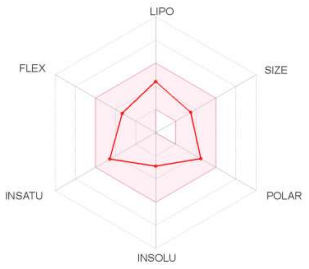
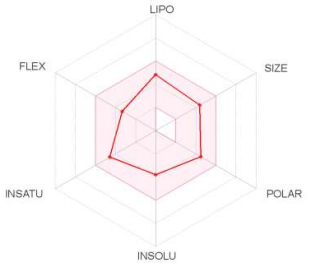
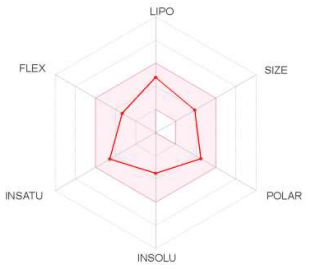
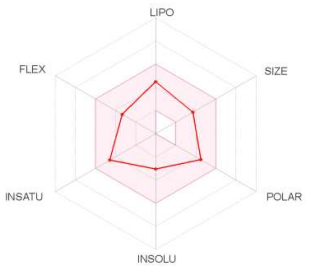
Supplementary Information

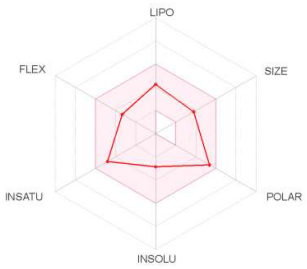
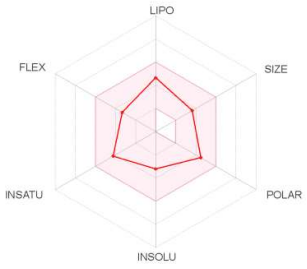
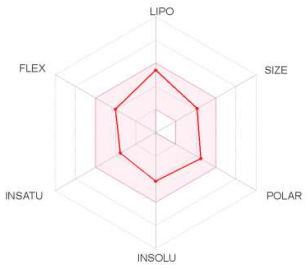
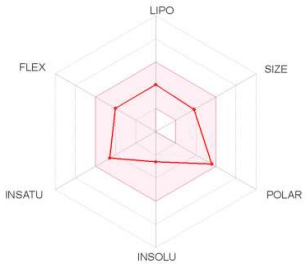
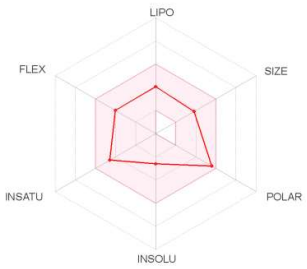
Stereoselective synthesis of tri-substituted tetrahydrothiophenes and their in silico binding against mycobacterial protein tyrosine phosphatase B

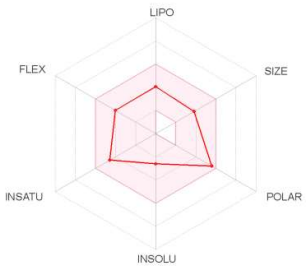
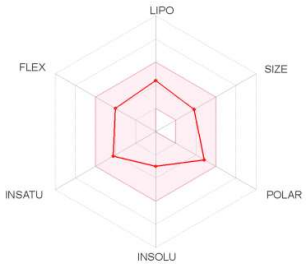
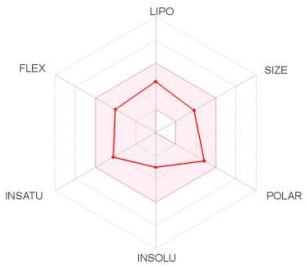
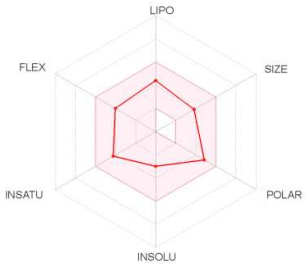
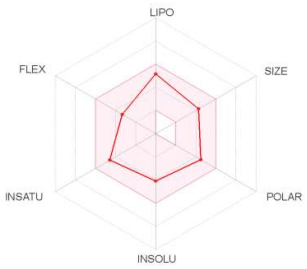
Anshul Jain,[a] Sushobhan Maji,[b] Khyati Shukla,[c] Akanksha Kumari,[a] Shivani Garg,[b] Ramesh K. Metre,[a] Sudipta Bhattacharyya,[*b] and Nirmal K. Rana,[*a]

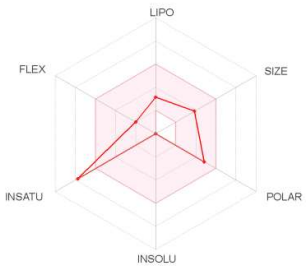
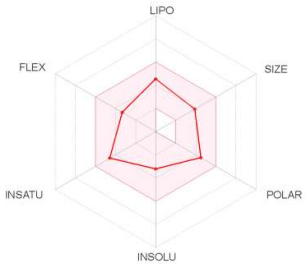
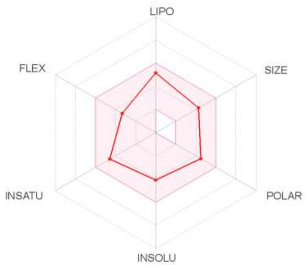
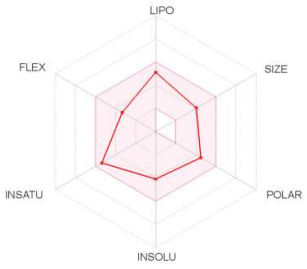
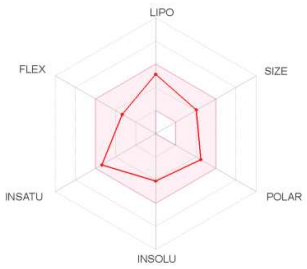
[a]Department of Chemistry, Indian Institute of Technology Jodhpur, Rajashtan-342037, India; [b]Department of Bioscience and Bioengineering, Indian Institute of Technology Jodhpur, Rajashtan-342037, India; [c]Department of Chemistry, Indian Institute of Technology Kanpur, Uttar Pradesh-208016, India.

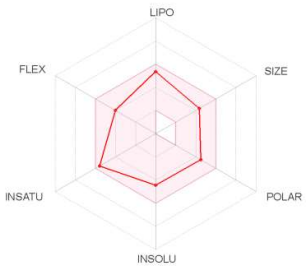
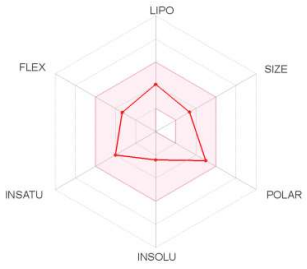
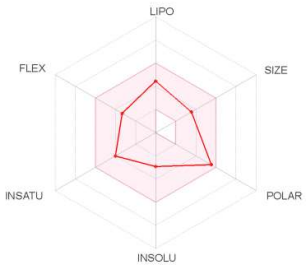
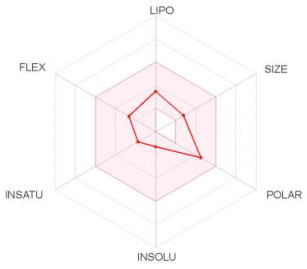
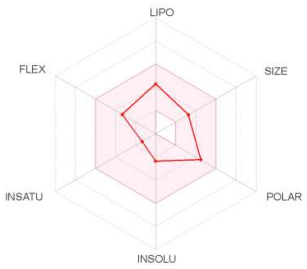
Table S1: *In silico* based analysis of standard pharmacokinetic properties and MptpB active site binding profiles of synthesized THT derivatives.

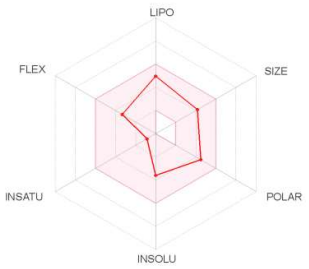
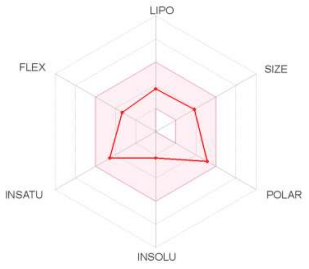
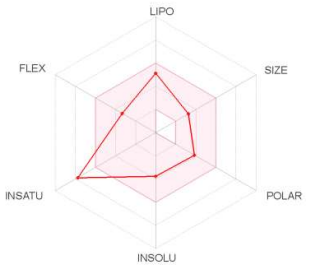
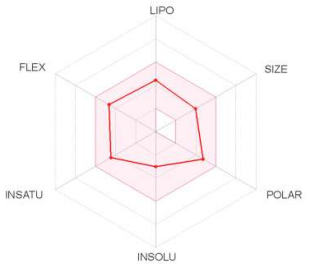
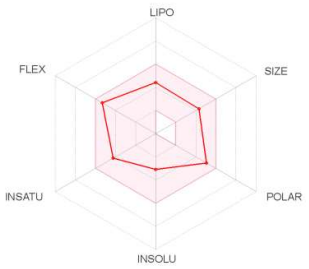
Ligand (Tetrahydrothiophenes derivatives)			**Binding affinity (Kcal/mol)**	
Molecules Number	**ADME plot**	**pKd**	**Swissdock**	**Autodock vina**
3a		5.91	-7.50	-8.5
3b		6.02	-8.21	-6.5
3c		5.72	-7.87	-7.8
3d		5.73	-7.80	-8.6

3e		5.78	-8.52	-8.5
3f		5.54	-8.30	-8.5
3g		6.18	-8.15	-7.7
3h		5.98	-8.57	-8.4
3i		5.89	-7.93	-8.6

3j		5.84	-8.10	-8.7
3k		6.26	-7.49	-8.2
3l		6.35	-8.47	-6.6
3m		6.25	-7.80	-6.4
3n		6.84	-8.65	-8.1

3o		6.46	-7.91	-8.4
3p		6.23	-8.10	-8.5
3q		6.80	-8.25	-8.3
3s		6.55	-7.79	-8.0
3t		4.84	-7.83	-8.0

3u		6.42	-8.10	-10.0
3v		5.06	-7.52	-6.2
3w		5.64	-7.33	-6.0
3x		4.35	-7.69	-6.4
3y		3.54	-7.53	-5.7

3z		5.25	-8.75	-7.6
4a		5.71	-7.38	-8.4
5a		5.68	-7.62	-6.7
6a		6.22	-7.52	-8.2
6k		6.13	-7.78	-8.9

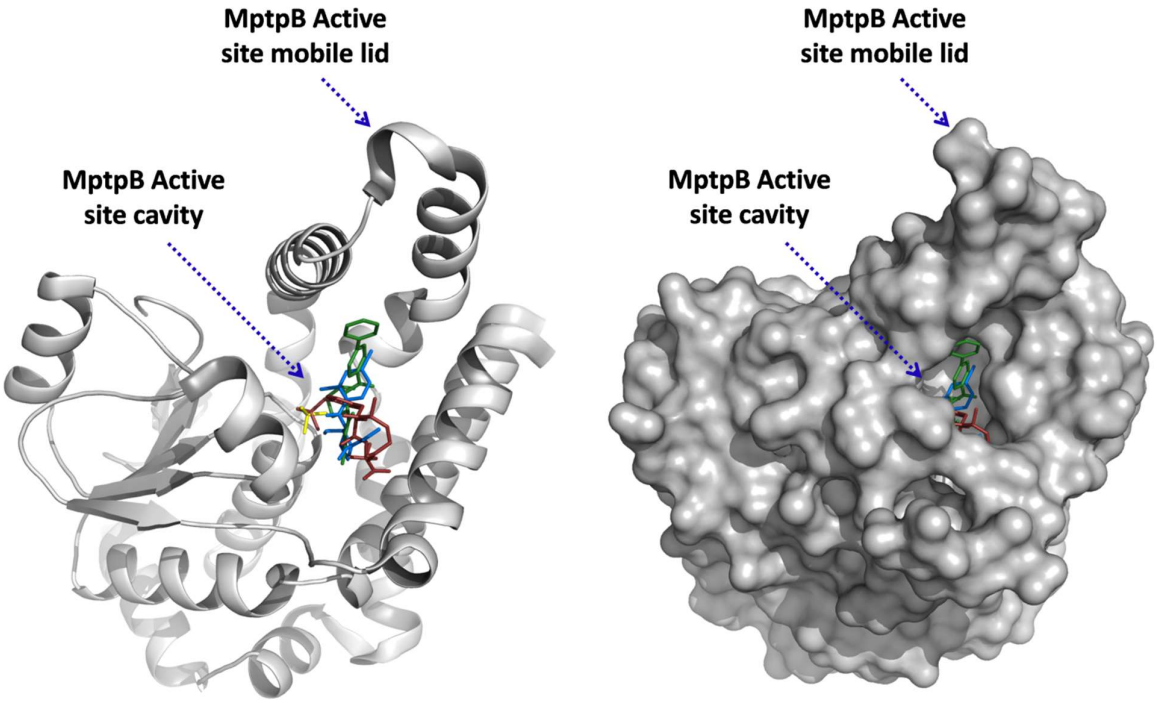


Figure S1. Mutually exclusive MptpB binding site of synthesized THT derivatives (compound **3n**, compound **3u**), physiological substrate mimicking phospho tyrosine containing tripeptide (pYL) and the product phosphate. All the ligands are represented as sticks at the active site cavity of MptpB; compound **3u** is colored green; compound **3n** is colored marine blue; phospho tyrosine containing tripeptide is colored ruby red; product phosphate is colored yellow. Other than the product phosphate molecule, which is derived from the crystal structure of MptpB bound with the product phosphate (PDB Id: 1YWF), all the other ligand molecules are docked at the active site cavity of MptpB (indicated by dashed arrow). The position of active site guarding mobile lid is also indicated by the dashed arrow.

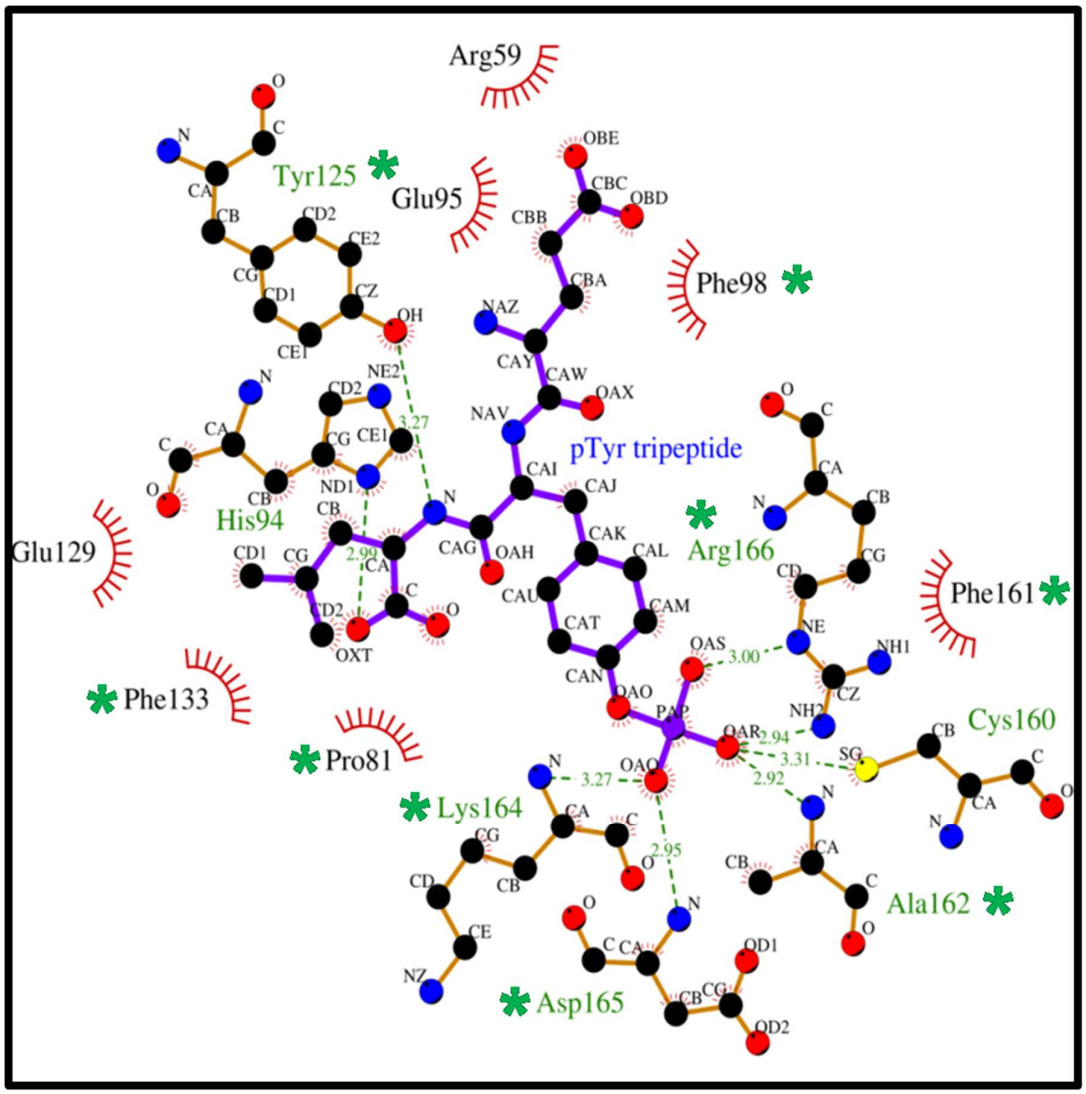


Fig. S2. Zoomed in view of Fig.1C right panel. The zoomed image clearly indicates the interaction profile of physiological substrate mimicking phosphotyrosyl tripeptide ligand (pYL) at the active site of MptpB. The common amino acid residues involved in pYL binding as well as binding of 3n and 3u THT ligands are highlighted with green asterisks. Green dotted lines indicate the formation of hydrogen bonds whereas red spiked arcs indicate hydrophobic interactions.

Molecular Dynamics (MD) Simulation

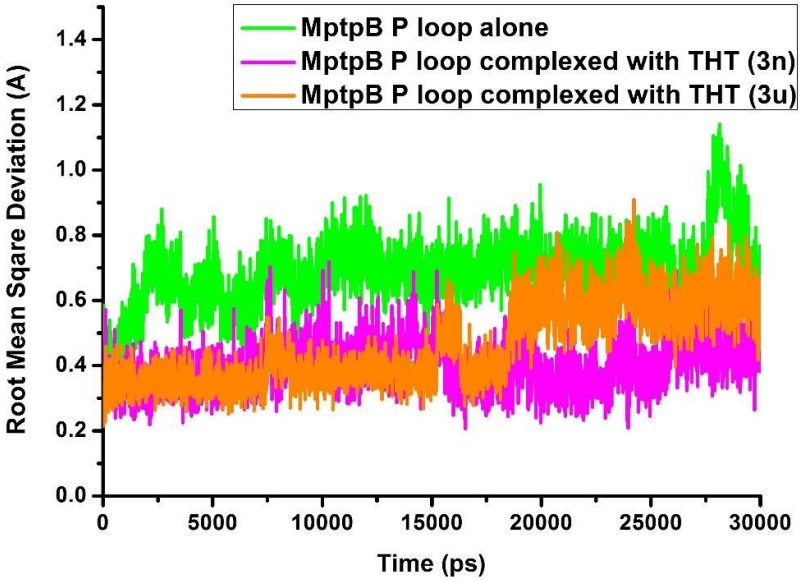
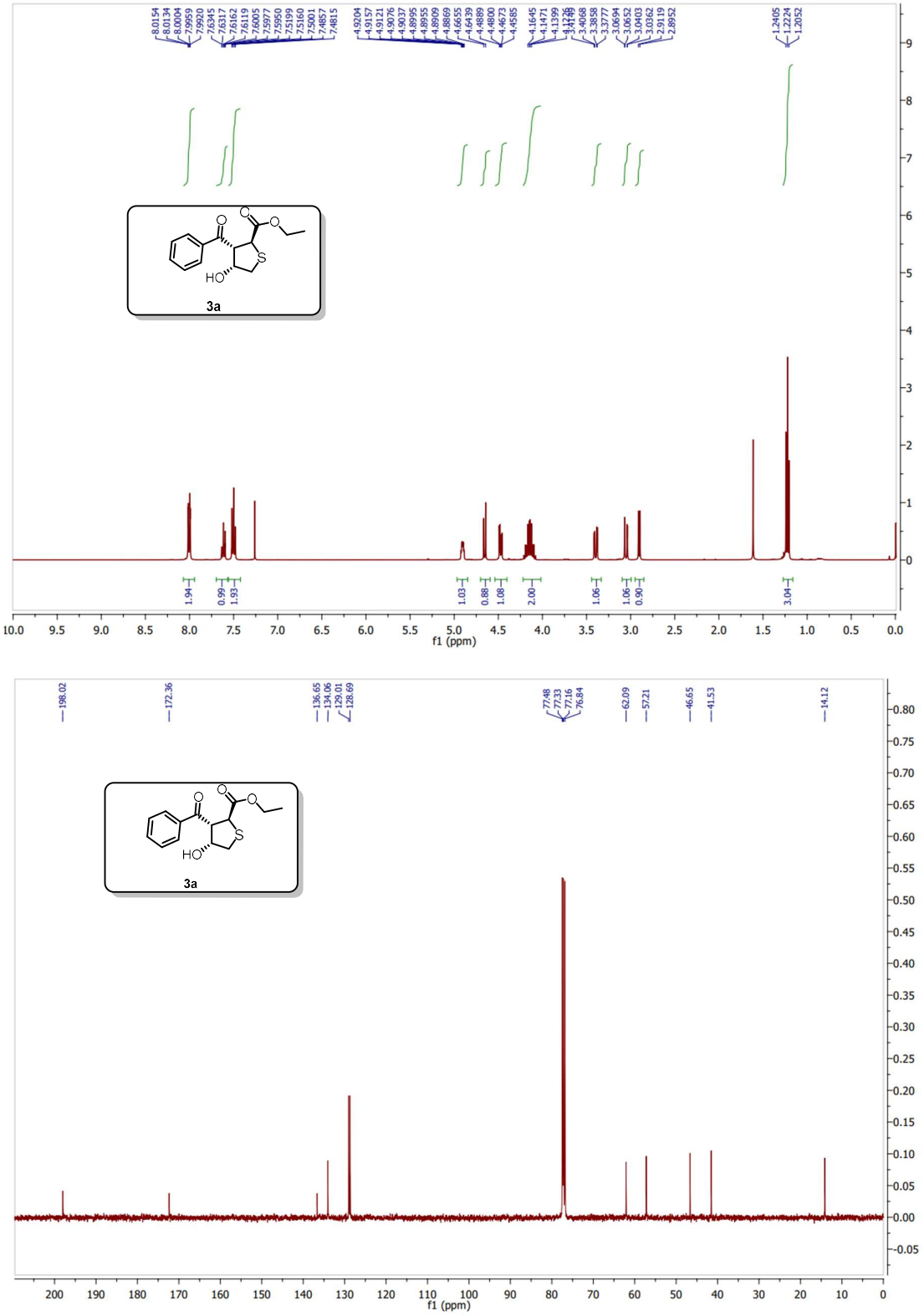
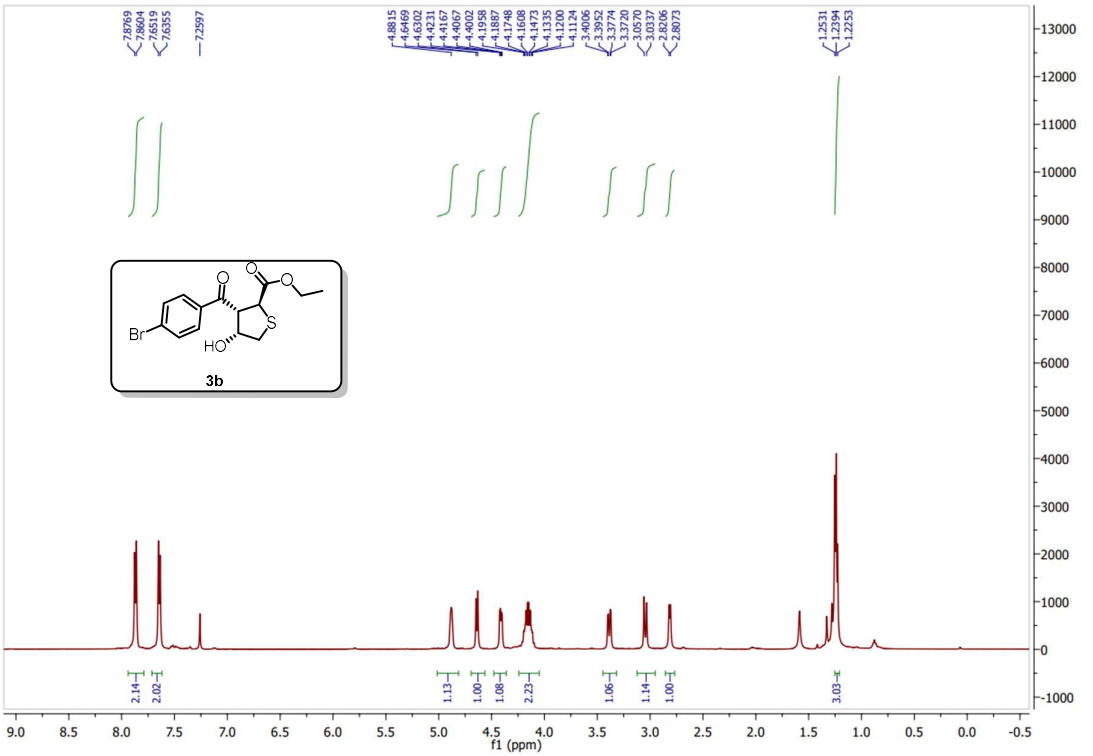


