

Supplementary Information

Design, synthesis and antiviral evaluation of triazole-linked 7-hydroxycoumarin – monoterpene conjugates as inhibitors of RSV replication

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1. NMR ¹H and ¹³C spectra of the compounds 10, 20 and 37-55.
2. HRMS spectra of the compounds 10, 20, and 37-55.
3. 2D spectra of compounds 37, 43, 50, 54Z, 54E
4. UHPLC of compounds.
5. Synthesis of compounds 23-31.
6. References

1. NMR ^1H and ^{13}C spectra of the compounds 10, 20 and 37-55.

Fig. S1. ^1H spectra of Compound 20

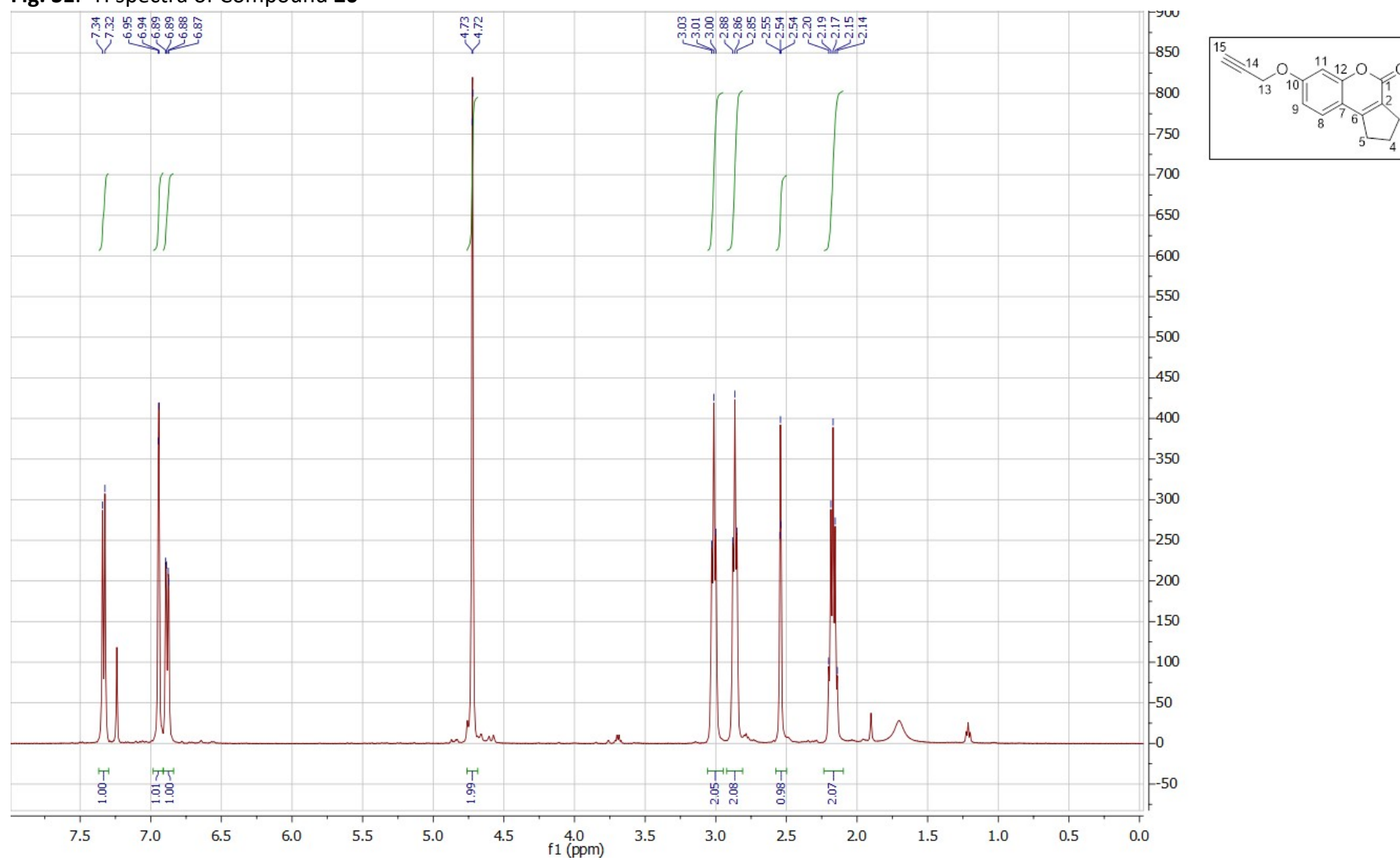


Fig. S2. ^{13}C spectra of Compound 20.

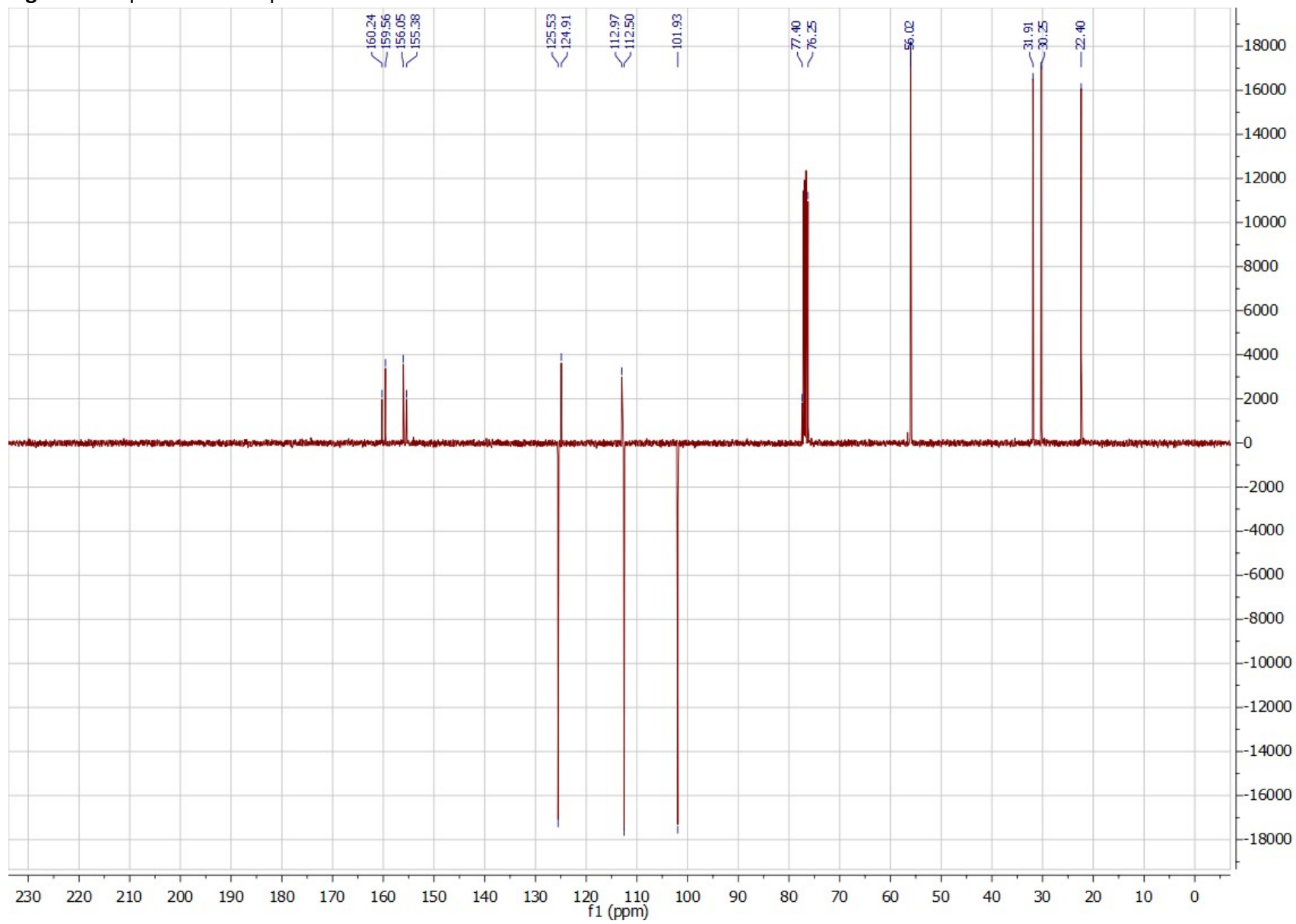


Fig. S3. ¹H spectra of Compound 10

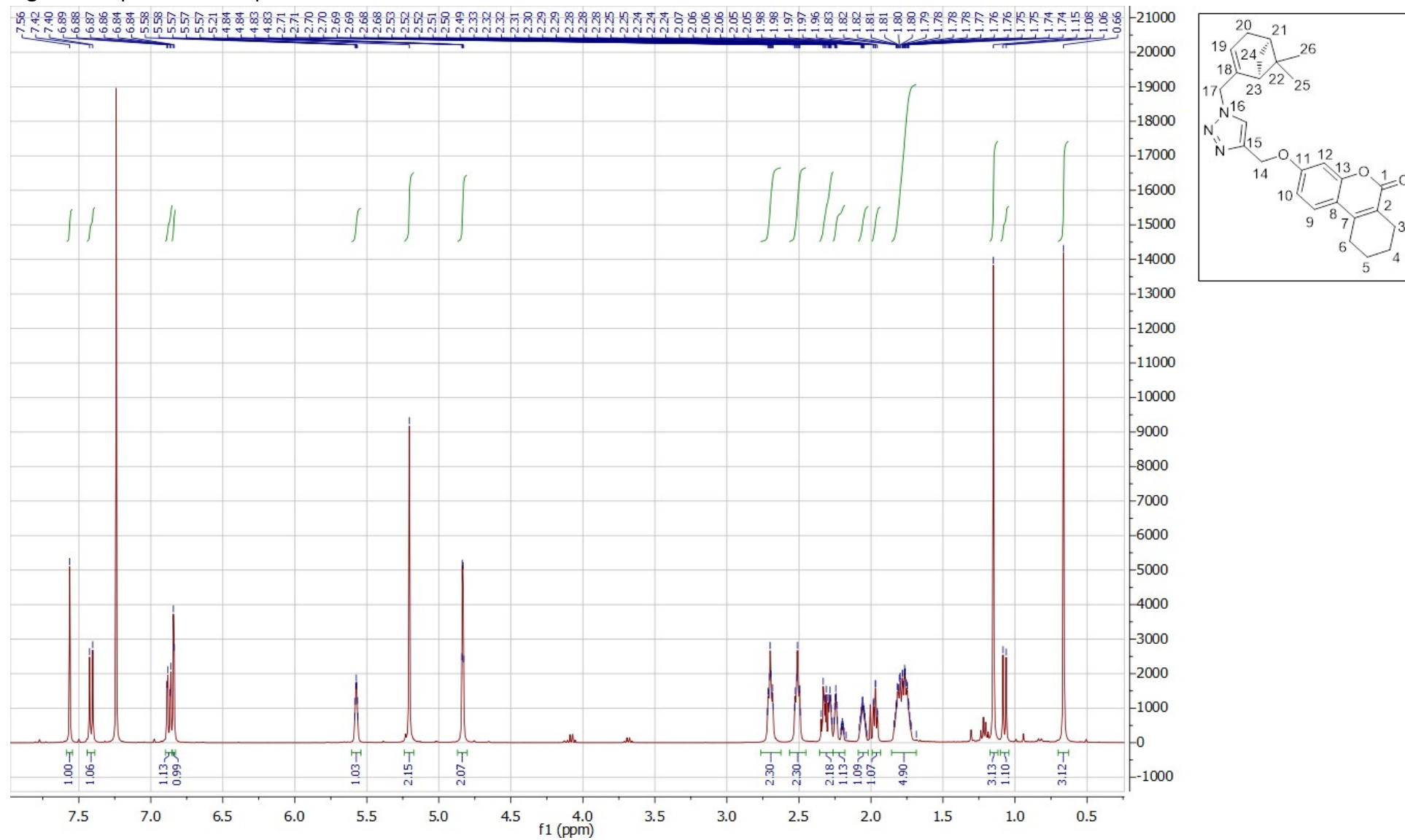


Fig. S4. ^{13}C spectra of Compound 10.

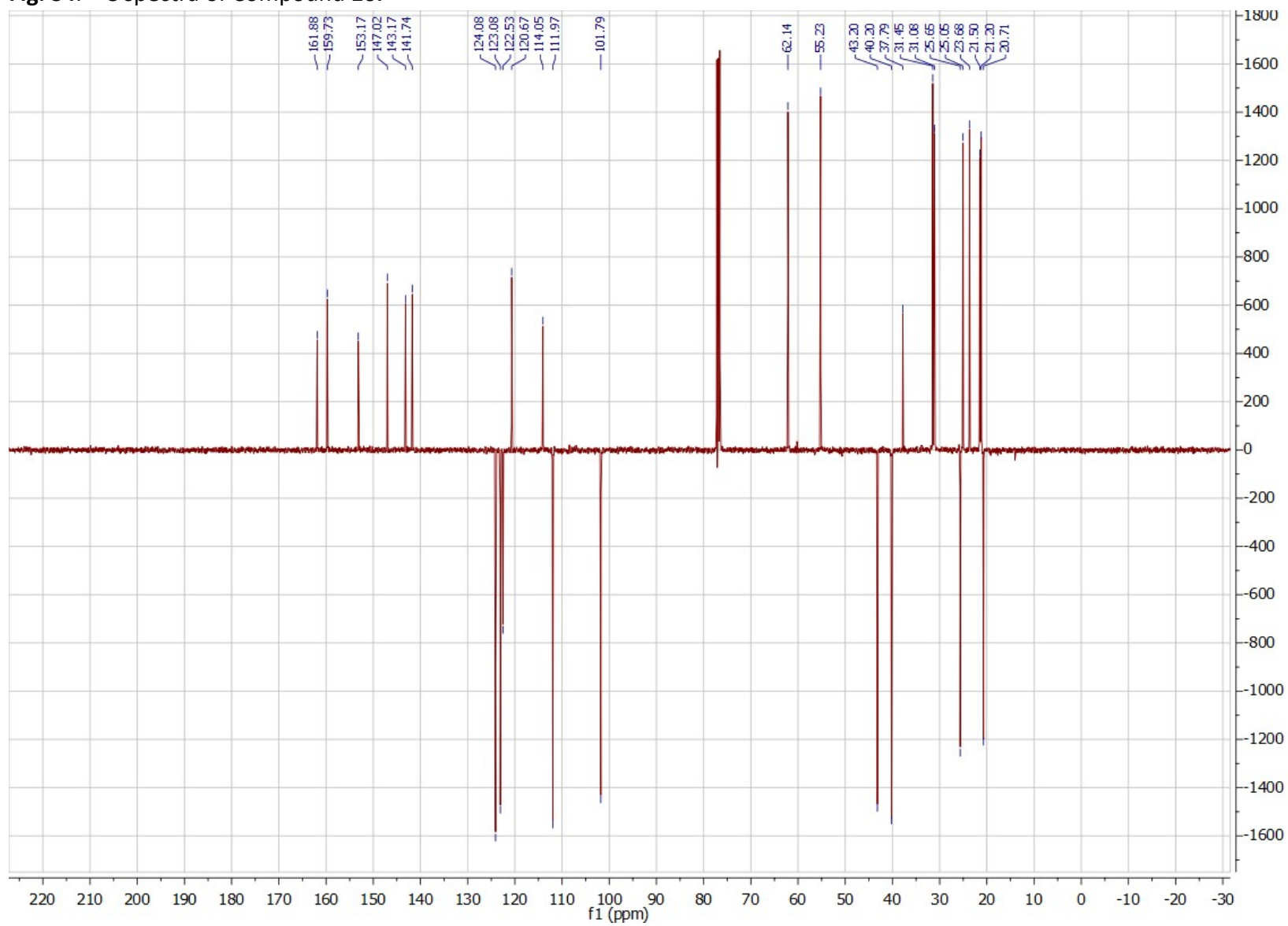


Fig. S5. ¹H spectra of Compound 38

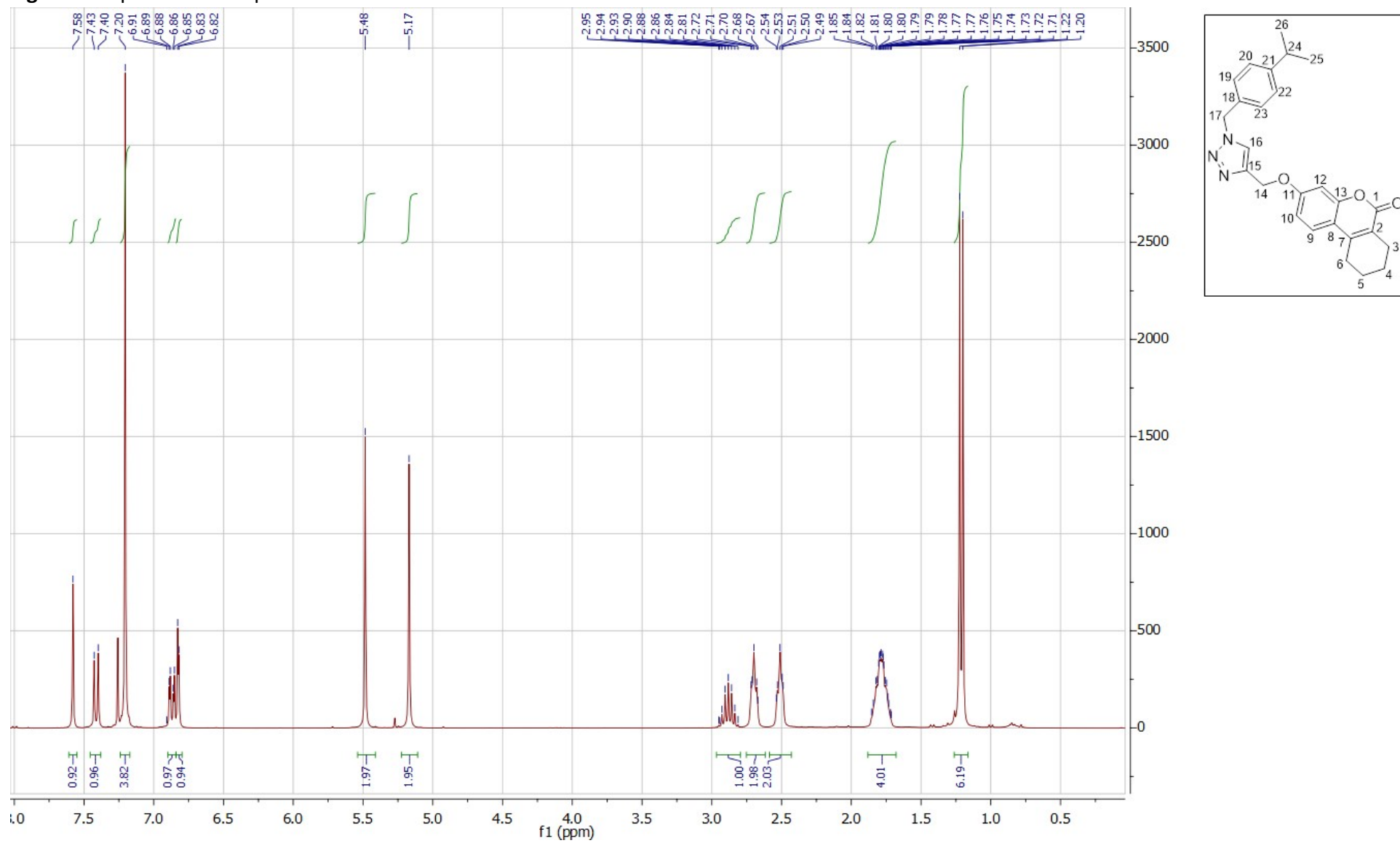


Fig. S6. ^{13}C spectra of Compound **38**

lfav-do-cyc16.137.fid
CYC 16; CDCl₃/dhd3

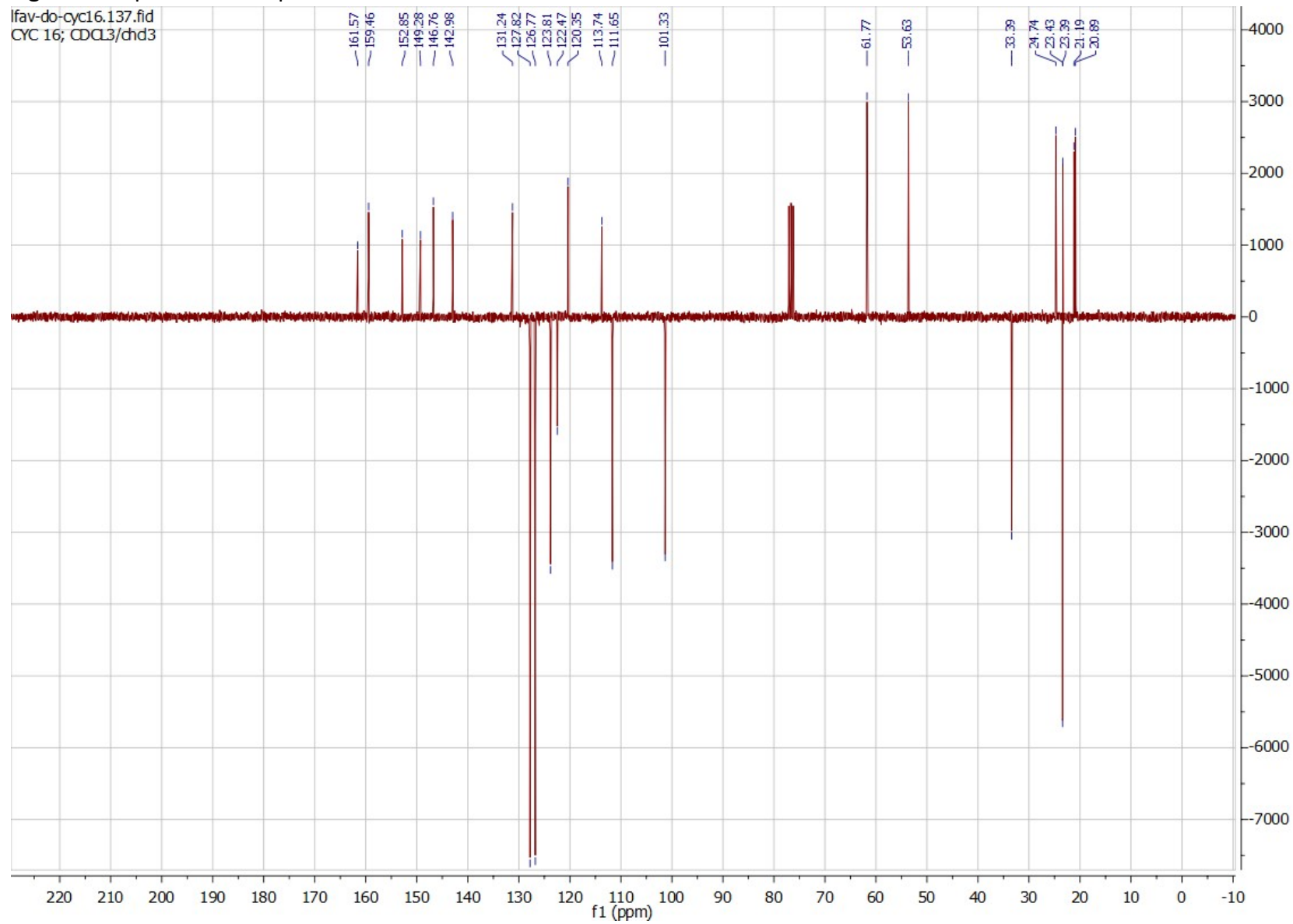


Fig. S7. ¹H spectra of Compound 39

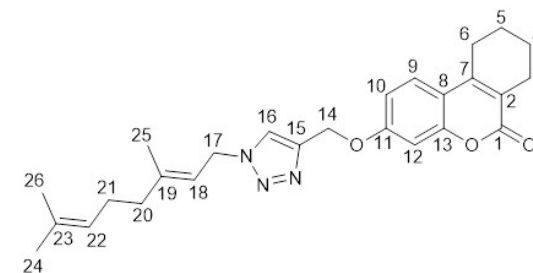
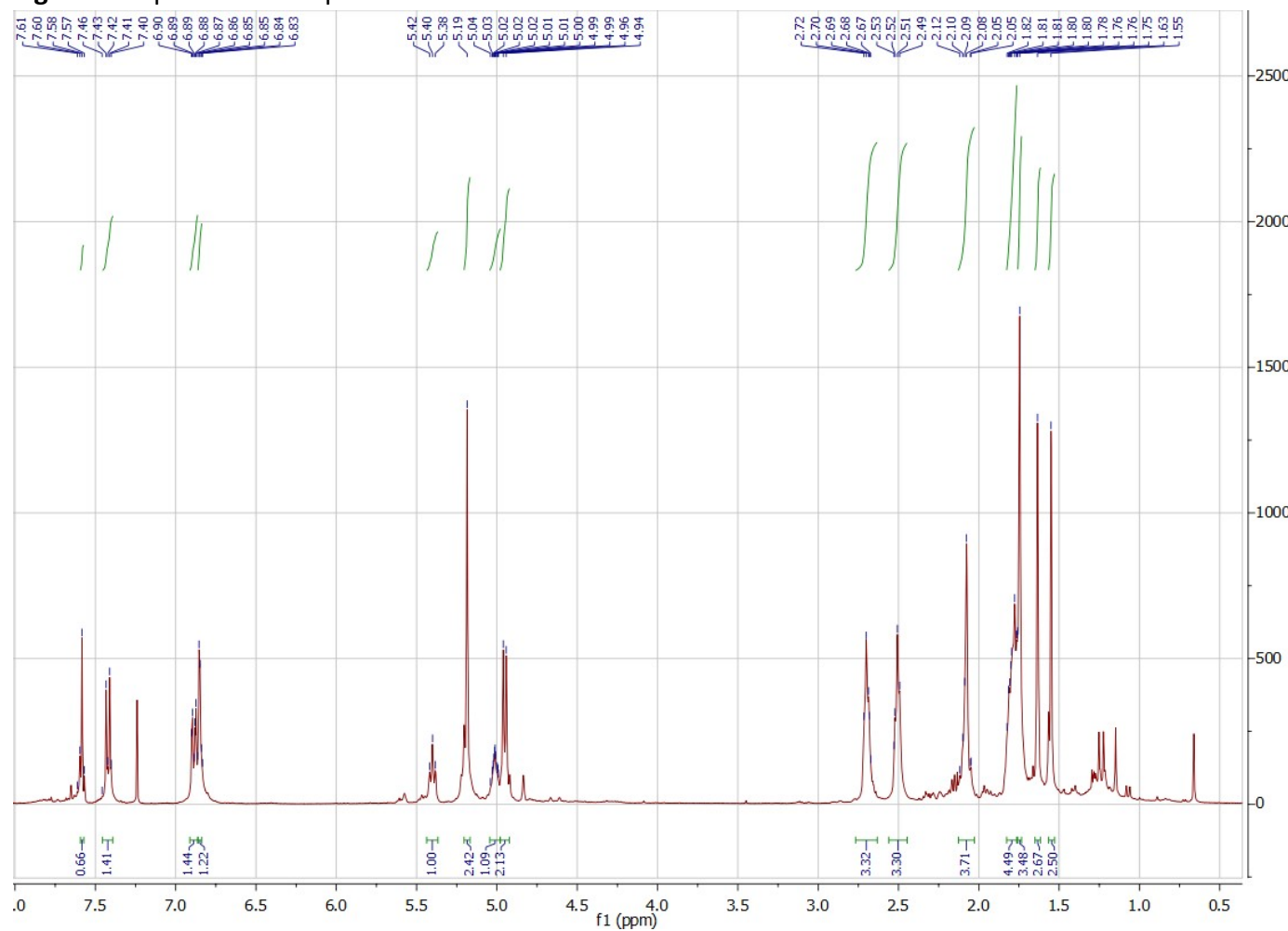


Fig. S8. ^{13}C spectra of Compound 39

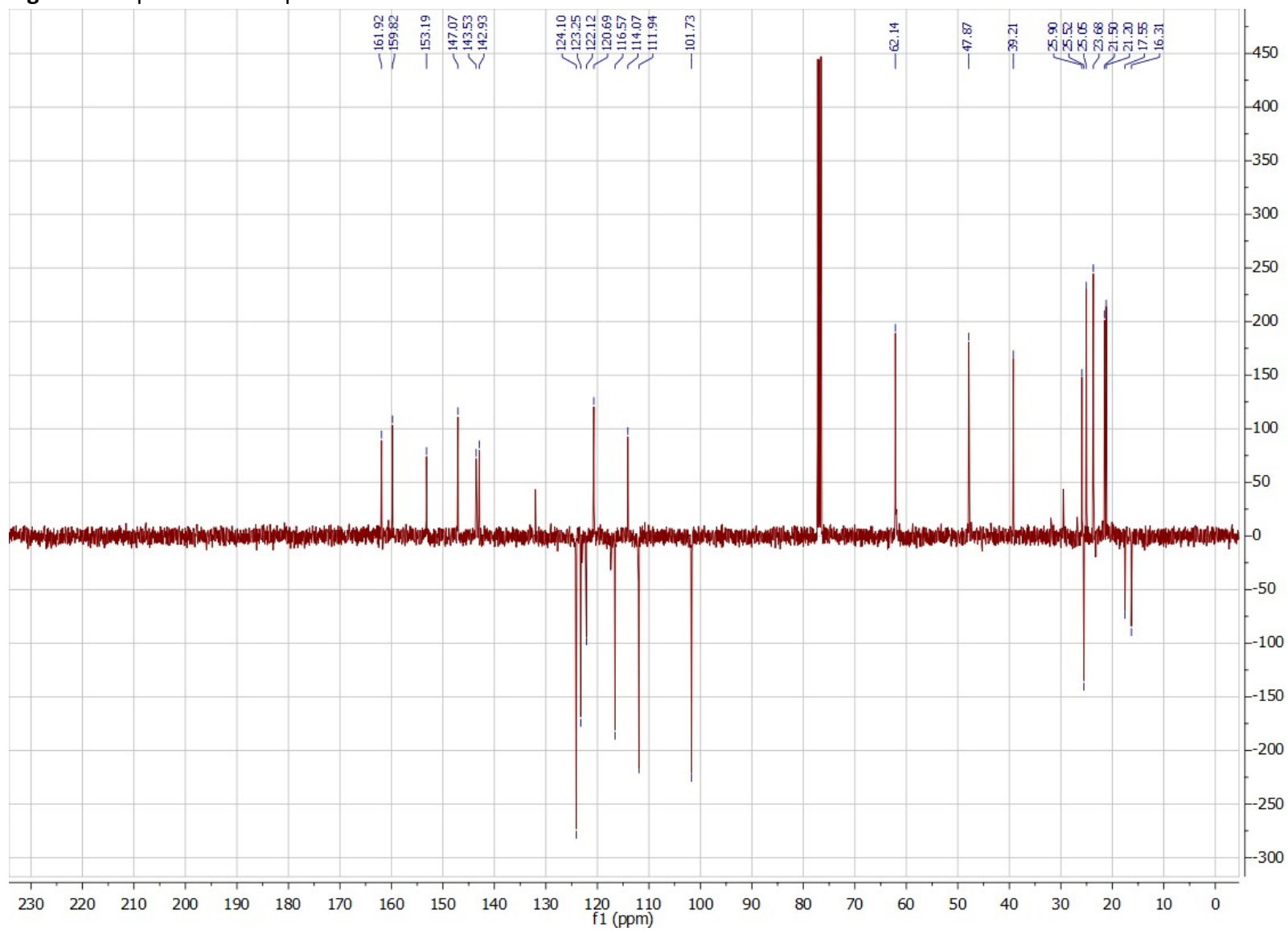


Fig. S9. ¹H spectra of Compound 40

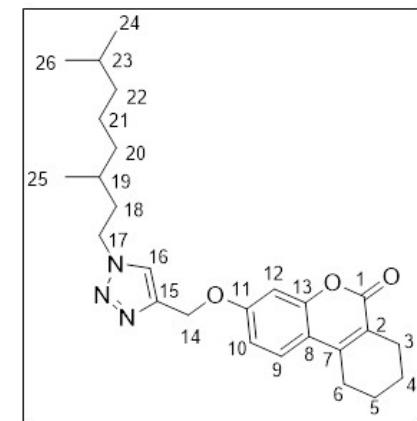
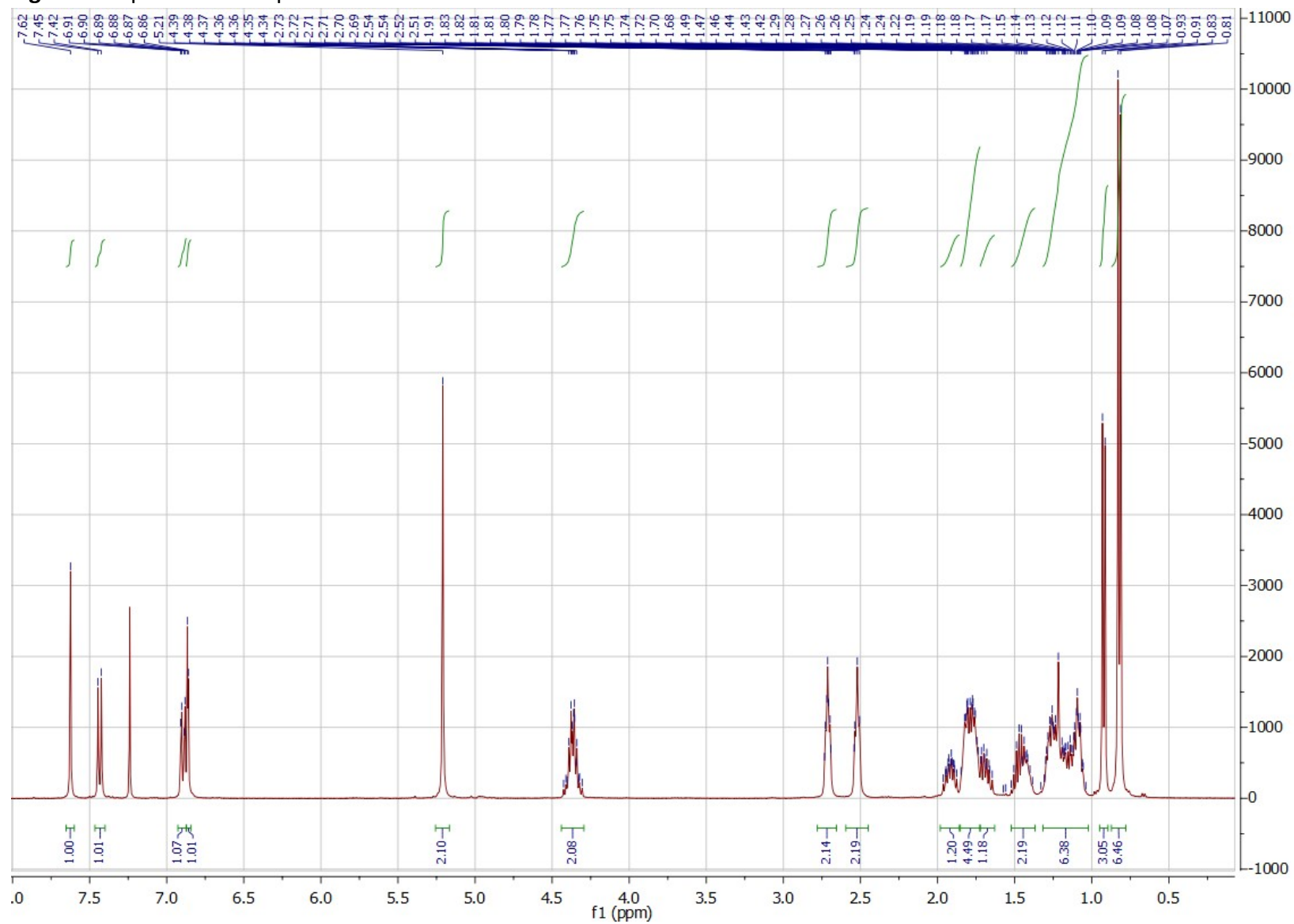


