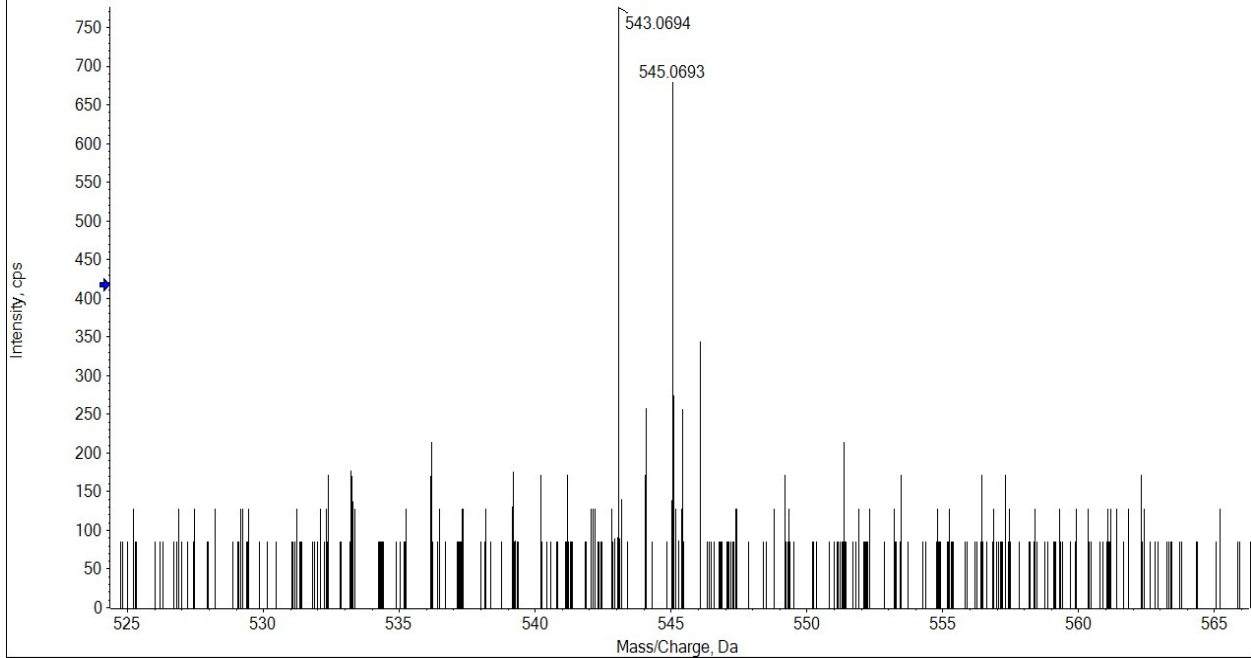
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NS        101
SOLVENT  CDCl3
DS        4
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FIDRES    1.173783 Hz
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RG        101
DN        13.000 usec
DE        6.50 usec
TE        303.1 K
D1        2.00000000 sec
D11       0.03000000 sec
TDD       1
SFO1      150.9873069 MHz
NUC1      13C
PQ        4.20 usec
PL        12.50 usec
PLW1      86.32800293 N
SFO2      600.4024016 MHz
NUC2      1H
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PCPD2     80.00 usec
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PLW13     0.30599001 W

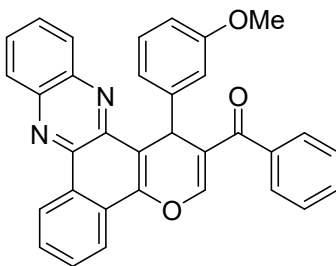
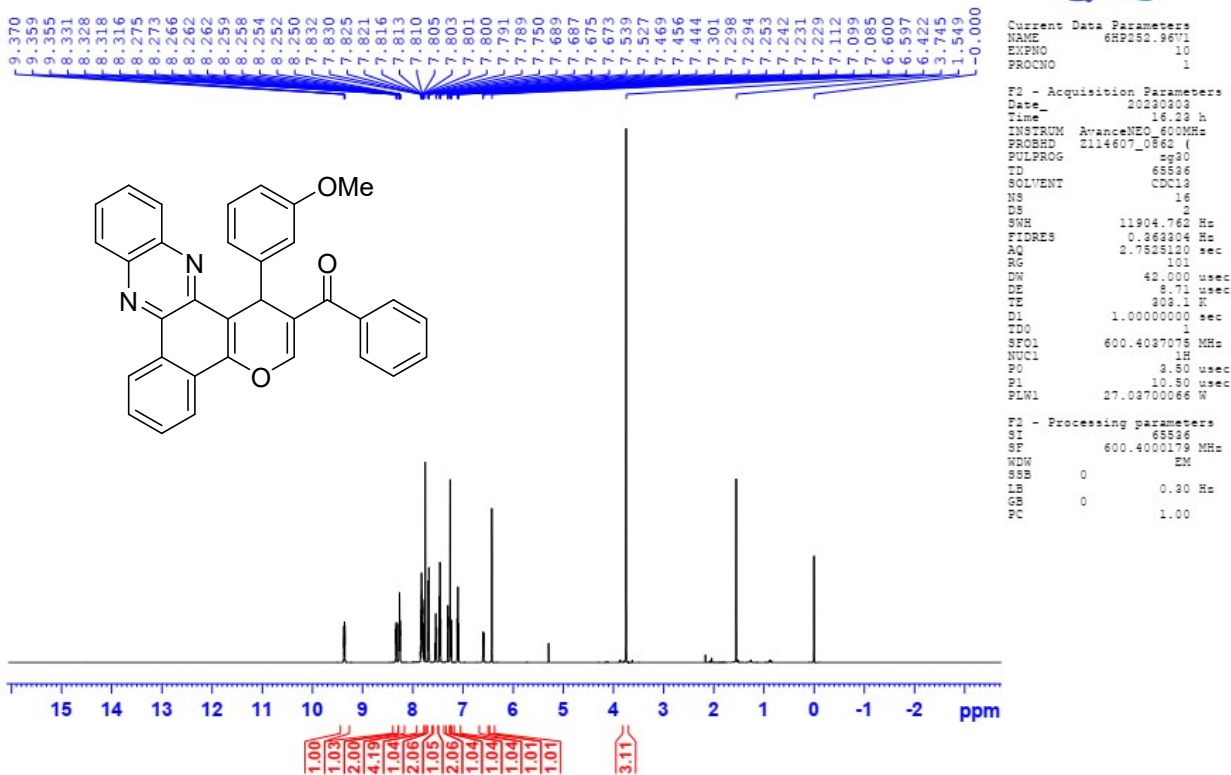
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Spectrum from 20230614Hang.wiff2 (sample 1) - HP252.91, Experiment 1, +IDA TOF MS (20 - 4500) from 0.193 min

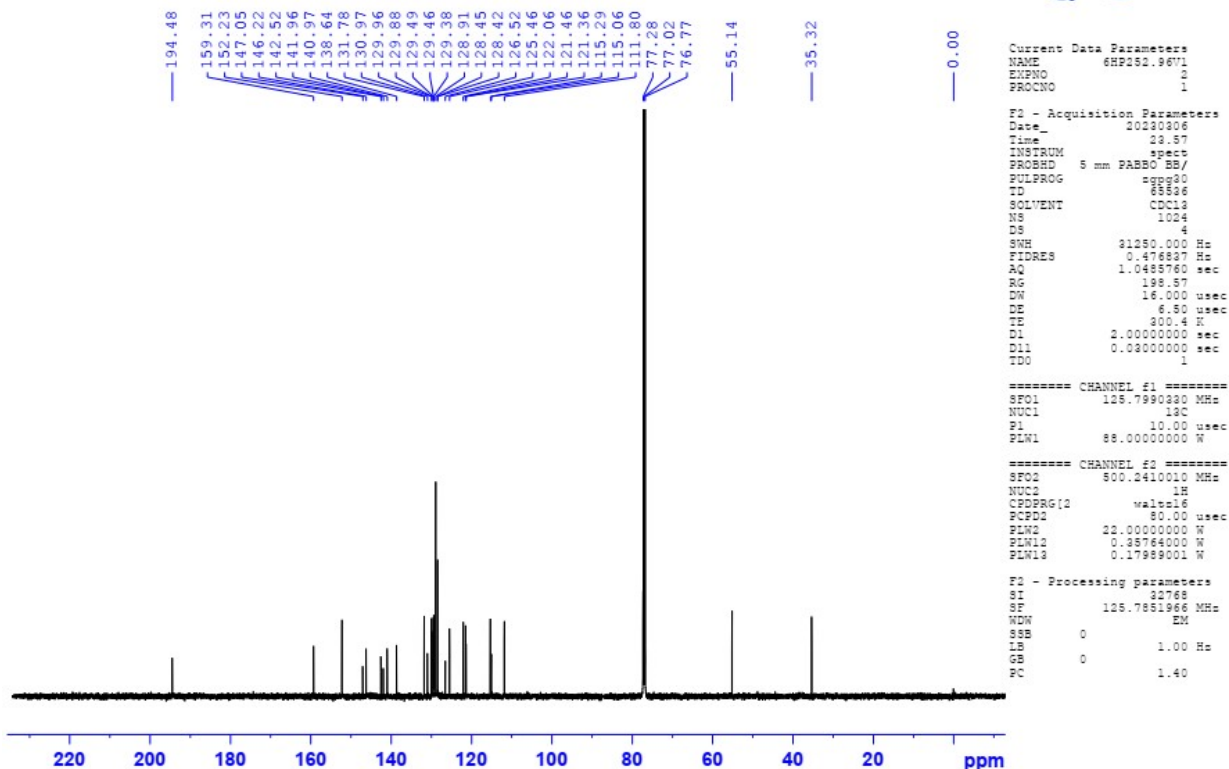


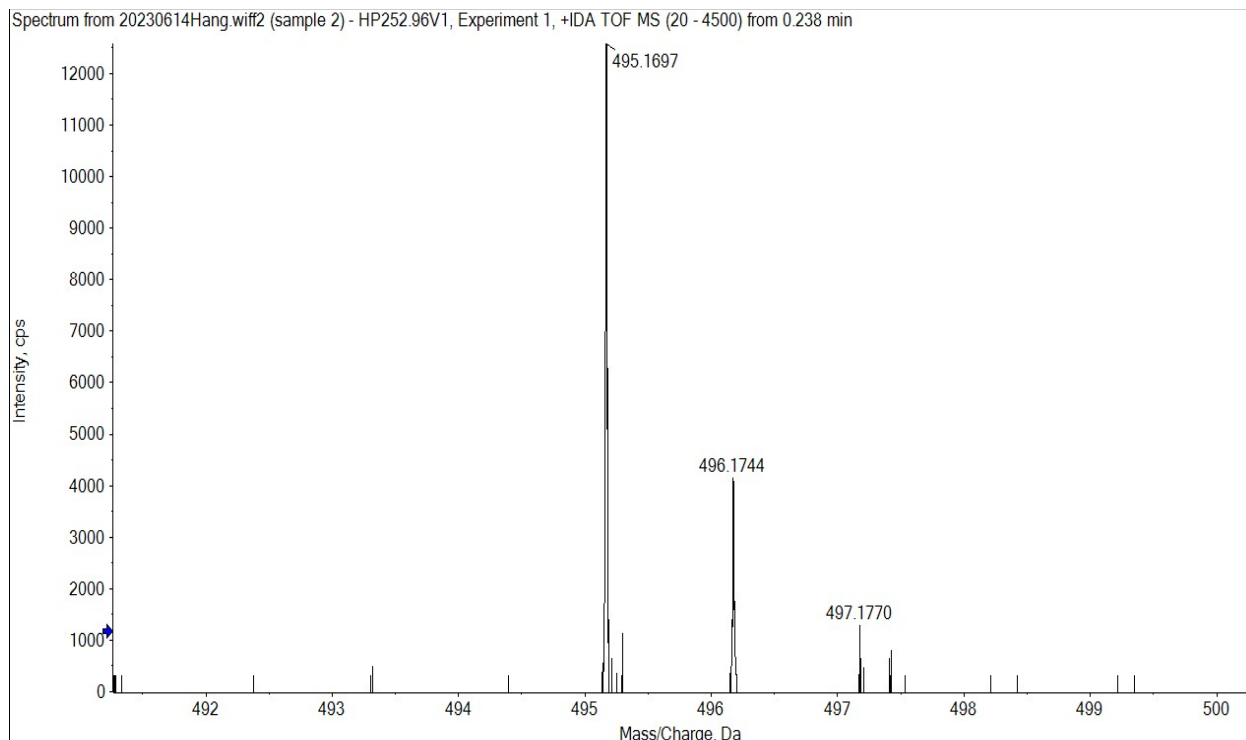
(1-(3-Methoxyphenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)(phenyl)methanone (7c).

