Supporting Information

Direct Reductive Amination of Aldehyde Bisulfite Adducts Induced by 2-Picoline Borane – Application to the Synthesis of a DPP-IV Inhibitor

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Chemical Process Research and Development

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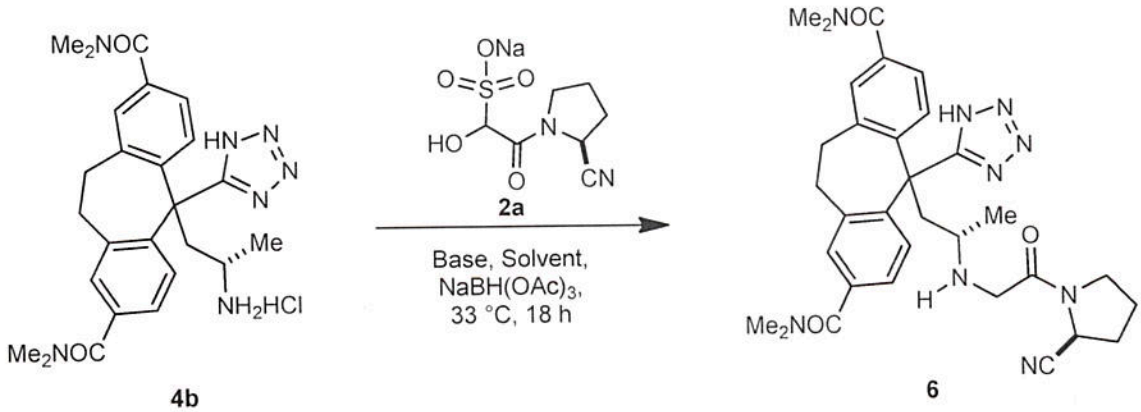
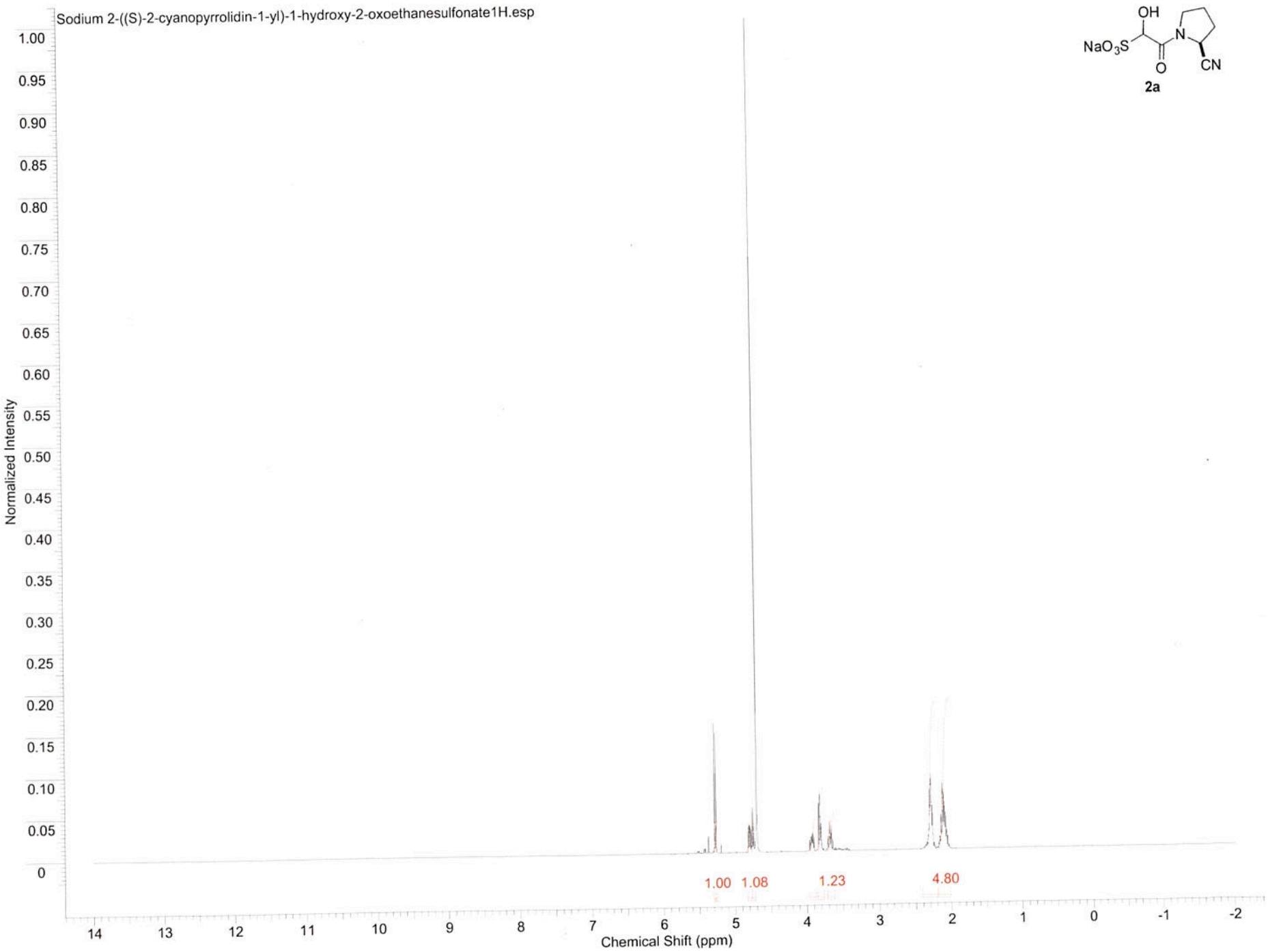
1.0 Base Screen

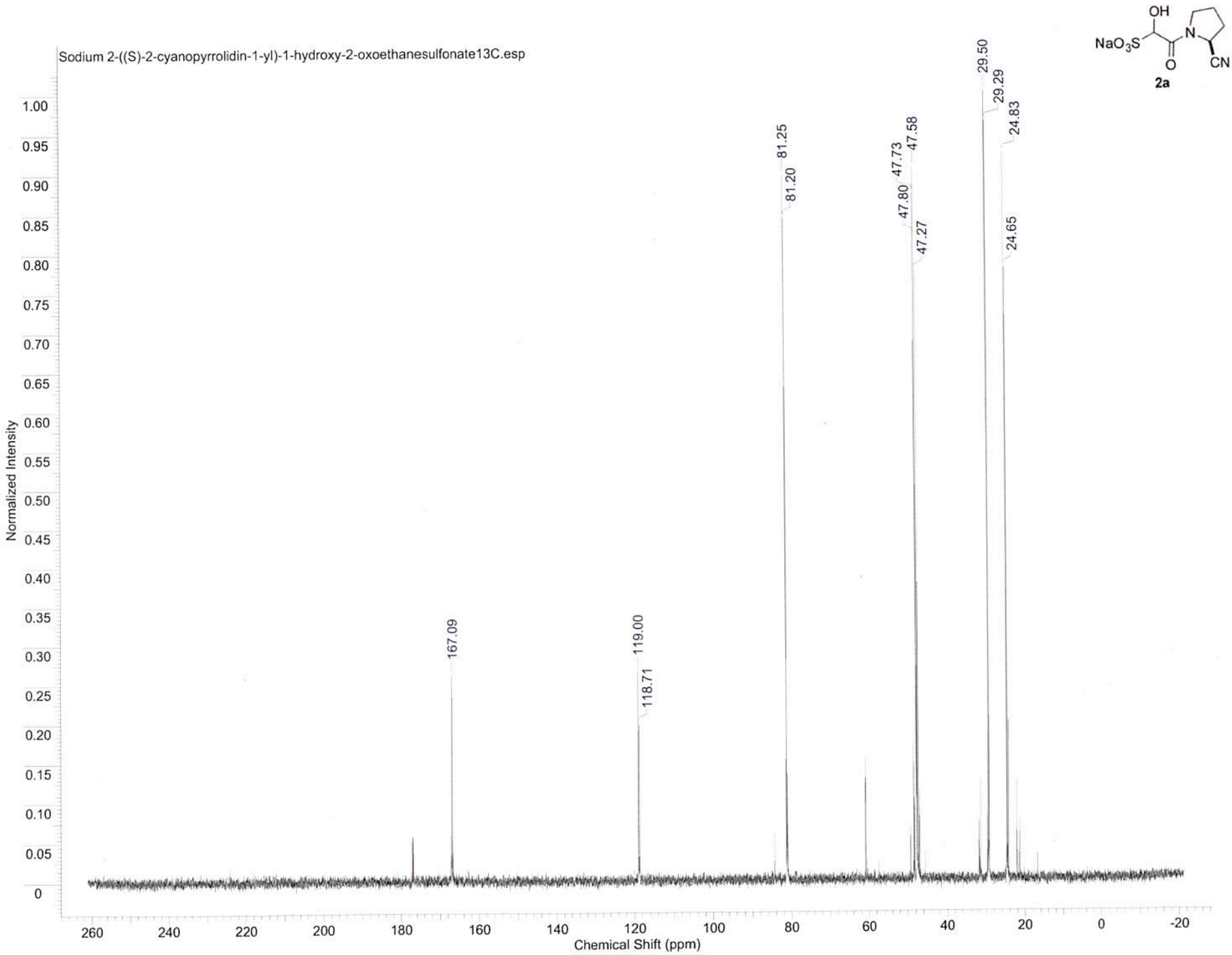


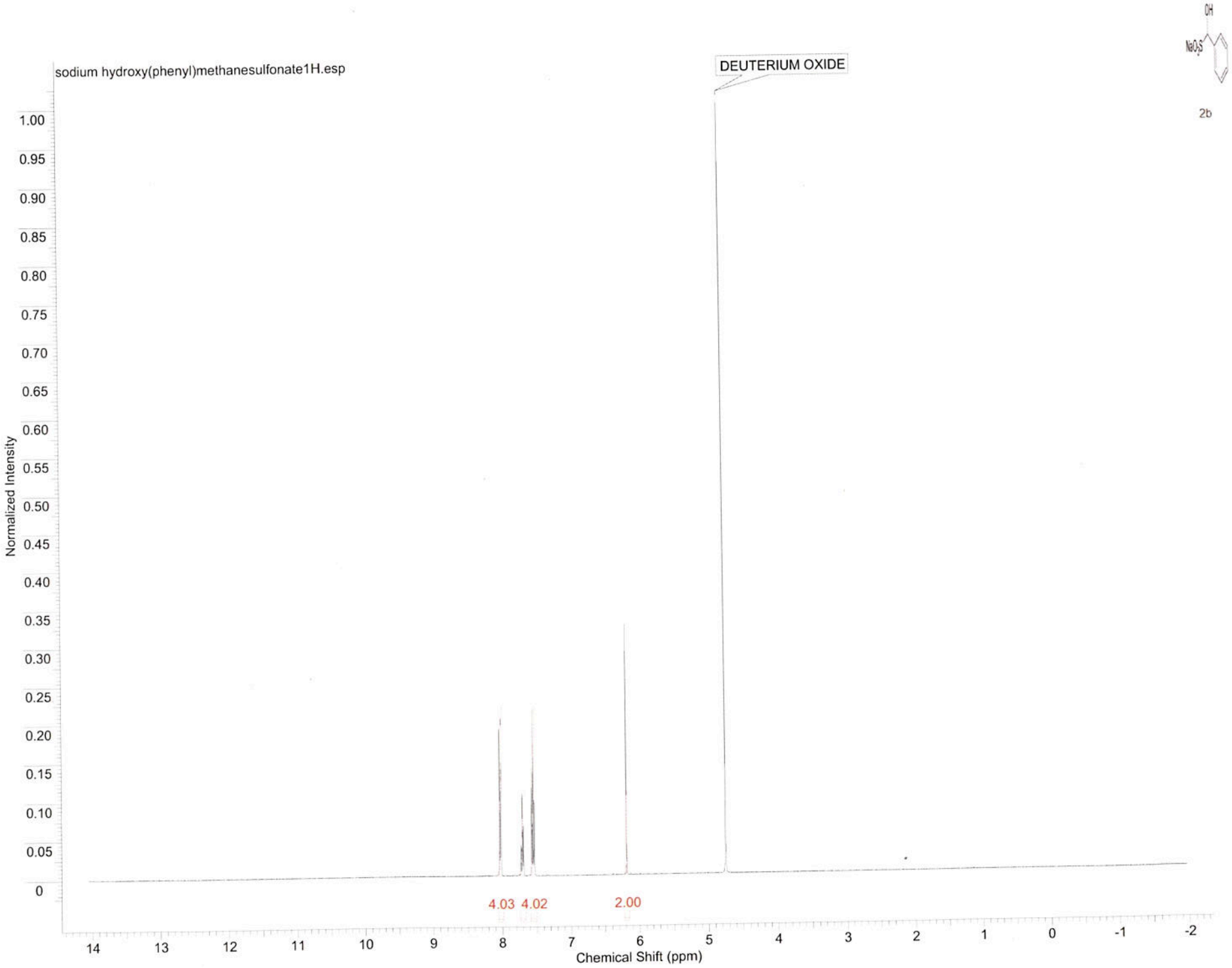
4b **6**

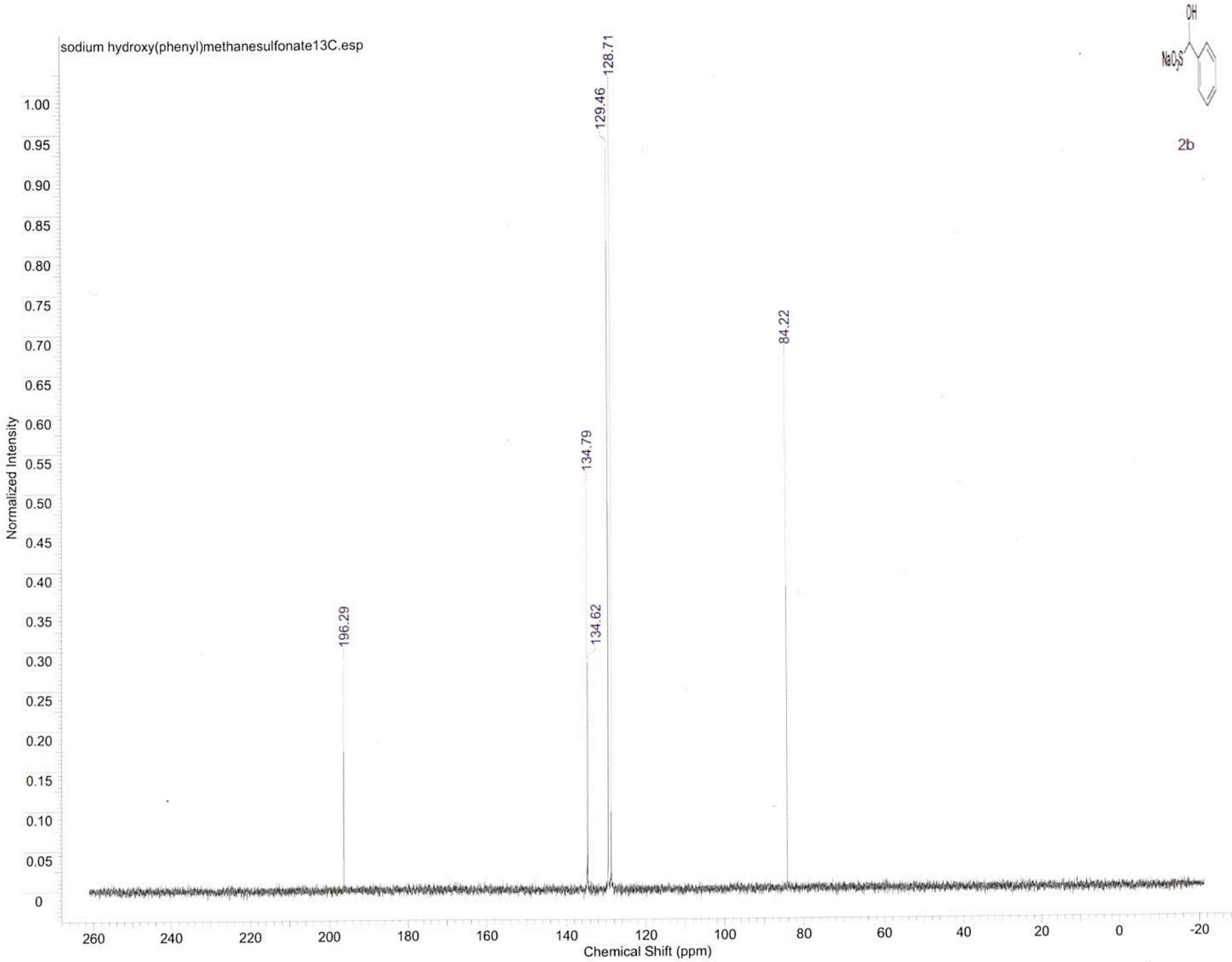
Entry[a]	Base	Solvent	Product Assay Yield[b]
1	Et_3N	ACN	63
2	NaOAc	ACN	50
3	$CHKO_2$	ACN	4.5
4	Et_3N	DCM	51
5	NaOAc	DCM	9
6	Et_3N	MeOH	83
7	NaOAc	MeOH	87
8	$CHKO_2$	MeOH	58
9	Et_3N	DMAC	67
10	NaOAc	DMAC	63
11	$CHKO_2$	DMAC	38
12	Et_3N	THF	8
13	NaOAc	THF	4
14	$CHKO_2$	THF	7.3
15	Et_3N	DMSO	75
16	NaOAc	DMSO	25
17	$CHKO_2$	DMSO	28

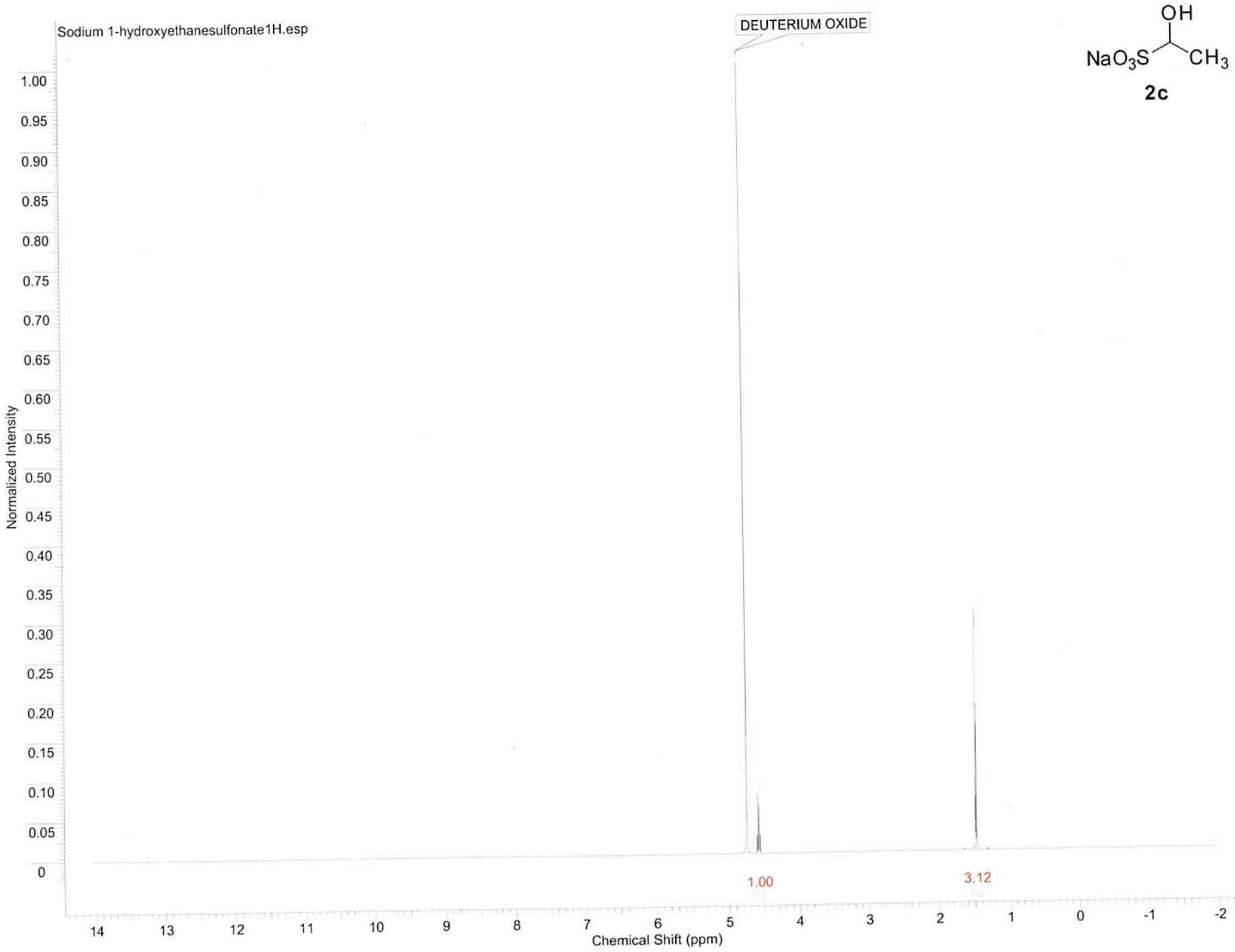
[a] Reactions conducted on 0.1 mmol scale with **2a** (2 eq), $NaBH(OAc)_3$ (2.5 eq) and base (8 eq)
[b] Weight % yield determined by quantitative HPLC analysis


Sodium 2-((S)-2-cyanopyrrolidin-1-yl)-1-hydroxy-2-oxoethanesulfonate1H.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.08
1.23
4.80
OH
NaO3S
N
O
CN
2a


Sodium 2-((S)-2-cyanopyrrolidin-1-yl)-1-hydroxy-2-oxoethanesulfonate13C.esp
OH
NaO3S
N
O
CN
2a
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
167.09
119.00
118.71
81.25
81.20
47.73
47.58
47.80
47.27
29.50
29.29
24.83
24.65
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


sodium hydroxy(phenyl)methanesulfonate1H.esp
DEUTERIUM OXIDE
OH
NaO3S
2b
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
4.03
4.02
2.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)


sodium hydroxy(phenyl)methanesulfonate13C.esp
OH
NaO3S
2b
128.71
129.46
84.22
134.79
134.62
196.29
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


Sodium 1-hydroxyethanesulfonate1H.esp
DEUTERIUM OXIDE
OH
NaO3S
CH3
2c
Normalized Intensity
1.00
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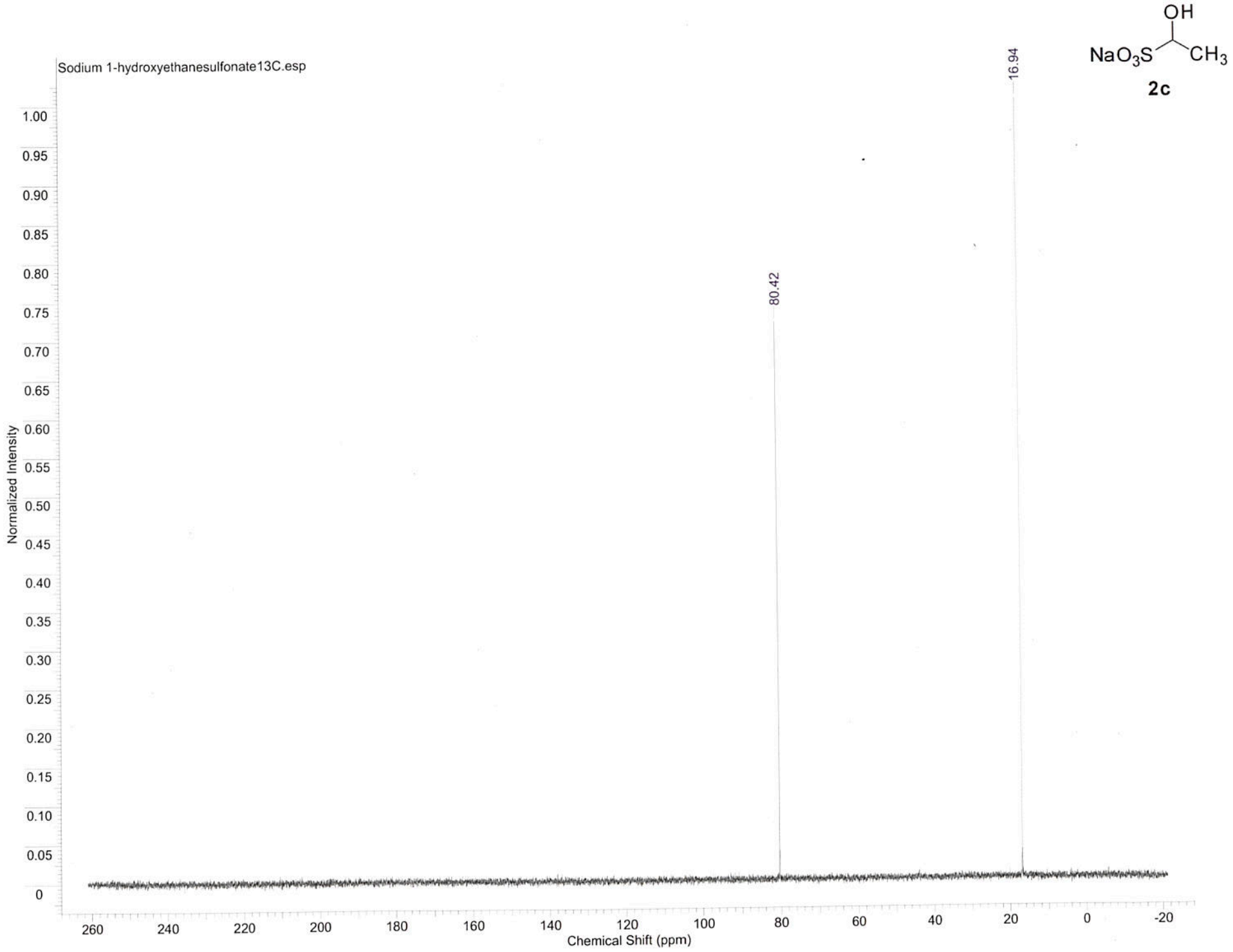
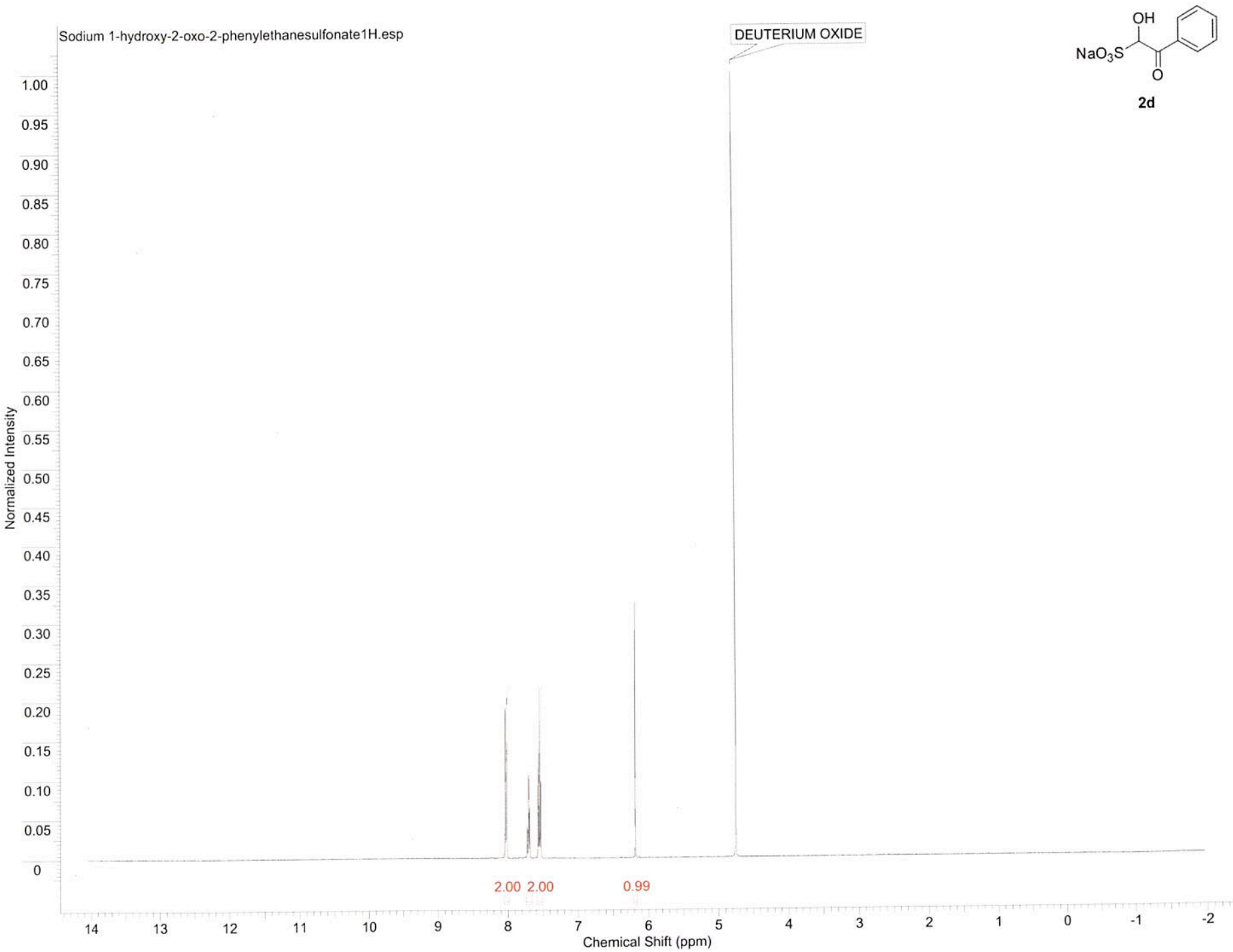
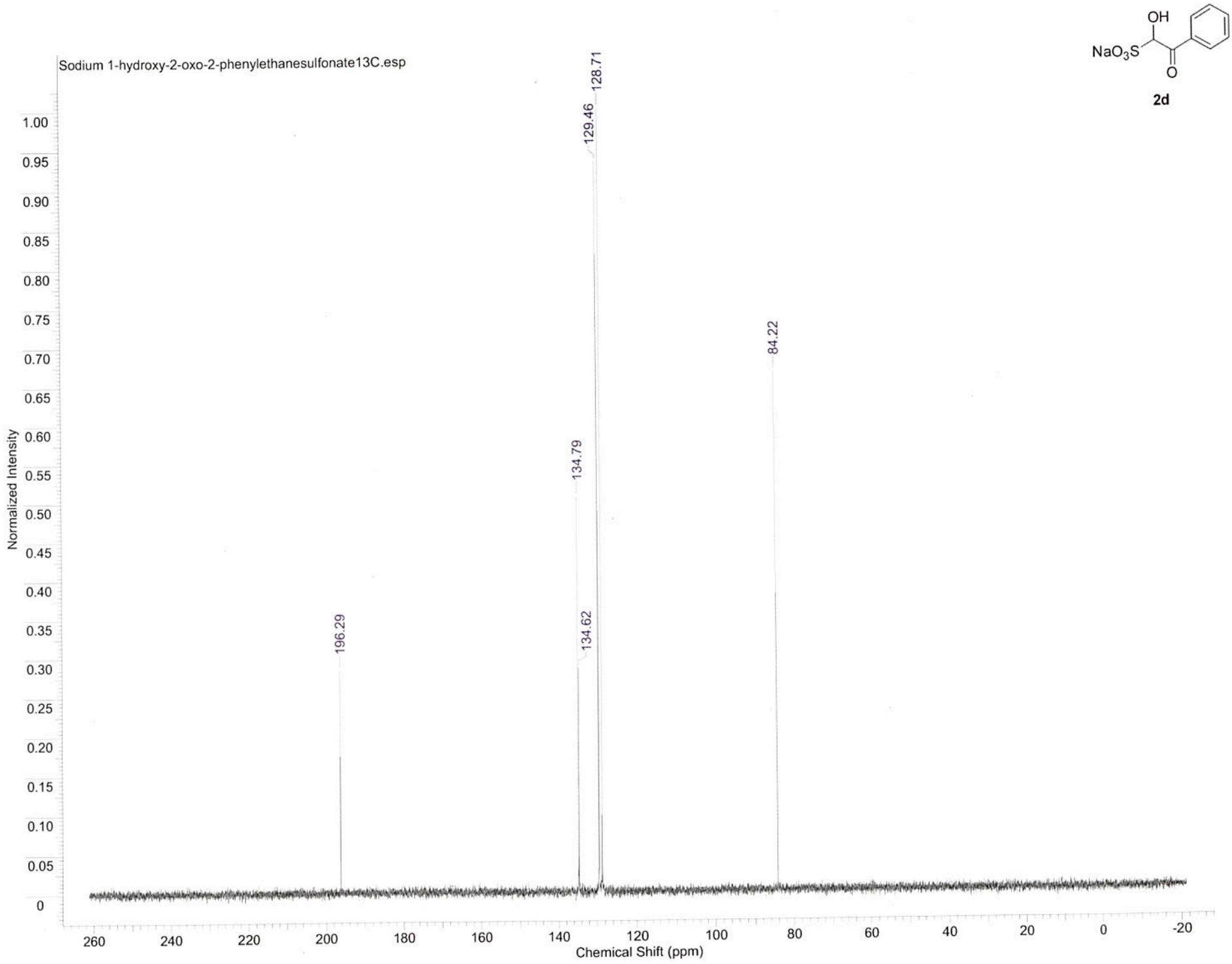
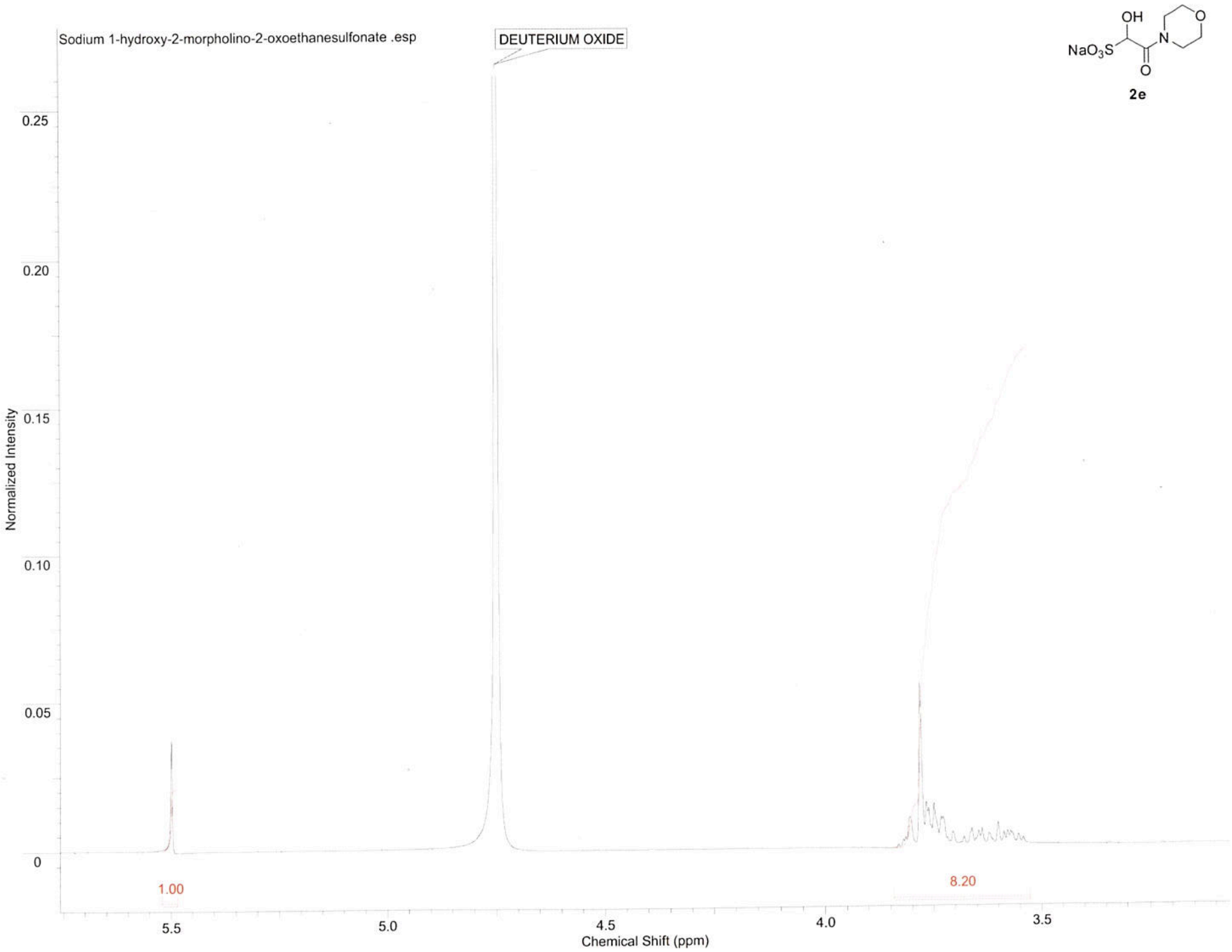
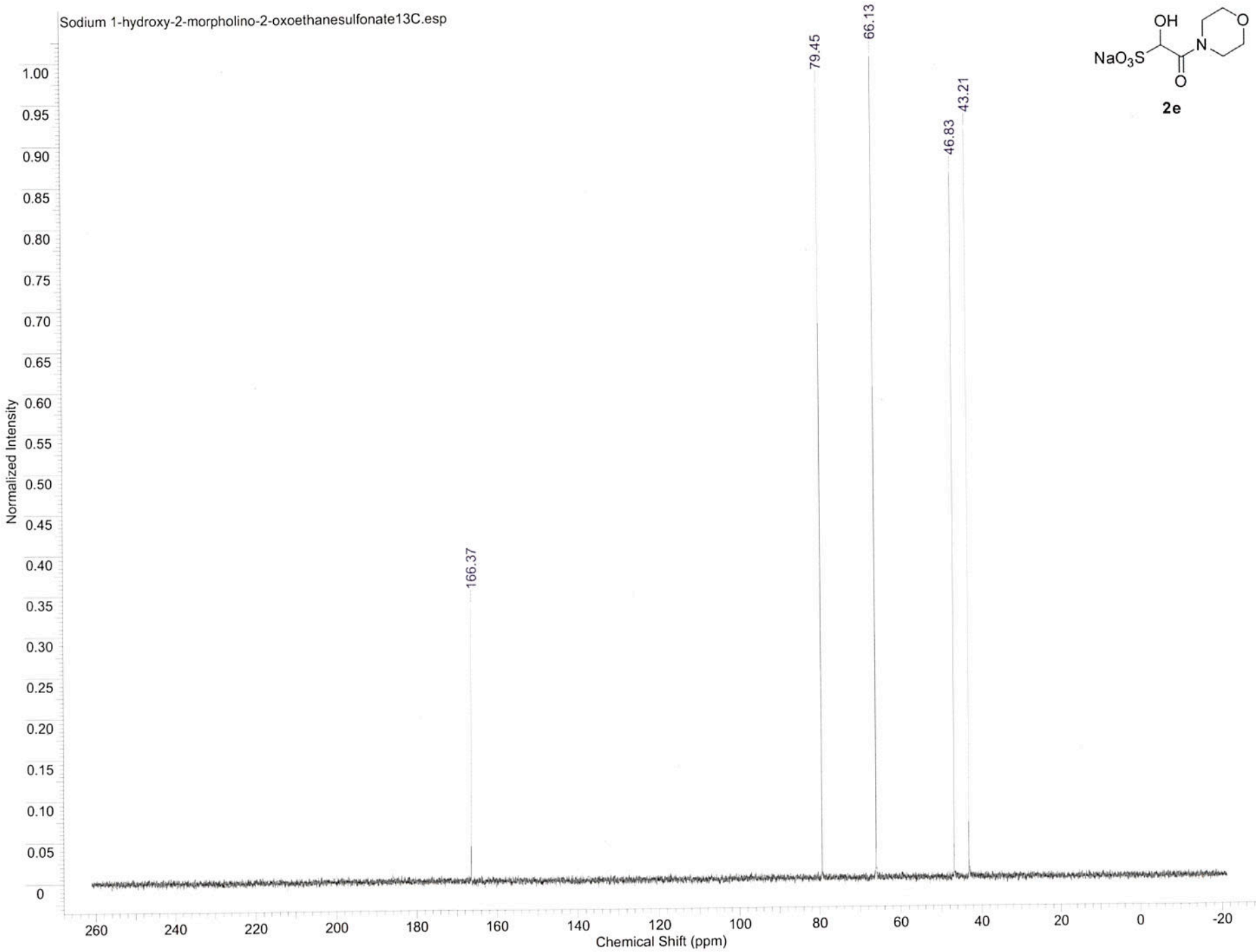
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.00
3.12
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

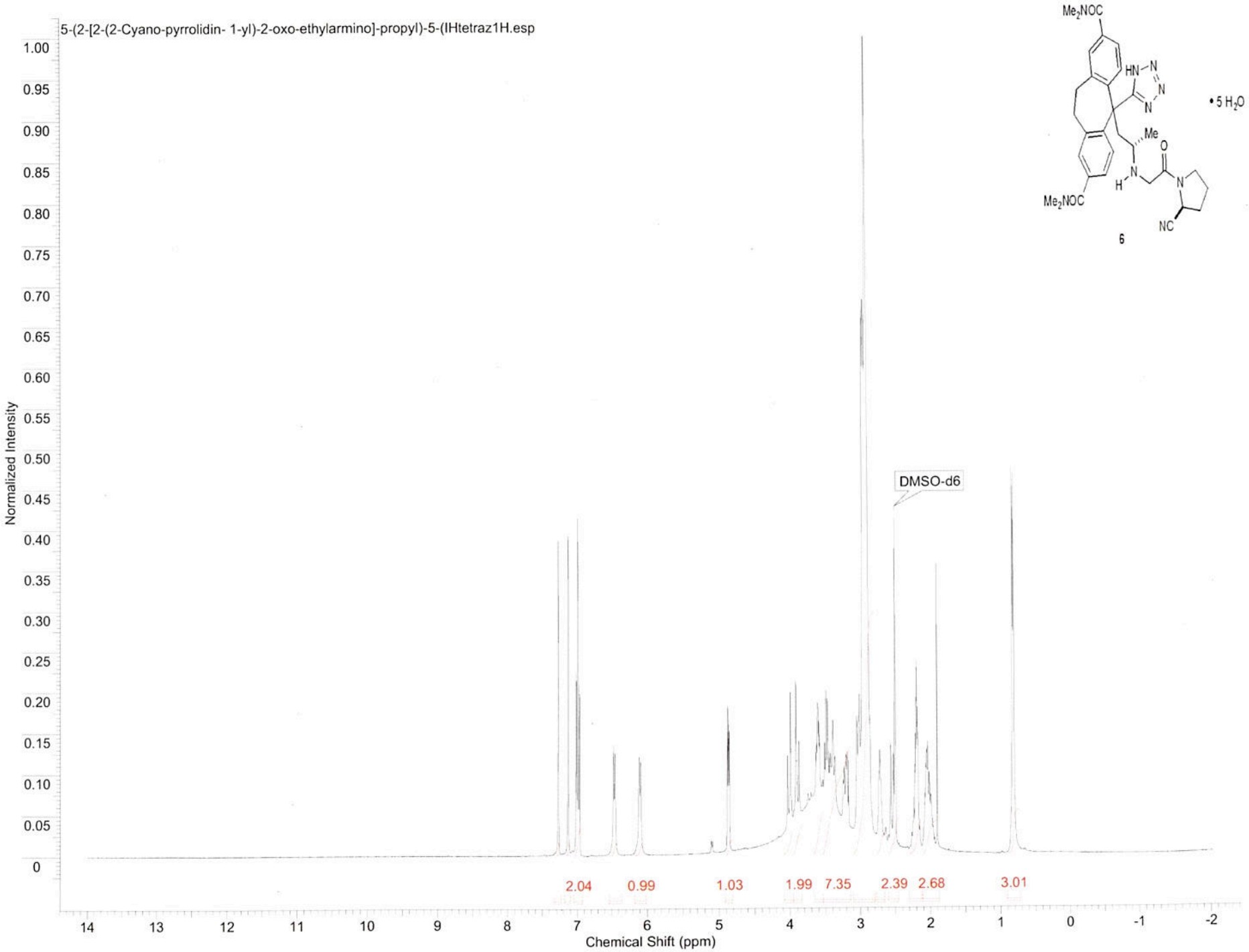

Sodium 1-hydroxyethanesulfonate13C.esp
16.94
80.42
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)
OH
NaO3S
CH3
2c


Sodium 1-hydroxy-2-oxo-2-phenylethanesulfonate1H.esp
DEUTERIUM OXIDE
OH
NaO3S
O
2d
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
2.00
2.00
0.99
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)


Sodium 1-hydroxy-2-oxo-2-phenylethanesulfonate13C.esp
OH
NaO3S
O
2d
128.71
129.46
84.22
134.79
134.62
196.29
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


Sodium 1-hydroxy-2-morpholino-2-oxoethanesulfonate .esp
DEUTERIUM OXIDE
OH
NaO3S
N
O
O
2e
0.25
0.20
0.15
0.10
0.05
0
Normalized Intensity
1.00
8.20
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)


Sodium 1-hydroxy-2-morpholino-2-oxoethanesulfonate13C.esp
79.45
66.13
46.83
43.21
166.37
Normalized Intensity
Chemical Shift (ppm)
OH
NaO3S
N
O
2e


5-(2-[2-(2-Cyano-pyrrolidin- 1-yl)-2-oxo-ethylarmino]-propyl)-5-(IHtetraz1H.esp
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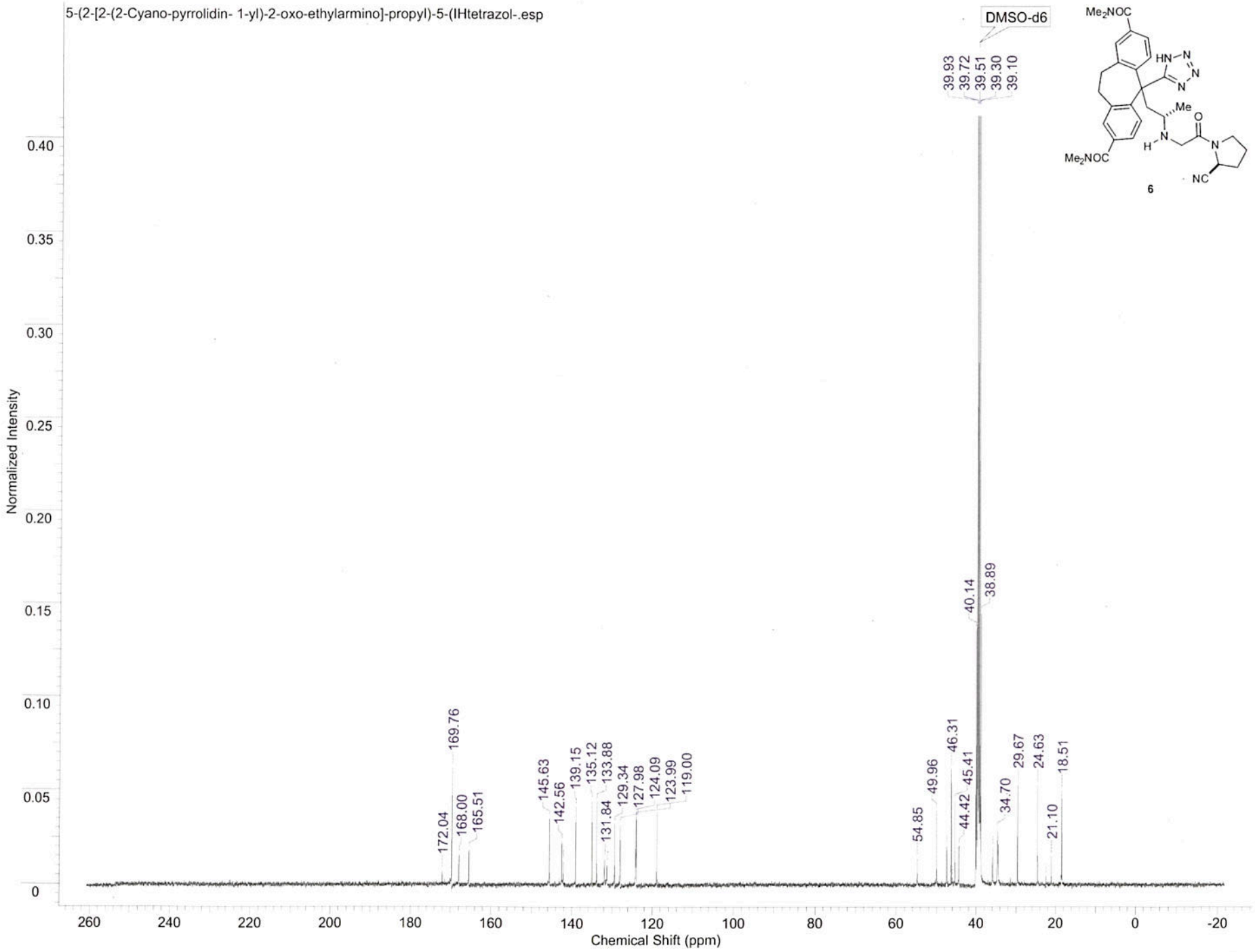
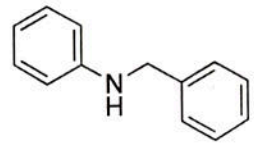
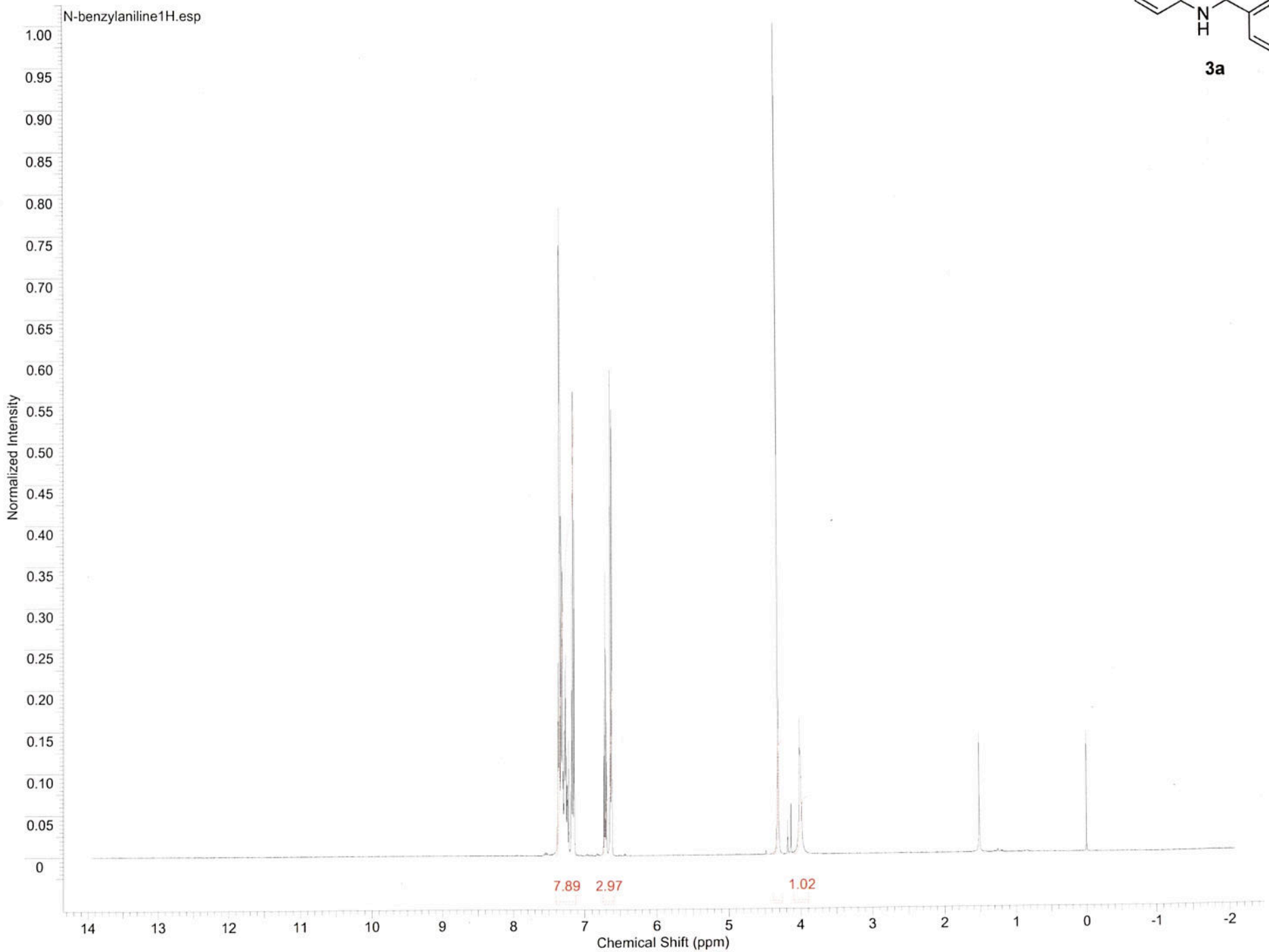
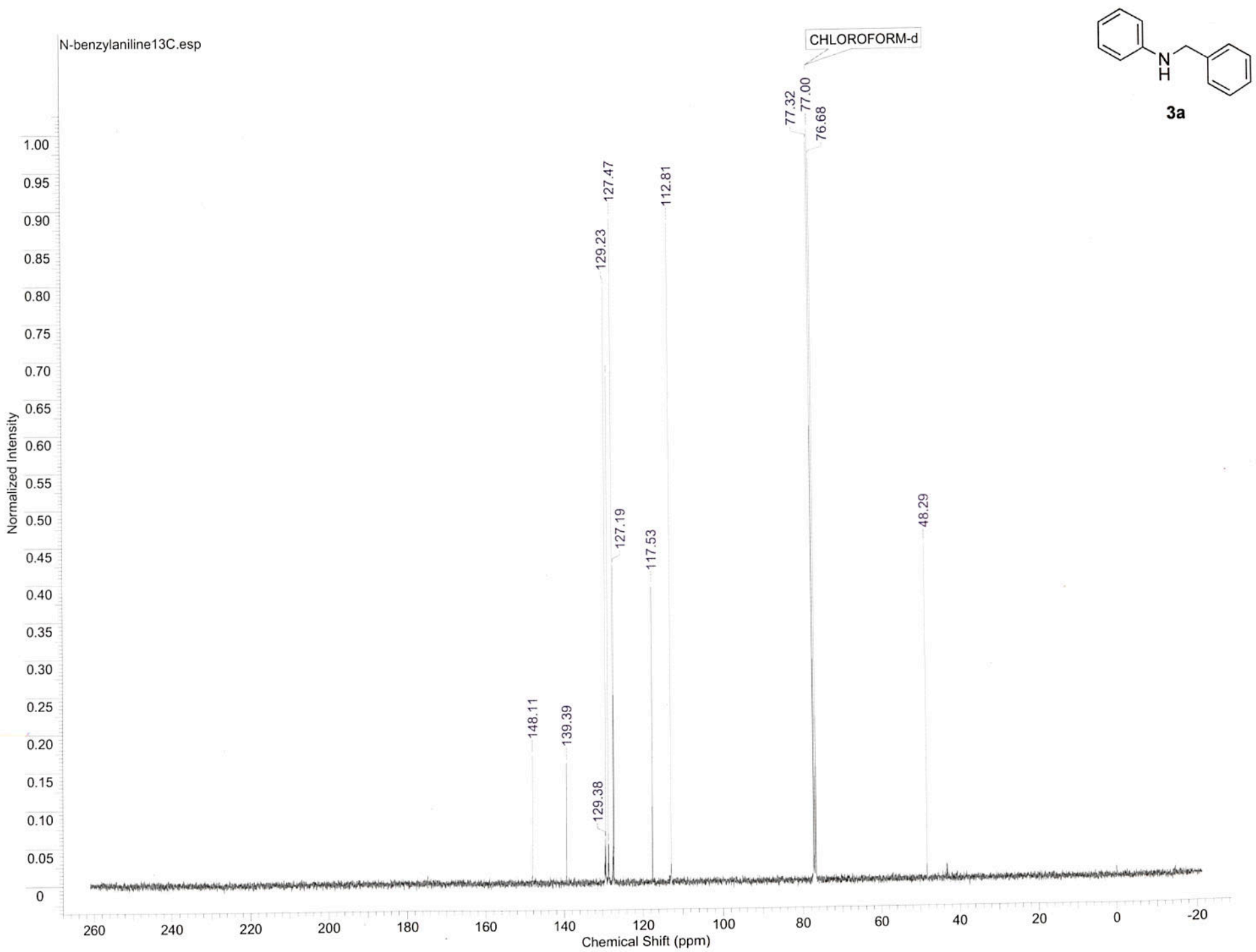
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
DMSO-d6
2.04
0.99
1.03
1.99
7.35
2.39
2.68
3.01
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)
Me2NOC
HN
N
N
N
• 5 H2O
Me
O
H
N
N
Me2NOC
NC
6


5-(2-[2-(2-Cyano-pyrrolidin- 1-yl)-2-oxo-ethylarmino]-propyl)-5-(IHtetrazol-.esp
DMSO-d6
39.93
39.72
39.51
39.30
39.10
Me2NOC
HN-N
N
N
Me
O
H-N
N
Me2NOC
NC
6
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
169.76
172.04
168.00
165.51
145.63
142.56
139.15
135.12
133.88
131.84
129.34
127.98
124.09
123.99
119.00
40.14
38.89
54.85
49.96
46.31
45.41
44.42
34.70
29.67
24.63
21.10
18.51
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)



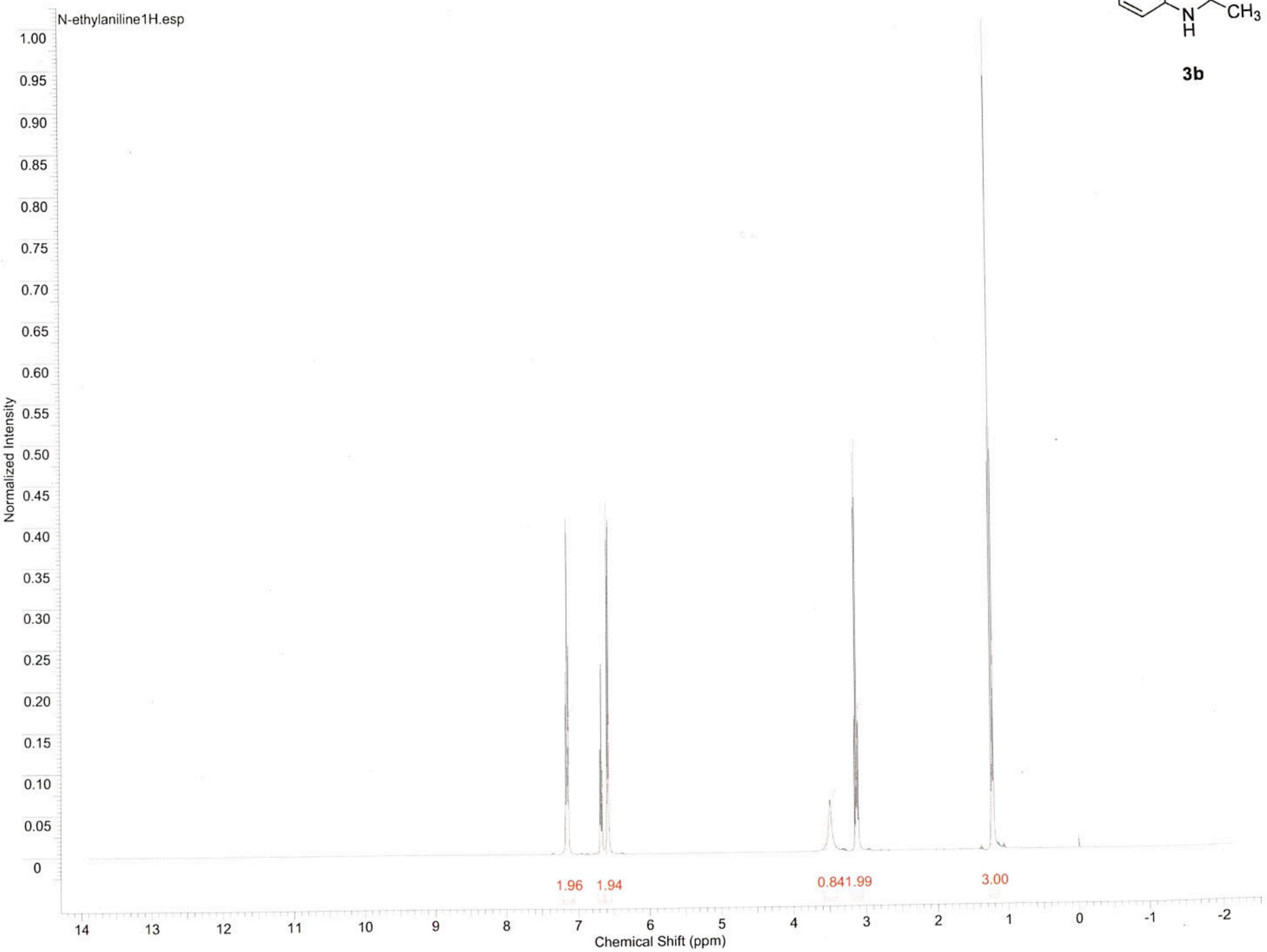
3a

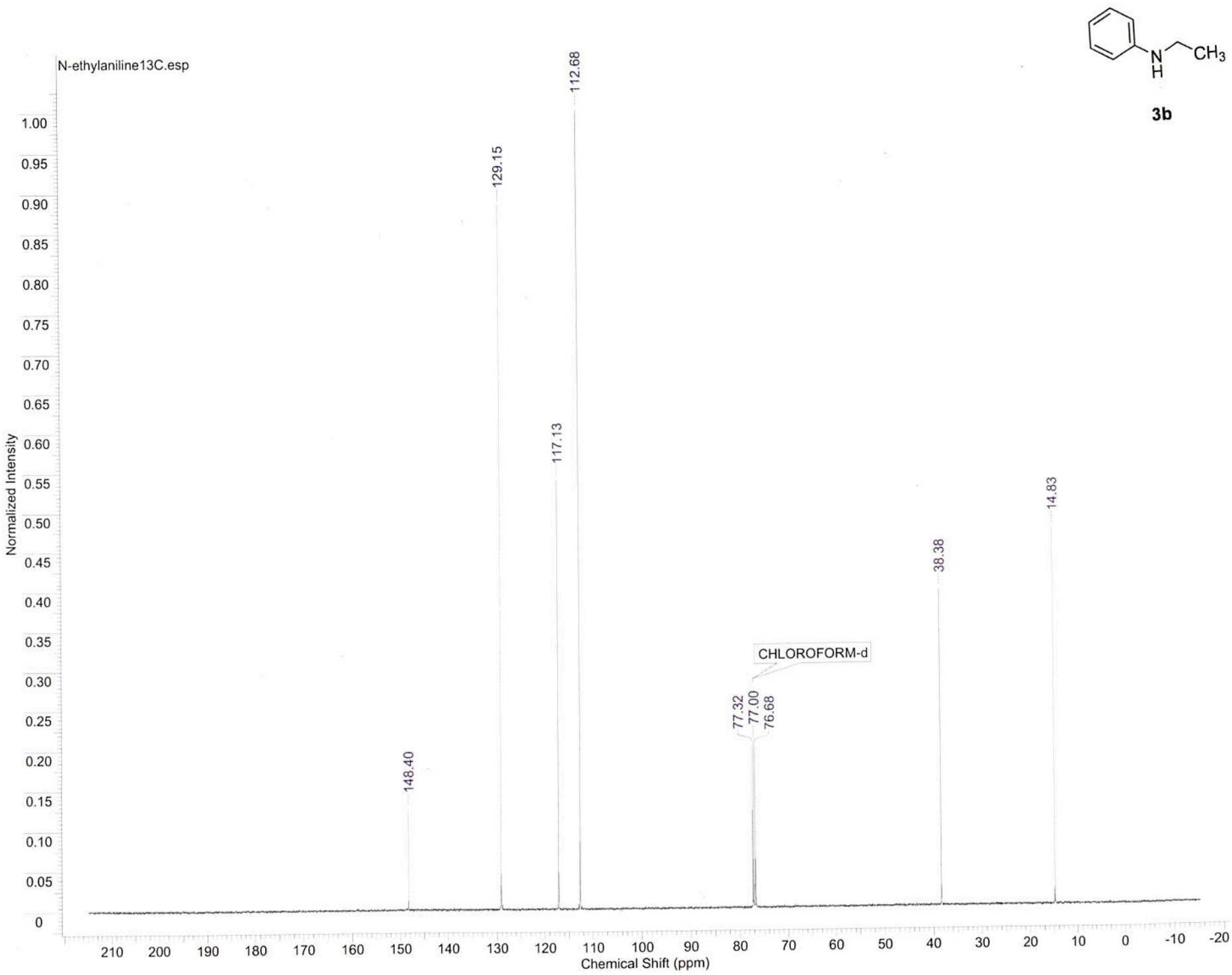

N-benzylaniline1H.esp
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
7.89
2.97
1.02
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)


