Semi-Syntheses and Interrogation of Indole-Substituted *Aspidosperma* Terpenoid Alkaloids**

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

* Corresponding author

** This manuscript is dedicated to the memory of our beloved colleague Dr. Rodrigo B. Andrade.

‡ Deceased May 24th, 2021.

Table of Contents

Supporting Figures

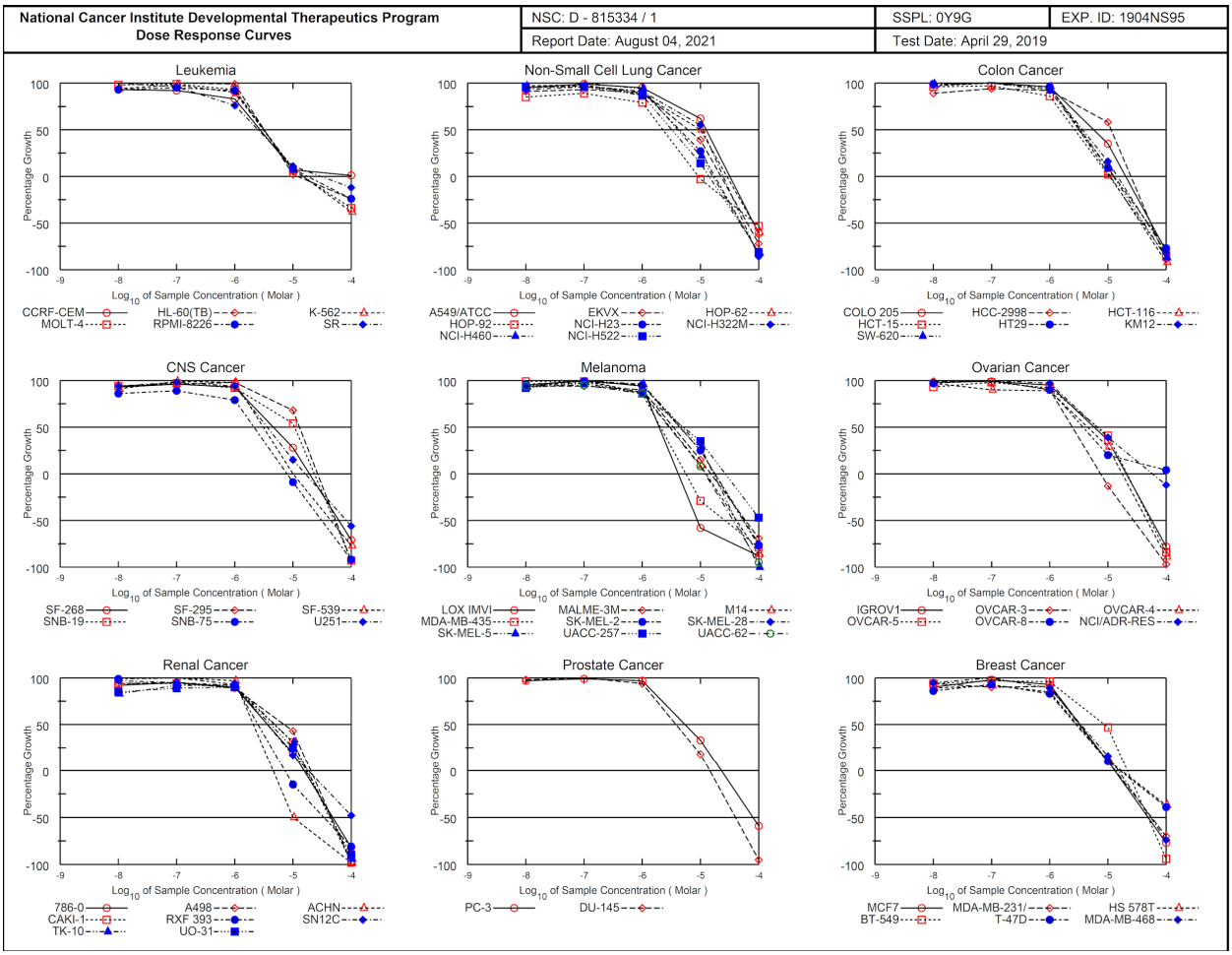


Fig. S1 Plots of tabersonine's growth inhibition activity on various human cancer cell lines. The compound was incubated with sixty cancer cell lines at five serial doses (100 μM, 10 μM, 1 μM, 0.1 μM, and 0.01 μM) for 48h.

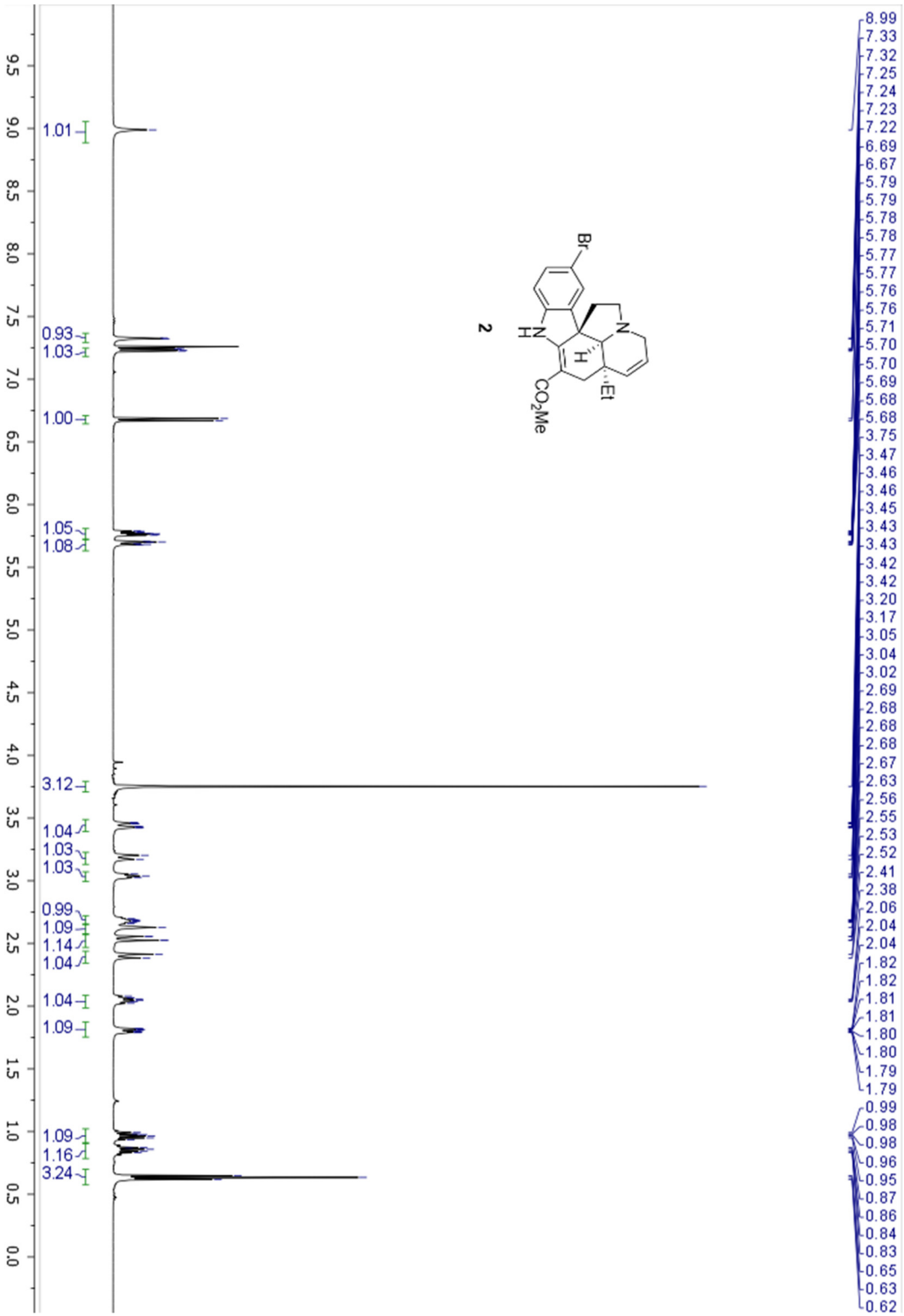
National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

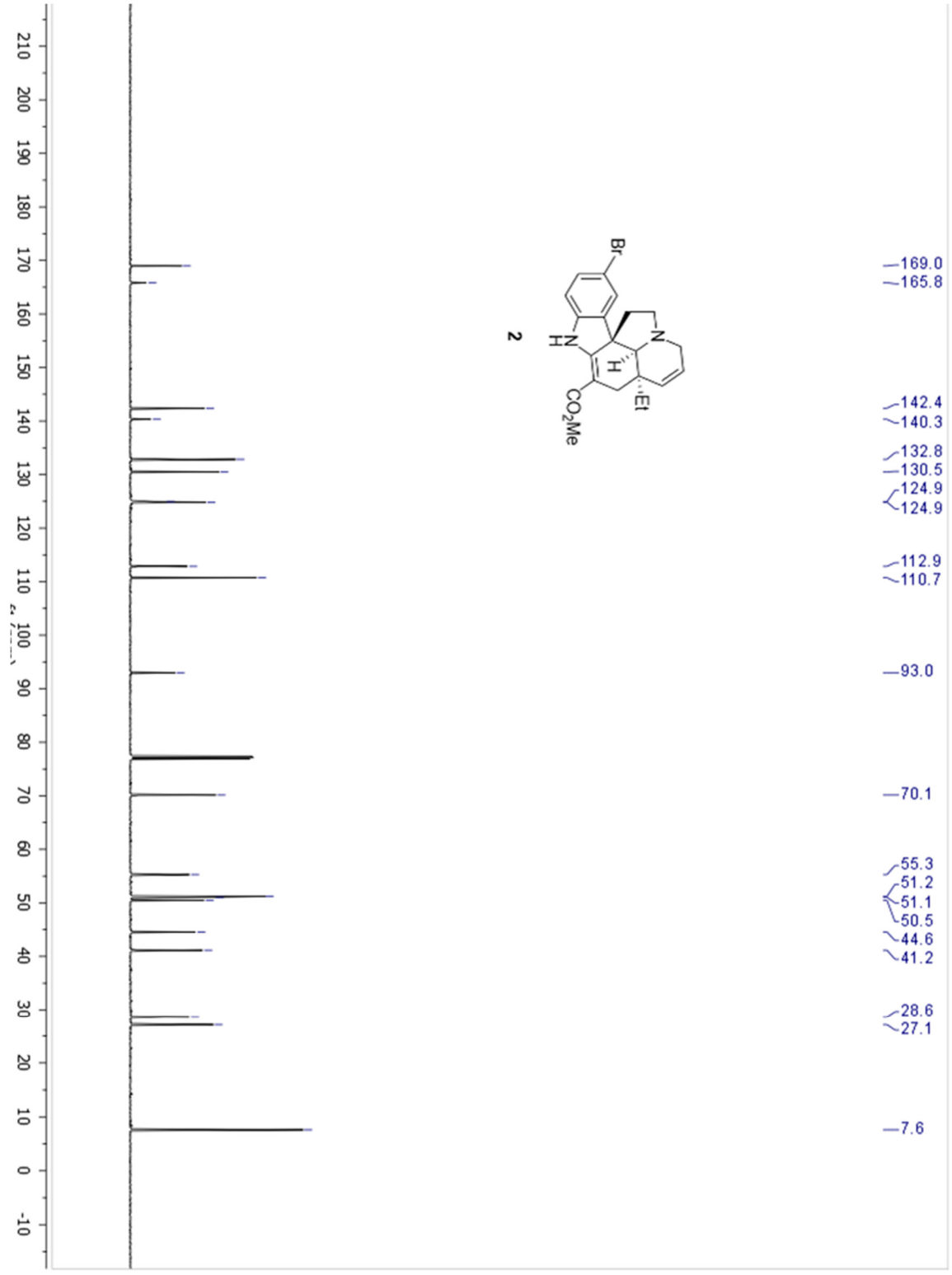
NSC : D - 815334 / 1	Experiment ID : 1904NS95	Test Type : 08	Units : Molar
Report Date : August 04, 2021	Test Date : April 29, 2019	QNS :	MC :
COMI : Tabersonine	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y9G	