Fig. S10. ^{13}C spectra of Compound 40

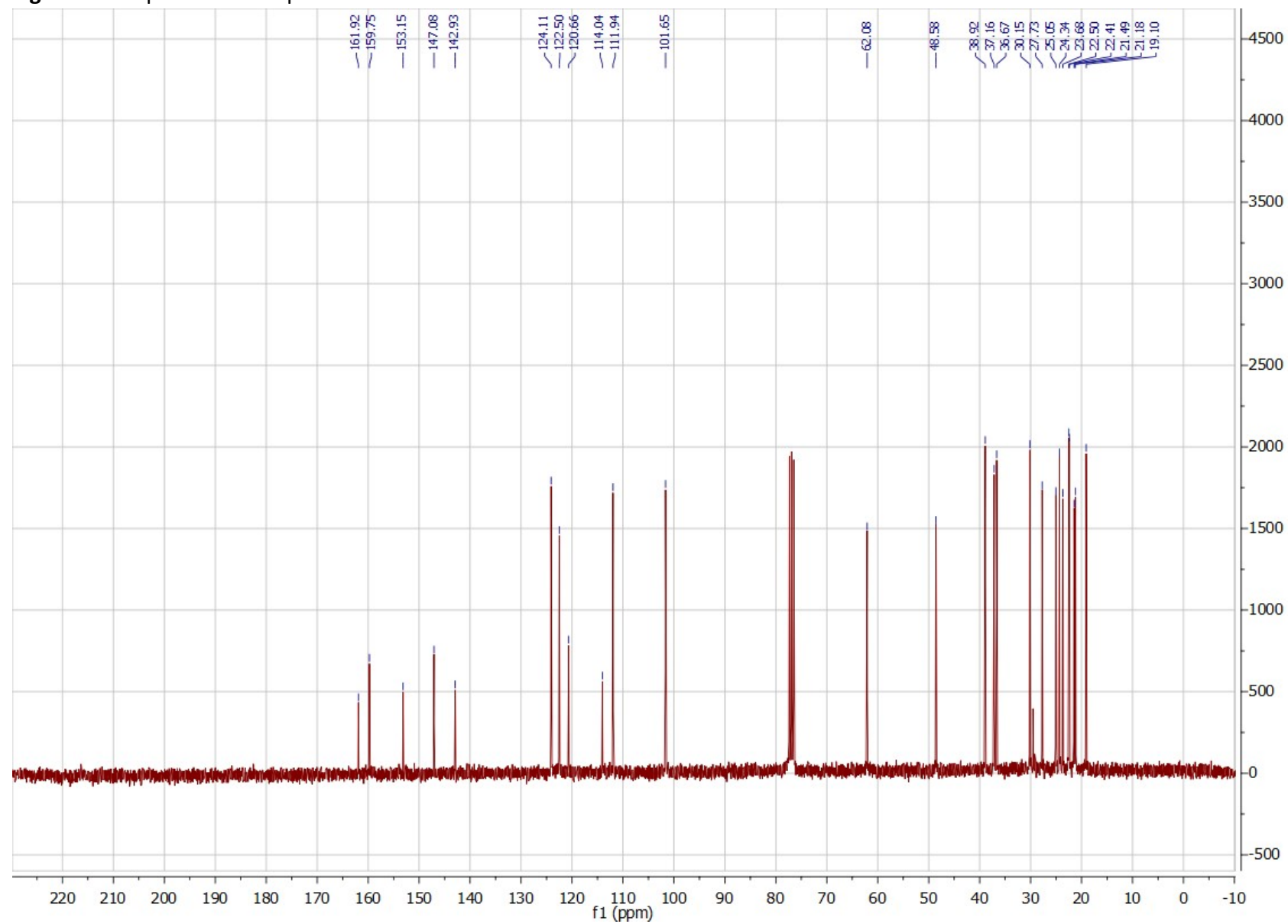


Fig. S11. ¹H spectra of Compound 41

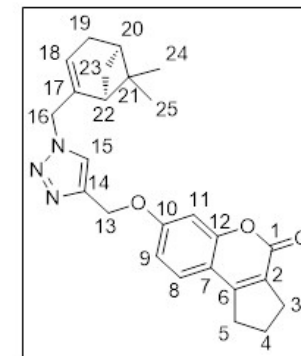
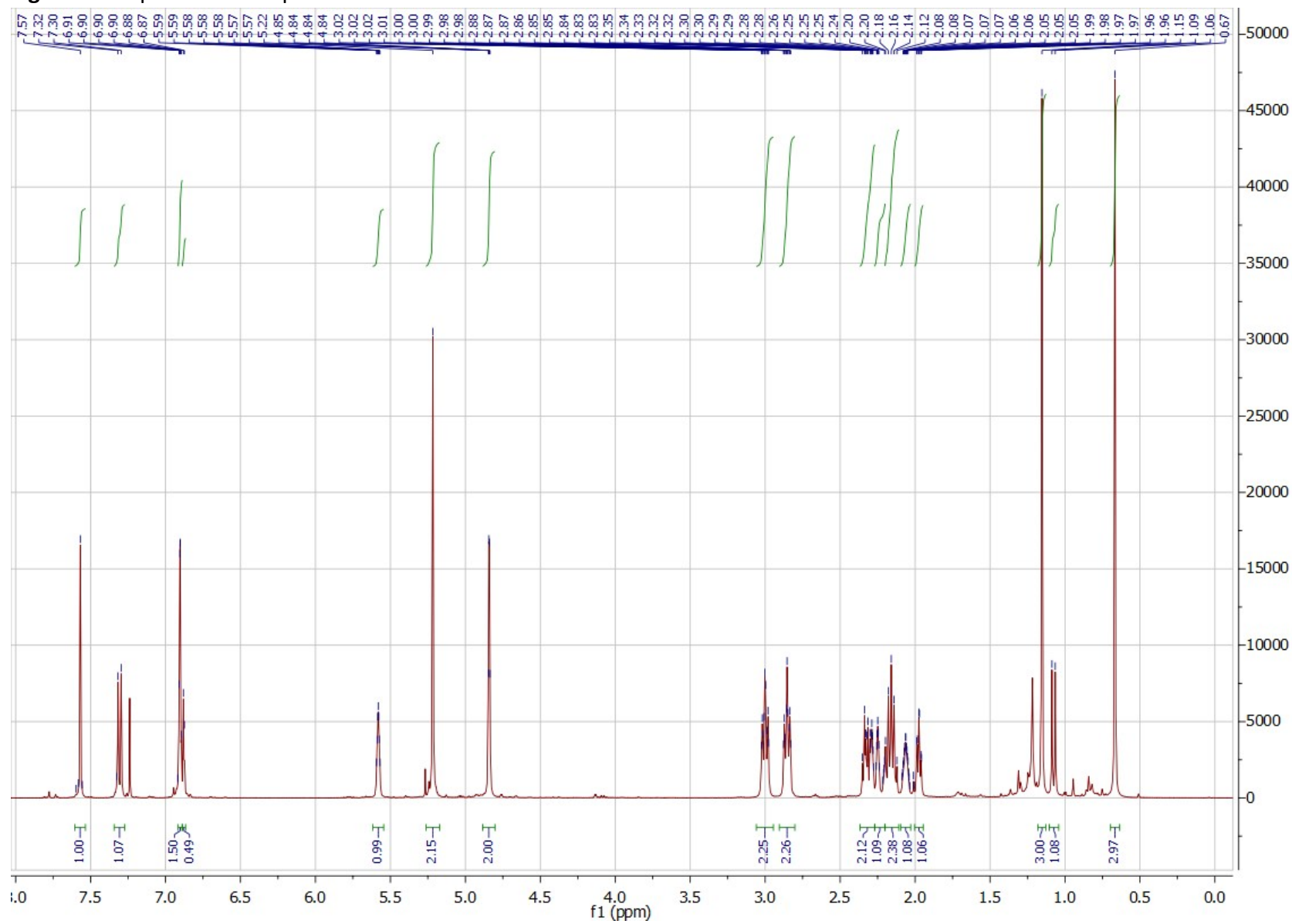


Fig. S12. ^{13}C spectra of Compound 41

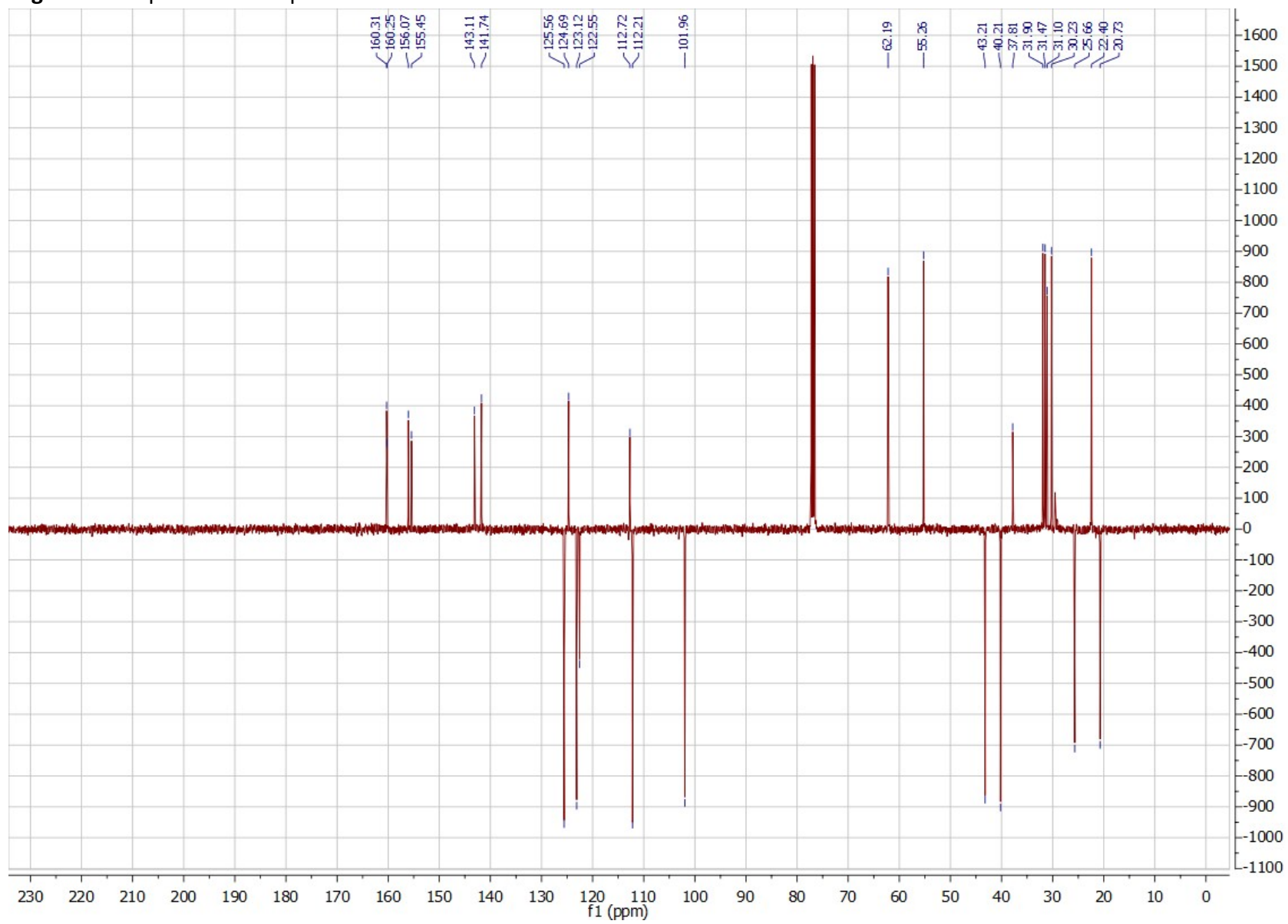


Fig. S13. ¹H spectra of Compound 43

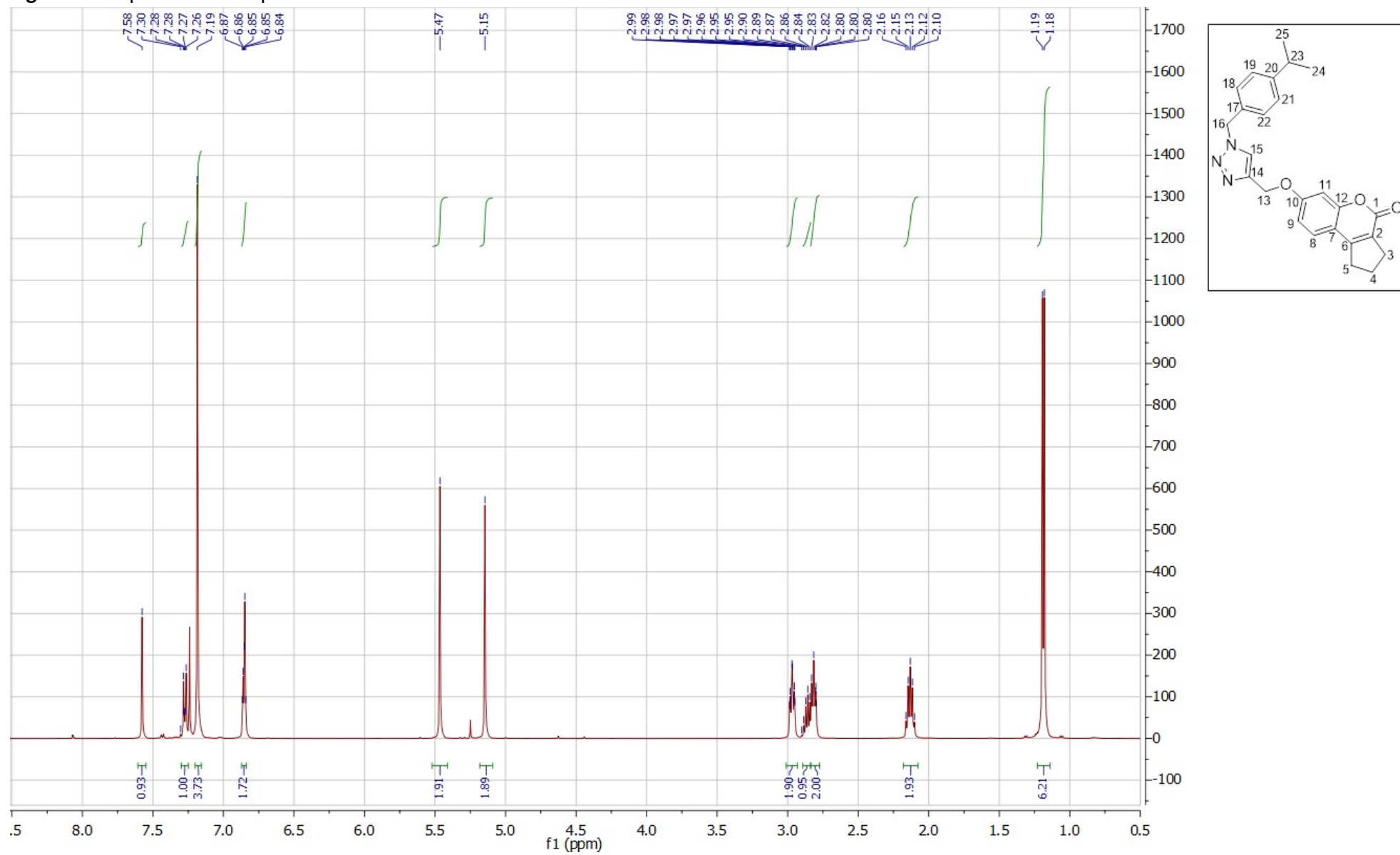


Fig. S14. ^1H spectra of Compound **43**

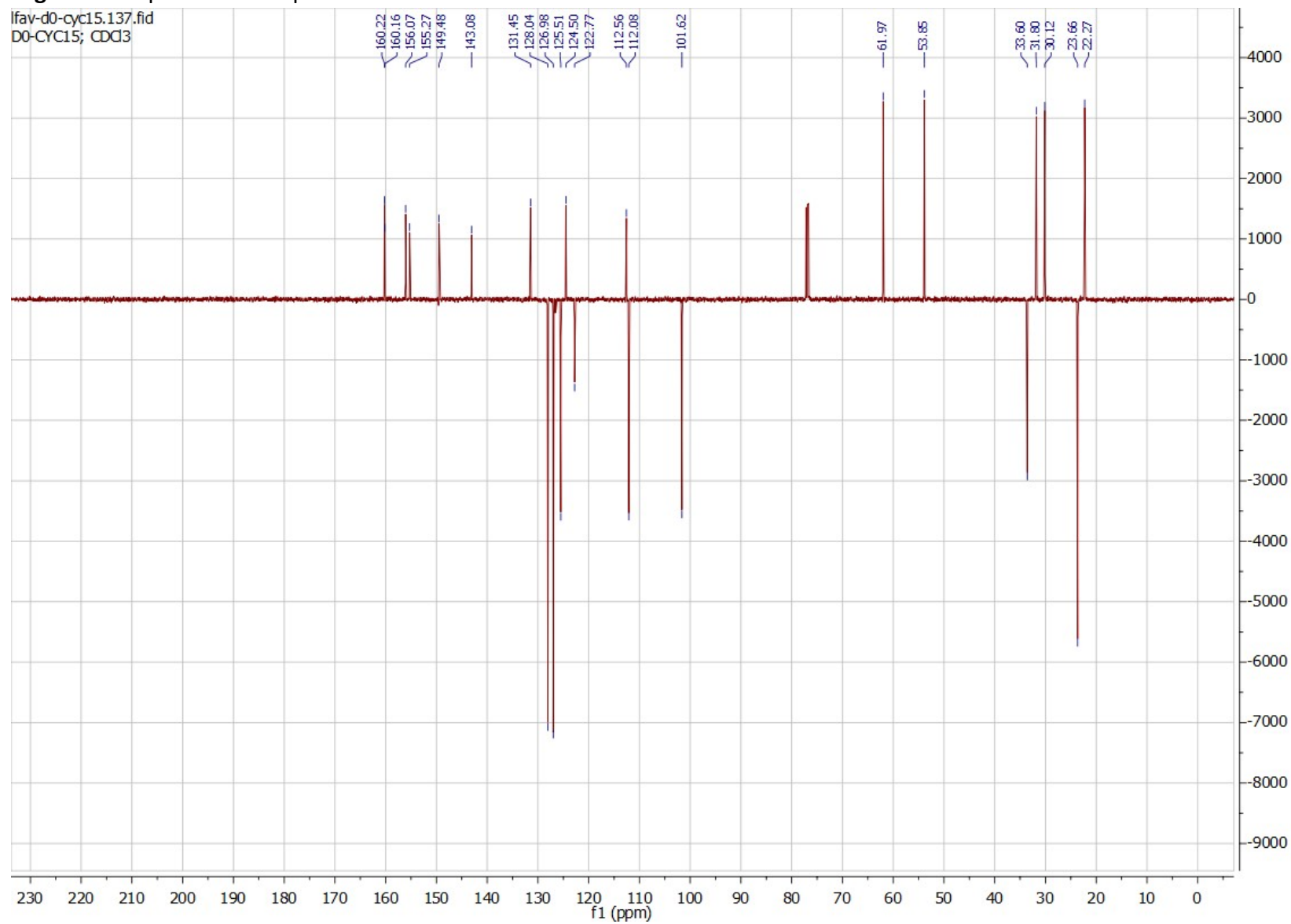


Fig. S15. ¹H spectra of Compound 44

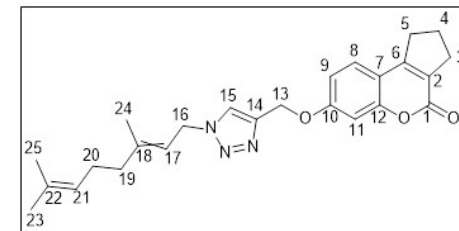
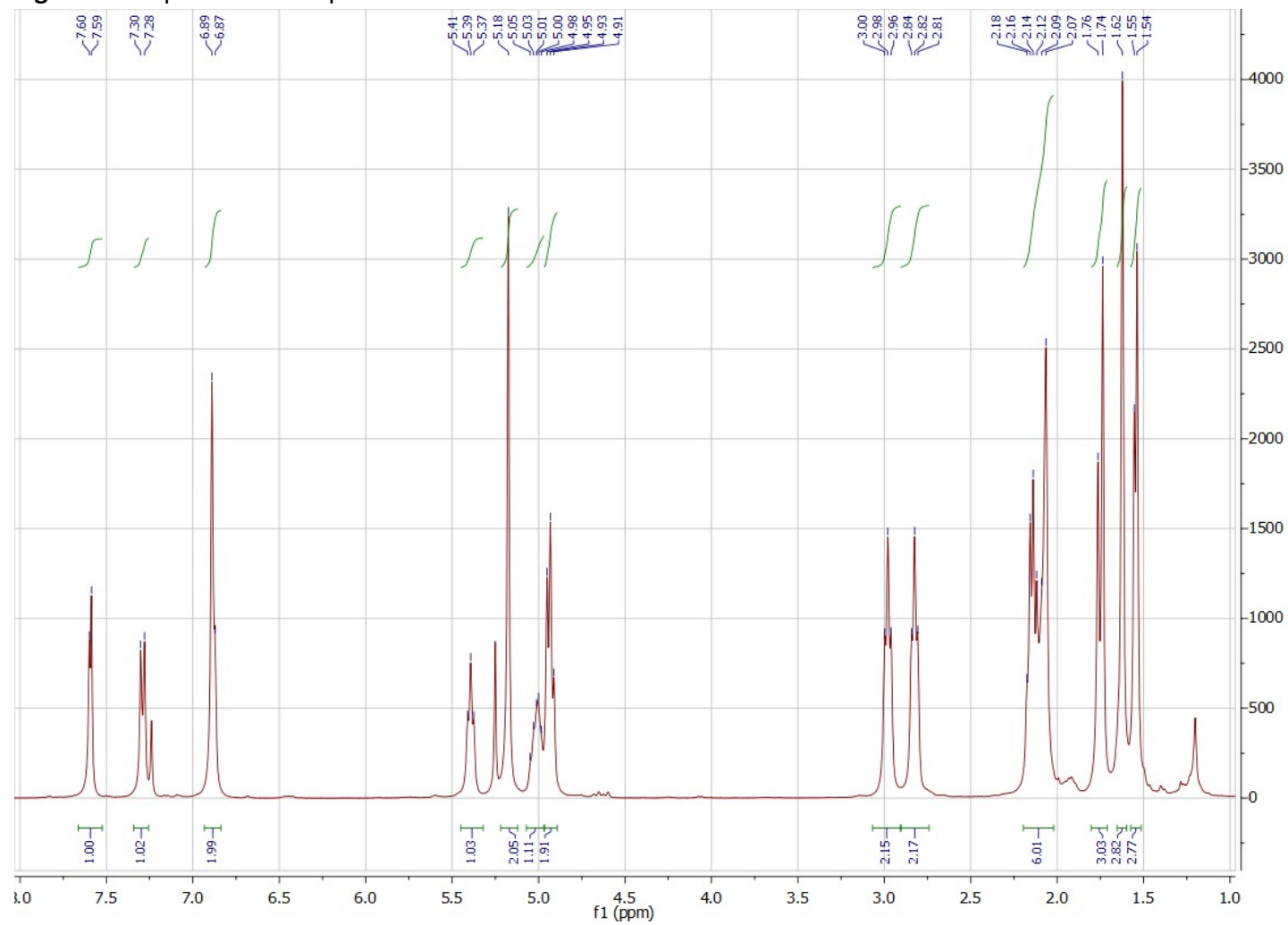


Fig. S16. ^{13}C spectra of Compound 44

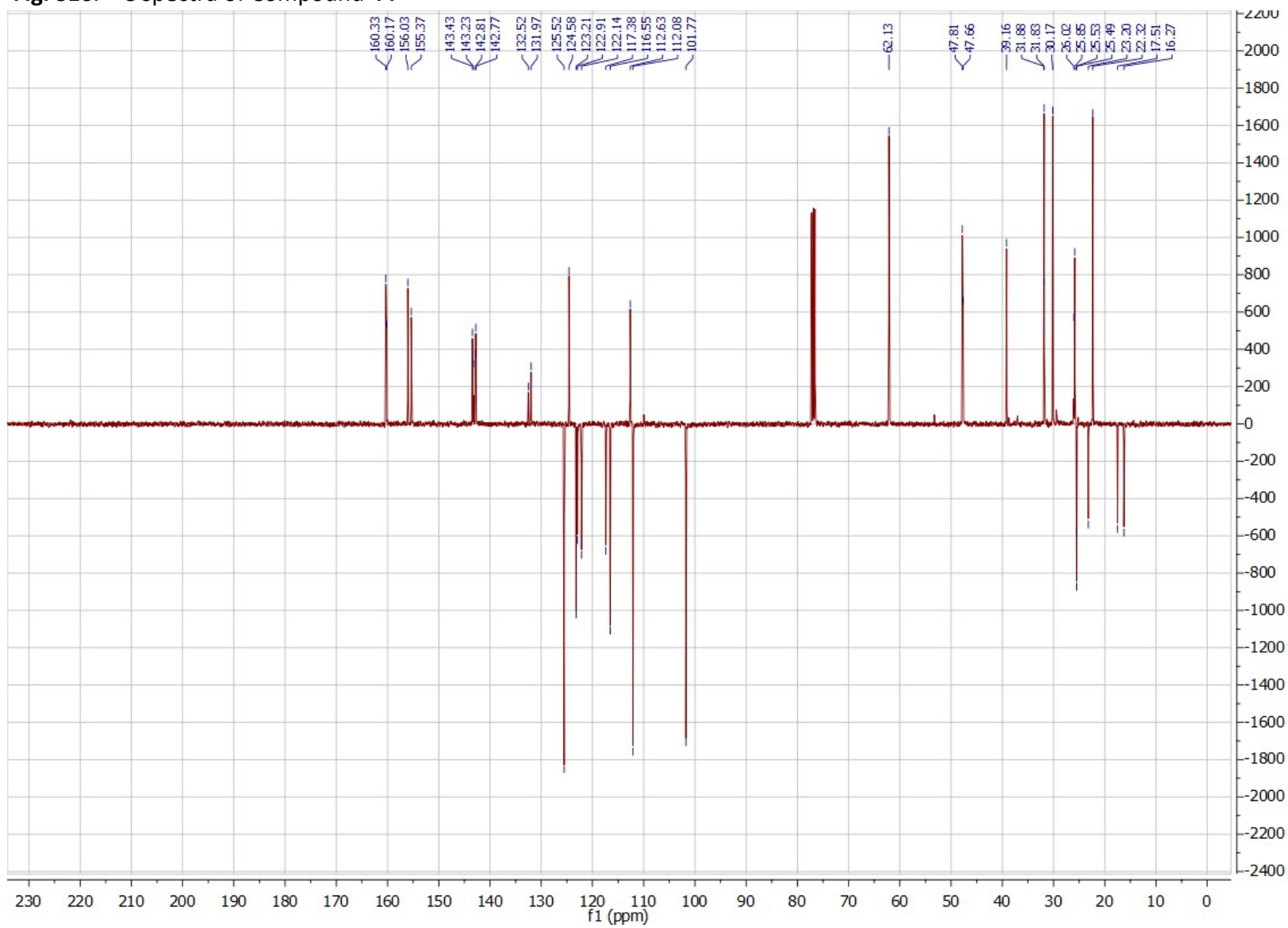


Fig. S17. ¹H spectra of Compound 45

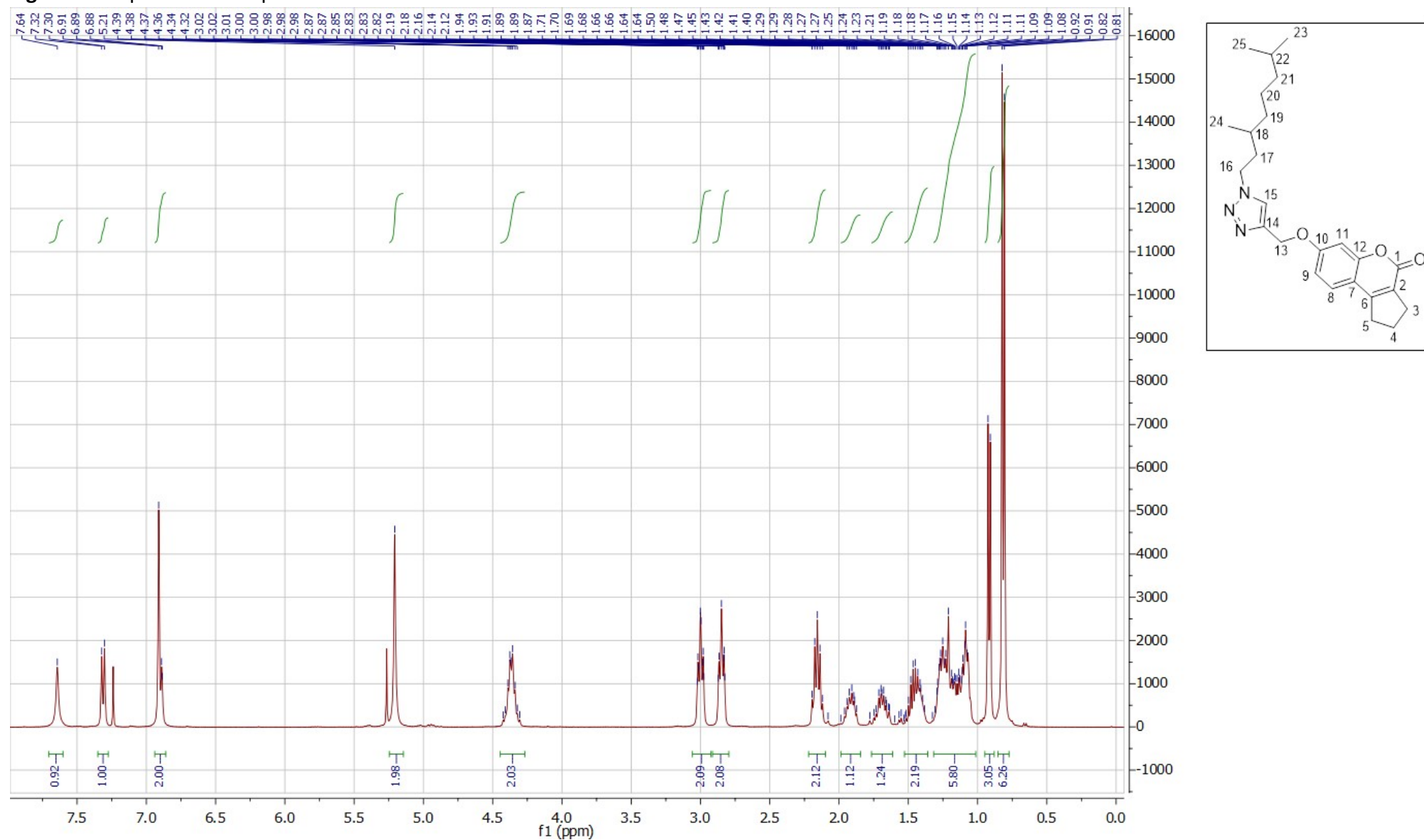


Fig. S18. ^{13}C spectra of Compound 45

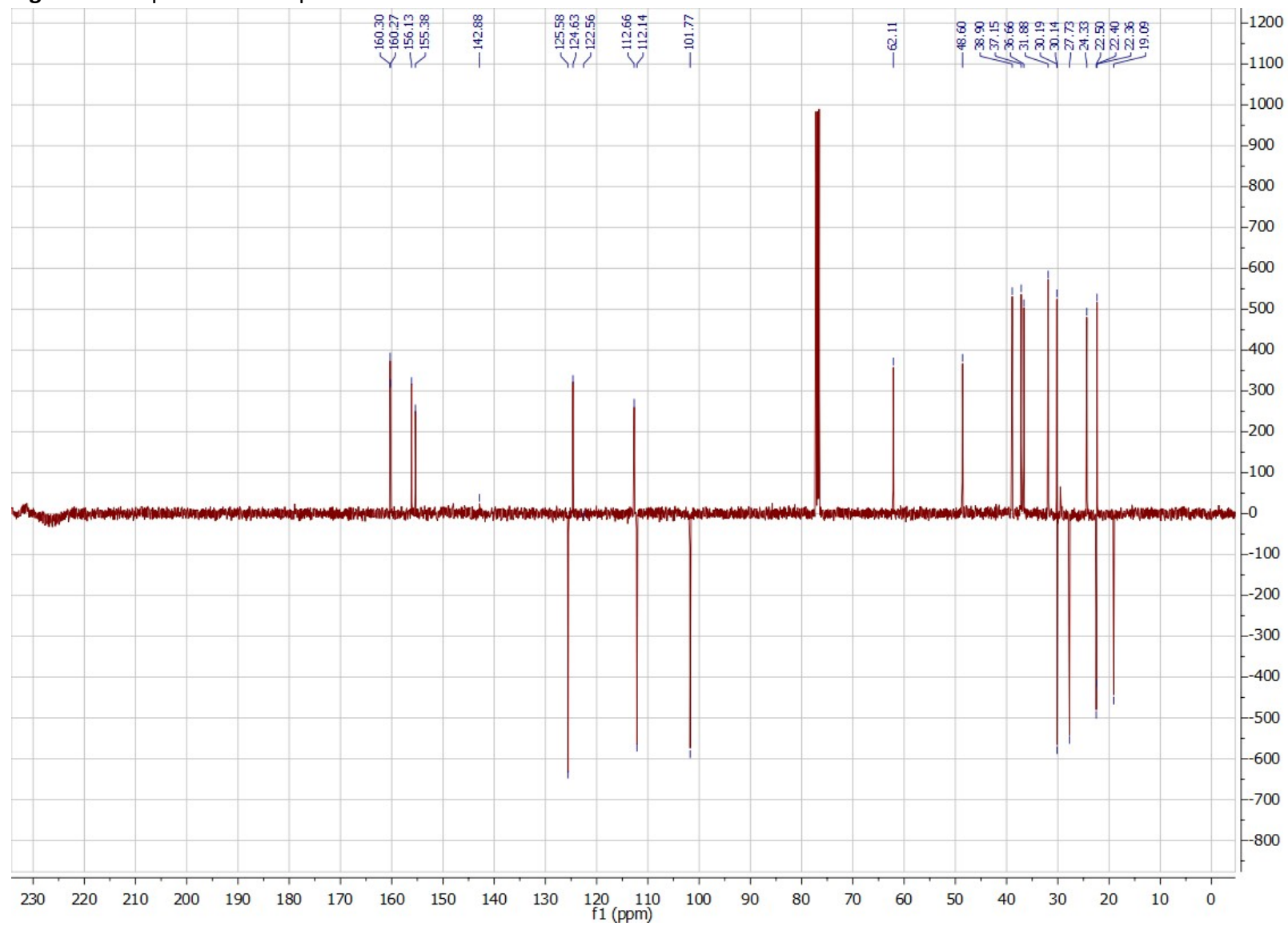


Fig. S20. ^{13}C spectra of Compound 46

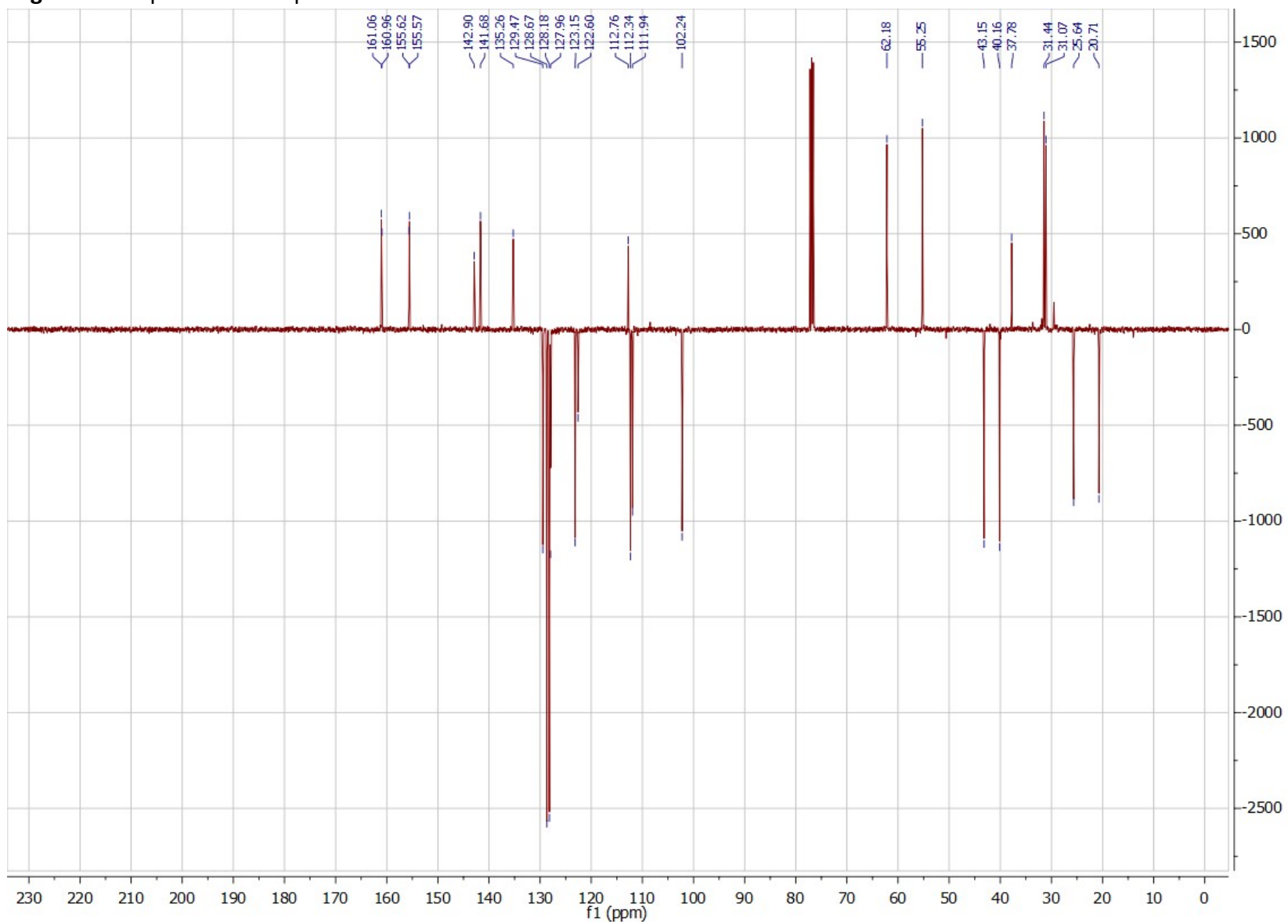


Fig. S21. ¹H spectra of Compound 48

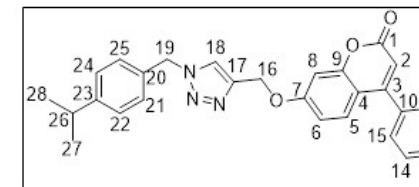
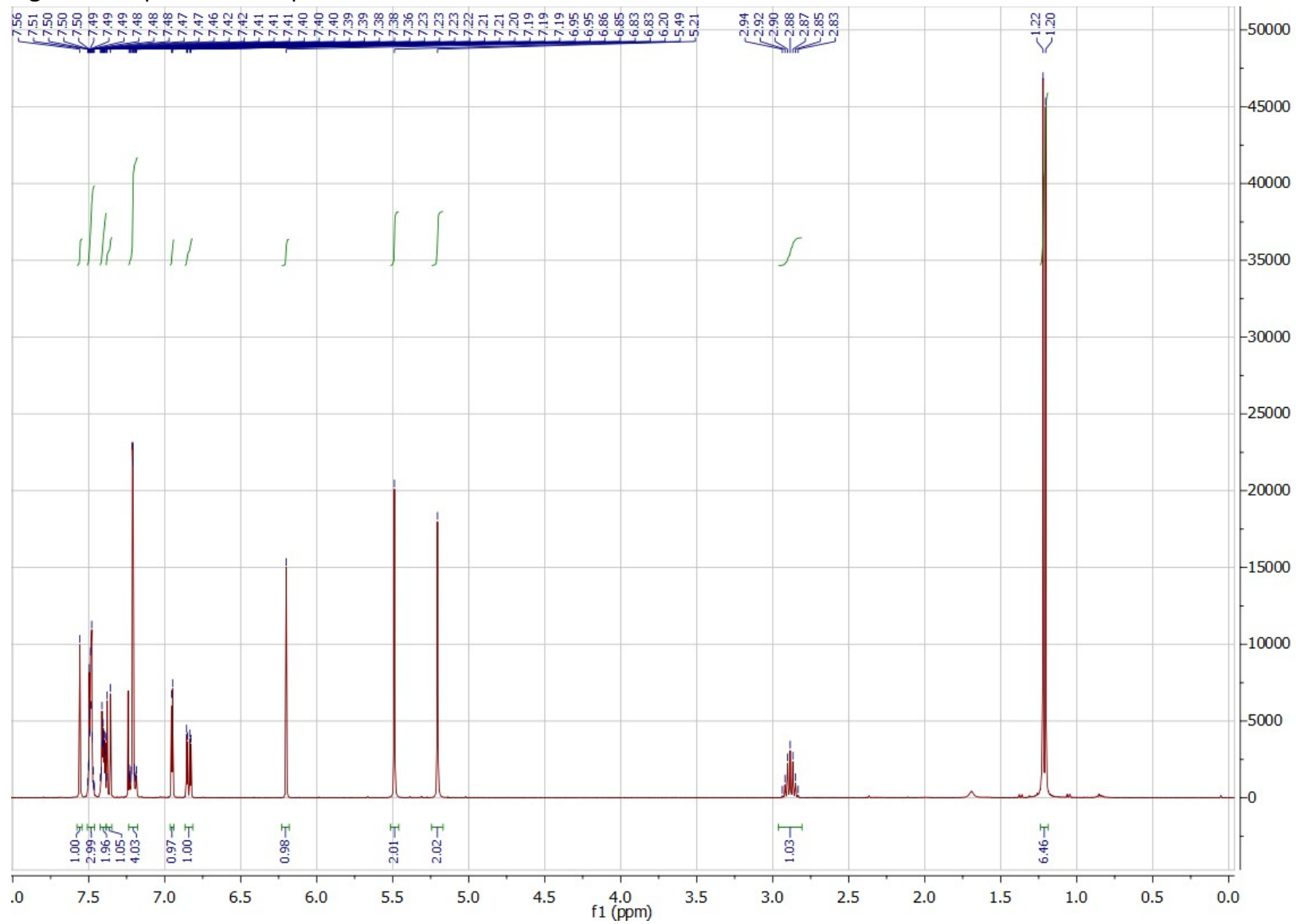