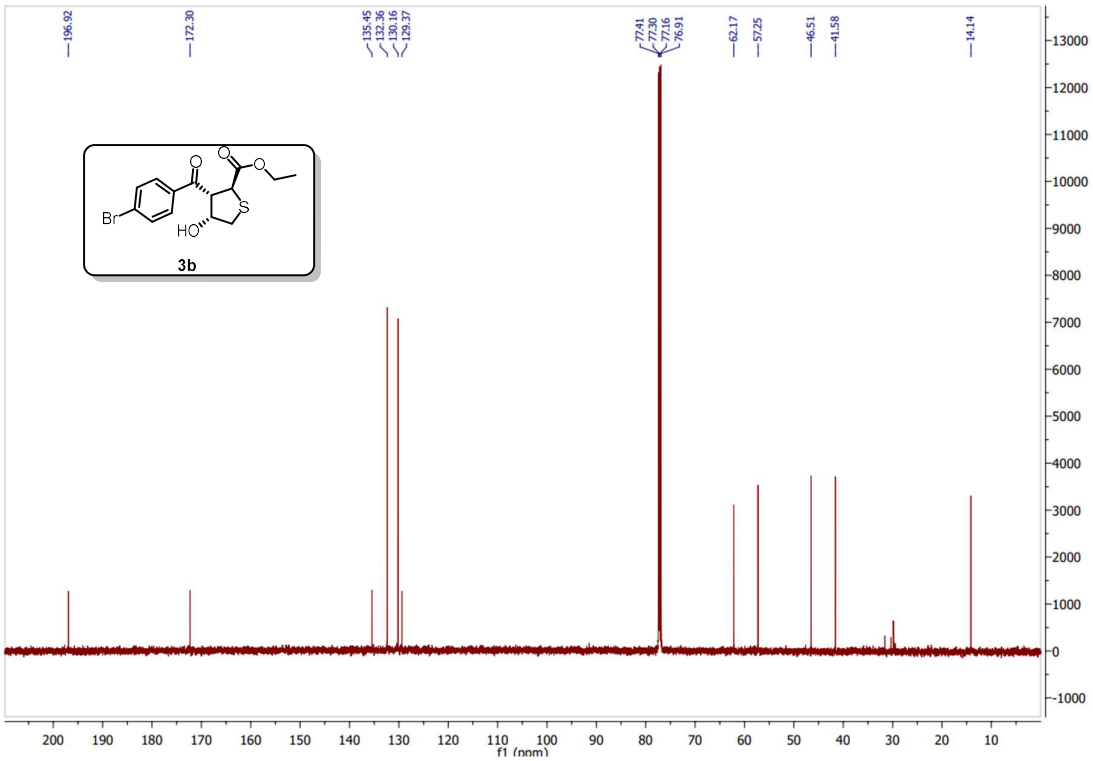
Fig. S3. Stability of MptpB active site P loop in presence of THT derivatives (3n and 3u).

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

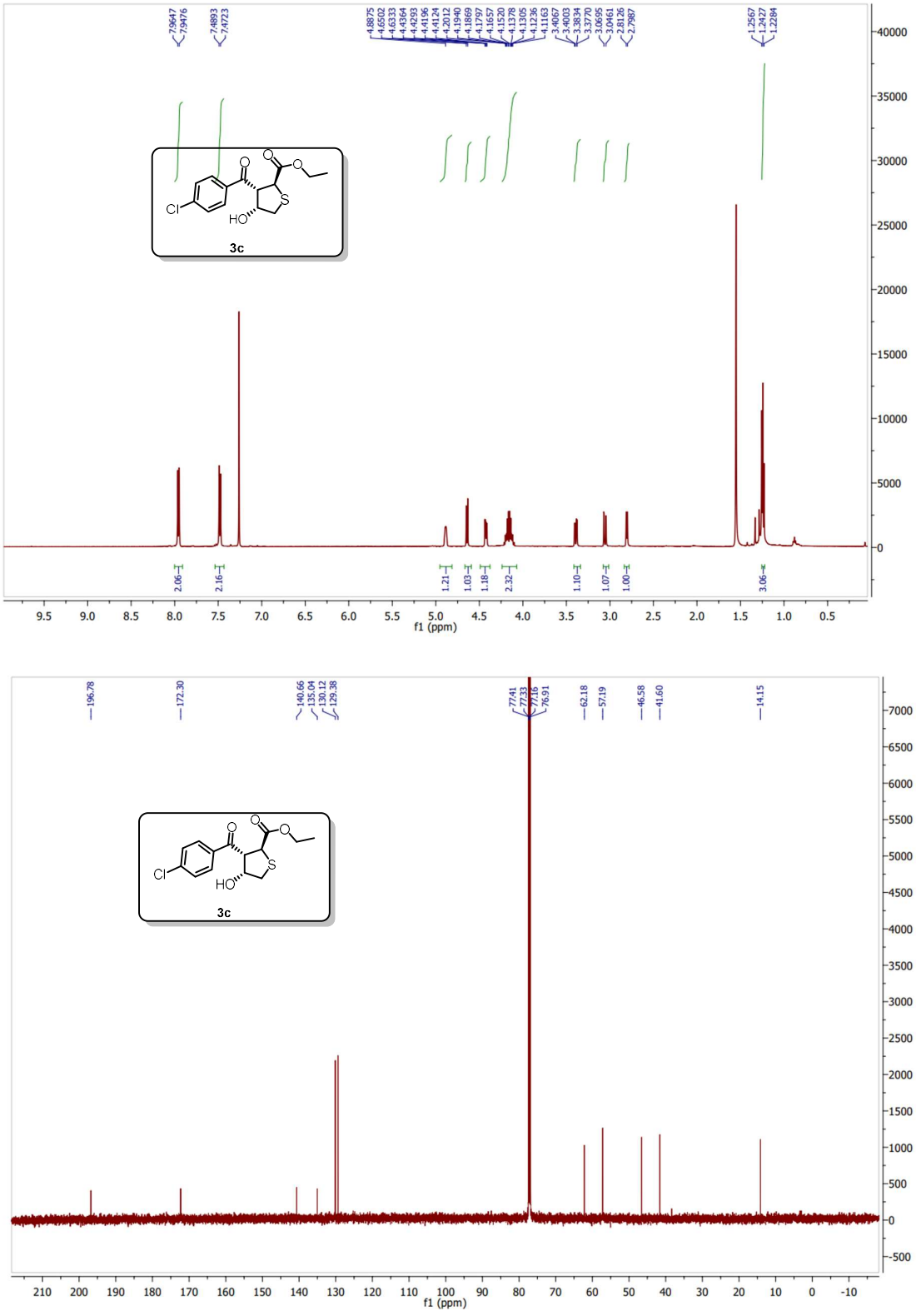


400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR Spectra of **3a**

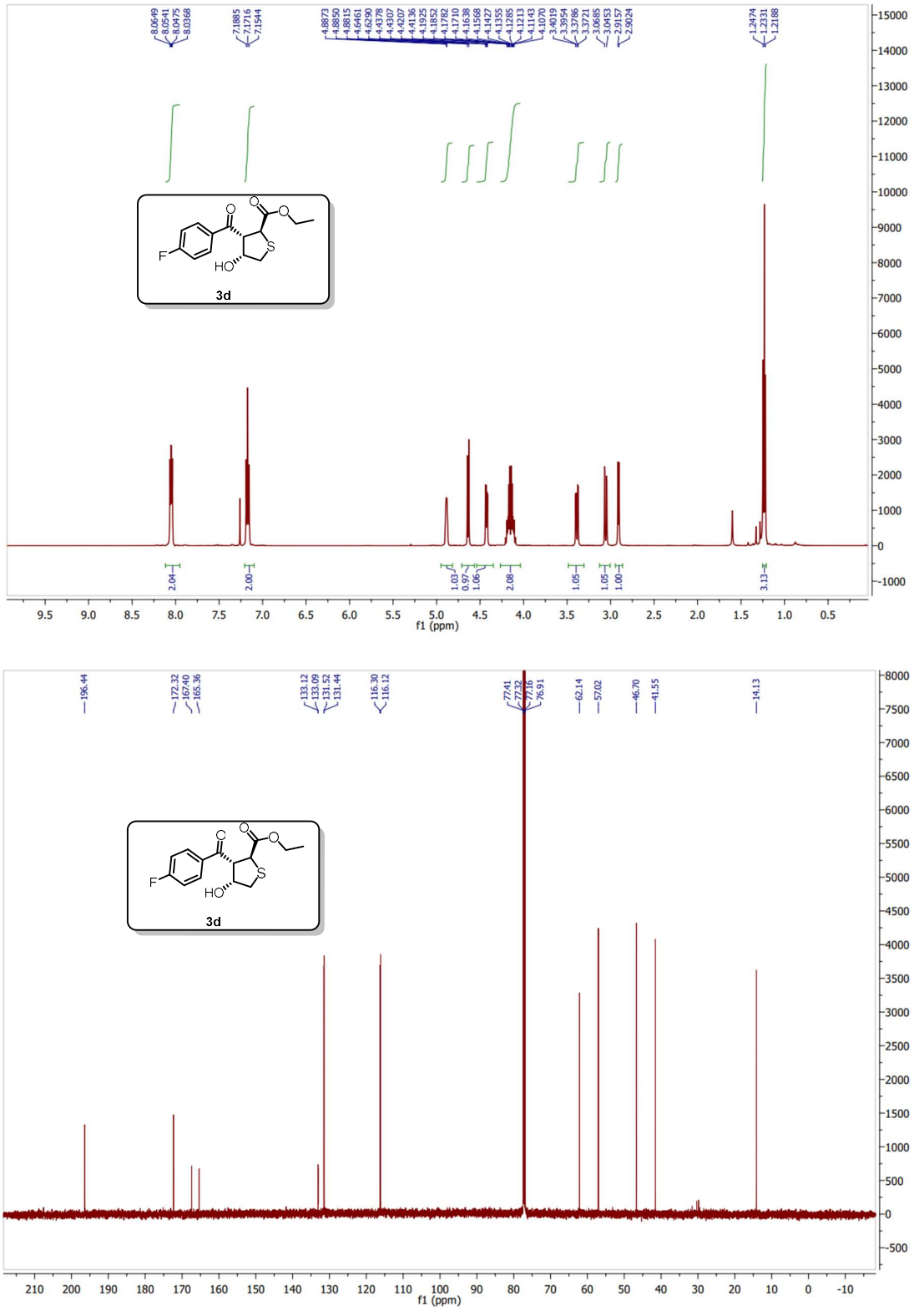




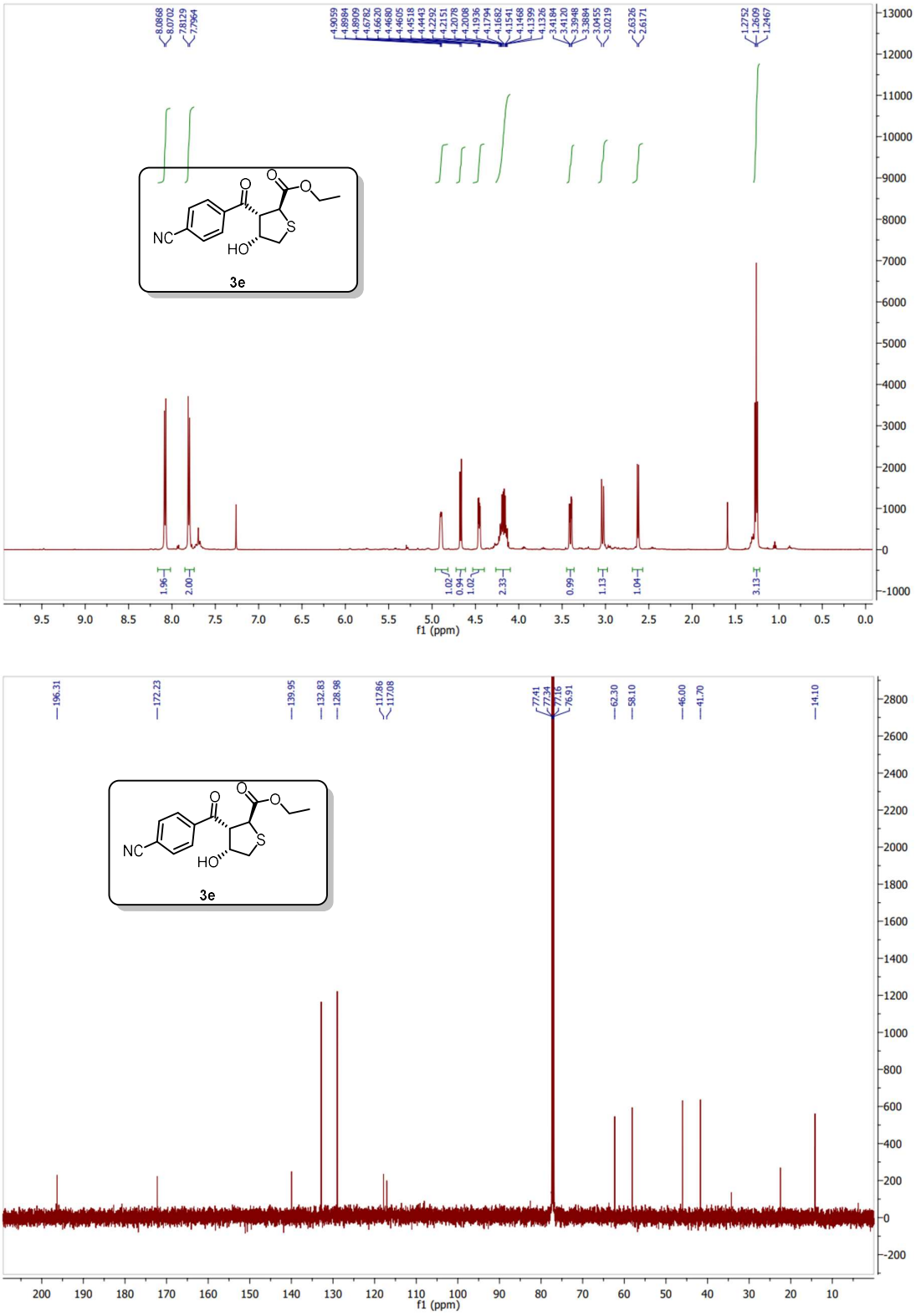
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3b**



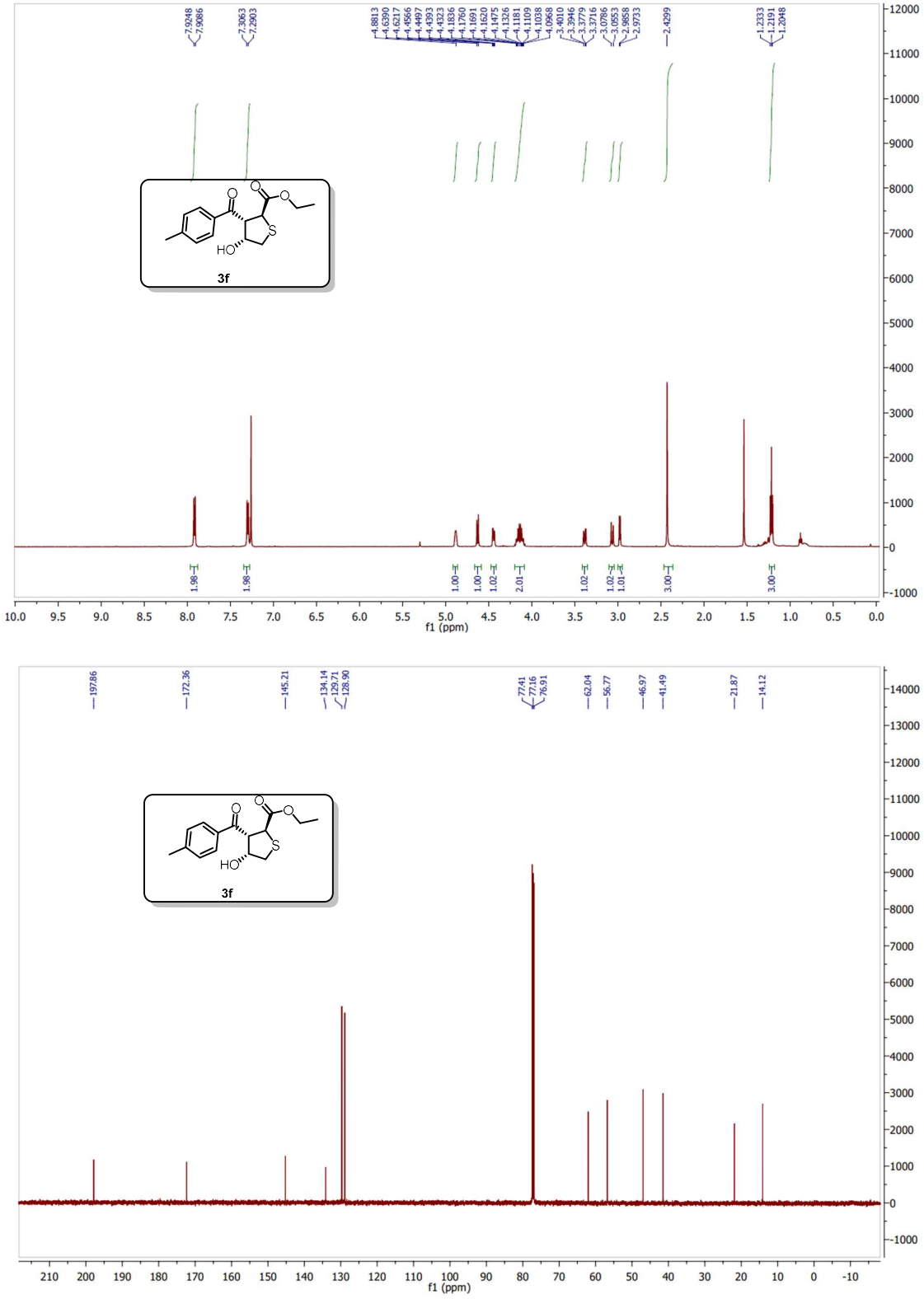
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3c**