		Log10 Concentration												
	Time	Mean Optical Densities						Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.495	2.715	2.557	2.546	2.337	0.657	0.521	93	92	83	7	1	2.73E-6	> 1.00E-4	> 1.00E-4
HL-60(TB)	1.121	3.393	3.397	3.406	3.365	1.157	0.852	100	101	99	2	-24	3.18E-6	1.15E-5	> 1.00E-4
K-562	0.276	2.750	2.604	2.695	2.496	0.482	0.171	94	98	90	8	-38	3.08E-6	1.51E-5	> 1.00E-4
MOLT-4	0.736	3.237	3.199	3.201	3.062	0.907	0.484	98	99	93	7	-34	3.15E-6	1.47E-5	> 1.00E-4
RPMI-8226	0.952	2.979	2.840	2.886	2.821	1.112	0.728	93	95	92	8	-24	3.17E-6	1.78E-5	> 1.00E-4
SR	0.263	0.952	0.955	0.924	0.790	0.342	0.232	100	96	76	11	-12	2.55E-6	3.07E-5	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.378	2.100	2.020	2.076	2.007	1.438	0.148	95	99	95	62	-61	1.24E-5	3.18E-5	8.15E-5
EKVX	0.793	2.340	2.194	2.228	2.186	1.390	0.225	91	93	90	39	-72	5.99E-6	2.24E-5	6.36E-5
HOP-62	0.675	2.356	2.300	2.319	2.147	1.509	0.271	97	98	88	50	-60	9.78E-6	2.84E-5	8.12E-5
HOP-92	1.309	2.007	1.905	1.927	1.863	1.274	0.612	85	89	79	-3	-53	2.28E-6	9.27E-6	8.62E-5
NCI-H23	0.639	2.238	2.162	2.188	2.087	1.075	0.109	95	97	91	27	-83	4.37E-6	1.77E-5	5.02E-5
NCI-H322M	0.743	2.063	1.967	2.016	1.945	1.472	0.105	93	96	91	55	-86	1.09E-5	2.46E-5	5.57E-5
NCI-H460	0.182	1.654	1.678	1.739	1.570	0.508	0.032	102	106	94	22	-82	4.11E-6	1.63E-5	4.90E-5
NCI-H522	0.894	2.692	2.614	2.627	2.465	1.150	0.167	96	96	87	14	-81	3.24E-6	1.41E-5	4.70E-5
Colon Cancer															
COLO 205	0.568	2.392	2.406	2.458	2.317	1.201	0.112	101	104	96	35	-80	5.62E-6	2.00E-5	5.45E-5
HCC-2998	0.975	2.968	2.747	2.856	2.814	2.137	0.108	89	94	92	58	-89	1.14E-5	2.49E-5	5.44E-5
HCT-116	0.286	2.563	2.503	2.609	2.477	0.371	0.023	97	102	96	4	-92	3.16E-6	1.09E-5	3.63E-5
HCT-15	0.259	1.740	1.685	1.691	1.537	0.282	0.038	96	97	86	2	-86	2.68E-6	1.04E-5	3.91E-5
HT29	0.367	2.531	2.509	2.559	2.454	0.567	0.086	99	101	96	9	-77	3.41E-6	1.28E-5	4.89E-5
KM12	0.535	2.463	2.419	2.502	2.344	0.840	0.096	98	102	94	16	-82	3.65E-6	1.45E-5	4.70E-5
SW-620	0.293	1.961	1.941	2.032	1.824	0.435	0.040	99	104	92	9	-87	3.18E-6	1.23E-5	4.13E-5
CNS Cancer															
SF-268	0.638	1.959	1.870	1.904	1.861	1.012	0.188	93	96	93	28	-71	4.60E-6	1.93E-5	6.19E-5
SF-295	0.883	3.176	3.038	3.093	3.122	2.450	0.064	94	96	98	68	-93	1.30E-5	2.66E-5	5.43E-5
SF-539	0.745	2.377	2.227	2.357	2.343	0.749	0.172	91	99	98	.	-77	3.09E-6	1.01E-5	4.48E-5
SNB-19	0.695	2.341	2.240	2.297	2.203	1.584	0.050	94	97	92	54	-93	1.07E-5	2.33E-5	5.11E-5
SNB-75	1.037	1.988	1.851	1.882	1.793	0.945	0.087	86	89	79	-9	-92	2.15E-6	7.93E-6	3.14E-5
U251	0.296	1.730	1.638	1.701	1.649	0.517	0.129	94	98	94	15	-56	3.64E-6	1.64E-5	8.14E-5
Melanoma															
LOX IMVI	0.244	1.806	1.731	1.889	1.707	0.102	0.030	95	105	94	-58	-88	1.94E-6	4.13E-6	8.81E-6
MALME-3M	0.712	1.888	1.815	1.816	1.769	0.892	0.219	94	94	90	15	-69	3.43E-6	1.52E-5	5.91E-5
M14	0.618	2.356	2.234	2.359	2.124	0.777	0.087	93	100	87	9	-86	2.97E-6	1.25E-5	4.18E-5
MDA-MB-435	0.505	2.228	2.204	2.208	1.983	0.361	0.108	99	99	86	-29	-79	2.06E-6	5.63E-6	2.68E-5
SK-MEL-2	1.287	2.823	2.757	2.814	2.750	1.678	0.293	96	99	95	25	-77	4.45E-6	1.77E-5	5.43E-5
SK-MEL-28	0.739	2.232	2.250	2.320	2.172	1.119	0.186	101	106	96	25	-75	4.49E-6	1.79E-5	5.65E-5
SK-MEL-5	1.015	3.035	2.904	2.999	2.964	1.598	0.005	94	98	96	29	-100	4.87E-6	1.68E-5	4.11E-5
UACC-257	1.272	2.732	2.609	2.682	2.531	1.780	0.670	92	97	86	35	-47	5.06E-6	2.65E-5	> 1.00E-4
UACC-62	0.958	3.067	2.940	2.959	2.768	1.131	0.053	94	95	86	8	-95	2.89E-6	1.20E-5	3.69E-5
Ovarian Cancer															
IGROV1	0.540	2.172	2.143	2.148	2.092	1.128	0.117	98	99	95	36	-78	5.80E-6	2.06E-5	5.64E-5
OVCAR-3	0.473	1.657	1.649	1.677	1.541	0.413	0.012	99	102	90	-13	-97	2.45E-6	7.51E-6	2.75E-5
OVCAR-4	0.711	1.653	1.623	1.562	1.547	0.980	0.077	97	90	89	29	-89	4.40E-6	1.75E-5	4.65E-5
OVCAR-5	0.540	1.428	1.365	1.414	1.354	0.901	0.089	93	98	92	41	-84	6.55E-6	2.12E-5	5.36E-5
OVCAR-8	0.450	2.231	2.182	2.243	2.055	0.812	0.526	97	101	90	20	4	3.75E-6	> 1.00E-4	> 1.00E-4
NCI/ADR-RES	0.624	2.077	2.083	2.128	2.030	1.187	0.550	100	104	97	39	-12	6.39E-6	5.81E-5	> 1.00E-4
Renal Cancer															
786-0	0.555	2.435	2.287	2.345	2.239	0.920	0.101	92	95	90	19	-82	3.66E-6	1.56E-5	4.85E-5
A498	1.210	2.093	2.041	2.051	1.999	1.592	0.027	94	95	89	43	-98	7.12E-6	2.02E-5	4.58E-5
ACHN	0.370	1.628	1.624	1.685	1.584	0.184	0.007	100	105	97	-50	-98	2.07E-6	4.54E-6	9.94E-6
CAKI-1	0.773	2.885	2.749	2.755	2.670	1.419	0.019	94	94	90	31	-98	4.70E-6	1.73E-5	4.25E-5
RXF 393	0.776	1.392	1.385	1.394	1.352	0.658	0.150	99	100	93	-15	-81	2.51E-6	7.24E-6	3.40E-5
SN12C	0.651	2.544	2.490	2.450	2.398	0.967	0.341	97	95	92	17	-48	3.63E-6	1.82E-5	> 1.00E-4
TK-10	0.767	1.928	1.733	1.839	1.840	1.123	0.043	83	92	92	31	-94	4.86E-6	1.76E-5	4.41E-5
UO-31	0.642	1.876	1.696	1.744	1.747	0.952	0.063	85	89	90	25	-90	4.11E-6	1.65E-5	4.48E-5
Prostate Cancer															
PC-3	0.618	2.577	2.523	2.552	2.515	1.257	0.255	97	99	97	33	-59	5.36E-6	2.28E-5	8.02E-5
DU-145	0.389	1.458	1.441	1.487	1.392	0.585	0.019	98	103	94	18	-95	3.81E-6	1.45E-5	4.00E-5
Breast Cancer															
MCF7	0.576	2.759	2.537	2.725	2.616	0.799	0.130	90	98	93	10	-77	3.33E-6	1.31E-5	4.86E-5
MDA-MB-231/ATCC	0.752	1.725	1.669	1.631	1.635	0.849	0.228	94	90	91	10	-70	3.19E-6	1.33E-5	5.66E-5
HS 578T	0.857	1.687	1.595	1.618	1.563	0.951	0.543	89	92	85	11	-37	2.99E-6	1.72E-5	> 1.00E-4
BT-549	1.598	2.687	2.623	2.659	2.649	2.110	0.103	94	97	96	47	-94	8.71E-6	2.16E-5	4.90E-5
T-47D	1.002	2.631	2.406	2.510	2.352	1.162	0.610	86	93	83	10	-39	2.82E-6	1.59E-5	> 1.00E-4
MDA-MB-468	0.819	1.777	1.727	1.778	1.668	0.971	0.210	95	100	89	16	-74	3.40E-6	1.50E-5	5.37E-5

Fig. S2 The quantitative summary including GI_{50}, TGI, and LC_{50} for the screening results of tabersonine on human cancer cell lines.

