Supplementary Materials

Structural investigations on 2-amidobenzimidazole derivatives as new inhibitors of protein kinase CK1 delta

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Table of Contents

Figure S1

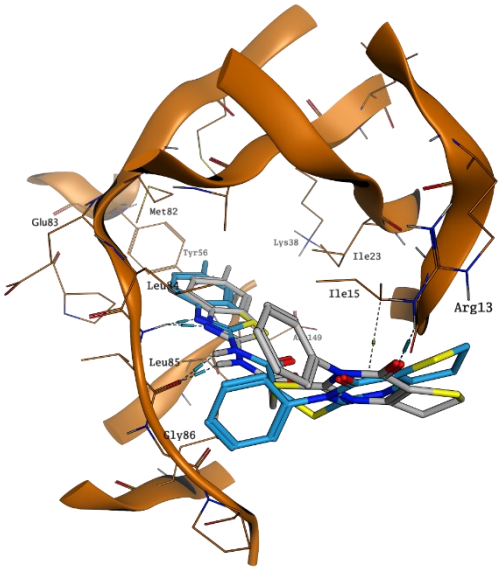


Figure S1. Comparison between the docking pose of the reference crystallographic ligand IWP-2 (blue) with its relative X-ray conformation (grey) within CK1δ (orange) binding site (PDB ID: 5OKT).

Table S1. *Physicochemical and pharmacokinetic parameters of derivatives **15**, **18**, **22**, **23***

Compound ID	**15**	**18**	**22**	**23**	**PF-670462***
logP (o/w)	2.814	1.557	3.160	1.573	3.882
logS	-4.421	-3.776	-4.989	-4.631	-5.839
logHERG	-5.369	-5.304	-5.198	-5.507	-5.324
Caco-2	376.9	43.2	319.4	81.8	753.7
logBB	-0.869	-2.058	-0.812	-1.798	-0.503
logKHSA	0.200	0.027	0.300	-0.075	0.687
HOA (%)	89 %	65 %	90 %	70 %	100

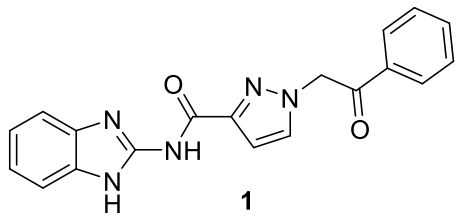
** Positive control used in the CK1δ Activity Assays.*

Legenda

- Good
- Average
- Bad

	Range or recommended values
logP (o/w): Predicted octanol/water partition coefficient.	–2.0 – 6.5
logS: Predicted aqueous solubility (mol dm^{-3}).	–6.5 – 0.5
logHERG: Predicted IC_{50} value for blockage of HERG K+ channels.	–5
Caco-2: Predicted apparent Caco-2 cell permeability in nm/sec.	<25 poor, >500 great
logBB: Predicted brain/blood partition coefficient.	–3.0 – 1.2
logKHSA: Prediction of binding to human serum albumin.	–1.5 – 1.5
HOA (%): Prediction of human oral absorption on 0 to 100% scale.	>80% is high, <25% is poor

