Supporting information

Synthesis and evaluation of influenza A viral neuraminidase candidate inhibitors based on a bicyclo[3.1.0]hexane scaffold

Cinzia Colombo,[†] [‡]*B. Mario Pinto,*[†] *Anna Bernardi,* [‡]*Andrew J. Bennet*[*,†]

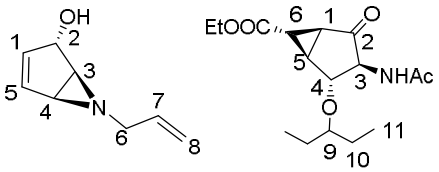
[†]Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia, Canada V5A 1S6; [‡] Università degli Studi di Milano, Dipartimento di Chimica, Via Golgi 19, I-20133 Milano, Italy.

[*]Address correspondence to Andrew J. Bennet, Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6. Tel: 778-782-8814 ; Fax: 778-782-3765; E-mail: bennet@sfu.ca

Table of contents

Products numbering for Spectral Assignment

The following numbering was adopted for products assignment. The final scaffold, a cyclopentane ring fused with a cyclopropane bearing the carboxylic acid function, was numbered as reported below. Numbering of the precursor units was adopted similarly, to conserve the carbon positions on the cyclopentene scaffold (see example below).



Stereochemical assignment for the Johnson-Corey-Chaykovsky products 20 and 30

Coupling constants for the cyclopropyl ring protons H_1, H_5, H_6 (Figure S3) give information about the exo and endo configuration at carbon C6, while the coupling constant between H_5 and the adjacent H_4 on the carbon bearing the 3-pentyl ether gives information about the relative configuration of the ether and the cyclopropane ring. Specifically, protons H_1 and H_5 are *cis* with coupling constants of 6.2 Hz and 6.1 Hz for **20** and **30**, respectively. The H_1-H_6 and H_5-H_6 coupling constants are consistent with a *trans* relationship, being in the range 2.5-3.8 Hz for both **20** and **30**, and as a consequence both are *exo*-products, in agreement with expectations.[1] In addition, compound **30** is consistent with an *exo-anti* configuration, showing no discernible coupling constant between H_4 and H_5 ($J_{4\text{-}5}$ ~ 0 Hz), typical of *trans* relationship, whereas, *exo-syn* **20** shows $J_{4\text{-}5}$ = 5.1 Hz and a deshielded H_1 resonance, relative to **30**, which are consistent with a *cis* relationship.[2- 3] Moreover, H_3 moves upfield in **20** as it is shielded by the cyclopropyl cone on the same side of the cyclopentane ring, a similar observation is made for H_4 in **30** (Figure S3).

Figure S1. ^{1}H-NMR spectra of compound **26** (top panel) to compound **31** (middle panel). Formation of propionaldehyde in $CDCl_3$ and formation of compound **32** (bottom panel).

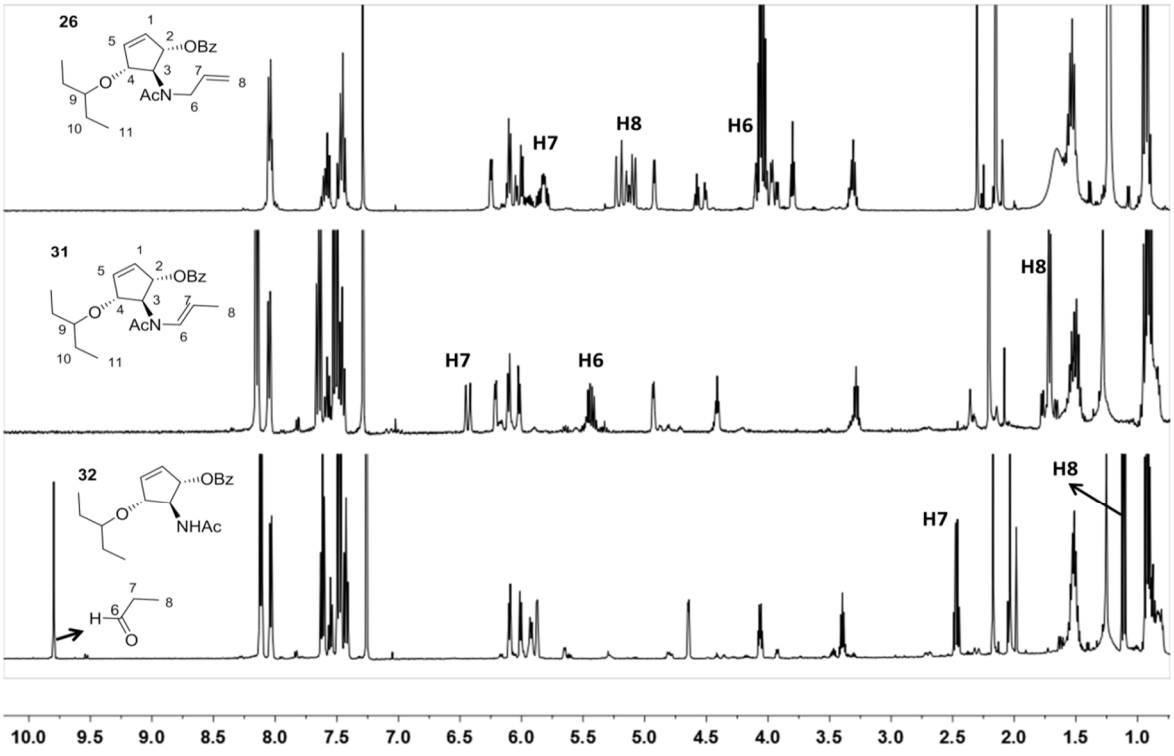


Figure S2. Conversion from compound **33** to compound **34** in $CDCl_3$.

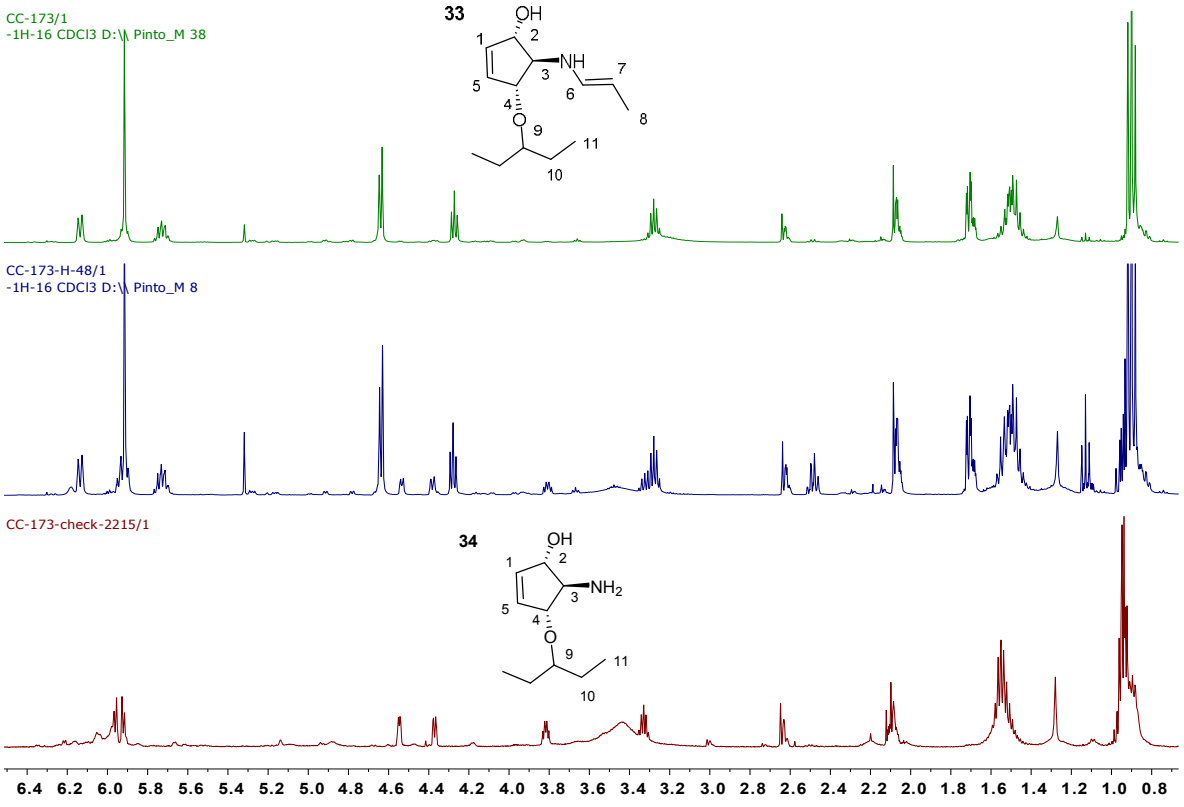
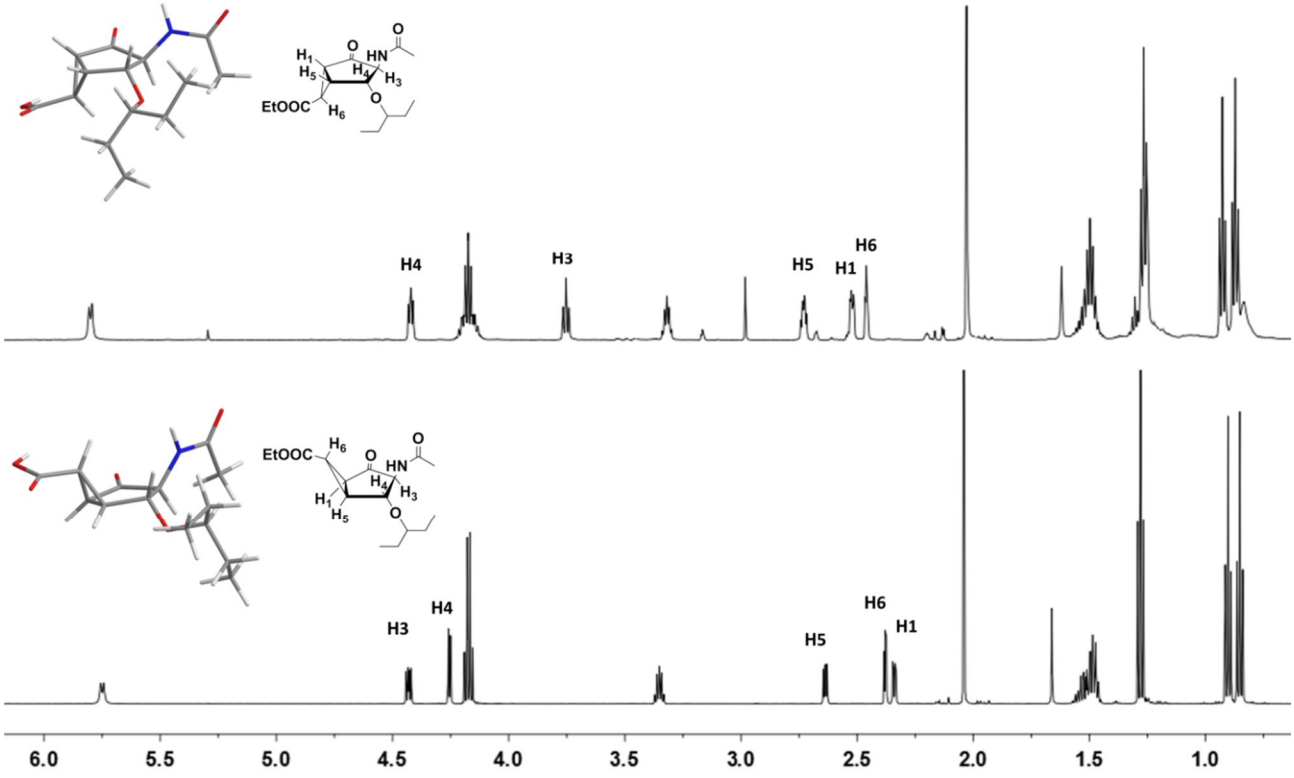


Figure S3. [1]H-NMR spectra of compound **20** (top panel) and compound **30** (bottom panel) and assignments of significant proton chemical shifts.



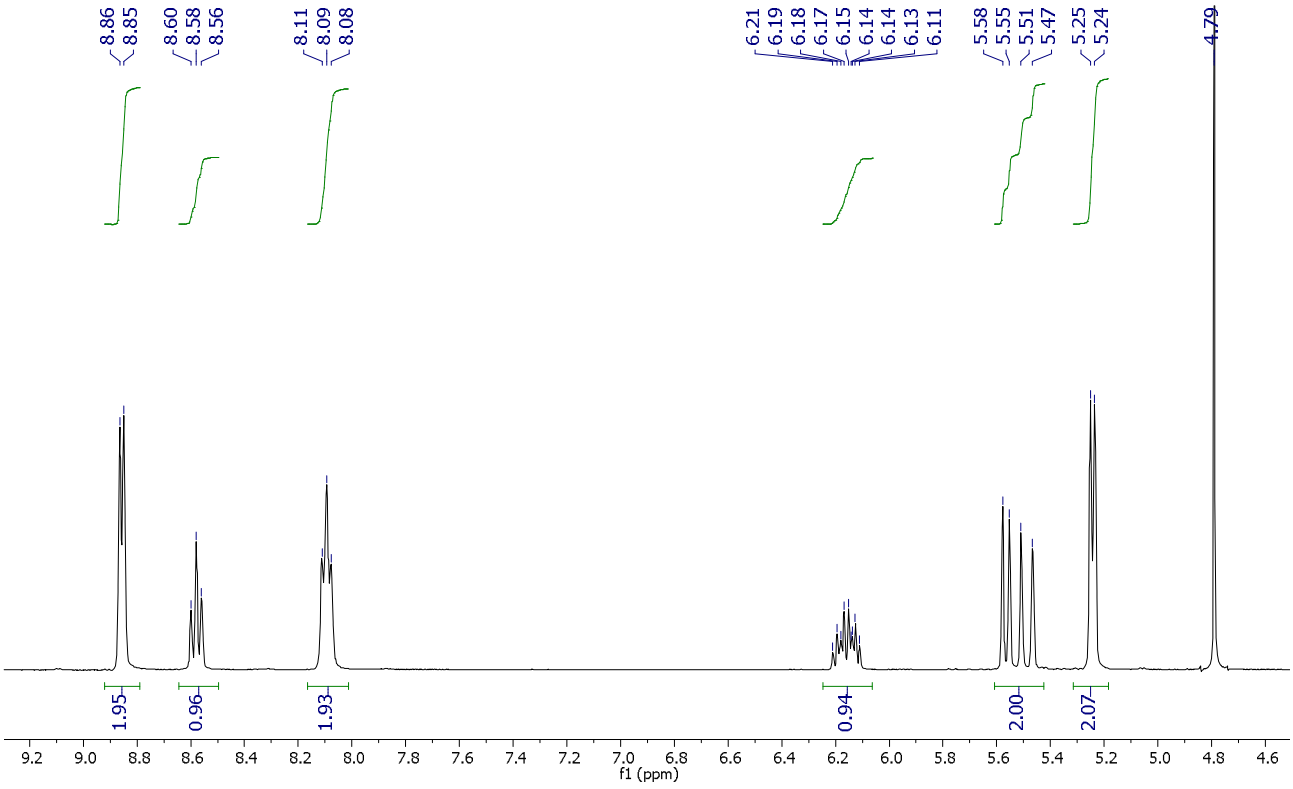
REFERENCES

(1) Romo, D.; Meyers, A. I. *Journal of Organic Chemistry* **1992**, *57*, 6265.

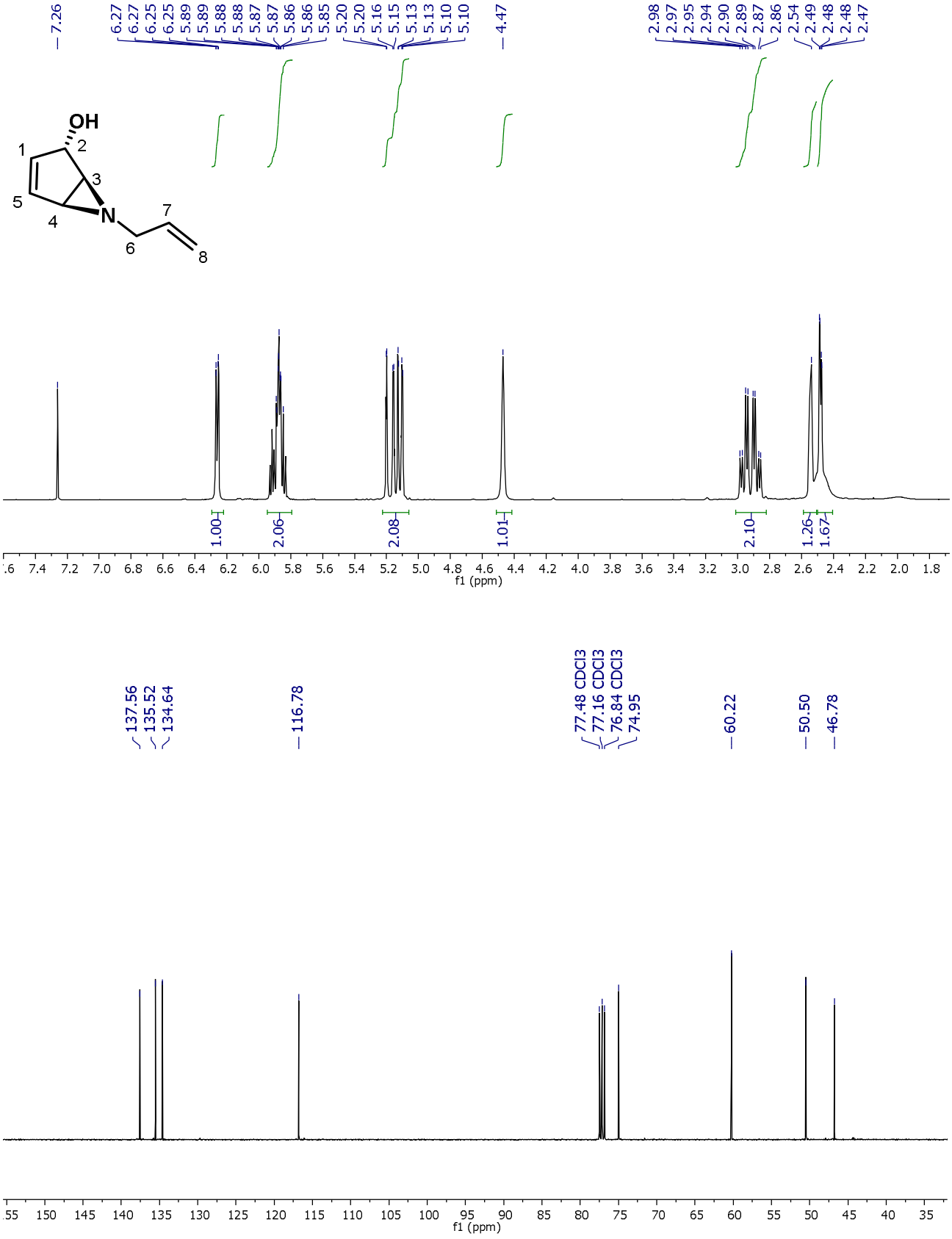
(2) Zhang, R.; Mamai, A.; Madalengoitia, J. S. *Journal of Organic Chemistry* **1999**, *64*, 547.

(3) Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. *Journal of Medicinal Chemistry* **2000**, *43*, 4893.

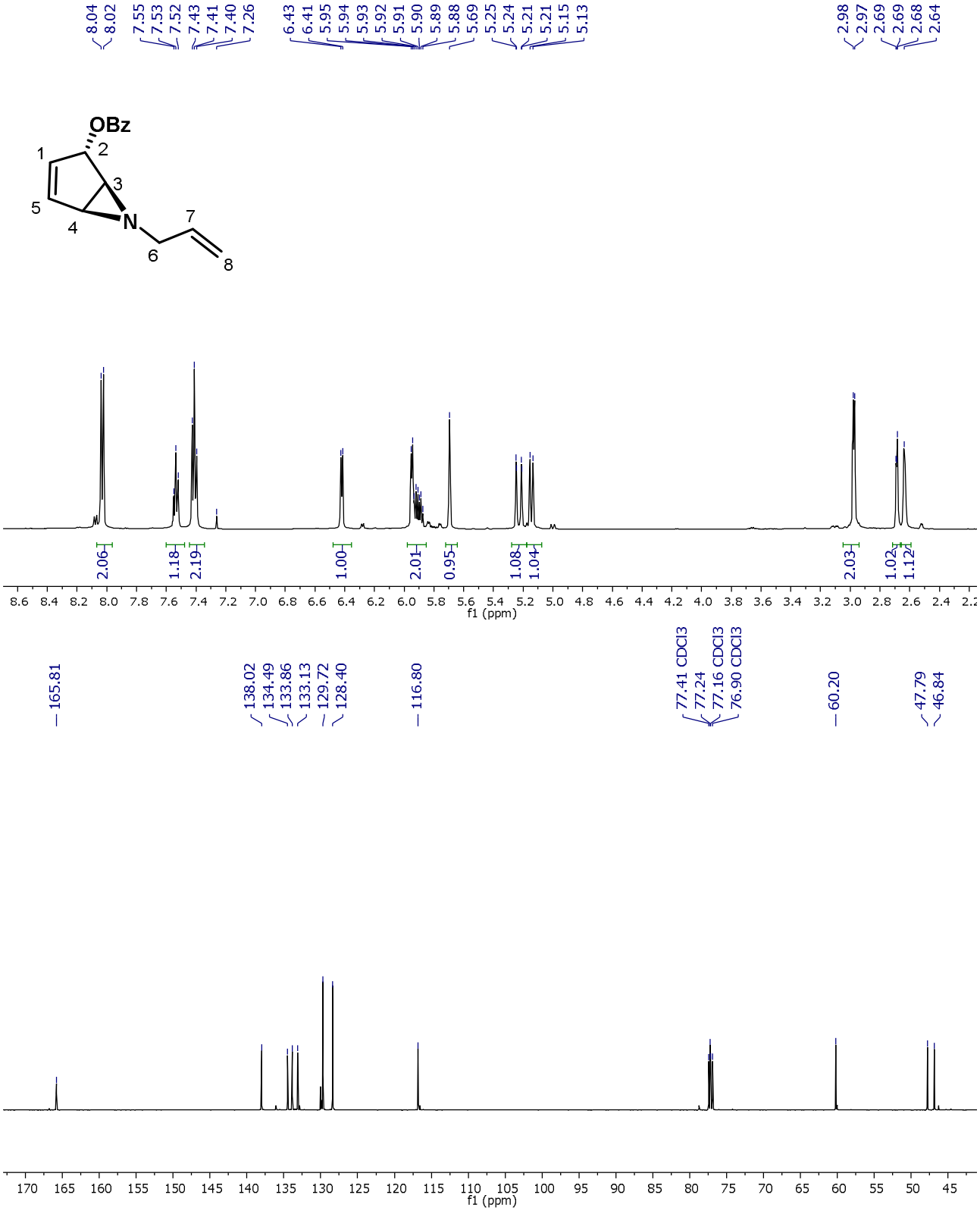
Compound 23


8.86
8.85
8.60
8.58
8.56
8.11
8.09
8.08
6.21
6.19
6.18
6.17
6.15
6.14
6.14
6.13
6.11
5.58
5.55
5.51
5.47
5.25
5.24
4.79
1.95
0.96
1.93
0.94
2.00
2.07
f1 (ppm)