N-benzylaniline13C.esp
CHLOROFORM-d
77.32
77.00
76.68
127.47
129.23
112.81
127.19
117.53
48.29
148.11
139.39
129.38
Normalized Intensity
Chemical Shift (ppm)
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20

N
H

3a


N-ethylaniline1H.esp
Normalized Intensity
Chemical Shift (ppm)
1.96
1.94
0.84
1.99
3.00
N
H
CH3
3b


N-ethylaniline13C.esp
112.68
129.15
117.13
148.40
77.32
77.00
76.68
CHLOROFORM-d
38.38
14.83
Normalized Intensity
Chemical Shift (ppm)
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
210
200
190
180
170
160
150
140
130
120
110
100
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40
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20
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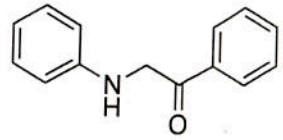
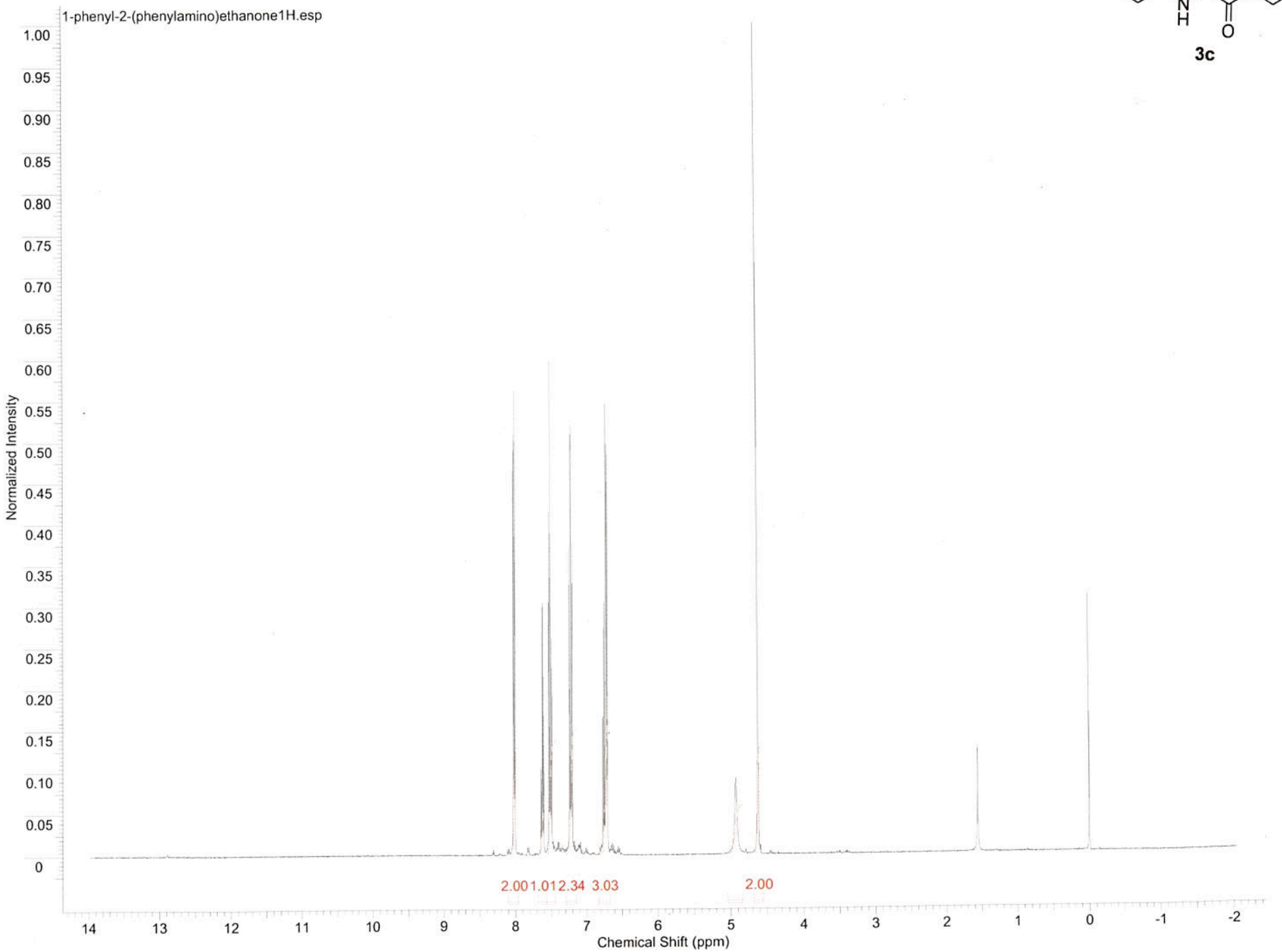
0
-10
-20

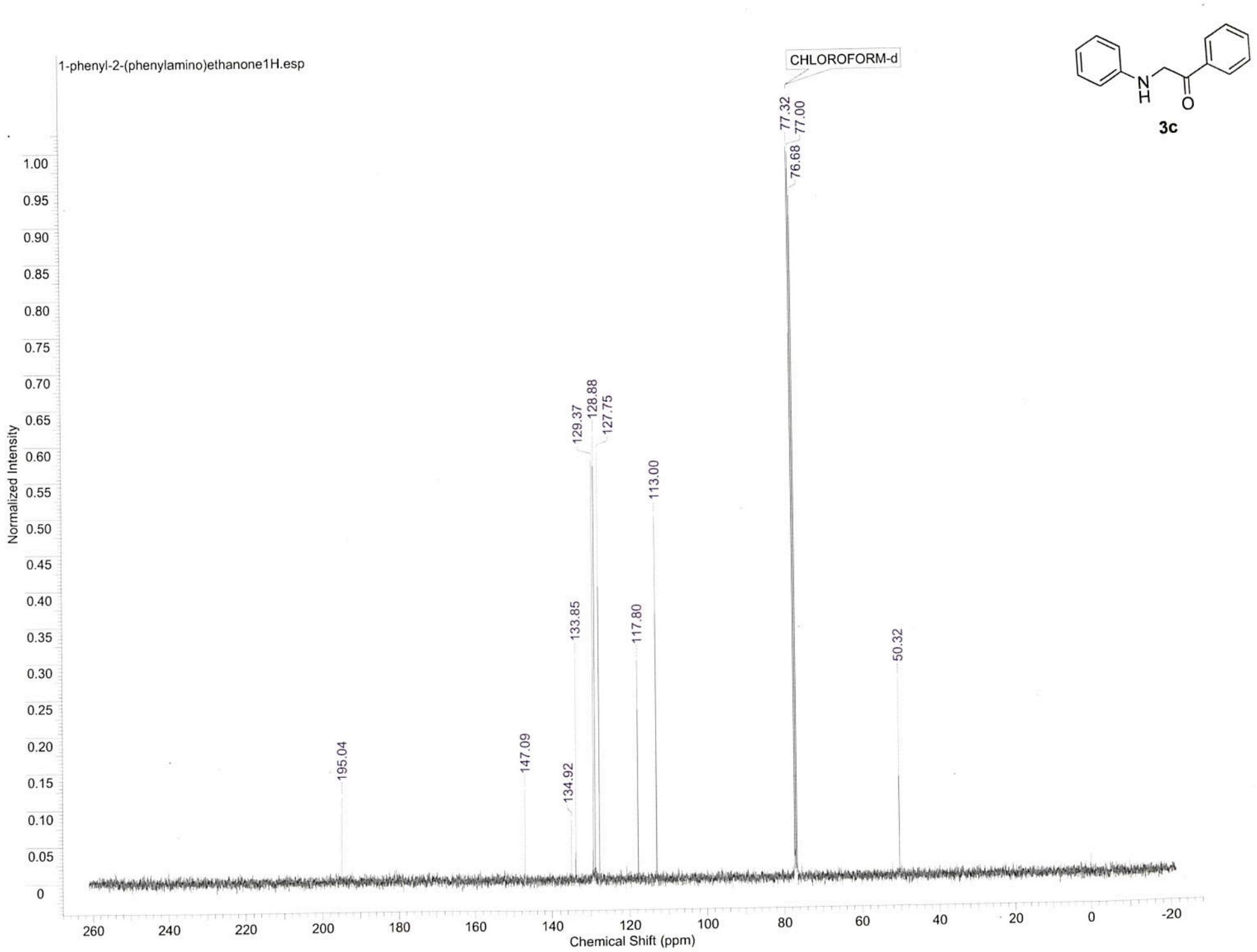
N
H
CH3

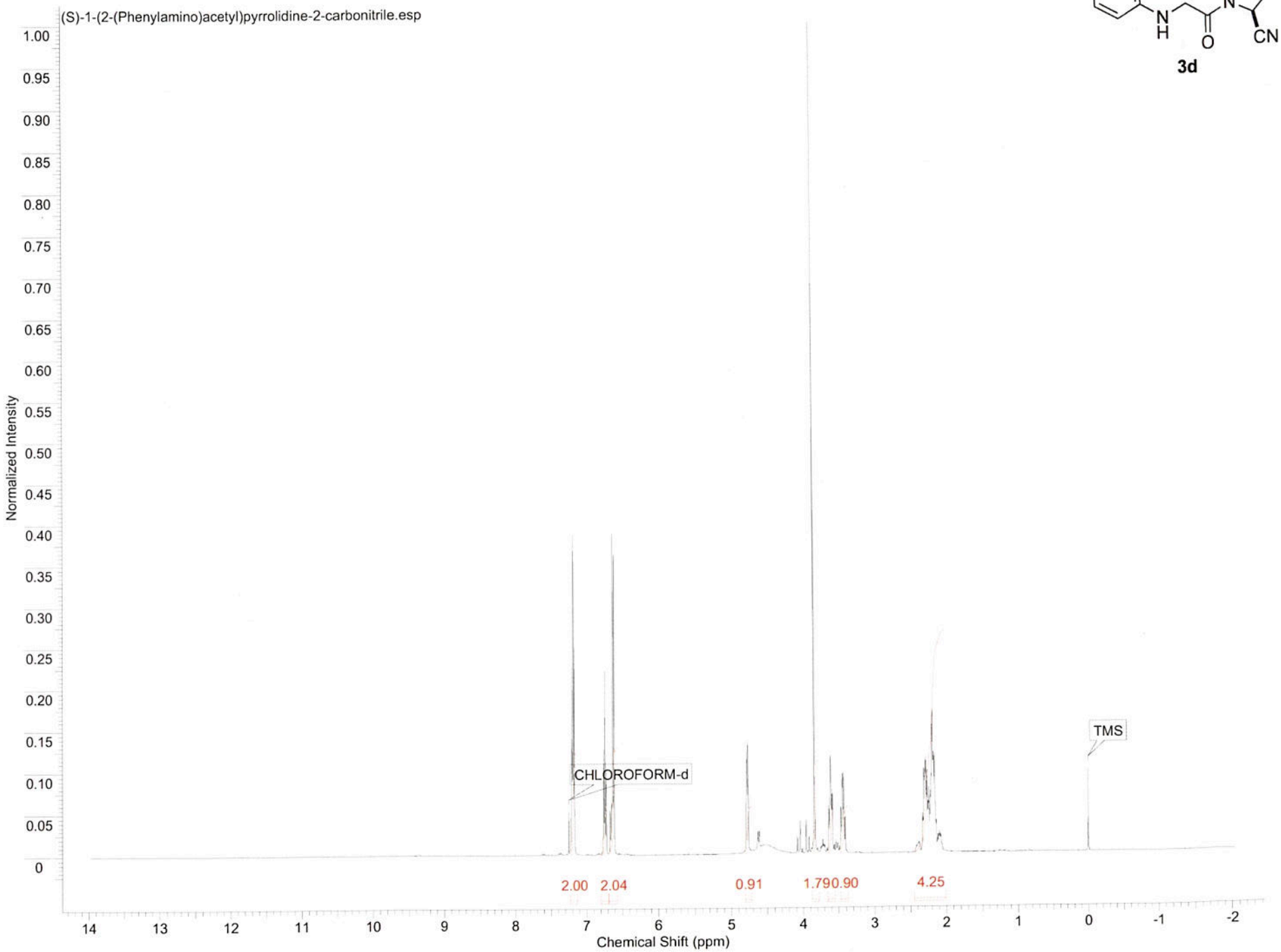
3b


N
H
O

3c

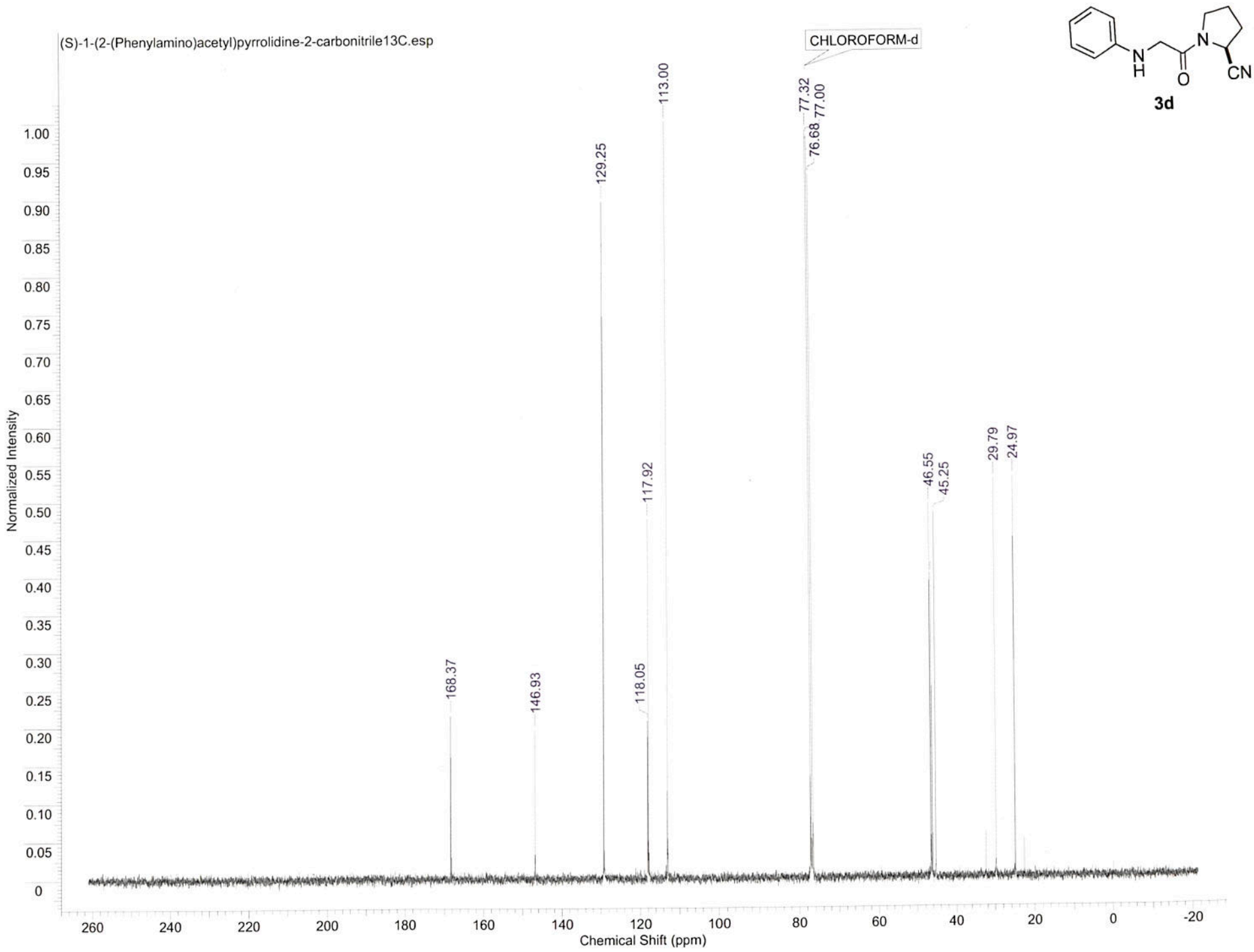

1-phenyl-2-(phenylamino)ethanone1H.esp
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
2.00 1.01 2.34 3.03
2.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