^{1}H NMR scanned spectra (DMSOd6) of derivatives 1-32.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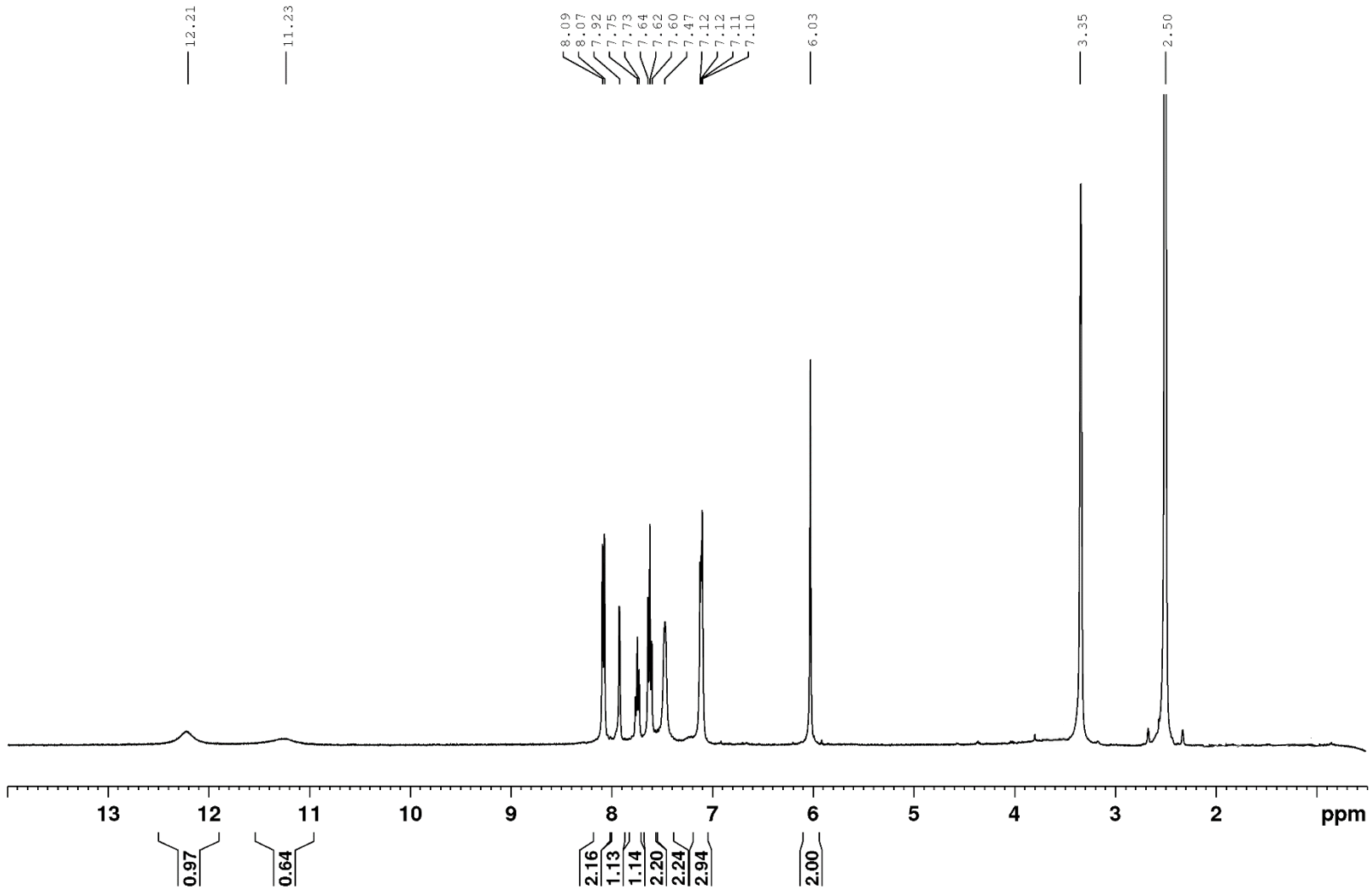
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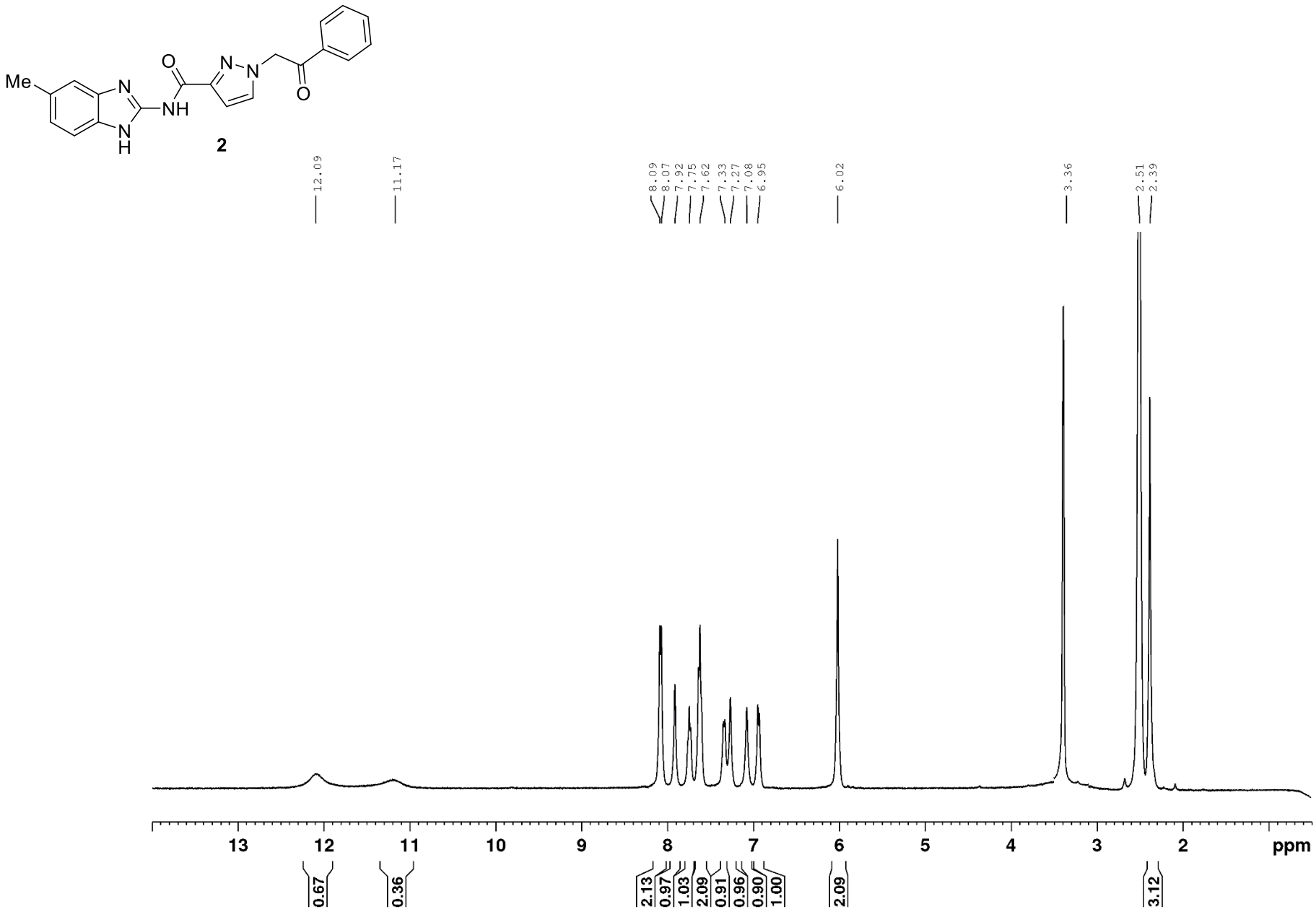
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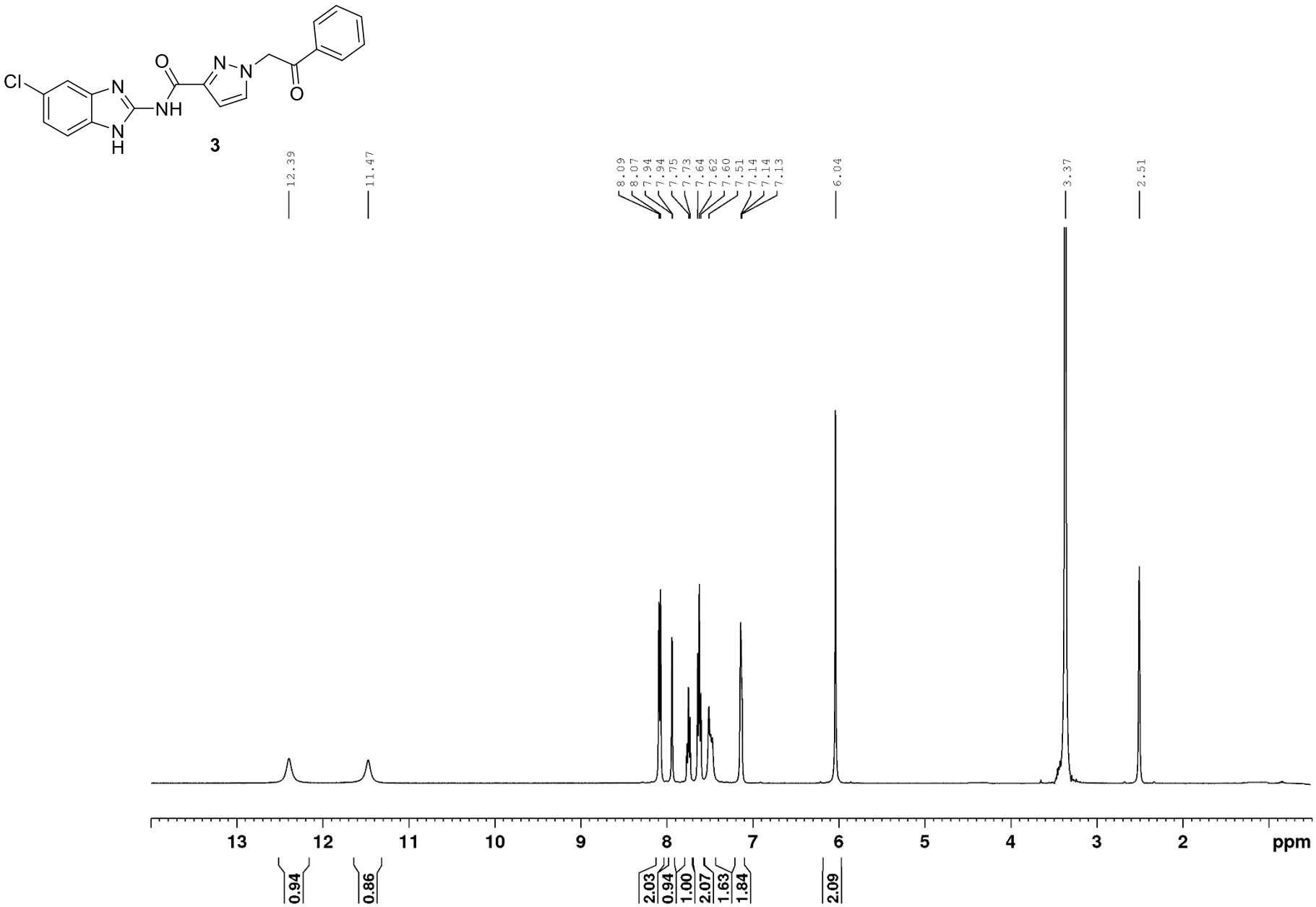
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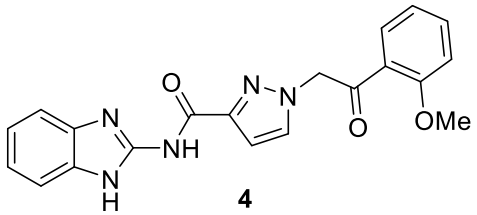
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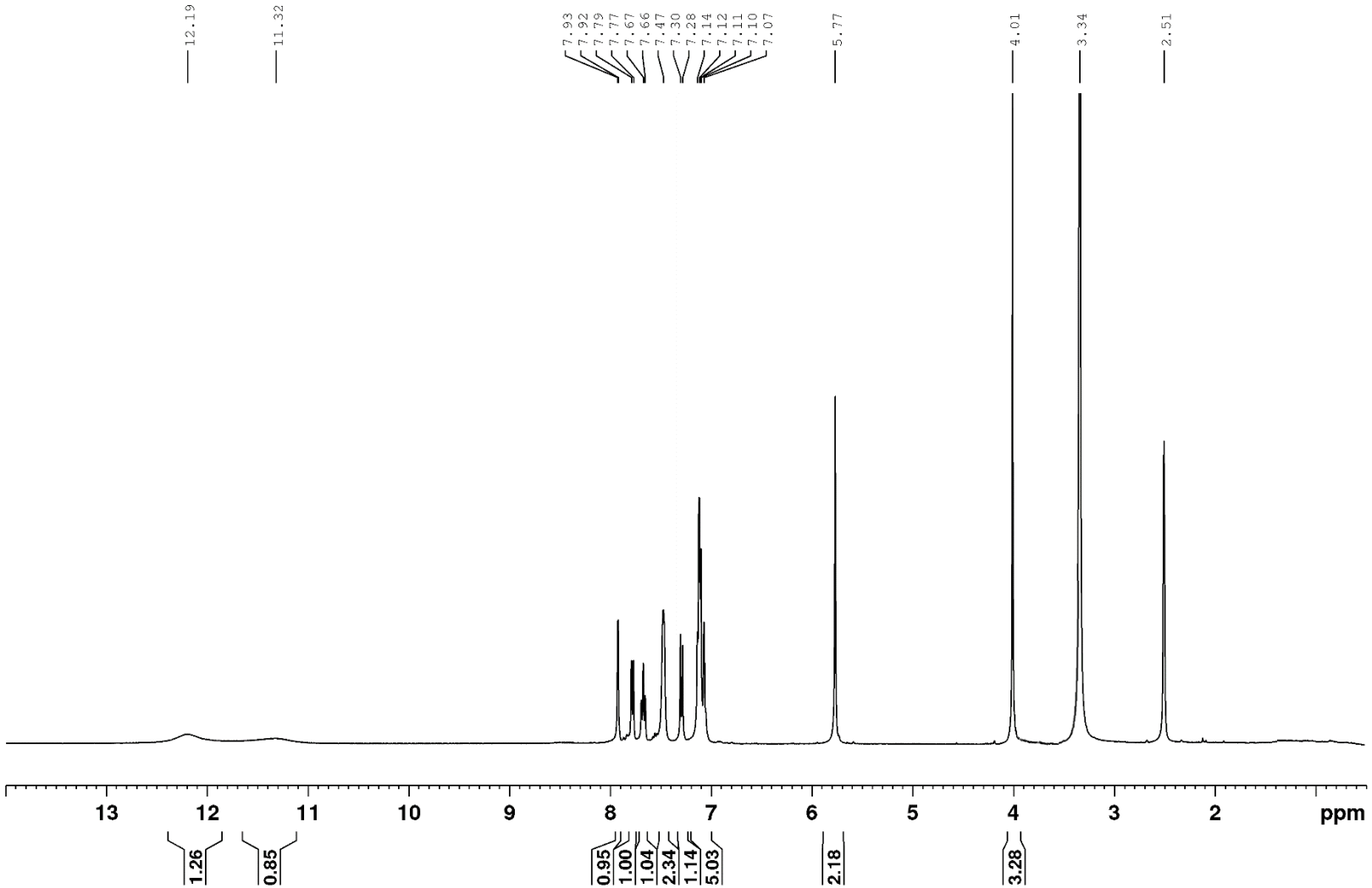
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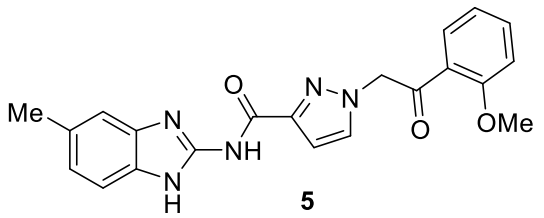
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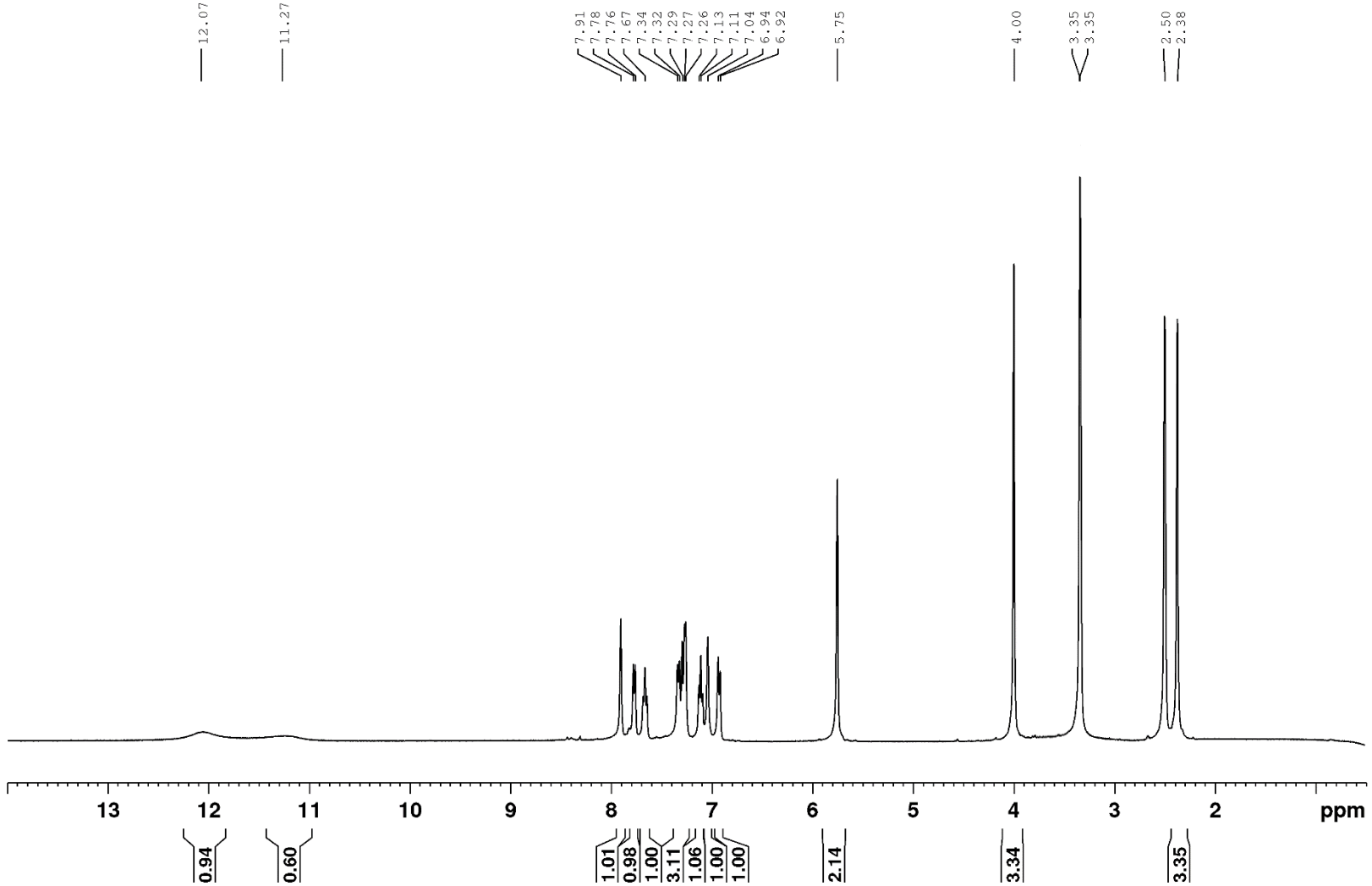
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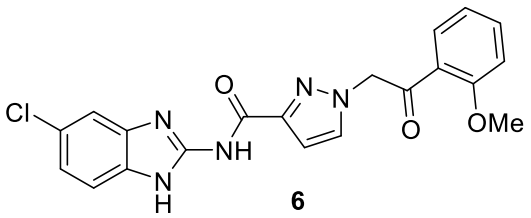