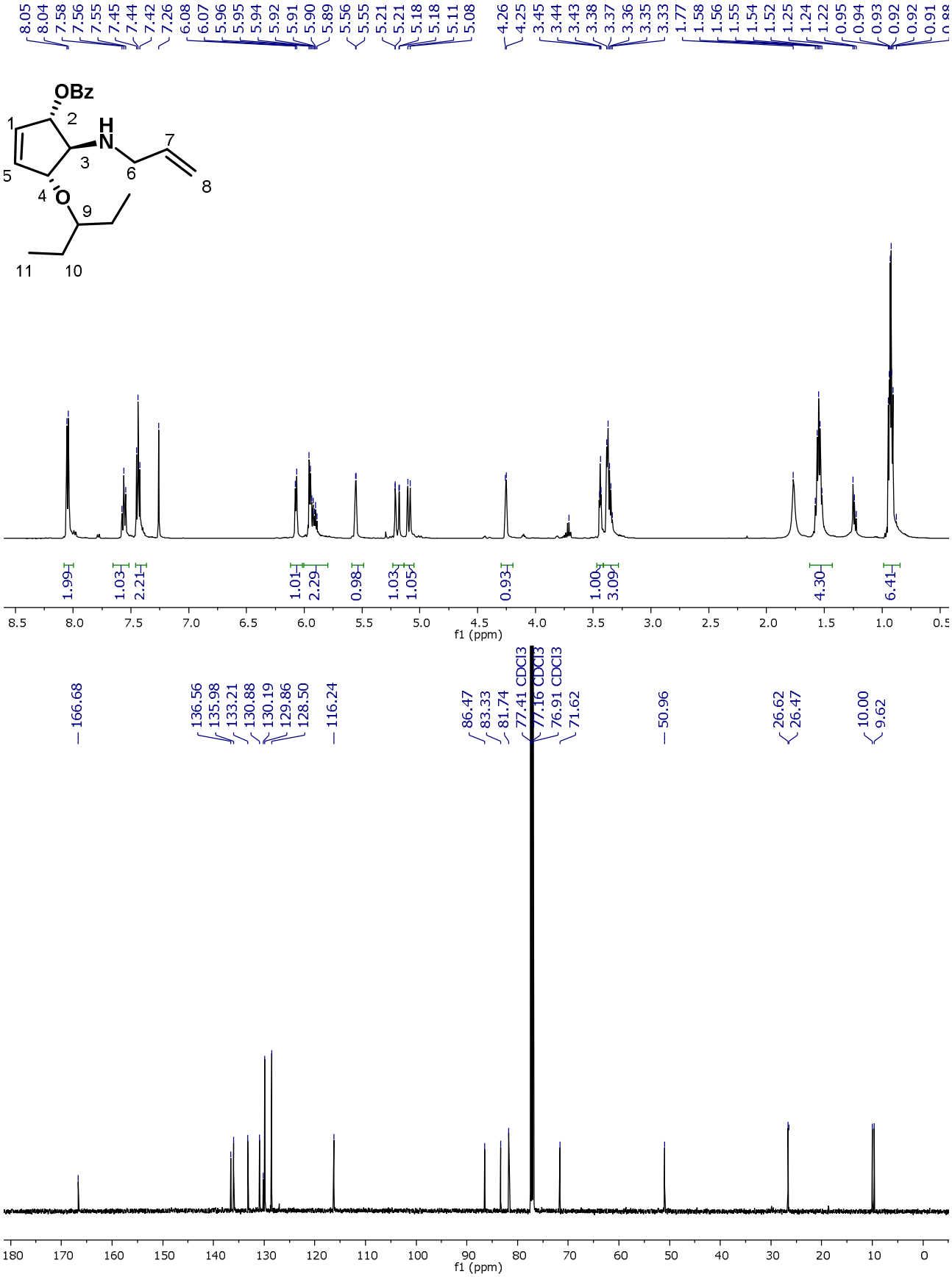
Compound 22


7.26
6.27
6.27
6.25
6.25
5.89
5.89
5.88
5.88
5.87
5.87
5.86
5.86
5.85
5.20
5.20
5.16
5.15
5.13
5.13
5.10
5.10
4.47
2.98
2.97
2.95
2.94
2.90
2.89
2.87
2.86
2.54
2.49
2.48
2.48
2.47
OH
1
2
3
4
5
6
7
8
N
1.00
2.06
2.08
1.01
2.10
1.26
1.67
f1 (ppm)
137.56
135.52
134.64
116.78
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
74.95
60.22
50.50
46.78
f1 (ppm)

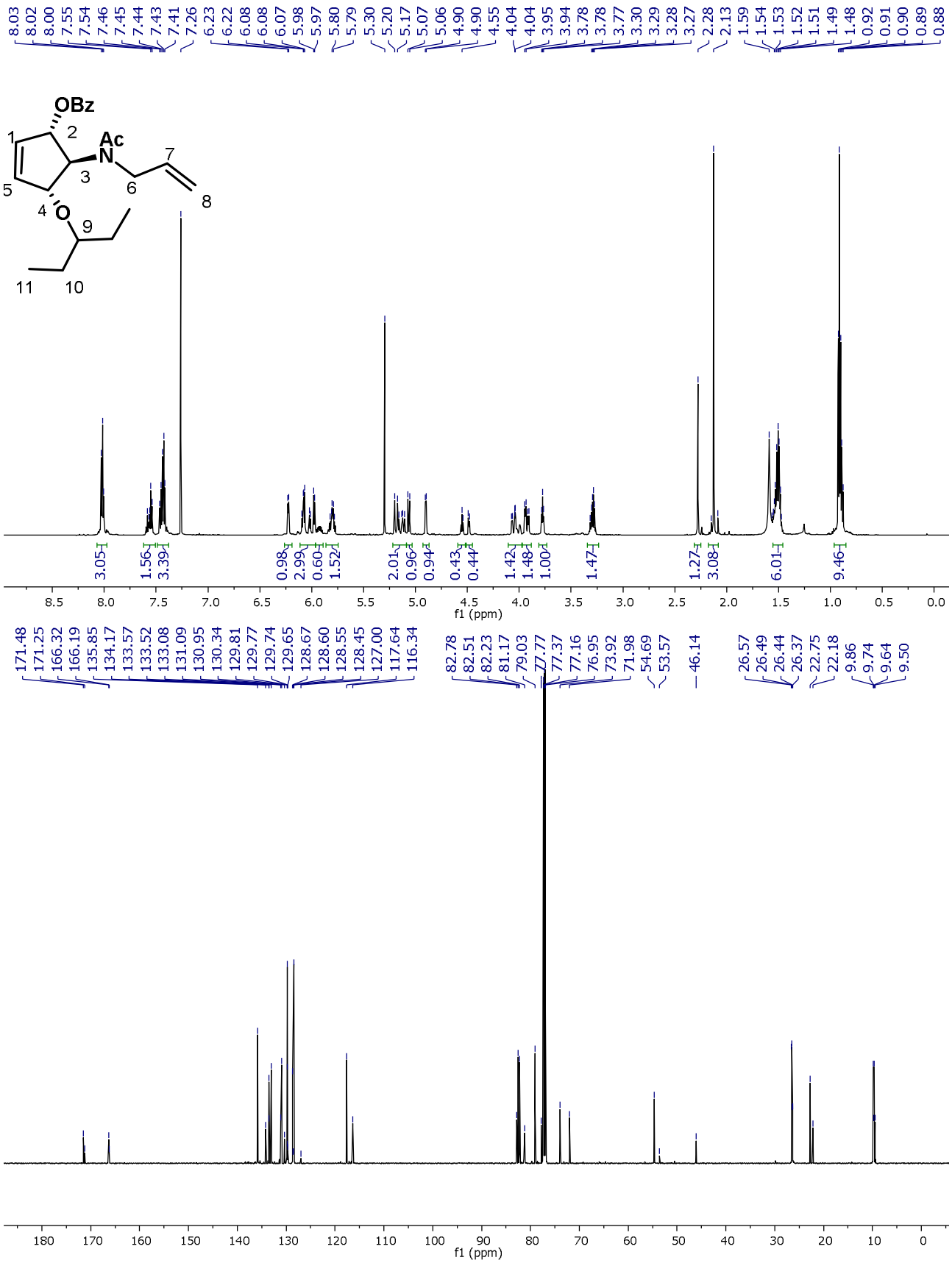
Compound 24


8.04
8.02
7.55
7.53
7.52
7.43
7.41
7.40
7.26
6.43
6.41
5.95
5.94
5.93
5.92
5.91
5.90
5.89
5.88
5.69
5.25
5.24
5.21
5.21
5.15
5.13
2.98
2.97
2.69
2.69
2.68
2.64
OBz
1
2
3
4
5
6
7
8
N
2.06
1.18
2.19
1.00
2.01
0.95
1.08
1.04
2.03
1.02
1.12
f1 (ppm)
165.81
138.02
134.49
133.86
133.13
129.72
128.40
116.80
77.41 CDCl3
77.24
77.16 CDCl3
76.90 CDCl3
60.20
47.79
46.84
f1 (ppm)

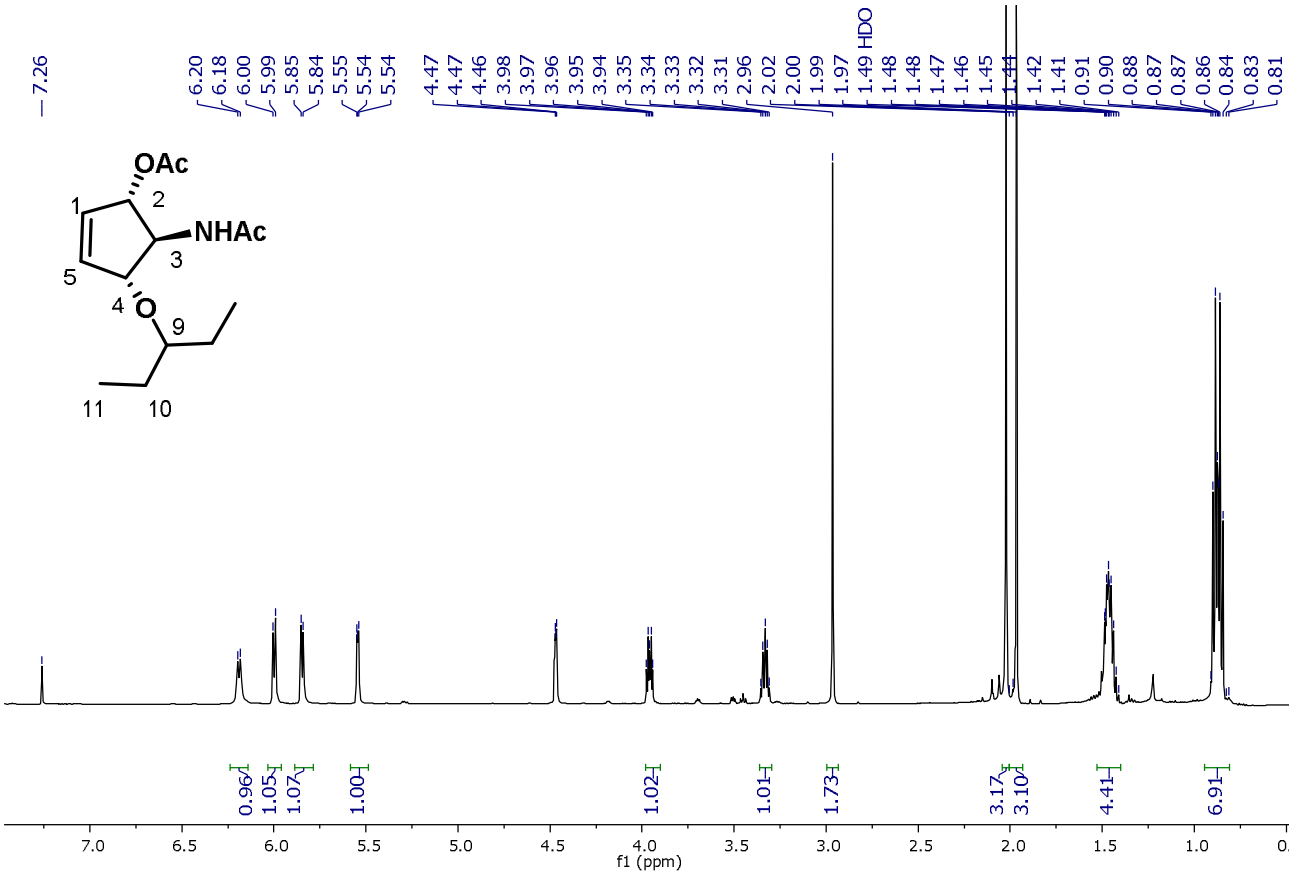
Compound 25

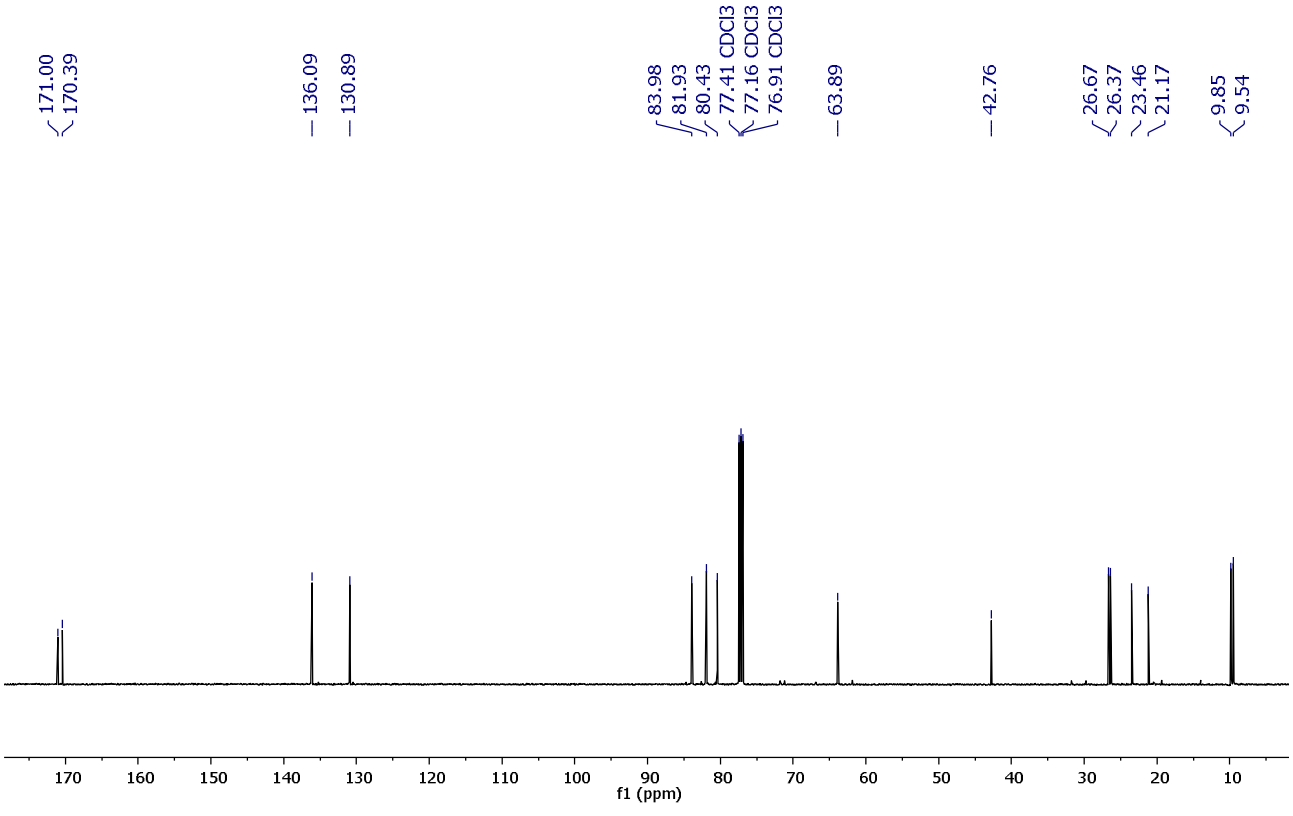

8.05 8.04 7.58 7.56 7.55 7.45 7.44 7.42 7.26 6.08 6.07 5.96 5.95 5.94 5.92 5.91 5.90 5.89 5.56 5.55 5.21 5.21 5.18 5.18 5.11 5.08 4.26 4.25 3.45 3.44 3.43 3.38 3.37 3.36 3.35 3.33 1.77 1.58 1.56 1.55 1.54 1.52 1.25 1.24 1.22 0.95 0.94 0.93 0.92 0.92 0.91
OBz
H
N
O
1 2 3 4 5 6 7 8 9 10 11
1.99 1.03 2.21 1.01 2.29 0.98 1.03 1.05 0.93 1.00 3.09 4.30 6.41
f1 (ppm)
166.68 136.56 135.98 133.21 130.88 130.19 129.86 128.50 116.24 86.47 83.33 81.74 77.41 CDCl3 77.16 CDCl3 76.91 CDCl3 71.62 50.96 26.62 26.47 10.00 9.62
f1 (ppm)

Compound 26

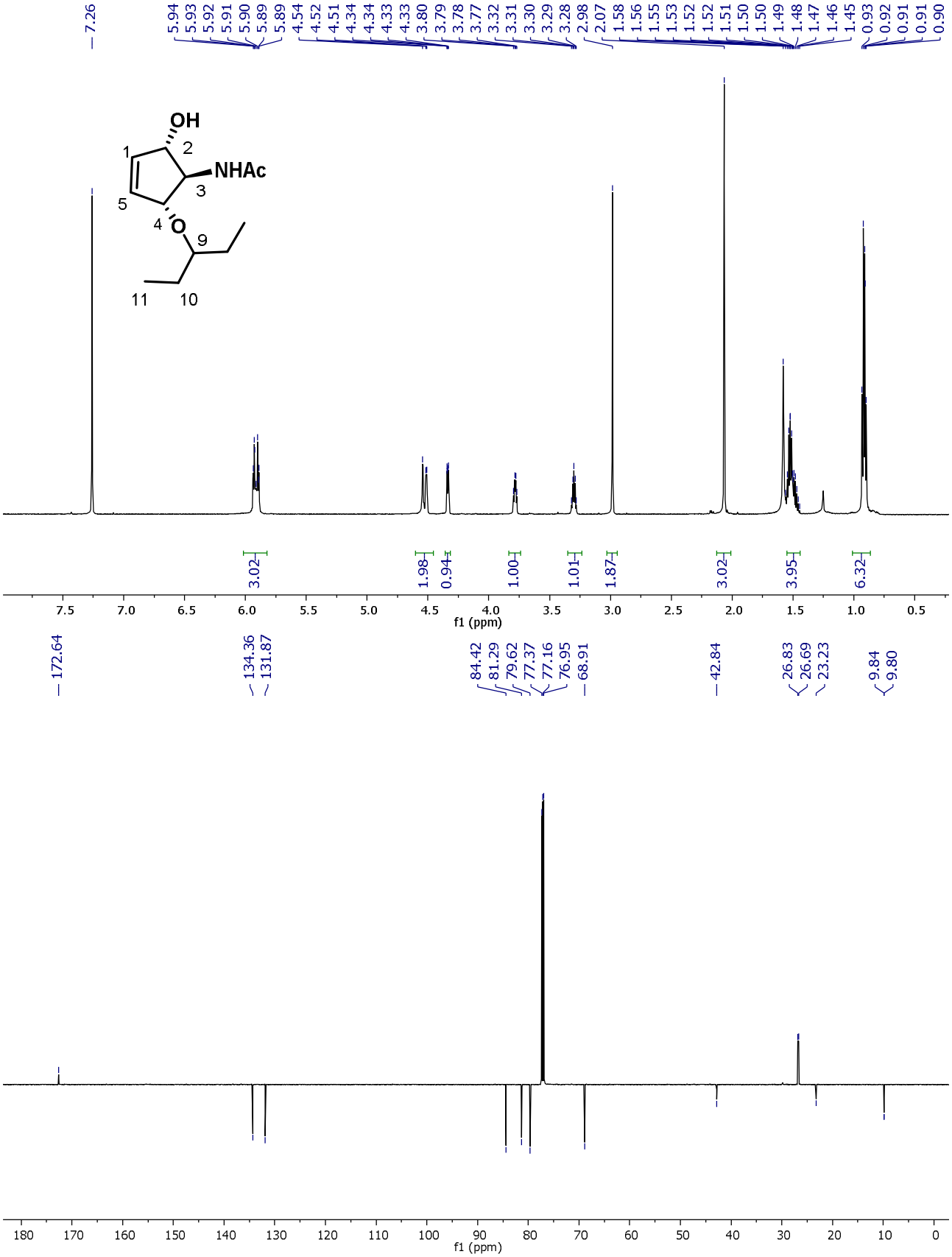

8.03 8.02 8.00 7.55 7.54 7.46 7.45 7.44 7.43 7.41 7.26 6.23 6.22 6.08 6.08 6.07 5.98 5.97 5.80 5.79 5.30 5.20 5.17 5.07 5.06 4.90 4.90 4.55 4.04 4.04 3.95 3.94 3.78 3.78 3.77 3.30 3.29 3.28 3.27 2.28 2.13 1.59 1.54 1.53 1.52 1.51 1.49 1.48 0.92 0.91 0.90 0.89 0.88
OBz
Ac
N
1
2
3
4
5
6
7
8
9
10
11
3.05 1.56 3.39 0.98 2.99 0.60 1.52 2.01 0.96 0.94 0.43 0.44 1.42 1.48 1.00 1.47 1.27 3.08 6.01 9.46
f1 (ppm)
171.48 171.25 166.32 166.19 135.85 134.17 133.57 133.52 133.08 131.09 130.95 130.34 129.81 129.77 129.74 129.65 128.67 128.60 128.55 128.45 127.00 117.64 116.34
82.78 82.51 82.23 81.17 79.03 77.77 77.37 77.16 76.95 73.92 71.98 54.69 53.57 46.14 26.57 26.49 26.44 26.37 22.75 22.18 9.86 9.74 9.64 9.50
f1 (ppm)

