Practical Synthesis of a Cathepsin S Inhibitor: Route Identification, Purification Strategies and Serendipitous Discovery of a Crystalline Salt Form

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Supporting information

1) General experimental methods *S-2*

2) Chiral HPLC chromatograms of compound **1** *S-3*

3) ^{1}H and ^{13}C NMR spectra *S-4*

General experimental methods:

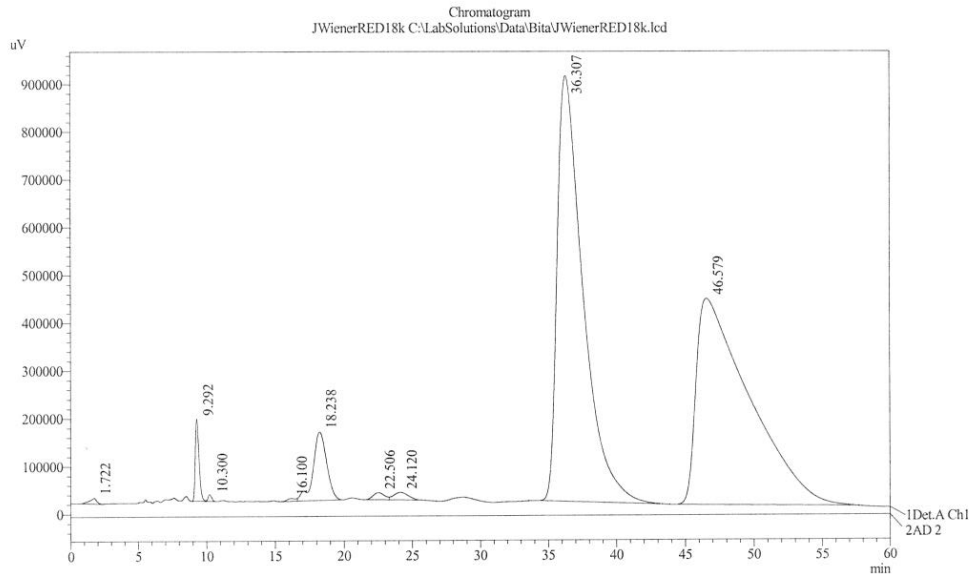
Proton and carbon NMR spectra were recorded at a 500 MHz or a 600 MHz NMR spectrometers. Flash column chromatography was performed using Merck silica gel 60. HRMS (ESI) was performed on a μTof apparatus. Powder X-ray Diffraction (PXRD) conditions: Philips X'PERT PRO with X'Celerator Cu detector equipped with a real time multiple strips X-ray detection technology. The samples were scanned from 4 ^{o} to 40 ^{o} 2θ, at a step size 0.0167 ^{o} 2θ and a time per step of 29.8450 seconds. The tube voltage and current were 45 kV and 40 mA, respectively. The samples were placed onto zero background holders and analyzed on a spinning stage. The thermogravimetric analyses (TGA) were performed on a TA Instruments model TGA Q 50 under a nitrogen purge. The samples were placed in aluminum pans and scanned at a rate of 10°C/min up to 400 °C. Differential Scanning Calorimetry (DSC) was performed on a DCS Q 100. Samples were scanned with a temperature ramp of 10 °C/min. Samples were placed in aluminum DSC pans with a single hole punched into the lid up to 350 ºC. Polarized Light Microscopy (PLM) was performed on a Olympus model BX51 polarizing microscope, equipped with a PAX-IT digital camera. The magnification was 500X.

Unless specified, all the reagents and solvents were purchased from commercial sources and used without further purification.

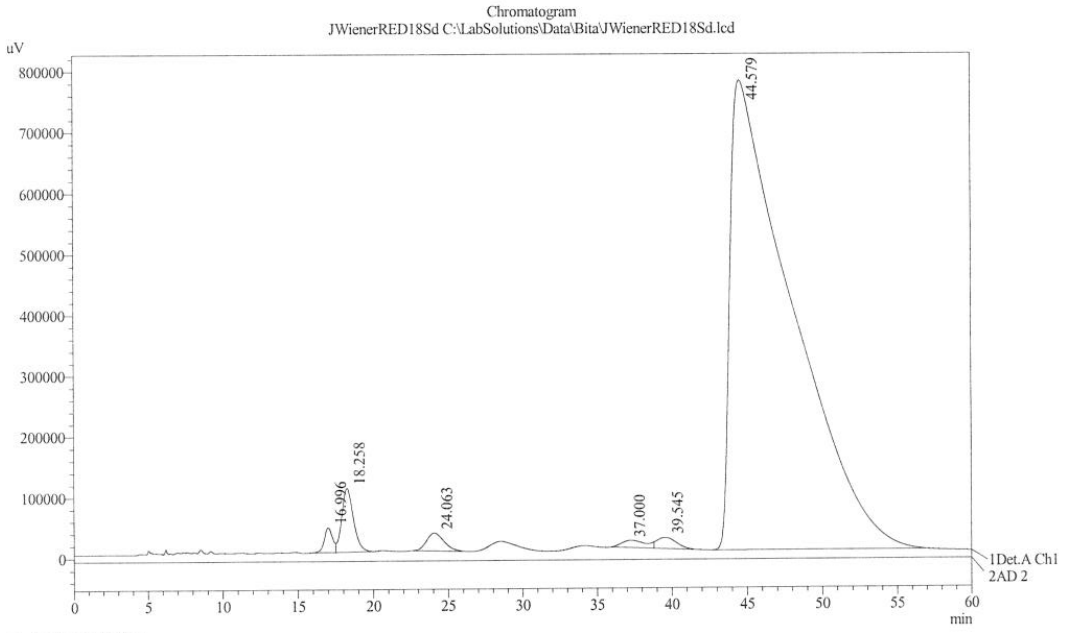
Chiral HPLC chromatograms of compound 1

Chiral separation conditions are: The Chiralpak AD-H 250 x 4.6 mm @ 40 Celsius, 50% MeOH: EtOH (1:1) with 0.1% diethylamine, 50% hexanes @ 0.5mL/min, Detection UV 214nm.

