

Supplementary Material

Synthesis of C4-substituted 1,2,3,4-tetrahydroisoquinolin-6-ols as potential estrogen receptor modulators

Tanya Mabank,^a Chan Vinh Lam,^{b,†} Luc Brunsveld,^b Ivan R. Green,^a and Willem A. L. van Otterlo^{a,*}

^a Department of Chemistry and Polymer Science, University of Stellenbosch, Private Bag X1, Matieland, ZA-7602 Stellenbosch, South Africa

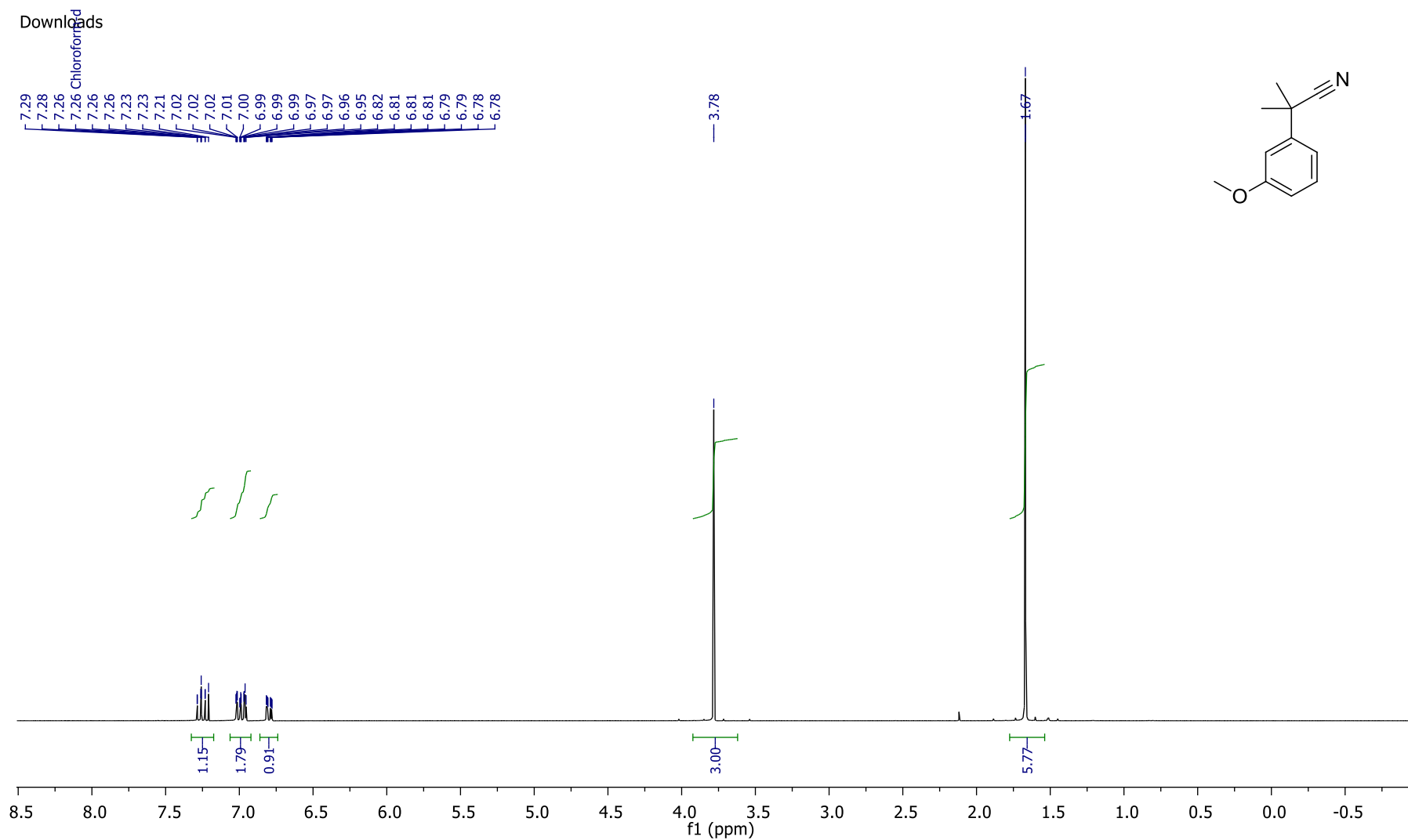
^b Laboratory of Chemical Biology, Department of Biomedical Engineering, Technische Universiteit Eindhoven, Den Dolech 2, 5612AZ, Eindhoven, The Netherlands

Email: wvo@sun.ac.za

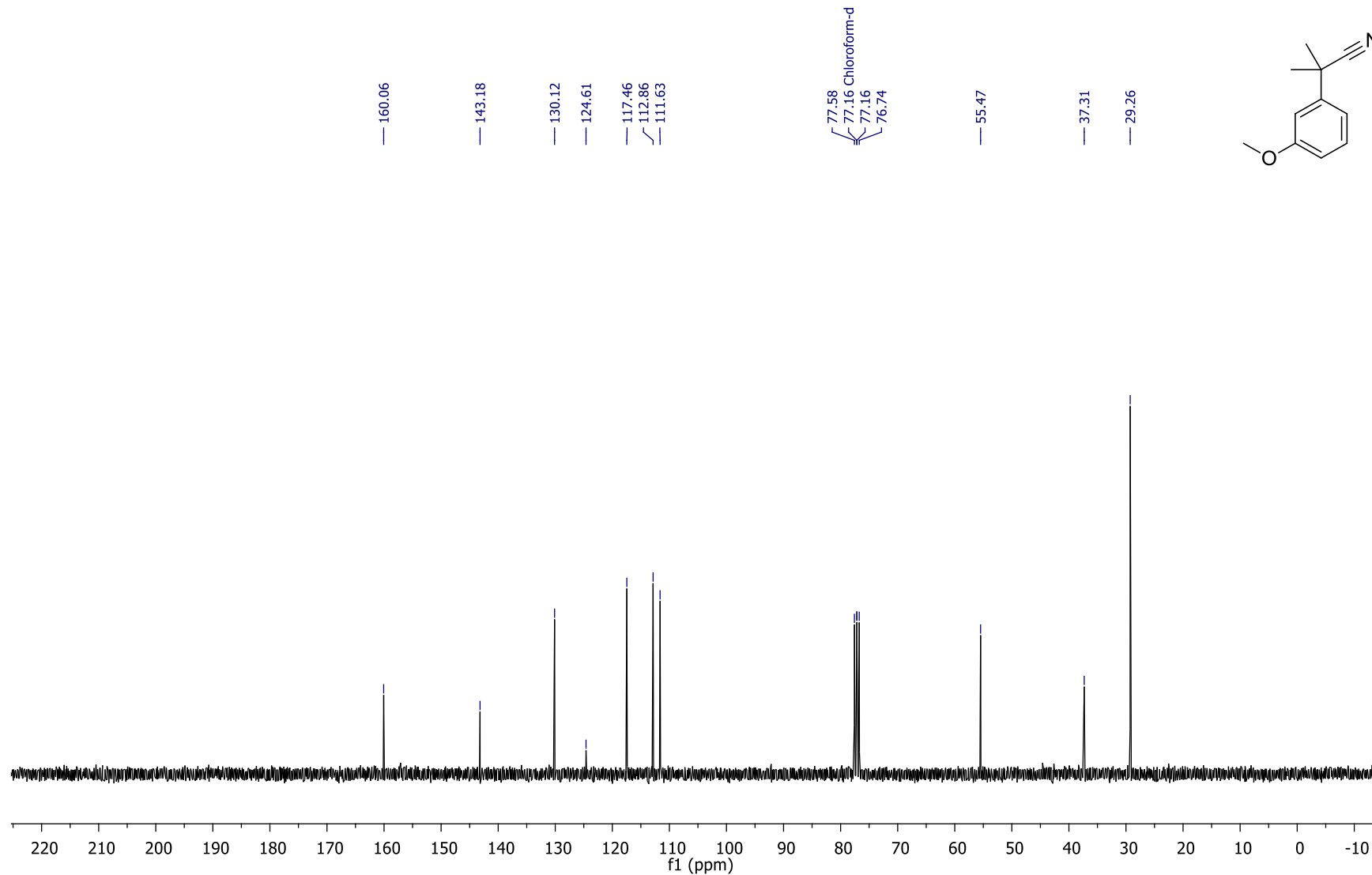
Table of Contents

¹H and ¹³C NMR spectra and selected HMRS data for the following compounds is supplied:

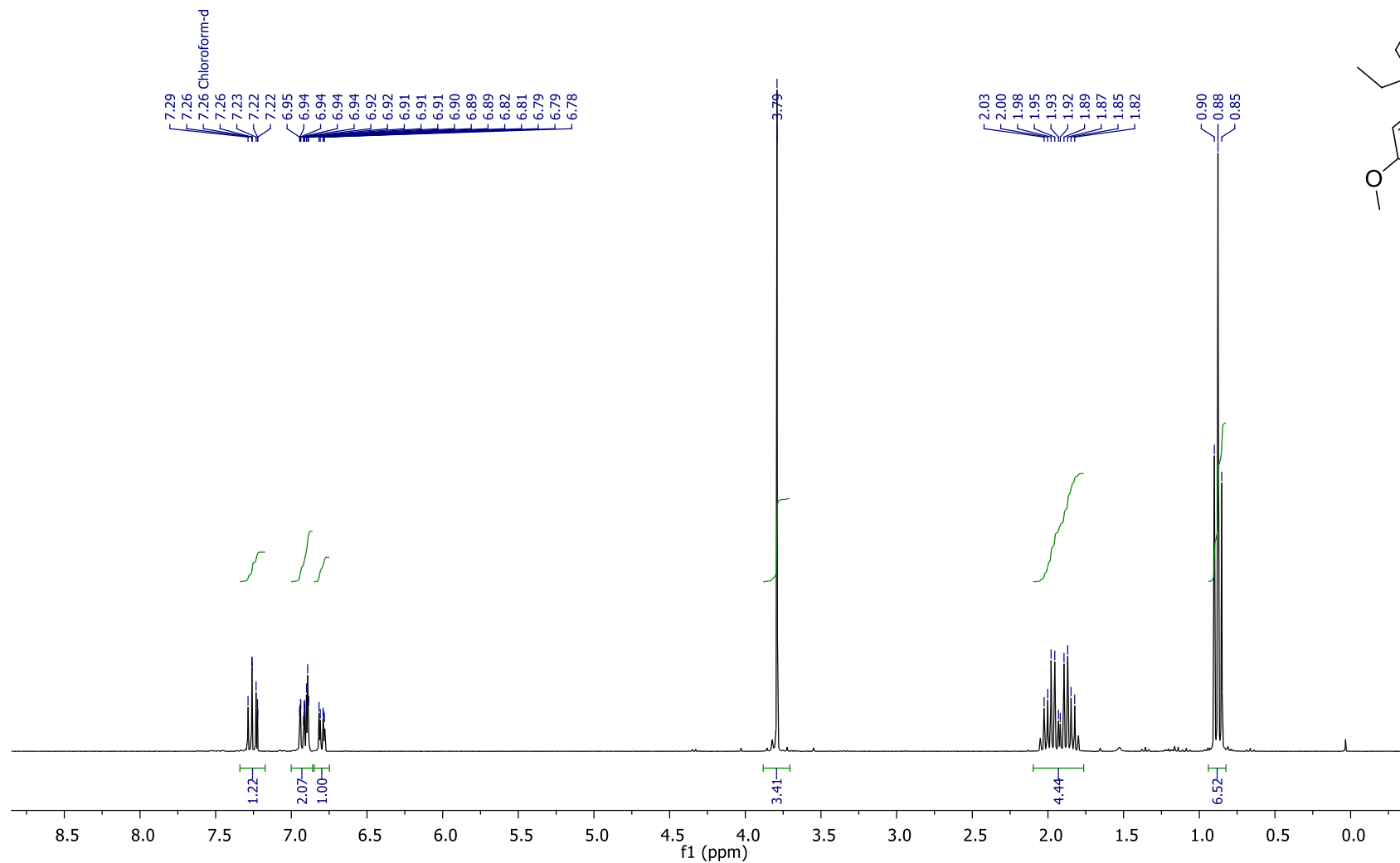
Compounds 11b-e	S2
Compounds 12b-e	S10
Compounds 14a-e	S18
Compounds 15a-e	S33
Compounds 9a-c,e	S45
EC ₅₀ results obtained for SUMO-tagged ER α cofactor peptide recruitment.	S56

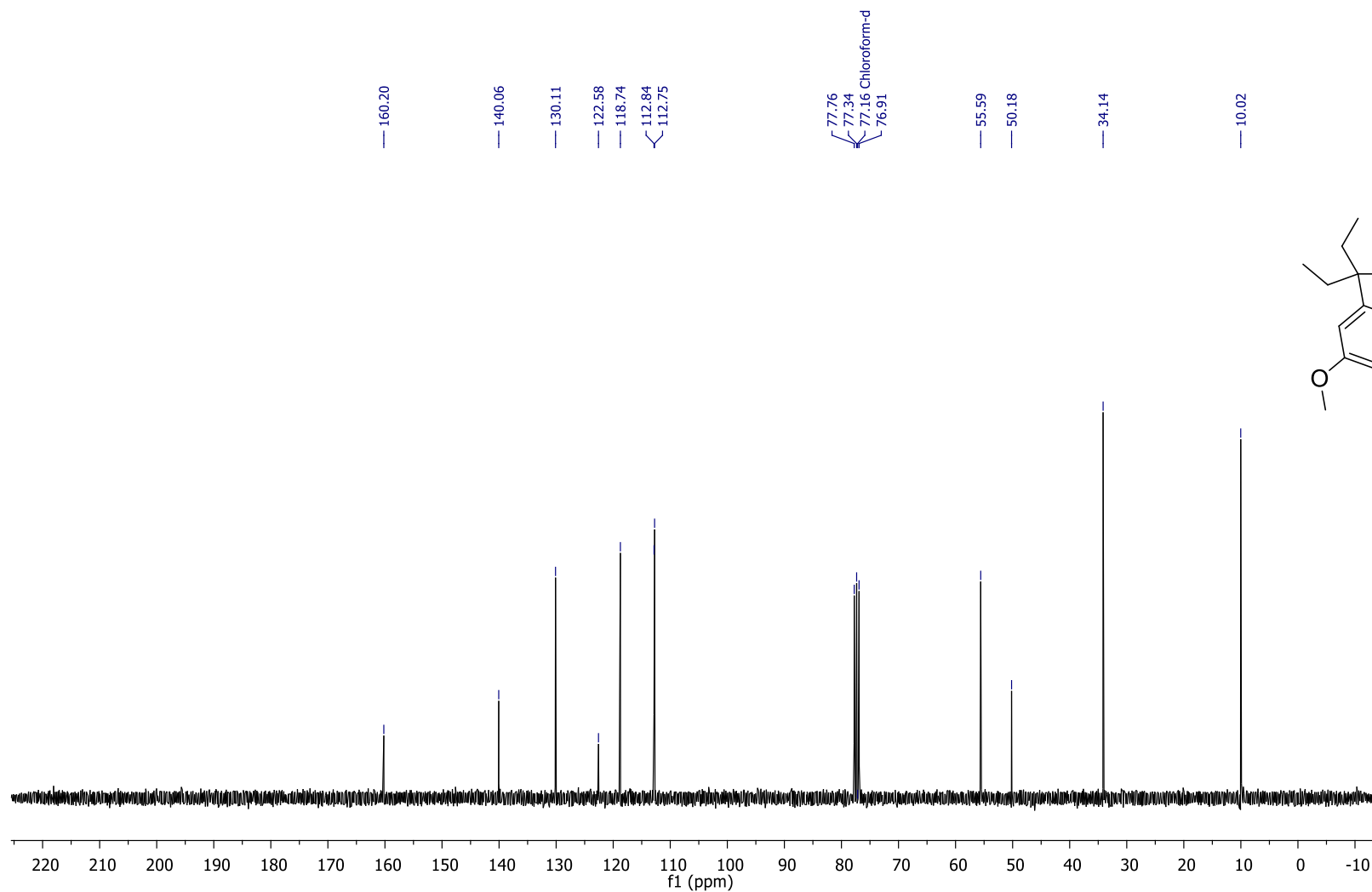


¹H-NMR (300 MHz) spectrum of **11b** in CDCl₃

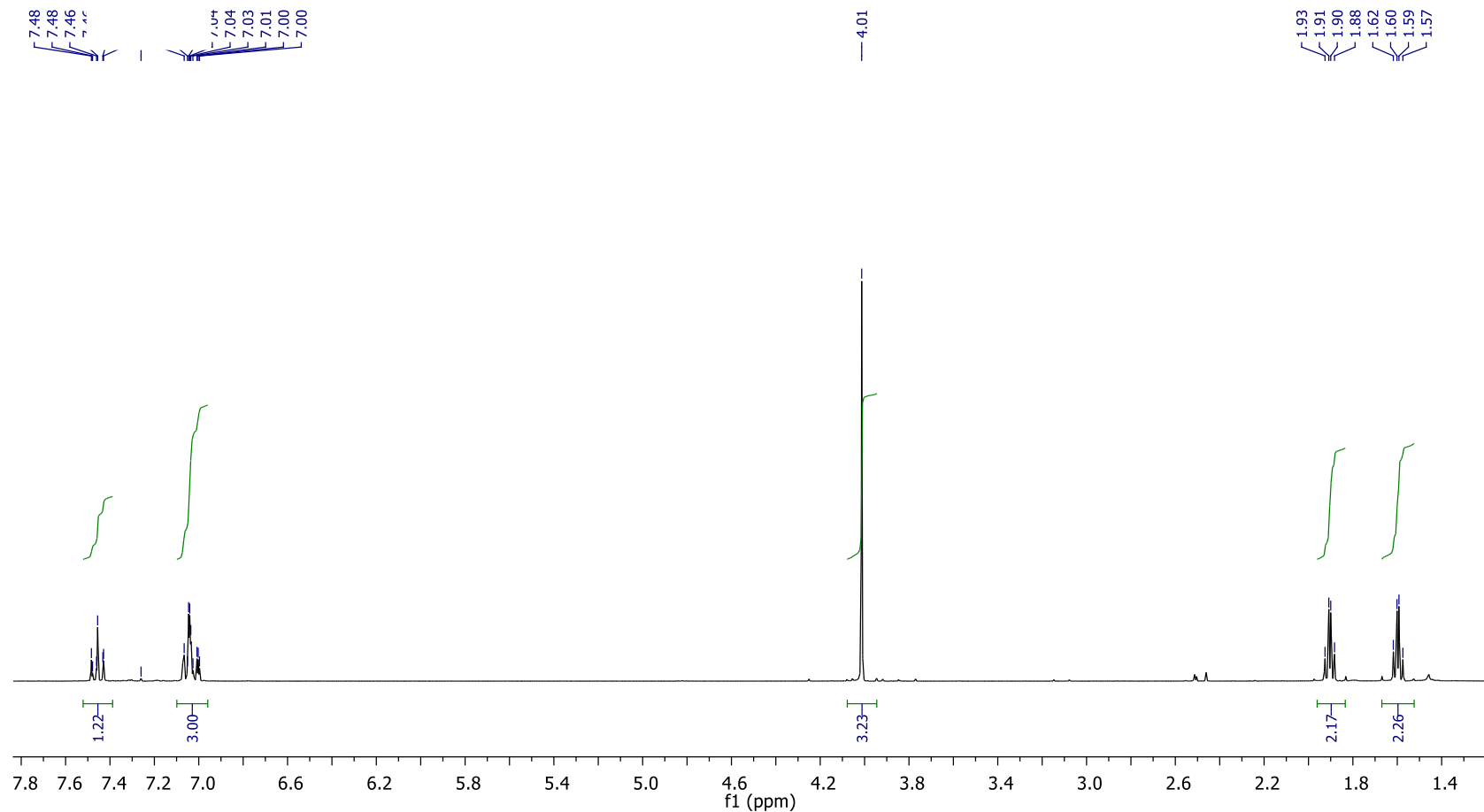
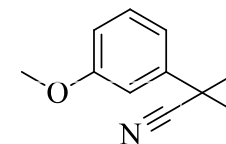


¹³C-NMR (75 MHz) spectrum of **11b** in CDCl₃

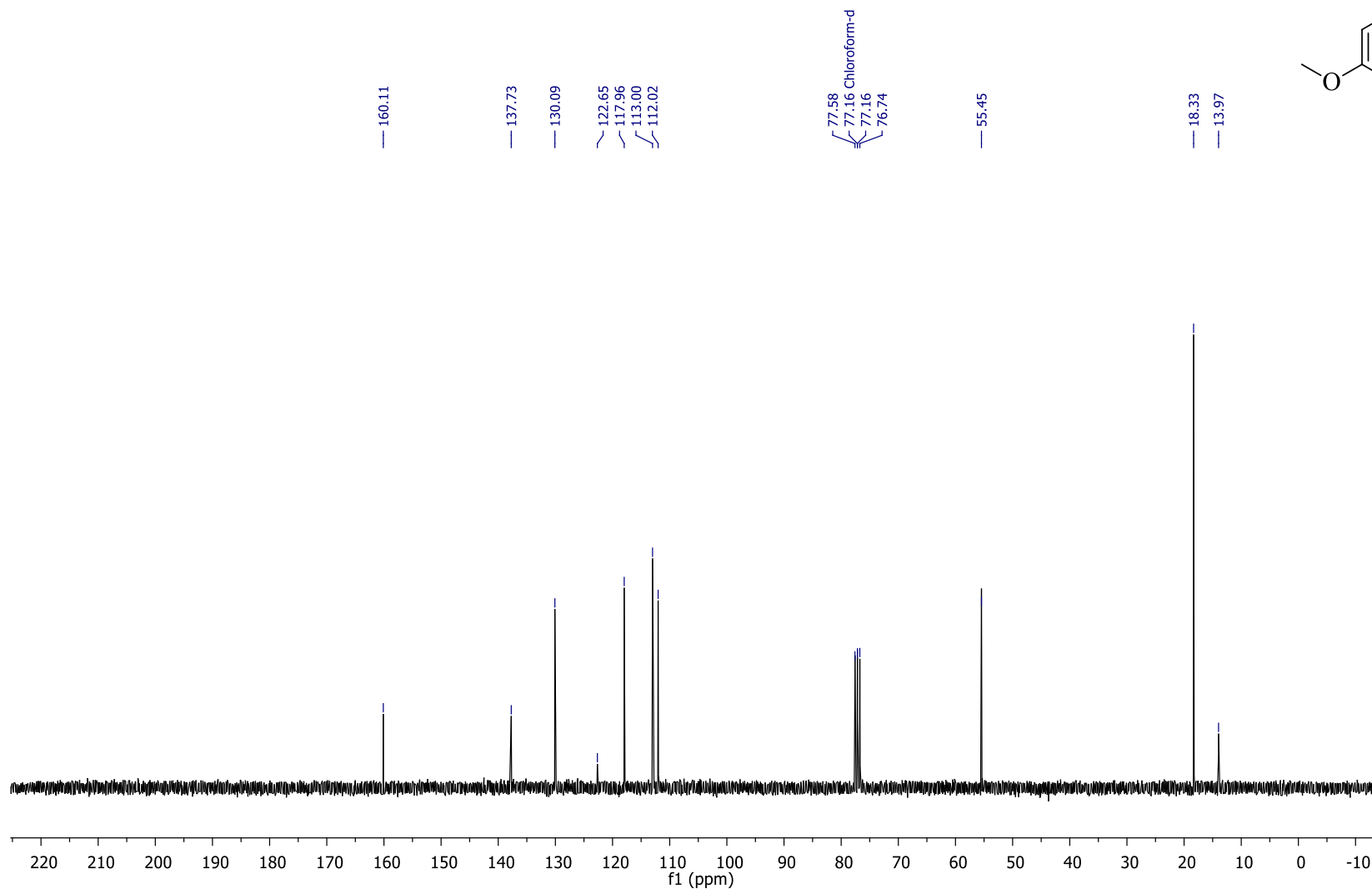




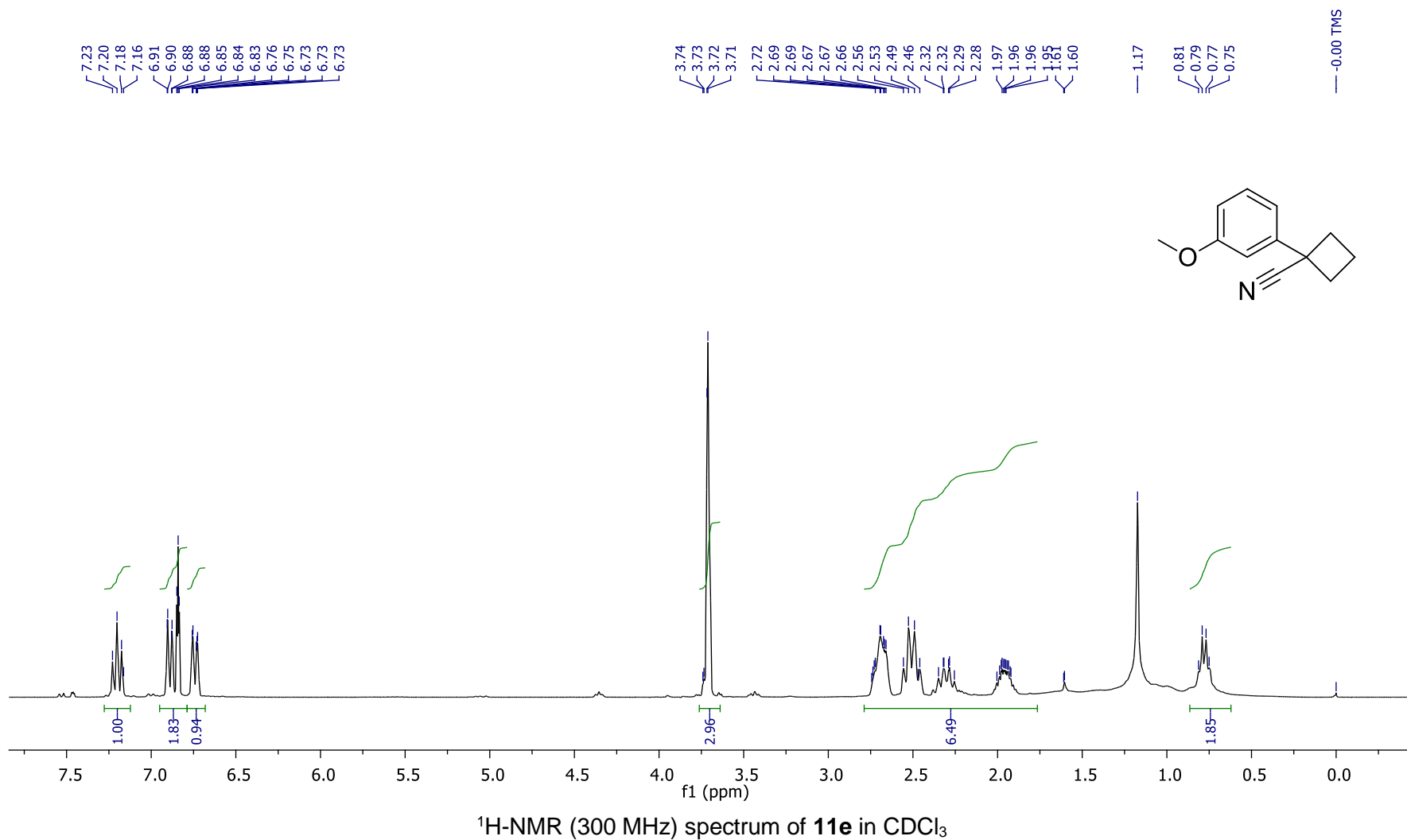
¹³C-NMR (75 MHz) spectrum of **11c** in CDCl₃

