Supplementary Information

Article

Synthesis and antiviral activity of camphene derivatives against different types of viruses

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Pharmacophore model

To create a pharmacophore model, we used the Pharmacophore Modeling module implemented in the Schrodinger Suite: Release 2020-4 software. As a result, two models were developed: (i) pharmacophore model based on assessing the contributions of amino acid residues located at M090-site, TBQH-site, and Toremifene-site; (ii) pharmacophore model based on assessing the complementarity of a ligand and a protein at a potential binding site. Also, the pharmacophore profile of the compounds **2a** and **7a** was evaluated (**Figure S1**).

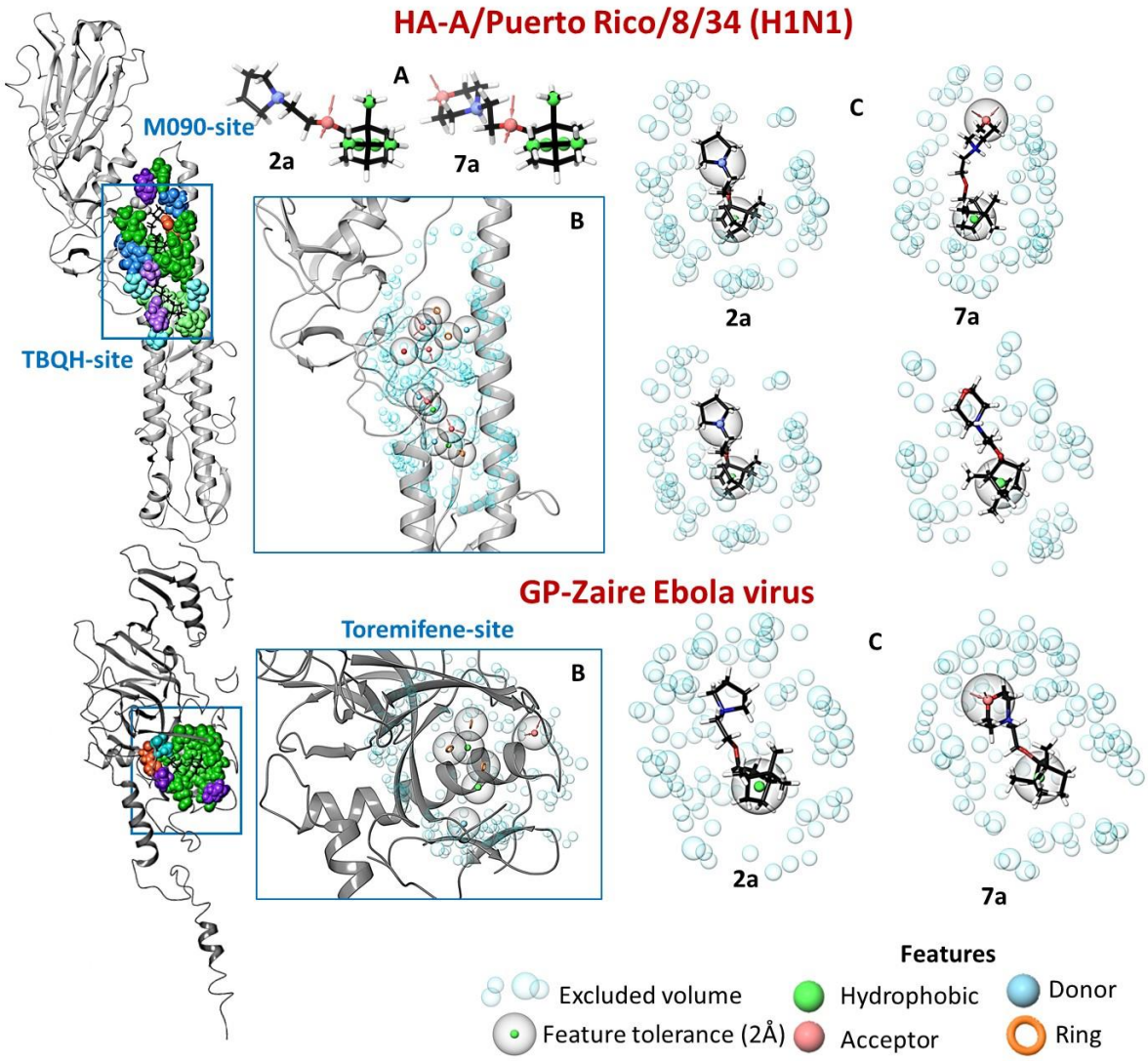


Figure S1. (**A**): the pharmacophore profile of the compounds **2a** and **7a**; (**B**): the pharmacophore model based on assessing the contributions of amino acid residues located at M090-site, TBQH-site, and Toremifene-site; **C** the pharmacophore model based on assessing the complementarity of a ligand and a protein.

Compounds **2a** and **7a** have a similar pharmacophore profile and include hydrophobic 1,7,7-trimethylbicyclo[2.2.1]heptan fragment, hydrogen bond acceptor (ether group), and

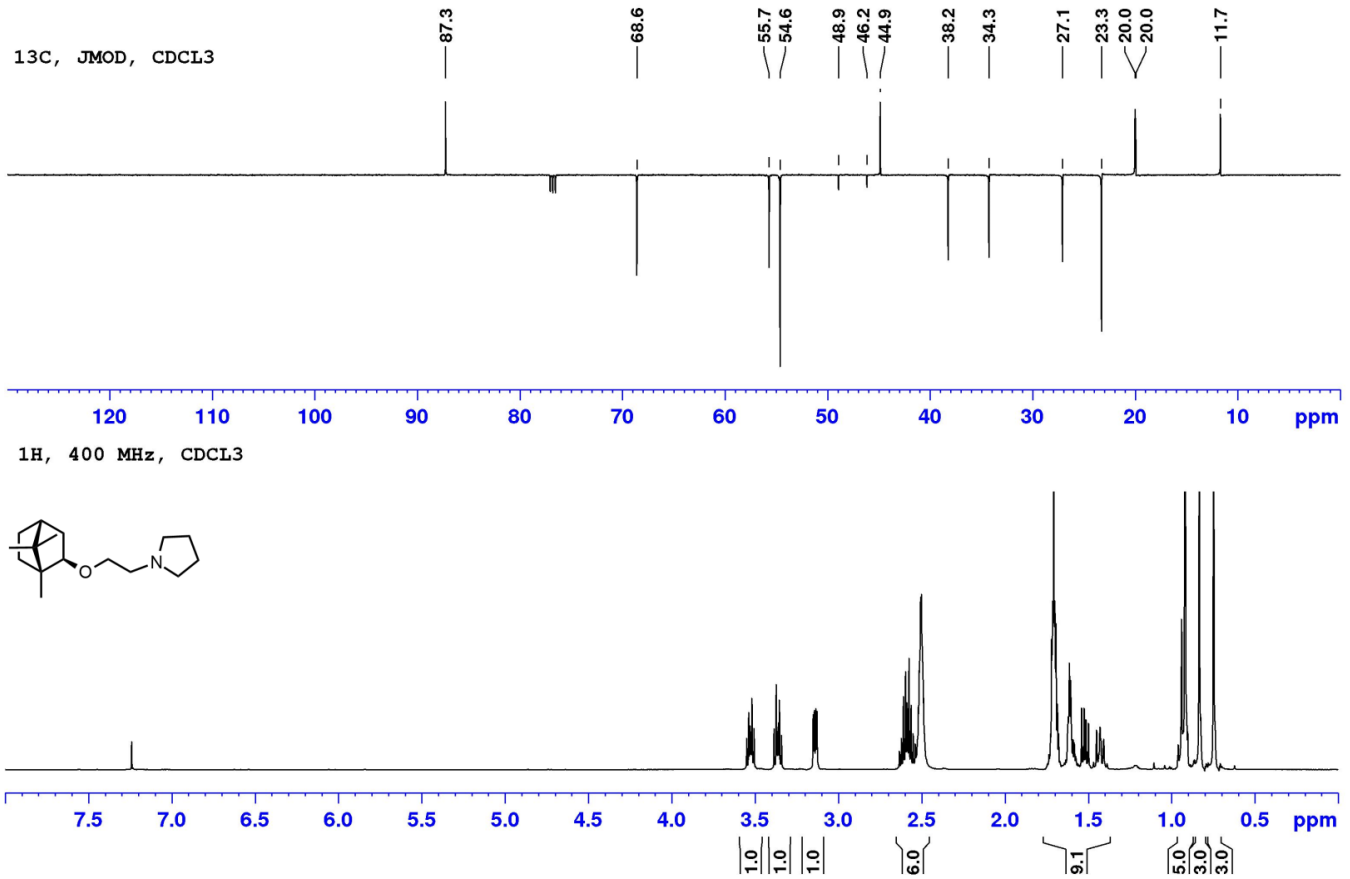
protonated nitrogen atoms that create an additional reaction center of the molecule capable of forming salt bridges and cation-π stacking interactions.

