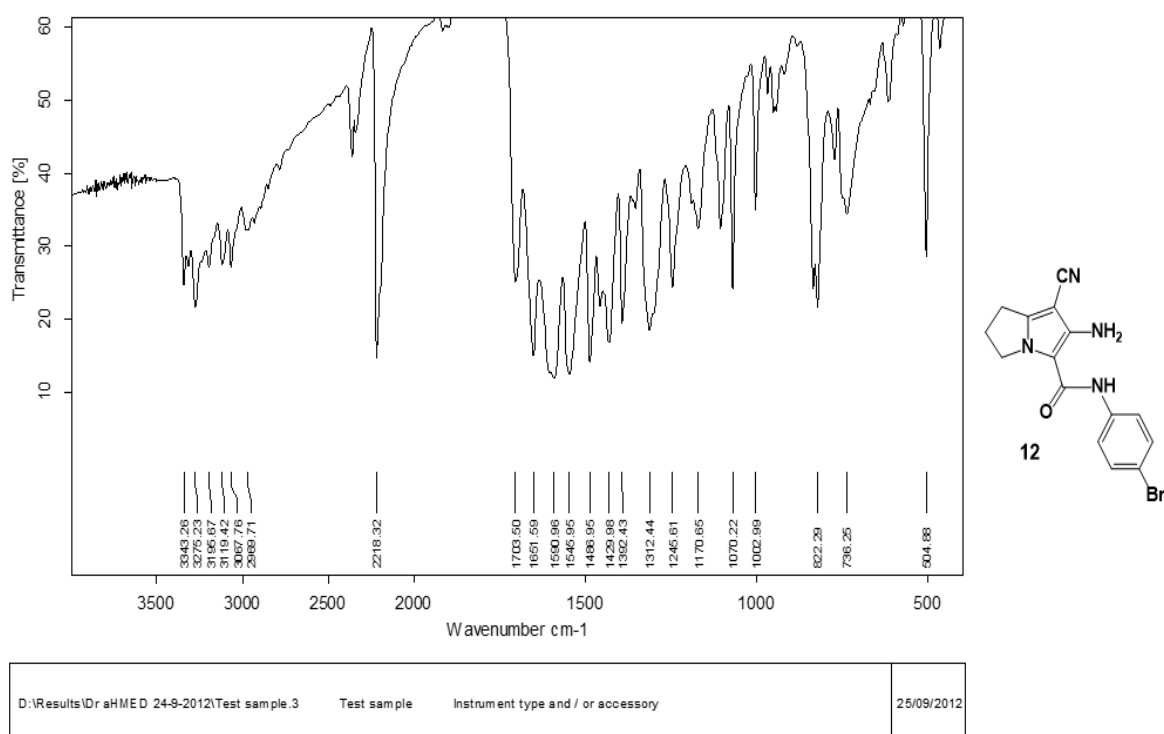


Supplementary Materials: Design, Synthesis, and Biological Evaluation of Some Novel Pyrrolizine Derivatives as COX Inhibitors with Anti-inflammatory/Analgesic Activities and Low Ulcerogenic Liability

Ahmed M. Gouda ^{1,2,*}, Hamed I. Ali ^{1,3}, Waleed H. Almalki ⁴, Mohamed A. Azim ^{1,5}, Mohammed A. S. Abourehab ⁶ and Ahmed H. Abdelazeem ²

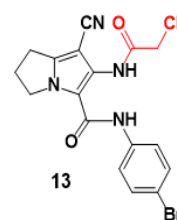
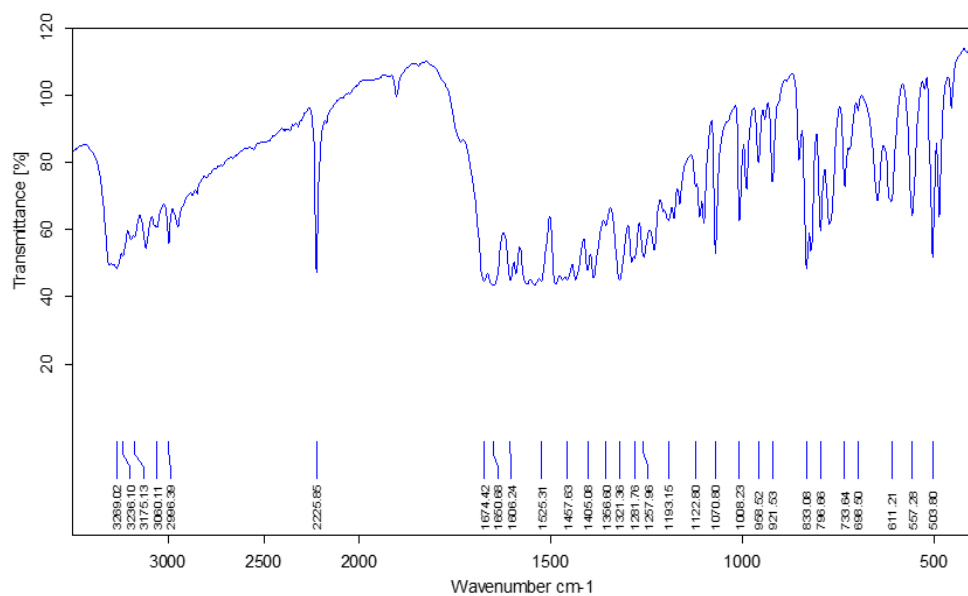
IR Spectra

Infrared spectra (IR) were done using BRUKER TENSOR 37 spectrophotometer and absorption were expressed in wave number (cm⁻¹) using KBr disc.



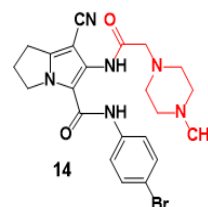
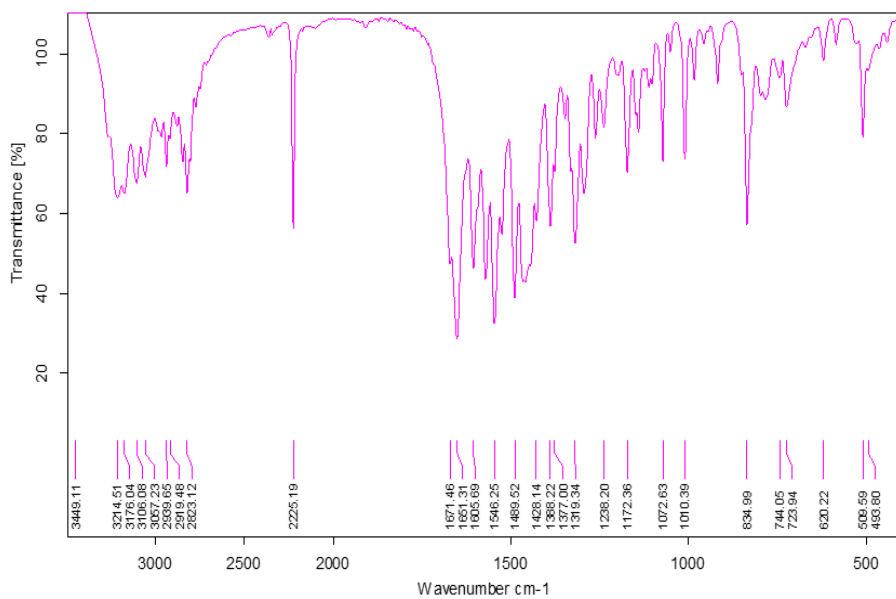
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Figure S1: IR spectrum of compound 12



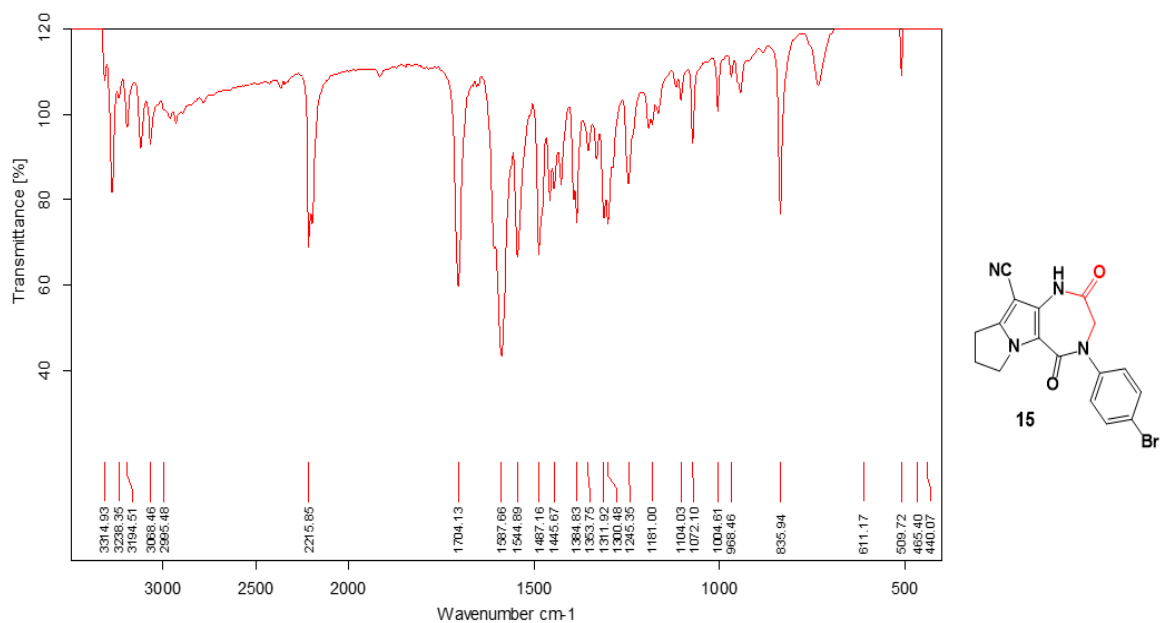
C:\Program Files\OPUS_65\MEAS\MET THY 2.2 MET THY 2 Instrument type and / or accessory 13/06/2015

Figure S2: IR spectrum of compound 13



C:\Program Files\OPUS_65\MEAS\MET THY 2.4 MET THY 2 Instrument type and / or accessory 13/06/2015

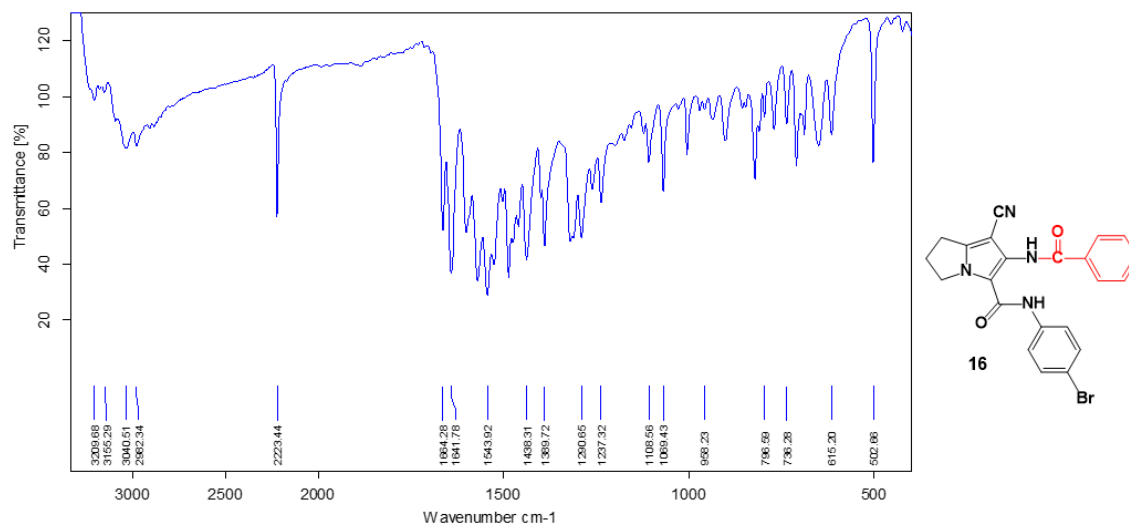
Figure S3: IR spectrum of compound 14



C:\Program Files\OPUS_65\MEAS\MET THY 2.3 MET THY 2 Instrument type and / or accessory 13/06/2015

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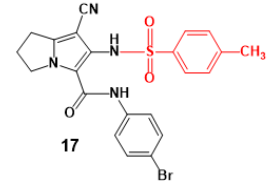
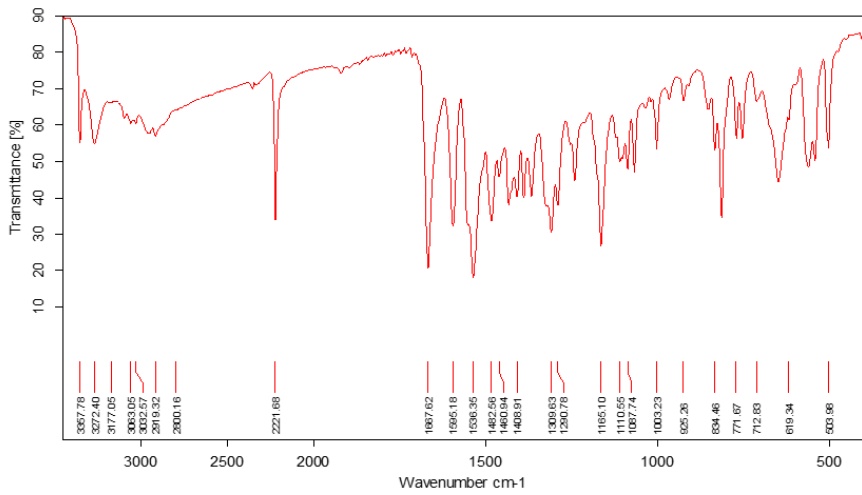
Figure S4: IR spectrum of compound 15



C:\Program Files\OPUS_65\MEAS\MLT.264 MLT Instrument type and / or accessory 01/06/2015

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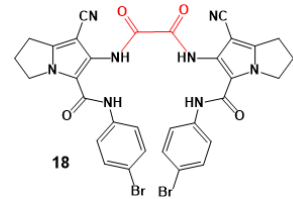
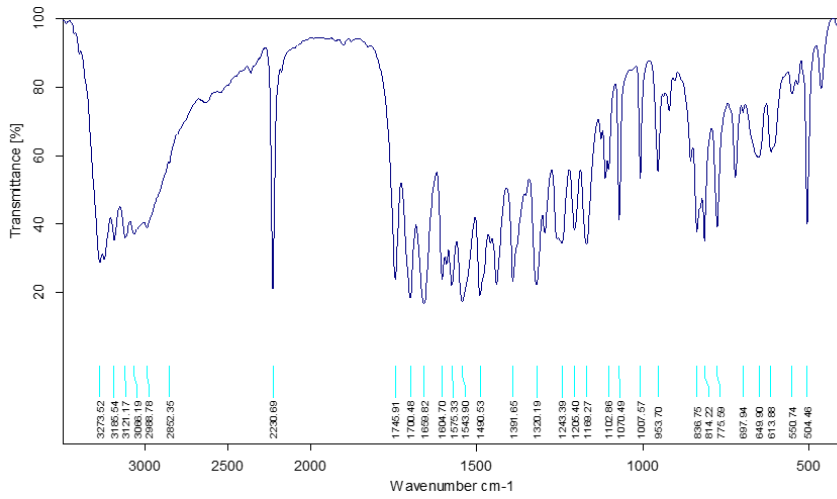
Figure S5: IR spectrum of compound 16



C:\Program Files\OPUS_05\MEAS\MLT 270 MLT Instrument type and / or accessory 02/08/2015

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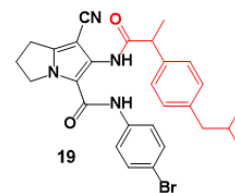
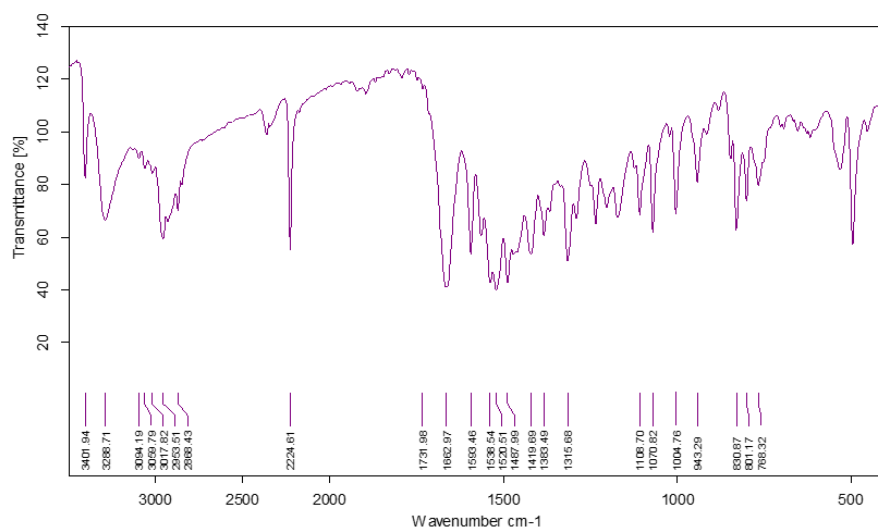
Figure S6: IR spectrum of compound 17



C:\Program Files\OPUS_05\MEAS\MET THY 2.6 MET THY 2 Instrument type and / or accessory 13/08/2015

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Figure S7: IR spectrum of compound 18



C:\Program Files\OPUS_65\MEAS\MLT.258	MLT	Instrument type and / or accessory	02/04/2015
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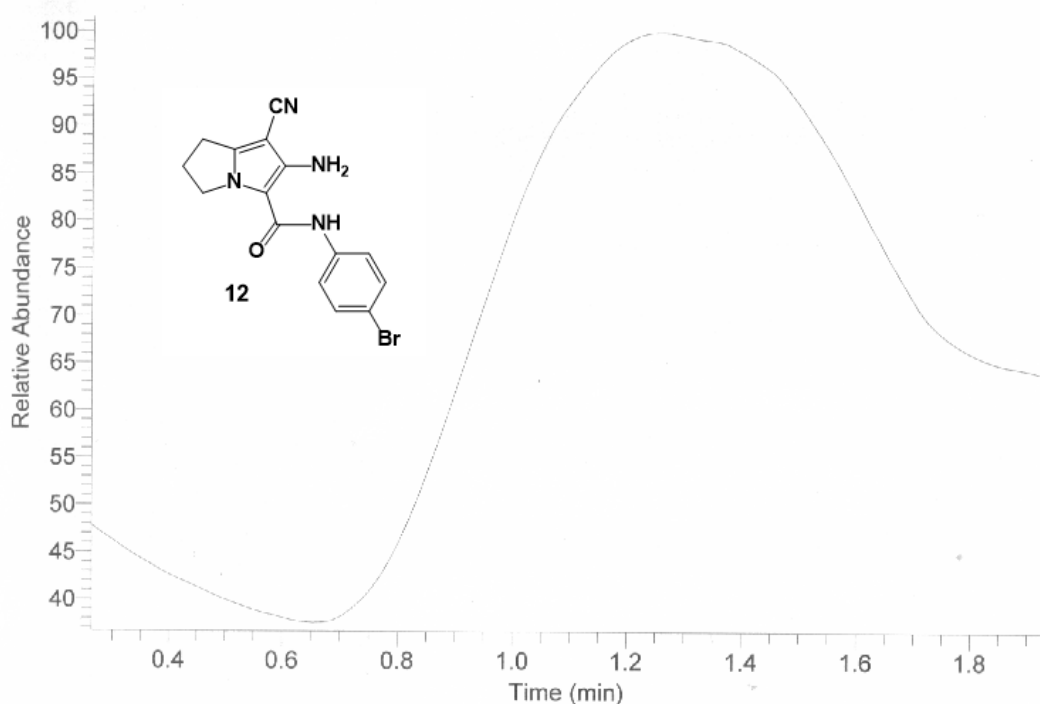
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Figure S8: IR spectrum of compound 19

Mass Spectra

Mass spectra were recorded on Shimadzu GCMS QP5050A spectrometer, at 70 eV (EI) at the regional center for mycology and biotechnology, Al-Azhar University.

RT: 0.26 - 1.93 SM: 15B



NL:
3.26E7
TIC MS
AHMED-
MAHMOU
-GAD-1D

AHMED-MAHMOUD-GAD-1D #73 RT: 1.24 AV: 1 SB: 2 0.57, 0.62 NL: 1.84E6
T: {0,0} + c EI Full ms [40.00-1000.00]

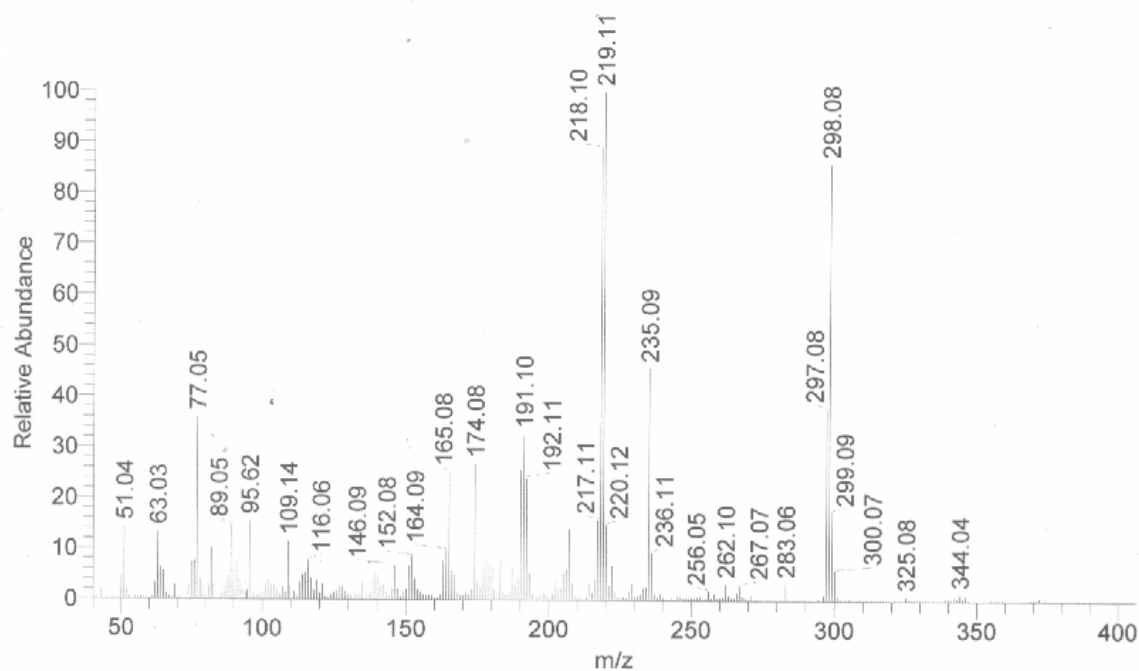
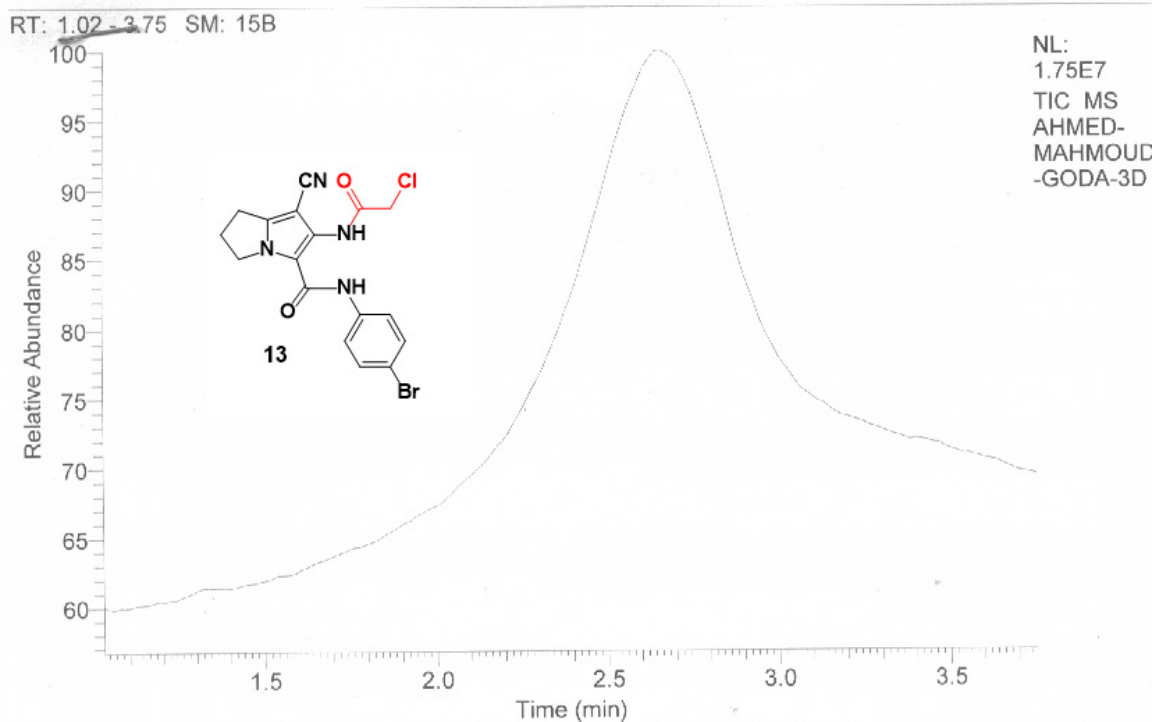


Figure S9: Mass spectrum of compound 12.



AHMED-MAHMOUD-GODA-3D #201 RT: 3.38 AV: 1 SB: 2 3.63 ; 3.67 NL: 2.54E4
T: {0,0} + c EI Full ms [40.00-1000.00]

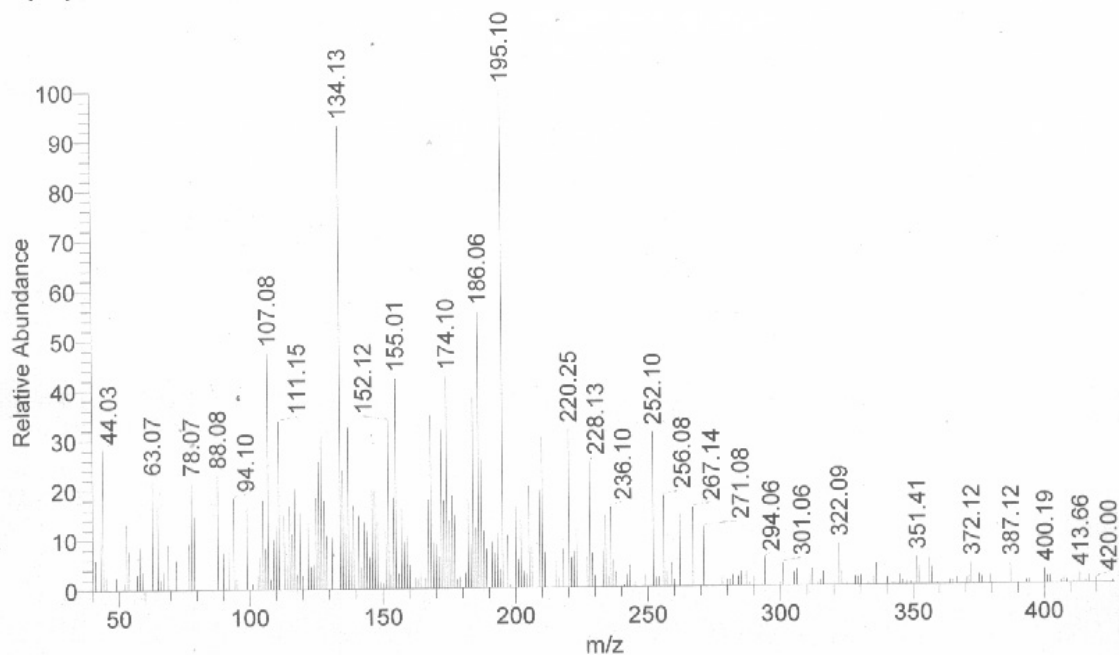
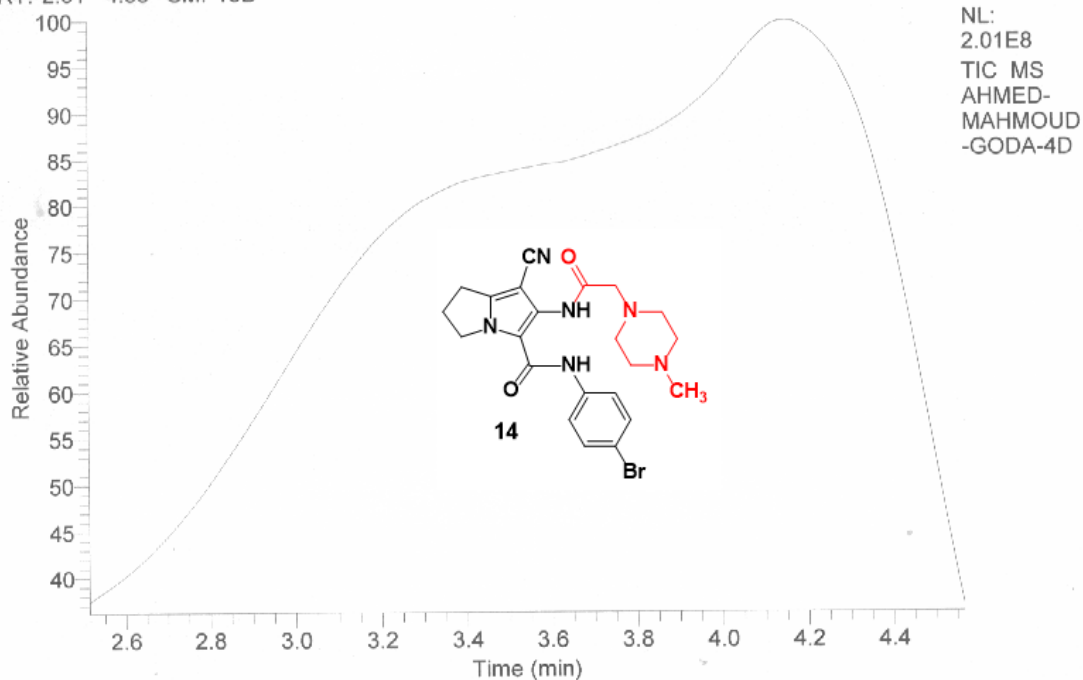


Figure S10: Mass spectrum of compound 13

RT: 2.51 - 4.56 SM: 15B



AHMED-MAHMOUD-GODA-4D #141 RT: 2.38 AV: 1 SB: 2 2.38 2.39 NL: 5.83E4
T: {0,0} + c EI Full ms [40.00-1000.00]