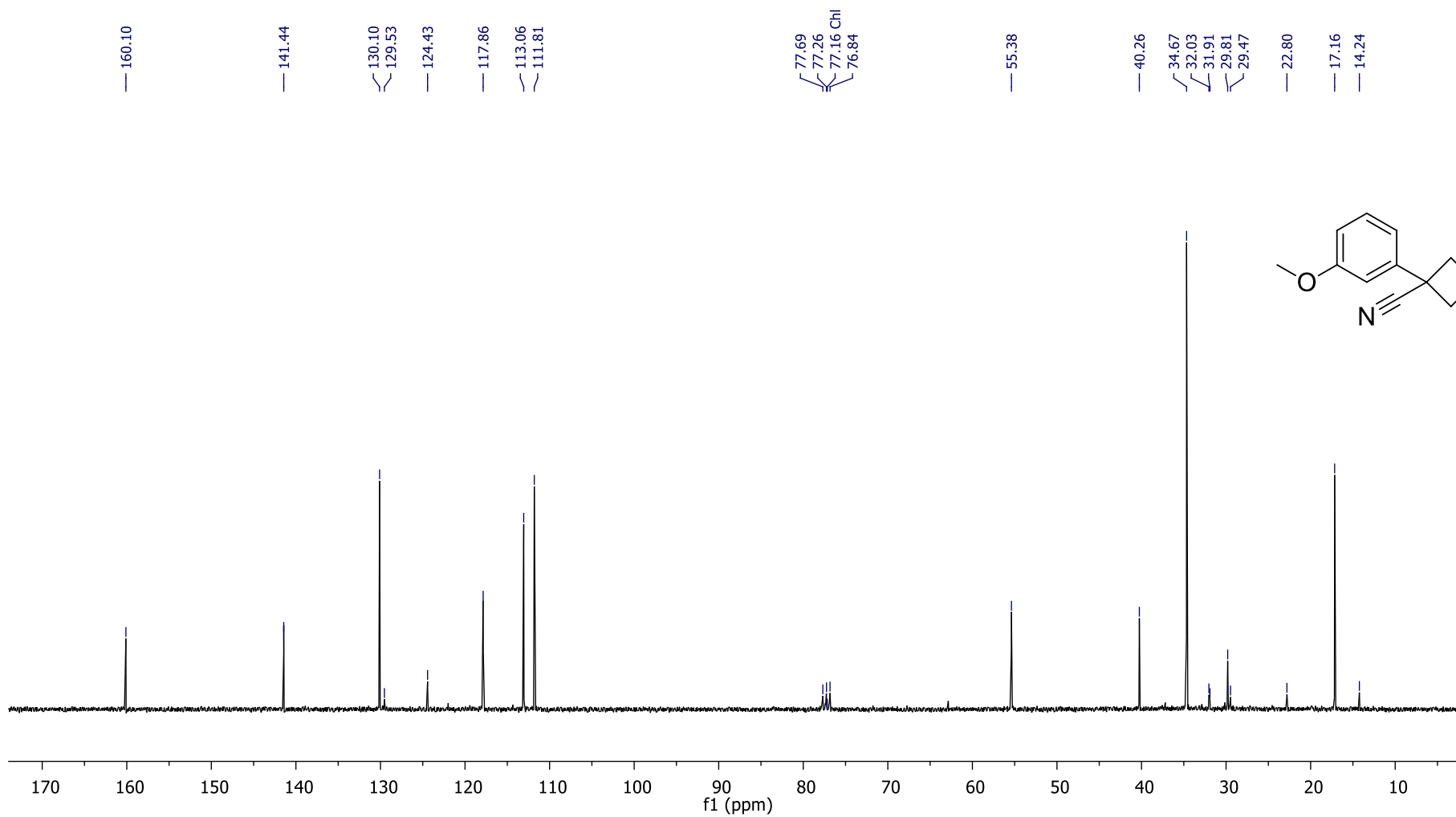


¹H-NMR (300 MHz) spectrum of **11d** in CDCl₃

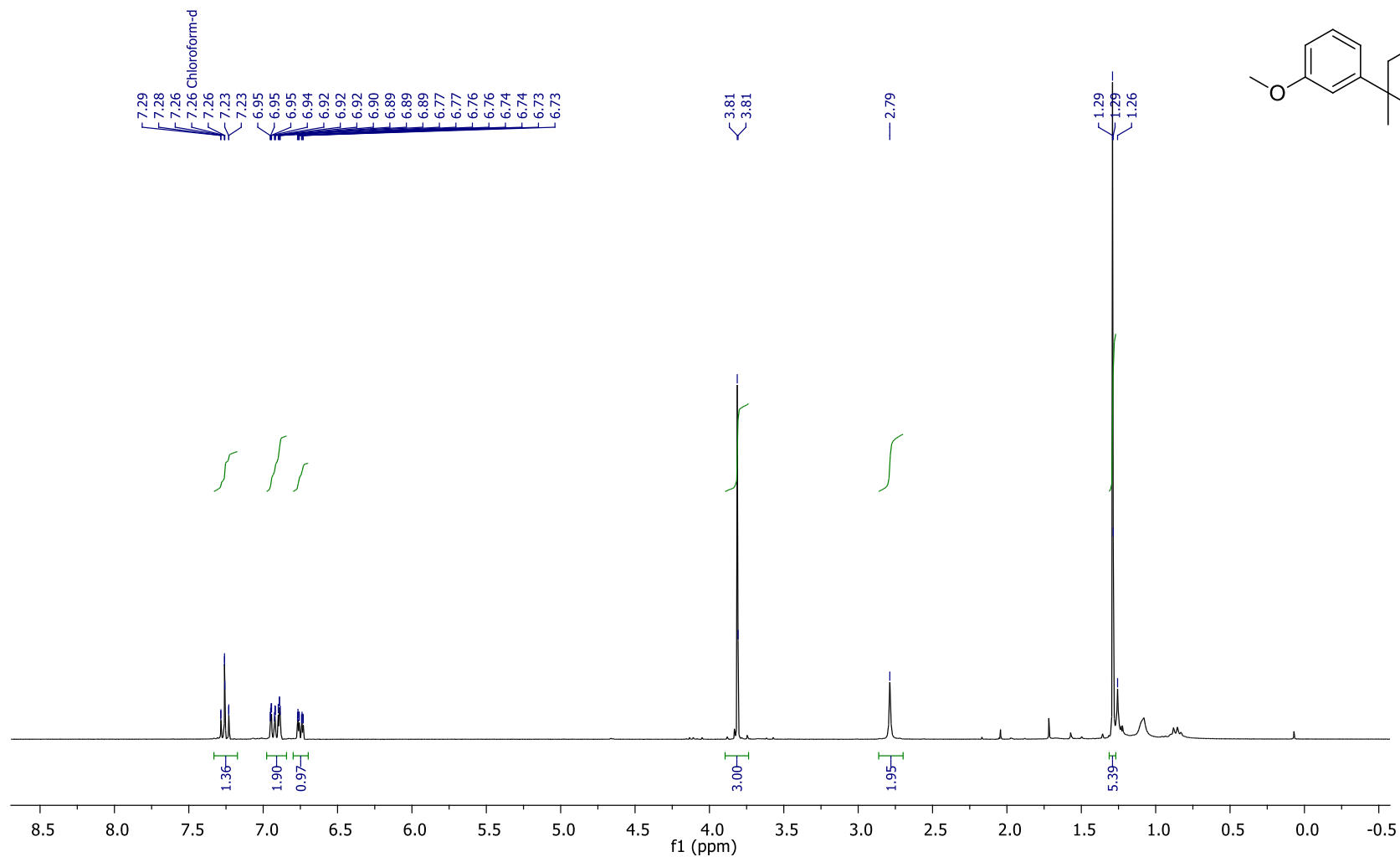


¹³C-NMR (75 MHz) spectrum of **11d** in CDCl₃

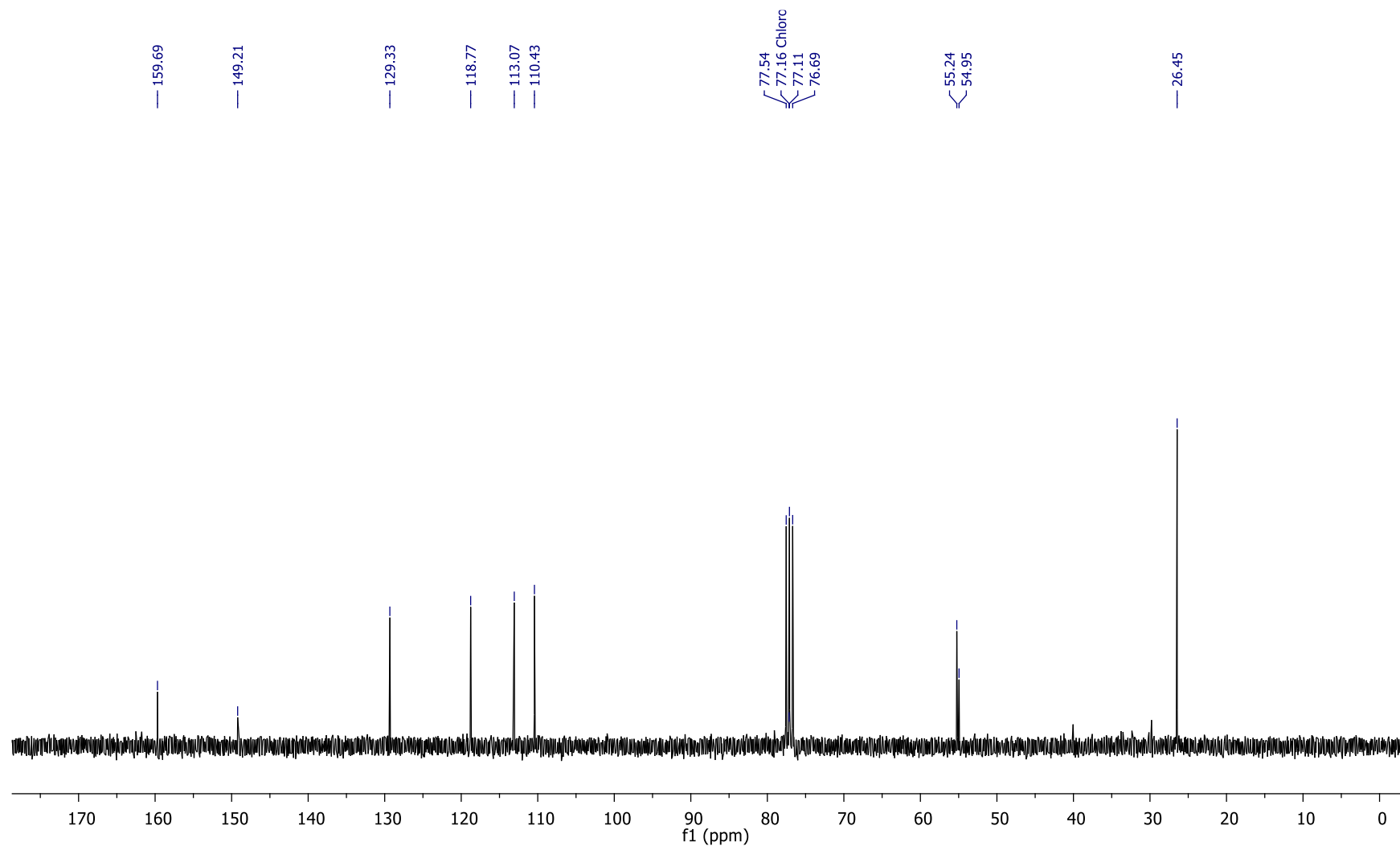




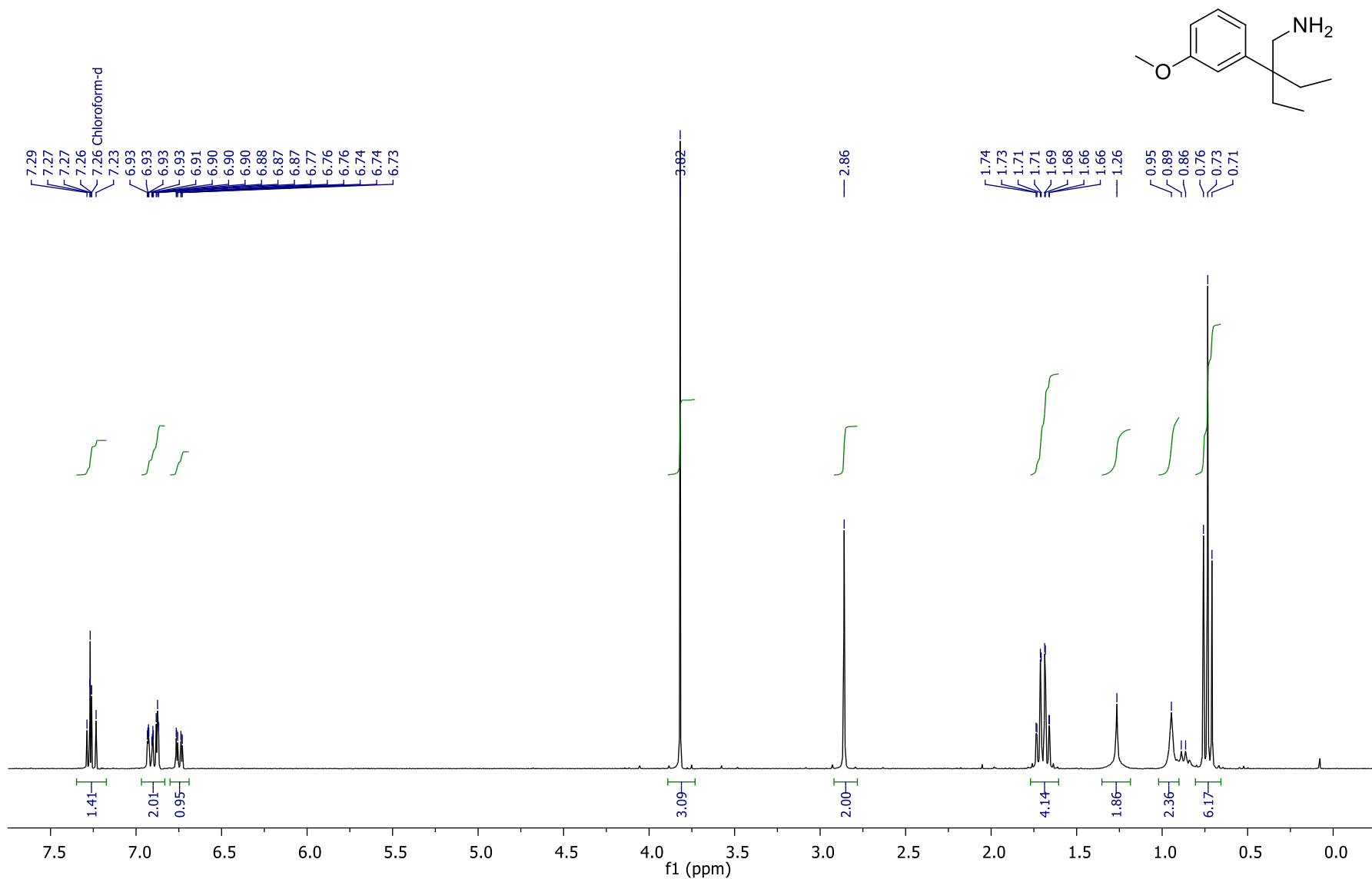
¹³C-NMR (75 MHz) spectrum of **11e** in CDCl₃

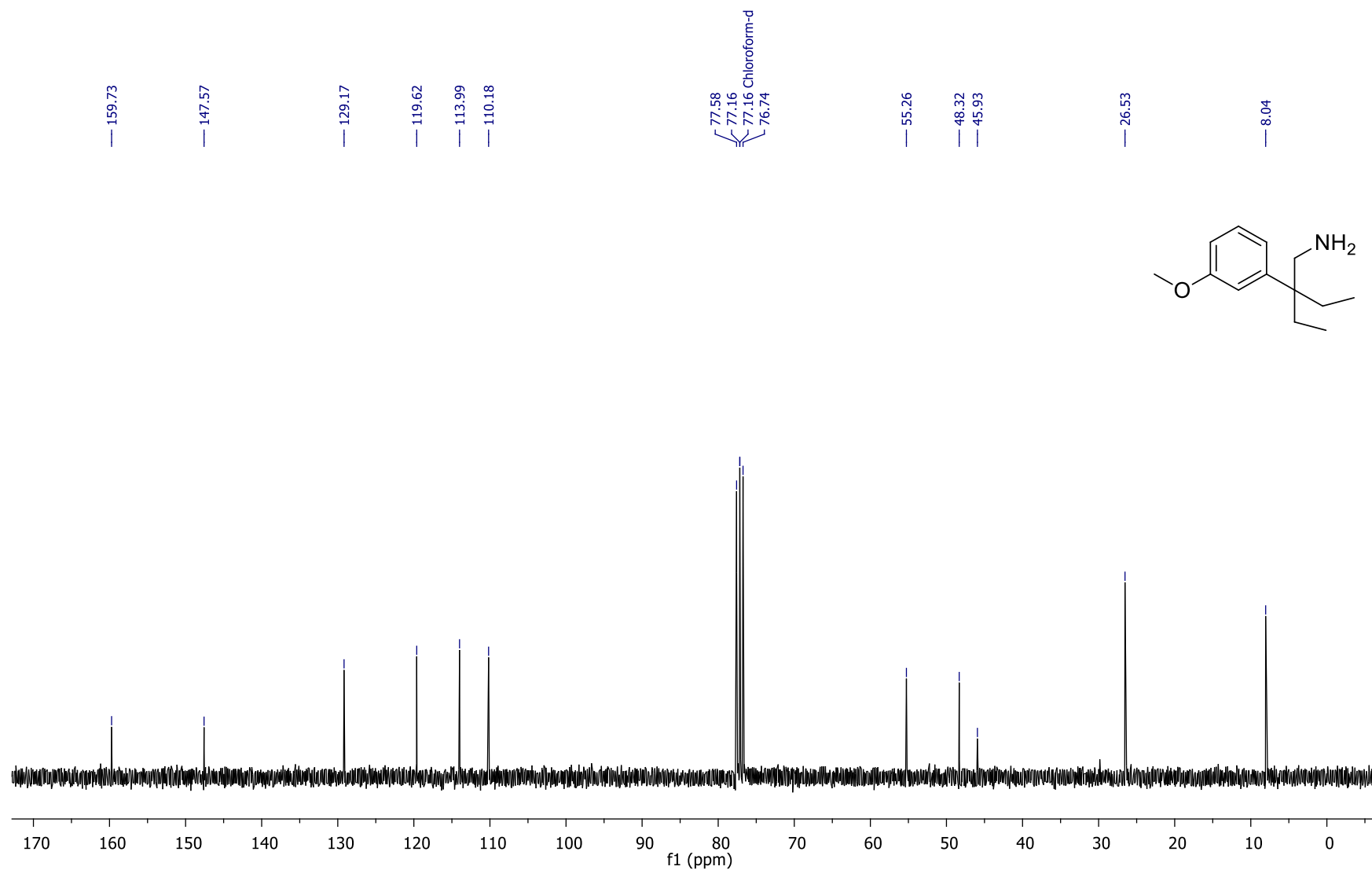


¹H-NMR (300MHz) spectrum of **12b** in CDCl₃

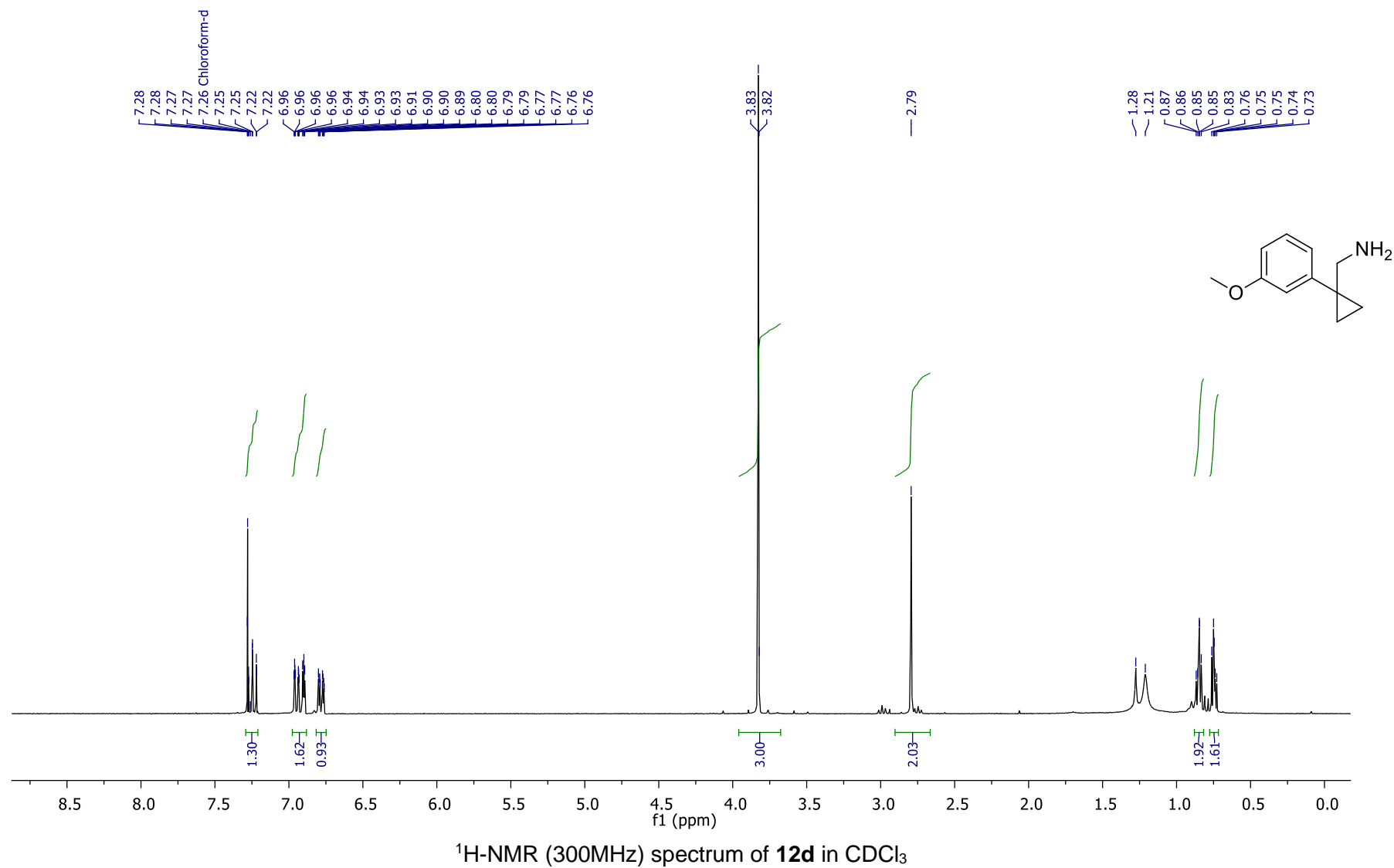


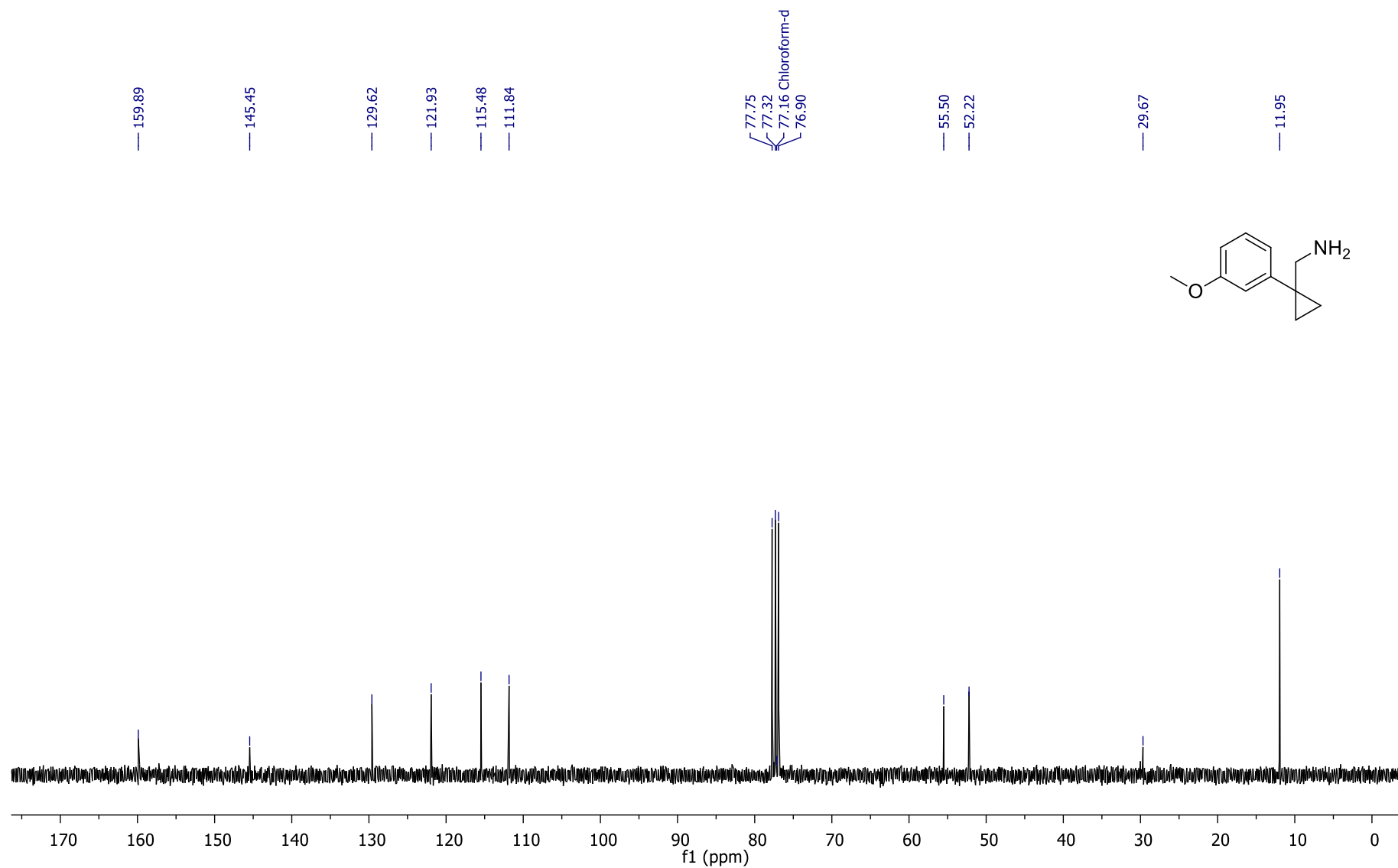
¹³C-NMR (300 MHz) spectrum of **12b** in CDCl₃

