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Supporting Information

Oxidative Radical Coupling of Hydroquinones and Thiols Using Chromic Acid: One-Pot Synthesis of Quinonyl Alkyl/Aryl Thioethers

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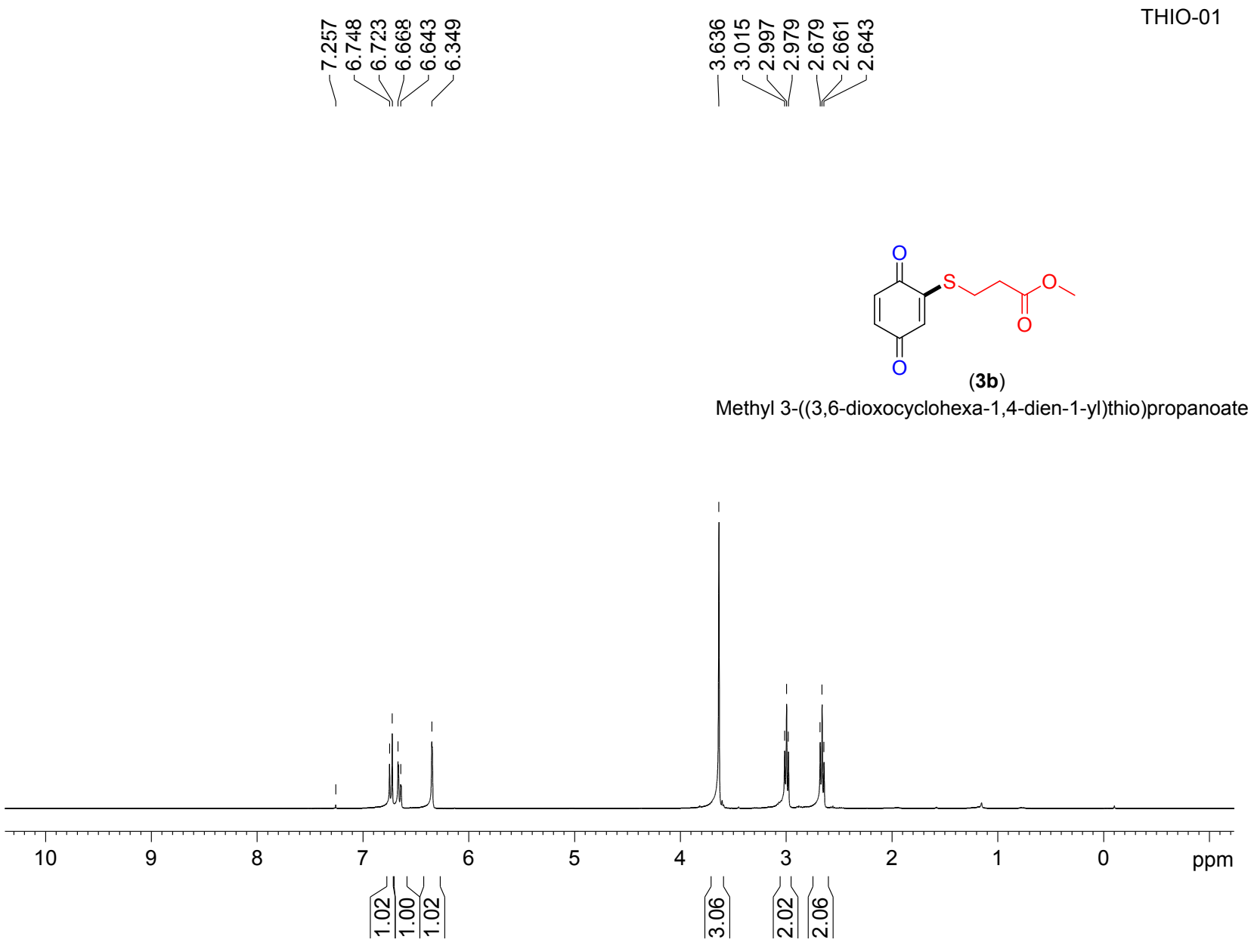

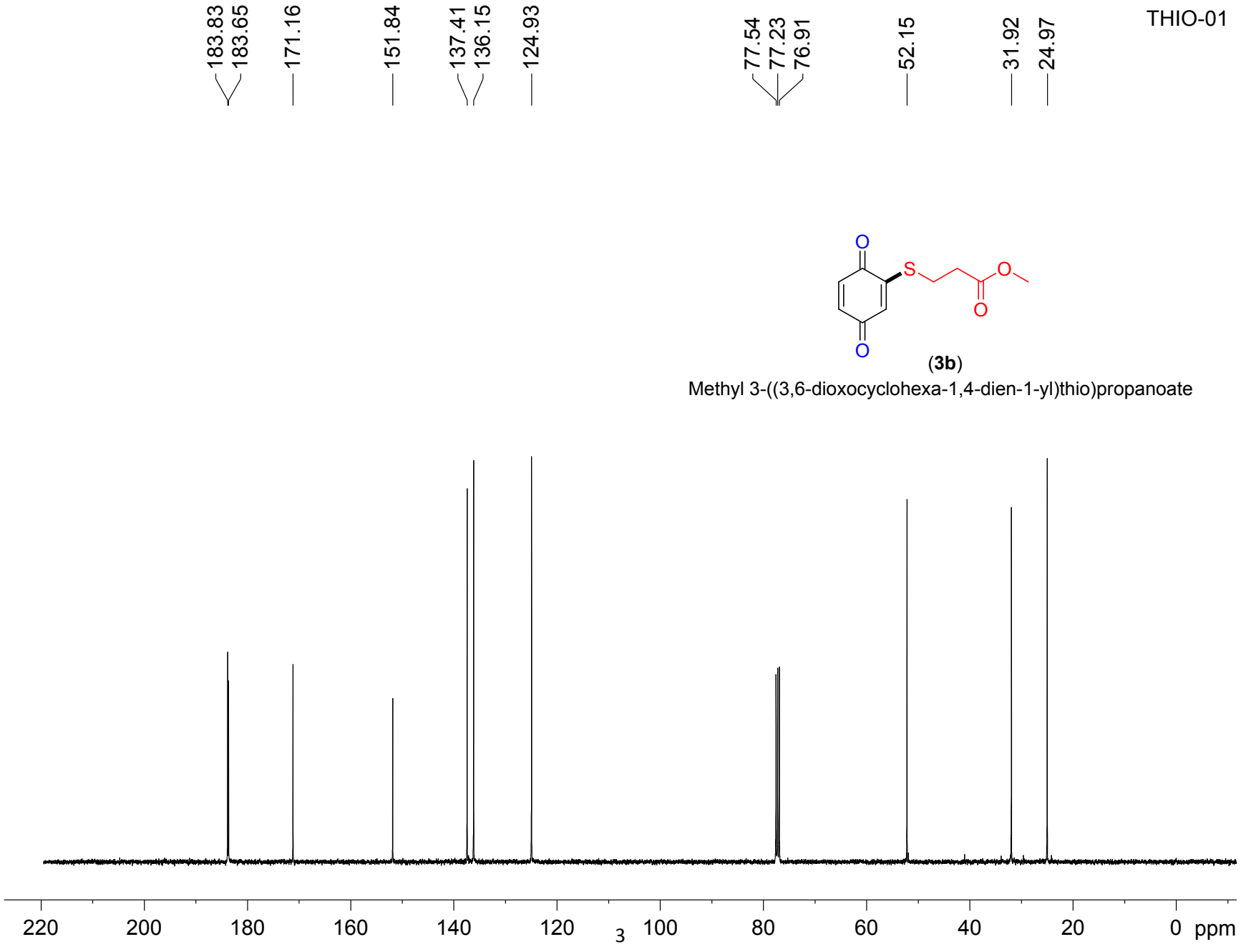

(**3b**)

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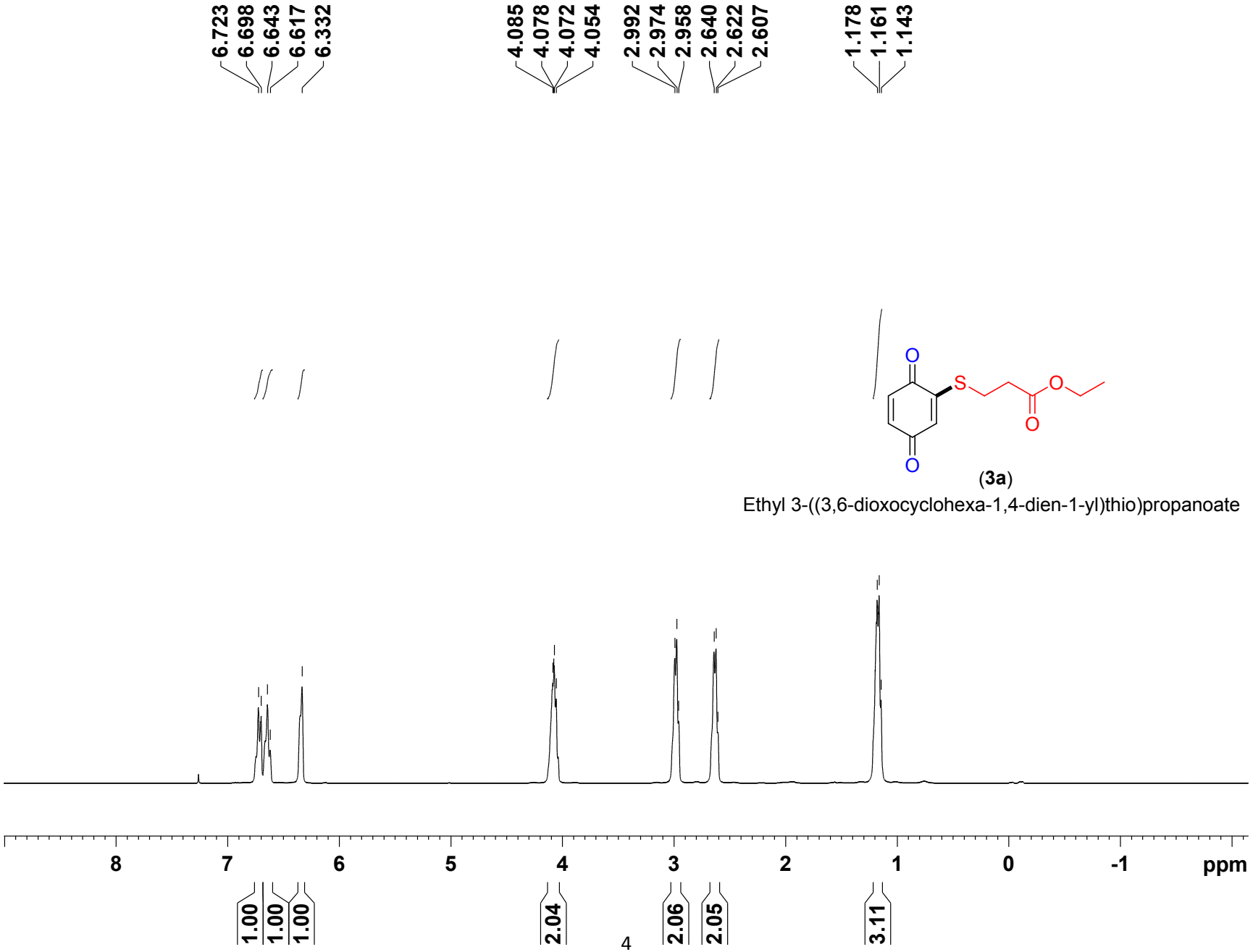

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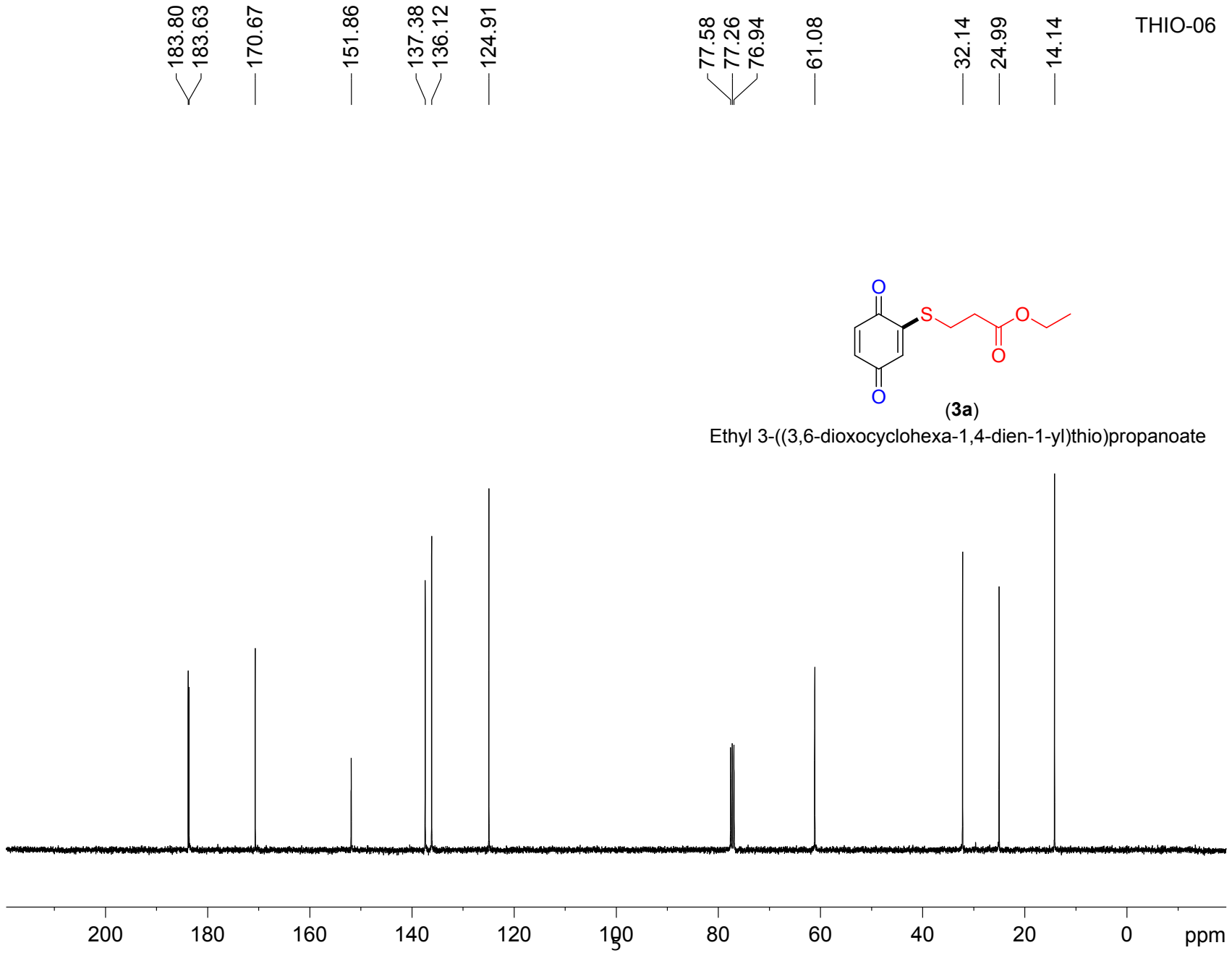
Ethyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate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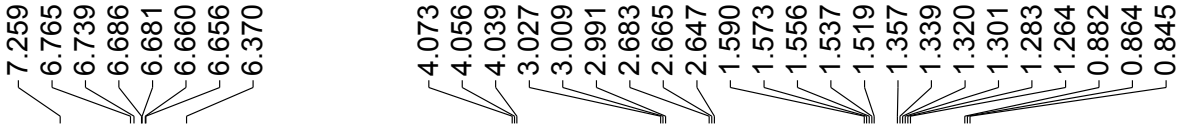
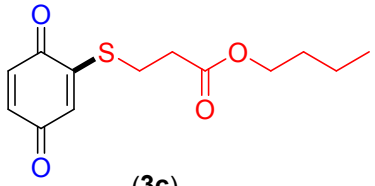
183.63
170.67
151.86
137.38
136.12
124.91
77.58
77.26
76.94
61.08
32.14
24.99
14.14
THIO-06
O
S
O
O
O
(3a)
Ethyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate
200
180
160
140
120
100
80
60
40
20
0
ppm

THIO-08





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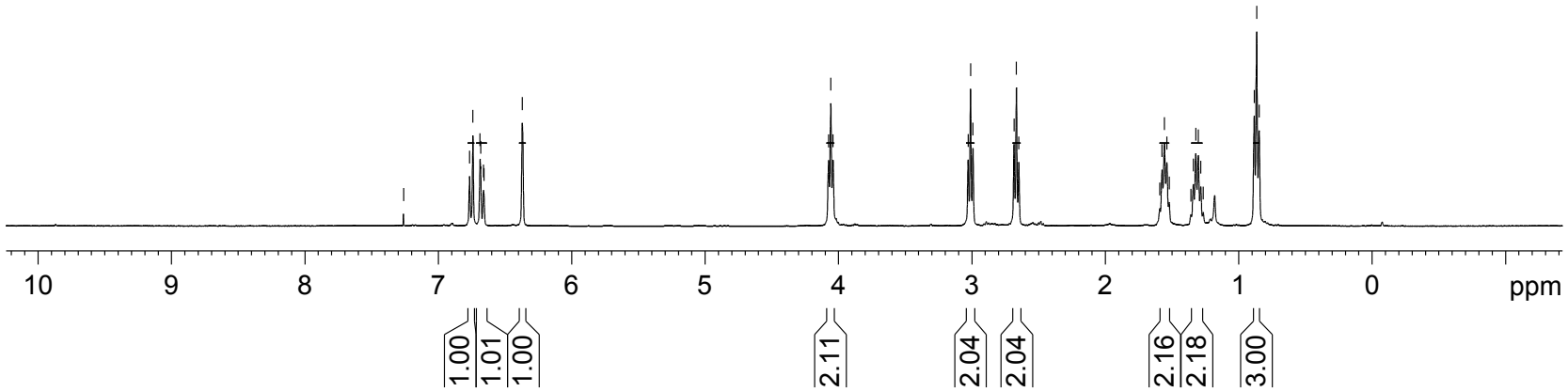
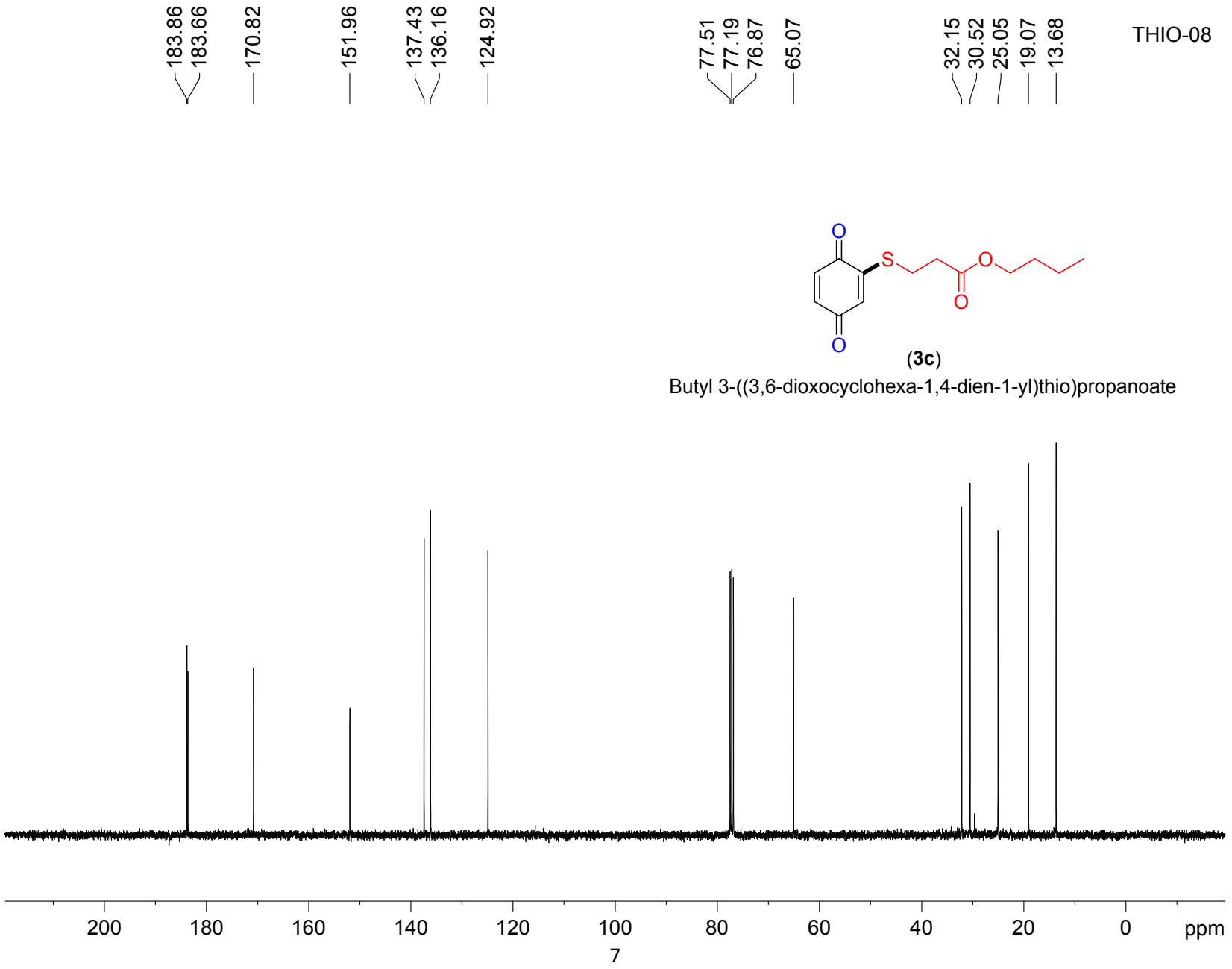
Butyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate

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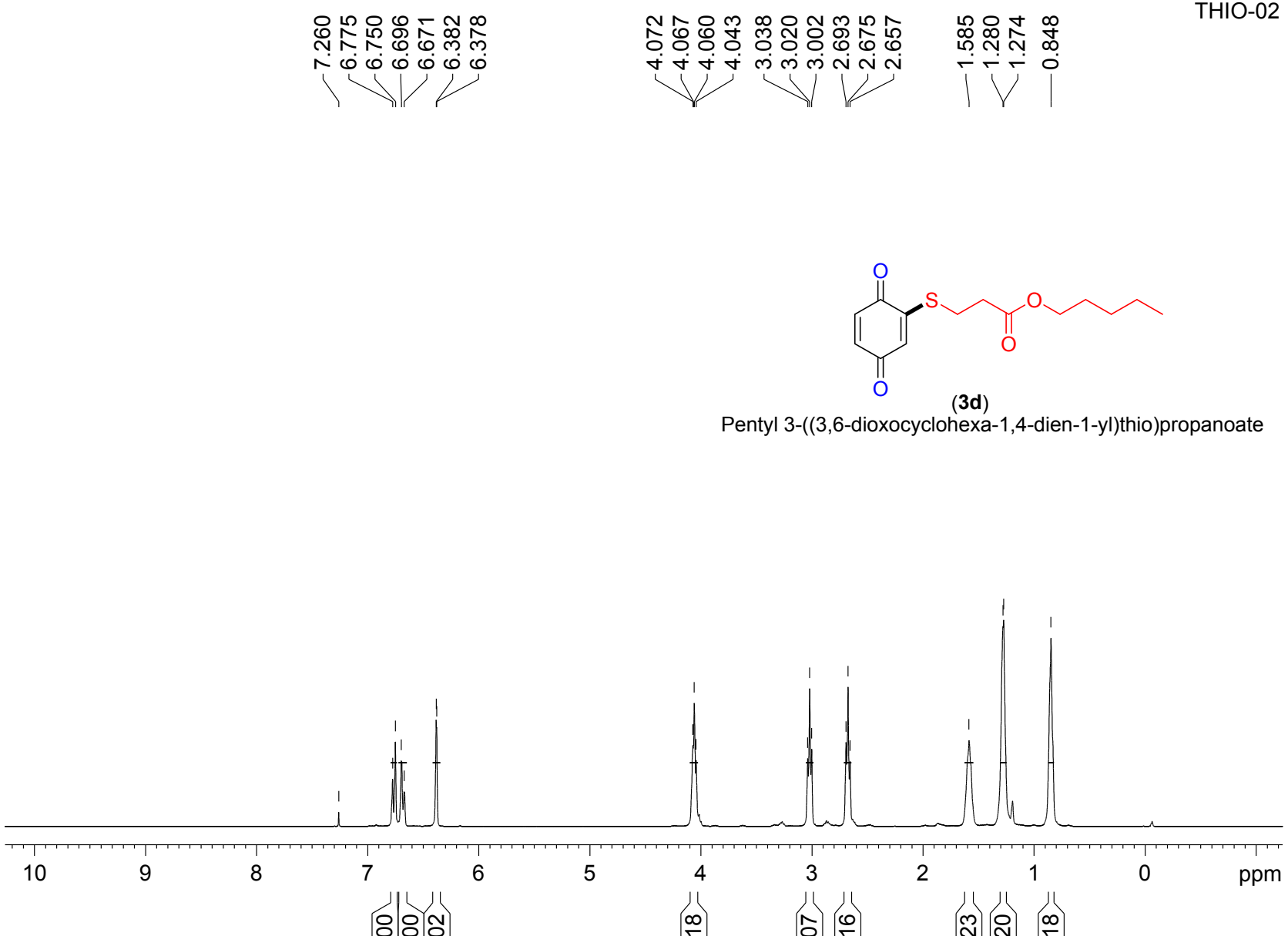
183.66
170.82
151.96
137.43
136.16
124.92
77.51
77.19
76.87
65.07
32.15
30.52
25.05
19.07
13.68
THIO-08
O
S
O
O
O
(3c)
Butyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate
200
180
160
140
120
100
80
60
40
20
0
ppm

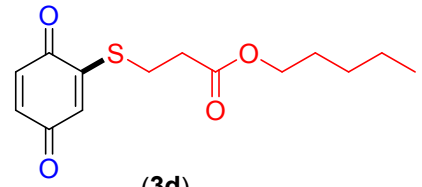
THIO-02



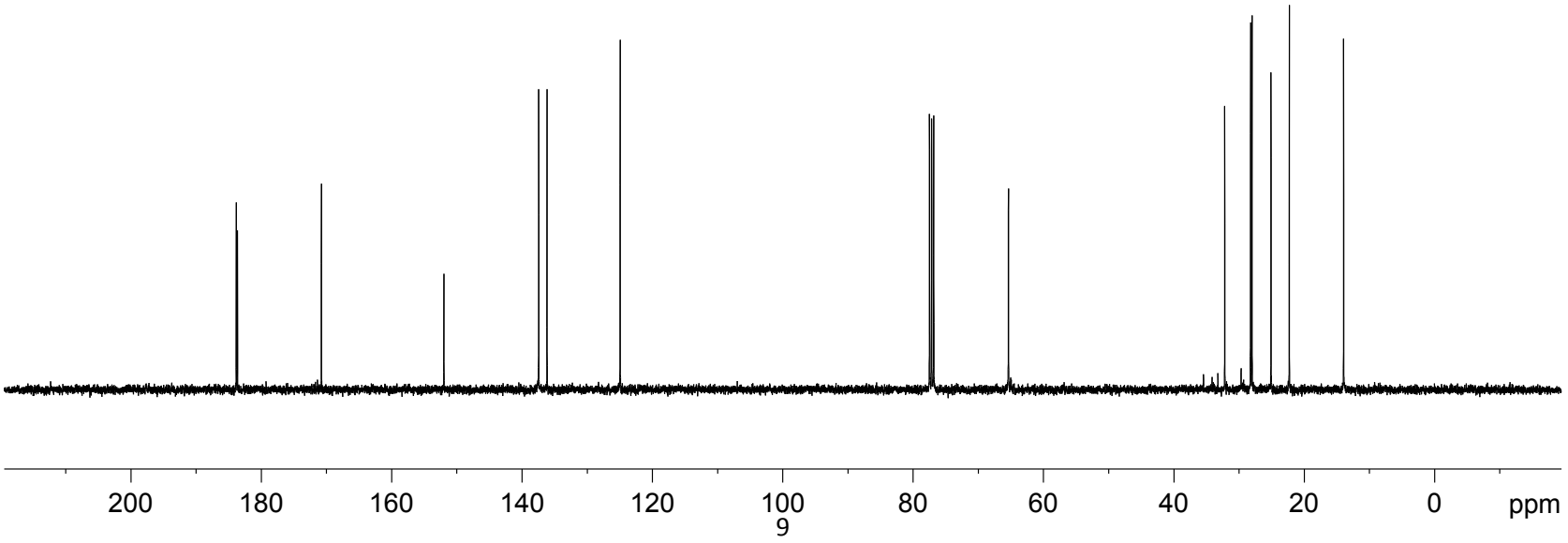
(**3d**)
Pentyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate

THIO-02

183.83
183.64
170.78
151.97
137.43
136.15
124.93
77.47
77.15
76.83
65.36
32.18
28.20
27.99
25.07
22.27
13.93



(**3d**)
Pentyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate



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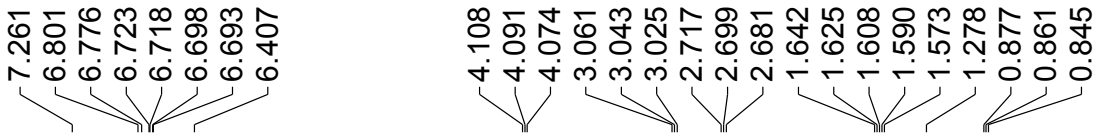
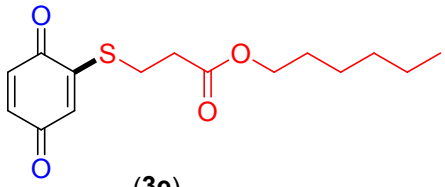
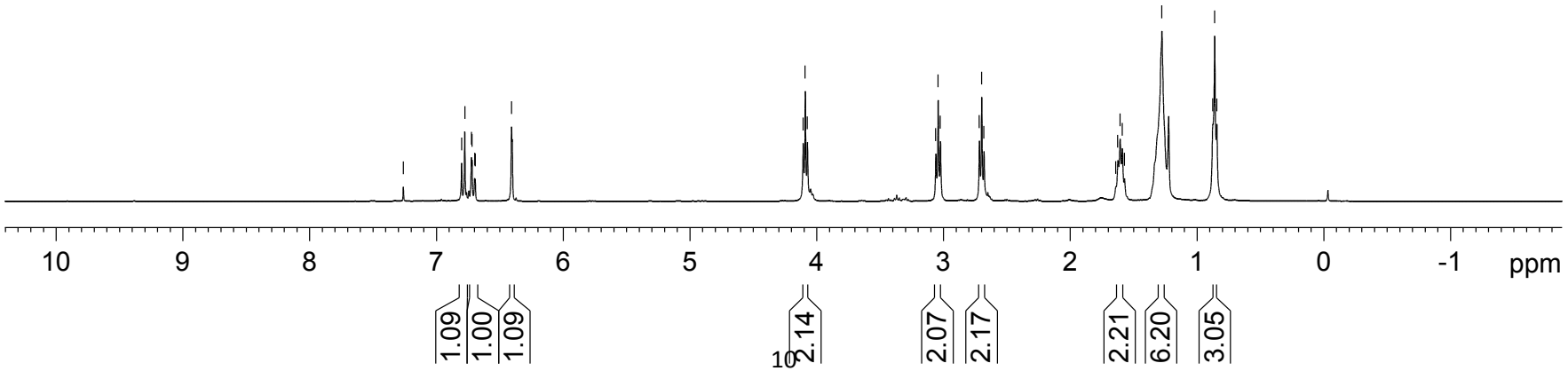




(**3e**)

Hexyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate



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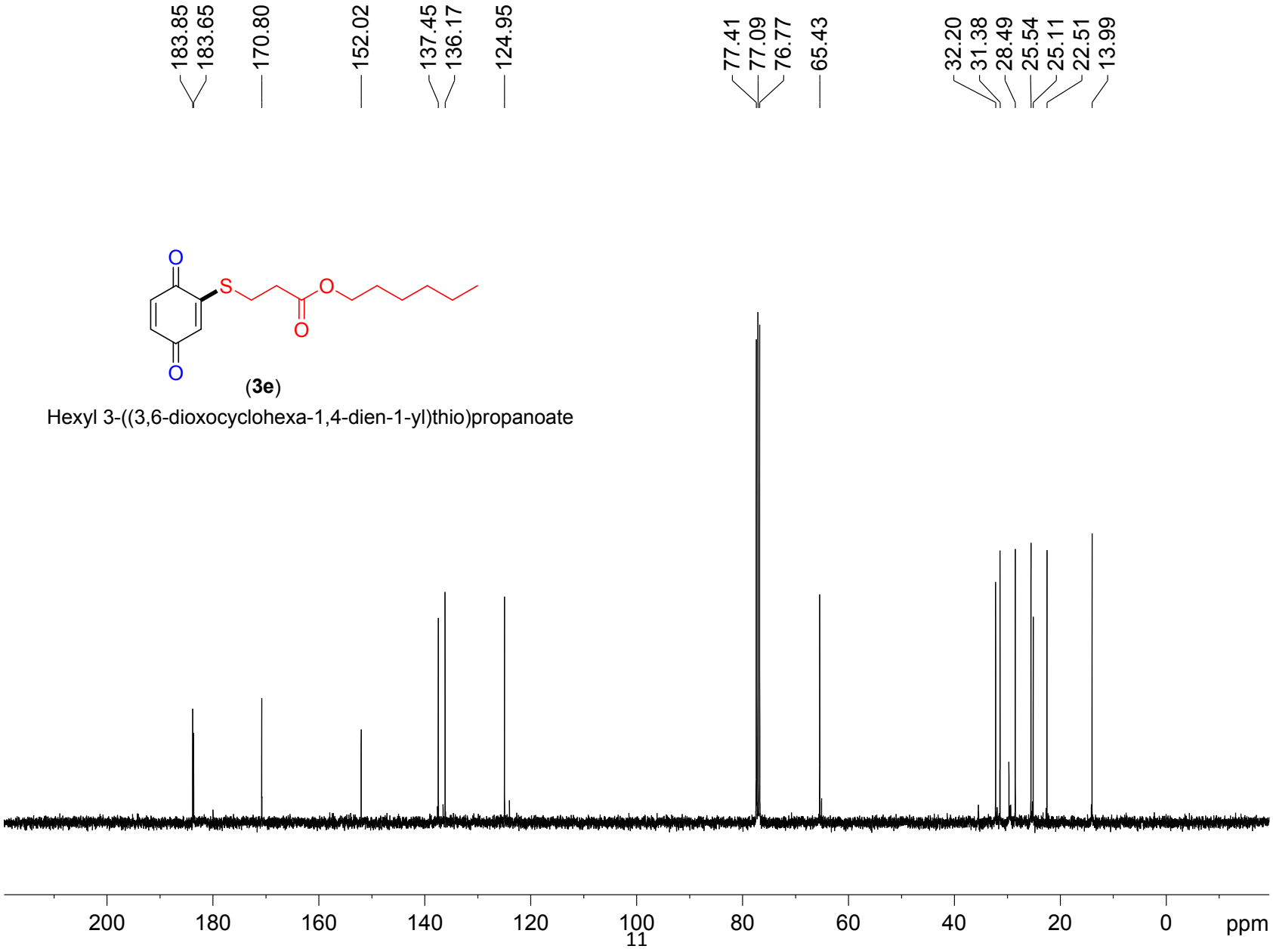
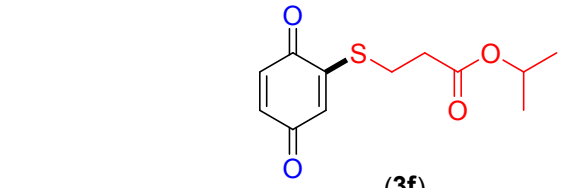


(**3e**)

Hexyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate

THIO-05



(**3f**)

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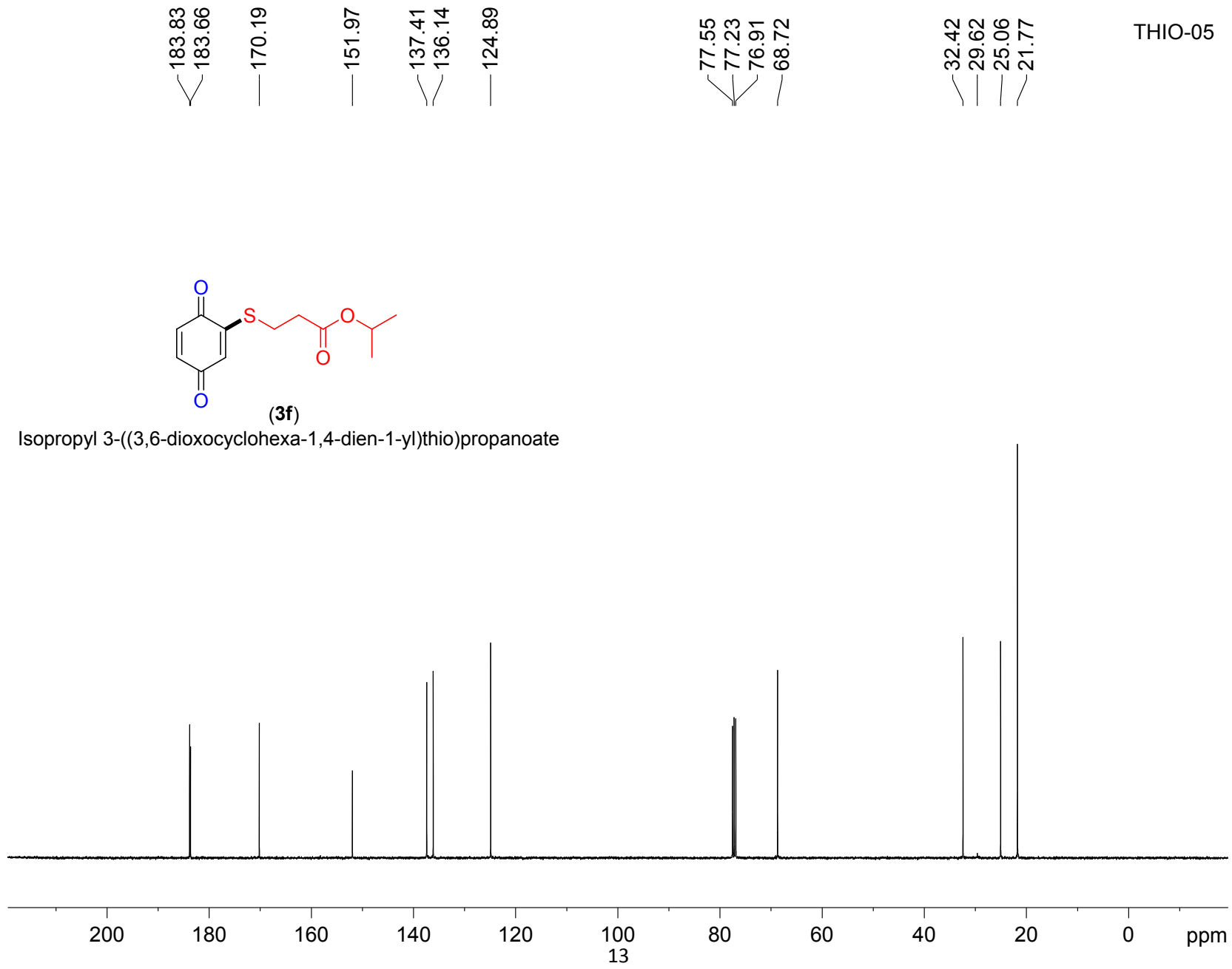
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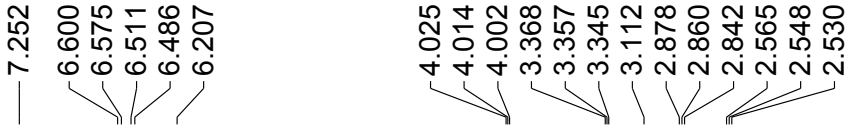
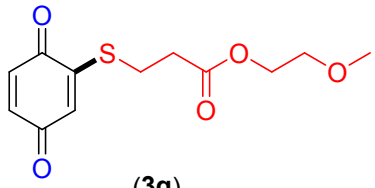
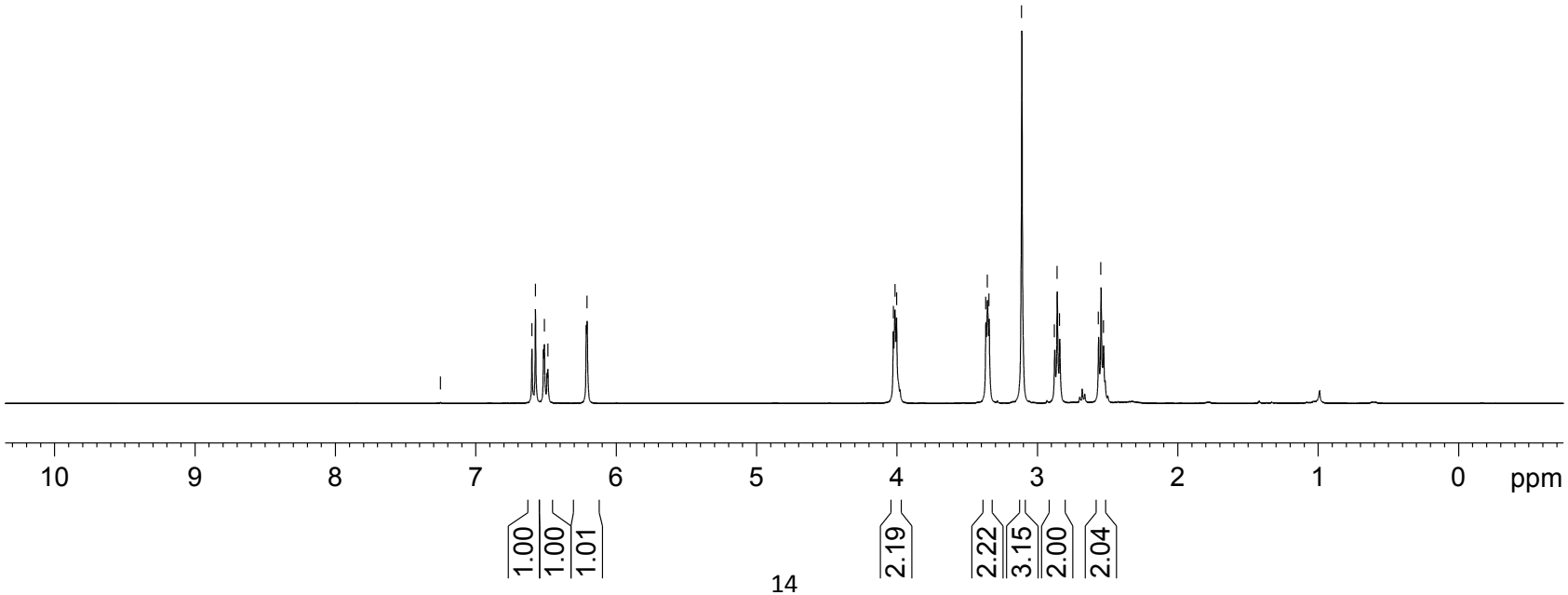
183.66
170.19
151.97
137.41
136.14
124.89
77.55
77.23
76.91
68.72
32.42
29.62
25.06
21.77
THIO-05
O
S
O
O
O
(3f)
Isopropyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate
200
180
160
140
120
100
80
60
40
20
0
ppm
13

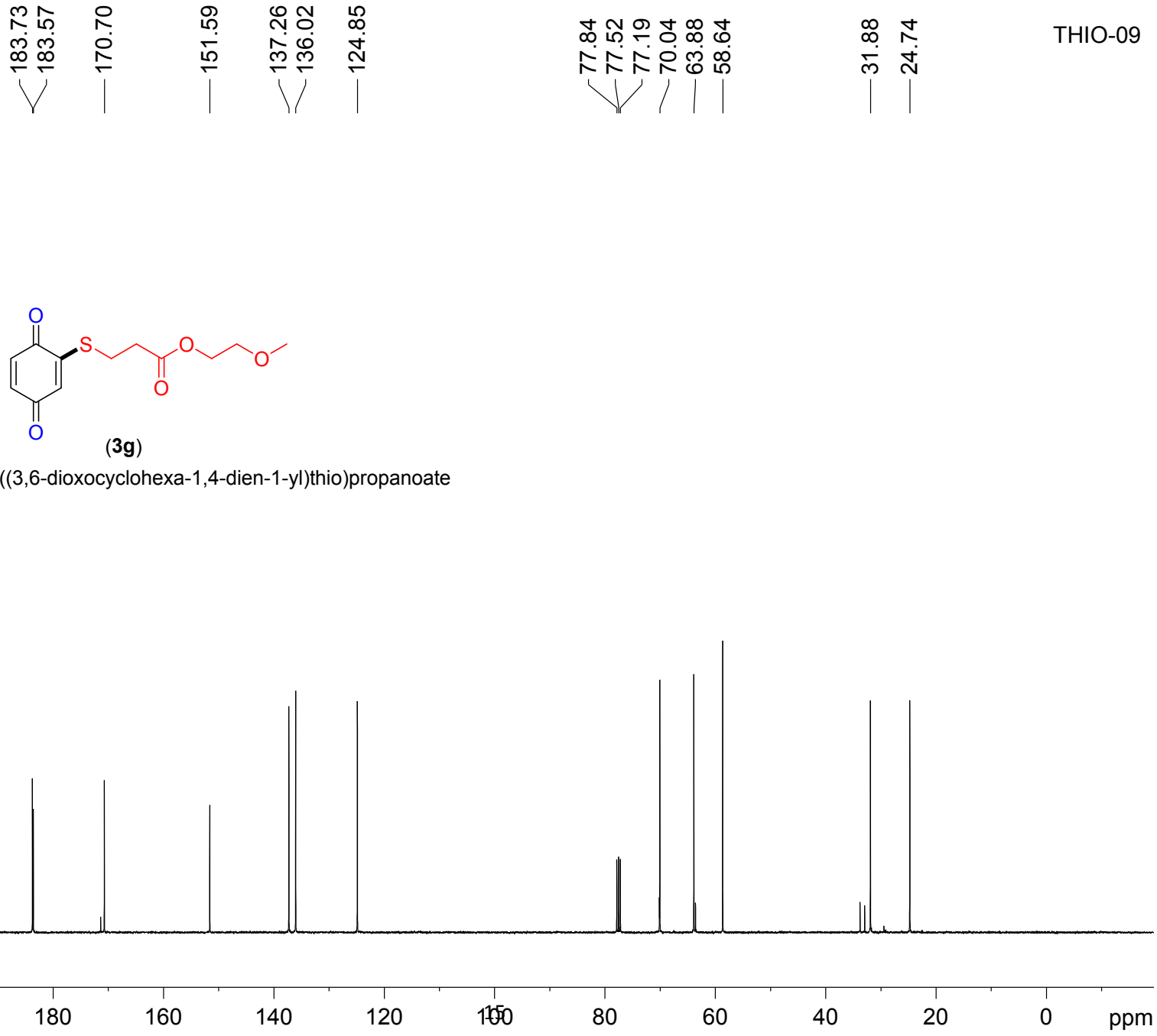




(**3g**)

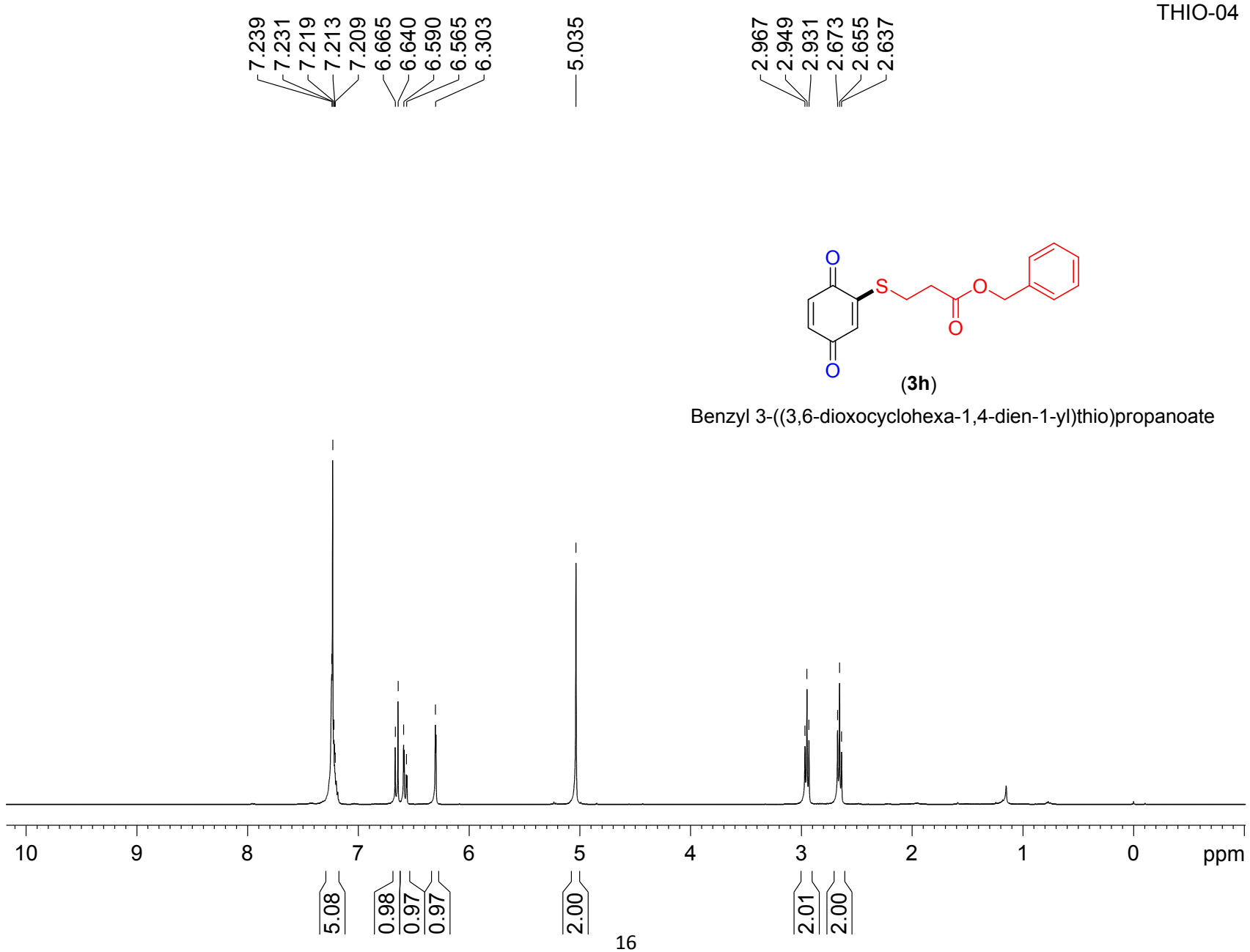
2-methoxyethyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate





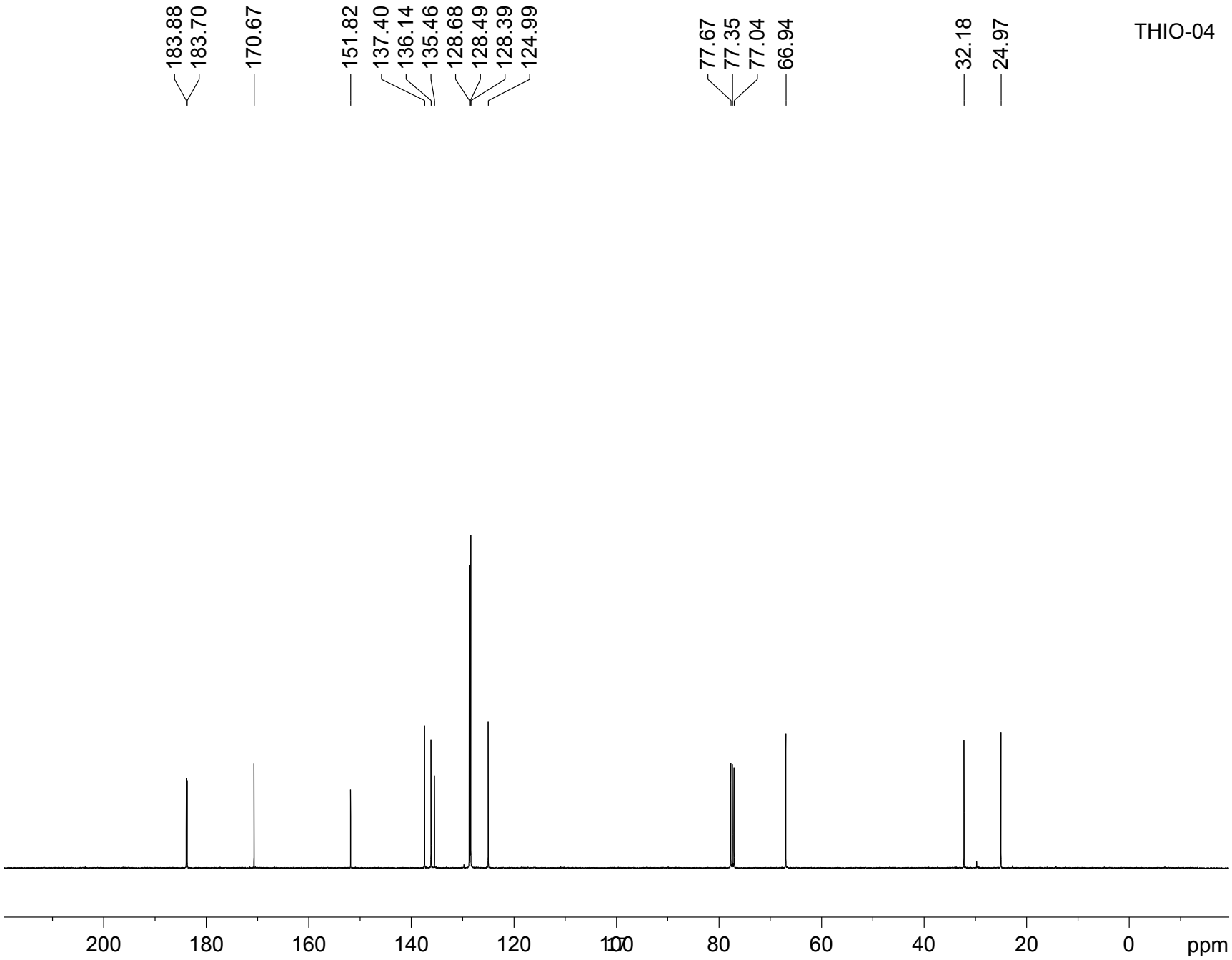
(**3g**)

2-methoxyethyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate



(**3h**)

Benzyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate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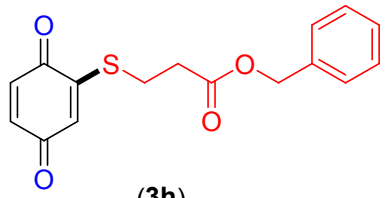
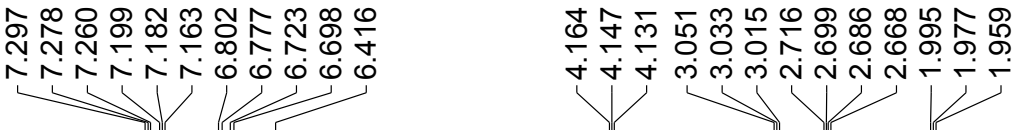
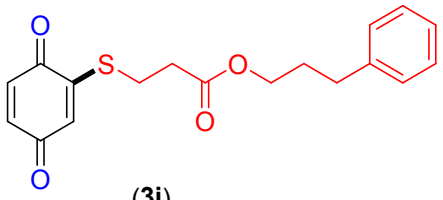
183.70
170.67
151.82
137.40
136.14
135.46
128.68
128.49
128.39
124.99
77.67
77.35
77.04
66.94
32.18
24.97
THIO-04
200
180
160
140
120
100
80
60
40
20
0
ppm



(**3h**)

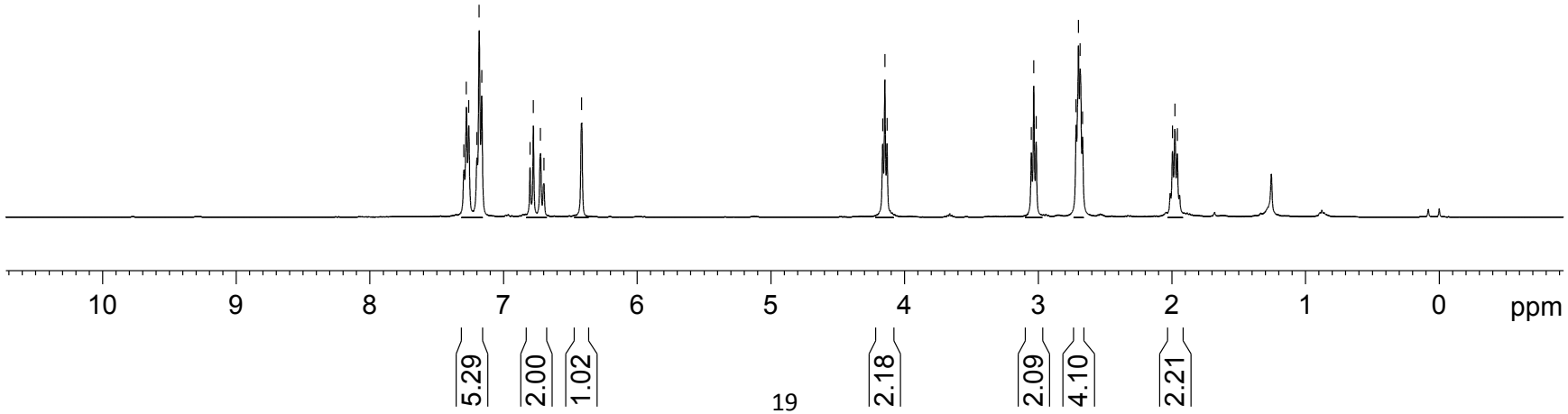
Benzyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate

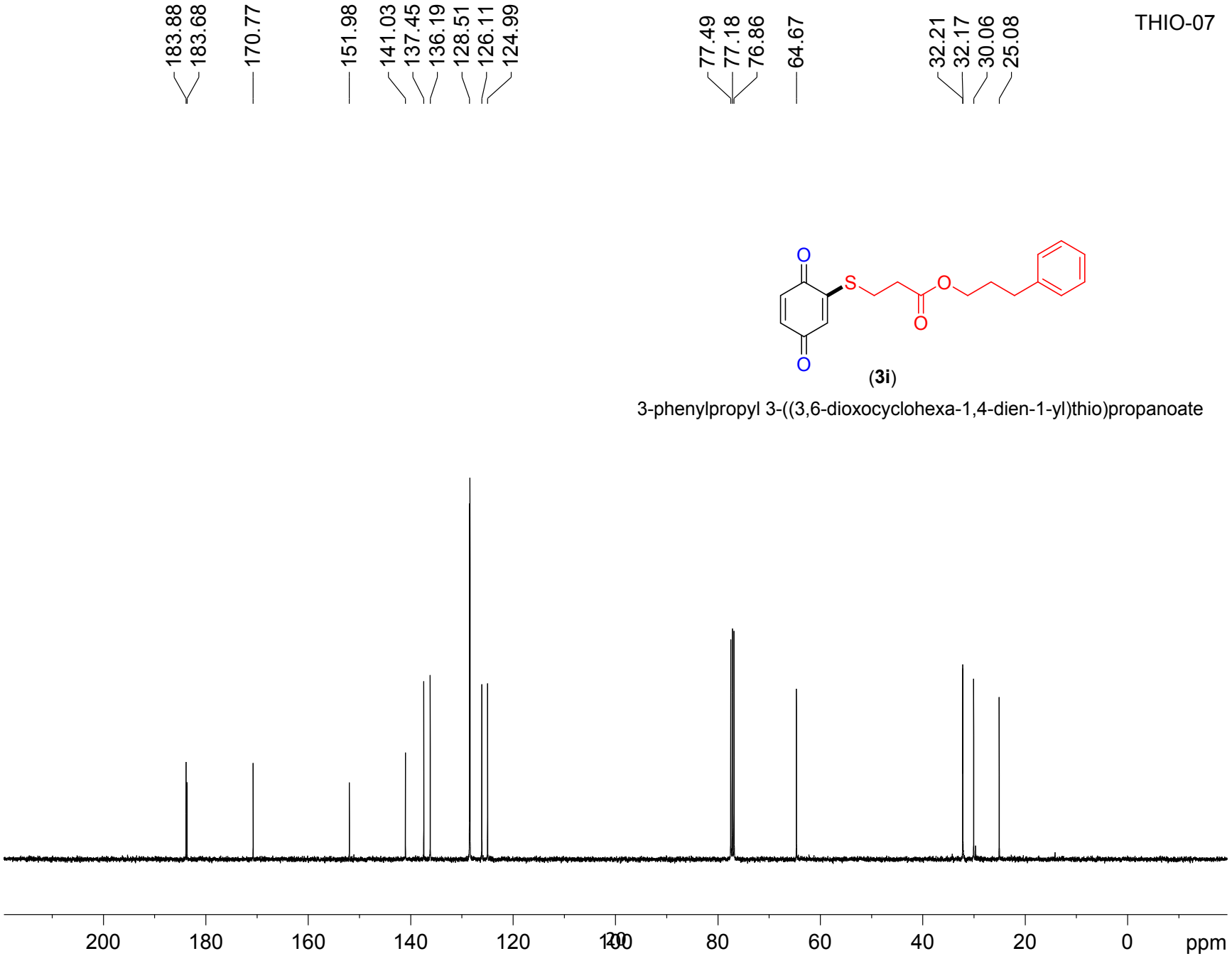




(**3i**)

3-phenylpropyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate





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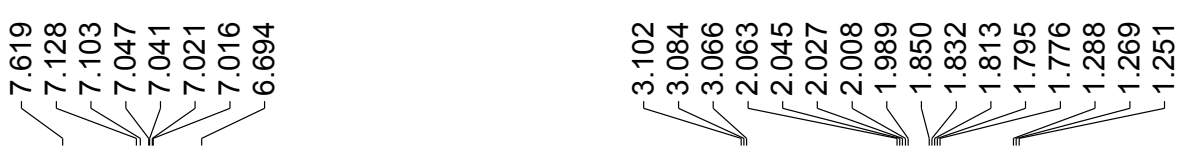
3-phenylpropyl 3-((3,6-dioxocyclohexa-1,4-dien-1-yl)thio)propanoate



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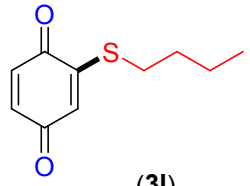
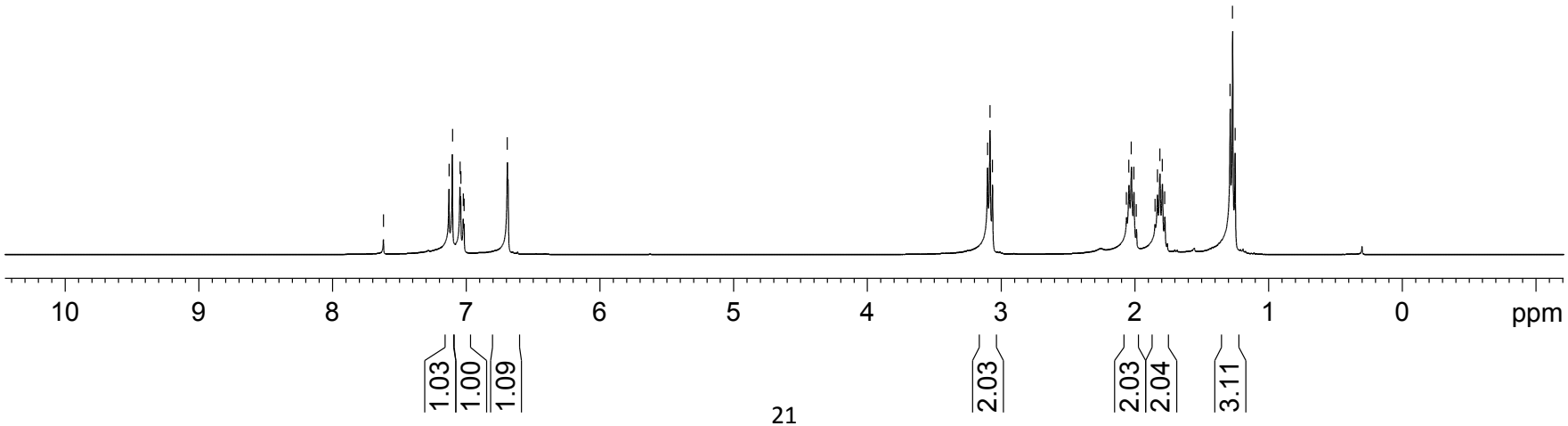
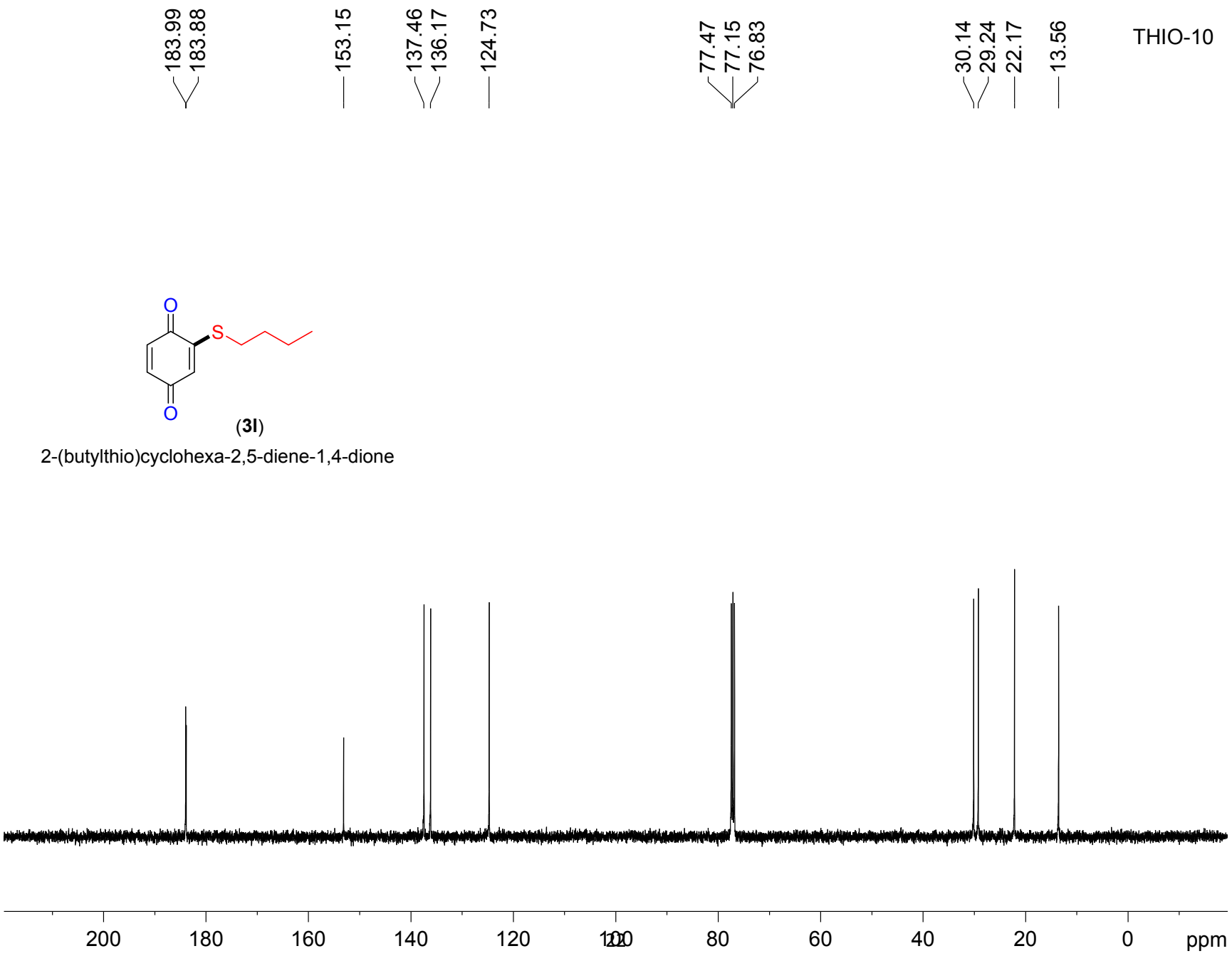


(**3l**)

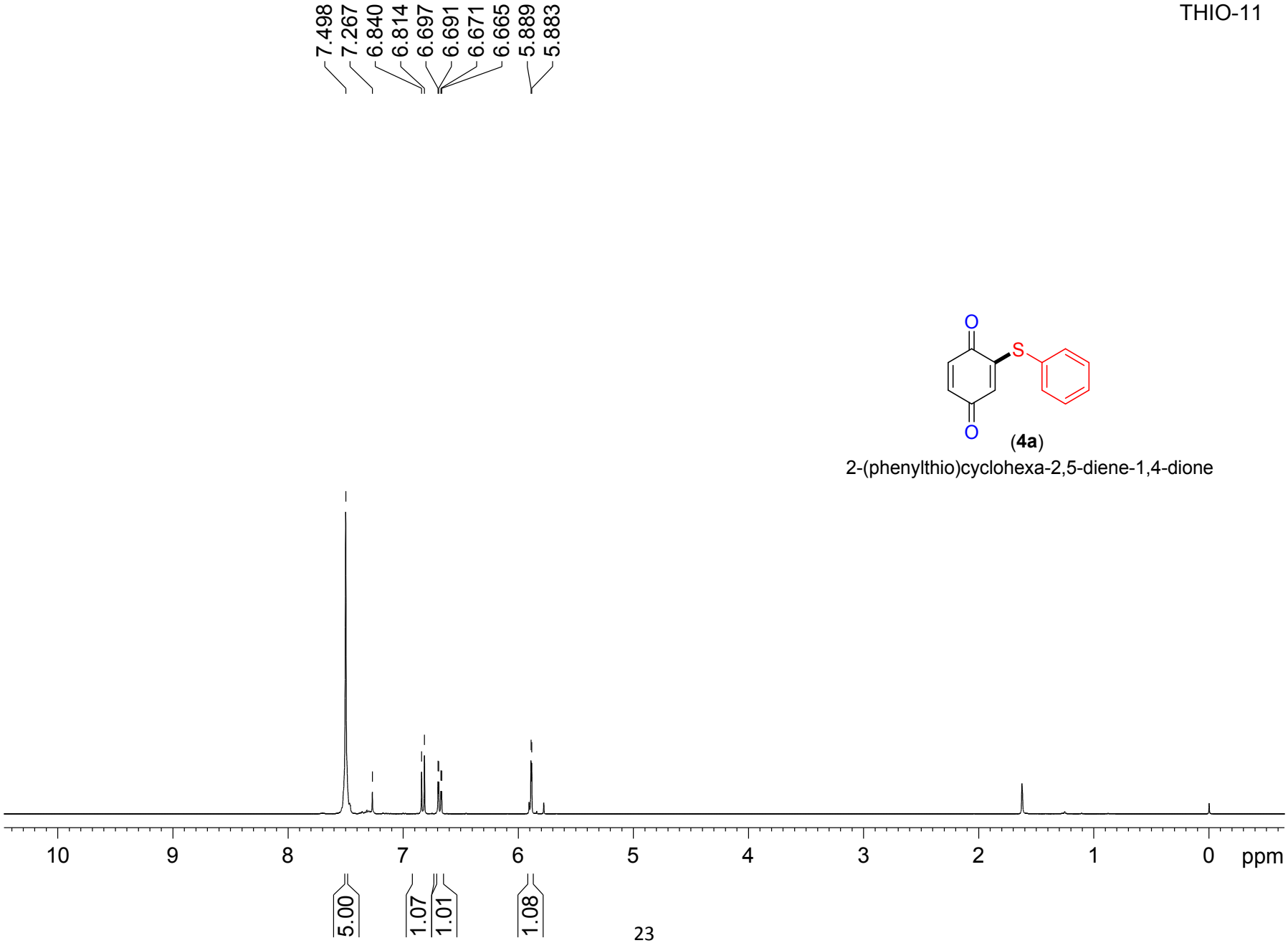
2-(butylthio)cyclohexa-2,5-diene-1,4-dione