Fig. S22. ^{13}C spectra of Compound 48

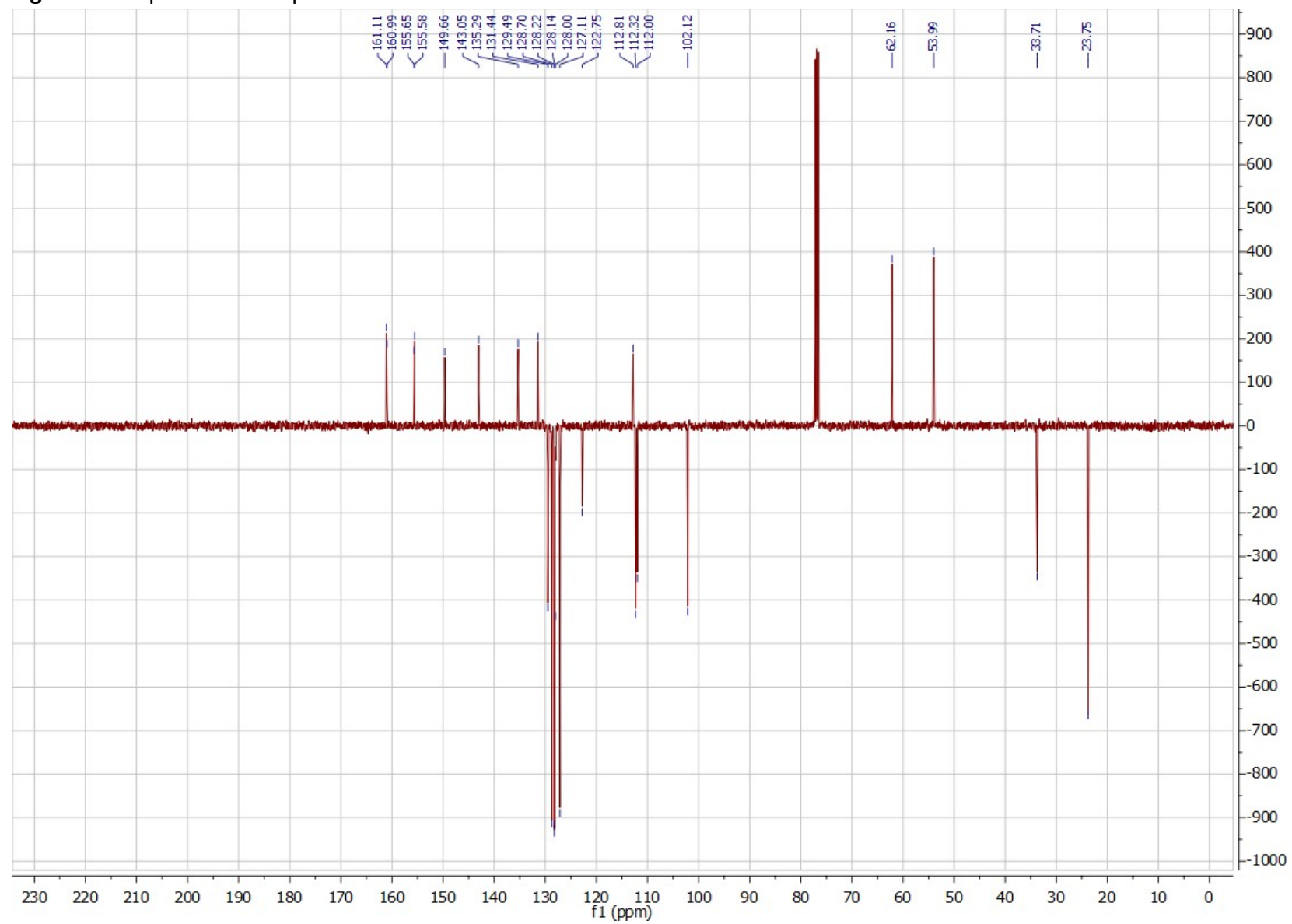


Fig. S23. ¹H spectra of Compound 49

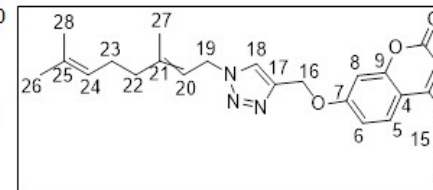
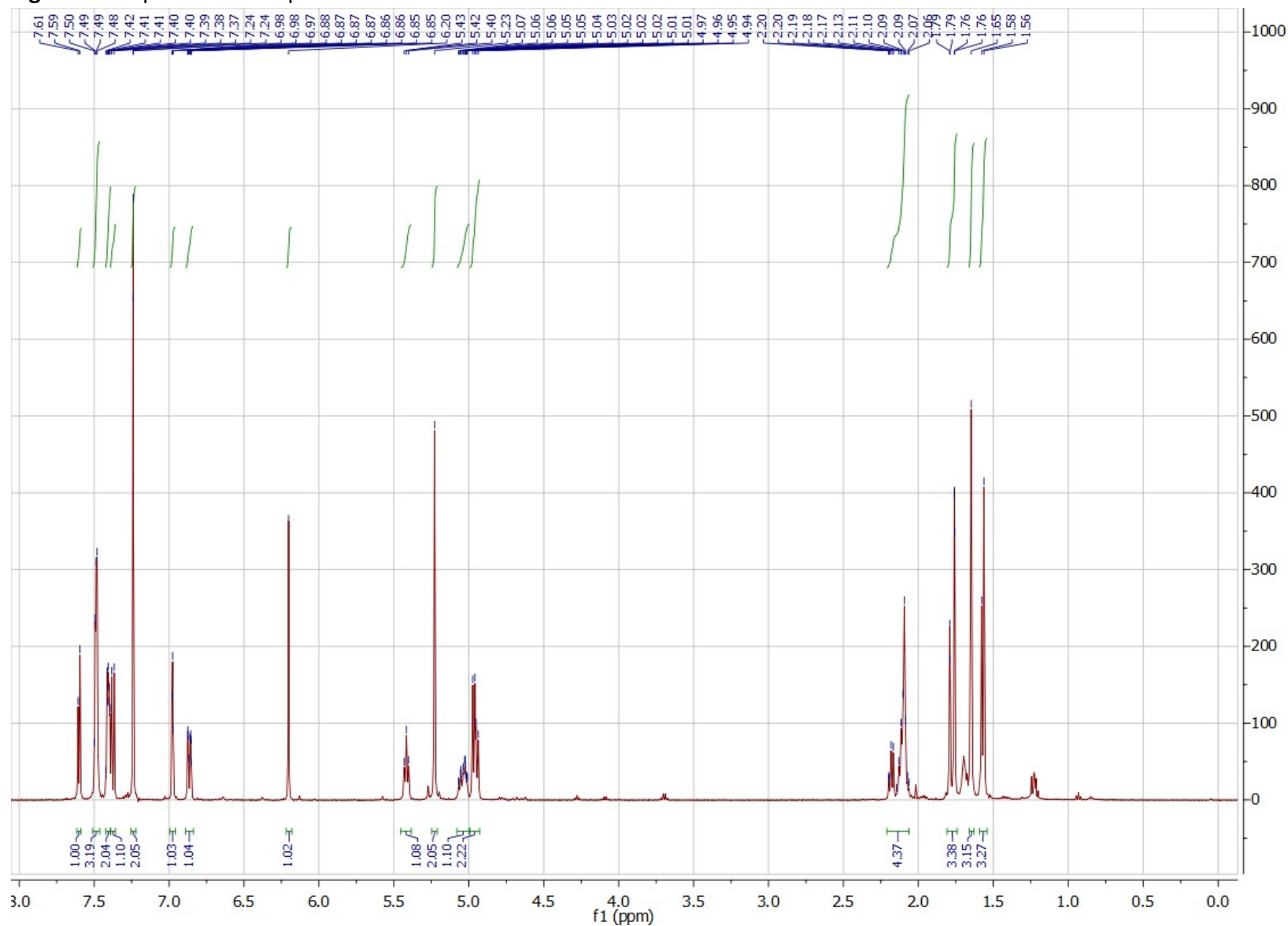


Fig. S24. ¹³C spectra of Compound 49

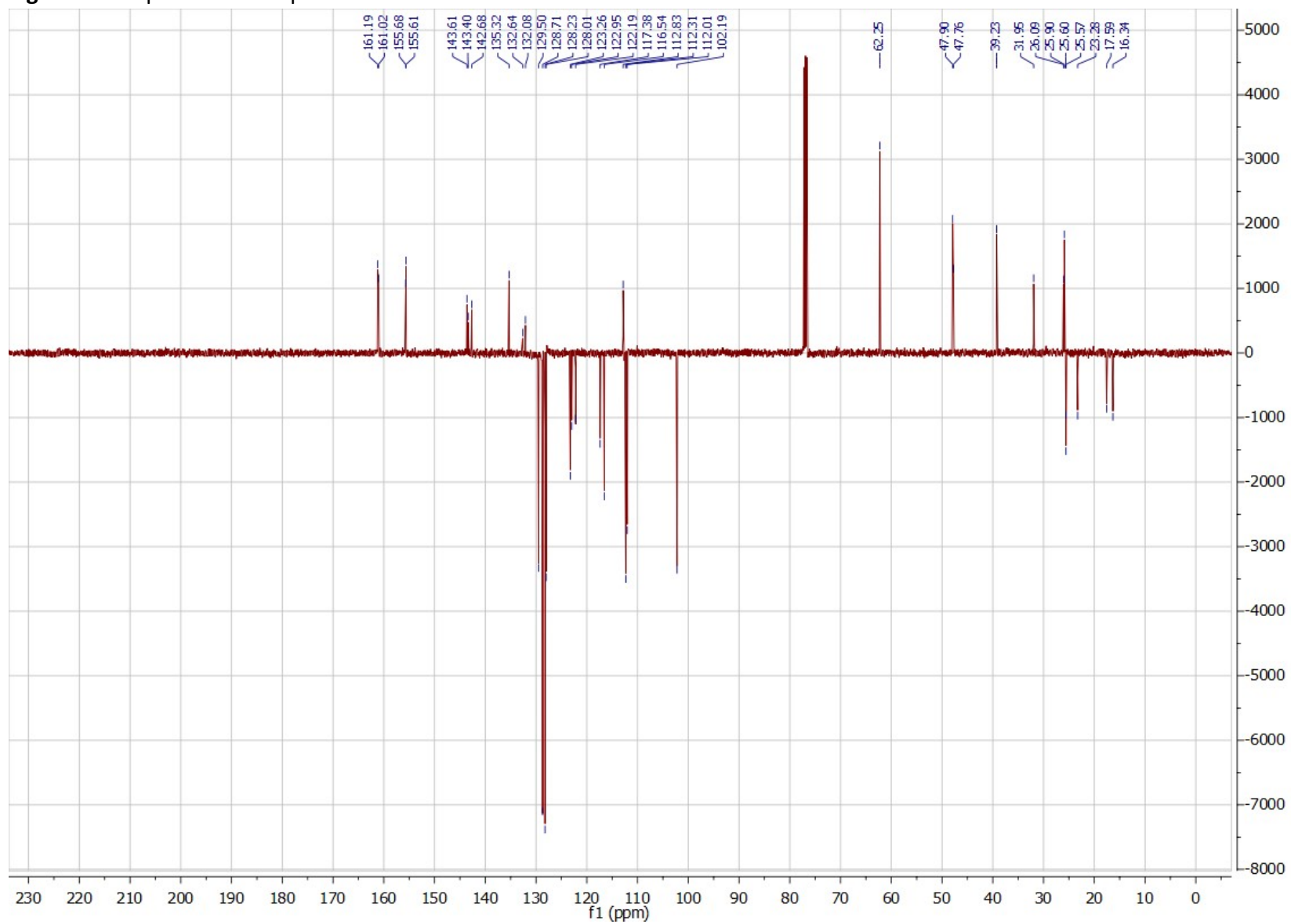


Fig. S25. ¹H spectra of Compound 50

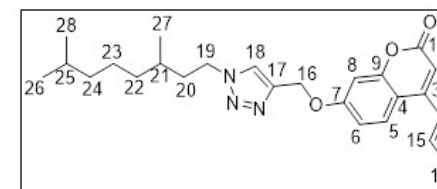
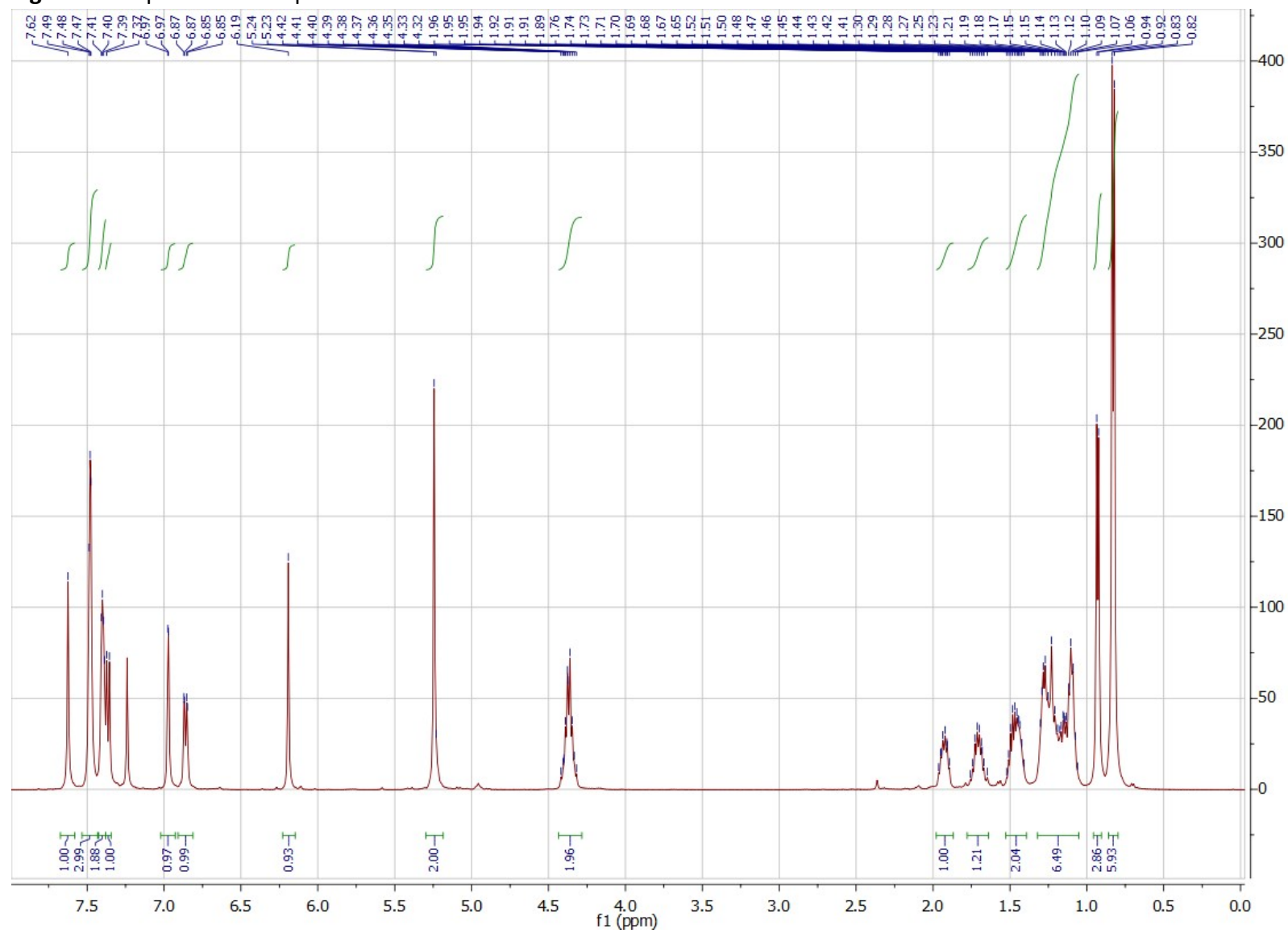


Fig. S26. ^{13}C spectra of Compound 50

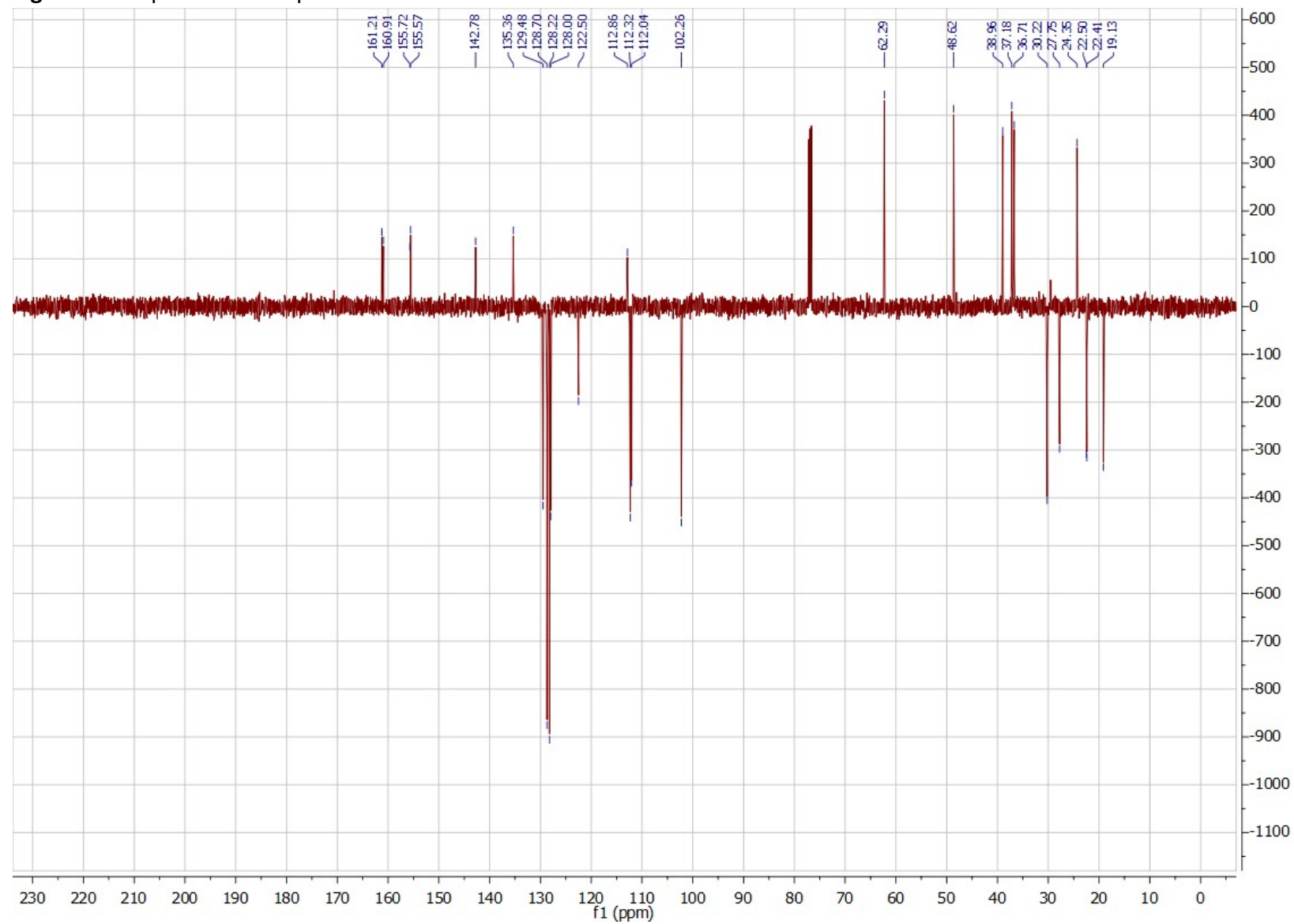


Fig. S27. ¹H spectra of Compound 51

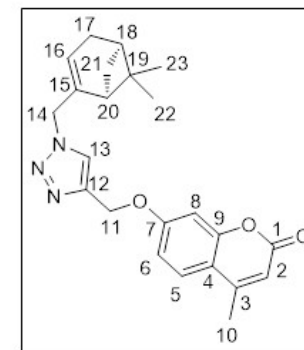
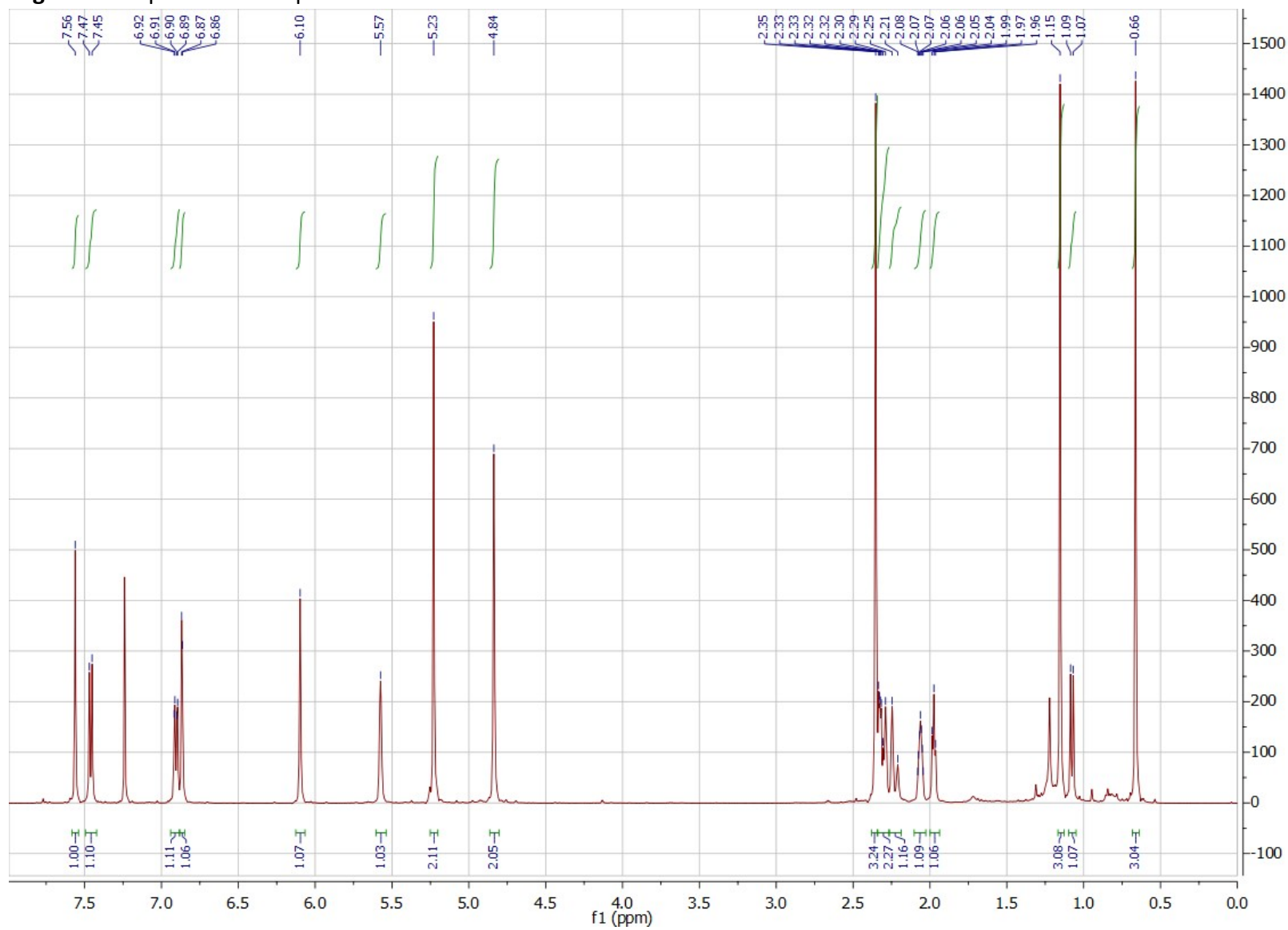


