Slight structural modulation around a pivotal bond: High impact on enantiomeric stability

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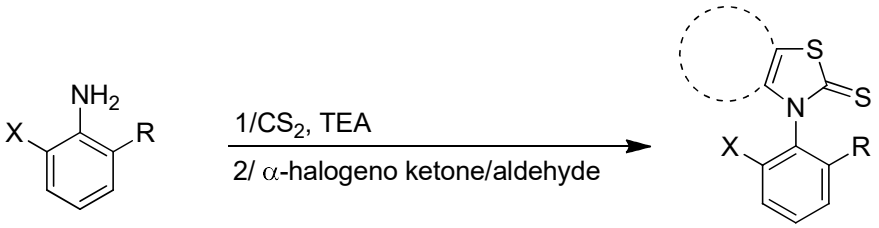
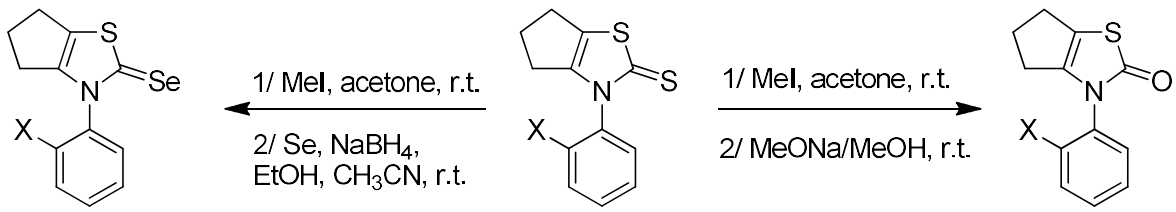
Supporting Information

Synthesis schemes



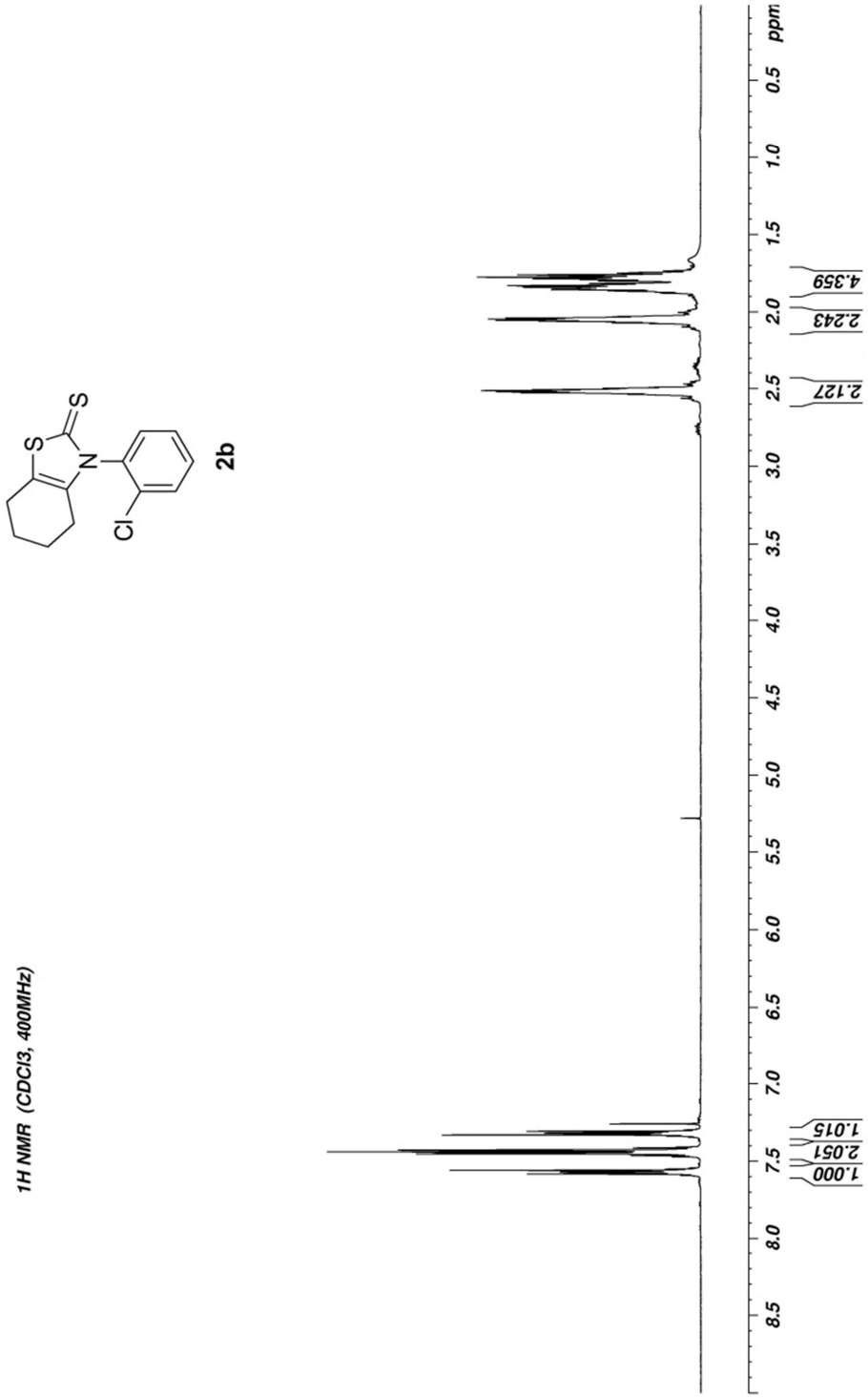
α-halogeno ketone/aldehyde	X	R	*N*-arylthiazoline-2-thione
2-chlorocyclopentanone	F	H	**1a**
	Cl	H	**1b**
	Br	H	**1c**
	I	H	**1d**
2-chlorocyclohexanone	F	H	**2a**
	Cl	H	**2b**
	Br	H	**2c**
	I	H	**2d**
chloroacetone	F	H	**3a**
	Cl	H	**3b**
	Br	H	**3c**
	I	H	**3d**
chloroacetaldehyde	I	H	**4d**
	F	Me	**5a**

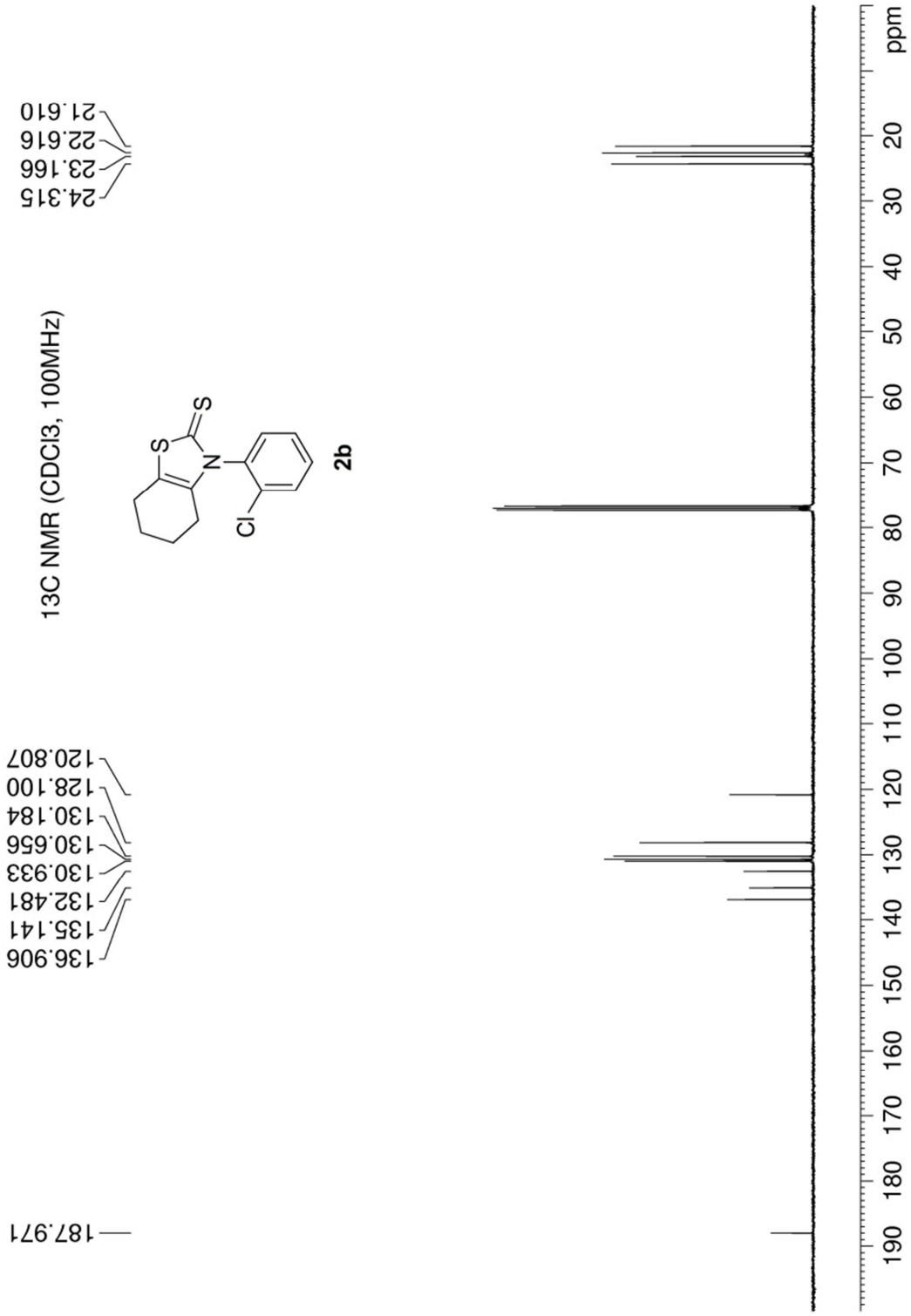


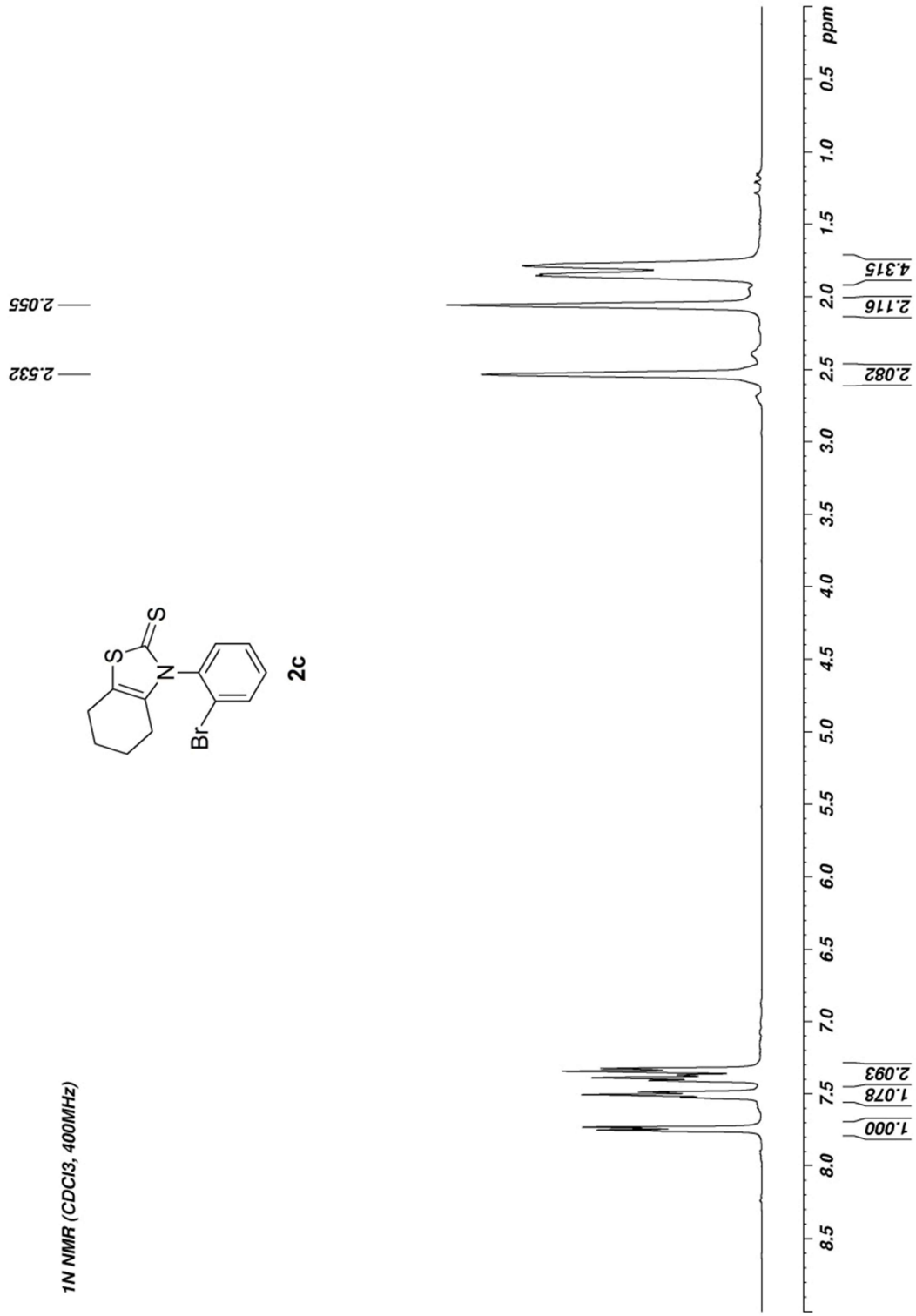
6 **1** **7**

X = F, Cl, Br or I

NMR Spectra


1H NMR (CDCl3, 400MHz)
S
S
N
Cl
2b
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
4.359
2.243
2.127
1.015
2.051
1.000


13C NMR (CDCl3, 100MHz)
2b
S
S
N
Cl
187.971
136.906
135.141
132.481
130.933
130.656
130.184
128.100
120.807
24.315
23.166
22.616
21.610
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


1N NMR (CDCl3, 400MHz)
2c
Br
S
S
N
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2.055
ppm
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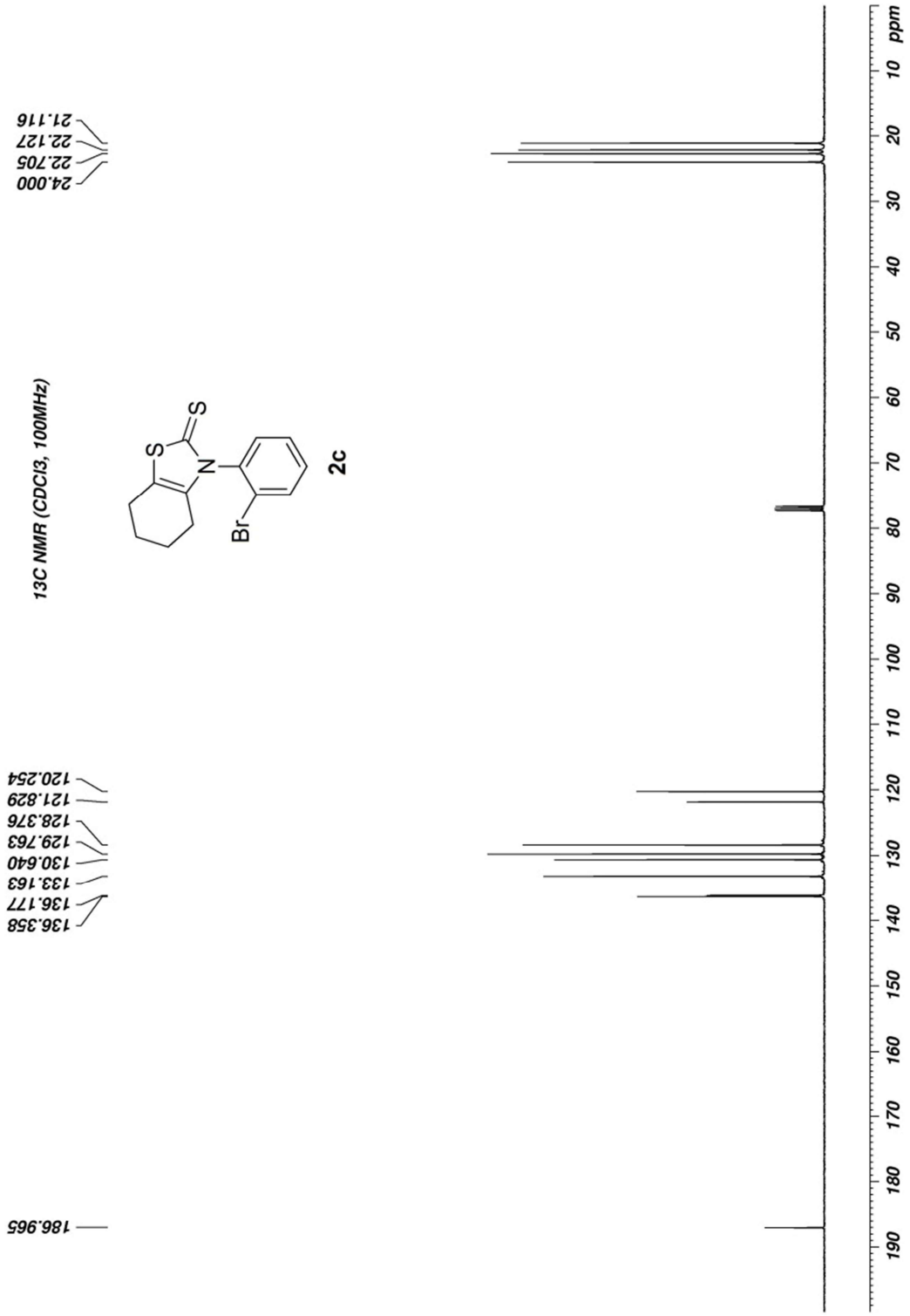
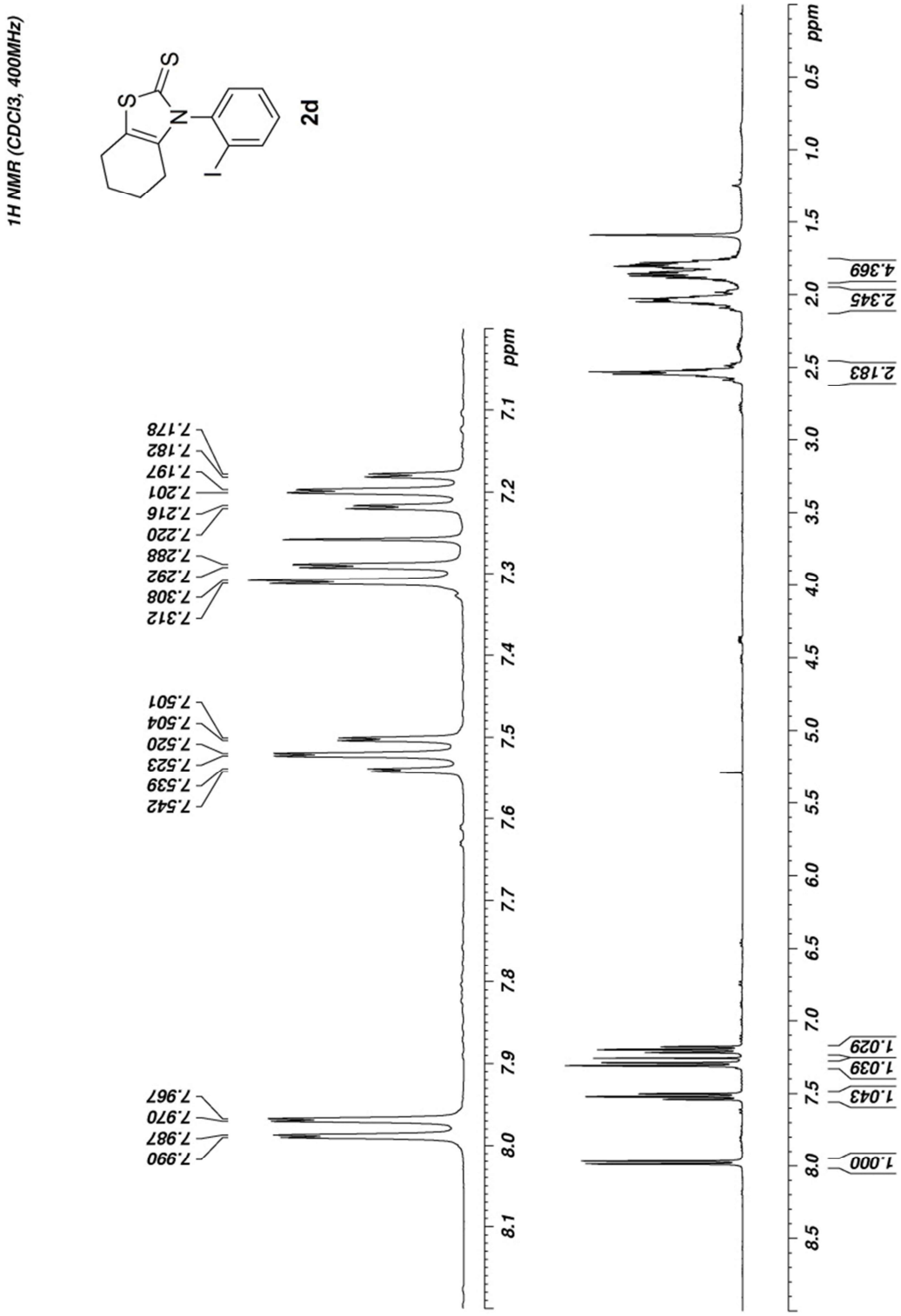
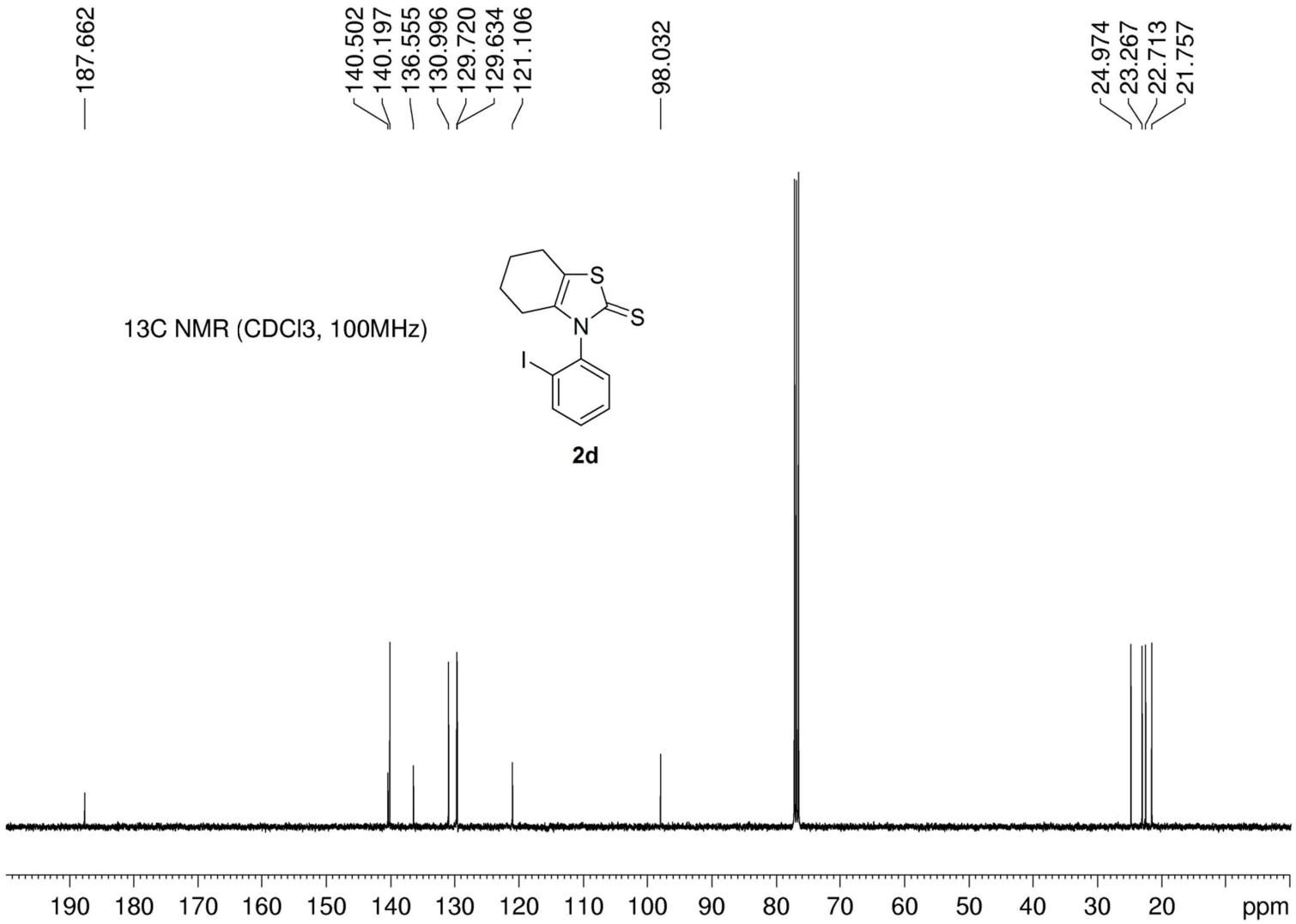
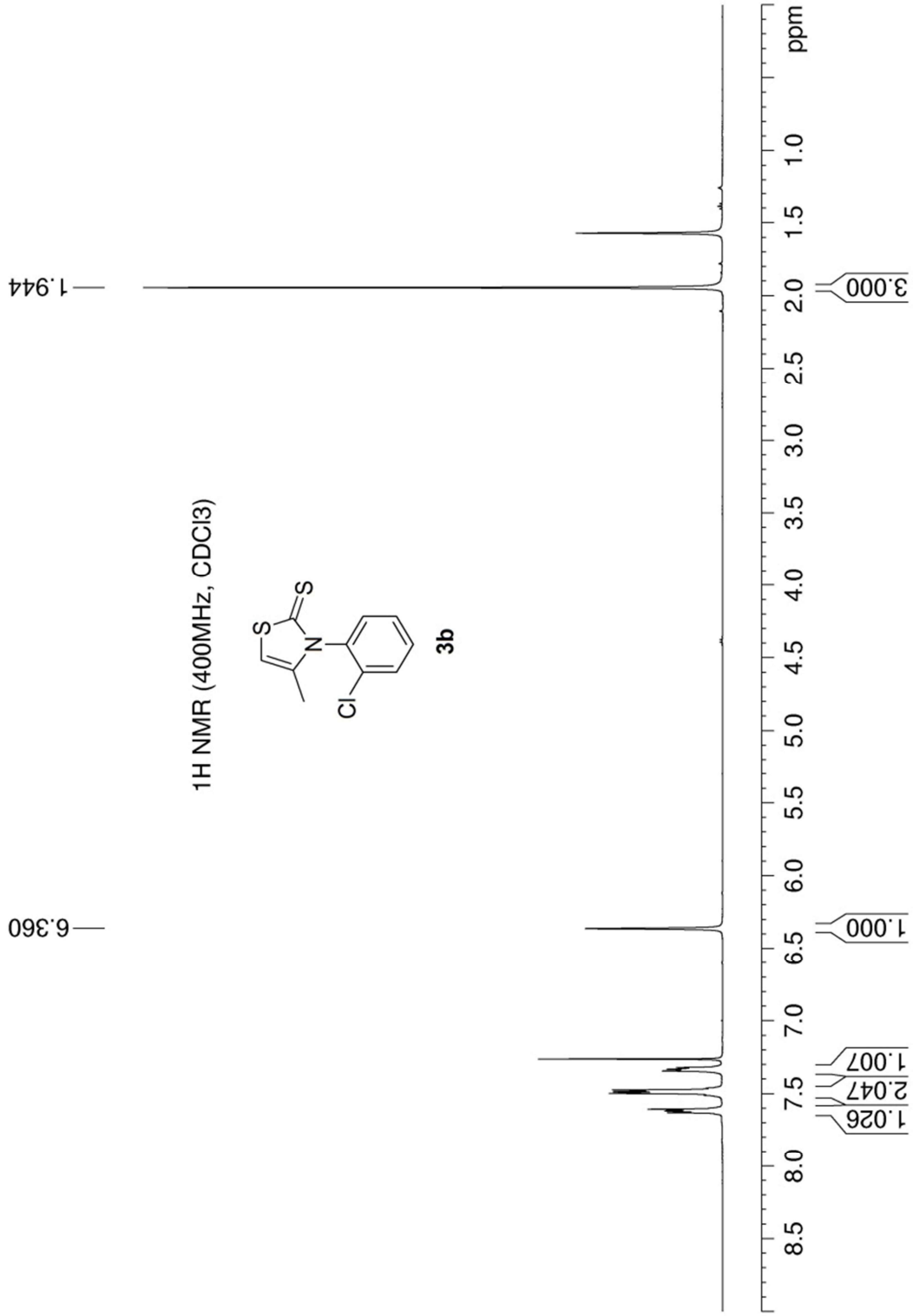
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
4.315
2.116
2.082
2.093
1.078
1.000

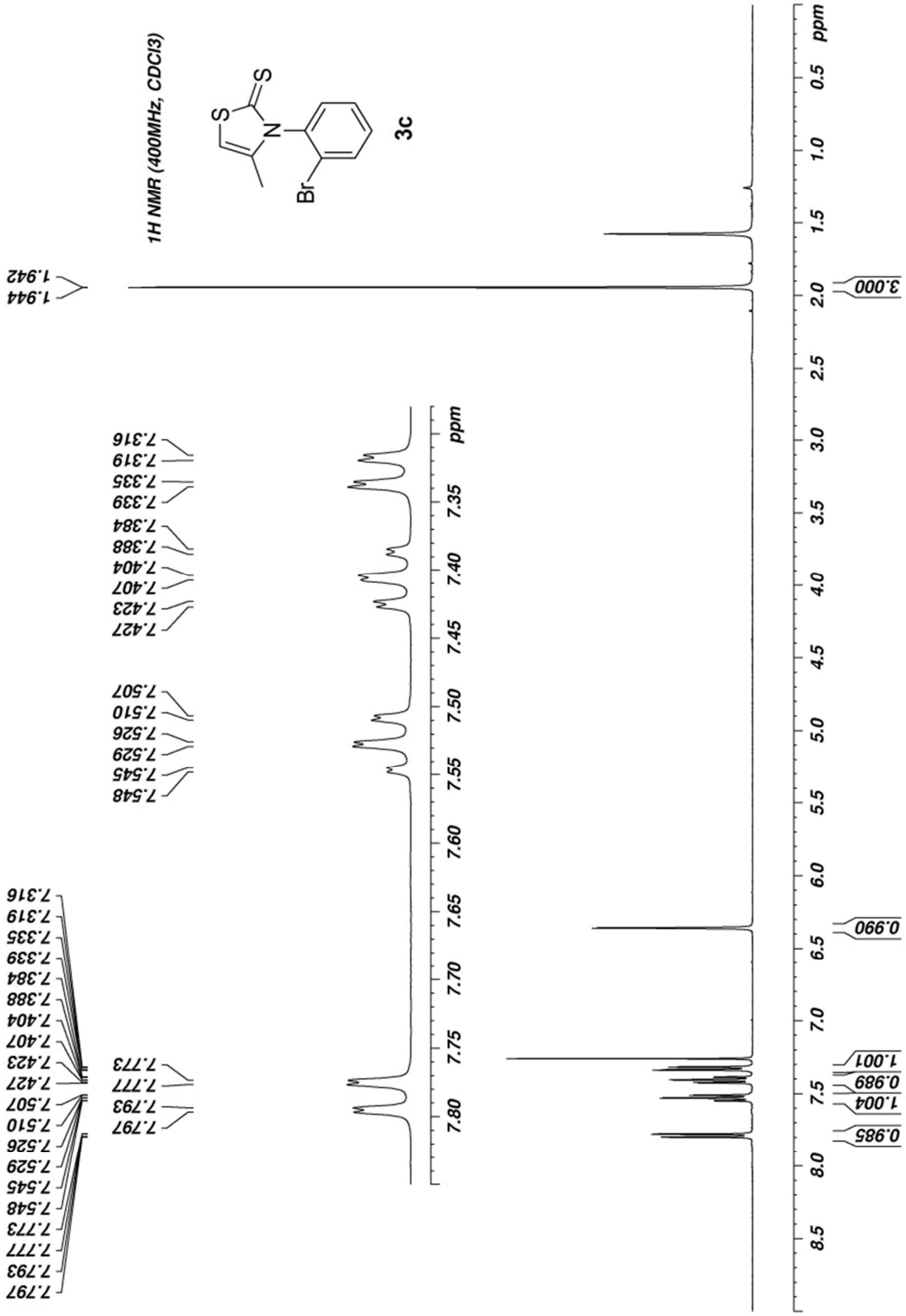

13C NMR (CDCl3, 100MHz)
S
S
N
Br
2c
186.965
136.358
136.177
133.163
130.640
129.763
128.376
121.829
120.254
24.000
22.705
22.127
21.116
ppm