^{1}H- and ^{13}C NMR Spectra

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H
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CO2Me
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112.9
110.7
93.0
70.1
55.3
51.2
51.1
50.5
44.6
41.2
28.6
27.1
7.6
210
200
190
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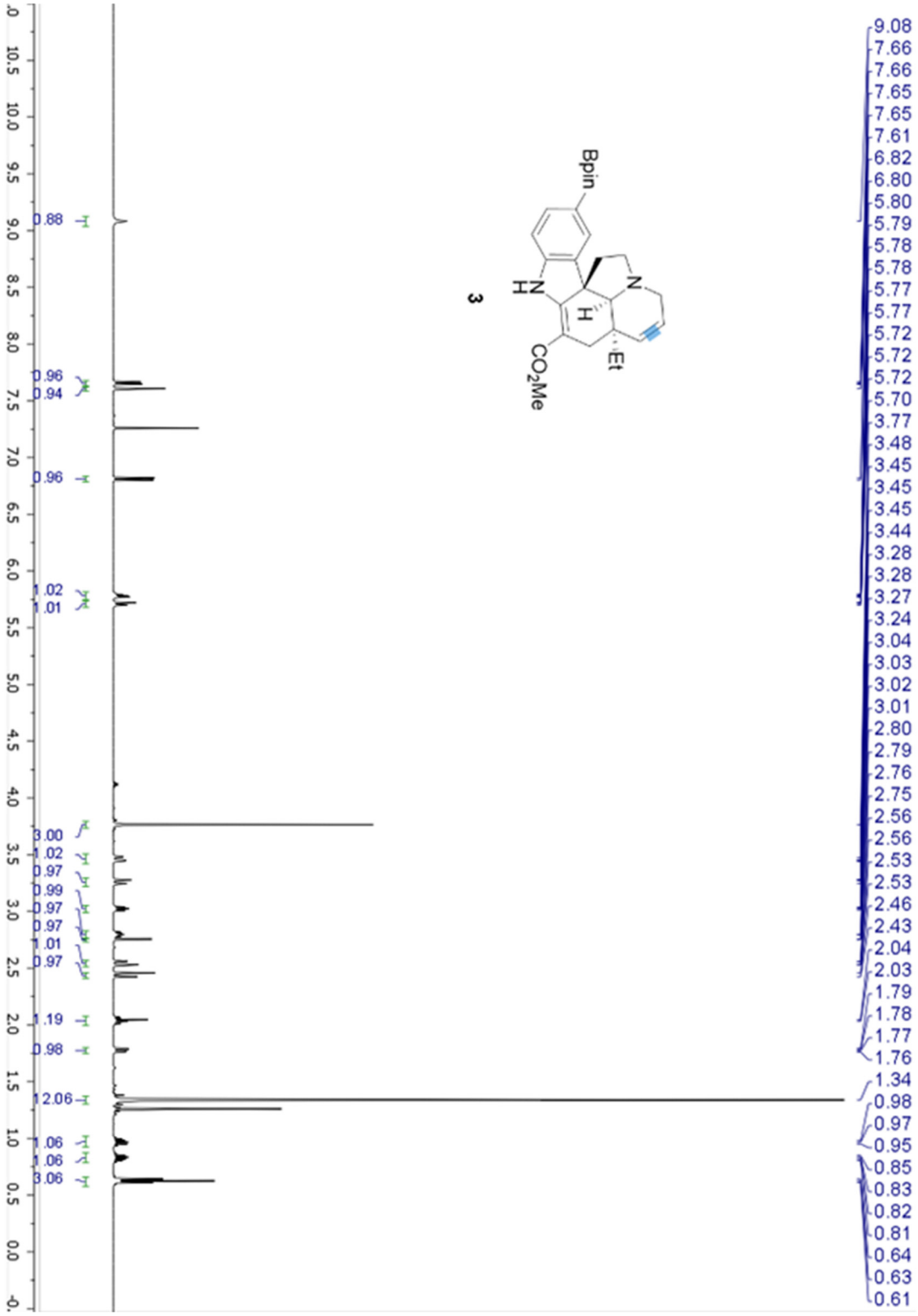
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5.72
5.72
5.72
5.70
3.77
3.48
3.45
3.45
3.45
3.44
3.28
3.28
3.27
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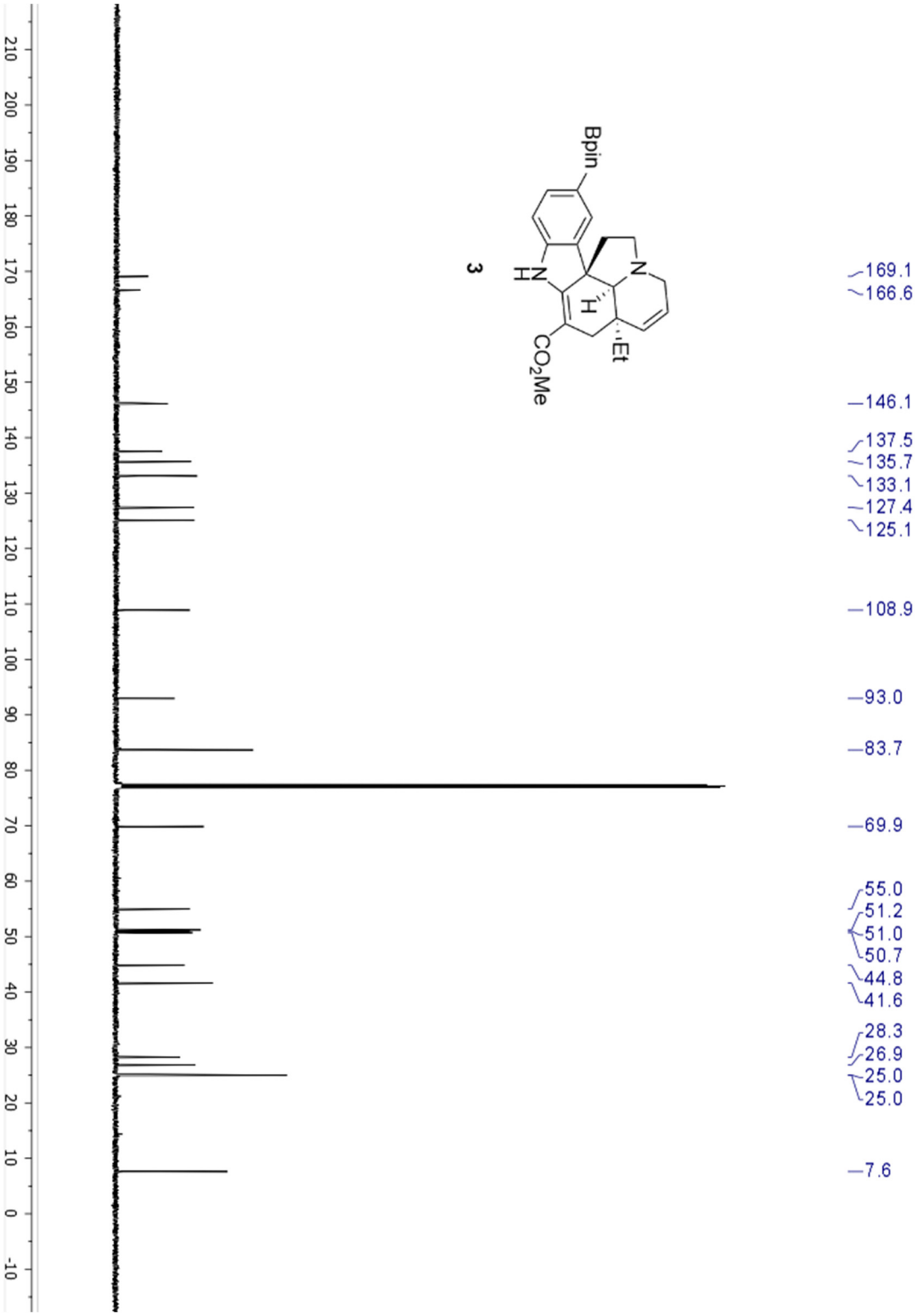
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CO2Me
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83.7
69.9
55.0
51.2
51.0
50.7
44.8
41.6
28.3
26.9
25.0
25.0
7.6
210
200
190
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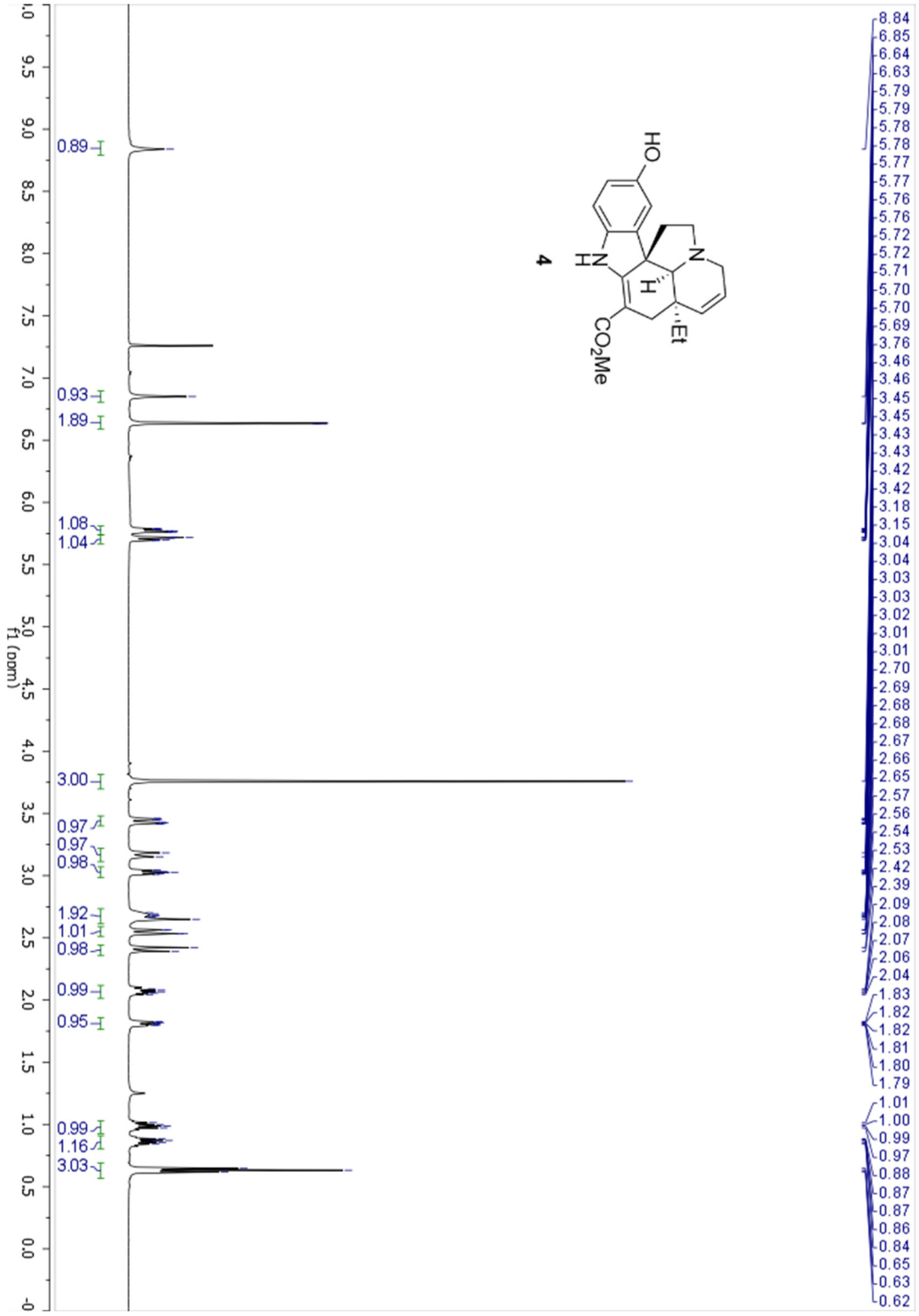
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1.08
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3.00
0.97
0.97
0.98
1.92
1.01
0.98
0.99
0.95
0.99
1.16
3.03
8.84
6.85
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5.79
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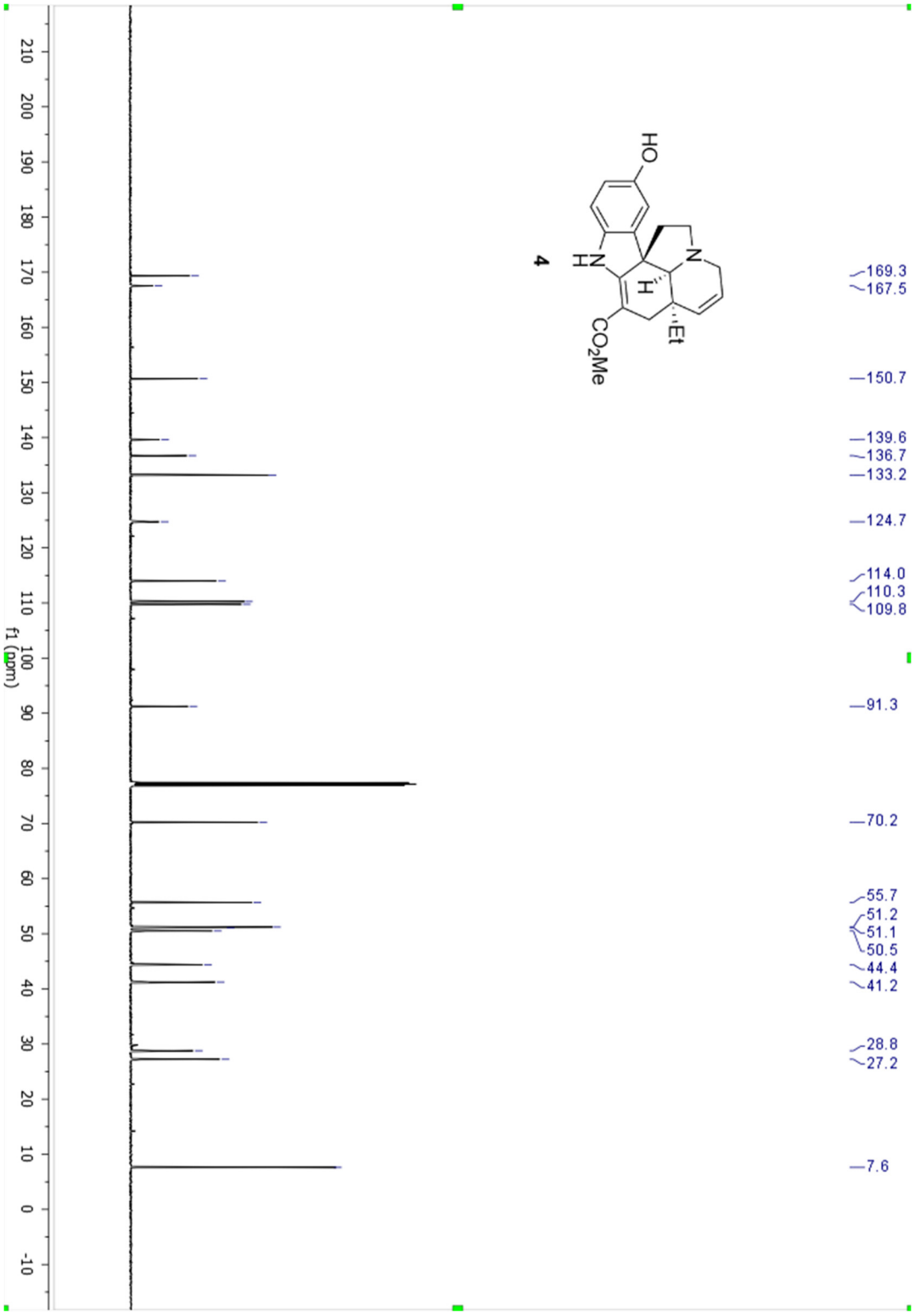
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110.3
109.8