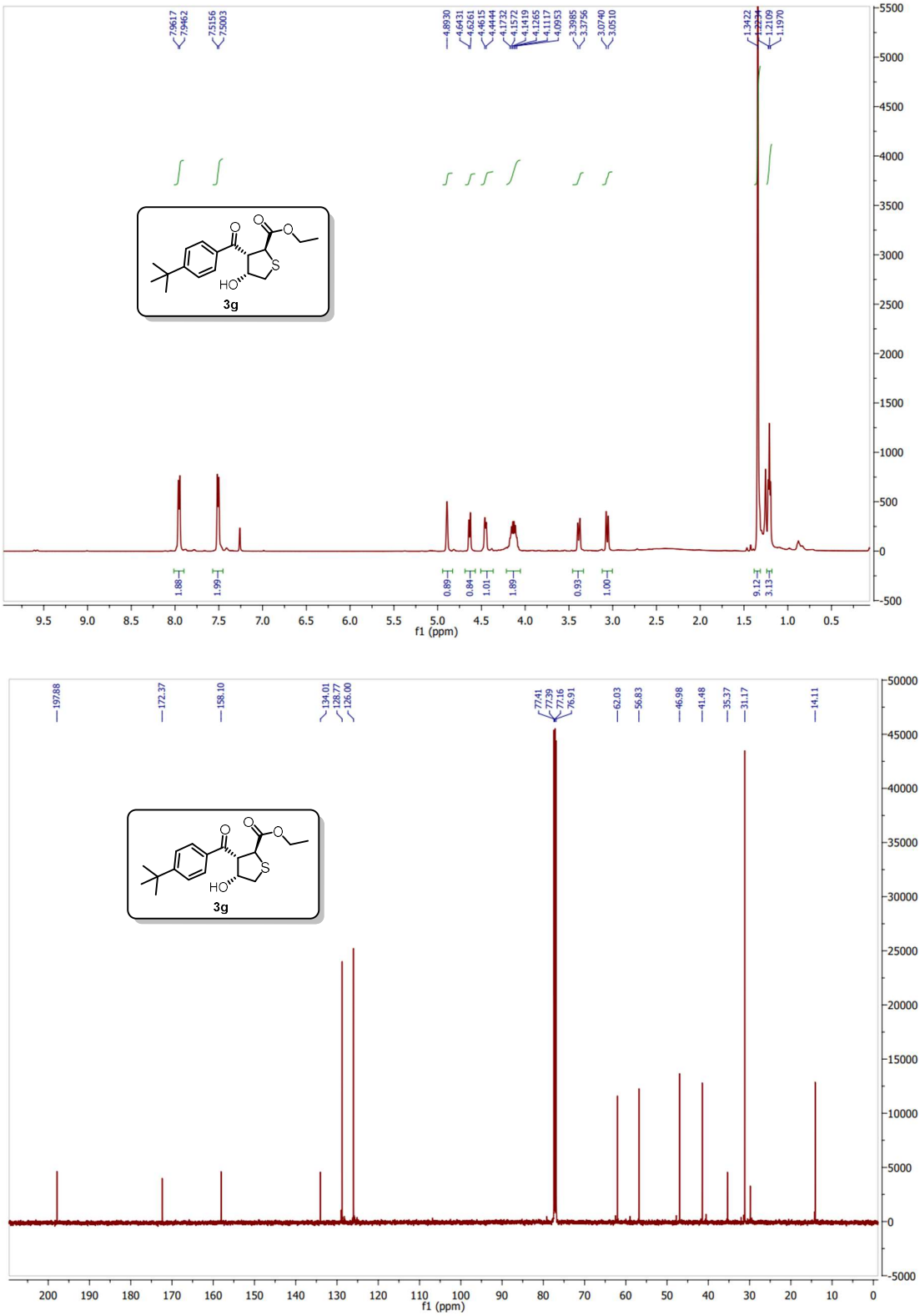
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3d**



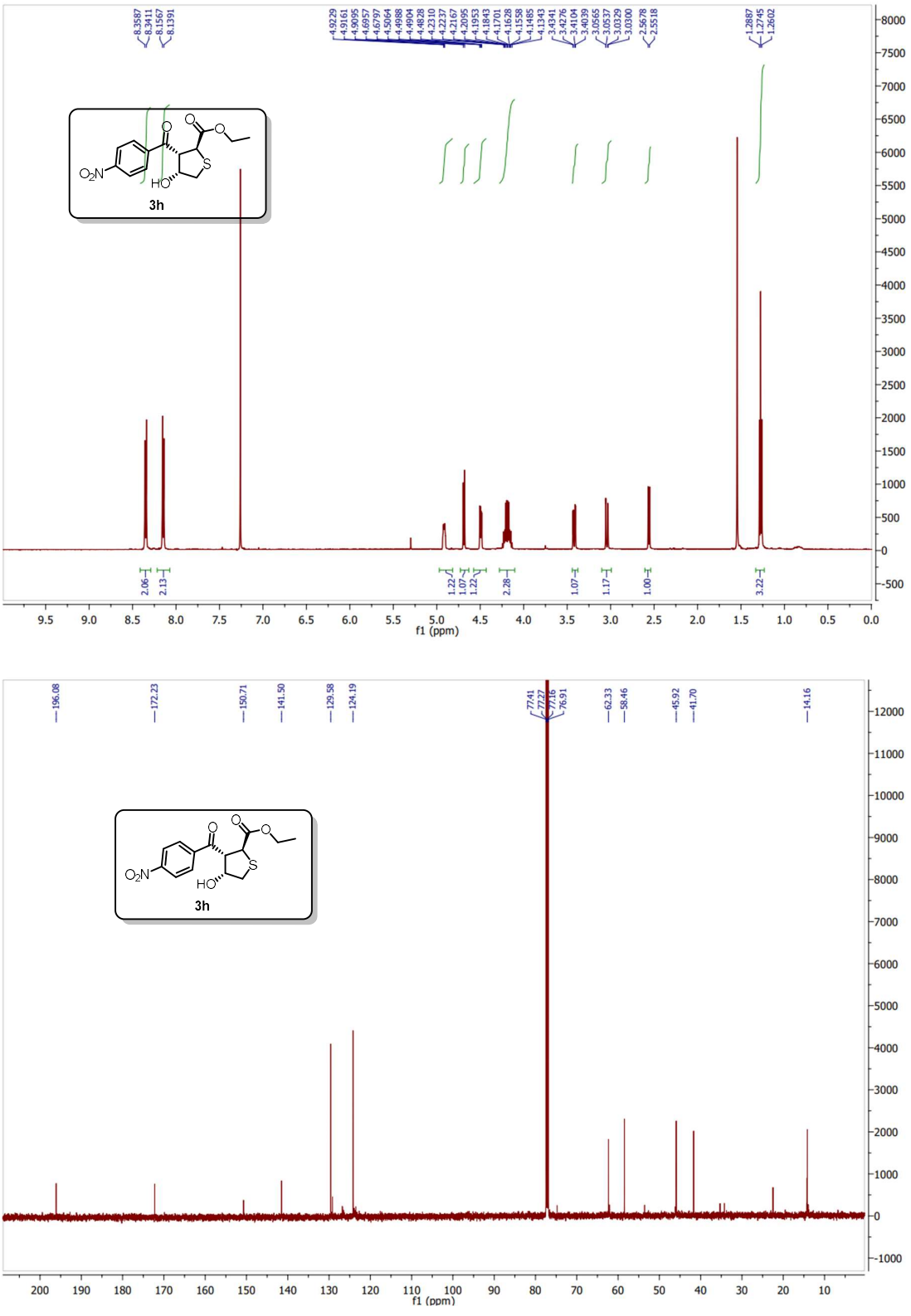
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3e**



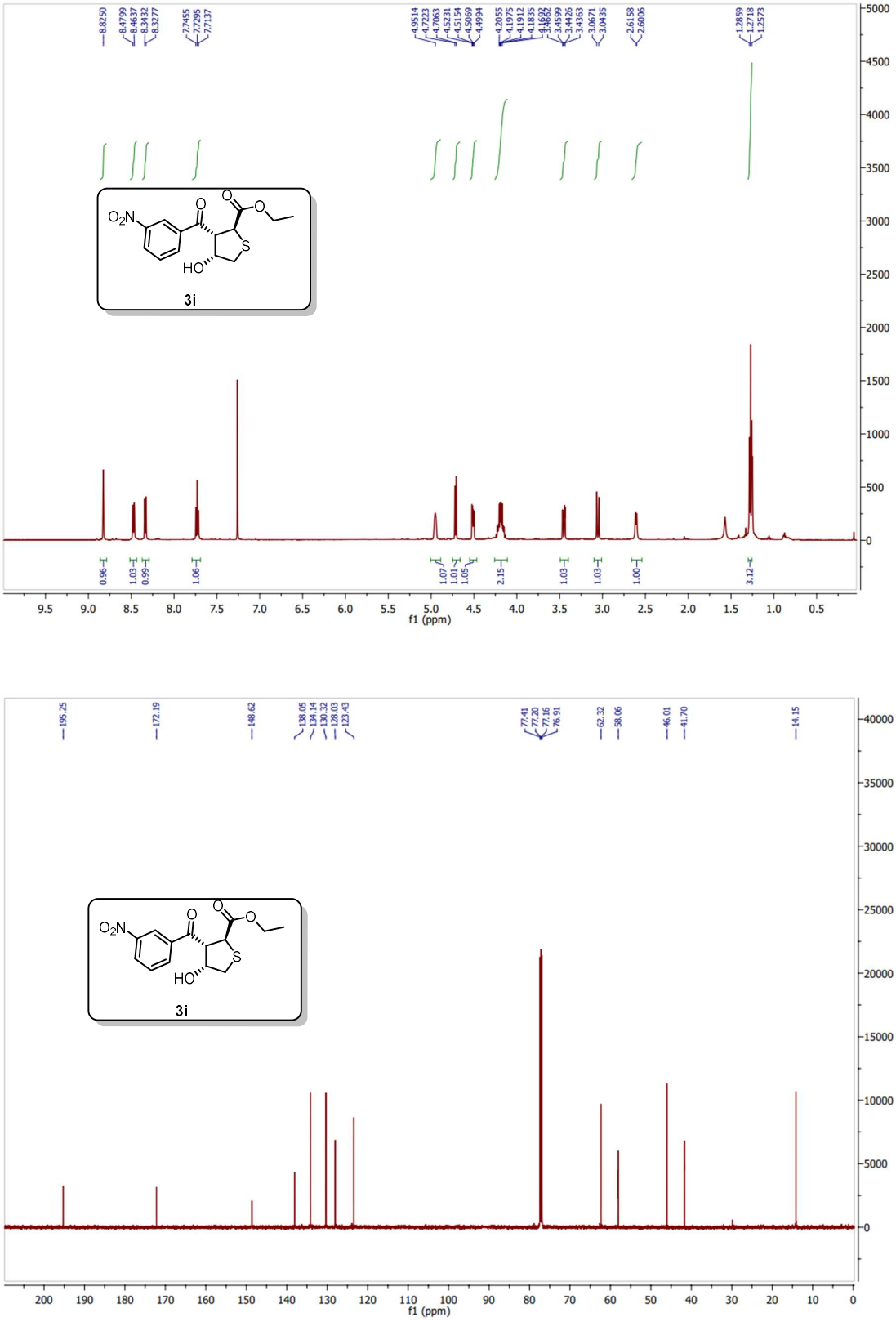
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3f**



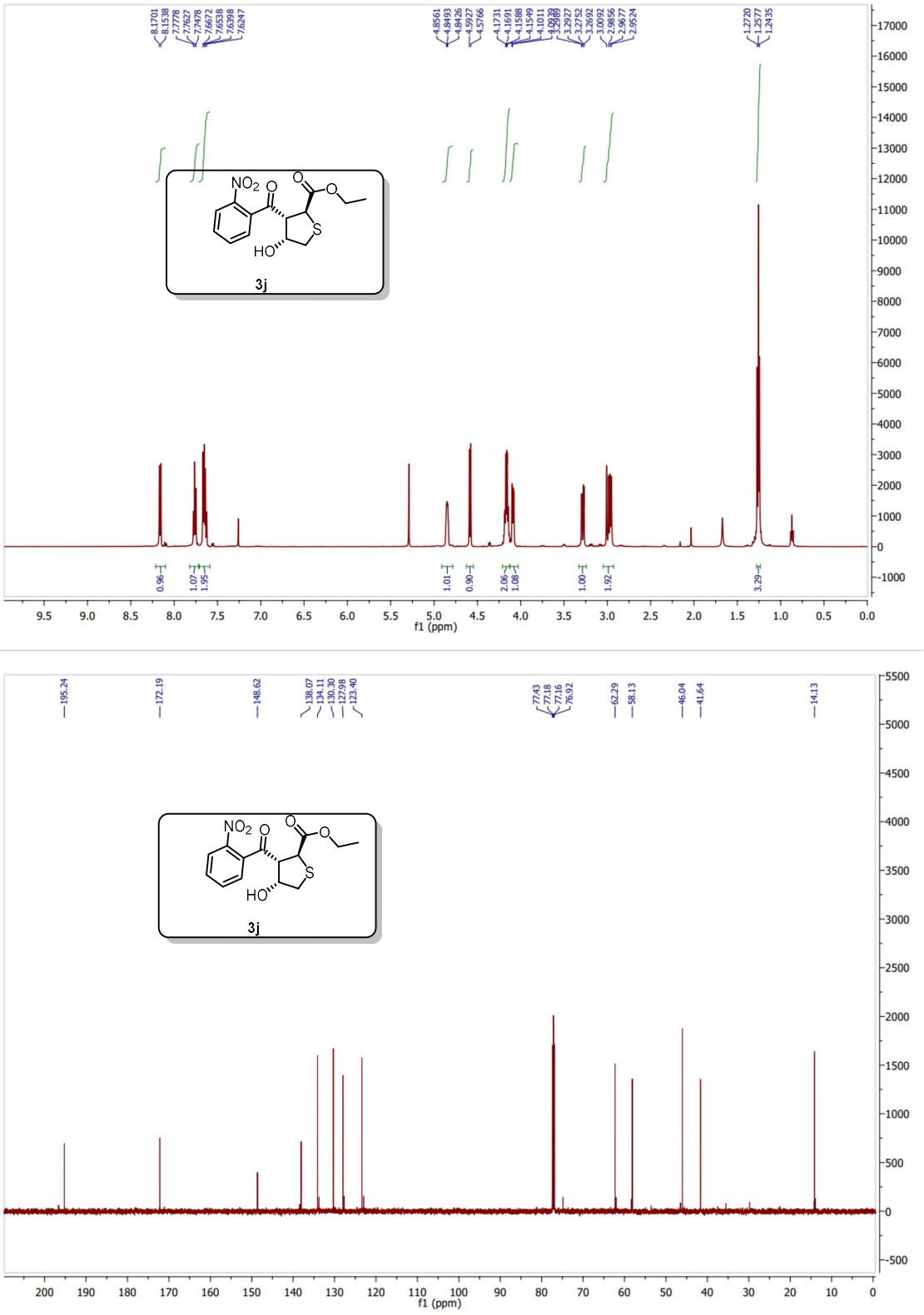
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3g**



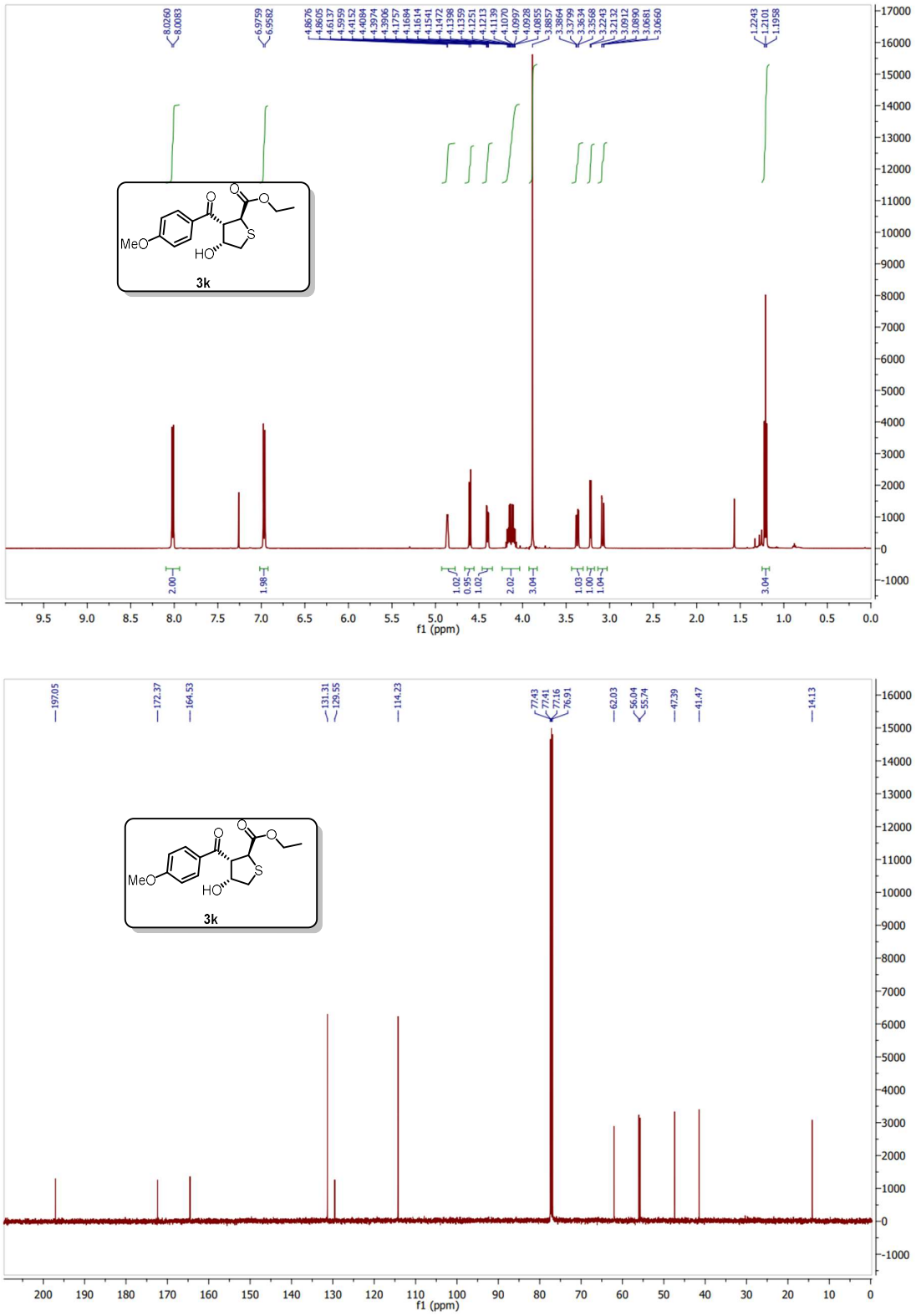
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3h**



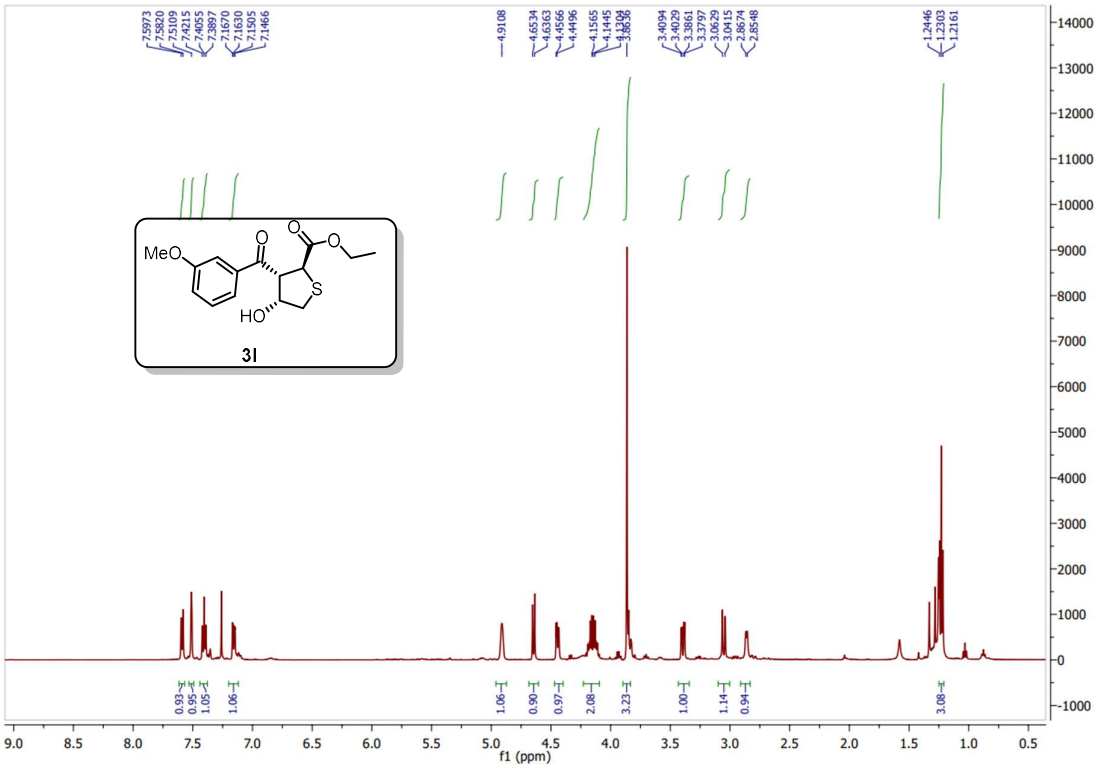
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3i**