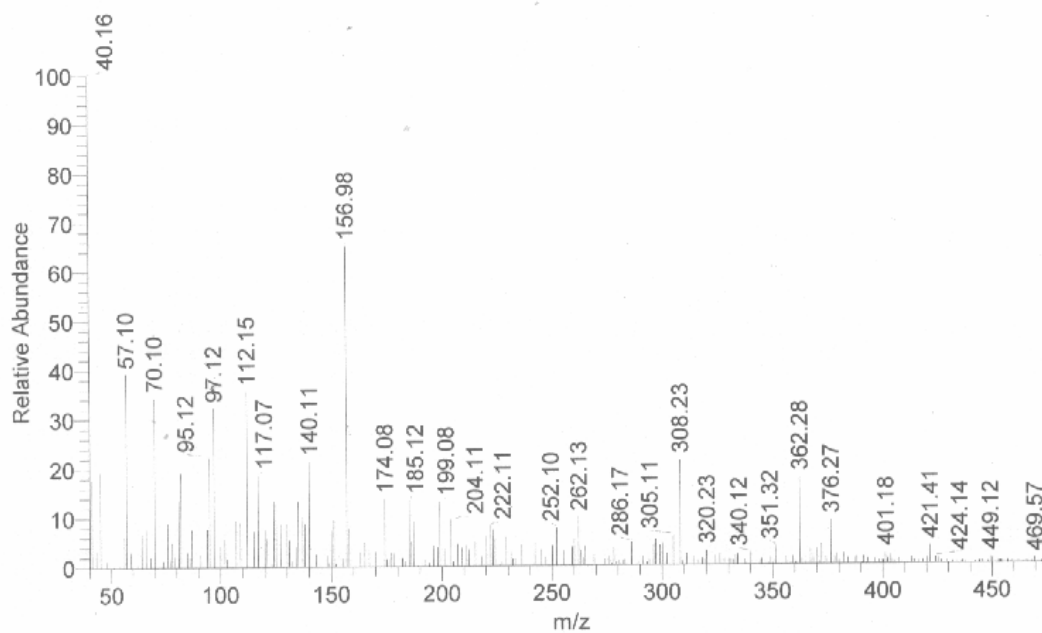
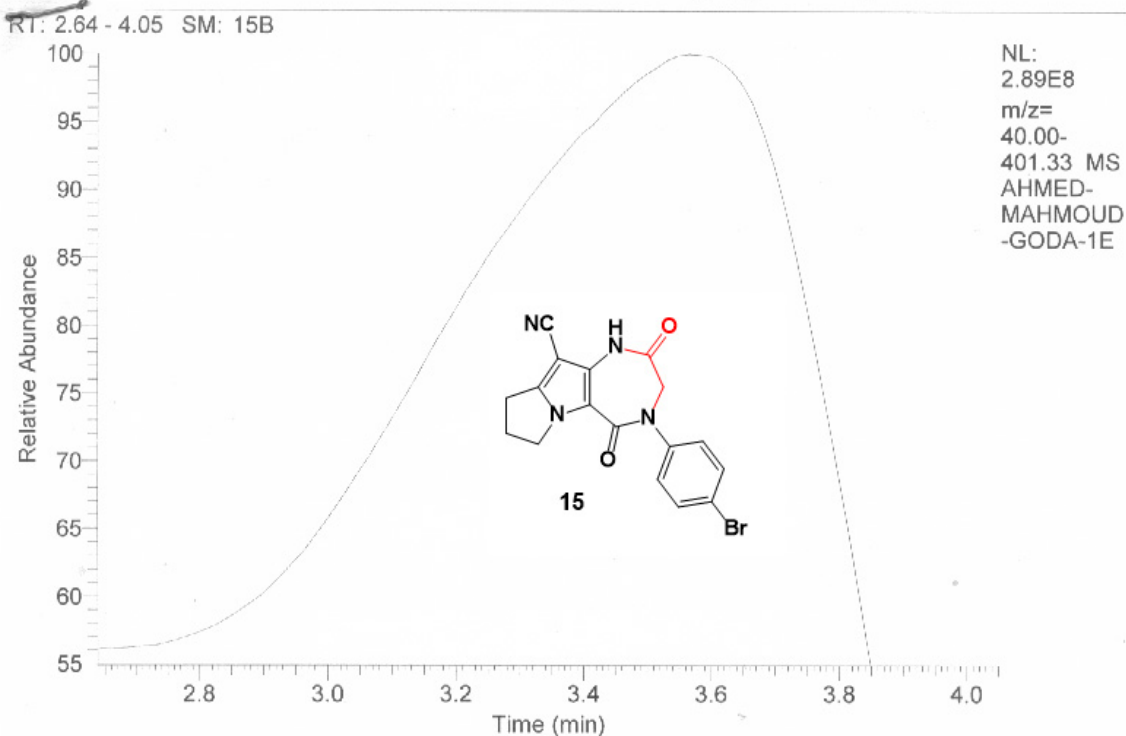


Figure S11: Mass spectrum of compound 14



AHMED-MAHMOUD-GODA-1E #148 RT: 2.49 AV: 1 SB: 2 2.38 , 2.39 NL: 2.16E6
T: {0,0} + c EI Full ms [40.00-1000.00]

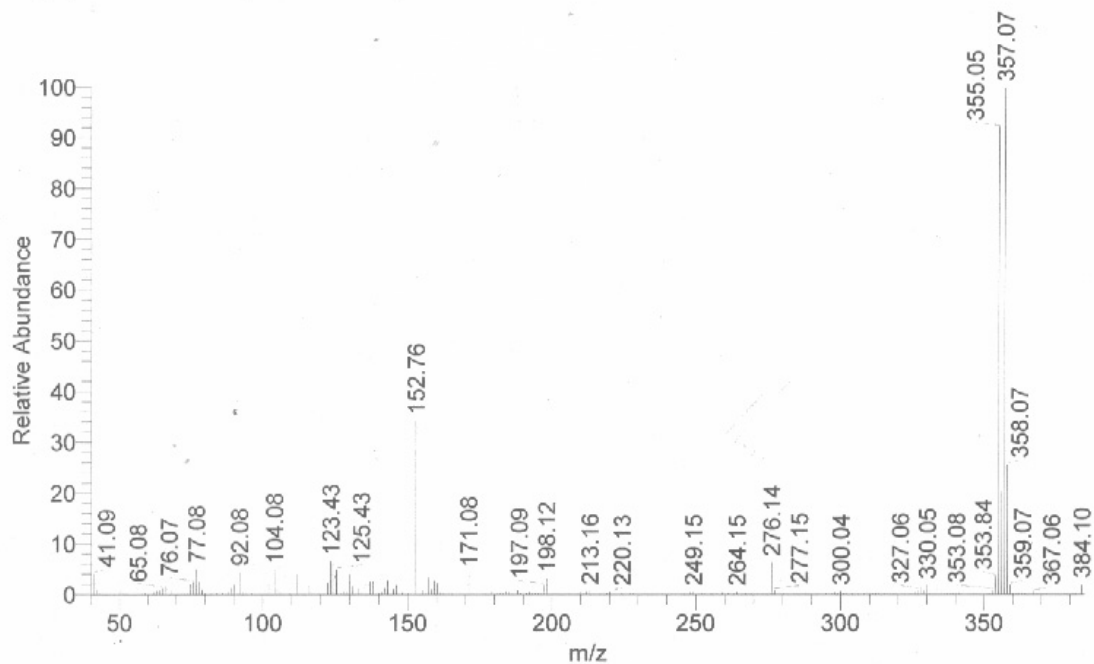
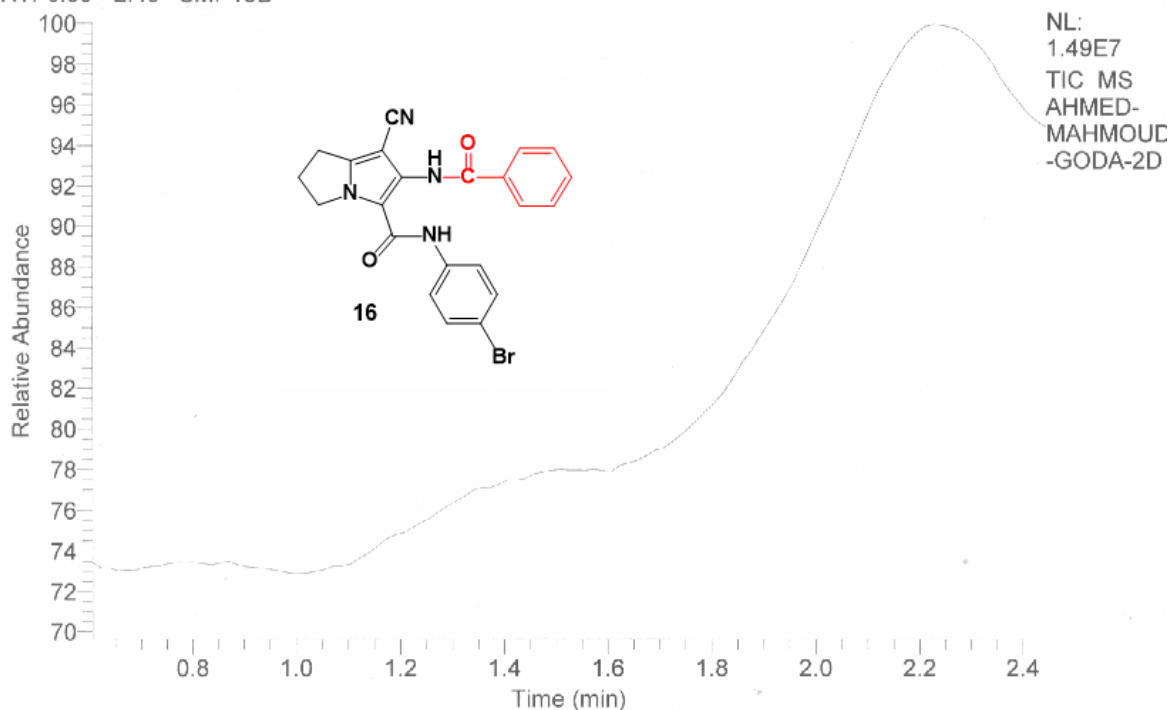


Figure S12: Mass spectrum of compound 15

RT: 0.60 - 2.45 SM: 15B



AHMED-MAHMOUD-GODA-2D #168 RT: 2.83 AV: 1 SB: 2 2.91, 2.90 NL: 5.85E4
T: {0,0} + c EI Full ms [40.00-1000.00]

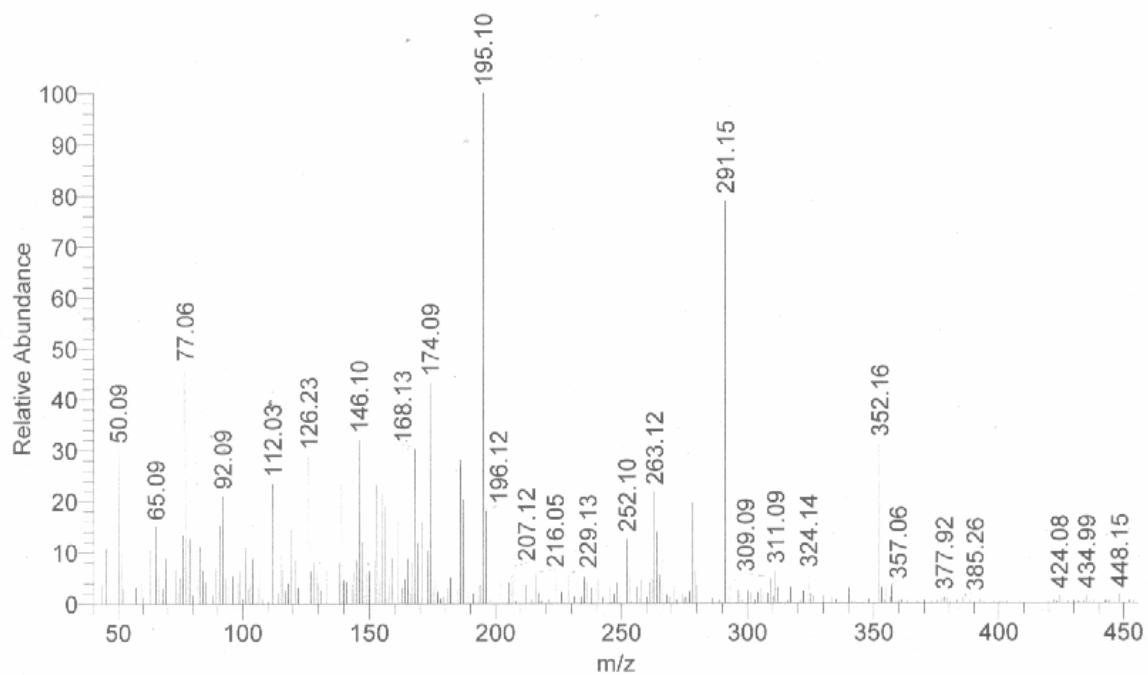
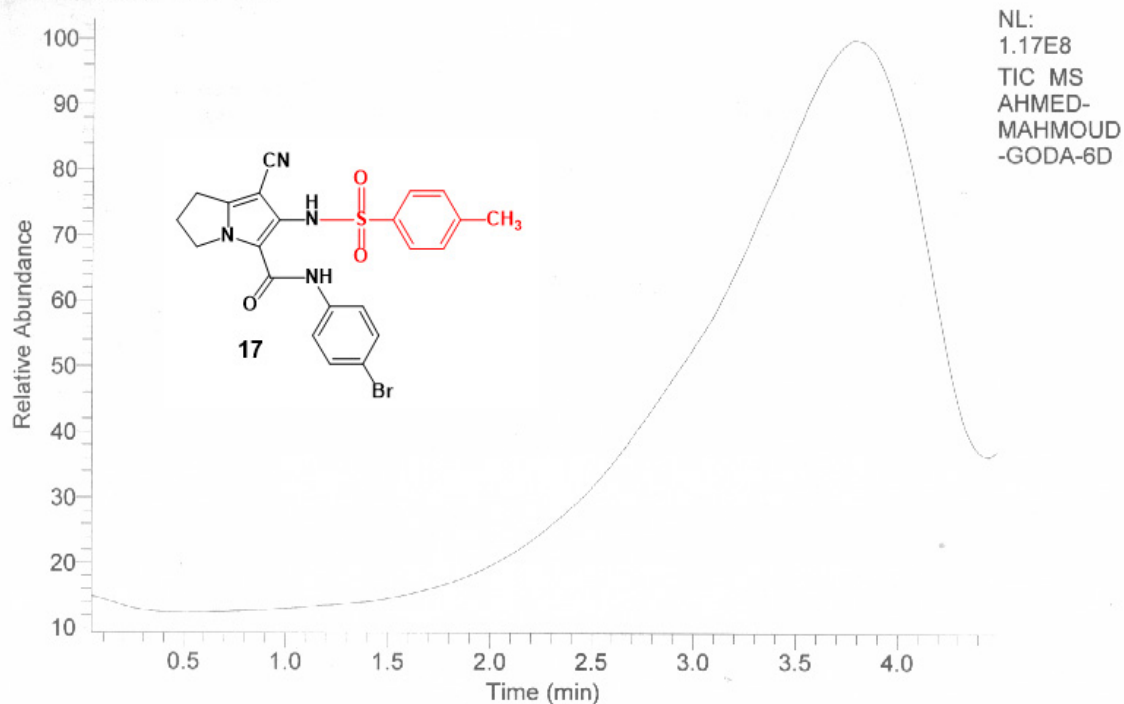


Figure S13: Mass spectrum of compound 16

RT: 0.04 - 4.49 SM: 15B



AHMED-MAHMOUD-GODA-6D #328 RT: 5.51 AV: 1 NL: 2.92E7
T: {0,0} + c EI Full ms [40.00-1000.00]

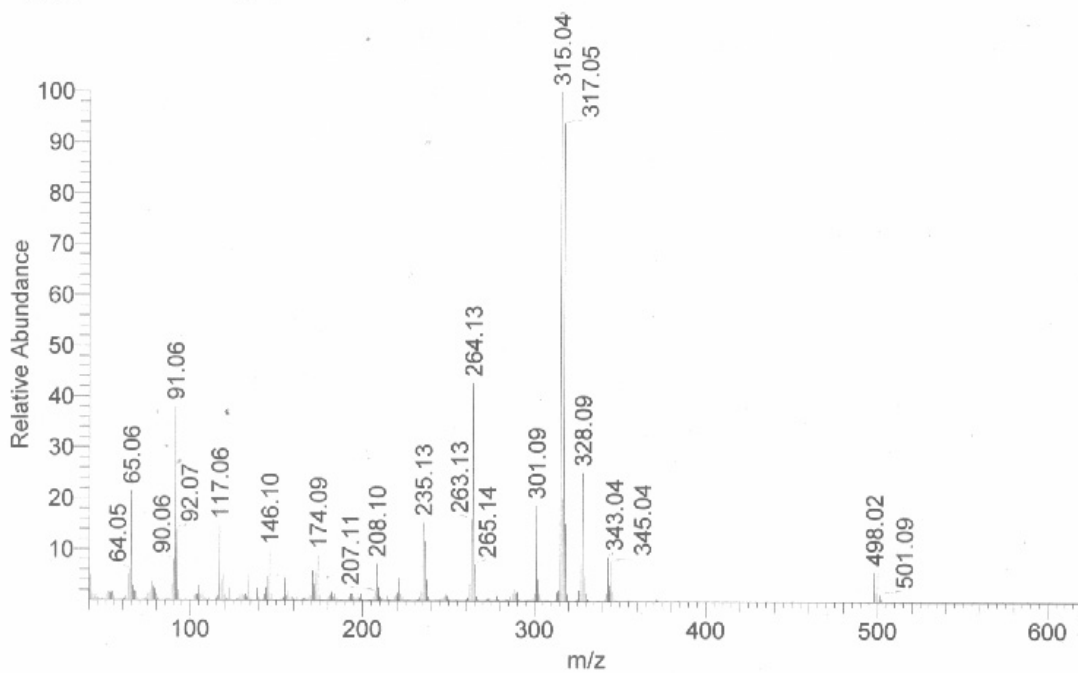
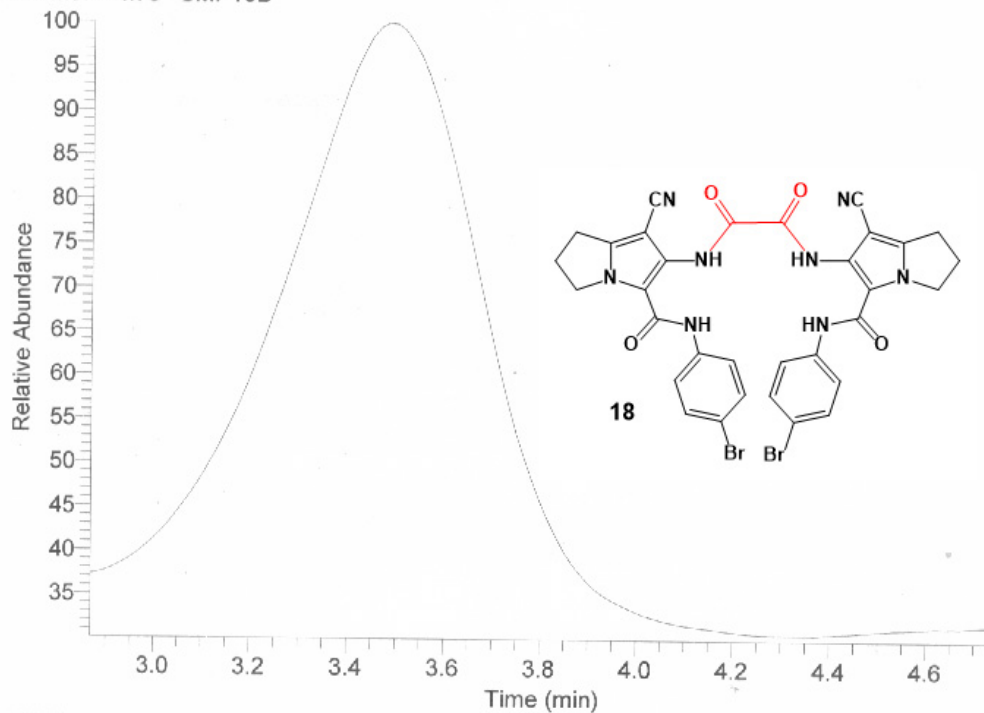


Figure S14: Mass spectrum of compound 17

RT: 2.87 - 4.75 SM: 15B



NL:
4.83E7
TIC MS
AHMED-
MAHMOUD
-GODA-7D

AHMED-MAHMOUD-GODA-7D #122 RT: 2.06 AV: 1 SB: 27 2.34,2.46 , 2.28-2.58 NL: 3.31E4
T: {0,0} + c EI Full ms [40.00-1000.00]

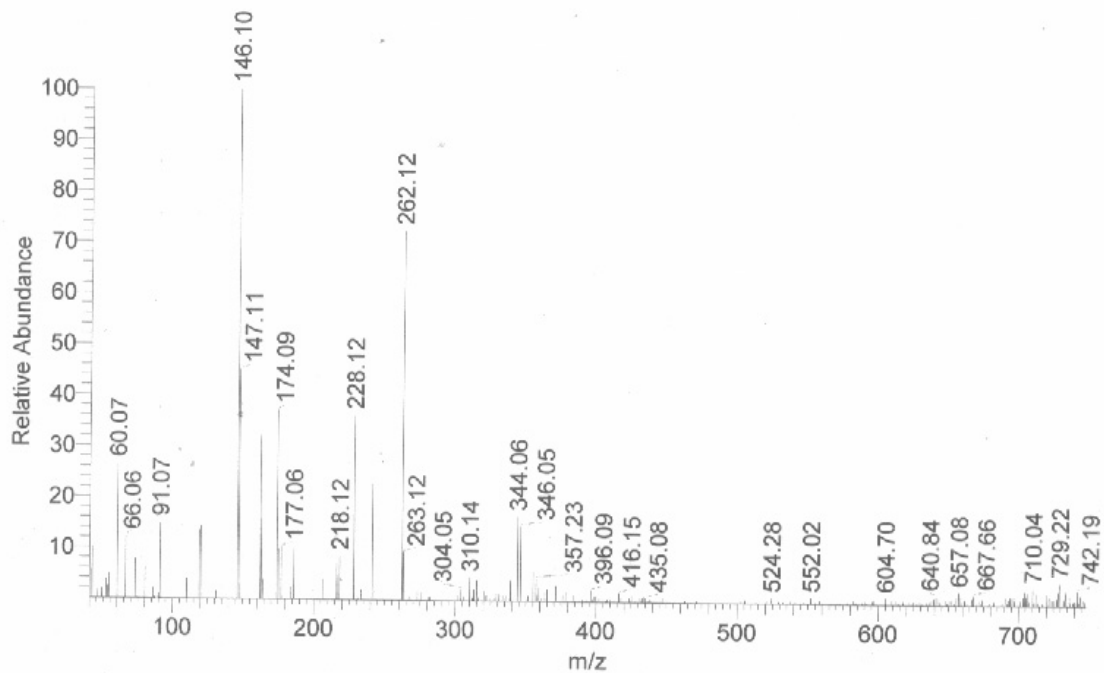
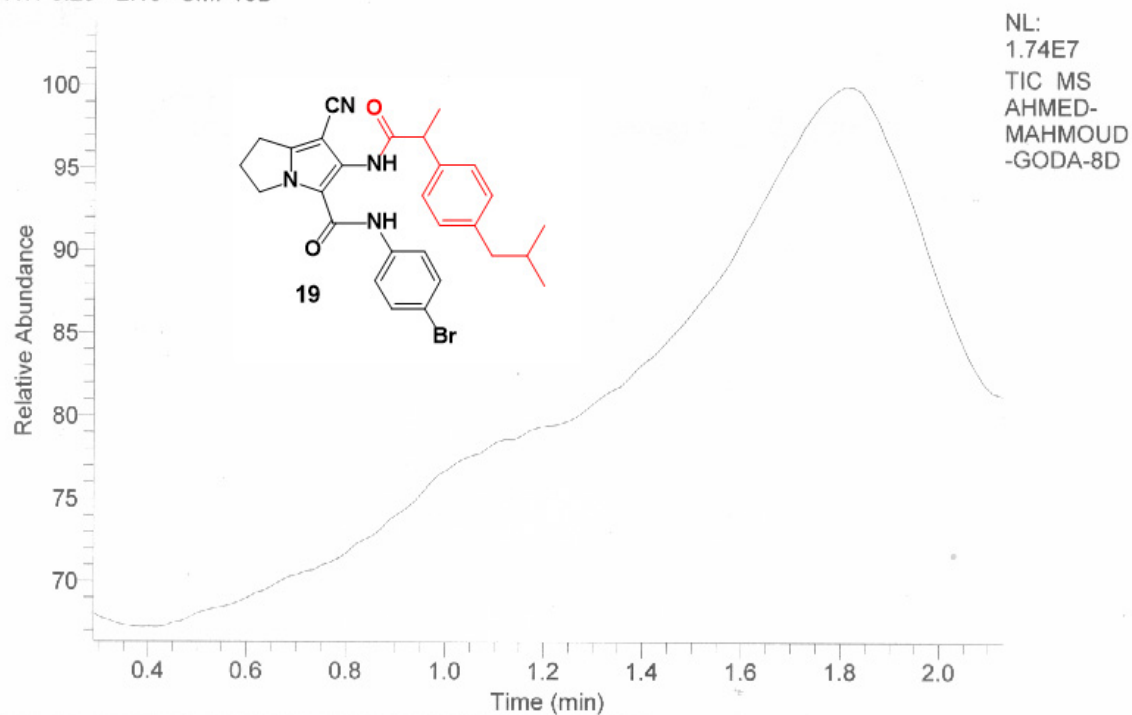


Figure S15: Mass spectrum of compound 18

RT: 0.29 - 2.13 SM: 15B



AHMED-MAHMOUD-GODA-8D #243 RT: 4.08 AV: 1 SB: 17 5.34-5.46, 5.27-5.41 NL: 3.33E4
T: {0,0} + c EI Full ms [40.00-1000.00]

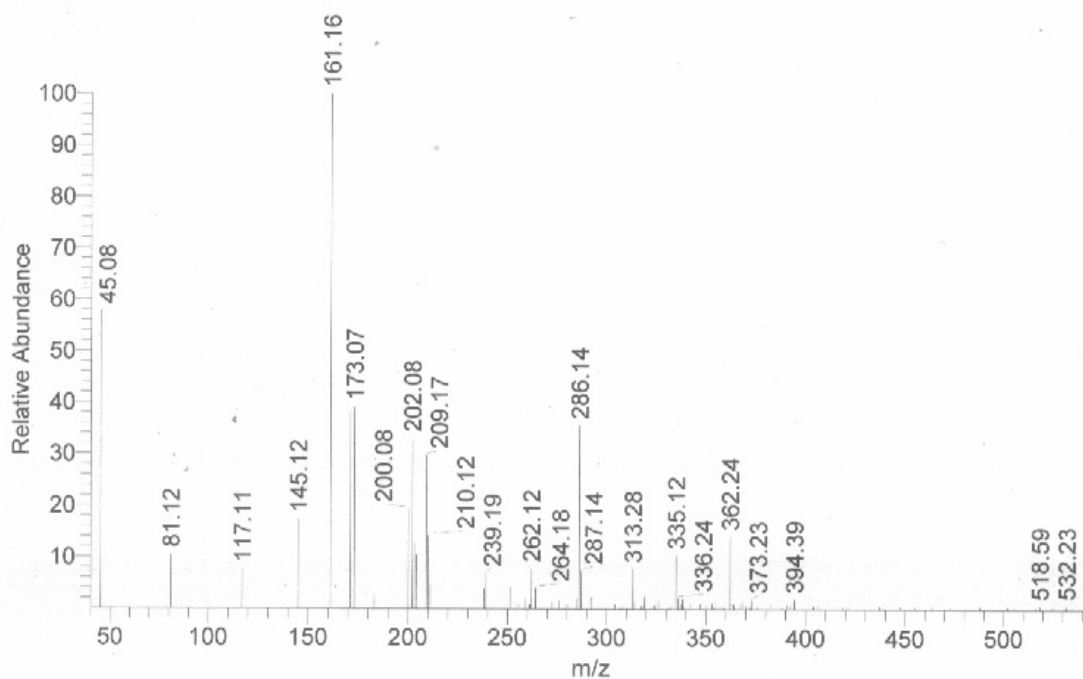


Figure S16: Mass spectrum of compound 19

¹H-NMR and ¹³C-NMR Spectra

¹H-NMR spectra were recorded on a BRUKER AVANCE II spectrometer (at the faculty of pharmacy, Umm Al-Qura University) at 500 MHz in the specified solvent, chemical shifts were reported on the δ scale and were related to that of the solvent and J values are given in Hz. ¹³C NMR and DEPT135 spectra were obtained on a BRUKER AVANCE II at 125 MHz (at the faculty of pharmacy, Umm Al-Qura University).