91.3
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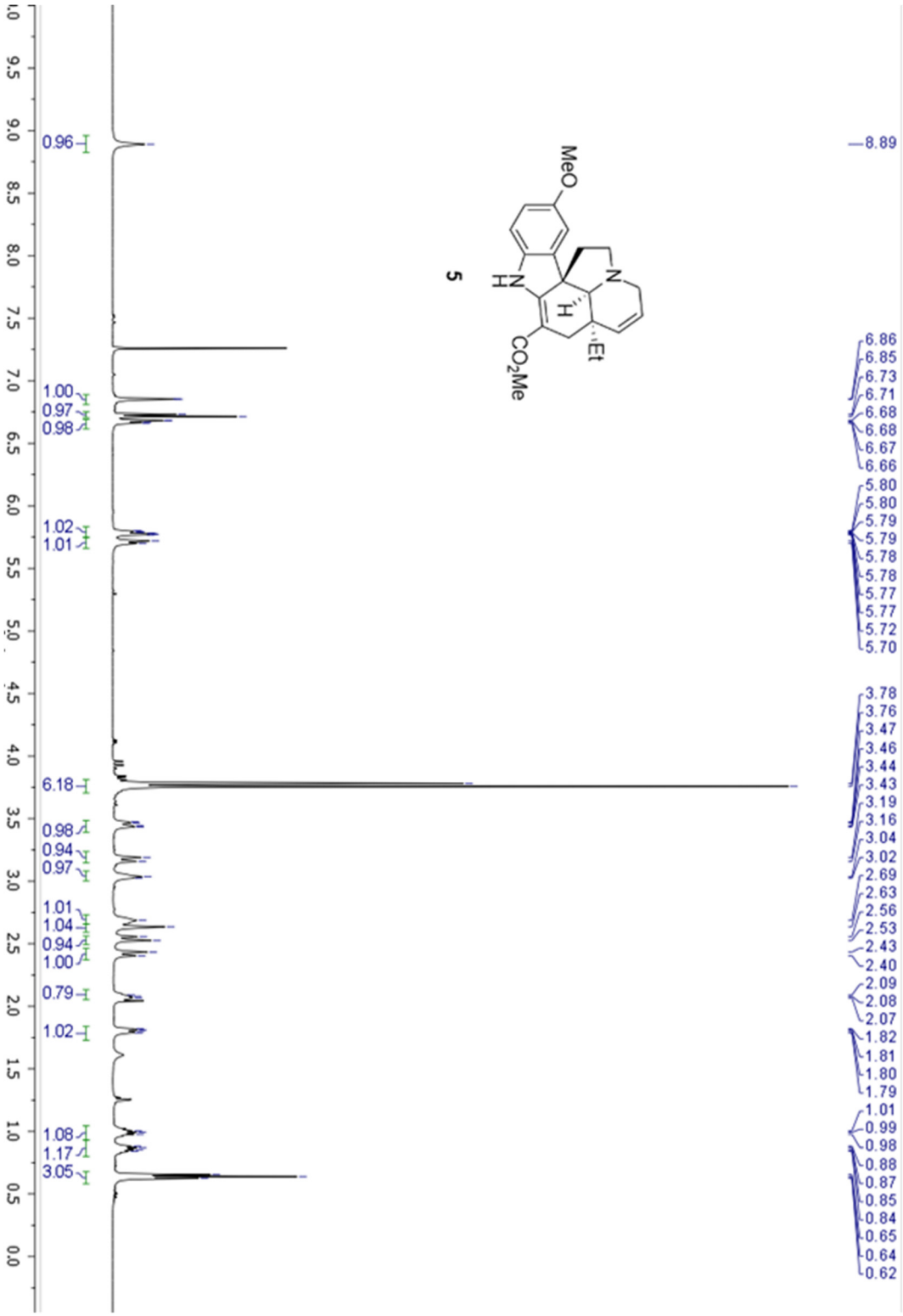
f1 (ppm)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5.77
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0.65
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0.97
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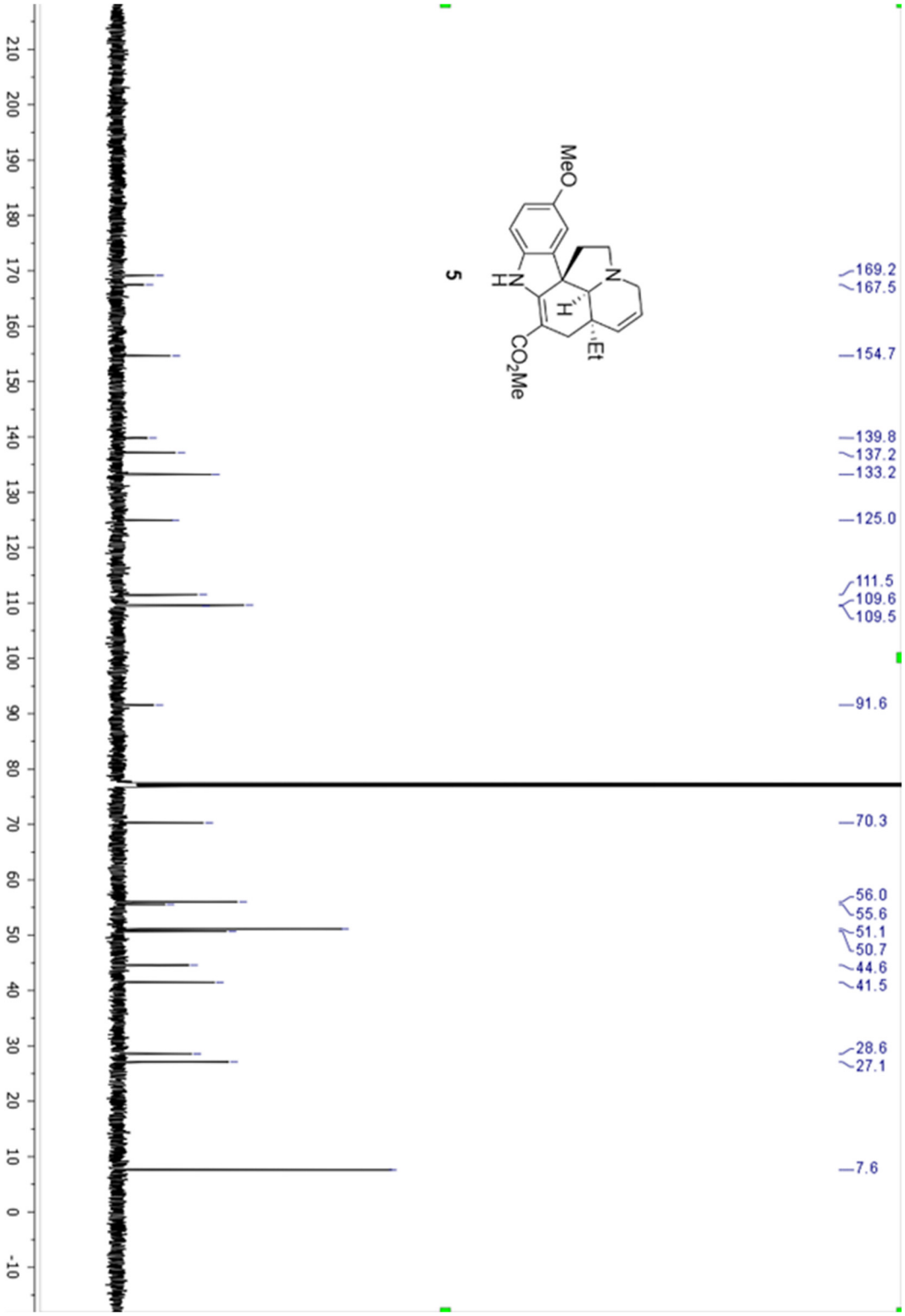
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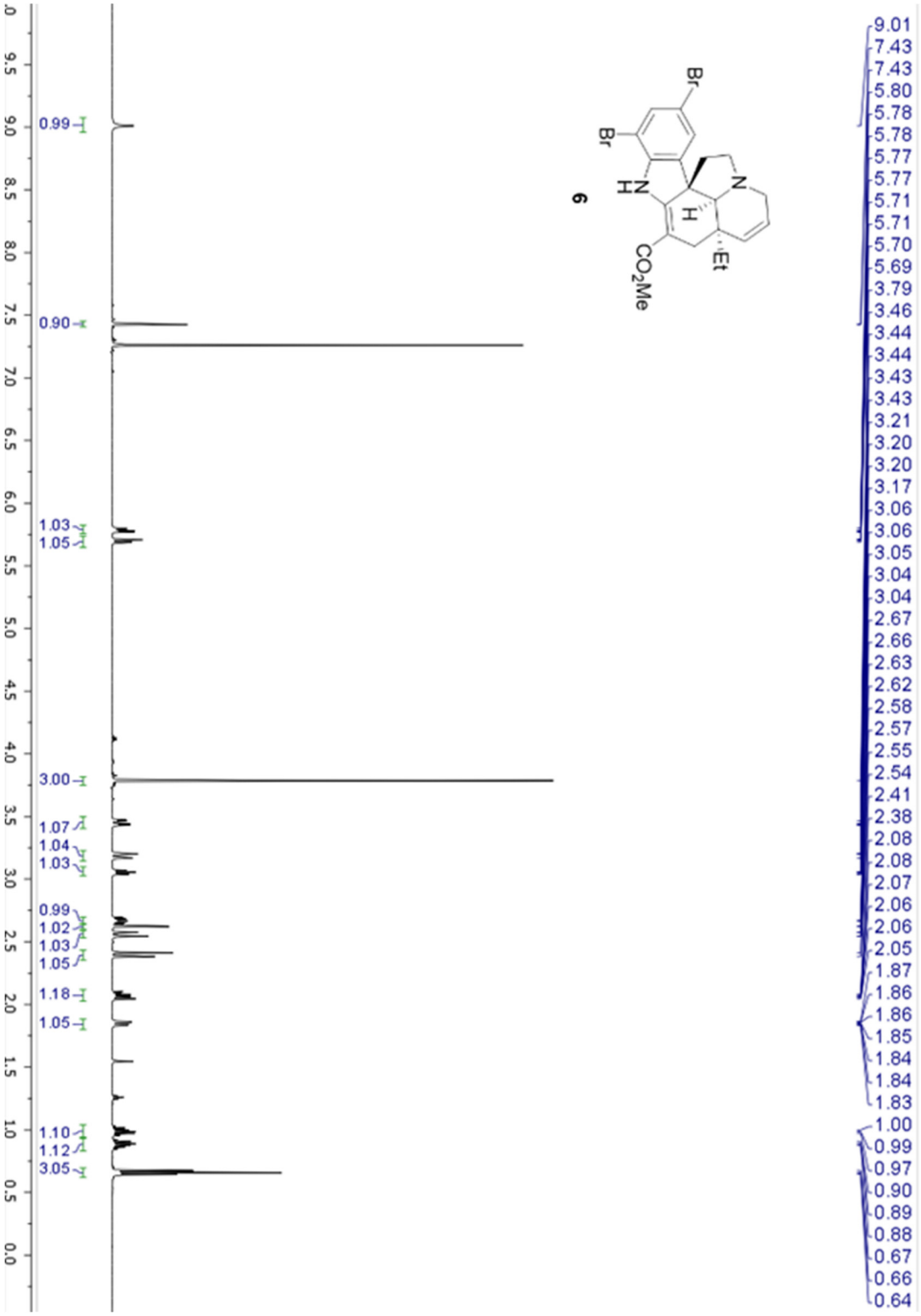
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2.06
2.05
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1.86
1.86
1.85
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0.97
0.90
0.89
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0.66
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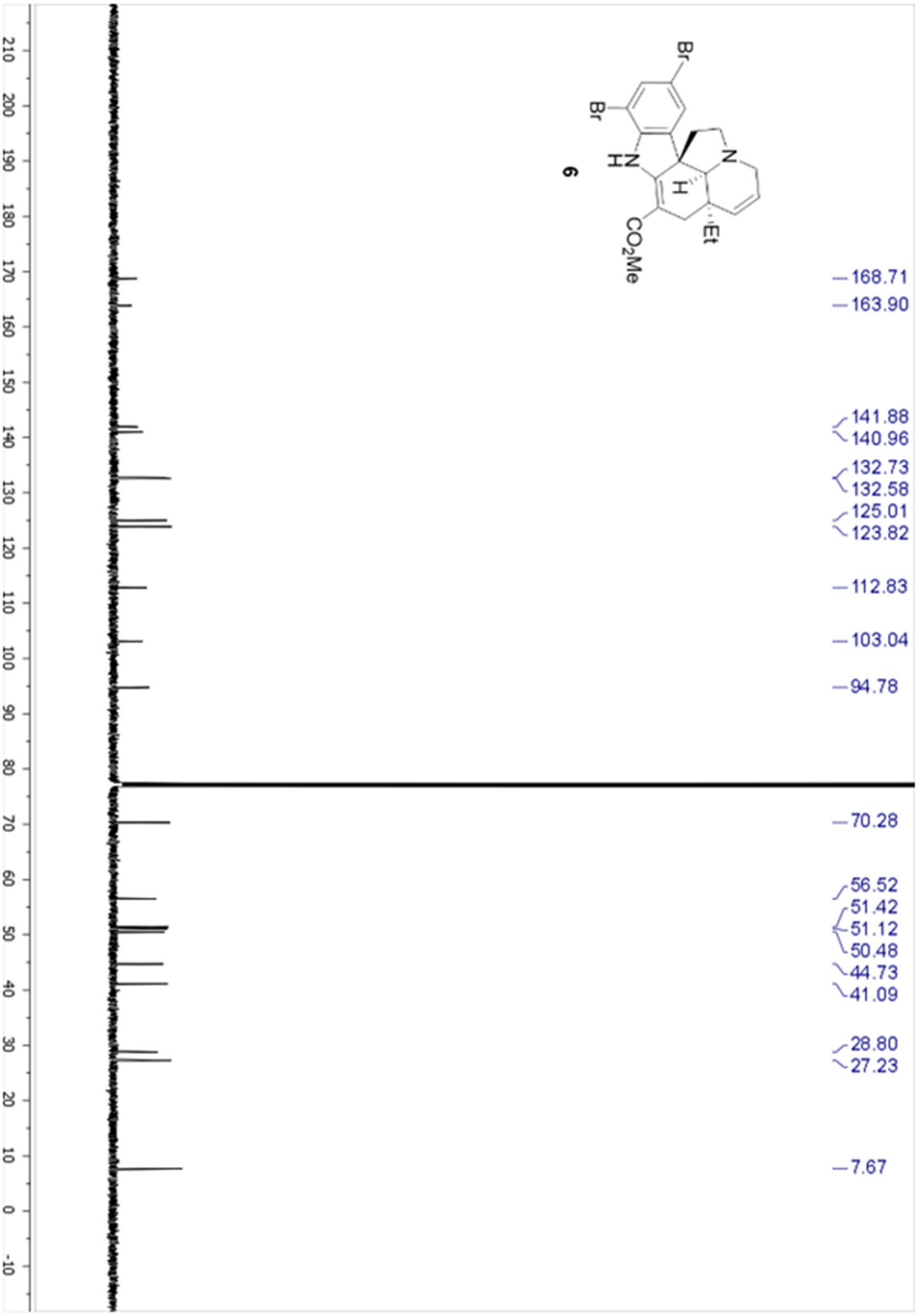
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Br
N
H
N
H
Et
CO2Me
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103.04
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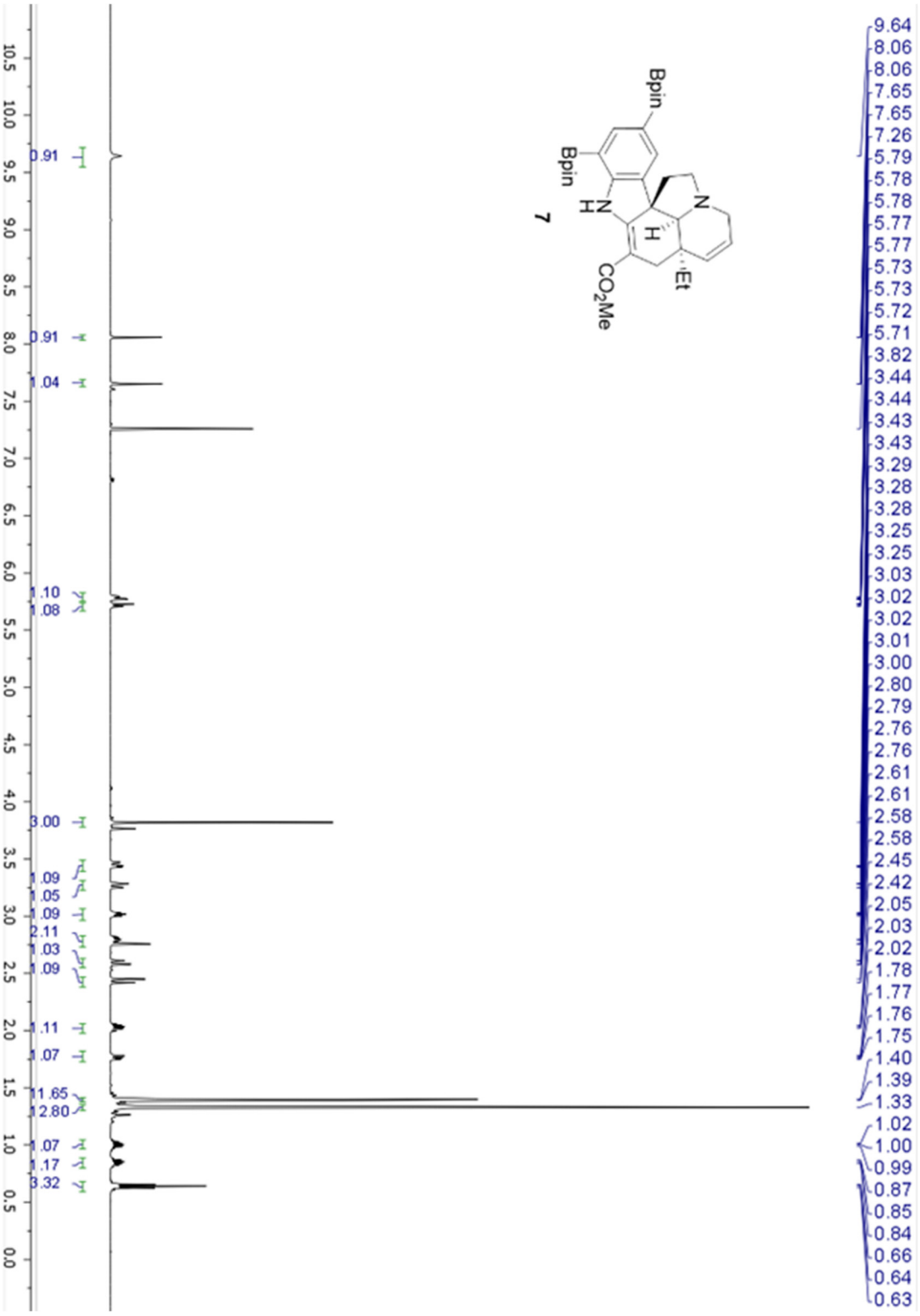
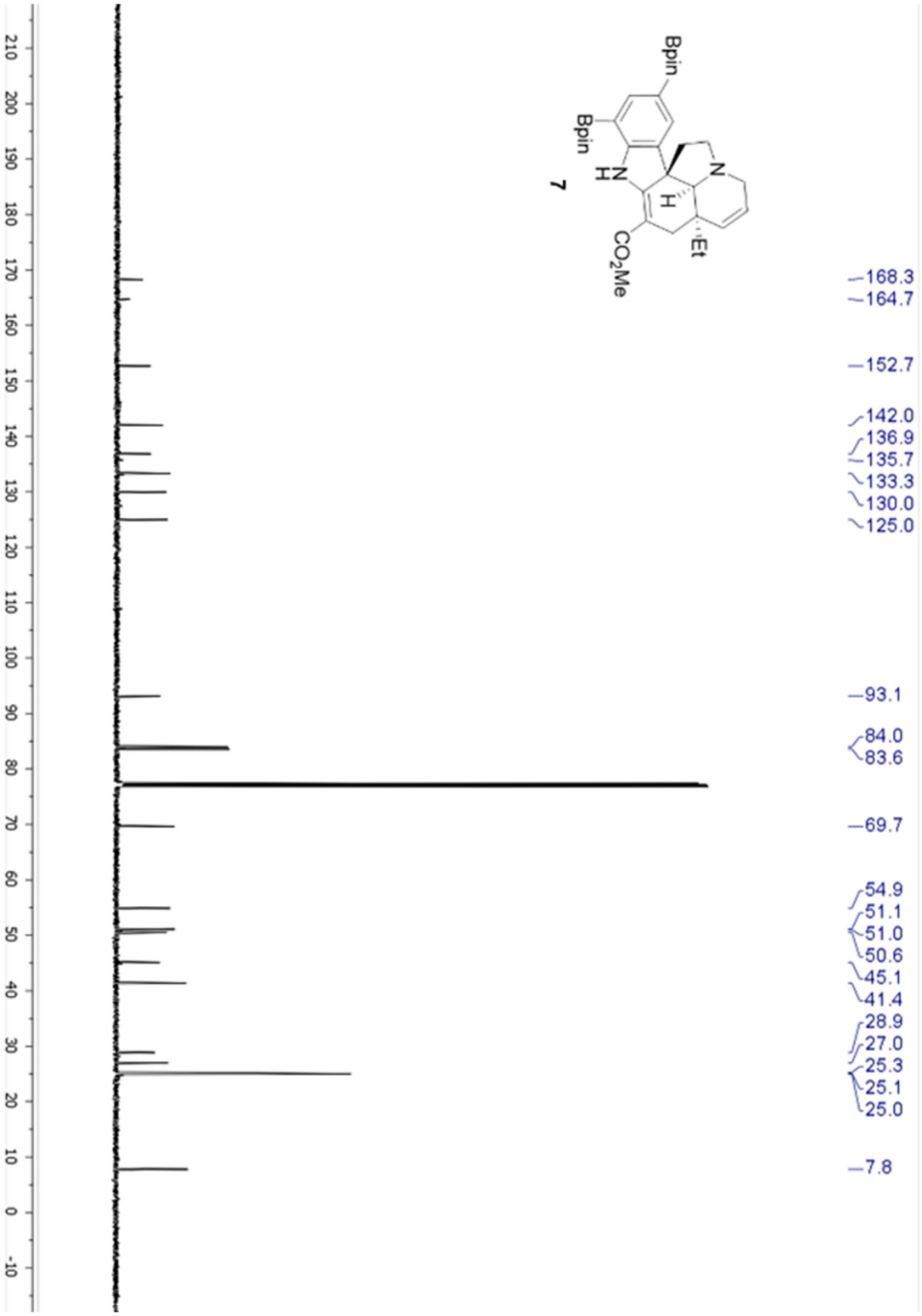
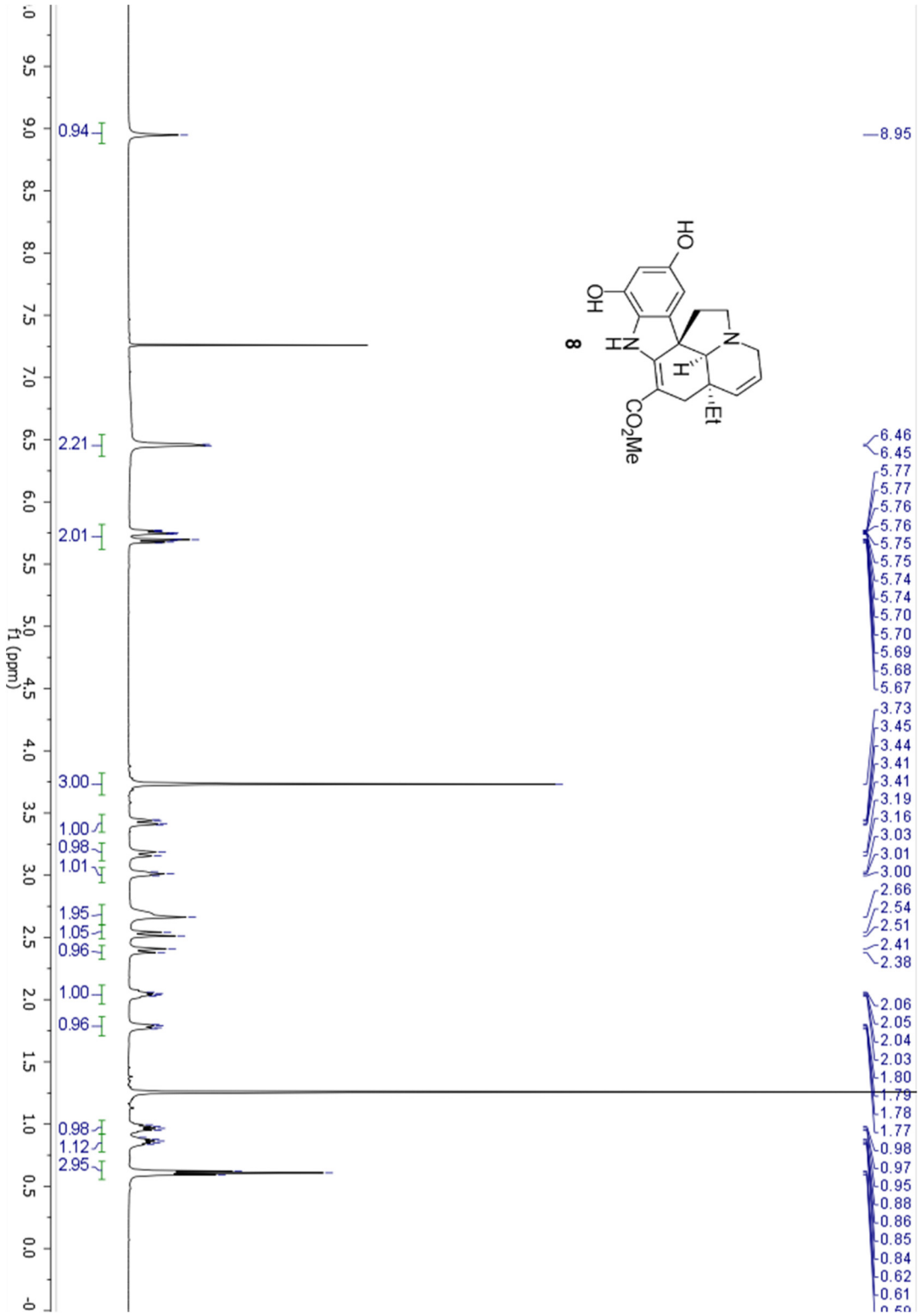
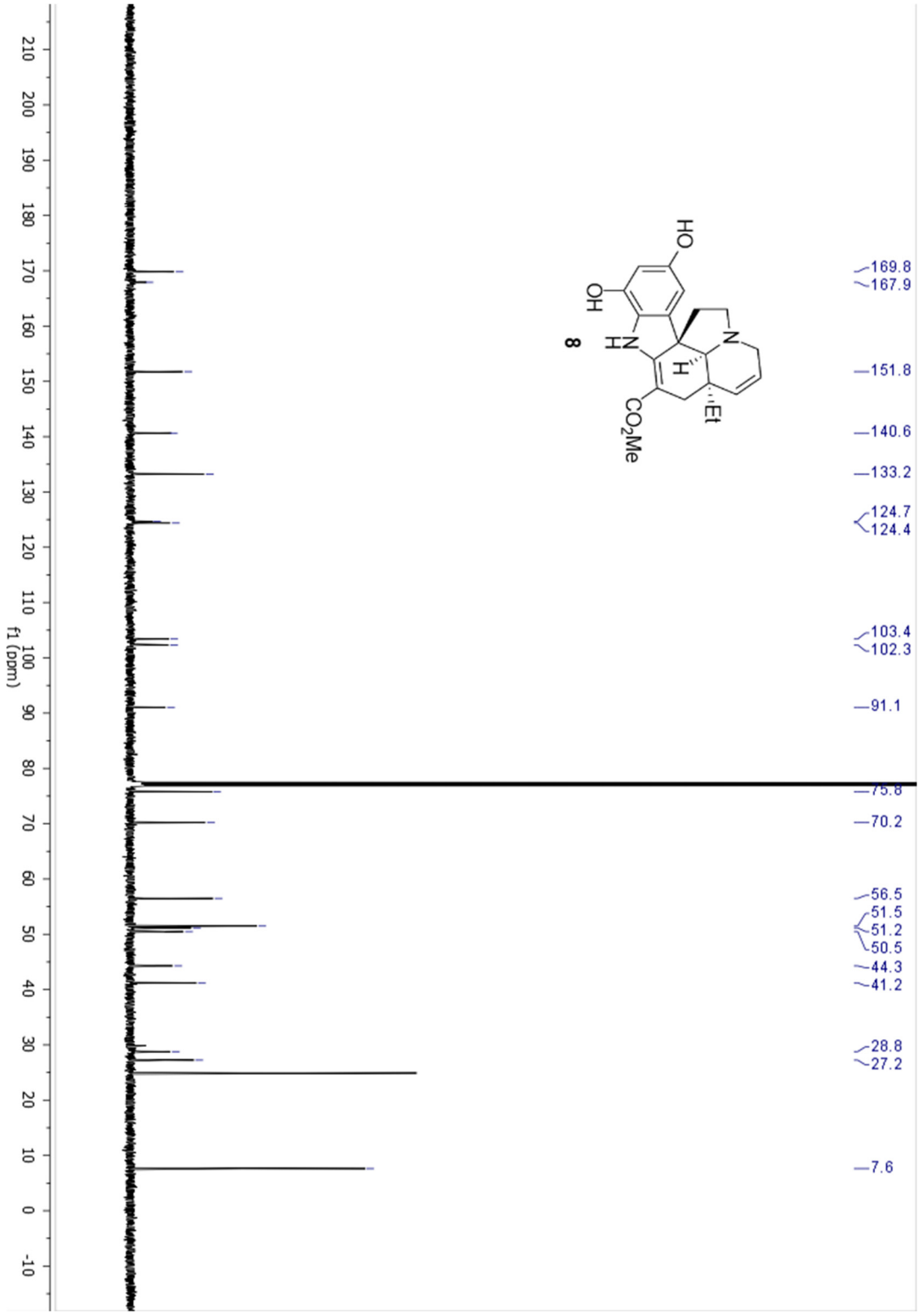
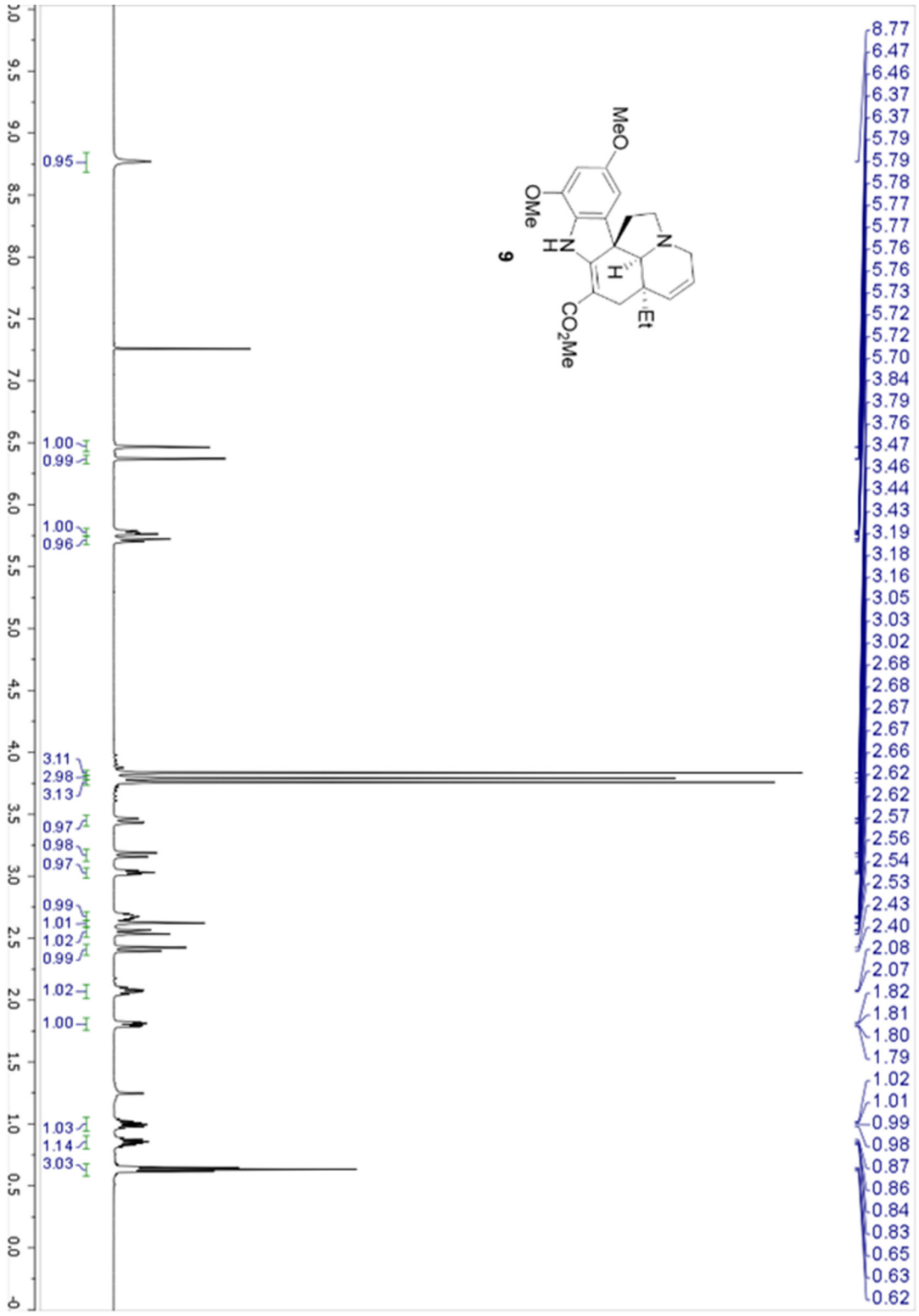
51.42
51.12
50.48
44.73
41.09
28.80
27.23
7.67