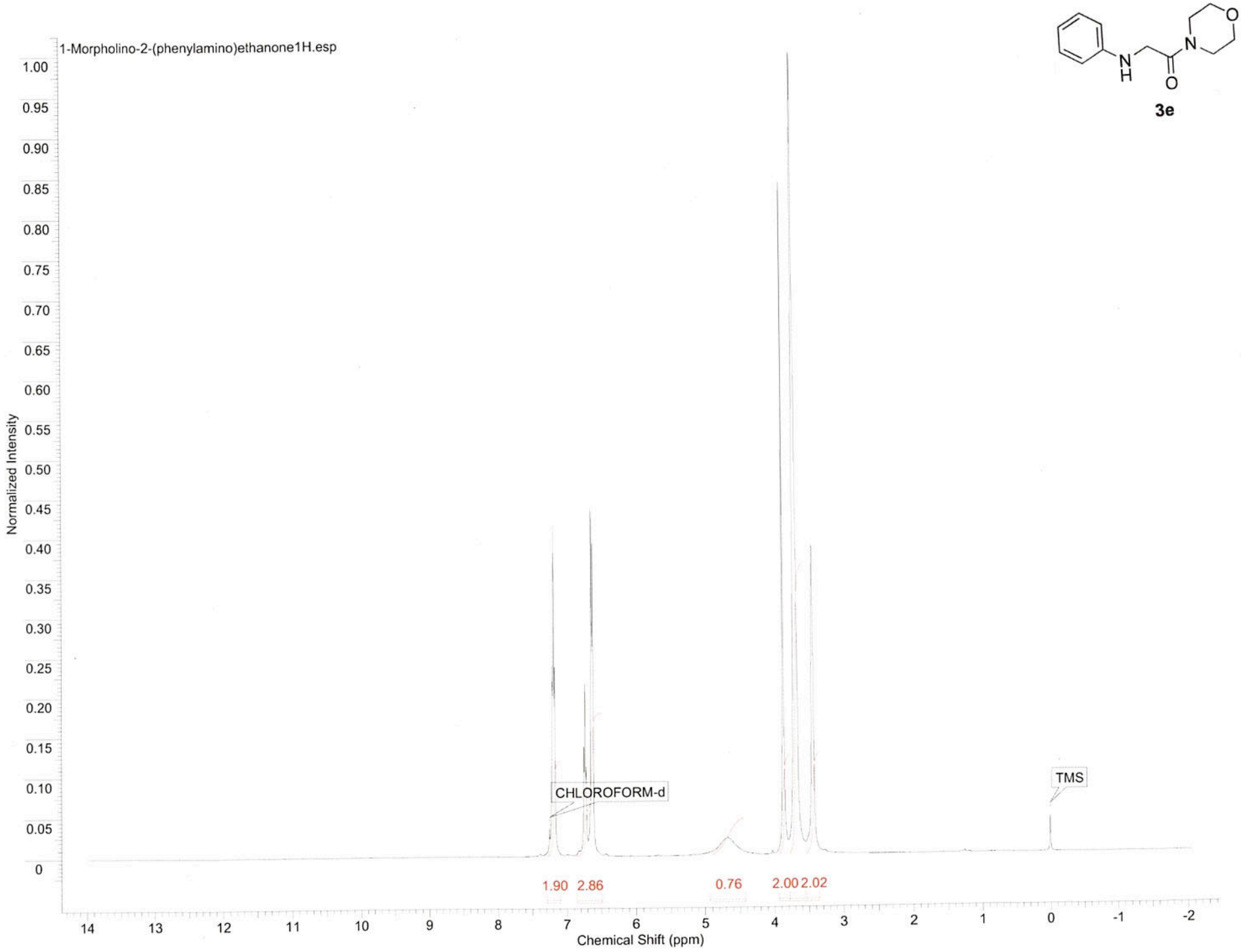

1-phenyl-2-(phenylamino)ethanone1H.esp
CHLOROFORM-d
77.32
77.00
76.68
129.37
128.88
127.75
113.00
133.85
117.80
50.32
195.04
147.09
134.92
Normalized Intensity
Chemical Shift (ppm)
3c


(S)-1-(2-(Phenylamino)acetyl)pyrrolidine-2-carbonitrile.esp
Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
TMS
2.00
2.04
0.91
1.79
0.90
4.25

N
H
O
N
CN

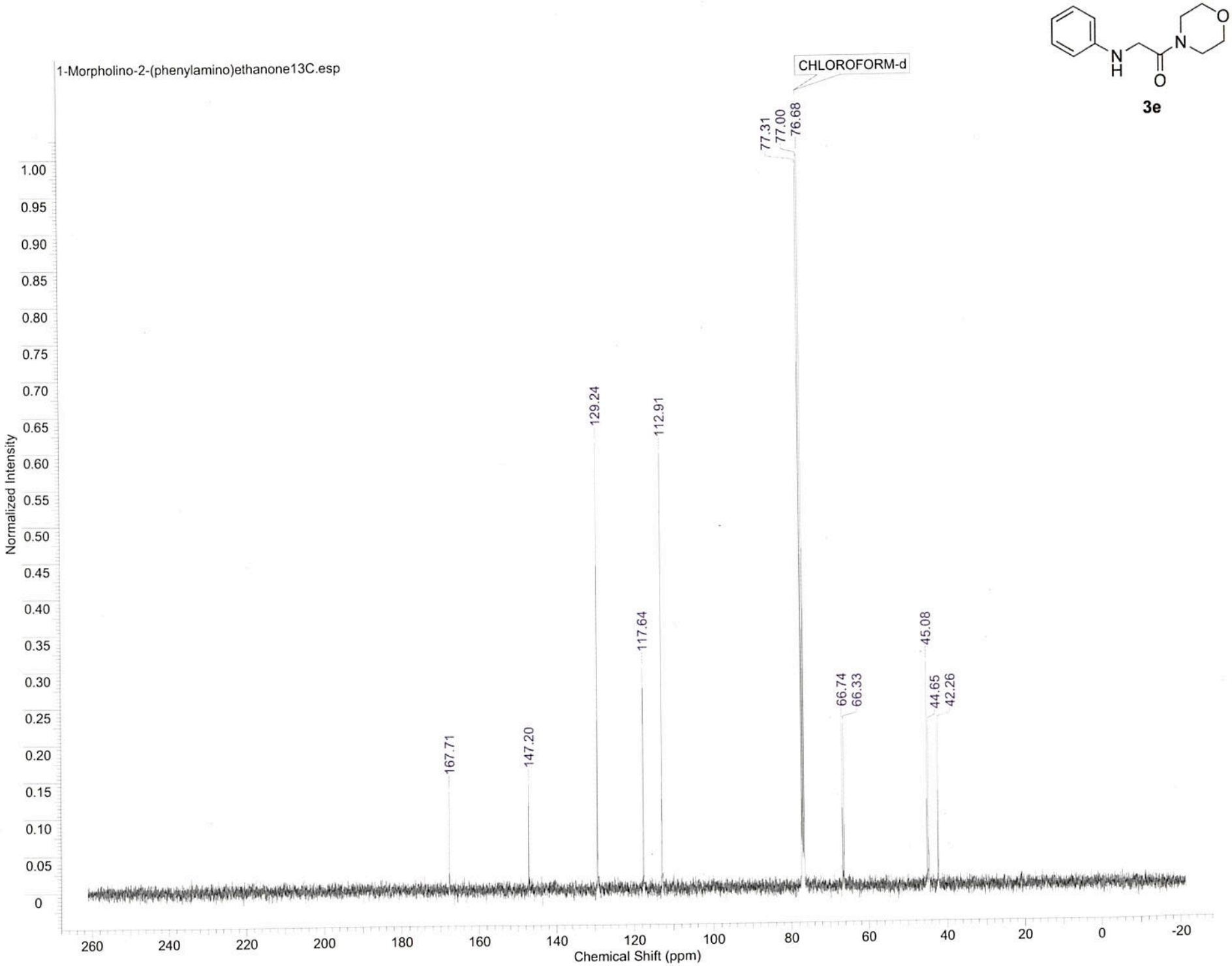
3d

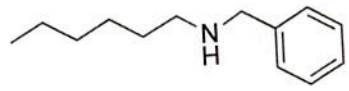

(S)-1-(2-(Phenylamino)acetyl)pyrrolidine-2-carbonitrile13C.esp
CHLOROFORM-d
3d
Normalized Intensity
Chemical Shift (ppm)
168.37
146.93
129.25
118.05
117.92
113.00
77.32
77.00
76.68
46.55
45.25
29.79
24.97


1-Morpholino-2-(phenylamino)ethanone1H.esp
Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
TMS
1.90
2.86
0.76
2.00
2.02

N
H
N
O
O

3e


1-Morpholino-2-(phenylamino)ethanone13C.esp
CHLOROFORM-d
77.31
77.00
76.68
129.24
112.91
117.64
167.71
147.20
66.74
66.33
45.08
44.65
42.26
Normalized Intensity
Chemical Shift (ppm)
3e