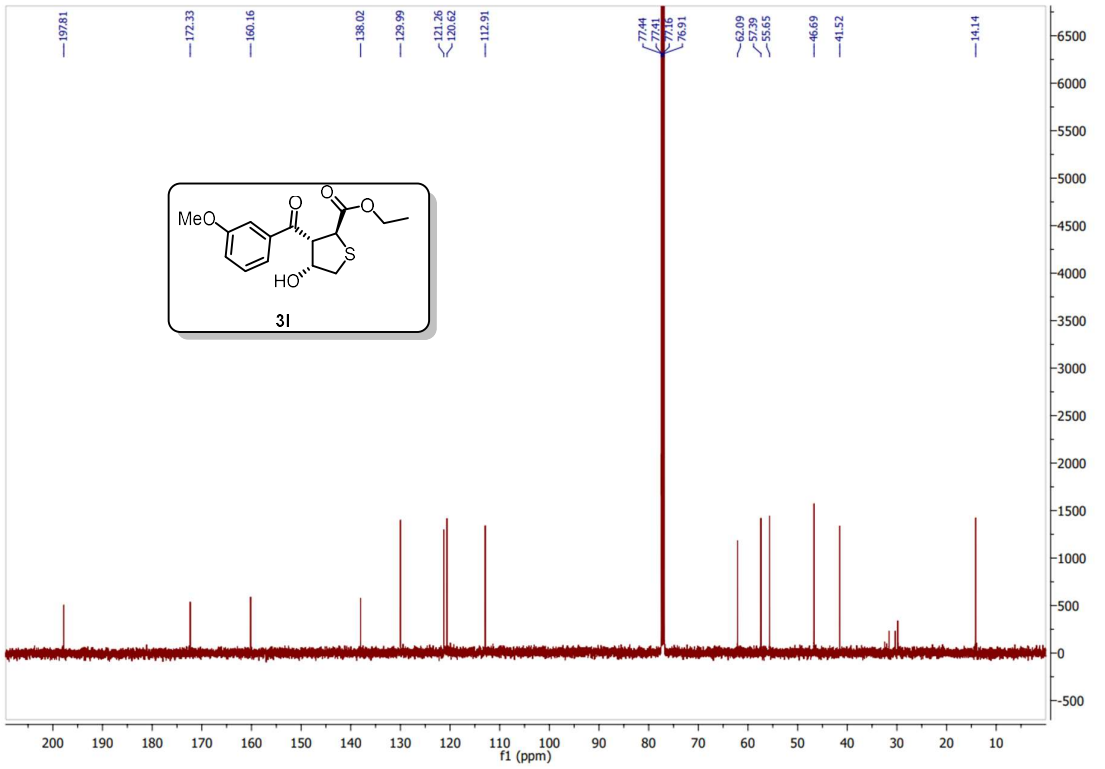


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3j**

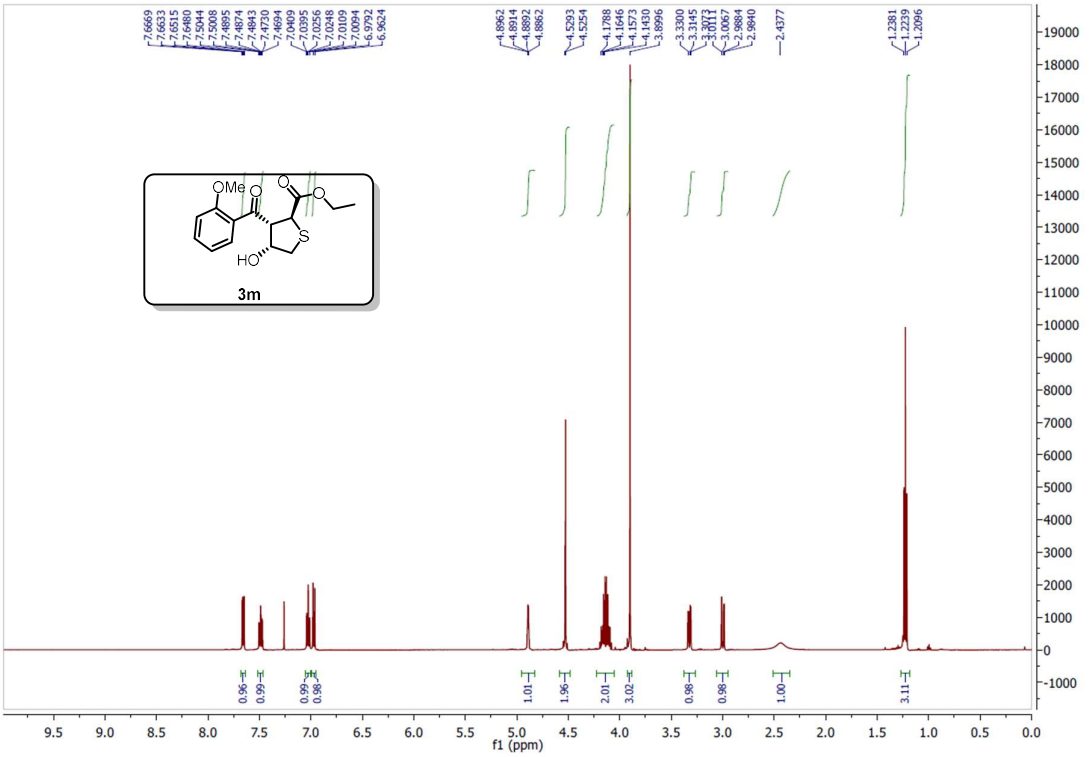


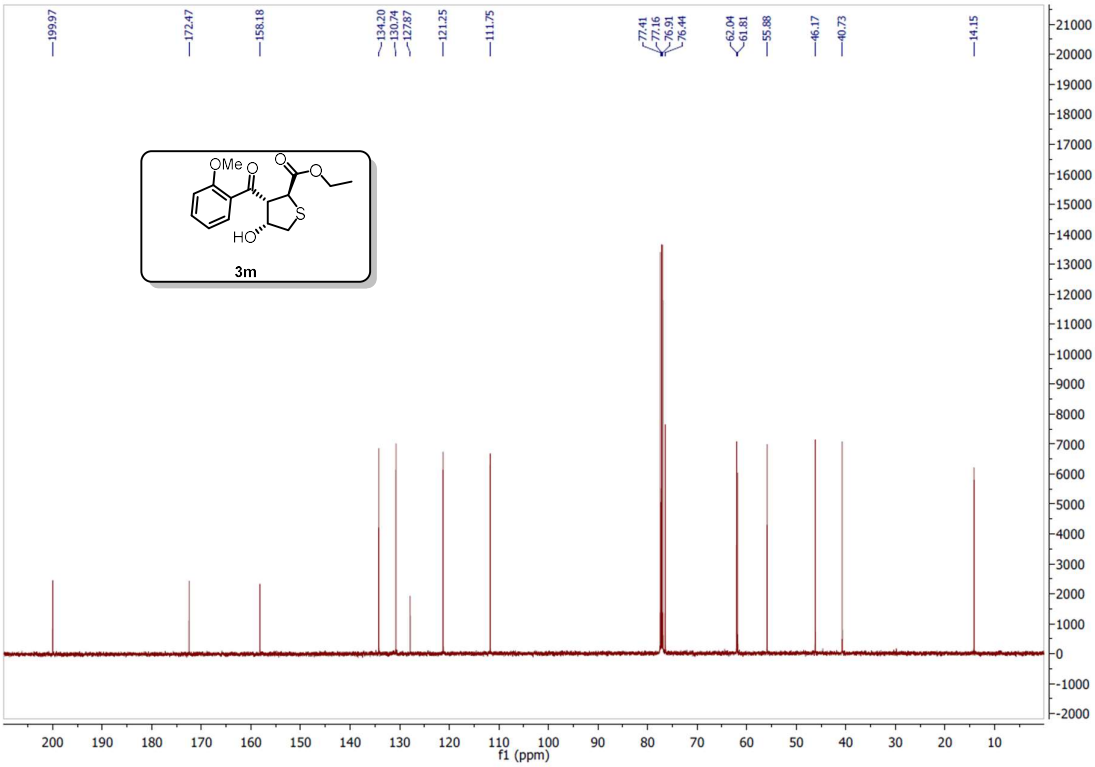
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3k**



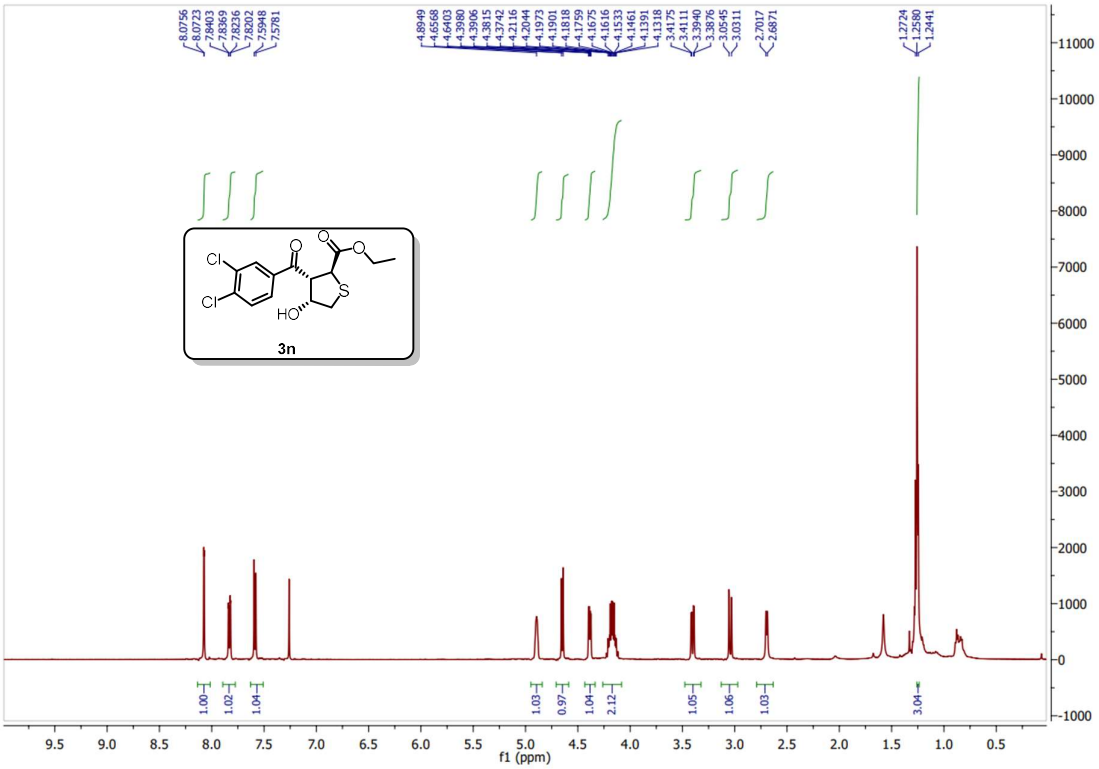


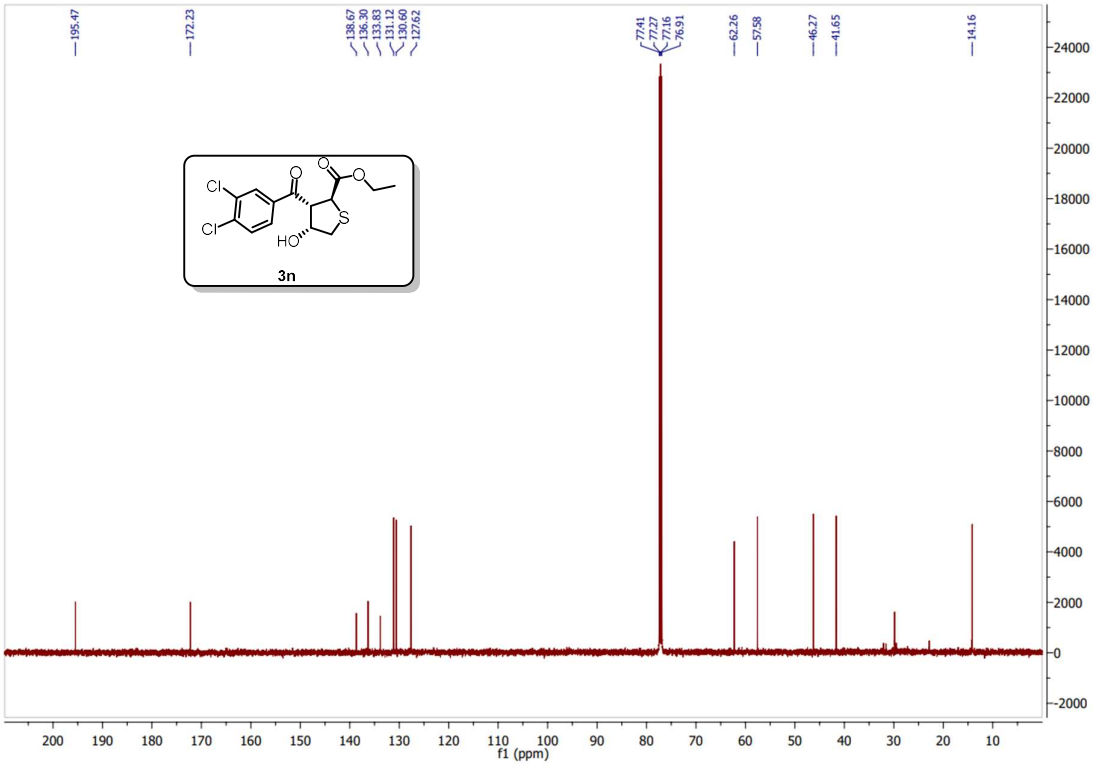
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3l**



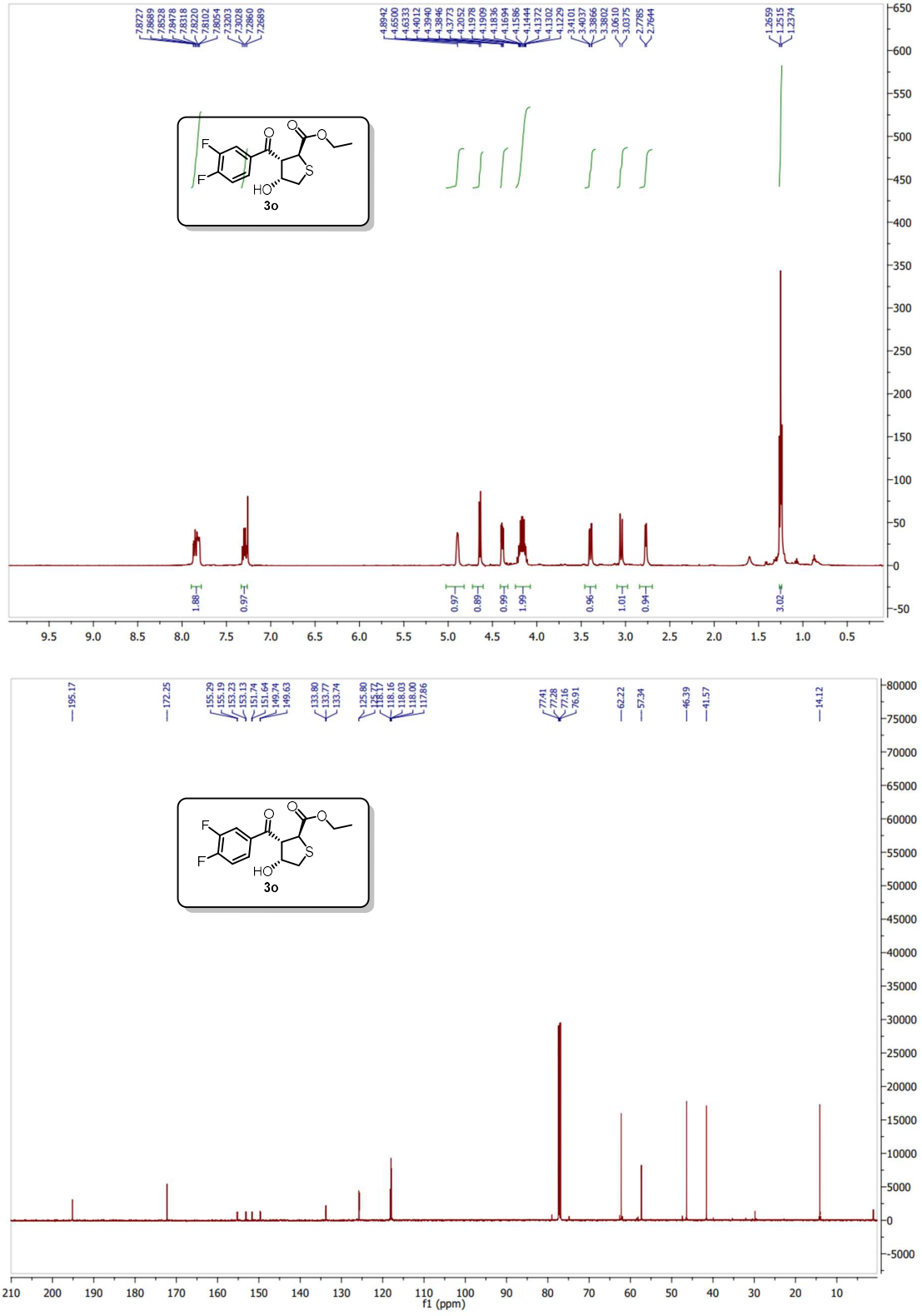


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3m**

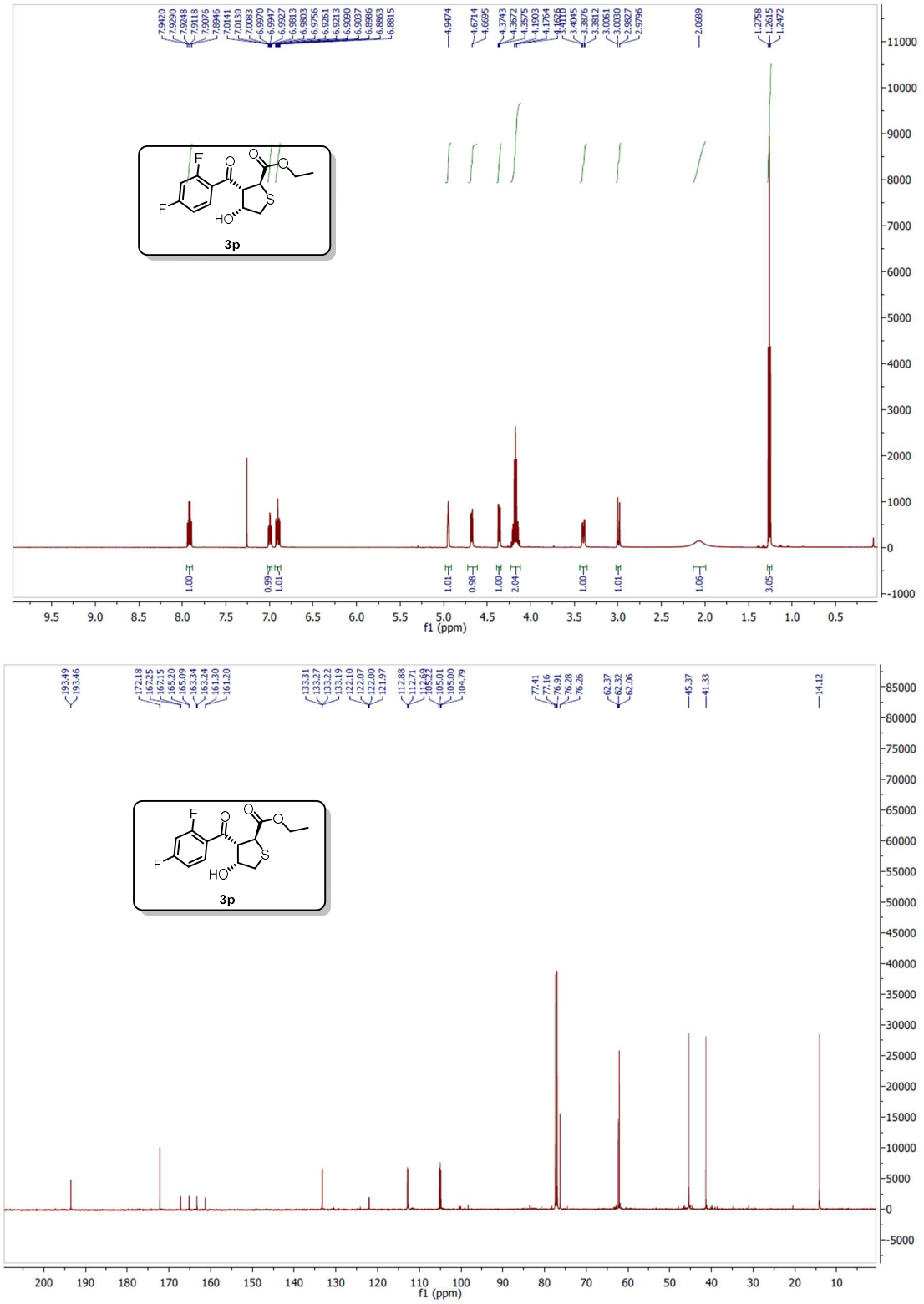




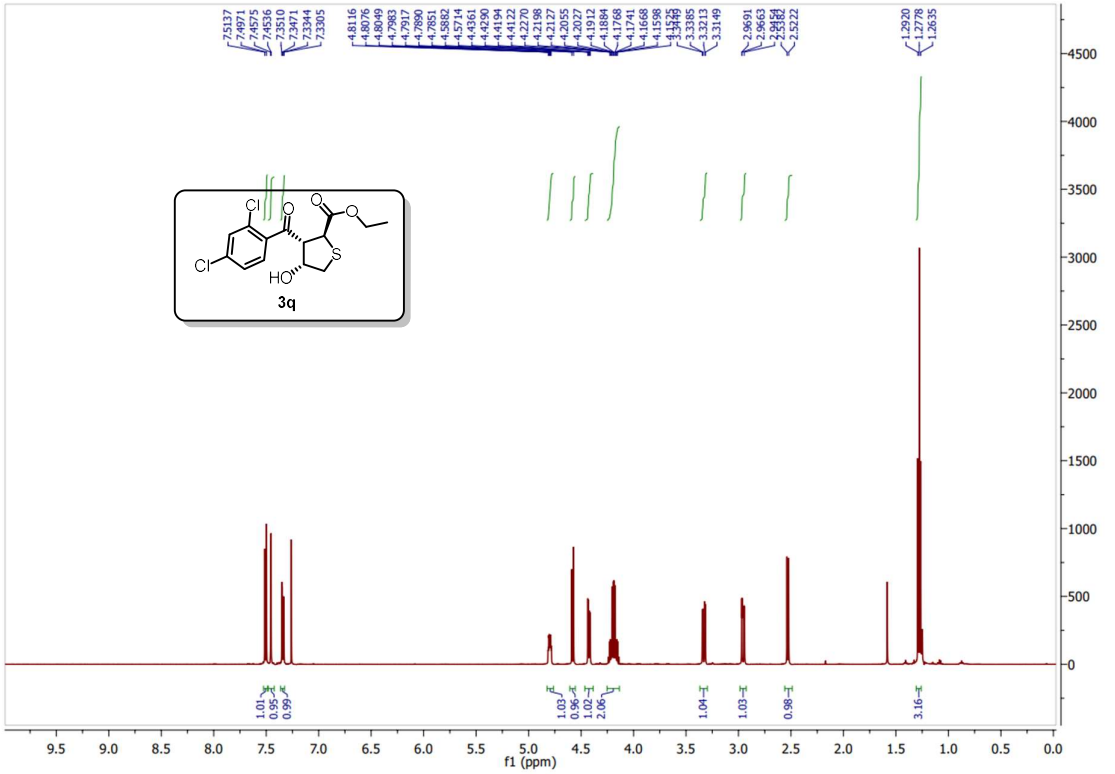
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3n**