HP252.96V1-CDC13-1H



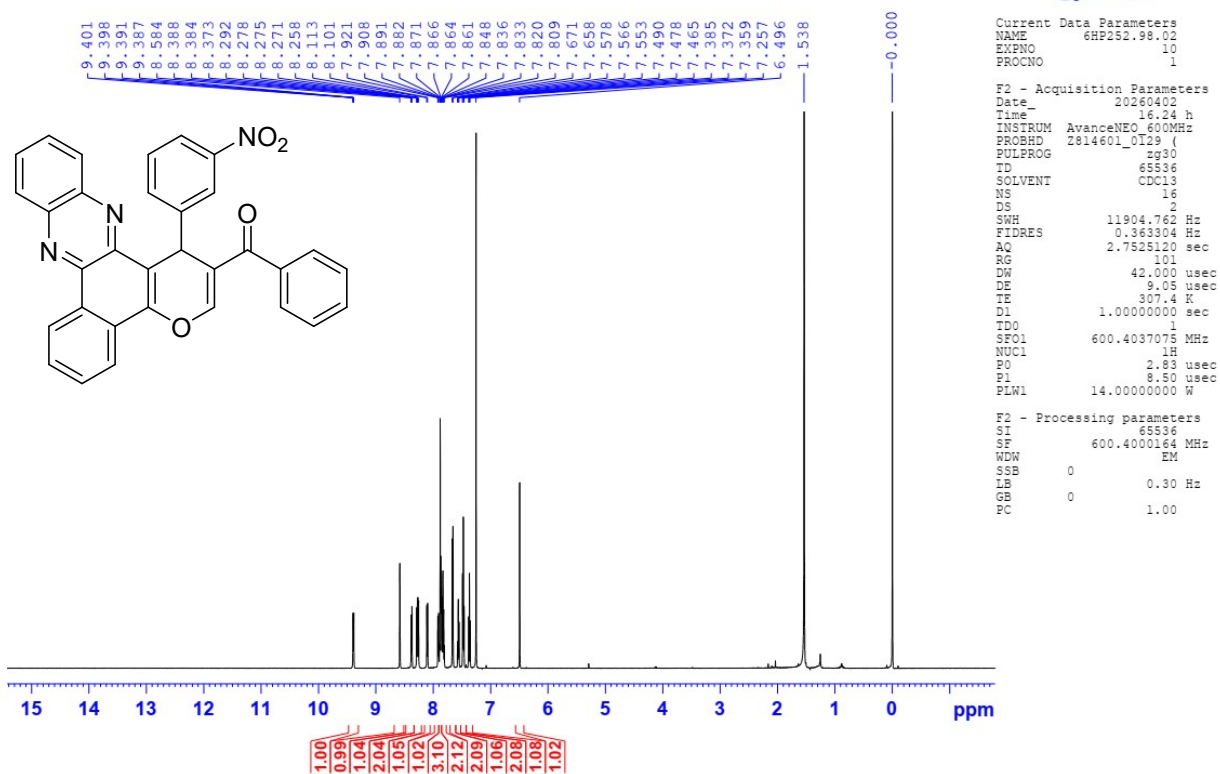
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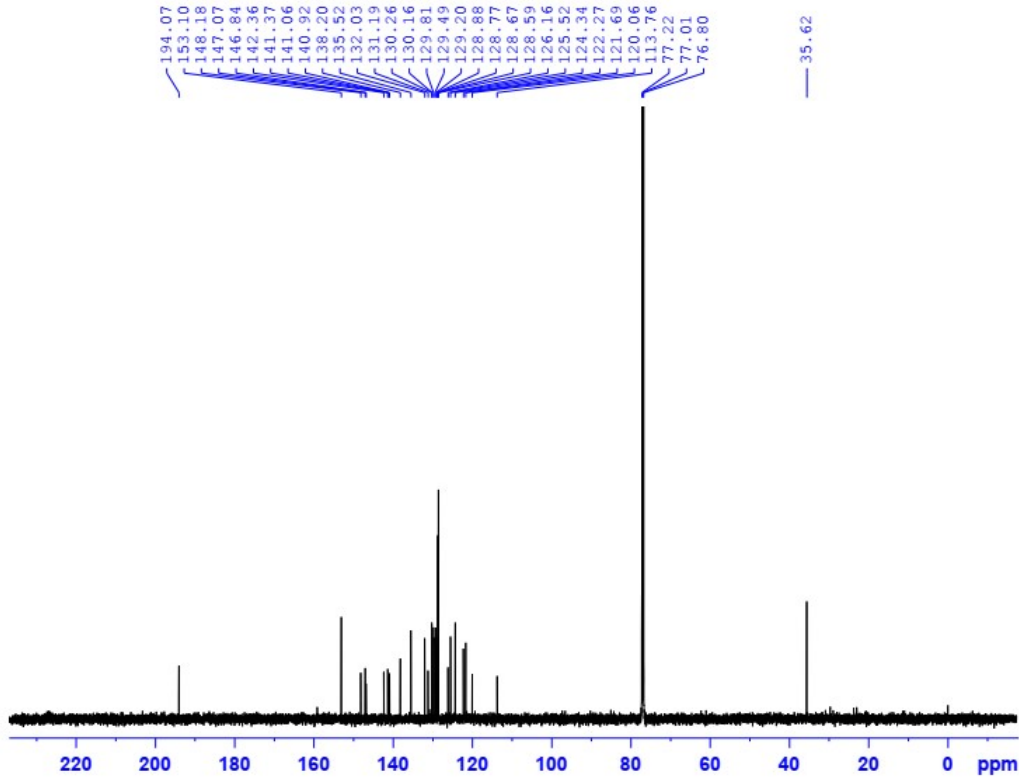


(1-(3-Nitrophenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)(phenyl)methanone (7d).

HP252.98.02-CDC13-1H



HP252.98V2-CDC13-C13CPD



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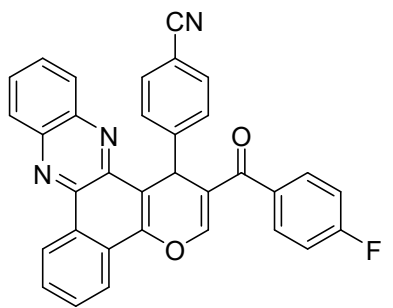
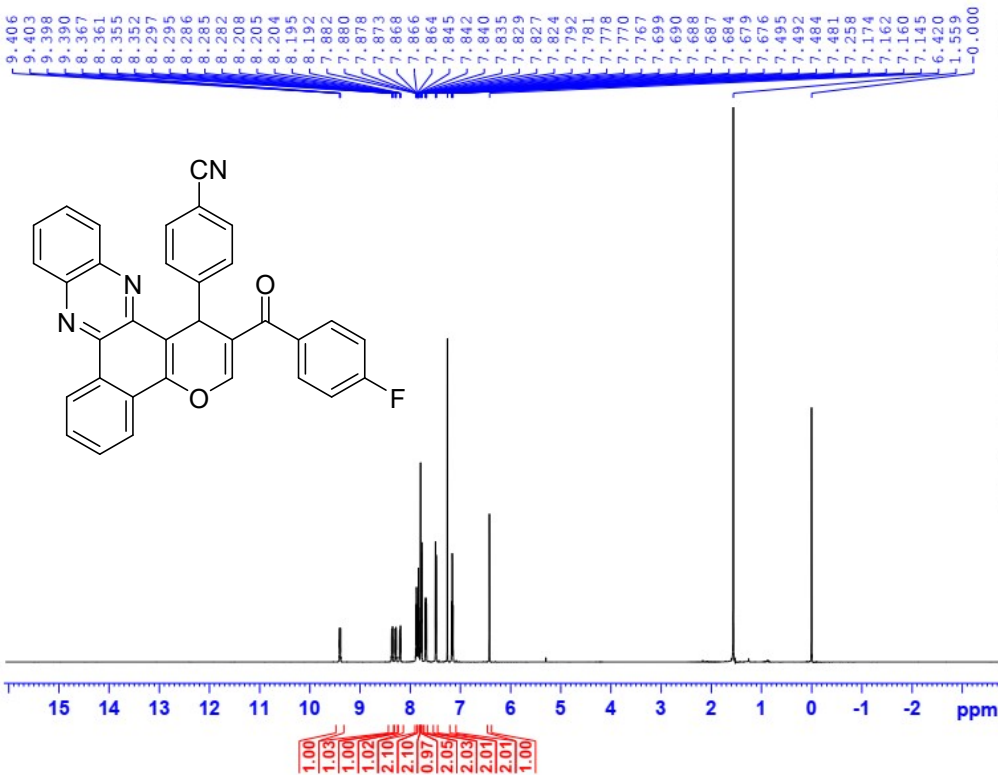
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PULPROG  zgpg30
TD       65536
SOLVENT  CDC13
NS       512
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SWH      38461.539 Hz
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RG       101
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DE       6.50 usec
TE       302.1 K
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D11      0.02000000 sec
TDO      1
SF01     150.9873069 MHz
NUC1     13C
P0       4.20 usec
P1       12.80 usec
PLW1     86.22820039 W
SF02     600.4024016 MHz
NUC2     1H
CPOPRG[2] waltz65
PCPD2    80.00 usec
PLW2     27.03700066 W
PLW12    0.46875001 W
PLW13    0.205599001 W

F2 - Processing parameters
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SF       150.9707001 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
    
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4-(2-(4-Fluorobenzoyl)-1H-benzo[a]pyrano[2,3-c]phenazin-1-yl)benzotrilee (7e).

HP03.27V1-CDC13-1H



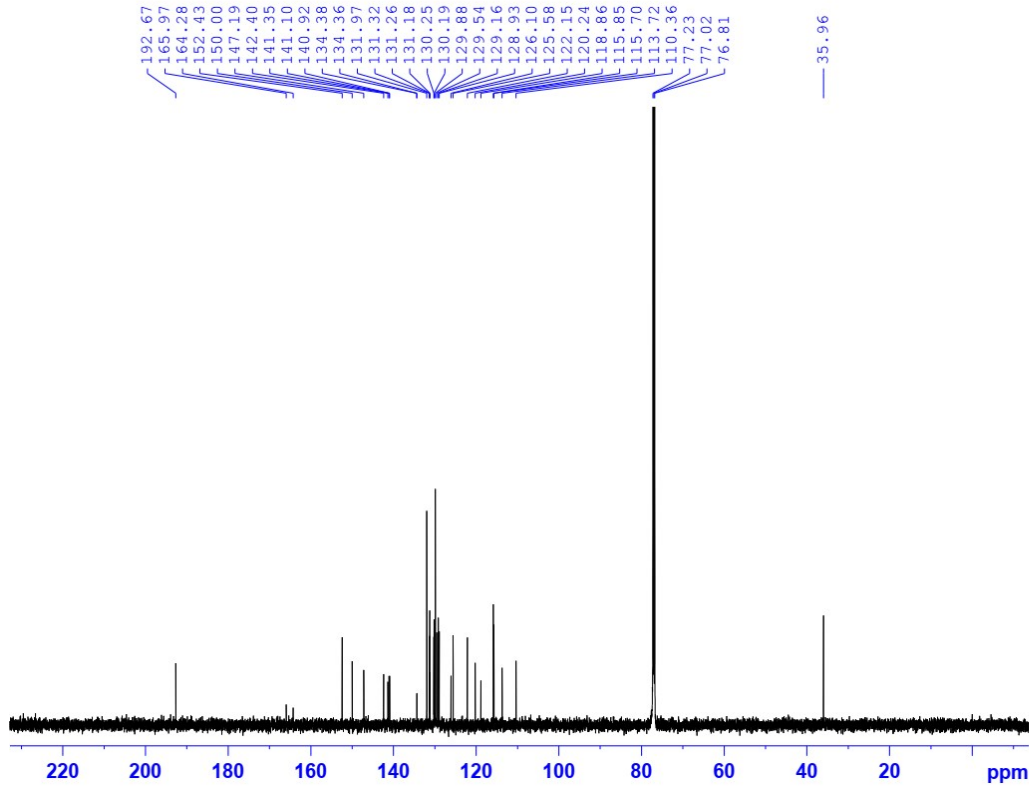
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PULPROG  zgpg30
TD       65536
SOLVENT  CDC13
NS       16
DS       2
SWH      11904.762 Hz
FIDRES   0.262304 Hz
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RG       101
DN       42.000 usec
DE       8.71 usec
TE       303.2 K
D1       1.00000000 sec
TDO      1
SF01     600.4037075 MHz
NUC1     1H
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P1       10.50 usec
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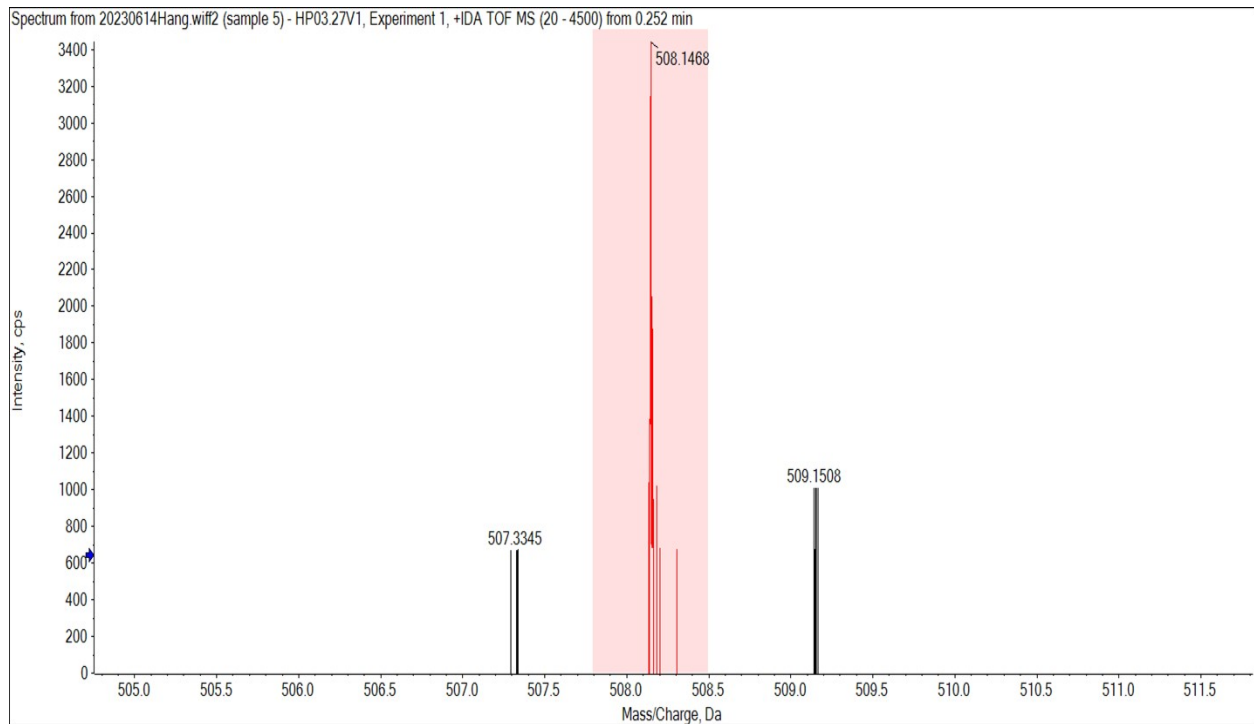
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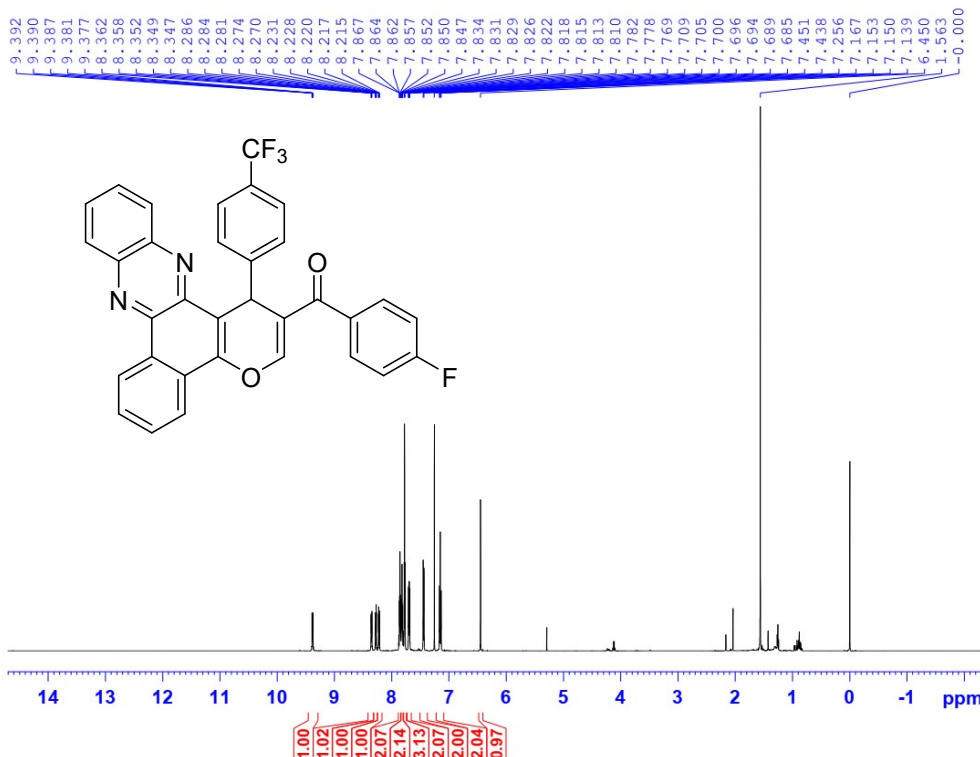
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PULPROG zpgp30
TD 65536
SOLVENT CDC13
NS 1024
DS 4
SWH 38461.539 Hz
FIDRES 1.173753 Hz
AQ 0.8519680 sec
RG 101
SW 13.000 usec
DE 6.50 usec
TE 300.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO
SFO1 150.9873069 MHz
NUC1 13C
PO 4.20 usec
P1 12.60 usec
PLW1 86.32800293 W
SFO2 600.4024016 MHz
NUC2 1H
CPDPRG[2] waltz65
PCPD2 80.00 usec
PLW2 27.03700066 W
PLW12 0.46575001 W
PLW13 0.30599001 W

F2 - Processing parameters
SI 32768
SF 150.9707001 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



(4-Fluorophenyl)(1-(4-(trifluoromethyl)phenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7f).