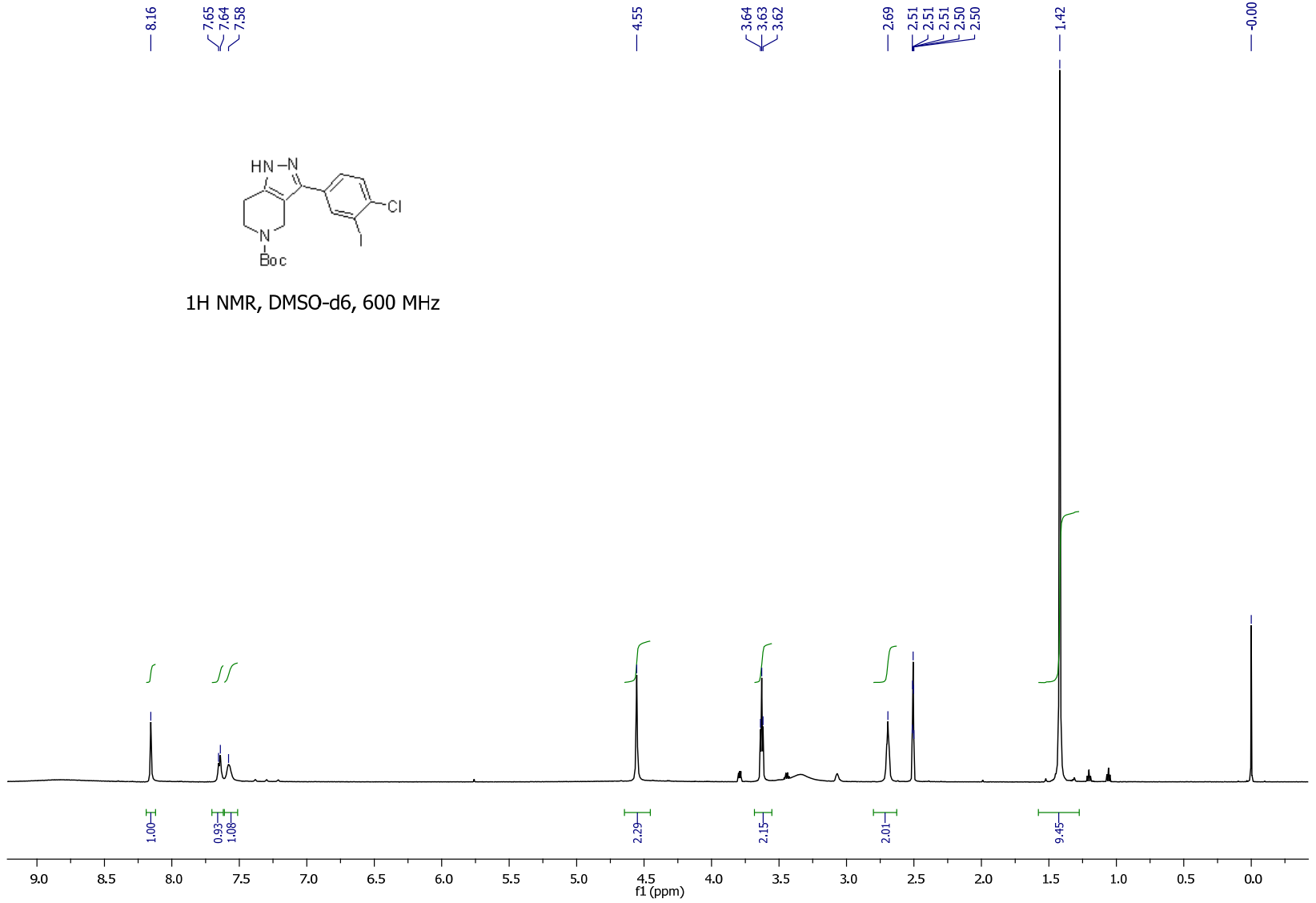
Racemic sample



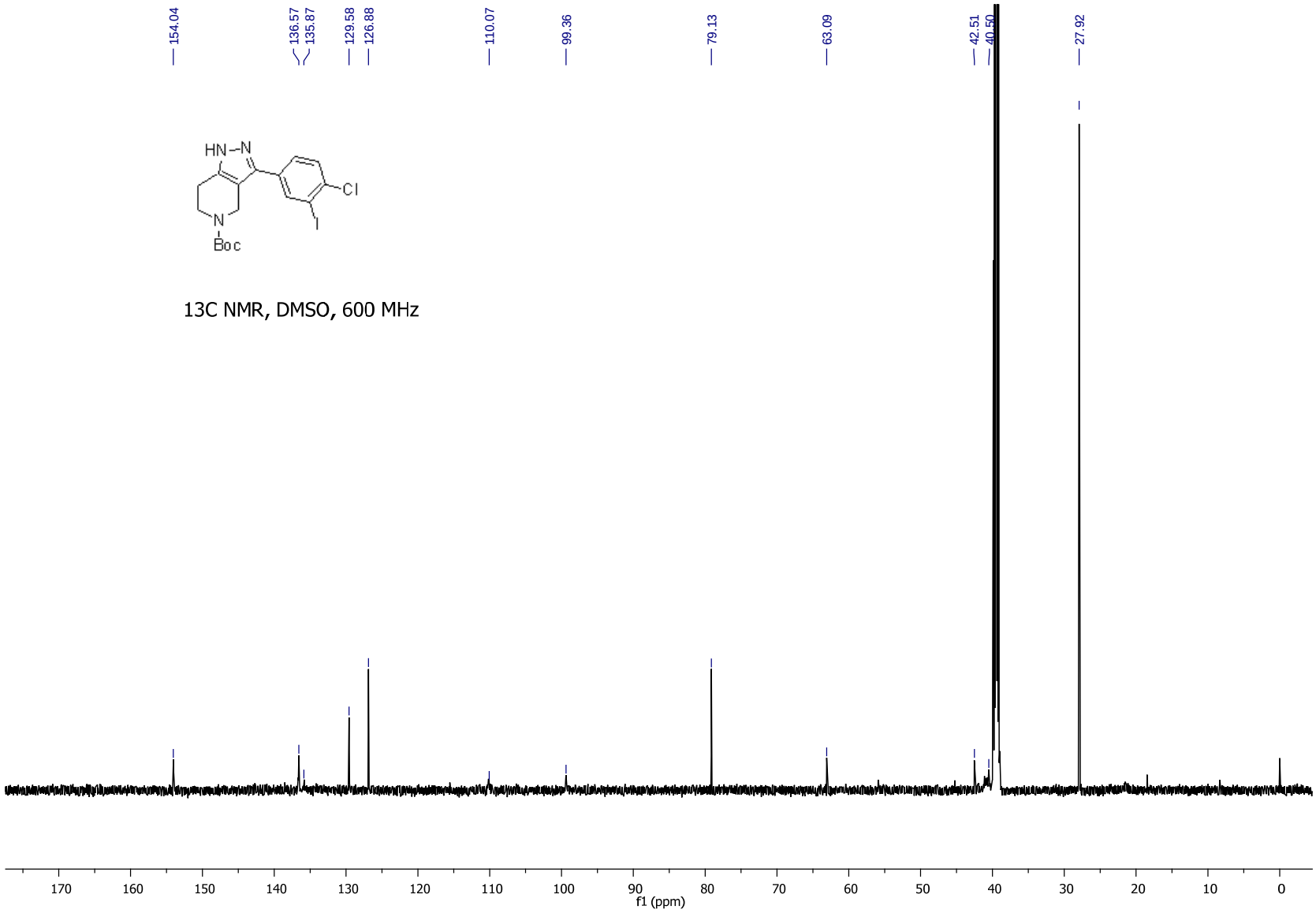
Compound **1**



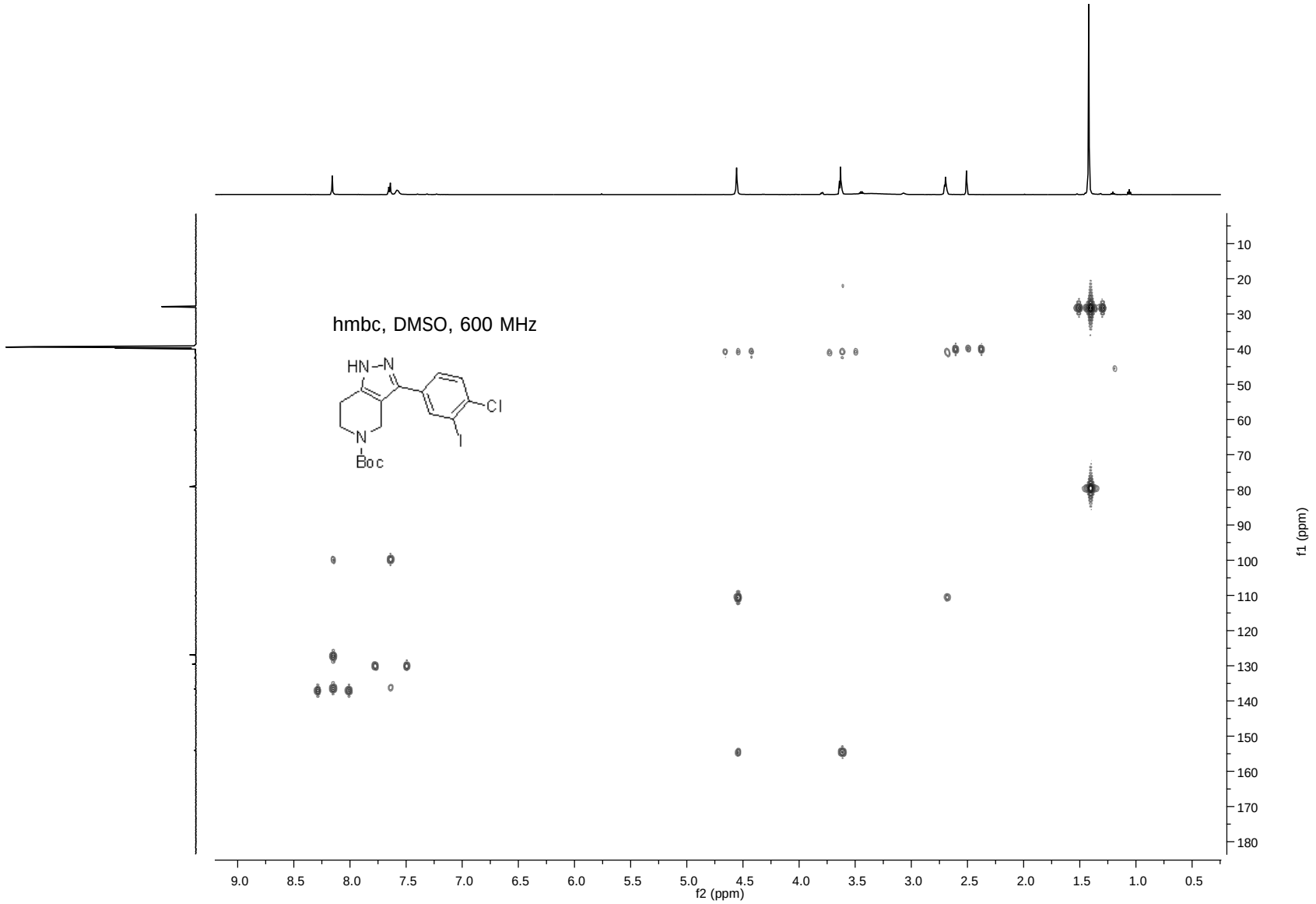
^{1}H NMR of compound **2**, DMSO-d6, 600 MHz