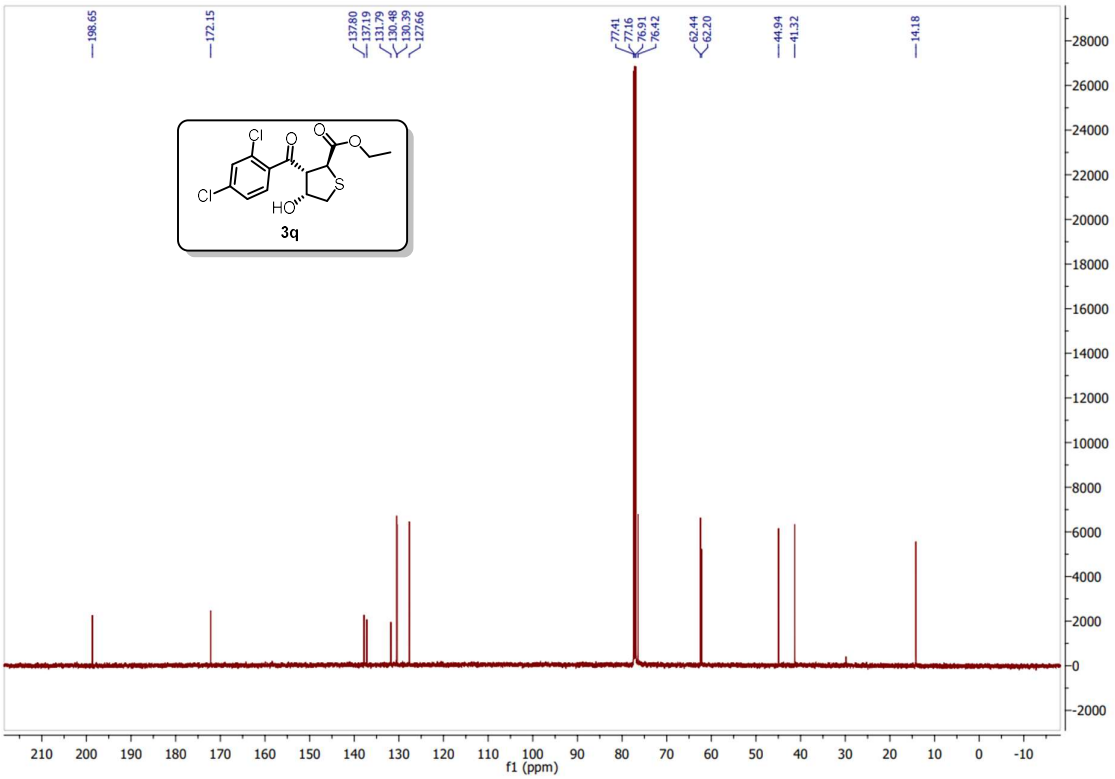


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3o**

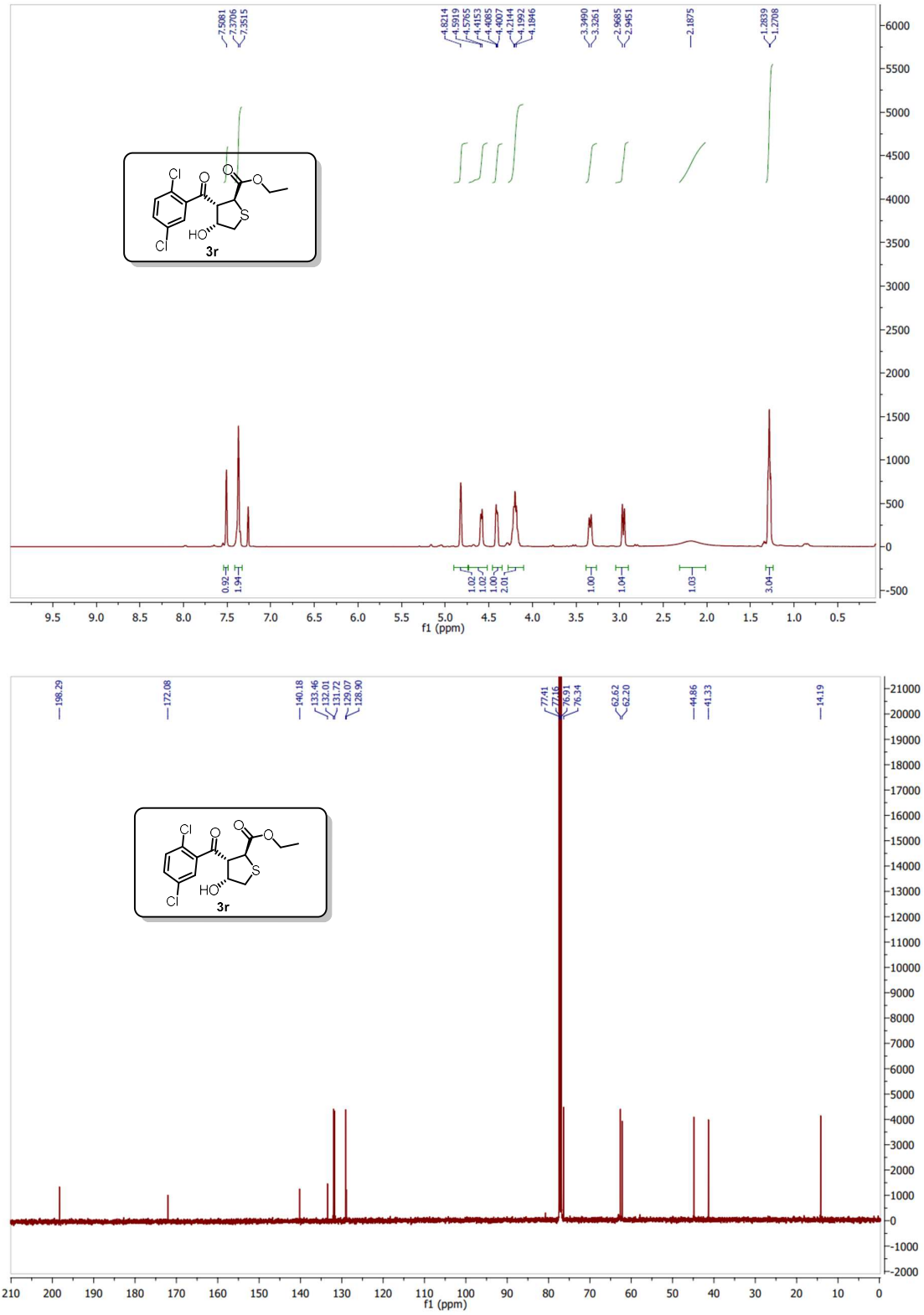


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3p**

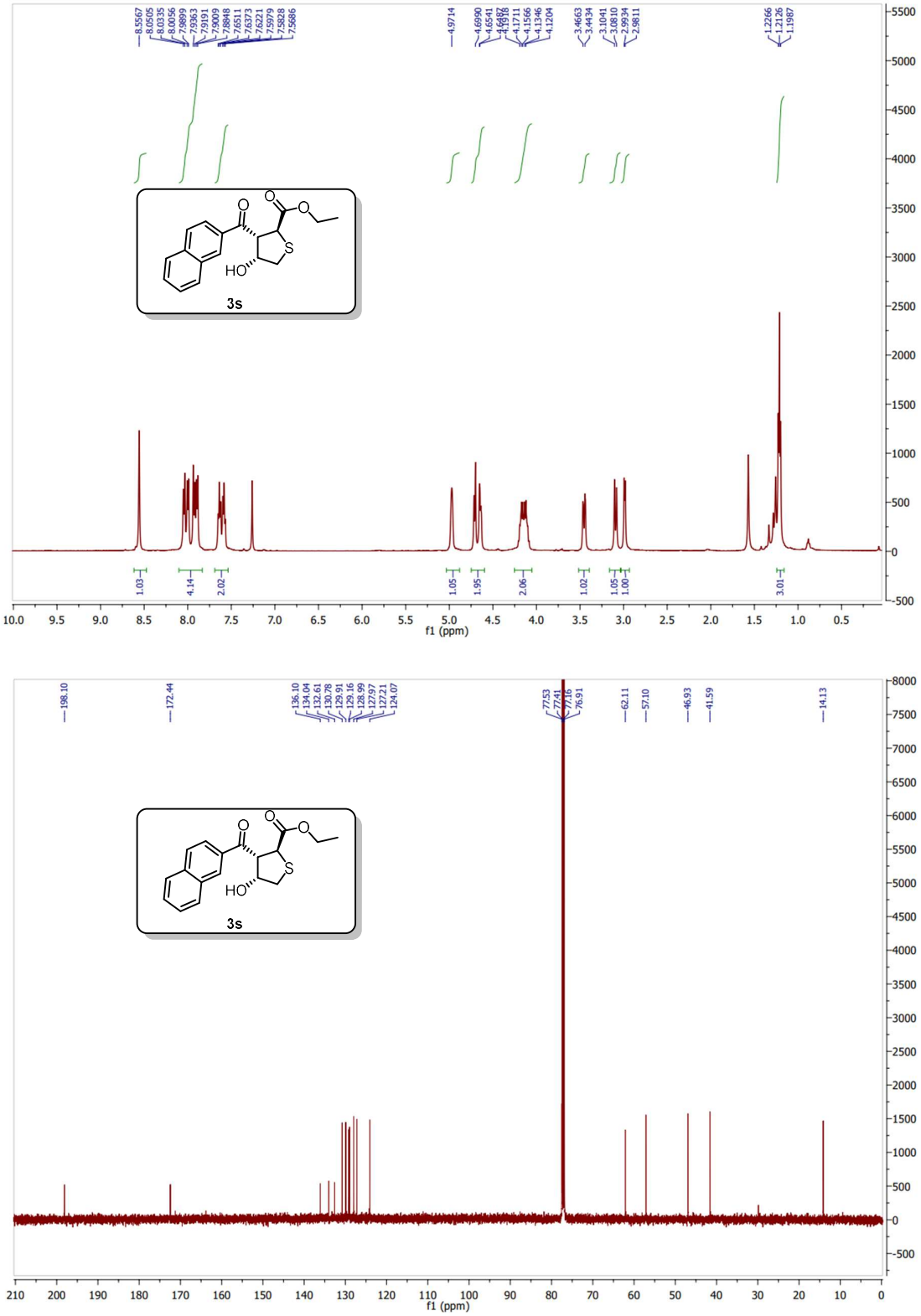




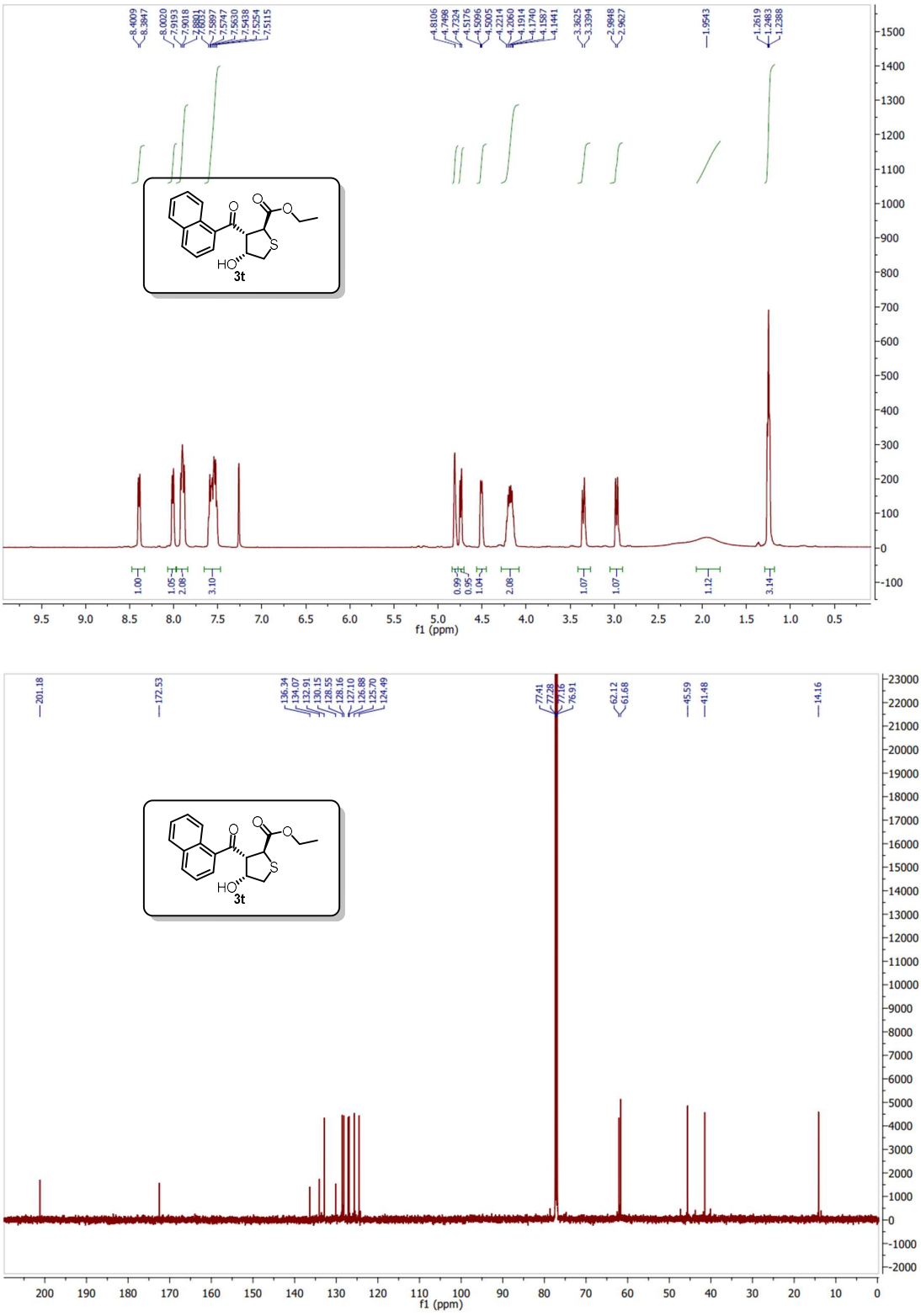
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3q**



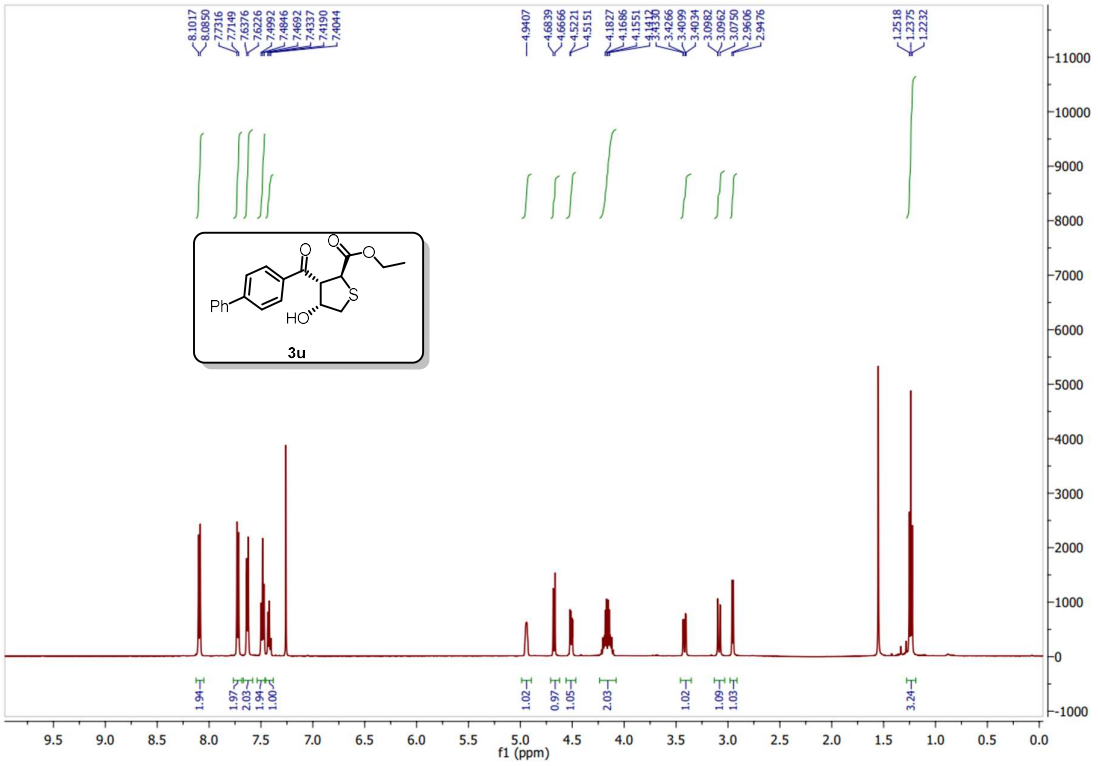
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3r**

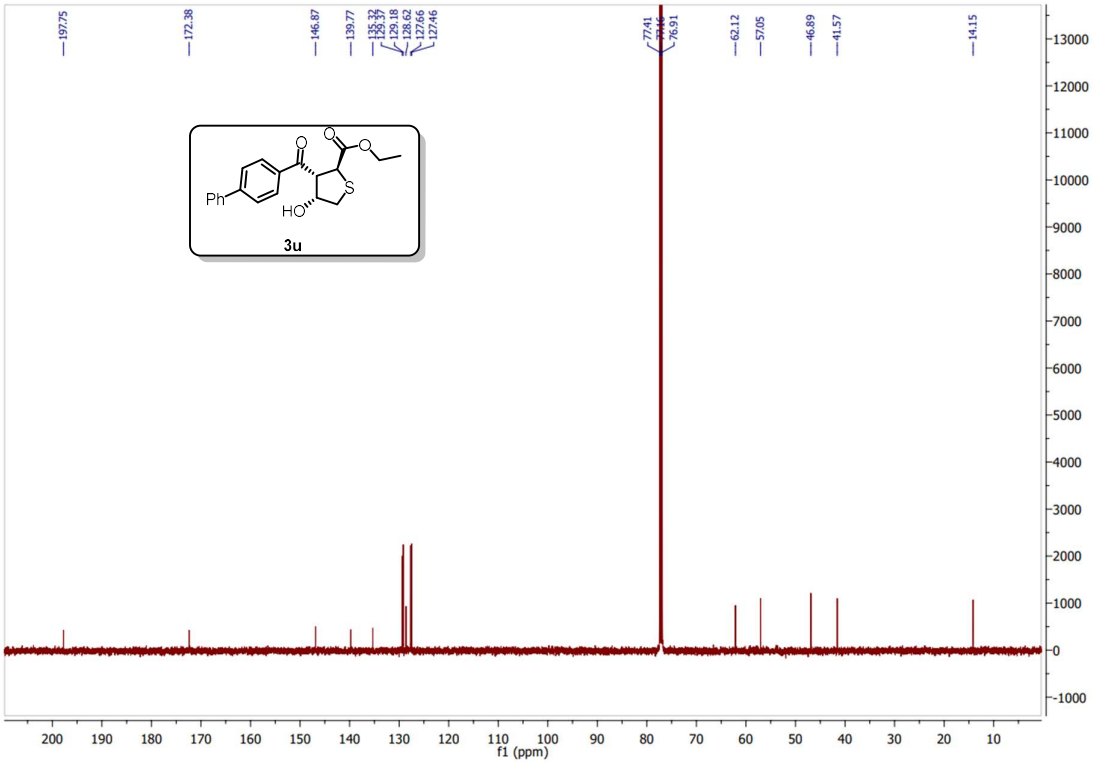


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3s**

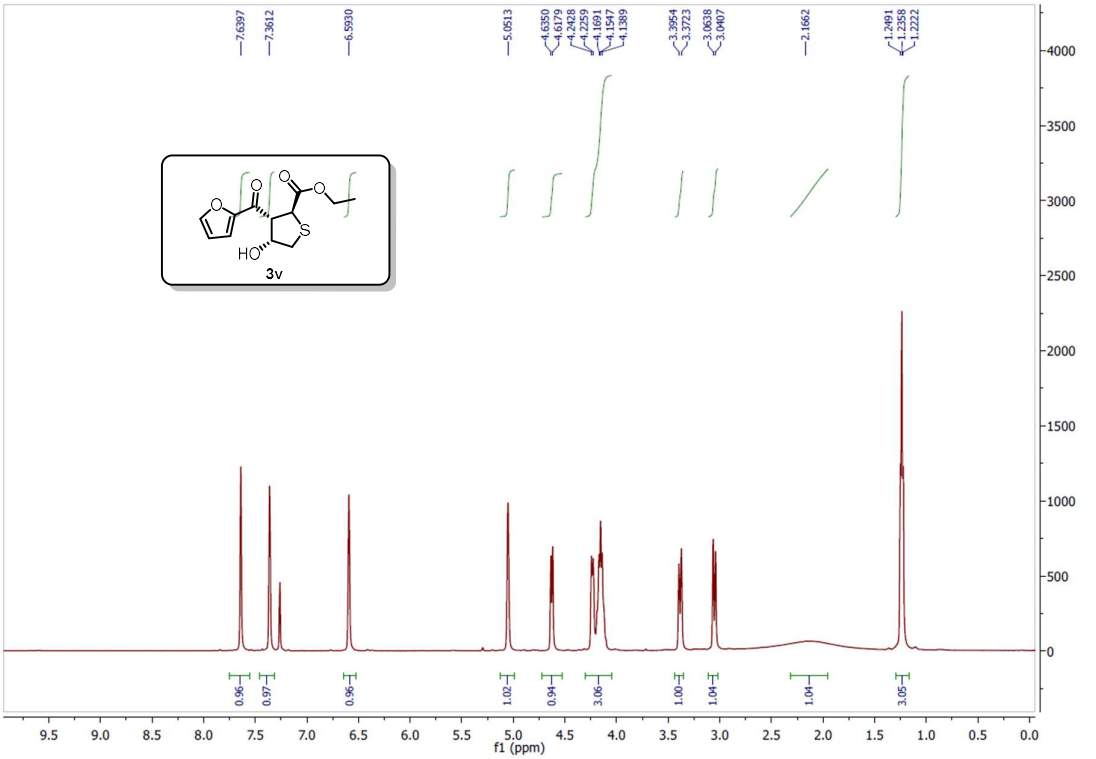


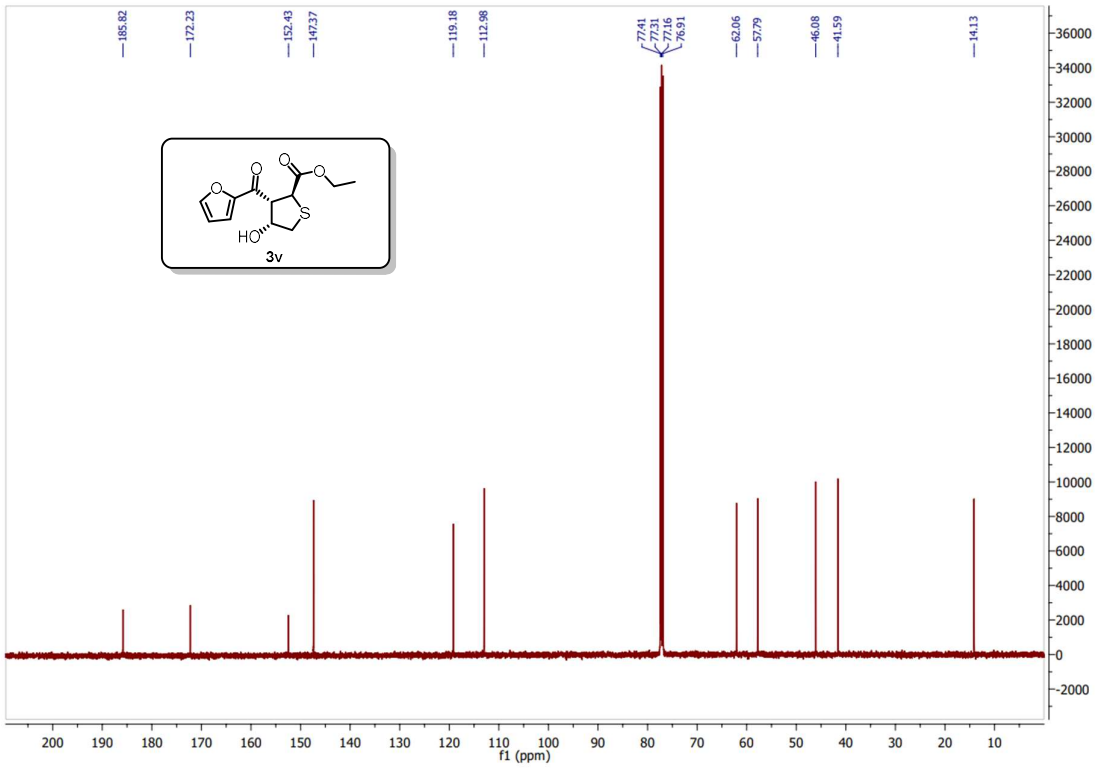
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3t**



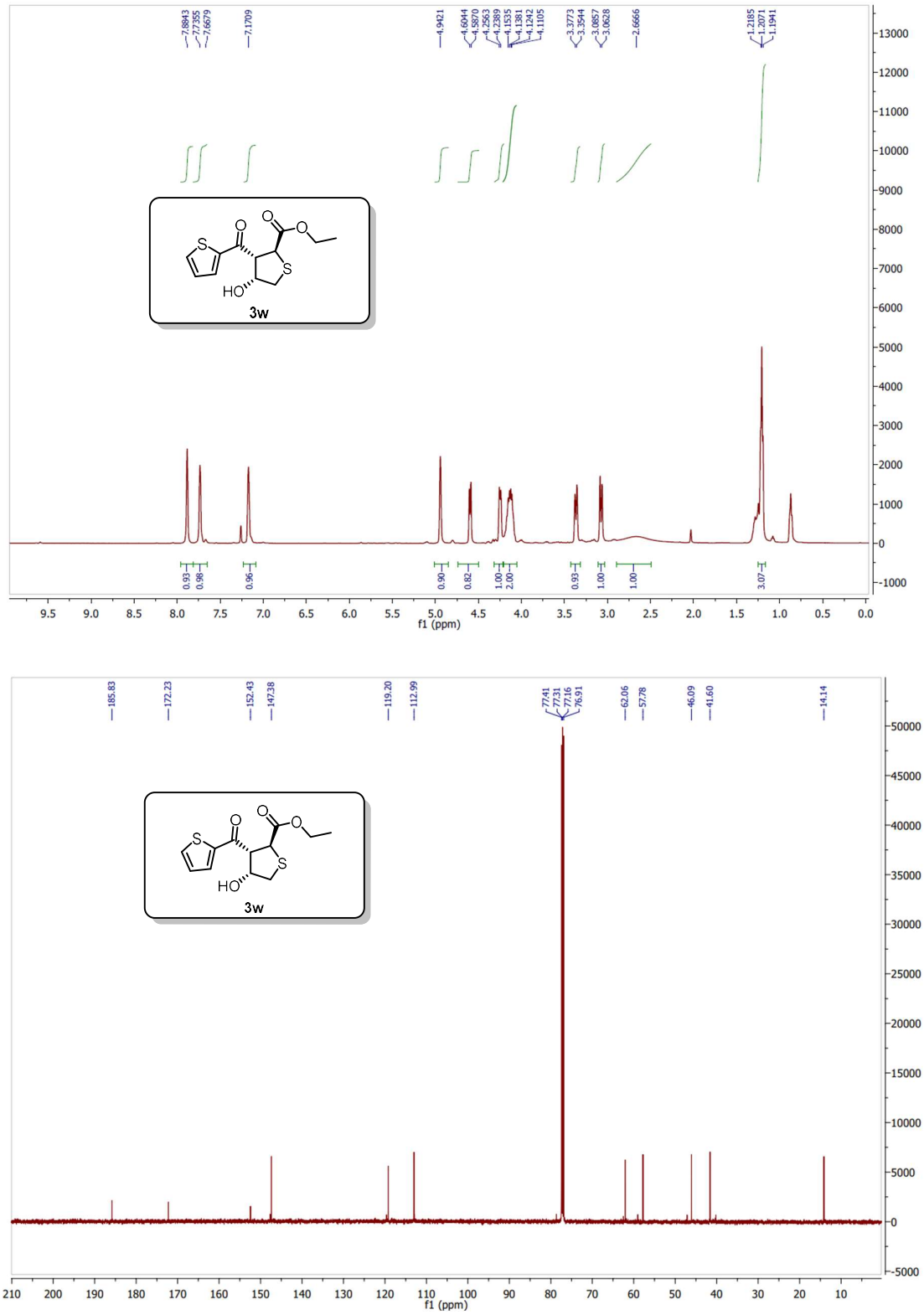


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3u**

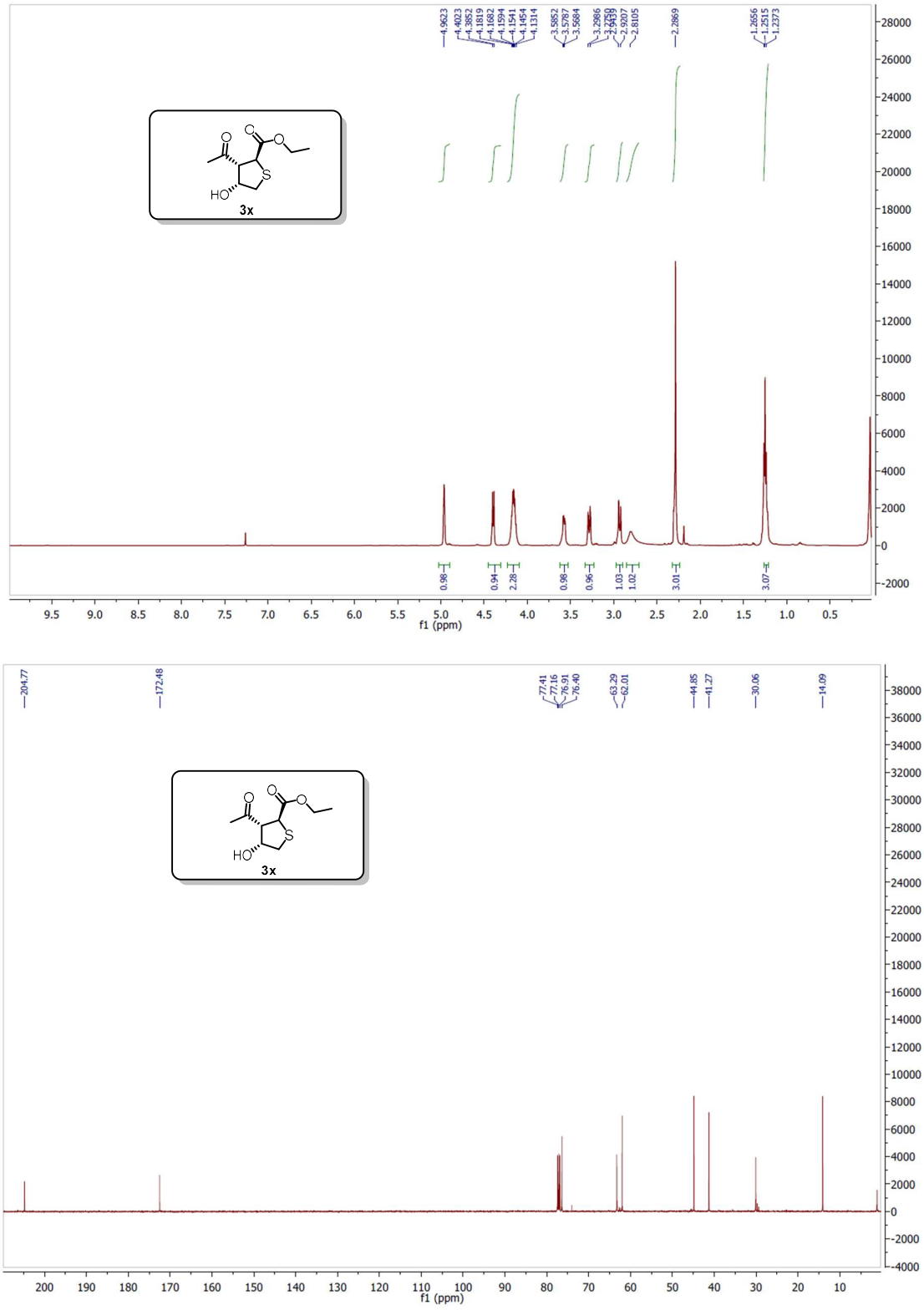




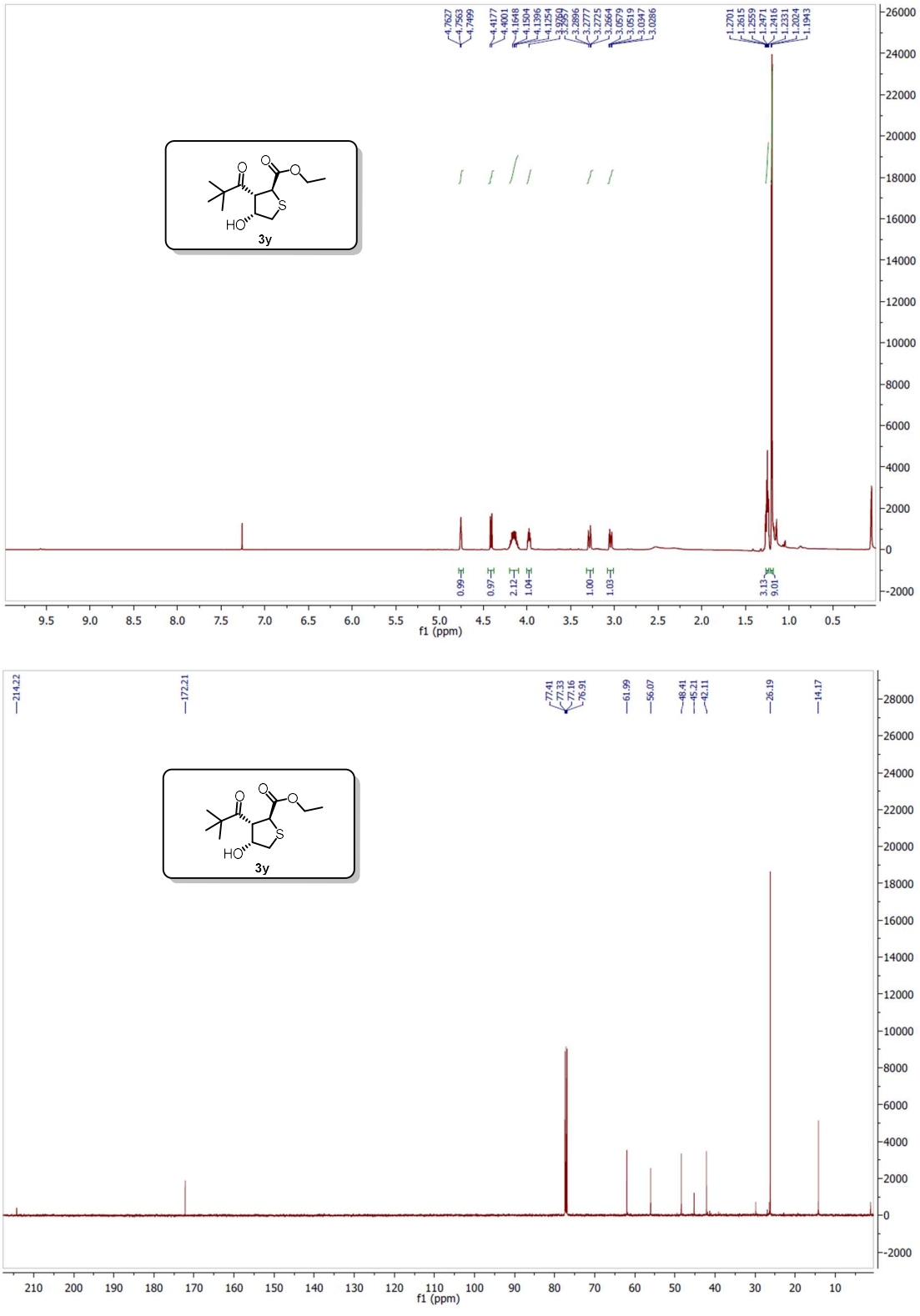
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3v**



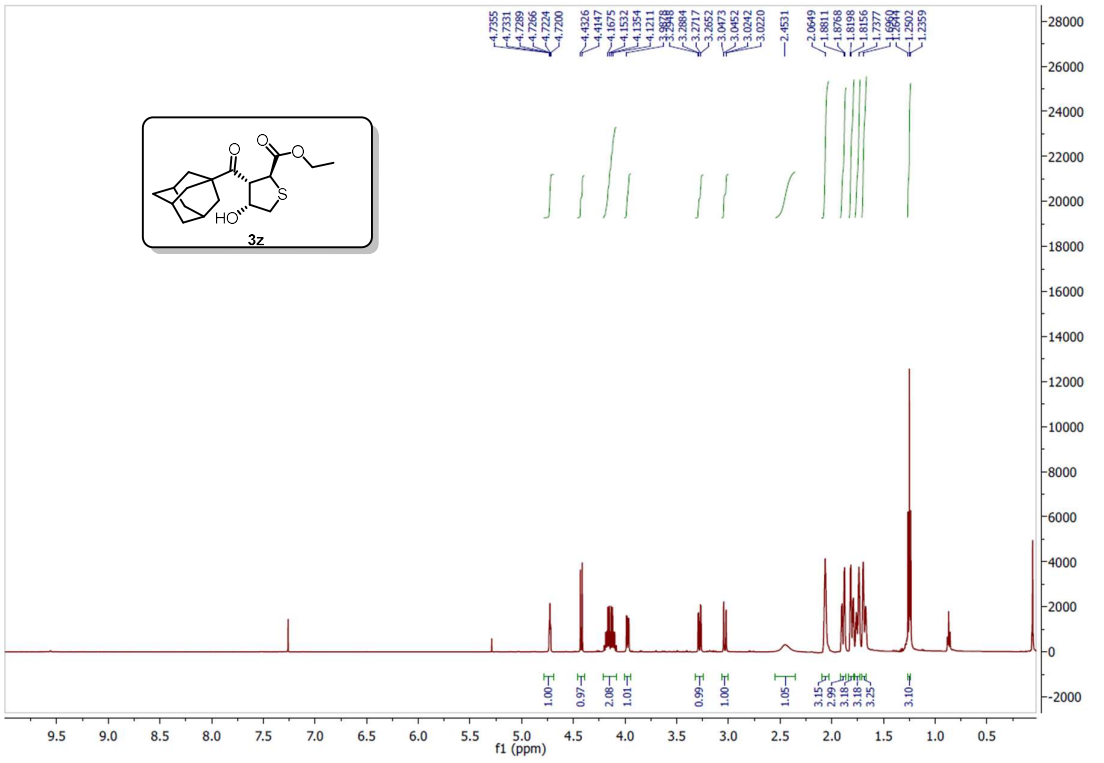
500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3w**