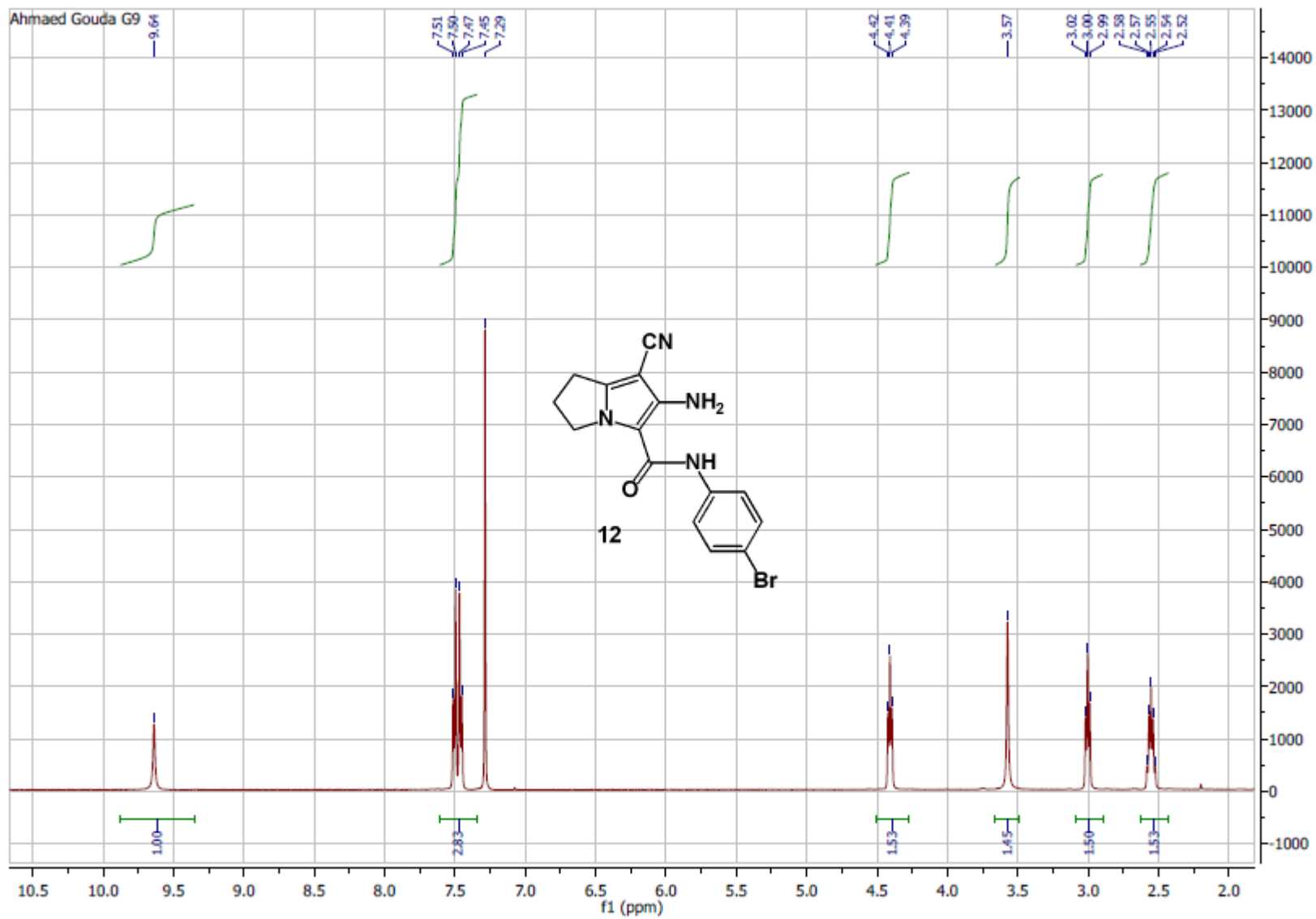


Figure S17a: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 12

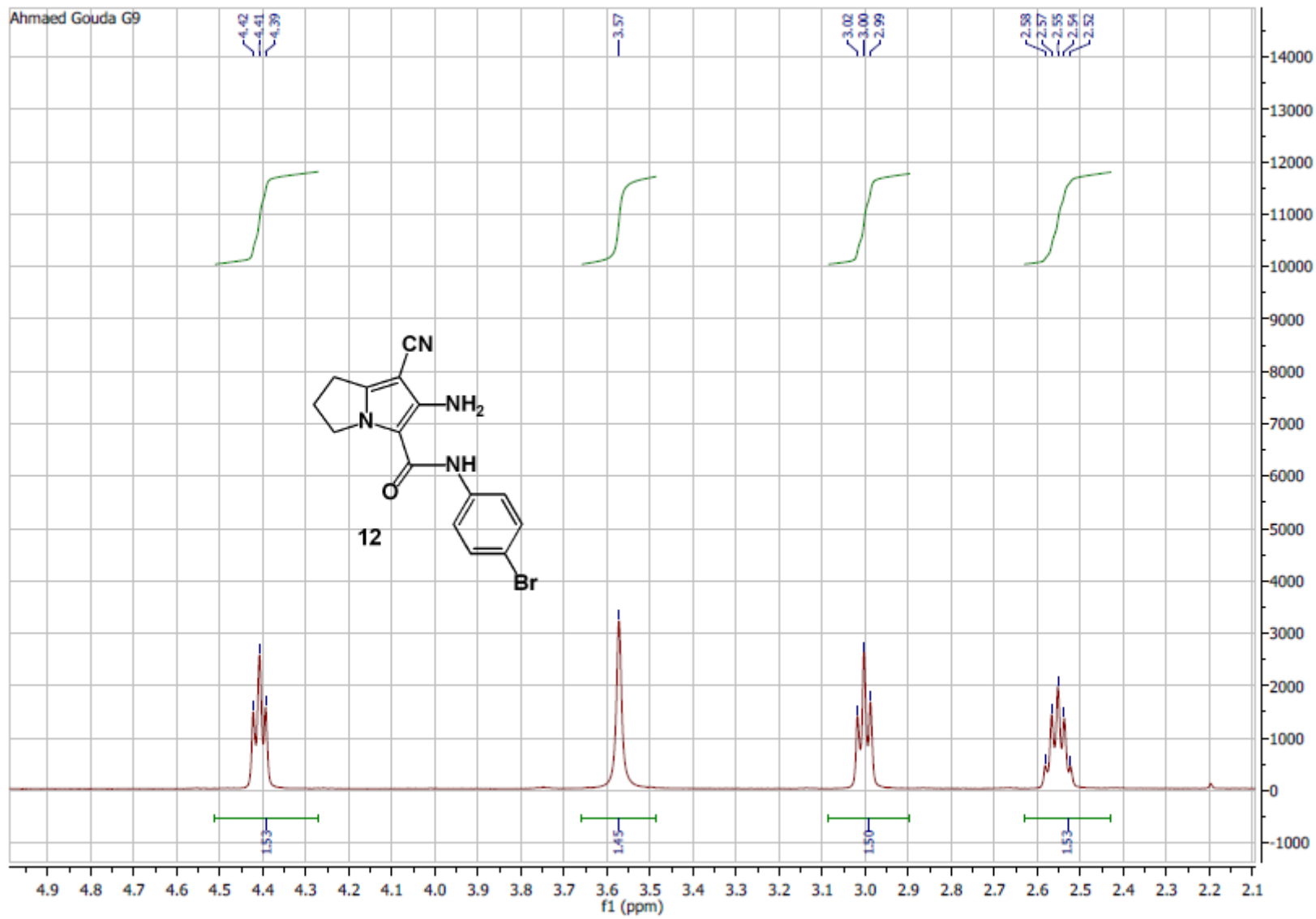


Figure S17b: ¹H-NMR (CDCl₃, 500 MHz, δ ppm) spectrum of compound 12 (ZOOM on Aliphatic Protons)

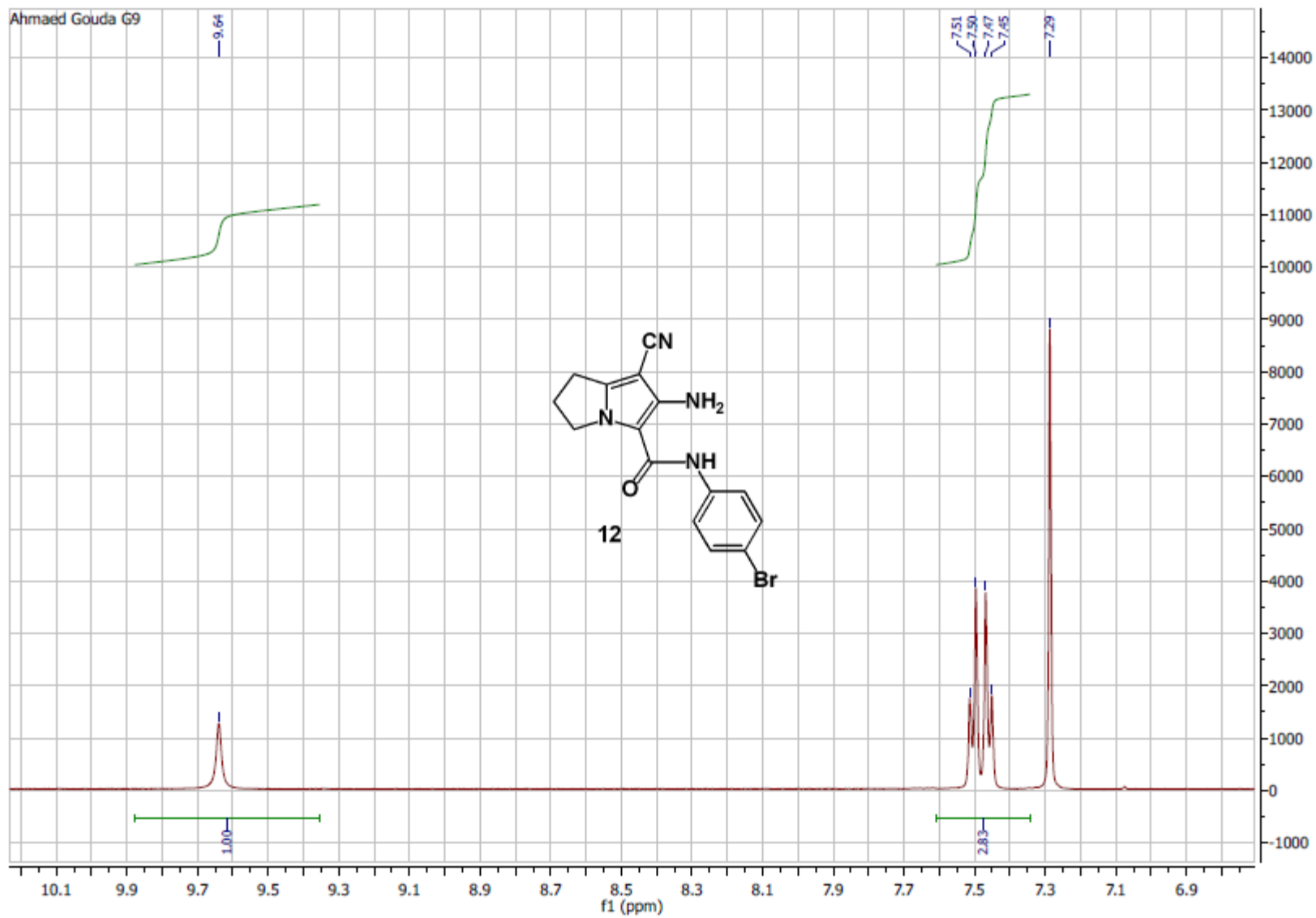


Figure S17c: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 12 (ZOOM on Aromatic Protons)

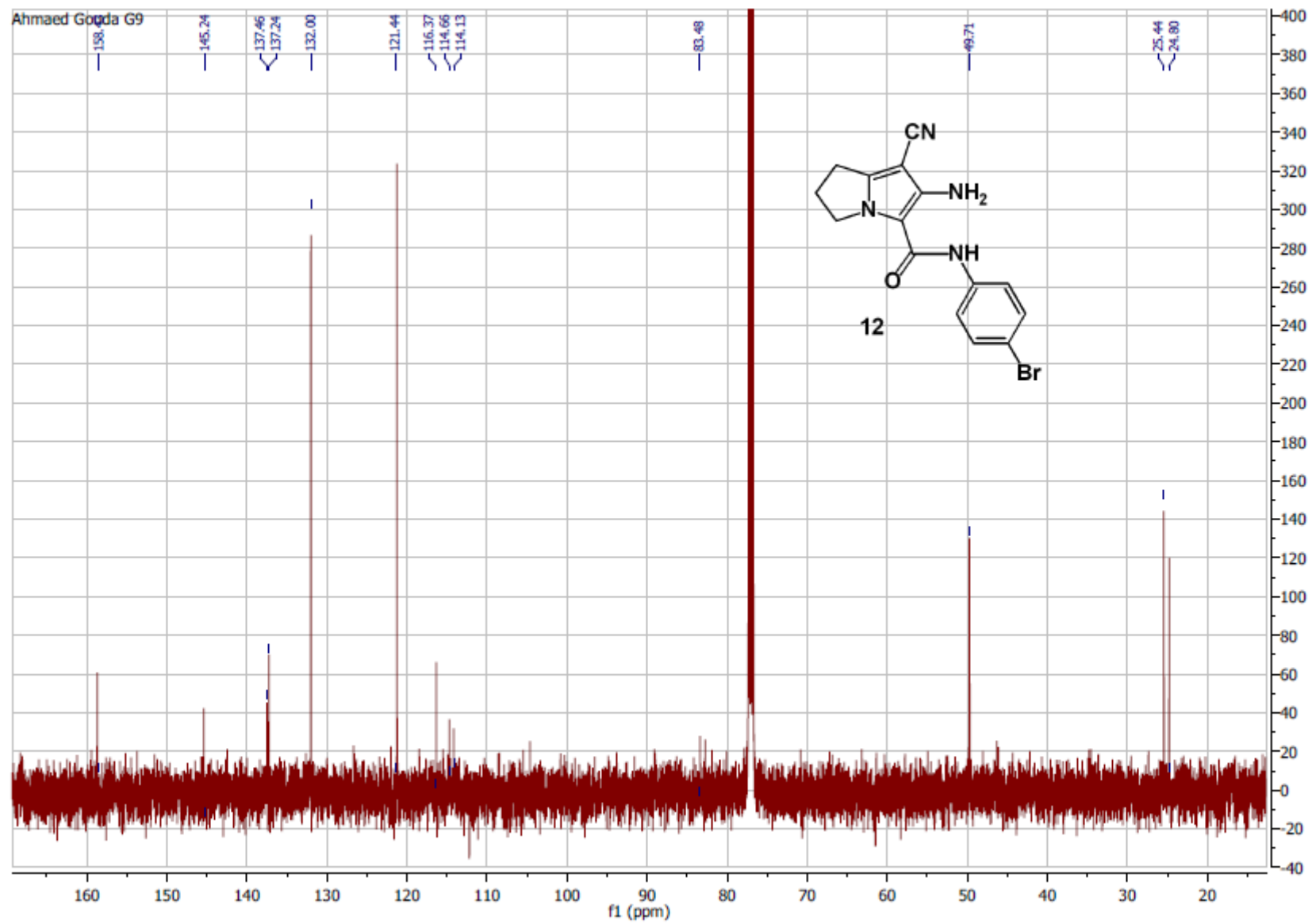


Figure S18a: ^{13}C -NMR (CDCl_3 , 125 MHz, δ ppm) spectrum of compound 12

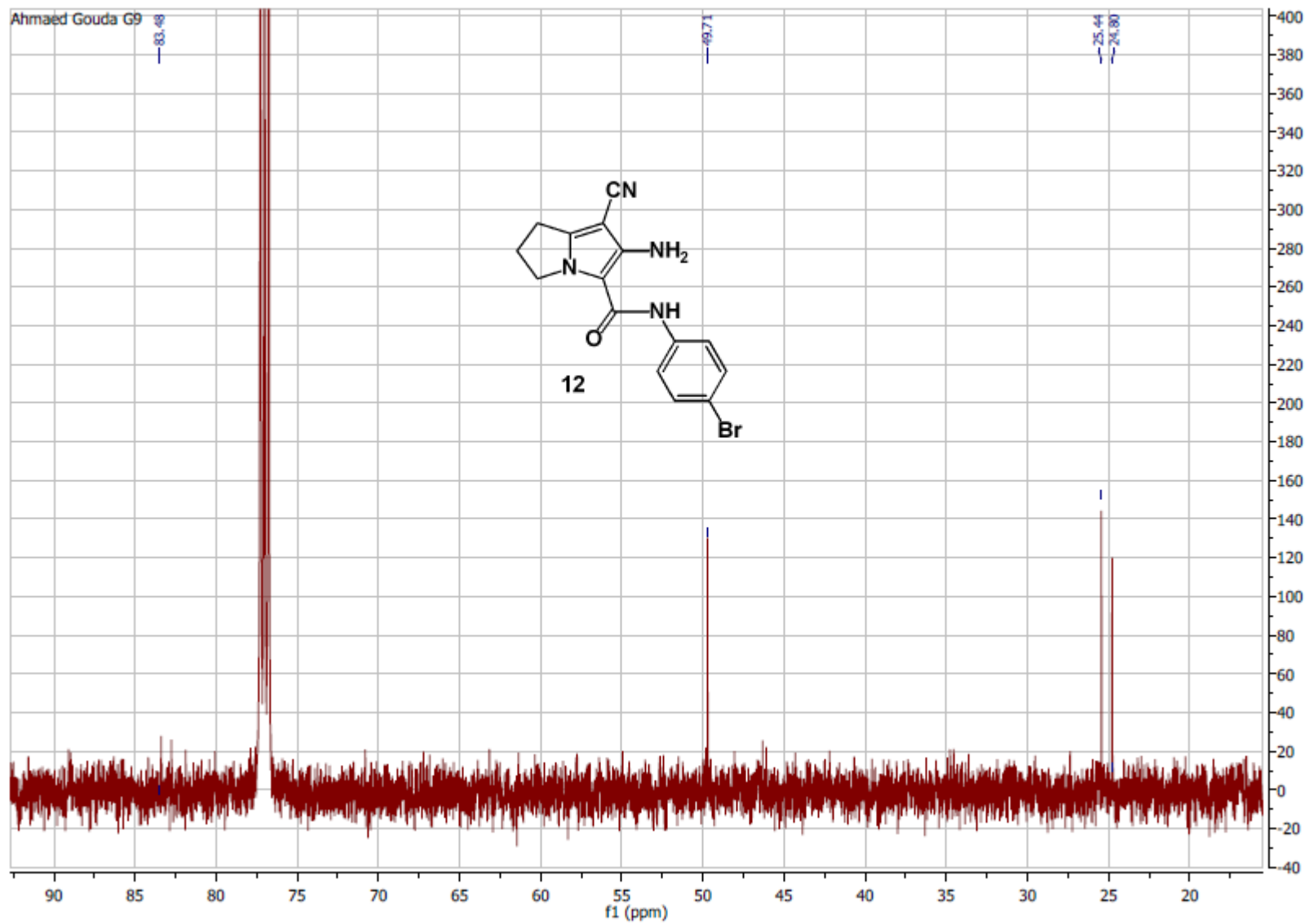


Figure S18b: ^{13}C -NMR (CDCl_3 , 125 MHz, δ ppm) spectrum of compound 12 (ZOOM on Aliphatic Carbons)

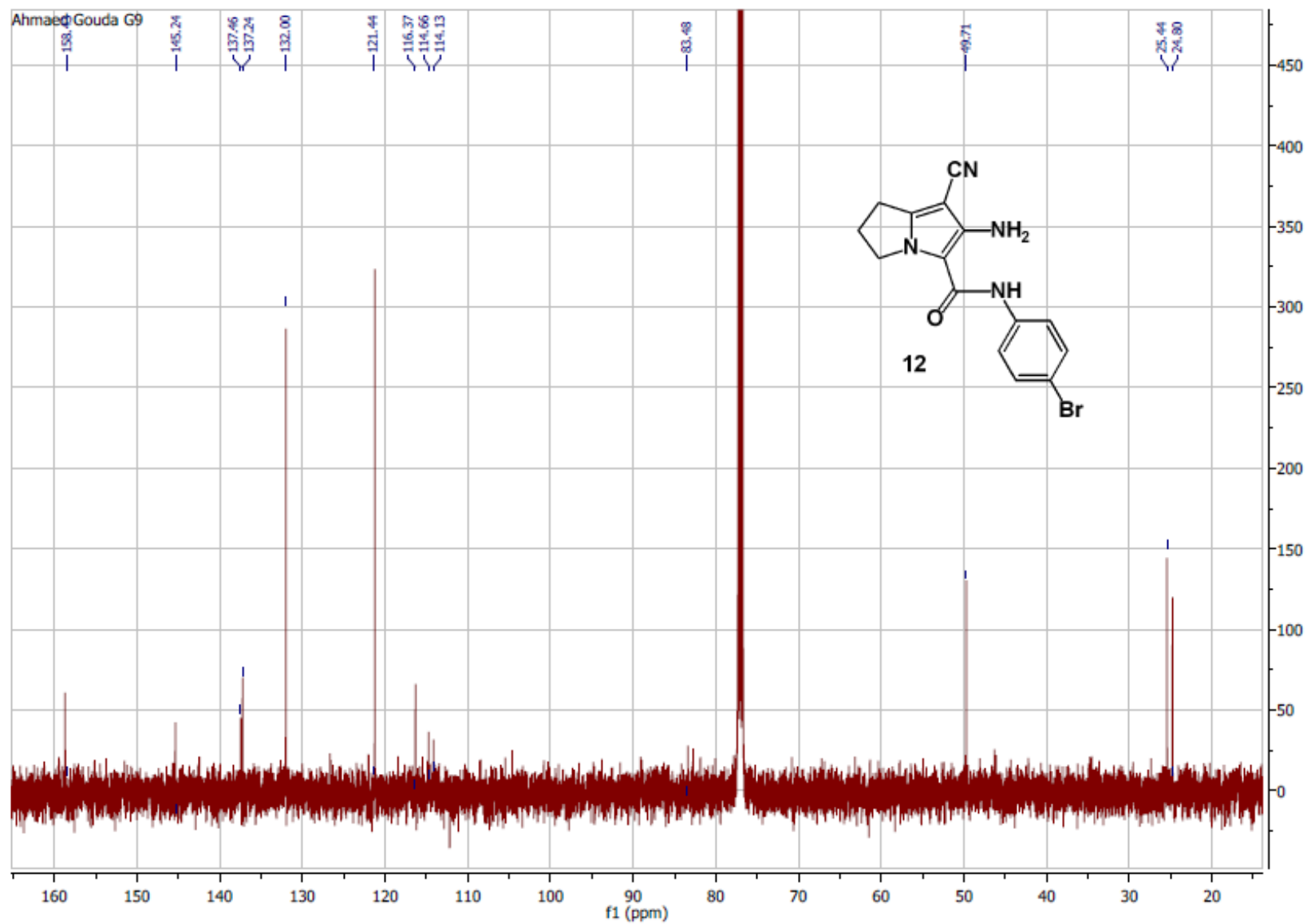


Figure S18c: ^{13}C -NMR (CDCl_3 , 125 MHz, δ ppm) spectrum of compound 12 (ZOOM on Aromatic Carbons)

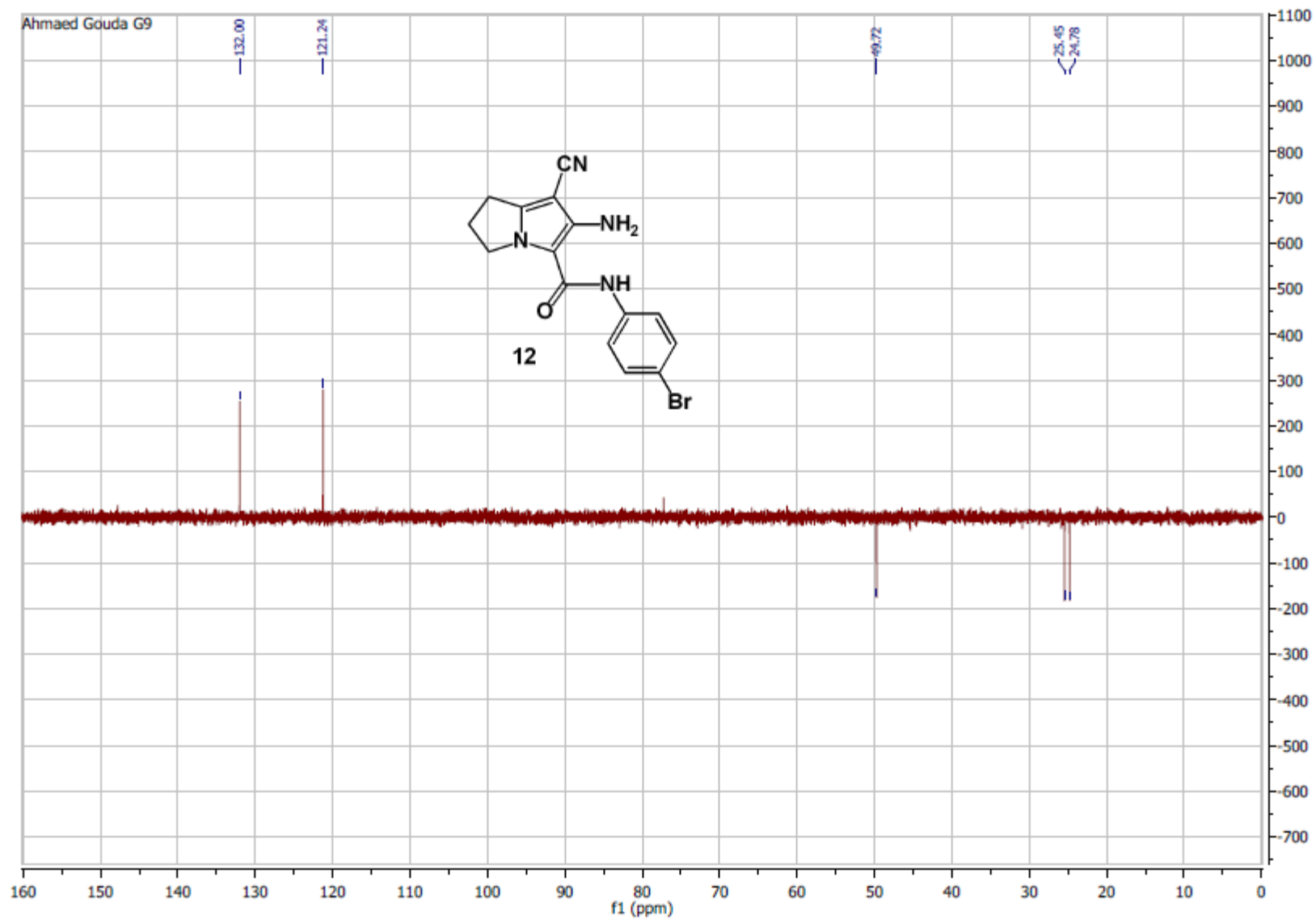


Figure S19: DEPT 135 of compound 12

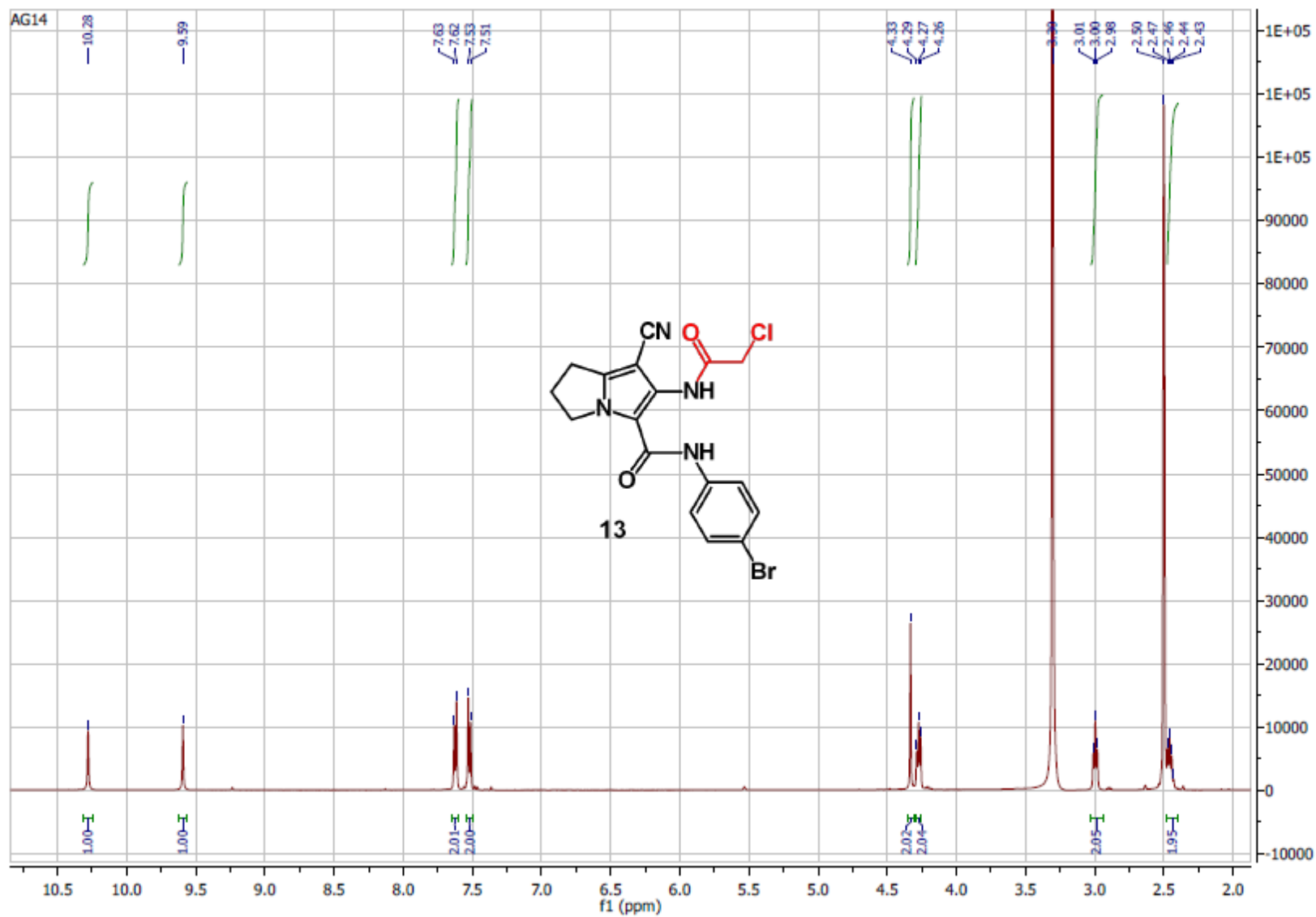


Figure S20a: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 13

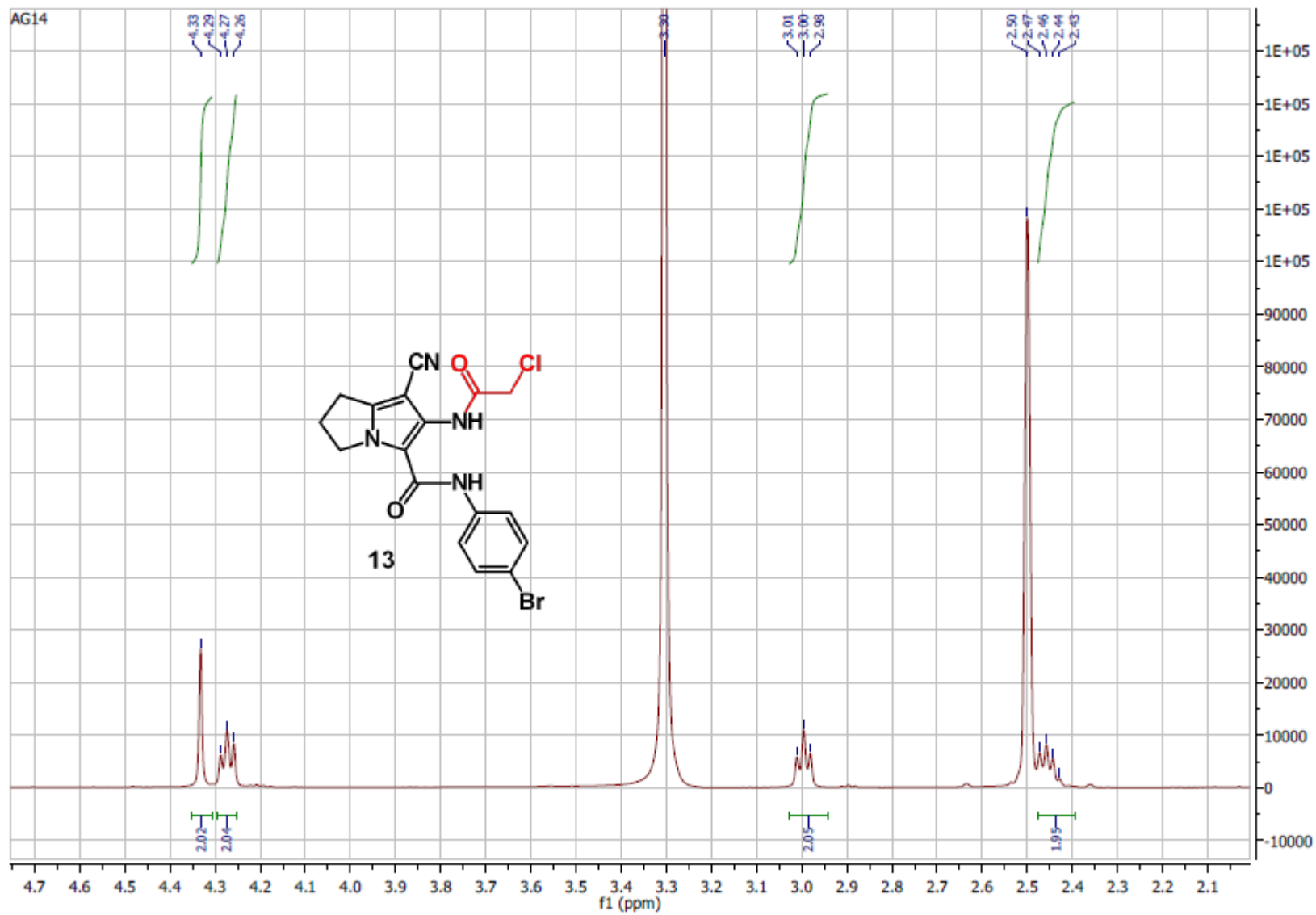


Figure S20b: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 13 (ZOOM on Aliphatic Protons)