A pharmacophore model of potential ligand-binding sites shows that surrounding amino acids have hydrophobic characteristics (shown in green in **Figure 1S-B**) and there are a number of amino acids that may contain atoms or groups of atoms exhibiting the properties of acceptors or donors of hydrogen bonds, as well as aromatic rings. The location of such features as hydrogen bond acceptors or donors, hydrophobic, and aromatic groups in the binding sites of influenza and Ebola viruses differ in space. However, saturation with hydrophobic amino acids increases the likelihood that compounds containing a hydrophobic moiety, such as 1,7,7-trimethylbicyclo[2.2.1]heptan moiety in compounds **2a** and **7a**, will bind. The presence of acceptor and donor features allows hydrogen and salt bridges to be formed, which are observed when compounds **2a** and **7a** bind at the described binding sites. In addition, aromatic amino acids can form stacking interactions with protonated pyrolidine and/or morpholic fragments of the compounds **2a** and **7a**.

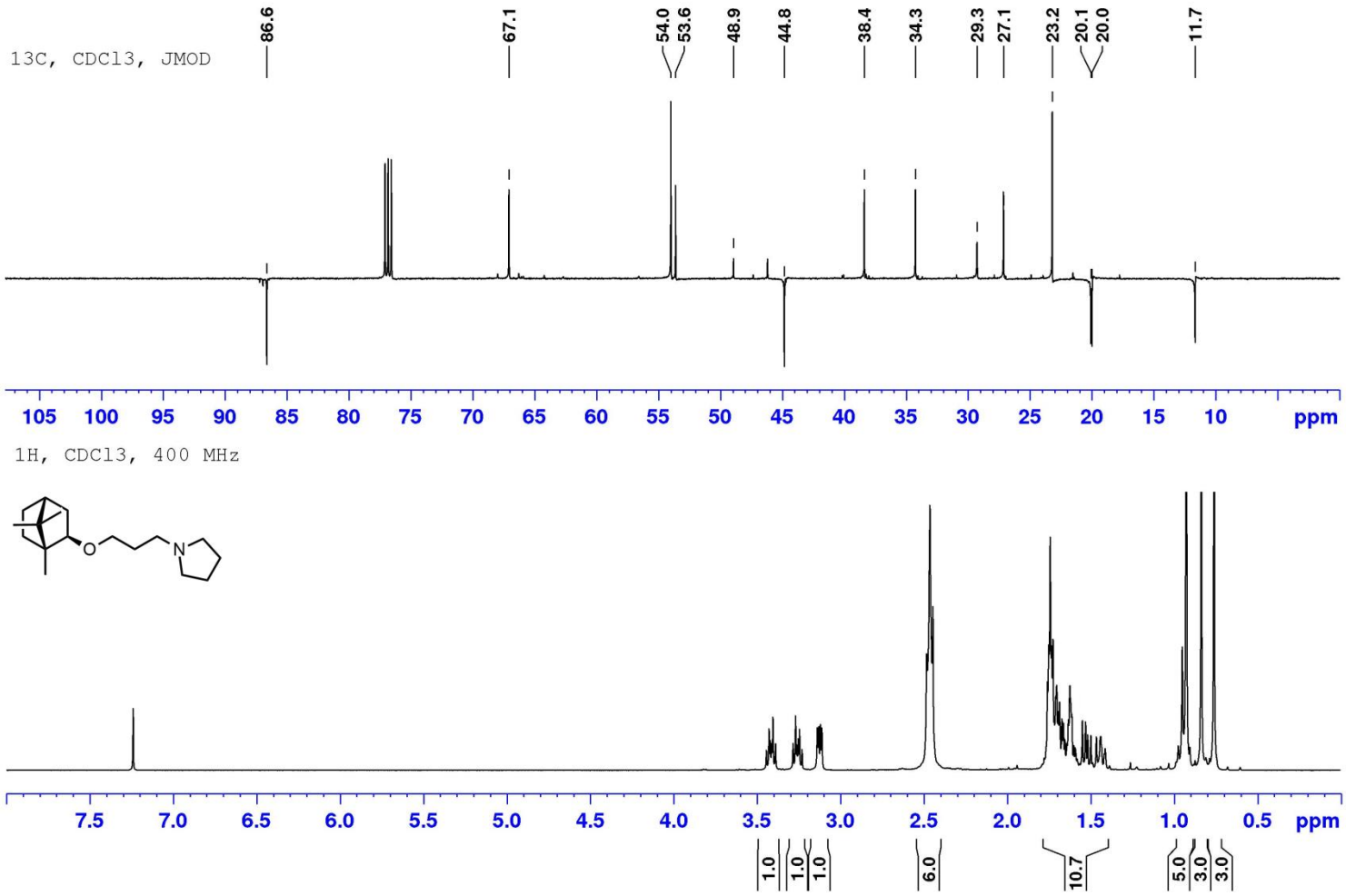
The pharmacophore model based on the principle of ligand-protein complementarity (**Figure 1S-C**) in all cases contains a hydrophobic feature: ligands bind to the binding sites by forming strong hydrophobic contacts with amino acids with similar features being formed.