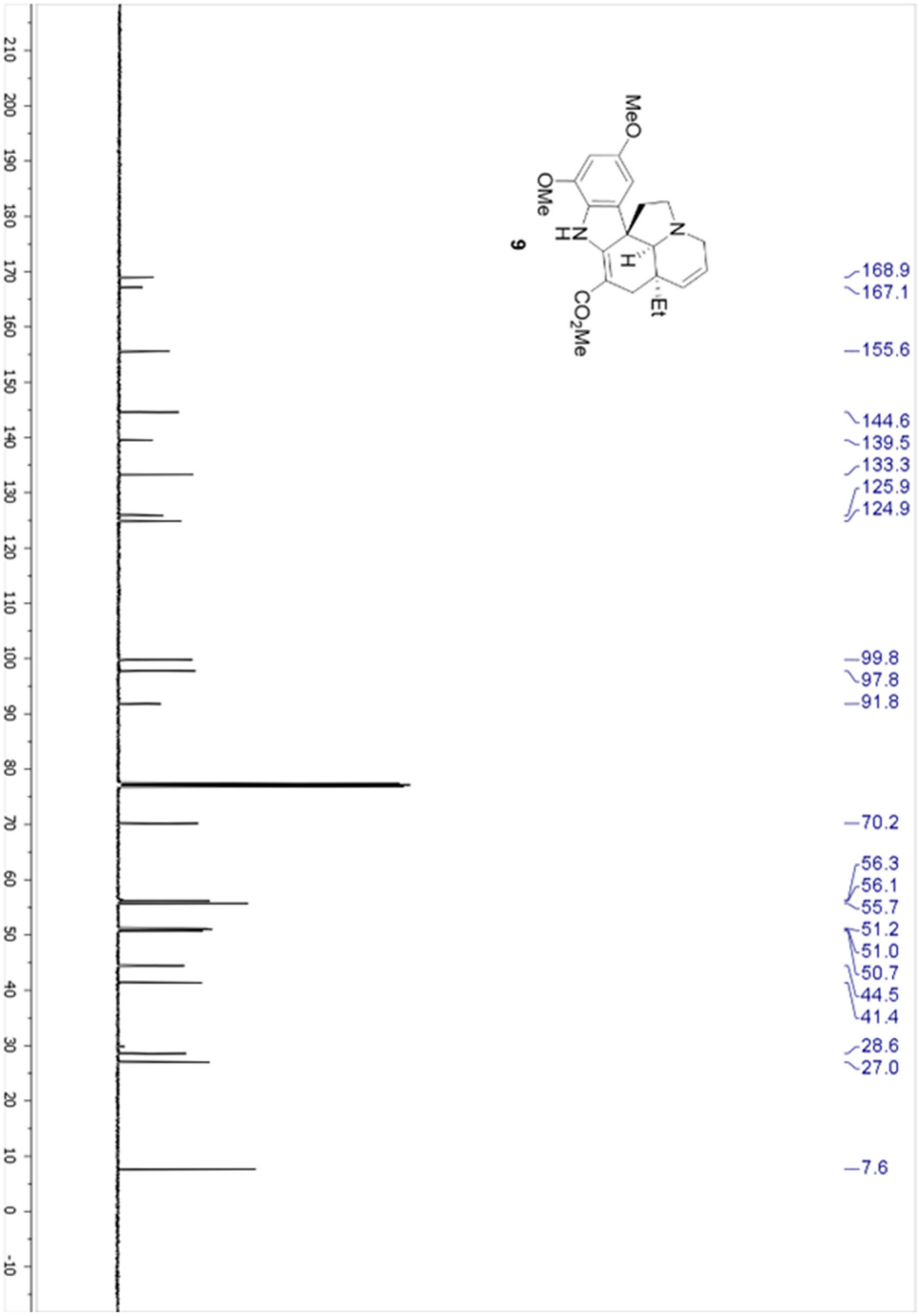

Bpin
Bpin
N
H
N
H
CO2Me
Et
7

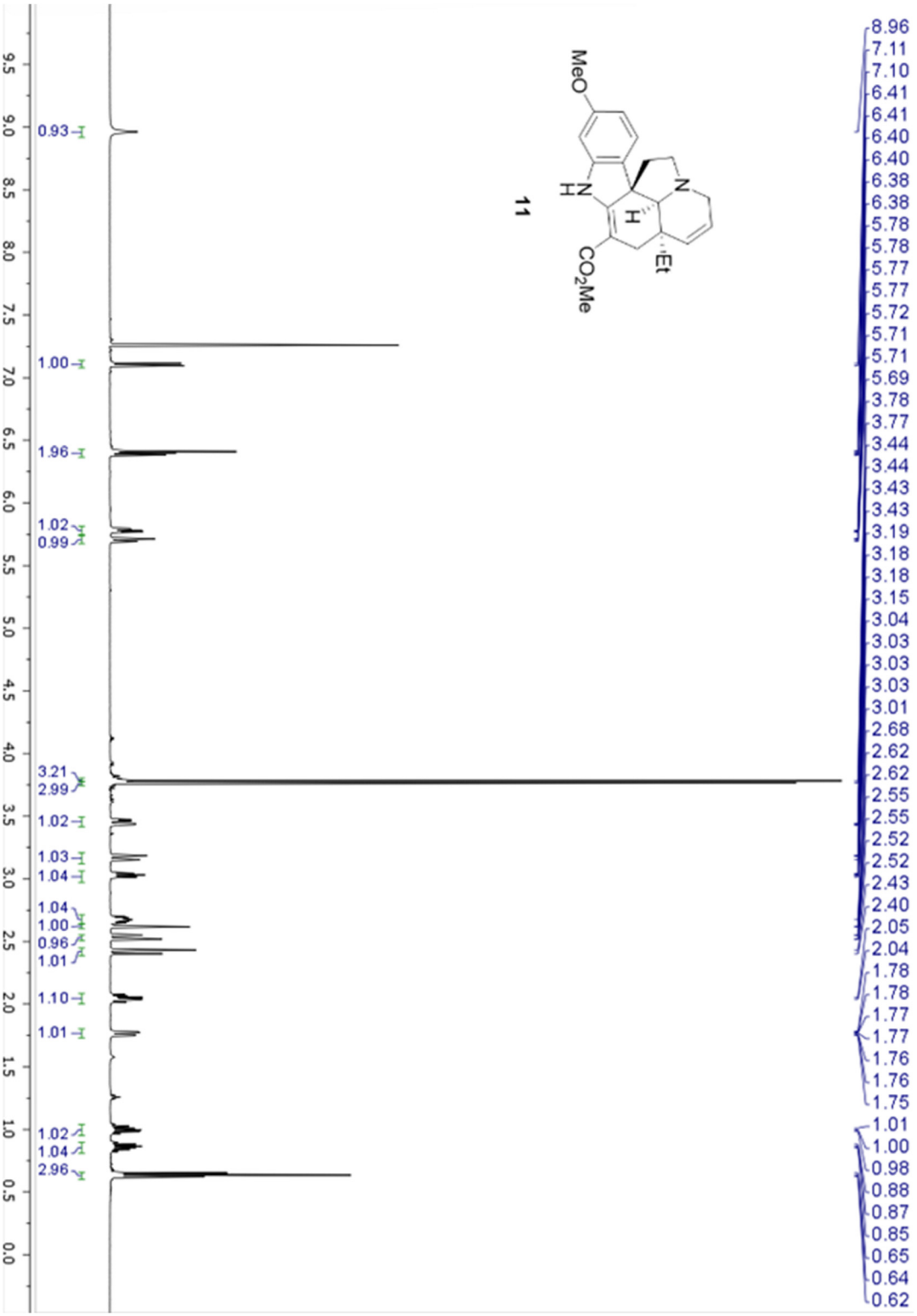

Bpin
Bpin
N
H
N
H
Et
CO2Me
7
168.3
164.7
152.7
142.0
136.9
135.7
133.3
130.0
125.0
93.1
84.0
83.6
69.7
54.9
51.1
51.0
50.6
45.1
41.4
28.9
27.0
25.3
25.1
25.0
7.8