HP03.28-CDC13-1H

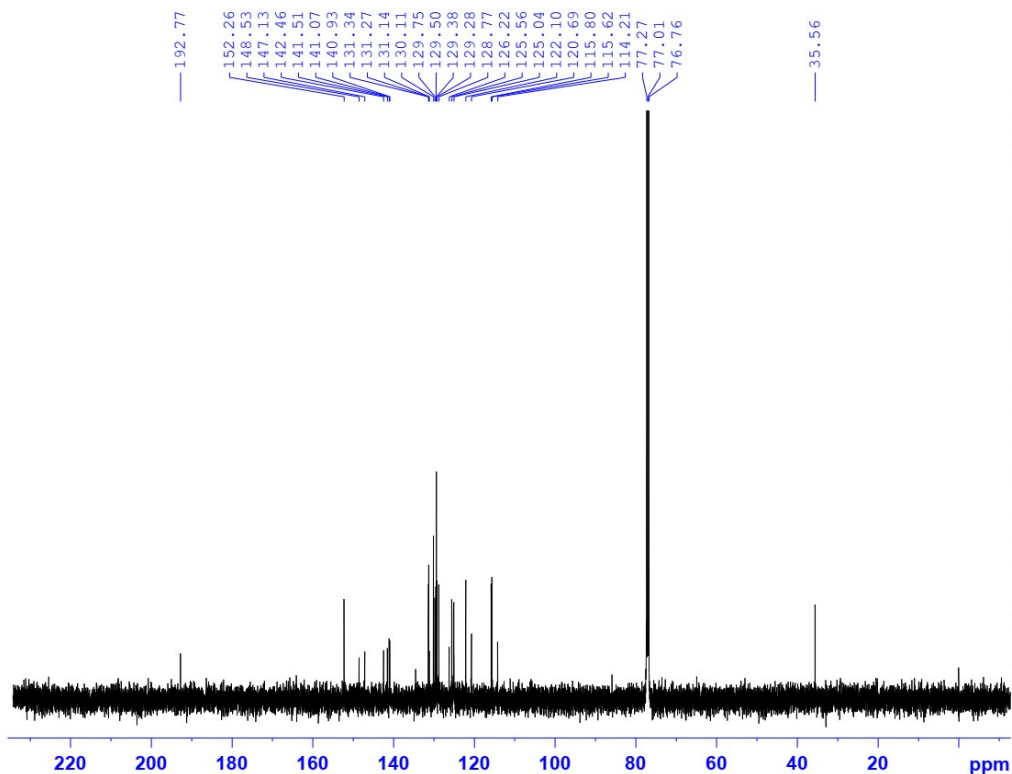


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EXPNO 10
PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 11904.762 Hz
FIDRES 0.363304 Hz
AQ 2.7525120 sec
RG 101
DW 42.000 usec
DE 8.71 usec
TE 303.1 K
D1 1.00000000 sec
TDO 1
SF01 600.4037075 MHz
NUC1 1H
PO 3.50 usec
P1 10.50 usec
PLW1 27.03700066 W

F2 - Processing parameters
SI 65536
SF 600.4000160 MHz
WDW EM
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GB 0
PC 1.00

HP03.28-CDC13-C13CPD



Current Data Parameters
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EXPNO 2
PROCNO 1

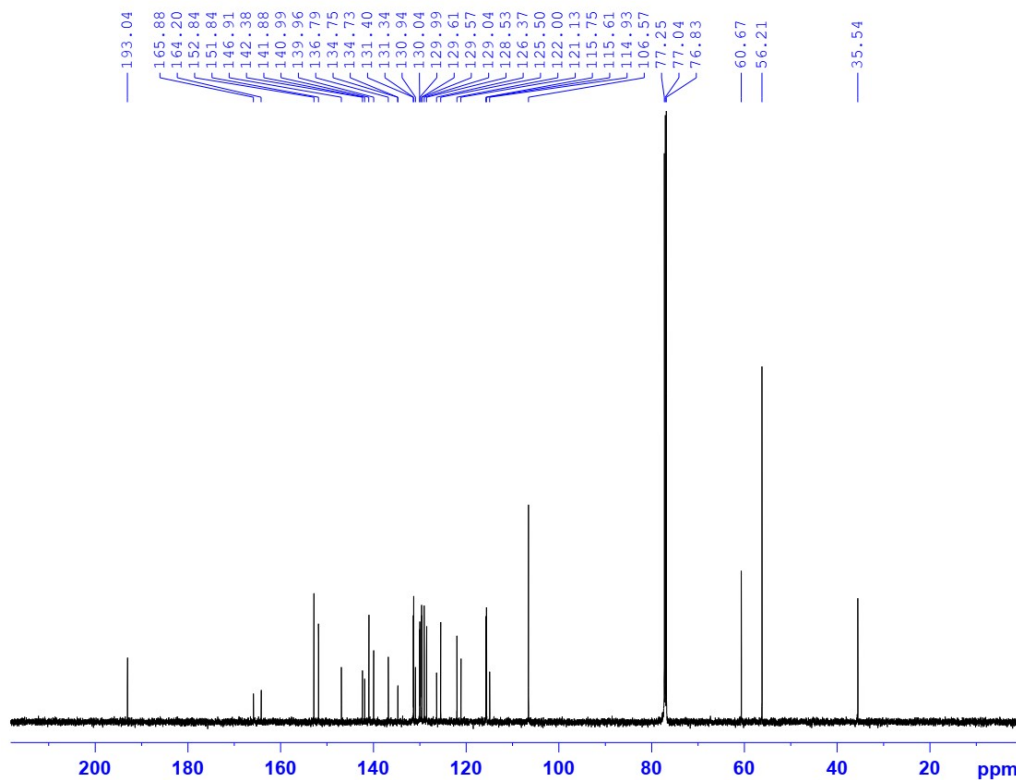
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FIDRES 0.476837 Hz
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RG 198.57
DW 16.000 usec
DE 6.50 usec
TE 301.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1

===== CHANNEL f1 =====
SF01 125.7990330 MHz
NUC1 13C
P1 10.00 usec
PLW1 88.00000000 W

===== CHANNEL f2 =====
SF02 500.2410010 MHz
NUC2 1H
CPDPRG[2] waltz16
PCPD2 80.00 usec
PLW2 22.00000000 W
PLW12 0.35764000 W
PLW13 0.17989001 W

F2 - Processing parameters
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SSB 0
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GB 0
PC 1.40

HP03.29-CDC13-C13CPD

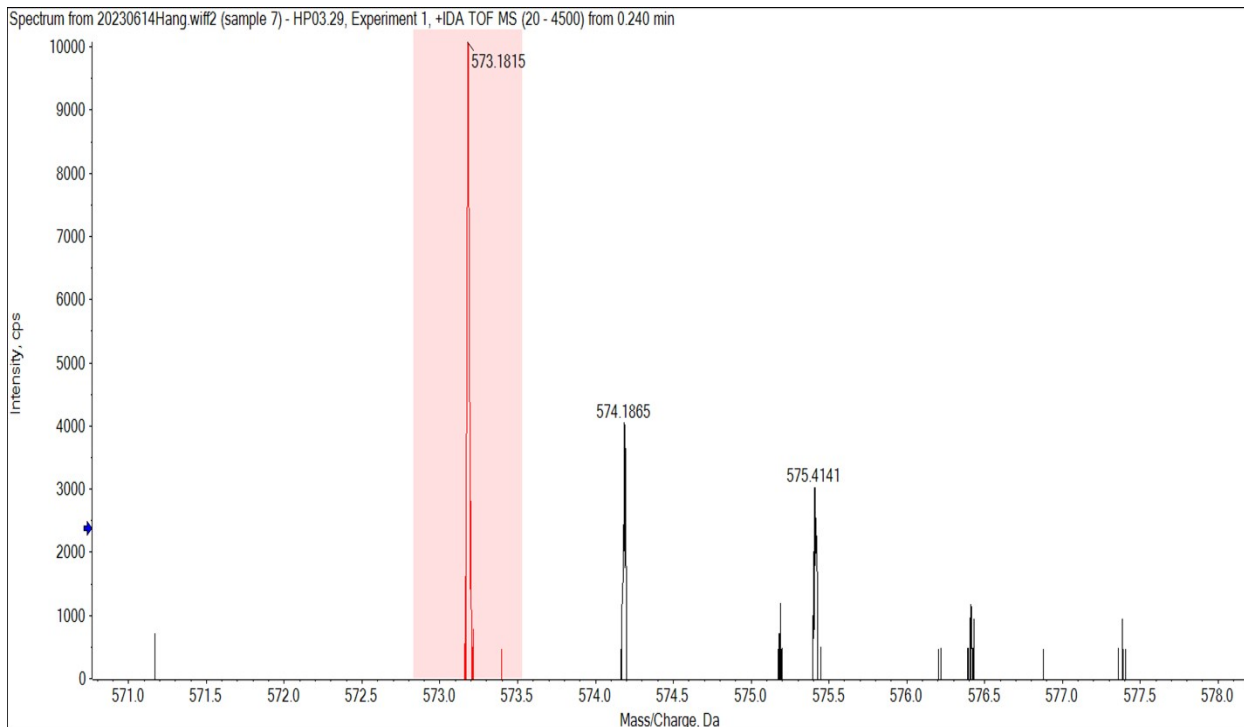


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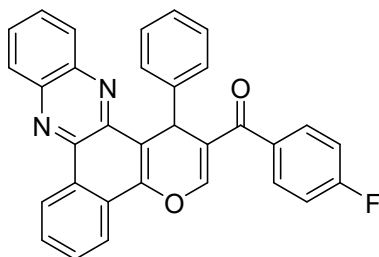
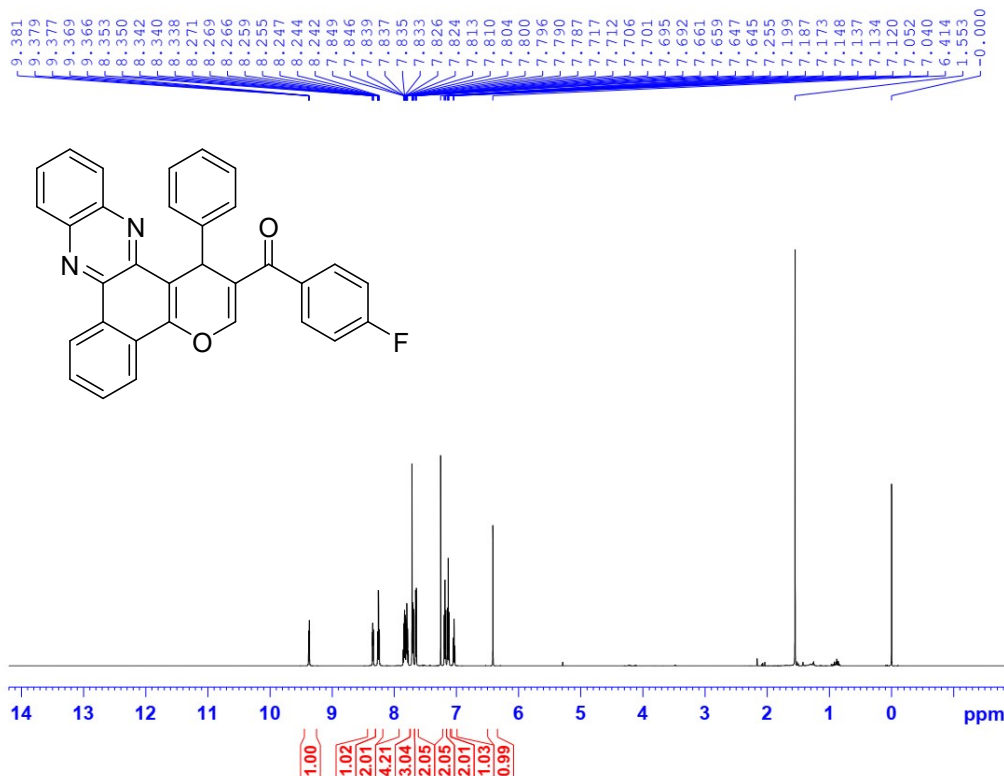
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PULPROG  _zgpg30
TD       65536
SOLVENT  CDC13
NS       258
DS       4
SWH      38461.539 Hz
FIDRES   1.173753 Hz
AQ       0.8519680 sec
RG       101
DM       13.000 usec
DE       6.50 usec
TE       300.1 K
D1       2.00000000 sec
d11      0.03000000 sec
TD0      1
SF01     150.9873069 MHz
NUC1     13C
P0       4.20 usec
P1       12.60 usec
PLW1     86.32800293 W
SF02     600.4024016 MHz
NUC2     1H
CPDPRG2  waltz65
PCPD2    80.00 usec
PLW2     27.03700066 W
PLW12    0.46375001 W
PLW13    0.30399001 W

F2 - Processing parameters
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SF       150.9707001 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
FC       1.40
    
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(4-Fluorophenyl)(1-phenyl-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7h).

HP03.32-CDC13-1H

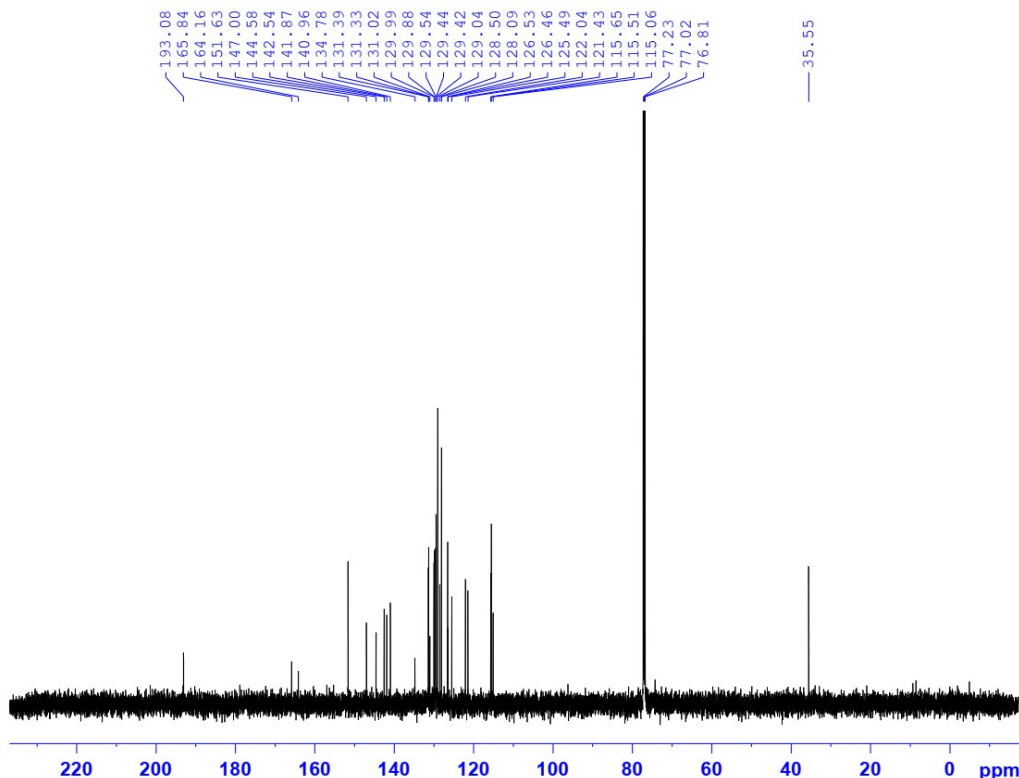


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 EXPNO 10
 PROCNO 1

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 TD 65536
 SOLVENT cdcl3
 NS 16
 DS 2
 SWH 11904.762 Hz
 FIDRES 0.363304 Hz
 AQ 2.7525120 sec
 RG 101
 DW 42.000 usec
 DE 8.71 usec
 TE 303.1 K
 D1 1.0000000 sec
 TDO 1
 SF01 600.4037075 MHz
 NUC1 1H
 P0 3.50 usec
 P1 10.50 usec
 PLW1 27.03700066 W

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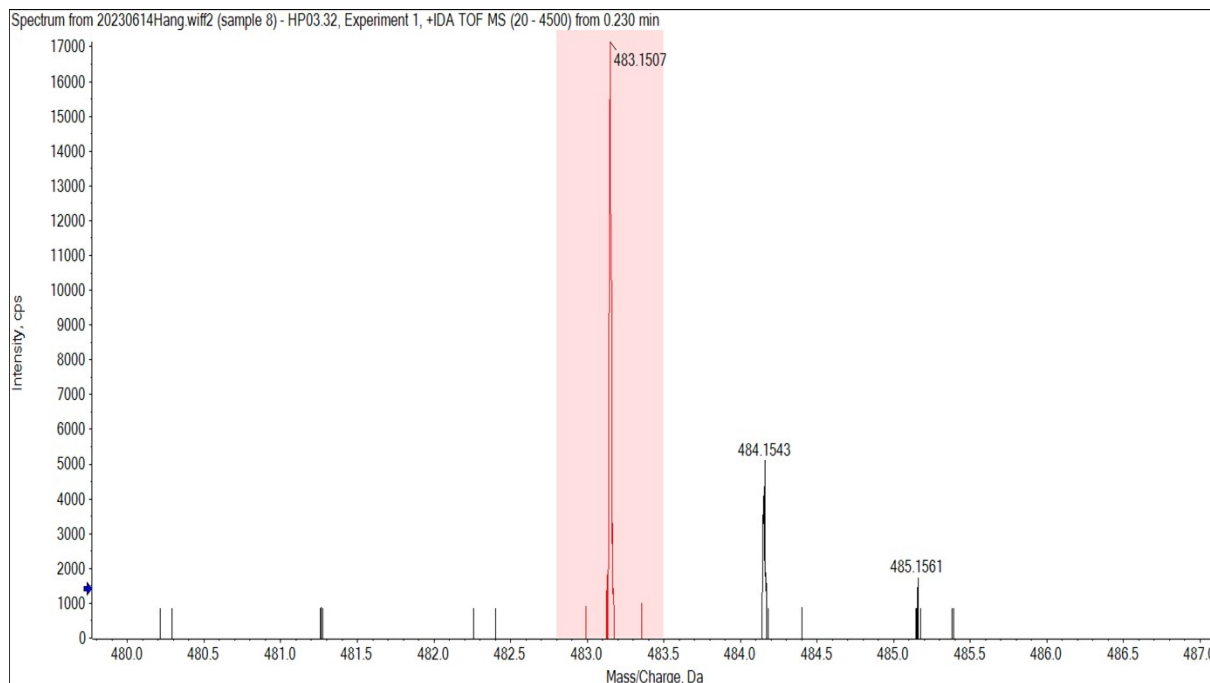
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Current Data Parameters
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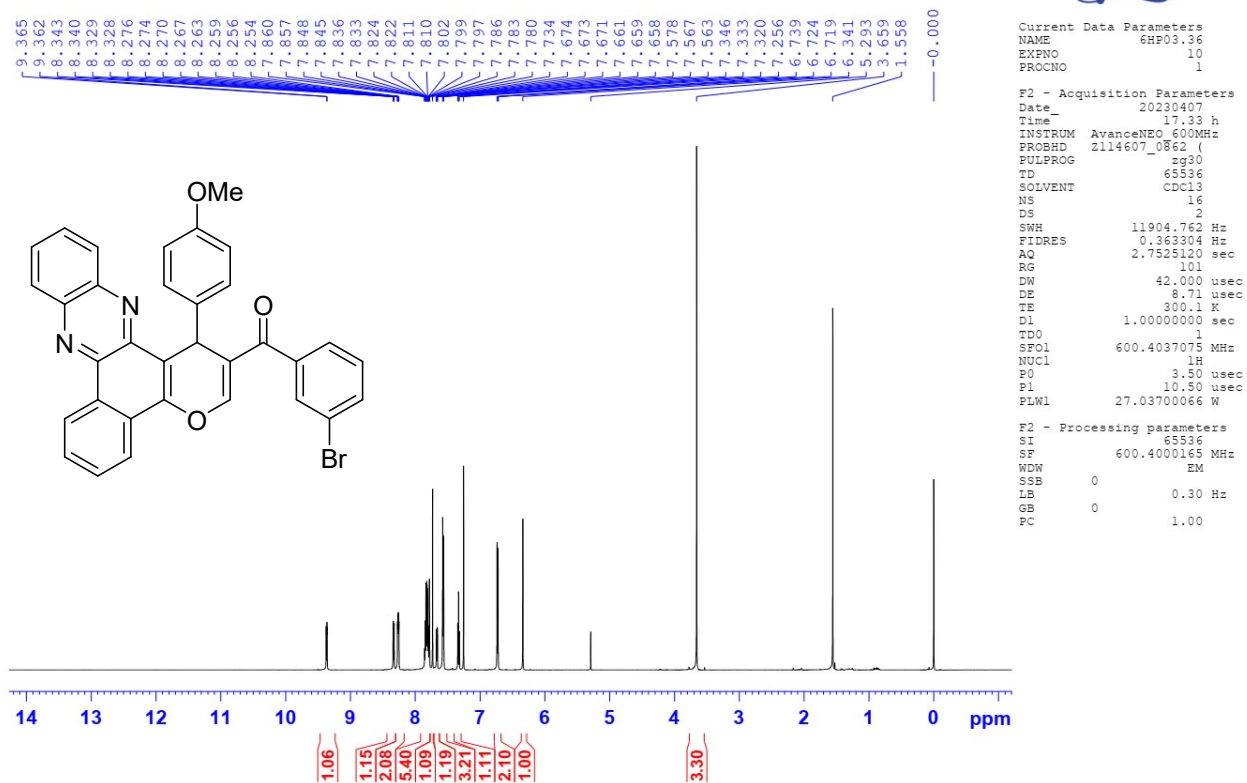
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 SOLVENT cdcl3
 NS 258
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 SWH 38461.539 Hz
 FIDRES 1.173753 Hz
 AQ 0.8519680 sec
 RG 101
 DW 13.000 usec
 DE 6.50 usec
 TE 300.1 K
 D1 2.0000000 sec
 D11 0.03000000 sec
 TDO 1
 SF01 150.9873069 MHz
 NUC1 13C
 P0 4.20 usec
 P1 12.60 usec
 PLW1 86.32800293 W
 SFO2 600.4024016 MHz
 NUC2 1H
 CPDPRG[2] waltz65
 PCPD2 80.00 usec
 PLW2 27.03700066 W
 PLW12 0.46575001 W
 PLW13 0.30599001 W

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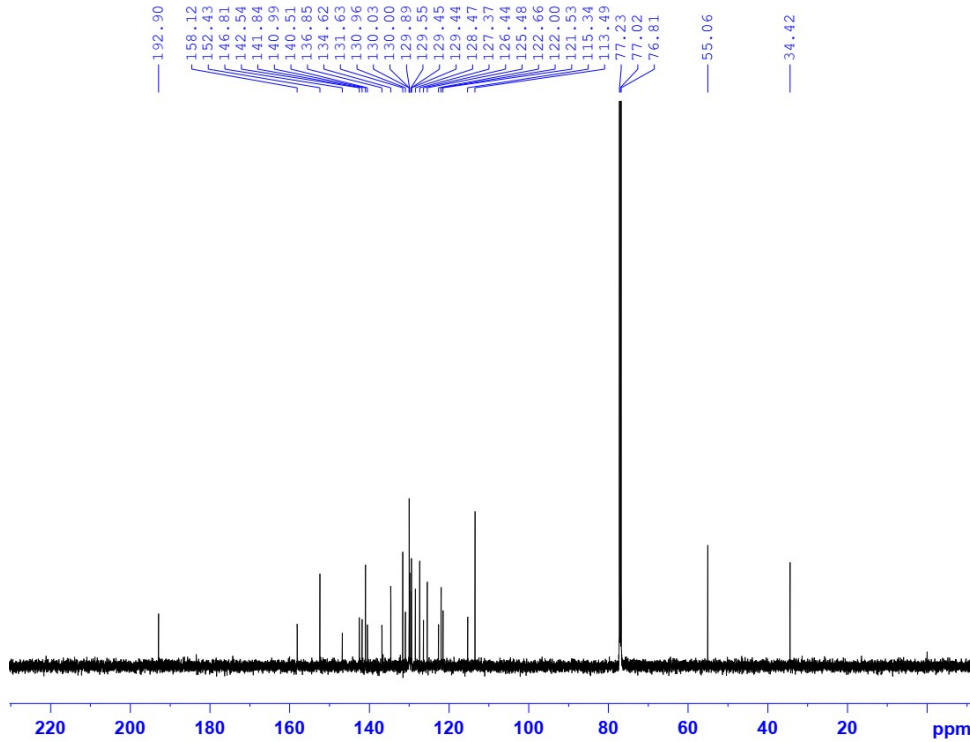


(3-Bromophenyl)(1-(4-methoxyphenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7i).

HP03.36-CDC13-1H



HP03.36-CDC13-C13CPD



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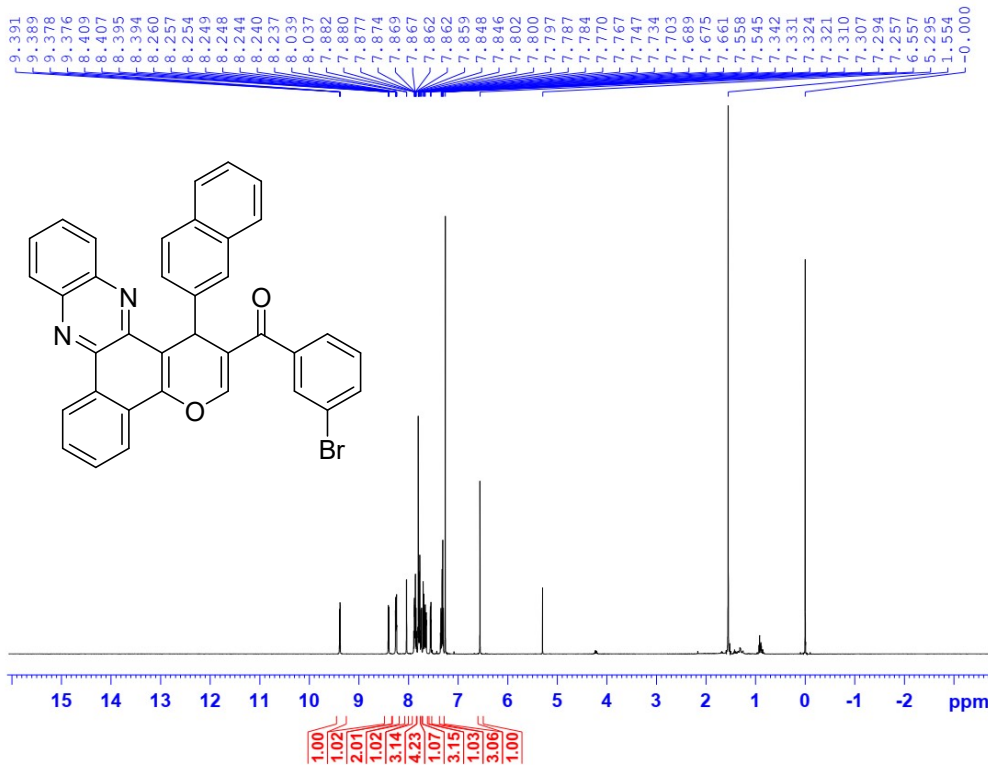
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PROCNO   1

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SOLVENT  CDCl3
NS        258
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FIDRES    1.173753 Hz
AQ         0.8519680 sec
RG         101
DW         13.000 usec
DE         6.50 usec
TE         300.1 K
D1         2.00000000 sec
D11        0.03000000 sec
TD0        1
SFO1      150.9873069 MHz
NUC1       13C
P0         4.20 usec
P1         12.60 usec
PLW1      86.32800293 W
SFO2      600.4024016 MHz
NUC2       1H
CPDPRG2   waltz65
PCPD2     80.00 usec
PLW2      27.03700066 W
PLW12     0.46575001 W
PLW13     0.305999001 W

F2 - Processing parameters
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SF         150.9707001 MHz
WDW        EM
SSB         0
LB         1.00 Hz
GB         0
PC         1.40
    
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(3-Bromophenyl)(1-(naphthalen-2-yl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7j).