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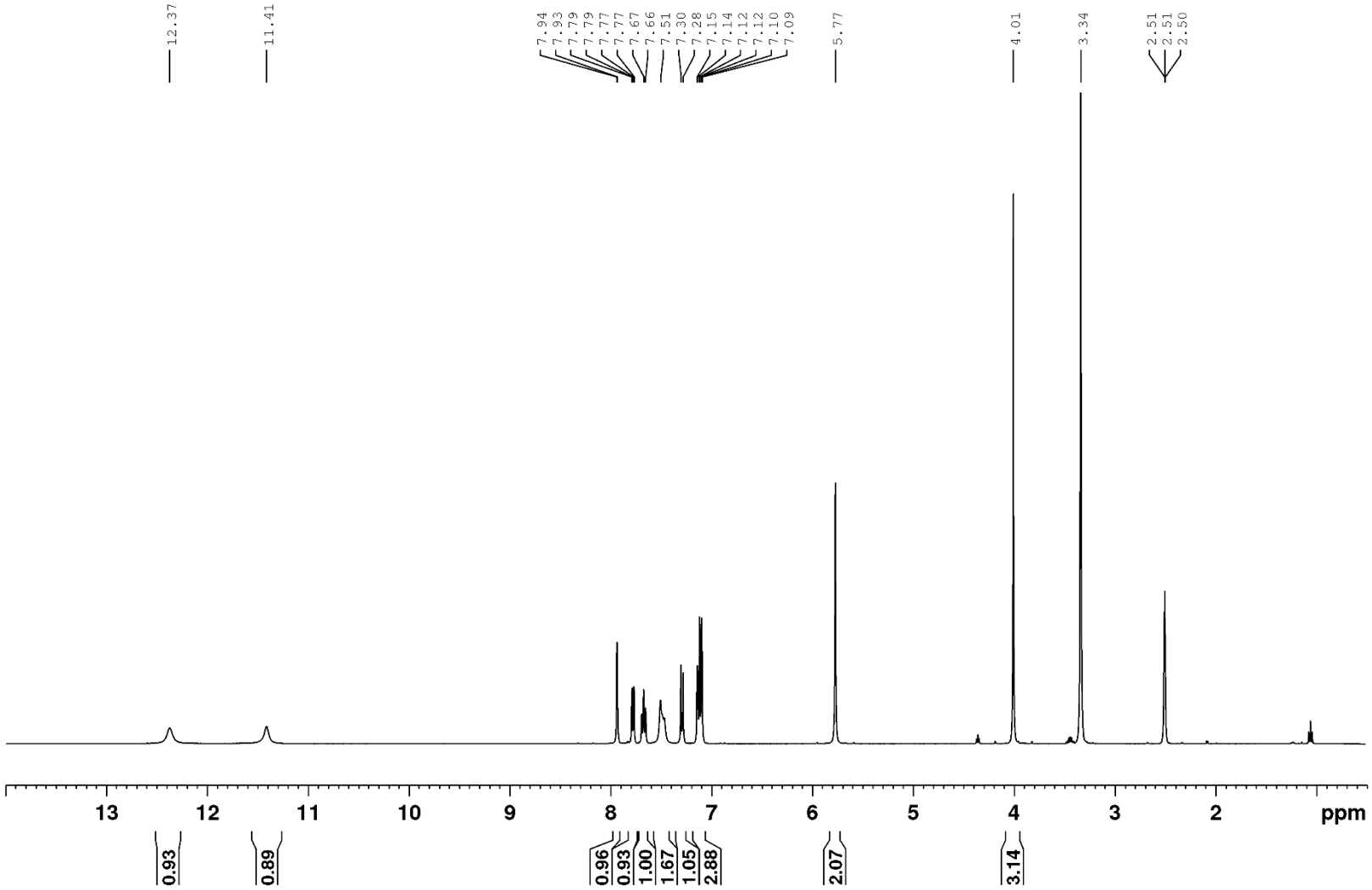
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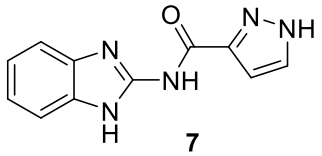
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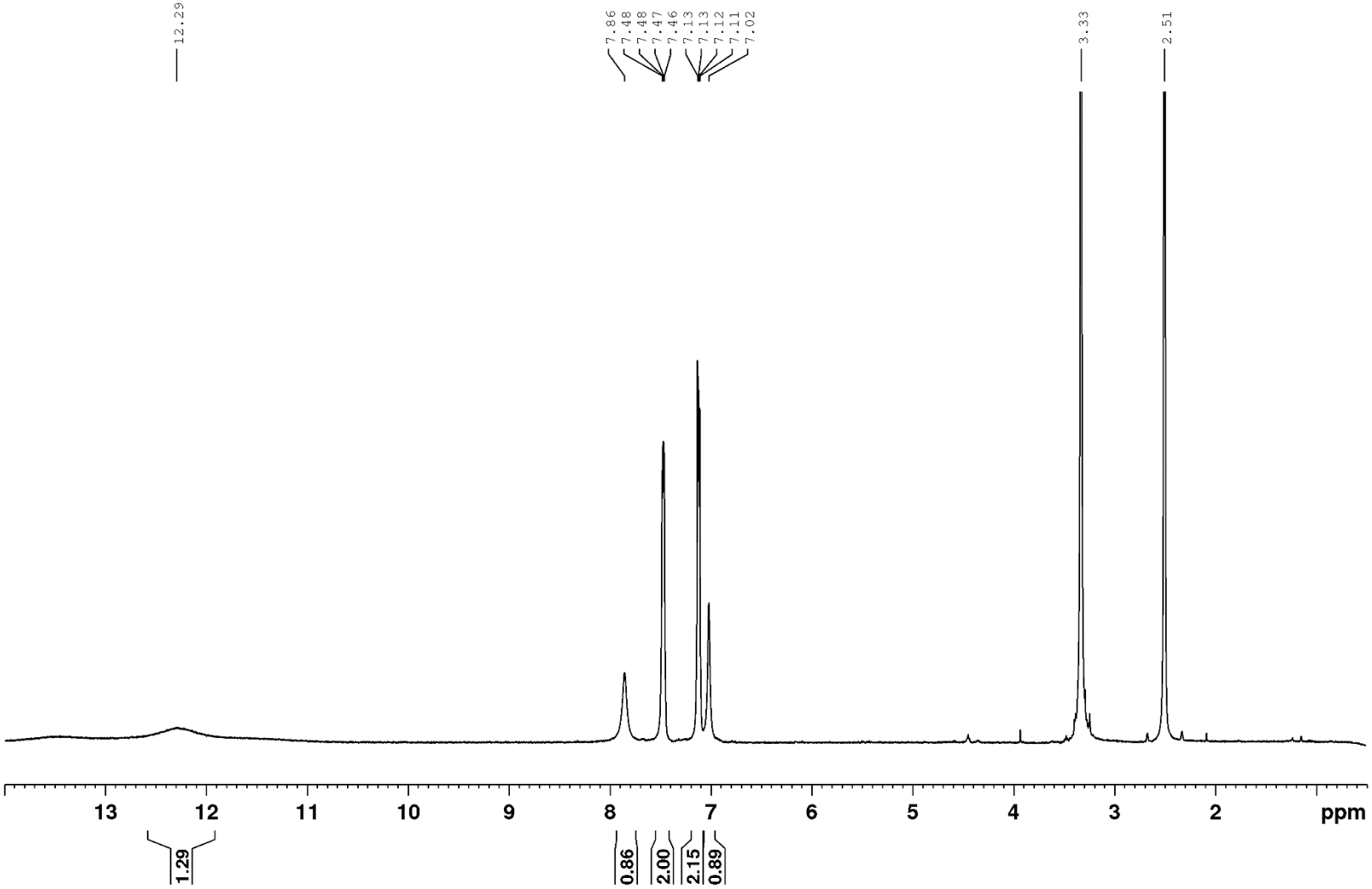
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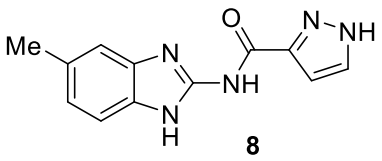
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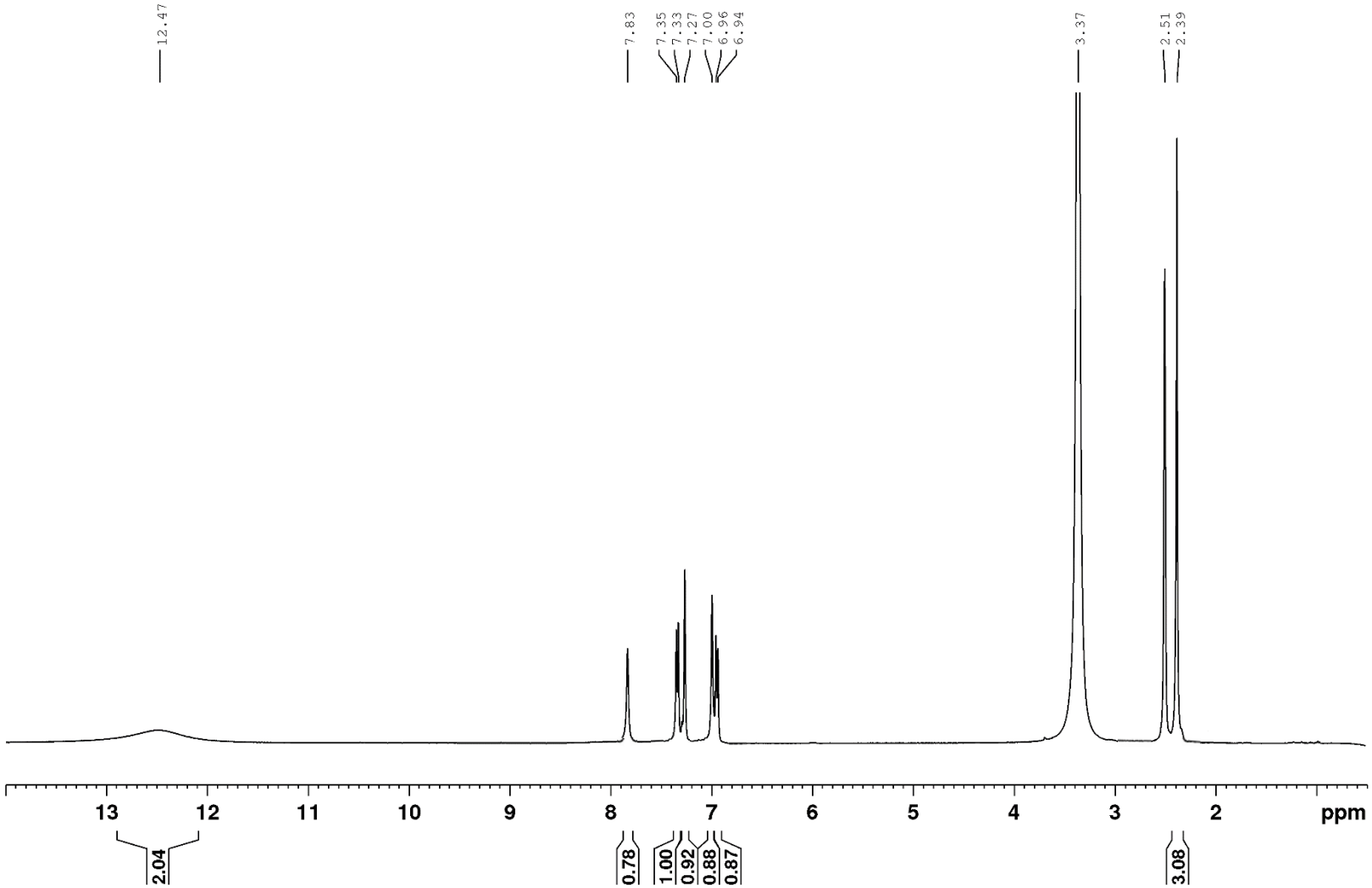
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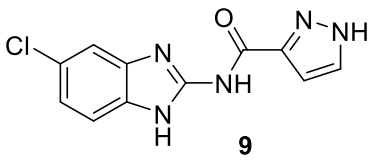
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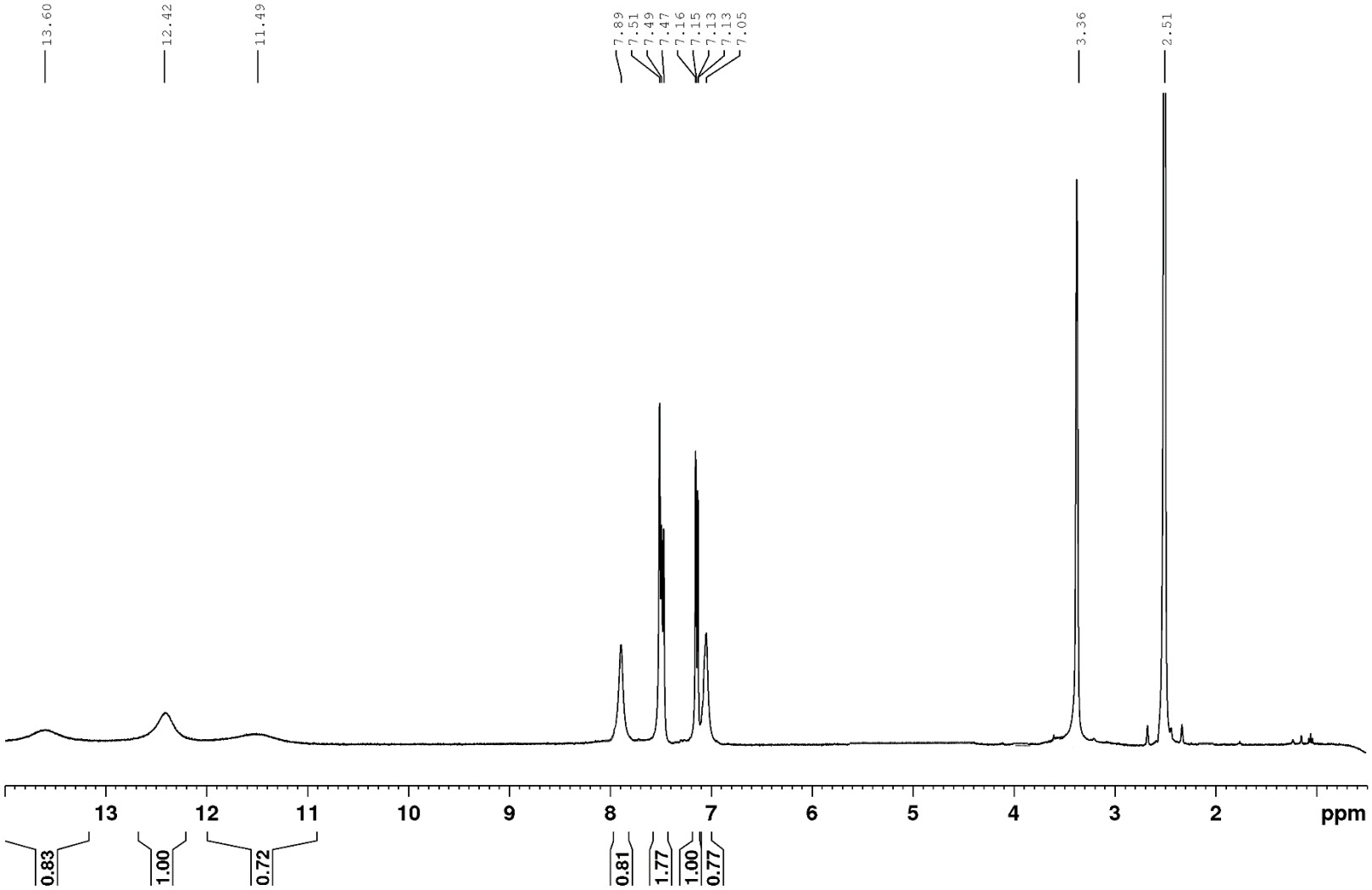
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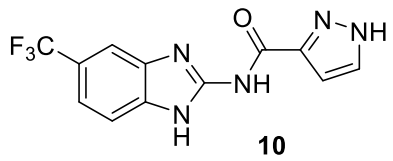
