Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
This journal is © The Royal Society of Chemistry 2017

Photochromic histone deacetylase inhibitors based on dithienylethenes and fulgimides

D. Wutz, D. Gluhacevic, A. Chakrabarti, K. Schmidtkunz, F. Erdmann, C. Romier, W. Sippl, M. Jung and B. König*

Supporting Information

Table of Contents

Additional photochemical data

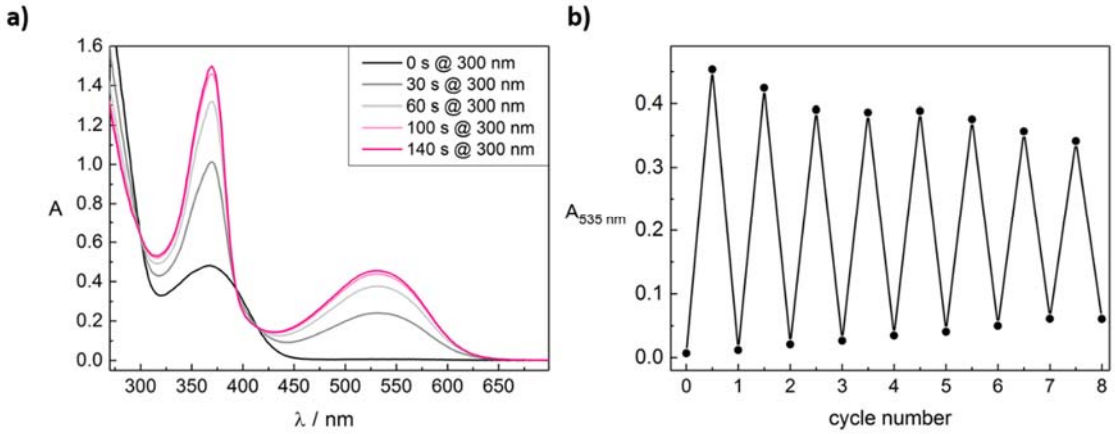


Figure S1. a) Changes in absorption spectra of DTE **10** (100 µM in DMSO) upon continuous irradiation for 0, 30, 60, 100 and 140 s with light of λ = 300 nm until the PSS is reached. **b)** Cycle performance of DTE **10** (100 µM in DMSO). Changes in absorption at 535 nm were measured during alternate irradiation with light of 300 nm for 140 s and 530 nm for 1 min.

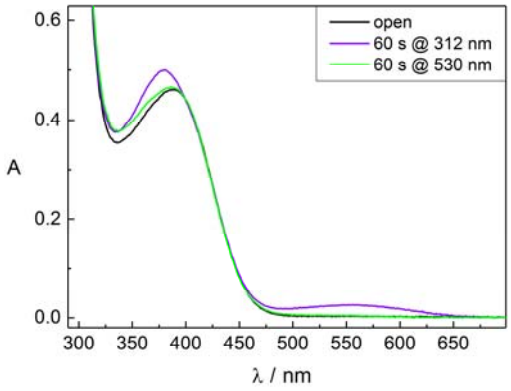


Figure S2. Absorption spectra of DTE **12** (100 µM in toluene/THF) open, after irradiation with λ = 312 nm for 60 s and subsequent irradiation with λ = 530 nm for 60 s.

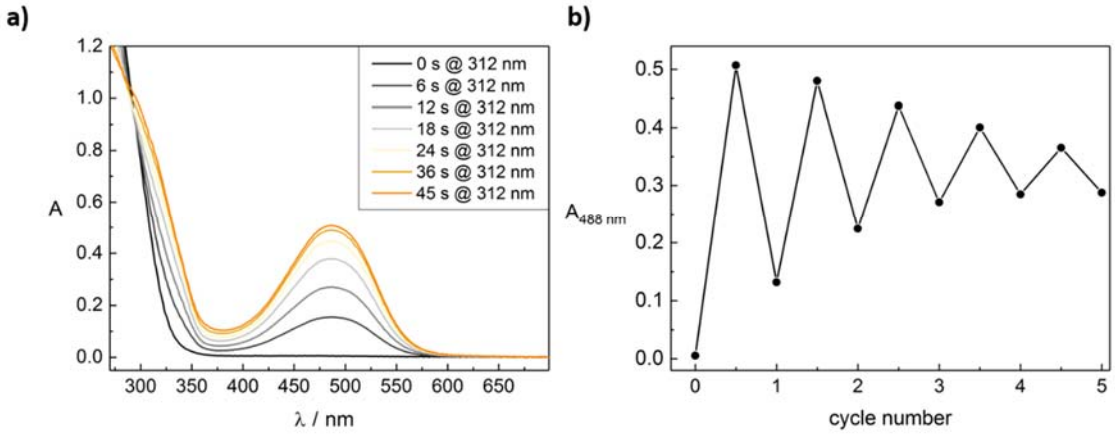


Figure S3. a) Changes in absorption spectra of DTE **3** (100 µM in DMSO) upon continuous irradiation for 0, 6, 12, 18, 24, 36 and 48 s with light of λ = 312 nm until the PSS is reached. **b)** Cycle performance of DTE **3** (100 µM in DMSO). Changes in absorption at 488 nm were measured during alternate irradiation with light of 312 nm for 48 s and 470 nm for 1 min.

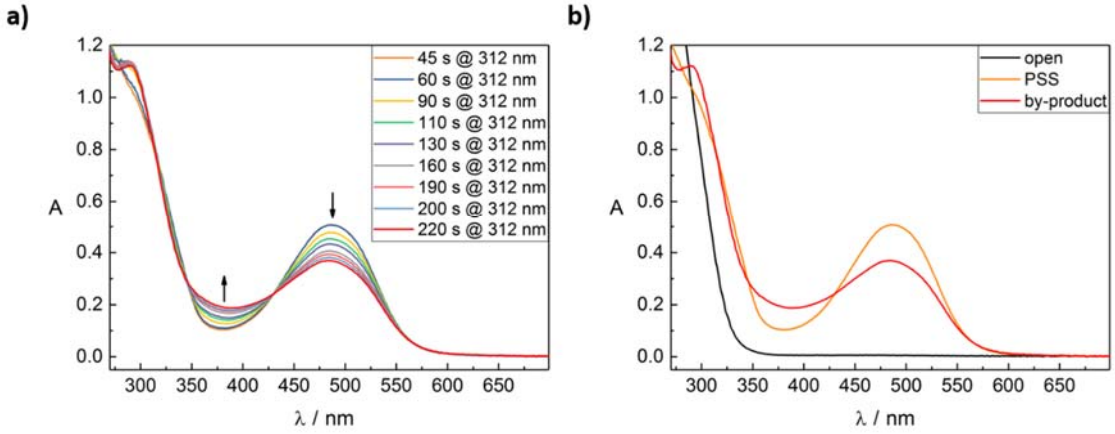


Figure S4. a) Changes in absorption spectra of DTE **3** (100 µM in DMSO) upon continuous irradiation for 48, 60, 92, 112, 132, 162, 192, 202 and 222 s with light of λ = 312 nm until the byproduct is completely formed. **b)** Comparison of the absorption spectra of the three occurring states/isomers of **3**: open (black), PSS (orange) and byproduct (red).

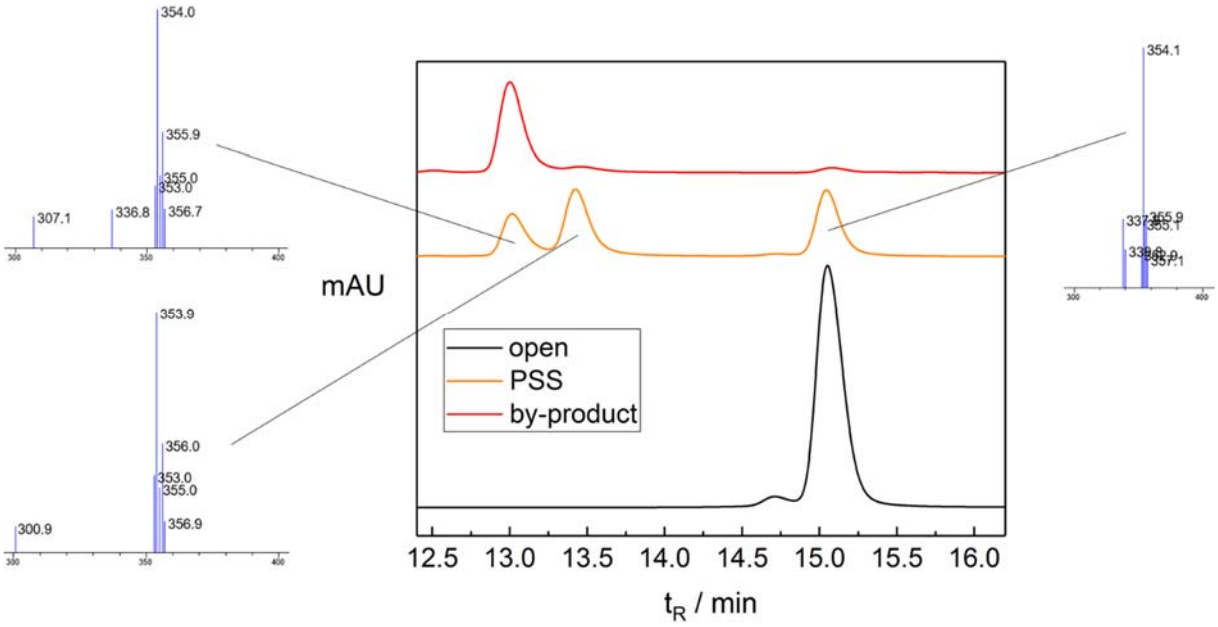


Figure S5. HPLC-MS traces recorded at 275 nm of the three different states/isomers of **3** (t_R open isomer: 15.05 min, m/z=354.1; t_R closed isomer: 13.42 min, m/z=353.9; t_R byproduct: 13.02 min, m/z=354.0; black: open isomer without irradiation; orange: PSS after 45 s of irradiation; red: byproduct after 220 s of irradiation). Upon reaching the PSS (orange) approximately 23% of the byproduct has already formed and its formation is completed after 220 s (red).

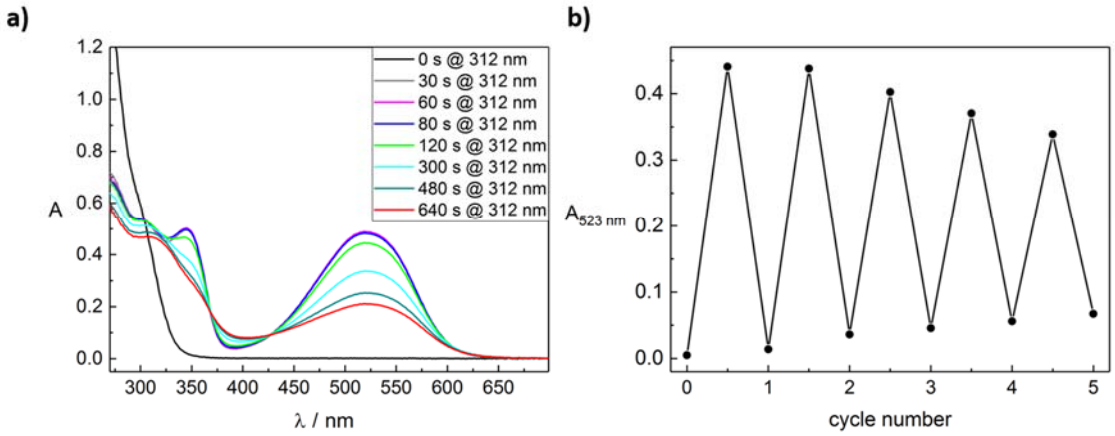


Figure S6. a) Changes in absorption spectra of DTE **6** (100 µM in DMSO) upon continuous irradiation for 0, 30, 60 (PSS), 80, 120, 300, 480 and 640 s (byproduct) with light of λ = 312 nm. b) Cycle performance of DTE **6** (100 µM in DMSO). Changes in absorption at 523 nm were measured during alternate irradiation with light of 312 nm for 60 s and 530 nm for 3 min.

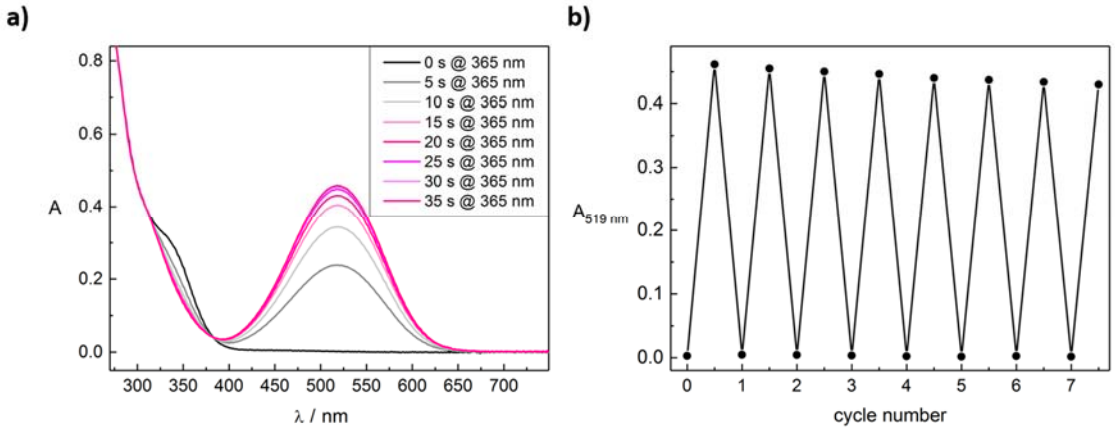


Figure S7. a) Changes in absorption spectra of fulgimide **18** (100 µM in DMSO) upon continuous irradiation for 0, 5, 10, 15, 20, 25, 30 and 35 s with light of λ = 365 nm until the PSS is reached. **b)** Cycle performance of fulgimide **18** (100 µM in DMSO). Changes in absorption at 519 nm were measured during alternate irradiation with light of 365 nm for 35 s and 530 nm for 5 min.

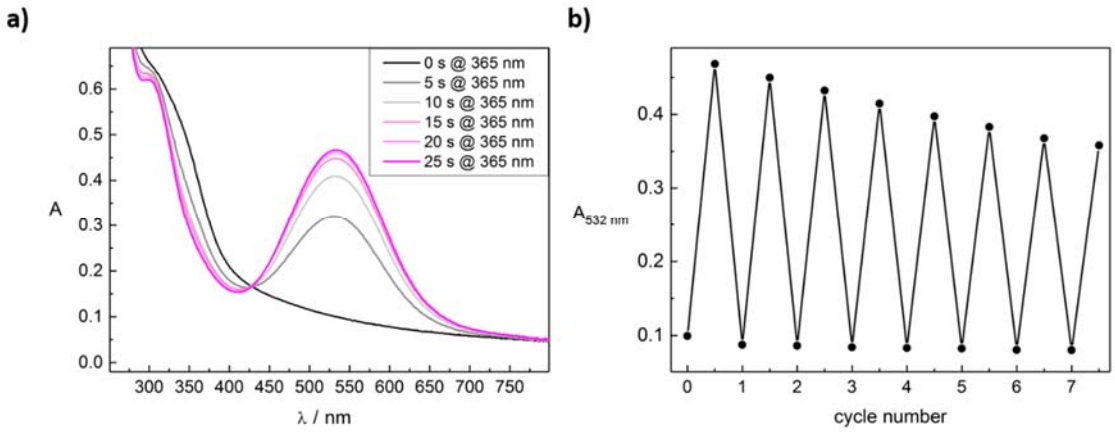


Figure S8. a) Changes in absorption spectra of fulgimide **20** (100 µM in PBS with 1% of DMSO, pH=7.4) upon continuous irradiation for 0, 5, 10, 15, 20 and 25 s with light of λ = 365 nm until the PSS is reached. **b)** Cycle performance of fulgimide **20** (100 µM in in PBS with 1% of DMSO, pH=7.4). Changes in absorption at 532 nm were measured during alternate irradiation with light of 365 nm for 25 s and 530 nm for 10 min.

