Supporting Information

End-to-End Continuous Flow Synthesis and Purification of Diphenhydramine Hydrochloride Featuring Atom Economy, In-Line Separation, and Flow of Molten Ammonium Salts

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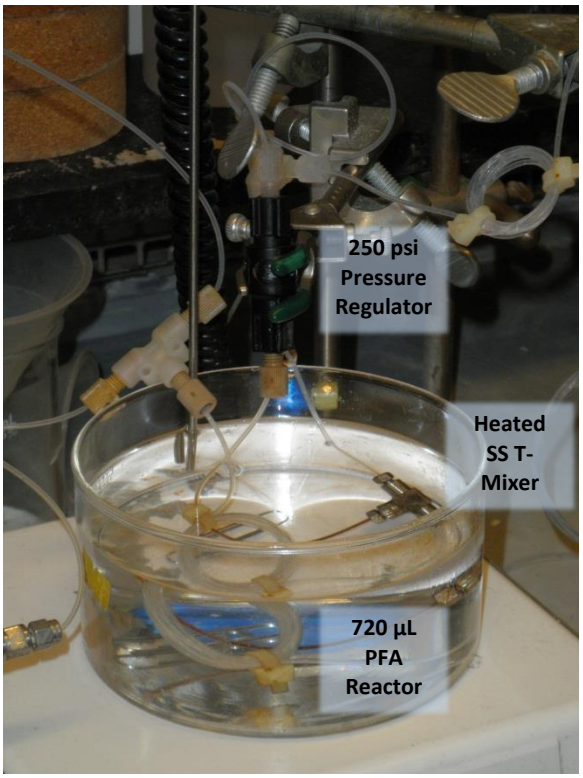
Cambridge, Massachusetts 02139, USA

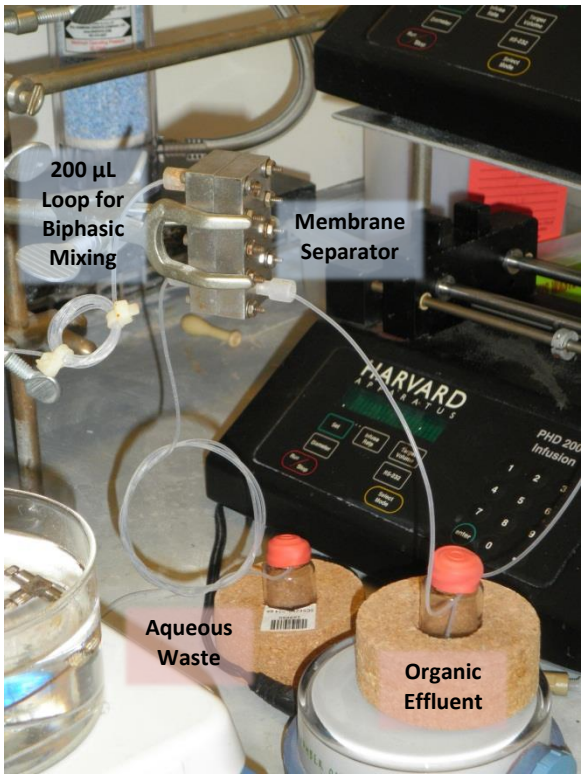
Contents

1) Reaction Set-up with Hexane Extraction and Precipitation of Diphenhydramine HCl:

Expanded View of Reactor:



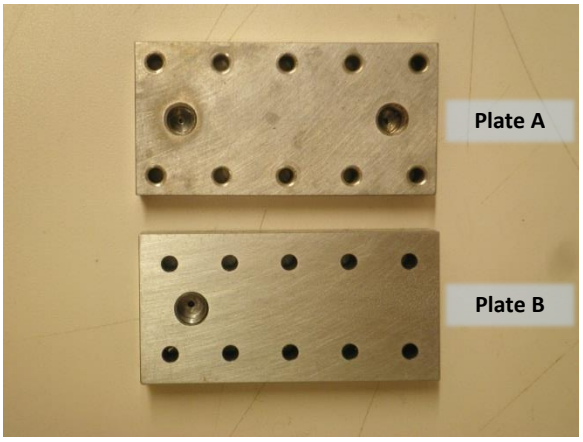
Expanded View of Separator and Acid Addition:



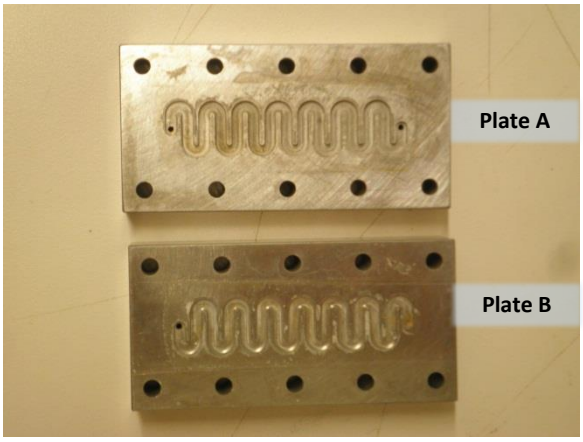
2) Photographic Illustration of Membrane Separator and Operation:

The separator employed was constructed from two stainless steel plates sandwiching a Zefluor membrane with 1.0 µM pores. Identical channels were etched into each stainless steel plate causing fluid to proceed through the path in a repeating U-shaped zig-zag pattern. The groove cut into each plate was 1 mm in depth, 2 mm wide, and had a total path length of 157 mm. One plate, designated as A, had two ports one at the beginning of the groove, the other at the end of the groove. The other plate, designated as B, had only one port which was at the end of the groove. A pressure differential was established across the membrane by placing different lengths of tubing at the exit ports. A 100 cm segment of tubing (0.03 in inner diameter) was placed at Exit Port A, and a 30 cm segment of tubing (0.03 in inner diameter) was placed at Exit Port B. The biphasic mixture entered the separation channel from the entry port on Plate A. The aqueous layer, after passing through the channel, exited the separator without wetting the Zefluor membrane through a port at the end of the groove also on Plate A. The organic layer wet the Zefluor membrane upon passing through the separation channel, and exited the extraction chamber through a port at the end of the groove on Plate B.

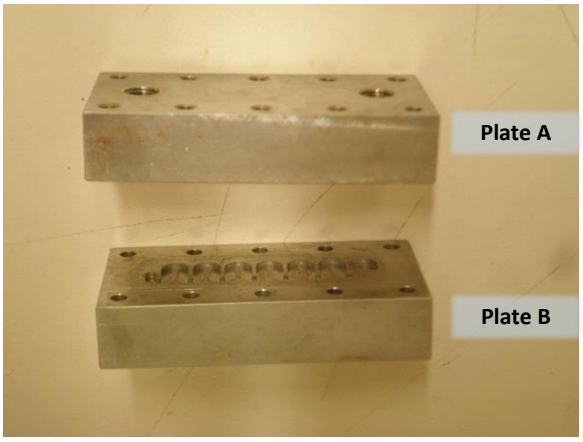
Exterior face blocks with inlet/outlet ports:



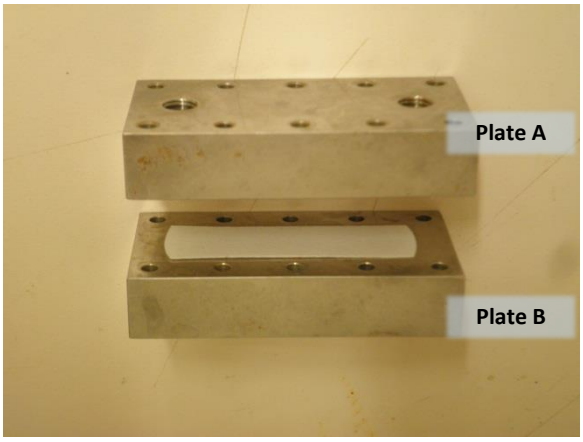
Interior solvent channel:



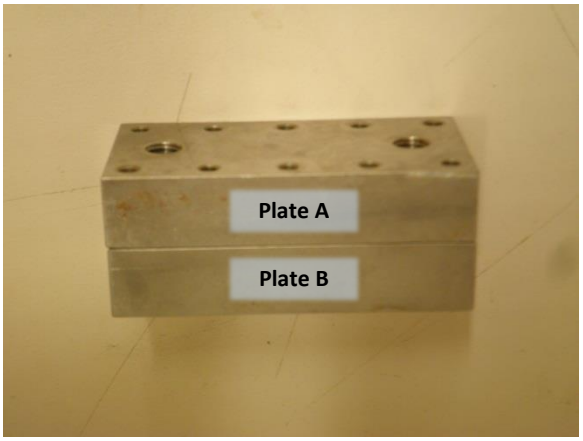
Symmetric channels aligned:



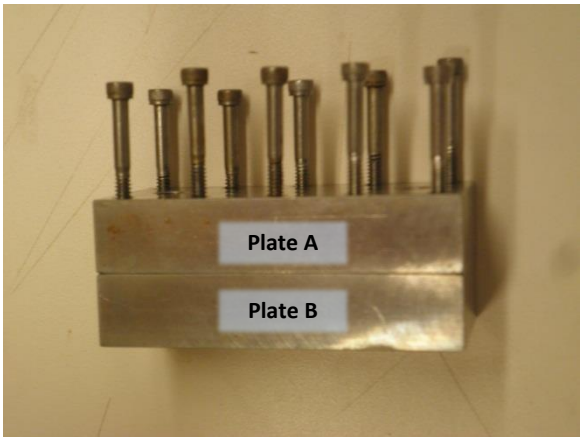
Zefluor membrane inserted:



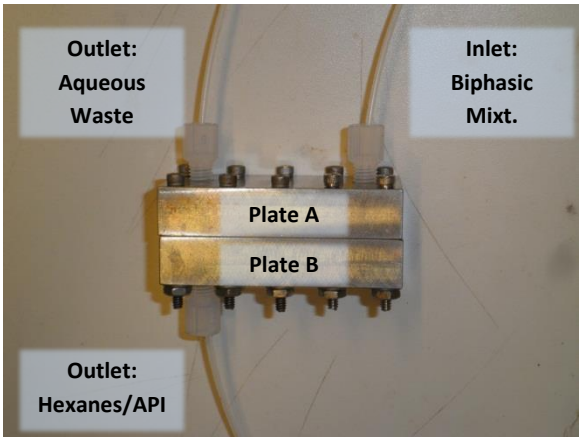
Stainless steel blocks sandwiched:



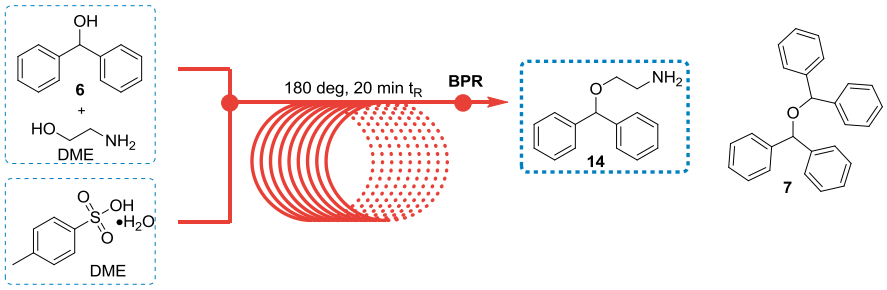
Blocks fastened via screws on perimeter:



Membrane separator assembled, with tubing:



3) Benzhydrol as a Precursor to Diphenhydramine



SI Table 1: Formation of ether *via* acid-promoted condensation.

Entry	equiv DMAE	BPR (psi)	14 : 6 : 7
1	2	-	3 : 96 : 1
2	2	75	73 : 8 : 19
3[a]	2	250	21 : 42 : 37
4	1	75	37 : 10 : 43
5	3	75	0 : 100 : 0

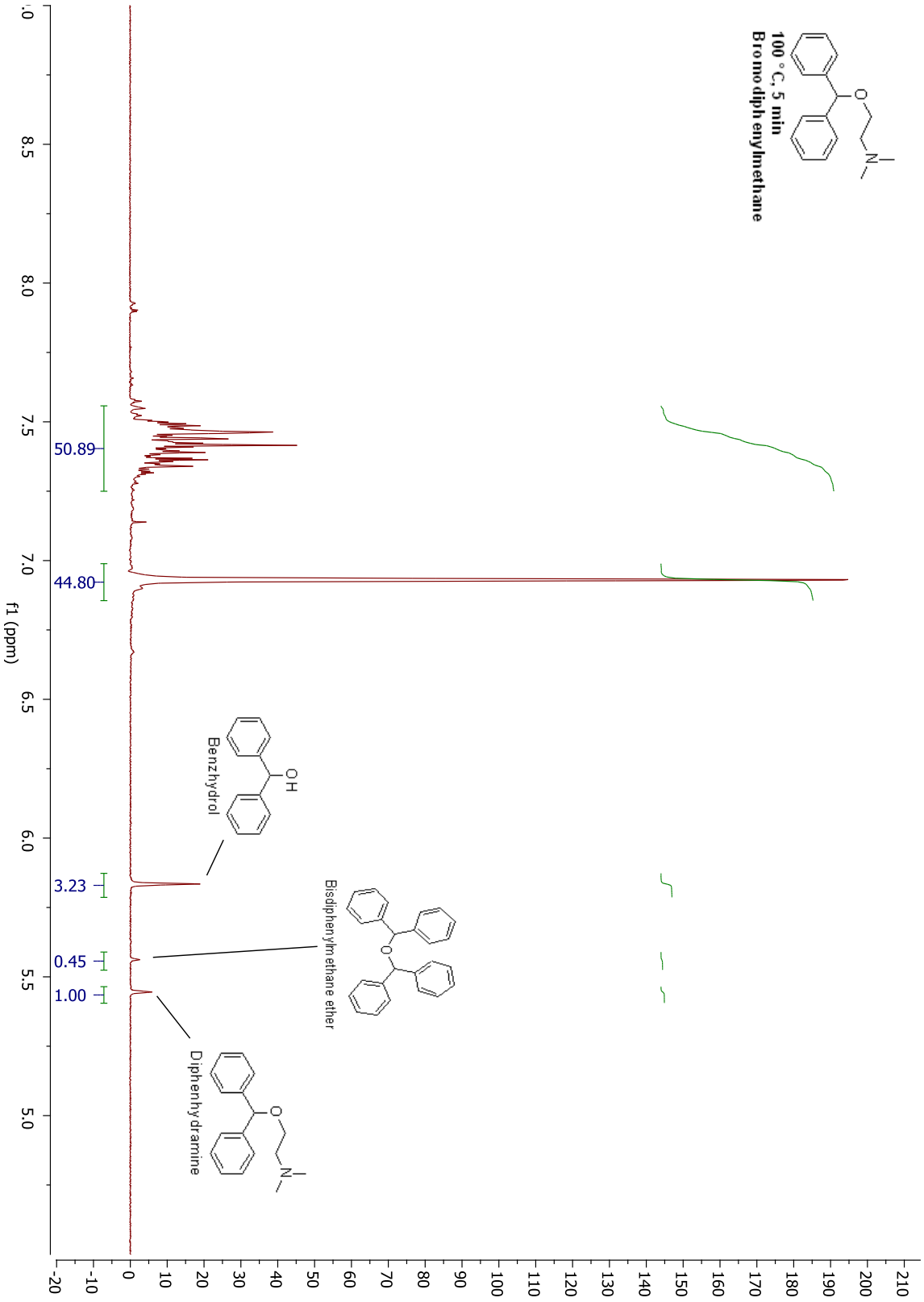
a) Reaction mixture becomes biphasic

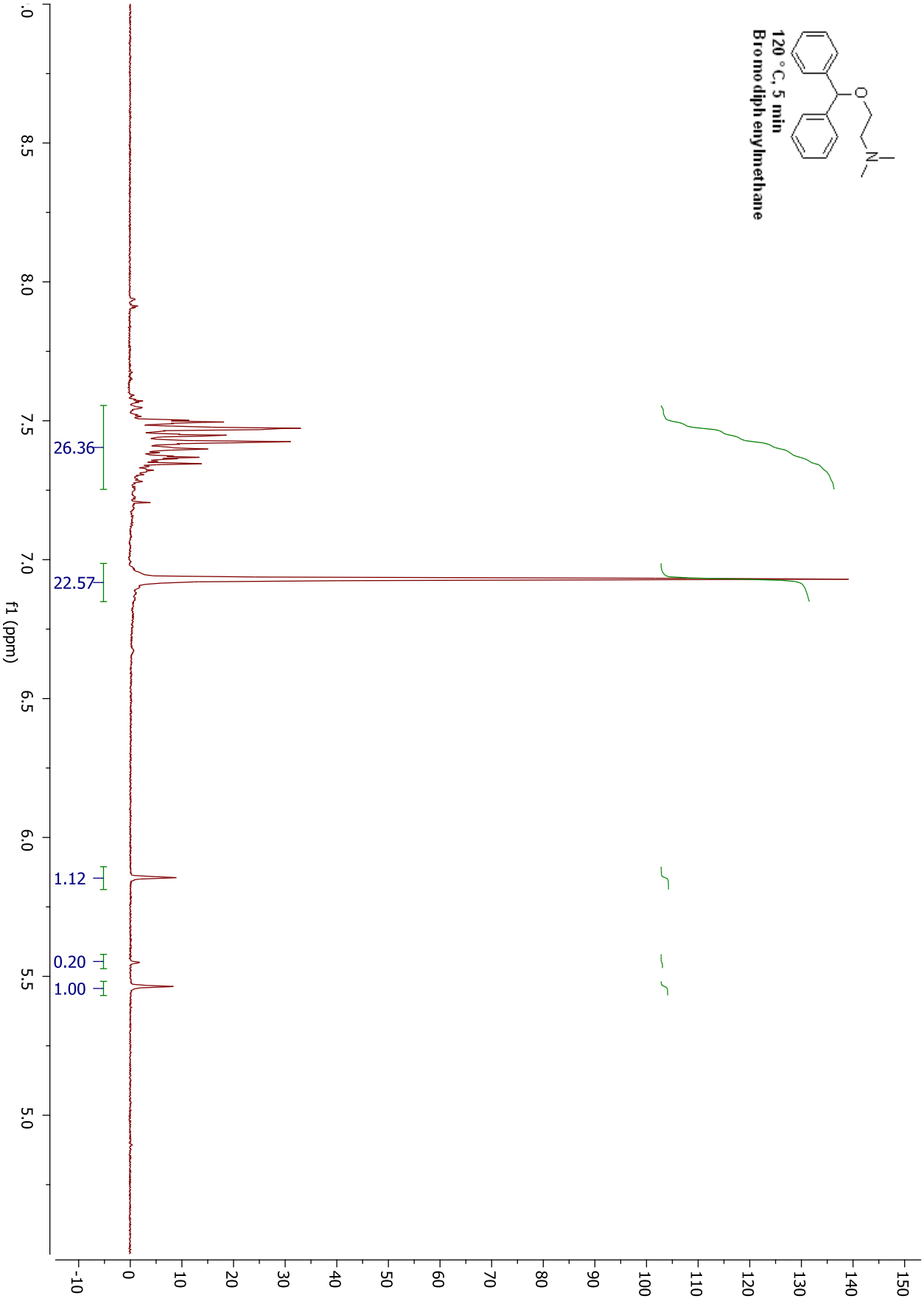
2-(benzhydryloxy)ethanamine:

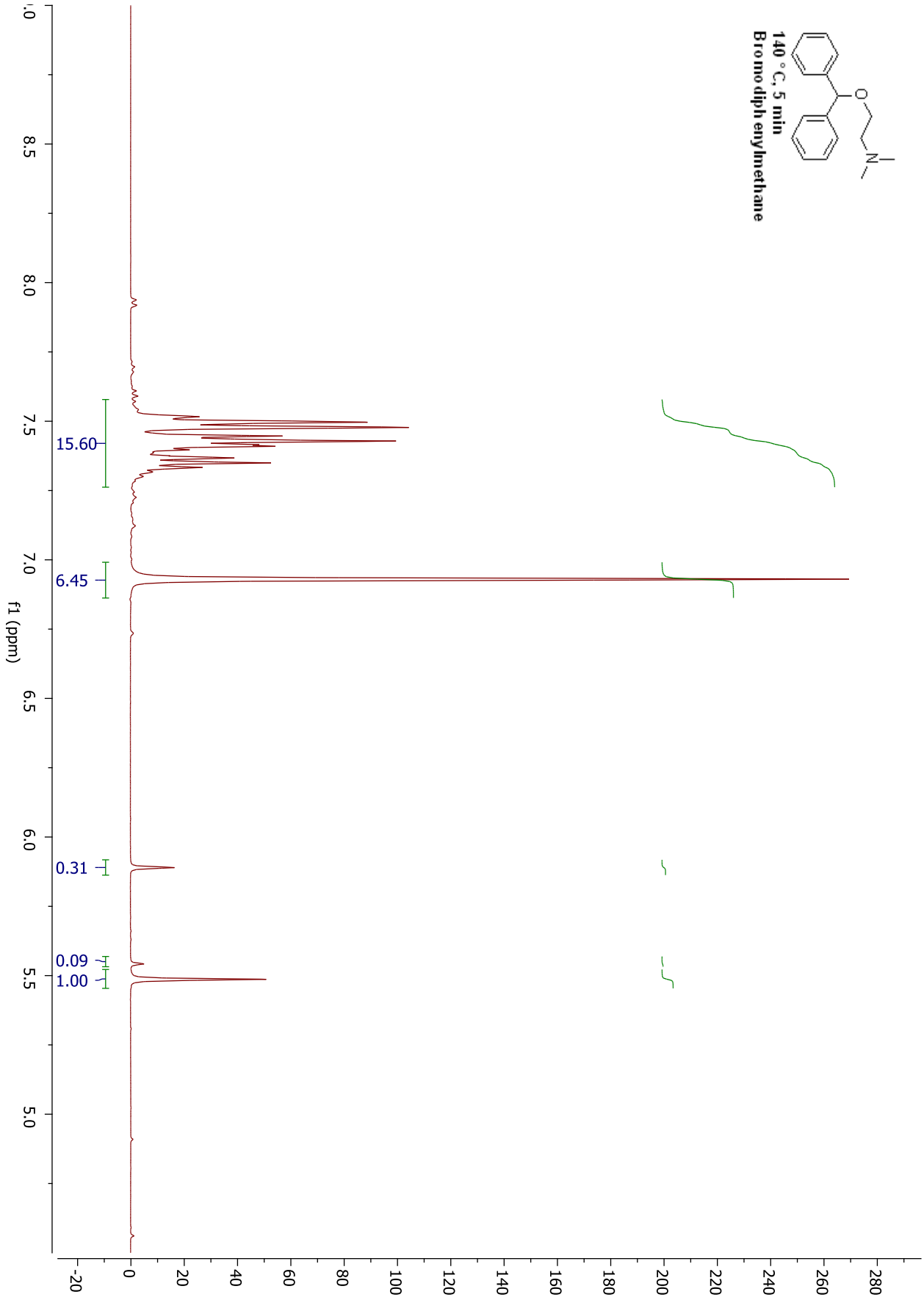
0.184 g (1.00 mmol) of benzhydrol was comined with 120 µL (2.00 mmol) of 2-aminoethanol. To these reagents was added DME to make a 2.5 mL solution which was 0.40 M in benzhydrol. A separate solution was made combining 0.418 g (2.20 mmol) of *p*-toluene sulfonic acid with DME to make 2.5 mL of a 0.88 M solution. A micro-reactor was constructed from high-purity PFA tubing (26.4 cm, 0.03" i.d.), and a 120 µL loop was made to serve as the reactor. The solutions were loaded into separate stainless steel syringes, connected by high-purity PFA tubing of the same dimensions and a PEEK T-mixer (0.02" i.d.) leading to the reactor. A back-pressure regulator (IDEX Health) was attached to the end of the reactor coil to prevent solvent boiling. The reactor coil was placed in a high-temperature oil bath heated to 180 °C, and both solutions were transported by a syringe pump (Harvard Apparatus PhD Ultra) at 3 µL/min giving a residence time of 20 min. After passing an initial volume of 360 µL (3 residence), sample was collected in a scintillation vial for 20 min. The sample was treated with saturated aqueous solution of sodium carbonate and extracted three times with ether. The combined organic fractions were dried with magnesium sulfate, filtered and concentrated. The crude sample was analyzed by ^{1}H NMR to determine the ratio of benzhydrol ether **6** to desired amine **14**. Proton NMR matched the values reported in literature.[1]

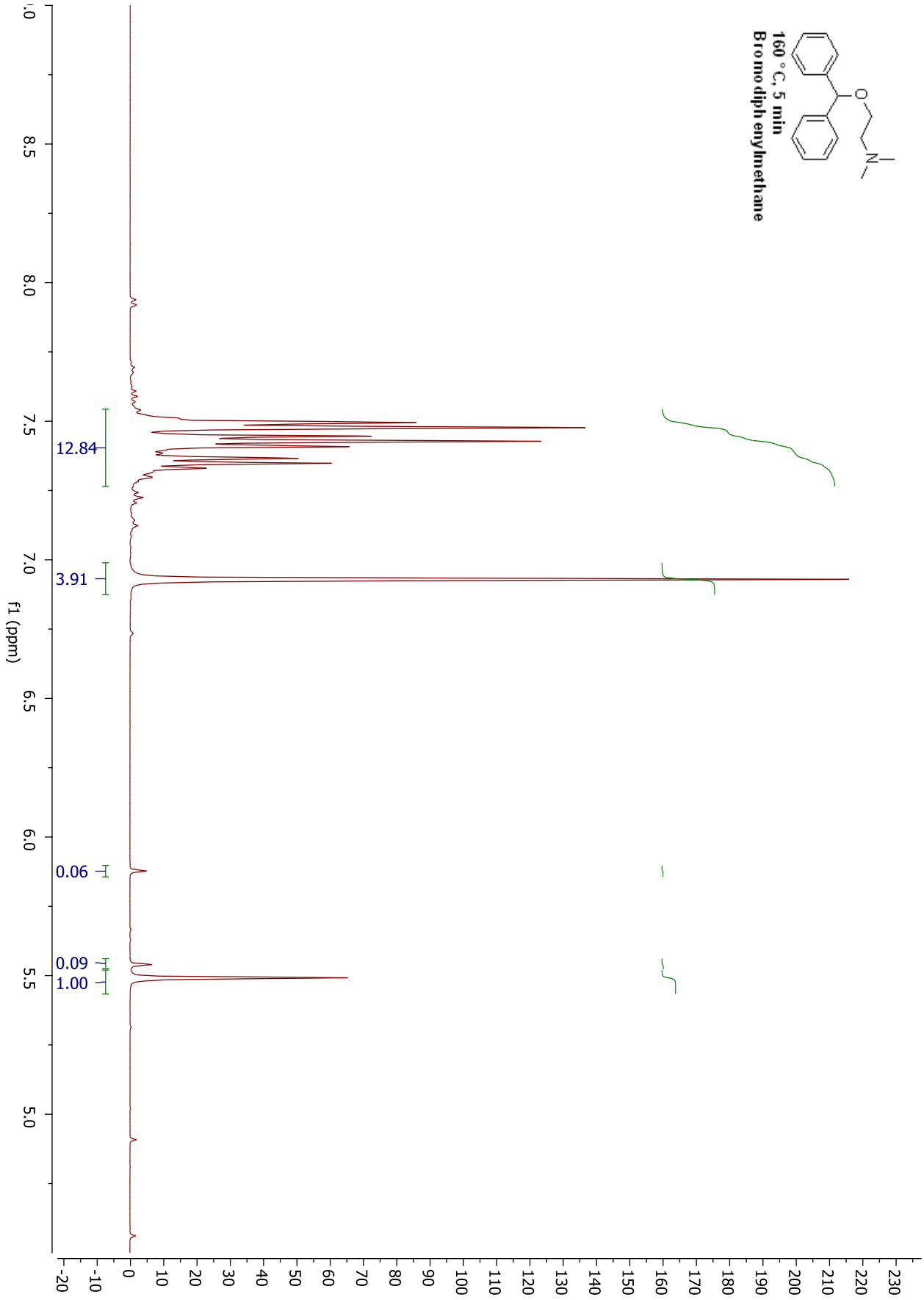
1) Corsano, S.; Strappaghetti, G.; Di Domenico, E.; Brasili, L.; Picchio, M. T. *Archiv. Pharm.* **1989**, *12*, 873-878.

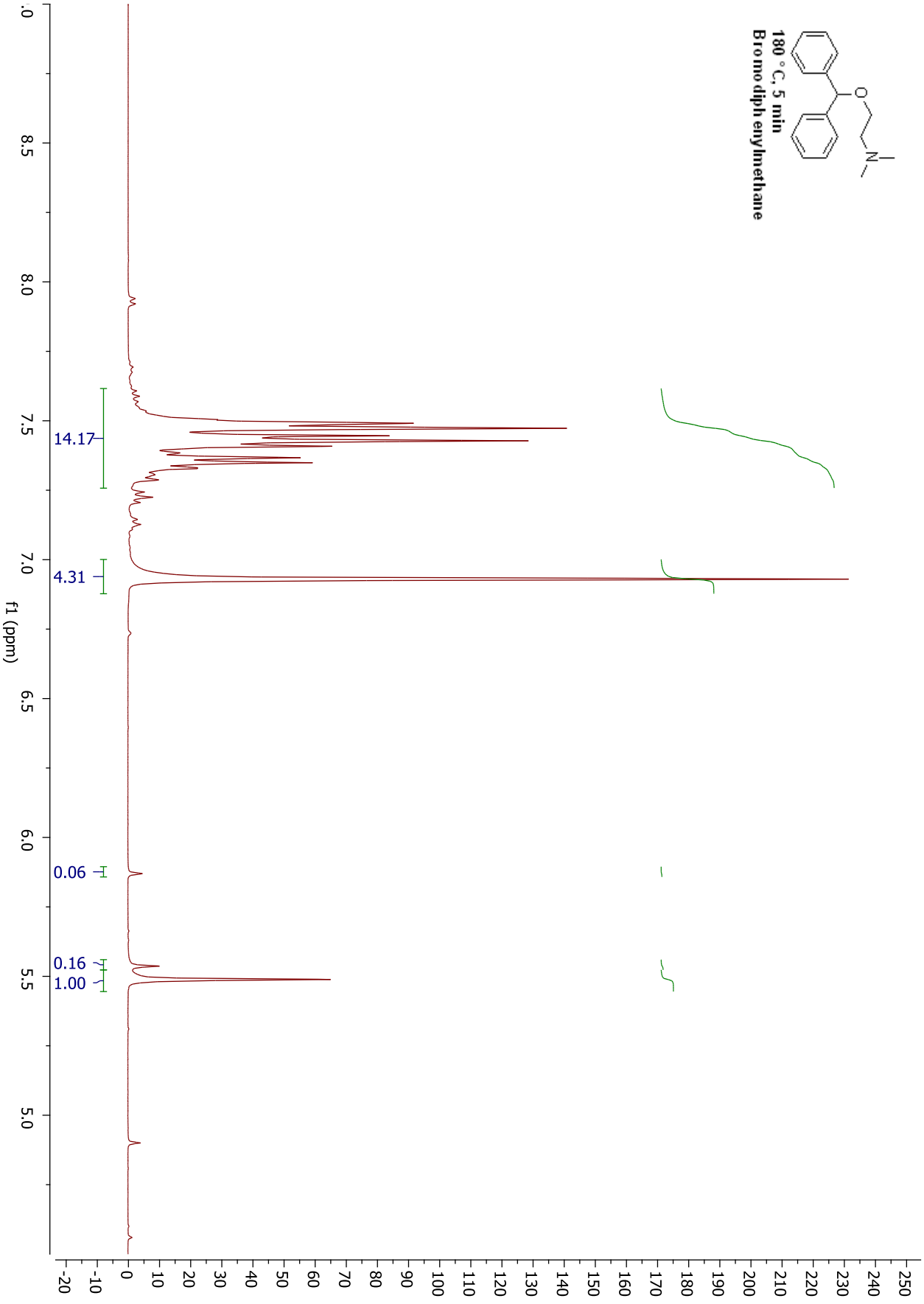
4) Spectra for Table 1:

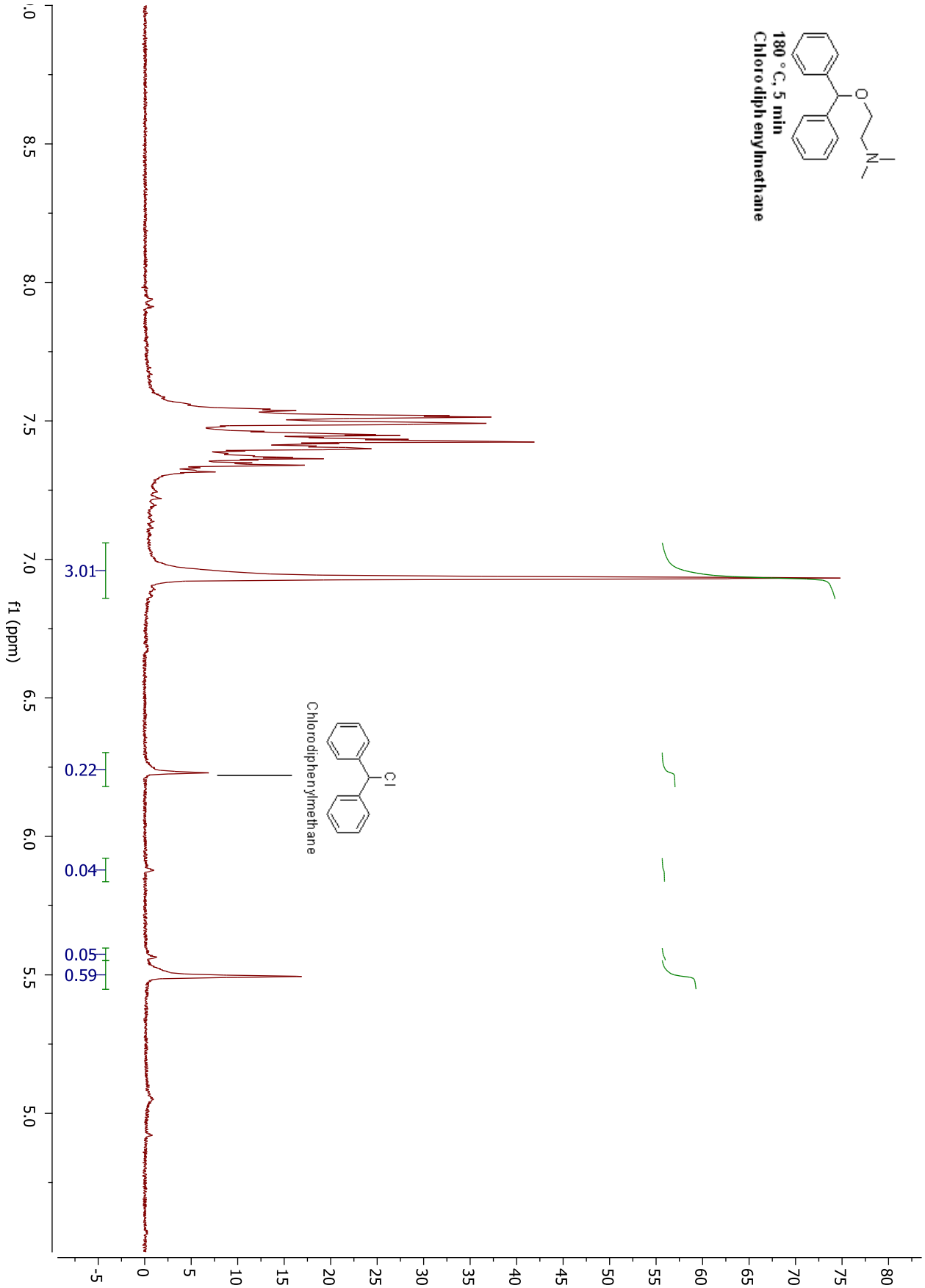


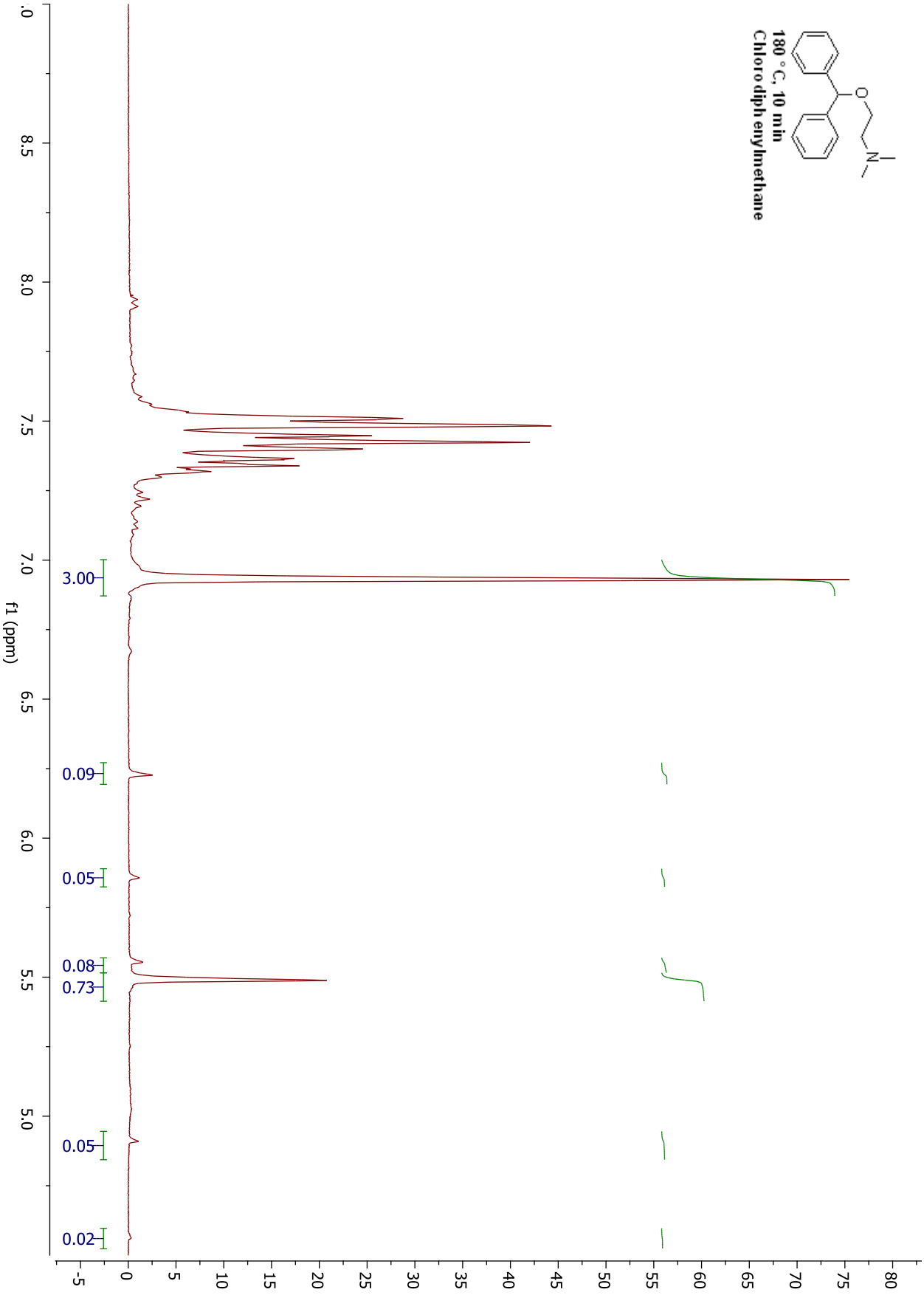


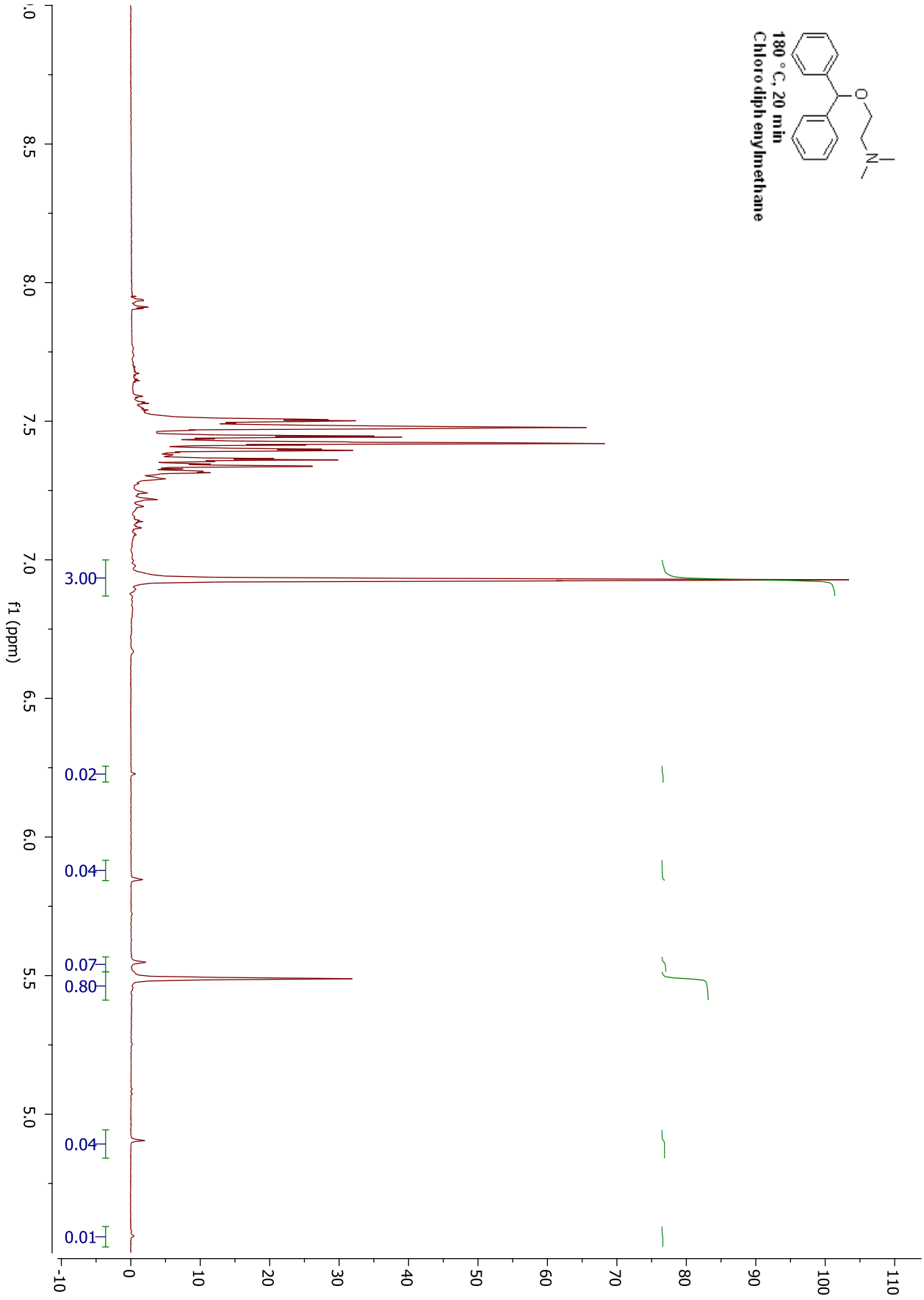




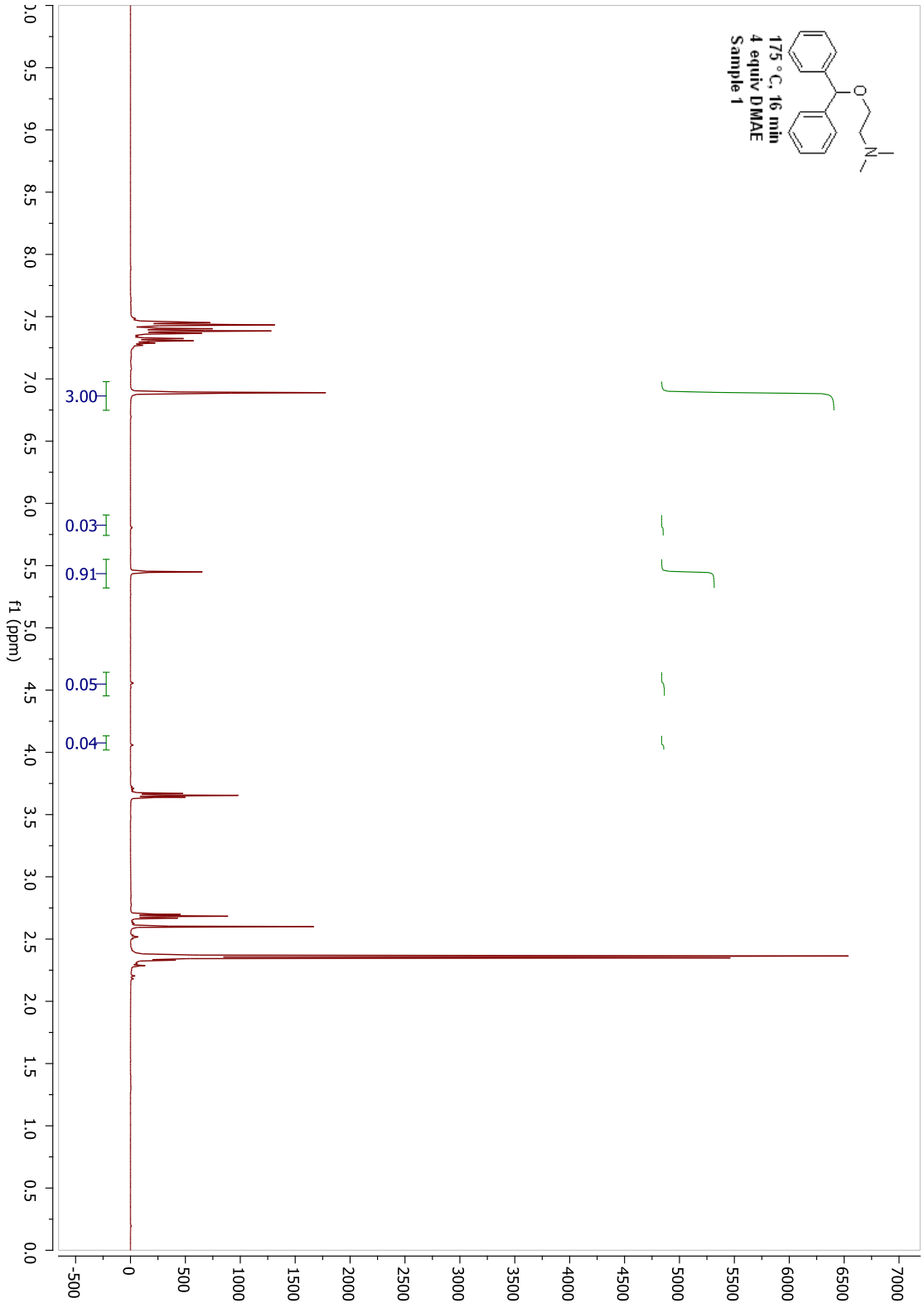


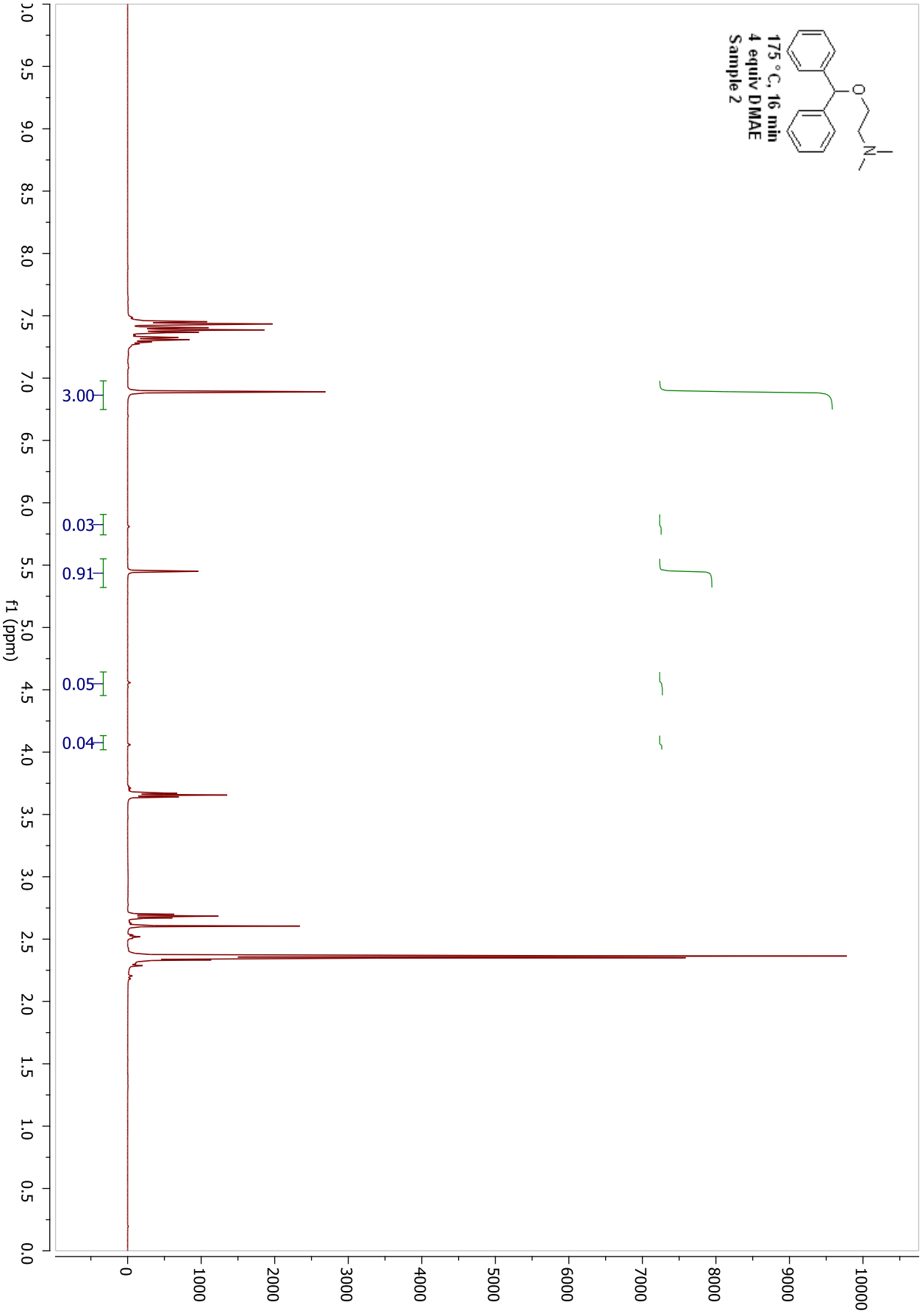


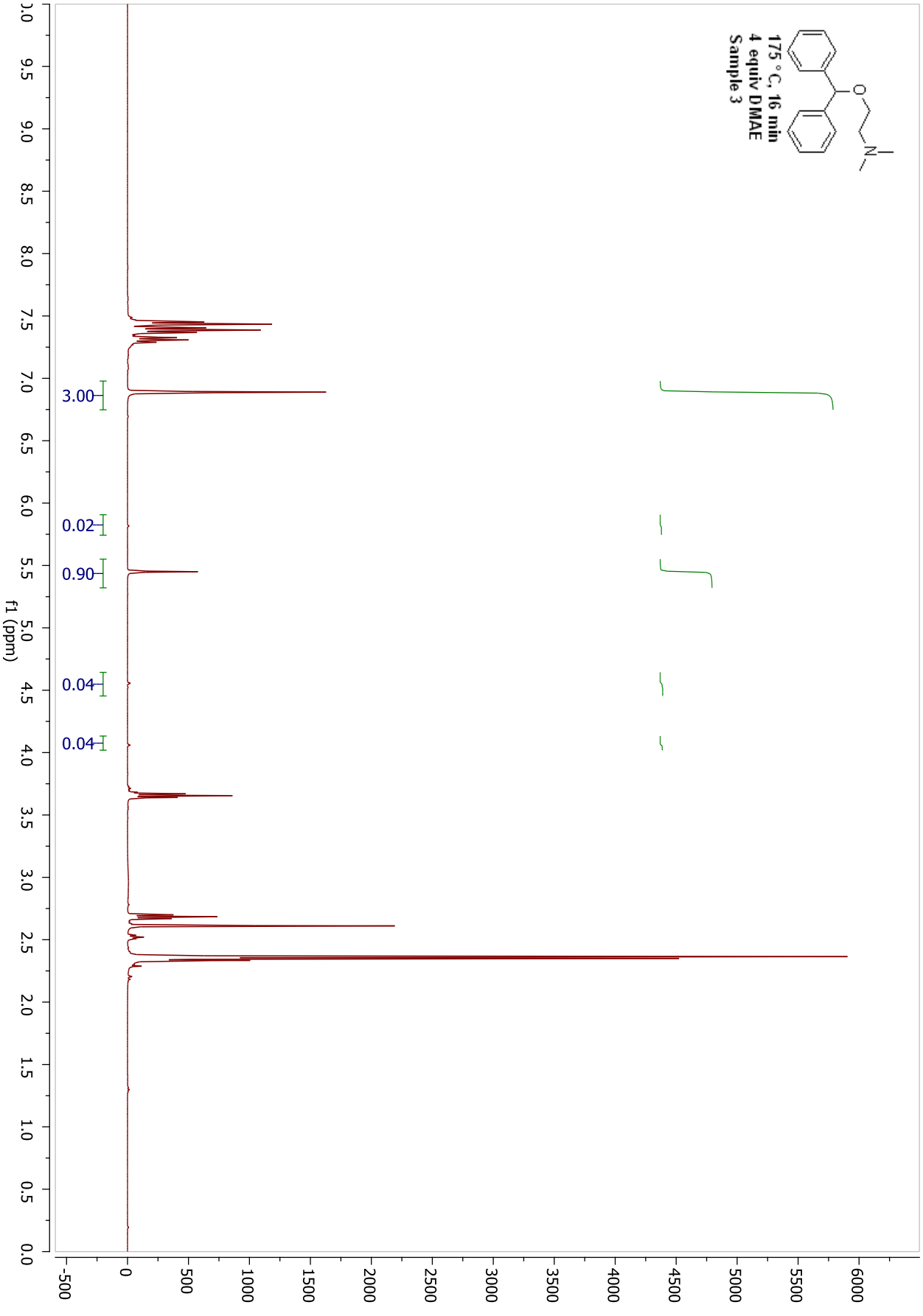


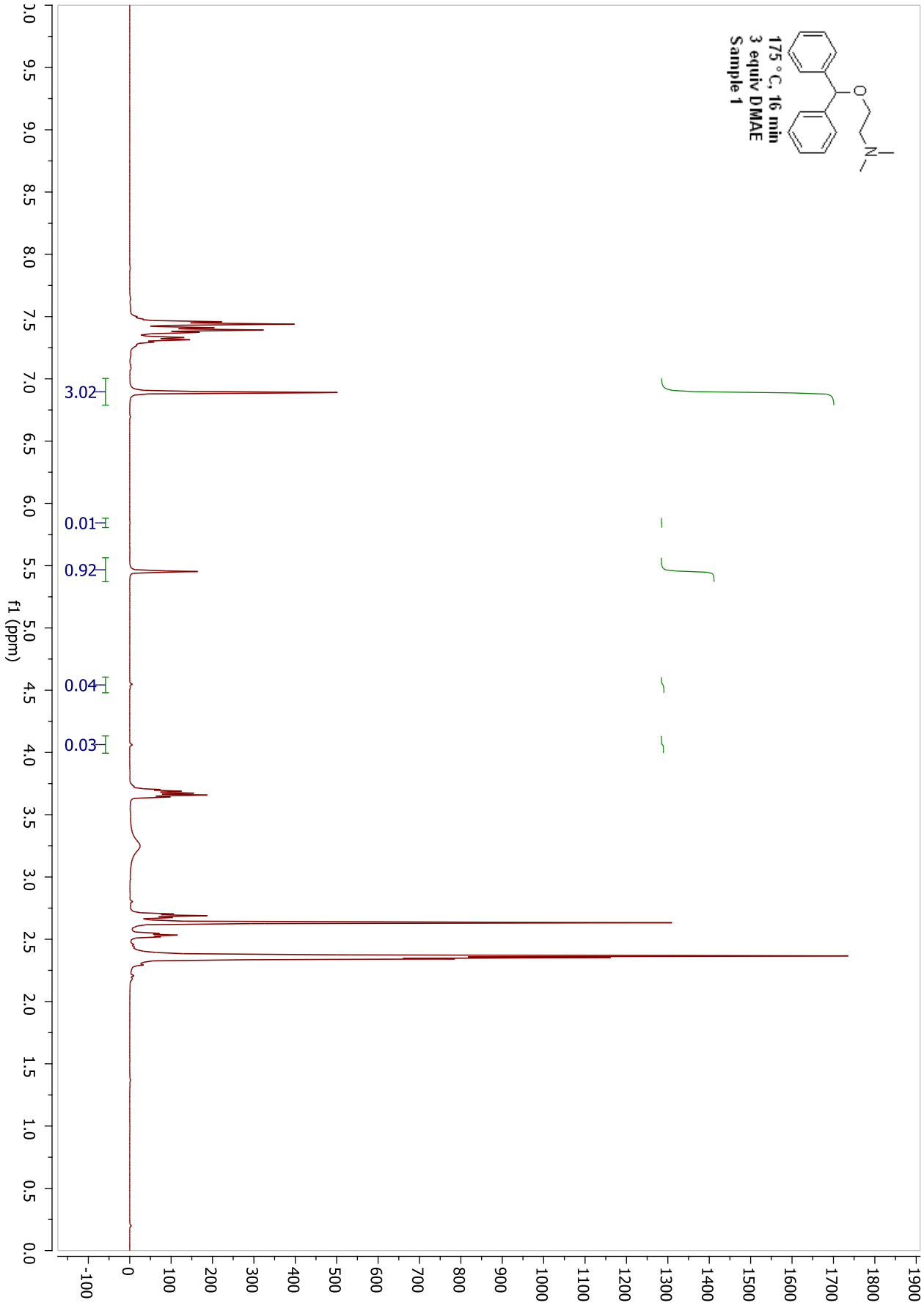


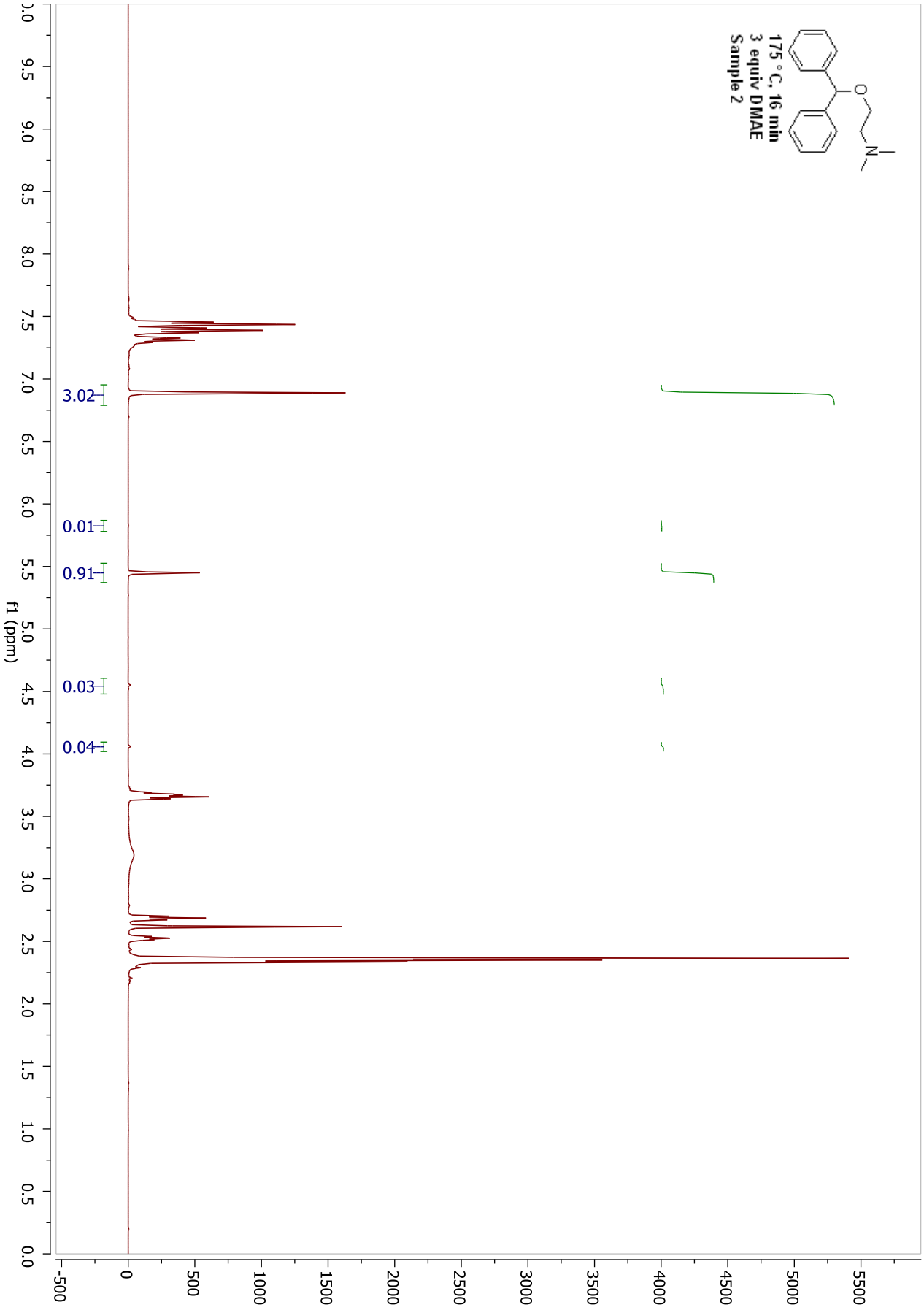
5) Spectra from Table 2:

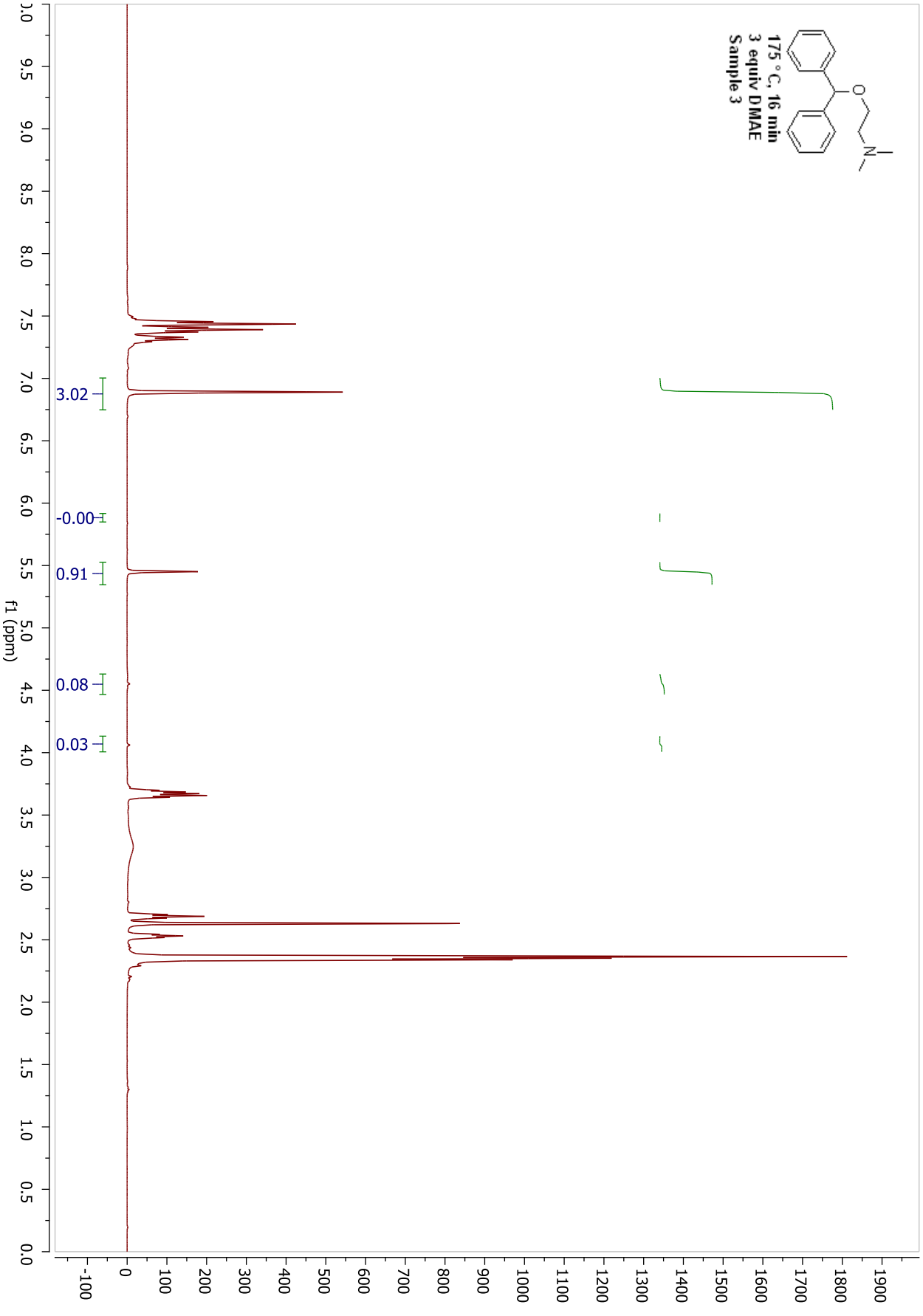


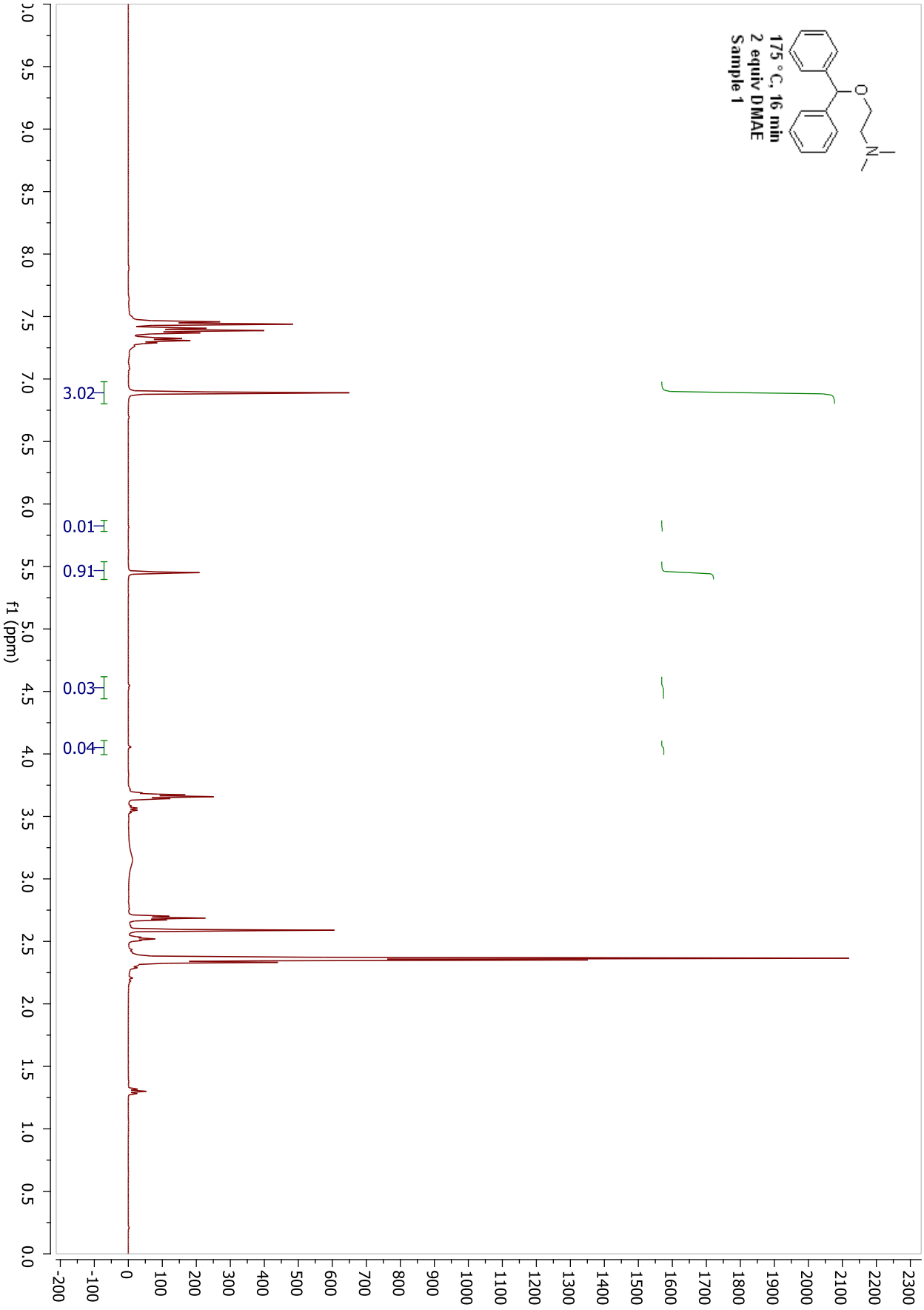


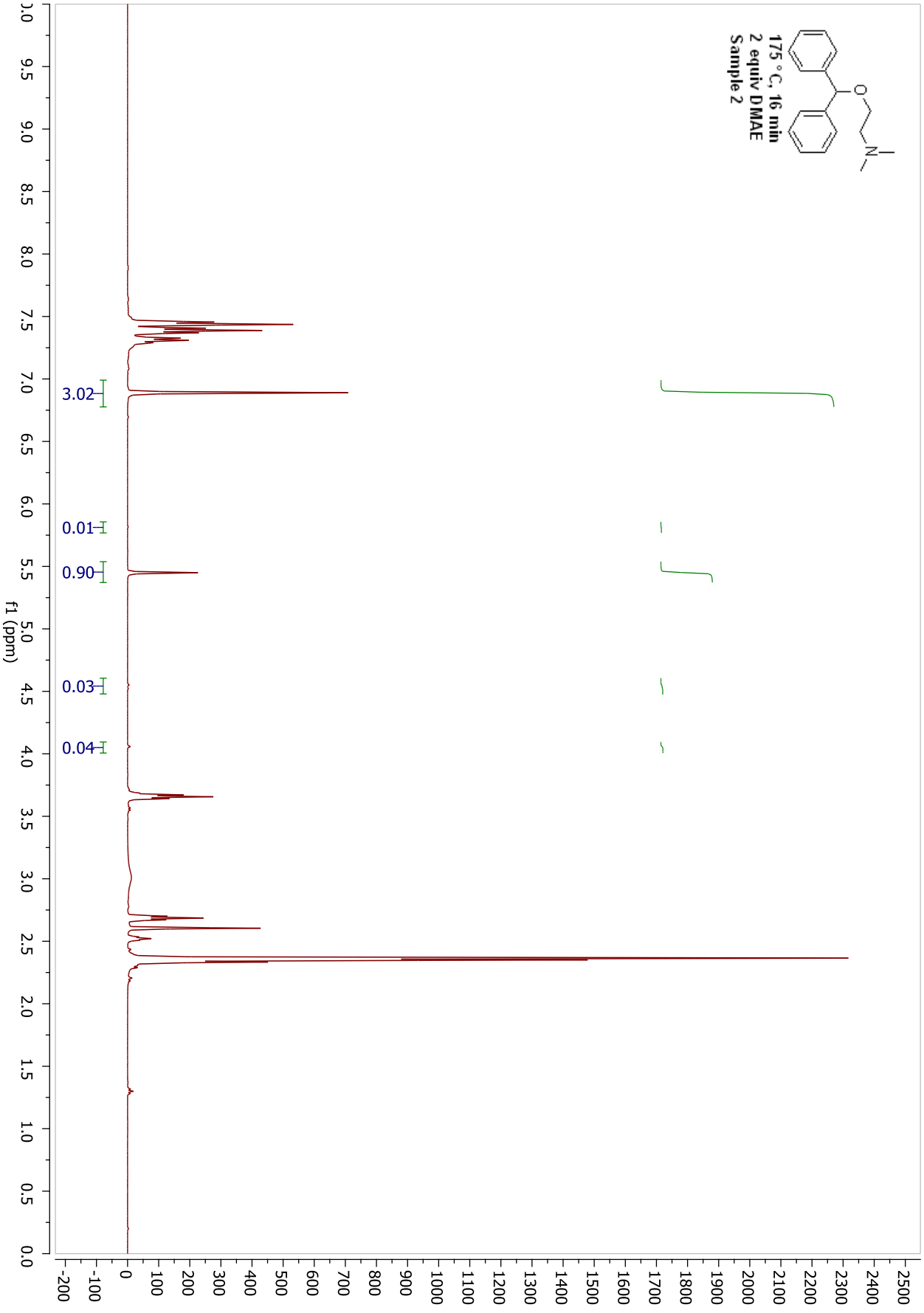


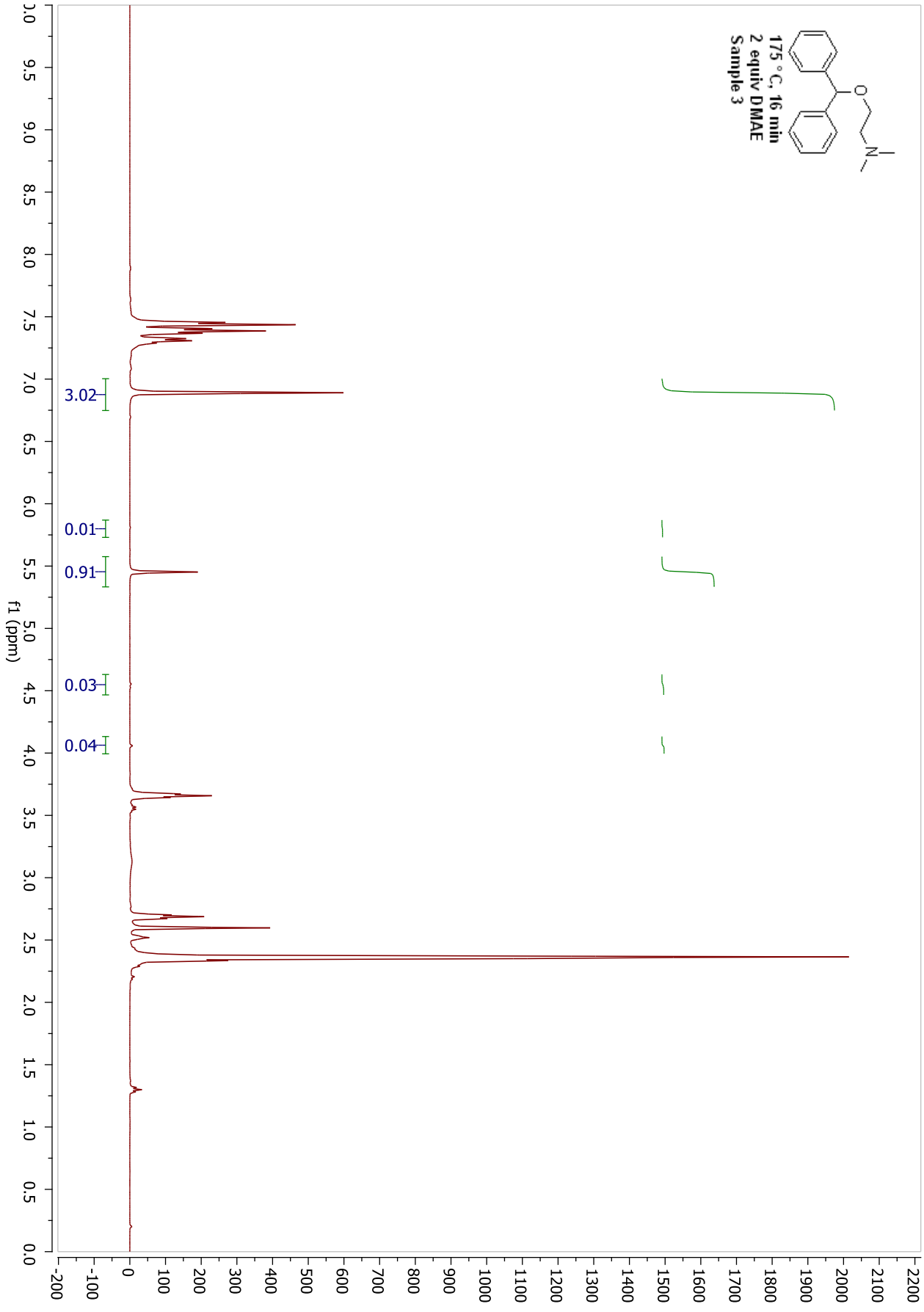


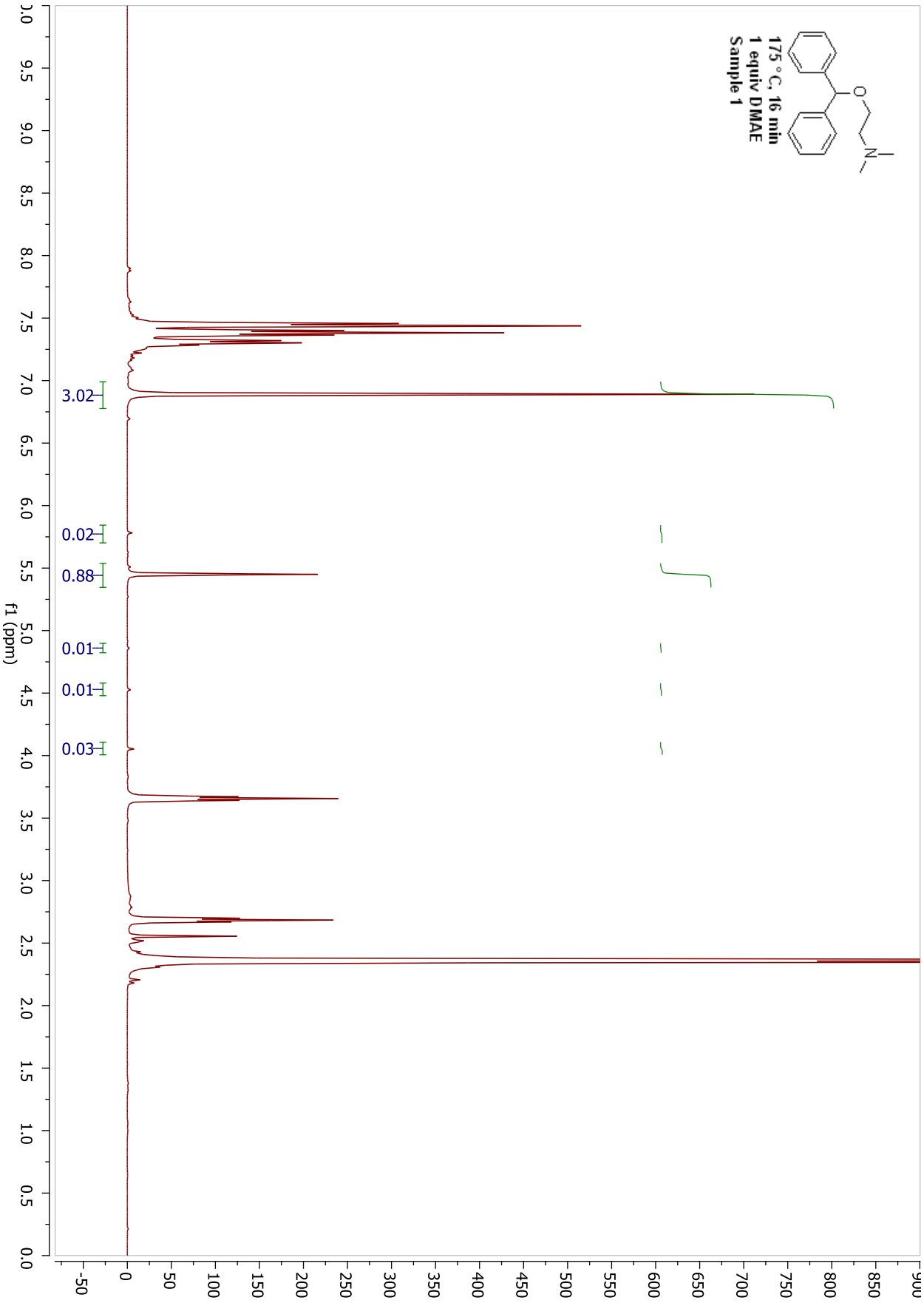


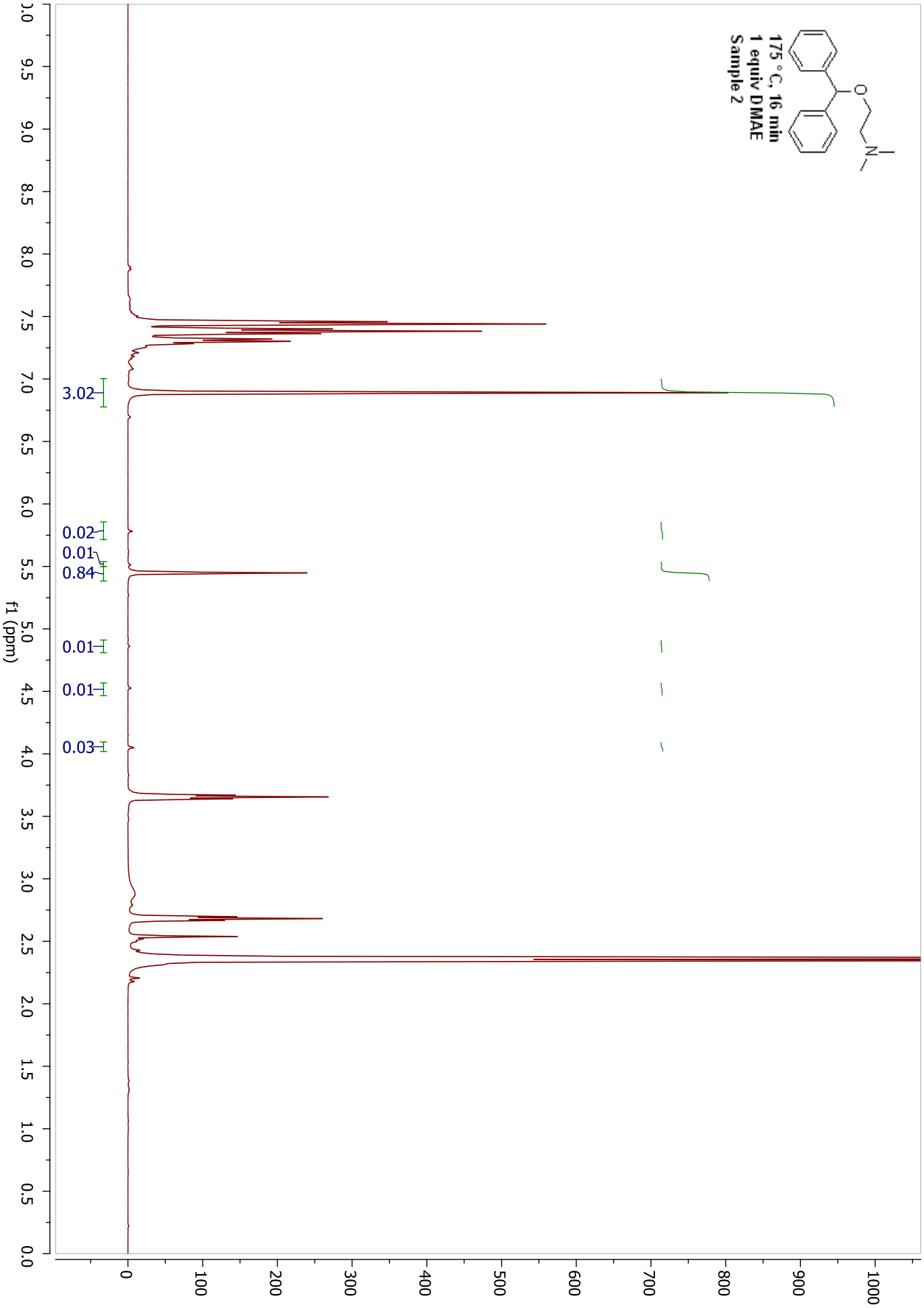