¹H-NMR (300MHz) spectrum of **12c** in CDCl₃

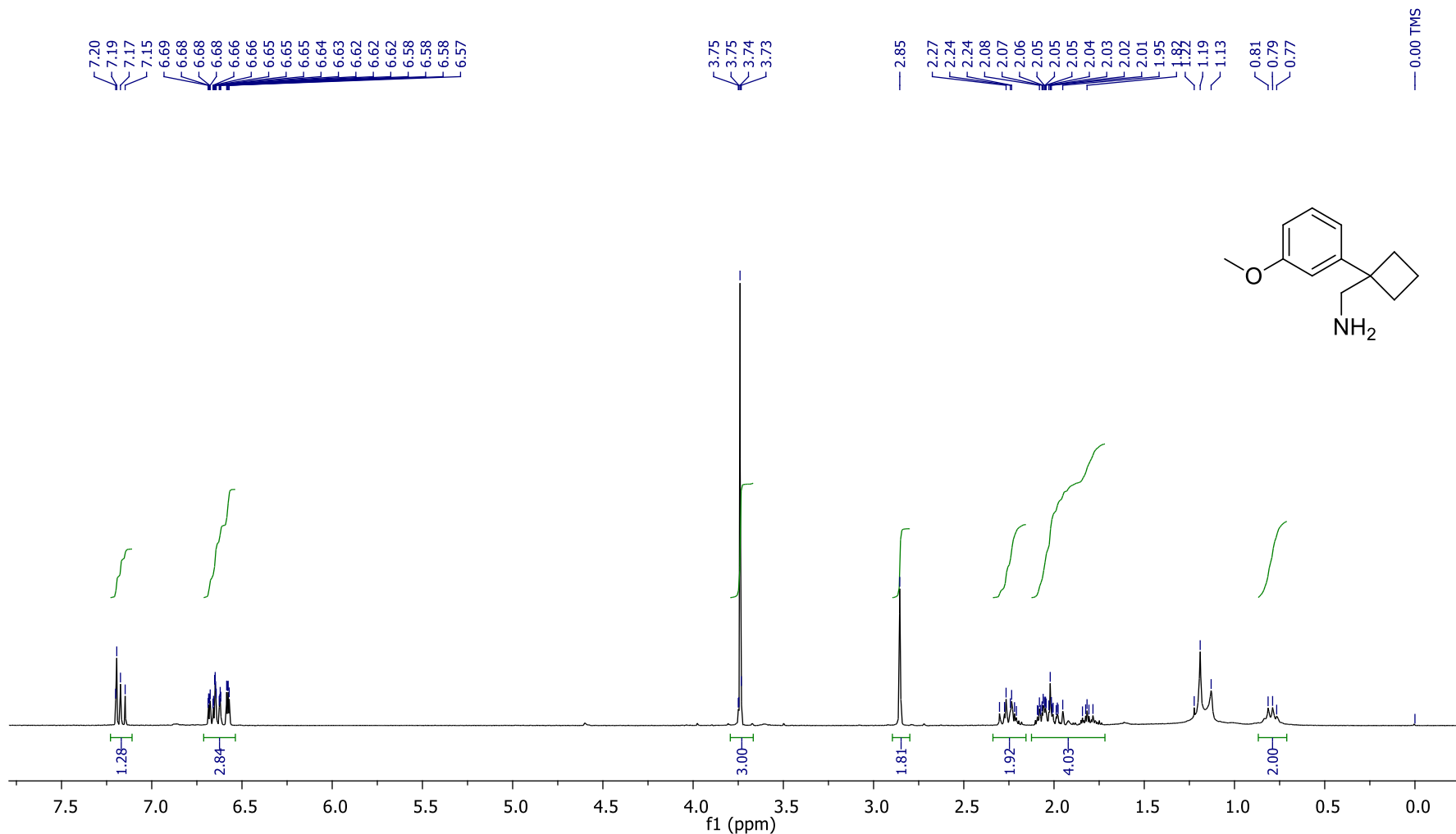


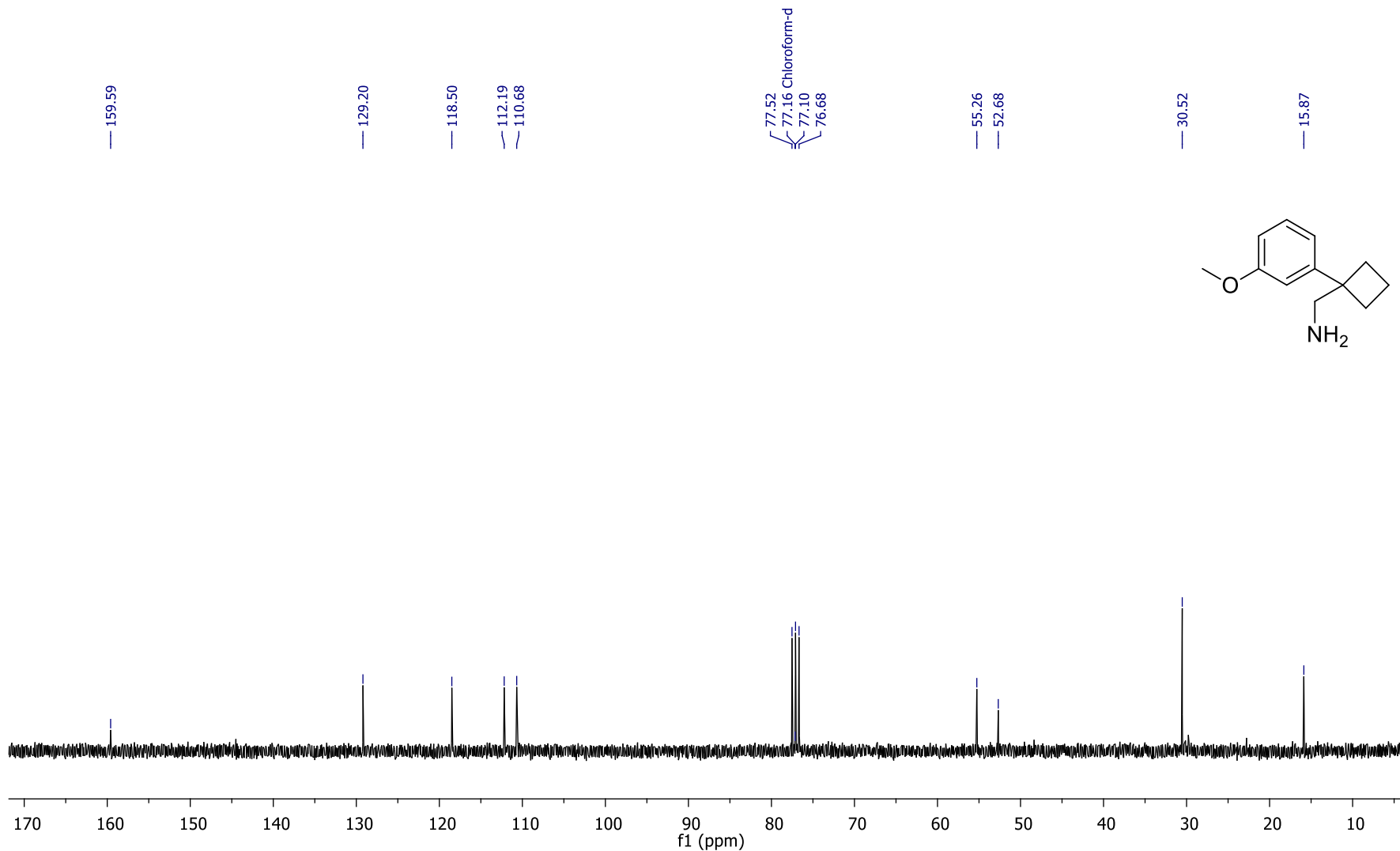
¹³C-NMR (75 MHz) spectrum of 12c in CDCl₃



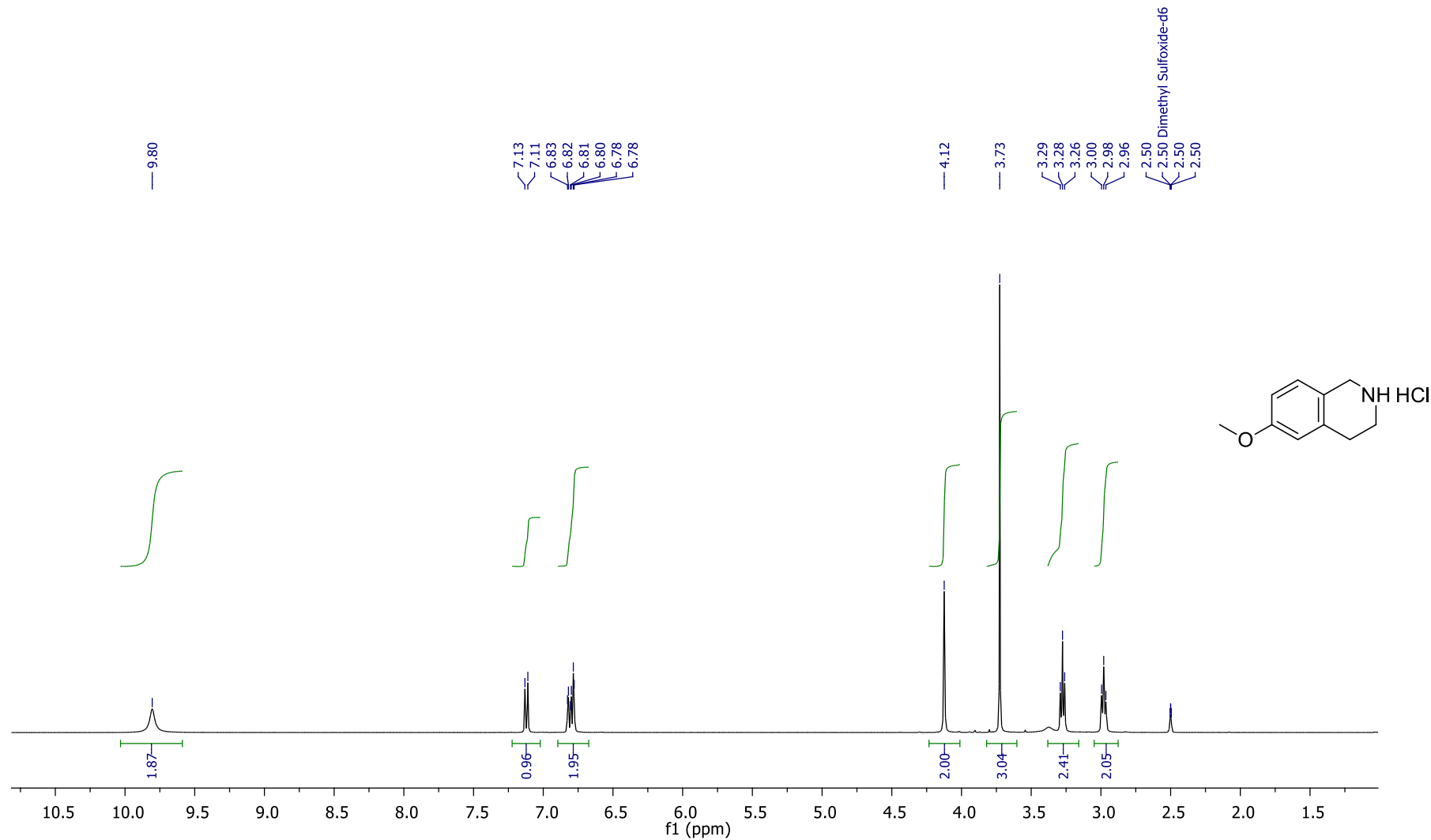


¹³C-NMR (75 MHz) spectrum of **12d** in CDCl₃

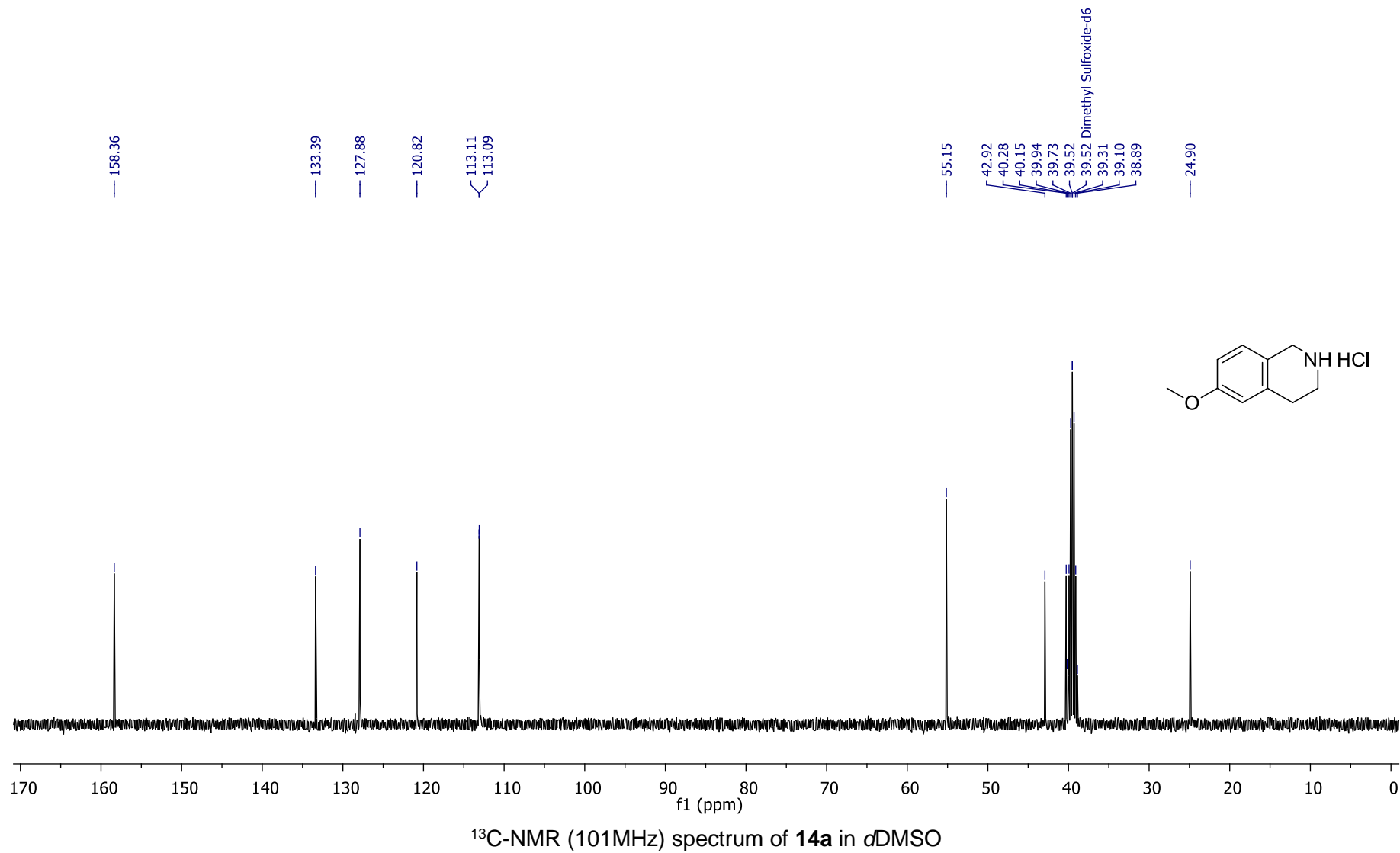


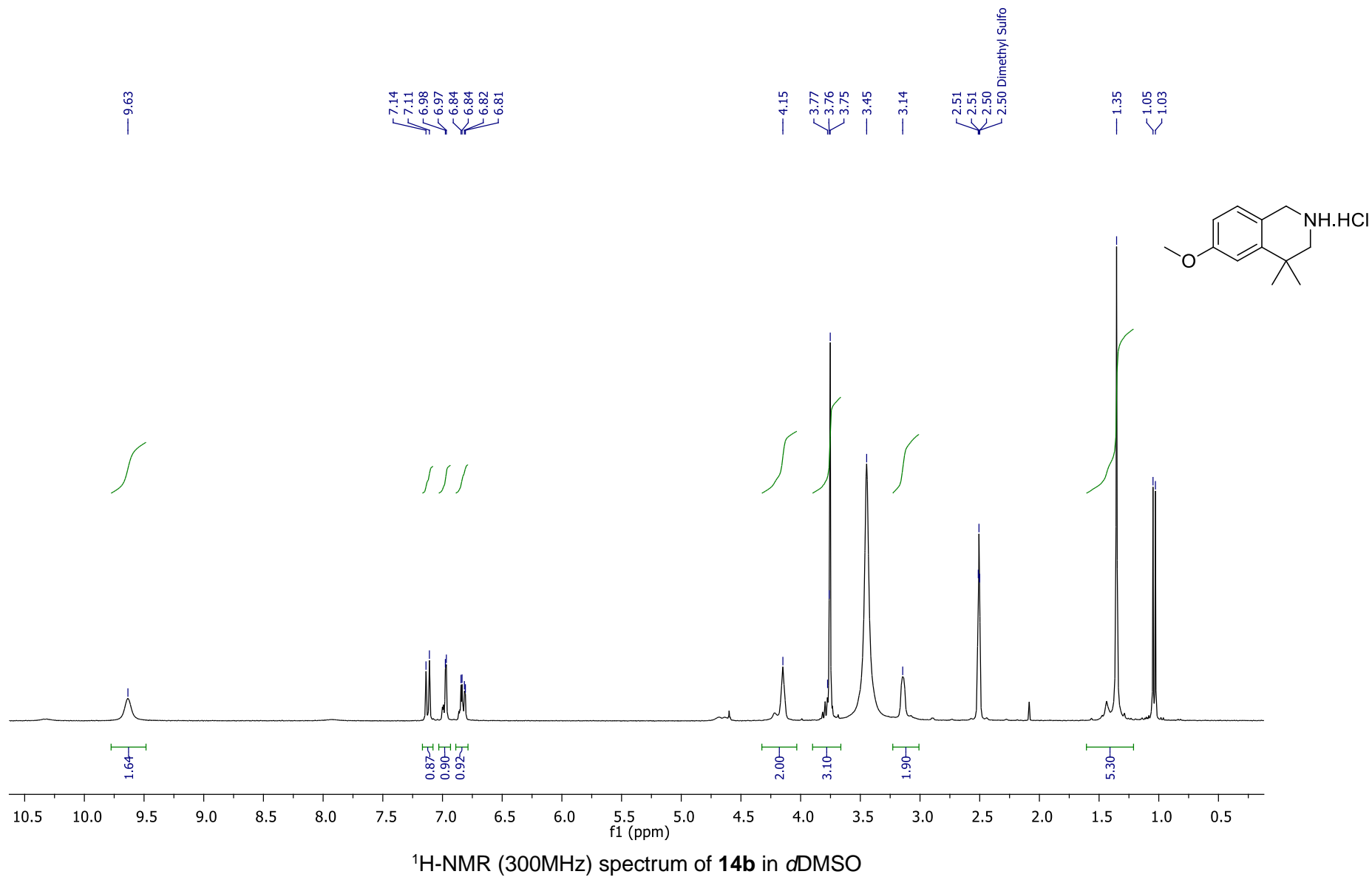


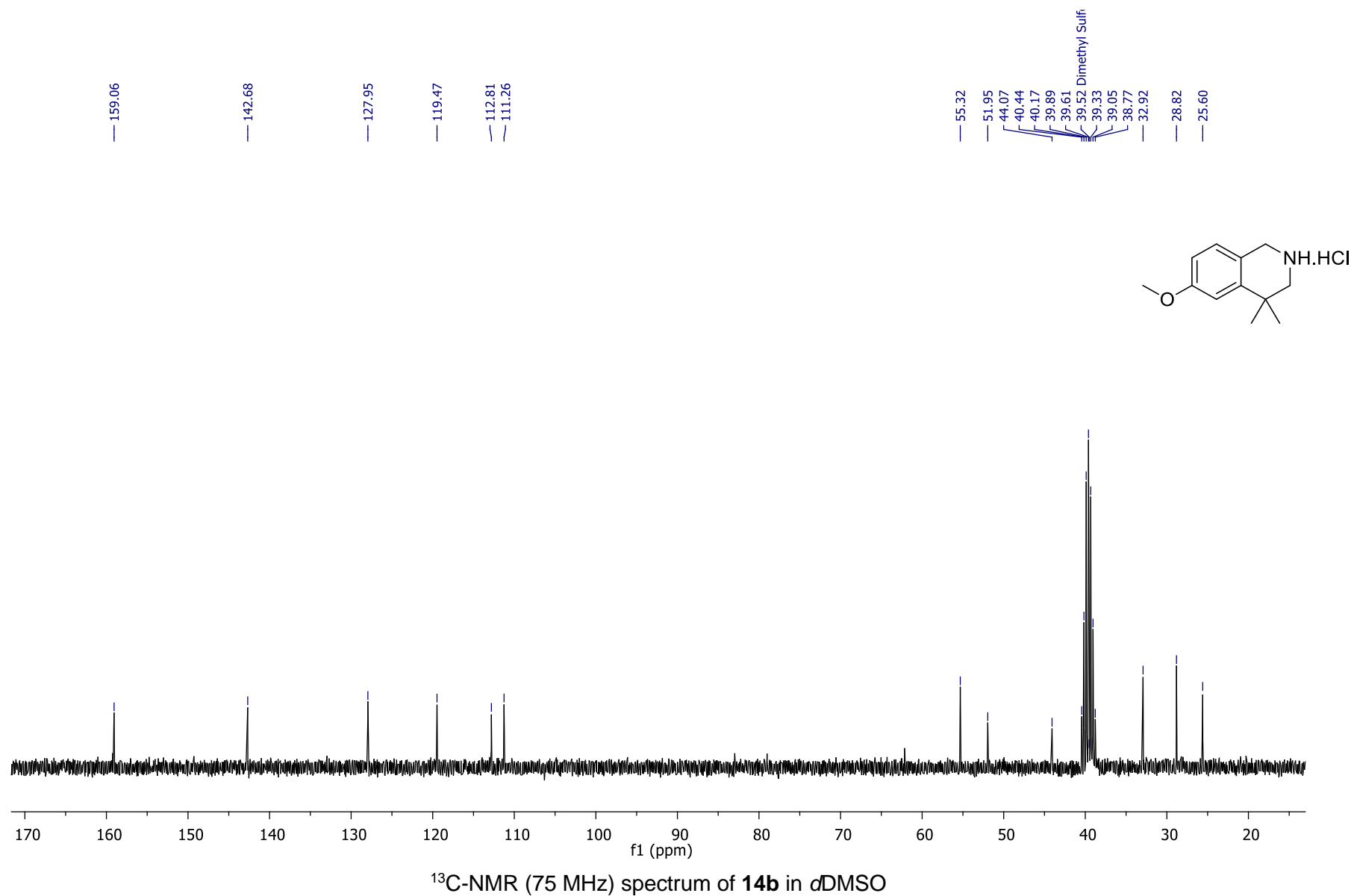
¹³C-NMR (75 MHz) spectrum of **12e** in CDCl₃

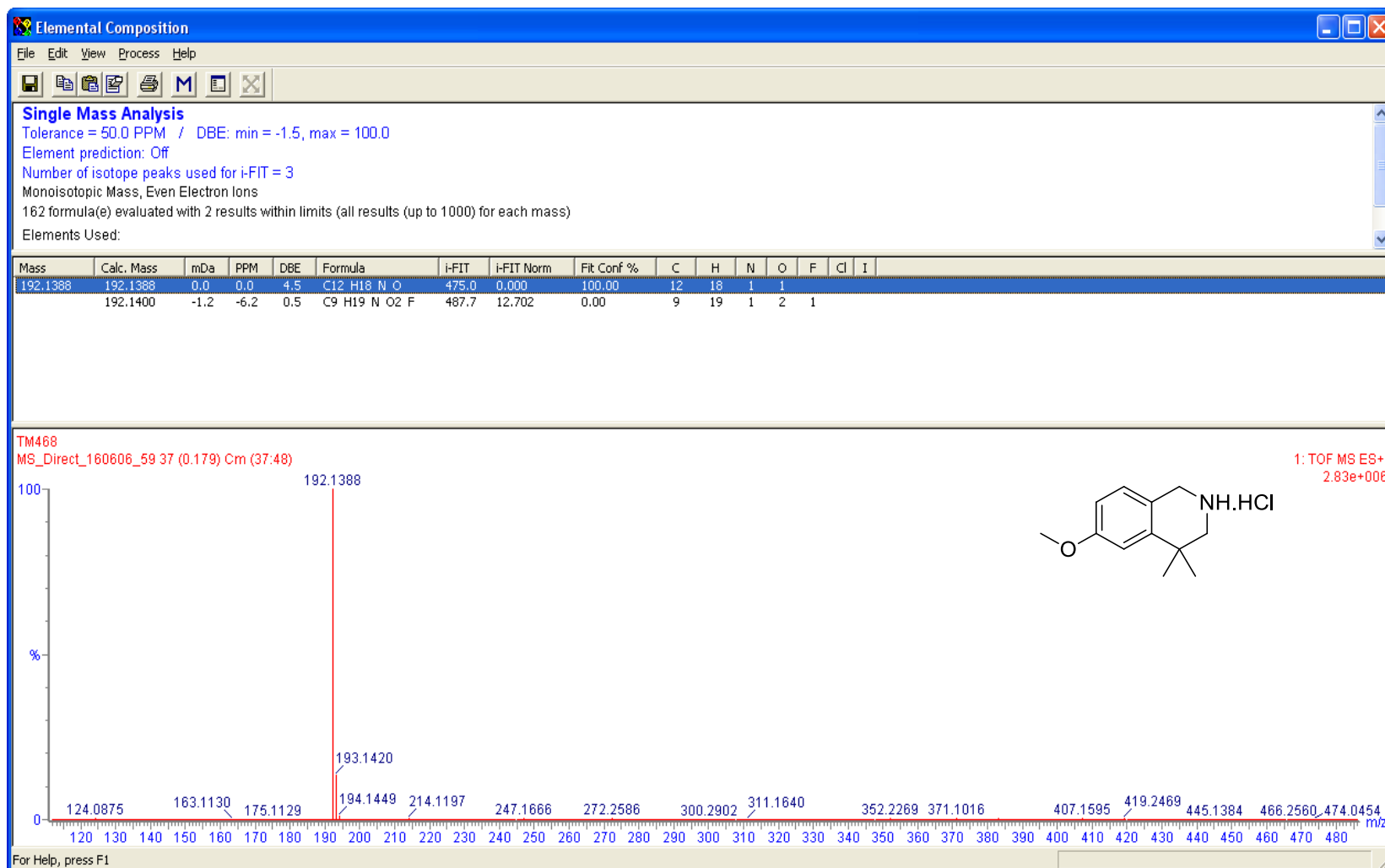


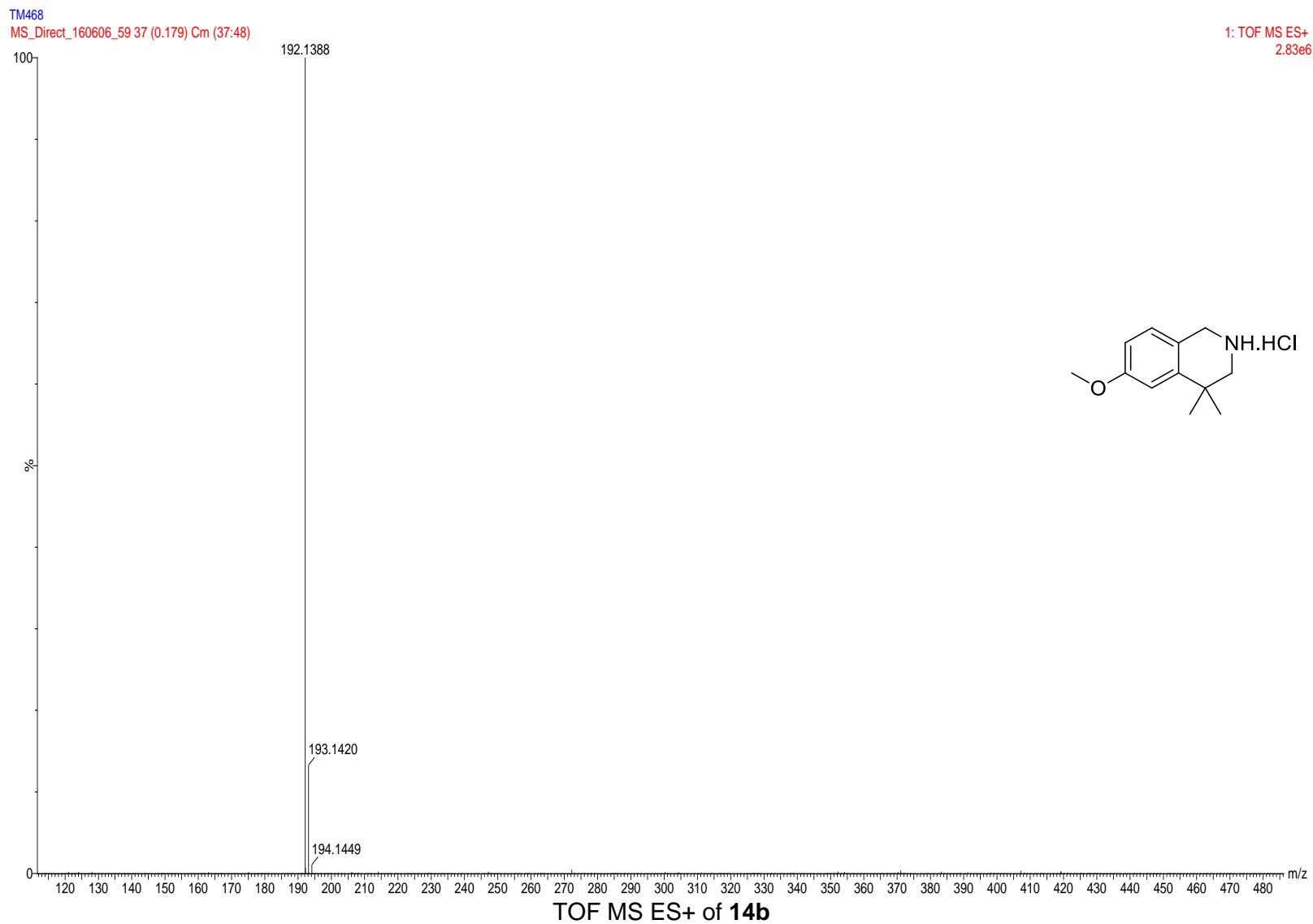
¹H-NMR (400MHz) spectrum of **14a** in *d*DMSO

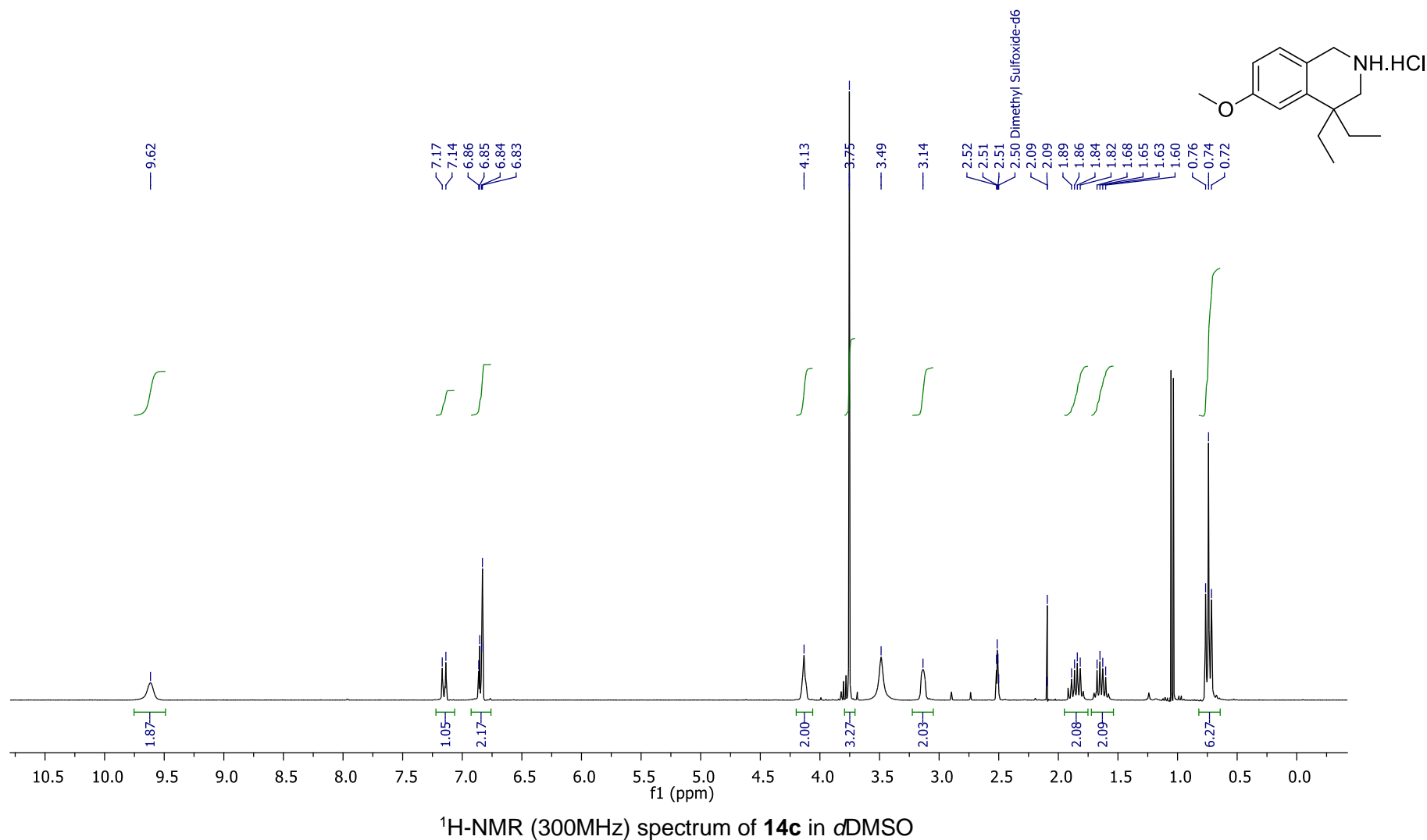


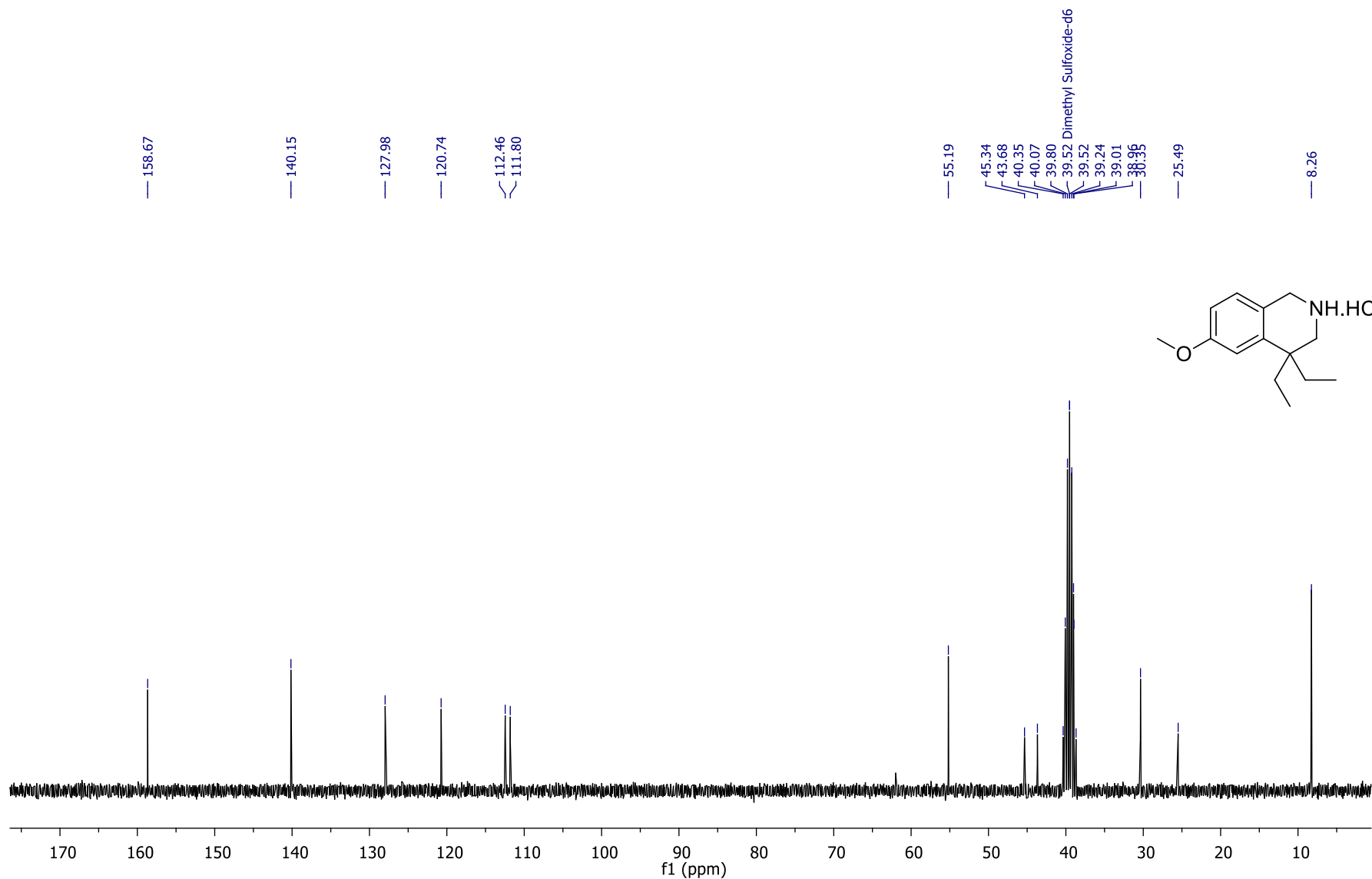




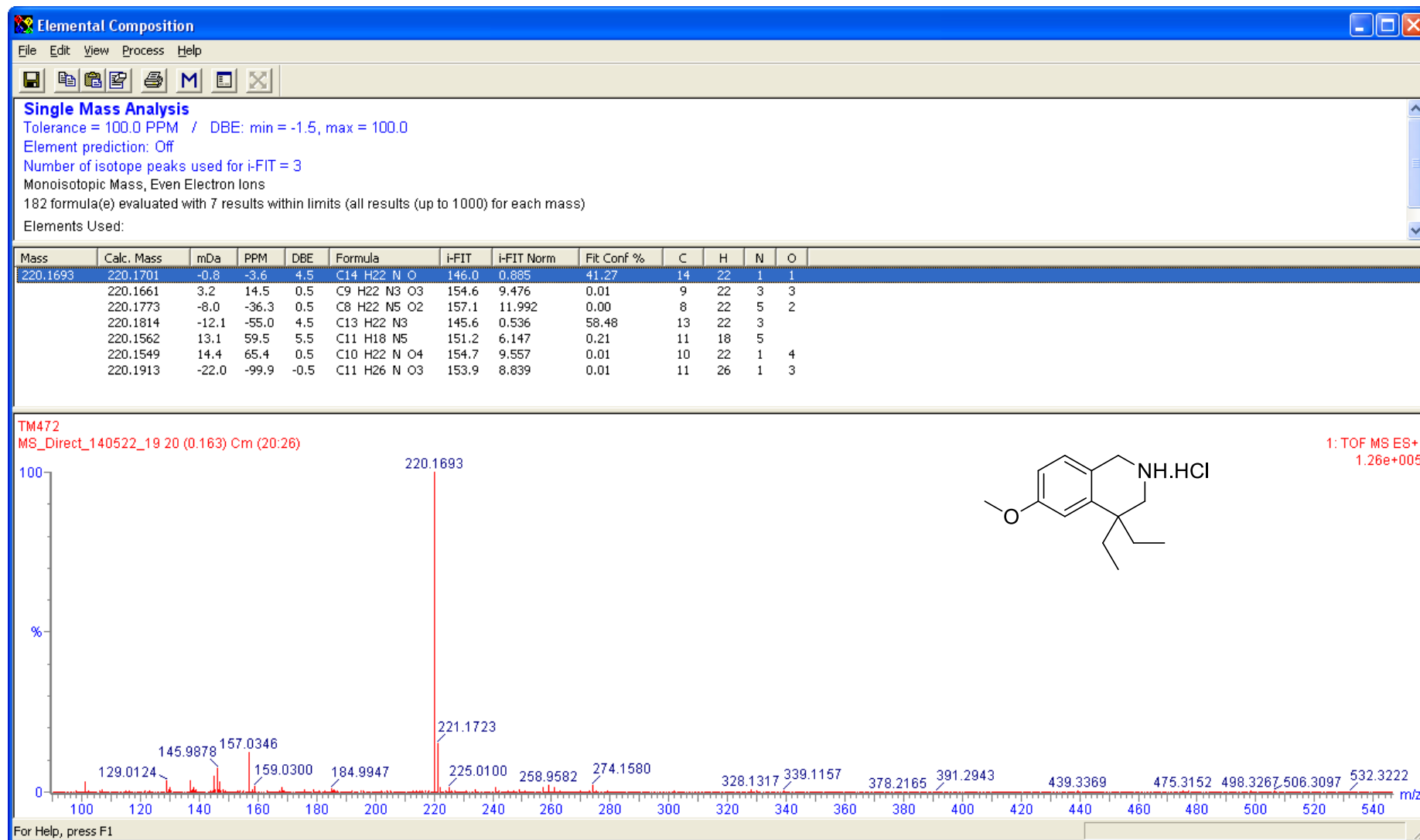
TOF MS ES+ of **14b**



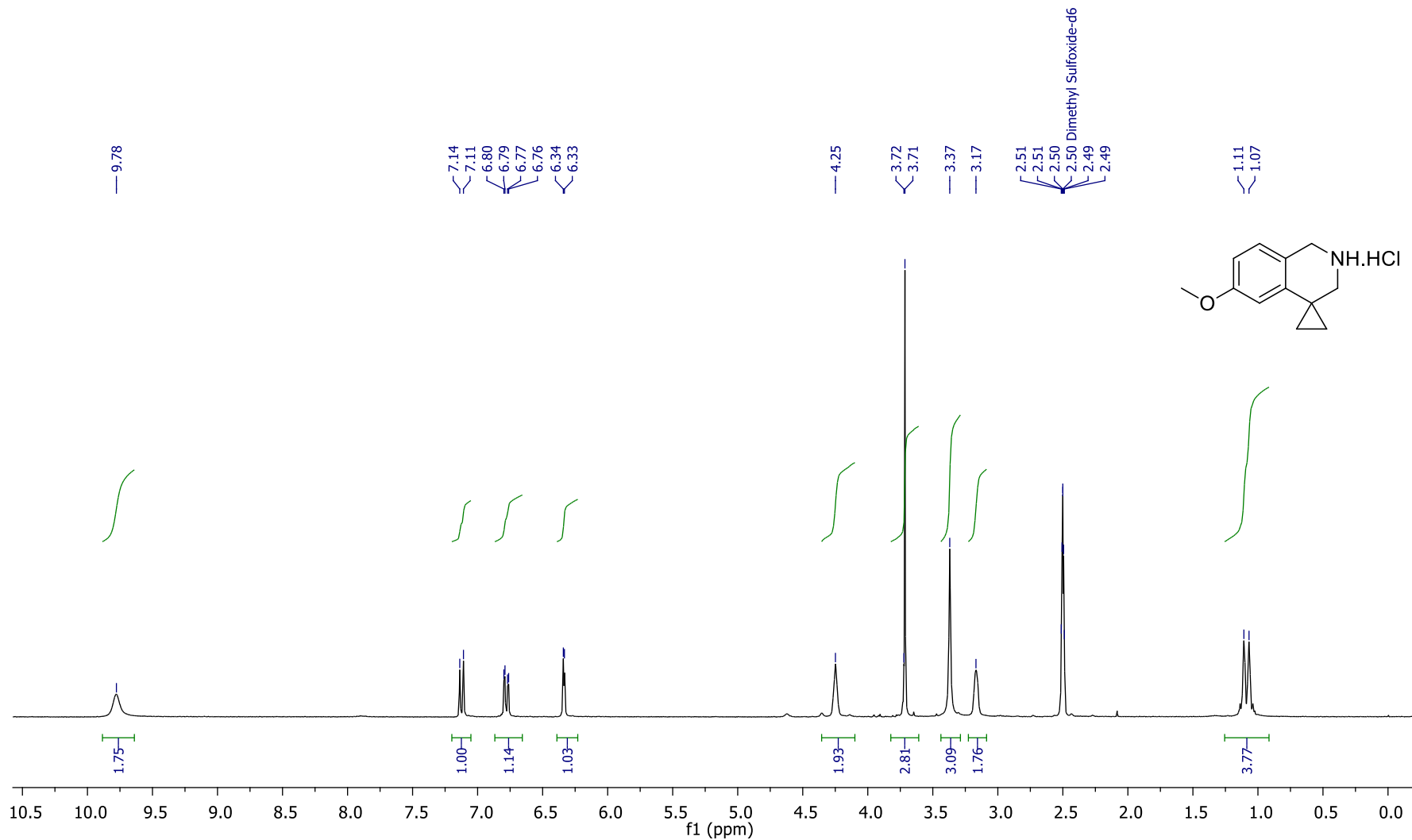




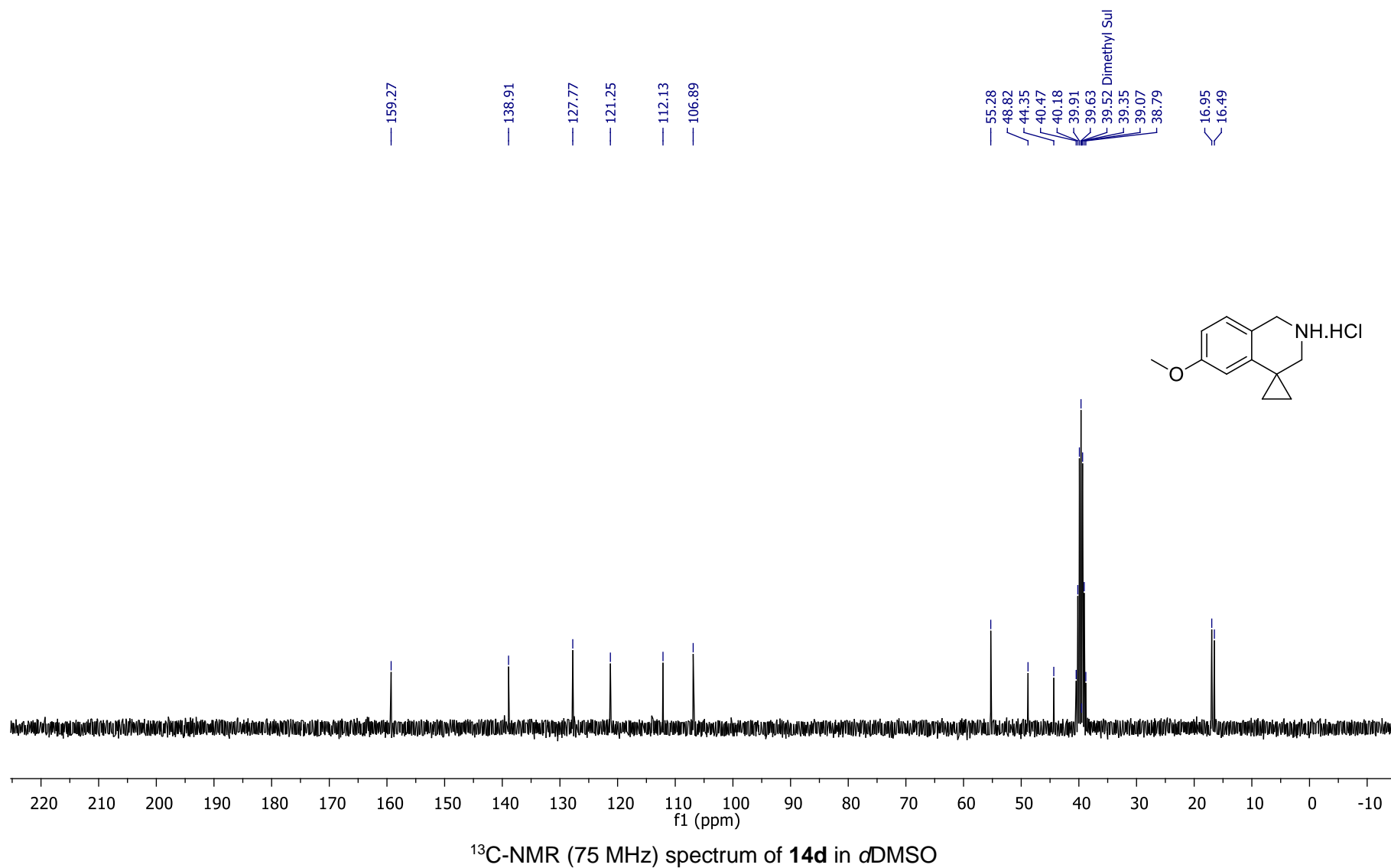
¹³C-NMR (75 MHz) spectrum of 14c in dDMSO

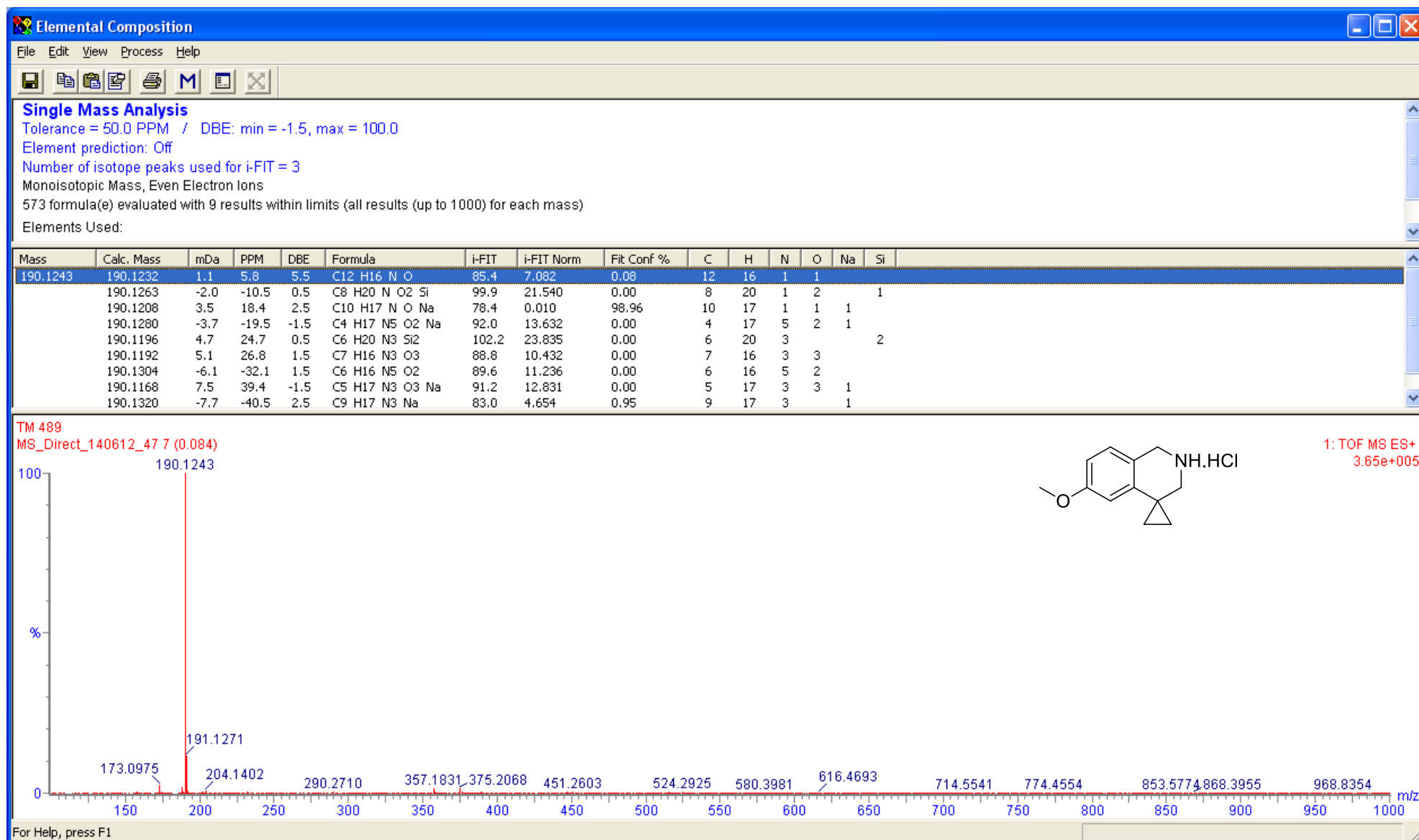


TOF MS ES+ of 14c

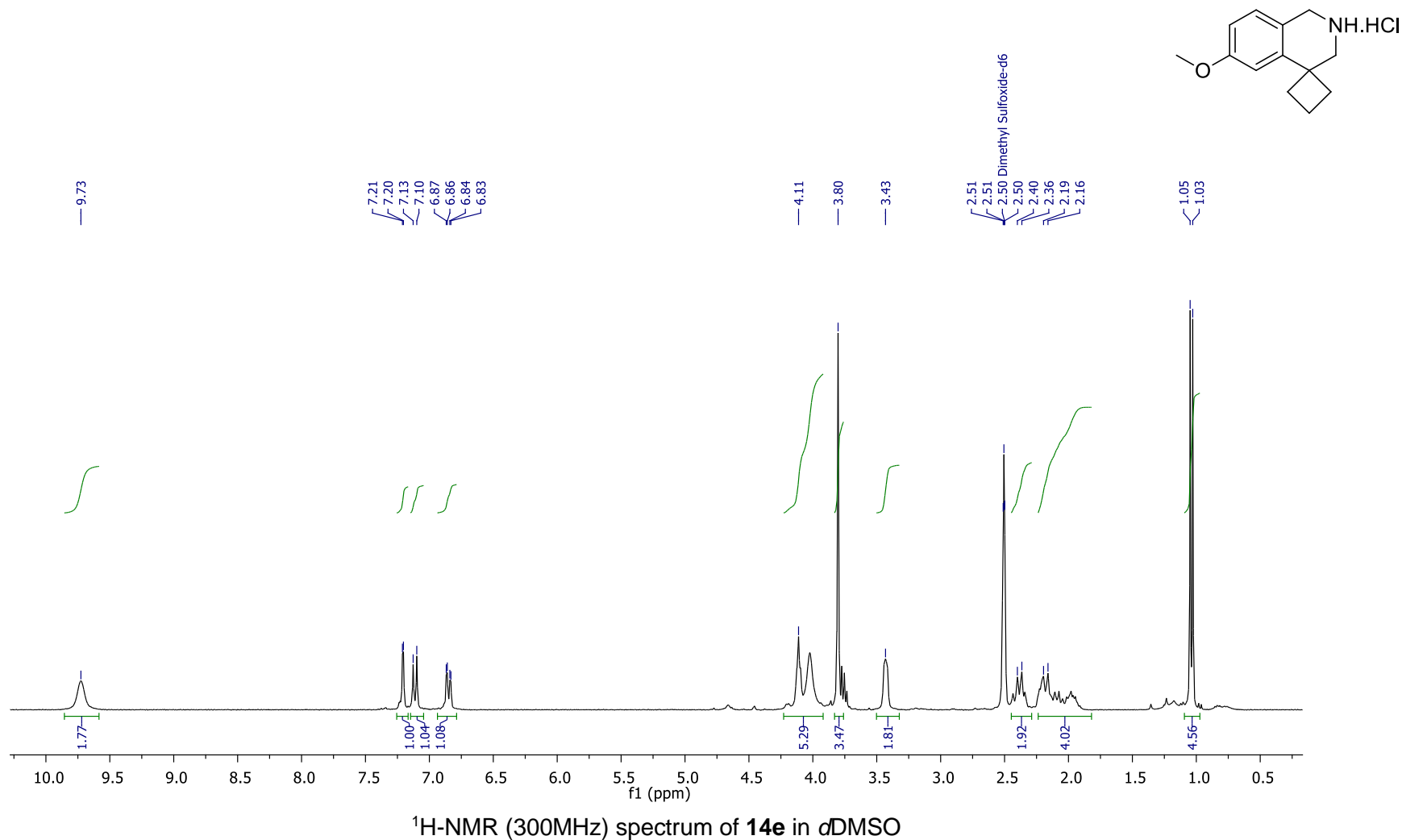


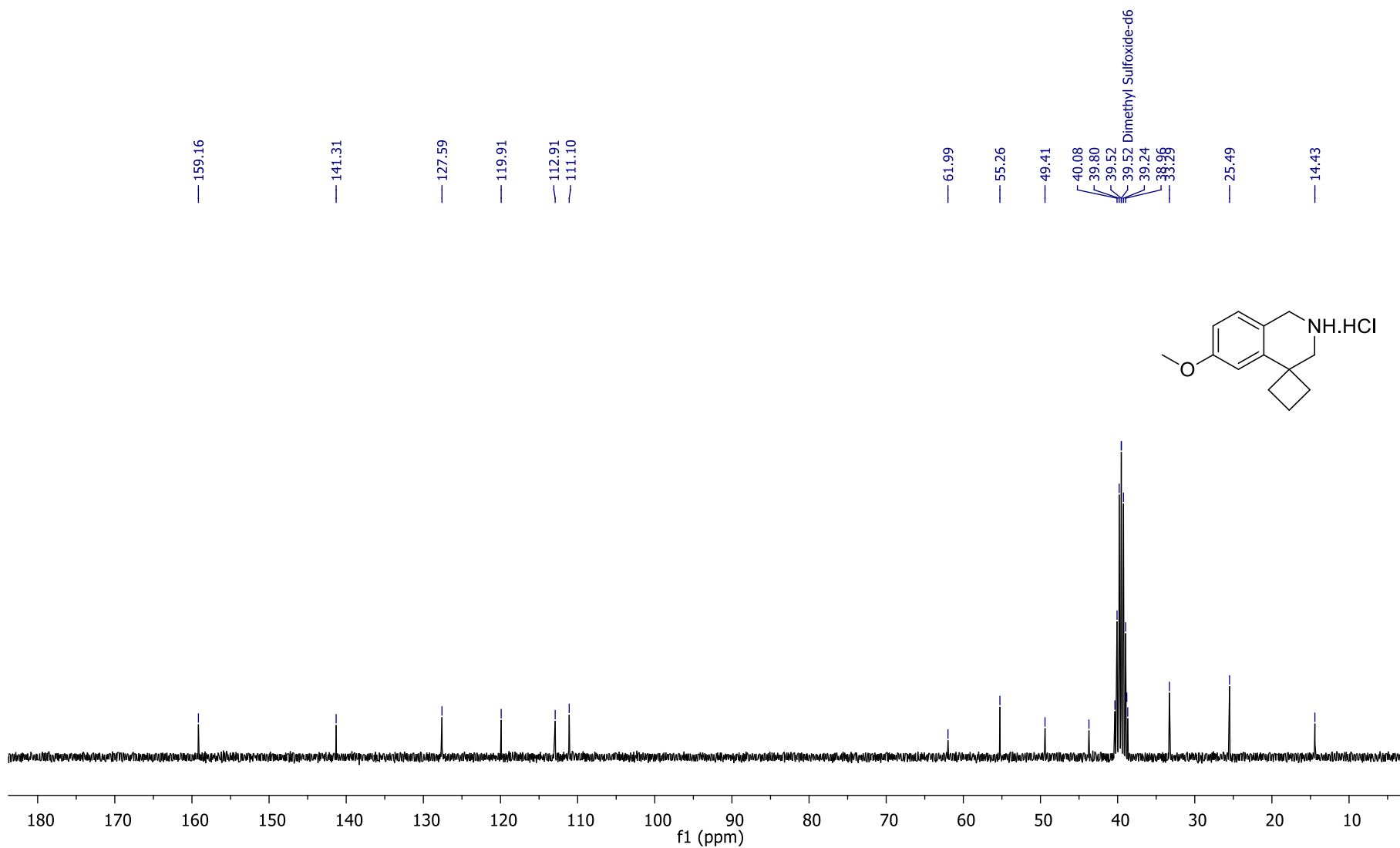
¹H-NMR (300MHz) spectrum of **14d** in dMSO





TOF MS ES+ of 14d



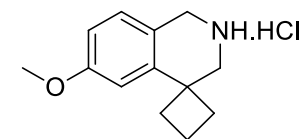
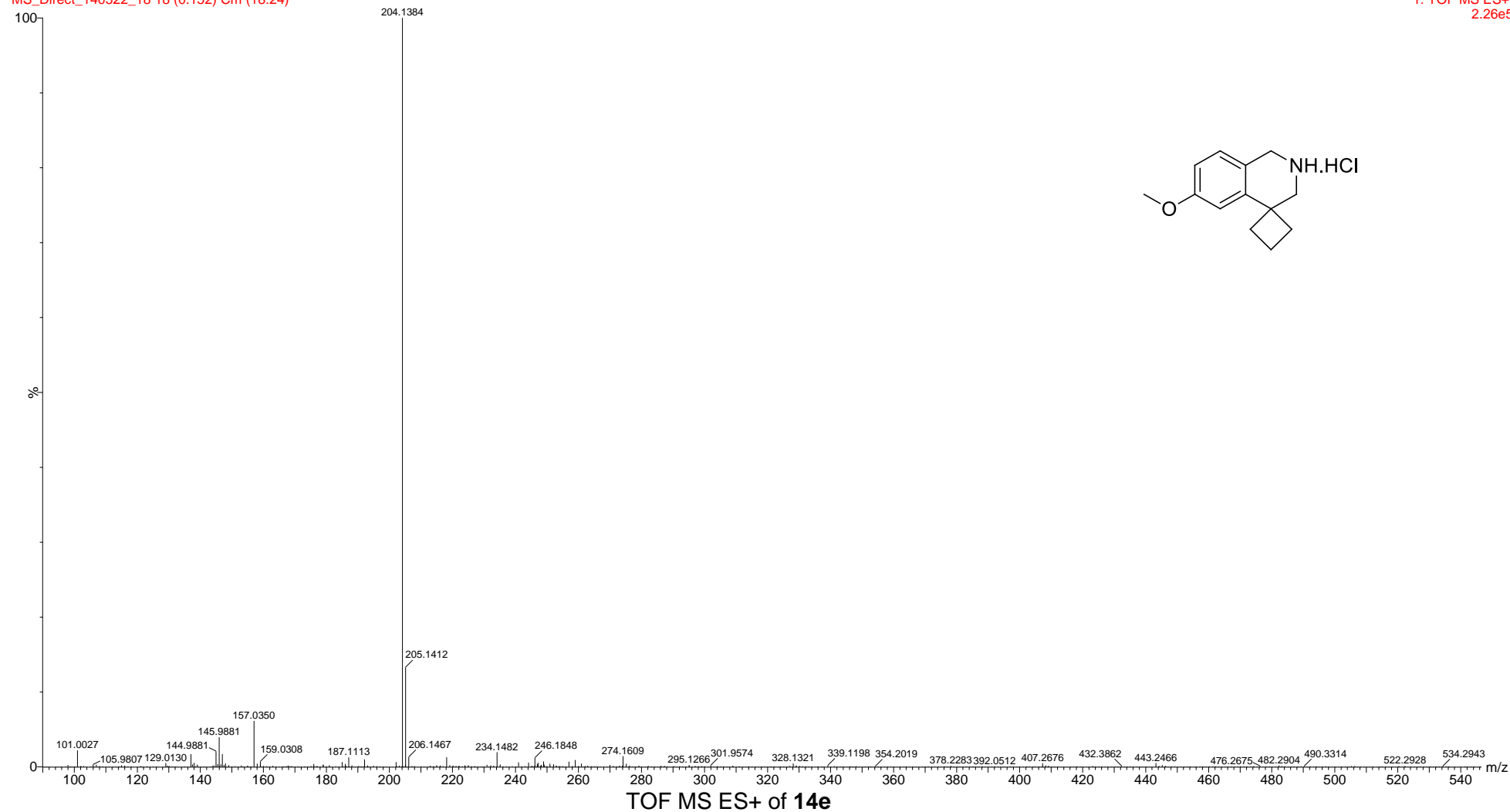


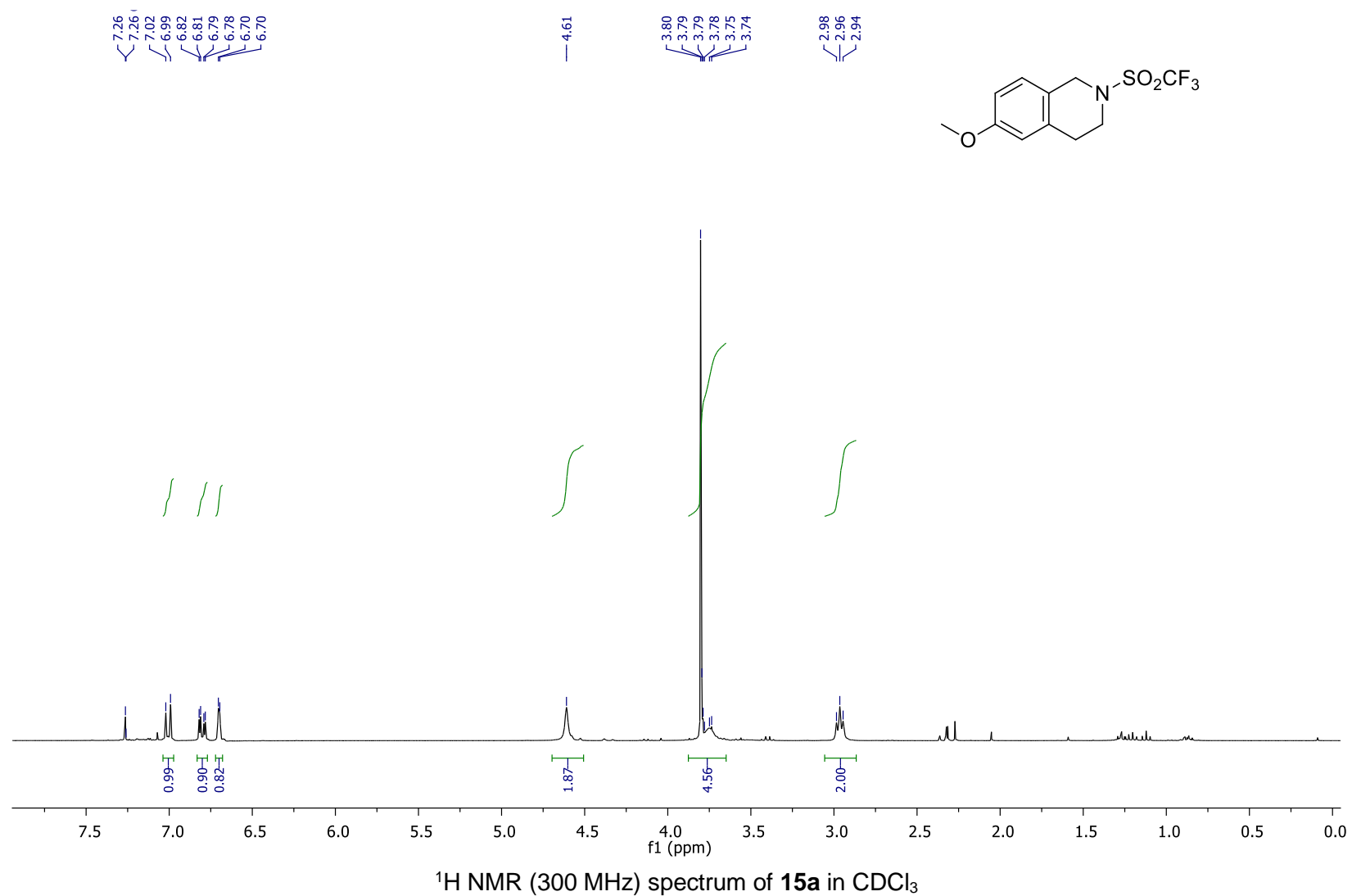
^{13}C -NMR (300 MHz) spectrum of **14e** in *d*DMSO

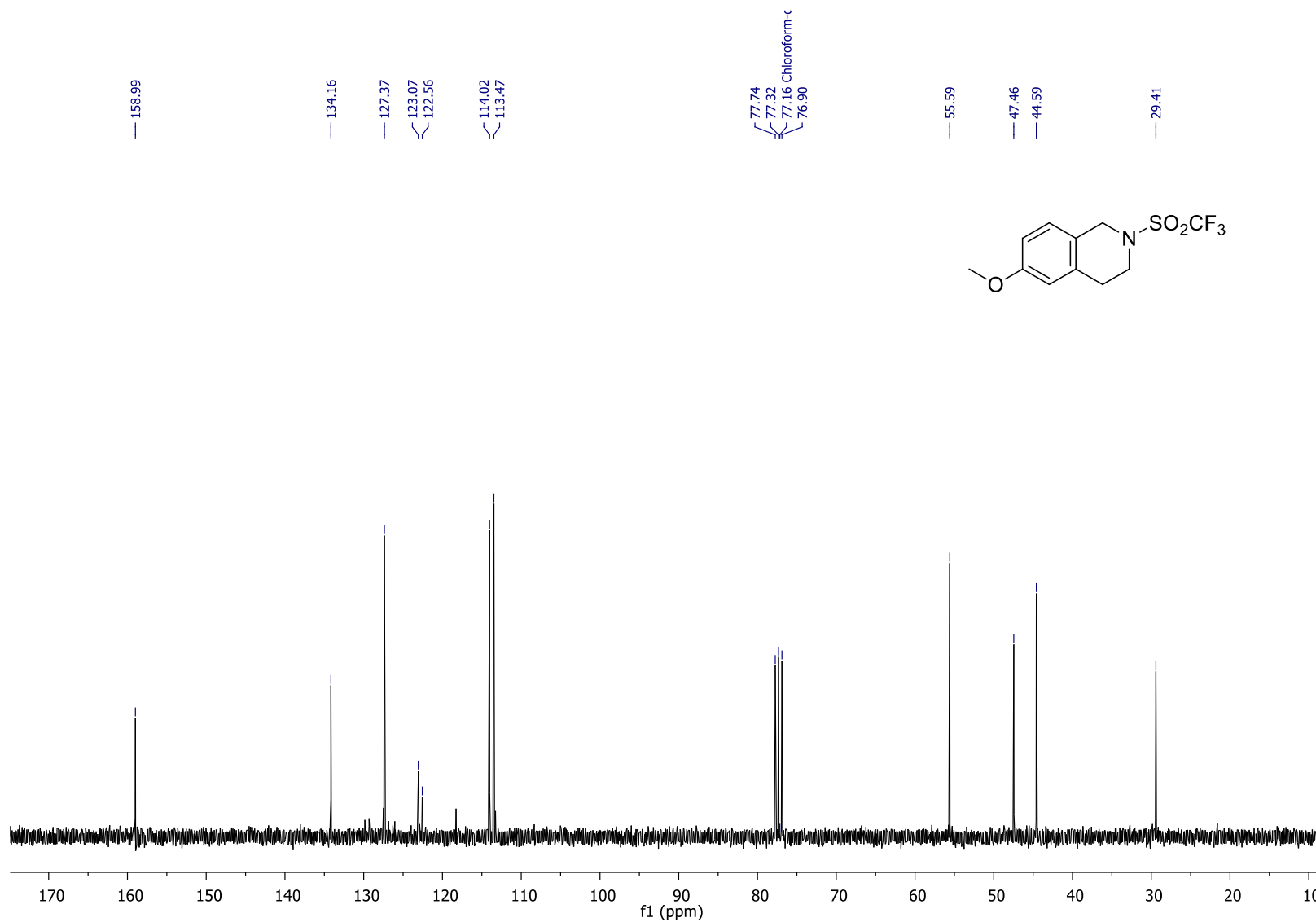
TM471

MS_Direct_140522_18 18 (0.152) Cm (18:24)

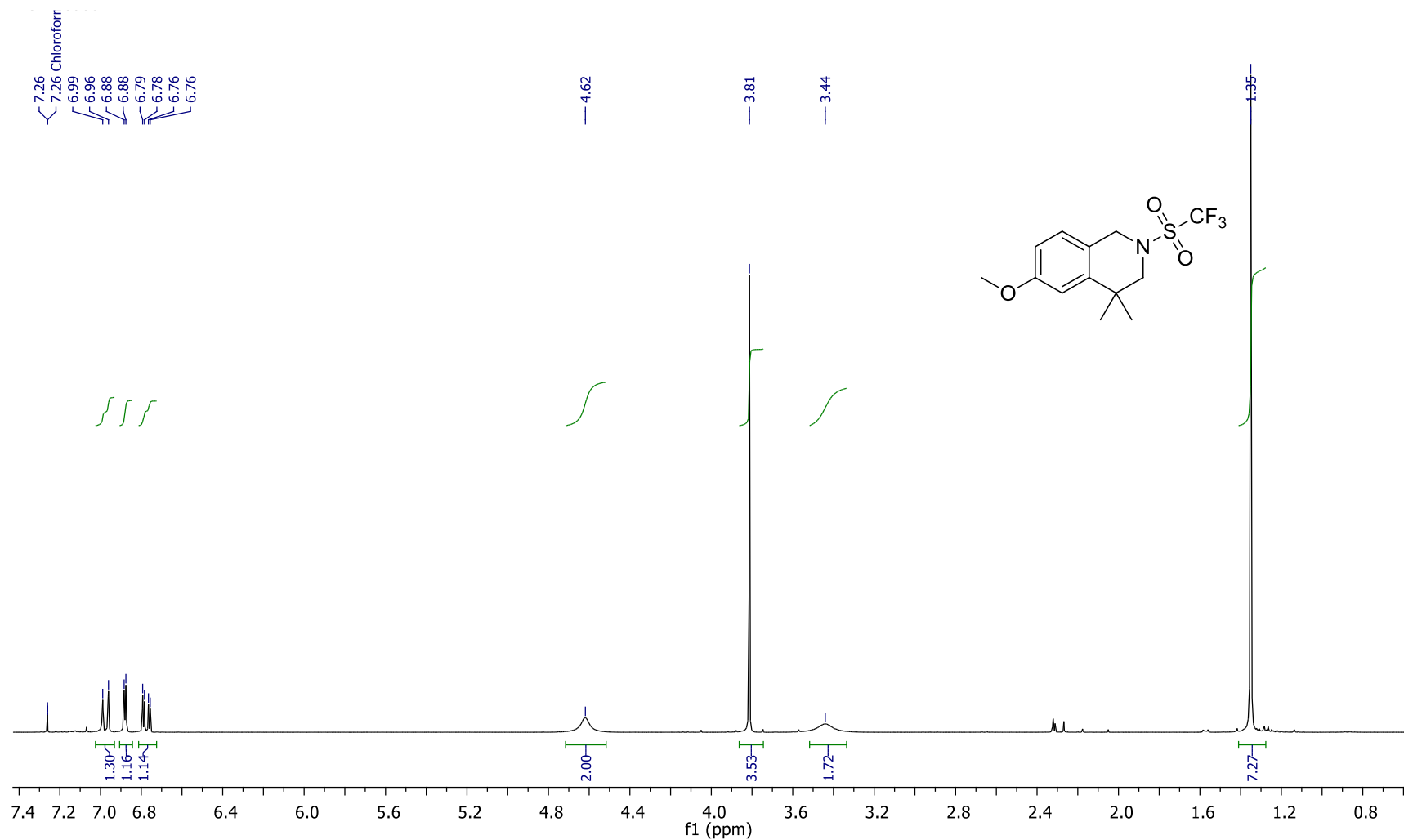
1: TOF MS ES+
2.26e5



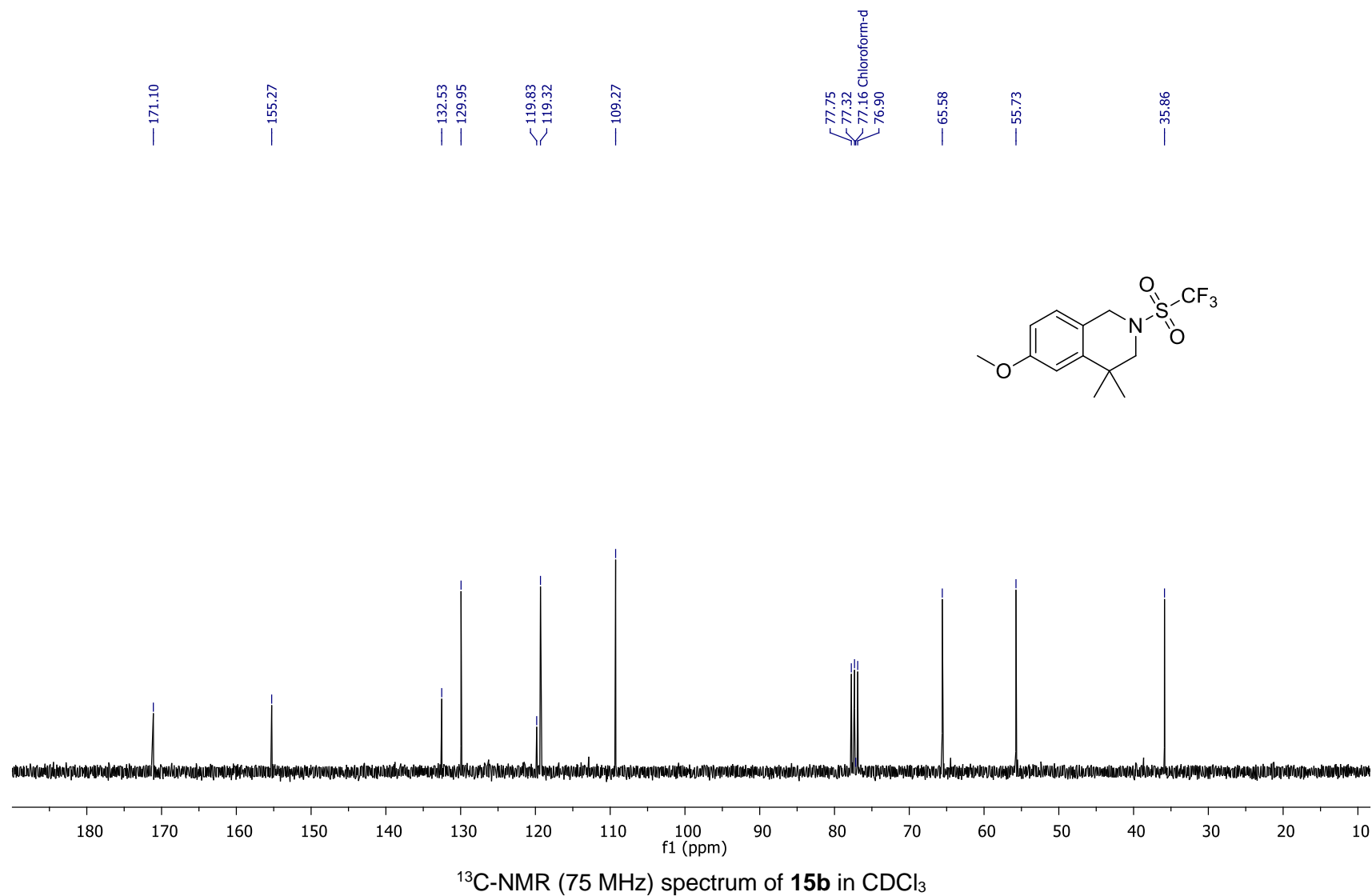


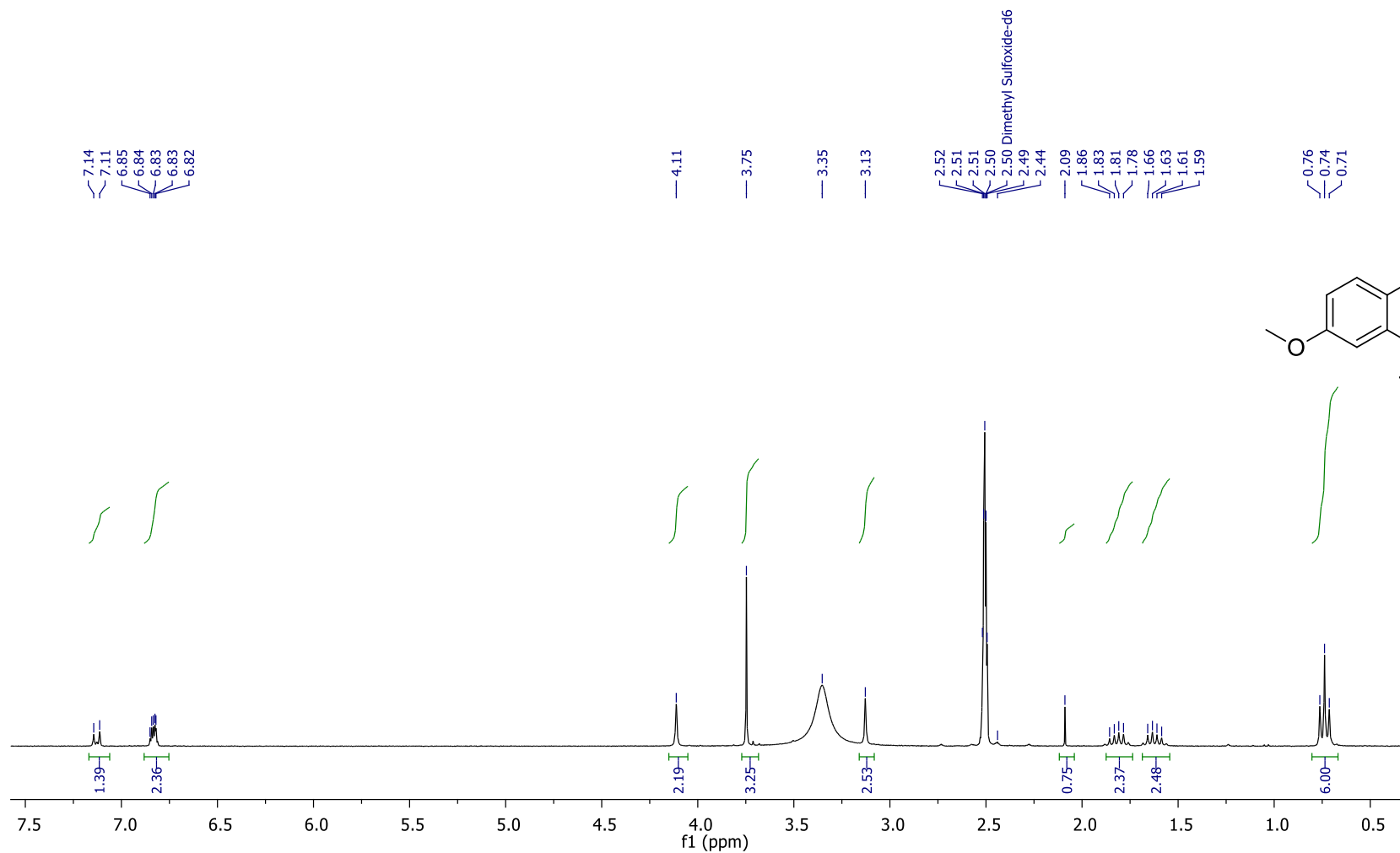


¹³C NMR (75 MHz) spectrum of **15a** in CDCl₃

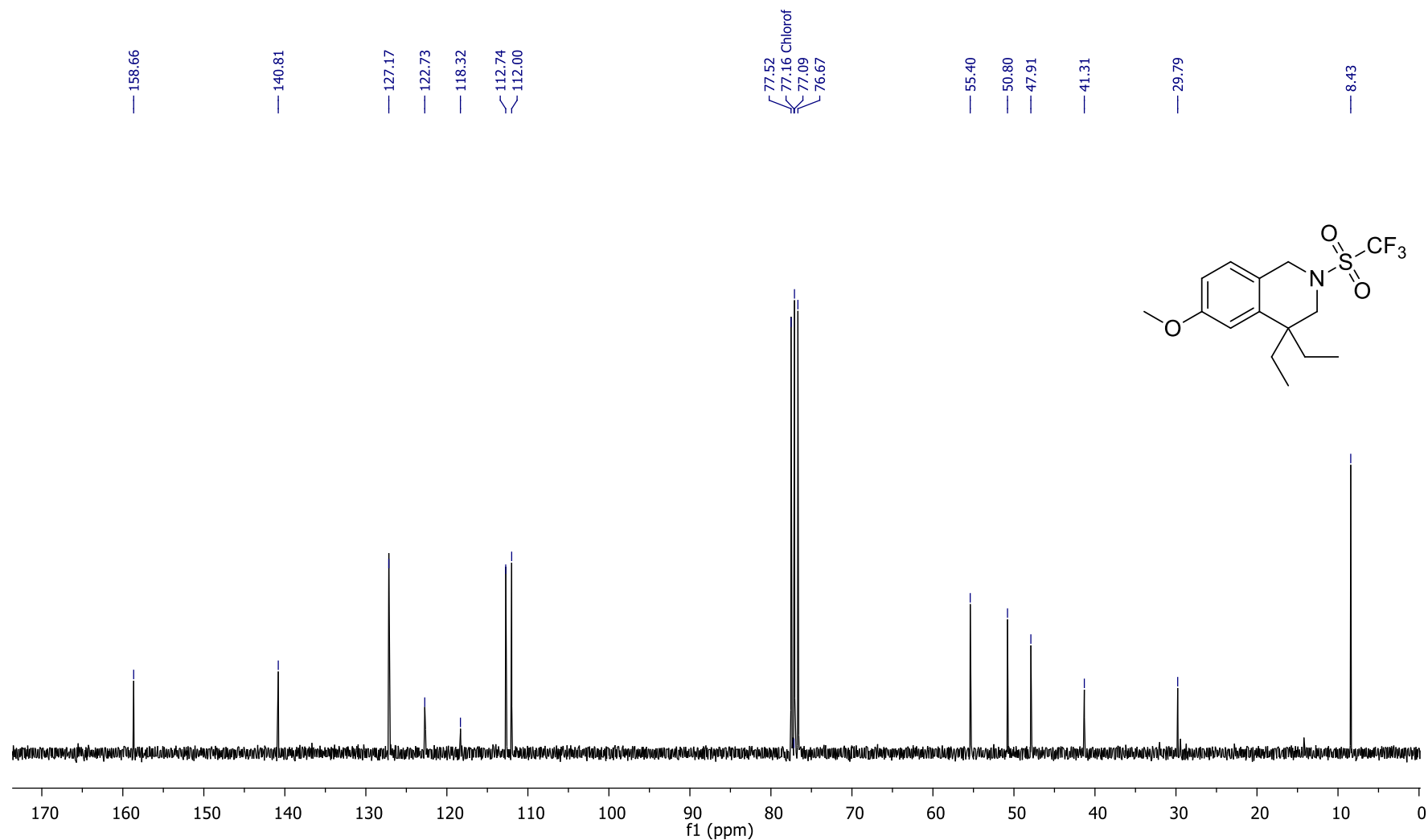


¹H-NMR (300MHz) spectrum of **15b** in CDCl₃

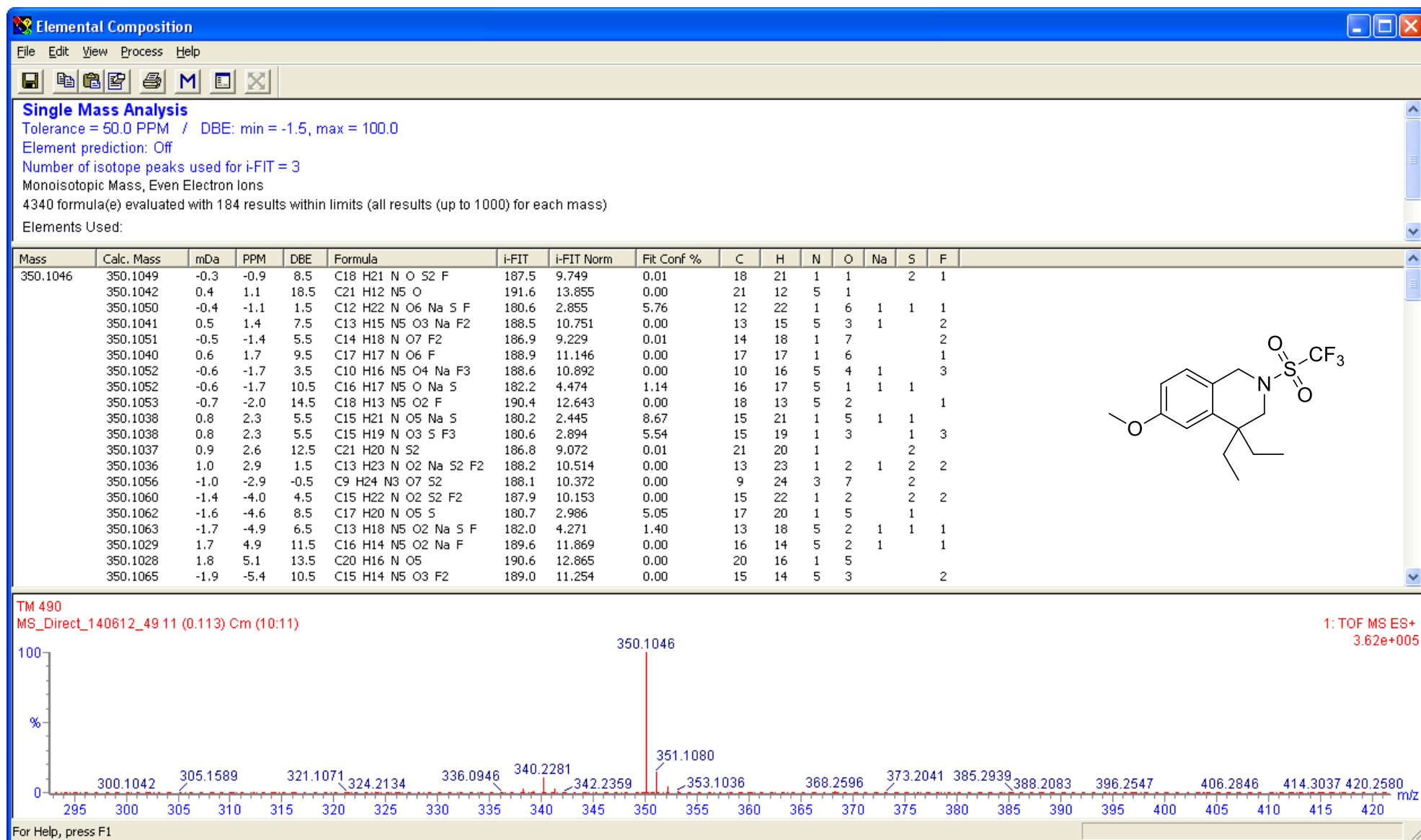




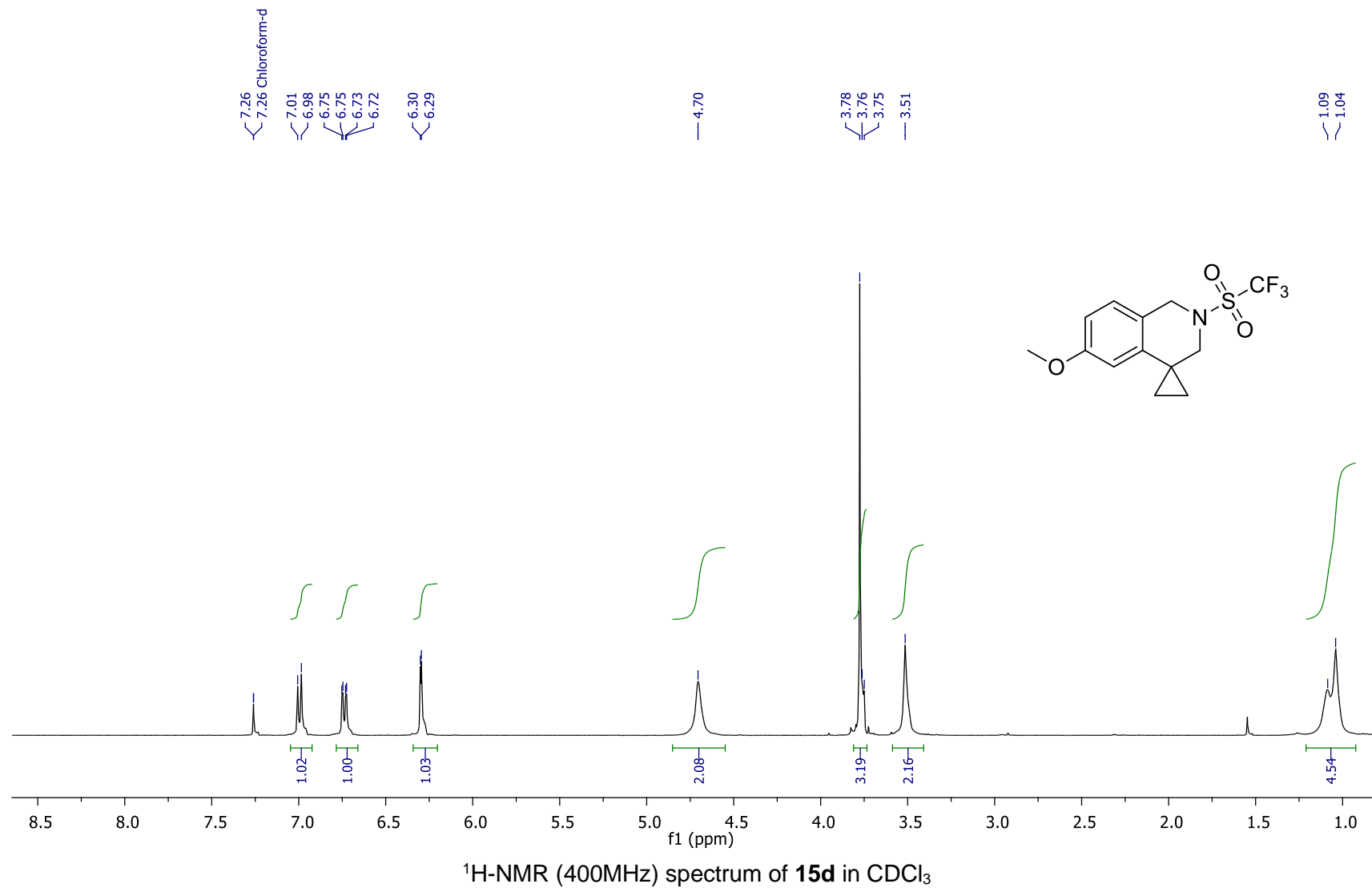
¹H NMR (300MHz) spectrum of 15c in dDMSO

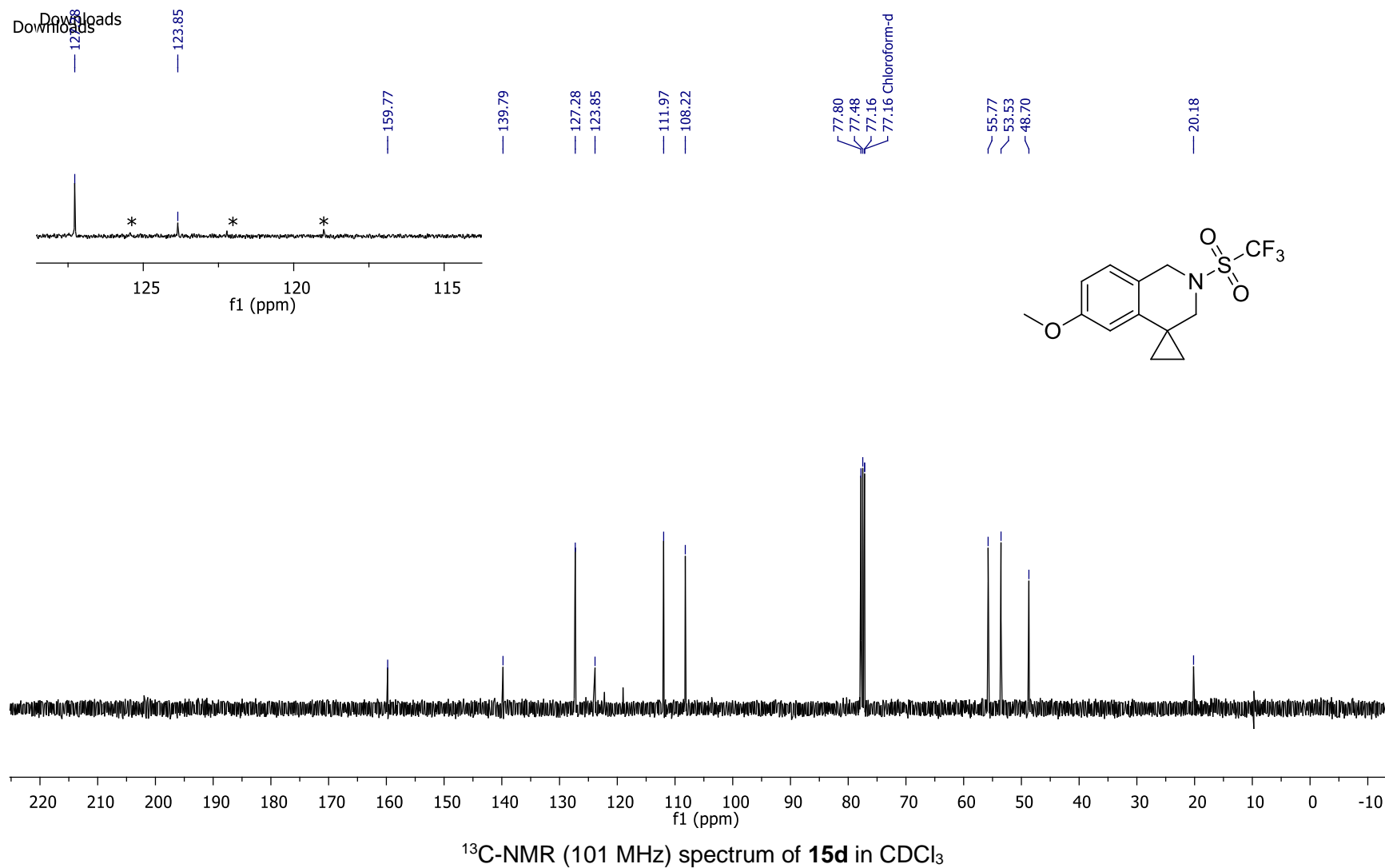


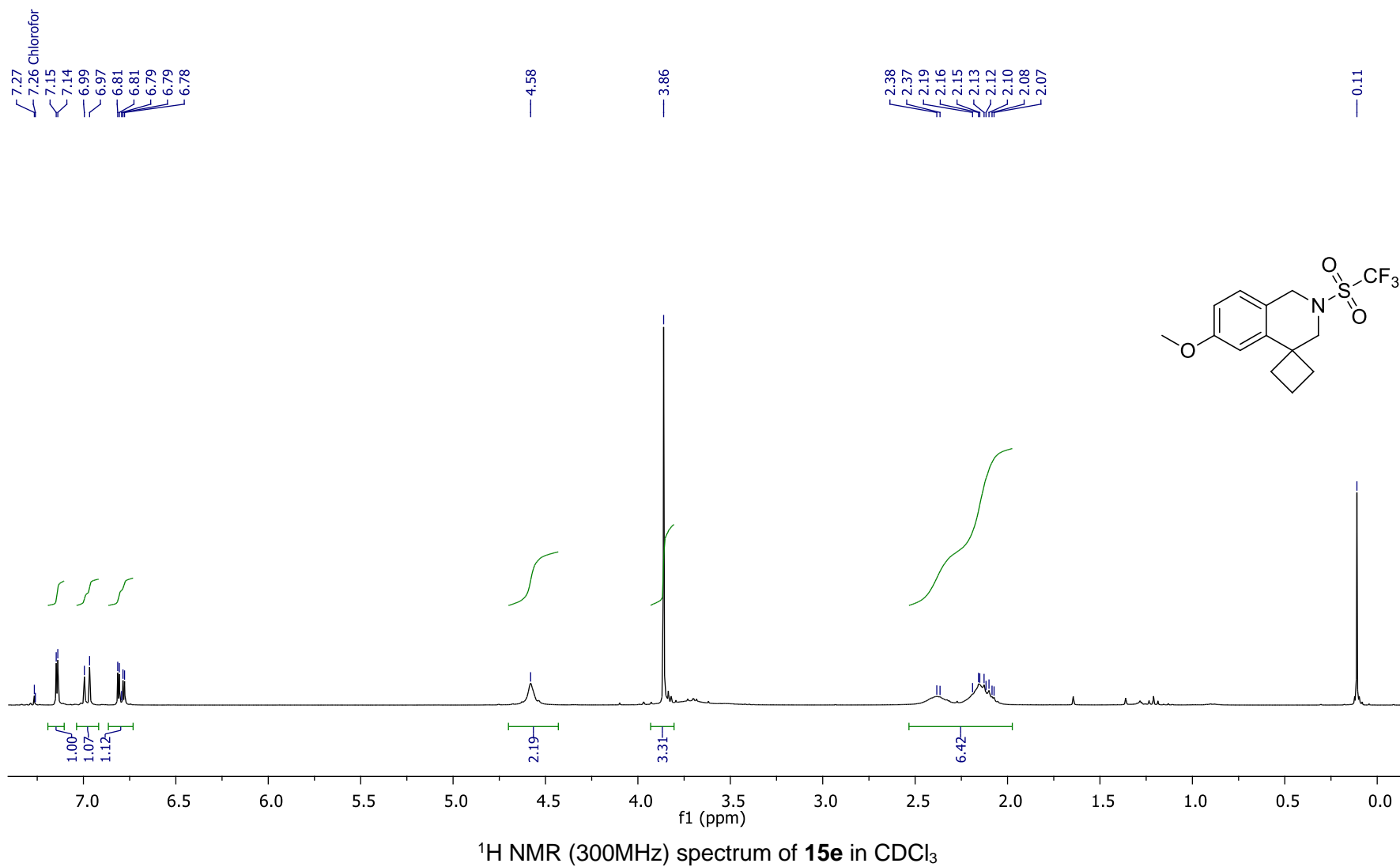
¹³C NMR (300 MHz) spectrum of **15c** in CDCl₃

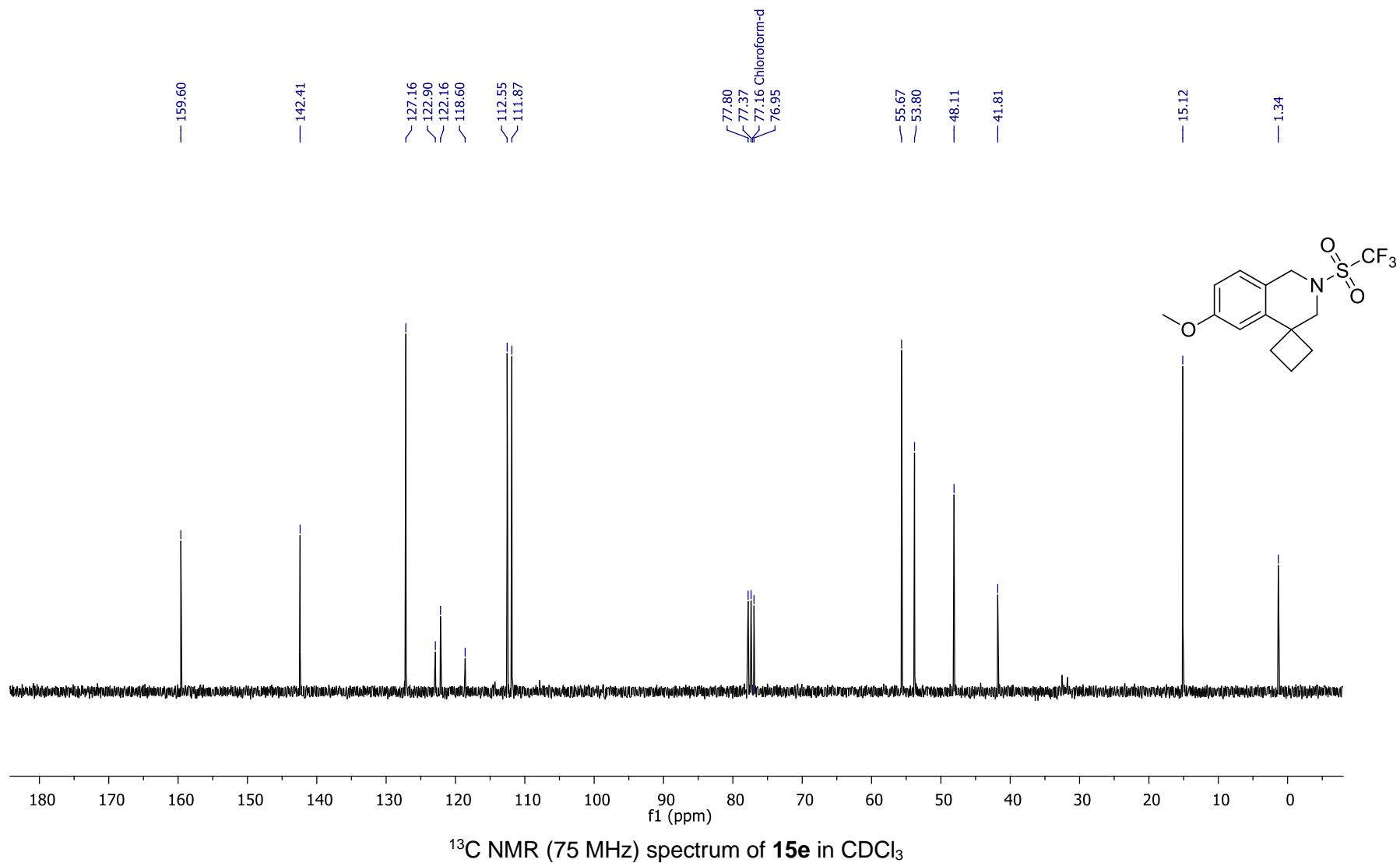


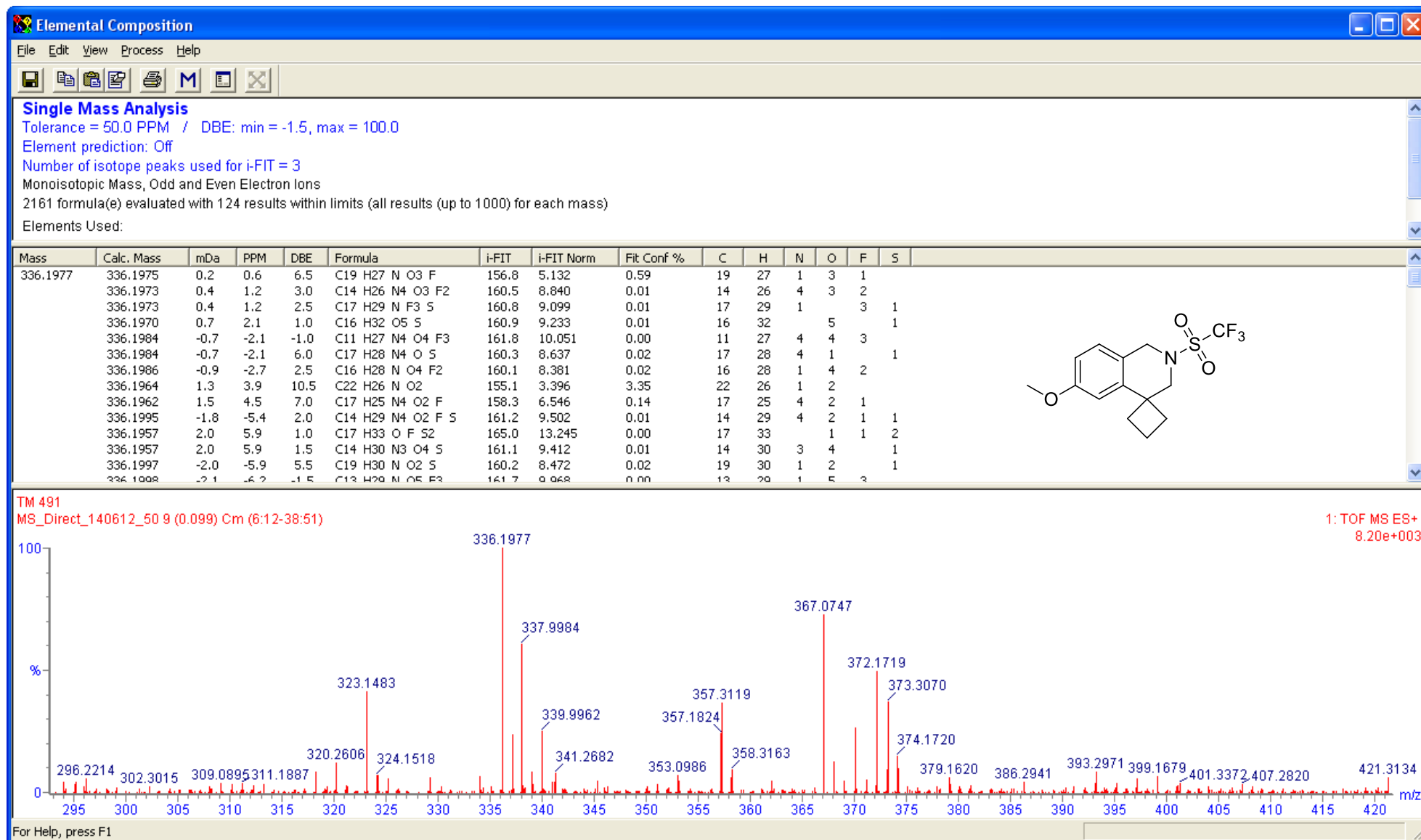
TOF MS ES+ of 15c



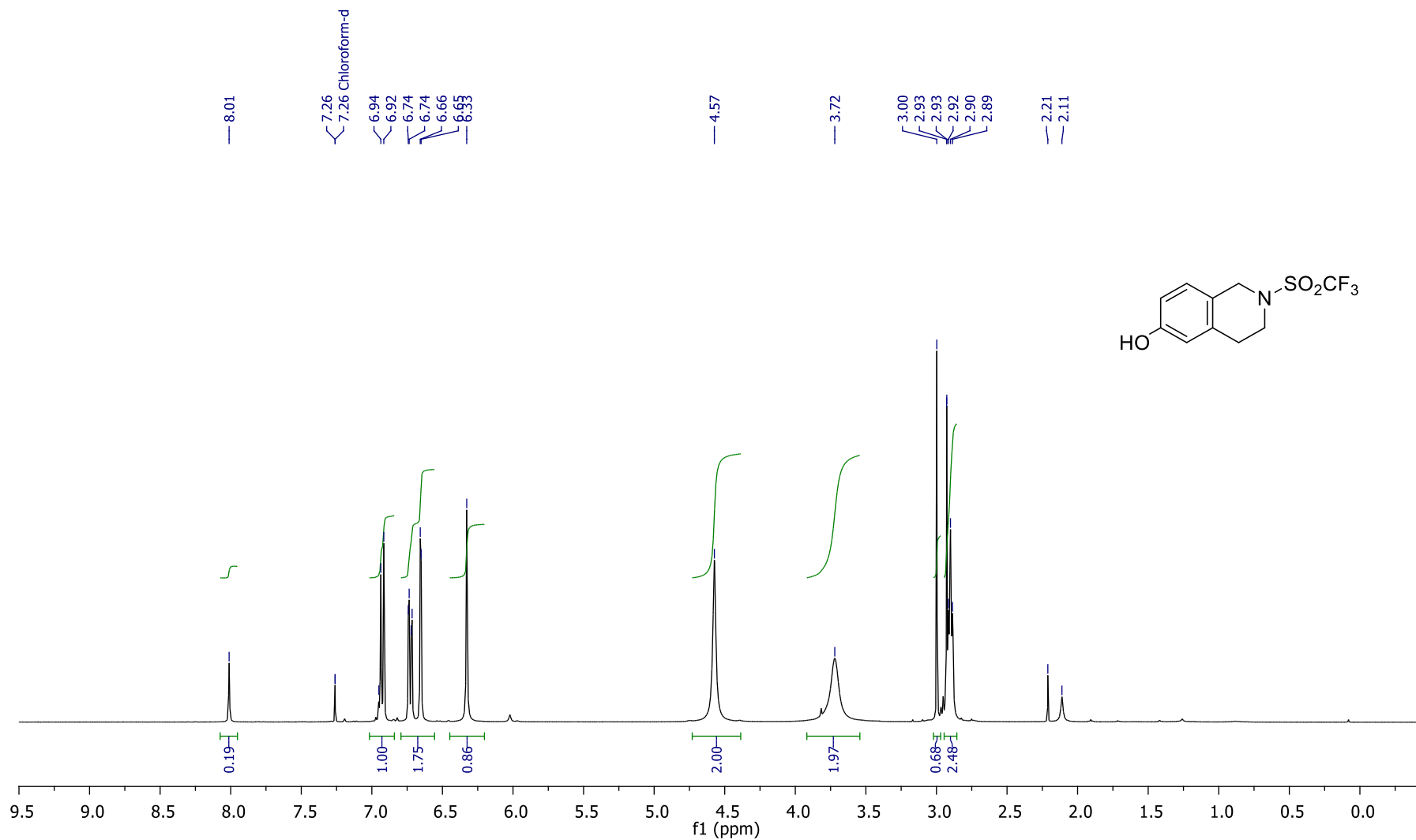




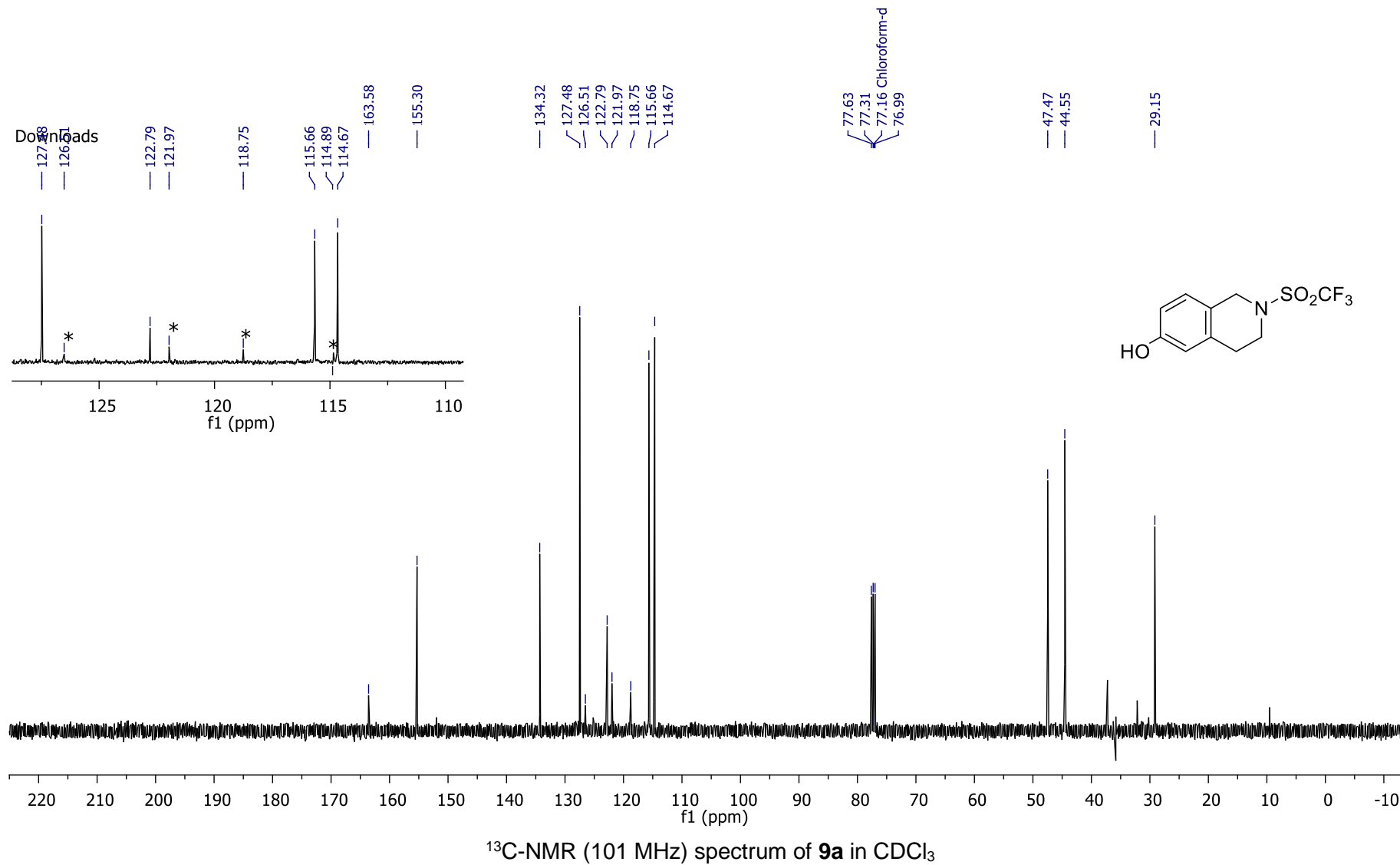


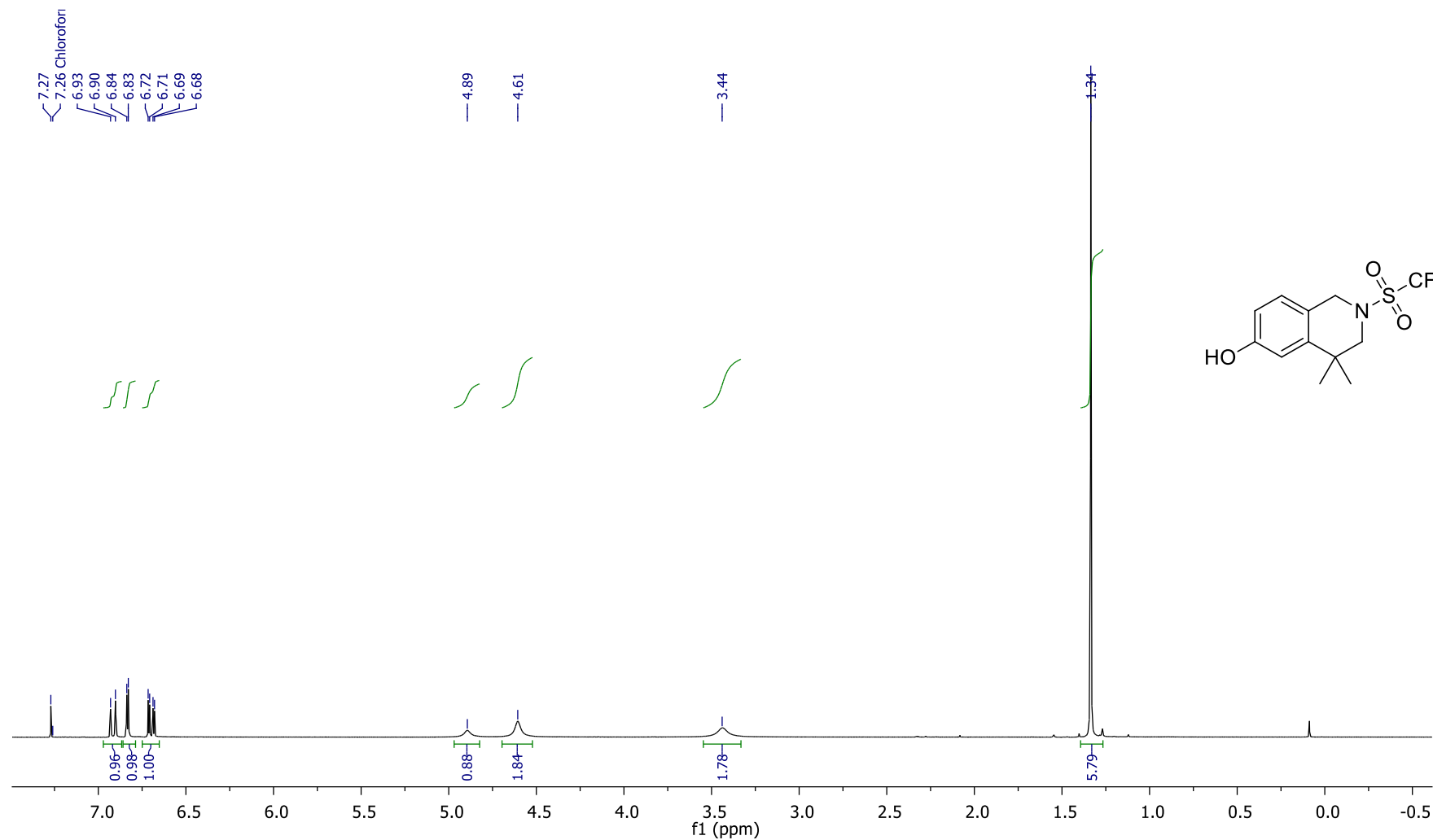


TOF MS ES+ of 15e

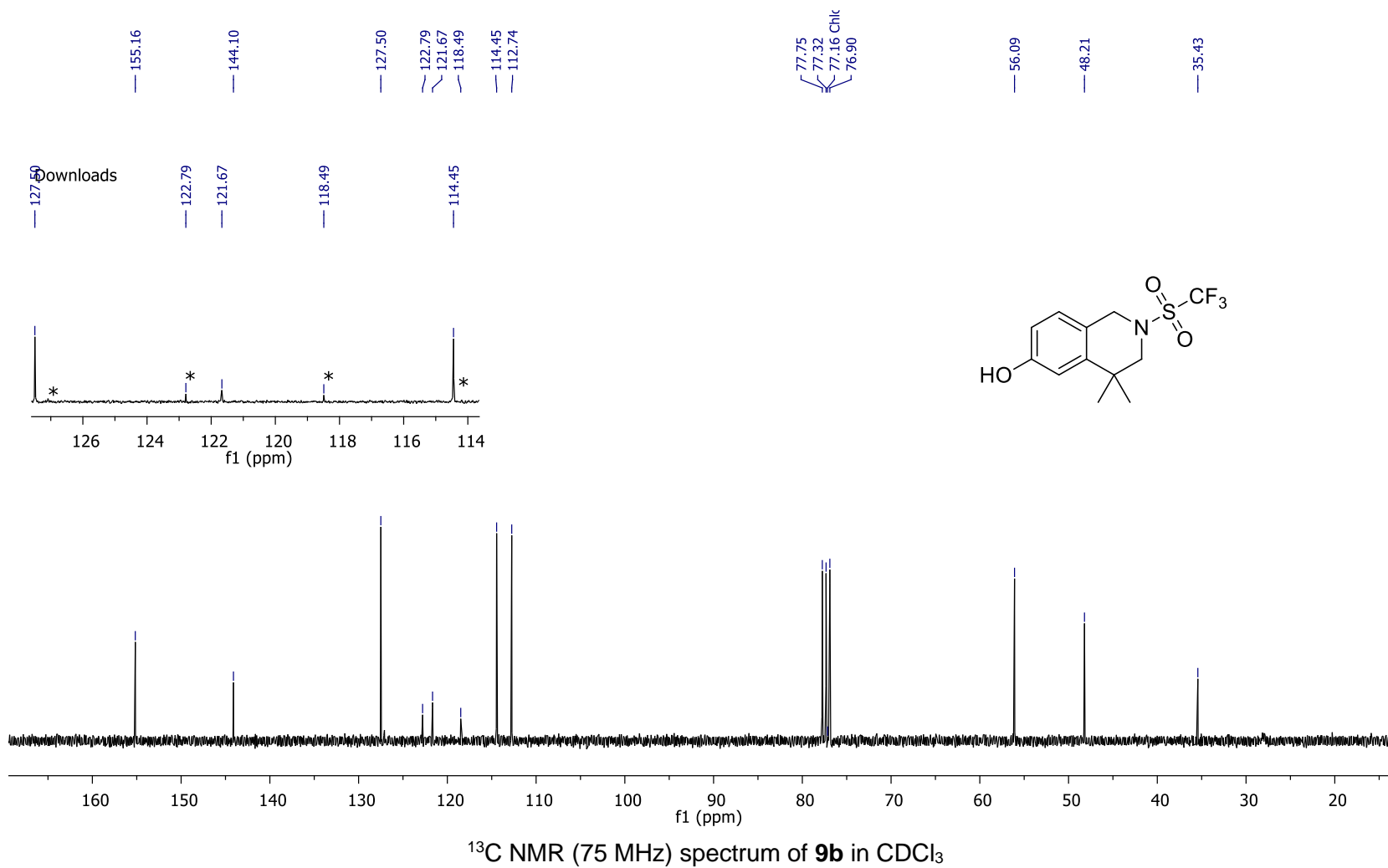


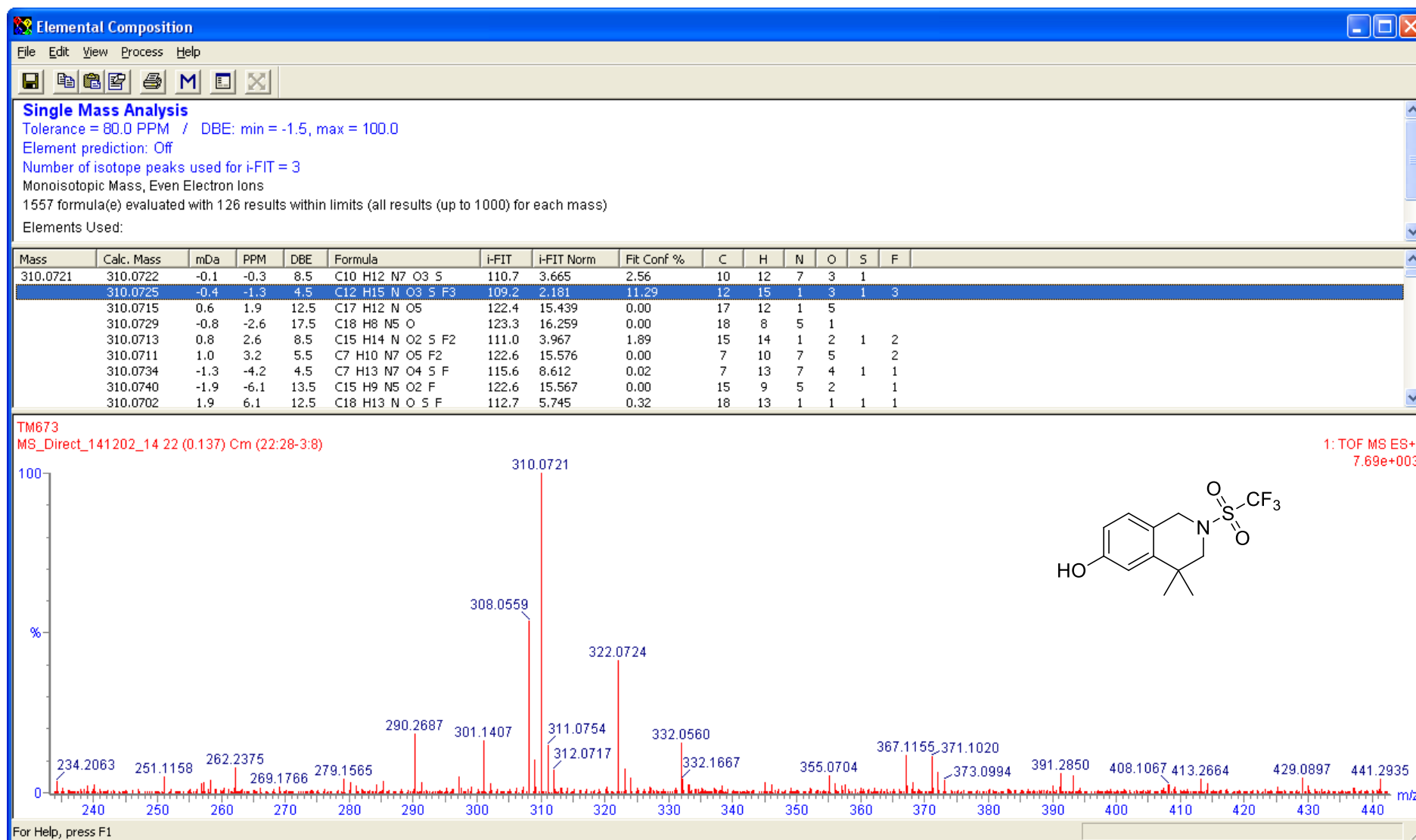
¹H-NMR (101 MHz) spectrum of **9a** in CDCl₃