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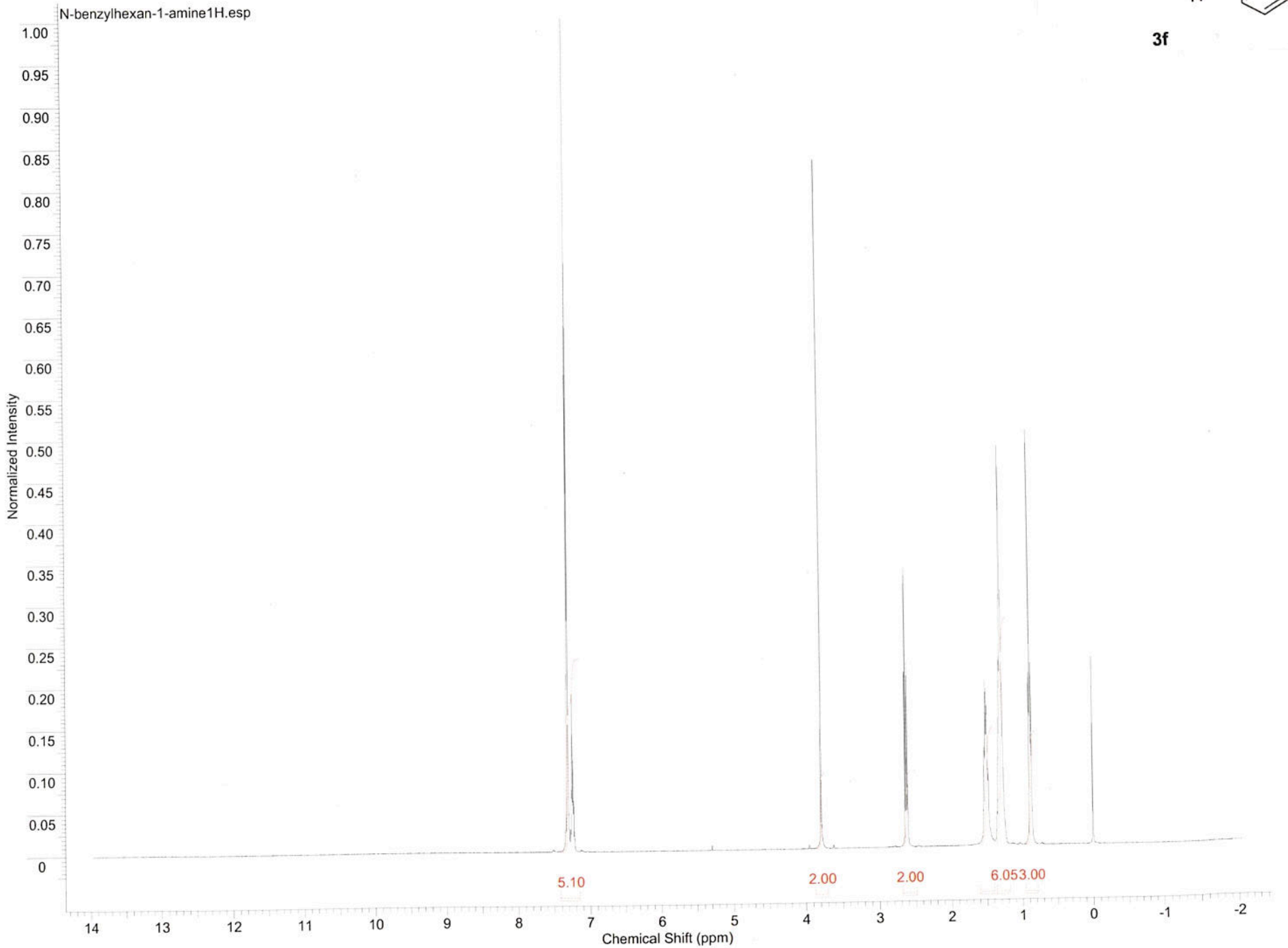
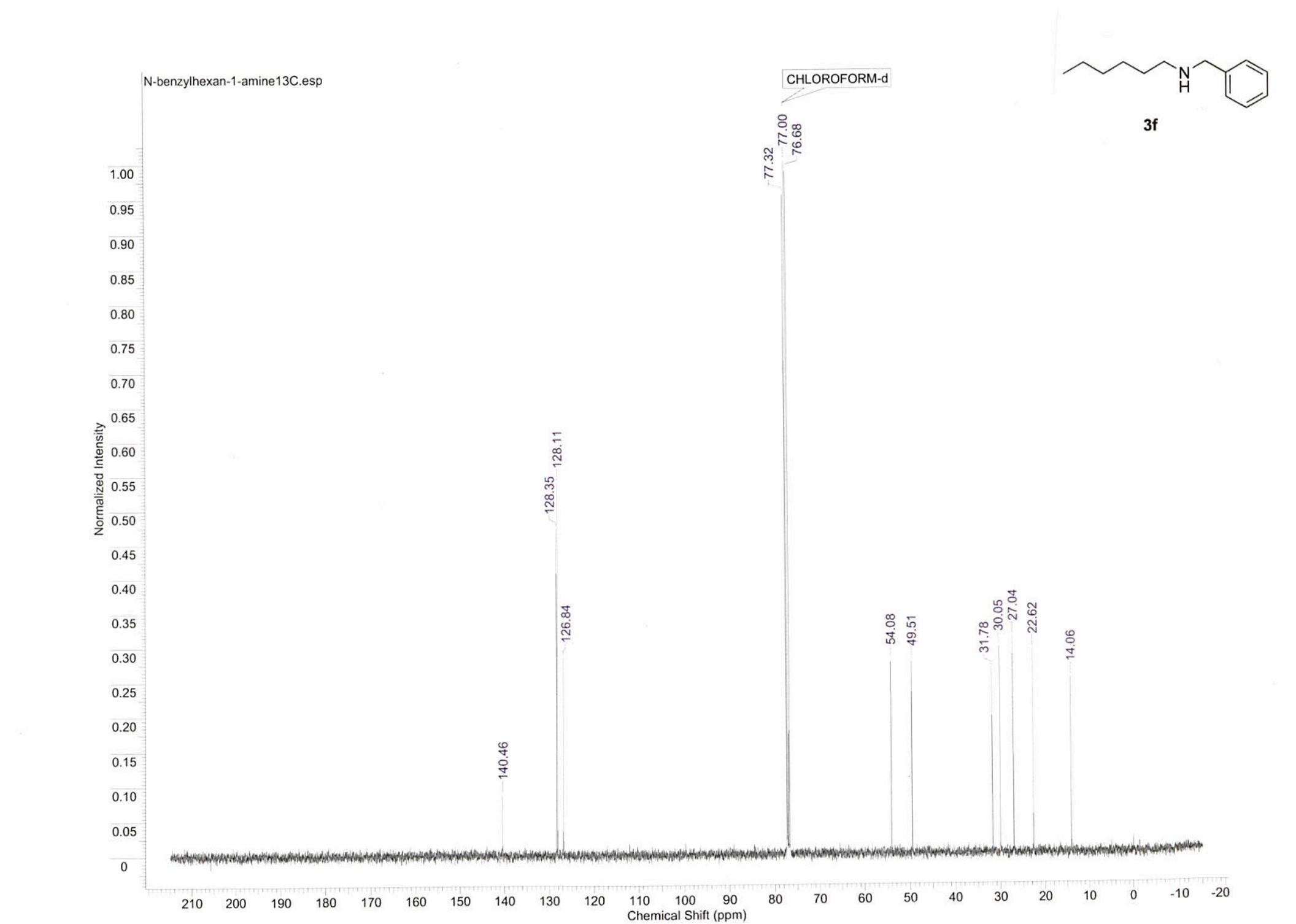
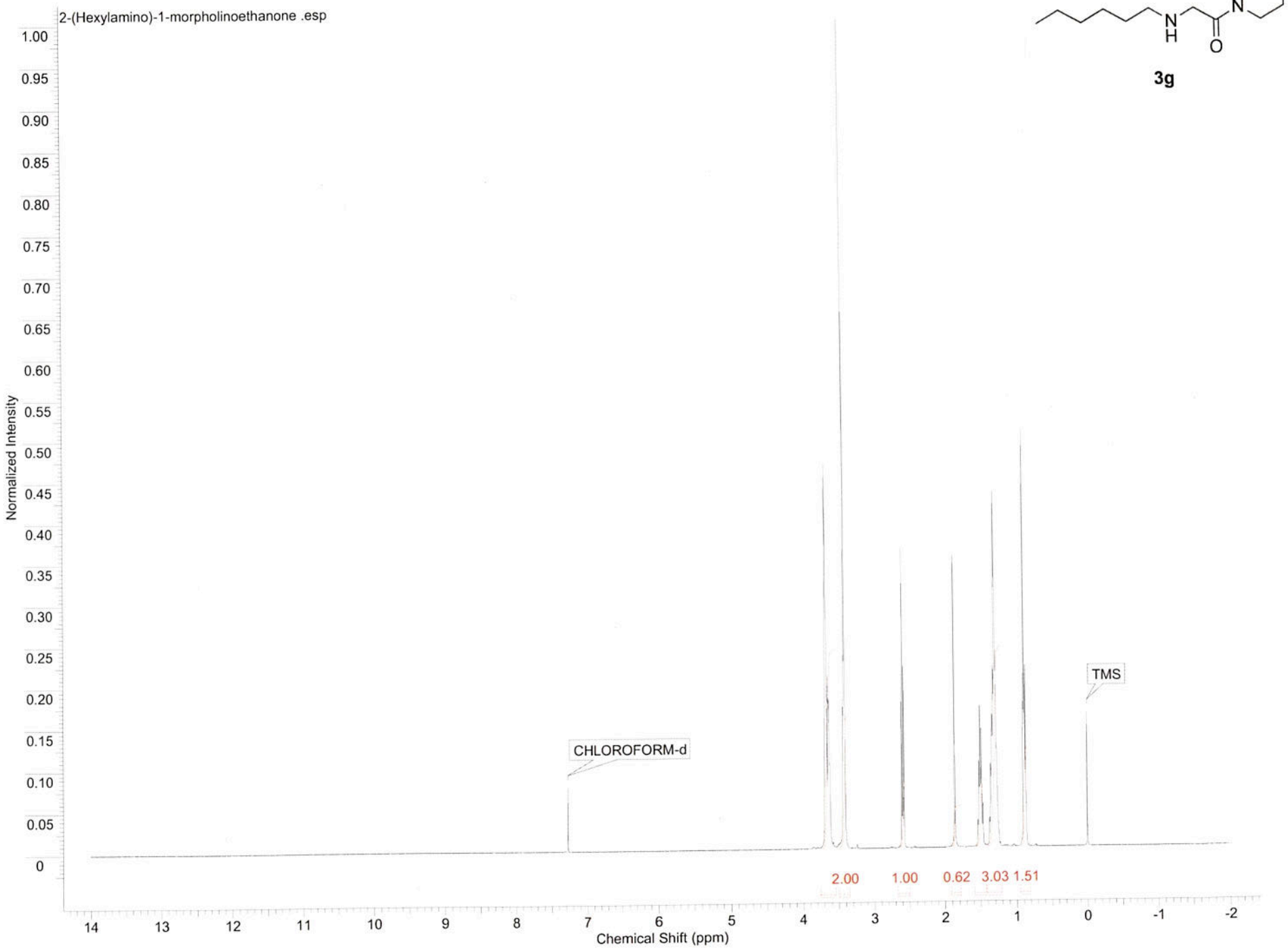
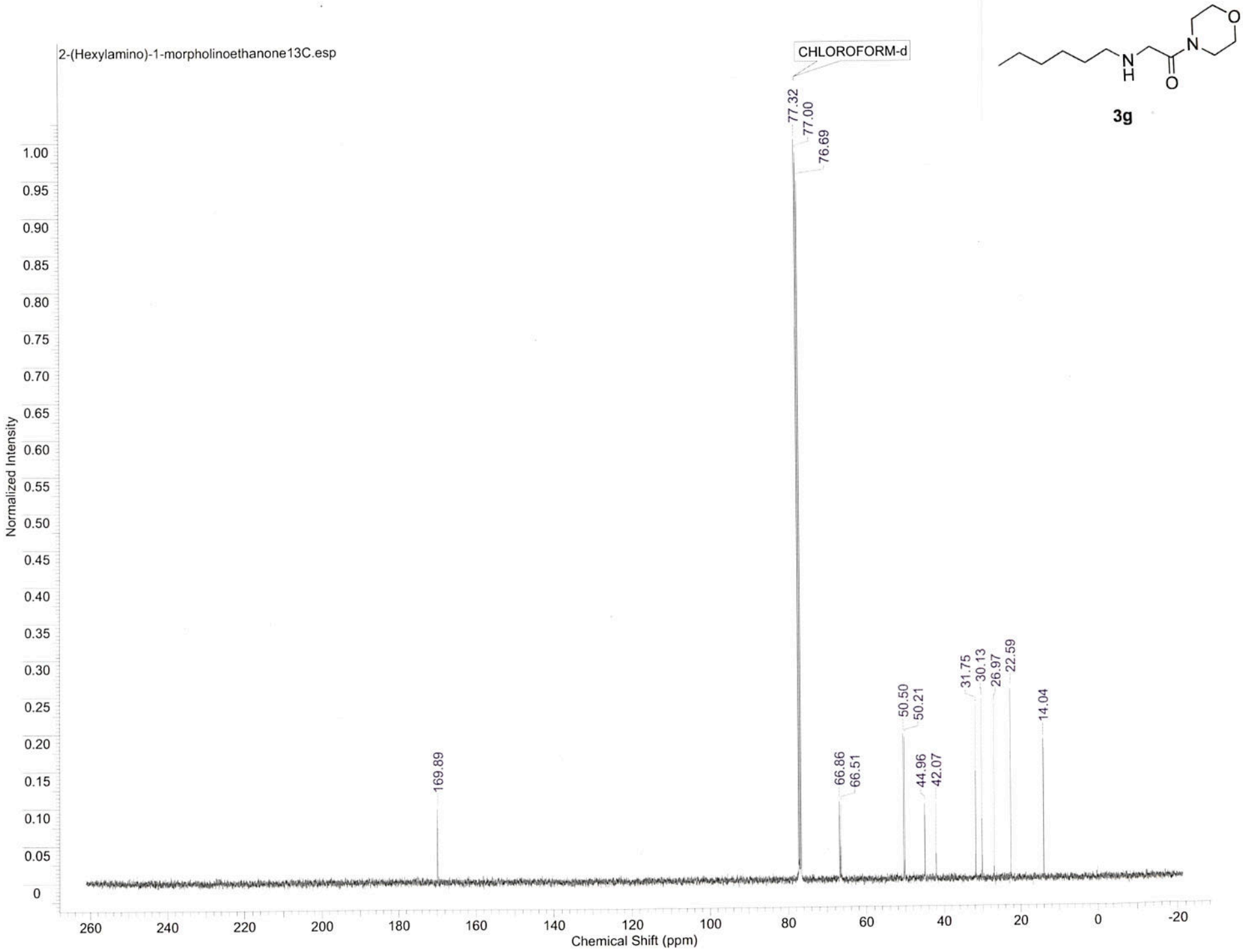
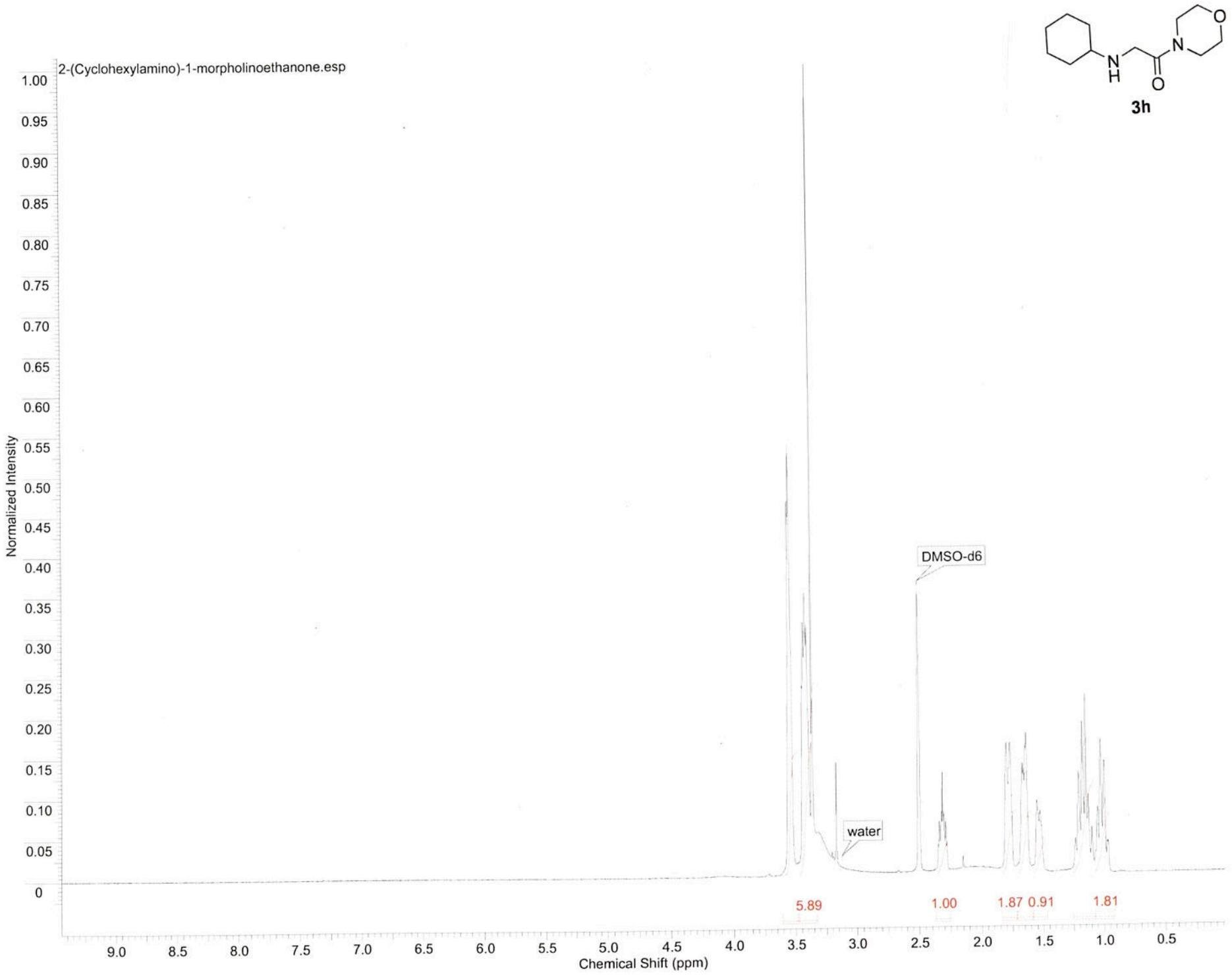

N-benzylhexan-1-amine1H.esp
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
5.10
2.00
2.00
6.05
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

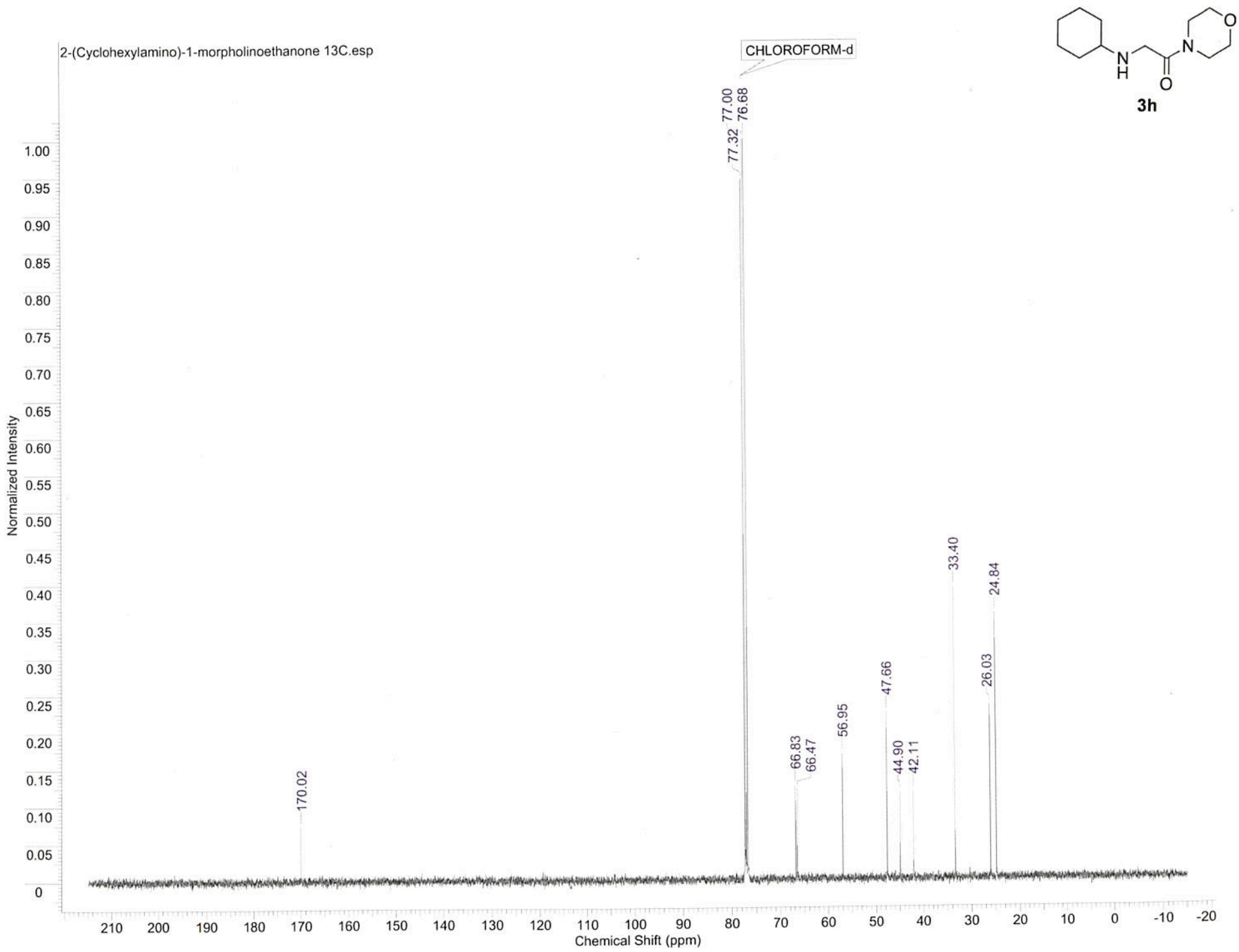

N-benzylhexan-1-amine13C.esp
CHLOROFORM-d
77.32
77.00
76.68
128.35
128.11
126.84
140.46
54.08
49.51
31.78
30.05
27.04
22.62
14.06
Normalized Intensity
Chemical Shift (ppm)
3f