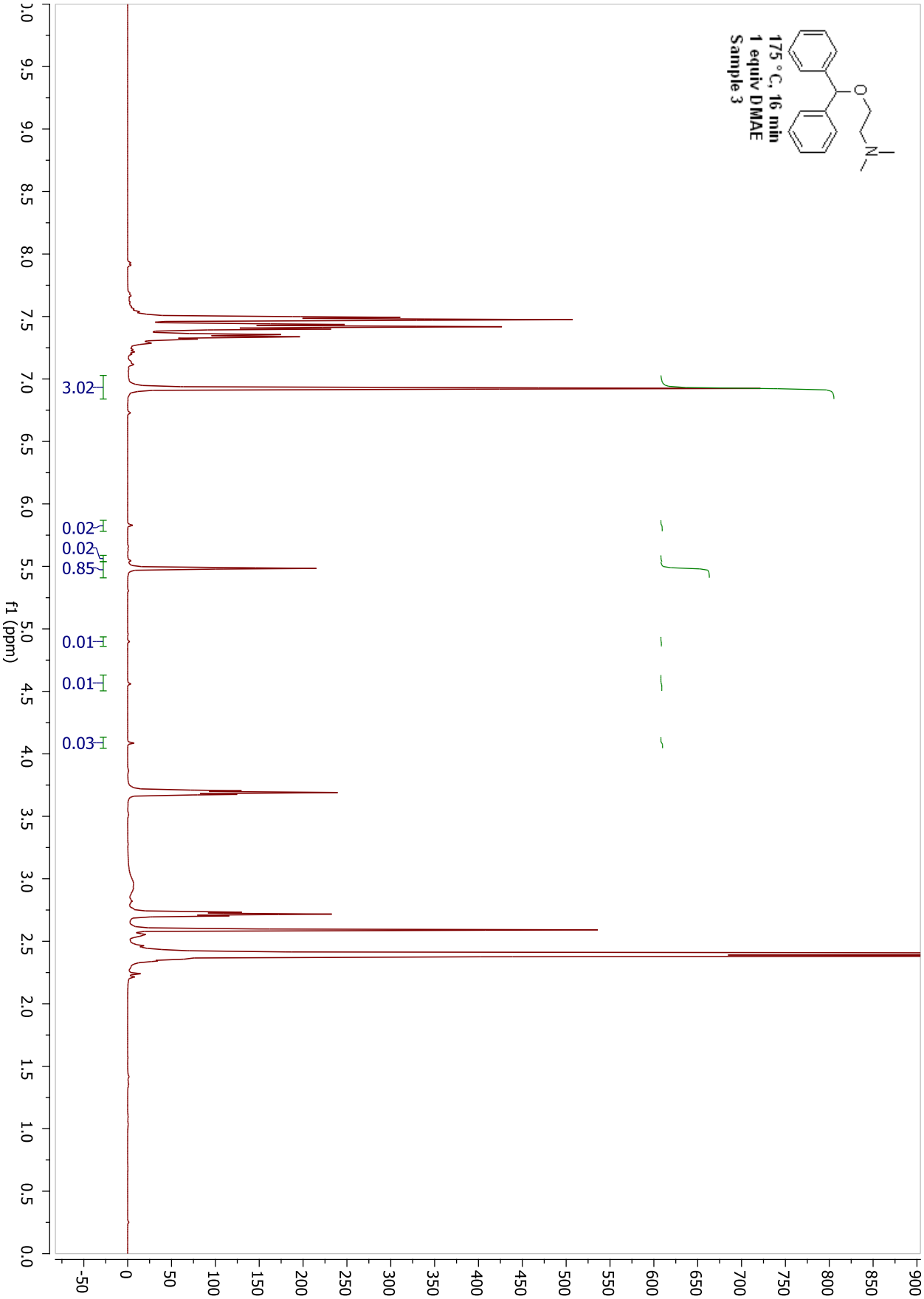


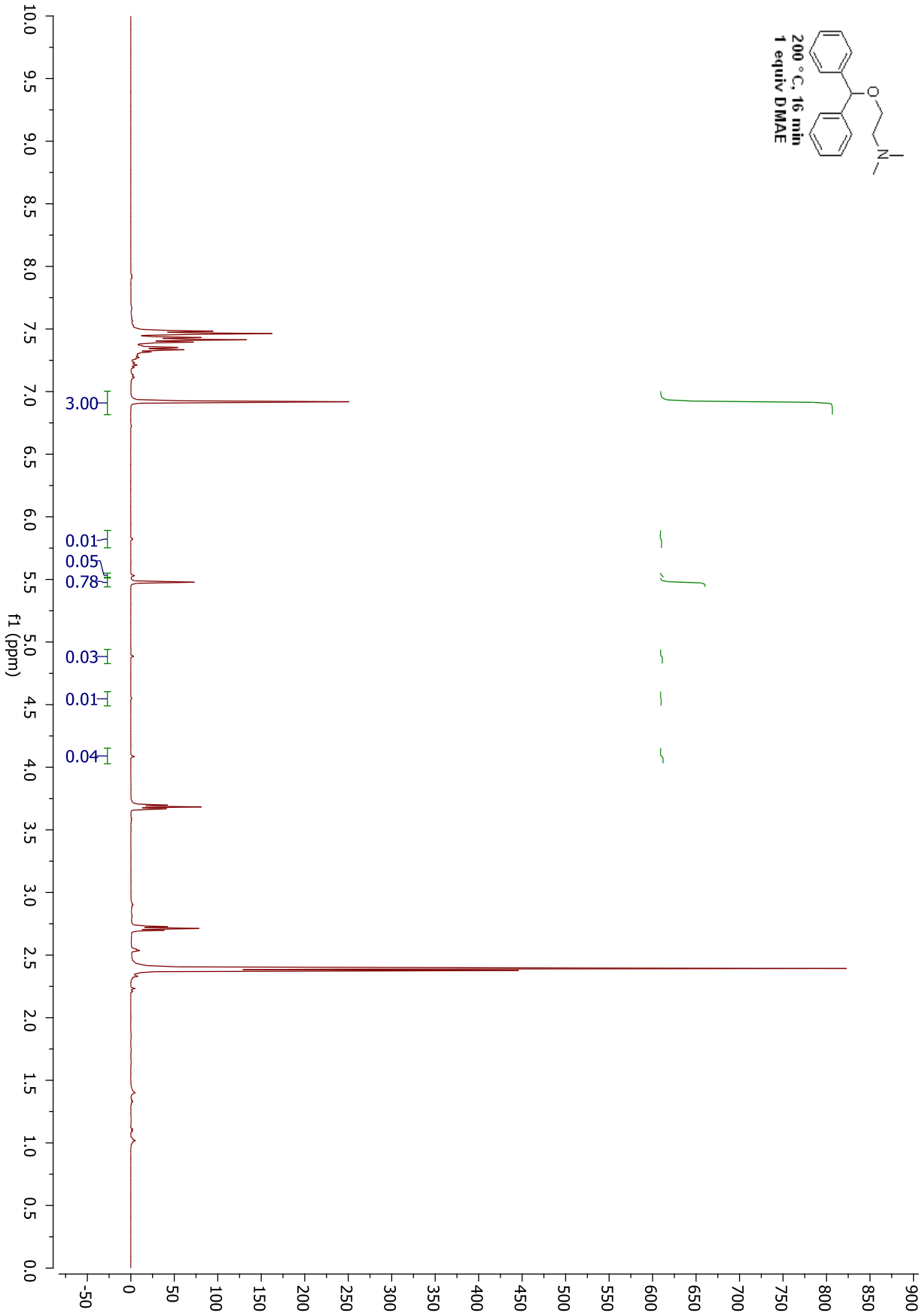


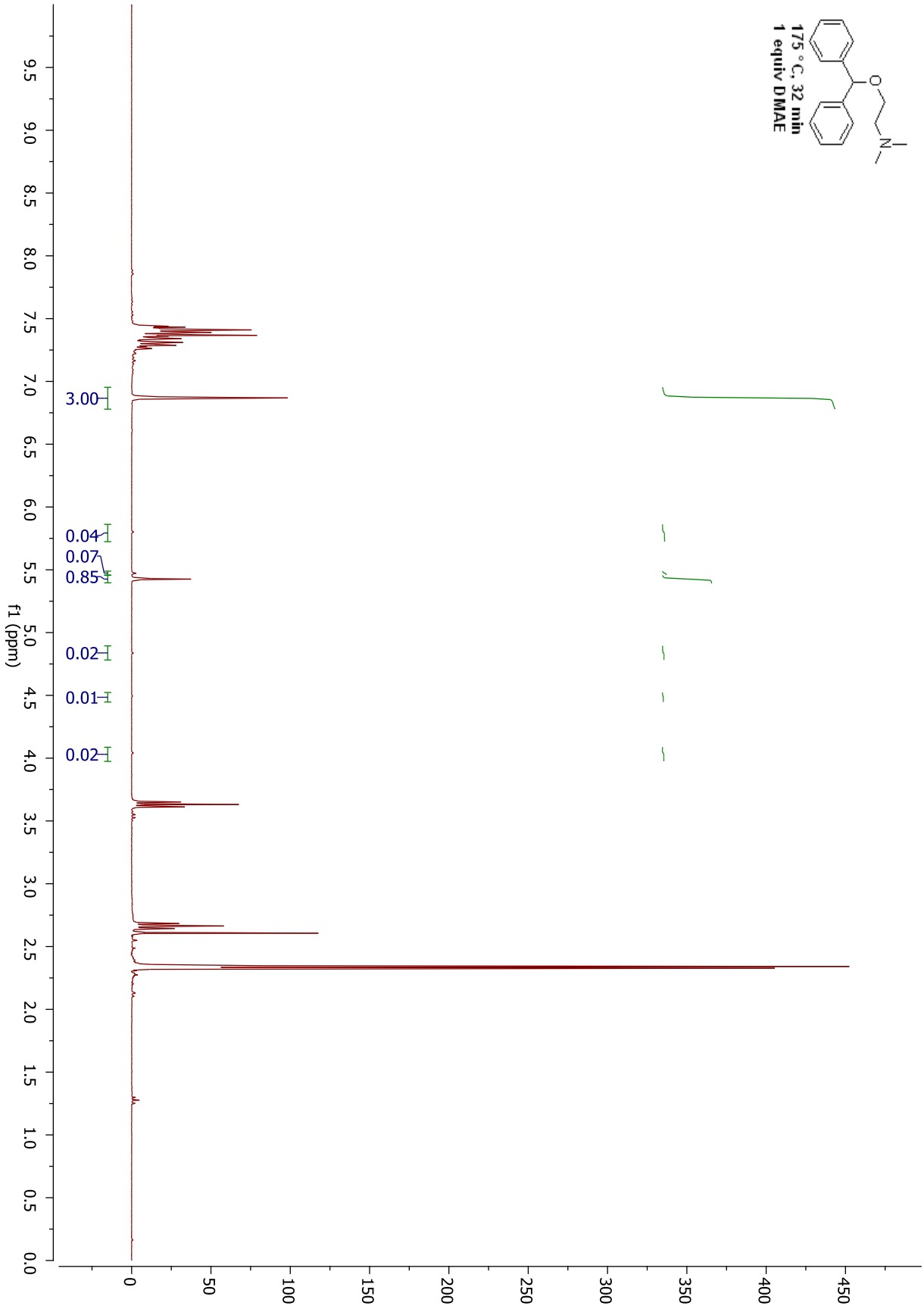












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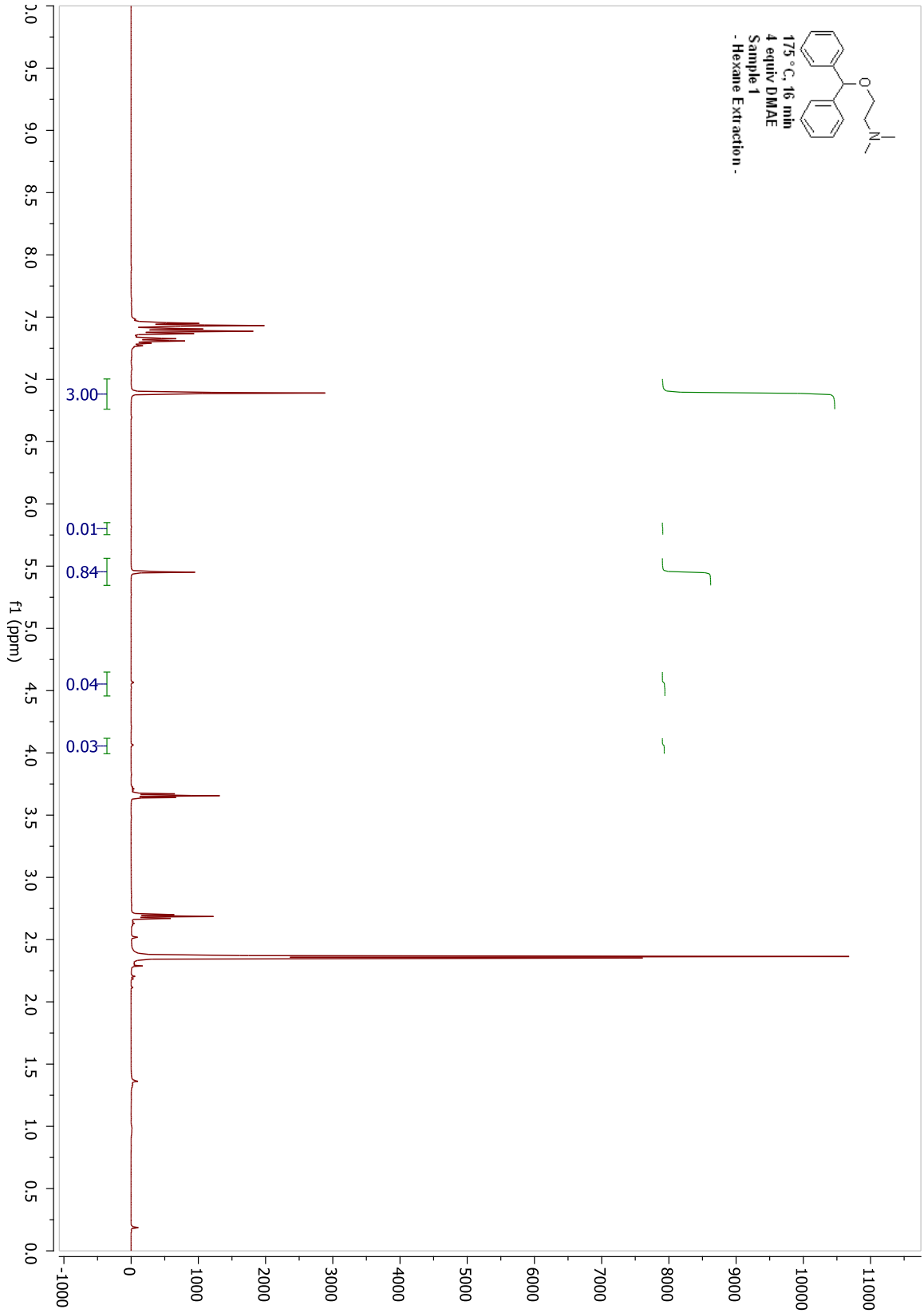