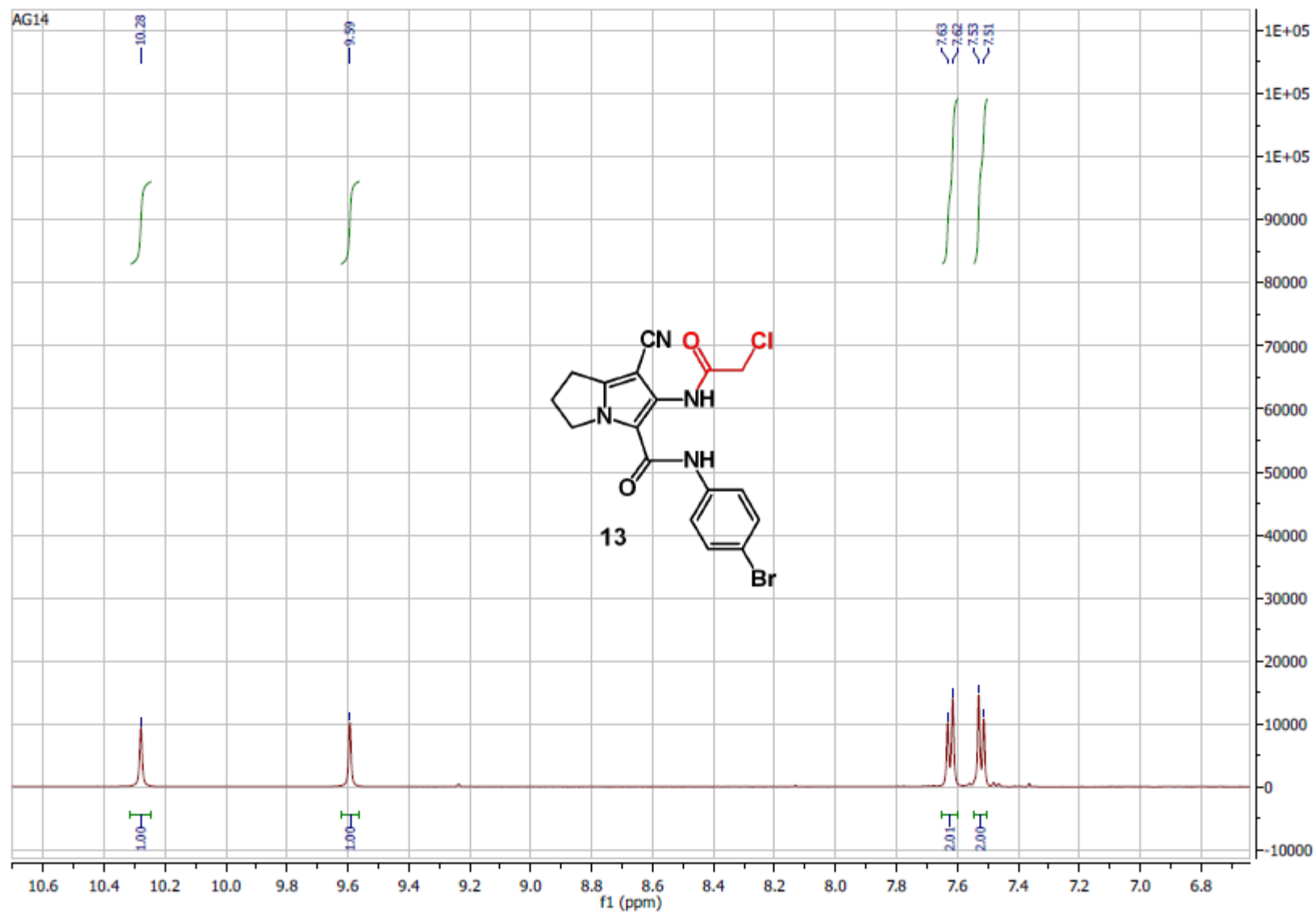


Figure S20c: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 13 (ZOOM on Aromatic Protons)

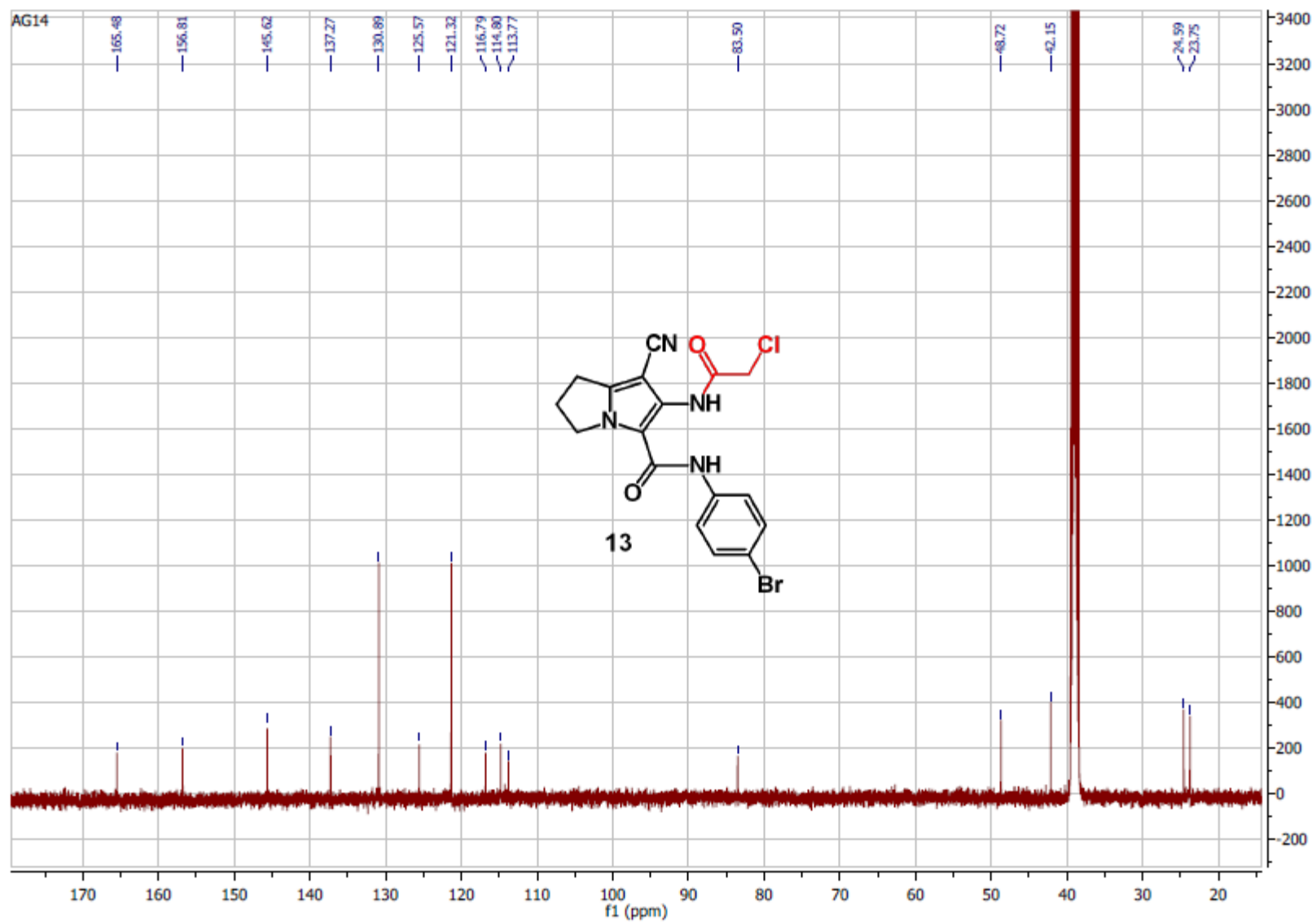


Figure S21a: ^{13}C -NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 13

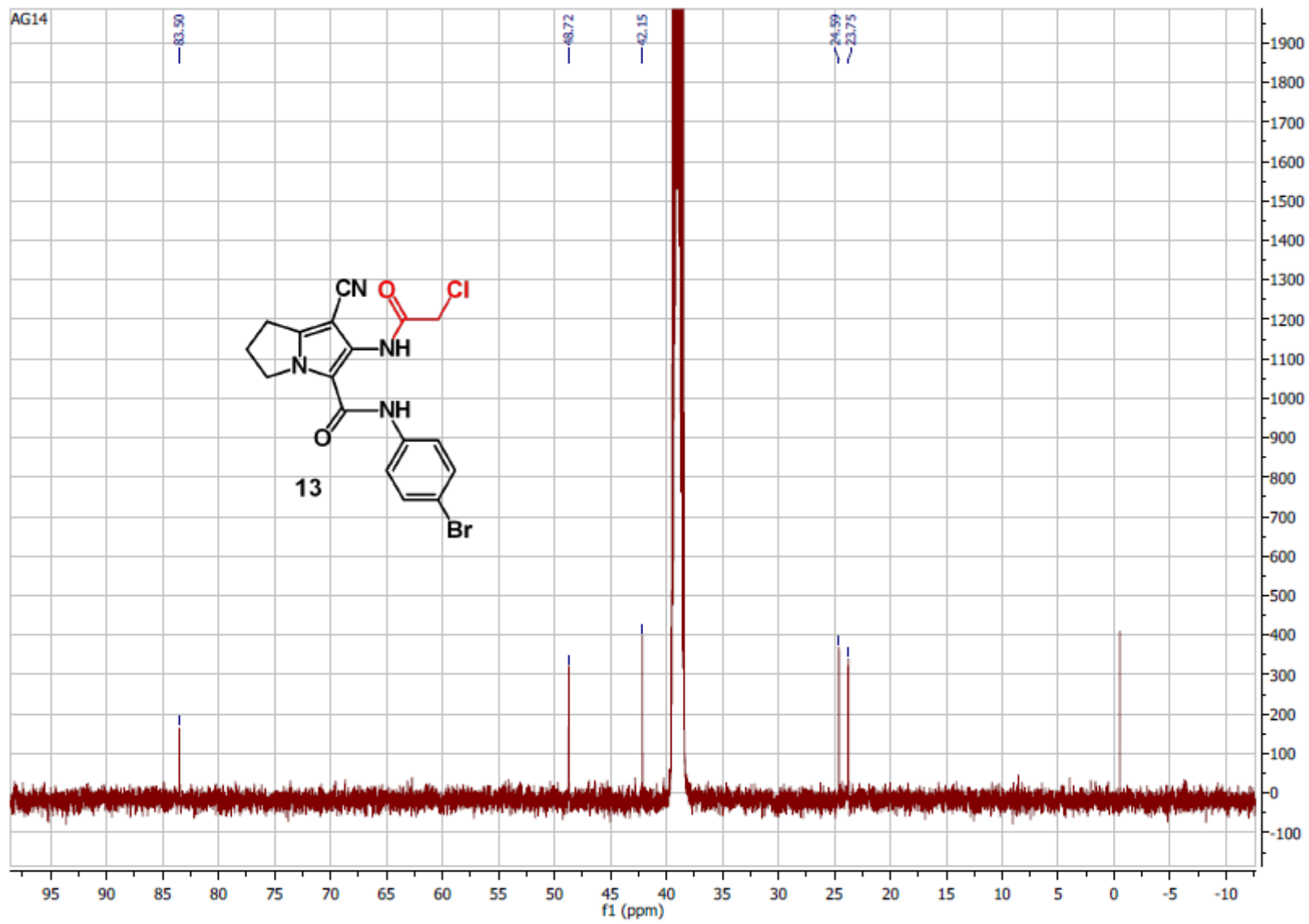


Figure S21b: ^{13}C -NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 13 (ZOOM on Aliphatic Carbons)

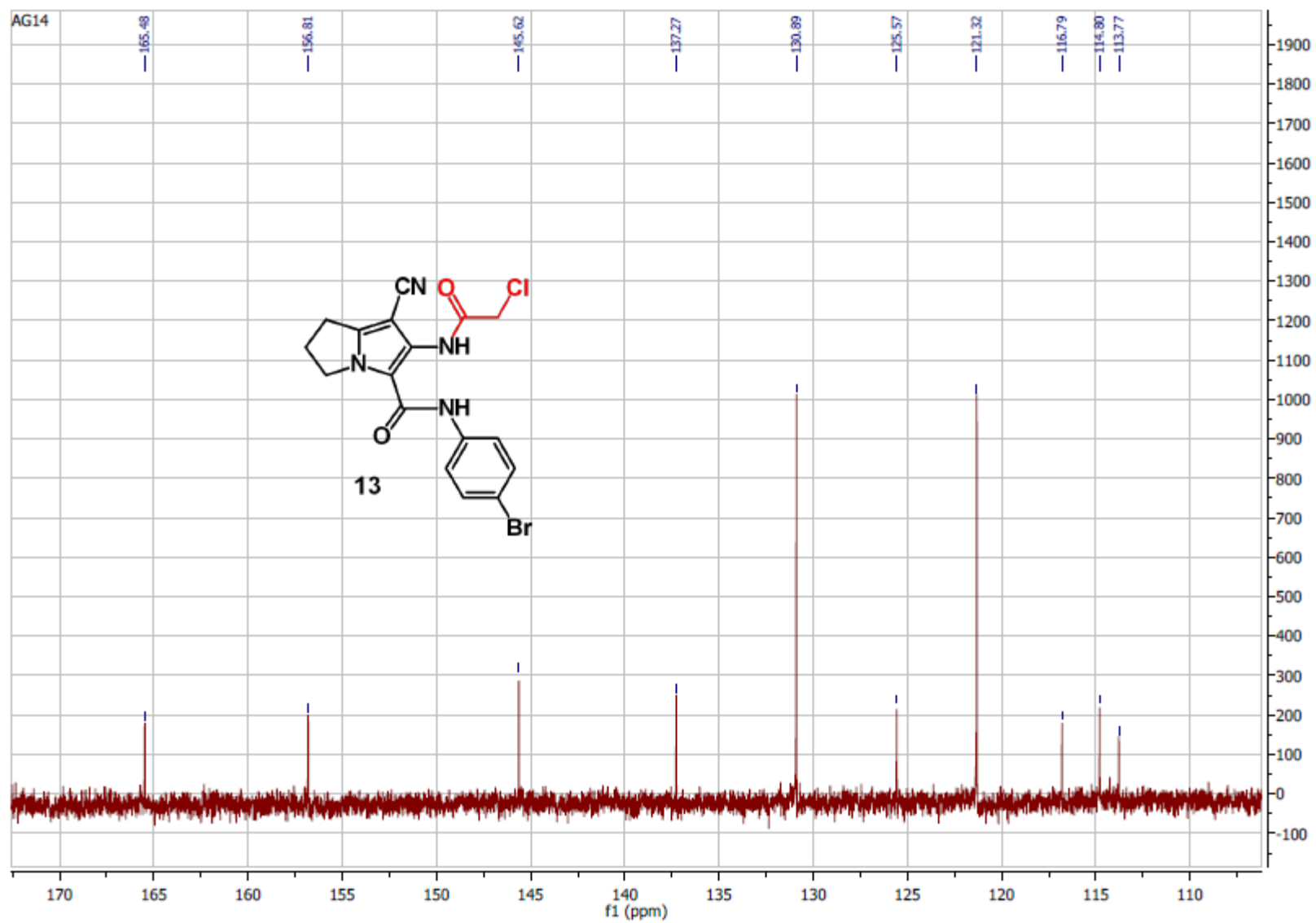


Figure S21c: ^{13}C -NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 13 (ZOOM on Aromatic Carbons)

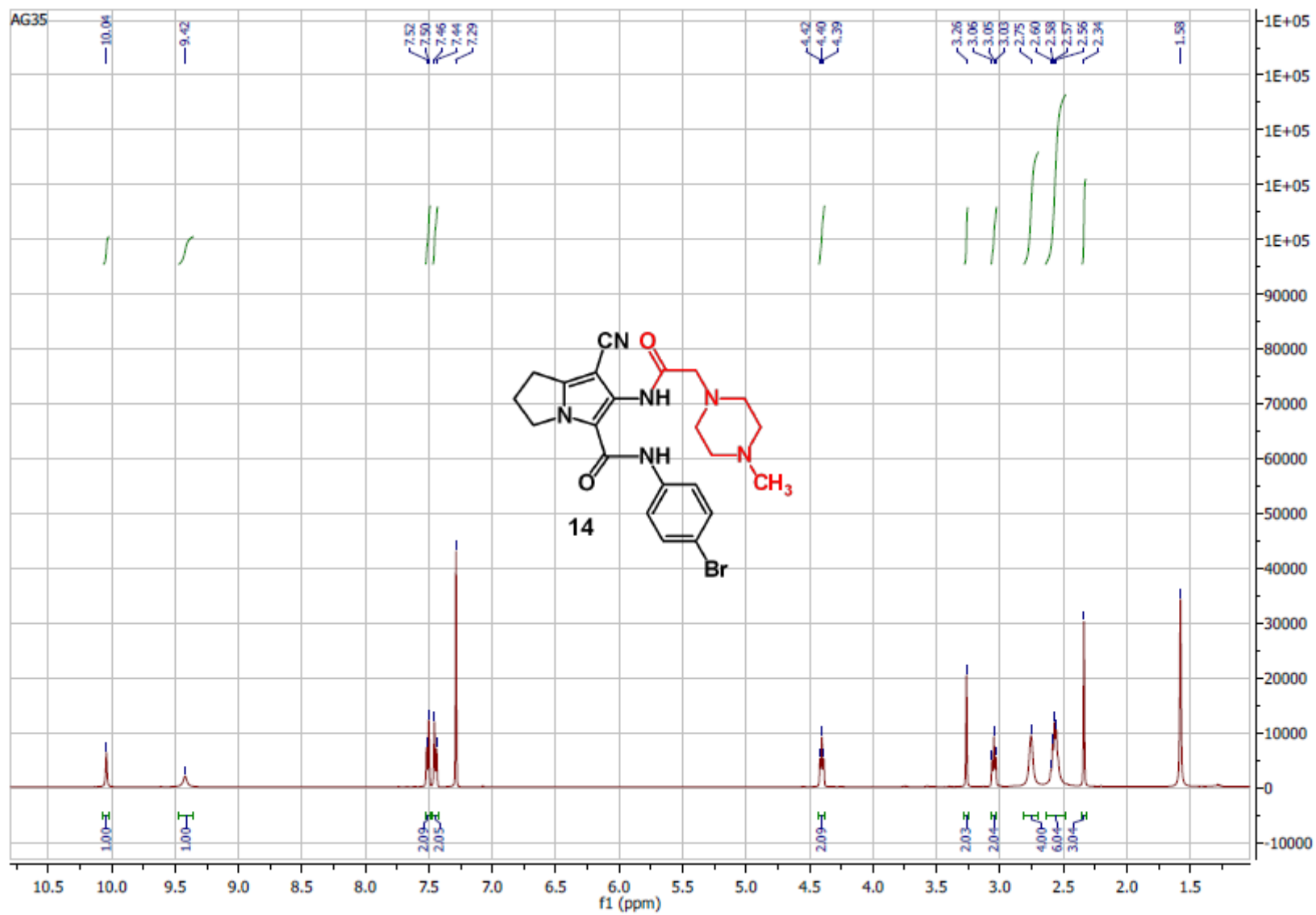


Figure S22a: ¹H-NMR (CDCl₃, 500 MHz, δ ppm) spectrum of compound 14

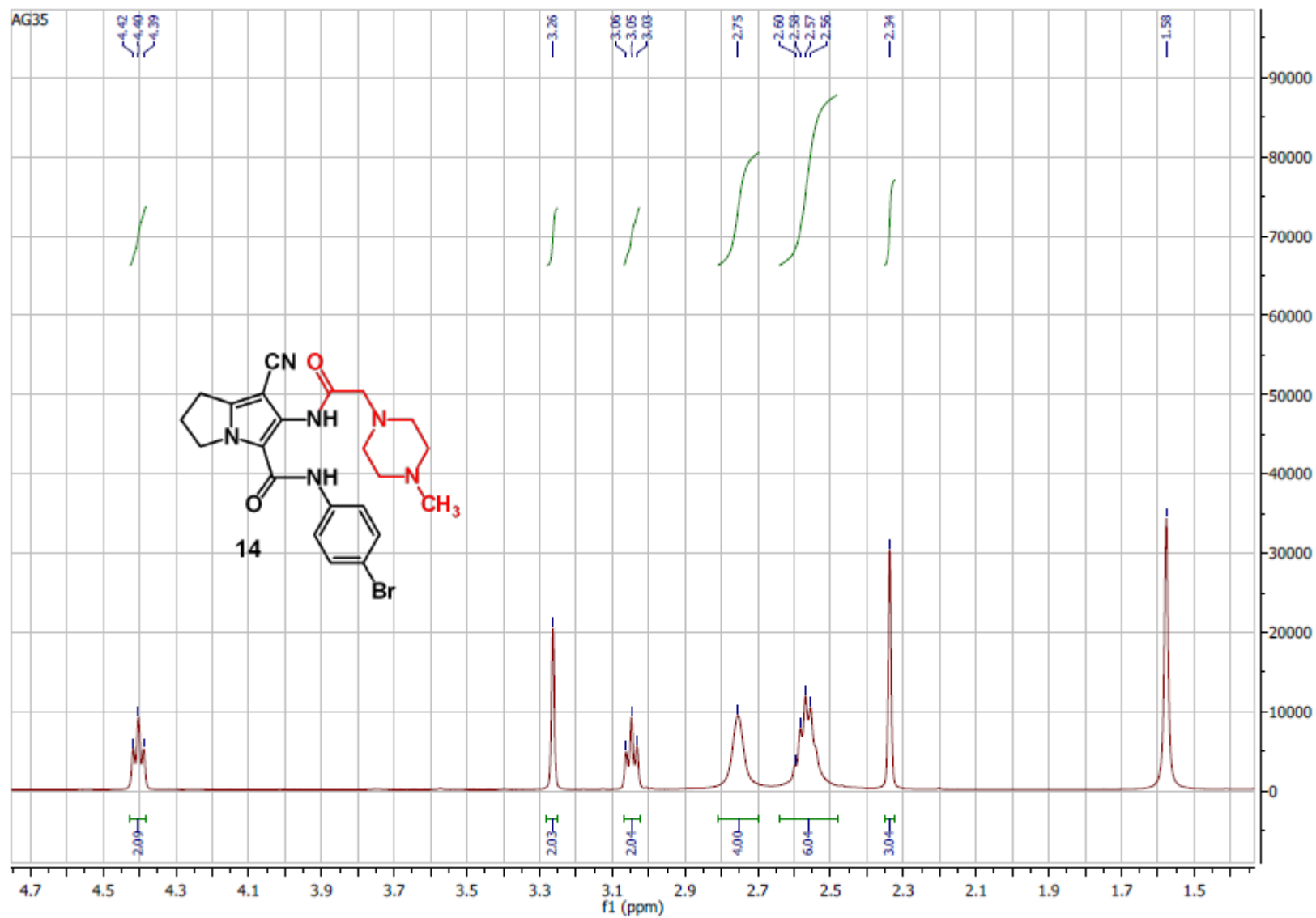


Figure S22b: ¹H-NMR (CDCl₃, 500 MHz, δ ppm) spectrum of compound 14 (ZOOM on Aliphatic Protons)

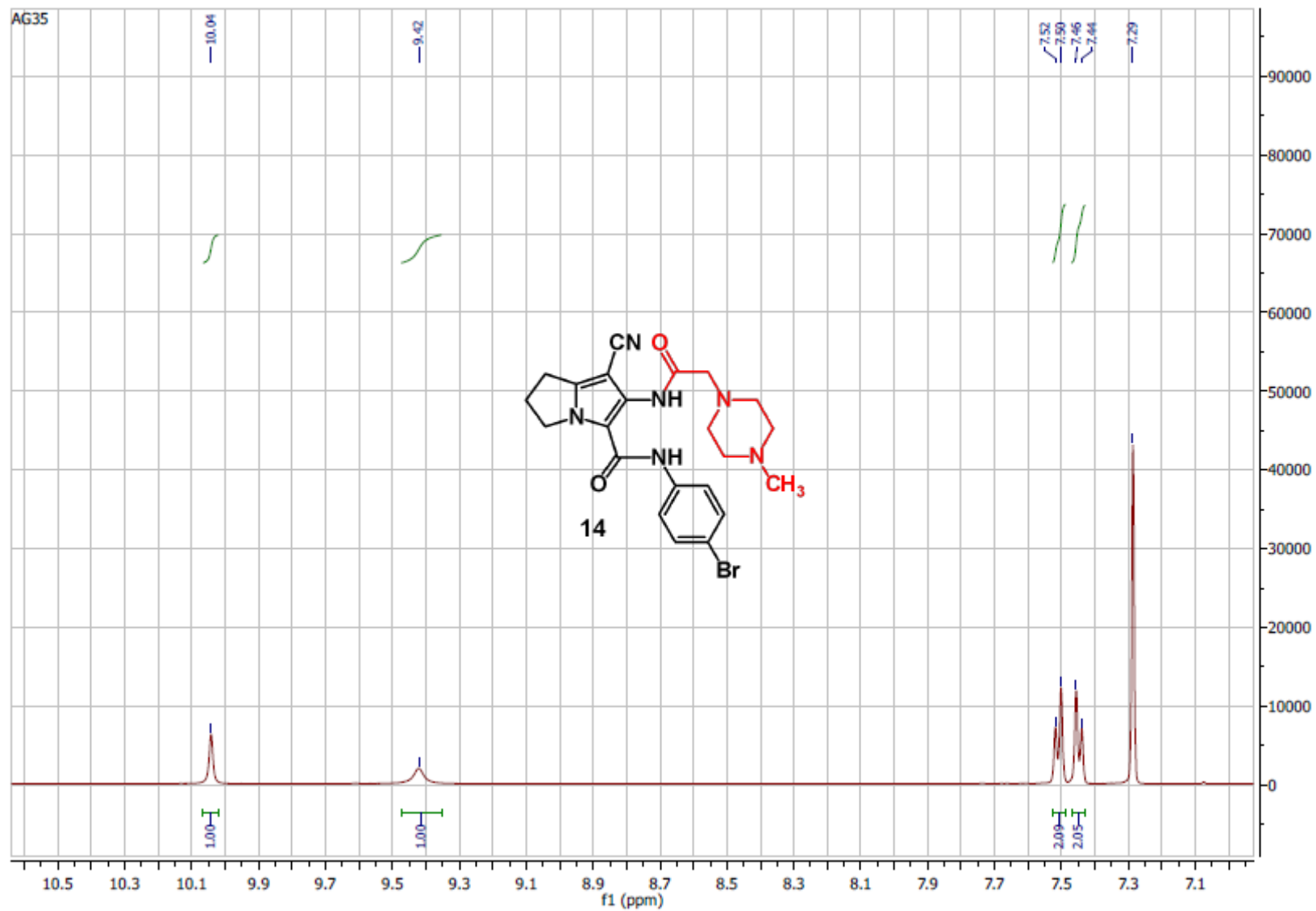


Figure S22c: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 14 (ZOOM on Aromatic Protons)

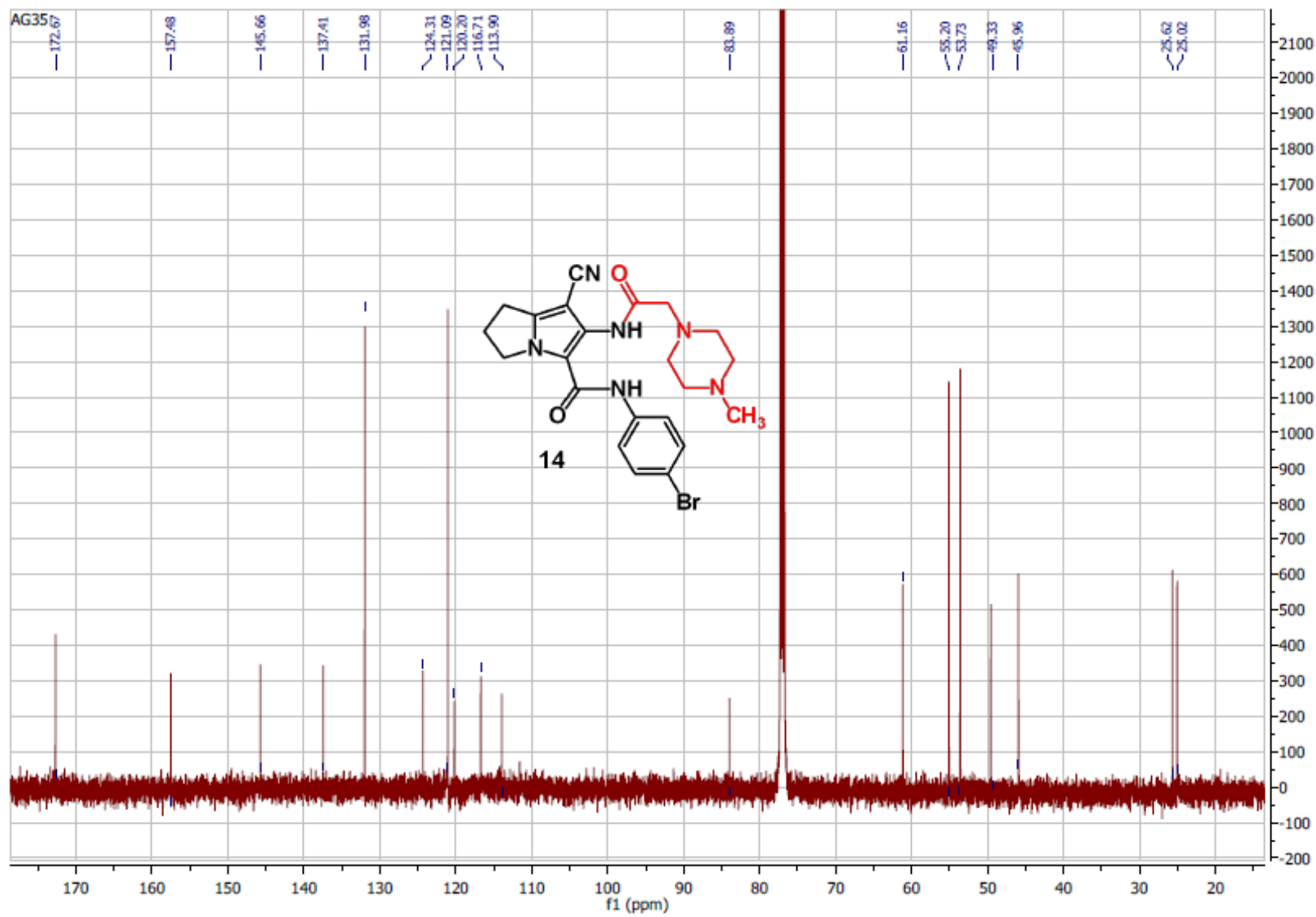


Figure S23a: ^{13}C -NMR (CDCl_3 , 125 MHz, δ ppm) spectrum of compound 14

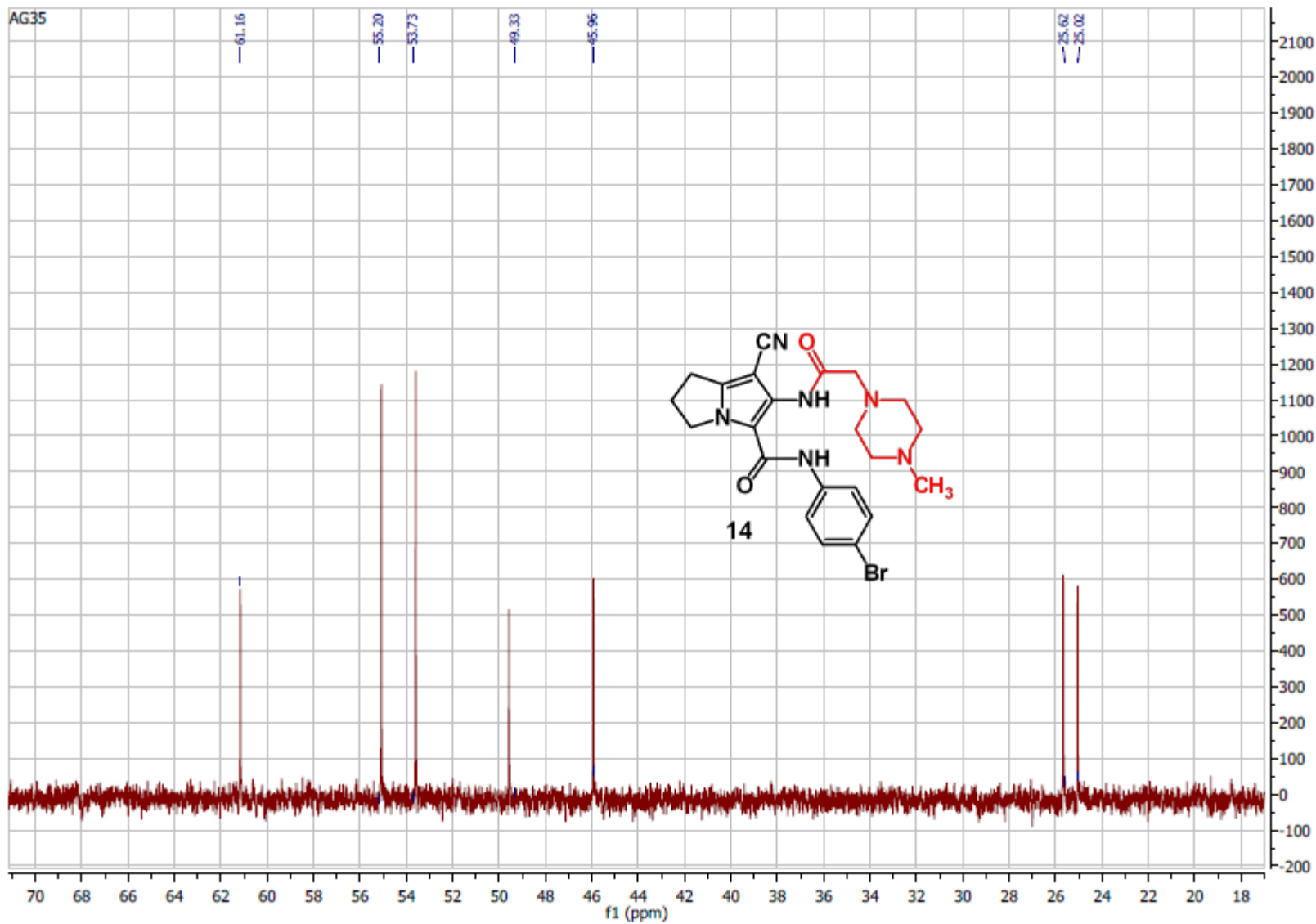


Figure S23b: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 14 (ZOOM on Aliphatic Carbons)