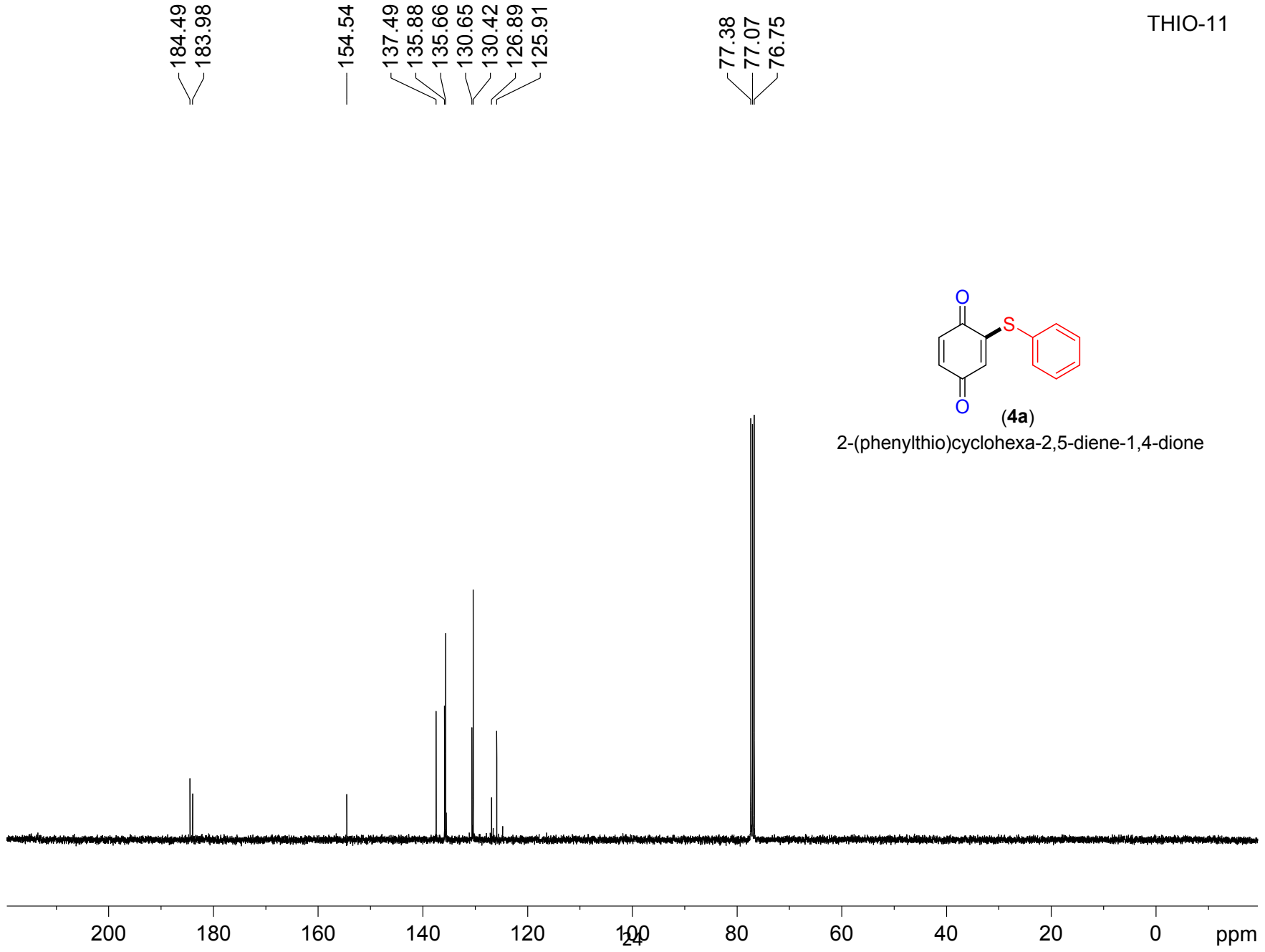
(**3l**)

2-(butylthio)cyclohexa-2,5-diene-1,4-dione



(**4a**)

2-(phenylthio)cyclohexa-2,5-diene-1,4-dione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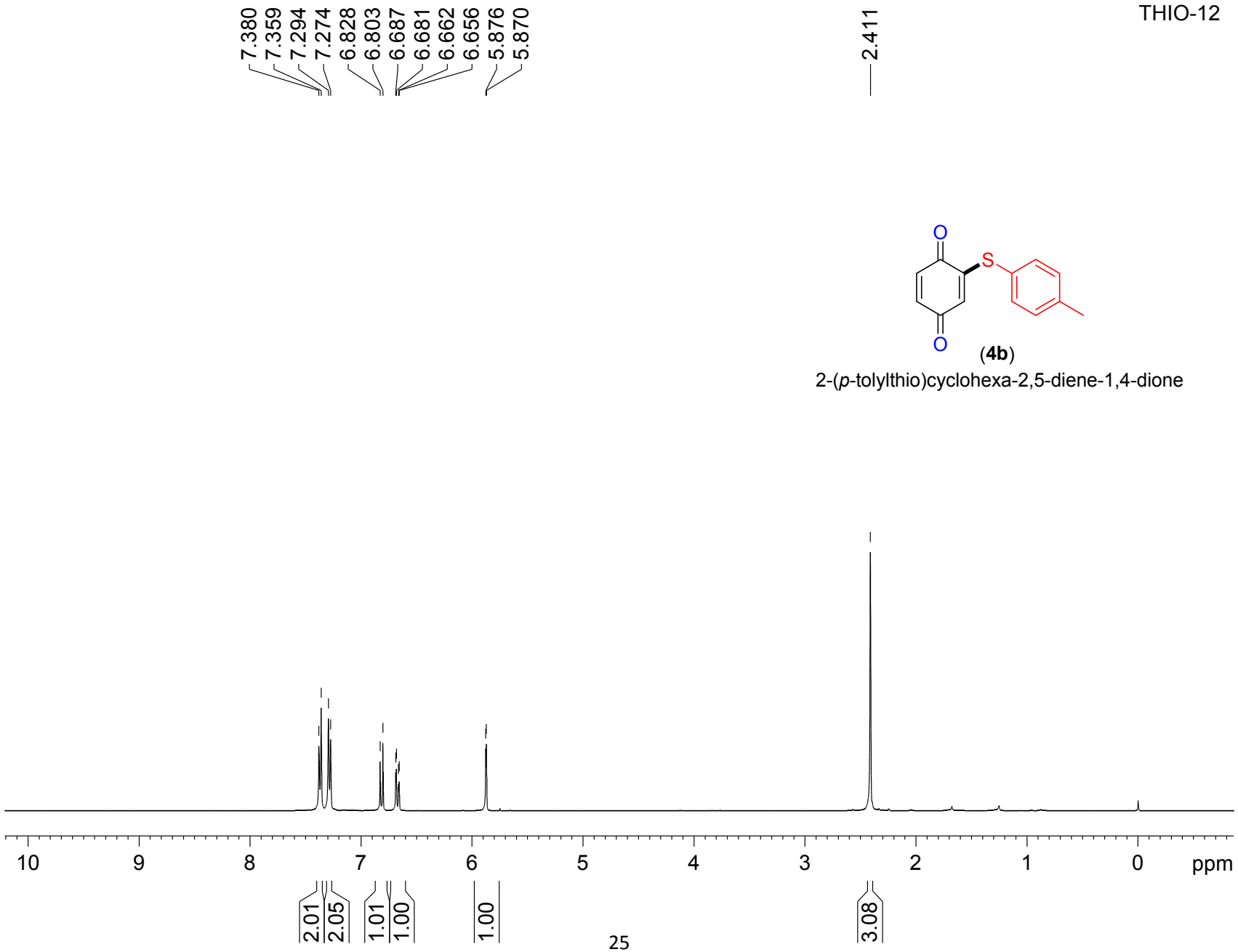
183.98
154.54
137.49
135.88
135.66
130.65
130.42
126.89
125.91
77.38
77.07
76.75
THIO-11
O
S
O
(4a)
2-(phenylthio)cyclohexa-2,5-diene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm



(**4b**)

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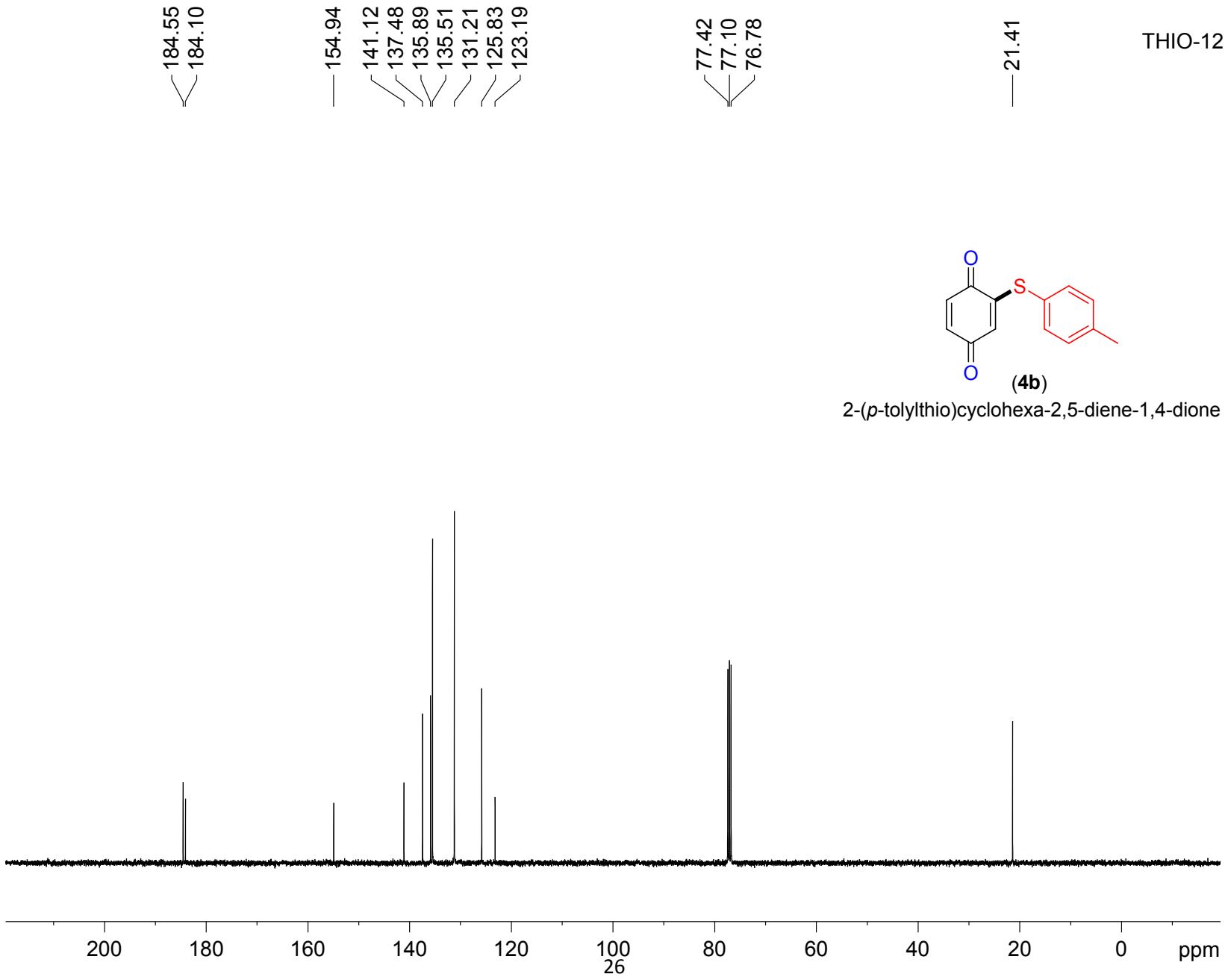
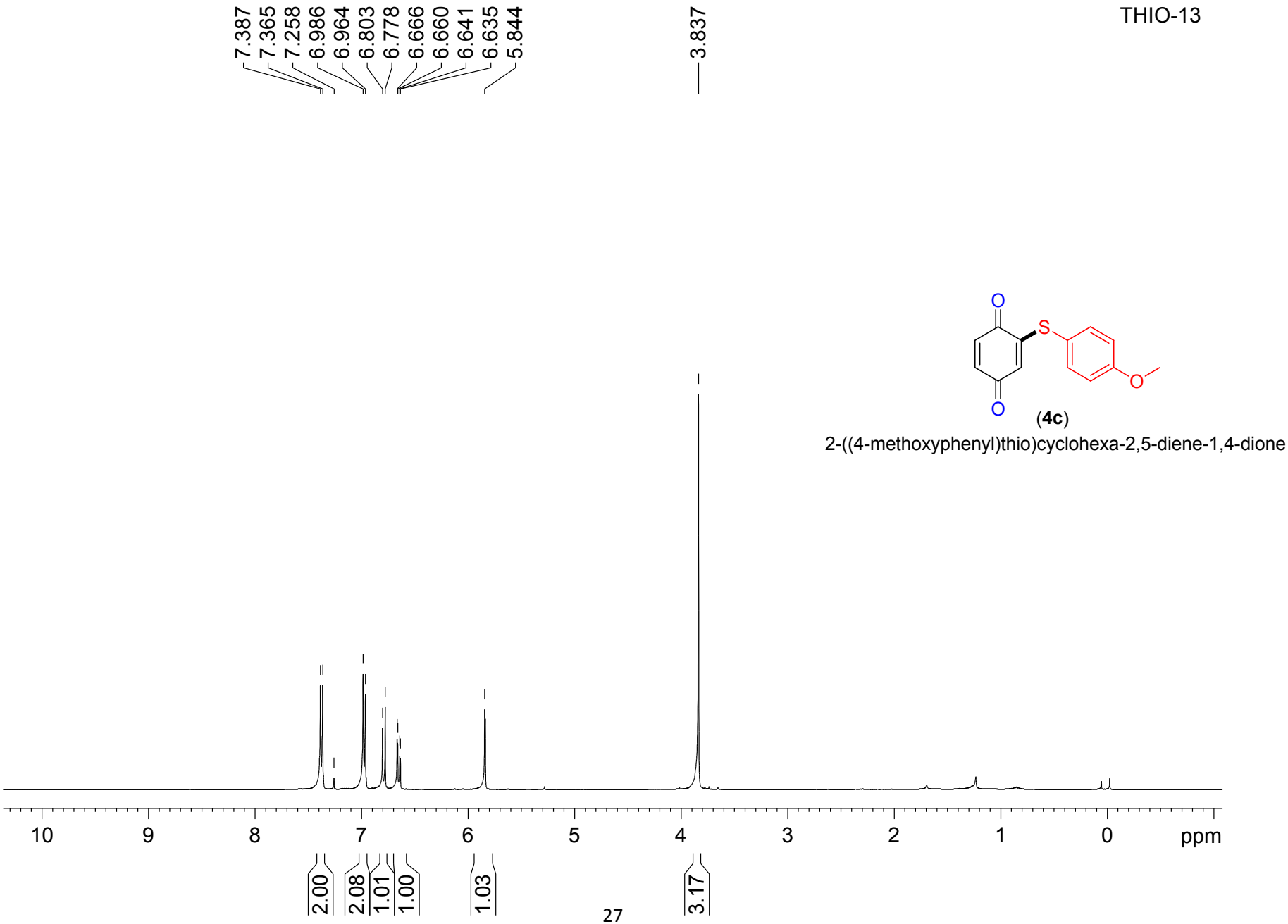
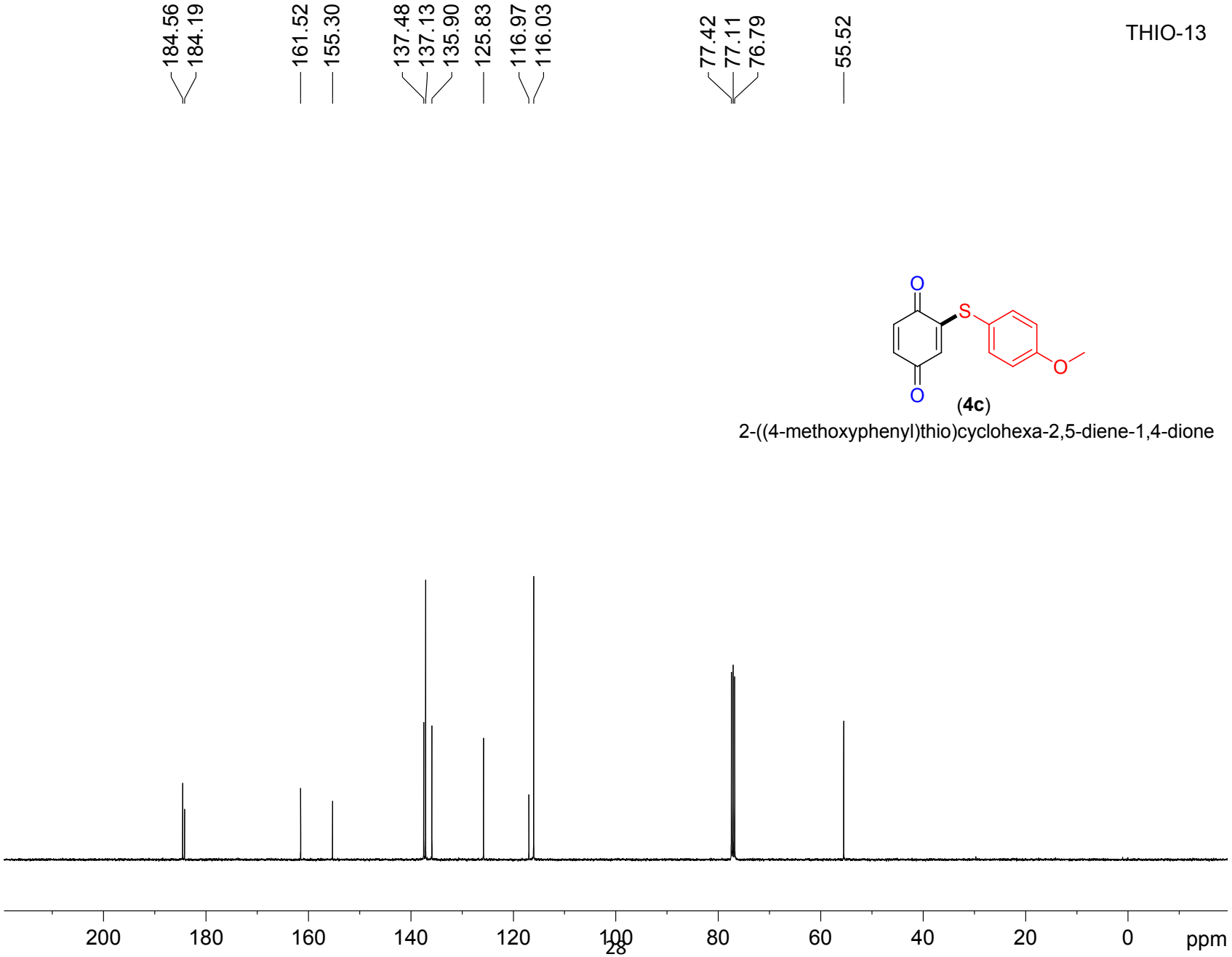
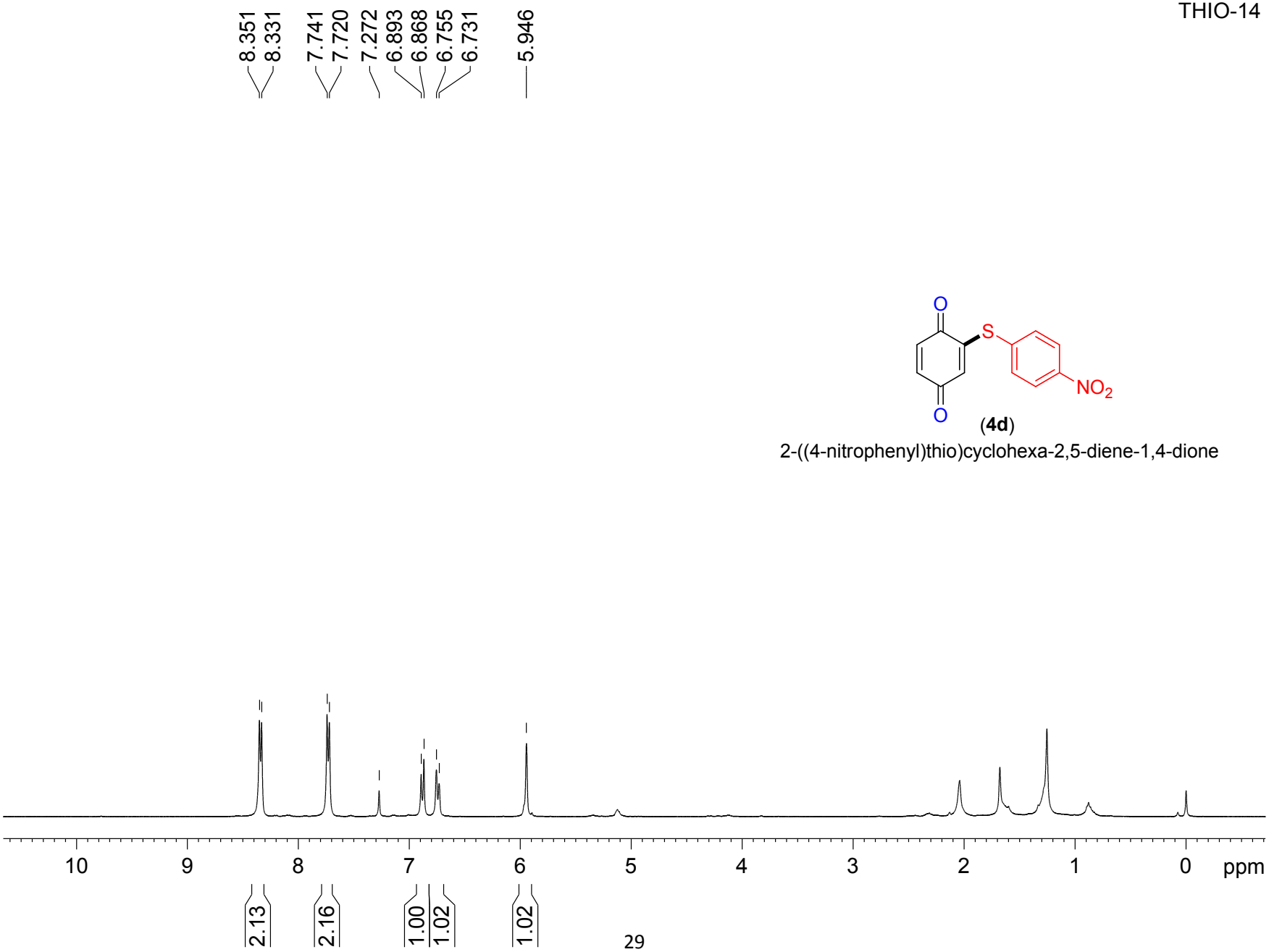

