Supporting Information for

ORIGINAL ARTICLE

Nobiletin and its derivatives overcome multidrug resistance (MDR) in cancer: total synthesis and discovery of potent MDR reversal agents

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[†]These authors made equal contributions to this work.

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Section 1 Docking and molecular dynamics simulation methods

The crystal structure of P-gp in complex with inhibitor QZ59-RRR (PDB ID 4M2S) was used for molecular docking. All of the residues in P-gp were protonated at pH 7.0. Partial charges of the atoms were assigned by the Sybyl force field. The protomol, which represents a set of molecular fragments to characterize the active site, was generated by a ligand-based approach, and the bound ligand was utilized for protomol generation. The proto-thresh and proto-bloat parameters represented how much the protomol could be buried within the protein and how far the protomol extended outside the cavity, respectively, which were assigned by the default values 0.5 and 0. For the reliability of the molecular docking method, the bound inhibitor QZ59-RRR was redocked back to the protein and the results showed an average RMSD of <1.5 Å between the docking poses and the ZQ59-RRR conformation in the crystal structure.

MD simulations were then applied for a more precise prediction of binding patterns using AMBER 14. Amber99SB force field and general amber force field (GAFF) were assigned for ligands and P-gp, respectively. The protonation states of each amino acid were set depending on an overall pH of 7.0. The systems of **29d**-(P-gp) and NOB-(P-gp) were solvated in an 8 Å TIP3P water box in the form of a truncated octahedron, and Cl- was added for electric neutrality. After energy minimization and heating in the NPT ensemble from 10 to 300 K over 25 ps, the systems were subjected to 8 ns MD simulations in the NPT ensemble with a constant pressure of 1 atm and temperature of 300 K in periodic boundary conditions. An 8 Å cutoff was assigned for long-range electrostatic interactions with particle mesh Ewald (PME) method. The time step was set to 2 fs with the SHAKE algorithm applied to bonds involving hydrogen atoms. Binding free energies of **29d** and NOB with P-gp were calculated using MM-PBSA method by extracting 100 snapshots of the last 1 ns trajectory with default parameters assigned.

Section 2 Cell viability assay, colony formation assay and animal models

1. Cell viability assay, colony formation assay

The degree of resistance was estimated by cytotoxicity using the sulforhodamine B (SRB) assay and by colony formation assay[1] for HCT8 human intestinal cancer cells, A549 human nonsmall cell lung cancer (NSCLC) cells and paclitaxel (PTX)-resistant cell lines HCT8/T and A549/T (KeyGen Biotech Co., Ltd., Nanjing, China). RPMI-1640 medium supplemented with 10% fetal bovine serum (GIBCO, Paisley, Scotland) was used for culturing cancer cells at 37 ℃ with a humidified 5% CO_2 atmosphere. To maintain drug resistance, PTX (0.94 μmol/L for A2780/T and 0.24 μmol/L for A549/T) was added to the culture medium. The reversal of resistance was defined as a ratio of the IC_{50} values for the PTX cells without and with test compound (10 μmol/L).

2. Apoptosis detection and cell cycle analysis

Flow cytometry analyses were performed to define the cell cycle distribution after treatment[7]. HCT8/T cells were harvested after 24 h of treatment and washed twice with ice-cold PBS, then fixed and permeabilized with 70% ice-cold ethanol overnight at 4 °C or 2 h at −20 °C. The cells were stained by a solution containing PI (20 μg/mL), RNase A (200 μg/mL) and 0.1% Triton X-100 (Sigma Aldrich) in PBS for 30 min at room temperature before analysis by a BD FACS Aria flow cytometer (BD Biosciences, San Jose, USA) with FlowJo software.

For the cell apoptosis assay, cells were collected, washed and suspended in 100 μL of binding buffer (10 mmol/L *N*-2-hydroxyethylpiperazine-*N*-2-ethane sulfonic acid/NaOH, 140 mmol/L NaCl, 2.5 mmol/L $CaCl_2$, pH 7.4). Apoptotic cells were identified by double supravital staining with 5 μL recombinant FITC (fluorescein isothiocyanate)-conjugated annexin-V and 5 μL PI (50 μg/mL) and analyzed by a BD FACSAria flow cytometer with FlowJo software.

3. Xenograft model establishment

All animal studies were approved by the Animal Care and Use Committee at Guangzhou University of Chinese Medicine (China, No #ZYYL20150807). Tumor-bearing mice were randomized into nine groups (n = 6): control group, 15 mg/kg PTX group, 50 mg/kg NOB group, 50 mg/kg **13** group, 50 mg/kg **29d** group, 50 mg/kg NOB + 15 mg/kg PTX group, 25 mg/kg **13** + 15 mg/kg PTX group, 50 mg/kg **13** + 15 mg/kg PTX group, 25 mg/kg **29d** + 15 mg/kg PTX group, and 50 mg/kg **29d** + 15 mg/kg PTX group. The mixture of 5 × 10^6 A549/T cells was resuspended in 50 μL of RPMI 1640 medium and 50 μL of matrigel was injected into the armpits of the right forepaws of 8-week-old nude mice. Five days later, the mice with tumor formation were given intraperitoneal injection (i.p.) every 3 days. The tumor volume was monitored every 3 days and calculated using the following equation:

volume = (width^2 × length)/2. On day 30, all nude mice were sacrificed, and the tumors were excised and then weighed using an electronic balance.

4. Western blotting

The total cellular samples were harvested and rinsed twice with ice-cold PBS buffer. After lysis, the protein expression levels of P-gp, NRF2, ERK and AKT, as well as their phosphorylation levels, were measured in A2780 or A2780/T cells in the absence or presence of NOB and its derivatives by Western blotting, as described previously[1].

5. LC–MS/MS analysis

Tumor fractions were homogenized in PBS solution and extracted with 3 volumes of methanol. After centrifugation, the supernatant was analyzed with an Agilent 6460 Triple Quadrupole LC/MS System (Agilent Technologies, Inc., USA) equipped with a Waters ACQUITY UPLC® HSS T3 C18 column (1.8 μm, 100 mm × 2.1 mm; Part No.186003539, Waters, Ireland). A linear gradient mobile phase composed of 0.1% aqueous formic acid (A) and 0.1% formic acid in acetonitrile (B) was optimized according to the following gradient program: 0–2 min (40% B); 2–8 min (40%–74% B); 8–8.5 min (74%–40% B). The injection volume was 10 μL, and the flow rate was 0.35 mL/min. MS parameters were as follows: capillary voltage, 4000 V; fragmentation voltage, 150 V; drying gas, 10 L/min; drying gas temperature, 325 ℃; nebulizer gas pressure, 40 psi; dwell time, 200 ms. Multiple reaction monitoring (MRM) was used for detection with the parent ion/product ion (*m*/*z*) for PTX at 876.9/308.1 (CE 25 V), docetaxel (DOX, internal standard) at 830.3/304.1 (CE 20 V), **29d** at 473.2/72.1 (CE 18 V) and NOB at 402.9/372.9 (CE 25 V). All UPLC–MS data were obtained by Agilent ChemStation Software (v6.03).

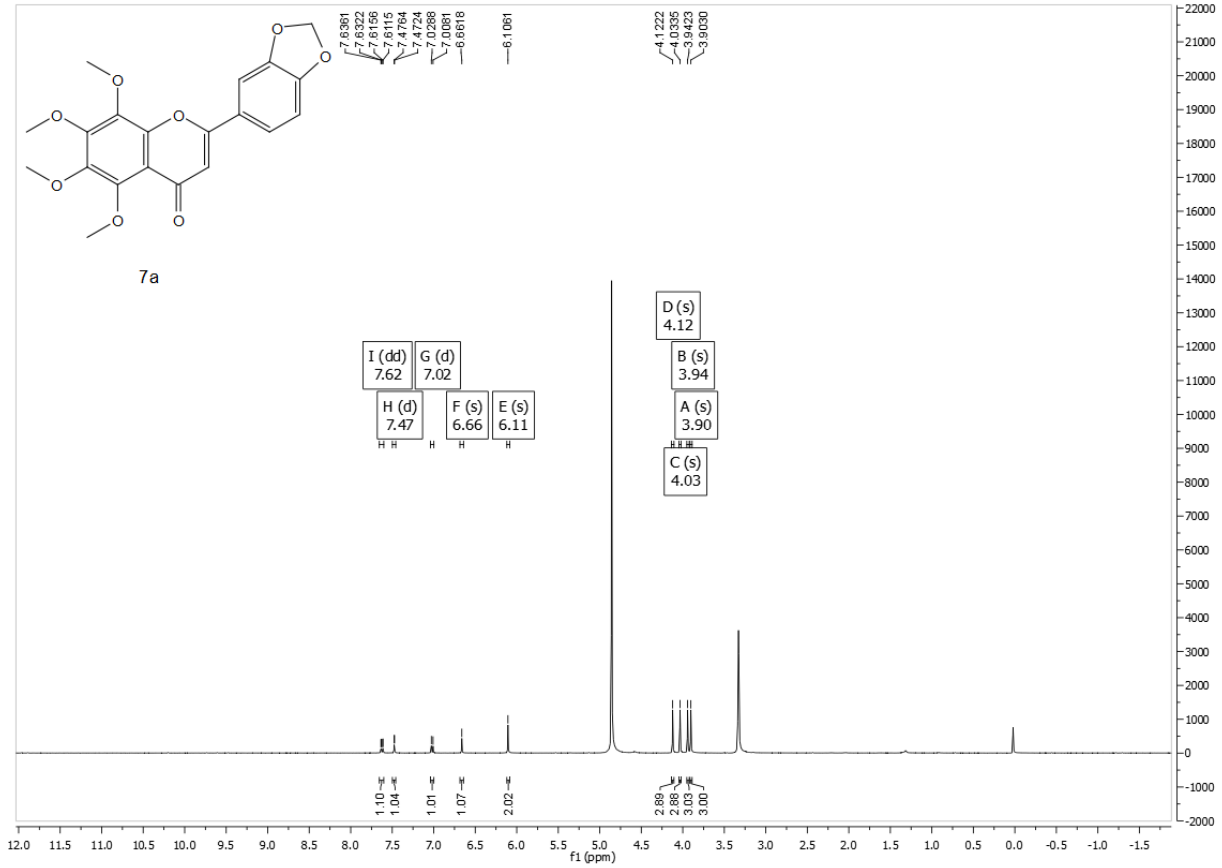
6. Statistical analysis

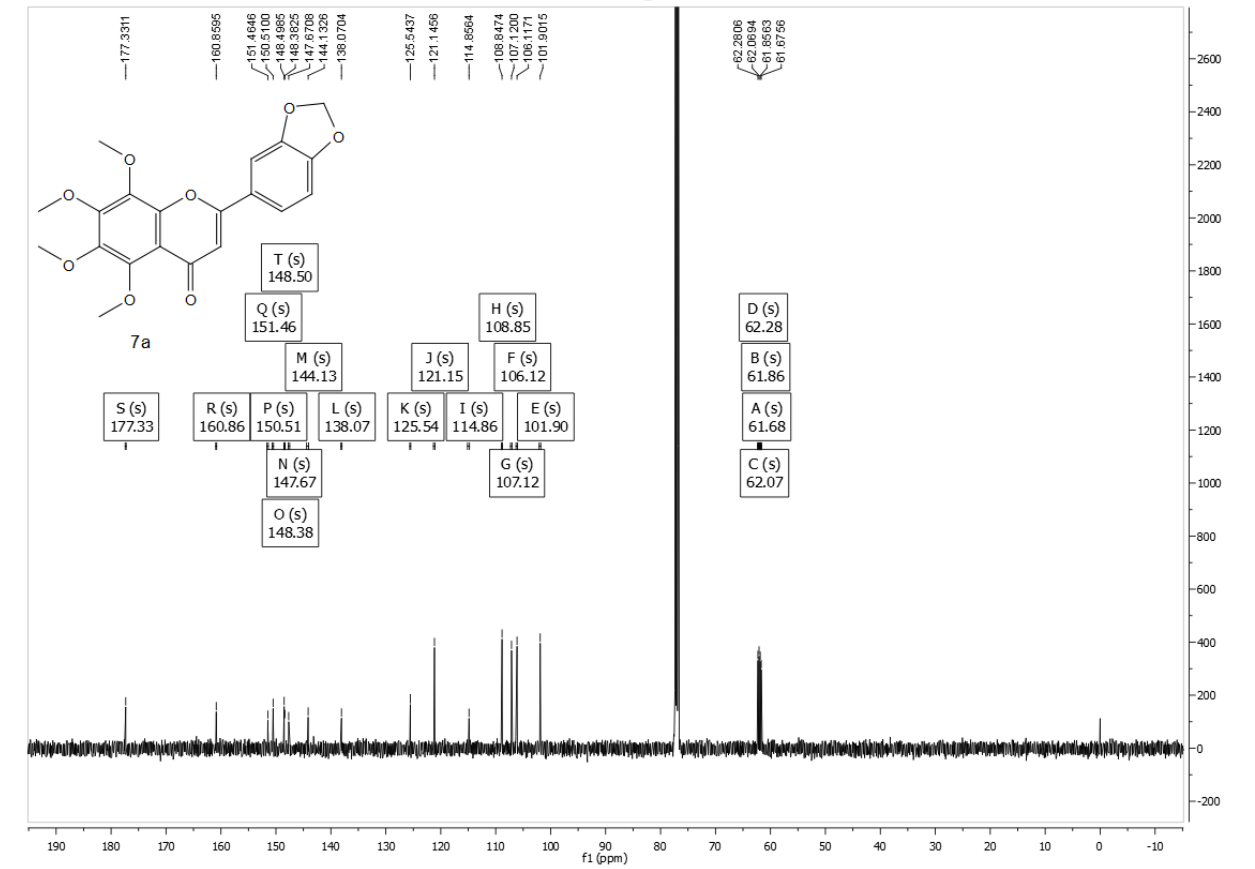
All data were repeated in a minimum of three separate experiments, and the data were presented as the mean ± SEM. *P* values were calculated using Student's *t*-test or one-way analysis of variance (ANOVA) followed by one-way ANOVA using GraphPad Software 6.0 (GraphPad Software, Inc., San Diego, USA). $P < 0.05$ was considered statistically significant.

Reference:

1. Wen Y, Zhao RQ, Gupta P, Fan YF, Zhang YK, Huang ZG, et al. The epigallocatechin gallate derivative Y-6 reverses drug resistance mediated by the ABCB1 transporter both *in vitro* and *in vivo*. *Acta Pharm Sin B* 2019;**9**:316-323.

Section 3 ^{1}H NMR and ^{13}C NMR data for tested compounds

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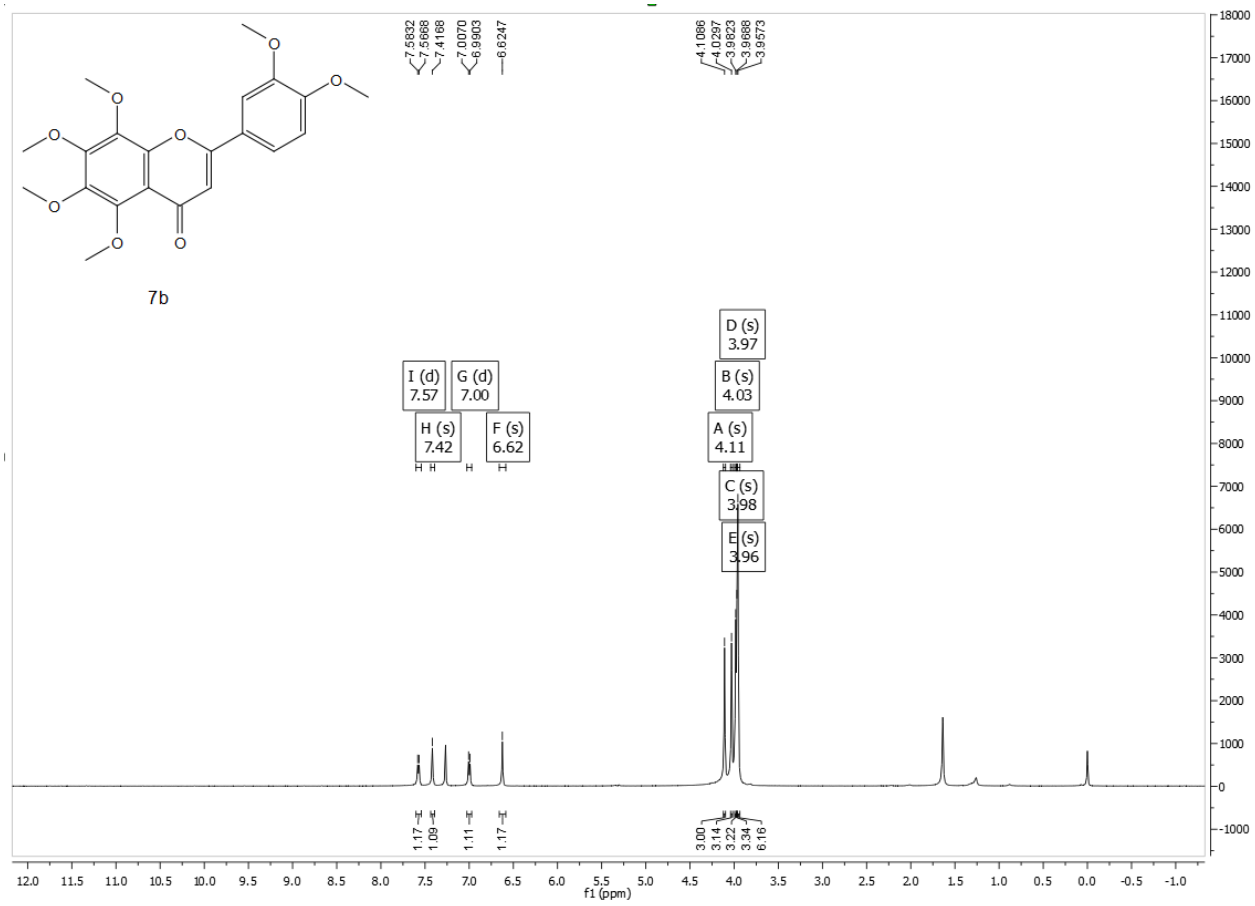
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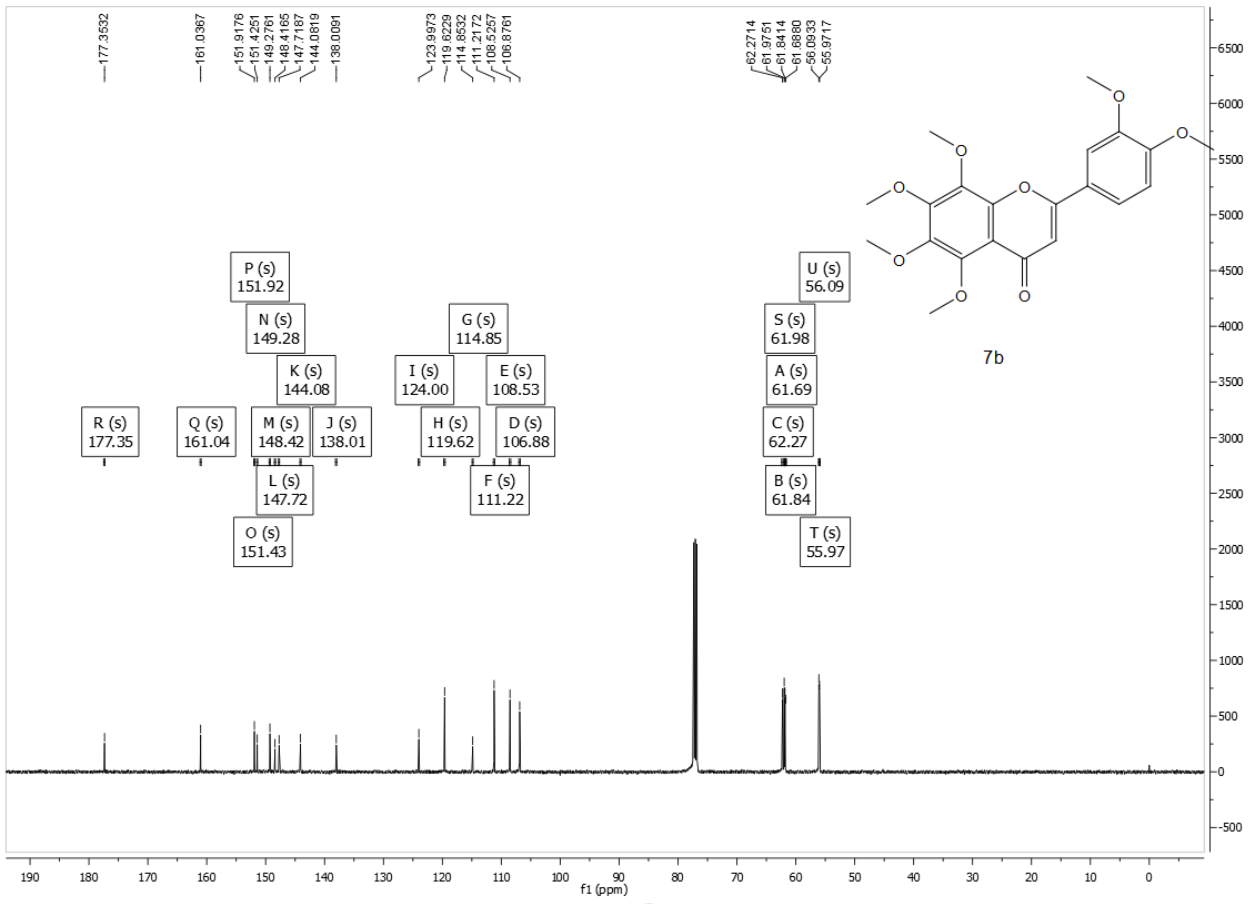
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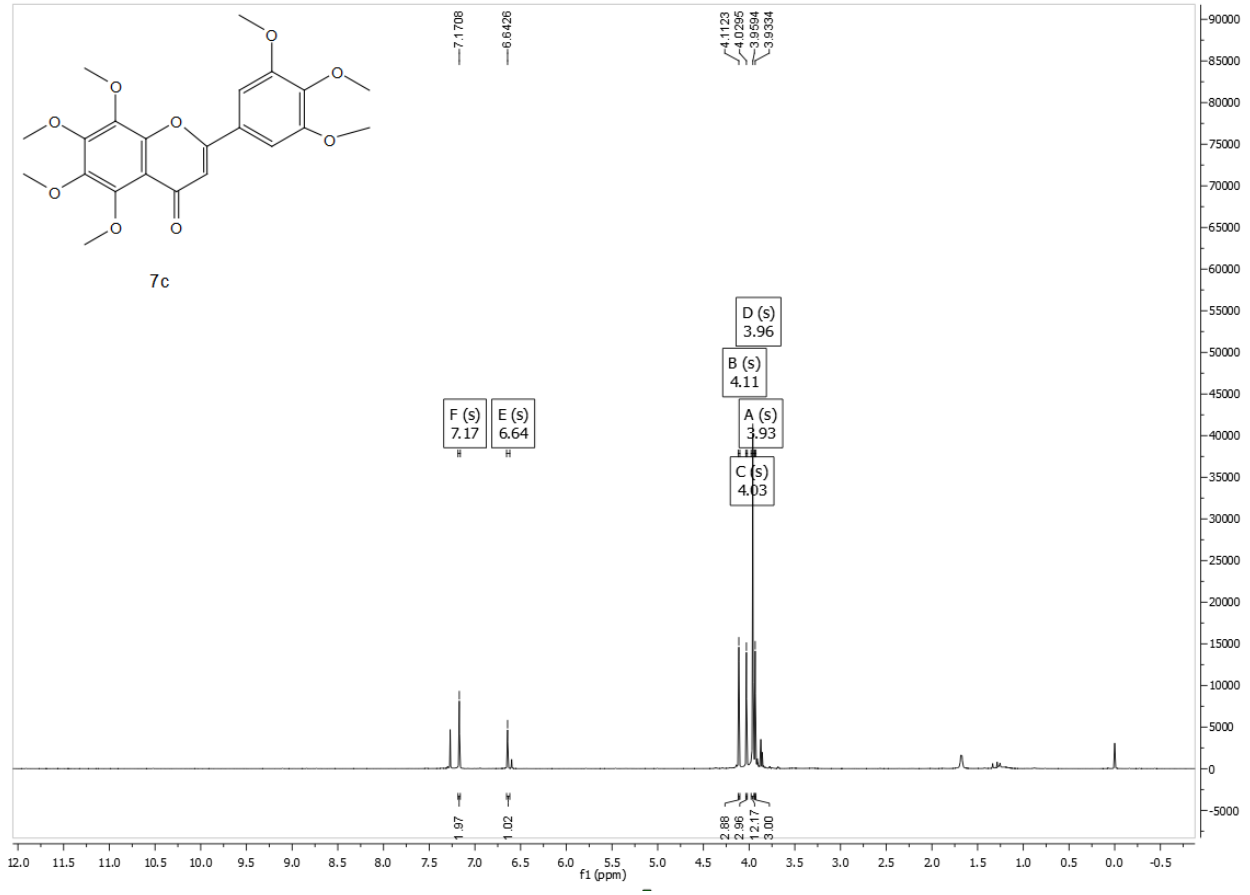
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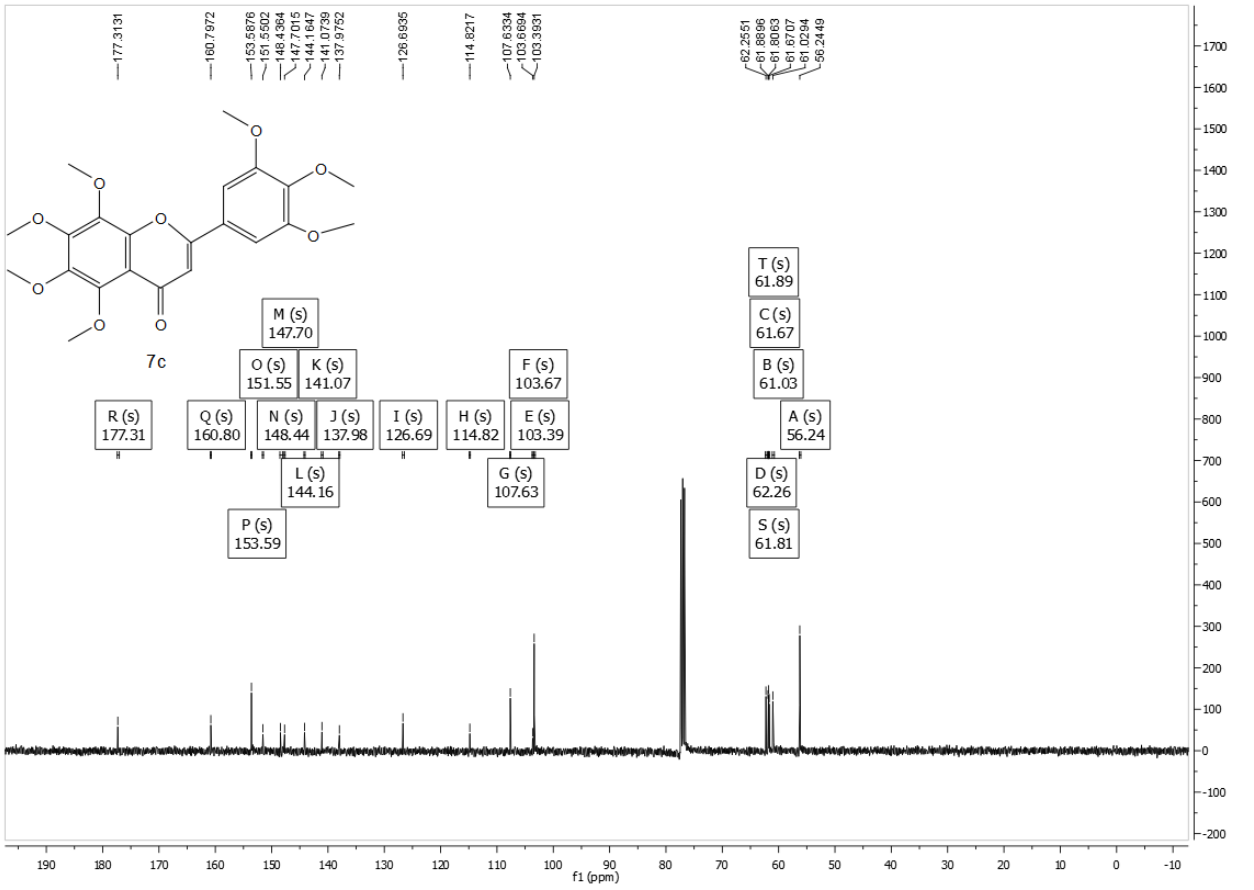
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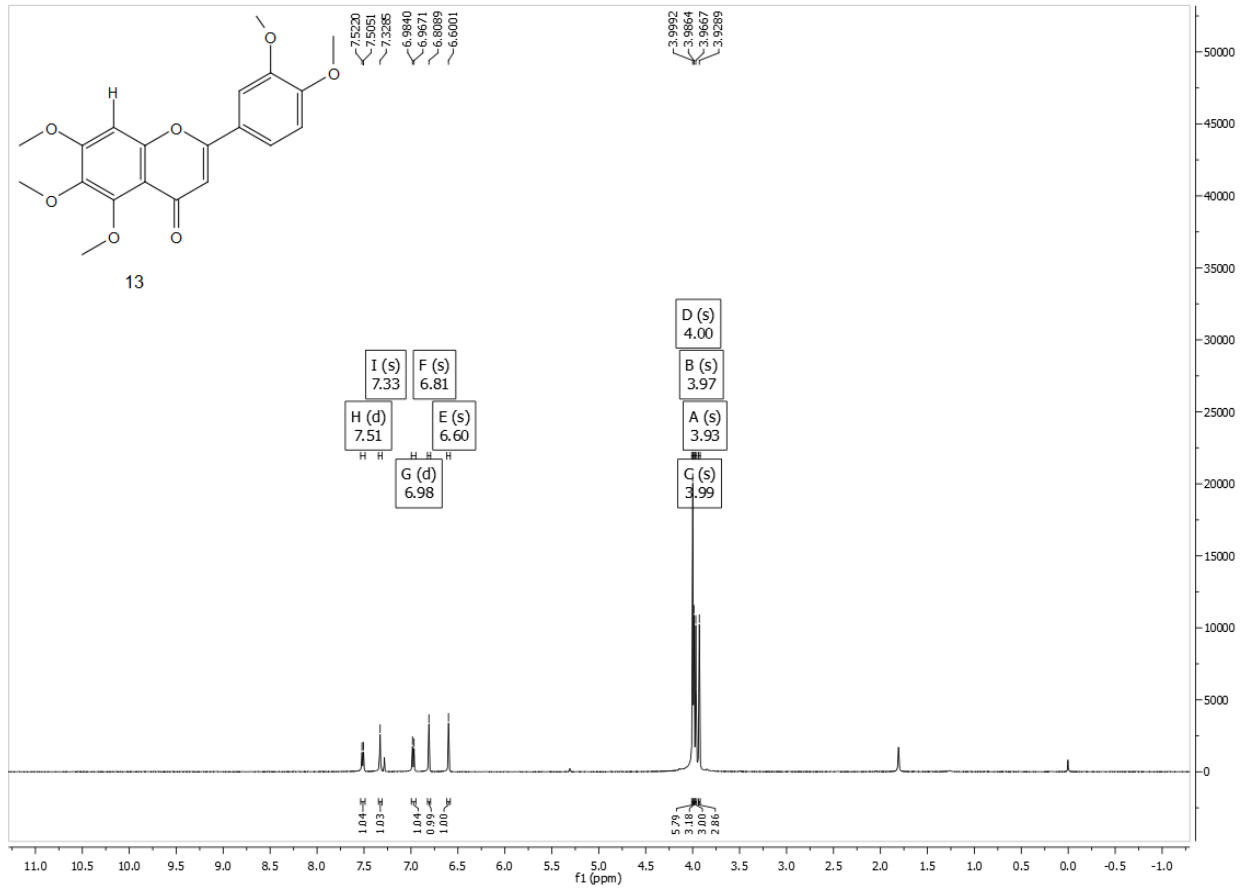
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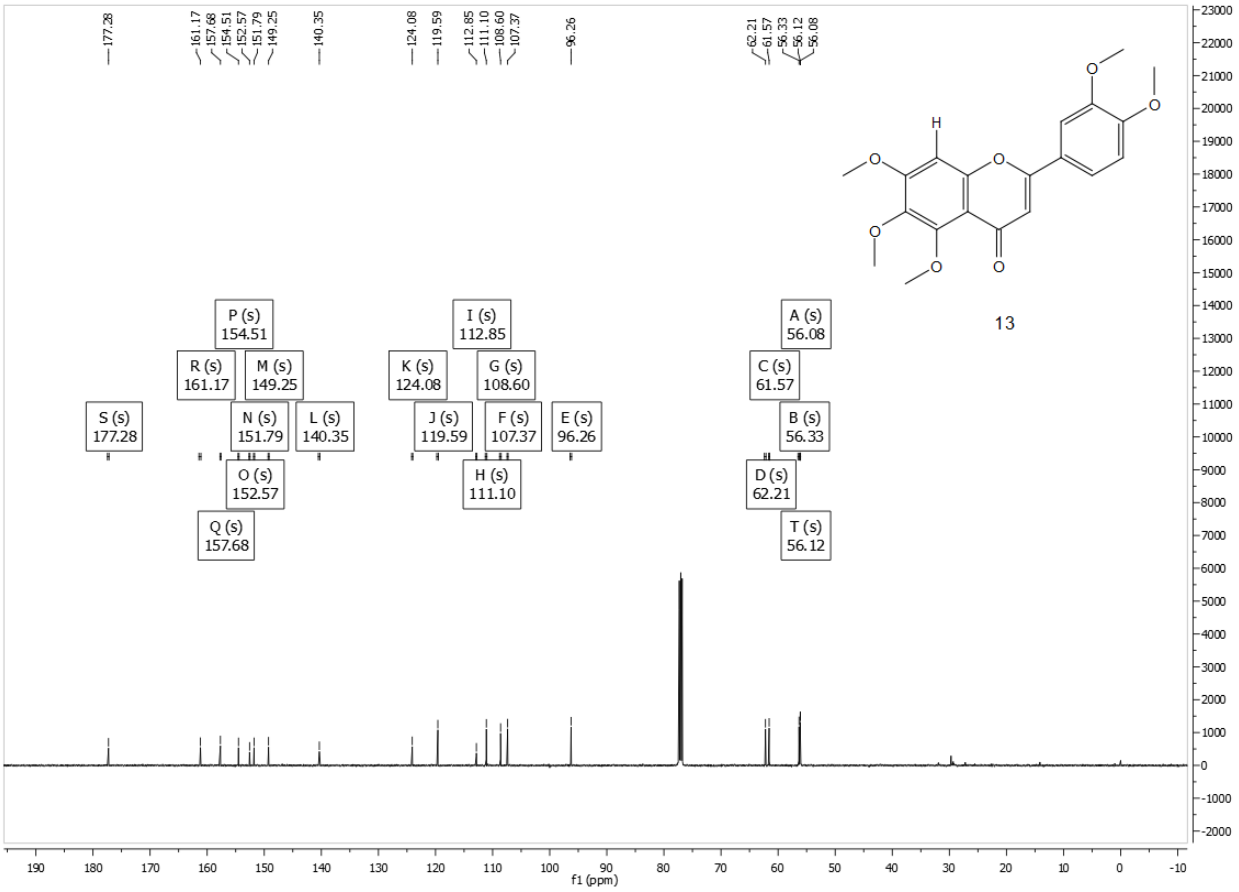
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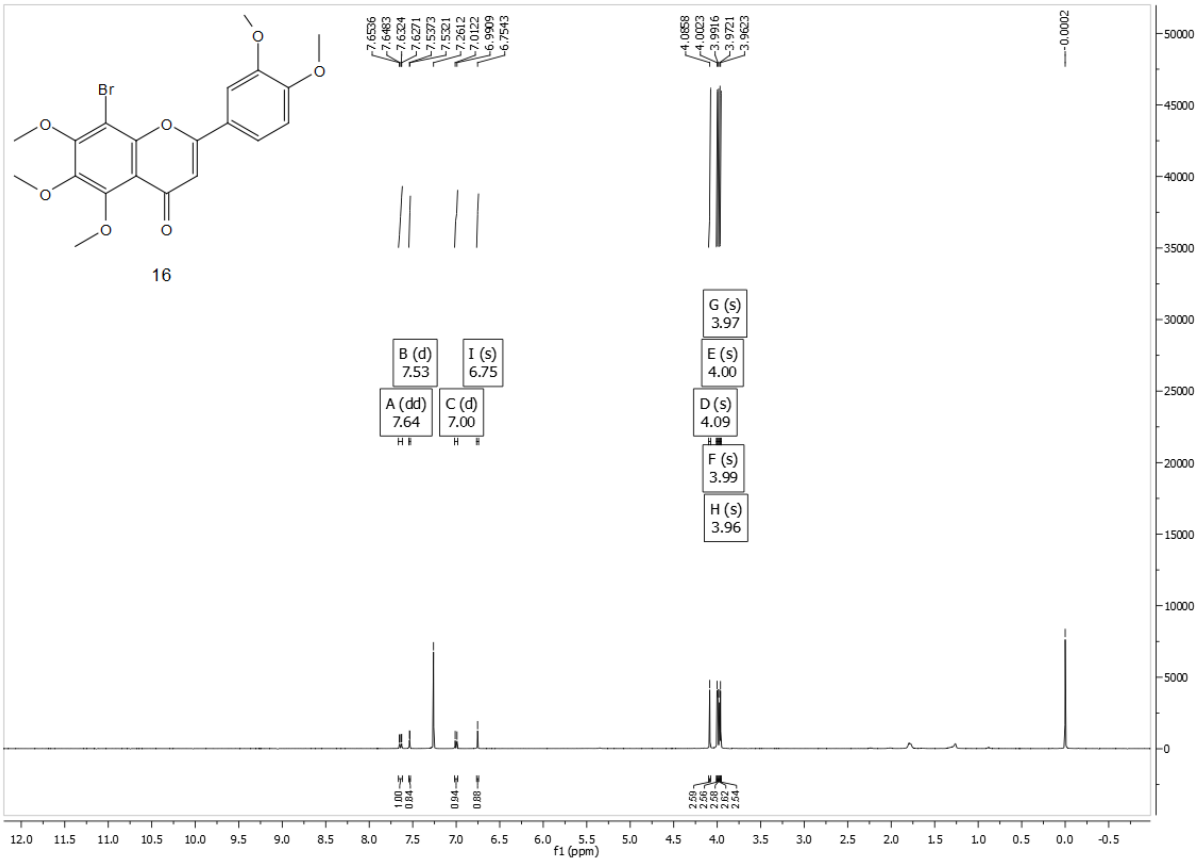
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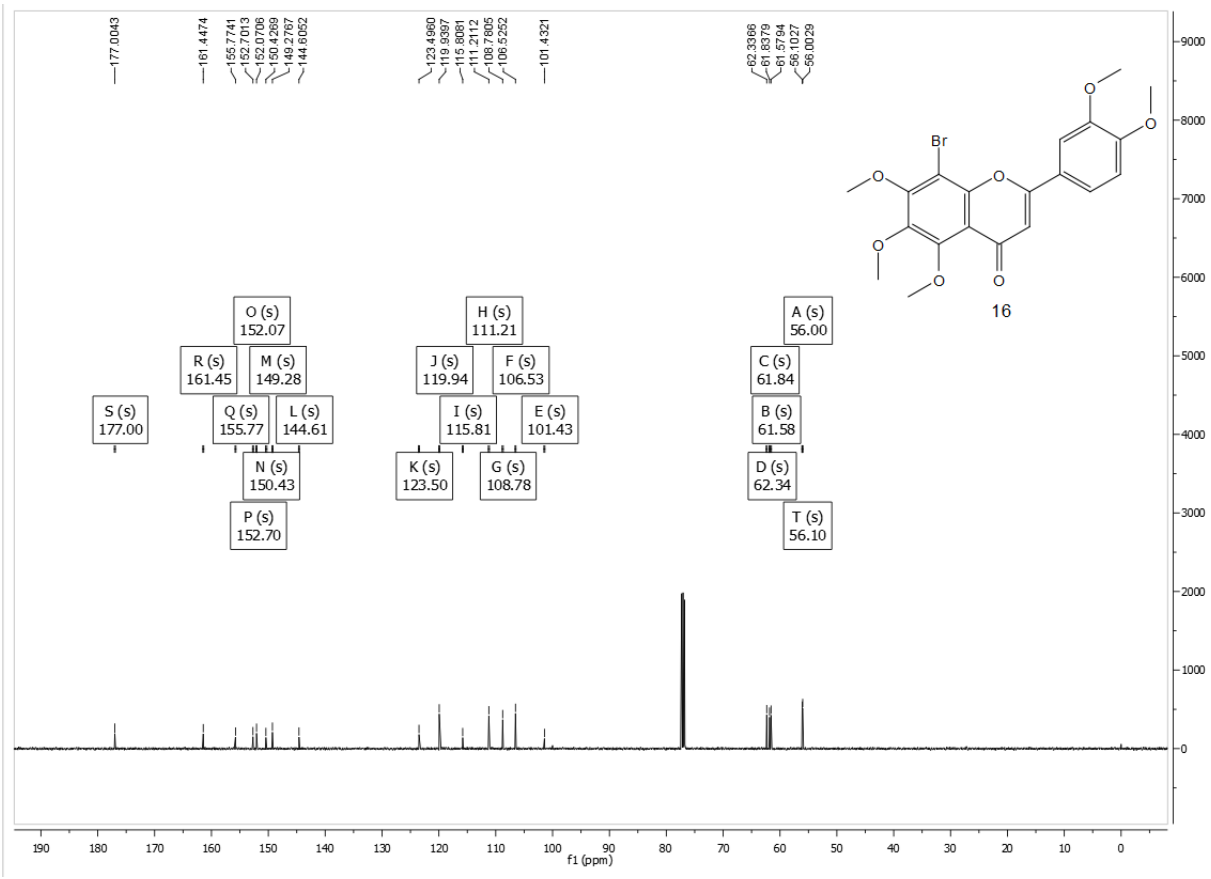
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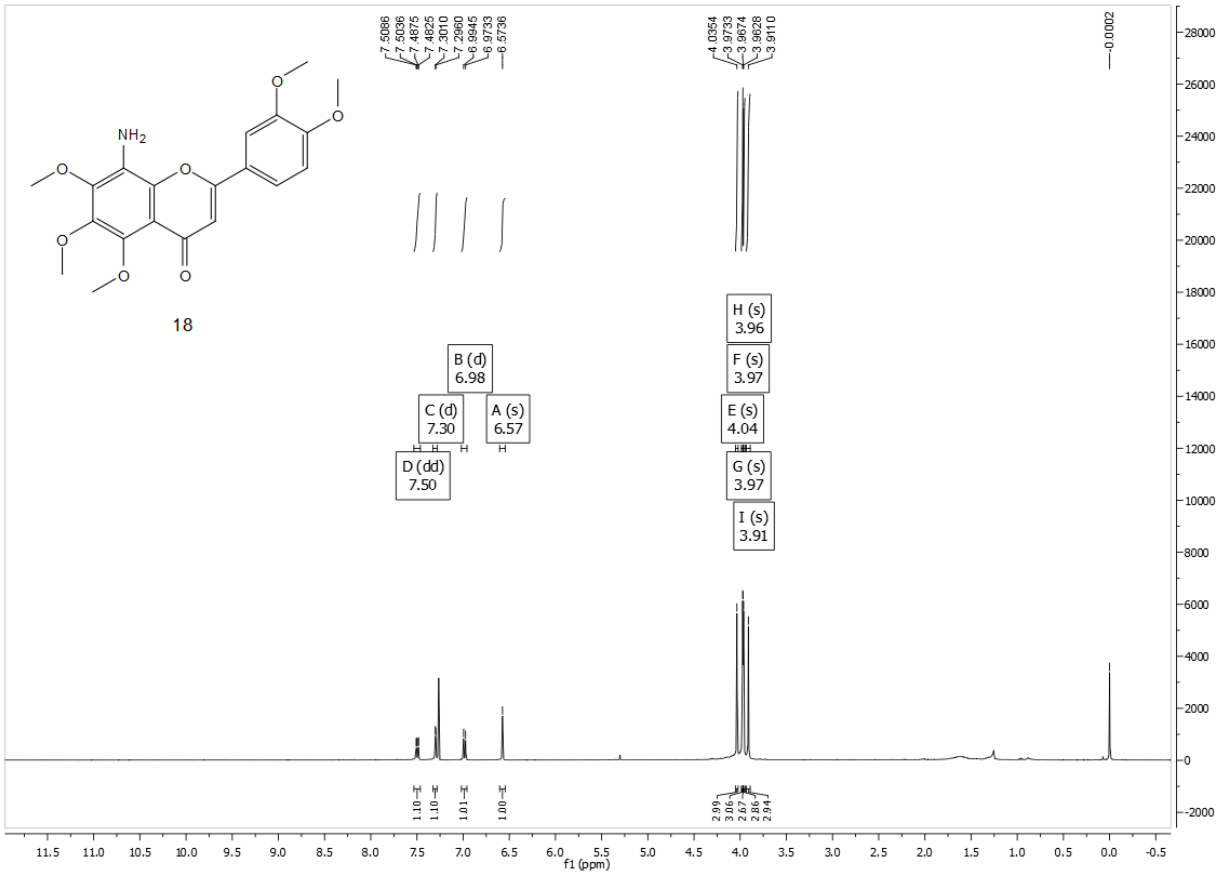
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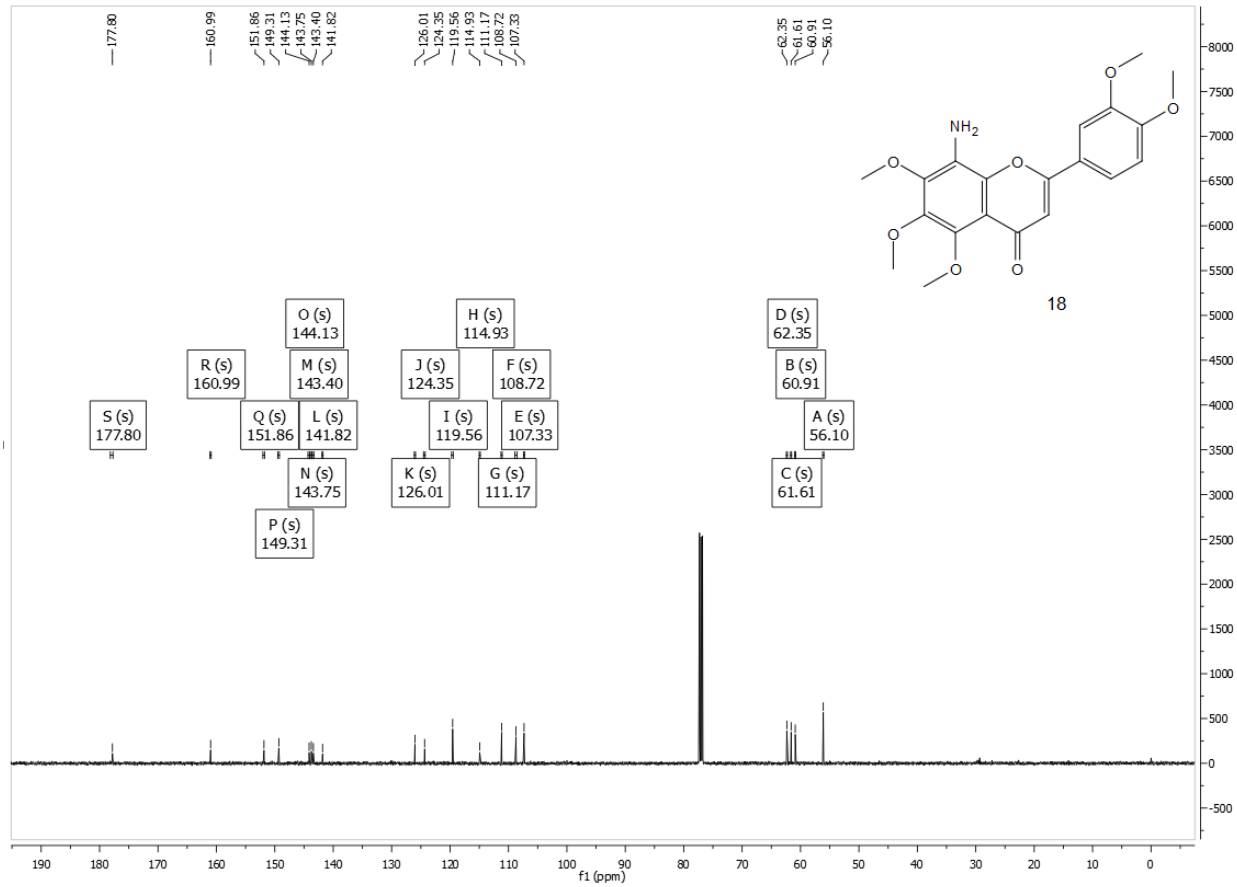
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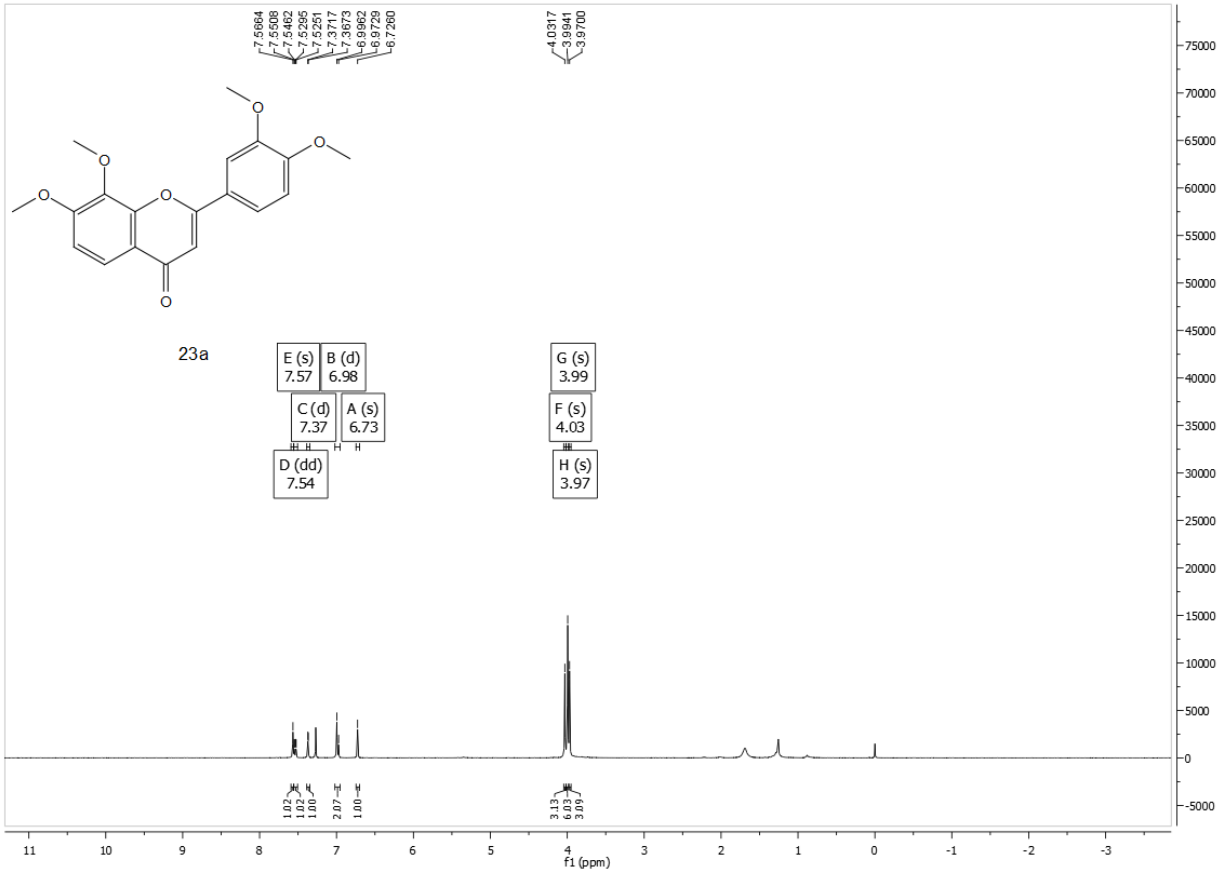
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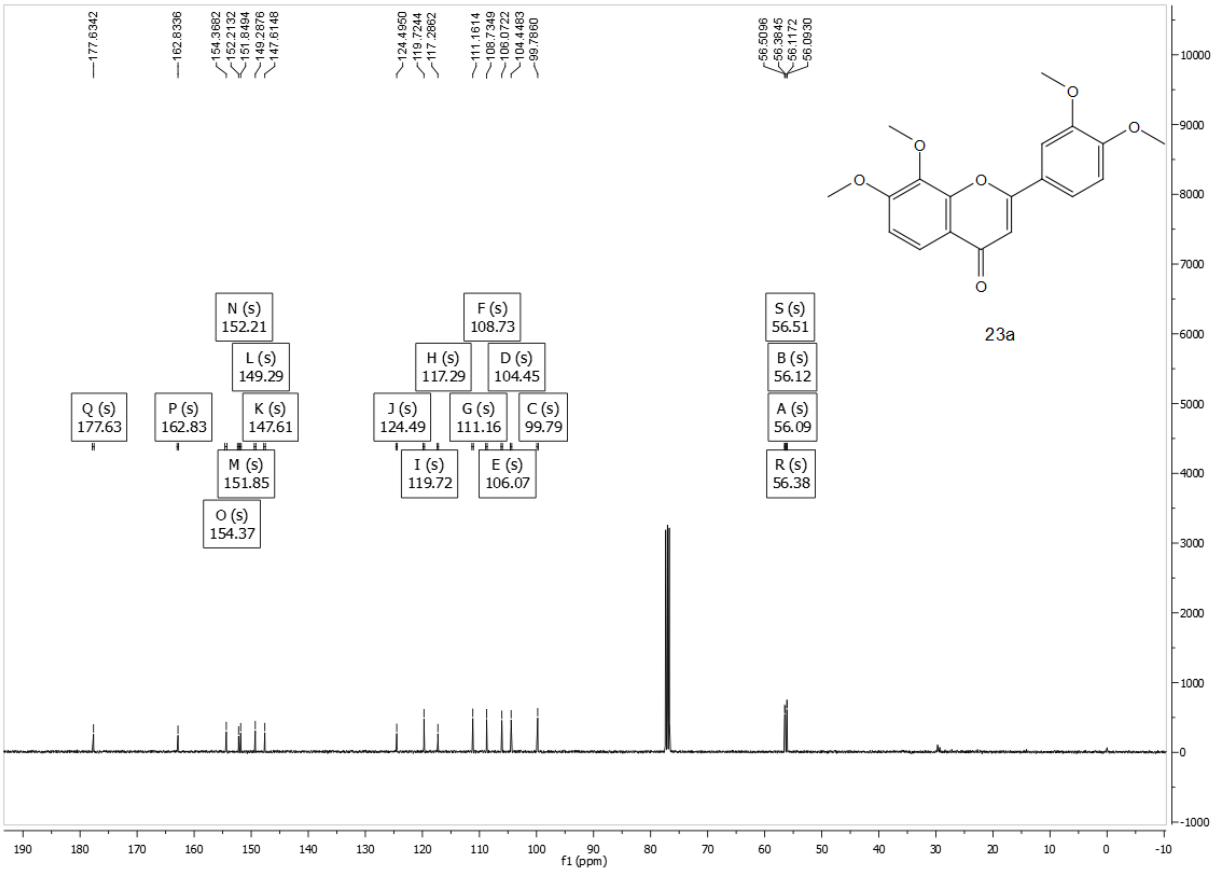
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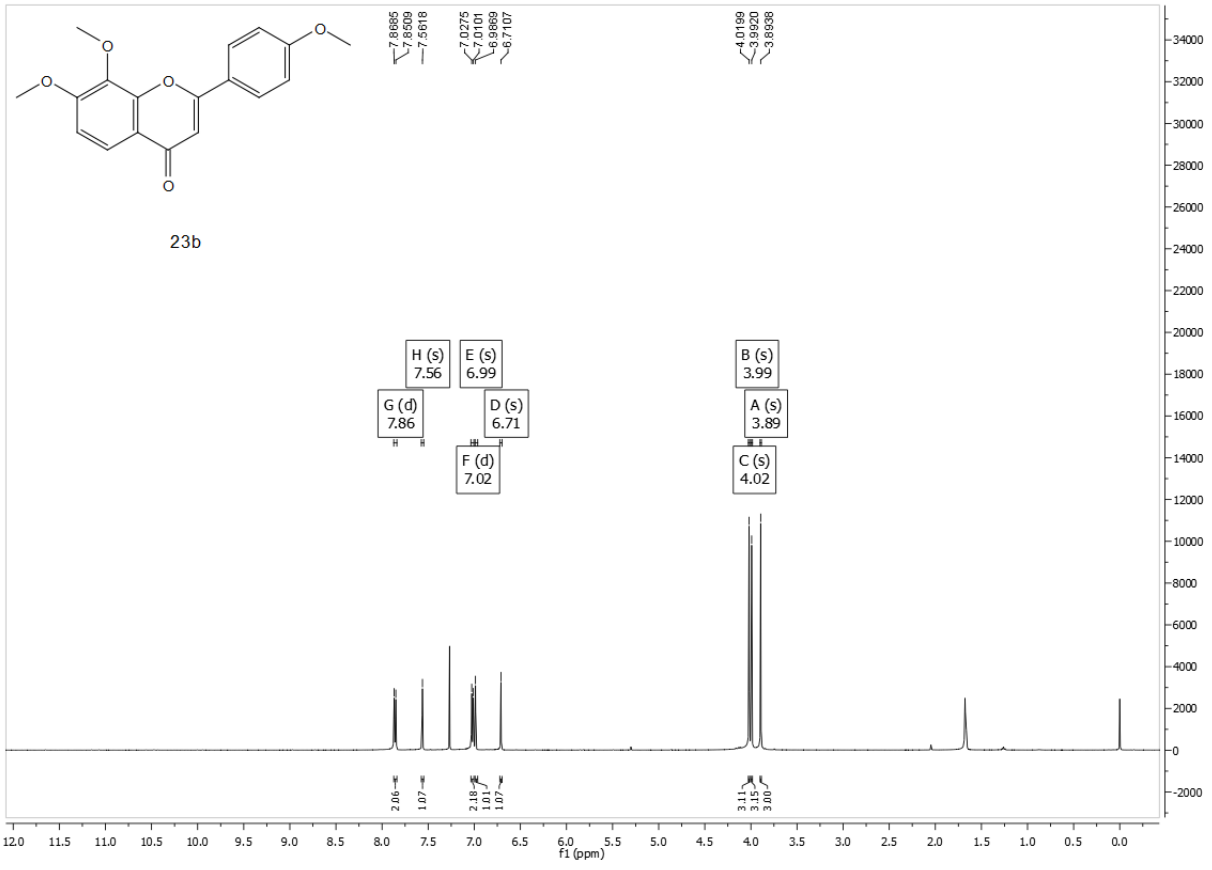
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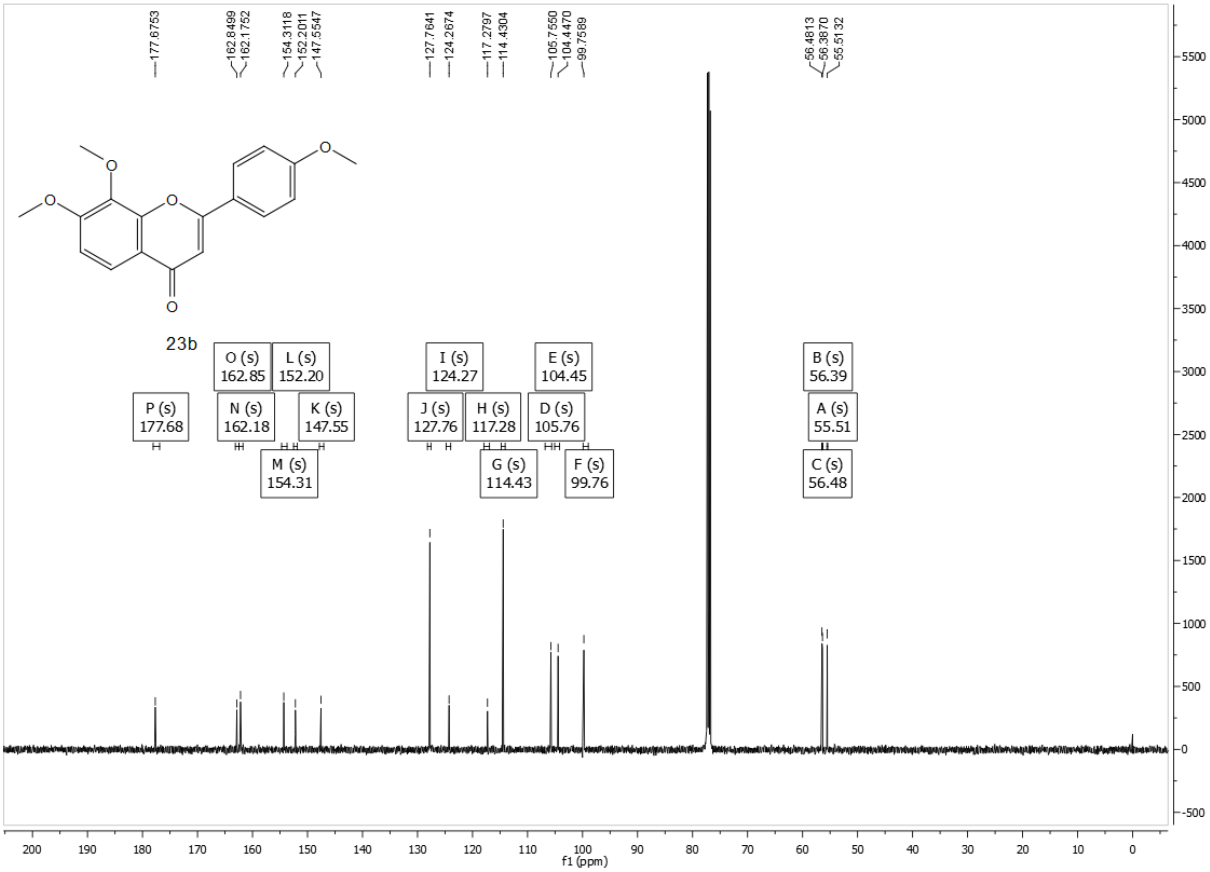
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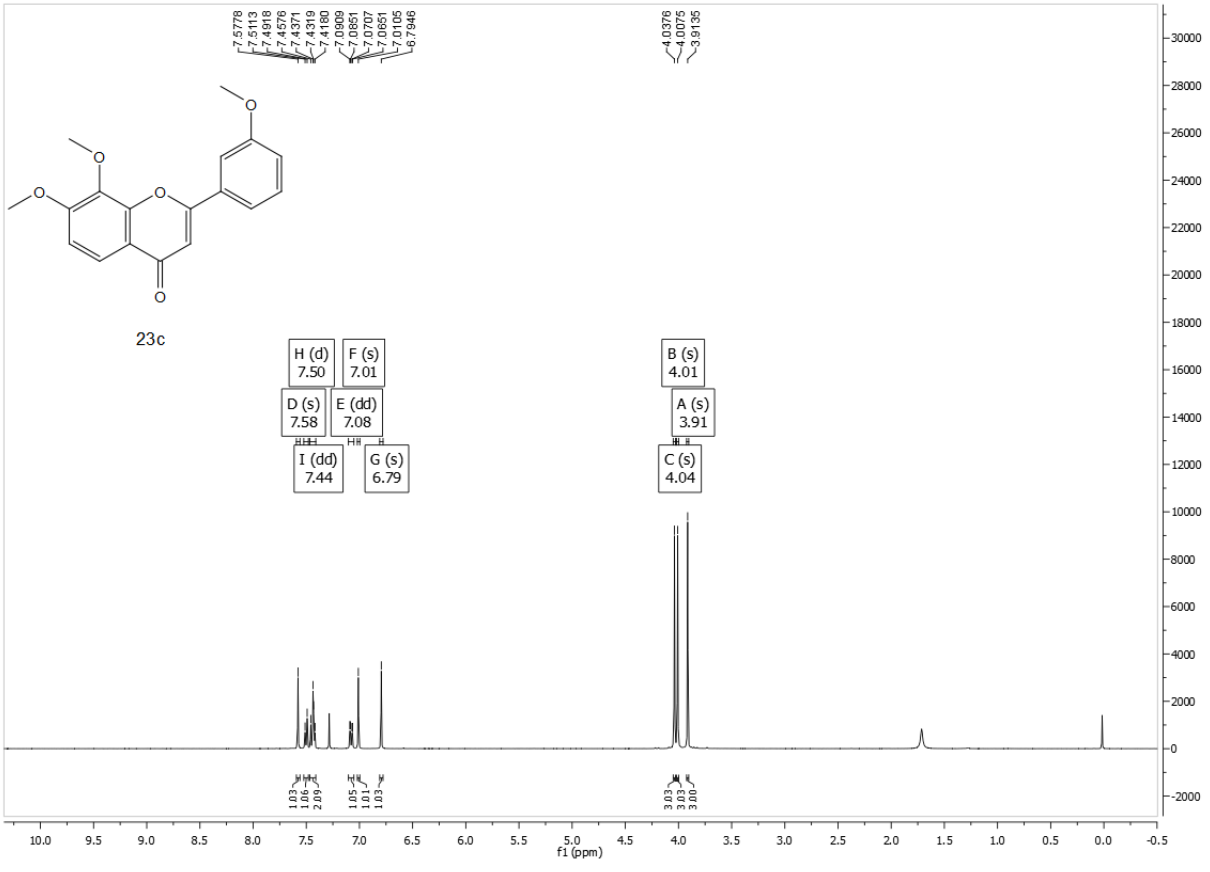
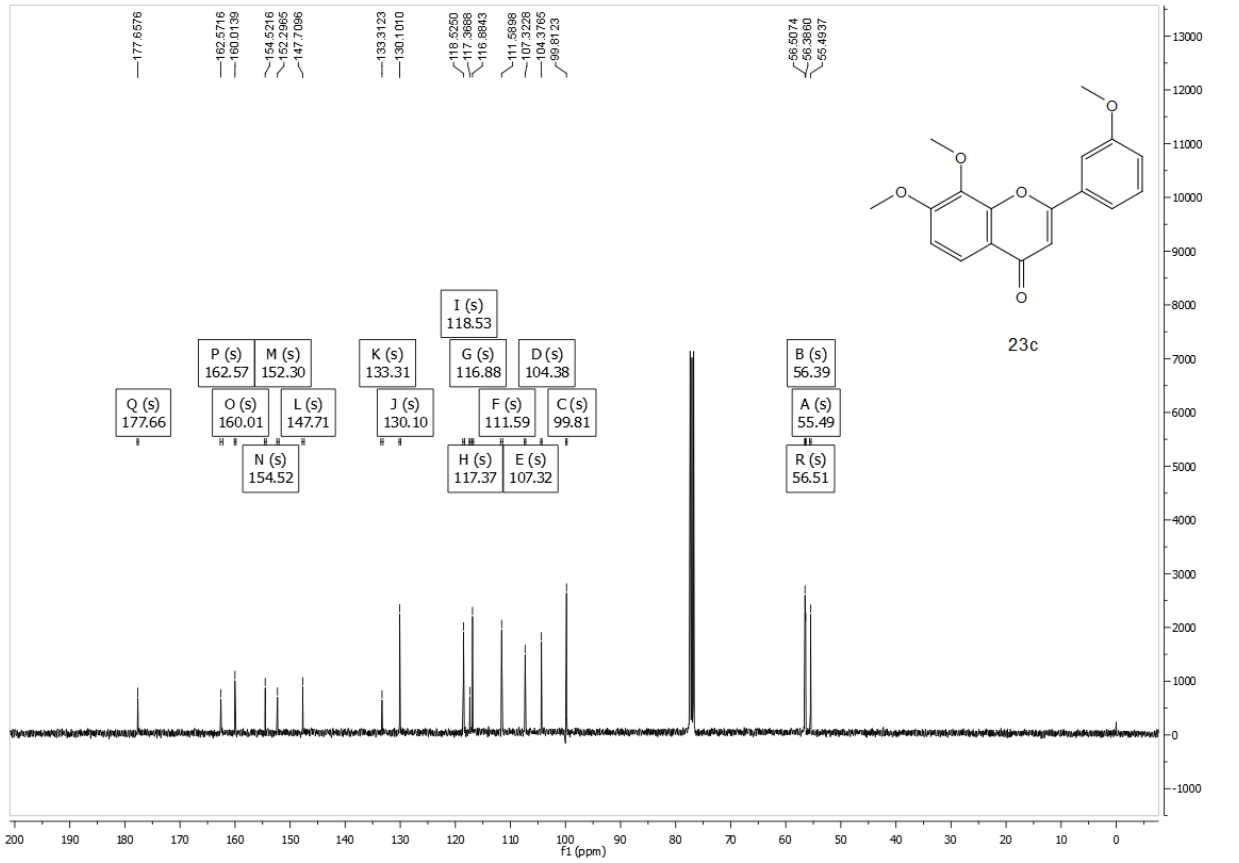
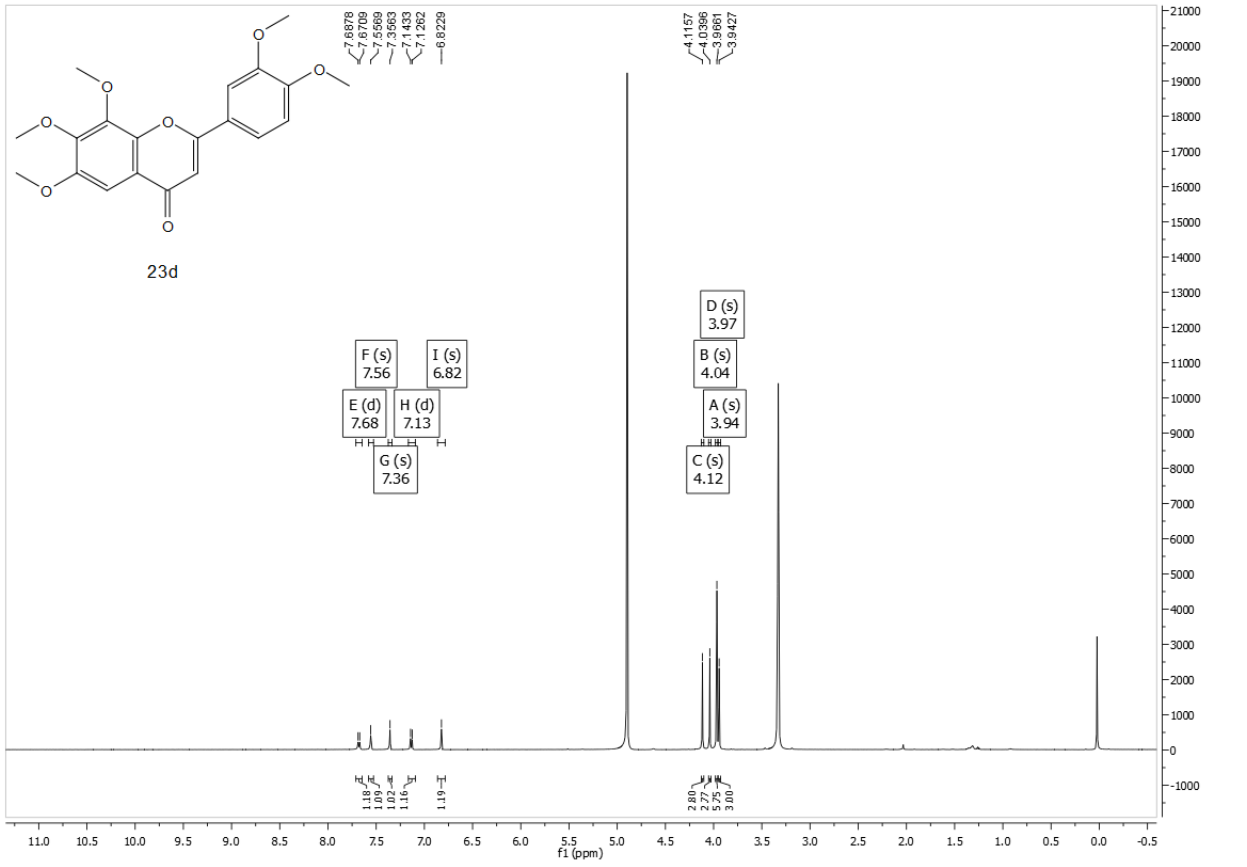
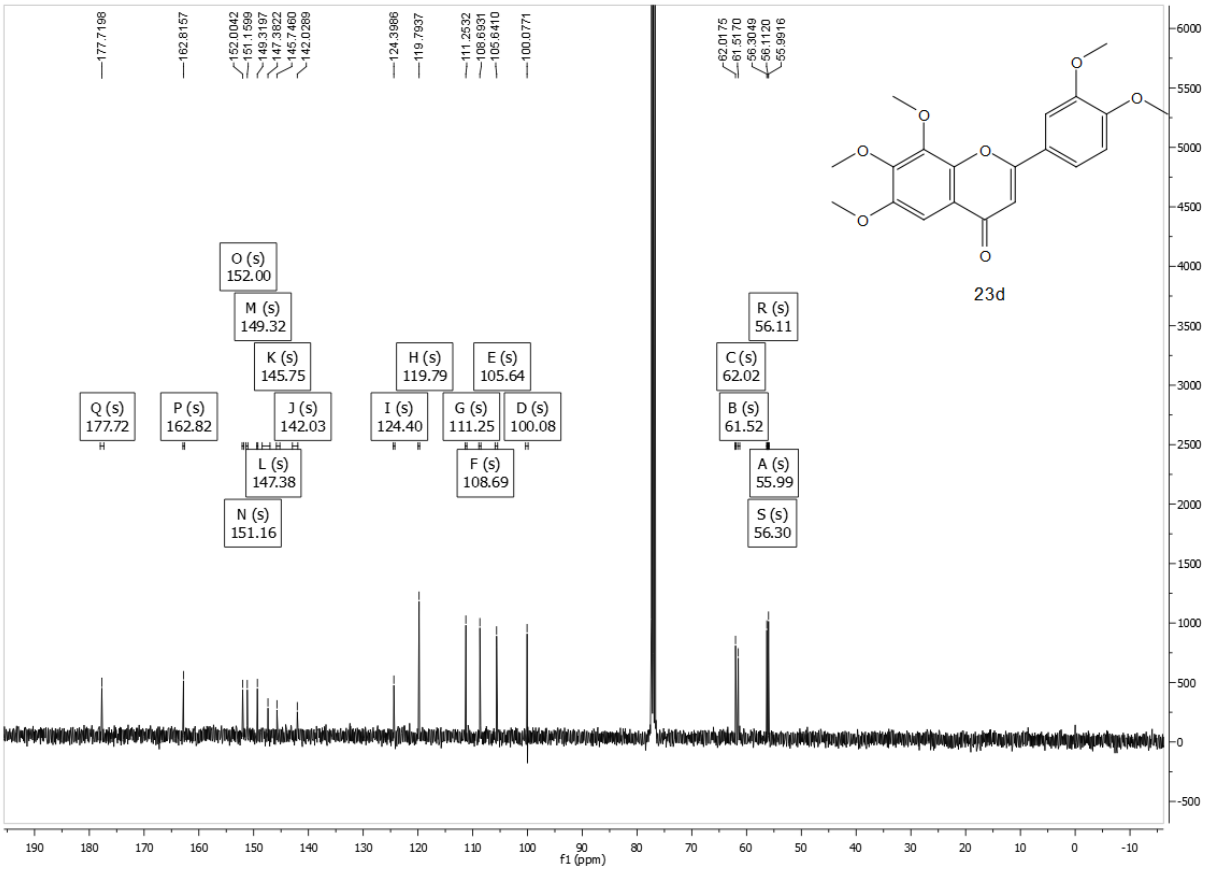
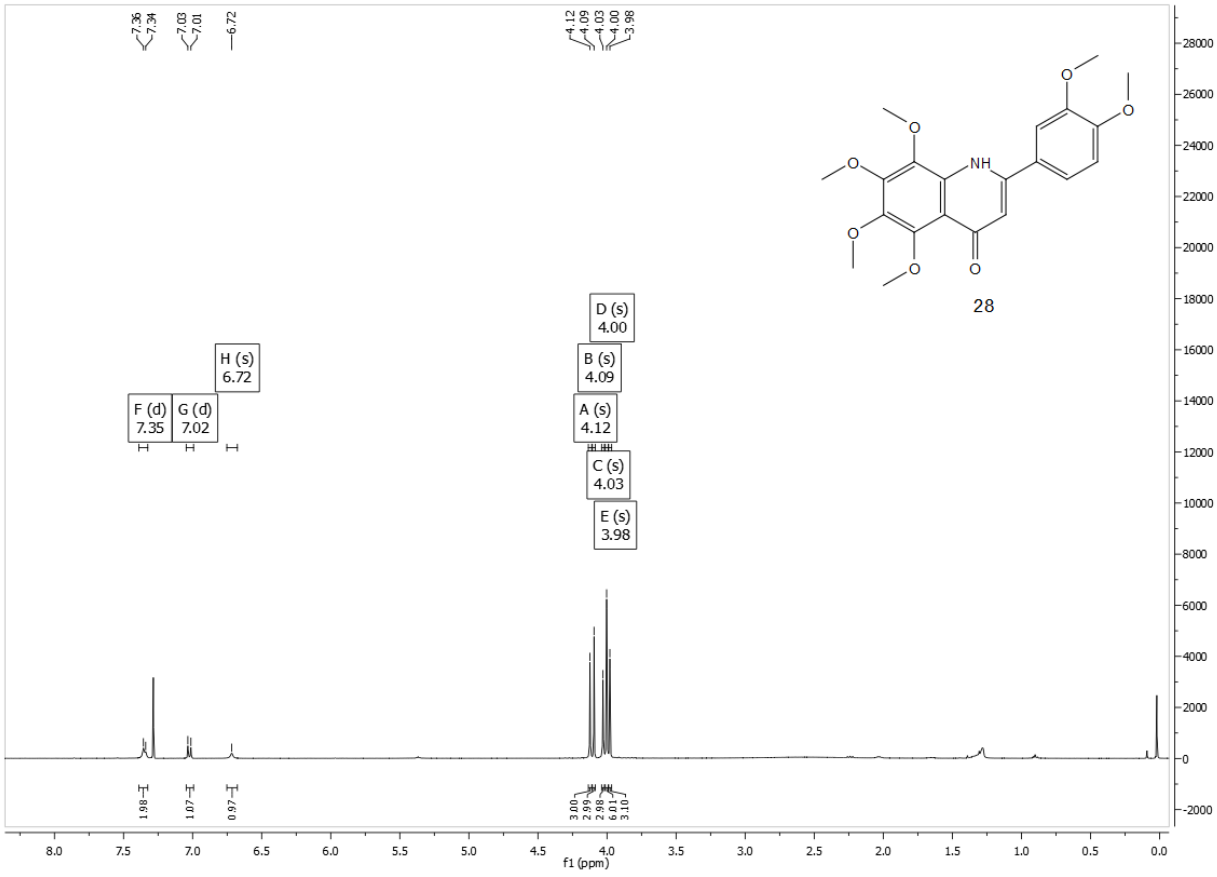
C (s) 56.48
f1 (ppm)

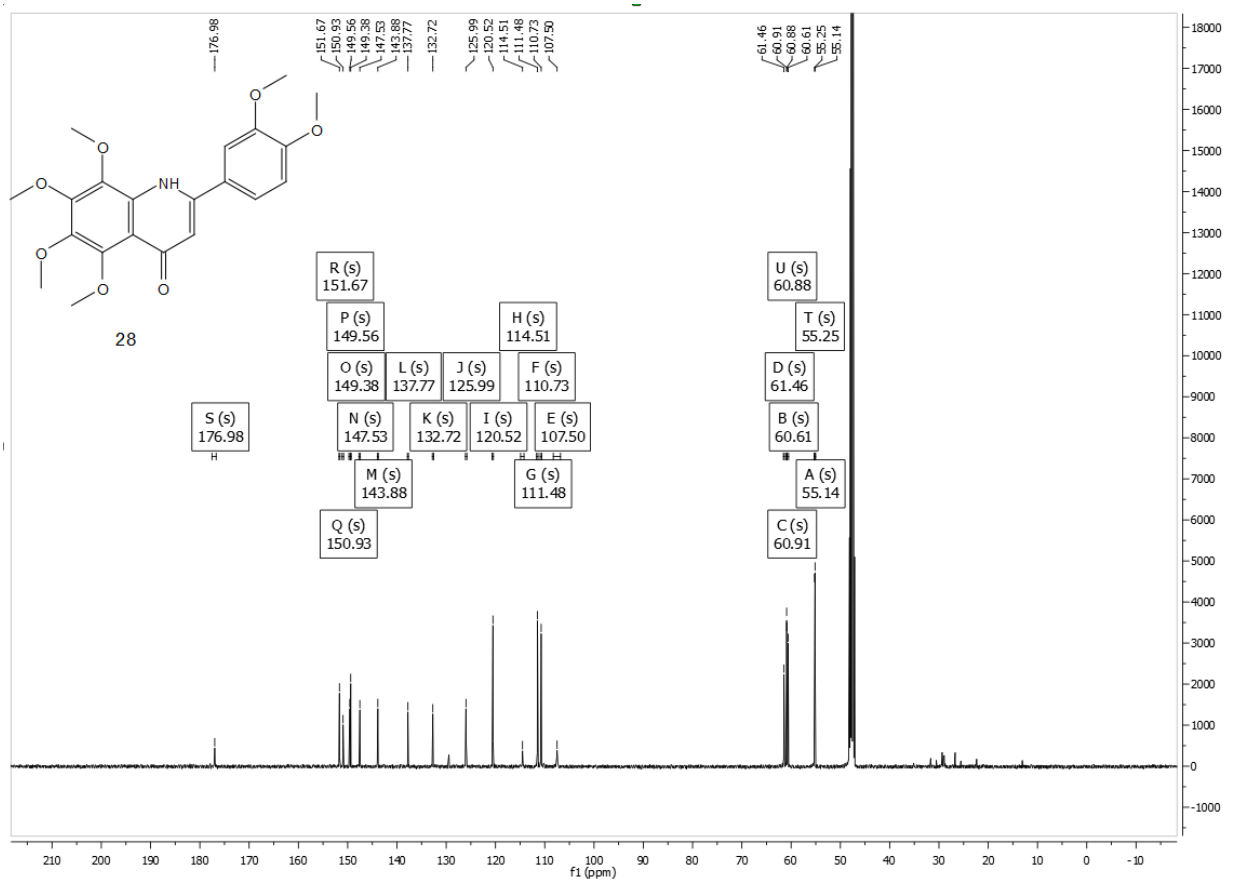

7.5778
7.5113
7.4918
7.4576
7.4371
7.4319
7.4180
7.0909
7.0851
7.0707
7.0651
7.0105
6.7946
4.0376
4.0075
3.9135
23c
H (d) 7.50
F (s) 7.01
B (s) 4.01
D (s) 7.58
E (dd) 7.08
A (s) 3.91
I (dd) 7.44
G (s) 6.79
C (s) 4.04
1.03
1.06
2.09
1.05
1.01
1.03
3.03
3.03
3.00
f1 (ppm)

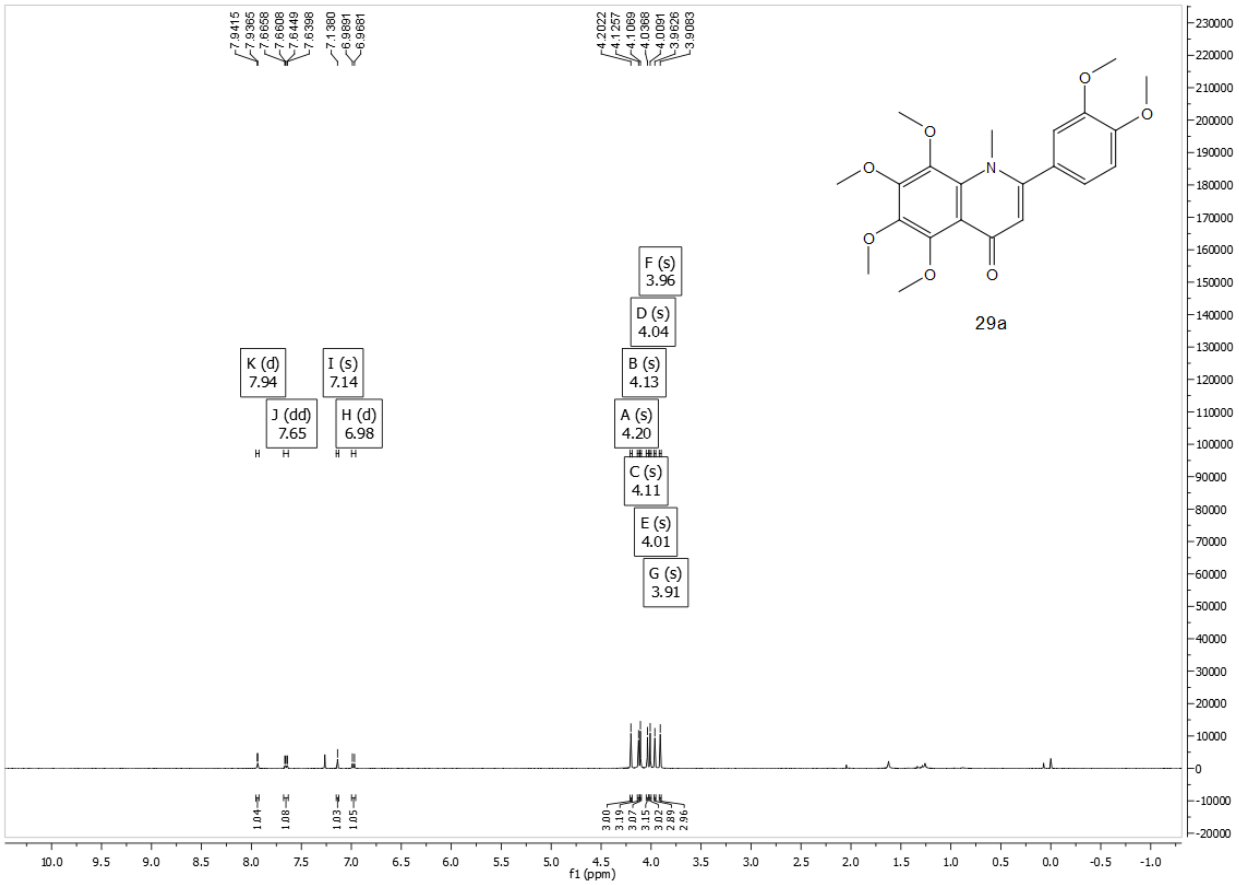

177.6576
162.5716
160.0139
154.5216
152.2965
147.7096
133.3123
130.1010
118.5250
117.3688
116.8843
111.5898
107.3228
104.3765
99.8123
56.5074
56.3860
55.4937
23c
Q (s) 177.66
P (s) 162.57
O (s) 160.01
N (s) 154.52
M (s) 152.30
L (s) 147.71
K (s) 133.31
J (s) 130.10
I (s) 118.53
G (s) 116.88
H (s) 117.37
F (s) 111.59
E (s) 107.32
D (s) 104.38
C (s) 99.81
B (s) 56.39
A (s) 55.49
R (s) 56.51
f1 (ppm)

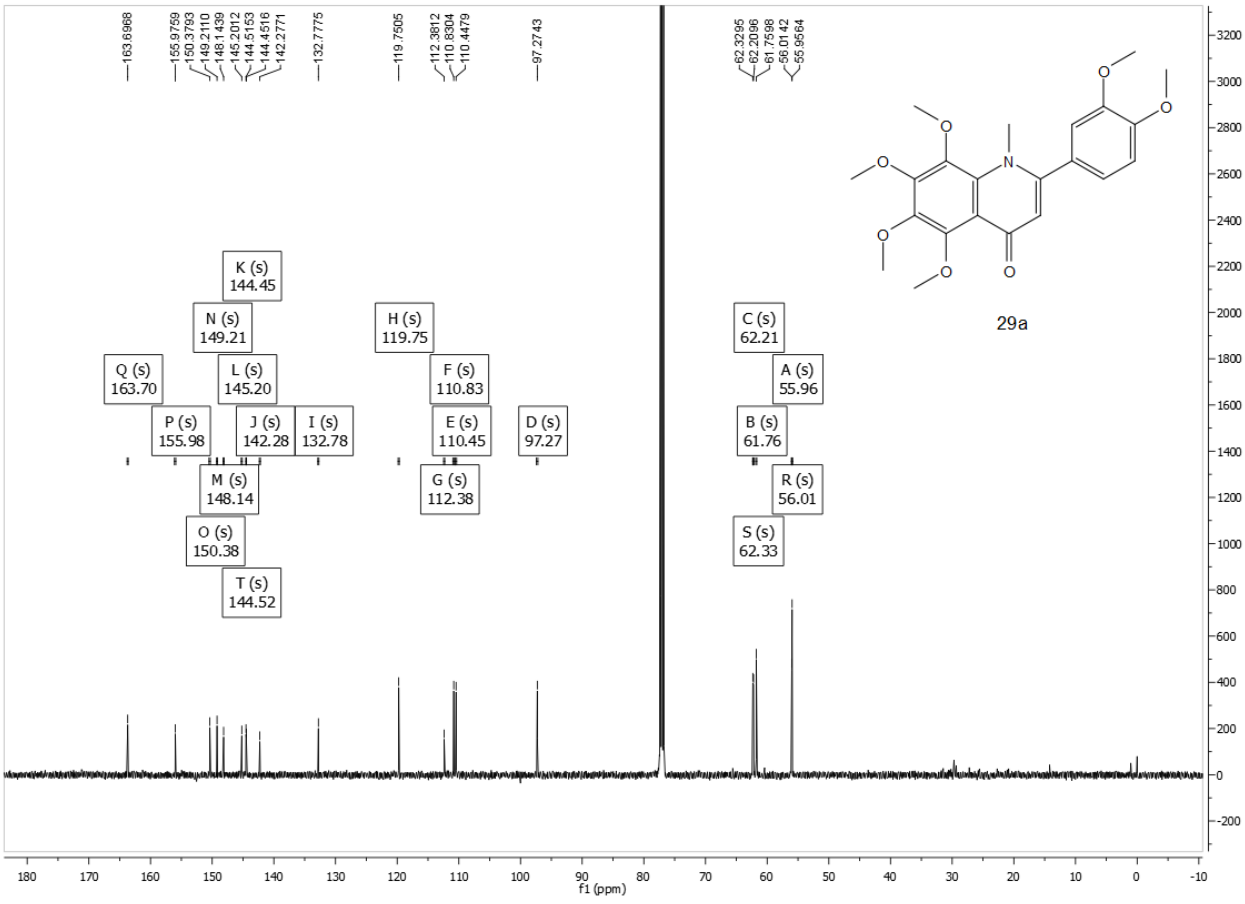

7.6878
7.6709
7.5569
7.3563
7.1433
7.1262
6.8229
4.1157
4.0396
3.9661
3.9427
23d
F (s) 7.56
E (d) 7.68
G (s) 7.36
H (d) 7.13
I (s) 6.82
D (s) 3.97
B (s) 4.04
A (s) 3.94
C (s) 4.12
1.18
1.09
1.02
1.16
1.19
2.80
2.77
5.75
3.00
f1 (ppm)

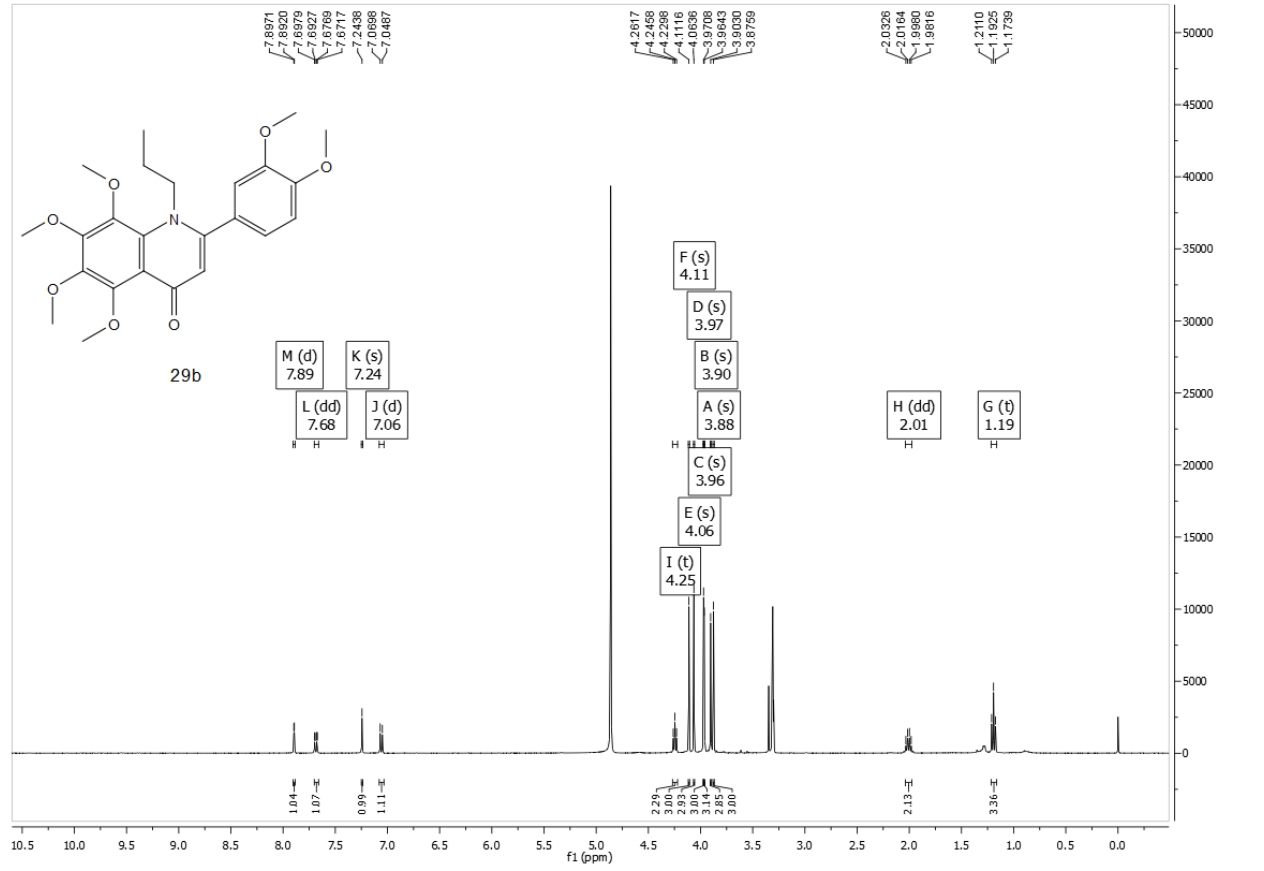

177.7198
162.8157
152.0042
151.1599
149.3197
147.3822
145.7460
142.0289
124.3986
119.7937
111.2532
108.6931
105.6410
100.0771
62.0175
61.5170
56.3049
56.1120
55.9916
O (s) 152.00
M (s) 149.32
K (s) 145.75
H (s) 119.79
E (s) 105.64
R (s) 56.11
C (s) 62.02
Q (s) 177.72
P (s) 162.82
J (s) 142.03
I (s) 124.40
G (s) 111.25
D (s) 100.08
B (s) 61.52
L (s) 147.38
F (s) 108.69
A (s) 55.99
N (s) 151.16
S (s) 56.30
23d
f1 (ppm)

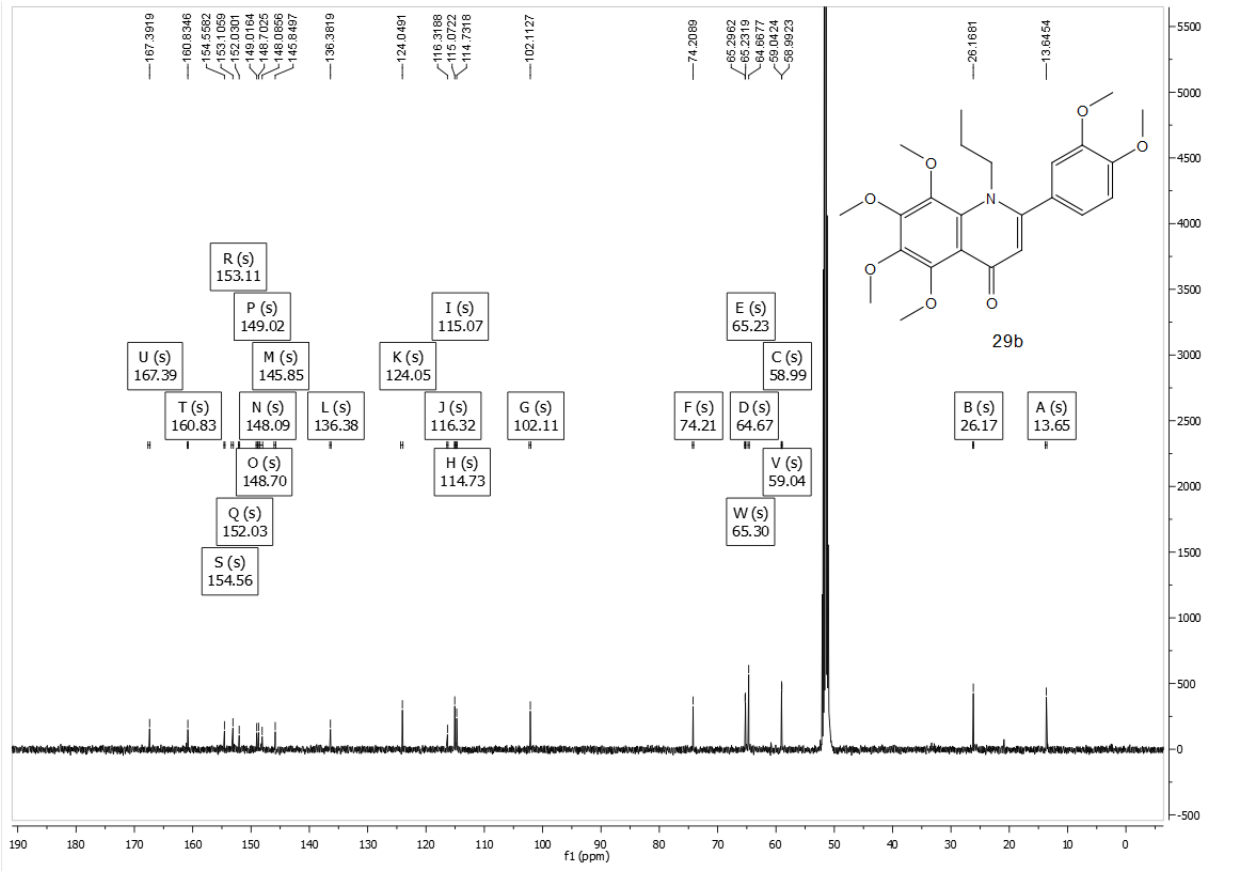

7.36
7.34
7.03
7.01
6.72
4.12
4.09
4.03
4.00
3.98
D (s) 4.00
H (s) 6.72
B (s) 4.09
F (d) 7.35
G (d) 7.02
A (s) 4.12
C (s) 4.03
E (s) 3.98
NH
28
1.98
1.07
0.97
3.00
2.99
2.98
6.01
3.10
f1 (ppm)

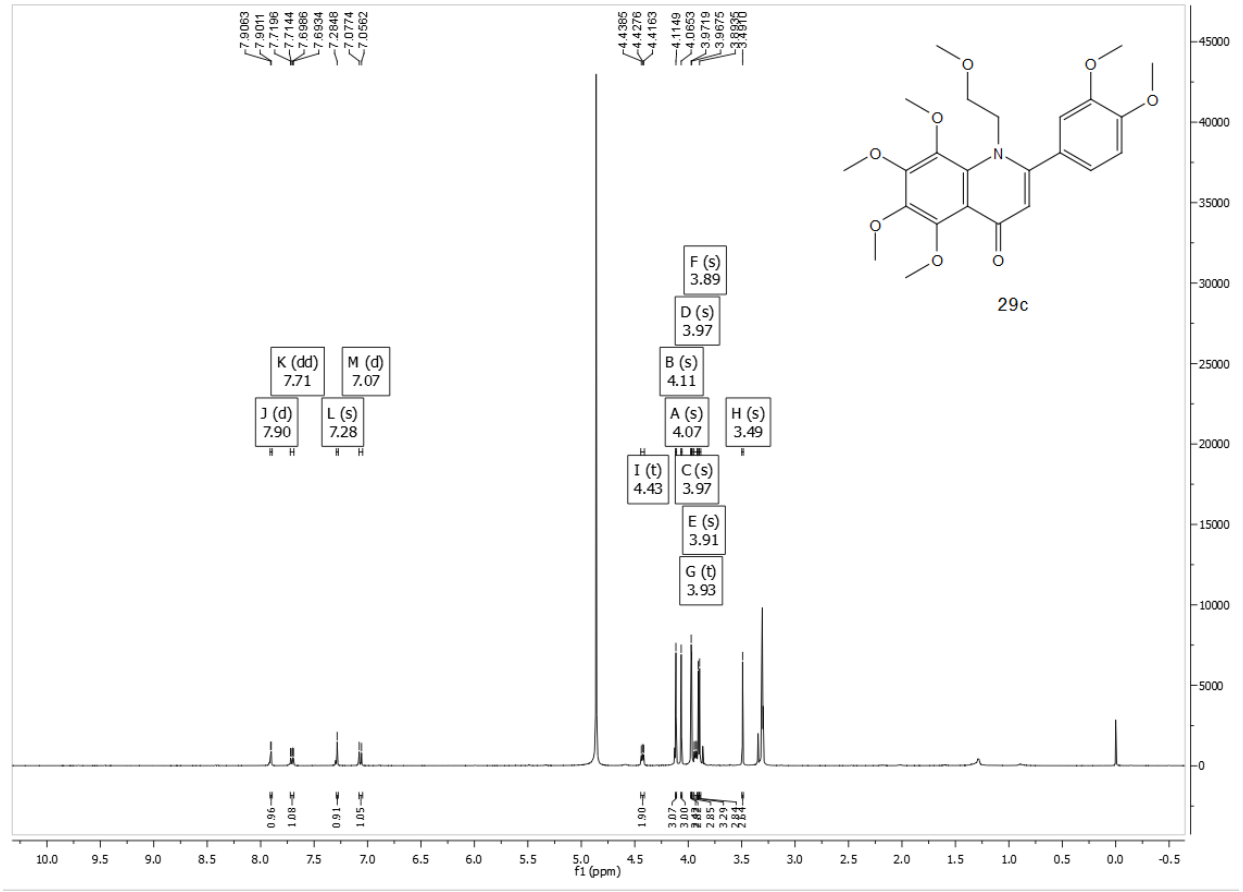

176.98
151.67
150.93
149.56
149.38
147.53
143.88
137.77
132.72
125.99
120.52
114.51
111.48
110.73
107.50
61.46
60.91
60.88
60.61
55.25
55.14
28
R (s) 151.67
P (s) 149.56
O (s) 149.38
L (s) 137.77
J (s) 125.99
H (s) 114.51
F (s) 110.73
S (s) 176.98
N (s) 147.53
K (s) 132.72
I (s) 120.52
E (s) 107.50
M (s) 143.88
G (s) 111.48
Q (s) 150.93
U (s) 60.88
T (s) 55.25
D (s) 61.46
B (s) 60.61
A (s) 55.14
C (s) 60.91
f1 (ppm)

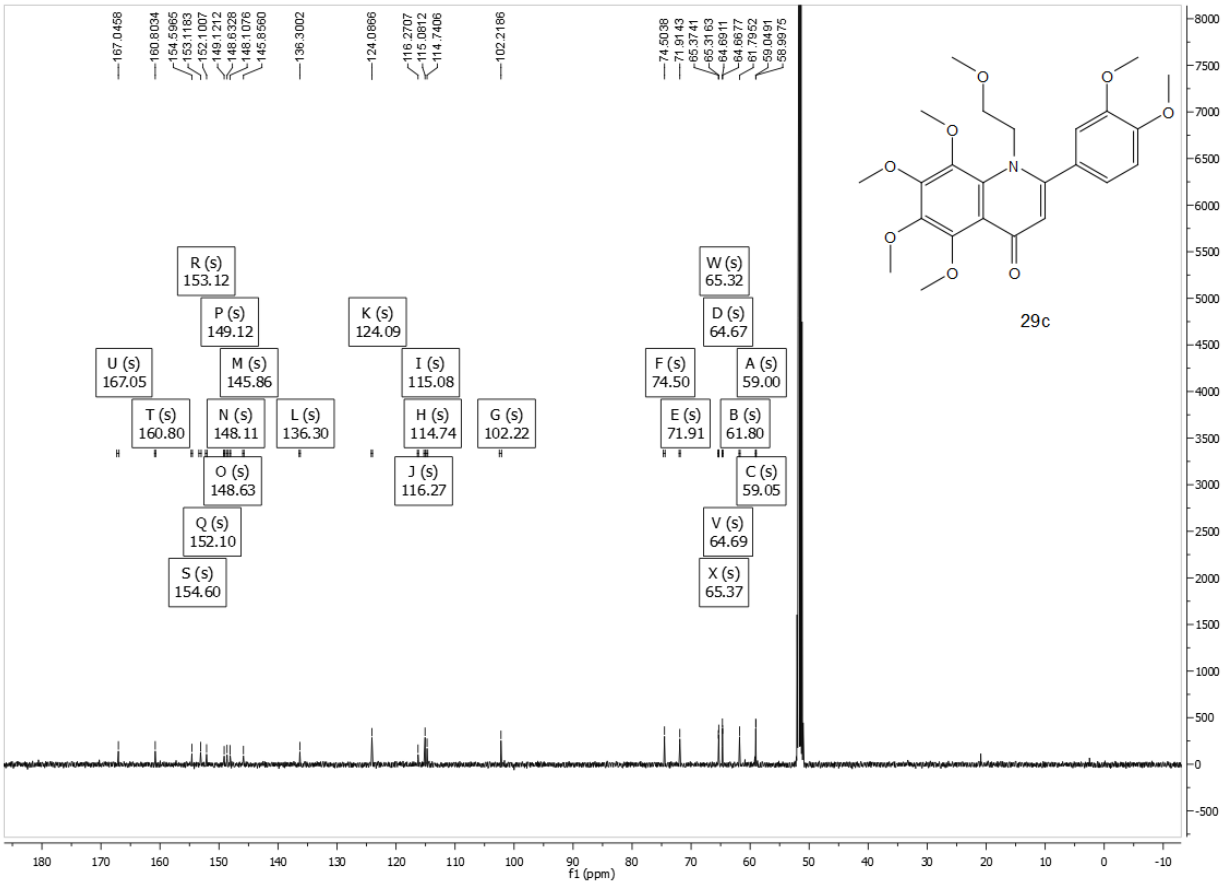

7.9415
7.9365
7.6658
7.6608
7.6449
7.6398
7.1380
6.9891
6.9681
4.2022
4.1257
4.1069
4.0368
4.0091
3.9826
3.9083
29a
K (d) 7.94
J (dd) 7.65
I (s) 7.14
H (d) 6.98
F (s) 3.96
D (s) 4.04
B (s) 4.13
A (s) 4.20
C (s) 4.11
E (s) 4.01
G (s) 3.91
1.04
1.08
1.03
1.05
3.00
3.19
3.07
3.15
3.02
2.89
2.96
f1 (ppm)

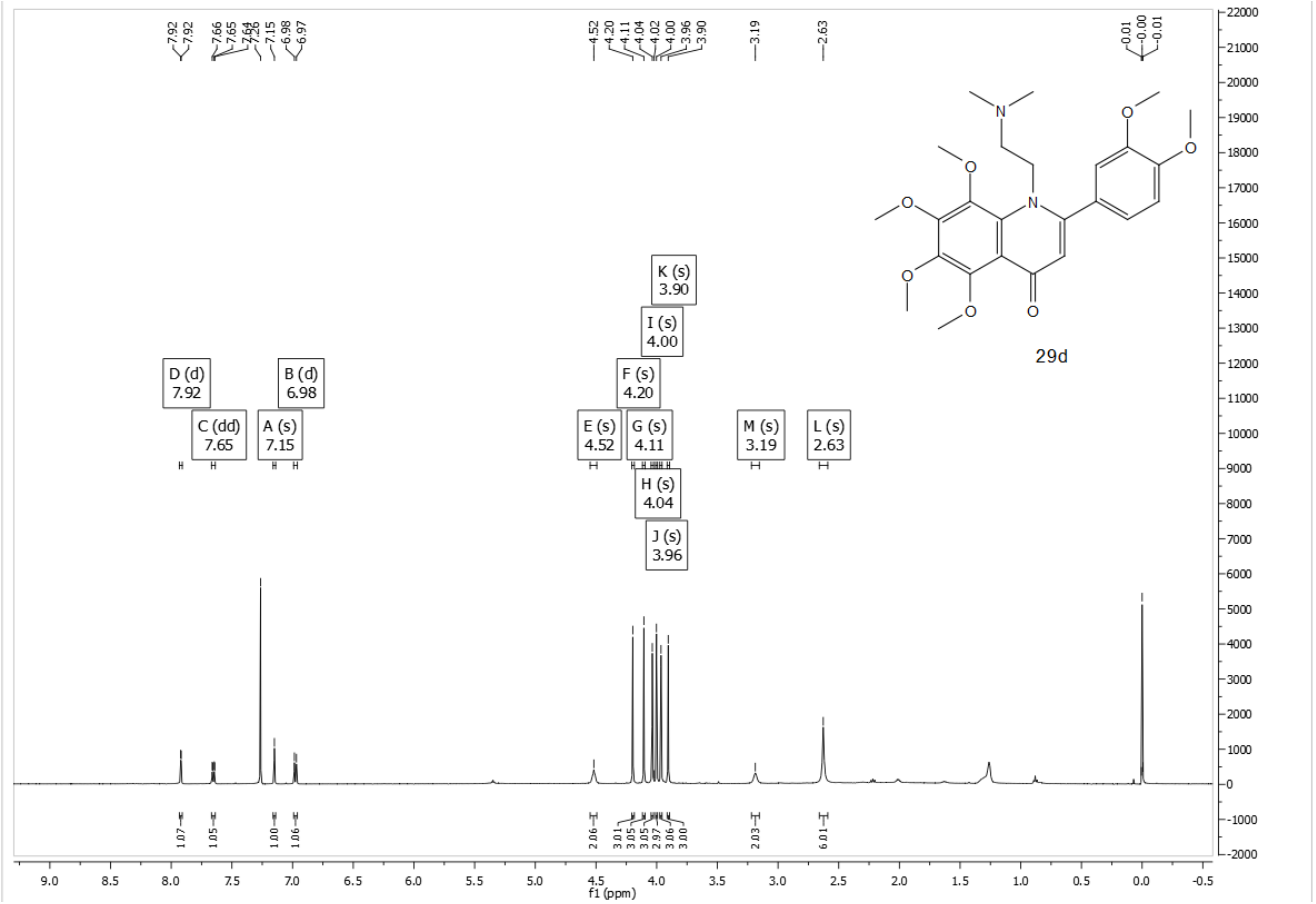

163.6988
155.9759
150.3793
149.2110
148.1439
145.2012
144.5153
144.4516
142.2771
132.7775
119.7505
112.3812
110.8304
110.4479
97.2743
62.3295
62.2096
61.7598
56.0142
55.9564
K (s) 144.45
N (s) 149.21
H (s) 119.75
C (s) 62.21
Q (s) 163.70
L (s) 145.20
F (s) 110.83
A (s) 55.96
P (s) 155.98
J (s) 142.28
I (s) 132.78
E (s) 110.45
D (s) 97.27
B (s) 61.76
M (s) 148.14
G (s) 112.38
R (s) 56.01
O (s) 150.38
S (s) 62.33
T (s) 144.52
29a
f1 (ppm)

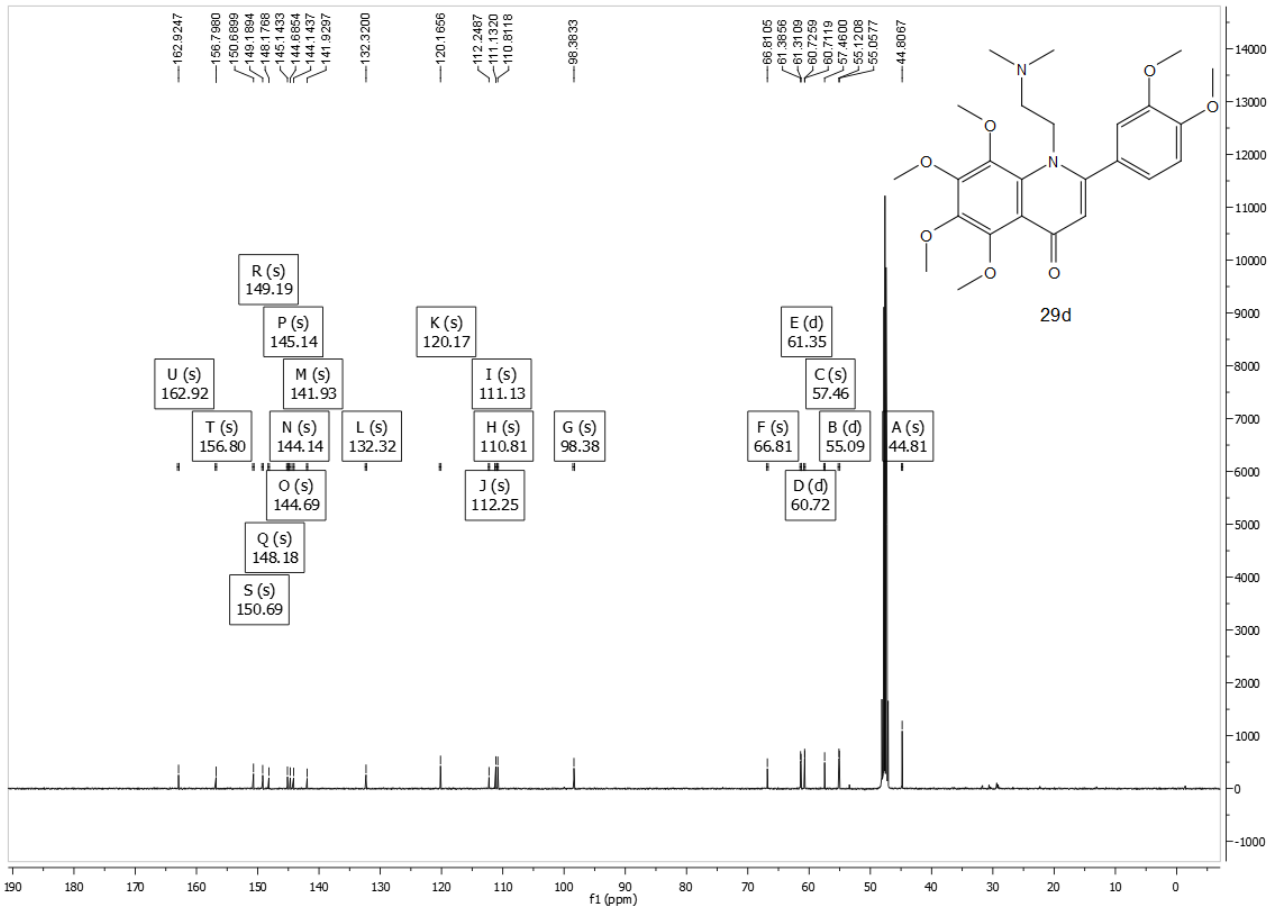

7.8971
7.8920
7.8979
7.8927
7.8769
7.8717
7.2438
7.0698
7.0487
4.2617
4.2458
4.2298
4.1116
4.0636
3.9708
3.9643
3.9030
3.8759
2.0326
2.0164
1.9980
1.9816
1.2110
1.1925
1.1739
F (s) 4.11
D (s) 3.97
B (s) 3.90
A (s) 3.88
C (s) 3.96
E (s) 4.06
I (t) 4.25
M (d) 7.89
K (s) 7.24
L (dd) 7.68
J (d) 7.06
H (dd) 2.01
G (t) 1.19
29b
1.04
1.07
0.99
1.11
2.29
3.00
2.93
3.00
3.14
2.85
3.00
2.13
3.36
f1 (ppm)


167.3919
160.8346
154.5582
153.1059
152.0301
149.0164
148.7025
148.0856
145.8497
136.3819
124.0491
116.3188
115.0722
114.7318
102.1127
74.2089
65.2962
65.2319
64.6677
59.0424
58.9923
26.1681
13.6454
R (s) 153.11
P (s) 149.02
U (s) 167.39
M (s) 145.85
K (s) 124.05
I (s) 115.07
E (s) 65.23
C (s) 58.99
T (s) 160.83
N (s) 148.09
L (s) 136.38
J (s) 116.32
G (s) 102.11
F (s) 74.21
D (s) 64.67
B (s) 26.17
A (s) 13.65
O (s) 148.70
H (s) 114.73
V (s) 59.04
Q (s) 152.03
W (s) 65.30
S (s) 154.56
29b
f1 (ppm)


7.9063
7.9011
7.7196
7.7144
7.6986
7.6934
7.2848
7.0774
7.0562
4.4365
4.4276
4.4163
4.1149
4.0653
3.9719
3.9675
3.8810
F (s) 3.89
D (s) 3.97
B (s) 4.11
K (dd) 7.71
M (d) 7.07
J (d) 7.90
L (s) 7.28
A (s) 4.07
H (s) 3.49
I (t) 4.43
C (s) 3.97
E (s) 3.91
G (t) 3.93
29c
f1 (ppm)


R (s) 153.12
P (s) 149.12
U (s) 167.05
M (s) 145.86
T (s) 160.80
N (s) 148.11
L (s) 136.30
K (s) 124.09
I (s) 115.08
H (s) 114.74
G (s) 102.22
O (s) 148.63
J (s) 116.27
Q (s) 152.10
S (s) 154.60
W (s) 65.32
D (s) 64.67
F (s) 74.50
A (s) 59.00
E (s) 71.91
B (s) 61.80
C (s) 59.05
V (s) 64.69
X (s) 65.37
29c
f1 (ppm)


K (s) 3.90
I (s) 4.00
D (d) 7.92
B (d) 6.98
F (s) 4.20
C (dd) 7.65
A (s) 7.15
E (s) 4.52
G (s) 4.11
M (s) 3.19
L (s) 2.63
H (s) 4.04
J (s) 3.96
29d
f1 (ppm)


162.9247
156.7980
150.6899
149.1894
148.1768
145.1433
144.6854
144.1437
141.9297
132.3200
120.1656
112.2487
111.1320
110.8118
98.3833
66.8105
61.3856
61.3109
60.7259
60.7119
57.4600
55.1208
55.0577
44.8067
R (s) 149.19
P (s) 145.14
U (s) 162.92
M (s) 141.93
T (s) 156.80
N (s) 144.14
L (s) 132.32
O (s) 144.69
Q (s) 148.18
S (s) 150.69
K (s) 120.17
I (s) 111.13
H (s) 110.81
G (s) 98.38
J (s) 112.25
E (d) 61.35
C (s) 57.46
F (s) 66.81
B (d) 55.09
A (s) 44.81
D (d) 60.72
29d
f1 (ppm)

Section 4 High-resolution mass spectra (HR-MS) data for tested compounds

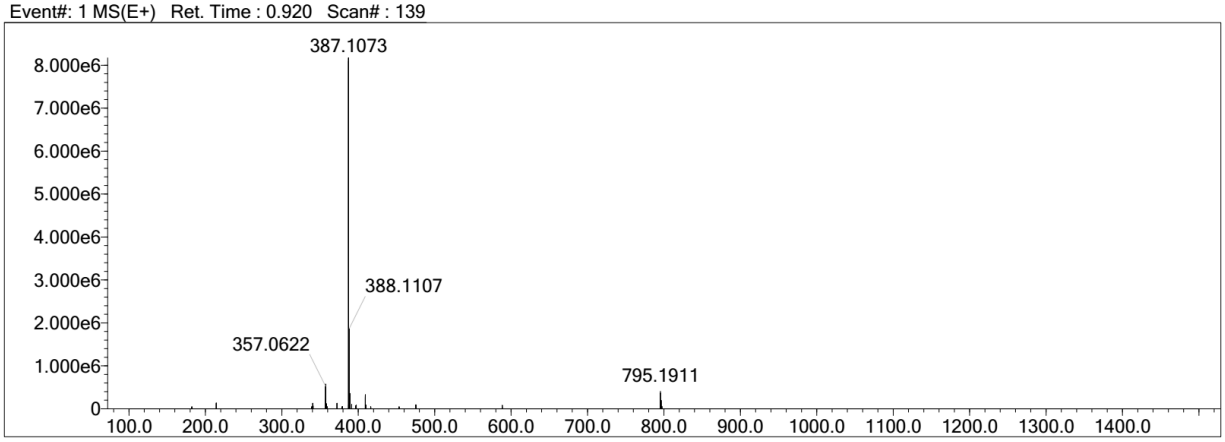
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	33	C	4	0	30	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	3	P	3	0	0	Se	2	0	0	Na
3H	1	0	0	O	2	0	8	S	2	0	0	Br	1	0	0	K
B	3	0	0	F	1	0	0	Cl	1	0	0	I	3	0	0	NH4

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

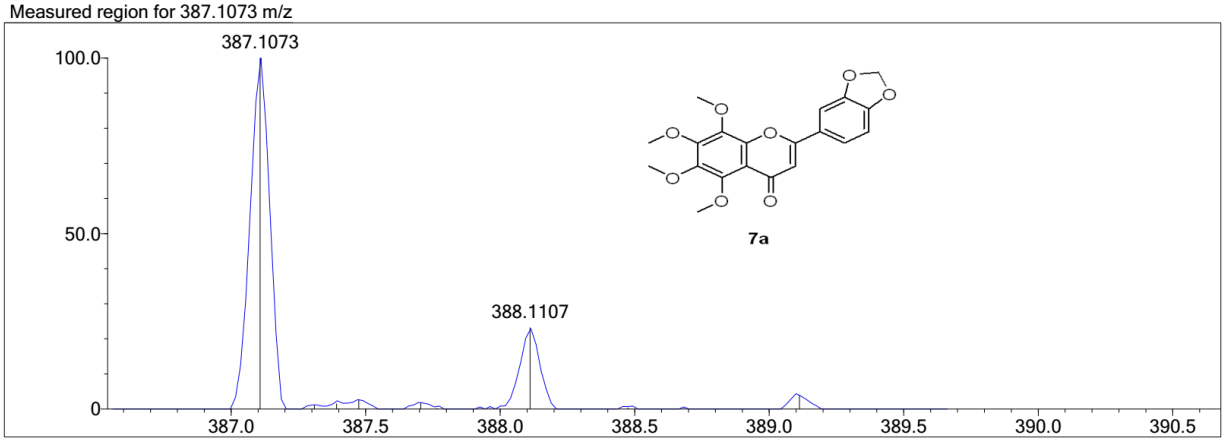
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

Event#: 1 MS(E+) Ret. Time : 0.920 Scan# : 139

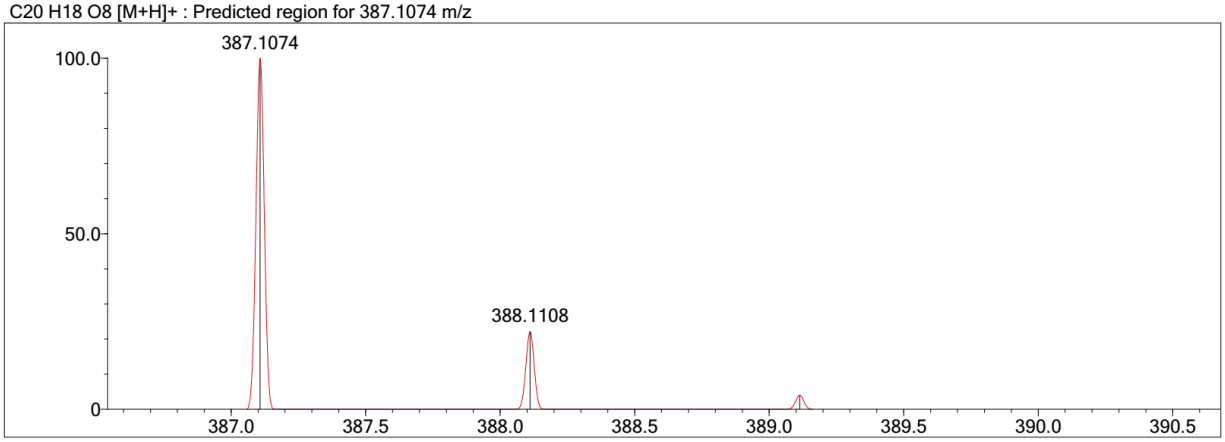


Measured region for 387.1073 m/z



7a

C20 H18 O8 [M+H]+ : Predicted region for 387.1074 m/z

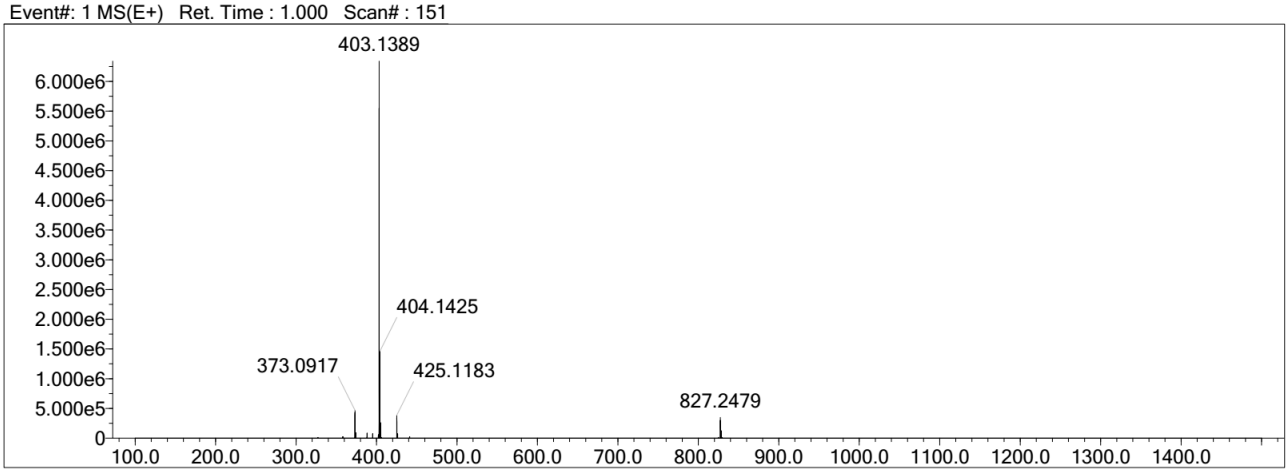


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	83.53	C20 H18 O8	[M+H]+	387.1073	387.1074	-0.1	-0.26	83.53	12.0

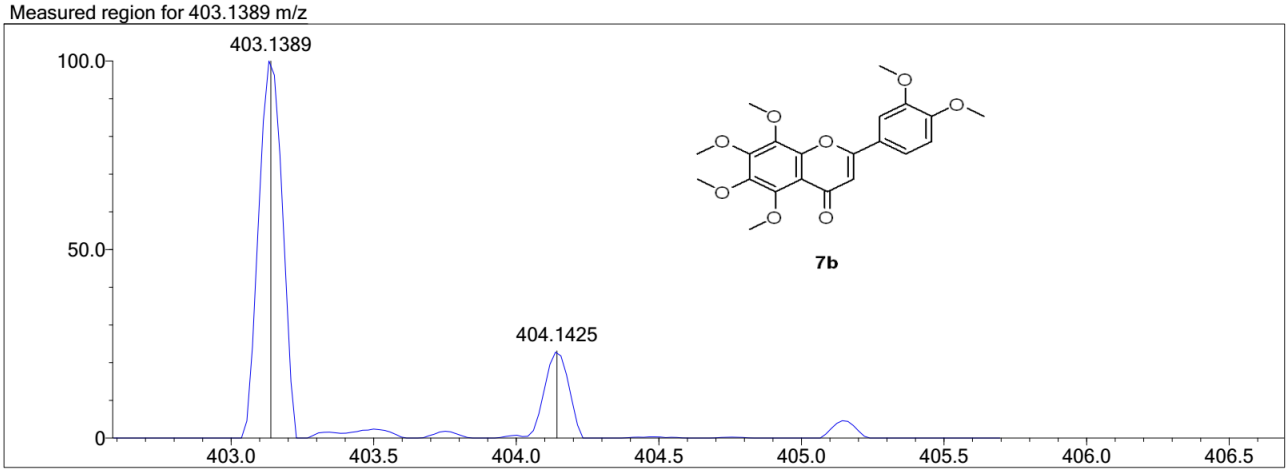
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	10	25	O	2	0	8	Cl	1	0	1	H
C	4	18	25	F	1	0	1	Br	1	0	1	Na
N	3	0	3	S	2	0	1	I	3	0	0	

Error Margin (ppm):	50	DBE Range:	-2.0 - 100.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	no	Use MSn Info:	no
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	15

Event#: 1 MS(E+) Ret. Time : 1.000 Scan# : 151

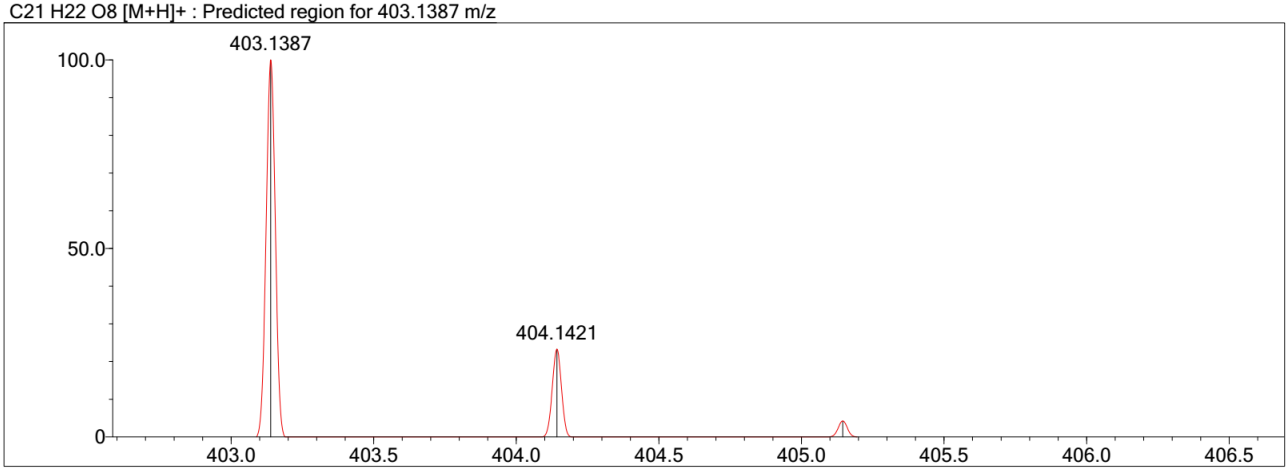


Measured region for 403.1389 m/z



7b

C21 H22 O8 [M+H]+ : Predicted region for 403.1387 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	81.30	C21 H22 O8	[M+H]+	403.1389	403.1387	0.2	0.50	81.30	11.0

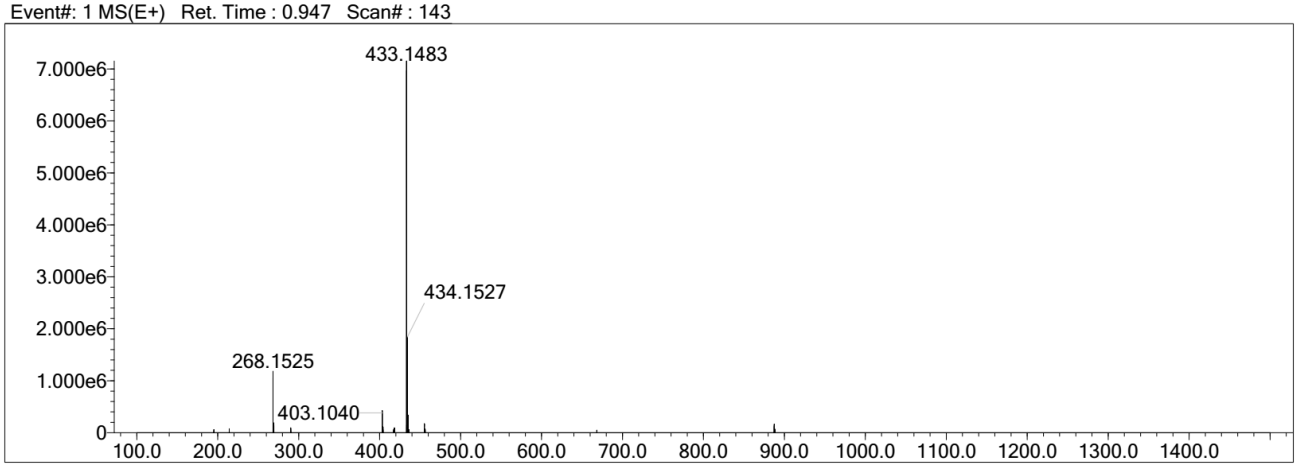
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	8	32	C	4	0	22	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	0	P	3	0	0	Se	2	0	0	
3H	1	0	0	O	2	0	10	S	2	0	0	Br	1	0	0	
B	3	0	0	F	1	0	0	Cl	1	0	1	I	3	0	0	

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

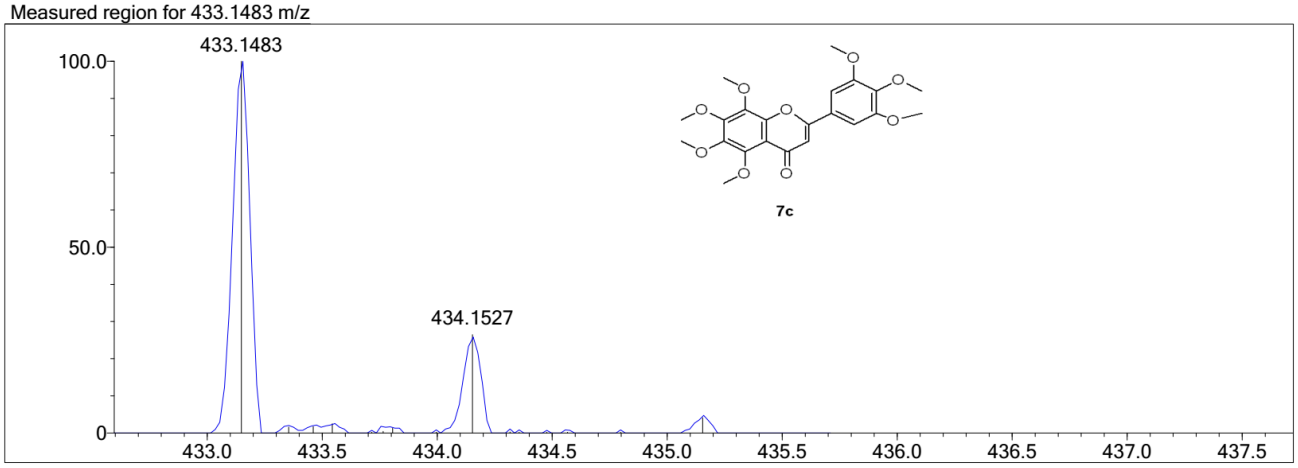
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

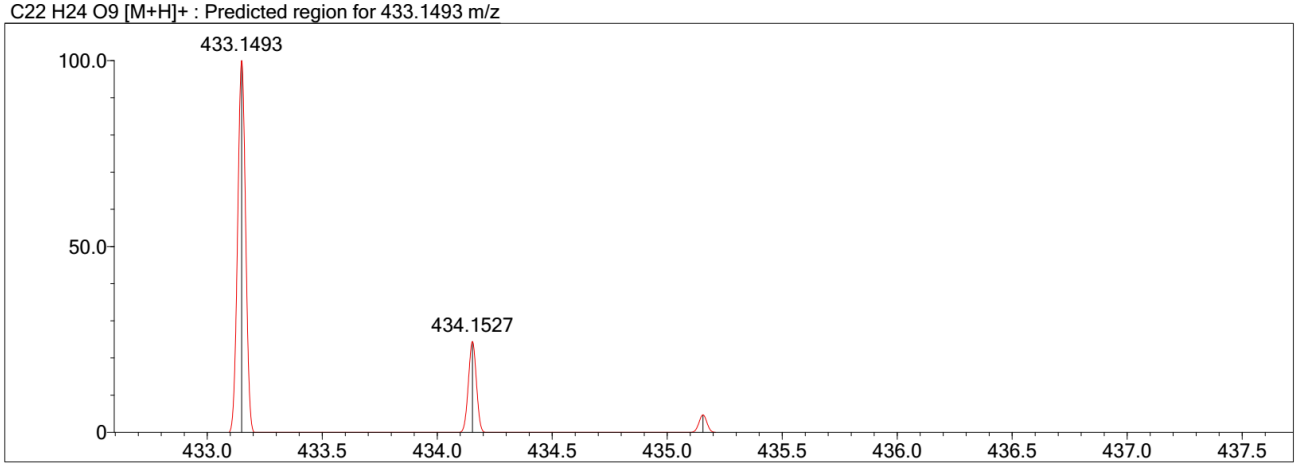
Event#: 1 MS(E+) Ret. Time : 0.947 Scan# : 143



Measured region for 433.1483 m/z



C22 H24 O9 [M+H]+ : Predicted region for 433.1493 m/z

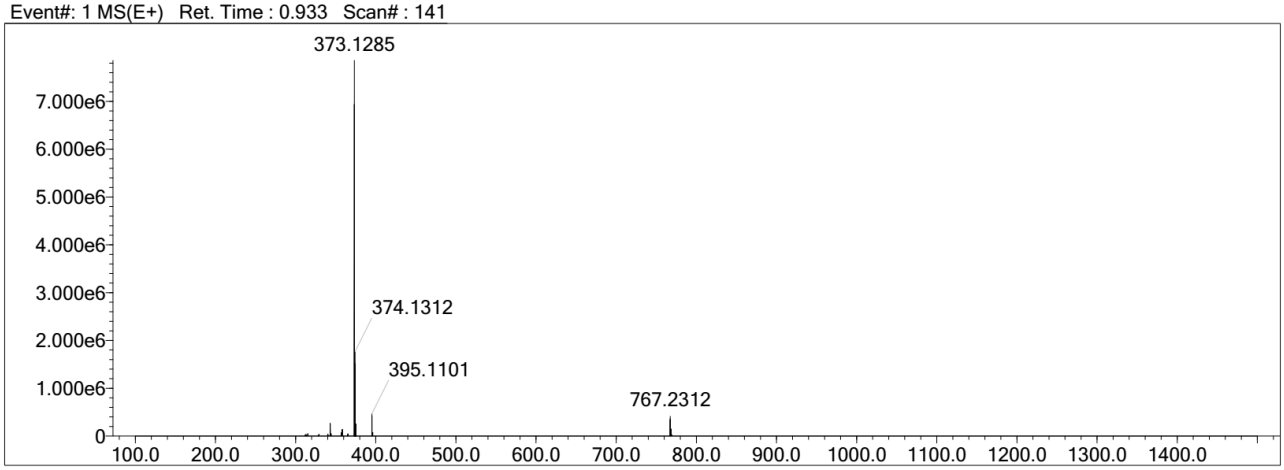


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	80.61	C22 H24 O9	[M+H]+	433.1483	433.1493	-1.0	-2.31	83.34	11.0

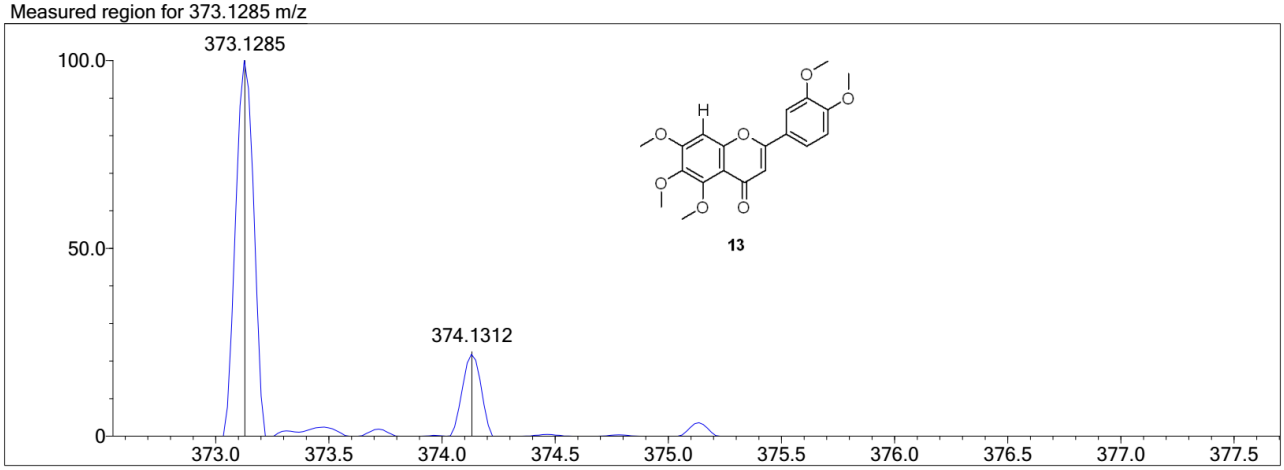
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	32	O	2	0	8	Cl	1	0	0	Na
C	4	18	25	F	1	0	0	Br	1	0	1	
N	3	0	2	S	2	0	0	I	3	0	0	

Error Margin (ppm):	100	DBE Range:	-1.0 - 1000.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	no	Use MSn Info:	no
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	30

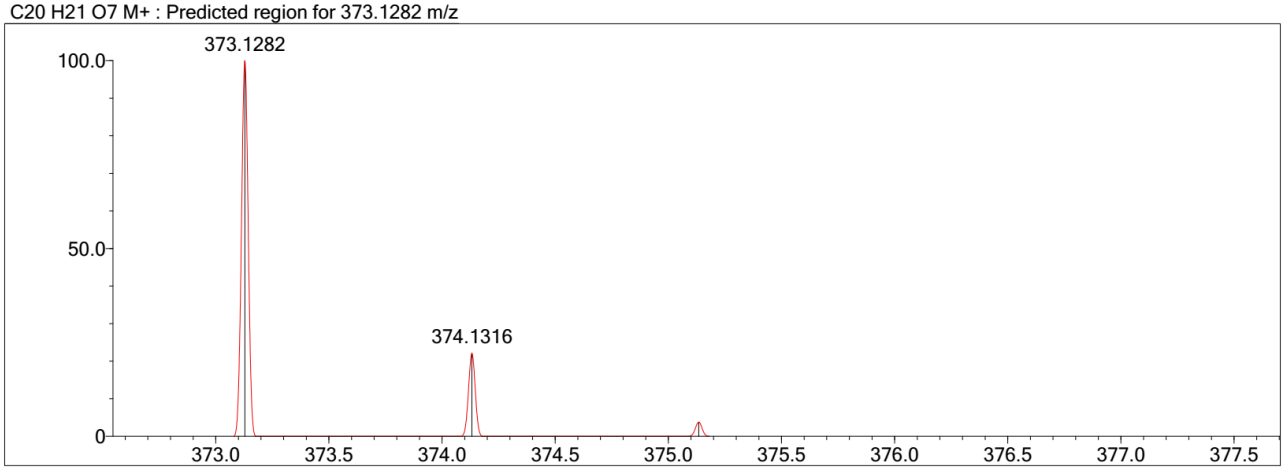
Event#: 1 MS(E+) Ret. Time : 0.933 Scan# : 141



Measured region for 373.1285 m/z



C20 H21 O7 M+ : Predicted region for 373.1282 m/z

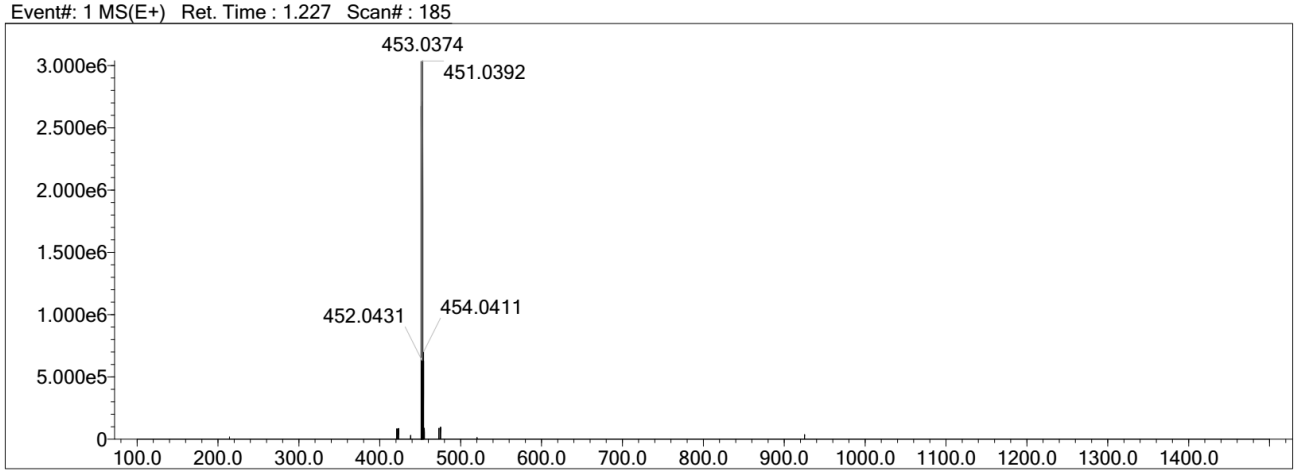


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	82.24	C20 H21 O7	M+	373.1285	373.1282	0.3	0.80	82.24	10.5

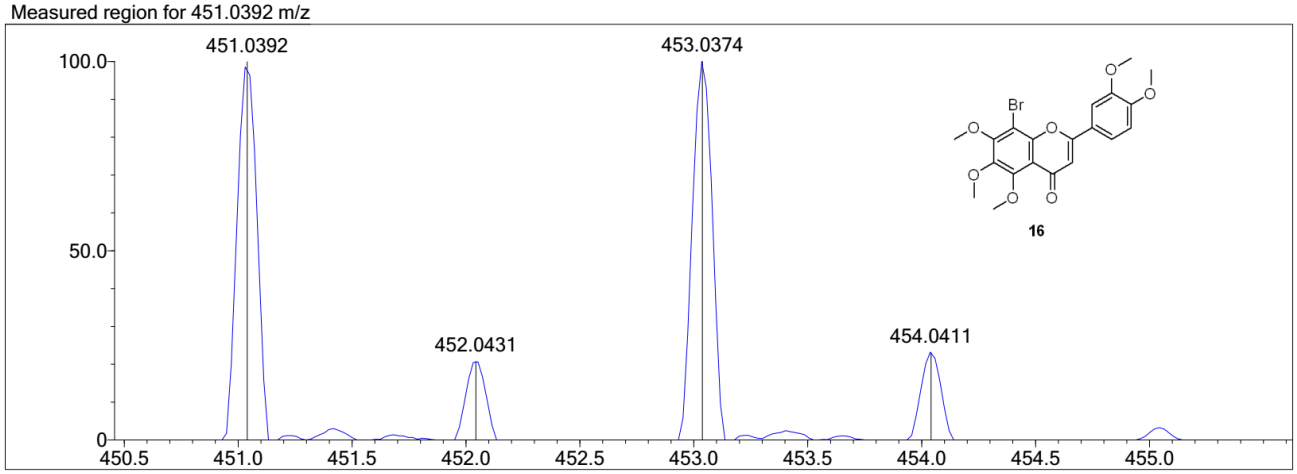
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	32	O	2	0	8	Cl	1	0	0	H
C	4	18	25	F	1	0	0	Br	1	0	1	Na
N	3	0	2	S	2	0	0	I	3	0	0	

Error Margin (ppm):	100	DBE Range:	-1.0 - 1000.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	no	Use MSn Info:	no
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	30

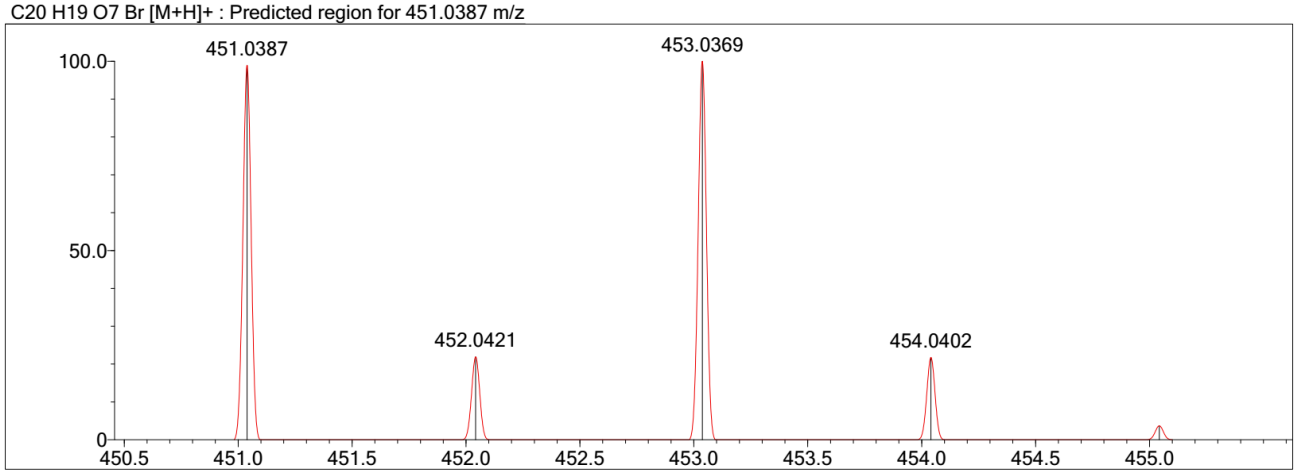
Event#: 1 MS(E+) Ret. Time : 1.227 Scan# : 185



Measured region for 451.0392 m/z



C20 H19 O7 Br [M+H]+ : Predicted region for 451.0387 m/z

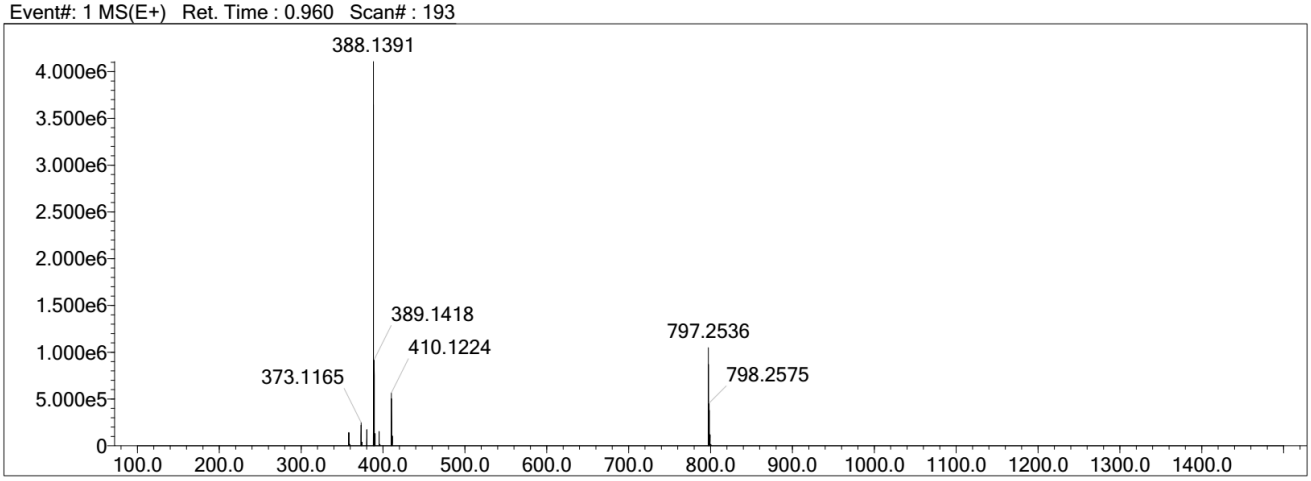


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	87.36	C20 H19 O7 Br	[M+H]+	451.0392	451.0387	0.5	1.11	87.60	11.0

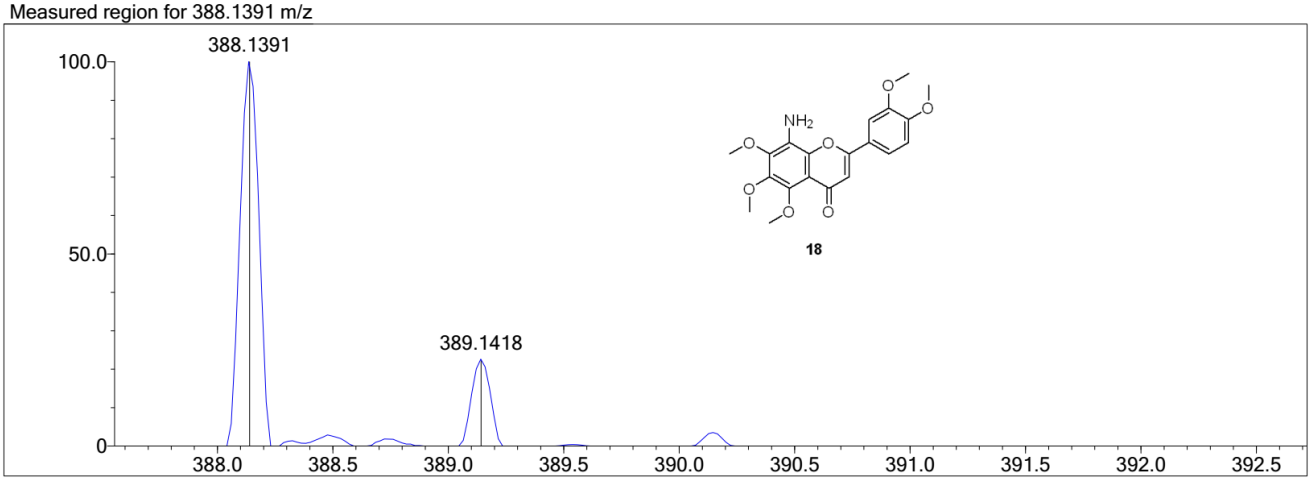
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	32	O	2	0	8	Cl	1	0	0	H
C	4	18	25	F	1	0	0	Br	1	0	1	Na
N	3	0	2	S	2	0	0	I	3	0	0	

Error Margin (ppm):	100	DBE Range:	-1.0 - 1000.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	no	Use MSn Info:	no
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	30

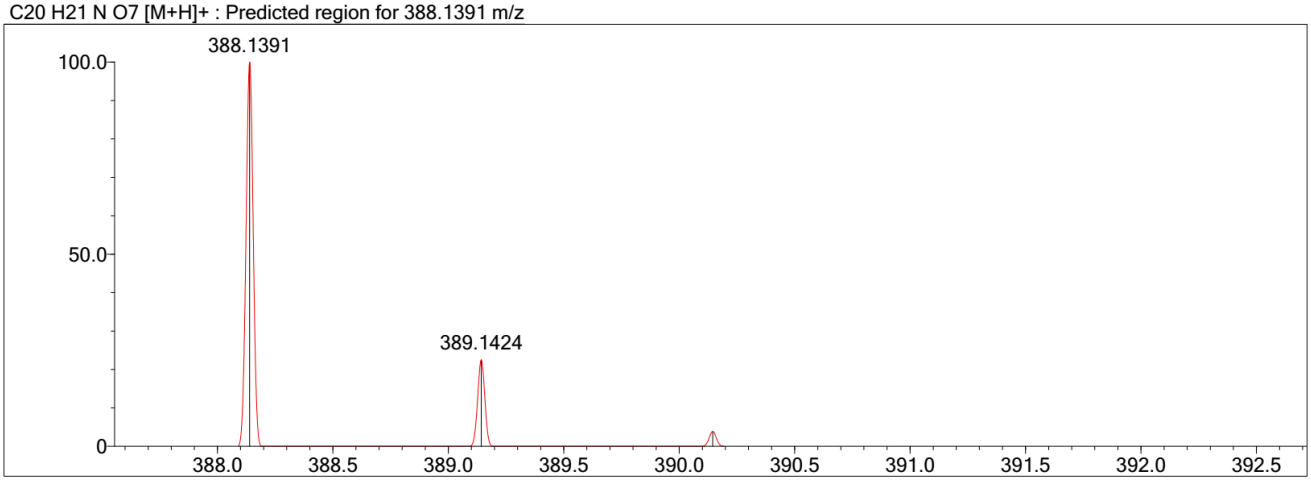
Event#: 1 MS(E+) Ret. Time : 0.960 Scan# : 193



Measured region for 388.1391 m/z



C20 H21 N O7 [M+H]+ : Predicted region for 388.1391 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	84.36	C20 H21 N O7	[M+H]+	388.1391	388.1391	0.0	0.00	84.36	11.0

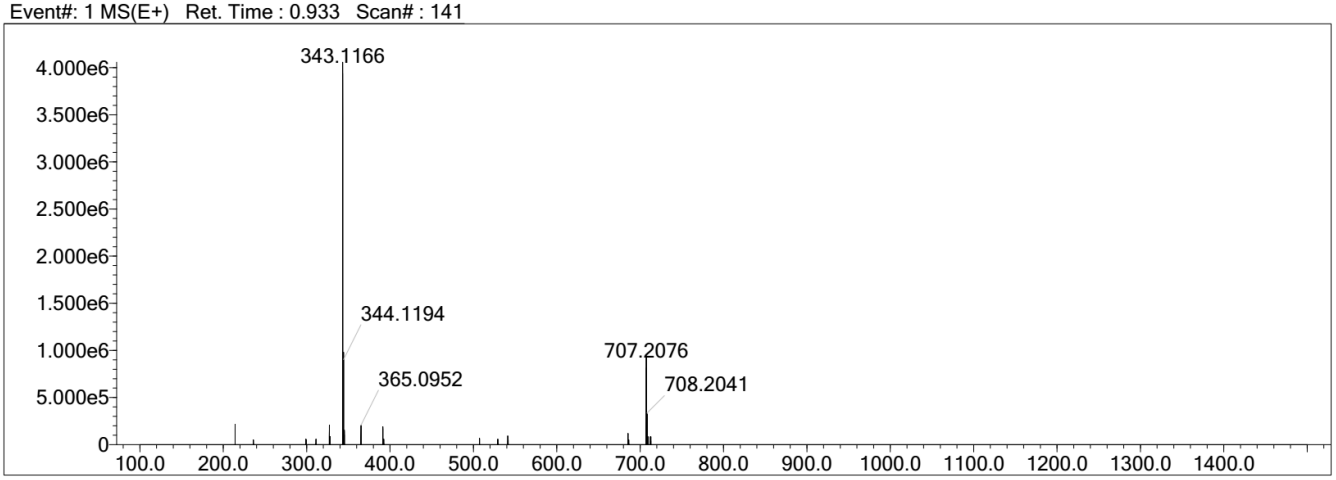
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	8	32	C	4	0	22	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	0	P	3	0	0	Se	2	0	0	
3H	1	0	0	O	2	0	10	S	2	0	0	Br	1	0	0	
B	3	0	0	F	1	0	0	Cl	1	0	1	I	3	0	0	

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

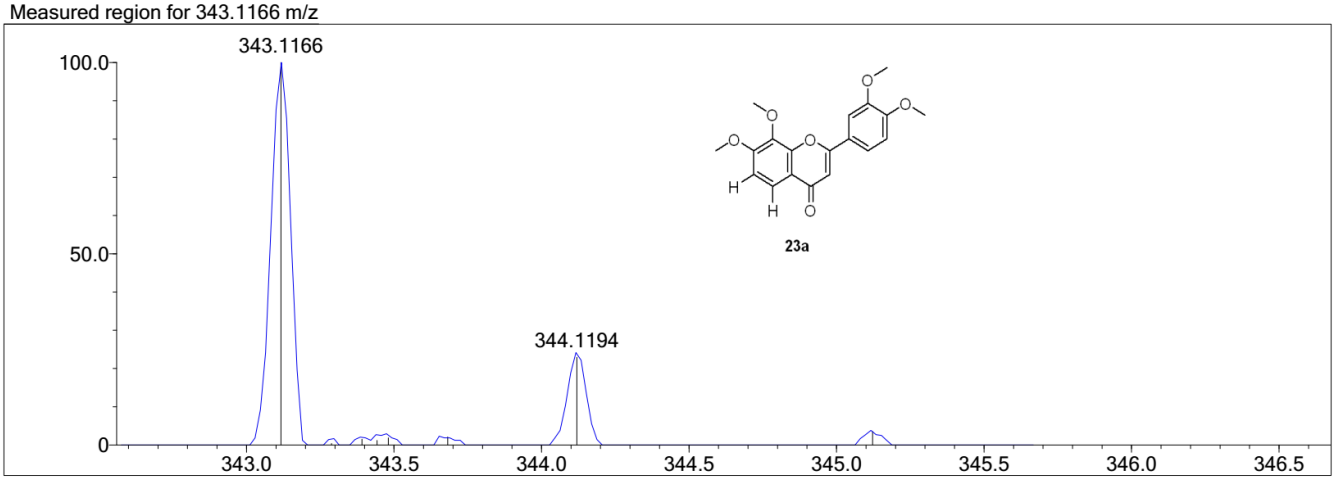
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

Event#: 1 MS(E+) Ret. Time : 0.933 Scan# : 141

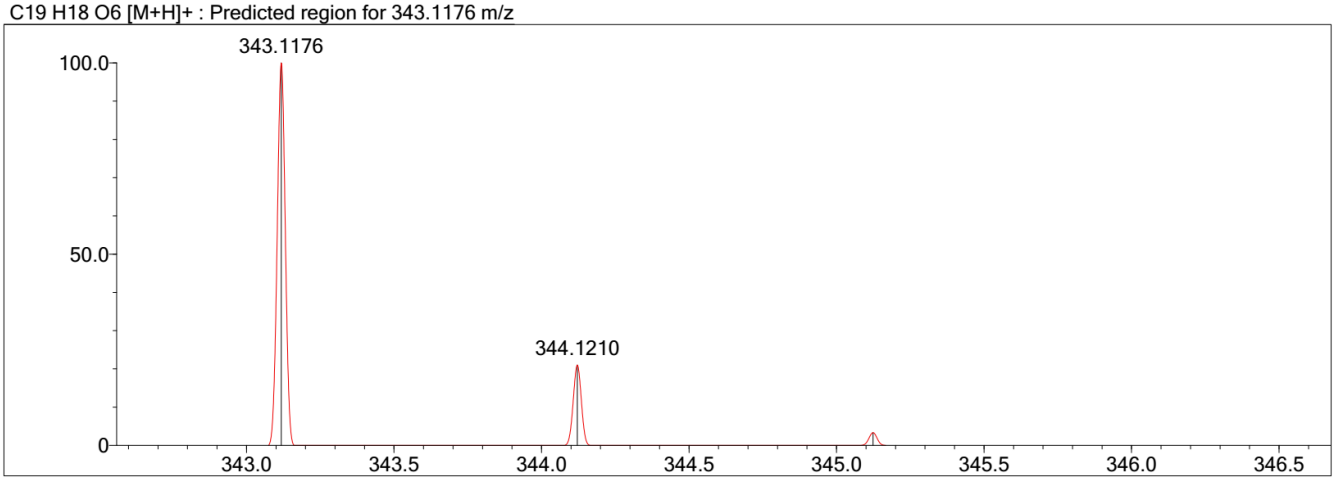


Measured region for 343.1166 m/z



23a

C19 H18 O6 [M+H]+ : Predicted region for 343.1176 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	73.86	C19 H18 O6	[M+H]+	343.1166	343.1176	-1.0	-2.91	77.57	11.0

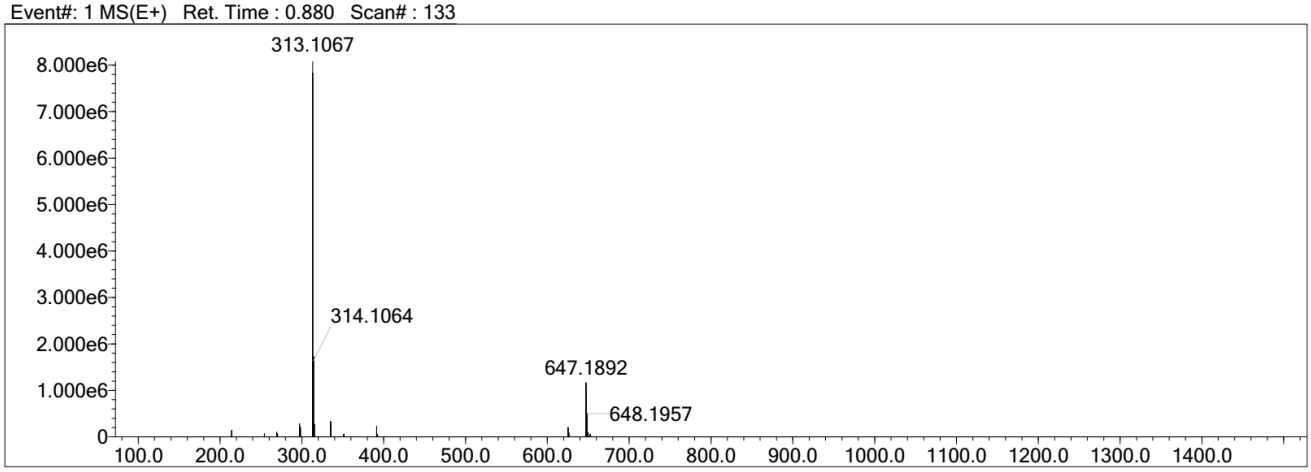
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	8	32	C	4	0	22	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	0	P	3	0	0	Se	2	0	0	
3H	1	0	0	O	2	0	10	S	2	0	0	Br	1	0	0	
B	3	0	0	F	1	0	0	Cl	1	0	1	I	3	0	0	

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

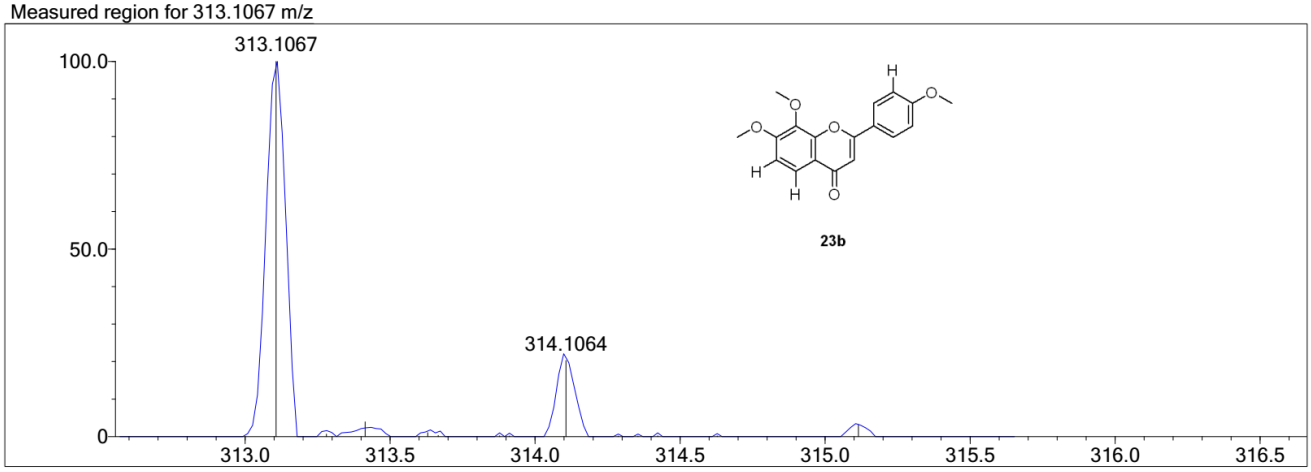
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

Event#: 1 MS(E+) Ret. Time : 0.880 Scan# : 133

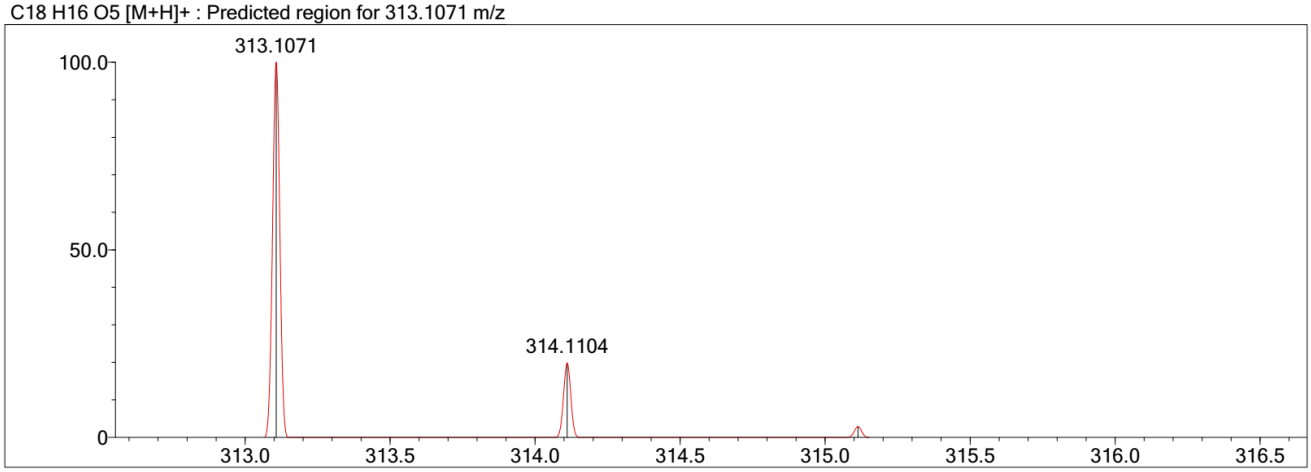


Measured region for 313.1067 m/z



23b

C18 H16 O5 [M+H]+ : Predicted region for 313.1071 m/z

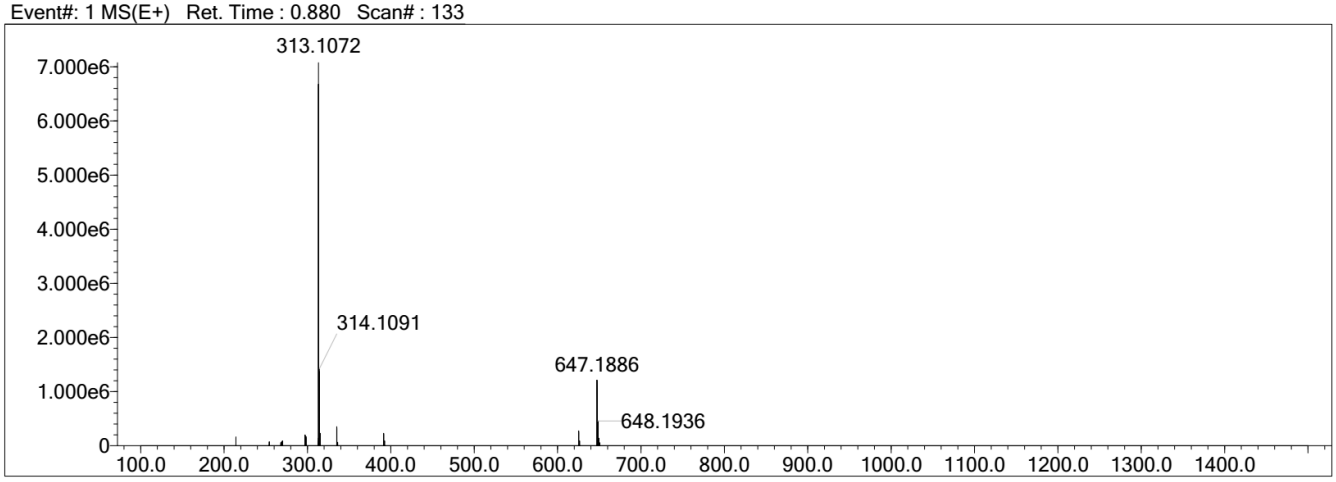


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	76.66	C18 H16 O5	[M+H]+	313.1067	313.1071	-0.4	-1.28	77.20	11.0

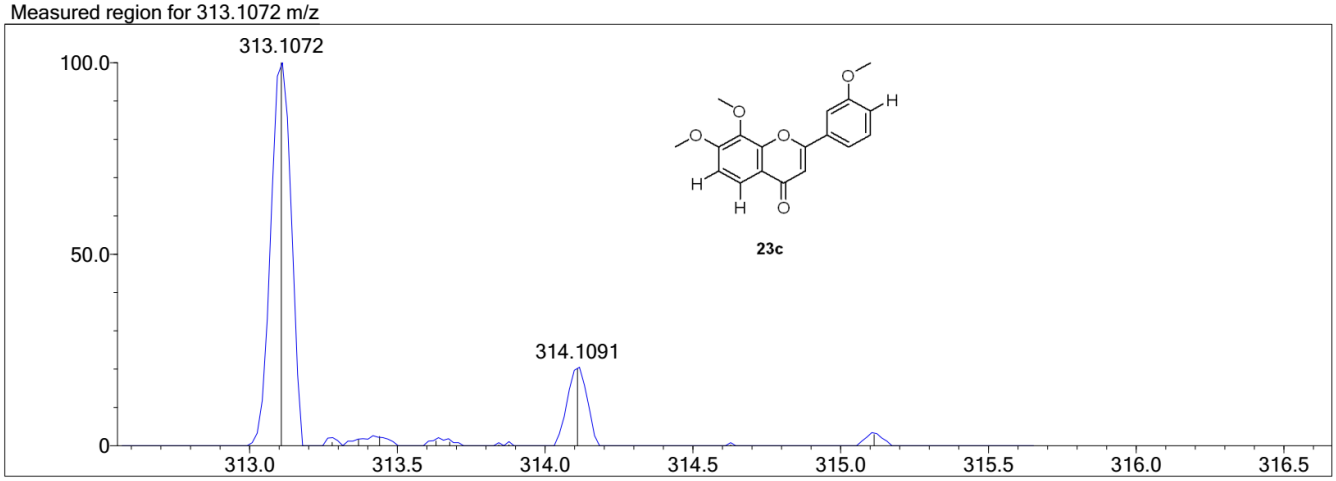
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	8	32	C	4	0	22	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	0	P	3	0	0	Se	2	0	0	
3H	1	0	0	O	2	0	10	S	2	0	0	Br	1	0	0	
B	3	0	0	F	1	0	0	Cl	1	0	1	I	3	0	0	

Error Margin (ppm):	50	DBE Range:	-50.0 - 50.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	yes	Use MSn Info:	no
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	500

Event#: 1 MS(E+) Ret. Time : 0.880 Scan# : 133

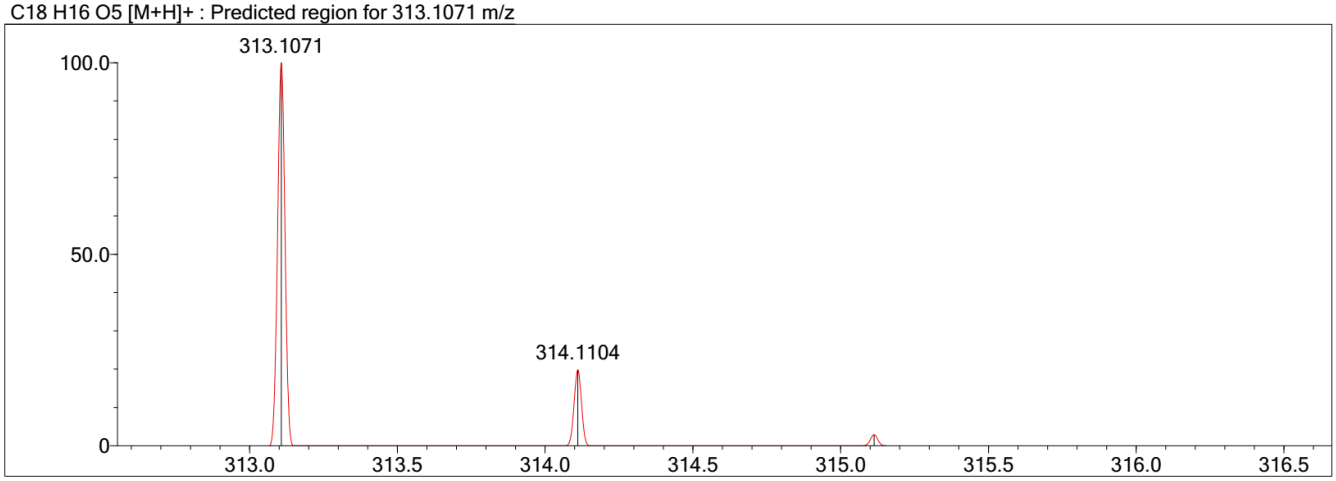


Measured region for 313.1072 m/z



23c

C18 H16 O5 [M+H]+ : Predicted region for 313.1071 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	78.59	C18 H16 O5	[M+H]+	313.1072	313.1071	0.1	0.32	78.59	11.0

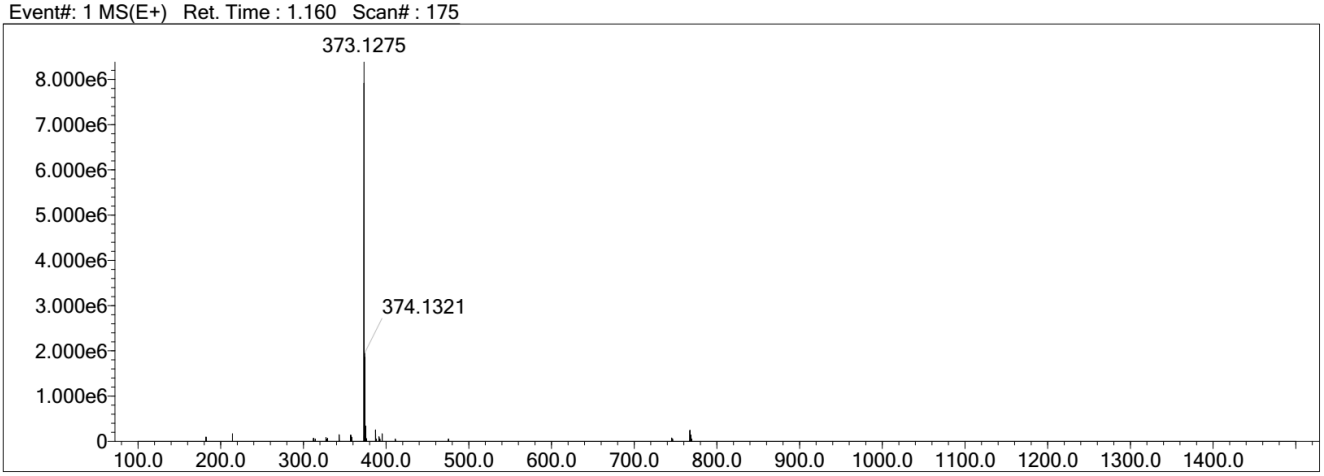
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	33	C	4	0	30	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	3	P	3	0	0	Se	2	0	0	Na
3H	1	0	0	O	2	0	8	S	2	0	0	Br	1	0	0	K
B	3	0	0	F	1	0	0	Cl	1	0	0	I	3	0	0	NH4

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

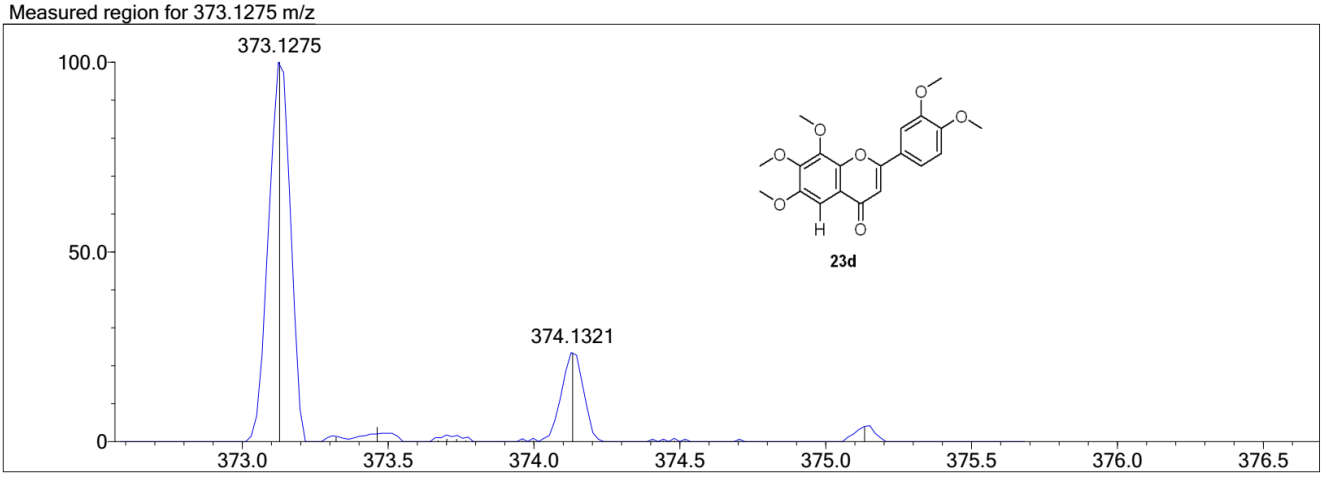
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

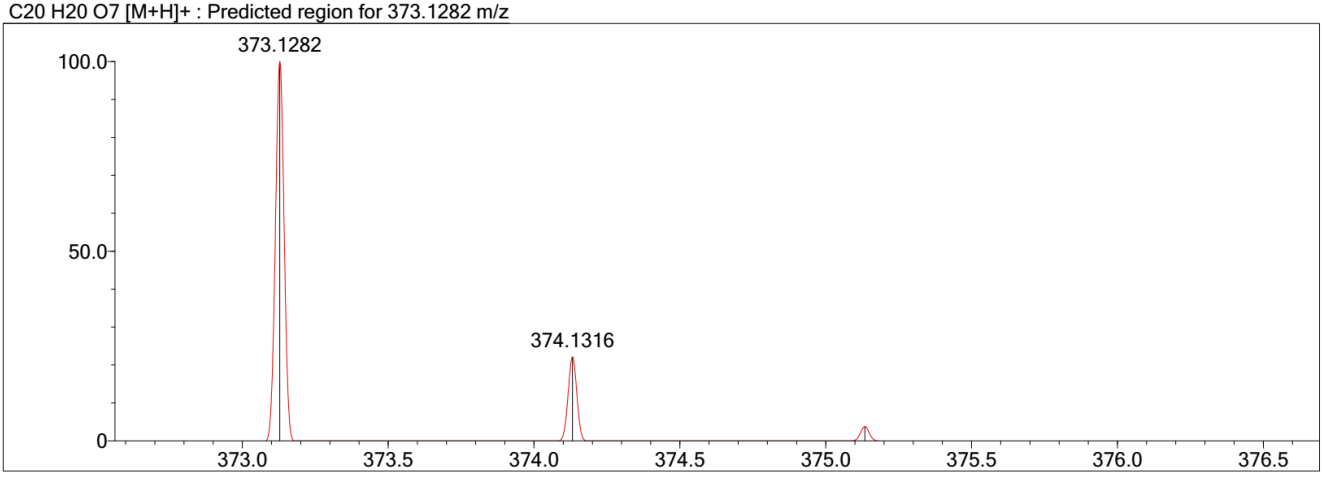
Event#: 1 MS(E+) Ret. Time : 1.160 Scan# : 175



Measured region for 373.1275 m/z



C20 H20 O7 [M+H]+ : Predicted region for 373.1282 m/z

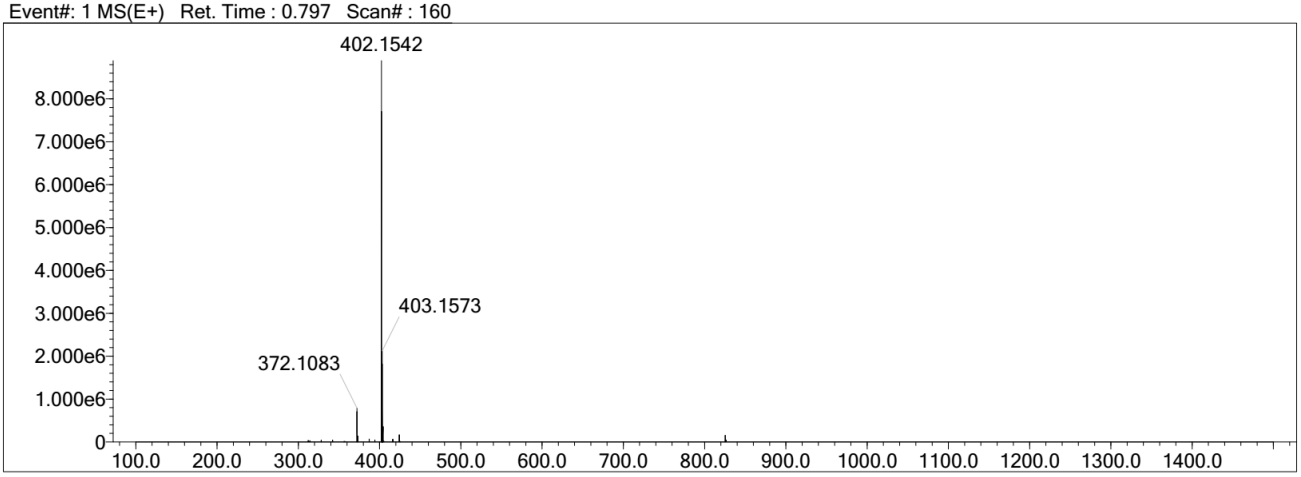


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
2	78.41	C20 H20 O7	[M+H]+	373.1275	373.1282	-0.7	-1.88	80.17	11.0

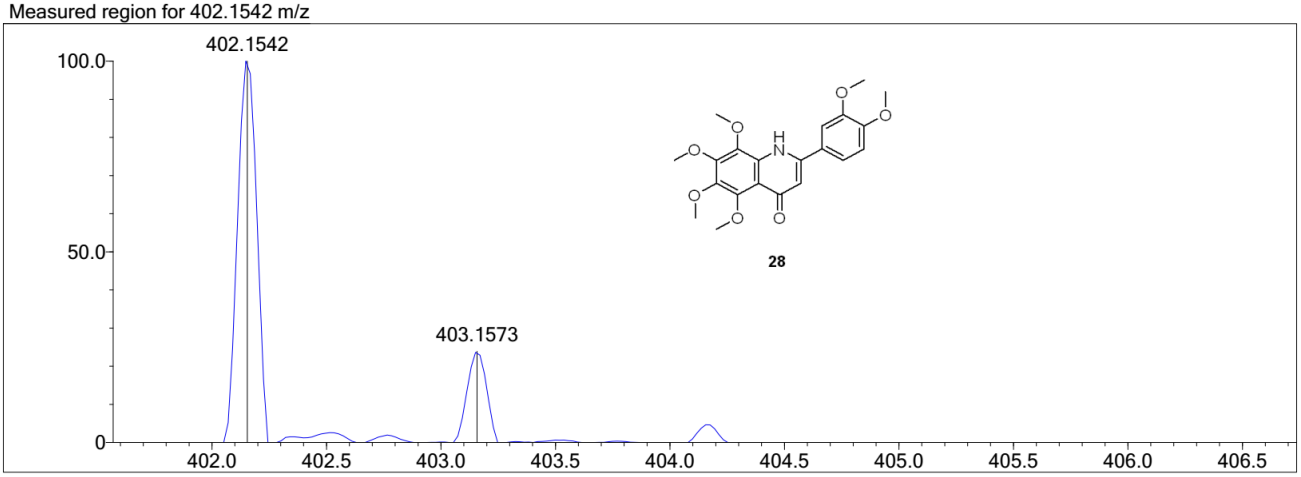
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	32	O	2	0	8	Cl	1	0	0	H
C	4	18	25	F	1	0	0	Br	1	0	1	Na
N	3	0	2	S	2	0	0	I	3	0	0	

Error Margin (ppm):	100	DBE Range:	-1.0 - 1000.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	no	Use MSn Info:	no
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	30

Event#: 1 MS(E+) Ret. Time : 0.797 Scan# : 160

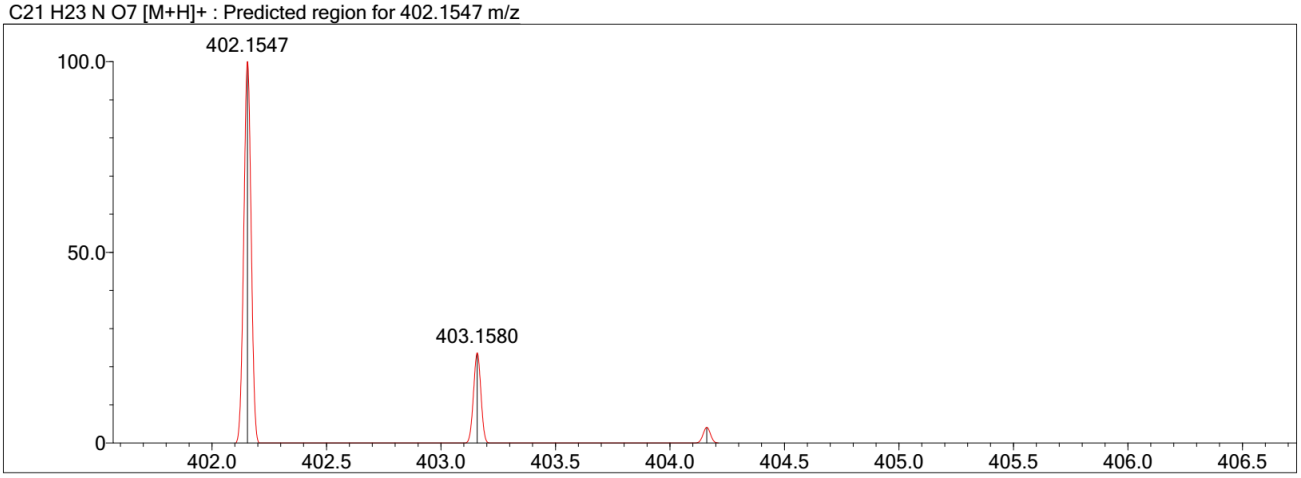


Measured region for 402.1542 m/z



28

C21 H23 N O7 [M+H]+ : Predicted region for 402.1547 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	78.28	C21 H23 N O7	[M+H]+	402.1542	402.1547	-0.5	-1.24	78.75	11.0

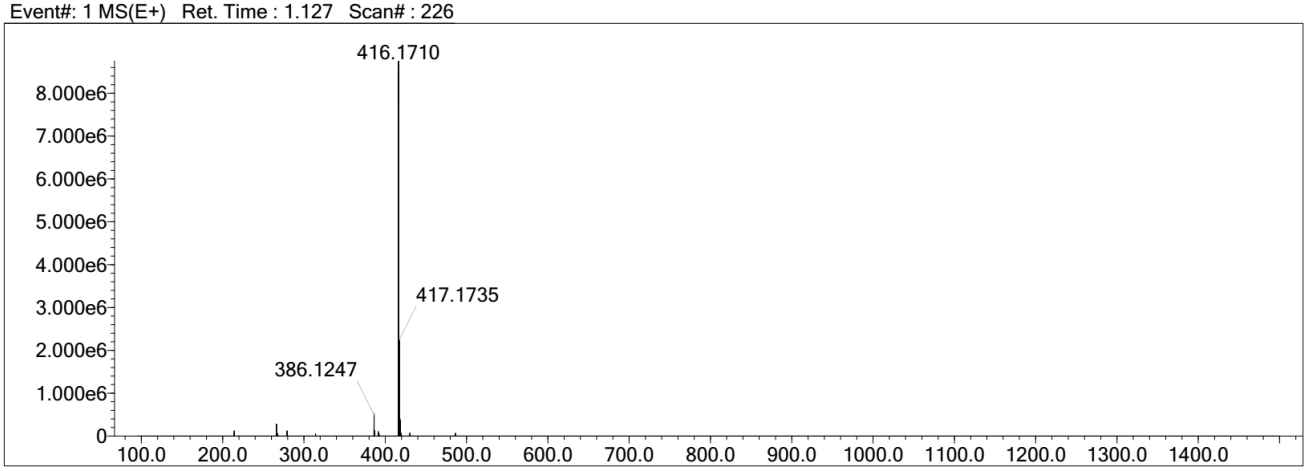
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	155	N	3	0	19	P	3	0	0	Se	2	0	0	H
2H	1	0	0	O	2	0	16	S	2	0	0	Br	1	0	0	
B	3	0	0	F	1	0	0	Cl	1	0	0	I	3	0	0	
C	4	0	99	Si	4	0	0	K	1	0	0					

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

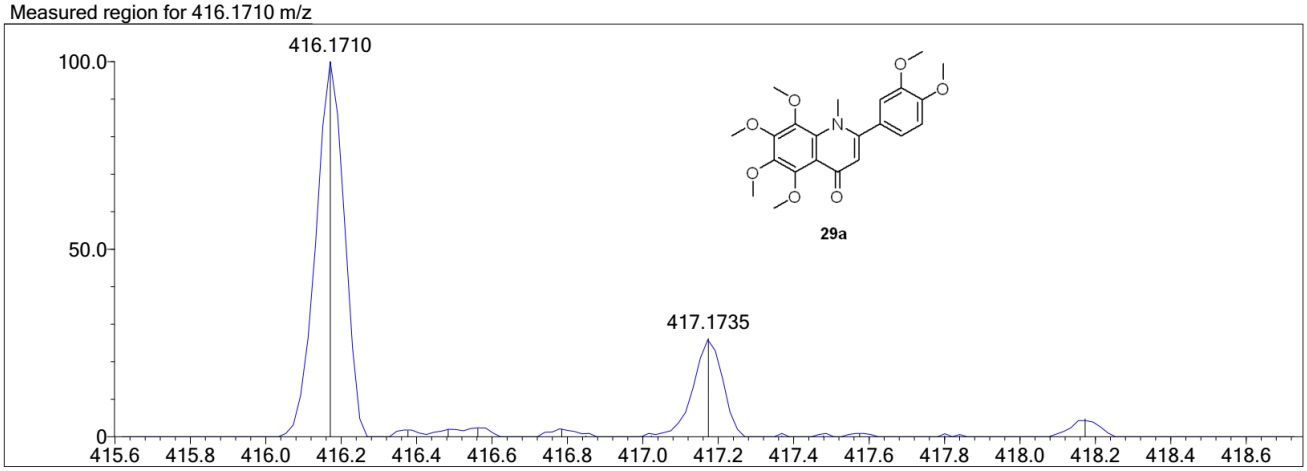
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

Event#: 1 MS(E+) Ret. Time : 1.127 Scan# : 226

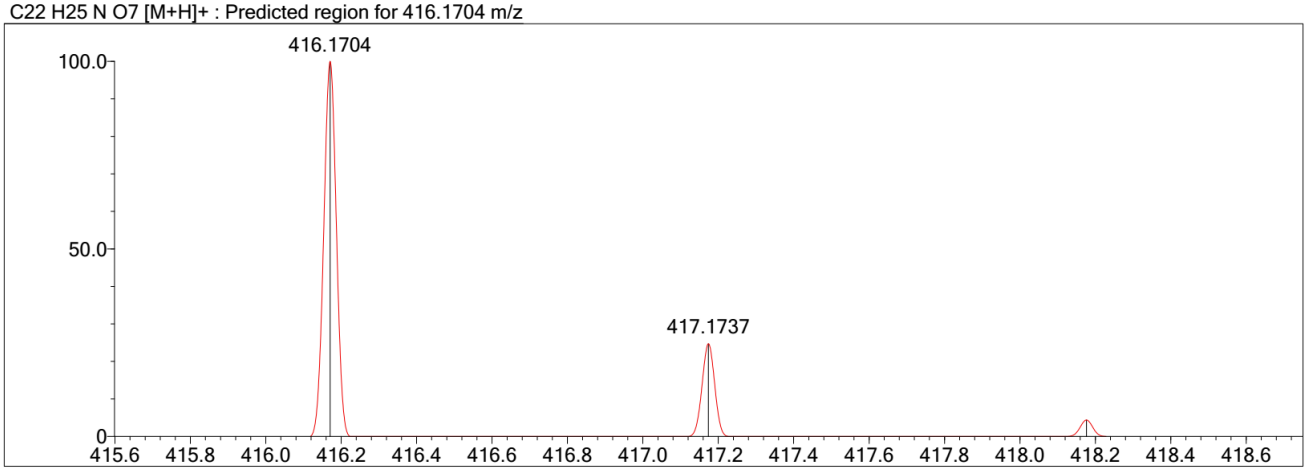


Measured region for 416.1710 m/z



29a

C22 H25 N O7 [M+H]+ : Predicted region for 416.1704 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
2	76.87	C22 H25 N O7	[M+H]+	416.1710	416.1704	0.6	1.44	77.73	11.0

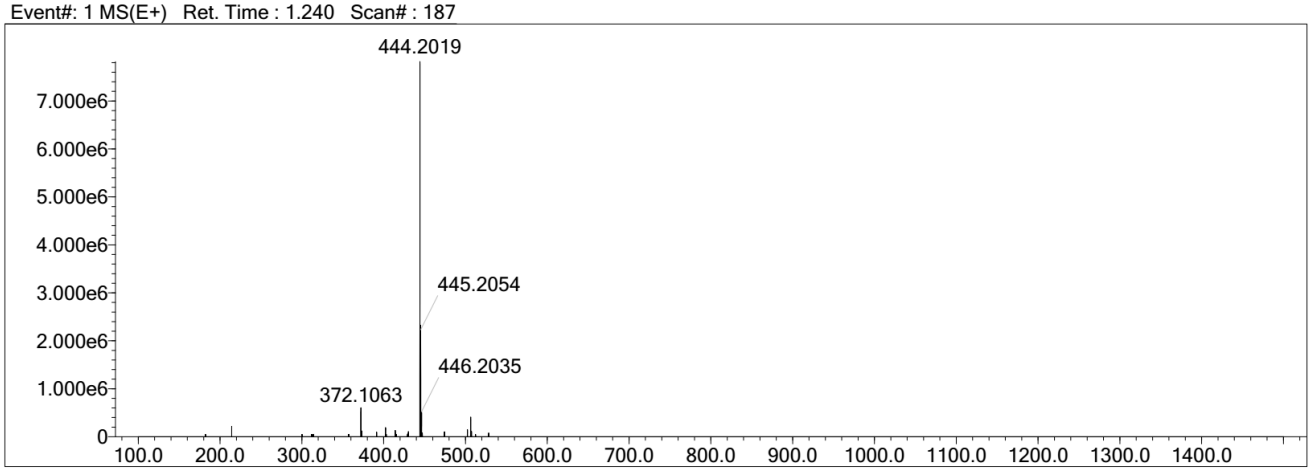
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	33	C	4	0	30	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	3	P	3	0	0	Se	2	0	0	Na
3H	1	0	0	O	2	0	8	S	2	0	0	Br	1	0	0	K
B	3	0	0	F	1	0	0	Cl	1	0	0	I	3	0	0	NH4

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

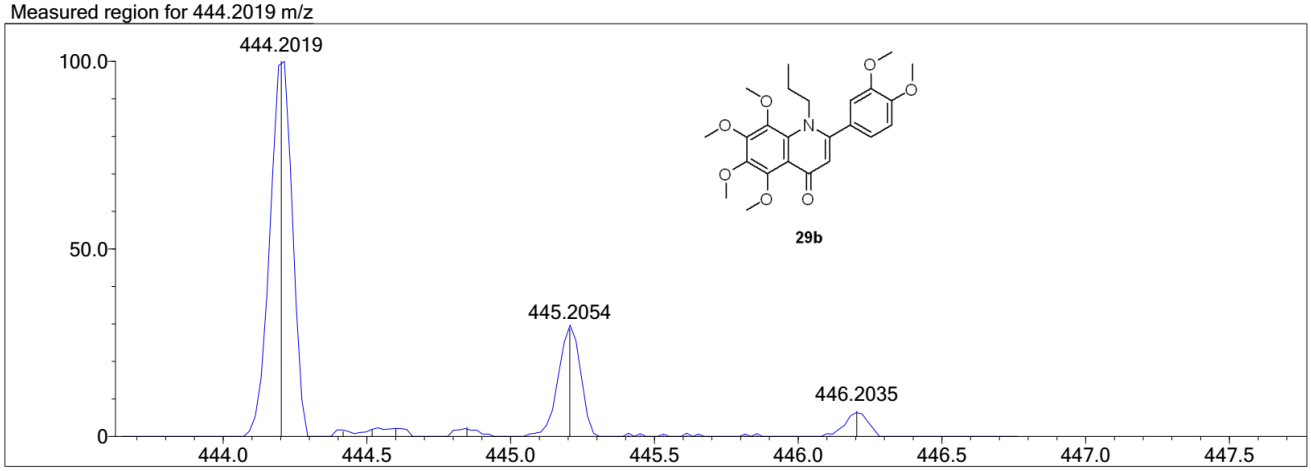
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

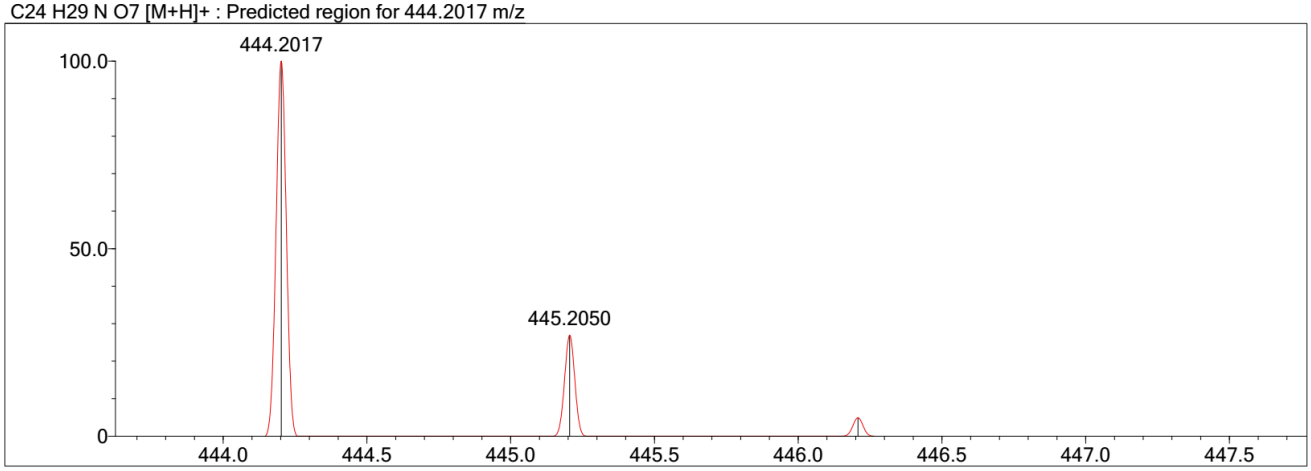
Event#: 1 MS(E+) Ret. Time : 1.240 Scan# : 187



Measured region for 444.2019 m/z



C24 H29 N O7 [M+H]+ : Predicted region for 444.2017 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	82.69	C24 H29 N O7	[M+H]+	444.2019	444.2017	0.2	0.45	82.69	11.0

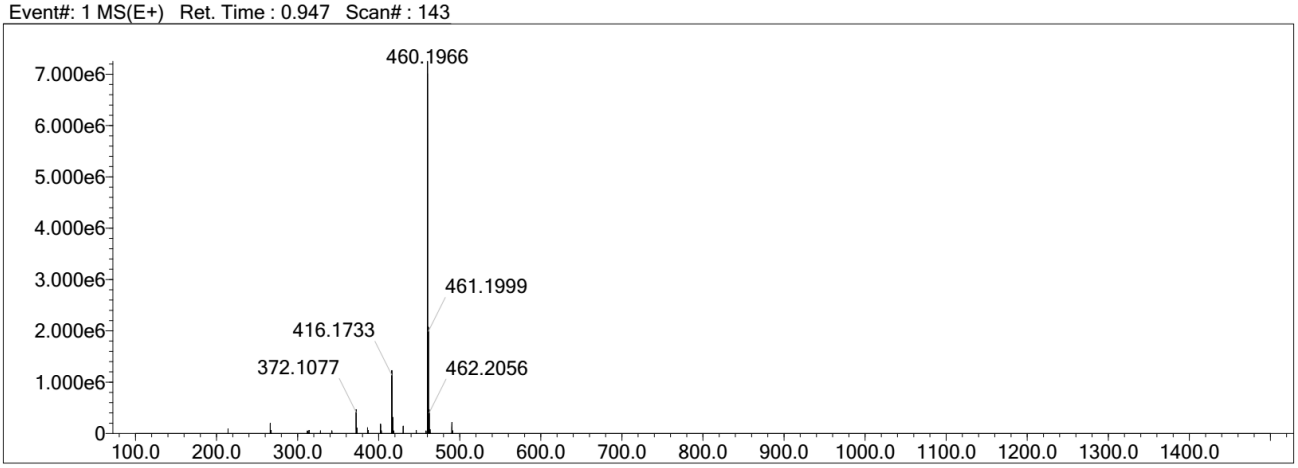
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	33	C	4	0	30	Si	4	0	0	K	1	0	0	H
2H	1	0	0	N	3	0	3	P	3	0	0	Se	2	0	0	Na
3H	1	0	0	O	2	0	8	S	2	0	0	Br	1	0	0	K
B	3	0	0	F	1	0	0	Cl	1	0	0	I	3	0	0	NH4

Error Margin (ppm): 50
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

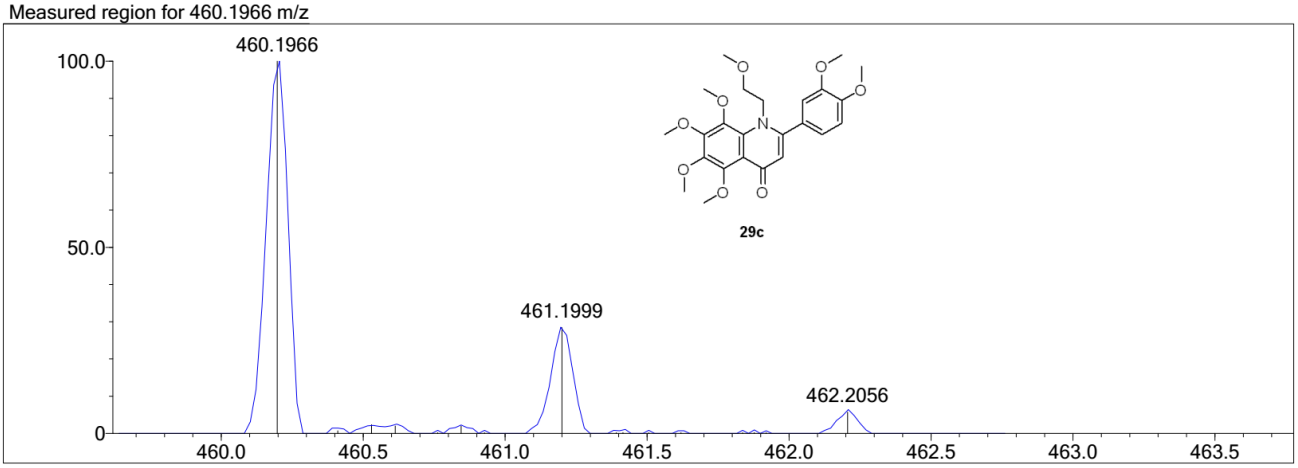
DBE Range: -50.0 - 50.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

Event#: 1 MS(E+) Ret. Time : 0.947 Scan# : 143

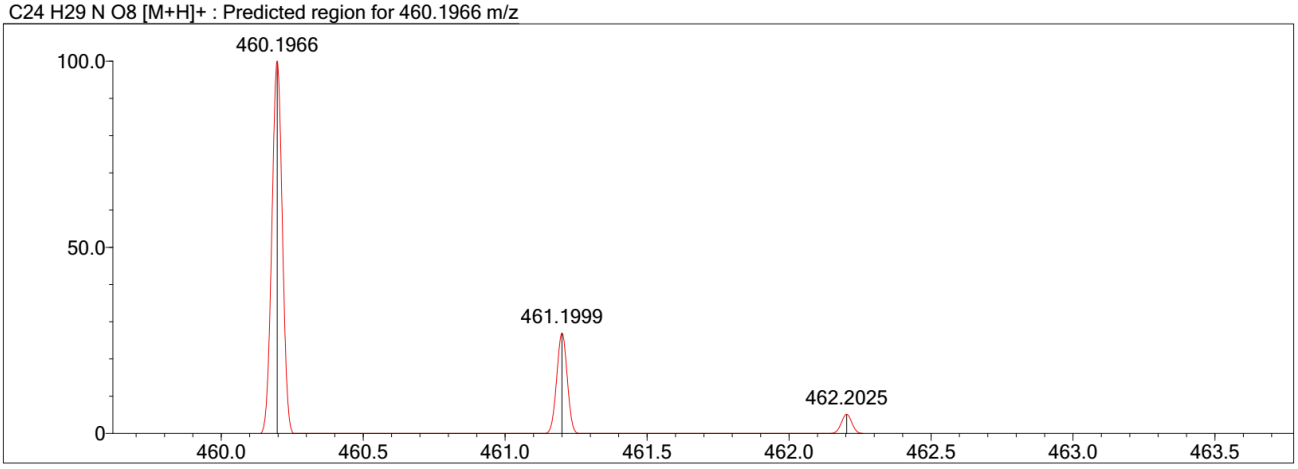


Measured region for 460.1966 m/z



29c

C24 H29 N O8 [M+H]+ : Predicted region for 460.1966 m/z

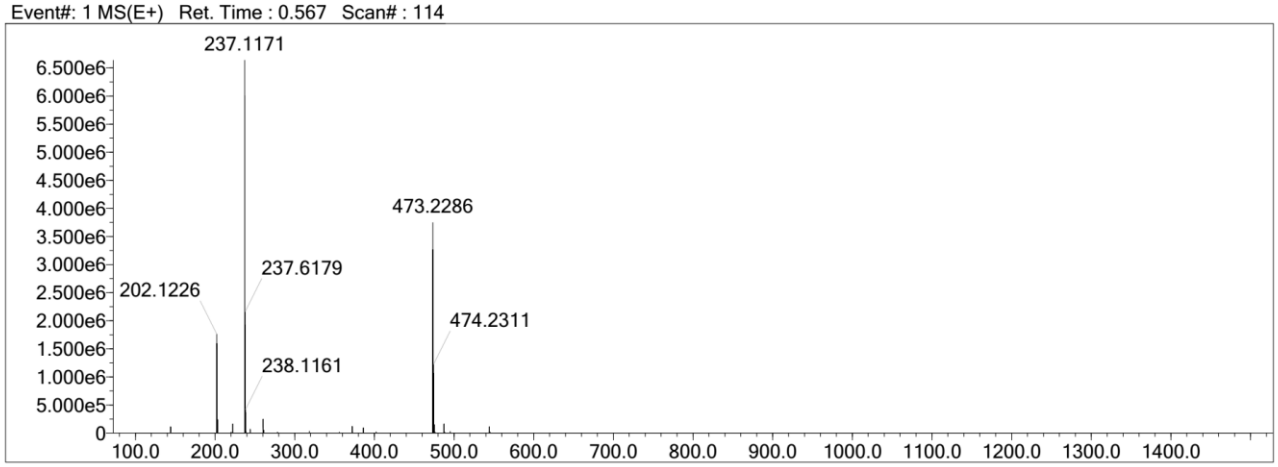


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	87.17	C24 H29 N O8	[M+H]+	460.1966	460.1966	0.0	0.00	87.17	11.0

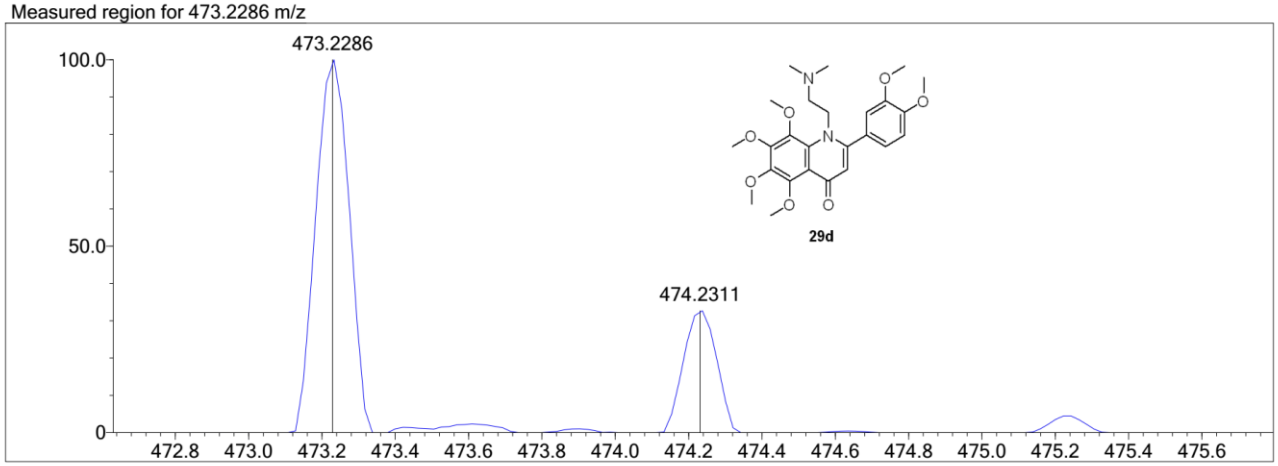
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	32	O	2	0	8	Cl	1	0	0	H
C	4	18	25	F	1	0	0	Br	1	0	1	Na
N	3	0	2	S	2	0	0	I	3	0	0	

Error Margin (ppm):	100	DBE Range:	-1.0 - 1000.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	no	Use MSn Info:	no
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	30

Event#: 1 MS(E+) Ret. Time : 0.567 Scan# : 114

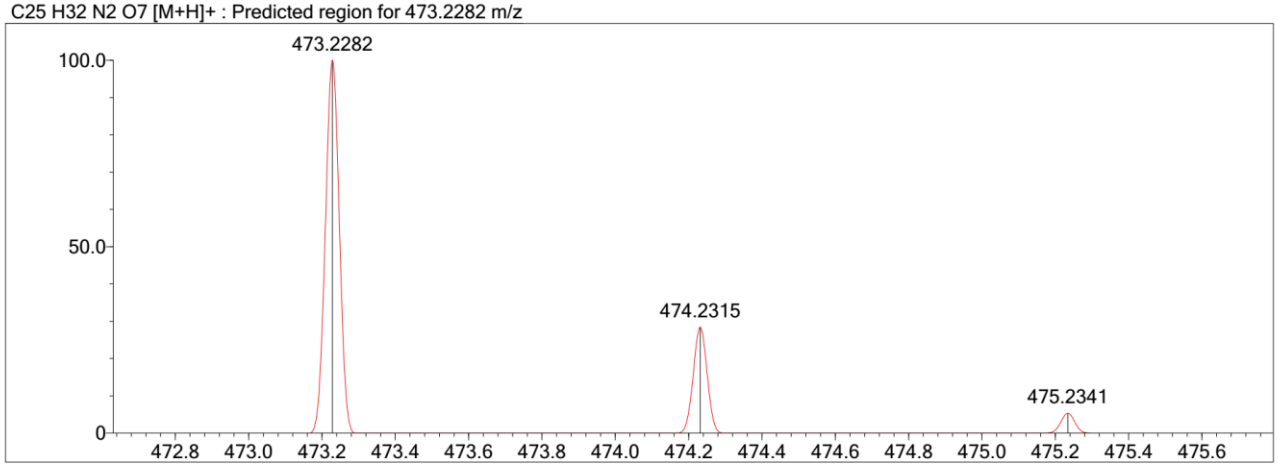


Measured region for 473.2286 m/z



29d

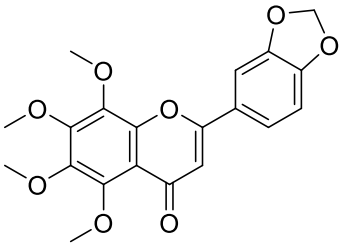
C25 H32 N2 O7 [M+H]+ : Predicted region for 473.2282 m/z



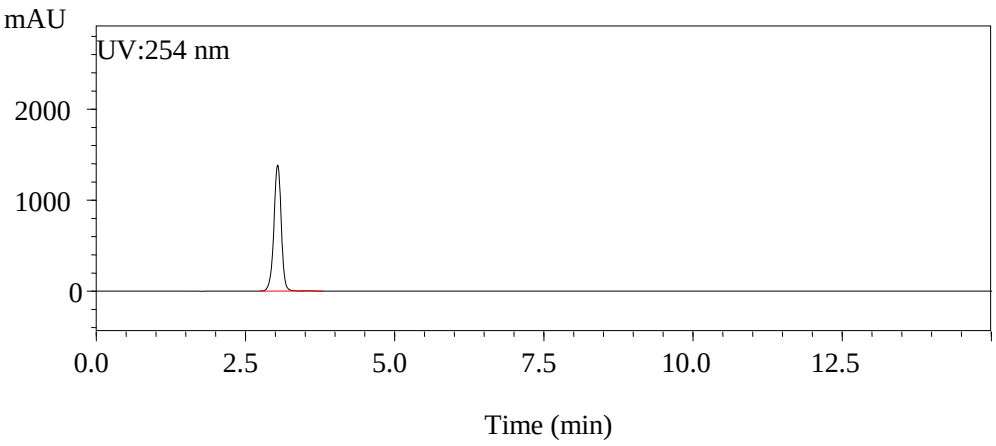
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	81.76	C25 H32 N2 O7	[M+H]+	473.2286	473.2282	0.4	0.85	81.76	11.0

Section 5 Purity data of tested compounds

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



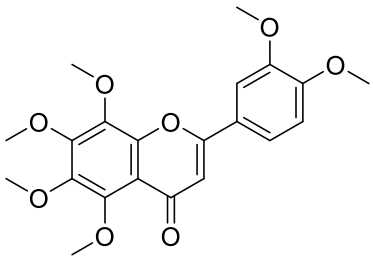
7a



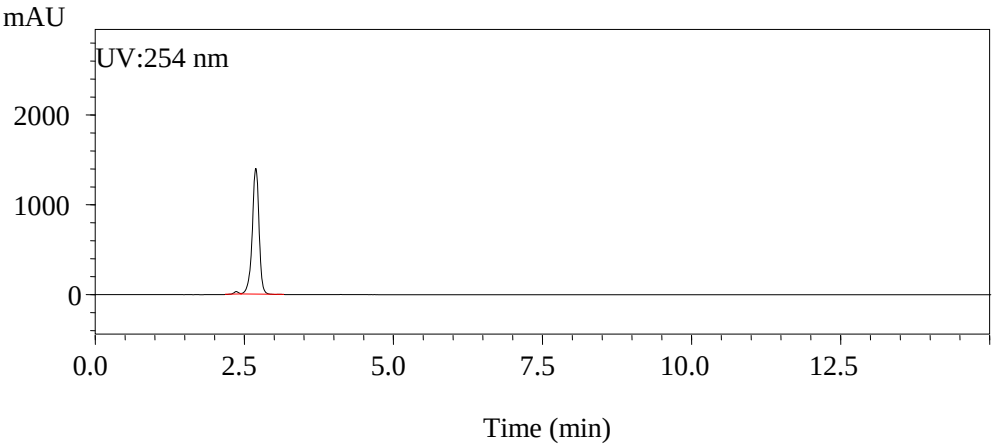
Peak#	Retention time (min)	Peak area	Peak height	Peak area%
1	3.035	11910155	1385792	99.8167
2	3.563	21872	2725	0.1833

Purity：99.8%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



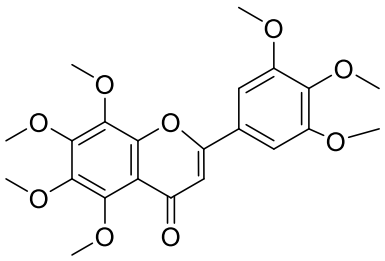
7b



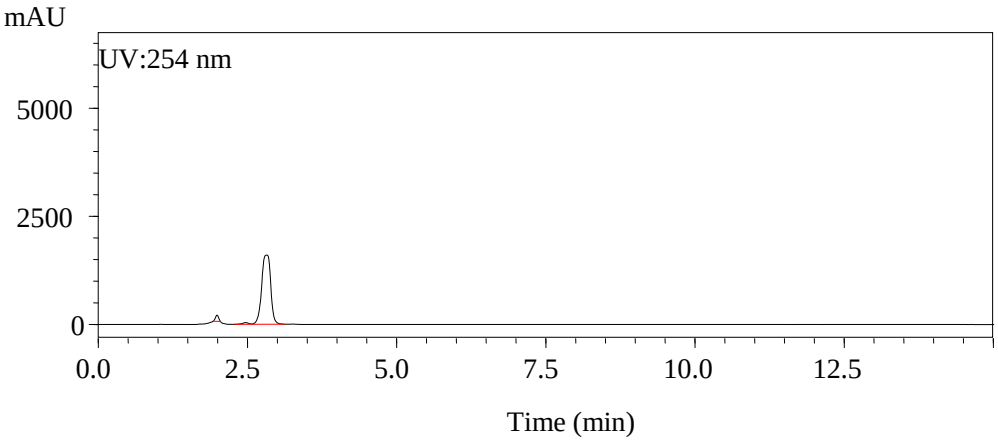
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.358	130890	26765	1.1622
2	2.687	11131199	1397896	98.8378

Purity：98.8%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*; T = 25 ℃; flow rate = 1.0 mL/min).



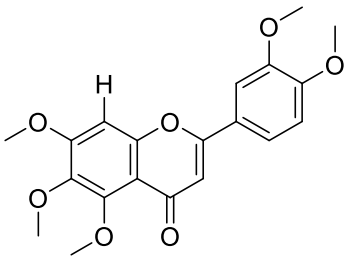
7c



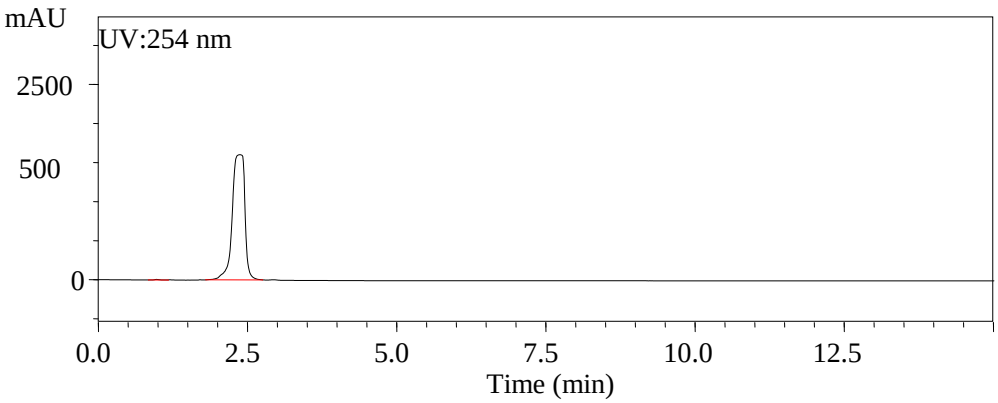
Peak#	Retention time	Peak area	Peak height	Peak area%
1	1.985	524440	138566	2.9658
2	2.816	17158713	1600144	97.0342

Purity：97.0%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



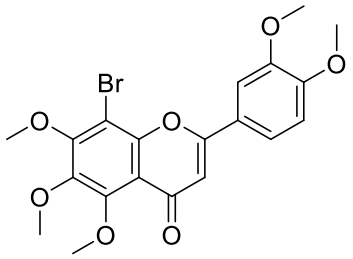
13



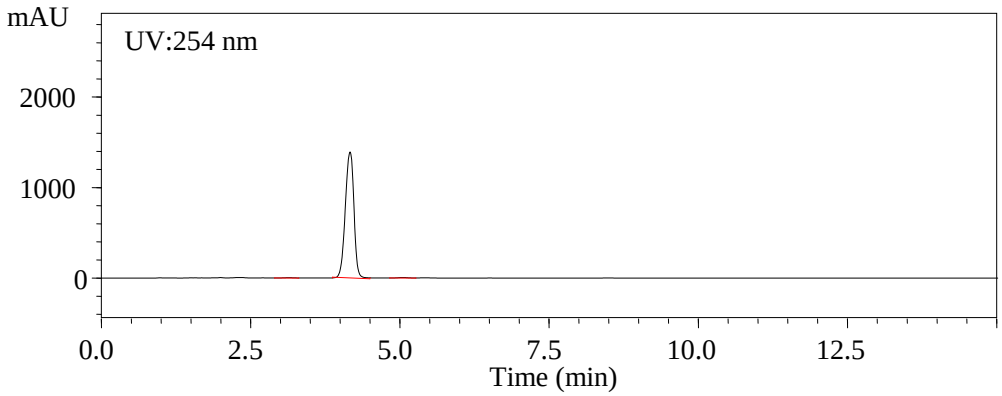
Peak#	Retention time	Peak area	Peak height	Peak area%
1	0.971	31640	6161	0.1339
2	2.365	23600585	1603305	99.8661

Purity：99.9%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



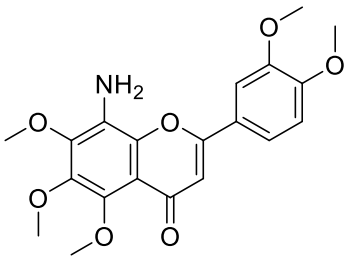
16



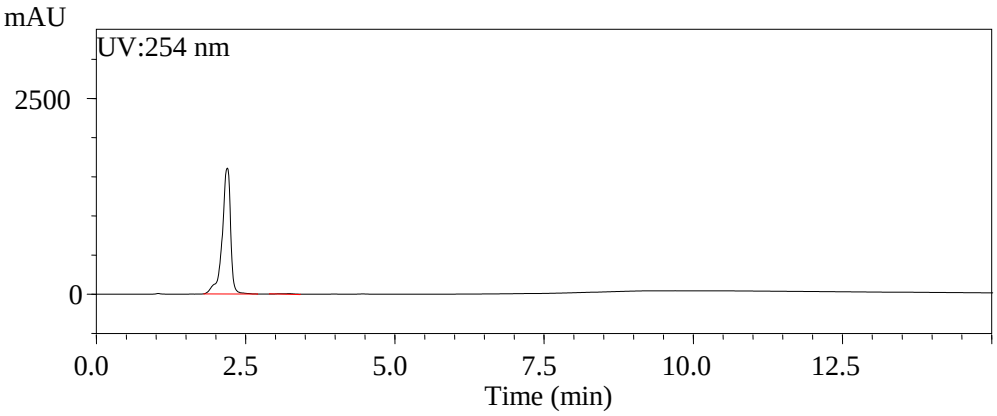
Peak#	Retention time	Peak area	Peak height	Peak area%
1	3.133	31094	2688	0.2226
2	4.161	13885159	1390251	99.3919
3	5.043	53865	4839	3.046

Purity：99.4%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



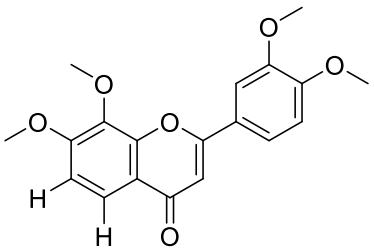
18



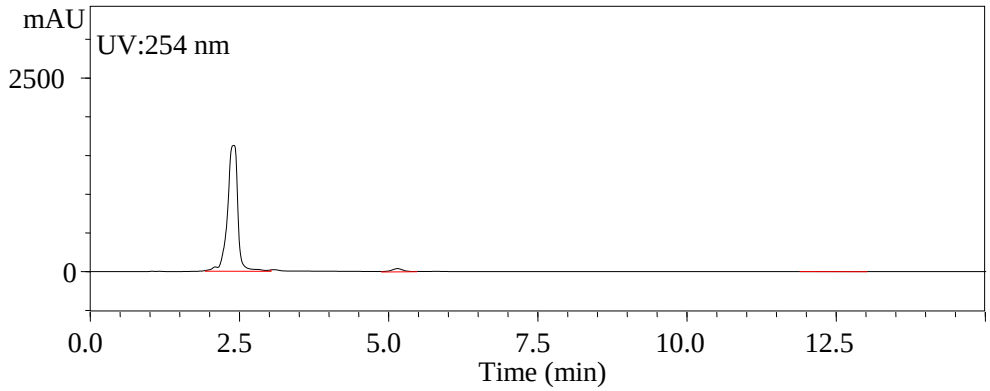
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.188	15851912	1607674	99.3798
2	3.222	98921	7140	3.013

Purity：99.4%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



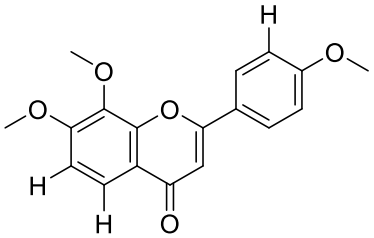
23a



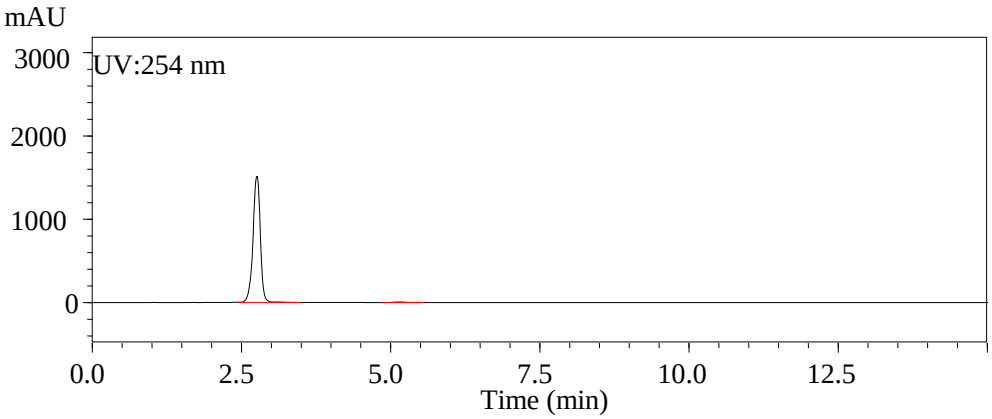
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.399	19613761	1624607	96.8674
2	5.142	609254	41997	3.0090
3	12.407	25030	917	0.1236

Purity：96.9%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



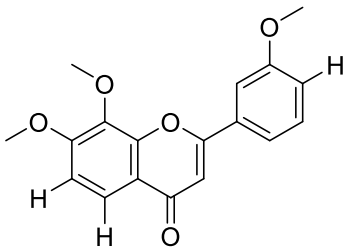
23b



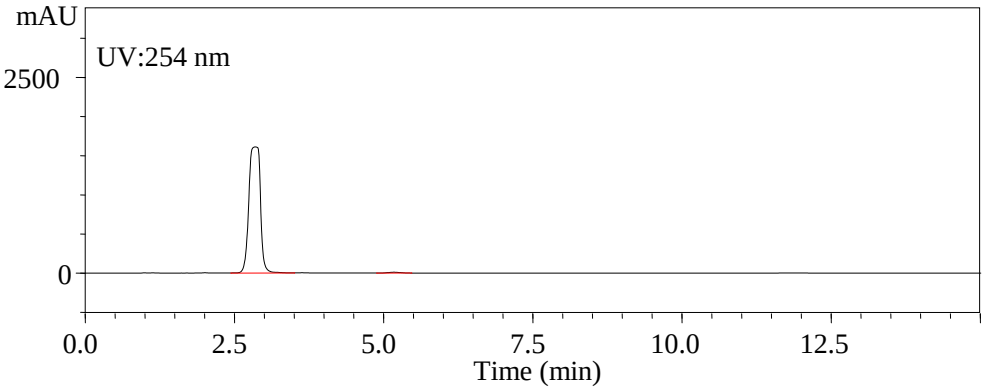
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.754	13032842	1513138	99.3539
2	5.142	84748	6719	0.6461

Purity：99.4%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



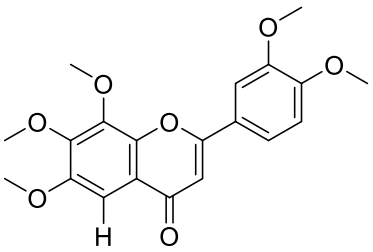
23c



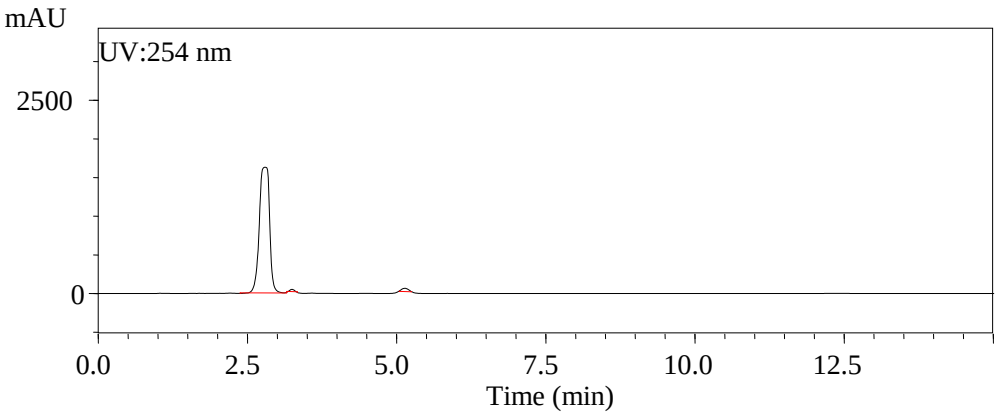
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.843	21751199	1612049	99.3968
2	5.170	131993	10479	0.6032

Purity：99.4%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



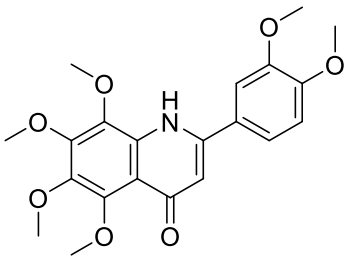
23d



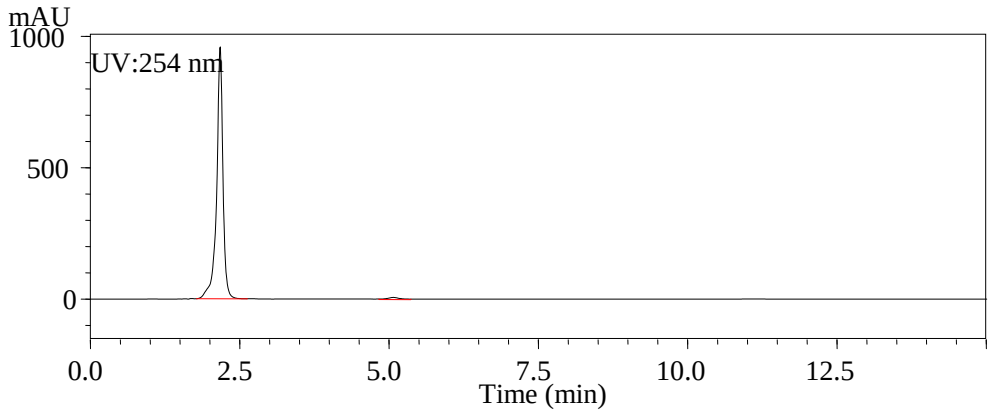
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.792	19339604	1623690	97.7101
2	3.241	120177	28551	0.6072
3	5.132	333061	42540	1.6827

Purity：97.7%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



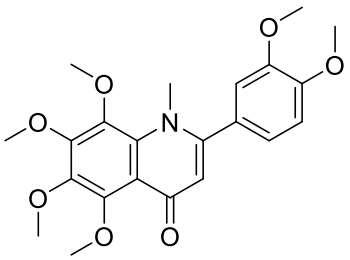
28



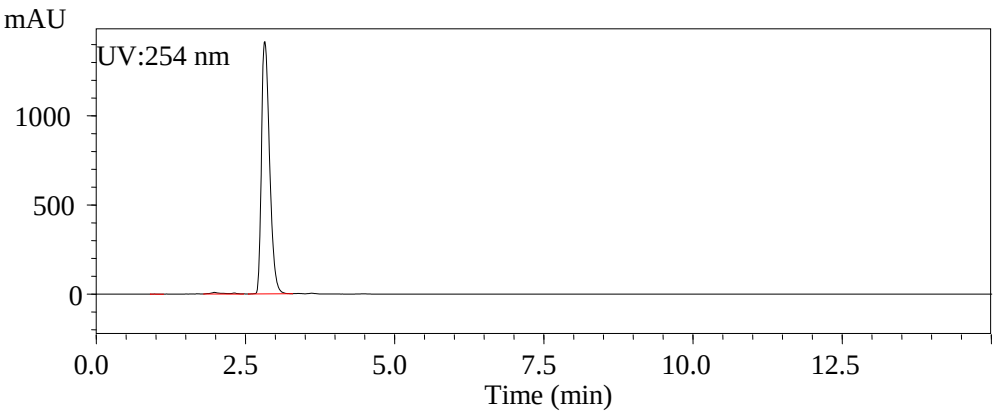
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.166	7075257	958401	98.3486
2	5.068	118799	7590	1.6514

Purity：98.3%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



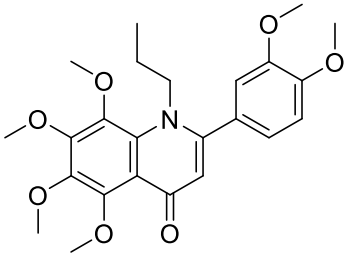
29a



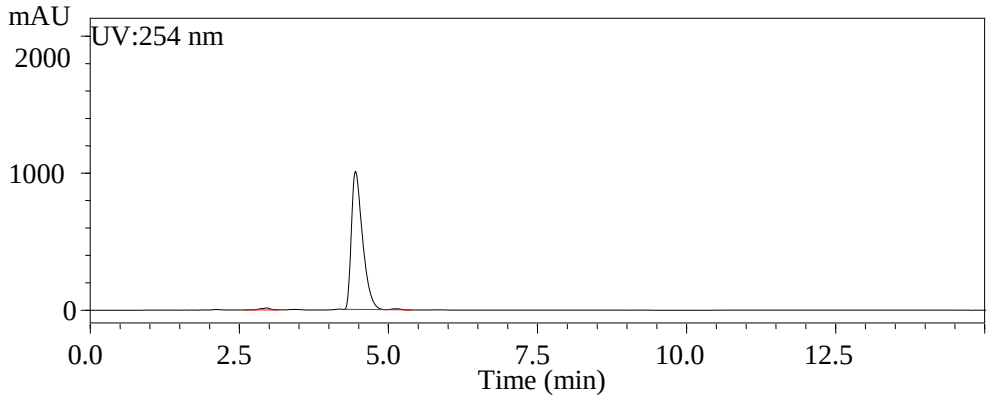
Peak#	Retention time	Peak area	Peak height	Peak area%
1	0.969	1213	233	0.0089
2	1.975	136747	8631	1.0083
3	2.817	13424673	1415032	98.9828

Purity：99.0%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



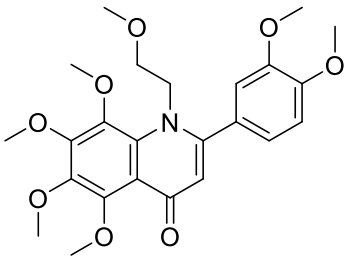
29b



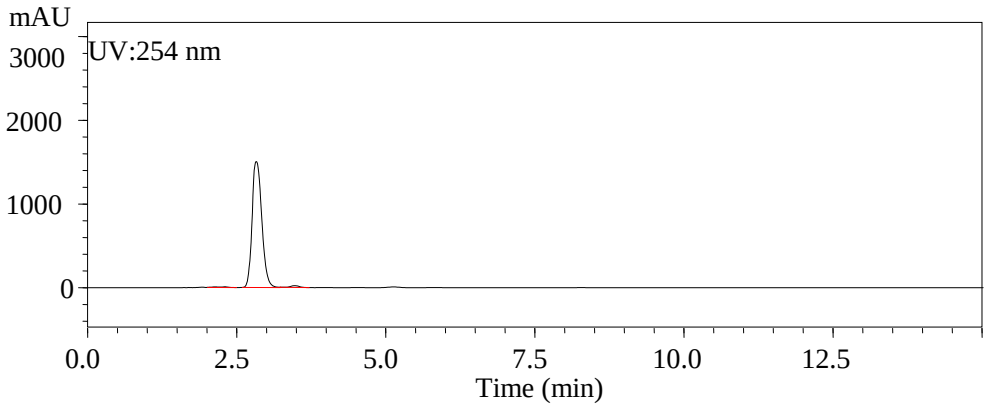
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.955	140708	13425	1.0579
2	4.443	13090370	1008949	98.4168
3	5.120	69879	7354	2.140

Purity：98.4%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (80%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



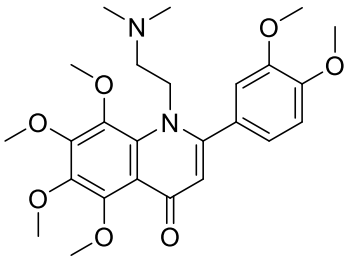
29c



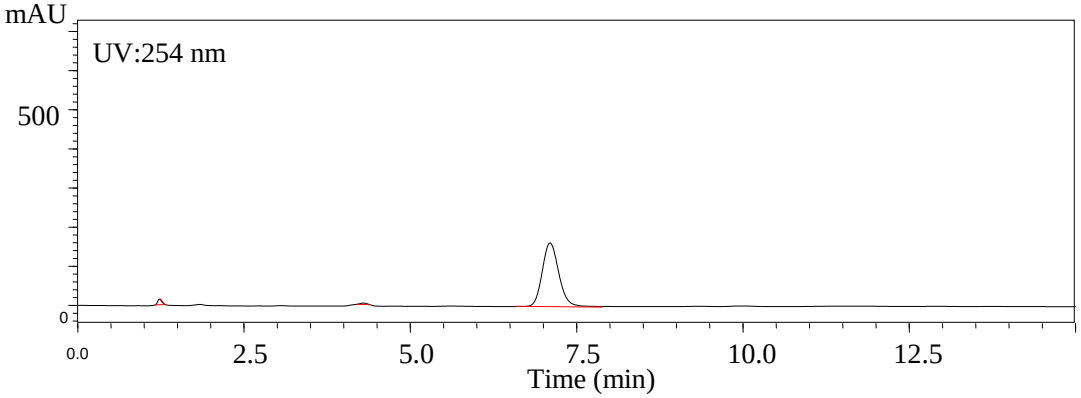
Peak#	Retention time	Peak area	Peak height	Peak area%
1	2.300	118554	8306	0.6820
2	2.823	17042033	1504978	98.0308
3	3.470	223772	22138	2.259

Purity：98.0%

SHIMADZU LC-20AT (column, Hypersil BDS C18, 5.0 μm, 150 mm × 4.6 mm (Elite); detector, SPD-20A UV/Vis detector, UV detection at 254 nm; elution, MeOH in water (55%, *v/v*); T = 25 ℃; flow rate = 1.0 mL/min).



29d



Peak#	Retention time	Peak area	Peak height	Peak area%
1	1.224	59197	14227	2.0274
2	4.291	23772	3478	0.8141
3	7.096	2836900	162964	97.1585

Purity：97.1%