Compound 27

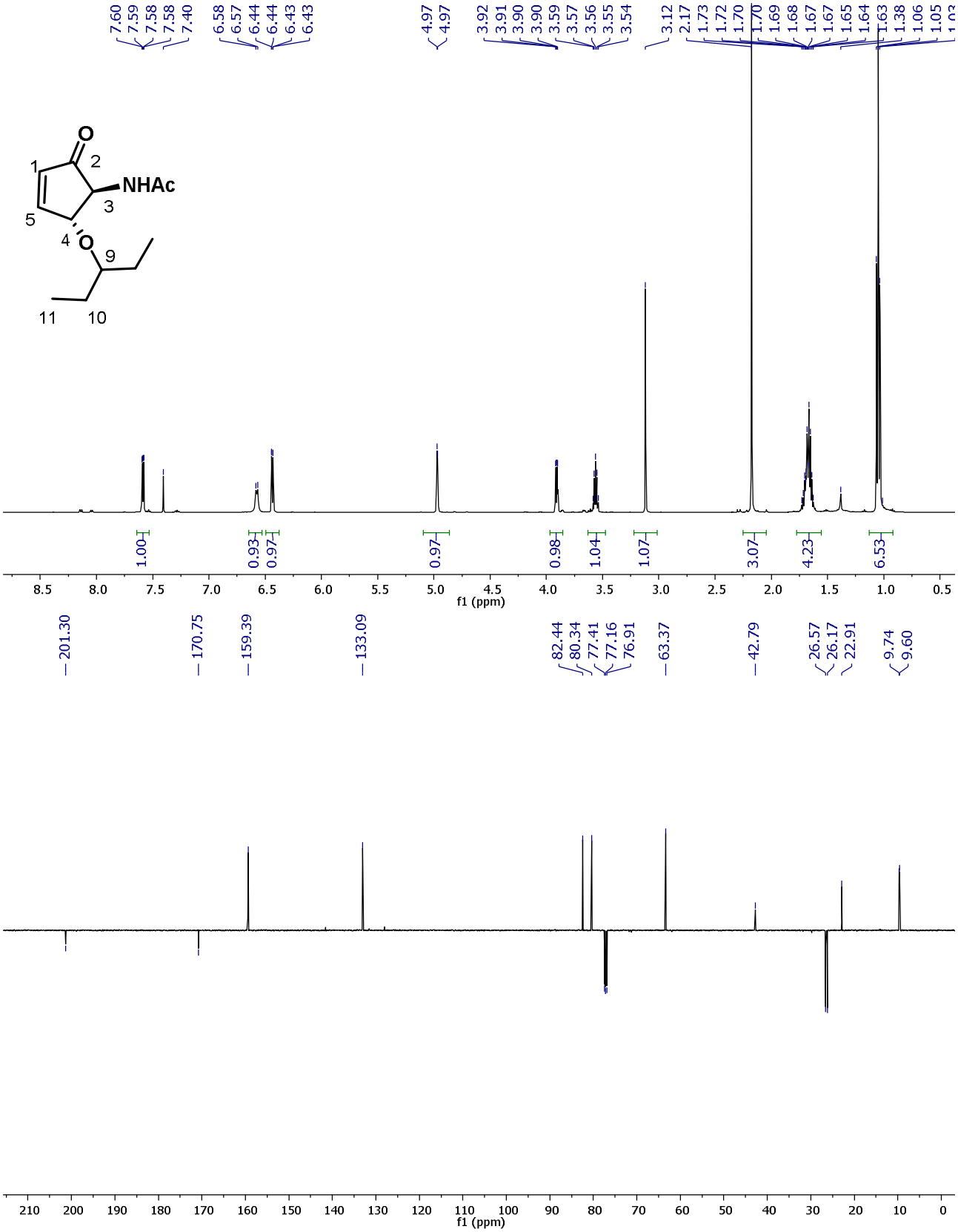

7.26
6.20
6.18
6.00
5.99
5.85
5.84
5.55
5.54
5.54
4.47
4.47
4.46
3.98
3.97
3.96
3.95
3.94
3.35
3.34
3.33
3.32
3.31
2.96
2.02
2.00
1.99
1.97
1.49 HDO
1.48
1.48
1.47
1.46
1.45
1.44
1.42
1.41
0.91
0.90
0.88
0.87
0.87
0.86
0.84
0.83
0.81
OAc
NHAc
O
0.96
1.05
1.07
1.00
1.02
1.01
1.73
3.17
3.10
4.41
6.91
f1 (ppm)


171.00
170.39
136.09
130.89
83.98
81.93
80.43
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
63.89
42.76
26.67
26.37
23.46
21.17
9.85
9.54
f1 (ppm)

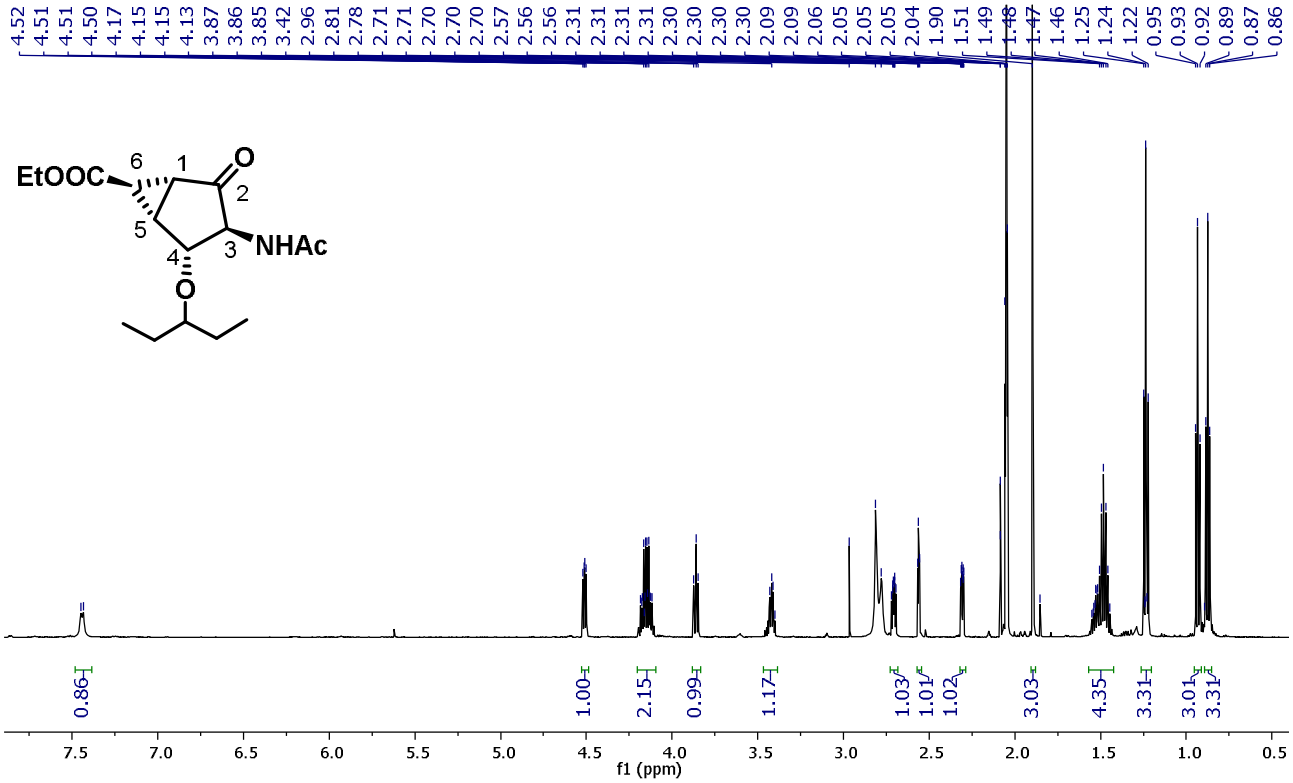
Compound 28

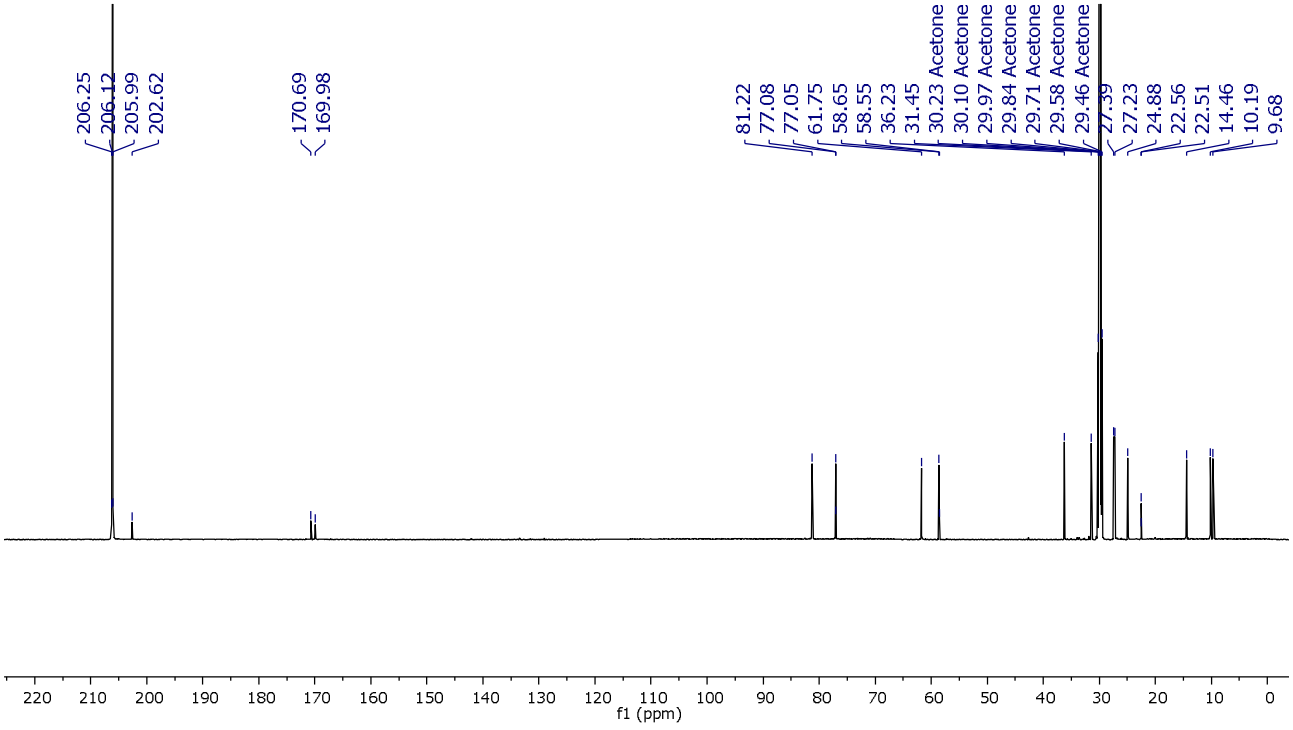

7.26
5.94
5.93
5.92
5.91
5.90
5.89
5.89
4.54
4.52
4.51
4.34
4.34
4.33
4.33
3.80
3.79
3.78
3.77
3.32
3.31
3.30
3.29
3.28
2.98
2.07
1.58
1.56
1.55
1.53
1.52
1.52
1.51
1.50
1.50
1.49
1.48
1.47
1.46
1.45
0.93
0.92
0.91
0.91
0.90
OH
NHAc
1
2
3
4
5
O
9
10
11
3.02
1.98
0.94
1.00
1.01
1.87
3.02
3.95
6.32
f1 (ppm)
172.64
134.36
131.87
84.42
81.29
79.62
77.37
77.16
76.95
68.91
42.84
26.83
26.69
23.23
9.84
9.80
f1 (ppm)

Compound 21

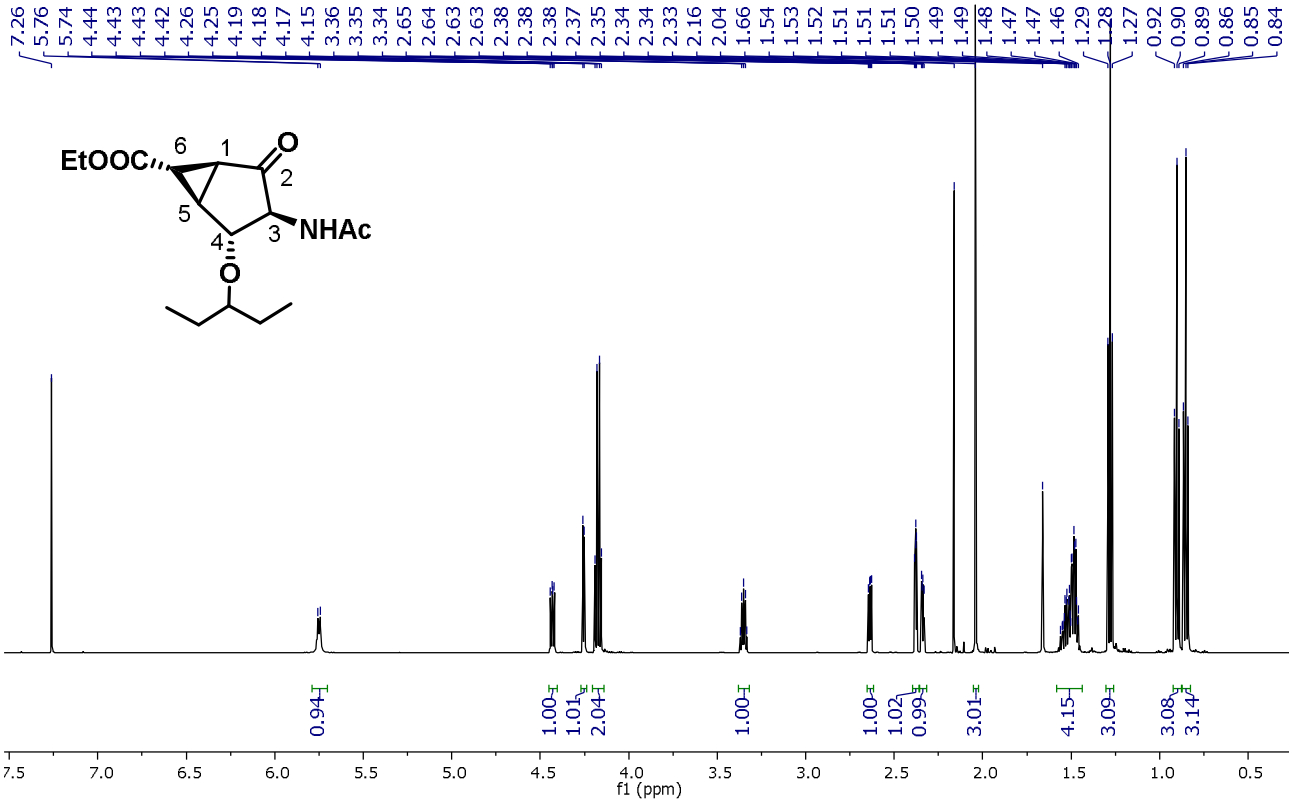

7.60
7.59
7.58
7.58
7.40
6.58
6.57
6.44
6.44
6.43
6.43
4.97
4.97
3.92
3.91
3.90
3.90
3.59
3.57
3.56
3.55
3.54
3.12
2.17
1.73
1.72
1.70
1.70
1.69
1.68
1.67
1.67
1.65
1.64
1.63
1.38
1.06
1.05
O
1
2
NHAc
3
5
4
O
9
11
10
1.00
0.93
0.97
0.97
0.98
1.04
1.07
3.07
4.23
6.53
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
201.30
170.75
159.39
133.09
82.44
80.34
77.41
77.16
76.91
63.37
42.79
26.57
26.17
22.91
9.74
9.60
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

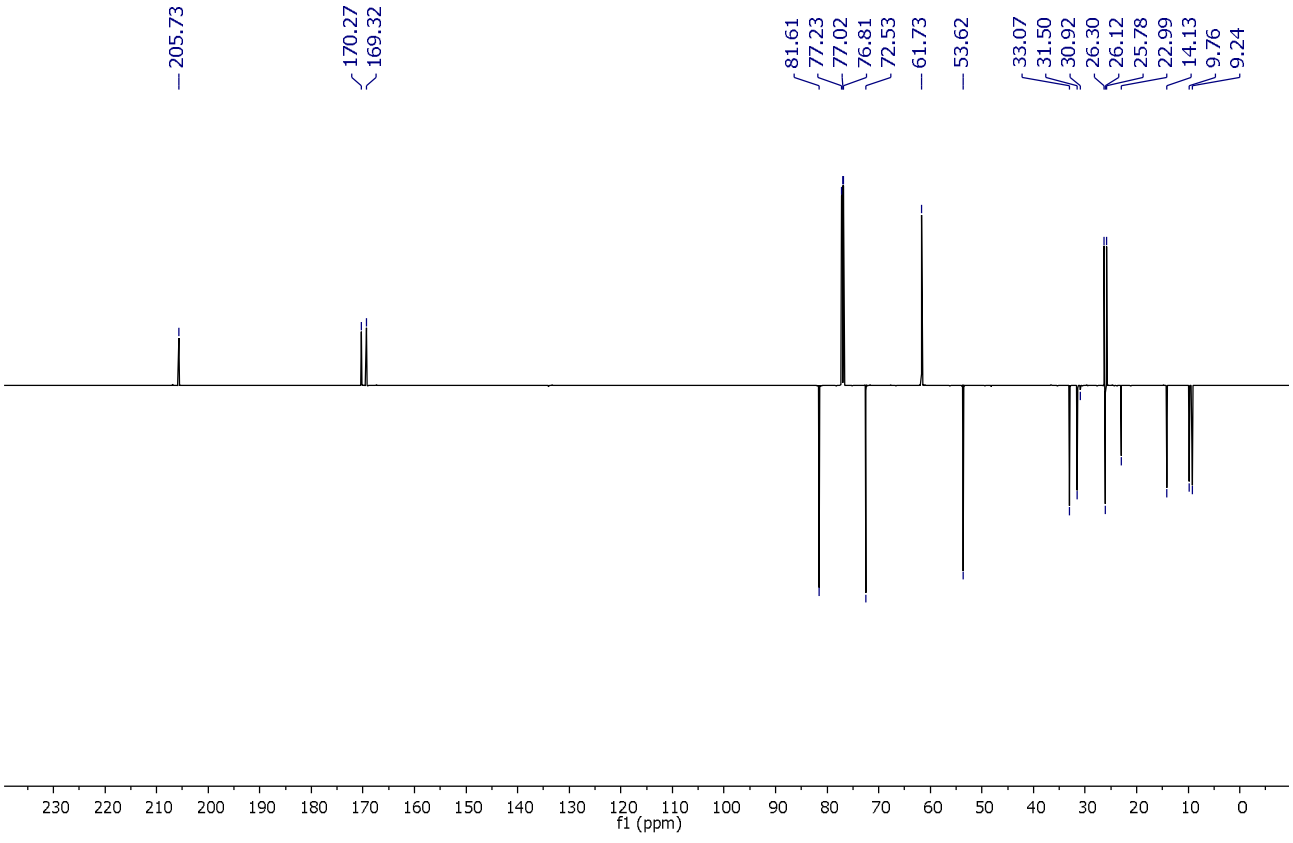
Compound 20


4.52 4.51 4.51 4.50 4.17 4.15 4.15 4.13 3.87 3.86 3.85 3.42 2.96 2.81 2.78 2.71 2.71 2.70 2.70 2.70 2.57 2.56 2.56 2.31 2.31 2.31 2.31 2.30 2.30 2.30 2.30 2.09 2.09 2.06 2.05 2.05 2.05 2.04 1.90 1.51 1.49 1.48 1.47 1.46 1.25 1.24 1.22 0.95 0.93 0.92 0.89 0.87 0.86
EtOOC
NHAc
0.86 1.00 2.15 0.99 1.17 1.03 1.01 1.02 3.03 4.35 3.31 3.01 3.31
f1 (ppm)

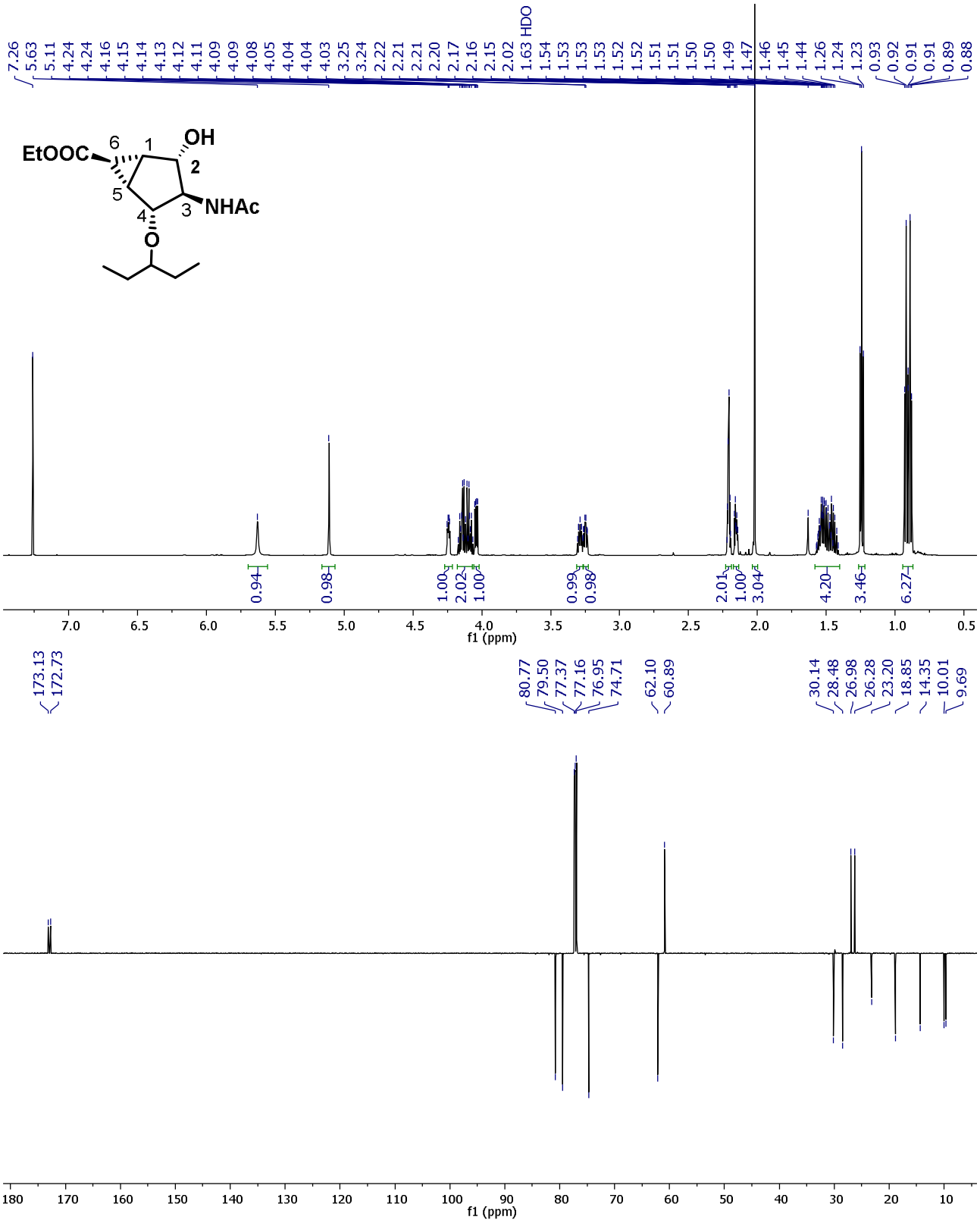

206.25 206.12 205.99 202.62 170.69 169.98 81.22 77.08 77.05 61.75 58.65 58.55 36.23 31.45 30.23 Acetone 30.10 Acetone 29.97 Acetone 29.84 Acetone 29.71 Acetone 29.58 Acetone 29.46 Acetone 27.39 27.23 24.88 22.56 22.51 14.46 10.19 9.68
f1 (ppm)