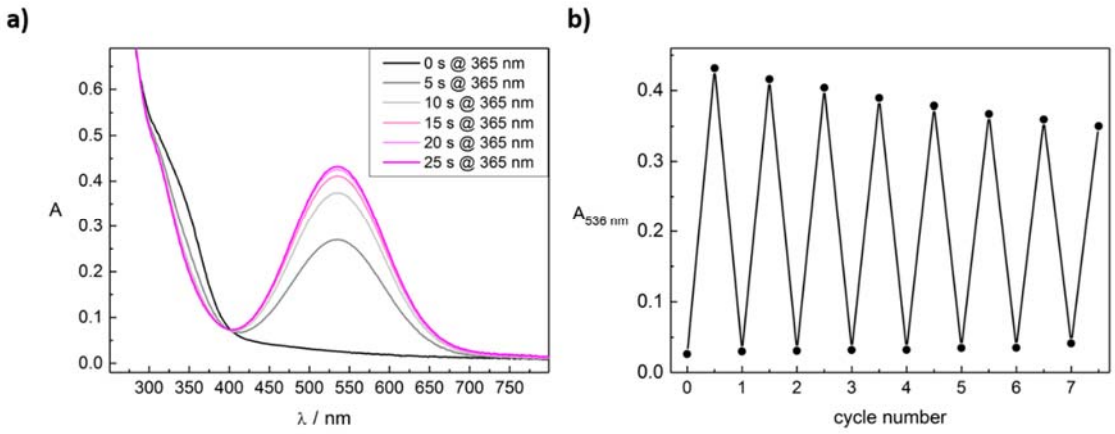


Figure S9. a) Changes in absorption spectra of fulgimide **18** (100 µM in PBS with 1% of DMSO, pH=7.4) upon continuous irradiation for 0, 5, 10, 15, 20 and 25 s with light of λ = 365 nm until the PSS is reached. **b)** Cycle performance of fulgimide **18** (100 µM in in PBS with 1% of DMSO, pH=7.4). Changes in absorption at 536 nm were measured during alternate irradiation with light of 365 nm for 25 s and 530 nm for 10 min.

Docking results and additional docking poses

Table S1. Docking scores calculated for *h*HDAC1 (PDB ID 5ICN).

Entry	Compound	IC_{50} *h*HDAC1 [µM]	pIC_{50} *h*HDAC1	E GBSA kcal/mol
1	**3 open**	15 ± 1 .2	4.82	-38.54
2	**3 byproduct** (*R,R*)	26 ± 2.5	4.59	-
3	**3 byproduct** (*S,S*)	26 ± 2.5	4.59	-
4	**6 open**	4.2 ± 0.7	5.38	-35.05
5	**6 closed** (*R,R*)	5.1 ± 0.8	5.29	-37.25
6	**6 closed** (*S,S*)	5.1 ± 0.8	5.29	-37.05
7	**18 open**	28.5 ± 10.9	4.55	-37.48
8	**18 closed** (*R*)	87.5 ± 53.0	4.06	-29.52
9	**18 closed** (*S*)	87.5 ± 53.0	4.06	-31.83
10	**20 open**	6.4 ± 1.0	5.19	-41.57
11	**20 closed** (*R*)	5.0 ± 1.0	5.30	-42.80
12	**20 closed** (*S*)	5.0 ± 1.0	5.30	-44.16

Table S2. Docking scores calculated for *h*HDAC6 (PDB ID 5G0I).

Entry	Compound	IC_{50} *h*HDAC6 [μM]	pIC_{50} *h*HDAC6	E GBSA kcal/mol
1	**3 open**	1.8 ± 0.2	5.74	-41.90
2	**3 byproduct** (*R,R*)	3.9 ± 0.2	5.41	-30.82
3	**3 byproduct** (*S,S*)	3.9 ± 0.2	5.41	-30.12
4	**6 open**	0.213 ± 0.018	6.67	-45.20
5	**6 closed** (*R,R*)	0.297 ± 0.041	6.53	-47.75
6	**6 closed** (*S,S*)	0.297 ± 0.041	6.53	-47.86
7	**18 open**	1.8 ± 0.5	5.74	-40.08
8	**18 closed** (*R*)	6.1 ± 1.7	5.21	-40.48
9	**18 closed** (*S*)	6.1 ± 1.7	5.21	-41.77
10	**20 open**	0.047 ± 0.032	7.33	-73.55
11	**20 closed** (*R*)	0.075 ± 0.047	7.12	-72.90
12	**20 closed** (*S*)	0.075 ± 0.047	7.12	-71.91

Table S3. Docking scores calculated for *h*HDAC8 (PDB ID 2V5X).

Entry	Compound	IC_{50} *h*HDAC8 [μM]	pIC_{50} *h*HDAC8	E GBSA kcal/mol
1	**3 open**	1.6 ± 0.6	5.80	-60.59
2	**3 byproduct** (*R,R*)	2.7 ± 0.9	5.57	-
3	**3 byproduct** (*S,S*)	2.7 ± 0.9	5.57	-
4	**6 open**	0.248 ± 0.29	6.61	-67.62
5	**6 closed** (*R,R*)	0.262 ± 0.36	6.58	-65.18
6	**6 closed** (*S,S*)	0.262 ± 0.36	6.58	-65.47
7	**18 open**	1.1 ± 0.2	5.96	-63.56
8	**18 closed** (*R*)	0.88 ± 0.07	6.06	-63.49
9	**18 closed** (*S*)	0.88 ± 0.07	6.06	-63.13
10	**20 open**	5.6 ± 1.3	5.25	-58.40
11	**20 closed** (*R*)	3.6 ± 1.0	5.44	-60.62
12	**20 closed** (*S*)	3.6 ± 1.0	5.44	-60.26

Table S4. Docking scores calculated for *sm*HDAC8 (PDB ID 5FUE).

Entry	Compound	IC_{50} *sm*HDAC8 [µM]	pIC_{50} *sm*HDAC8	E GBSA kcal/mol
1	**3 open**	5.8 ± 1.1	5.24	-59.32
2	**3 byproduct** (*R,R*)	22 ± 3.9	4.66	-
3	**3 byproduct** (*S,S*)	22 ± 3.9	4.74	-
4	**6 open**	18 ± 2.1	4.74	-45.25
5	**6 closed** (*R,R*)	4.5 ± 0.8	5.35	-60.97
6	**6 closed** (*S,S*)	4.5 ± 0.8	5.35	-61.06
7	**18 open**	1.1 ± 0.2	5.96	-70.29
8	**18 closed** (*R*)	1.1 ± 0.1	5.96	-70.84
9	**18 closed** (*S*)	1.1 ± 0.1	5.96	-72.22
10	**20 open**	8.9 ± 3.1	5.05	-63.50
11	**20 closed** (*R*)	5.7 ± 2.0	5.24	-60.15
12	**20 closed** (*S*)	5.7 ± 2.0	5.24	-60.28

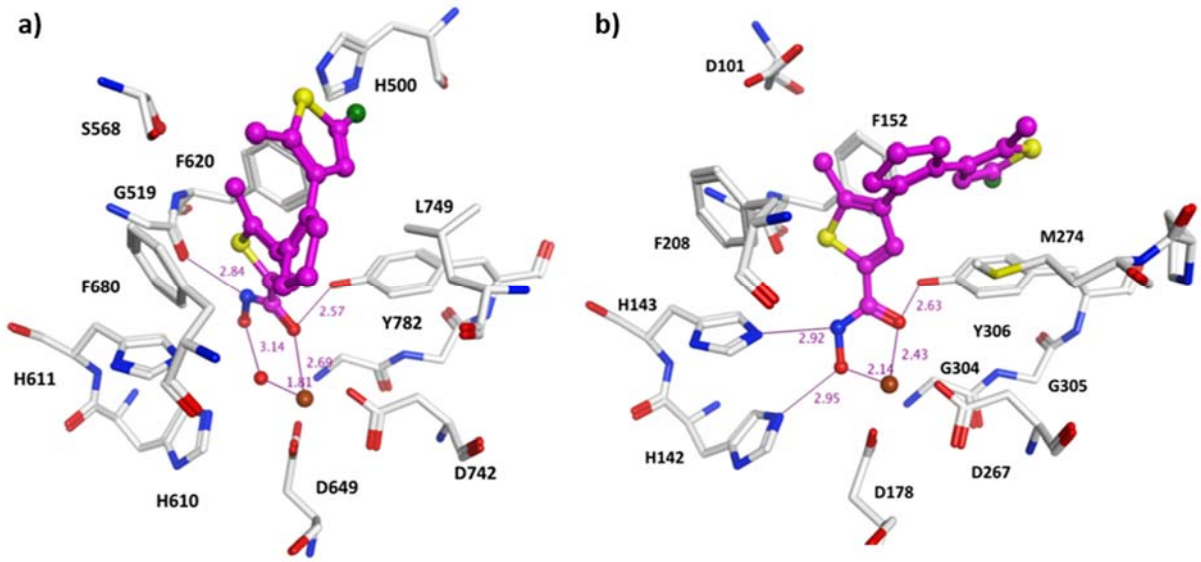


Figure S10. Docking poses of DTE **3 open** for *h*HDAC6 (**a**) and *h*HDAC8 (**b**). Only the interacting residues of the binding pocket are displayed. The zinc ion is shown as brown ball. The water molecule bridging the coordination to the zinc ion in **a)** is shown as red ball. Distances of the metal coordination and hydrogen bonds are given in Å and are shown as lines colored in magenta.

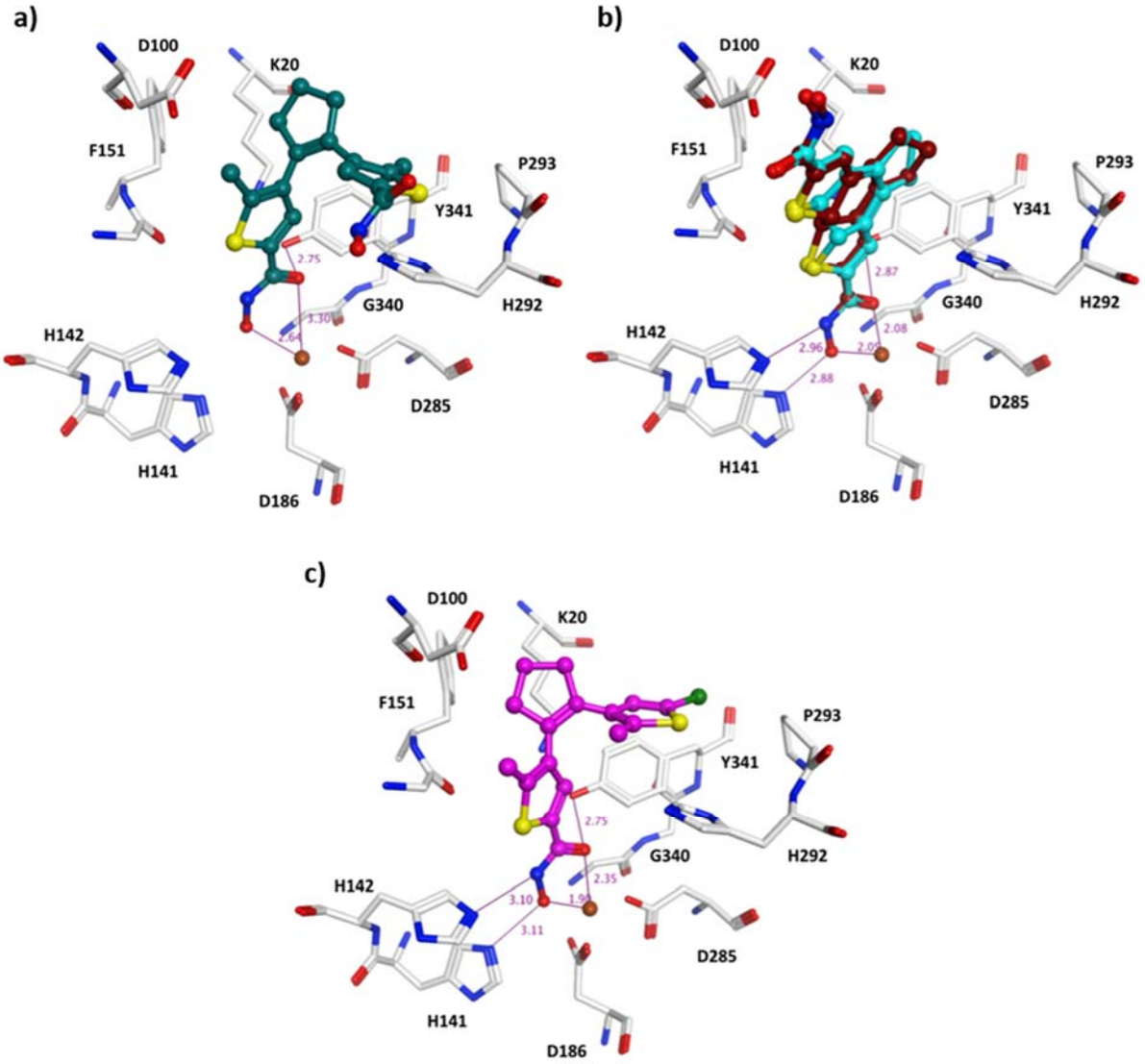


Figure S11. Docking poses of DTEs for *sm*HDAC8. **a) 6 open** colored dark green, **b) 6 closed** (*R,R*) colored cyan and **6 closed** (*S,S*) colored brown, **c) 3 open** colored magenta. Only the interacting residues of the binding pocket are displayed. The zinc ion is shown as brown ball. Distances of the metal coordination and hydrogen bonds are given in Å and are shown as lines colored in magenta.