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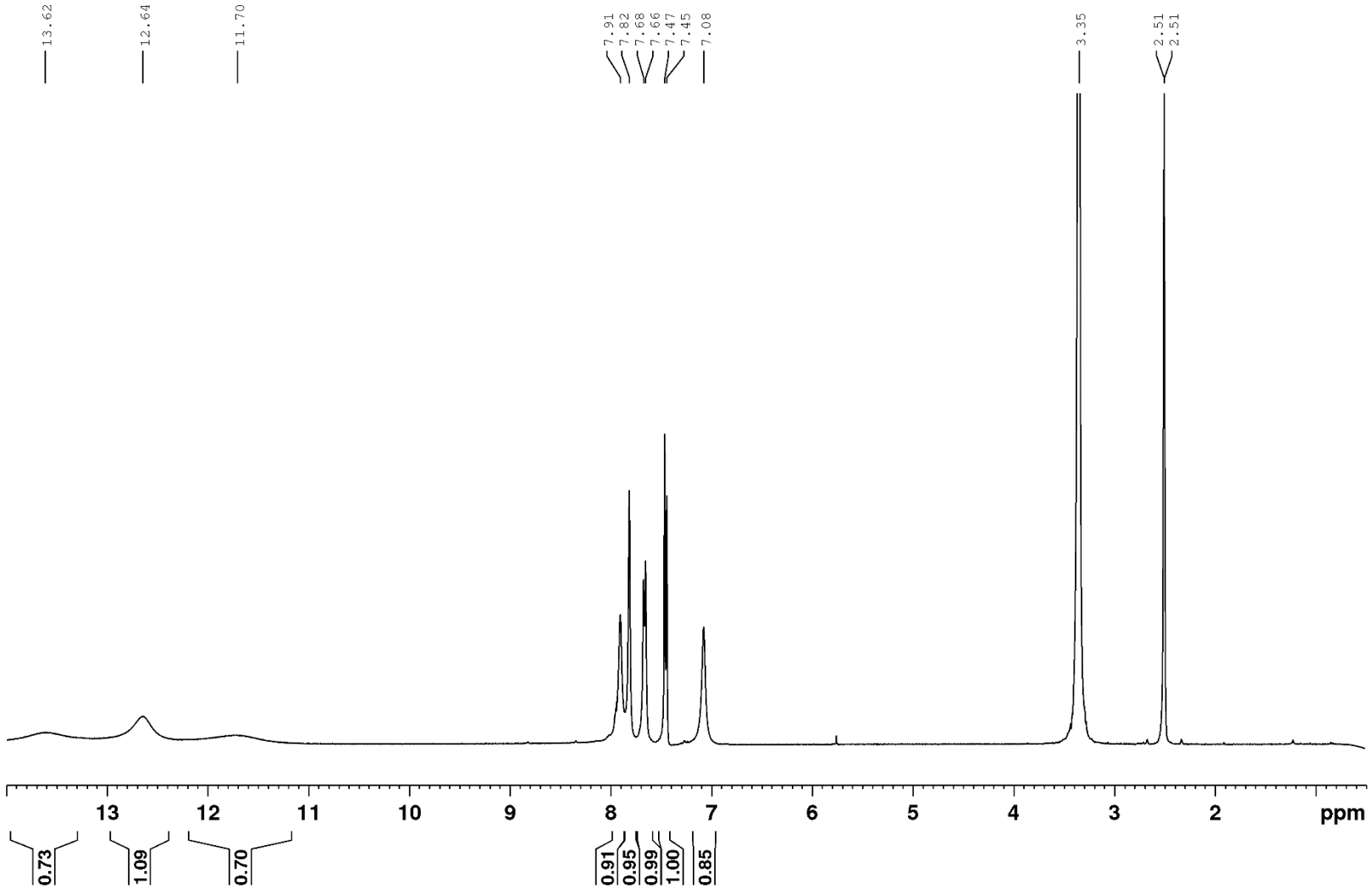
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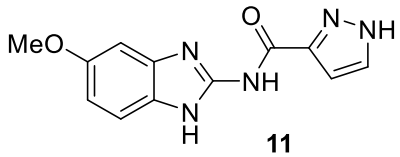
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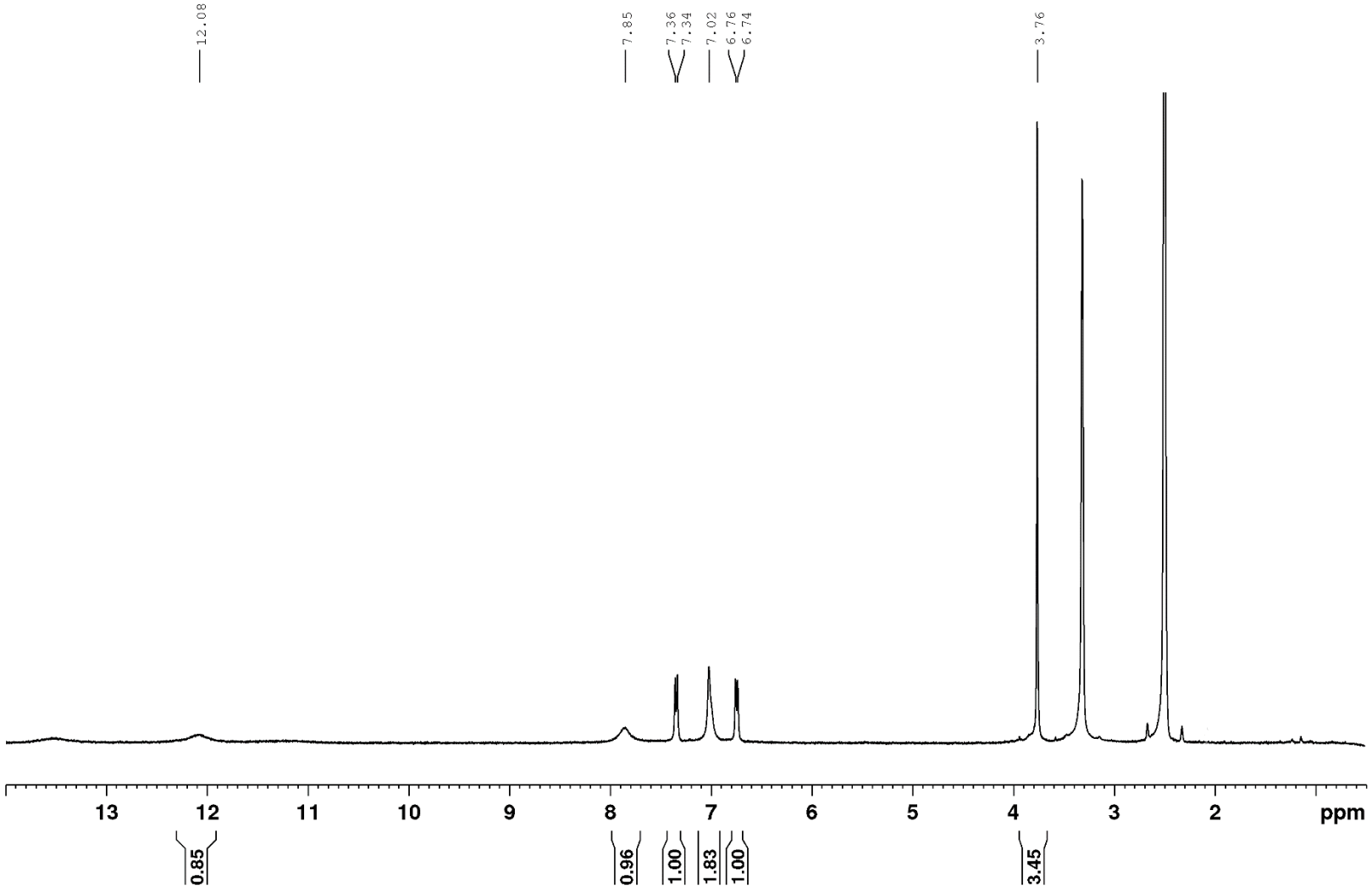
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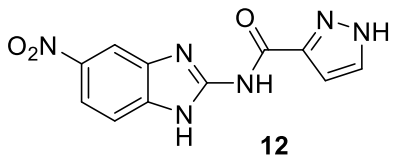
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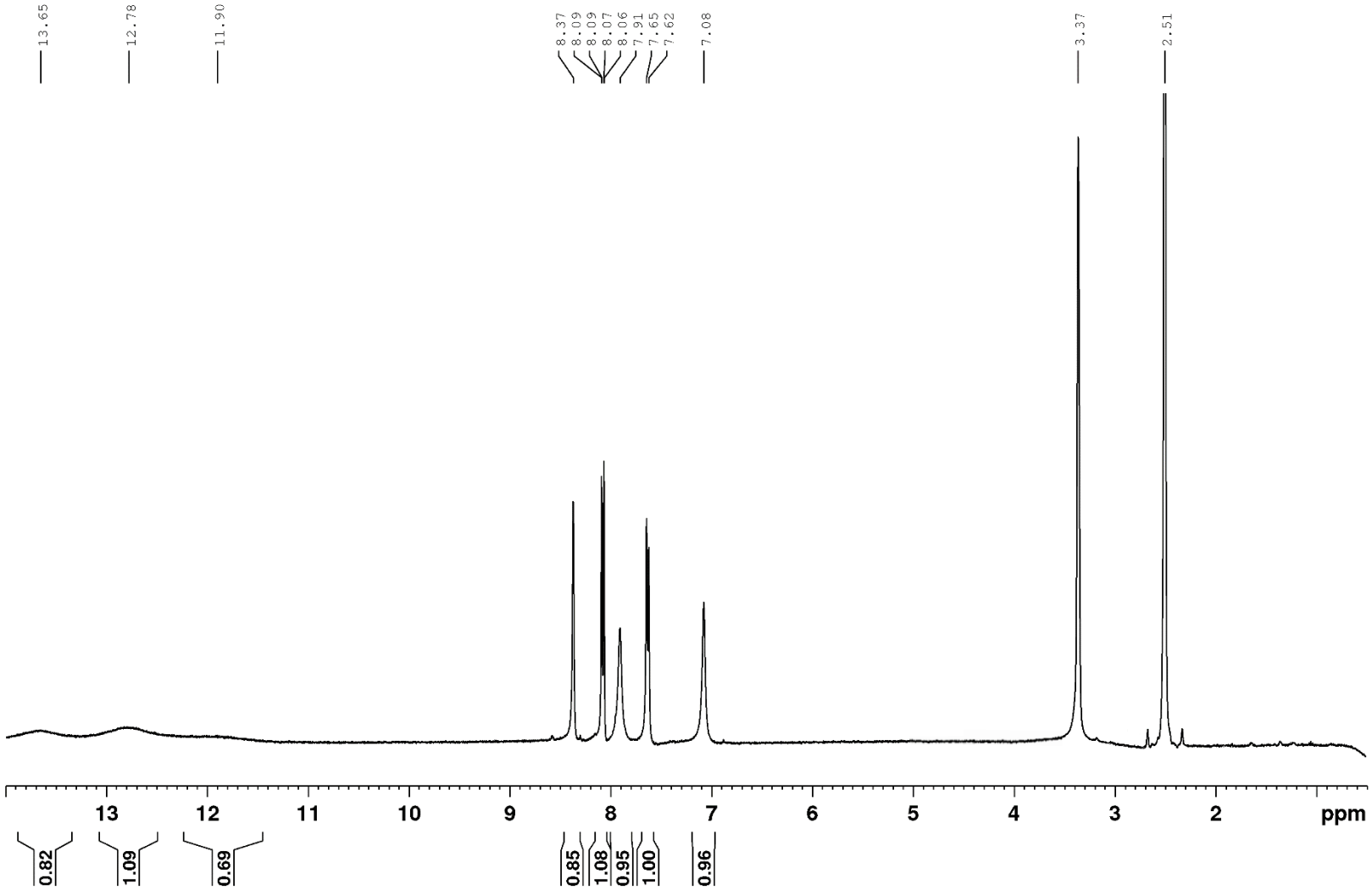
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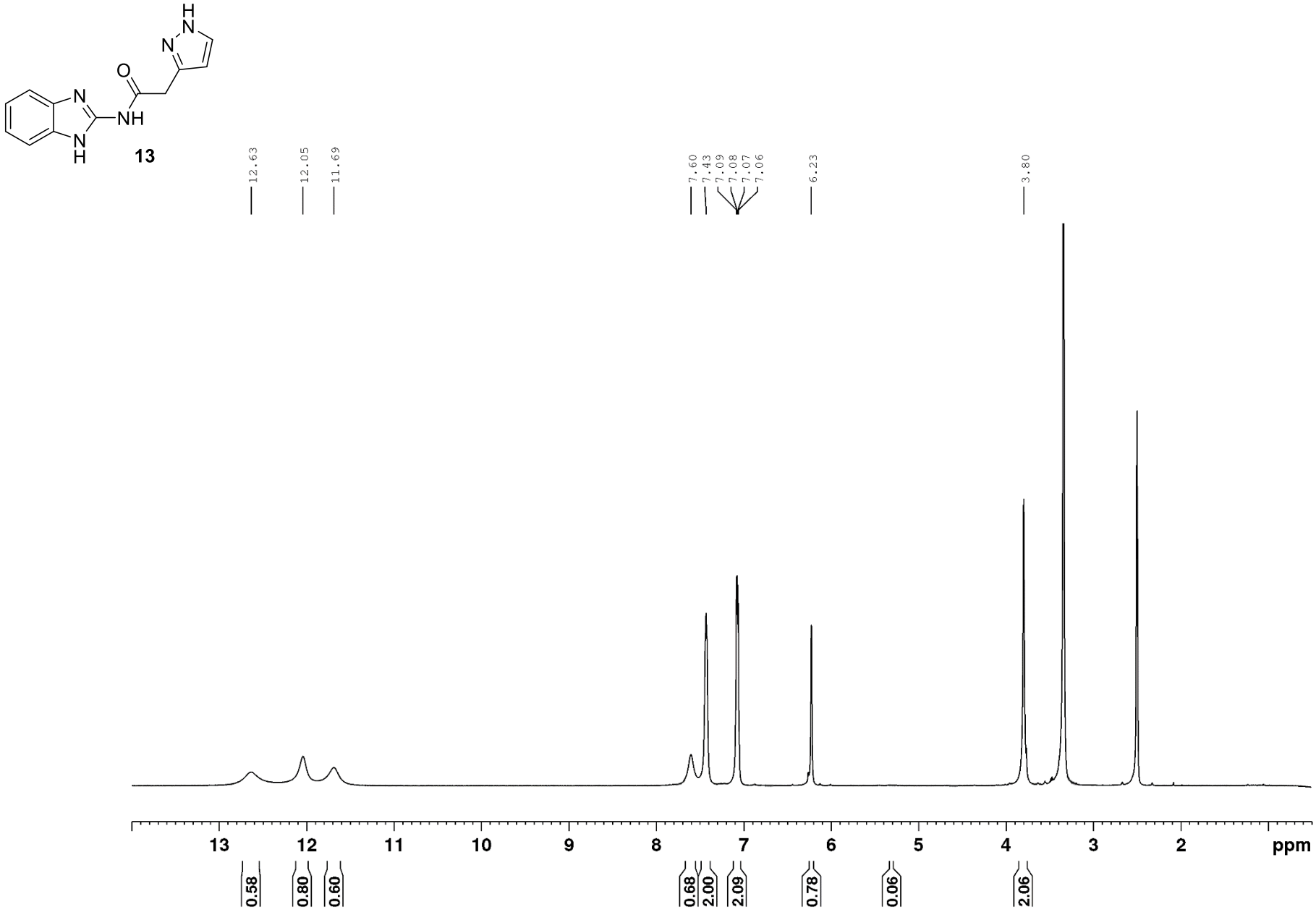
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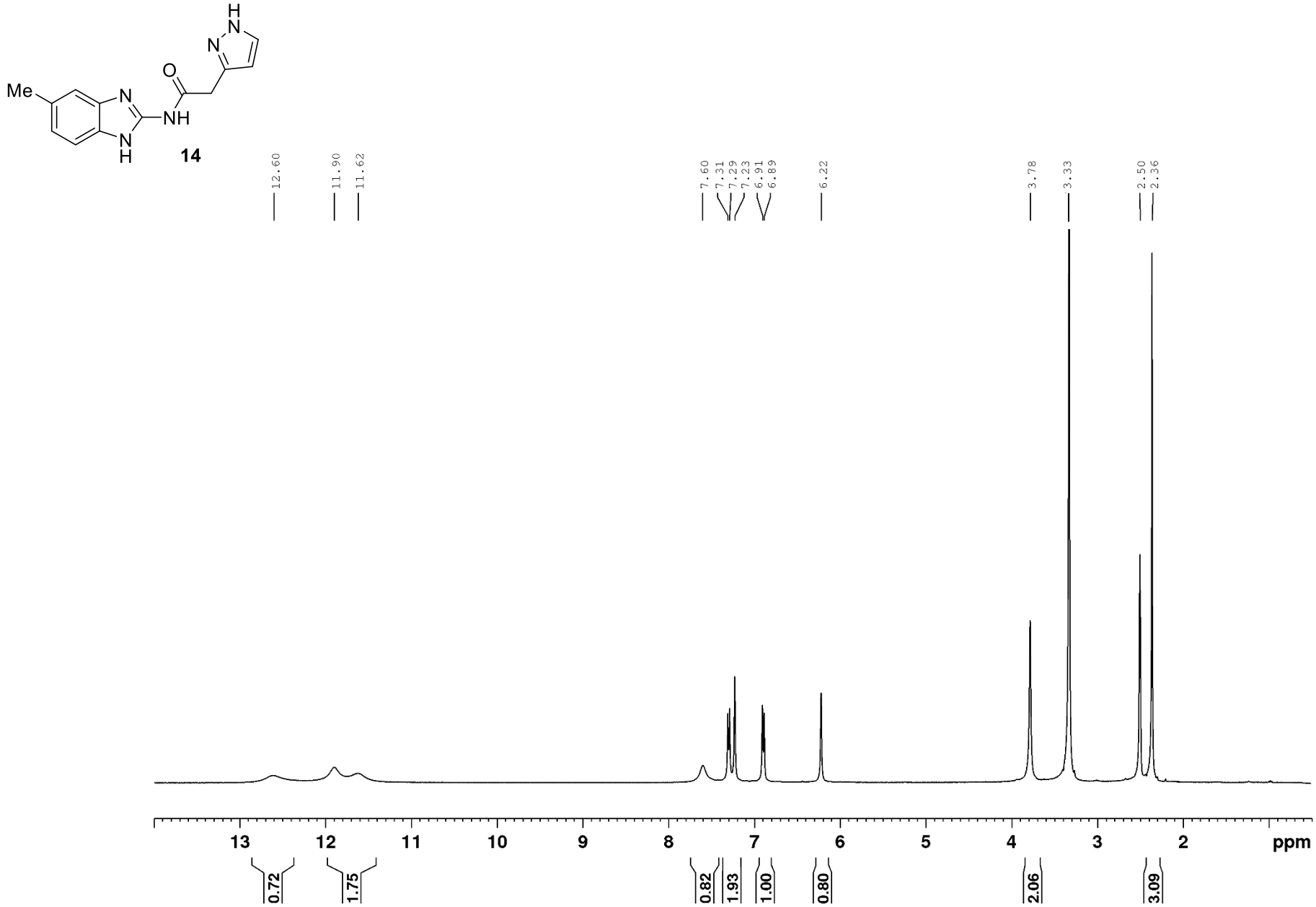
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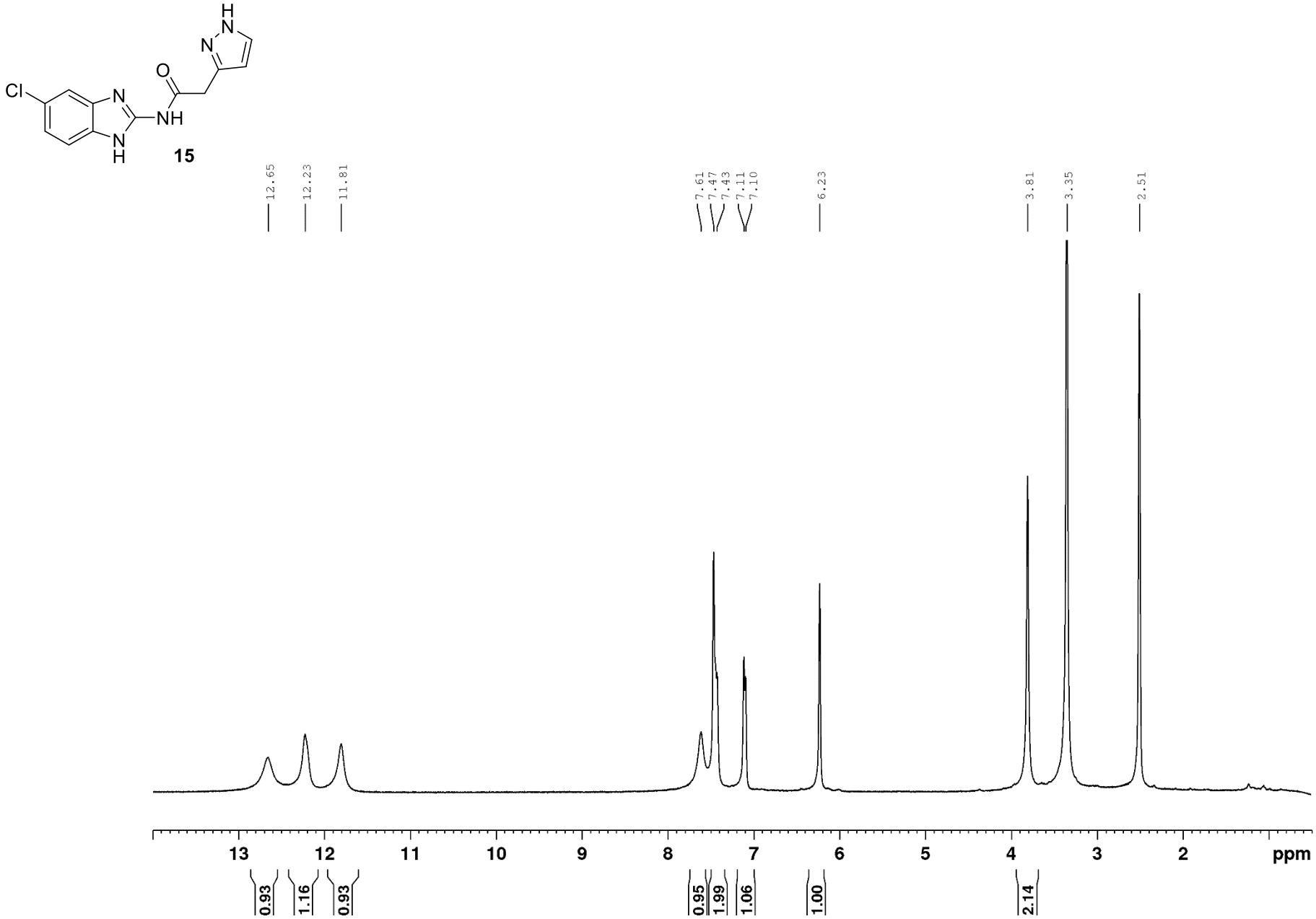