Compound 30

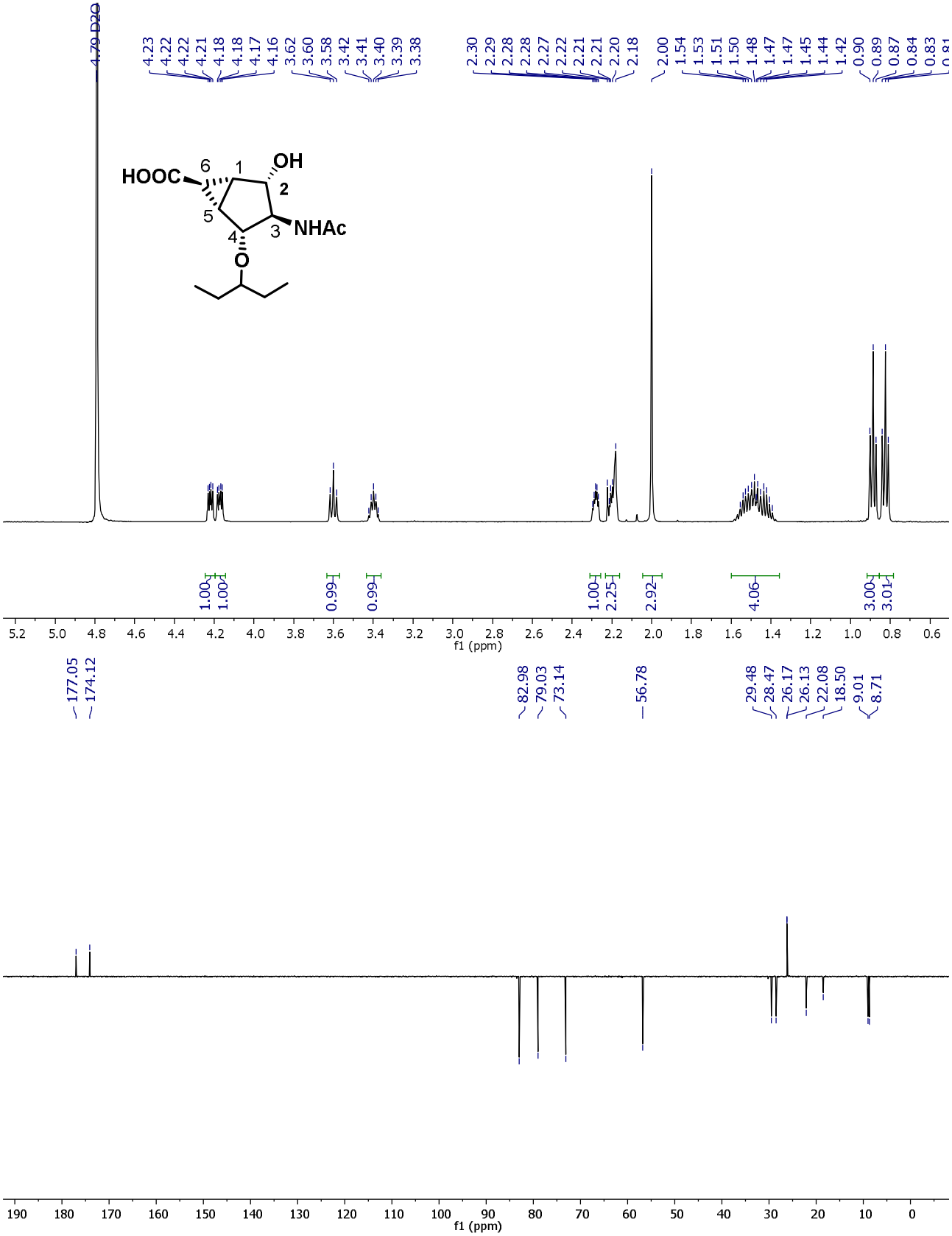

7.26 5.76 5.74 4.44 4.43 4.42 4.26 4.25 4.19 4.18 4.17 4.15 3.36 3.35 3.34 2.65 2.64 2.63 2.63 2.38 2.38 2.38 2.37 2.35 2.34 2.34 2.33 2.16 2.04 1.66 1.54 1.53 1.52 1.51 1.51 1.51 1.50 1.49 1.49 1.48 1.47 1.47 1.46 1.29 1.28 1.27 0.92 0.90 0.89 0.86 0.85 0.84
EtOOC
NHAc
0.94 1.00 1.01 2.04 1.00 1.00 1.02 0.99 3.01 4.15 3.09 3.08 3.14
f1 (ppm)


205.73
170.27 169.32
81.61 77.23 77.02 76.81 72.53 61.73 53.62 33.07 31.50 30.92 26.30 26.12 25.78 22.99 14.13 9.76 9.24
f1 (ppm)

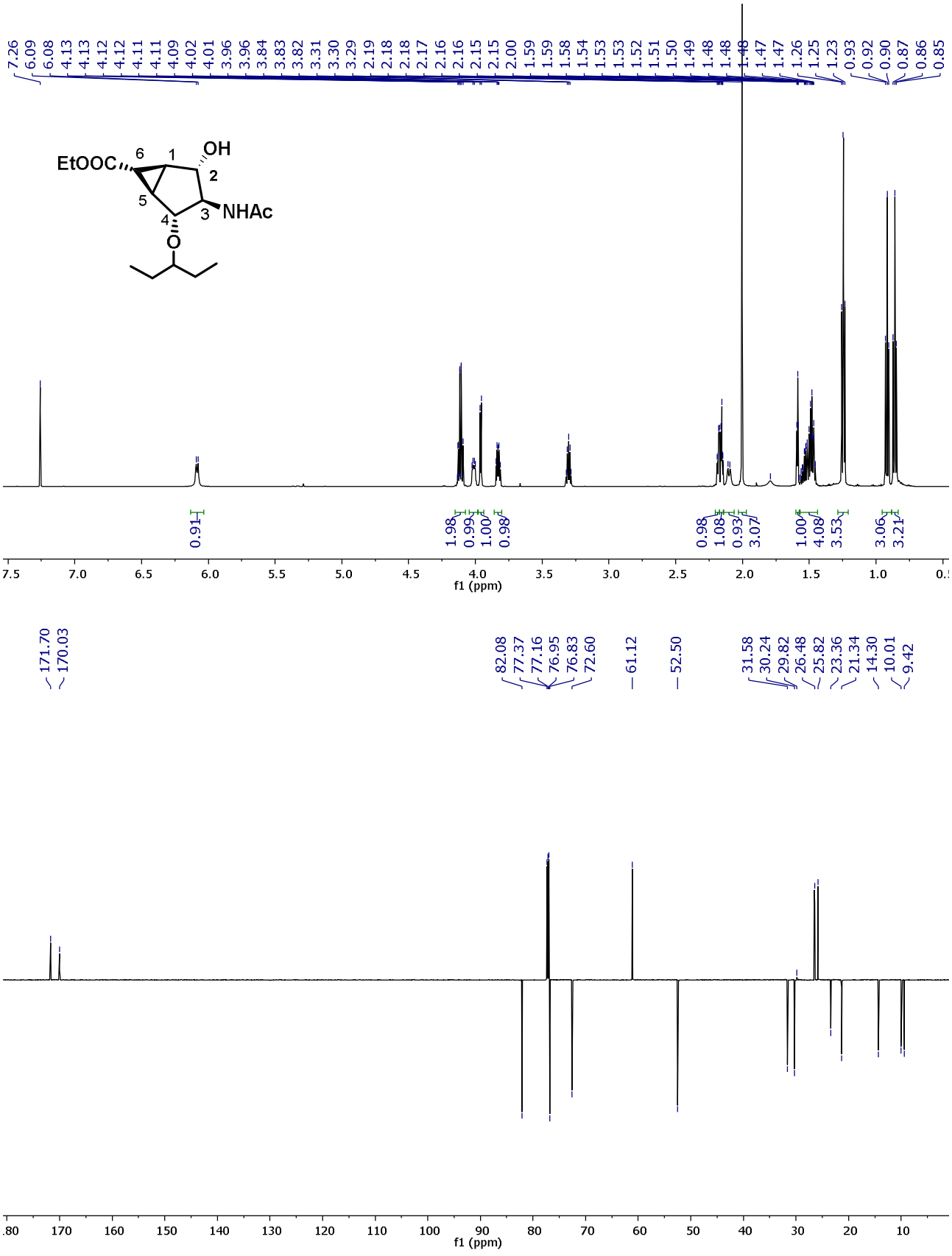
Compound 35


7.26 5.63 5.11 4.24 4.24 4.16 4.15 4.14 4.13 4.12 4.11 4.09 4.09 4.08 4.05 4.04 4.04 4.03 3.25 3.24 2.22 2.21 2.21 2.20 2.17 2.16 2.15 2.02 1.63 HDO 1.54 1.53 1.53 1.53 1.52 1.52 1.51 1.51 1.50 1.50 1.49 1.47 1.46 1.45 1.44 1.26 1.24 1.23 0.93 0.92 0.91 0.91 0.89 0.88
EtOOC
OH
NHAc
O
0.94 0.98 1.00 2.02 1.00 0.99 0.98 2.01 1.00 3.04 4.20 3.46 6.27
f1 (ppm)
173.13 172.73 80.77 79.50 77.37 77.16 76.95 74.71 62.10 60.89 30.14 28.48 26.98 26.28 23.20 18.85 14.35 10.01 9.69
f1 (ppm)

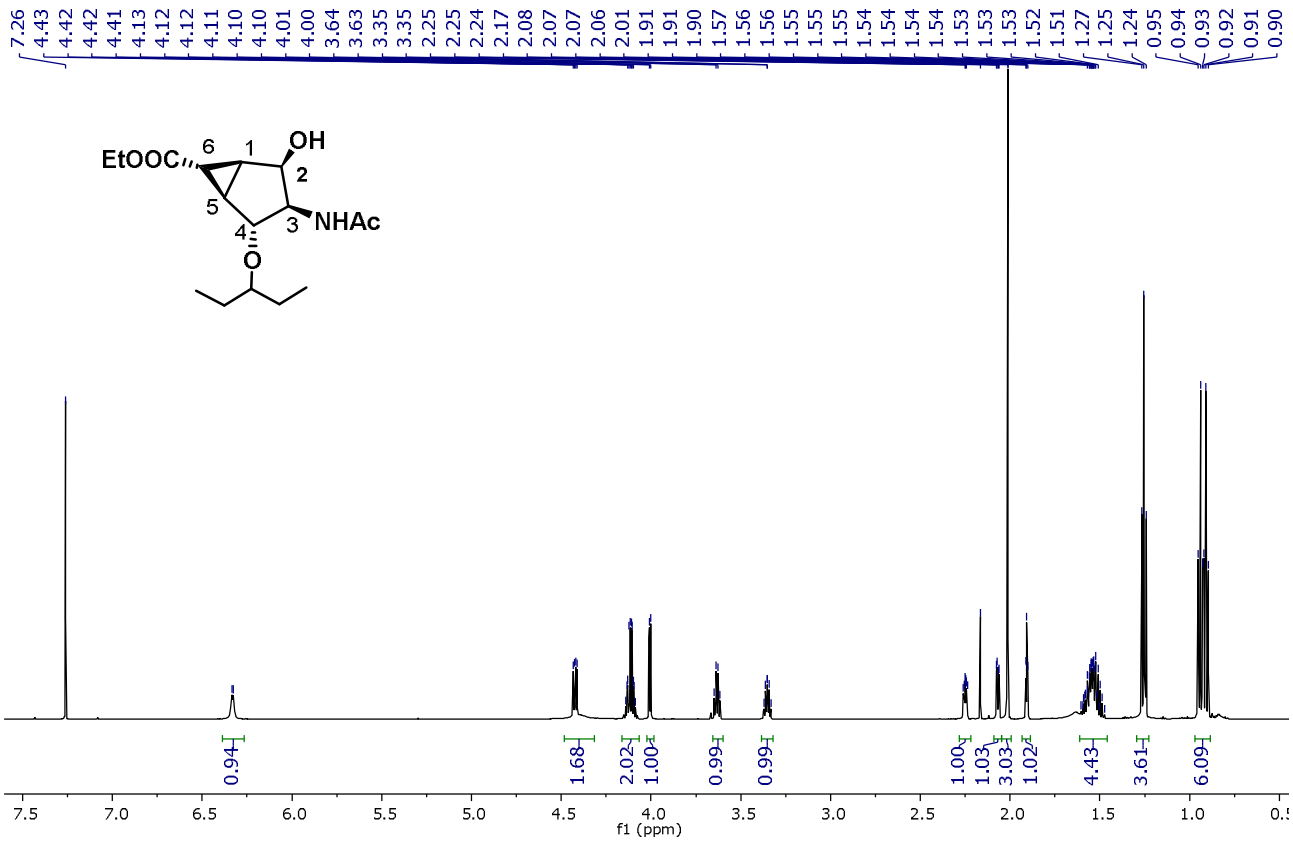
Compound 13

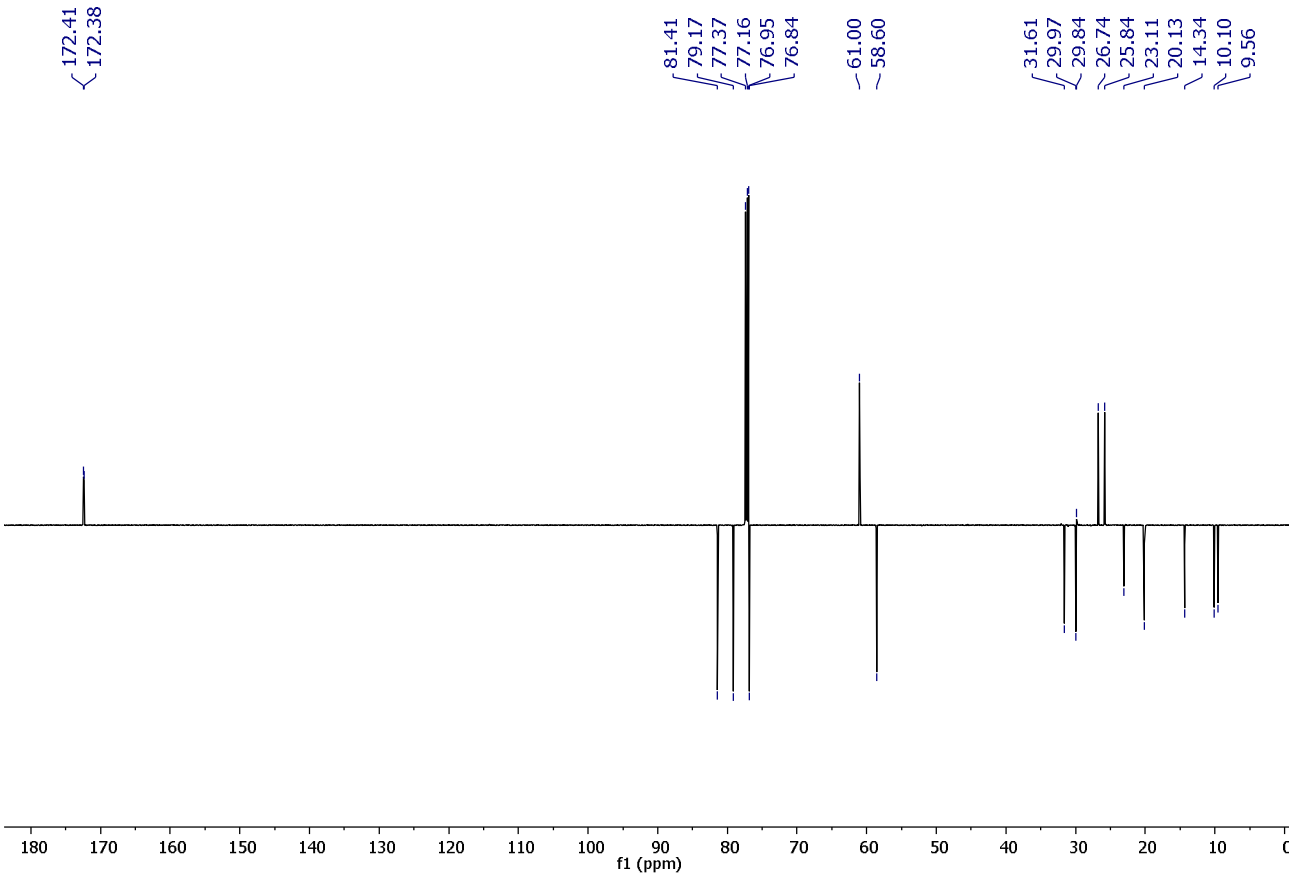

4.79 D2O
4.23 4.22 4.22 4.21 4.18 4.18 4.17 4.16 3.62 3.60 3.58 3.42 3.41 3.40 3.39 3.38
2.30 2.29 2.28 2.28 2.27 2.22 2.21 2.21 2.20 2.18 2.00 1.54 1.53 1.51 1.50 1.48 1.47 1.47 1.45 1.44 1.42 0.90 0.89 0.87 0.84 0.83
HOOC
OH
NHAc
O
1.00 1.00 0.99 0.99 1.00 2.25 2.92 4.06 3.00 3.01
f1 (ppm)
177.05 174.12 82.98 79.03 73.14 56.78 29.48 28.47 26.17 26.13 22.08 18.50 9.01 8.71
f1 (ppm)

Compound 36

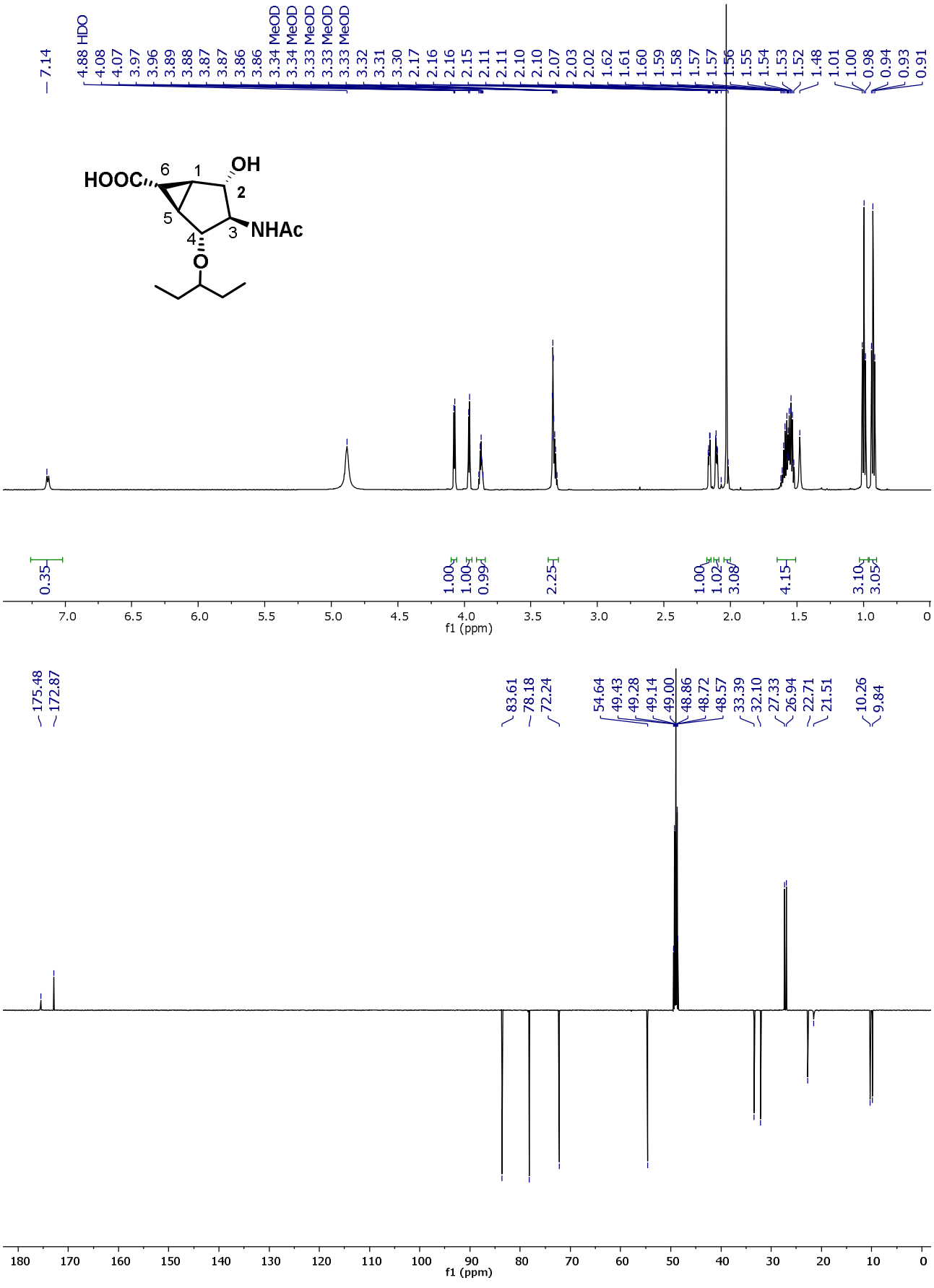

7.26 6.09 6.08 4.13 4.13 4.12 4.12 4.11 4.11 4.09 4.02 4.01 3.96 3.96 3.84 3.83 3.82 3.31 3.30 3.29 2.19 2.18 2.18 2.17 2.16 2.16 2.15 2.15 2.00 1.59 1.59 1.58 1.54 1.53 1.53 1.52 1.51 1.50 1.49 1.48 1.48 1.48 1.47 1.47 1.26 1.25 1.23 0.93 0.92 0.90 0.87 0.86 0.85
EtOOC
OH
NHAc
O
0.91 1.98 0.99 1.00 0.98 0.98 1.08 0.93 3.07 1.00 4.08 3.53 3.06 3.21
f1 (ppm)
171.70 170.03 82.08 77.37 77.16 76.95 76.83 72.60 61.12 52.50 31.58 30.24 29.82 26.48 25.82 23.36 21.34 14.30 10.01 9.42
f1 (ppm)