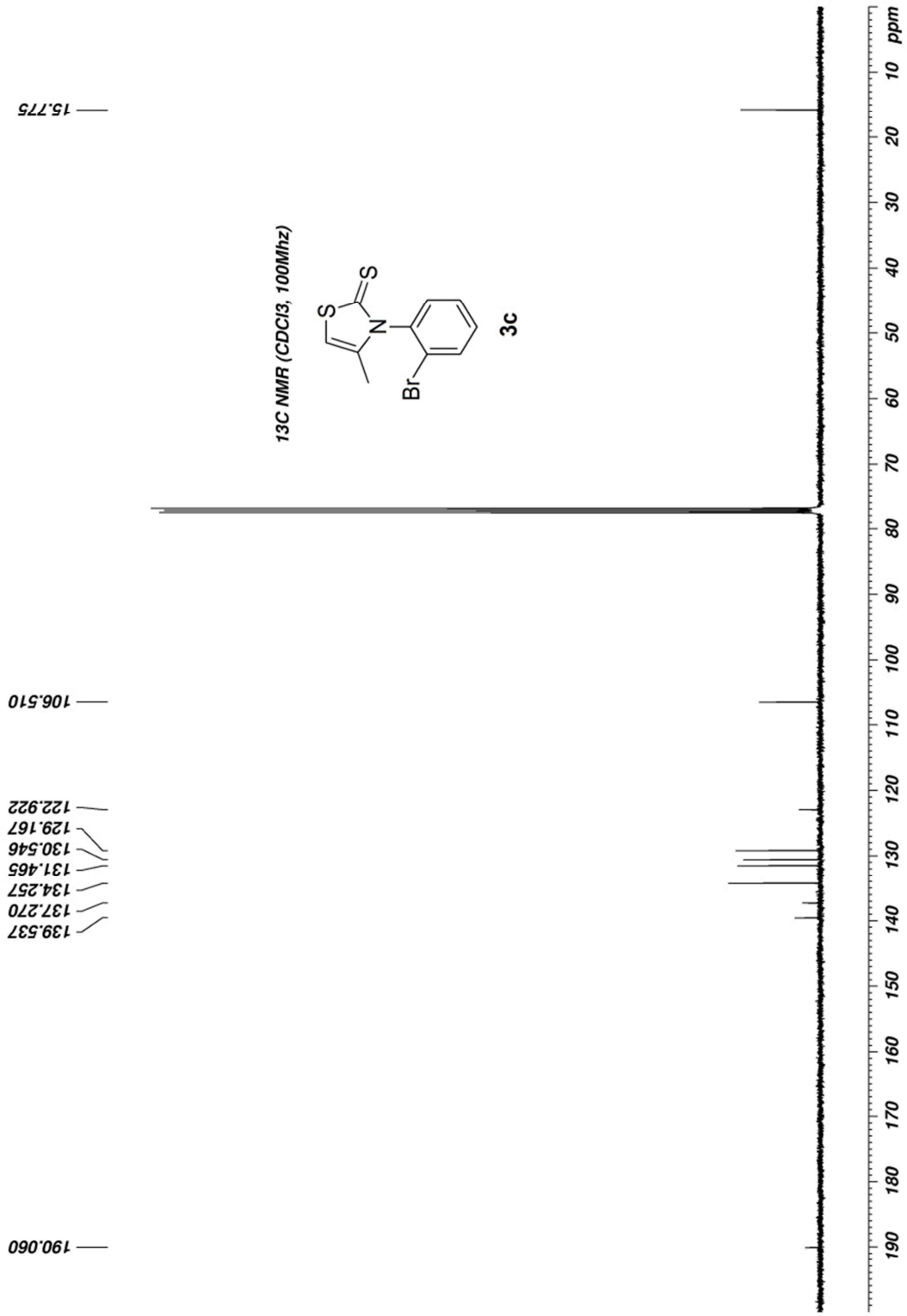

1H NMR (CDCl3, 400MHz)
2d
7.990
7.987
7.970
7.967
7.542
7.539
7.523
7.520
7.504
7.501
7.312
7.308
7.292
7.288
7.220
7.216
7.201
7.197
7.182
7.178
ppm
1.000
1.043
1.039
1.029
2.183
2.345
4.369


13C NMR (CDCl3, 100MHz)
2d
187.662
140.502
140.197
136.555
130.996
129.720
129.634
121.106
98.032
24.974
23.267
22.713
21.757
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


1H NMR (400MHz, CDCl3)
3b
1.944
6.360
3.000
1.000
1.007
2.047
1.026
ppm


13C NMR (CDCl3, 100MHz)
3b
190.199
139.640
135.557
132.883
131.323
131.038
130.511
128.455
106.472
15.573
ppm


1H NMR (400MHz, CDCl3)
3c
Br
S
S
N
ppm
1.944
1.942
7.797
7.793
7.777
7.773
7.548
7.545
7.529
7.526
7.510
7.507
7.427
7.423
7.407
7.404
7.388
7.384
7.339
7.335
7.319
7.316
3.000
0.990
1.001
0.989
1.004
0.985


13C NMR (CDCl3, 100Mhz)
3c
Br
S
S
N
190.060
139.537
137.270
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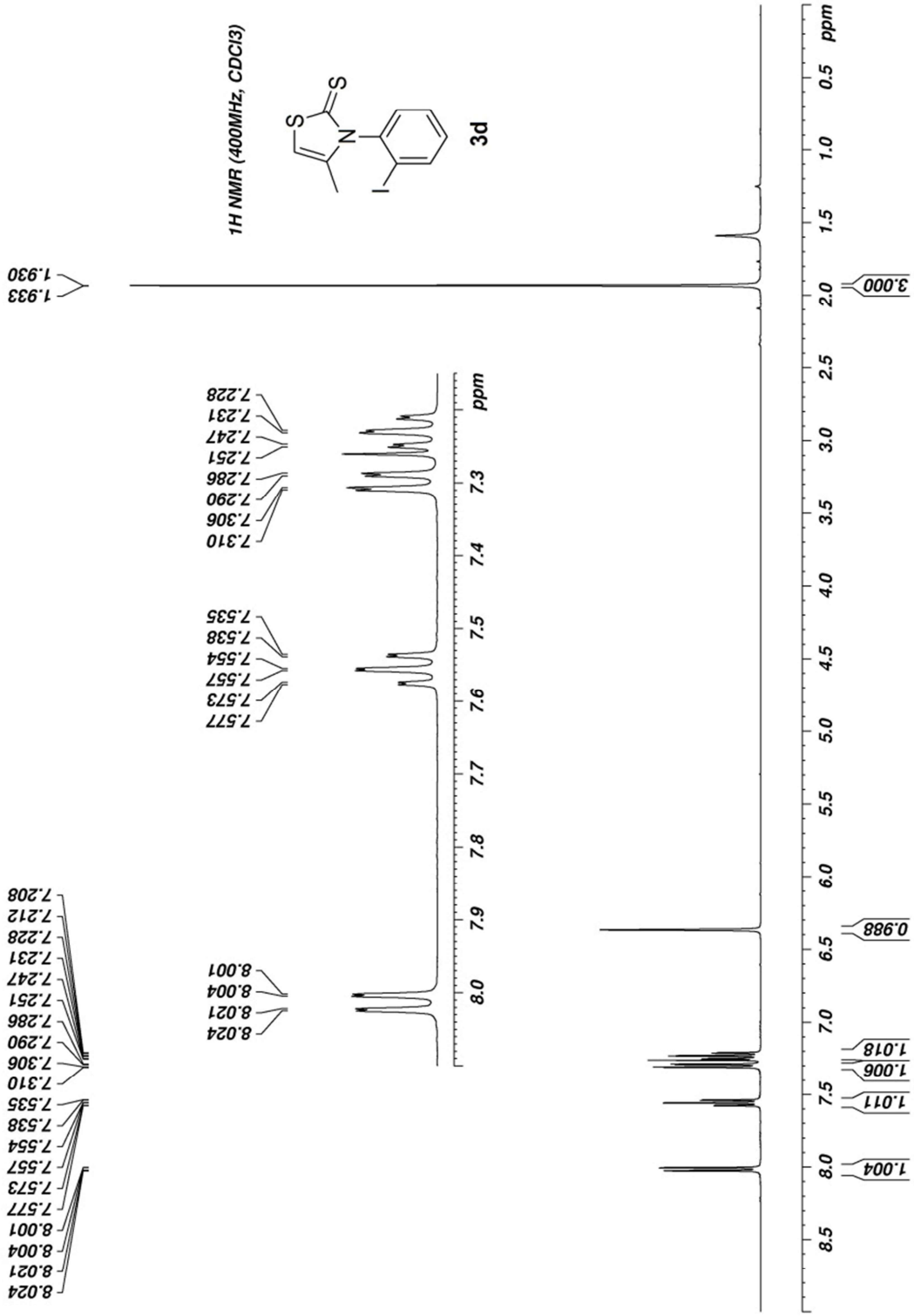
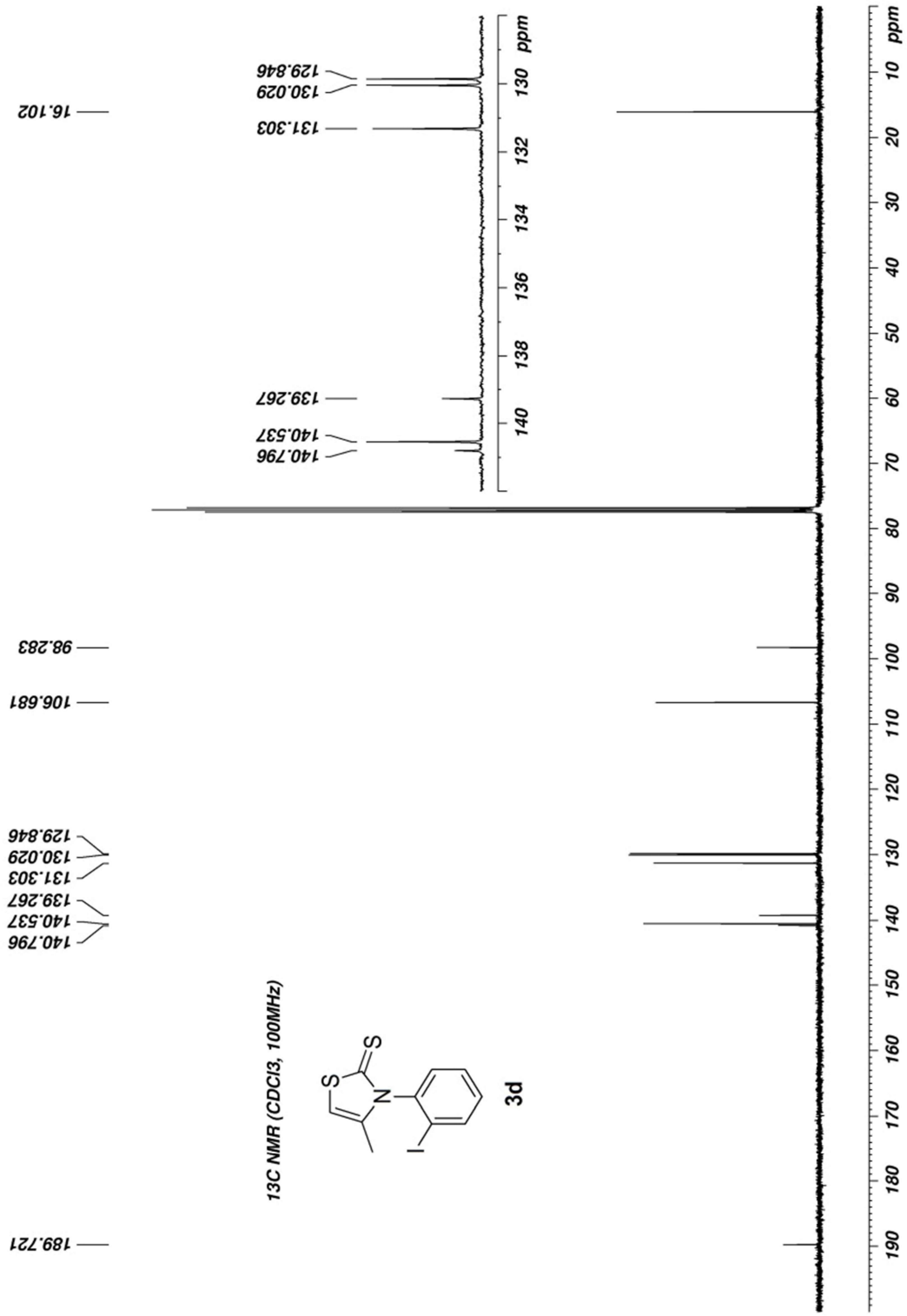
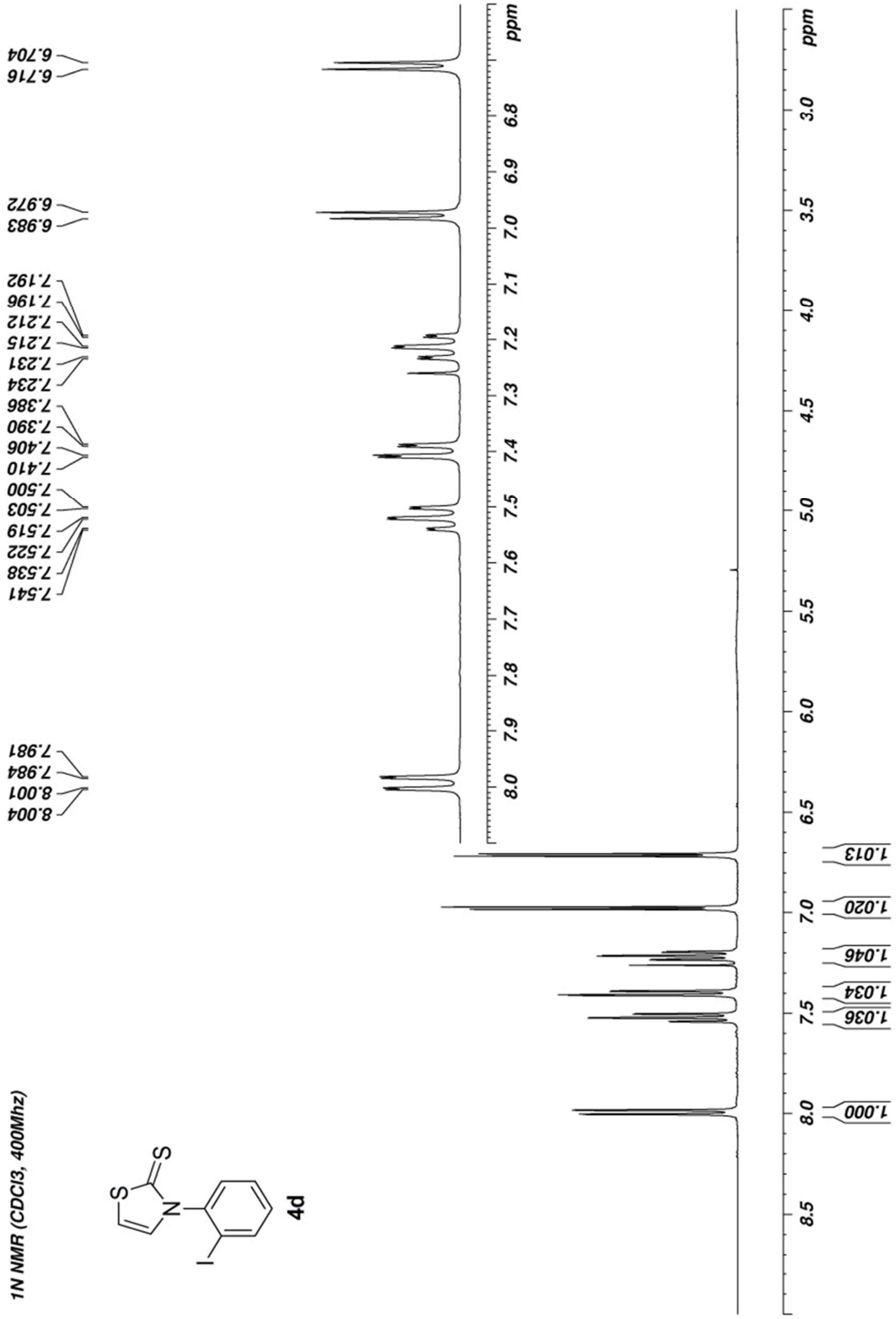
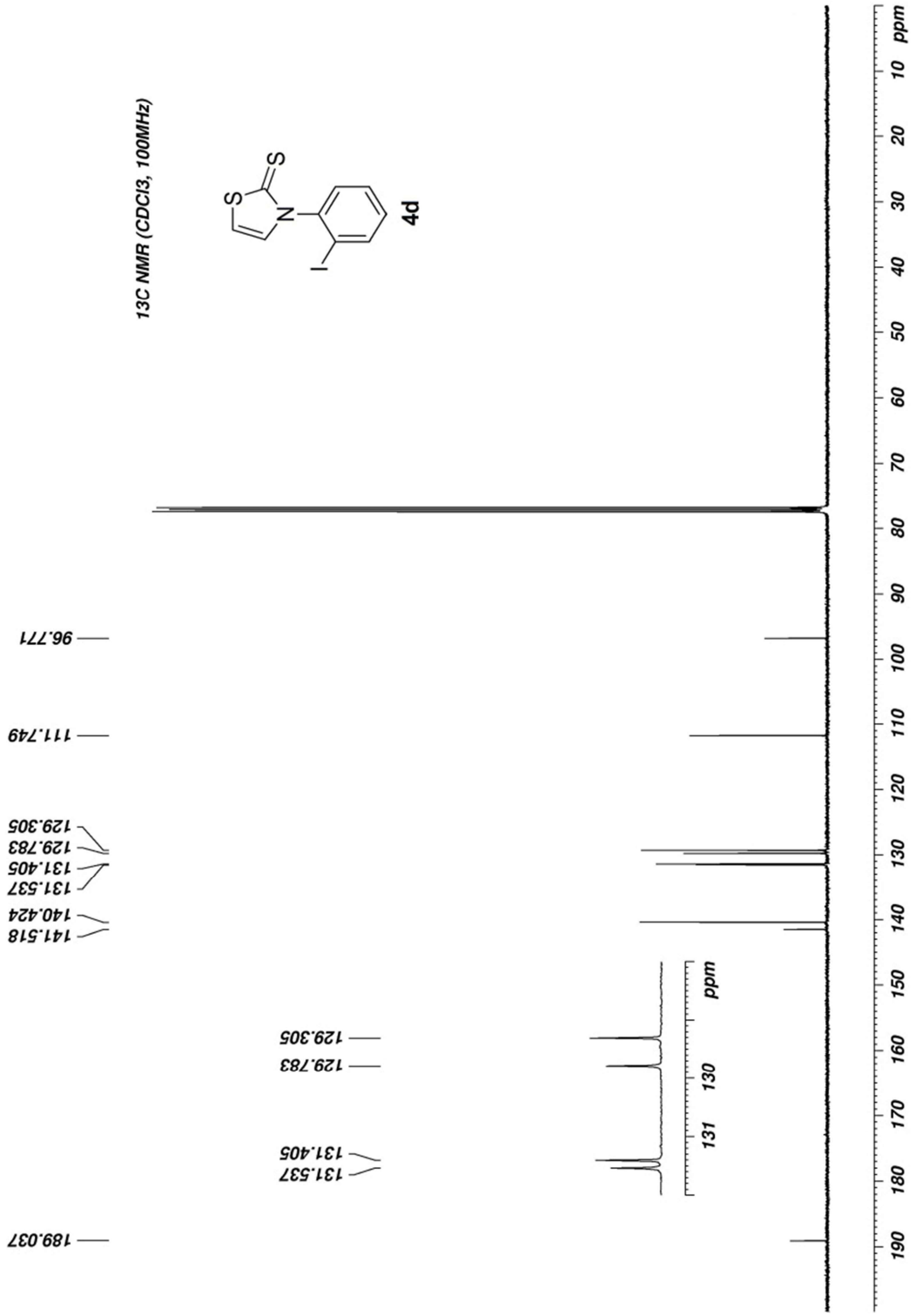
131.465
130.546
129.167
122.922
106.510
15.775
ppm


1H NMR (400MHz, CDCl3)
3d
S
S
N
I
ppm
8.024
8.021
8.004
8.001
7.577
7.573
7.557
7.554
7.538
7.535
7.310
7.306
7.290
7.286
7.251
7.247
7.231
7.228
7.208
1.933
1.930
1.004
1.011
1.006
1.018
0.988
3.000


13C NMR (CDCl3, 100MHz)
3d
189.721
140.796
140.537
139.267
131.303
130.029
129.846
106.681
98.283
16.102
ppm


1N NMR (CDCl3, 400Mhz)
4d
8.004
8.001
7.984
7.981
7.541
7.538
7.522
7.519
7.503
7.500
7.410
7.406
7.390
7.386
7.234
7.231
7.215
7.212
7.196
7.192
6.983
6.972
6.716
6.704
1.000
1.036
1.034
1.046
1.020
1.013
ppm


13C NMR (CDCl3, 100MHz)
4d
189.037
131.537
131.405
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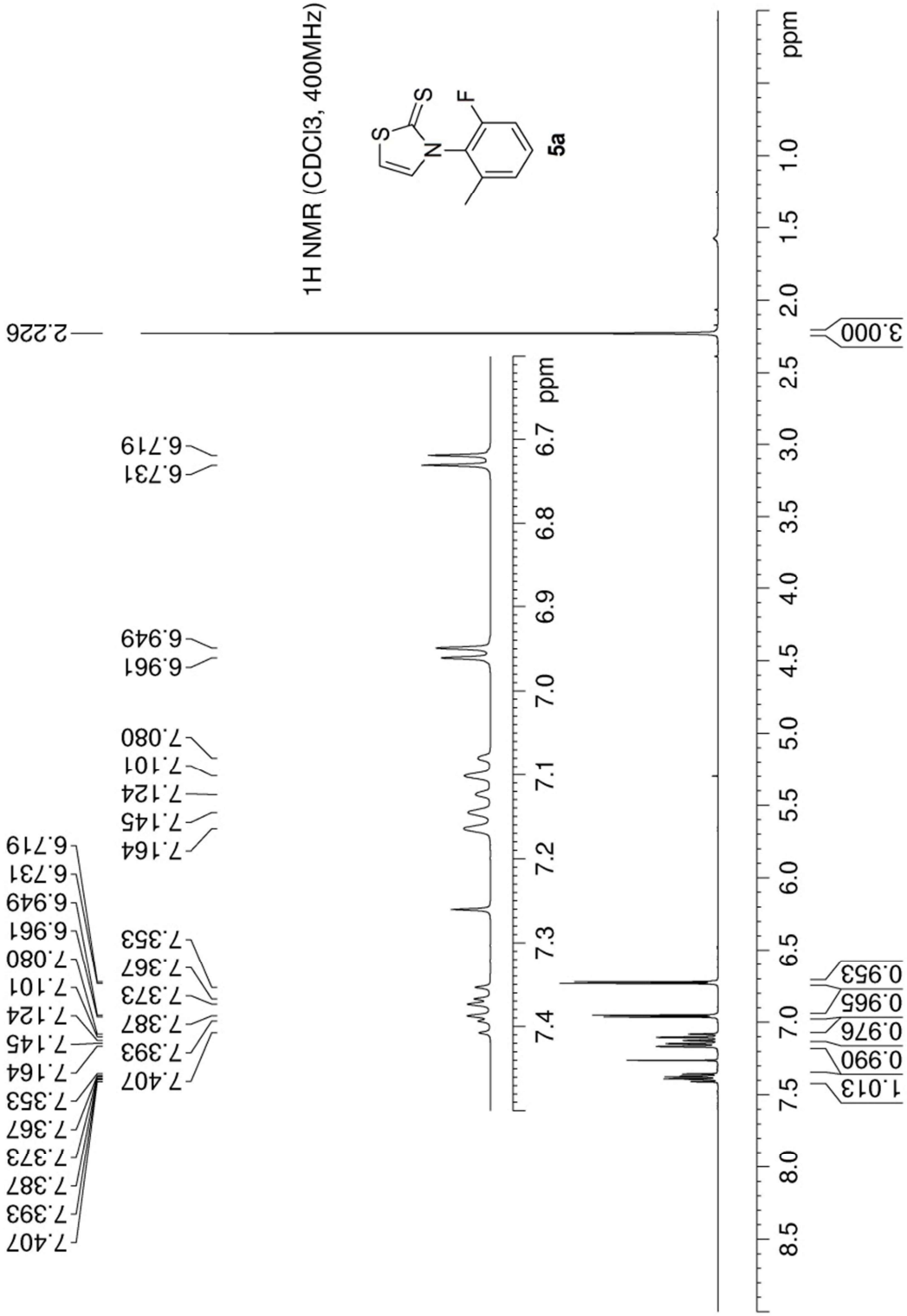
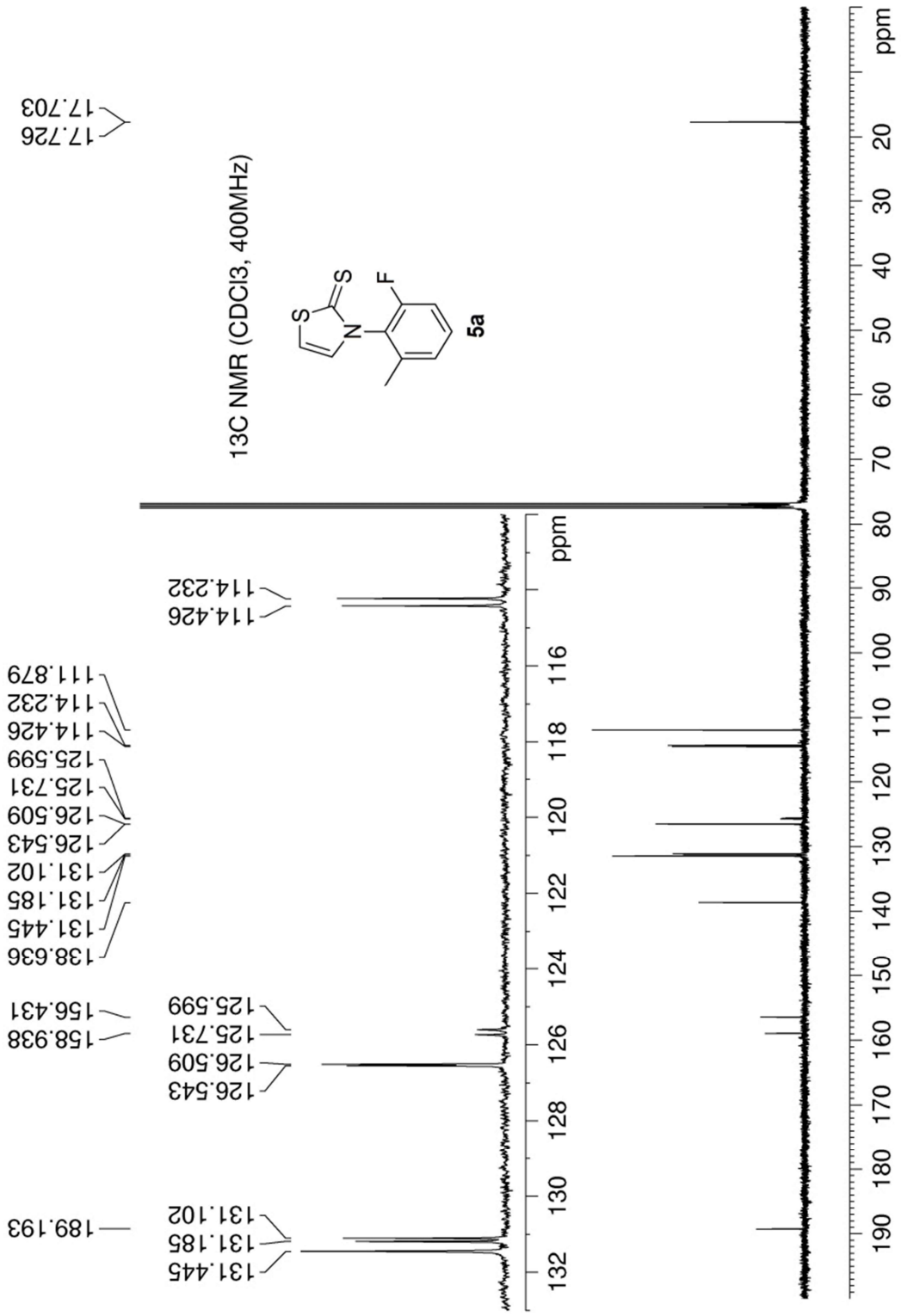
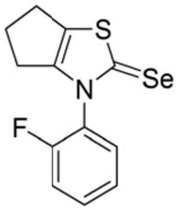
129.305
141.518
140.424
131.537
131.405
129.783
129.305
111.749
96.771
ppm

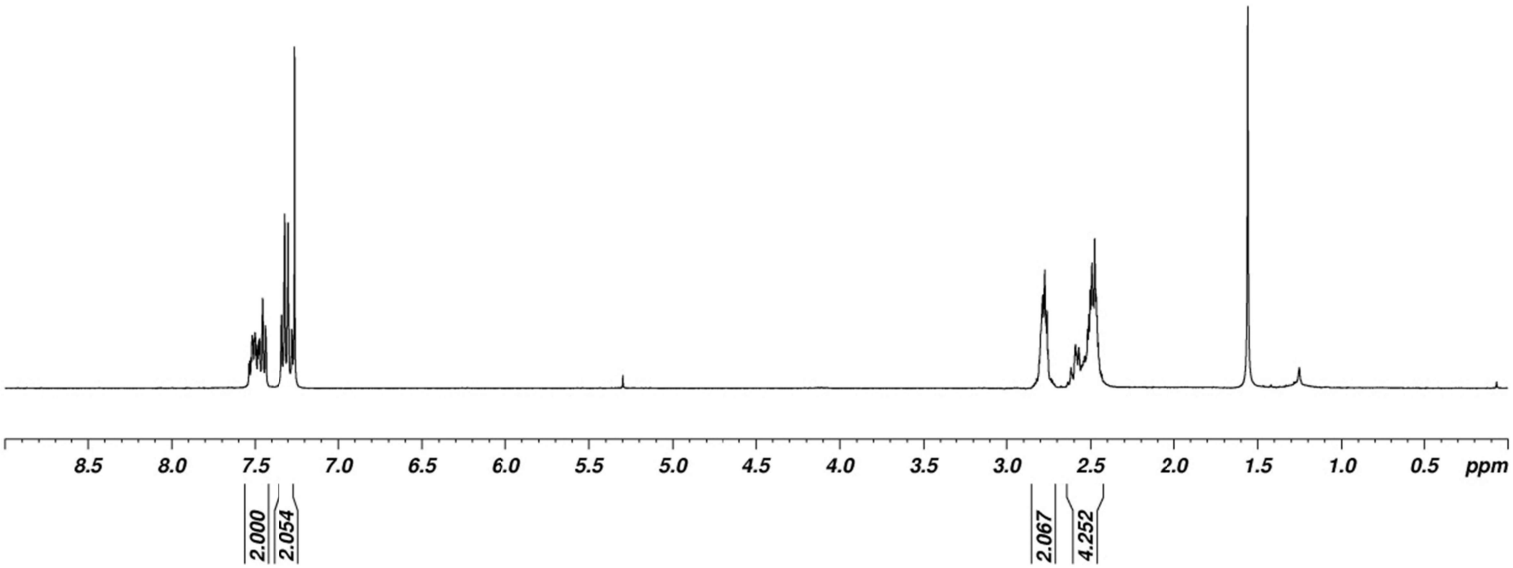

1H NMR (CDCl3, 400MHz)
5a
2.226
7.407
7.393
7.387
7.373
7.367
7.353
7.164
7.145
7.124
7.101
7.080
6.961
6.949
6.731
6.719
3.000
1.013
0.990
0.976
0.965
0.953
ppm

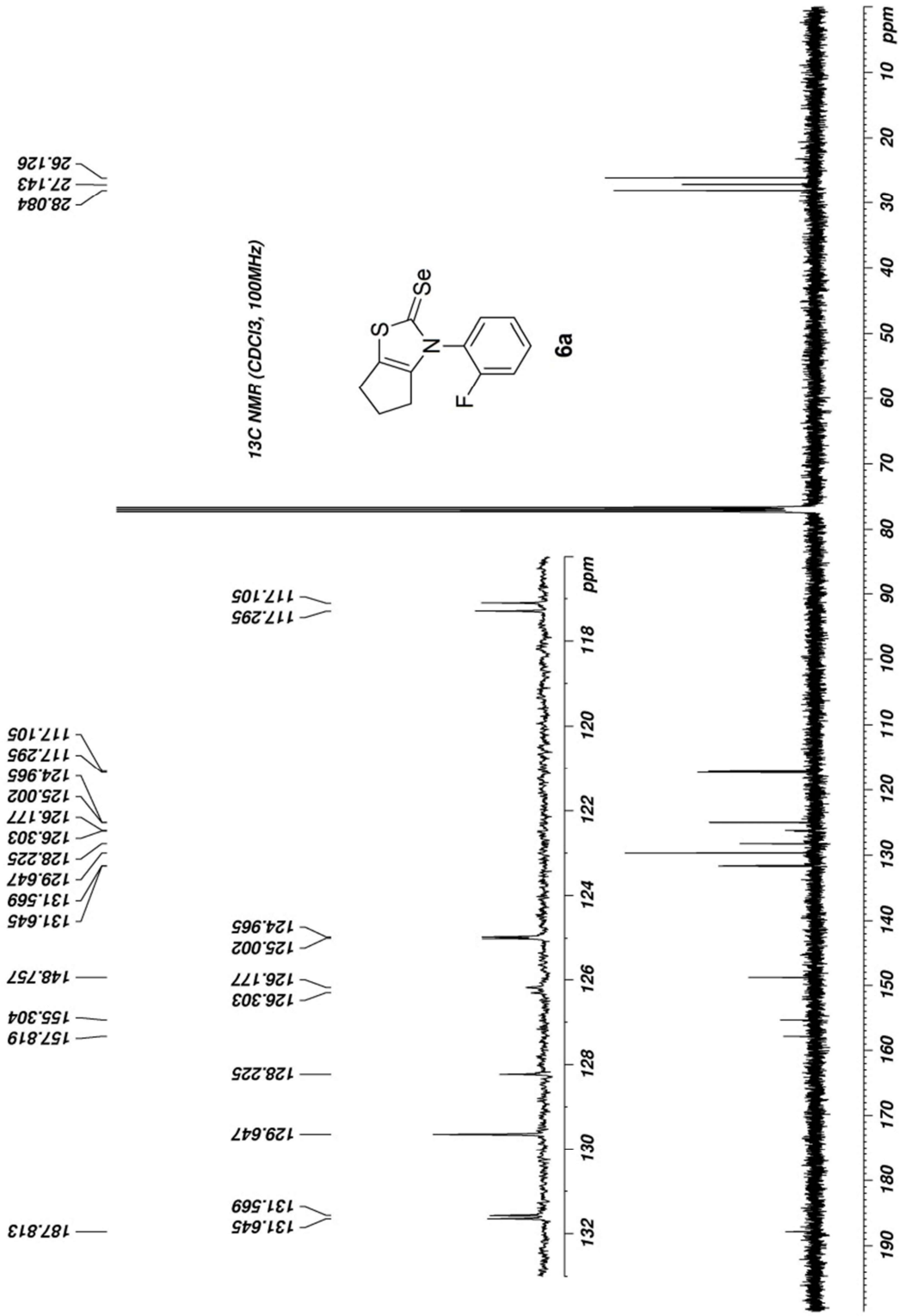

13C NMR (CDCl3, 400MHz)
5a
S
S
N
F
ppm
17.726
17.703
114.426
114.232
111.879
114.232
114.426
125.599
125.731
126.509
126.543
138.636
131.445
131.185
131.102
156.431
158.938
125.599
125.731
126.509
126.543
189.193
131.445
131.185
131.102

