

Supporting Information

Mycophenolic Acid Derivatives with Immunosuppressive Activity from the Coral-Derived Fungus *Penicillium bialowiezense*

Qing Zhang, Beiye Yang, Fengli Li, Mengting Liu, Shuang Lin, Jianping Wang, Yongbo Xue, Hucheng Zhu, Weiguang Sun*, Zhengxi Hu*, and Yonghui Zhang*

Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Tongji

Medical College, Huazhong University of Science and Technology, Wuhan 430030, People's Republic of China

* Corresponding author Tel.: (86) 27-83692892

E-mail: zhangyh@mails.tjmu.edu.cn (Y.Z.); weiguang_s@hust.edu.cn (W.S.); hzx616@126.com (Z.H.)

Contents of Supporting Information

Figure S1. ^1H NMR spectrum of compound 1 (Recorded in CD_3OD).....	5
Figure S2. ^{13}C NMR spectrum of compound 1 (Recorded in CD_3OD)	6
Figure S3. DEPT spectrum of compound 1 (Recorded in CD_3OD).....	7
Figure S4. HSQC spectrum of compound 1 (Recorded in CD_3OD).....	8
Figure S5. HMBC spectrum of compound 1 (Recorded in CD_3OD).....	9
Figure S6. ^1H - ^1H COSY spectrum of compound 1 (Recorded in CD_3OD)	10
Figure S7. HRESIMS spectrum of compound 1	11
Figure S8. IR spectrum of compound 1	12
Figure S9. UV spectrum of compound 1	13
Figure S10. ^1H NMR spectrum of compound 2 (Recorded in CD_3OD).....	14
Figure S11. ^{13}C NMR spectrum of compound 2 (Recorded in CD_3OD)	15
Figure S12. DEPT spectrum of compound 2 (Recorded in CD_3OD).....	16
Figure S13. HSQC spectrum of compound 2 (Recorded in CD_3OD).....	17
Figure S14. HMBC spectrum of compound 2 (Recorded in CD_3OD).....	18
Figure S15. ^1H - ^1H COSY spectrum of compound 2 (Recorded in CD_3OD)	19
Figure S16. HRESIMS spectrum of compound 2	20
Figure S17. IR spectrum of compound 2	21
Figure S18. UV spectrum of compound 2	22
Figure S19. ^1H NMR spectrum of compound 3 (Recorded in CD_3OD).....	23
Figure S20. ^{13}C NMR spectrum of compound 3 (Recorded in CD_3OD)	24
Figure S21. DEPT spectrum of compound 3 (Recorded in CD_3OD).....	25
Figure S22. HSQC spectrum of compound 3 (Recorded in CD_3OD).....	26
Figure S23. HMBC spectrum of compound 3 (Recorded in CD_3OD).....	27
Figure S24. ^1H - ^1H COSY spectrum of compound 3 (Recorded in CD_3OD)	28
Figure S25. HRESIMS spectrum of compound 3	29
Figure S26. IR spectrum of compound 3	30
Figure S27. UV spectrum of compound 3	31
Figure S28. ^1H NMR spectrum of compound 4 (Recorded in CD_3OD).....	32
Figure S29. ^{13}C NMR spectrum of compound 4 (Recorded in CD_3OD)	33
Figure S30. HSQC spectrum of compound 4 (Recorded in CD_3OD).....	34
Figure S31. HMBC spectrum of compound 4 (Recorded in CD_3OD).....	35
Figure S32. ^1H - ^1H COSY spectrum of compound 4 (Recorded in CD_3OD)	36
Figure S33. HRESIMS spectrum of compound 4	37
Figure S34. IR spectrum of compound 4	38
Figure S35. UV spectrum of compound 4	39
Figure S36. ^1H NMR spectrum of compound 5 (Recorded in CD_3OD).....	40

Figure S37. ^{13}C NMR spectrum of compound 5 (Recorded in CD_3OD)	41
Figure S38. DEPT spectrum of compound 5 (Recorded in CD_3OD).....	42
Figure S39. HSQC spectrum of compound 5 (Recorded in CD_3OD).....	43
Figure S40. HMBC spectrum of compound 5 (Recorded in CD_3OD).....	44
Figure S41. ^1H - ^1H COSY spectrum of compound 5 (Recorded in CD_3OD)	45
Figure S42. HRESIMS spectrum of compound 5.....	46
Figure S43. IR spectrum of compound 5	47
Figure S44. UV spectrum of compound 5	48
Figure S45. ^1H NMR spectrum of compound 6 (Recorded in CD_3OD).....	49
Figure S46. ^{13}C NMR spectrum of compound 6 (Recorded in CD_3OD)	50
Figure S47. DEPT spectrum of compound 6 (Recorded in CD_3OD).....	51
Figure S48. HSQC spectrum of compound 6 (Recorded in CD_3OD).....	52
Figure S49. HMBC spectrum of compound 6 (Recorded in CD_3OD).....	53
Figure S50. ^1H - ^1H COSY spectrum of compound 6 (Recorded in CD_3OD)	54
Figure S51. HRESIMS spectrum of compound 6.....	55
Figure S52. IR spectrum of compound 6	56
Figure S53. UV spectrum of compound 6	57
Figure S54. ^1H NMR spectrum of compound 7 (Recorded in CD_3OD).....	58
Figure S55. ^{13}C NMR spectrum of compound 7 (Recorded in CD_3OD)	59
Figure S56. DEPT spectrum of compound 7 (Recorded in CD_3OD).....	60
Figure S57. HSQC spectrum of compound 7 (Recorded in CD_3OD).....	61
Figure S58. HMBC spectrum of compound 7 (Recorded in CD_3OD).....	62
Figure S59. ^1H - ^1H COSY spectrum of compound 7 (Recorded in CD_3OD)	63
Figure S60. HRESIMS spectrum of compound 7.....	64
Figure S61. IR spectrum of compound 7	65
Figure S62. UV spectrum of compound 7	66
Figure S63. ^1H NMR spectrum of compound 8 (Recorded in CD_3OD).....	67
Figure S64. ^{13}C NMR spectrum of compound 8 (Recorded in CD_3OD)	68
Figure S65. DEPT spectrum of compound 8 (Recorded in CD_3OD).....	69
Figure S66. HSQC spectrum of compound 8 (Recorded in CD_3OD).....	70
Figure S67. HMBC spectrum of compound 8 (Recorded in CD_3OD).....	71
Figure S68. ^1H - ^1H COSY spectrum of compound 8 (Recorded in CD_3OD)	72
Figure S69. HRESIMS spectrum of compound 8.....	73
Figure S70. IR spectrum of compound 8	74
Figure S71. UV spectrum of compound 8	75
Figure S72. ^1H NMR spectrum of compound 9 (Recorded in CD_3OD).....	76
Figure S73. ^{13}C NMR spectrum of compound 9 (Recorded in CD_3OD)	77
Figure S74. DEPT spectrum of compound 9 (Recorded in CD_3OD).....	78

Figure S75. HSQC spectrum of compound 9 (Recorded in CD ₃ OD).....	79
Figure S76. HMBC spectrum of compound 9 (Recorded in CD ₃ OD).....	80
Figure S77. ¹ H– ¹ H COSY spectrum of compound 9 (Recorded in CD ₃ OD)	81
Figure S78. HRESIMS spectrum of compound 9	82
Figure S79. IR spectrum of compound 9	83
Figure S80. UV spectrum of compound 9	84
Figure S81. ¹ H NMR spectrum of compound 10 (Recorded in CD ₃ OD).....	85
Figure S82. ¹³ C NMR spectrum of compound 10 (Recorded in CD ₃ OD)	86
Figure S83. DEPT spectrum of compound 10 (Recorded in CD ₃ OD).....	87
Figure S84. HSQC spectrum of compound 10 (Recorded in CD ₃ OD).....	88
Figure S85. HMBC spectrum of compound 10 (Recorded in CD ₃ OD).....	89
Figure S86. ¹ H– ¹ H COSY spectrum of compound 10 (Recorded in CD ₃ OD)	90
Figure S87. HRESIMS spectrum of compound 10	91
Figure S88. IR spectrum of compound 10	92
Figure S89. UV spectrum of compound 10	93
Structure elucidation of compounds 1, 2, and 8–10	94
The physical and chemical constants of compounds 1, 2, and 8–10	96
¹H and ¹³C NMR data for compounds 1, 2, and 8–10	97

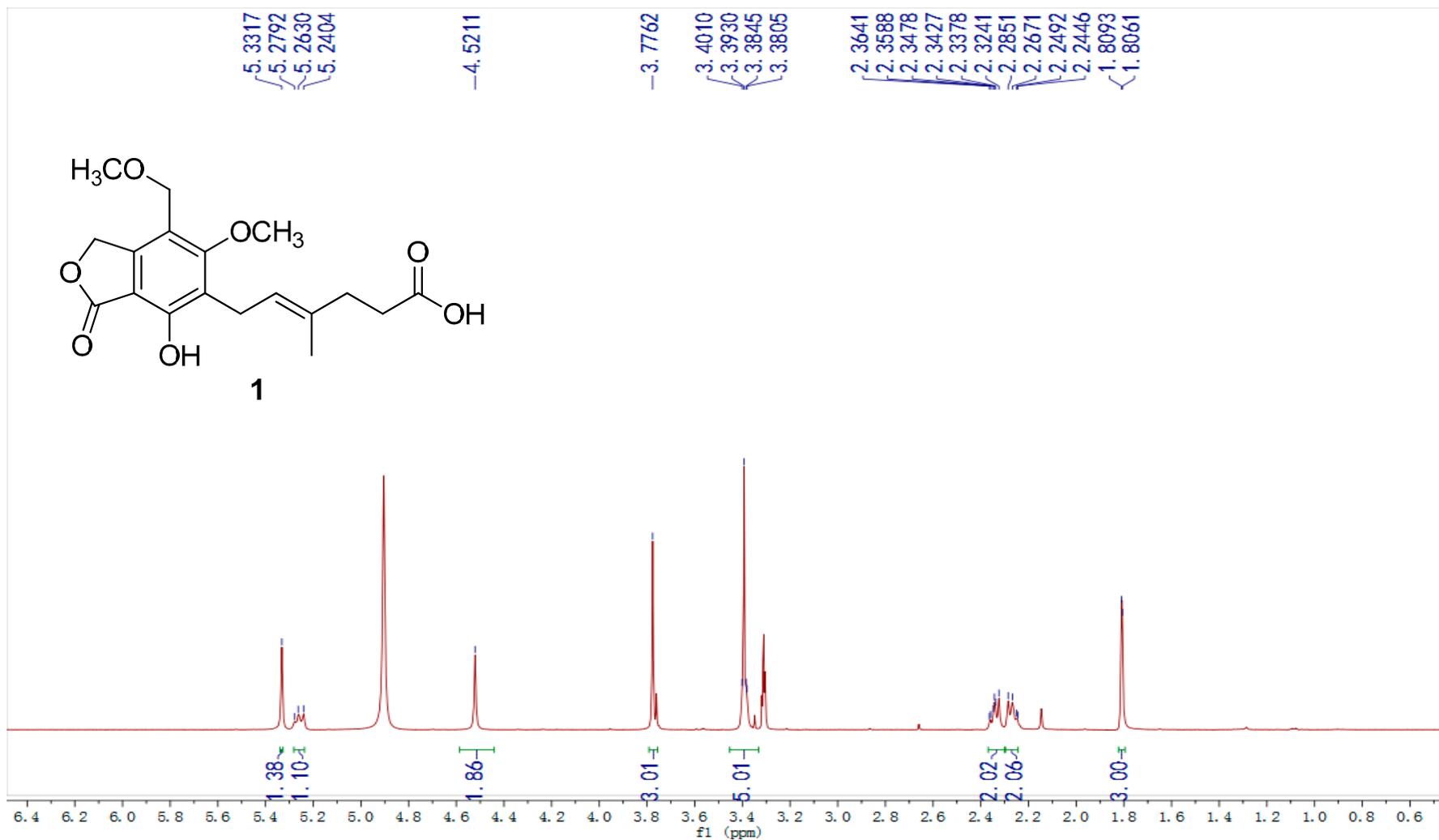


Figure S1. ¹H NMR spectrum of compound 1 (Recorded in CD₃OD)

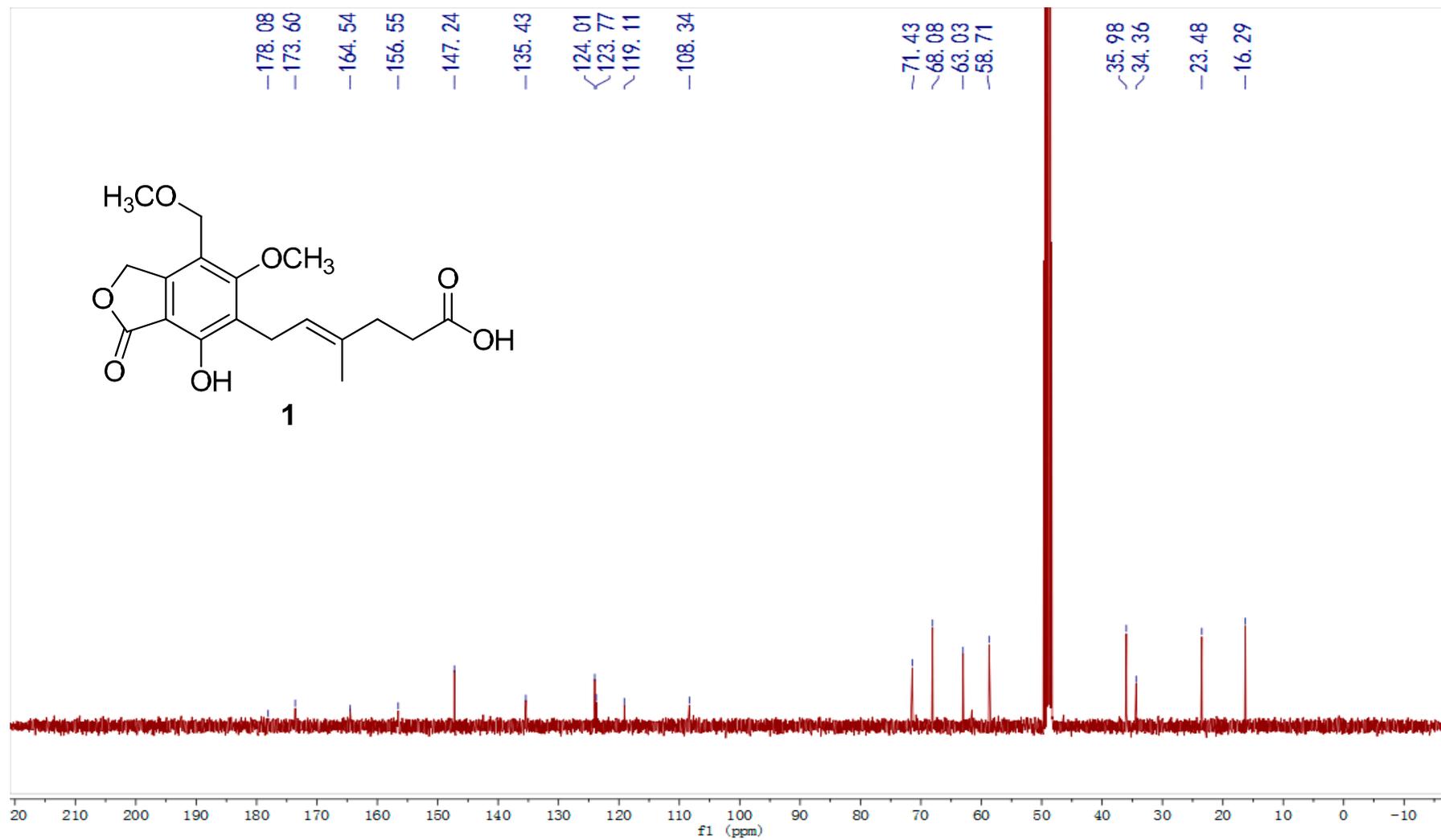


Figure S2. ^{13}C NMR spectrum of compound 1 (Recorded in CD_3OD)

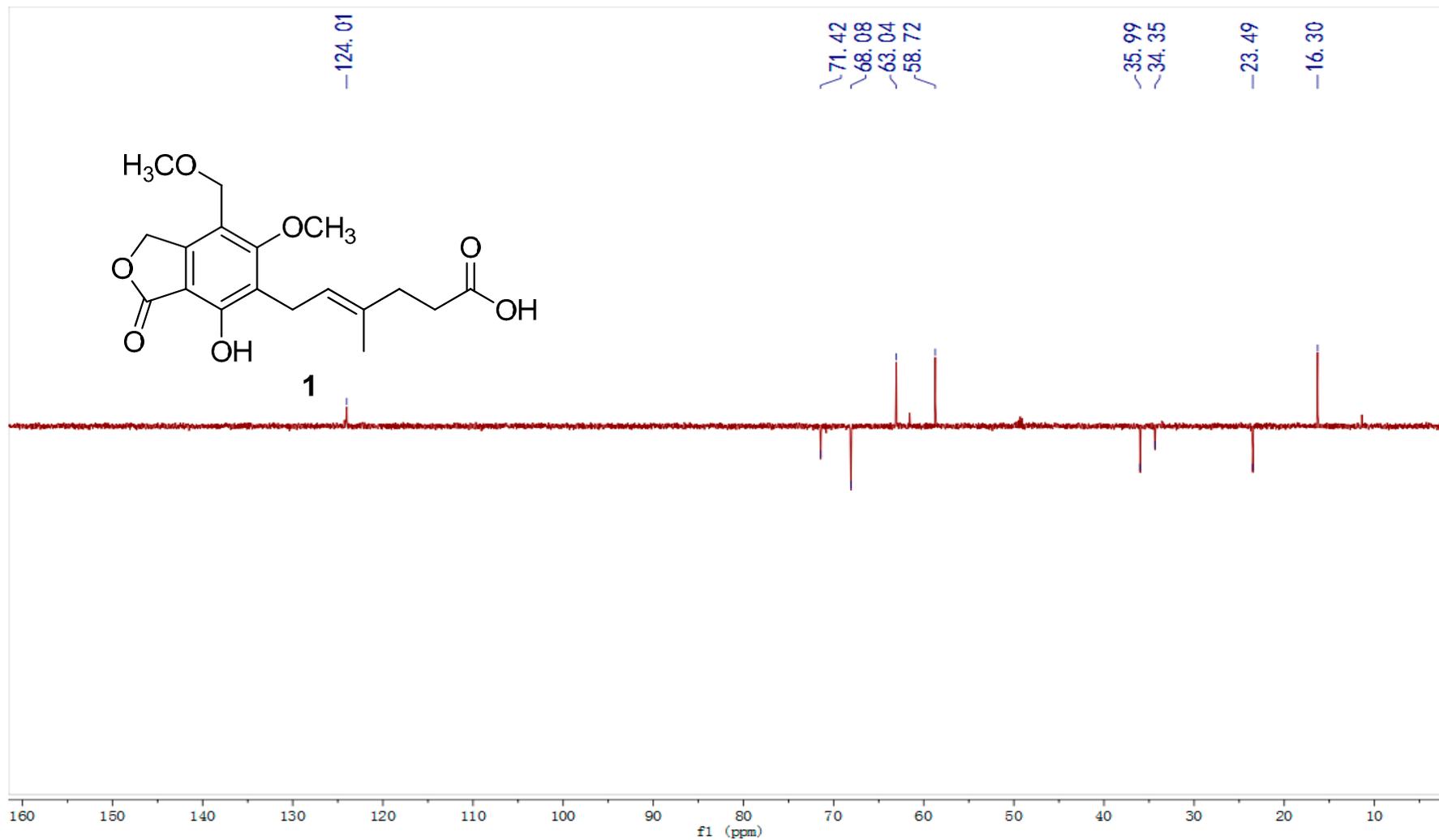


Figure S3. DEPT spectrum of compound 1 (Recorded in CD₃OD)

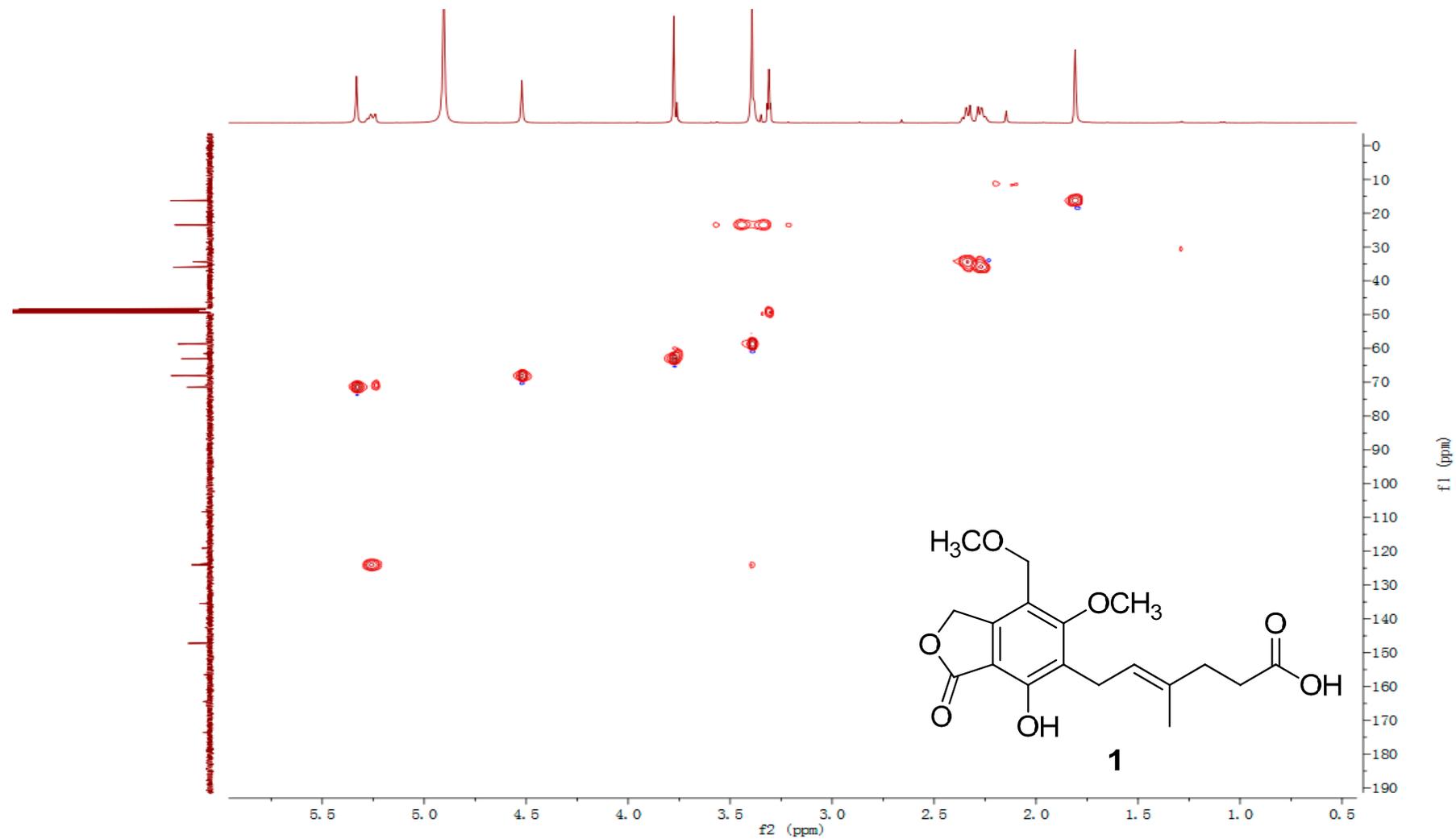


Figure S4. HSQC spectrum of compound 1 (Recorded in CD₃OD)

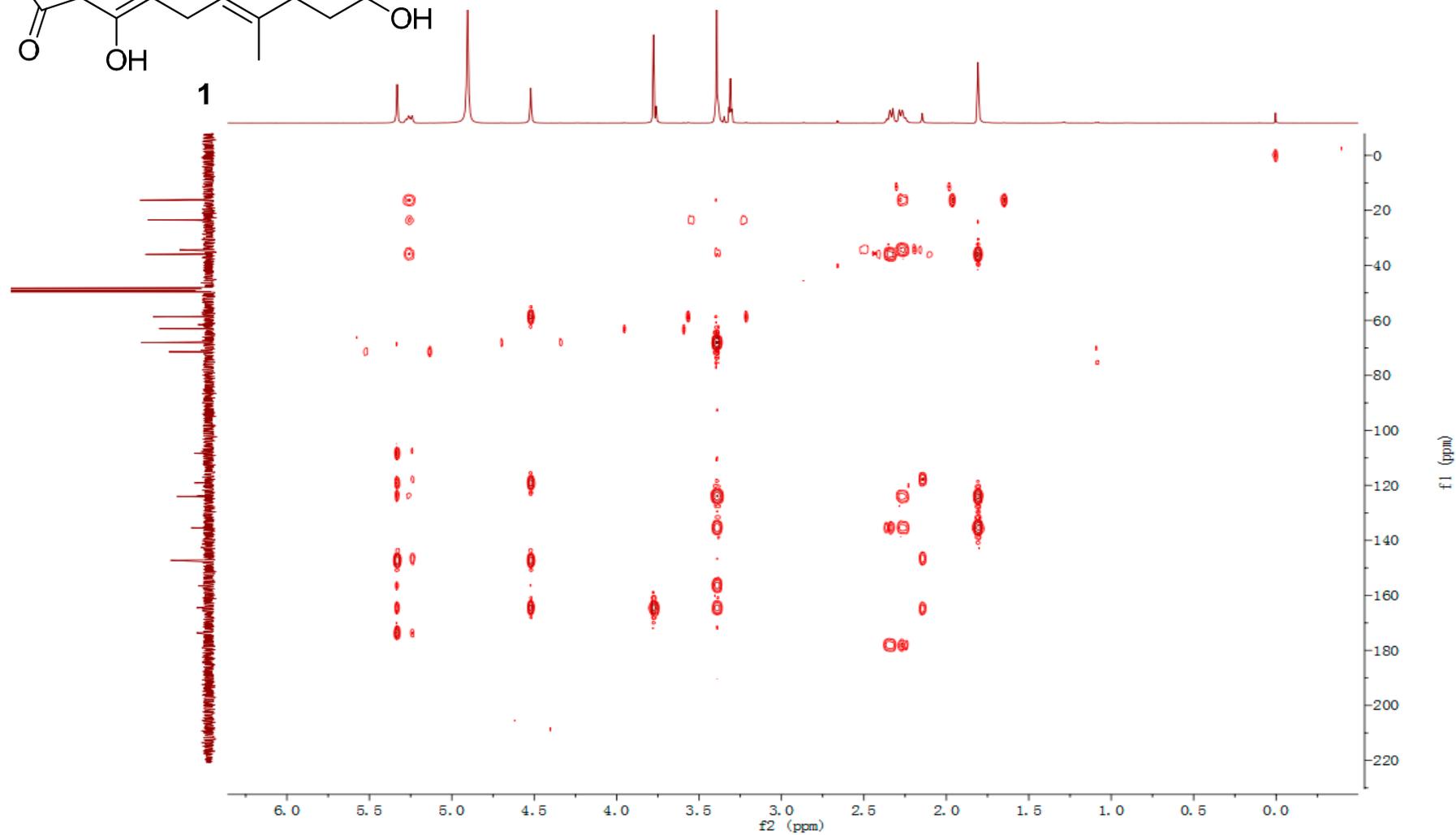
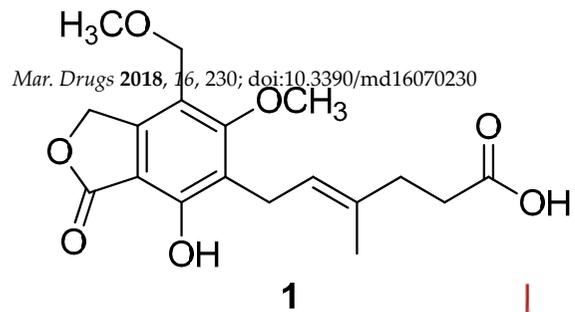


Figure S5. HMBC spectrum of compound **1** (Recorded in CD₃OD)

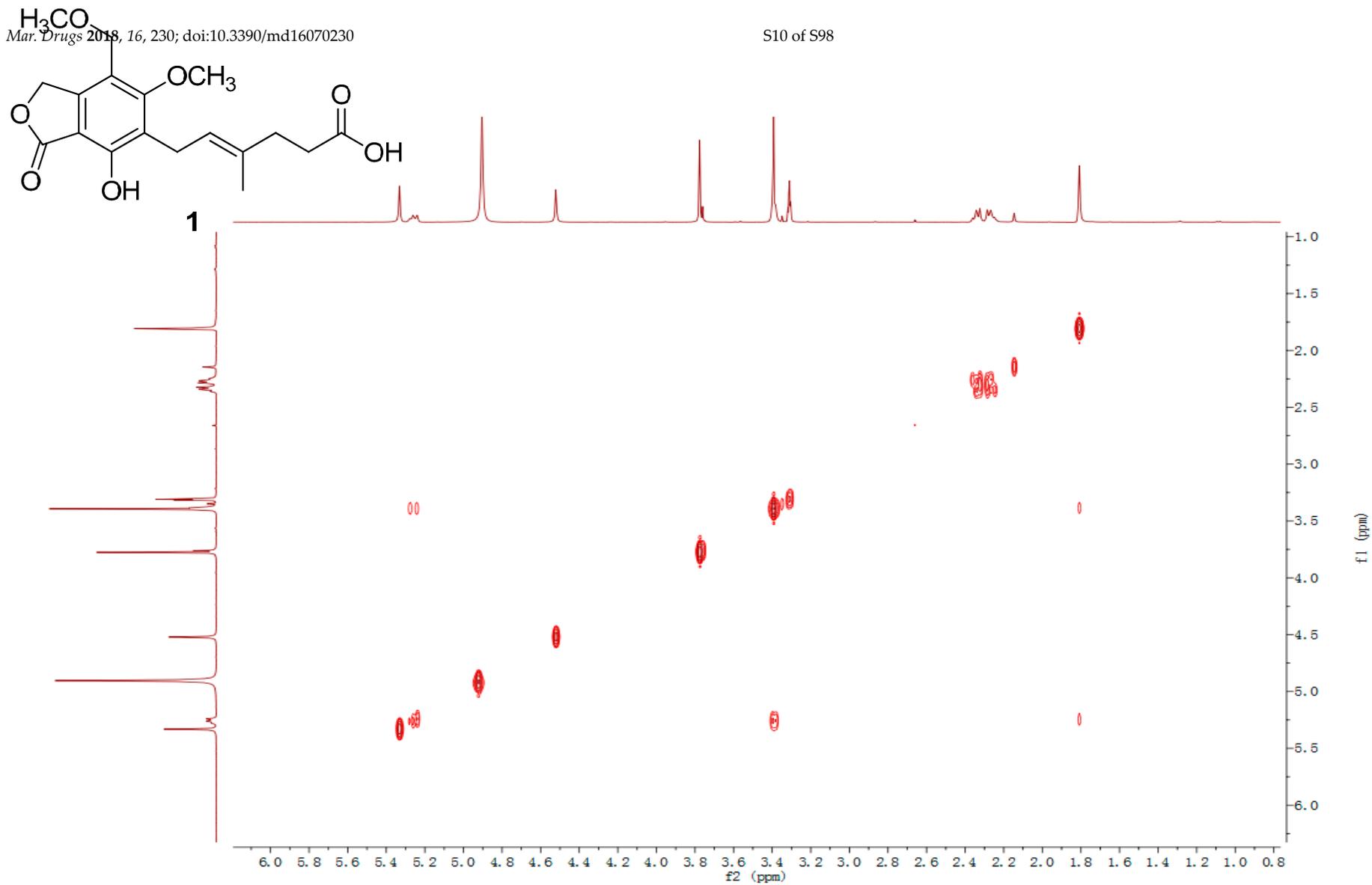


Figure S6. ^1H - ^1H COSY spectrum of compound **1** (Recorded in CD_3OD)

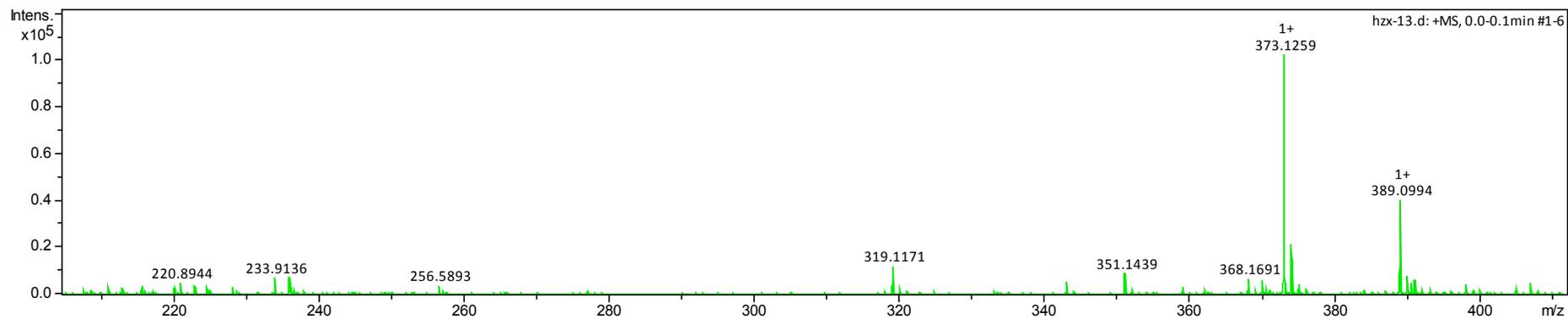
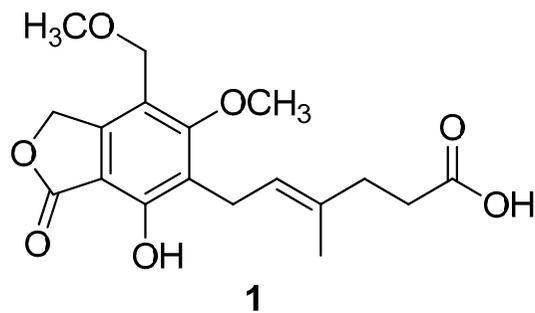


Figure S7. HRESIMS spectrum of compound 1



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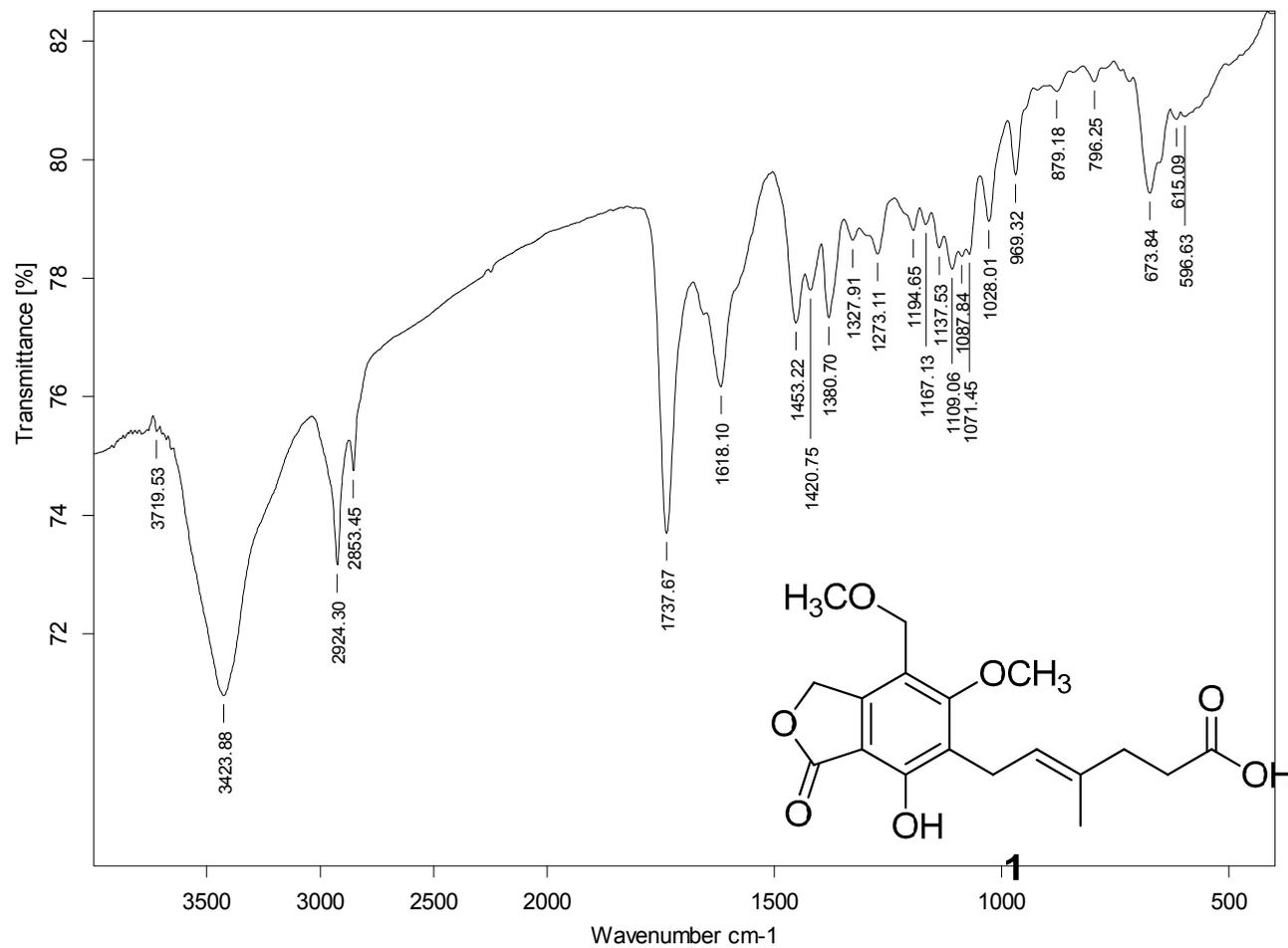


Figure S8. IR spectrum of compound 1

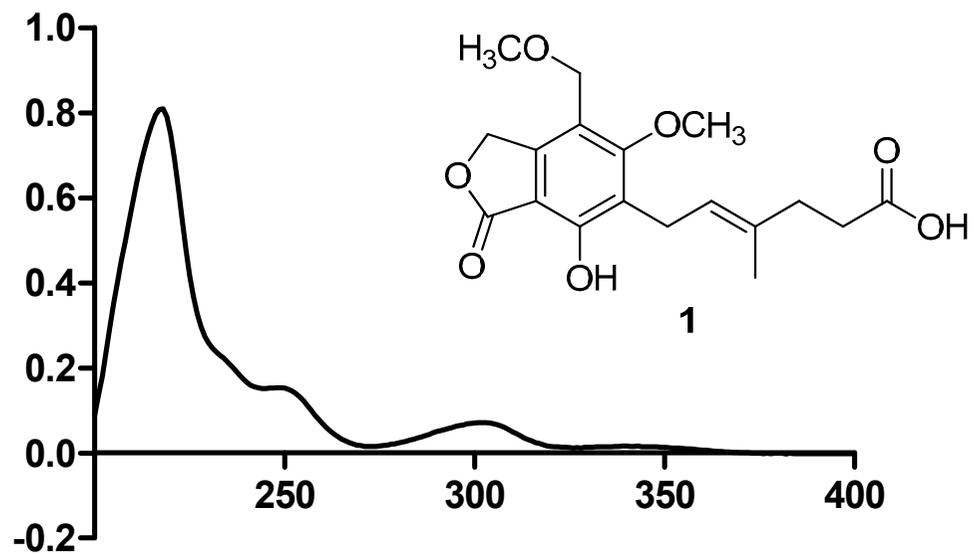


Figure S9. UV spectrum of compound 1

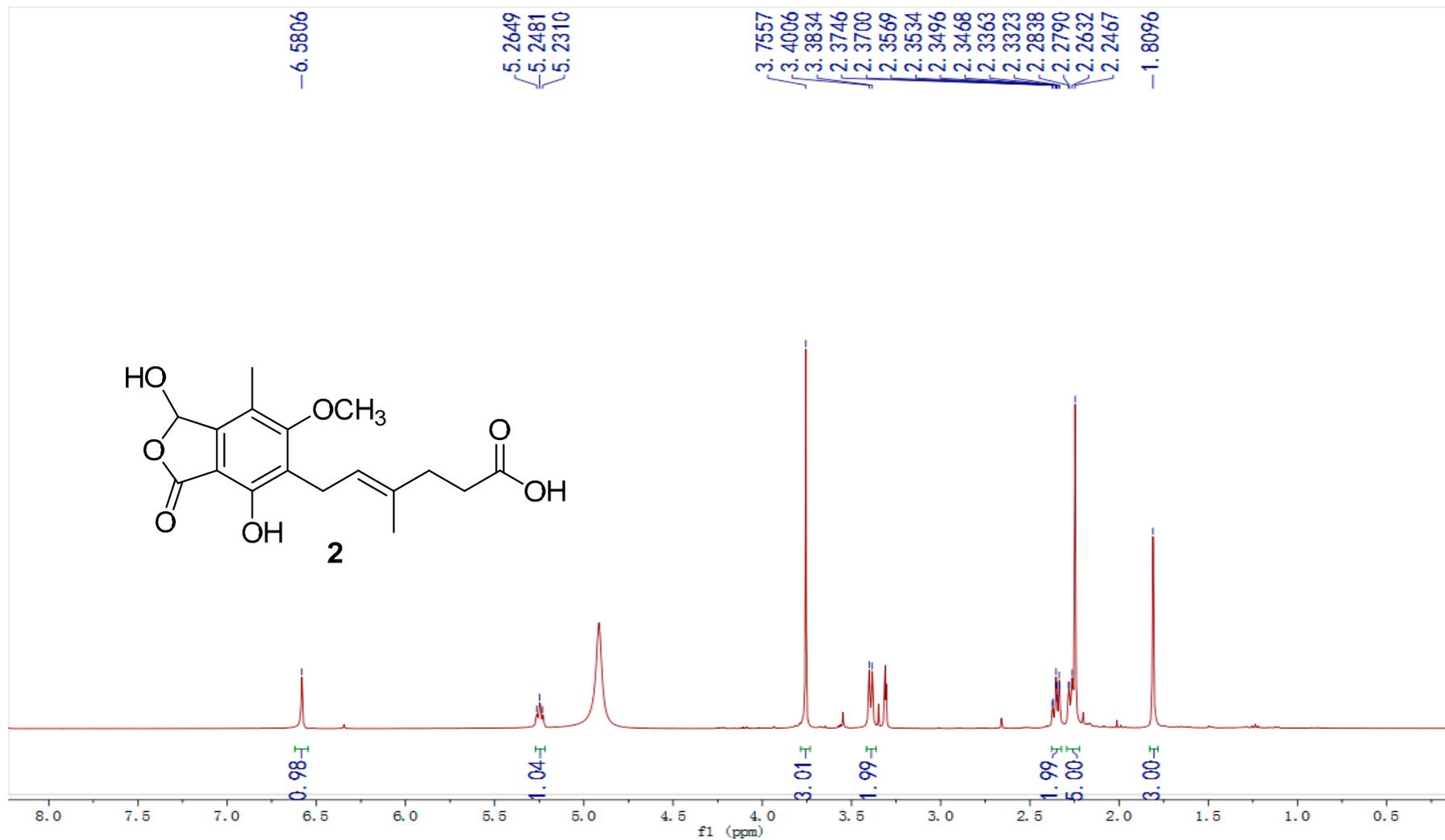


Figure S10. ¹H NMR spectrum of compound 2 (Recorded in CD₃OD)

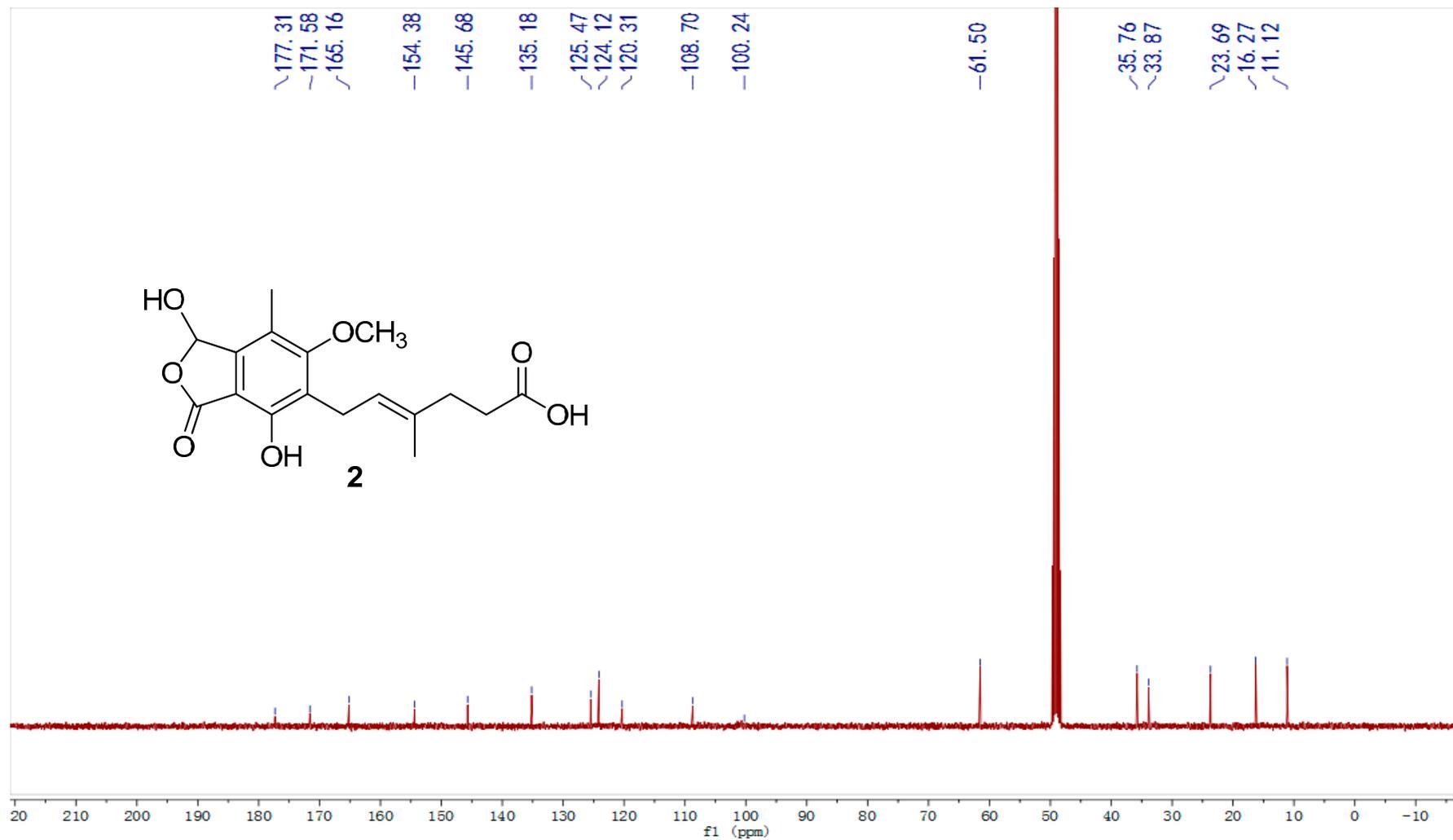


Figure S11. ¹³C NMR spectrum of compound 2 (Recorded in CD₃OD)

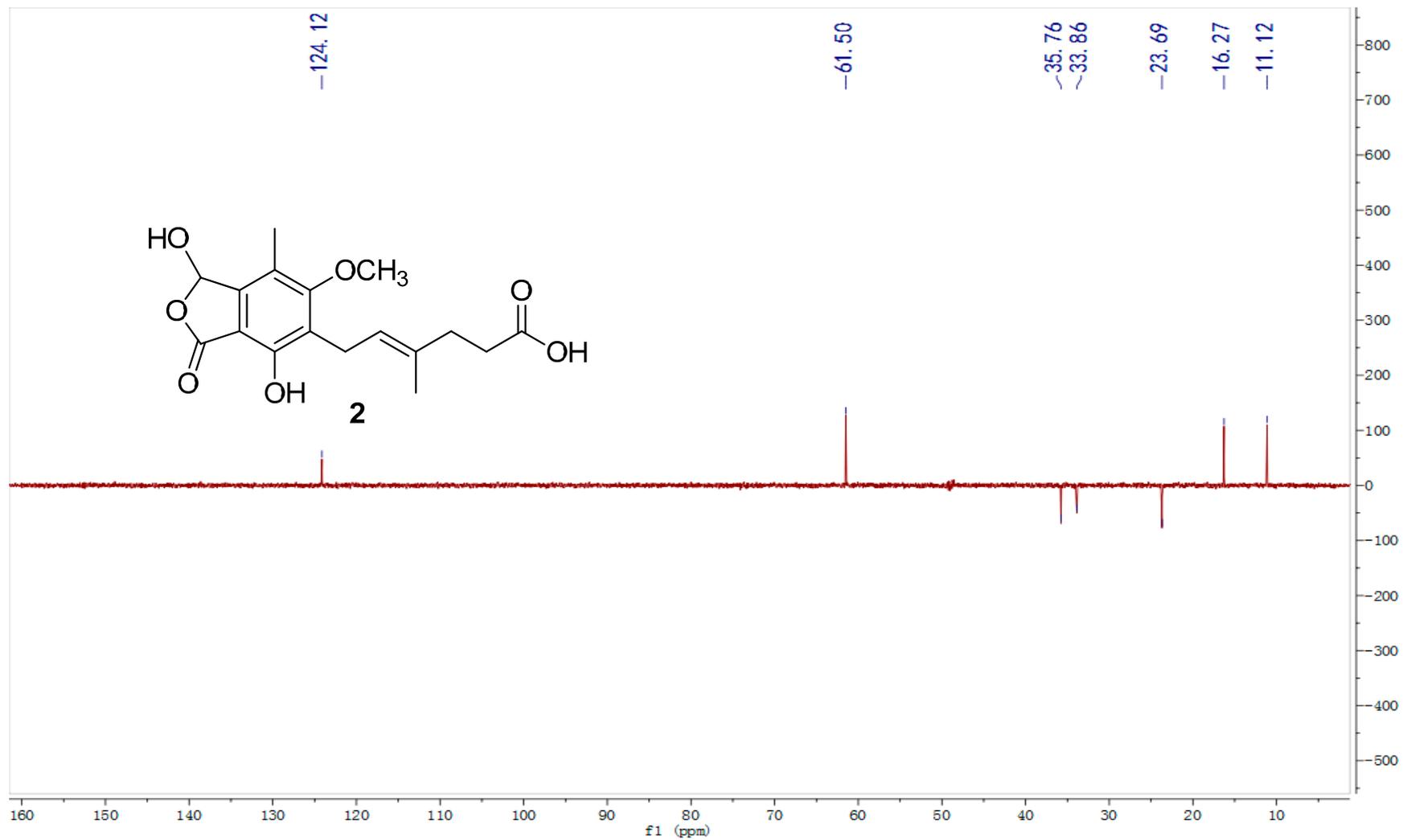
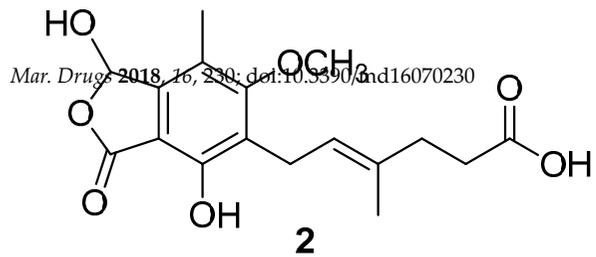


Figure S12. DEPT spectrum of compound 2 (Recorded in CD₃OD)



S17 of S98

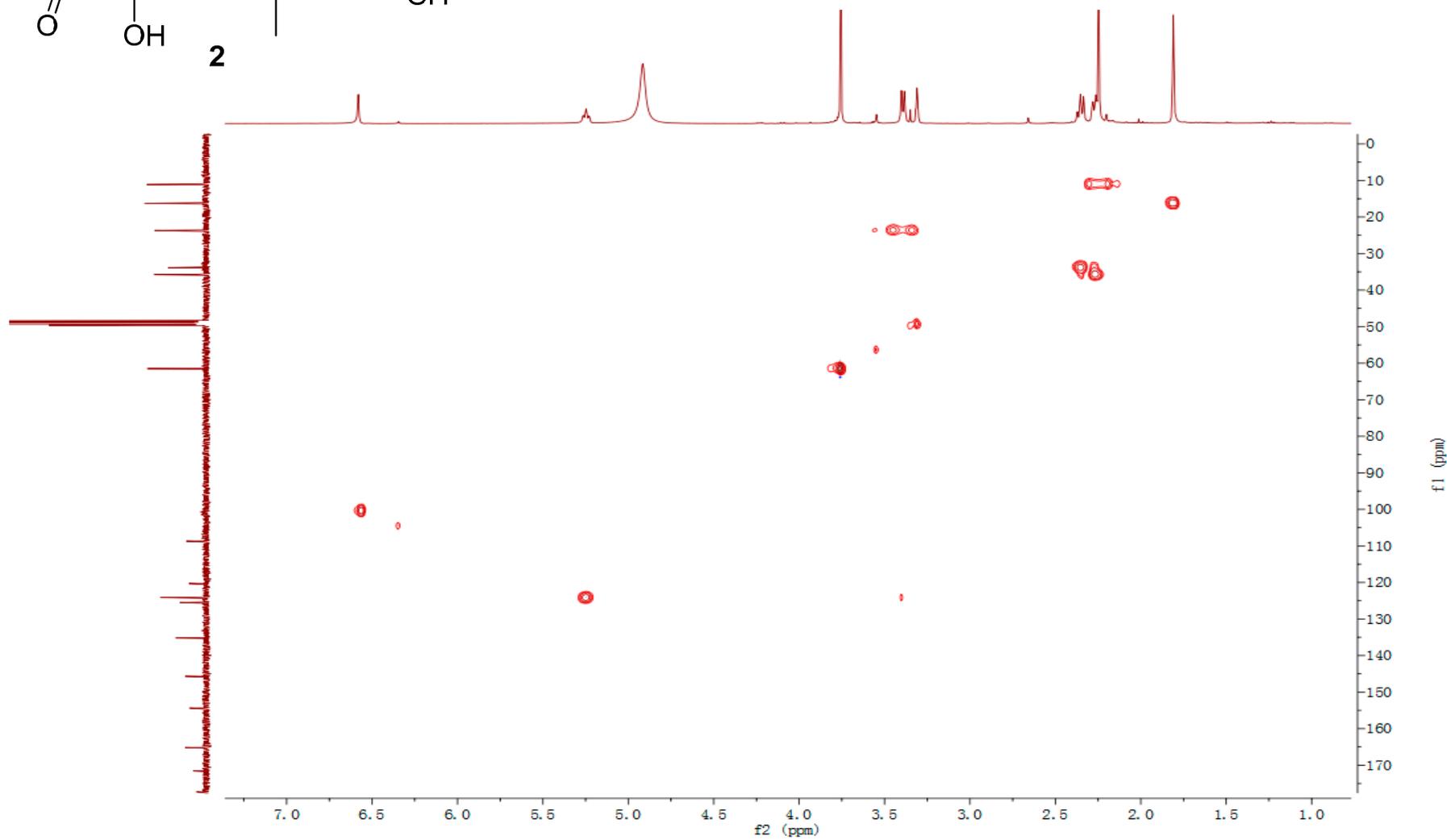
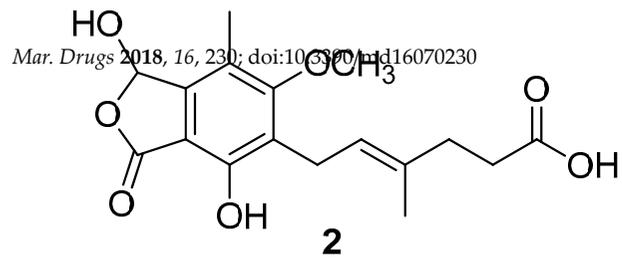


Figure S13. HSQC spectrum of compound 2 (Recorded in CD_3OD)



S18 of S98

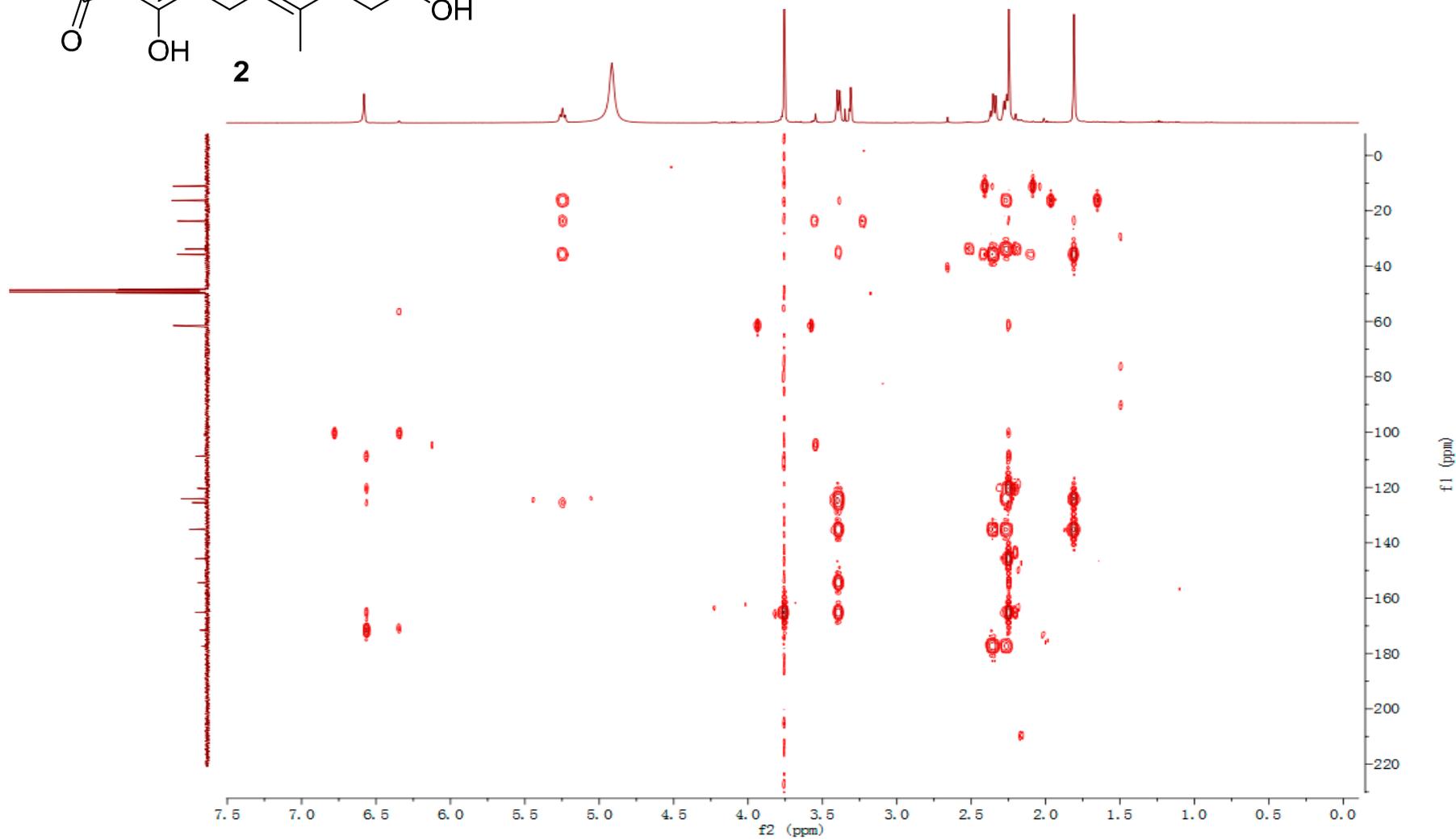
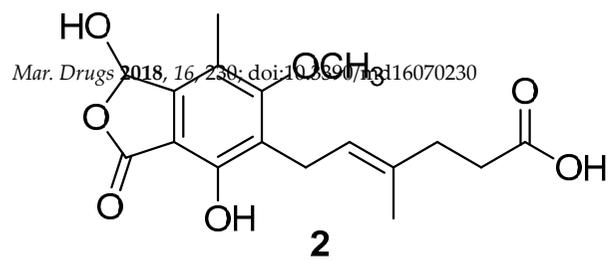


Figure S14. HMBC spectrum of compound 2 (Recorded in CD₃OD)



S19 of S98

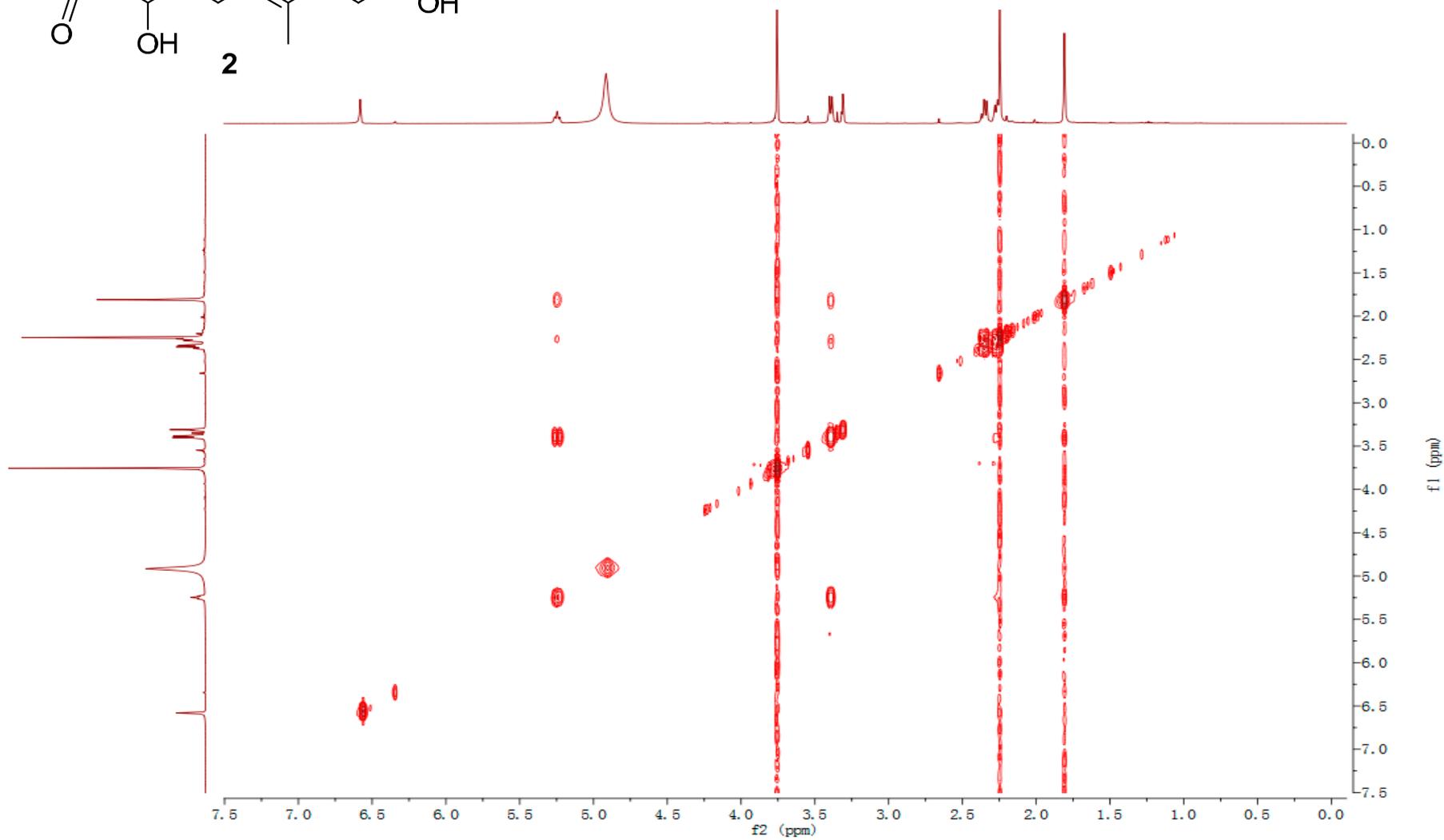


Figure S15. ^1H - ^1H COSY spectrum of compound 2 (Recorded in CD_3OD)

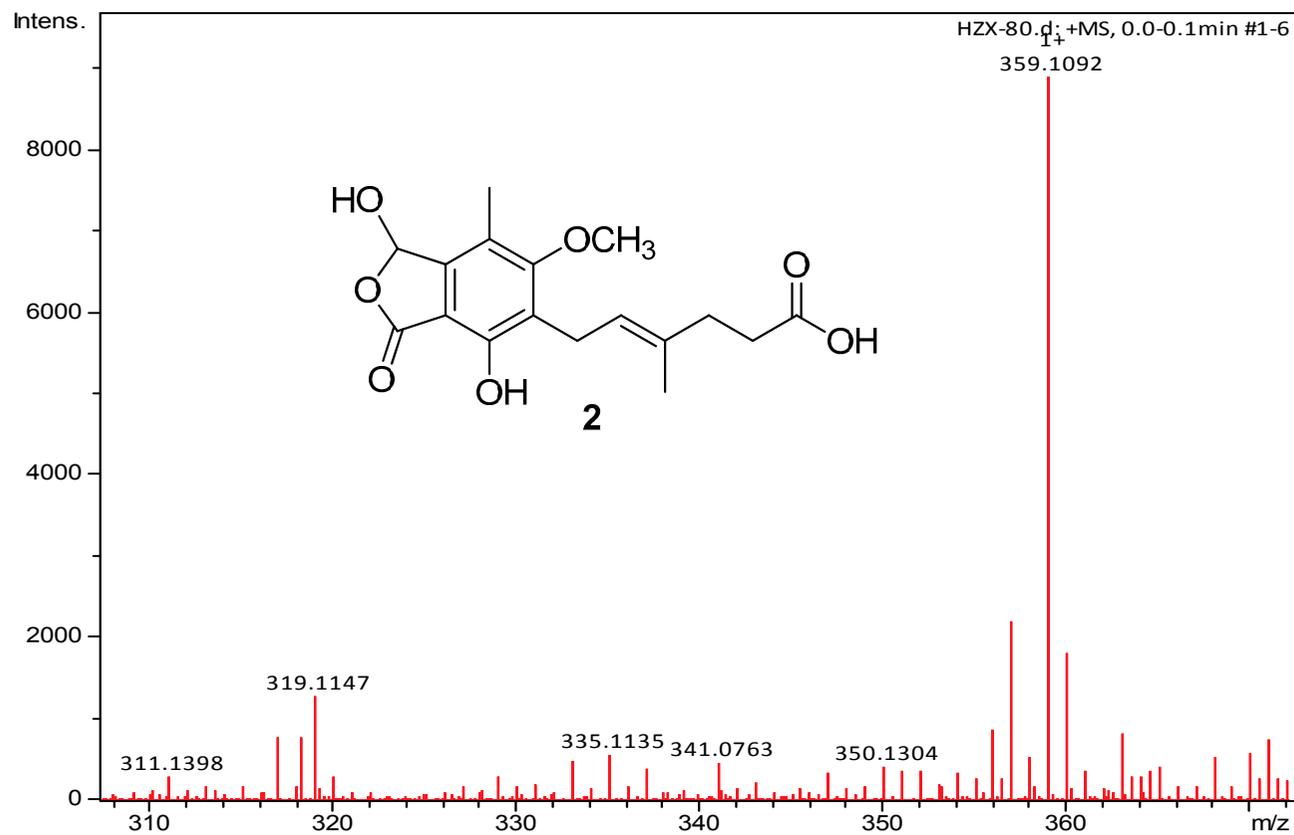


Figure S16. HRESIMS spectrum of compound 2

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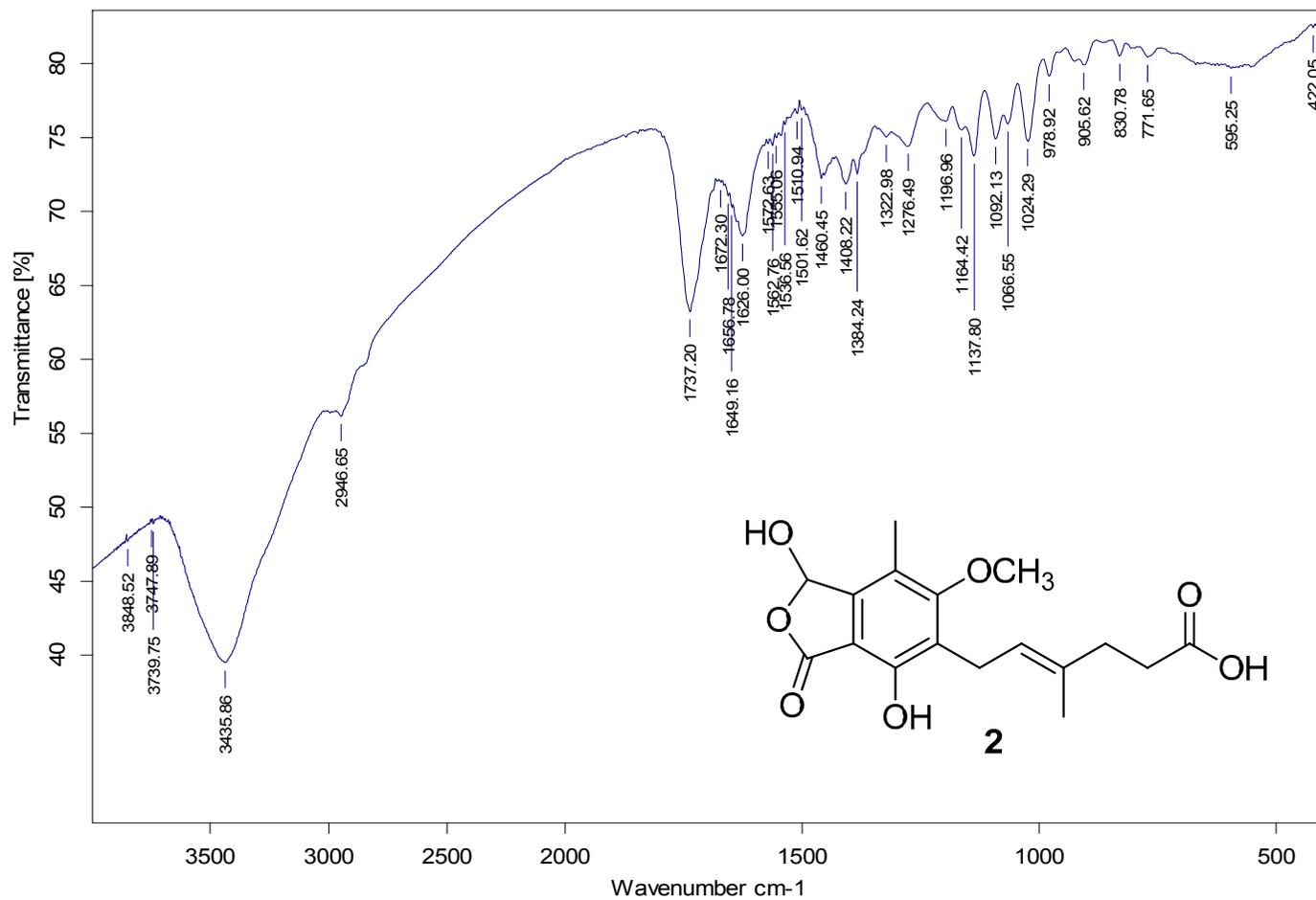


Figure S17. IR spectrum of compound 2

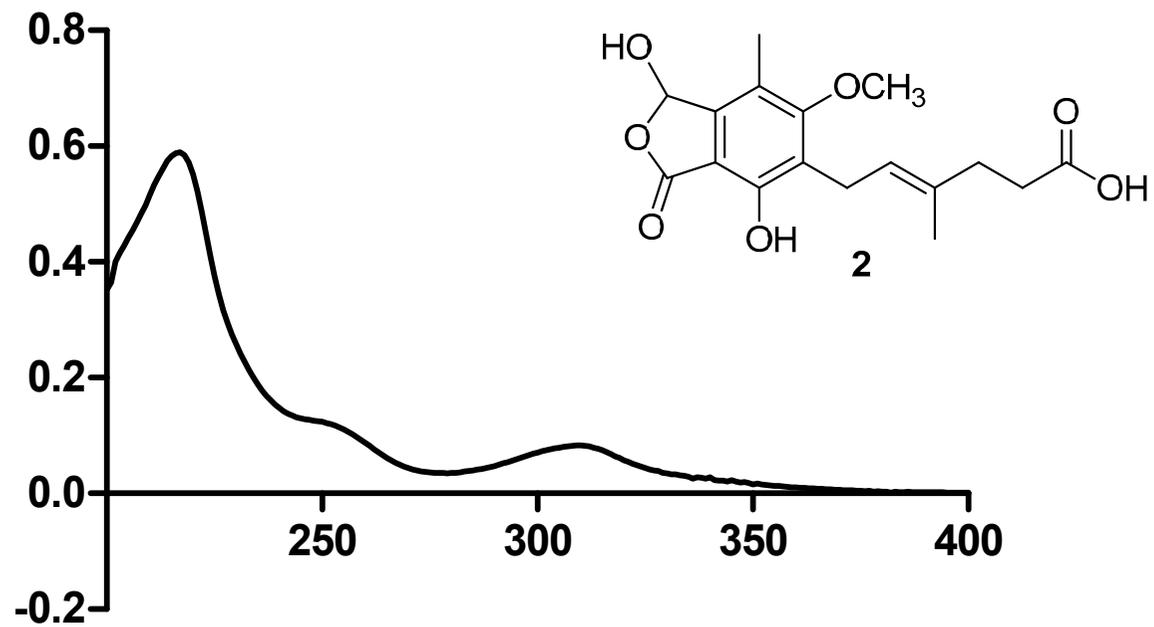


Figure S18. UV spectrum of compound 2

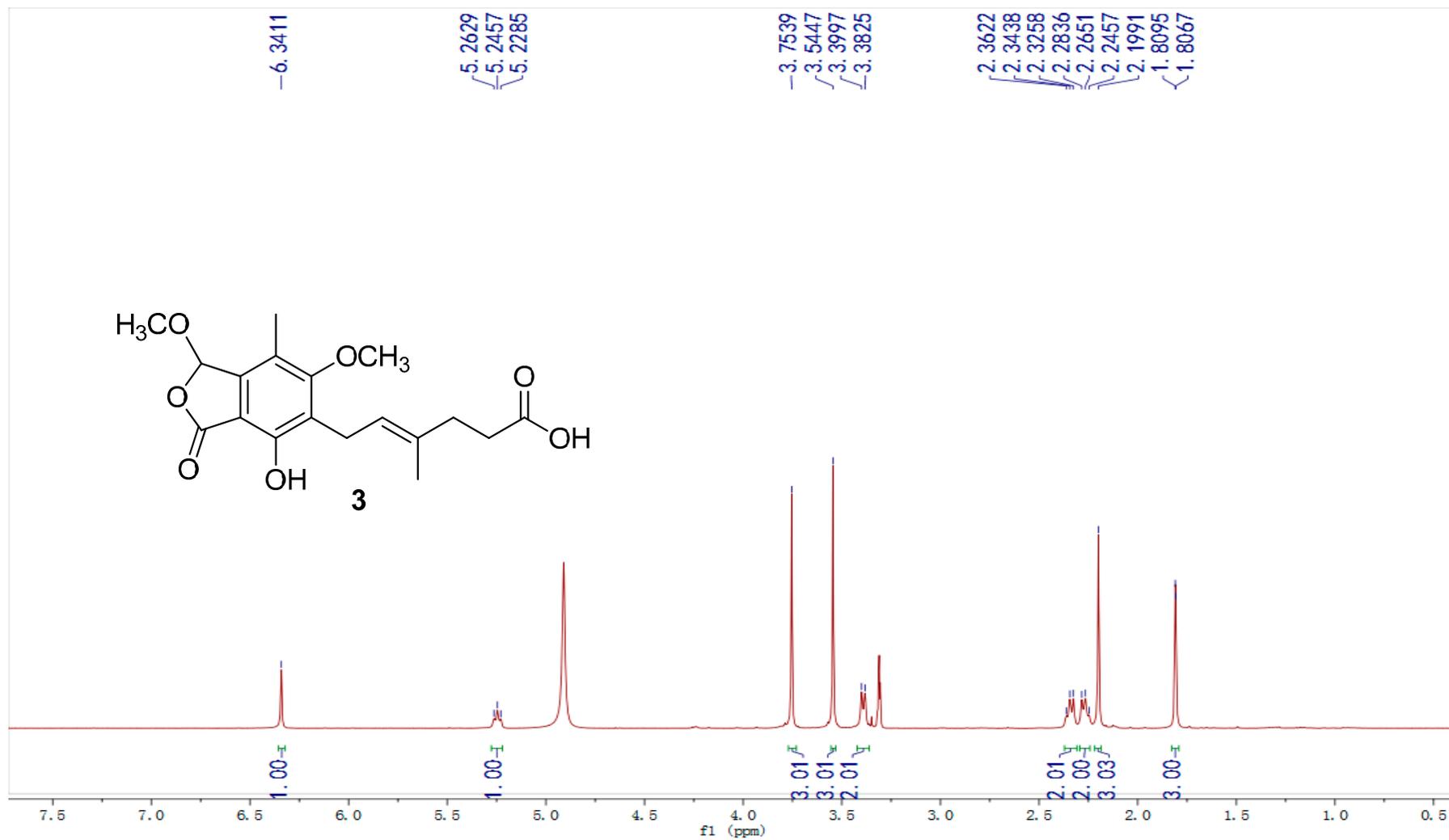


Figure S19. ¹H NMR spectrum of compound 3 (Recorded in CD₃OD)

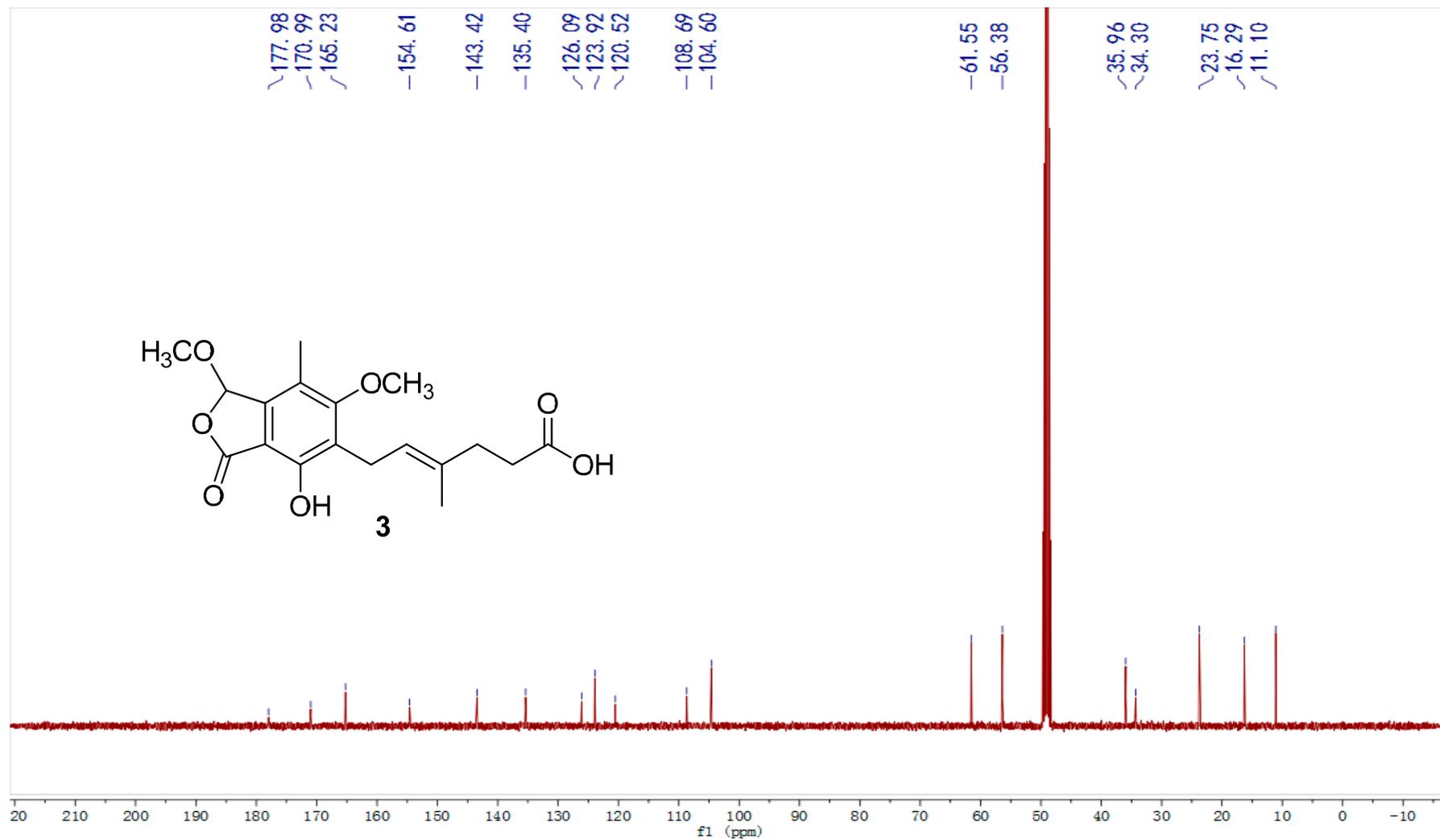


Figure S20. ¹³C NMR spectrum of compound 3 (Recorded in CD₃OD)

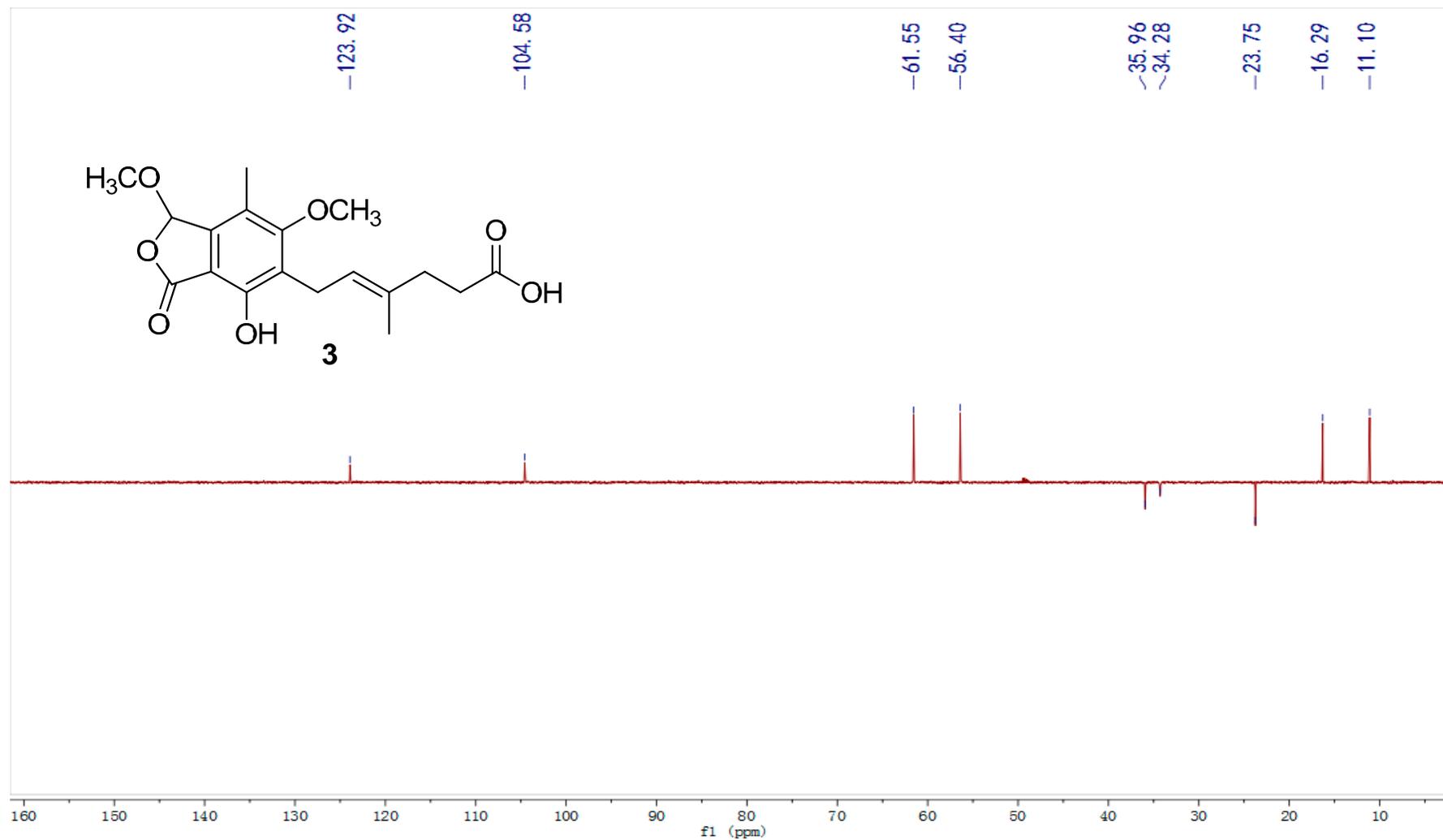
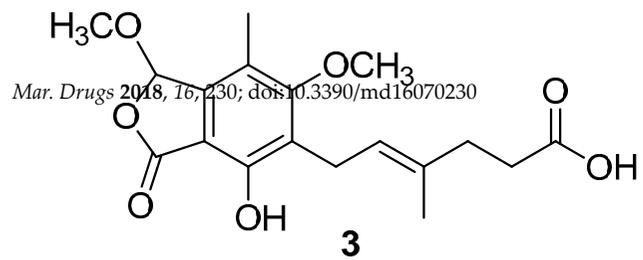


Figure S21. DEPT spectrum of compound 3 (Recorded in CD₃OD)



S26 of S98

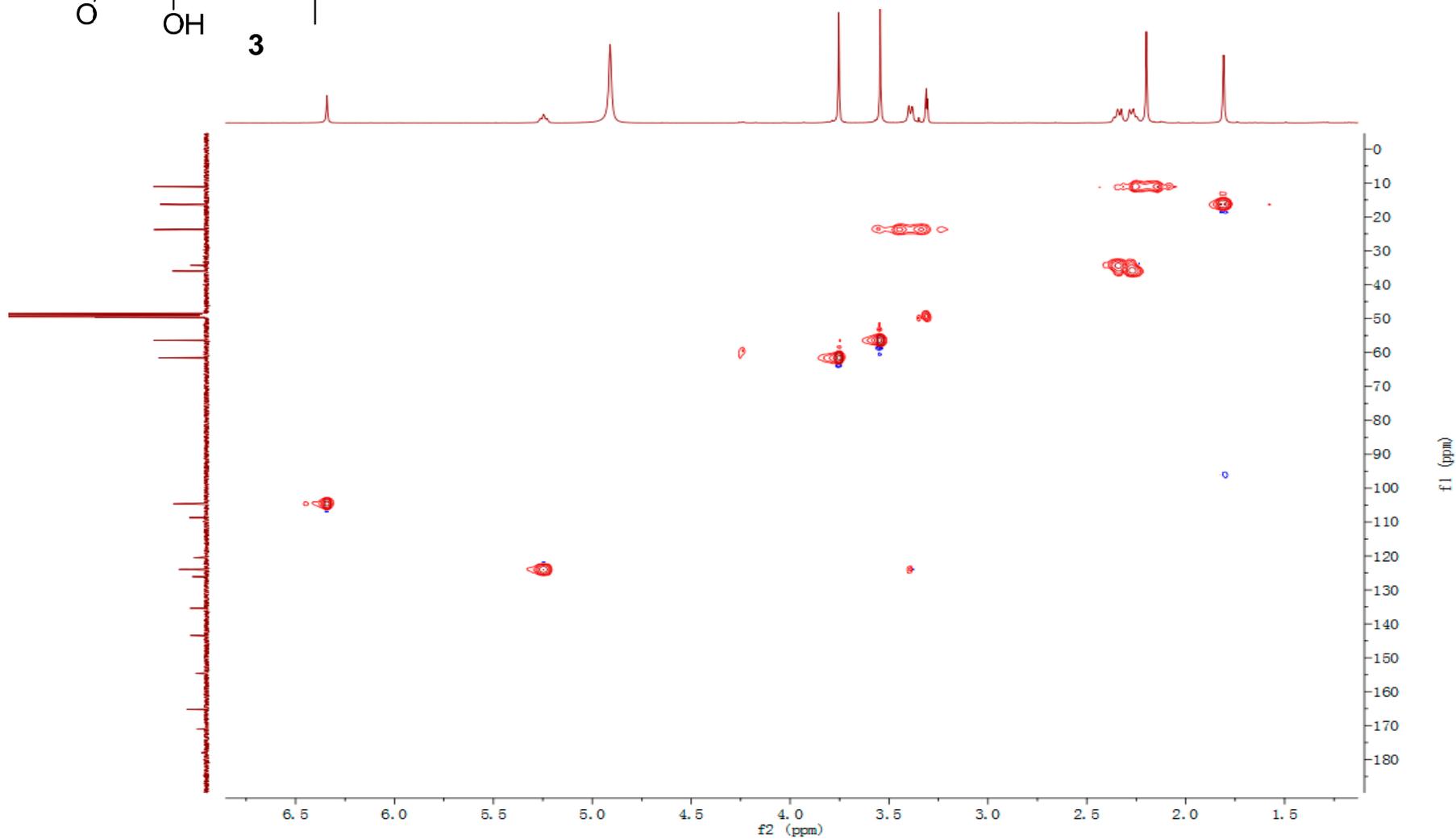
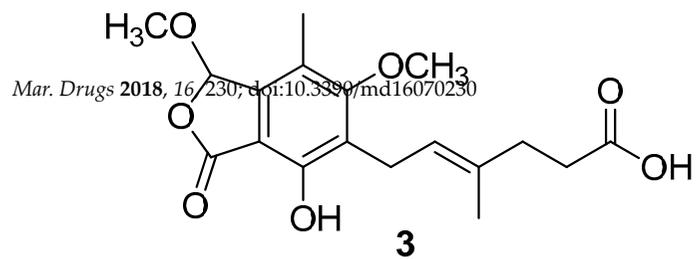


Figure S22. HSQC spectrum of compound 3 (Recorded in CD₃OD)



S27 of S98

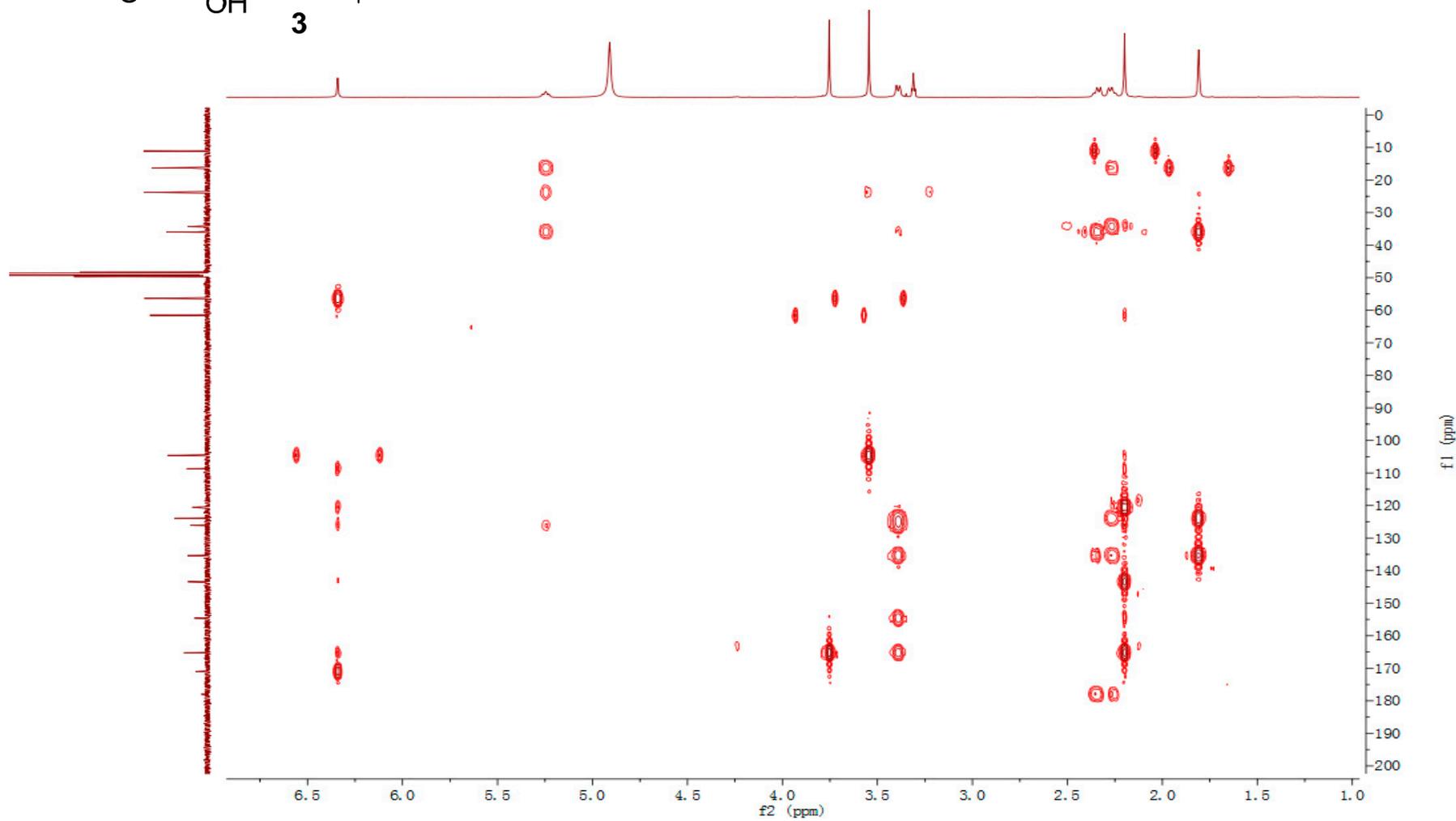


Figure S23. HMBC spectrum of compound **3** (Recorded in CD₃OD)

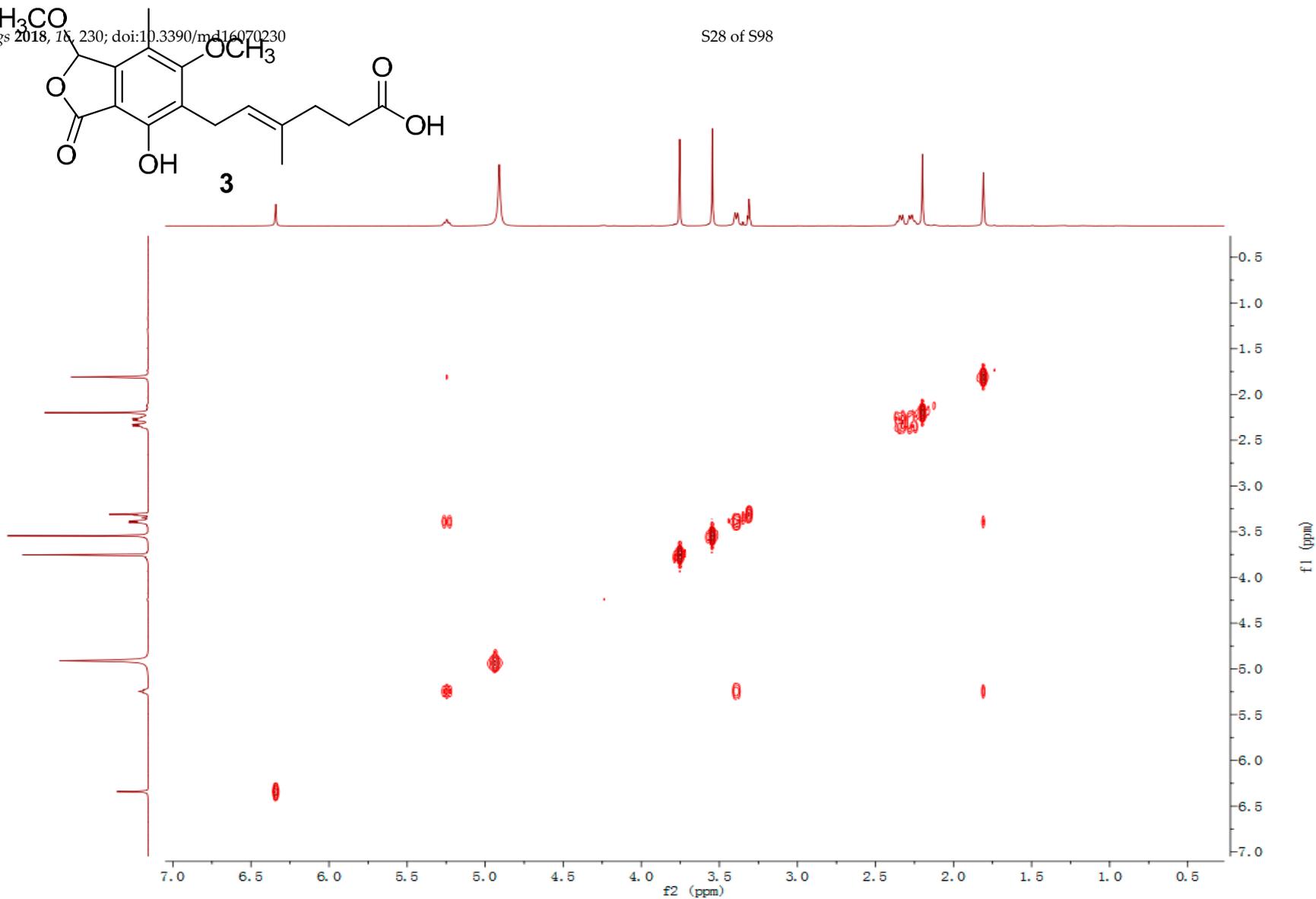


Figure S24. ¹H-¹H COSY spectrum of compound 3 (Recorded in CD₃OD)

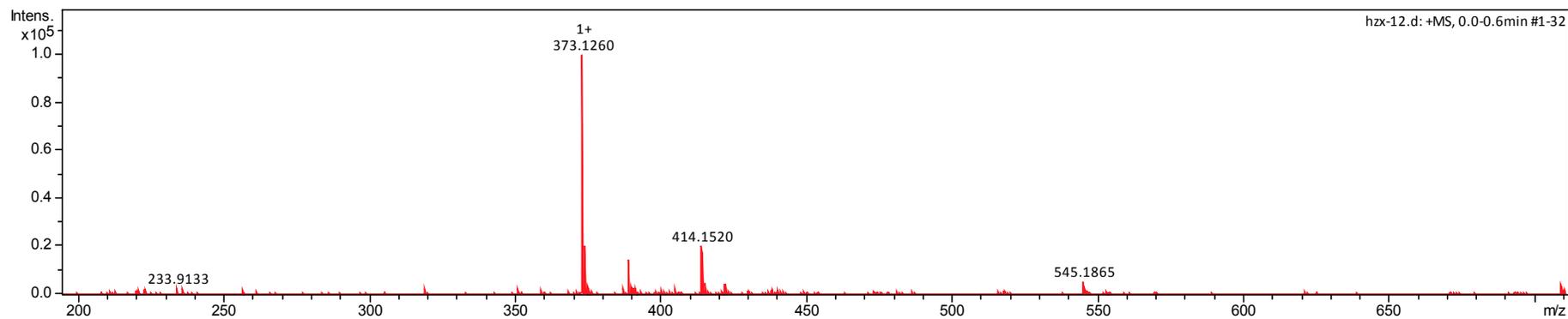
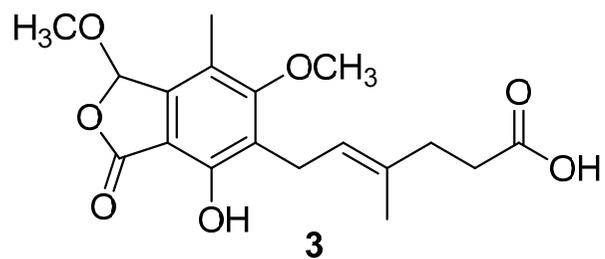


Figure S25. HRESIMS spectrum of compound 3



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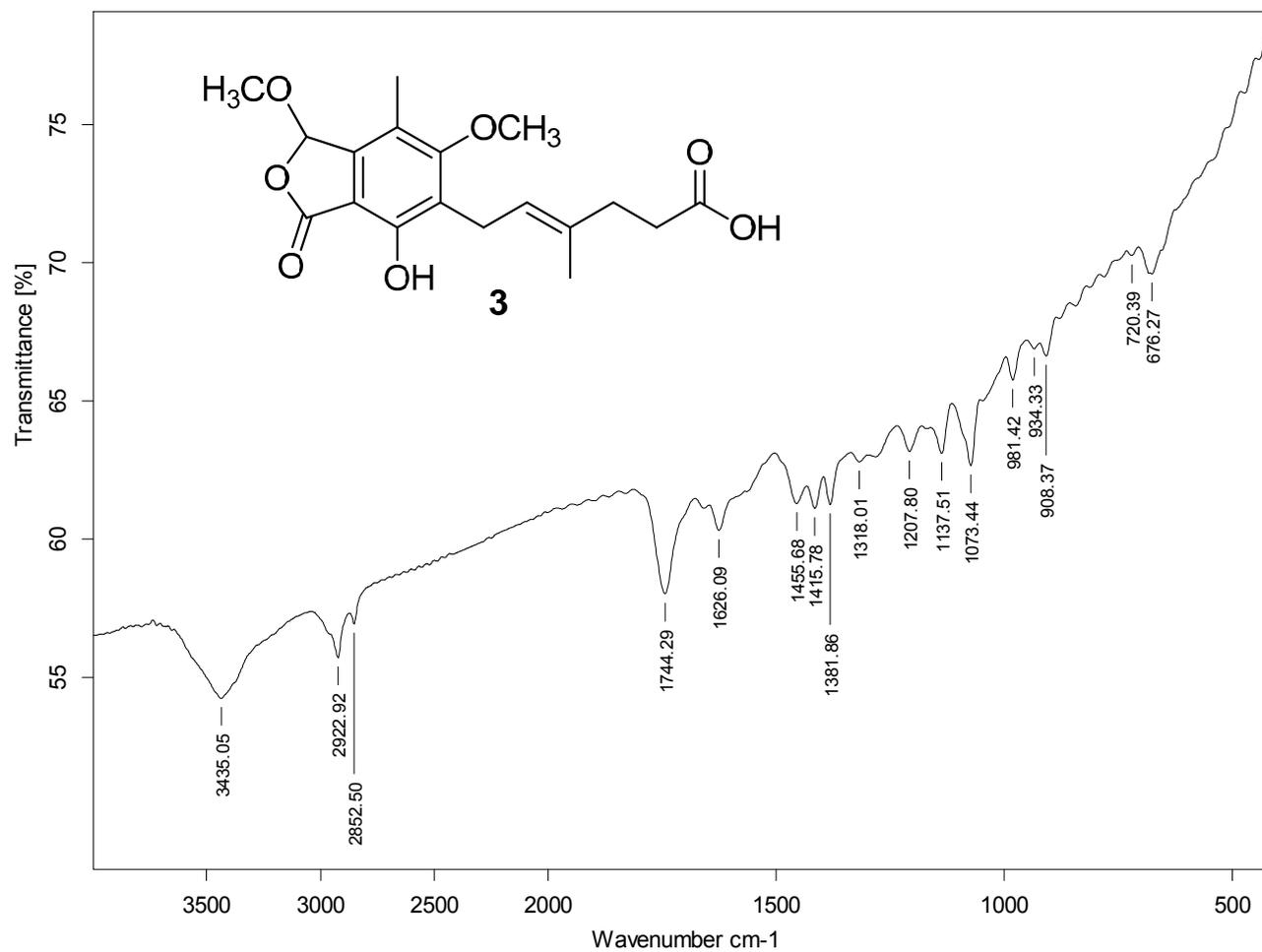


Figure S26. IR spectrum of compound 3

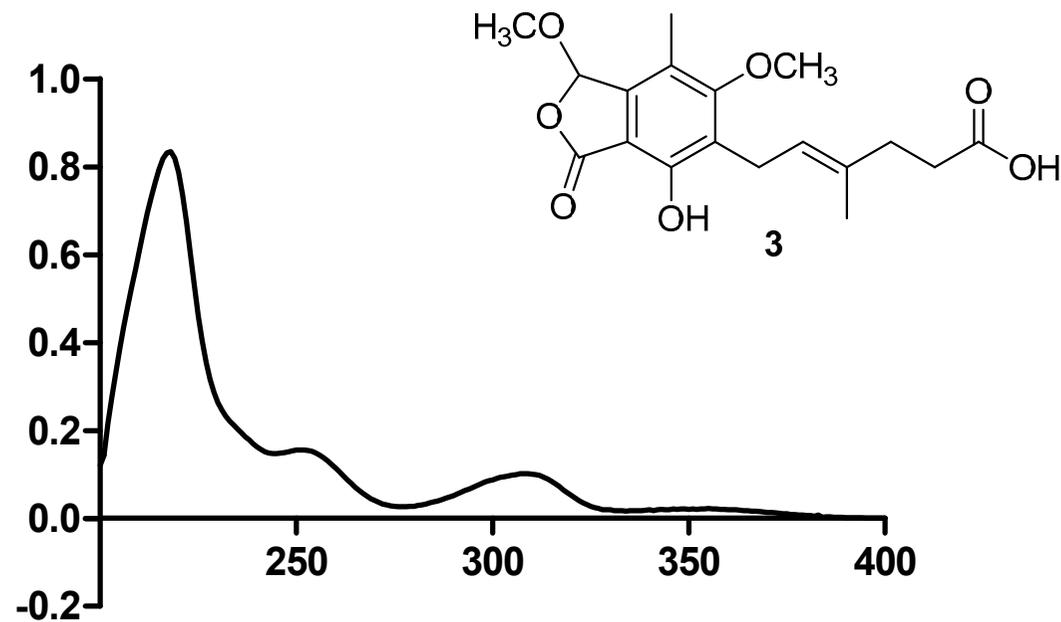


Figure S27. UV spectrum of compound 3

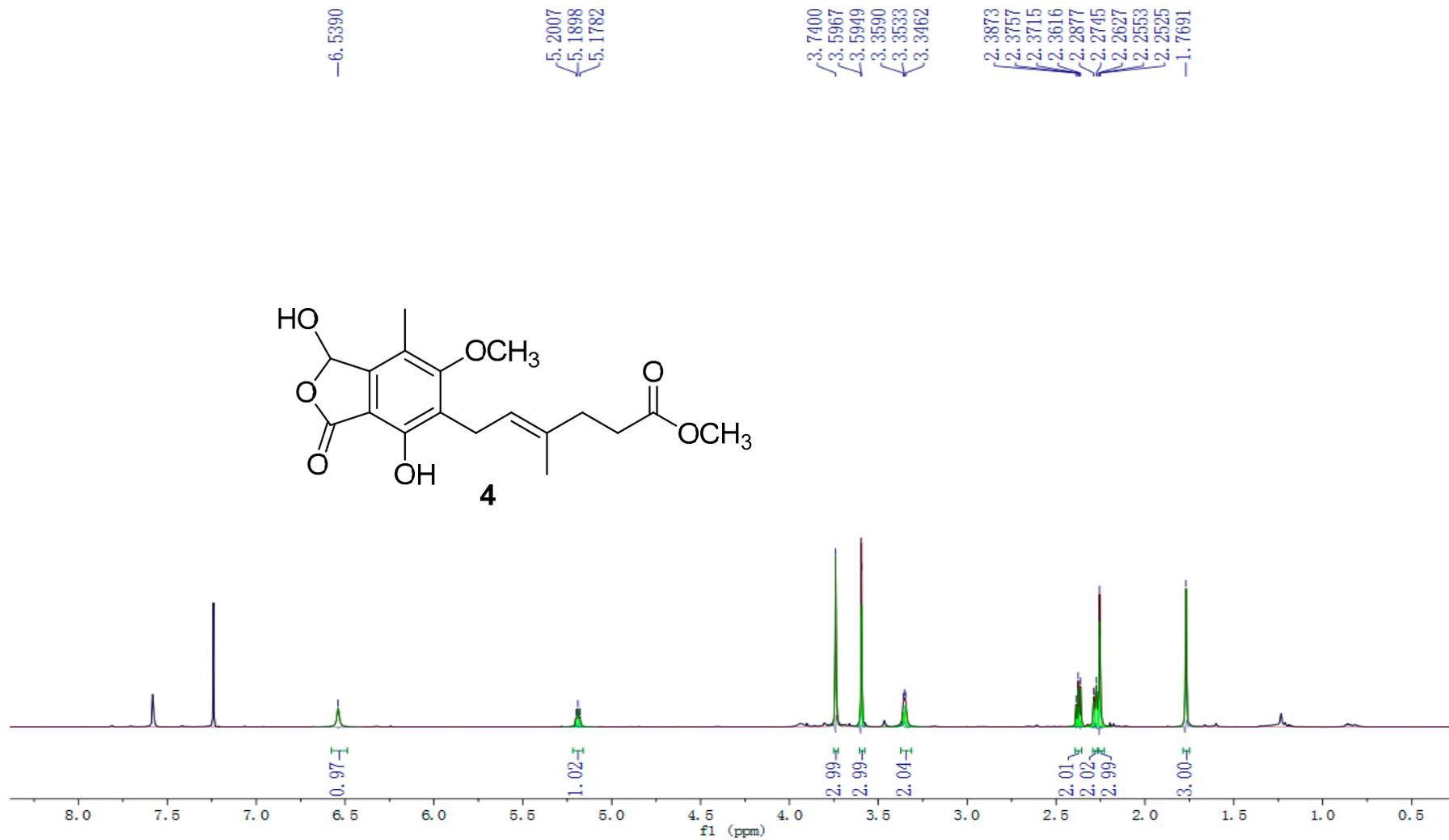


Figure S28. ¹H NMR spectrum of compound 4 (Recorded in CD₃OD)

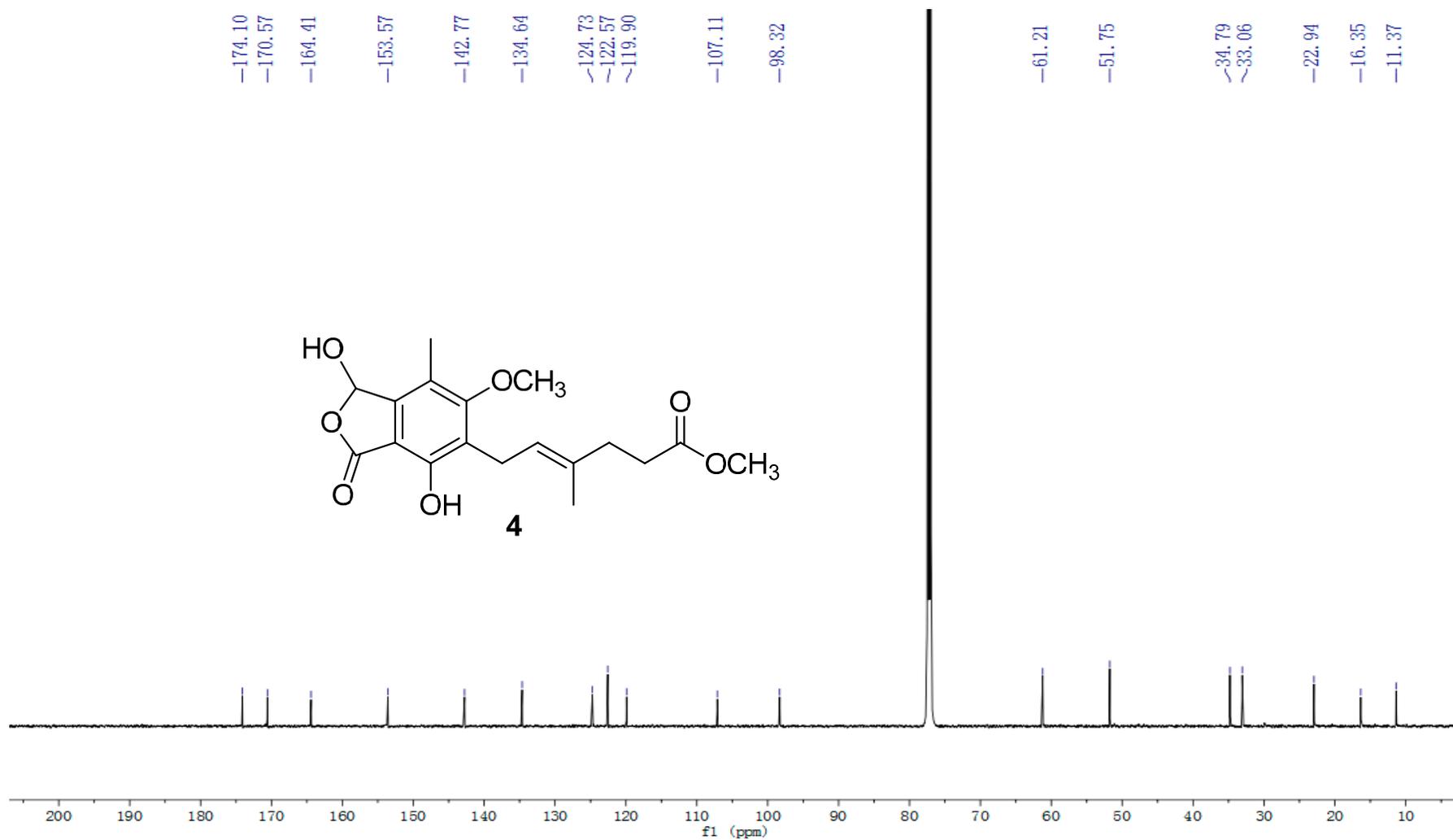


Figure S29. ¹³C NMR spectrum of compound 4 (Recorded in CD₃OD)

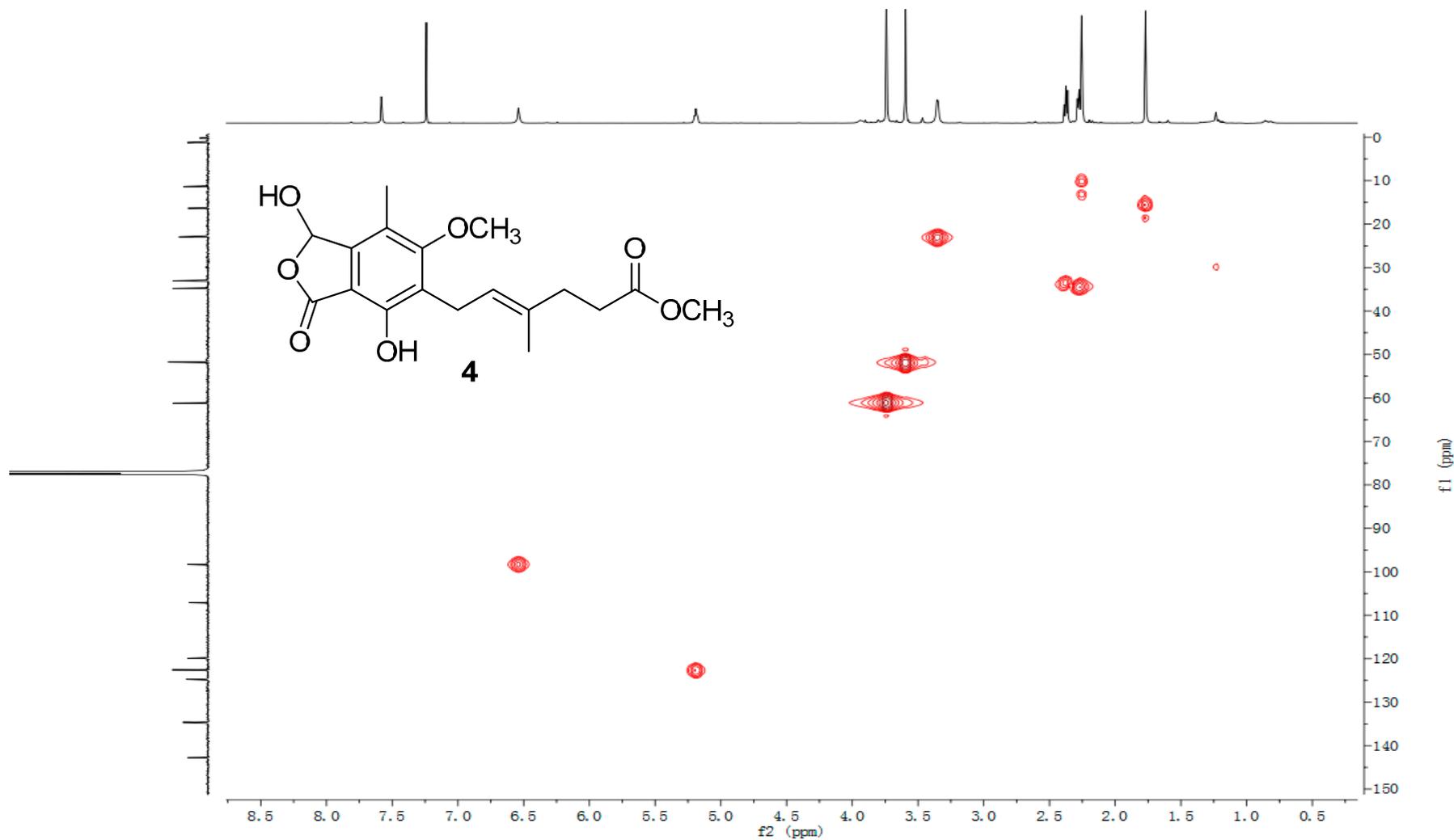


Figure S30. HSQC spectrum of compound 4 (Recorded in CD₃OD)

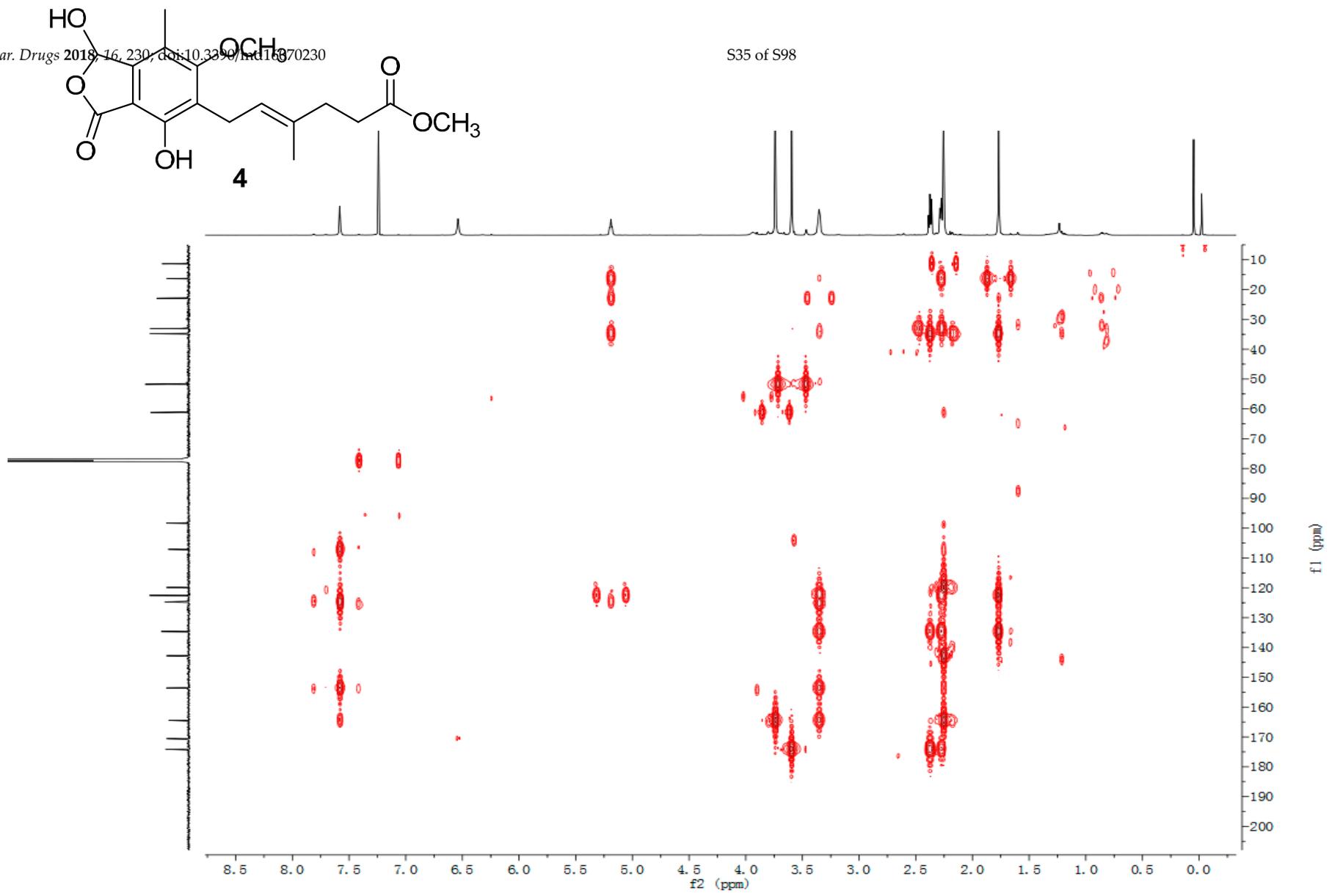
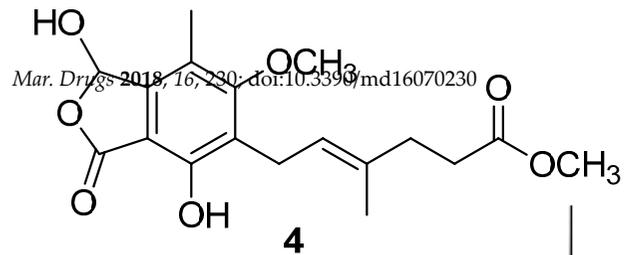


Figure S31. HMBC spectrum of compound 4 (Recorded in CD₃OD)



S36 of S98

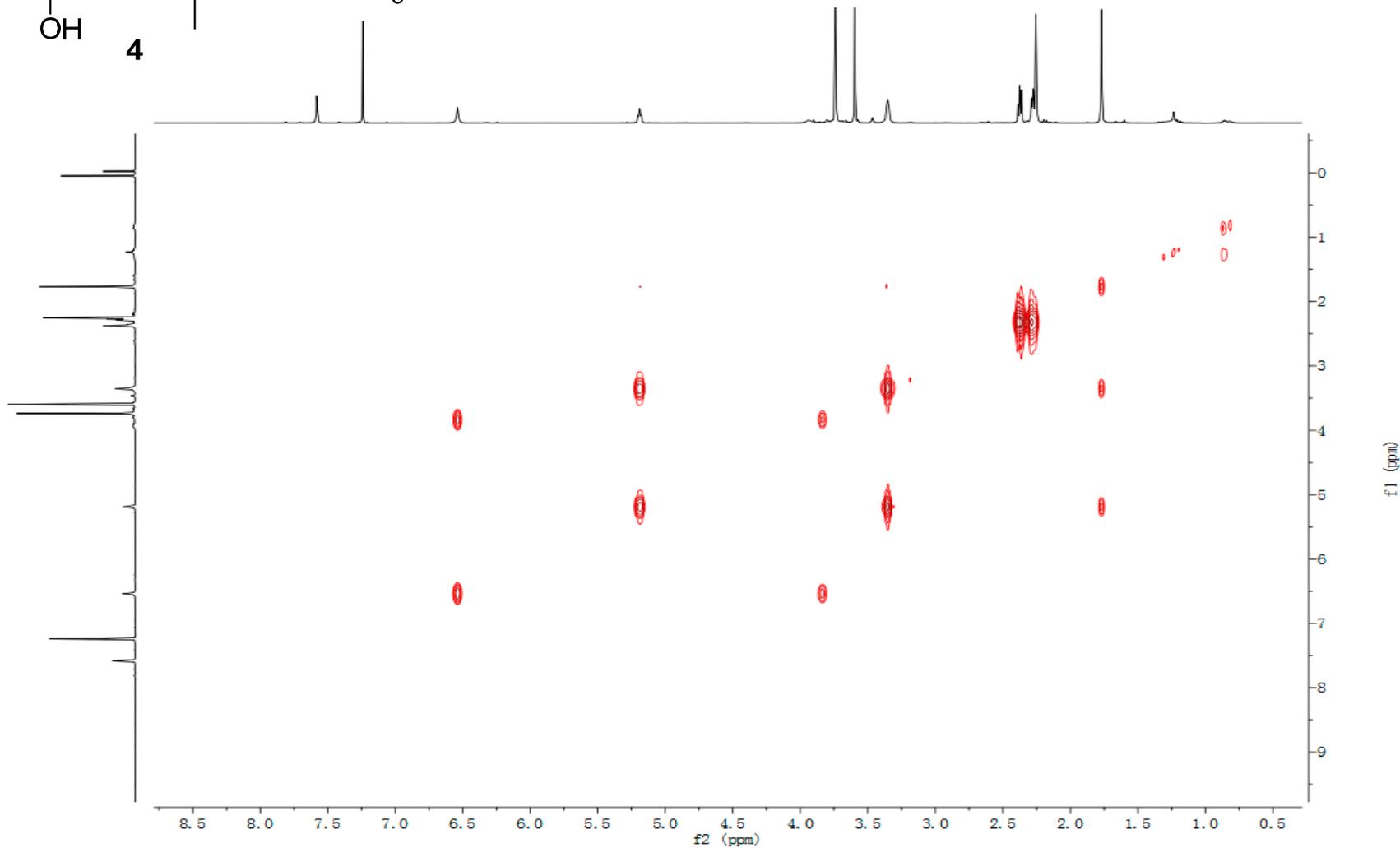


Figure S32. ^1H - ^1H COSY spectrum of compound **4** (Recorded in CD_3OD)

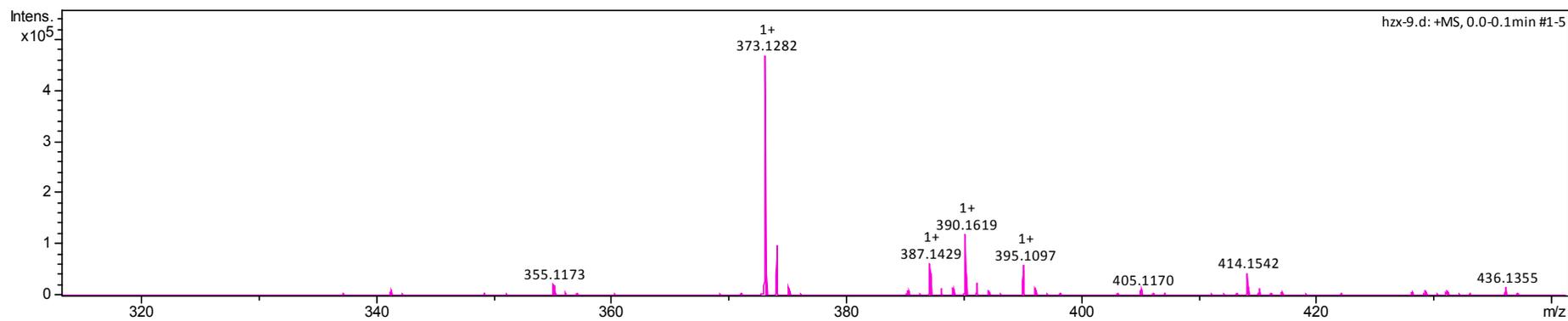
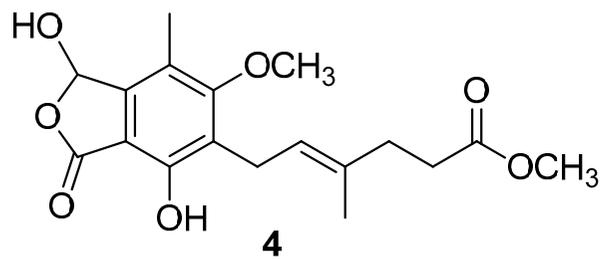


Figure S33. HRESIMS spectrum of compound 4



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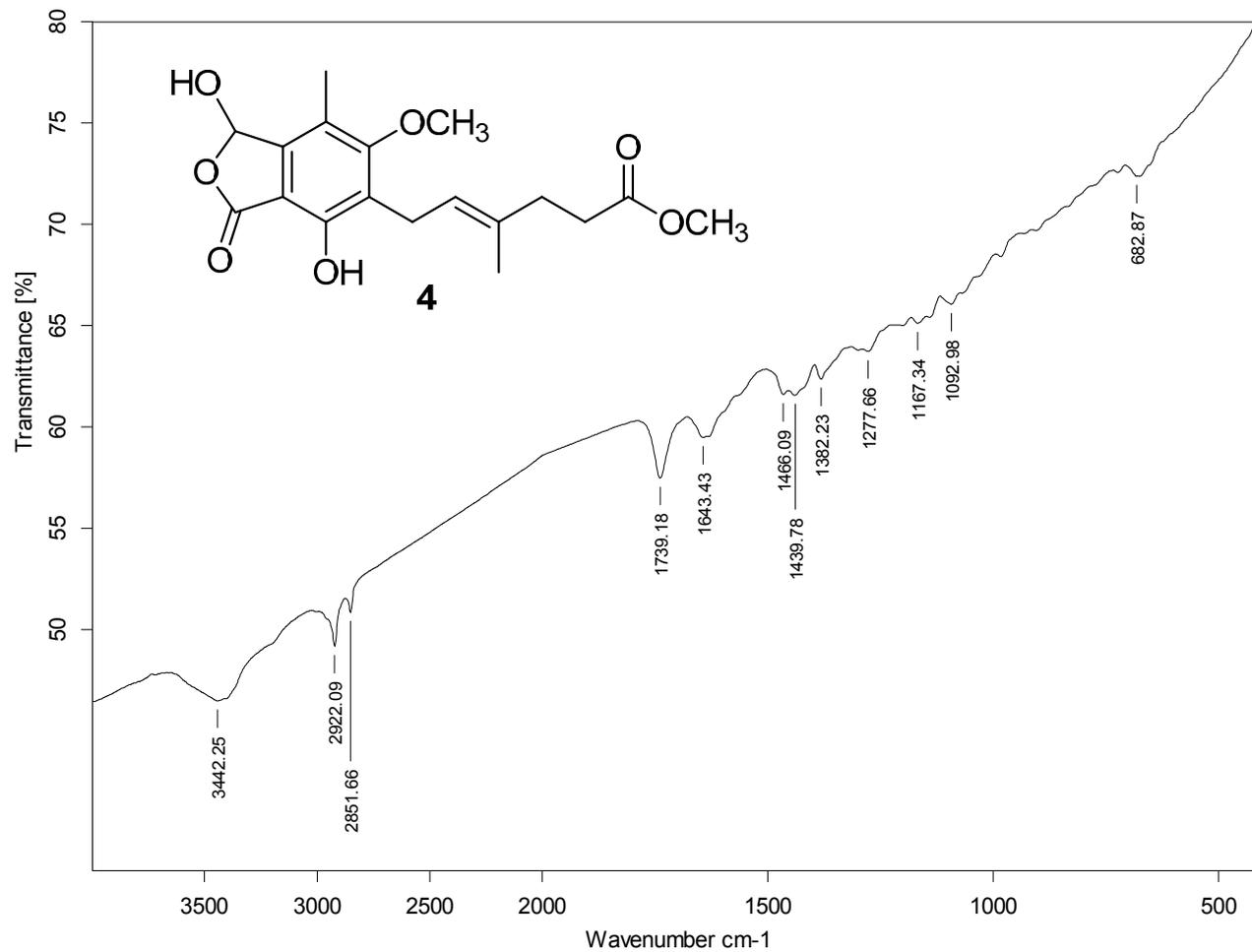


Figure S34. IR spectrum of compound 4

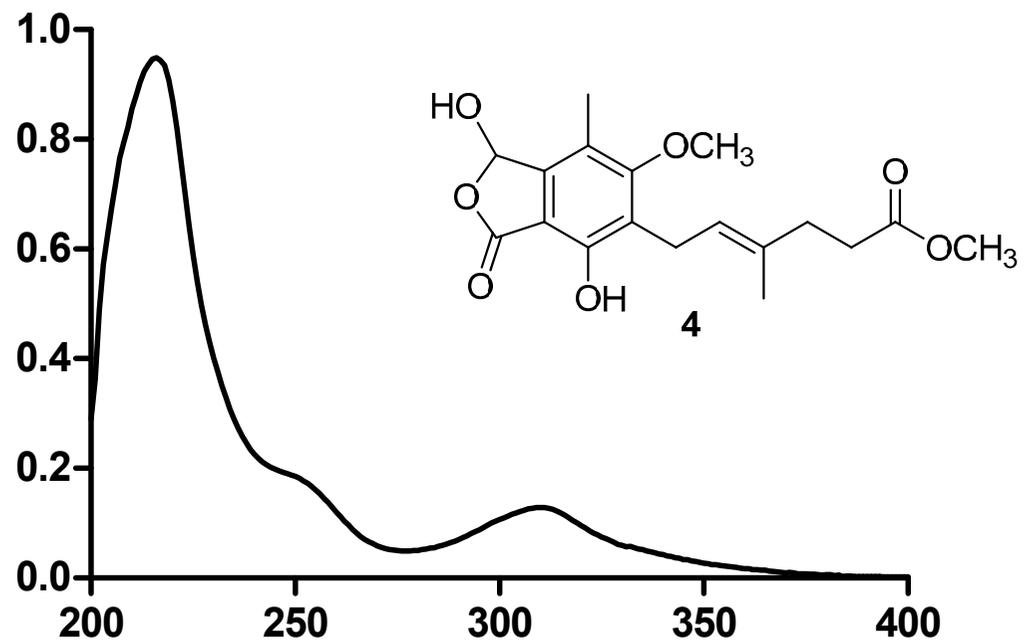


Figure S35. UV spectrum of compound 4

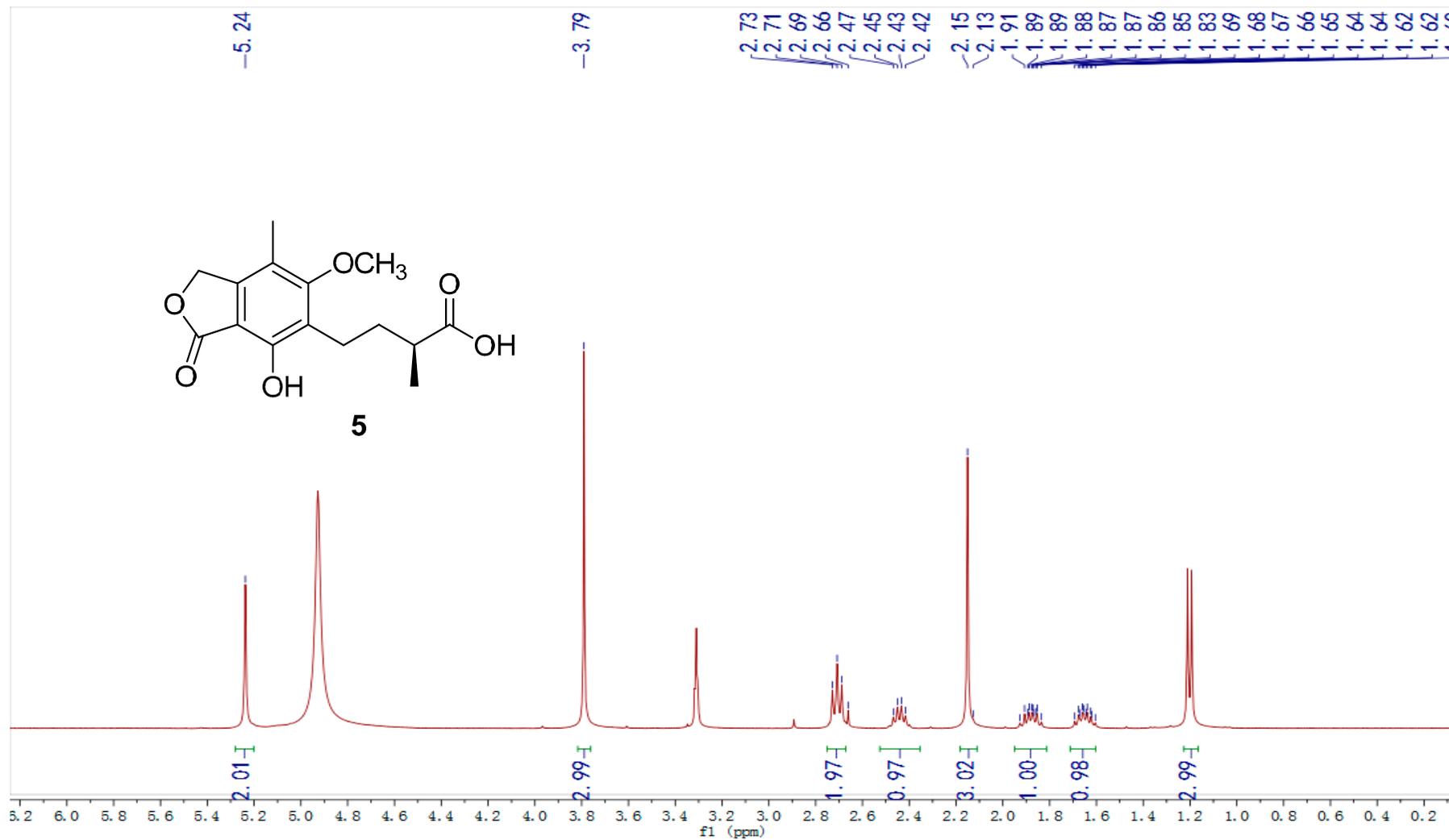


Figure S36. ¹H NMR spectrum of compound 5 (Recorded in CD₃OD)

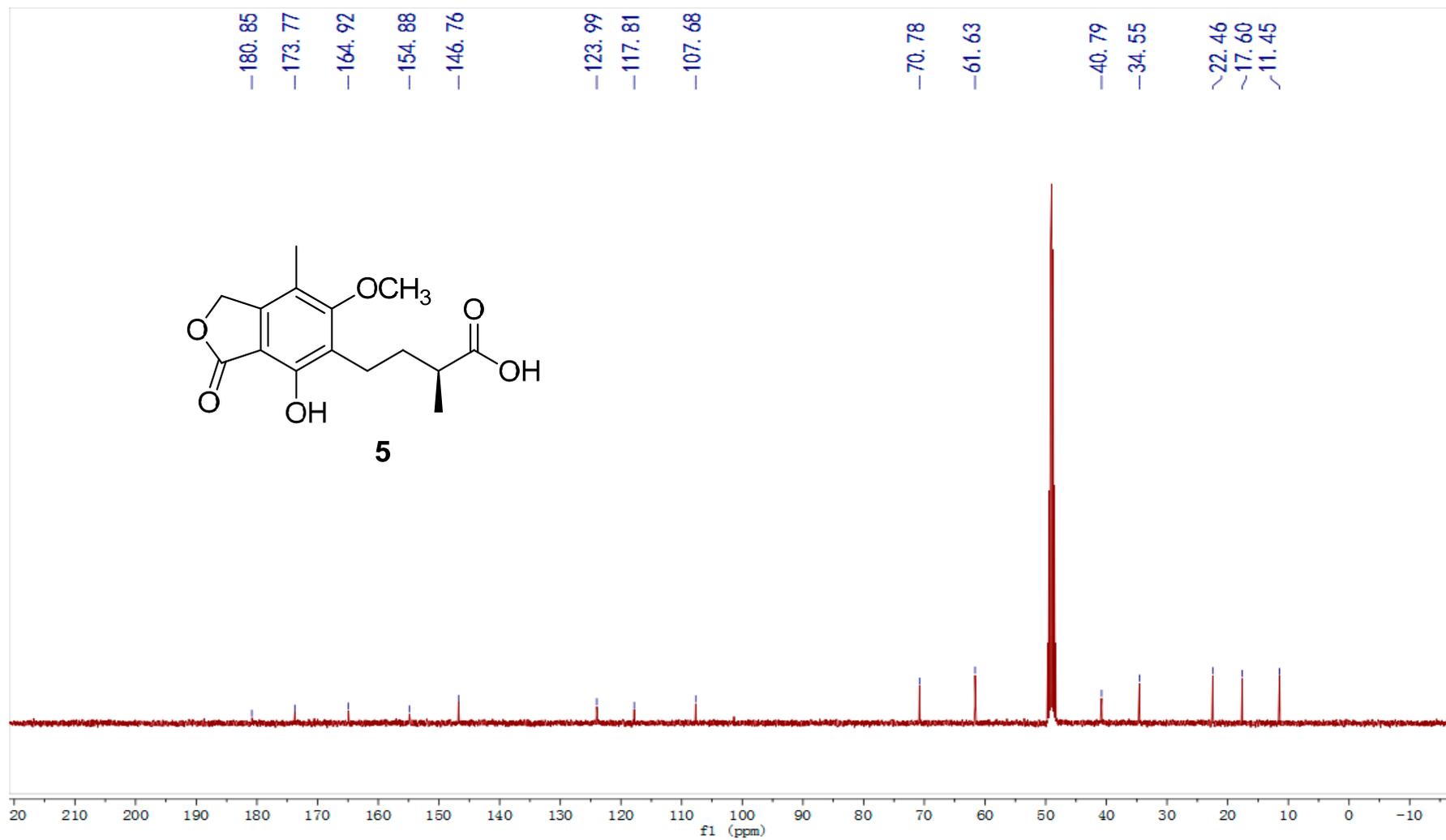


Figure S37. ^{13}C NMR spectrum of compound 5 (Recorded in CD_3OD)

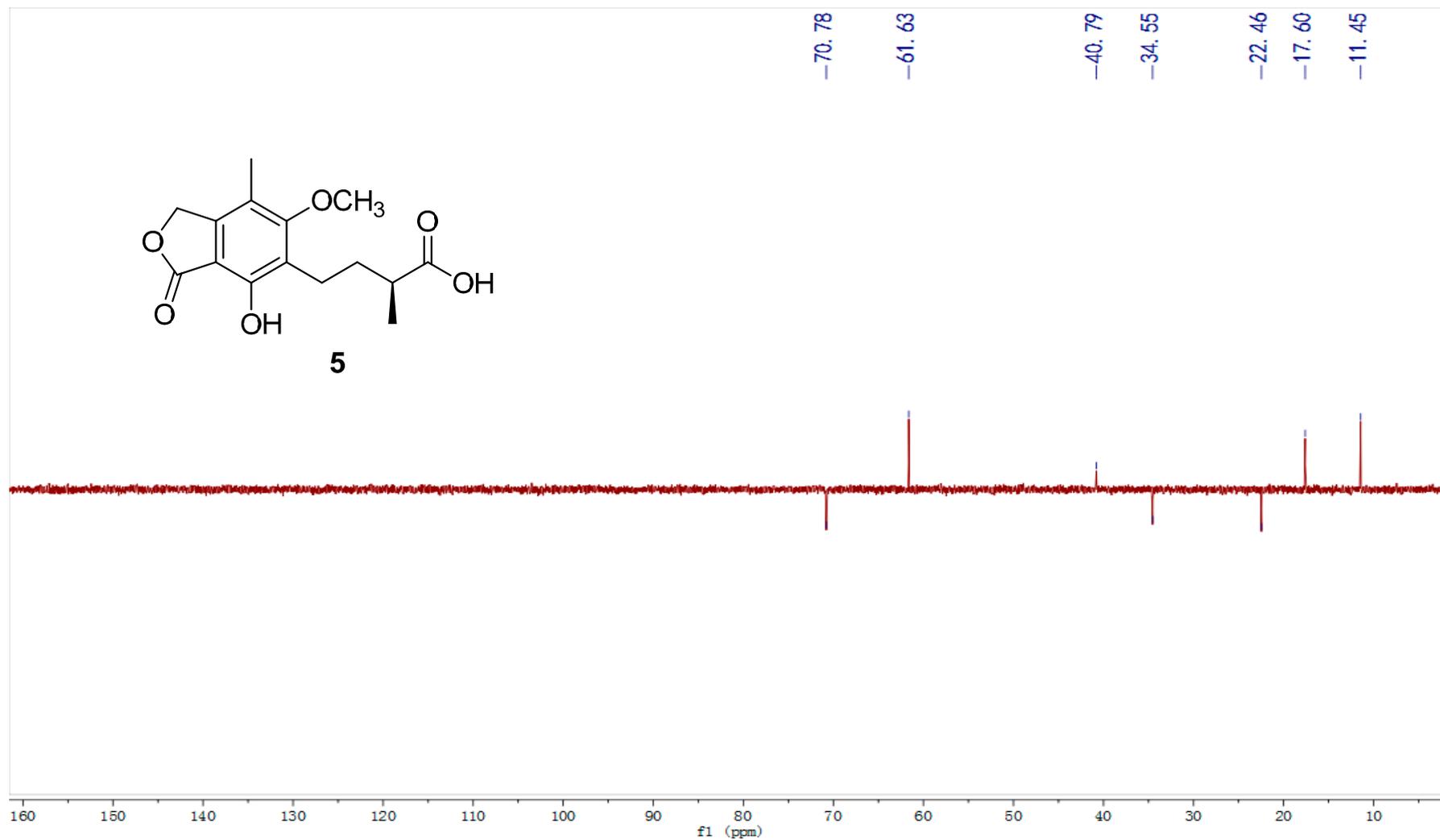


Figure S38. DEPT spectrum of compound 5 (Recorded in CD₃OD)

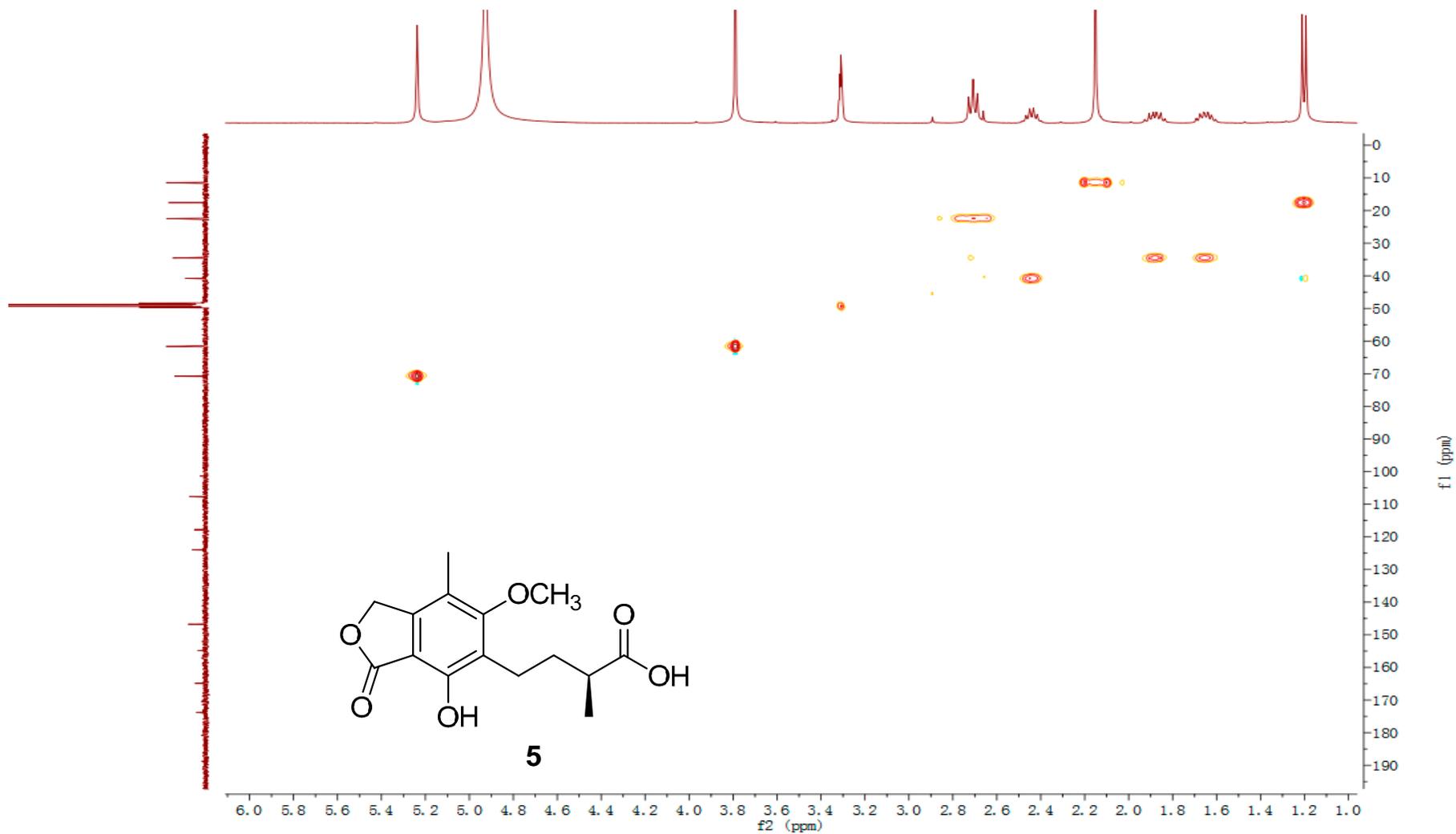


Figure S39. HSQC spectrum of compound 5 (Recorded in CD₃OD)

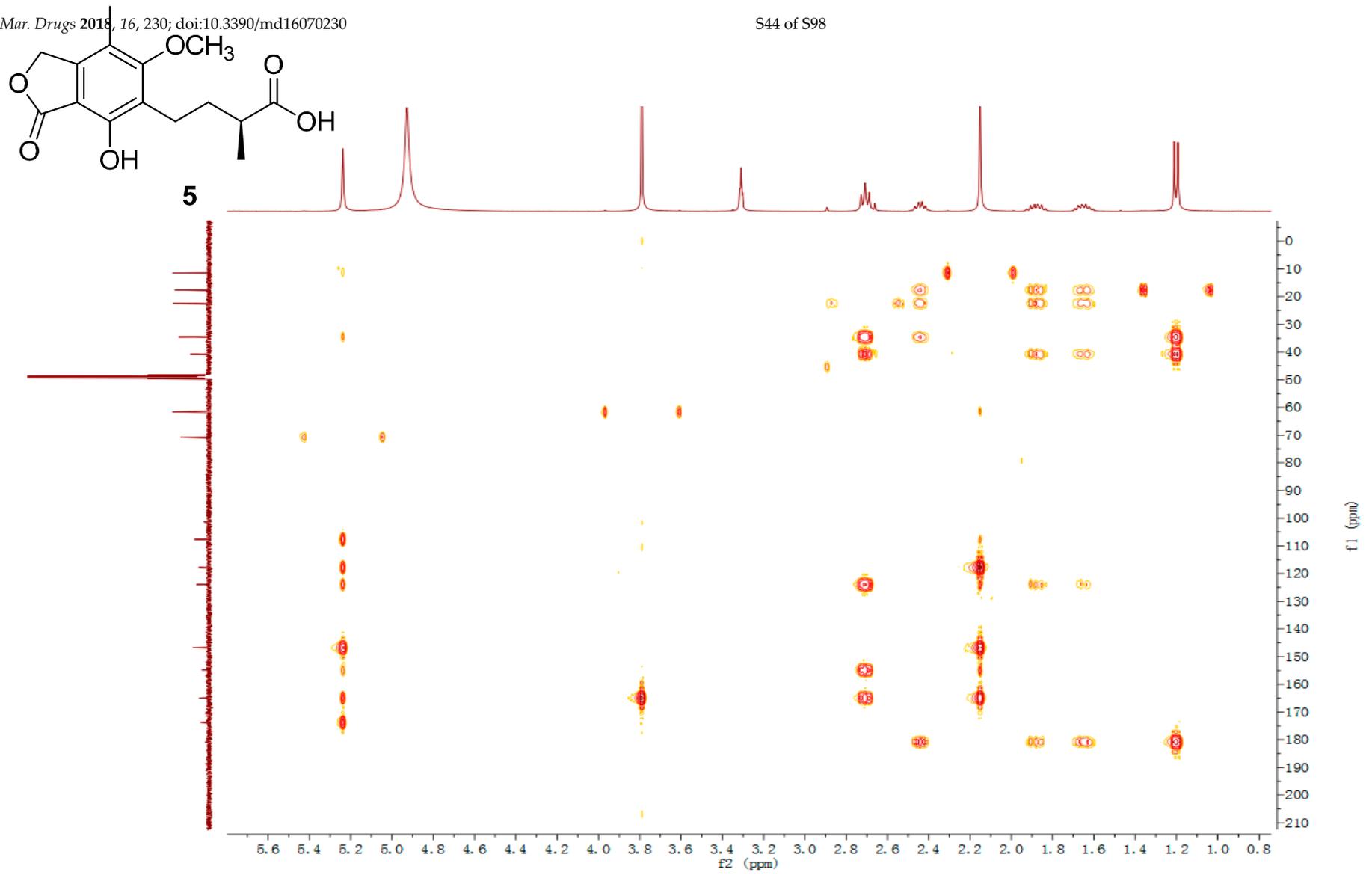


Figure S40. HMBC spectrum of compound 5 (Recorded in CD₃OD)

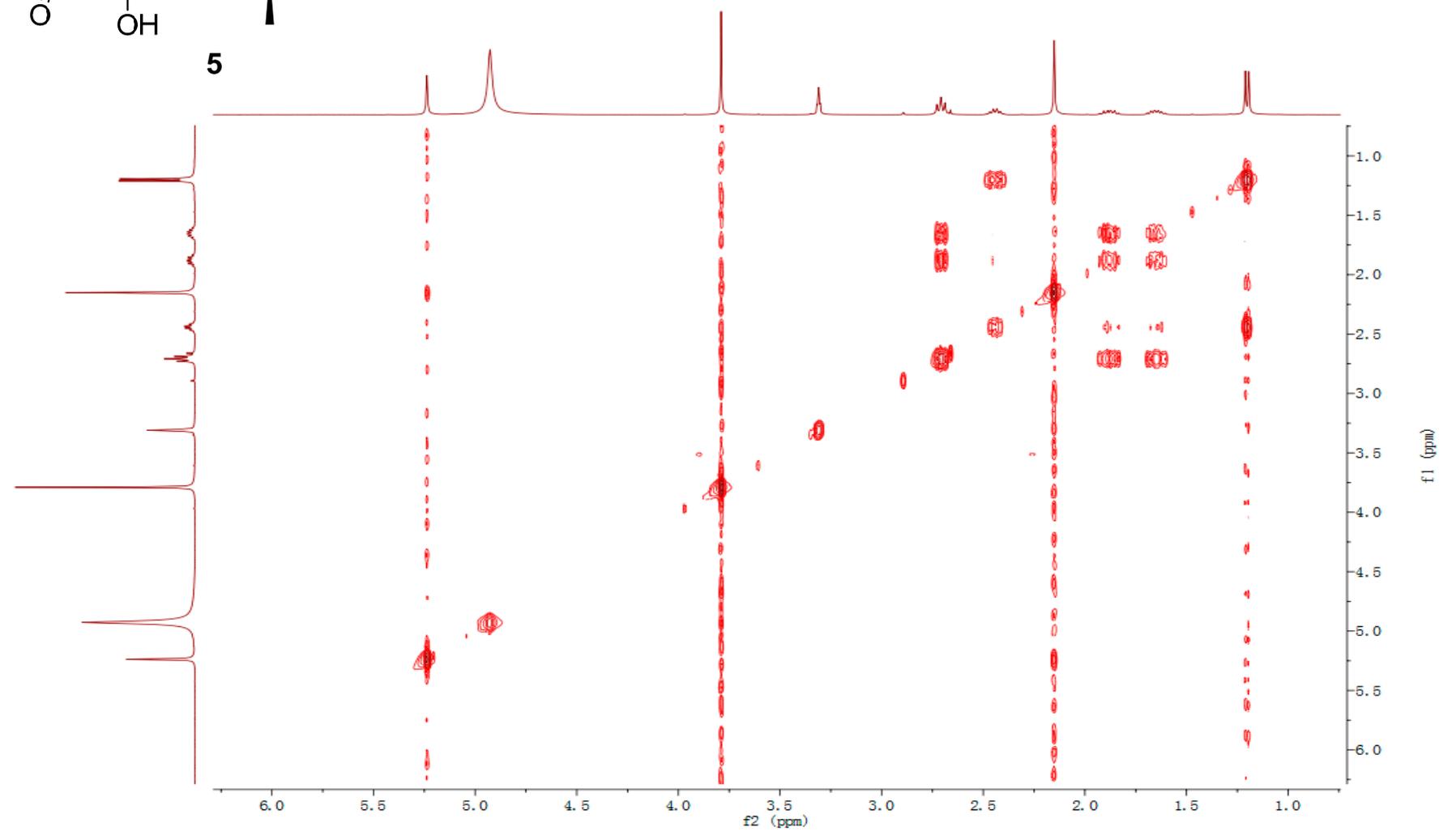
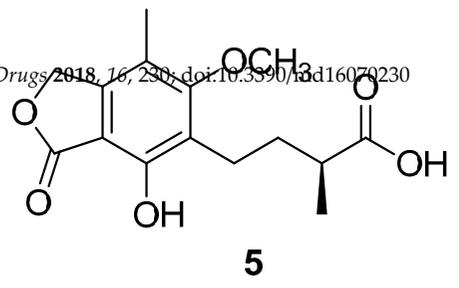


Figure S41. ¹H-¹H COSY spectrum of compound 5 (Recorded in CD₃OD)

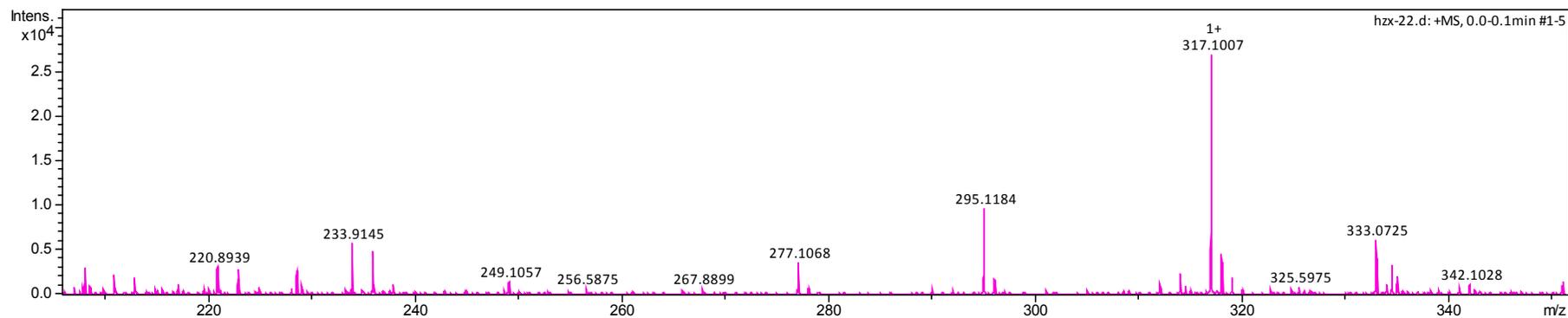
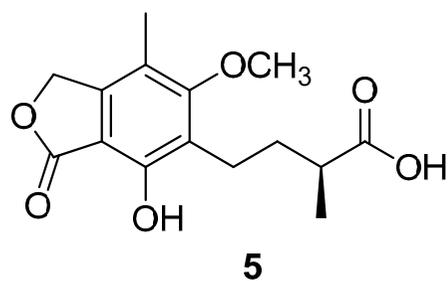


Figure S42. HRESIMS spectrum of compound 5



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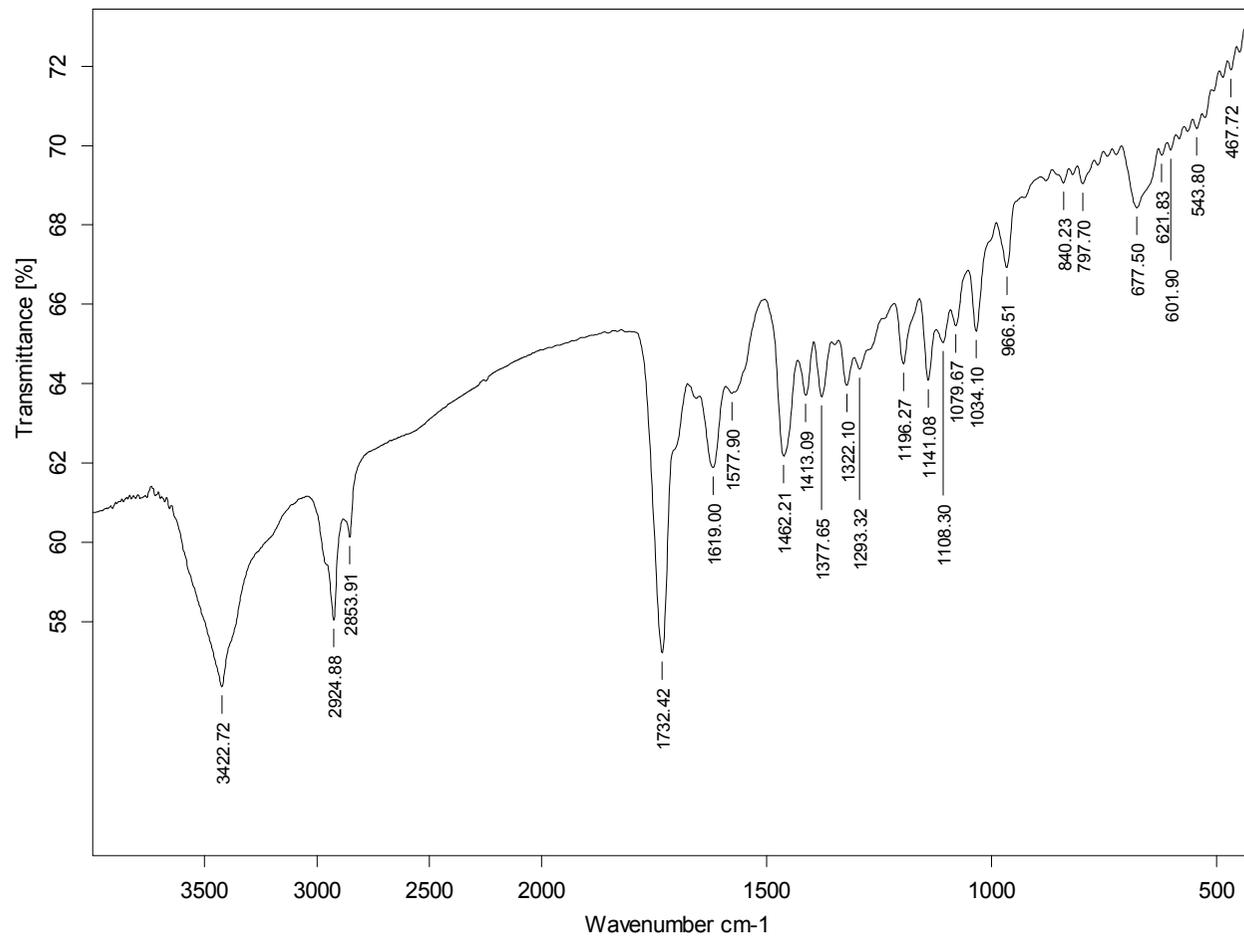
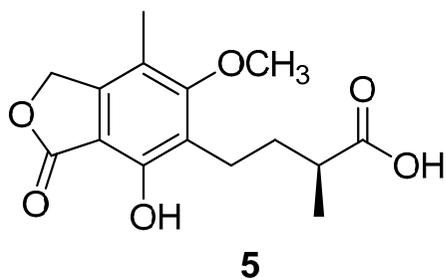


Figure S43. IR spectrum of compound 5

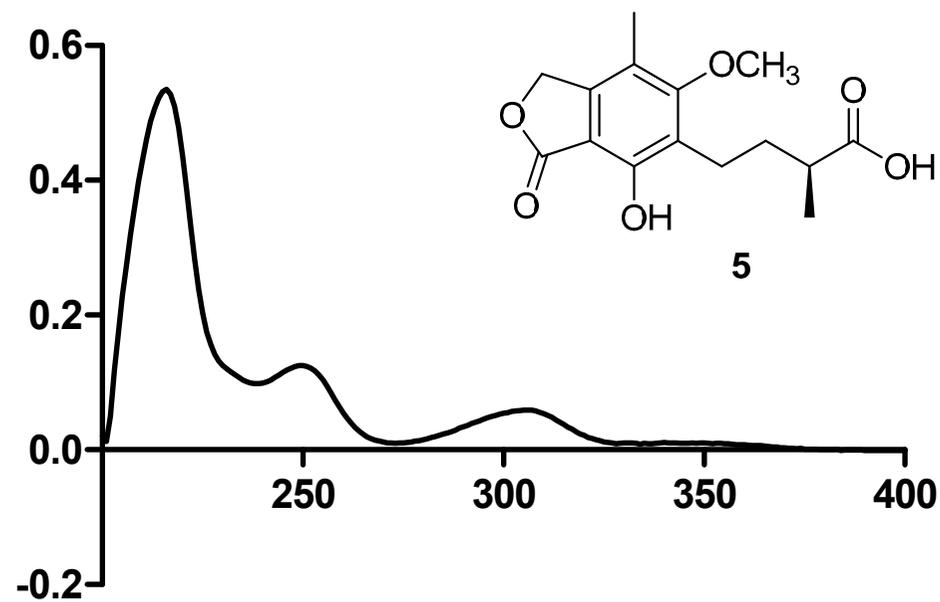


Figure S44. UV spectrum of compound 5

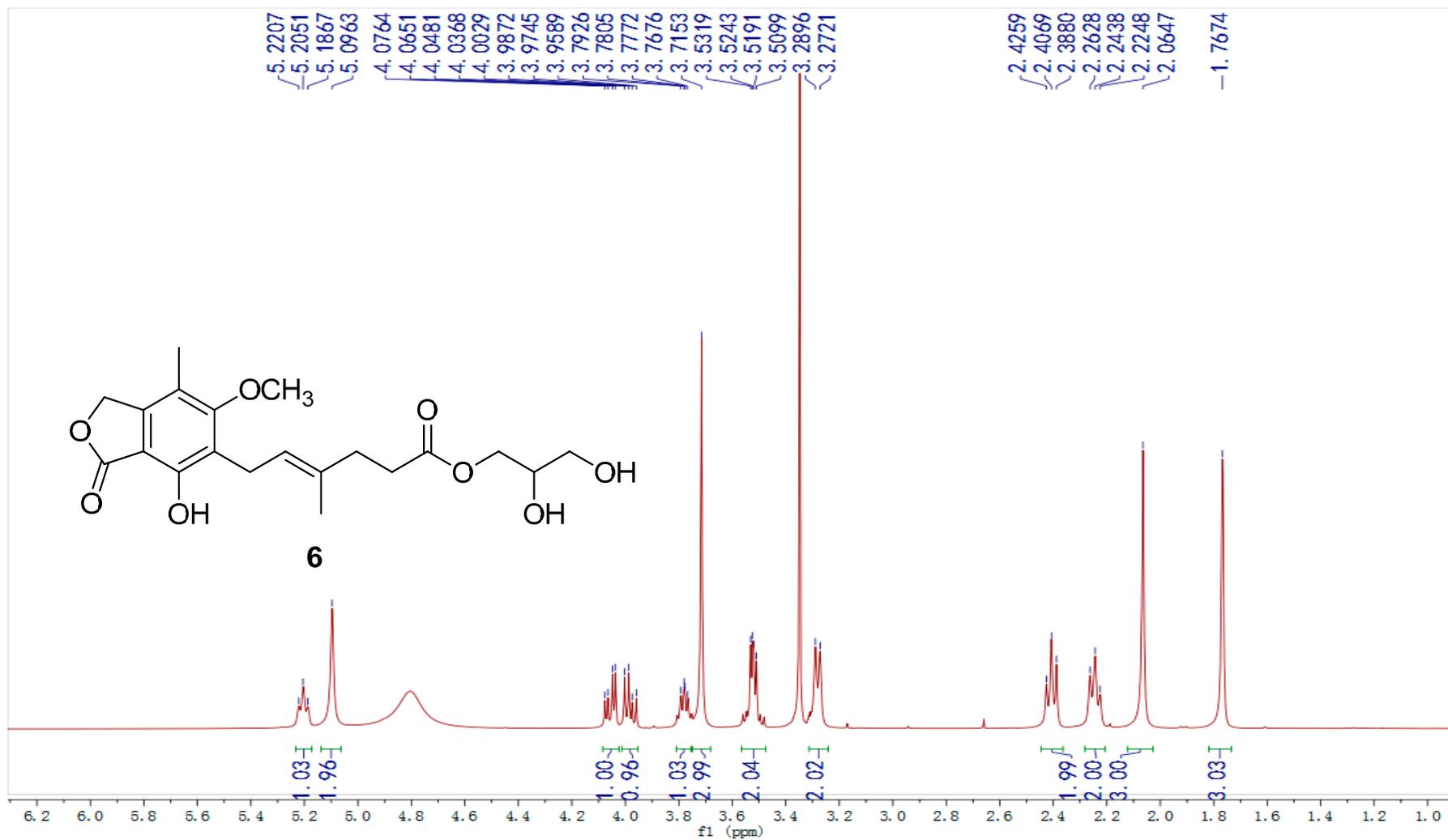


Figure S45. ¹H NMR spectrum of compound 6 (Recorded in CD₃OD)

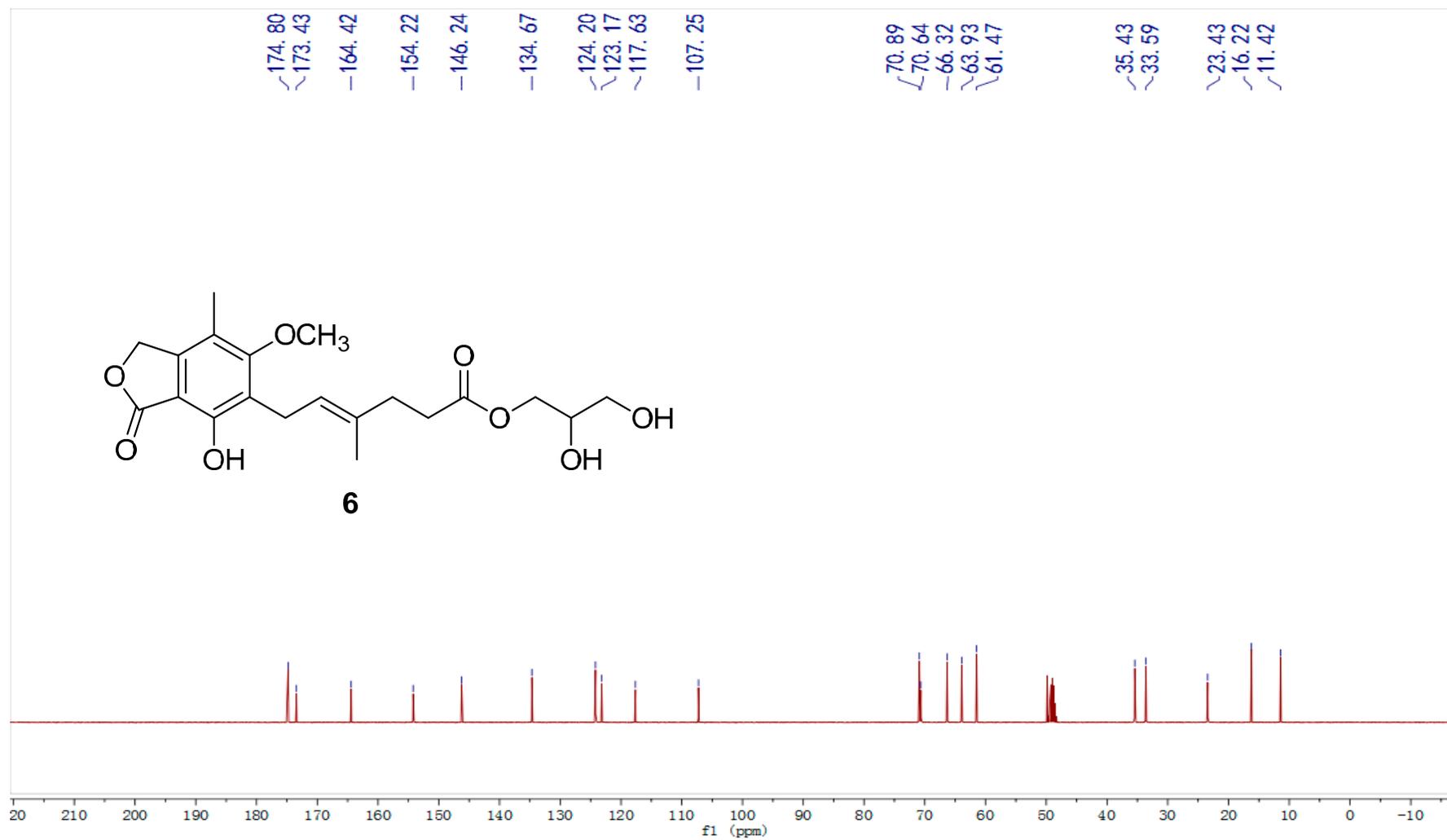


Figure S46. ^{13}C NMR spectrum of compound 6 (Recorded in CD_3OD)

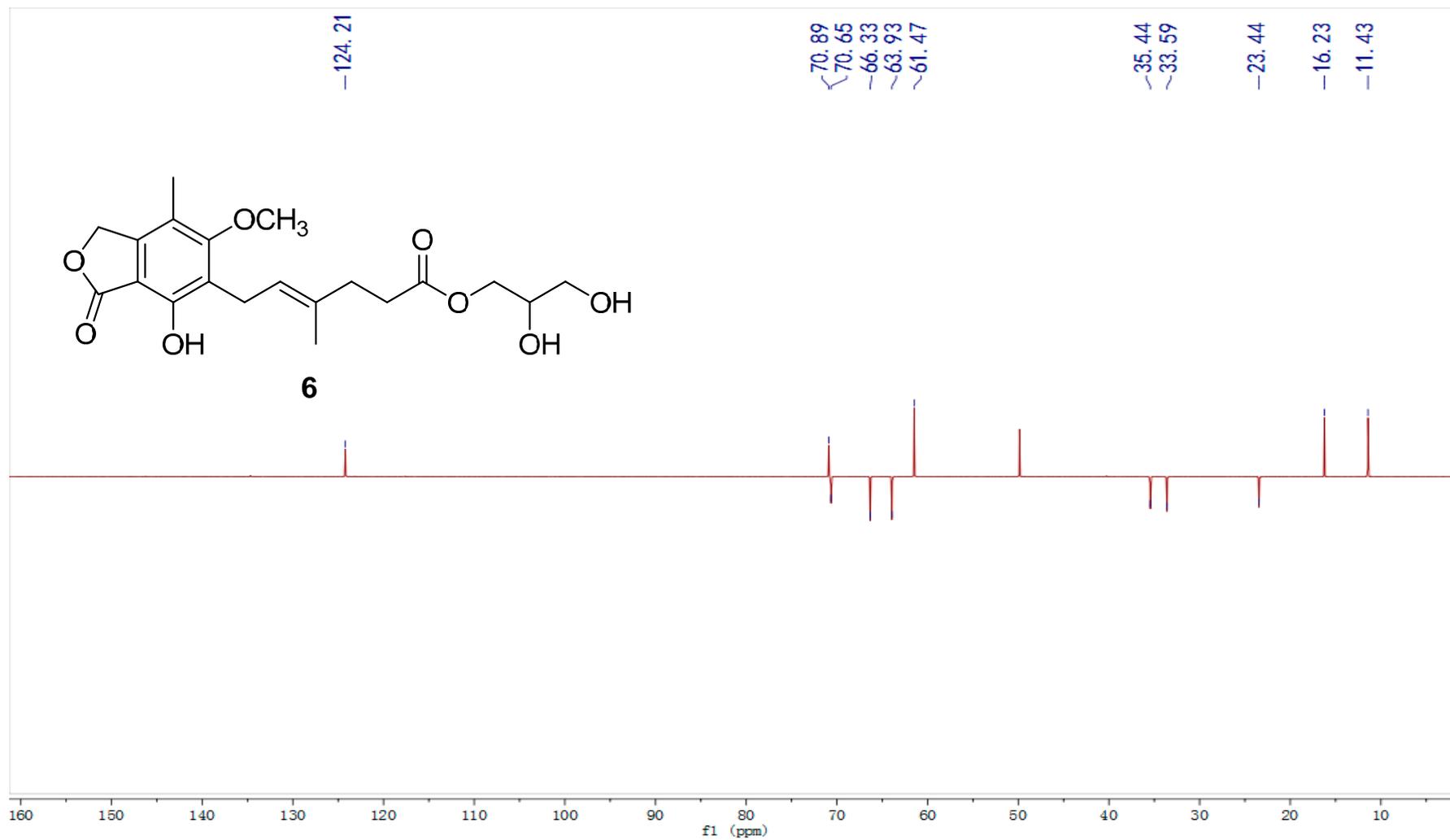


Figure S47. DEPT spectrum of compound 6 (Recorded in CD₃OD)

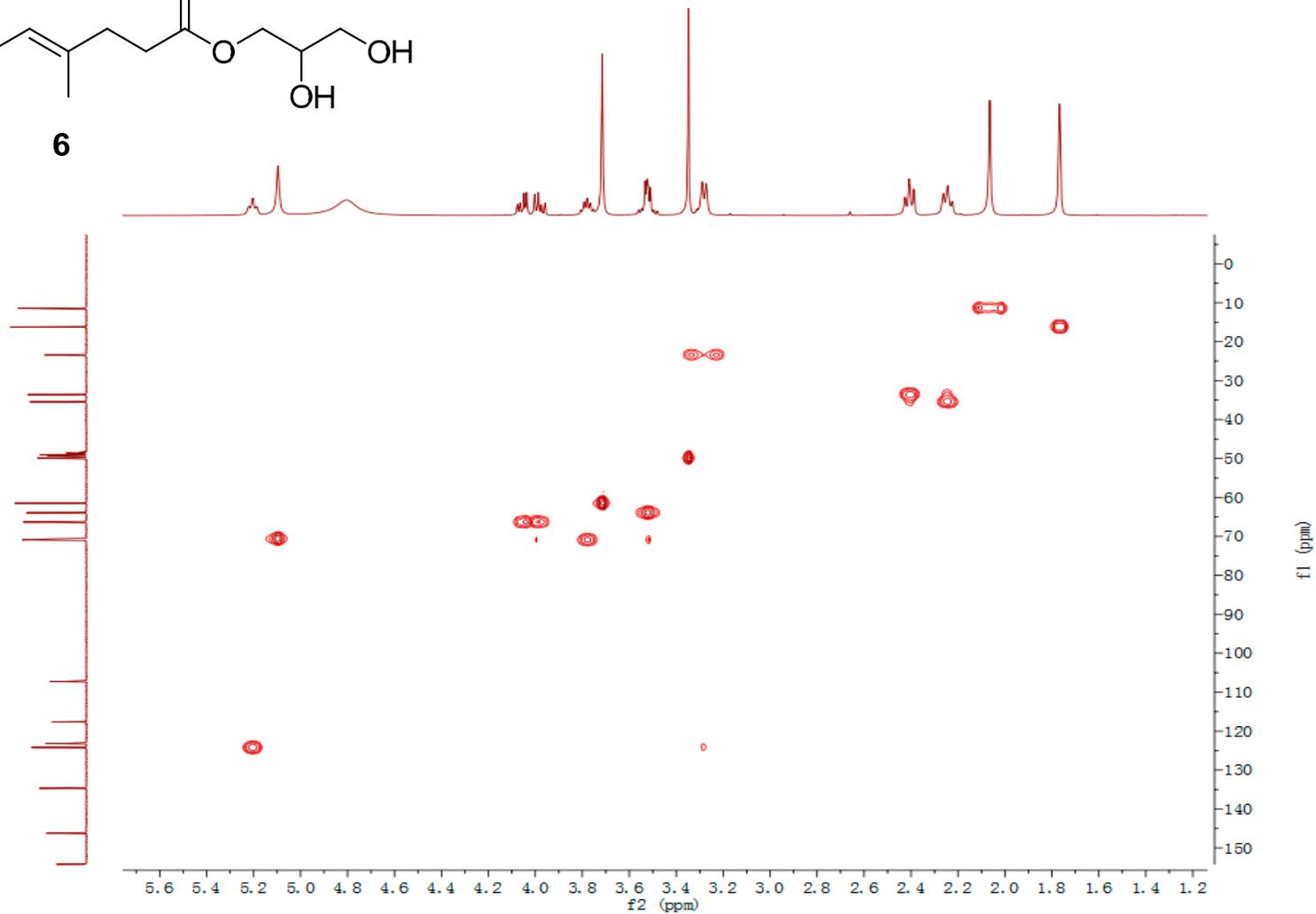
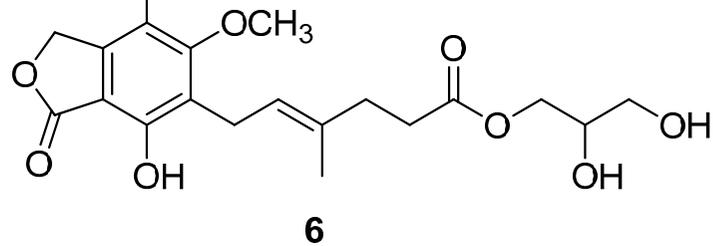


Figure S48. HSQC spectrum of compound **6** (Recorded in CD₃OD)

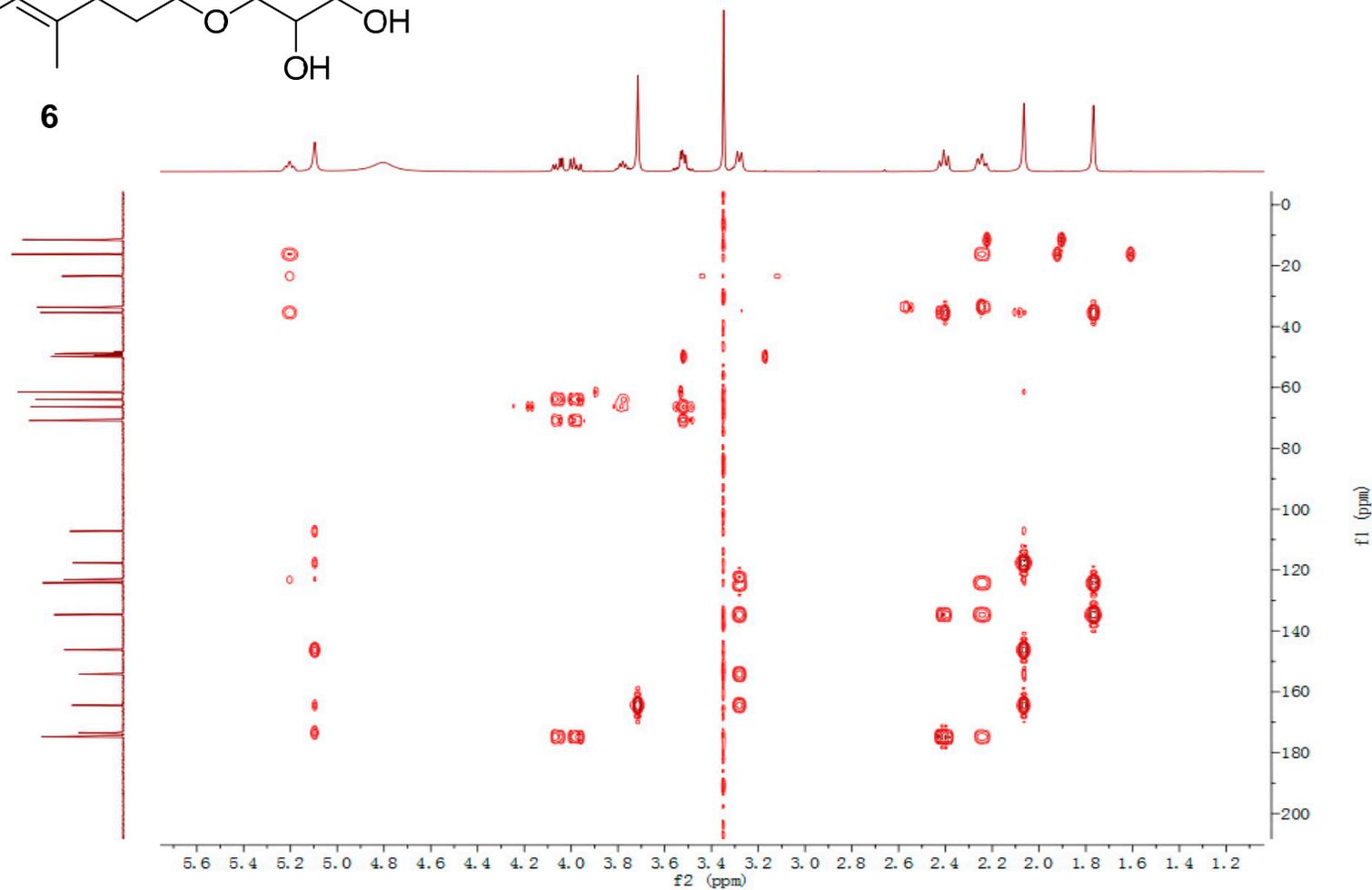
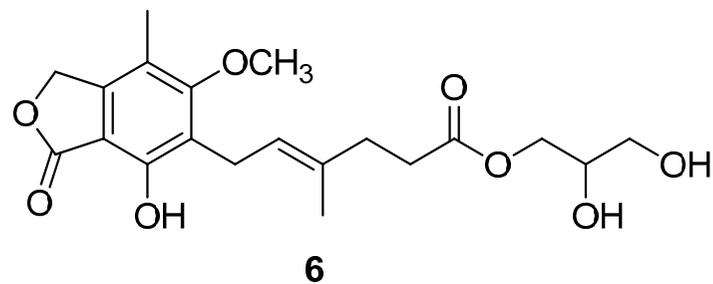


Figure S49. HMBC spectrum of compound **6** (Recorded in CD₃OD)

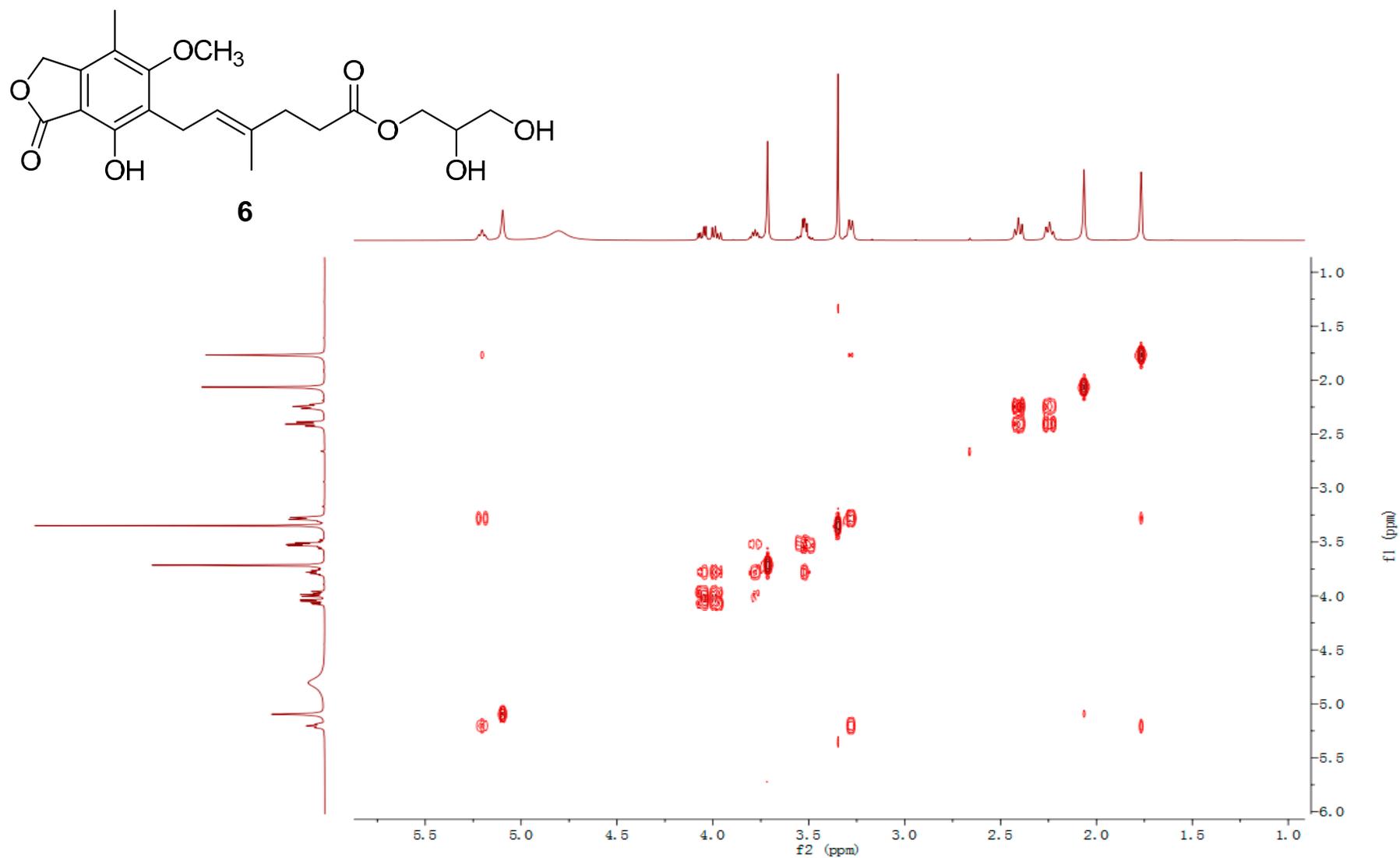


Figure S50. ¹H-¹H COSY spectrum of compound 6 (Recorded in CD₃OD)

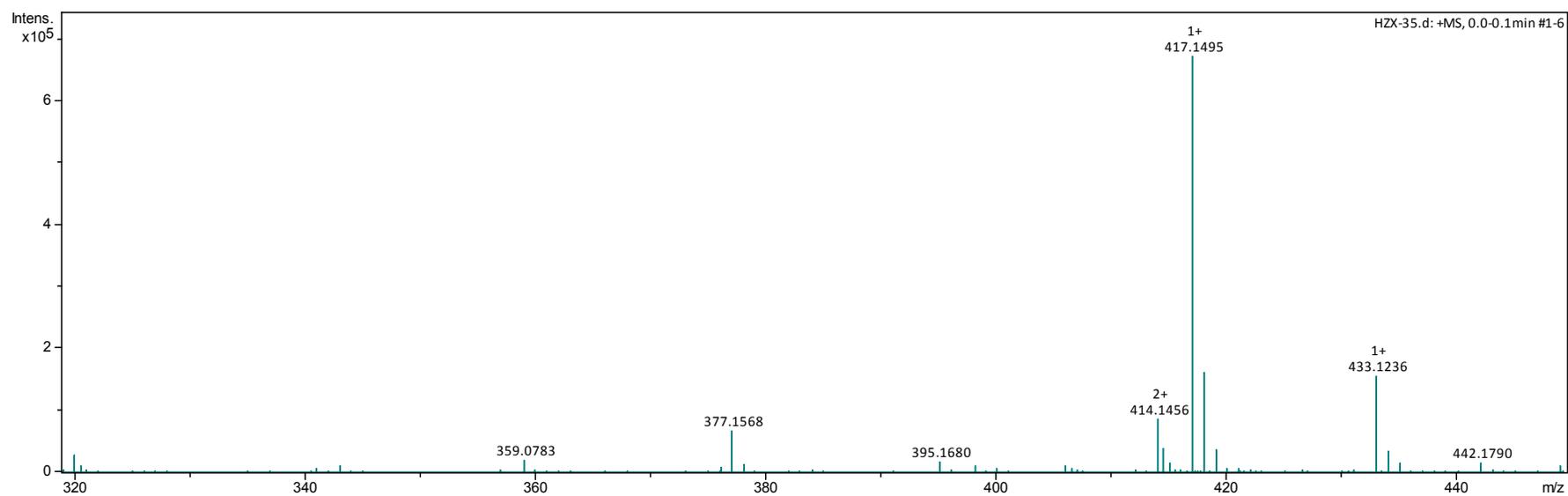
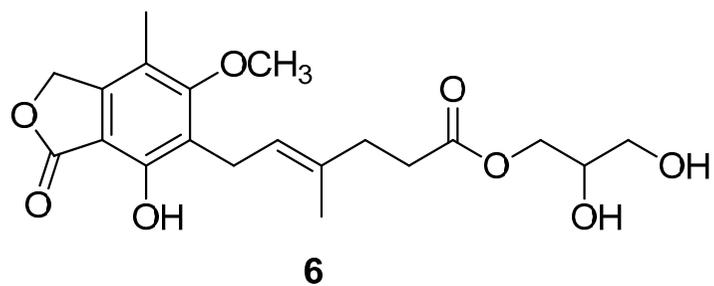


Figure S51. HRESIMS spectrum of compound 6



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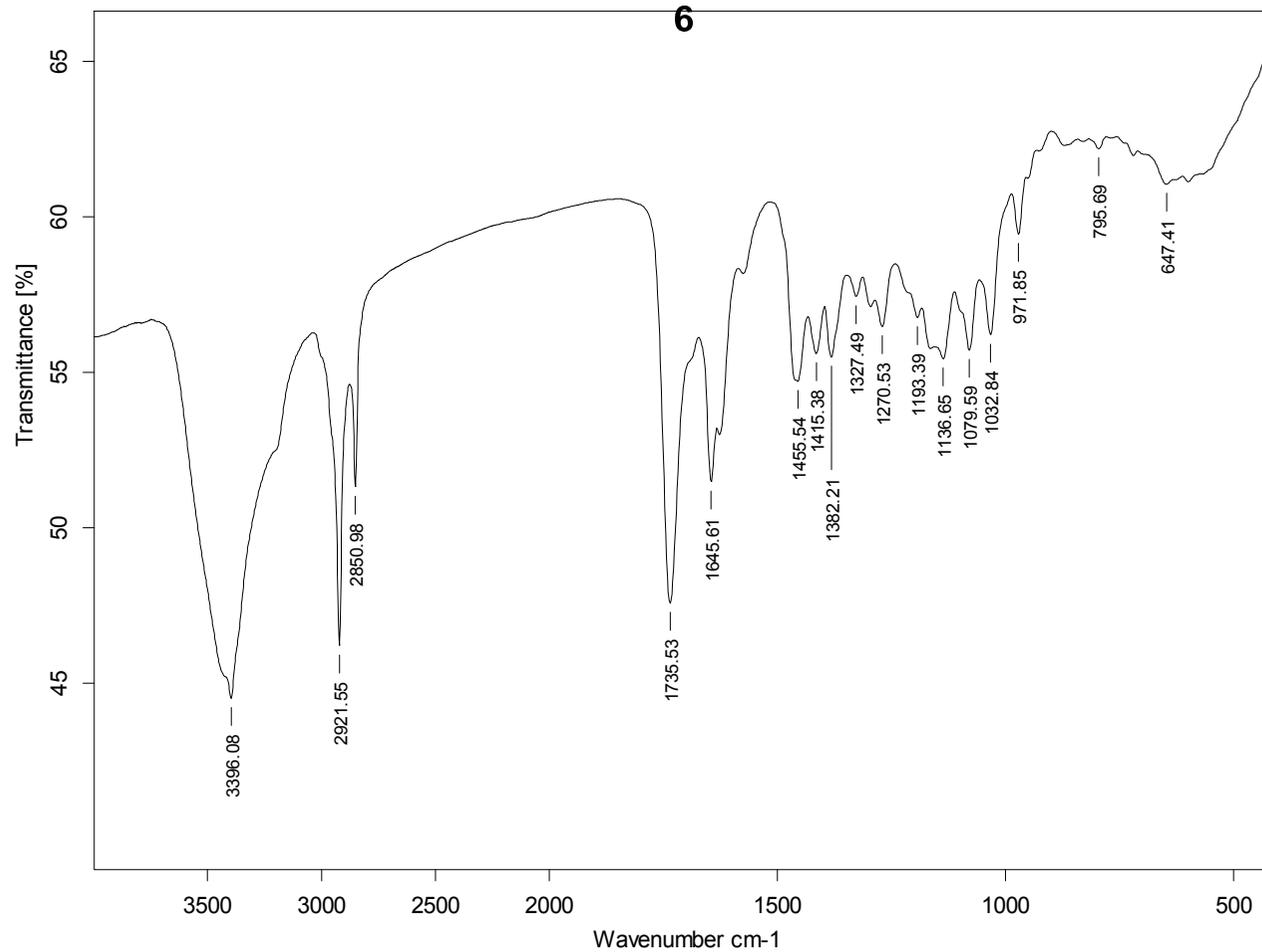
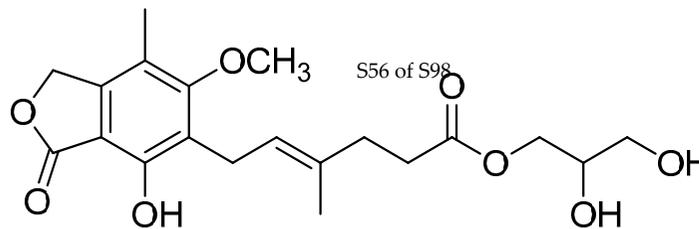


Figure S52. IR spectrum of compound 6

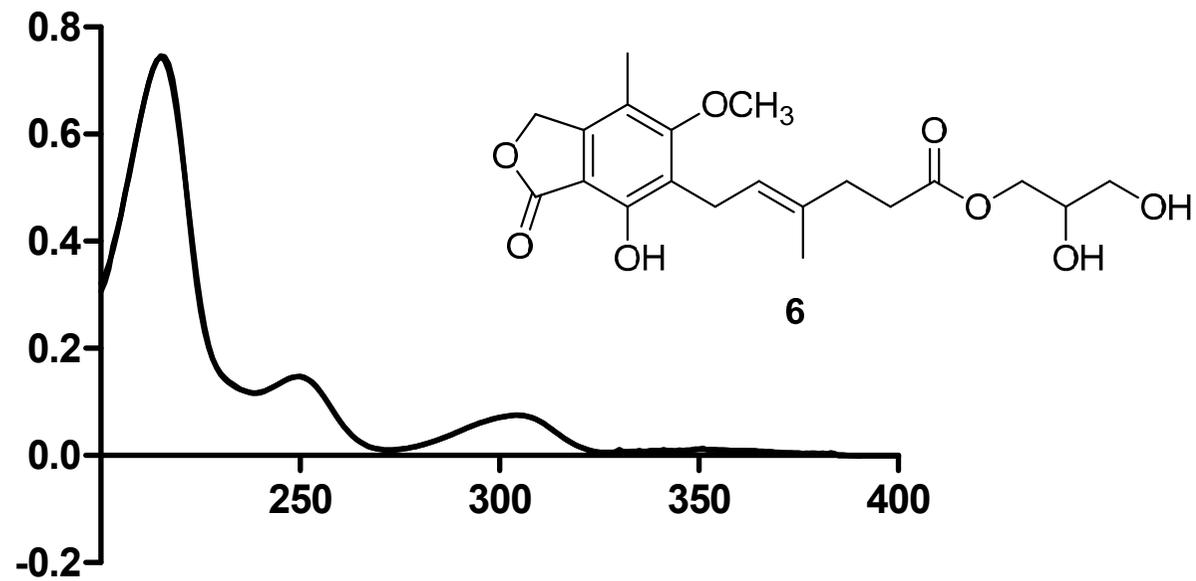


Figure S53. UV spectrum of compound 6

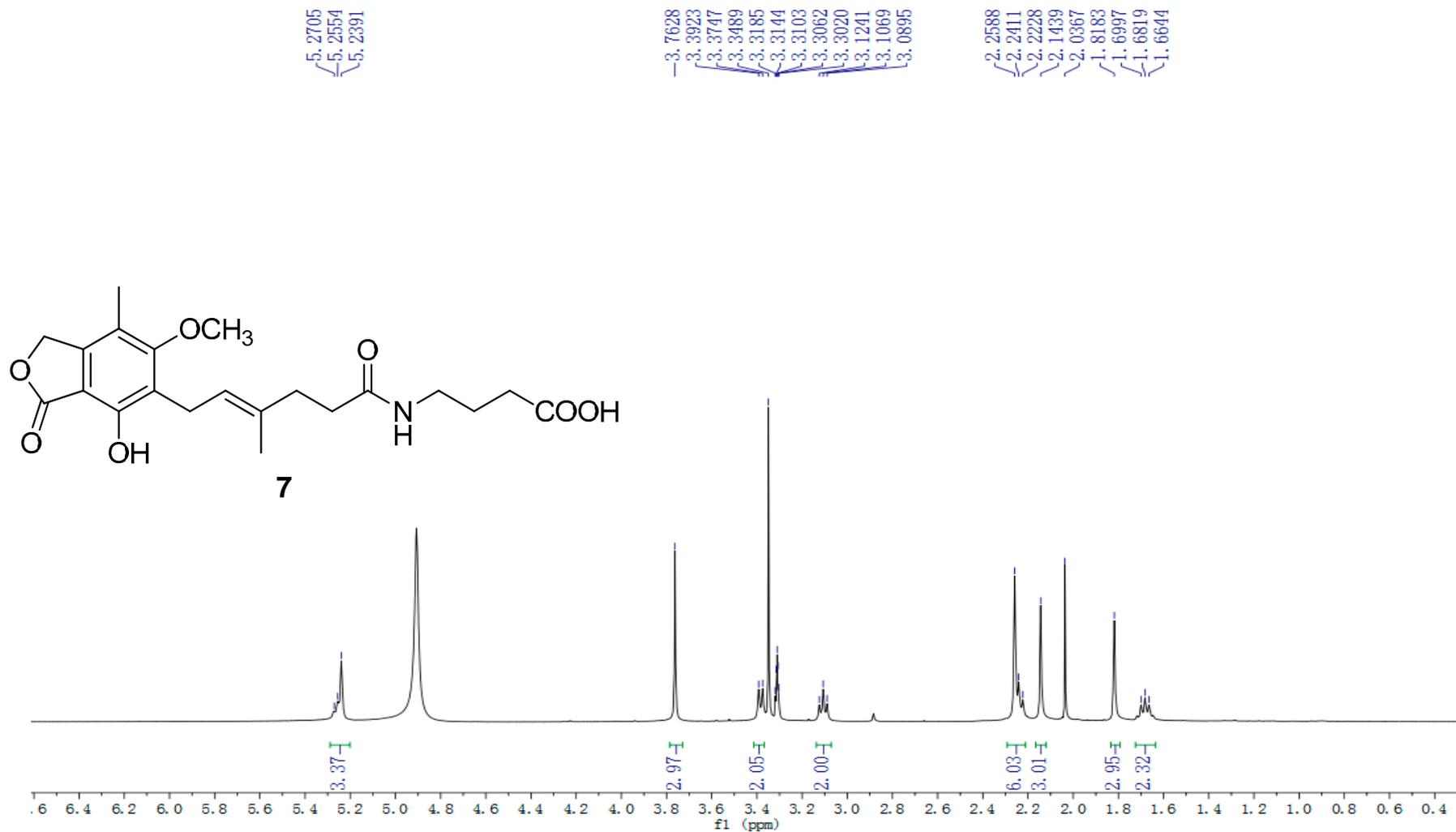


Figure S54. ¹H NMR spectrum of compound 7 (Recorded in CD₃OD)

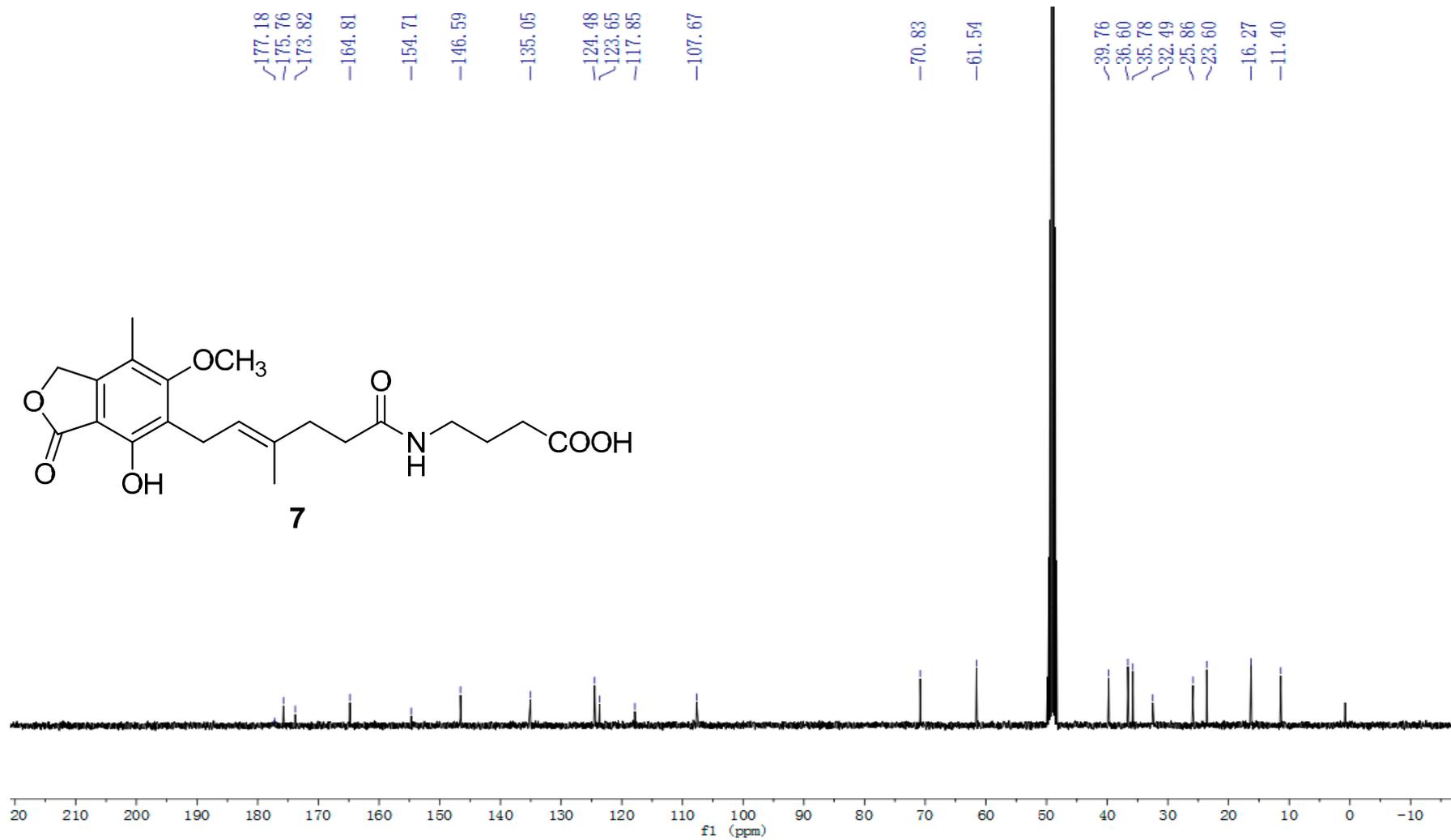


Figure S55. ¹³C NMR spectrum of compound 7 (Recorded in CD₃OD)

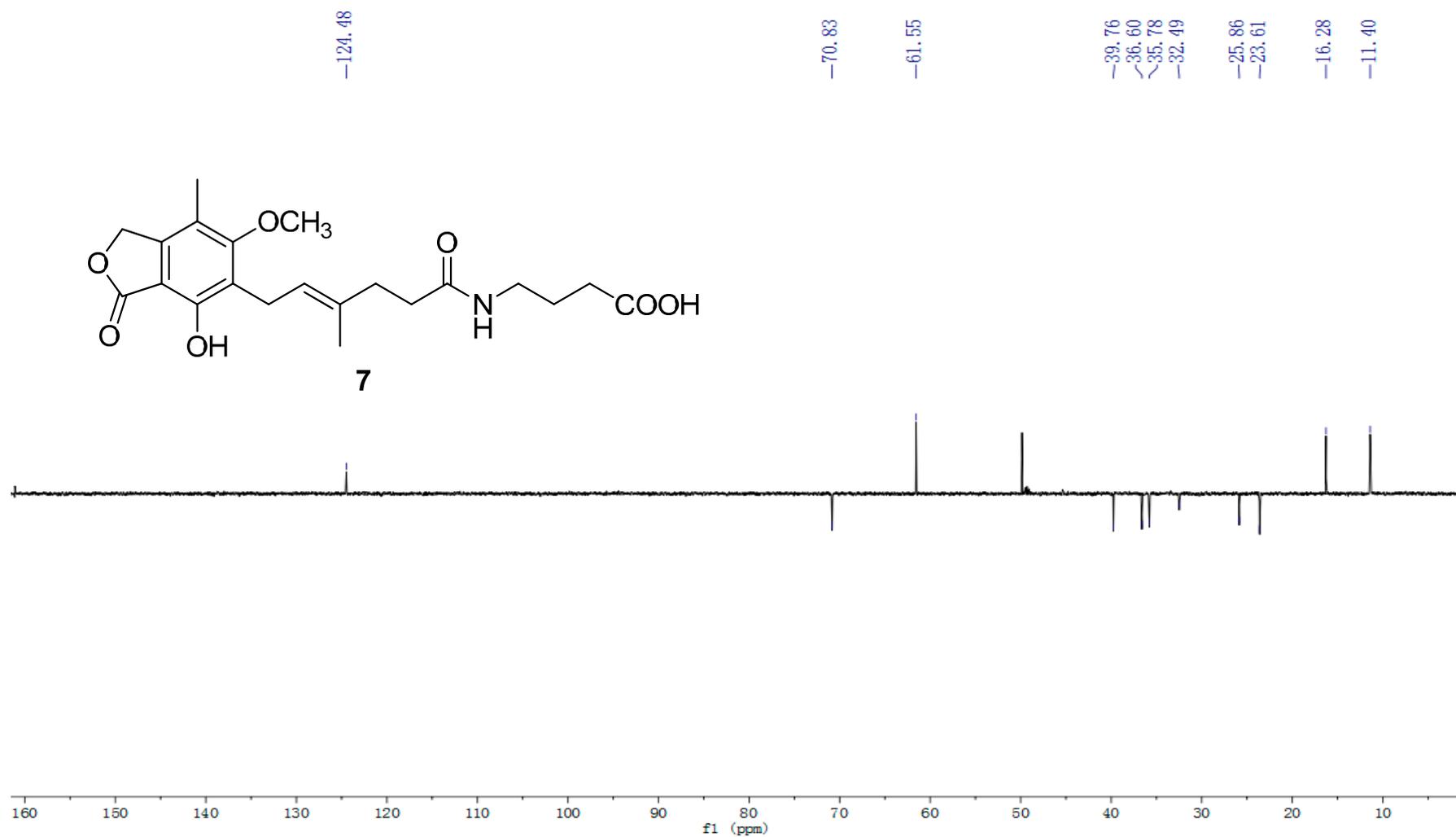


Figure S56. DEPT spectrum of compound 7 (Recorded in CD₃OD)

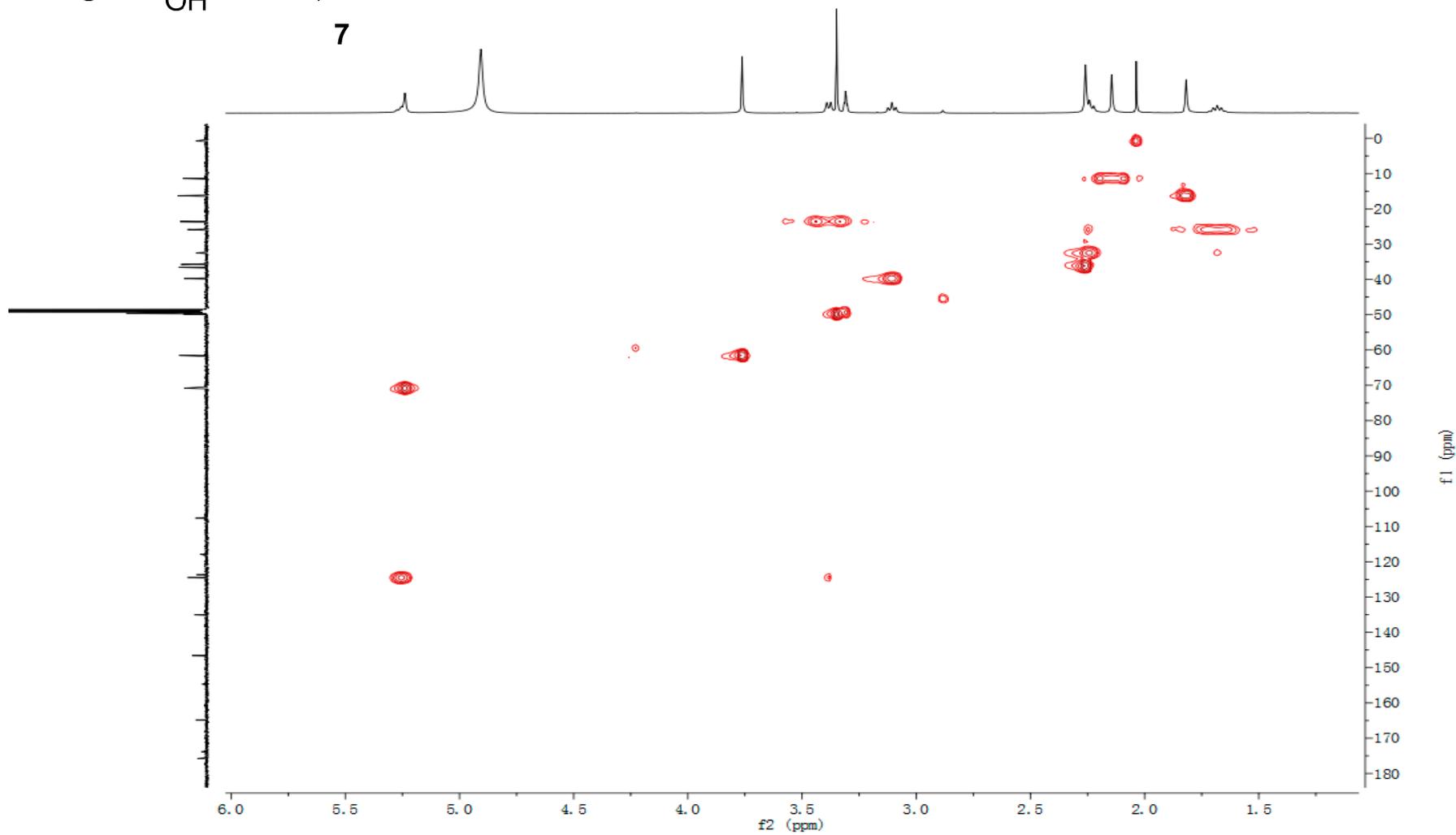
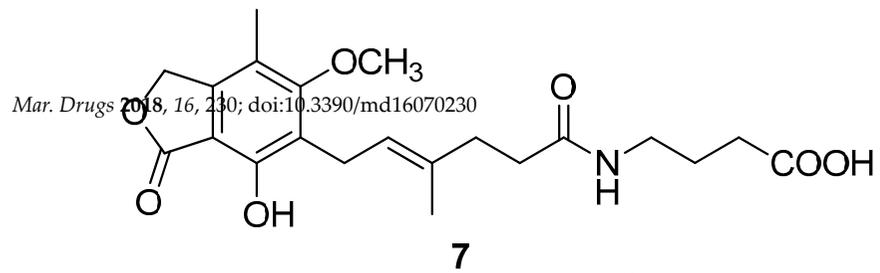
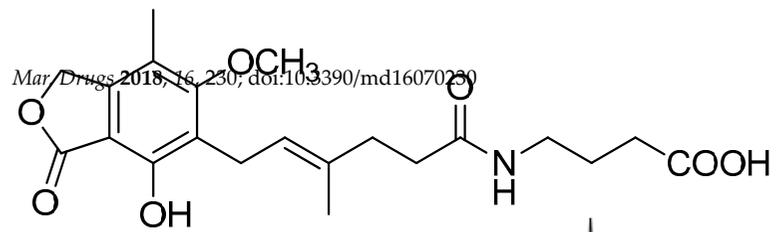


Figure S57. HSQC spectrum of compound 7 (Recorded in CD₃OD)



S62 of S98

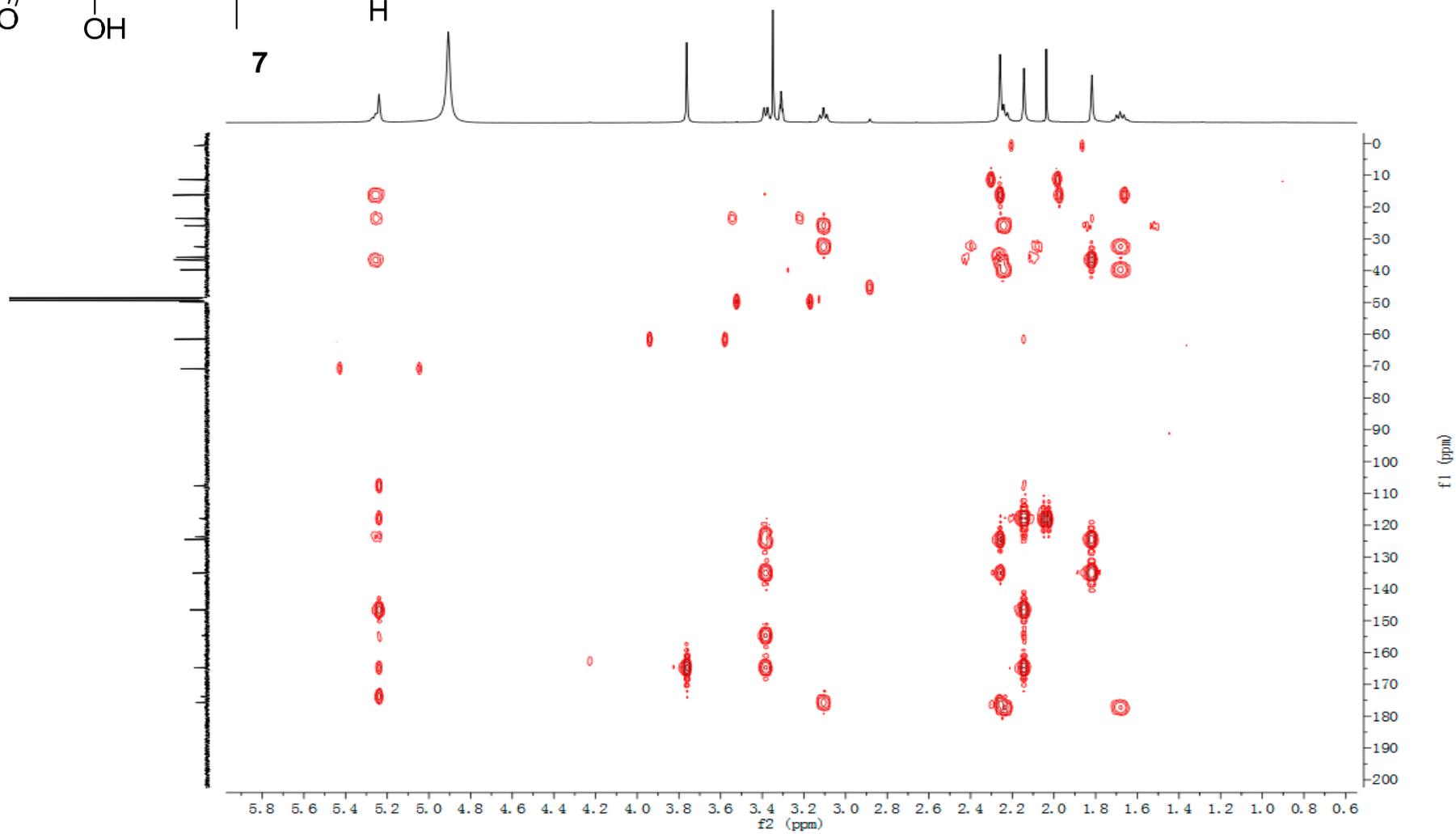
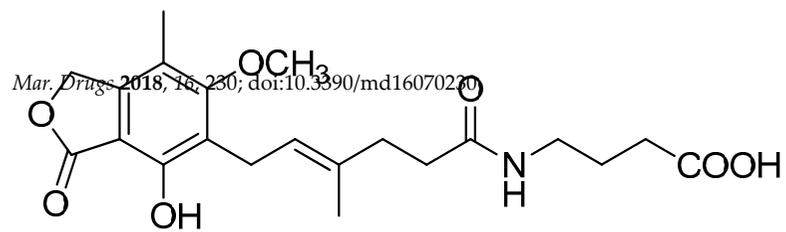


Figure S58. HMBC spectrum of compound 7 (Recorded in CD₃OD)



S63 of S98

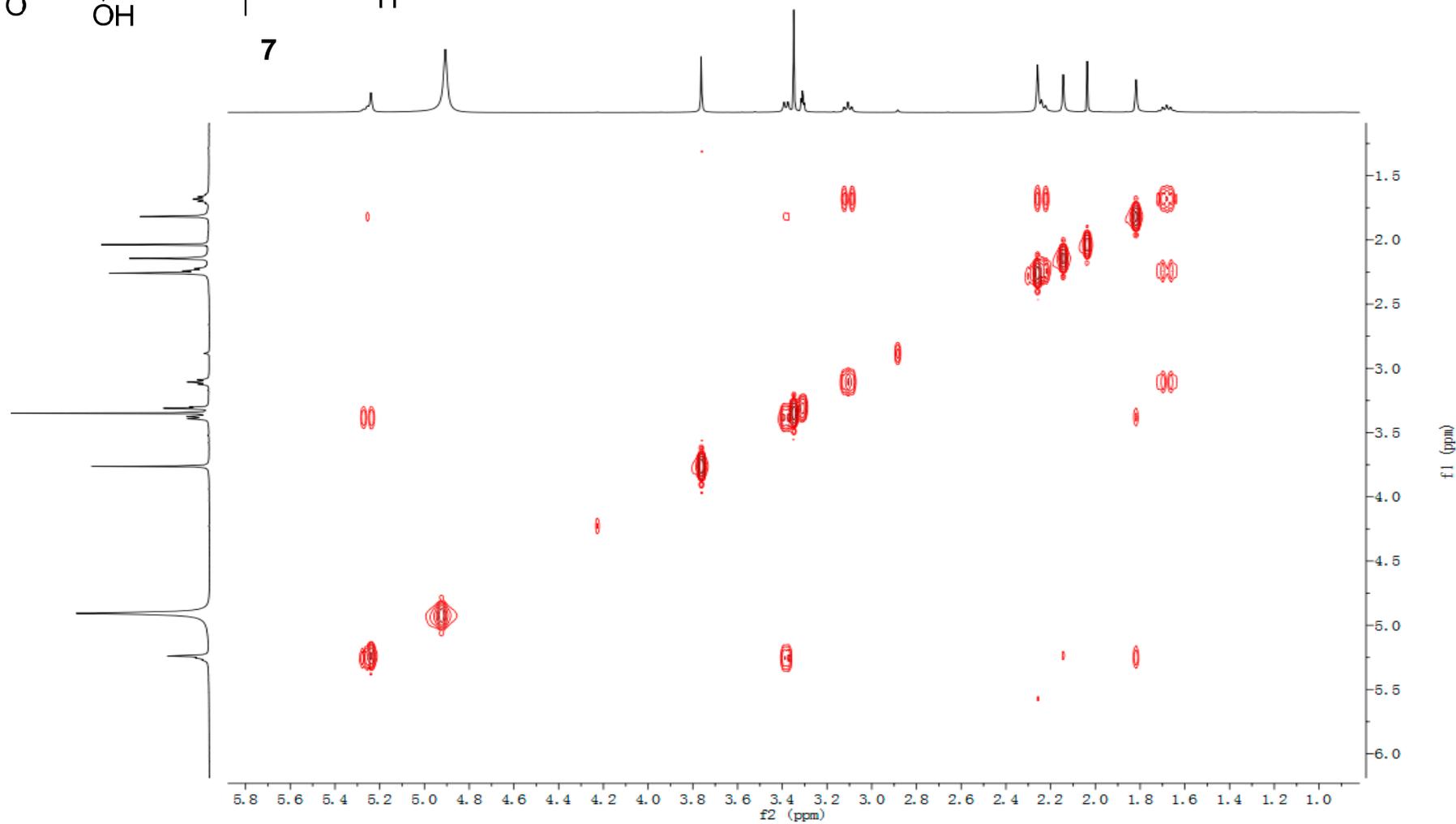


Figure S59. ^1H - ^1H COSY spectrum of compound 7 (Recorded in CD_3OD)

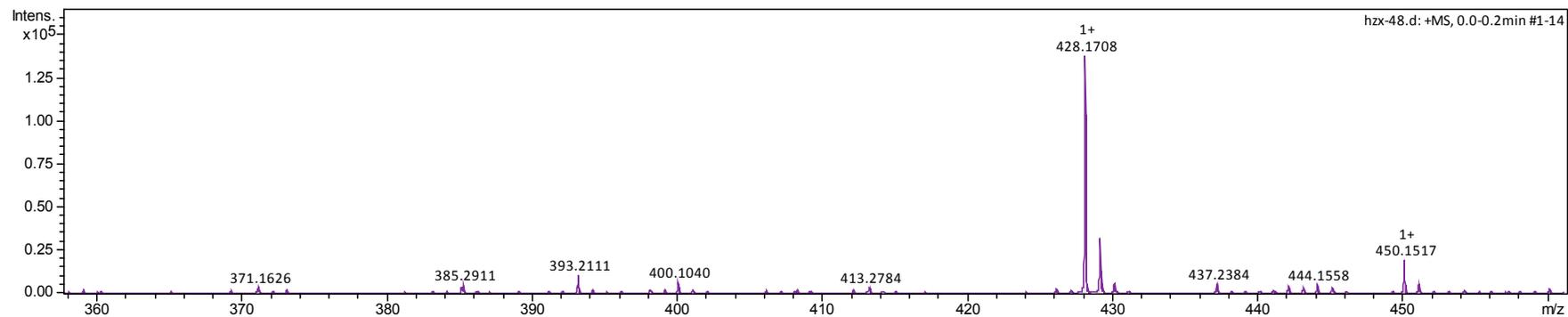
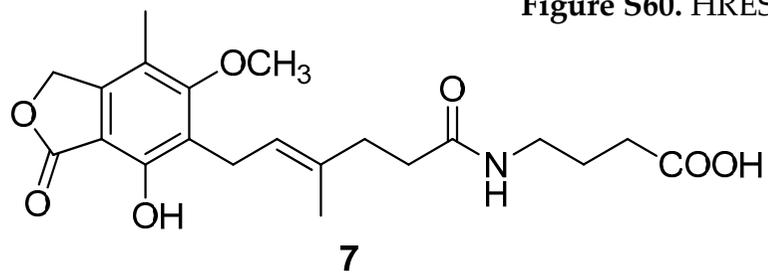
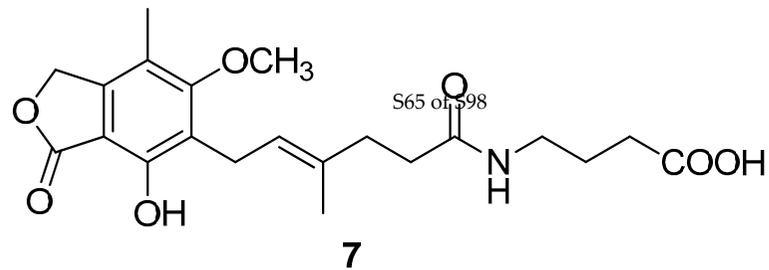


Figure S60. HRESIMS spectrum of compound 7





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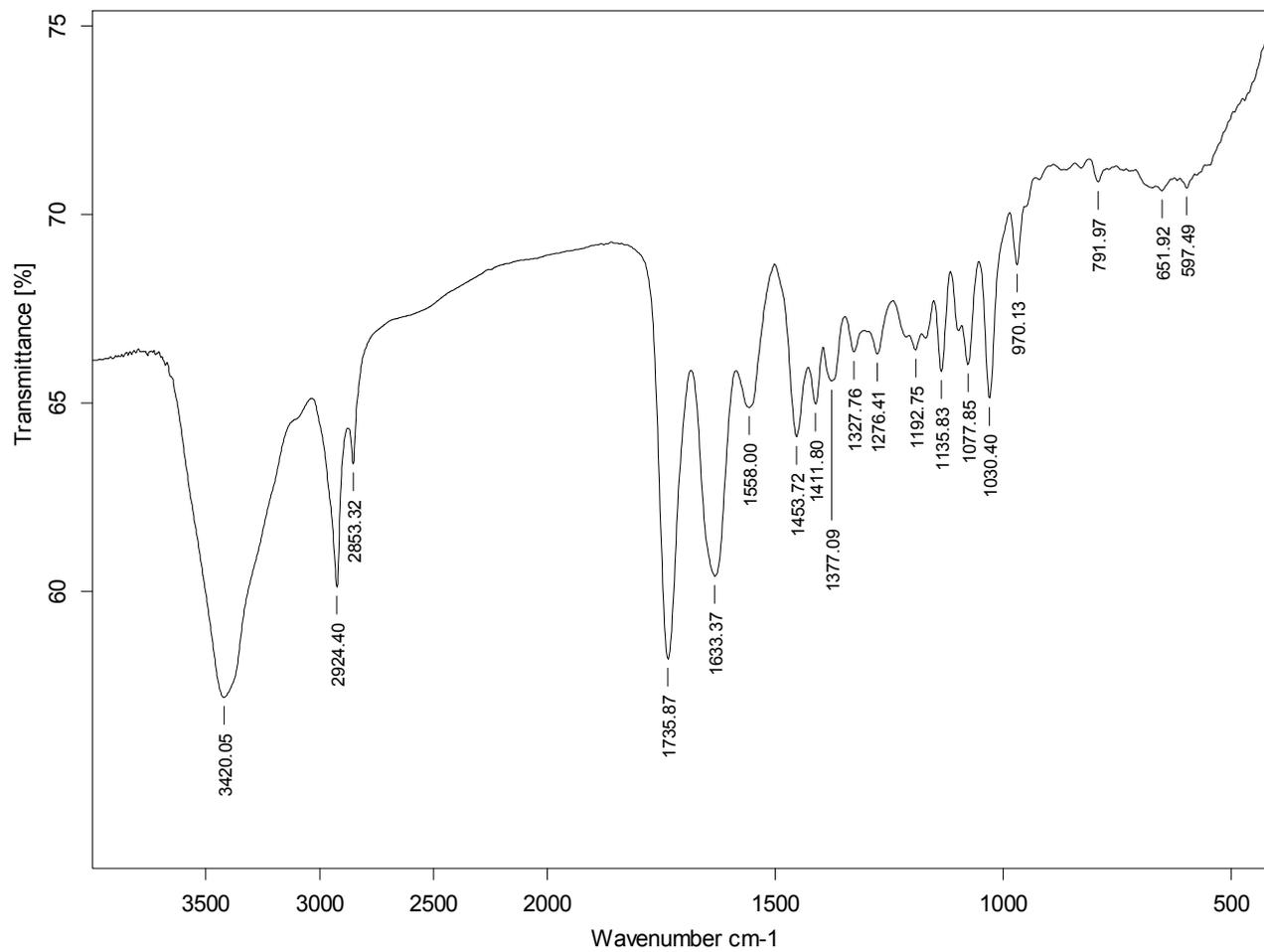


Figure S61. IR spectrum of compound 7

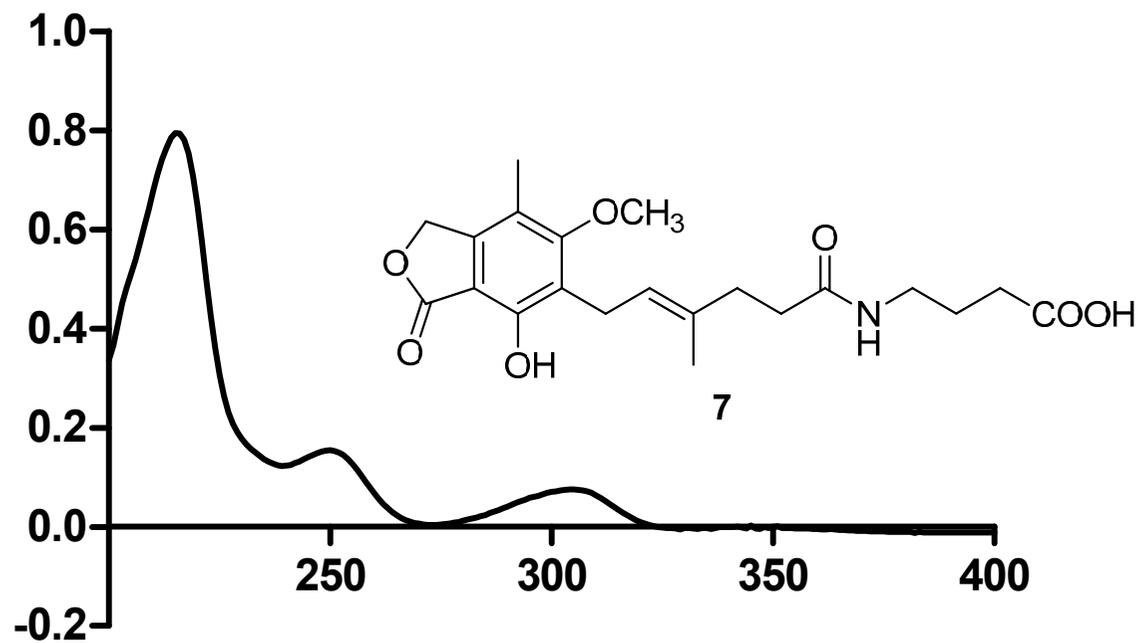


Figure S62. UV spectrum of compound 7

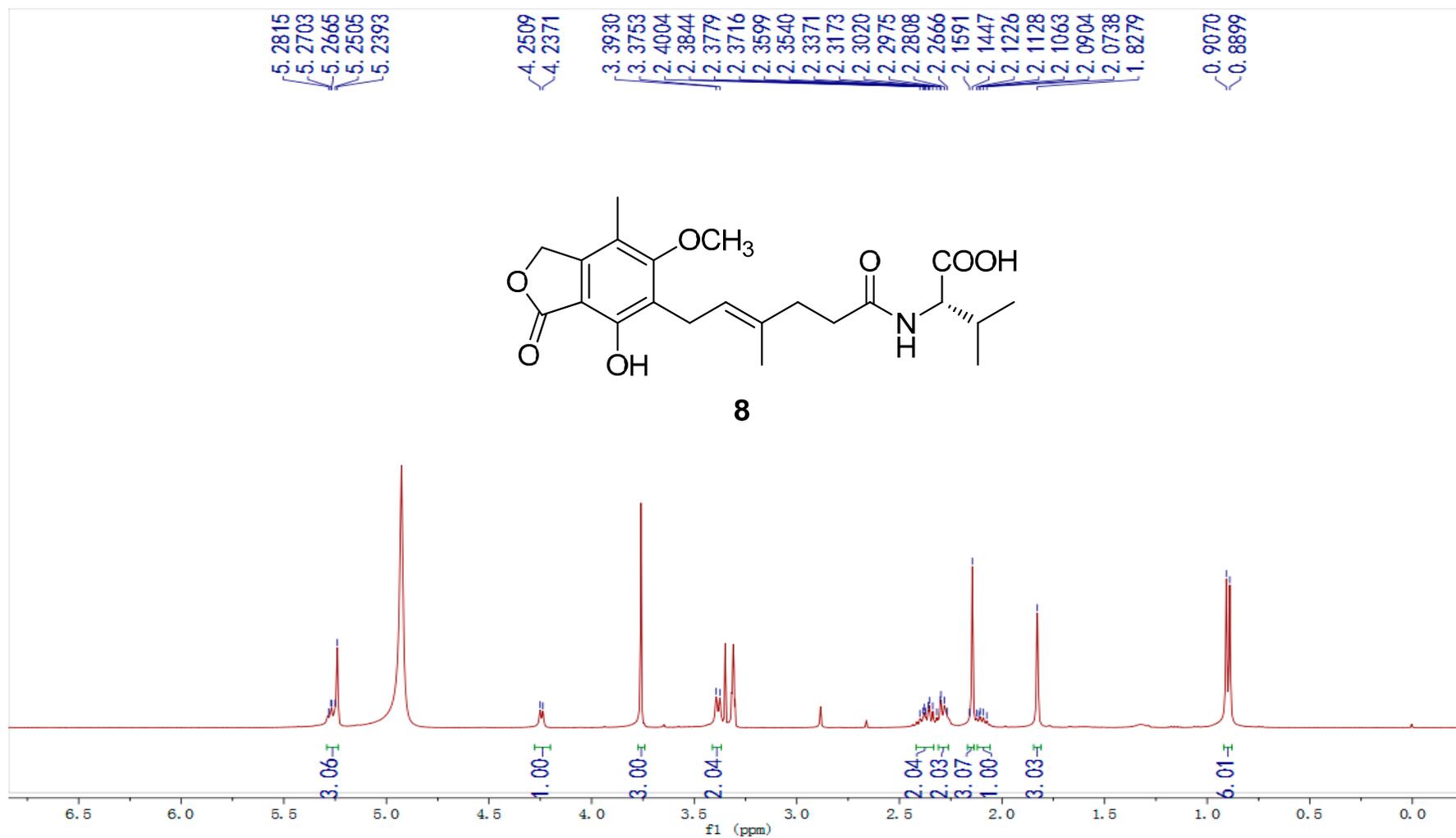


Figure S63. ¹H NMR spectrum of compound 8 (Recorded in CD₃OD)

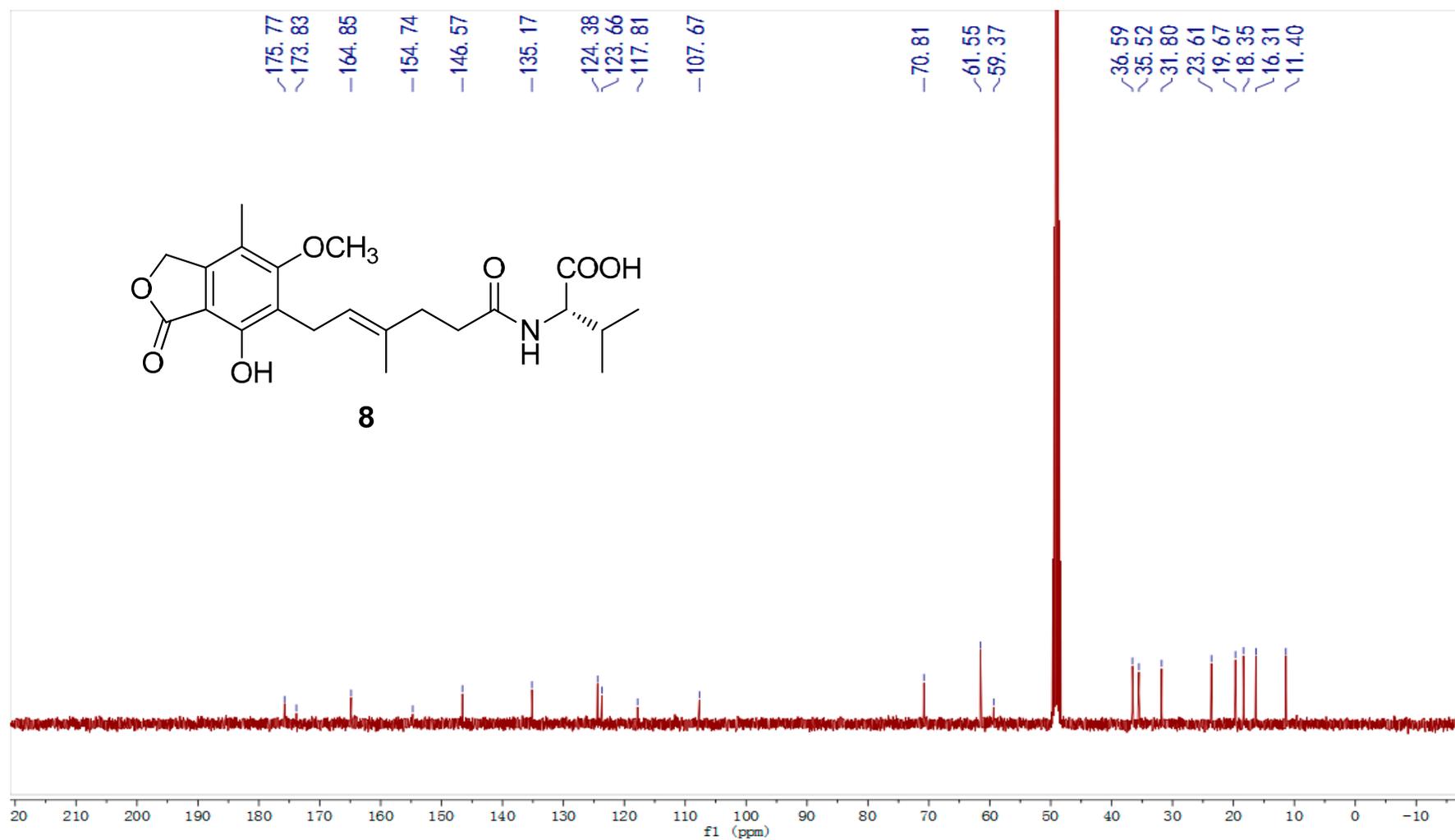


Figure S64. ¹³C NMR spectrum of compound 8 (Recorded in CD₃OD)

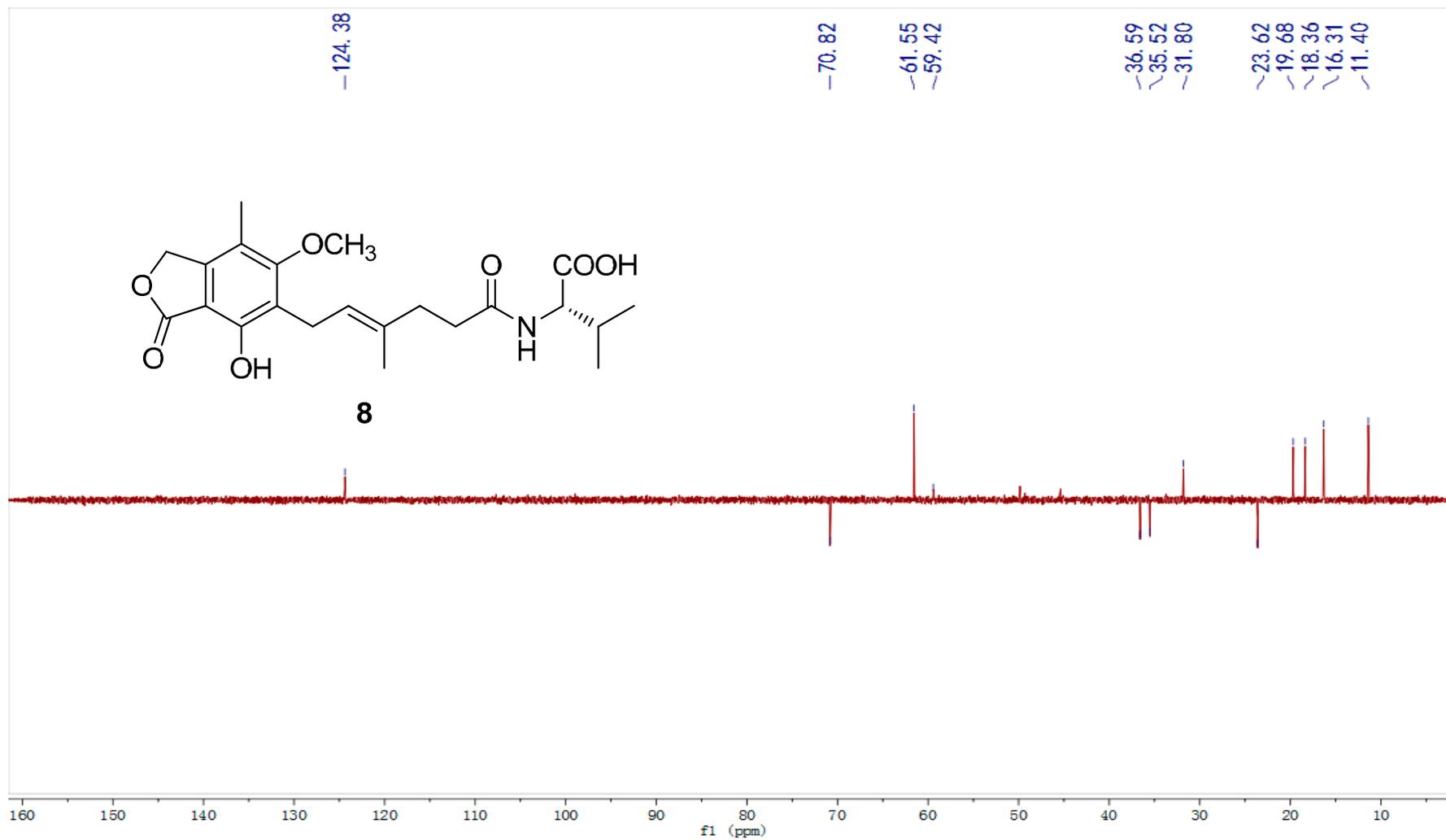


Figure S65. DEPT spectrum of compound 8 (Recorded in CD₃OD)

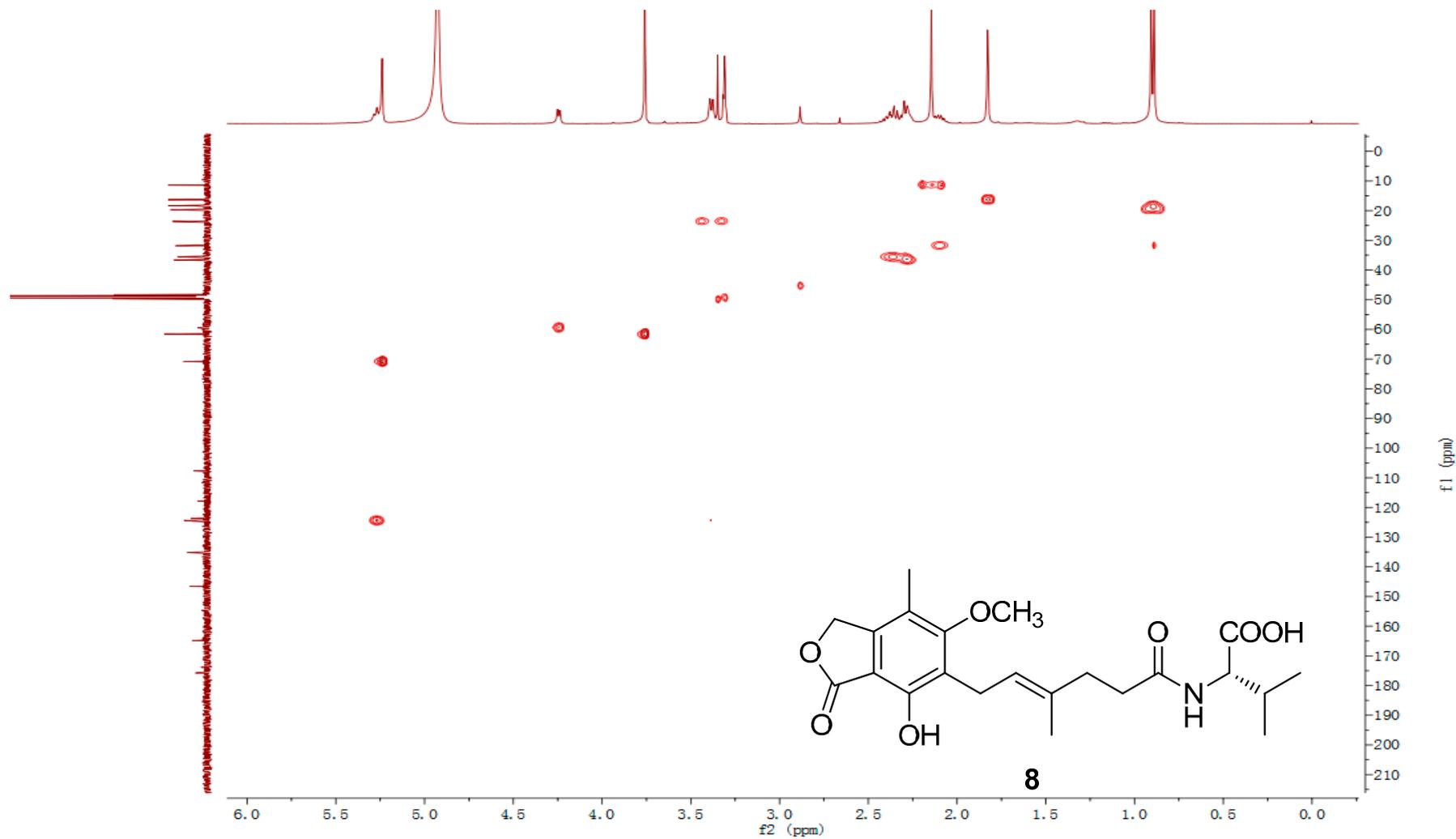
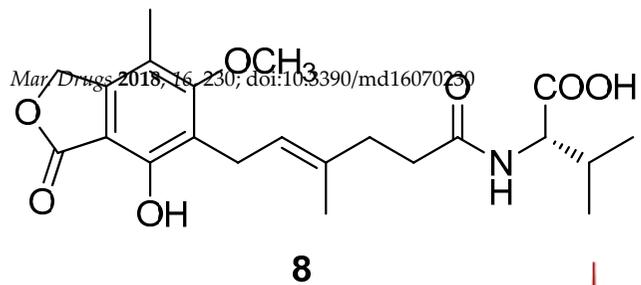


Figure S66. HSQC spectrum of compound 8 (Recorded in CD_3OD)



S71 of S98

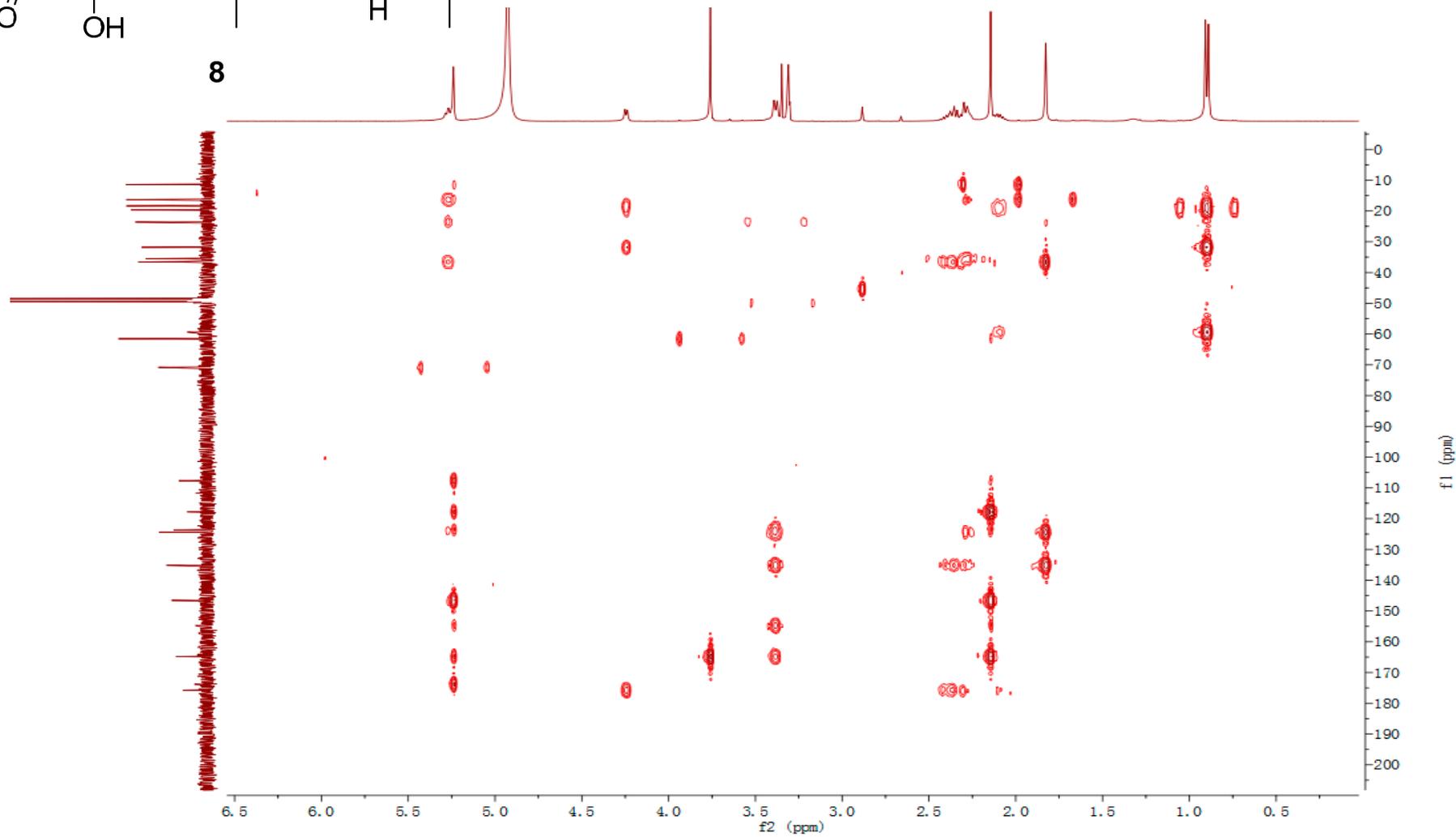
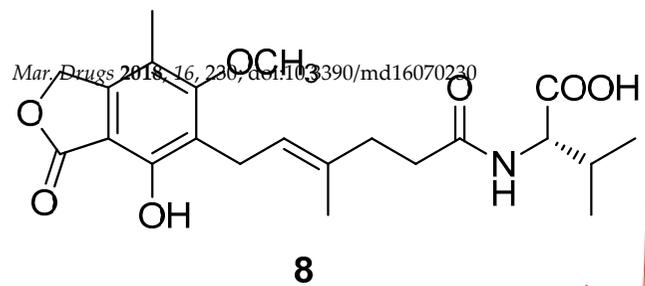


Figure S67. HMBC spectrum of compound **8** (Recorded in CD₃OD)



S72 of S98

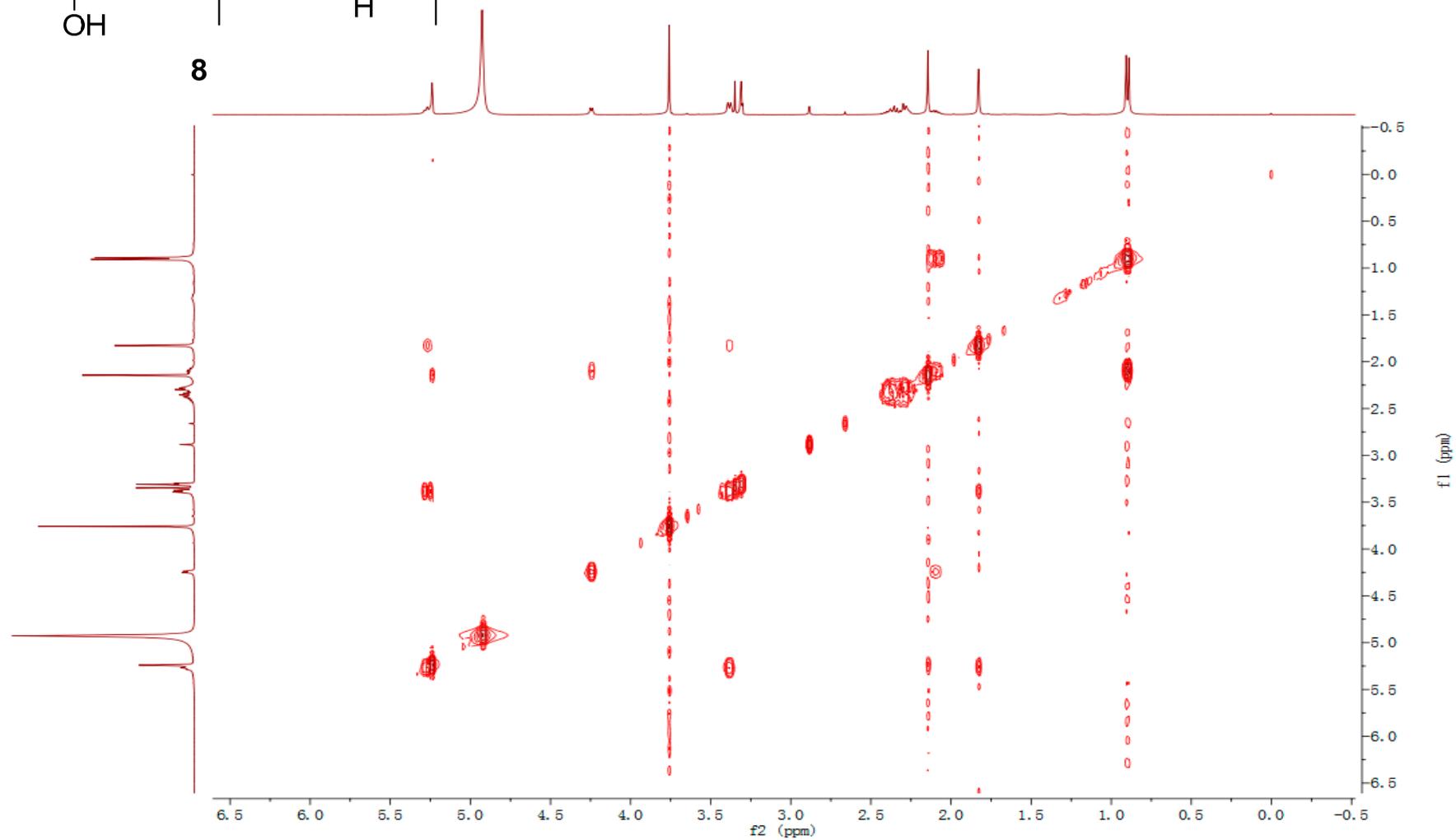


Figure S68. ^1H - ^1H COSY spectrum of compound **8** (Recorded in CD_3OD)

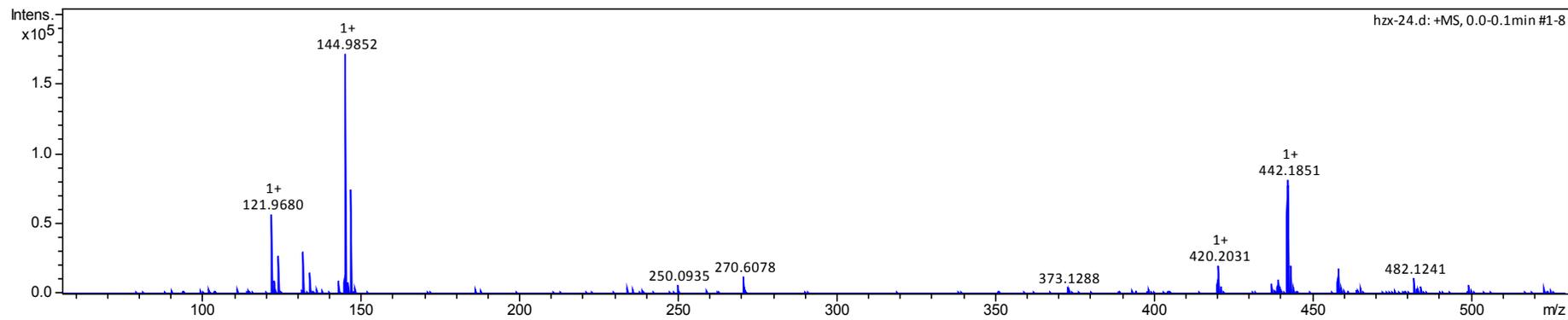
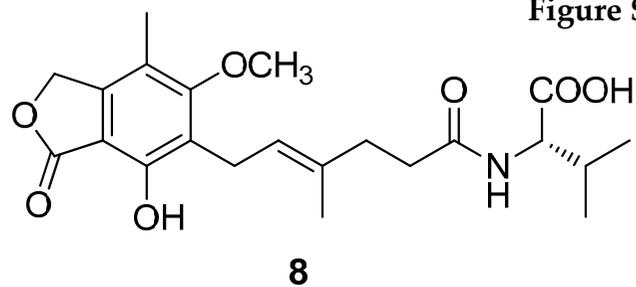


Figure S69. HRESIMS spectrum of compound 8



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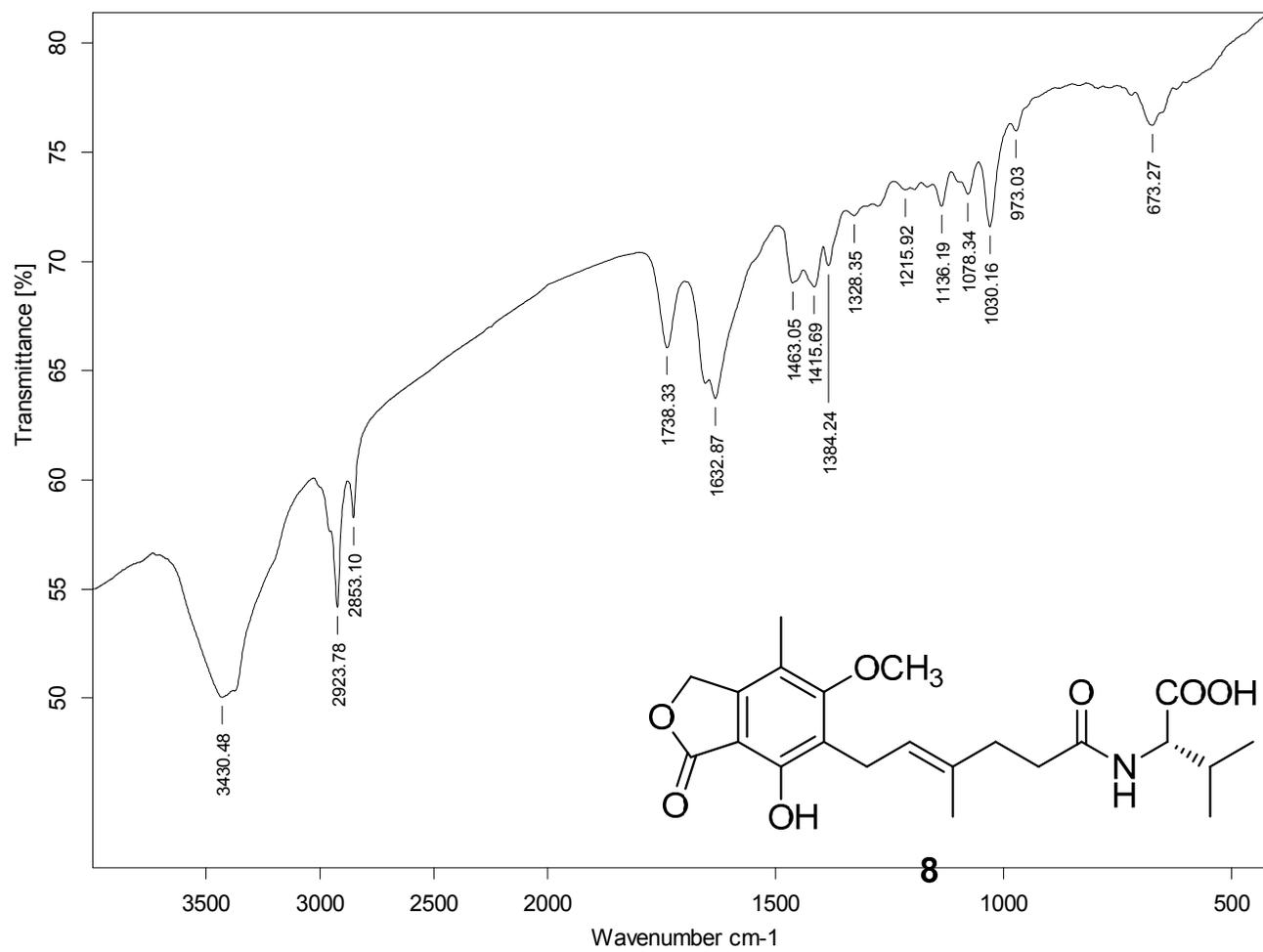


Figure S70. IR spectrum of compound 8

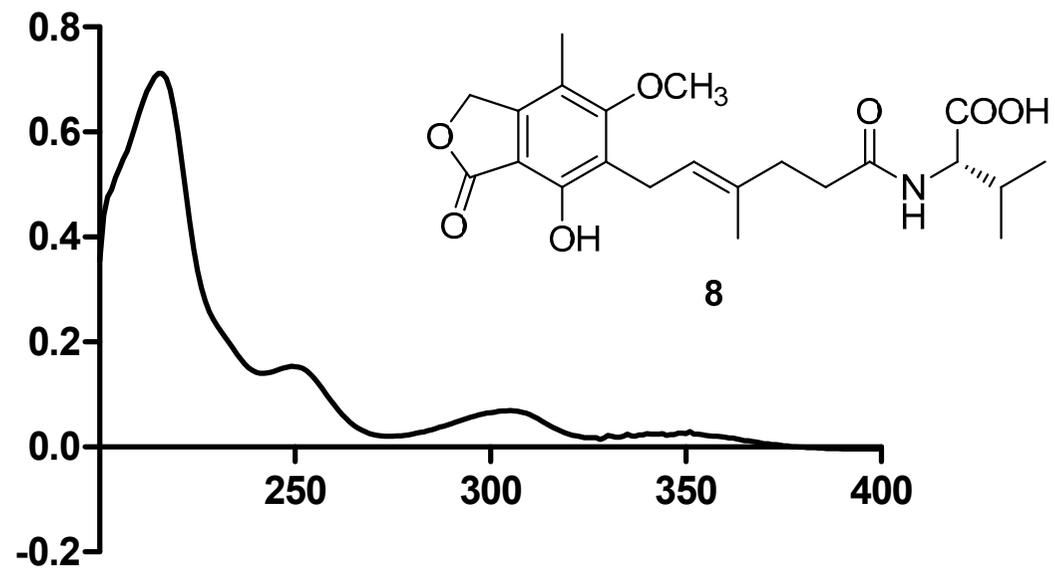


Figure S71. UV spectrum of compound 8

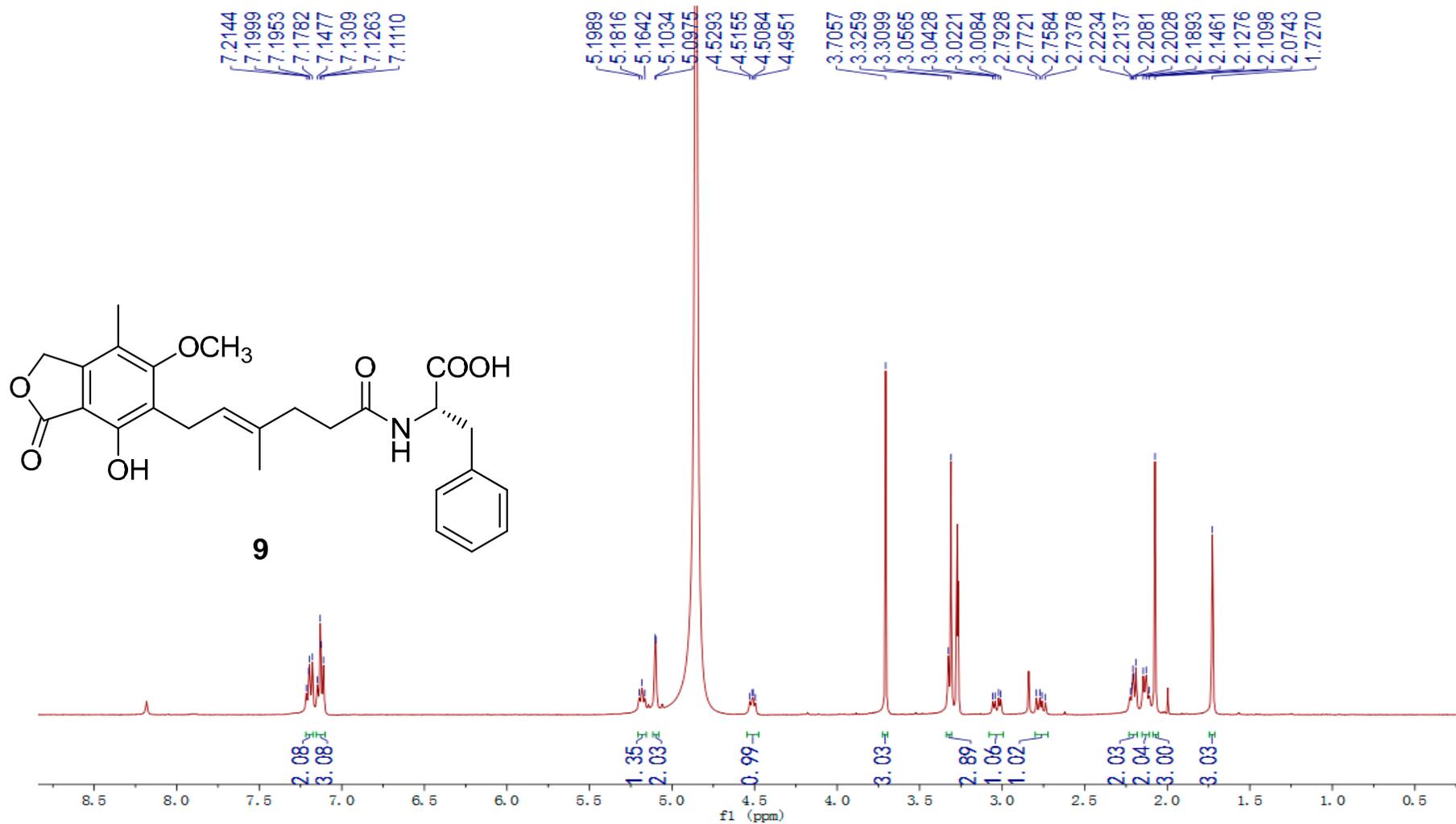


Figure S72. ¹H NMR spectrum of compound 9 (Recorded in CD₃OD)

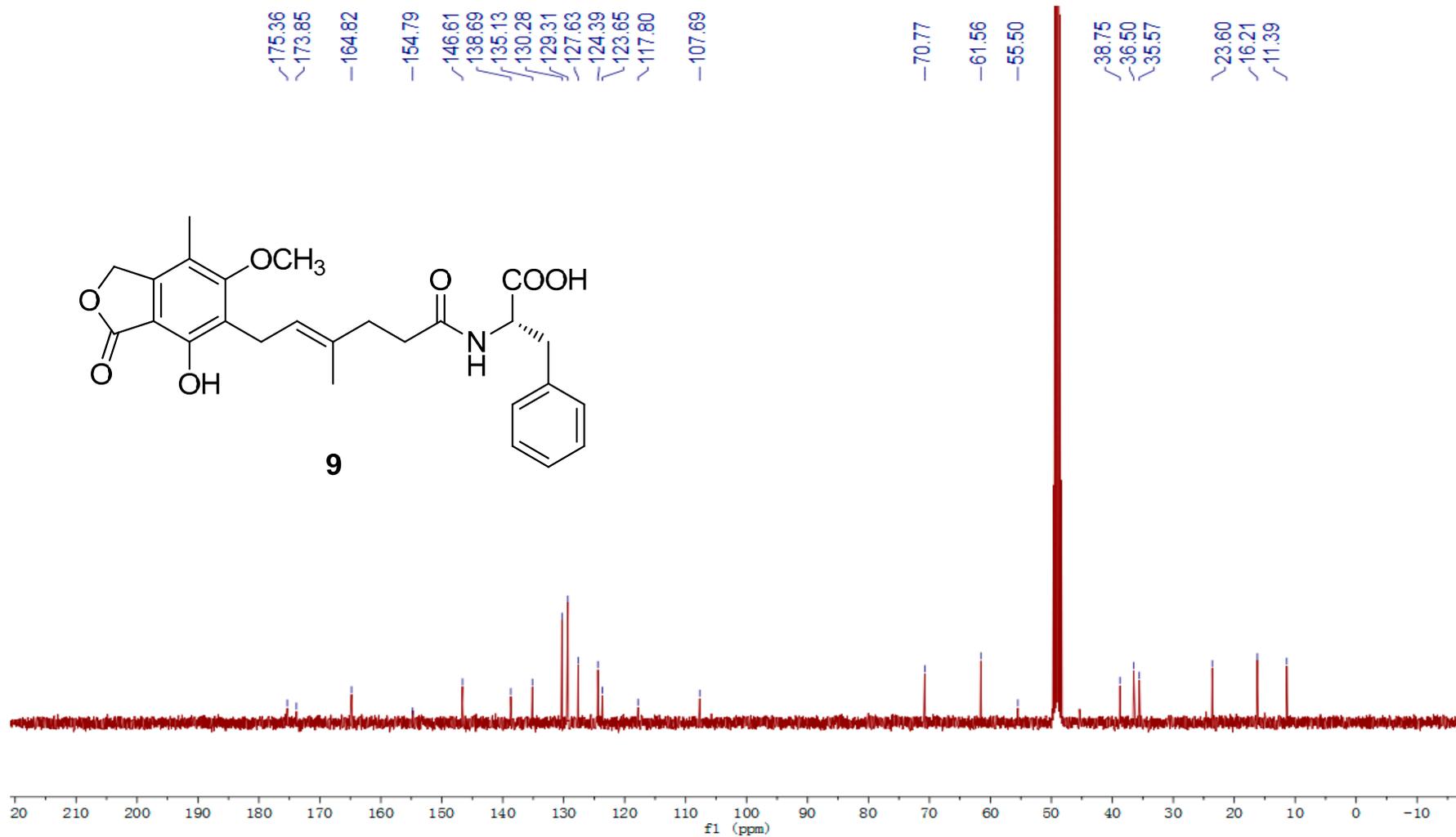


Figure S73. ¹³C NMR spectrum of compound 9 (Recorded in CD₃OD)

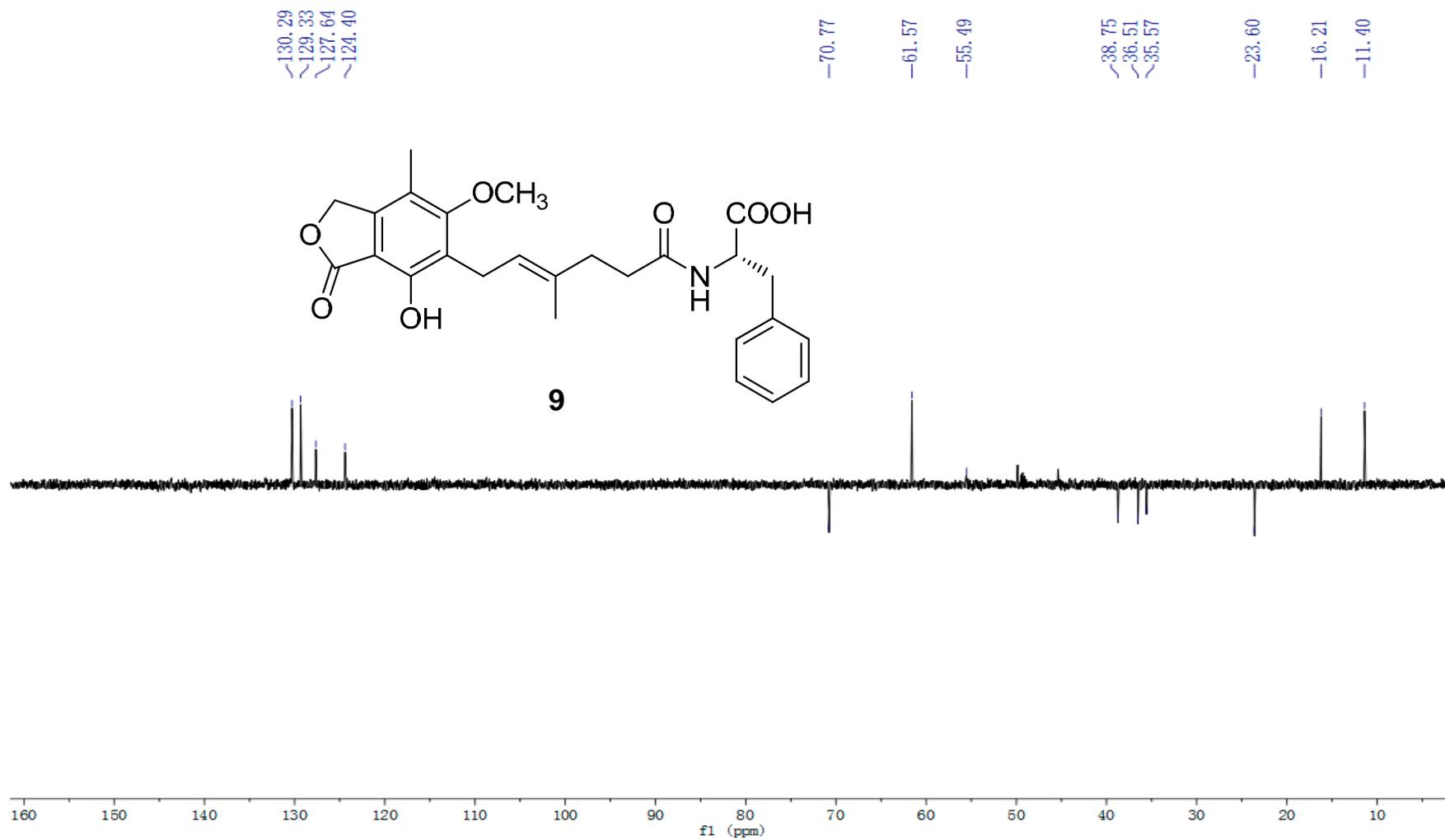


Figure S74. DEPT spectrum of compound 9 (Recorded in CD₃OD)

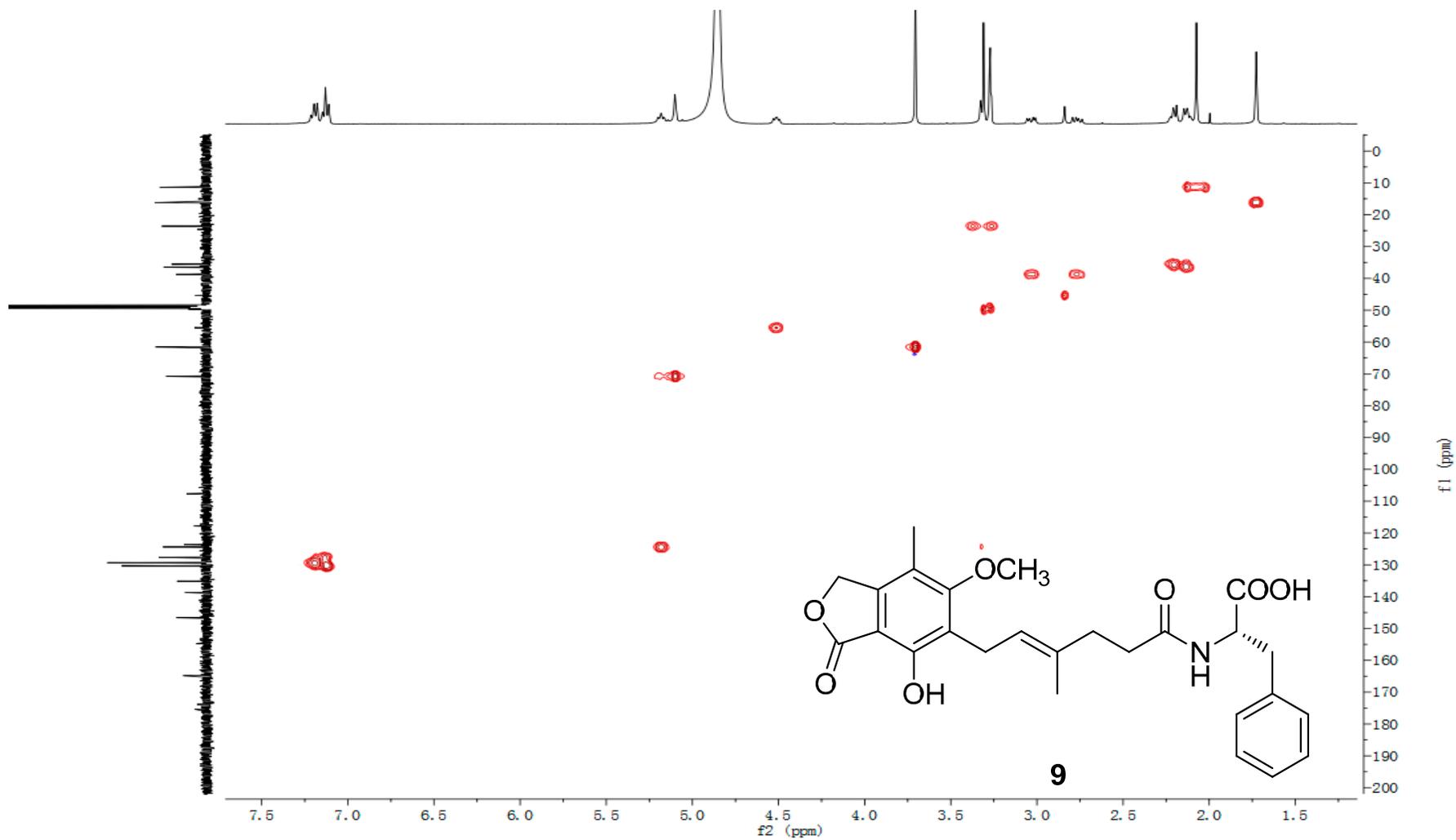
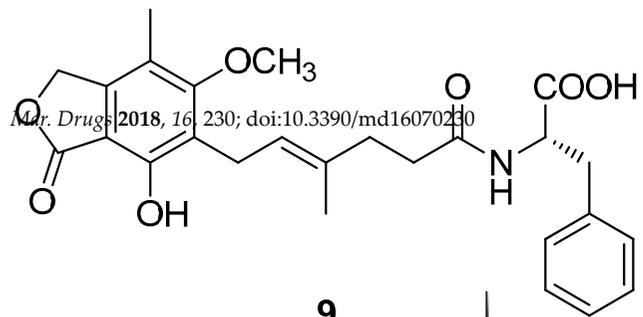


Figure S75. HSQC spectrum of compound 9 (Recorded in CD₃OD)



S80 of S98

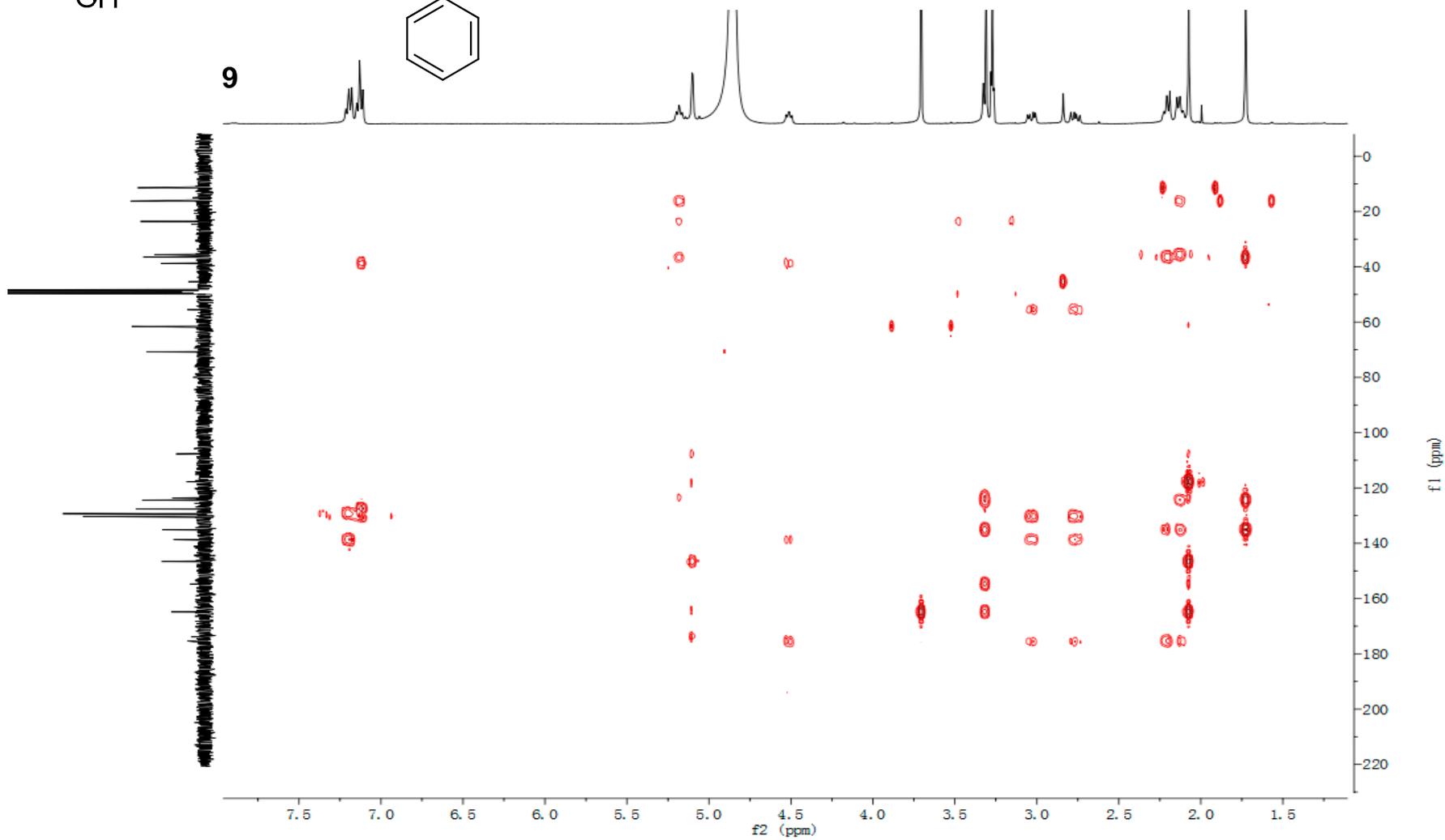
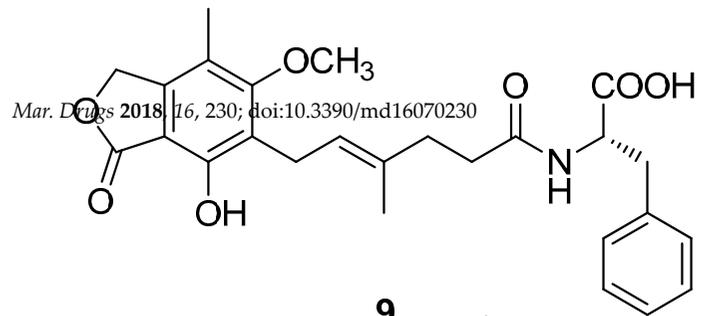


Figure S76. HMBC spectrum of compound 9 (Recorded in CD₃OD)



S81 of S98

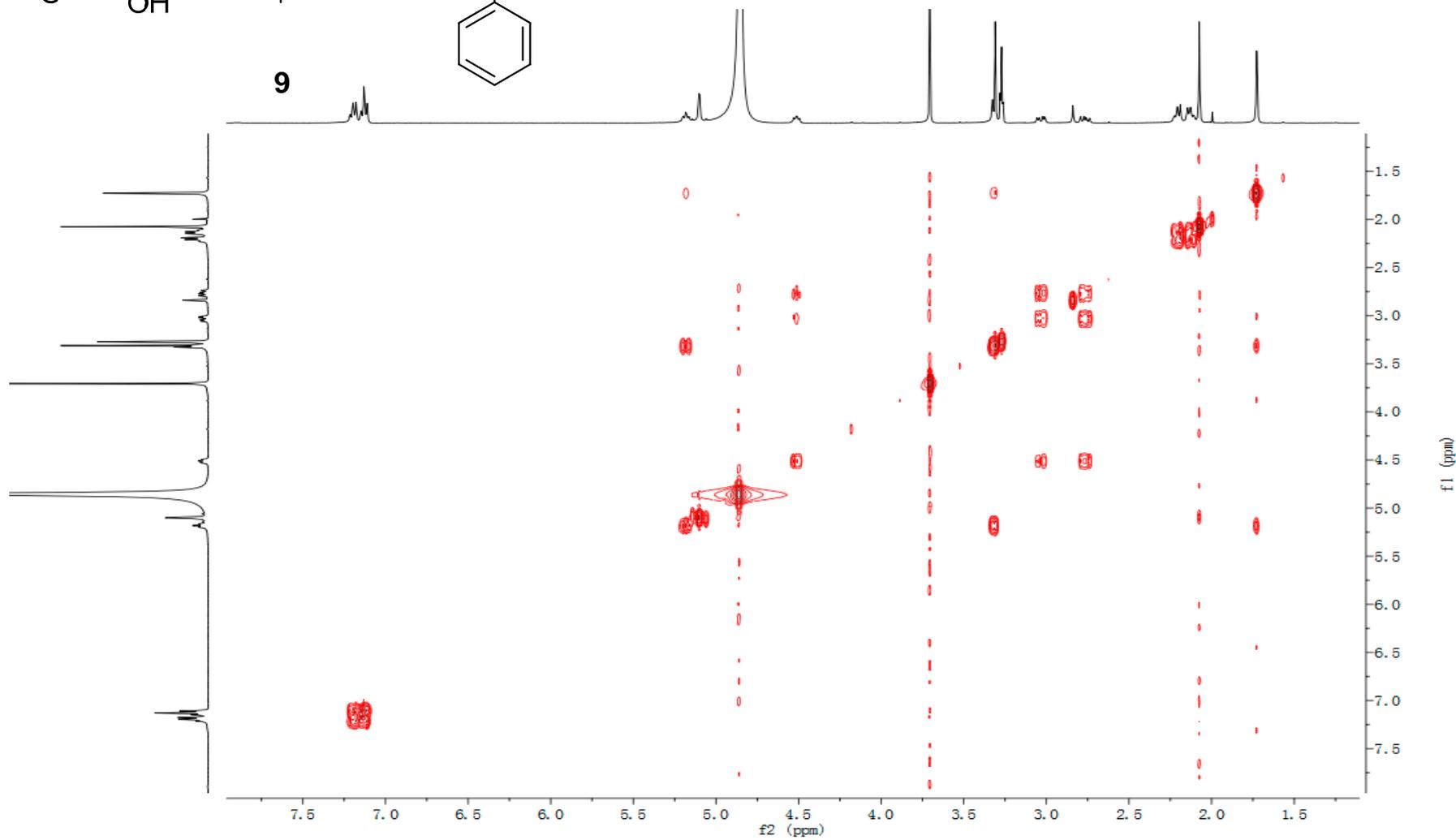


Figure S77. ^1H - ^1H COSY spectrum of compound 9 (Recorded in CD_3OD)

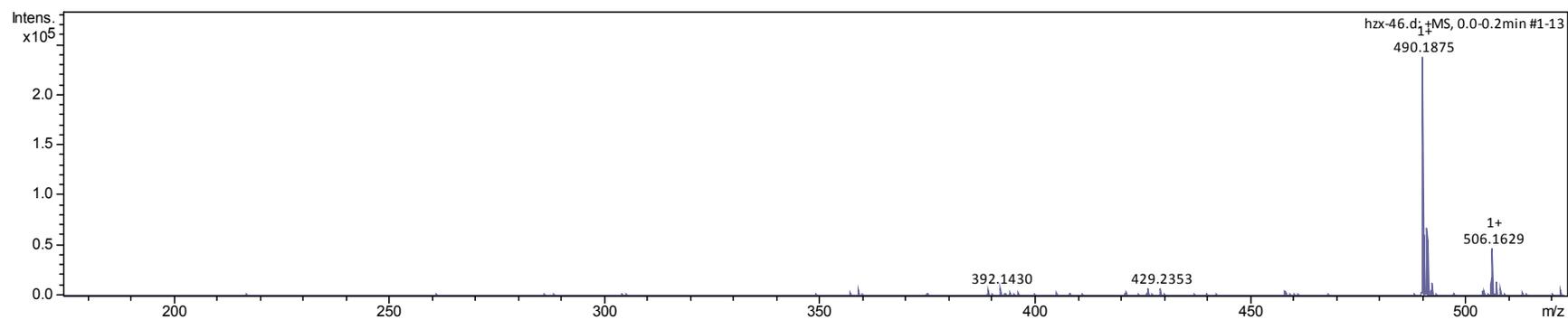
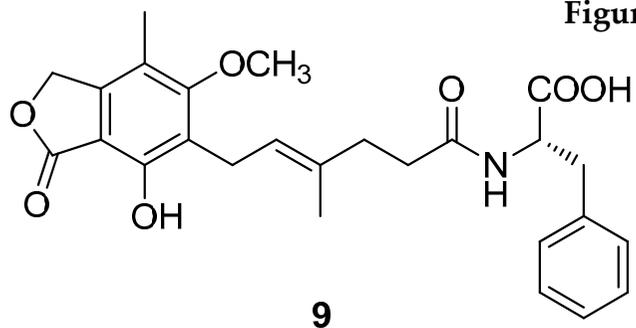


Figure S78. HRESIMS spectrum of compound 9



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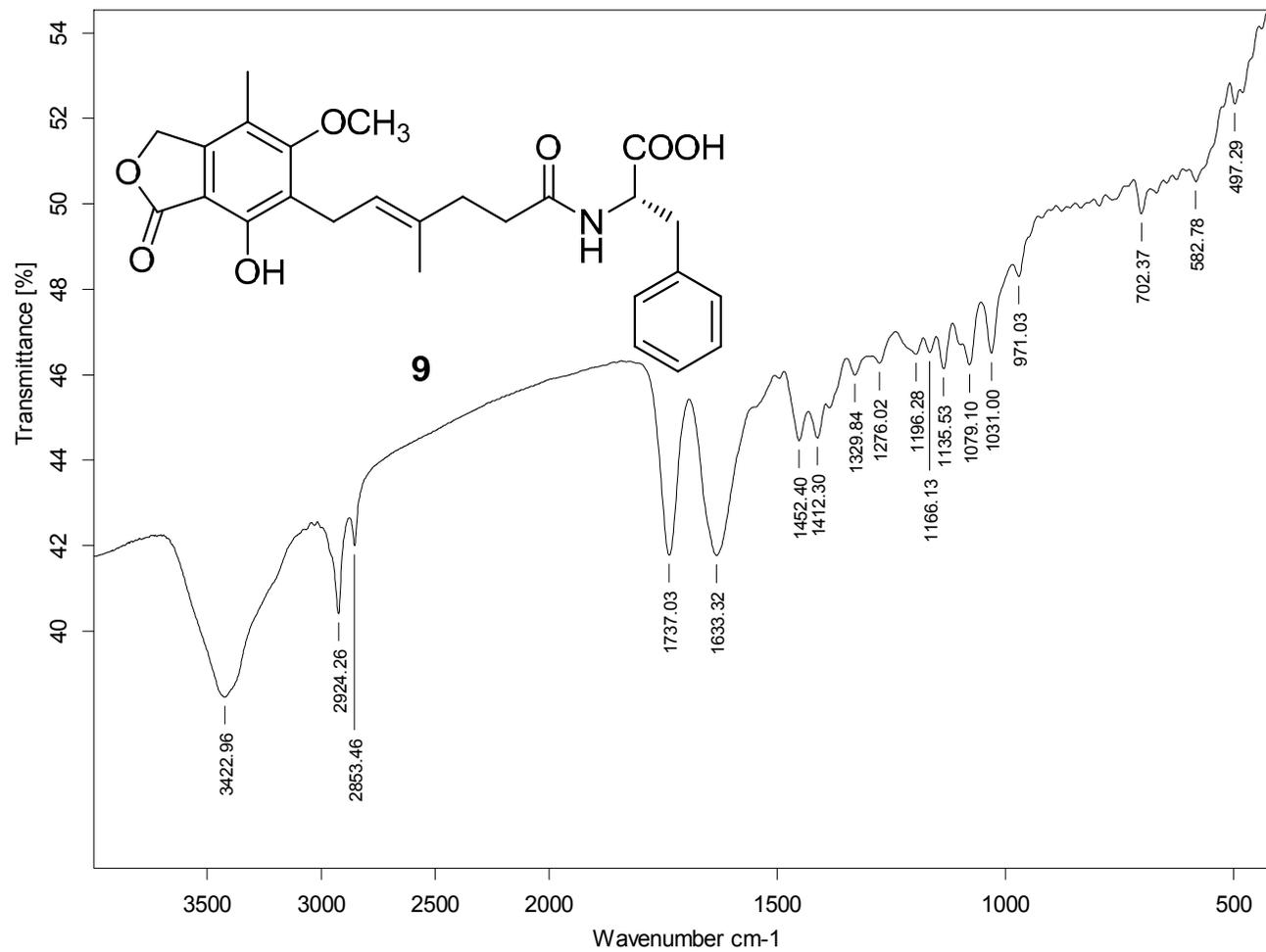


Figure S79. IR spectrum of compound 9

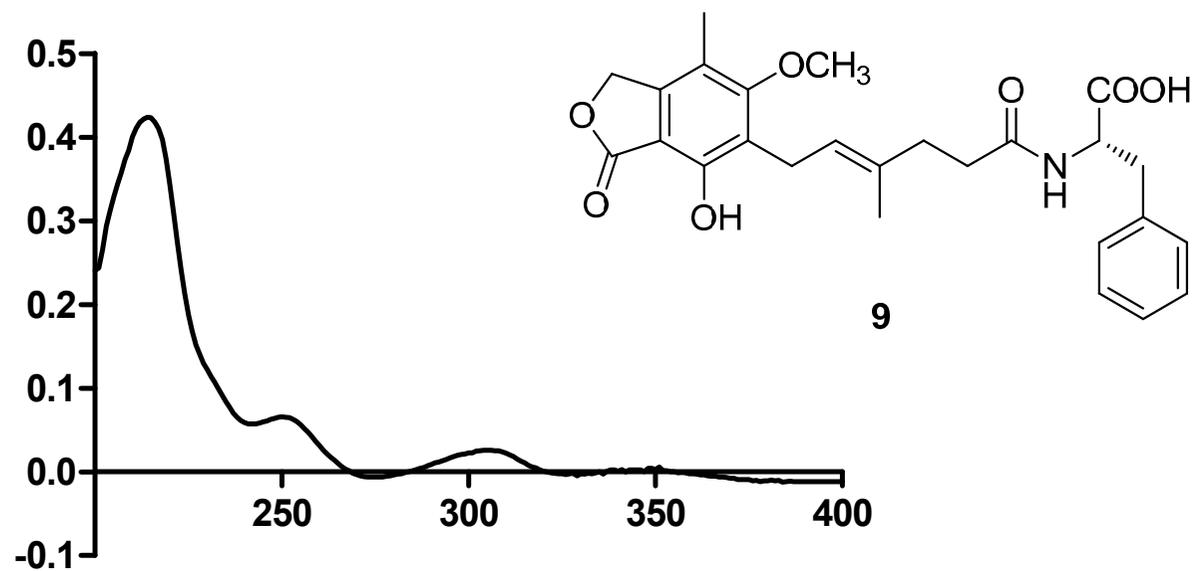


Figure S80. UV spectrum of compound 9

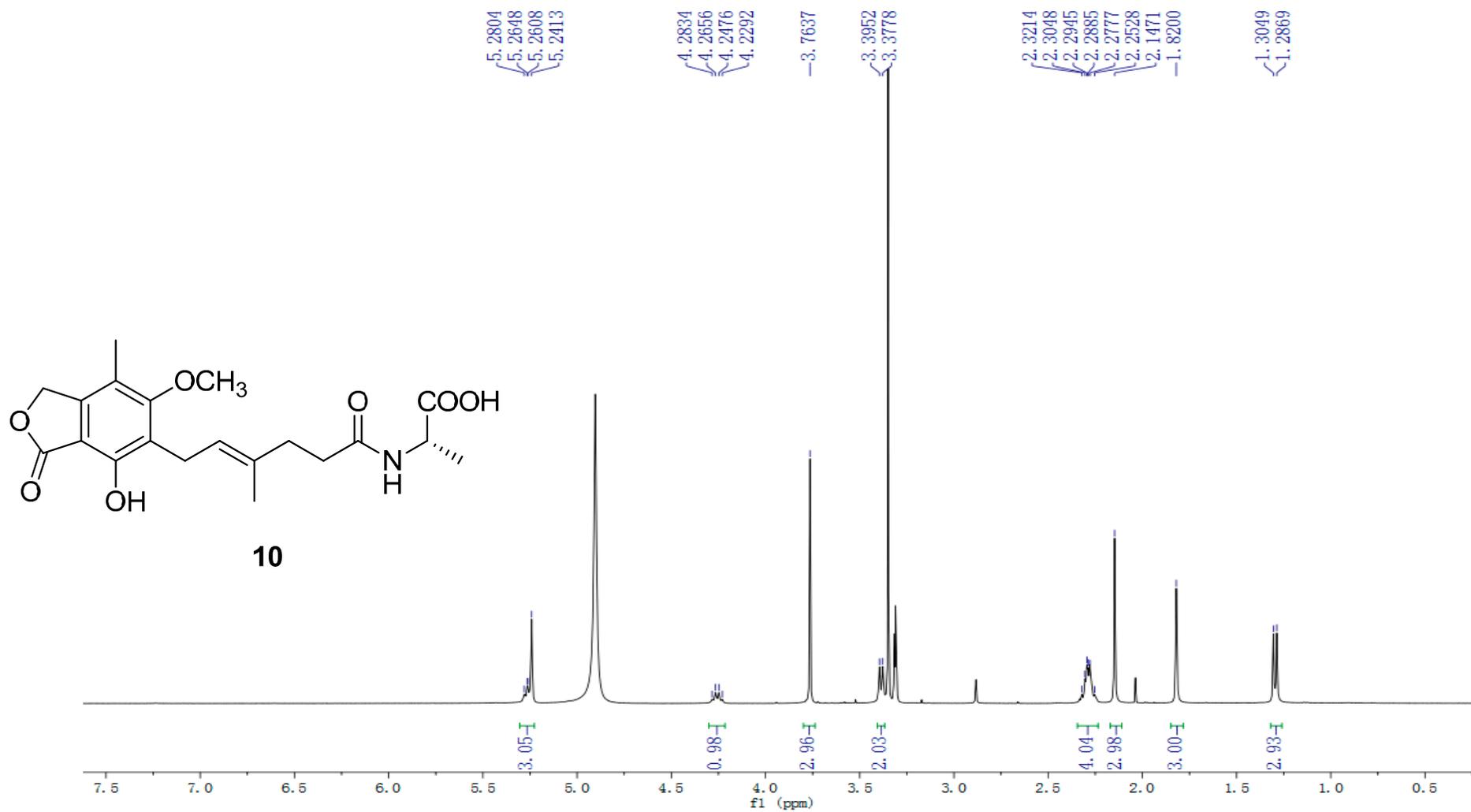


Figure S81. ¹H NMR spectrum of compound 10 (Recorded in CD₃OD)

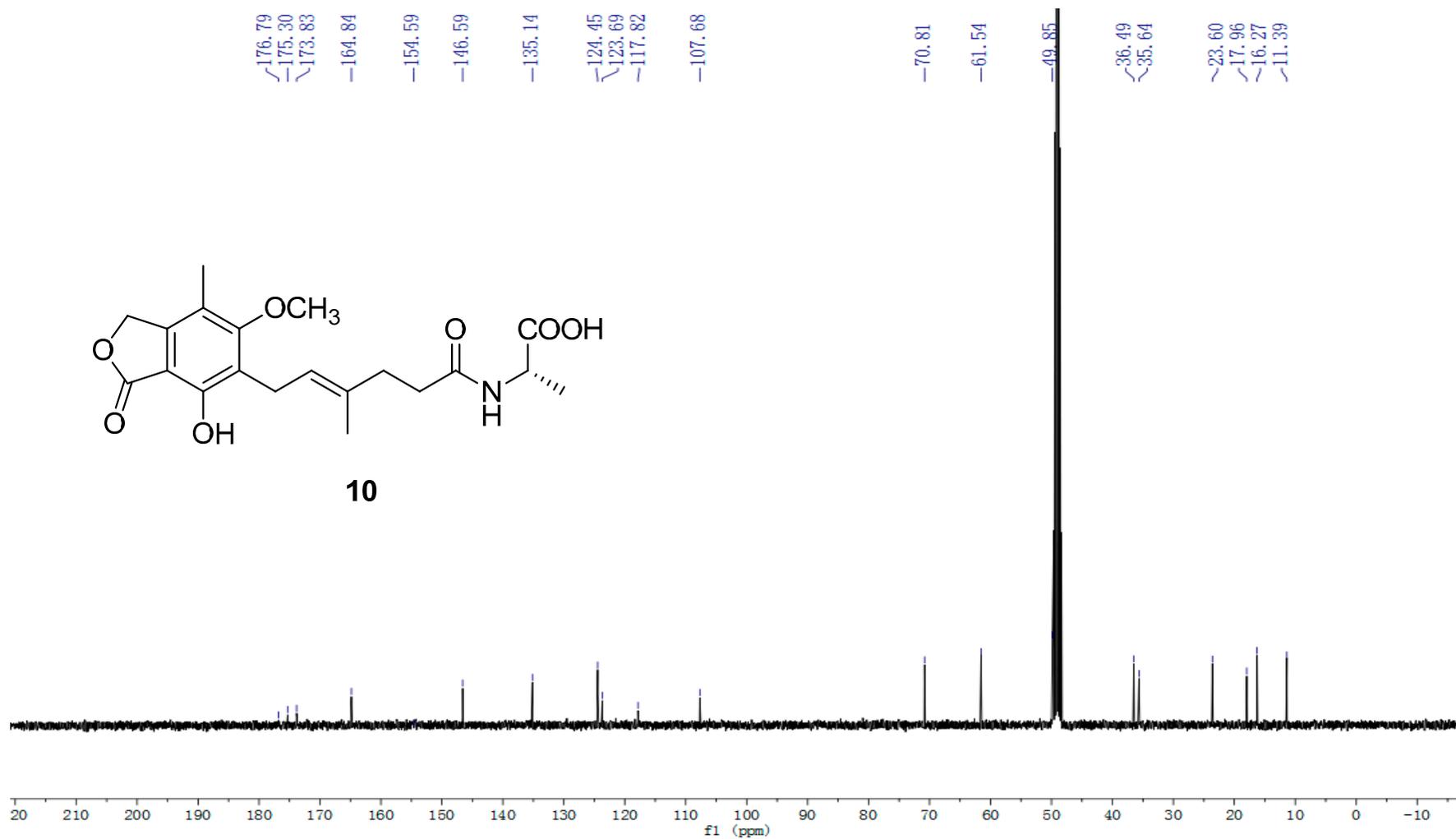


Figure S82. ¹³C NMR spectrum of compound 10 (Recorded in CD₃OD)

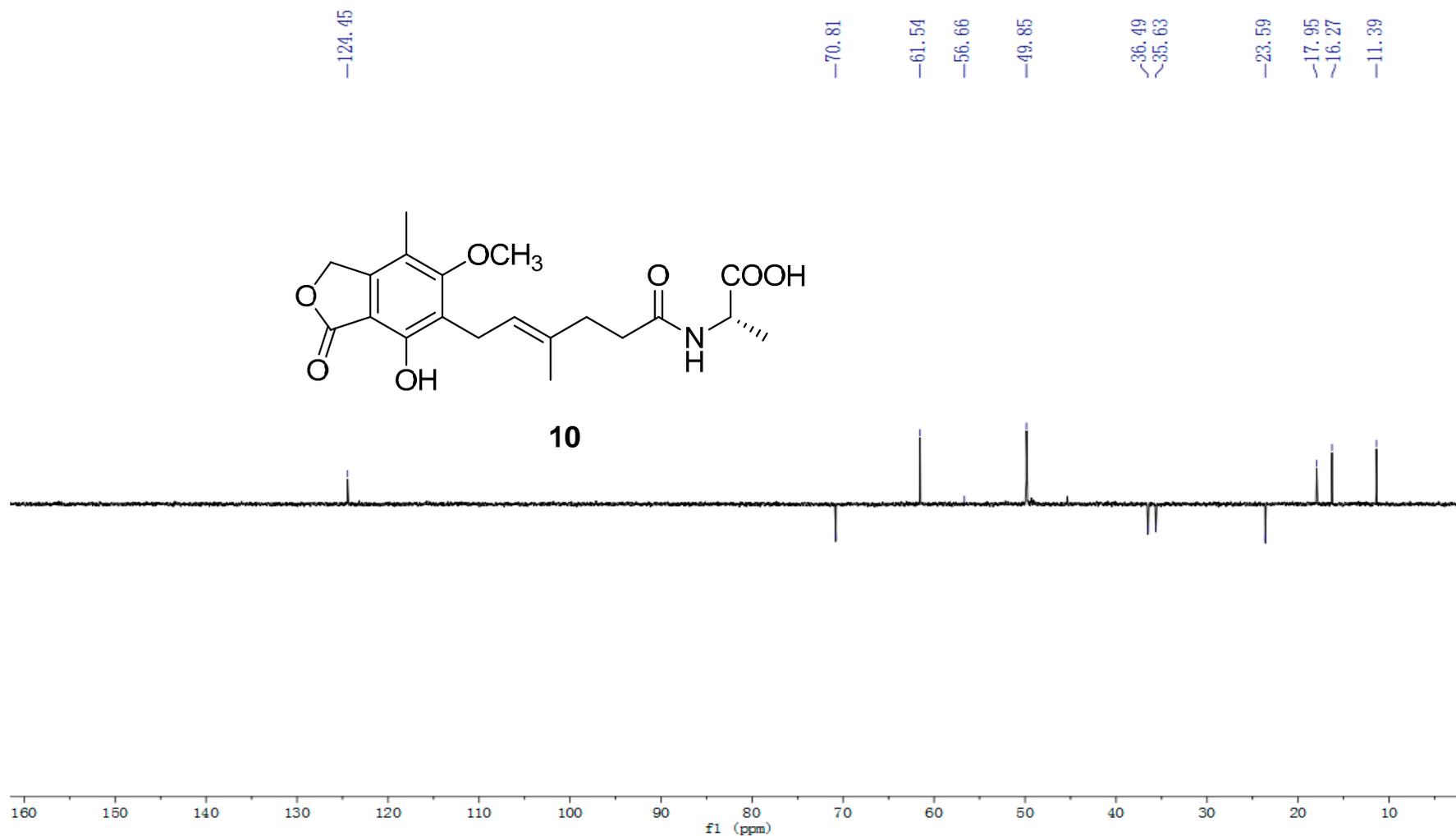


Figure S83. DEPT spectrum of compound 10 (Recorded in CD₃OD)

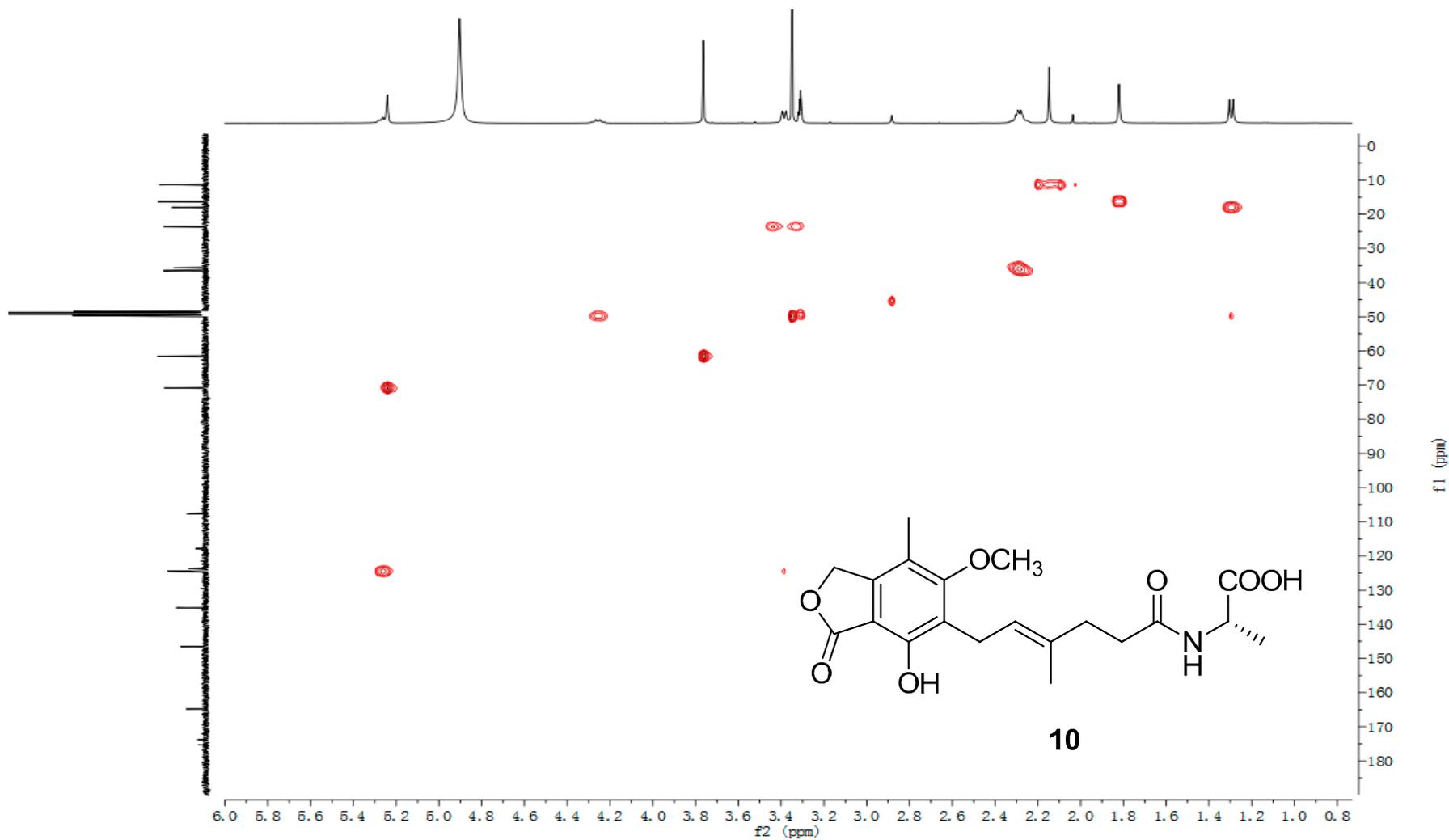


Figure S84. HSQC spectrum of compound 10 (Recorded in CD₃OD)

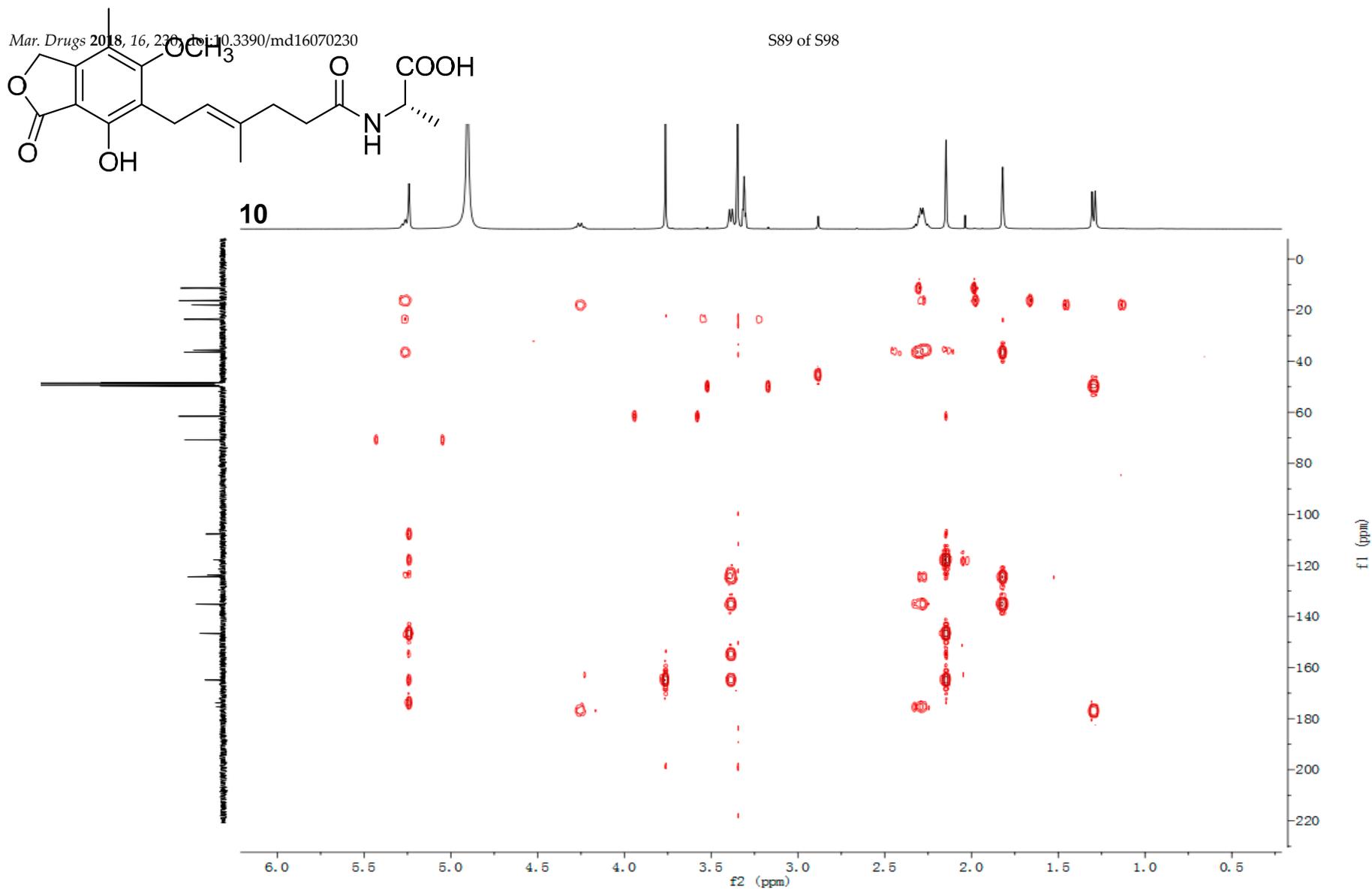
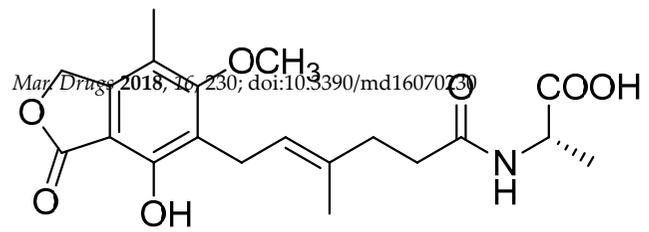


Figure S85. HMBC spectrum of compound 10 (Recorded in CD_3OD)



S90 of S98

10

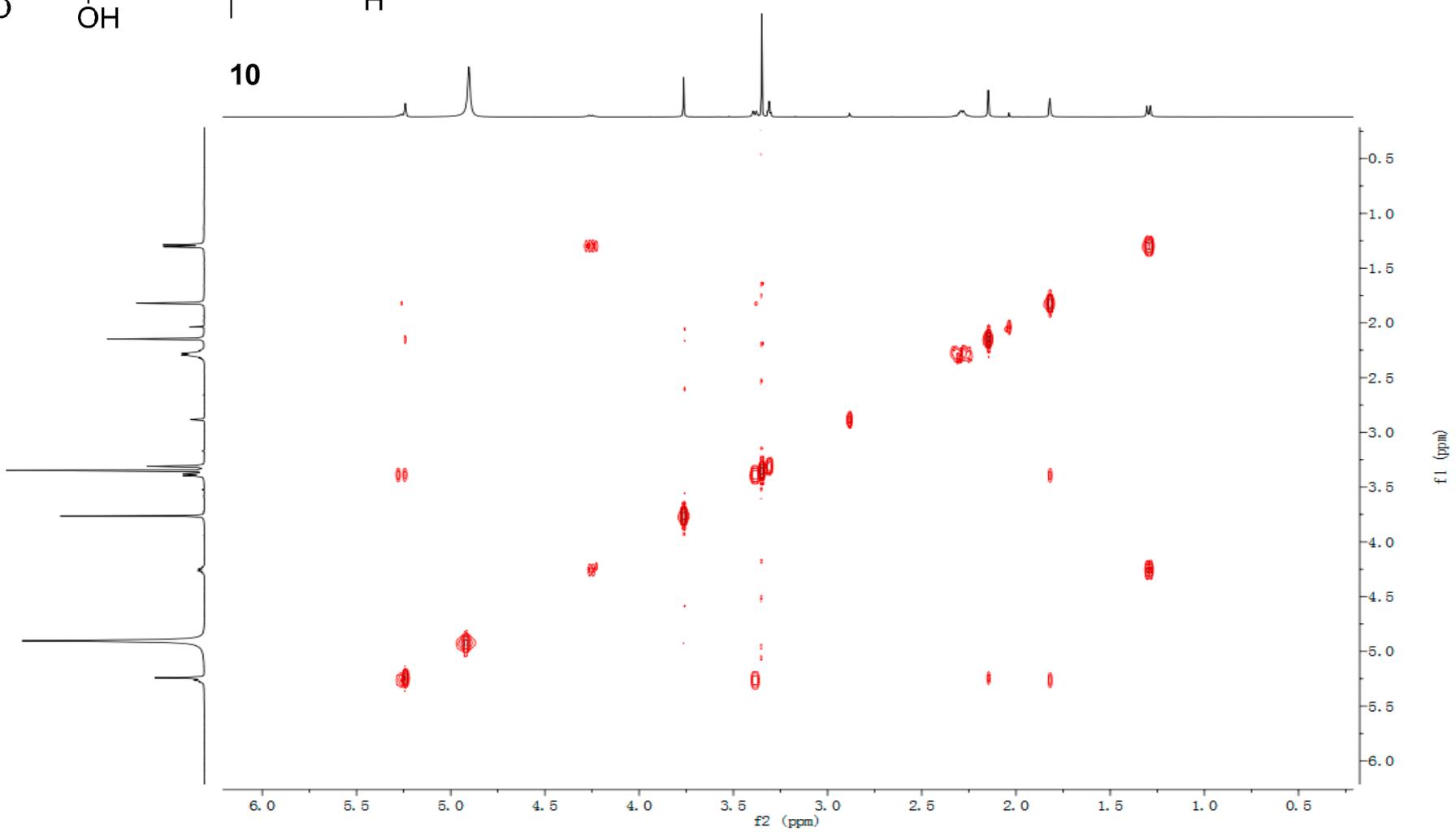


Figure S86. ^1H - ^1H COSY spectrum of compound 10 (Recorded in CD_3OD)

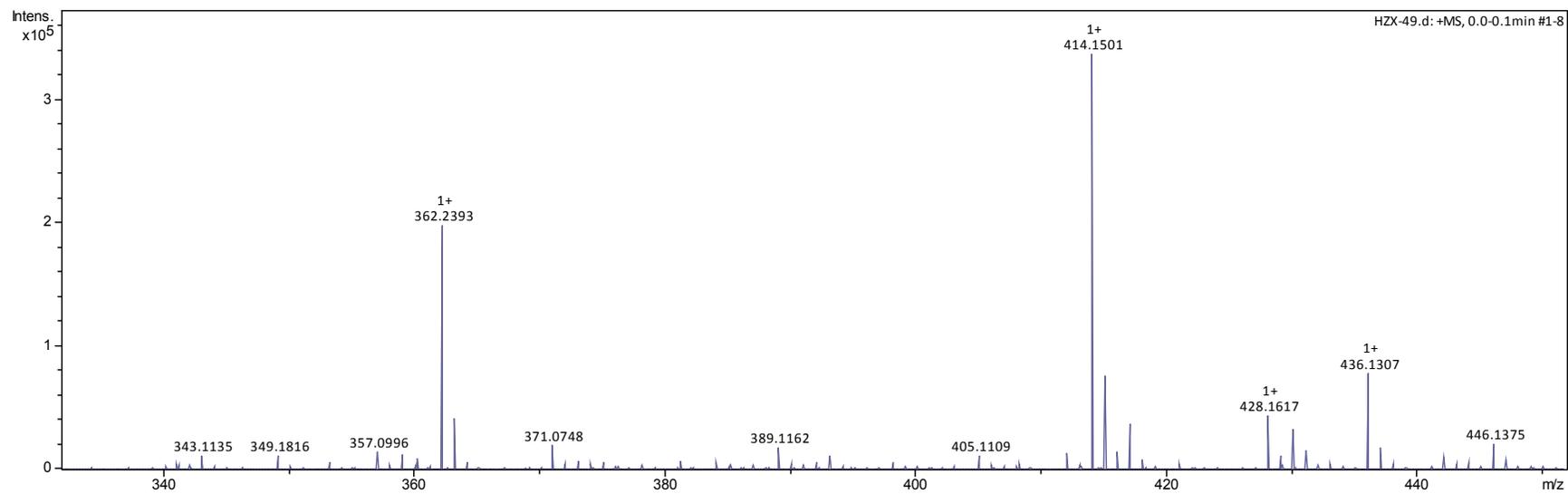
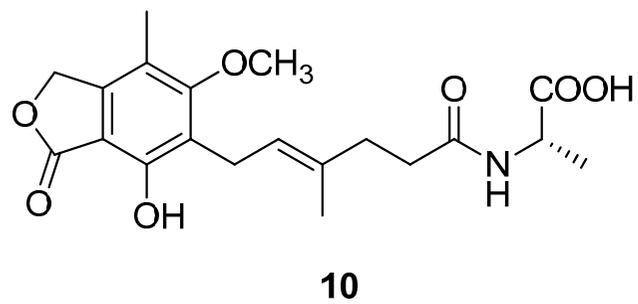


Figure S87. HRESIMS spectrum of compound 10



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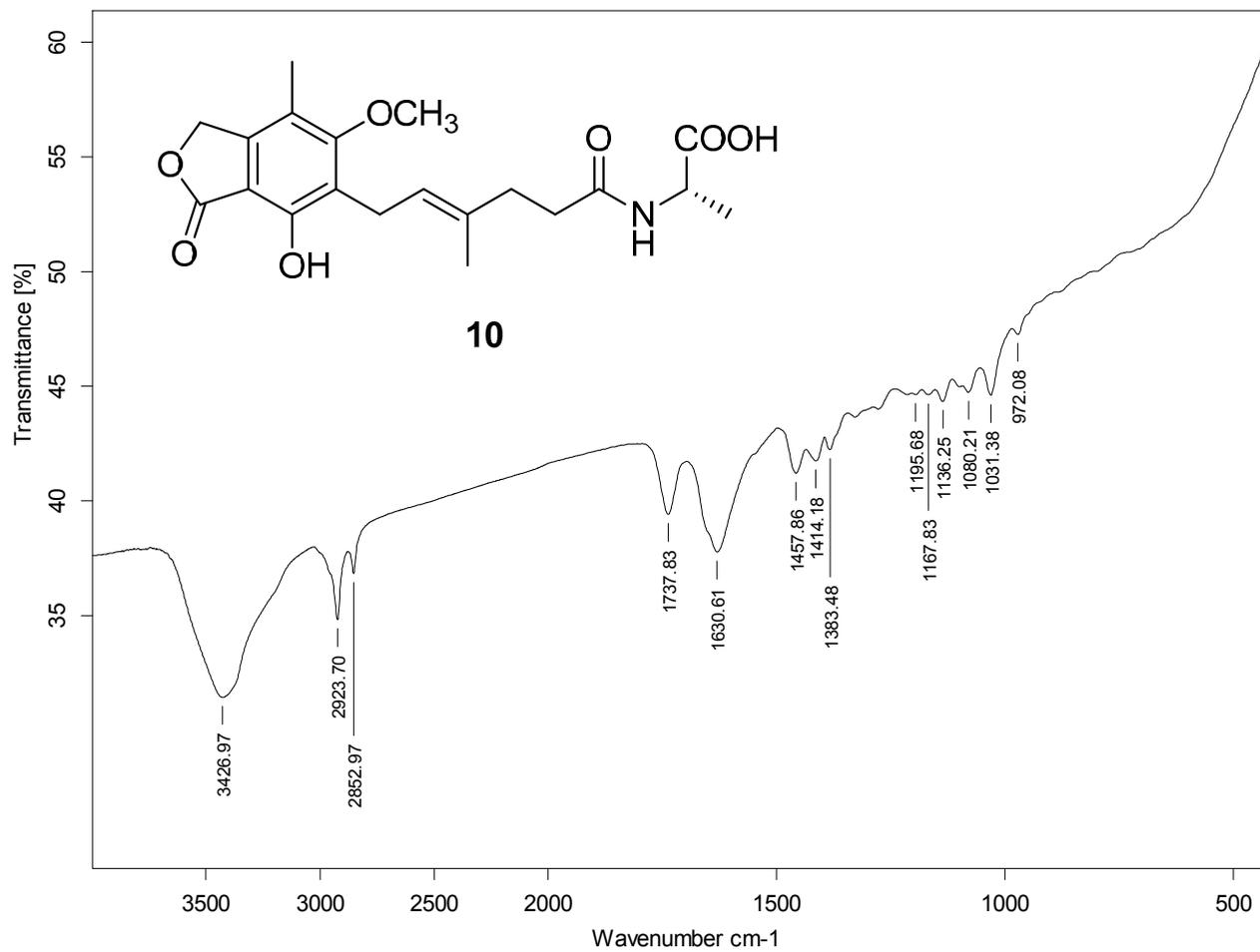


Figure S88. IR spectrum of compound 10

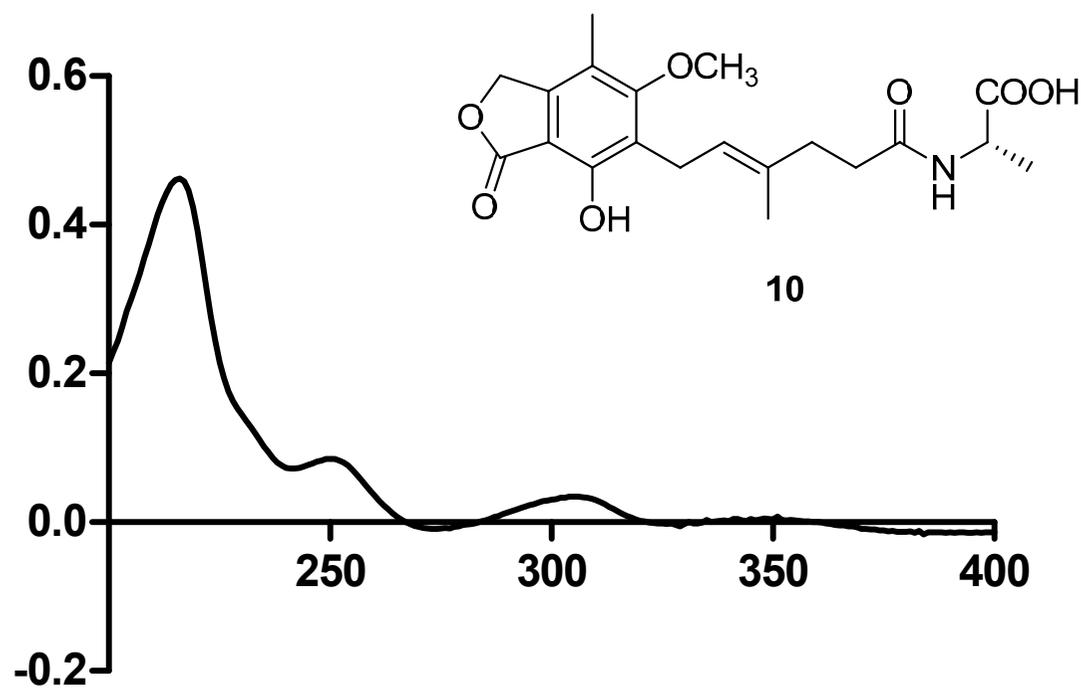


Figure S89. UV spectrum of compound 10

Structure elucidation of compounds 1, 2, and 8–10

Compound **1** was isolated as a white powder, and its molecular formula was assigned as $C_{18}H_{22}O_7$, based on the HRESIMS data at m/z 373.1259 ($[M + Na]^+$, calcd for 373.1263) and ^{13}C NMR data, requiring eight indices of hydrogen deficiency. Detailed analysis of the 1H and ^{13}C NMR data (Table S1) of **1** and **11** suggested that both compounds possessed the similar structural features, with the only difference that a methyl group at C-8 in **11** was replaced by a $-CH_2OCH_3$ group in **1**, as supported by the HMBC correlations from H-8 to C-3a (δ_c 147.2), C-4 (δ_c 119.1), C-5 (δ_c 164.5), and the methoxyl carbon (δ_c 58.7). Moreover, the planar structure was defined by the 2D NMR analysis, including HMBC and 1H - 1H COSY correlations. Thus, the structure of **1** was identified and named 8-*O*-methyl mycophenolic acid.

Compound **2** was also isolated as a white powder. Its molecular formula $C_{17}H_{20}O_7$ was determined by the HRESIMS m/z 359.1092 $[M + Na]^+$ (calcd for $C_{17}H_{20}O_7Na$, 359.1107). The 1H and ^{13}C NMR data (Table S1) showed high similarity to those of **11**, differing in that the C-3 methylene in **11** was hydroxylated in **2**, as verified by its molecular formula and the chemical shift values of CH-3 (δ_H 6.58; δ_c 100.2). This conclusion was further confirmed by the HMBC correlations from H-3 to C-1 (δ_c 171.6), C-3a (δ_c 145.7), C-4 (δ_c 120.3), and C-7a (δ_c 108.7). Compound **2** was optically inactive and no apparent Cotton effects were observed in its experimental CD spectrum despite the presence of an α,β -unsaturated carbonyl chromophore, suggesting that it was a racemic mixture. Moreover, an attempt to separate the two enantiomers was failed. Thus, the structure of **2** was defined and named 3-hydroxy mycophenolic acid.

Compound **8** was determined to have the molecular formula $C_{22}H_{29}NO_7$, according to its HRESIMS m/z 442.1851 $[M + Na]^+$ (calcd for $C_{22}H_{29}NO_7Na$, 442.1842). The 1H and ^{13}C NMR data (Table S2) were similar to those of **11**, except for the presence the valine residue which formed an amide bond with C-6', as supported by the COSY correlations from H-2'' (δ_H 4.24) to H-4'' (δ_H 2.10) and from H-4'' to H-5'' (δ_H 0.90) and H-6'' (δ_H 0.90) and HMBC correlations from H-2'' to C-6' and C-3'' and from H-4'' to C-3''. The specific rotation of **8** $\{[\alpha]_D^{23}: +5.3$ (c 0.08, MeOH) $\}$ was dextrorotatory, the same to that of the synthetic product *N*-mycophenoyl-*L*-valine $\{[\alpha]_D^{25}: +2.0$ (c 1, acetone) $\}$ [1], suggesting the presence of a *L*-valine in **8**. Thus, the structure of **8** was identified as *N*-mycophenoyl-*L*-valine.

Compounds **9** and **10** were also identified as the natural mycophenolic acid-amino acid conjugates. And their molecular formulas were determined to be $C_{26}H_{29}NO_7$ and $C_{20}H_{25}NO_7$, respectively, based on the HRESIMS analysis as well as ^{13}C NMR data. Detailed analysis of the 1D and 2D NMR data (Table S2) of **9** and **10** with those of **8** revealed the obvious differences that **9** had a phenylalanine amide unit and **10** had an alanine amide unit, as supported by the key 2D NMR analysis. Compound **9** was measured with a specific rotation, $[\alpha]_D^{23}: +2.5$ (c 0.1, MeOH), which was identical to that of the synthetic product *N*-mycophenoyl-*L*-phenylalanine $\{[\alpha]_D^{25}: +2.0$ (c 1, MeOH) $\}$ [1], suggesting the presence of a *L*-phenylalanine amide unit

in **9**. Similarly, comparing the specific rotation of **10** $\{[\alpha]_D^{25}: -6.4 (c 0.08, \text{MeOH})\}$ with that of the synthetic product *N*-mycophenoyl-L-alanine $\{[\alpha]_D^{25}: -2.0 (c 1, \text{acetone})\}$ [1], the similar negative values indicated the presence of a L-alanine amide unit in **10**. Thus, the structures of **9** and **10** were defined and named *N*-mycophenoyl-L-phenylalanine and *N*-mycophenoyl-L-alanine, respectively.

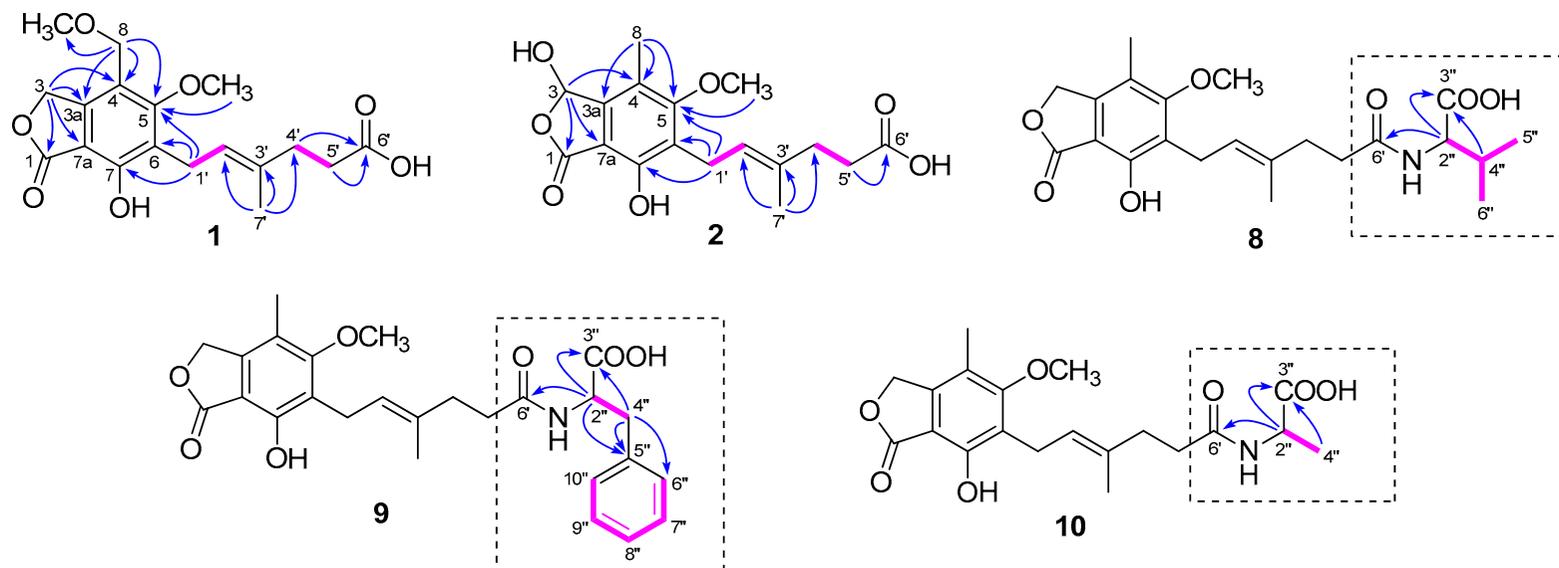


Figure S90. Key ^1H - ^1H COSY (pink lines) and HMBC (blue arrows) correlations of **1**-**2** and **8**-**10**.

Ref: [1] Iwaszkiewicz-Grzes, D.; Cholewinski, G.; Kot-Wasik, A.; Trzonkowski, P.; Dzierzbicka, K. Synthesis and biological activity of mycophenolic acid-amino acid derivatives. *Eur. J. Med. Chem.* **2013**, *69*, 863–871.

The physical and chemical constants of compounds 1, 2, and 8–10

8-O-Methyl mycophenolic acid (1): white powder; UV (MeOH) λ_{\max} (log ϵ): 219 (4.57), 253 (3.81), and 305 (3.51) nm; IR (ν_{\max}): 3424, 2924, 2853, 1738, 1618, 1453, 1421, 1381, 1273, 1109, 1028, 969, 674 cm^{-1} ; HRESIMS m/z 373.1259 [M + Na]⁺ (calcd for C₁₈H₂₂O₇Na, 373.1263); ¹H and ¹³C NMR data, see Table S1.

3-Hydroxy mycophenolic acid (2): white powder; $[\alpha]_{\text{D}}^{23}$: 0 (*c* 0.15, MeOH); UV (MeOH) λ_{\max} (log ϵ): 218 (4.41), 251 (3.73), and 311 (3.56) nm; IR (ν_{\max}): 3436, 2947, 1737, 1626, 1460, 1408, 1276, 1138, 1092, 1024, 595 cm^{-1} ; HRESIMS m/z 359.1092 [M + Na]⁺ (calcd for C₁₇H₂₀O₇Na, 359.1107); ¹H and ¹³C NMR data, see Table S1.

N-Mycophenoyl-L-valine (8): white powder; $[\alpha]_{\text{D}}^{23}$: +5.3 (*c* 0.08, MeOH); UV (MeOH) λ_{\max} (log ϵ): 217 (4.24), 251 (3.49), and 307 (3.16) nm; IR (ν_{\max}): 3430, 2924, 2853, 1738, 1633, 1463, 1416, 1384, 1136, 1078, 1030, 973, 673 cm^{-1} ; HRESIMS m/z 442.1851 [M + Na]⁺ (calcd for C₂₂H₂₉NO₇Na, 442.1842); ¹H and ¹³C NMR data, see Table S2.

N-Mycophenoyl-L-phenyloalanine (9): white powder; $[\alpha]_{\text{D}}^{23}$: +2.5 (*c* 0.1, MeOH); UV (MeOH) λ_{\max} (log ϵ): 215 (4.39), 253 (3.64), and 308 (3.17) nm; IR (ν_{\max}): 3423, 2924, 2853, 1737, 1633, 1452, 1412, 1330, 1136, 1079, 1031, 971, 702, 583 cm^{-1} ; HRESIMS m/z 490.1875 [M + Na]⁺ (calcd for C₂₆H₂₉NO₇Na, 490.1842); ¹H and ¹³C NMR data, see Table S2.

N-Mycophenoyl-L-alanine (10): white powder, $[\alpha]_{\text{D}}^{23}$: -6.4 (*c* 0.08, MeOH); UV (MeOH) λ_{\max} (log ϵ): 218 (4.29), 253 (3.58), and 307 (3.16) nm; IR (ν_{\max}): 3427, 2924, 2853, 1738, 1631, 1458, 1414, 1383, 1136, 1080, 1031, 972 cm^{-1} ; HRESIMS m/z 414.1501 [M + Na]⁺ (calcd for C₂₀H₂₅NO₇Na, 414.1529); ¹H and ¹³C NMR data, see Table S2.

¹H and ¹³C NMR data for compounds 1, 2, and 8–10

Table S1. ¹H and ¹³C NMR data for 1 and 2 in CD₃OD (δ in ppm, J in Hz).

No.	1		2	
	$\delta_{\text{H}}^{a,b}$	δ_{C}^c	$\delta_{\text{H}}^{a,b}$	δ_{C}^c
1	-	173.6 CO	-	171.6 CO
3	5.33 (2H, s)	71.4 CH ₂	6.58 (1H, s)	100.2 CH
3a	-	147.2 C	-	145.7 C
4	-	119.1 C	-	120.3 C
5	-	164.5 C	-	165.2 C
6	-	123.8 C	-	125.5 C
7	-	156.6 C	-	154.4 C
7a	-	108.3 C	-	108.7 C
8	4.52 (2H, s)	68.1 CH ₂	2.25 (3H, s)	11.1 CH ₃
3-OMe	-	-	-	-
5-OMe	3.78 (3H, s)	63.0 CH ₃	3.76 (3H, s)	61.5 CH ₃
8-OMe	3.39 (3H, s)	58.7 CH ₃	-	-
1'	3.39 (2H, m)	23.5 CH ₂	3.39 (2H, br d, $J = 6.9$ Hz)	23.7 CH ₂
2'	5.26 (1H, t, $J = 7.0$ Hz)	124.0 CH	5.25 (1H, t, $J = 6.9$ Hz)	124.1 CH
3'	-	135.4 C	-	135.2 C
4'	2.27 (2H, m)	36.0 CH ₂	2.26 (2H, m)	35.8 CH ₂
5'	2.34 (2H, m)	34.4 CH ₂	2.35 (2H, m)	33.9 CH ₂
6'	-	178.1 C	-	177.3 C
7'	1.81 (3H, s)	16.3 CH ₃	1.81 (3H, s)	16.3 CH ₃
6'-OMe	-	-	-	-

^a Recorded at 400 MHz; ^b "m" means overlapped or multiplet with other signals; ^c Recorded at 100 MHz.

Table S2. ¹H and ¹³C NMR data for 8–10 in CD₃OD (δ in ppm, J in Hz).

No.	8		9		10	
	δ _H ^{a,b}	δ _C ^c	δ _H ^{a,b}	δ _C ^c	δ _H ^{a,b}	δ _C ^c
1	-	173.8 C	-	173.9 C	-	173.8 C
3	5.24 (2H, s)	70.8 CH ₂	5.10 (2H, s)	70.8 CH ₂	5.24 (2H, s)	70.8 CH ₂
3a	-	146.6 C	-	146.6 C	-	146.6 C
4	-	117.8 C	-	117.8 C	-	117.8 C
5	-	164.9 C	-	164.8 C	-	164.8 C
6	-	123.7 C	-	123.7 C	-	123.7 C
7	-	154.7 C	-	154.8 C	-	154.6 C
7a	-	107.7 C	-	107.7 C	-	107.7 C
8	2.14 (3H, s)	11.4 CH ₃	2.07 (3H, s)	11.4 CH ₃	2.15 (3H, s)	11.4 CH ₃
5-OMe	3.76 (3H, s)	61.6 CH ₃	3.71 (3H, s)	61.6 CH ₃	3.76 (3H, s)	61.5 CH ₃
1'	3.38 (2H, br d, J = 7.1 Hz)	23.6 CH ₂	3.32 (2H, br d, J = 6.9 Hz)	23.6 CH ₂	3.39 (2H, br d, J = 7.0 Hz)	23.6 CH ₂
2'	5.27 (1H, t, J = 7.1 Hz)	124.4 CH	5.18 (1H, t, J = 6.9 Hz)	124.4 CH	5.26 (1H, t, J = 7.0 Hz)	124.5 CH
3'	-	135.2 C	-	135.1 C	-	135.1 C
4'	2.28 (2H, m)	36.6 CH ₂	2.13 (2H, m)	36.5 CH ₂	2.27 (2H, m)	36.5 CH ₂
5'	2.36 (2H, m)	35.5 CH ₂	2.21 (2H, m)	35.6 CH ₂	2.30 (2H, m)	35.6 CH ₂
6'	-	175.8 C	-	175.4 C	-	175.3 C
7'	1.83 (3H, s)	16.3 CH ₃	1.73 (3H, s)	16.2 CH ₃	1.82 (3H, s)	16.3 CH ₃
2''	4.24 (1H, d, J = 5.5 Hz)	59.4 CH	4.51 (1H, dd, J = 5.4, 8.2 Hz)	55.5 CH	4.26 (1H, q, J = 7.2 Hz)	49.9 CH
3''	-	175.8 C	-	175.4 C	-	176.8 C
4''	2.10 (1H, m)	31.8 CH	2.77 (1H, dd, J = 8.2, 13.7 Hz); 3.03 (1H, dd, J = 5.4, 13.7 Hz)	38.8 CH ₂	1.30 (3H, d, J = 7.2 Hz)	18.0 CH ₃
5''	0.90 (3H, d, J = 6.8 Hz)	19.7 CH ₃	-	138.7 C	-	-
6''	0.90 (3H, d, J = 6.8 Hz)	18.4 CH ₃	7.12 (1H, m)	130.3 C	-	-
7''	-	-	7.19 (1H, m)	129.3 C	-	-
8''	-	-	7.14 (1H, m)	127.6 C	-	-
9''	-	-	7.19 (1H, m)	129.3 C	-	-
10''	-	-	7.12 (1H, m)	130.3 C	-	-

^a Recorded at 400 MHz; ^b "m" means overlapped or multiplet with other signals; ^c Recorded at 100 MHz.