Compound 37

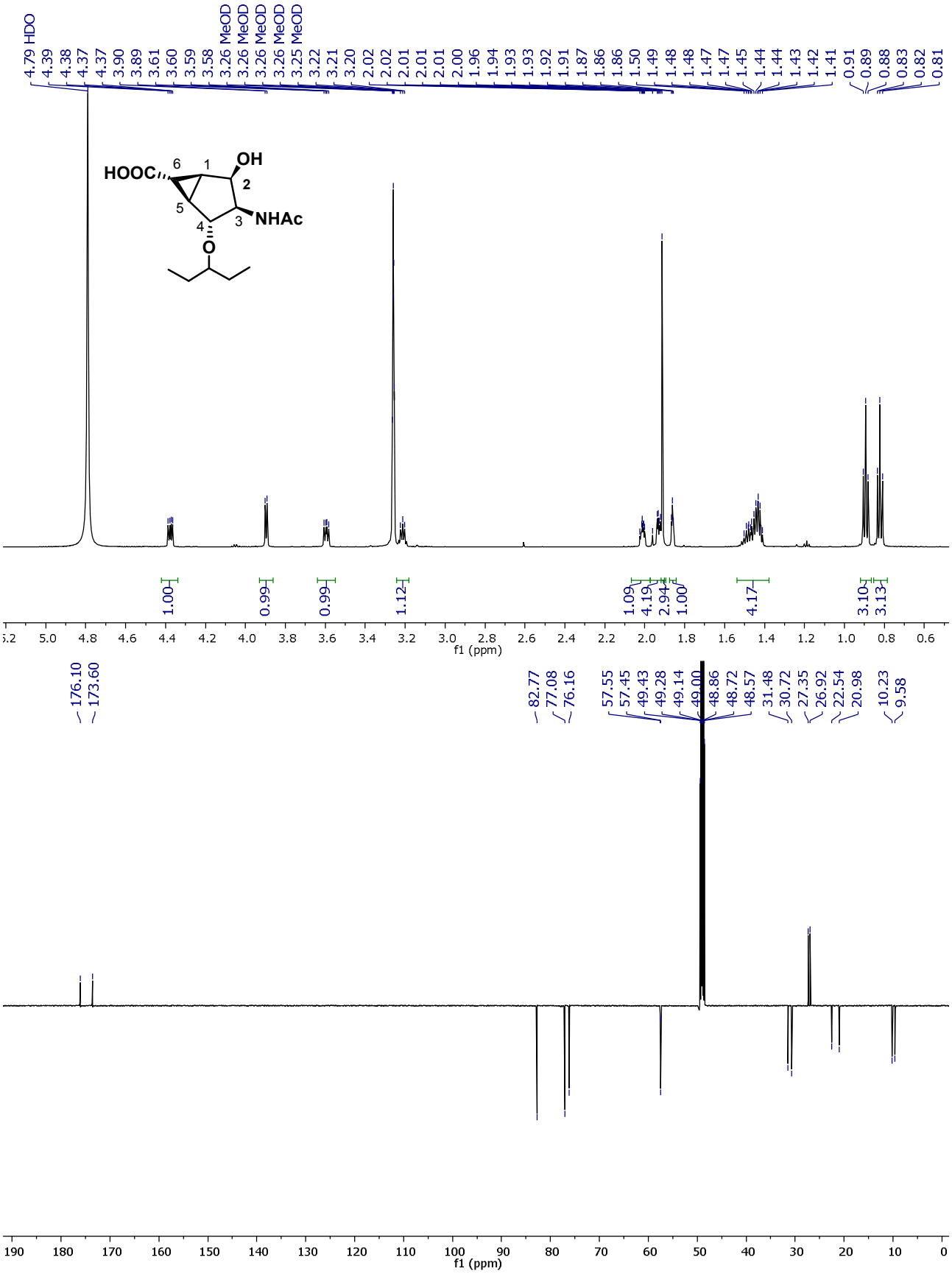

7.26 4.43 4.42 4.42 4.41 4.13 4.12 4.12 4.11 4.10 4.10 4.01 4.00 3.64 3.63 3.35 3.35 2.25 2.25 2.24 2.17 2.08 2.07 2.07 2.06 2.01 1.91 1.91 1.90 1.57 1.56 1.56 1.55 1.55 1.55 1.54 1.54 1.54 1.54 1.53 1.53 1.53 1.52 1.51 1.27 1.25 1.24 0.95 0.94 0.93 0.92 0.91 0.90
EtOOC
6
1
OH
2
5
3
NHAc
4
O
0.94 1.68 2.02 1.00 0.99 0.99 1.00 1.03 3.03 1.02 4.43 3.61 6.09
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
f1 (ppm)


172.41 172.38
81.41 79.17 77.37 77.16 76.95 76.84
61.00 58.60
31.61 29.97 29.84 26.74 25.84 23.11 20.13 14.34 10.10 9.56
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

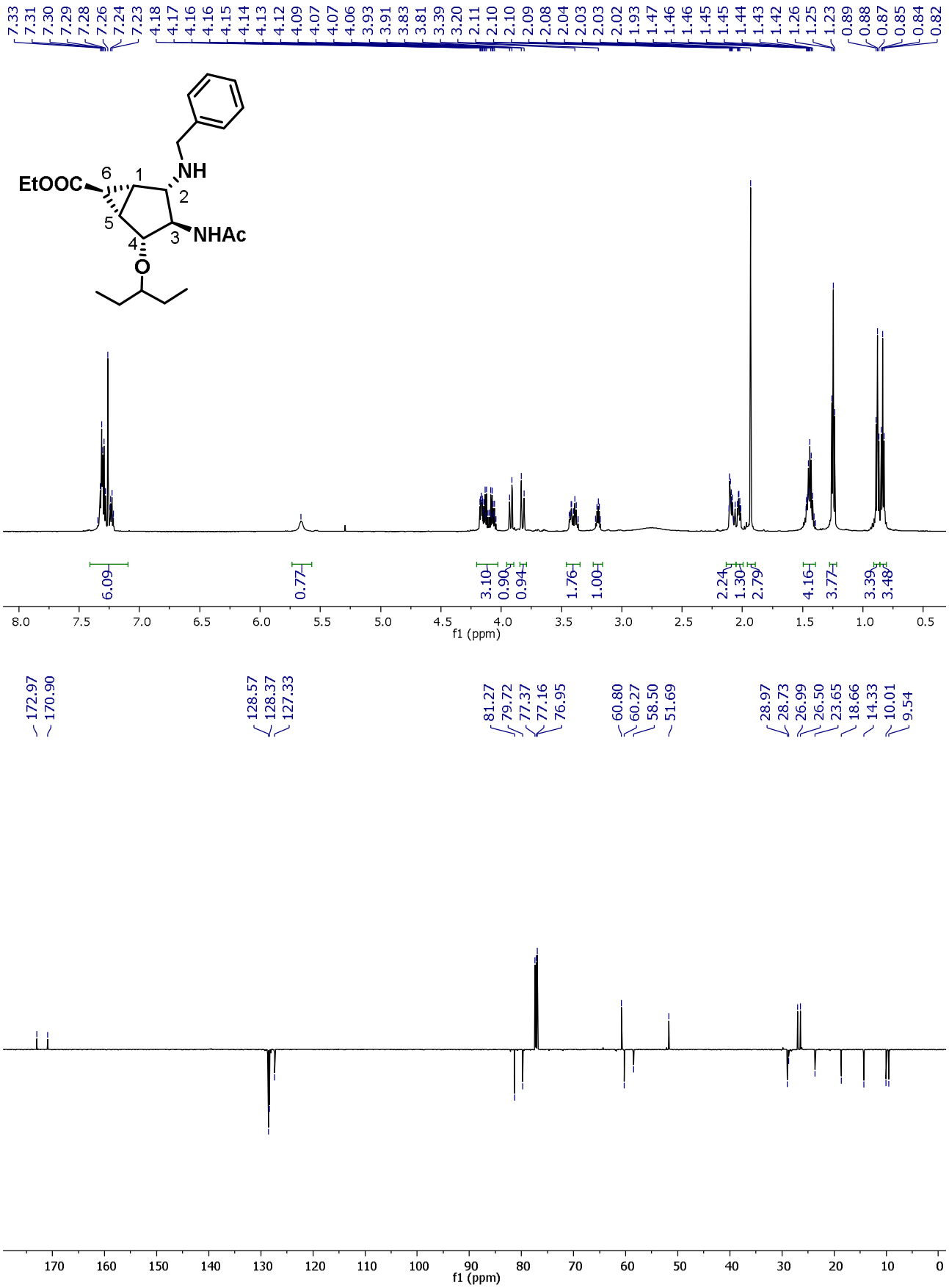
Compound 14


7.14
4.88 HDO
4.08
4.07
3.97
3.96
3.89
3.88
3.87
3.87
3.86
3.86
3.34 MeOD
3.34 MeOD
3.33 MeOD
3.33 MeOD
3.33 MeOD
3.32
3.31
3.30
2.17
2.16
2.16
2.15
2.11
2.11
2.10
2.10
2.07
2.03
2.02
1.62
1.61
1.60
1.59
1.58
1.57
1.57
1.56
1.55
1.54
1.53
1.52
1.48
1.01
1.00
0.98
0.94
0.93
0.91
HOOC
OH
NHAc
O
0.35
1.00
1.00
0.99
2.25
1.00
1.02
3.08
4.15
3.10
3.05
f1 (ppm)
175.48
172.87
83.61
78.18
72.24
54.64
49.43
49.28
49.14
49.00
48.86
48.72
48.57
33.39
32.10
27.33
26.94
22.71
21.51
10.26
9.84
f1 (ppm)

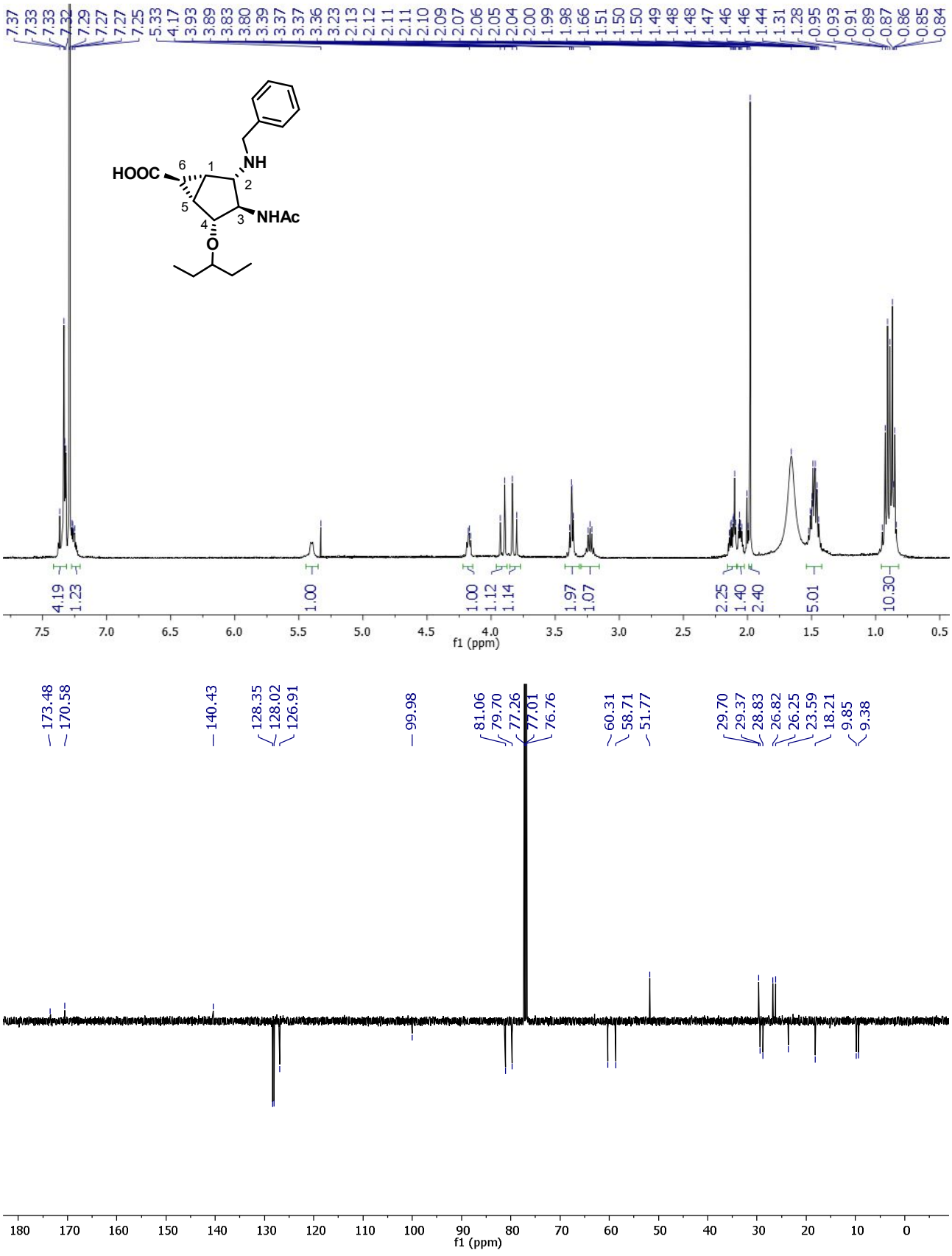
Compound 15


4.79 HDO
4.39
4.38
4.37
4.37
3.90
3.89
3.61
3.60
3.59
3.58
3.26 MeOD
3.26 MeOD
3.26 MeOD
3.26 MeOD
3.25 MeOD
3.22
3.21
3.20
2.02
2.02
2.01
2.01
2.01
2.00
1.96
1.94
1.93
1.93
1.92
1.91
1.87
1.86
1.86
1.50
1.49
1.48
1.48
1.47
1.47
1.45
1.44
1.44
1.43
1.42
1.41
0.91
0.89
0.88
0.83
0.82
0.81
HOOC
OH
NHAc
O
1.00
0.99
0.99
1.12
1.09
4.19
2.94
1.00
4.17
3.10
3.13
f1 (ppm)
176.10
173.60
82.77
77.08
76.16
57.55
57.45
49.43
49.28
49.14
49.00
48.86
48.72
48.57
31.48
30.72
27.35
26.92
22.54
20.98
10.23
9.58
f1 (ppm)

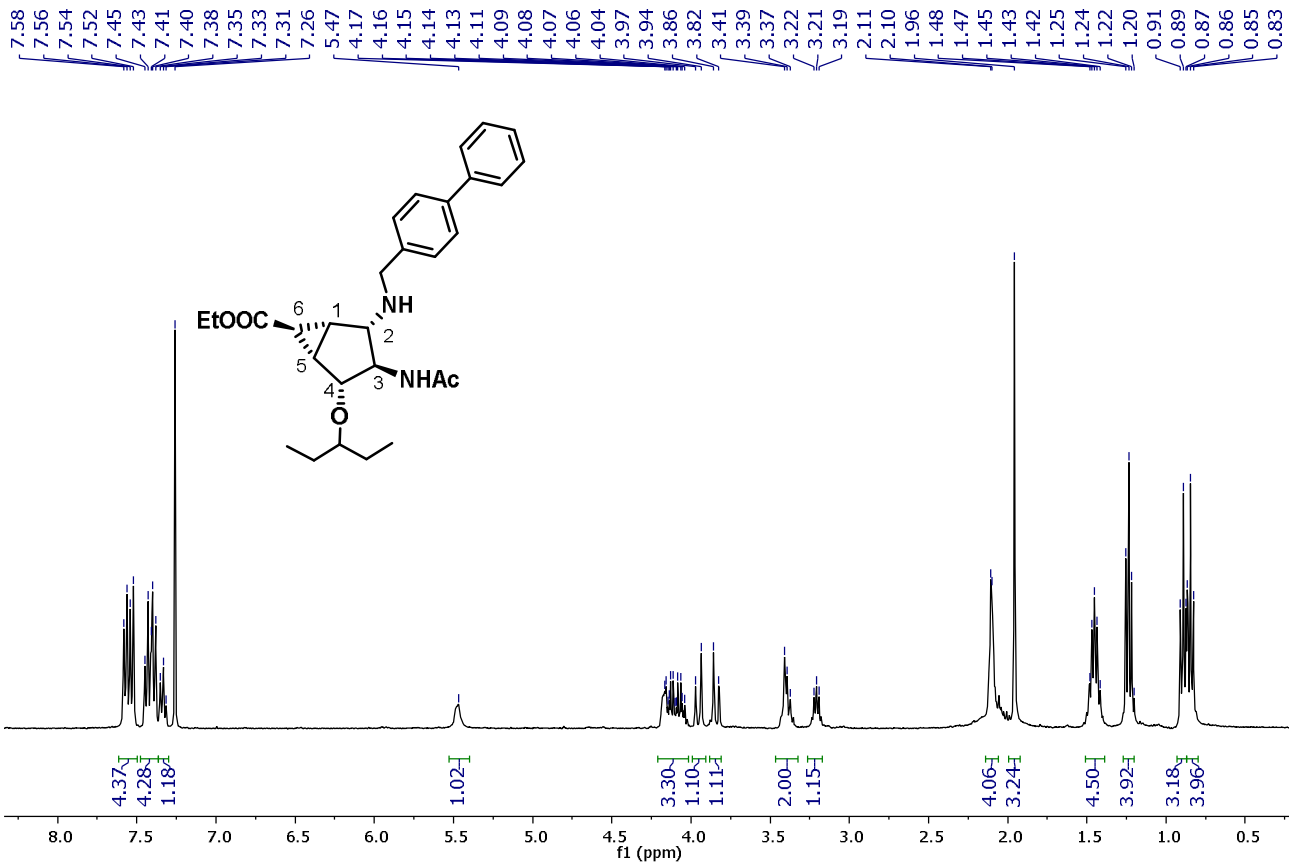
Compound 38

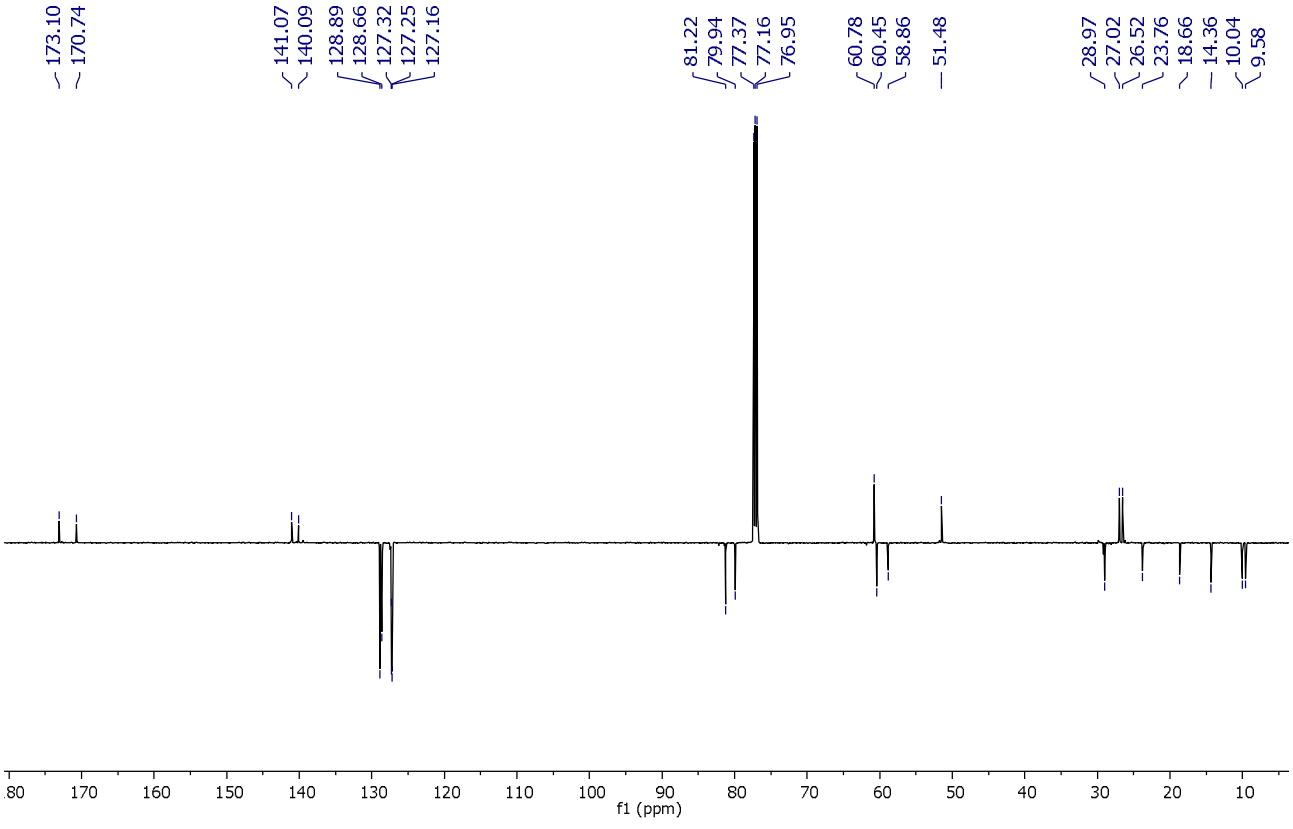

7.33 7.31 7.30 7.29 7.28 7.26 7.24 7.23 4.18 4.17 4.16 4.16 4.15 4.14 4.13 4.12 4.09 4.07 4.07 4.06 3.93 3.91 3.83 3.81 3.39 3.20 2.11 2.10 2.10 2.09 2.08 2.04 2.03 2.03 2.02 1.93 1.47 1.46 1.46 1.45 1.45 1.44 1.43 1.42 1.26 1.25 1.23 0.89 0.88 0.87 0.85 0.84 0.82
EtOOC
NH
NHAc
O
6.09 0.77 3.10 0.90 0.94 1.76 1.00 2.24 1.30 2.79 4.16 3.77 3.39 3.48
f1 (ppm)
172.97 170.90 128.57 128.37 127.33 81.27 79.72 77.37 77.16 76.95 60.80 60.27 58.50 51.69 28.97 28.73 26.99 26.50 23.65 18.66 14.33 10.01 9.54
f1 (ppm)