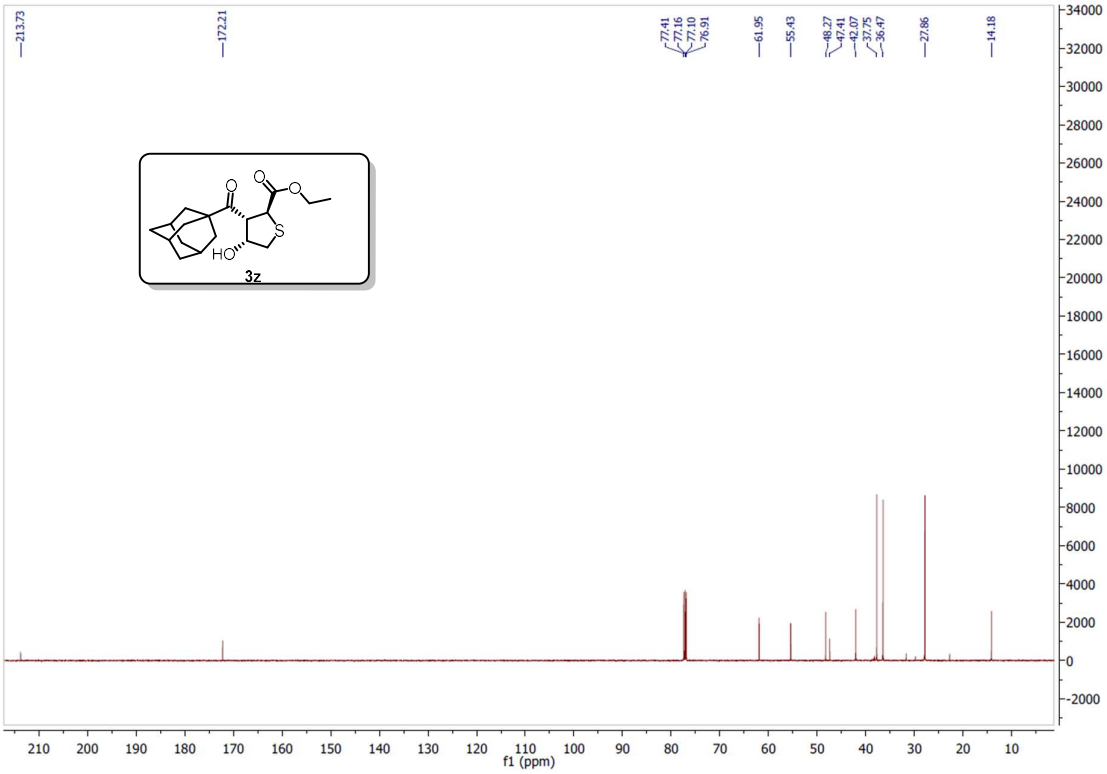


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3x**

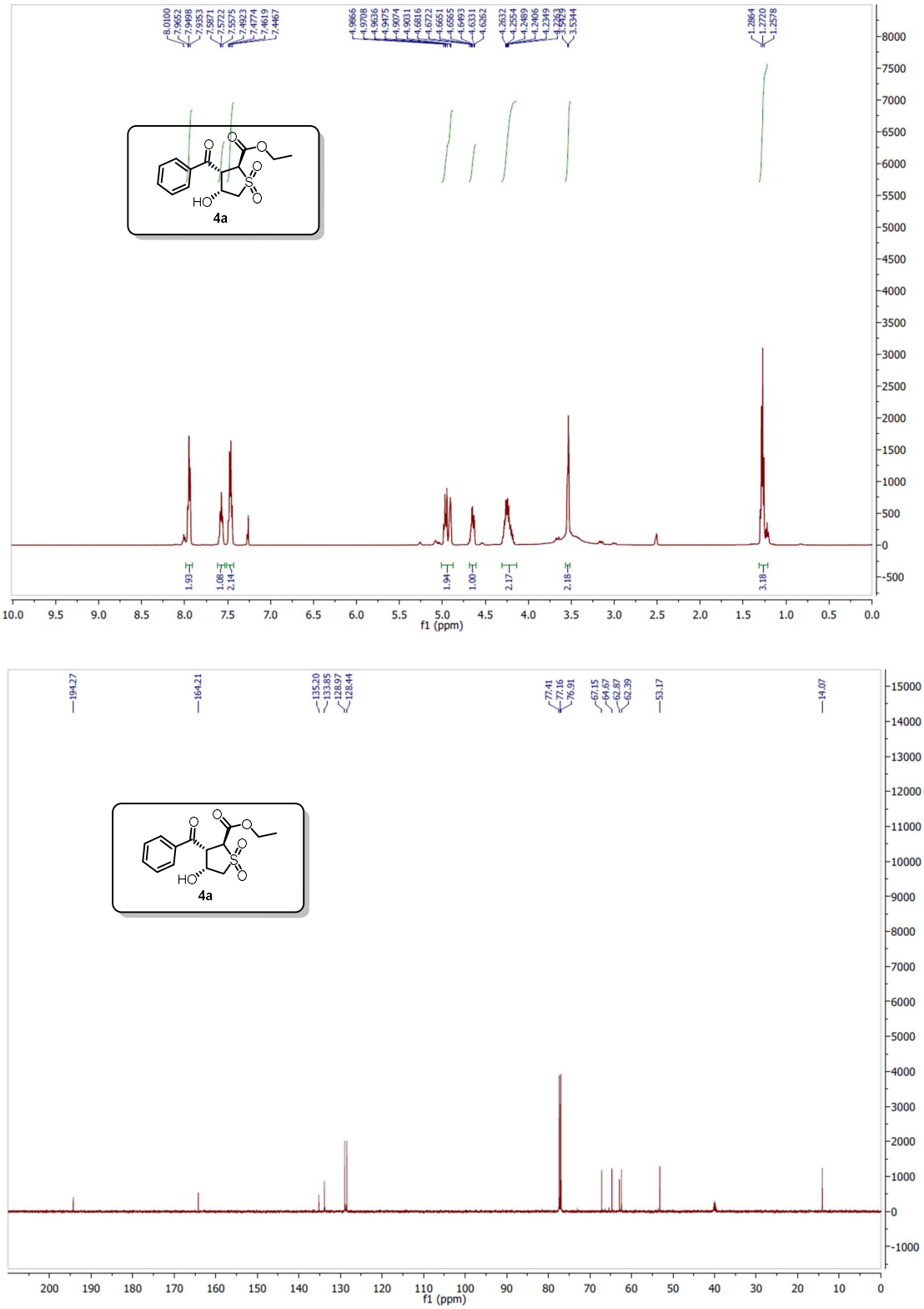


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3y**

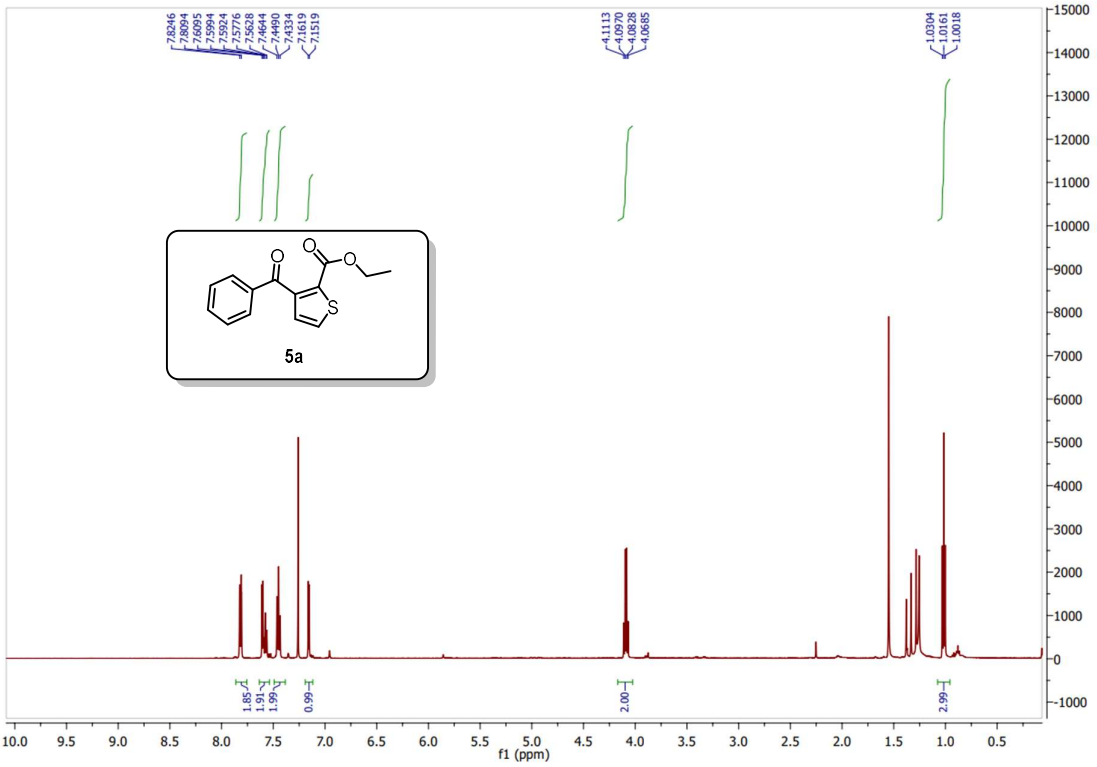


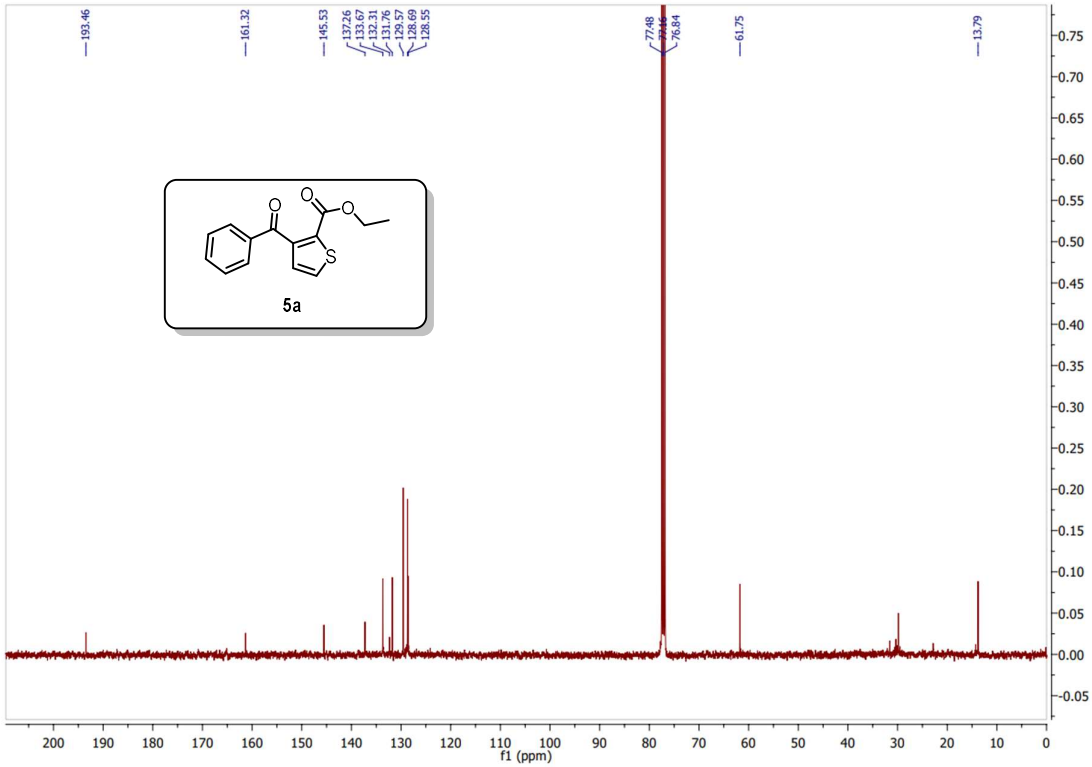


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **3z**

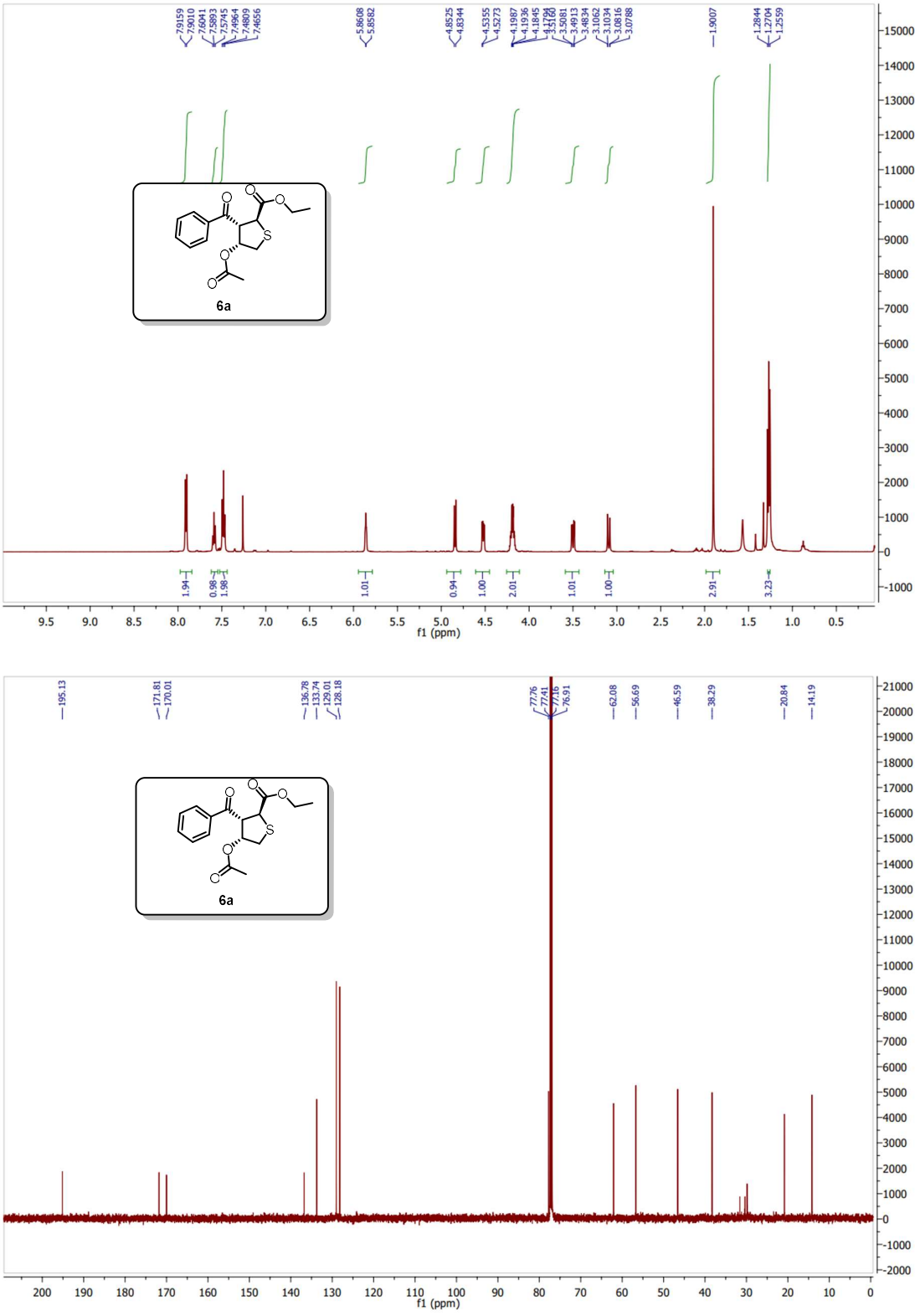


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **4a**

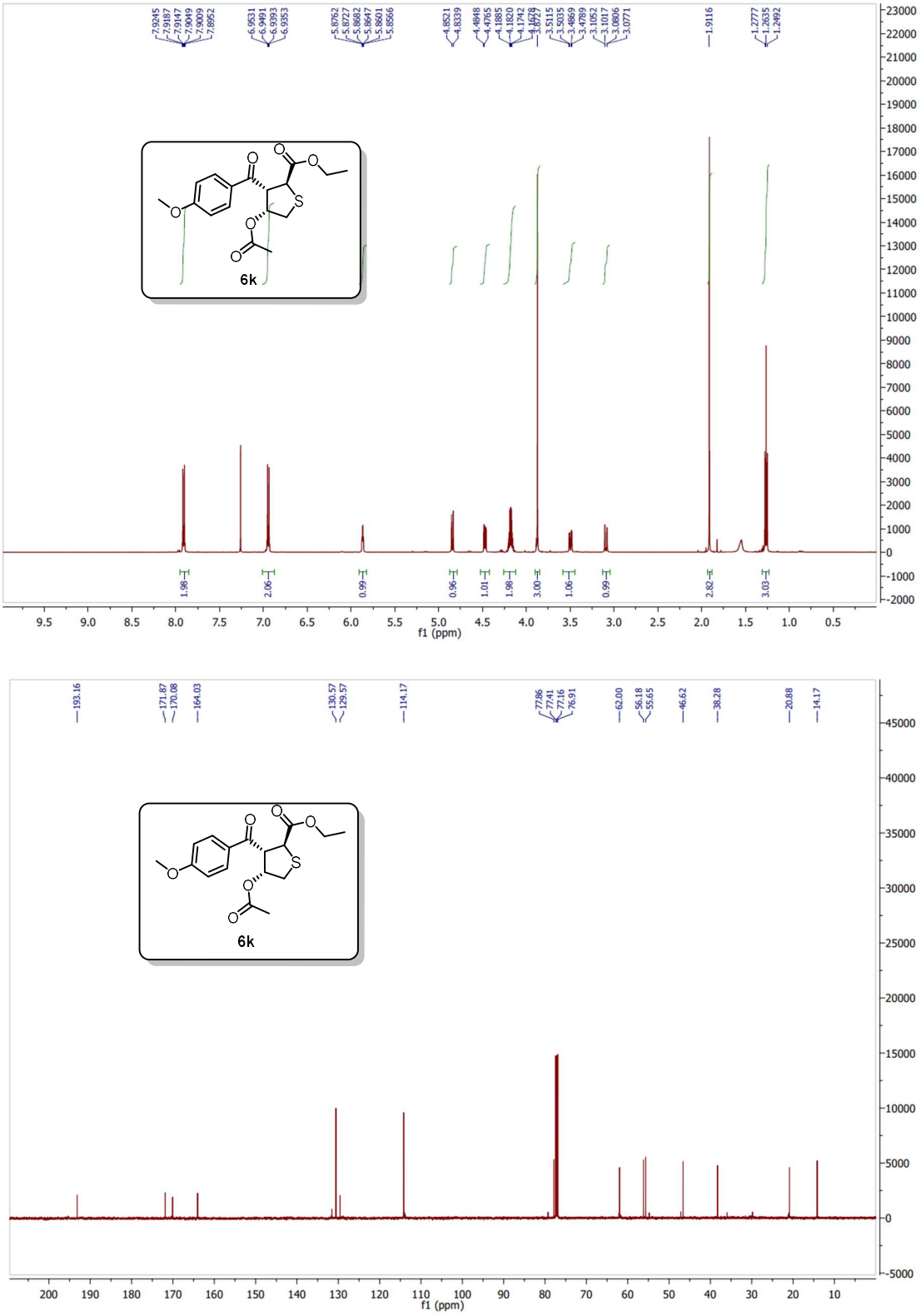




500 MHz ^{1}H NMR and 100 MHz ^{13}C NMR Spectra of **5a**

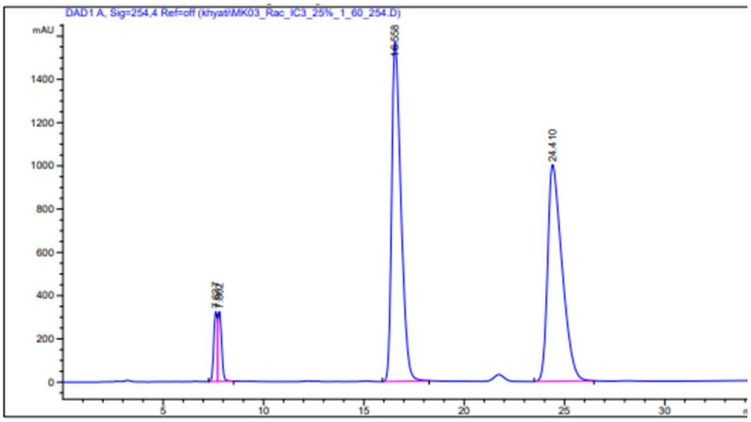


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **6a**

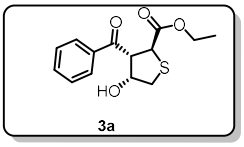


500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR Spectra of **6k**

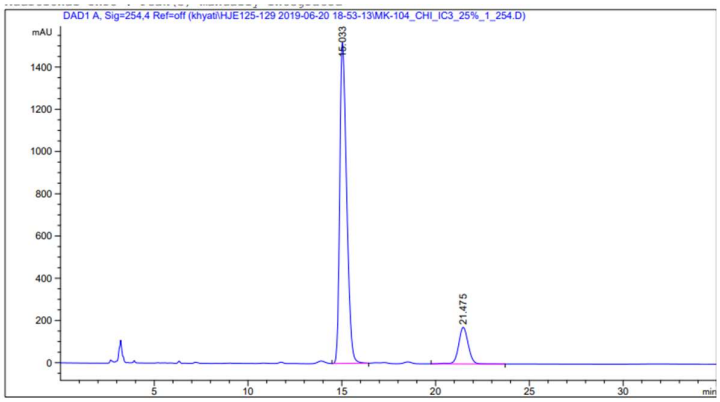
HPLC graph:




```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.627 BV    0.1793 3863.86987  323.51205   3.5698
   2   7.802 VB    0.1967 4230.09033  323.14145   3.9081
   3  16.558 BB    0.4847 5.02198e4  1572.03320  46.3972
   4  24.410 BB    0.7432 4.99252e4  1002.22754  46.1250

Totals :                 1.08239e5  3220.91425
```

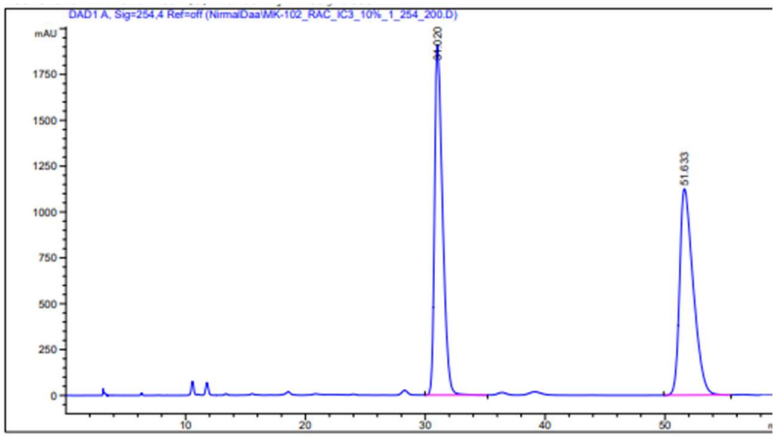


HPLC graph of racemic **3a**

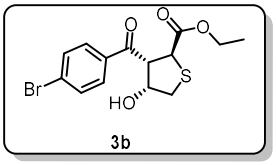



```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.033 BB    0.3903 3.86096e4  1520.19019  86.2927
   2  21.475 BB    0.5473 6133.00342  173.11958  13.7073

Totals :                 4.47426e4  1693.30977
```

HPLC graph of enantioenriched **3a**

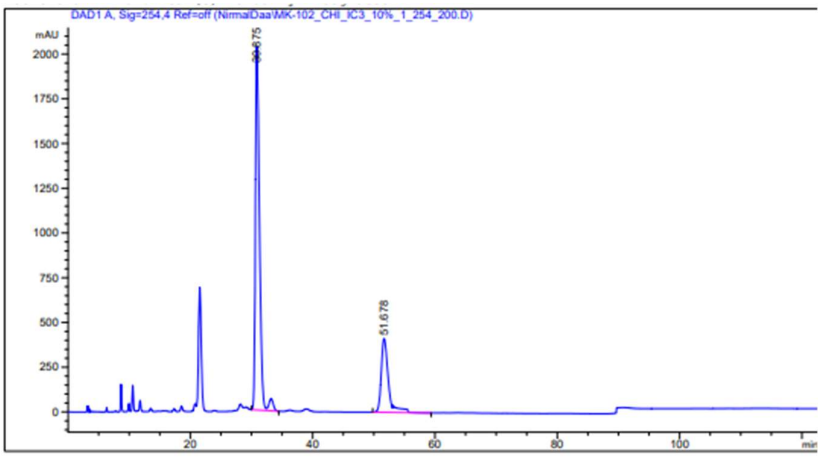



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.020 BB    0.6954 8.83379e4  1910.70789  49.8815
   2  51.633 BB    1.1600 8.87576e4  1125.56543  50.1185

Totals :                 1.77096e5  3036.27332
```



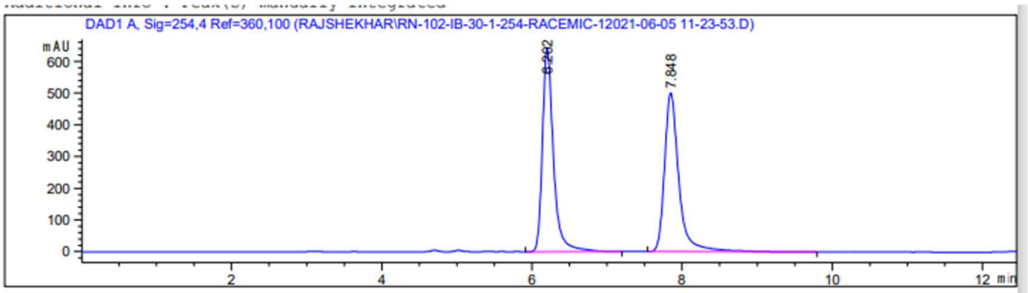
3b

HPLC graph of racemic **3b**



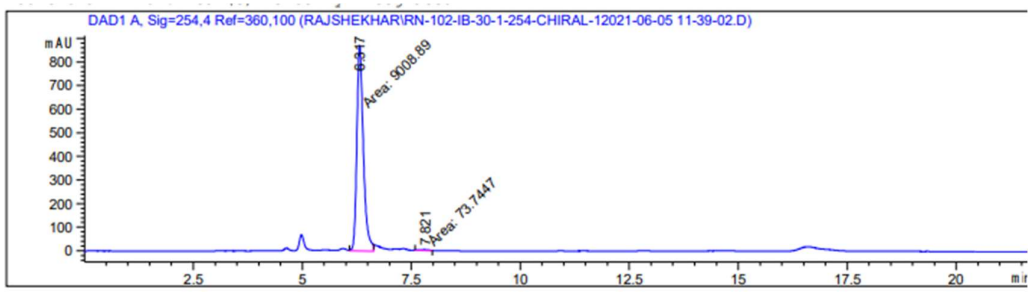

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  30.875 BV R  0.6865 9.54271e4  2032.93164  74.1747
   2  51.678 BV R  1.1071 3.32248e4   412.78293  25.8253

Totals :                 1.28652e5  2445.71457
```