HP03.38-CDC13-1H



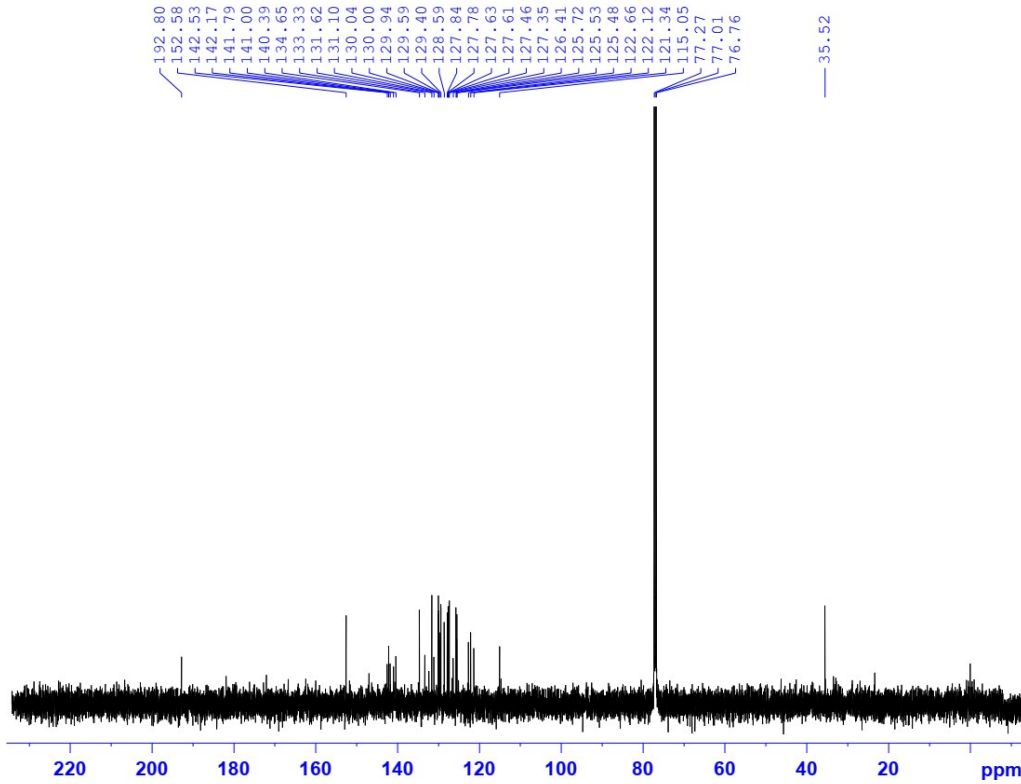
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TD        65536
SOLVENT  CDCl3
NS        16
DS         2
SWH       11904.762 Hz
FIDRES    0.363304 Hz
AQ         2.7525120 sec
RG         101
DW         42.000 usec
DE         8.71 usec
TE         300.1 K
D1         1.00000000 sec
TD0        1
SFO1      600.4037075 MHz
NUC1       1H
P0         3.50 usec
P1         10.50 usec
PLW1      27.03700066 W

F2 - Processing parameters
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SF         600.4000158 MHz
WDW        EM
SSB         0
LB         0.30 Hz
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HP03.38-CDC13-C13CPD



Current Data Parameters
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 PROCNO 1

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 Date_ 20230410
 Time 17.23
 INSTRUM spect
 PROBHD 5 mm PABBO BB/
 PULPROG zgpg30
 TD 65536
 SOLVENT CDC13
 NS 256
 DS 4
 SWH 31250.000 Hz
 FIDRES 0.476837 Hz
 AQ 1.0485760 sec
 RG 198.57
 DW 16.000 usec
 DE 6.50 usec
 TE 301.6 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1

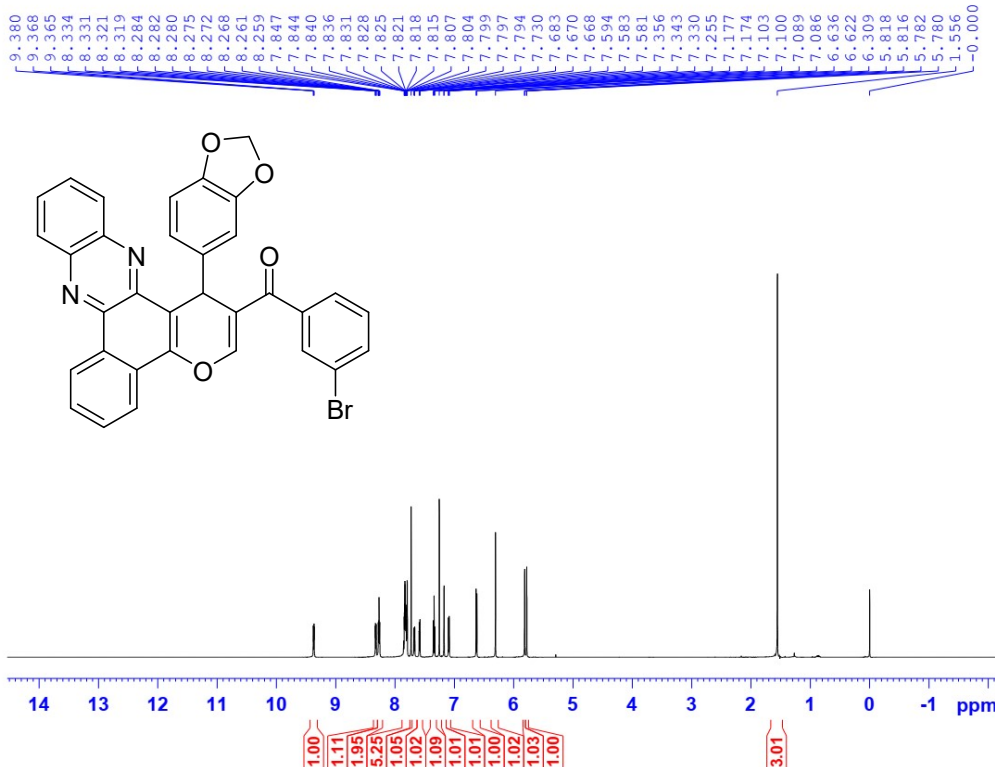
==== CHANNEL f1 =====
 SFO1 125.7990330 MHz
 NUC1 13C
 P1 10.00 usec
 PLW1 88.00000000 W

==== CHANNEL f2 =====
 SFO2 500.2410010 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 80.00 usec
 PLN2 22.00000000 W
 PLW2 0.35764000 W
 PLW12 0.17989001 W
 PLW13 0.17989001 W

F2 - Processing parameters
 SI 32768
 SF 125.7851966 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

(1-(Benzo[d][1,3]dioxol-5-yl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)(3-bromophenyl)methanone (7k).

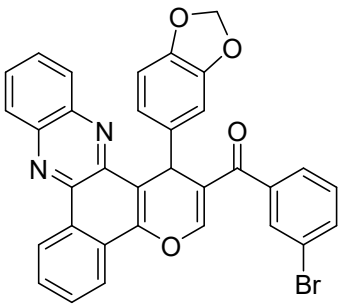
HP03.48-CDC13-1H



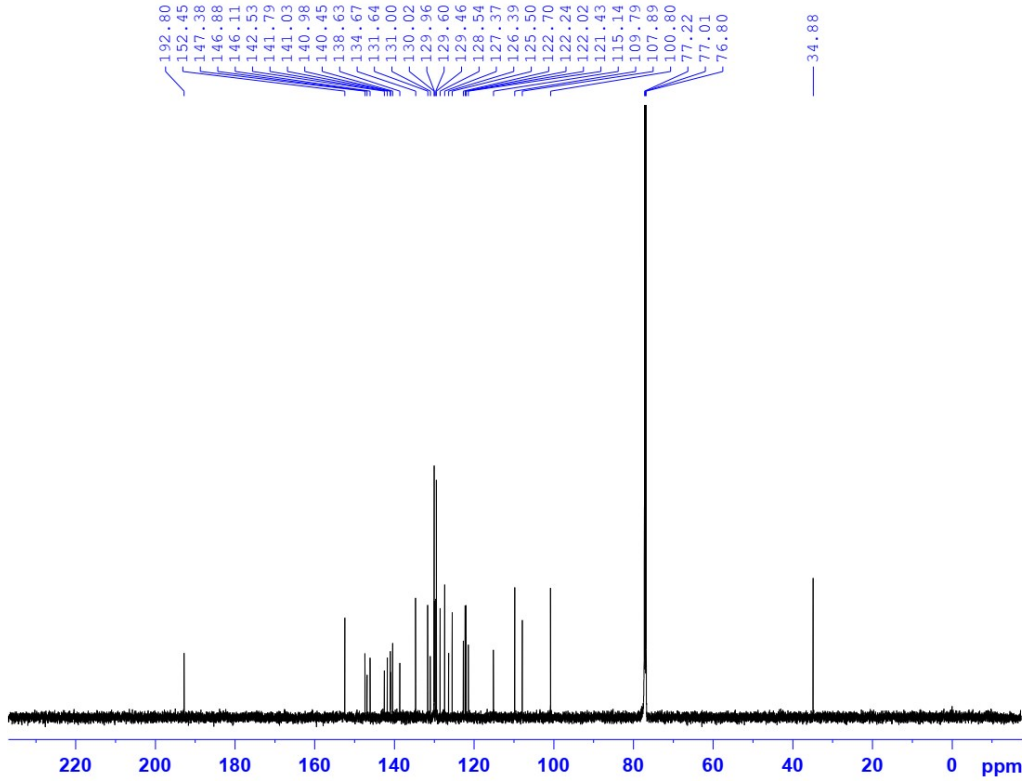
Current Data Parameters
 NAME 6HP03.48
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20230417
 Time 17.30 h
 INSTRUM AvanceNeo 600MHz
 PROBHD 2114607_D862 (4
 PULPROG zg30
 TD 65536
 SOLVENT CDC13
 NS 16
 DS 2
 SWH 11904.762 Hz
 FIDRES 0.363304 Hz
 AQ 2.7525120 sec
 RG 101
 DW 42.000 usec
 DE 8.71 usec
 TE 303.1 K
 D1 1.00000000 sec
 TD0 1
 SFO1 600.4037075 MHz
 NUC1 1H
 P0 3.50 usec
 P1 10.50 usec
 PLW1 27.03700066 W

F2 - Processing parameters
 SI 65536
 SF 600.4000171 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00



HP03.48-CDC13-C13CPD

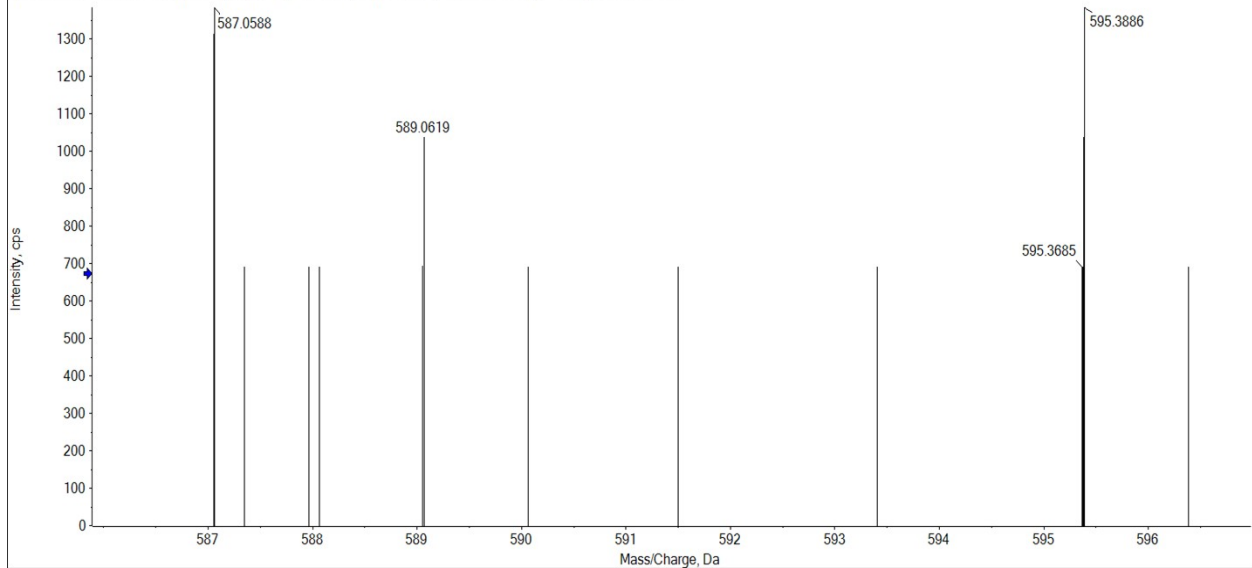


Current Data Parameters
NAME 6HP03.48
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230418
Time 21.18 h
INSTRUM AvanceNEO 600MHz
PROBHD 2114607_0862 (
PULPROG zgpg30
TD 65536
SOLVENT cdc13
NS 1024
DS 4
SWH 38461.539 Hz
FIDRES 1.173753 Hz
AQ 0.8519680 sec
RG 101
DW 13.000 usec
DE 6.50 usec
TE 303.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9873069 MHz
NUC1 13C
P0 4.20 usec
P1 12.60 usec
PLM1 86.32800293 W
SFO2 600.4024016 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 80.00 usec
PLW2 27.03700066 W
PLM2 0.46575001 W
PLW3 0.30599001 W

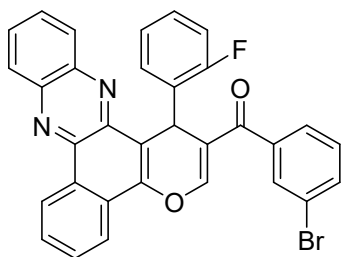
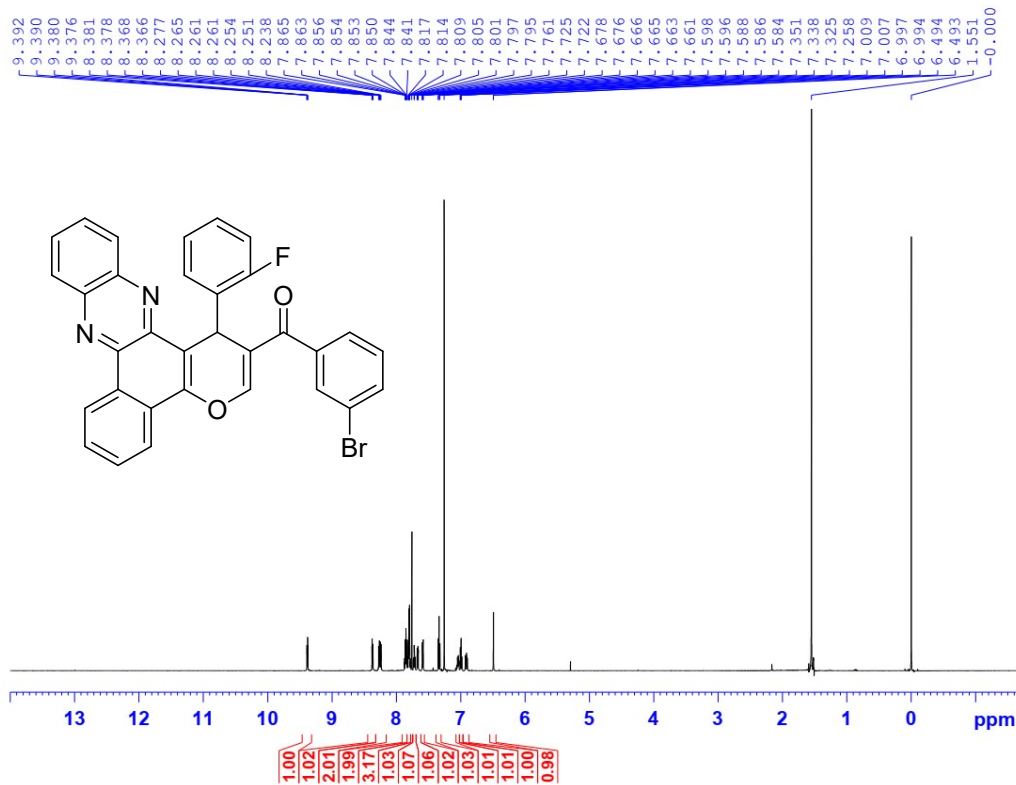
F2 - Processing parameters
SI 32768
SF 150.9707001 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Spectrum from 20230614Hang.wif2 (sample 11) - HP03.48, Experiment 1, +IDA TOF MS (20 - 4500) from 0.297 min