1H NMR (CDCl3, 400MHz)



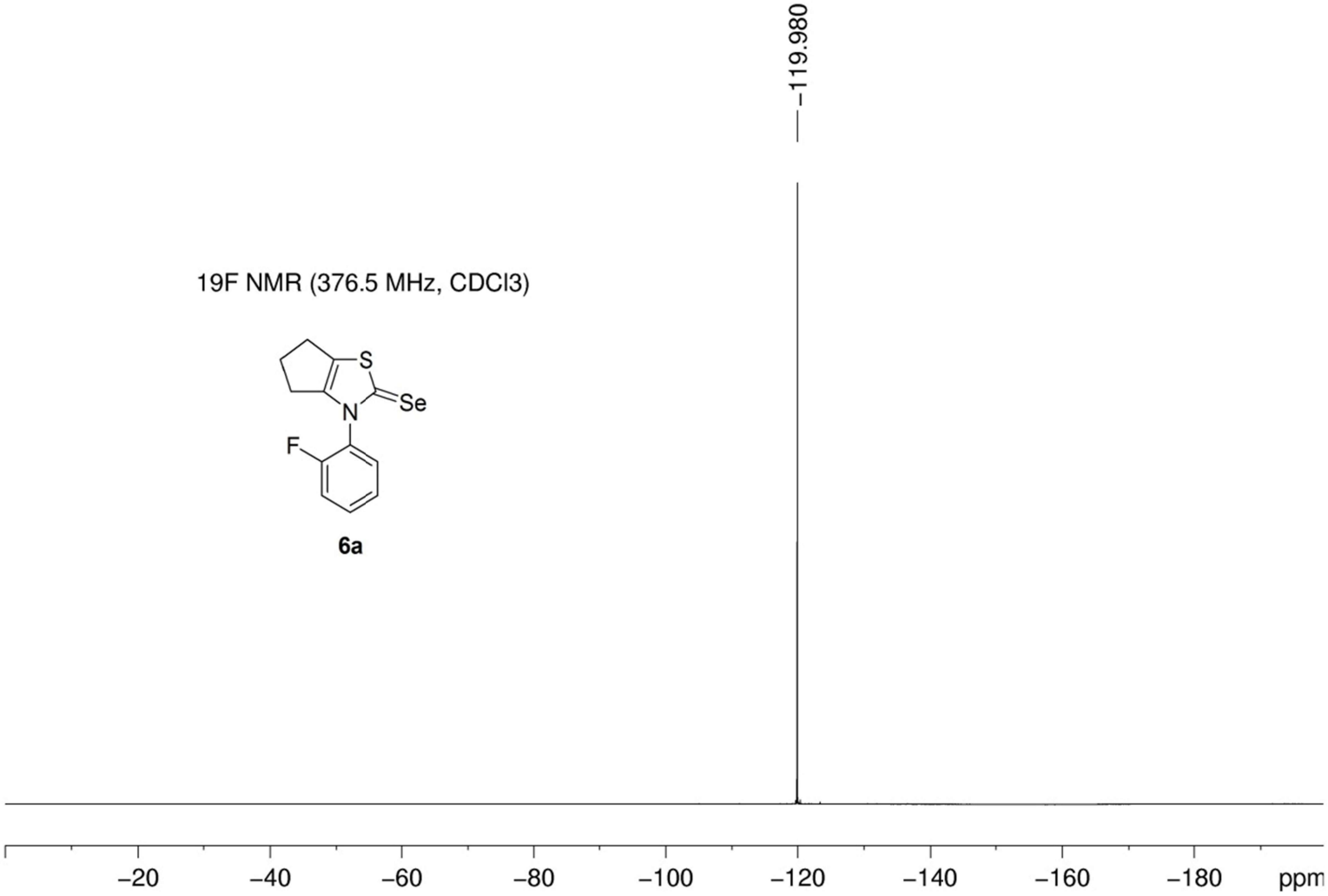
6a

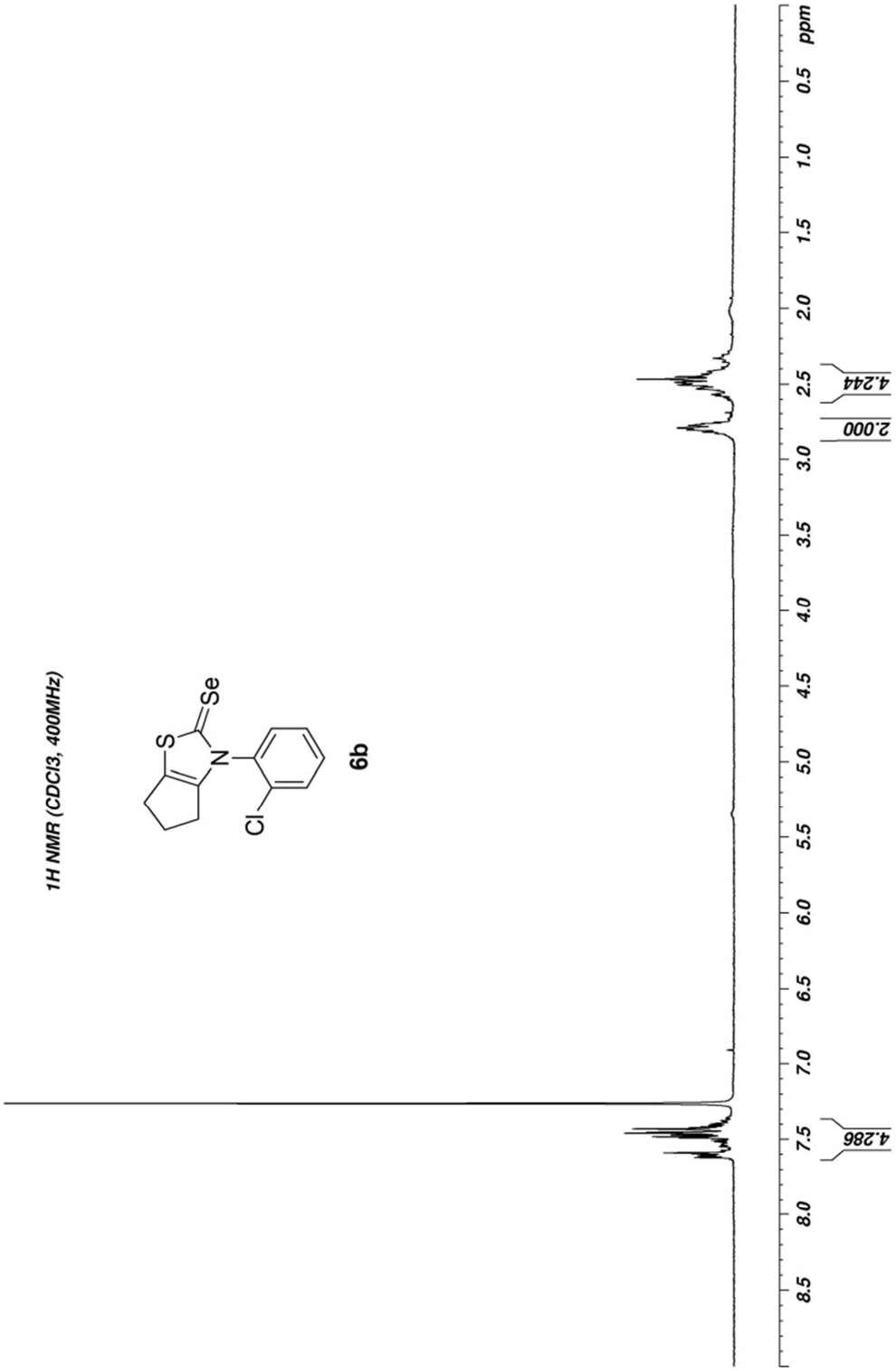


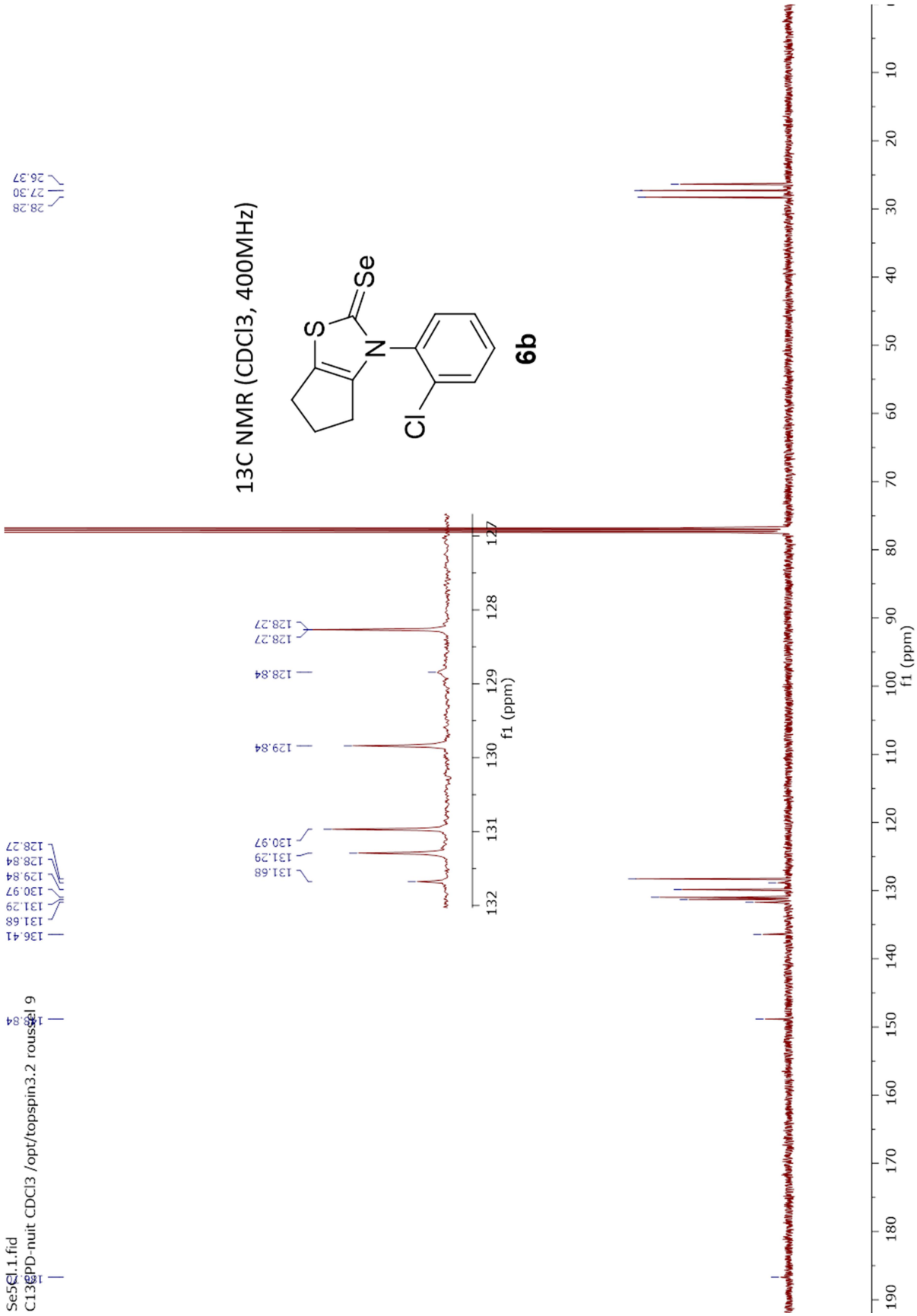

13C NMR (CDCl3, 100MHz)
6a
Se
S
N
F
ppm
187.813
148.757
155.304
157.819
131.645
131.569
129.647
128.225
126.303
126.177
125.002
124.965
117.295
117.105
131.645
131.569
129.647
128.225
126.303
126.177
125.002
124.965
117.295
117.105
28.084
27.143
26.126

19F NMR (376.5 MHz, CDCl3)

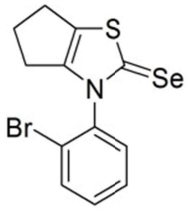
6a



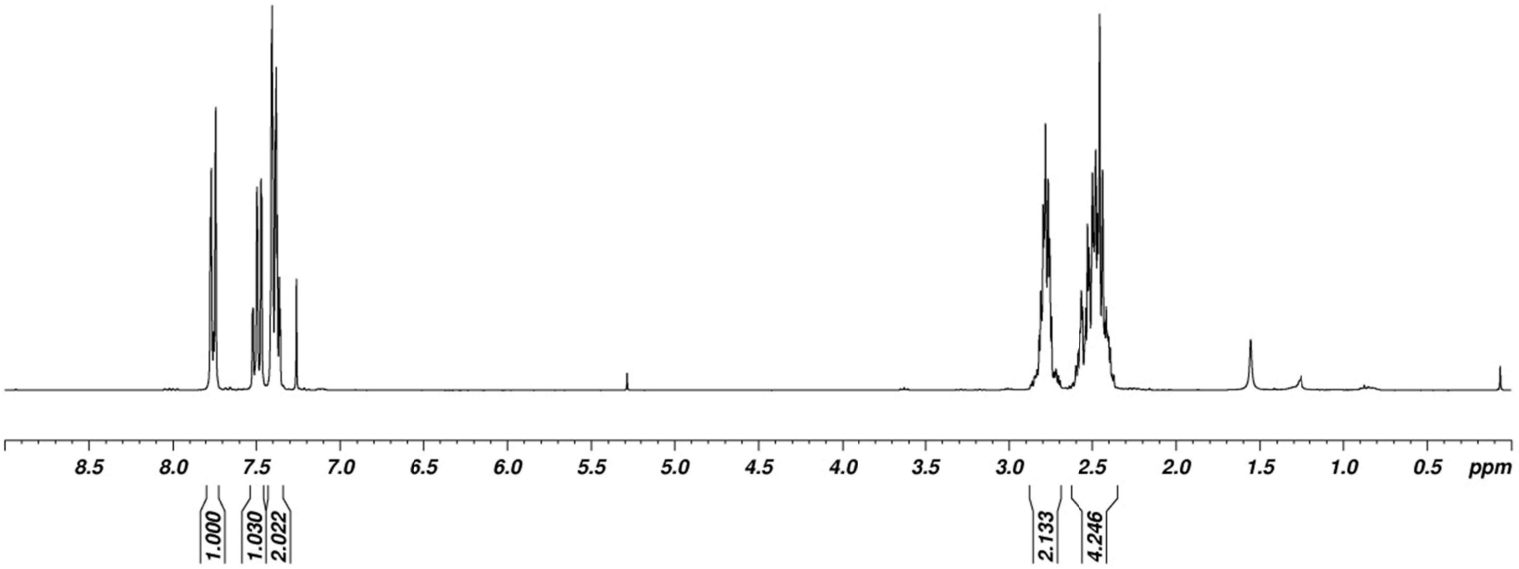

1H NMR (CDCl3, 400MHz)
S
Se
N
Cl
6b
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
4.286
2.000
4.244

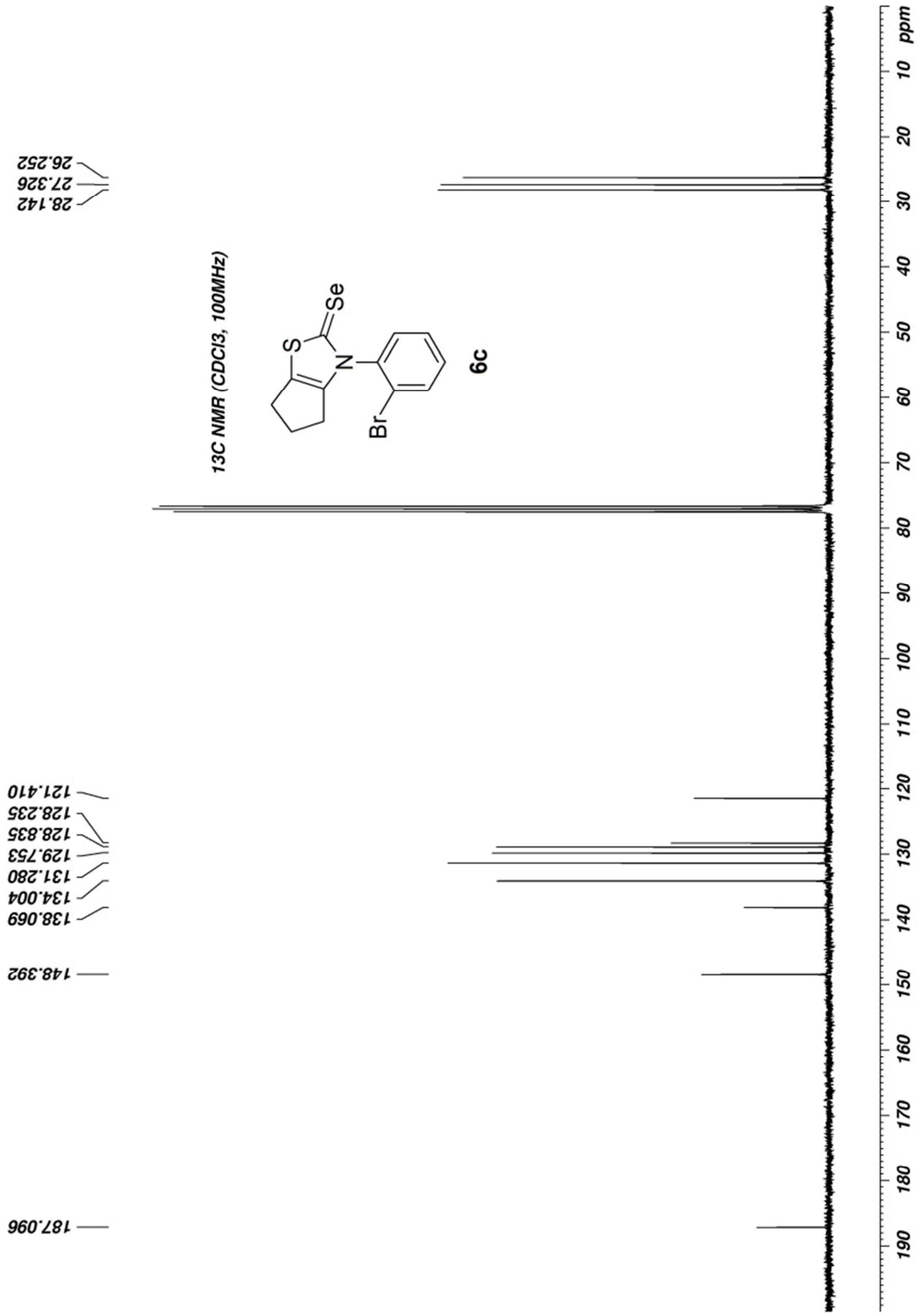

13C NMR (CDCl3, 400MHz)
6b
Se5Cl.1.fid
C13CPD-nuit CDCl3 /opt/topspin3.2 roussel 9
f1 (ppm)

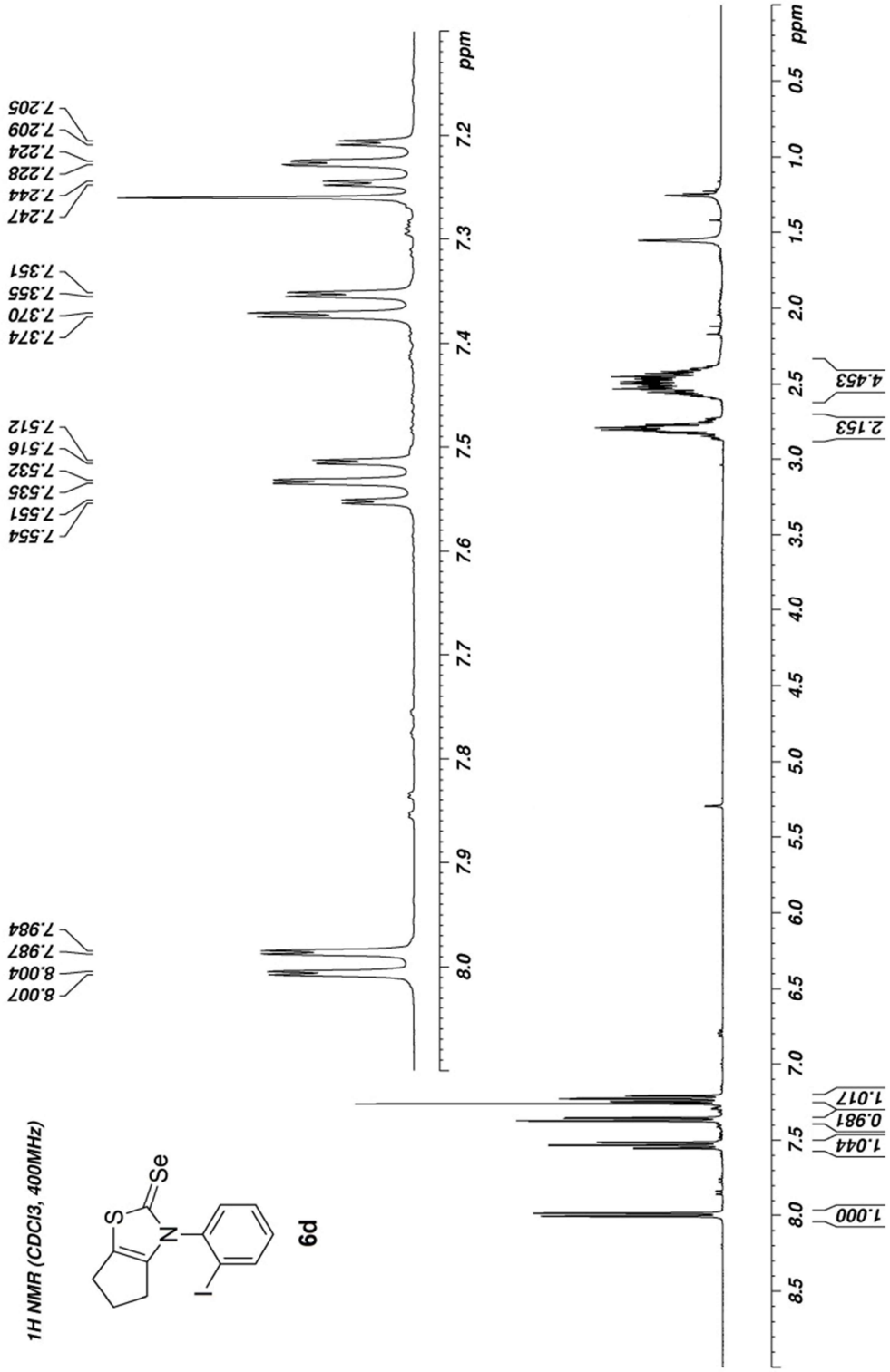
1H NMR (CDCl3, 400MHz)



6c




13C NMR (CDCl3, 100MHz)
6c
Br
N
S
Se
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
26.252
27.326
28.142
121.410
128.235
128.835
129.753
131.280
134.004
138.069
148.392
187.096


1H NMR (CDCl3, 400MHz)
6d
8.007
8.004
7.987
7.984
7.554
7.551
7.535
7.532
7.516
7.512
7.374
7.370
7.355
7.351
7.247
7.244
7.228
7.224
7.209
7.205
ppm
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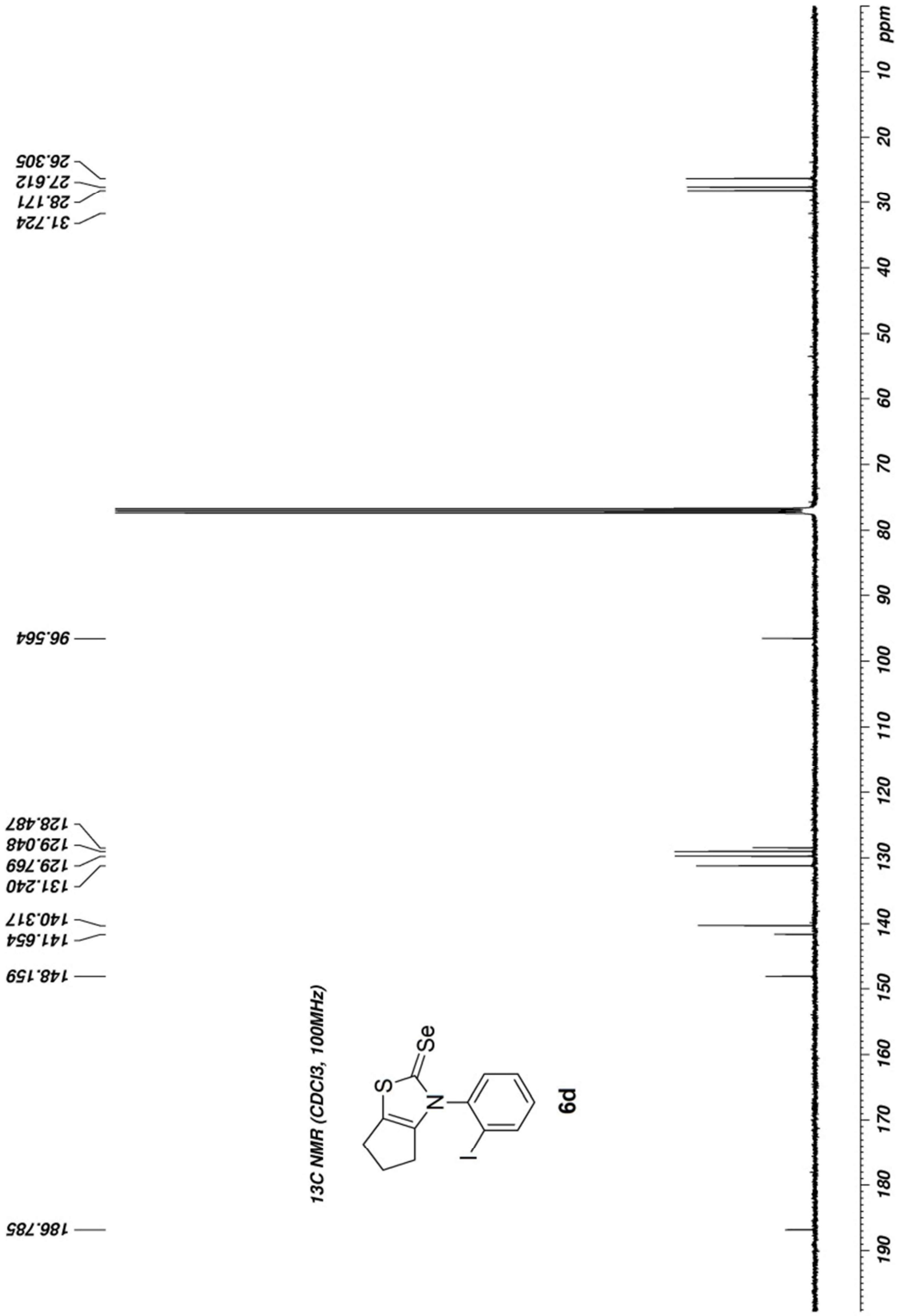
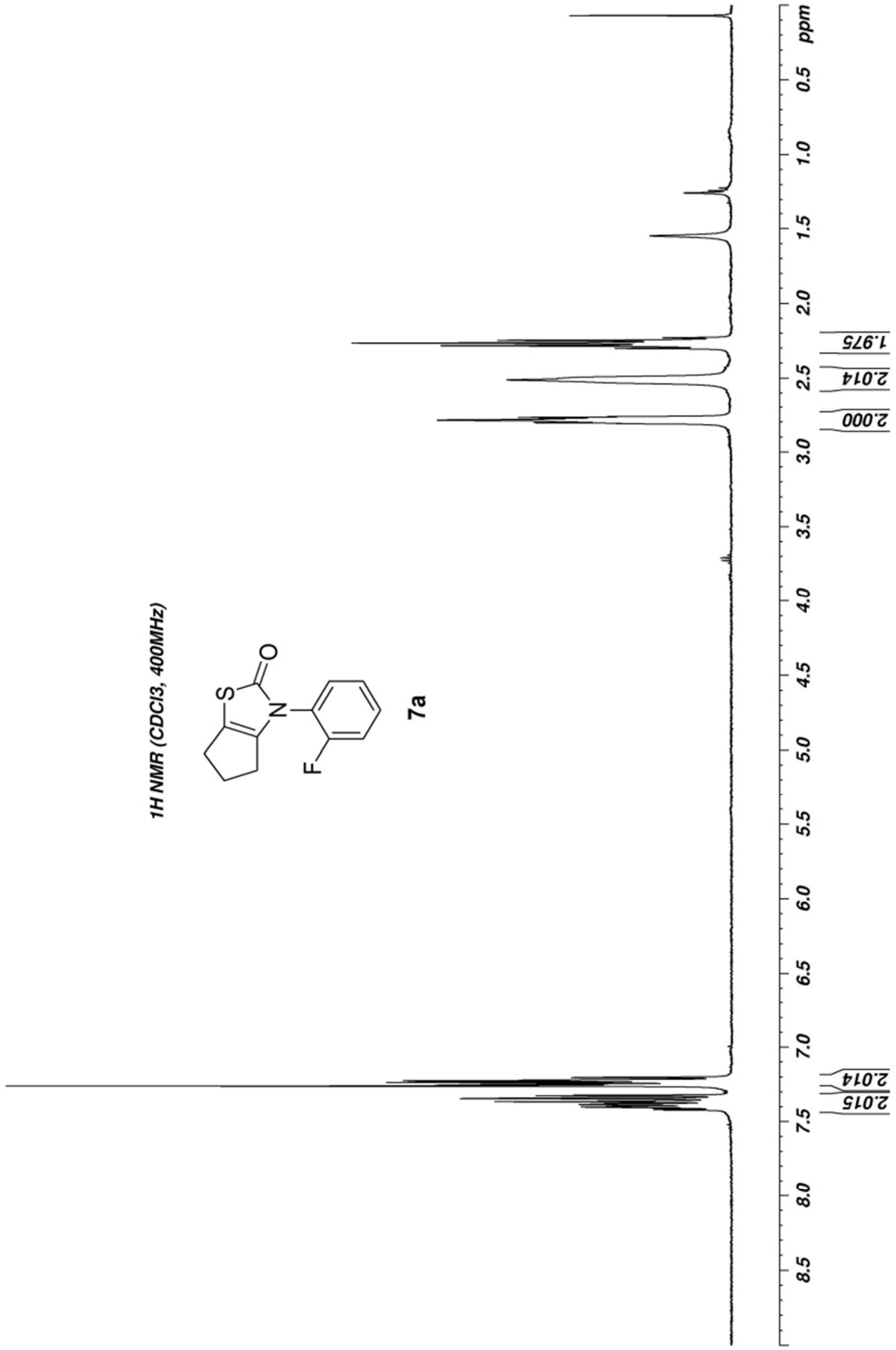
1.044
0.981
1.017
4.453
2.153


13C NMR (CDCl3, 100MHz)
6d
186.785
148.159
141.654
140.317
131.240
129.769
129.048
128.487
96.564
31.724
28.171
27.612
26.305
ppm