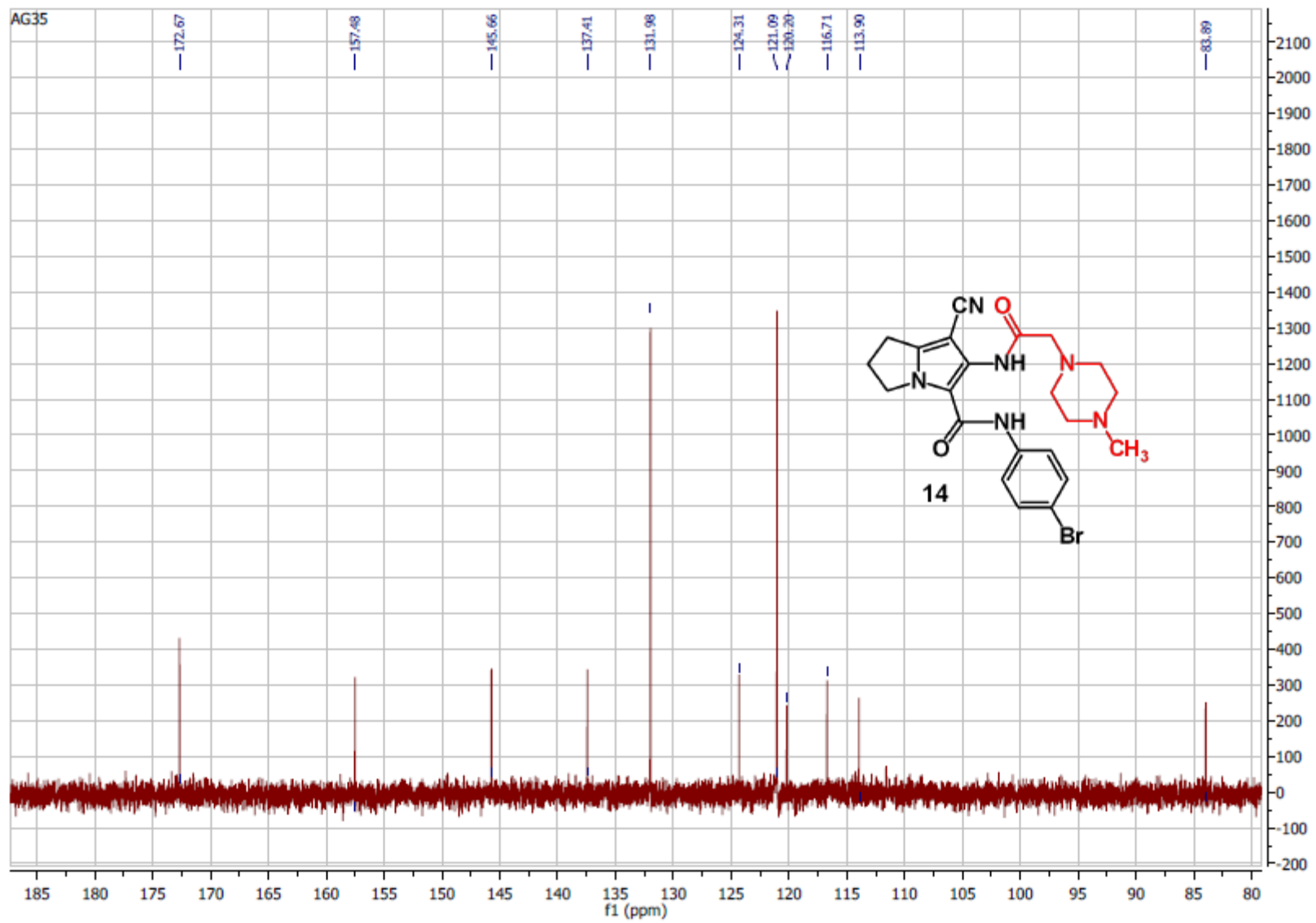


Figure S23c: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 14 (ZOOM on Aromatic Carbons)

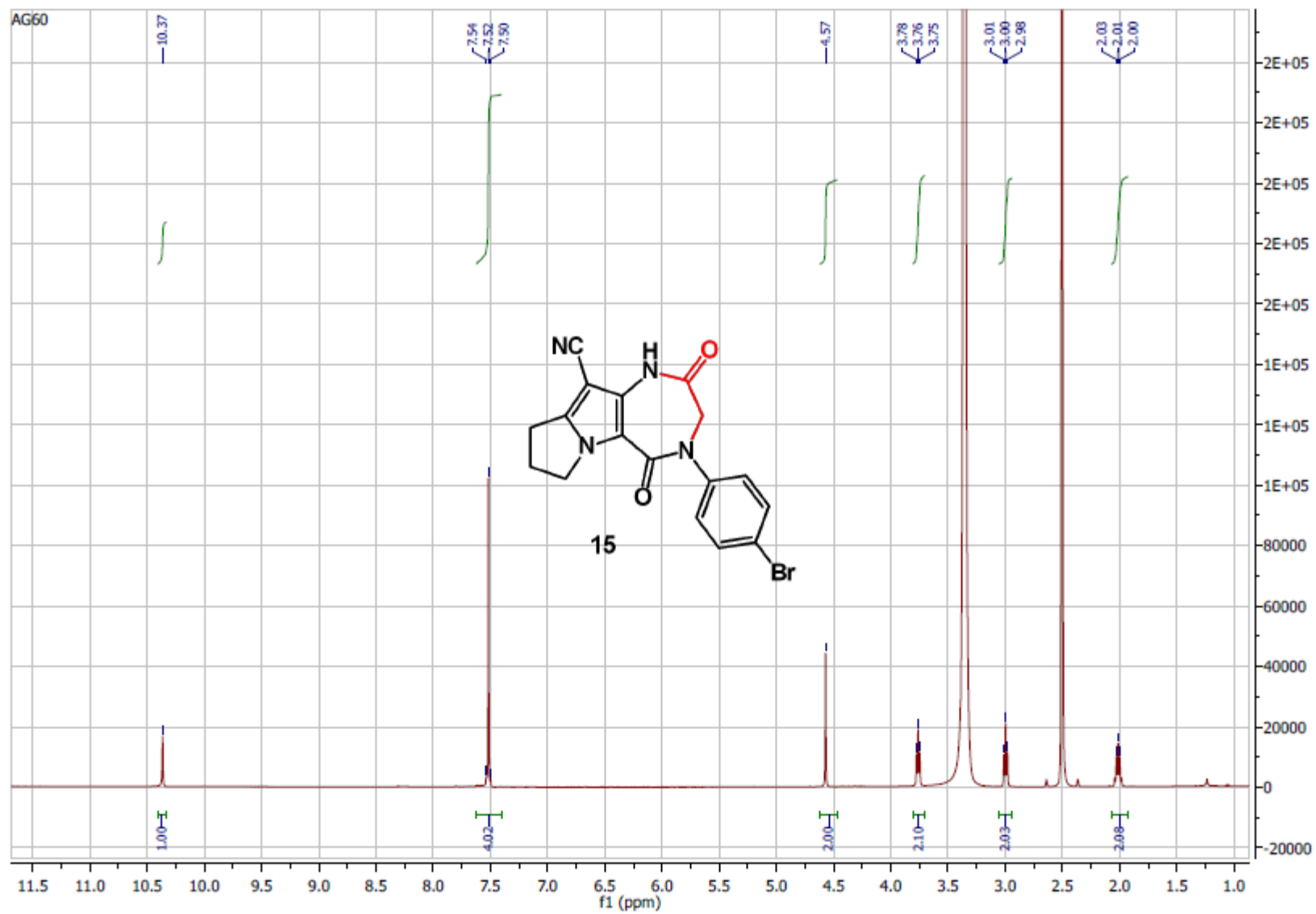


Figure S24a: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 15

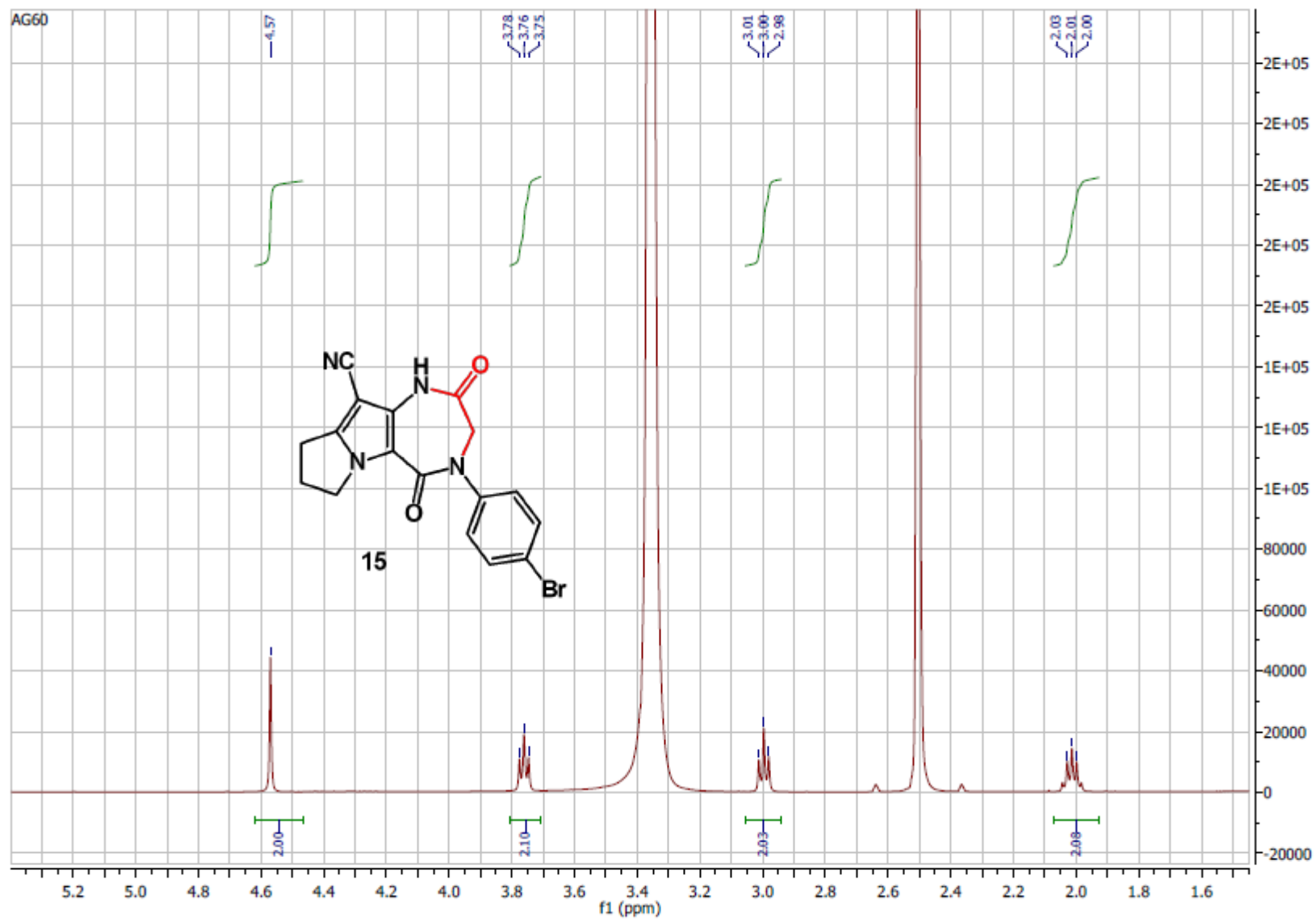


Figure S24b: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 15 (ZOOM on Aliphatic Protons)

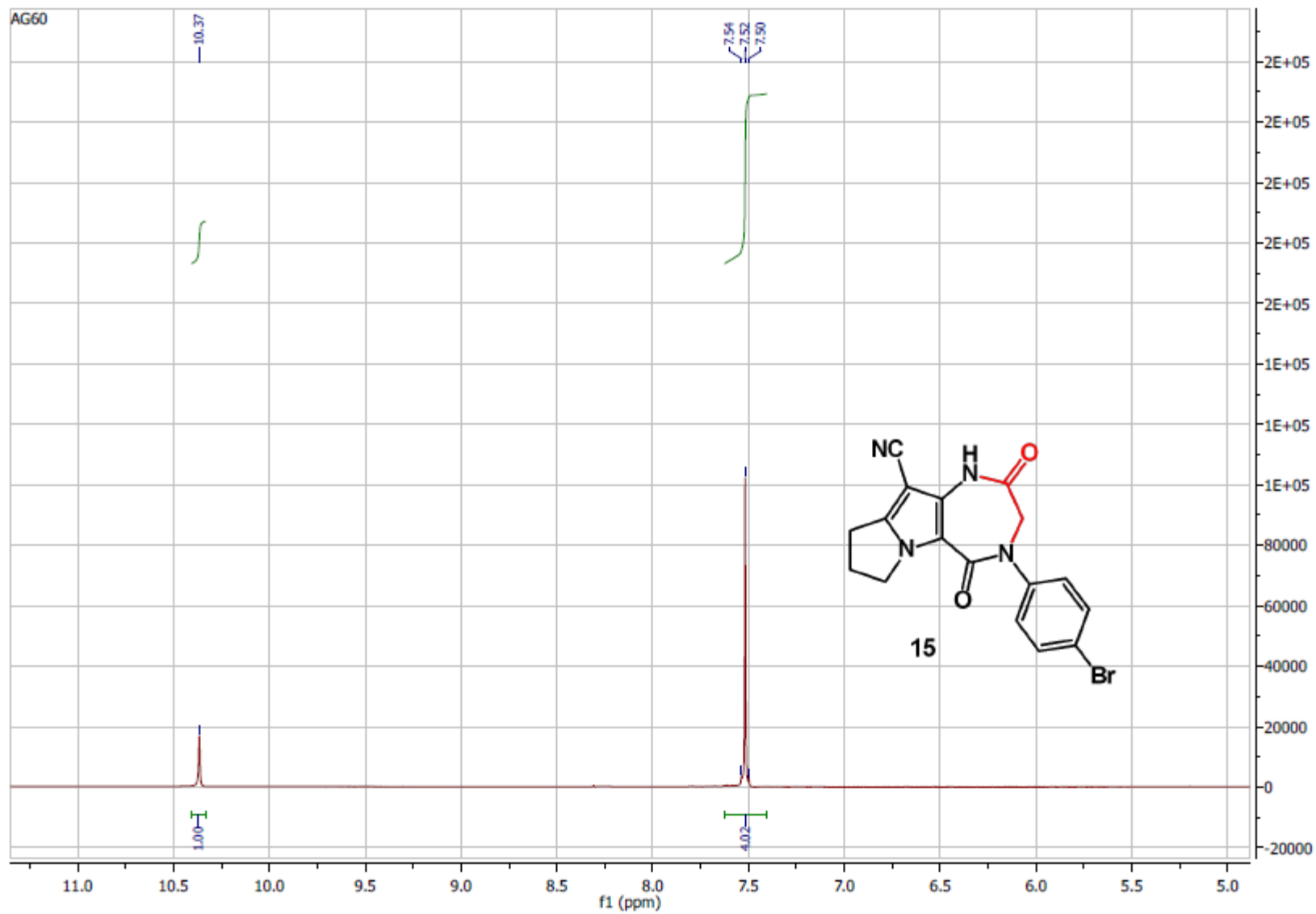


Figure S24c: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 15 (ZOOM on Aromatic Protons)

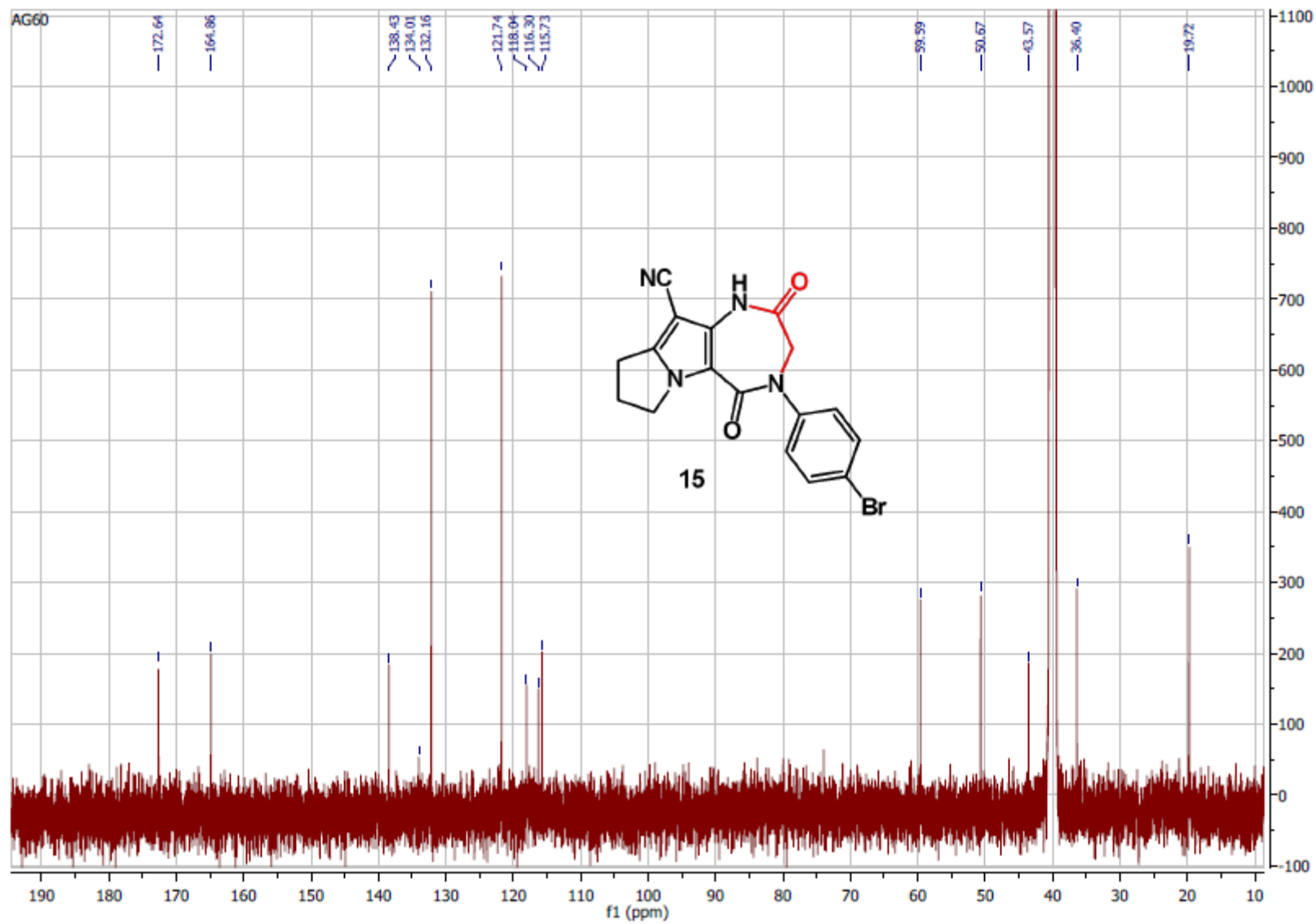


Figure S25a: ^{13}C -NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 15

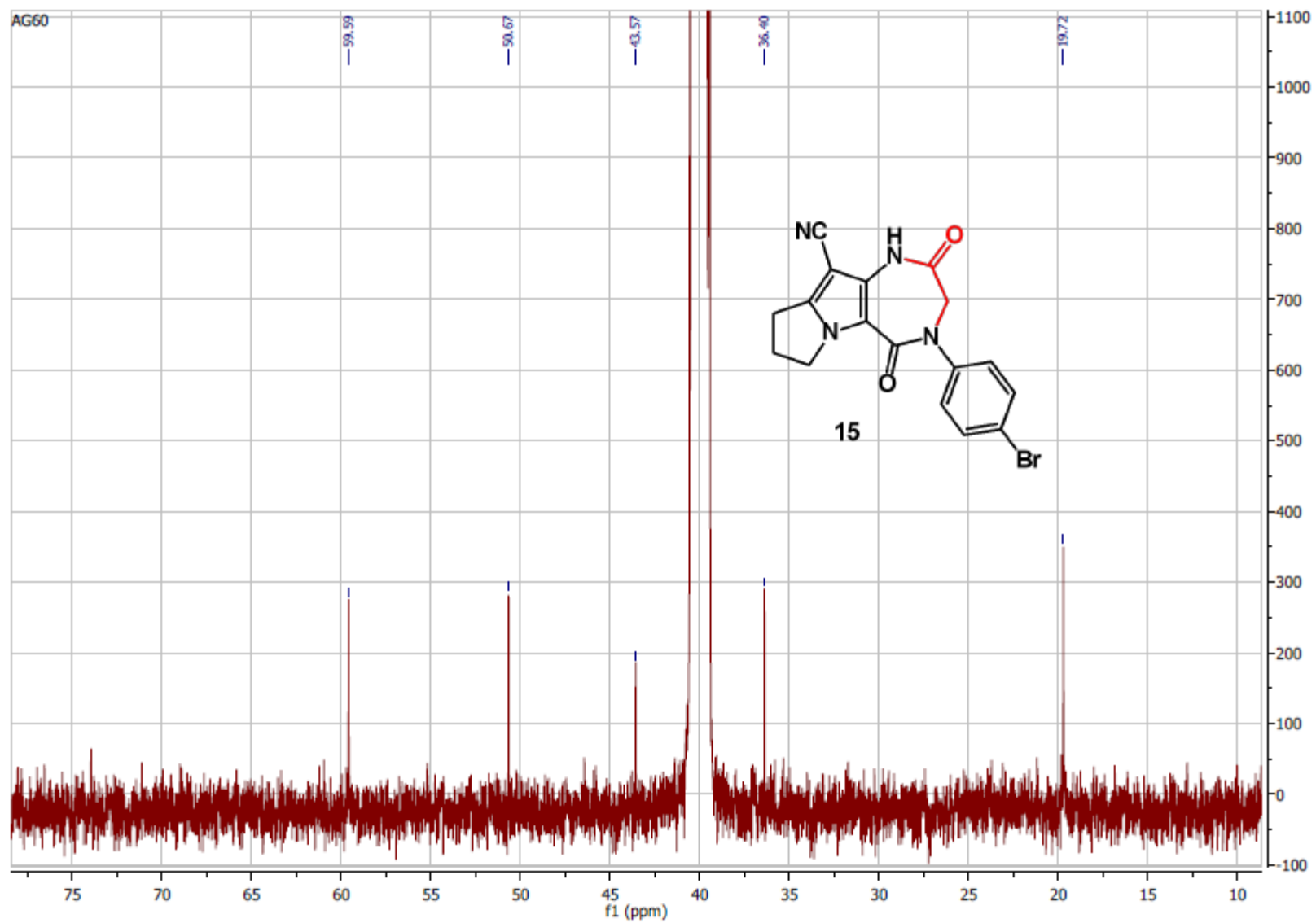


Figure S25b: ^{13}C -NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 15 (ZOOM on Aliphatic Carbons)

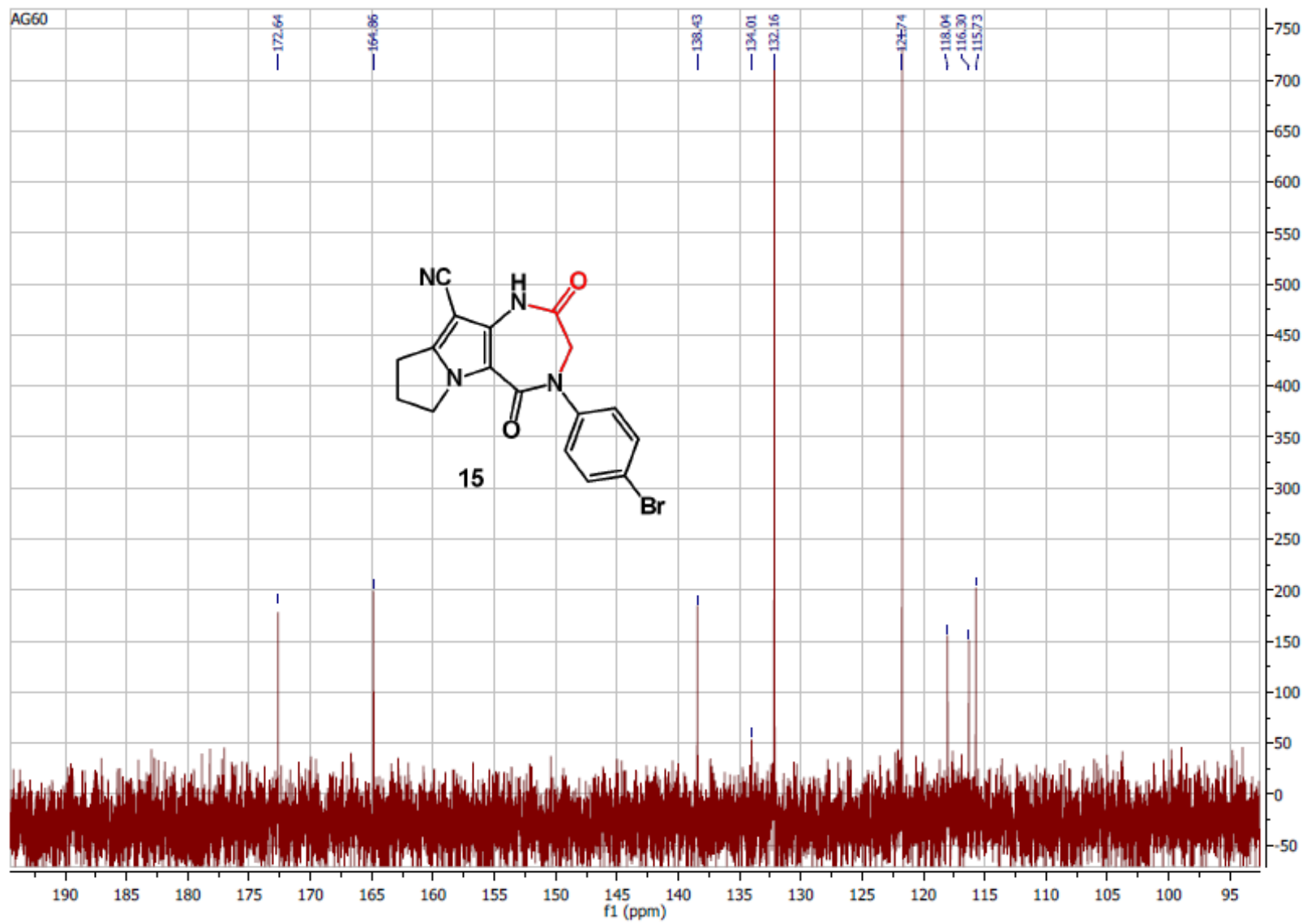


Figure S25c: ^{13}C -NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 15 (ZOOM on Aromatic Carbons)

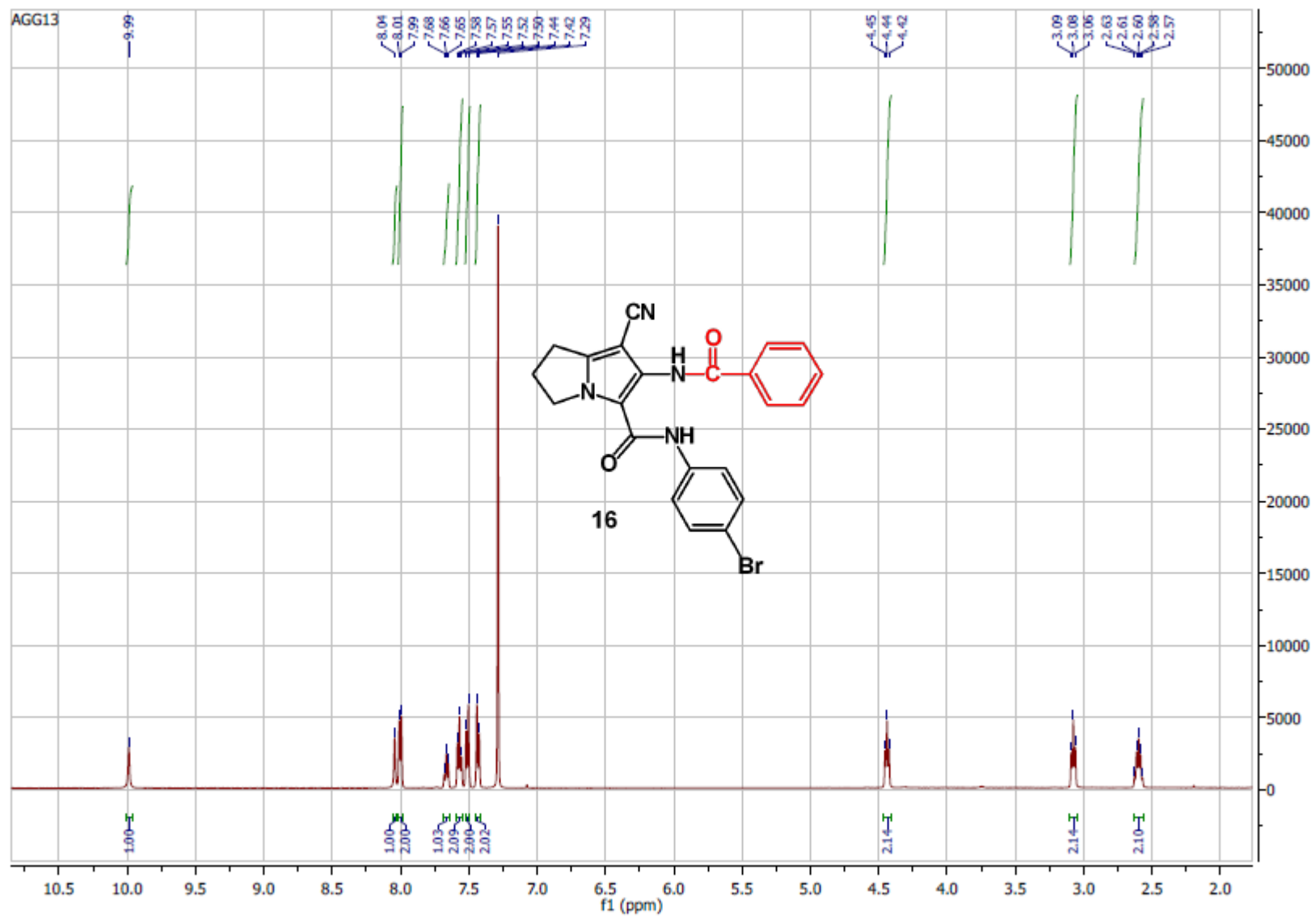


Figure S26a: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 16

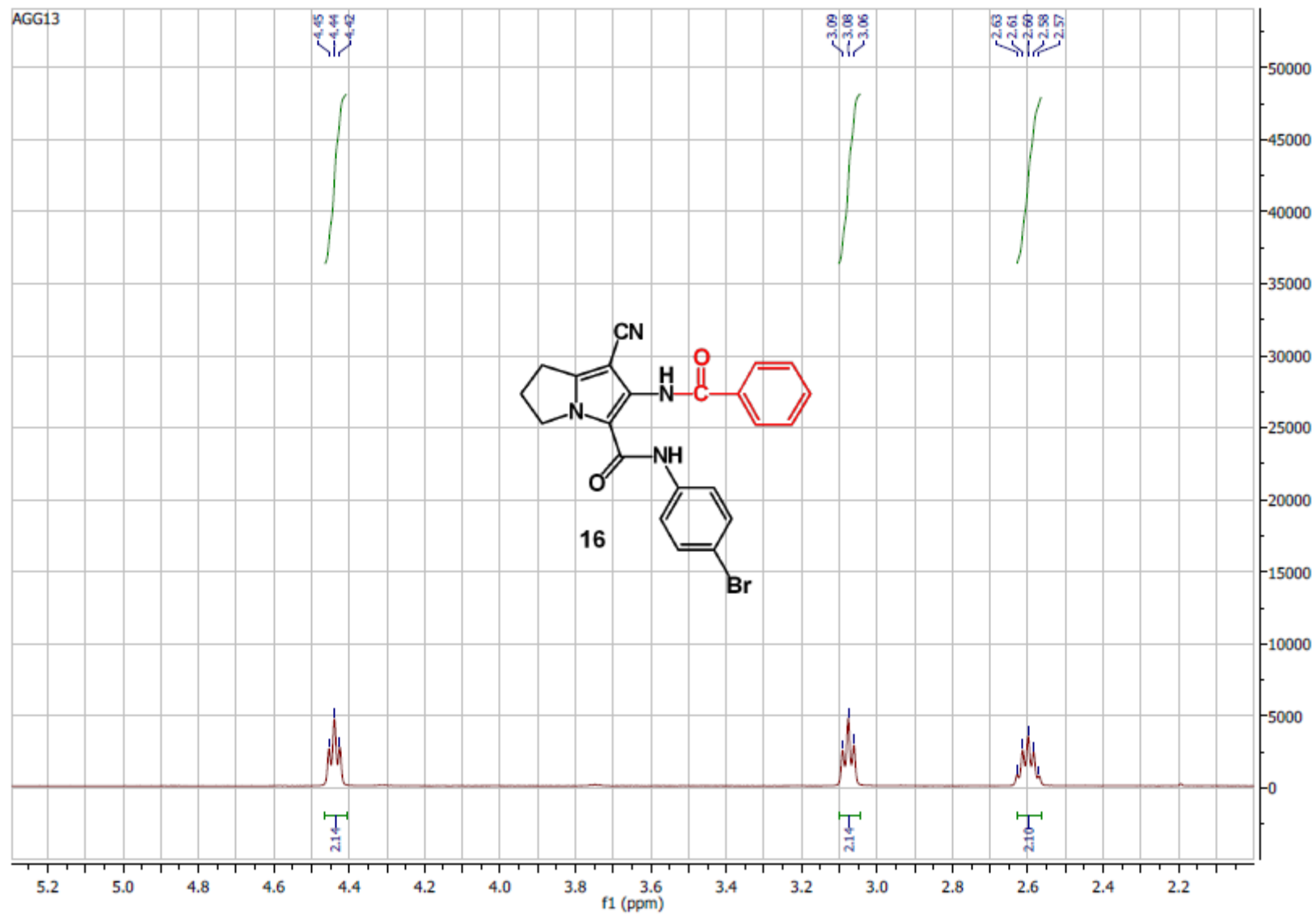


Figure S26b: ¹H-NMR (CDCl₃, 500 MHz, δ ppm) spectrum of compound 16 (ZOOM on Aliphatic Protons)