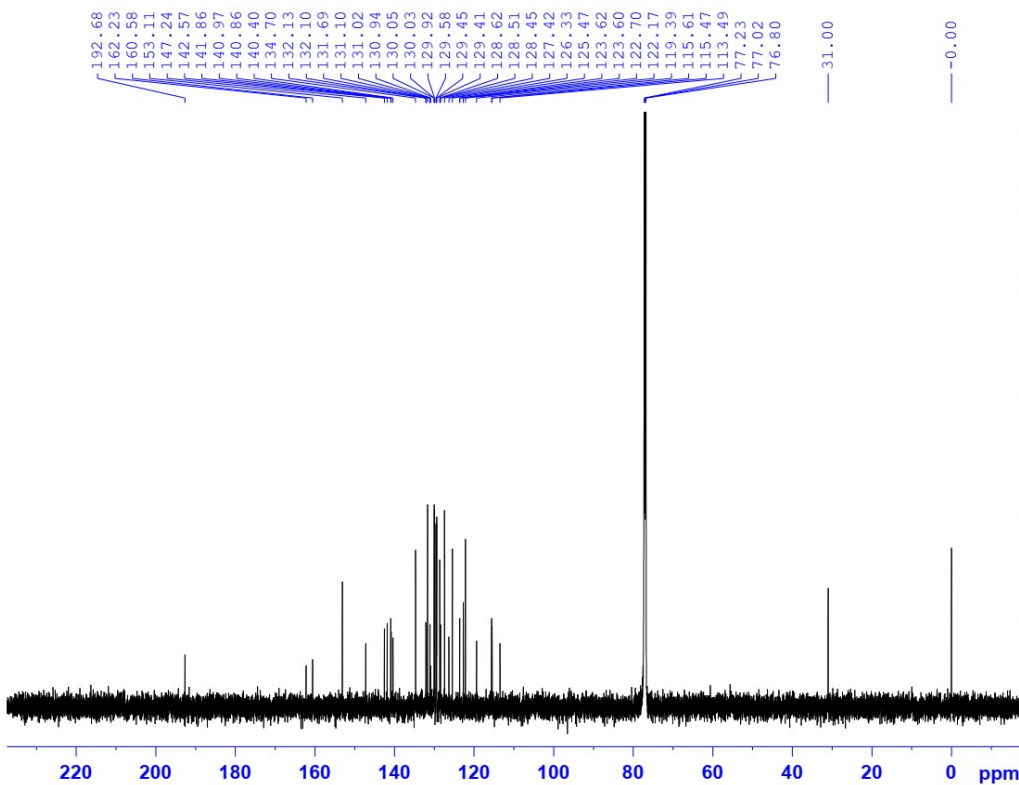


(3-Bromophenyl)(1-(2-fluorophenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7I).

DH03.50-CDC13-1H

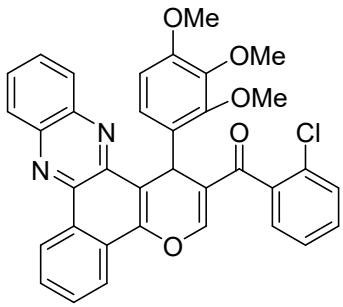
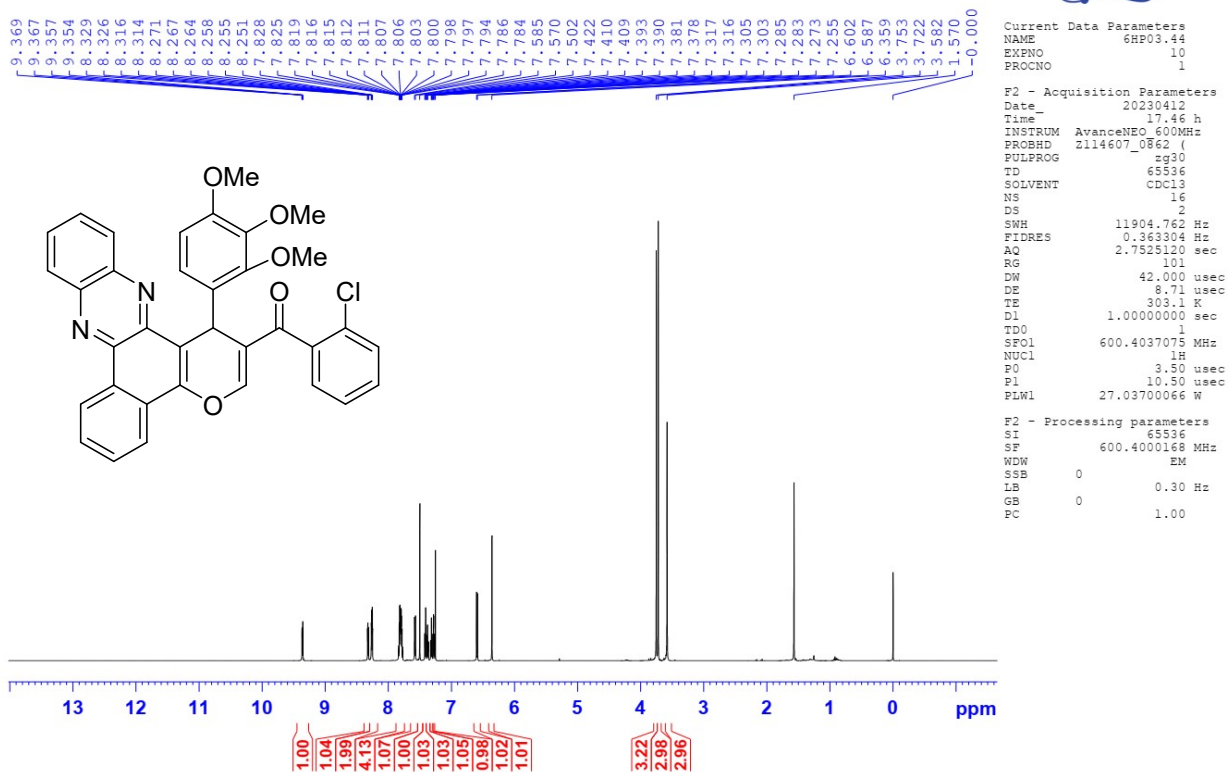


DH03.50-CDC13-C13CPD

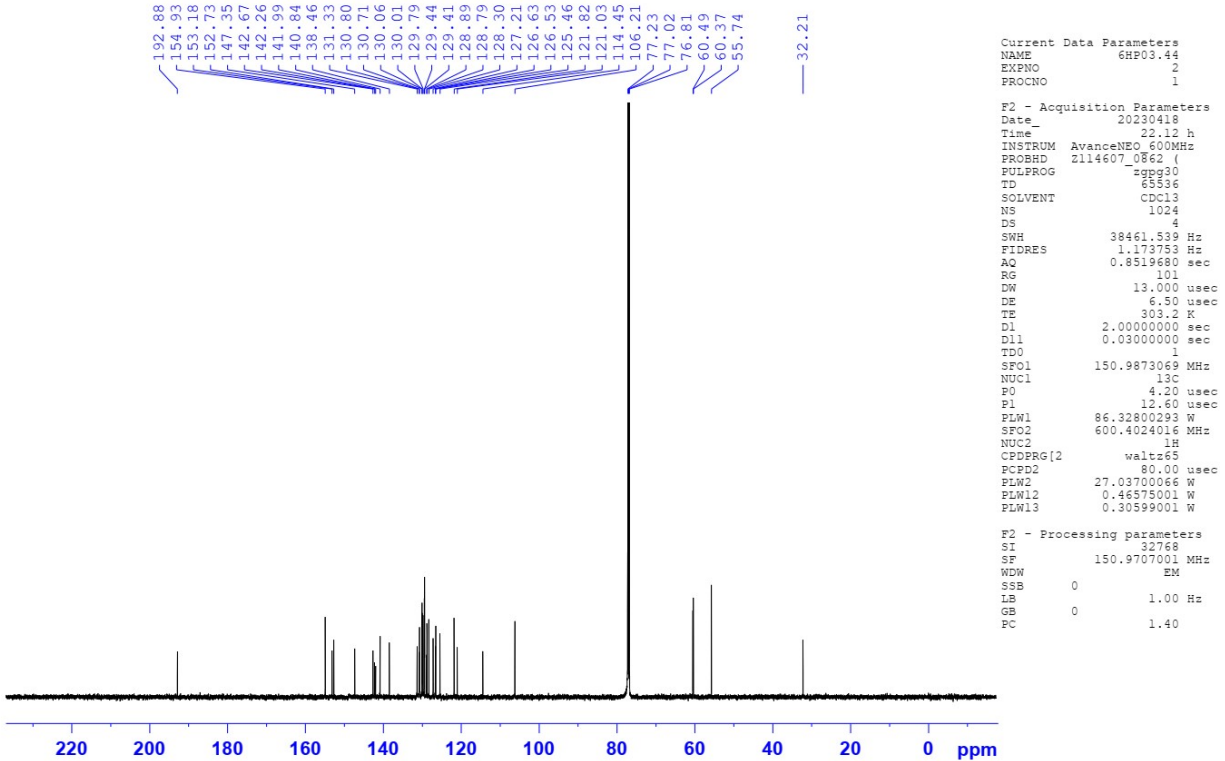


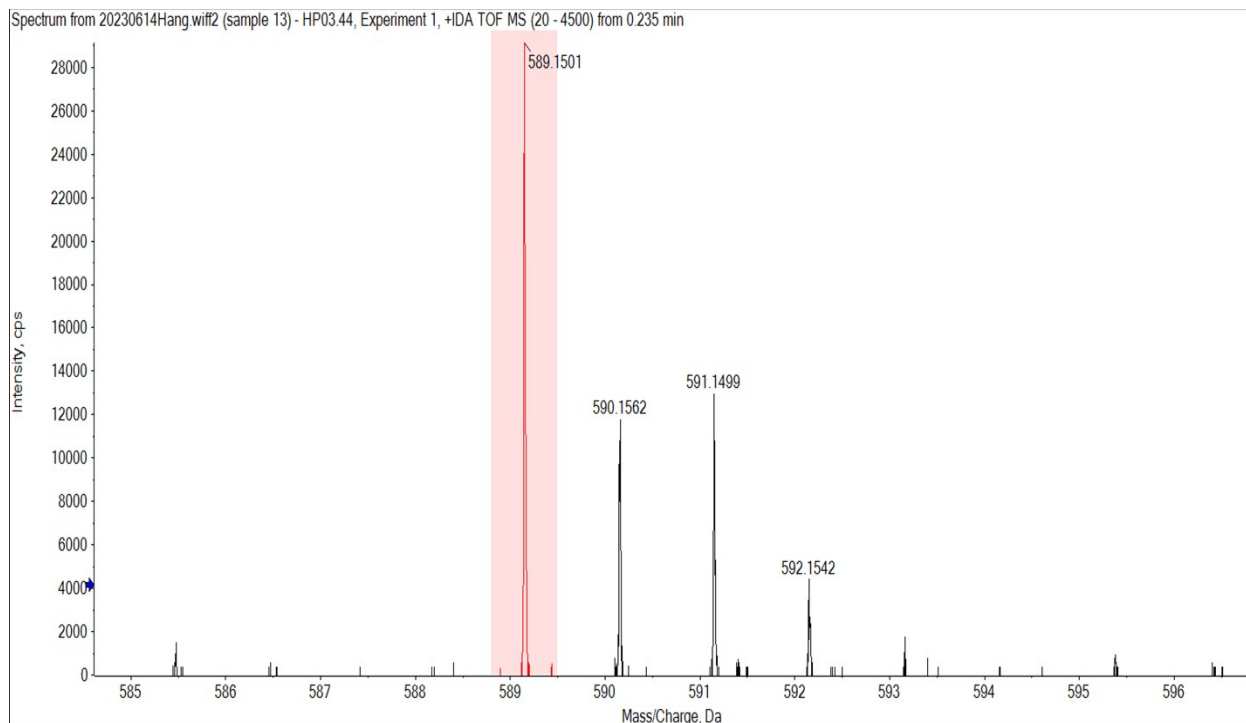
(2-Chlorophenyl)(1-(2,3,4-trimethoxyphenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7m).