Compound 16

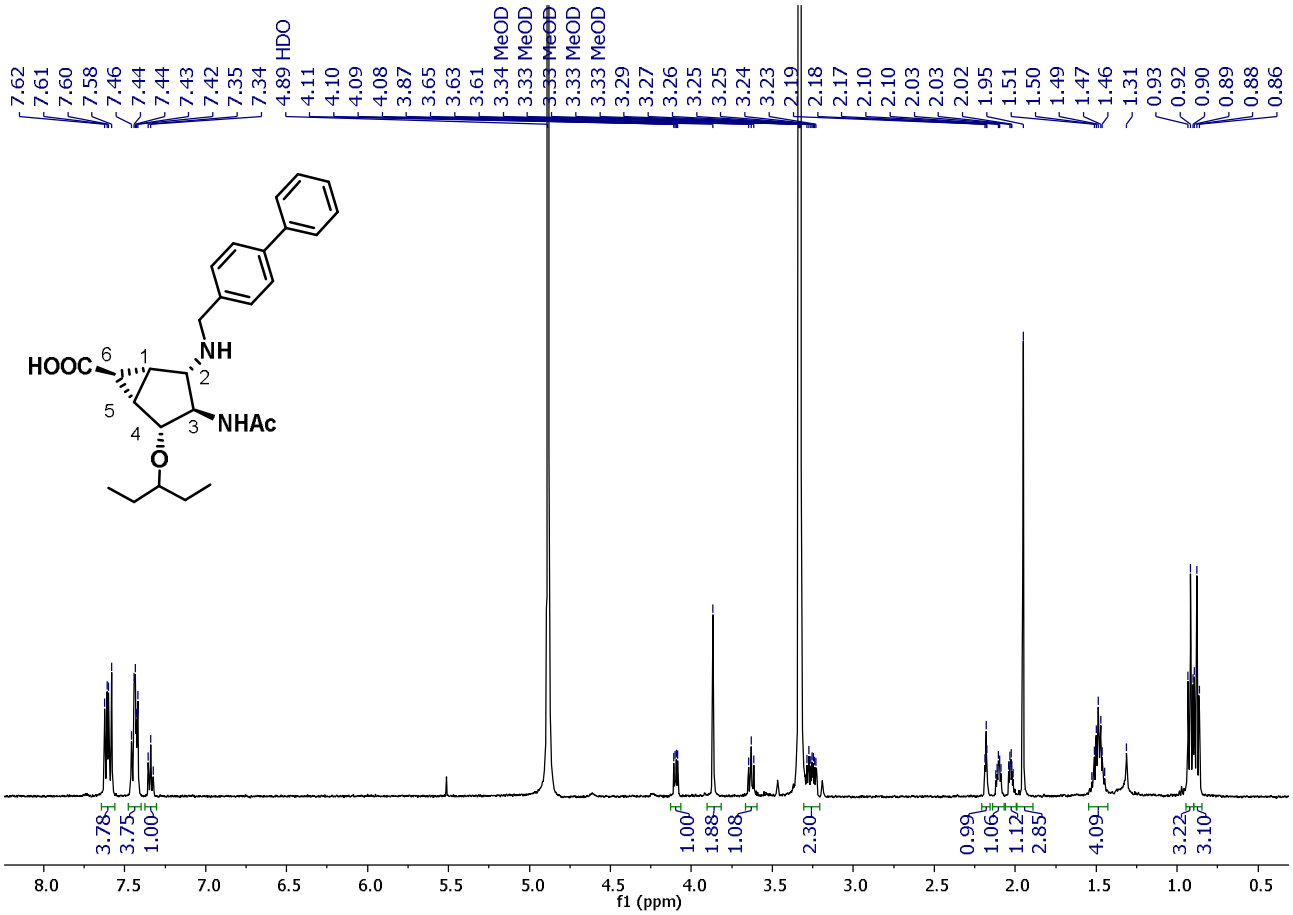


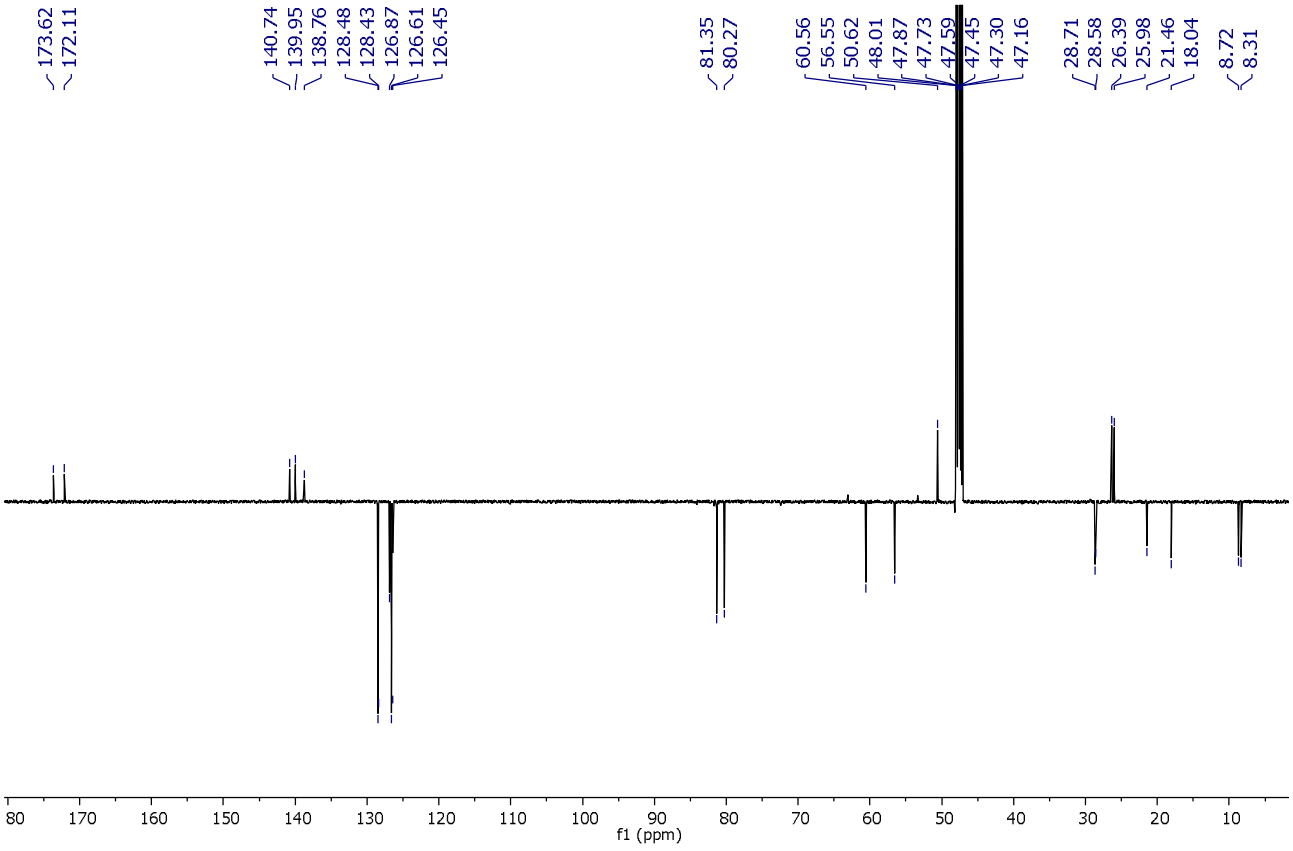
Compound 39


7.58 7.56 7.54 7.52 7.45 7.43 7.41 7.40 7.38 7.35 7.33 7.31 7.26
5.47 4.17 4.16 4.15 4.14 4.13 4.11 4.09 4.08 4.07 4.06 4.04 3.97 3.94 3.86 3.82 3.41 3.39 3.37 3.22 3.21 3.19
2.11 2.10 1.96 1.48 1.47 1.45 1.43 1.42 1.25 1.24 1.22 1.20 0.91 0.89 0.87 0.86 0.85 0.83
EtOOC
NH
NHAc
O
4.37 4.28 1.18 1.02 3.30 1.10 1.11 2.00 1.15 4.06 3.24 4.50 3.92 3.18 3.96
f1 (ppm)


173.10 170.74
141.07 140.09 128.89 128.66 127.32 127.25 127.16
81.22 79.94 77.37 77.16 76.95
60.78 60.45 58.86 51.48
28.97 27.02 26.52 23.76 18.66 14.36 10.04 9.58
f1 (ppm)

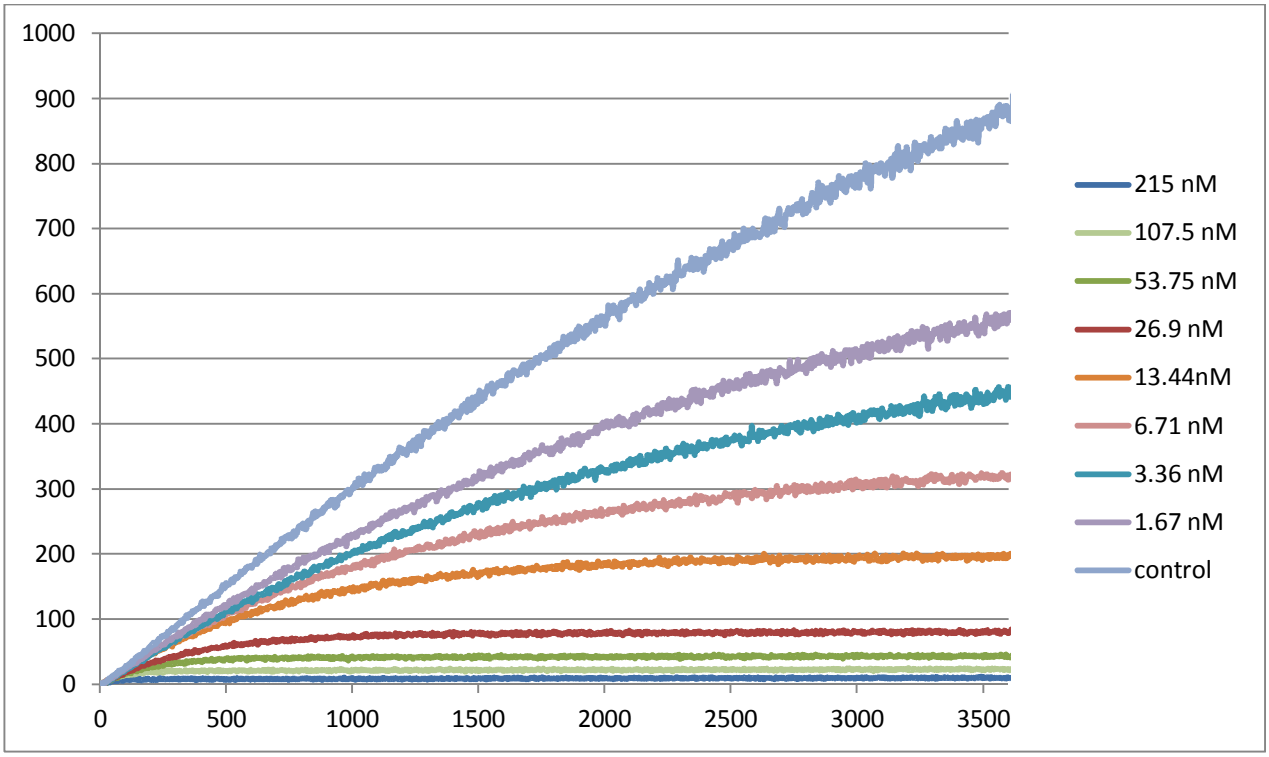
Compound 17


7.62 7.61 7.60 7.58 7.46 7.44 7.44 7.43 7.42 7.35 7.34 4.89 HDO 4.11 4.10 4.09 4.08 3.87 3.65 3.63 3.61 3.34 MeOD 3.33 MeOD 3.33 MeOD 3.33 MeOD 3.33 MeOD 3.29 3.27 3.26 3.25 3.25 3.24 3.23 2.19 2.18 2.17 2.10 2.10 2.03 2.03 2.02 1.95 1.51 1.50 1.49 1.47 1.46 1.31 0.93 0.92 0.90 0.89 0.88 0.86
HOOC
NH
NHAc
O
3.78 3.75 1.00 1.00 1.88 1.08 2.30 0.99 1.06 1.12 2.85 4.09 3.22 3.10
f1 (ppm)

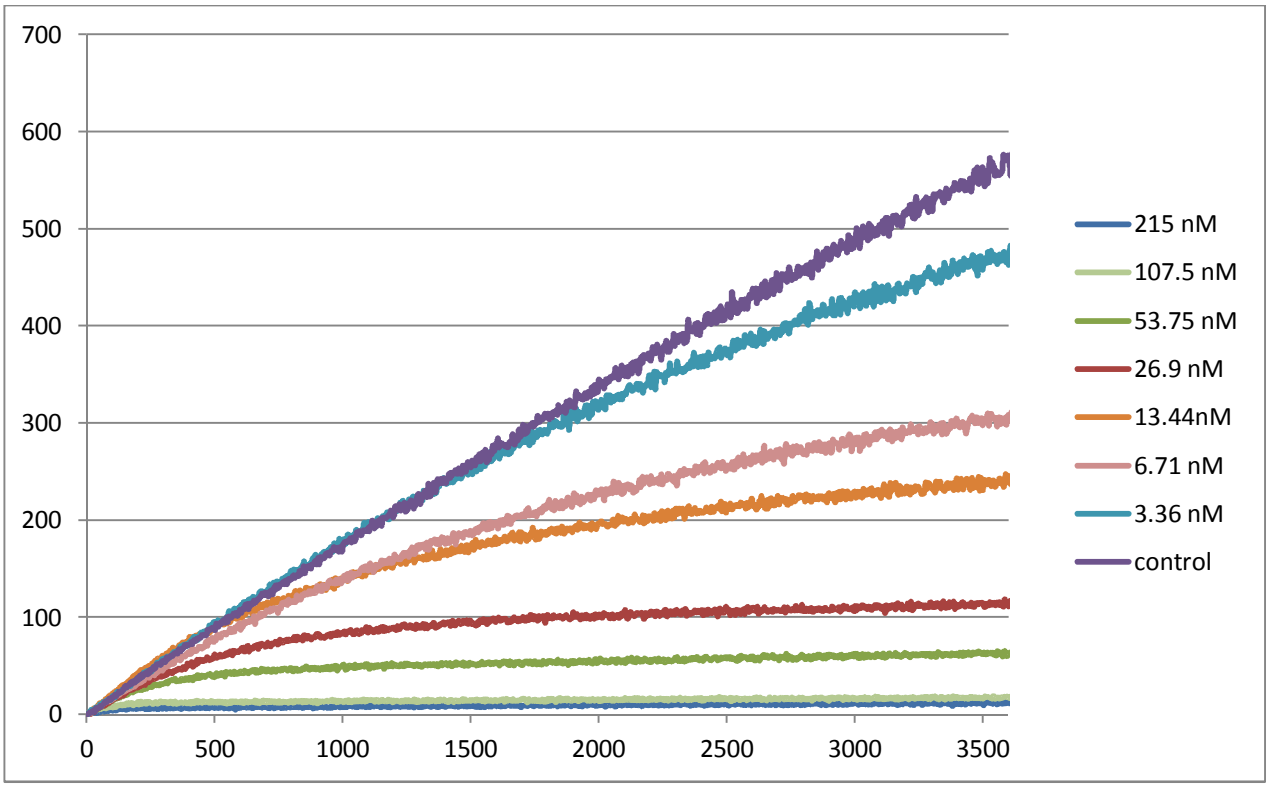

173.62 172.11 140.74 139.95 138.76 128.48 128.43 126.87 126.61 126.45 81.35 80.27 60.56 56.55 50.62 48.01 47.87 47.73 47.59 47.45 47.30 47.16 28.71 28.58 26.39 25.98 21.46 18.04 8.72 8.31
f1 (ppm)

No preincubation kinetics curves:

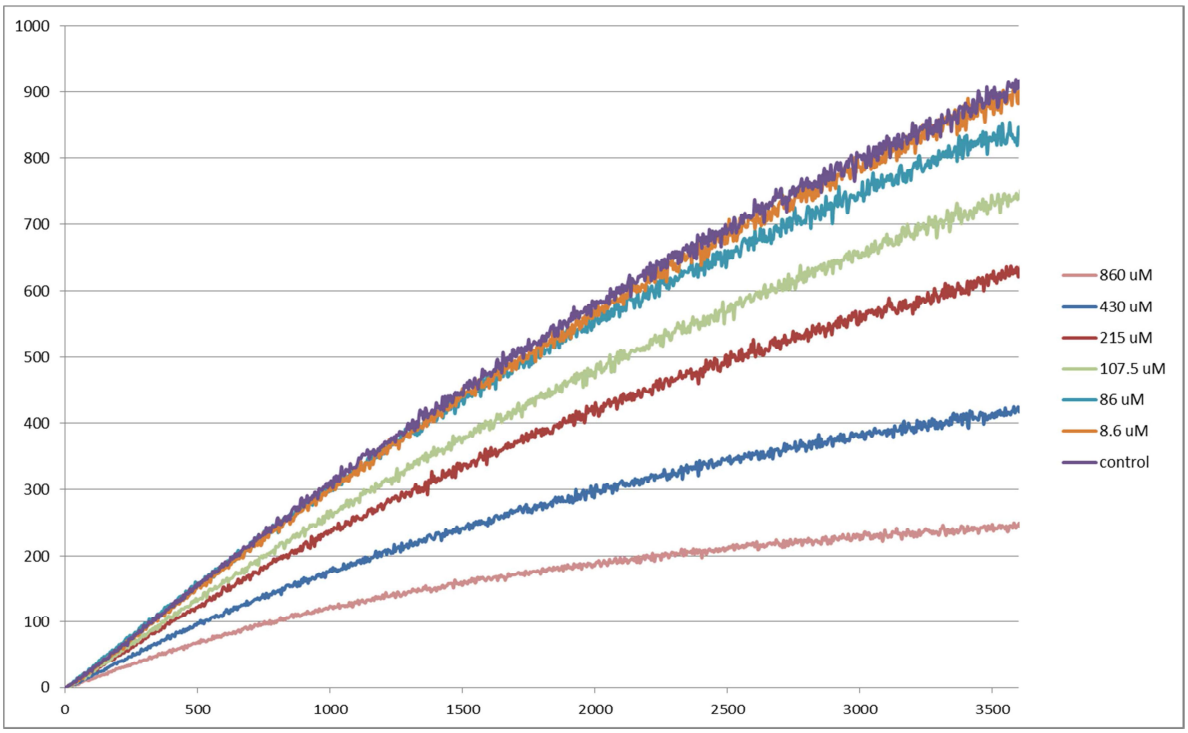
Compound 4, H9N2.



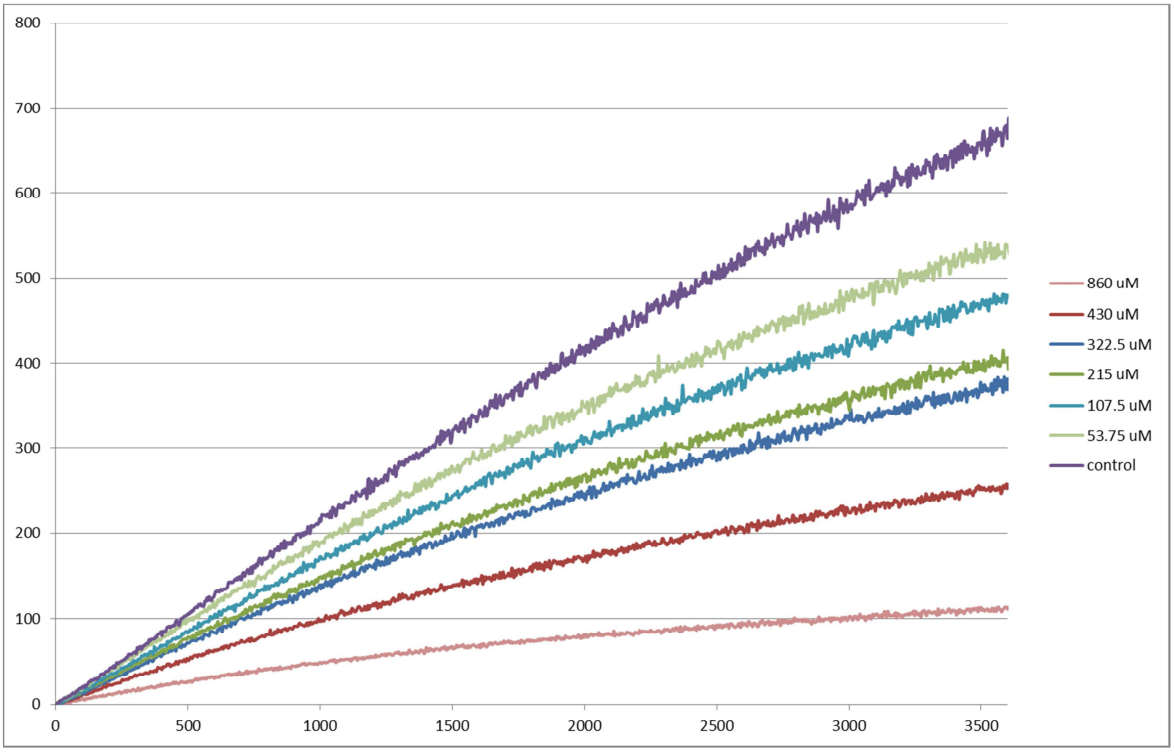
Compound 4, H5N1.



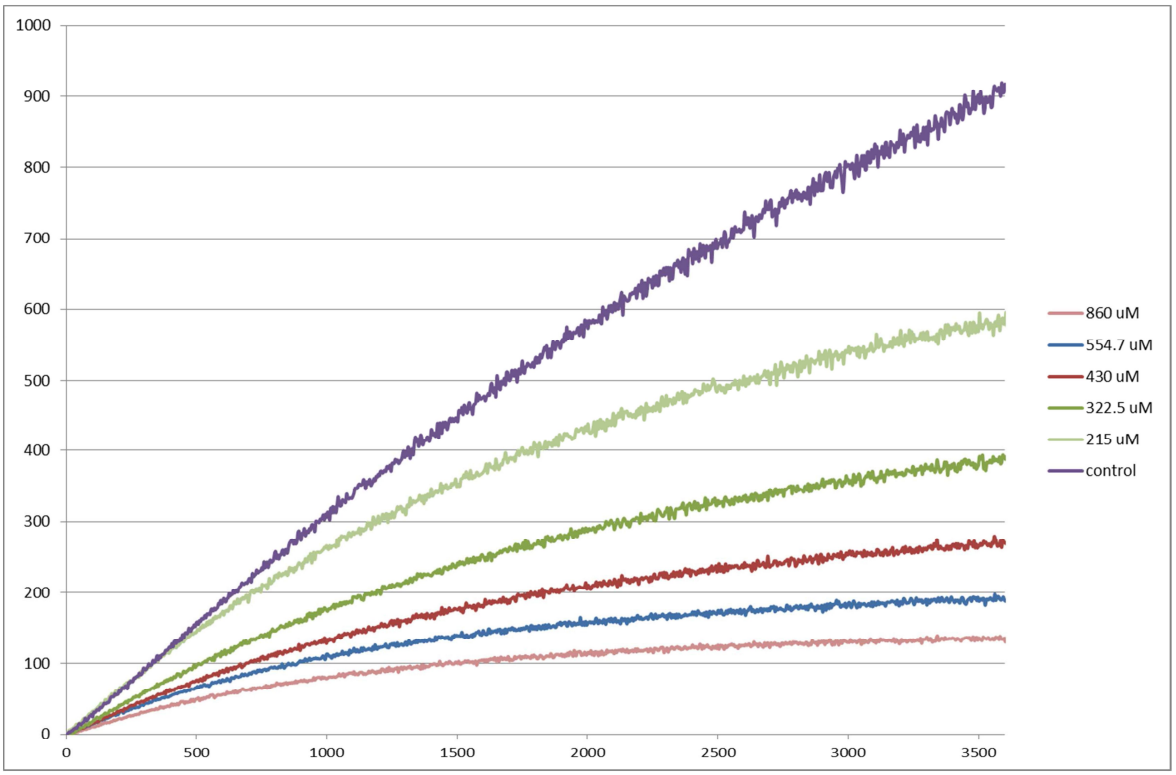
Compound 13, H9N2.