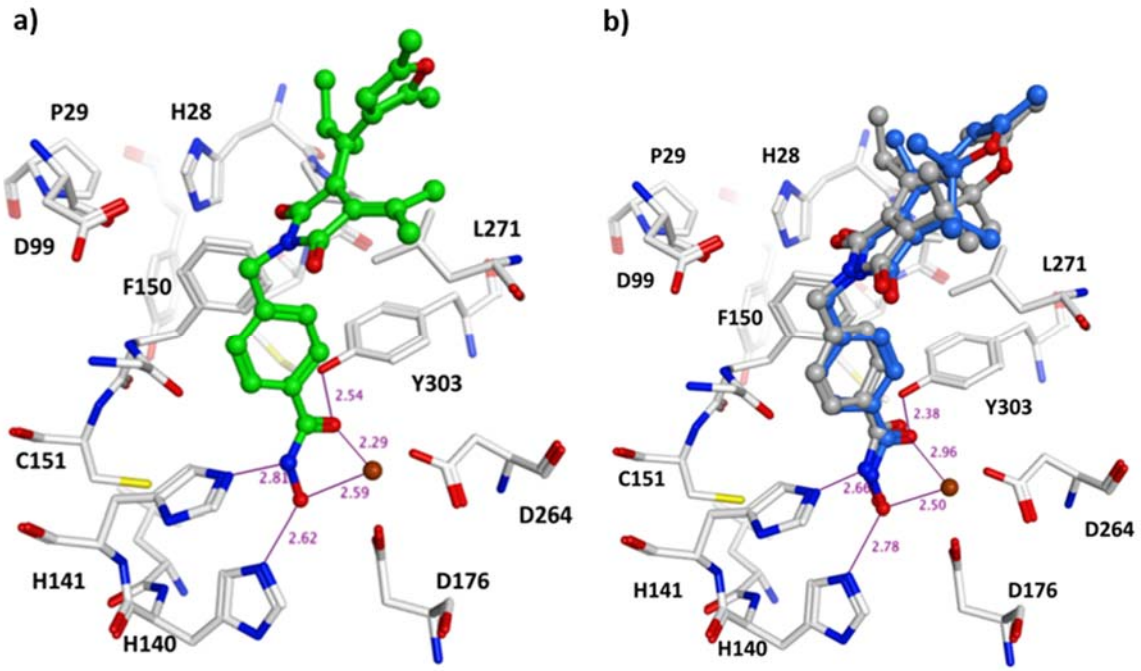


Figure S12. Docking poses of the fulgimide **20** for *h*HDAC1. **a) 20 open** colored green, **b) 20 closed** (*R*) colored blue and **20** closed (*S*) colored light grey). The zinc ion is shown as brown ball. Distances of the metal coordination and hydrogen bonds are given in Å and are shown as lines colored in magenta.

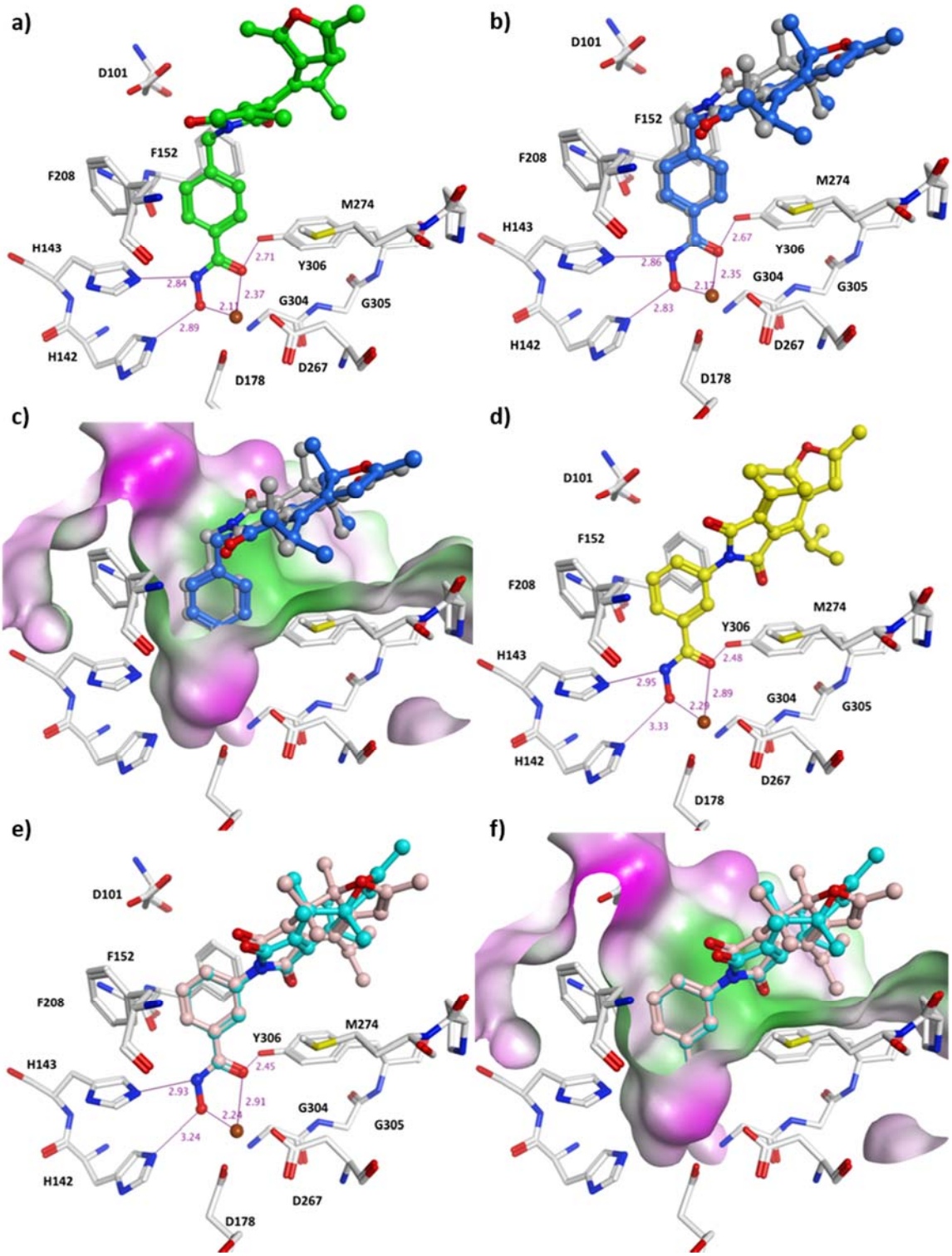
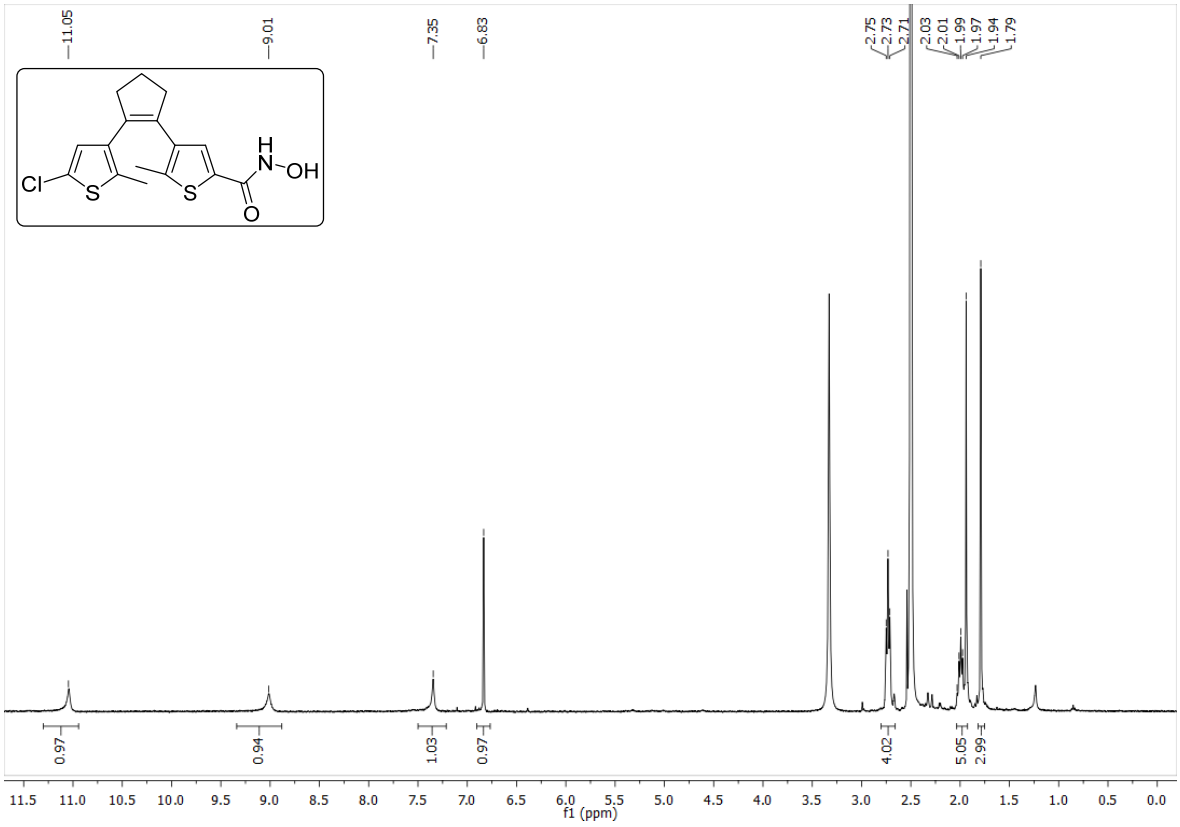
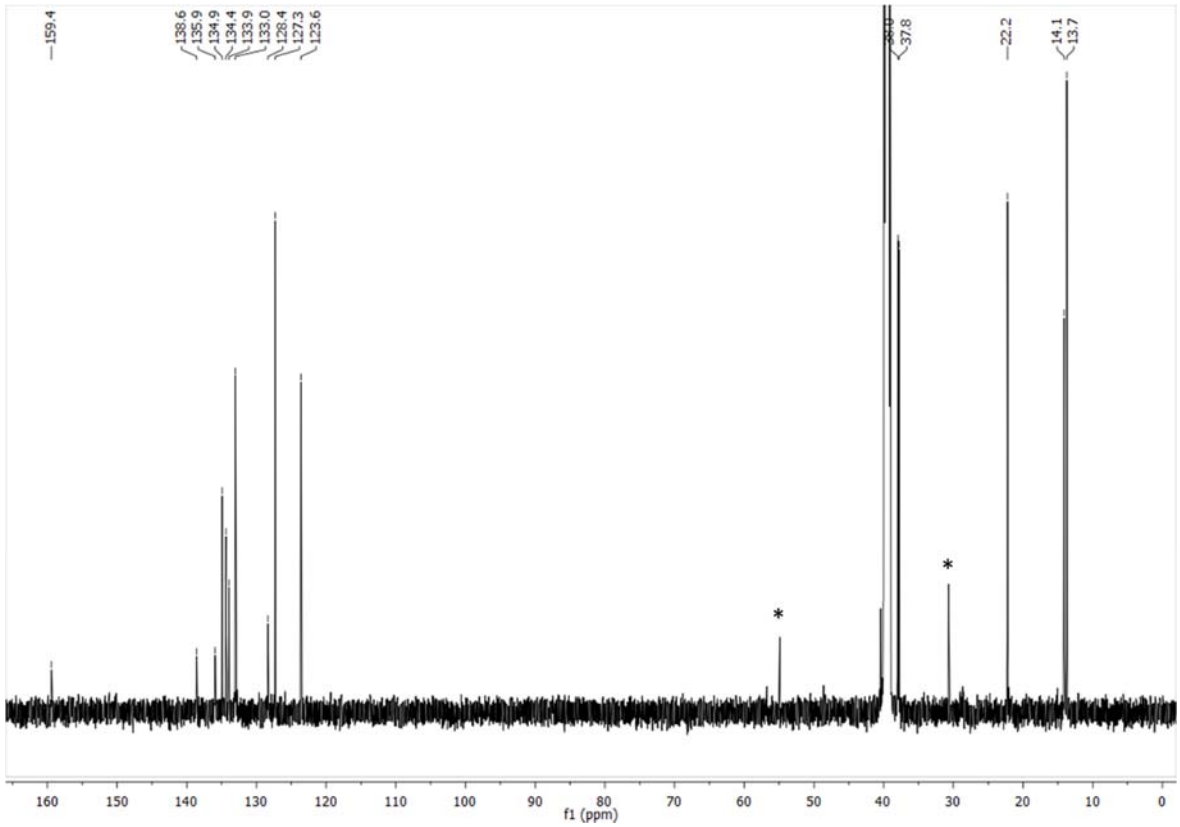


Figure S13. Docking poses of the fulgimides (**20 open** colored green, **20 closed** (*R*) colored blue, **20 closed** (*S*) colored light grey**, 18 open** colored yellow, **18 closed** (*R*) colored cyan and **18 closed** (*S*) colored salmon) for *h*HDAC8. The zinc ion is shown as brown ball and the water molecule bridging the coordination to the zinc ion is shown as red ball. Distances of the metal coordination and hydrogen bonds are given in Å and are shown as lines colored in magenta. The molecular surface of the *h*HDAC8 binding pocket in **c)** and **f)** is colored according to the hydrophobicity (hydrophobic regions are colored green, polar regions are colored magenta).

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

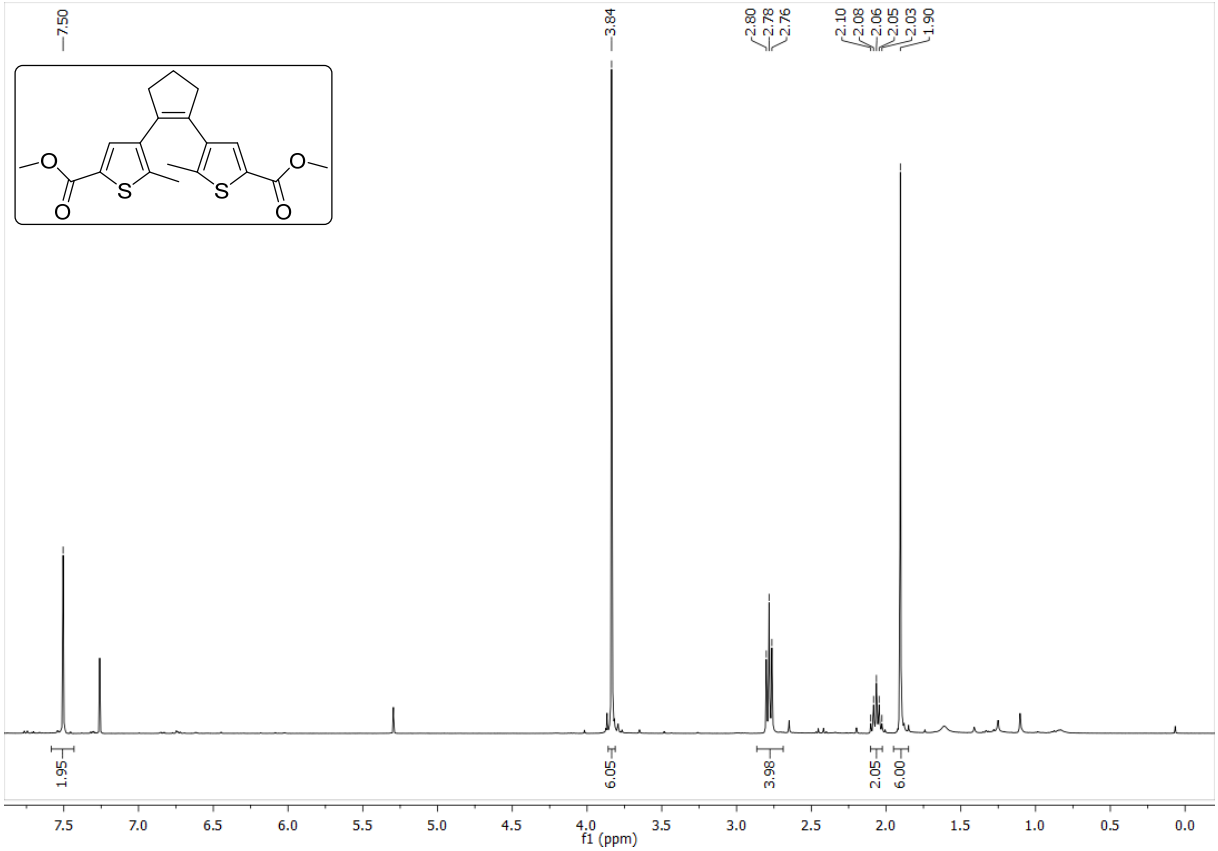
Compound **3**[A]