NMR ^{1}H and ^{13}C spectra

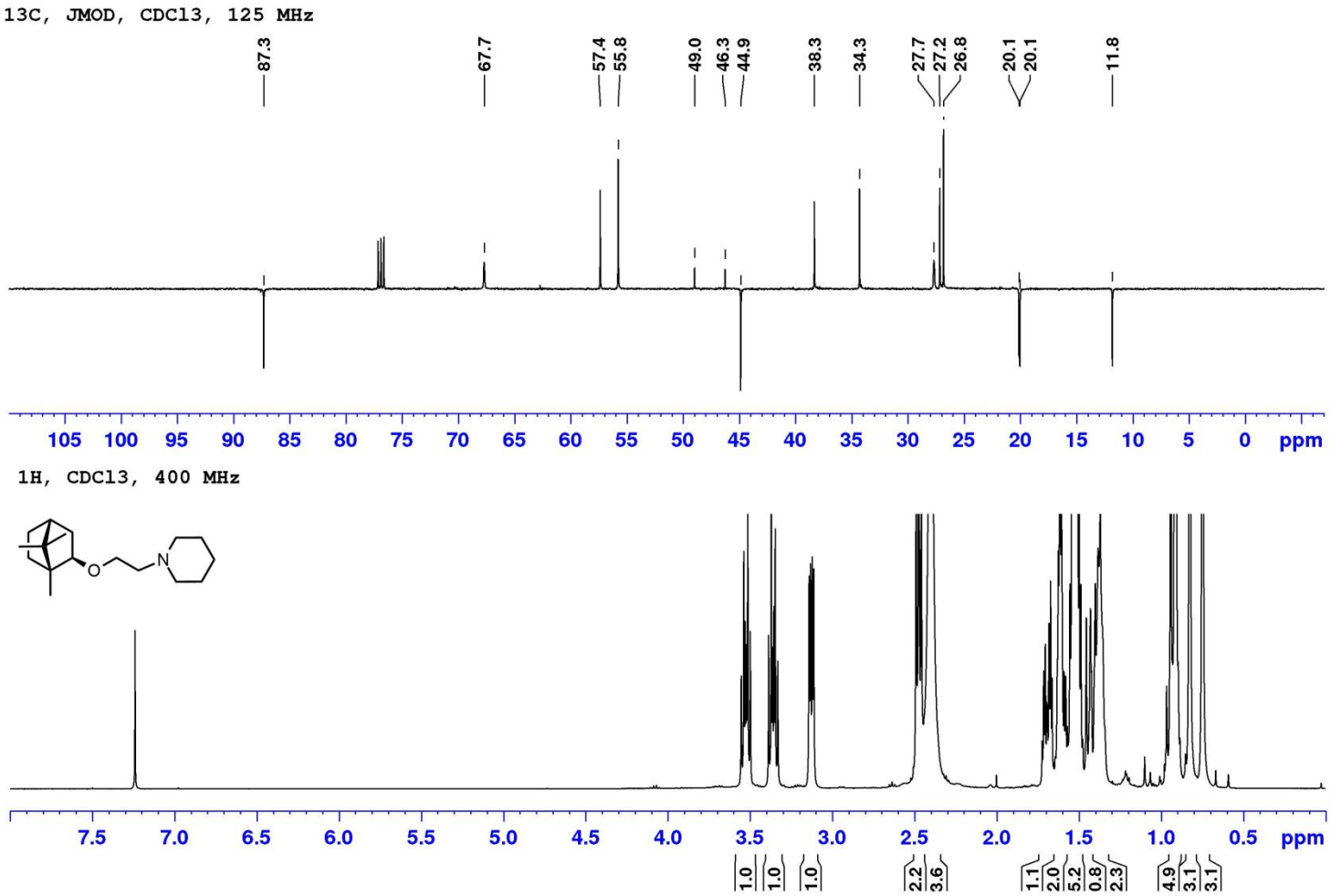
Compound 2a



Compound 2b


13C, CDCl3, JMOD
86.6
67.1
54.0
53.6
48.9
44.8
38.4
34.3
29.3
27.1
23.2
20.1
20.0
11.7
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm
1H, CDCl3, 400 MHz
O
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0
1.0
1.0
6.0
10.7
5.0
3.0
3.0

Compound 3a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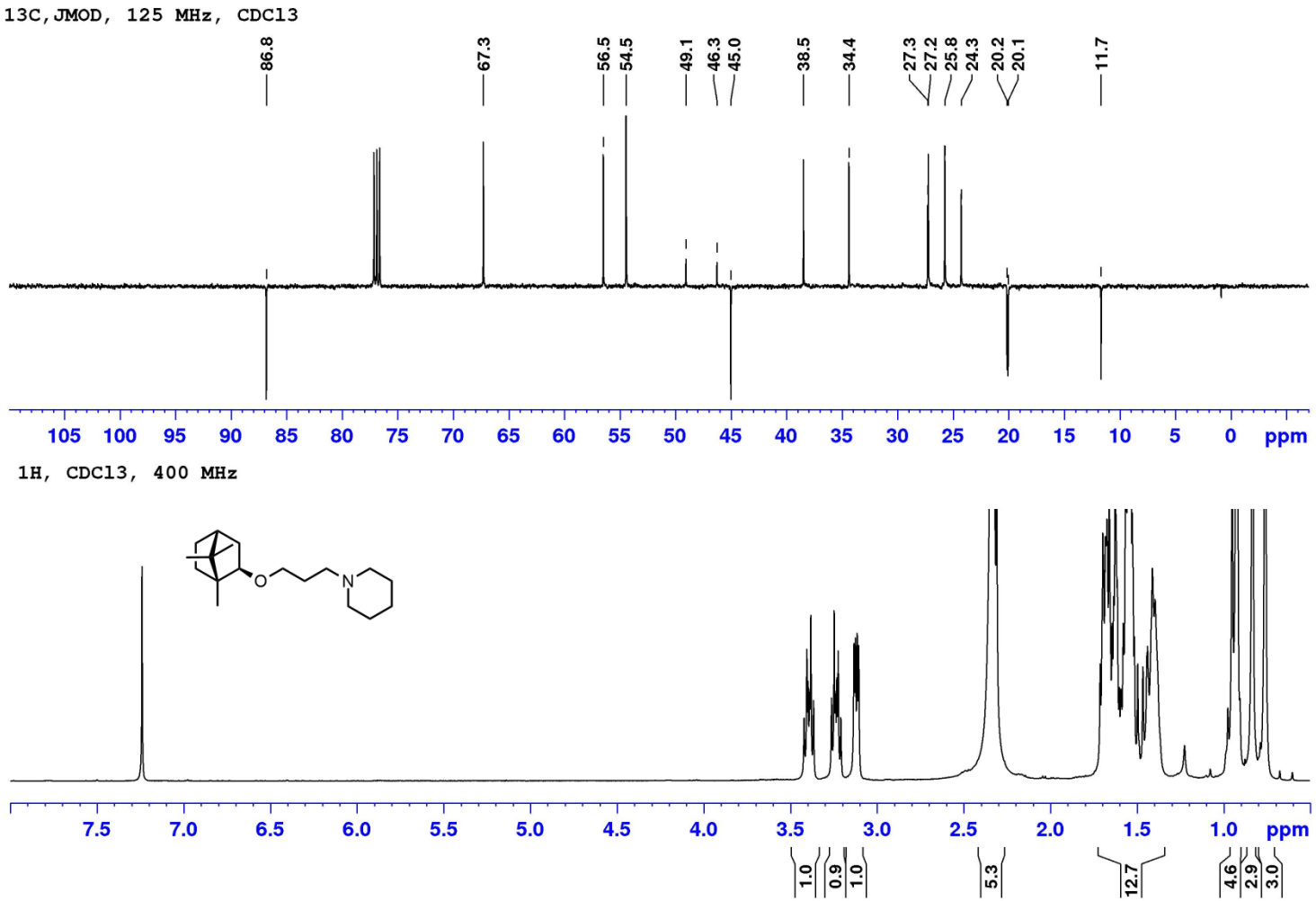
67.7
57.4
55.8
49.0
46.3
44.9
38.3
34.3
27.7
27.2
26.8
20.1
20.1
11.8
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
1H, CDCl3, 400 MHz
O
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0
1.0
1.0
2.2
3.6
1.1
2.0
5.2
0.8
2.3
4.9
3.1
3.1

Compound 3b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54.5
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46.3
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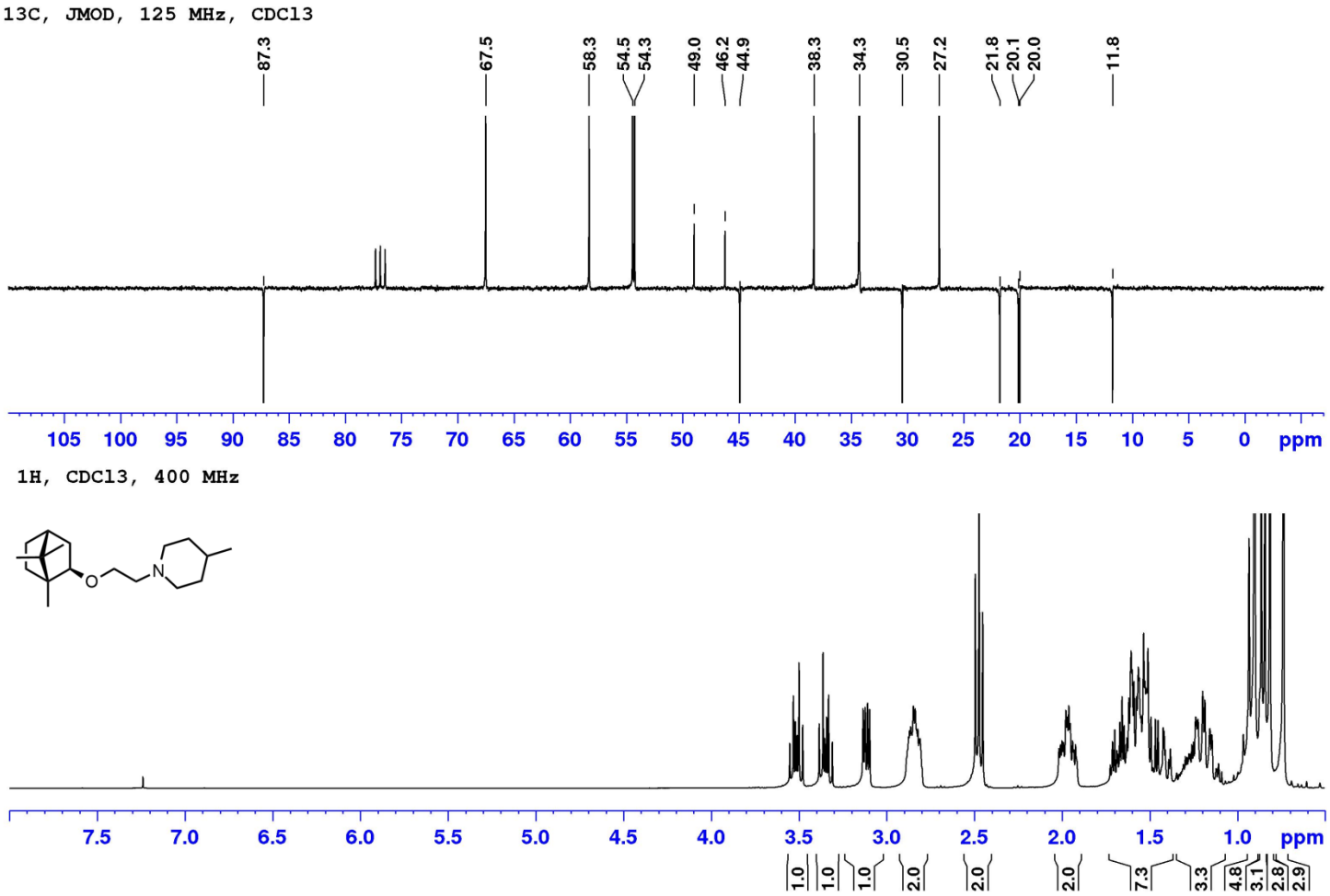
38.5
34.4
27.3
27.2
25.8
24.3
20.2
20.1
11.7
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
1H, CDCl3, 400 MHz
O
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.0
0.9
1.0
5.3
12.7
4.6
2.9
3.0

Compound 4a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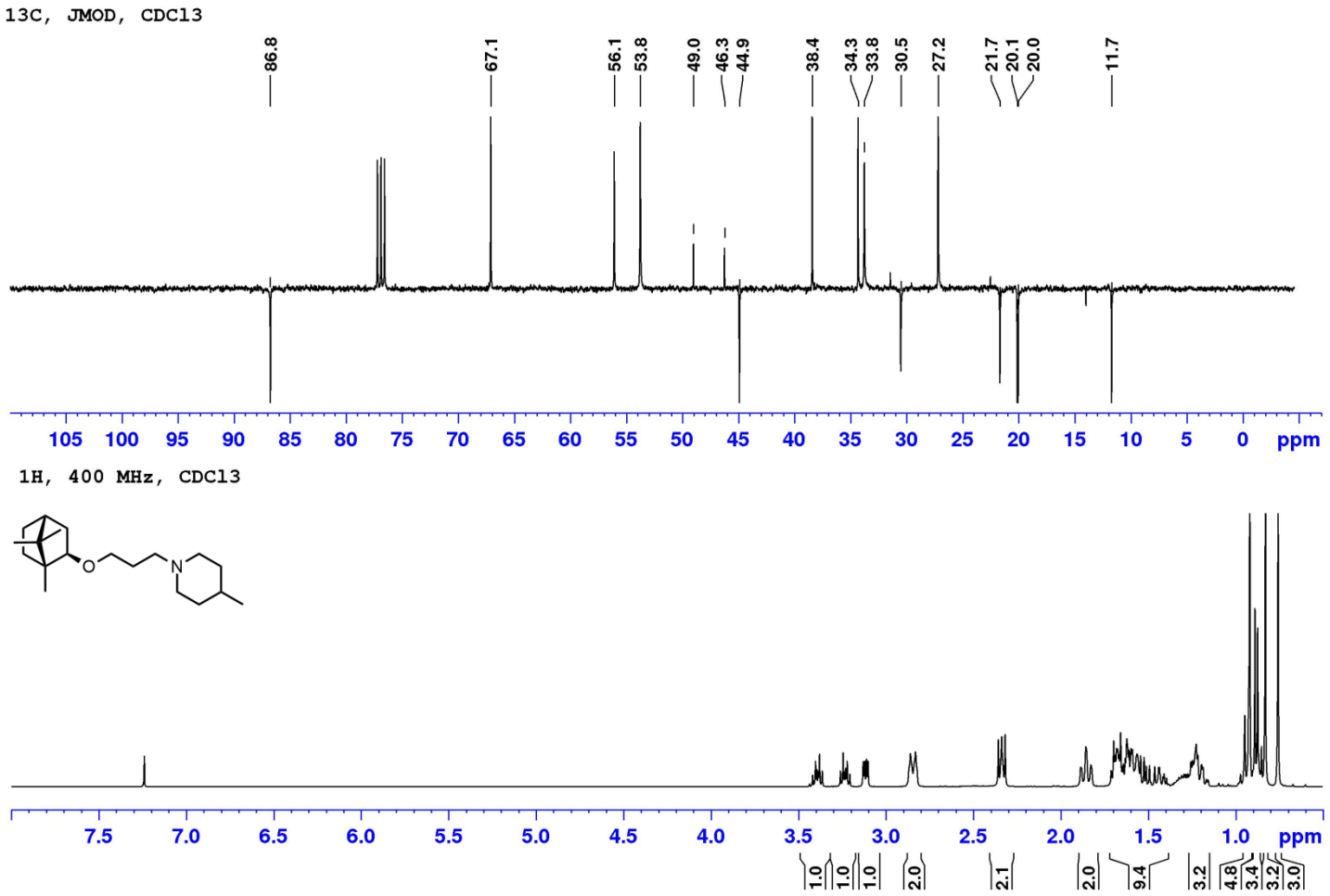
58.3
54.5
54.3
49.0
46.2
44.9
38.3
34.3
30.5
27.2
21.8
20.1
20.0
11.8
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
1H, CDCl3, 400 MHz
O
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.0 1.0 1.0 2.0 2.0 2.0 7.3 3.3 4.8 3.1 2.8 2.9

Compound 4b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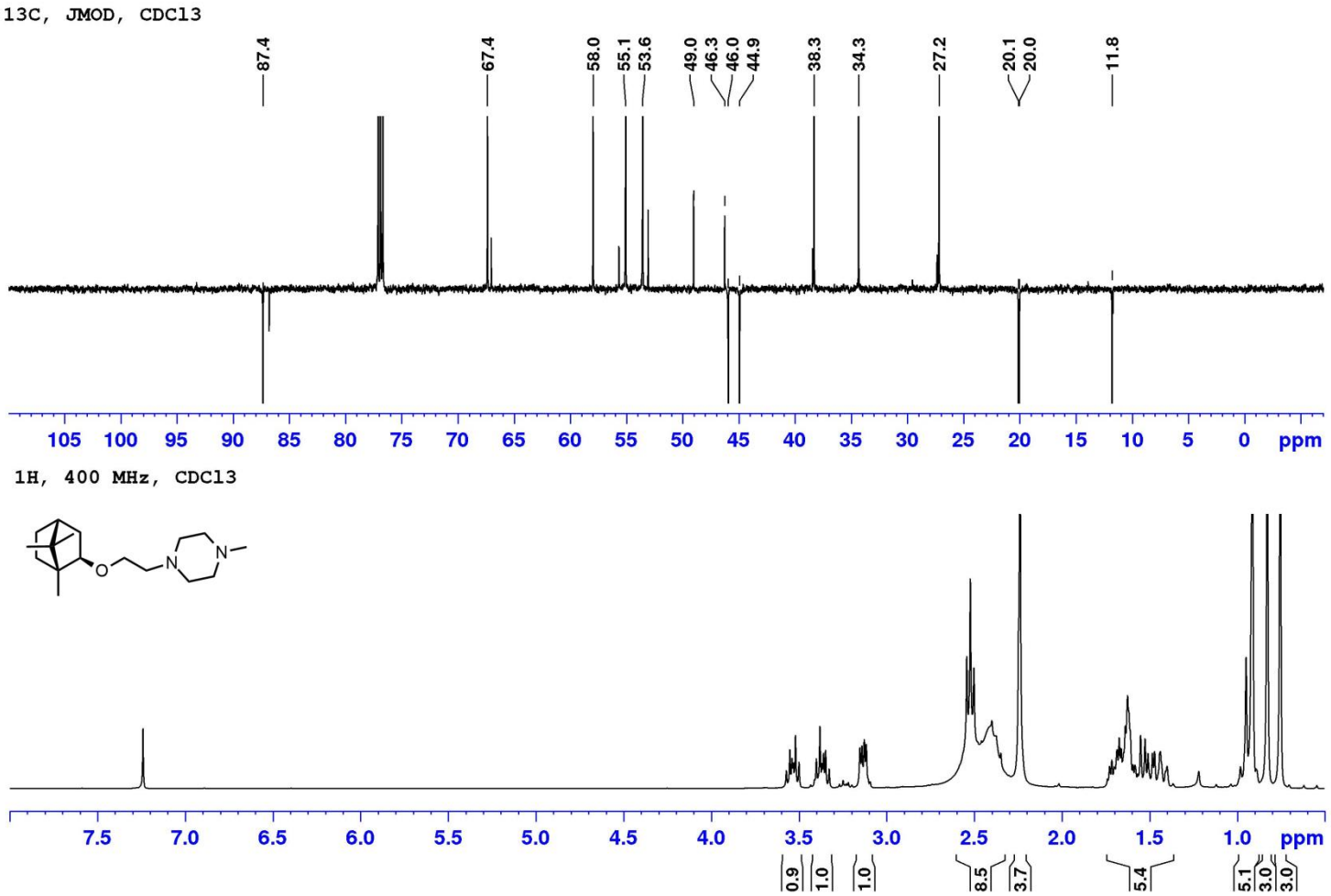
56.1
53.8
49.0
46.3
44.9
38.4
34.3
33.8
30.5
27.2
21.7
20.1
20.0
11.7
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
1H, 400 MHz, CDCl3
O
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.0 1.0 1.0 2.0 2.1 2.0 9.4 3.2 4.8 3.4 3.2 3.0

Compound 5a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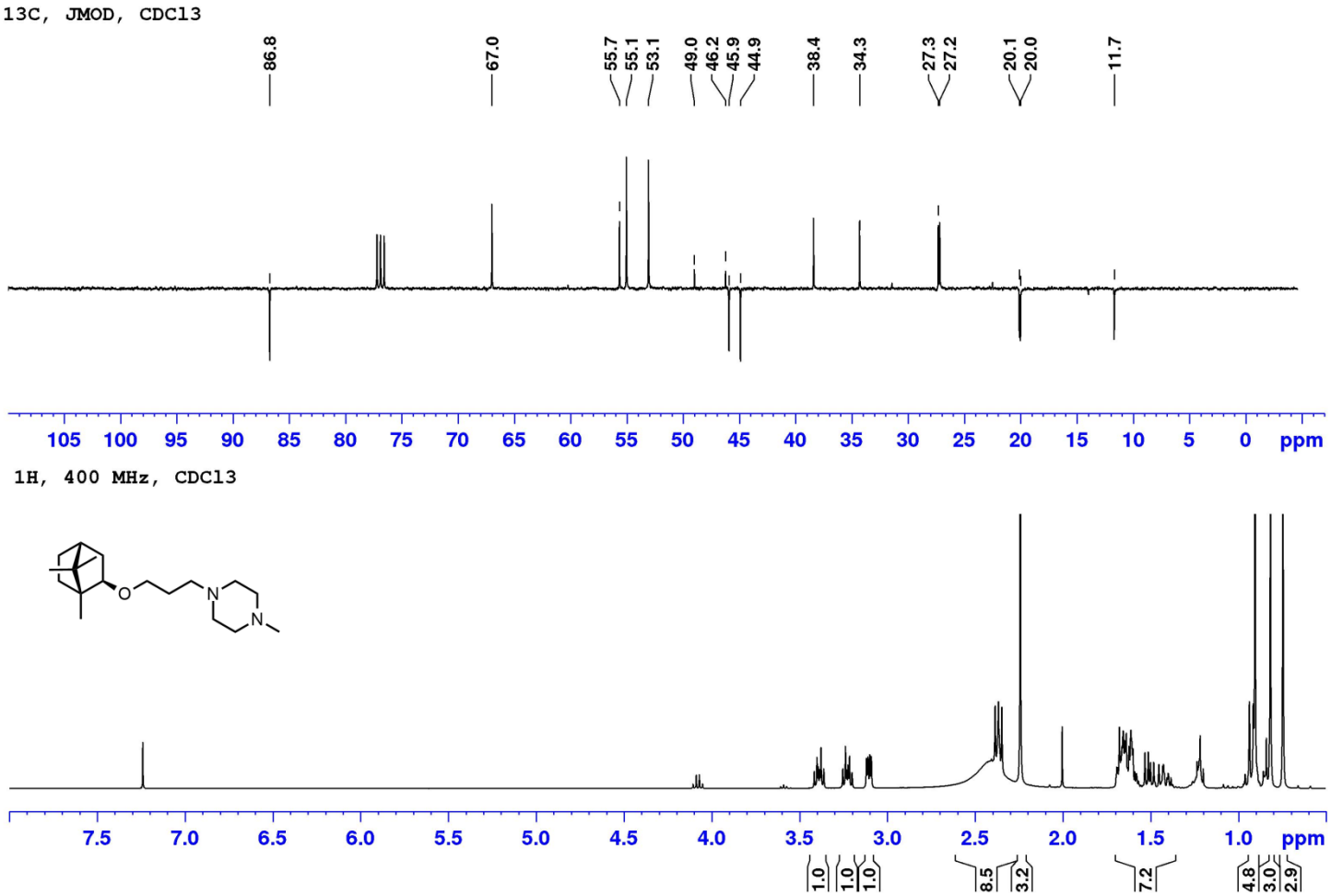
58.0
55.1
53.6
49.0
46.3
46.0
44.9
38.3
34.3
27.2
20.1
20.0
11.8
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
1H, 400 MHz, CDCl3
O
N
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.9
1.0
1.0
8.5
3.7
5.4
5.1
3.0
3.0