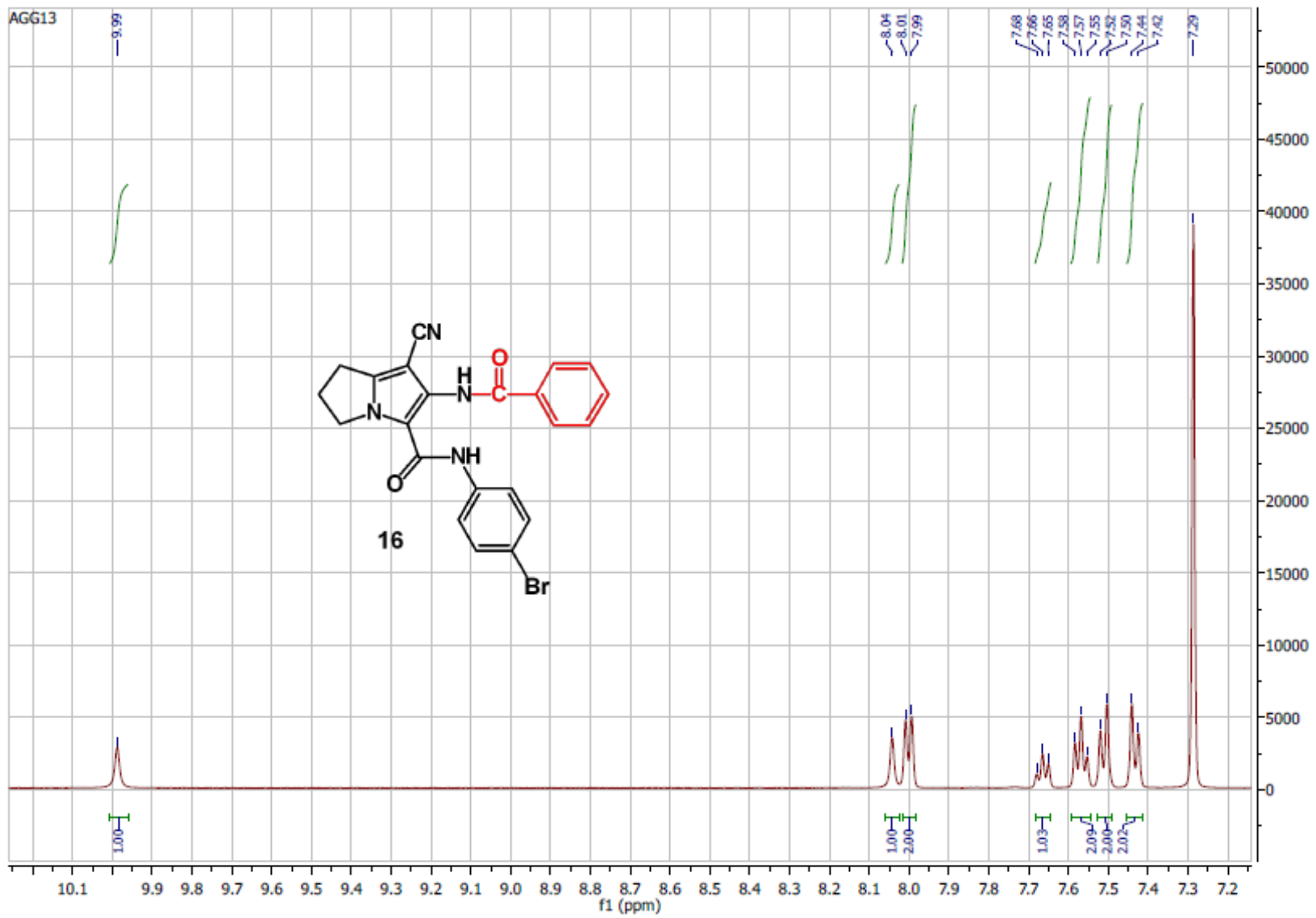


Figure S26c: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 16 (ZOOM on Aromatic Protons)

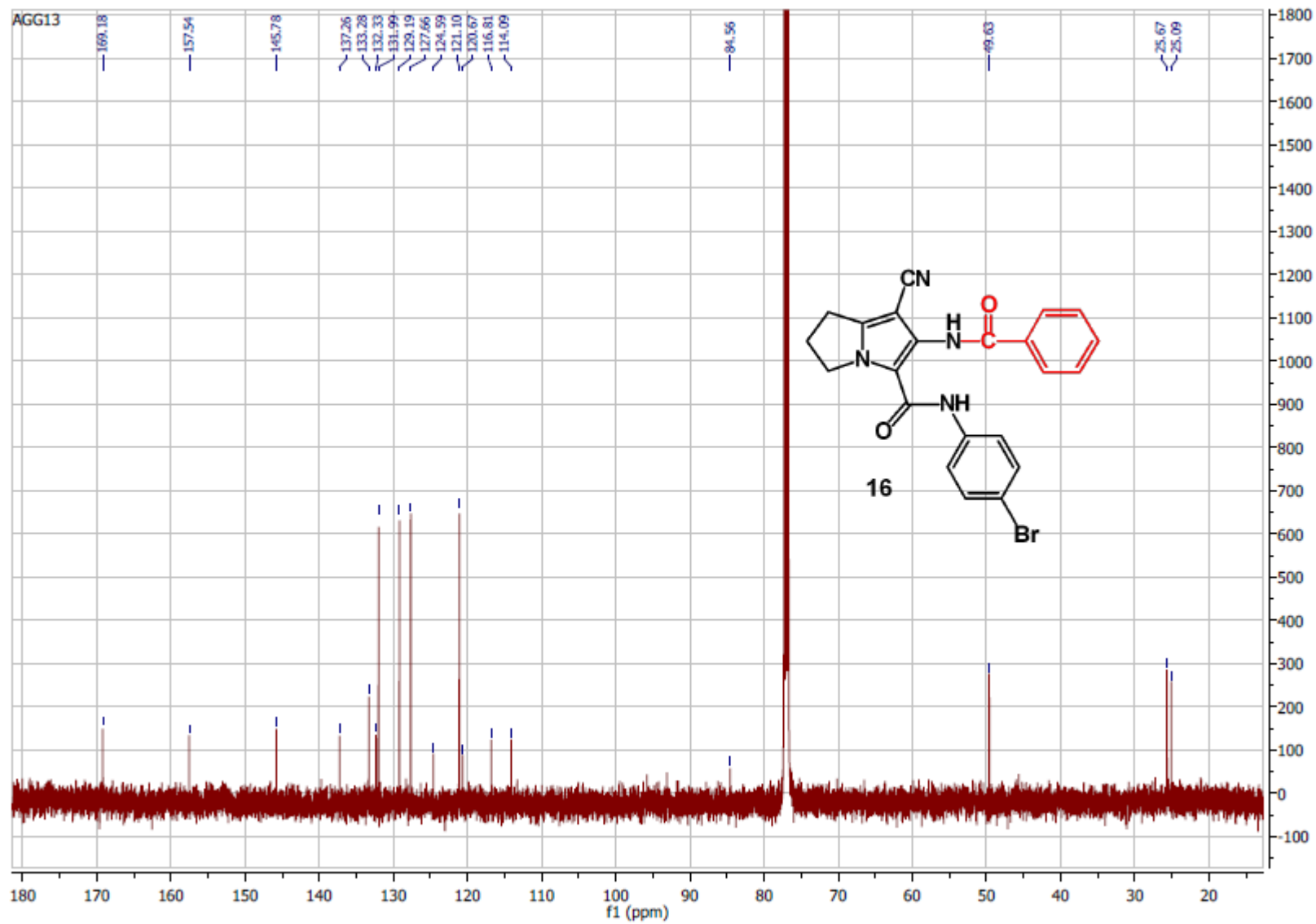


Figure S27a: ^{13}C -NMR (CDCl_3 , 125 MHz, δ ppm) spectrum of compound 16

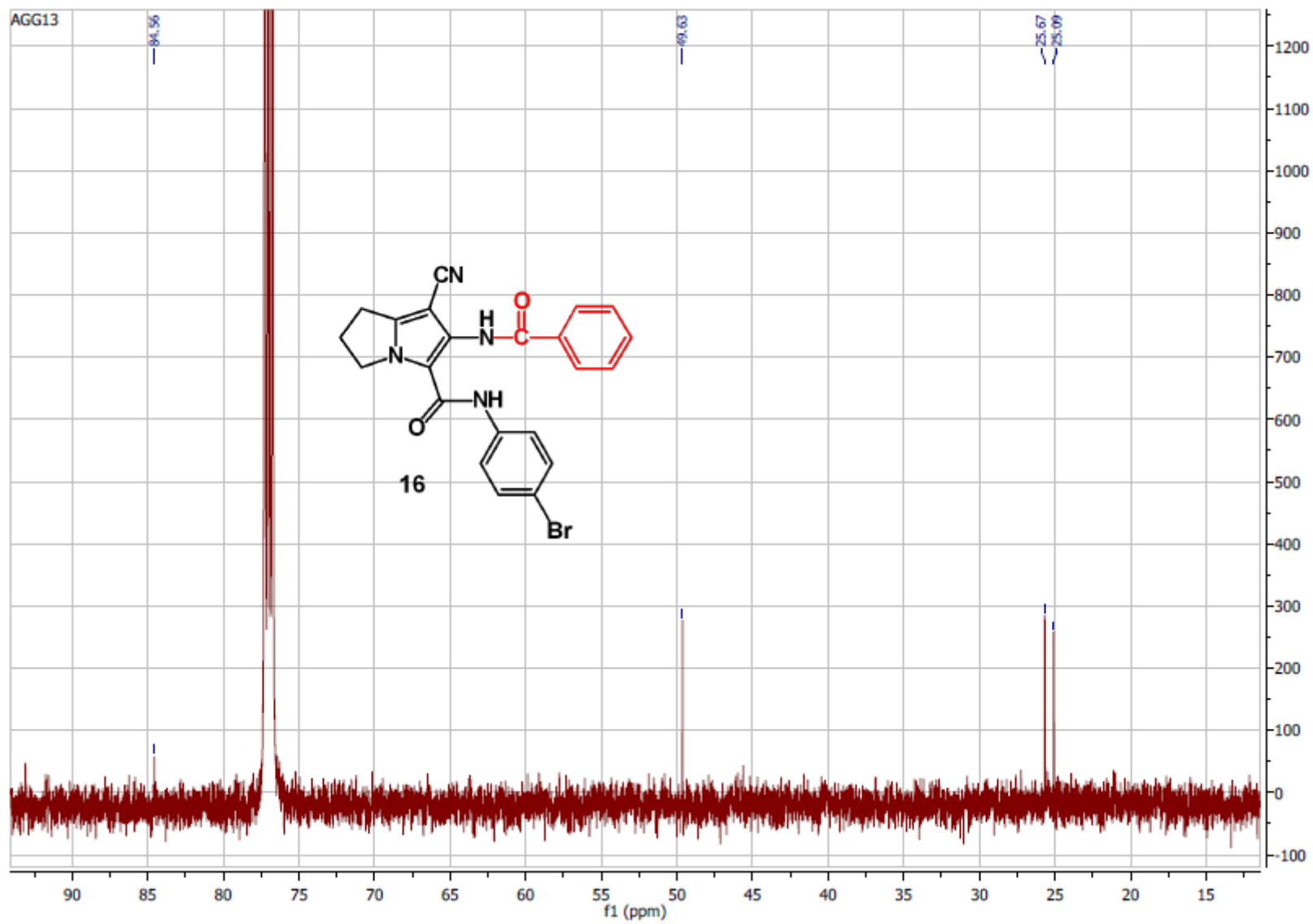


Figure S27b: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 16 (ZOOM on Aliphatic Carbons)

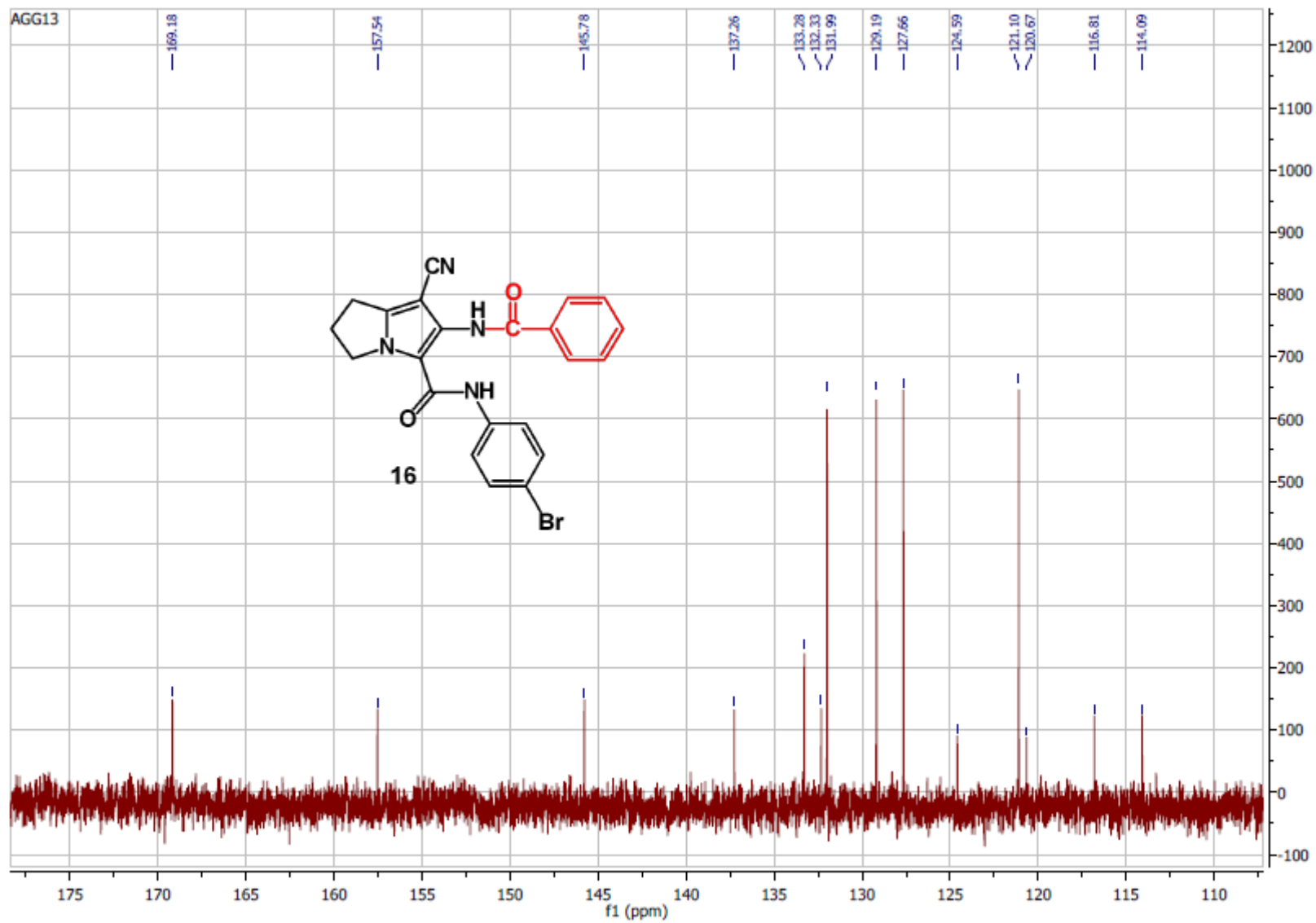


Figure S27c: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm): spectrum of compound 16 (ZOOM on Aromatic Carbons)

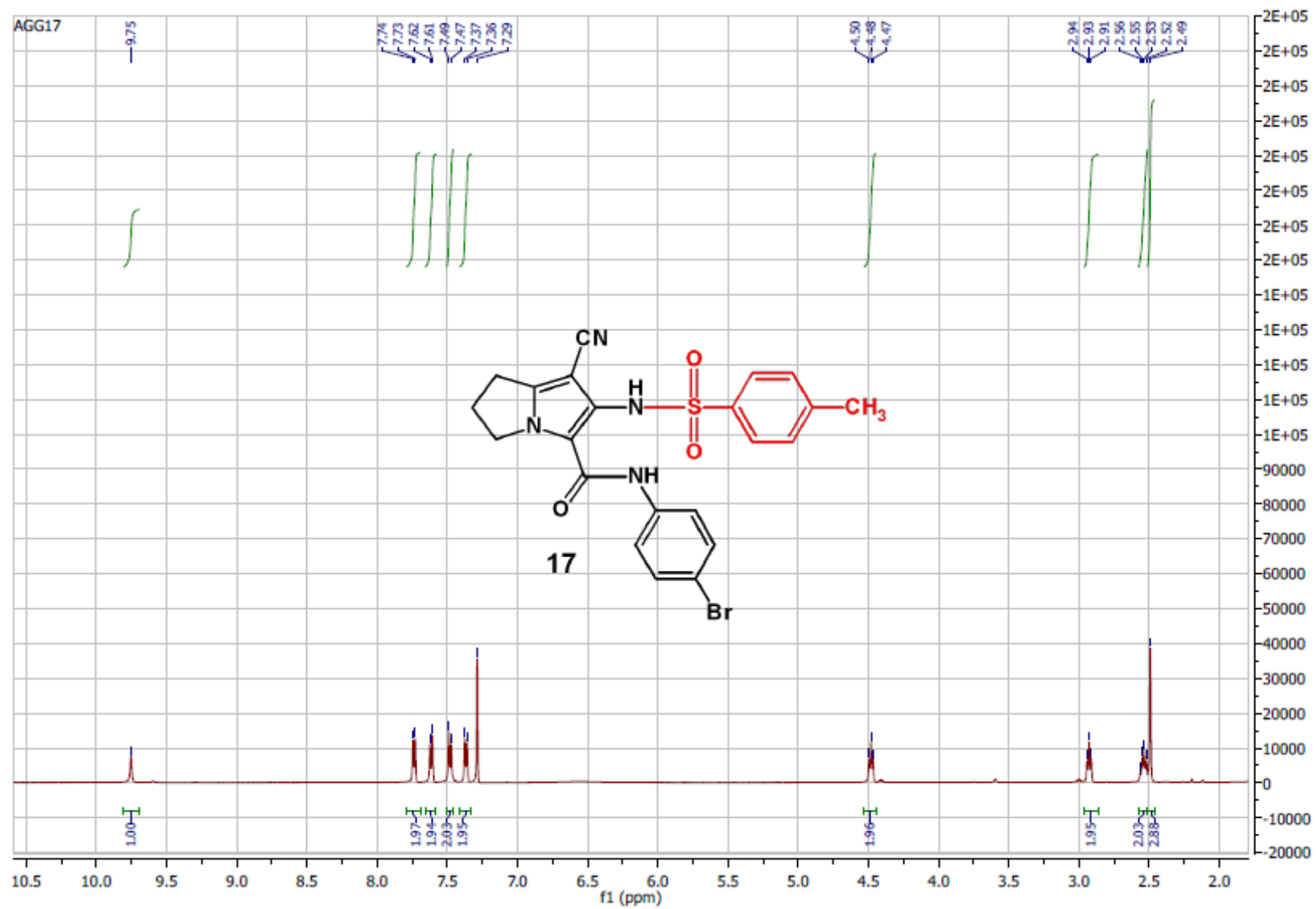


Figure S28a: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 17

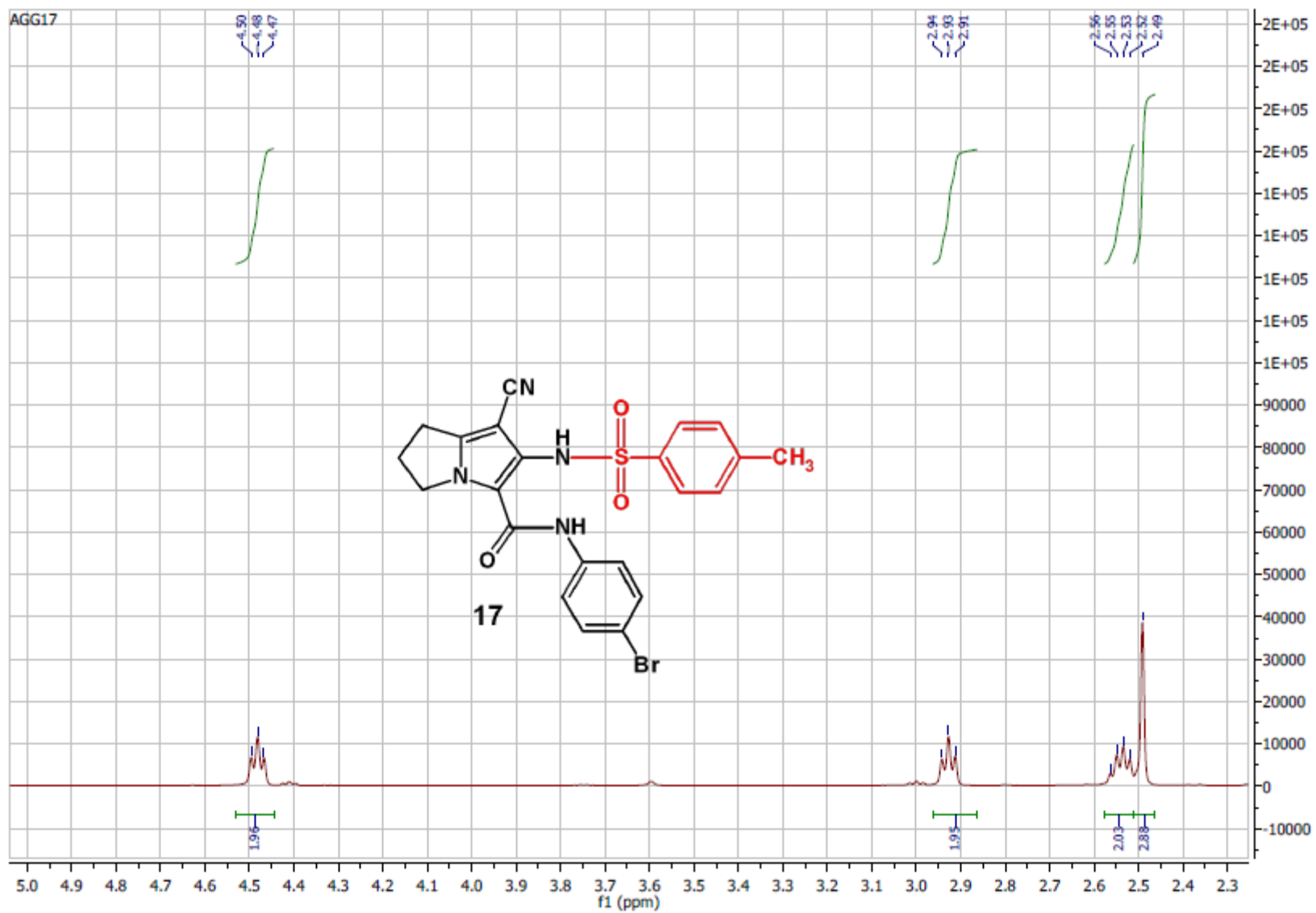


Figure S28b: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 17 (ZOON on Aliphatic Protons)

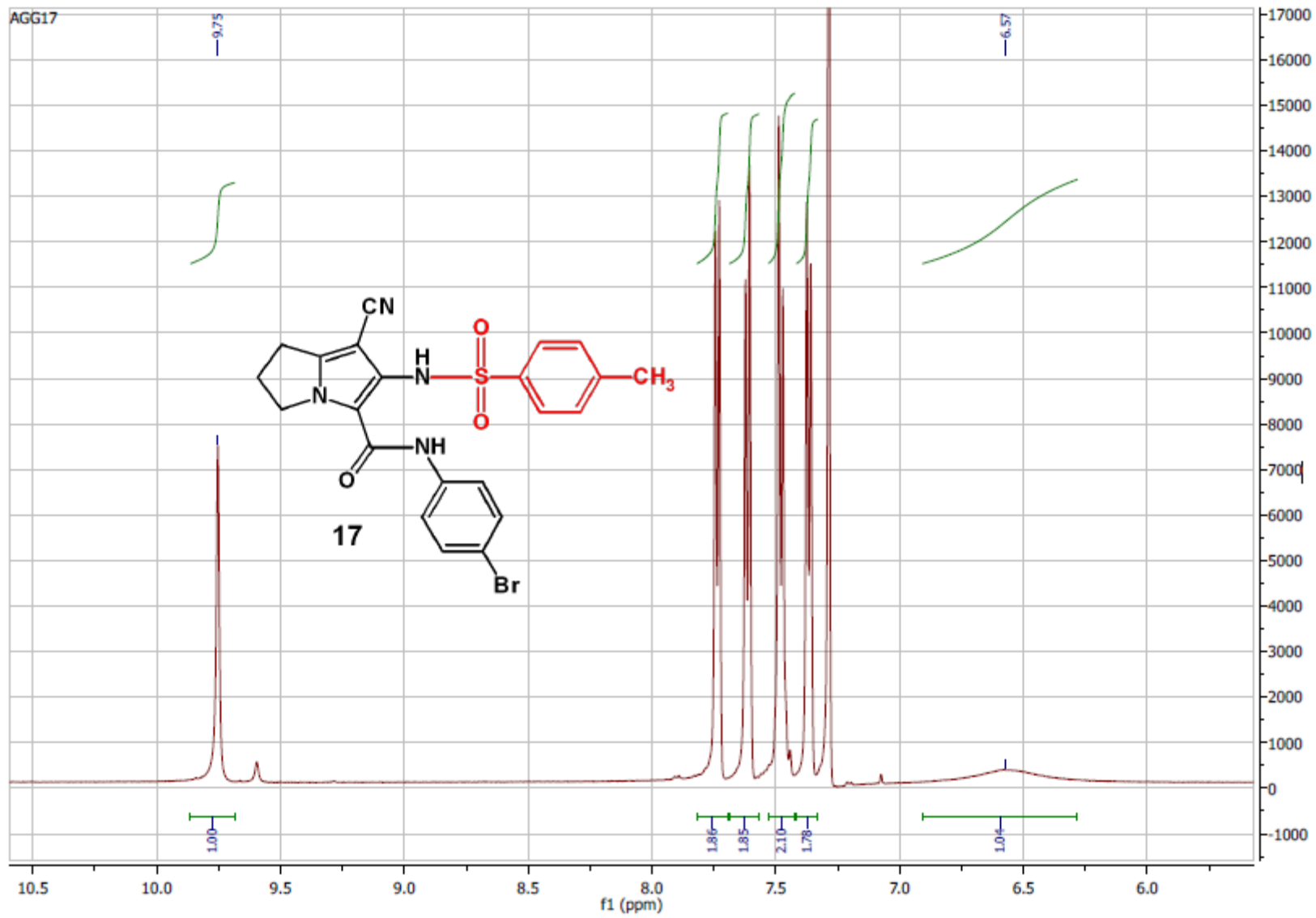


Figure S28c: ¹H-NMR (CDCl₃, 500 MHz, δ ppm) spectrum of compound 17 (ZOON on NHs + Aromatic Protons)