HP03.44-CDC13-1H



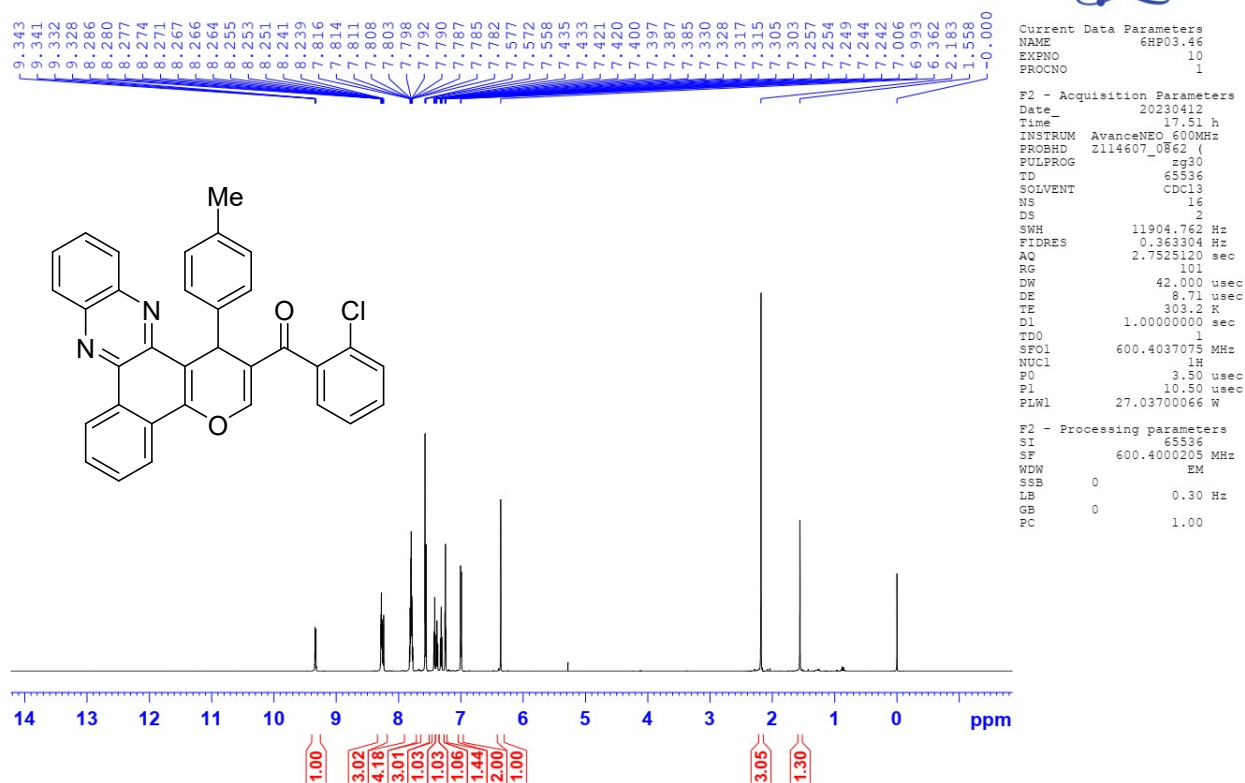
HP03.44-CDC13-C13CPD



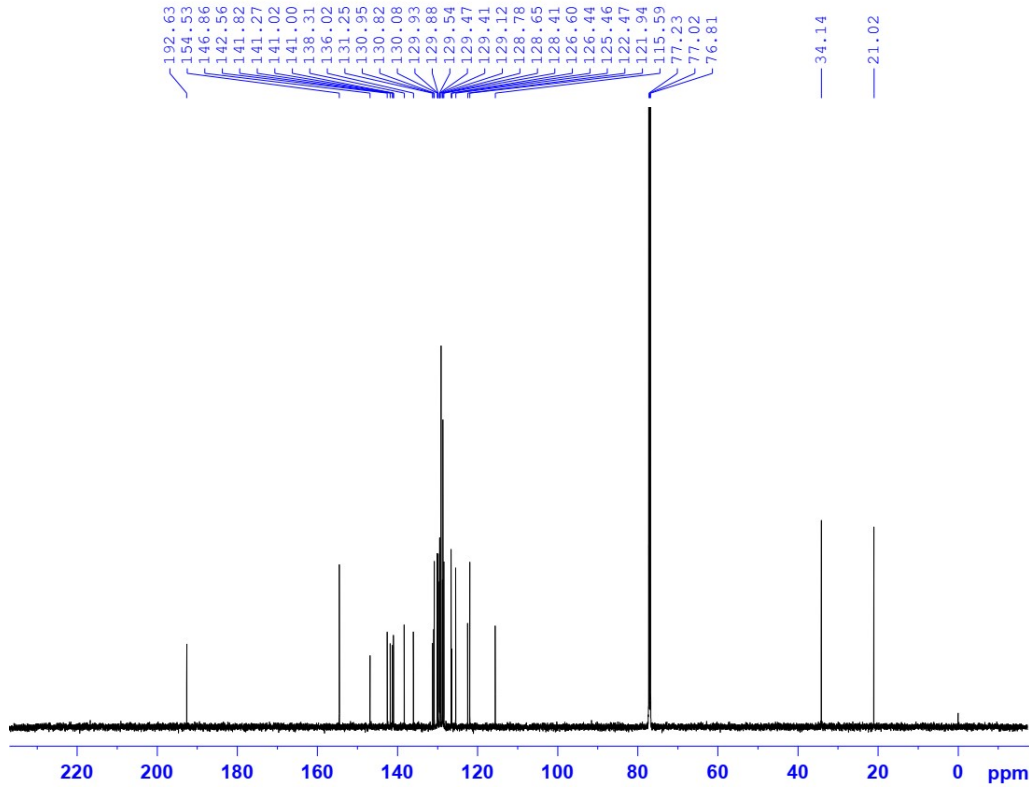


(2-Chlorophenyl)(1-(p-tolyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7n).

HP03.46-CDCl3-1H



HP03.46-CDC13-C13CPD

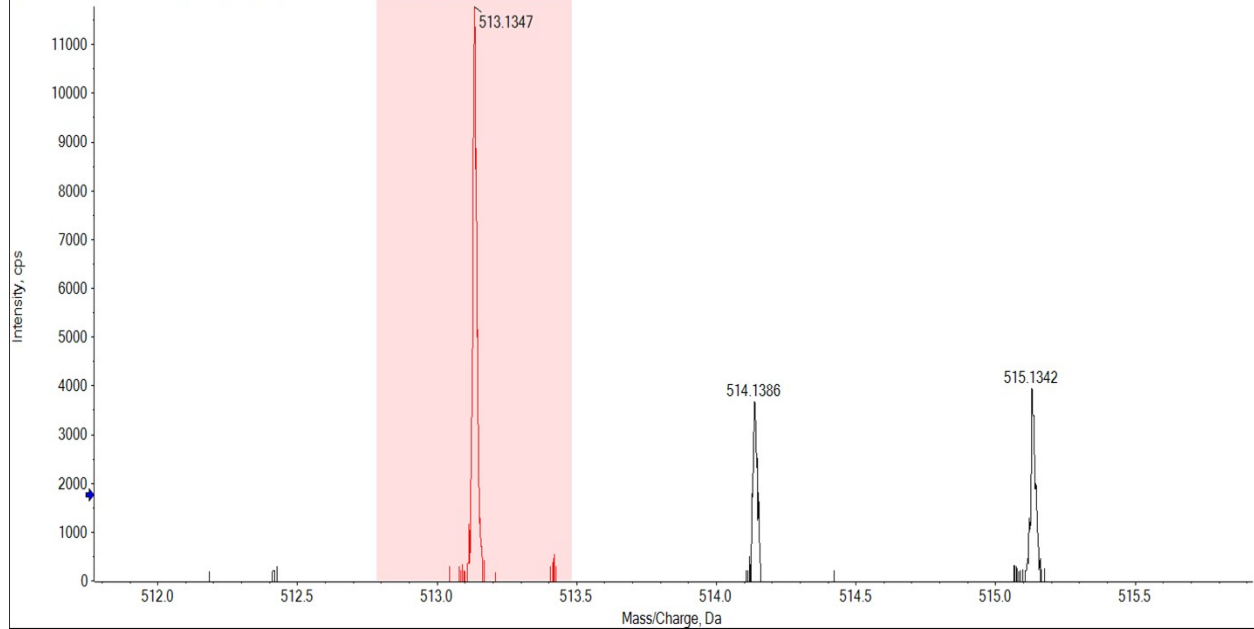


Current Data Parameters
NAME 6HP03.46
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230418
Time 23.08 h
INSTRUM AvanceNEO 600MHz
PROBHD zll4607_0862 (1
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 1024
DS 4
SWH 38461.539 Hz
FIDRES 1.173753 Hz
AQ 0.8519680 sec
RG 101
DM 13.000 usec
DE 6.50 usec
TE 303.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SF01 150.9873069 MHz
NUC1 13C
PO 4.20 usec
P1 12.60 usec
PLW1 86.32800293 W
SFO2 600.4024016 MHz
NUC2 1H
CPDPRG[2] waltz65
PCPD2 80.00 usec
PLW2 27.03700066 W
PLW12 0.46575001 W
PLW13 0.30599001 W

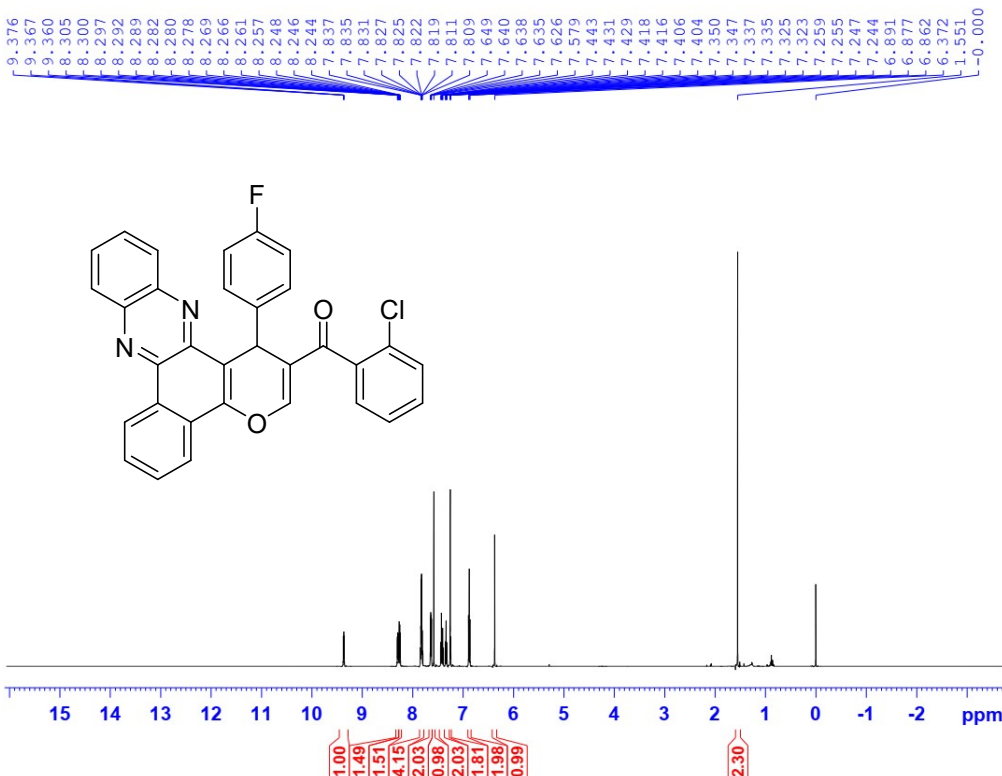
F2 - Processing parameters
SI 32768
SF 150.9707001 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Spectrum from 20230614Hang.wiff2 (sample 14) - HP03.46, Experiment 1, +IDA TOF MS (20 - 4500) from 0.210 min



(2-Chlorophenyl)(1-(4-fluorophenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7o).

HP03.47-CDC13-1H



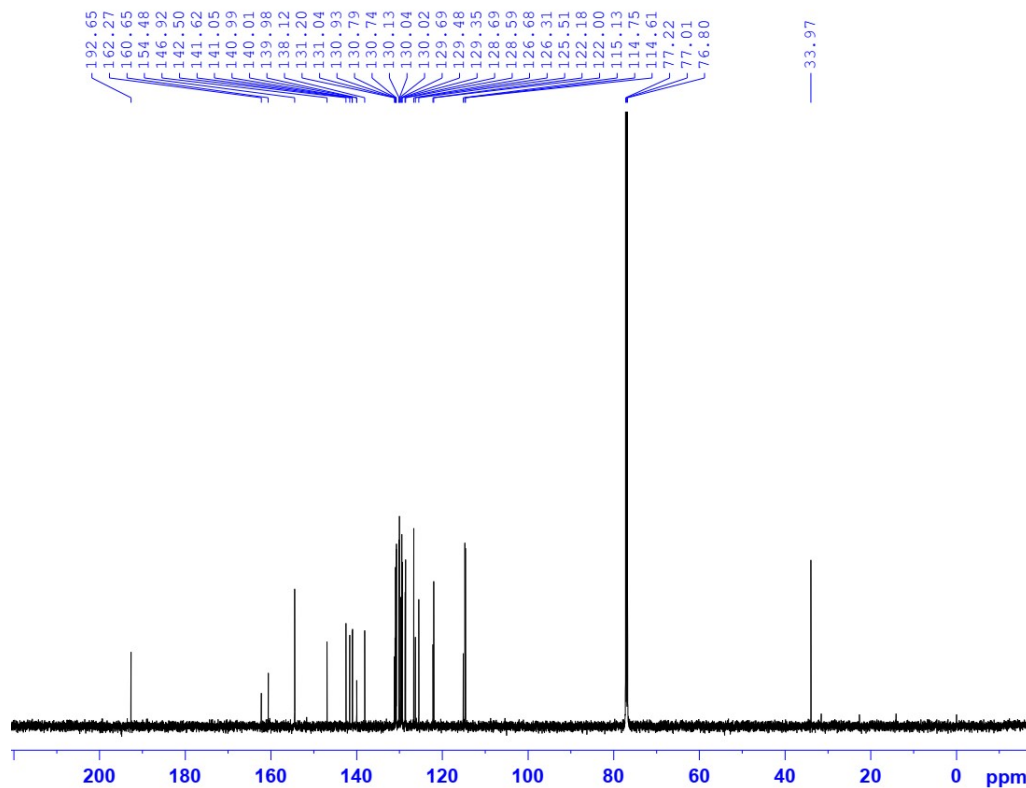
```

Current Data Parameters
NAME      6HP03.47
EXPNO    1
PROCNO   1

F2 - Acquisition Parameters
Date_    20230417
Time     17.25 h
INSTRUM  AvanceNEO 600MHz
PROBHD   Z114607_0862 (
PULPROG  zg30
TD       65536
SOLVENT  CDCl3
NS       16
DS       2
SWH      11904.762 Hz
FIDRES   0.363304 Hz
AQ       2.7525120 sec
RG       101
DM       42.000 usec
DE       8.71 usec
TE       303.1 K
D1       1.00000000 sec
TD0      1
SF01     600.4037075 MHz
NUC1     1H
PC       3.50 usec
P1       10.50 usec
PLW1     27.03700066 W

F2 - Processing parameters
SI       65536
SF       600.4000168 MHz
WDW      EM
SSB      0
LB       0.30 Hz
GB       0
PC       1.00
    
```

HP03.47-CDC13-C13CPD

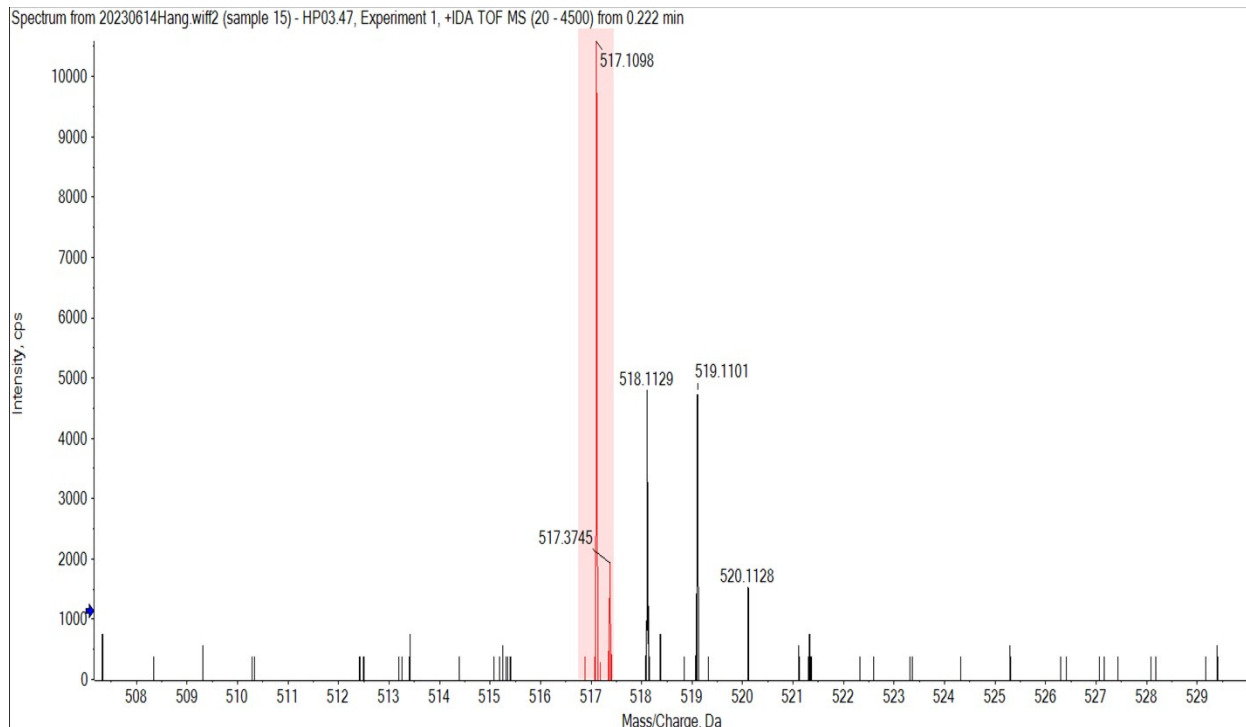


```

Current Data Parameters
NAME      6HP03.47
EXPNO    2
PROCNO   1

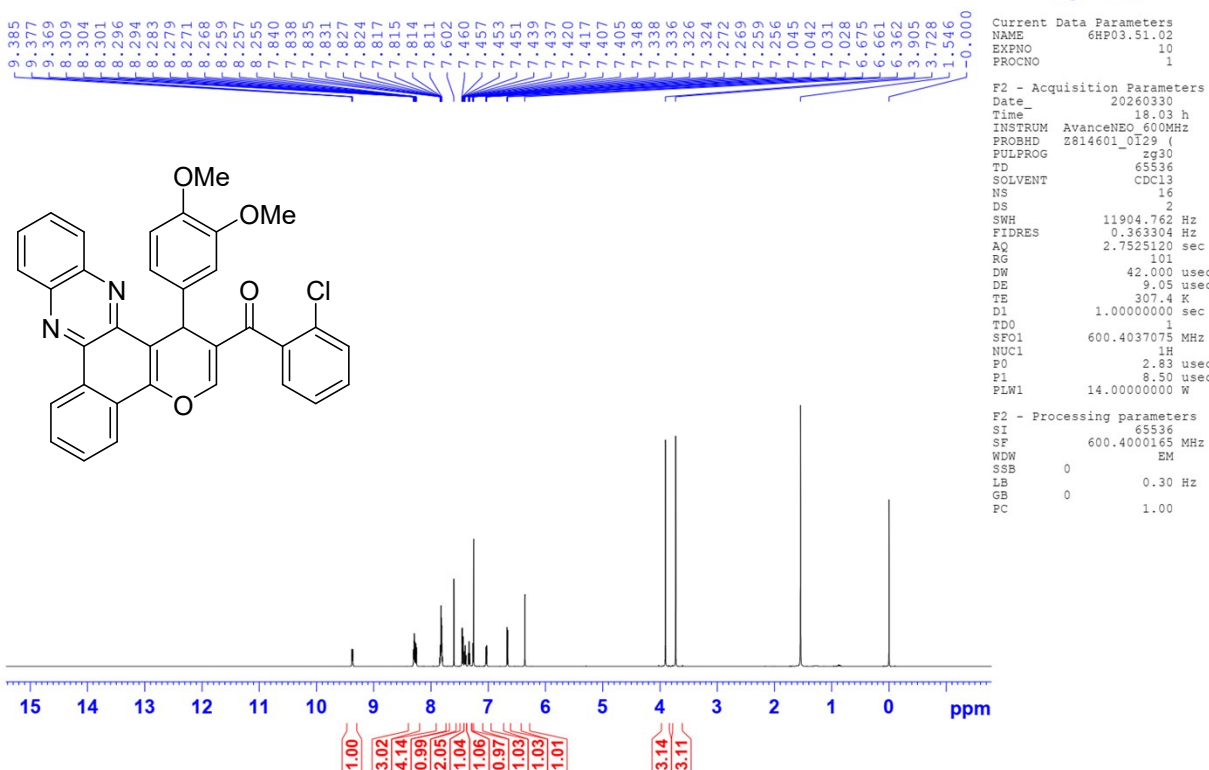
F2 - Acquisition Parameters
Date_    20230419
Time     0.02 h
INSTRUM  AvanceNEO 600MHz
PROBHD   Z114607_0862 (
PULPROG  zgpg30
TD       65536
SOLVENT  CDCl3
NS       1024
DS       4
SWH      38461.539 Hz
FIDRES   1.173753 Hz
AQ       0.8519680 sec
RG       101
DM       13.000 usec
DE       6.50 usec
TE       303.2 K
D1       2.00000000 sec
D11      0.03000000 sec
TD0      1
SF01     150.9873069 MHz
NUC1     13C
PC       4.20 usec
P1       12.60 usec
PLW1     86.32800293 W
SF02     600.4024016 MHz
NUC2     1H
CPDPRG2  waltz65
PCPD2    80.00 usec
PLW2     27.03700066 W
PLW12    0.46575001 W
PLW13    0.30599001 W

F2 - Processing parameters
SI       32768
SF       150.9707001 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
    
```

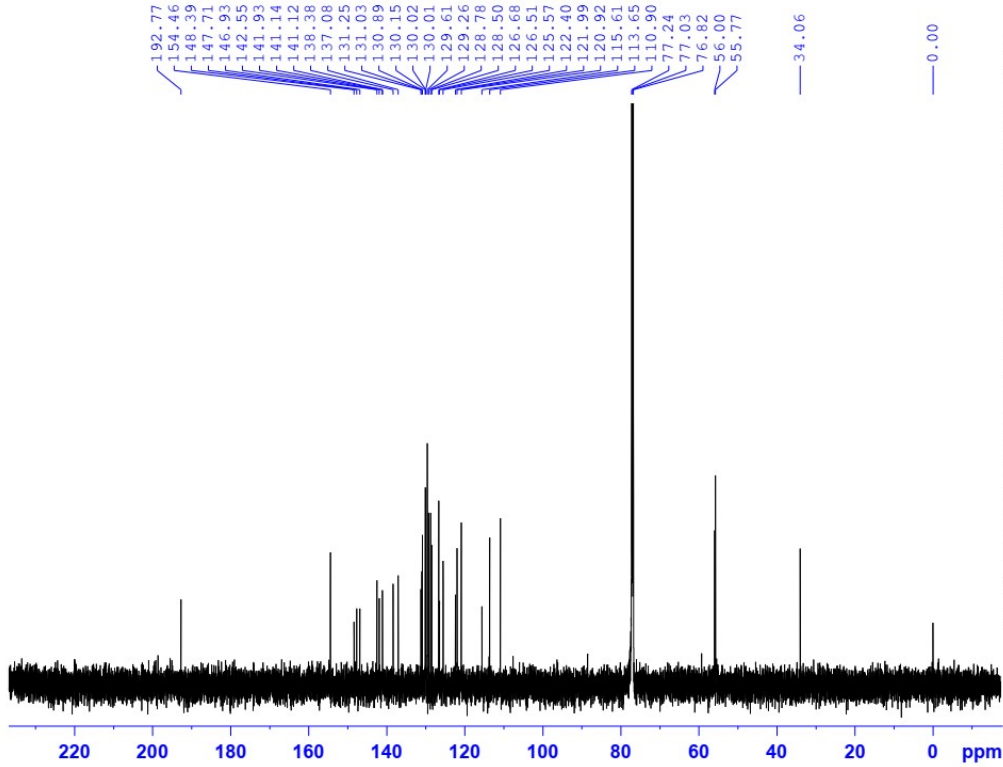


(2-chlorophenyl)(1-(3,4-dimethoxyphenyl)-1H-benzo[a]pyrano[2,3-c]phenazin-2-yl)methanone (7p).

HP03.51.02-CDCl3-1H



HP03.51.02-CDC13-C13CPD



Current Data Parameters
 NAME 6HP03.51.02
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20260331
 Time_ 8.12 h
 INSTRUM AvanceNEO 600MHz
 PROBRD Z814601_0129 (600)30
 PULPROG zgpg30
 TD 65536
 SOLVENT CDC13
 NS 1024
 DS 4
 SWH 38461.539 Hz
 FIDRES 1.173753 Hz
 AQ 0.8519680 sec
 RG 101
 DW 13.000 usec
 DE 6.50 usec
 TE 309.3 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 150.9873069 MHz
 NUCL1 13C
 P0 5.63 usec
 P1 16.90 usec
 PLW1 126.55000305 W
 SFO2 600.4024016 MHz
 NUCL2 1H
 CPDPRG2 waltz65
 PCPD2 70.00 usec
 PLW2 14.00000000 W
 PLW12 0.20643000 W
 PLW13 0.10383000 W

F2 - Processing parameters
 SI 32768
 SF 150.9706931 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

Spectrum from 20230614Hang.wiff2 (sample 16) - HP03.51, Experiment 1, +IDA TOF MS (20 - 4500) from 0.300 min

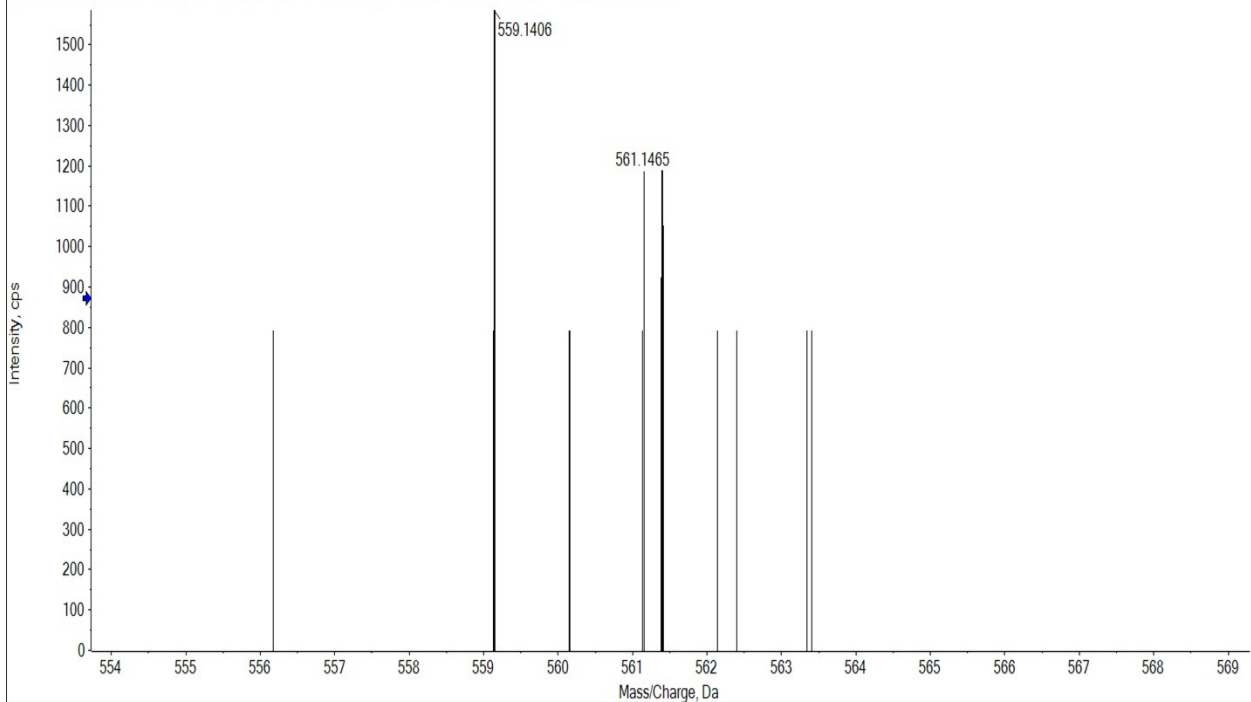


Table S1. Inhibitory effect of 7a-p on NO production in LPS-mediated macrophage RAW 264.7 cells and cell viability of RAW 264.7 cells

Entry	Compound	Concentration (µg/ml)	NO inhibition (%)	Cell viability (%)
1.	7a	64	80	96
		16	72	100
		4	64	100
		1	46	100
		0.25	35	100
		IC₅₀	1.67±0.2	
2.	7b	64	66	87
		16	60	92
		4	55	94
		1	42	95
		0.25	6	95
		IC₅₀	2.85±0.32	
3.	7c	64	81	85
		16	69	96
		4	58	100
		1	51	100
		0.25	31	100
IC₅₀	0.96±0.05			
4.	7d	64	67	93
		16	61	100
		4	55	100
		1	54	100
		0.25	48	100
		IC₅₀	0.5±0.05	
5.	7e	64	72	78
		16	66	87
		4	62	88
		1	48	90
		0.25	41	93
		IC₅₀	1.43±0.08	
6.	7f	64	66	88
		16	52	96
		4	40	97
		1	21	100
		0.25	0	100
		IC₅₀	14.00±1.20	
7.	7g	64	85	81
		16	82	100

Entry	Compound	Concentration (µg/ml)	NO inhibition (%)	Cell viability (%)
		4	71	100
		1	55	100
		0.25	31	100
		IC₅₀	0.84±0.07	
8.	7h	64	64	74
		16	59	100
		4	53	100
		1	50	100
		0.25	36	100
		IC₅₀	1.0±0.15	
9.	7i	64	66	70
		16	57	72
		4	44	84
		1	6	91
		0.25	0	100
		IC₅₀	9.54±0.5	
10.	7j	64	70	80
		16	59	94
		4	20	100
		1	6	100
		0.25	0	100
		IC₅₀	13.23±1.44	
11.	7k	64	76	100
		16	60	100
		4	54	100
		1	22	100
		0.25	11	100
		IC₅₀	3.63±0.15	
12.	7l	64	82	70
		16	60	75
		4	59	85
		1	57	92
		0.25	12	93
		IC₅₀	0.88±0.05	
13.	7m	64	75	80
		16	71	84
		4	66	90
		1	24	91
		0.25	11	92
		IC₅₀	2.86±0.19	
14.	7n	64	65	67
		16	61	76
		4	30	94

Entry	Compound	Concentration (µg/ml)	NO inhibition (%)	Cell viability (%)
		1	9	96
		0.25	0	97
		IC₅₀	11.74±0.85	
15.	7o	64	70	89
		16	69	93
		4	37	99
		1	35	100
		0.25	29	100
		IC₅₀	8.88±0.5	
16.	7p	64	76	65
		16	65	87
		4	55	88
		1	43	90
		0.25	26	90
		IC₅₀	2.75±0.31	
	Reference:	128	92	90
	N ^G -Methyl-L-arginine acetate	32	85	99
	(L-NMMA)	8	63	99
		2	29	100
		0.5	16	100
		IC₅₀	5.71±0.5	