184.55
184.10
154.94
141.12
137.48
135.89
135.51
131.21
125.83
123.19
77.42
77.10
76.78
21.41
THIO-12
O
S
O
(4b)
2-(p-tolylthio)cyclohexa-2,5-diene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

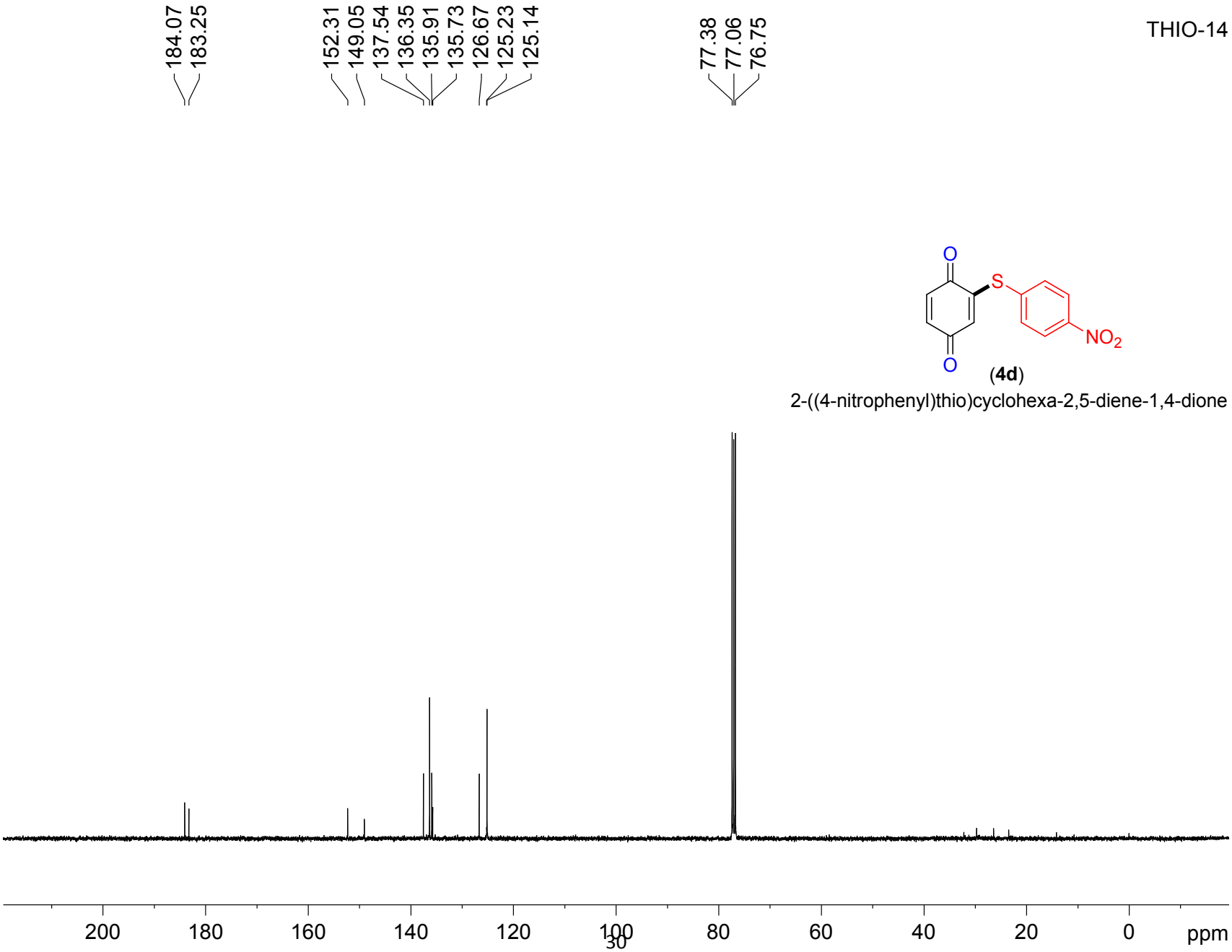

7.387
7.365
7.258
6.986
6.964
6.803
6.778
6.666
6.660
6.641
6.635
5.844
3.837
THIO-13
O
S
O
O
(4c)
2-((4-methoxyphenyl)thio)cyclohexa-2,5-diene-1,4-dione
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.08
1.01
1.00
1.03
3.17

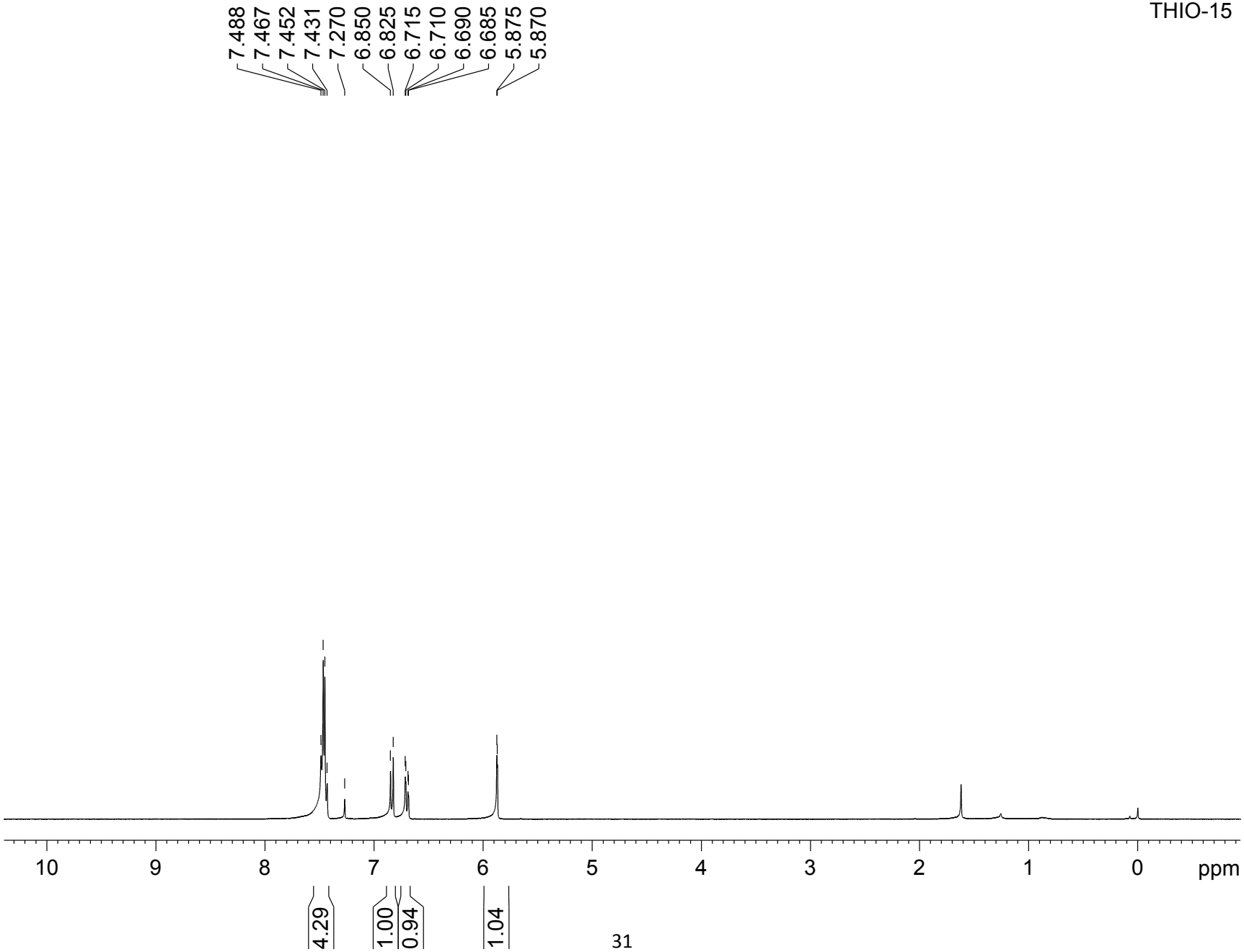

184.56
184.19
161.52
155.30
137.48
137.13
135.90
125.83
116.97
116.03
77.42
77.11
76.79
55.52
THIO-13
O
S
O
O
(4c)
2-((4-methoxyphenyl)thio)cyclohexa-2,5-diene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

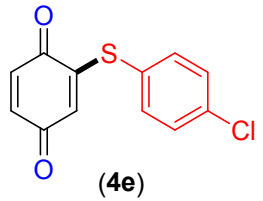


(**4d**)

2-((4-nitrophenyl)thio)cyclohexa-2,5-diene-1,4-dione

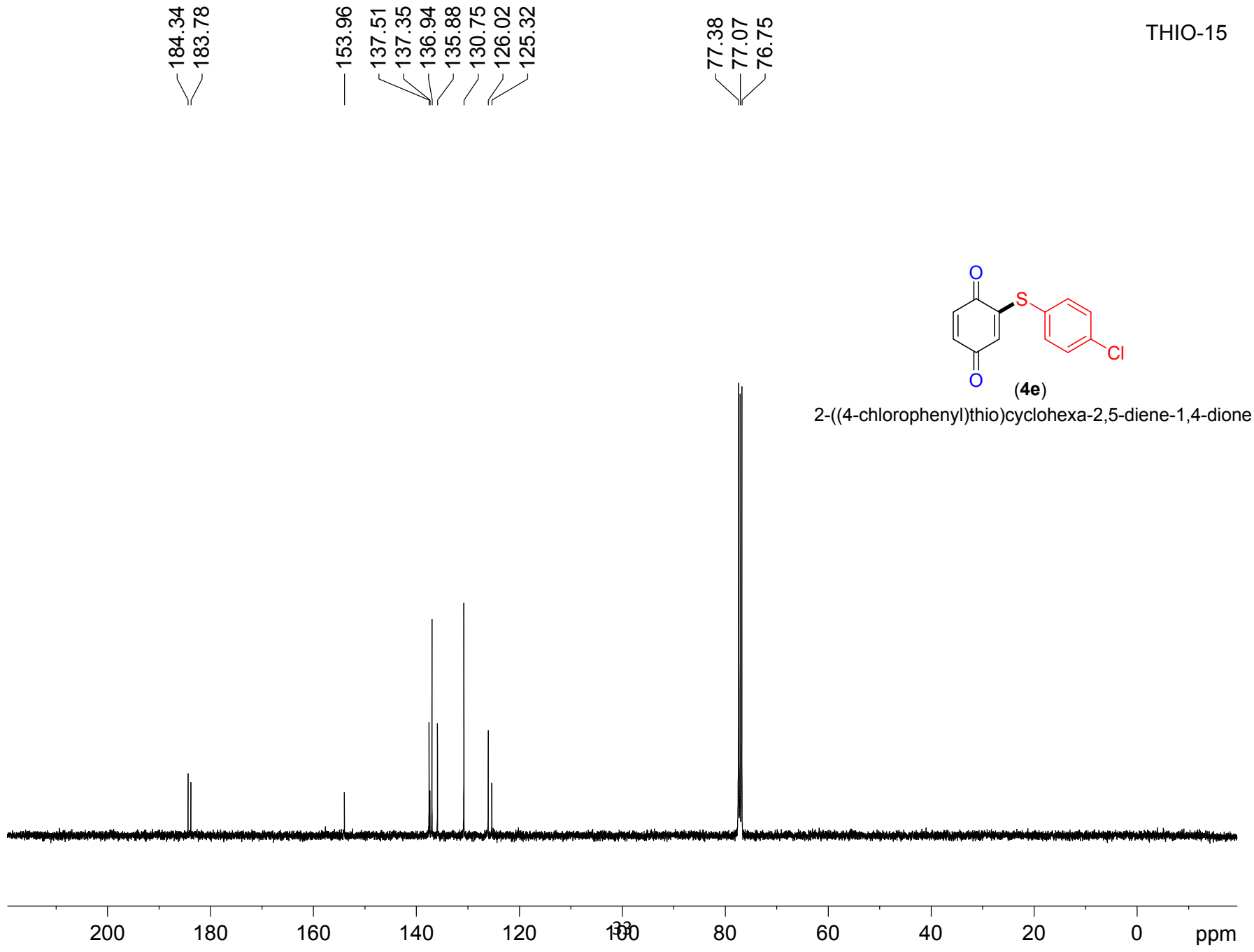

184.07
183.25
152.31
149.05
137.54
136.35
135.91
135.73
126.67
125.23
125.14
77.38
77.06
76.75
THIO-14
O
S
NO2
O
(4d)
2-((4-nitrophenyl)thio)cyclohexa-2,5-diene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

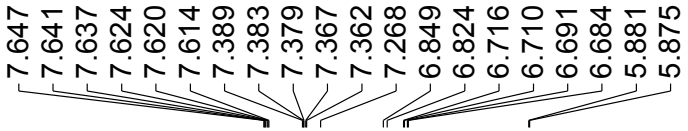

7.488
7.467
7.452
7.431
7.270
6.850
6.825
6.715
6.710
6.690
6.685
5.875
5.870
THIO-15
10
9
8
7
6
5
4
3
2
1
0
ppm
4.29
1.00
0.94
1.04

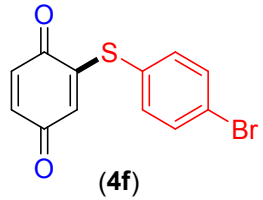


(**4e**)

2-((4-chlorophenyl)thio)cyclohexa-2,5-diene-1,4-dione

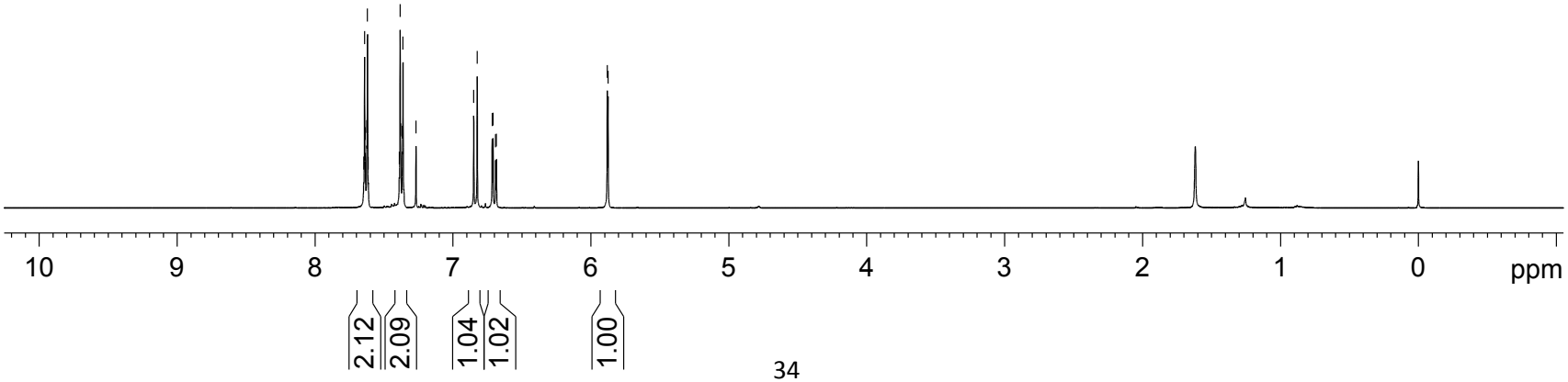

184.34
183.78
153.96
137.51
137.35
136.94
135.88
130.75
126.02
125.32
77.38
77.07
76.75
THIO-15
O
S
Cl
O
(4e)
2-((4-chlorophenyl)thio)cyclohexa-2,5-diene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

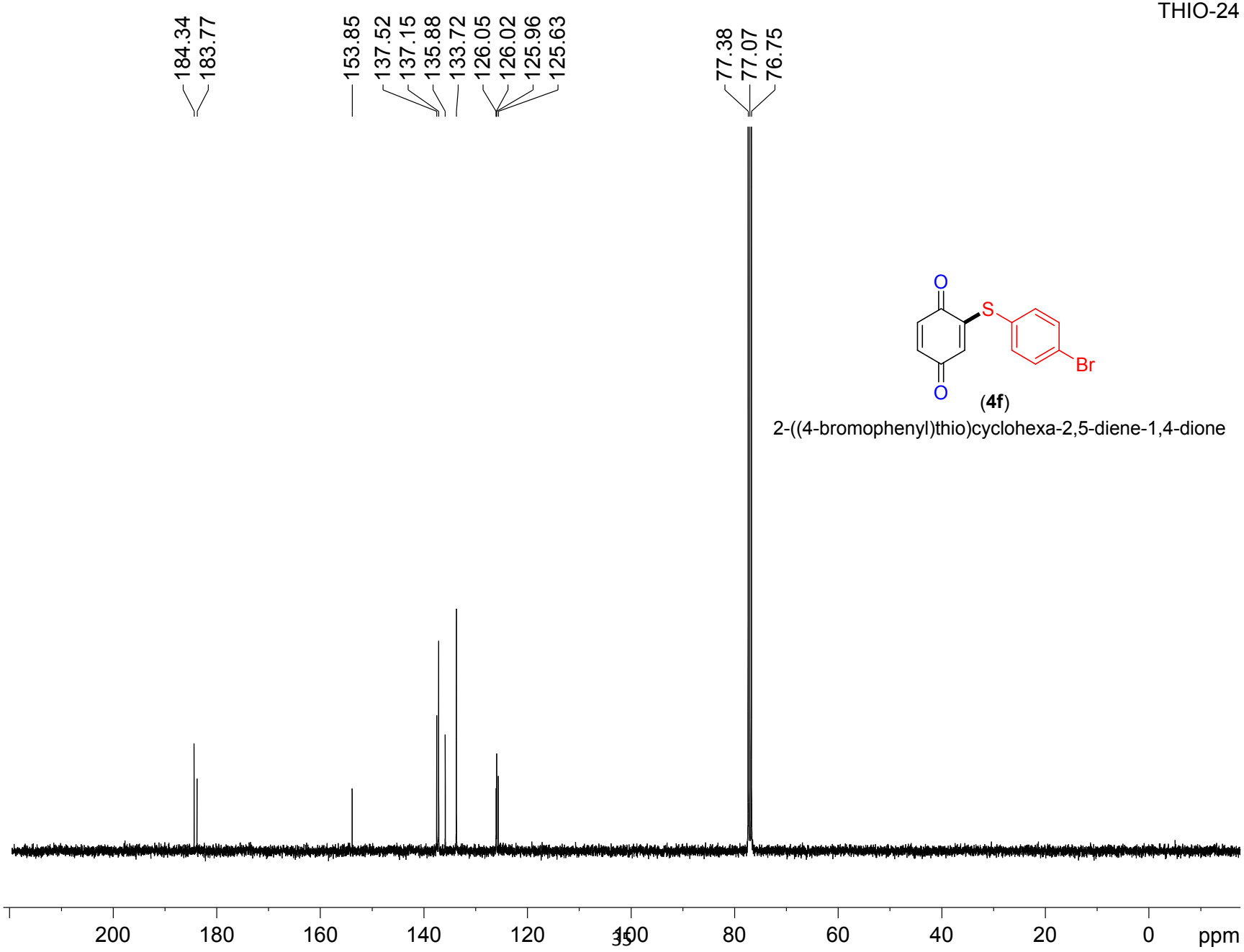




(**4f**)

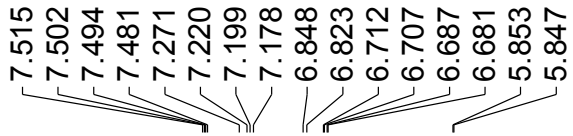
2-((4-bromophenyl)thio)cyclohexa-2,5-diene-1,4-dione

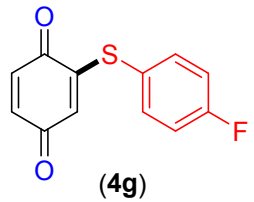




(**4f**)

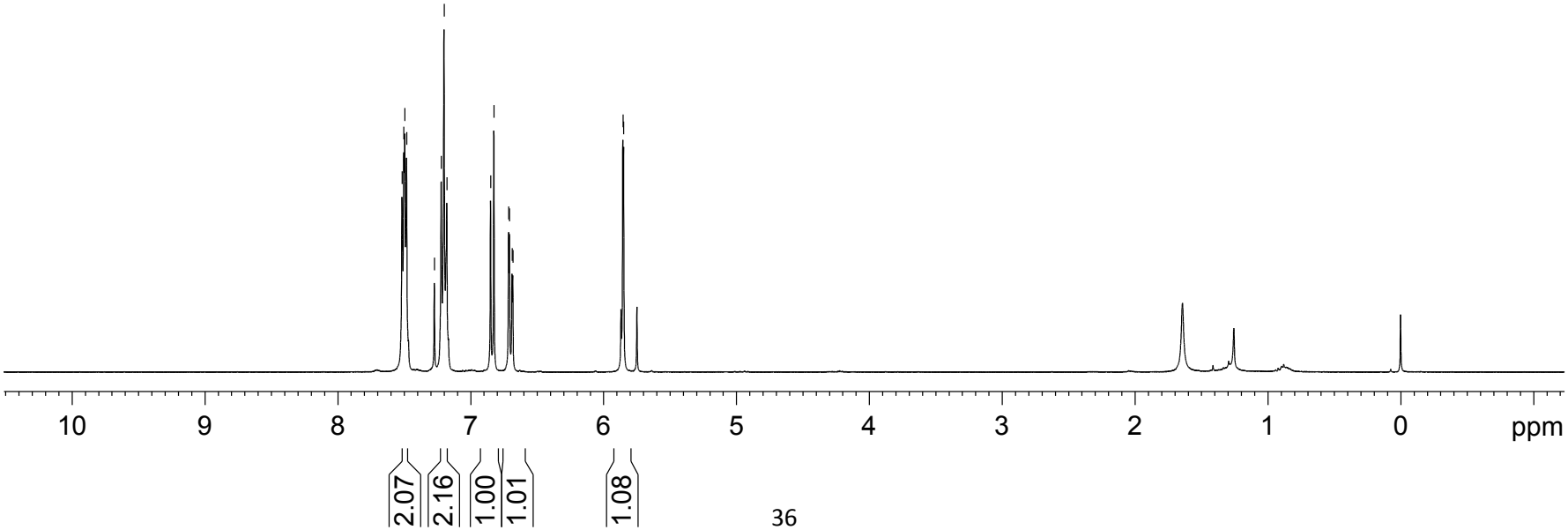
2-((4-bromophenyl)thio)cyclohexa-2,5-diene-1,4-dione

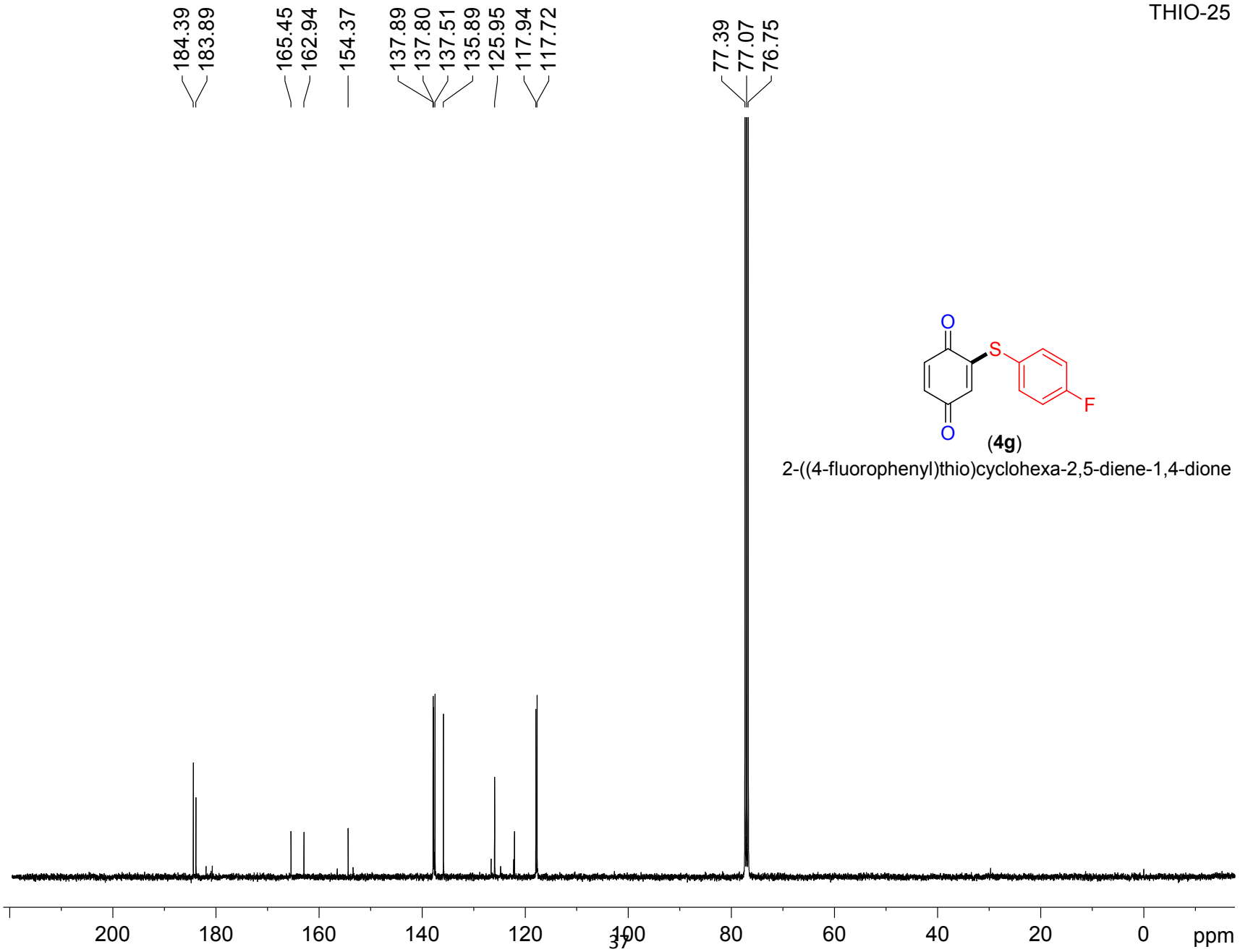




(**4g**)

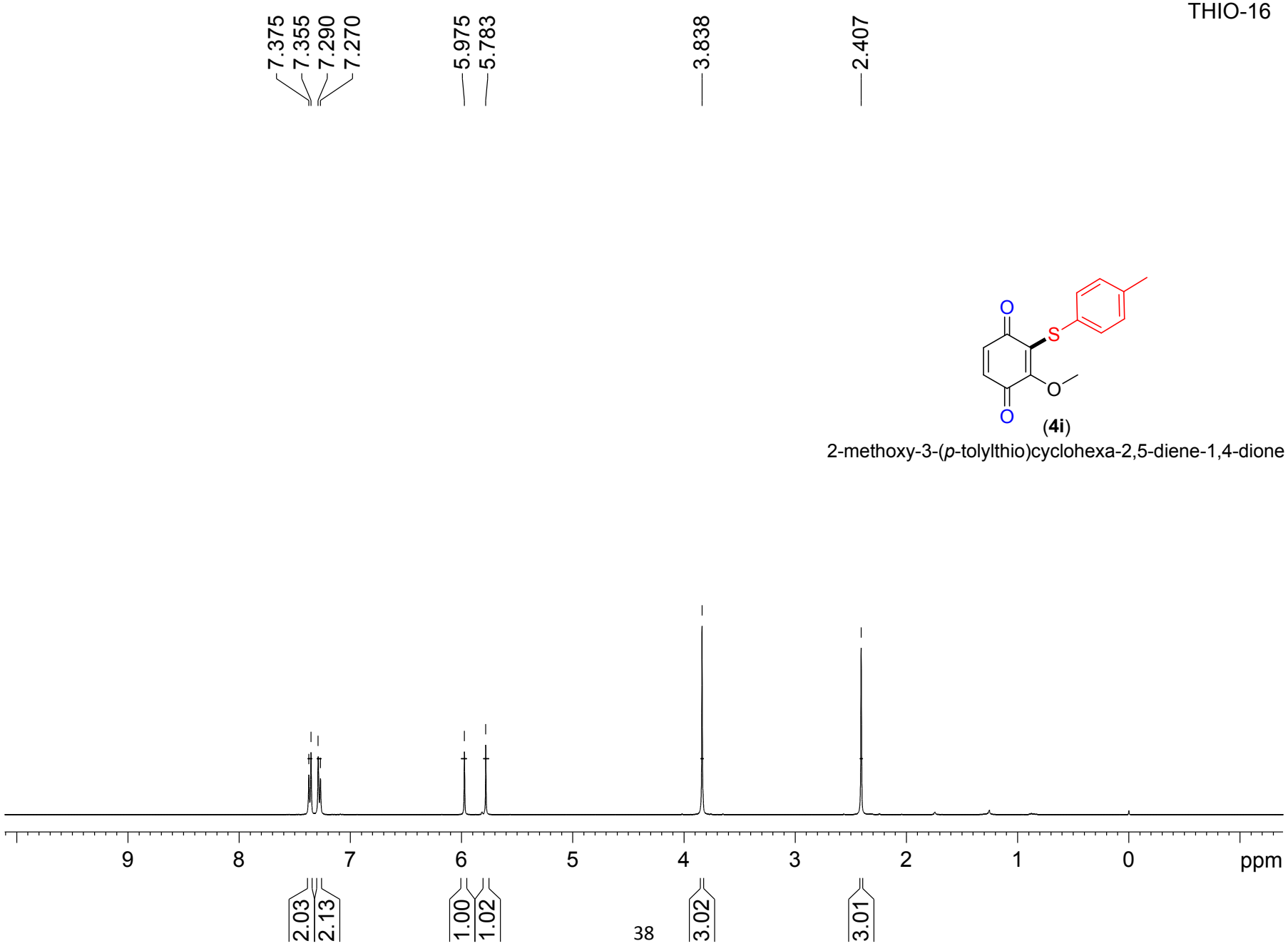
2-((4-fluorophenyl)thio)cyclohexa-2,5-diene-1,4-dione





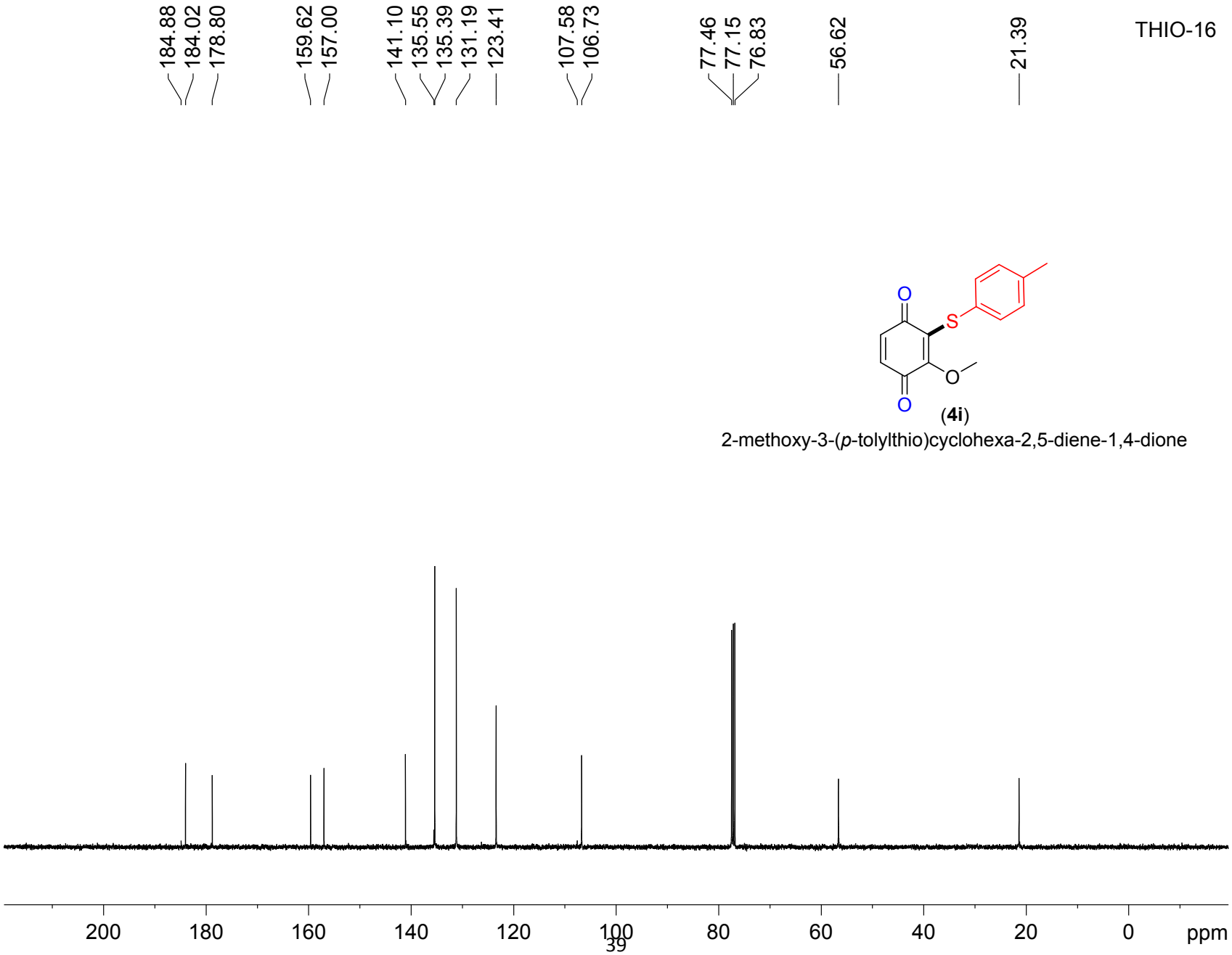
(**4g**)

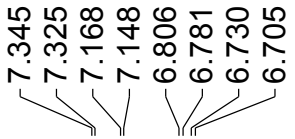
2-((4-fluorophenyl)thio)cyclohexa-2,5-diene-1,4-dione

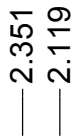


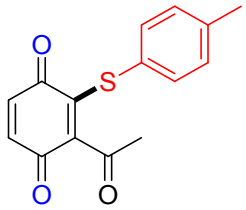
(**4i**)

2-methoxy-3-(*p*-tolylthio)cyclohexa-2,5-diene-1,4-dione


184.88
184.02
178.80
159.62
157.00
141.10
135.55
135.39
131.19
123.41
107.58
106.73
77.46
77.15
76.83
56.62
21.39
THIO-16
O
S
O
O
(4i)
2-methoxy-3-(p-tolylthio)cyclohexa-2,5-diene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

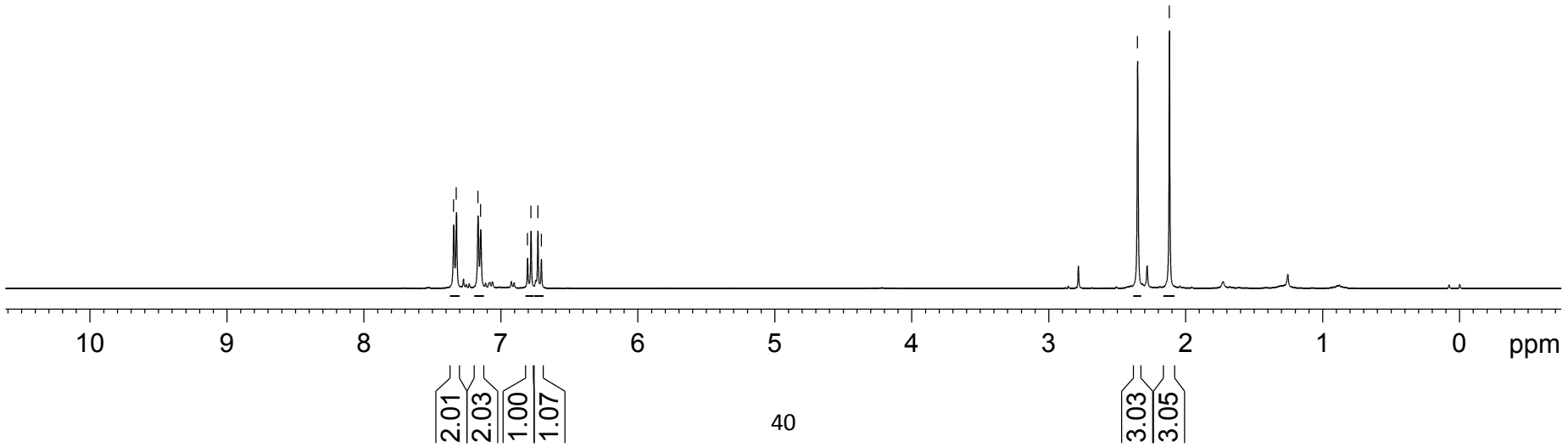




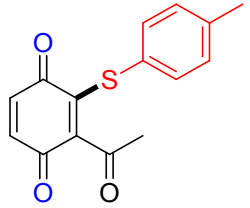


(**4j**)

2-acetyl-3-(*p*-tolylthio)cyclohexa-2,5-diene-1,4-dione

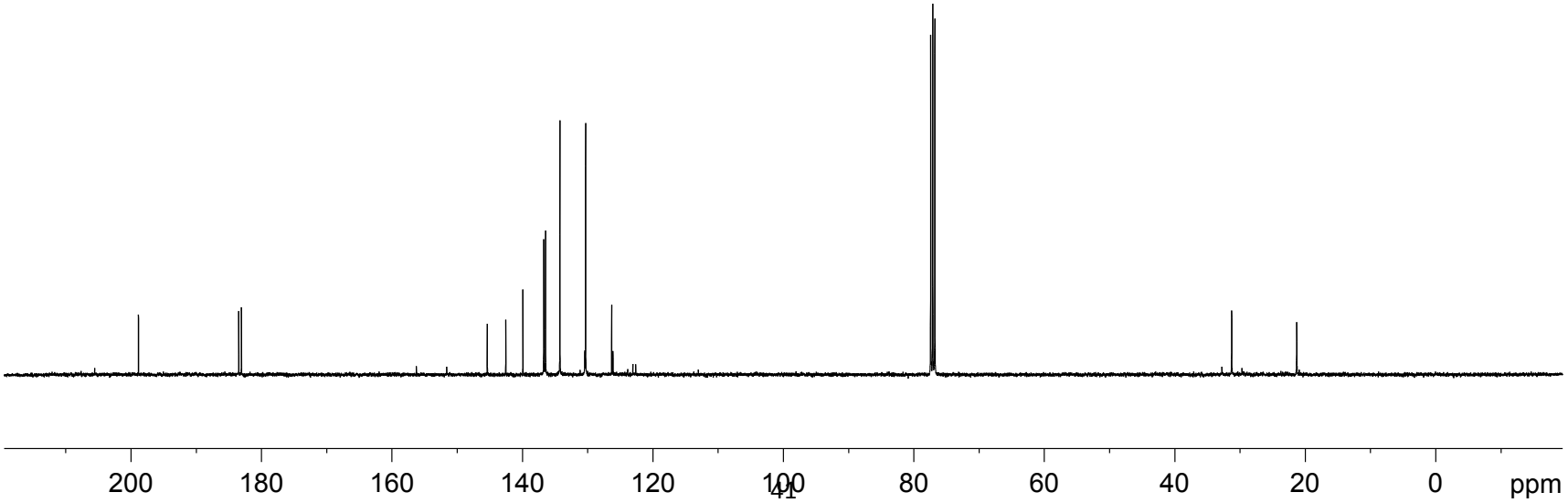


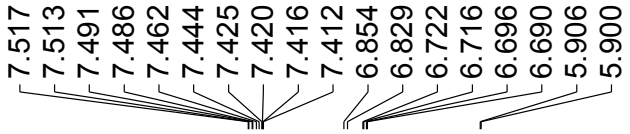
THIO-17

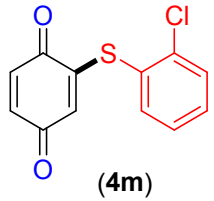


(**4j**)

2-acetyl-3-(*p*-tolylthio)cyclohexa-2,5-diene-1,4-dione

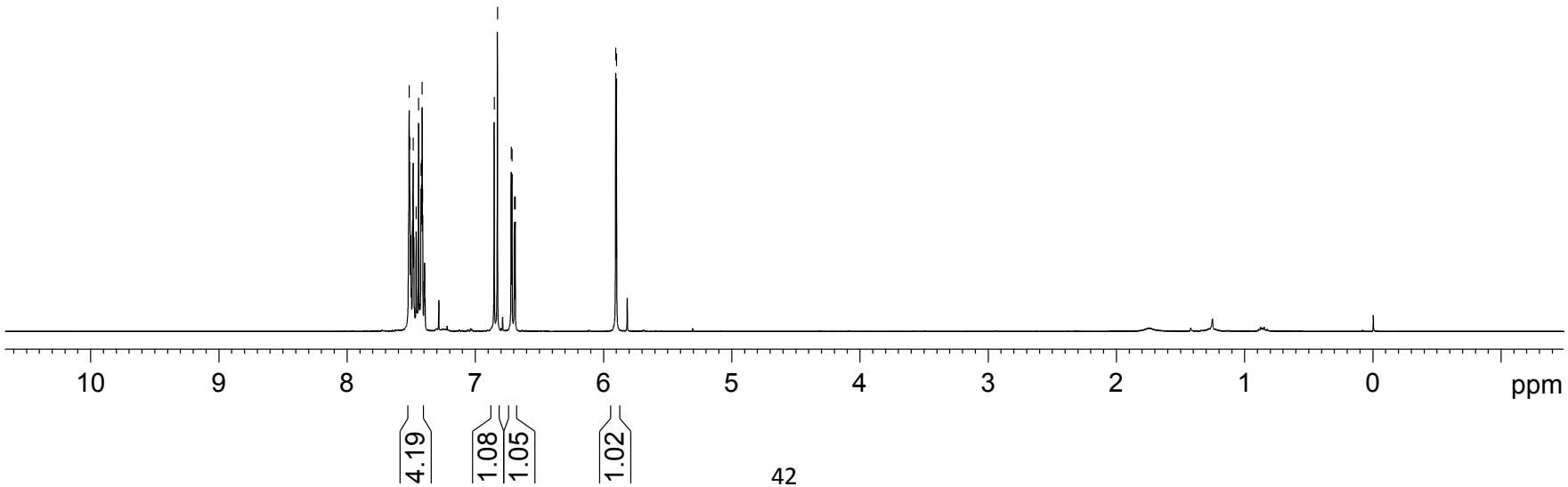


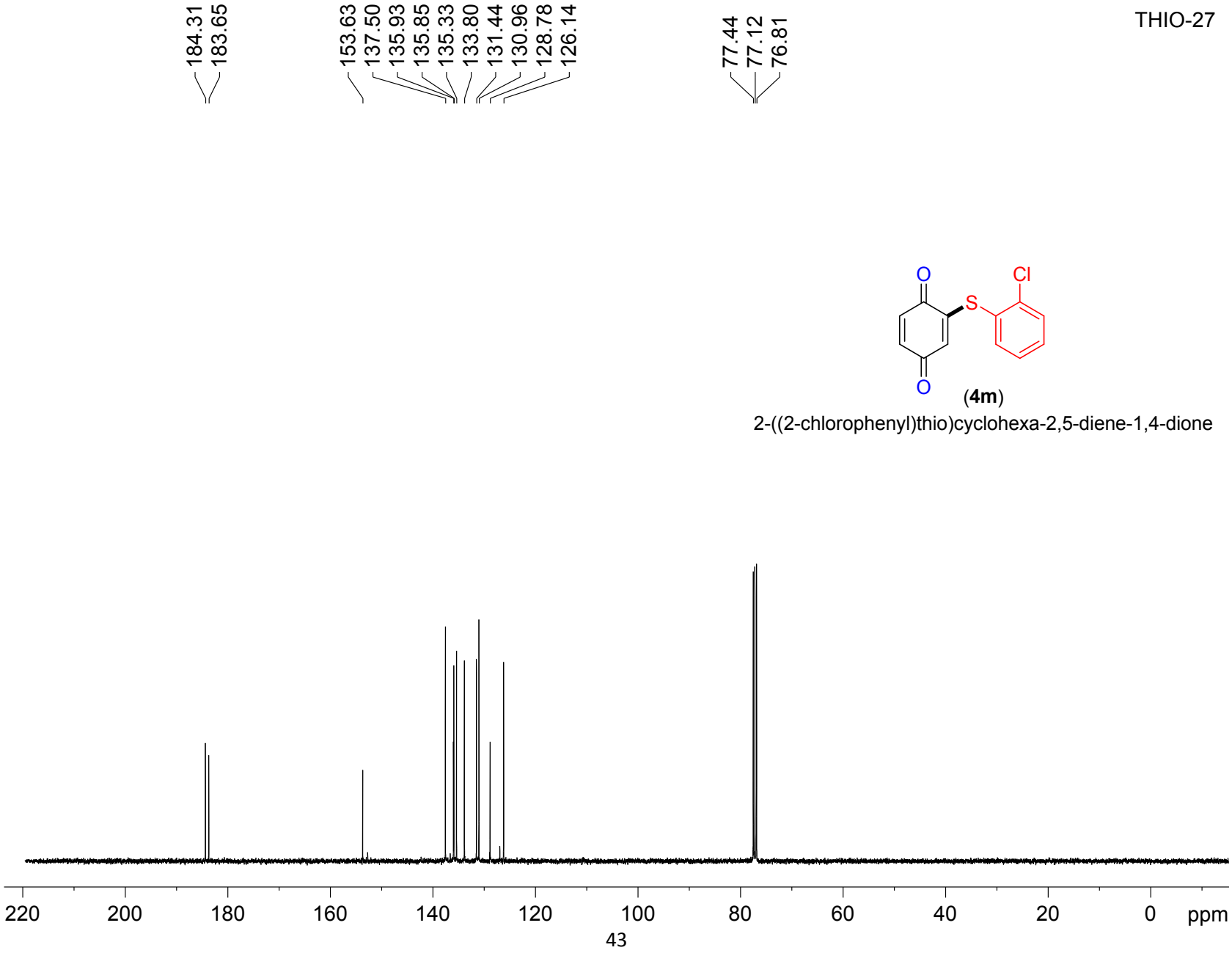


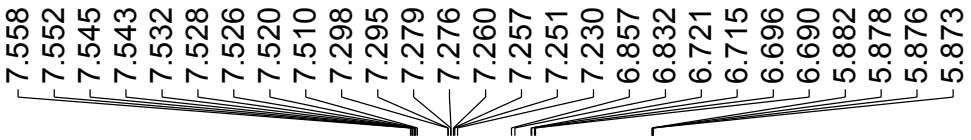


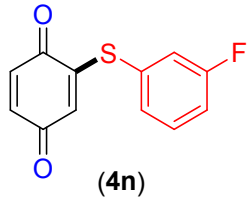
(**4m**)

2-((2-chlorophenyl)thio)cyclohexa-2,5-diene-1,4-dione



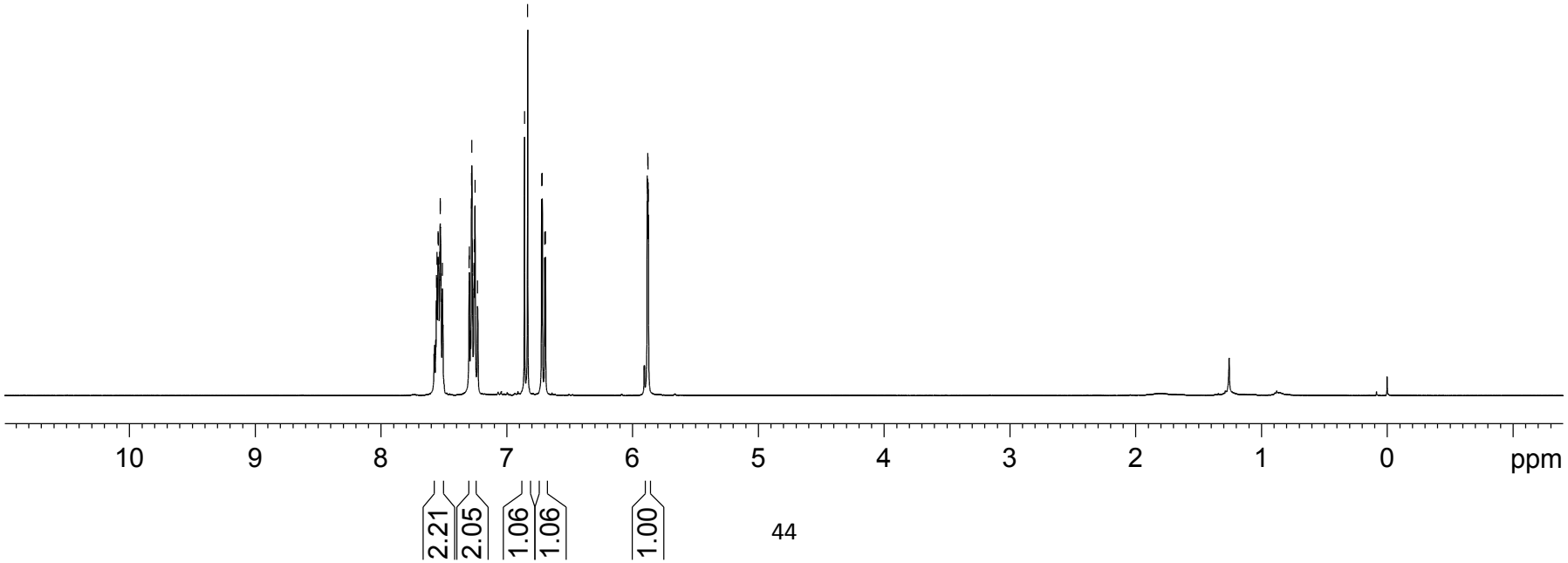

184.31
183.65
153.63
137.50
135.93
135.85
135.33
133.80
131.44
130.96
128.78
126.14
77.44
77.12
76.81
THIO-27
O
Cl
S
O
(4m)
2-((2-chlorophenyl)thio)cyclohexa-2,5-diene-1,4-dione
220
200
180
160
140
120
100
80
60
40
20
0
ppm

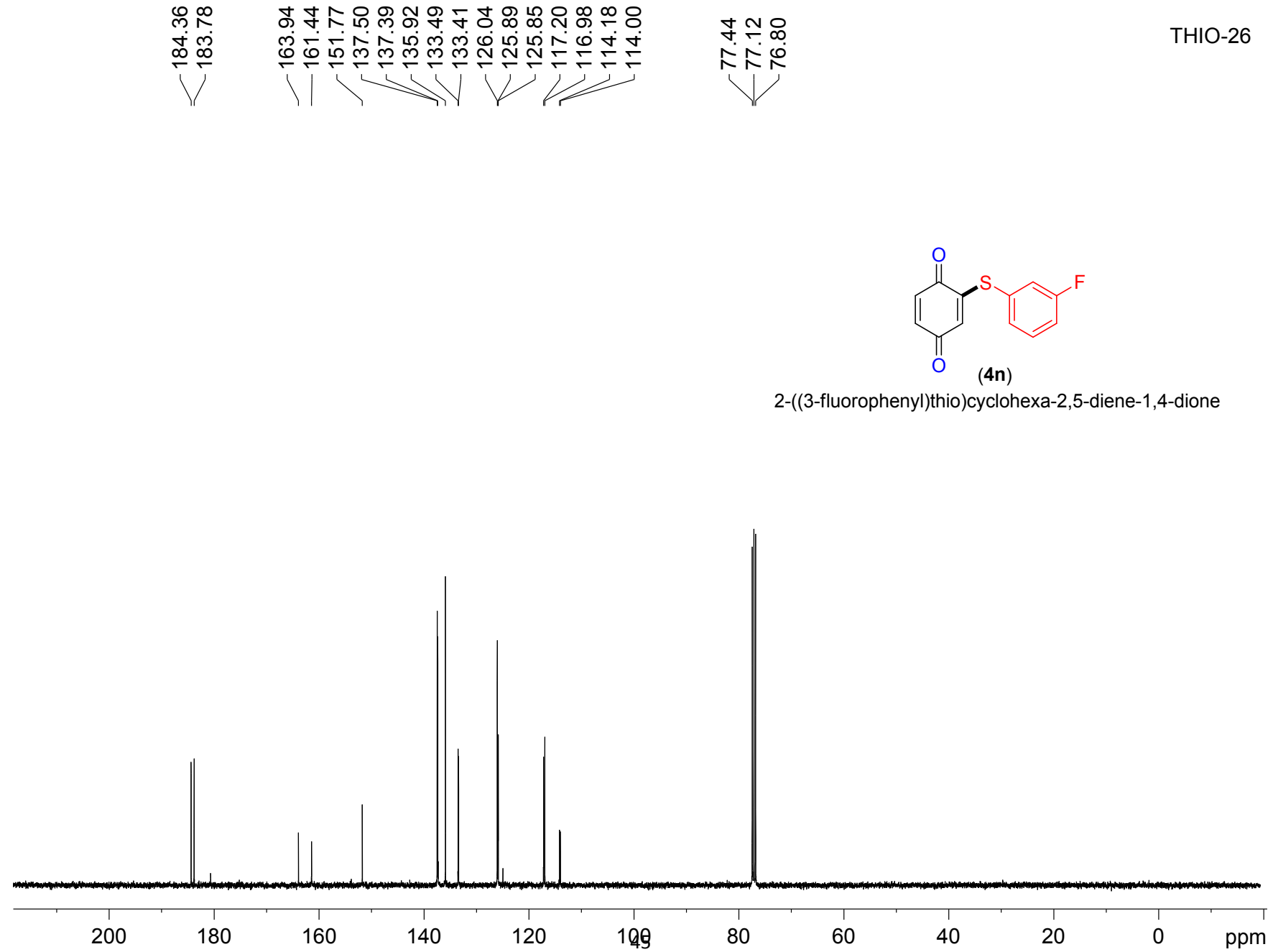


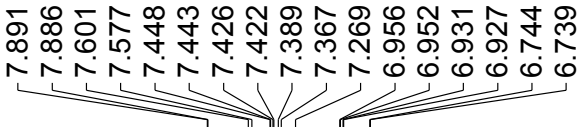


(**4n**)

2-((3-fluorophenyl)thio)cyclohexa-2,5-diene-1,4-dione

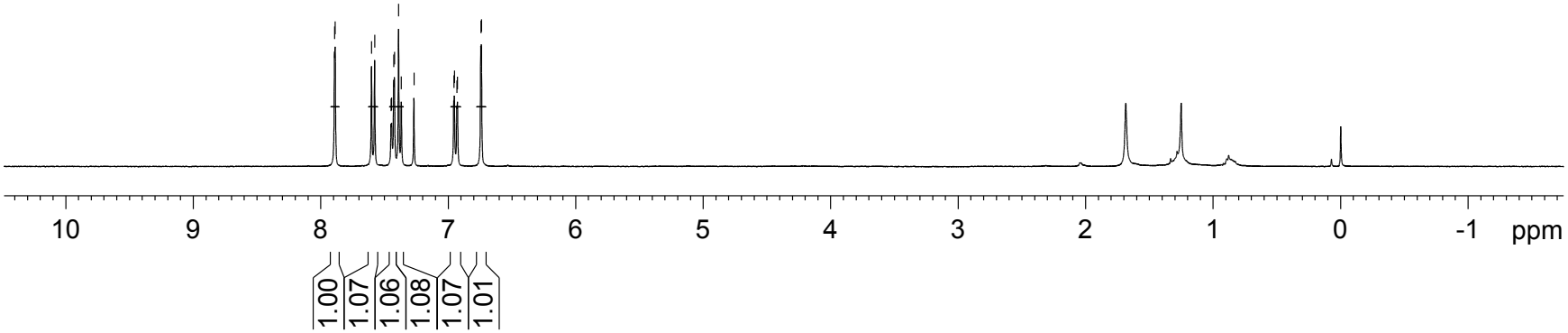


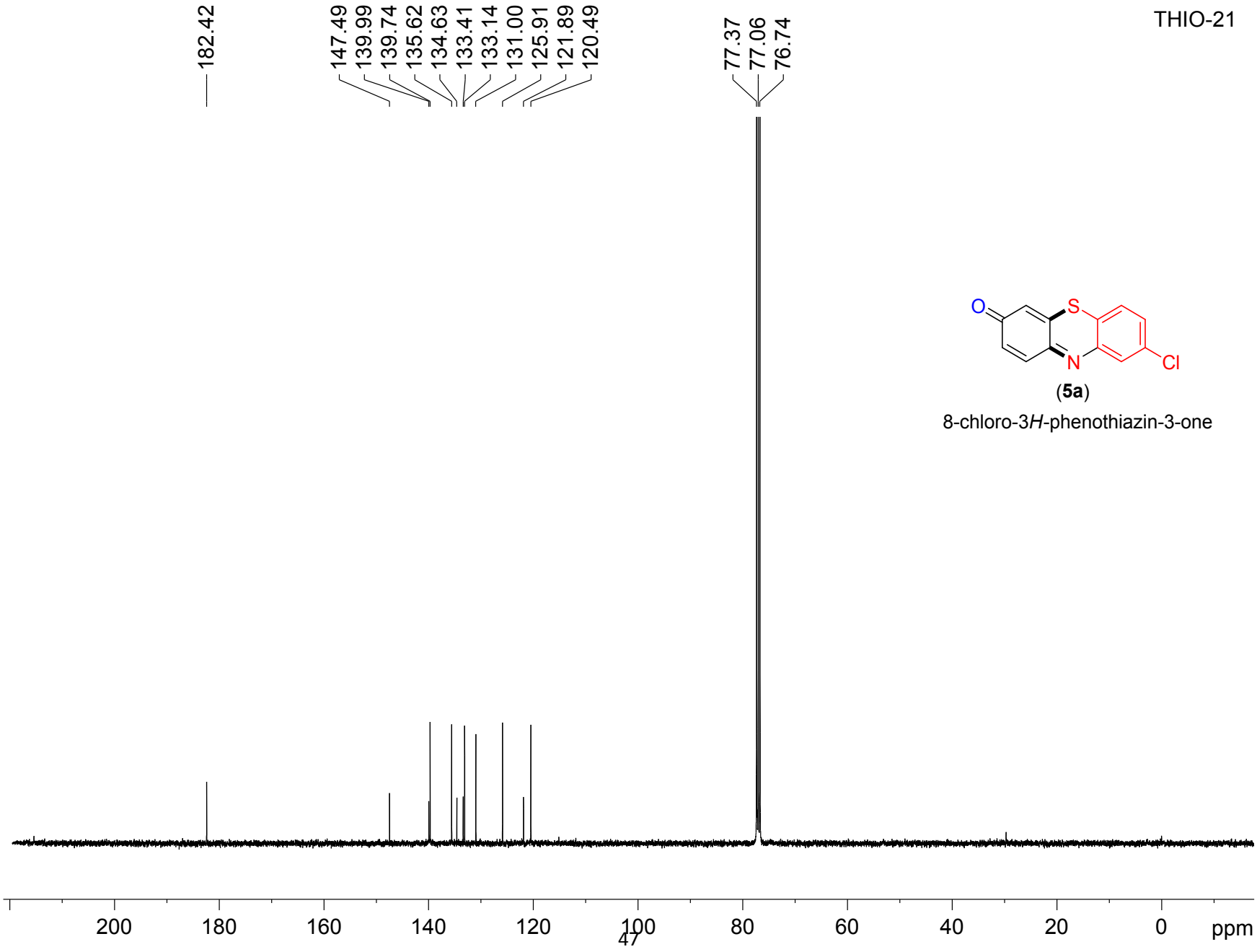

184.36
183.78
163.94
161.44
151.77
137.50
137.39
135.92
133.49
133.41
126.04
125.89
125.85
117.20
116.98
114.18
114.00
77.44
77.12
76.80
THIO-26
O
S
F
O
(4n)
2-((3-fluorophenyl)thio)cyclohexa-2,5-diene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

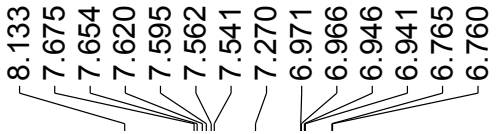


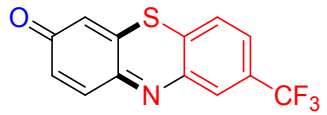
(**5a**)

8-chloro-3*H*-phenothiazin-3-one



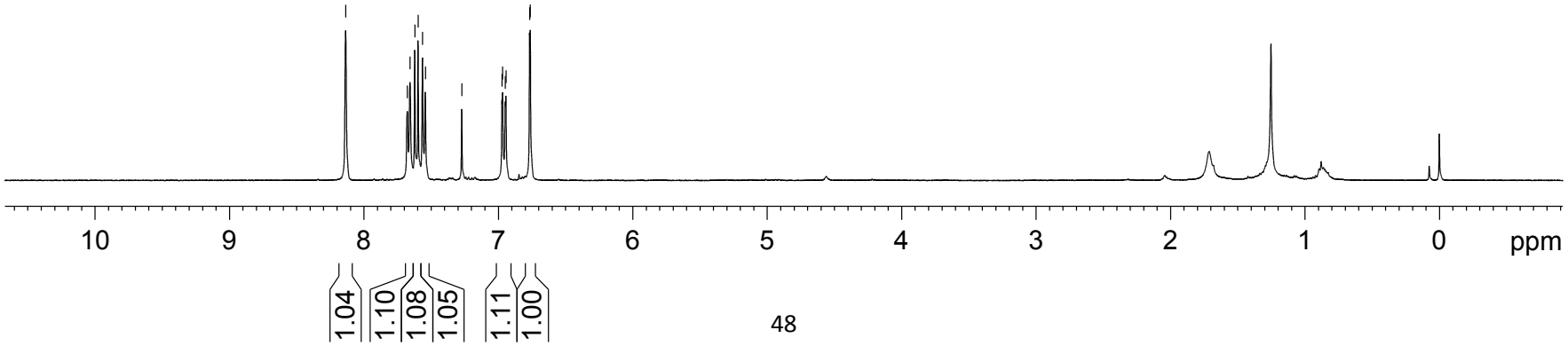

182.42
147.49
139.99
139.74
135.62
134.63
133.41
133.14
131.00
125.91
121.89
120.49
77.37
77.06
76.74
THIO-21
O
S
N
Cl
(5a)
8-chloro-3H-phenothiazin-3-one
200
180
160
140
120
100
80
60
40
20
0
ppm

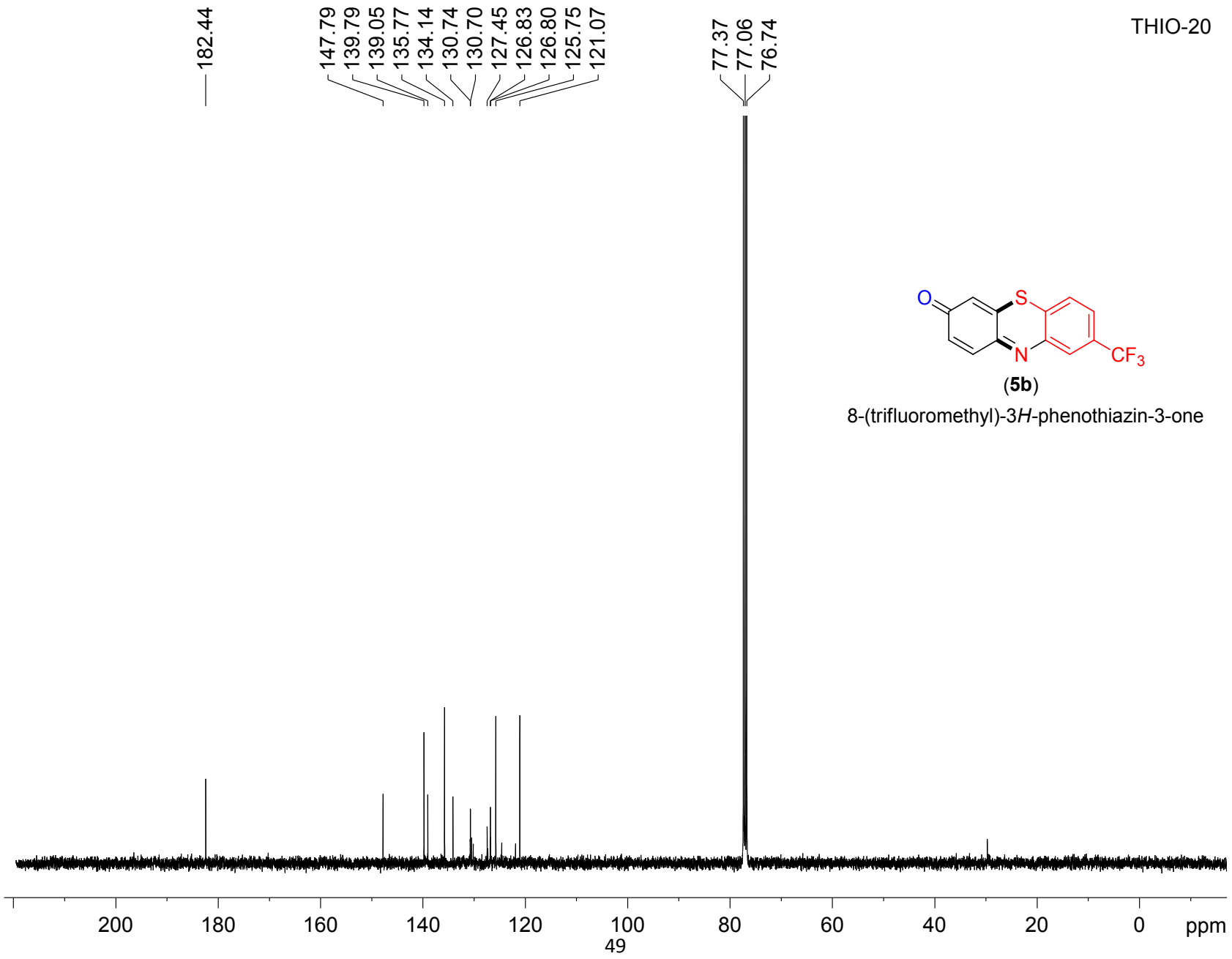


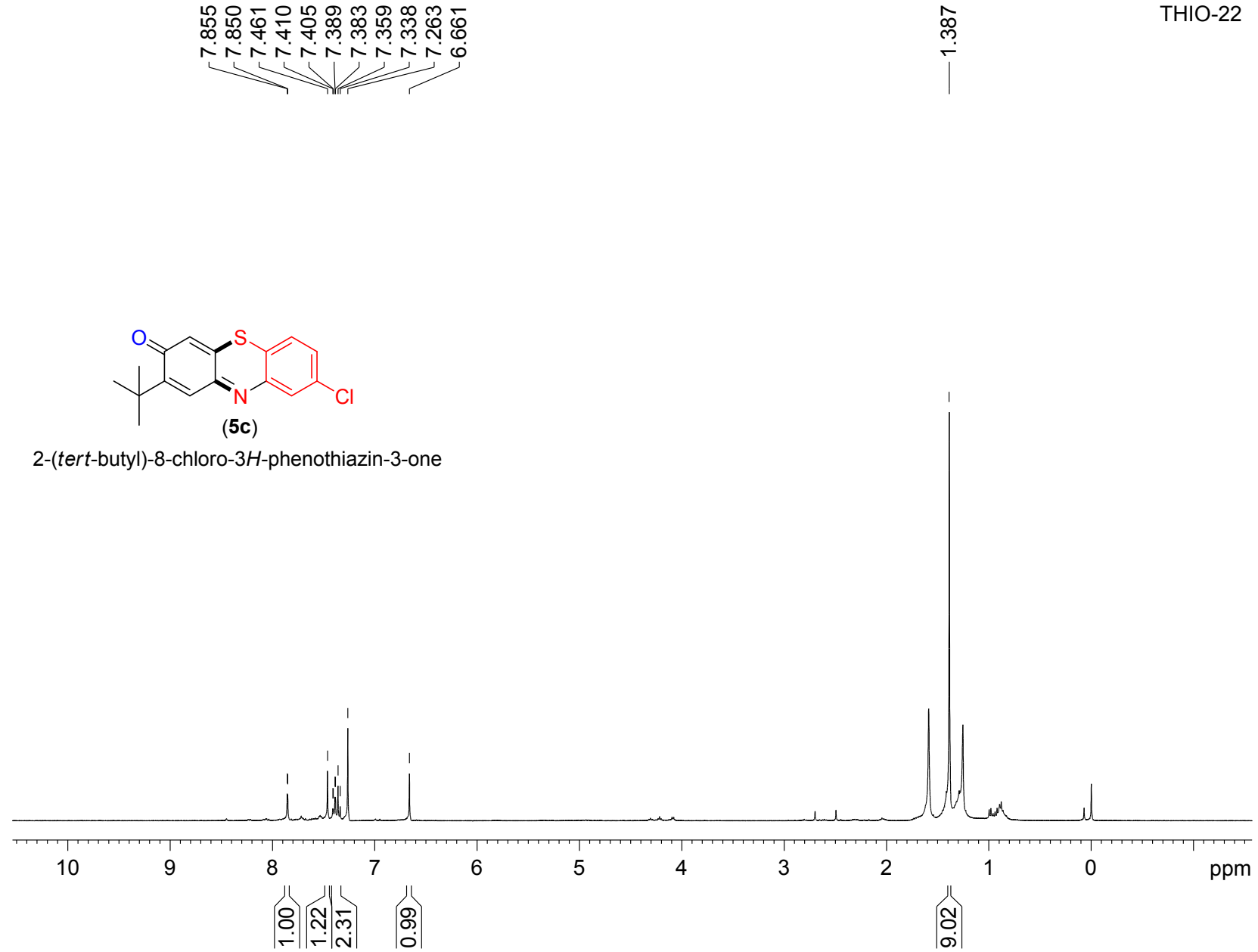


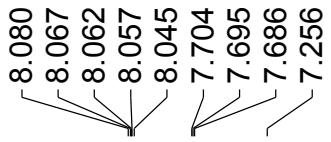
(**5b**)

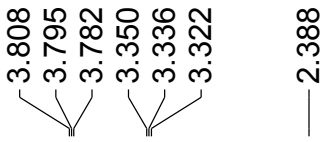
8-(trifluoromethyl)-3*H*-phenothiazin-3-one

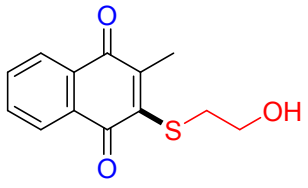



182.44
147.79
139.79
139.05
135.77
134.14
130.74
130.70
127.45
126.83
126.80
125.75
121.07
77.37
77.06
76.74
THIO-20
O
S
N
CF3
(5b)
8-(trifluoromethyl)-3H-phenothiazin-3-one
200
180
160
140
120
100
80
60
40
20
0
ppm