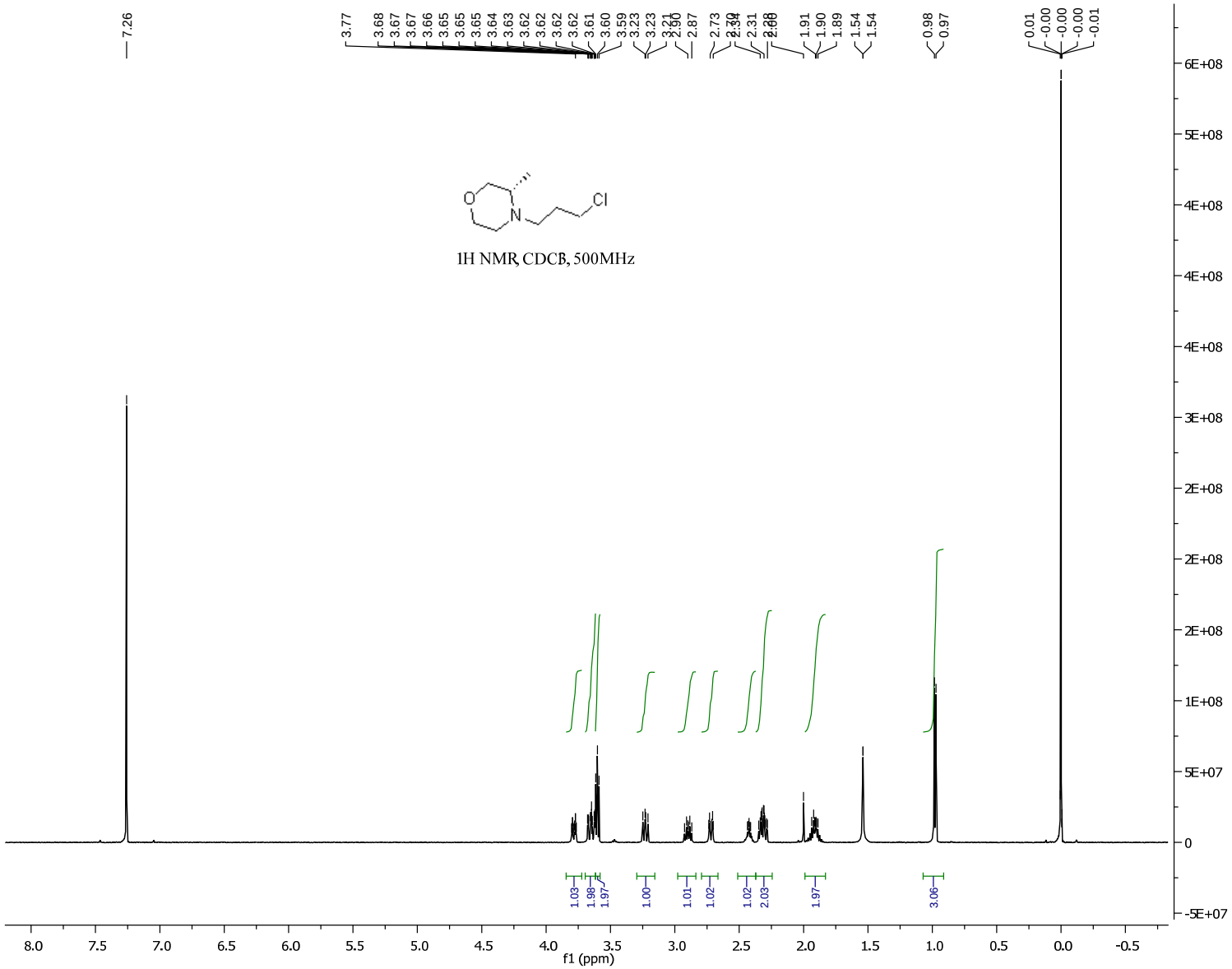
^{13}C NMR of compound **2**, DMSO-d6, 600 MHz



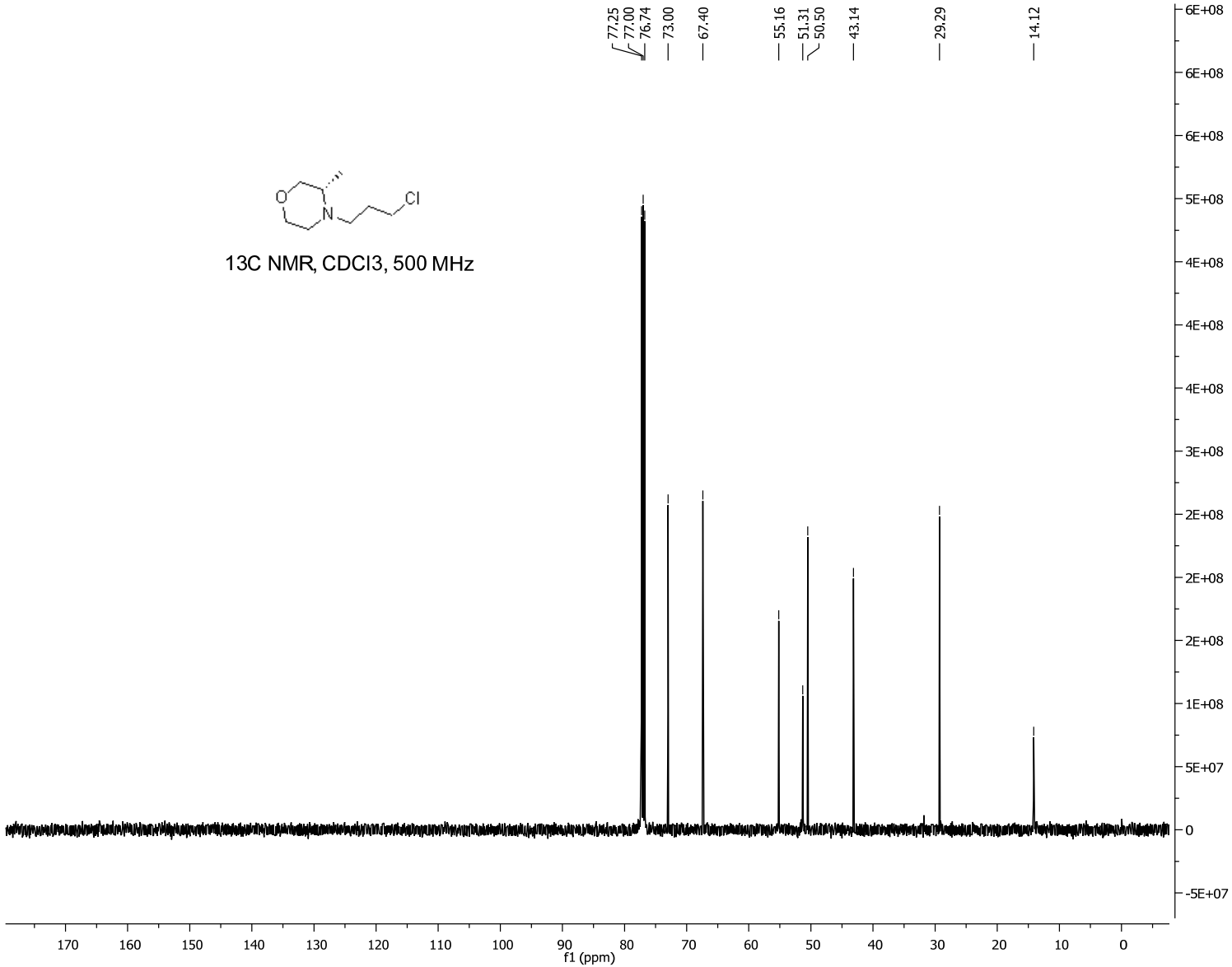
hmbc of compound **2**, DMSO-d6, 600 MHz



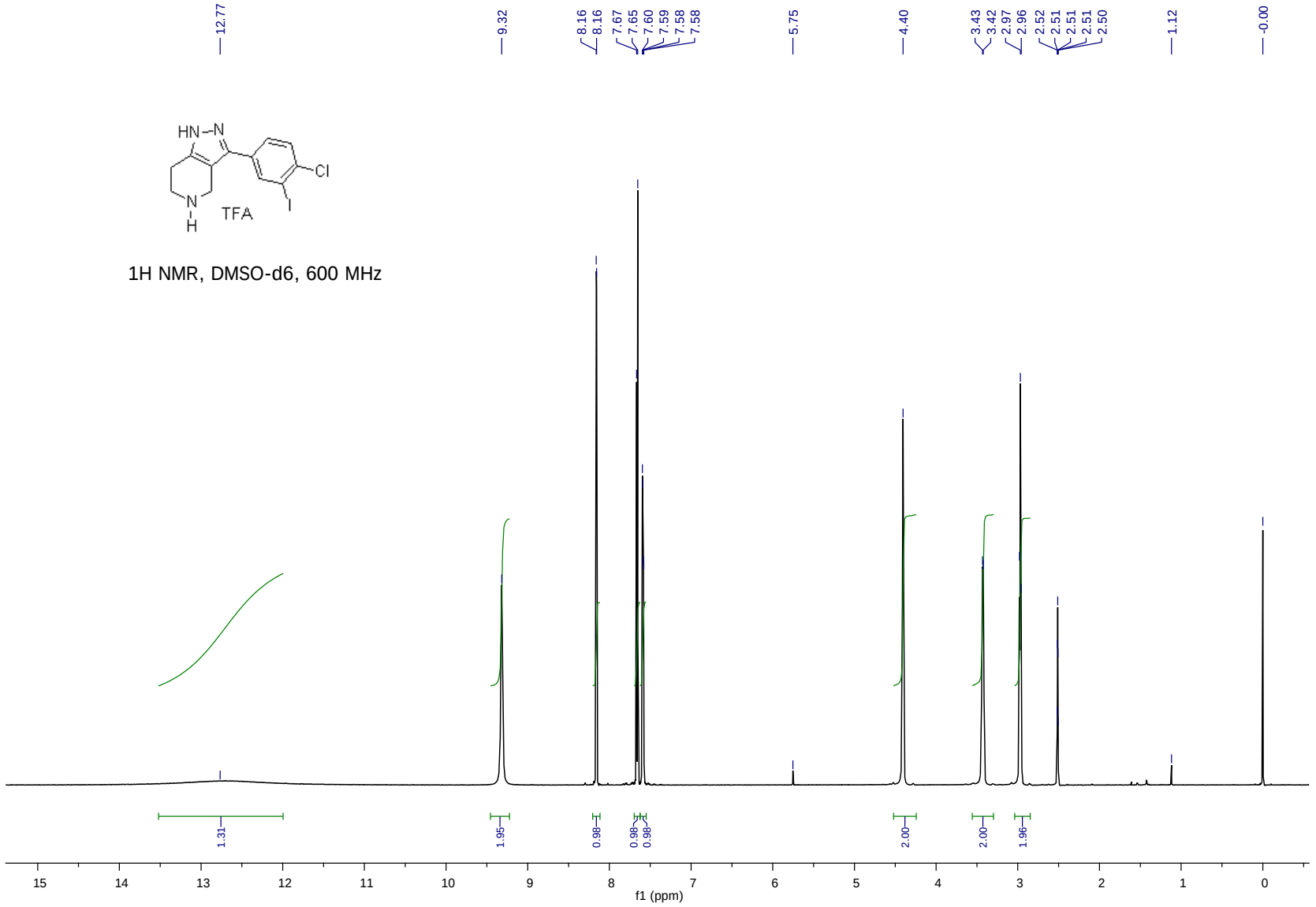
^{1}H NMR of compound **3**, $CDCl_3$, 500 MHz



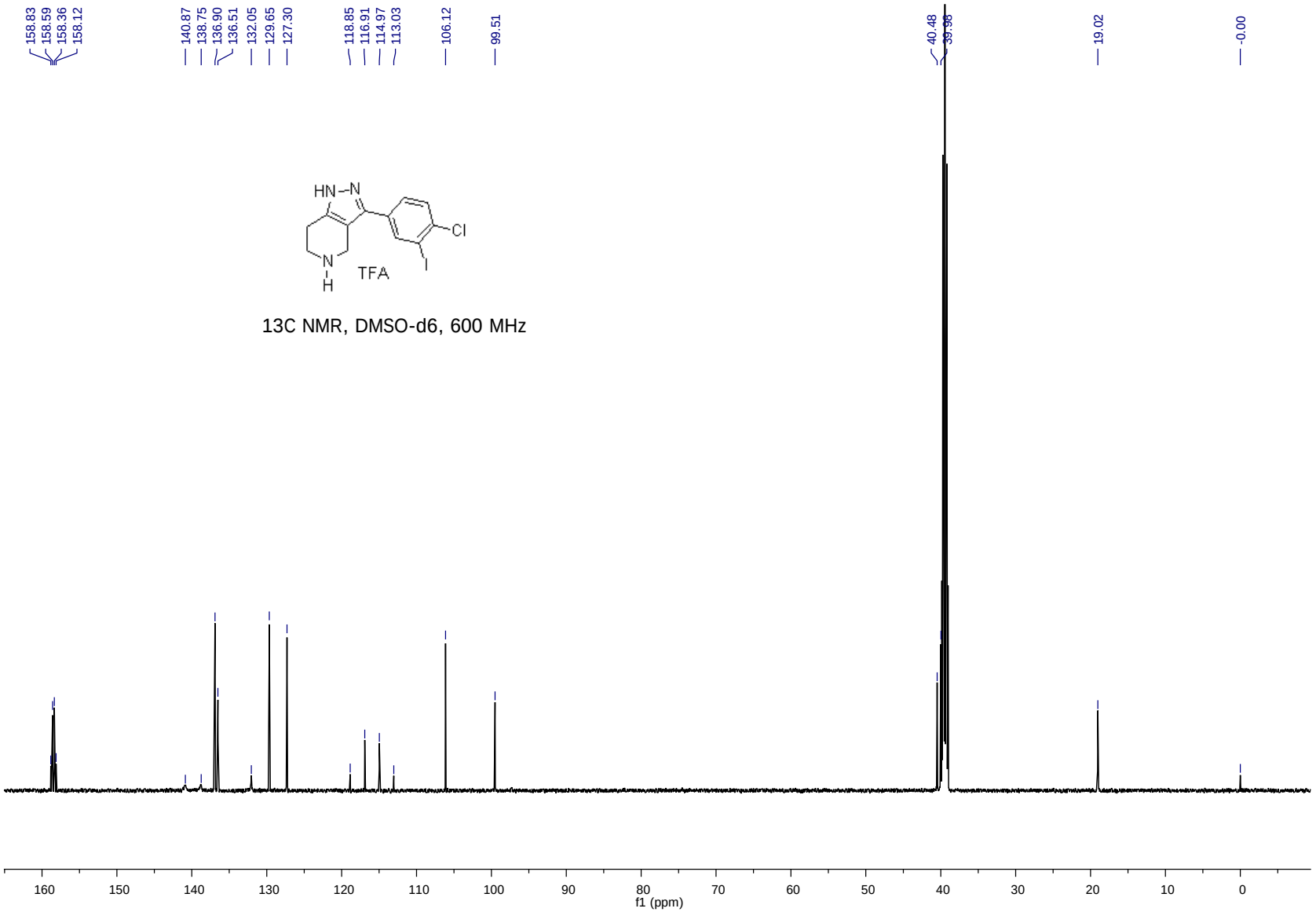
^{13}C NMR of compound **3**, $CDCl_3$, 500 MHz



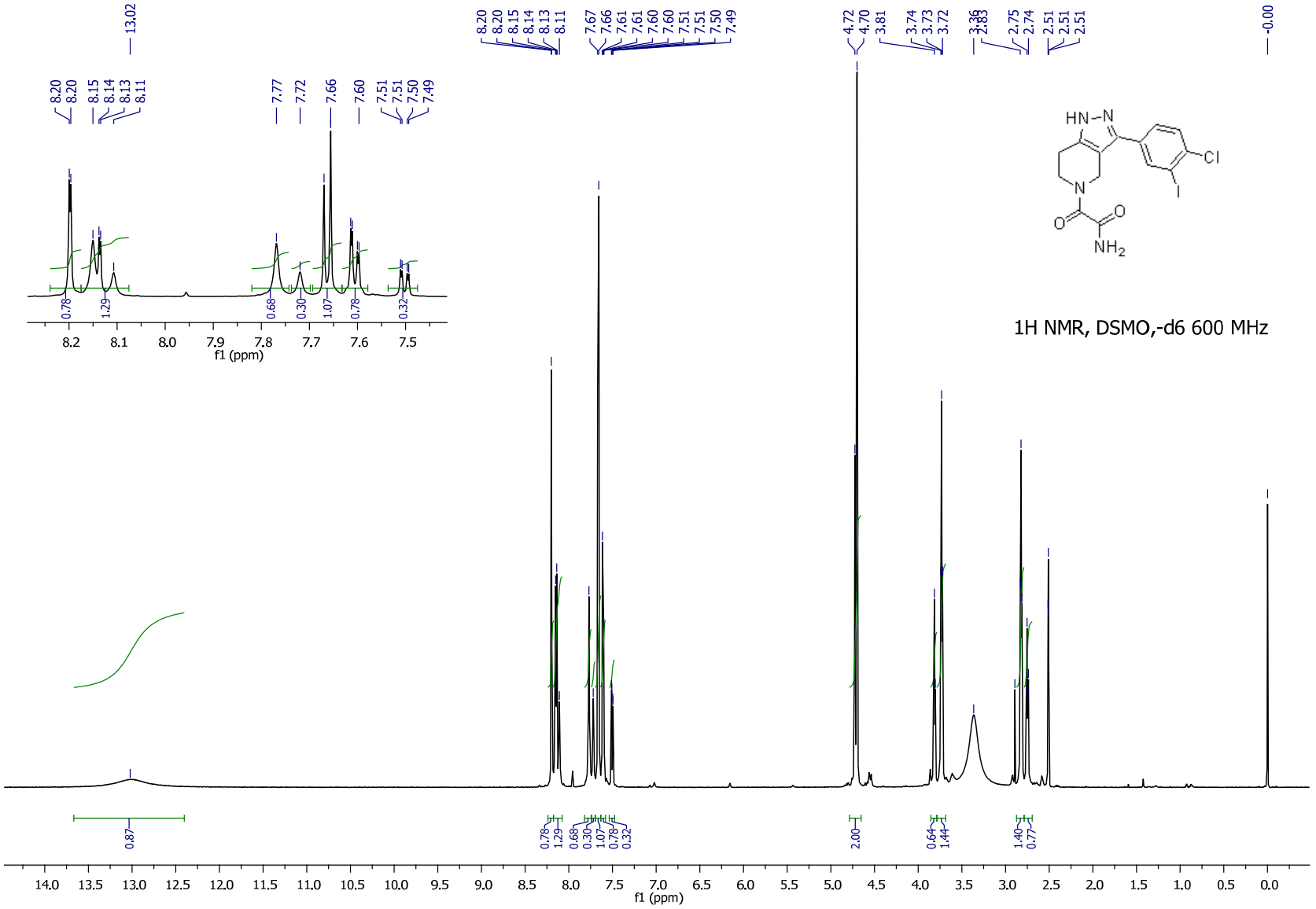
^{1}H NMR of compound **8**, TFA salt, DMSO-d6, 600 MHz



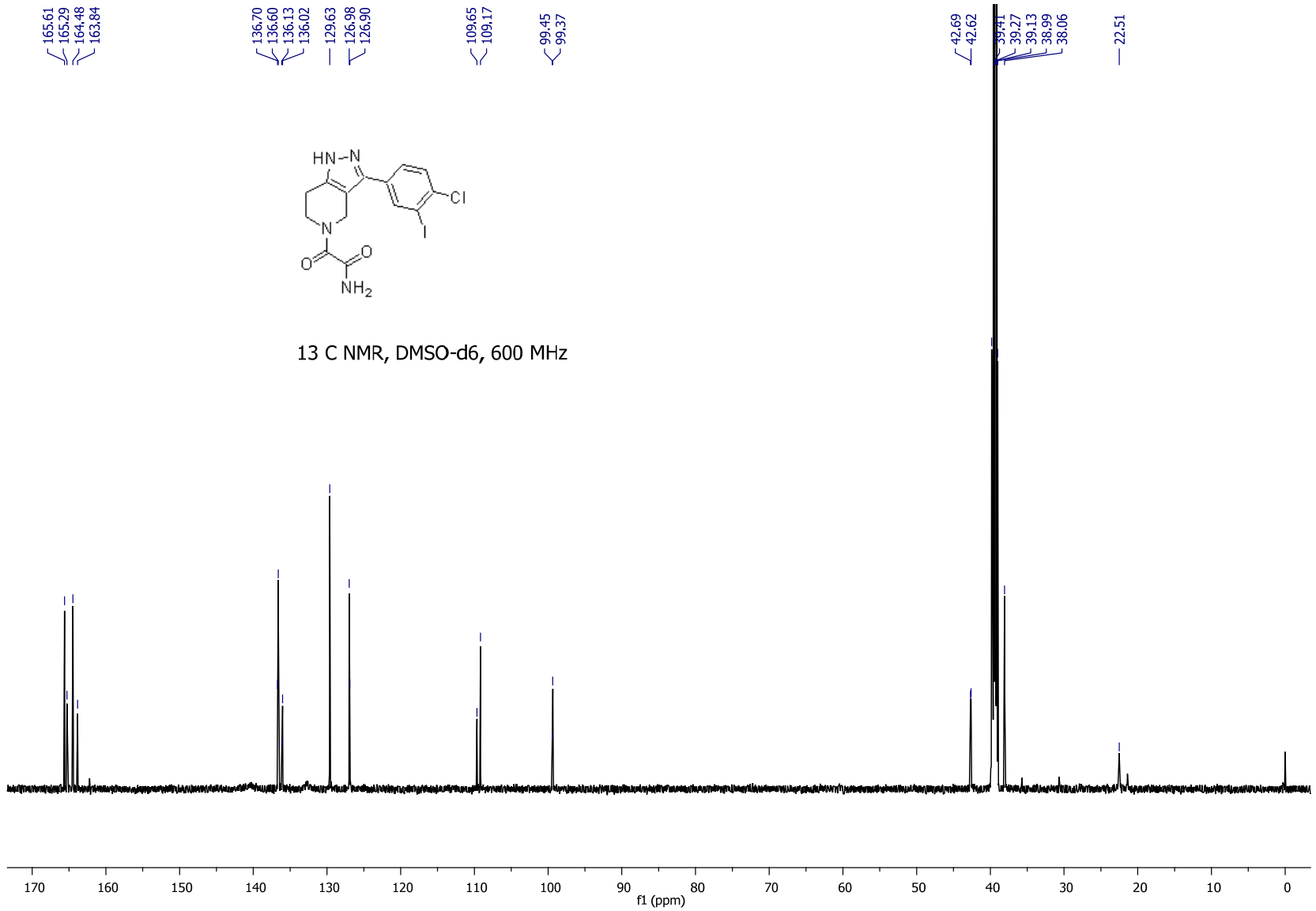
^{13}C NMR of compound **8**, TFA salt, DMSO-d6, 600 MHz



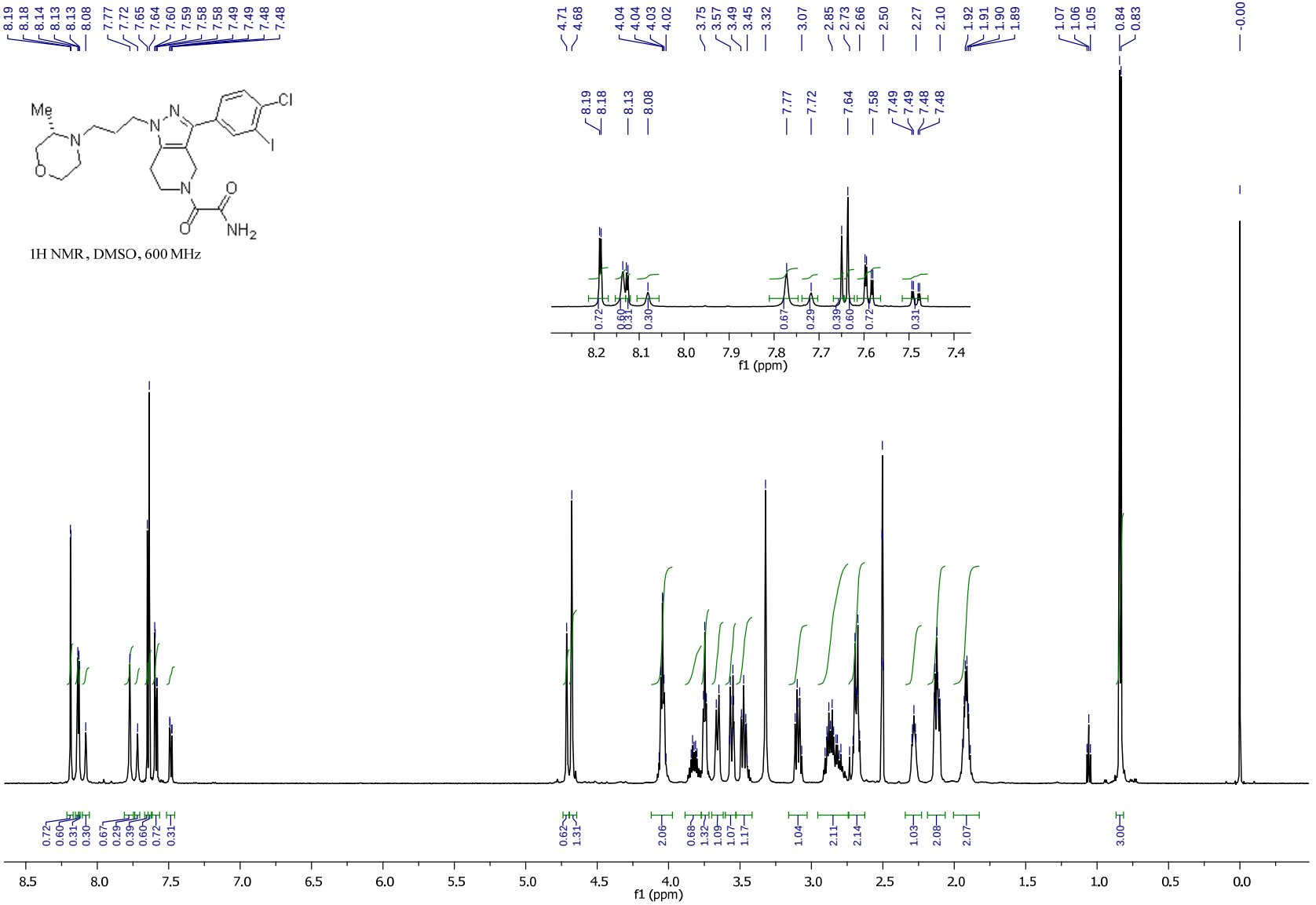
^{1}H NMR of compound **9**, DMSO-d6, 600 MHz



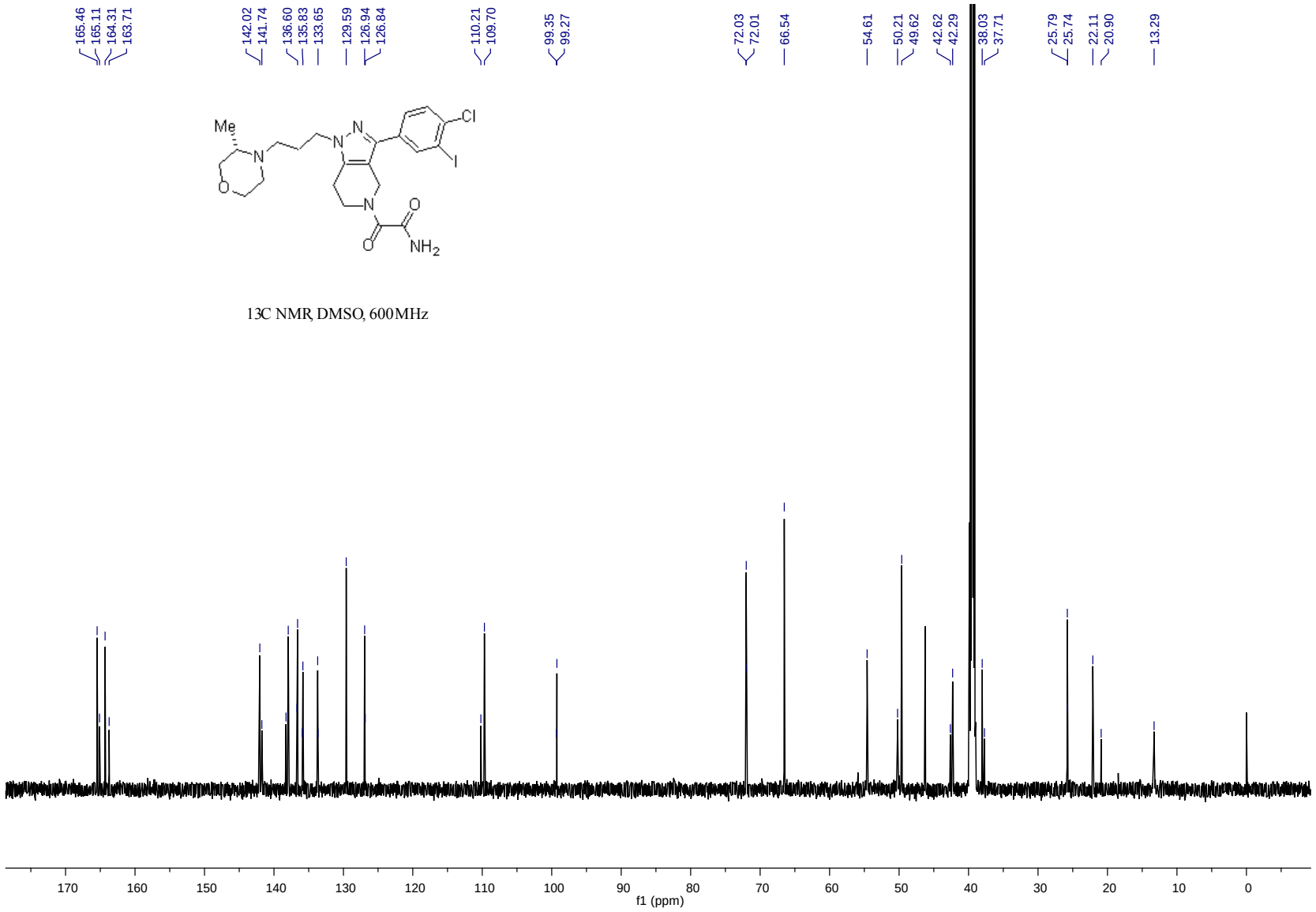
^{13}C NMR of compound **9**, DMSO-d6, 600 MHz



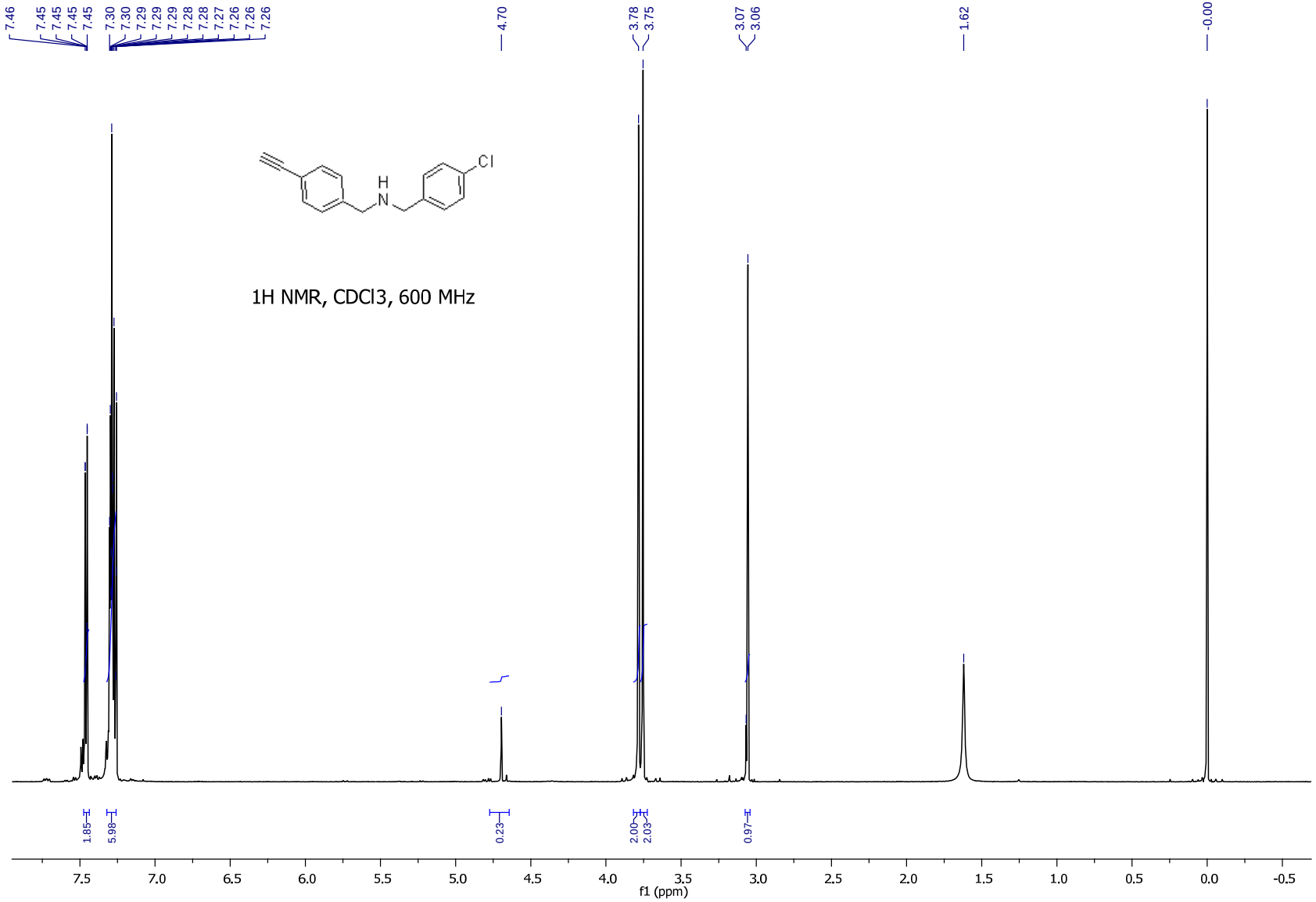
^{1}H NMR of compound **10**, DMSO-d6, 600 MHz



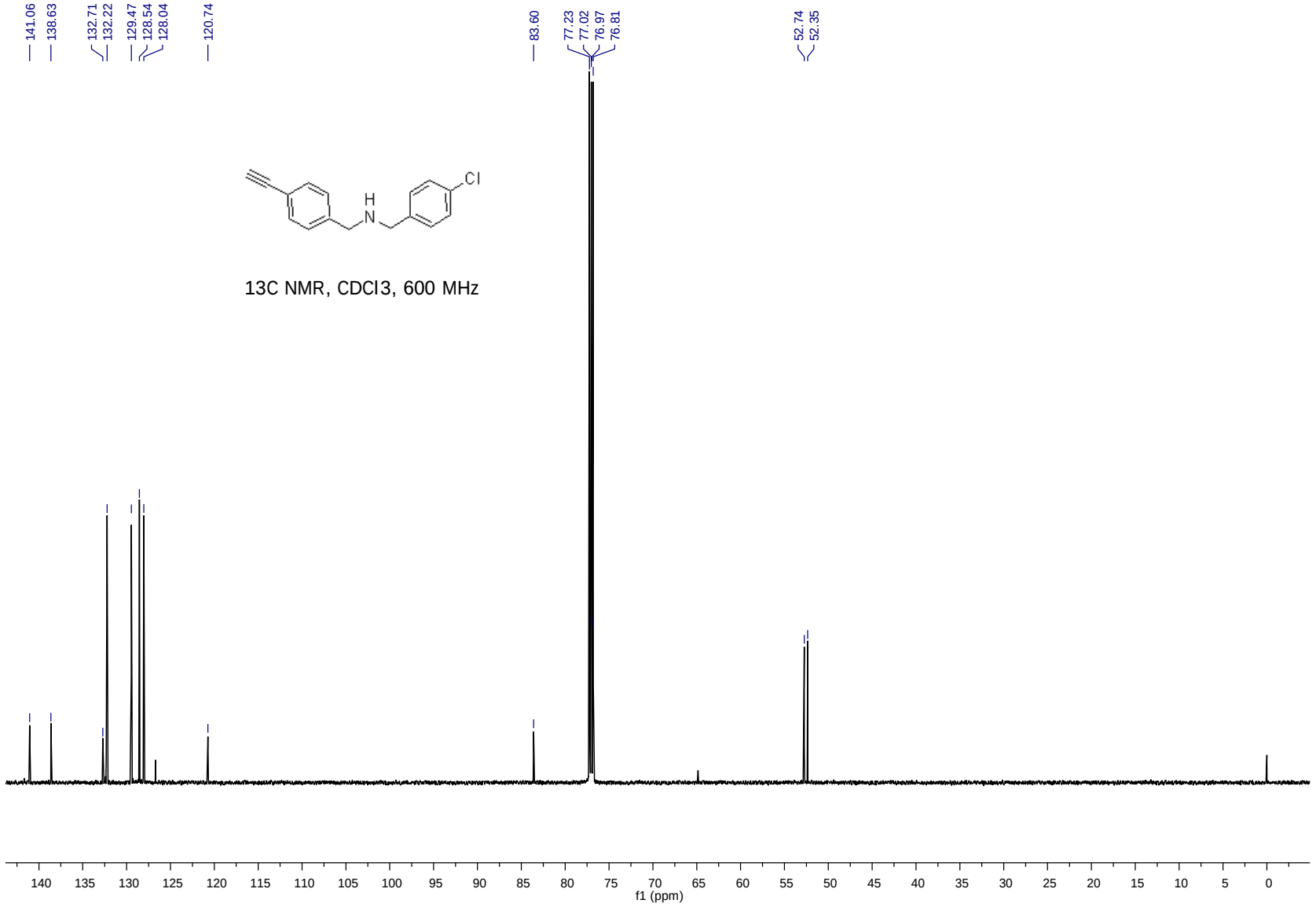
^{13}C NMR of compound **10**, DMSO-d6, 600 MHz



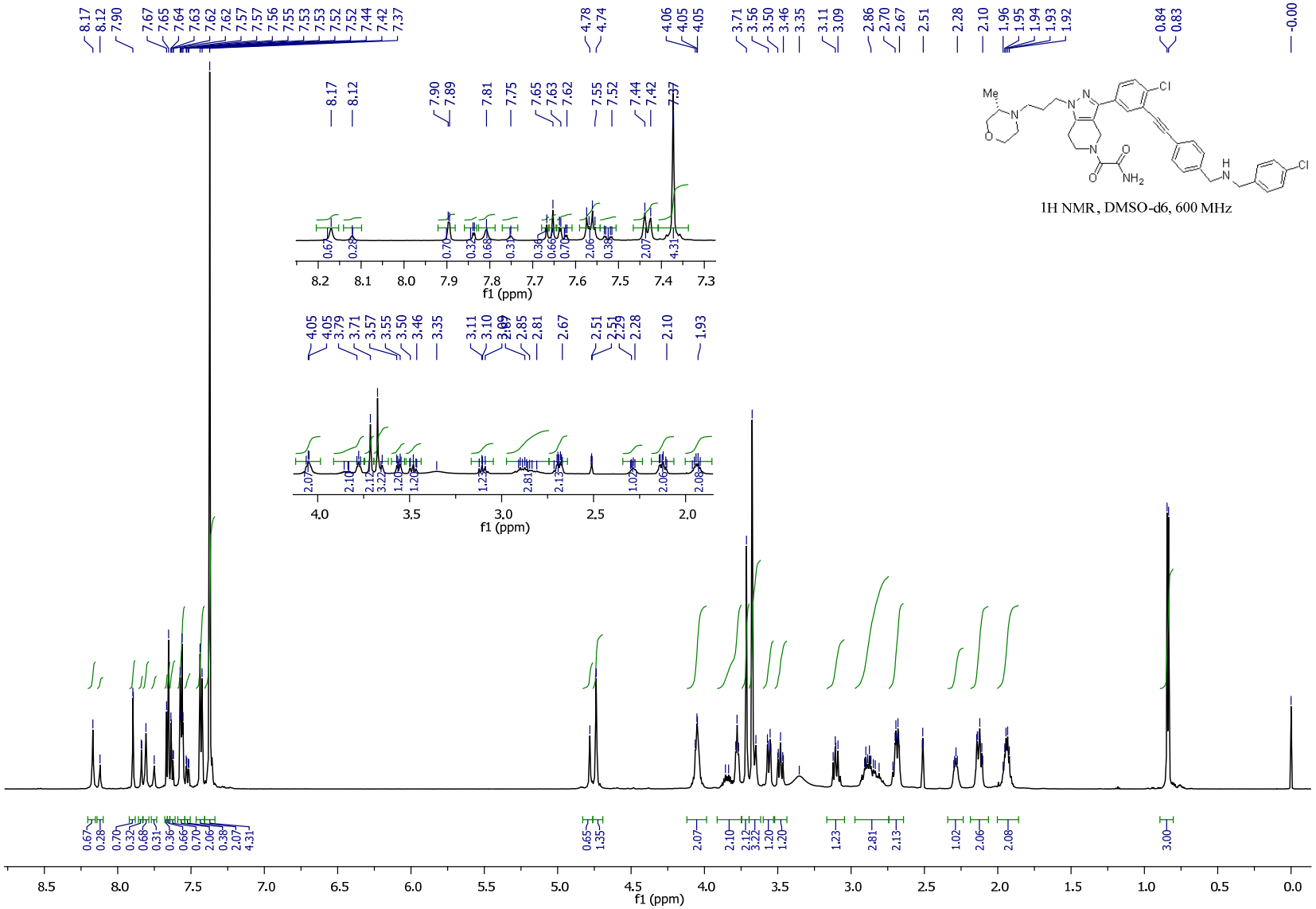
^{1}H NMR of compound **4**, $CDCl_3$, 600 MHz



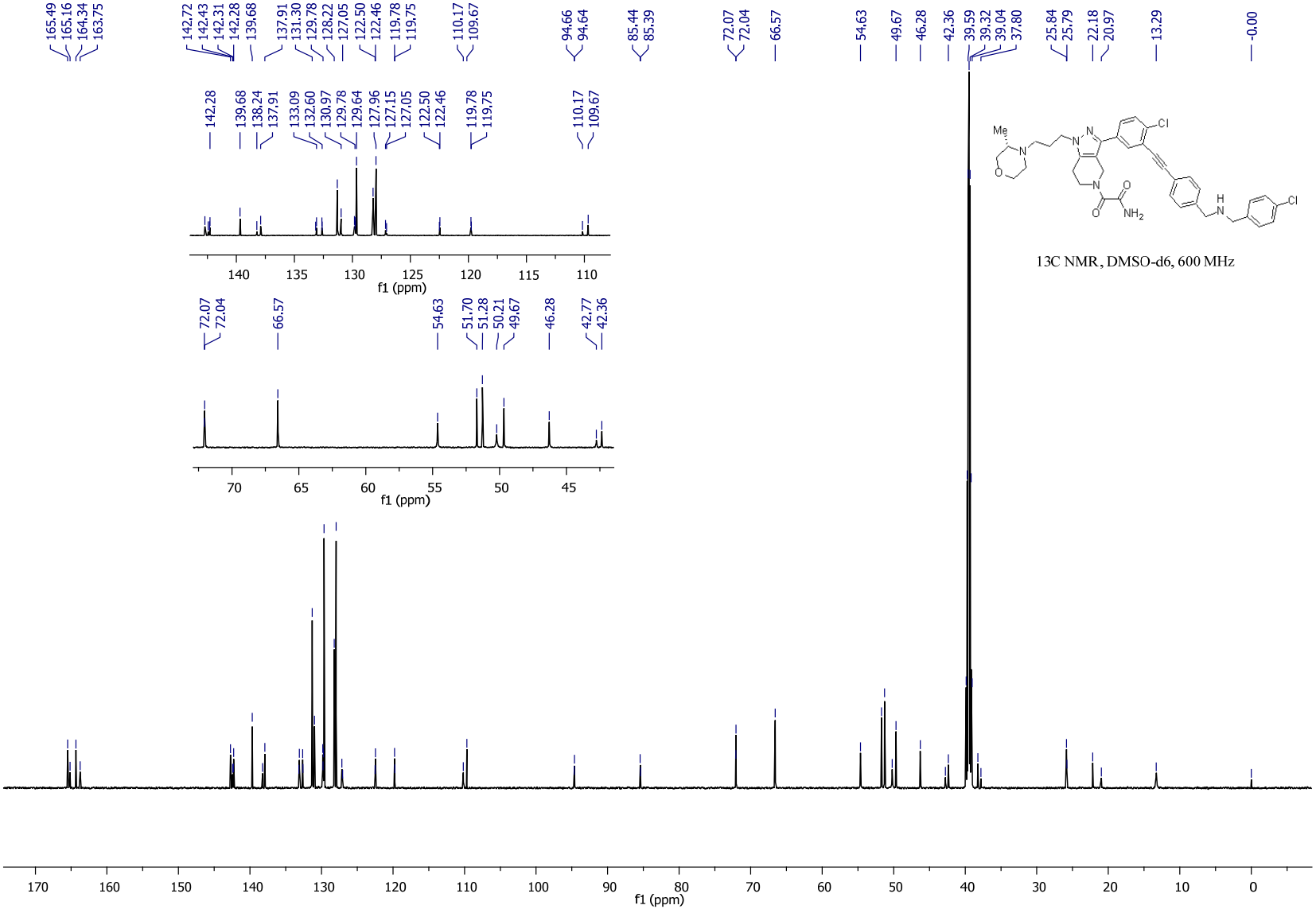
^{13}C NMR of compound **4**, $CDCl_3$, 600 MHz



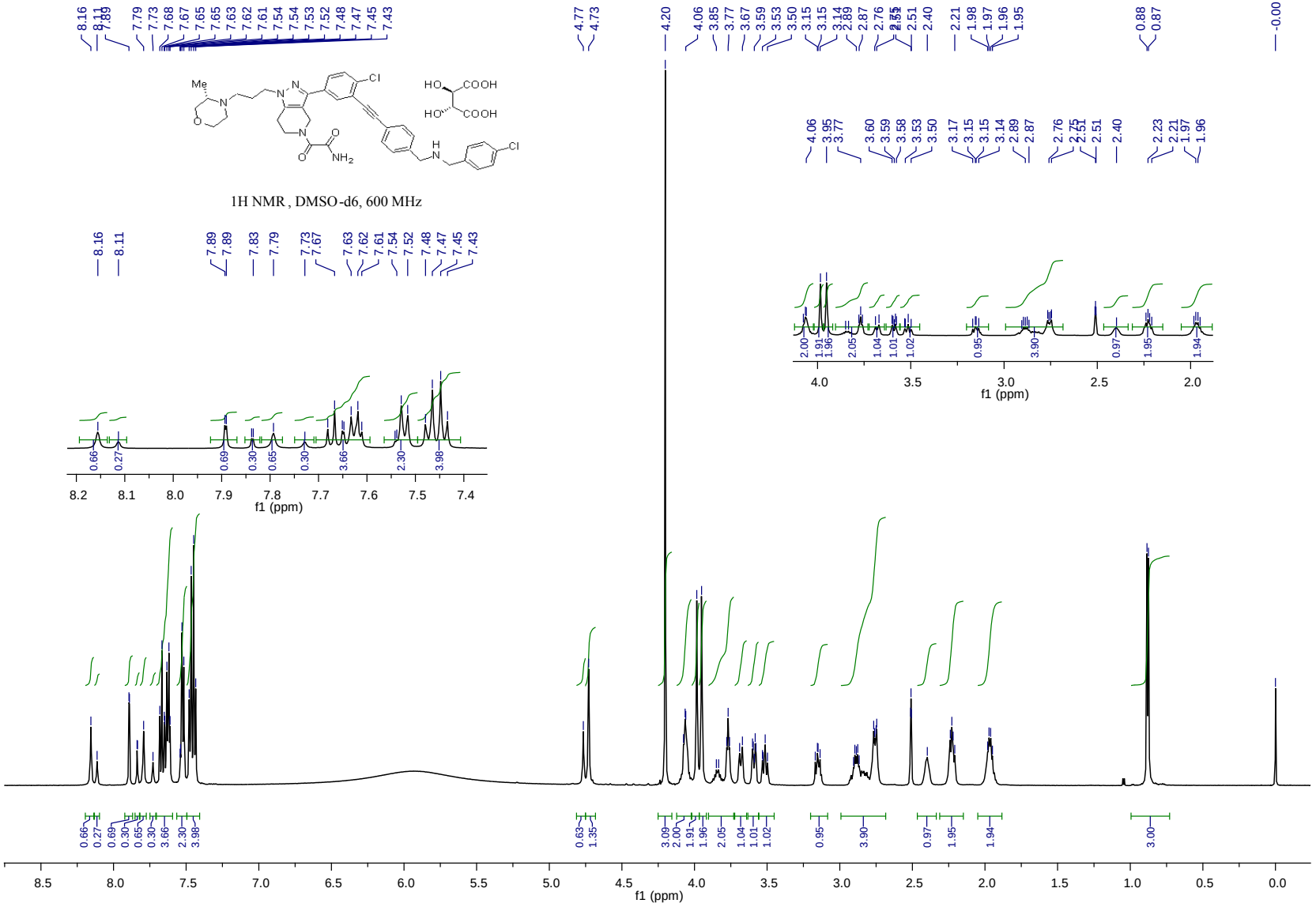
^{1}H NMR of compound **1**, DMSO-d6, 600 MHz



