

Synthesis and Antimalarial Evaluation of Amide and Urea Derivatives Based on the Thiaplakortone A Natural Product Scaffold

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General Experimental Procedures. Unless otherwise specified, proton ^1H and carbon ^{13}C NMR spectra were recorded at 30 °C in DMSO- d_6 on Varian INOVA 500 or 600 MHz NMR spectrometers. The latter spectrometer was equipped with a triple resonance cold probe. The ^1H and ^{13}C NMR chemical shifts were referenced to the solvent peak for DMSO- d_6 at δ_{H} 2.50 and δ_{C} 39.5. LRESIMS were recorded on an Agilent 6120 quadrupole LCMS system. ^1H NMR data are recorded as follows: chemical shift (d) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Compounds for biological studies were placed under high vacuum (0.05 mmHg) for several hours before testing.

Chart of Analogues (pg 1)

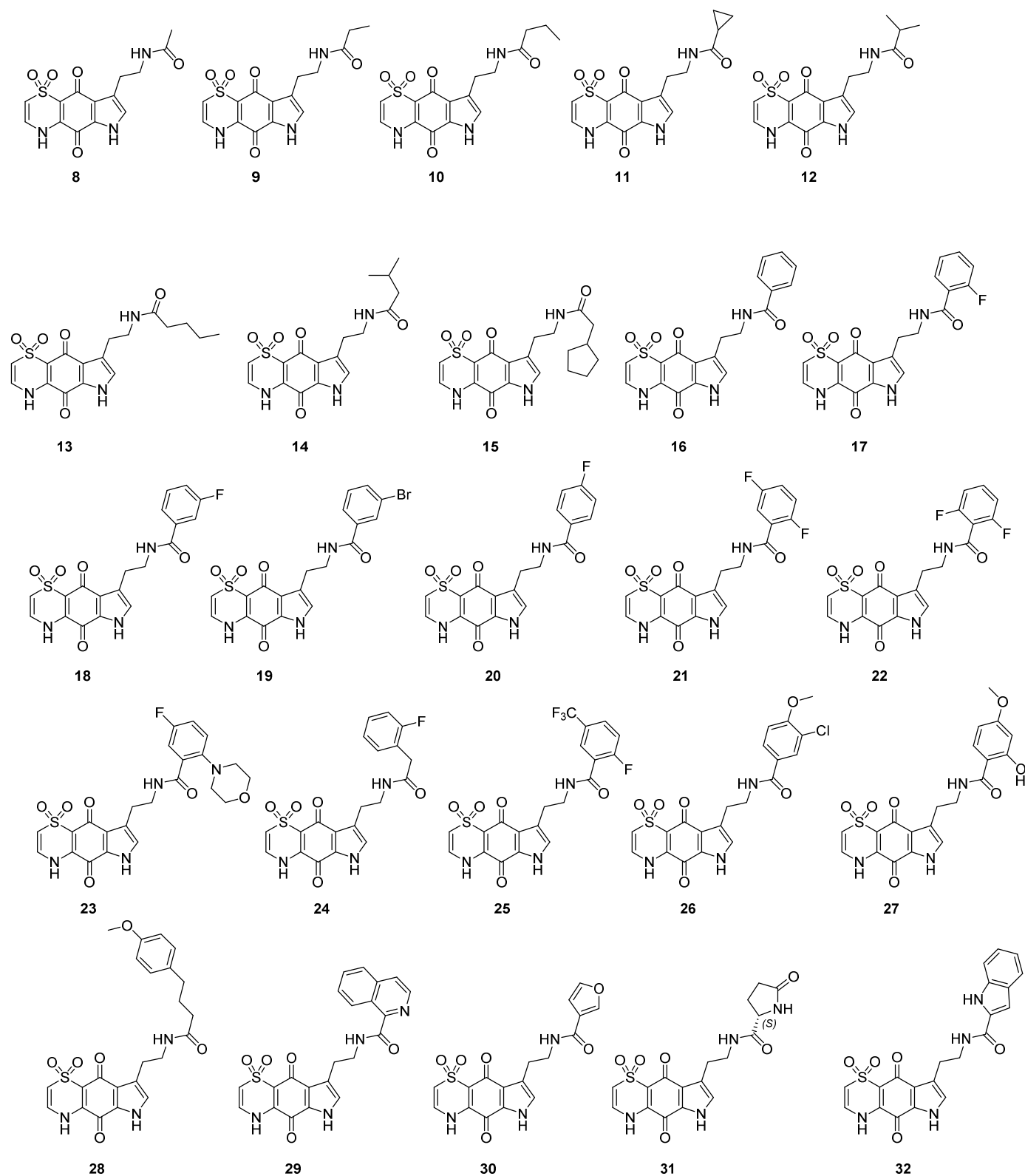
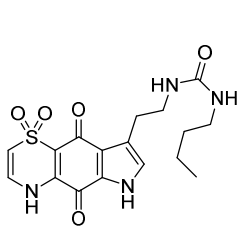
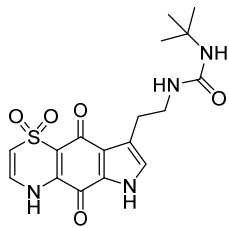


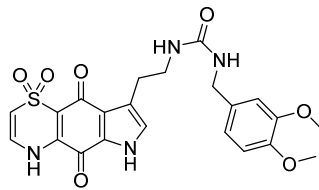
Chart of Analogues (pg 2)



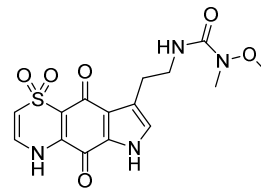
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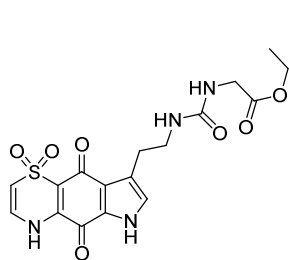
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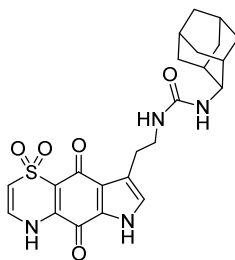
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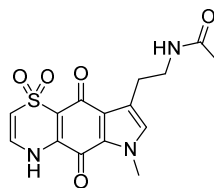
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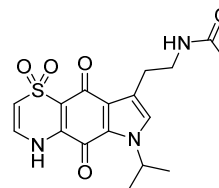
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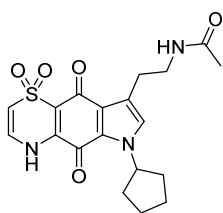
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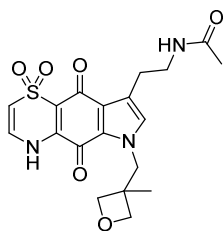
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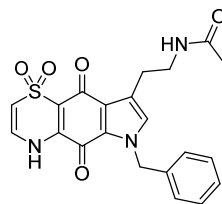
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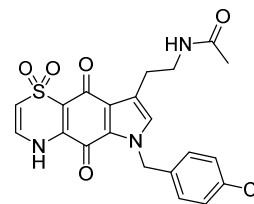
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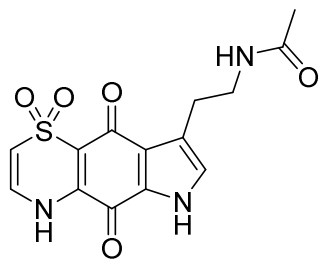
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44



45

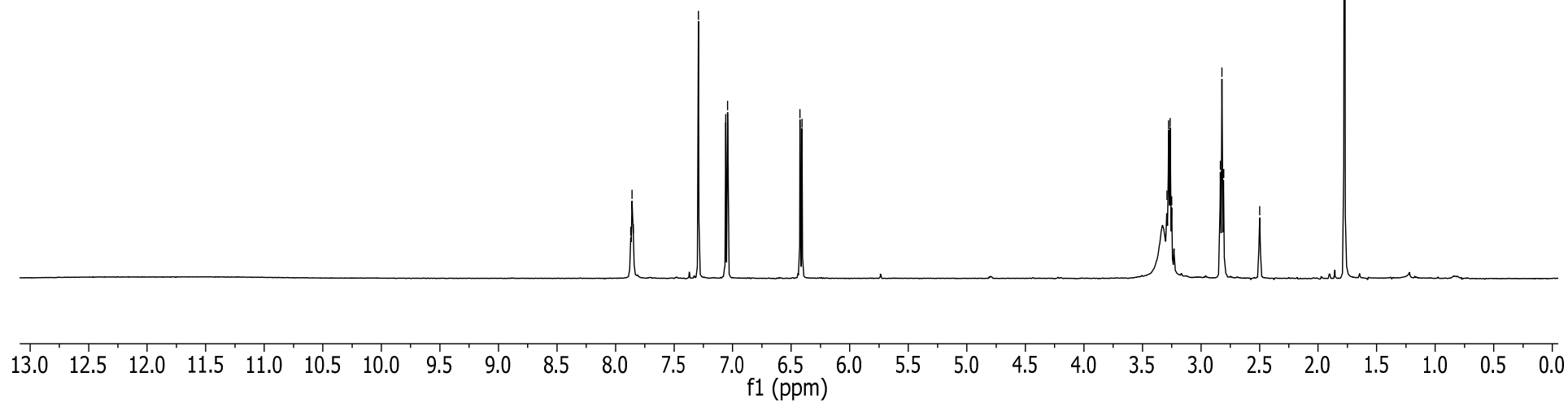


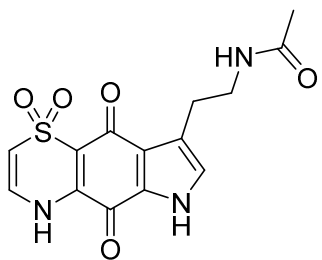
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7.86
7.85
7.29
7.06
7.04
6.42
6.41

3.29
3.28
3.26
3.25
2.84
2.82
2.81
2.50

1.78

500 MHz ^1H NMR spectrum of compound **8** in DMSO- d_6





— 178.41

— 169.03

— 167.54

— 139.92

— 130.14

— 128.79

— 127.71

— 124.62

— 123.25

— 114.21

— 111.53

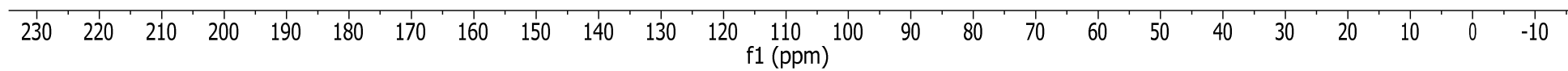
— 39.50

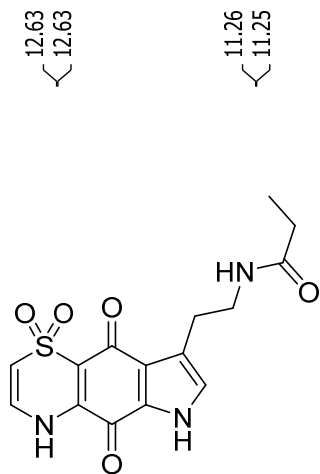
— 38.42

— 25.33

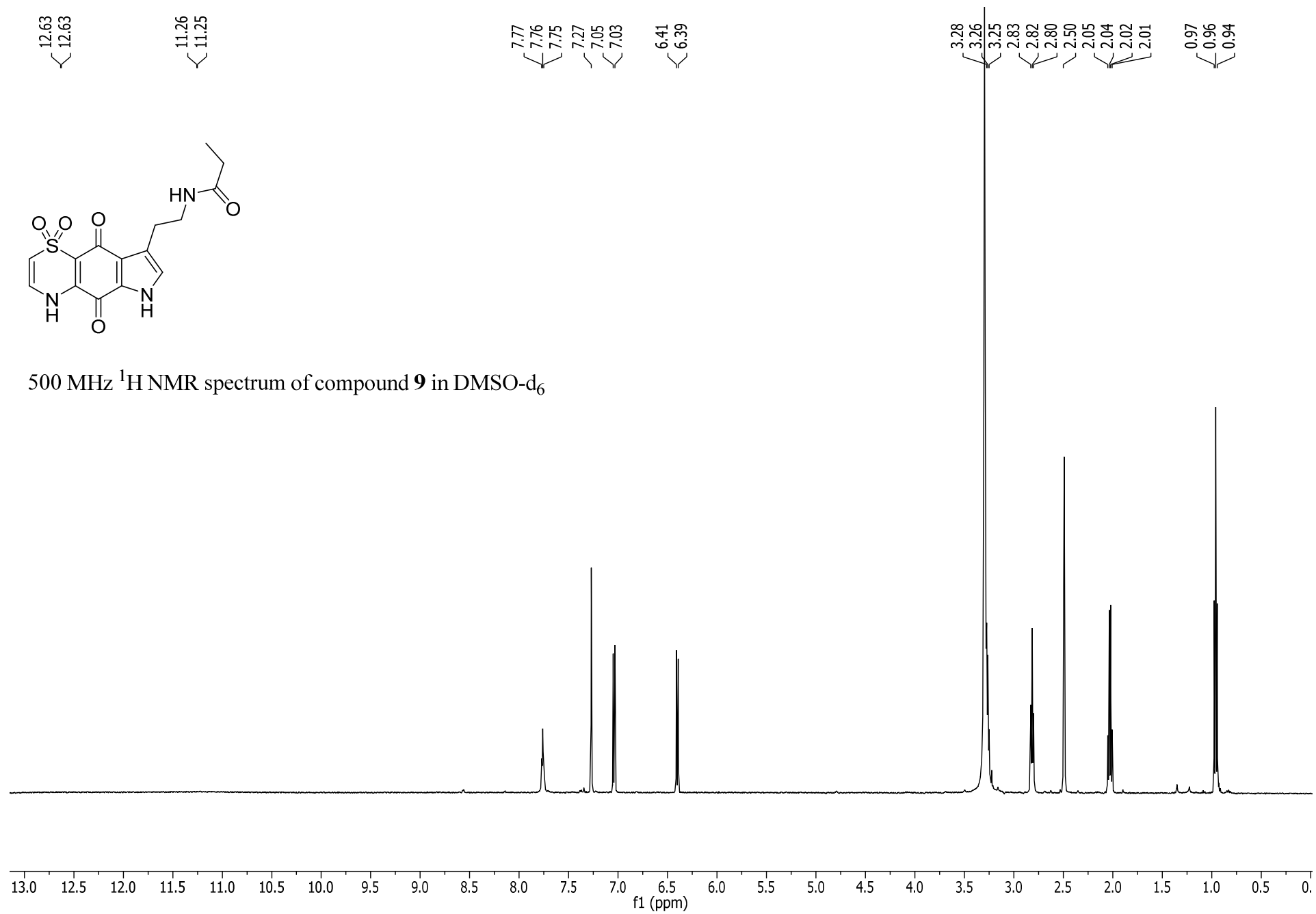
— 22.57

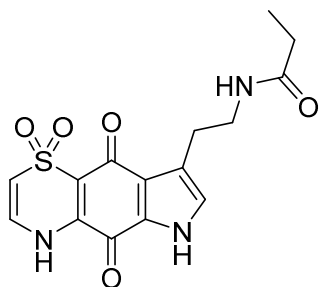
125 MHz ^{13}C NMR spectrum of compound **8** in DMSO- d_6





500 MHz ^1H NMR spectrum of compound **9** in DMSO-d_6





178.41
172.69
167.66

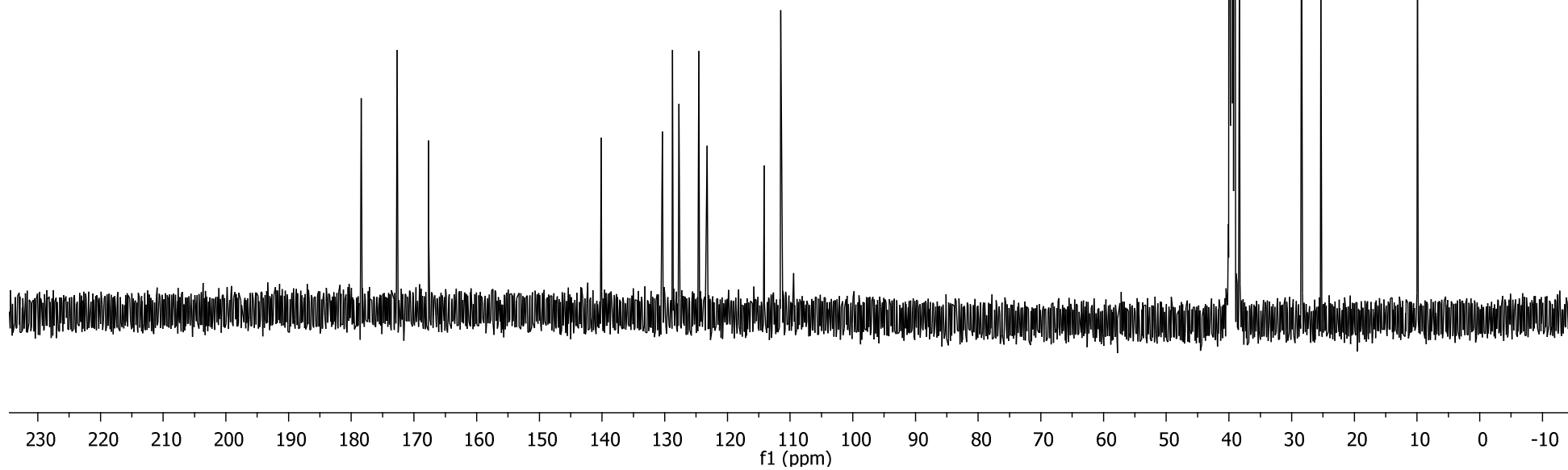
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130.35
128.74
127.74
124.56
123.25
114.15
111.51

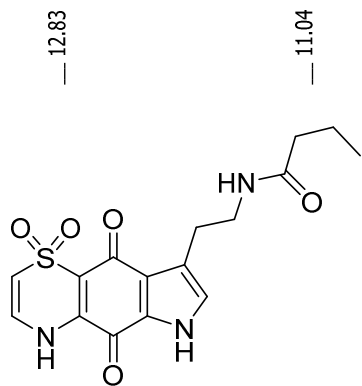
38.30

28.45
25.33

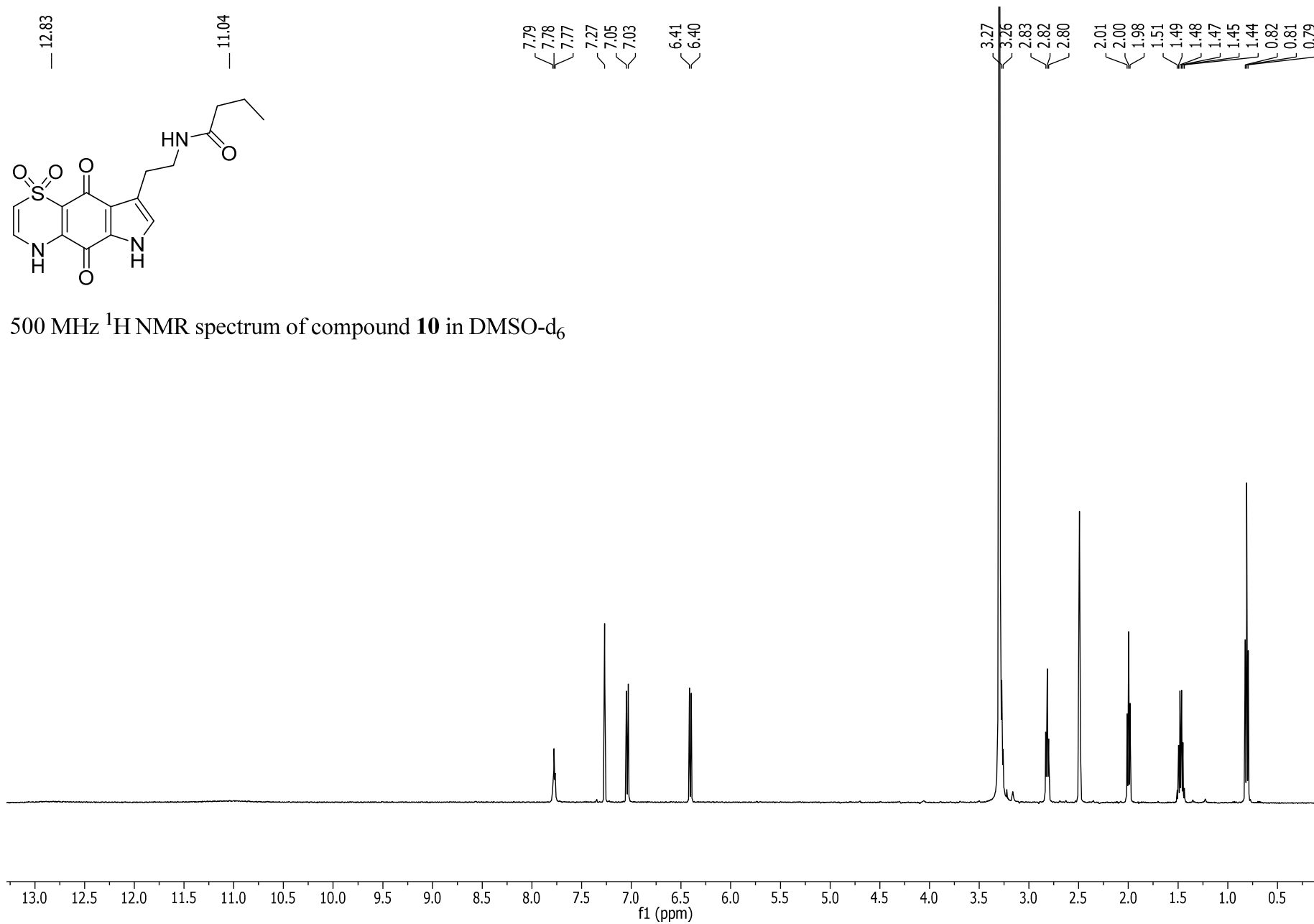
9.91

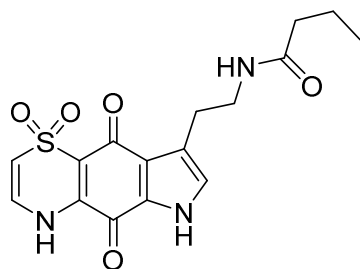
125 MHz ^{13}C NMR spectrum of compound **9** in DMSO- d_6



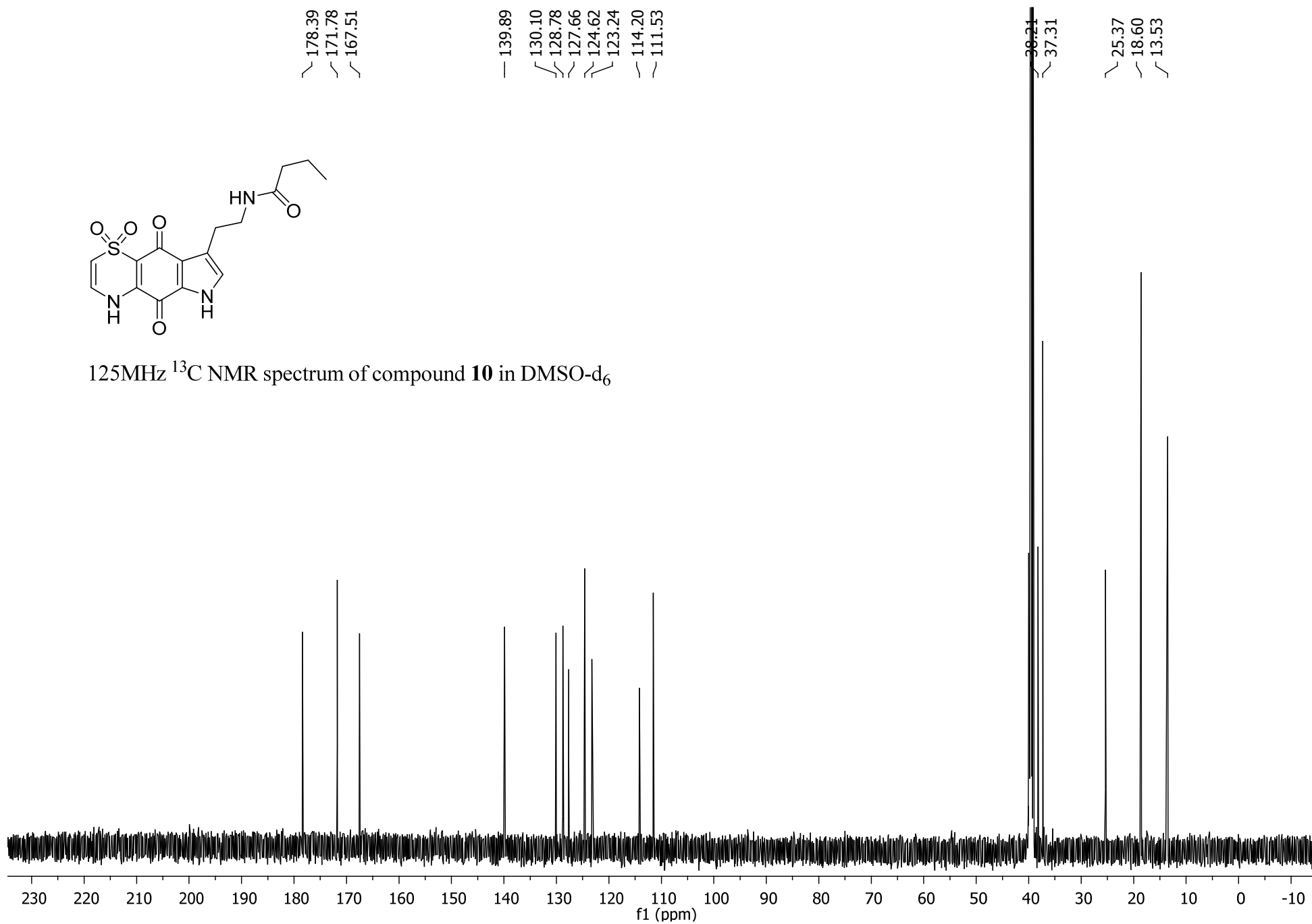


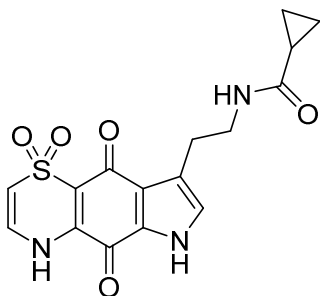
500 MHz ^1H NMR spectrum of compound **10** in DMSO-d_6



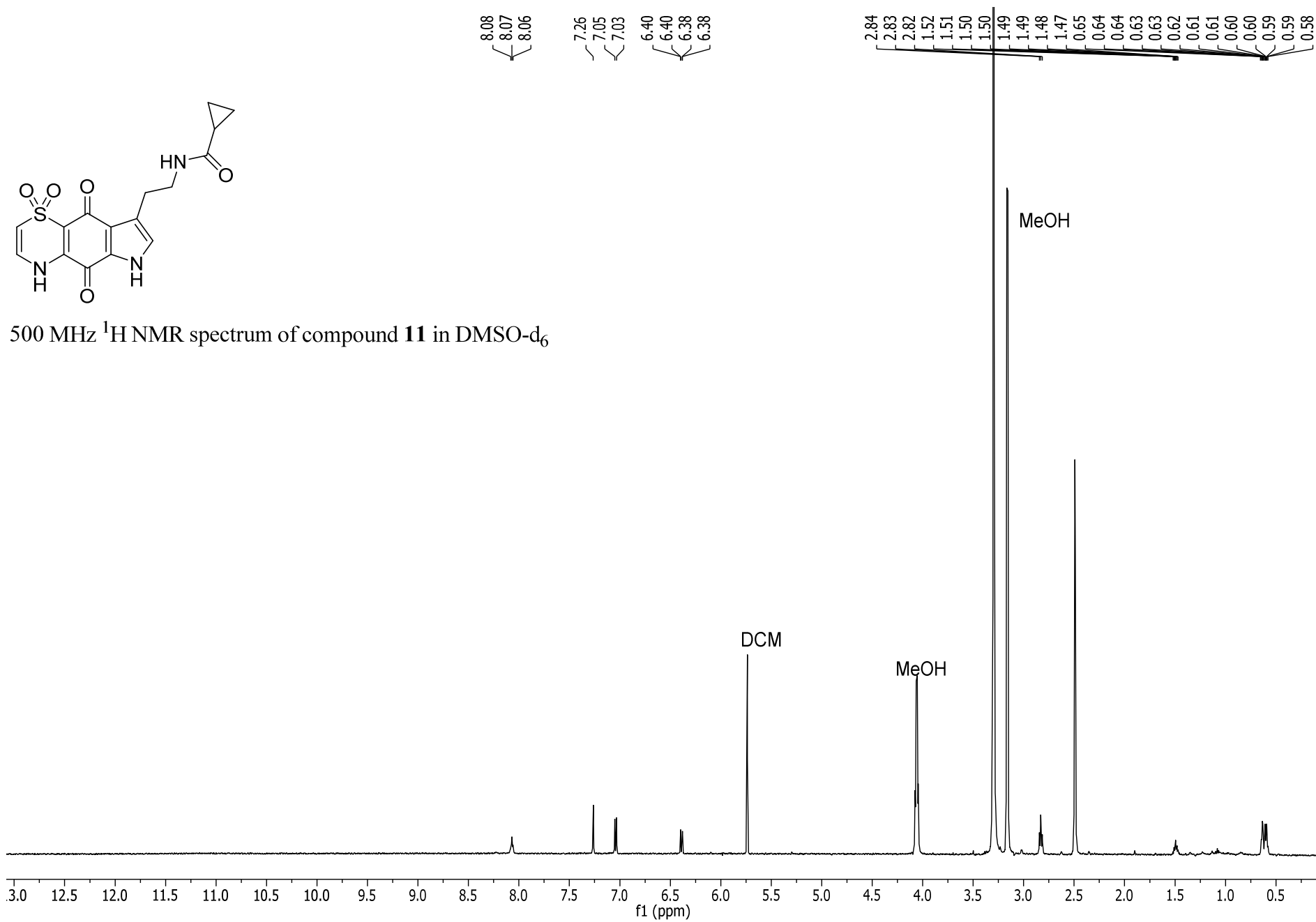


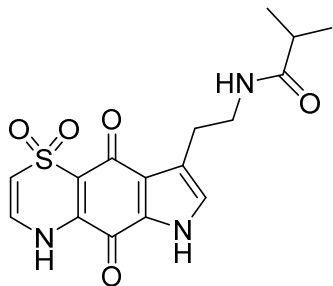
125MHz ^{13}C NMR spectrum of compound **10** in DMSO- d_6



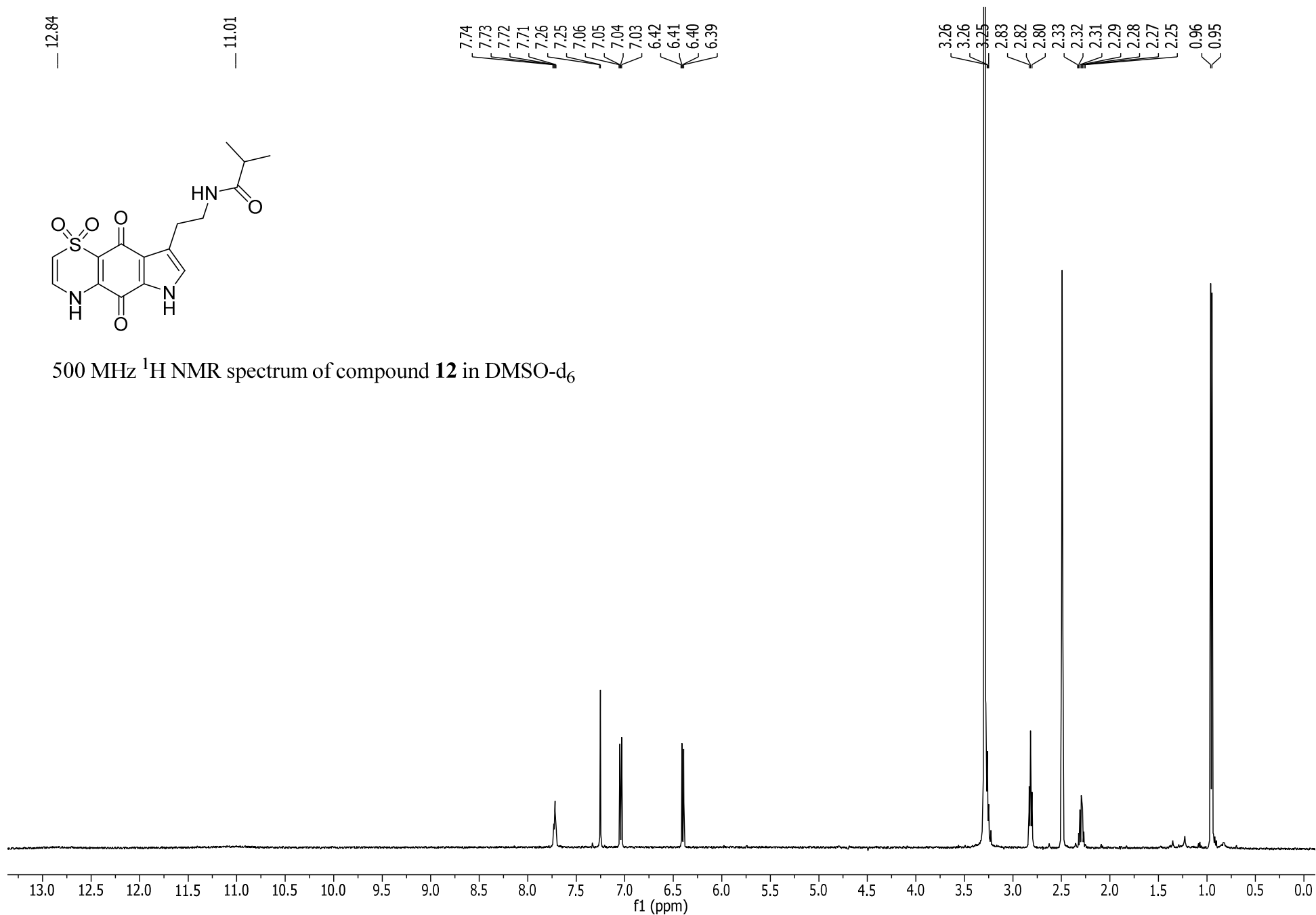


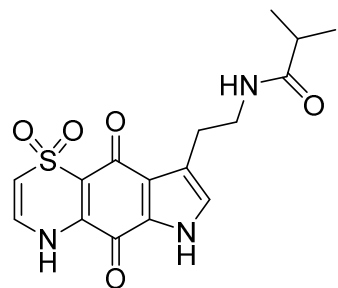
500 MHz ^1H NMR spectrum of compound **11** in DMSO-d_6



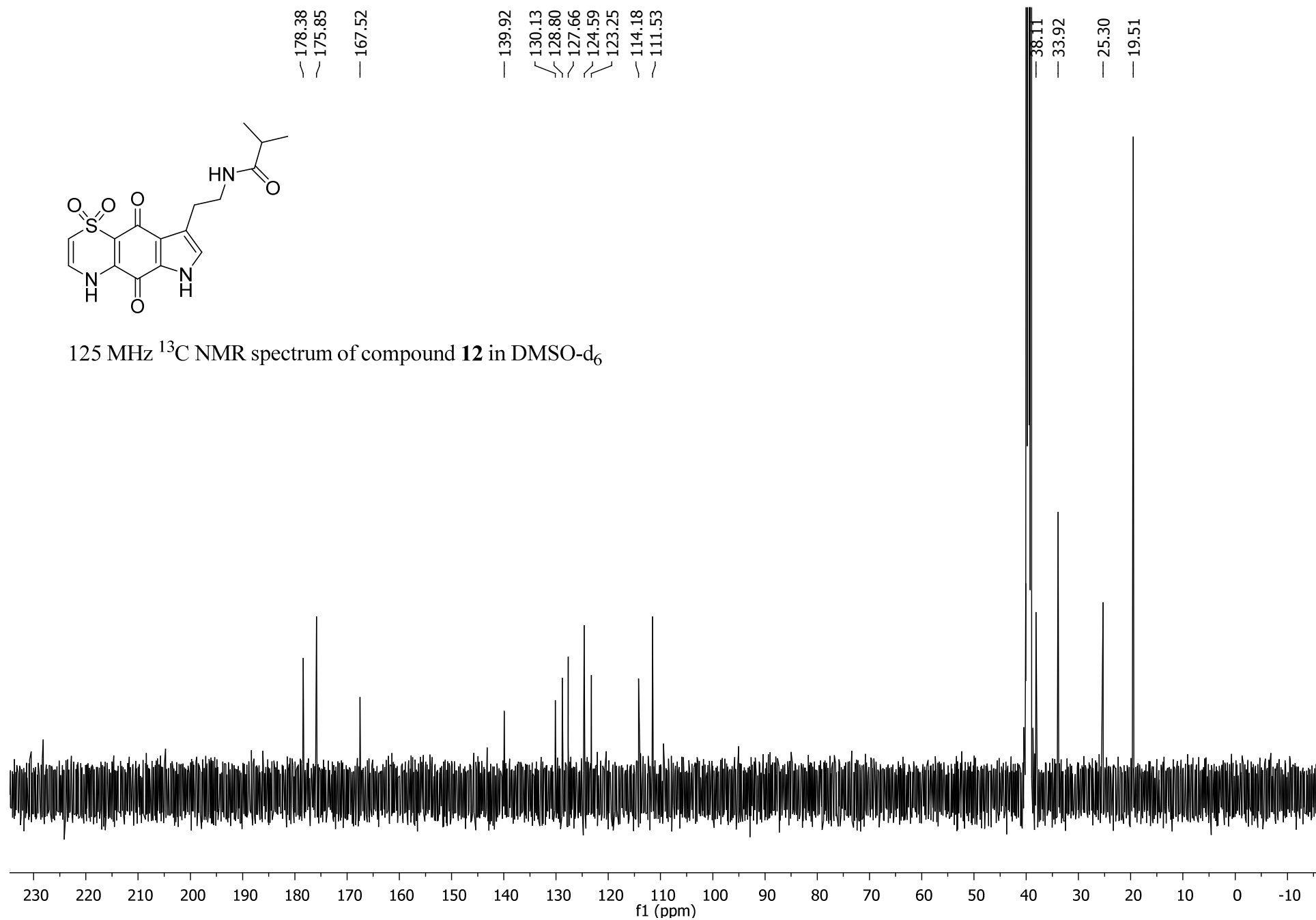


500 MHz ^1H NMR spectrum of compound **12** in DMSO-d_6





125 MHz ^{13}C NMR spectrum of compound **12** in DMSO-d_6

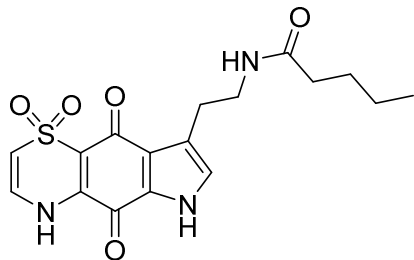


12.90
12.89

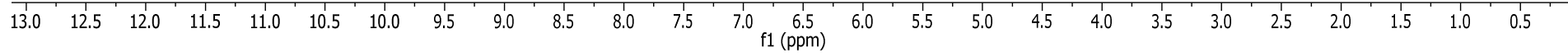
11.06
11.06

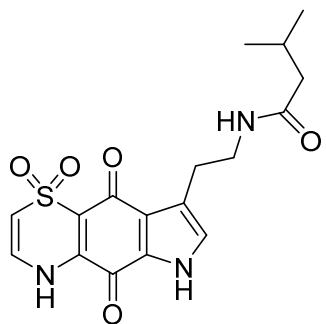
7.79
7.79
7.78
7.78
7.77
7.76
7.27
7.27
7.06
7.05
7.04
7.03
6.42
6.42
6.41
6.40

3.31
3.28
3.27
3.26
2.83
2.81
2.80
2.03
2.02
2.00
1.46
1.45
1.43
1.42
1.40
1.24
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1.21
1.20
1.18
1.17
0.84
0.83
0.81

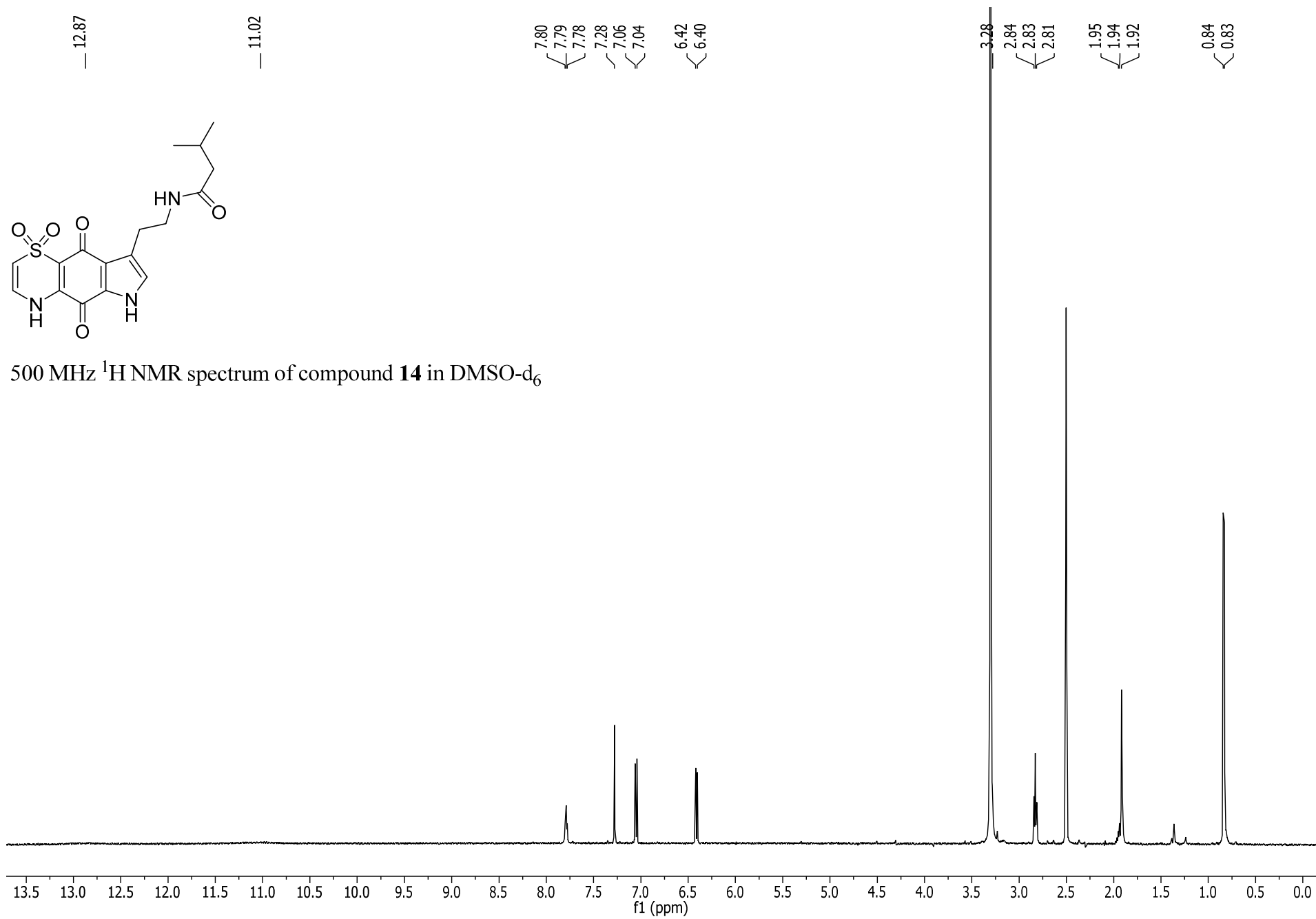


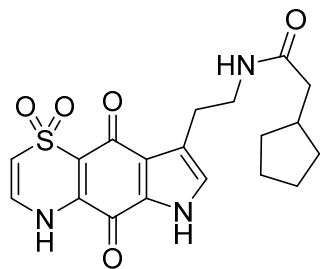
500 MHz ^1H NMR spectrum of compound **13** in DMSO-d_6



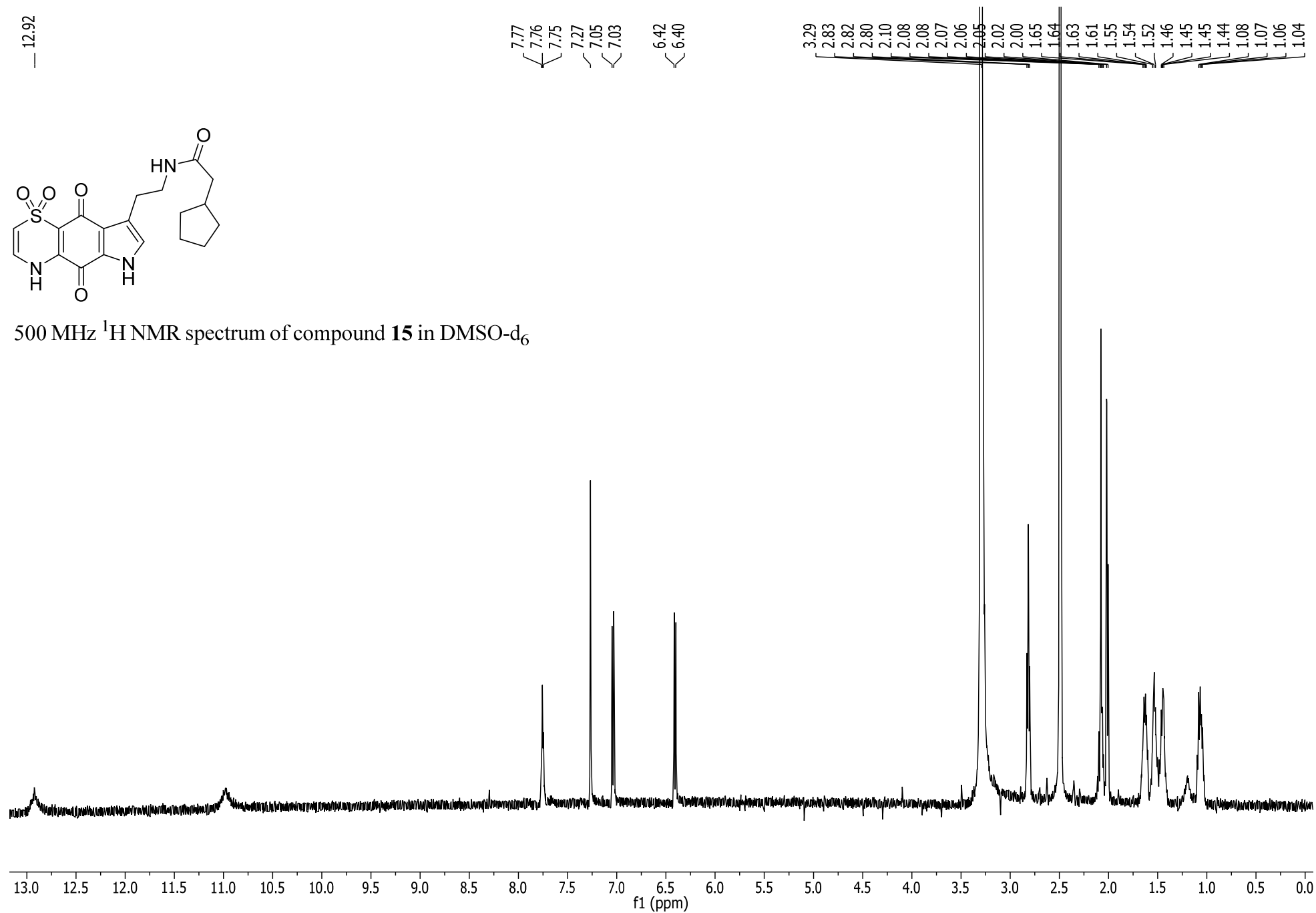


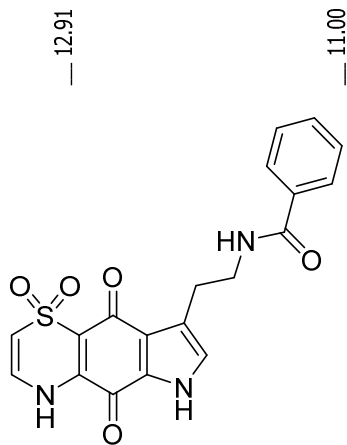
500 MHz ^1H NMR spectrum of compound **14** in DMSO-d_6



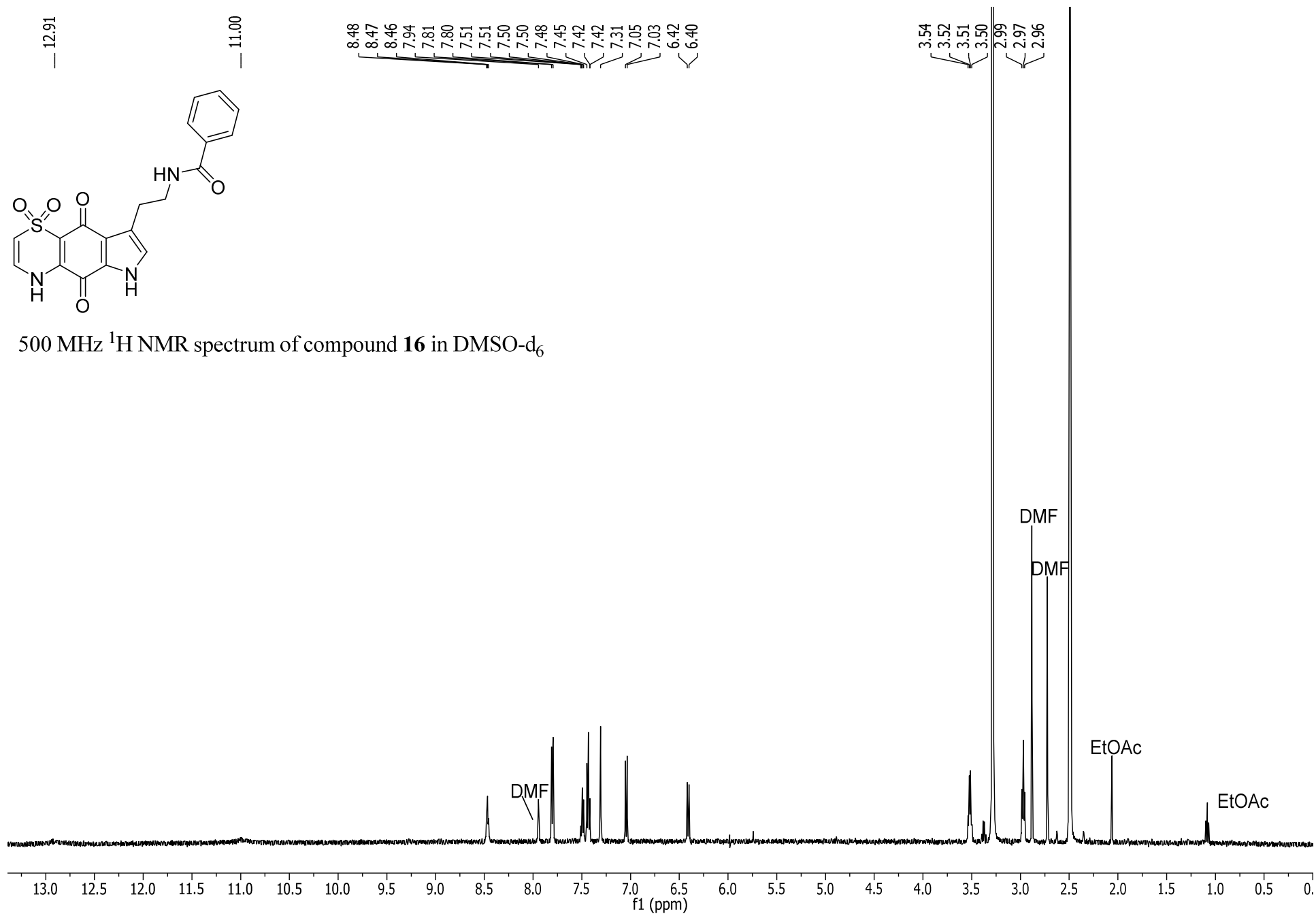


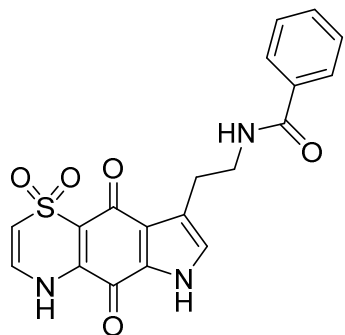
500 MHz ^1H NMR spectrum of compound **15** in DMSO-d_6



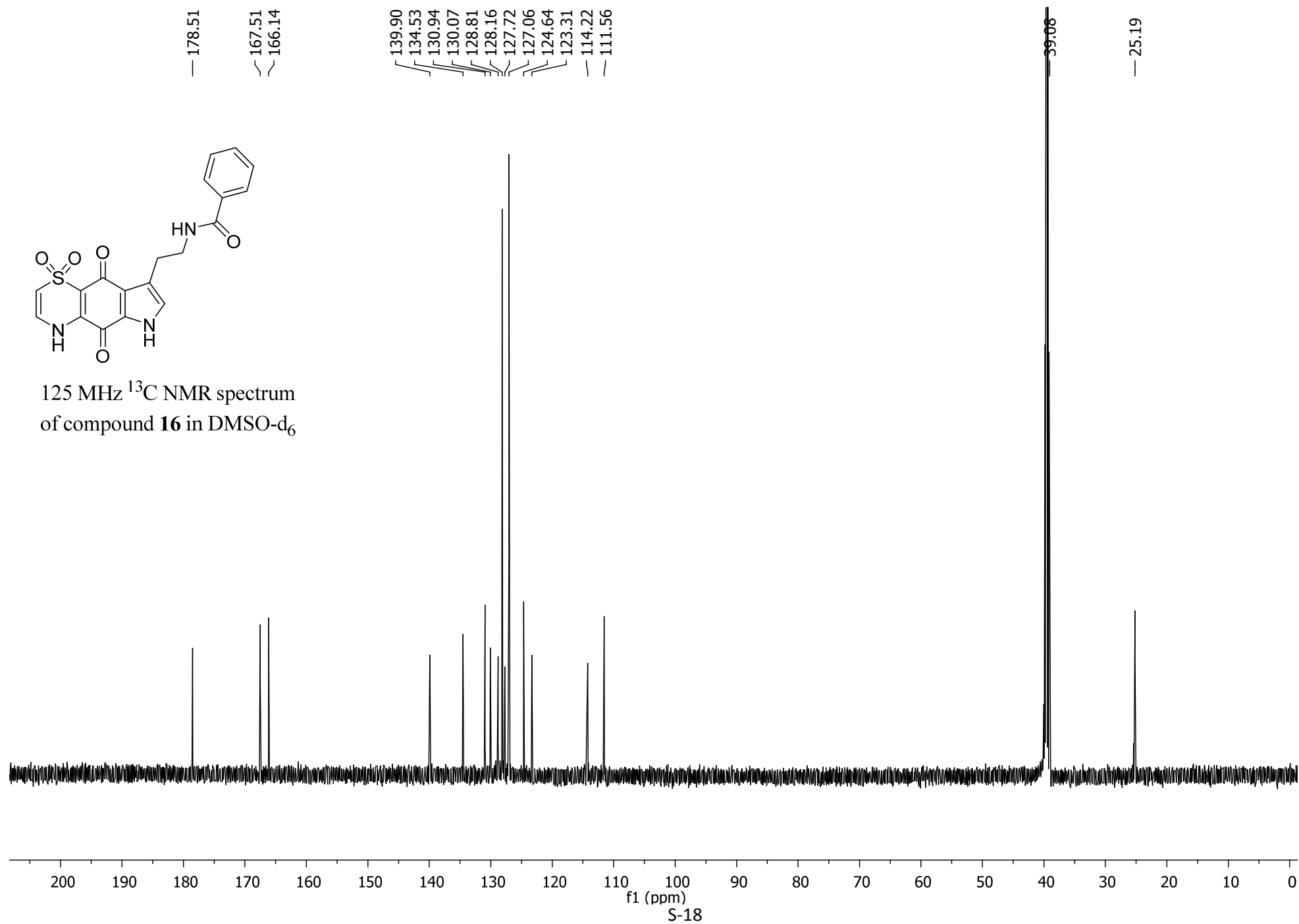


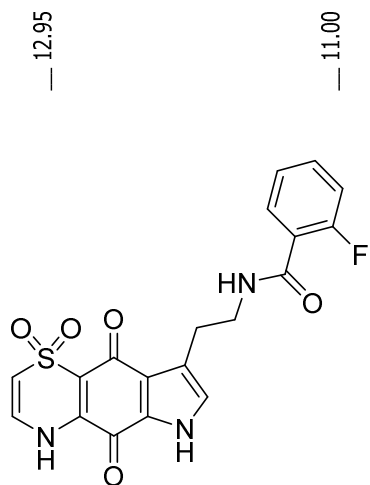
500 MHz ^1H NMR spectrum of compound **16** in DMSO-d_6



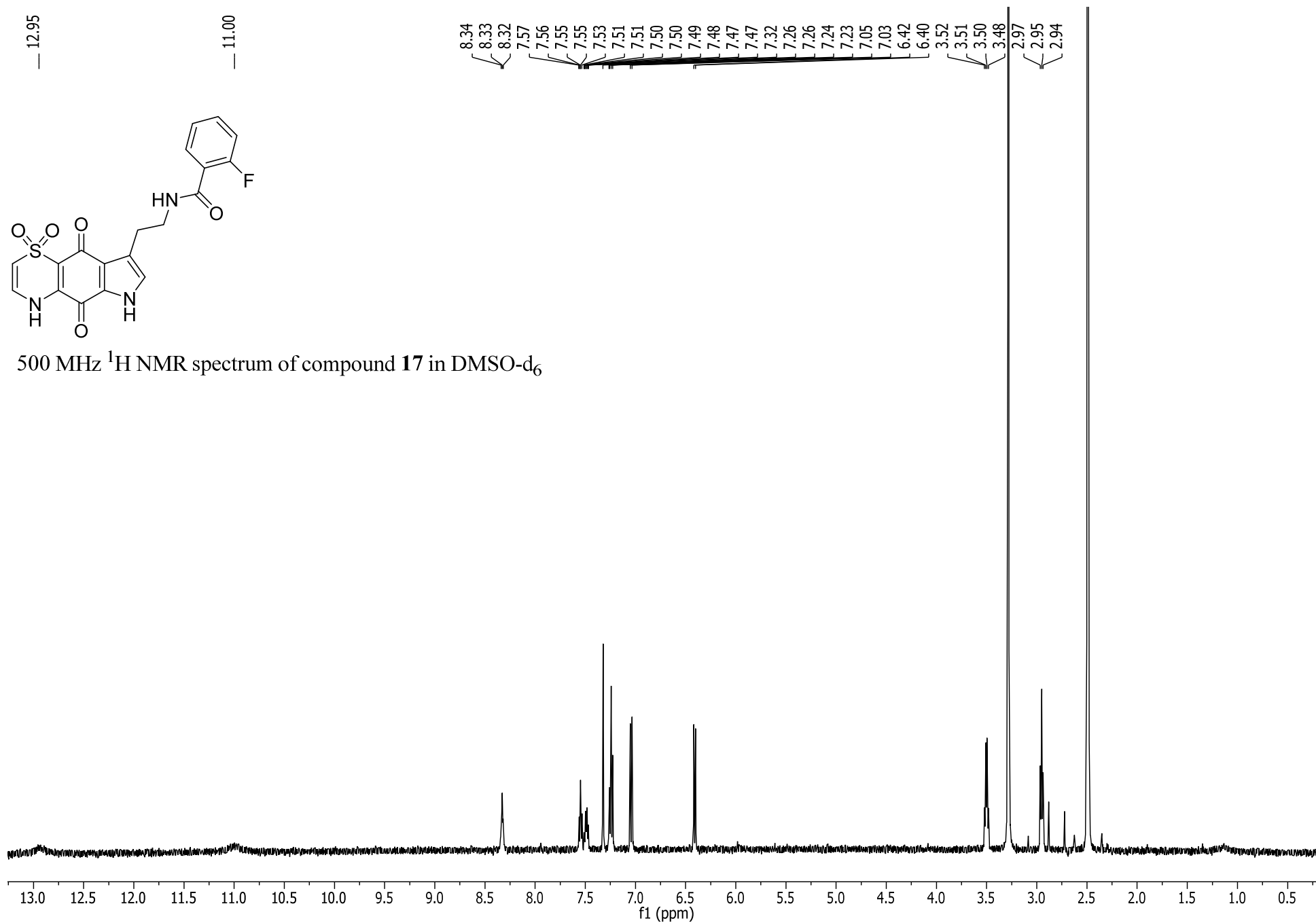


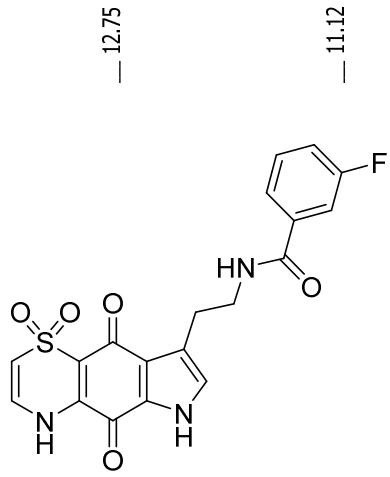
125 MHz ^{13}C NMR spectrum
of compound **16** in DMSO-d_6



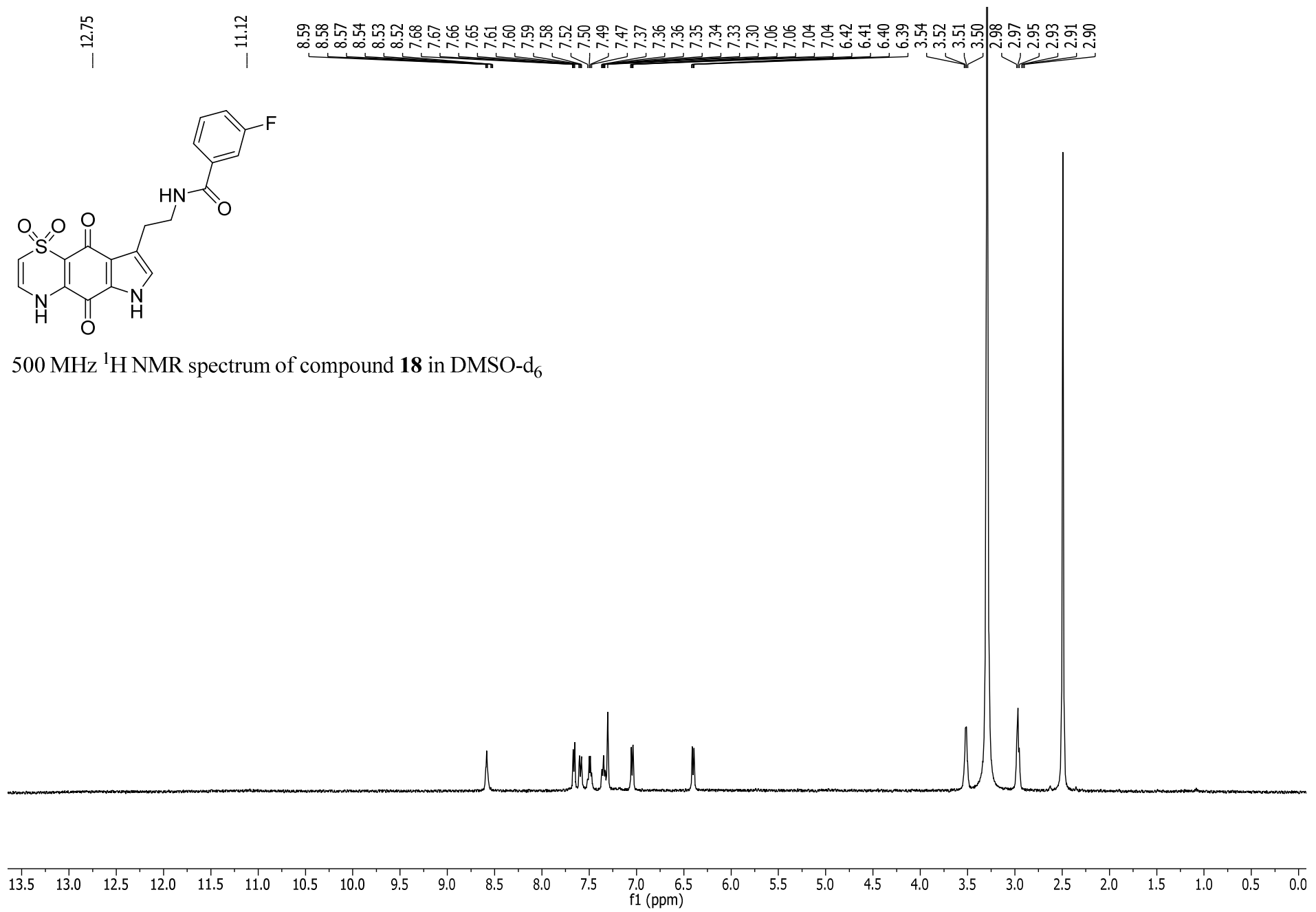


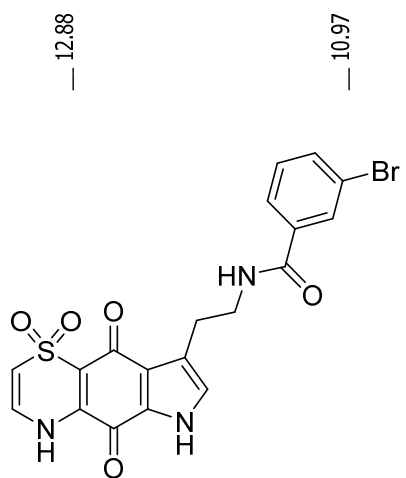
500 MHz ^1H NMR spectrum of compound **17** in DMSO-d_6



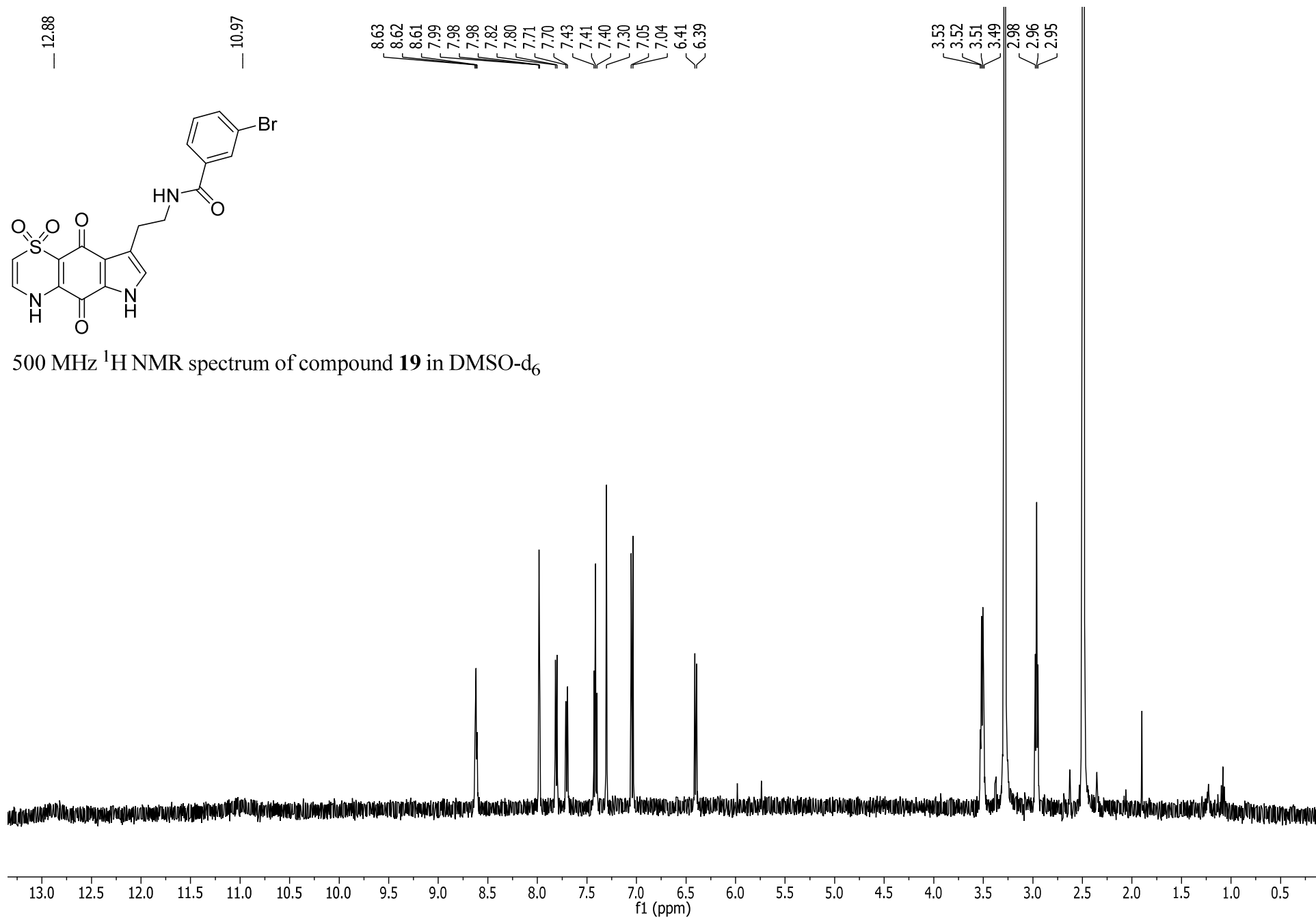


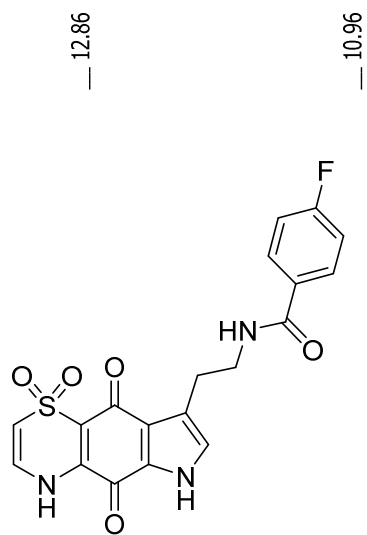
500 MHz ^1H NMR spectrum of compound **18** in DMSO-d_6



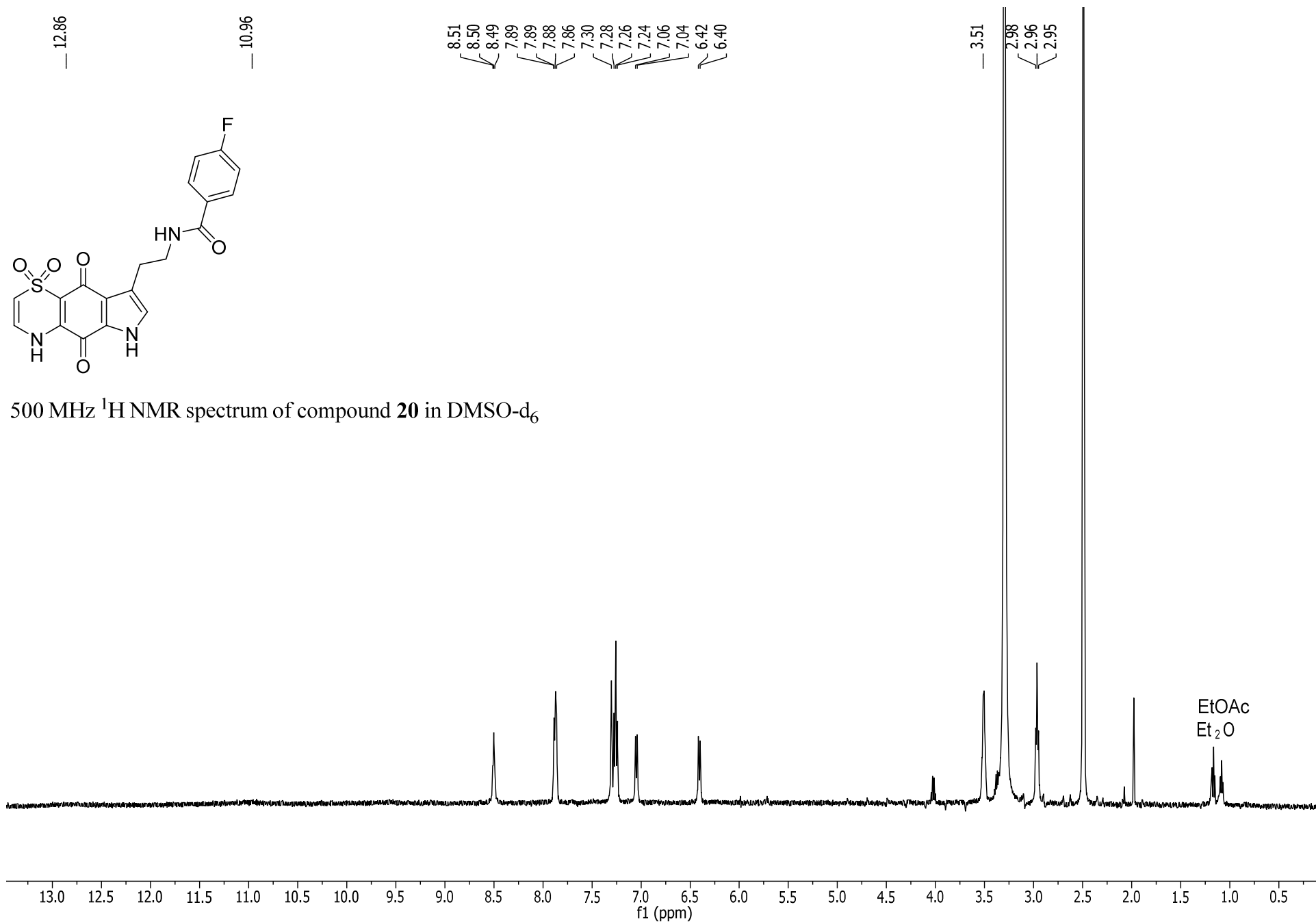


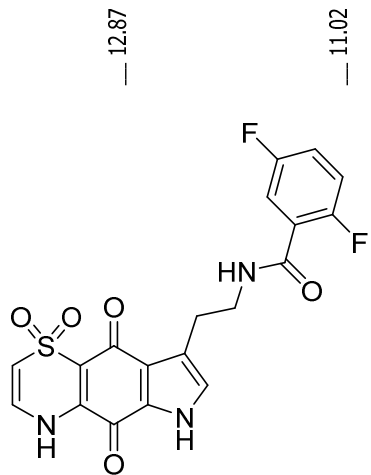
500 MHz ^1H NMR spectrum of compound **19** in DMSO-d_6



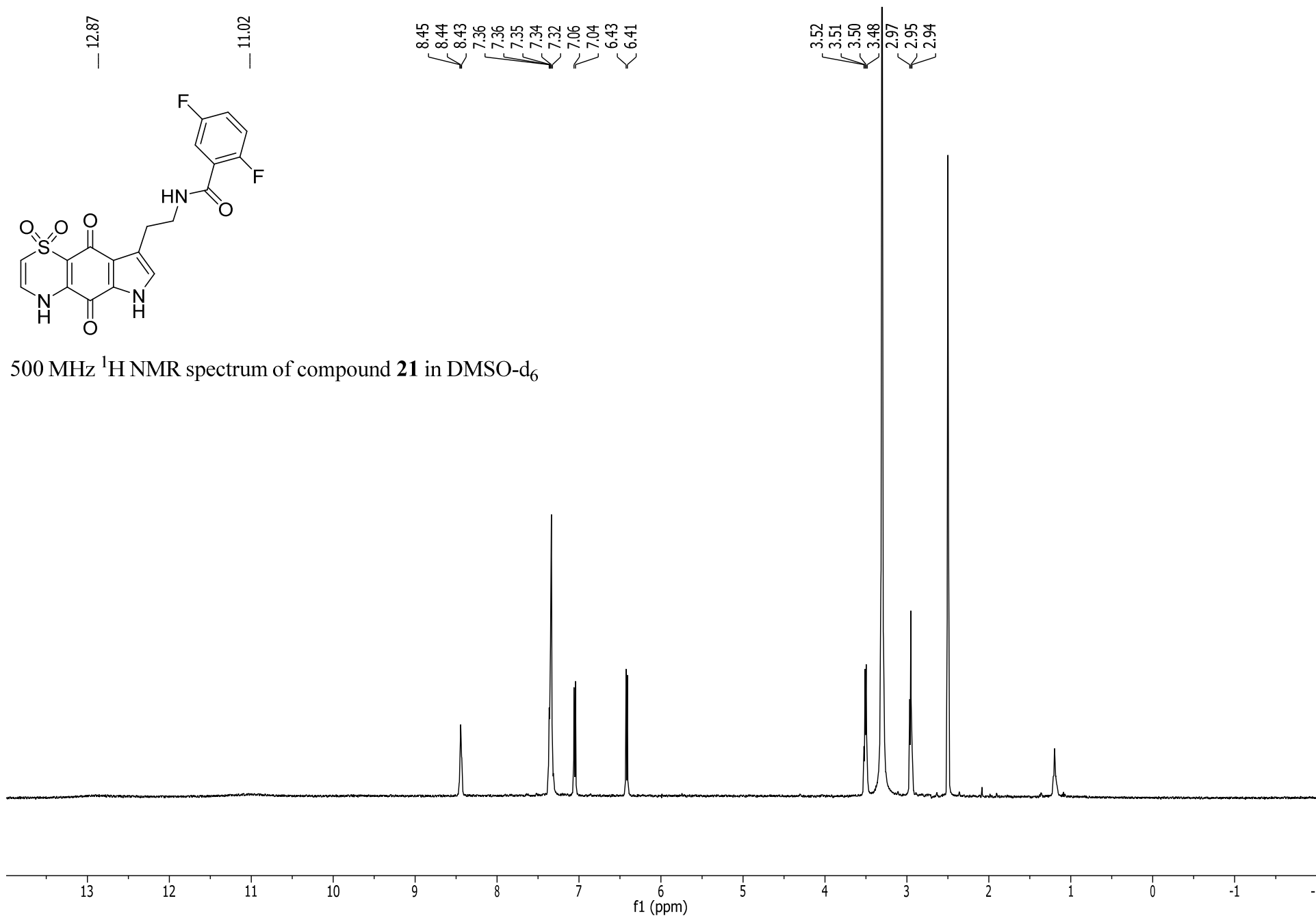


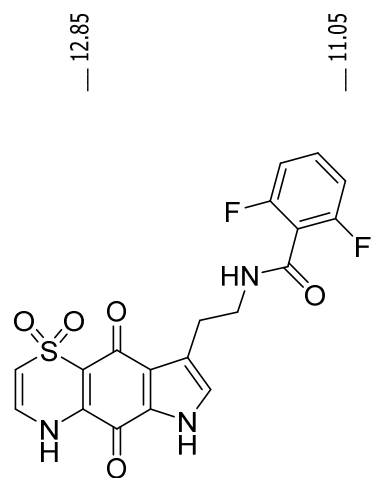
500 MHz ^1H NMR spectrum of compound **20** in DMSO-d_6



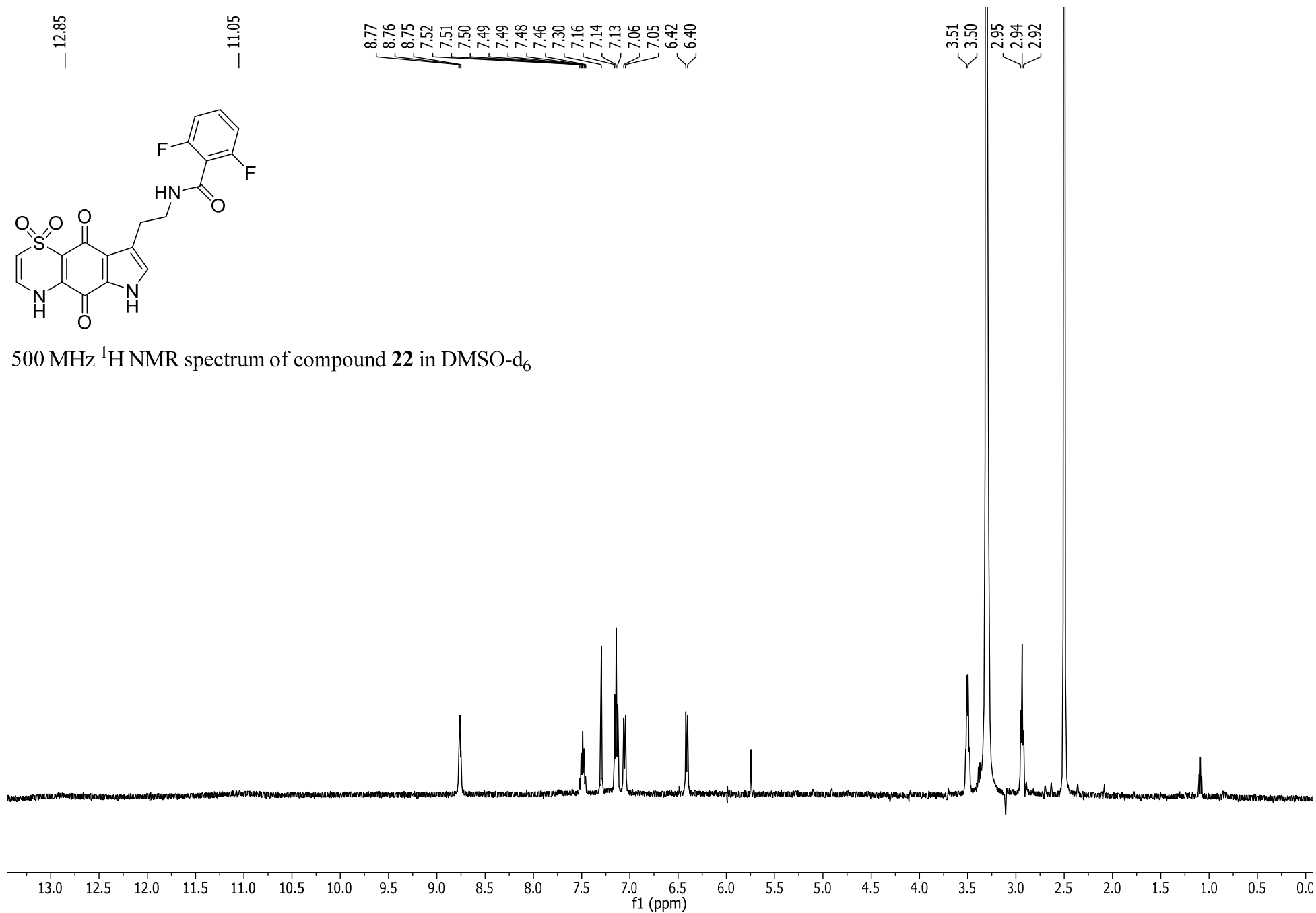


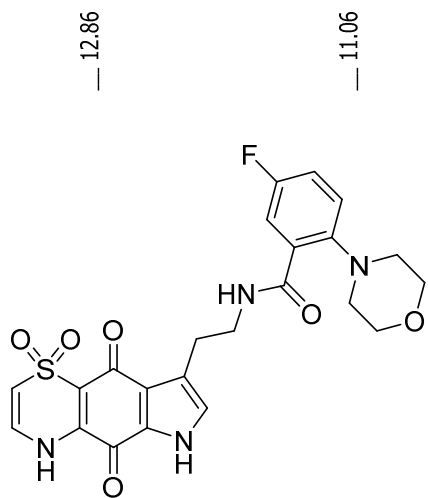
500 MHz ^1H NMR spectrum of compound **21** in DMSO-d_6



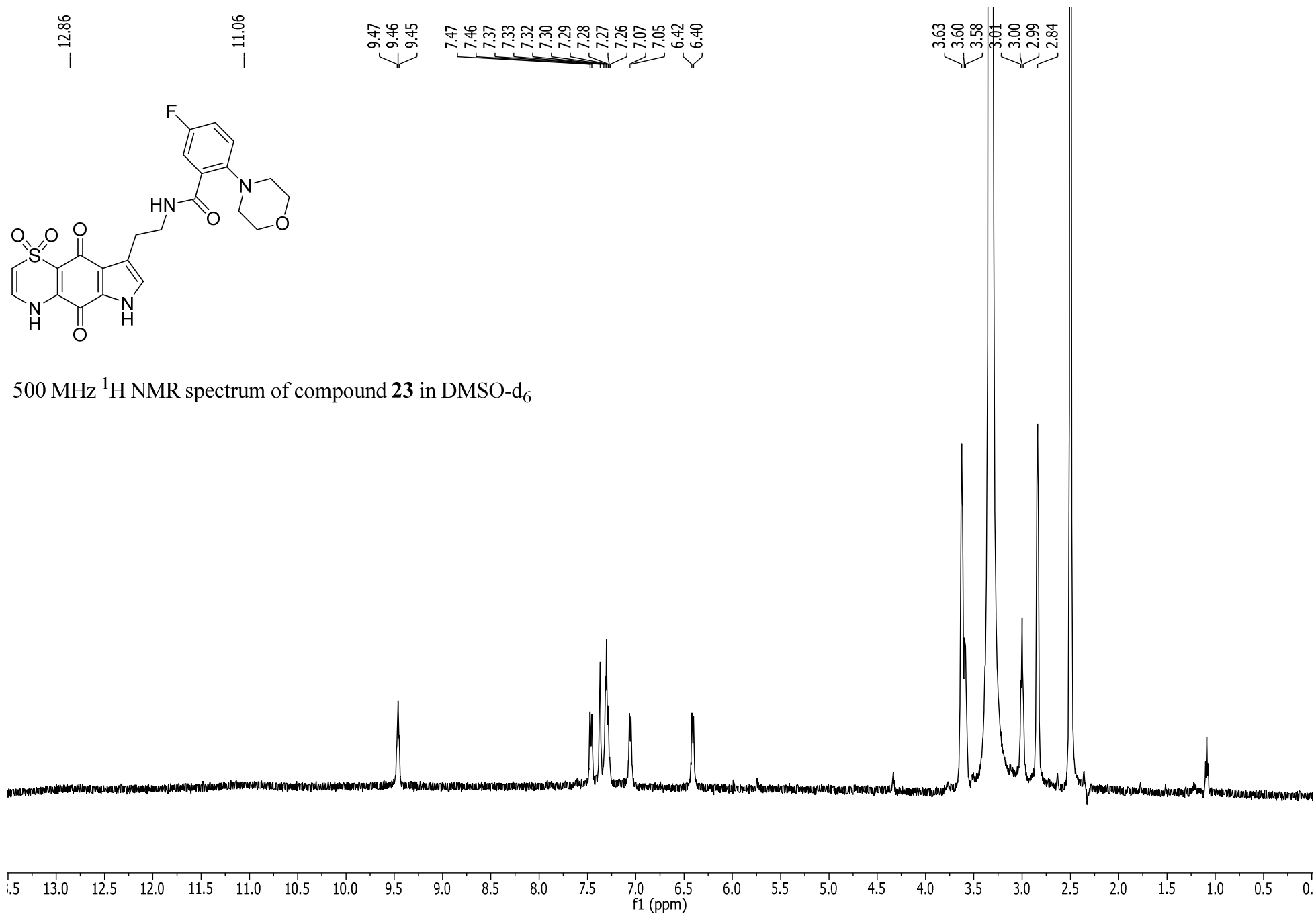


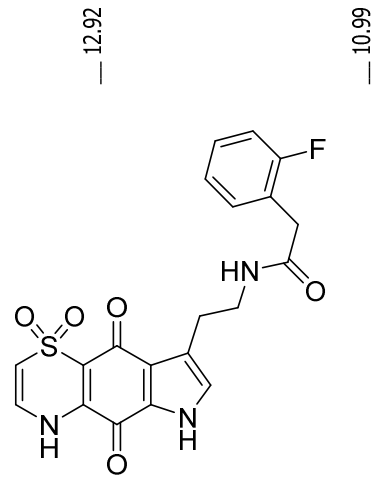
500 MHz ^1H NMR spectrum of compound **22** in DMSO- d_6



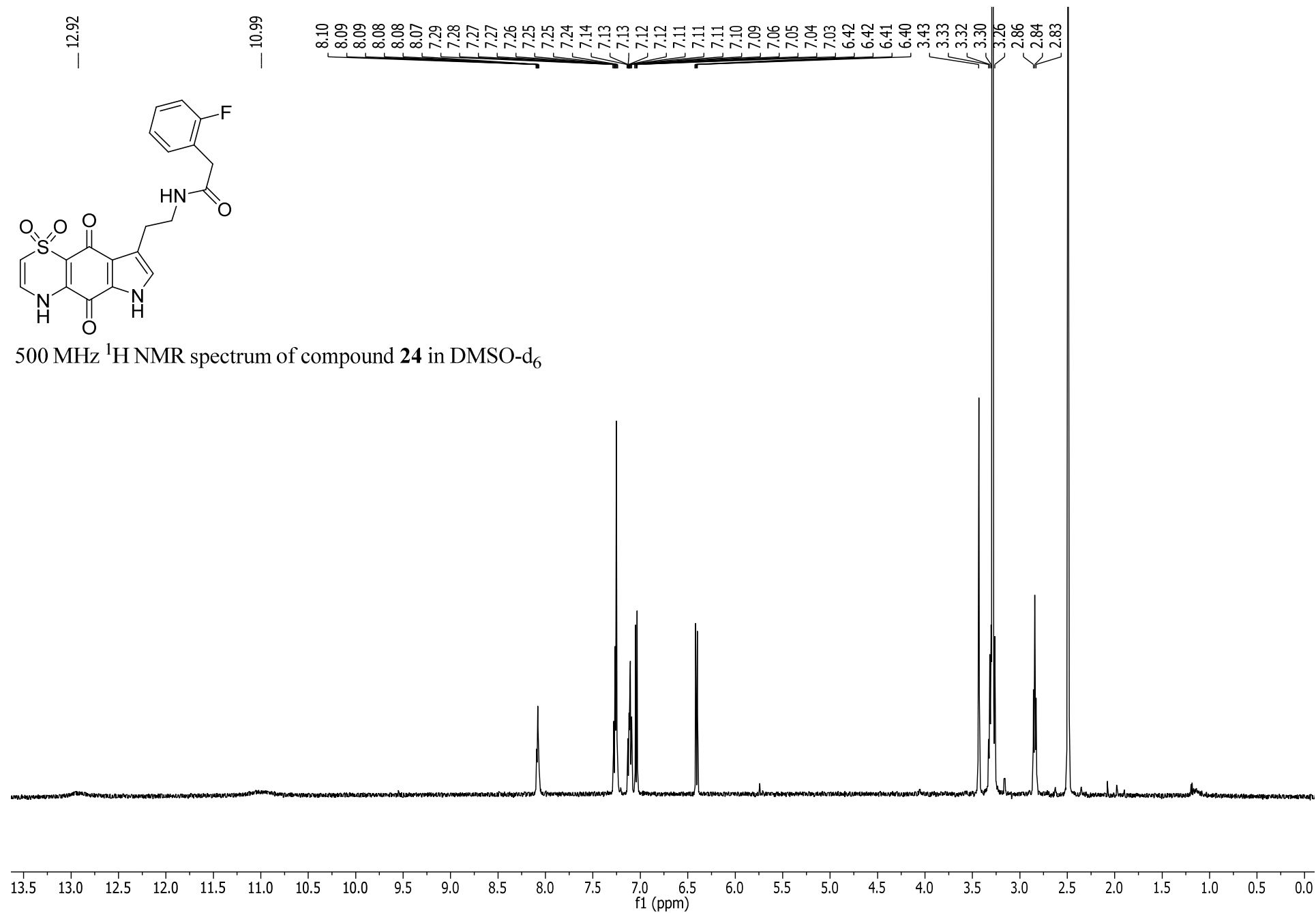


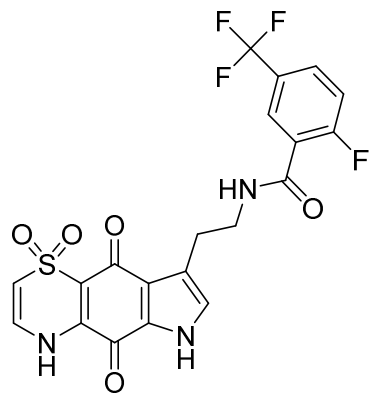
500 MHz ^1H NMR spectrum of compound **23** in DMSO- d_6





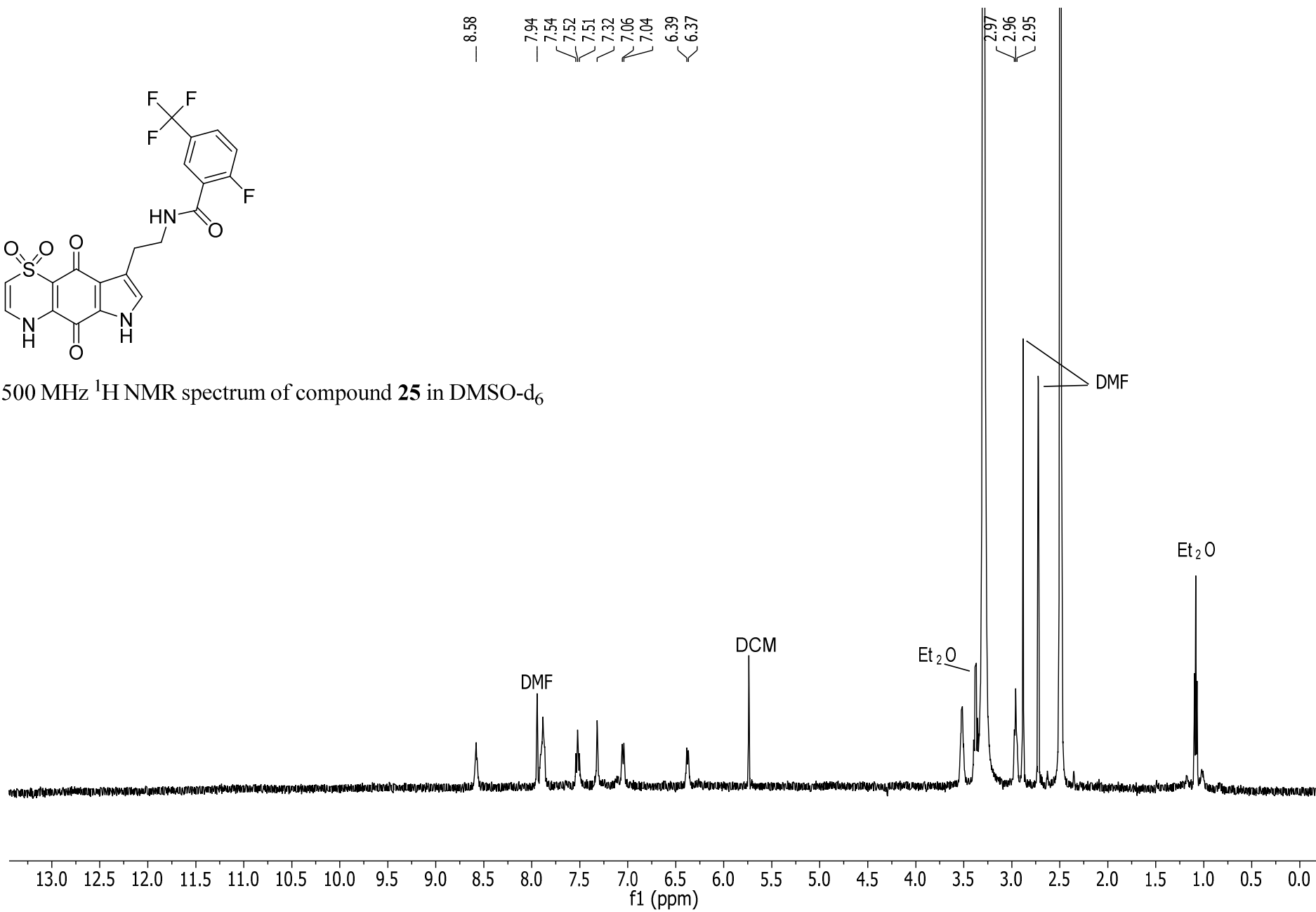
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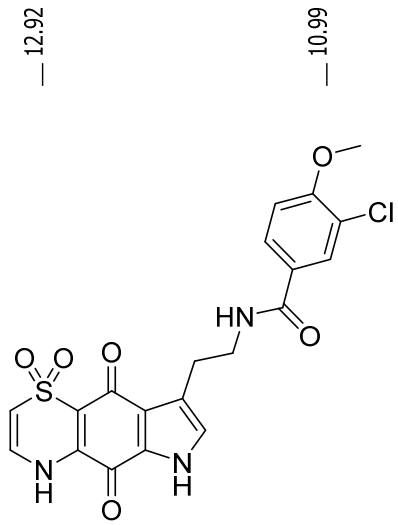




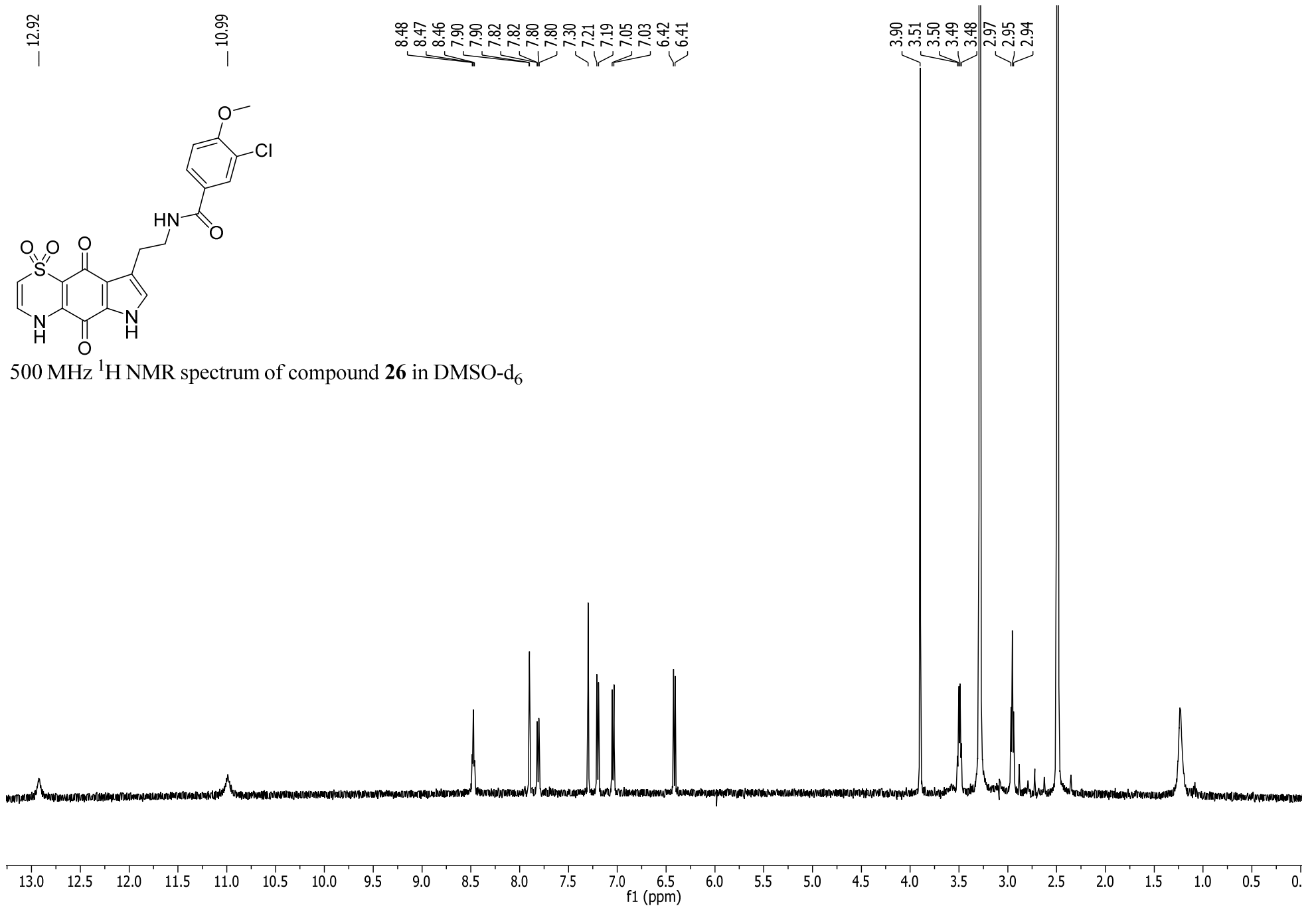
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7.04
6.39
6.37

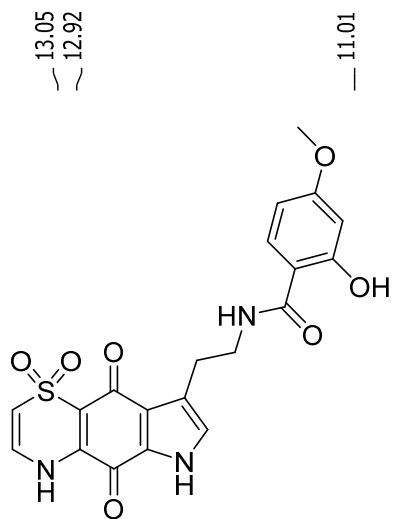
500 MHz ^1H NMR spectrum of compound **25** in DMSO-d_6



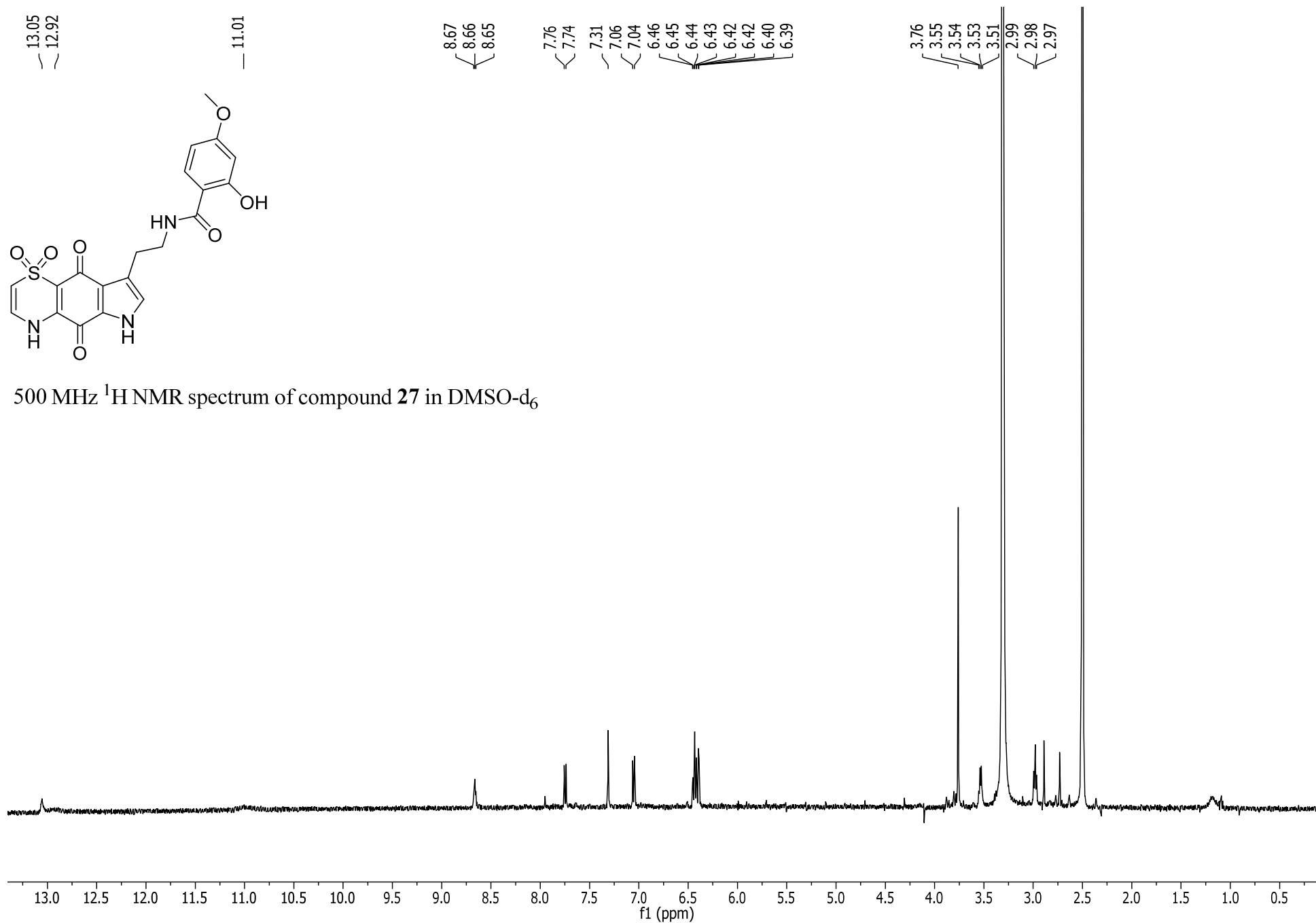


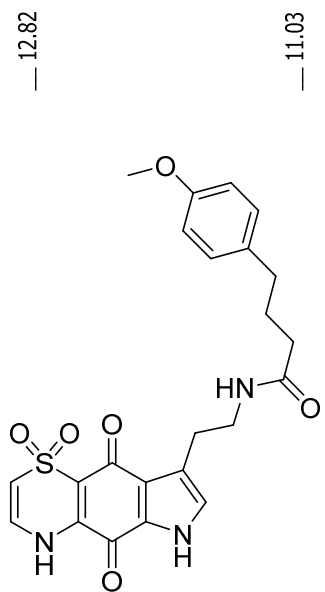
500 MHz ^1H NMR spectrum of compound **26** in DMSO-d_6



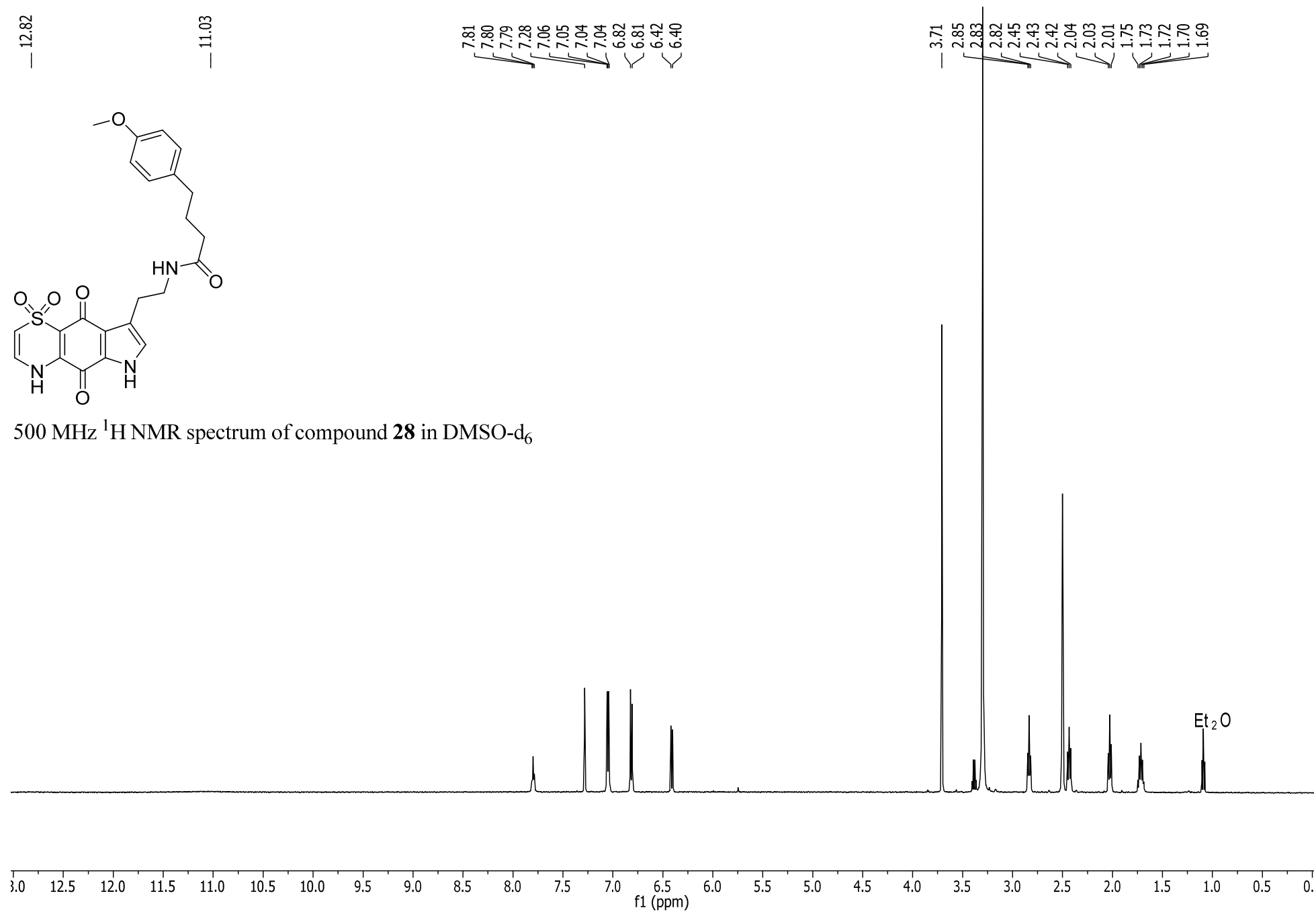


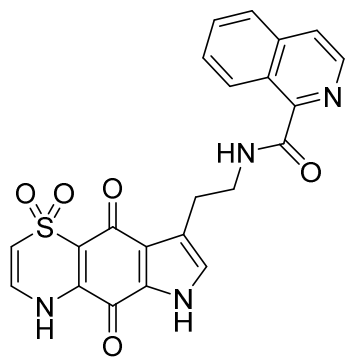
500 MHz ^1H NMR spectrum of compound **27** in DMSO-d_6



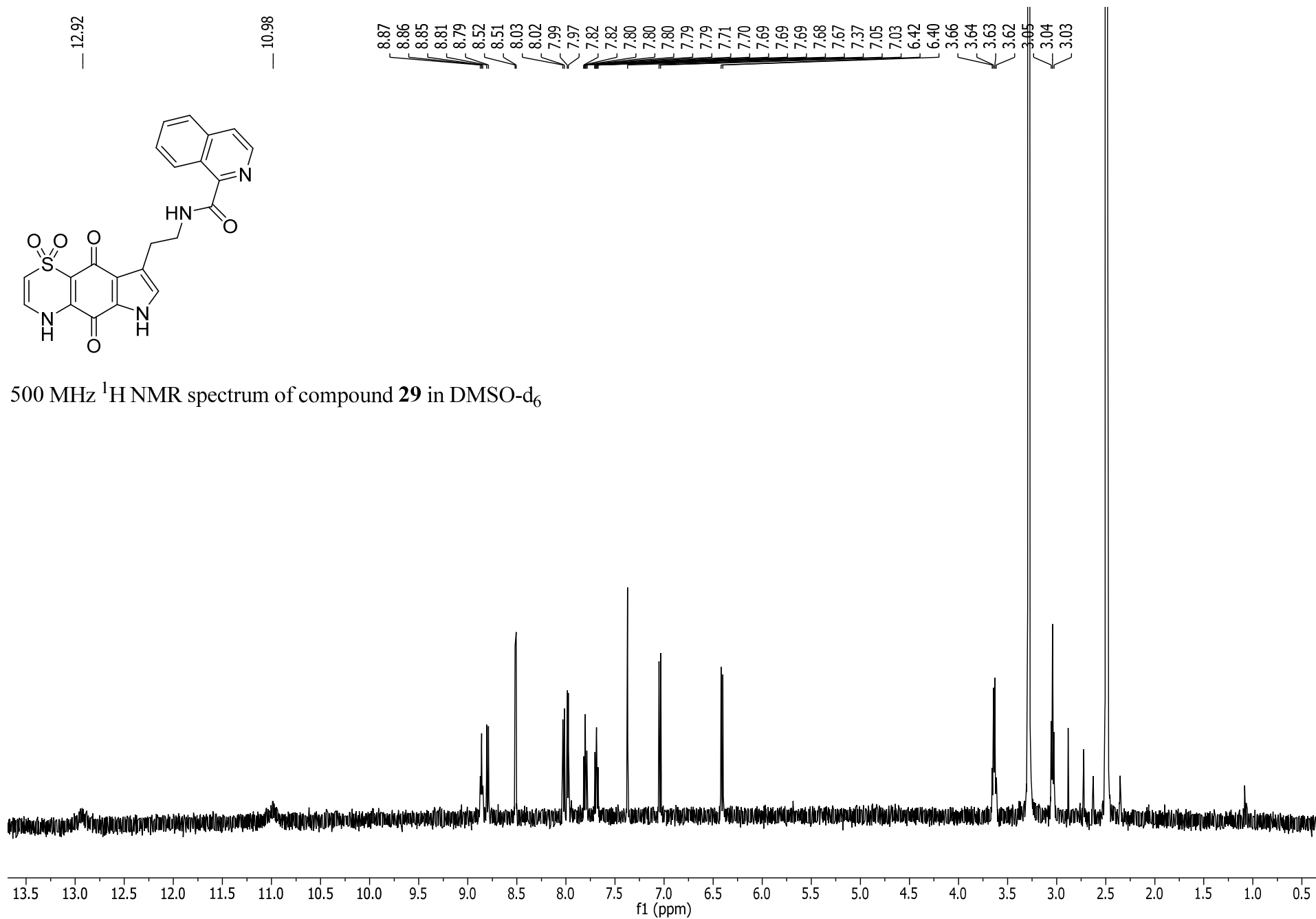


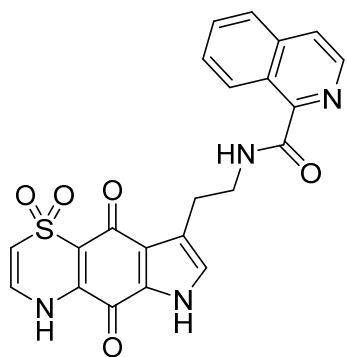
500 MHz ^1H NMR spectrum of compound **28** in DMSO-d_6



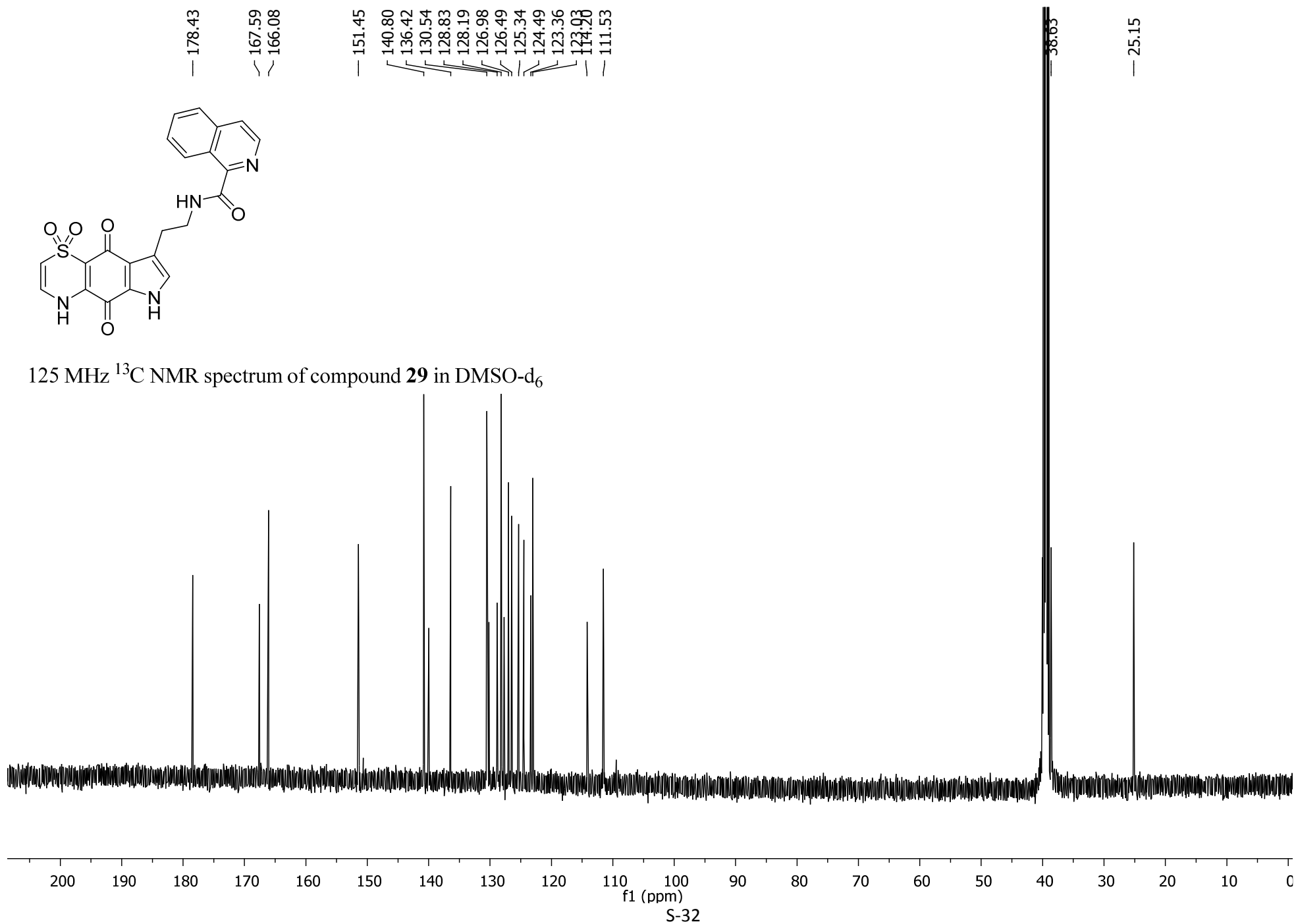


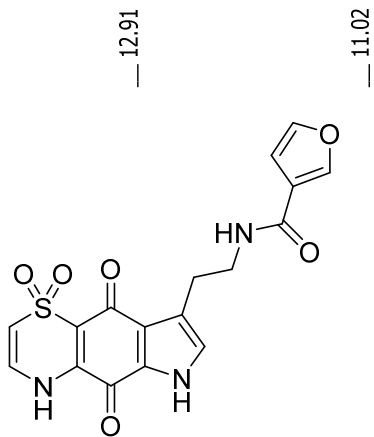
500 MHz ^1H NMR spectrum of compound **29** in DMSO-d_6



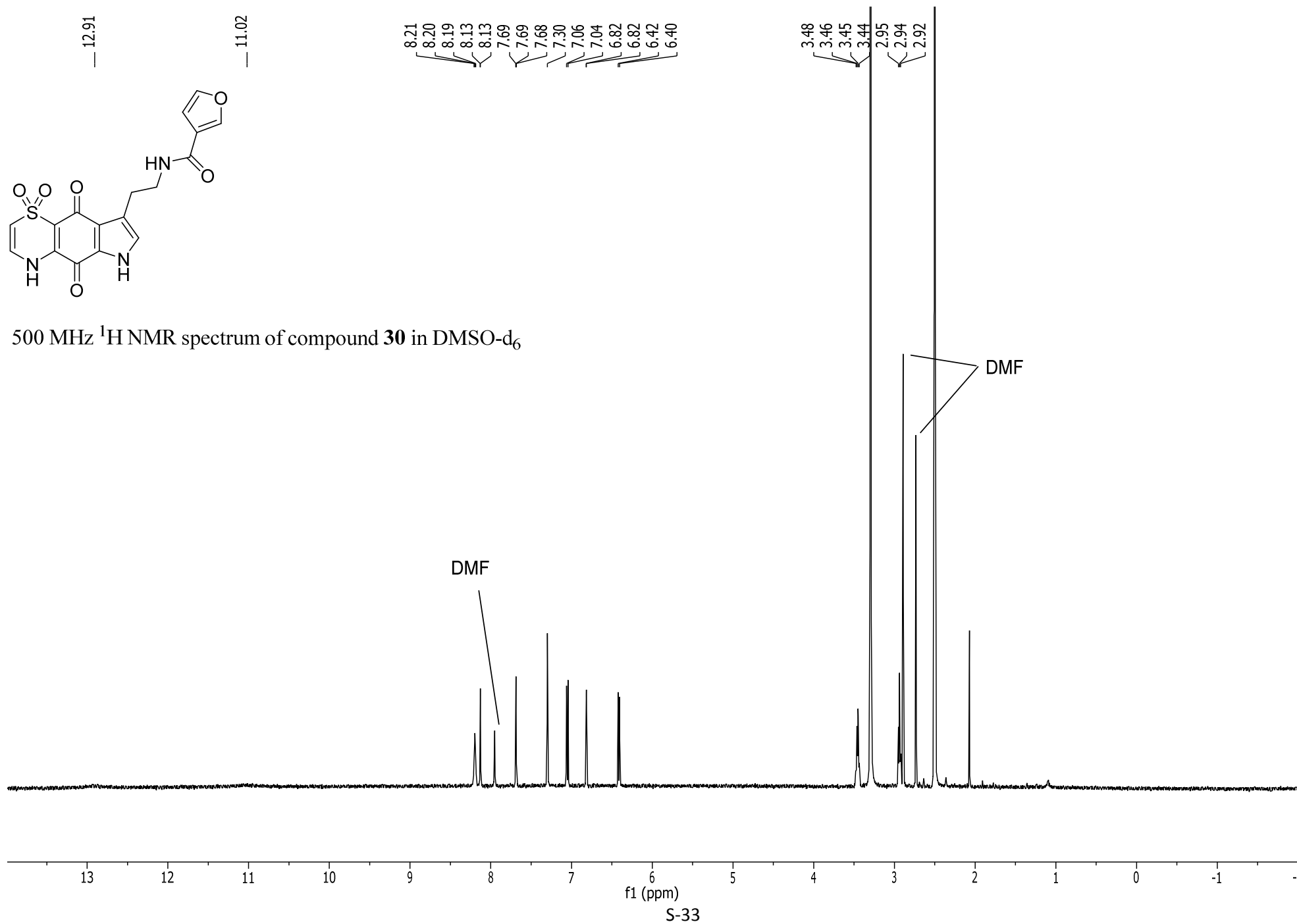


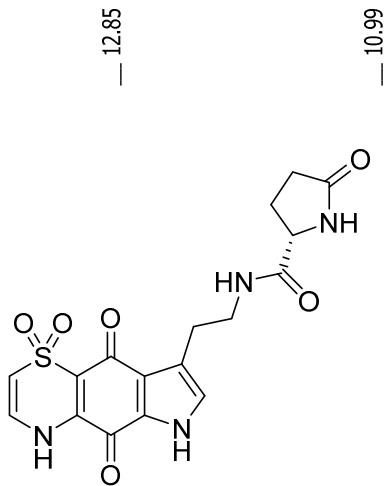
125 MHz ^{13}C NMR spectrum of compound **29** in DMSO-d_6



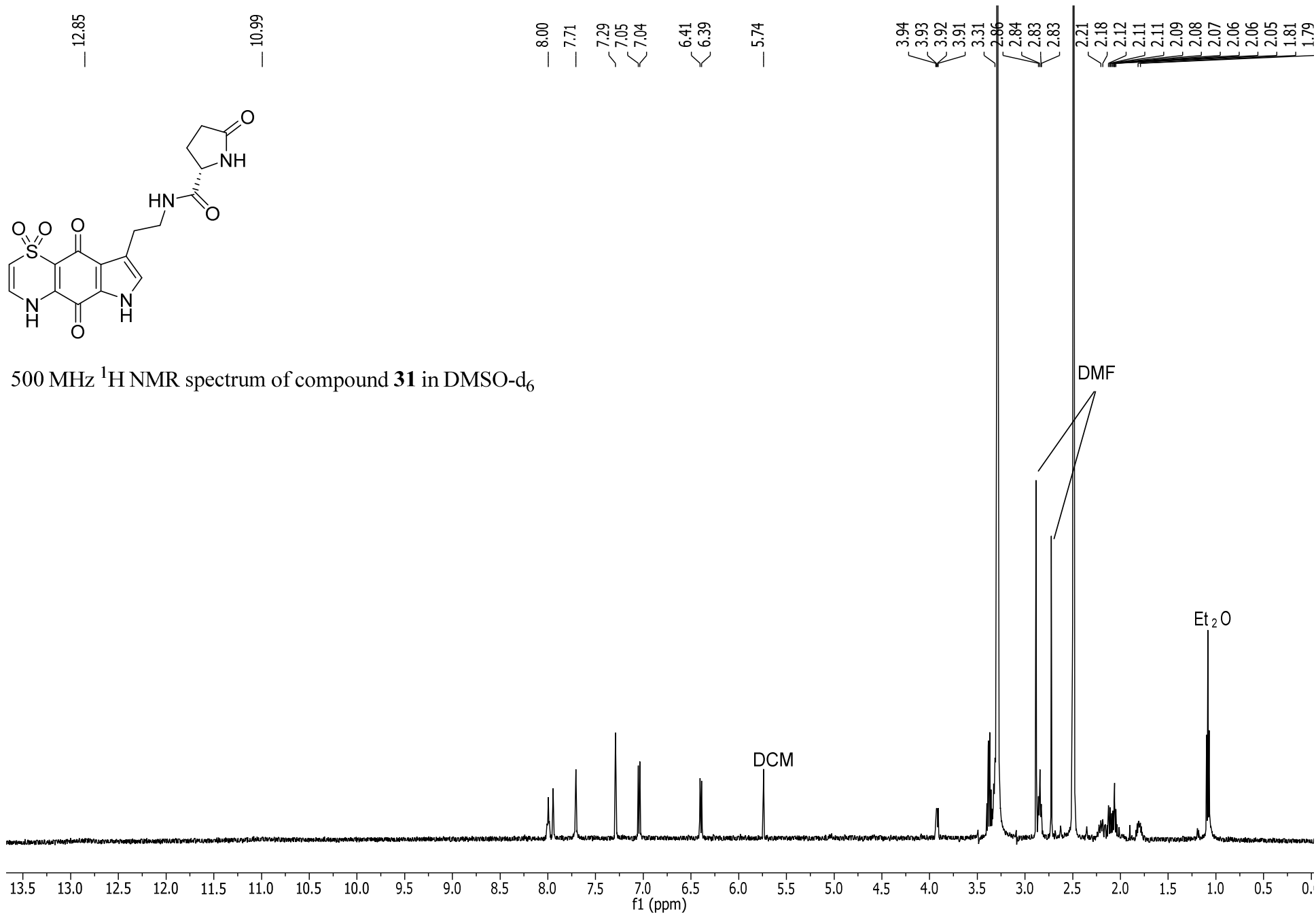


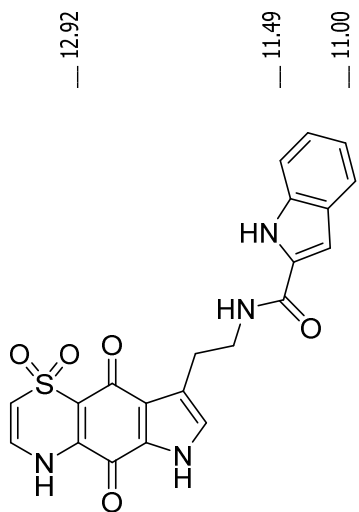
500 MHz ^1H NMR spectrum of compound **30** in DMSO-d_6



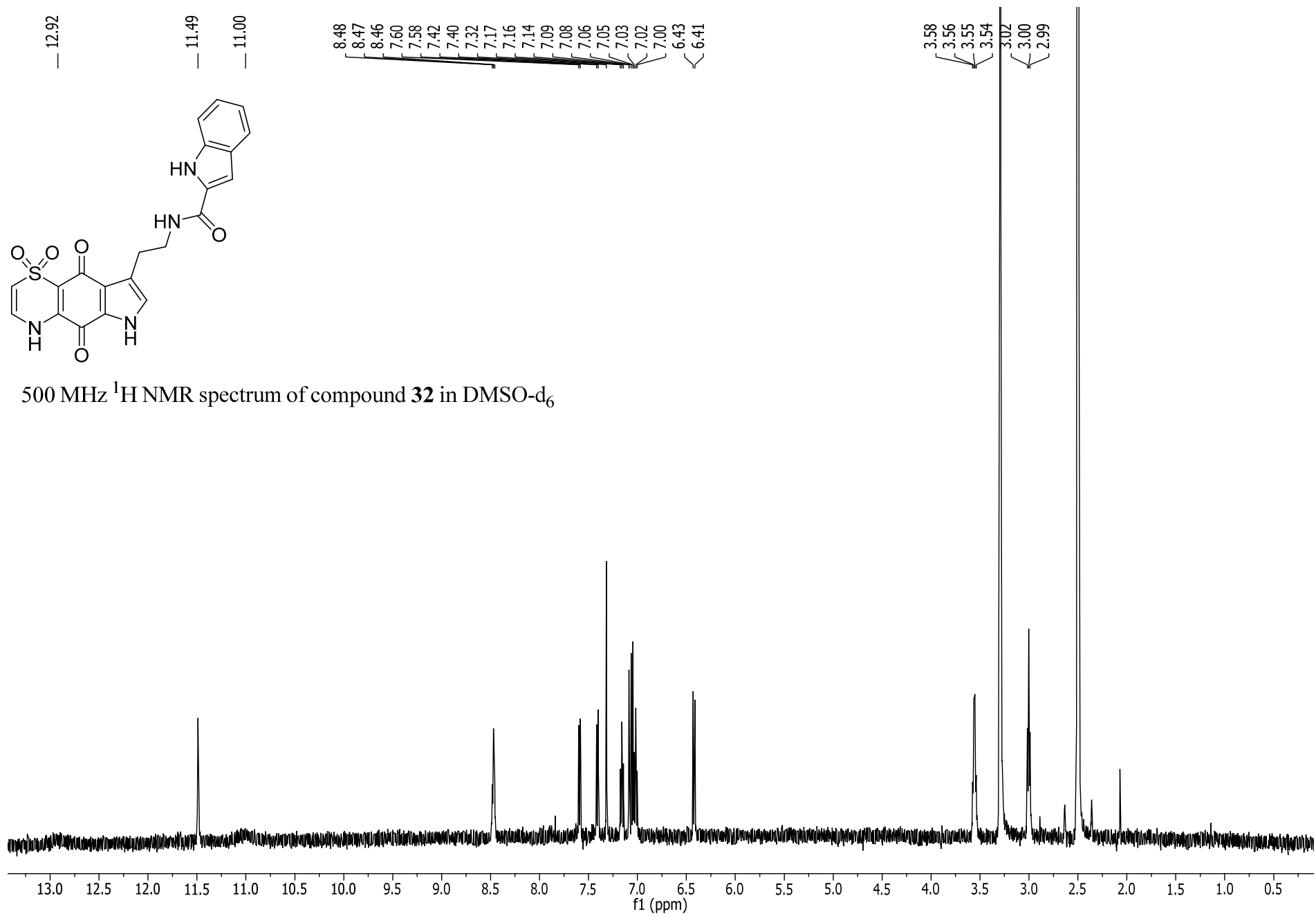


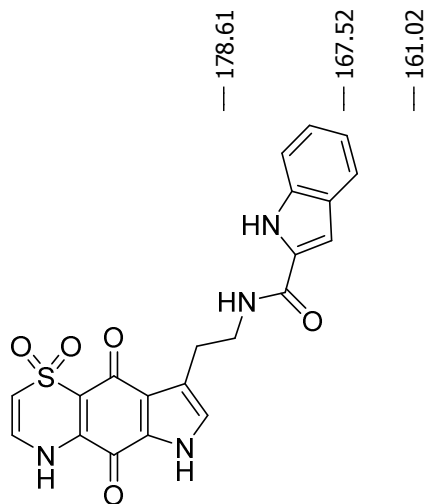
500 MHz ^1H NMR spectrum of compound **31** in DMSO-d_6



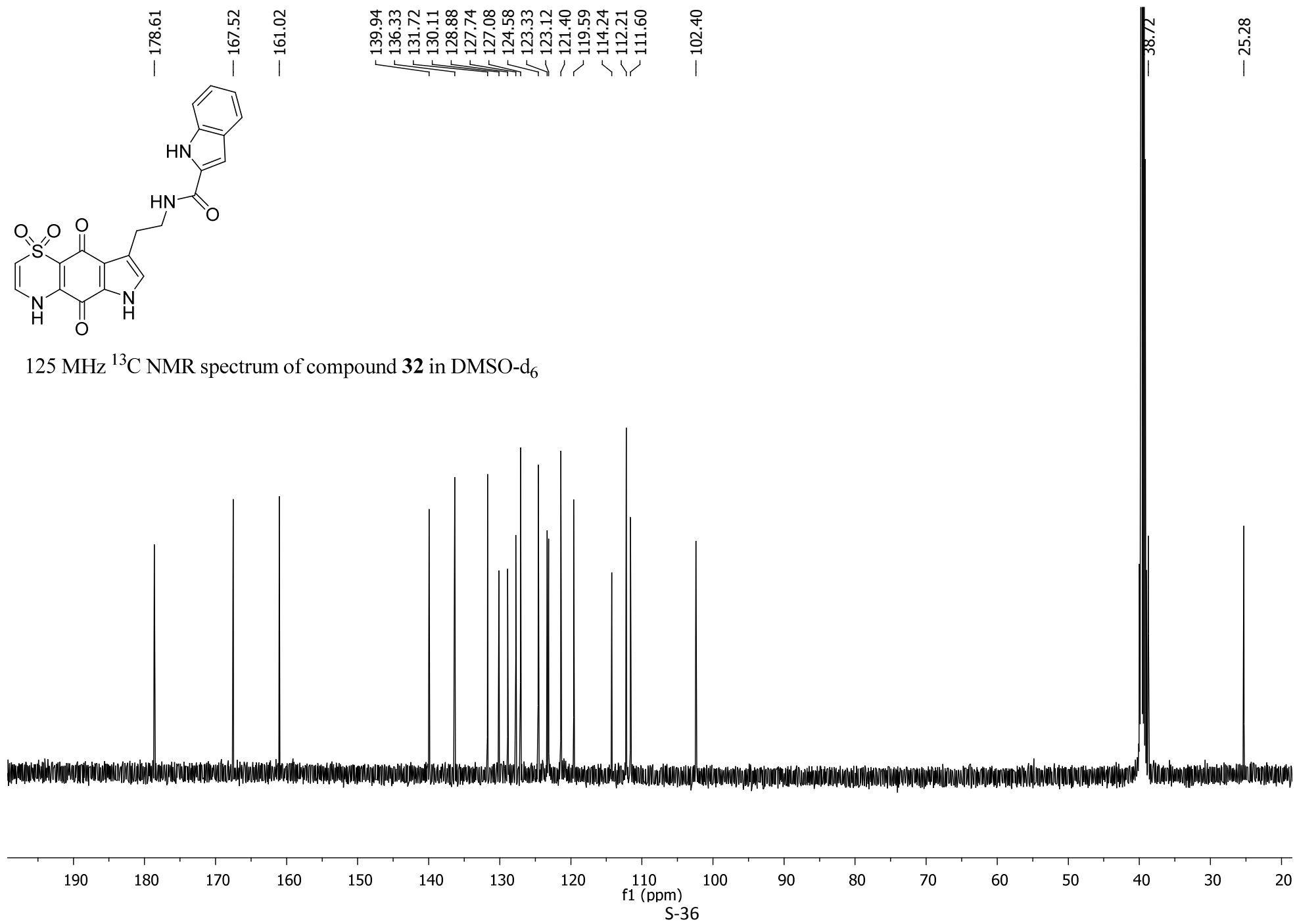


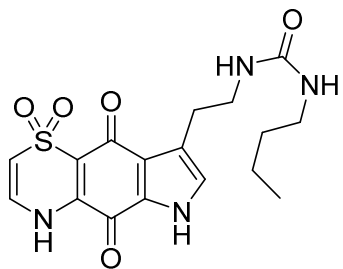
500 MHz ^1H NMR spectrum of compound **32** in DMSO-d_6



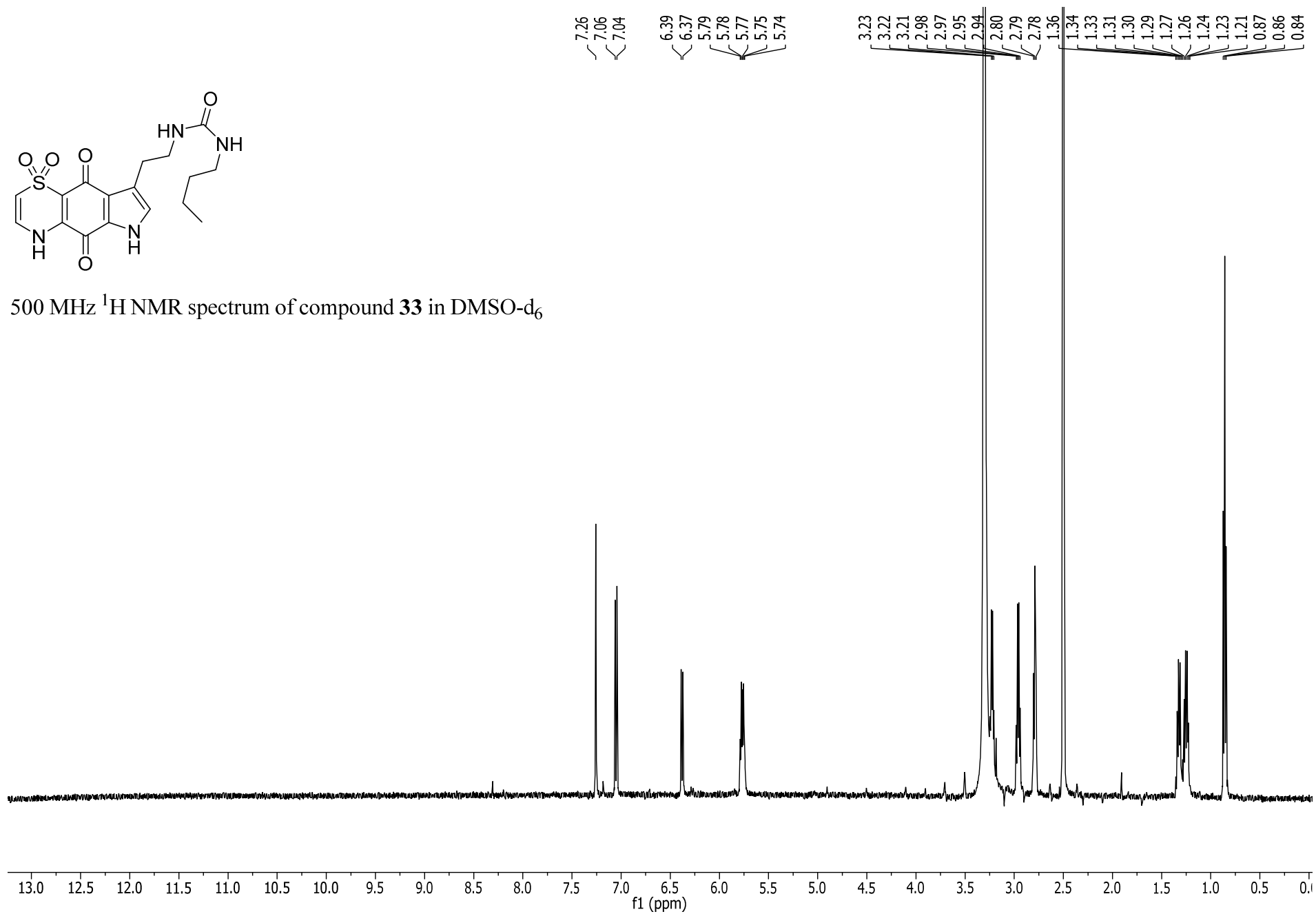


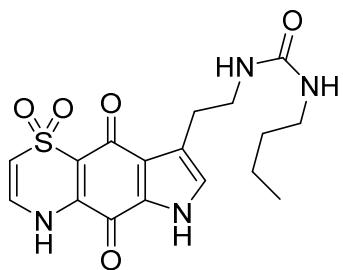
125 MHz ^{13}C NMR spectrum of compound **32** in DMSO-d_6



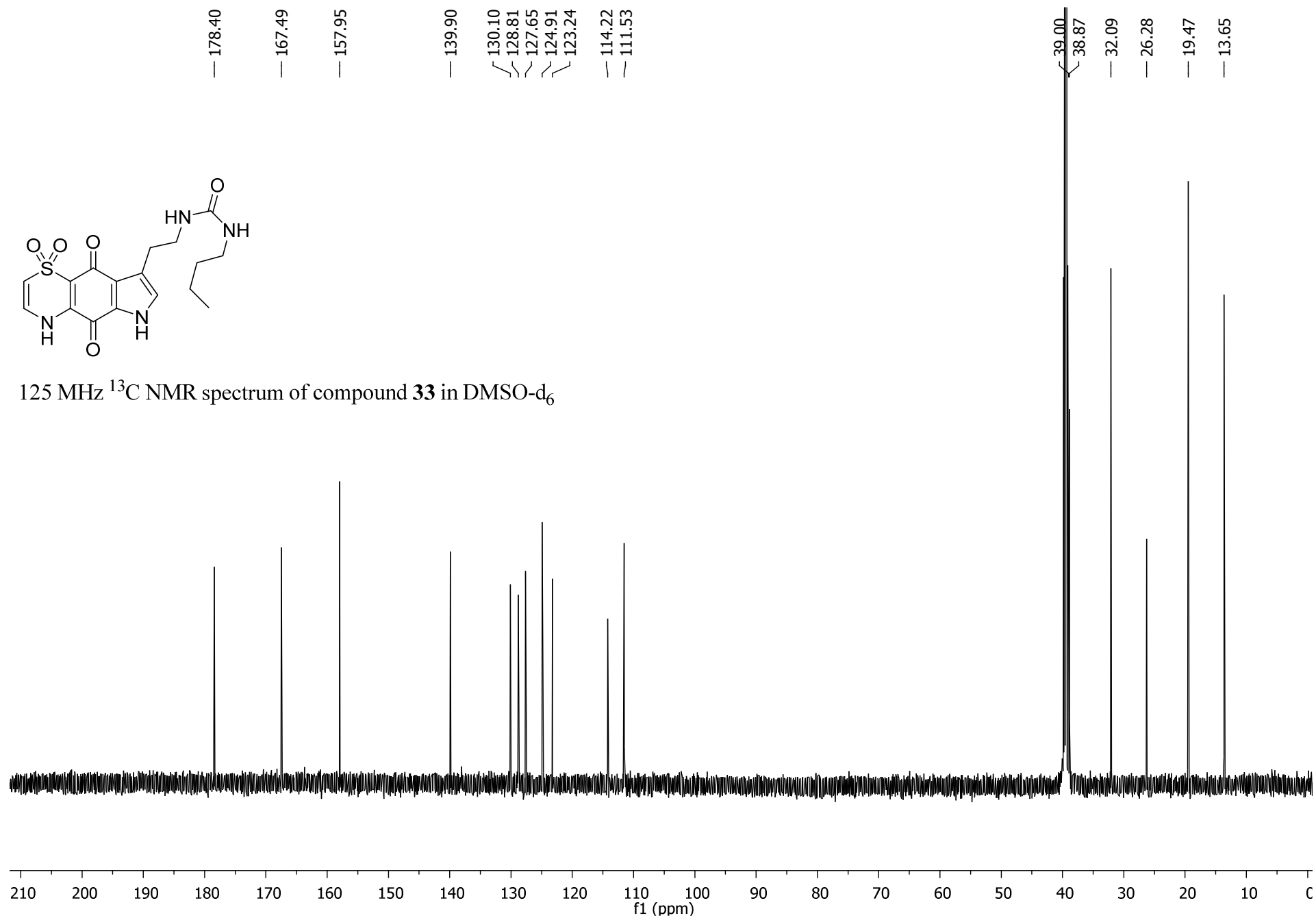


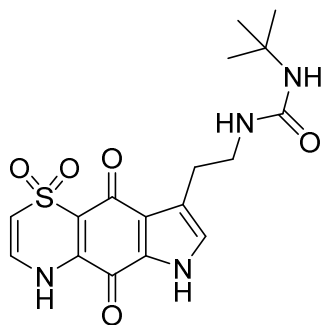
500 MHz ^1H NMR spectrum of compound **33** in DMSO-d_6



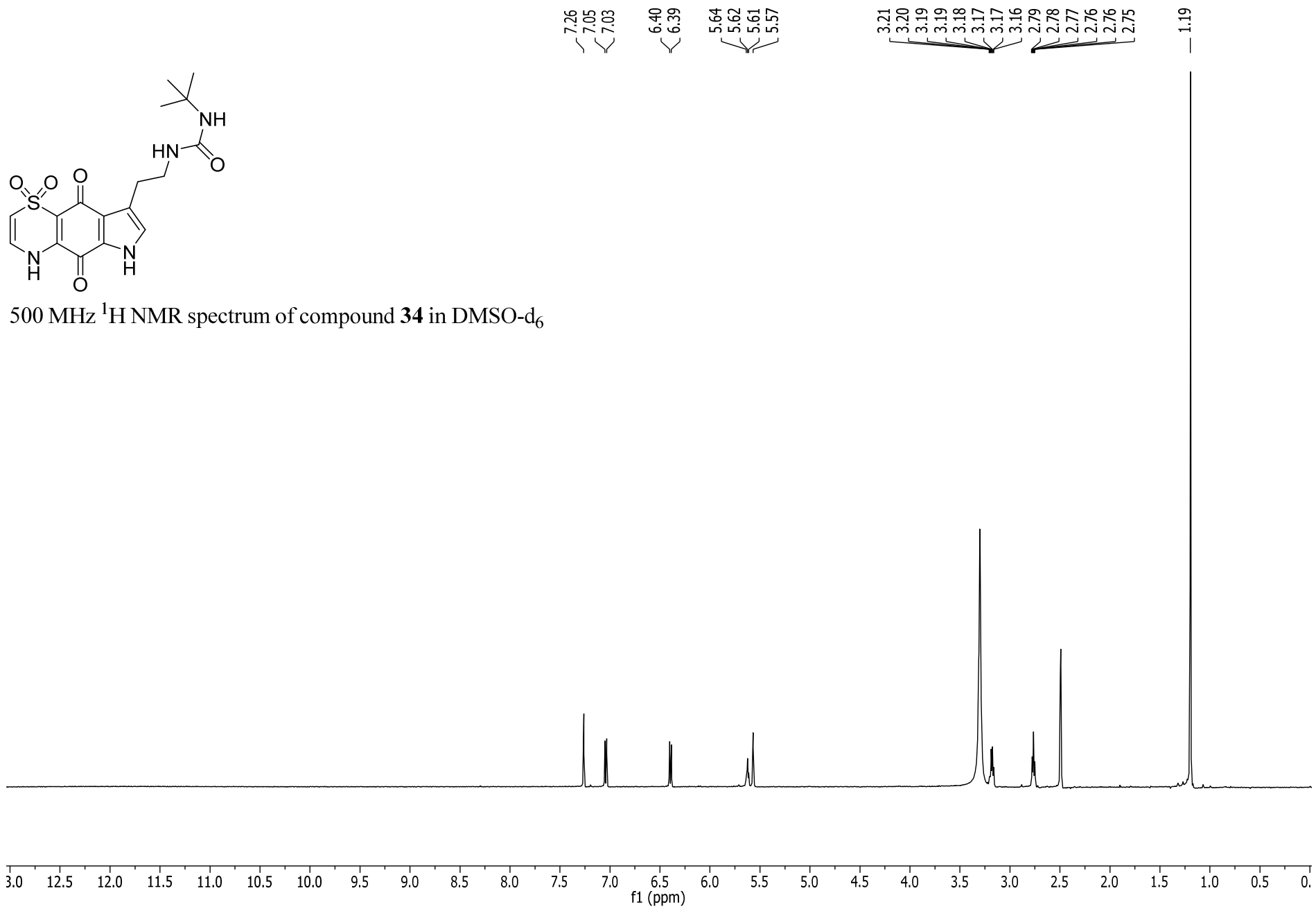


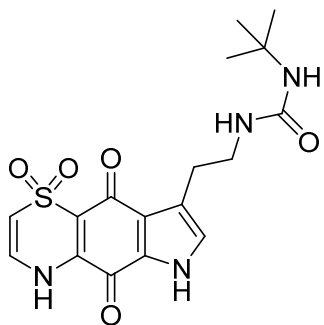
125 MHz ^{13}C NMR spectrum of compound **33** in DMSO-d_6



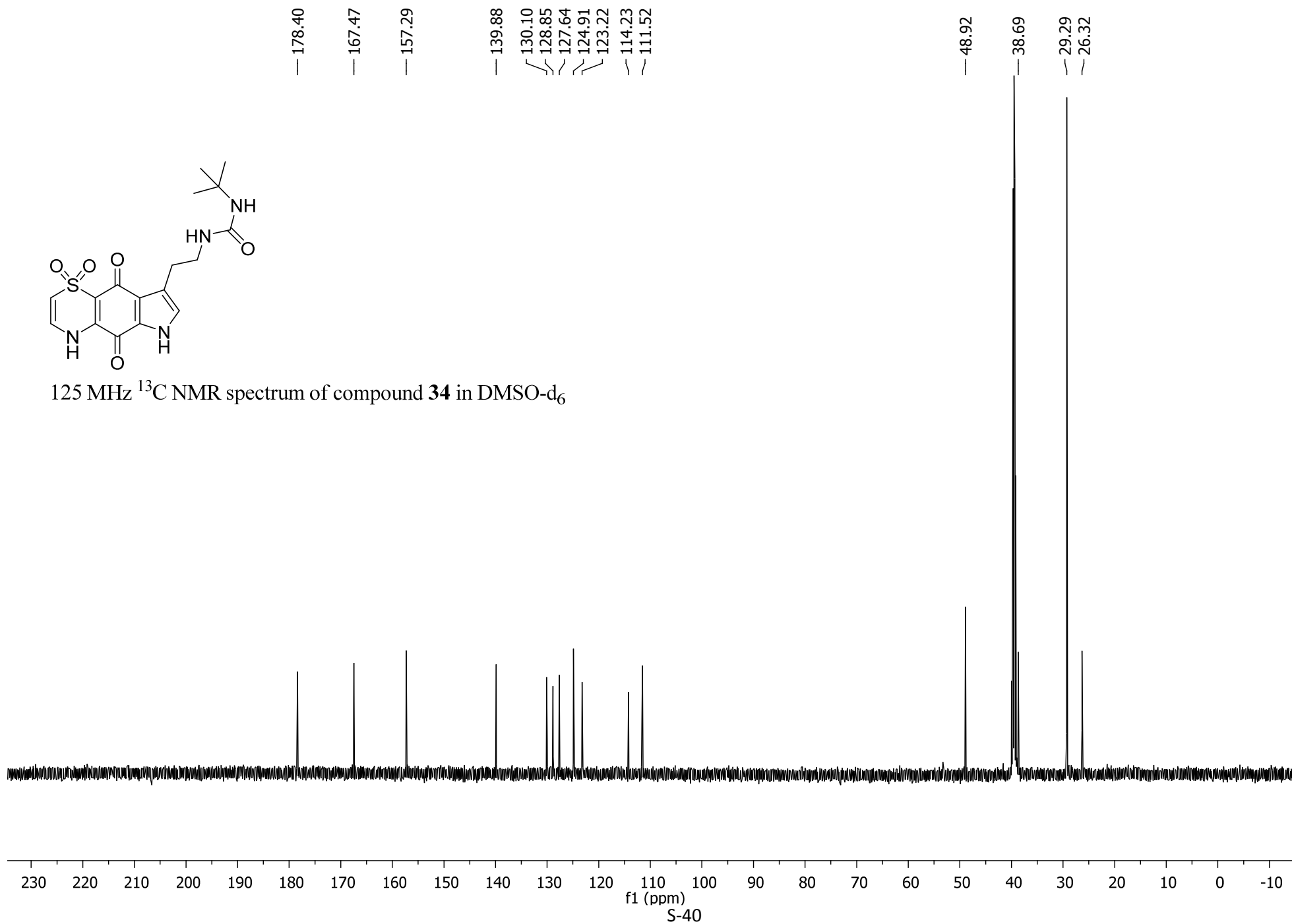


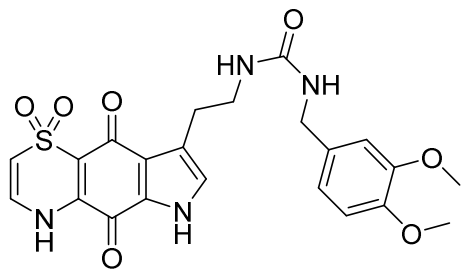
500 MHz ^1H NMR spectrum of compound **34** in DMSO-d_6



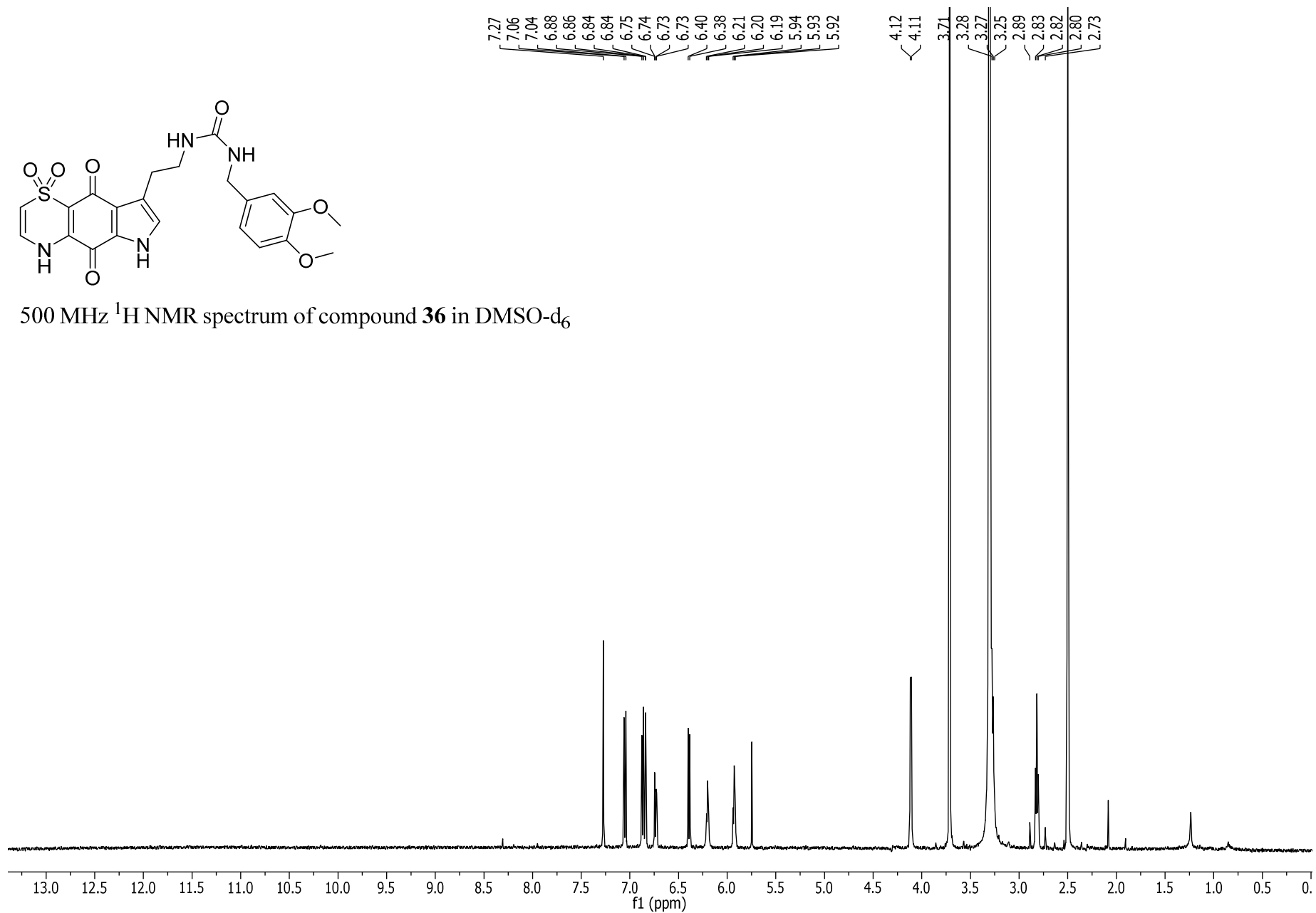


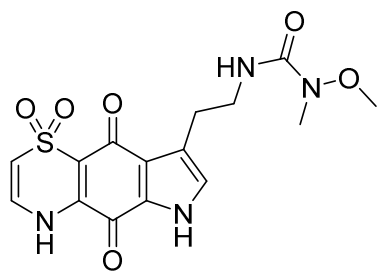
125 MHz ^{13}C NMR spectrum of compound **34** in DMSO-d_6



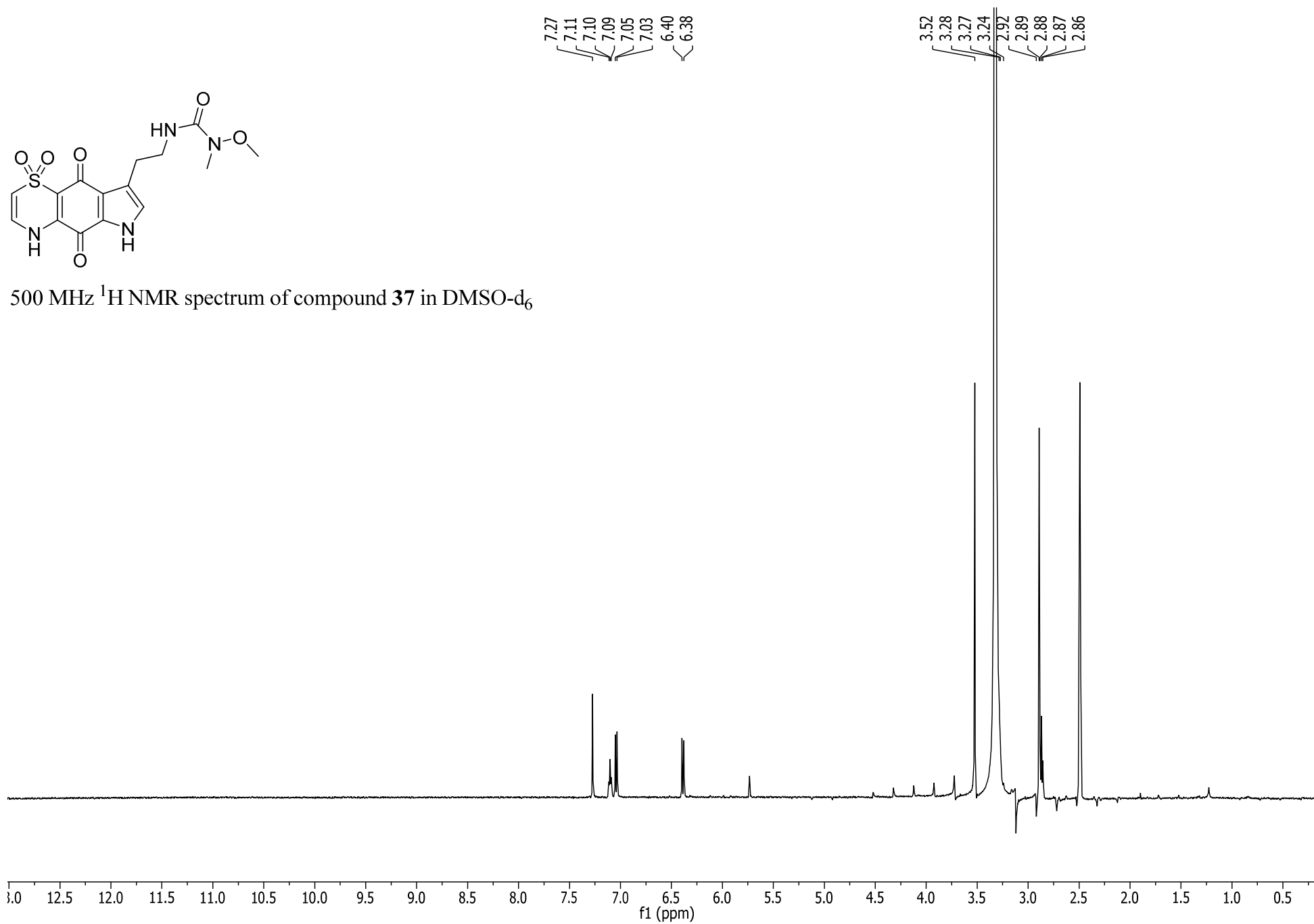


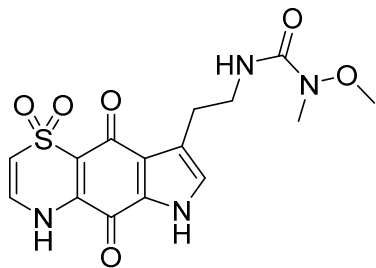
500 MHz ^1H NMR spectrum of compound **36** in DMSO-d_6



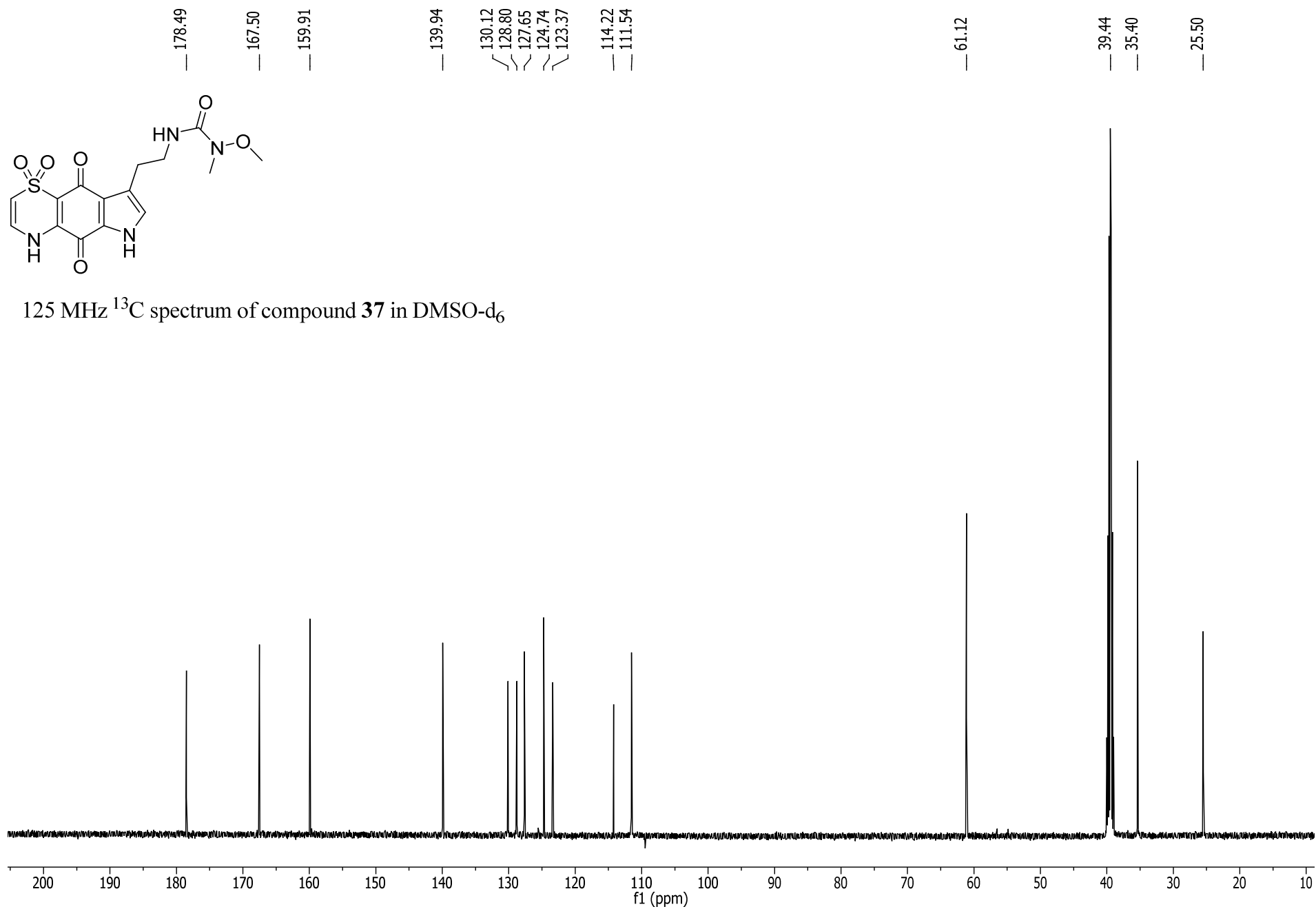


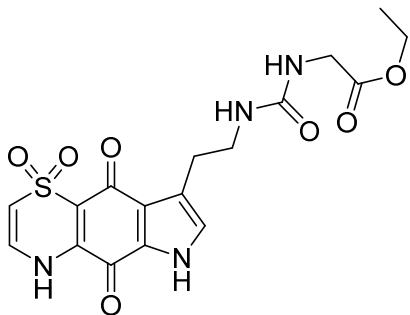
500 MHz ^1H NMR spectrum of compound **37** in DMSO-d_6



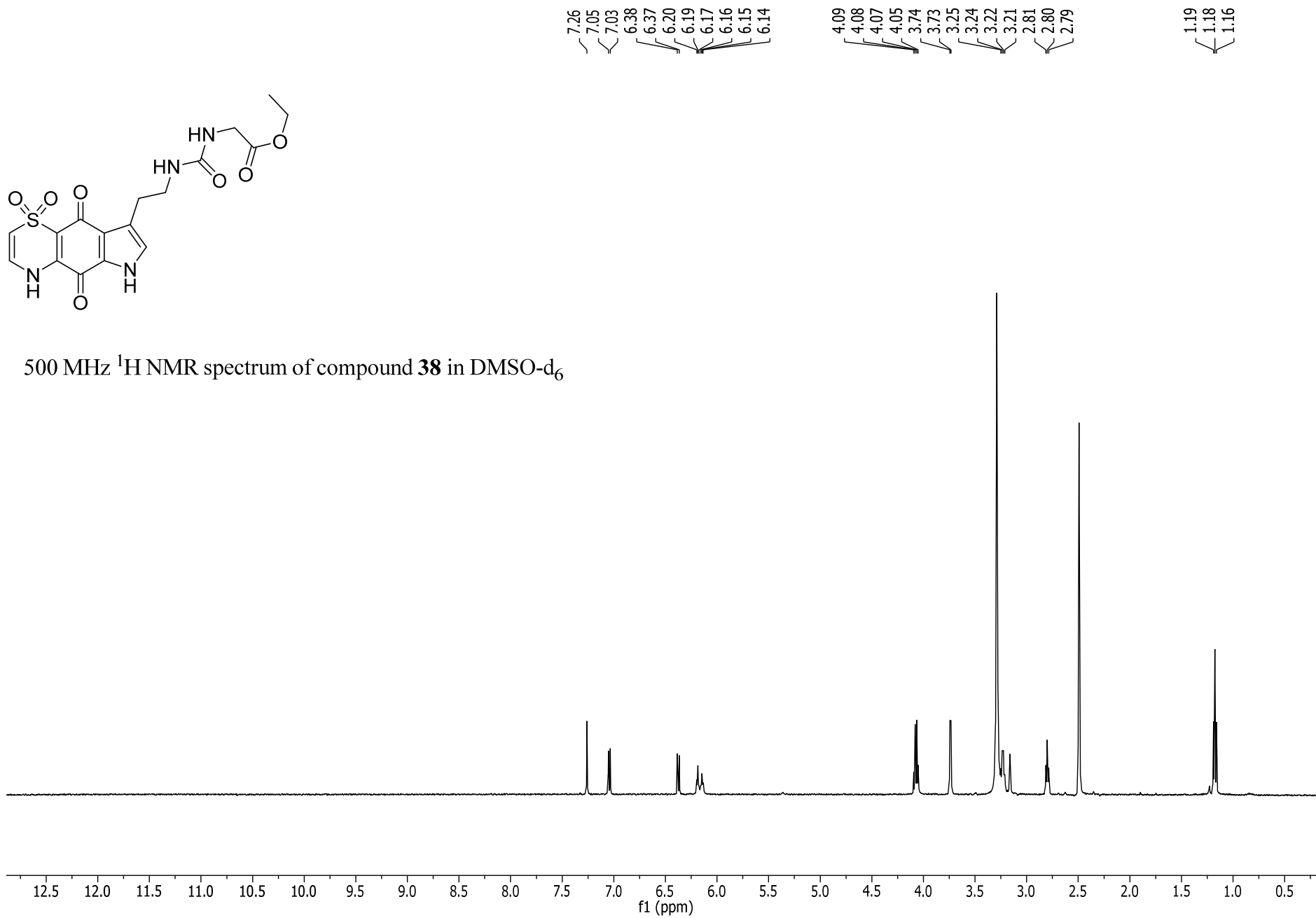


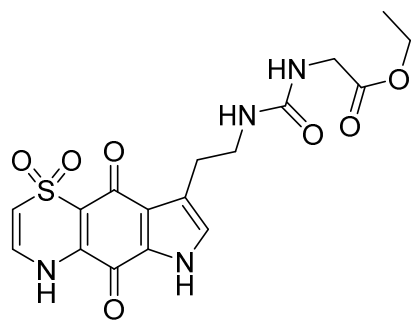
125 MHz ^{13}C spectrum of compound **37** in DMSO-d_6



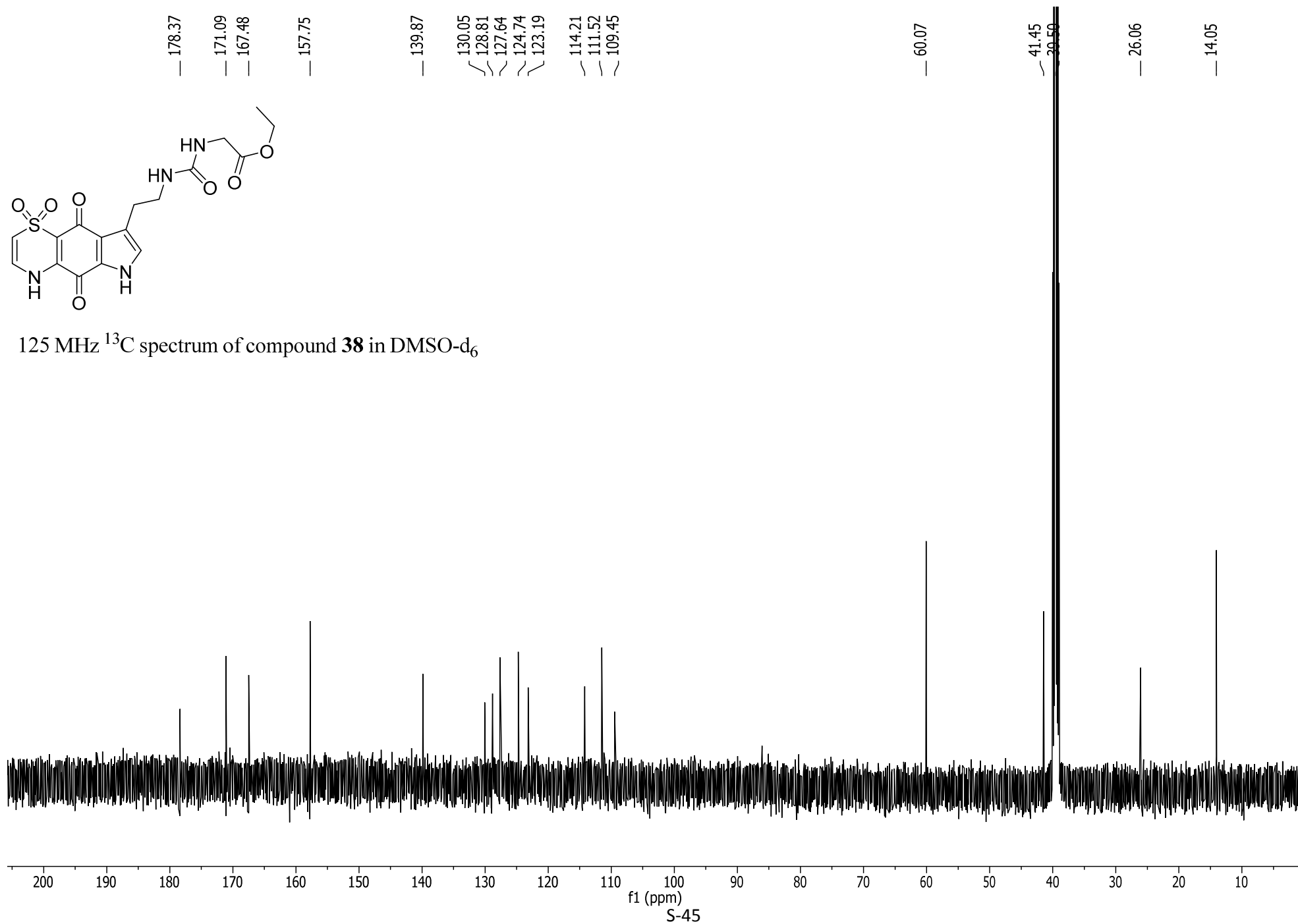


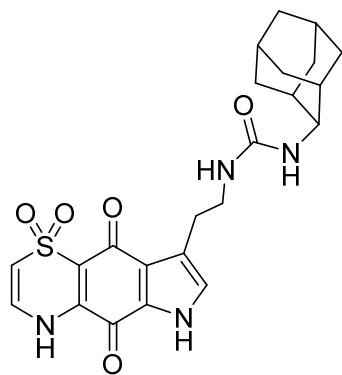
500 MHz ^1H NMR spectrum of compound **38** in DMSO- d_6



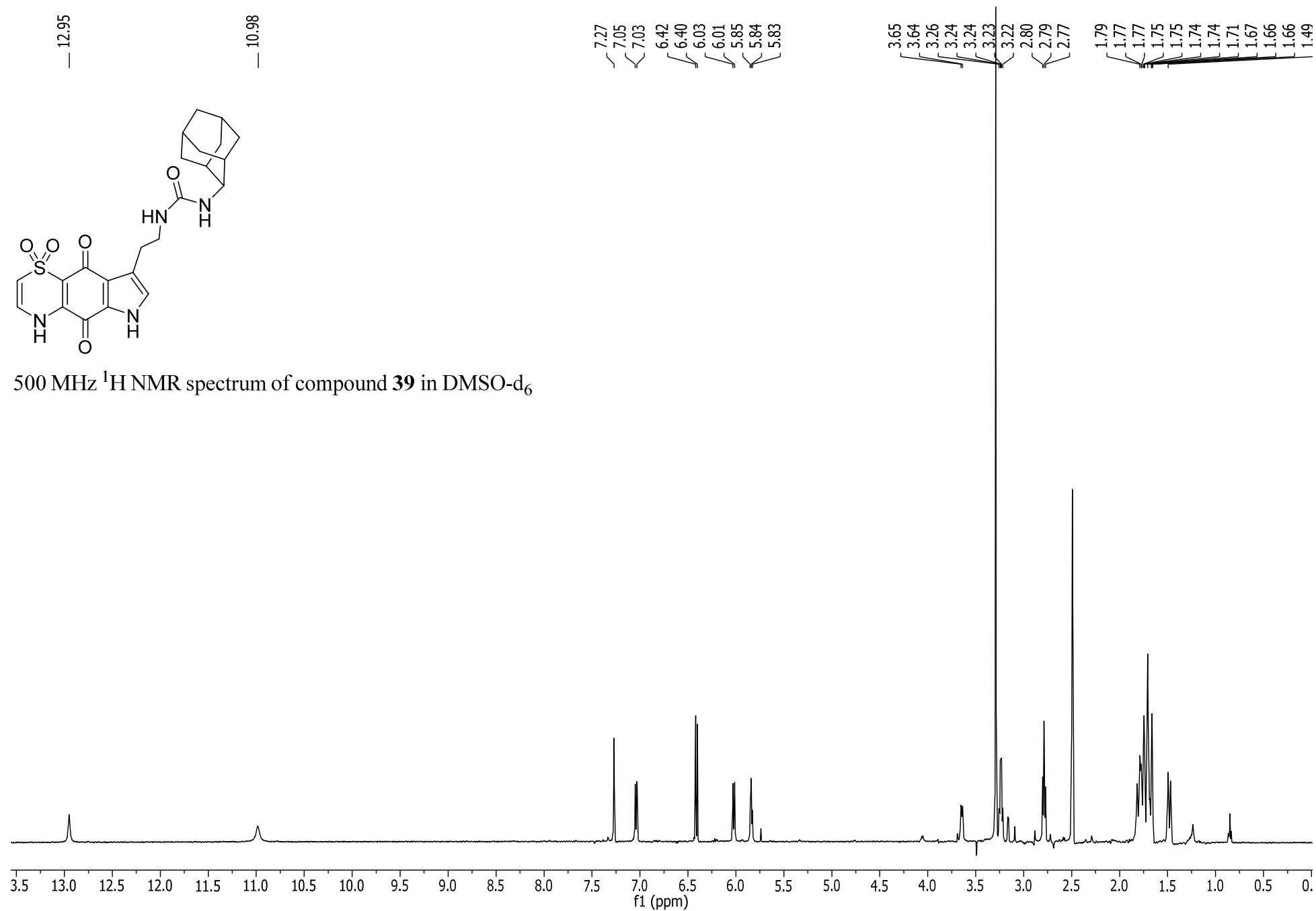


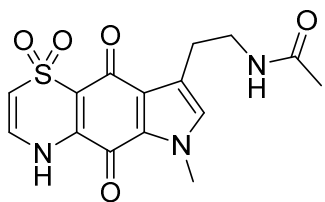
125 MHz ^{13}C spectrum of compound **38** in DMSO- d_6



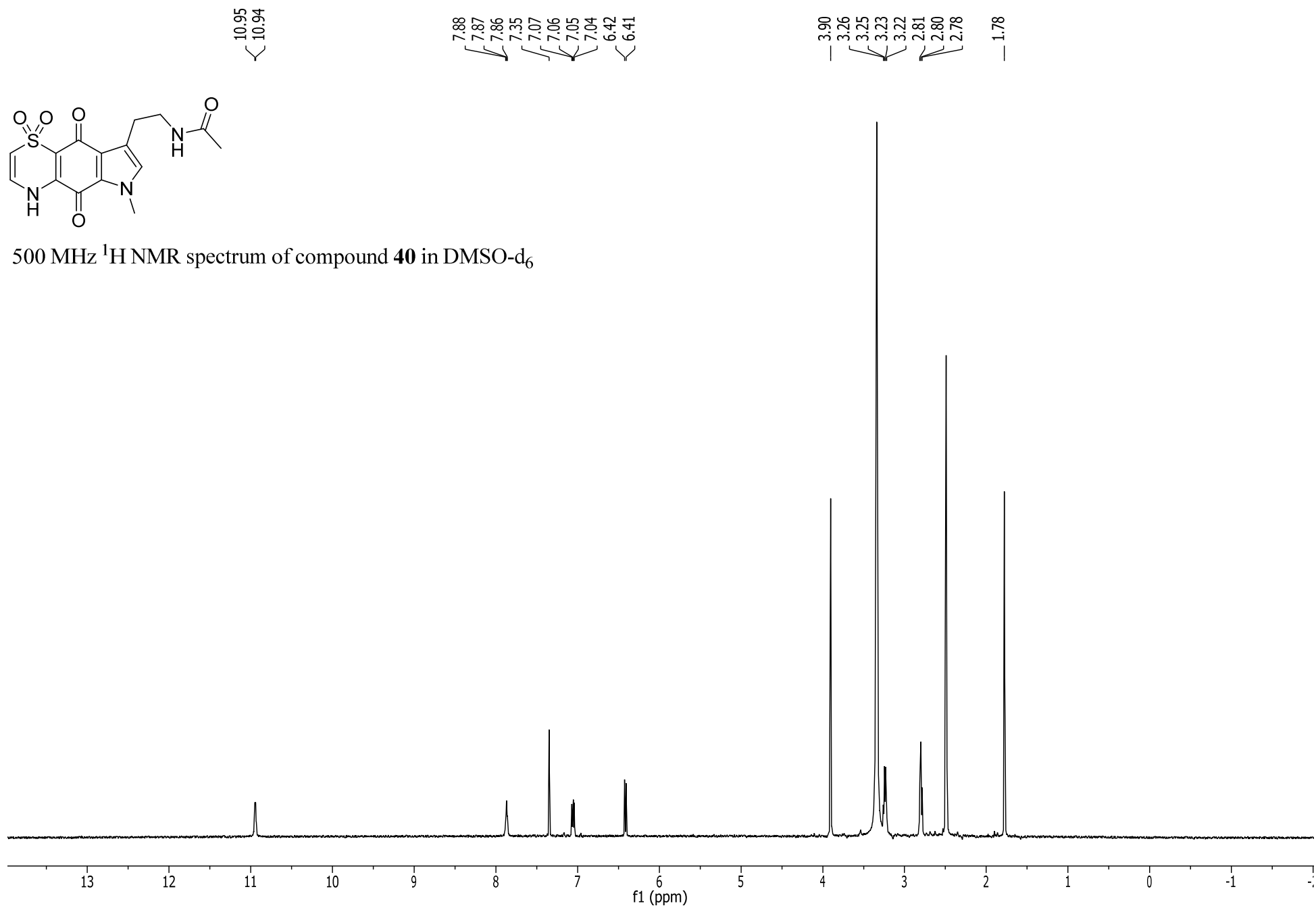


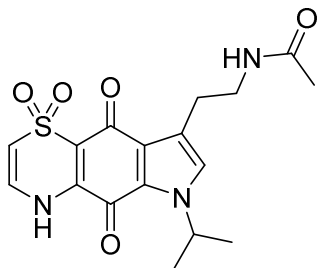
500 MHz ^1H NMR spectrum of compound **39** in DMSO-d_6



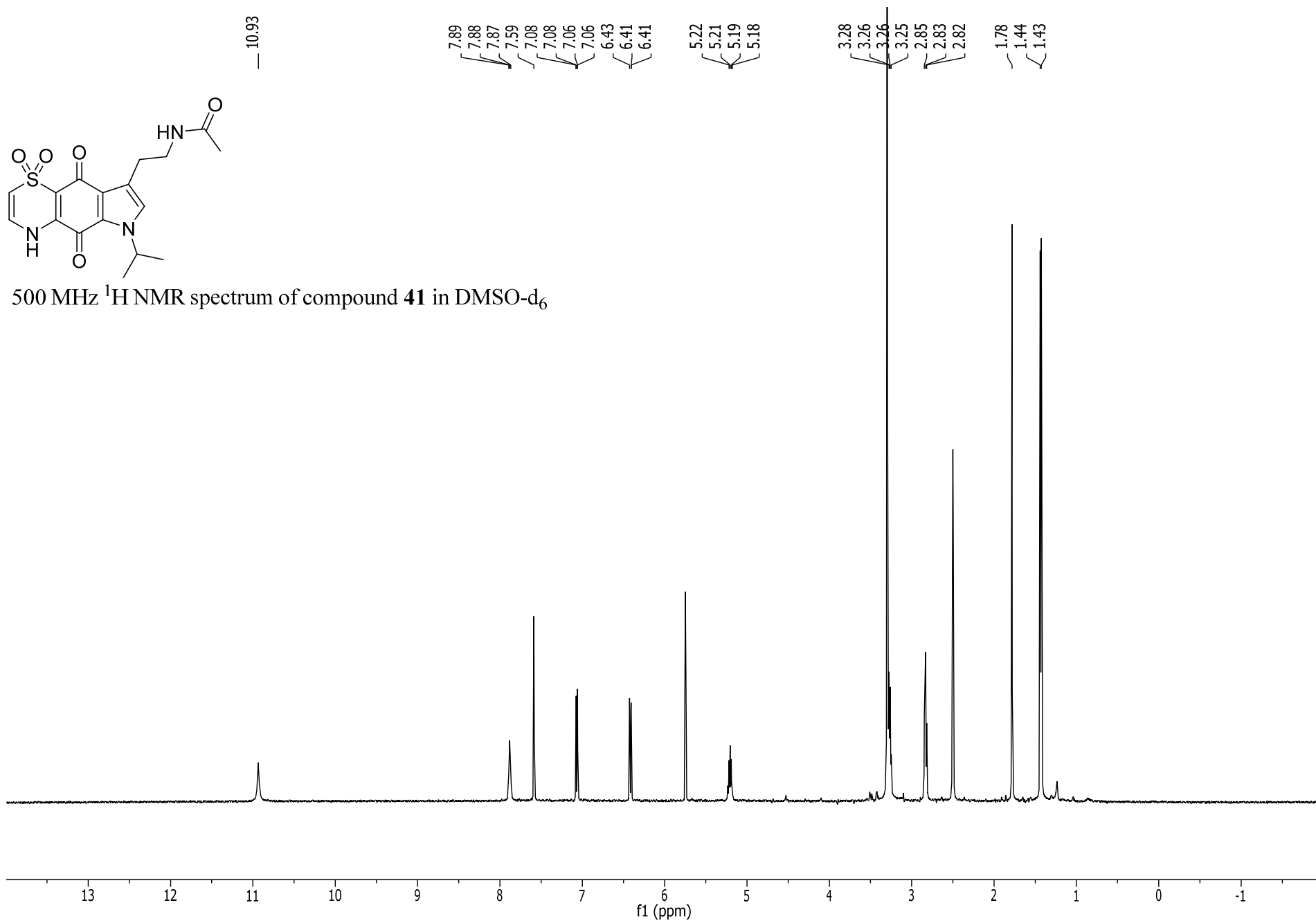


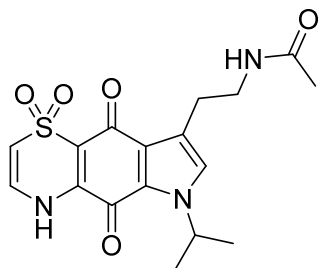
500 MHz ^1H NMR spectrum of compound **40** in DMSO- d_6



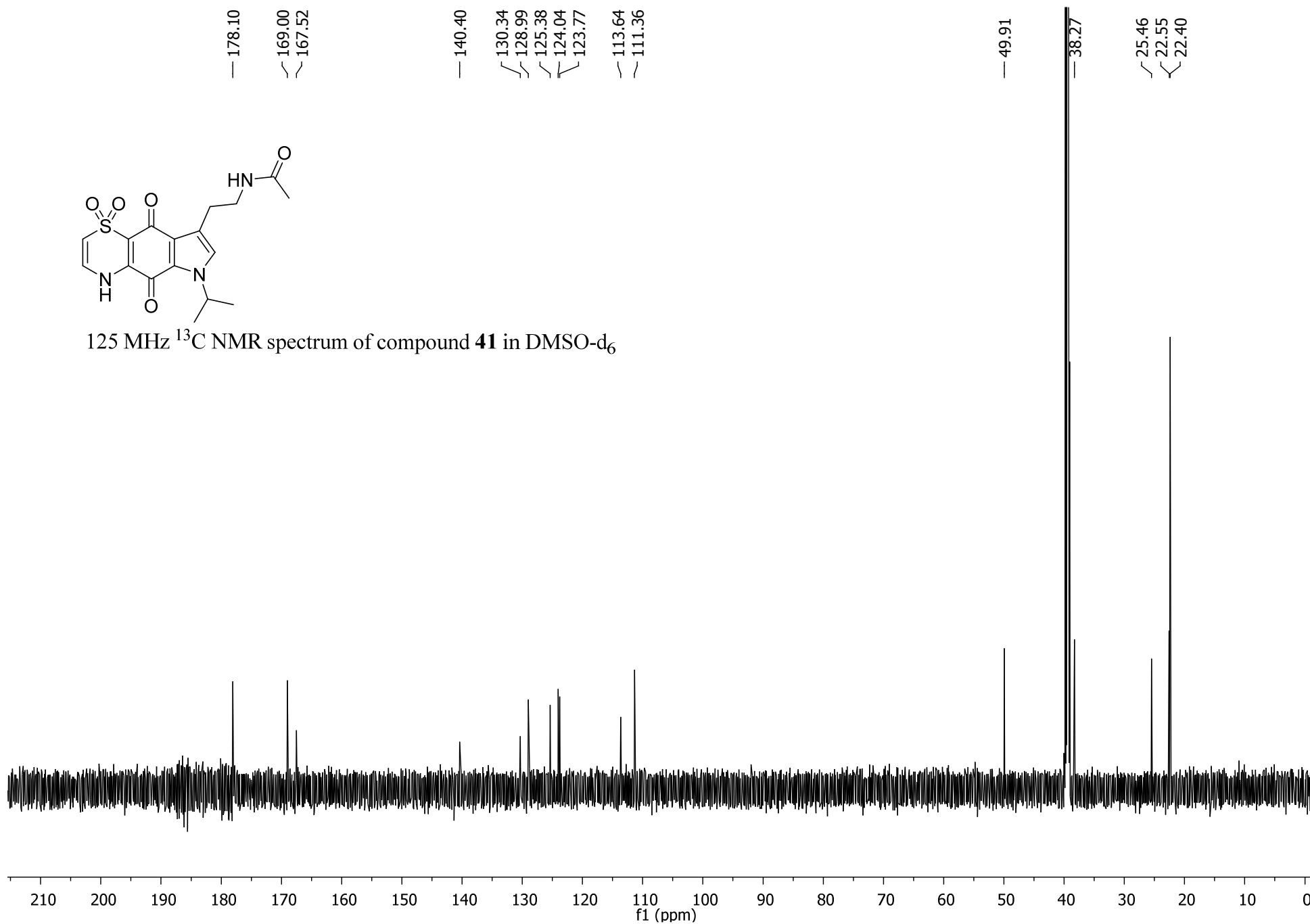


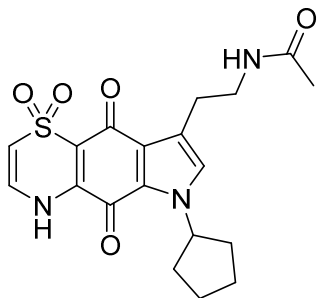
500 MHz ^1H NMR spectrum of compound **41** in DMSO- d_6



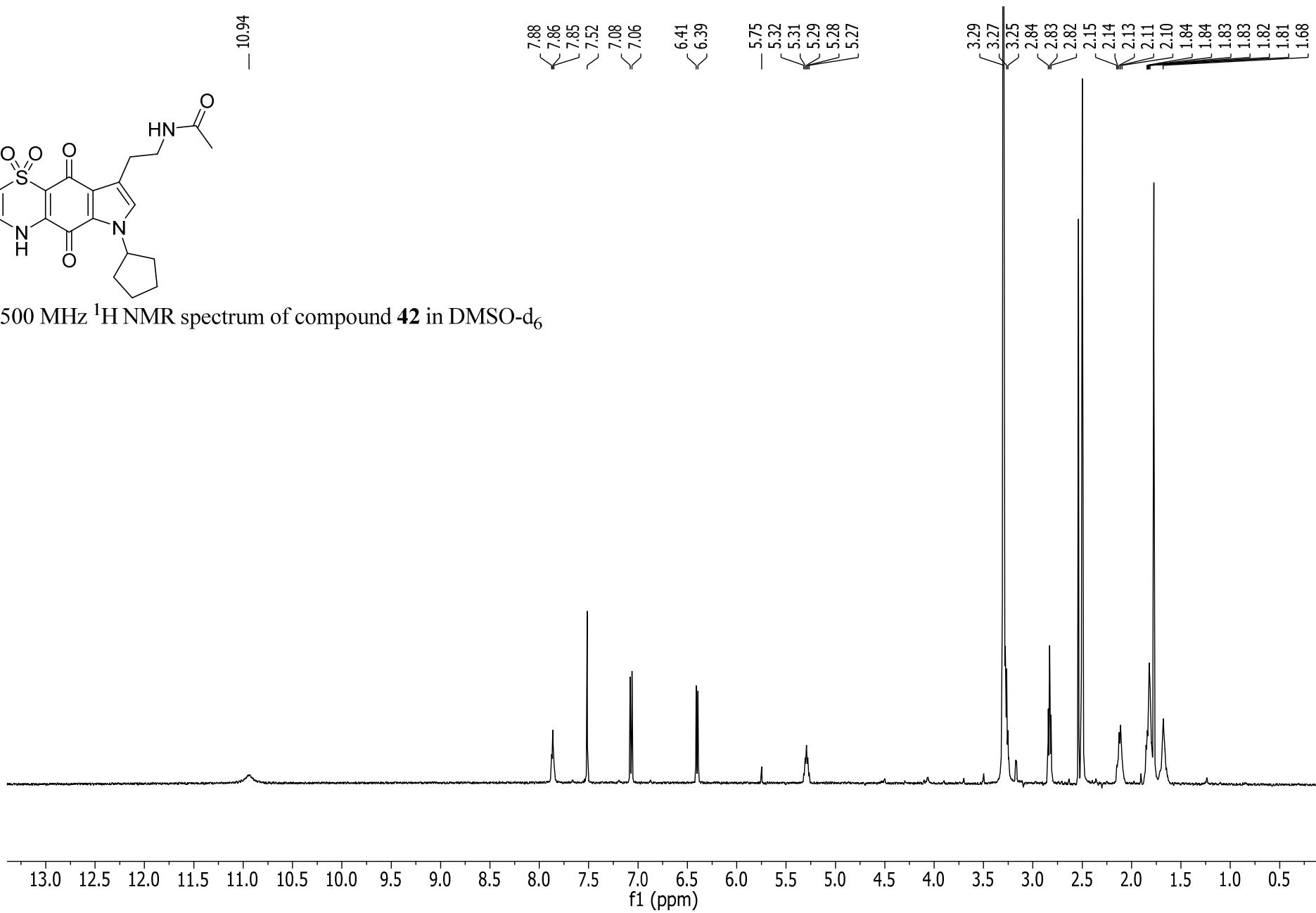


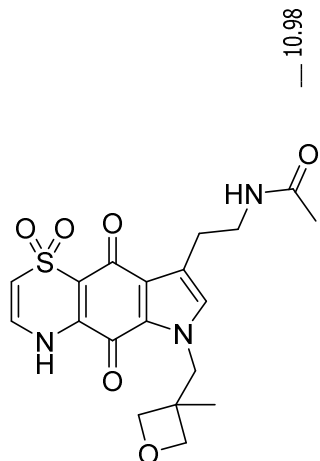
125 MHz ^{13}C NMR spectrum of compound **41** in DMSO-d_6



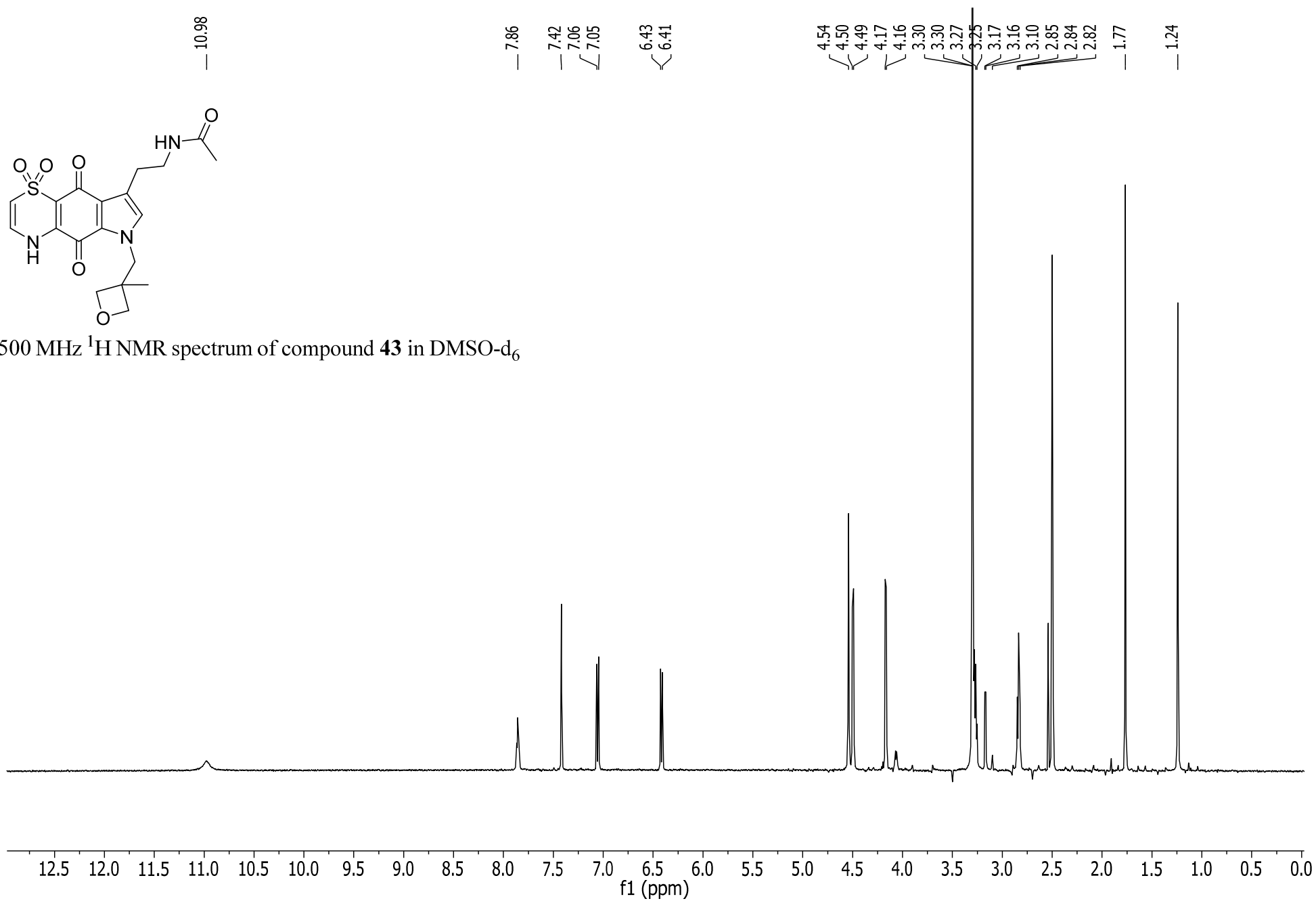


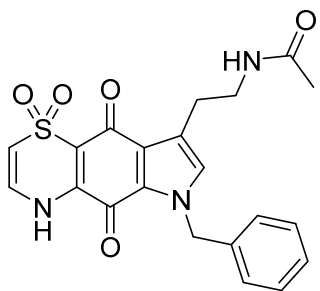
500 MHz ^1H NMR spectrum of compound **42** in DMSO-d_6



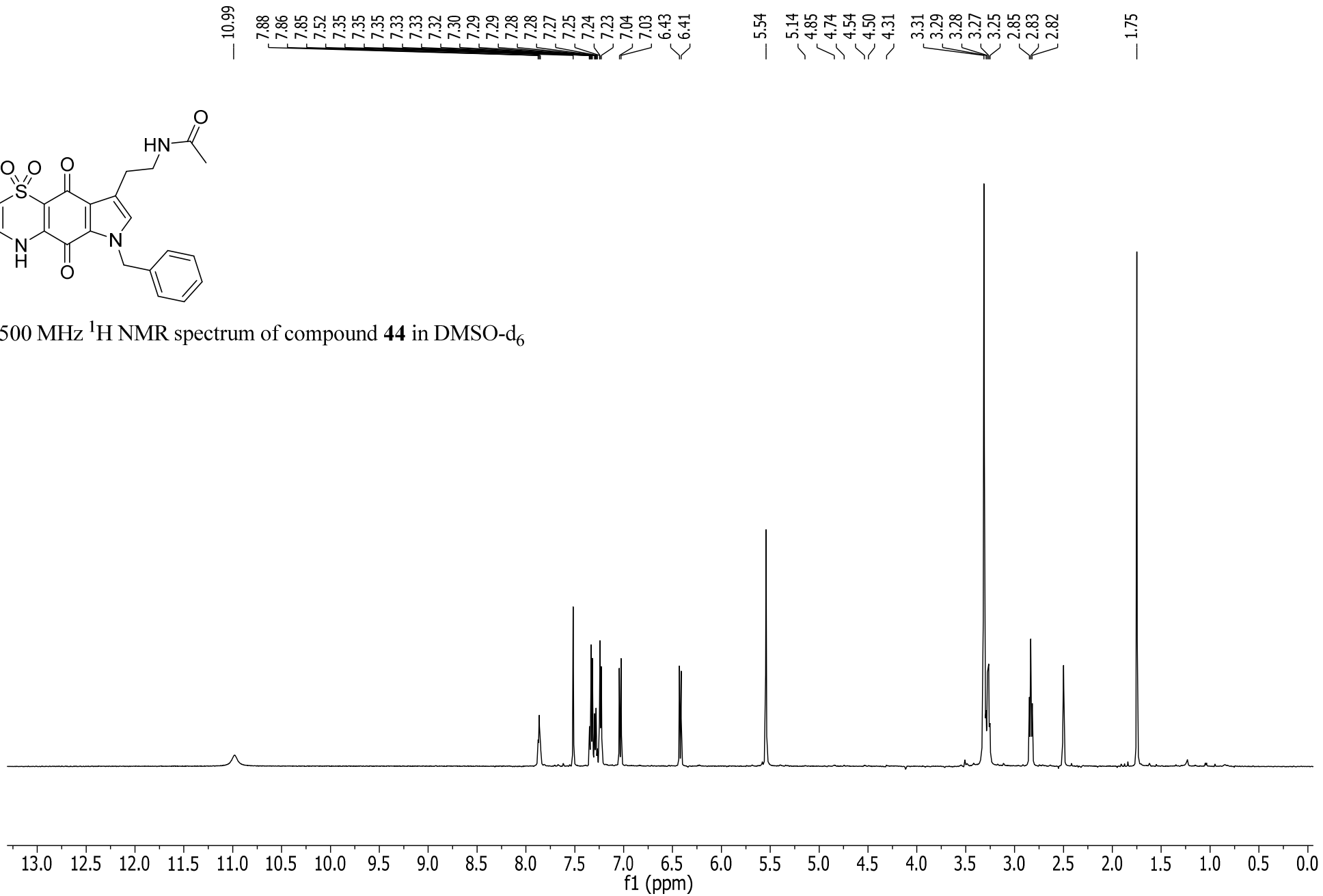


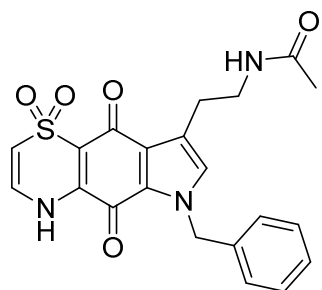
500 MHz ^1H NMR spectrum of compound **43** in DMSO-d_6



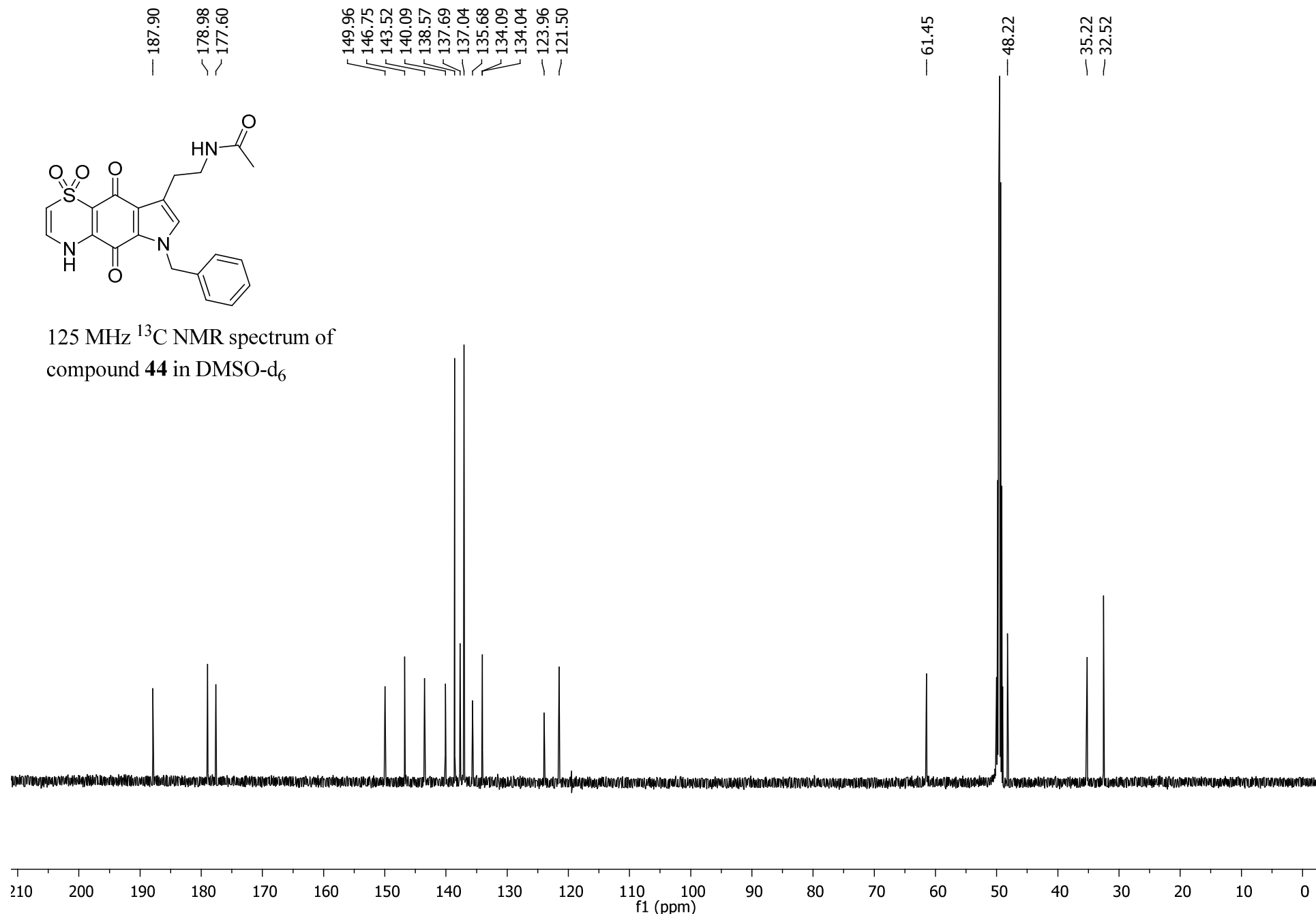


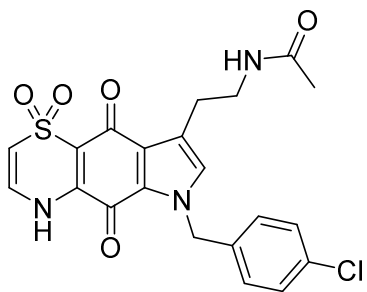
500 MHz ^1H NMR spectrum of compound **44** in DMSO- d_6



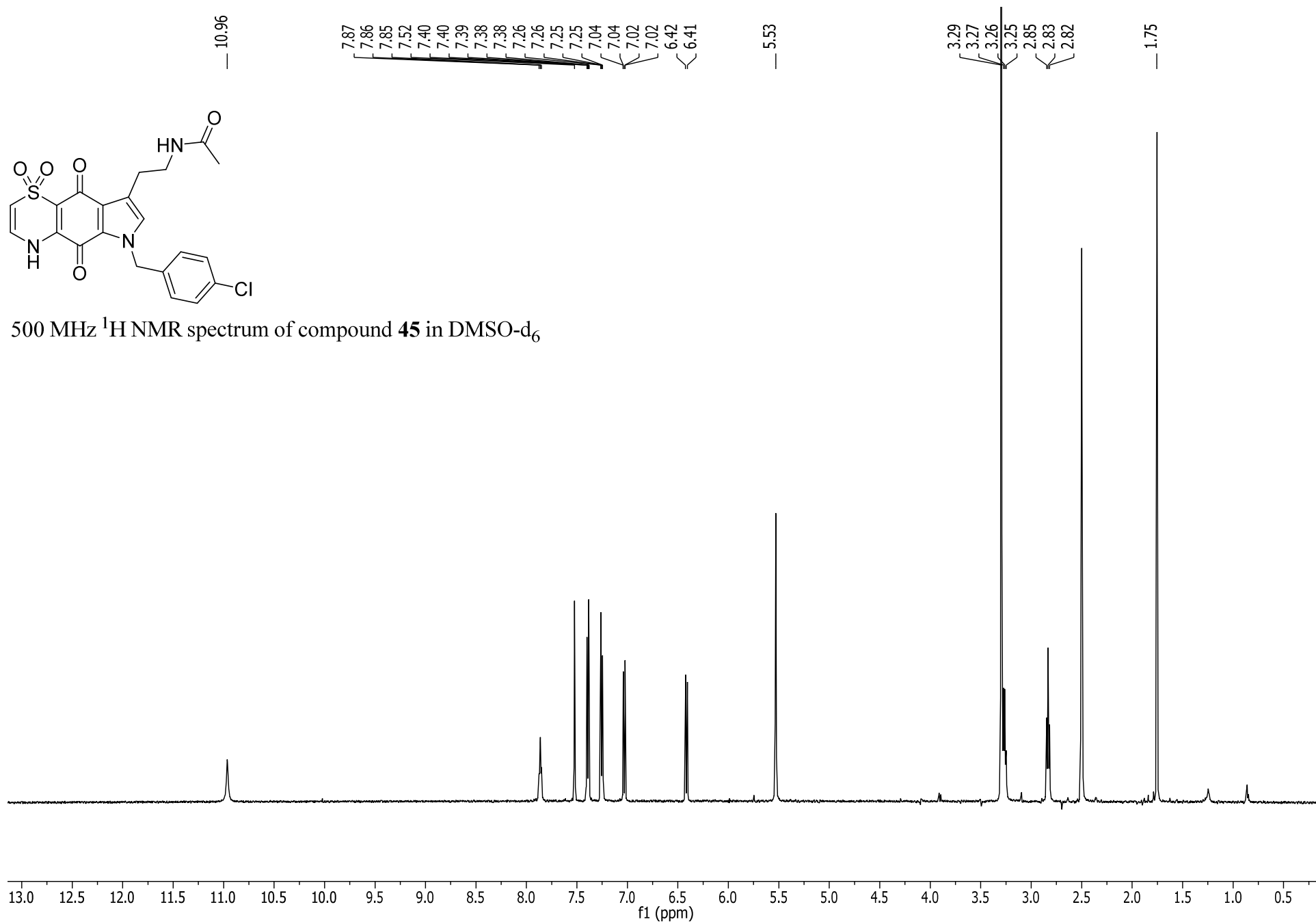


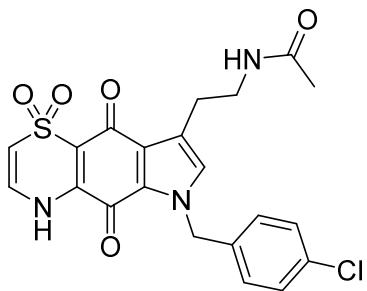
125 MHz ^{13}C NMR spectrum of compound **44** in DMSO- d_6



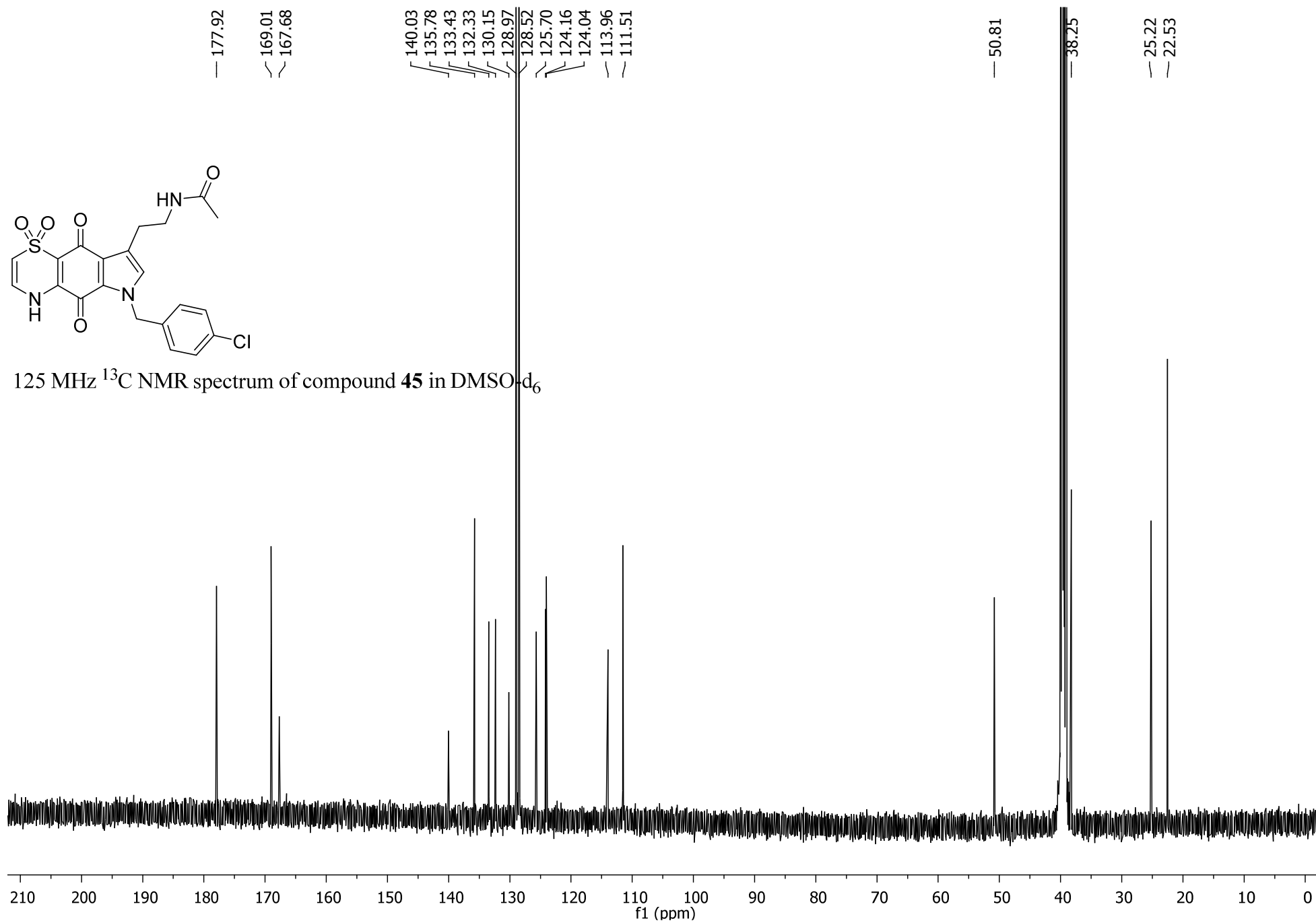


500 MHz ^1H NMR spectrum of compound **45** in DMSO-d_6





125 MHz ^{13}C NMR spectrum of compound **45** in DMSO-d_6



X-ray crystallography

Crystal data for (1)

[C₁₂H₁₂N₃O₄S]Cl·2H₂O, $M_r = 365.8$. Orthorhombic, space group *Pbca*, $a = 14.5655(5)$, $b = 8.3351(3)$, $c = 26.0998(10)$ Å, $V = 3168.6(2)$ Å³. D_c ($Z = 8$) = 1.53 g cm⁻³. $\mu_{MO} = 0.41$ mm; specimen: 0.35 x 0.25 x 0.10 mm; $T'_{\min/\max} = 0.87/0.96$. $2\theta_{\max} = 55.0^\circ$; $N_t = 8729$, $N = 2640$ ($R_{\text{int}} = 0.031$), $N_o = 2950$; $R_1 = 0.052$, $wR_2 = 0.1229$; $S = 1.11$.

Crystal data for (9)

C₁₅H₁₅N₃O₅S·C₂H₆OS, $M_r = 427.5$. Monoclinic, space group *P2₁/c* $a = 10.0722(6)$, $b = 24.948(2)$, $c = 7.5588(5)$ Å, $\beta = 99.053(6)$, $V = 1875.7(2)(2)$ Å³. D_c ($Z = 4$) = 1.51 g cm⁻³. $\mu_{MO} = 0.33$ mm; specimen: 0.31 x 0.17 x 0.04 mm; $T'_{\min/\max} = 0.91/0.99$. $2\theta_{\max} = 55.0^\circ$; $N_t = 7560$, $N = 4251$ ($R_{\text{int}} = 0.037$), $N_o = 3062$; $R_1 = 0.053$, $wR_2 = 0.125$; $S = 1.06$.