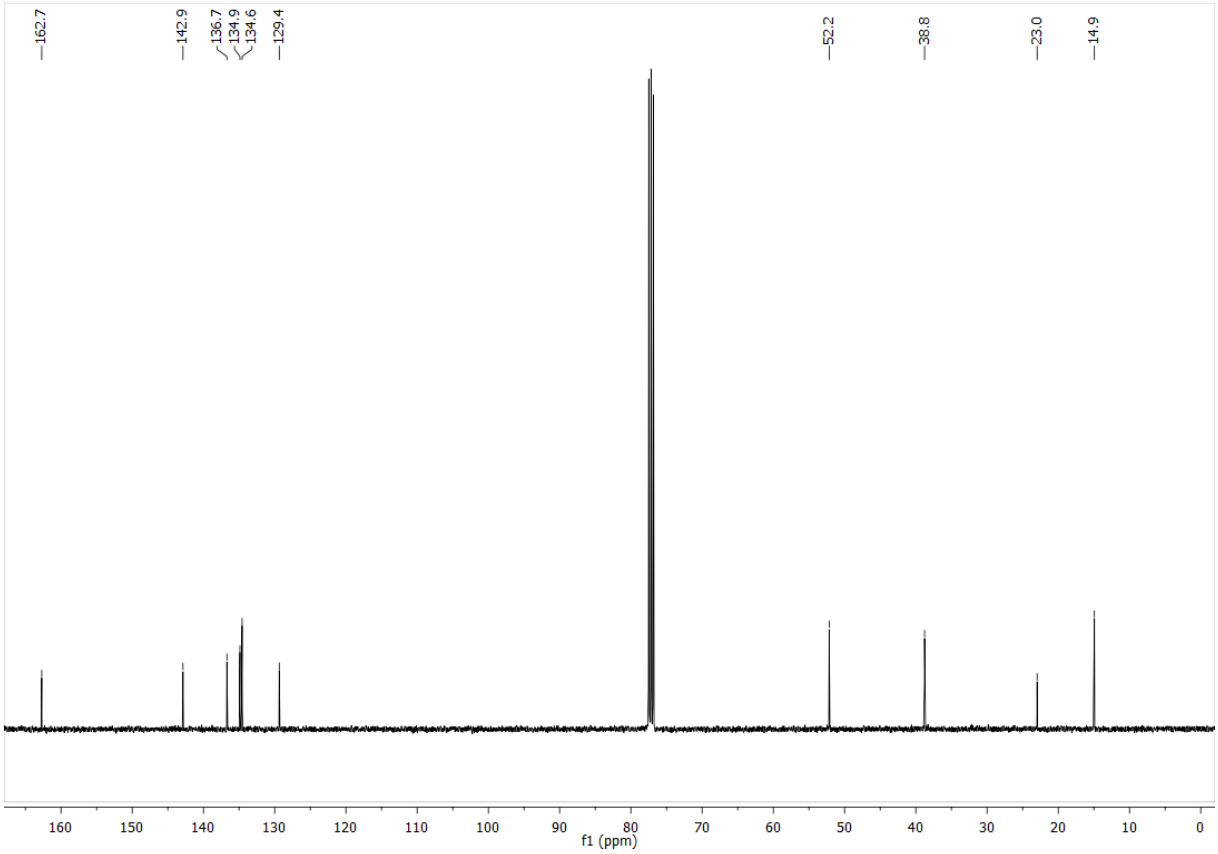




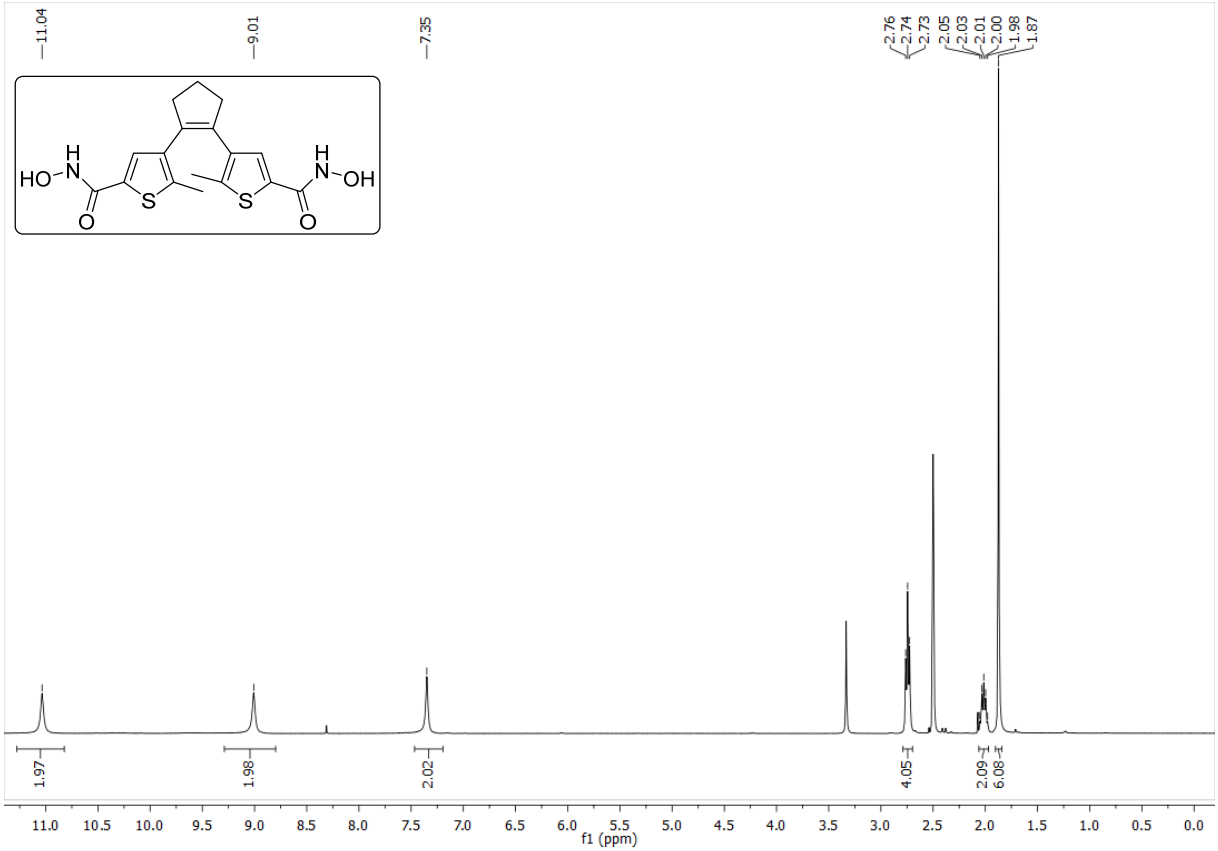
[A] ^{13}C-NMR-spectrum contains traces of acetone and CH_2Cl_2; signals are marked with *

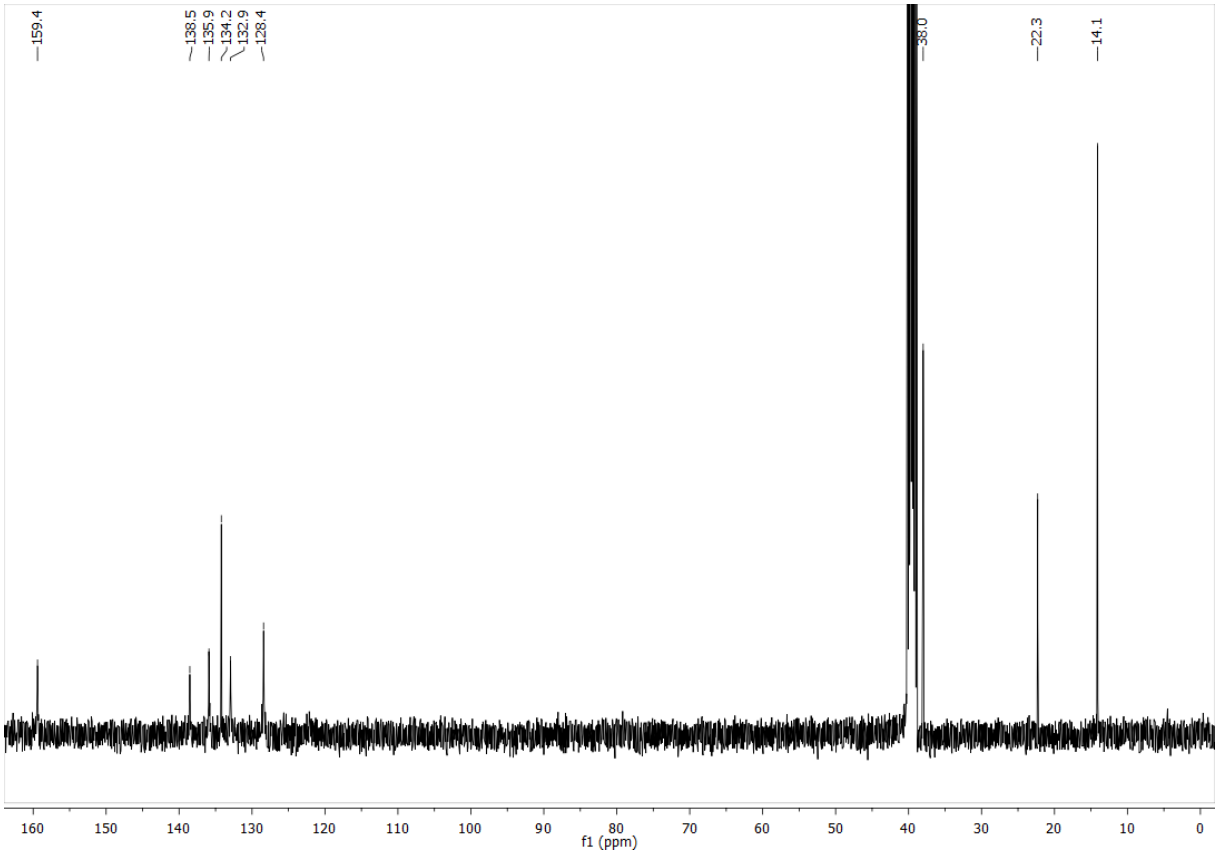
Compound **5**


7.50
3.84
2.80
2.78
2.76
2.10
2.08
2.06
2.05
2.03
1.90
1.95
6.05
3.98
2.05
6.00
f1 (ppm)

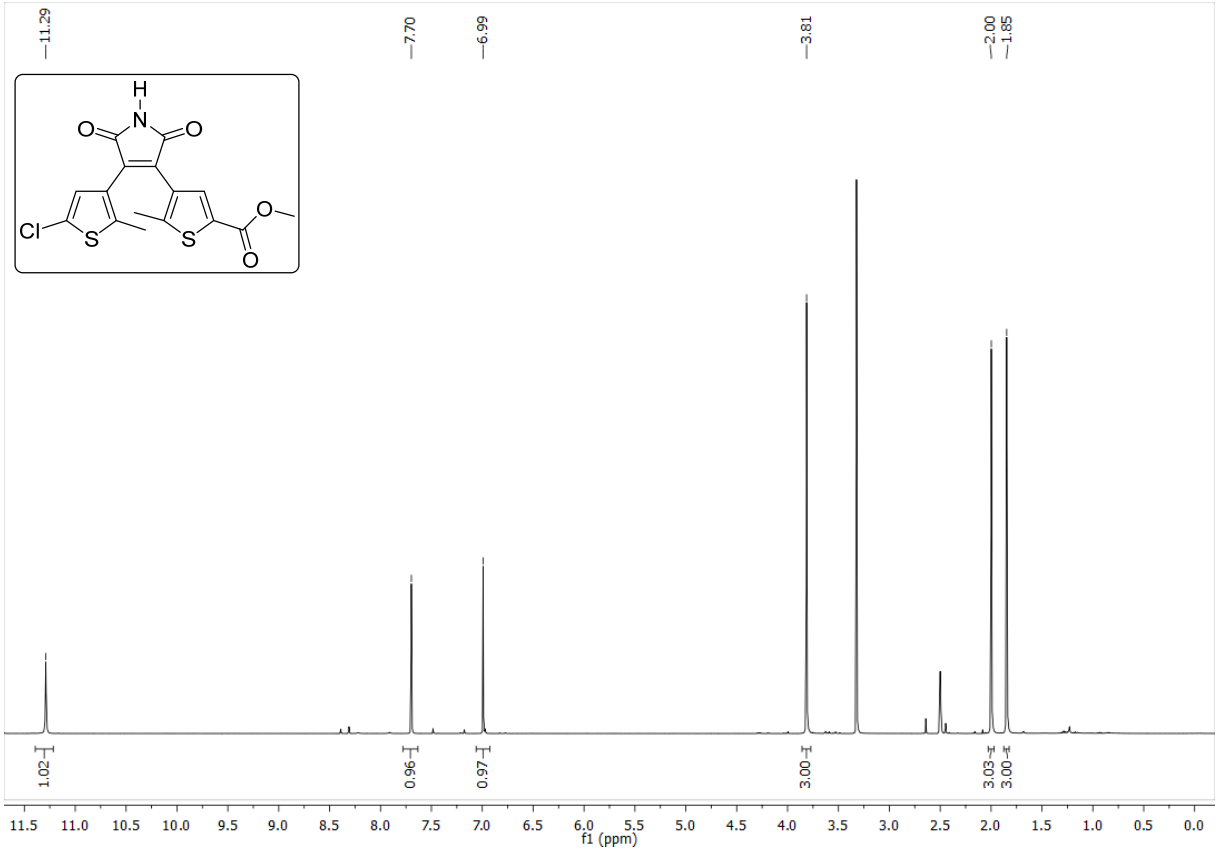

162.7
142.9
136.7
134.9
134.6
129.4
52.2
38.8
23.0
14.9
f1 (ppm)

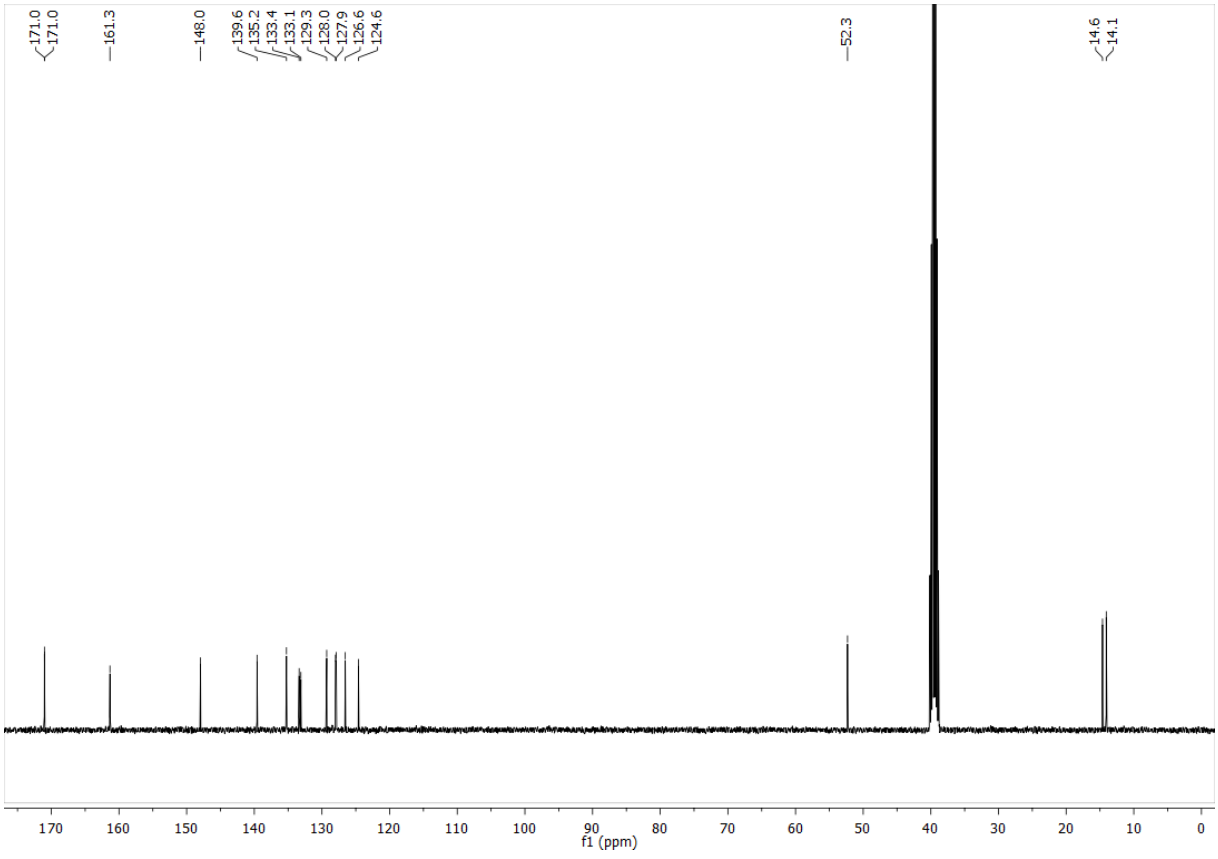
Compound **6**


11.04
9.01
7.35
2.76
2.74
2.73
2.05
2.03
2.01
2.00
1.98
1.87
HO
H
N
O
S
S
N
H
OH
O
1.97
1.98
2.02
4.05
2.09
6.08
f1 (ppm)

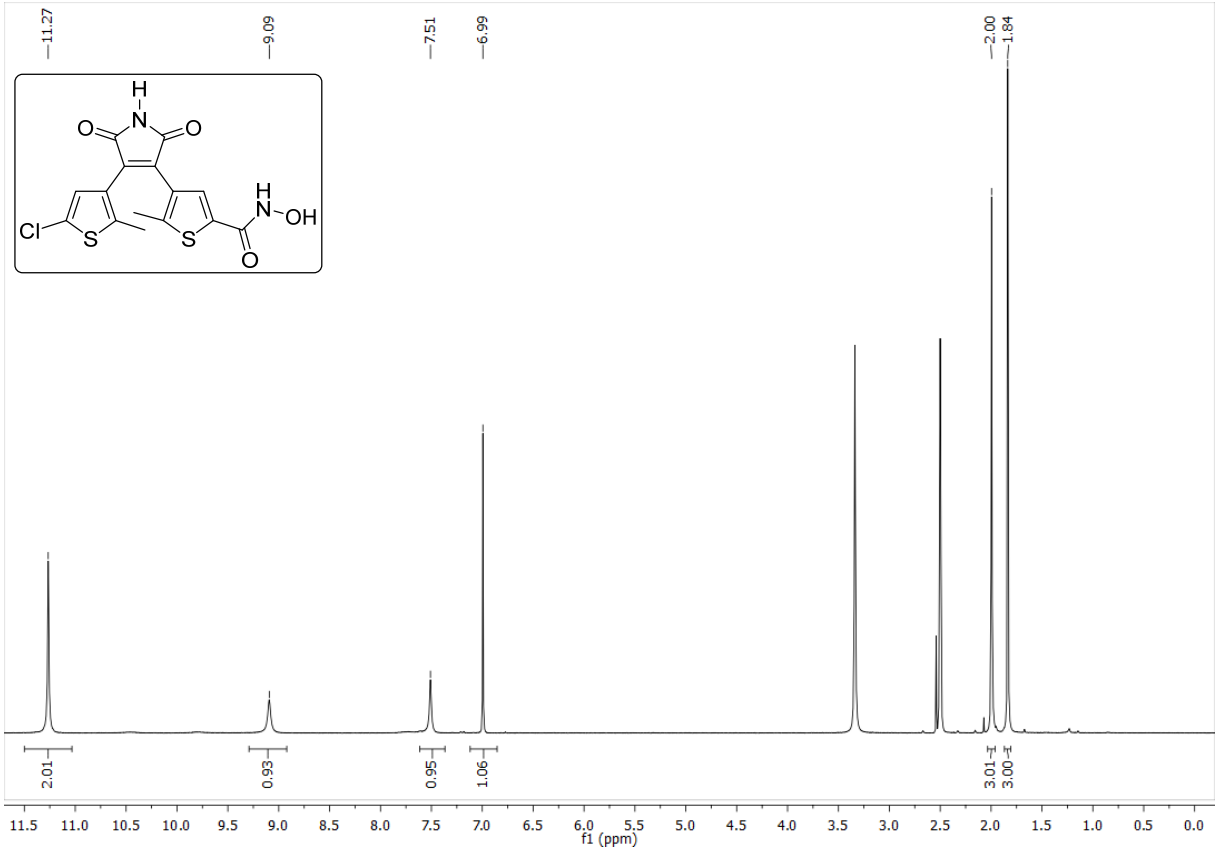

159.4
138.5
135.9
134.2
132.9
128.4
38.0
22.3
14.1
f1 (ppm)

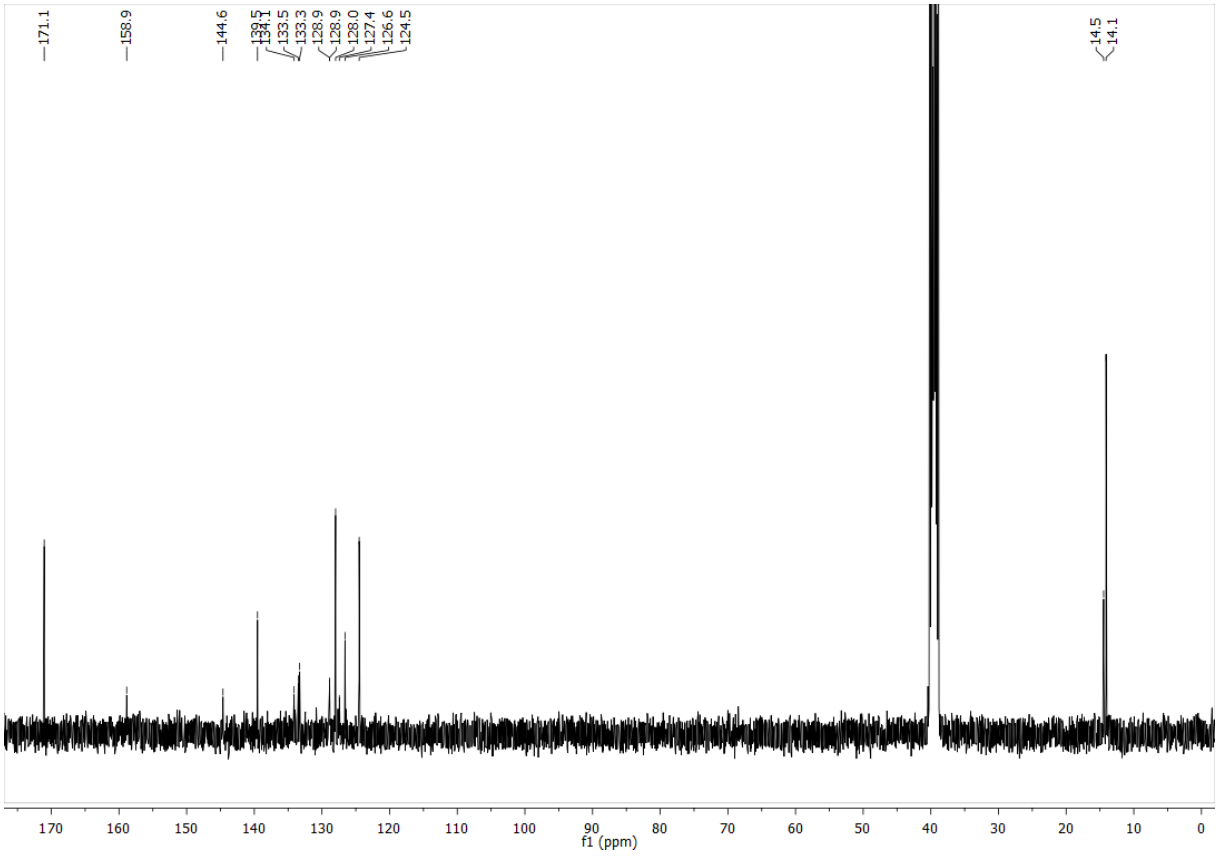
Compound **9**


11.29
7.70
6.99
3.81
2.00
1.85
1.02
0.96
0.97
3.00
3.03
3.00
f1 (ppm)

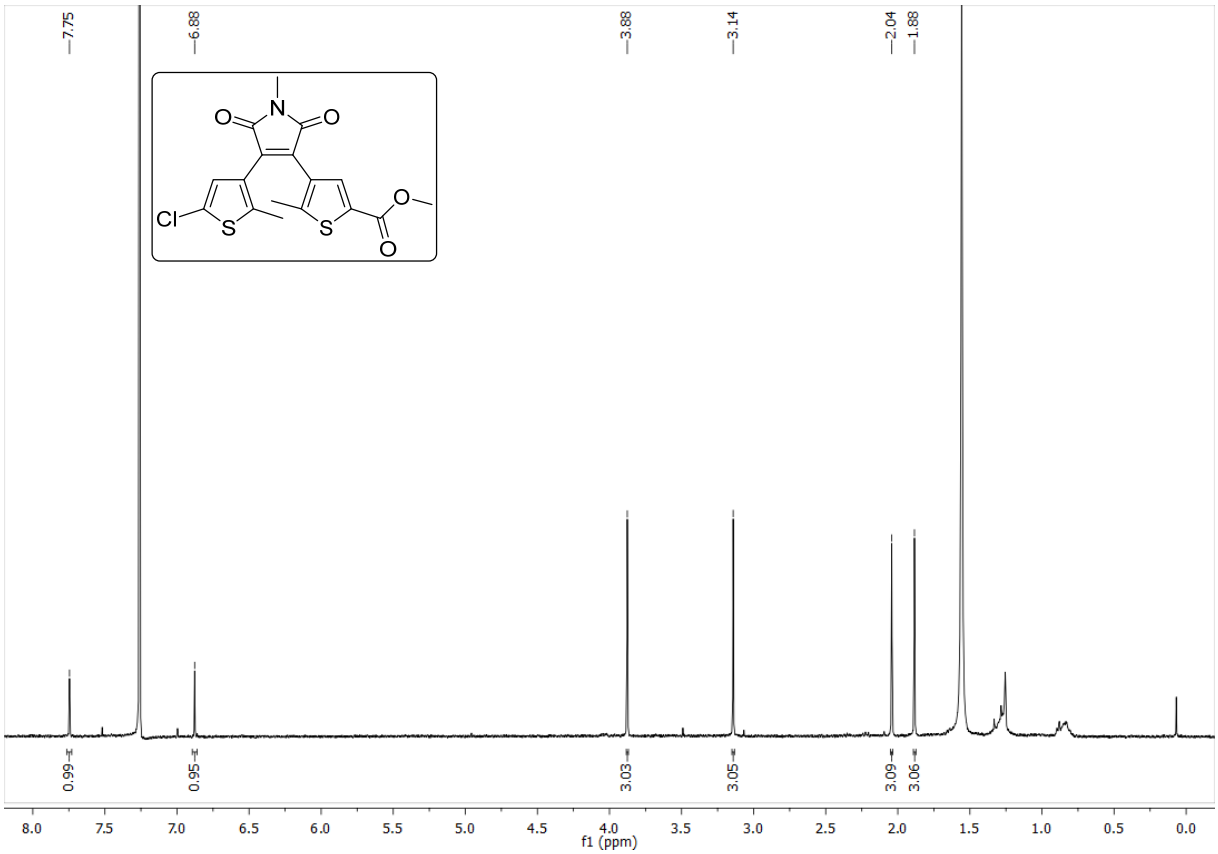

171.0
171.0
161.3
148.0
139.6
135.2
133.4
133.1
129.3
128.0
127.9
126.6
124.6
52.3
14.6
14.1
f1 (ppm)

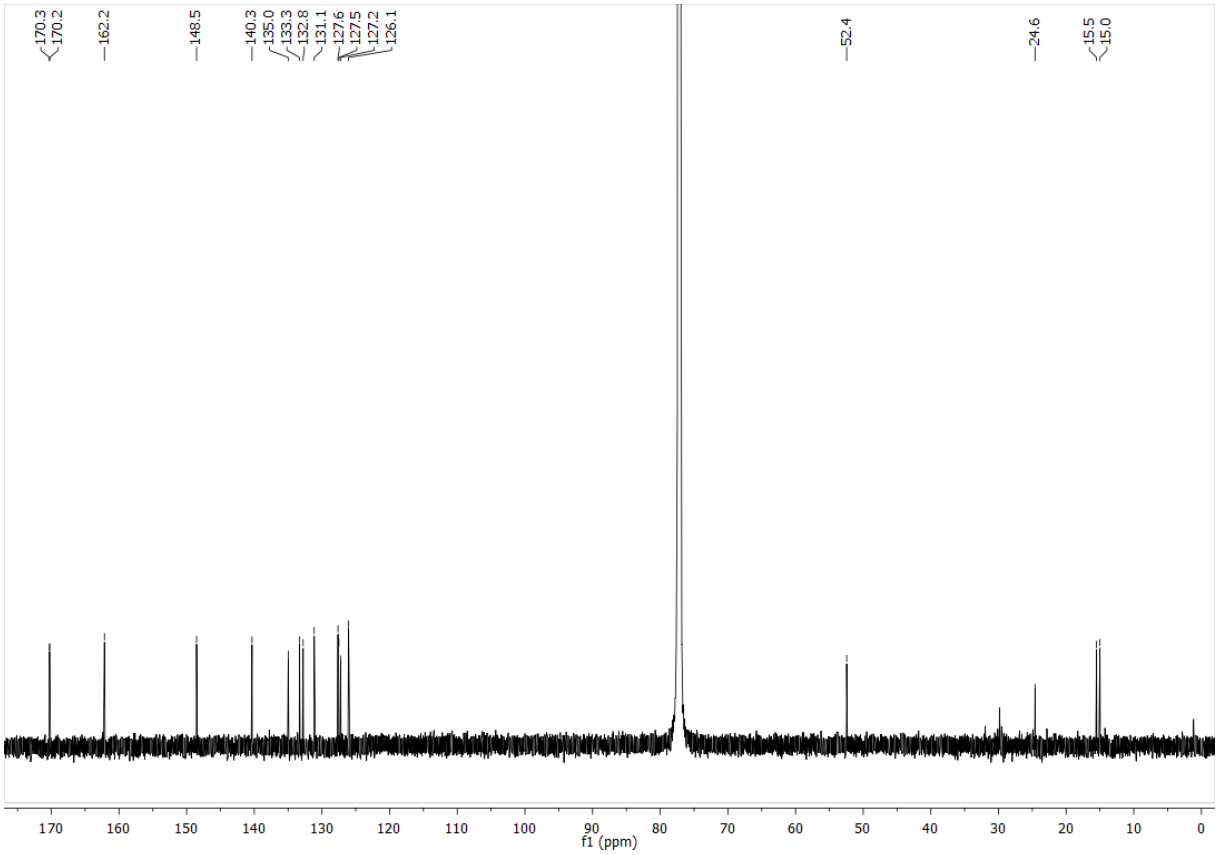
Compound **10**


11.27
9.09
7.51
6.99
2.00
1.84
2.01
0.93
0.95
1.06
3.01
3.00
f1 (ppm)

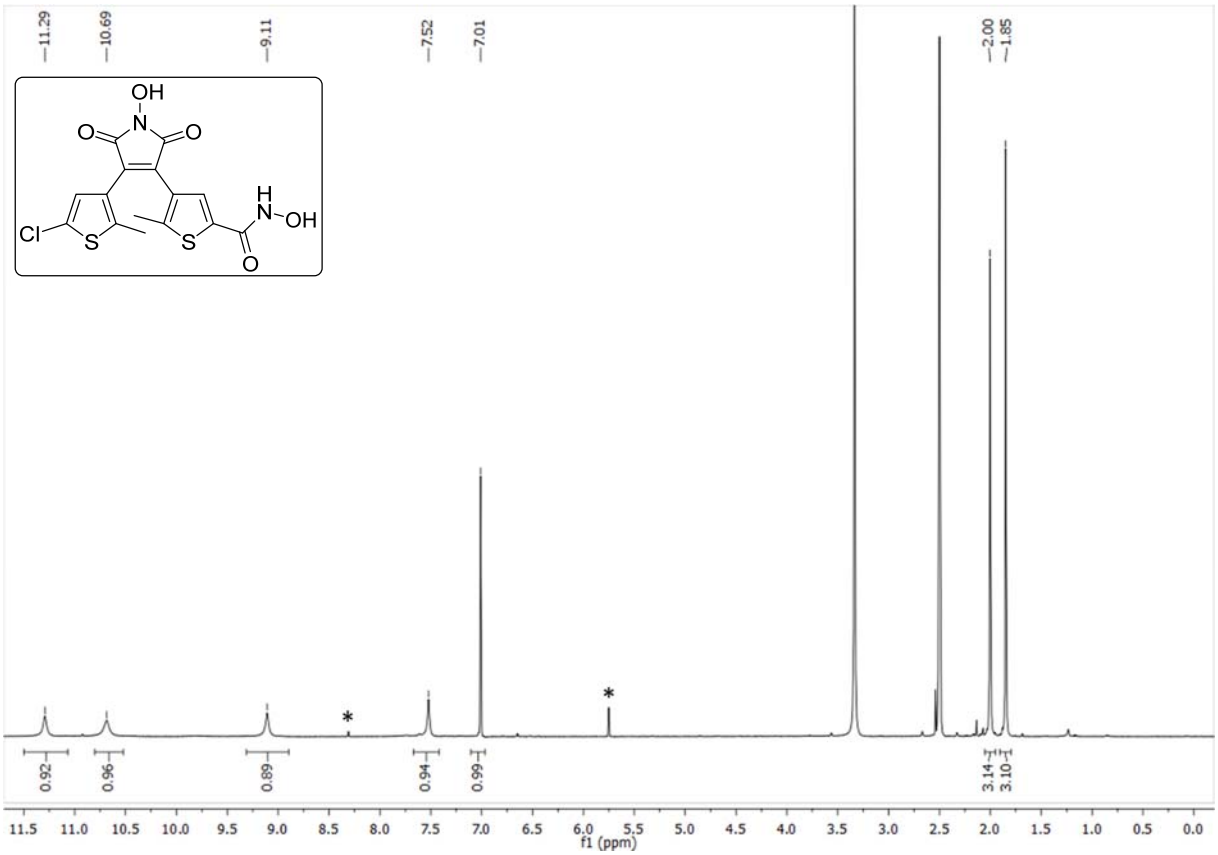

171.1
158.9
144.6
139.5
134.1
133.5
133.3
128.9
128.9
128.0
127.4
126.6
124.5
14.5
14.1
f1 (ppm)

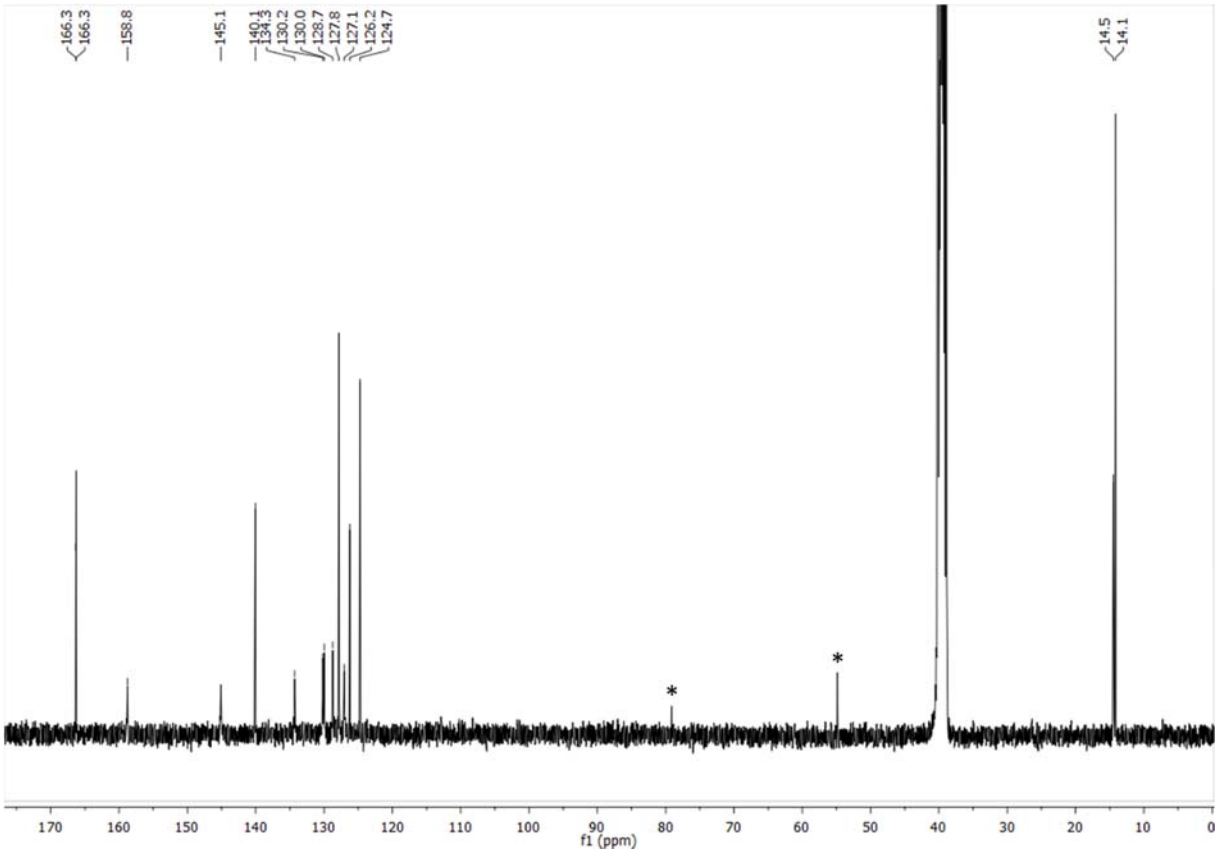
Compound **11**


7.75
6.88
3.88
3.14
2.04
1.88
0.99
0.95
3.03
3.05
3.09
3.06
f1 (ppm)


170.3
170.2
162.2
148.5
140.3
135.0
133.3
132.8
131.1
127.6
127.5
127.2
126.1
52.4
24.6
15.5
15.0
f1 (ppm)

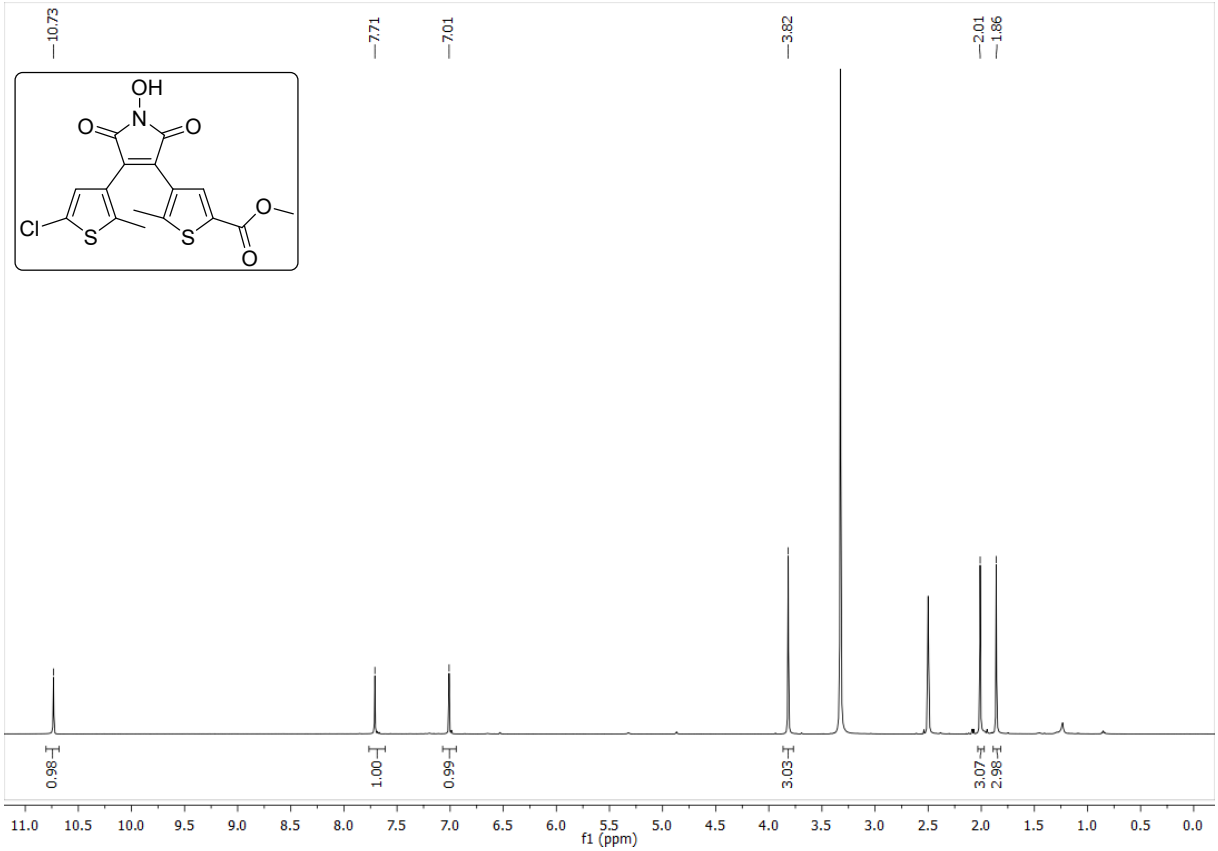
Compound **12**[B]

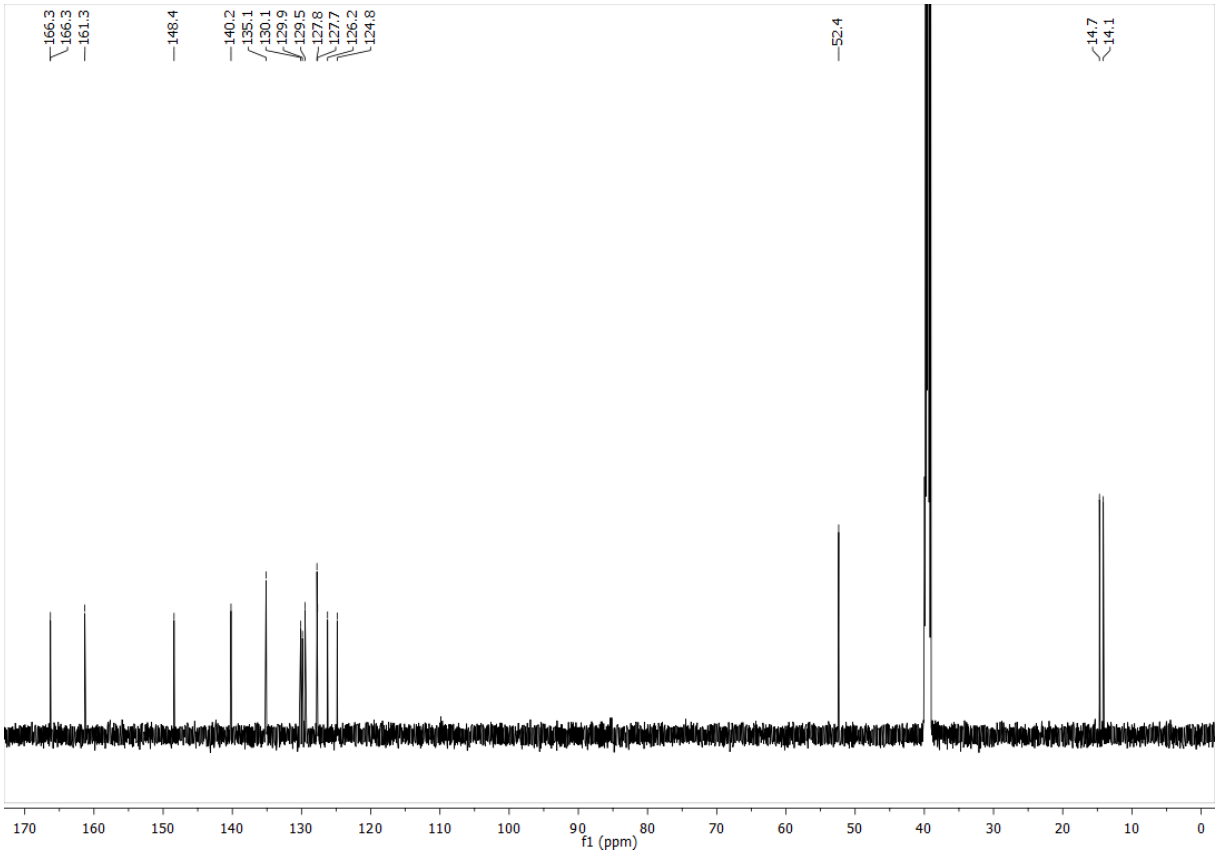




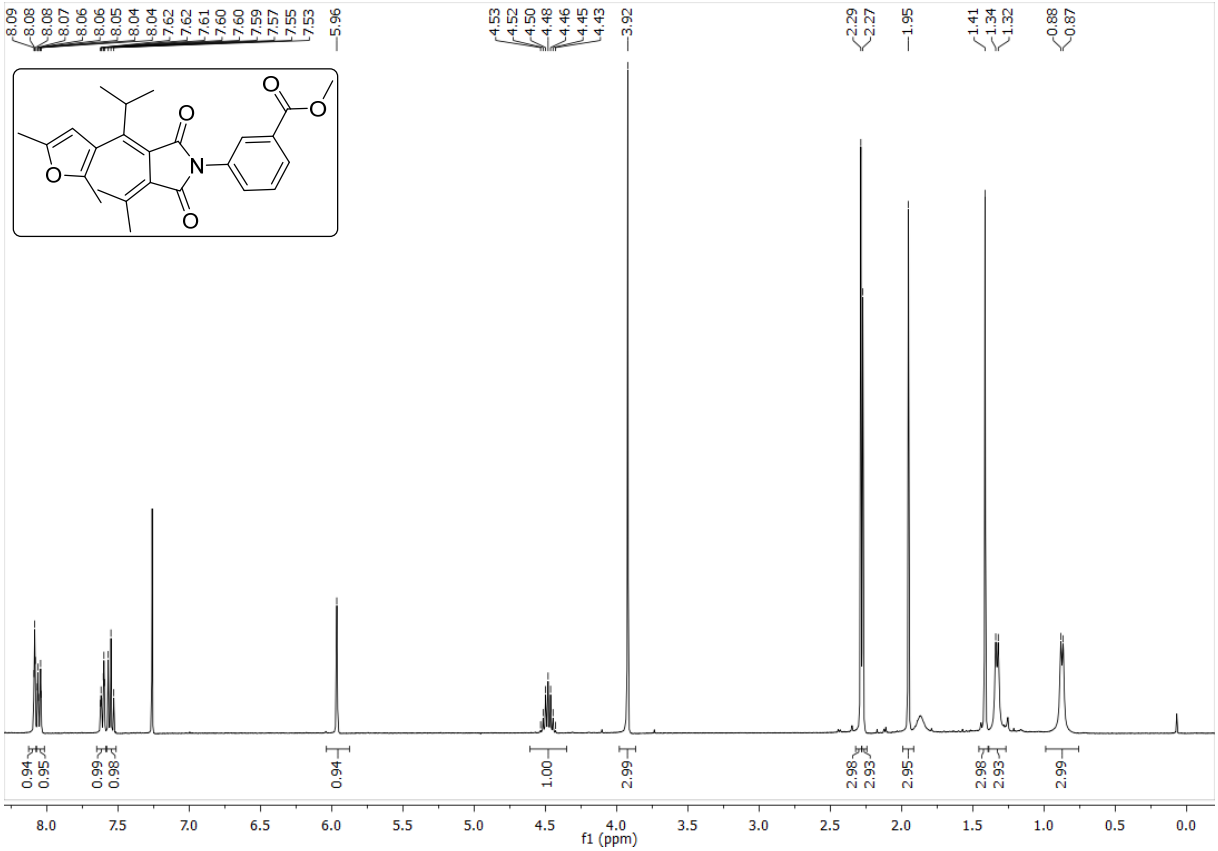
[B] NMR-spectra contain traces of $CHCl_3$ and CH_2Cl_2; signals are marked with *

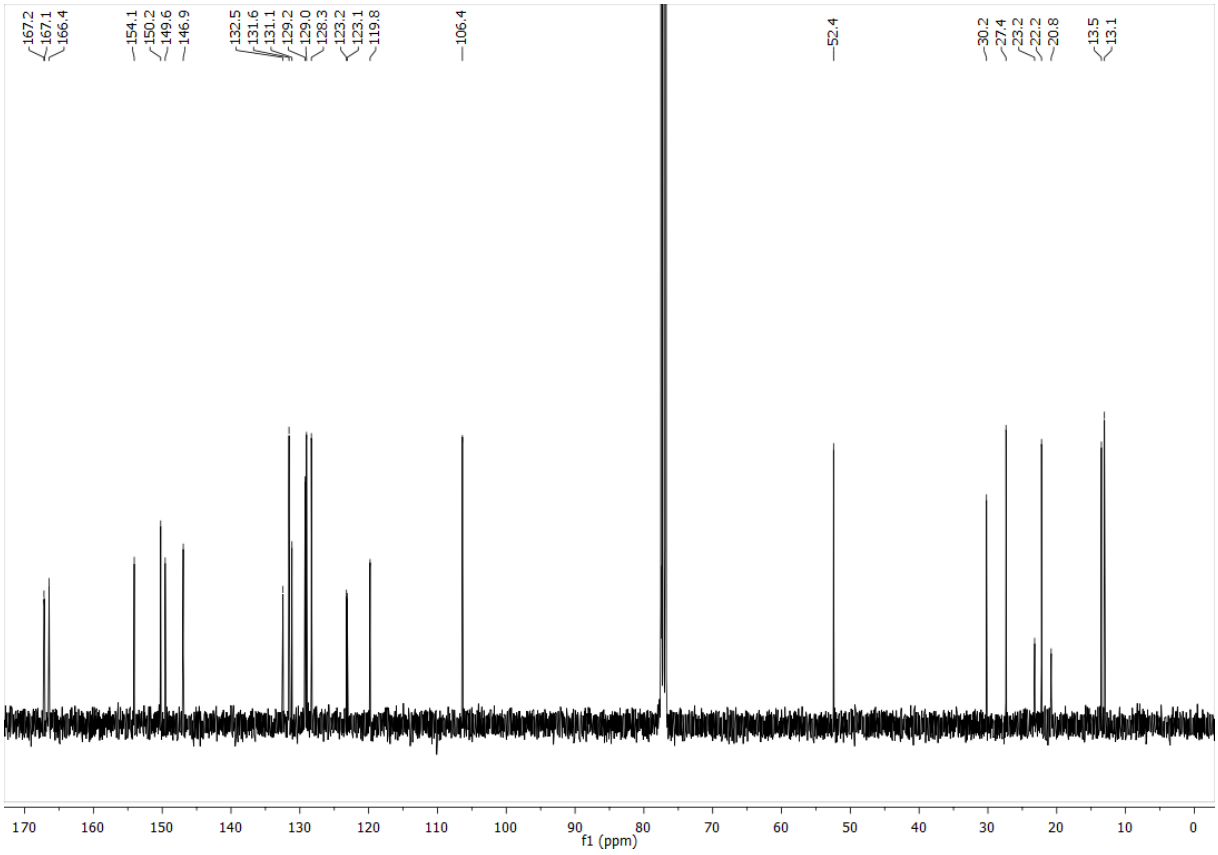
Compound **13**


10.73
7.71
7.01
3.82
2.01
1.86
OH
N
O
O
Cl
S
S
O
O
0.98
1.00
0.99
3.03
3.07
2.98
f1 (ppm)

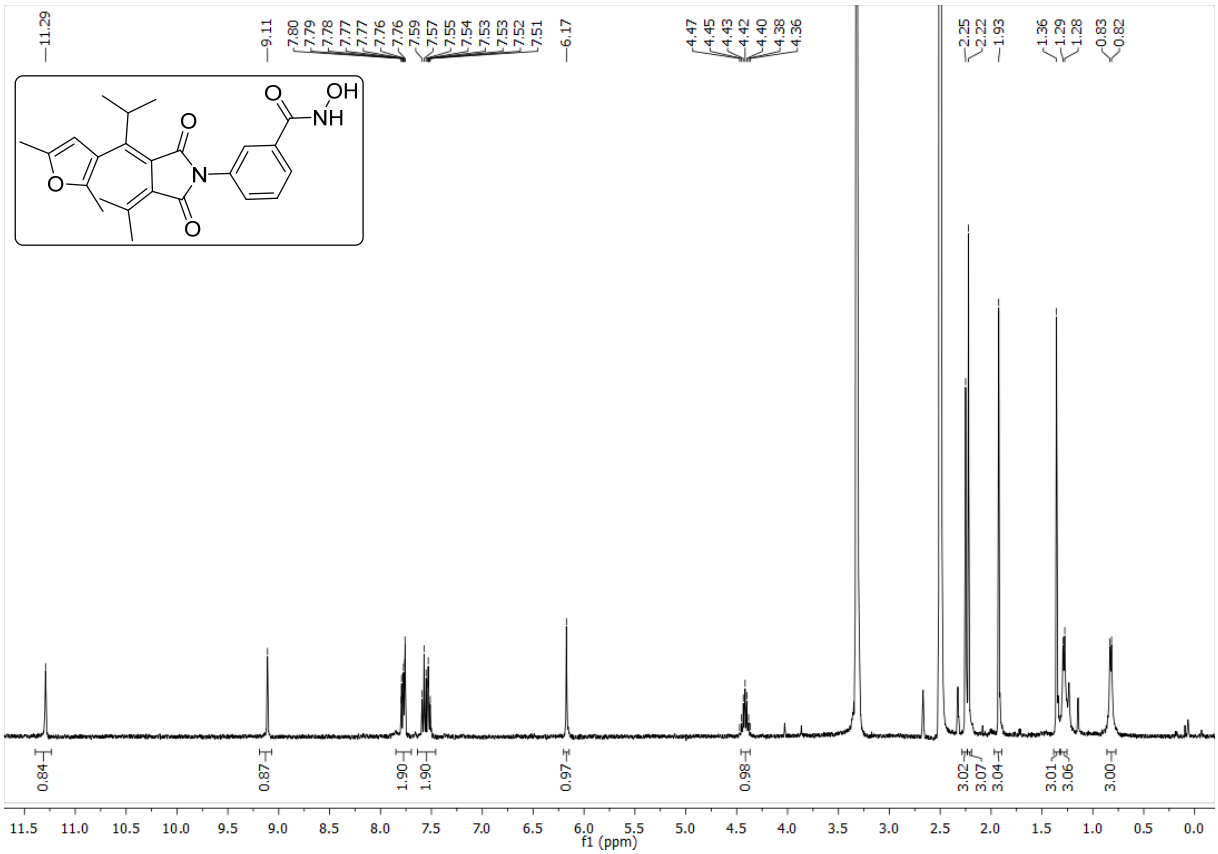

166.3
166.3
161.3
148.4
140.2
135.1
130.1
129.9
129.5
127.8
127.7
126.2
124.8
52.4
14.7
14.1
f1 (ppm)

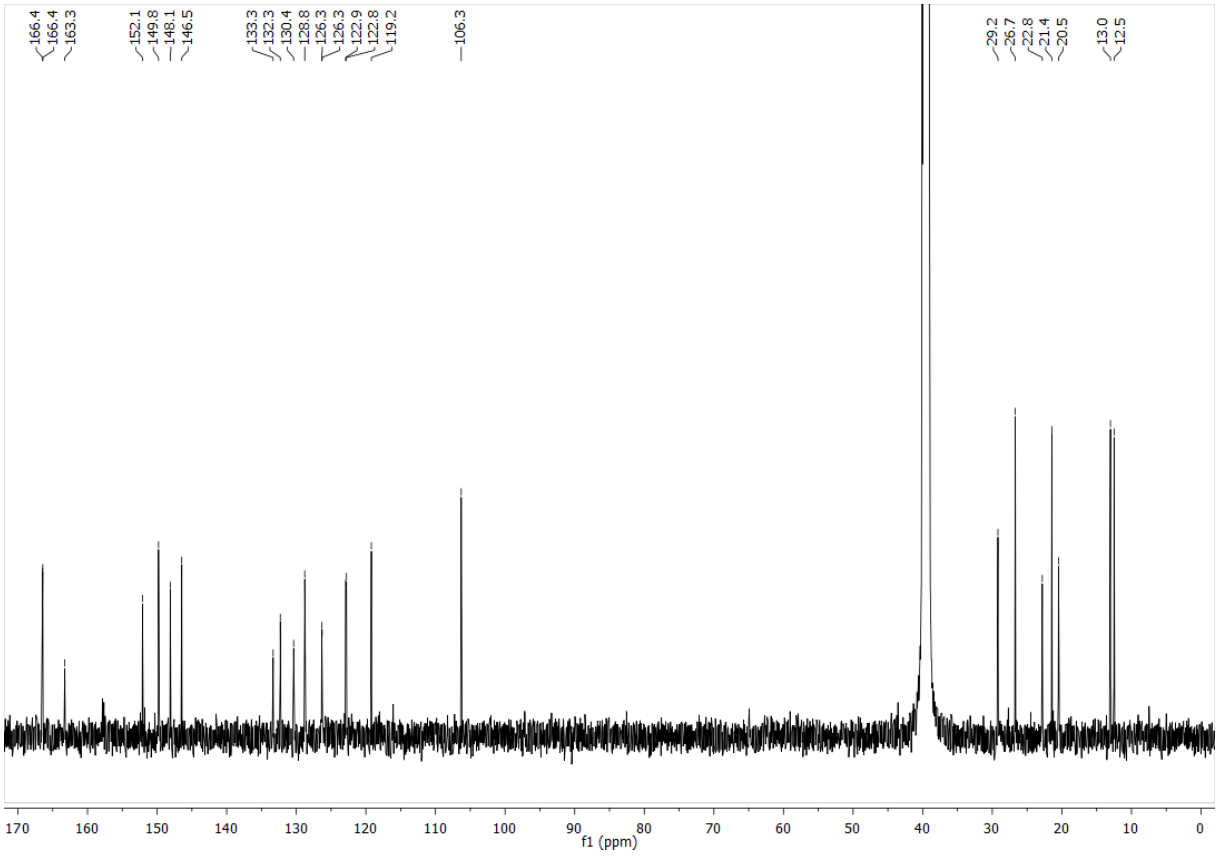
Compound **17**


8.09
8.08
8.08
8.07
8.06
8.06
8.06
8.05
8.04
8.04
7.62
7.62
7.61
7.60
7.60
7.59
7.57
7.55
7.53
5.96
4.53
4.52
4.50
4.48
4.46
4.45
4.43
3.92
2.29
2.27
1.95
1.41
1.34
1.32
0.88
0.87
0.94
0.95
0.99
0.98
0.94
1.00
2.99
2.98
2.93
2.95
2.98
2.93
2.99
f1 (ppm)

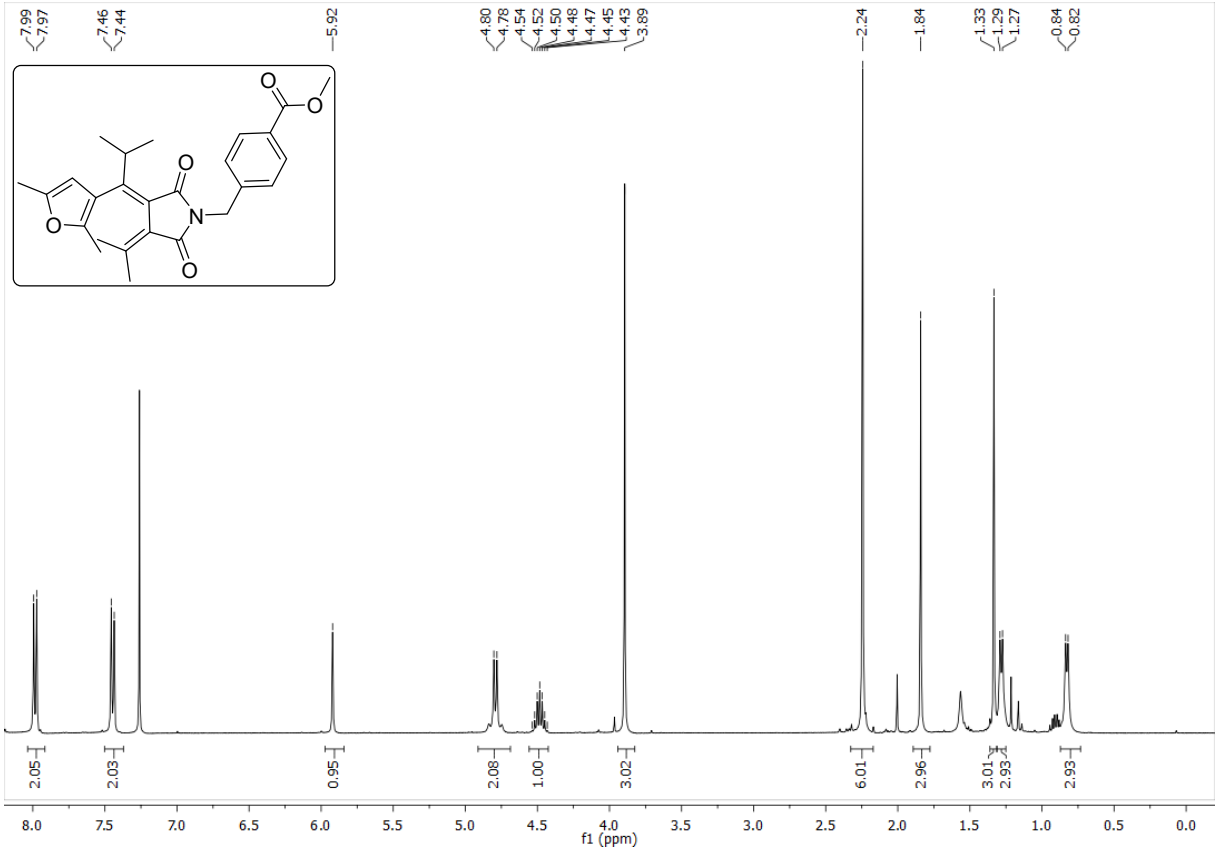

167.2
167.1
166.4
154.1
150.2
149.6
146.9
132.5
131.6
131.1
129.2
129.0
128.3
123.2
123.1
119.8
106.4
52.4
30.2
27.4
23.2
22.2
20.8
13.5
13.1
f1 (ppm)

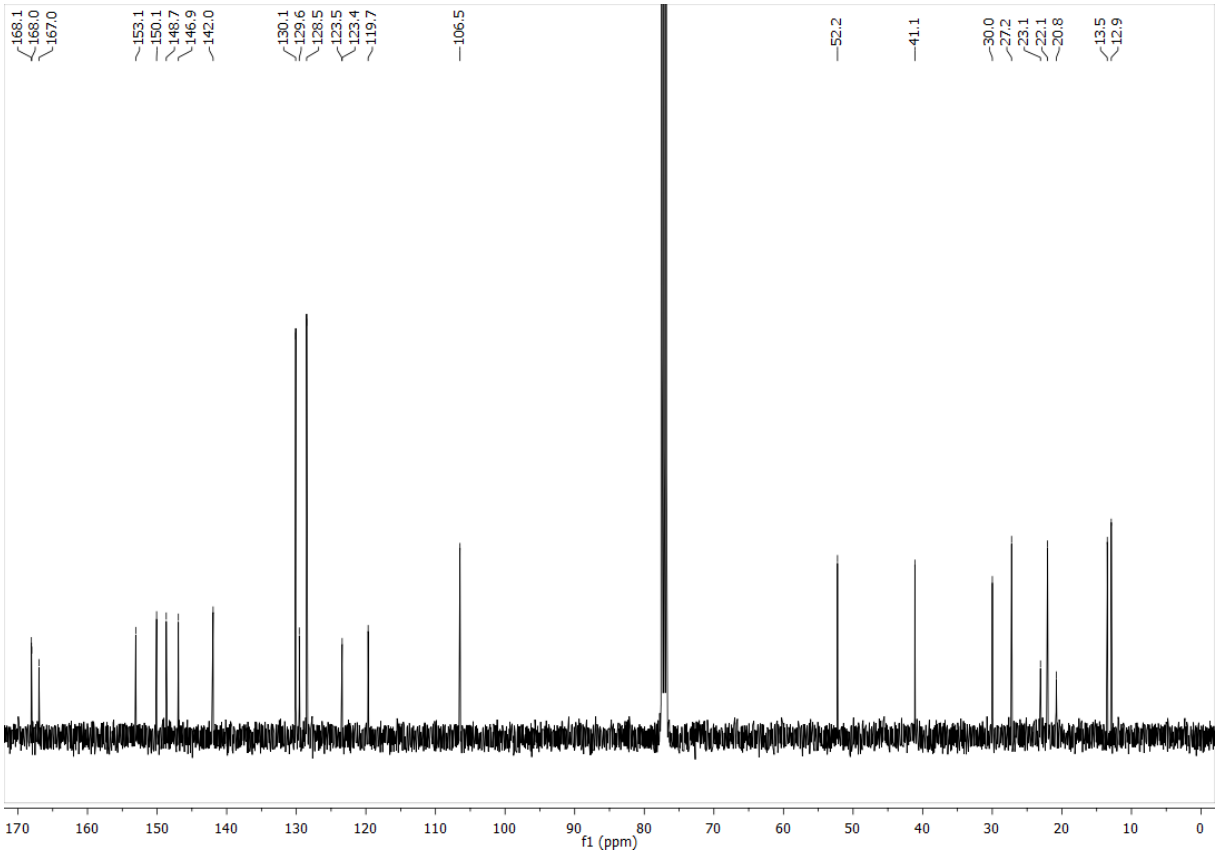
Compound **18**


11.29
9.11
7.80
7.79
7.78
7.77
7.77
7.76
7.76
7.59
7.57
7.55
7.54
7.53
7.53
7.52
7.51
6.17
4.47
4.45
4.43
4.42
4.40
4.38
4.36
2.25
2.22
1.93
1.36
1.29
1.28
0.83
0.82
O
OH
NH
O
N
O
O
0.84
0.87
1.90
1.90
0.97
0.98
3.02
3.07
3.04
3.01
3.06
3.00
f1 (ppm)

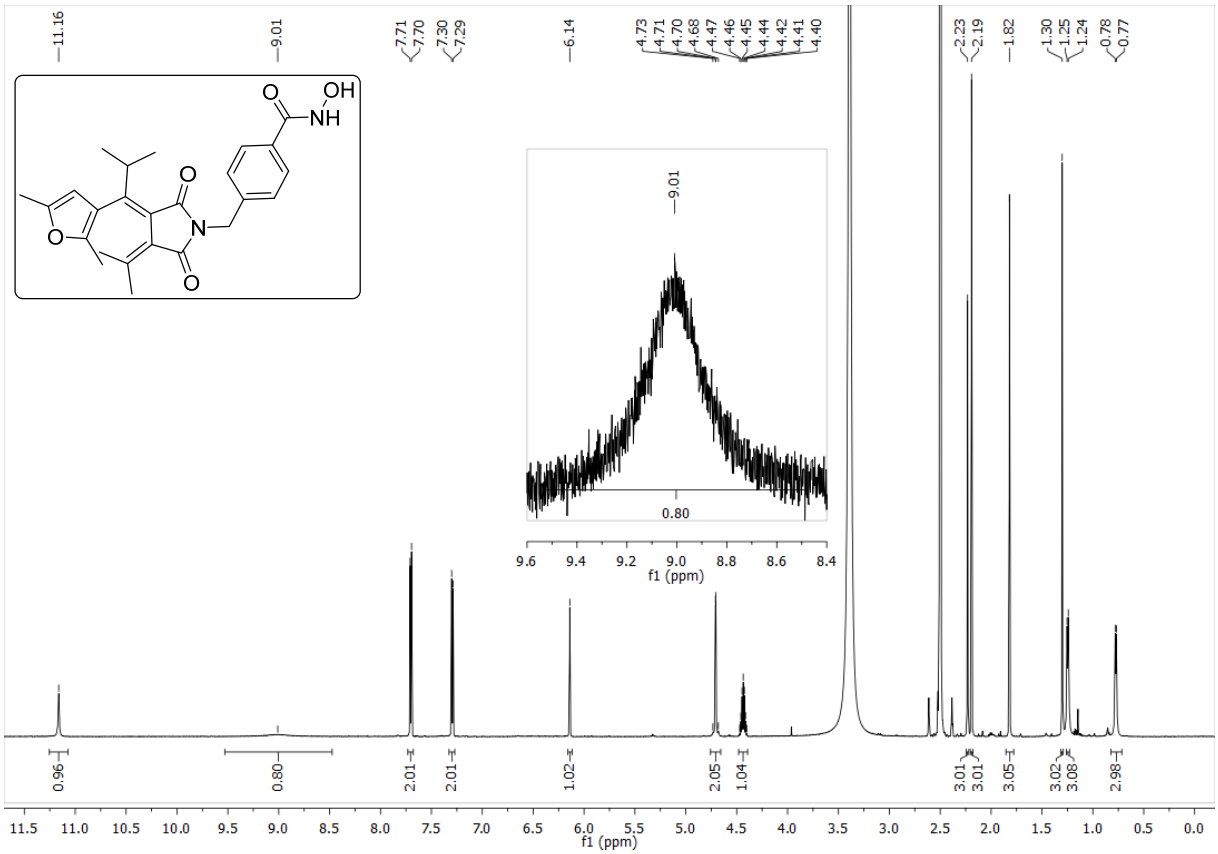

166.4
166.4
163.3
152.1
149.8
148.1
146.5
133.3
132.3
130.4
128.8
126.3
126.3
122.9
122.8
119.2
106.3
29.2
26.7
22.8
21.4
20.5
13.0
12.5
f1 (ppm)

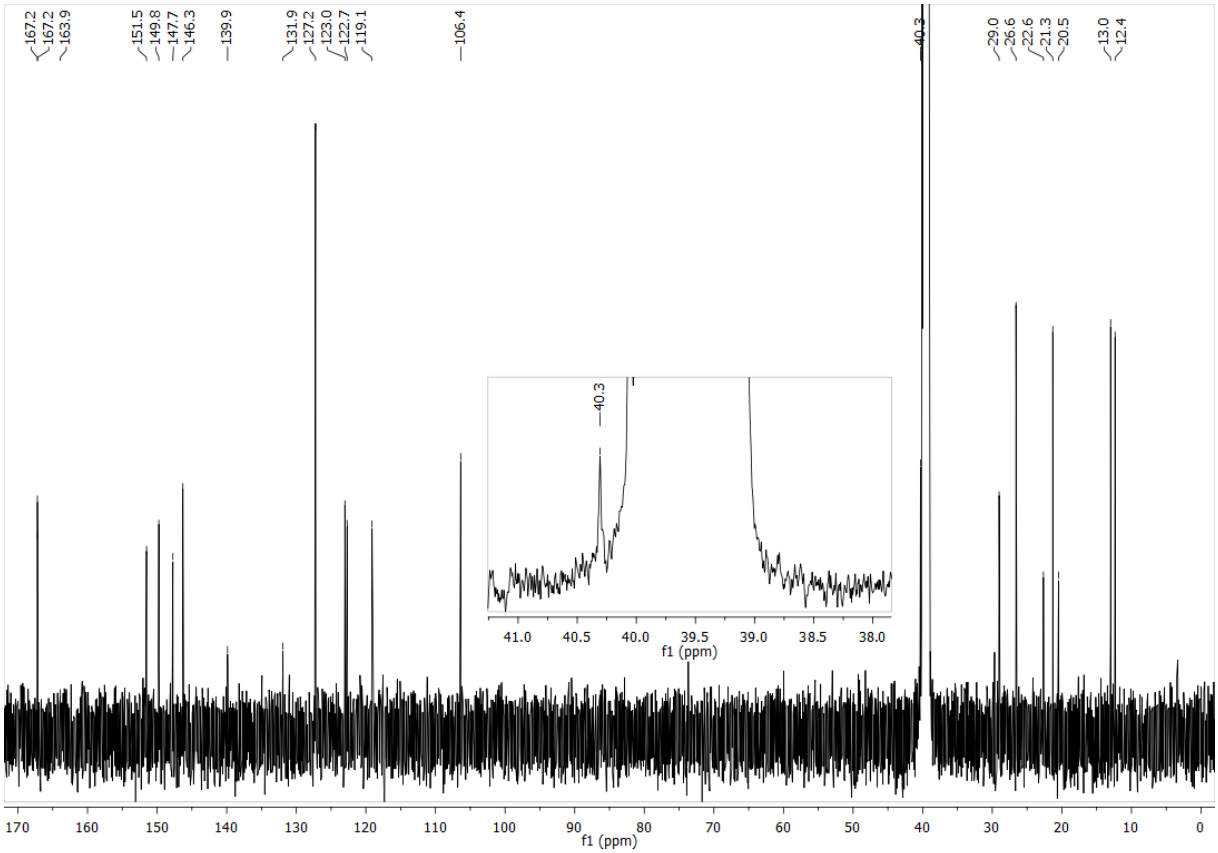
Compound **19**


7.99
7.97
7.46
7.44
5.92
4.80
4.78
4.54
4.52
4.50
4.48
4.47
4.45
4.43
3.89
2.24
1.84
1.33
1.29
1.27
0.84
0.82
O
O
O
N
O
O
2.05
2.03
0.95
2.08
1.00
3.02
6.01
2.96
3.01
2.93
2.93
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)


168.1
168.0
167.0
153.1
150.1
148.7
146.9
142.0
130.1
129.6
128.5
123.5
123.4
119.7
106.5
52.2
41.1
30.0
27.2
23.1
22.1
20.8
13.5
12.9
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Compound **20**


11.16
9.01
7.71
7.70
7.30
7.29
6.14
4.73
4.71
4.70
4.68
4.47
4.46
4.45
4.44
4.42
4.41
4.40
2.23
2.19
1.82
1.30
1.25
1.24
0.78
0.77
OH
NH
O
O
O
N
O
0.80
f1 (ppm)
0.96
0.80
2.01
2.01
1.02
2.05
1.04
3.01
3.01
3.05
3.02
3.08
2.98
f1 (ppm)


167.2
167.2
163.9
151.5
149.8
147.7
146.3
139.9
131.9
127.2
123.0
122.7
119.1
106.4
40.3
29.0
26.6
22.6
21.3
20.5
13.0
12.4
40.3
f1 (ppm)
f1 (ppm)