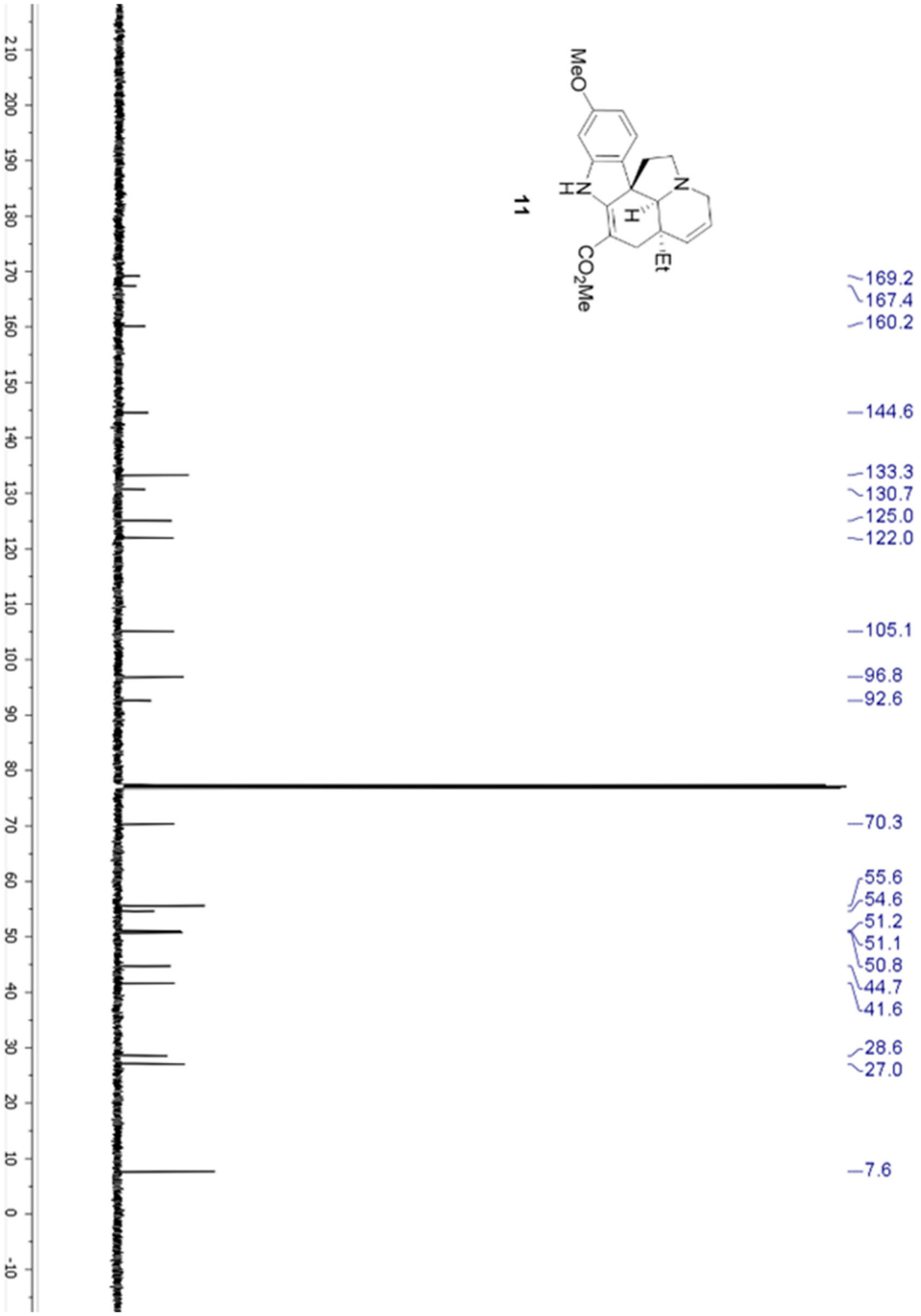

f1 (ppm)
0.94
2.21
2.01
3.00
1.00
0.98
1.01
1.95
1.05
0.96
1.00
0.96
0.98
1.12
2.95
8.95
6.46
6.45
5.77
5.77
5.76
5.76
5.75
5.75
5.74
5.74
5.70
5.70
5.69
5.68
5.67
3.73
3.45
3.44
3.41
3.41
3.19
3.16
3.03
3.01
3.00
2.66
2.54
2.51
2.41
2.38
2.06
2.05
2.04
2.03
1.80
1.79
1.78
1.77
0.98
0.97
0.95
0.88
0.86
0.85
0.84
0.62
0.61
HO
OH
N
H
N
H
Et
CO2Me
8

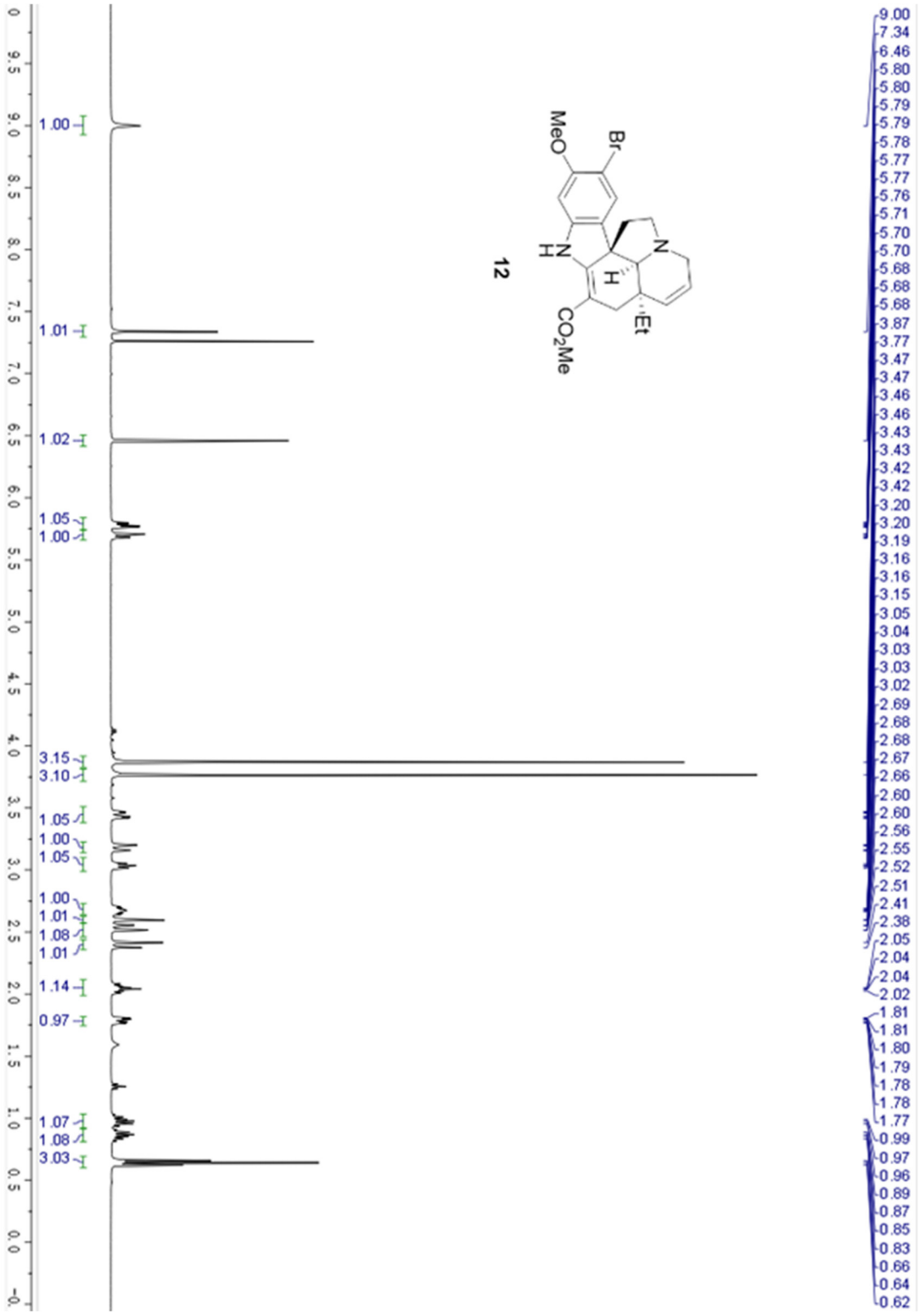

f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
169.8
167.9
151.8
140.6
133.2
124.7
124.4
103.4
102.3
91.1
75.8
70.2
56.5
51.5
51.2
50.5
44.3
41.2
28.8
27.2
7.6
HO
OH
N
H
N
H
Et
CO2Me
8

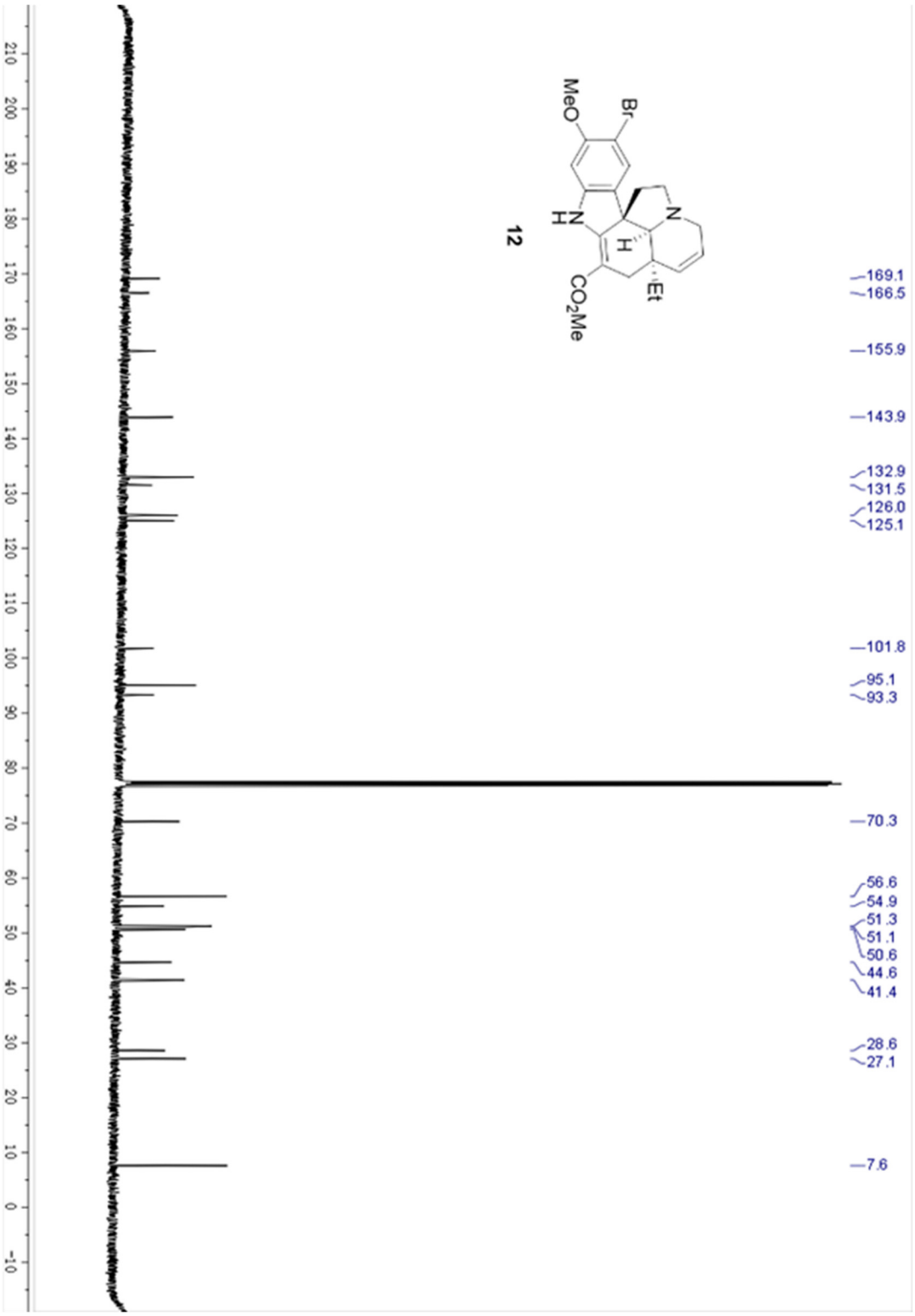

MeO
OMe
N
H
N
H
Et
CO2Me
9
0.95
1.00
0.99
1.00
0.96
3.11
2.98
3.13
0.97
0.98
0.97
0.99
1.01
1.02
0.99
1.02
1.00
1.03
1.14
3.03
8.77
6.47
6.46
6.37
6.37
5.79
5.79
5.78
5.77
5.77
5.76
5.76
5.73
5.72
5.72
5.70
3.84
3.79
3.76
3.47
3.46
3.44
3.43
3.19
3.18
3.16
3.05
3.03
3.02
2.68
2.68
2.67
2.67
2.66
2.62
2.62
2.57
2.56
2.54
2.53
2.43
2.40
2.08
2.07
1.82
1.81
1.80
1.79
1.02
1.01
0.99
0.98
0.87
0.86
0.84
0.83
0.65
0.63
0.62

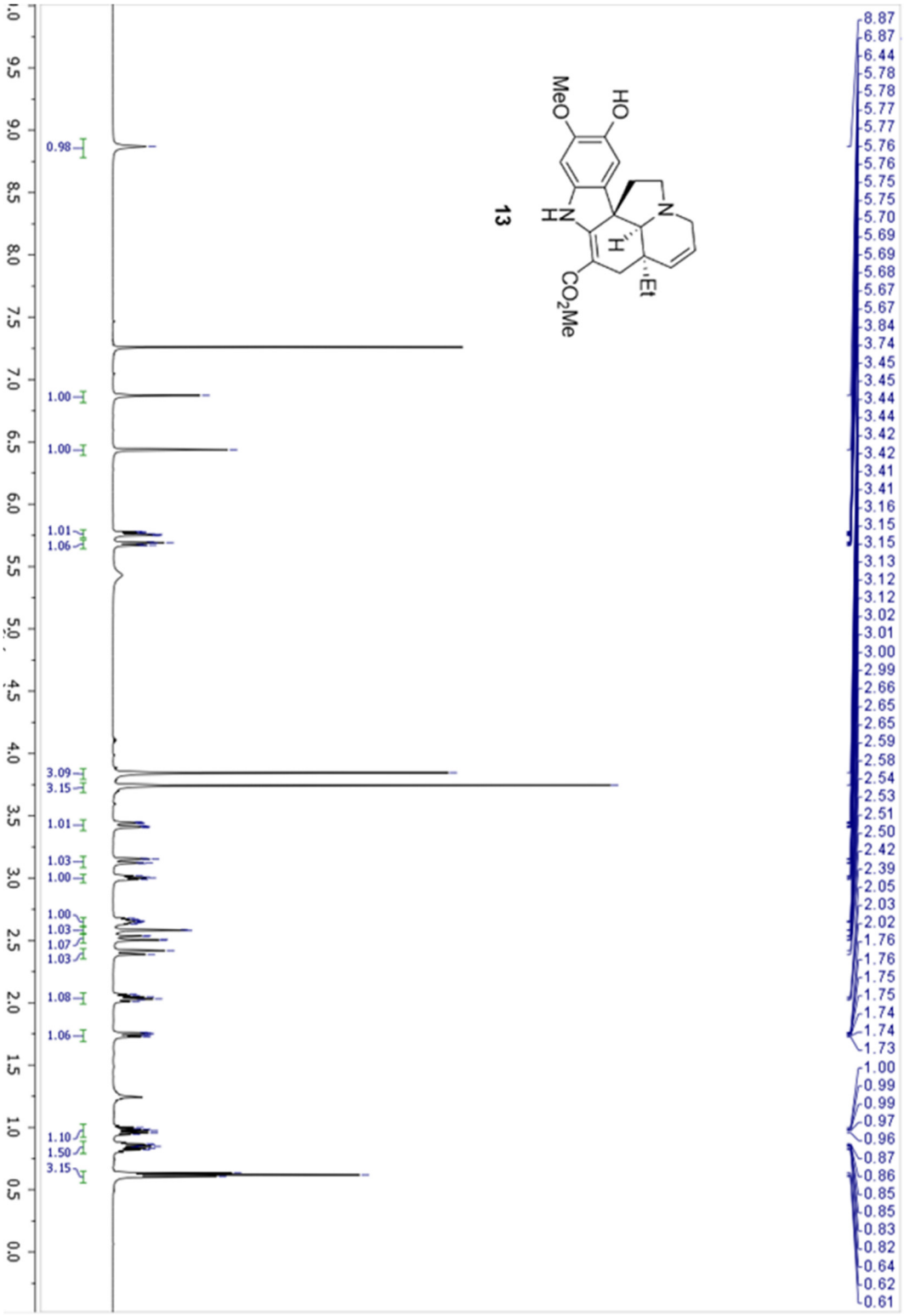

MeO
OMe
H
N
N
H
Et
CO2Me
9
168.9
167.1
155.6
144.6
139.5
133.3
125.9
124.9
99.8
97.8
91.8
70.2
56.3
56.1
55.7
51.2
51.0
50.7
44.5
41.4
28.6
27.0
7.6

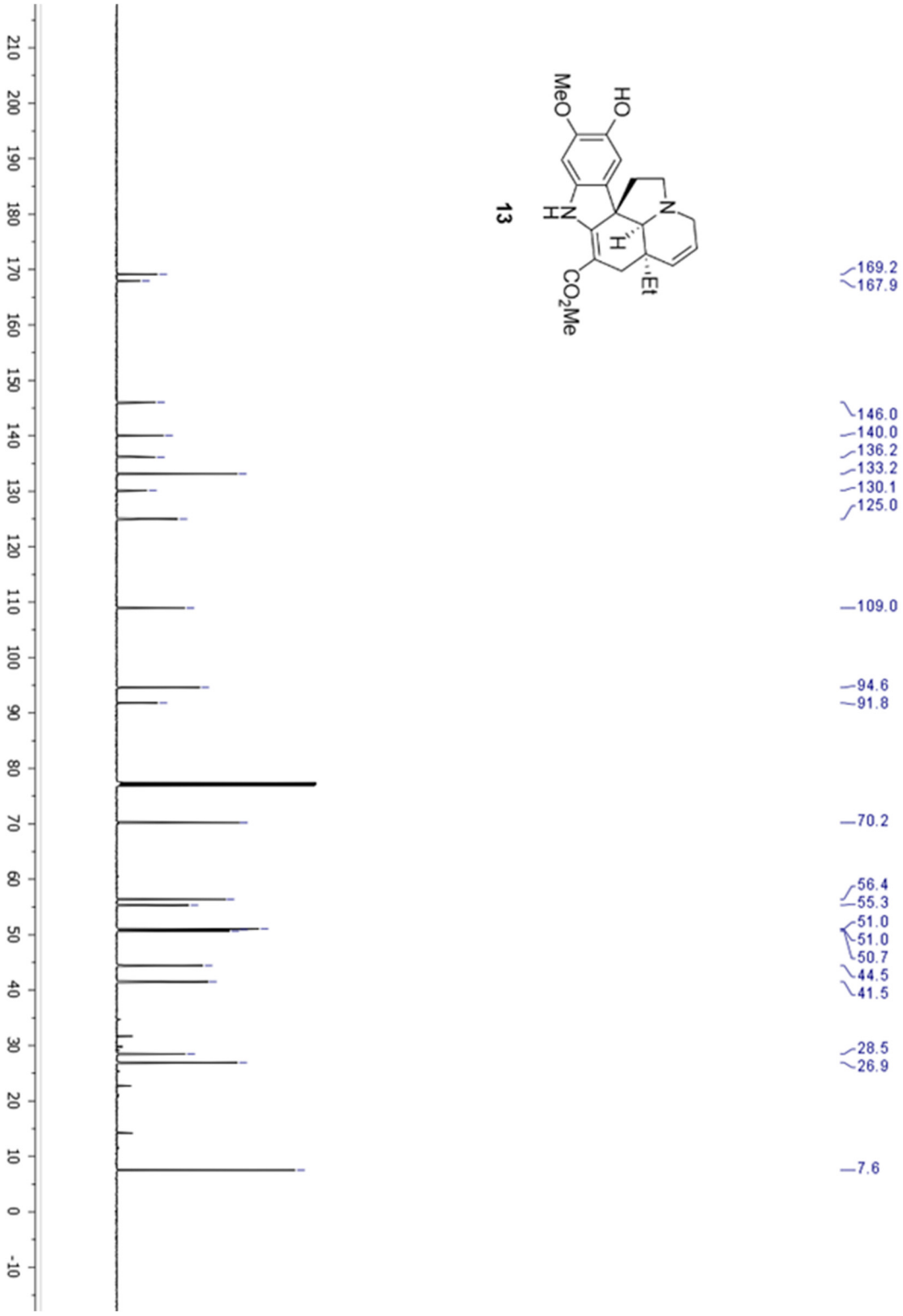

MeO
N
H
N
H
Et
CO2Me
11
0.93
1.00
1.96
1.02
0.99
3.21
2.99
1.02
1.03
1.04
1.04
1.00
0.96
1.01
1.10
1.01
1.02
1.04
2.96
8.96
7.11
7.10
6.41
6.41
6.40
6.40
6.38
6.38
5.78
5.78
5.77
5.77
5.72
5.71
5.71
5.69
3.78
3.77
3.44
3.44
3.43
3.43
3.19
3.18
3.18
3.15
3.04
3.03
3.03
3.03
3.01
2.68
2.62
2.62
2.55
2.55
2.52
2.52
2.43
2.40
2.05
2.04
1.78
1.78
1.77
1.77
1.76
1.76
1.75
1.01
1.00
0.98
0.88
0.87
0.85
0.65
0.64
0.62

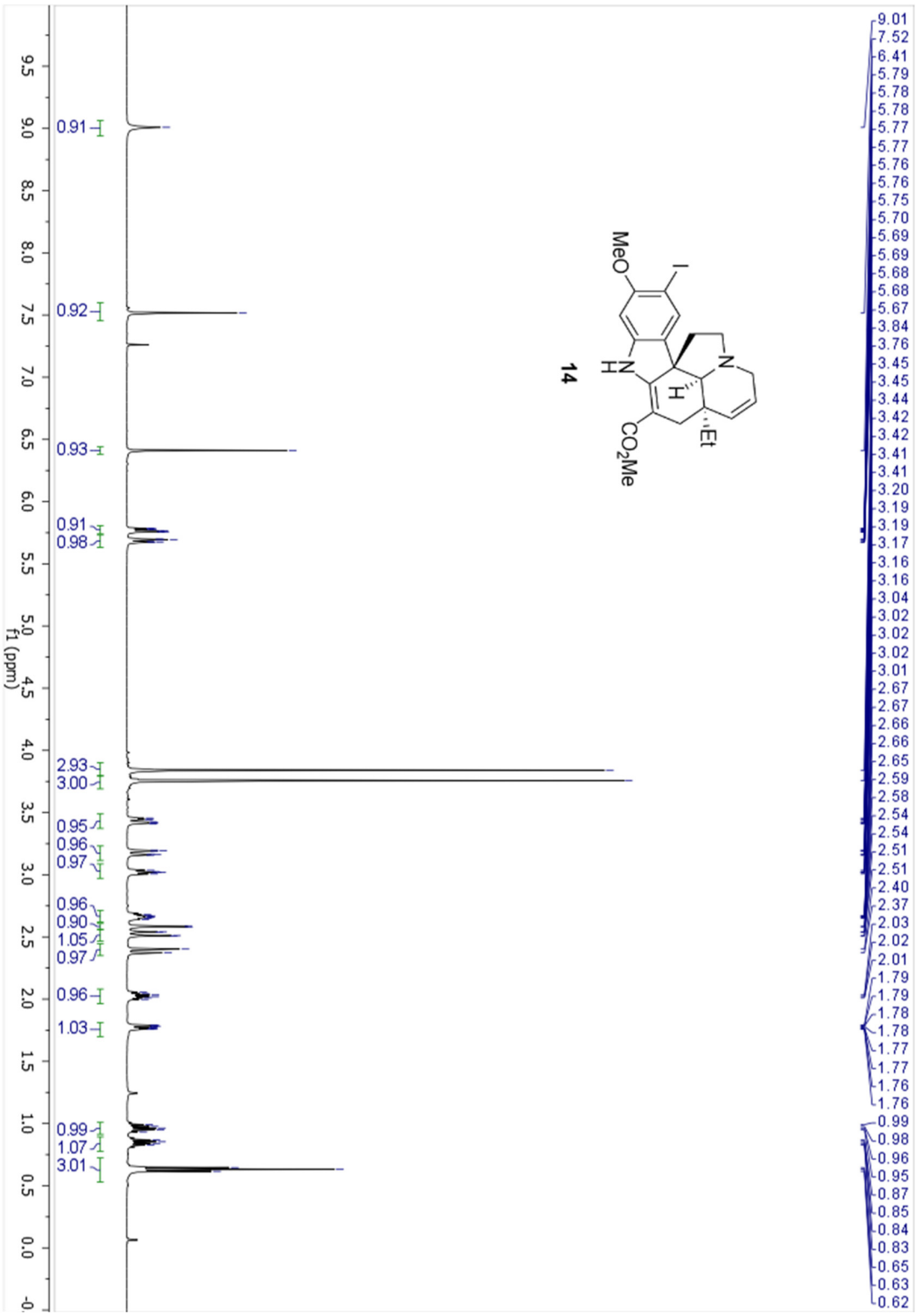

MeO
N
H
N
H
Et
CO2Me
11
169.2
167.4
160.2
144.6
133.3
130.7
125.0
122.0
105.1
96.8
92.6
70.3
55.6
54.6
51.2
51.1
50.8
44.7
41.6
28.6
27.0
7.6

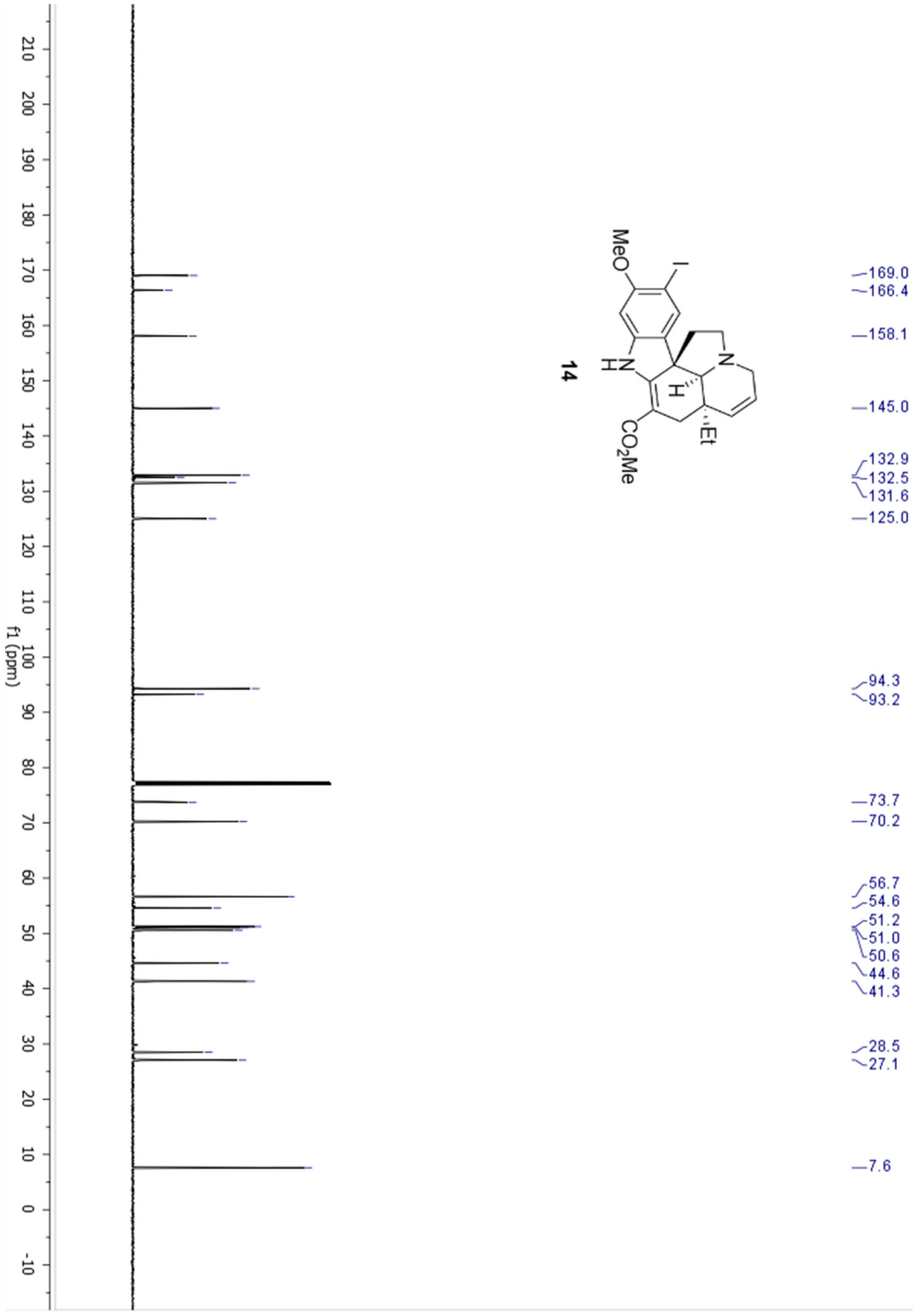

MeO
Br
N
H
N
H
Et
CO2Me
12
1.00
1.01
1.02
1.05
1.00
3.15
3.10
1.05
1.00
1.05
1.00
1.01
1.08
1.01
1.14
0.97
1.07
1.08
3.03

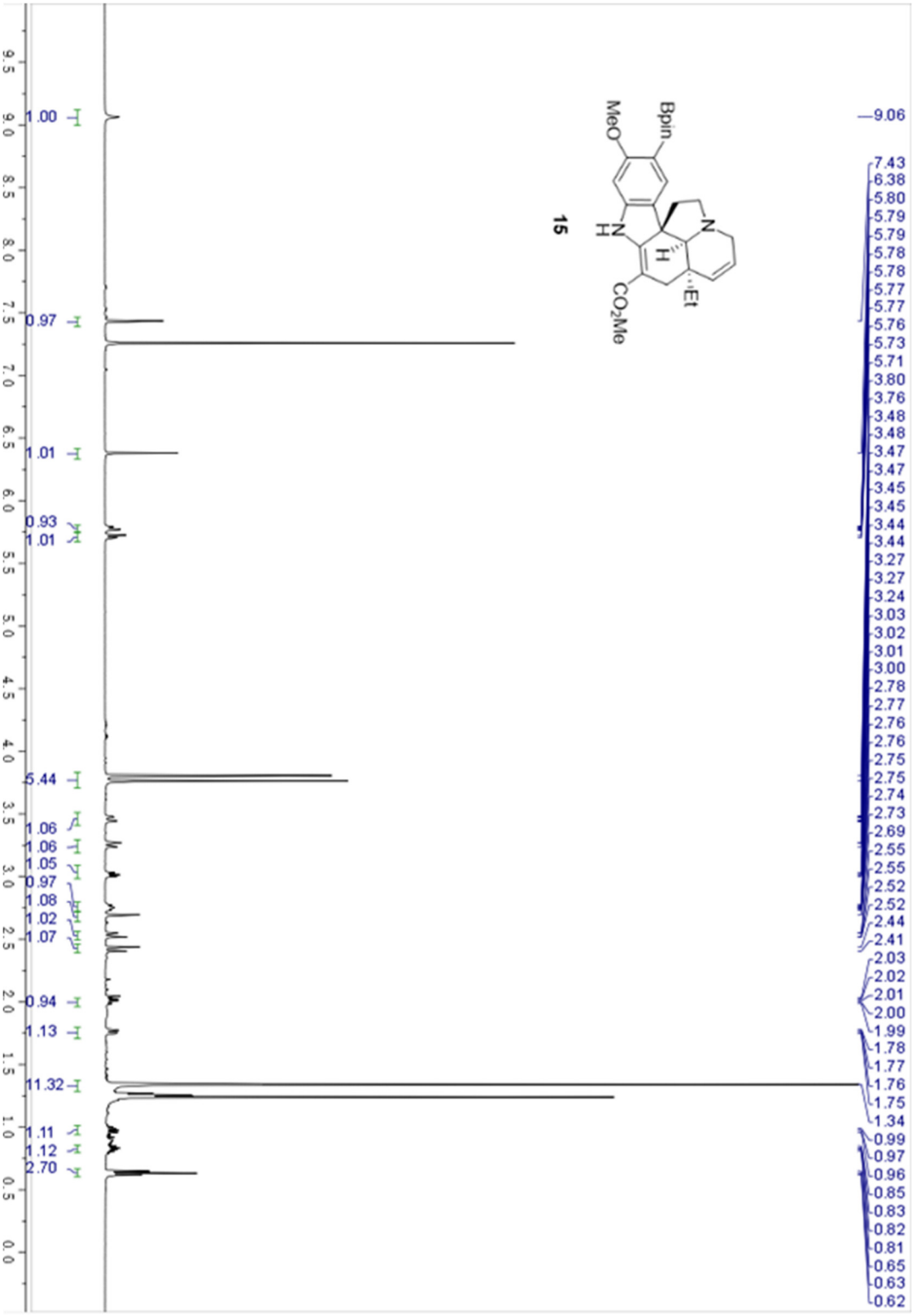

MeO
Br
N
H
N
H
Et
CO2Me
12
169.1
166.5
155.9
143.9
132.9
131.5
126.0
125.1
101.8
95.1
93.3
70.3
56.6
54.9
51.3
51.1
50.6
44.6
41.4
28.6
27.1
7.6