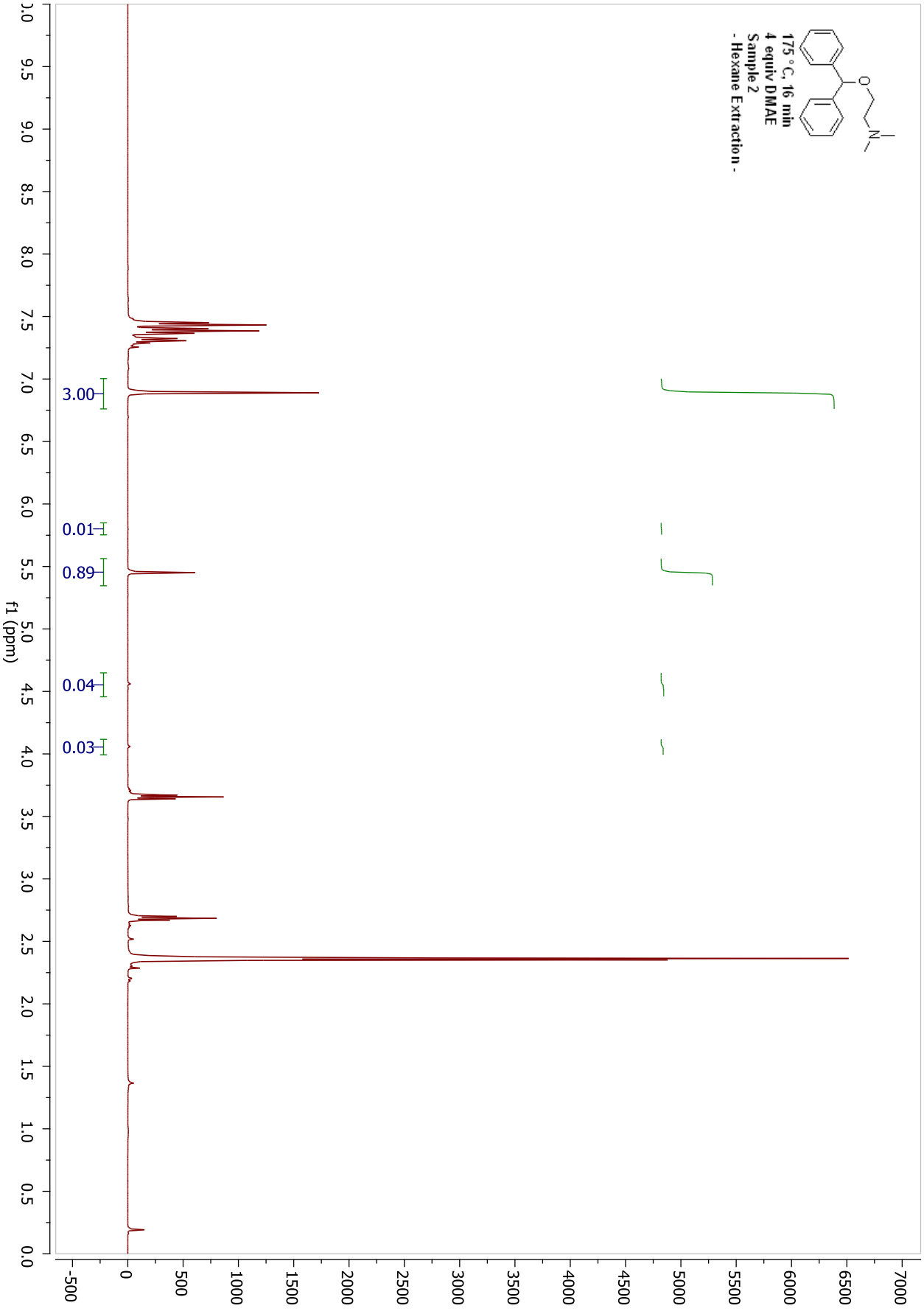

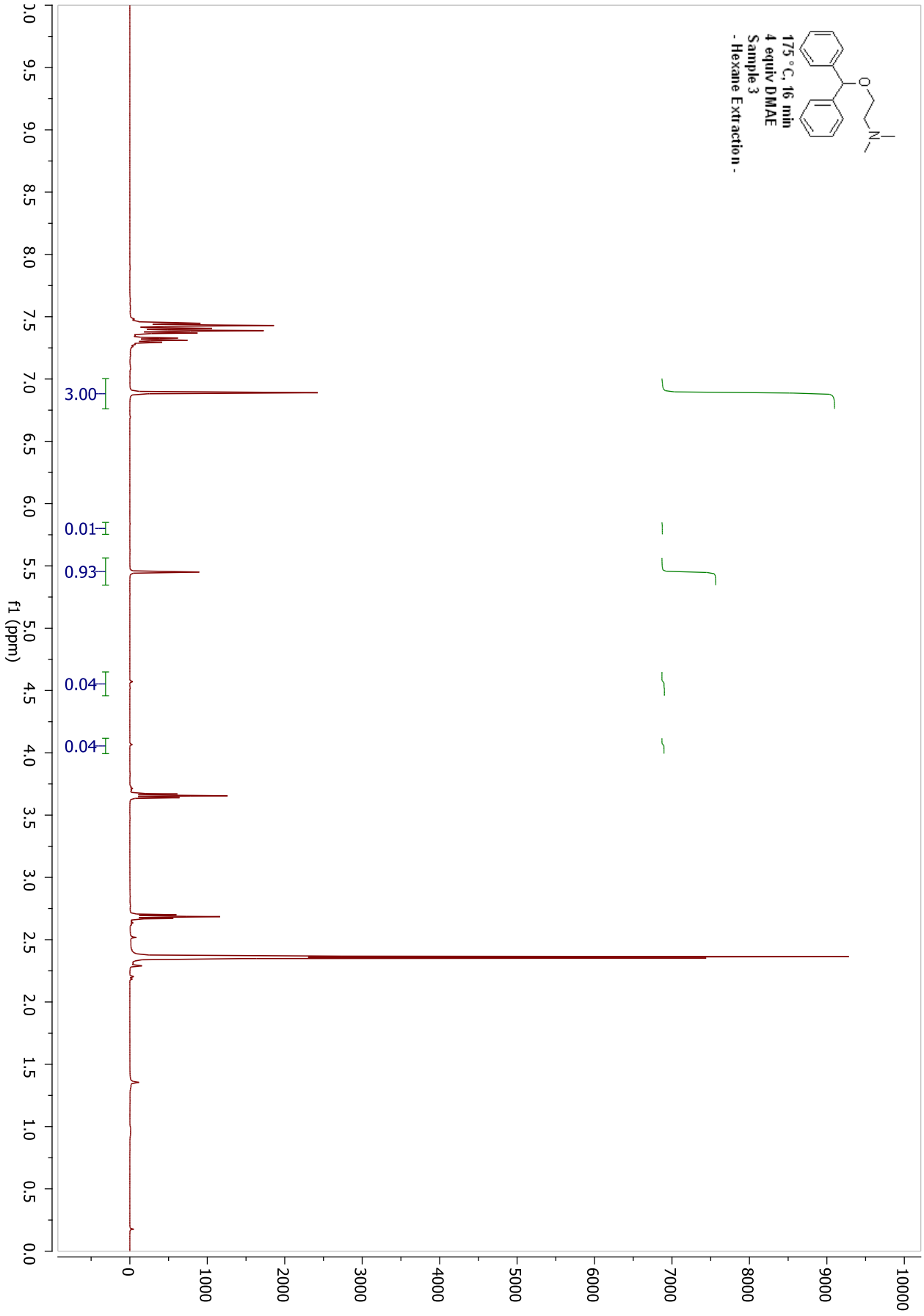

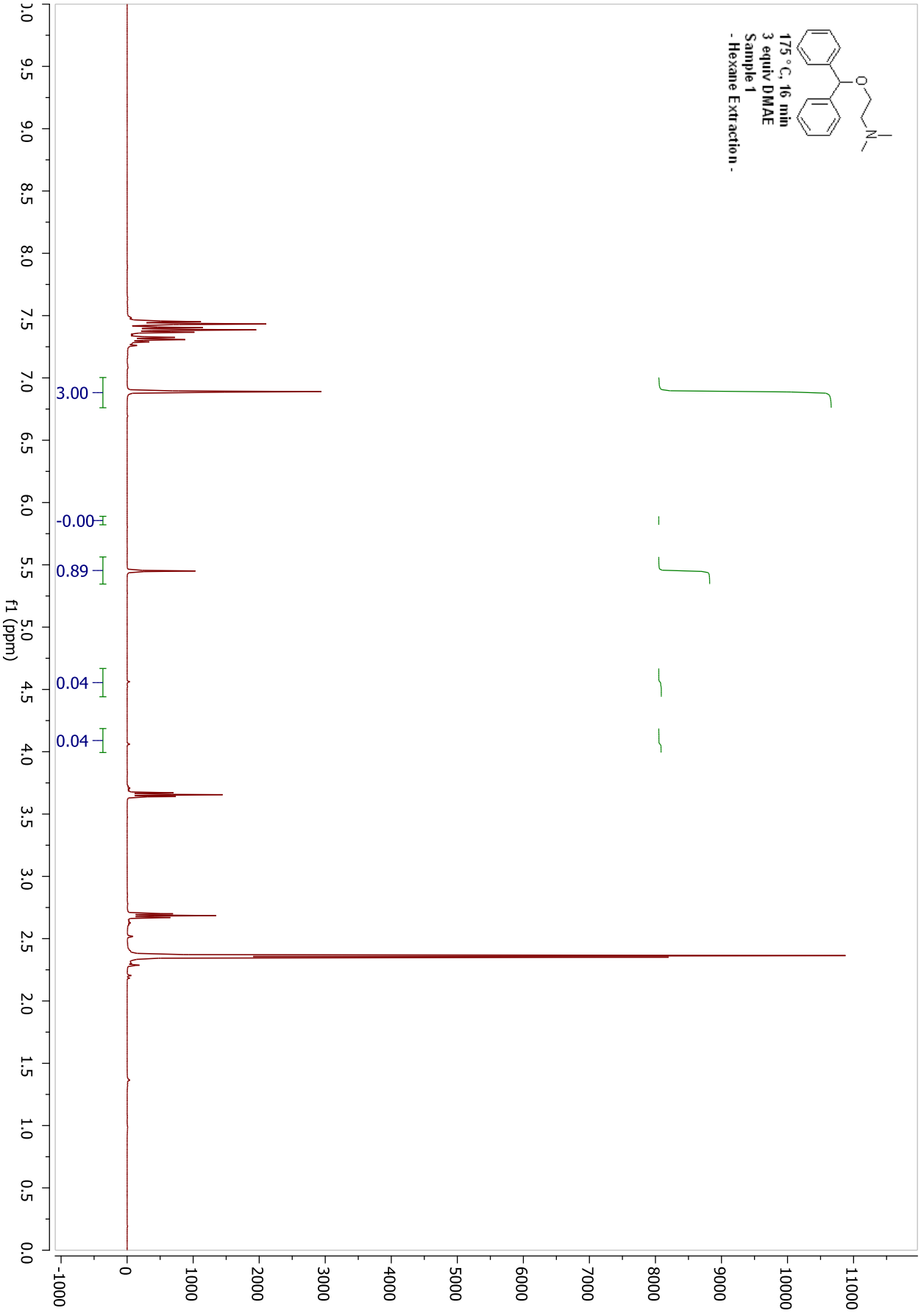

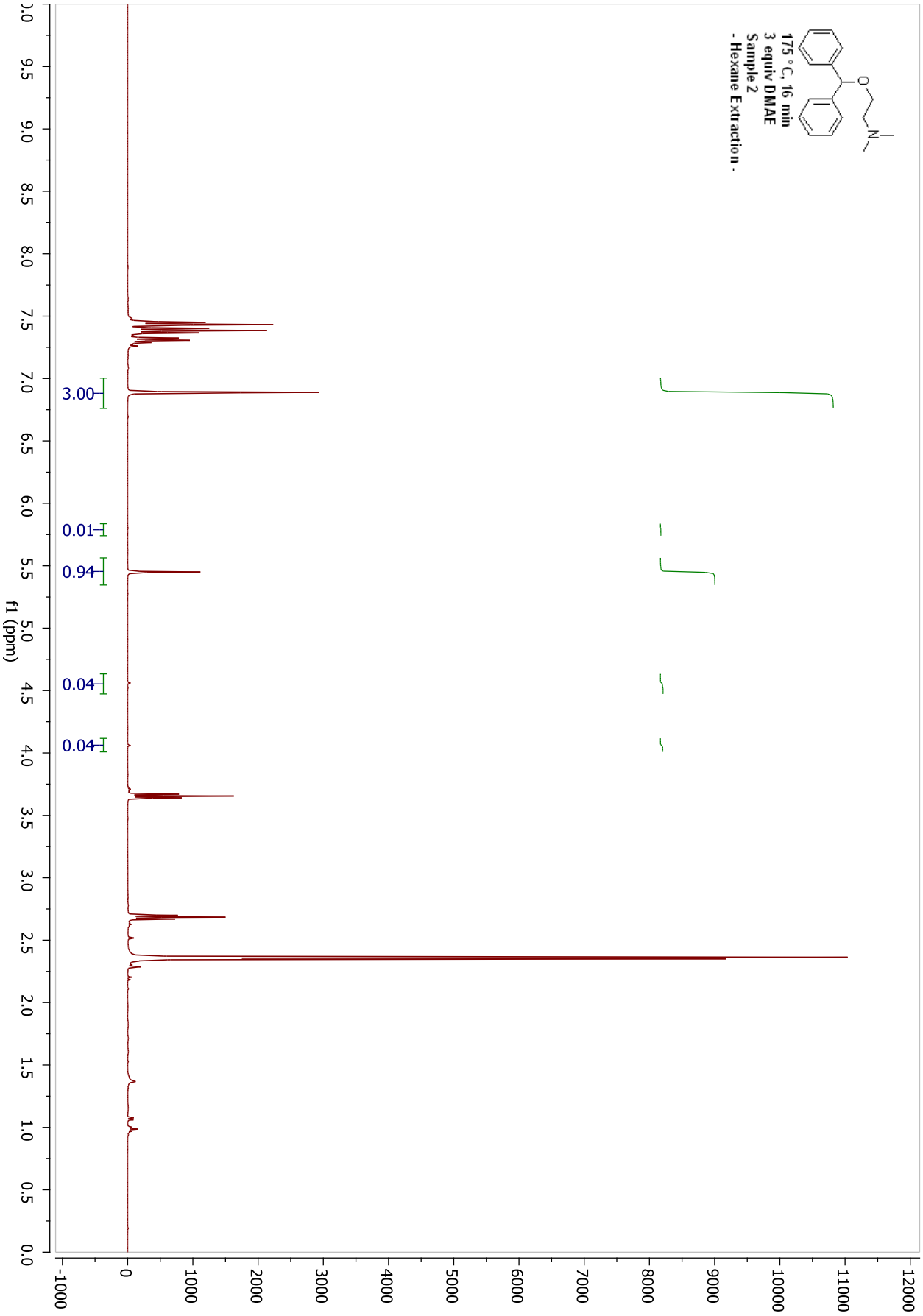

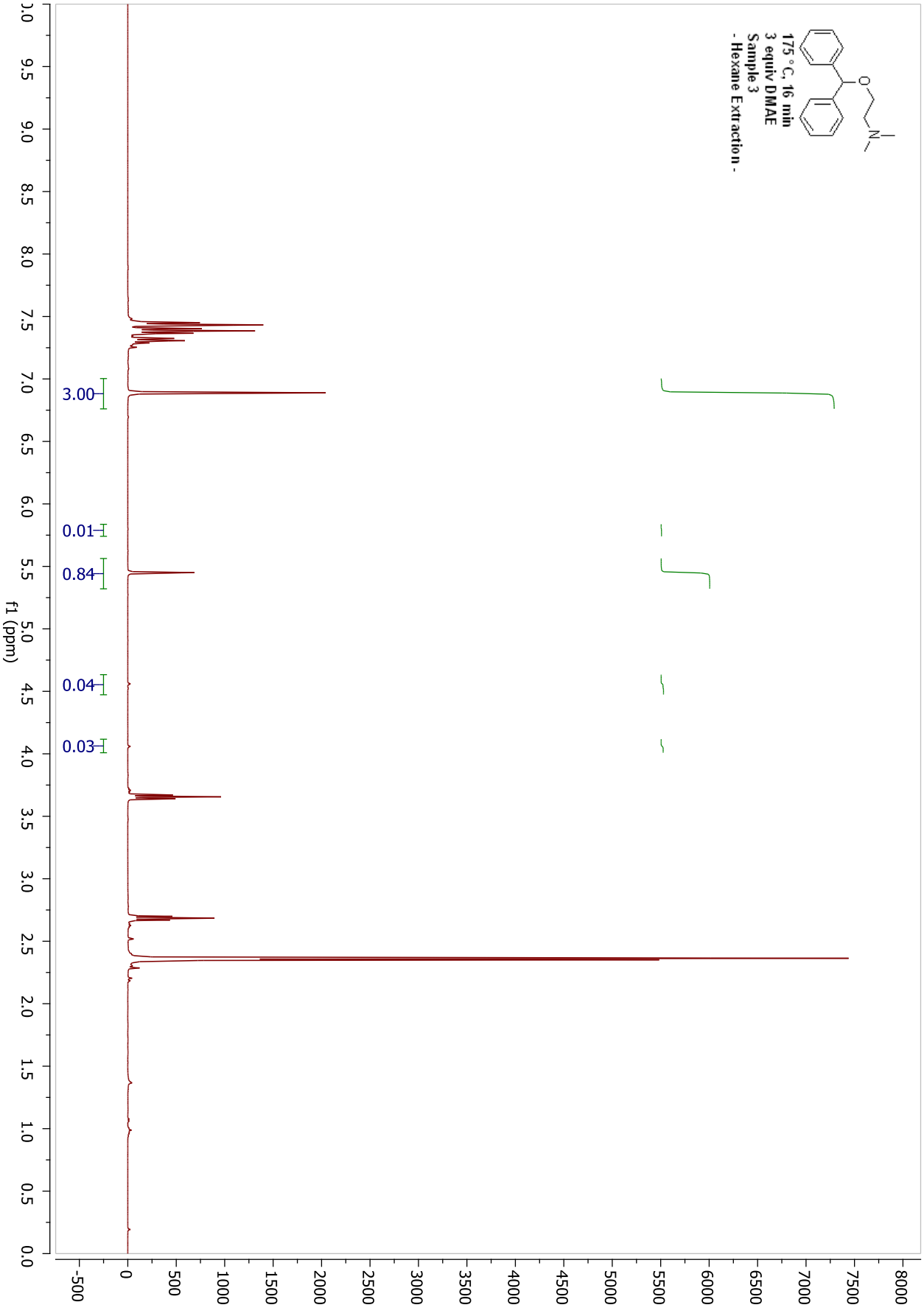