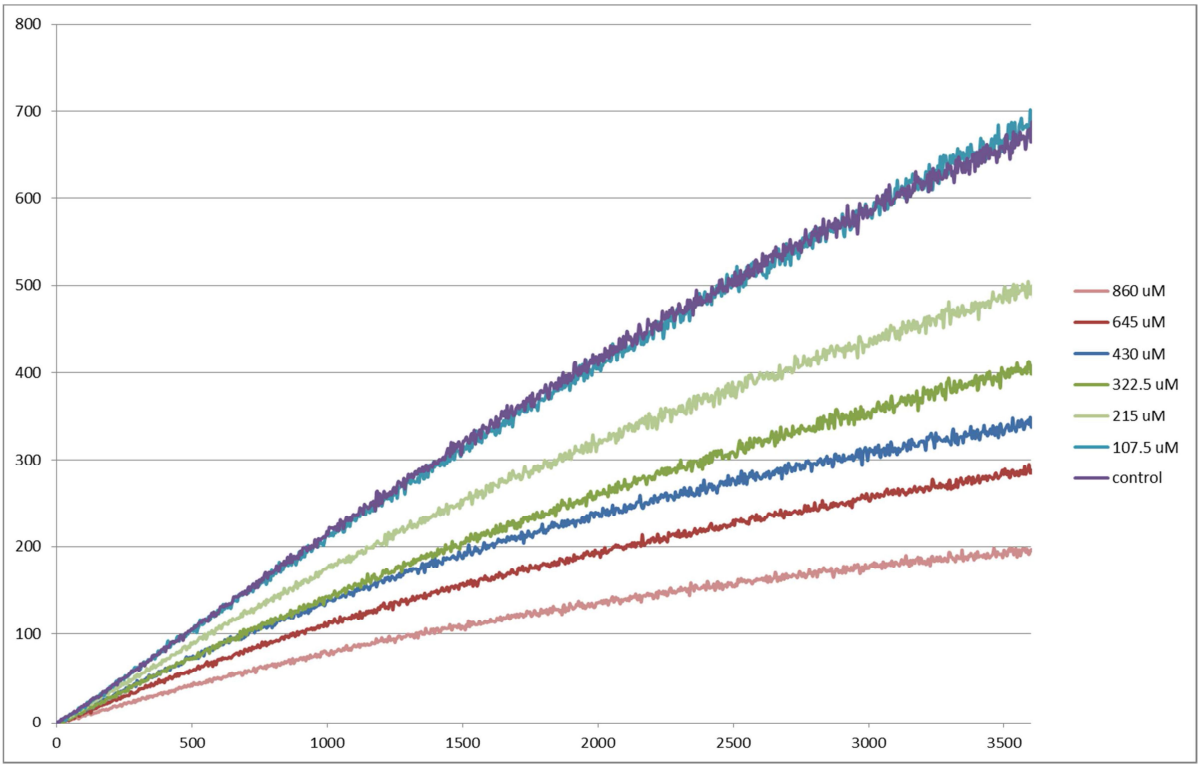
Compound 13, H5N1.



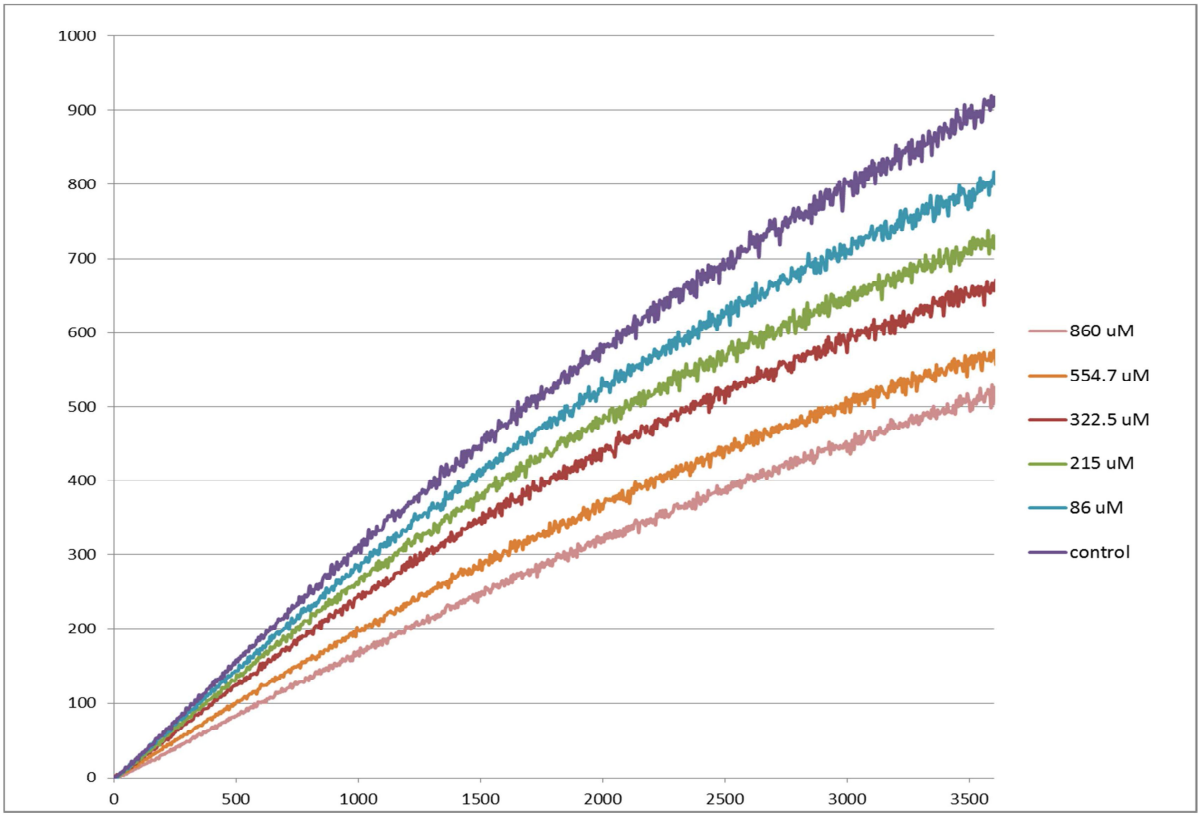
Compound 14, H9N2.



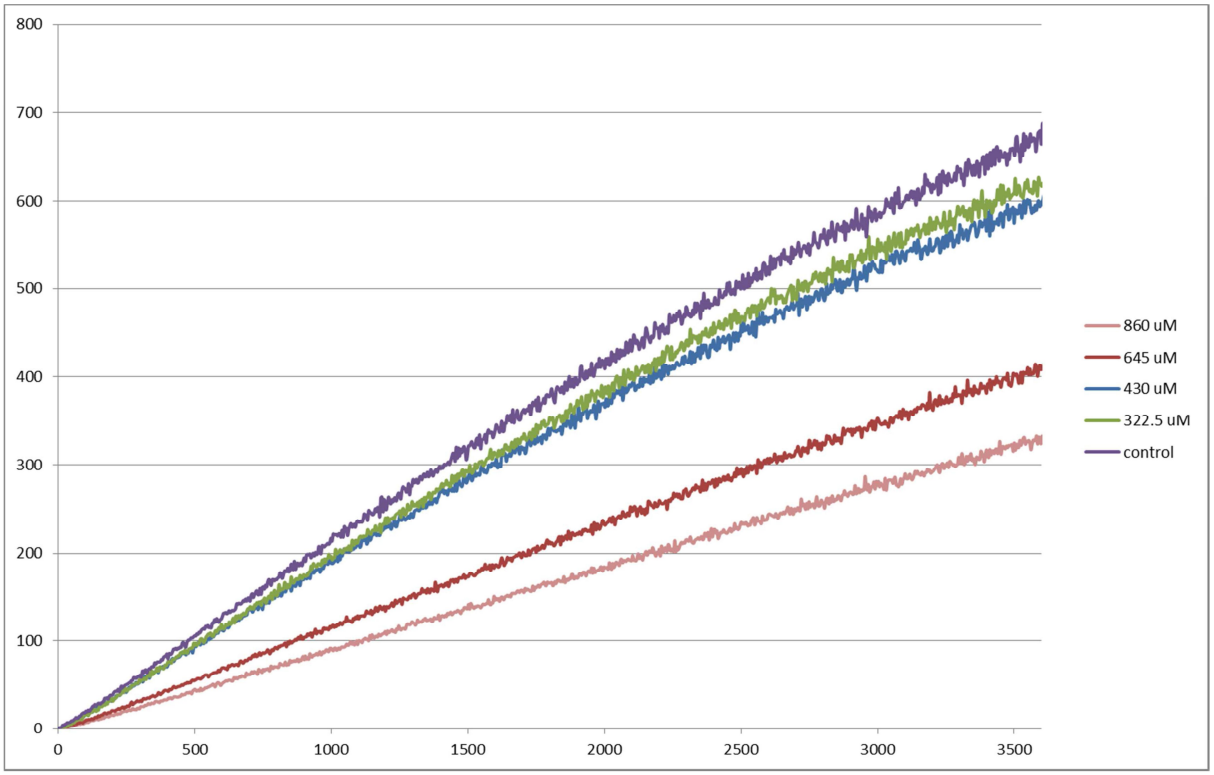
Compound 14, H5N1.



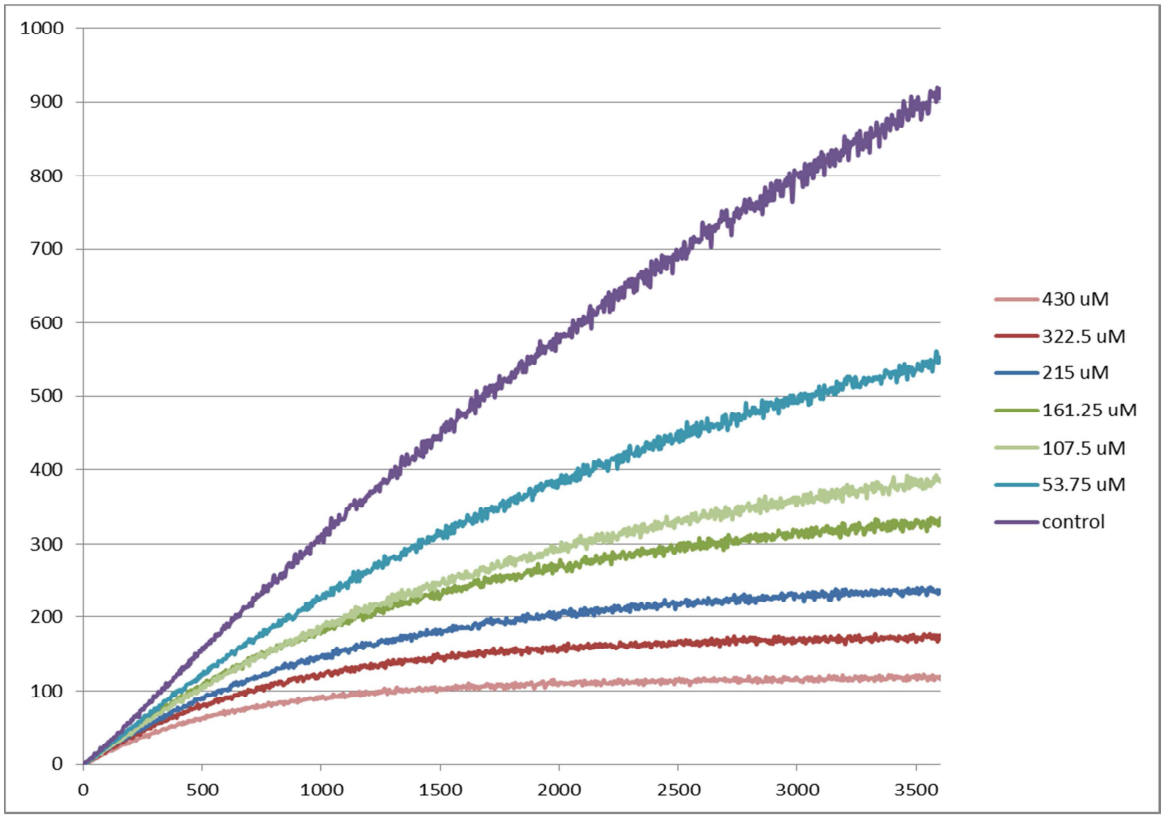
Compound 15, H9N2.



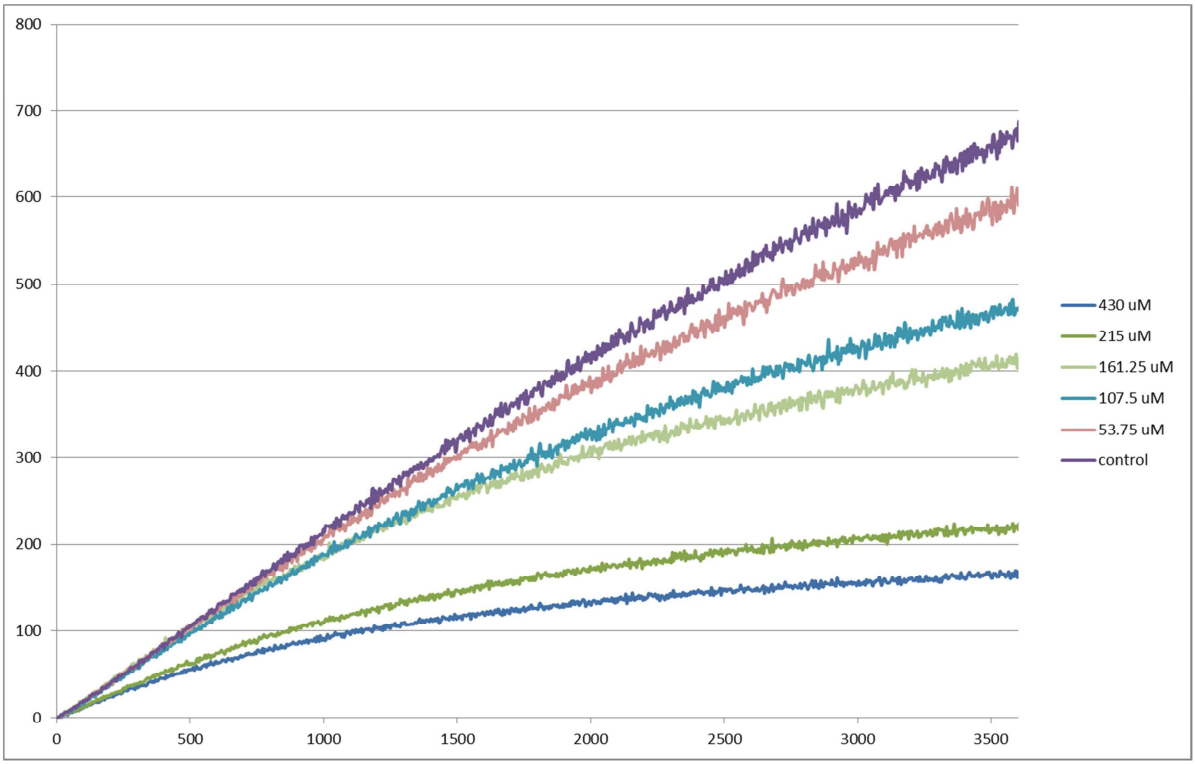
Compound 15, H5N1.



Compound 17, H9N2.

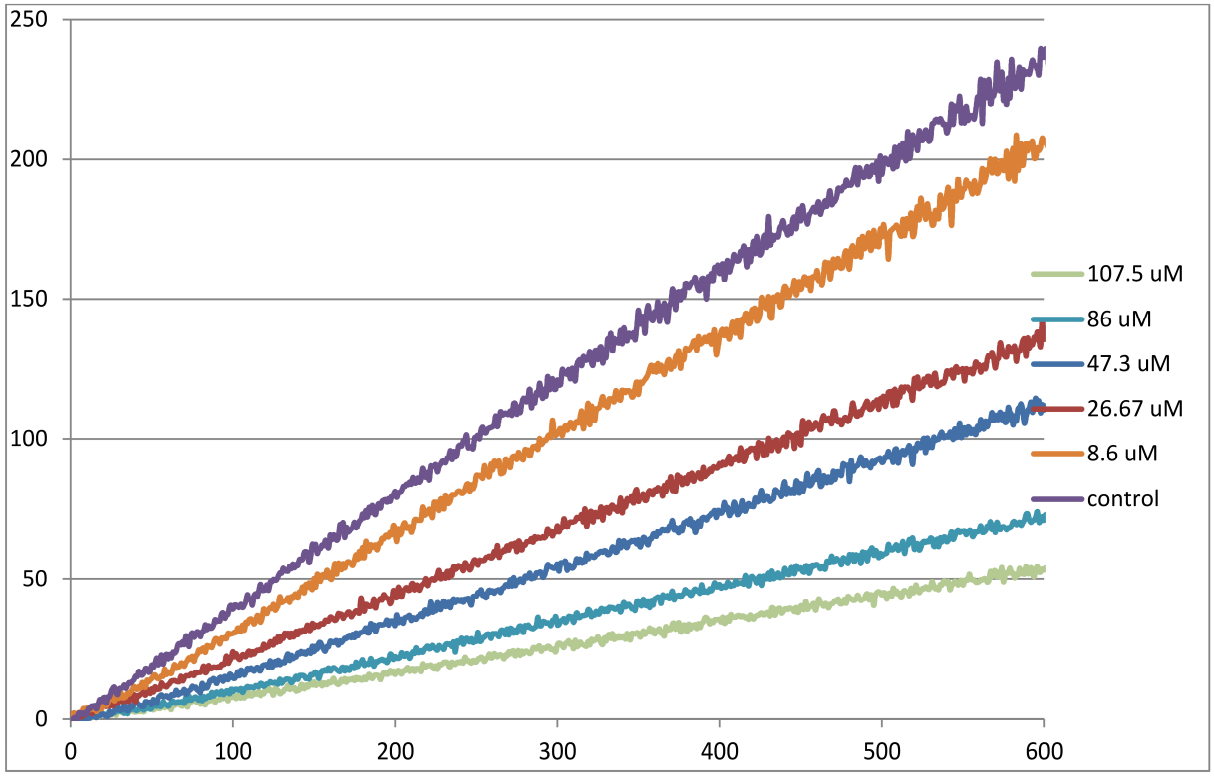


Compound 17, H5N1.

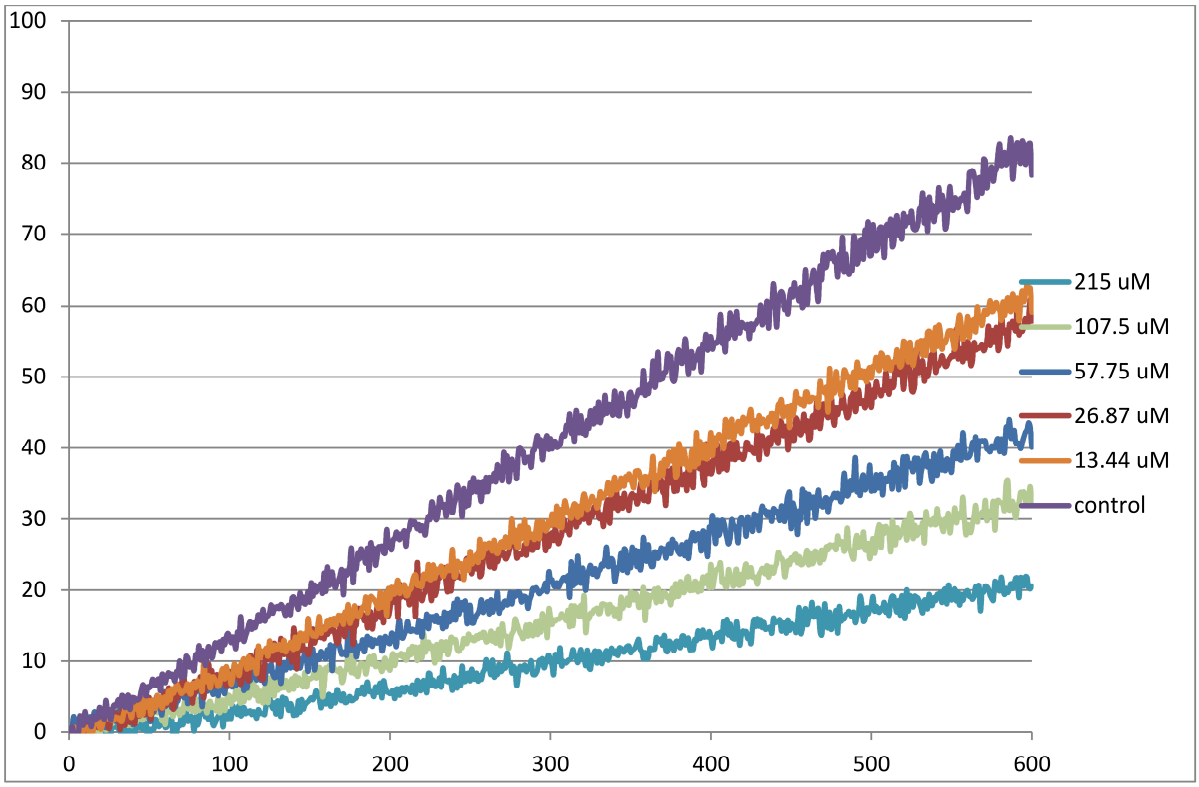


Preincubation kinetics curves:

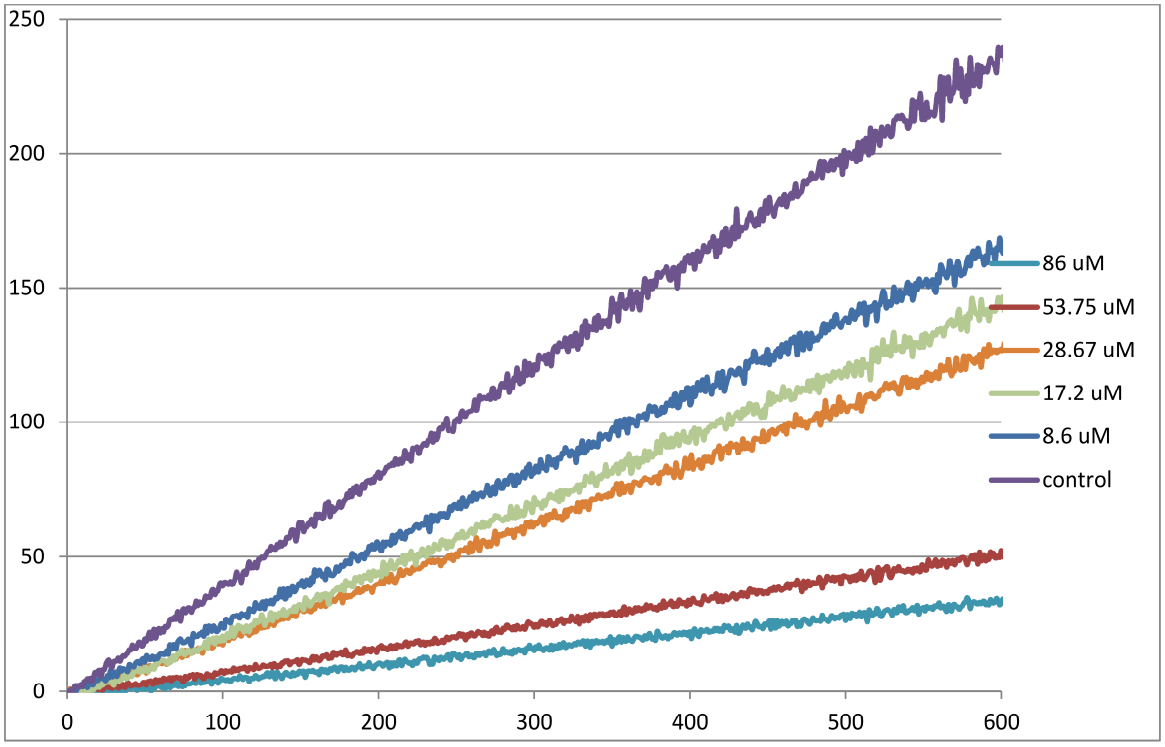
Compound 13, H9N2.