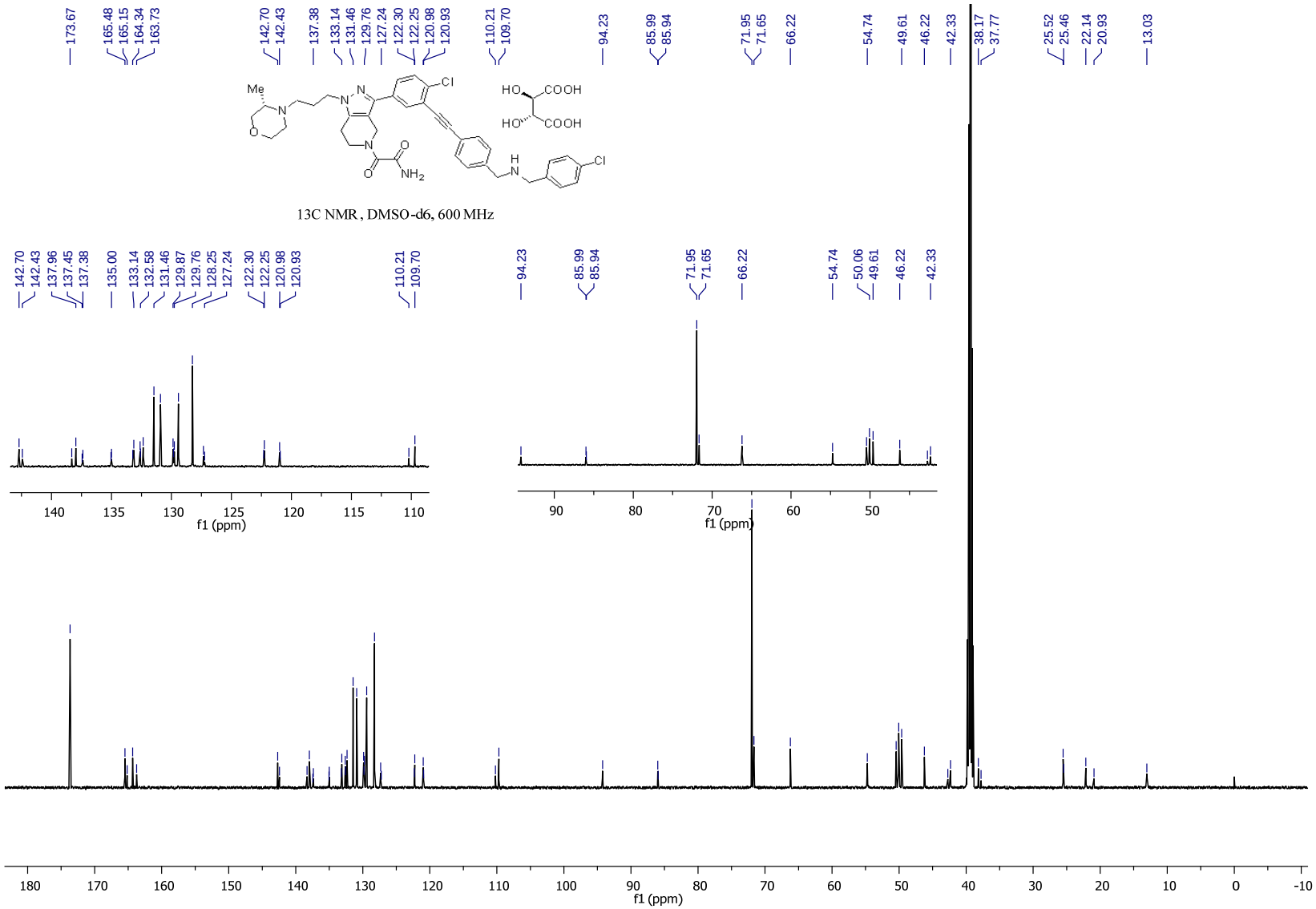
^{13}C NMR of compound **1**, DMSO-d6, 600 MHz



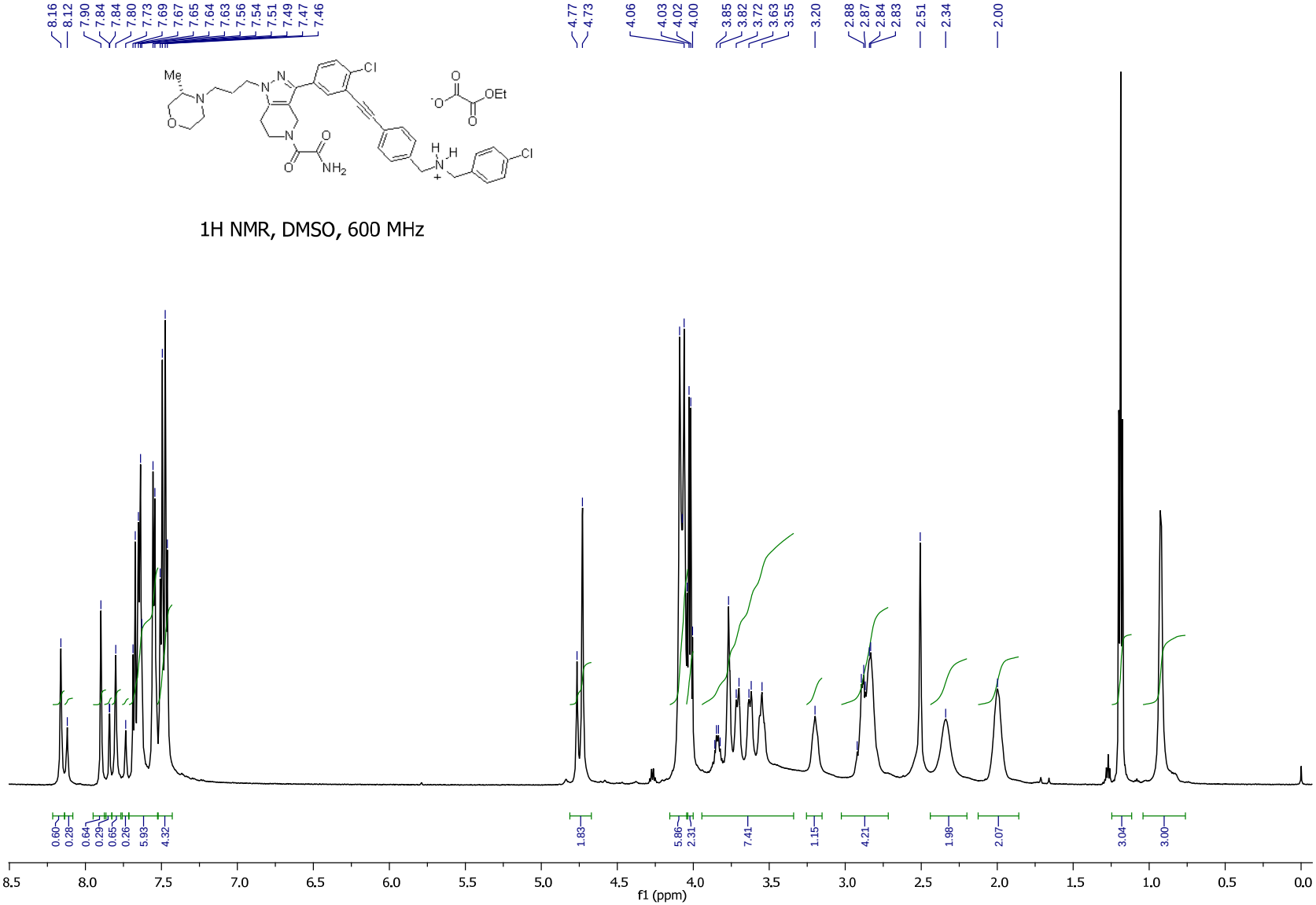
^{1}H NMR of compound **1, L-tartrate**, DMSO-d6, 600 MHz



^{13}C NMR of compound **1, L-tartrate**, DMSO-d6, 600 MHz



^{1}**H** NMR of compound 1**2**, DMSO-d6, 600 MHz



^{13}C NMR of compound **12**, DMSO-d6, 600 MHz