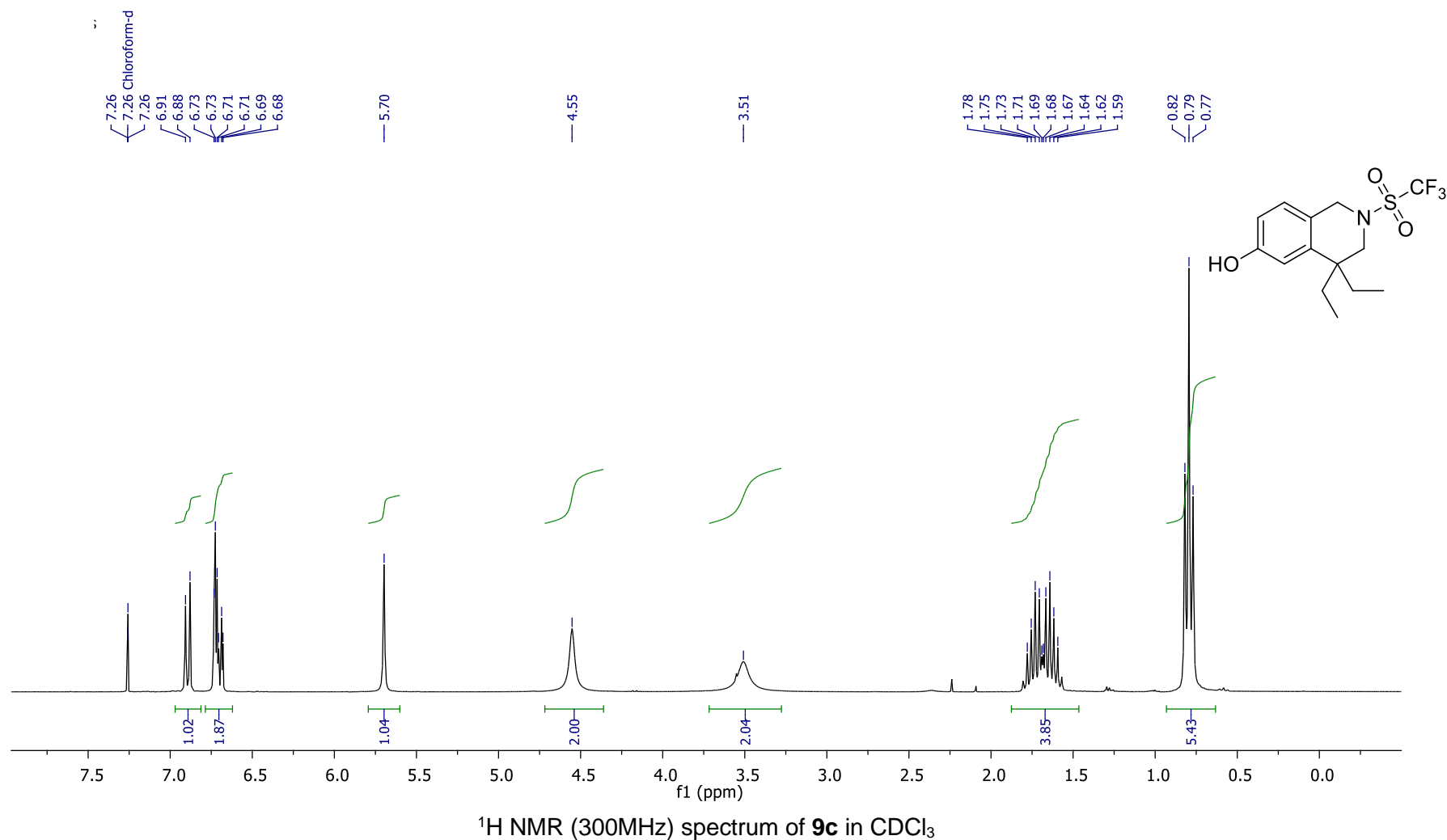


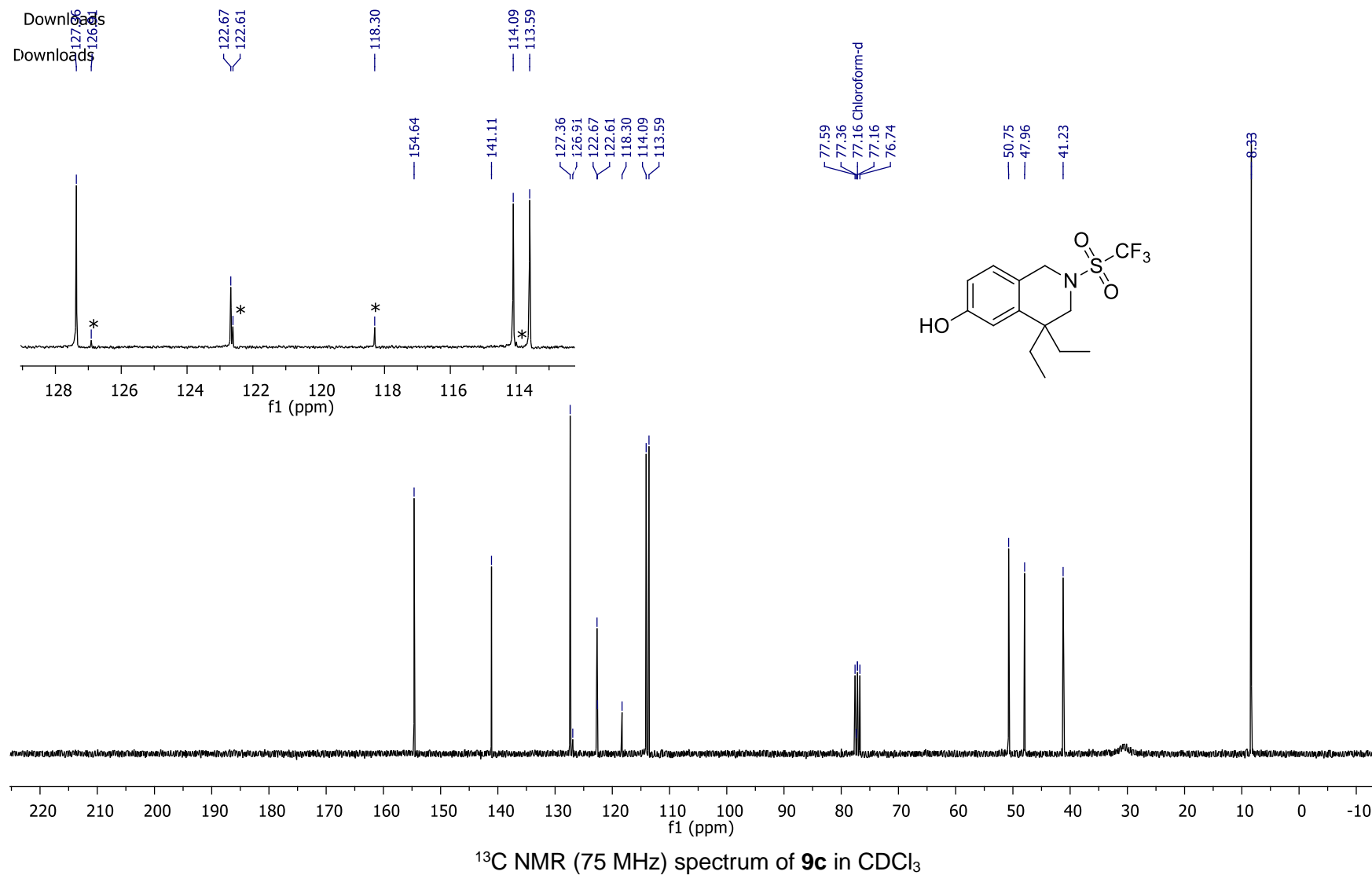


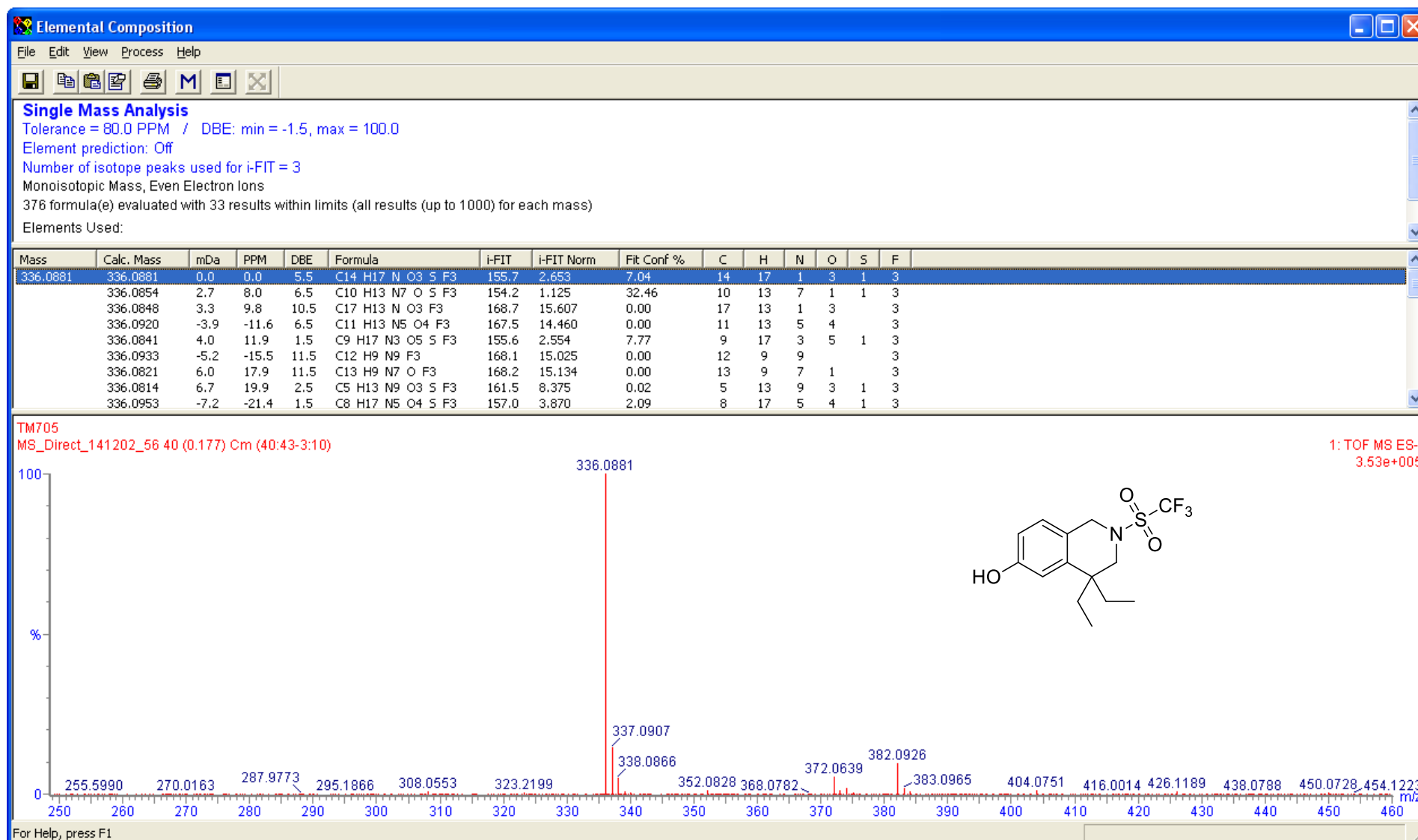
¹H NMR (300MHz) spectrum of **9b** in CDCl₃



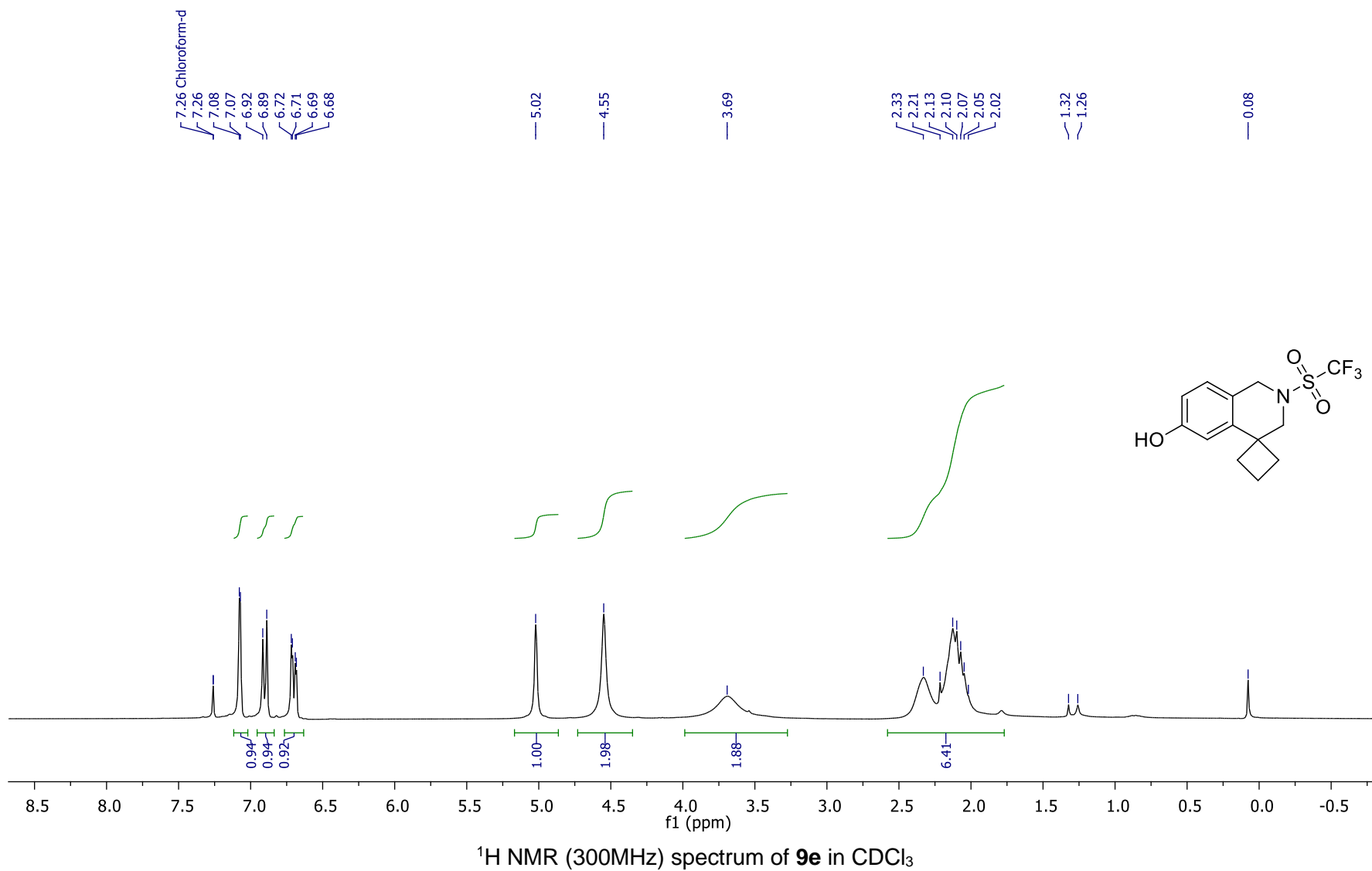
TOF MS ES+ of **9b**

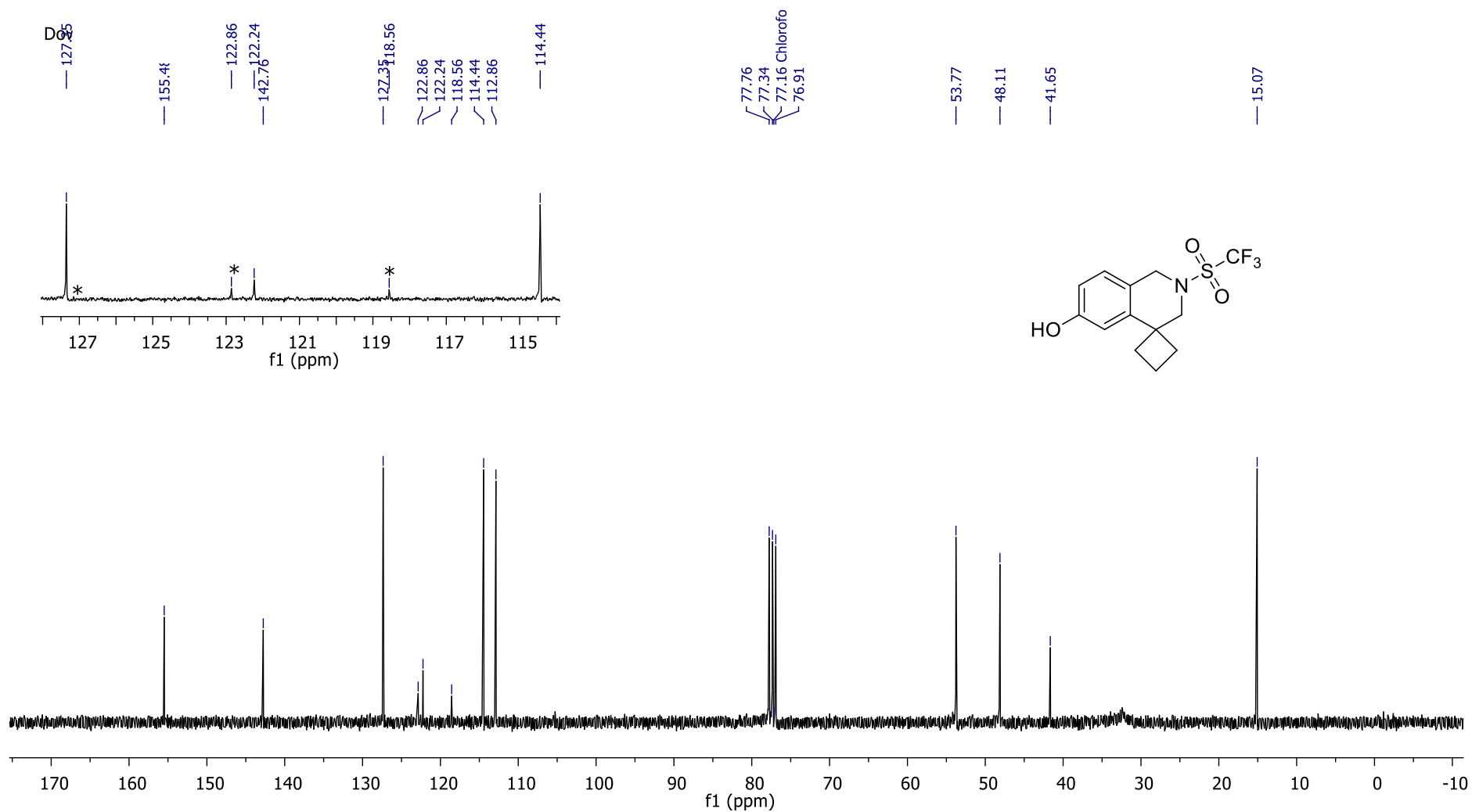






TOF MS ES+ of 9c





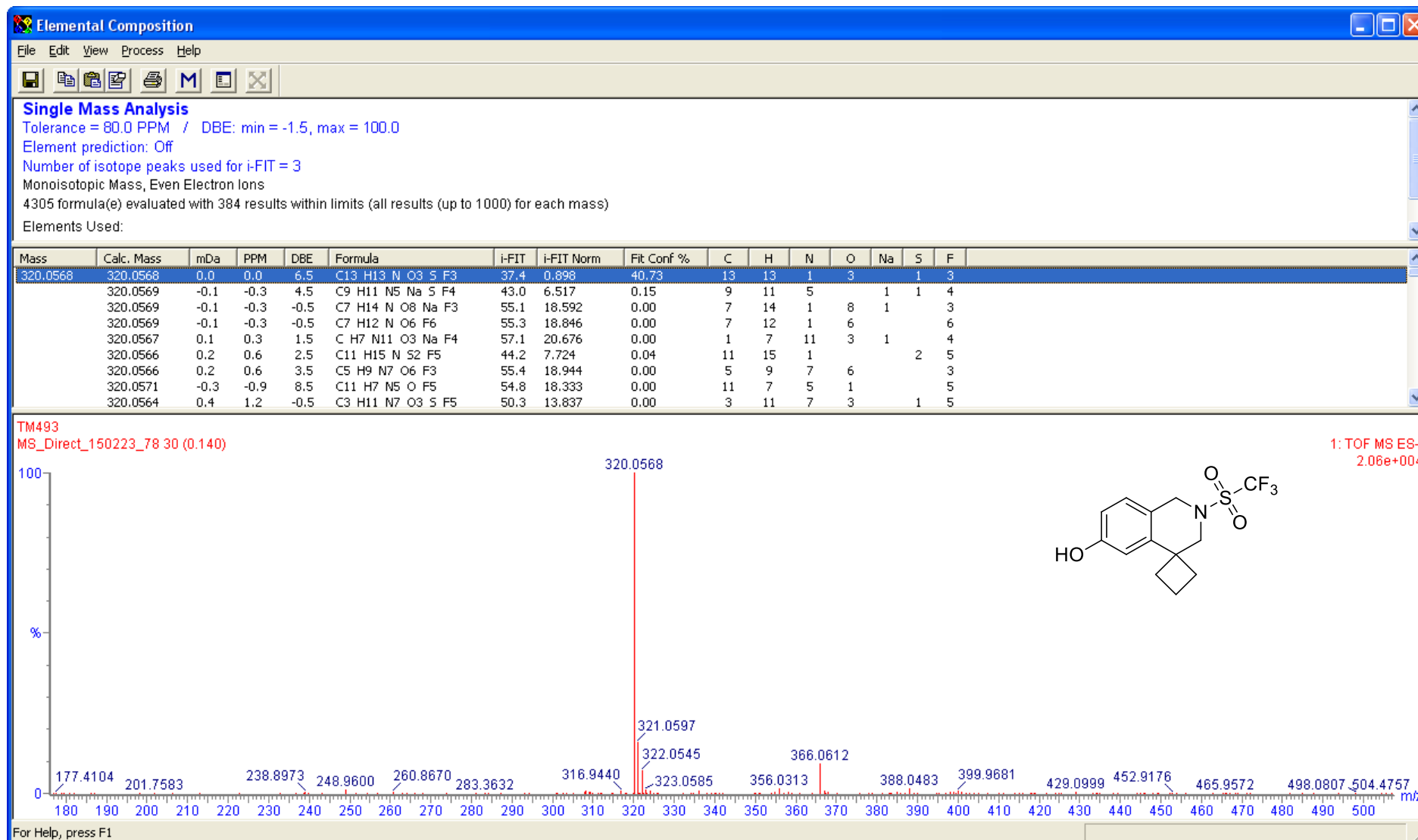
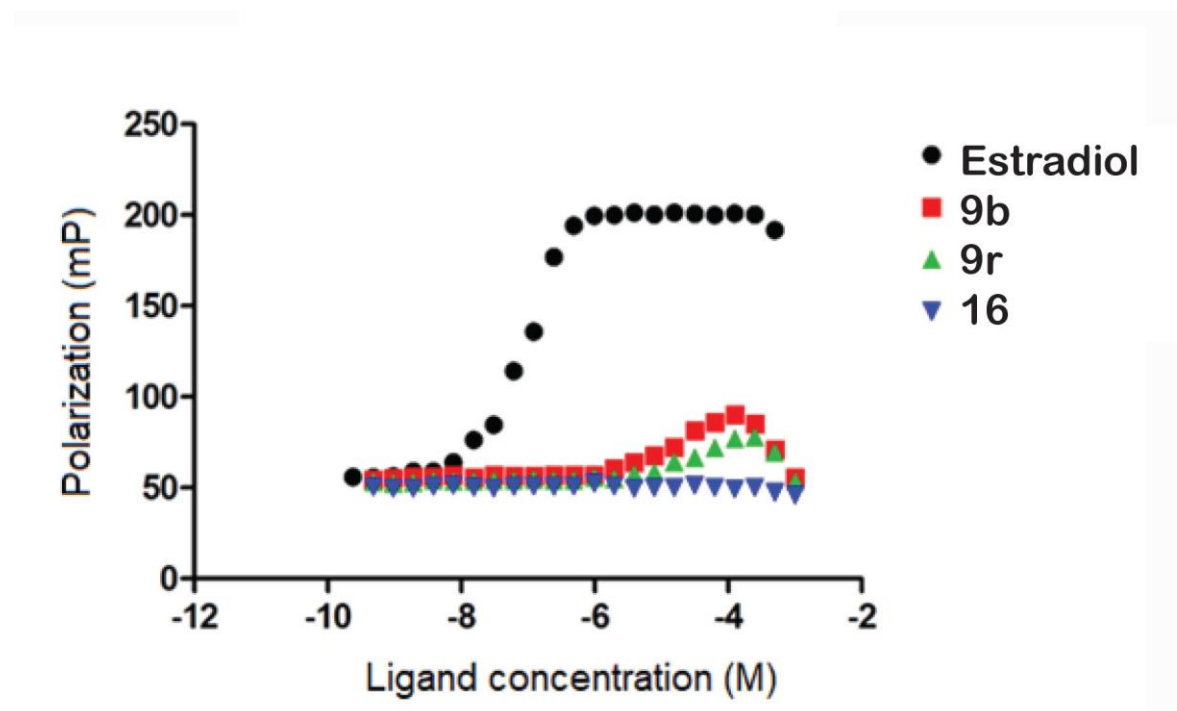


Figure S1. EC₅₀ results obtained for SUMO-tagged ER α cofactor peptide recruitment. Fluorescein-labelled LXXLL peptide fluorescence polarization curves upon increasing ligand concentration. Tested compounds **9b**, **9e** and **16** (compound **16** is from a previous library – see reference 26 in manuscript) result in a decrease in fluorescence polarization upon comparison to estradiol.



In this bioevaluation, a 1 μ M solution of SUMO-ER α , 0.1 μ M fluorescein-labelled SRC1-Box2 peptide and a 10 mM DMSO stock solution was prepared for each of the test compounds and during the experiment it was ensured that the final DMSO content was maintained at a constant 10% in each well. The measurements were performed in triplicate in coregulator buffer E in black 384 round-bottomed well plates. The results are shown above, where it should be noted that error bars are included but are obscured by the actual symbols.

The data measured for estradiol was analyzed using a non-linear regression graph, with single-site binding and used to calculate the EC₅₀ value of 86 nM (± 5 nM), in reasonable agreement with the value reported for estradiol versus ER α calculated in the related previous work (EC₅₀ value of 0.13 μ M ± 0.04 μ M from reference 25 in manuscript). As shown in the Figure, the synthesized compounds **9b** and **9e** rather disappointingly appeared to only induce a partial response (i.e. at a fraction of the maximum response induced by estradiol) at concentrations above 1 μ M. The activity of neither compounds plateaued at higher concentrations, which meant that determining an EC₅₀ for all the THIQ-based compounds was unfortunately not possible.