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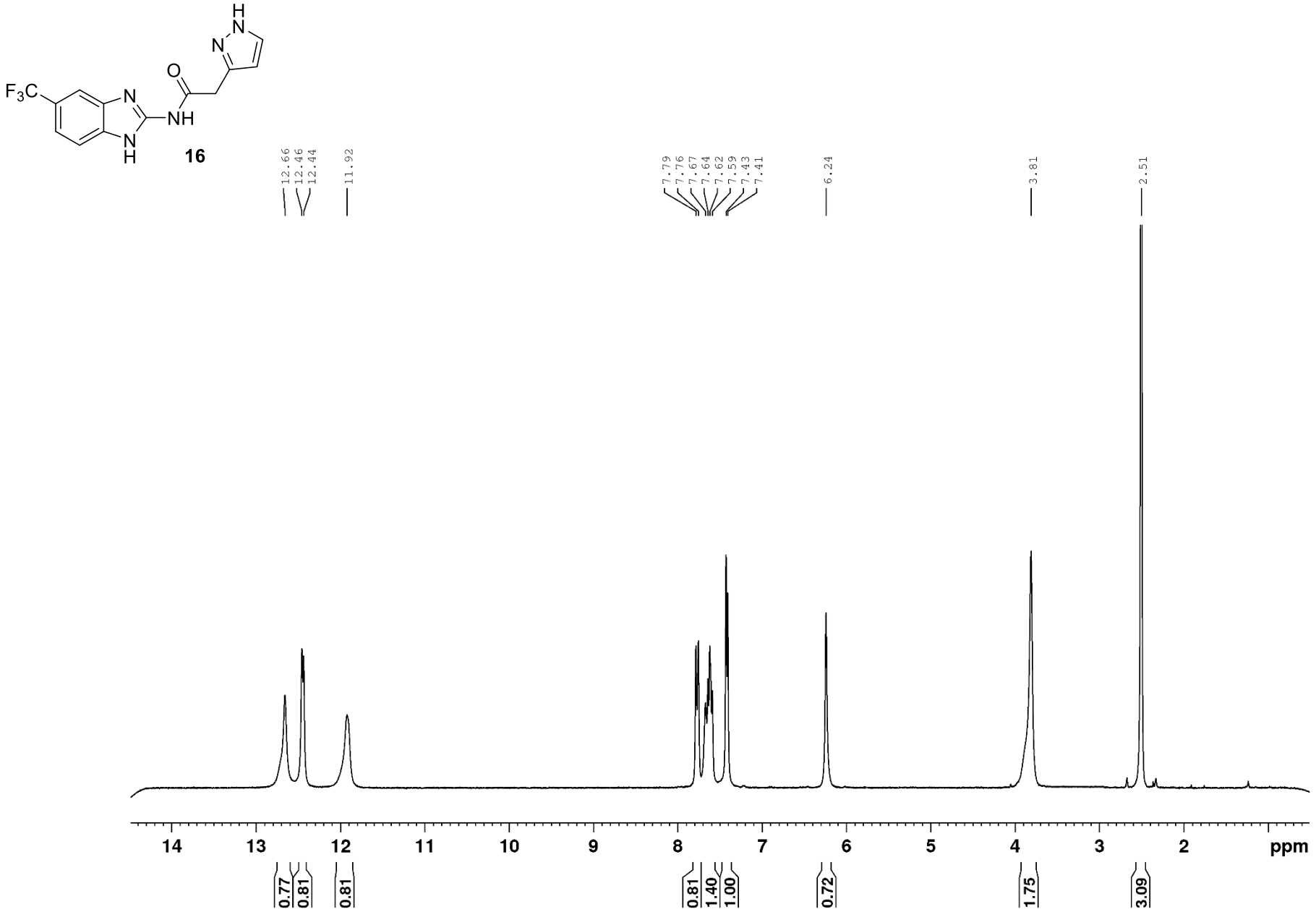
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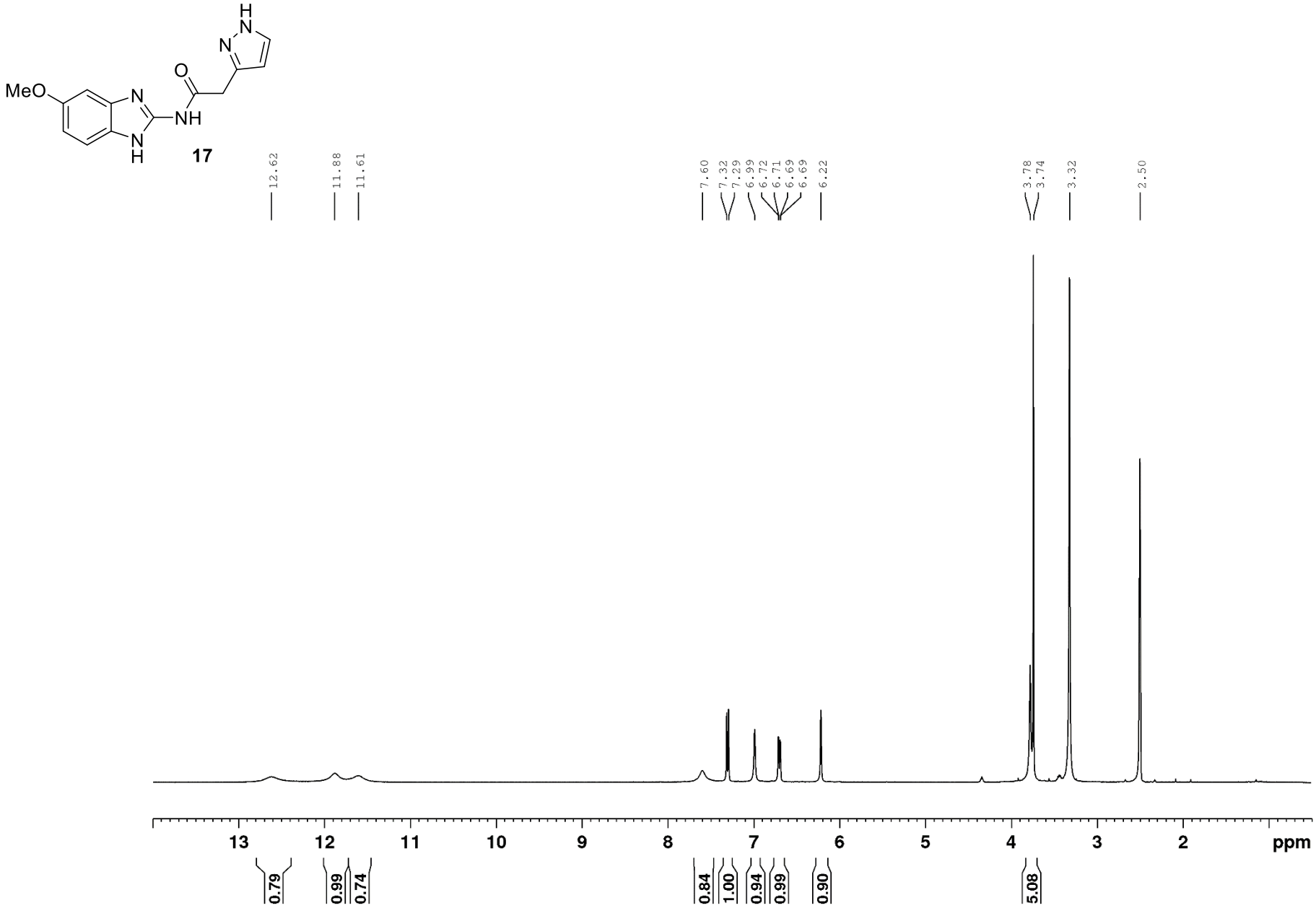
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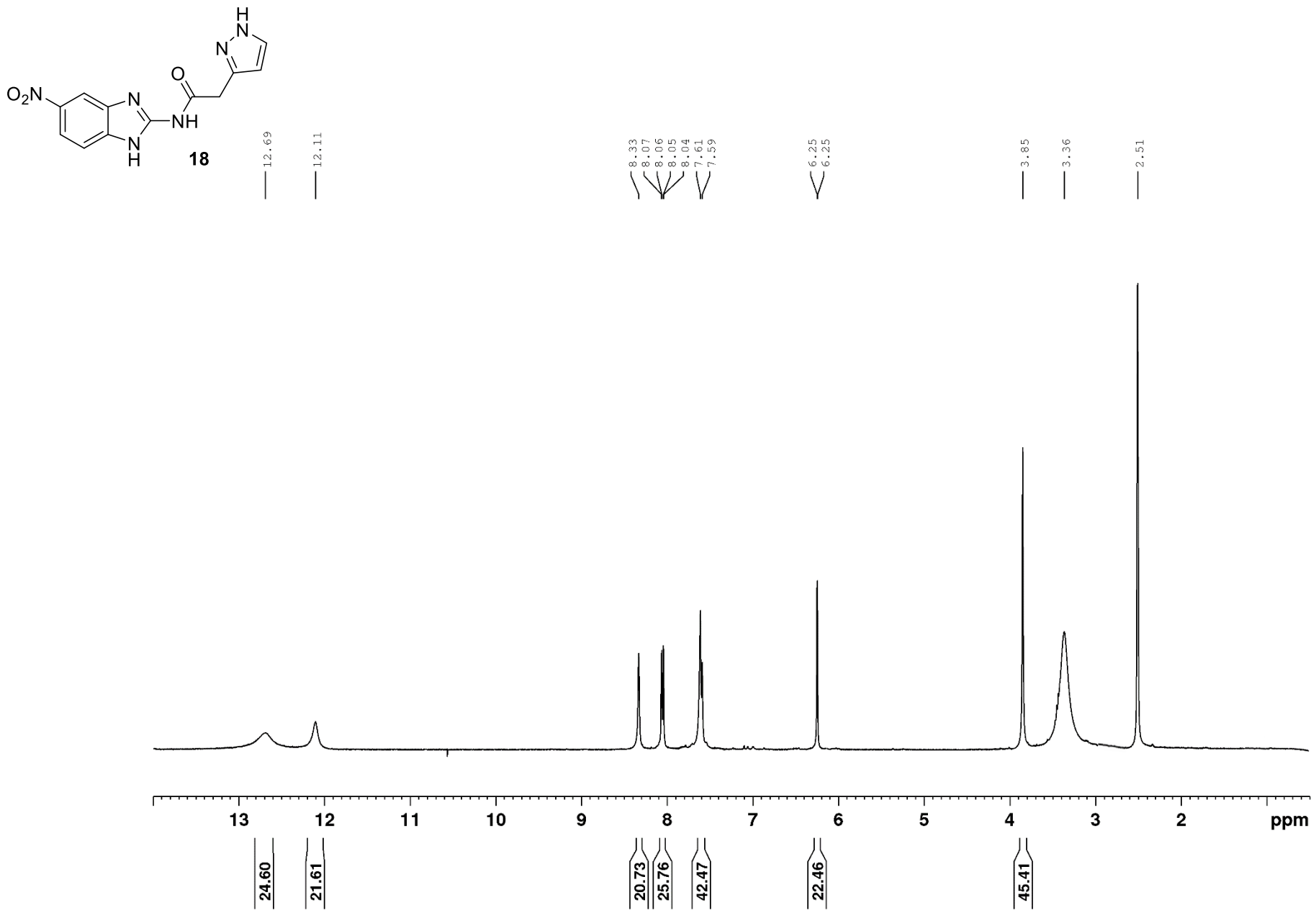
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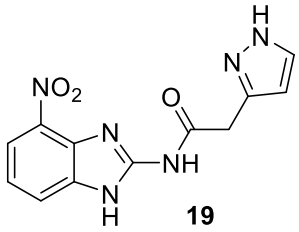
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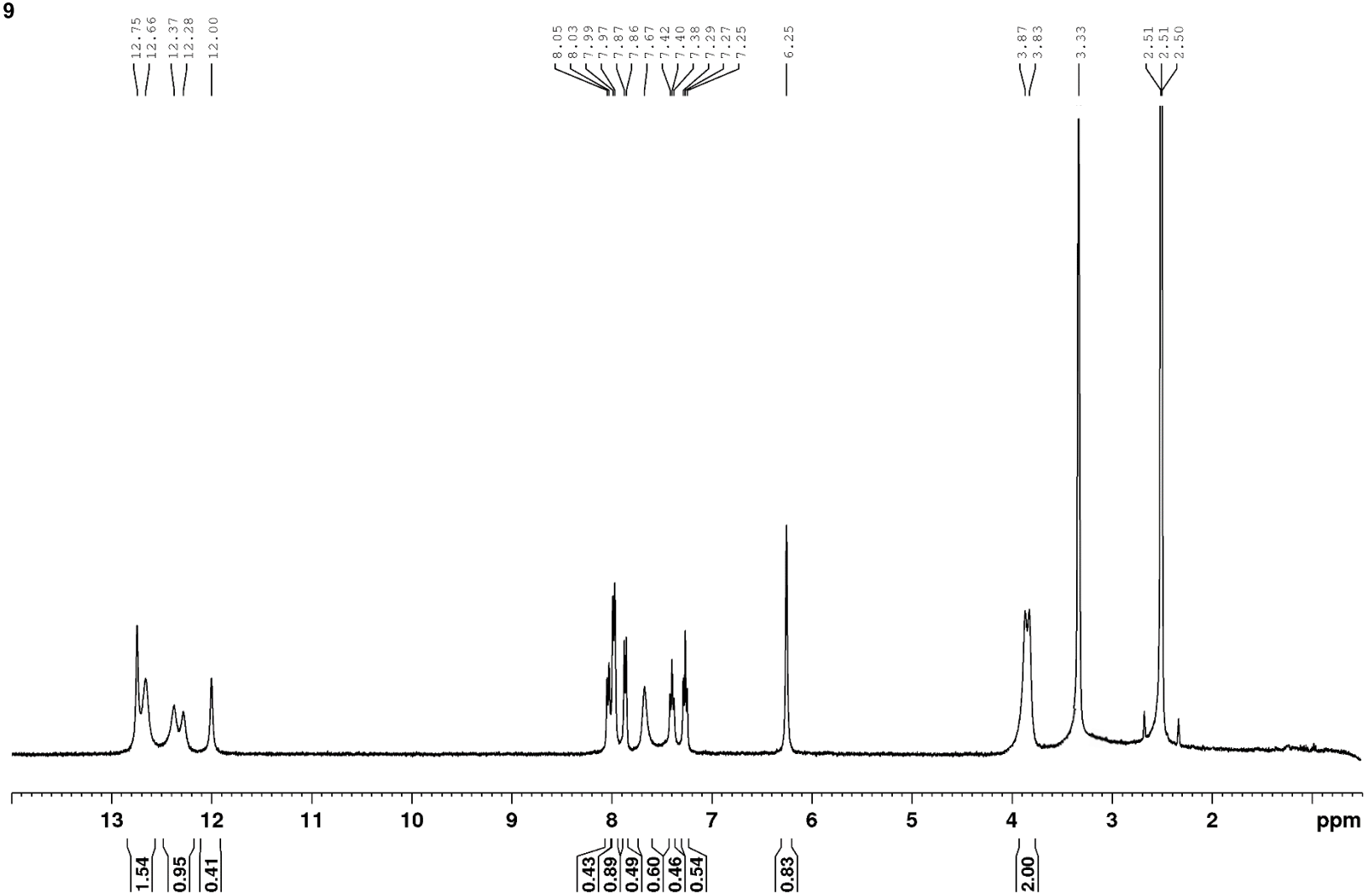
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2.51
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13
12
11
10
9
8
7
6
5
4
3
2
ppm
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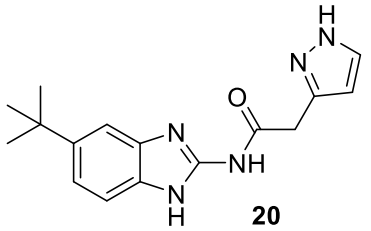
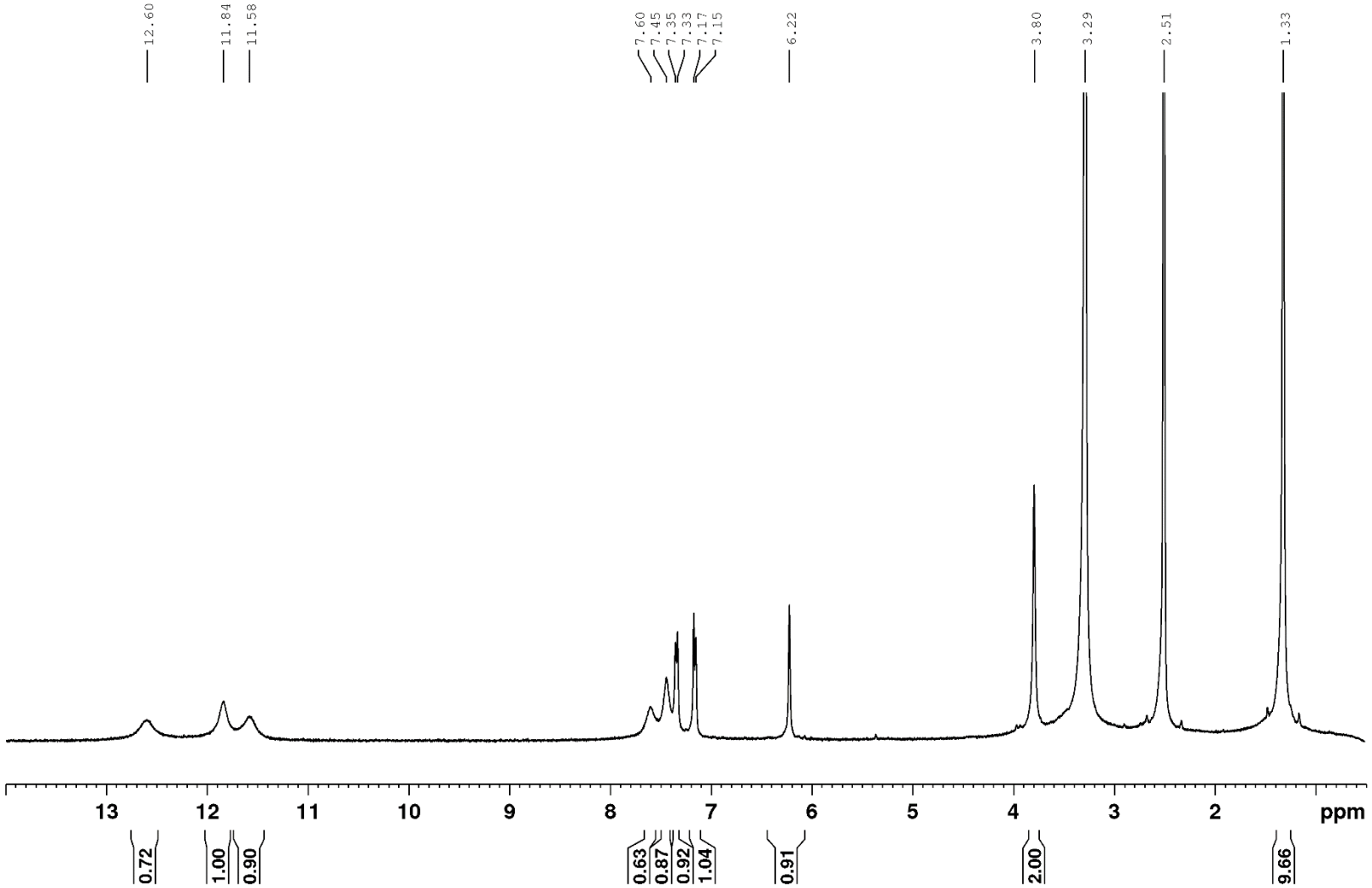
0.41
0.43
0.89
0.49
0.60
0.46
0.54
0.83
2.00