Compound 5b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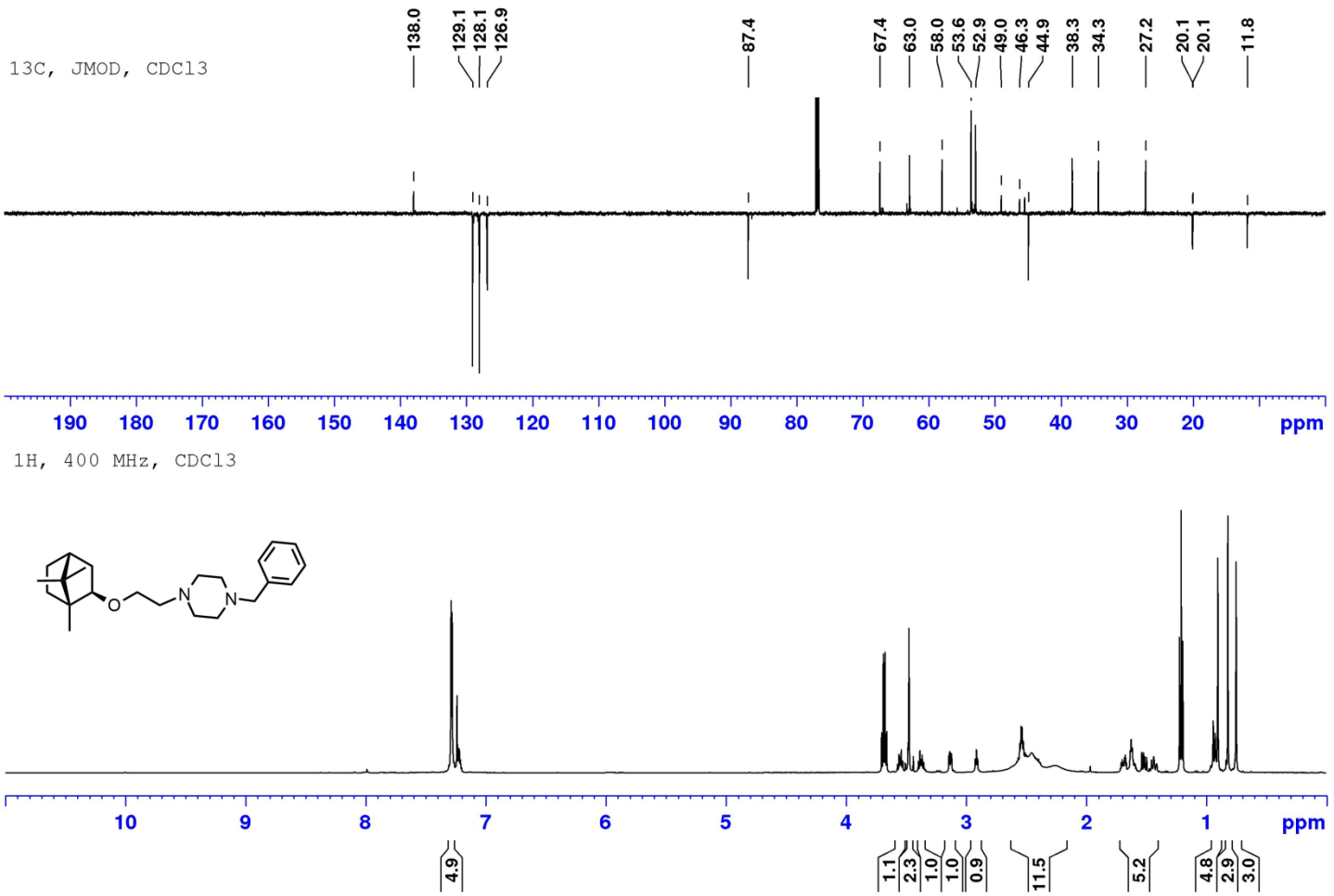
55.7
55.1
53.1
49.0
46.2
45.9
44.9
38.4
34.3
27.3
27.2
20.1
20.0
11.7
105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 ppm
1H, 400 MHz, CDCl3
O
N
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.0
1.0
1.0
8.5
3.2
7.2
4.8
3.0
2.9

Compound 6a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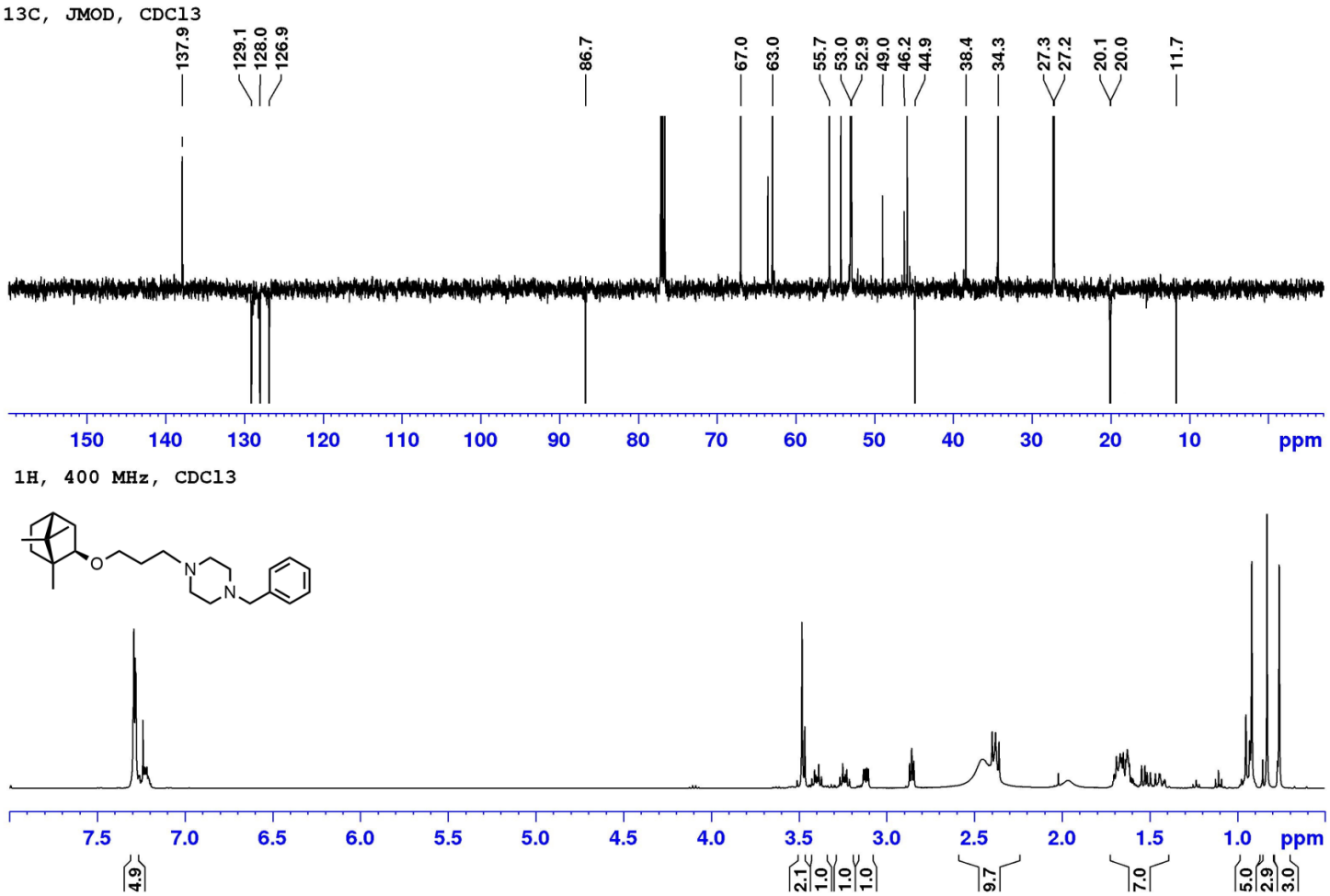
129.1
128.1
126.9
87.4
67.4
63.0
58.0
53.6
52.9
49.0
46.3
44.9
38.3
34.3
27.2
20.1
20.1
11.8
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm
1H, 400 MHz, CDCl3
10 9 8 7 6 5 4 3 2 1 ppm
4.9
1.1
2.3
1.0
1.0
0.9
11.5
5.2
4.8
2.9
3.0