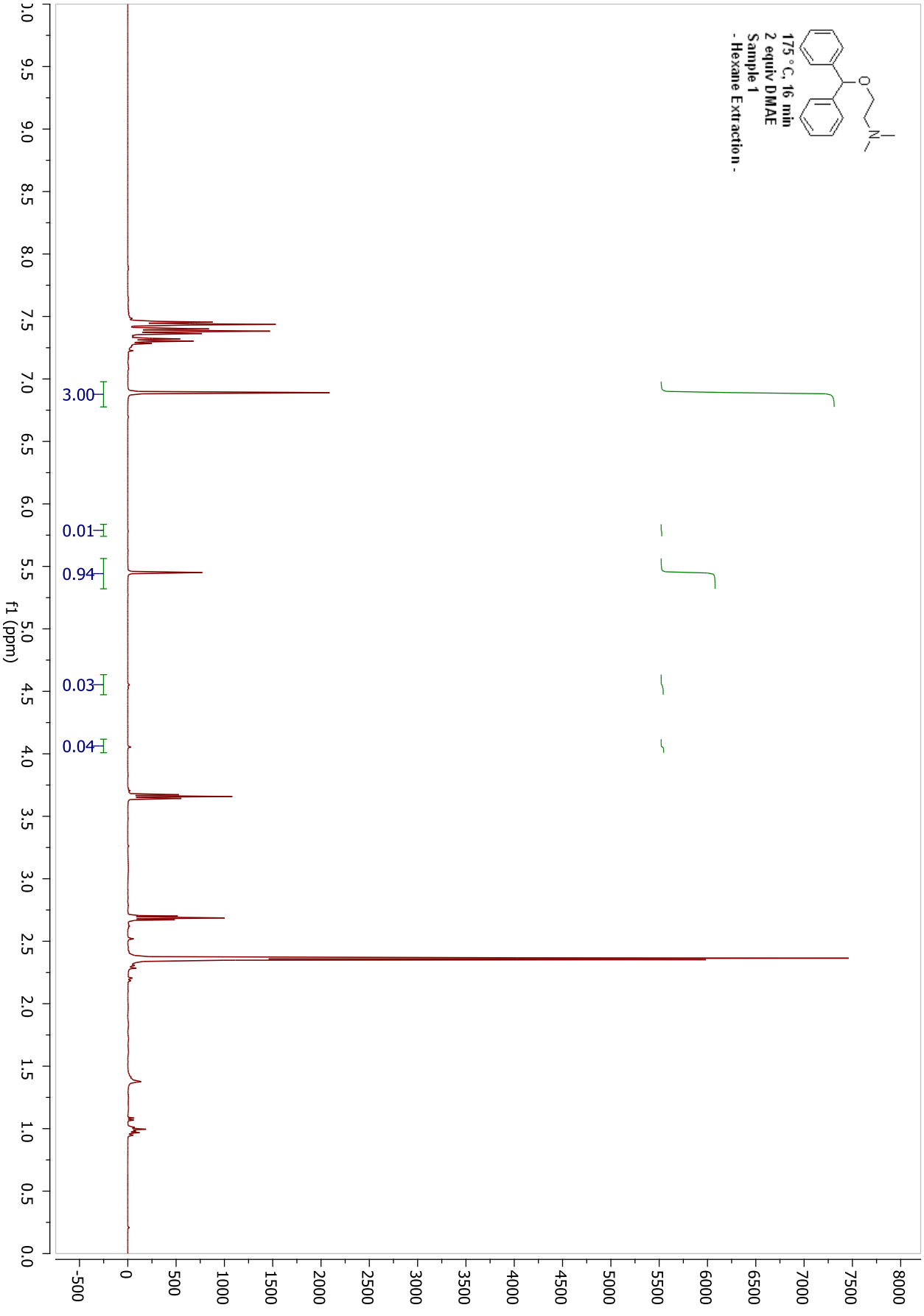

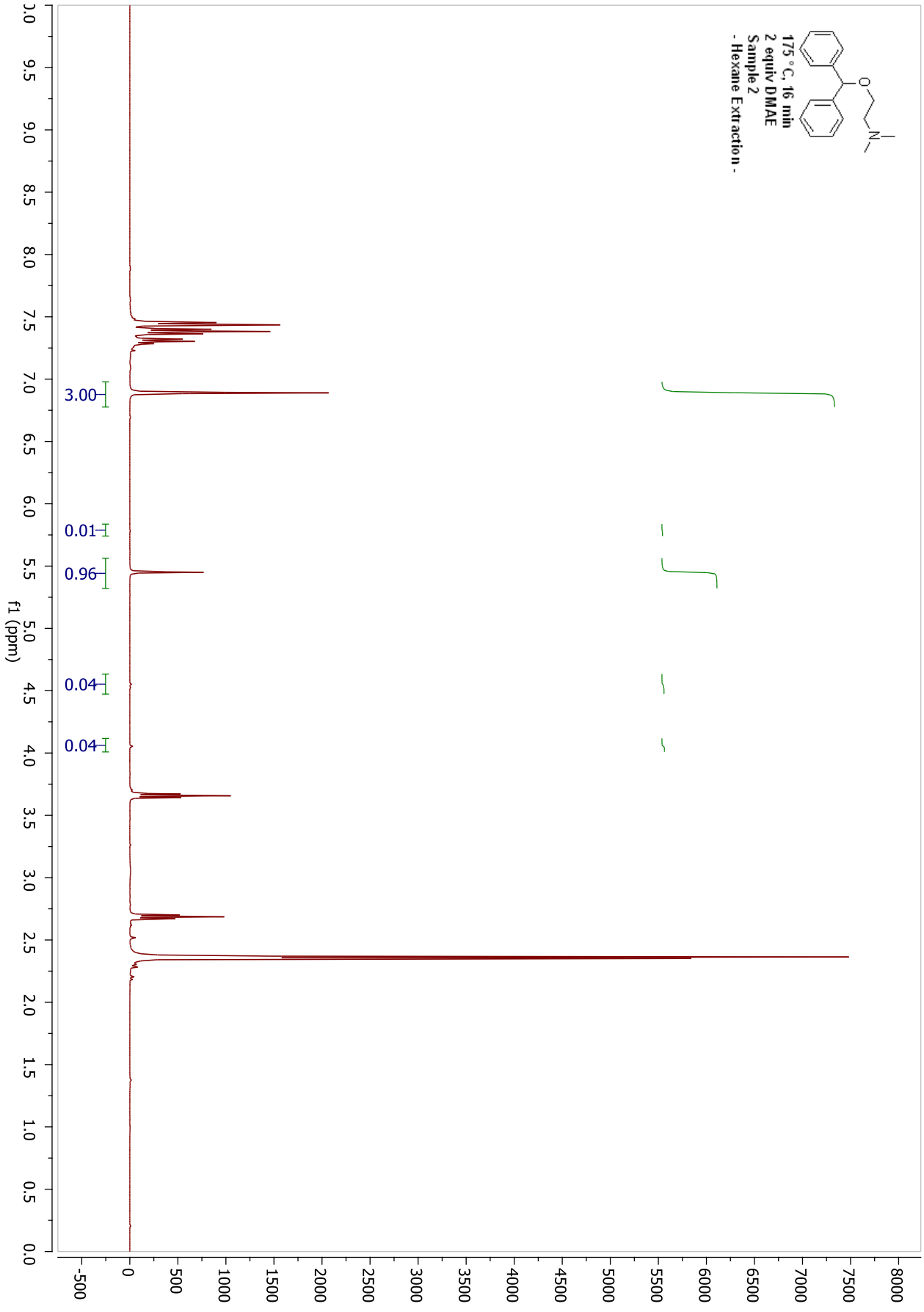

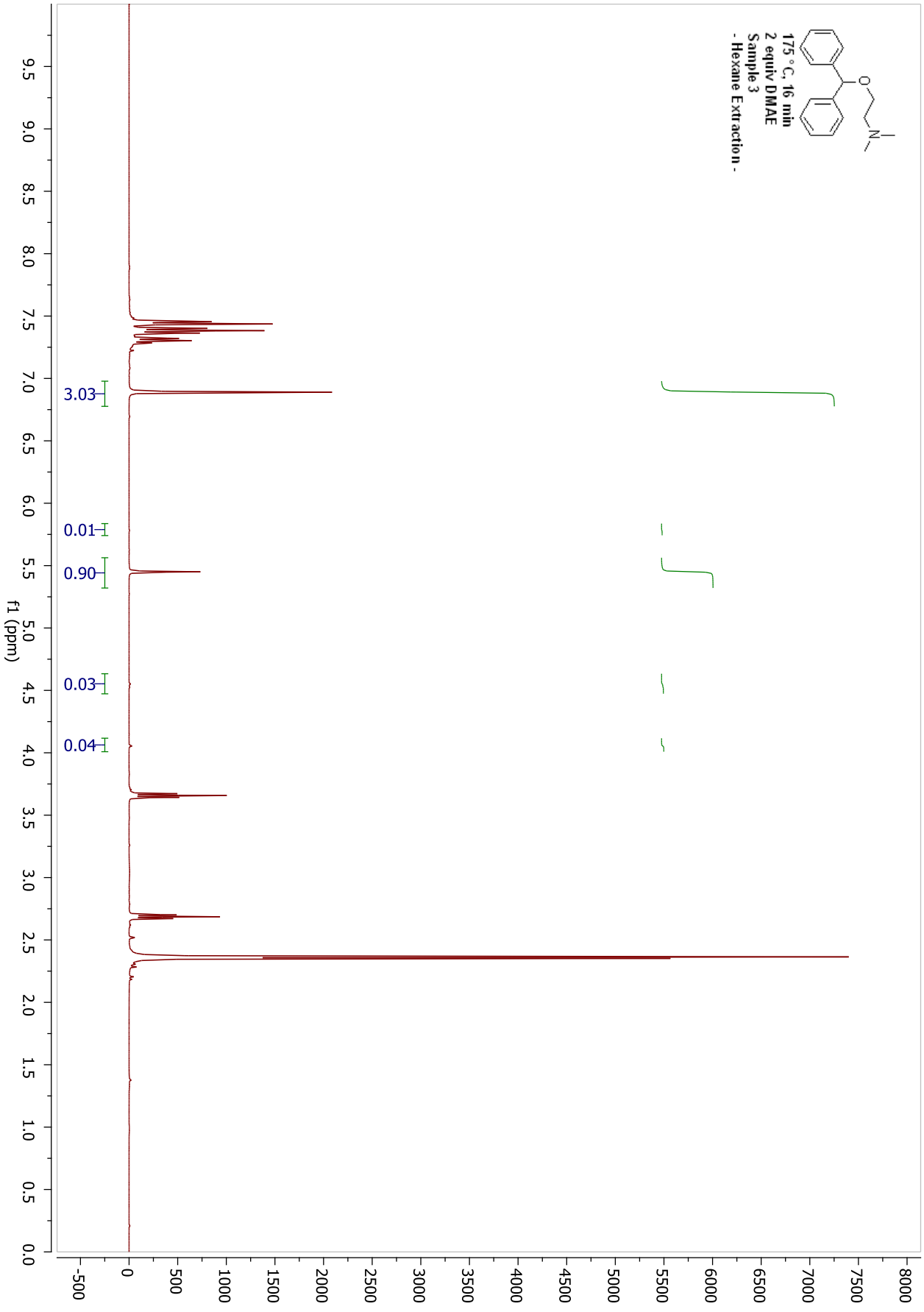

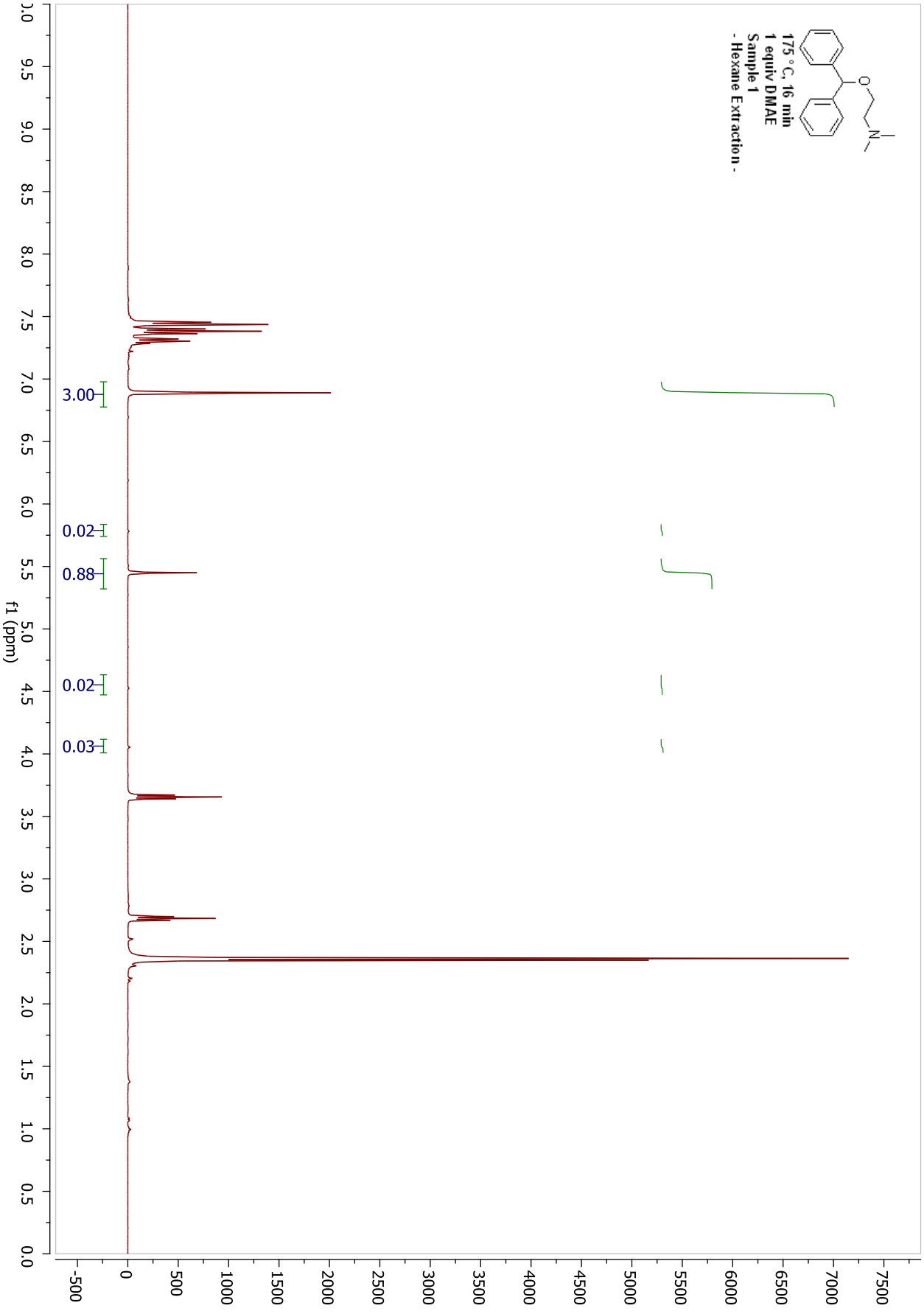

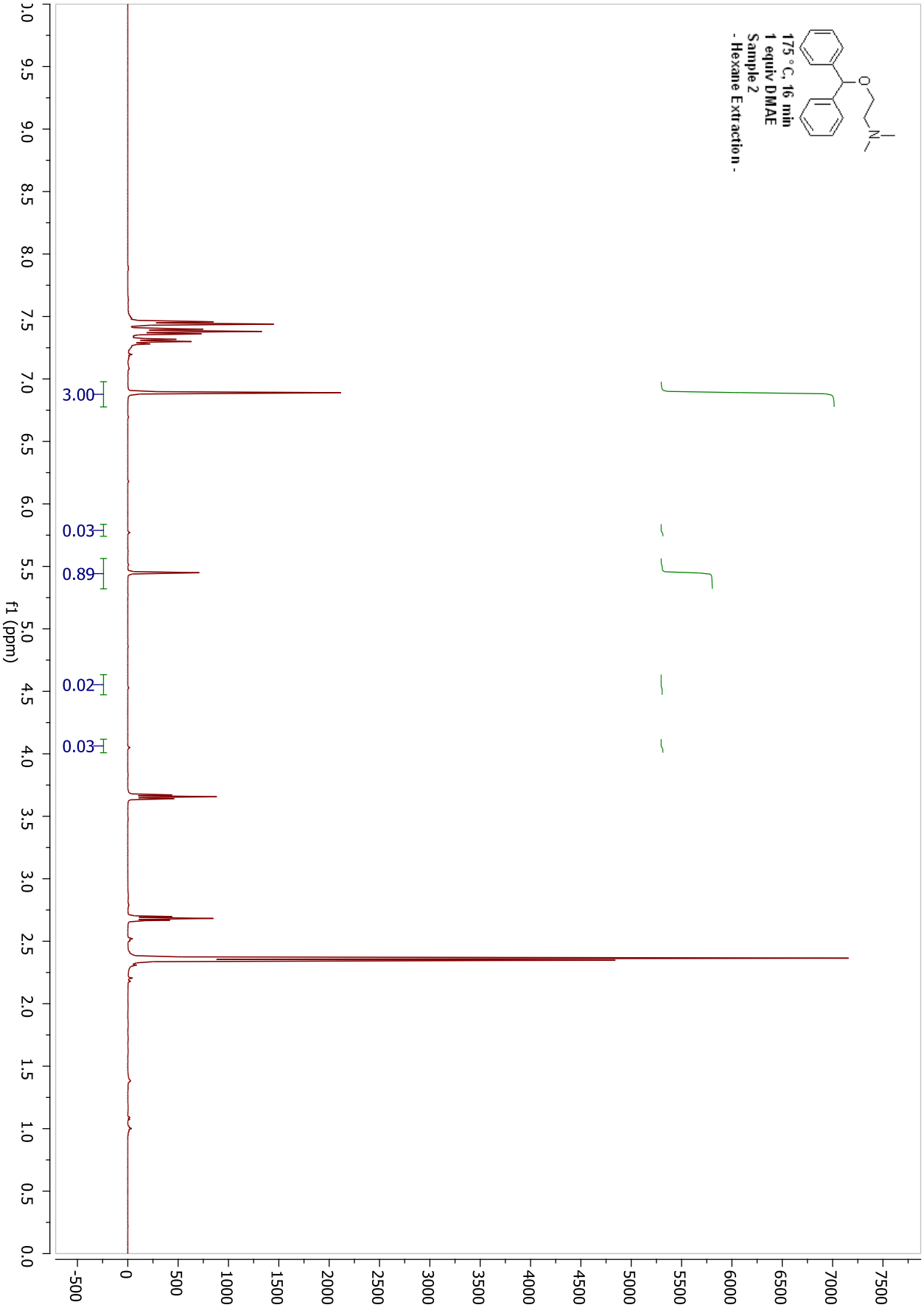