H
N
N
O
N
NH
N
H

20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11.84
11.58
7.60
7.45
7.35
7.33
7.17
7.15
6.22
3.80
3.29
2.51
1.33
13
12
11
10
9
8
7
6
5
4
3
2
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0.72
1.00
0.90
0.63
0.87
0.92
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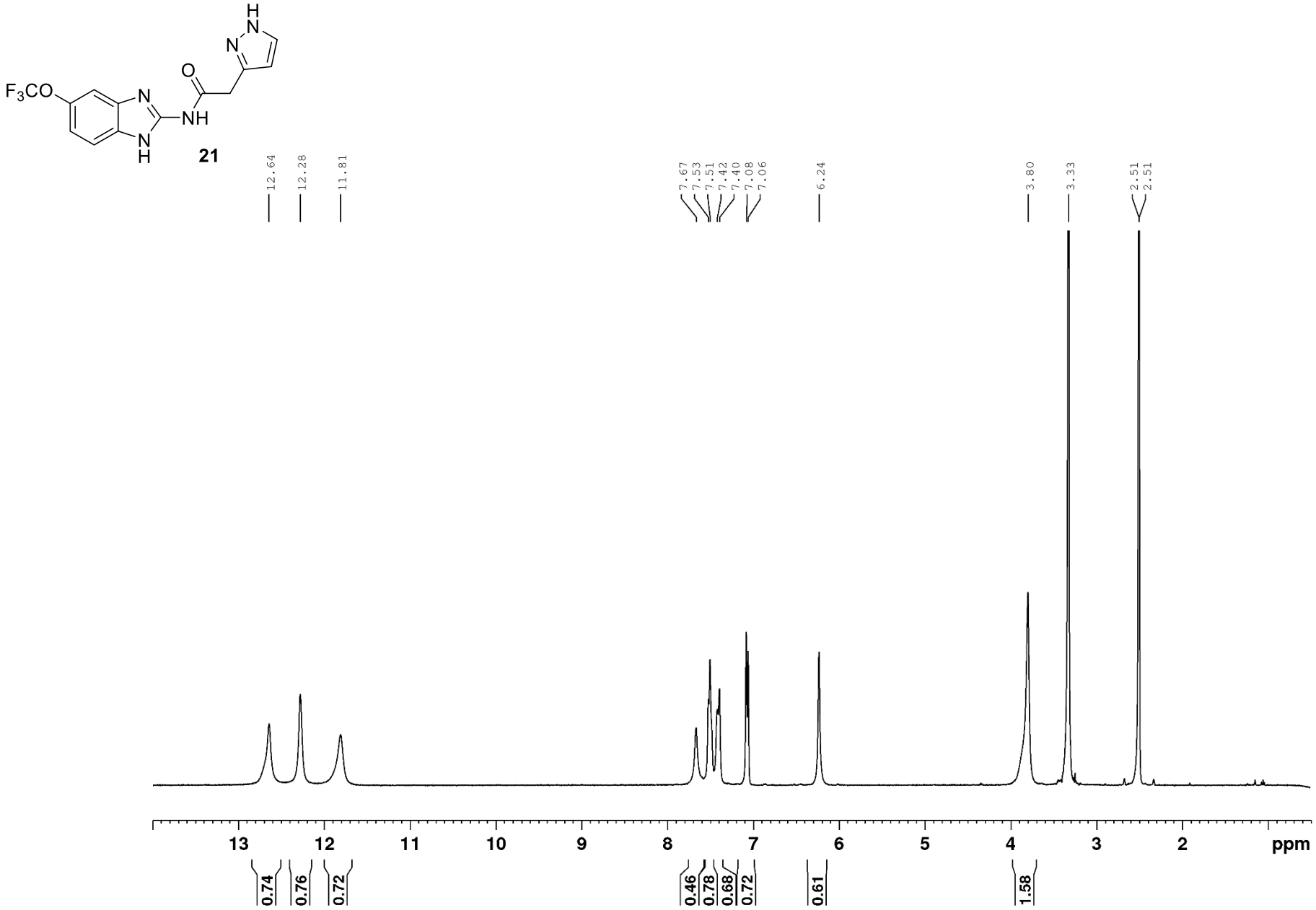
0.91
2.00
9.66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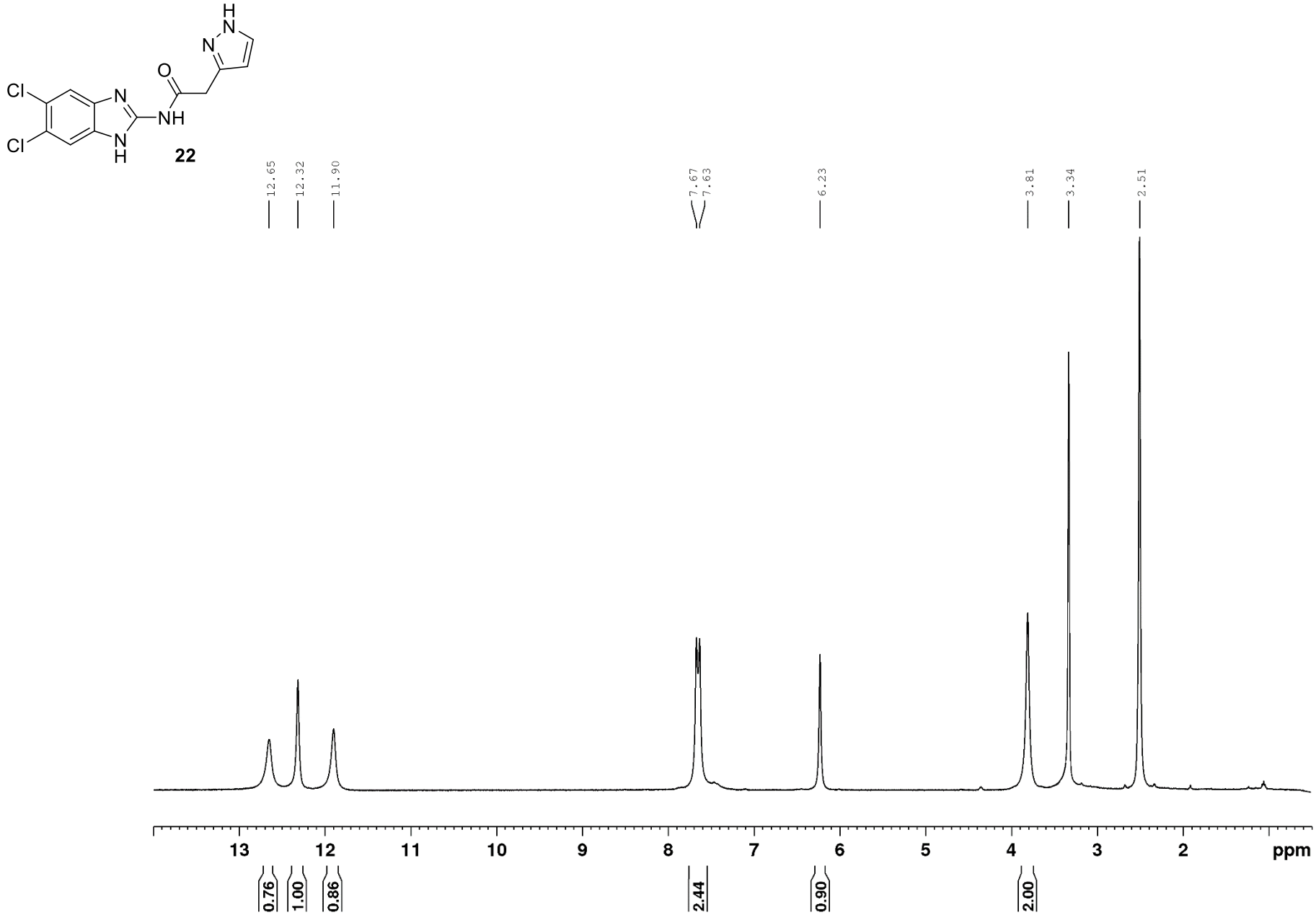
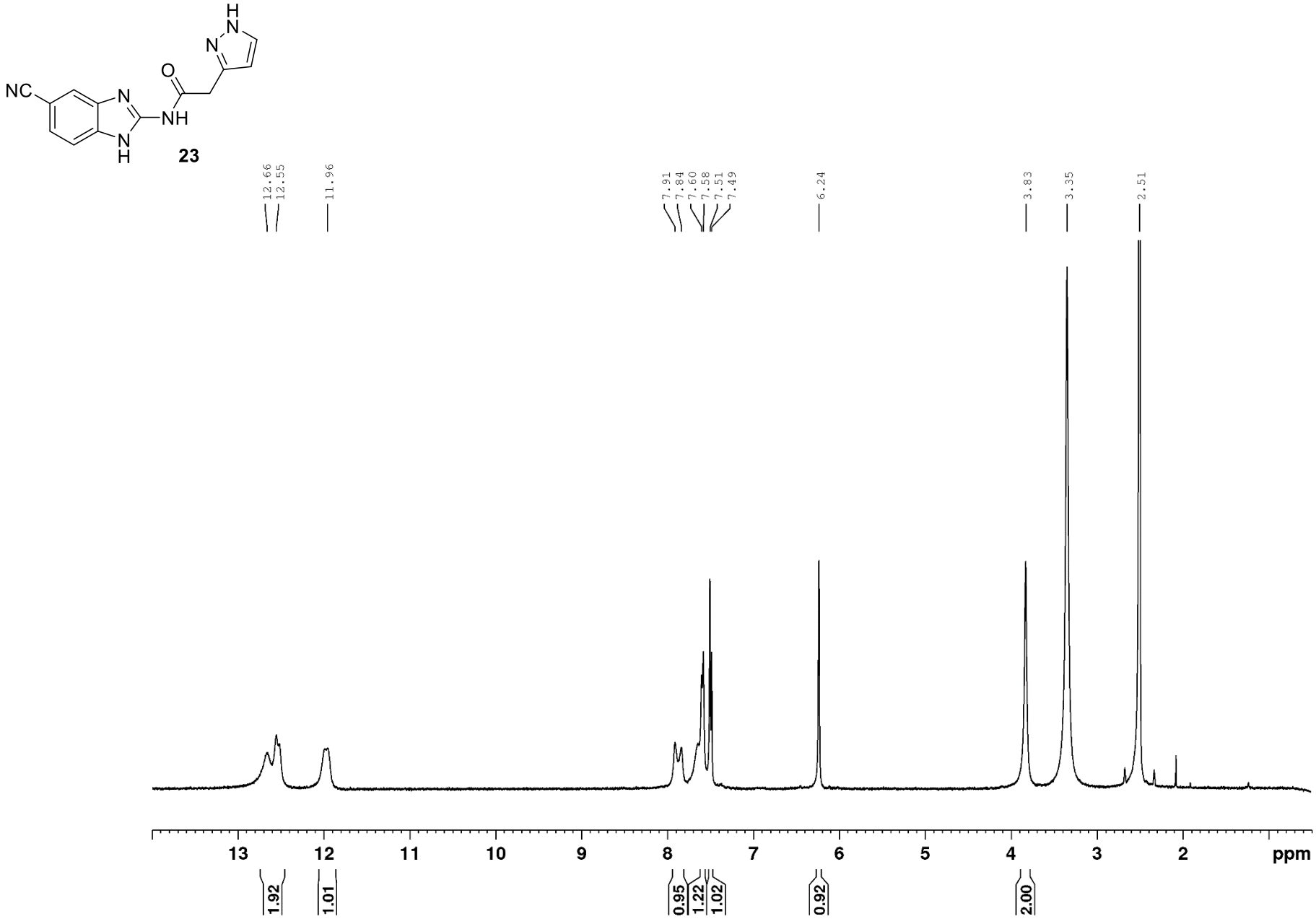
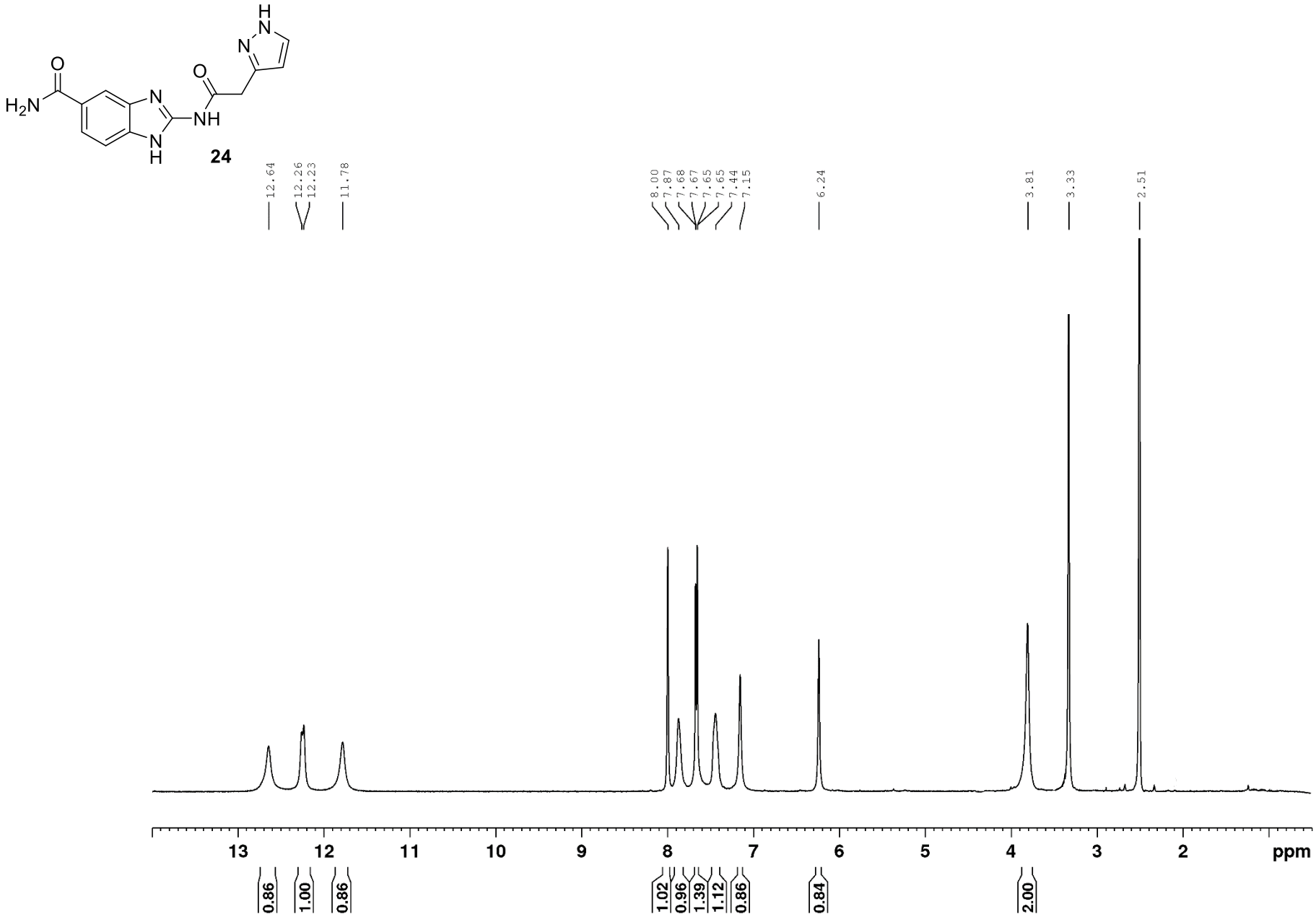
11.81
7.67
7.53
7.51
7.42
7.40
7.08
7.06
6.24
3.80
3.33
2.51
2.51
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.74
0.76
0.72
0.46
0.78
0.68
0.72
0.61
1.58


Cl
Cl
N
NH
N
H
O
N
H
22
12.65
12.32
11.90
7.67
7.63
6.23
3.81
3.34
2.51
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.76
1.00
0.86
2.44
0.90
2.00


NC
N
NH
N
H
O
H
N
N
23
12.66
12.55
11.96
7.91
7.84
7.60
7.58
7.51
7.49
6.24
3.83
3.35
2.51
13
12
11
10
9
8
7
6
5
4
3
2
ppm
1.92
1.01
0.95
1.22
1.02
0.92
2.00