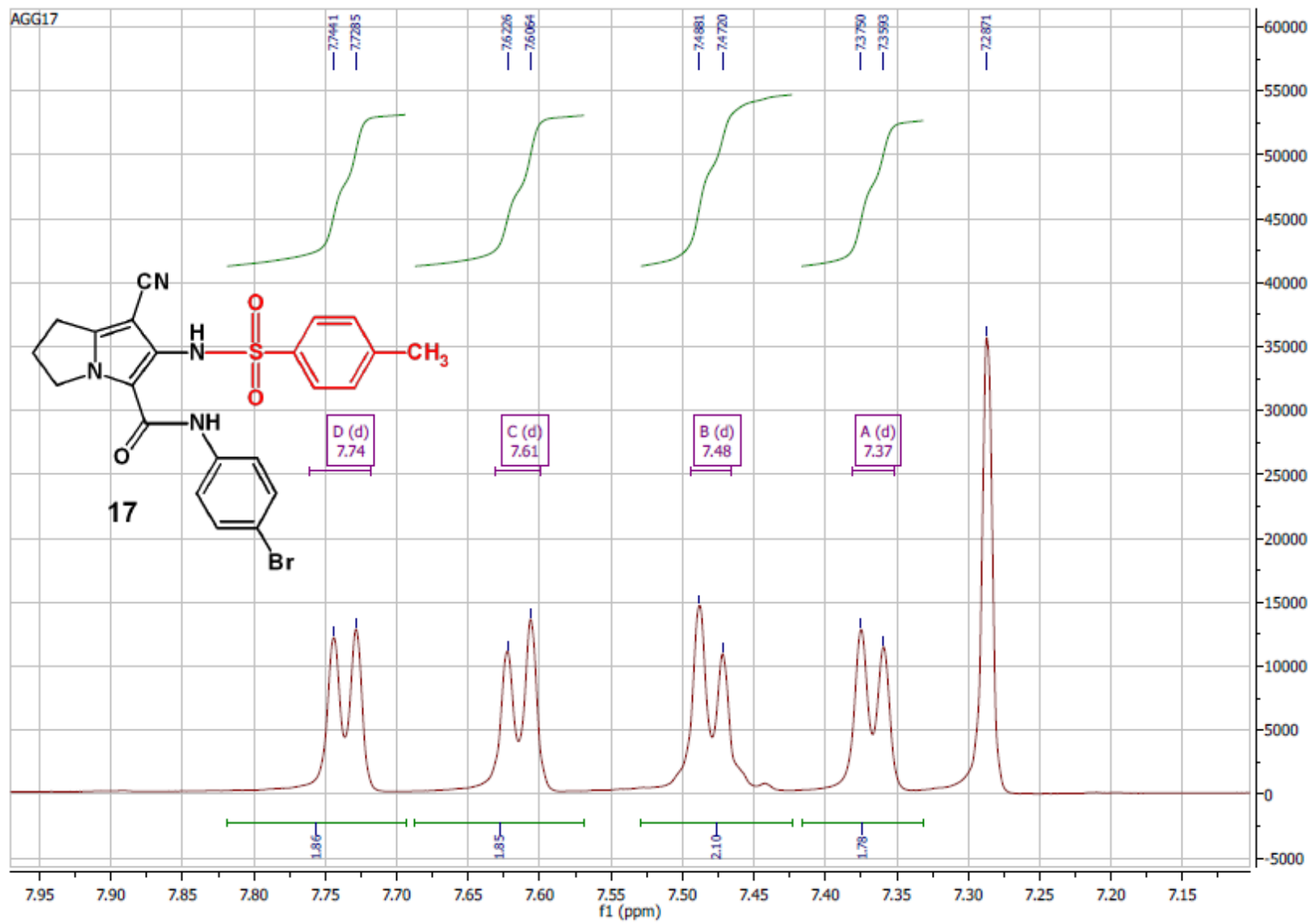


Figure S28d: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 17 (ZOON on Aromatic Protons)

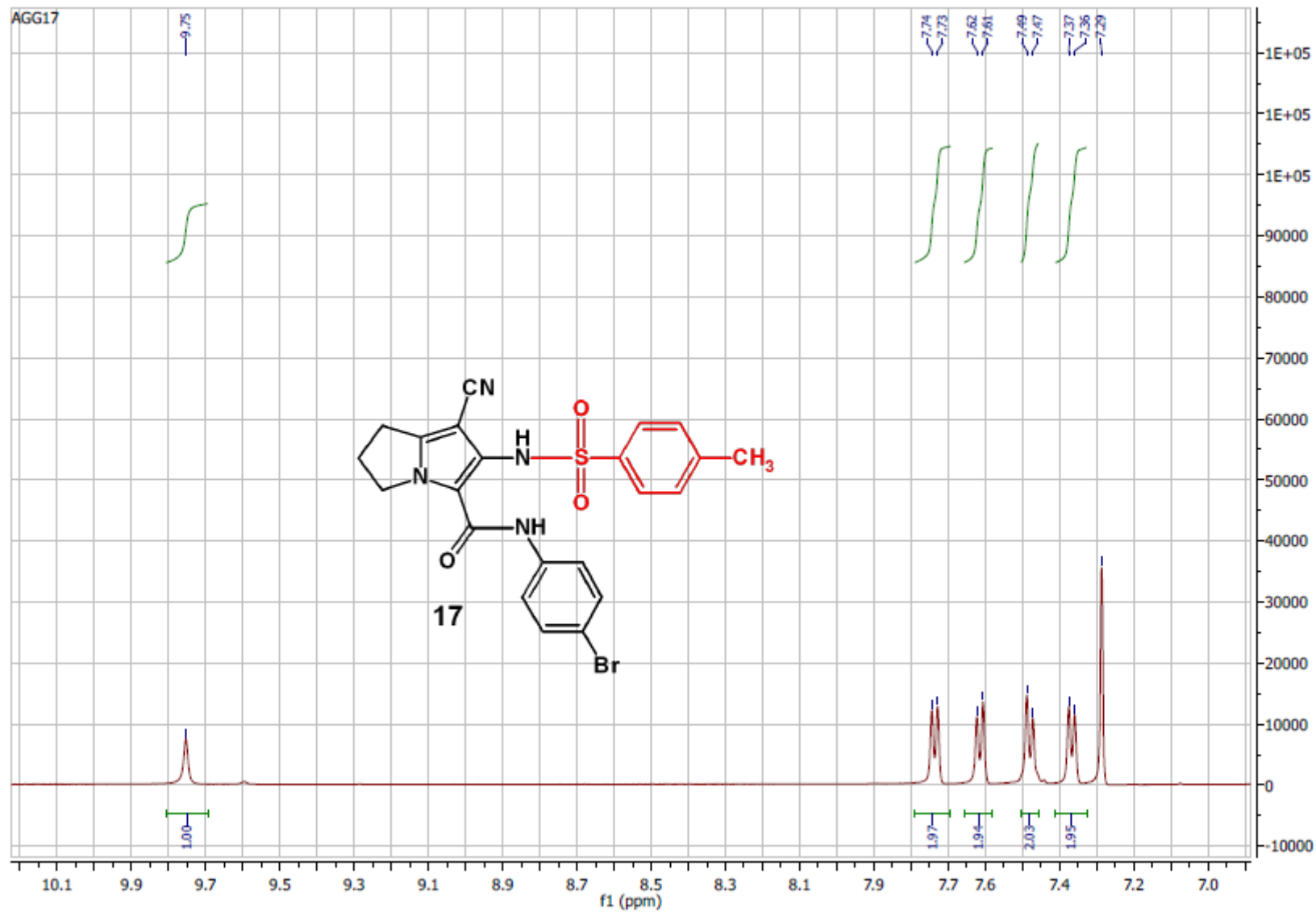


Figure S28e: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 17 (ZOON on Aromatic Protons)

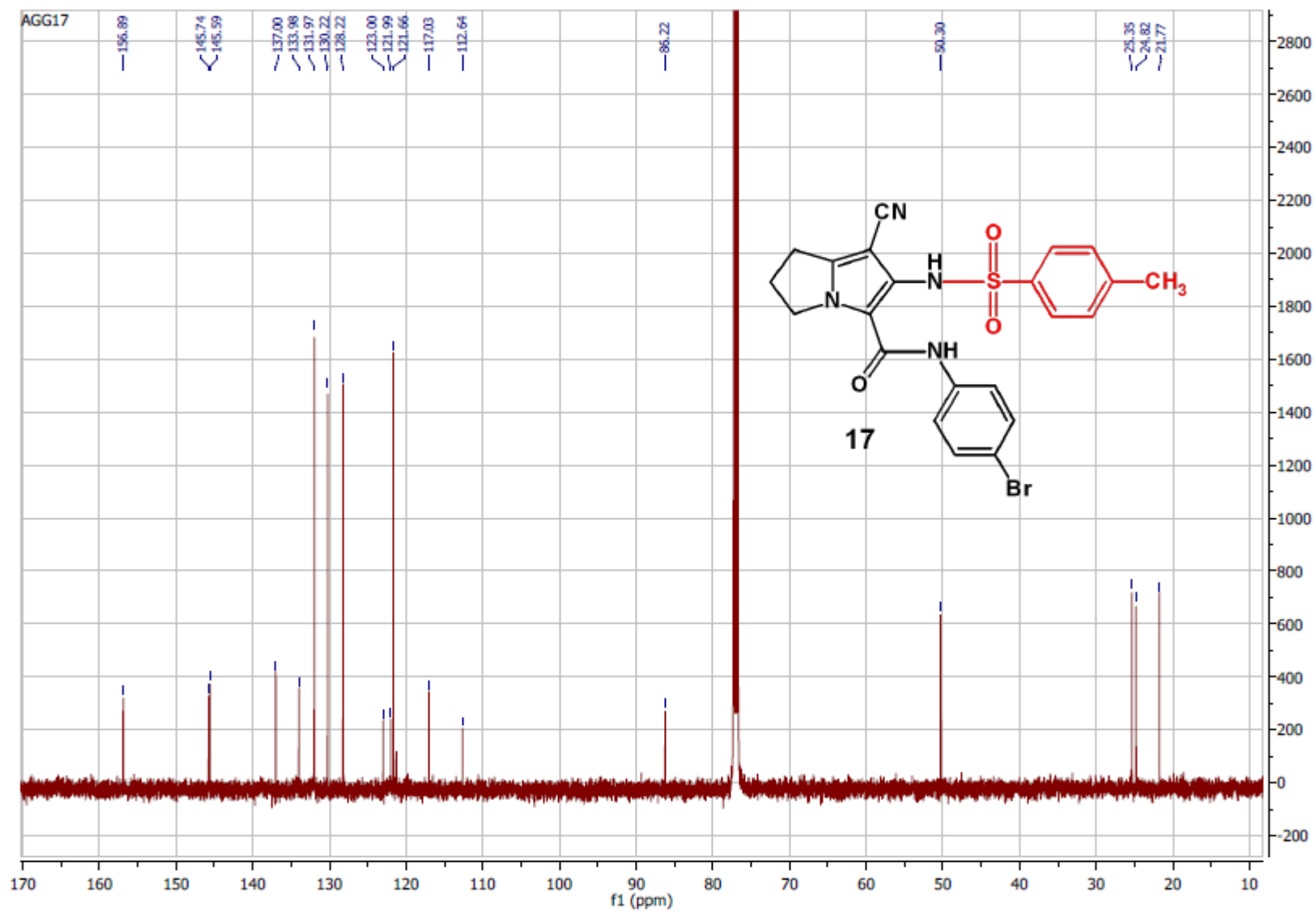


Figure S29a: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 17

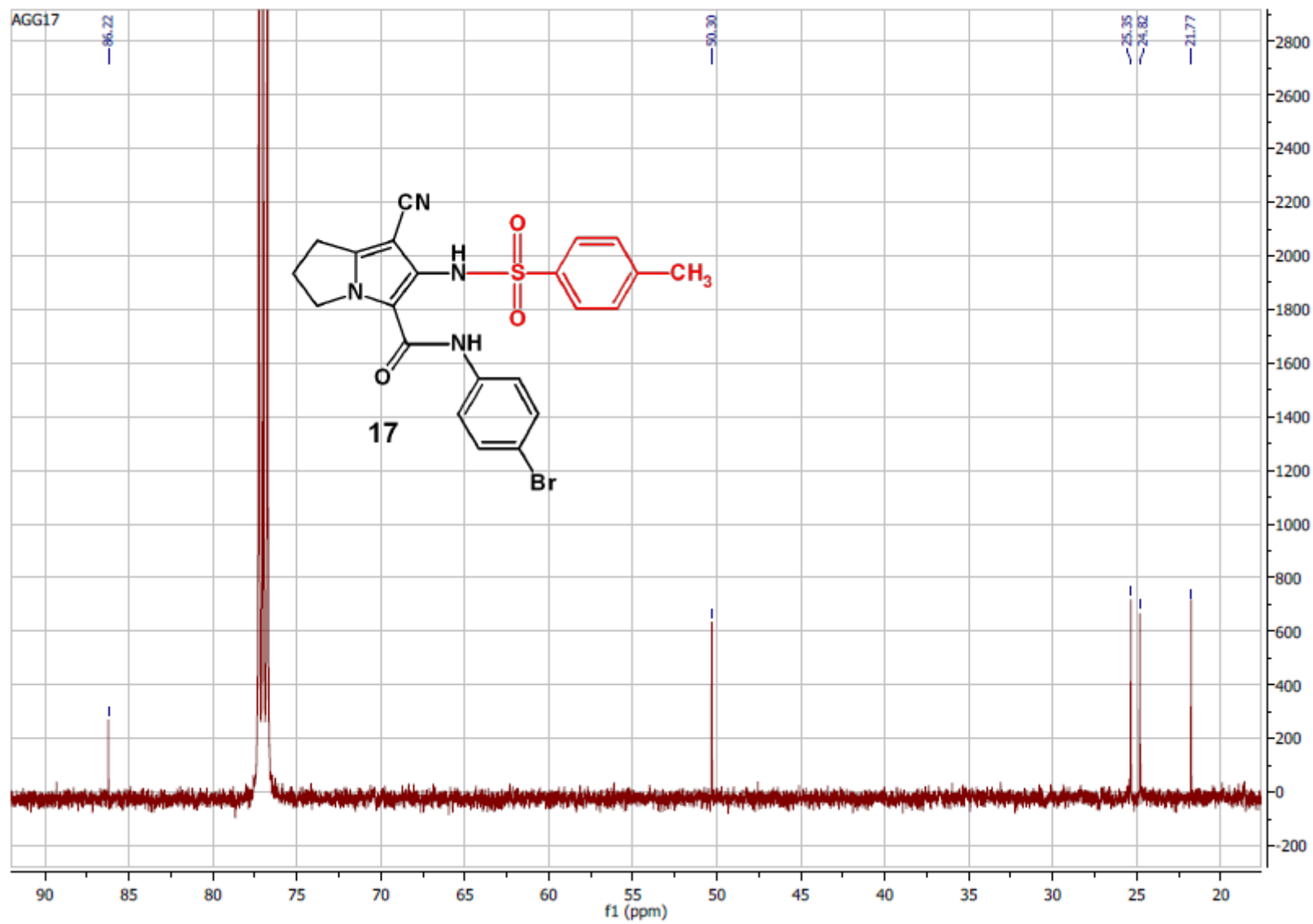


Figure S29b: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 17 (ZOOM on Aliphatic Carbons)

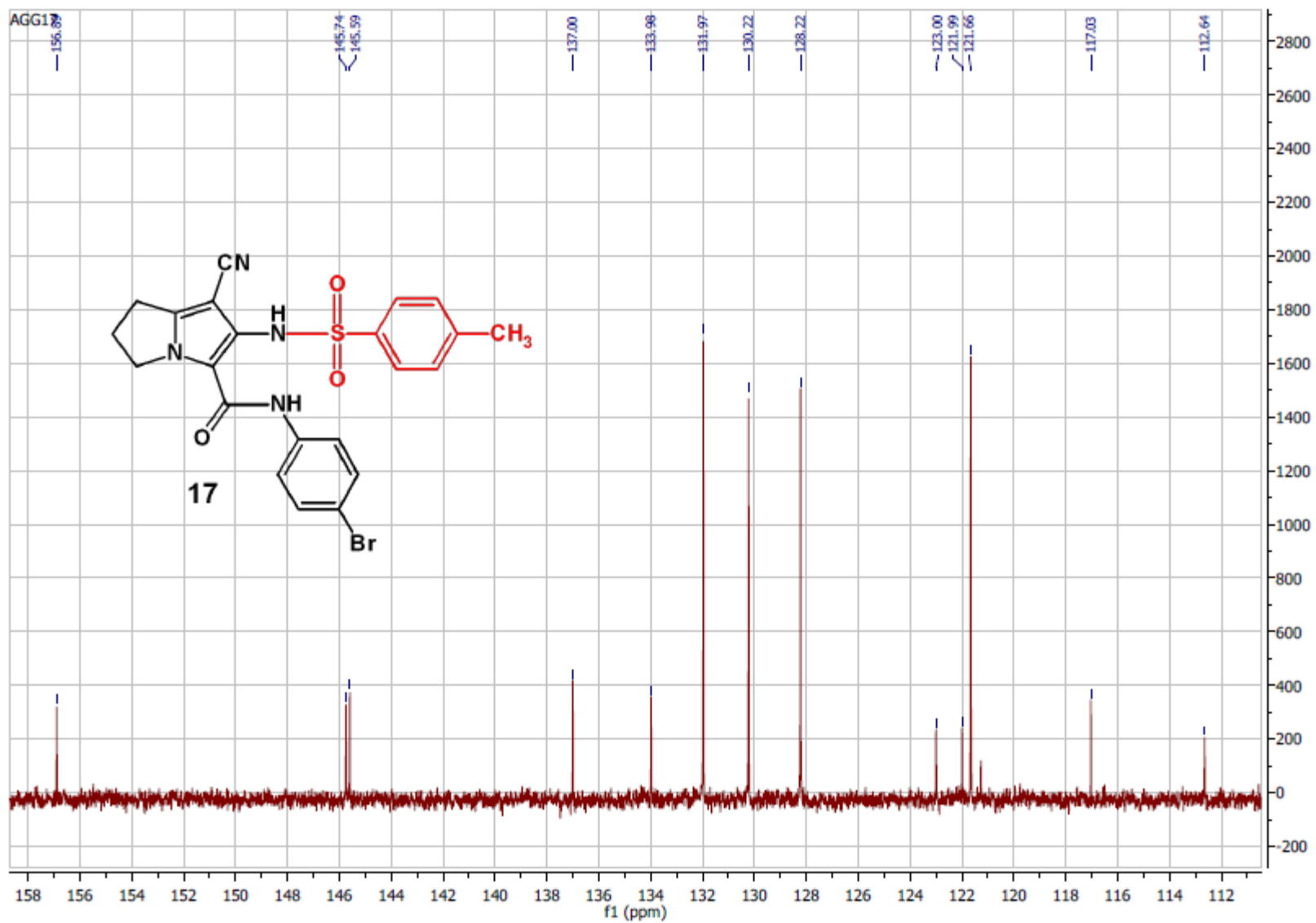


Figure S29c: 13C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 17 (ZOOM on Aromatic Carbons)

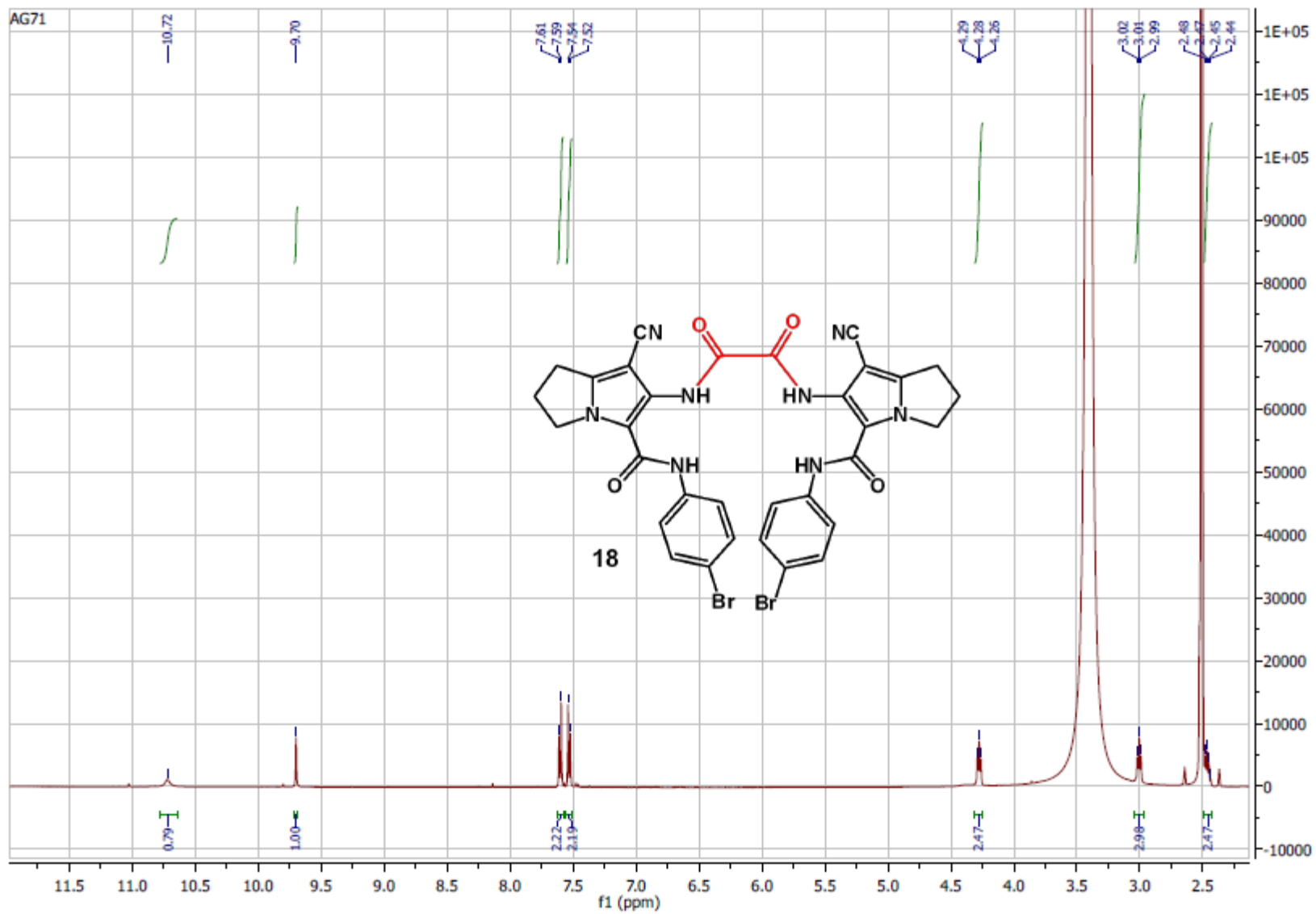


Figure S30a: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 18

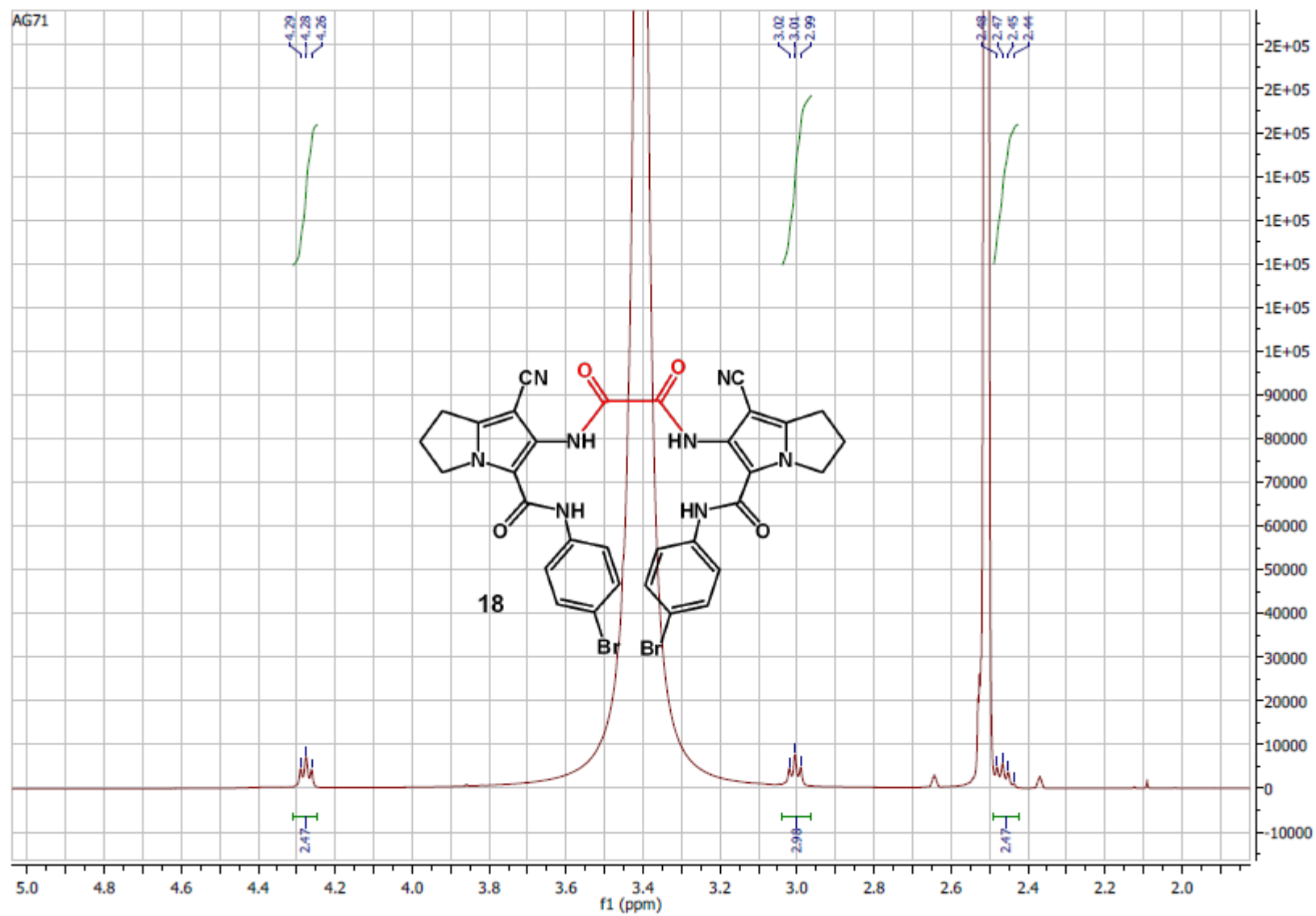


Figure S30b: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 18 (ZOOM on Aliphatic Protons)

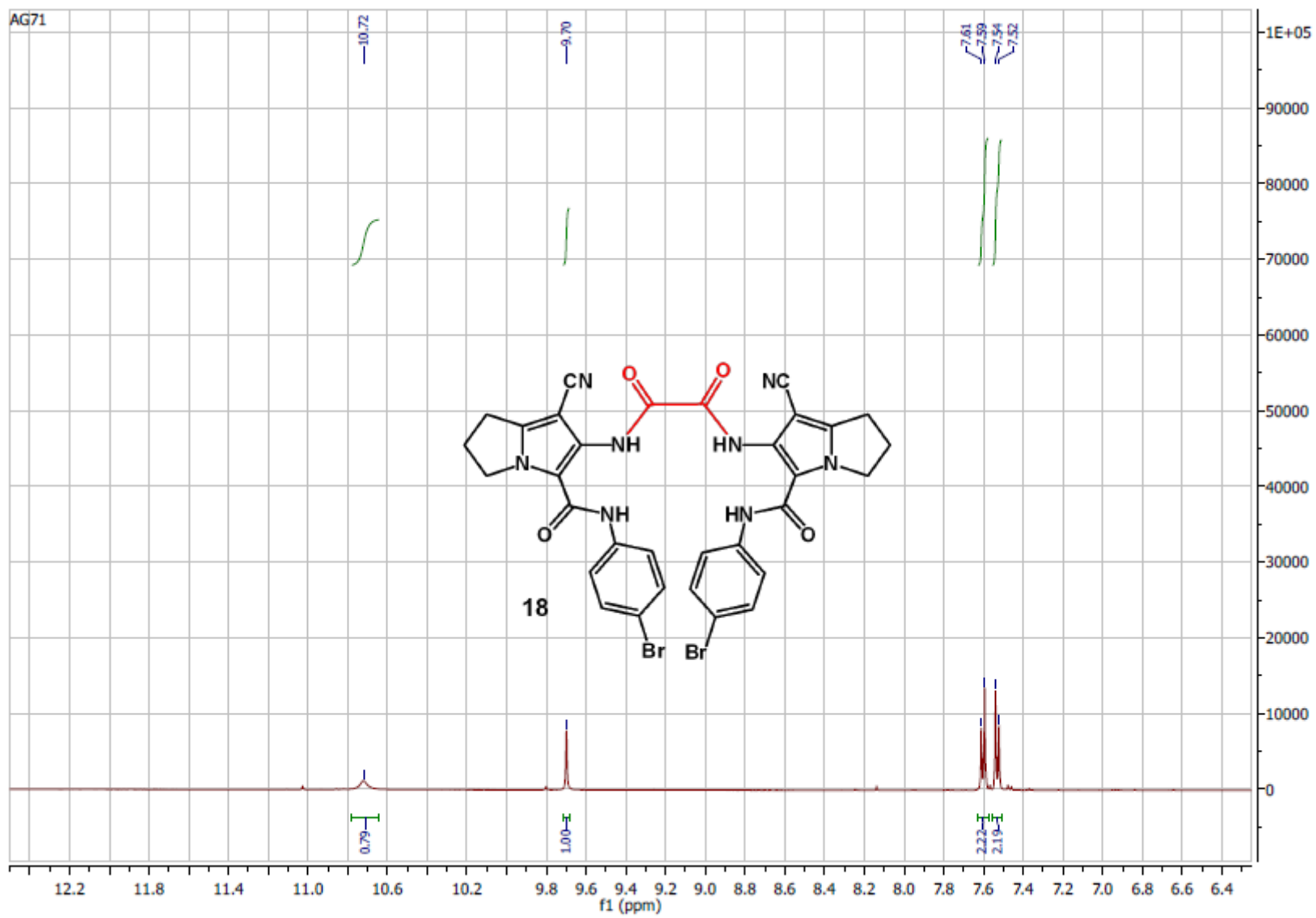


Figure S30c: $^1\text{H-NMR}$ (DMSO, 500 MHz, δ ppm) spectrum of compound 18 (ZOOM on Aromatic Protons)