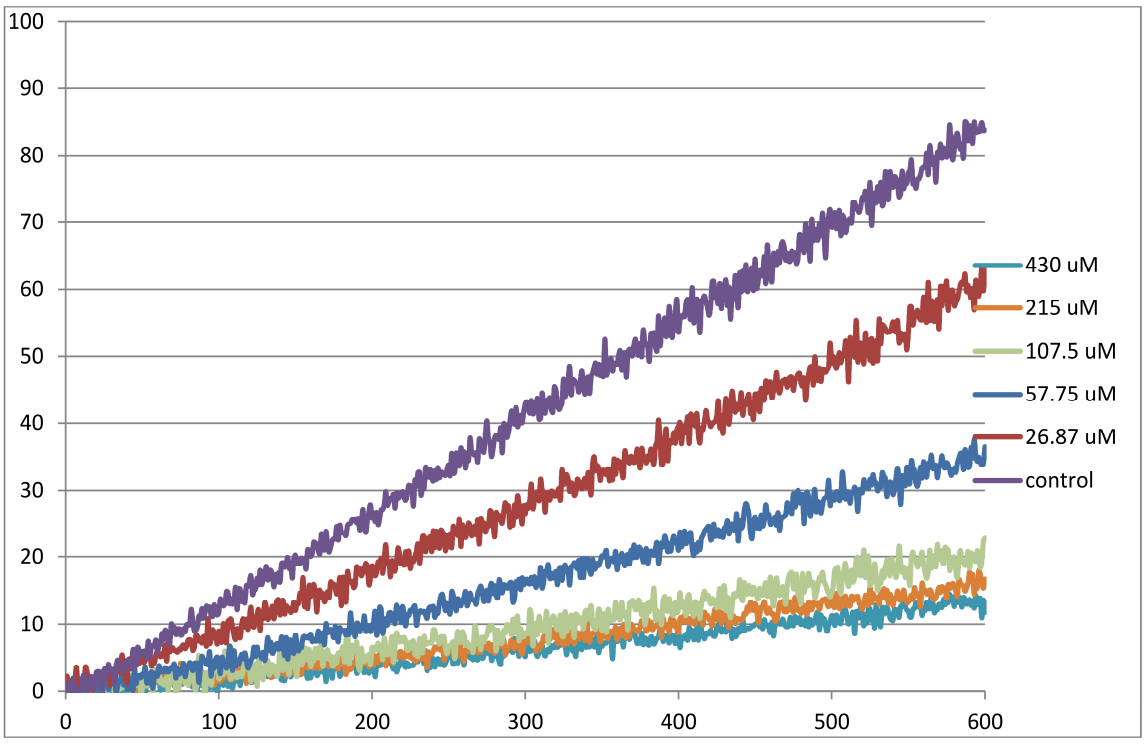
Compound 13, H5N1.



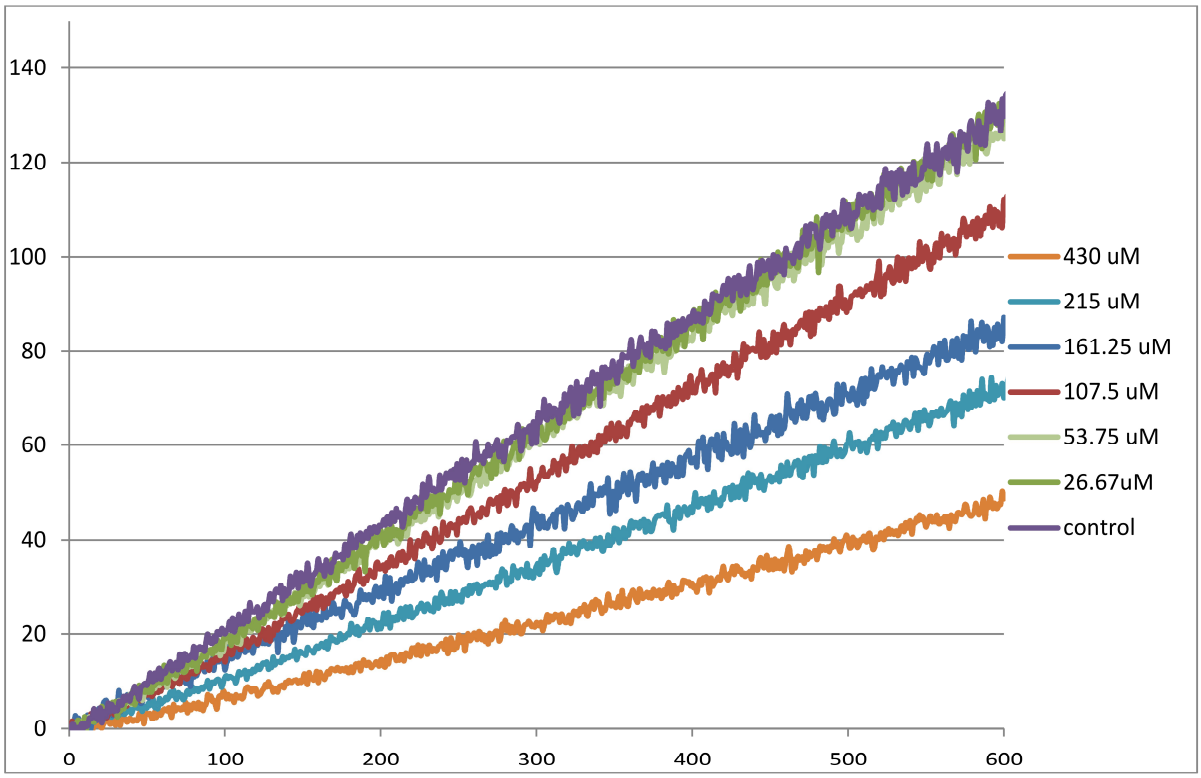
Compound 14, H9N2.



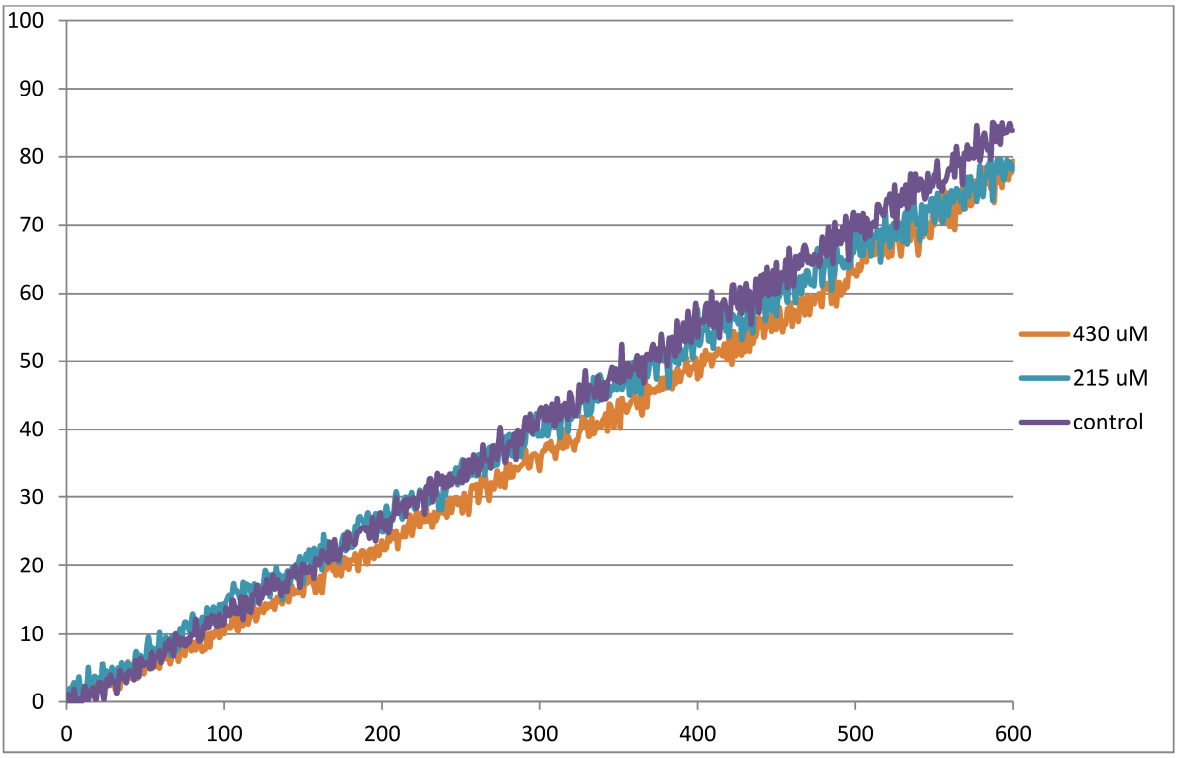
Compound 14, H5N1.



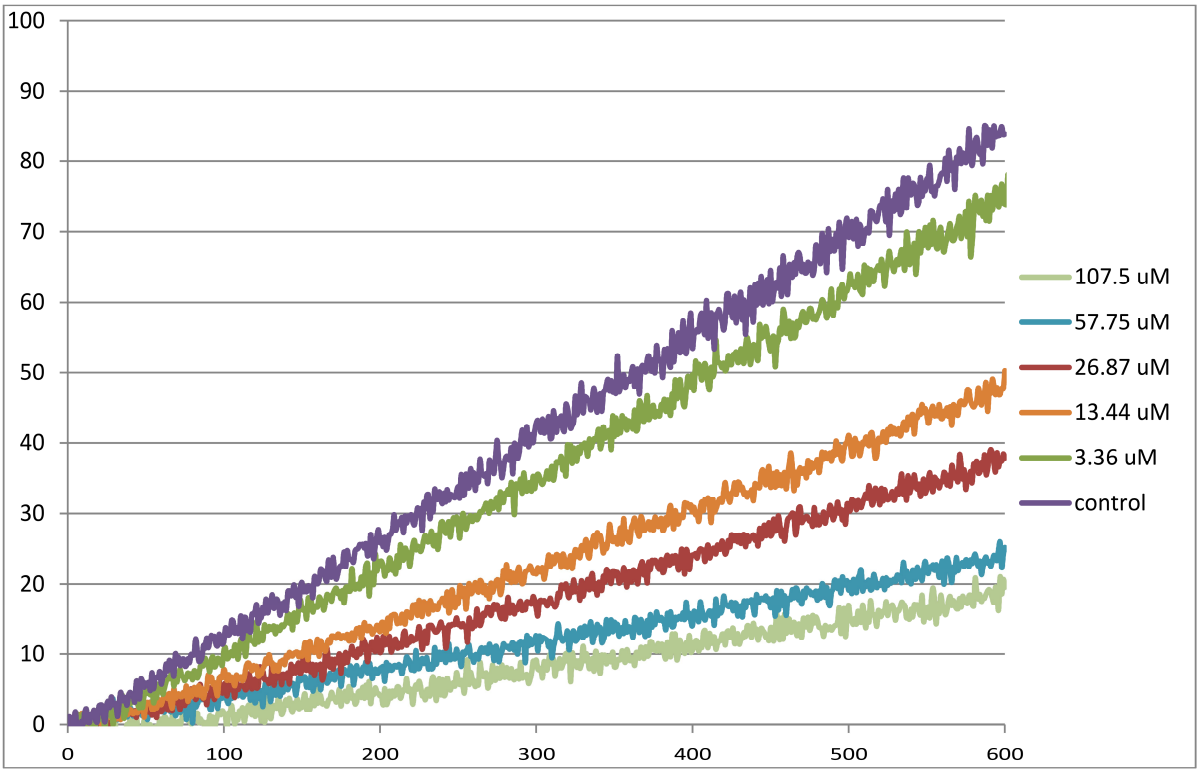
Compound 15, H9N2.



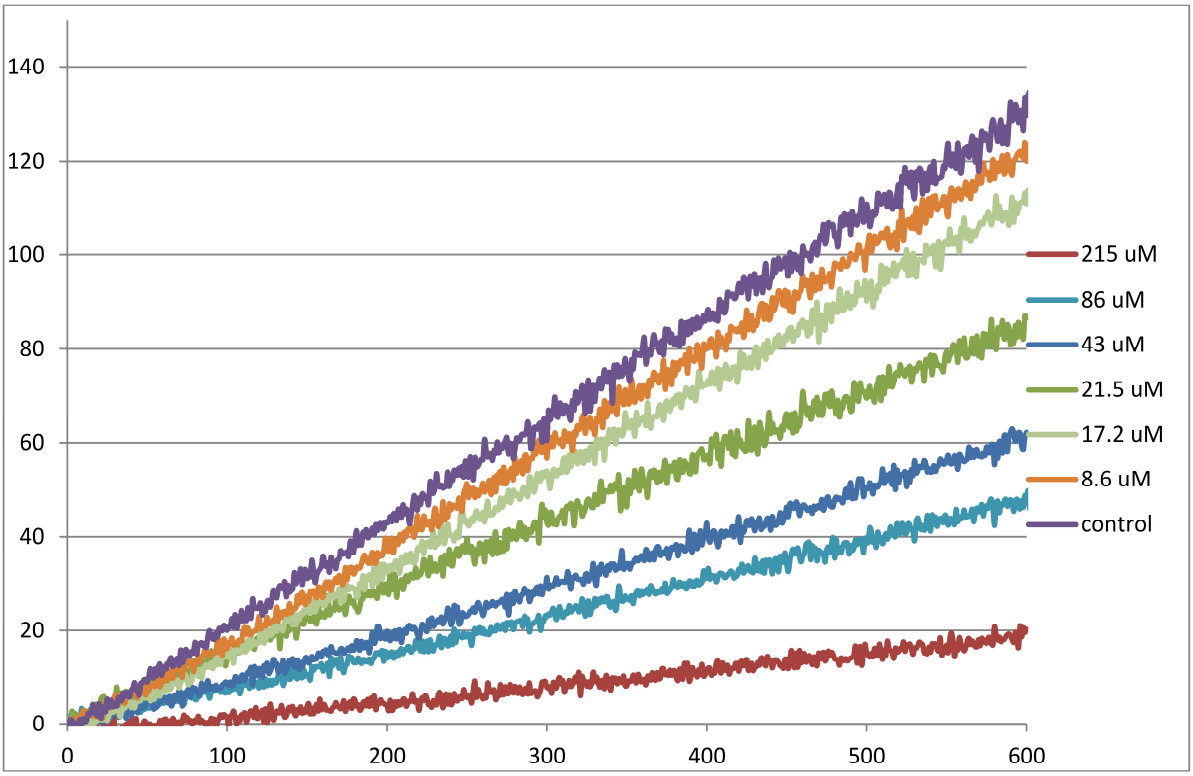
Compound 15, H5N1.



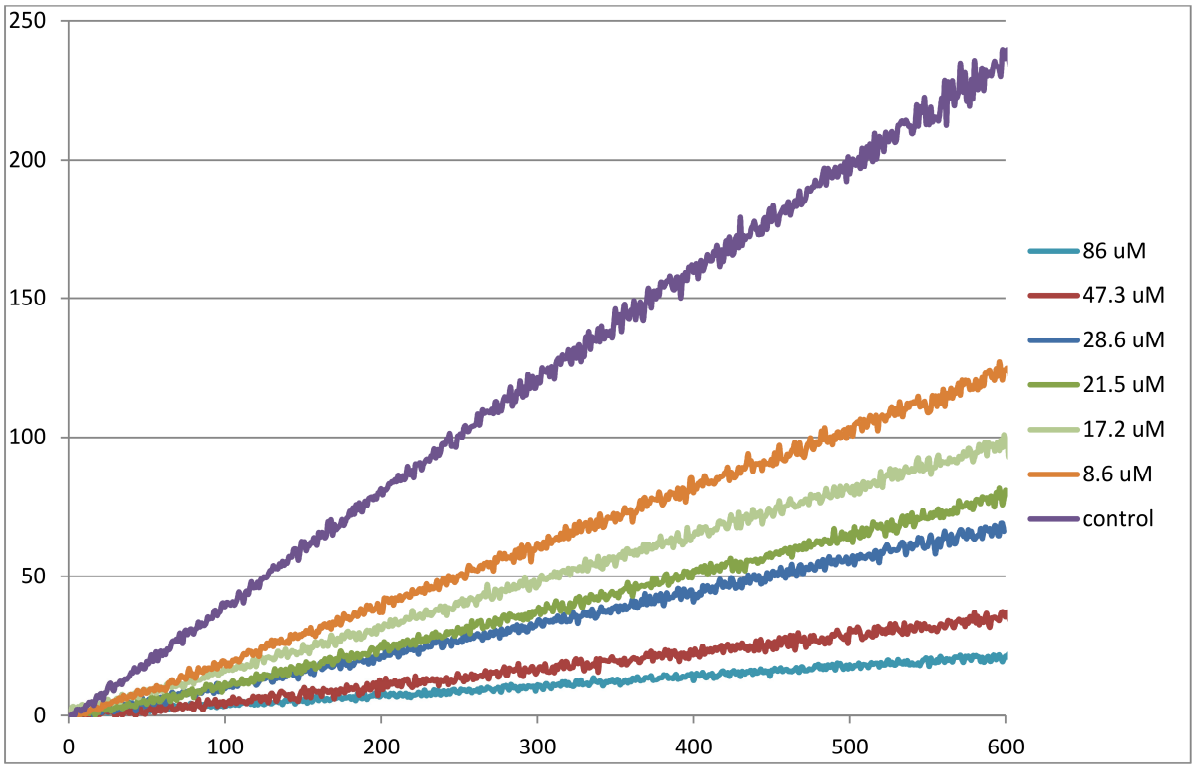
Compound 16, H9N2.



Compound 16, H5N1.

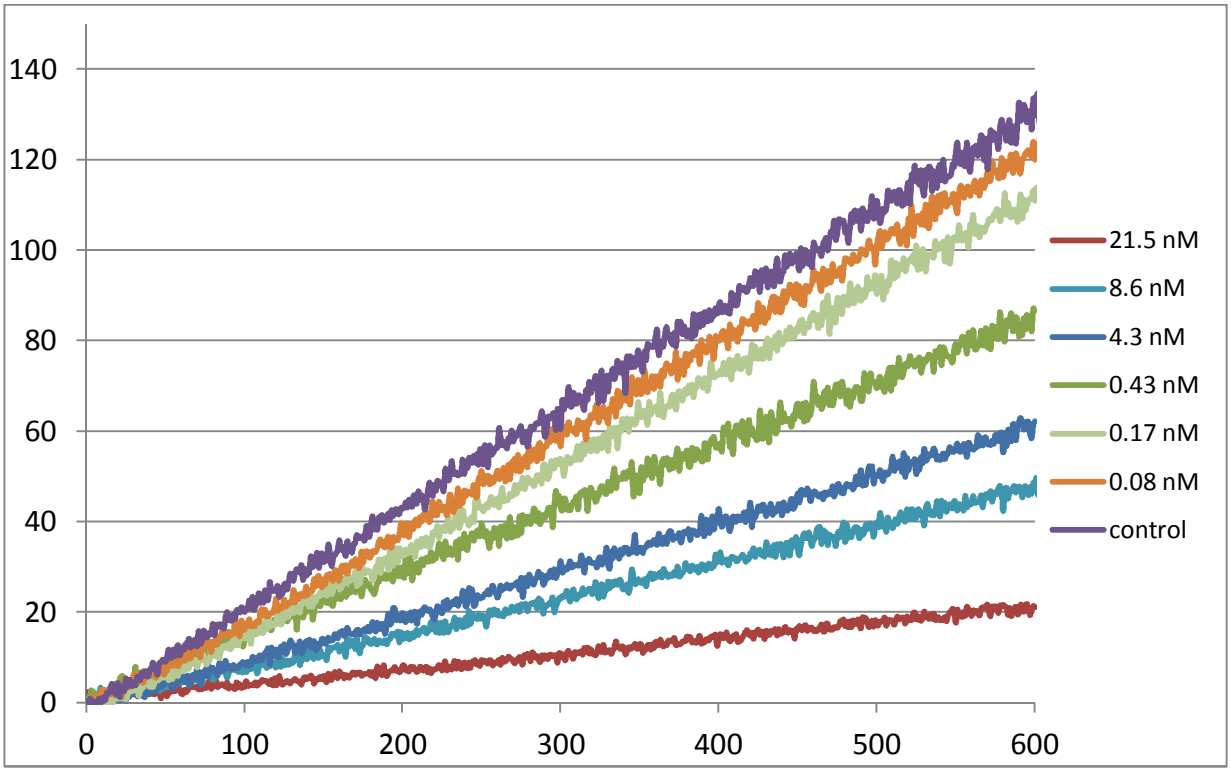


Compound 17, H9N2.



Compound 17, H5N1.

Compound 4, H9N2.



Compound 4, H5N1.