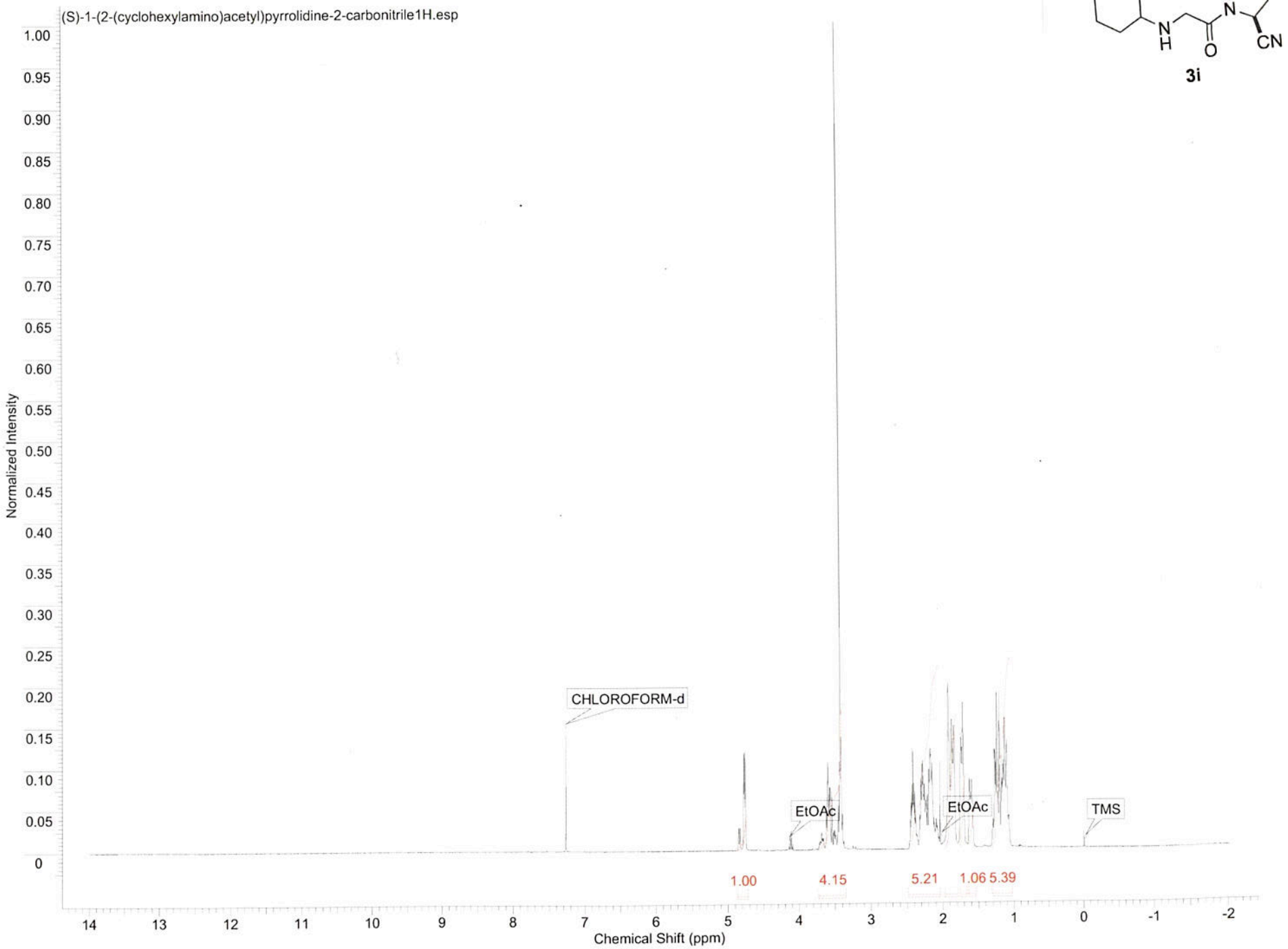

2-(Hexylamino)-1-morpholinoethanone .esp
Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
TMS
2.00
1.00
0.62
3.03
1.51

3g


2-(Hexylamino)-1-morpholinoethanone13C.esp
CHLOROFORM-d
77.32
77.00
76.69
169.89
66.86
66.51
50.50
50.21
44.96
42.07
31.75
30.13
26.97
22.59
14.04
Normalized Intensity
Chemical Shift (ppm)
3g

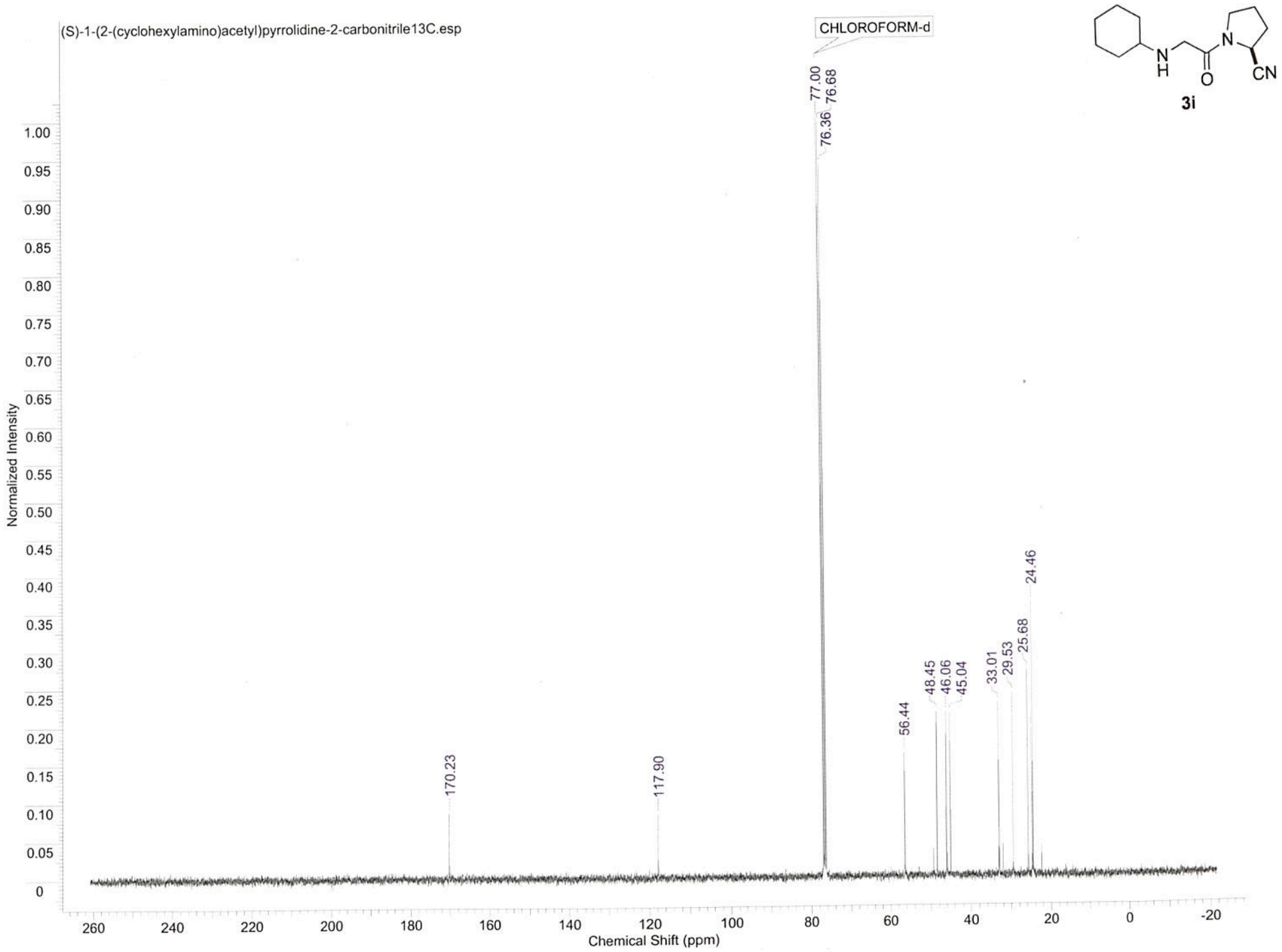

2-(Cyclohexylamino)-1-morpholinoethanone.esp
3h
Normalized Intensity
Chemical Shift (ppm)
DMSO-d6
water
5.89
1.00
1.87
0.91
1.81

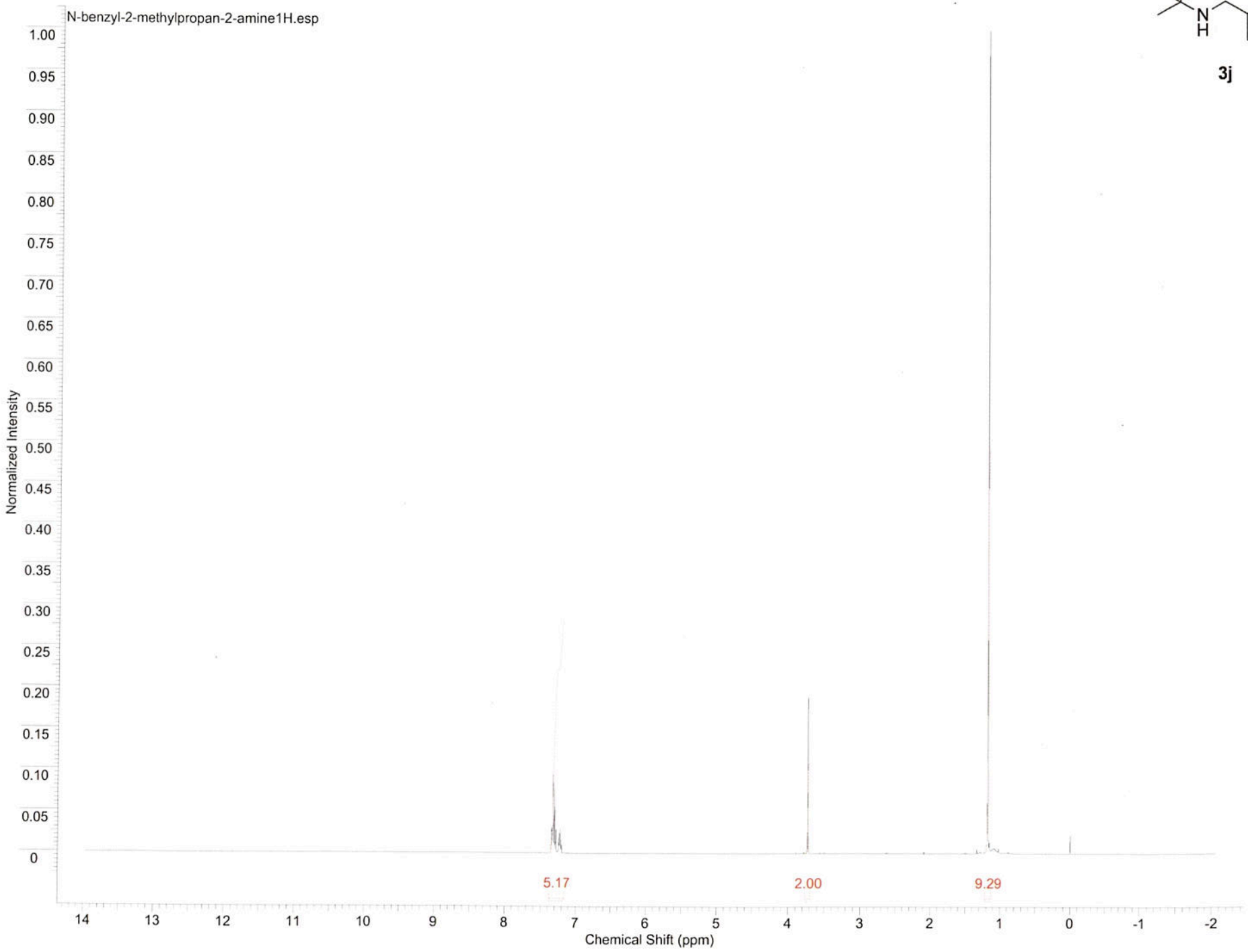

2-(Cyclohexylamino)-1-morpholinoethanone 13C.esp
CHLOROFORM-d
77.00
76.68
77.32
170.02
66.83
66.47
56.95
47.66
44.90
42.11
33.40
26.03
24.84
Normalized Intensity
Chemical Shift (ppm)
3h

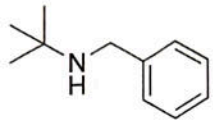

(S)-1-(2-(cyclohexylamino)acetyl)pyrrolidine-2-carbonitrile1H.esp
Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
EtOAc
EtOAc
TMS
1.00
4.15
5.21
1.06
5.39

N
H
O
N
CN

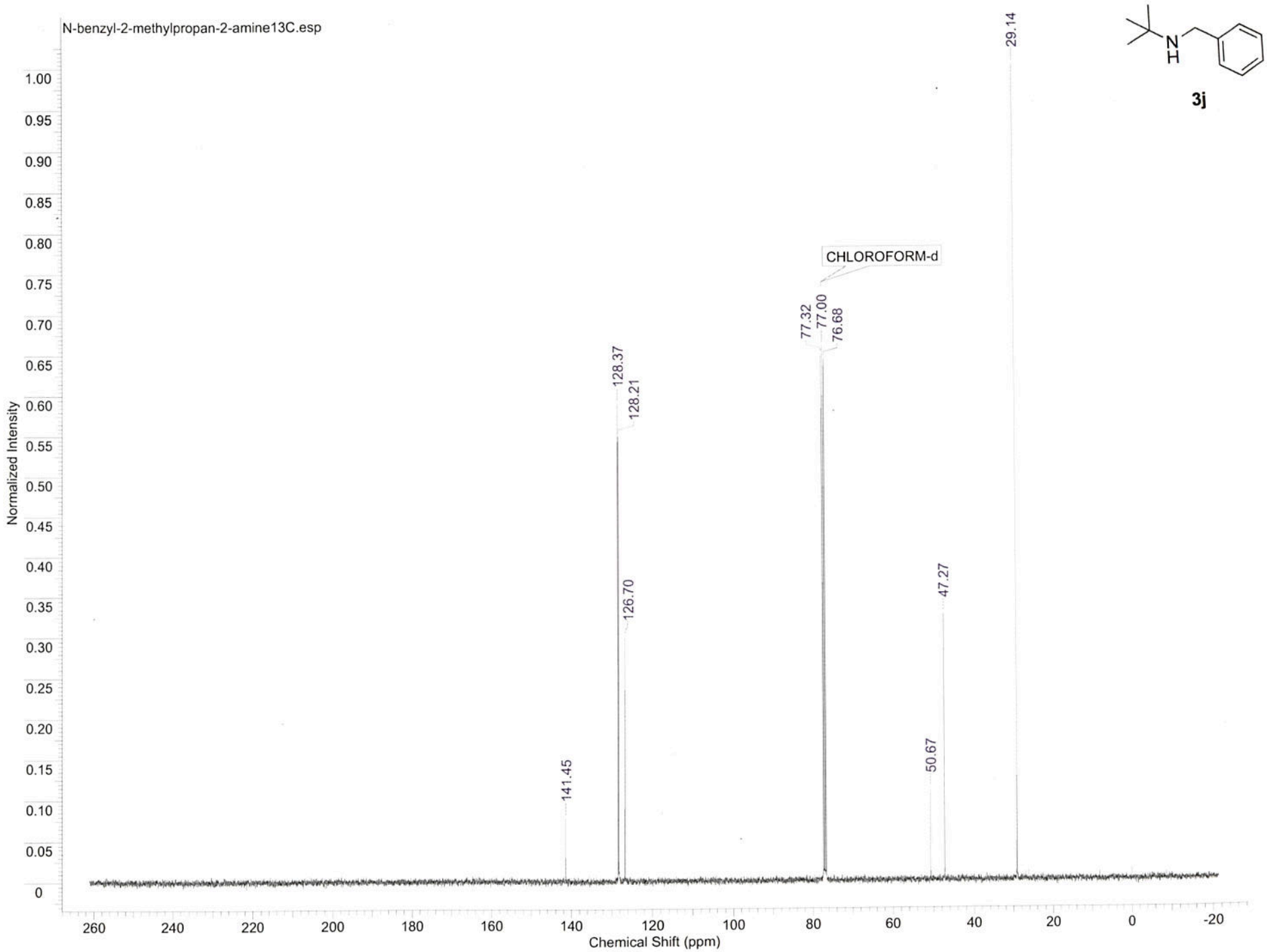
3i


(S)-1-(2-(cyclohexylamino)acetyl)pyrrolidine-2-carbonitrile13C.esp
CHLOROFORM-d
77.00
76.68
76.36
170.23
117.90
56.44
48.45
46.06
45.04
33.01
29.53
25.68
24.46
Normalized Intensity
Chemical Shift (ppm)
3i


N-benzyl-2-methylpropan-2-amine1H.esp
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
5.17
2.00
9.29
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)


N
H

3j


N-benzyl-2-methylpropan-2-amine13C.esp
3j
29.14
CHLOROFORM-d
77.32
77.00
76.68
128.37
128.21
126.70
141.45
47.27
50.67
Normalized Intensity
Chemical Shift (ppm)