1H NMR (CDCl3, 400MHz)
S
O
N
F
7a
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
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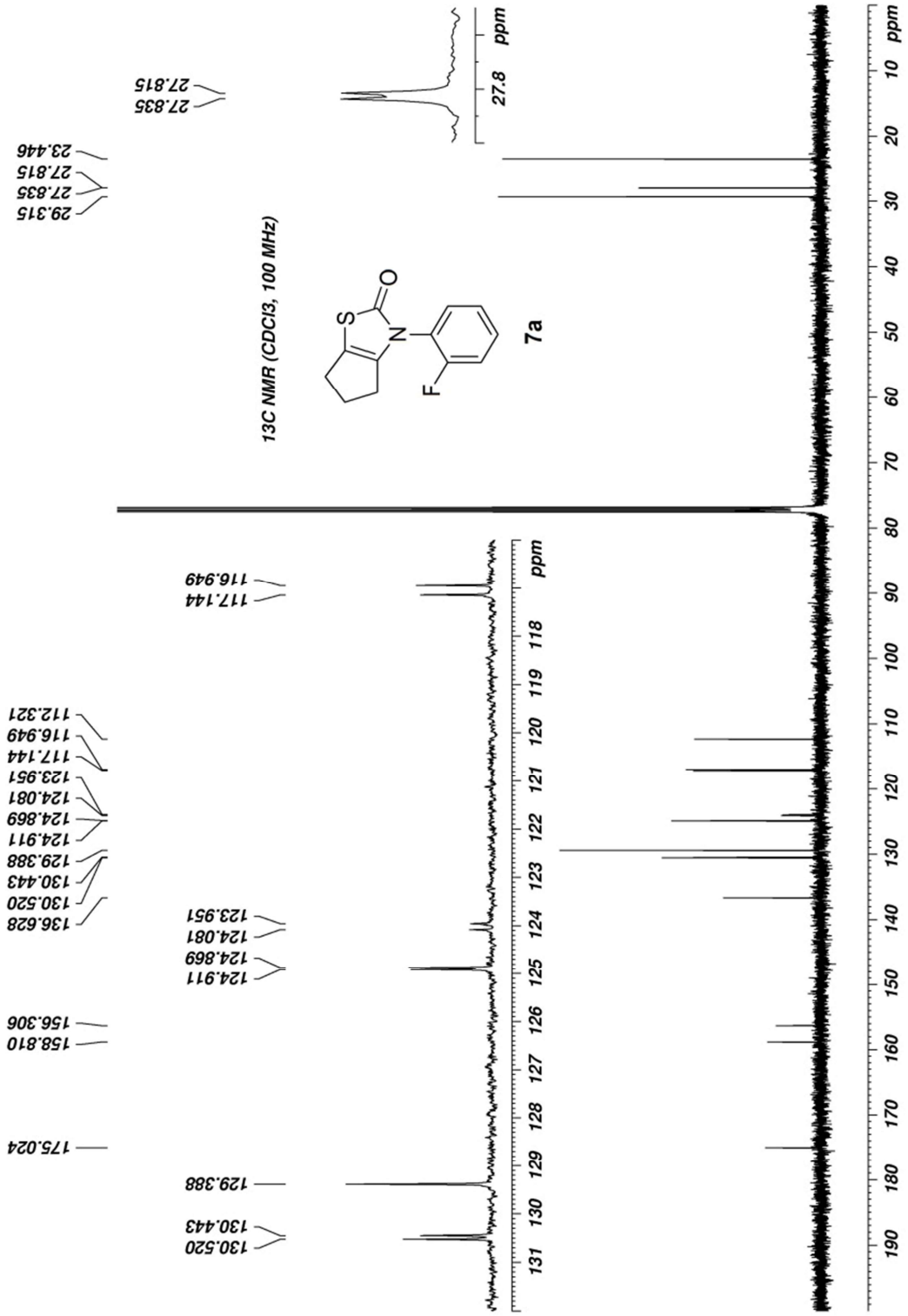
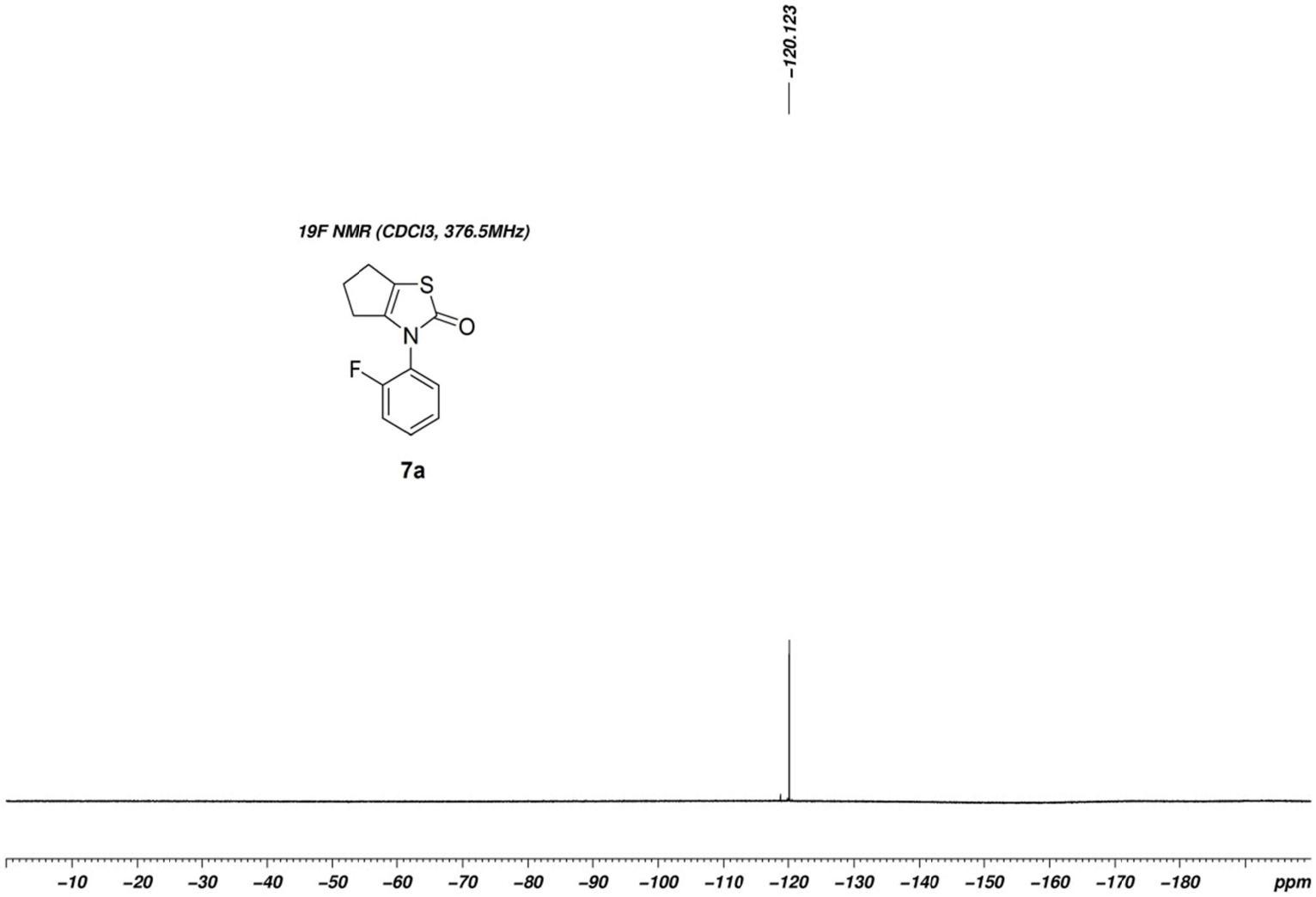
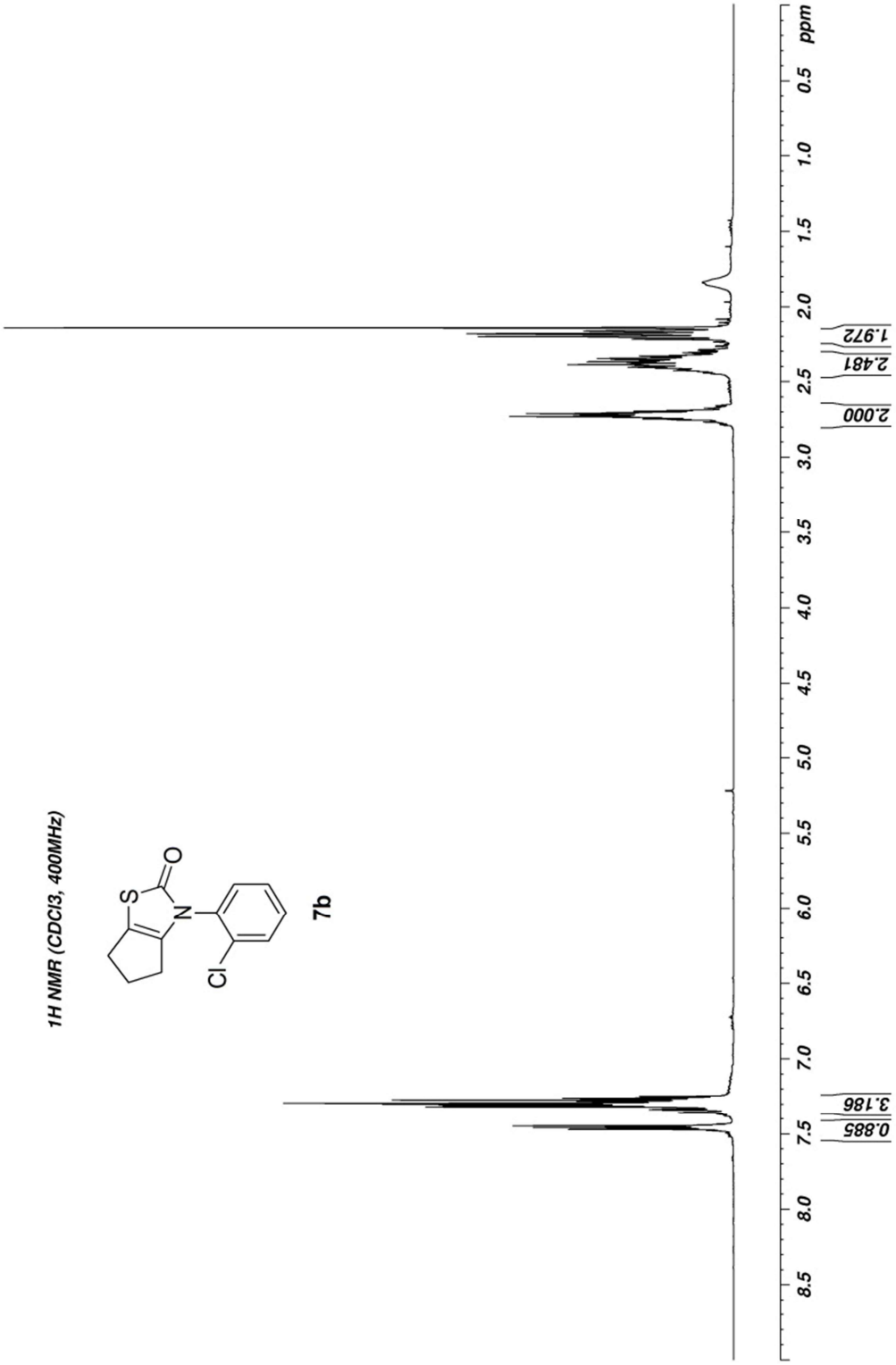
7.0
7.5
8.0
8.5
2.015
2.014
2.000
2.014
1.975

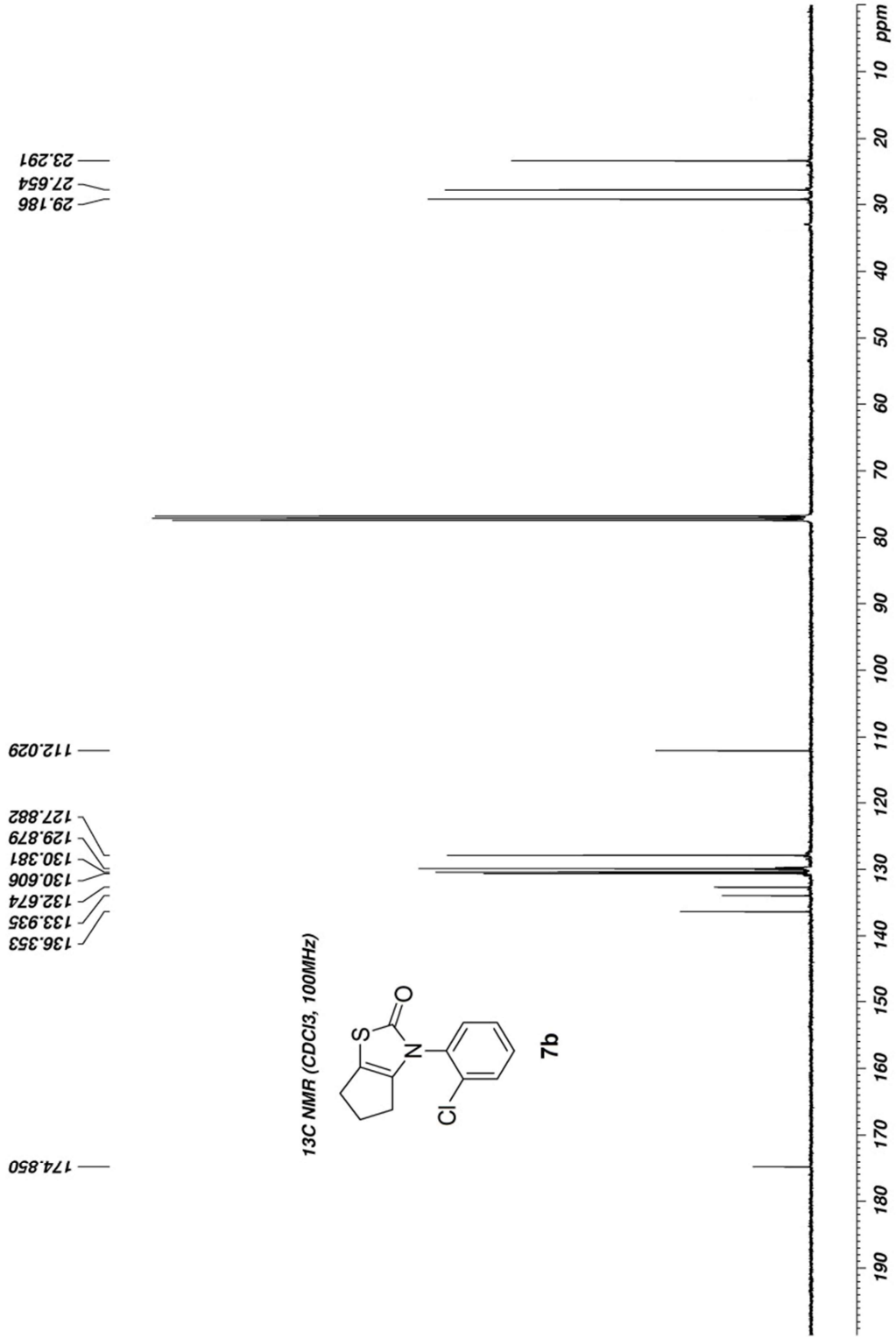

13C NMR (CDCl3, 100 MHz)
7a
S
O
N
F
ppm
27.8
27.835
27.815
23.446
29.315
27.835
27.815
116.949
117.144
130.520
130.443
129.388
175.024
158.810
156.306
124.911
124.869
124.081
123.951
136.628
130.520
130.443
129.388
124.911
124.869
124.081
123.951
117.144
116.949
112.321

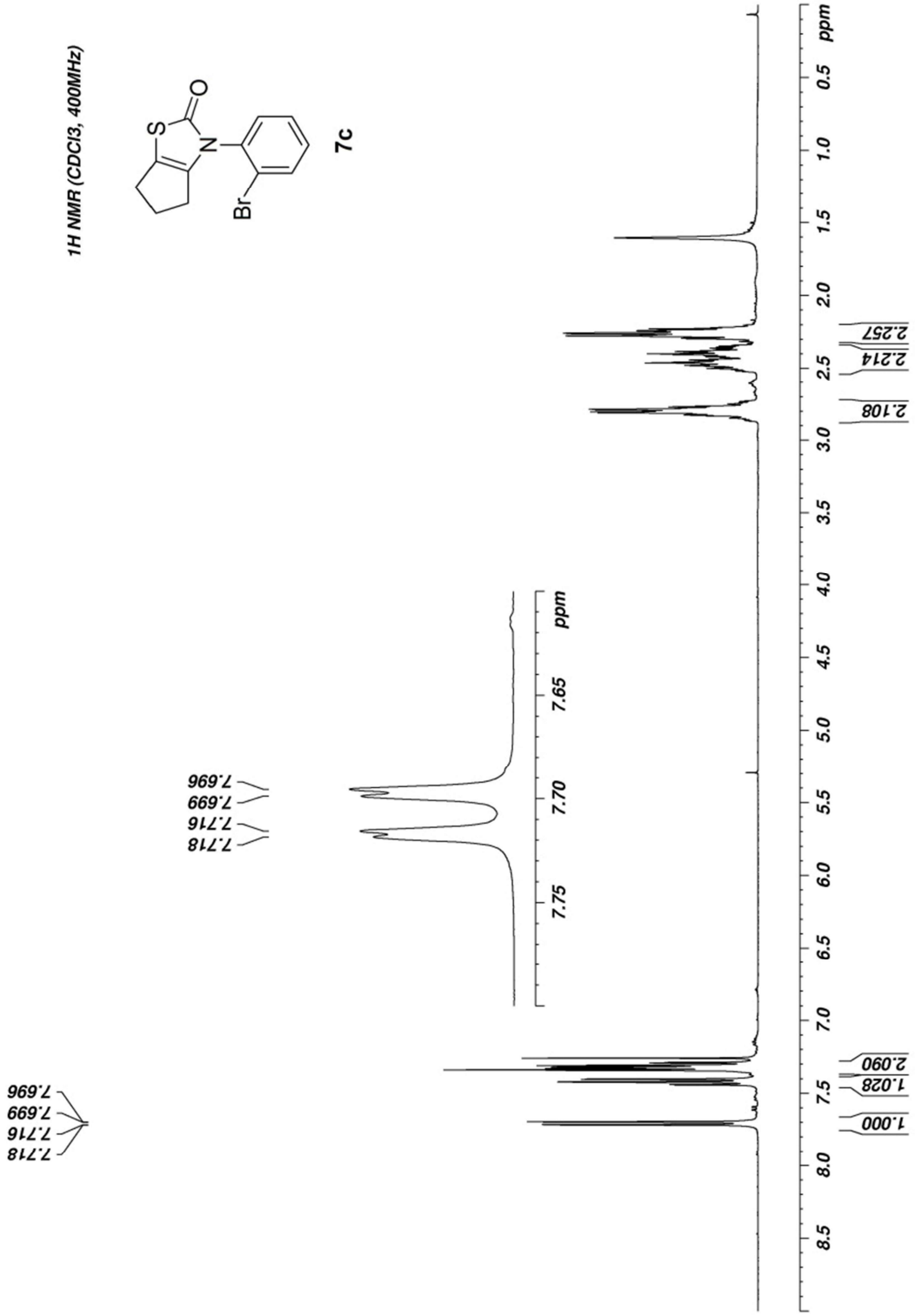
19F NMR (CDCl3, 376.5MHz)

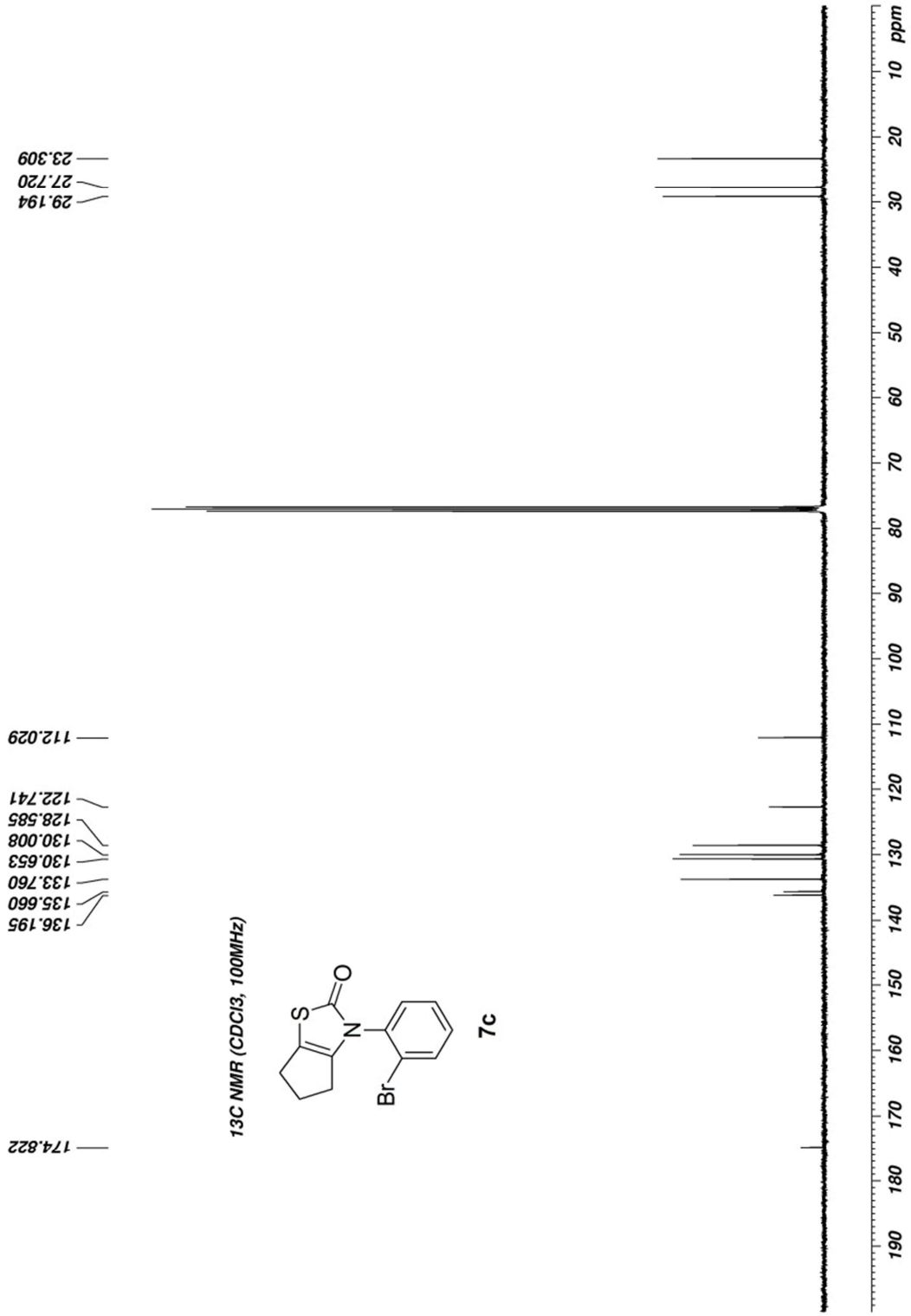
7a

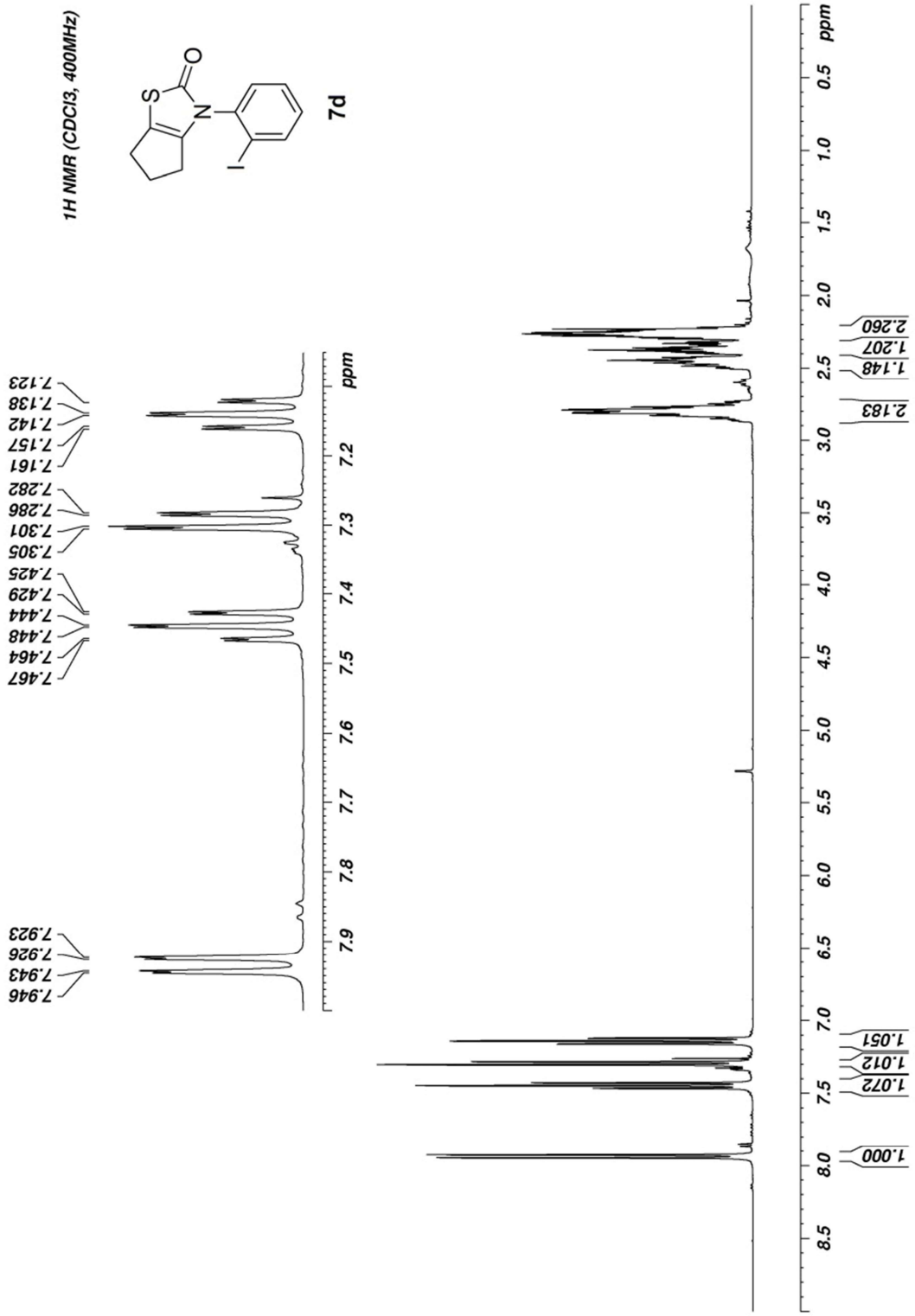


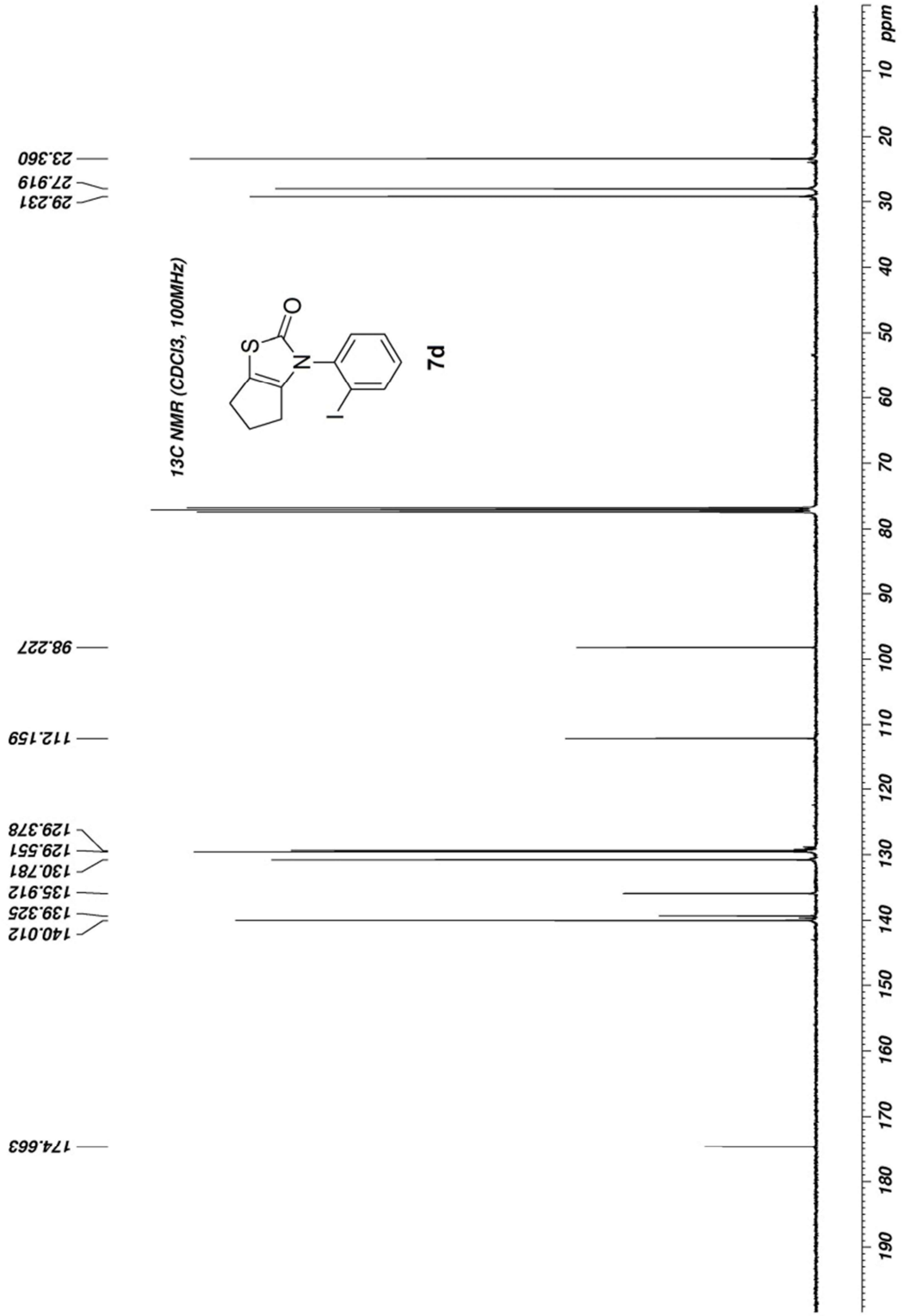

1H NMR (CDCl3, 400MHz)
S
O
N
Cl
7b
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
3.186
0.885
2.000
2.481
1.972


13C NMR (CDCl3, 100MHz)
7b
174.850
136.353
133.935
132.674
130.606
130.381
129.879
127.882
112.029
29.186
27.654
23.291
ppm


1H NMR (CDCl3, 400MHz)
7c
S
O
N
Br
7.718
7.716
7.699
7.696
7.718
7.716
7.699
7.696
ppm
7.75
7.70
7.65
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
2.257
2.214
2.108
2.090
1.028
1.000


13C NMR (CDCl3, 100MHz)
7c
174.822
136.195
135.660
133.760
130.653
130.008
128.585
122.741
112.029
29.194
27.720
23.309
ppm

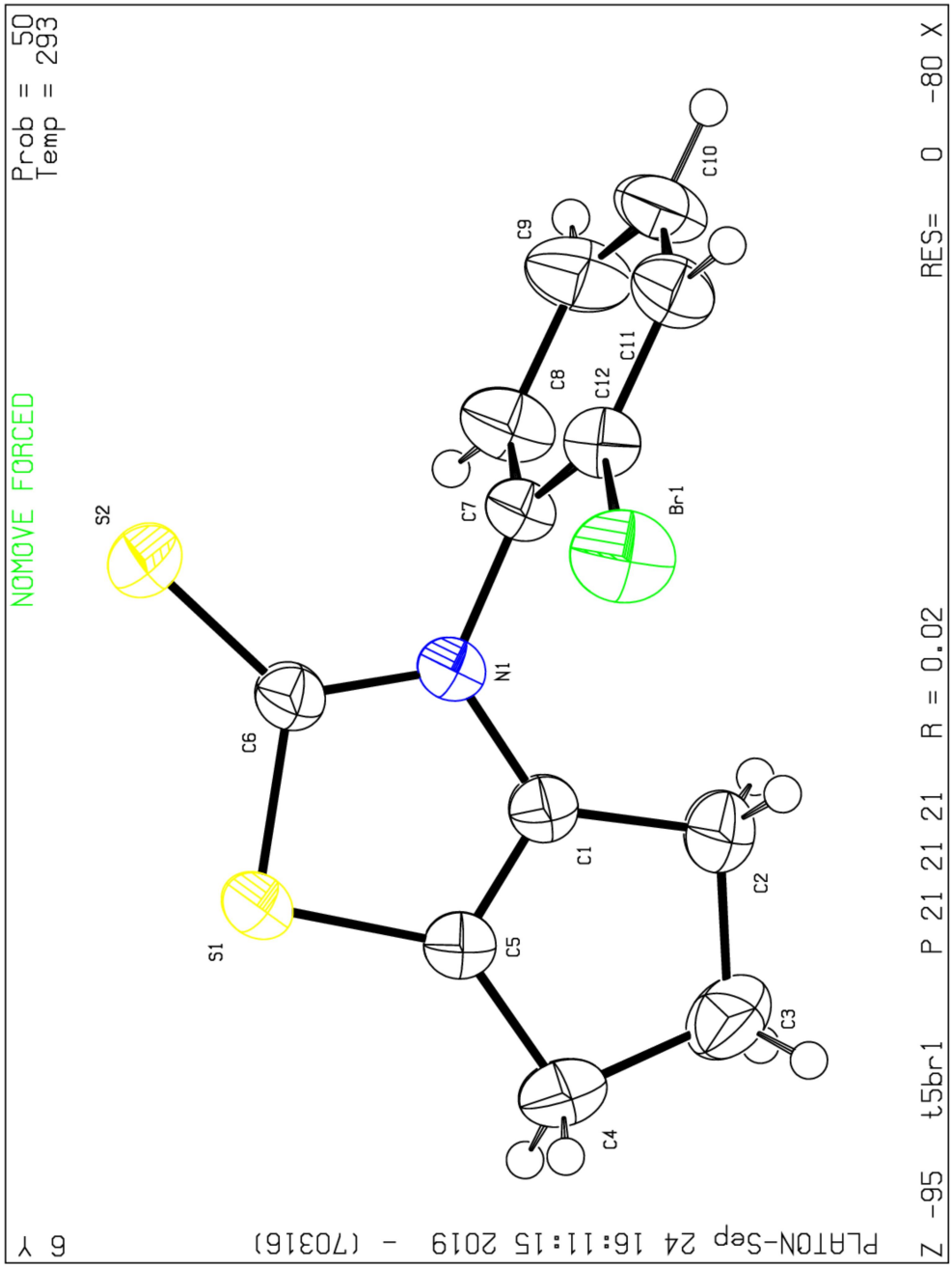

1H NMR (CDCl3, 400MHz)
7d
7.946
7.943
7.926
7.923
7.467
7.464
7.448
7.444
7.429
7.425
7.305
7.301
7.286
7.282
7.161
7.157
7.142
7.138
7.123
ppm
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
1.000
1.072
1.012
1.051
2.260
1.207
1.148
2.183
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


13C NMR (CDCl3, 100MHz)
7d
174.663
140.012
139.325
135.912
130.781
129.551
129.378
112.159
98.227
29.231
27.919
23.360
ppm