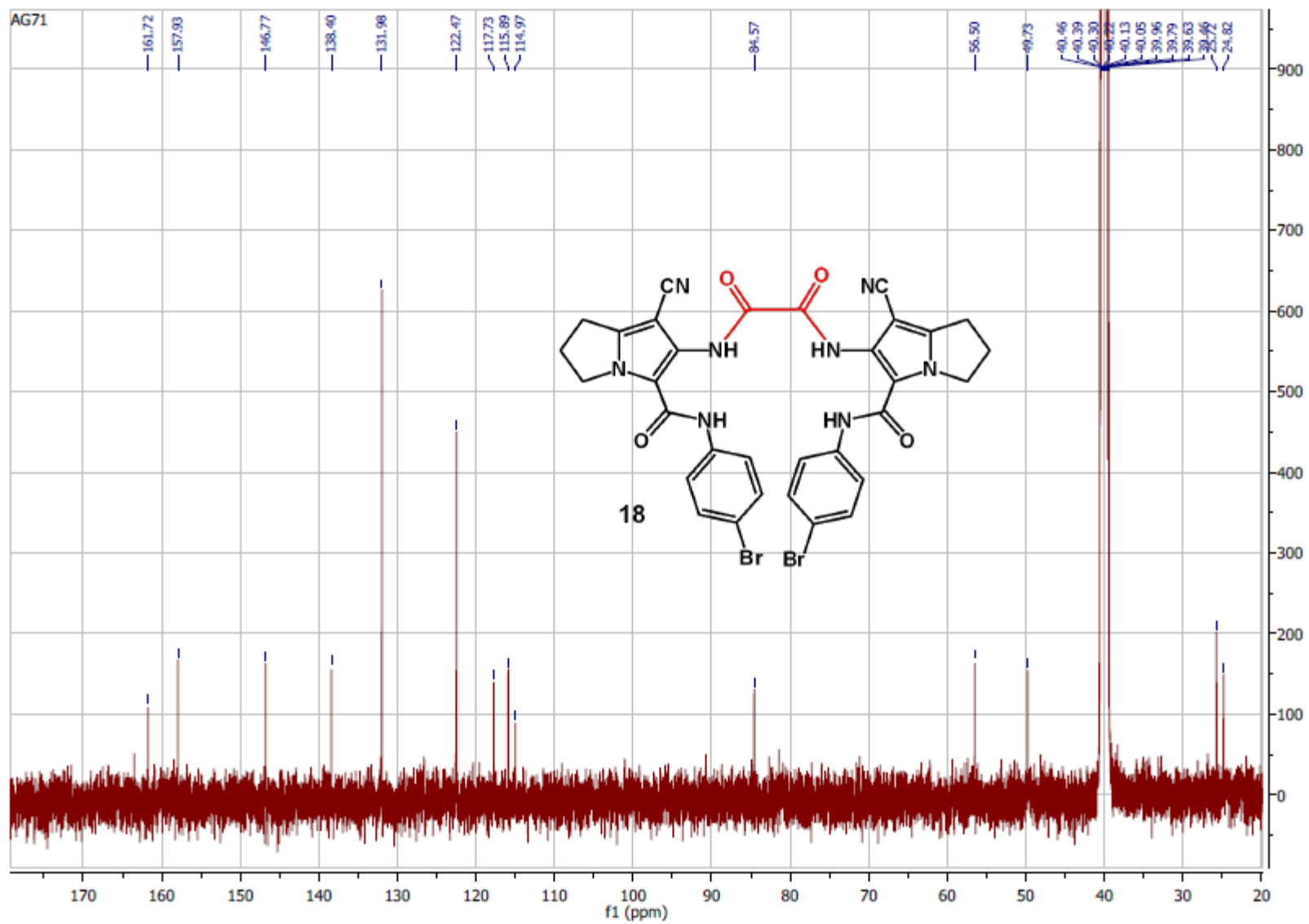


Figure S31: ^{13}C -NMR (DMSO, 125 MHz, δ ppm) spectrum of compound 18

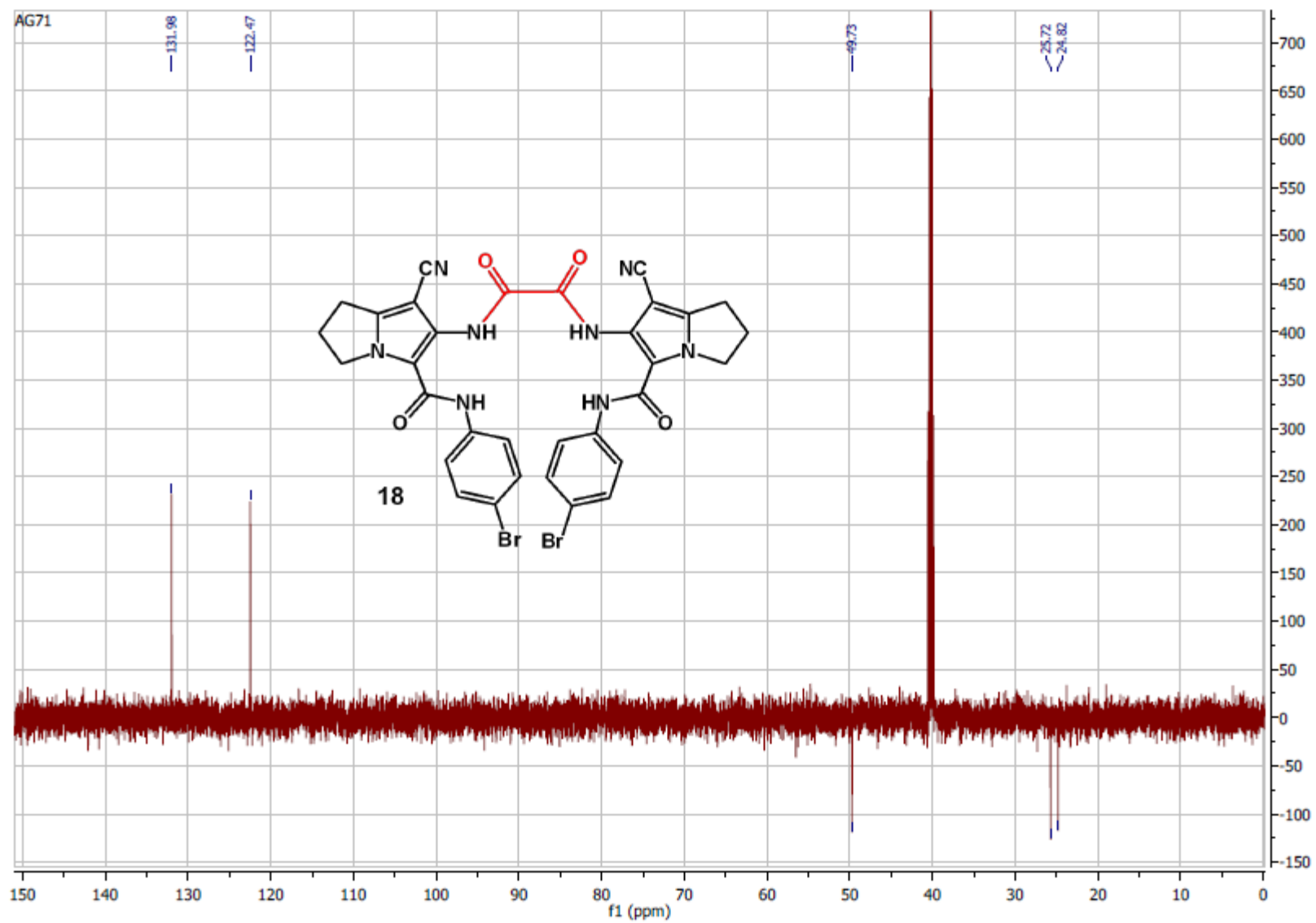


Figure S32: DEPT 135 spectrum of compound 18

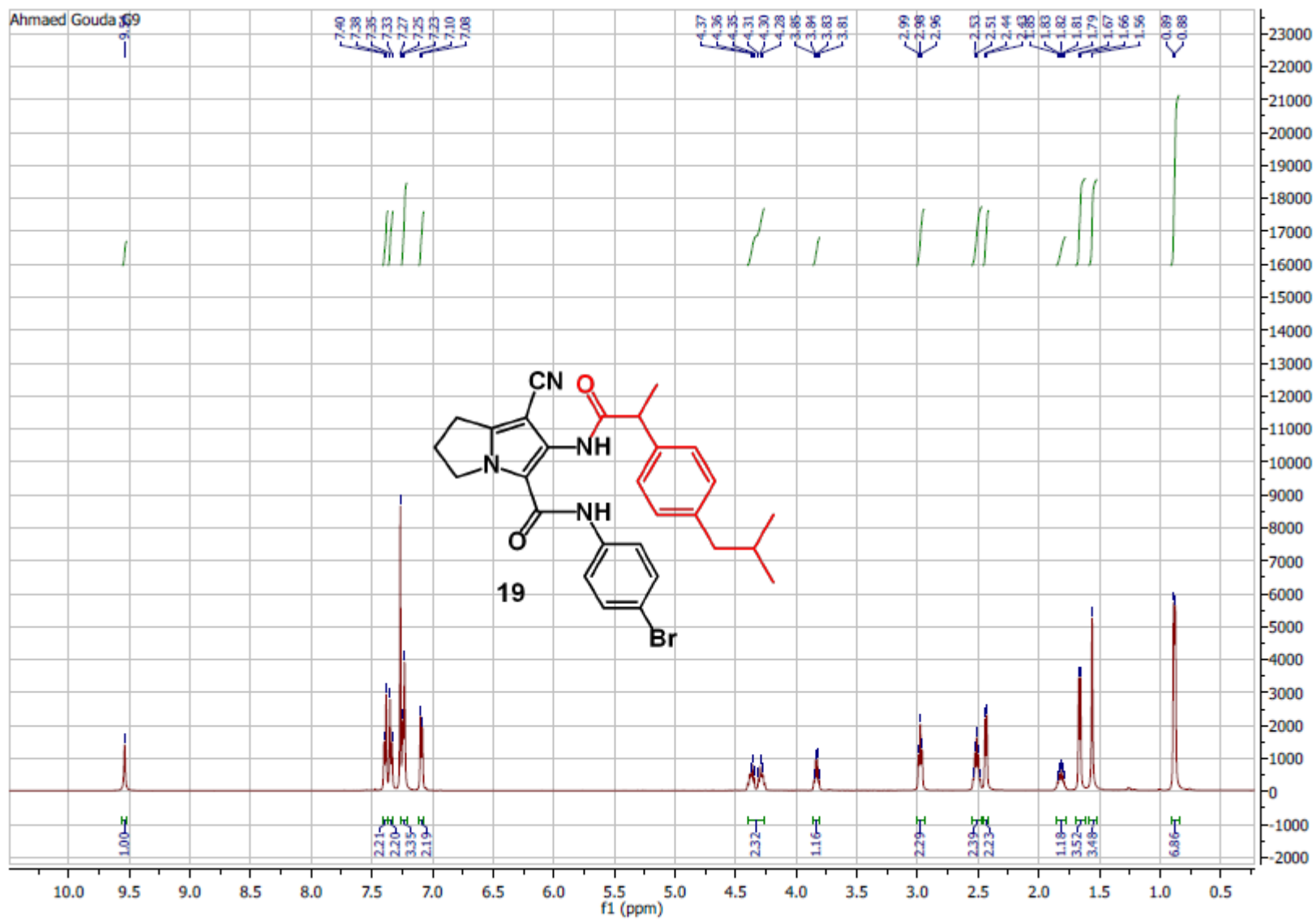


Figure S33a: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 19

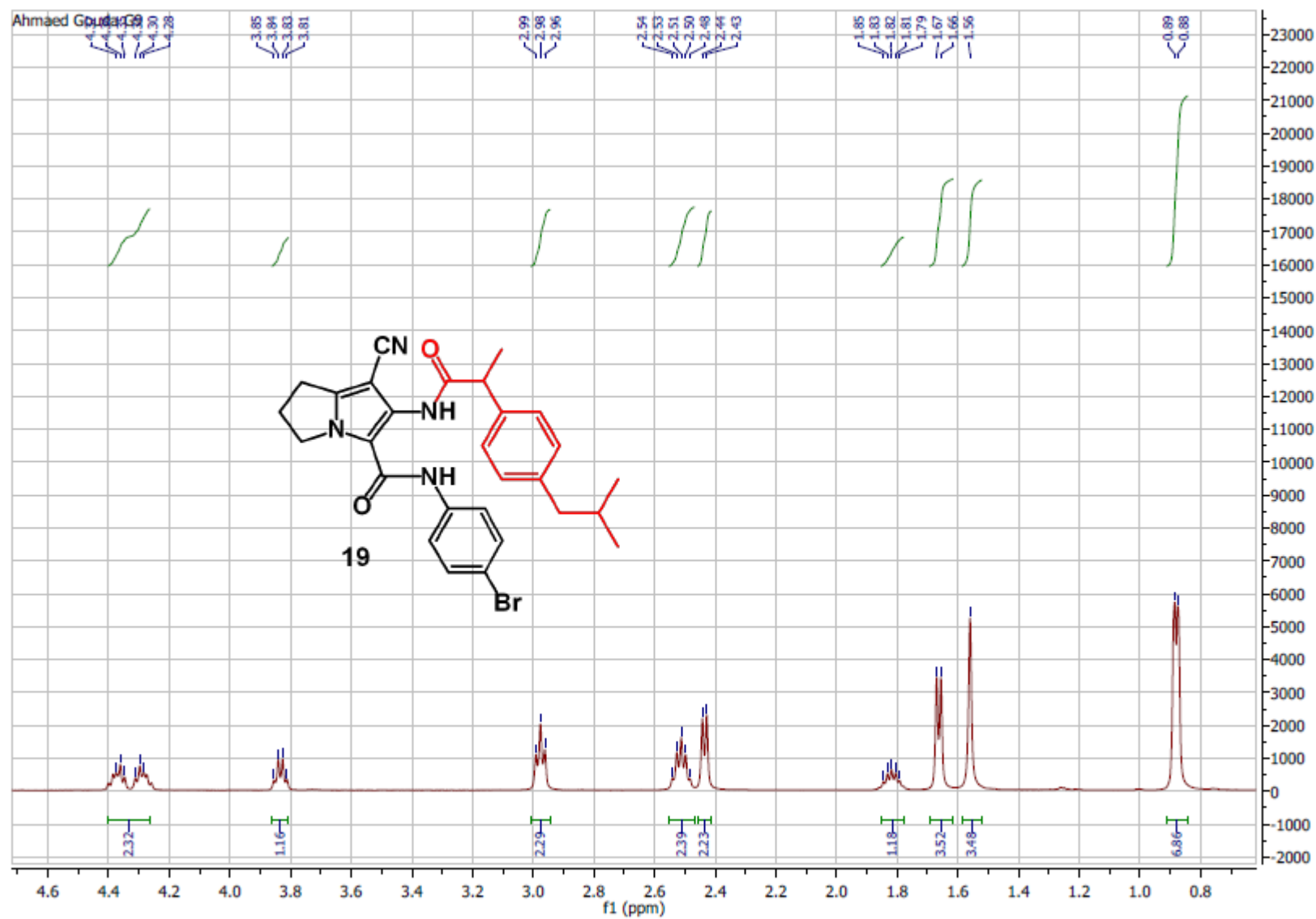


Figure S33b: ¹H-NMR (CDCl₃, 500 MHz, δ ppm) spectrum of compound 19 (ZOOM on Aliphatic Protons)

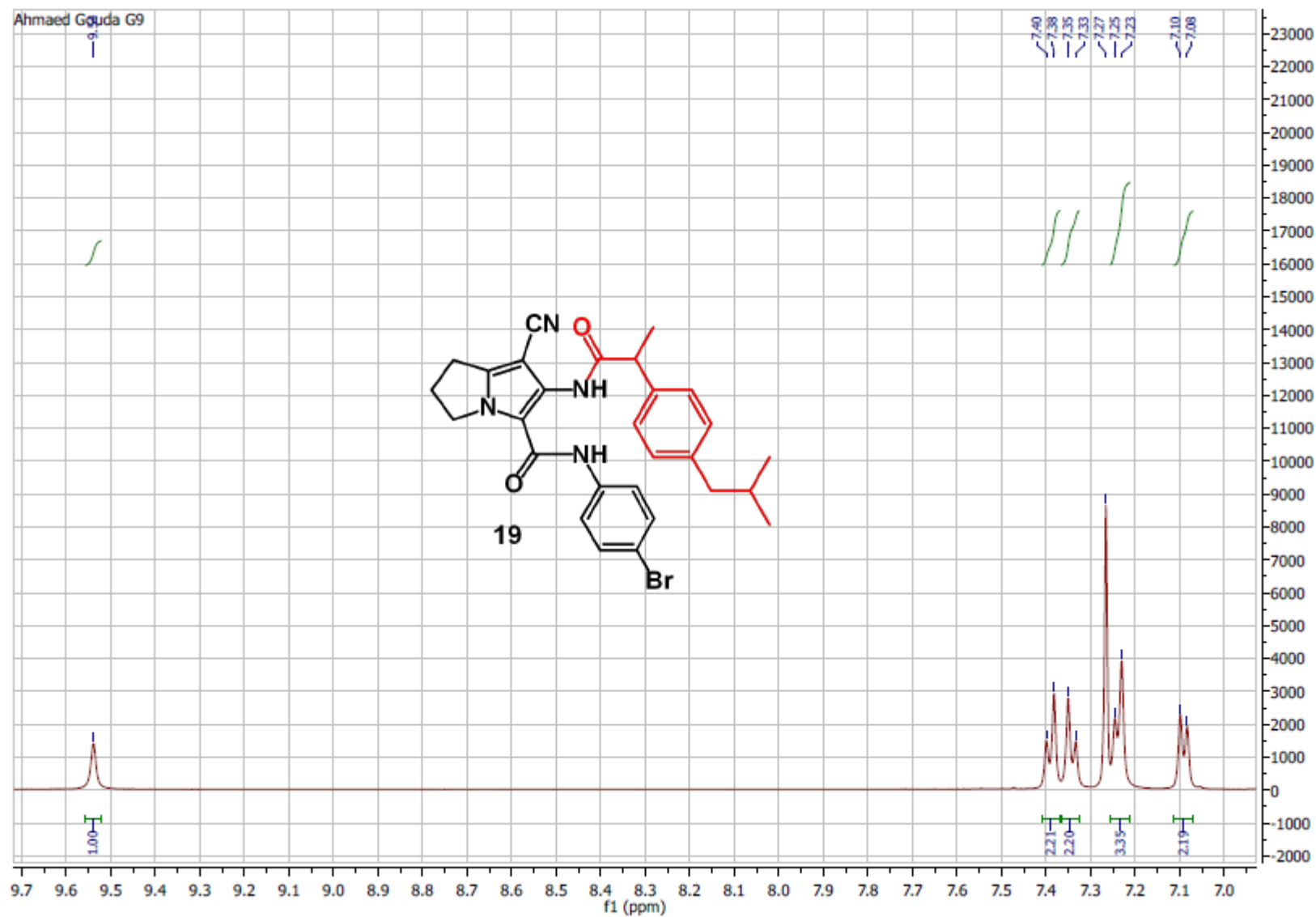


Figure S33c: $^1\text{H-NMR}$ (CDCl_3 , 500 MHz, δ ppm) spectrum of compound 19 (ZOOM on Aromatic Protons)

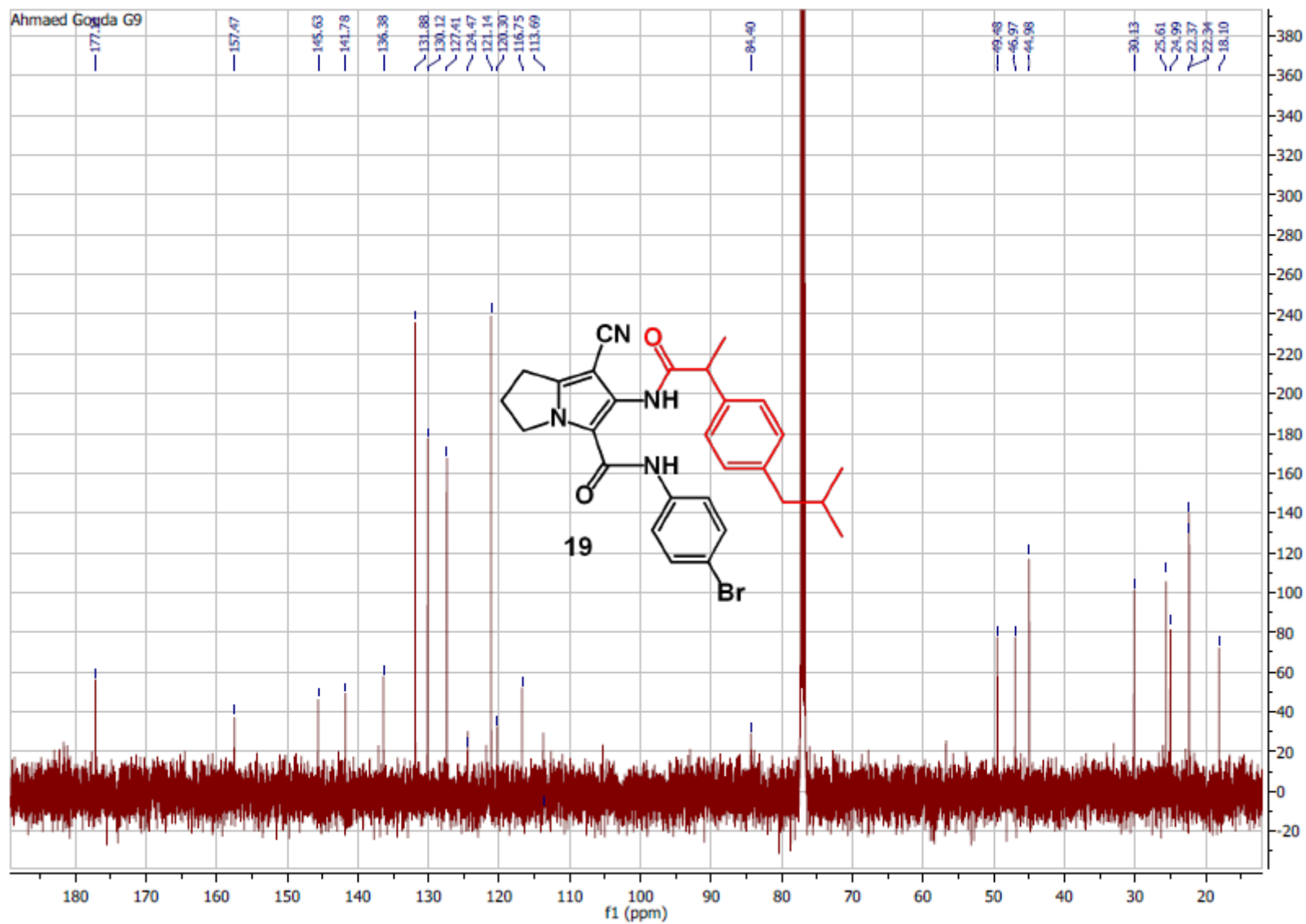


Figure S34a: ^{13}C -NMR (CDCl_3 , 125 MHz, δ ppm) spectrum of compound 19

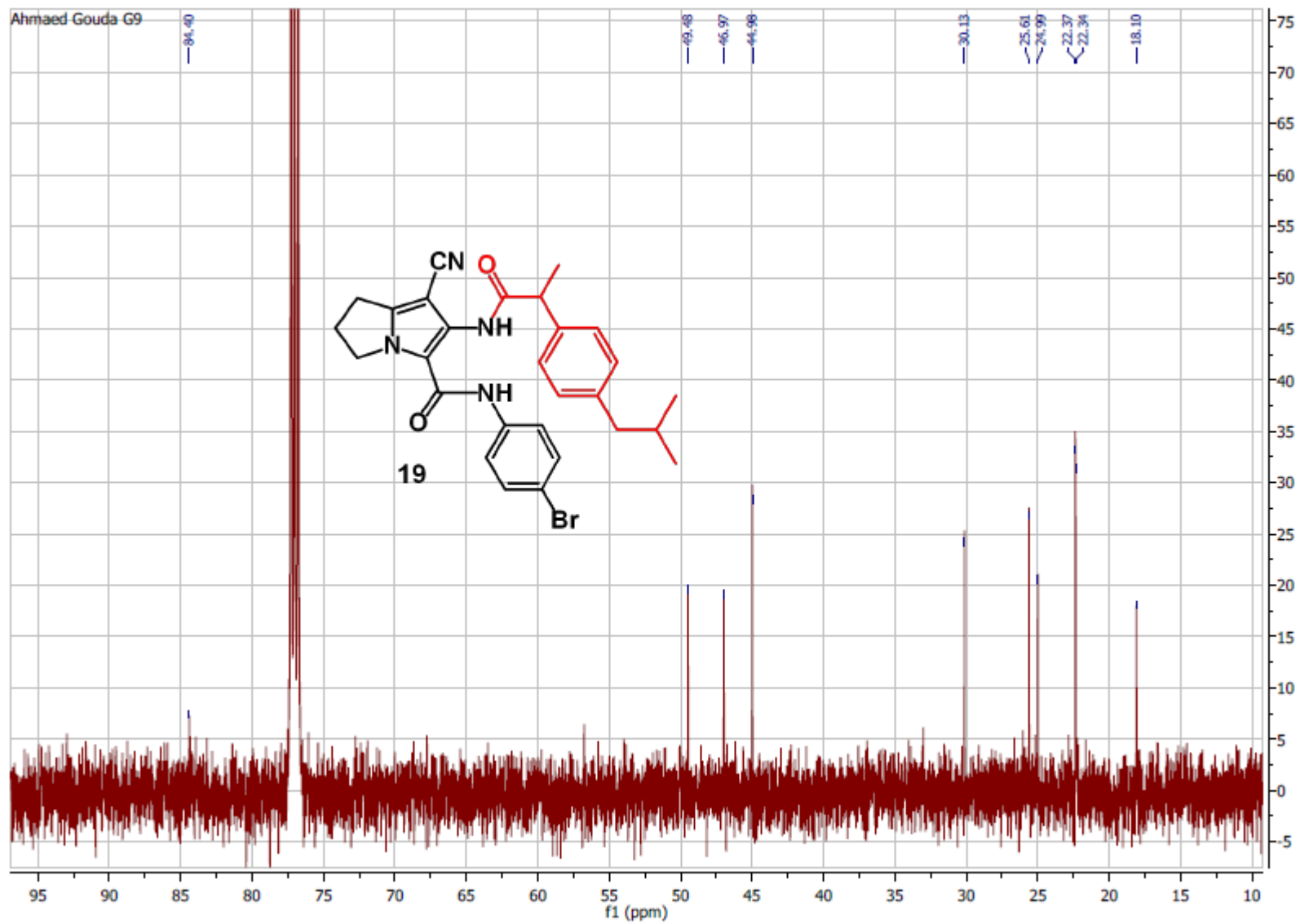


Figure S34b: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 19 (ZOOM on Aliphatic Carbons)

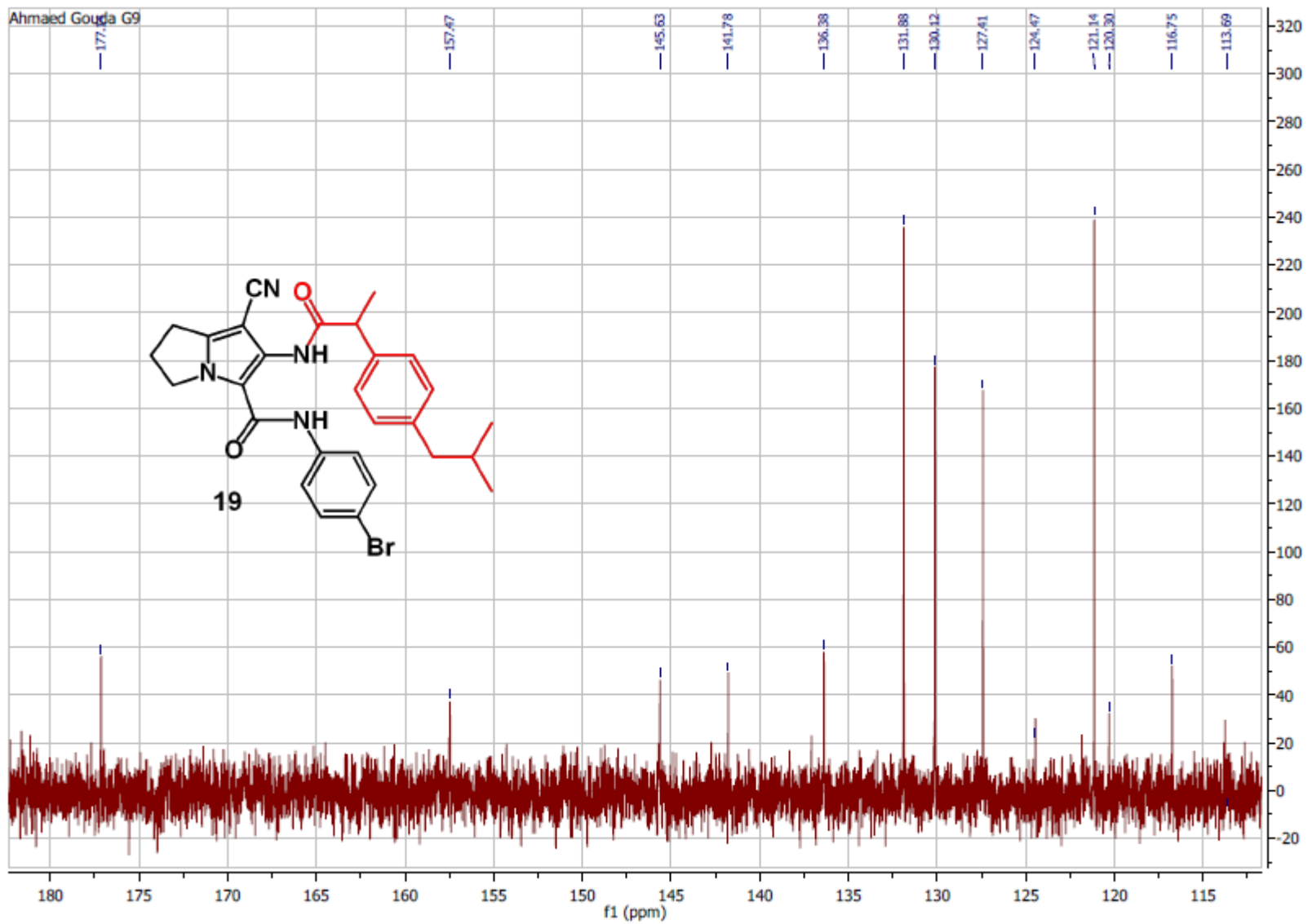


Figure S34c: ¹³C-NMR (CDCl₃, 125 MHz, δ ppm) spectrum of compound 19 (ZOOM on Aromatic Carbons)

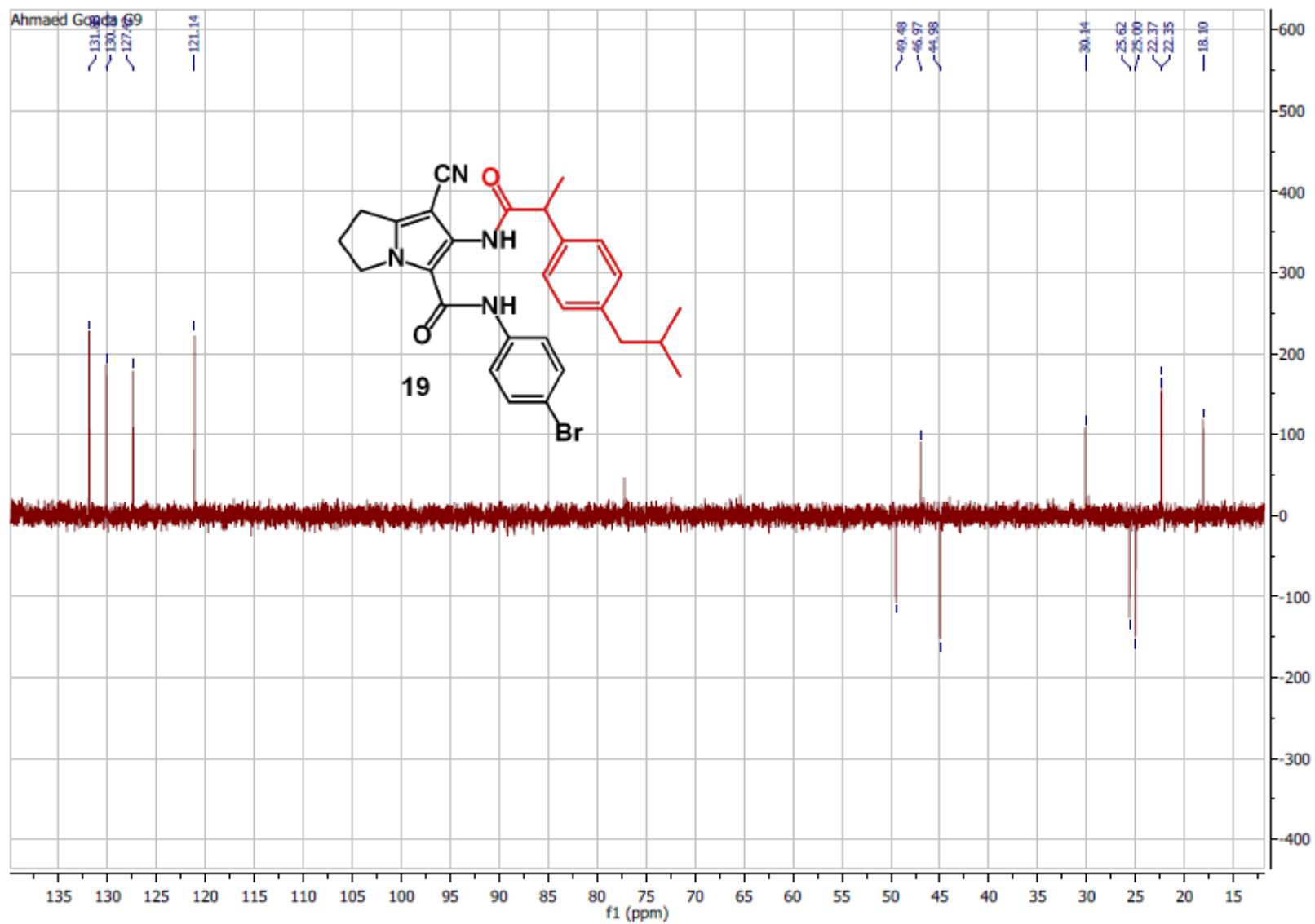


Figure S35: DEPT 135 spectrum of compound 19