Compound 6b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129.1
128.0
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53.0
52.9
49.0
46.2
44.9
38.4
34.3
27.3
27.2
20.1
20.0
11.7
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
1H, 400 MHz, CDCl3
O
N
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.9
2.1
1.0
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1.0
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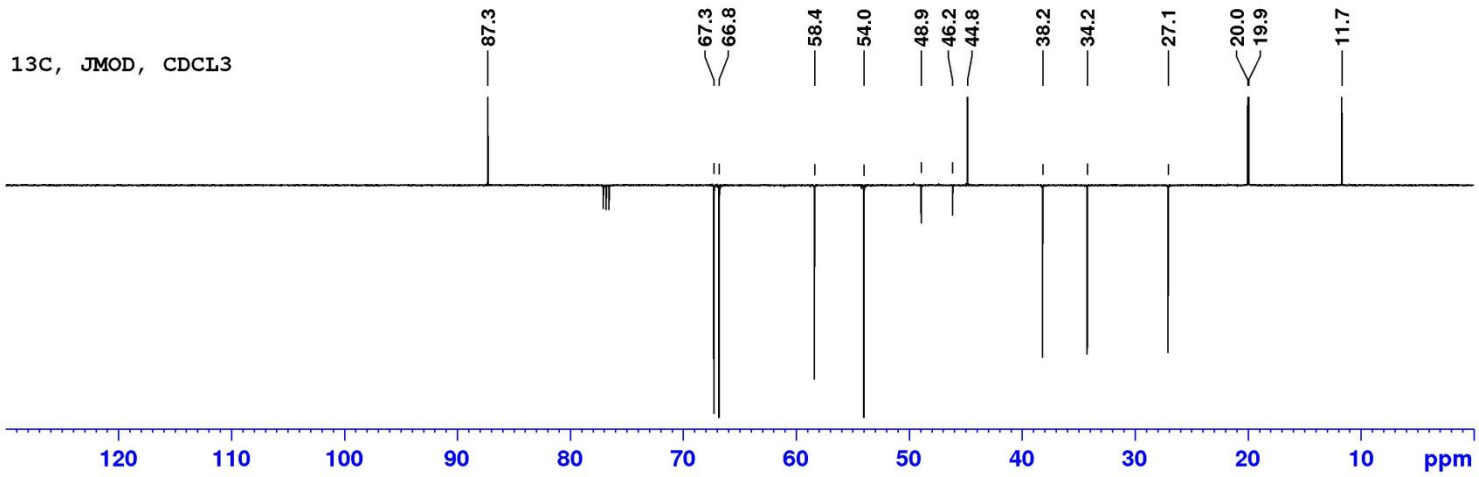
7.0
5.0
2.9
3.0

Compound 7a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67.3
66.8
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48.9
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44.8
38.2
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30
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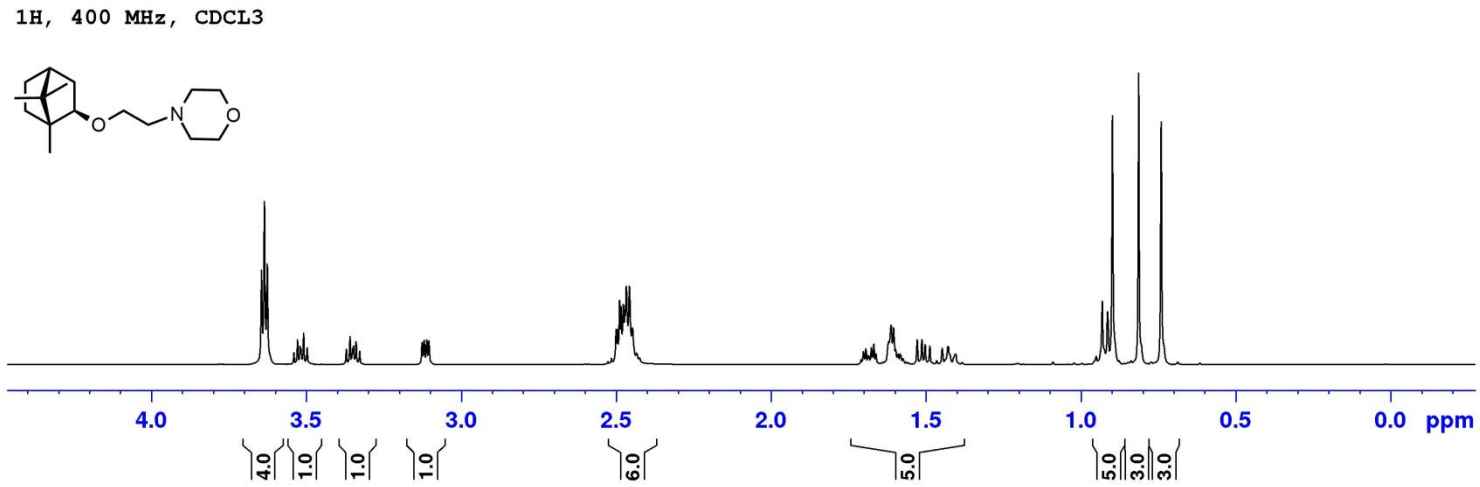
10
ppm


1H, 400 MHz, CDCL3
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N
O
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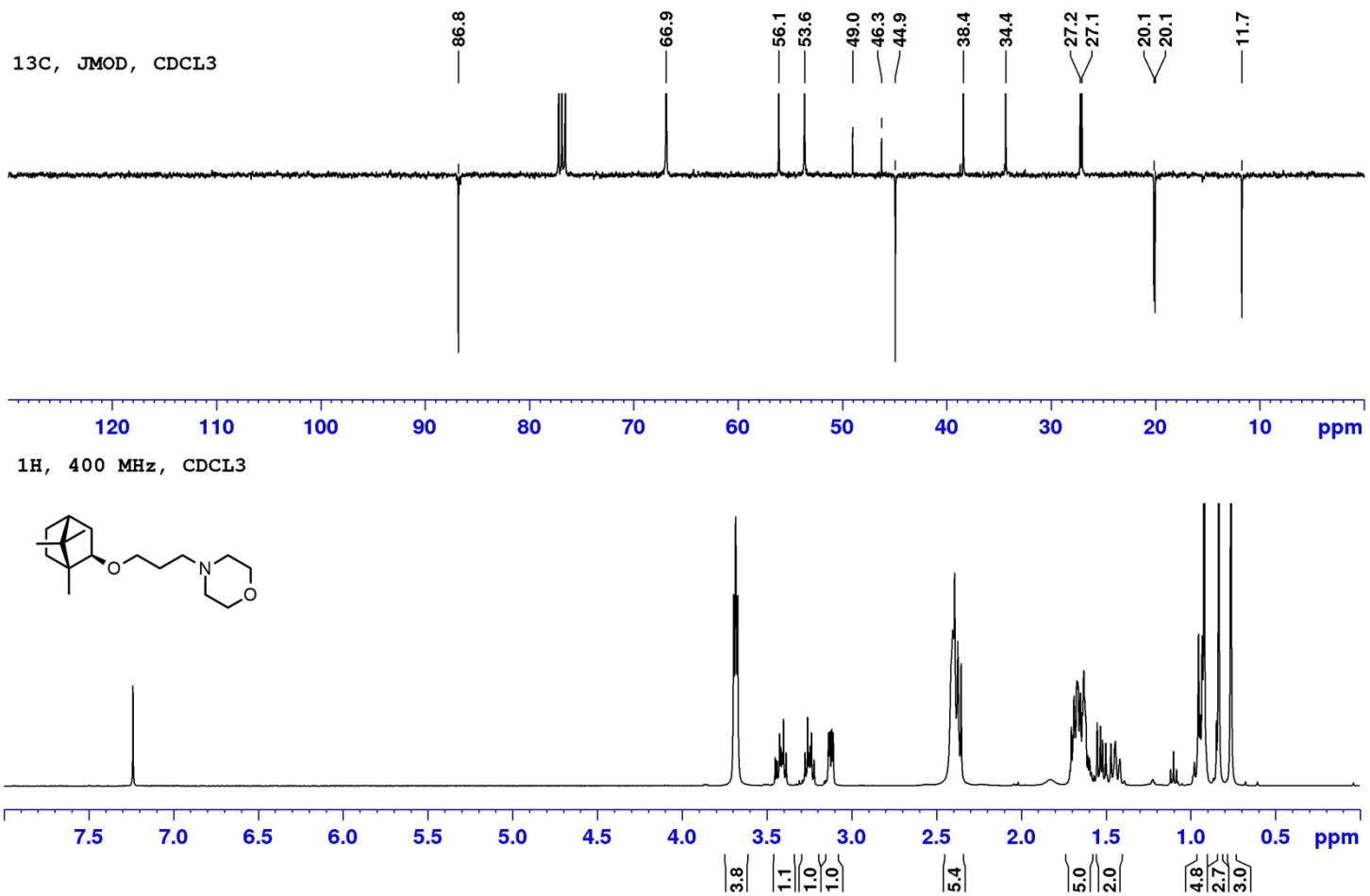
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.0
1.0
1.0
1.0
6.0
5.0
5.0
3.0
3.0