X-Ray Data

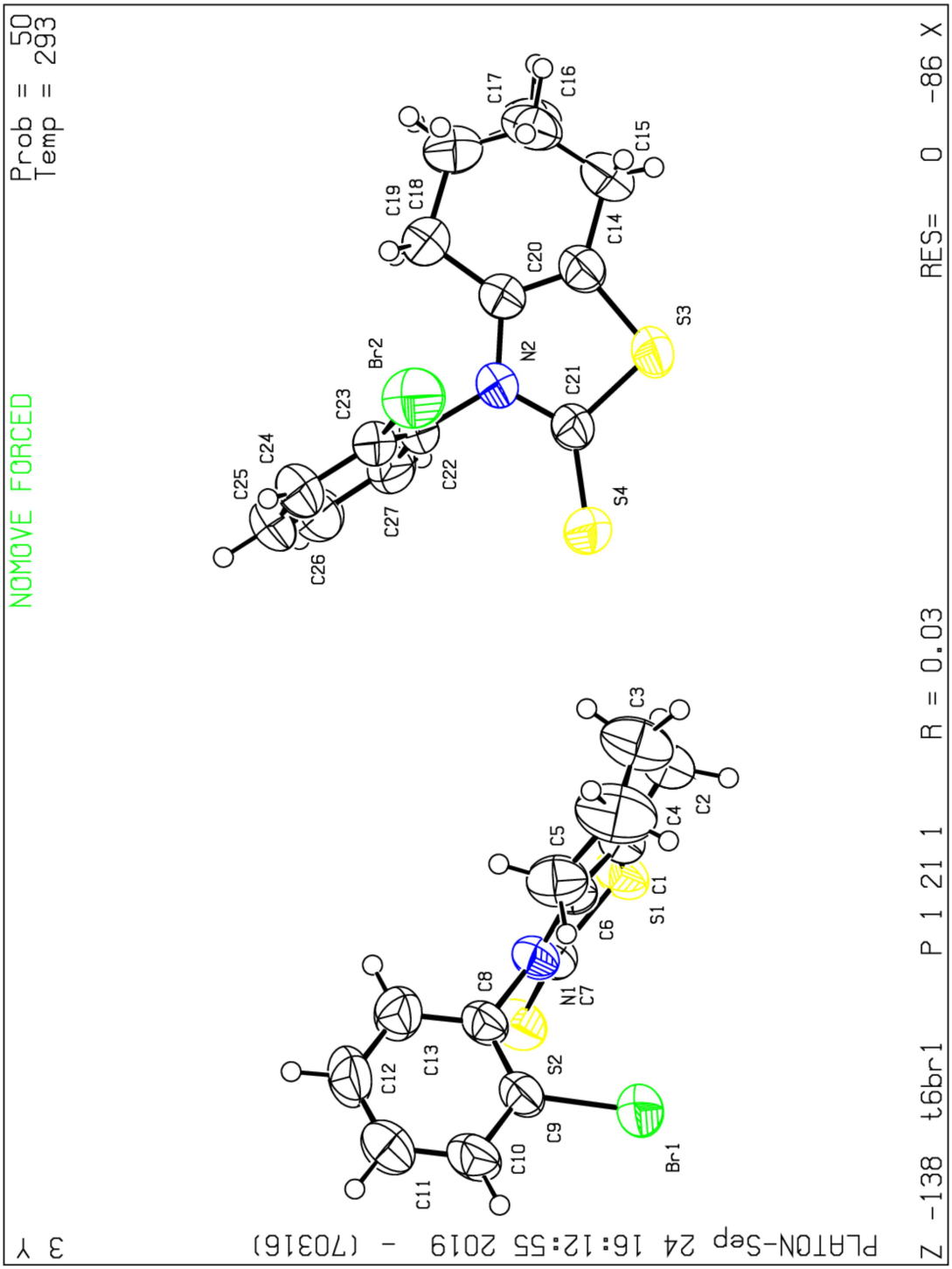
X-Ray Data of (S_a)-**1c**

CCDC number: 1955660



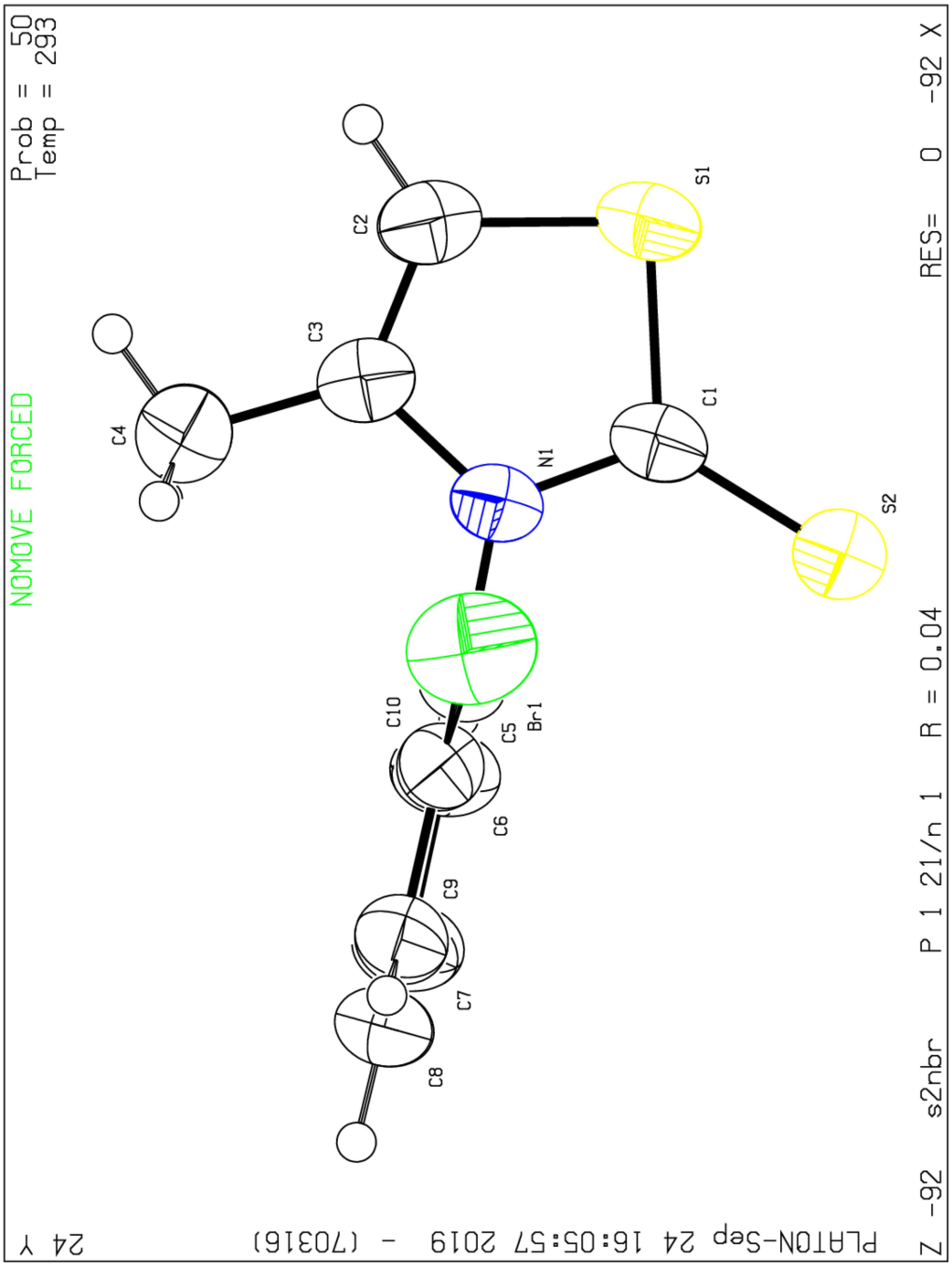
X-Ray Data of (*Sa*)-**2c**

CCDC number: 1955661



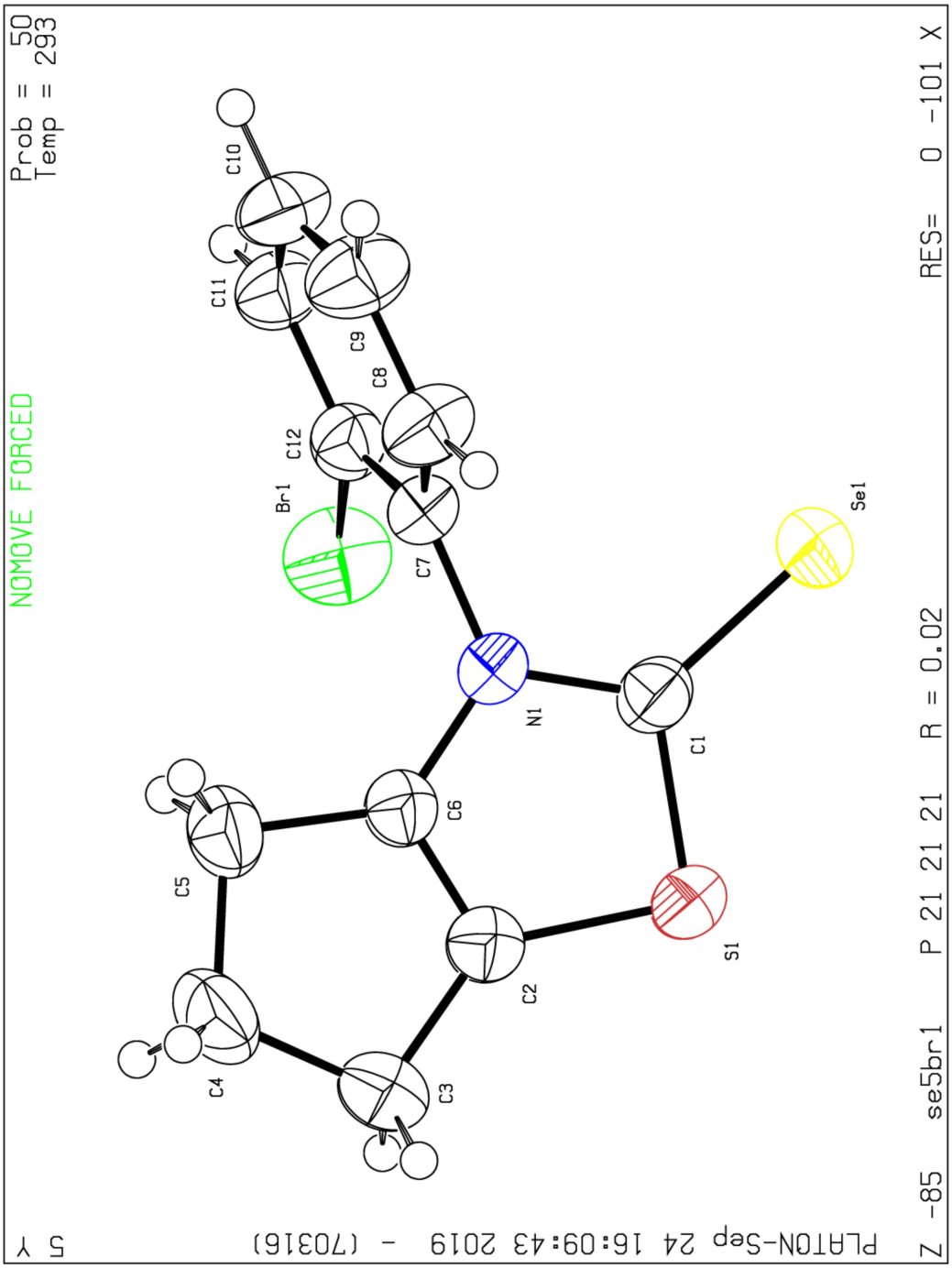
X-Ray Data of (S_a)-**3c**

CCDC number: 1955658



X-Ray Data of (S_a)-**6c**

CCDC number: 1955659



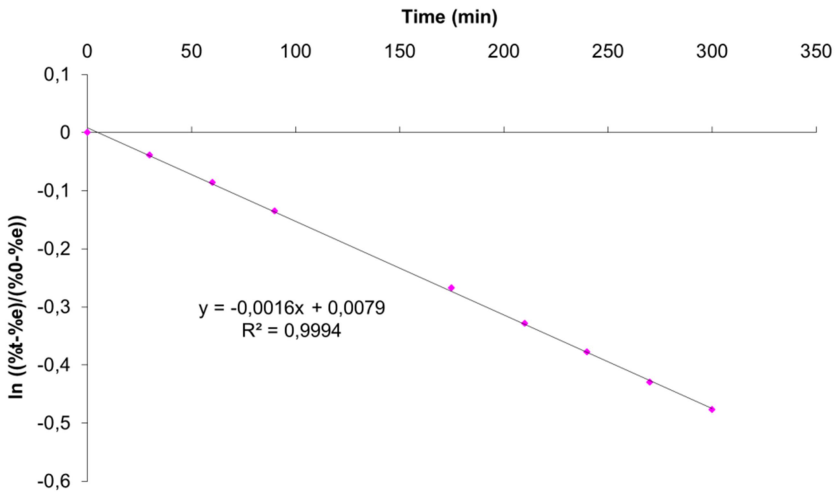
Determination of rotational barriers

Solvent : 1,2-dichlorobenzene

Temperature : 62°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	97,704	0
30	95,91	-0,038332294
60	93,797	-0,08544993
90	91,663	-0,135401807
175	86,518	-0,267209962
210	84,353	-0,328325901
240	82,7	-0,377640174
270	81,029	-0,430093001
300	79,603	-0,477139544

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



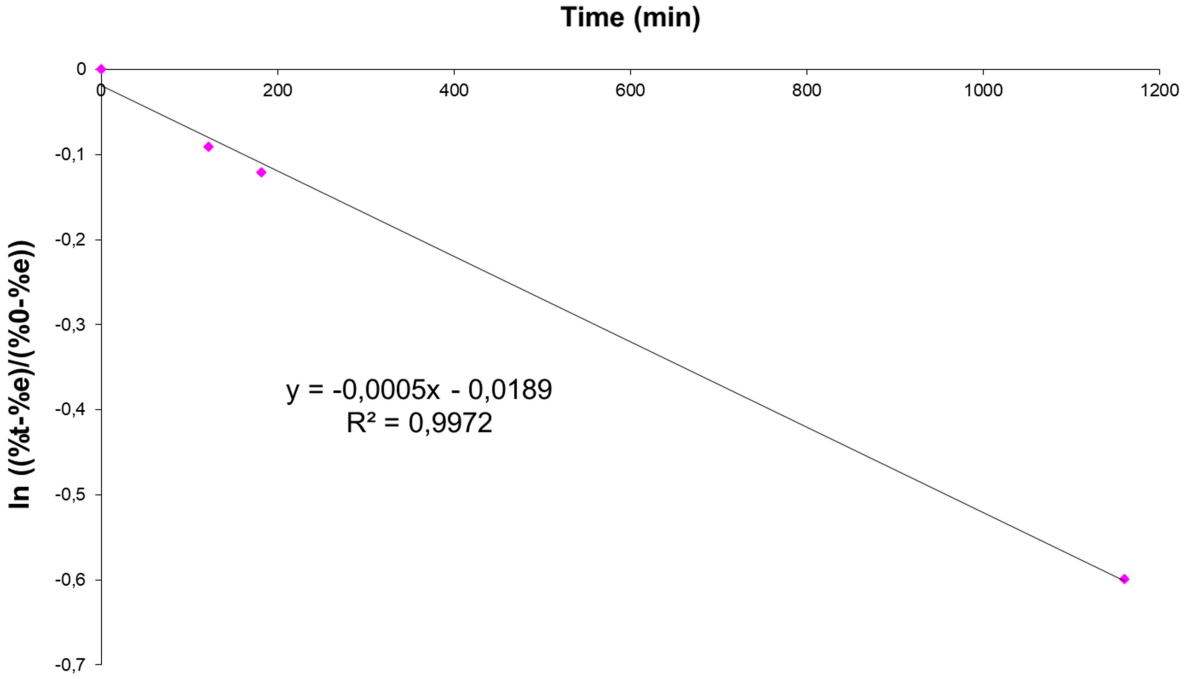
$k_{enantiomerisation}$ = 1.3400E-05 s^{-1} (62°C, 1,2-dichlorobenzene)
$\Delta G^{\neq}$ = 113.7 kJ/mol (62°C, 1,2-dichlorobenzene)
$t_{1/2}$ = 7.18 h (62°C, 1,2-dichlorobenzene)

Solvent : 1,2-dichlorobenzene

Temperature : 180°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	95,76	0
122	91,77	-0,091231969
182	90,54	-0,121121206
1160	75,14	-0,598950144

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



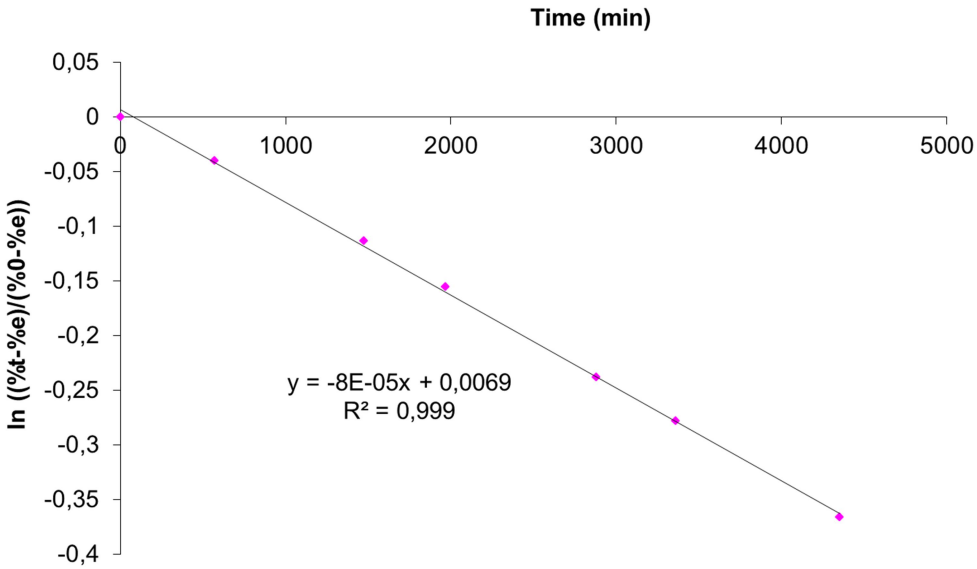
$k_{enantiomerisation}$ = 4,1873E-06 s^{-1} (180°C, 1,2-dichlorobenzene)
$\Delta G^{\neq}$ = 159.2 kJ/mol (180°C, 1,2-dichlorobenzene)
$t_{1/2}$ = 22.99 h (180°C, 1,2-dichlorobenzene)

Solvent : 1,2-dichlorobenzene

Temperature : 180°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	97,3	0
572	95,45	-0,039897475
1474	92,22	-0,113616253
1967	90,5	-0,155208321
2879	87,27	-0,238321582
3361	85,81	-0,278283111
4353	82,81	-0,365776949

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



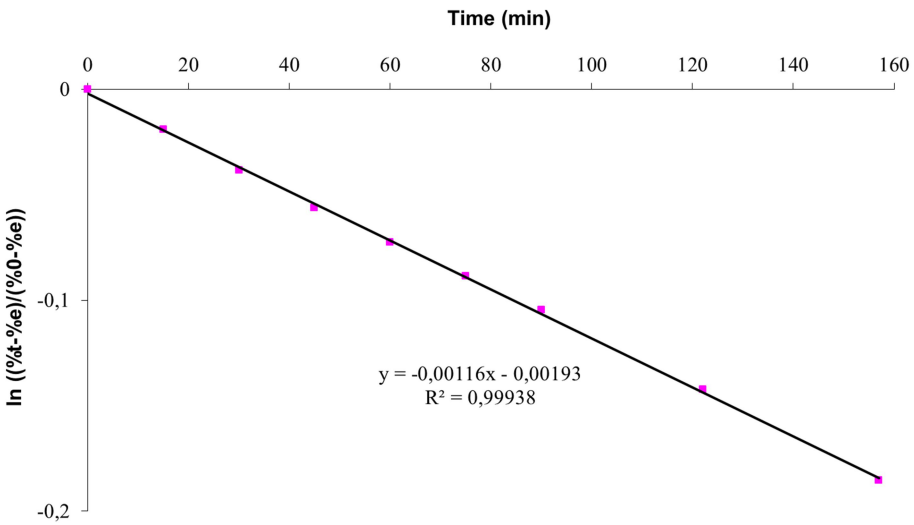
$k_{enantiomerisation}$ = 7,0701E-07 s^{-1} (180°C, 1,2-dichlorobenzene)
$\Delta G^{\neq}$ = 165.9 kJ/mol (180°C, 1,2-dichlorobenzene)
$t_{1/2}$ = 136.2 h (180°C, 1,2-dichlorobenzene)

Solvent : 1,2,4-trichlorobenzene

Temperature : 214°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	99,50	0,00000
15	98,56	-0,01917
30	97,63	-0,03851
45	96,80	-0,05609
60	96,04	-0,07246
75	95,30	-0,08867
90	94,58	-0,10469
122	92,94	-0,14217
157	91,13	-0,18523

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



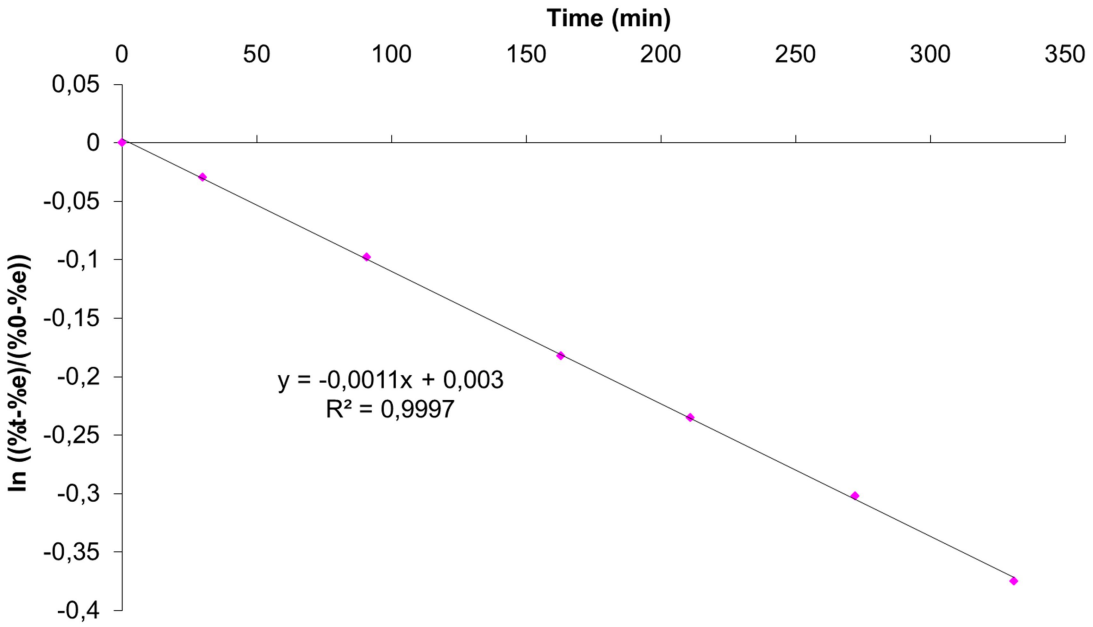
$k_{enantiomerisation}$ = 9,6742E-06 s^{-1} (214°C, 1,2,4-trichlorobenzene)
$\Delta G^{\neq}$ = 168.1 kJ/mol (214°C, 1,2,4-trichlorobenzene)
$t_{1/2}$ = 9.95 h (214°C, 1,2,4-trichlorobenzene)

Solvent : 1,2-dichlorobenzene

Temperature : 62°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	95,976	0
30	94,623	-0,0298701
91	91,69	-0,097858229
163	88,313	-0,182330257
211	86,343	-0,235117908
272	83,981	-0,302317976
331	81,595	-0,375120641

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



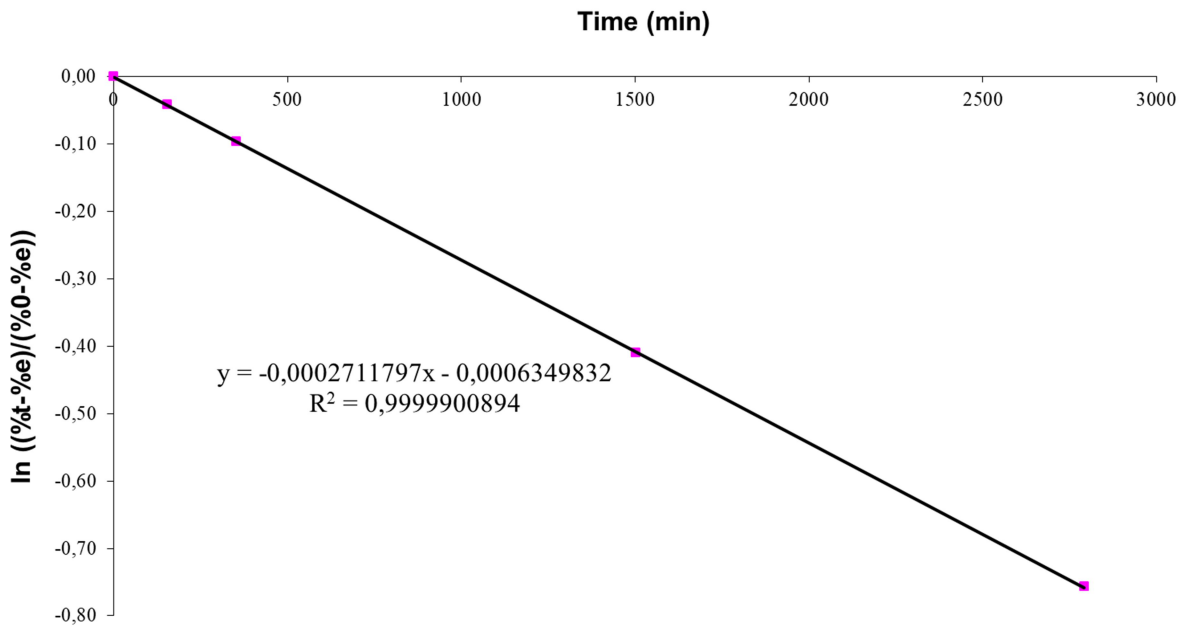
$k_{enantiomerisation}$ = 9,4401E-06 s^{-1} (62°C, 1,2-dichlorobenzene)
$\Delta G^{\neq}$ = 114.7 kJ/mol (62°C, 1,2-dichlorobenzene)
$t_{1/2}$ = 10.20 h (62°C, 1,2-dichlorobenzene)

Solvent : 1,2-dichlorobenzene

Temperature : 180°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	99,240	0,0000
154	97,200	-0,0423
353	94,720	-0,0963
1502	82,690	-0,4096
2792	73,100	-0,7569

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



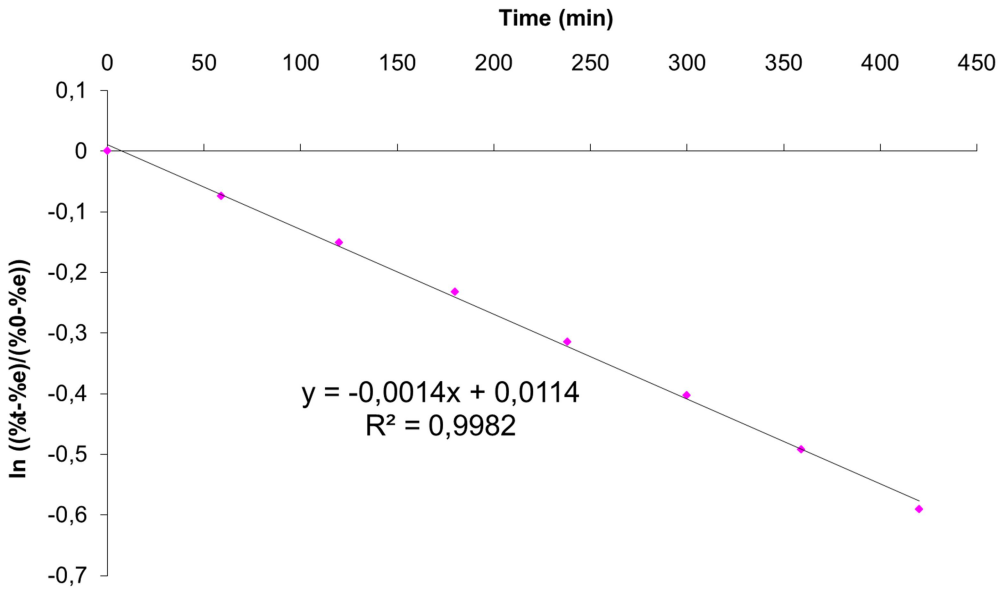
$k_{enantiomerisation}$ = 2,2598E-06 s^{-1} (180°C, 1,2-dichlorobenzene)
$\Delta G^{\neq}$ = 161.6 kJ/mol (180°C, 1,2-dichlorobenzene)
$t_{1/2}$ = 42.60 h (180°C, 1,2-dichlorobenzene)

Solvent : 1,2,4-trichlorobenzene

Temperature : 214°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	96,69	0
59	93,34	-0,074454013
120	90,14	-0,151156666
180	87,03	-0,231801614
238	84,1	-0,314232625
300	81,23	-0,402150838
359	78,54	-0,492223397
420	75,88	-0,590059539

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



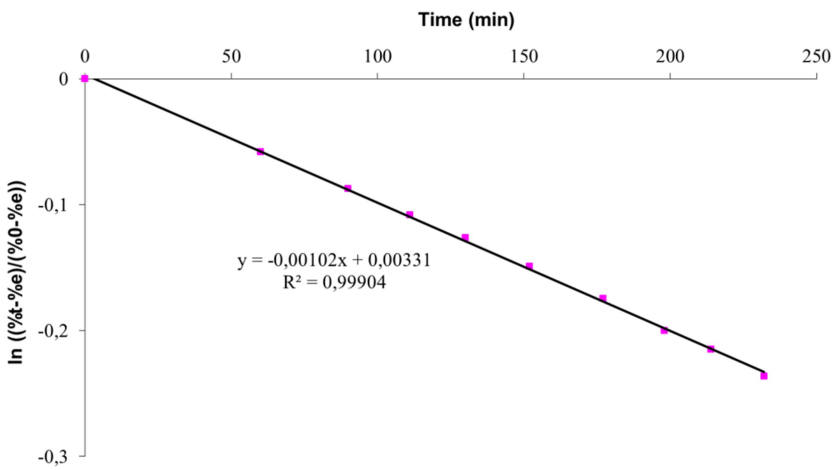
$k_{enantiomerisation}$ = 1,1670E-05 s^{-1} (214°C, 1,2,4-trichlorobenzene)
$\Delta G^{\neq}$ = 167.3 kJ/mol (214°C, 1,2,4-trichlorobenzene)
$t_{1/2}$ = 8.25 h (214°C, 1,2,4-trichlorobenzene)

Solvent : 1,2,4-trichlorobenzene

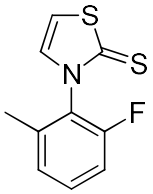
Temperature : 214°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	92,57	0,00000
60	90,17	-0,05803
90	89,01	-0,08733
111	88,21	-0,10805
130	87,52	-0,12628
152	86,67	-0,14919
177	85,75	-0,17460
198	84,85	-0,20010
214	84,34	-0,21484
232	83,61	-0,23633

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



$k_{enantiomerisation}$ = 8,4787E-06 s^{-1} (214°C, 1,2,4-trichlorobenzene)
$\Delta G^{\neq}$ = 168.6 kJ/mol (214°C, 1,2,4-trichlorobenzene)
$t_{1/2}$ = 11.35 h (214°C, 1,2,4-trichlorobenzene)



5a

Solvent : 1,2-dichlorobenzene

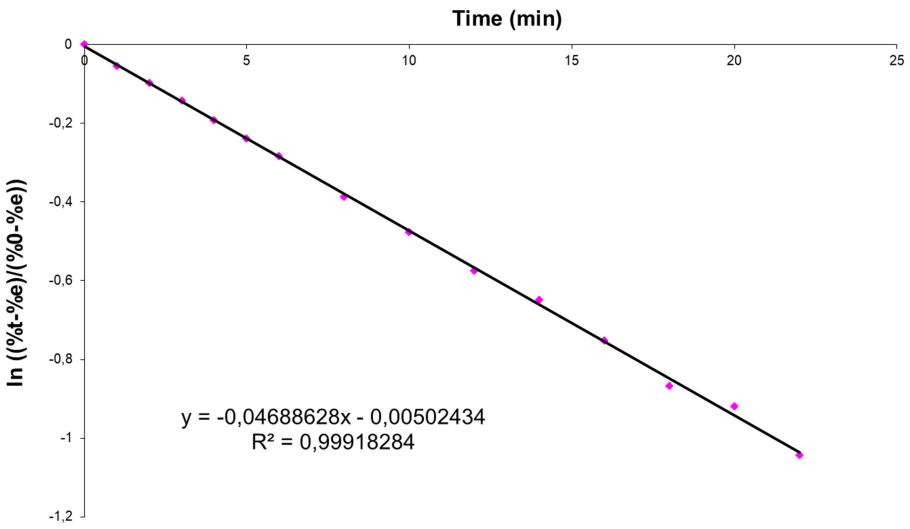
Temperature : 180°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	94,52	0
1	92,16	-0,054466622
2	90,37	-0,097851592
3	88,58	-0,143204519
4	86,69	-0,193434288
5	85,05	-0,239162913
6	83,5	-0,284393088
8	80,21	-0,387765531
10	77,61	-0,4777605
12	75,05	-0,575064699
14	73,27	-0,648773549
16	70,96	-0,753322667
18	68,69	-0,867949905
20	67,76	-0,918989789
22	65,67	-1,04419047