Fig. S28. ^{13}C spectra of Compound 51

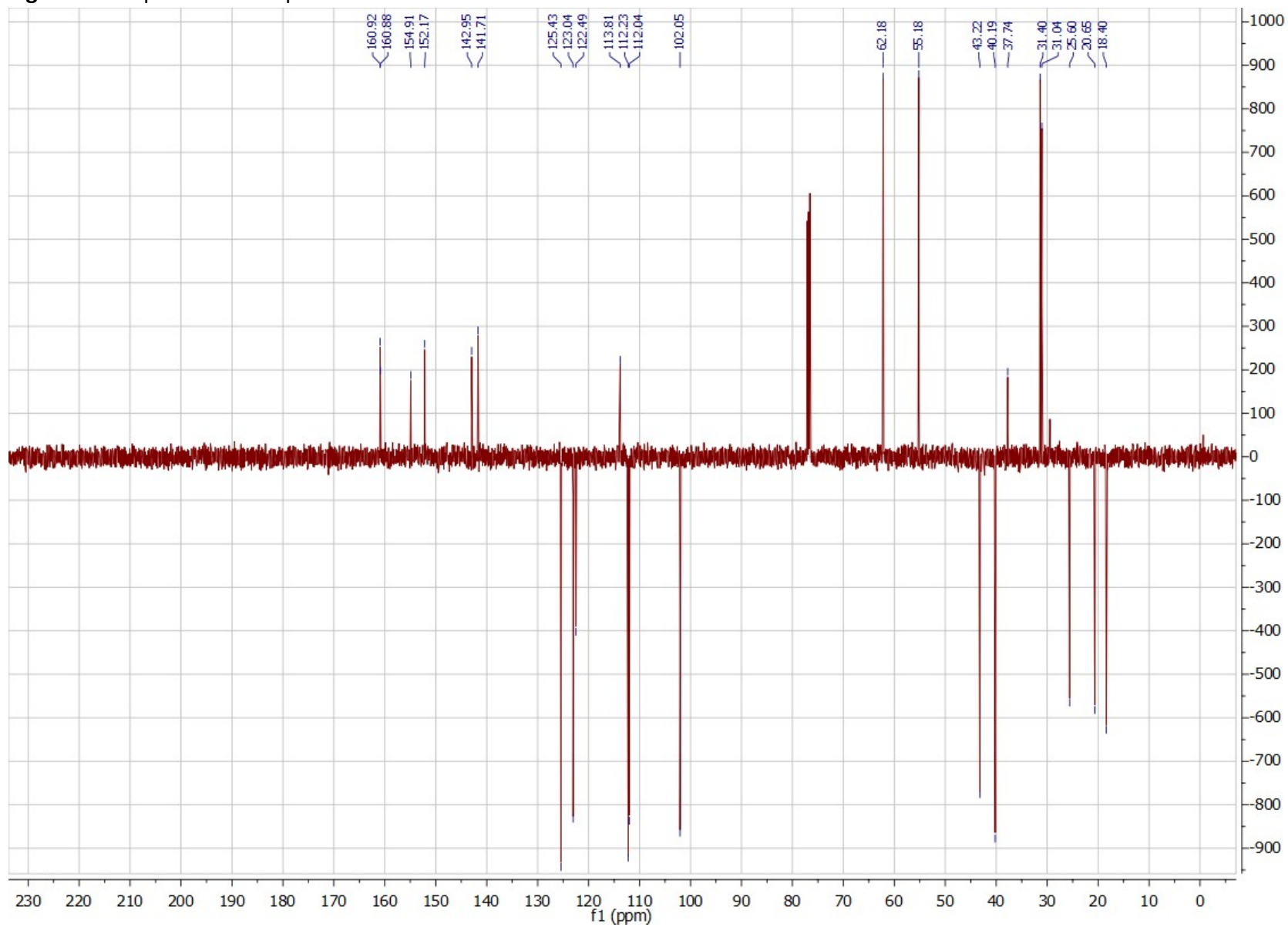


Fig. S29. ¹H spectra of Compound 53

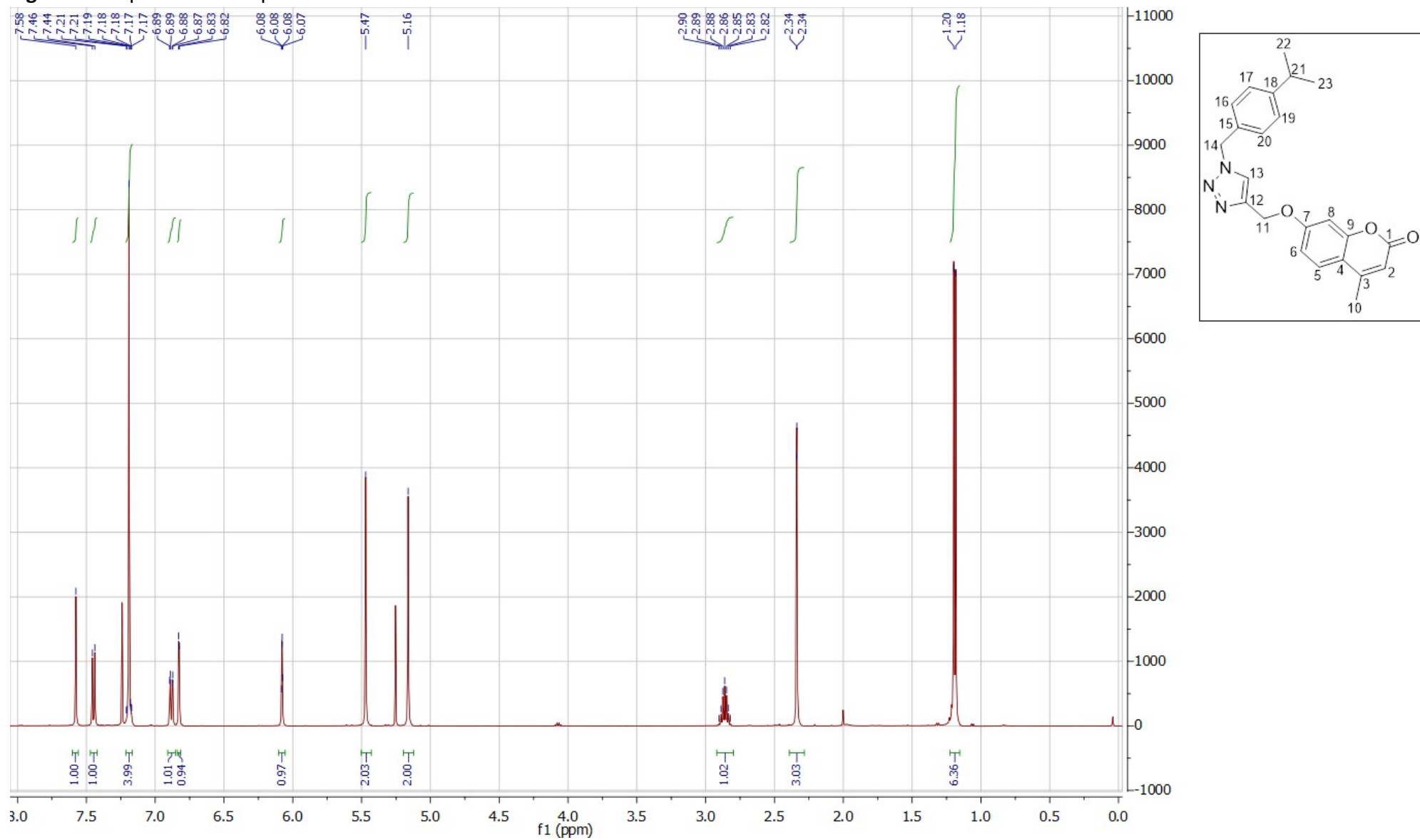


Fig. S30. ^{13}C spectra of Compound 53

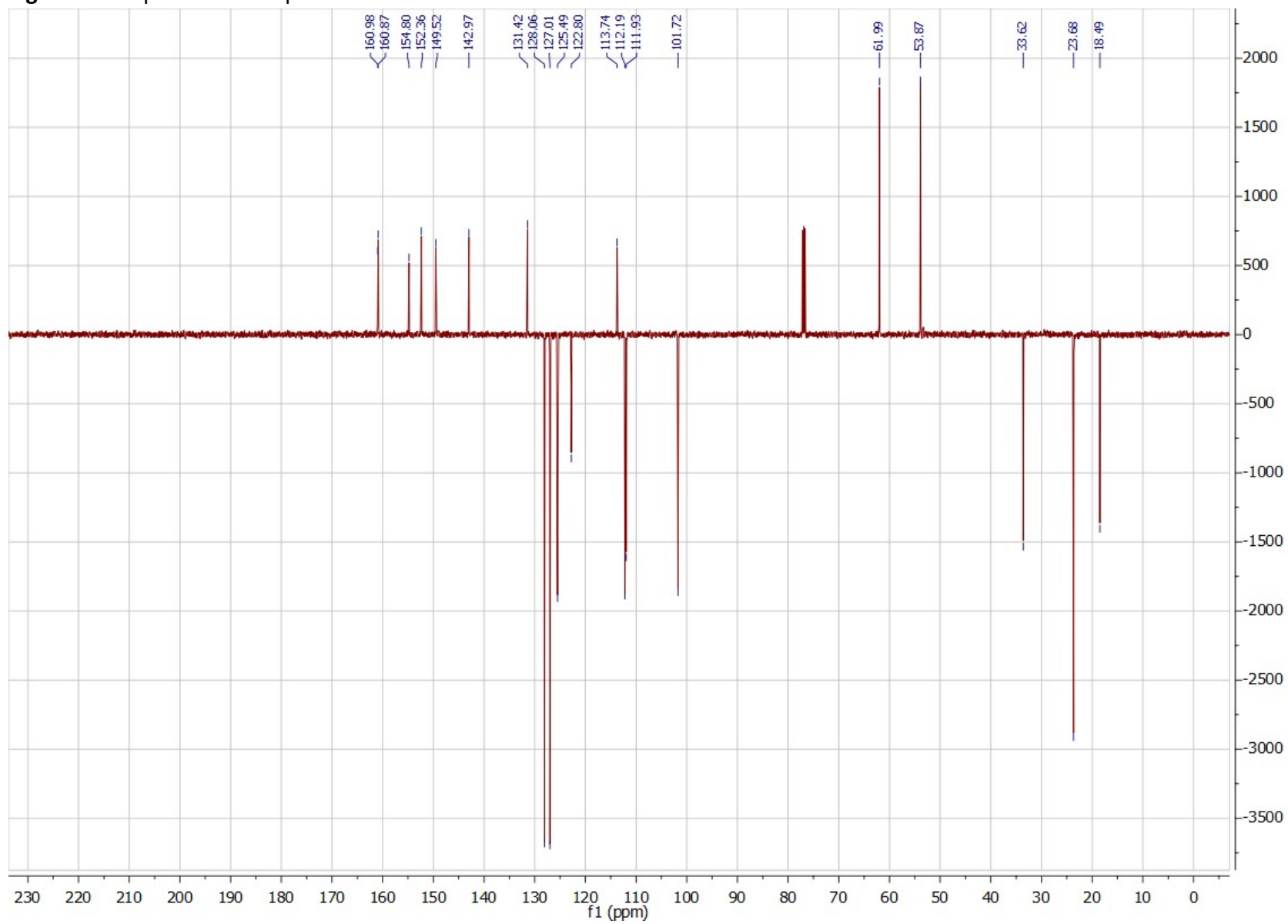


Fig. S31. ¹H spectra of Compound 54-E

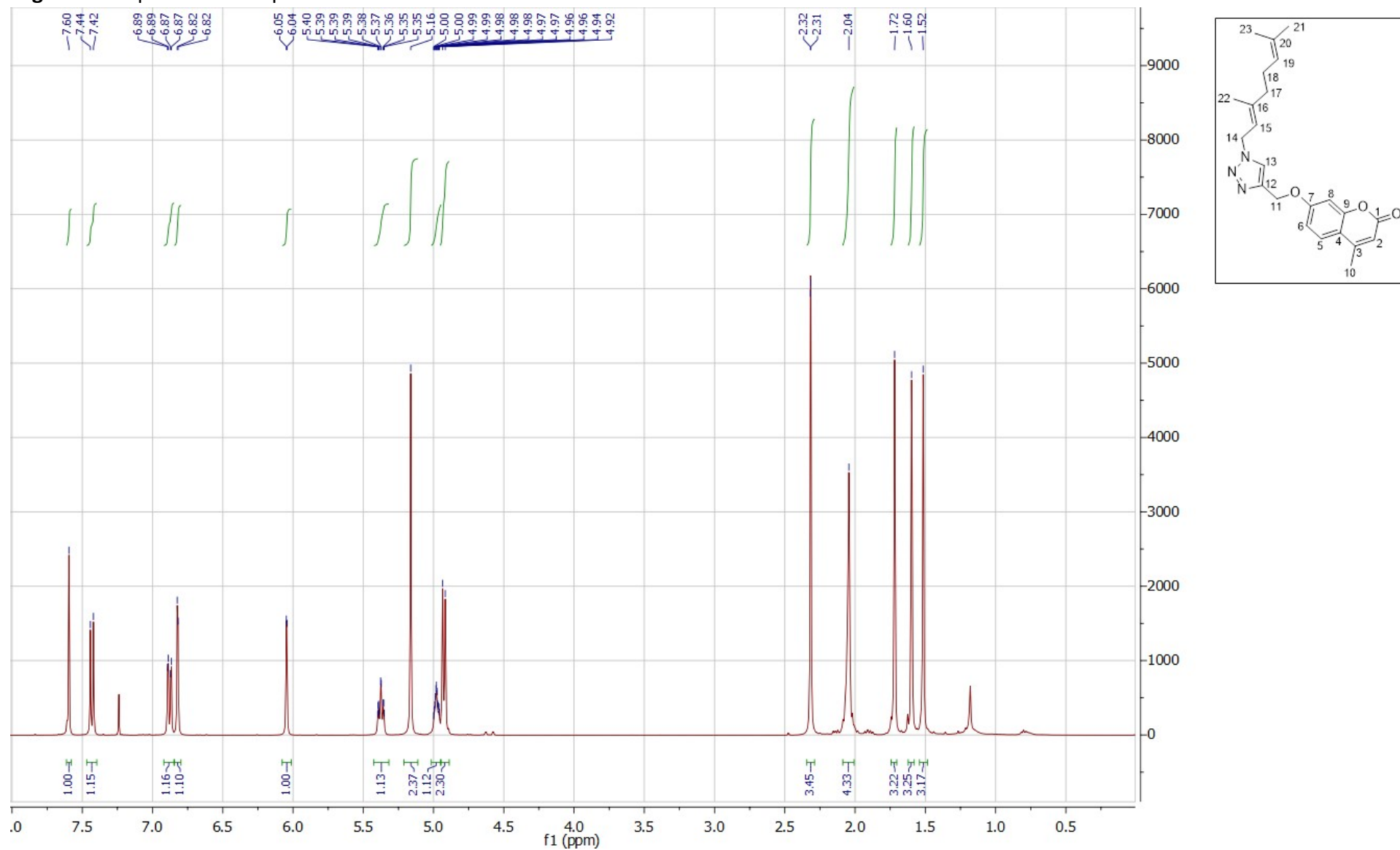


Fig. S32. ^{13}C spectra of Compound 54-E

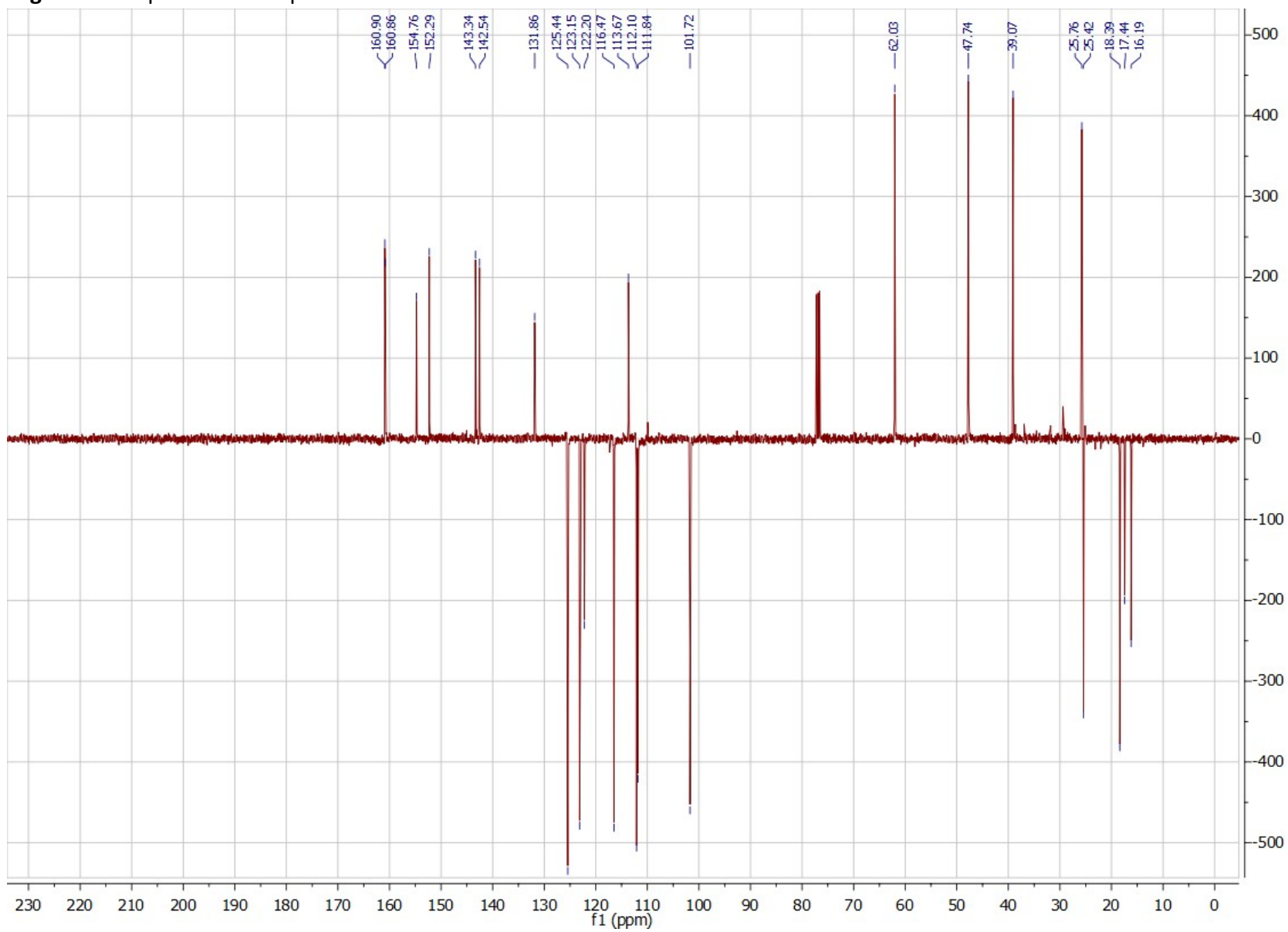


Fig. S33. ¹H spectra of Compound 54-Z

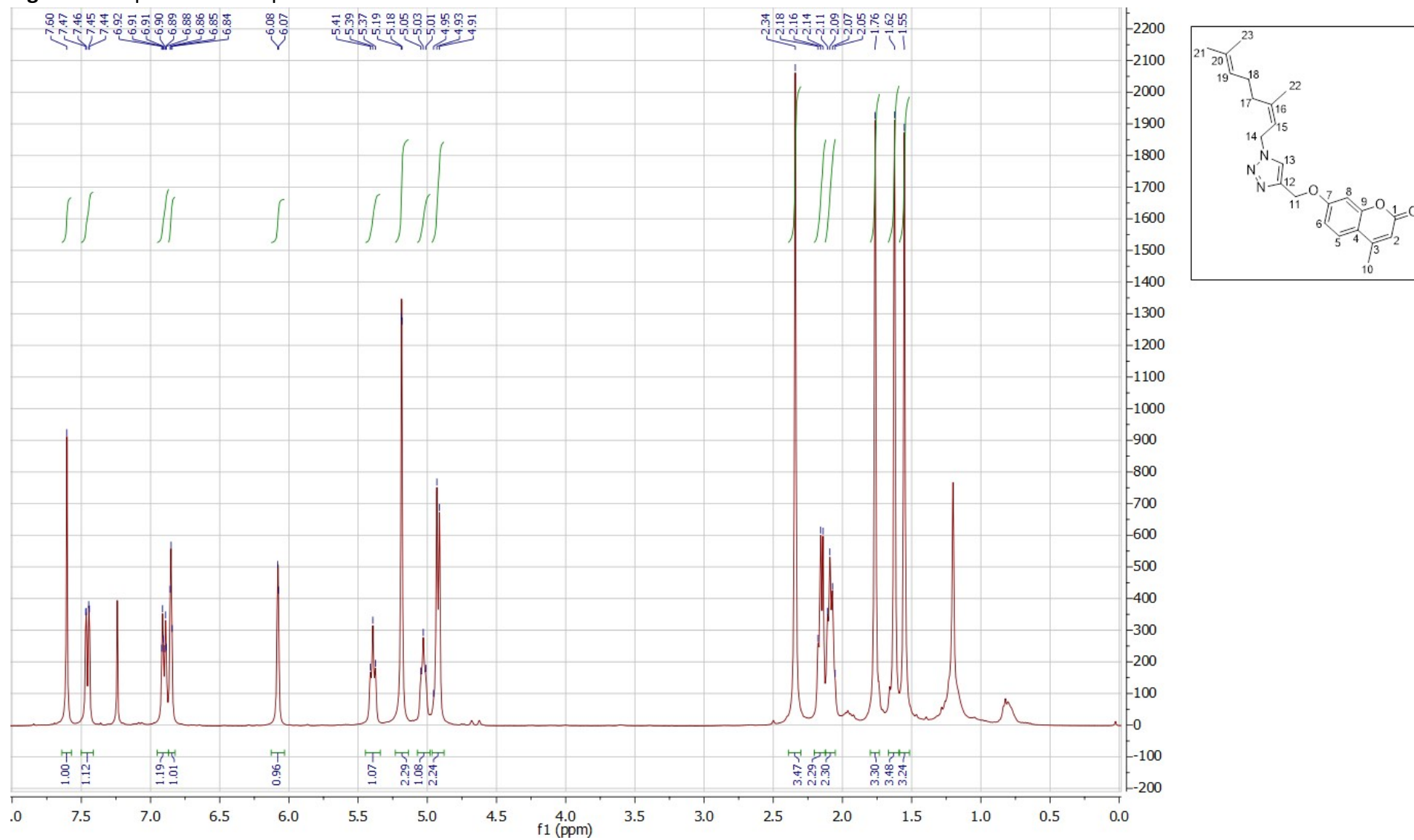


Fig. S34. ^{13}C spectra of Compound 54-Z

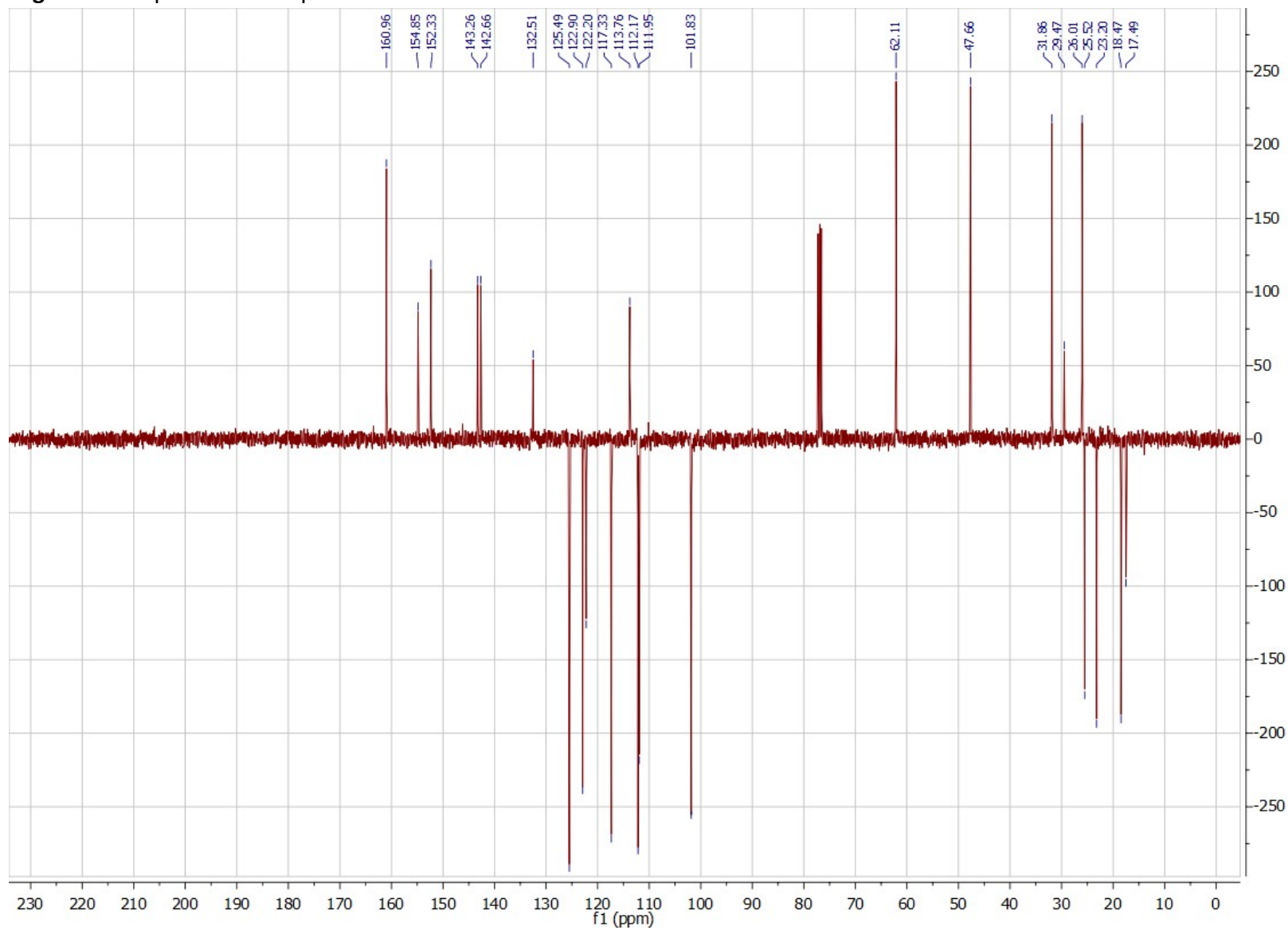


Fig. S35. ¹H spectra of Compound 55

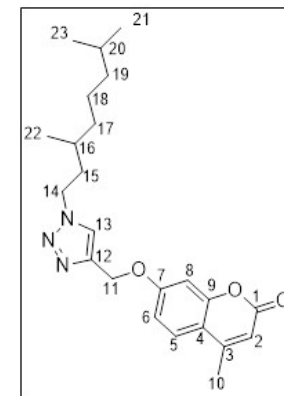
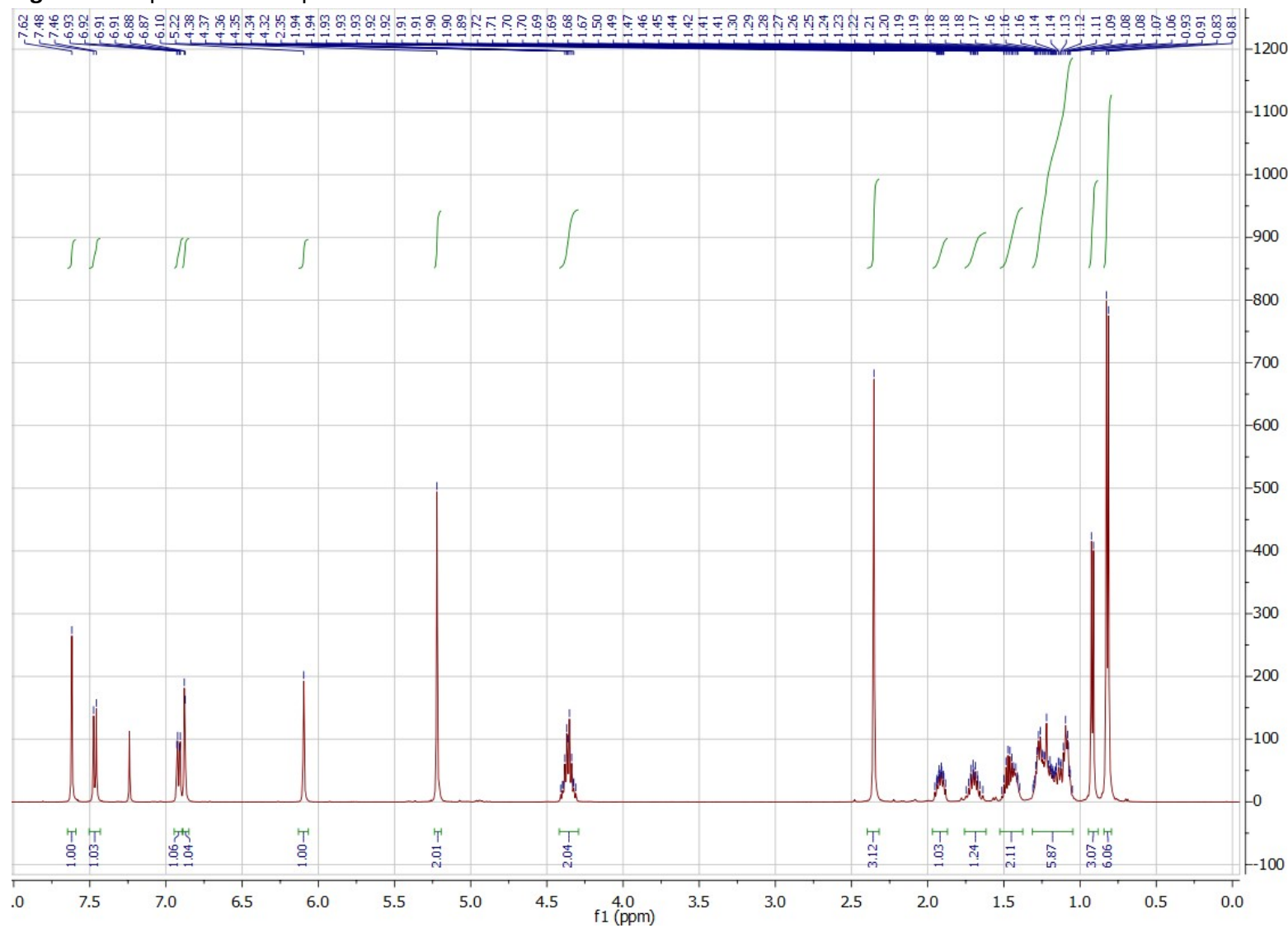
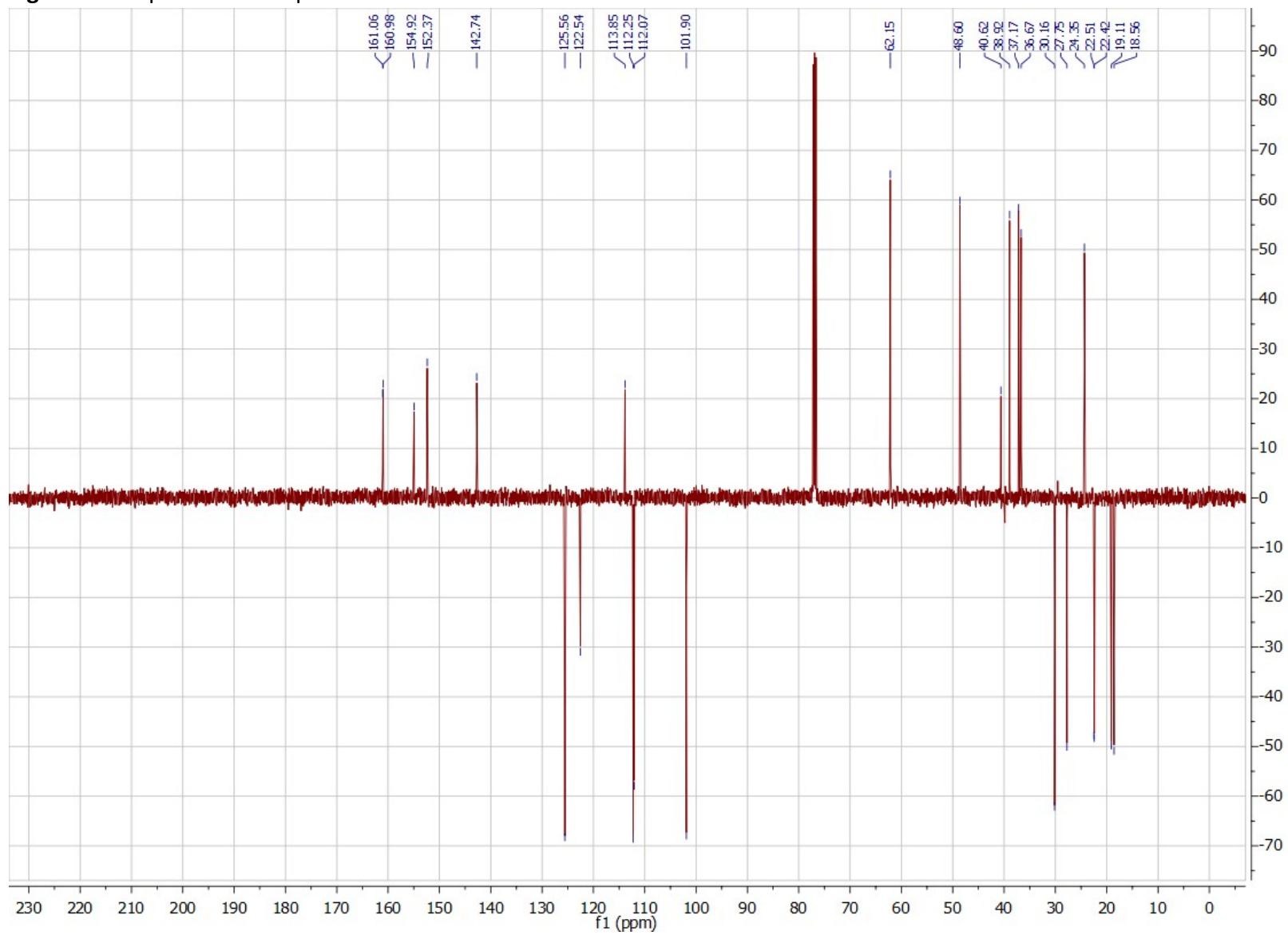


Fig. S36. ^{13}C spectra of Compound 55



2. HRMS spectra of the compounds 10, 19 and 37-55.

Fig. S37. HRMS Spectra of the compound **20**.

DO-PEC-CP #4 RT: 0.18 AV: 1 NL: 1.58E6
T: + c EI Full ms [14.50-260.50]

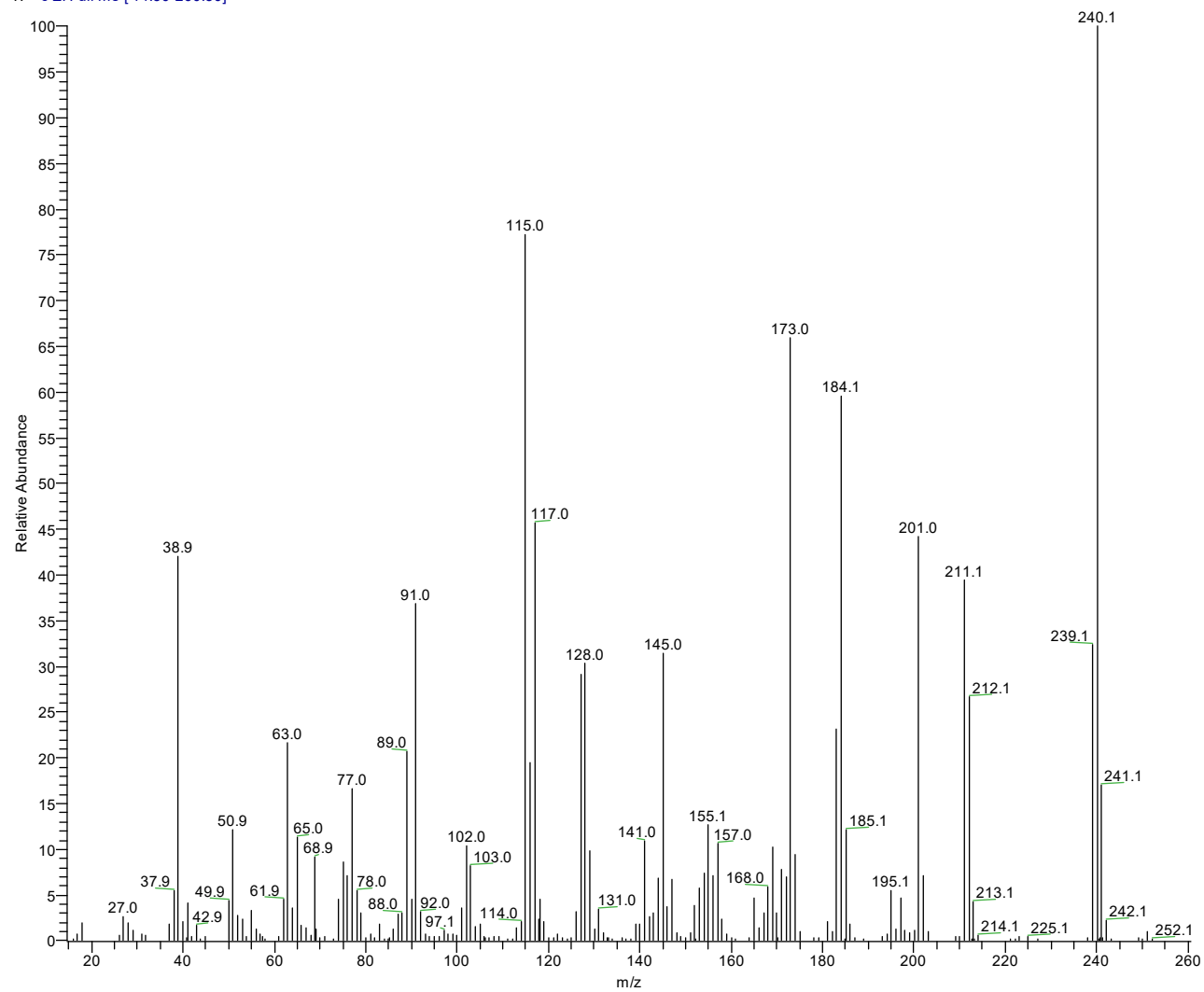


Fig. S38. HRMS Spectra of the compound **20**.

DO-CYC7 #5 RT: 0.32 AV: 1 NL: 1.31E7

T: + c EI Full ms [14.50-460.50]

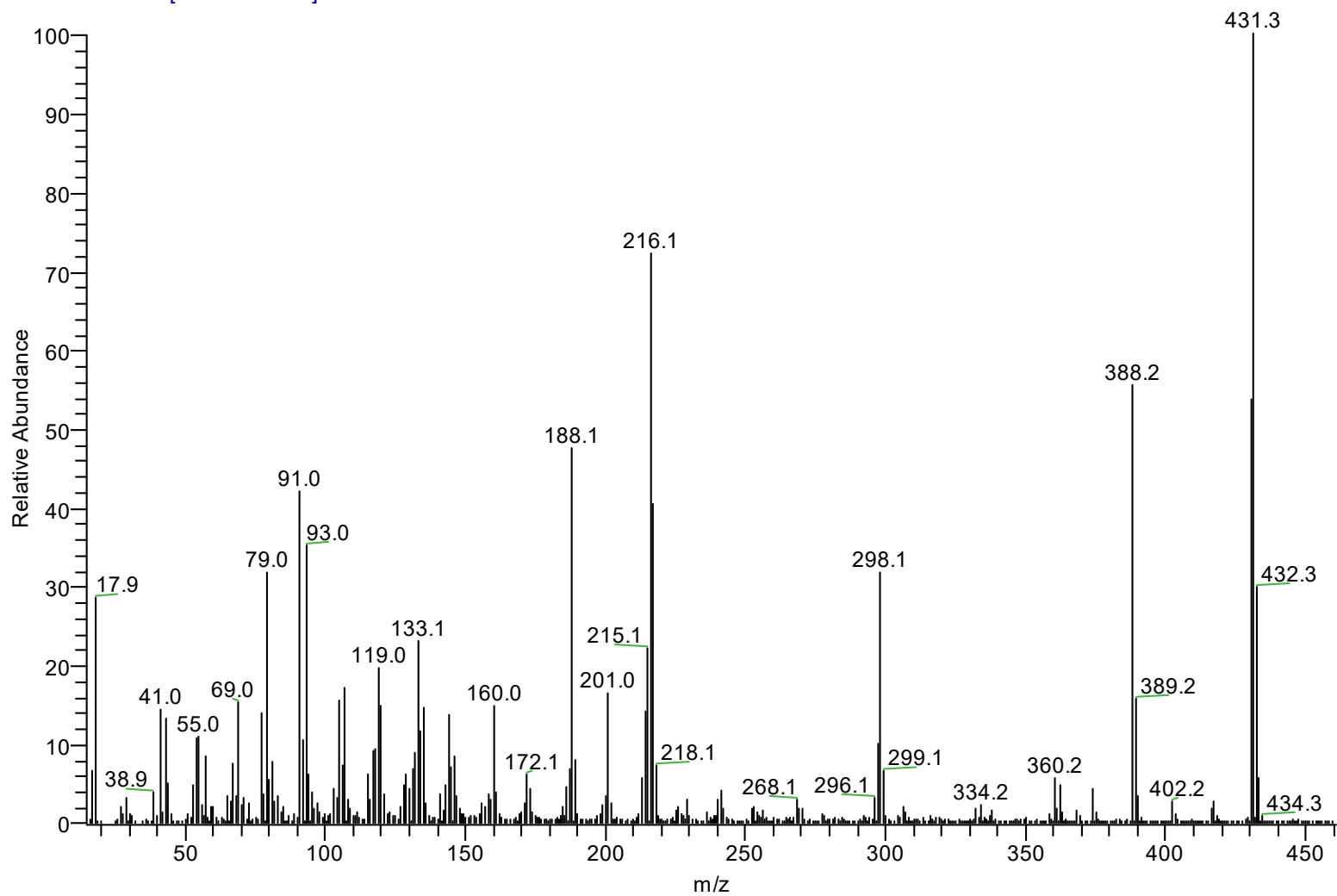


Fig. S39. HRMS Spectra of the compound **37**.

Do-cyc-2-2 #3 RT: 0.13 AV: 1 NL: 1.69E5
T: + c EI Full ms [32.50-460.50]

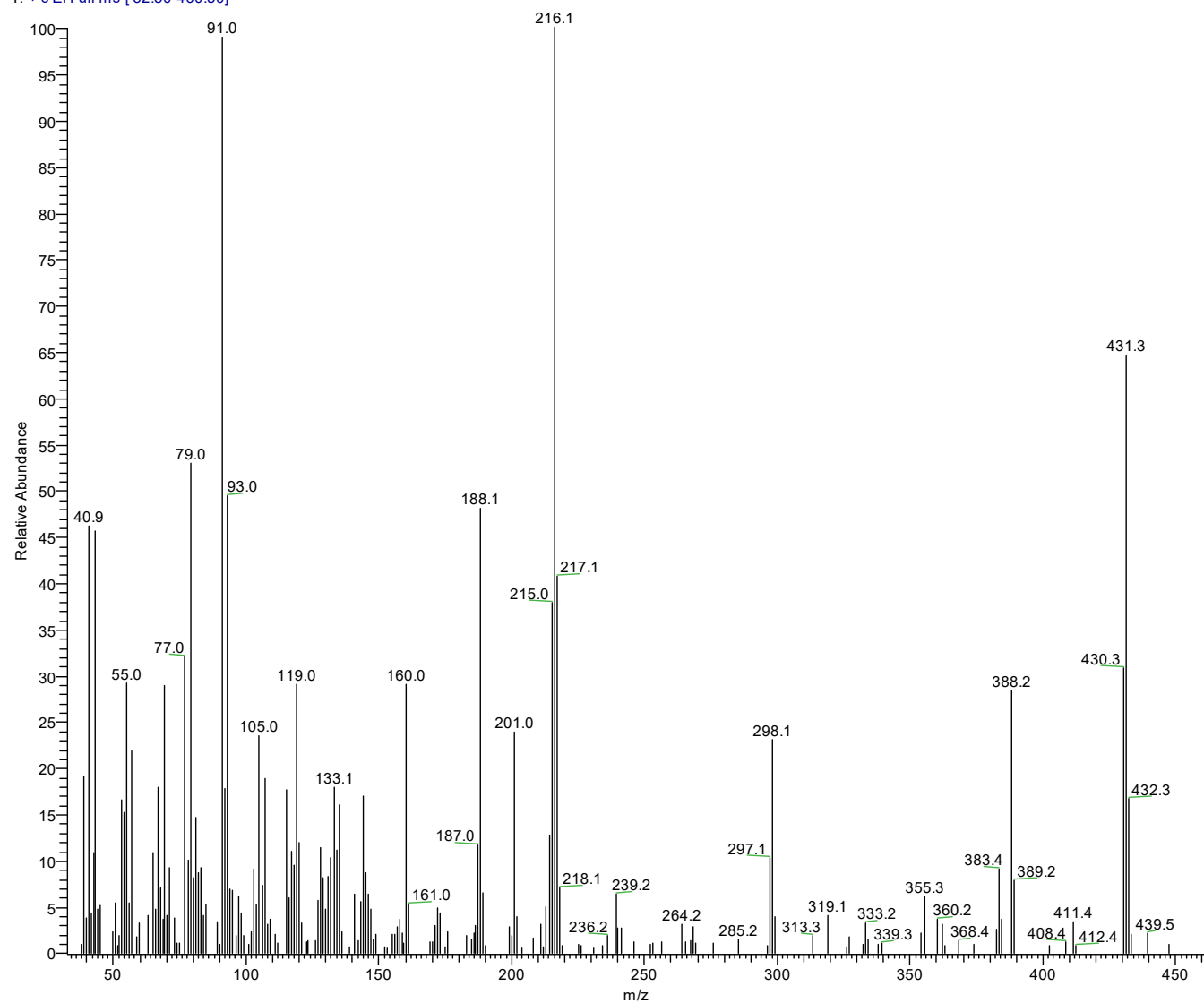


Fig. S40. HRMS Spectra of the compound **38**.

DO-CYC-16_230411140139 #1 RT: 0.00 AV: 1 NL: 7.66E6
T: + c EI Full ms [32.50-450.50]

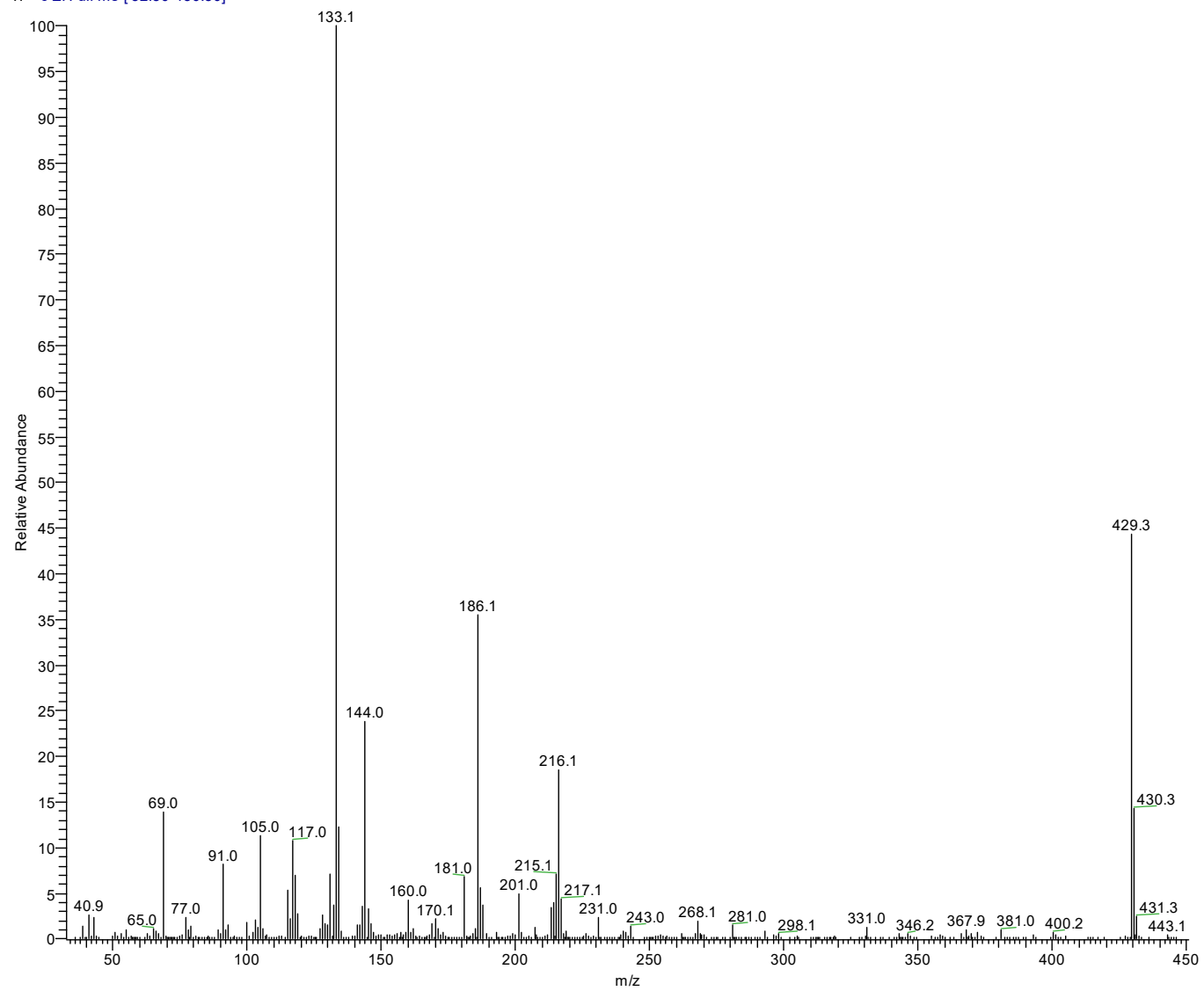


Fig. S41. HRMS Spectra of the compound **39**.

DO-CYC-3 #5 RT: 0.32 AV: 1 NL: 1.94E5
T: + c EI Full ms [14.50-460.50]

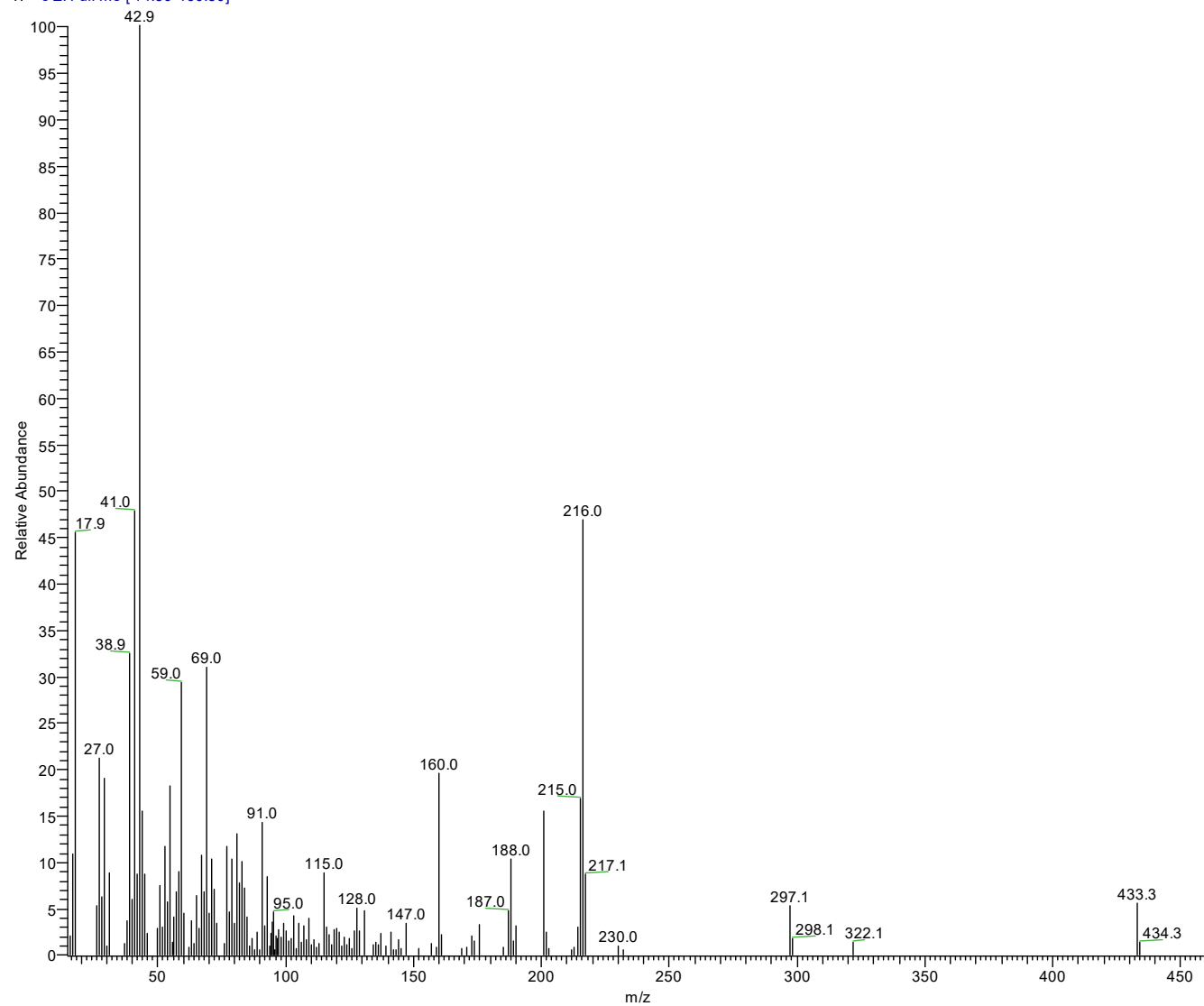


Fig. S42. HRMS Spectra of the compound **40**.

DO-CYC-21 #2 RT: 0.07 AV: 1 NL: 3.38E6
T: + c EI Full ms [32.50-470.50]

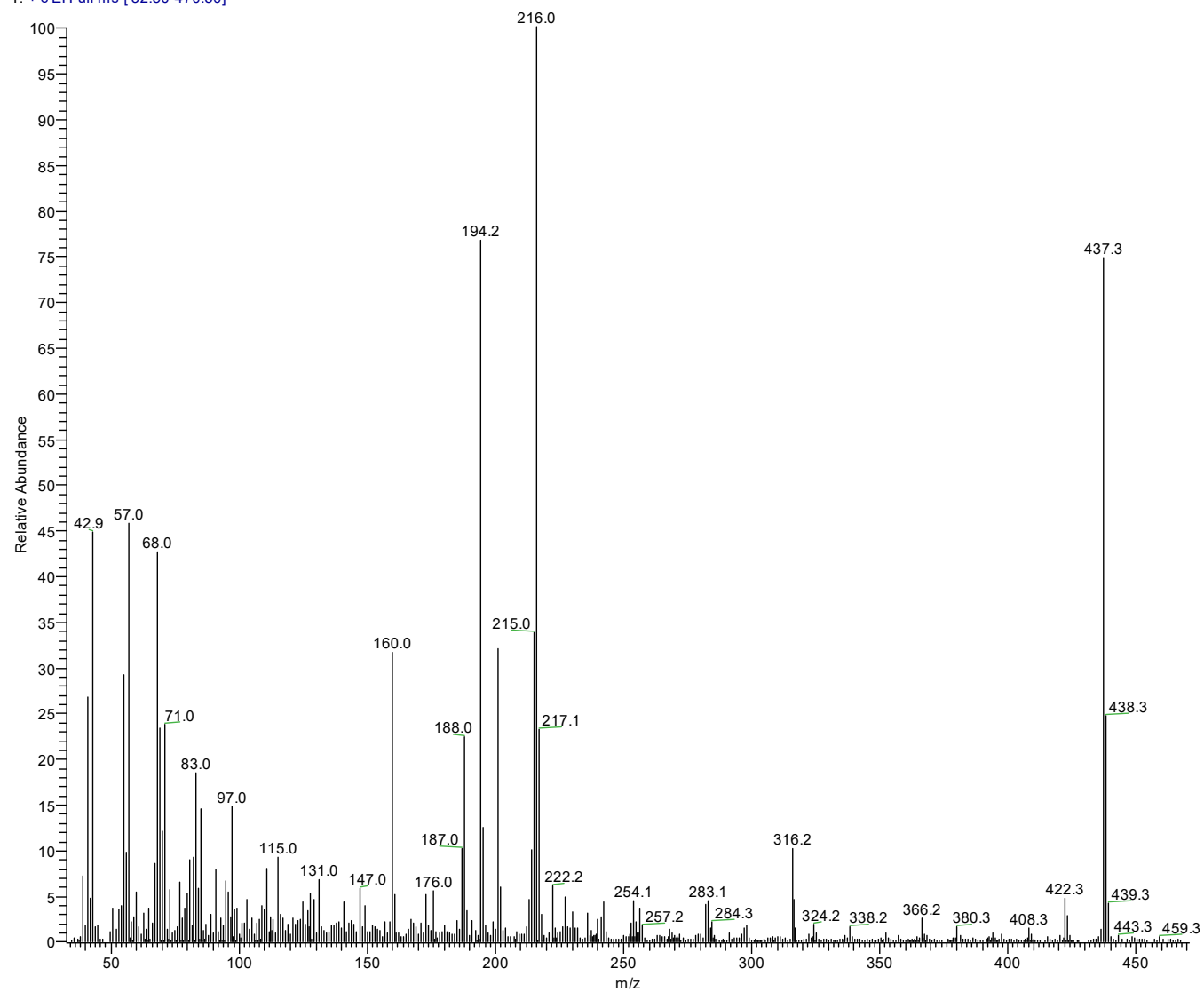


Fig. S43. HRMS Spectra of the compound **41**.

DO-CYC-5 #29 RT: 2.13 AV: 1 NL: 8.29E5
T: + c EI Full ms [14.50-430.50]

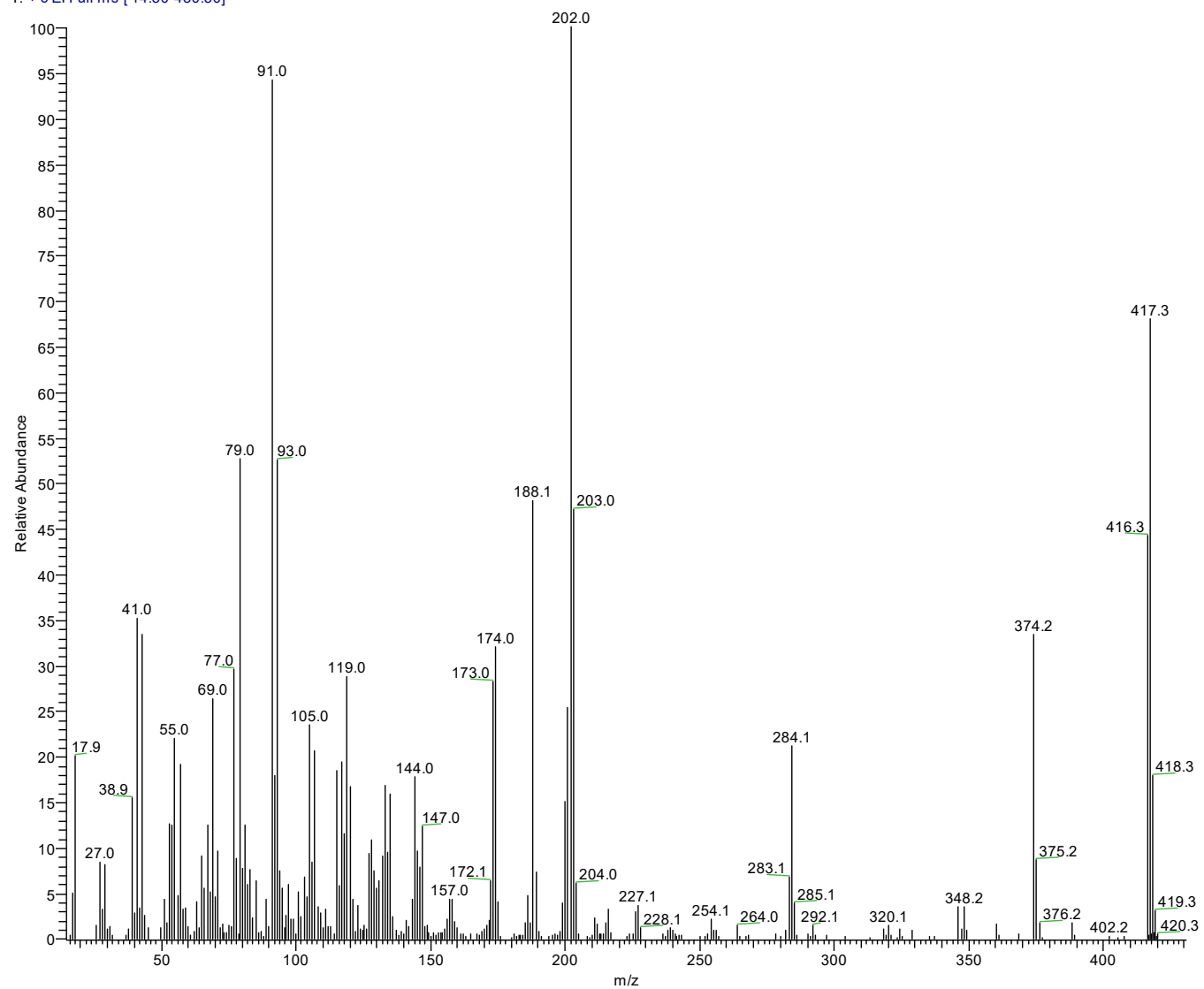


Fig. S44. HRMS Spectra of the compound **42**.

DO-CYC-6 #6 RT: 0.31 AV: 1 NL: 5.12E4
T: + c EI Full ms [32.50-450.50]

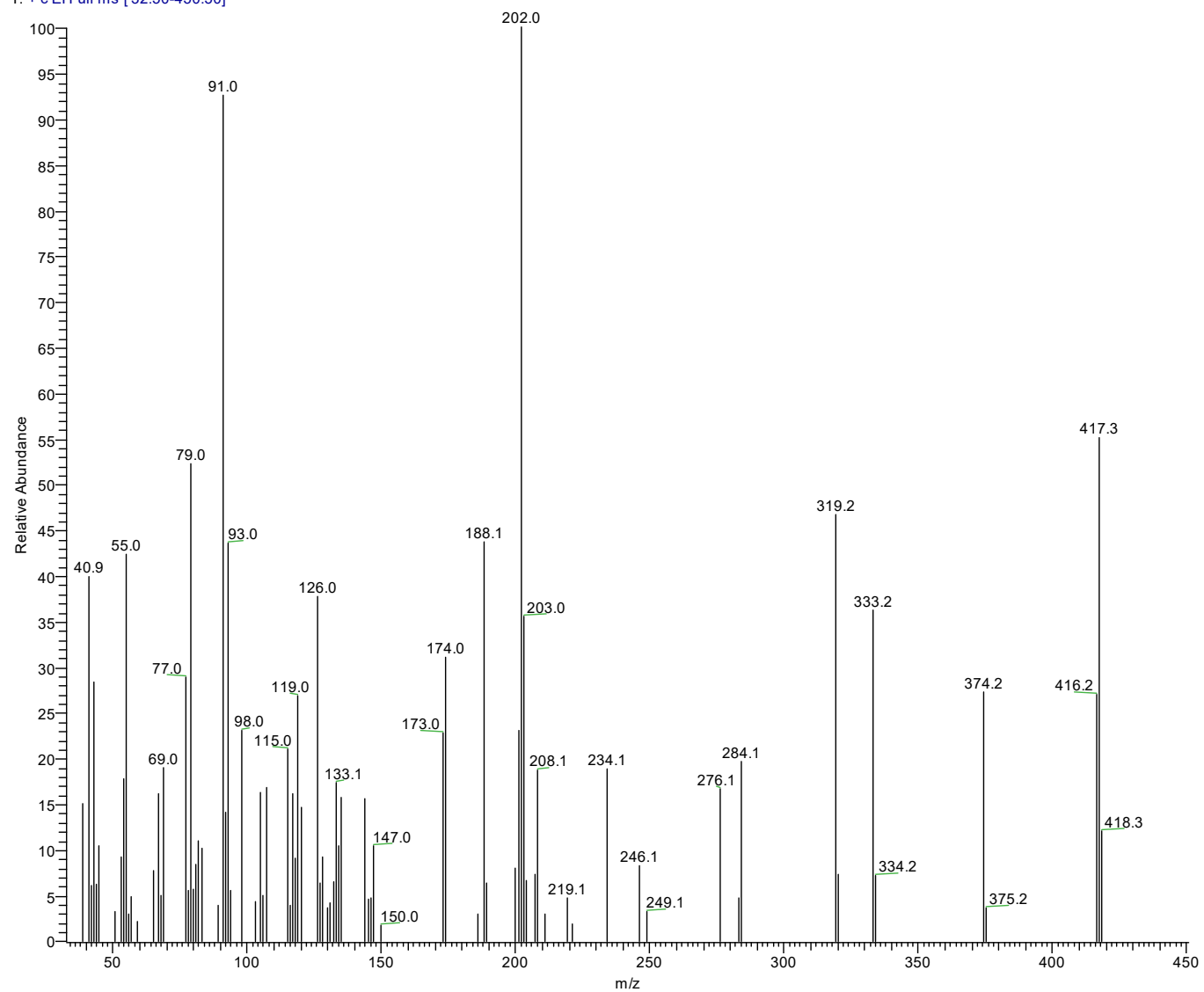


Fig. S45. HRMS Spectra of the compound **43**.

DO-CYC-15 #4 RT: 0.19 AV: 1 NL: 8.95E5
T: + c EI Full ms [32.50-450.50]

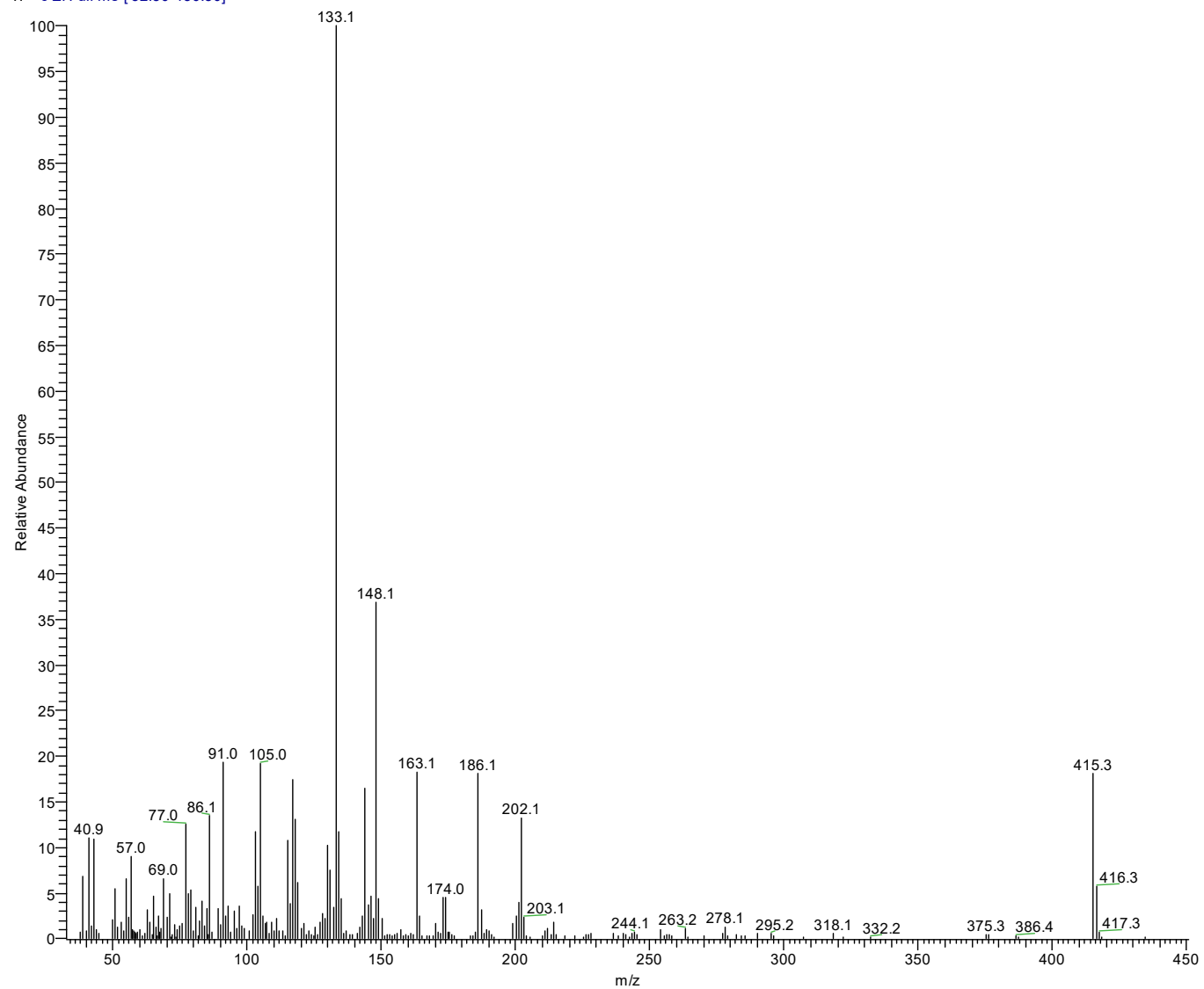


Fig. S46. HRMS Spectra of the compound **44**.

DO-CYC-4_#10 RT: 0.67 AV: 1 NL: 2.71E5
T: + c EI Full ms [14.50-440.50]

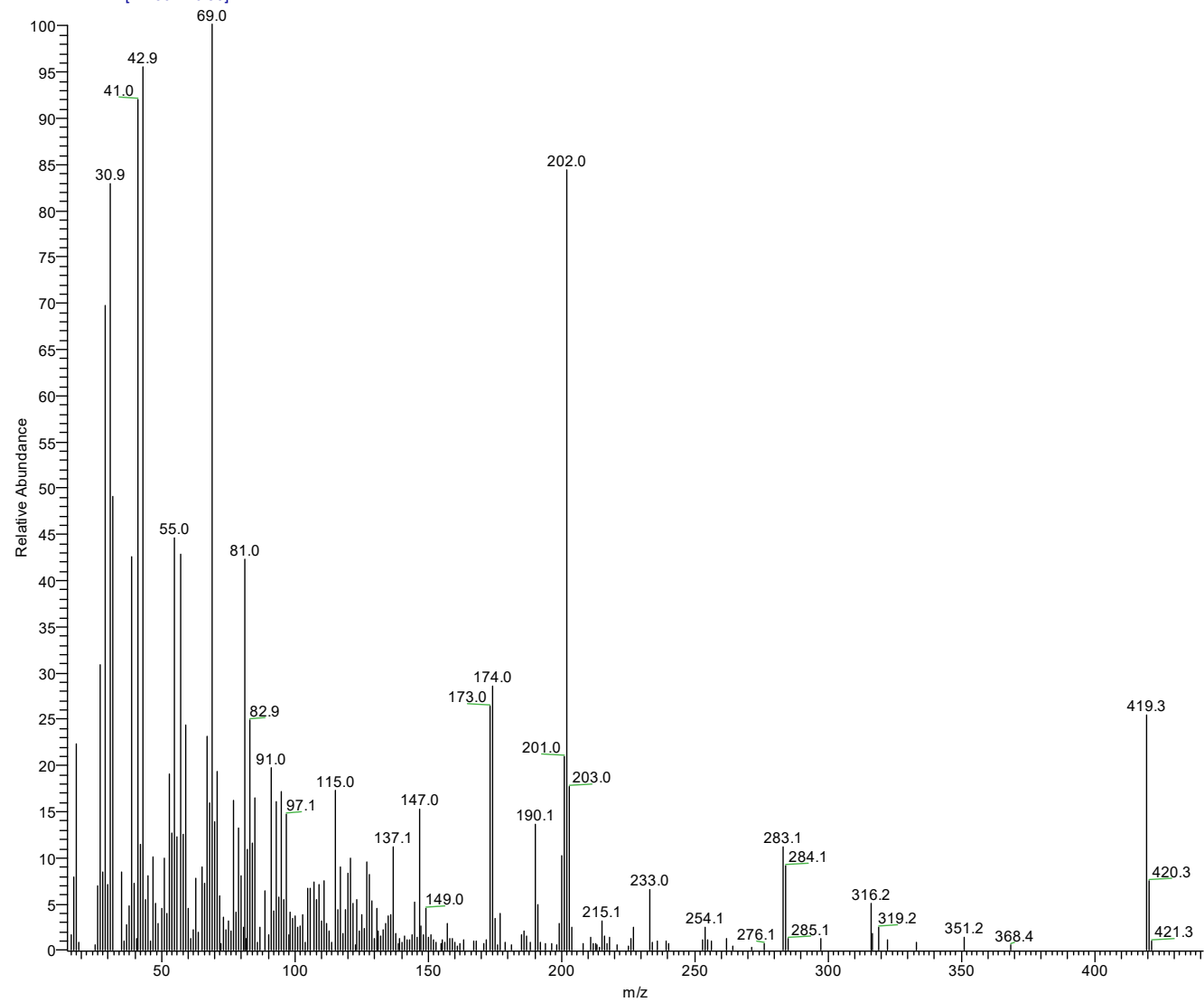


Fig. S47. HRMS Spectra of the compound **45**.

DO-CYC-24 #3 RT: 0.16 AV: 1 NL: 4.63E6
T: + c EI Full ms [14.50-430.50]

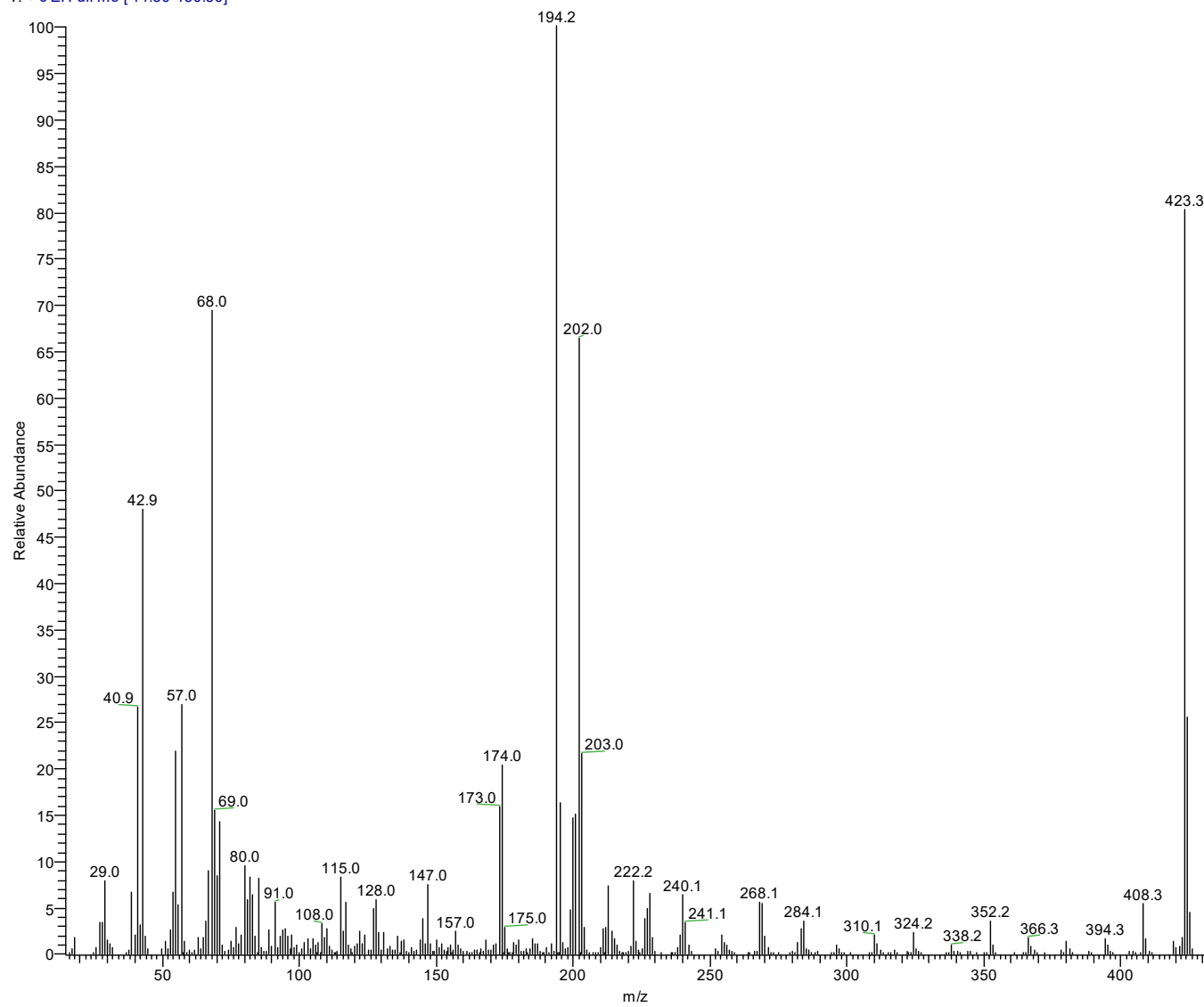


Fig. S48. HRMS Spectra of the compound **46**.

DO-CYC-10_230330142051 #12 RT: 0.88 AV: 1 NL: 9.23E4
T: + c EI Full ms [14.50-470.50]

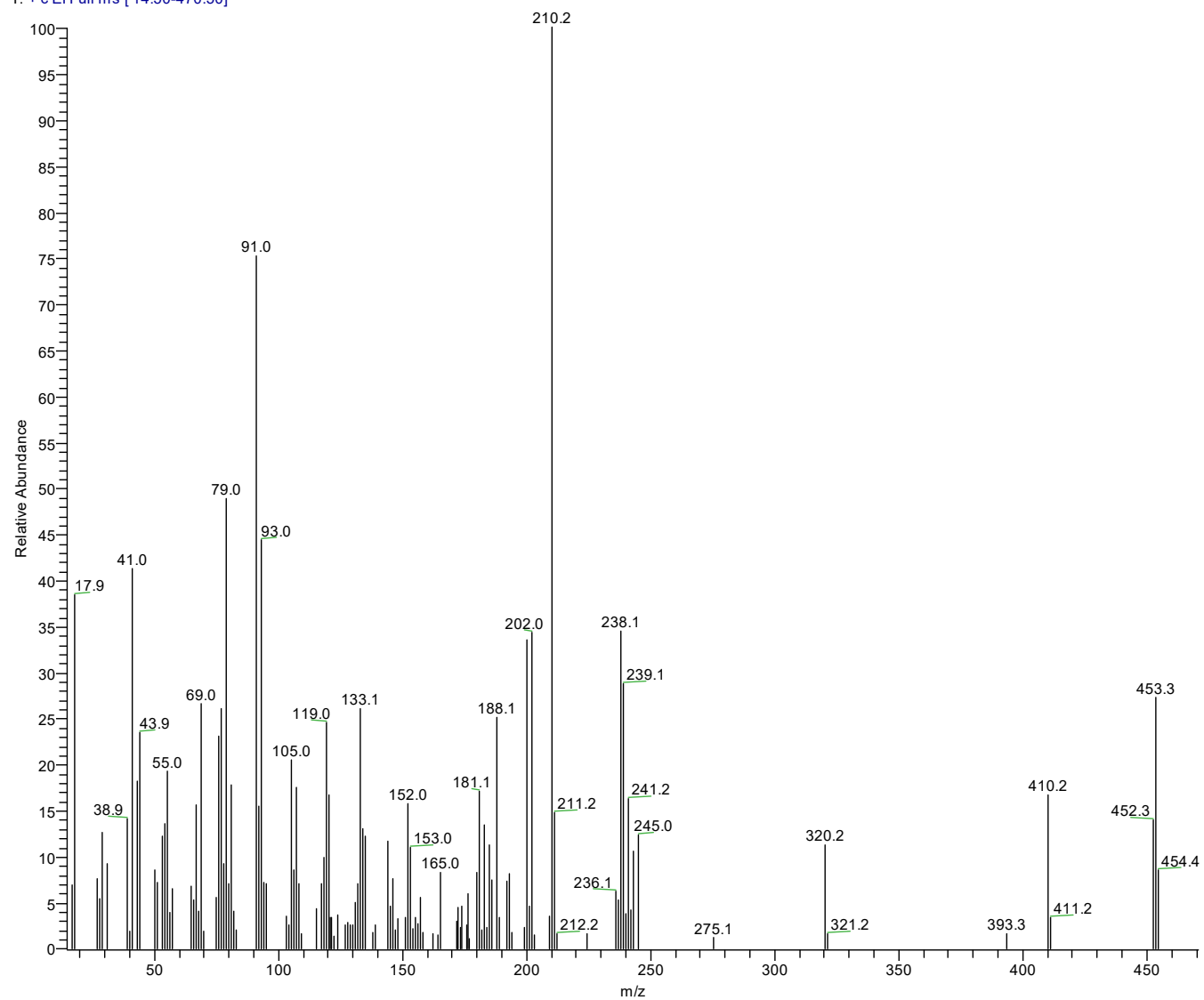


Fig. S49. HRMS Spectra of the compound **47**.

DO-CYC-9 #3 RT: 0.16 AV: 1 NL: 3.04E4
T: + c EI Full ms [14.50-480.50]

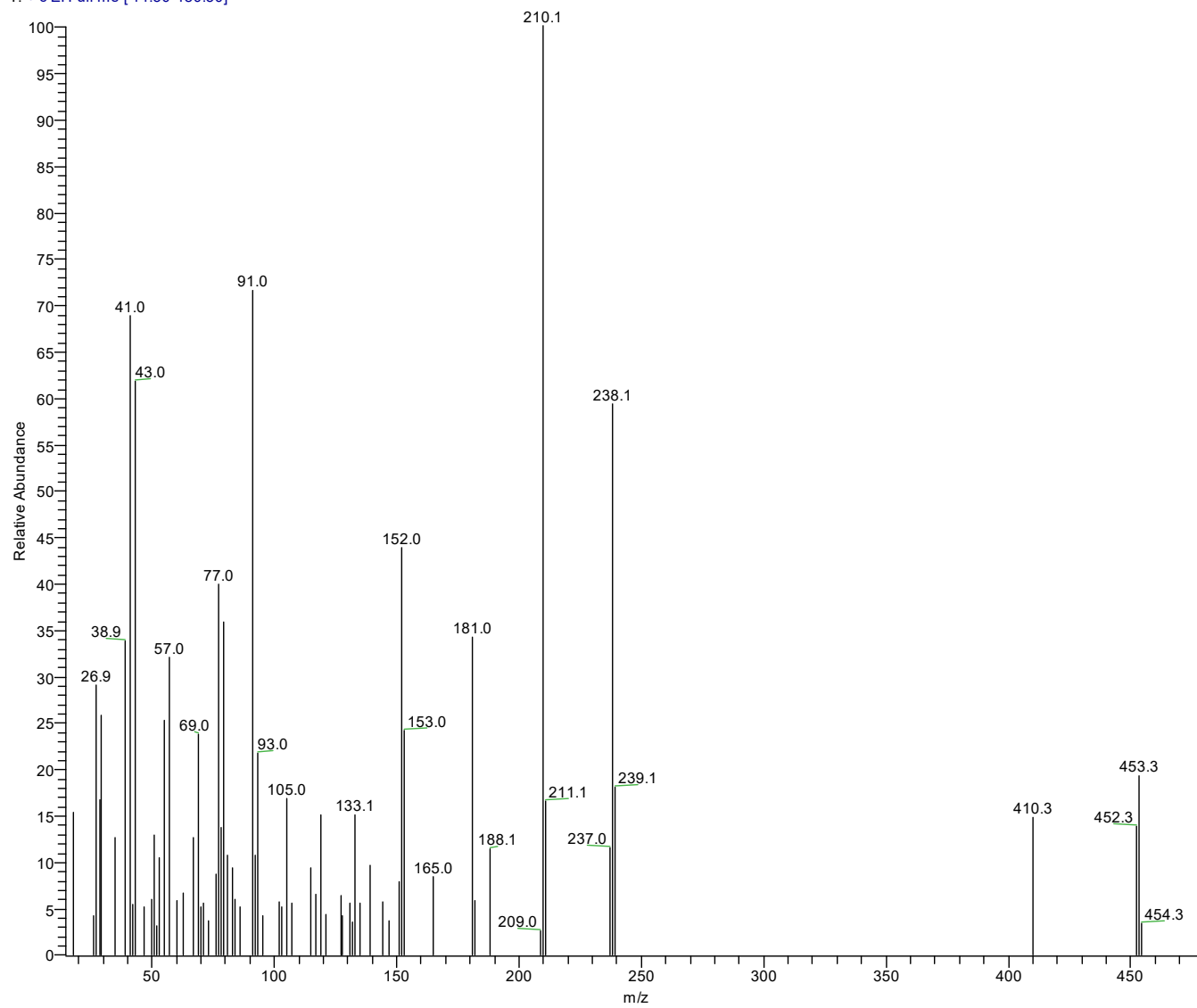


Fig. S50. HRMS Spectra of the compound **48**.

DO-CYC-18 #3 RT: 0.16 AV: 1 NL: 1.89E6
T: + c EI Full ms [14.50-480.50]

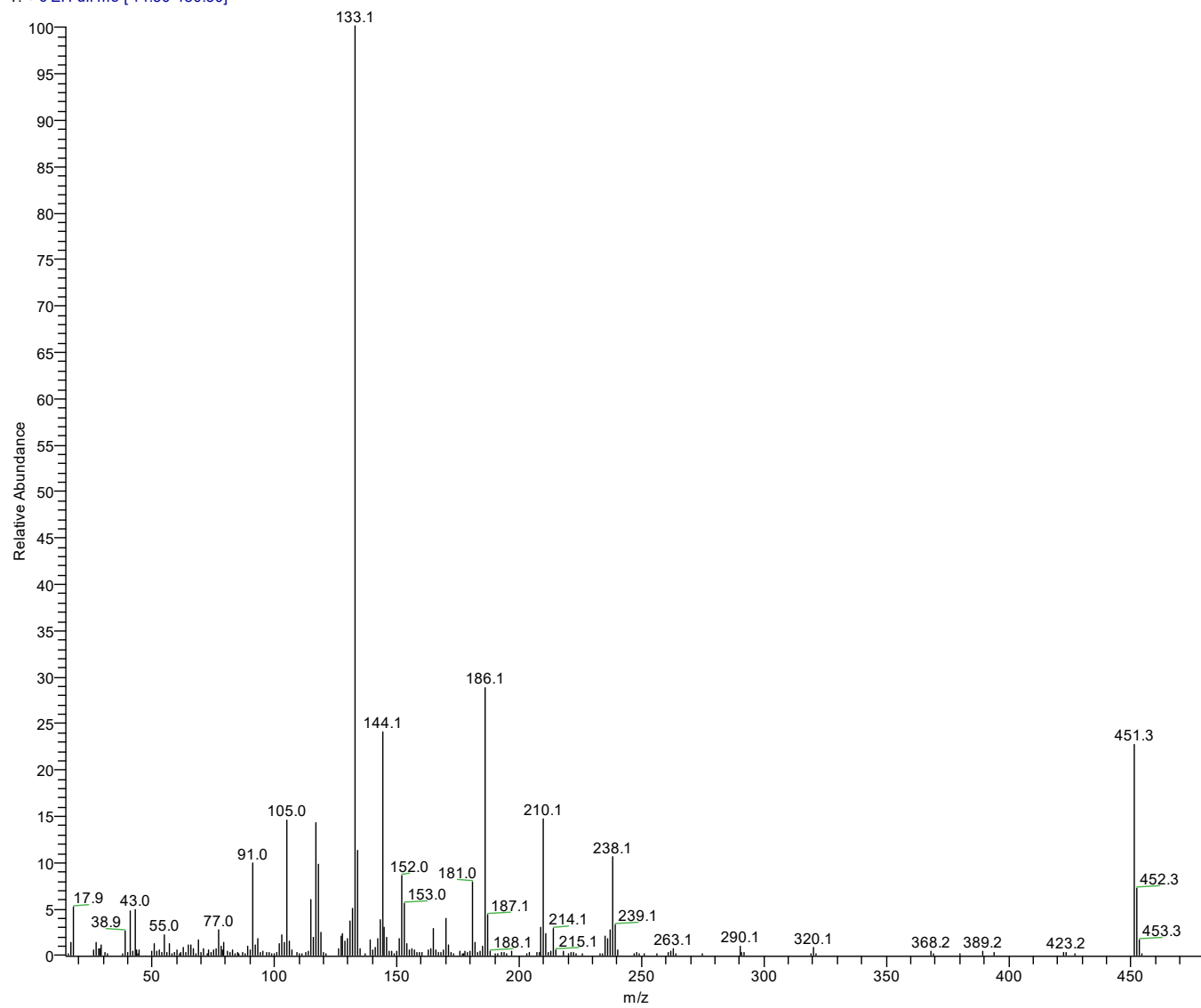


Fig. S51. HRMS Spectra of the compound **49**.

DO-CYC-8 #8 RT: 0.44 AV: 1 NL: 4.32E5
T: + c EI Full ms [32.50-480.50]

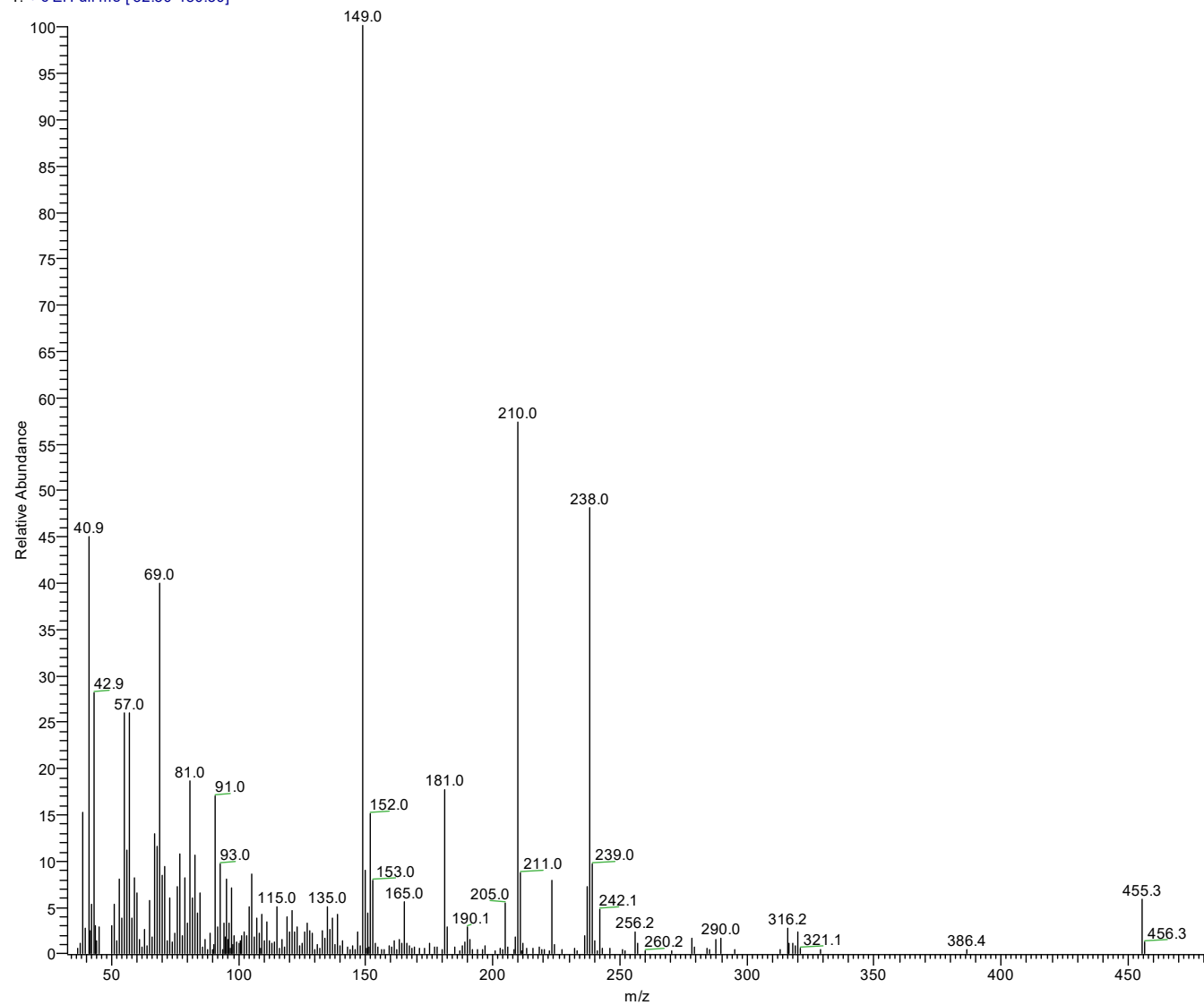


Fig. S52. HRMS Spectra of the compound **50**.

DO-CYC-23 #5 RT: 0.26 AV: 1 NL: 6.52E6
T: + c EI Full ms [32.50-500.50]

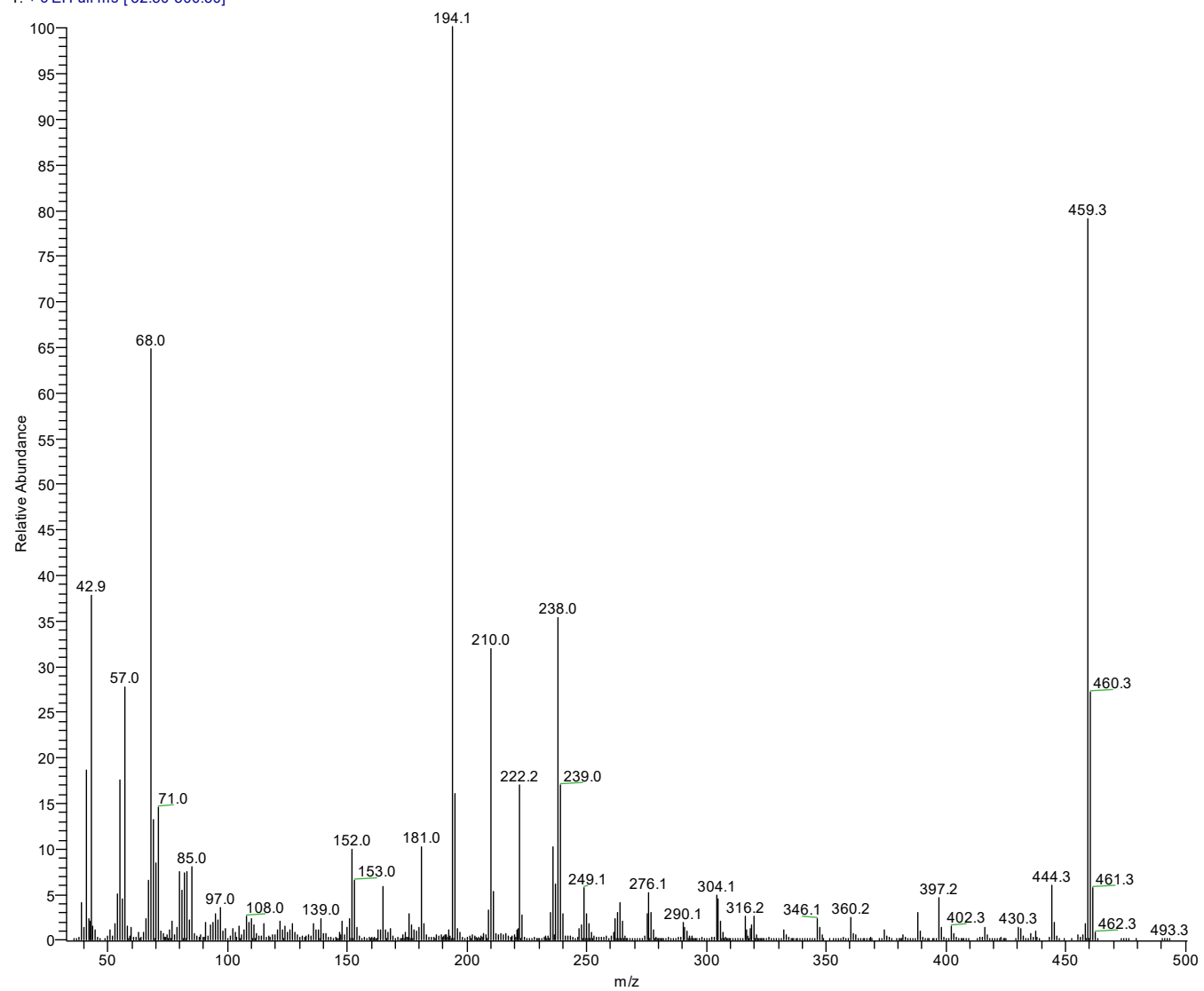


Fig. S53. HRMS Spectra of the compound **51**.

DO-CYC-20 #1 RT: 0.00 AV: 1 NL: 7.29E5
T: + c EI Full ms [14.50-400.50]

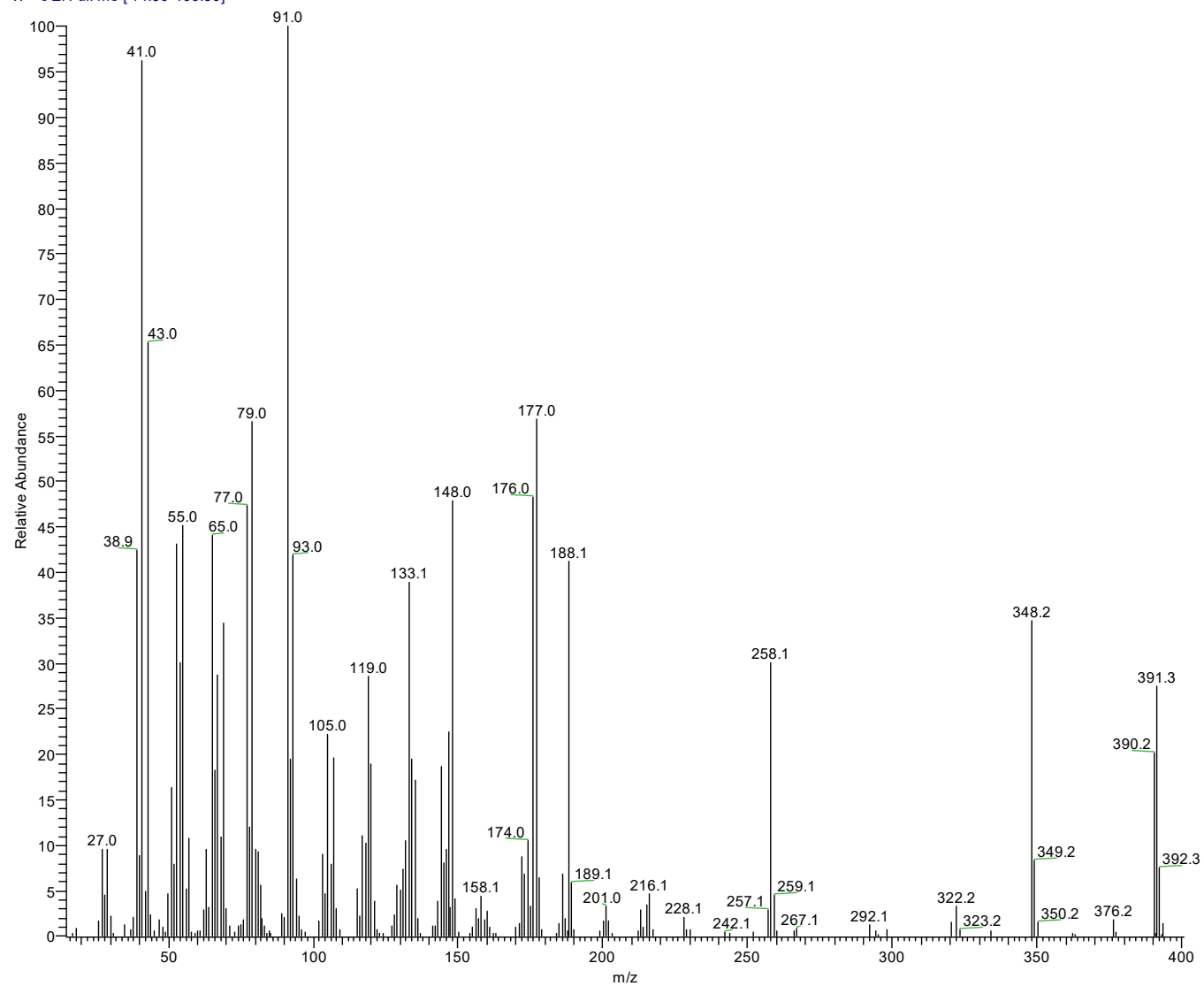


Fig. S54. HRMS Spectra of the compound **52**.

DO-CYC12 #10 RT: 0.70 AV: 1 NL: 7.30E6
T: + c EI Full ms [32.50-430.50]

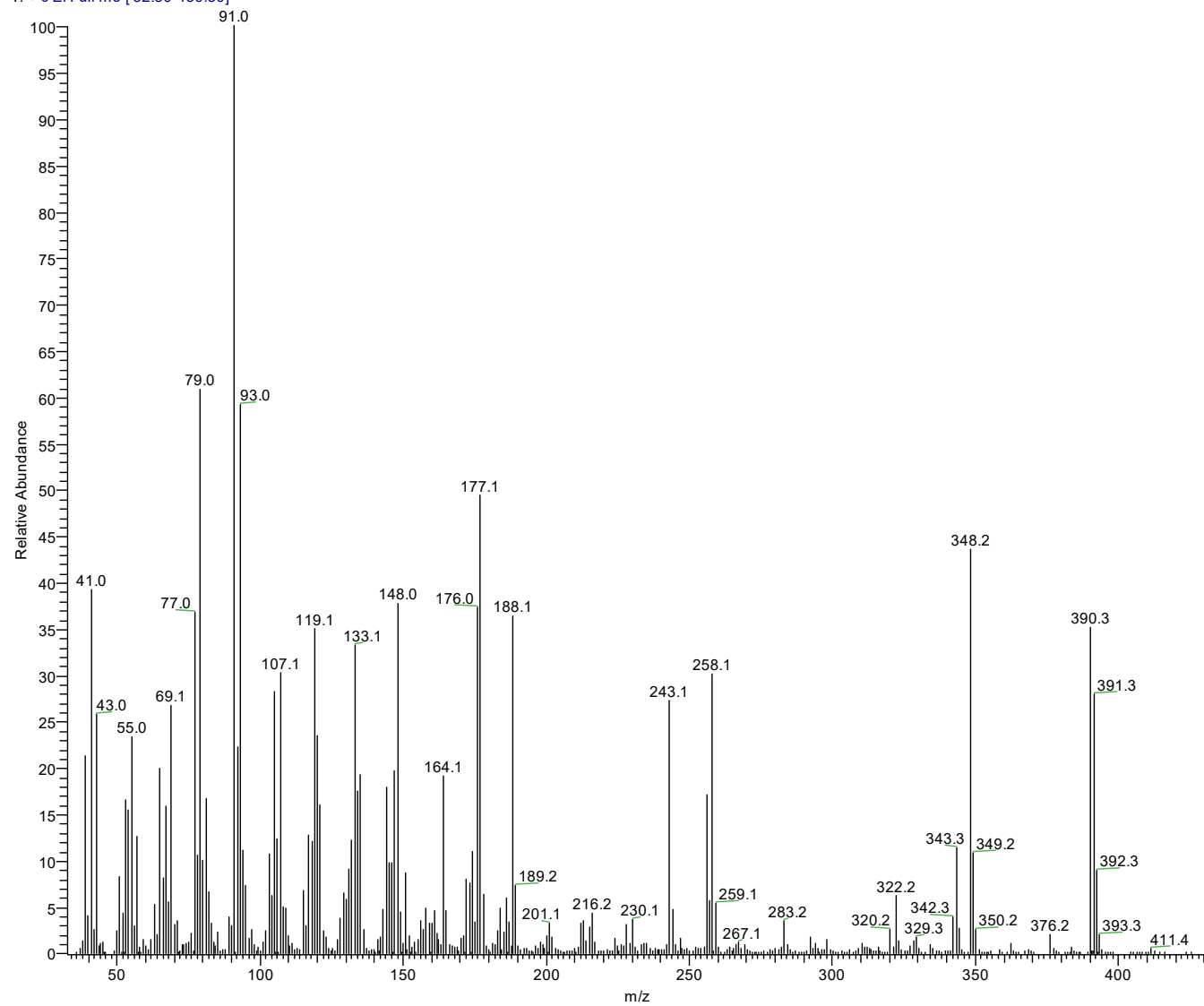


Fig. S55. HRMS Spectra of the compound **53**.

DO-CYC-17_230408142605 #3 RT: 0.16 AV: 1 NL: 8.93E6
T: + c EI Full ms [14.50-420.50]

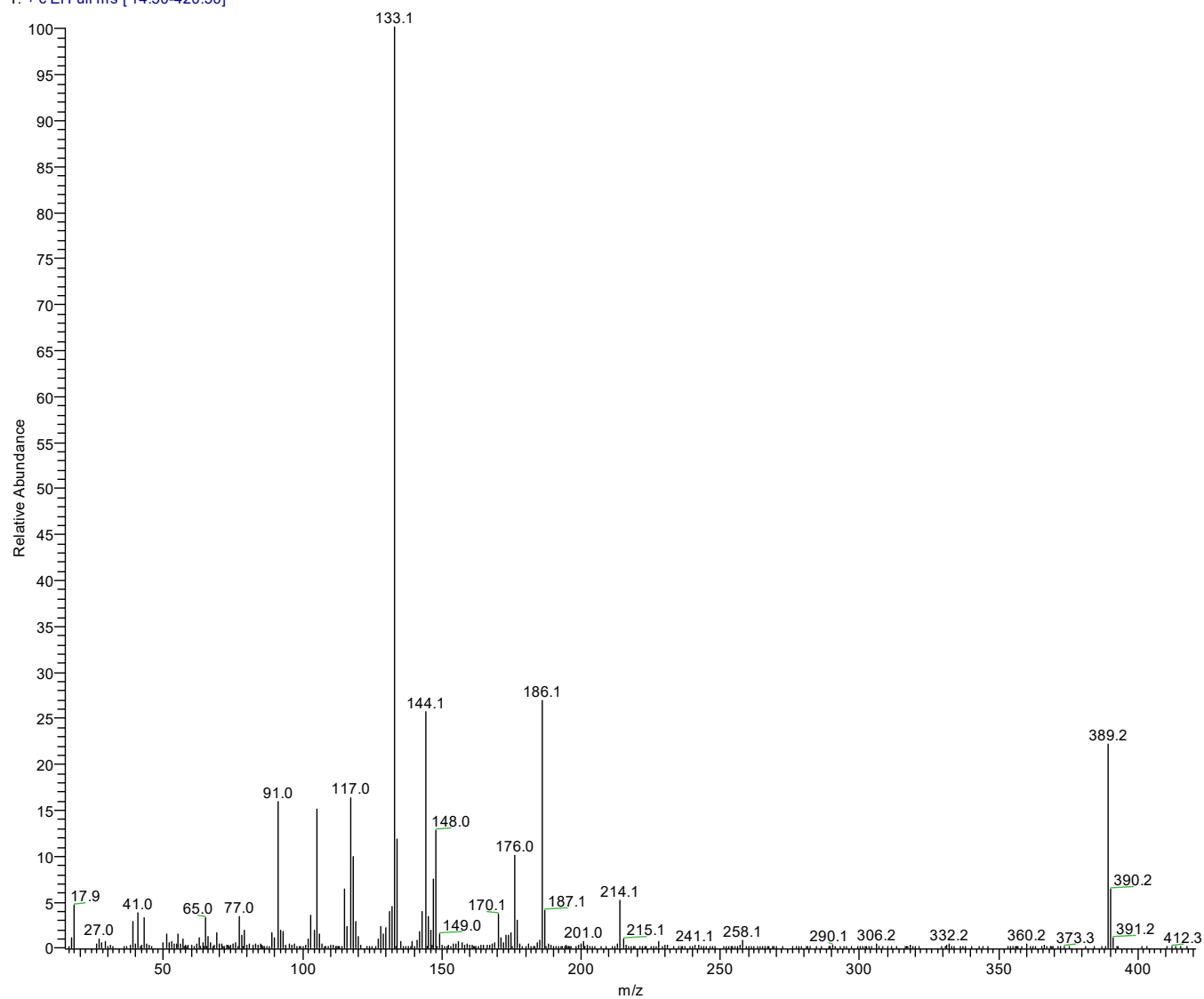


Fig. S56. HRMS Spectra of the compound **54-E**.

DO-CYC11-I-2 #2 RT: 0.08 AV: 1 NL: 3.29E5
T: + c EI Full ms [14.50-420.50]

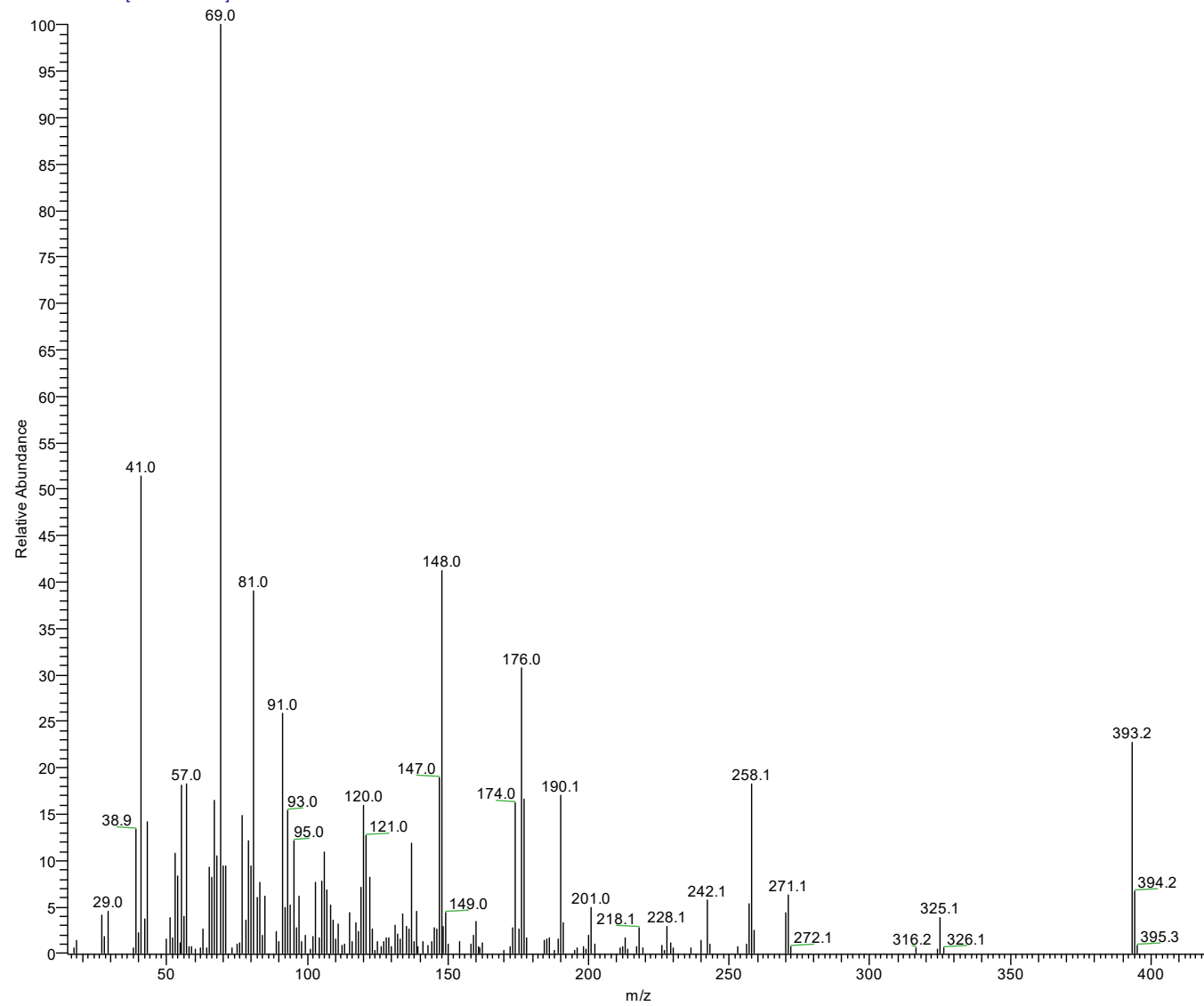


Fig. S57. HRMS Spectra of the compound **54-Z**.

DO-CYC-11-11 #17 RT: 0.96 AV: 1 NL: 9.63E4
T: + c EI Full ms [32.50-420.50]

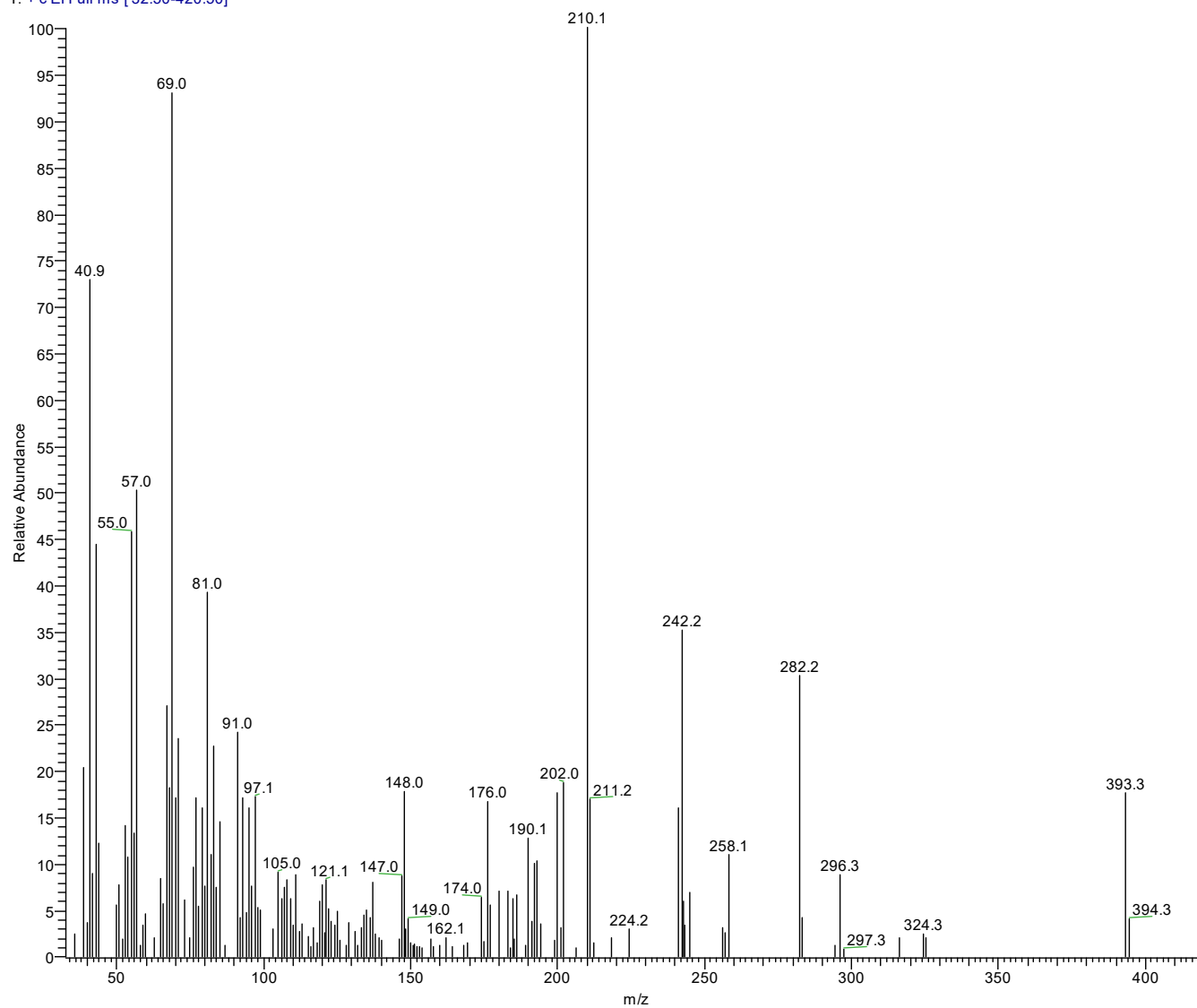
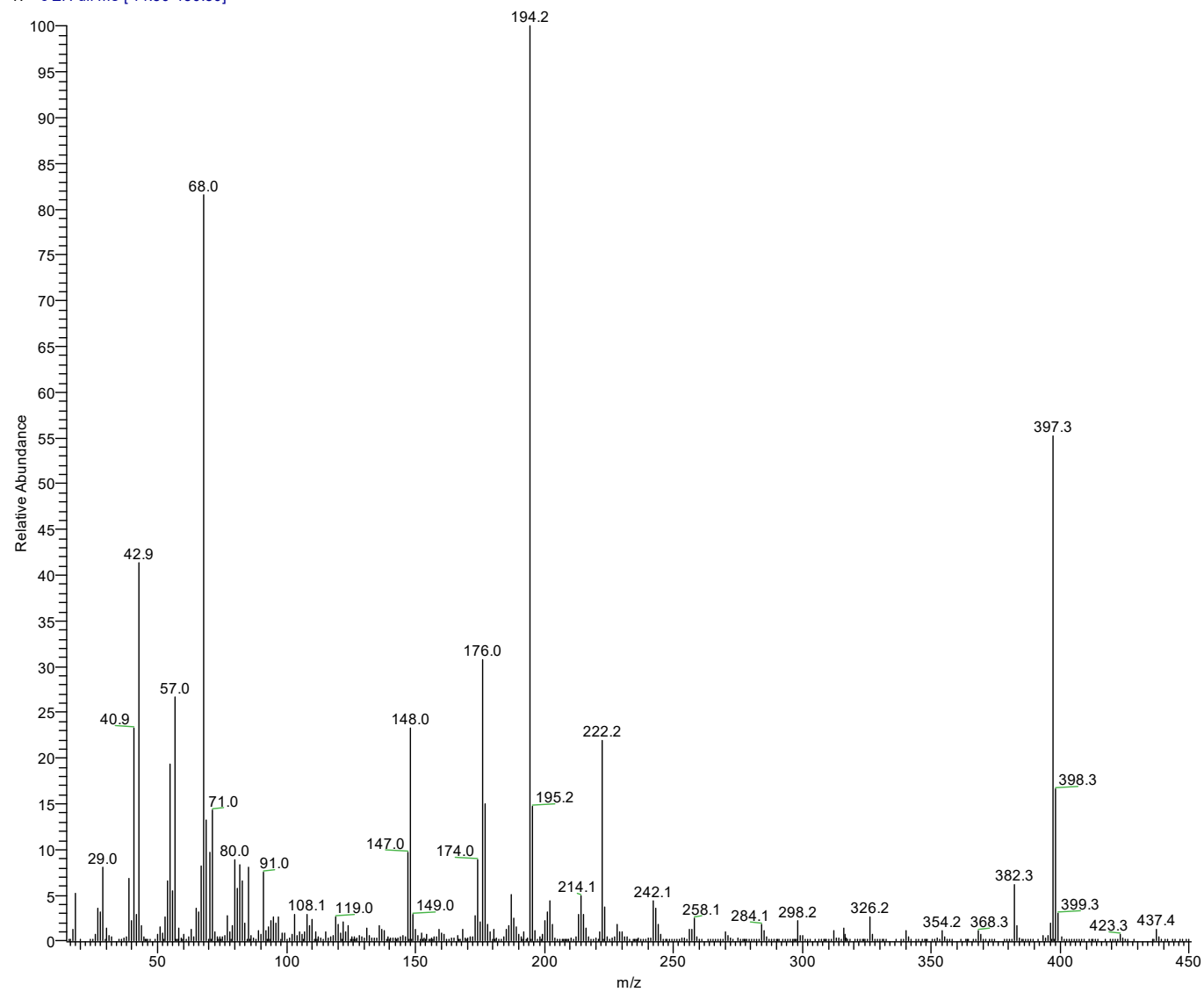


Fig. S58. HRMS Spectra of the compound **55**.

DO_CYC_22 #10 RT: 0.71 AV: 1 NL: 1.56E7
T: + c EI Full ms [14.50-450.50]



3. 2D spectra of compounds 37, 43, 50, 54Z, 54E

Fig. S59. ^1H - ^1H COSY spectra of the compound 37.

lfav-Tsyp-DO-CYC-2.4.ser — AV-600, 1H-1H cosy, Tsypyshev, — DO-CYC 2 in CDCl₃, 20.5mg

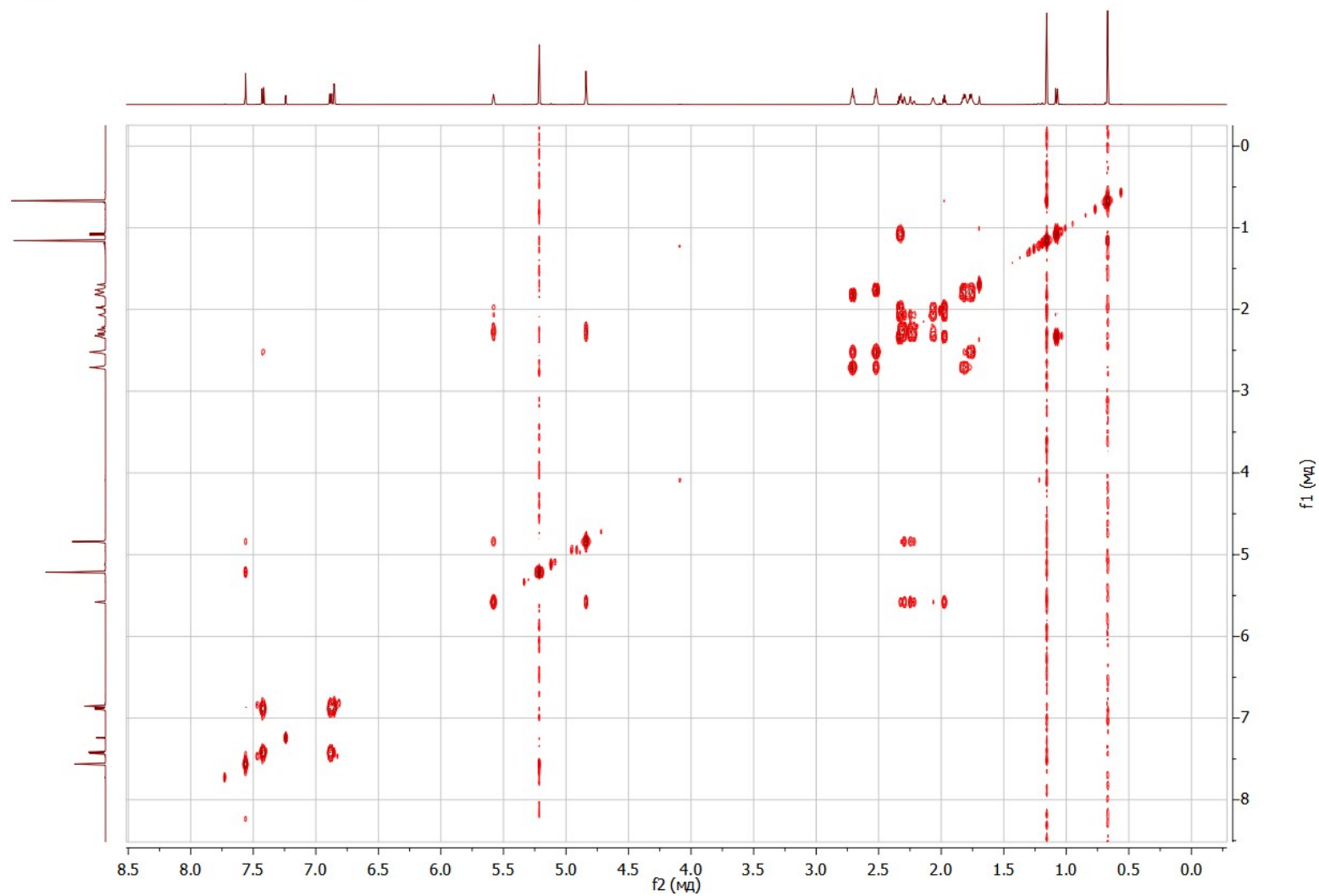


Fig. S60. ^1H - ^1H NOESY spectra of the compound **37**.

lfav-Tsyp-DO-CYC-2.7.ser — AV-600, 1H-1H noesy, Tsypyshev, — DO-CYC 2 in CDCl_3 , 20.5 mg

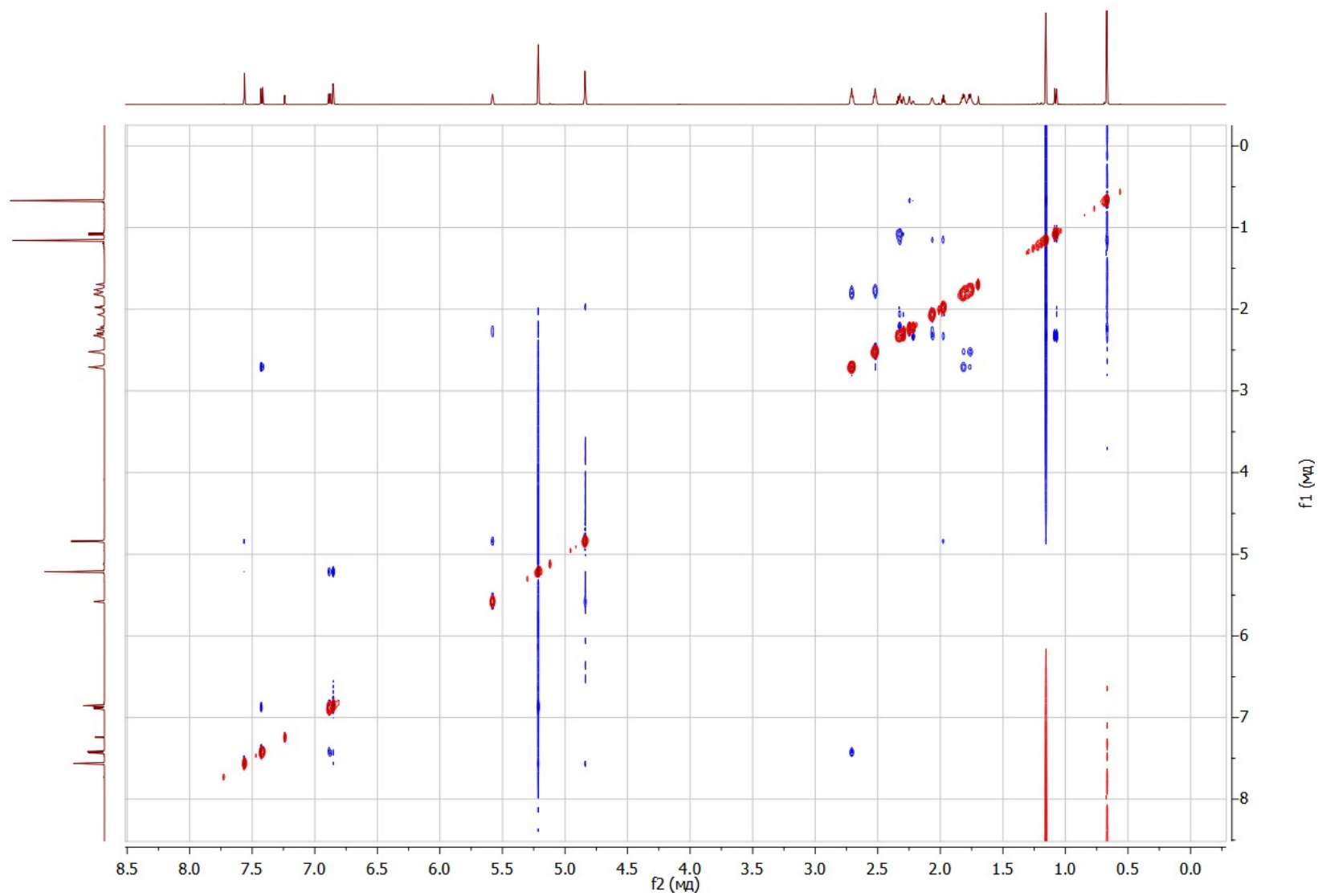


Fig. S61. ^1H - ^{13}C HSQC spectra of the compound **37**.

lfav-Tsyp-DO-CYC-2.5.ser — AV-600, ^{13}C - ^1H hsqc, Tsypyshev, — DO-CYC 2 in CDCl_3 , 20.5 mg

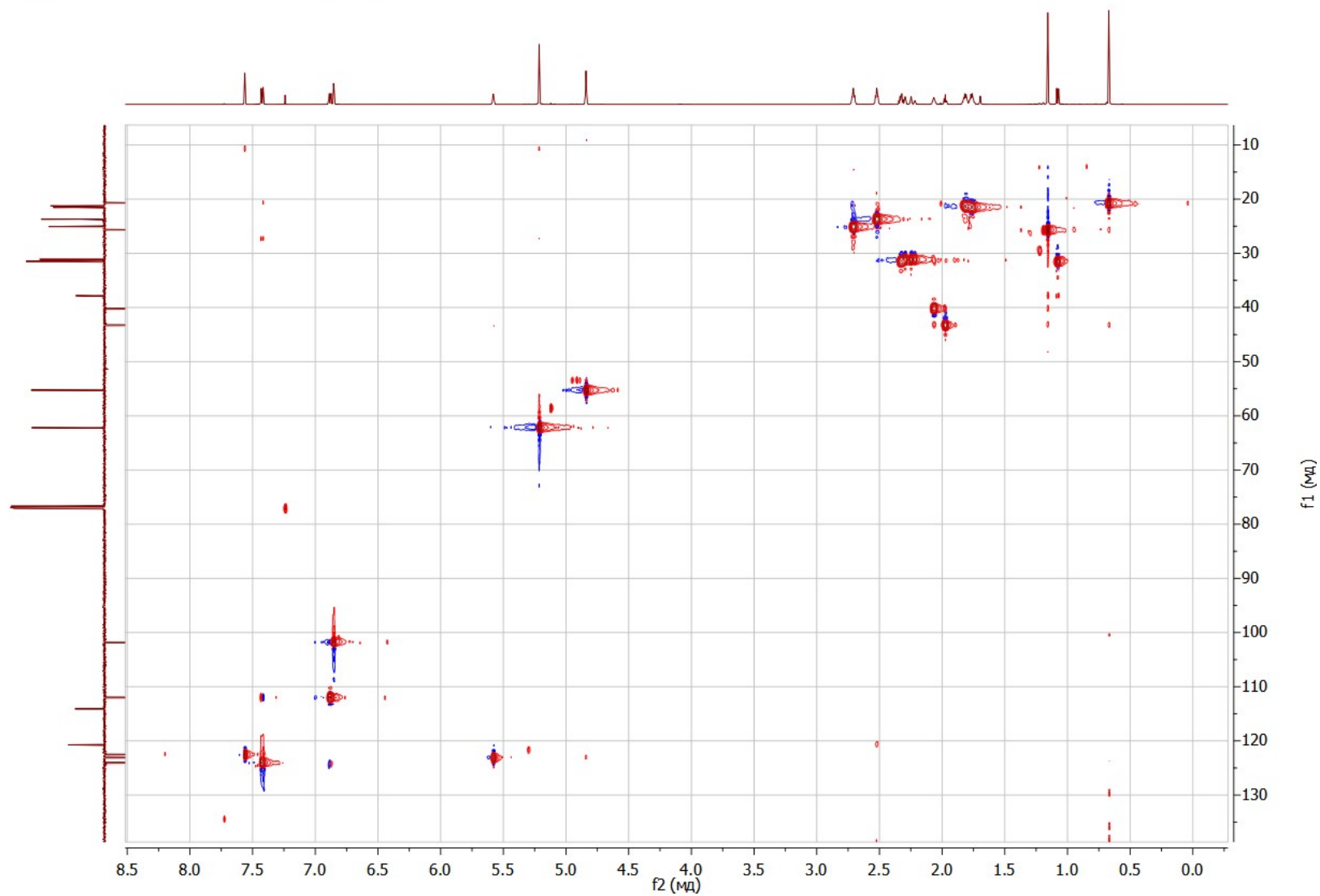


Fig. S62. ^1H - ^{13}C HMBC spectra of the compound **37**.

lfav-Tsyp-DO-CYC-2.6.ser — AV-600, 13C-1H hmbc, Tsypyshev, — DO-CYC 2 in CDCl_3 , 20.5 mg

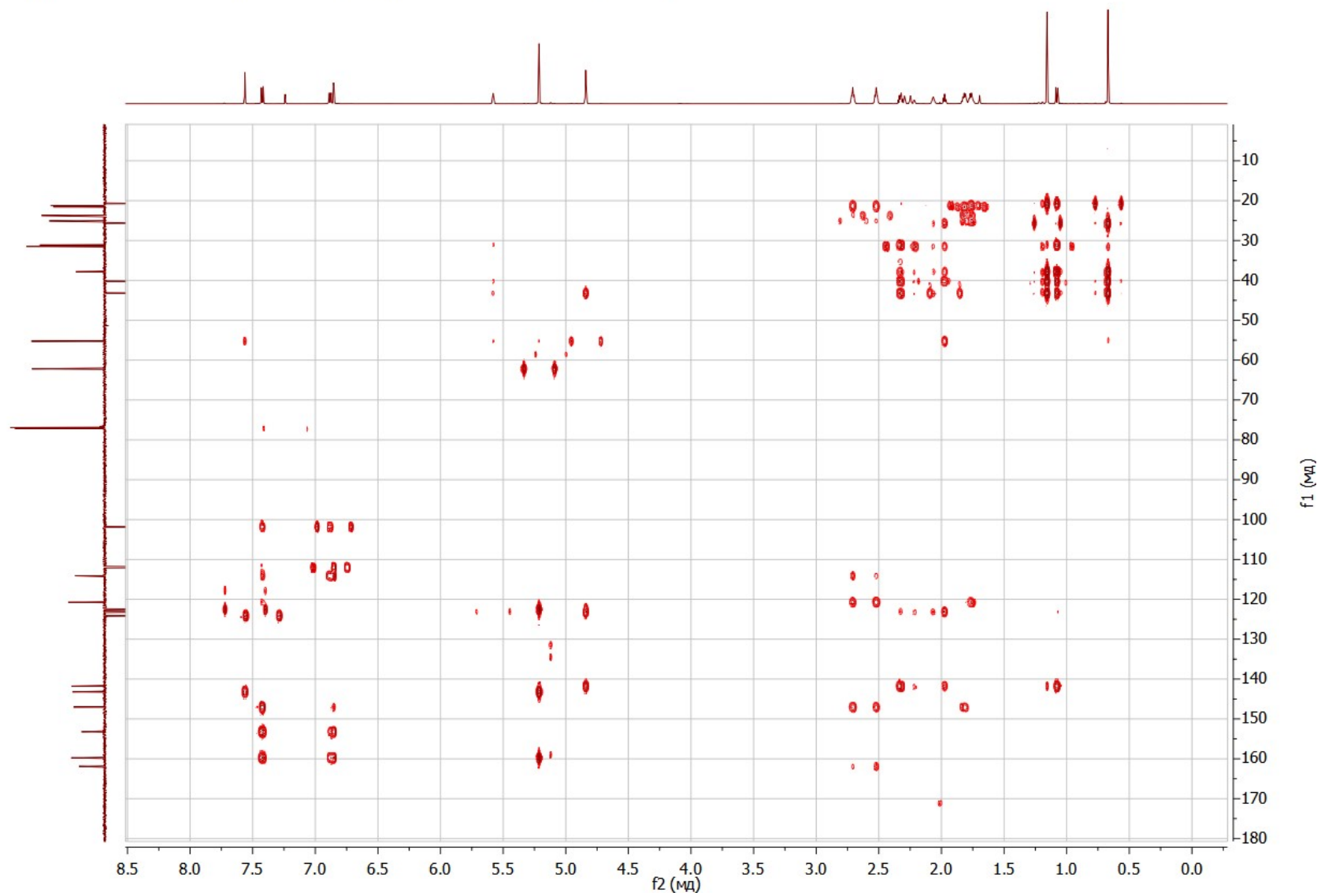


Fig. S63. ^1H - ^1H COSY spectra of the compound **43**

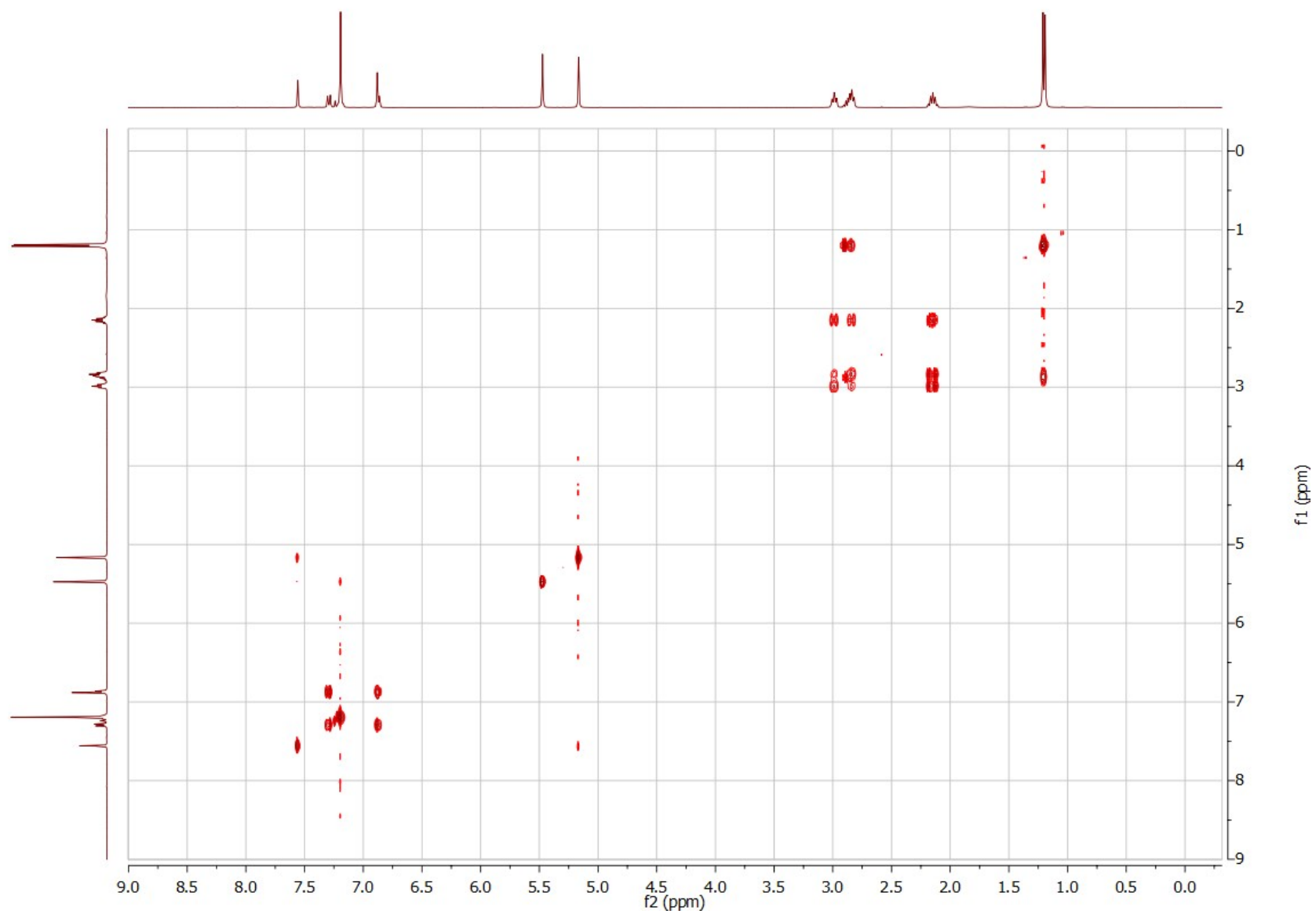


Fig. S64. ^1H - ^1H NOESY spectra of the compound 43

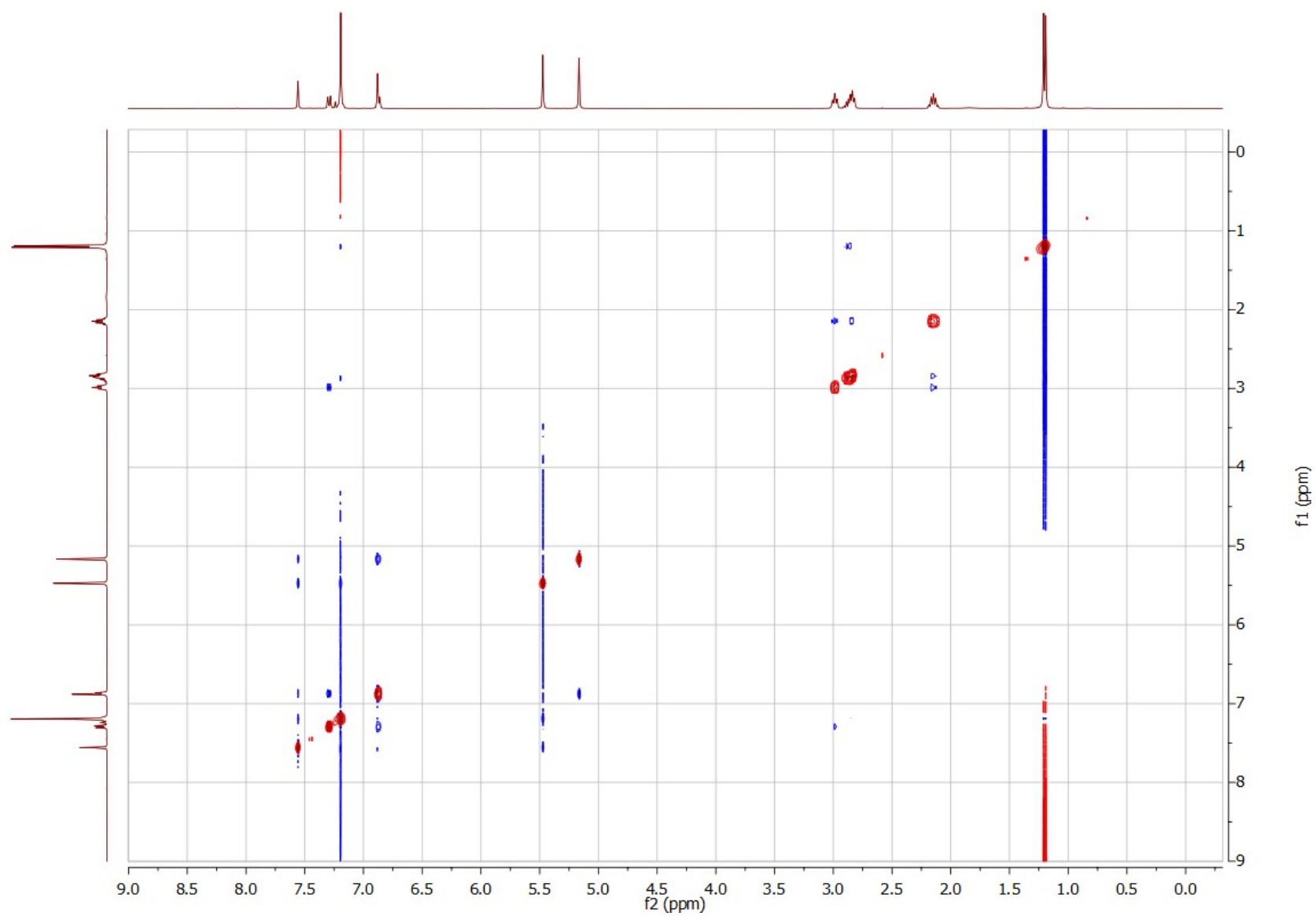


Fig. S65. ^1H - ^{13}C HSQC spectra of the compound 43



Fig. S66. ^1H - ^{13}C HMBC spectra of the compound 43

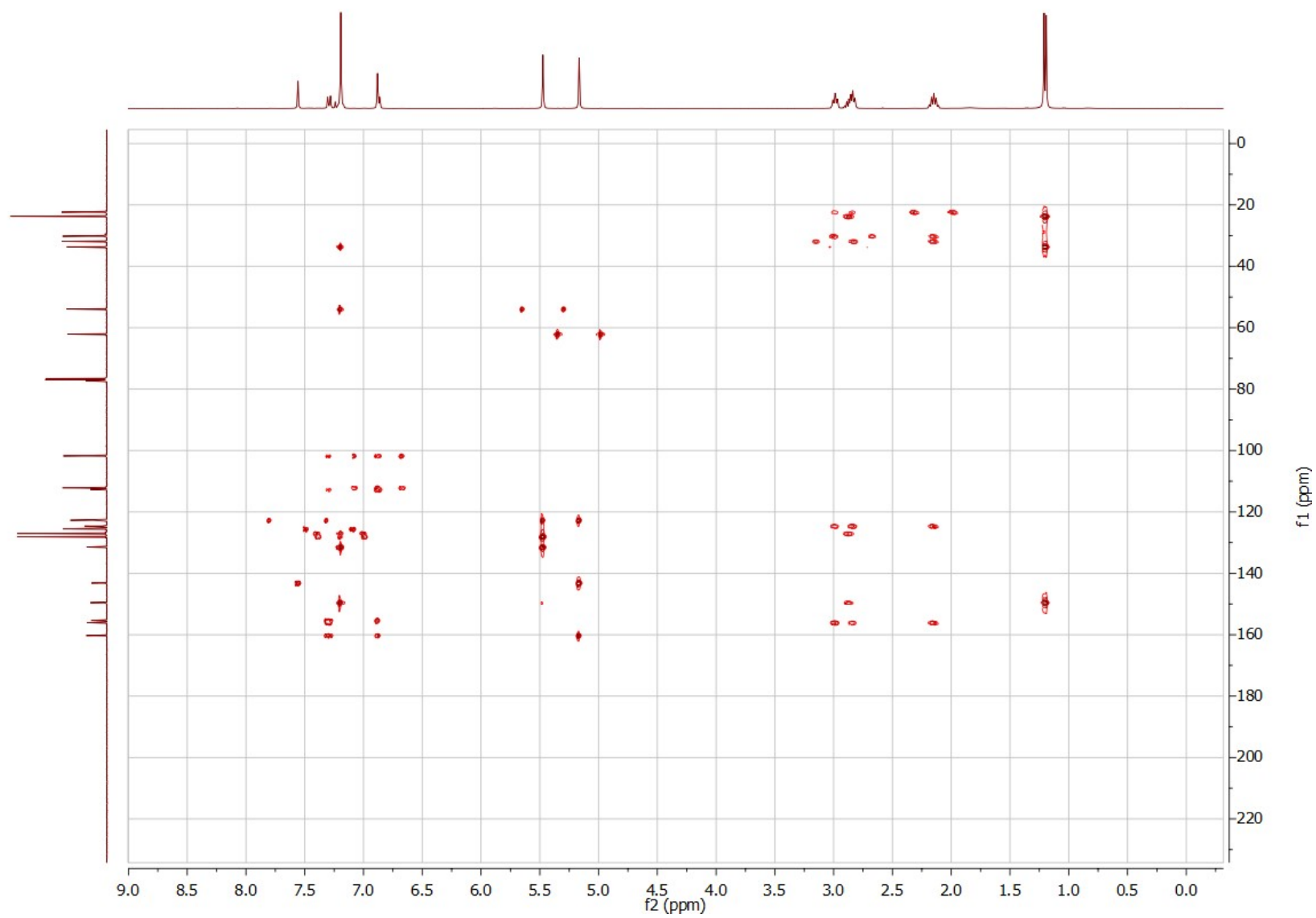


Fig. S67. ^1H - ^1H COSY spectra of the compound 50

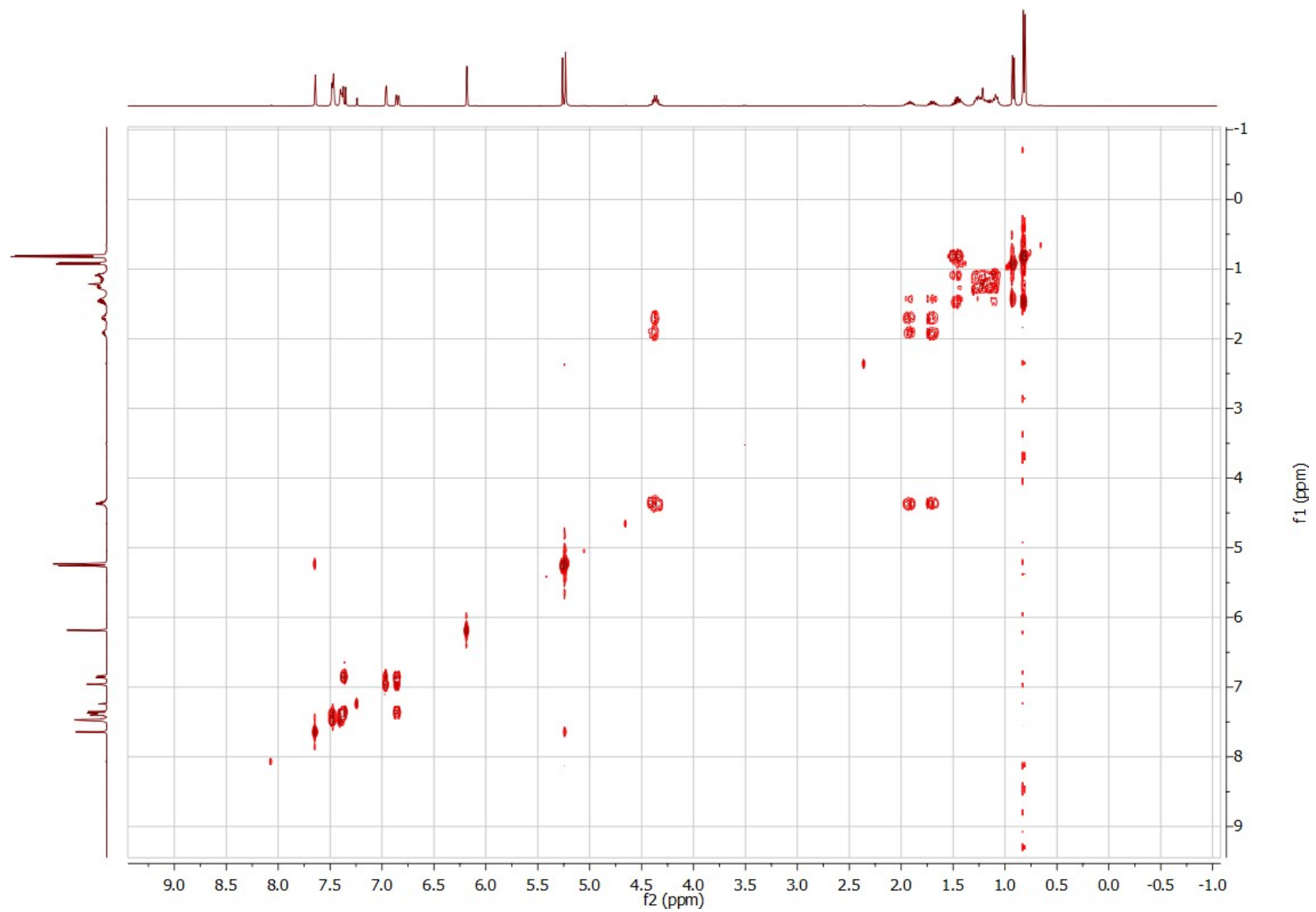


Fig. S68. ^1H - ^1H NOESY spectra of the compound 50

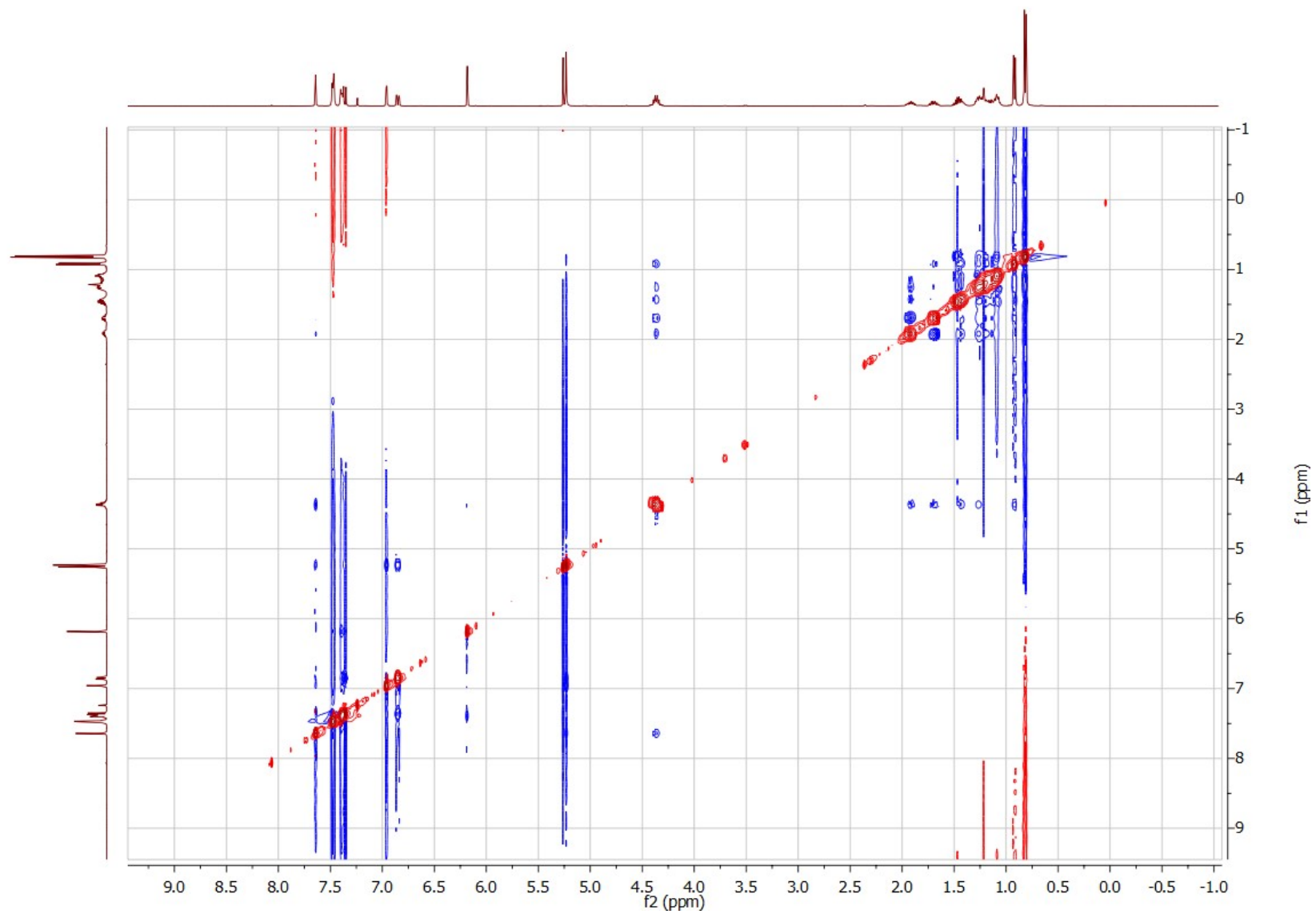


Fig. S69. ^1H - ^{13}C HSQC spectra of the compound 50

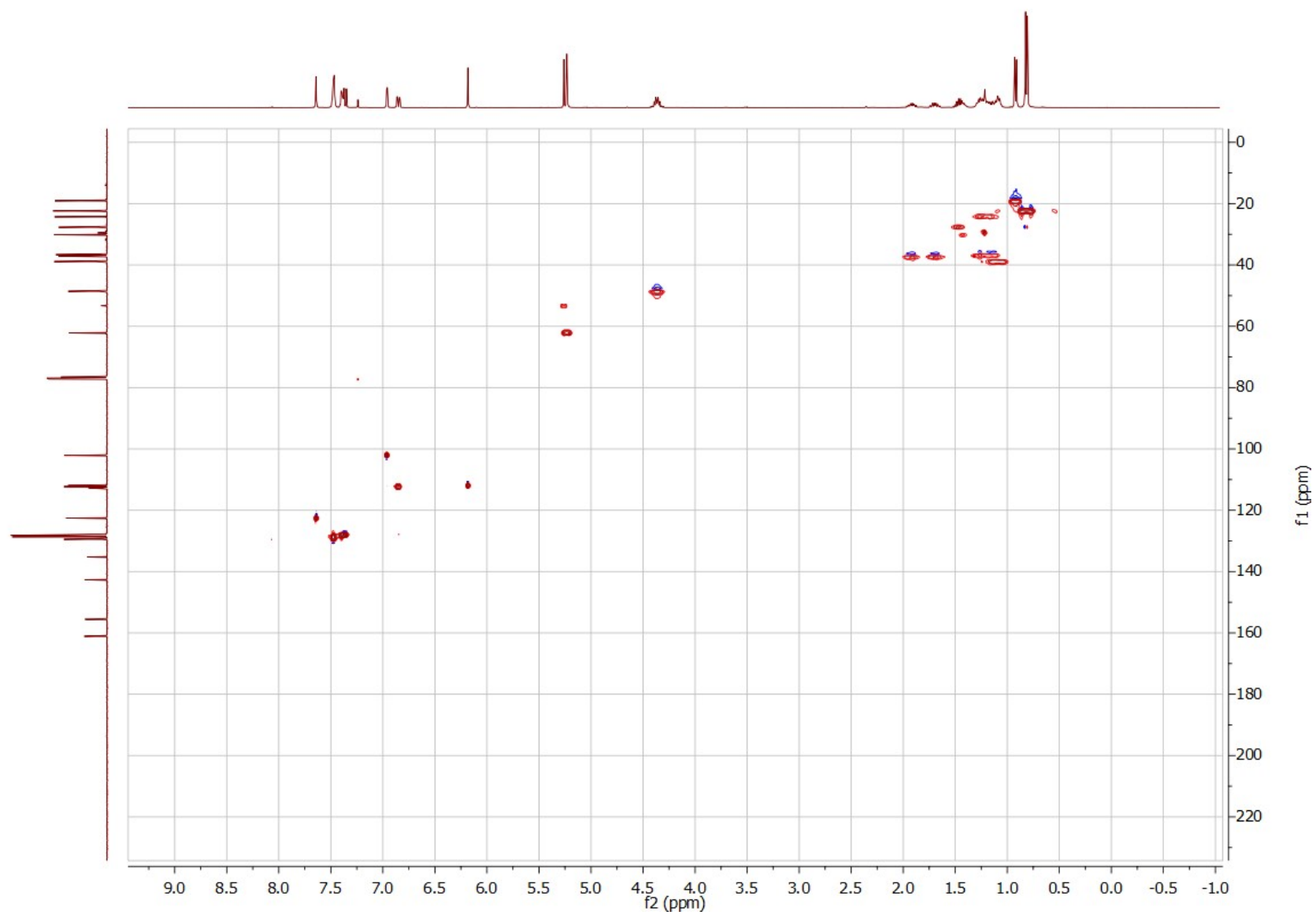


Fig. S70. ^1H - ^{13}C HMBC spectra of the compound **50**

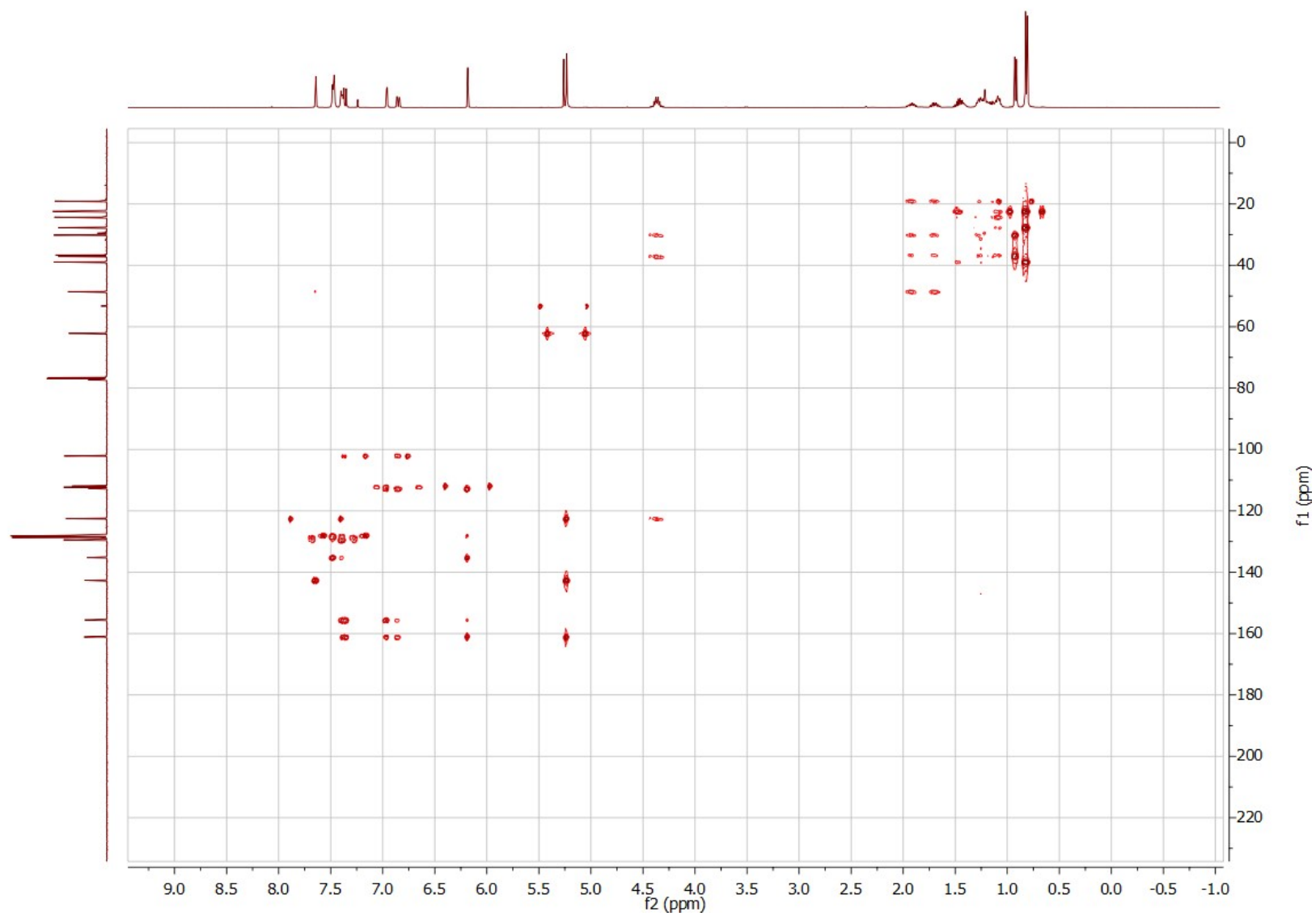


Fig. S71. ^1H - ^1H COSY spectra of the compound **54Z**.

lfav-do-cyc11-i1-2d.3.ser — D0-CYC11-i1-2D; CDCl_3 — ^1H - ^1H COSY

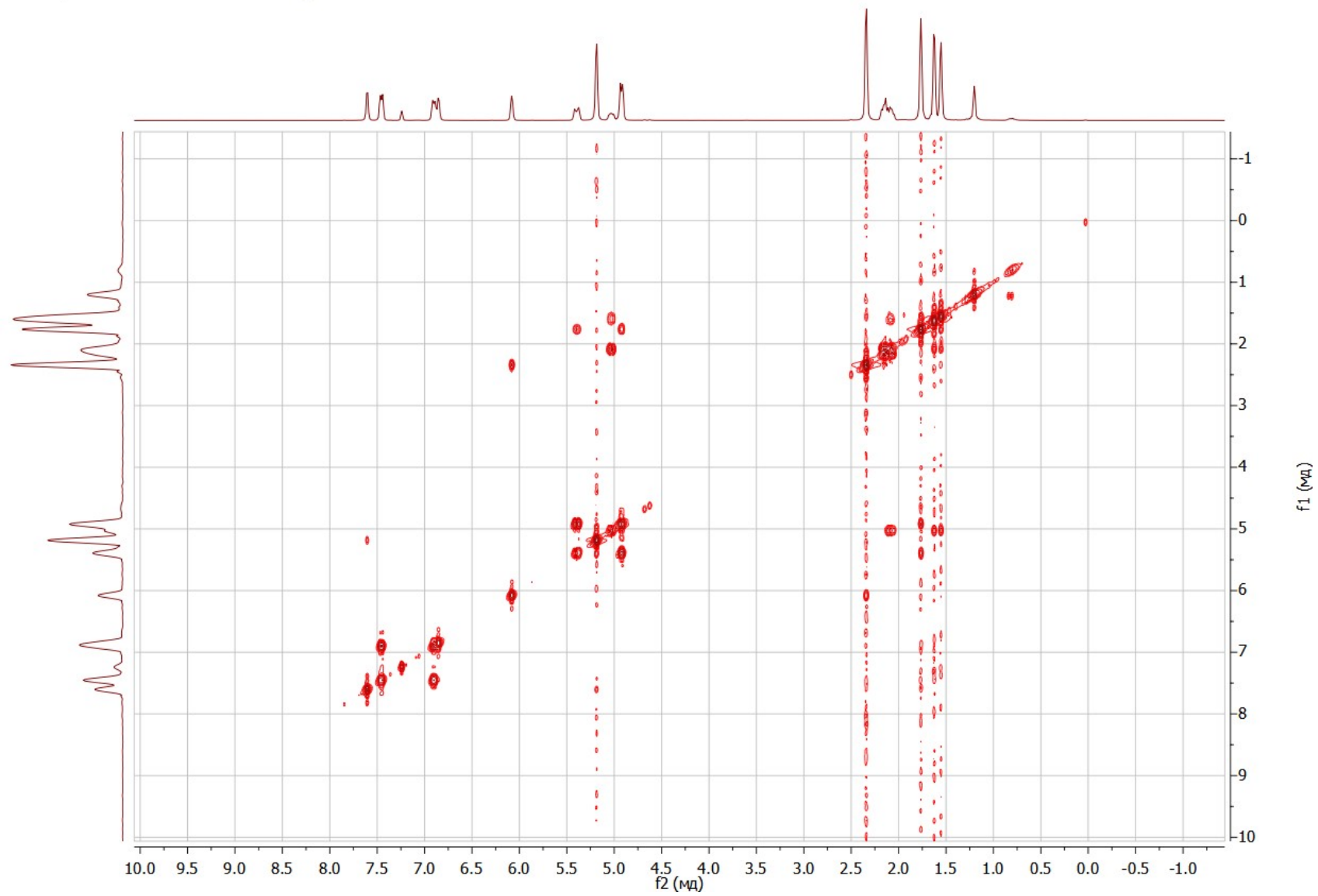


Fig. S72. ^1H - ^1H NOESY spectra of the compound **54Z**.

lfav-do-cyc11-i1-2d.4.ser — D0-CYC11-i1-2D; CDCl₃ — 1H-1H NOESY

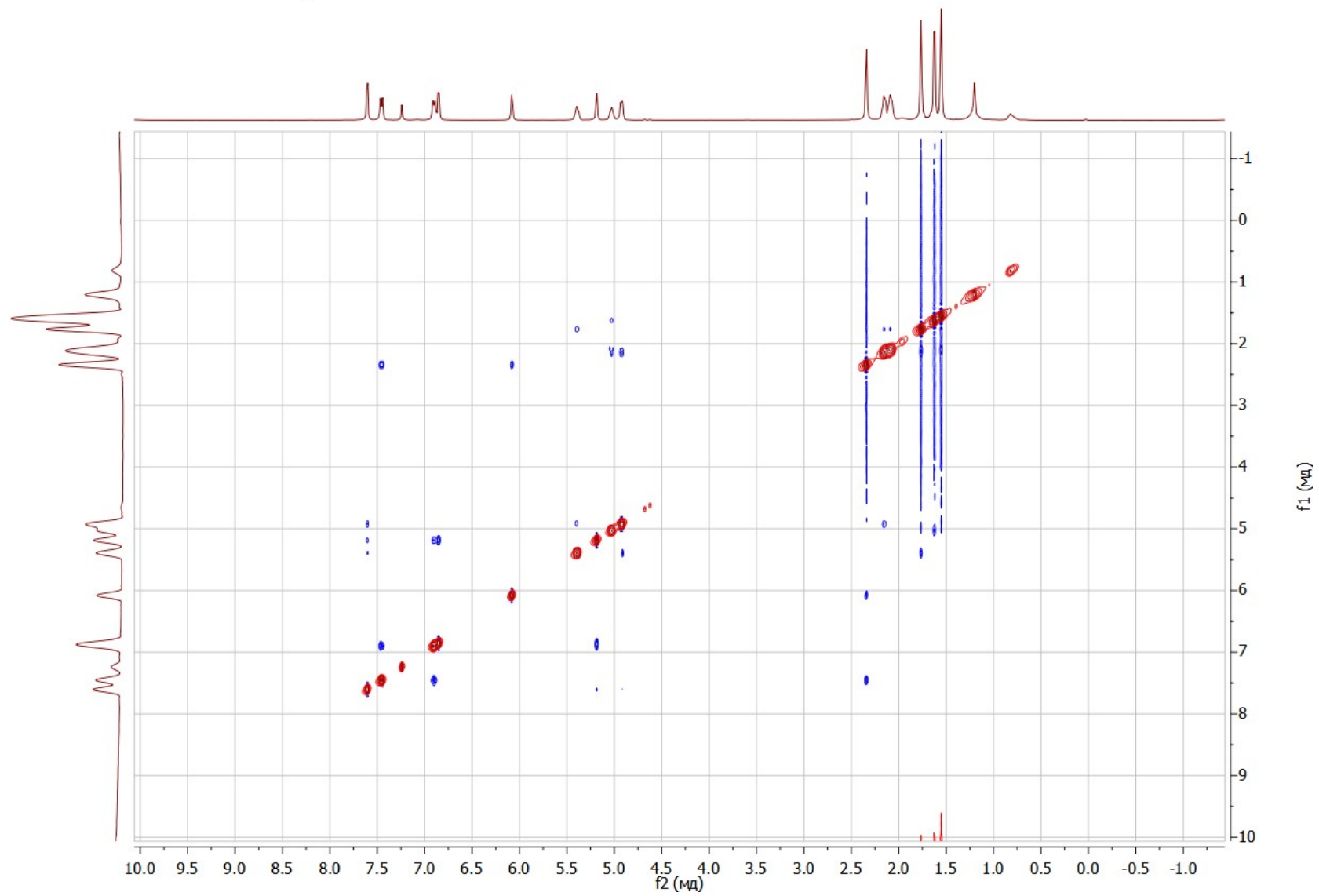


Fig. S73. ^1H - ^{13}C HSQC spectra of the compound **54Z**.

lfav-do-cyc11-i1-2d.5.ser — D0-CYC11-i1-2D; CDCl_3 — ^1H - ^{13}C HSQC

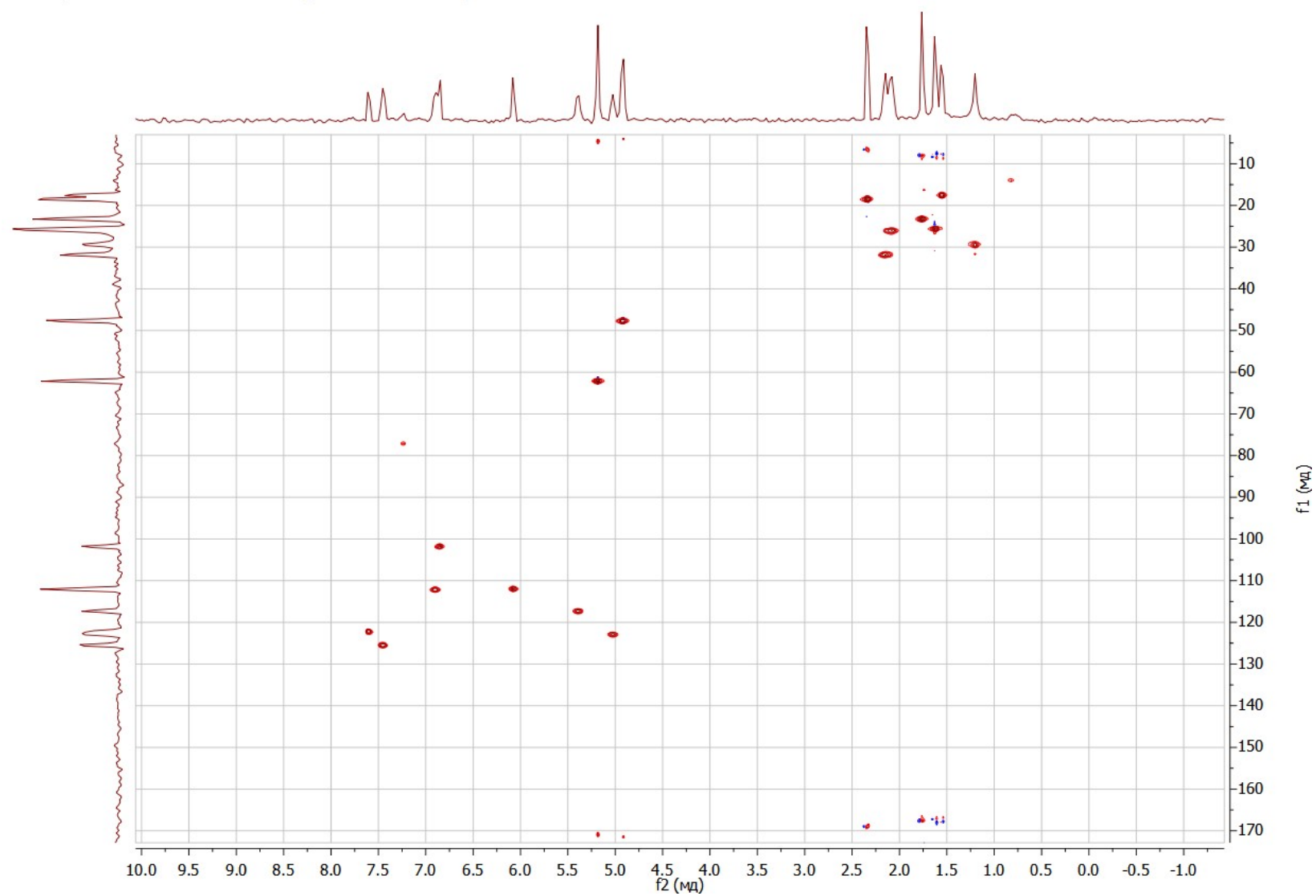


Fig. S74. ^1H - ^{13}C HMBC spectra of the compound **54Z**.

lfav-do-cyc11-i1-2d.6.ser — D0-CYC11-i1-2D; CDCl₃ — ^1H - ^{13}C HMBC

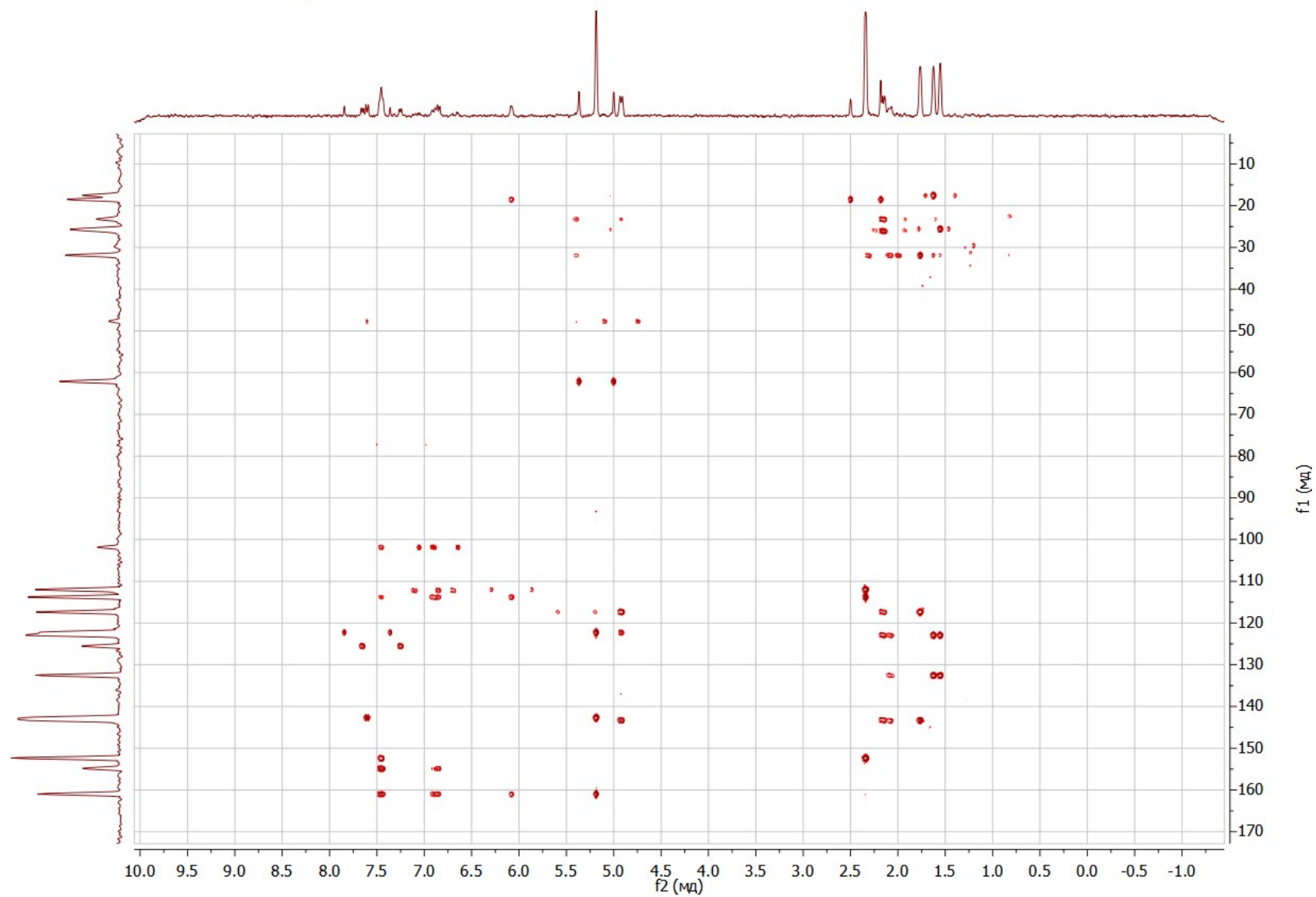


Fig. S75. ^1H - ^1H COSY spectra of the compound **54E**.

lfav-do-cyc11-i2-2d.3.ser — D0-CYC11-I2-2D; CDCl₃ — 1H-1H COSY

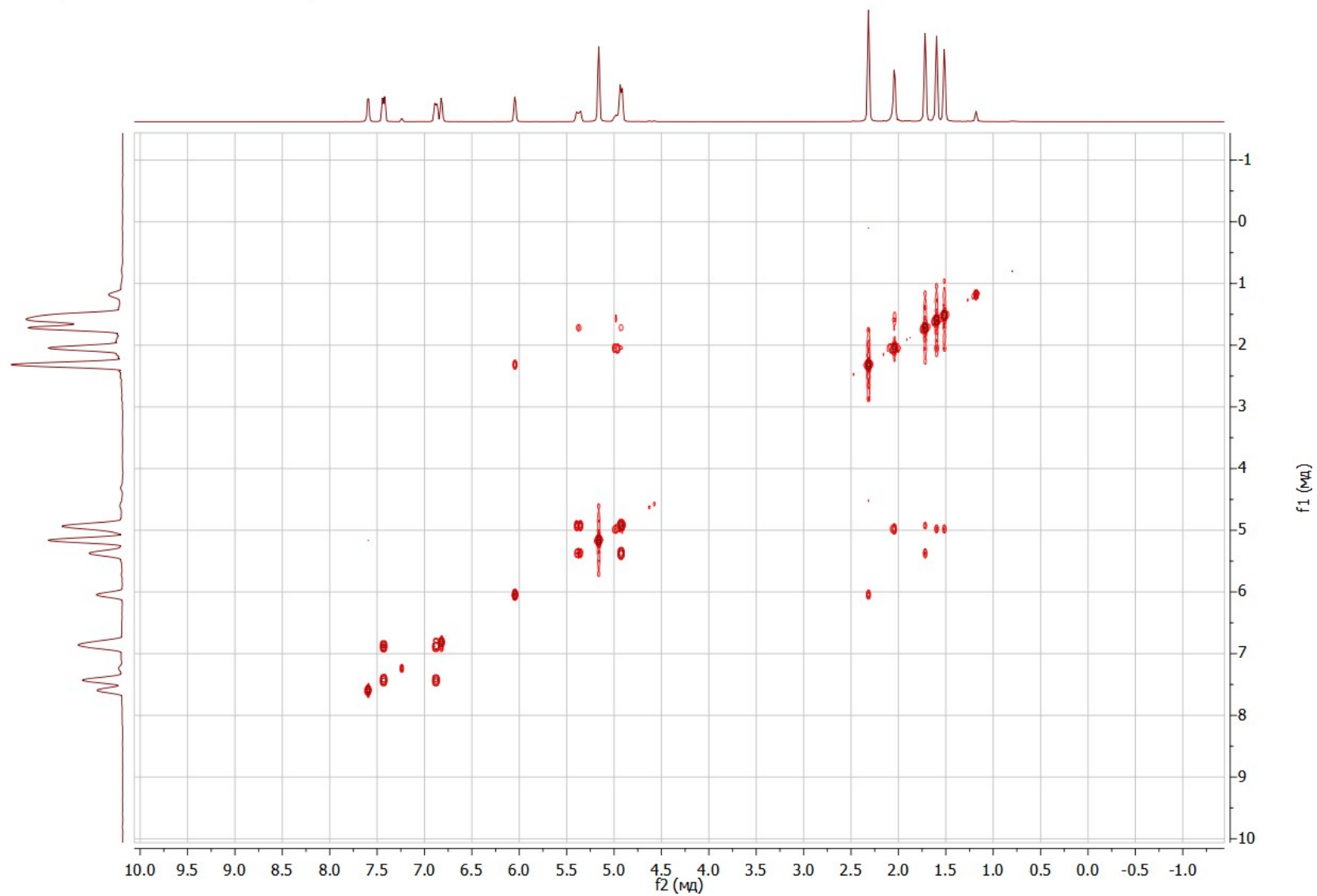


Fig. S76. ^1H - ^1H NOESY spectra of the compound **54E**.

lfav-do-cyc11-i2-2d.4.ser — D0-CYC11-I2-2D; CDCl₃ — ^1H - ^1H NOESY

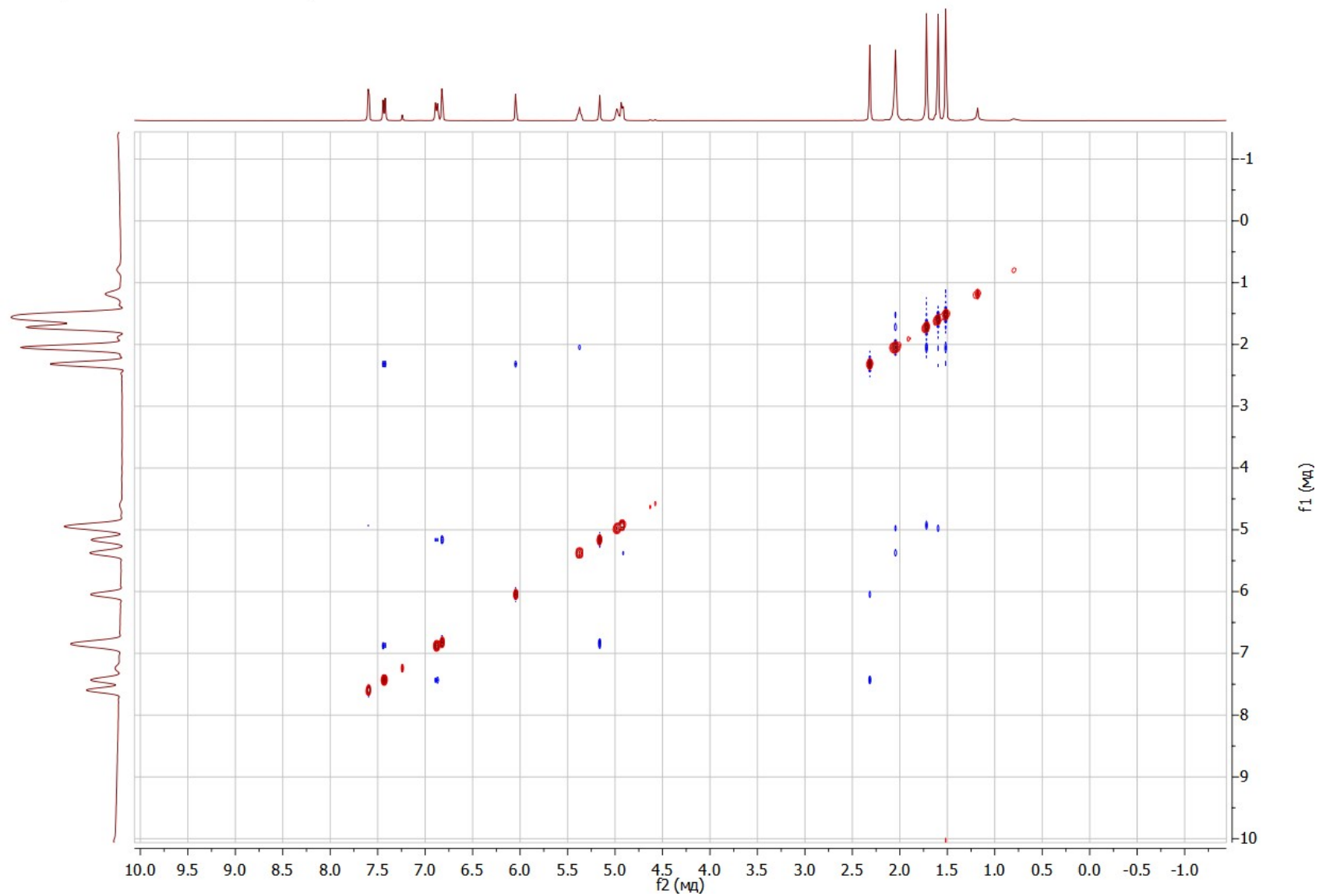


Fig. S77. ^1H - ^{13}C HSQC spectra of the compound **54E**.

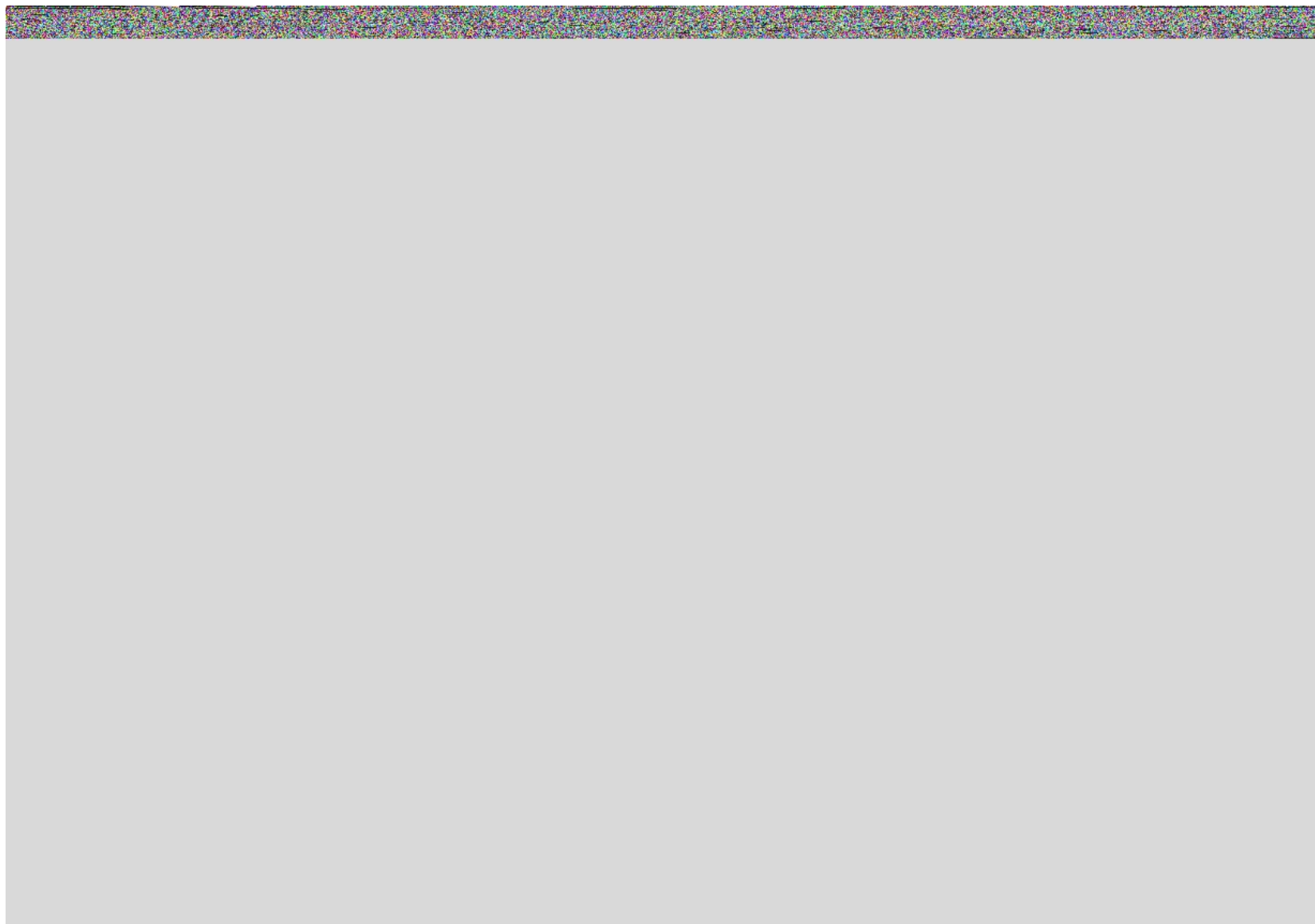
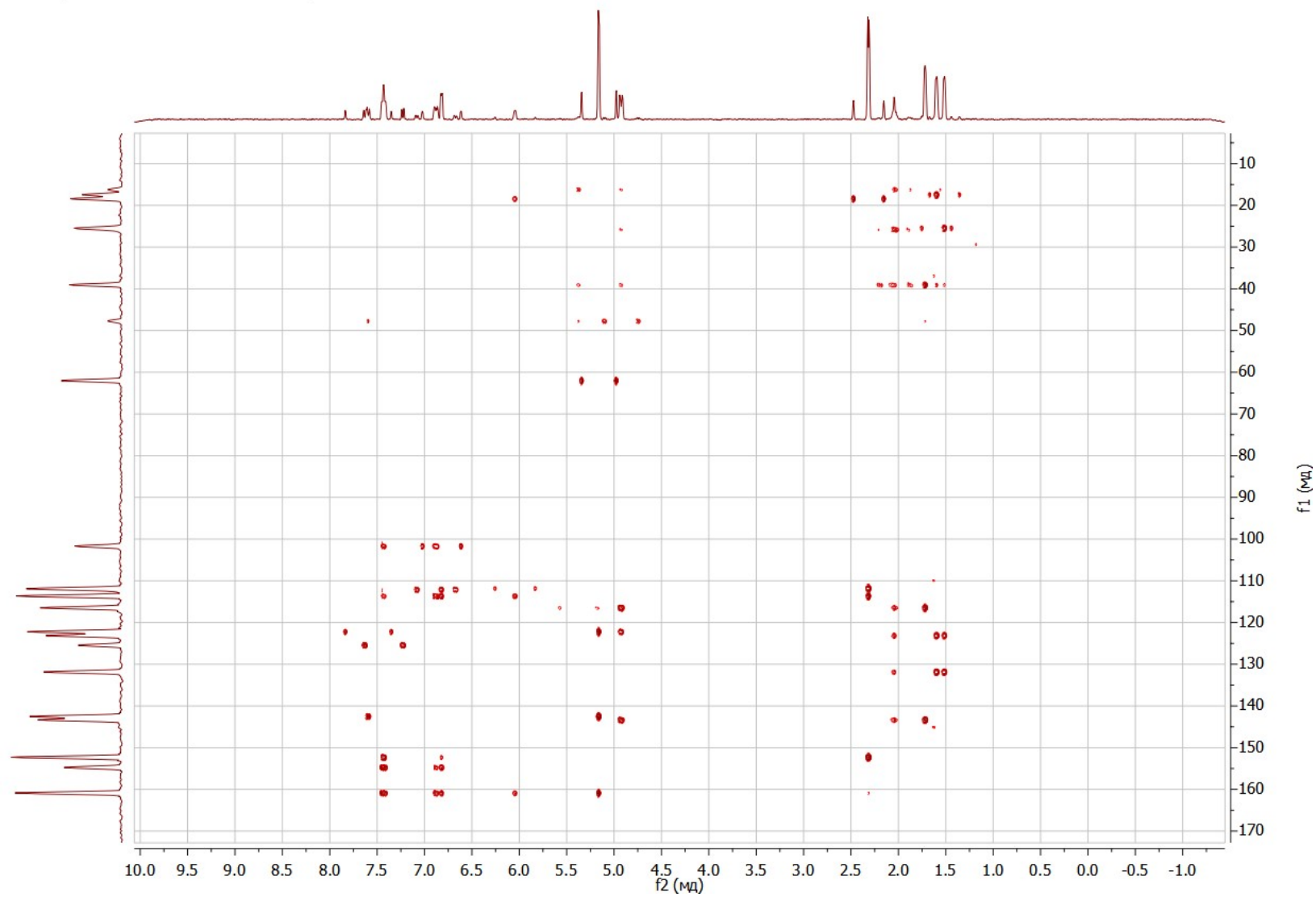


Fig. S78. ^1H - ^{13}C HMBC spectra of the compound **54E**.

lfav-do-cyc11-i2-2d.6.ser — D0-CYC11-I2-2D; CDCl₃ — ^1H - ^{13}C HMBC



4. UHPLC of compounds

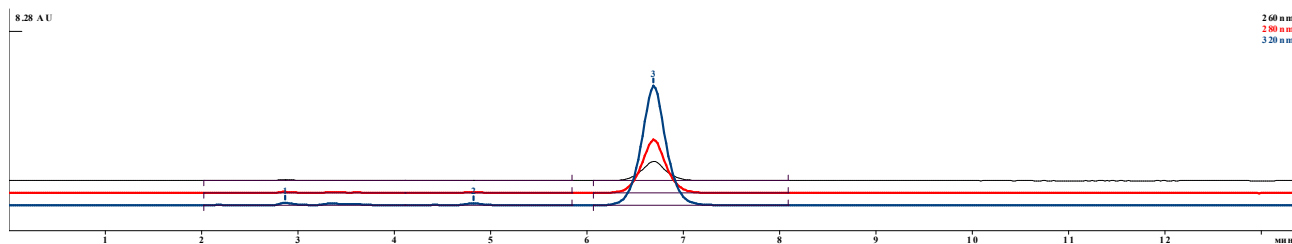


Fig. S79. UHPLC of the compound **10**, 94.47% [320 nm]

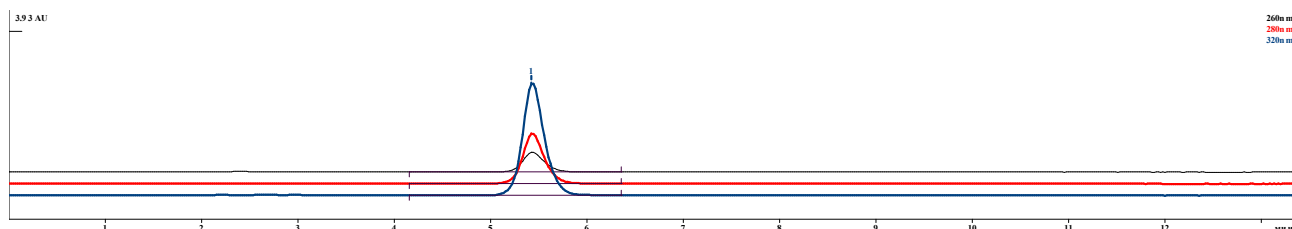


Fig. S80. UHPLC of the compound **39**, 98.28% [320 nm]

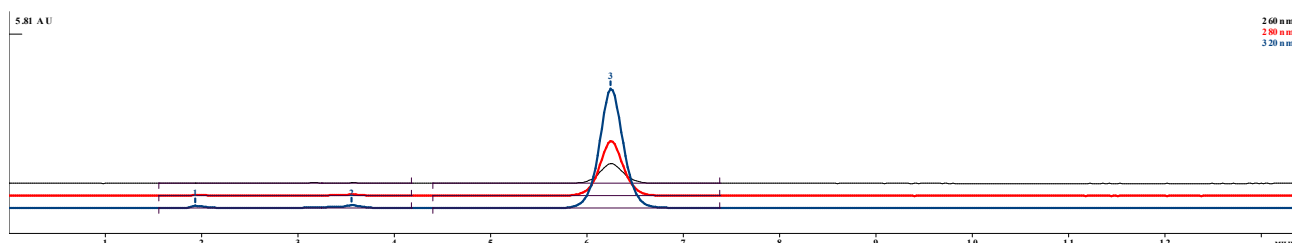


Fig. S81. UHPLC of the compound **40**, 95.11% [320 nm]

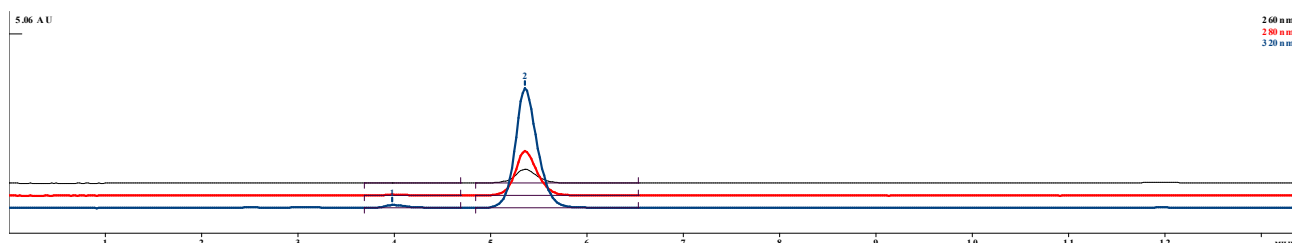


Fig. S82. UHPLC of the compound **41**, 97.58% [320 nm]

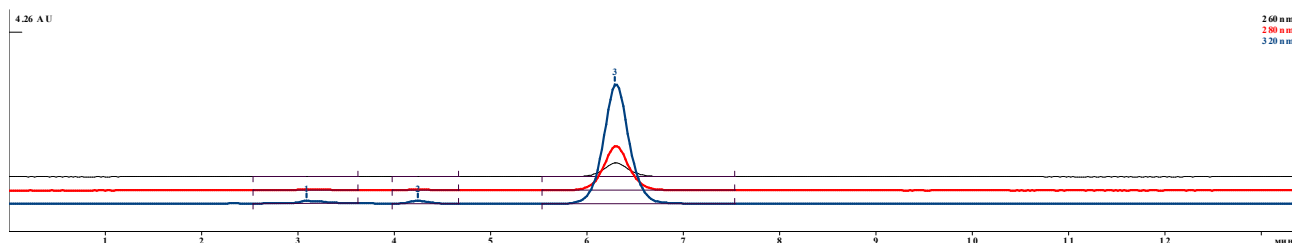


Fig. S83. UHPLC of the compound **43**, 95.96% [320 nm]

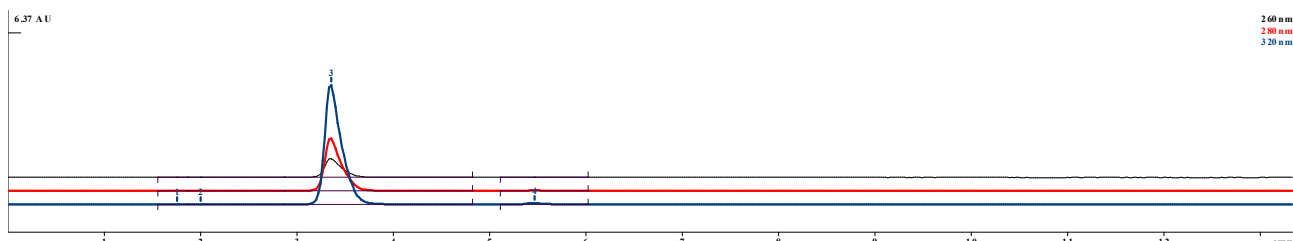


Fig. S84. UHPLC of the compound **44**, 97.62% [320 nm]

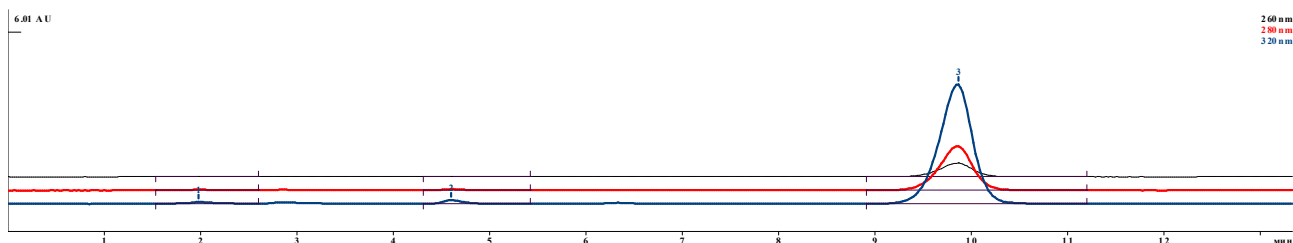


Fig. S85. UHPLC of the compound **45**, 96.86 % [320 nm]

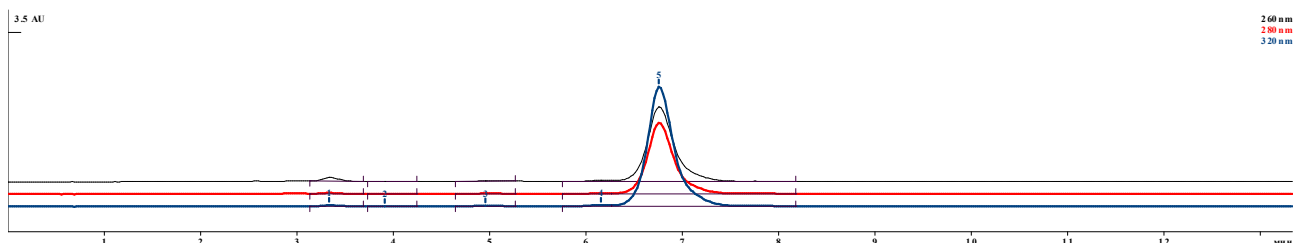


Fig. S86. UHPLC of the compound **46**, 98.02% [320 nm]

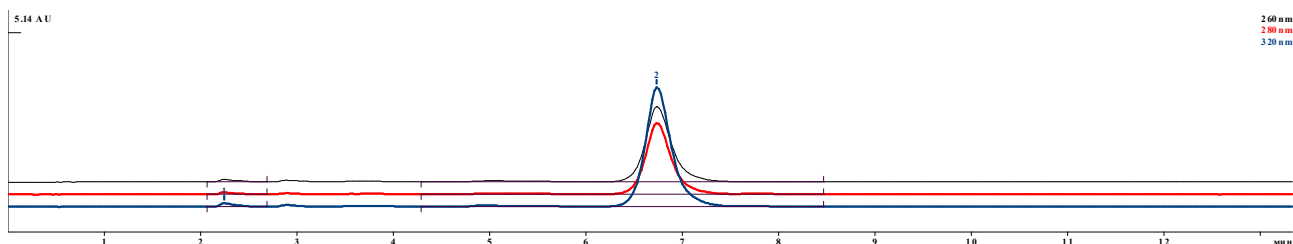


Fig. S87. UHPLC of the compound **47**, 98.39% [320 nm], 70%

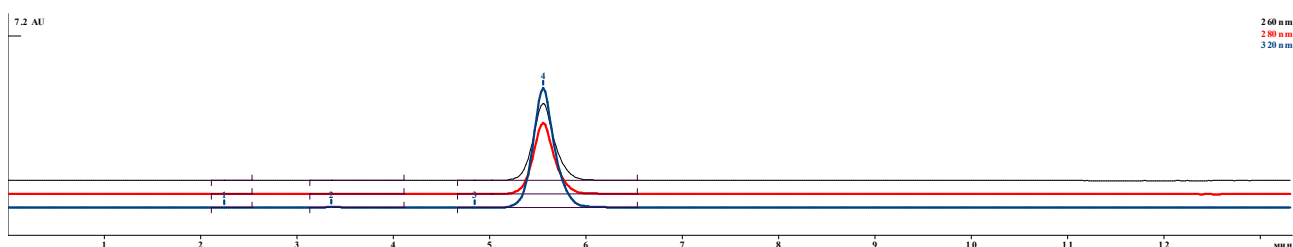


Fig. S88. UHPLC of the compound **48**, 99.04% [320]

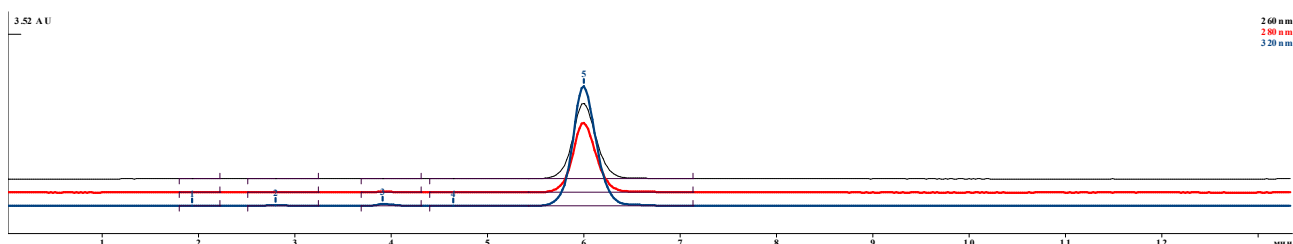


Fig. S89. UHPLC of the compound **50**, 97.35% [320 nm]

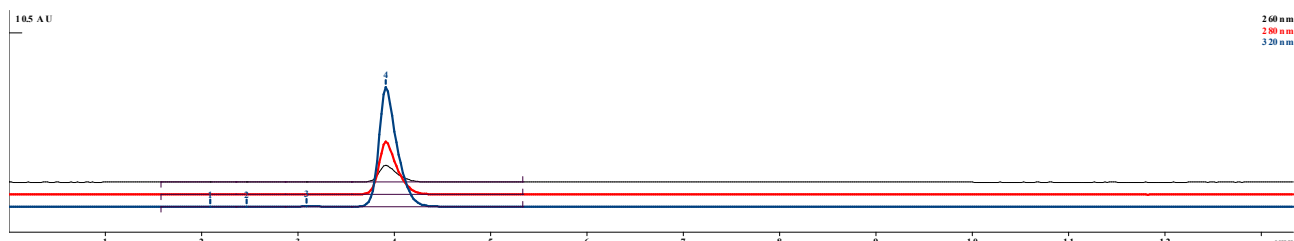


Fig. S90. UHPLC of the compound **51**, 98.31% [320 nm]

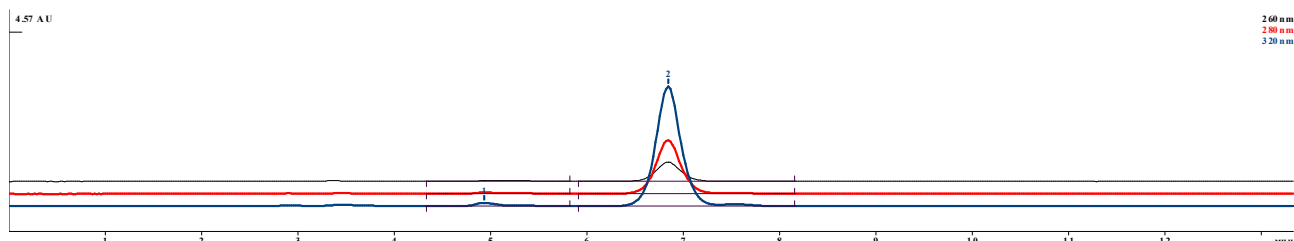


Fig. S91. UHPLC of the compound **52**, 97.18% [320 nm]

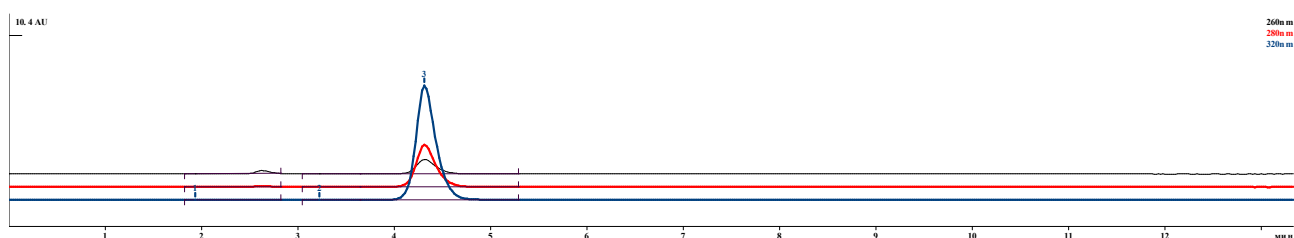


Fig. S92. UHPLC of the compound **53**, 99.96% [320 nm]

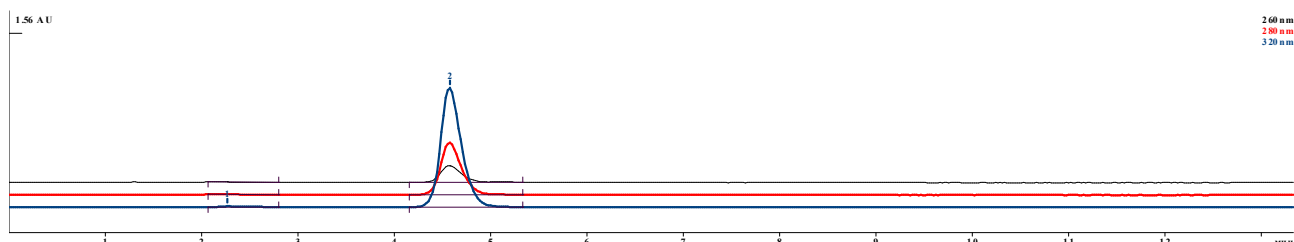


Fig. S93. UHPLC of the compound **54 (Z)**, 99.1 % [320 nm]

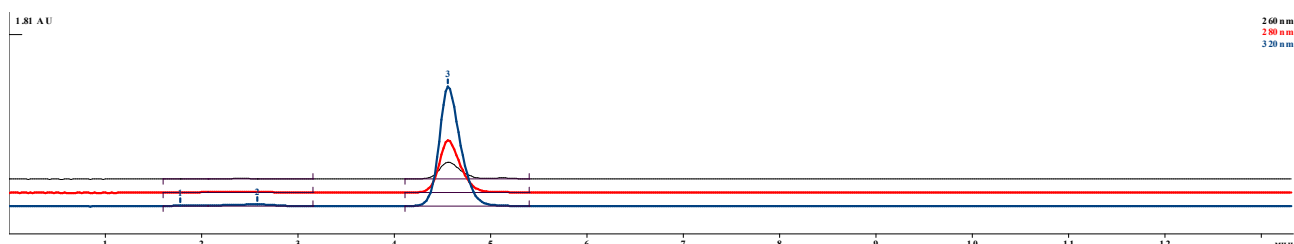


Fig. S94. UHPLC of the compound **54 (E)**, 95.90% [320 nm]

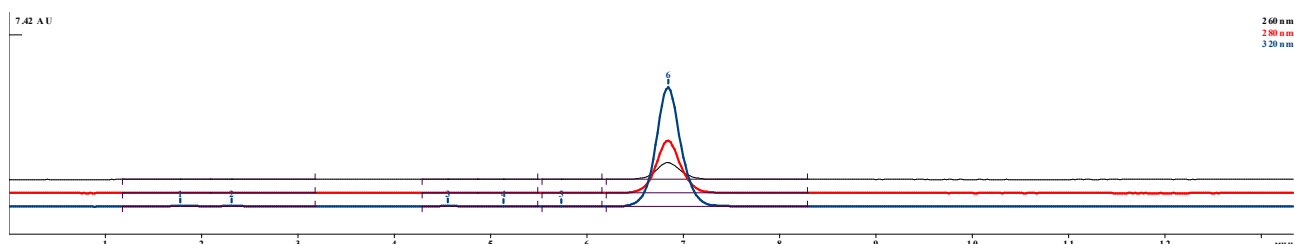


Fig. S95. UHPLC of the compound **55**, 97.30% [320]

5. Synthesis of compounds 23 to 31.

i. Synthesis of (+)-Myrtenal 23

50 mL of the aqueous solution of tert-butyl hydroperoxide (70%) was extracted with DCM. To the 50 mL of DCM extract of tert-butyl hydroperoxide were added selenium dioxide (7 mmol) and (+)- α -pinene (88 mmol). The mixture was stirred under reflux for 12 hours. Then, the reaction mixture was slowly neutralized using 10% solution of sodium peroxide, and dried over sodium sulphate. Then, the drying agent was filtered out, the solvent was evaporated, and the leftover mixture was purified using column chromatography (SiO₂, using mixture of hexane and chloroform with gradually increasing concentration of chloroform from 10 to 100%) The yield of **23** was 70%. Properties of the synthesized alcohol align with the previously published literary data[S1]

ii. Synthesis of alcohols 24-26.

To the stirred and cooled to 0-5 °C solution of the of **23**, (-)-myrtenal, or cuminaldehyde (61.6 mmol) in 100 mL of methanol, sodium borohydride (61.6 mmol) was added in small portions. Stirring continued for the next 3 hours, then 5% solution of hydrochloric acid was added slowly, until the target pH of 4 to 5 was achieved. Methanol was evaporated, the reaction mixture was subsequently extracted with diethyl ether, and the extract was then dried over sodium sulphate. The drying agent was filtered off, and diethyl ether was evaporated. The yields of **24**, **25**, and **26** were 55%, 72%, and 90% respectively. Properties of the synthesized alcohols align with the previously published literary data[S2-S4]

iii. Synthesis of bromides 27-31.

To the stirred and cooled to 0-5 °C solution of **24**, **25**, **26**, geraniol, or 3,7-dimethyloctanol (27.7 mmol) in 30 mL of dry diethyl ether, phosphorus tribromide (8.9 mmol) was added dropwise. Stirring was continued for 1 hour under low temperature, then continued for two hours under room temperature. After the completion of the reaction, the aqueous solution of sodium bicarbonate was added to the reaction mixture until the unreacted phosphorus tribromide was completely neutralized. The organic layer was separated, washed with brine, and subsequently evaporated. The yields of compounds **27** to **31** were 75%, 64%, 90%, 96%, and 88% respectively. Properties of the synthesized bromides align with the previously published literary data[S5-S8]

6. References.

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