24
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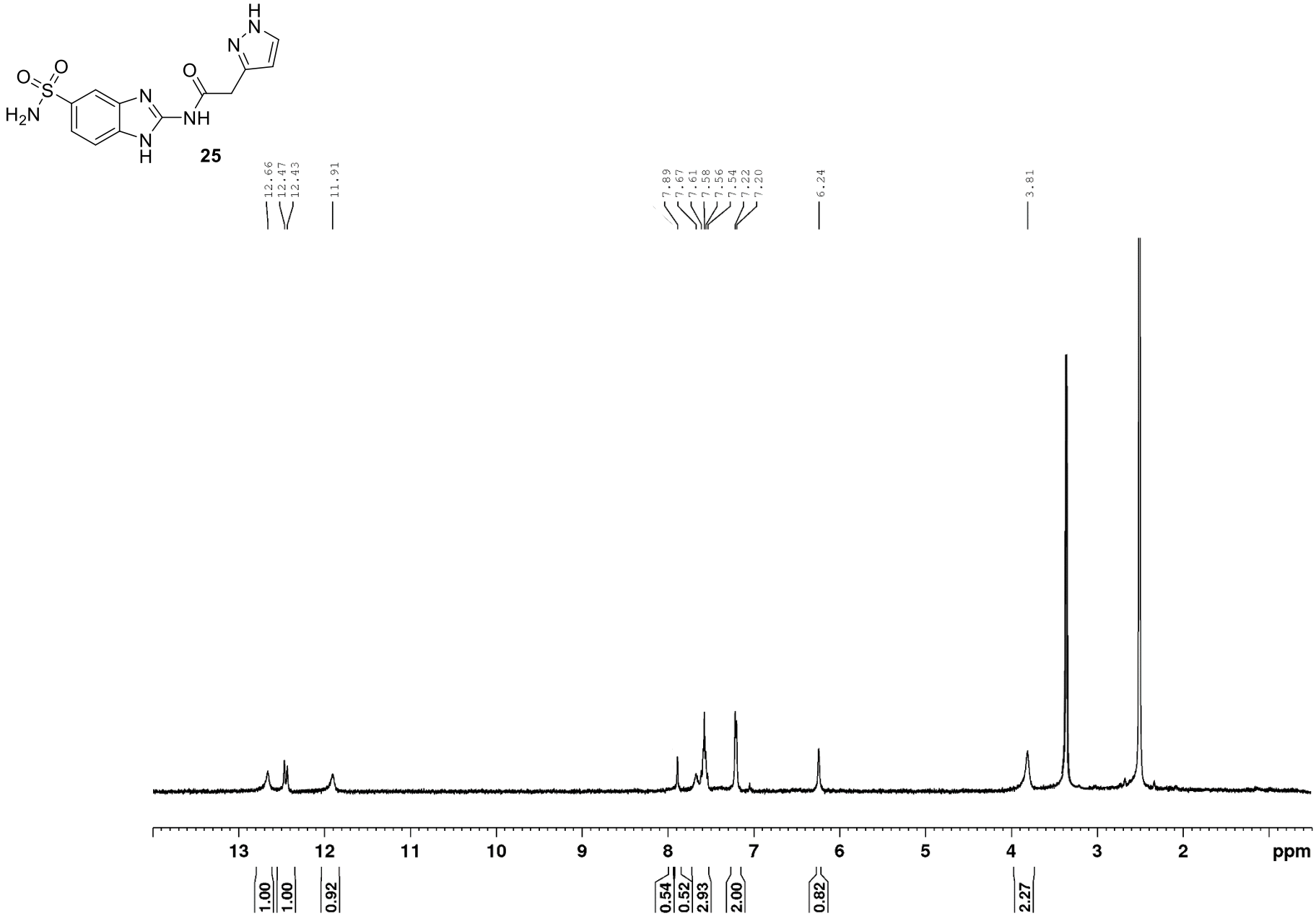
12.26
12.23
11.78
8.00
7.87
7.68
7.67
7.65
7.65
7.44
7.15
6.24
3.81
3.33
2.51
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.86
1.00
0.86
1.02
0.96
1.39
1.12
0.86
0.84
2.00


25
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12.47
12.43
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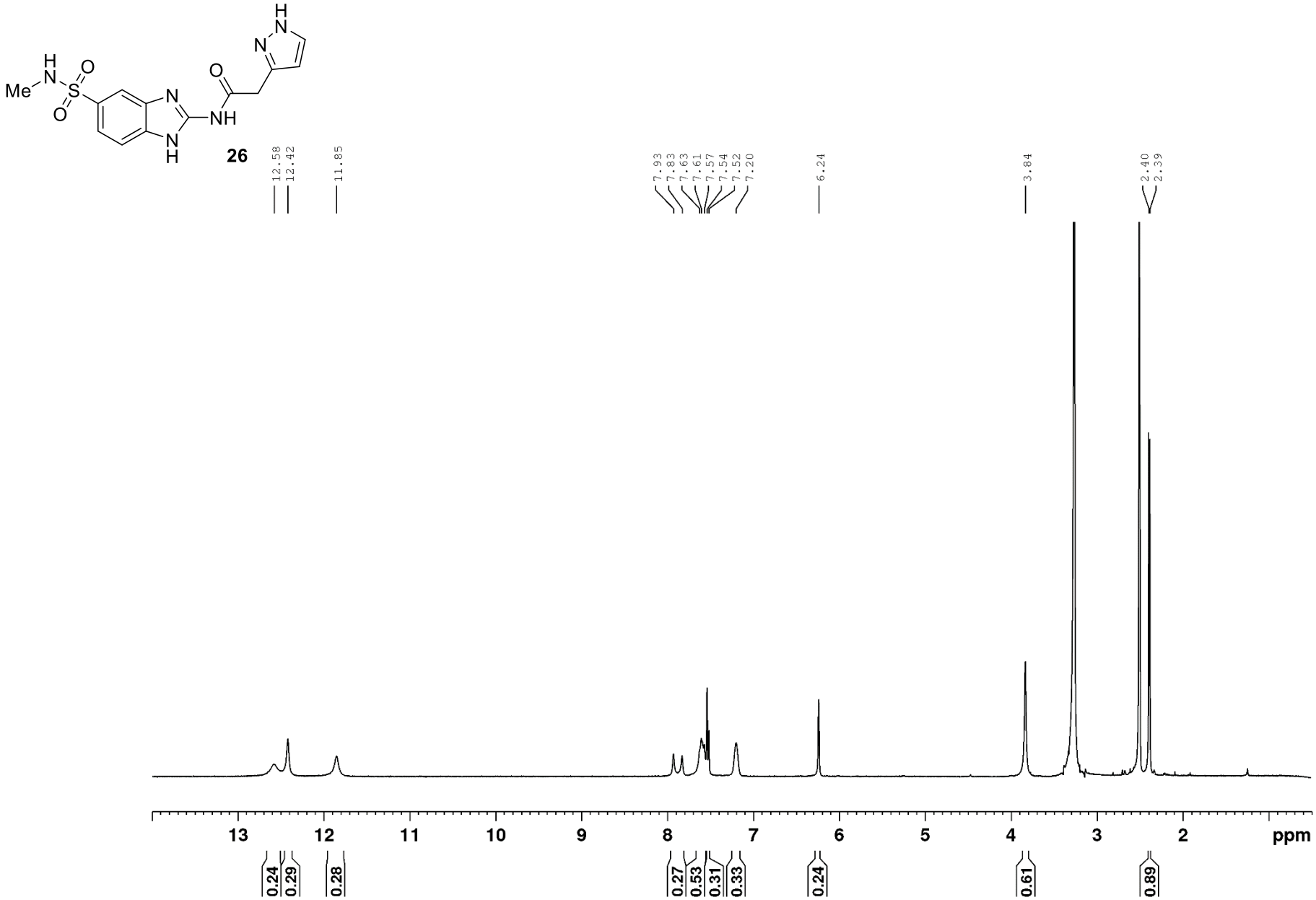
7.89
7.67
7.61
7.58
7.56
7.54
7.22
7.20
6.24
3.81
13
12
11
10
9
8
7
6
5
4
3
2
ppm
1.00
1.00
0.92
0.54
0.52
2.93
2.00
0.82
2.27


26
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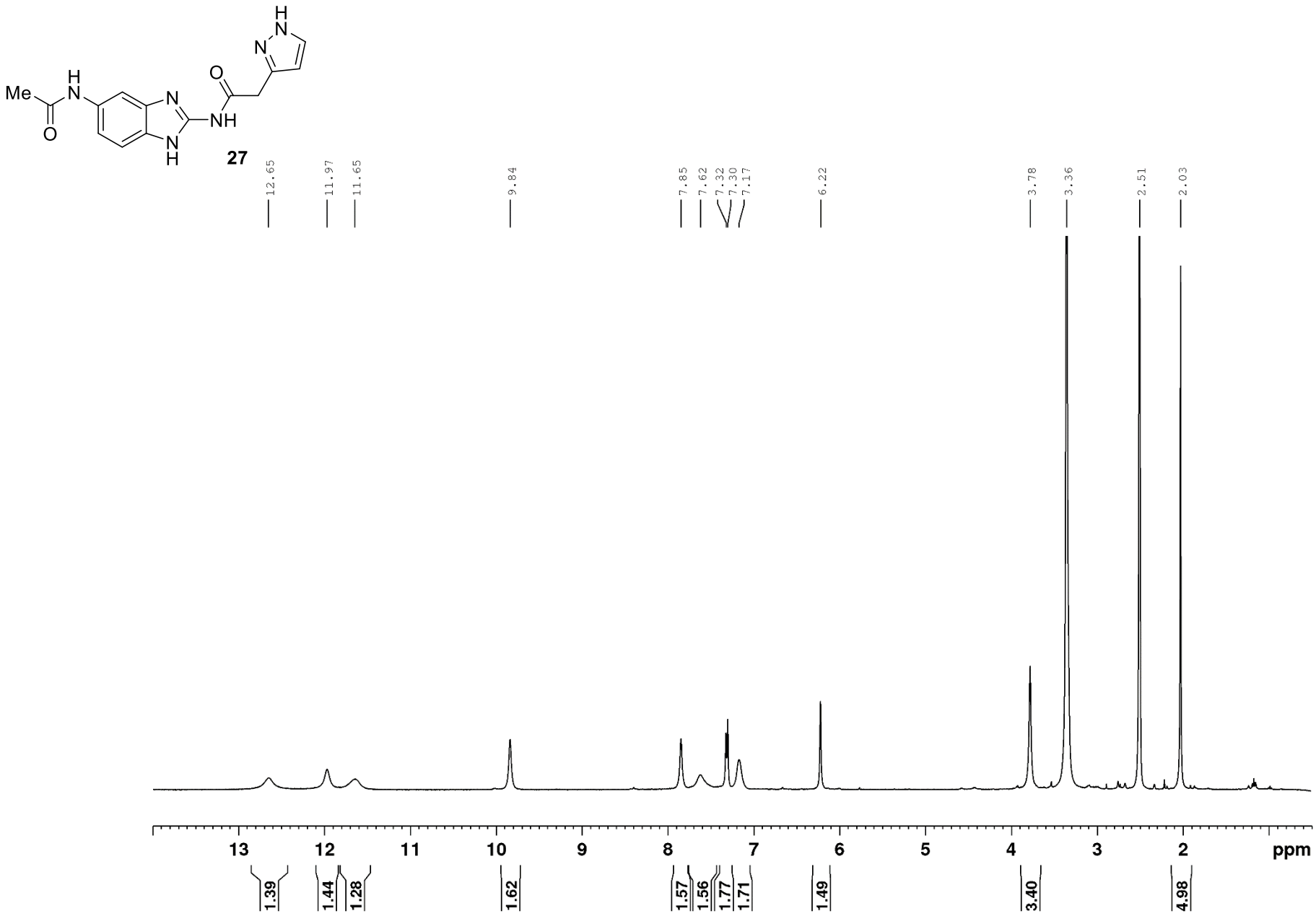
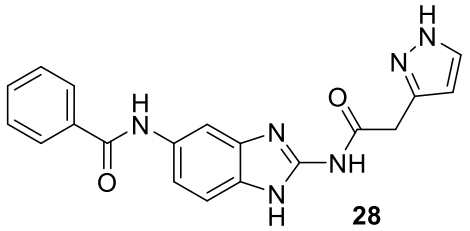
7.83
7.63
7.61
7.57
7.54
7.52
7.20
6.24
3.84
2.40
2.39
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.24
0.29
0.28
0.27
0.53
0.31
0.33
0.24
0.61
0.89


Me
H
N
O
N
H
N
N
NH
H
N
O
27
12.65
11.97
11.65
9.84
7.85
7.62
7.32
7.30
7.17
6.22
3.78
3.36
2.51
2.03
13
12
11
10
9
8
7
6
5
4
3
2
ppm
1.39
1.44
1.28
1.62
1.57
1.56
1.77
1.71
1.49
3.40
4.98