7.855
7.850
7.461
7.410
7.405
7.389
7.383
7.359
7.338
7.263
6.661
1.387
THIO-22
O
S
N
Cl
(5c)
2-(tert-butyl)-8-chloro-3H-phenothiazin-3-one
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.22
2.31
0.99
9.02



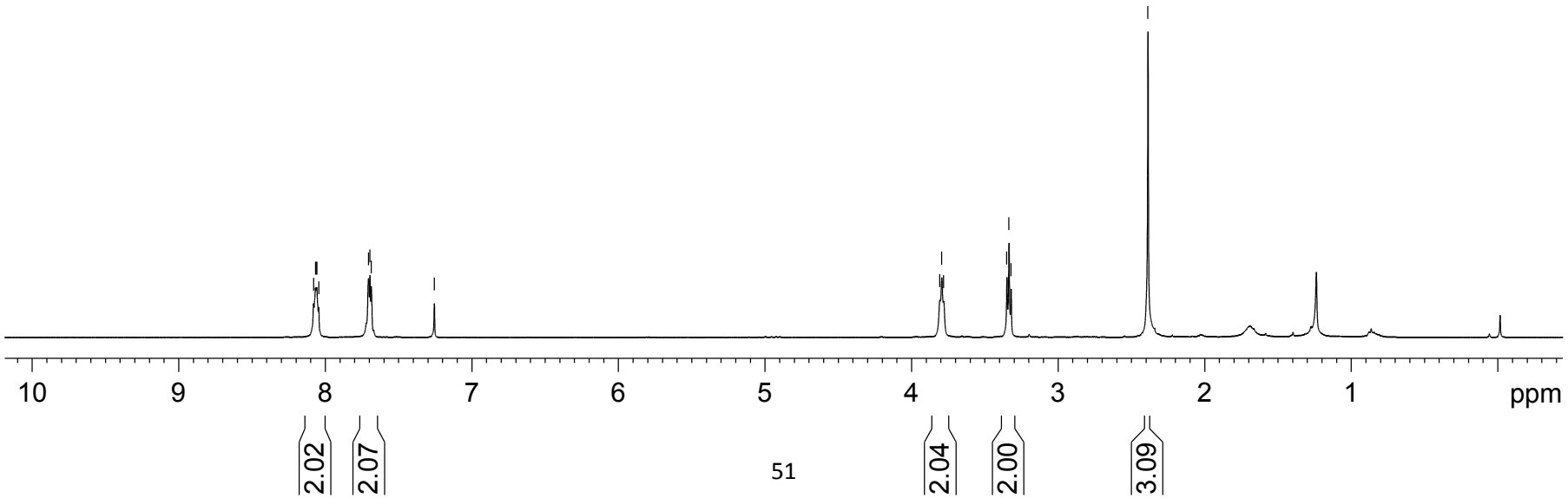


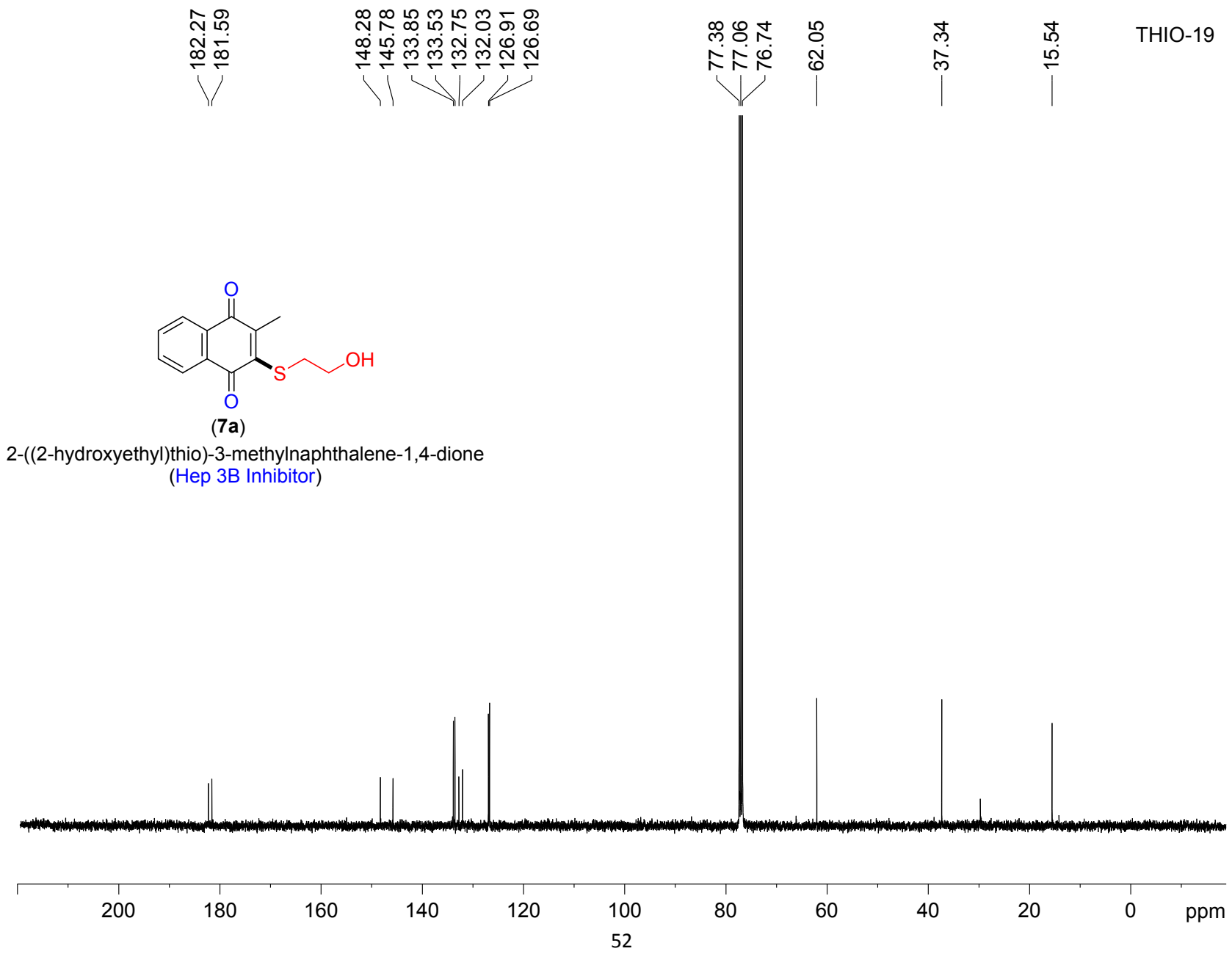


(**7a**)

2-((2-hydroxyethyl)thio)-3-methylnaphthalene-1,4-dione

(Hep 3B Inhibitor)



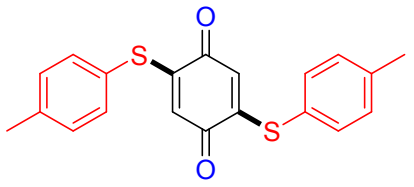


(**7a**)

2-((2-hydroxyethyl)thio)-3-methylnaphthalene-1,4-dione

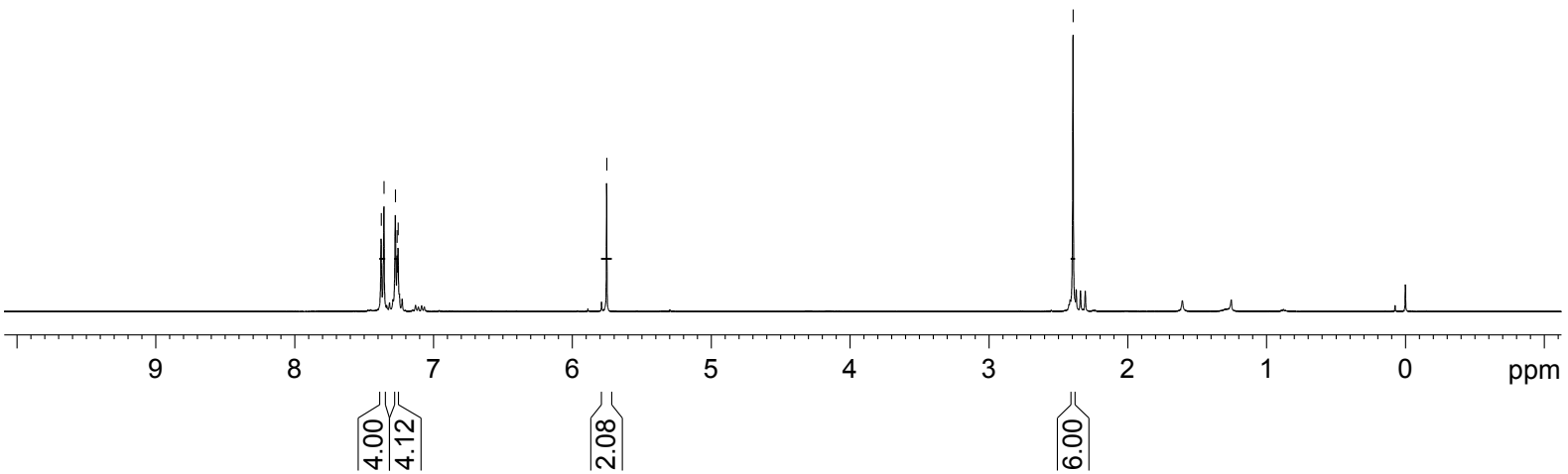
(Hep 3B Inhibitor)

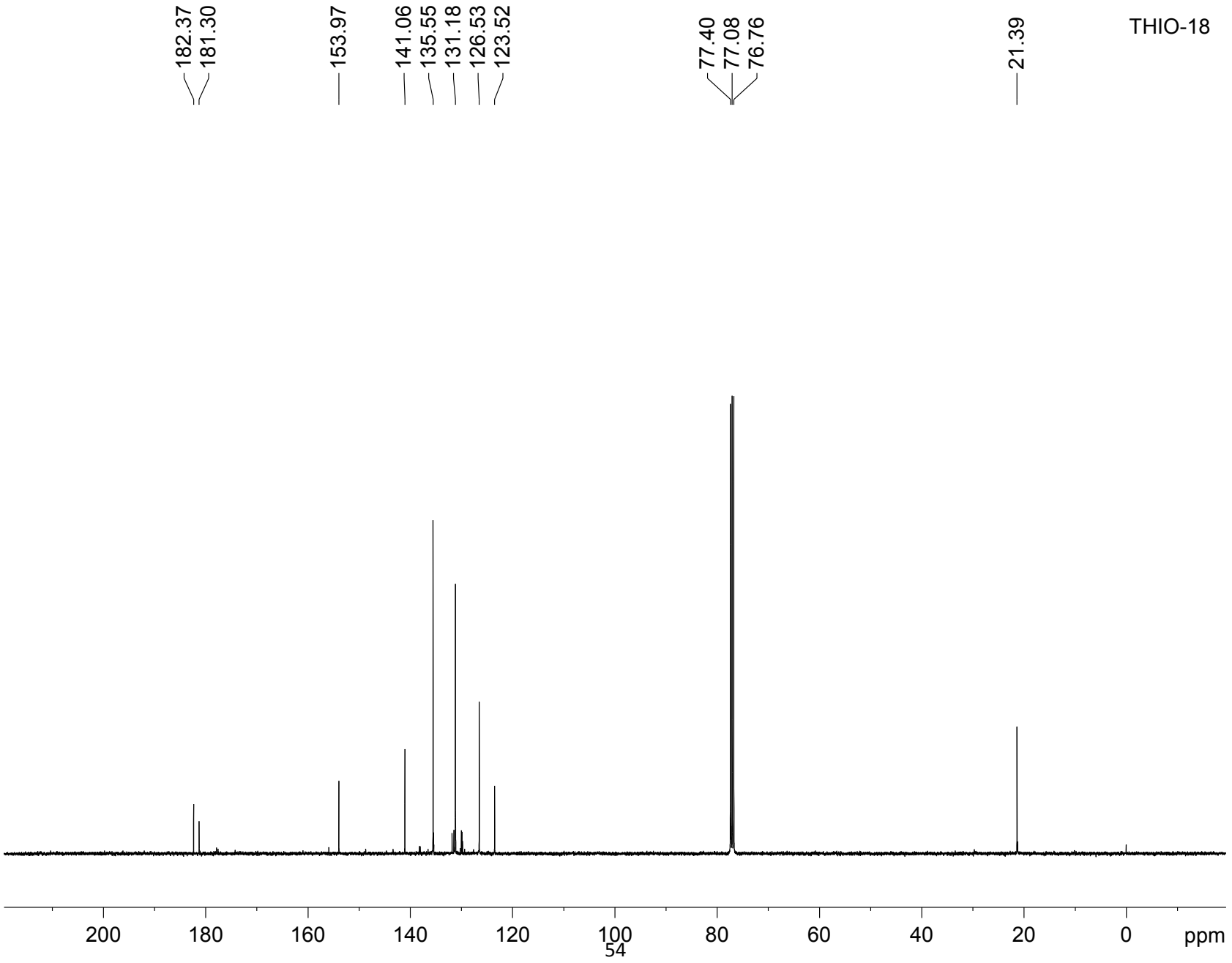
THIO-18

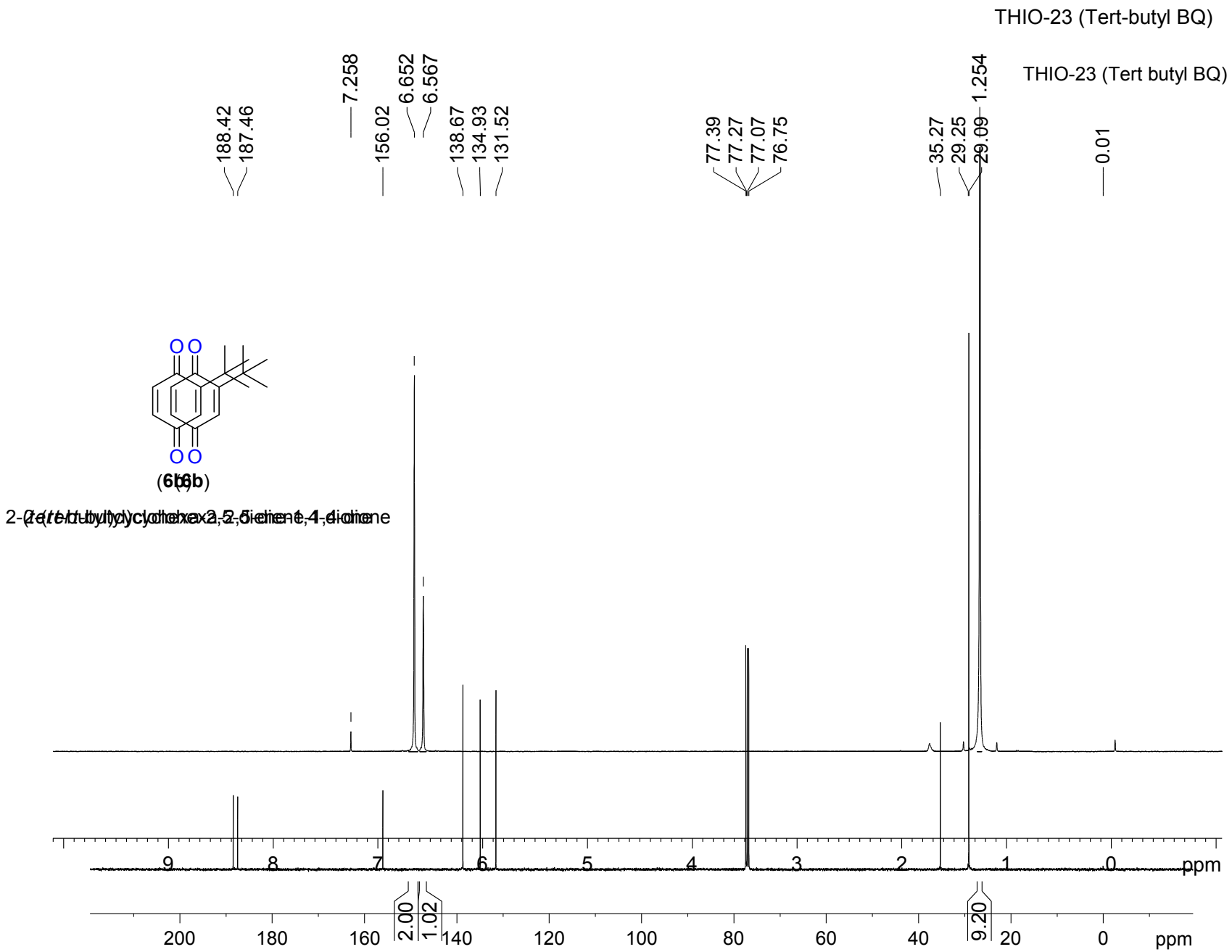


(**4o**)

2,5-bis(*p*-tolylthio)cyclohexa-2,5-diene-1,4-dione




182.37
181.30
153.97
141.06
135.55
131.18
126.53
123.52
77.40
77.08
76.76
21.39
THIO-18
200
180
160
140
120
100
80
60
40
20
0
ppm

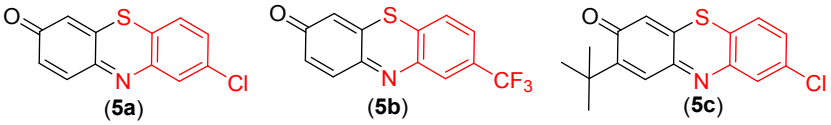

THIO-23 (Tert-butyl BQ)
THIO-23 (Tert butyl BQ)
188.42
187.46
7.258
156.02
6.652
6.567
138.67
134.93
131.52
77.39
77.27
77.07
76.75
35.27
29.25
29.09
1.254
0.01
(6b)
2-(tert-butyl)cyclohexa-2,5-diene-1,4-dione
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.02
9.20
200
180
160
140
120
100
80
60
40
20
0
ppm

2. ADME-PK properties and molecular characterization

Computational methods are being used to filter and select compounds based on different molecular characteristics that are considered to be relevant to predict the drug-likeness of molecules. Without the aid of computational methods, the drug development process would be more time-consuming and less efficient, however, it is important to mention that the filtering rules employed by these methods are not absolute answers to the problem and that experimental confirmation is compulsory. A number of compounds fail during clinical phases due to poor pharmacokinetic and safety properties, therefore, the growing number of public and commercial *in silico* tools to predict ADMET (absorption, distribution, metabolism, excretion and toxicity) parameters is not surprising.

Pharmacokinetics and drug-likeness prediction for the synthesized compounds **5a-c** were performed by online tool SwissADME[1a] of Swiss Institute of Bioinformatics (http://www.sib.swiss).[1b] 2D structural models were drawn in ChemBioDraw Ultra version 15.0 (Cambridge Software) and SMILES of **5a-c** was translated into molfile by online SMILES translator and structure file generator found in Online tool SwissADME. The analysis task was done to check whether the compound were inhibitor of isoforms of Cytochrome P450 (CYP) family such as CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. In addition, pharmacokinetics (such as gastrointestinal absorption, P-glycoprotein and blood brain barrier) and drug-likeness prediction such as Lipinski, Ghose and Veber rules and bioavailability score.[1c-e] The Lipinski, Ghose, Egan, Mugges and Veber rules were applied to assess drug likeness to predict whether a compound is likely to be a bioactive according to some important parameters such as molecular weight, Log *P*, number of HPA and HBD. The SwissADME tool used vector machine algorithm (SVM)[2f] with fastidiously cleaned large datasets of known inhibitors/non-inhibitors as well as substrates/non-substrates.

Table-1 Pharmacokinetic studies of compound **5a-c**



(**5a**) (**5b**) (**5c**)

Pharmacokinetics properties										
GI absorption		**BBB permeation**	**Log *p*** $_{o/w}$	**P-*gp***	**Inhibition of cytochrome P450**					**Log *Kp***
					CYP1A2	***CYP2C19***	***CYP2C9***	***CYP3A4***	***CYP2D6***	
5a	**High**	**Yes**	**3.11**	**No**	×	√	×	×	×	**-5.93 cm/s**
5b	**High**	**Yes**	**3.61**	**No**	√	√	×	×	×	**-5.95 cm/s**
5c	**High**	**Yes**	**3.61**	**No**	√	√	√	×	×	**-5.08 cm/s**

GI-Gastrointestinal absorption
BBB- Blood brain barrier permeability
Log P $_{o/w}$-Lipophilicity
P-gp- P-glycoprotein substrate
Log *Kp*- Skin permeation

Table-2 Drug-likeness and Medicinal Chemistry

Drug-likeness and Medicinal Chemistry											
Log *s*		Drug-likeness					Bio-availability	Medicinal properties			Synthetic accessibility
		Lipinski	*Ghose*	*Veber*	*Egan*	*Mugge*		TPSA (A^2)	PAINS (alert)	lead likeness	
5a	**-3.69**	√	√	√	√	√	**0.55**	**58.20**	**0**	**No** (MW<350)	**2.67**
5b	**-3.90**	√	√	√	√	√	**0.55**	**58.20**	**0**	**Yes**	**2.81**
5c	**-4.90**	√	√	√	√	√	**0.55**	**58.20**	**0**	**No** XLOGP3>3.5	**3.07**

Log s-Solubility class
TPSA- Topological polar surface area
PAINS- Pan assay interference structure

3. Molecular docking studies of compound 5b with AChE target

The docking analyses were performed using Glide tool of Schrödinger-Maestro (ver10.7) package (Schrödinger, LLC, New York, NY, 2013). The compound **5a** was sketched by using Chemdraw 12.0 software and converted to .mol file format with the standard settings and processed with default parameters of Ligprep tool from Schrodinger,[2] described by Greenwood *et al.,* 2010. In this study, the compound 5a was docked with active site of AChE (PDB ID- 1EVE). The 3D structure of proteins were downloaded from the RSCB- Protein Data Bank (PDB) website and prepared for the docking by removing of all water molecules. For grid generation, the hydrogen's were added, bond orders were assigned and water molecules beyond 5Å from the hetero groups were deleted in the imported protein and sitemap tool was used to locate the binding sites. For protein-ligand docking, the formation of H-bond between the ligand and the residues of the active site and its length along with Glide XP score,[3] were recorded with the help of Glide-Ligand docking tool of Maestro in cluster node of High-Performance Computing Facility (HPC).

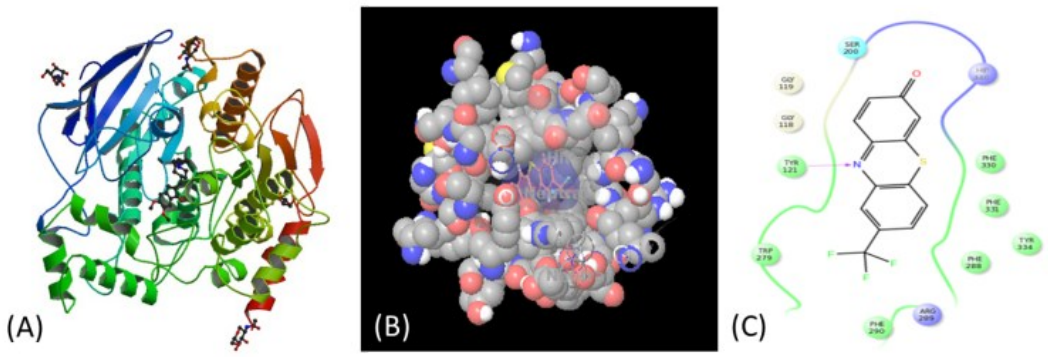


Figure 1. (**A**) Acetylcholinesterase (AChE) proteins; (**B**) 3D and (**C**) 2D structure of protein-ligand interaction.

Table-3 Binding interactions of the protein-ligand complexes

Mole.	PDB ID	Interactions	Residues	Distance (Å)	Glide XP Score (Kcal/mol)	Glide emodel score
5b	1EVE	H-bond	Tyr 121	1.80	-7.30	-44.18
PBD- Protein Data Bank						

4. Reference

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