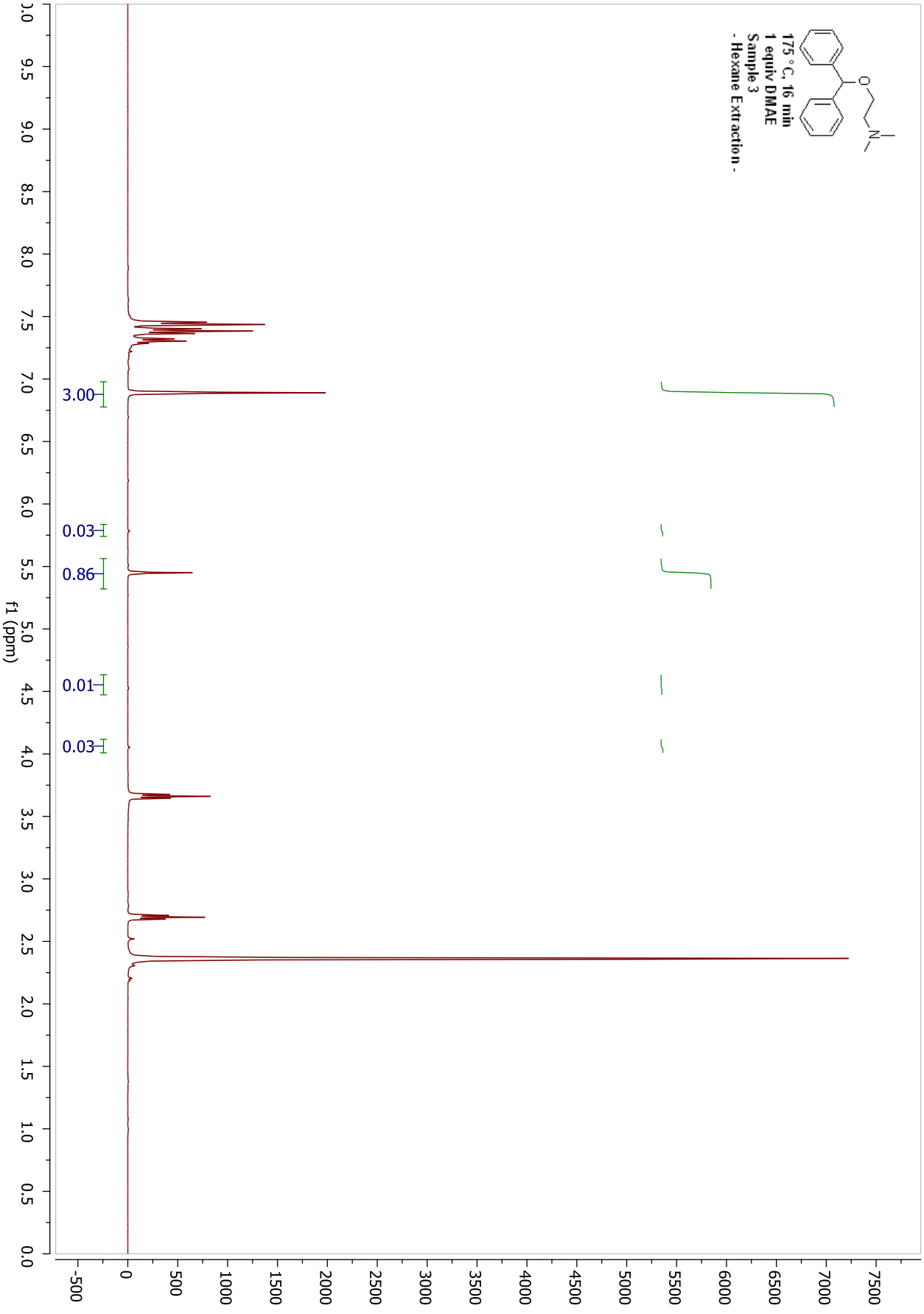

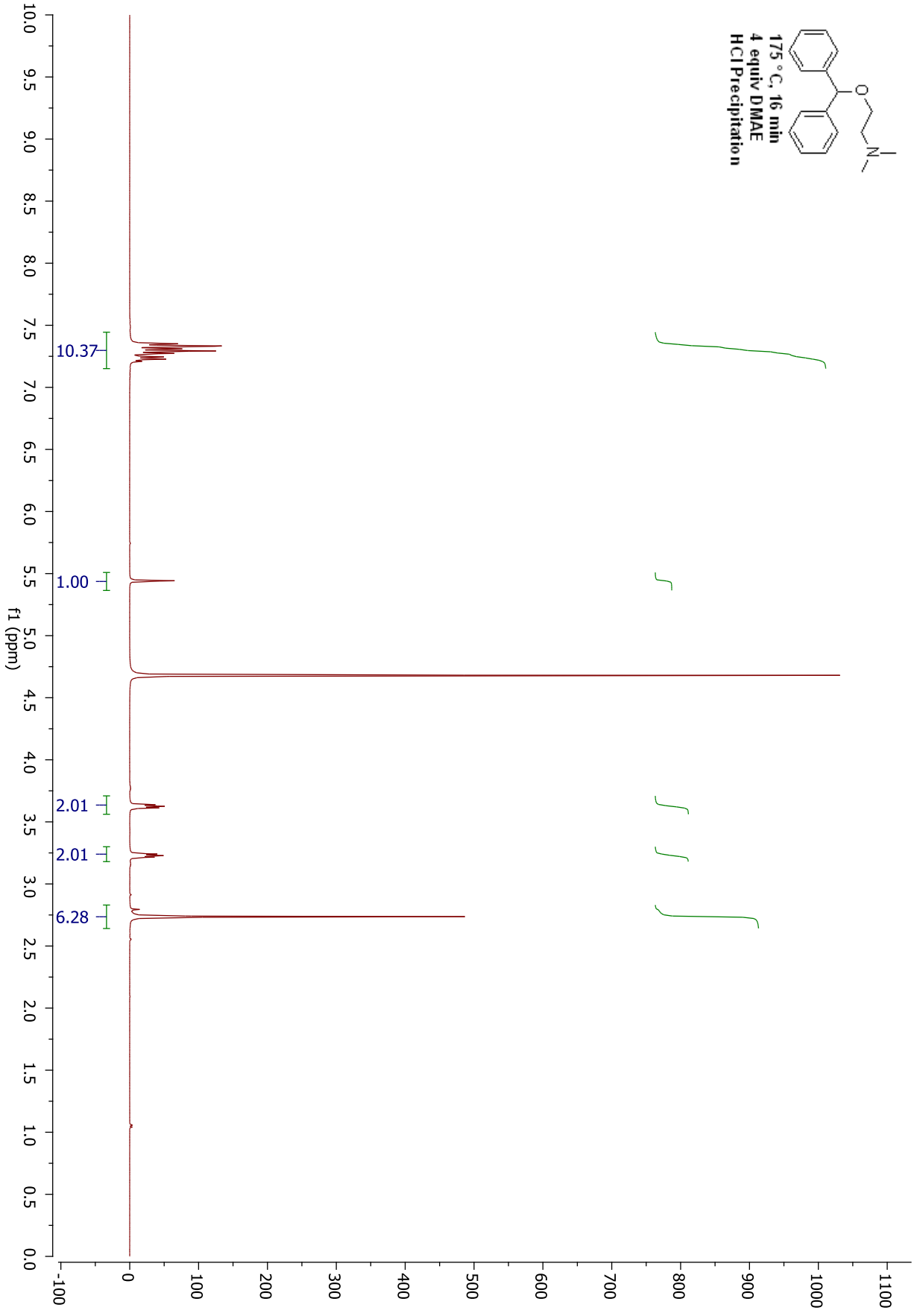

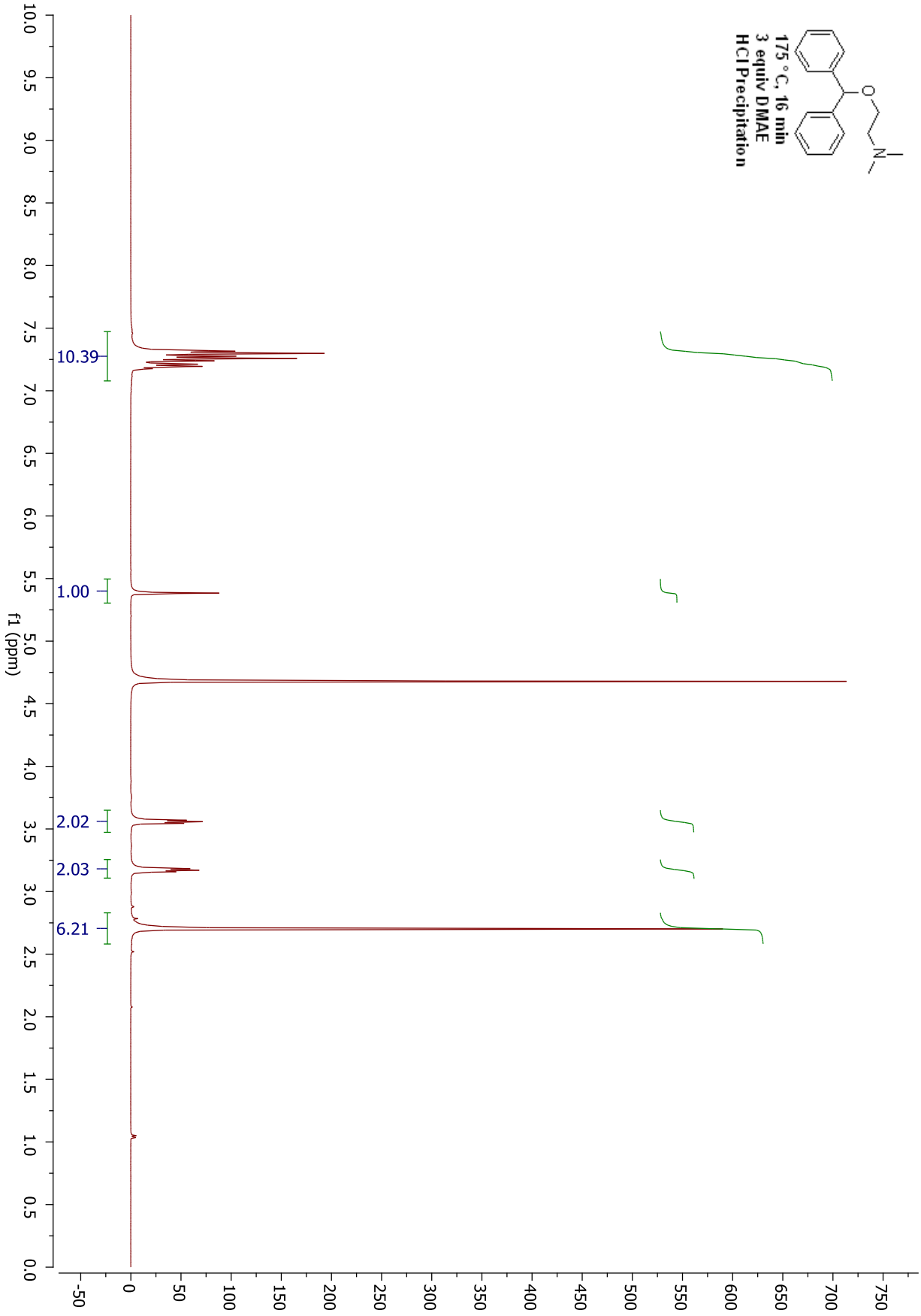

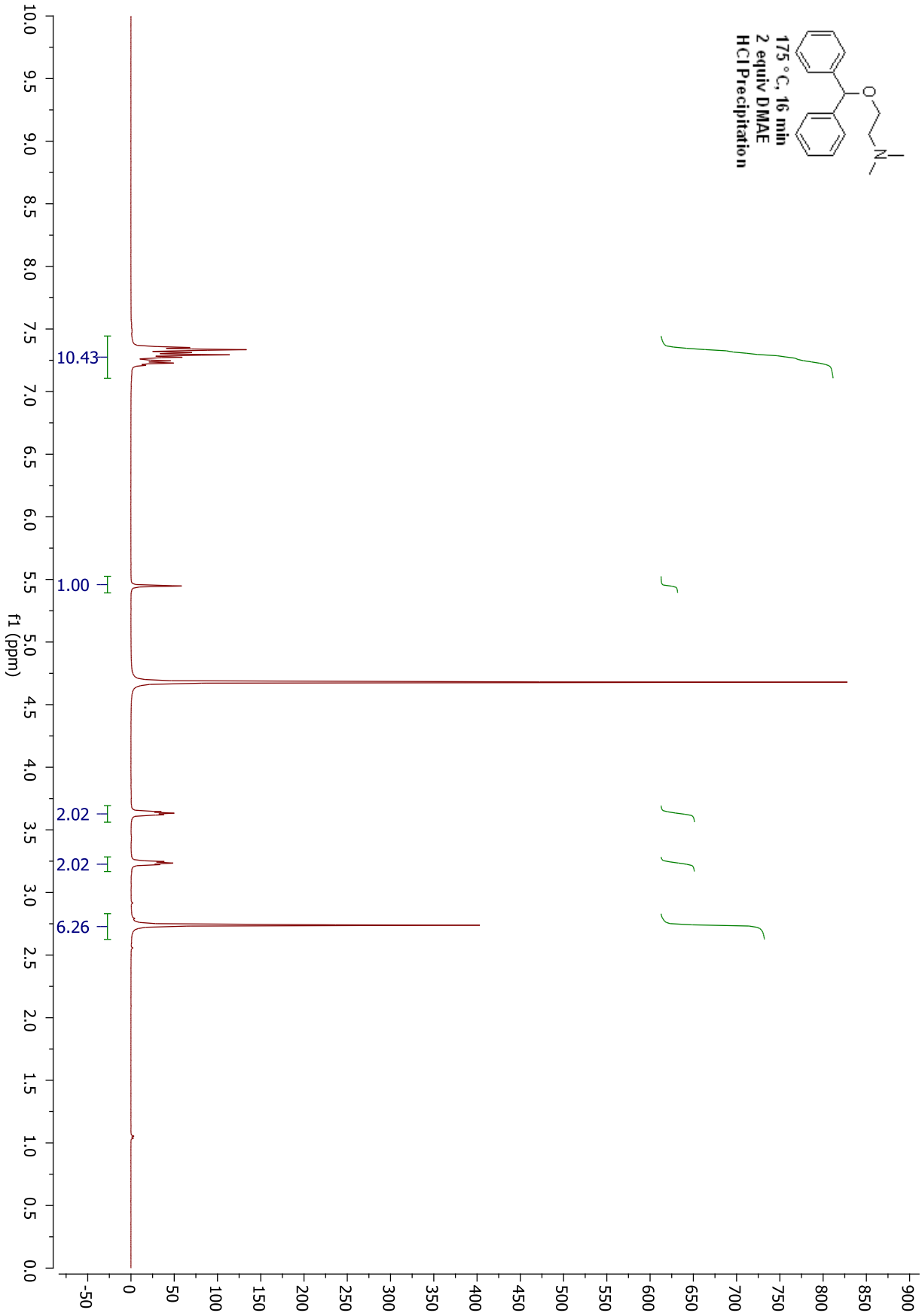

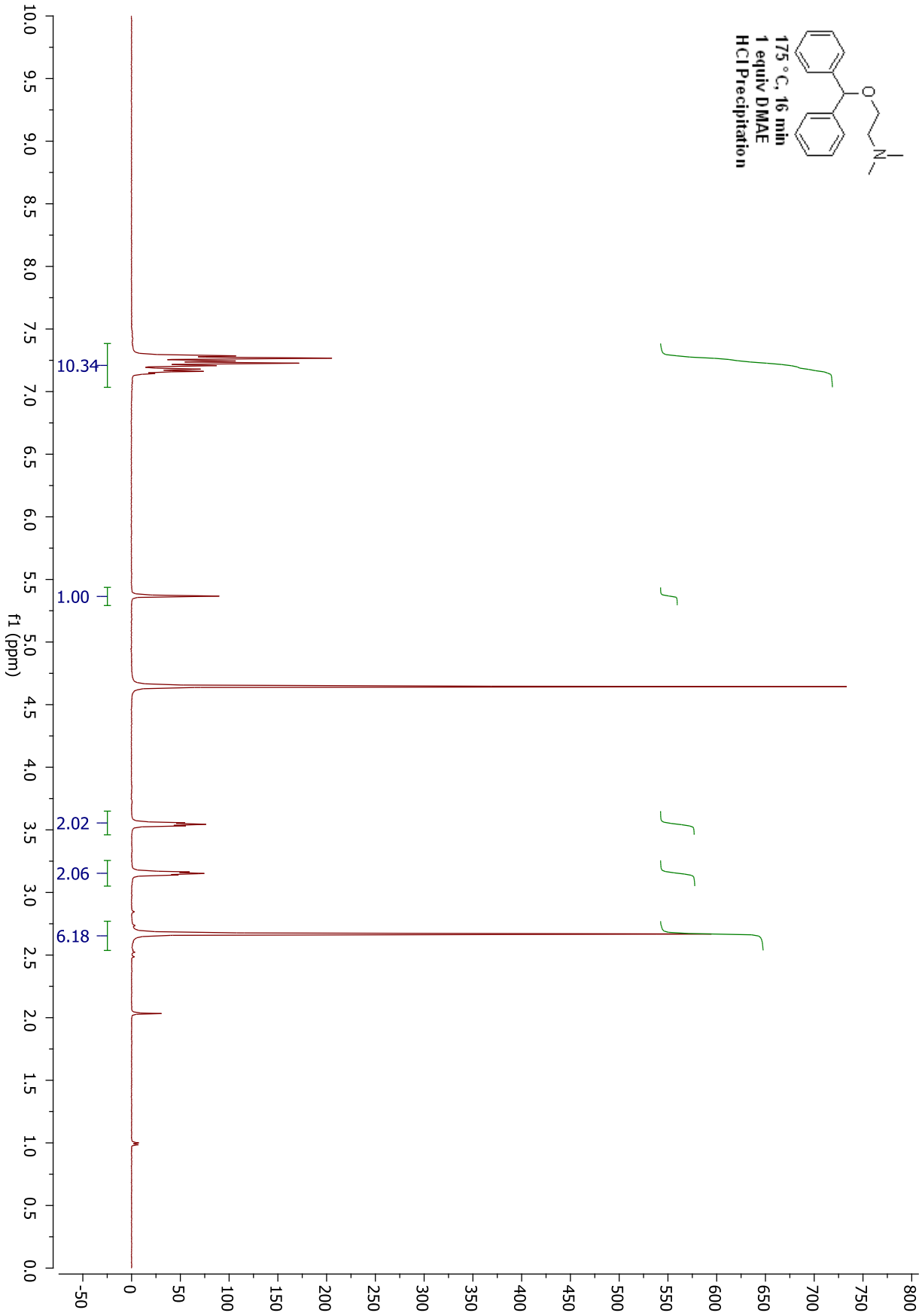

7) Spectra for Table 4: