Supplementary material

for

Multistep Synthesis and *In Vitro* Anticancer Evaluation of 2-Pyrazolyl-Estradiol Derivatives, Pyrazolocoumarin-Estradiol Hybrids and Analogous Compounds

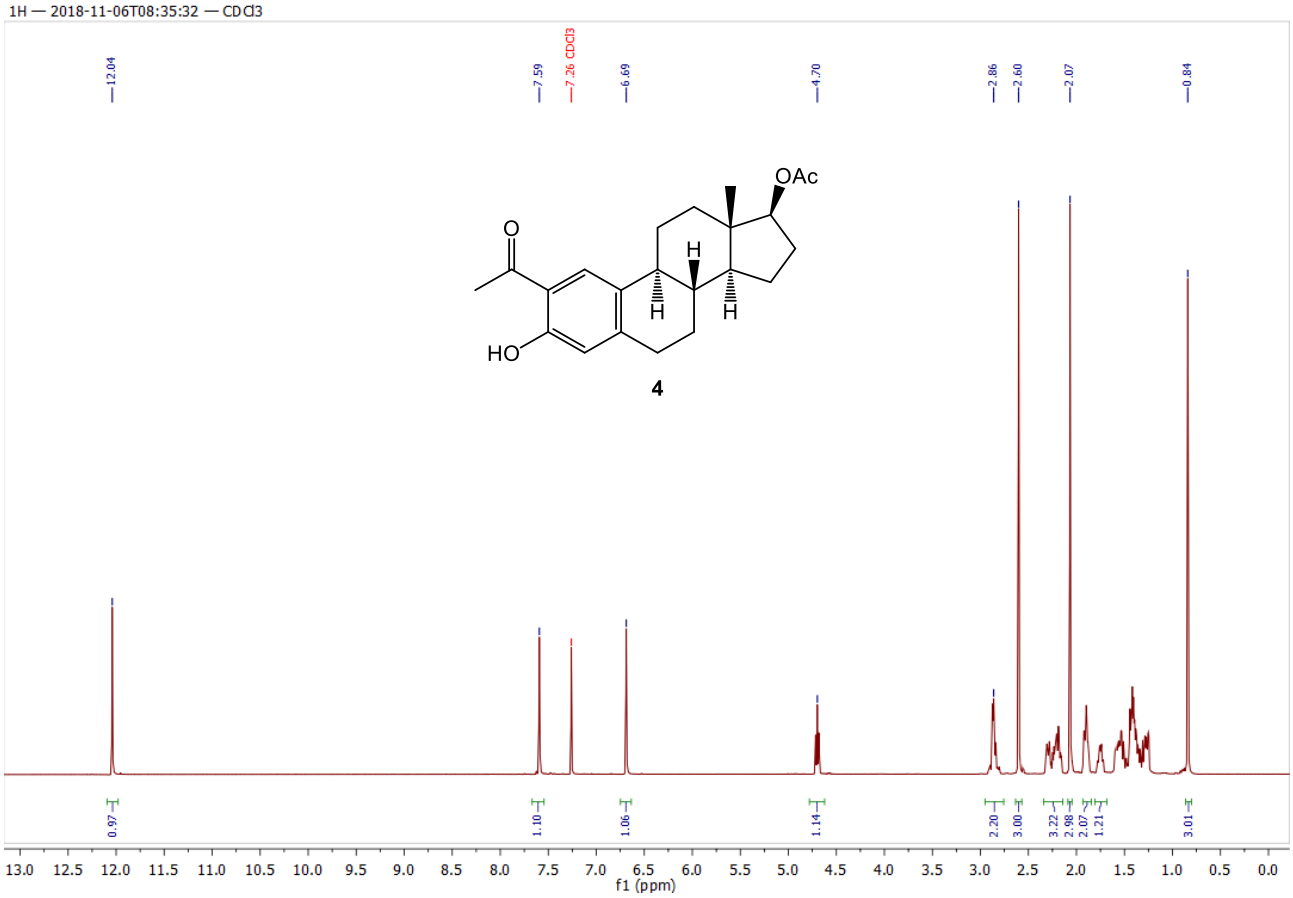
Barnabás Molnár [1], Mohana Krishna Gopisetty [2], Dóra Izabella Adamecz [2], Mónika Kiricsi [2] and Éva Frank [1,*]

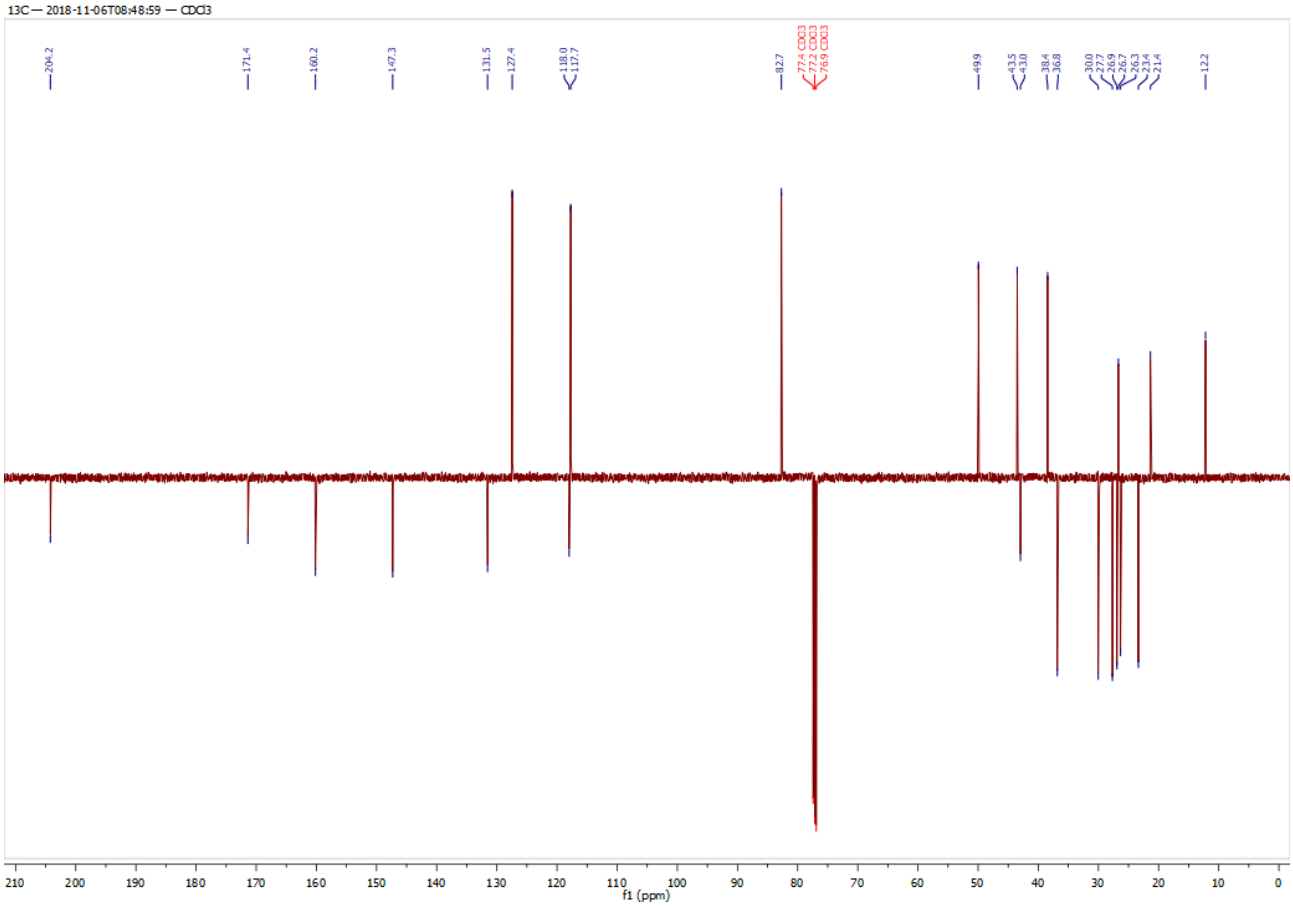
[1] *Department of Organic Chemistry, Doctoral School of Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary*

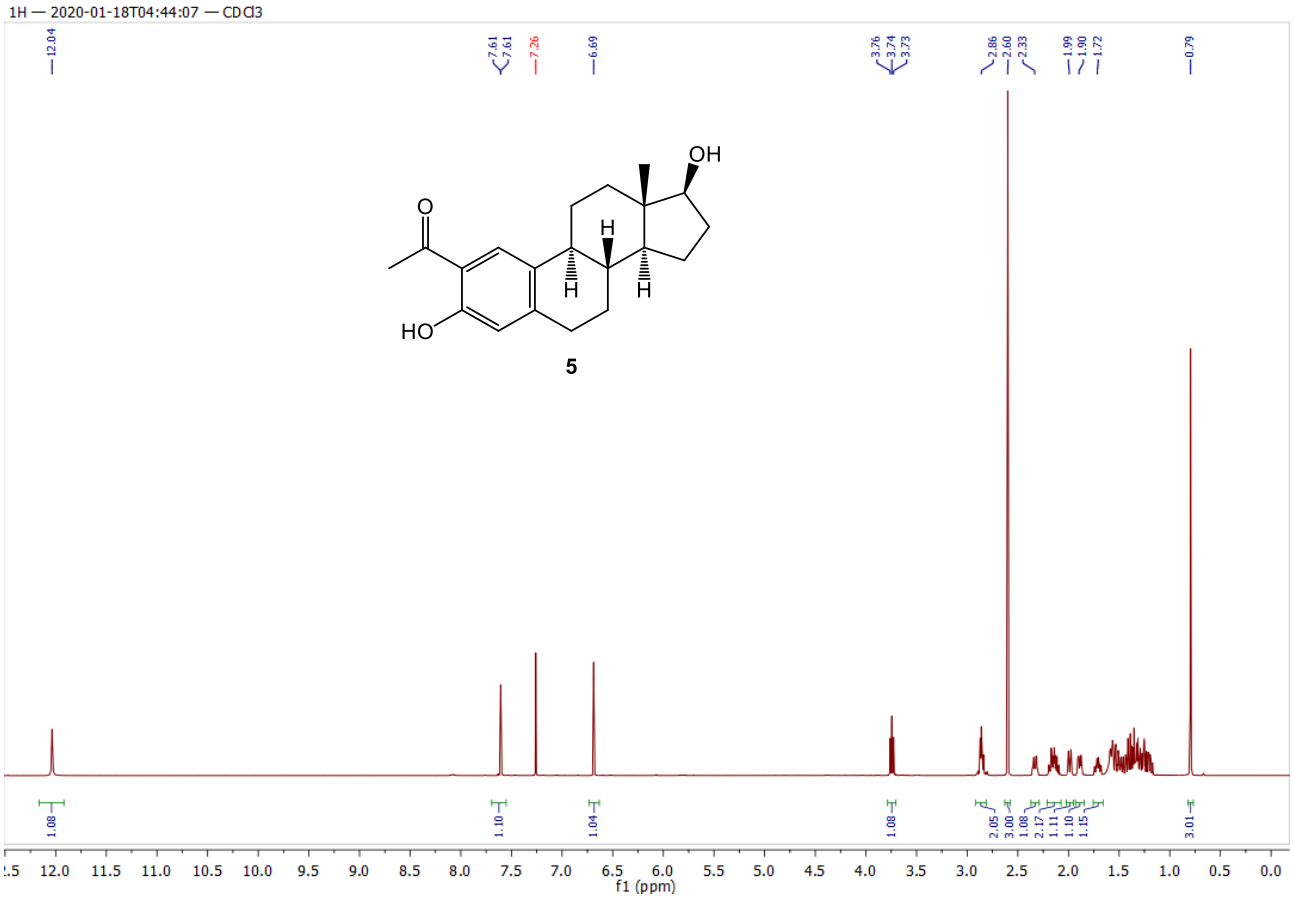
[2] *Department of Biochemistry and Molecular Biology, Doctoral School of Biology, University of Szeged, Közép fasor 52, H-6726, Szeged, Hungary*

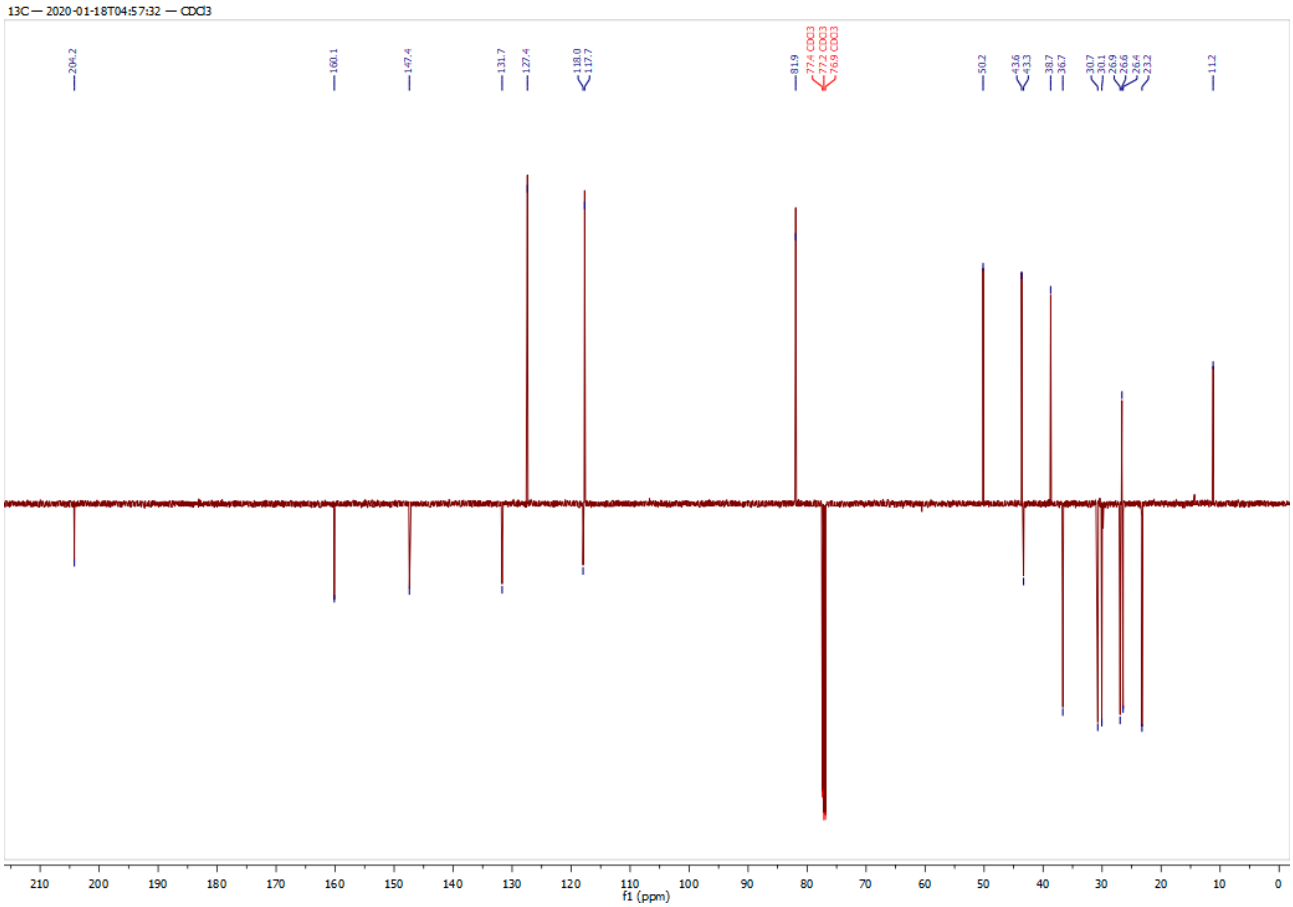
*Corresponding author. E-mail address: frank@chem.u-szeged.hu

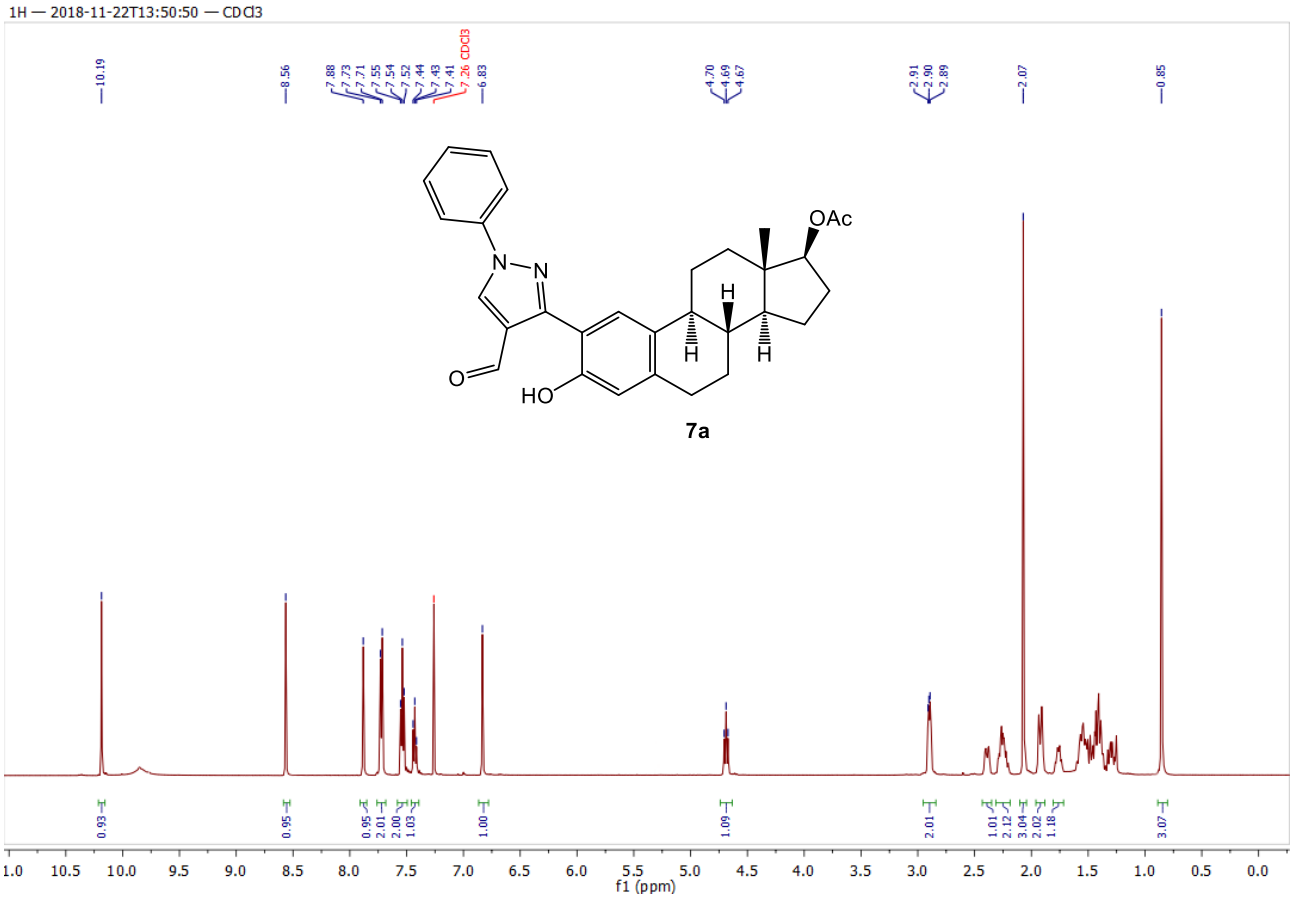
Table of Contents


1H — 2018-11-06T08:35:32 — CDCl3
12.04
7.59
7.26 CDCl3
6.69
4.70
2.86
2.60
2.07
0.84
OAc
O
H
H
H
HO
4
0.97
1.10
1.06
1.14
2.20
3.00
3.22
2.98
2.07
1.21
3.01
f1 (ppm)

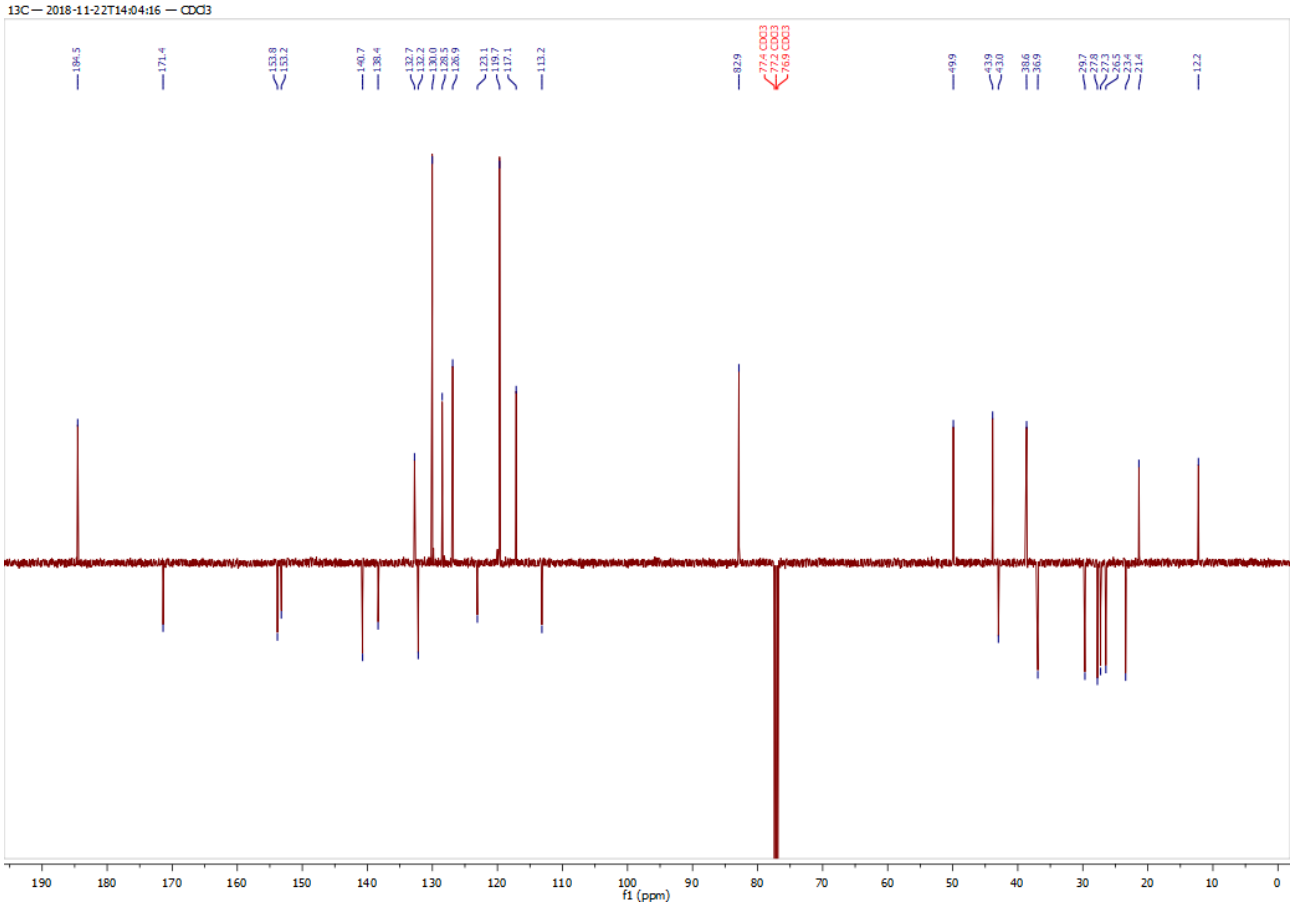

13C — 2018-11-06T08:48:59 — CDCl3
204.2
171.4
160.2
147.3
131.5
127.4
118.0
117.7
82.7
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
49.9
43.5
43.0
38.4
36.8
30.0
27.7
26.8
26.7
26.3
23.4
21.4
12.2
f1 (ppm)

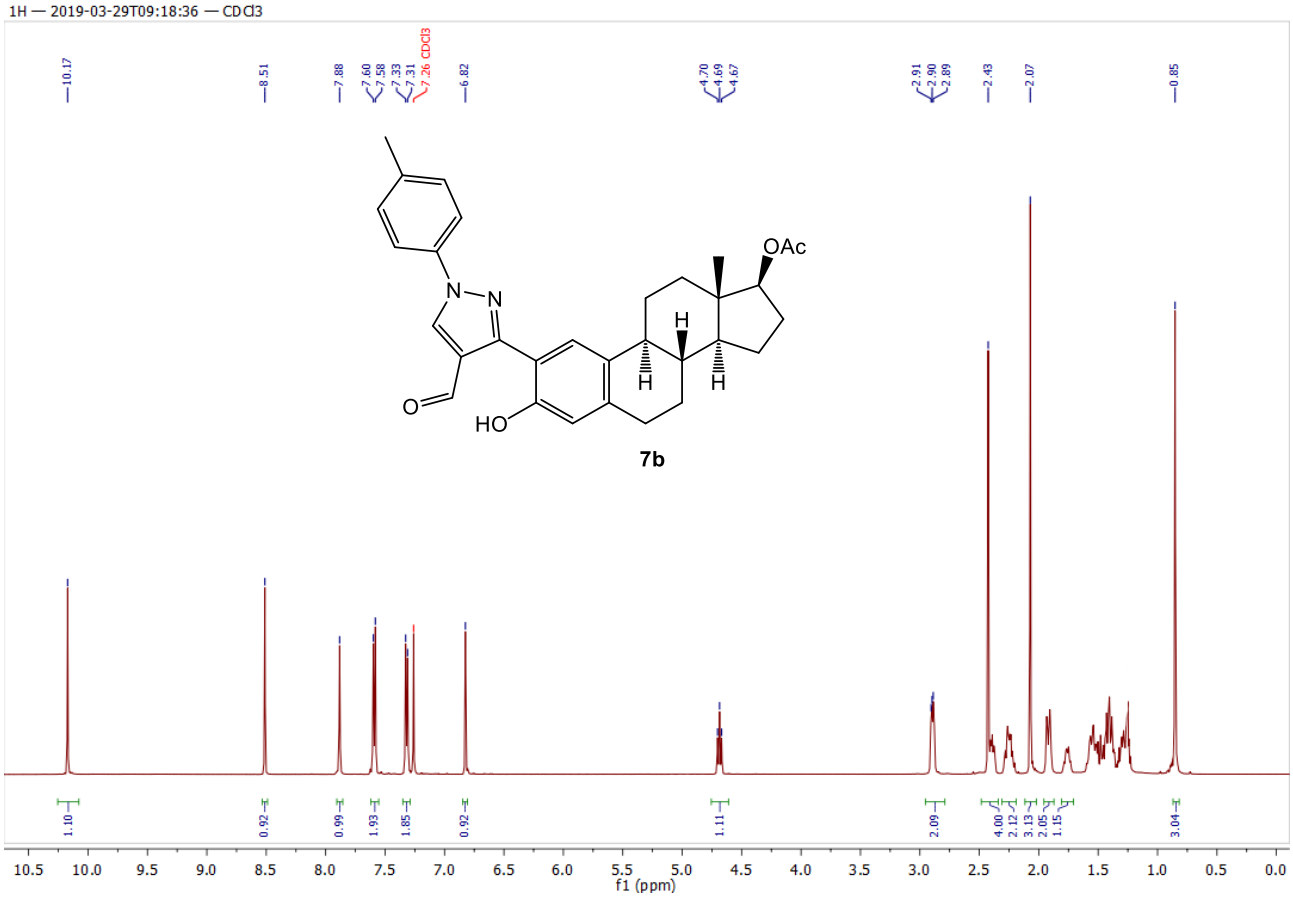

1H — 2020-01-18T04:44:07 — CDCl3
12.04
7.61
7.61
7.26
6.69
3.76
3.74
3.73
2.86
2.60
2.33
1.99
1.90
1.72
0.79
OH
O
H
H
H
HO
5
1.08
1.10
1.04
1.08
2.05
3.00
1.08
2.17
1.11
1.10
1.15
3.01
f1 (ppm)


13C — 2020-01-18T04:57:32 — CDCl3
204.2
160.1
147.4
131.7
127.4
118.0
117.7
81.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
50.2
43.6
43.3
38.7
36.7
30.7
30.1
28.8
26.6
26.4
23.2
11.2
f1 (ppm)

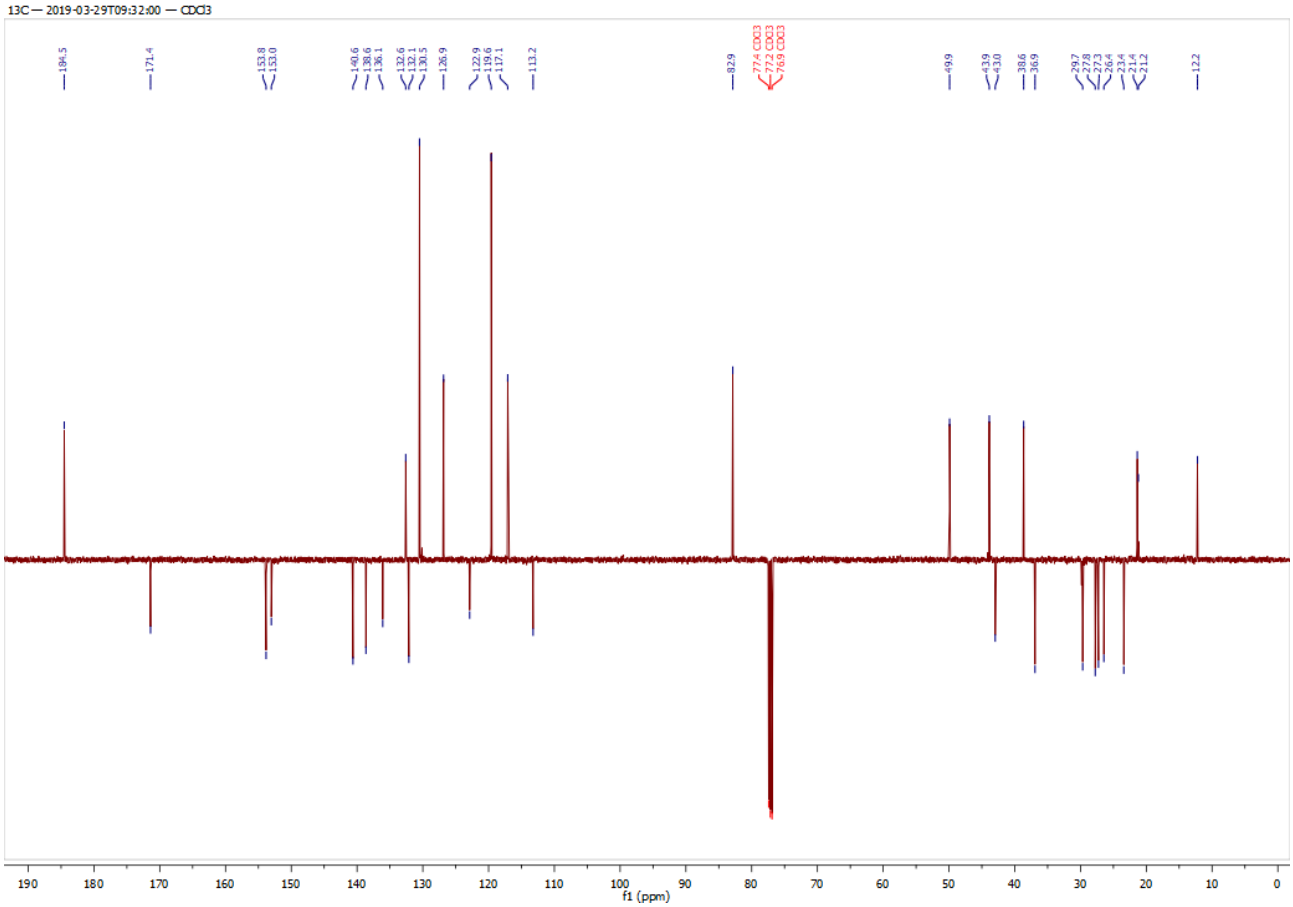

1H — 2018-11-22T13:50:50 — CDCl3
10.19
8.56
7.88
7.73
7.71
7.55
7.54
7.52
7.44
7.43
7.41
7.26 CDCl3
6.83
4.70
4.69
4.67
2.91
2.90
2.89
2.07
0.85
OAc
N
N
H
H
H
O
HO
0.93
0.95
0.95
2.01
2.00
1.03
1.00
1.09
2.01
1.01
2.12
3.04
2.02
1.18
3.07
f1 (ppm)

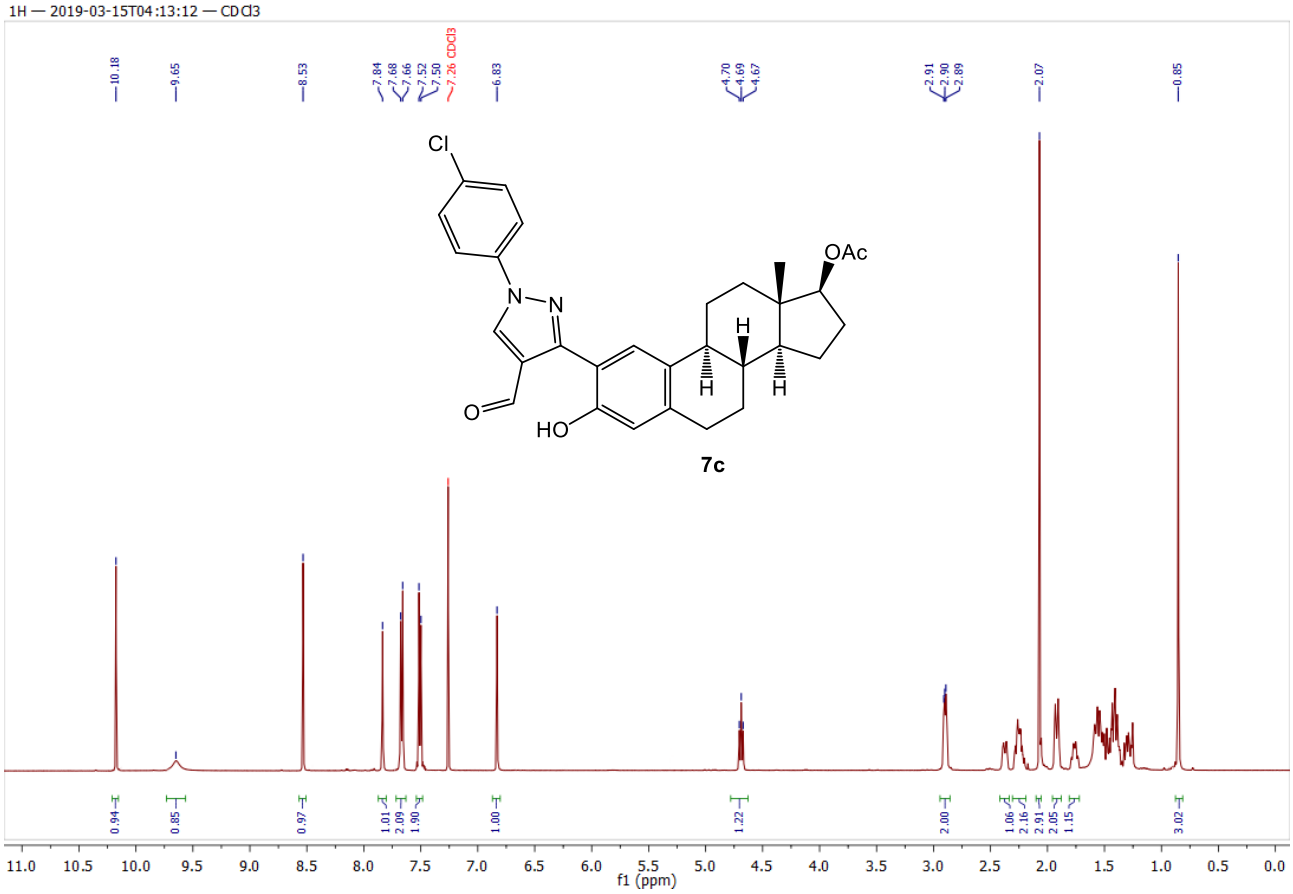
7a


13C — 2018-11-22T14:04:16 — CDCl3
194.5
171.4
153.8
153.2
140.7
138.4
132.7
132.2
130.0
128.5
126.9
123.1
119.7
117.1
113.2
82.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
49.9
43.9
43.0
38.6
36.9
29.7
27.8
27.3
26.5
23.4
21.4
12.2
f1 (ppm)

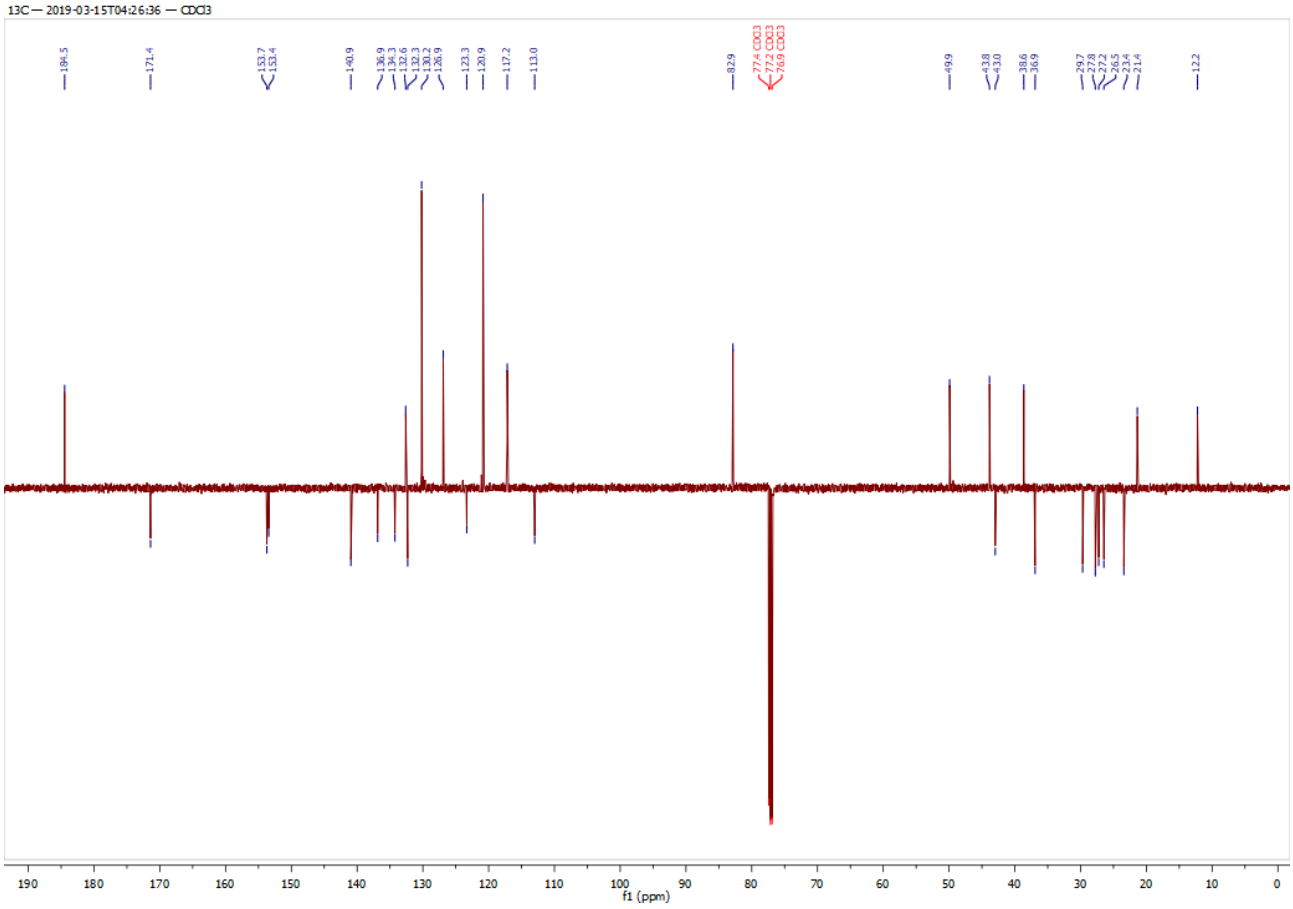

1H — 2019-03-29T09:18:36 — CDCl3
10.17
8.51
7.88
7.60
7.58
7.33
7.31
7.26 CDCl3
6.82
4.70
4.69
4.67
2.91
2.90
2.89
2.43
2.07
0.85
OAc
N
N
H
H
H
O
HO
1.10
0.92
0.99
1.93
1.85
0.92
1.11
2.09
4.00
2.12
3.13
2.05
1.15
3.04
f1 (ppm)

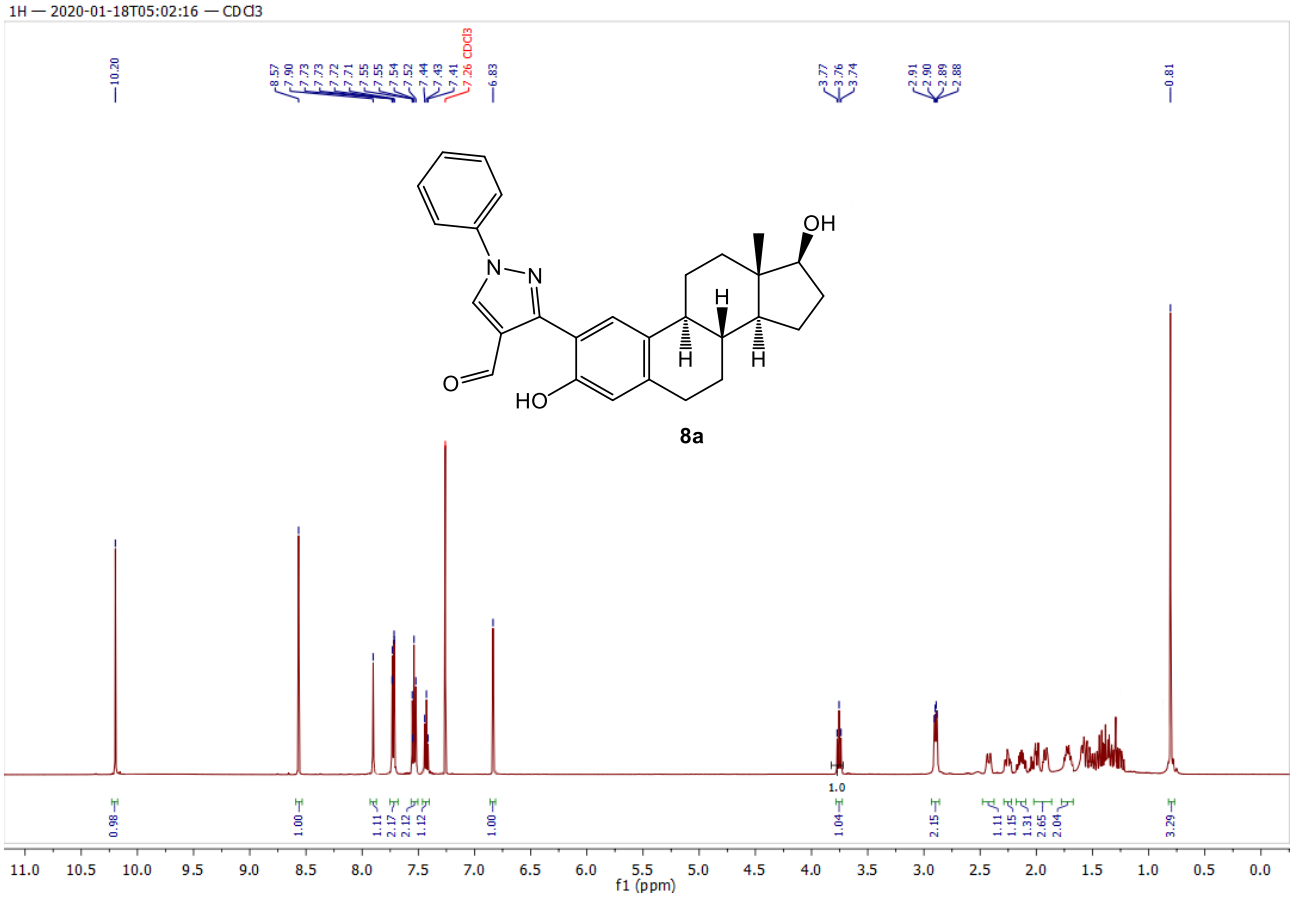
7b

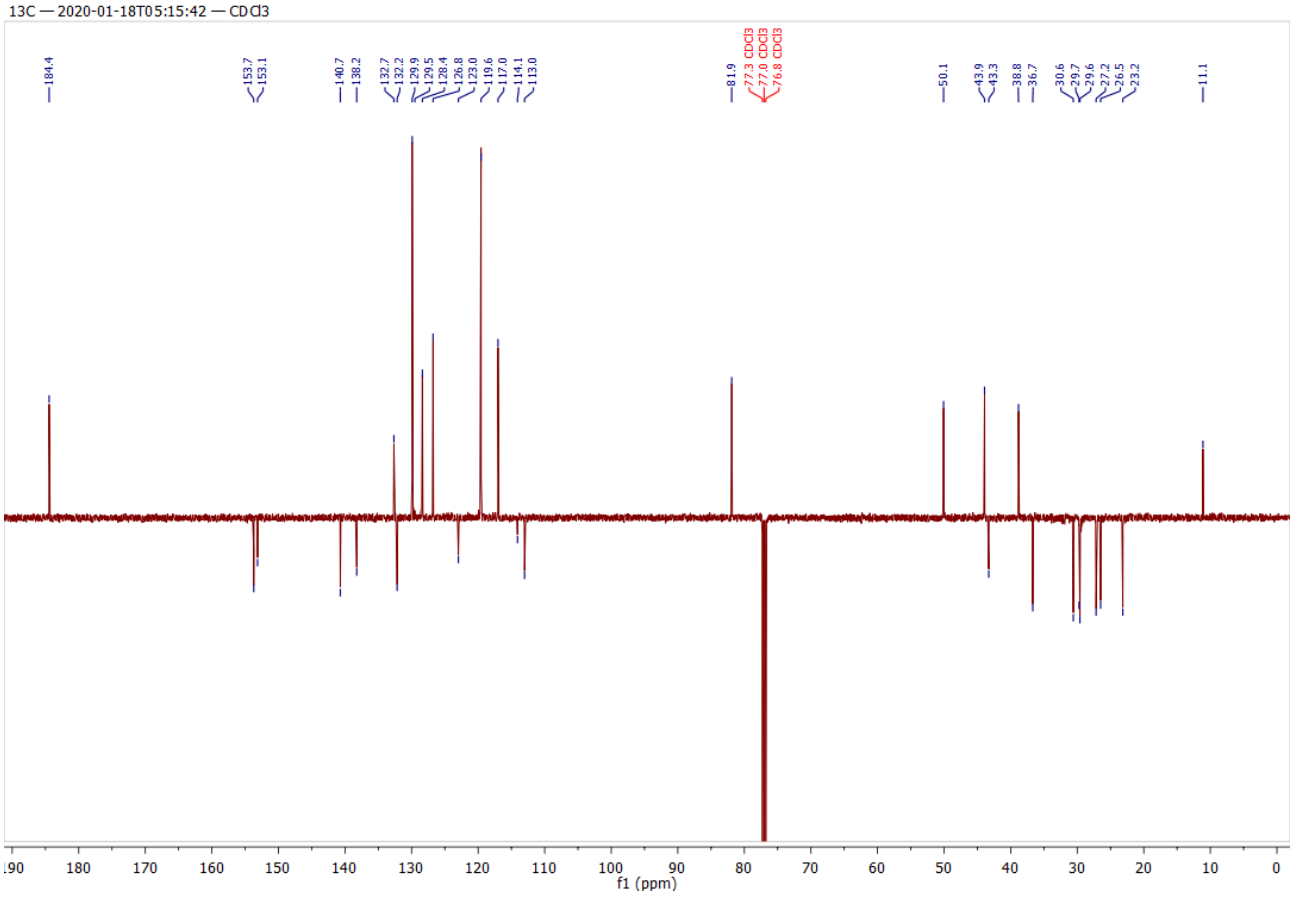

13C — 2019-03-29T09:32:00 — CDCl3
194.5
171.4
153.8
153.0
140.6
138.6
136.1
132.6
132.1
130.5
126.9
122.9
119.6
117.1
113.2
82.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
49.9
43.9
43.0
38.6
36.9
29.7
27.8
27.3
26.4
23.4
21.4
21.2
12.2
f1 (ppm)

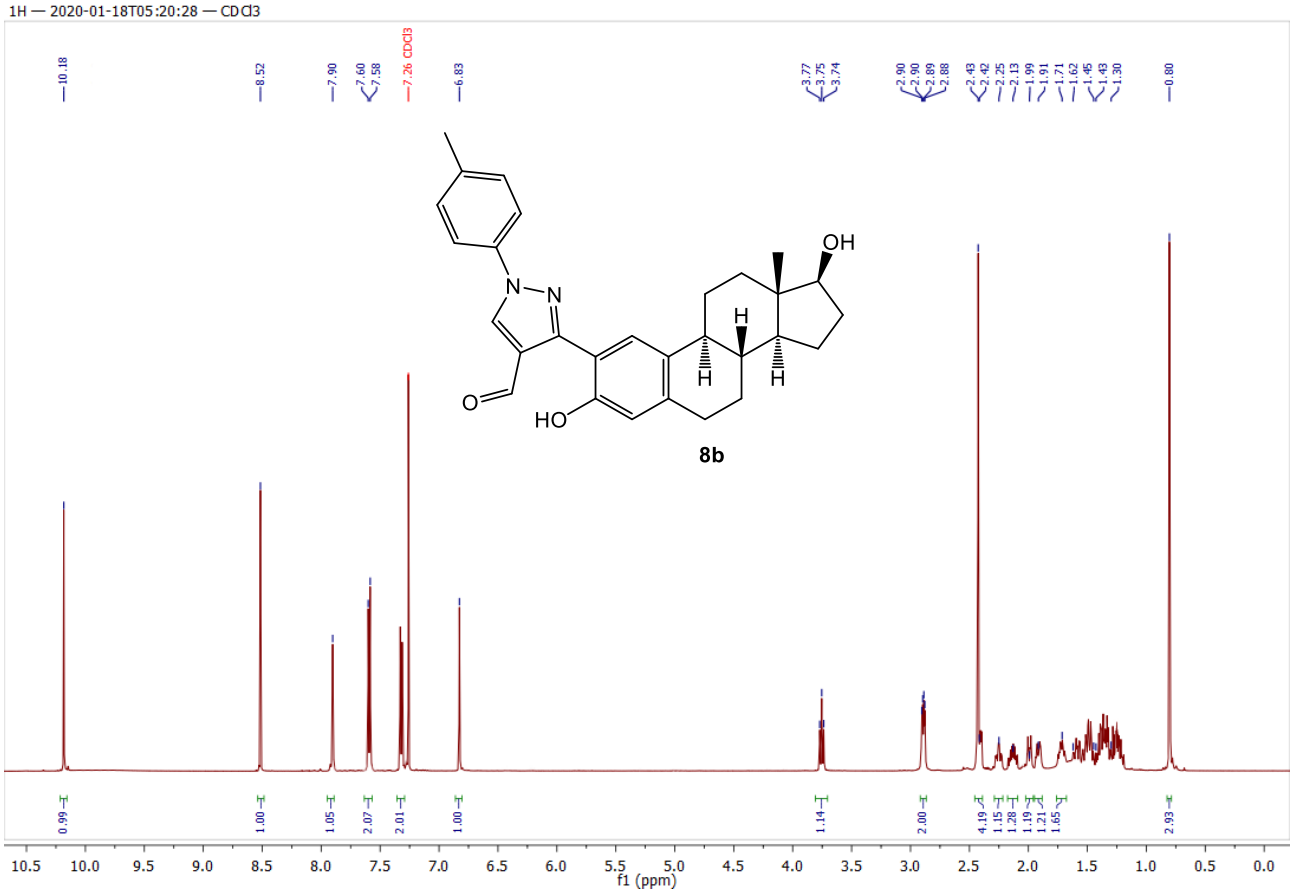

1H — 2019-03-15T04:13:12 — CDCl3
10.18
9.65
8.53
7.84
7.68
7.66
7.52
7.50
7.26 CDCl3
6.83
4.70
4.69
4.67
2.91
2.90
2.89
2.07
0.85
Cl
N
N
OAc
H
H
H
O
HO
0.94
0.85
0.97
1.01
2.09
1.90
1.00
1.22
2.00
1.06
2.16
2.91
2.05
1.15
3.02
f1 (ppm)

7c

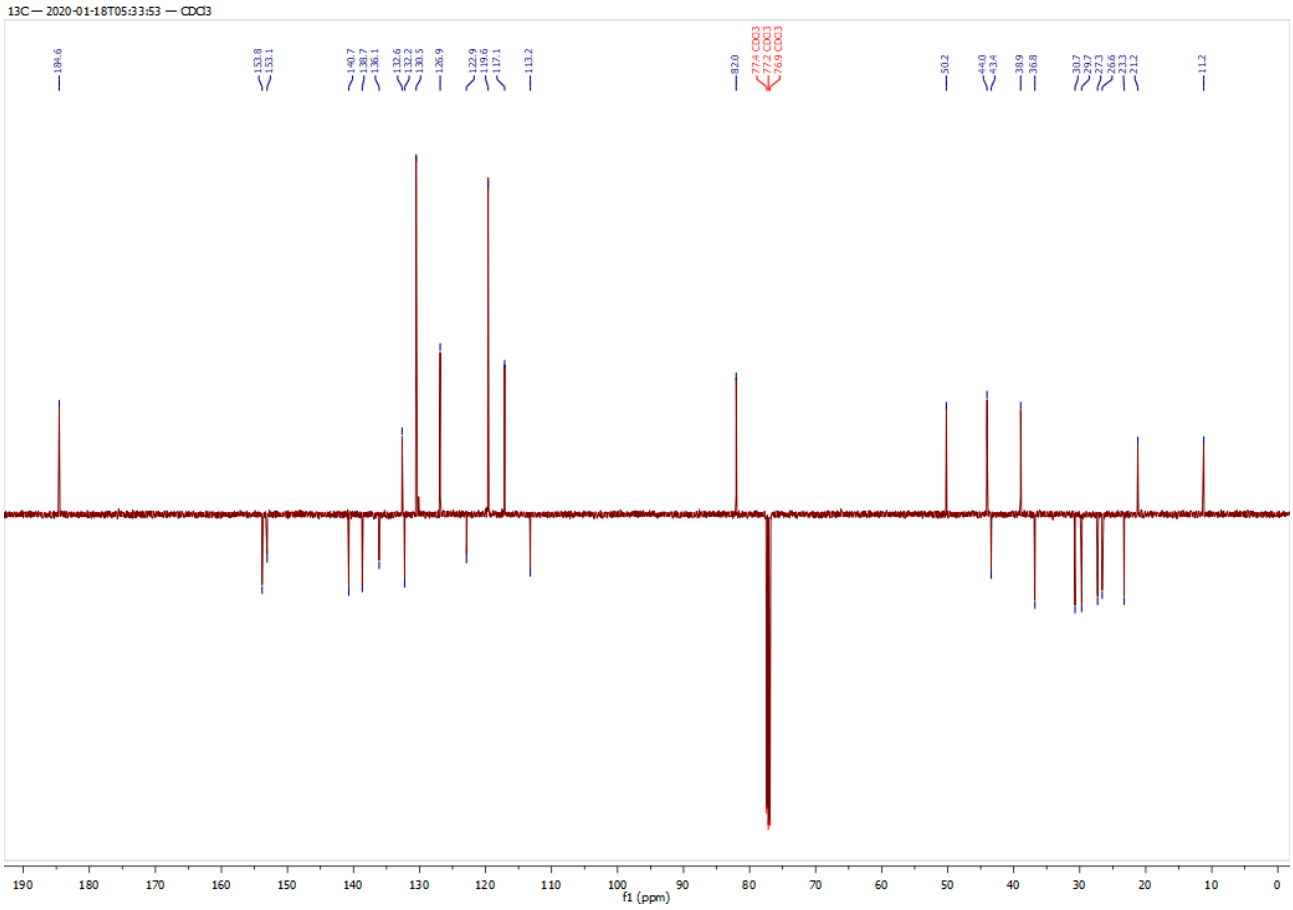

13C — 2019-03-15T04:26:36 — CDCl3
184.5
171.4
153.7
153.4
140.9
136.9
134.3
132.6
132.3
130.2
128.9
123.3
120.9
117.2
113.0
82.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
49.9
43.8
43.0
38.6
36.9
29.7
27.8
27.2
26.5
24.4
21.4
12.2
f1 (ppm)

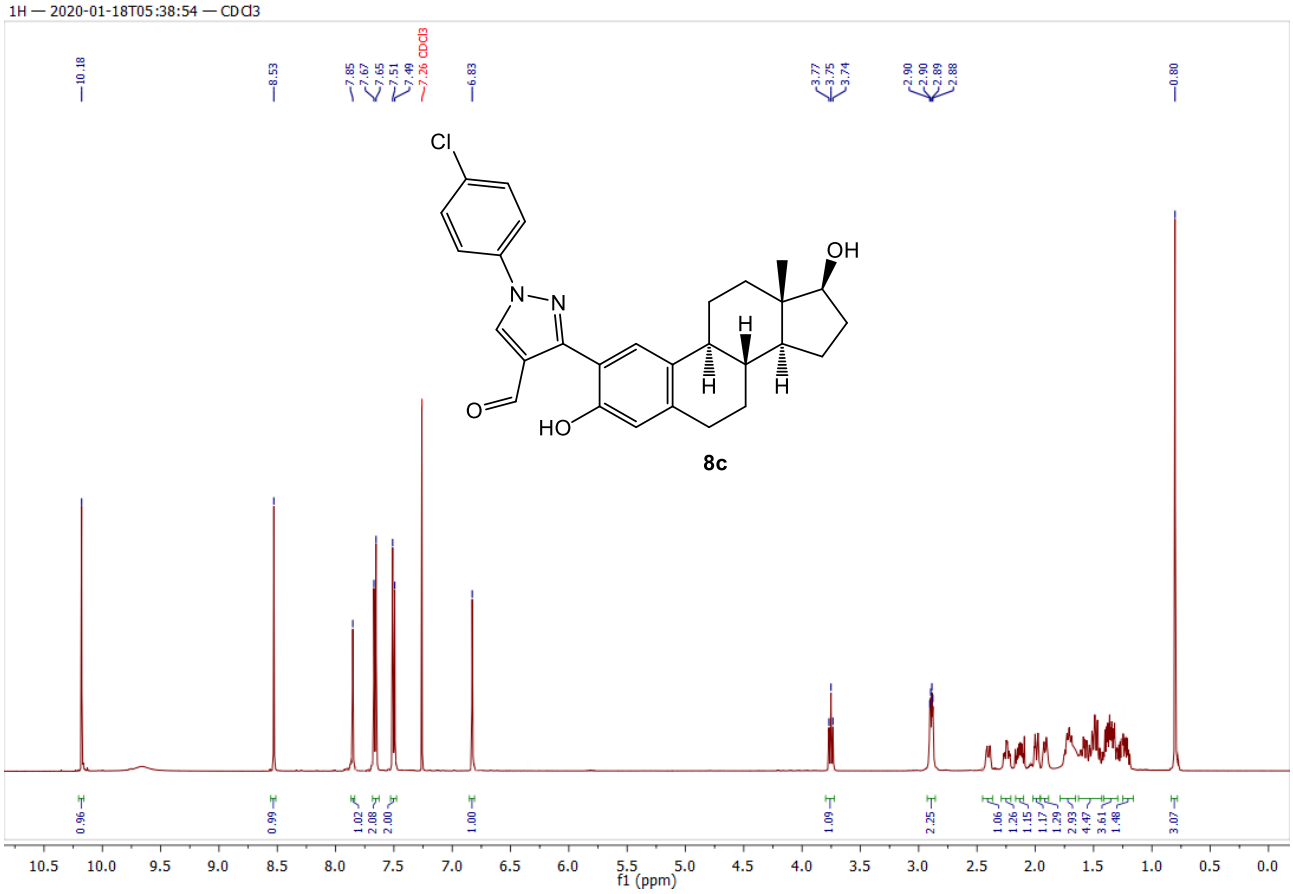

1H — 2020-01-18T05:02:16 — CDCl3
10.20
8.57
7.90
7.73
7.73
7.72
7.71
7.55
7.55
7.54
7.52
7.44
7.43
7.41
7.26 CDCl3
6.83
3.77
3.76
3.74
2.91
2.90
2.89
2.88
0.81
OH
N
N
H
H
H
O
HO
8a
0.98
1.00
1.11
2.17
2.12
1.12
1.00
1.0
1.04
2.15
1.11
1.15
1.31
2.65
2.04
3.29
f1 (ppm)


13C — 2020-01-18T05:15:42 — CDCl3
184.4
153.7
153.1
140.7
138.2
132.7
132.2
129.9
129.5
128.4
126.8
123.0
119.6
117.0
114.1
113.0
81.9
77.3 CDCl3
77.0 CDCl3
76.8 CDCl3
50.1
43.9
43.3
38.8
36.7
30.6
29.7
29.6
27.2
26.5
23.2
11.1
f1 (ppm)

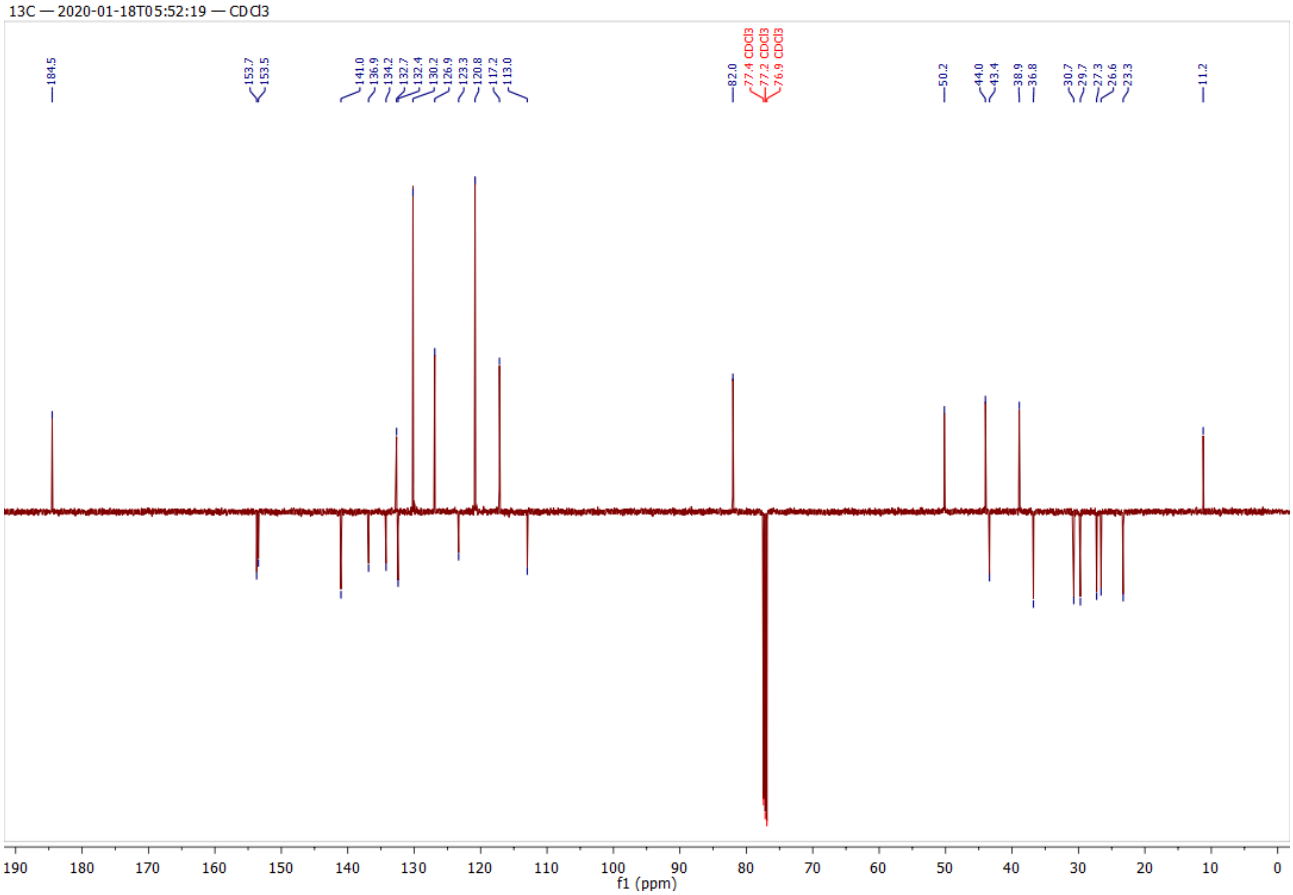

1H — 2020-01-18T05:20:28 — CDCl3
10.18
8.52
7.90
7.60
7.58
7.26 CDCl3
6.83
3.77
3.75
3.74
2.90
2.90
2.89
2.88
2.43
2.42
2.25
2.13
1.99
1.91
1.71
1.62
1.45
1.43
1.30
0.80
OH
N
N
H
H
H
O
HO
0.99
1.00
1.05
2.07
2.01
1.00
1.14
2.00
4.19
1.15
1.28
1.19
1.21
1.65
2.93
f1 (ppm)

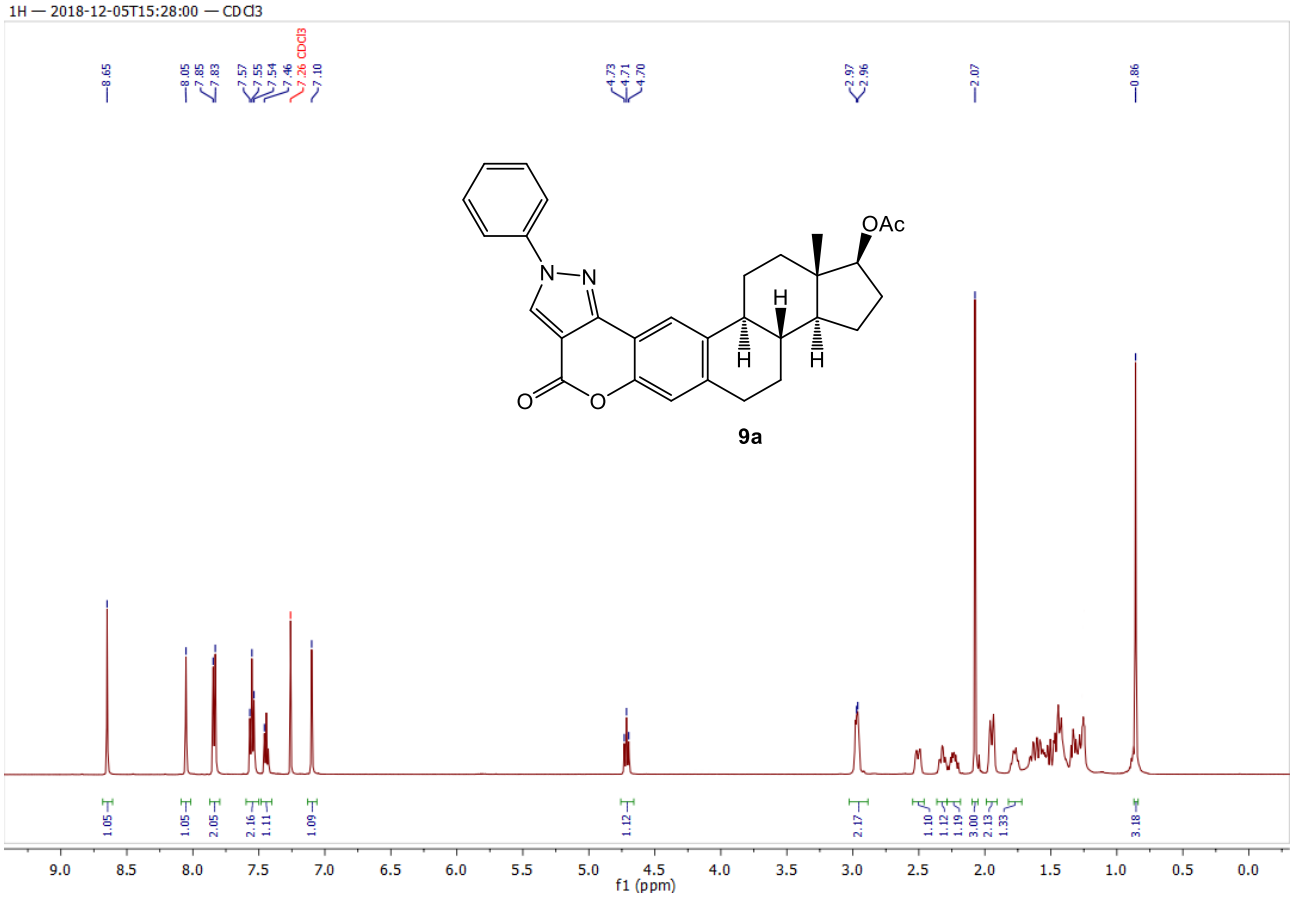
8b

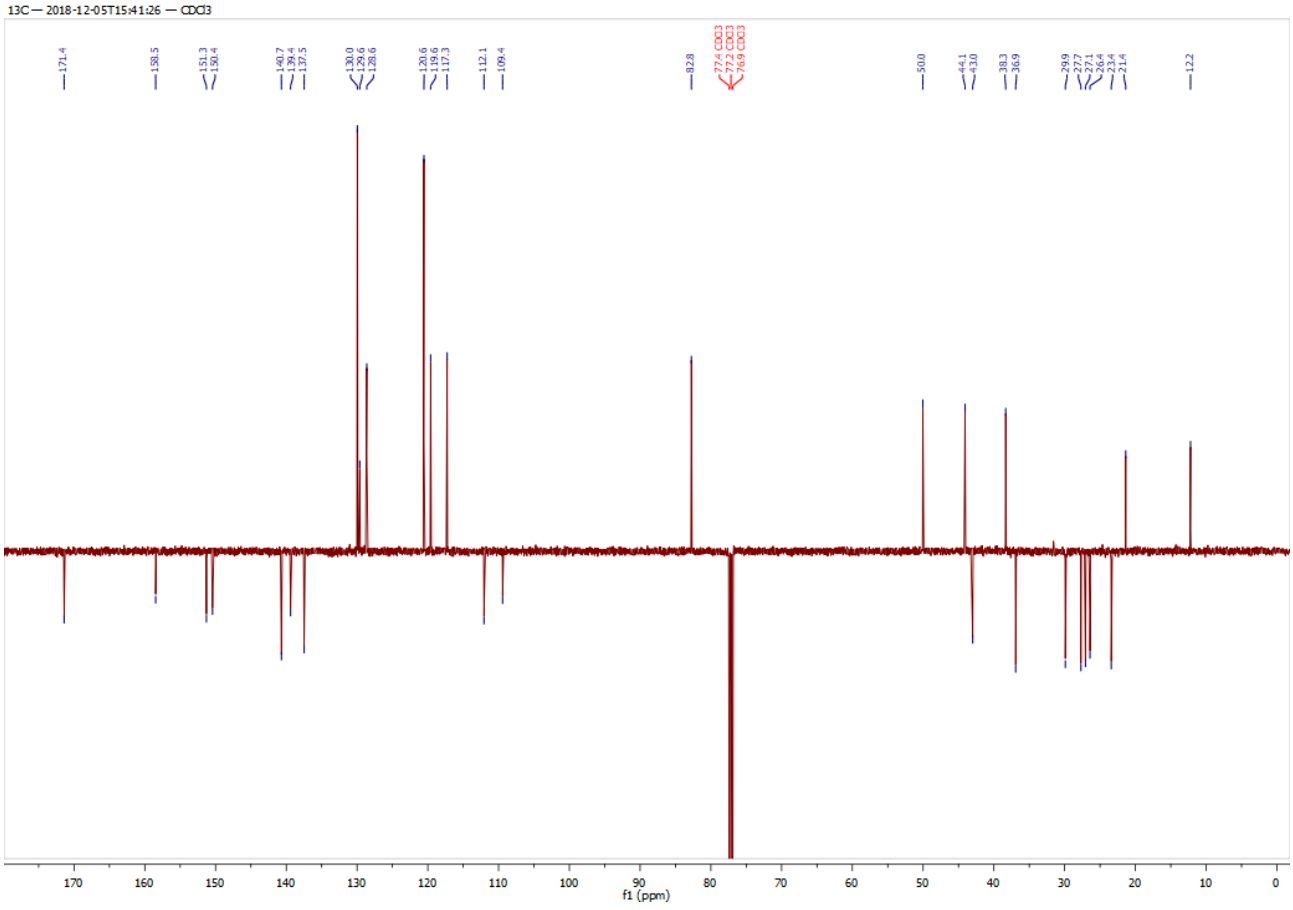

13C — 2020-01-18T05:33:53 — CDCl3
194.6
153.8
153.1
140.7
138.7
136.1
132.6
132.2
130.5
126.9
122.9
119.6
117.1
113.2
82.0
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
50.2
44.0
43.4
38.9
36.8
30.7
29.7
27.3
26.6
23.3
21.2
11.2
f1 (ppm)

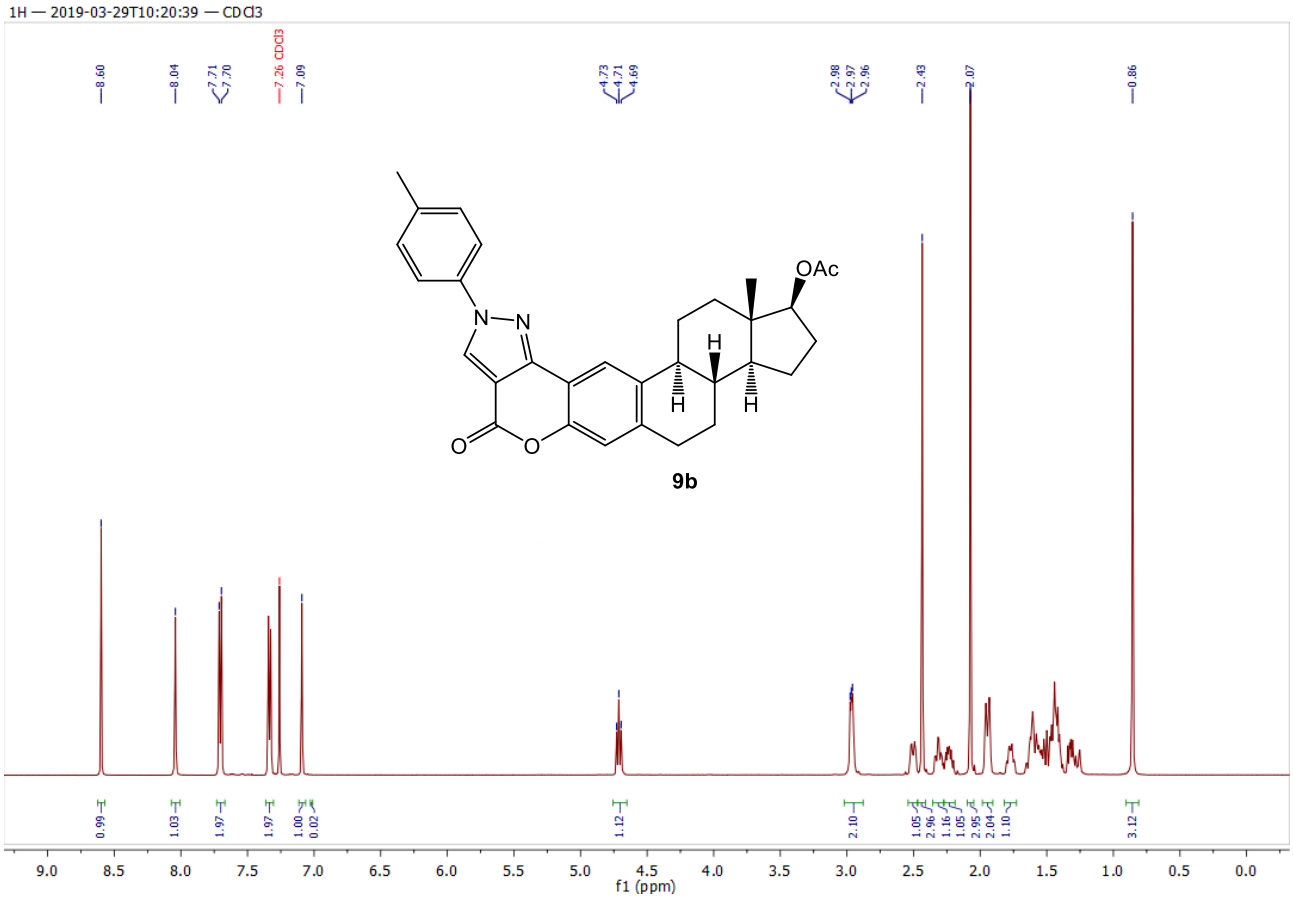

1H — 2020-01-18T05:38:54 — CDCl3
10.18
8.53
7.85
7.67
7.65
7.51
7.49
7.26 CDCl3
6.83
3.77
3.75
3.74
2.90
2.90
2.89
2.88
0.80
Cl
N
N
OH
H
H
H
O
HO
0.96
0.99
1.02
2.08
2.00
1.00
1.09
2.25
1.06
1.26
1.15
1.17
1.29
2.93
4.47
3.61
1.48
3.07
f1 (ppm)

8c

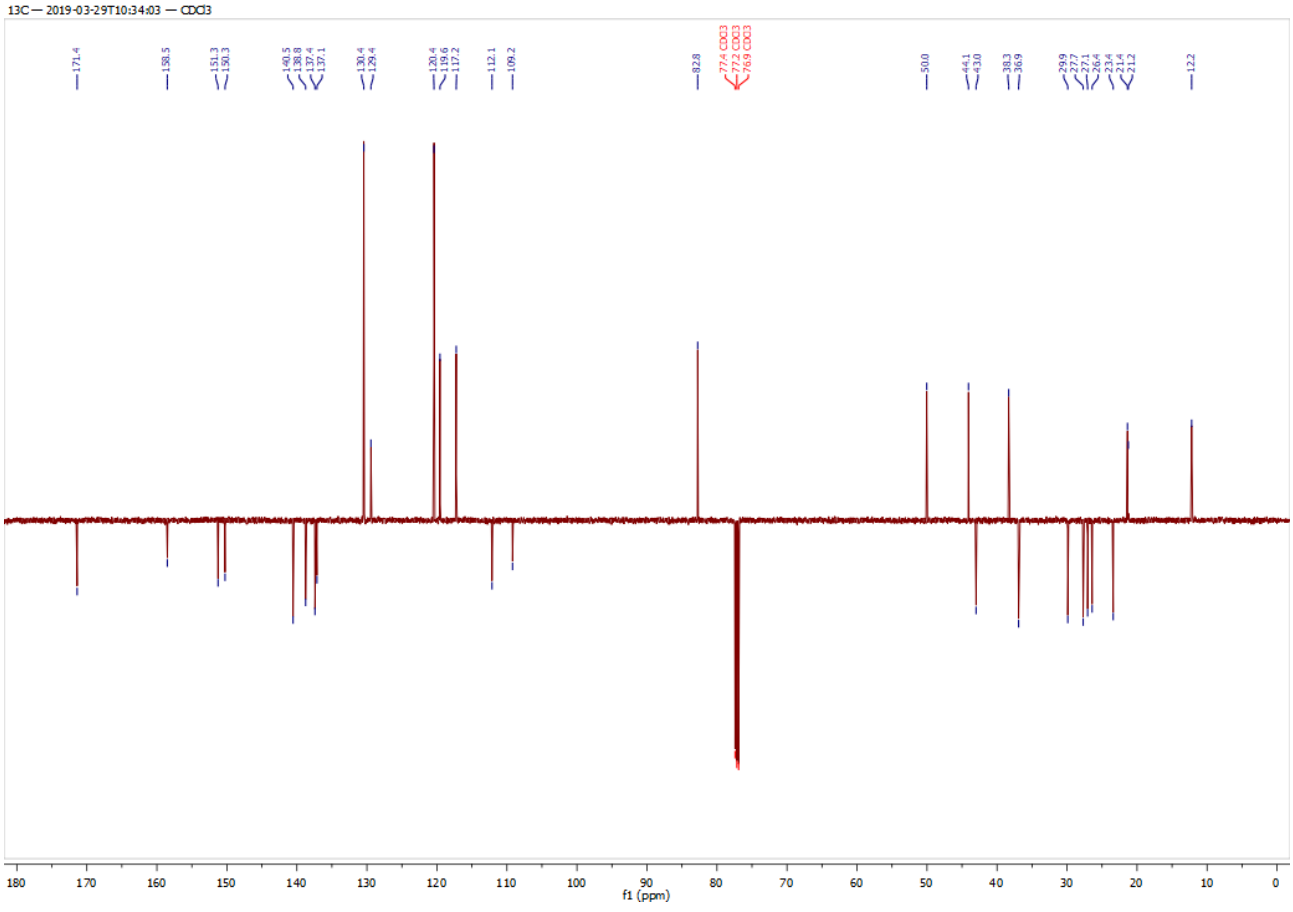

13C — 2020-01-18T05:52:19 — CDCl3
184.5
153.7
153.5
141.0
136.9
134.2
132.7
132.4
130.2
126.9
123.3
120.8
117.2
113.0
82.0
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
50.2
44.0
43.4
38.9
36.8
30.7
29.7
27.3
26.6
23.3
11.2
f1 (ppm)

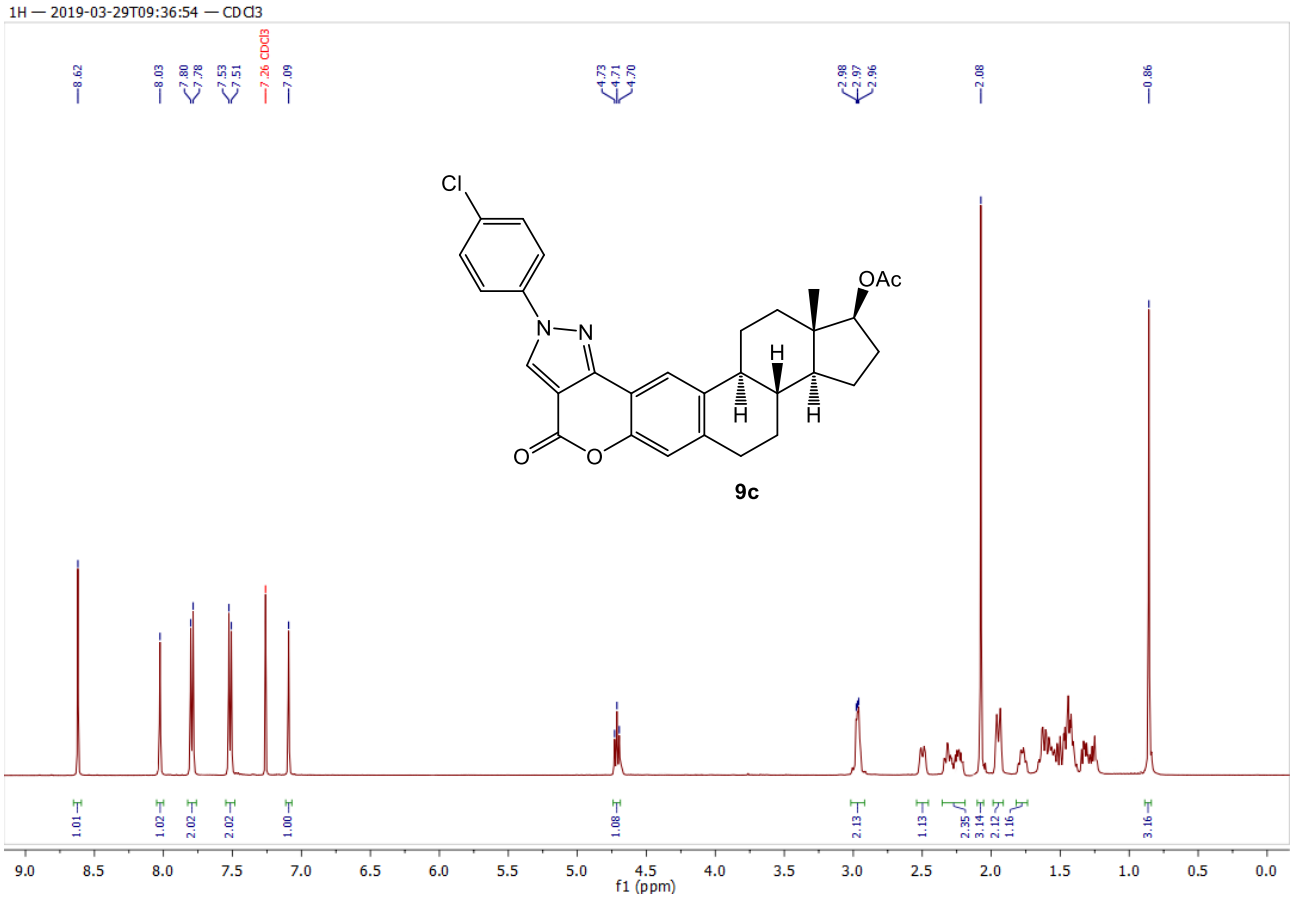

1H — 2018-12-05T15:28:00 — CDCl3
8.65
8.05
7.85
7.83
7.57
7.55
7.54
7.46
7.26 CDCl3
7.10
4.73
4.71
4.70
2.97
2.96
2.07
0.86
OAc
N
N
H
H
H
O
O
9a
1.05
1.05
2.05
2.16
1.11
1.09
1.12
2.17
1.10
1.12
1.19
3.00
2.13
1.33
3.18
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


13C — 2018-12-05T15:41:26 — CDCl3
171.4
158.5
151.3
150.4
140.7
139.4
137.5
130.0
129.6
128.6
120.6
119.6
117.3
112.1
109.4
82.8
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
50.0
44.1
43.0
38.3
36.9
29.9
27.7
27.1
25.4
24.4
21.4
12.2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

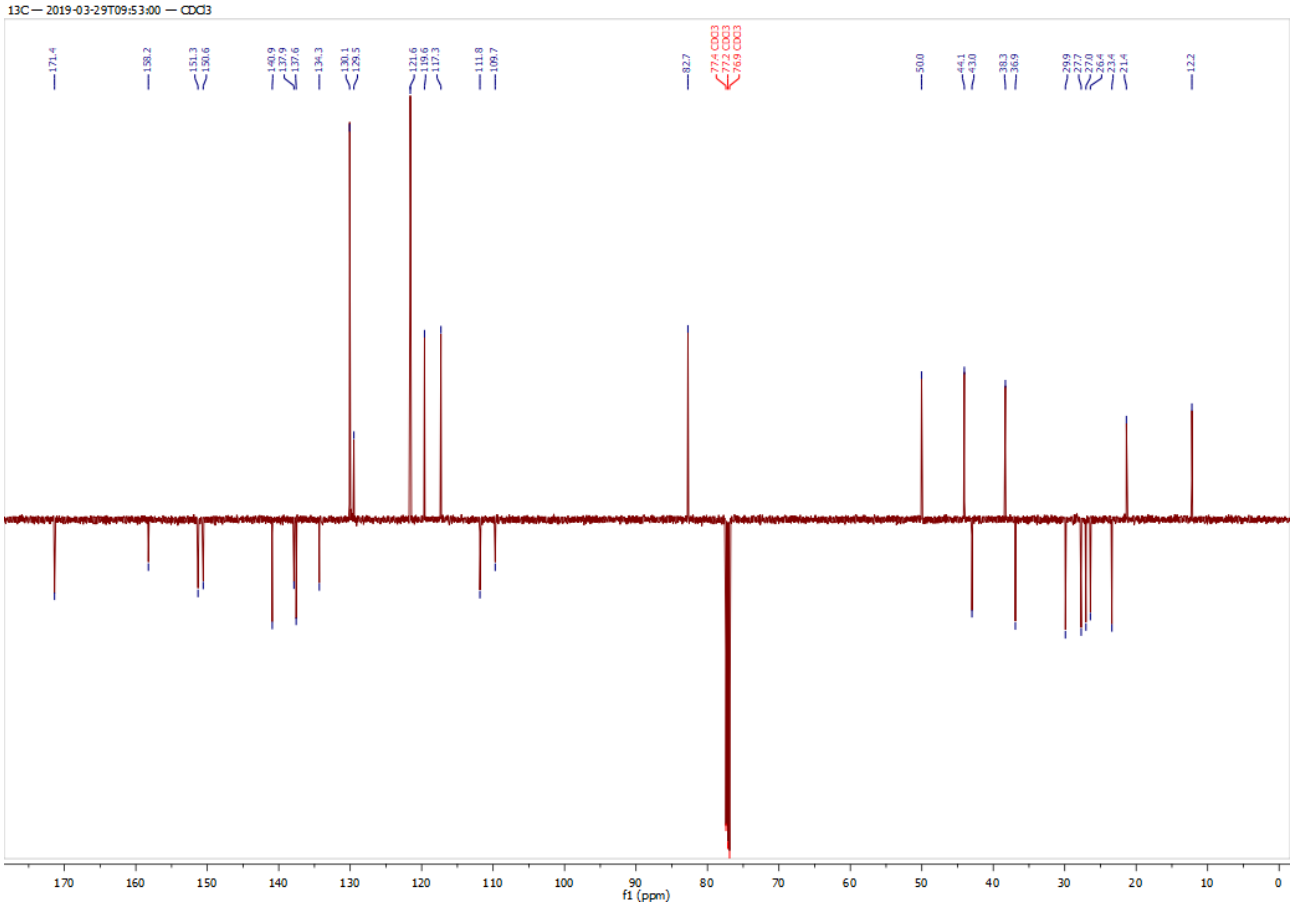

1H — 2019-03-29T10:20:39 — CDCl3
8.60
8.04
7.71
7.70
7.26 CDCl3
7.09
4.73
4.71
4.69
2.98
2.97
2.96
2.43
2.07
0.86
OAc
N
N
H
H
H
O
O
0.99
1.03
1.97
1.97
1.00
0.02
1.12
2.10
1.05
2.96
1.16
1.05
2.95
2.04
1.10
3.12
f1 (ppm)

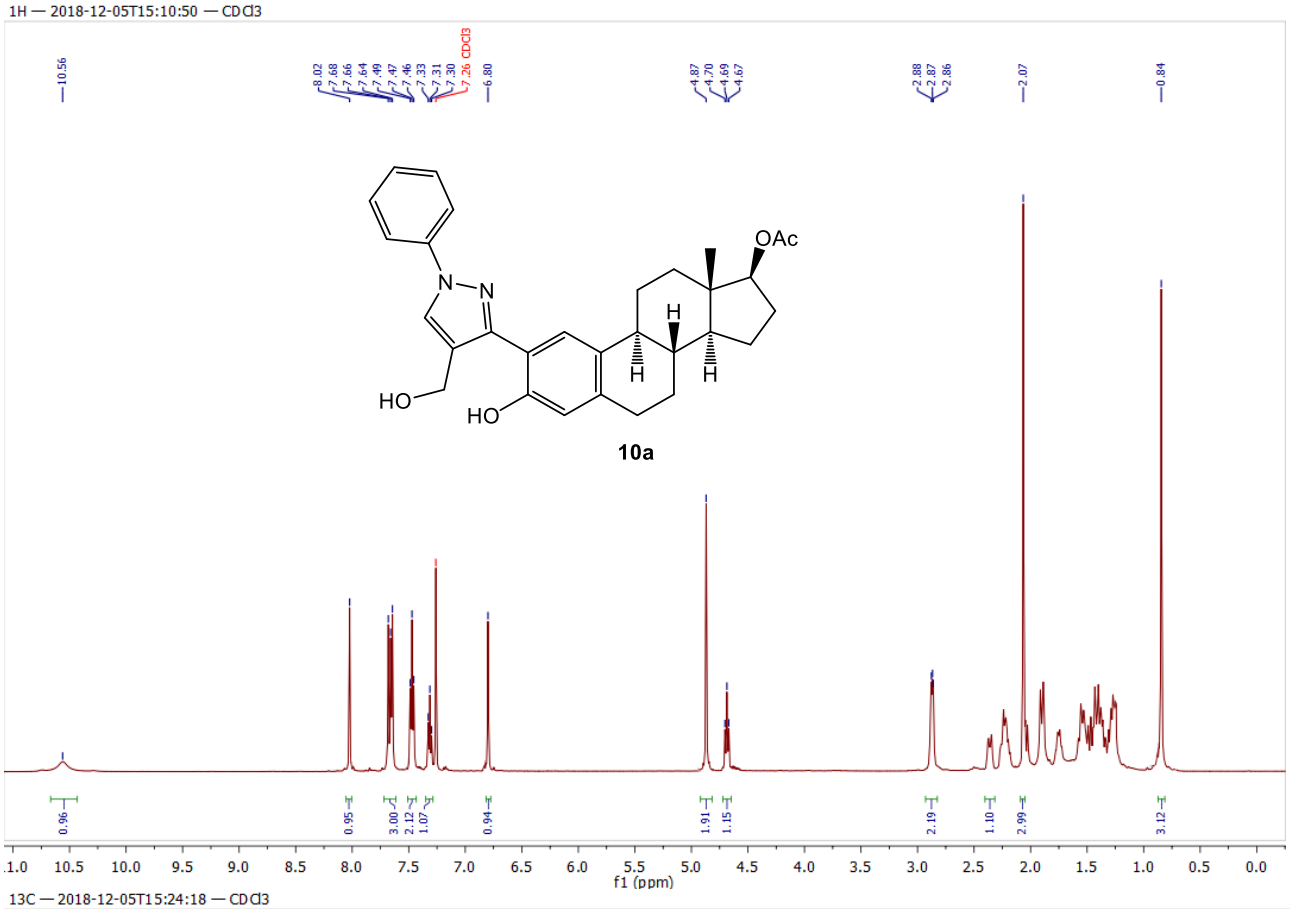
9b


13C — 2019-03-29T10:34:03 — CDCl3
171.4
150.5
151.3
150.3
140.5
138.8
137.4
137.1
130.4
129.4
120.4
119.6
117.2
112.1
109.2
82.8
77.4 CDCl3
77.3 CDCl3
76.9 CDCl3
50.0
44.1
43.0
38.3
36.9
29.9
27.7
27.1
26.4
23.4
21.4
21.2
12.2
f1 (ppm)

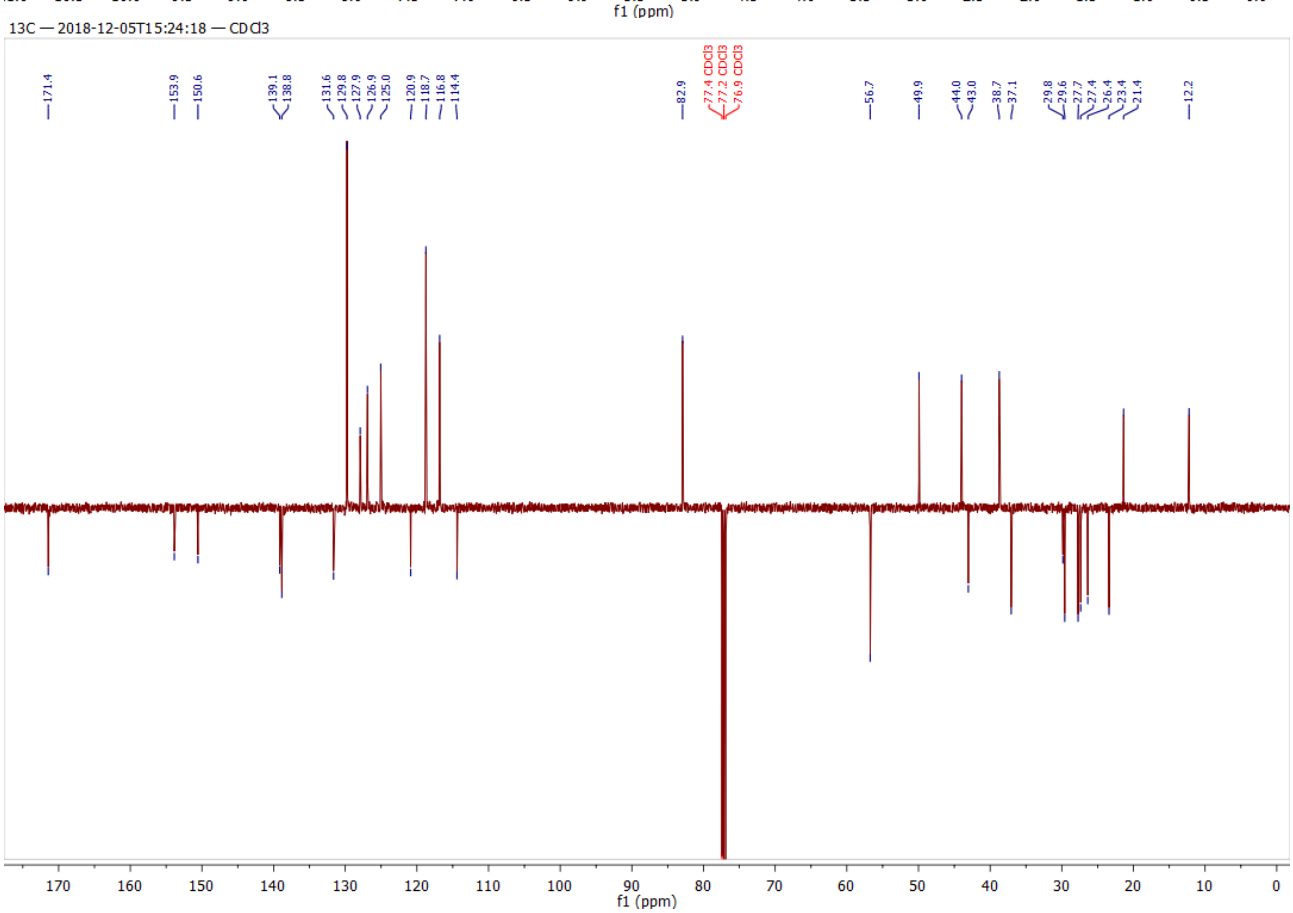

1H — 2019-03-29T09:36:54 — CDCl3
8.62
8.03
7.80
7.78
7.53
7.51
7.26 CDCl3
7.09
4.73
4.71
4.70
2.98
2.97
2.96
2.08
0.86
Cl
N
N
OAc
H
H
H
O
O
1.01
1.02
2.02
2.02
1.00
1.08
2.13
1.13
2.35
3.14
2.12
1.16
3.16
f1 (ppm)

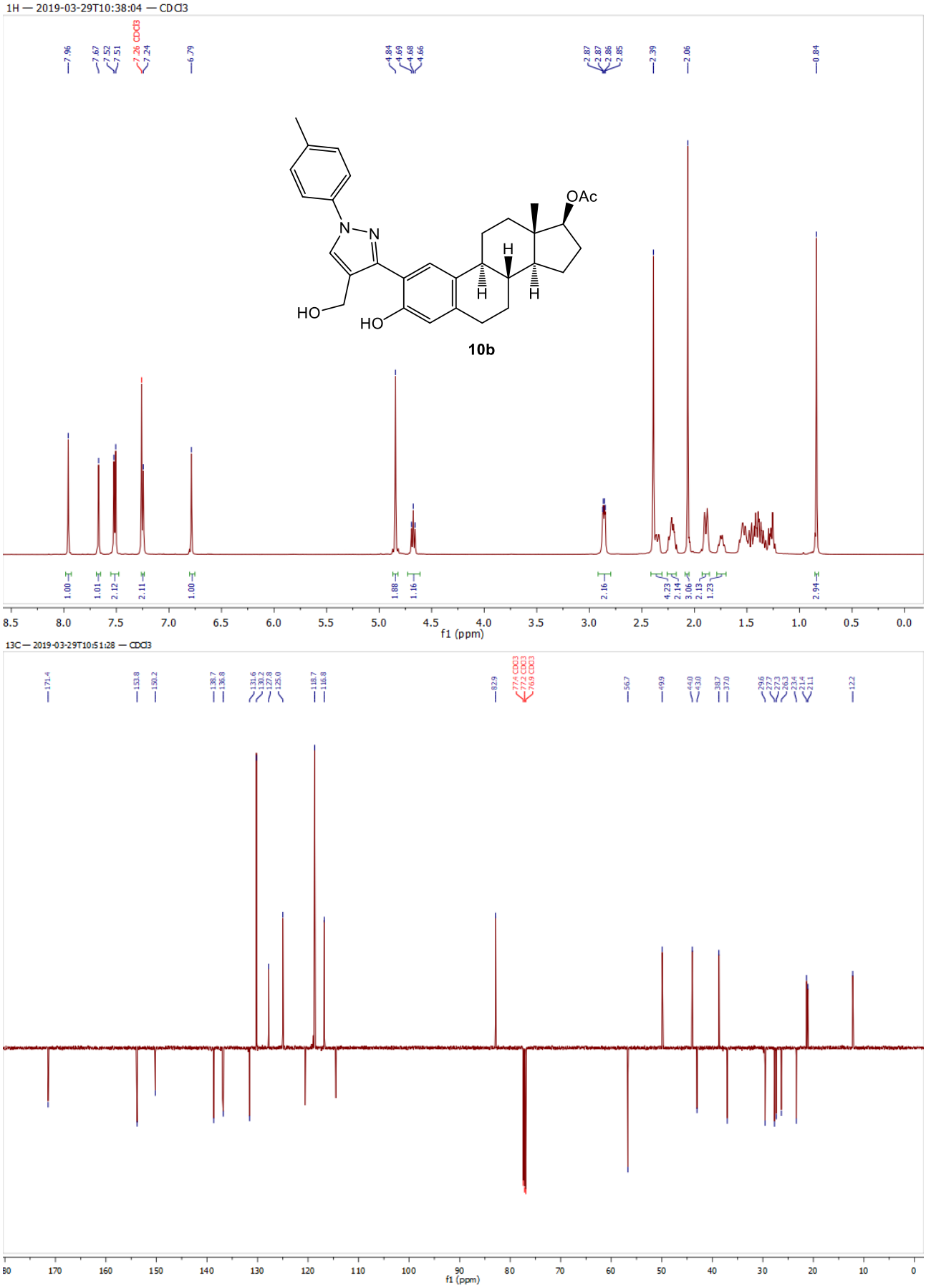
9c

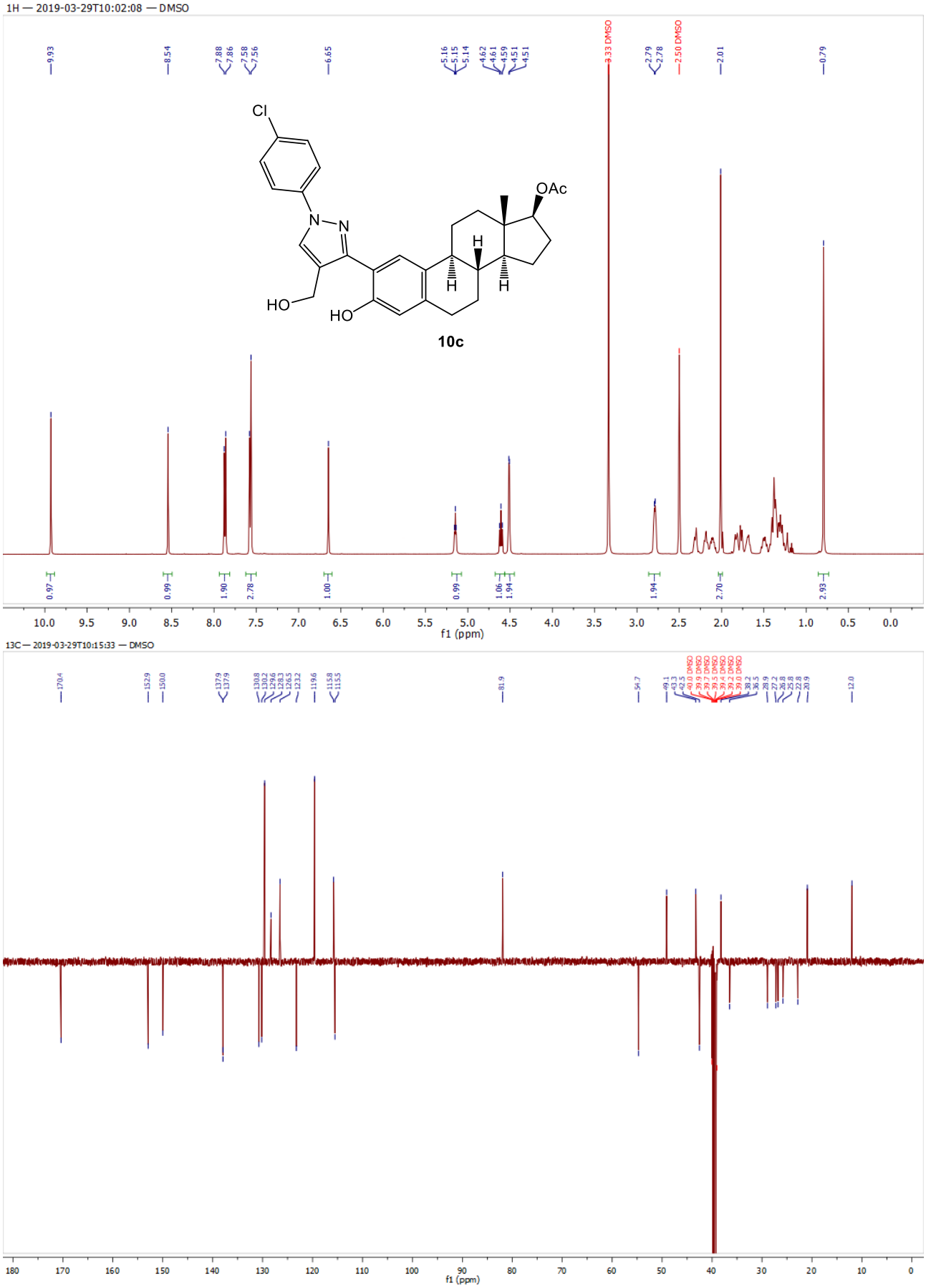

13C — 2019-03-29T09:53:00 — CDCl3
171.4
158.2
151.3
150.6
140.9
137.9
137.6
134.3
130.1
125.5
121.6
119.6
117.3
111.8
109.7
82.7
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
50.0
44.1
43.0
38.3
36.9
29.9
27.7
27.0
26.4
23.4
21.4
12.2
f1 (ppm)

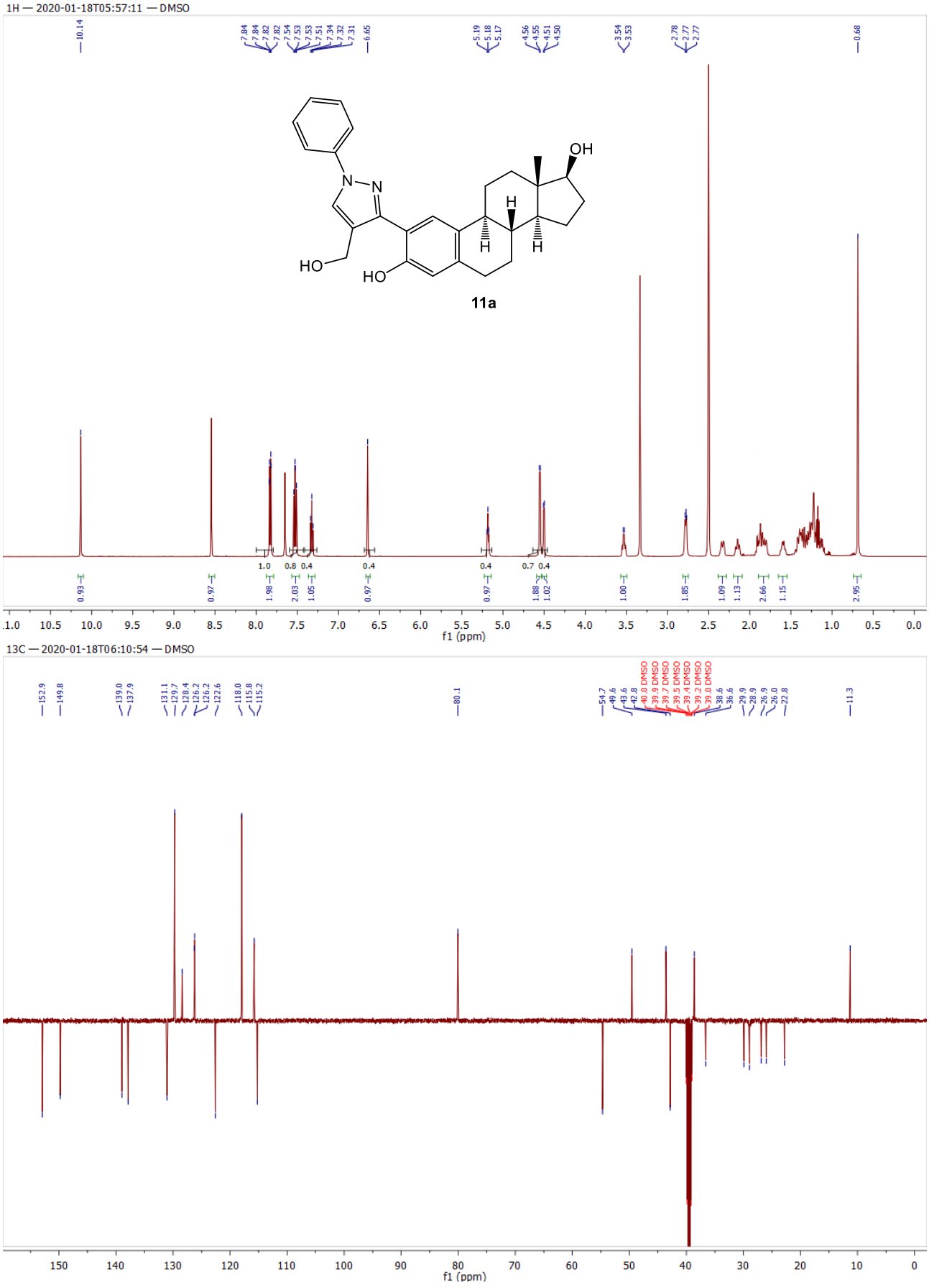

1H — 2018-12-05T15:10:50 — CDCl3
10.56
8.02
7.68
7.66
7.64
7.49
7.47
7.46
7.33
7.31
7.30
7.26 CDCl3
6.80
4.87
4.70
4.69
4.67
2.88
2.87
2.86
2.07
0.84
OAc
N
N
H
H
H
HO
HO
0.96
0.95
3.00
2.12
1.07
0.94
1.91
1.15
2.19
1.10
2.99
3.12
f1 (ppm)

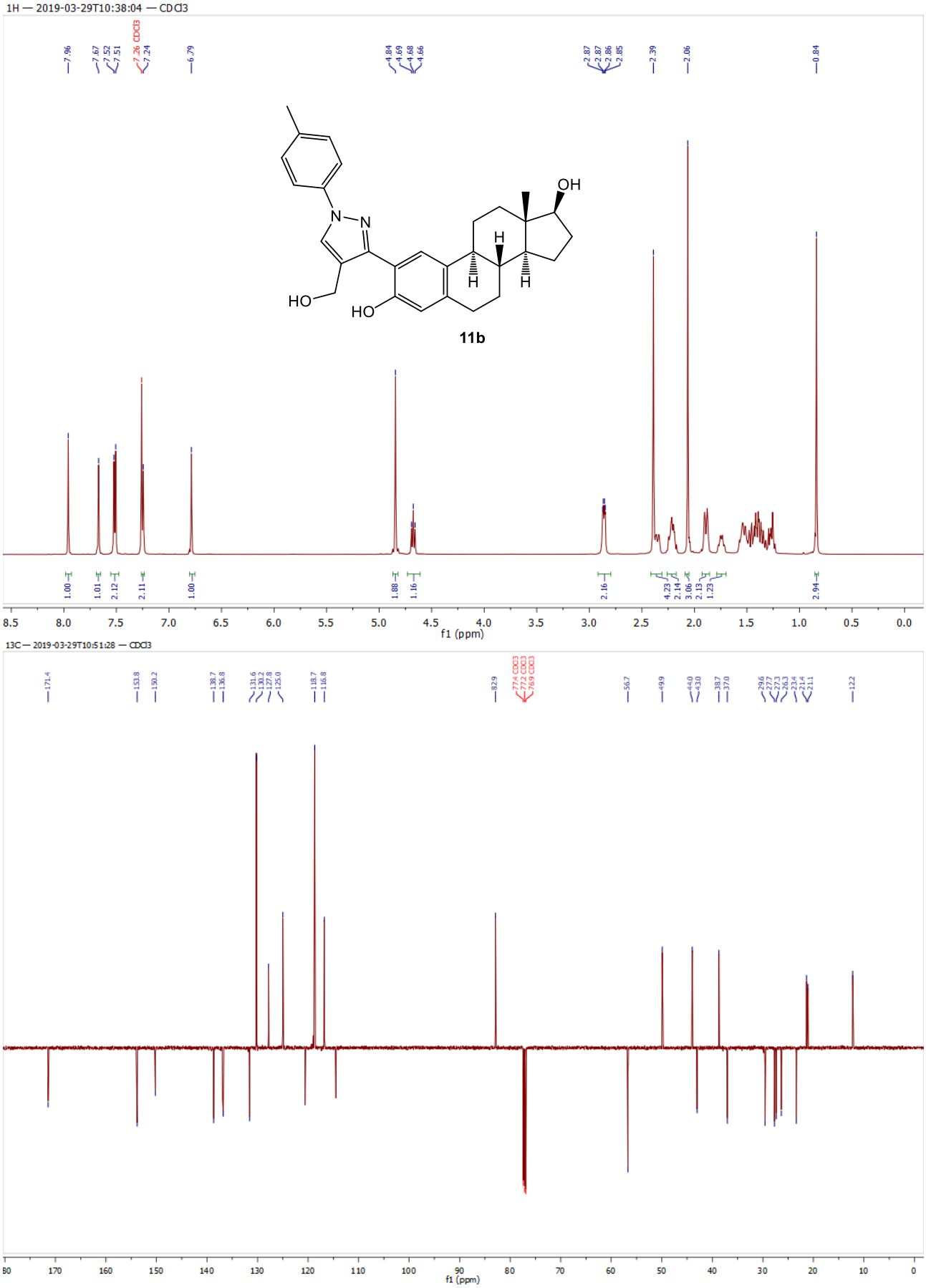
10a

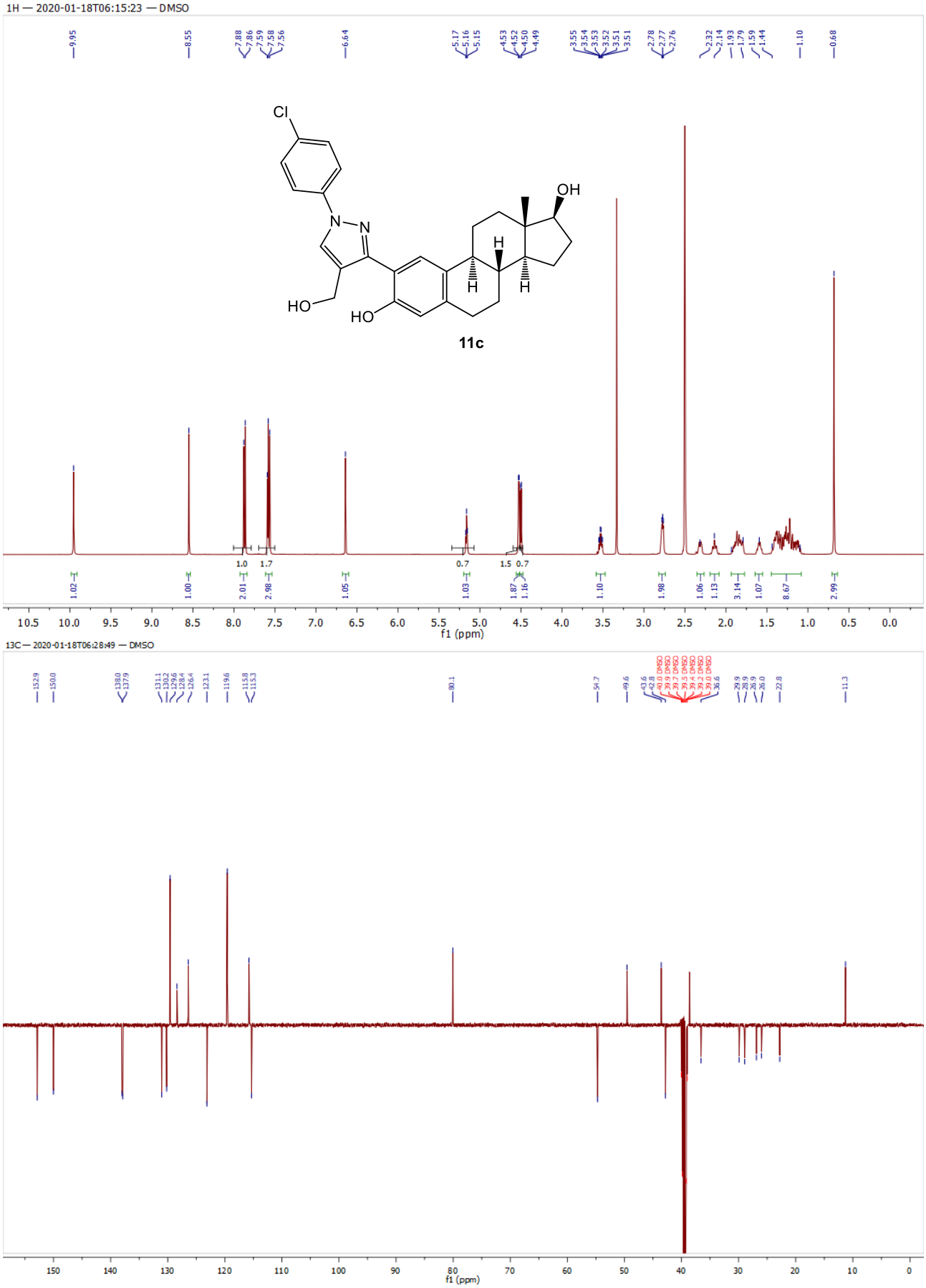

13C — 2018-12-05T15:24:18 — CDCl3
171.4
153.9
150.6
139.1
138.8
131.6
129.8
127.9
126.9
125.0
120.9
118.7
116.8
114.4
82.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
56.7
49.9
44.0
43.0
38.7
37.1
29.8
29.6
27.7
27.4
26.4
23.4
21.4
12.2
f1 (ppm)

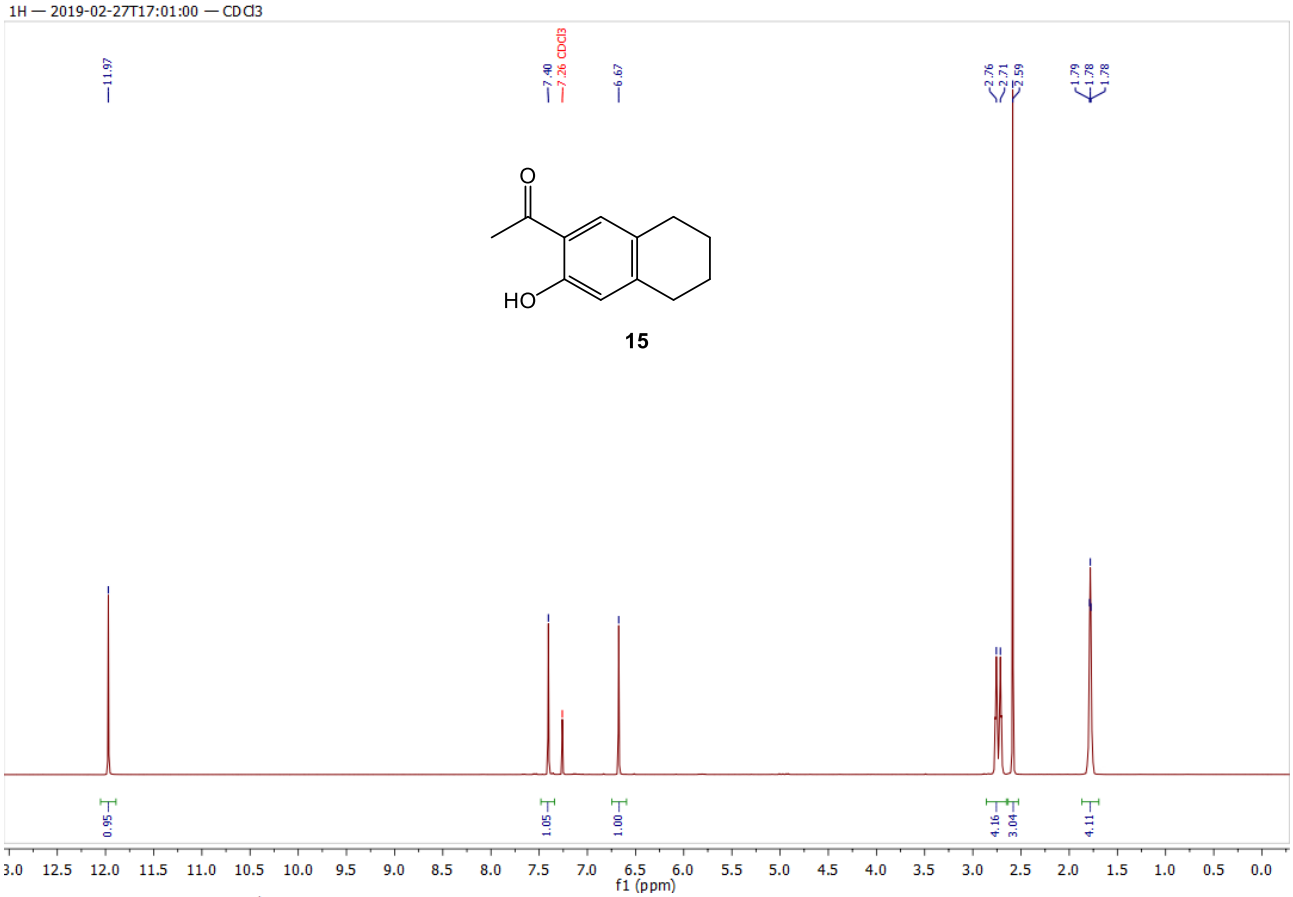

1H — 2019-03-29T10:38:04 — CDCl3
7.96
7.67
7.52
7.51
7.26 CDCl3
7.24
6.79
4.84
4.69
4.68
4.66
2.87
2.87
2.86
2.85
2.39
2.06
0.84
OAc
N
N
H
H
H
HO
HO
10b
1.00
1.01
2.12
2.11
1.00
1.88
1.16
2.16
4.23
2.14
3.06
2.13
1.23
2.94
f1 (ppm)
13C — 2019-03-29T10:51:28 — CDCl3
171.4
153.8
150.2
138.7
136.8
131.6
130.2
127.8
125.0
118.7
116.8
82.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
56.7
49.9
44.0
43.0
38.7
37.0
29.6
27.7
27.3
26.3
23.4
21.4
21.1
12.2
f1 (ppm)


1H — 2019-03-29T10:02:08 — DMSO
9.93
8.54
7.88
7.86
7.58
7.56
6.65
5.16
5.15
5.14
4.62
4.61
4.59
4.51
4.51
3.33 DMSO
2.79
2.78
2.50 DMSO
2.01
0.79
Cl
N
N
OAc
H
H
H
HO
HO
10c
0.97
0.99
1.90
2.78
1.00
0.99
1.06
1.94
1.94
2.70
2.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
13C — 2019-03-29T10:15:33 — DMSO
170.4
152.9
150.0
137.9
137.9
130.8
130.2
129.6
128.3
126.5
123.2
119.6
115.8
115.5
81.9
54.7
49.1
43.3
42.5
40.0 DMSO
39.9 DMSO
39.7 DMSO
39.5 DMSO
39.4 DMSO
39.2 DMSO
39.0 DMSO
38.2
36.5
28.9
27.2
26.8
25.8
22.8
20.9
12.0
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

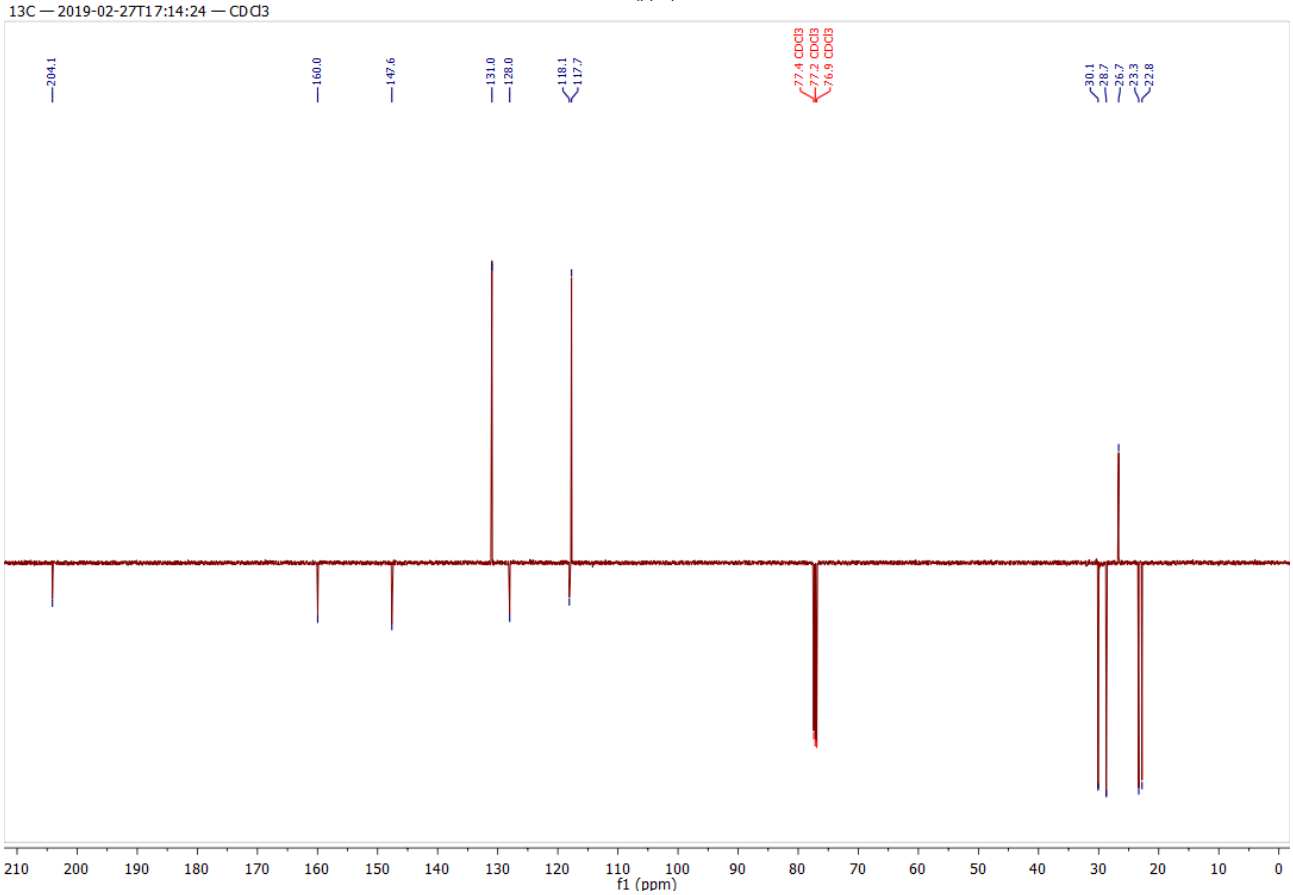

1H — 2020-01-18T05:57:11 — DMSO
OH
N
N
H
H
H
HO
HO
11a
f1 (ppm)
13C — 2020-01-18T06:10:54 — DMSO
f1 (ppm)

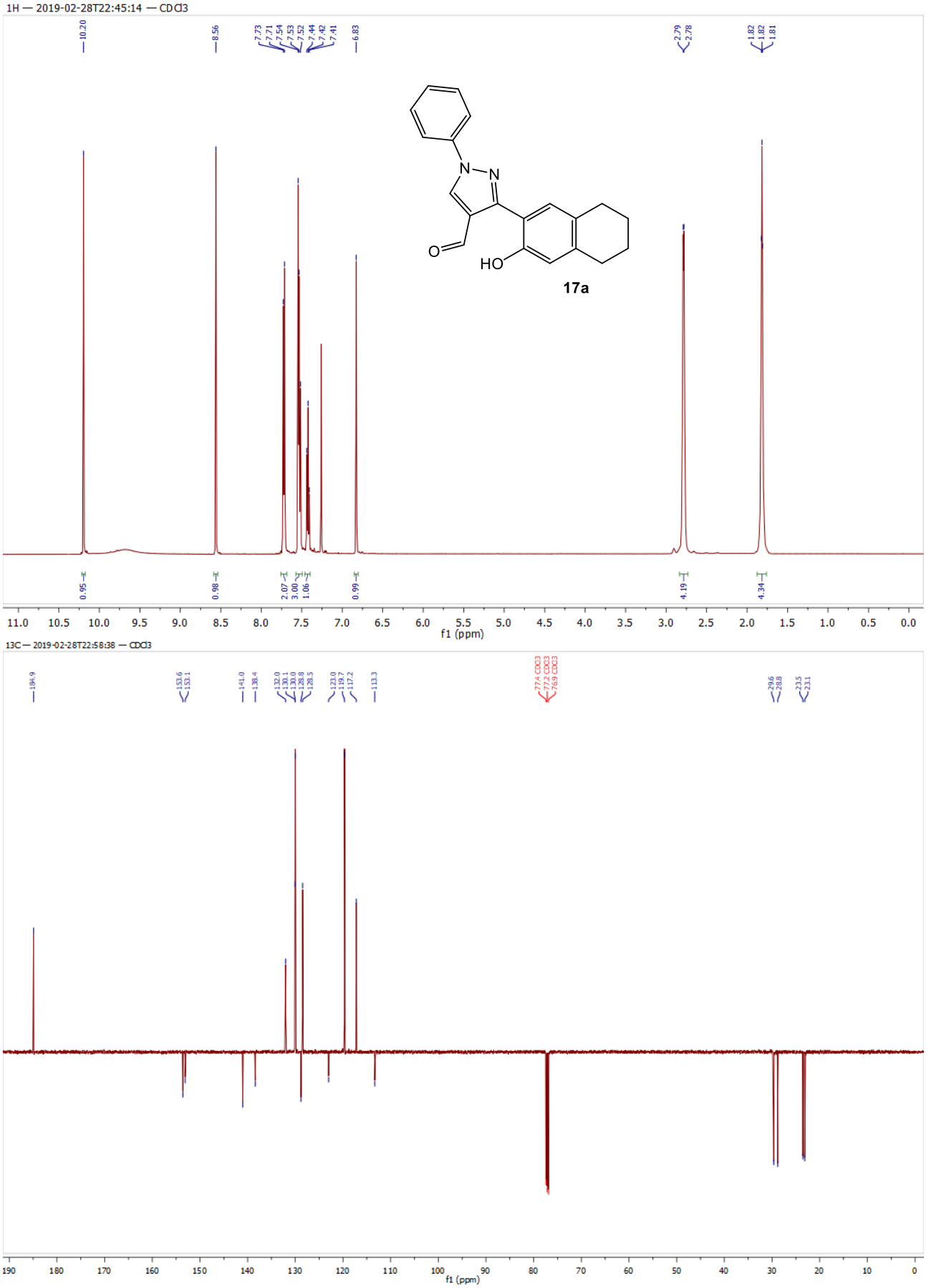

1H — 2019-03-29T10:38:04 — CDCl3
7.96
7.67
7.52
7.51
7.26 CDCl3
7.24
6.79
4.84
4.69
4.68
4.66
2.87
2.87
2.86
2.85
2.39
2.06
0.84
OH
N
N
H
H
H
HO
HO
11b
1.00
1.01
2.12
2.11
1.00
1.88
1.16
2.16
4.23
2.14
3.06
2.13
1.23
2.94
f1 (ppm)
13C — 2019-03-29T10:51:28 — CDCl3
171.4
153.8
150.2
138.7
136.8
131.6
130.2
127.8
125.0
118.7
116.8
82.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
56.7
49.9
44.0
43.0
38.7
37.0
29.6
27.7
27.3
26.3
23.4
21.4
21.1
12.2
f1 (ppm)


1H — 2020-01-18T06:15:23 — DMSO
Cl
N
N
OH
H
H
H
HO
HO
11c
f1 (ppm)
13C — 2020-01-18T06:28:49 — DMSO
f1 (ppm)


1H — 2019-02-27T17:01:00 — CDCl3
11.97
7.40
7.26 CDCl3
6.67
2.76
2.71
2.59
1.79
1.78
1.78
O
HO
0.95
1.05
1.00
4.16
3.04
4.11
f1 (ppm)

15

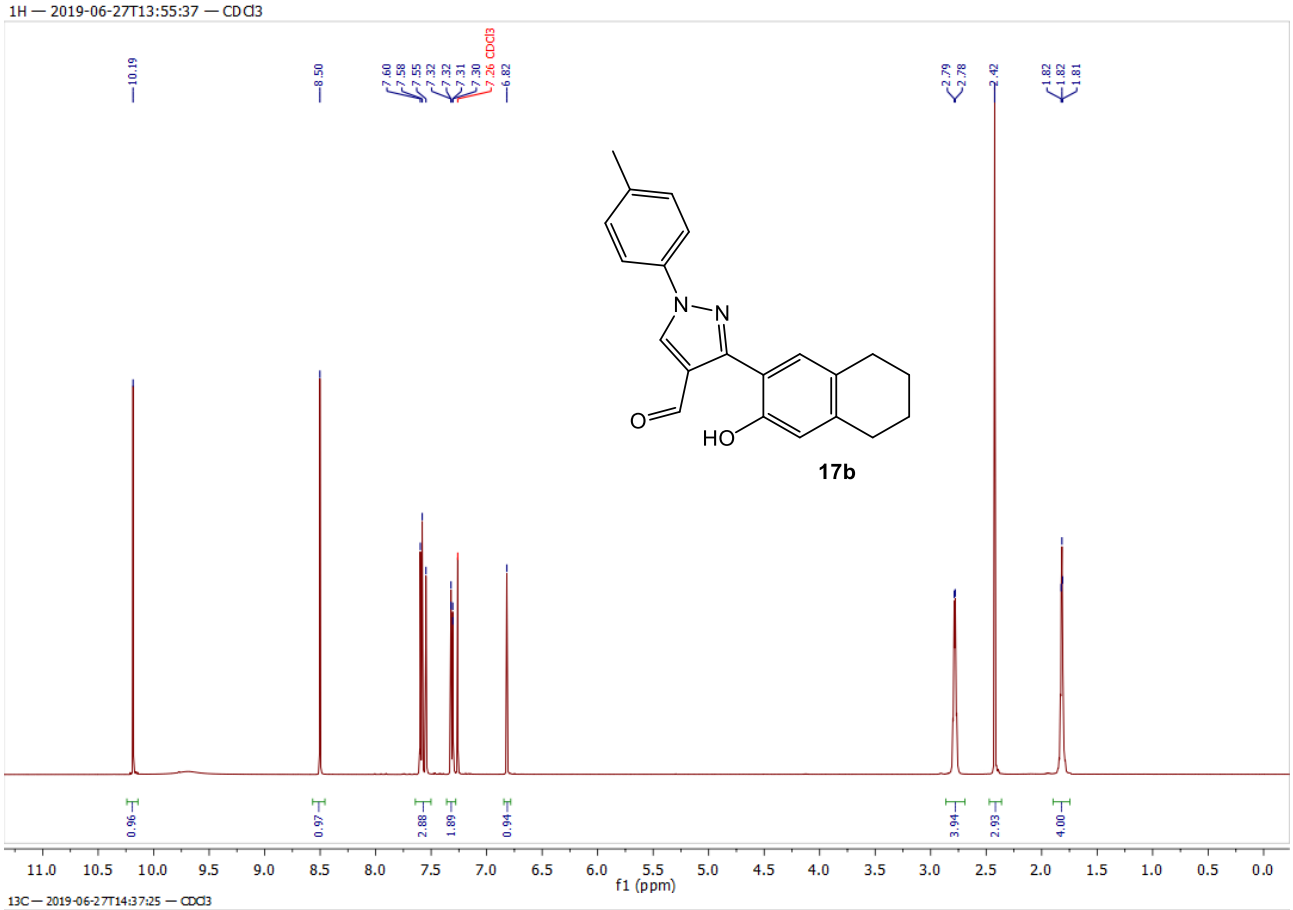

13C — 2019-02-27T17:14:24 — CDCl3
204.1
160.0
147.6
131.0
128.0
118.1
117.7
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
30.1
28.7
26.7
23.3
22.8
f1 (ppm)


1H — 2019-02-28T22:45:14 — CDCl3
10.20
8.56
7.73
7.71
7.54
7.53
7.52
7.44
7.42
7.41
6.83
2.79
2.78
1.82
1.82
1.81
0.95
0.98
2.07
3.00
1.06
0.99
4.19
4.34
f1 (ppm)
13C — 2019-02-28T22:58:38 — CDCl3
184.9
153.6
153.1
141.0
138.4
132.0
131.1
130.0
128.8
128.5
123.0
119.7
117.2
113.3
77.4 CDCl3
77.0 CDCl3
76.9 CDCl3
29.6
28.8
23.5
23.1
f1 (ppm)

N
N
O
HO

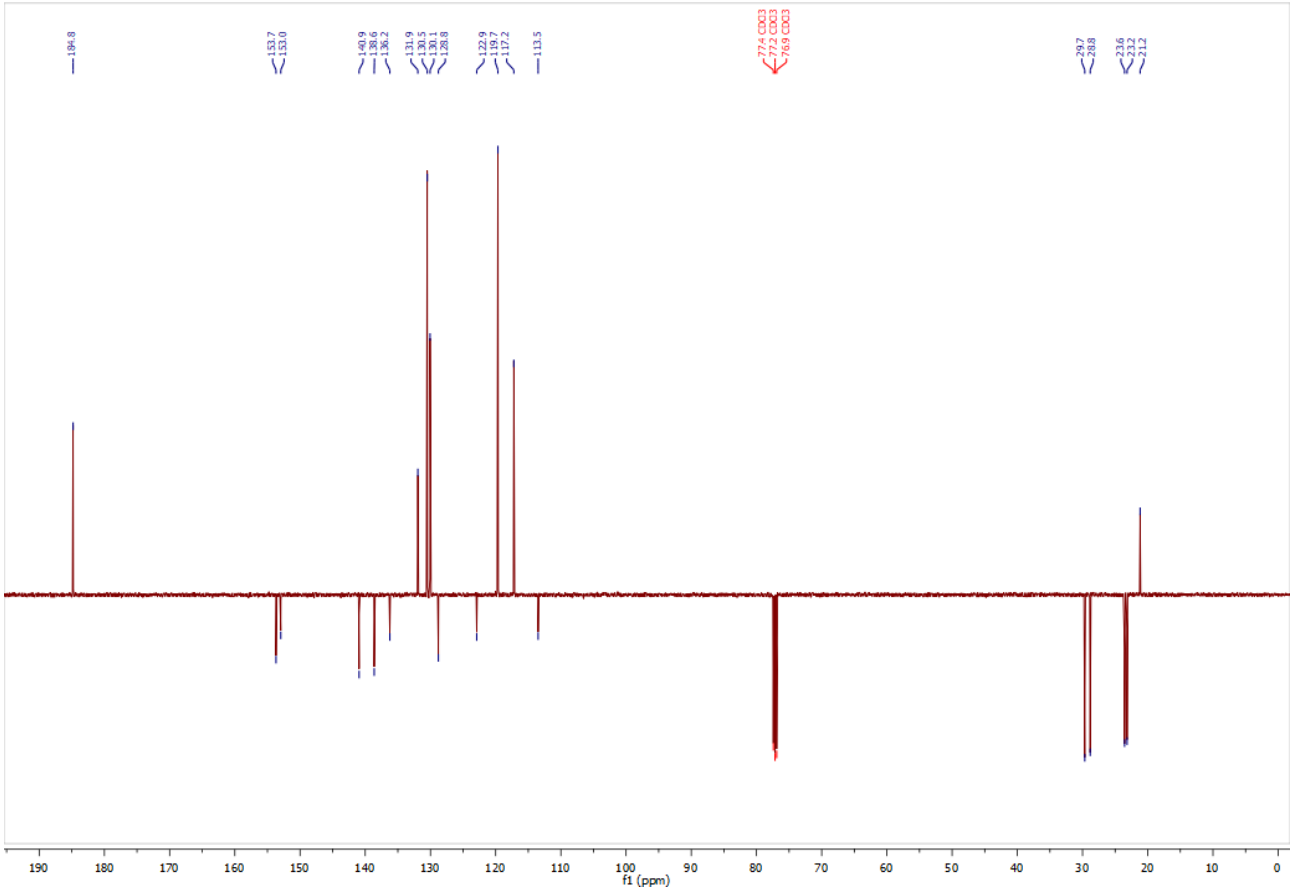
17a

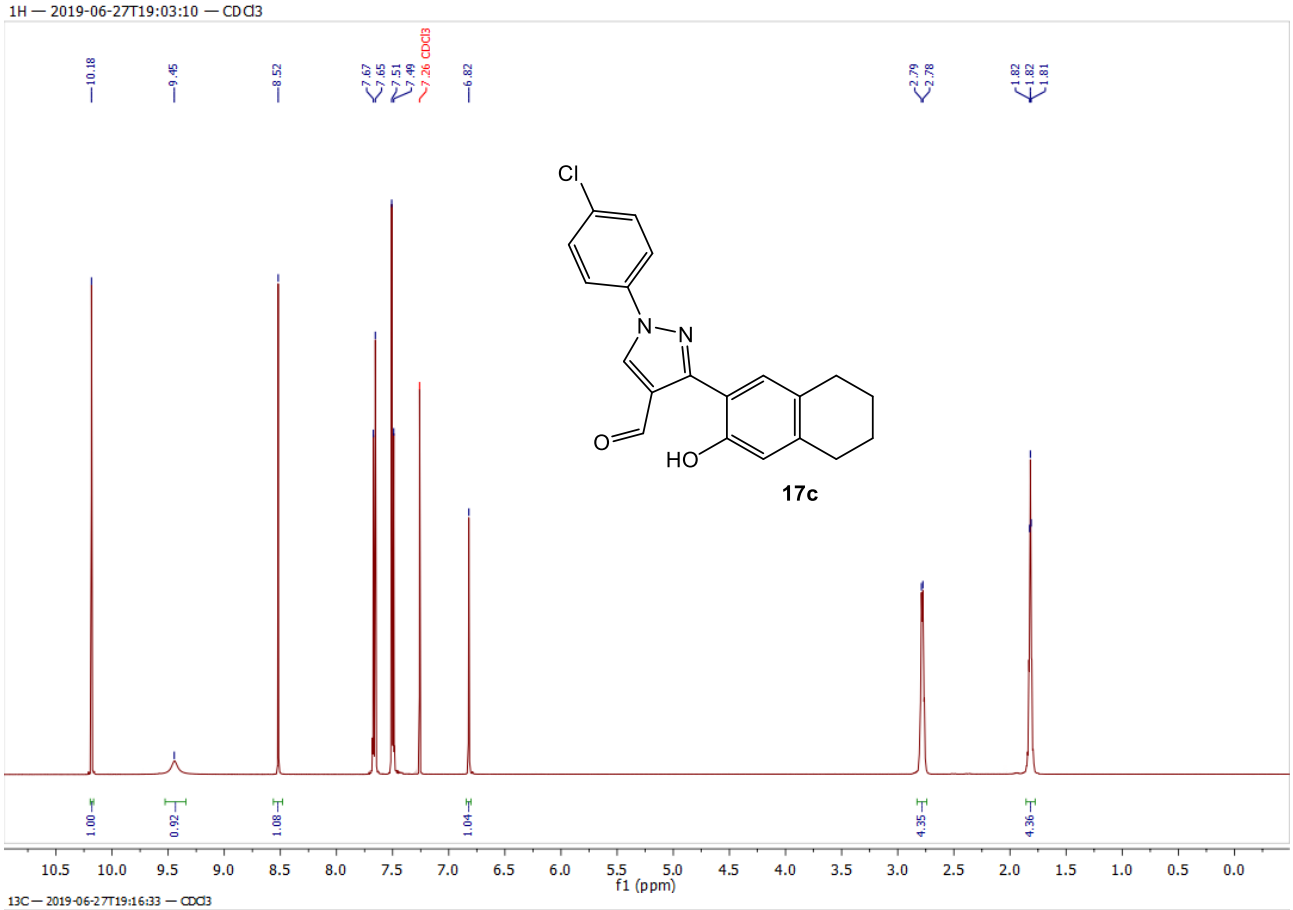
1H — 2019-06-27T13:55:37 — CDCl3

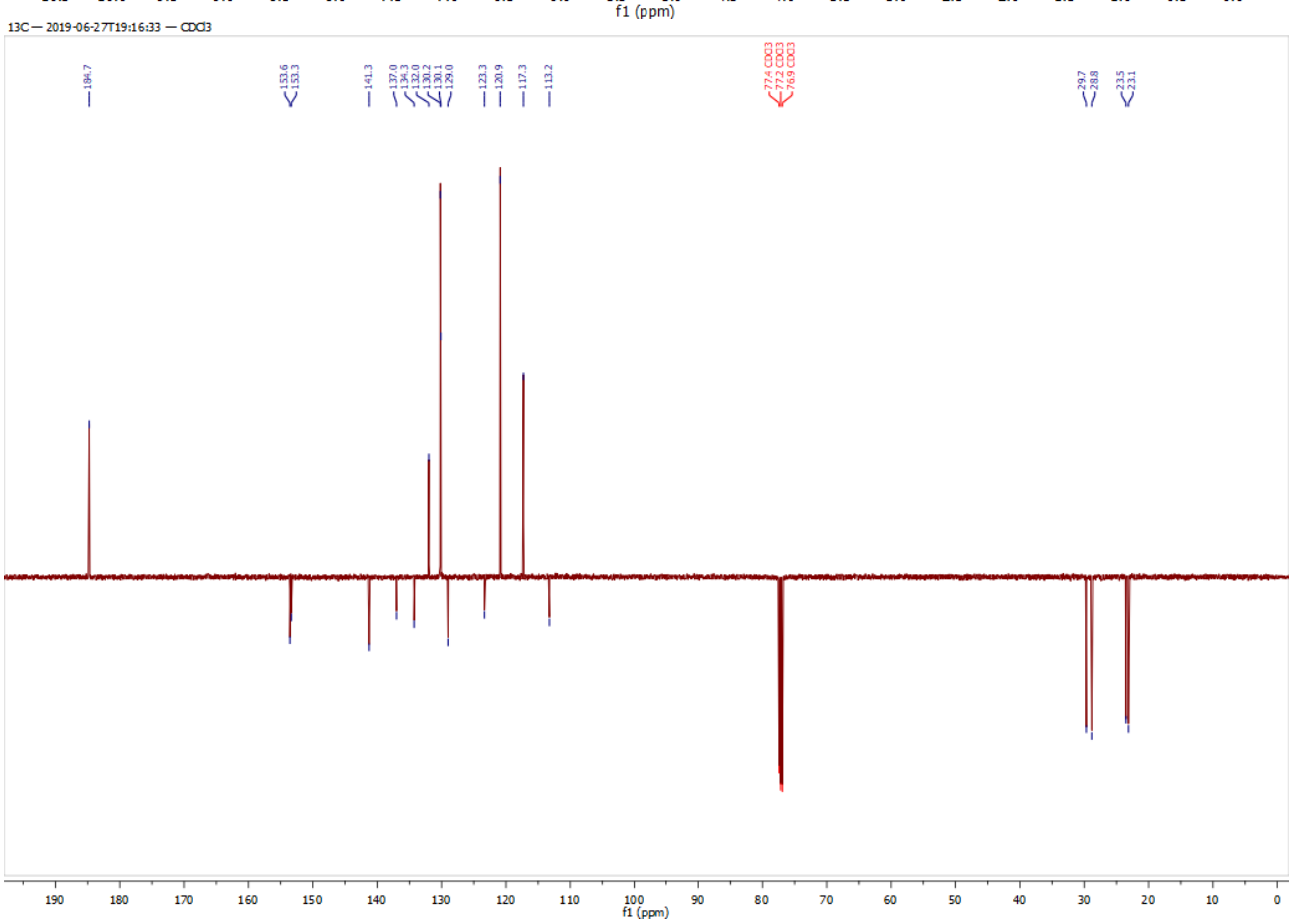


17b

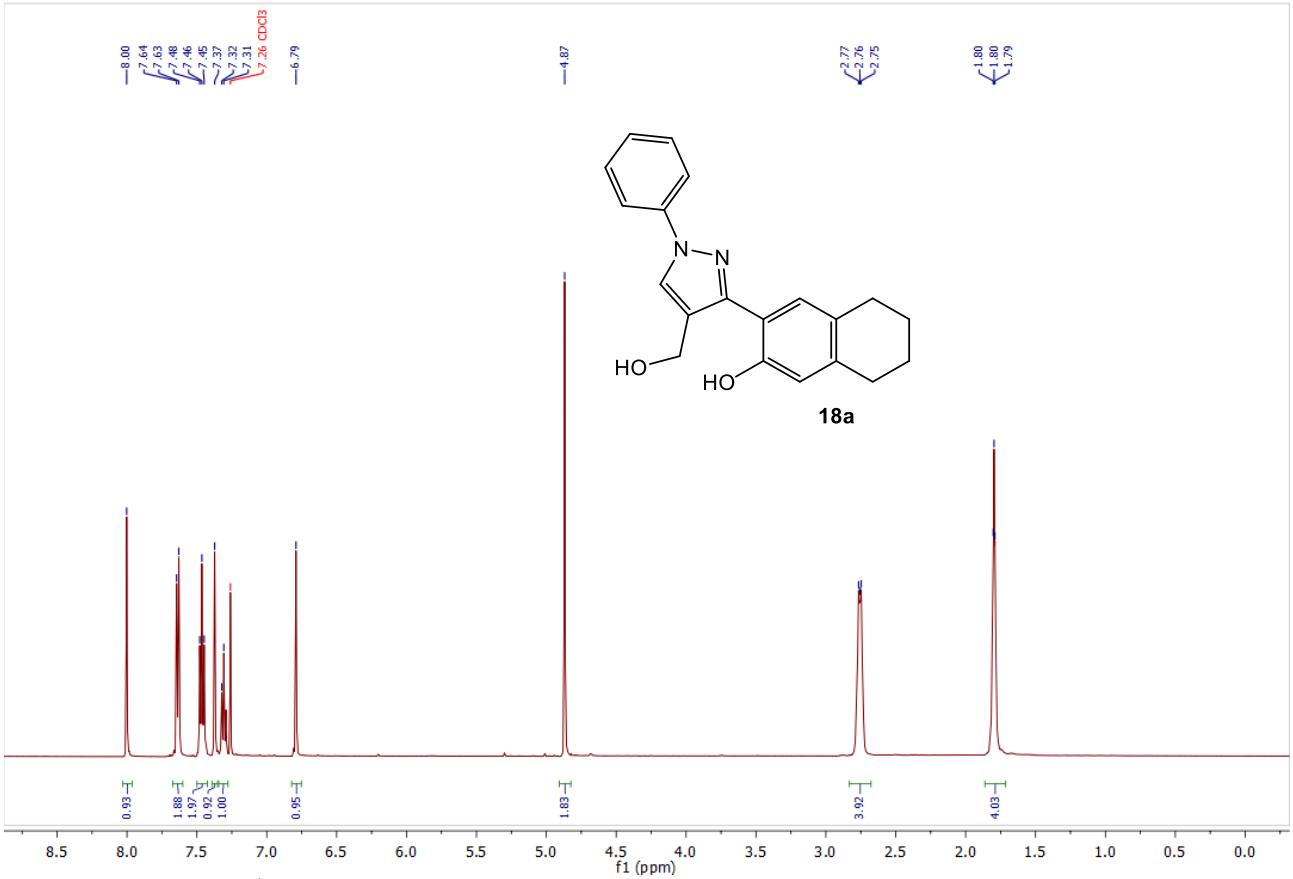
13C — 2019-06-27T14:37:25 — CDCl3




1H — 2019-06-27T19:03:10 — CDCl3
10.18
9.45
8.52
7.67
7.65
7.51
7.49
7.26 CDCl3
6.82
2.79
2.78
1.82
1.82
1.81
Cl
N
N
O
HO
17c
1.00
0.92
1.08
1.04
4.35
4.36
f1 (ppm)

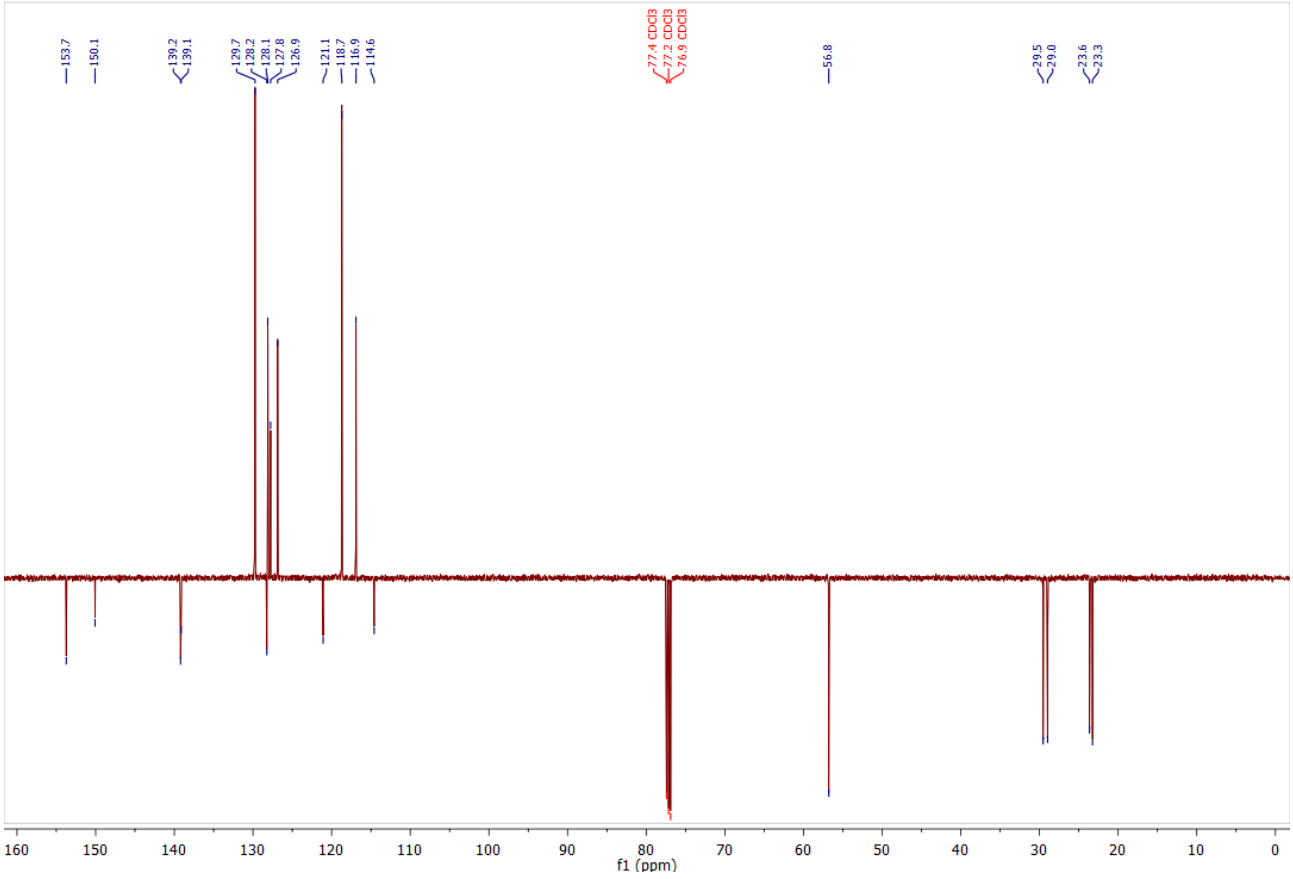

13C — 2019-06-27T19:16:33 — CDCl3
194.7
153.6
153.3
141.3
137.0
134.3
132.0
130.2
130.1
129.0
123.3
120.9
117.3
113.2
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
29.7
28.8
23.5
23.1
f1 (ppm)

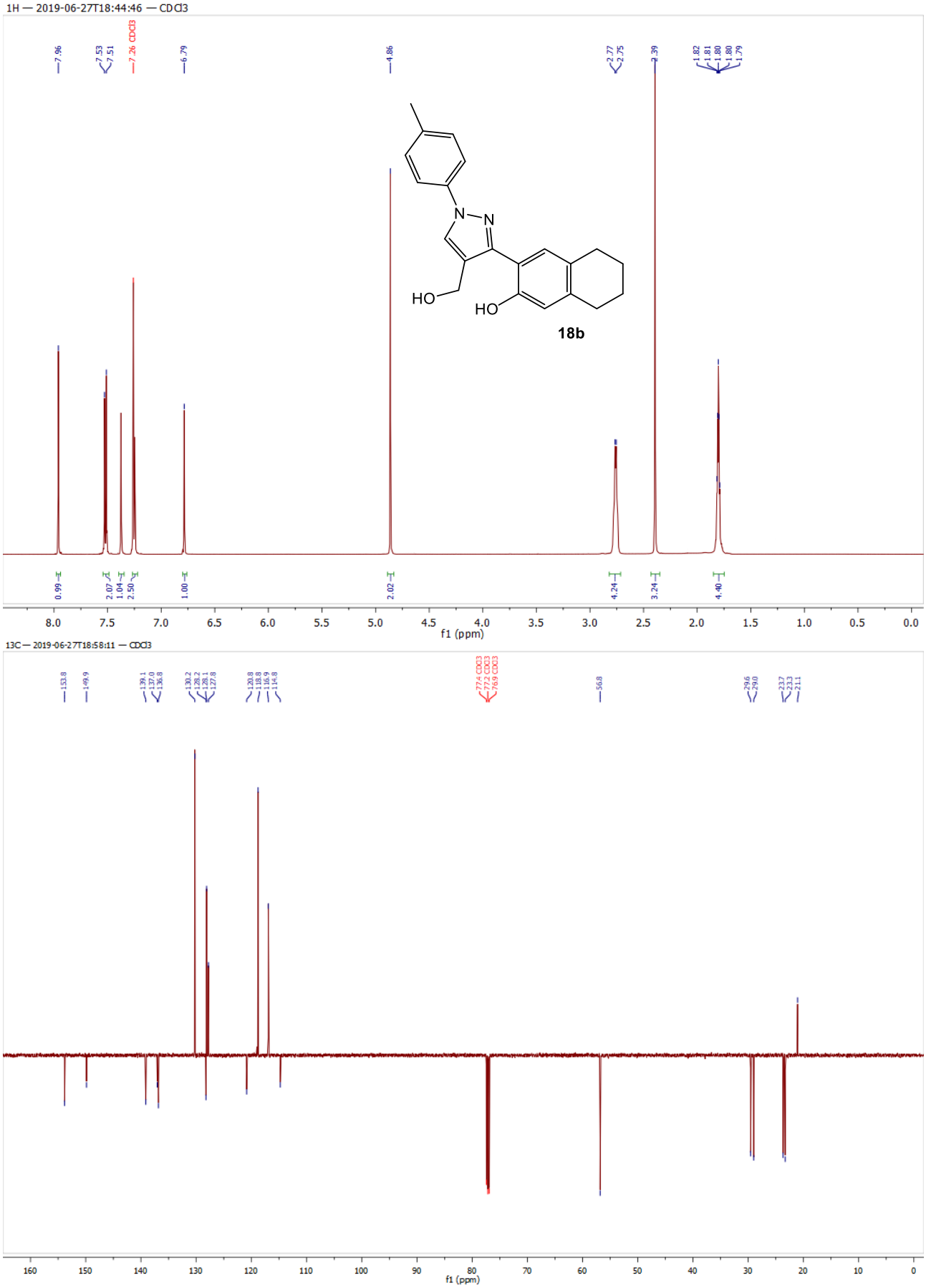
1H — 2019-04-18T21:21:00 — CDCl3

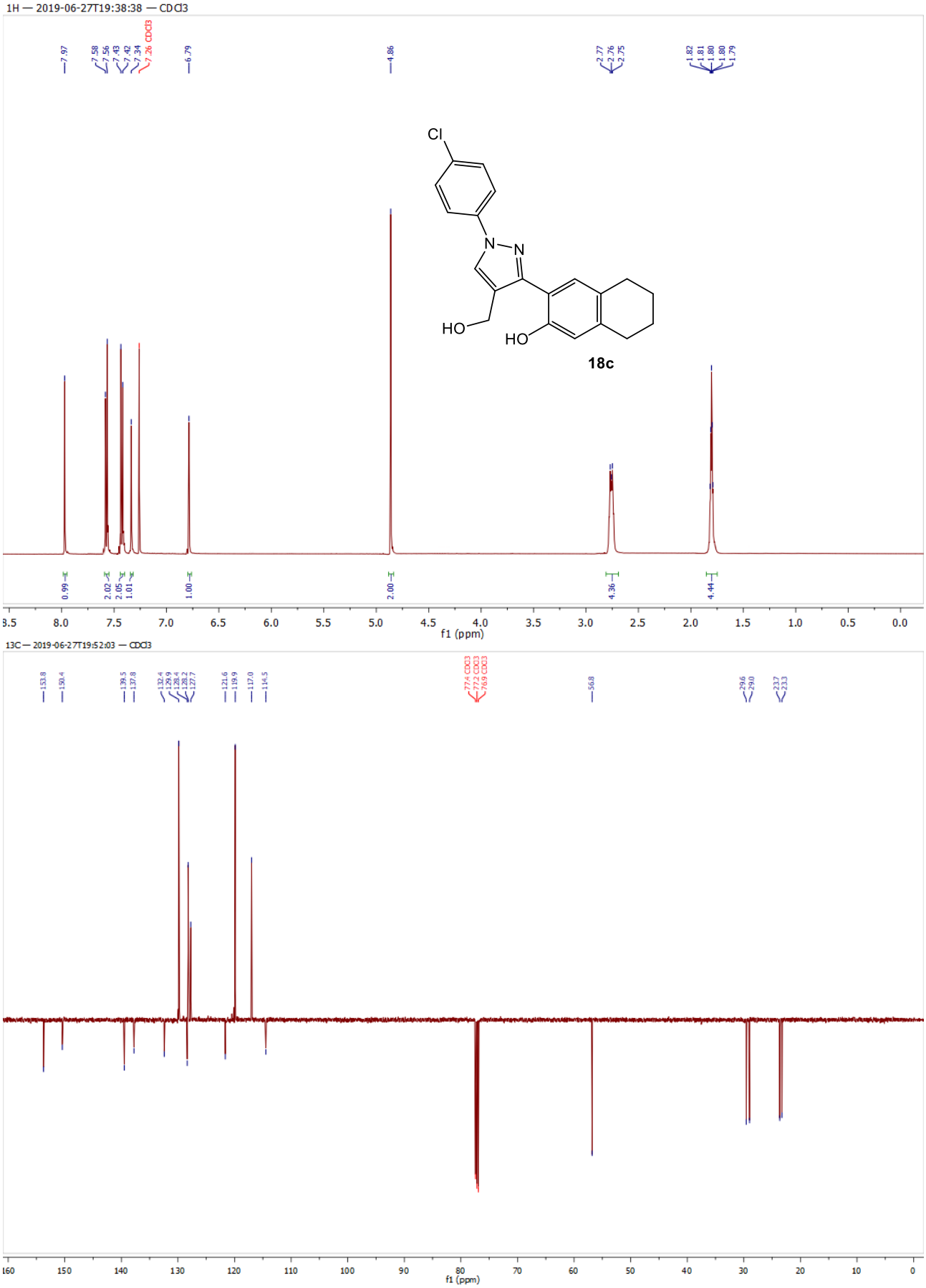


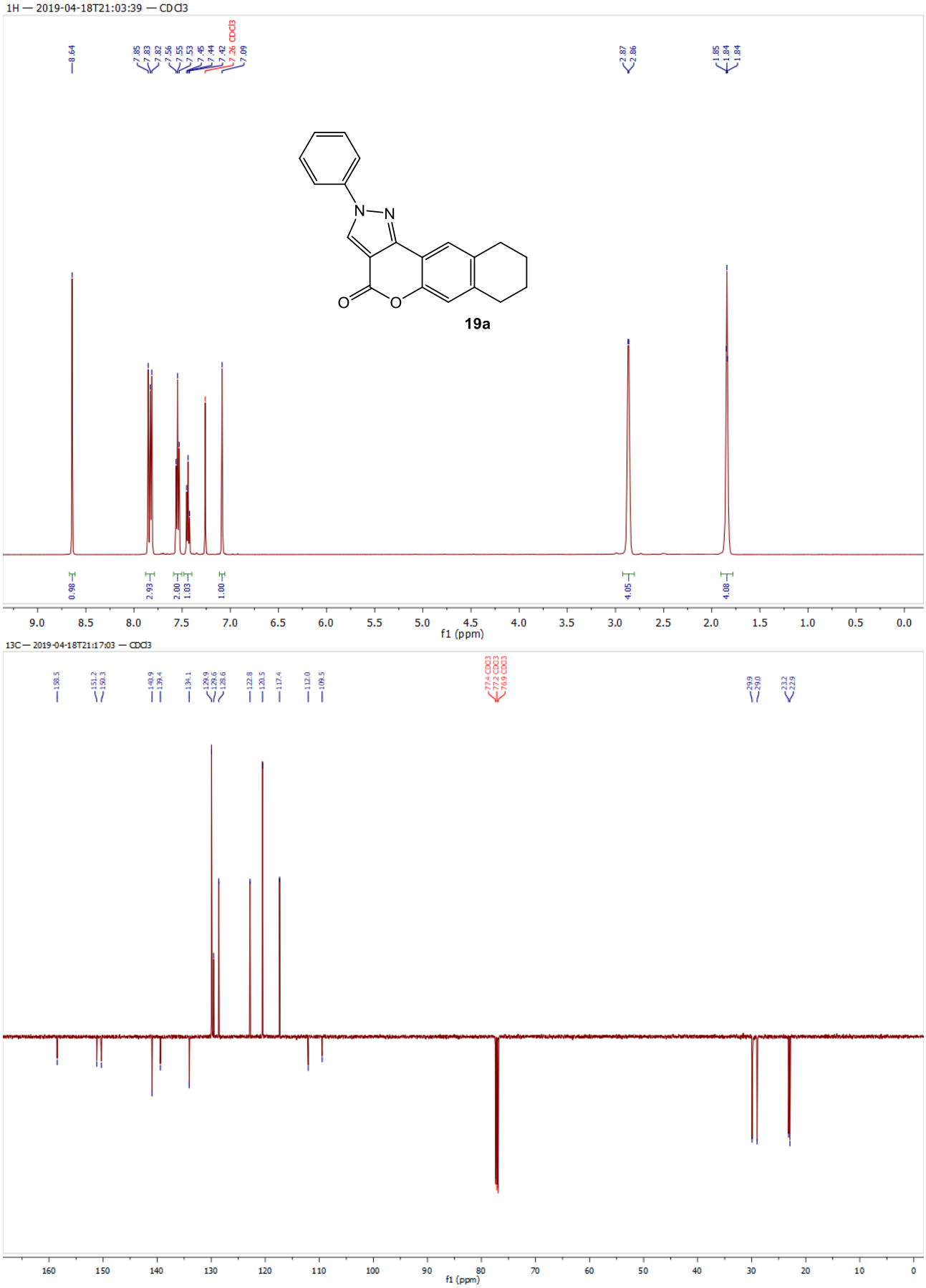
18a

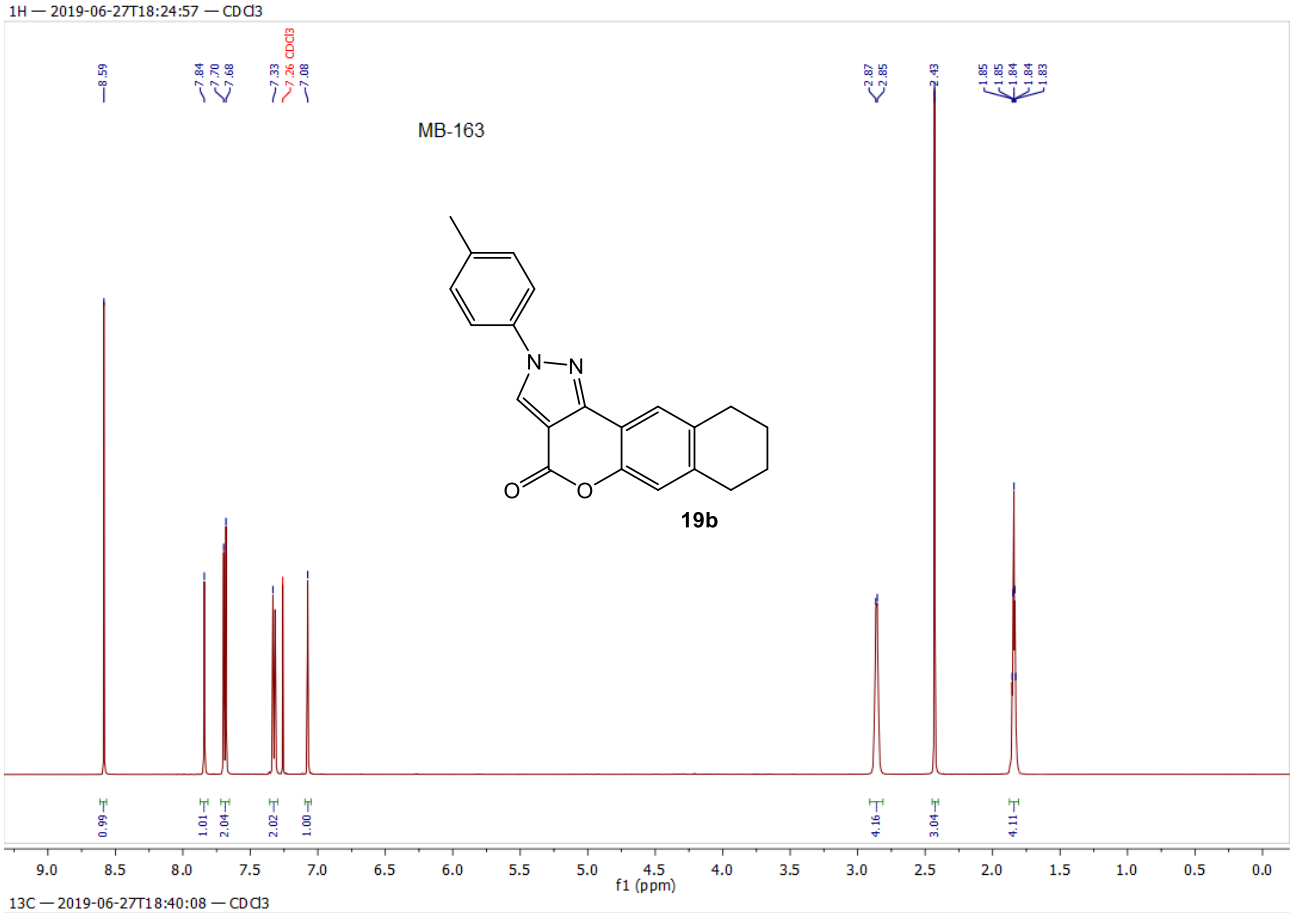
13C — 2019-04-18T21:34:25 — CDCl3

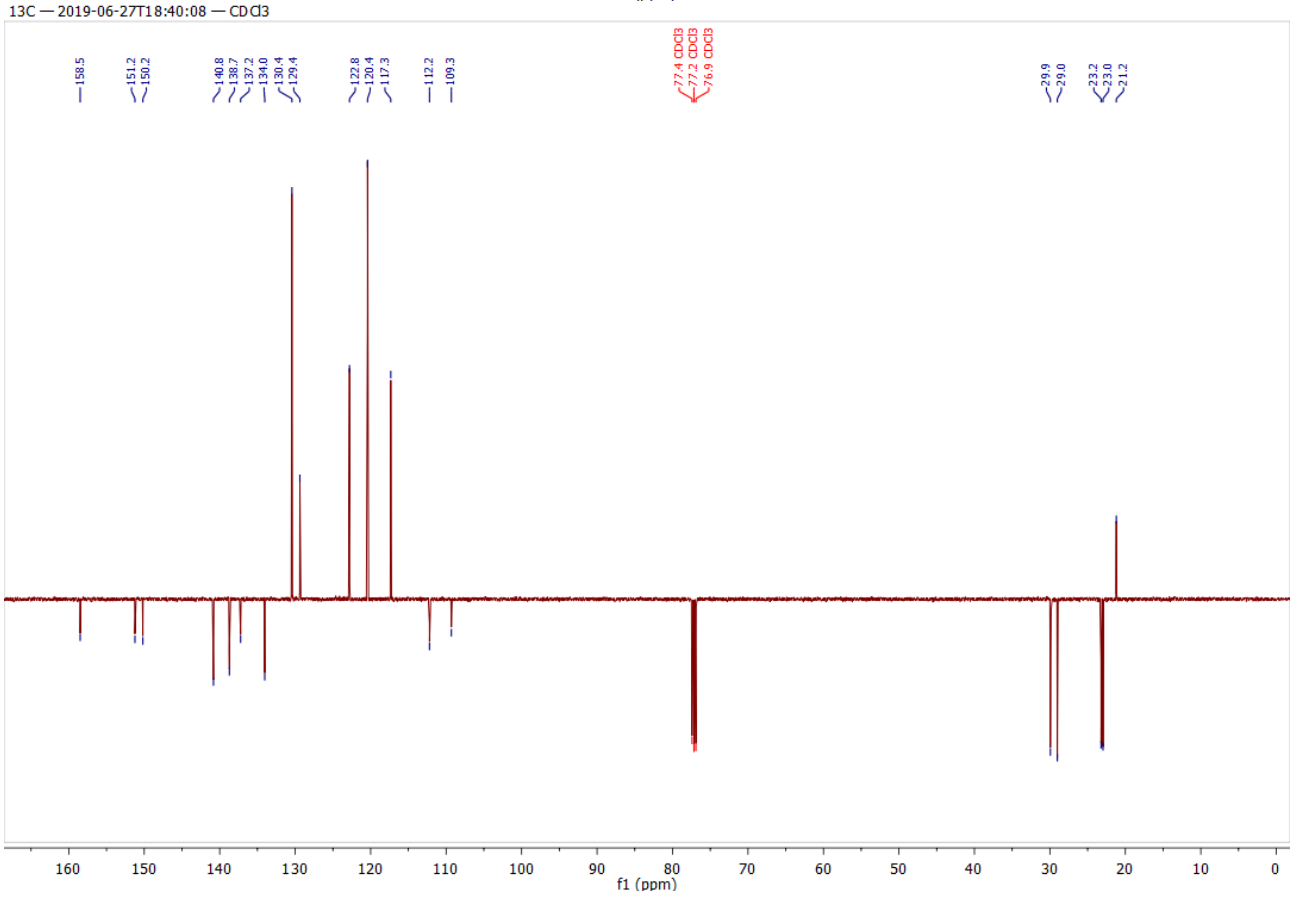


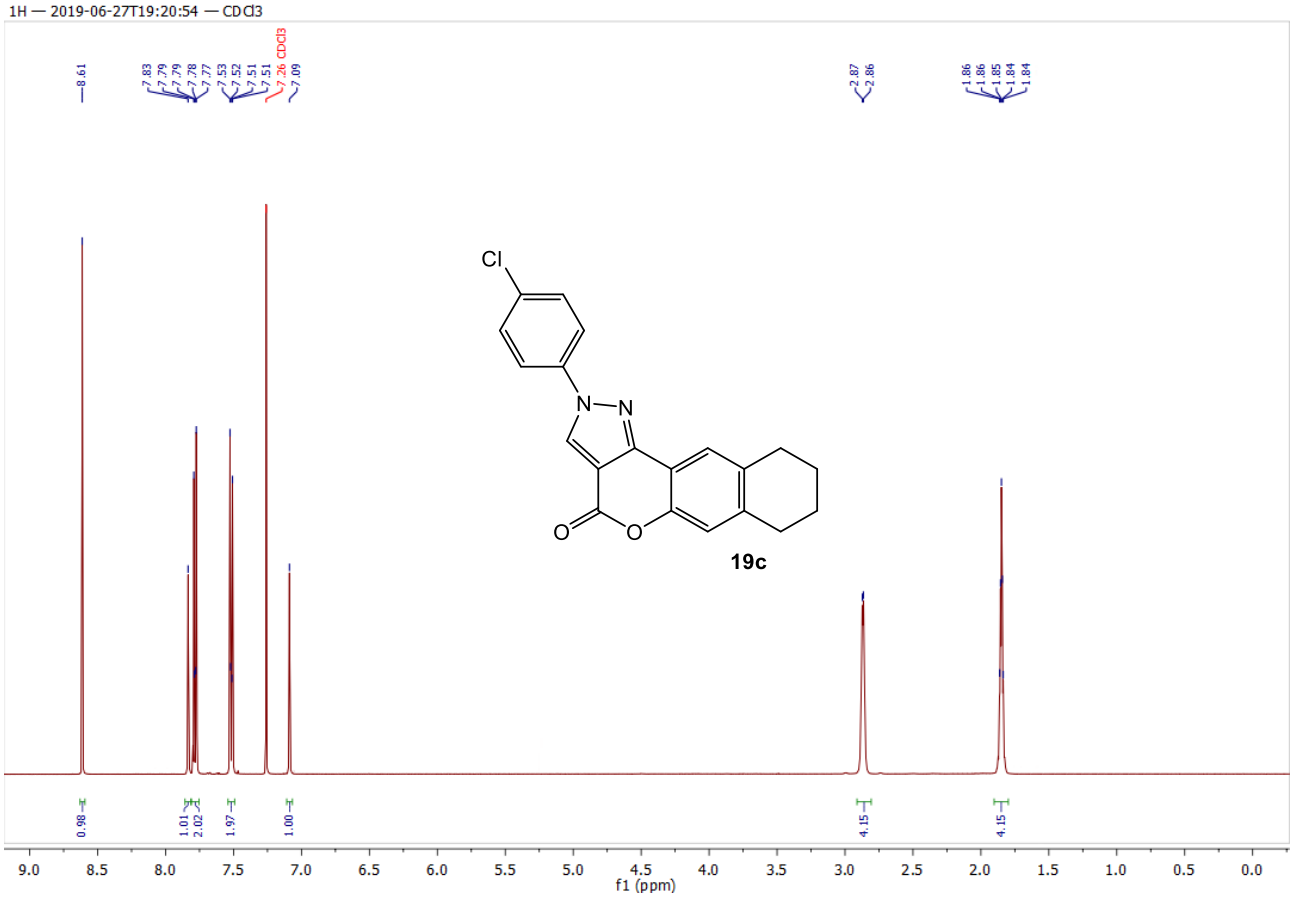

1H — 2019-06-27T18:44:46 — CDCl3
7.96
7.53
7.51
7.26 CDCl3
6.79
4.86
2.77
2.75
2.39
1.82
1.81
1.80
1.80
1.79
HO
HO
18b
0.99
2.07
1.04
2.50
1.00
2.02
4.24
3.24
4.40
f1 (ppm)
13C — 2019-06-27T18:58:11 — CDCl3
153.8
149.9
139.1
137.0
136.8
130.2
128.2
128.1
127.8
120.8
118.8
116.9
114.8
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
56.8
29.6
29.0
23.7
23.3
21.1
f1 (ppm)


1H — 2019-06-27T19:38:38 — CDCl3
7.97
7.58
7.56
7.43
7.42
7.34
7.26 CDCl3
6.79
4.86
2.77
2.76
2.75
1.82
1.81
1.80
1.80
1.79
Cl
N
N
HO
HO
18c
0.99
2.02
2.05
1.01
1.00
2.00
4.36
4.44
f1 (ppm)
13C — 2019-06-27T19:52:03 — CDCl3
153.8
150.4
139.5
137.8
132.4
129.9
128.4
128.2
127.7
121.6
119.9
117.0
114.5
77.4 CDCl3
77.0 CDCl3
76.9 CDCl3
56.8
29.6
29.0
23.7
23.3
f1 (ppm)


1H — 2019-04-18T21:03:39 — CDCl3
8.64
7.85
7.83
7.82
7.56
7.55
7.53
7.45
7.44
7.42
7.26 CDCl3
7.09
2.87
2.86
1.85
1.84
1.84
N
N
O
O
19a
0.98
2.93
2.00
1.03
1.00
4.05
4.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
13C — 2019-04-18T21:17:03 — CDCl3
158.5
151.2
150.3
140.9
139.4
134.1
129.9
129.6
128.6
122.8
120.5
117.4
112.0
109.5
77.4 CDCl3
77.0 CDCl3
76.9 CDCl3
29.9
29.0
23.2
22.9
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


1H — 2019-06-27T18:24:57 — CDCl3
MB-163
19b
f1 (ppm)


13C — 2019-06-27T18:40:08 — CDCl3
f1 (ppm)


1H — 2019-06-27T19:20:54 — CDCl3
8.61
7.83
7.79
7.79
7.78
7.77
7.53
7.52
7.51
7.51
7.26 CDCl3
7.09
2.87
2.86
1.86
1.86
1.85
1.84
1.84
Cl
N
N
O
O
19c
0.98
1.01
2.02
1.97
1.00
4.15
4.15
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

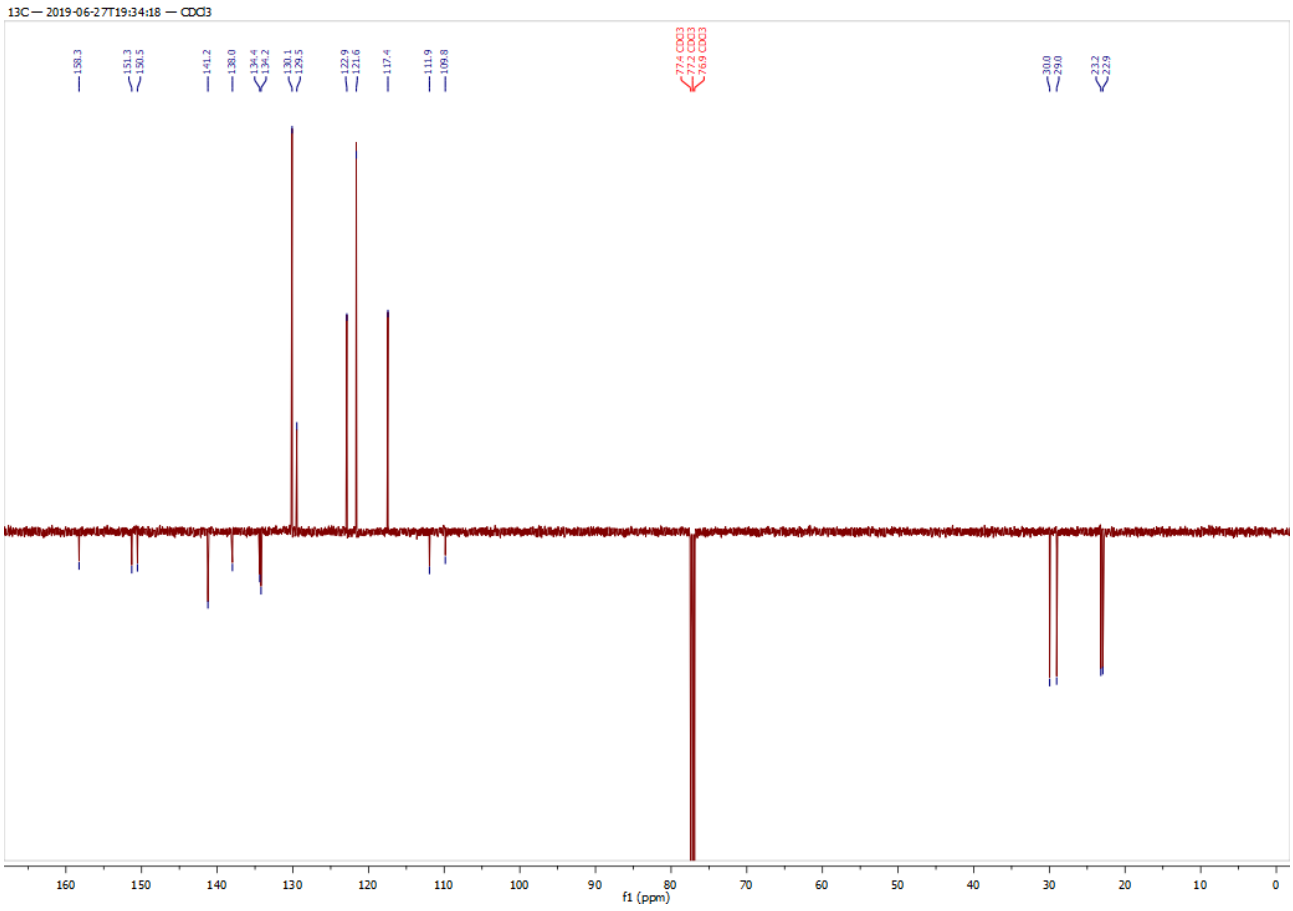

13C — 2019-06-27T19:34:18 — CDCl3
158.3
151.3
150.5
141.2
138.0
134.4
134.2
130.1
129.5
122.9
121.6
117.4
111.9
109.8
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
30.0
29.0
23.2
22.9
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Table S1: Mean±SD values of primary growth inhibitory screen (given as cell viability) used to construct the heat map

	MRC-5	MCF-7	HeLa	PC-3	DU145
Control	99.9±7.2	100±3.6	100.0±3.1	99.9±7.6	100.0±13.9
4	≥100±6.6	92.7±2.2	90.0±4.3	88.5±6.5	94.2±8.6
5	≥100±7	87.5±	99.6±3.5	79.0±3.8	100.6±6.5
7a	≥100±5.7	98.6±5.2	102.7±2.7	87.8±7.1	108.7±9.1
7b	100.4±5.1	≥100±4.3	100.1±2.1	98.2±6.5	98.7±15.6
7c	78.9±4.3	57.4±10.6	94.1±1.9	36.0±4.5	70.4±3.6
8a	99.9±3.3	100.9±4.8	100.4±1.6	54.9±3.0	108.8±4.1
8b	≥100±2.4	≥100±8.2	92.2±8.5	67.8±3.8	≥100±10.2
8c	≥100±3.3	≥100±5.3	83.1±6.2	94.8±4.0	≥100±5.0
9a	≥100±8.1	≥100±2.4	73.8±0.6	82.0±2.2	≥100±5.8
9b	≥100±4.2	≥100±0.8	68.0±0.4	86.2±2.4	≥100±4.5
9c	89.5±8.7	91.1±3.1	75.7±1.7	94.1±4.2	≥100±0.9
10a	93.6±1.7	73.5±7.2	83.2±2.0	63.6±17.8	≥100±15.8
10b	96.9±3.8	87.6±0.7	68.3±2.2	88.0±5.6	≥100±6.8
10c	96.4±10.1	63.2±2.2	72.4±4.2	81.6±6.8	77.3±6.3
11a	≥100±8.2	93.4±3.7	75.4±1.1	59.7±3.2	98.2±5.4
11b	≥100±2.2	80.4±2.9	70.1±4.5	74.3±2.3	97.5±10.1
11c	≥100±8.4	≥100±0.7	77.9±1.5	87.1±3.8	127.1±4.9
15	≥100±3.7	≥100±1.9	53.8±8.3	≥100±2.2	≥100±6.7
17a	≥100±7.3	≥100±2.3	53.7±3.3	71.0±20.9	≥100±6.4
17b	≥100±14.5	93.2±6.0	≥100±3.9	≥100±3.0	≥100±16.8
17c	≥100±4.0	77.5±4.6	≥100±4.0	61.9±2.8	80.3±10.8
18a	≥100±0.1	98.0±7.1	≥100±6.5	91.5±12.9	87.0±18.2
18b	≥100±2.6	≥100±5.3	≥100±8.7	99.6±7.7	45.3±2.5
18c	≥100±2.3	≥100±4.7	≥100±6.6	90.9±3.0	≥100±4.3
19a	≥100±3.0	≥100±3.9	≥100±8.7	95.4±1.3	21.6±0.5
19b	≥100±0	≥100±4.8	≥100±2.4	84.1±5.2	100.6±6.3
19c	≥100±2.5	≥100±3.8	≥100±8.3	79.1±7.8	≥100.6±10.8

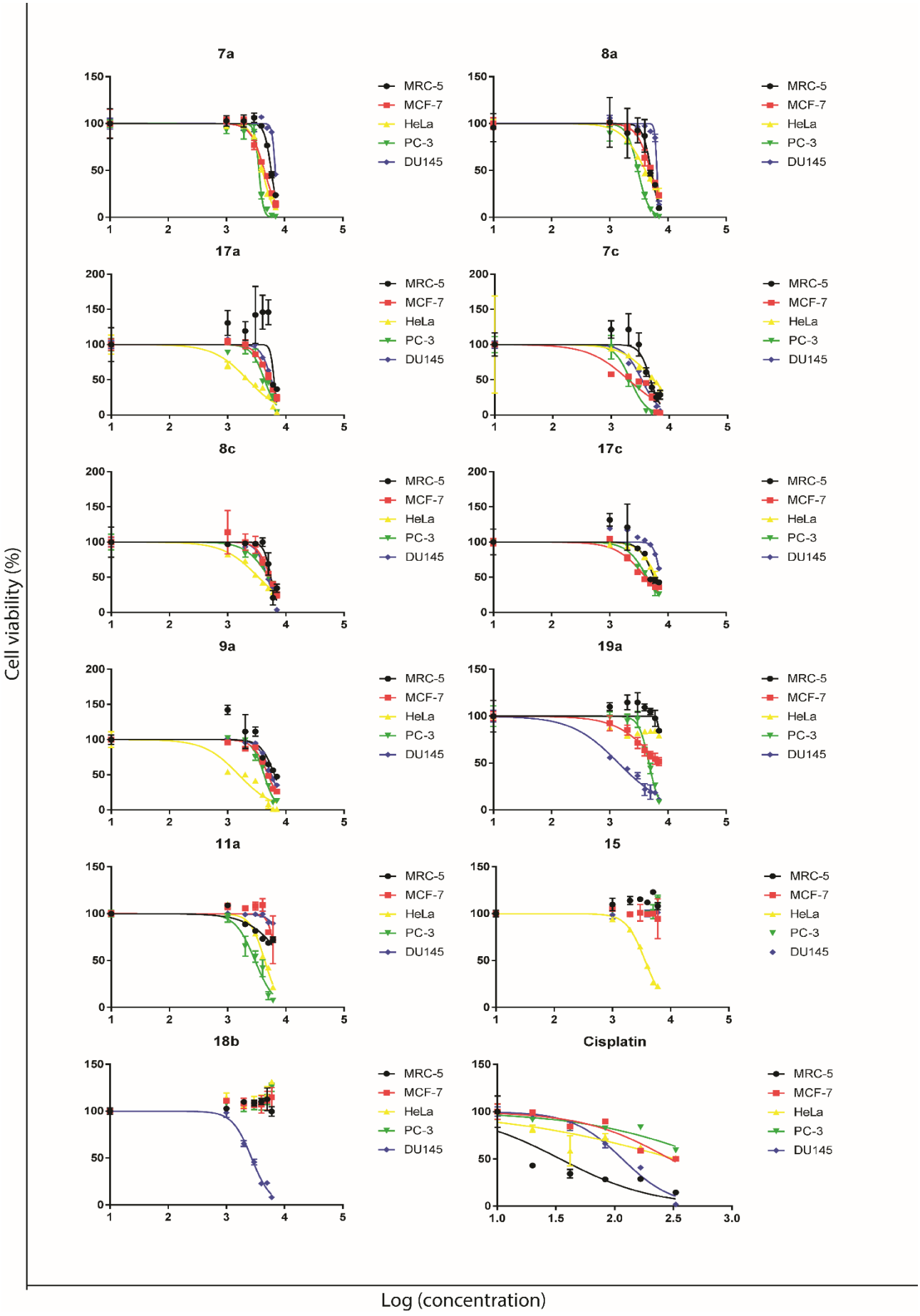


Figure S1: Dose response curves used to evaluate IC_{50} concentrations of selected compounds. X-axis represents nM concentrations of the test compound and μM concentration of cisplatin on logarithmic scale and Y-axis represents cell viability normalized to untreated control.