* Enantiomeric ratios determined by chiral HPLC on Chiralpak IE

Solvent : 1,2-dichlorobenzene

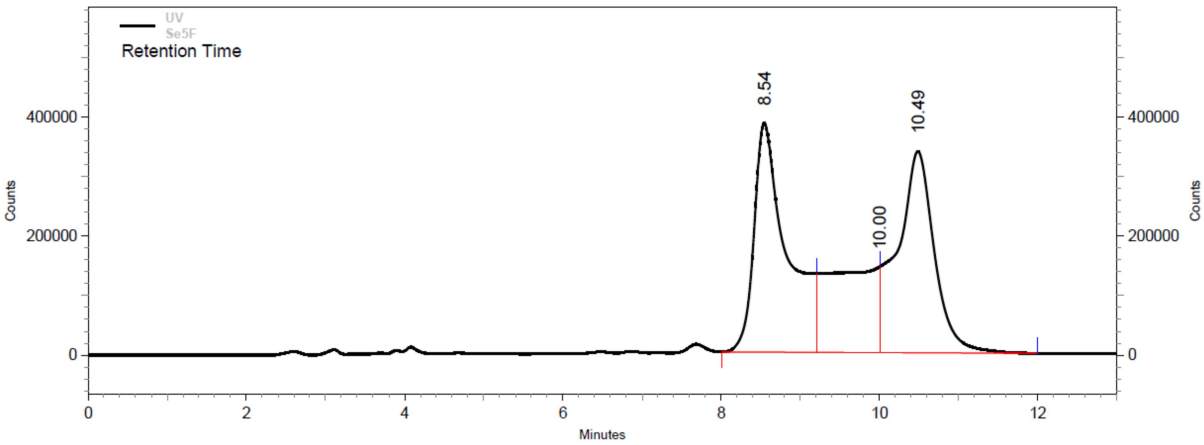
Temperature : 180°C



$k_{enantiomerisation}$ = 3.9702E-04 s^{-1} (180°C, 1,2-dichlorobenzene)
$\Delta G^{\neq}$ = 142.1 kJ/mol (180°C, 1,2-dichlorobenzene)
$t_{1/2}$ = 14.55 min (180°C, 1,2-dichlorobenzene)

Barrier determined by dynamic chiral HPLC:
Solvent: Heptane/Ethanol 60/40
Temperature: 10°C
Column: (*S*,*S*)-Whelk-O1

Temperature (°C)	10
Rt1 (min)	8,54
Rt2 (min)	10,49
ω1 (min)	0,36
ω2 (min)	0,47
N1	2919
N2	2821
h1 (µV)	384728
h2 (µV)	338563
hplateau (mV)	144114



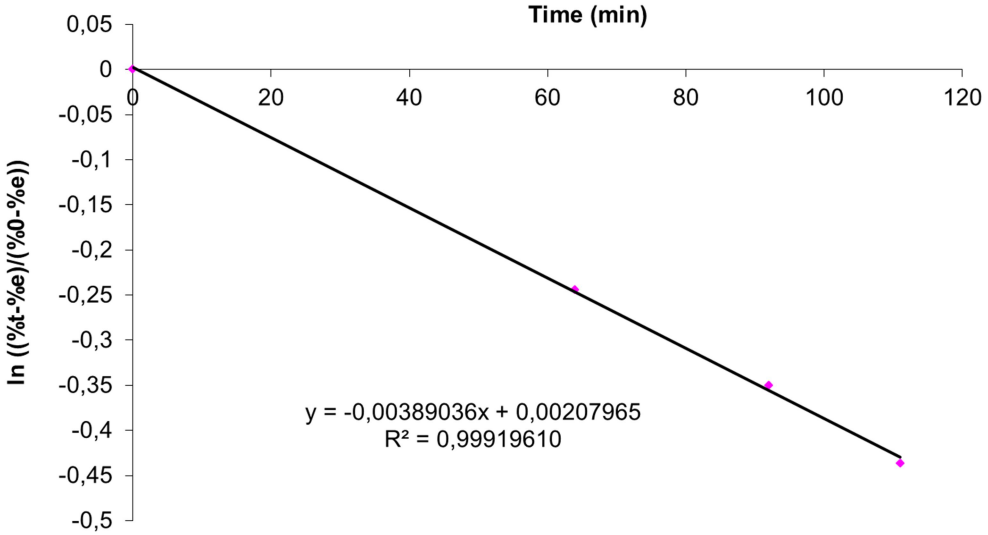
$k_{enantiomerisation}$ = 1,187E-03 s^{-1} (10°C, heptane/ethanol 60/40)
$\Delta G^{\neq}$ = 85.1 kJ/mol (10°C, heptane/ethanol 60/40)
$t_{1/2}$ = 9.74 min (10°C, heptane/ethanol 60/40)

Solvent : chlorobenzene

Temperature : 131°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	96,4	0
64	86,34	-0,244380396
92	82,7	-0,349924381
111	80	-0,436102078

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



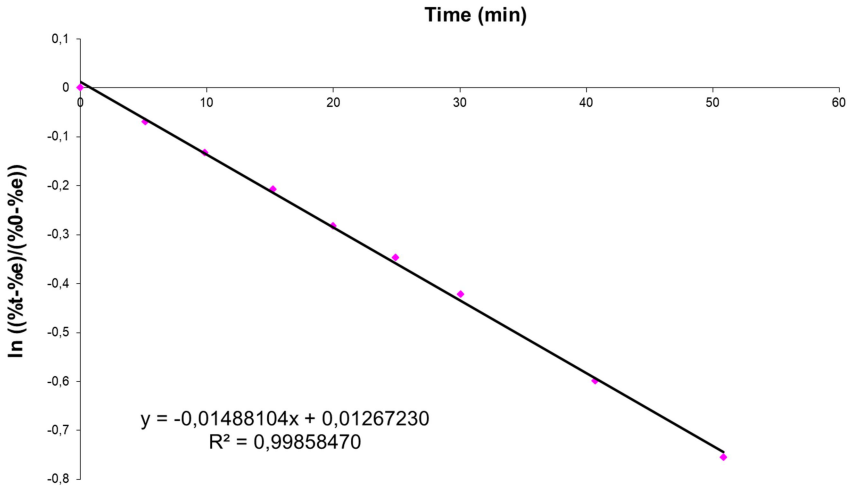
$k_{enantiomerisation}$ = 3,2141E-05 s^{-1} (131°C, chlorobenzene)
$\Delta G^{\neq}$ = 134.8 kJ/mol (131°C, chlorobenzene)
$t_{1/2}$ = 3.00 h (131°C, chlorobenzene)

Solvent : 1,2-dichlorobenzene

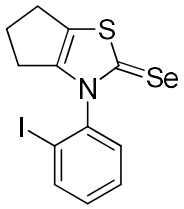
Temperature : 180°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	96,78	0
5	93,66	-0,06902341
10	90,96	-0,13285978
15	88	-0,207869601
20	85,28	-0,28213953
25	83,05	-0,347434195
30	80,69	-0,421518893
41	75,7	-0,598964769
51	71,98	-0,755322812

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



$k_{enantiomerisation}$ = 1,2401E-04 s^{-1} (180°C, 1,2-dichlorobenzene)
$\Delta G^{\neq}$ = 146.5 kJ/mol (180°C, 1,2-dichlorobenzene)
$t_{1/2}$ = 46.58 min (180°C, 1,2-dichlorobenzene)



6d

Solvent : 1,2,4-trichlorobenzene

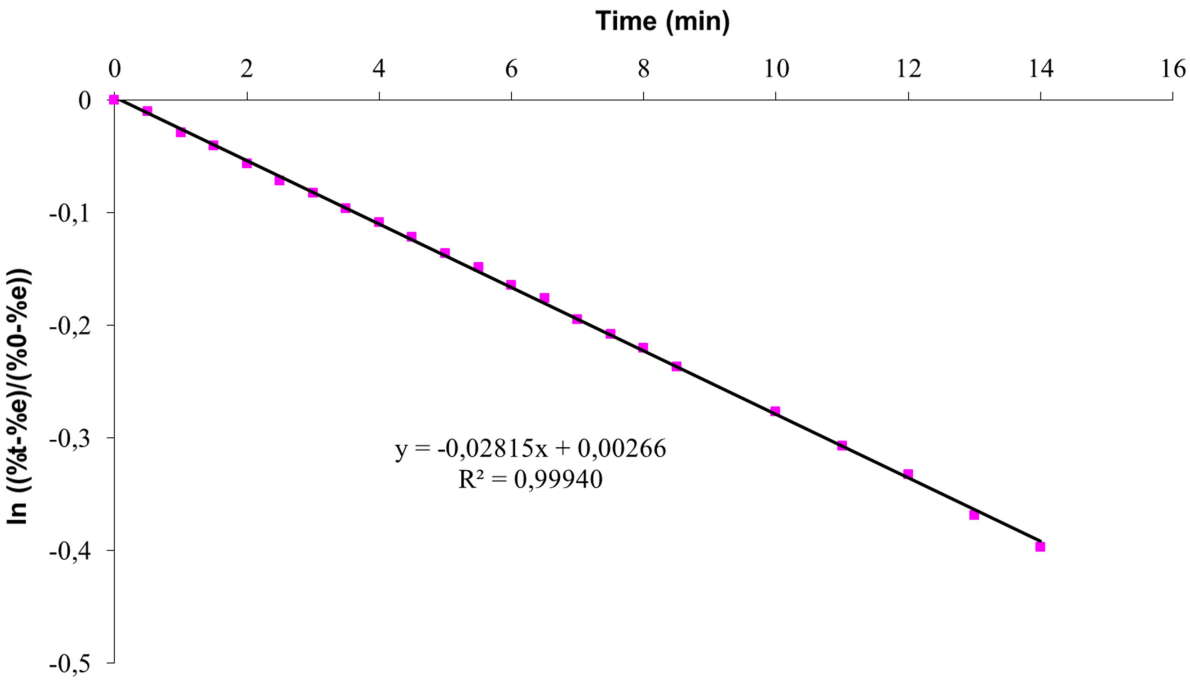
Temperature : 214°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0,000	97,10	0,00000
0,500	96,62	-0,01024
1,000	95,75	-0,02908
1,500	95,24	-0,04029
2,000	94,52	-0,05633
2,500	93,85	-0,07150
3,000	93,36	-0,08274
3,500	92,77	-0,09644
4,000	92,25	-0,10867
4,500	91,72	-0,12129
5,000	91,12	-0,13578
5,500	90,60	-0,14850
6,000	89,97	-0,16414
6,500	89,51	-0,17572
7,000	88,77	-0,19463
7,500	88,27	-0,20761
8,000	87,79	-0,22023
8,500	87,18	-0,23650
10,000	85,73	-0,27628
11,000	84,64	-0,30726
12,000	83,77	-0,33270
13,000	82,57	-0,36888
14,000	81,68	-0,39659

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1

Solvent : 1,2,4-trichlorobenzene

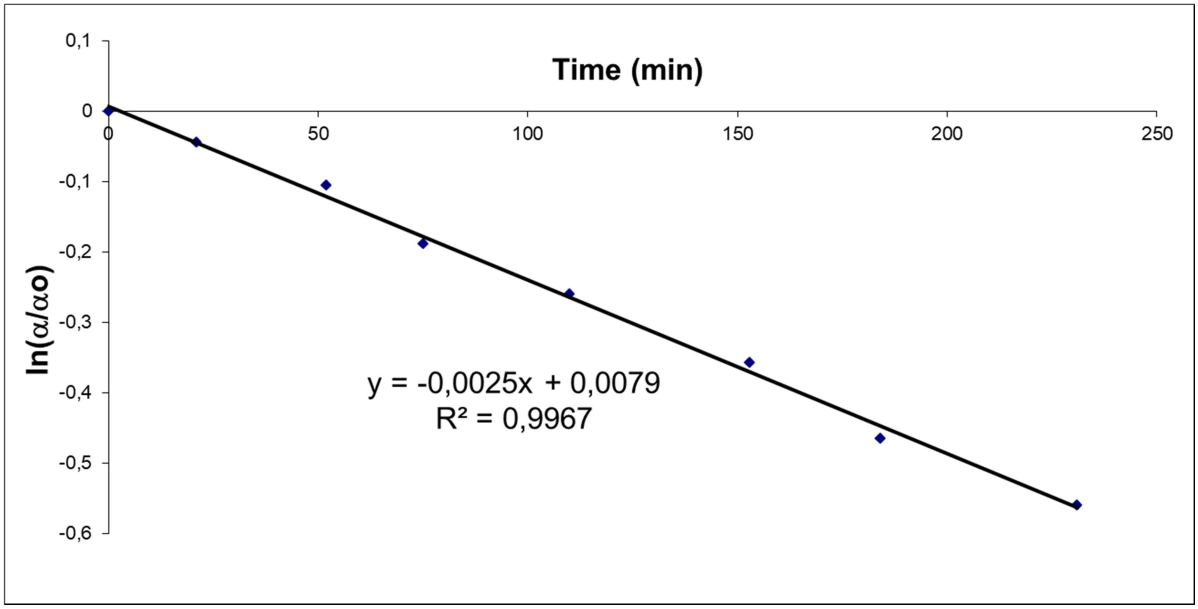
Temperature : 214°C



$k_{enantiomerisation}$ = 2,3459E-04 s^{-1} (214°C, 1,2,4-trichlorobenzene)
$\Delta G^{\neq}$ = 155.2 kJ/mol (214°C, 1,2,4-trichlorobenzene)
$t_{1/2}$ = 24.62 min (214°C, 1,2,4-trichlorobenzene)

Barrier determined by polarimetry: the decrease of the rotatory power is monitored.
Solvent: chloroform
Temperature: 35°C

α	α/α0	t (s)	ln(α/α0)
0,070	1	0	0
0,067	0,957142857	1260	-0,04380262
0,063	0,9	3120	-0,10536052
0,058	0,828571429	4500	-0,18805223
0,054	0,771428571	6600	-0,2595112
0,049	0,7	9180	-0,35667494
0,044	0,628571429	11040	-0,46430561
0,040	0,571428571	13860	-0,55961579



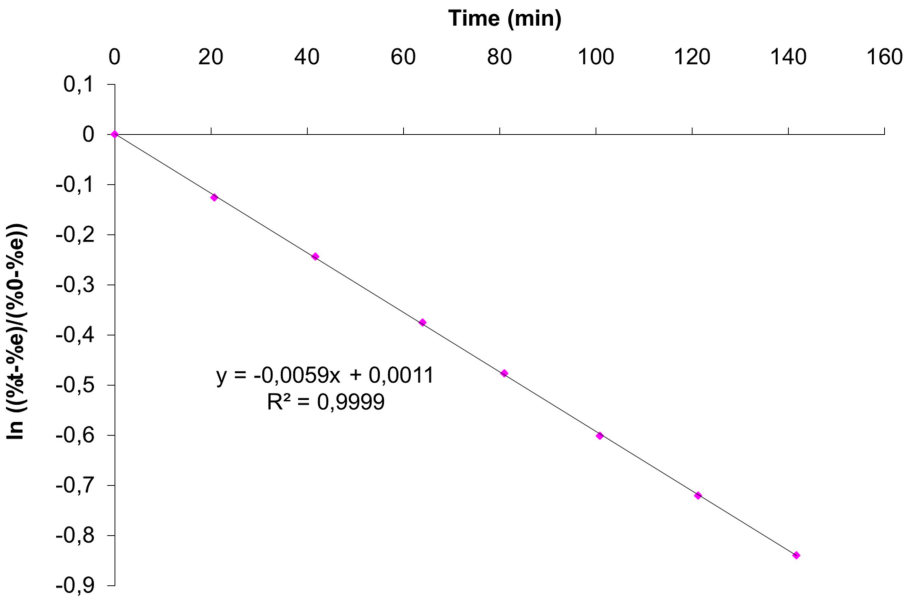
$k_{enantiomerisation}$ = 2,0587E-05 s^{-1} (35°C, chloroform)
$\Delta G^{\neq}$ = 103.2 kJ/mol (35°C, chloroform)
$t_{1/2}$ = 4.68 h (35°C, chloroform)

Solvent : chloroform

Temperature : 61°C

Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	96,9	0
21	91,35	-0,125945254
42	86,76	-0,243607378
64	82,21	-0,375740712
81	79,12	-0,476592452
101	75,71	-0,601137654
121	72,82	-0,720380331
142	70,25	-0,839862882

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1



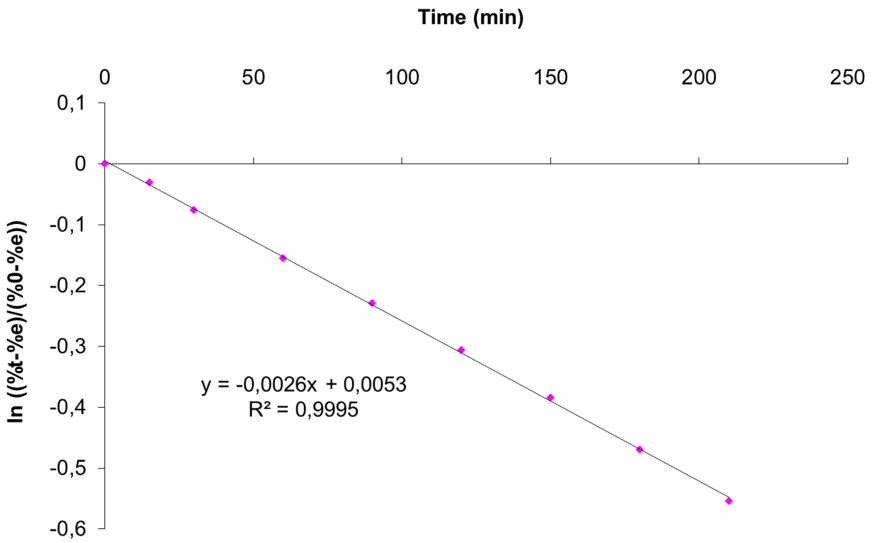
$k_{enantiomerisation}$ = 4,9457E-05 s^{-1} (61°C, chloroform)
$\Delta G^{\neq}$ = 109.7 kJ/mol (61°C, chloroform)
$t_{1/2}$ = 1.95 h (61°C, chloroform)

Solvent : chloroform

Temperature : 61°C

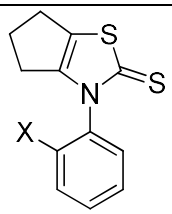
Time (min)	% major enantiomer*	ln ((%t-%e)/(%0-%e))
0	96,95	0
15	95,54	-0,030492145
30	93,534	-0,075540964
60	90,215	-0,154843145
90	87,343	-0,228937728
120	84,572	-0,3060391
150	81,977	-0,384066311
180	79,339	-0,470165517
210	76,985	-0,55380205

* Enantiomeric ratios determined by chiral HPLC on (*S*,*S*)-Whelk-O1

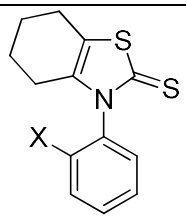


$k_{enantiomerisation}$ = 2,1947E-05 s^{-1} (61°C, chloroform)
$\Delta G^{\neq}$ = 112.0 kJ/mol (61°C, chloroform)
$t_{1/2}$ = 4.39 h (61°C, chloroform)

Experimental rotational barriers

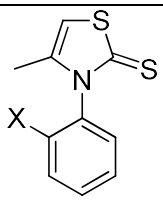


1



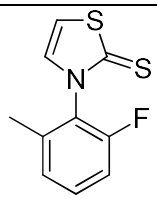
2

X	**1**	$\Delta G^{\neq}_{rot}$ (kJ/mol)	Solvent	Temperature	**2**	$\Delta G^{\neq}_{rot}$ (kJ/mol)	Solvent	Temperature
F	**1a**	82.5	Hexane/Ethanol 7/3	5°C	**2a**	113.7	1,2-Dichlorobenzene	62°C
Cl	**1b**	133.3	Chlorobenzene	131°C	**2b**	159.2	1,2-Dichlorobenzene	180°C
Br	**1c**	145.5	1,2-Dichlorobenzene	182°C	**2c**	165.9	1,2-Dichlorobenzene	180°C
I	**1d**	155.5	1,2-Dichlorobenzene	182°C	**2d**	168.1	1,2,4-Trichlorobenzene	214°C



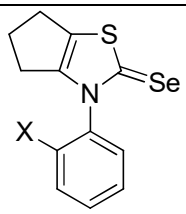
3

X	**3**	$\Delta G^{\neq}_{rot}$ (kJ/mol)	Solvent	Temperature
F	**3a**	114.7	1,2-Dichlorobenzene	62°C
Cl	**3b**	161.6	1,2-Dichlorobenzene	180°C
Br	**3c**	167.3	1,2,4-Trichlorobenzene	214°C
I	**3d**	168.6	1,2,4-Trichlorobenzene	214°C

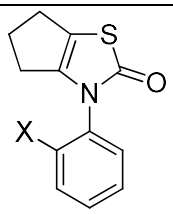


5a

$\Delta G^{\neq}_{rot}$ (kJ/mol)	Solvent	Temperature
142.1	1,2-Dichlorobenzene	180°C



6



7

X	**6**	$\Delta G^{\neq}_{rot}$ (kJ/mol)	Solvent	Temperature	**7**	$\Delta G^{\neq}_{rot}$ (kJ/mol)	Solvent	Temperature
F	**6a**	85.1	Heptane/Ethanol 6/4	10°C	**7a**	< 80	-	-
Cl	**6b**	134.8	Chlorobenzene	131°C	**7b**	103.2	Chloroform	35°C
Br	**6c**	146.4	1,2-Dichlorobenzene	180°C	**7c**	109.7	Chloroform	61°C
I	**6d**	155.2	1,2,4-Trichlorobenzene	214°C	**7d**	112.0	Chloroform	61°C

Computational methods of calculated rotational barriers

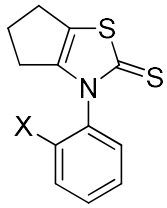
Computational details for the calculations of the rotational barriers: all the ground states (GS) and the transition states (TS) were calculated using DFT with B3LYP/6-311G(3d,3p), M06-2X/6-311G(3d,3p) and PBE0/def2-TZVPP methods, with LanL2DZ pseudopotential for iodine and without solvent model. GS and TS were checked by a frequency calculation: with respectively none and a single imaginary frequency. Their energy was calculated at the temperature experimentally used for the rotational barrier determination. Intrinsic reaction coordinate (IRC) calculations have been performed on each TS on both direction in order to validate the reaction path. All calculations were performed using Gaussian 16 package.[1]

[1] Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

Calculated rotational barriers with different functional/basis sets

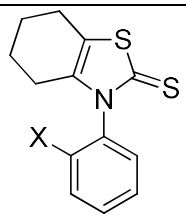
Rotational barriers are reported in kJ/mol.

Method X: PBE0 functional and def2-TZVPP basis set.
Method Y: M06-2X functional and 6-311G(3d,3p) basis set.
Method Z: B3LYP functional and 6-311G(3d,3p) basis set.



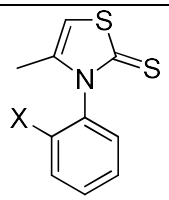
1

X	**1**	$\Delta G^{\neq}_{rot}$	$\Delta G^{\neq}_{calc}$ via A			$\Delta G^{\neq}_{calc}$ via B		
			Method X	Method Y	Method Z	Method X	Method Y	Method Z
F	**1a**	**82.5**	83.7	85.6	85.0	112.9	115.0	114.8
Cl	**1b**	**133.3**	137.8	145.7	143.3	154.1	160.2	157.7
Br	**1c**	**145.5**	152.3	161.4	157.1	163.1	170.5	166.6
I	**1d**	**155.5**	167.4	175.3	169.6	171.6	178.6	173.1



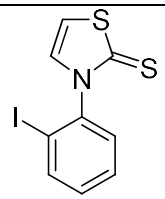
2

X	**2**	$\Delta G^{\neq}_{rot}$	$\Delta G^{\neq}_{calc}$ via A			$\Delta G^{\neq}_{calc}$ via B		
			Method X	Method Y	Method Z	Method X	Method Y	Method Z
F	**2a**	**113.7**	113.7	115.9	113.1	143.1	145.6	141.0
Cl	**2b**	**159.2**	163.7	171.6	165.6	175.2	181.5	176.1
Br	**2c**	**165.9**	175.2	184.5	176.8	181.0	189.2	182.2
I	**2d**	**168.1**	189.5	200.9	189.1	189.4	198.4	188.9



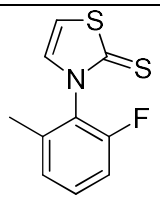
3

X	**3**	$\Delta G^{\neq}_{rot}$	$\Delta G^{\neq}_{calc}$ via A			$\Delta G^{\neq}_{calc}$ via B		
			Method X	Method Y	Method Z	Method X	Method Y	Method Z
F	**3a**	**114.7**	117.2	119.6	116.4	138.2	140.0	137.0
Cl	**3b**	**161.6**	167.5	175.1	168.7	173.8	180.5	175.3
Br	**3c**	**167.3**	178.4	187.0	179.1	179.9	188.6	181.5
I	**3d**	**168.6**	191.6	199.1	189.8	187.4	194.3	187.0



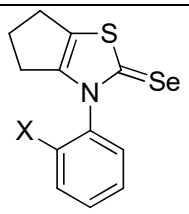
4d

$\Delta G^{\neq}_{rot}$	$\Delta G^{\neq}_{calc}$ via A			$\Delta G^{\neq}_{calc}$ via B		
	Method X	Method Y	Method Z	Method X	Method Y	Method Z
< 80	77.3	89.4	79.3	149.8	158.4	151.9



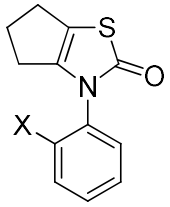
5a

$\Delta G^{\neq}_{rot}$	$\Delta G^{\neq}_{calc}$ via A			$\Delta G^{\neq}_{calc}$ via B		
	Method X	Method Y	Method Z	Method X	Method Y	Method Z
142.1	152.9	157.5	153.5	153,1	157.4	153.5



6

X	**6**	$\Delta G^{\neq}_{rot}$	$\Delta G^{\neq}_{calc}$ via A			$\Delta G^{\neq}_{calc}$ via B		
			Method X	Method Y	Method Z	Method X	Method Y	Method Z
F	**6a**	**85.1**	86.1	89.3	86.7	118.4	122.3	119.7
Cl	**6b**	**134.8**	140.5	150.5	145.1	163.5	172.5	166.0
Br	**6c**	**146.4**	154.9	165.9	159.3	173.4	183.9	175.9
I	**6d**	**155.2**	170.5	180.9	172.3	184.2	192.2	184.2

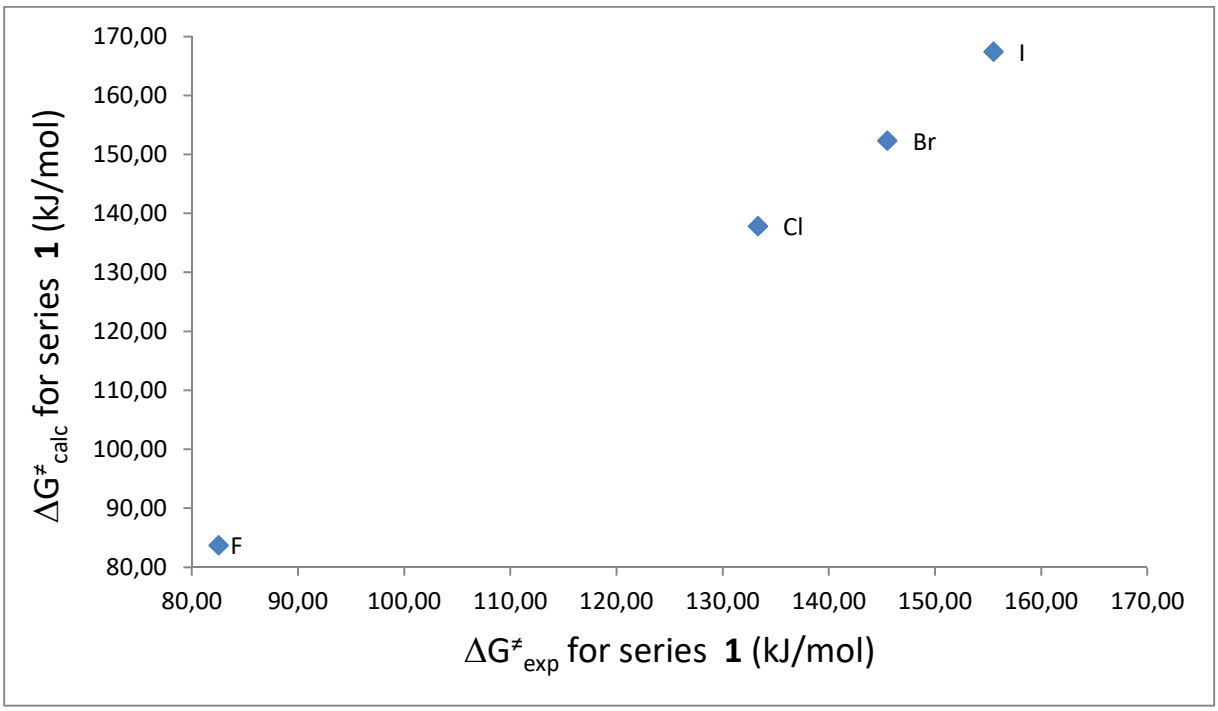


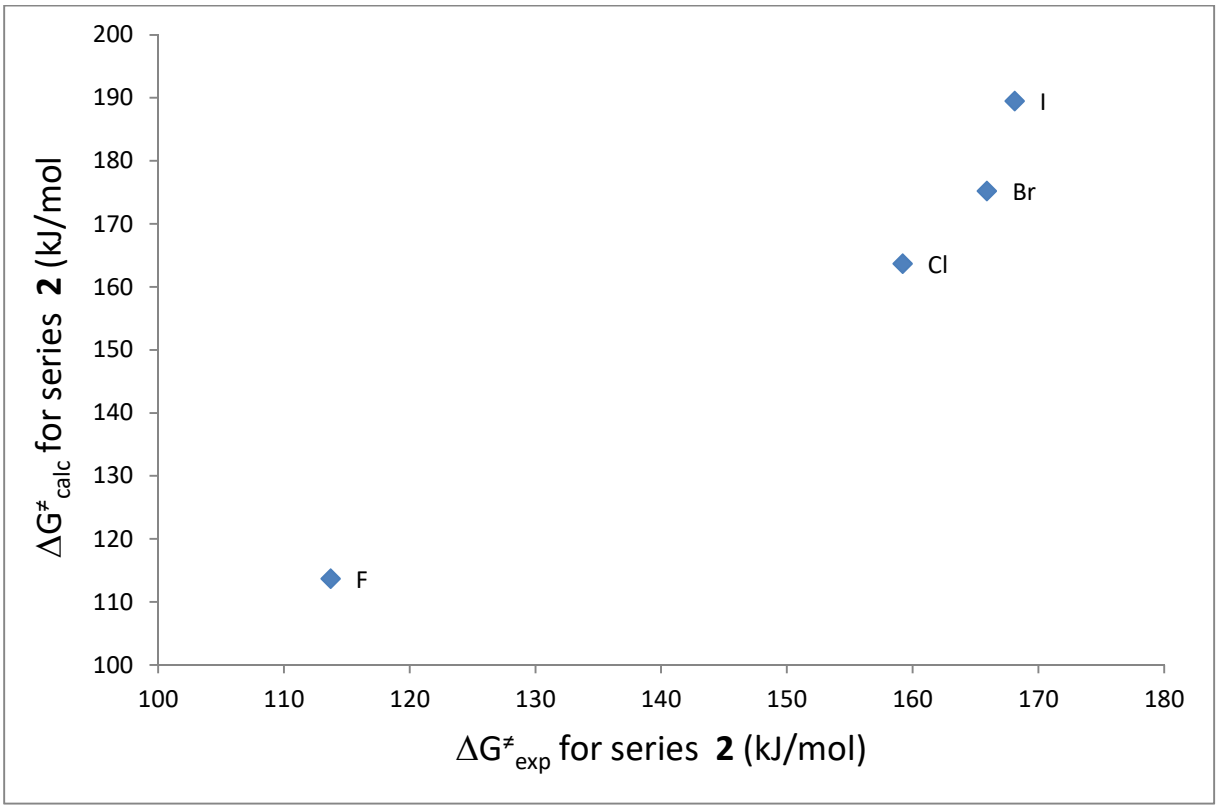
7

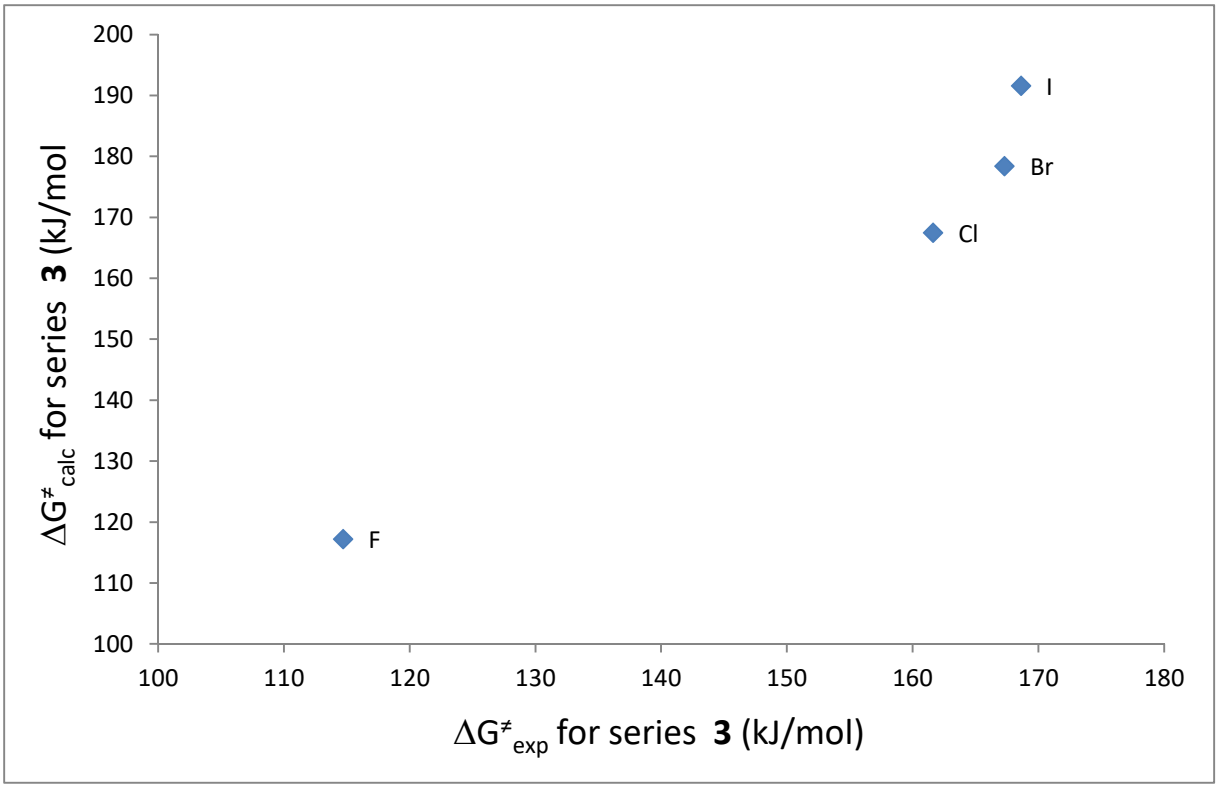
X	**7**	$\Delta G^{\neq}_{rot}$	$\Delta G^{\neq}_{calc}$ via A			$\Delta G^{\neq}_{calc}$ via B		
			Method X	Method Y	Method Z	Method X	Method Y	Method Z
F	**7a**	**< 80**	56.1	52.6	53.6	78.2	79.5	80.1
Cl	**7b**	**103.2**	102.6	103.8	104.4	109.3	110.8	110.1
Br	**7c**	**109.7**	116.6	118.4	118.5	116.3	118.3	118.5
I	**7d**	**112.0**	133.6	134.7	133.4	123.0	123.8	123.4

Experimental vs Calculated rotational barriers

$\Delta G^{\neq}_{calc}$ plotted herein correspond to the most favourable TS.