HPLC graph of enantioenriched **3b**



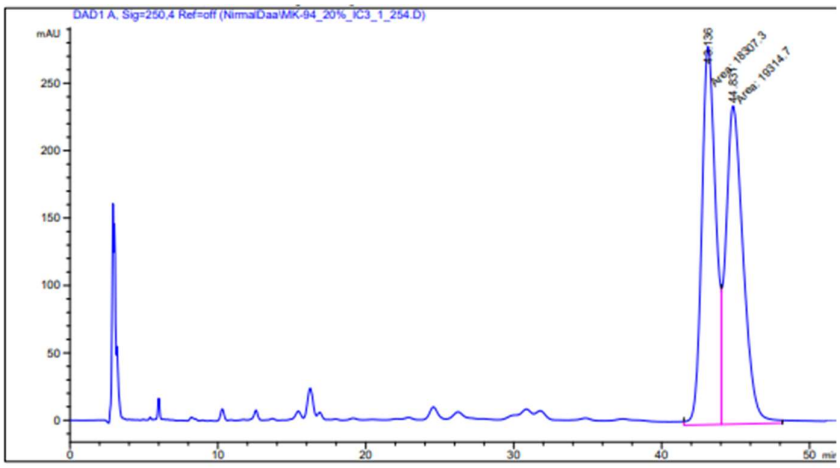

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.202 BB    0.1538 6557.01172  638.72516  49.4936
   2   7.848 BB    0.1997 6691.18213  501.35687  50.5064

Totals :                  1.32482e4  1140.08203
```

HPLC graph of racemic **3b (for recrystallization)**

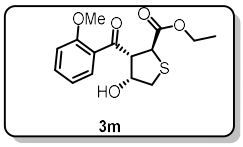



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.317 MM    0.1726 9008.89355  870.02698  99.1881
   2   7.821 MM    0.2964   73.74472    4.14723   0.8119

Totals :                  9082.63828  874.17420
```

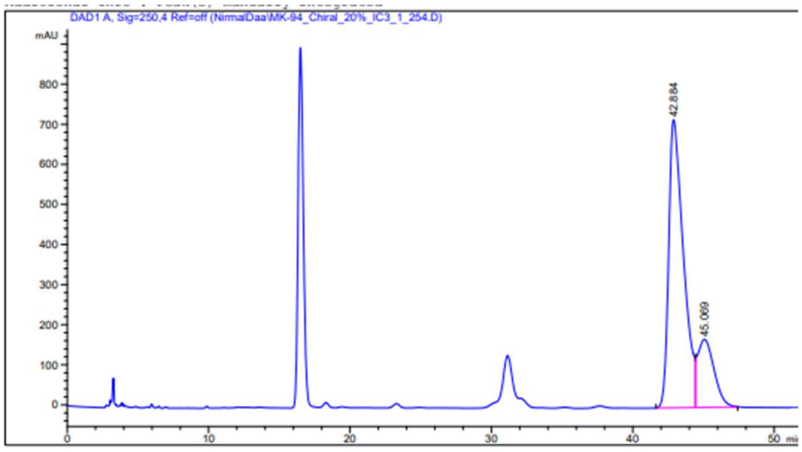
HPLC graph of enantioenriched **3b (after recrystallization)**




```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  43.136 MF    1.0875 1.83073e4   280.56085  48.6612
   2  44.831 FM    1.3636 1.93147e4   236.07501  51.3388

Totals :                  3.76220e4   516.63586
```

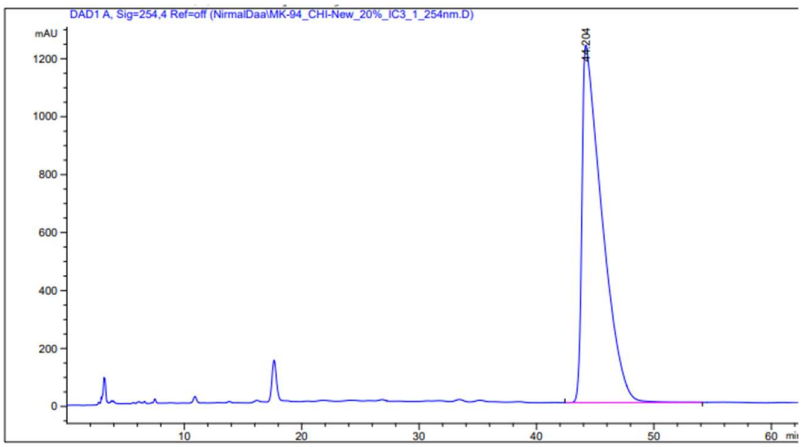


HPLC graph of racemic **3m**



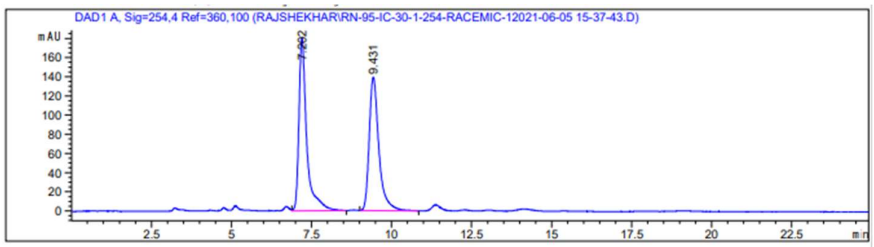

```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  42.884 BV    1.0555 5.19492e4   718.48883  78.9995
   2  45.069 VB    1.2063 1.38097e4   169.89090  21.0005

Totals :                  6.57589e4   888.37973
```

HPLC graph of enantioenriched **3m**



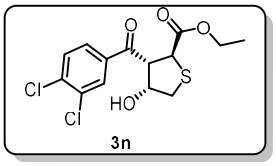

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  44.204 BB    1.5867 1.45802e5  1233.77698 100.0000

Totals :                  1.45802e5  1233.77698
```

HPLC graph of enantioenriched **3m (after recrystallization)**

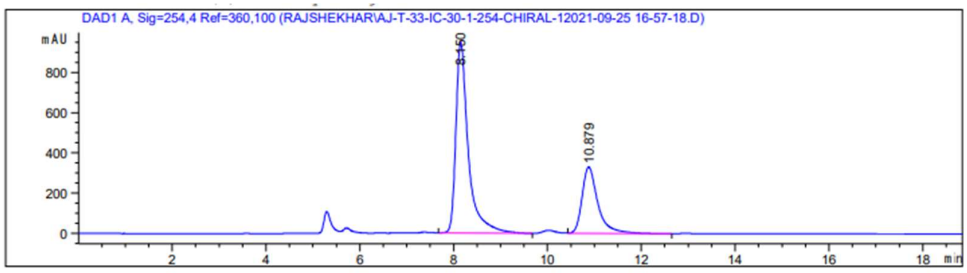



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.202 VB    0.2504 3051.45972  179.46701  51.1071
   2   9.431 BB    0.3144 2919.25635  139.37350  48.8929

Totals :                  5970.71606  318.84052
```

HPLC graph of racemic **3n**

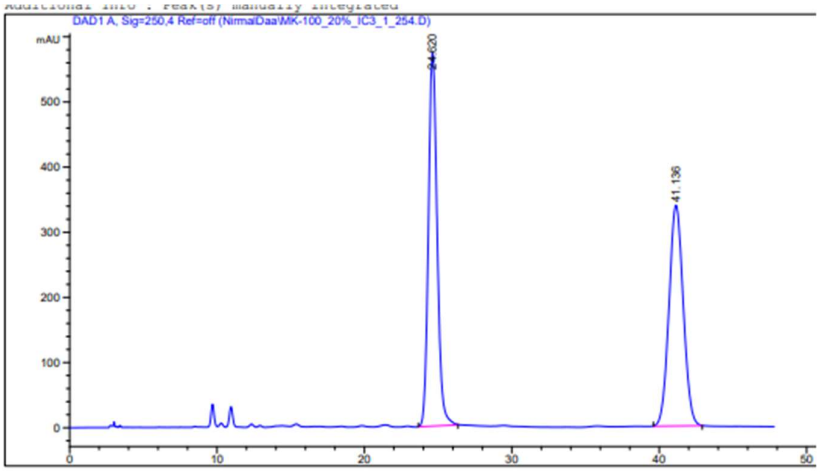


3n

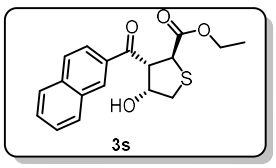



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.150 BB    0.2727 1.74857e4   950.23273  69.1736
   2  10.879 VB    0.3526 7792.32031  331.09695  30.8264

Totals :                  2.52781e4  1281.32968
```

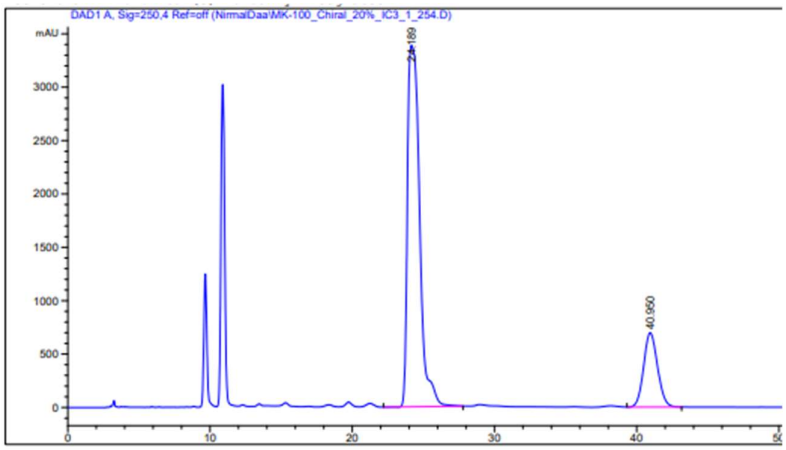
HPLC graph of enantioenriched **3n**




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  24.620 BB    0.6300 2.35055e4   573.65973  50.7912
   2  41.136 BB    1.0395 2.27732e4   339.11902  49.2088

Totals :                  4.62788e4   912.77875
```

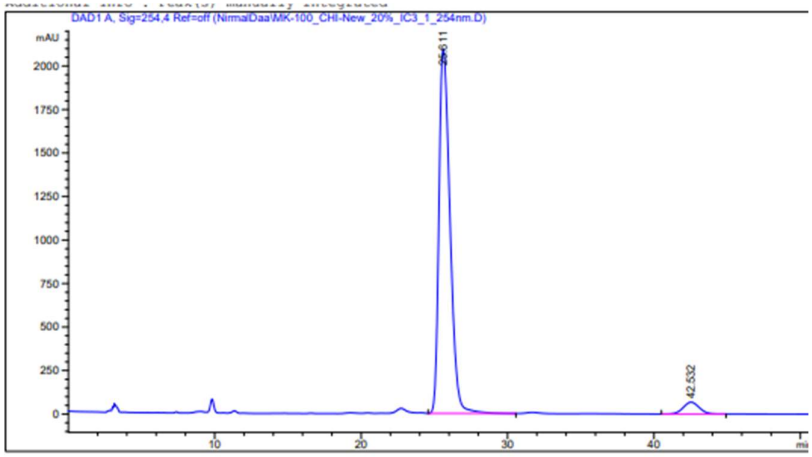


HPLC graph of racemic **3s**




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  24.189 VB     0.7066 2.00900e5  3384.09497  80.9167
   2  40.950 VB     1.0508 4.73800e4   697.24231  19.0833

Totals :                  2.48280e5  4081.33728
```

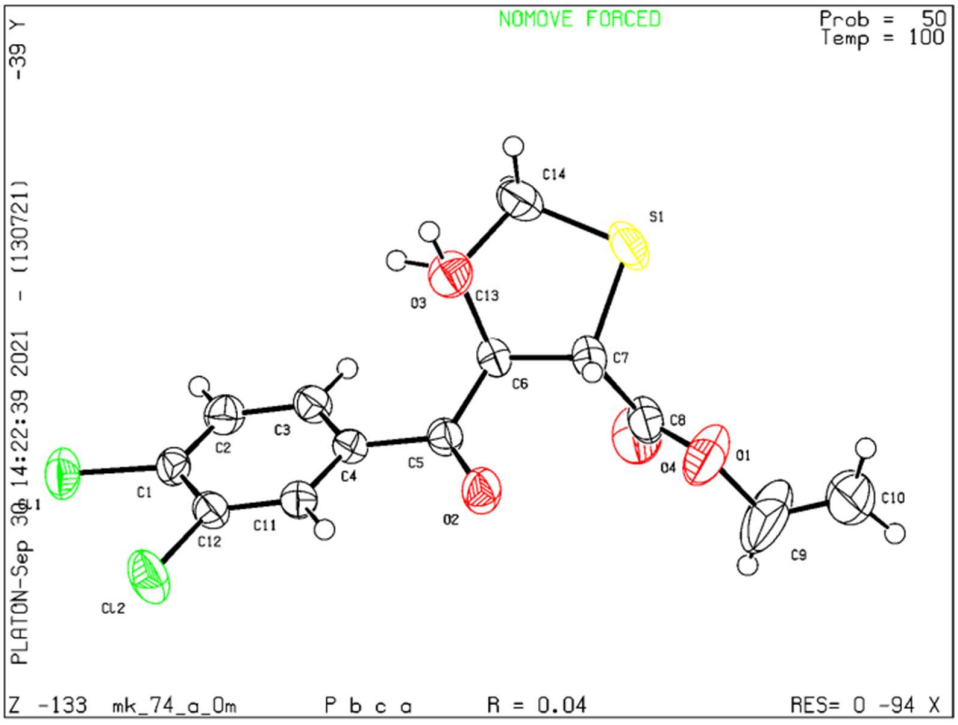
HPLC graph of enantioenriched **3s**



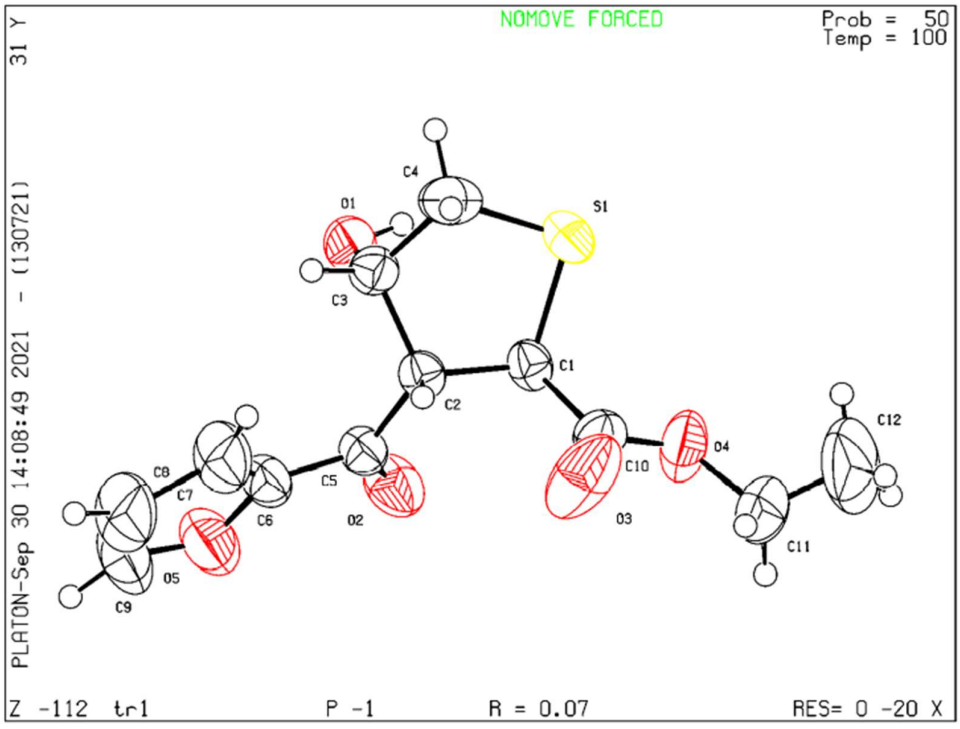

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  25.611 BB     0.8150 1.09639e5  2093.54980  95.5466
   2  42.532 BB     1.1599 5110.30469   67.91466   4.4534

Totals :                  1.14750e5  2161.46446
```

HPLC graph of enantioenriched **3s (after recrystallization)**

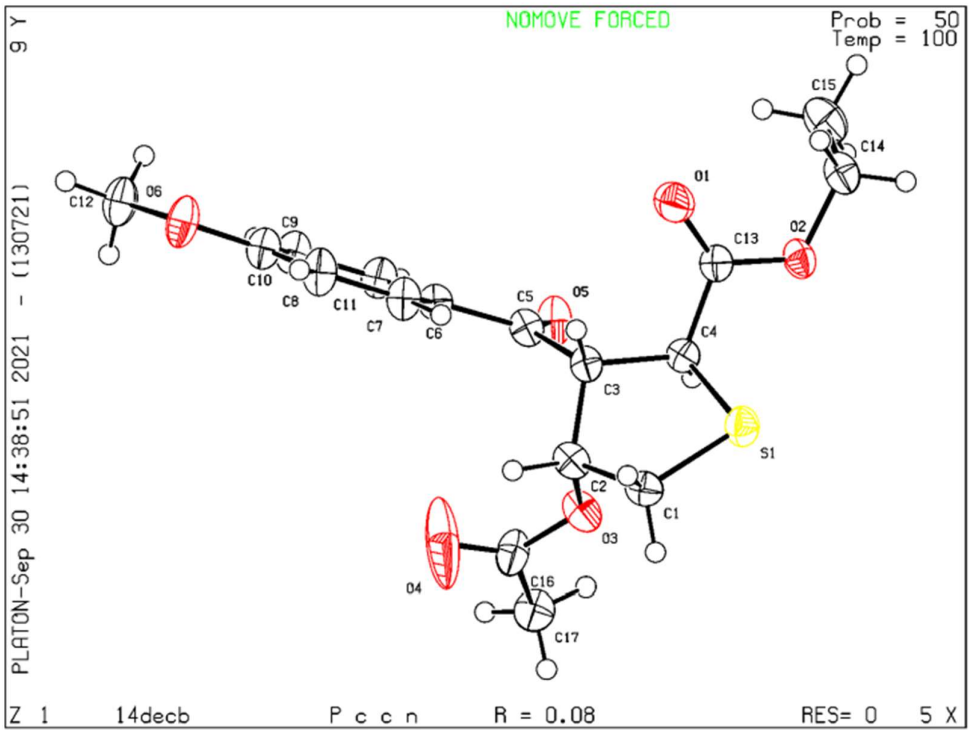
X-ray crystal structure of 3n, 3v, 6k



ORTEP Diagram of **3n** (CCDC 2113761)



ORTEP Diagram of **3v** (CCDC 2113762)



ORTEP Diagram of **6k** (CCDC 2113760)

Table S2: Crystal data and structure refinement for 3n, 3v, 6k

Identification code	**3n**	**3v**	**6k**
Empirical formula	$C_{14}H_{12}O_4SCl_2$	$C_{12}H_{14}O_5S$	$C_{17}H_{20}O_6S$
Formula weight	347.20	270.29	352.39
Temperature/K	100	100	100
Crystal system	orthorhombic	triclinic	orthorhombic
Space group	Pbca	P-1	Pccn
a/Å	6.7389(12)	6.8434(7)	41.990(11)
b/Å	14.205(3)	10.0084(8)	7.821(2)
c/Å	32.179(6)	10.5726(9)	10.606(3)
α/°	90	73.419(3)	90
β/°	90	75.274(4)	90
γ/°	90	72.063(3)	90
Volume/Å^3	3080.4(10)	649.21(10)	3483.0(16)
Z	8	12	8
ρ_{calc}g/cm^3	1.497	1.403	1.133
μ/mm^{-1}	0.568	0.201	0.085
F(000)	1424.0	280.0	1312.0
Crystal size/mm^3	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.1	0.2 × 0.2 × 0.2
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	2.532 to 58.472	6.64 to 57.396	5.822 to 56.95
Index ranges	-9 ≤ h ≤ 9, -19 ≤ k ≤ 19, -43 ≤ l ≤ 43	-9 ≤ h ≤ 9, -13 ≤ k ≤ 13, -14 ≤ l ≤ 14	-55 ≤ h ≤ 56, -10 ≤ k ≤ 10, -14 ≤ l ≤ 14
Reflections collected	78009	17407	38806
Independent reflections	4079 [R_{int} = 0.0373, R_{sigma} = 0.0147]	3211 [R_{int} = 0.0929, R_{sigma} = 0.0633]	4006 [R_{int} = 0.1118, R_{sigma} = 0.0550]
Data/restraints/parameters	4079/0/193	3211/0/165	4006/0/220
Goodness-of-fit on F^2	1.090	1.385	1.292
Final R indexes [I>=2σ (I)]	R_1 = 0.0447, wR_2 = 0.1163	R_1 = 0.0735, wR_2 = 0.1965	R_1 = 0.0795, wR_2 = 0.1819
Final R indexes [all data]	R_1 = 0.0572, wR_2 = 0.1231	R_1 = 0.1037, wR_2 = 0.2237	R_1 = 0.1094, wR_2 = 0.2053
Largest diff. peak/hole / e Å^{-3}	0.45/-0.31	0.35/-0.29	0.96/-0.54