13
MeO
HO
N
H
N
H
Et
CO2Me
0.98
1.00
1.00
1.01
1.06
3.09
3.15
1.01
1.03
1.00
1.00
1.03
1.07
1.03
1.08
1.06
1.10
1.50
3.15


13
MeO
HO
N
H
H
N
Et
CO2Me
169.2
167.9
146.0
140.0
136.2
133.2
130.1
125.0
109.0
94.6
91.8
70.2
56.4
55.3
51.0
51.0
50.7
44.5
41.5
28.5
26.9
7.6


MeO
I
N
H
N
H
Et
CO2Me
14
f1 (ppm)
0.91
0.92
0.93
0.91
0.98
2.93
3.00
0.95
0.96
0.97
0.96
0.90
1.05
0.97
0.96
1.03
0.99
1.07
3.01


MeO
I
N
H
N
H
Et
CO2Me
14
169.0
166.4
158.1
145.0
132.9
132.5
131.6
125.0
94.3
93.2
73.7
70.2
56.7
54.6
51.2
51.0
50.6
44.6
41.3
28.5
27.1
7.6
f1 (ppm)


MeO
Bpin
N
H
H
N
Et
CO2Me
15
9.06
7.43
6.38
5.80
5.79
5.79
5.78
5.78
5.77
5.77
5.76
5.73
5.71
3.80
3.76
3.48
3.48
3.47
3.47
3.45
3.45
3.44
3.44
3.27
3.27
3.24
3.03
3.02
3.01
3.00
2.78
2.77
2.76
2.76
2.75
2.75
2.74
2.73
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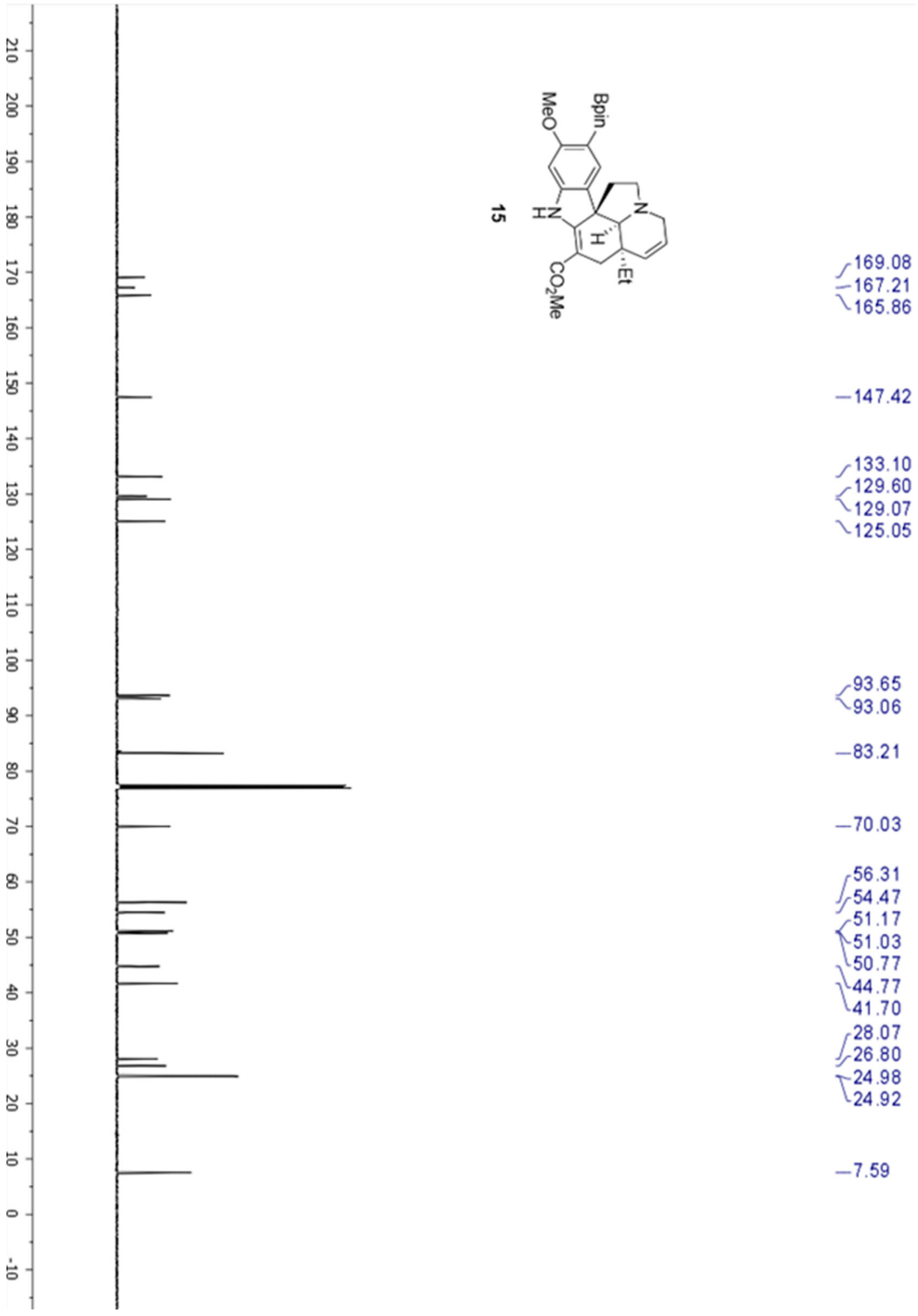
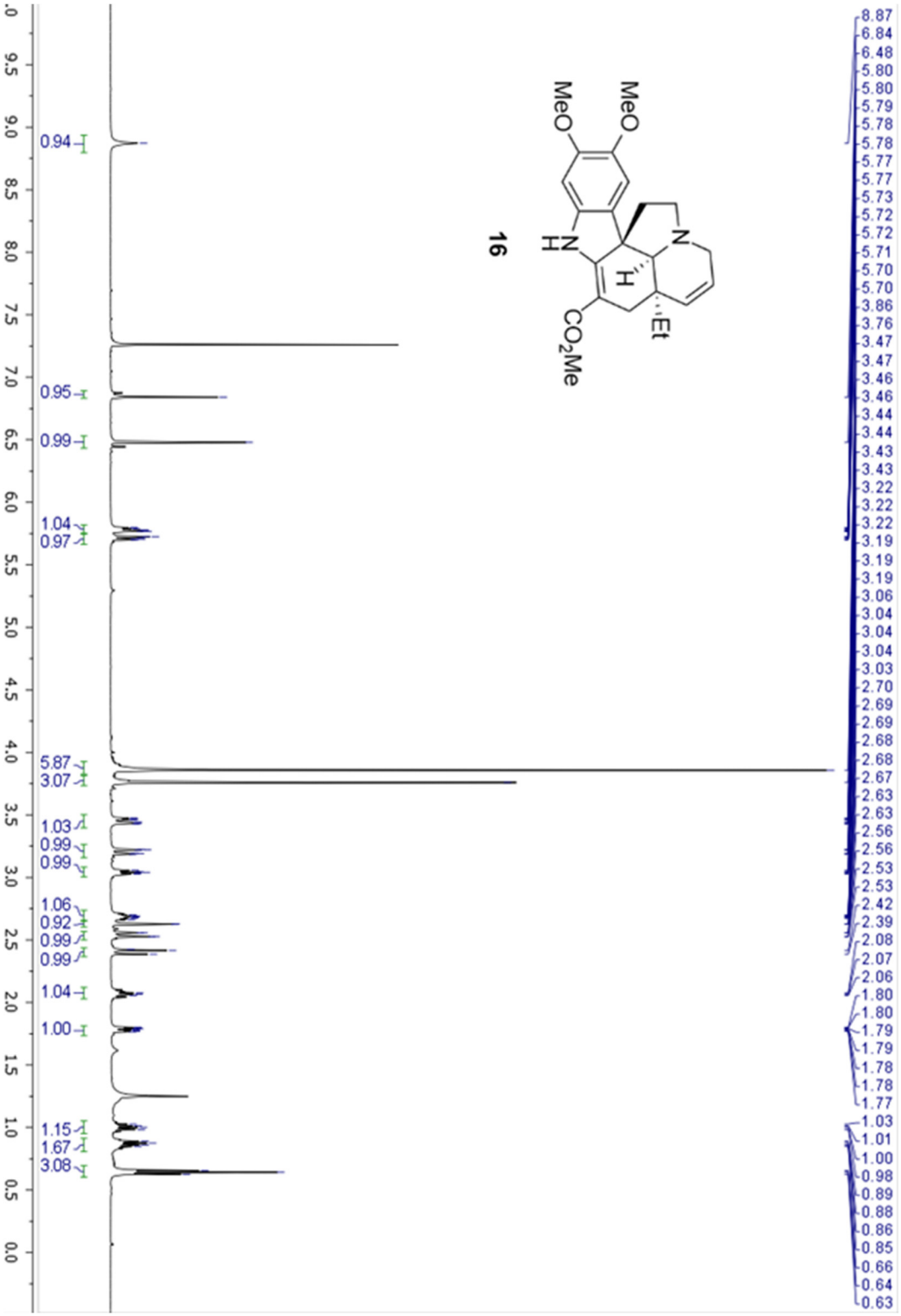
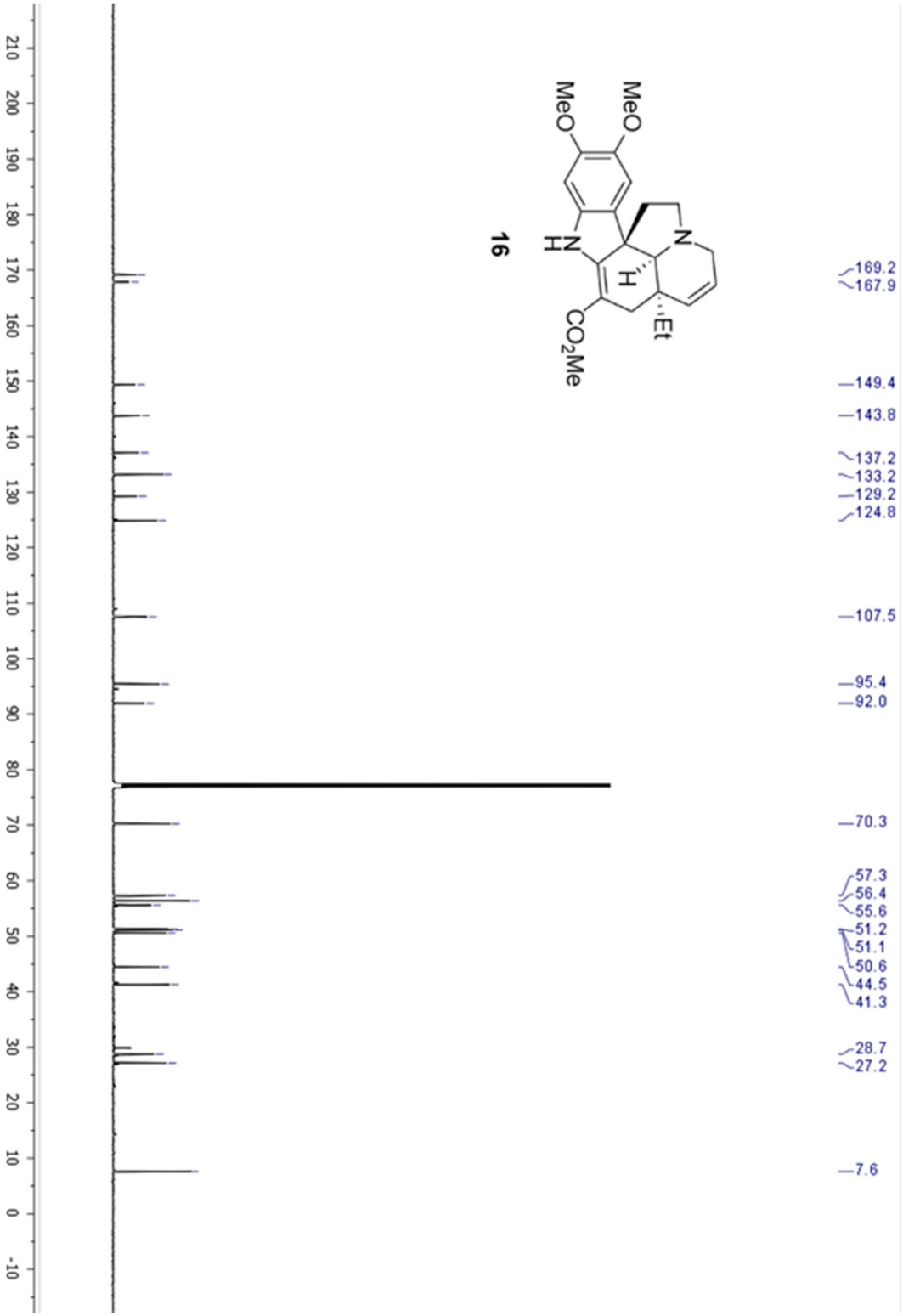
2.55
2.55
2.52
2.52
2.44
2.41
2.03
2.02
2.01
2.00
1.99
1.78
1.77
1.76
1.75
1.34
0.99
0.97
0.96
0.85
0.83
0.82
0.81
0.65
0.63
0.62
1.00
0.97
1.01
0.93
1.01
5.44
1.06
1.06
1.05
0.97
1.08
1.02
1.07
0.94
1.13
11.32
1.11
1.12
2.70


15
MeO
Bpin
N
H
N
H
Et
CO2Me
169.08
167.21
165.86
147.42
133.10
129.60
129.07
125.05
93.65
93.06
83.21
70.03
56.31
54.47
51.17
51.03
50.77
44.77
41.70
28.07
26.80
24.98
24.92
7.59


MeO
MeO
N
H
N
H
Et
CO2Me
16
0.94
0.95
0.99
1.04
0.97
5.87
3.07
1.03
0.99
0.99
1.06
0.92
0.99
0.99
1.04
1.00
1.15
1.67
3.08


MeO
MeO
N
H
H
N
Et
CO2Me
16
169.2
167.9
149.4
143.8
137.2
133.2
129.2
124.8
107.5
95.4
92.0
70.3
57.3
56.4
55.6
51.2
51.1
50.6
44.5
41.3
28.7
27.2
7.6