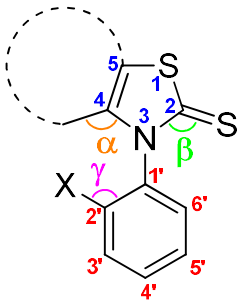





200
190
180
170
160
150
140
130
120
110
100
100
110
120
130
140
150
160
170
180
I
Br
Cl
F
ΔG≠calc for series 3 (kJ/mol
ΔG≠exp for series 3 (kJ/mol)

Angles and bond lengths from computational study and X-Ray Analysis

For GS and TSs, angles and bond lengths are reported from PBE0 functional and def2-TZVPP basis set.



		Angle α				Angle β				Angle γ			
		GS	TS1	TS2	RX	GS	TS1	TS2	RX	GS	TS1	TS2	RX
series **1**	**1a**	131.9	136.4	135.1		127.6	135.0	134.2		119.1	122.8	124.3	
	1b	131.9	136.5	131.3		127.2	134.9	131.7		120.4	127.8	127.3	
	1c	131.9	136.2	131.2	131.3	127.1	134.7	131.3	127.8	120.5	129.5	128.8	120.6
	1d	131.9	135.9	131.2		127.1	134.5	130.7		121.2	131.2	131.0	
series **2**	**2a**	122.5	126.5	123.7		127.6	133.7	130.5		119.1	123.1	122.8	
	2b	122.5	125.6	123.1		127.3	132.6	129.9		120.3	127.6	126.5	
	2c	122.5	125.3	123.0	122.3	127.2	132.6	129.6	127.2	120.5	129.4	127.9	120.5
	2d	122.5	125.1	122.9		127.2	132.7	129.2		121.1	131.5	129.9	
series **3**	**3a**	120.6	128.6	124.6		127.4	134.1	132.0		119,0	123.1	123.4	
	3b	120.5	126.5	123.0		127.1	132.0	130.9		120.3	127.4	127.2	
	3c	120.5	125.6	122.7	120.4	127.1	131.7	130.5	127.8	120.4	129.2	128.7	120.5
	3d	120.5	125.6	122.6		127.1	131.7	130,0		121.1	131.3	130.8	
4d		118.7	119.5	119.4		127.4	135.3	133.1		121.4	132.1	132.2	
5a		118.7	120.0	119.2		127.4	135.1	134.7		118.7	121.7	122.0	
series **6**	**6a**	132.1	136.6	135.4		127.8	136.9	136.7		119.1	122.9	123.7	
	6b	132.1	136.9	131.4		127.3	137,0	133.2		120.4	128,0	127.0	
	6c	132.1	136.6	131.3	131.3	127.2	136.8	132.7	128.5	120.6	129.6	128.6	120.2
	6d	132.1	136.2	131.3		127.2	136.5	132.1		121.2	131.2	130.9	
series **7**	**7a**	131.3	135.7	134.8		126.4	128.6	129.0		119.2	122.1	124.6	
	7b	131.2	136.3	134.5		126.4	129.0	128.8		120.5	127.3	128.8	
	7c	131.3	136,0	134.5		126.4	129.0	128.4		120.7	129.4	130.4	
	7d	131.3	135.7	134.5		126.3	129.0	127.9		121.3	131.8	132.5	

		C2-N3-C1'-C6' Dihedral Angle ϕ		C1'-C6'-C4'-C3' Dihedral Angle ψ				N3-C4-C5-S1 Dihedral Angle				C4-N3-C2=S Dihedral Angle			
		GS	RX	GS	TS1	TS2	RX	GS	TS1	TS2	RX	GS	TS1	TS2	RX
series **1**	**1a**	67.2		0.2	1.2	3.1		0.4	2.4	2.8		179.7	168.9	161.3	
	1b	78.1		0.3	4.3	6.6		0.3	3.7	5.7		179.0	160.3	148.4	
	1c	80.6	79.0	0.3	6.1	7.2	0.8	0.3	3.8	5.5	0.2	178.8	159.5	148.6	178.3
	1d	83.4		0.3	8.1	8.0		0.2	3.6	5.4		178.4	159.7	149.4	
series **2**	**2a**	72.2		0.3	2.1	5.1		0.3	5.5	7.4		179.6	159.7	146.9	
	2b	80.7		0.3	4.8	7.4		0.4	6.8	7.6		179.8	152.9	142.1	
	2c	82.2	79.9	0.3	6.3	7.9	0.4	0.4	6.9	7.3	0.8	179.6	152.7	142.1	179.7
	2d	84.2		0.3	8.1	8.5		0.5	6.7	7.0		179.2	153.5	142.6	
series **3**	**3a**	75.2		0.3	1.9	4.5		0.2	4.8	6.4		179.6	161.4	149.8	
	3b	82.7		0.3	4.5	6.9		0.1	8.0	7.1		179.9	153.0	143.7	
	3c	84.1	89.5	0.3	5.6	7.5	0.3	0.0	8.4	7.0	0.5	179.7	152.5	143.8	179.3
	3d	85.6		0.3	7.2	8.3		0.1	8.4	6.8		179.2	152.8	144.5	
4d		77.6		0.3	0.0	7.9		0.2	0.0	3.6		179.8	180.0	158.7	
5a		79.5		0.2	11.7	10.3		0.4	3.4	3.8		178.5	159.8	157.4	
series **6**	**6a**	68.4		0.2	1.3	3.0		0.4	2.4	3.1		179.9	168.8	160.7	
	6b	78.7		0.2	4.8	6.8		0.3	3.7	6.2		179.1	160.4	146.2	
	6c	81.1	80.8	0.2	6.5	7.4	0.4	0.2	3.7	6.1	0.4	178.8	159.6	146.2	179.1
	6d	83.3		0.2	8.3	8.2		0.1	3.5	5.9		178.3	159.6	147.0	
series **7**	**7a**	57.2		0.3	0.4	1.7		0.2	1.3	1.4		179.3	174.7	170.1	
	7b	66.5		0.5	1.5	4.4		0.3	2.5	1.9		179.6	166.8	163.0	
	7c	68.7		0.5	2.6	5.2		0.3	2.7	1.9		179.7	165.2	163.1	
	7d	72.9		0.5	5.5	6.1		0.3	2.8	1.9		179.7	164.7	163.8	

		Bond length C1'-N3 (pm)			
		GS	TS1	TS2	RX
series **1**	**1a**	142	144	144	
	1b	142	145	143	
	1c	142	145	143	144
	1d	142	144	143	
series **2**	**2a**	142	144	142	
	2b	142	145	142	
	2c	142	144	142	144
	2d	142	144	142	
series **3**	**3a**	142	145	143	
	3b	142	145	142	
	3c	142	145	142	144
	3d	142	144	142	
4d		142	144	144	
5a		142	144	143	
series **6**	**6a**	142	144	144	
	6b	142	145	143	
	6c	142	145	143	144
	6d	142	145	143	
series **7**	**7a**	141	144	143	
	7b	141	145	143	
	7c	142	145	143	
	7d	142	144	143	

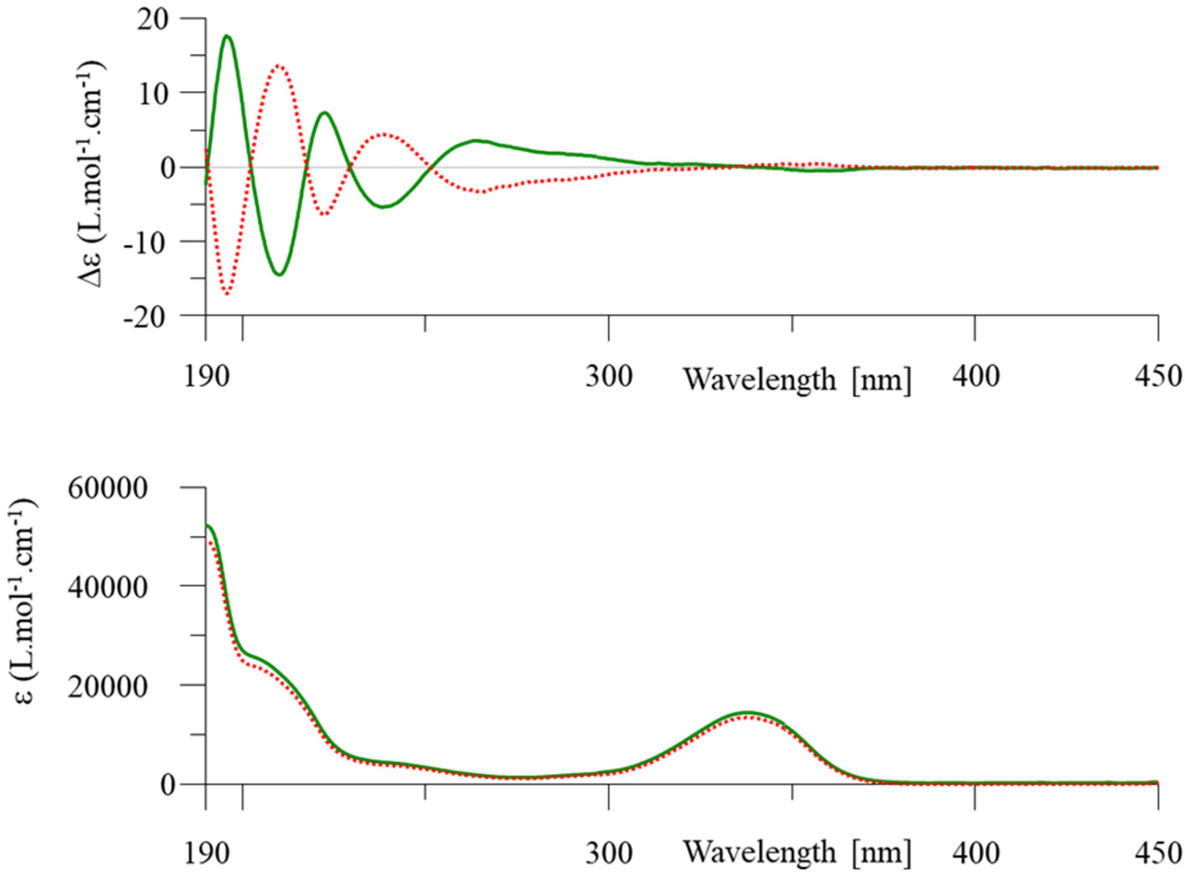
ECD and UV Spectra

ECD and UV spectra were measured on a JASCO J-815 spectrometer equipped with a JASCO Peltier cell holder PTC-423 to maintain the temperature at 25.0 ± 0.2°C. A CD quartz cell of 1 mm of optical pathlength was used. The CD spectrometer was purged with nitrogen before recording each spectrum, which was baseline subtracted.

The baseline was always measured for the same solvent and in the same cell as the samples.

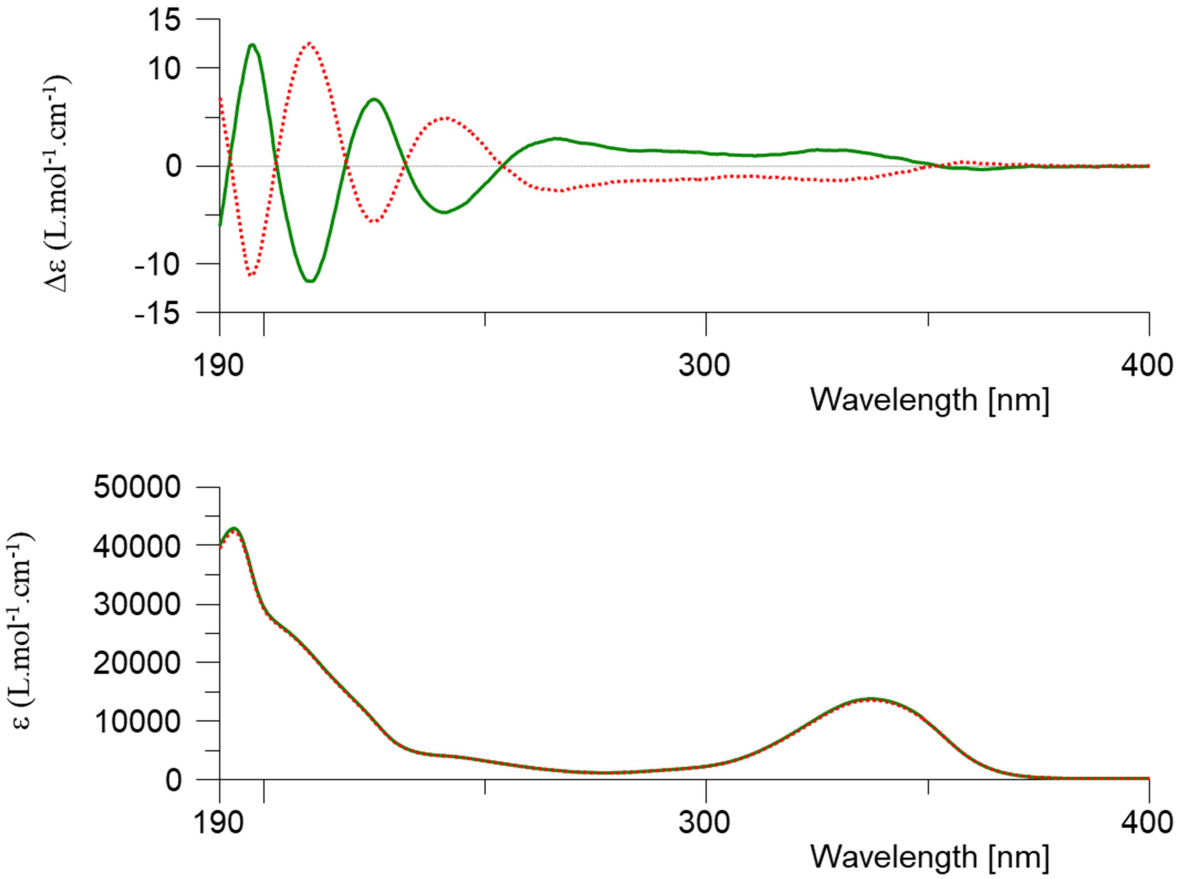
The spectra are presented without smoothing and further data processing.

Acquisition parameters used: 0.1 nm as intervals, scanning speed 50 nm/min, band width 2 nm, and 3 accumulations per sample.



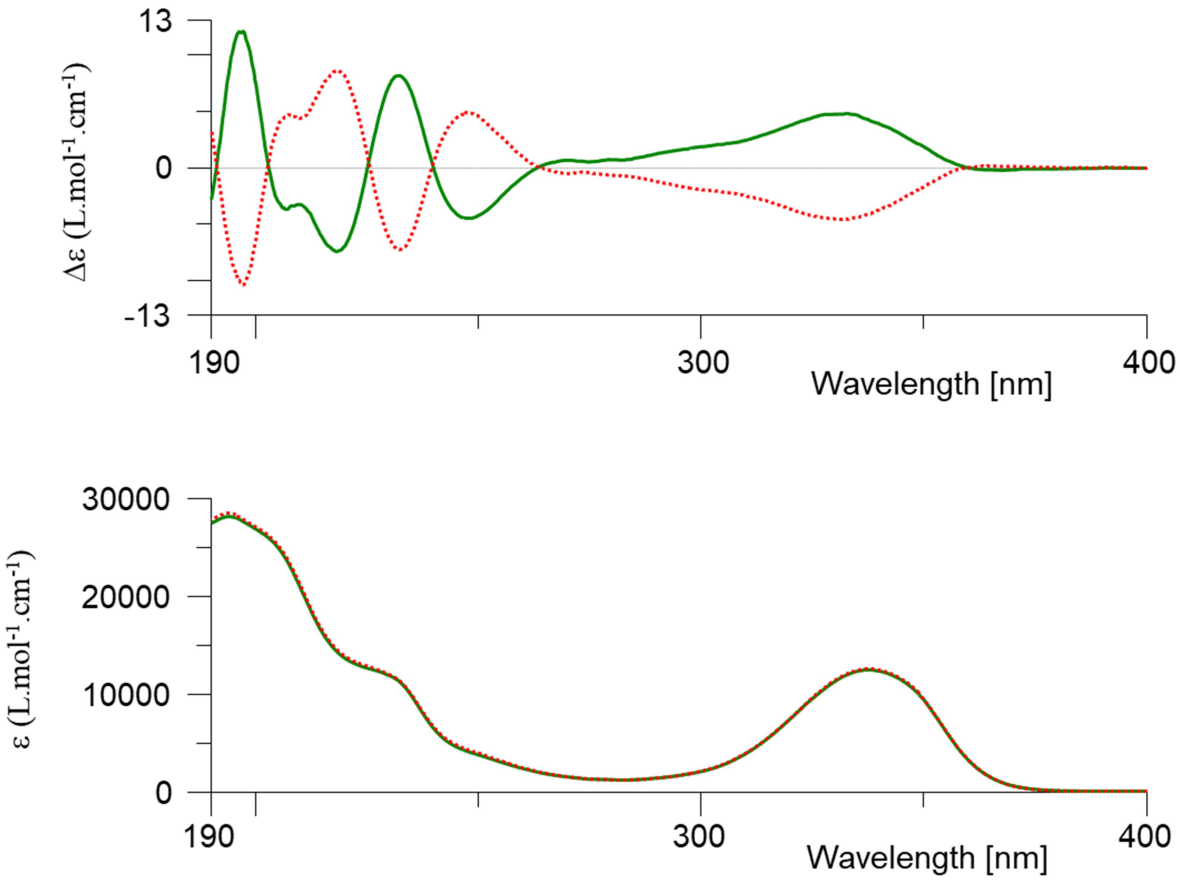
- first eluted enantiomer: green solid line, concentration = 0.346 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.349 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **1b**



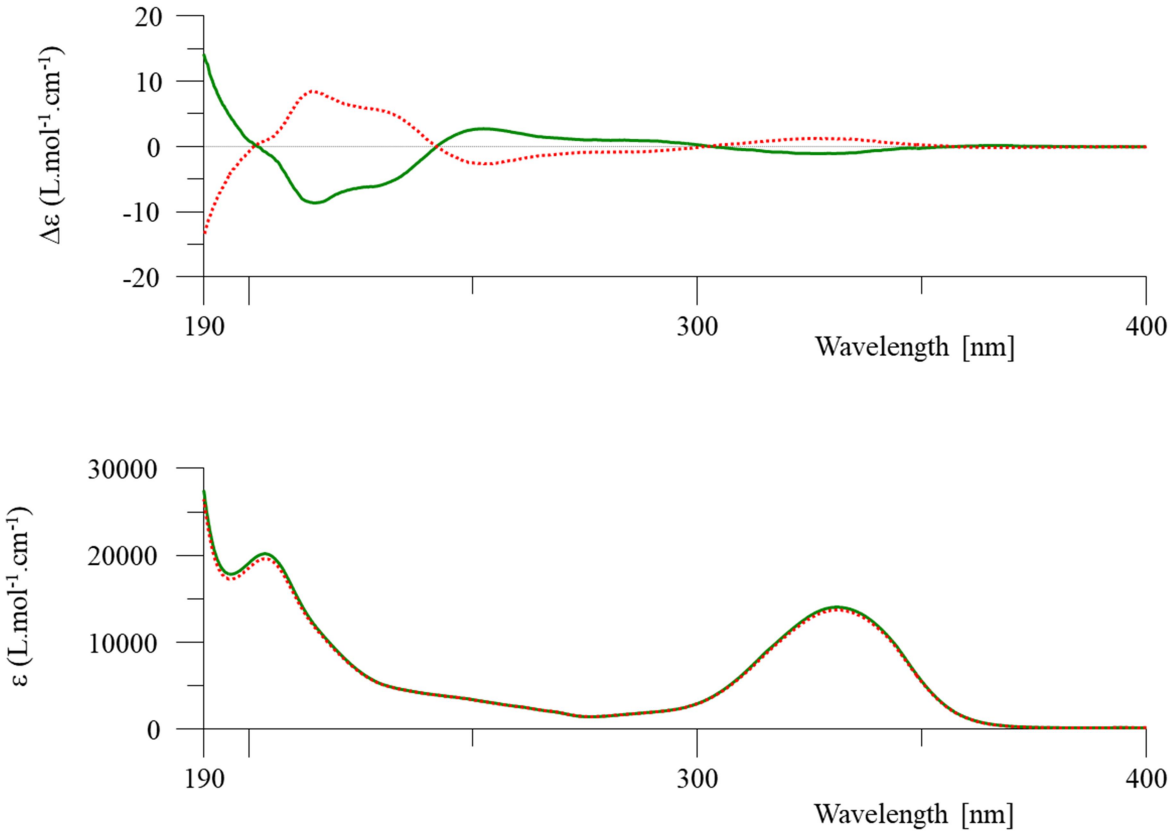
- first eluted enantiomer: green solid line, concentration = 0.403 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.415 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **1c**



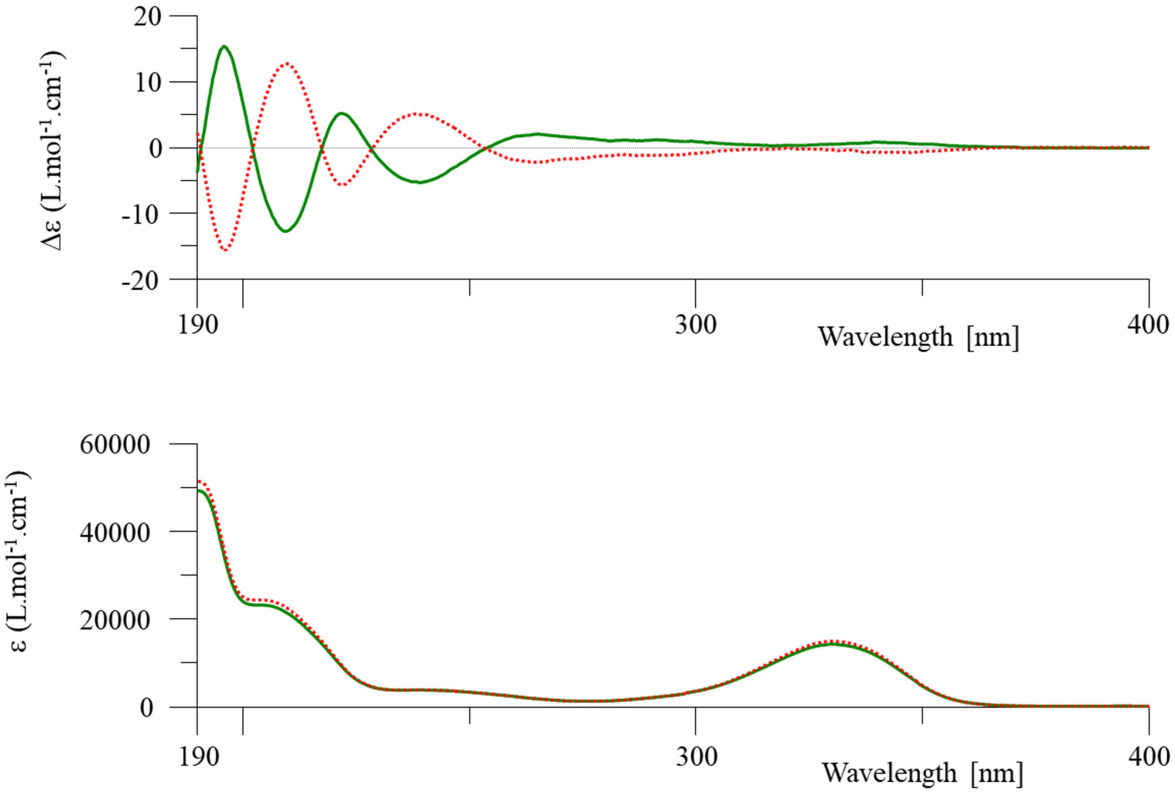
- first eluted enantiomer: green solid line, concentration = 0.647 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.602 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **1d**



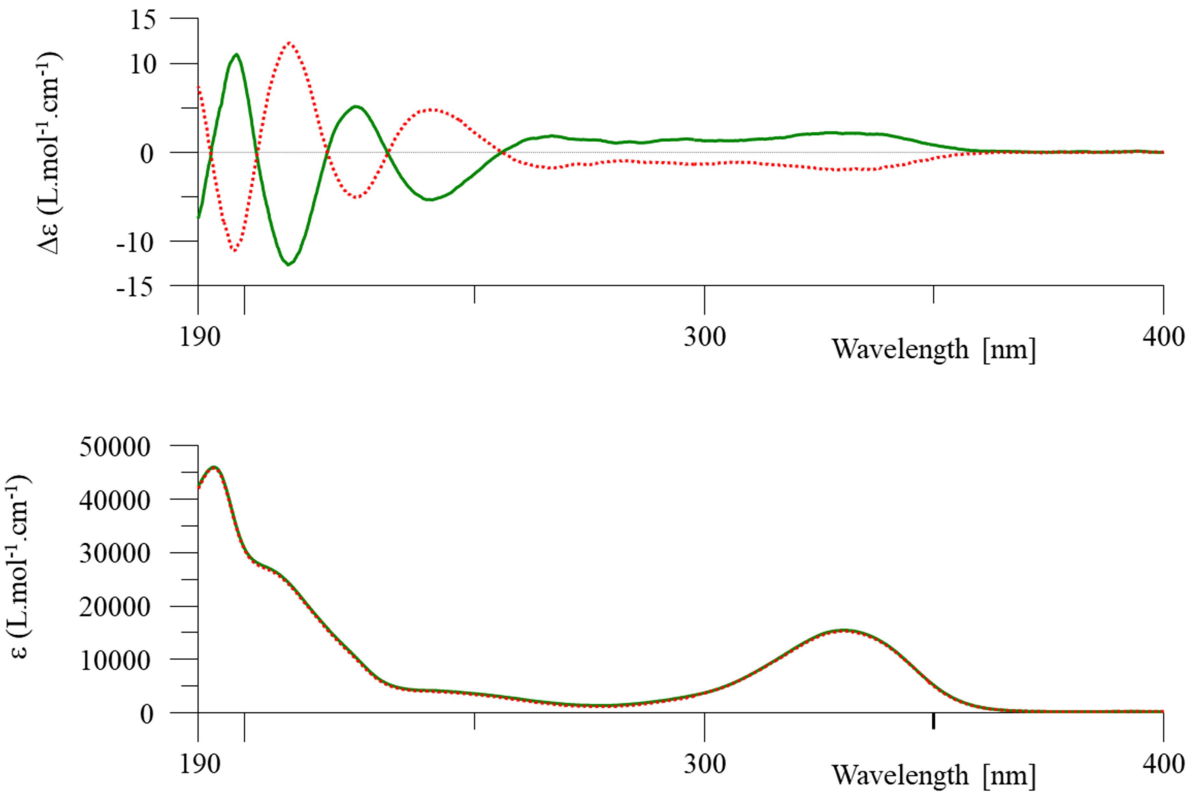
- first eluted enantiomer: green solid line, concentration = 0.638 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.624 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **2a**



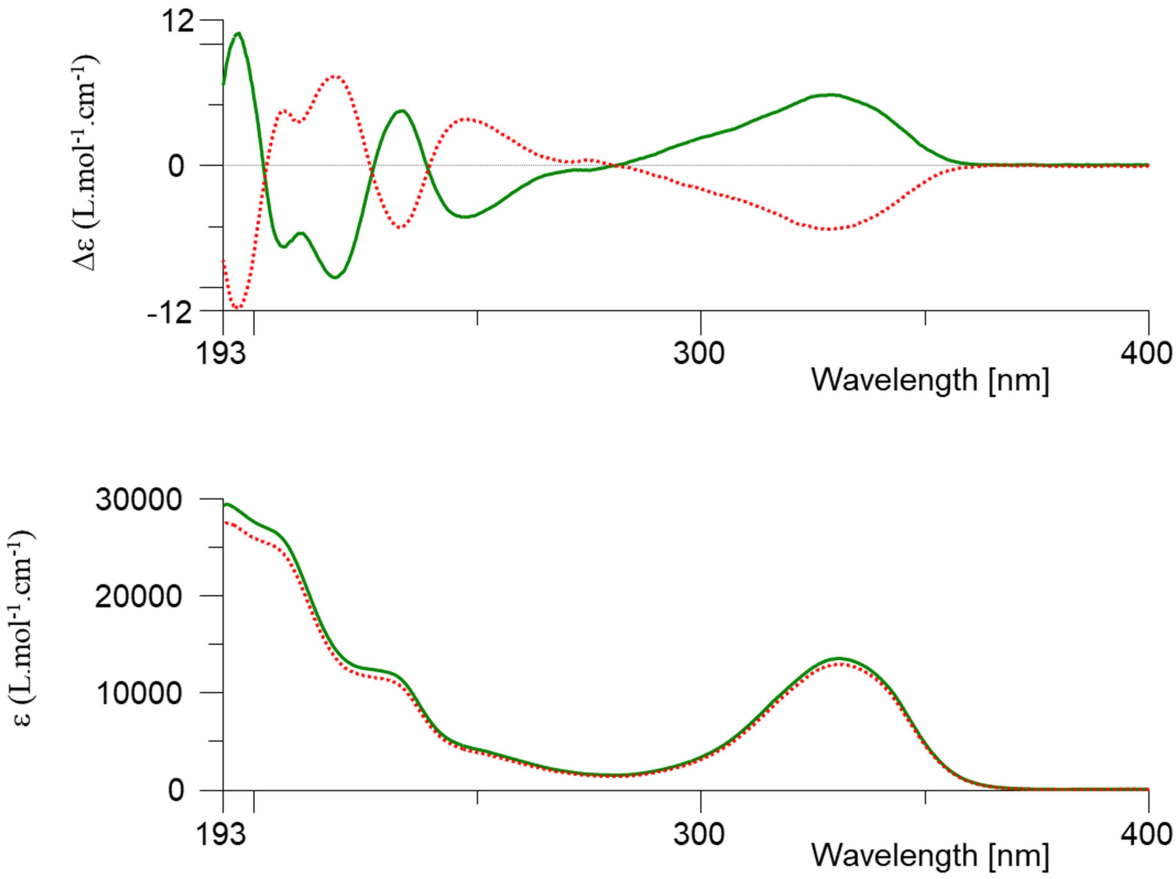
- first eluted enantiomer: green solid line, concentration = 0.324 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.344 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **2b**



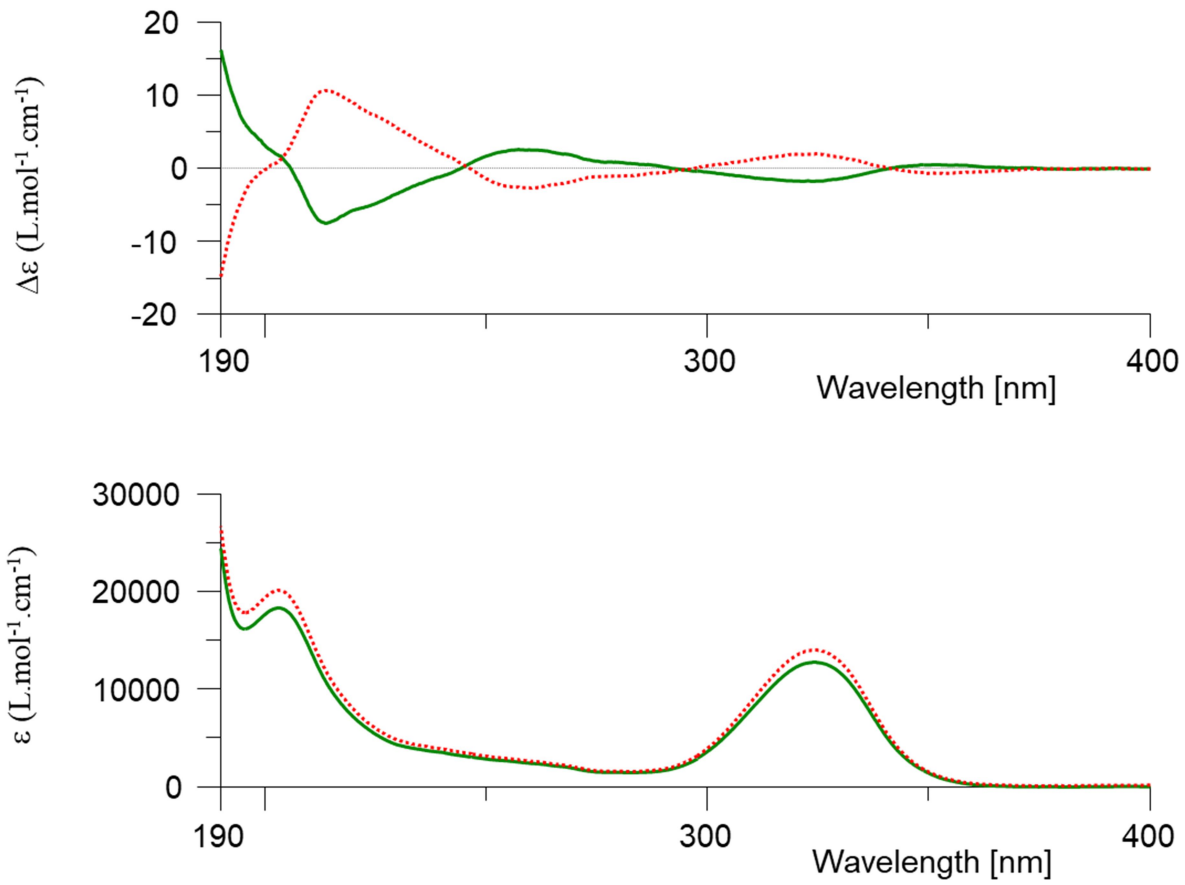
- first eluted enantiomer: green solid line, concentration = 0.392 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.362 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **2c**



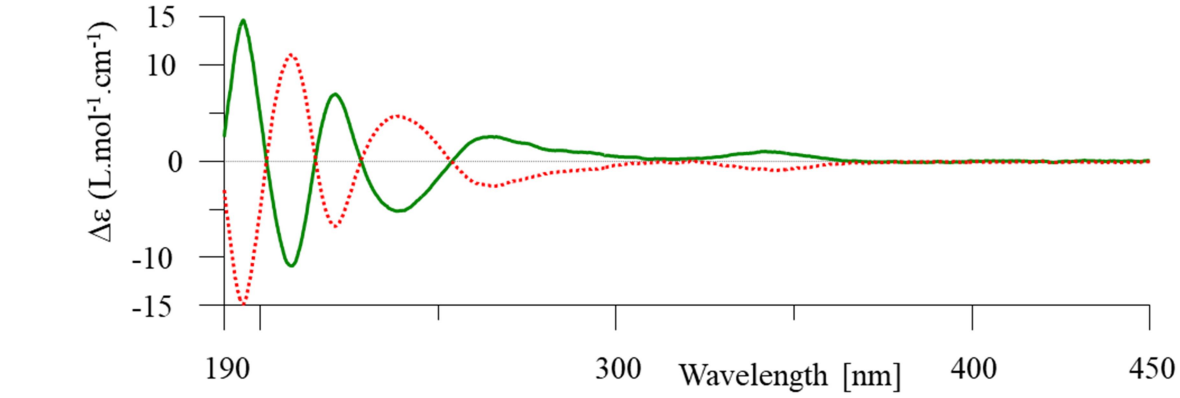
- first eluted enantiomer: green solid line, concentration = 0.618 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.612 mmol.L^{-1} in acetonitrile.

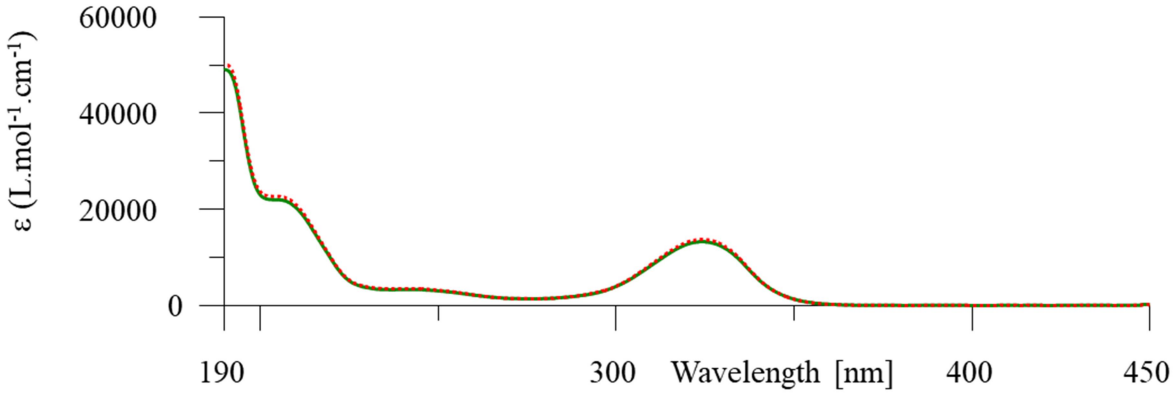
ECD (up) and UV (down) spectra of **2d**



- first eluted enantiomer: green solid line, concentration = 0.397 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.400 mmol.L^{-1} in acetonitrile.

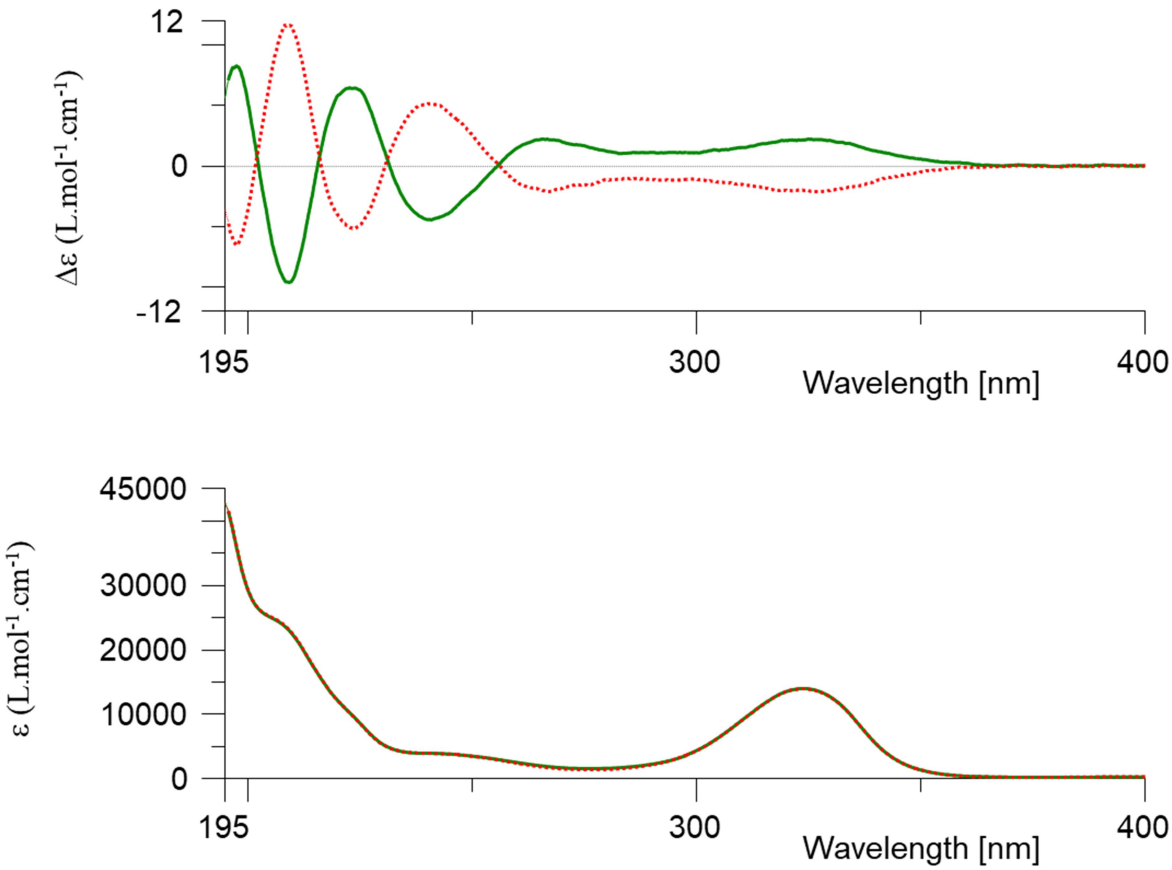
ECD (up) and UV (down) spectra of **3a**





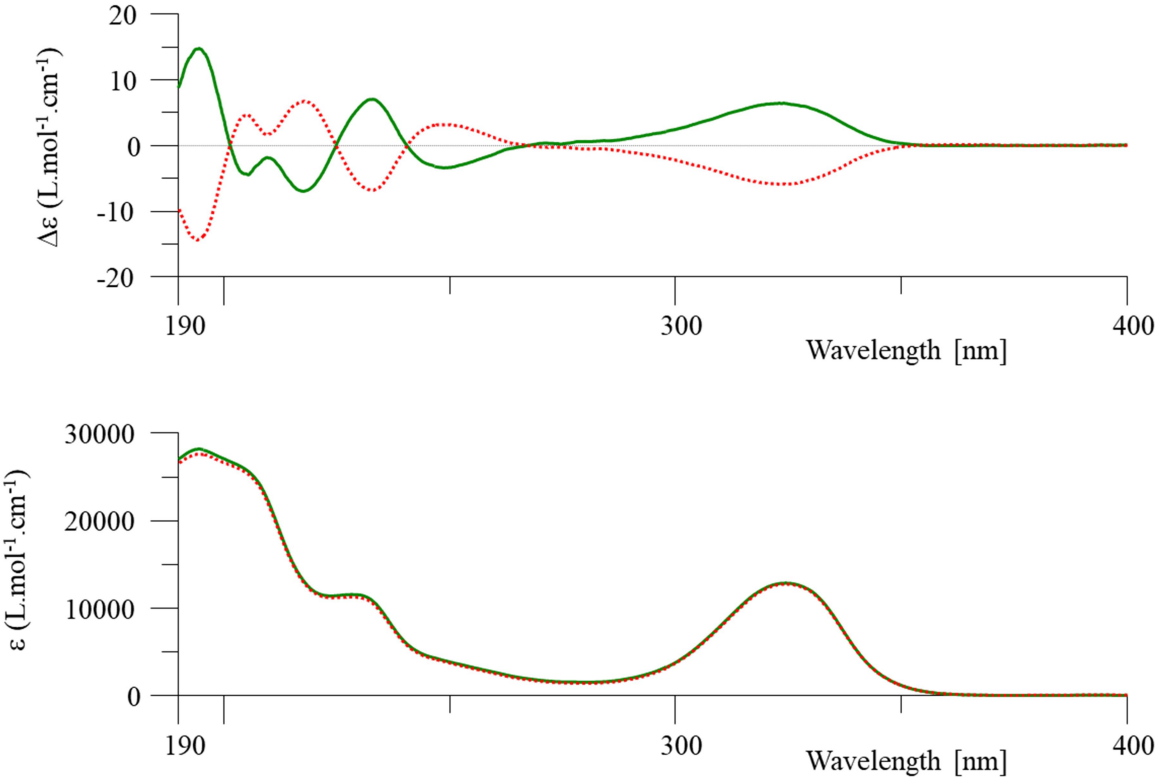
- first eluted enantiomer: green solid line, concentration = 0.357 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.361 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **3b**



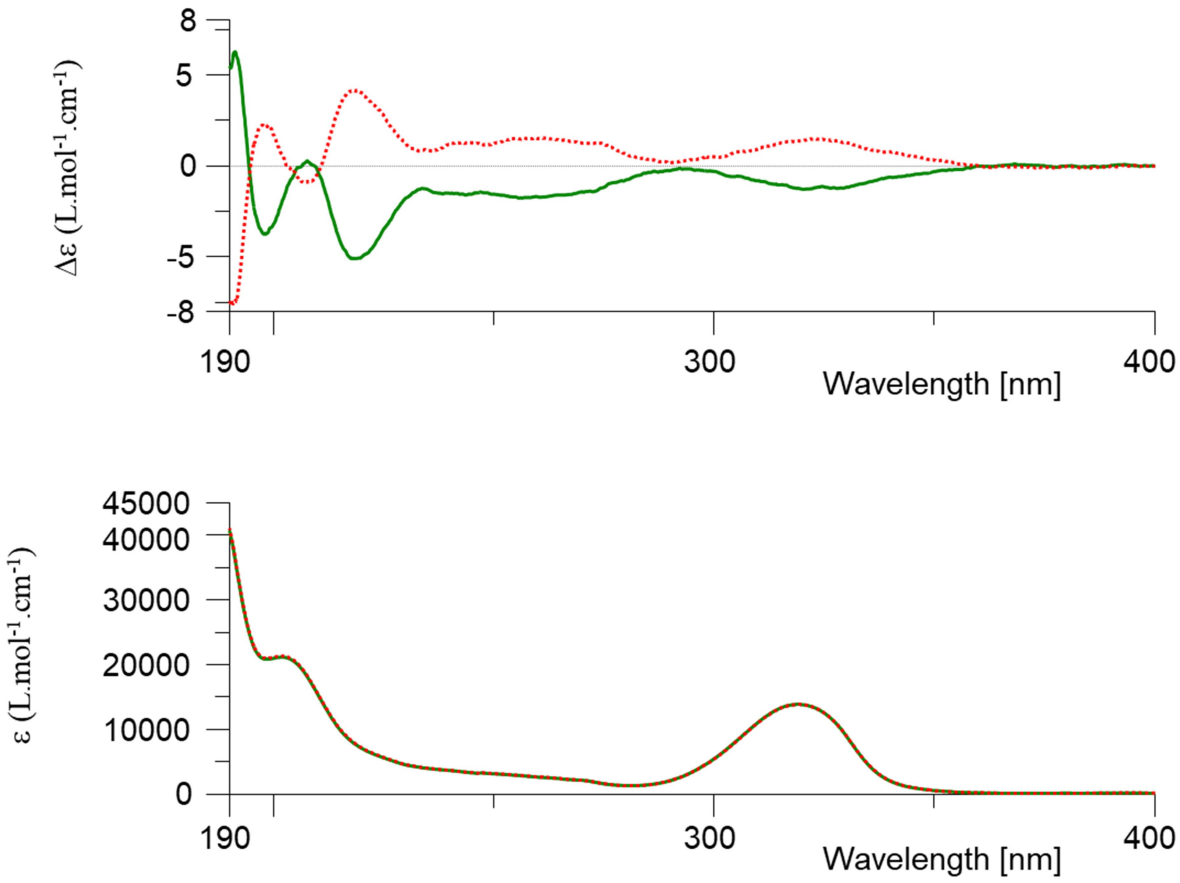
- first eluted enantiomer: green solid line, concentration = 0.387 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.387 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **3c**



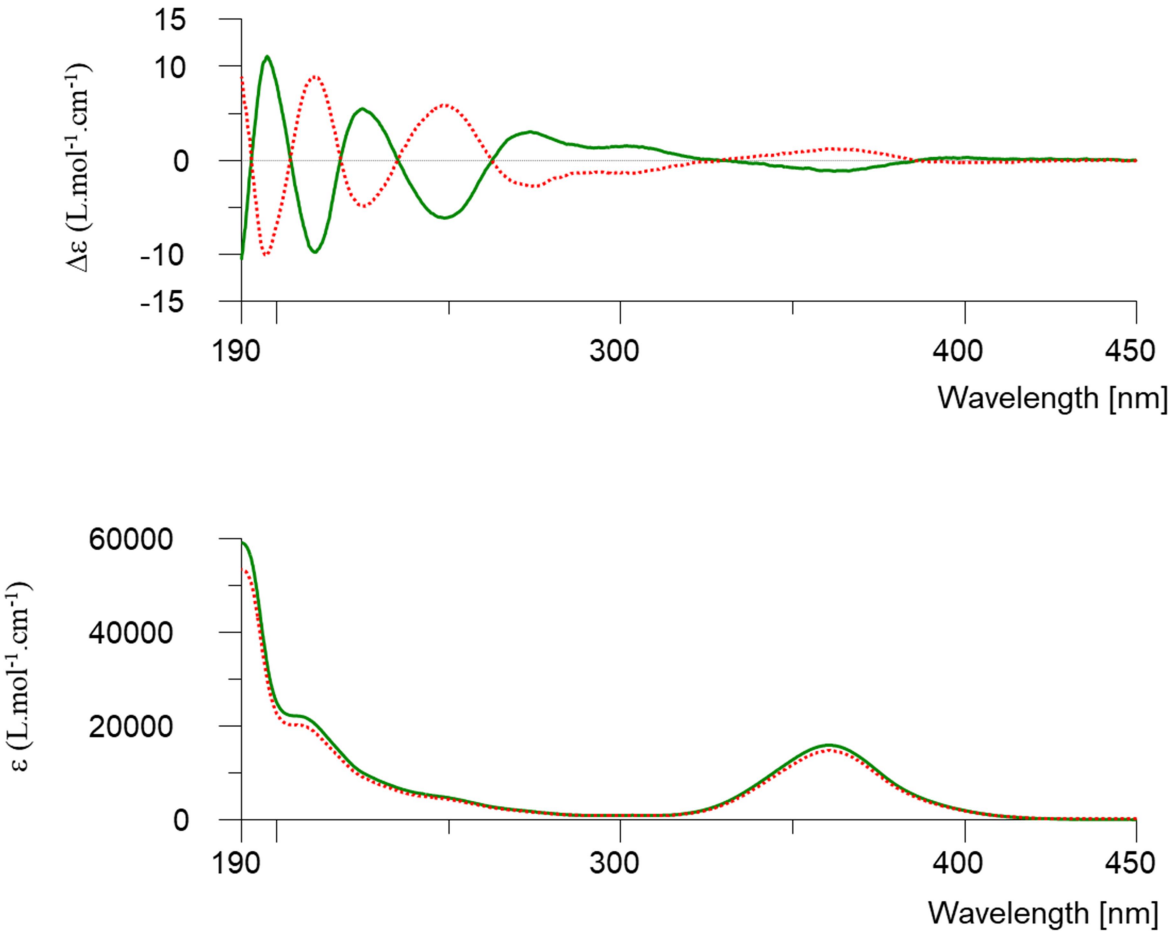
- first eluted enantiomer: green solid line, concentration = 0.500 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.496 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **3d**



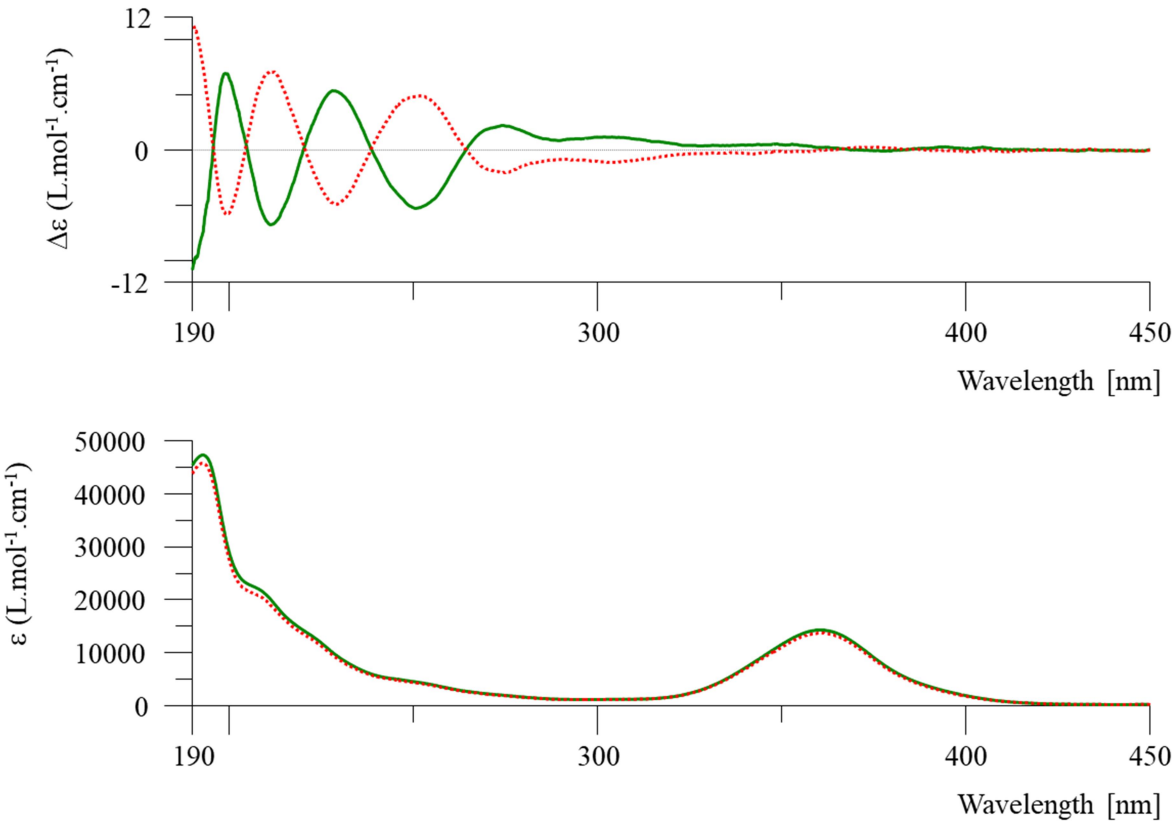
- first eluted enantiomer: green solid line, concentration = 0.402 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.405 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **5a**



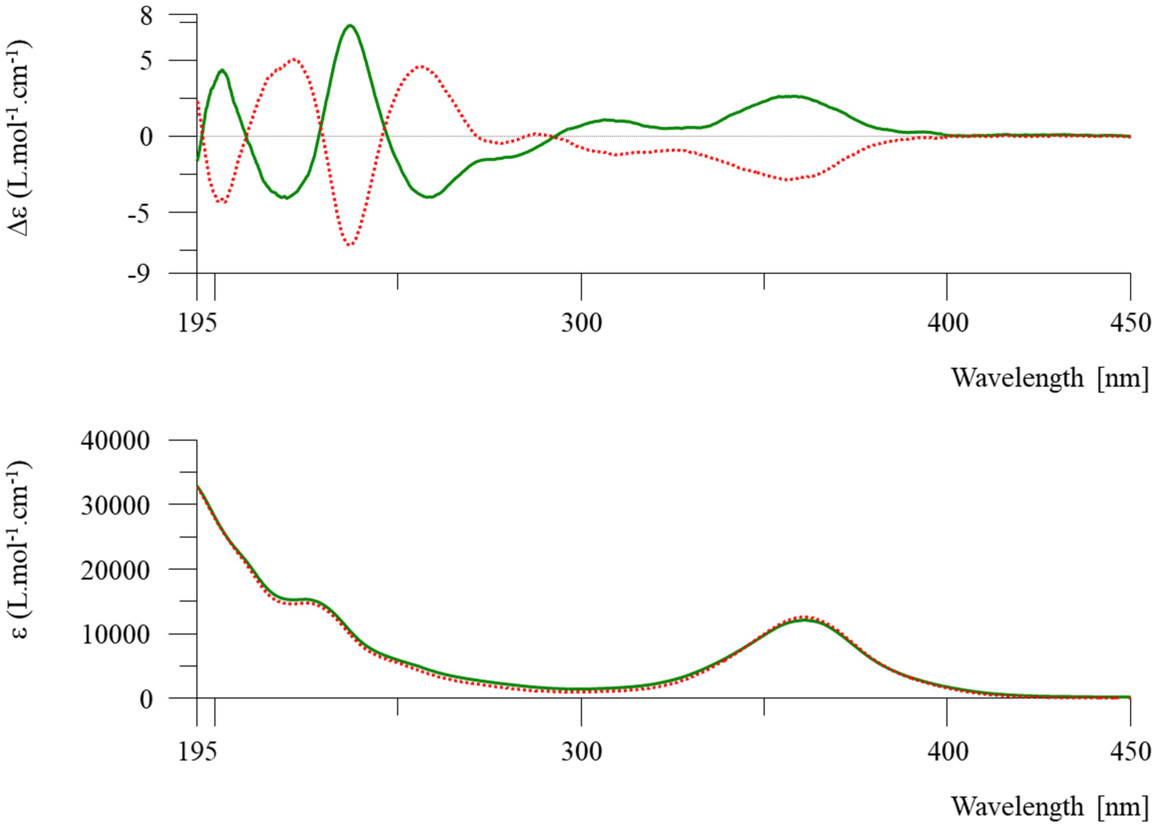
- first eluted enantiomer: green solid line, concentration = 0.284 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.350 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **6b**



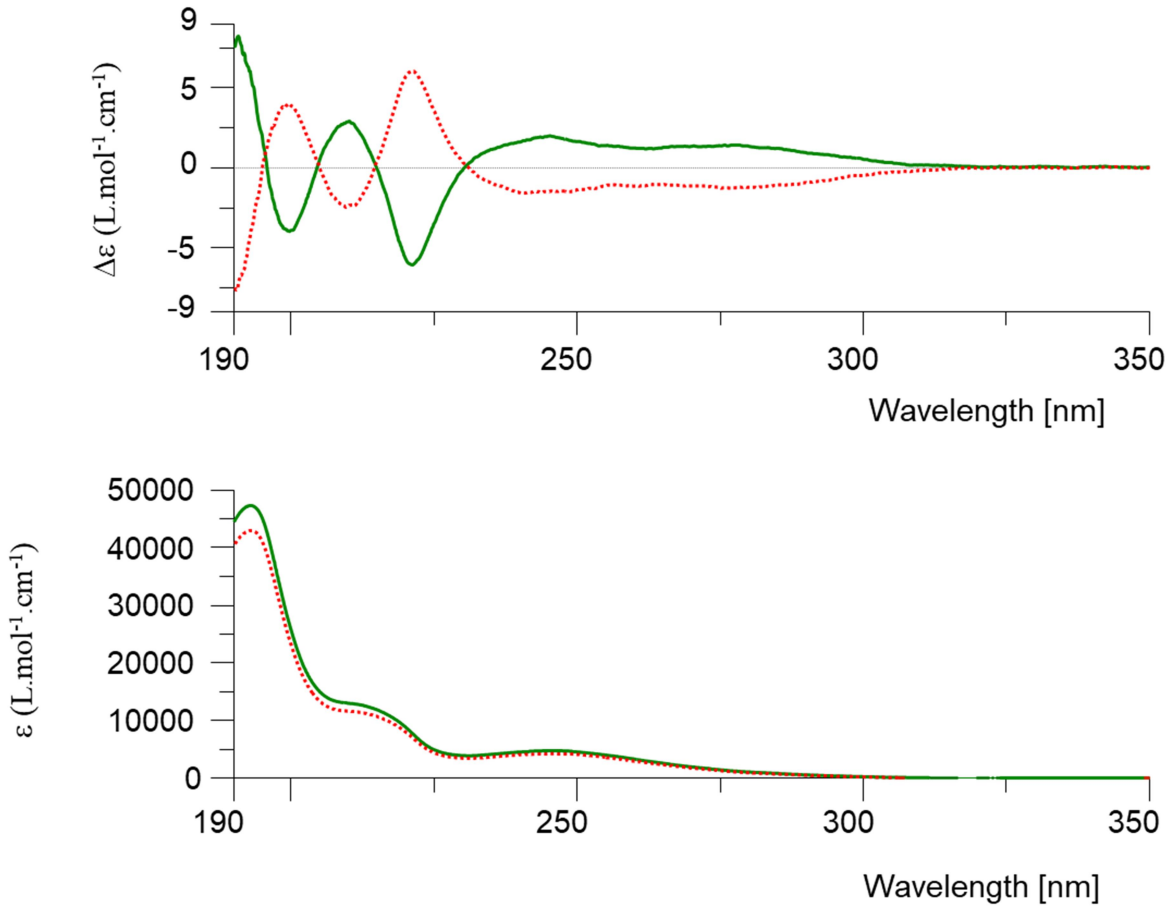
- first eluted enantiomer: green solid line, concentration = 0.412 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.374 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **6c**



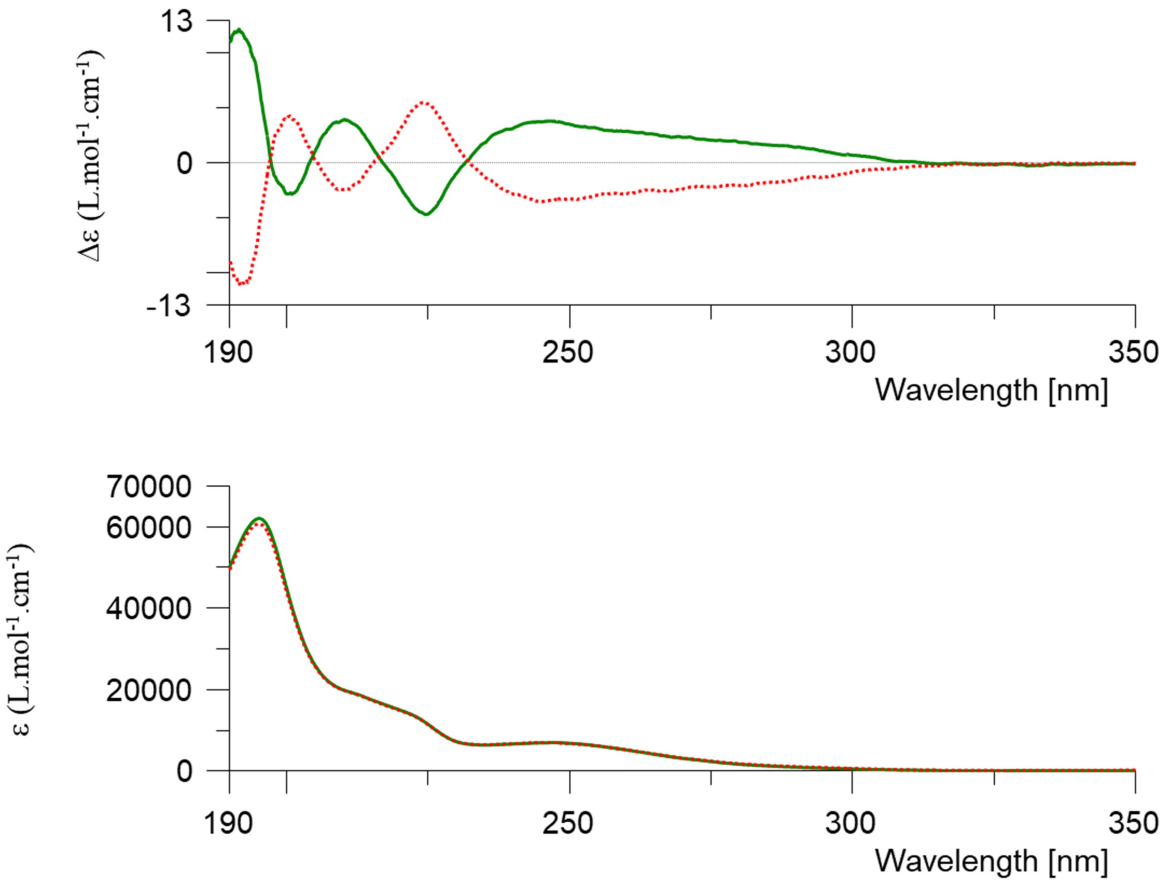
- first eluted enantiomer: green solid line, concentration = 0.564 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.447 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **6d**



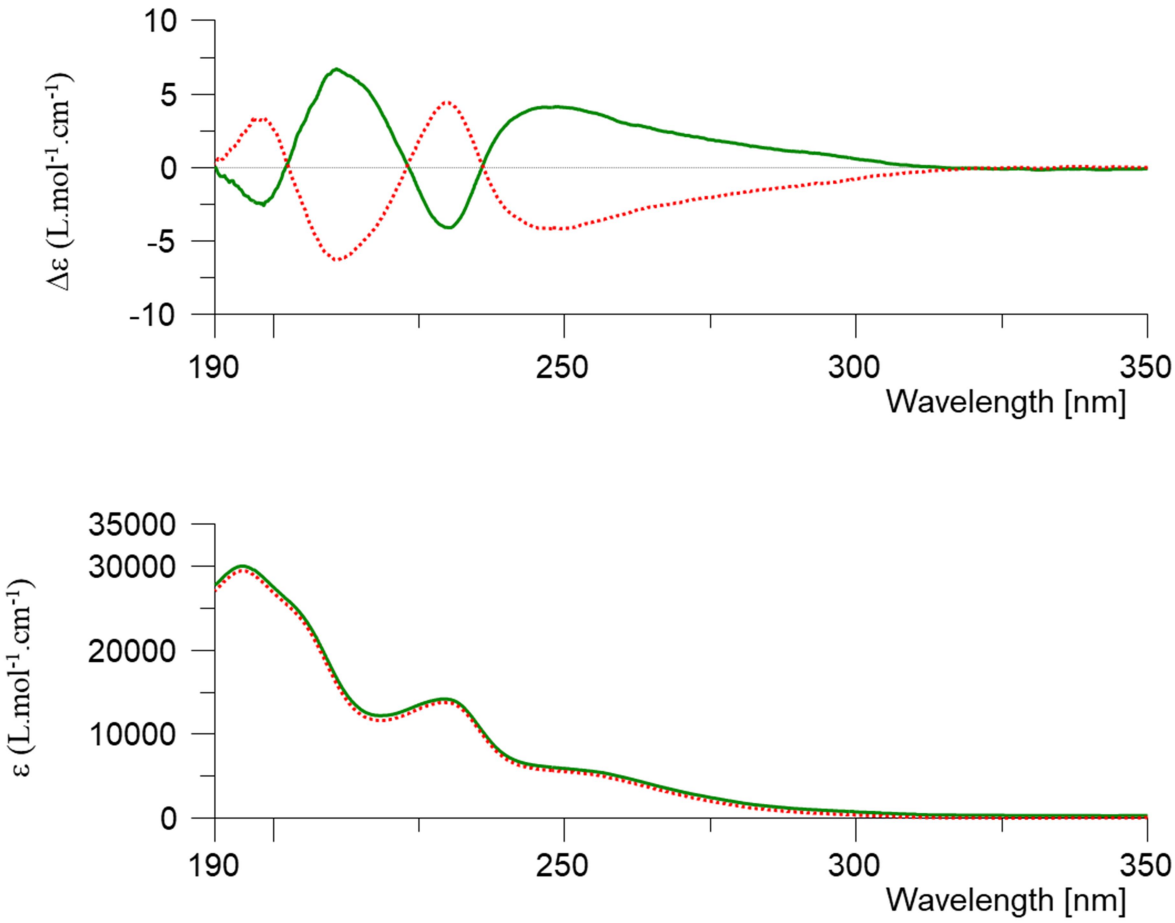
- first eluted enantiomer: green solid line, concentration = 0.421 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.484 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **7b**



- first eluted enantiomer: green solid line, concentration = 0.305 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.297 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **7c**



- first eluted enantiomer: green solid line, concentration = 0.540 mmol.L^{-1} in acetonitrile.
- second eluted enantiomer: red dotted line, concentration = 0.532 mmol.L^{-1} in acetonitrile.

ECD (up) and UV (down) spectra of **7d**