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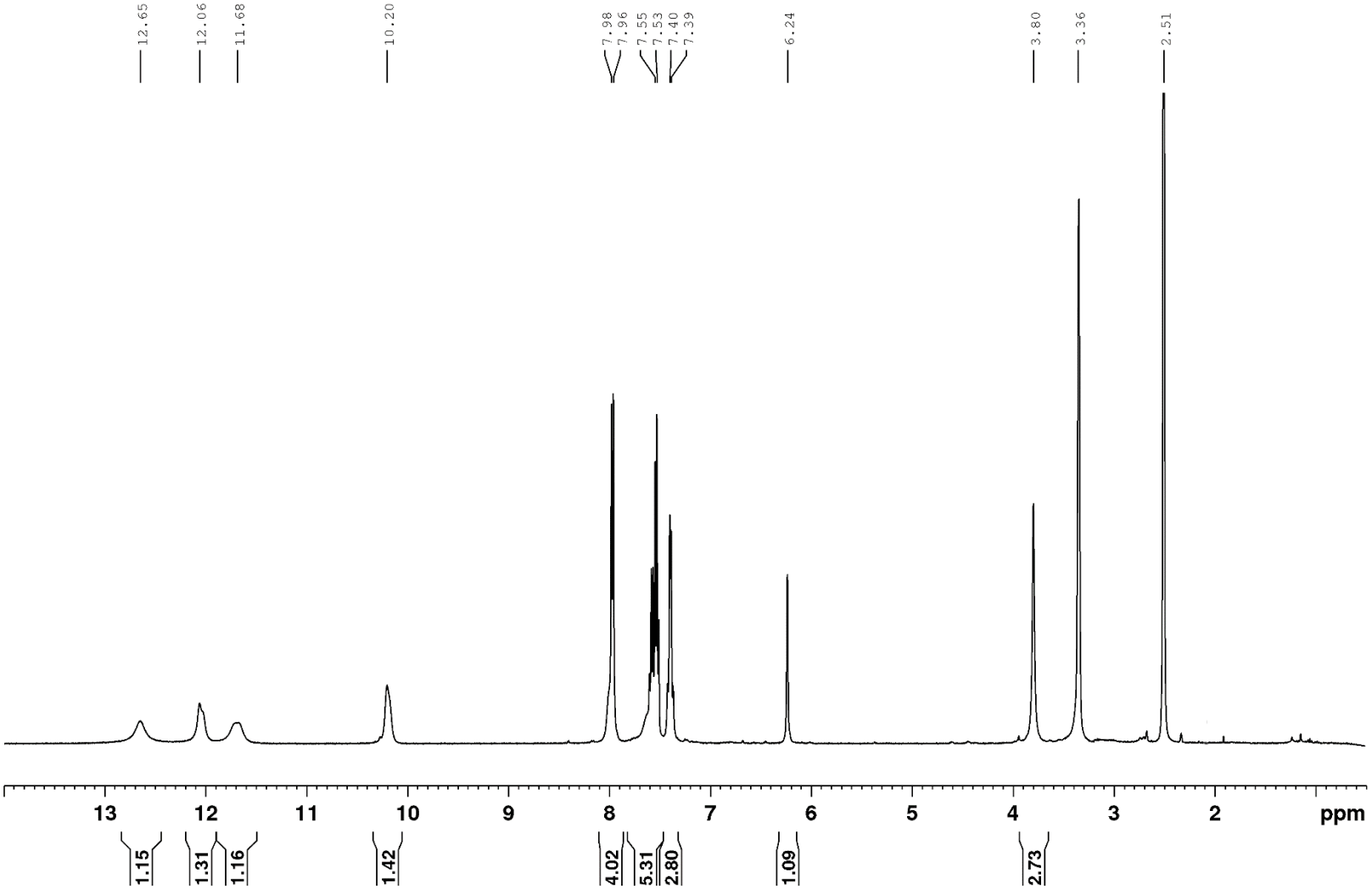
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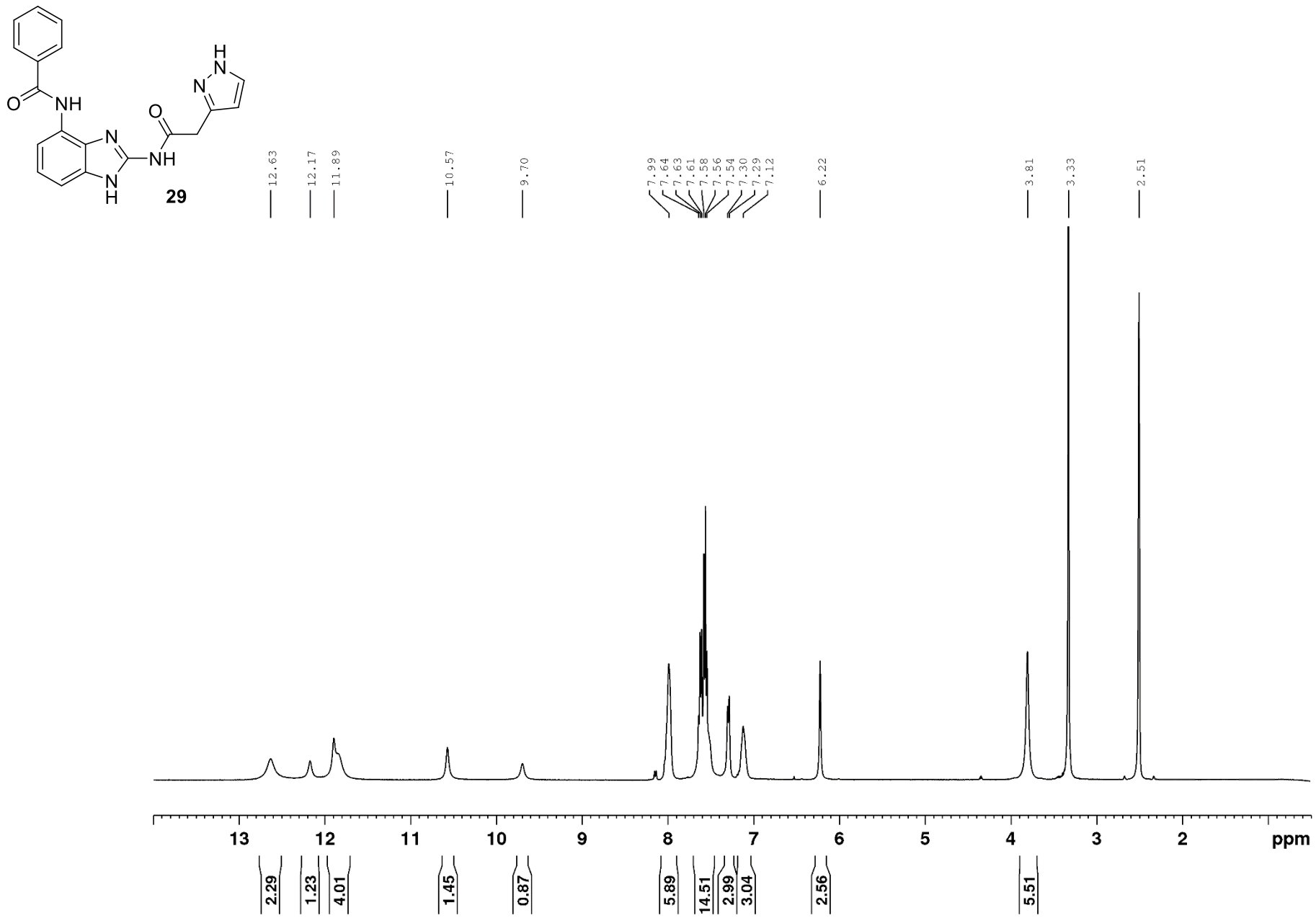
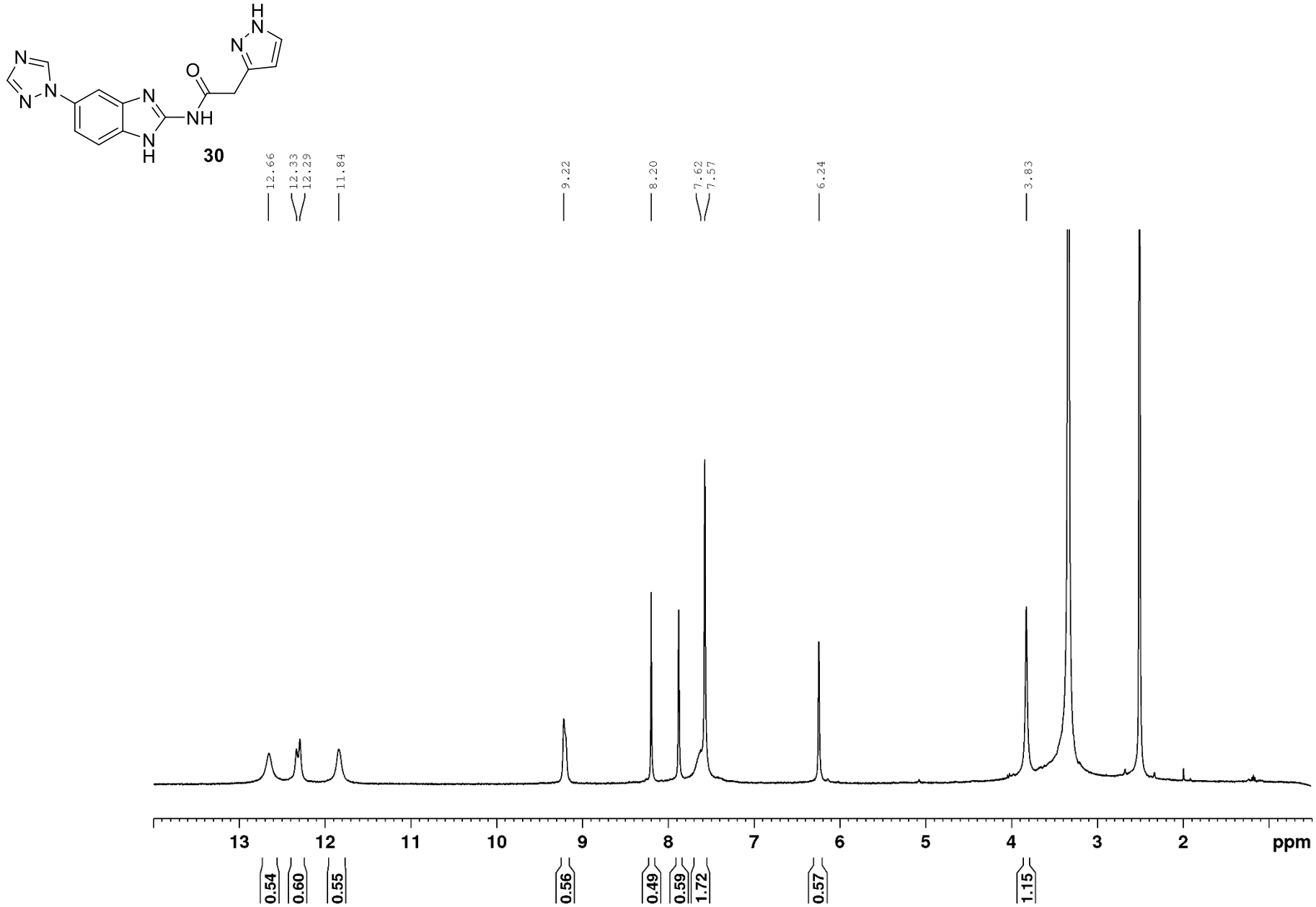
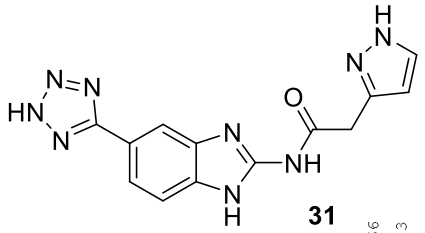
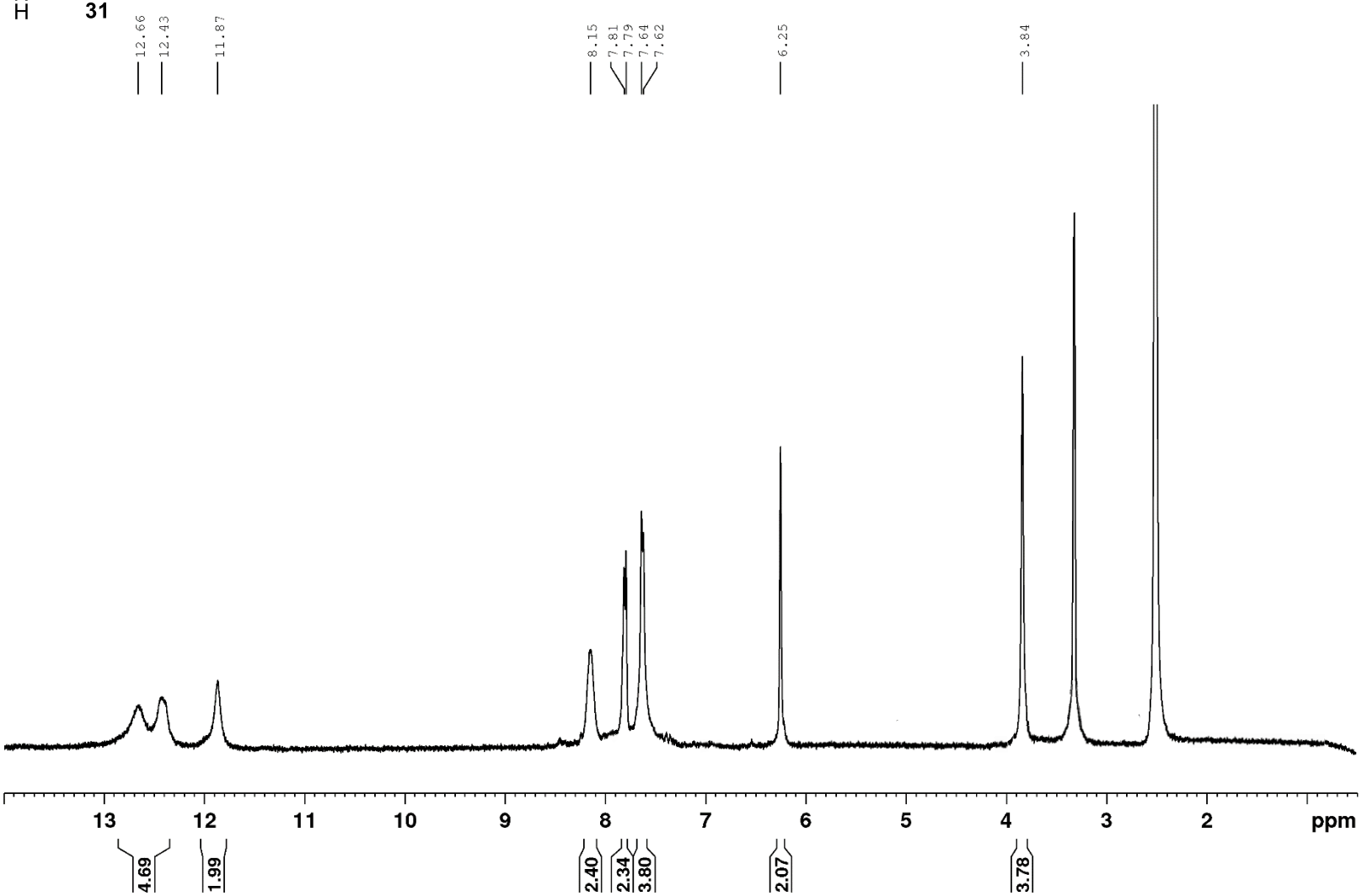
7.96
7.55
7.53
7.40
7.39
6.24
3.80
3.36
2.51
13
12
11
10
9
8
7
6
5
4
3
2
ppm
1.15
1.31
1.16
1.42
4.02
5.31
2.80
1.09
2.73


29
12.63
12.17
11.89
10.57
9.70
7.99
7.64
7.63
7.61
7.58
7.56
7.54
7.30
7.29
7.12
6.22
3.81
3.33
2.51
13
12
11
10
9
8
7
6
5
4
3
2
ppm
2.29
1.23
4.01
1.45
0.87
5.89
14.51
2.99
3.04
2.56
5.51


30
12.66
12.33
12.29
11.84
9.22
8.20
7.62
7.57
6.24
3.83
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.54
0.60
0.55
0.56
0.49
0.59
1.72
0.57
1.15



31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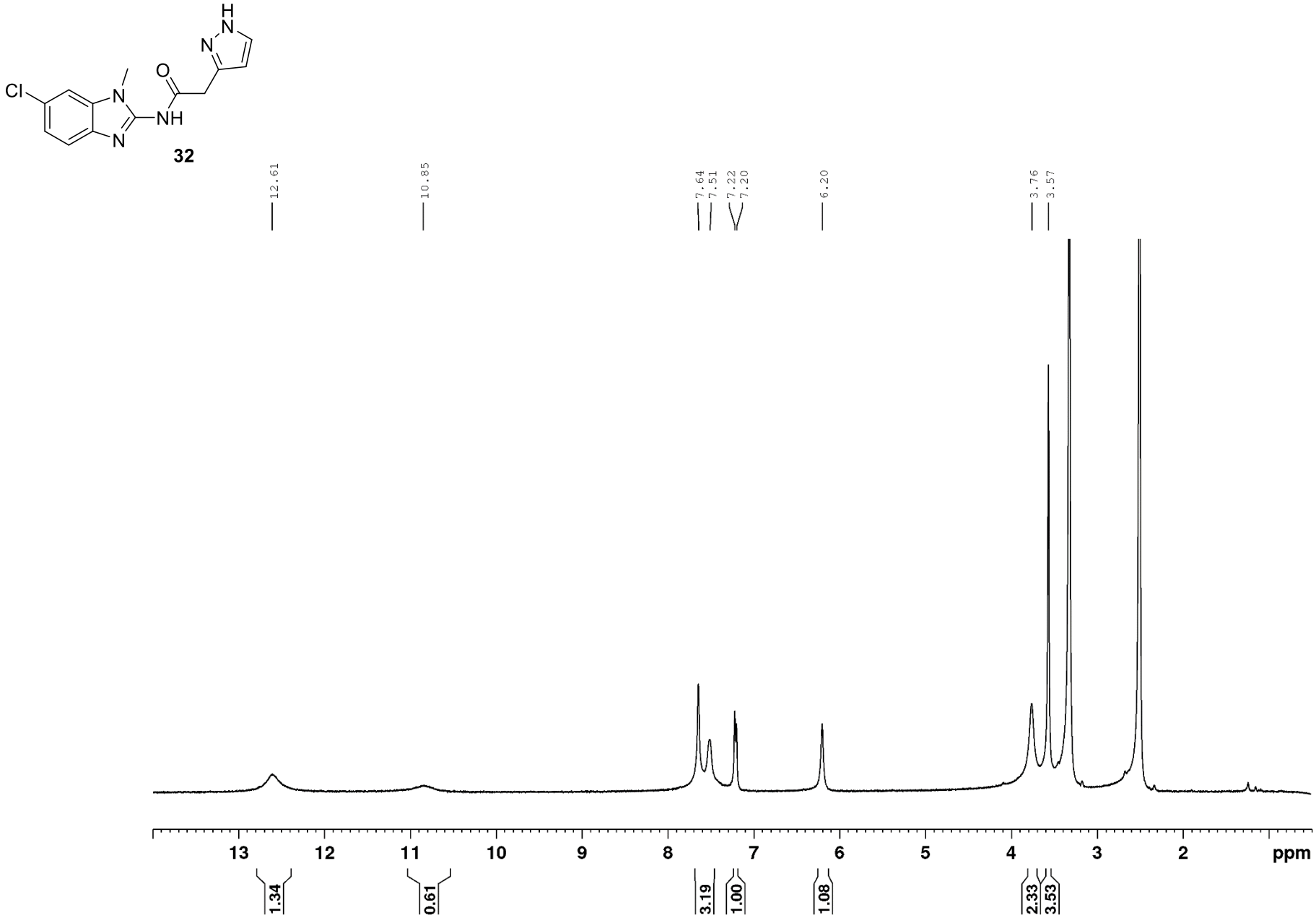
11.87
8.15
7.81
7.79
7.64
7.62
6.25
3.84
13
12
11
10
9
8
7
6
5
4
3
2
ppm
4.69
1.99
2.40
2.34
3.80
2.07
3.78


Cl
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O
NH
N
H
N
32
12.61
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7.51
7.22
7.20
6.20
3.76
3.57
13
12
11
10
9
8
7
6
5
4
3
2
ppm
1.34
0.61
3.19
1.00
1.08
2.33
3.53