Compound 7b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110
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90
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70
60
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40
30
20
10
ppm
1H, 400 MHz, CDCL3
O
N
O
7.5
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6.5
6.0
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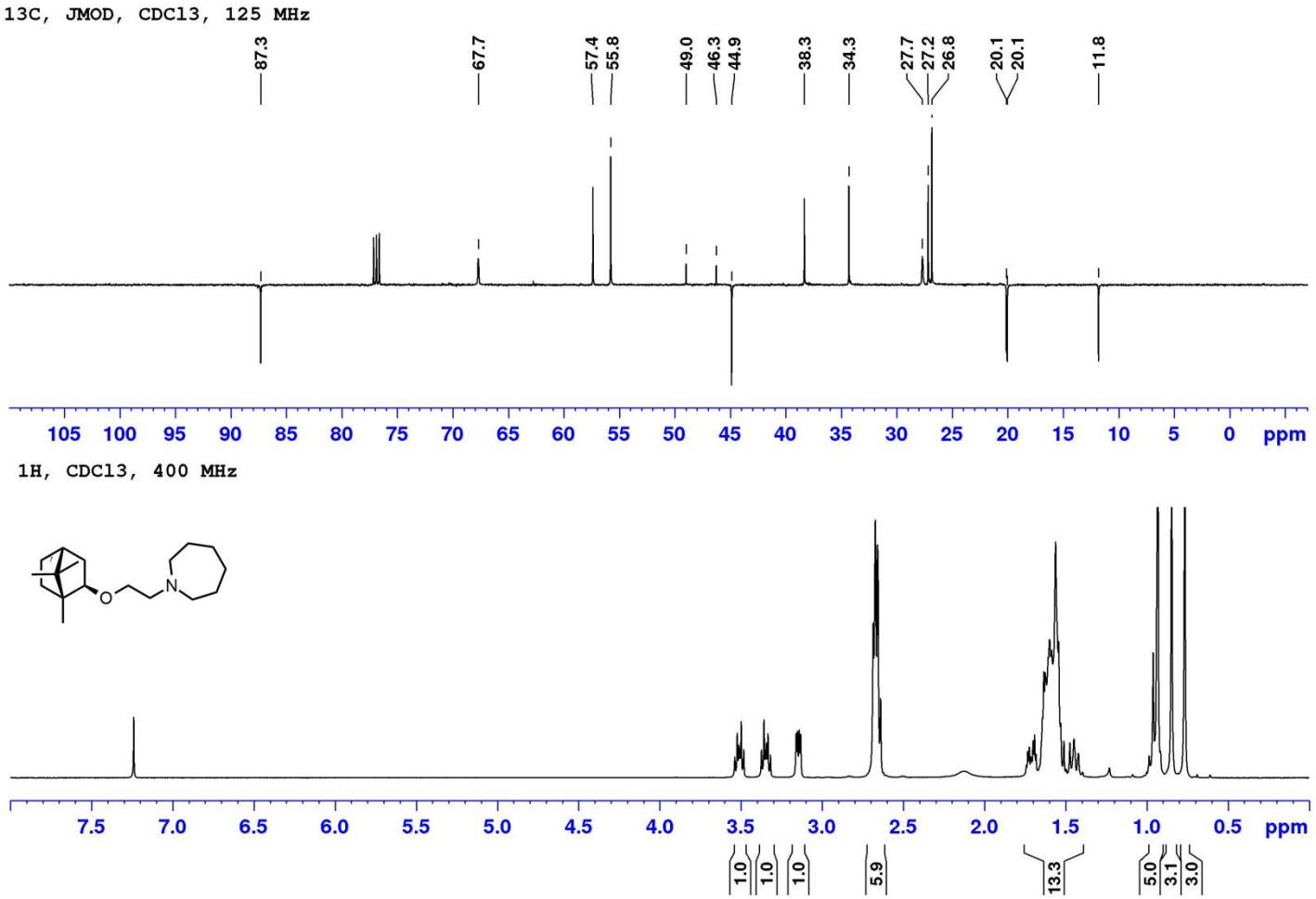
Compound 8a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27.2
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20.1
11.8
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1H, CDCl3, 400 MHz
O
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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13.3
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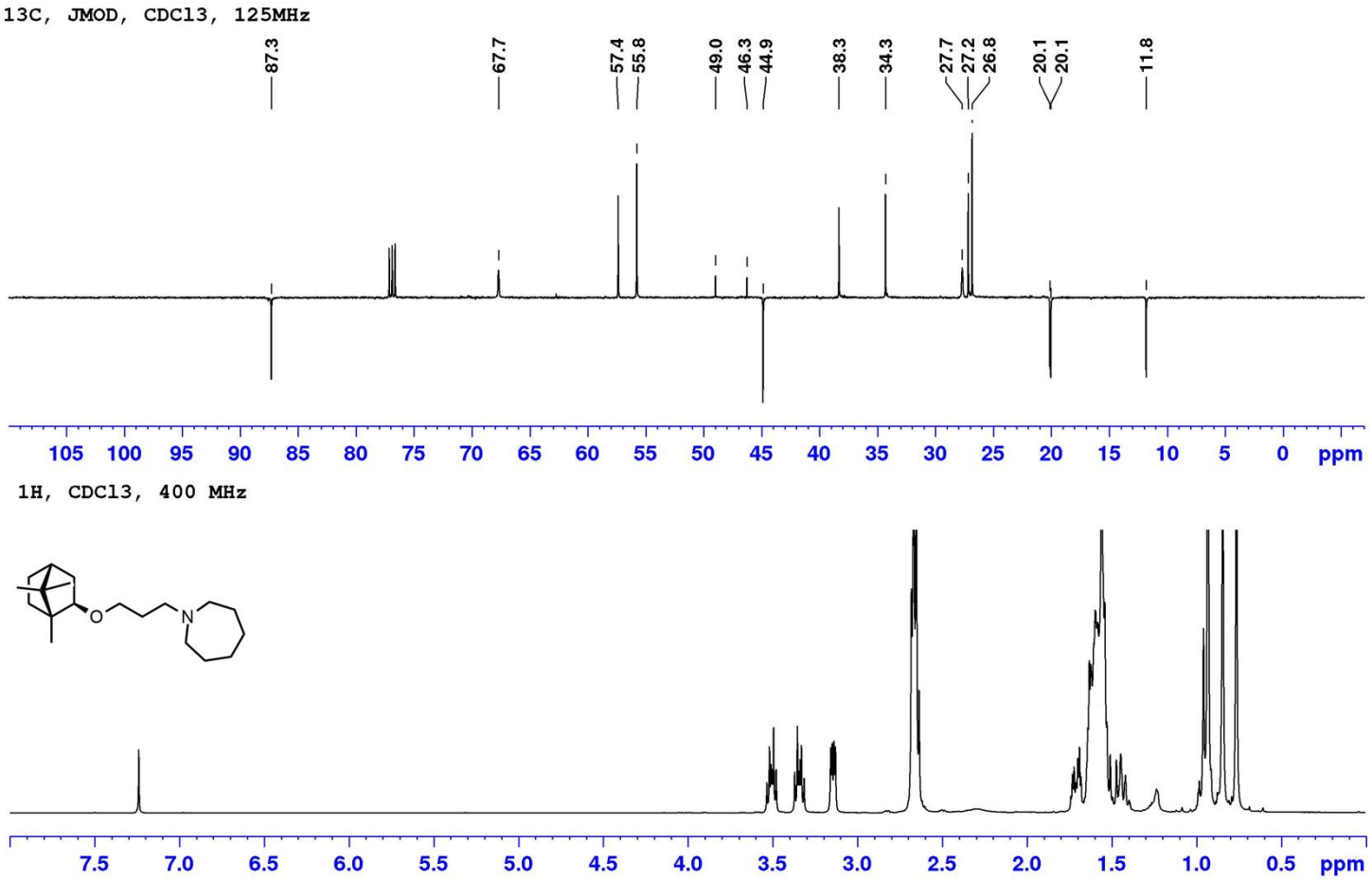
Compound 8b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1H, CDCl3, 400 MHz
O
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm