γ- and δ-Lactams from the Leaves of *Clausena lansium*

De-Yang Shen,[†,#] Thi Ngan Nguyen,[‡,#] Shwu-Jen Wu,[§] Young-Ji Shiao,[⊥] Hsin-Yi Hung,[∥] Ping-Chung Kuo,[▽] Daih-Huang Kuo,[○] Tran Dinh Thang,[‡,*] and Tian-Shung Wu,[∥,○,*]

[†] Department of Chemistry and [∥] School of Pharmacy, National Cheng Kung University, Tainan 70101, Taiwan

[‡] Department of Chemistry, Vinh University, Vinh City, Vietnam

[§] Department of Medical Laboratory Science and Biotechnology, Chung Hwa University of Medical Technology, Tainan 71703, Taiwan

[⊥] Division of Basic Chinese Medicine, National Research Institute of Chinese Medicine, Taipei 112, Taiwan

[▽] Department of Biotechnology, National Formosa University, Yunlin 63201, Taiwan

[○] Department of Pharmacy and Graduate Institute of Pharmaceutical Technology, Tajen University, Pingtung 90741, Taiwan

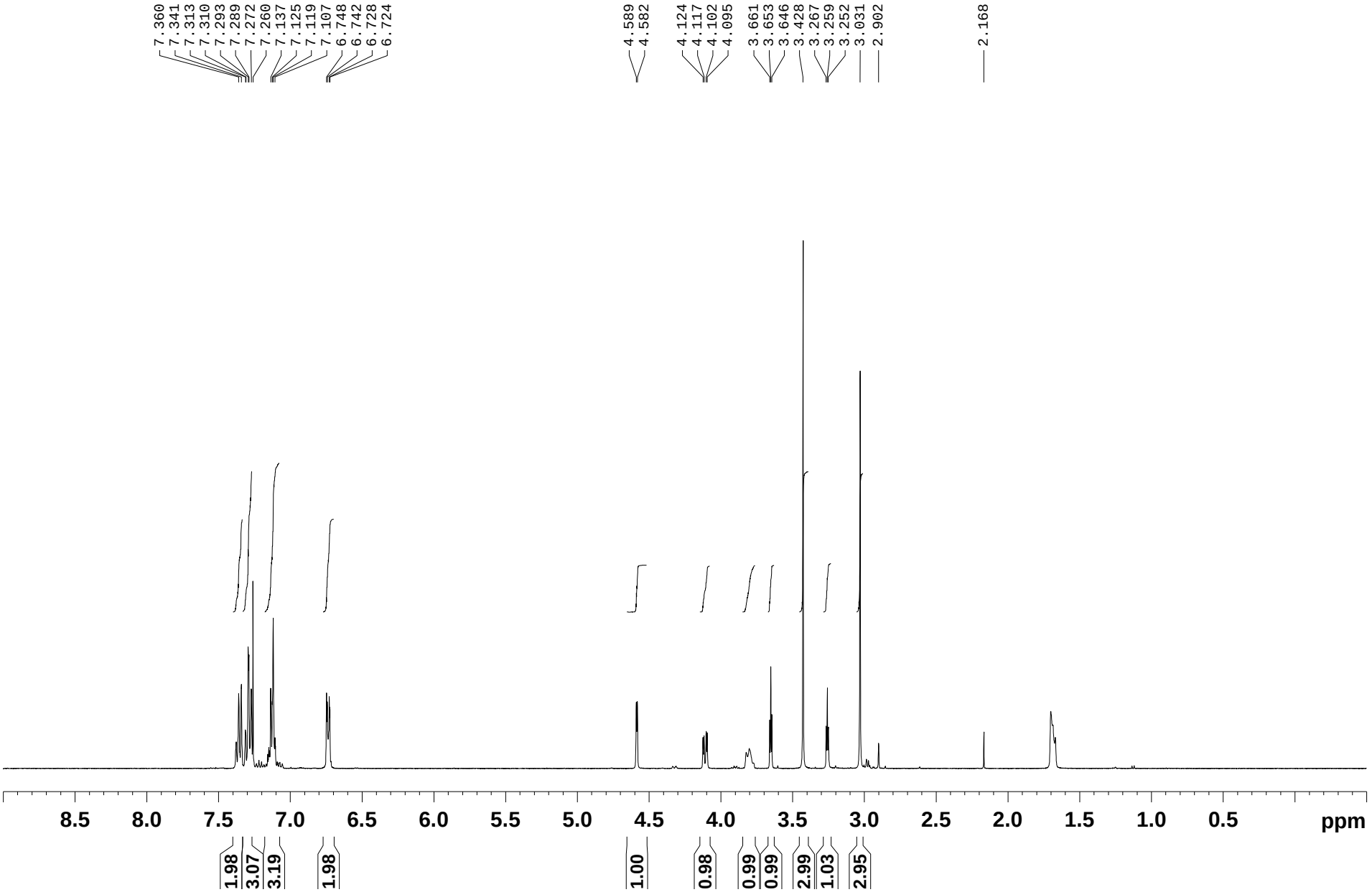
Table of Content

S 1 ^{1}H NMR (400 MH, $CDCl_3$) spectrum of the new compound **1.** 6
S 2 ^{13}C NMR (100 MH, $CDCl_3$) spectrum of the new compound **1.** 7
S 3 COSY spectrum of the new compound **1.** 8
S 4 NOESY spectrum of the new compound **1.** 9
S 5 HSQC spectrum of the new compound **1.** 10
S 6 HMBC spectrum of the new compound **1.** 11
S 7 CD spectrum of the new compound **1.** 12
S 8 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **2.** 13
S 9 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **2.** 14
S 10 COSY spectrum of the new compound **2.** 15
S 11 NOESY spectrum of the new compound **2.** 17
S 12 HSQC spectrum of the new compound **2.** 18
S 13 HMBC spectrum of the new compound **2.** 19
S 14 CD spectrum of the new compound **2.** 20
S 15 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **3.** 21
S 16 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **3.** 22
S 17 COSY spectrum of the new compound **3.** 23
S 18 NOESY spectrum of the new compound **3.** 24
S 19 HSQC spectrum of the new compound **3.** 25
S 20 HMBC spectrum of the new compound **3.** 26
S 21 CD spectrum of the new compound **3.** 27
S 22 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **4.** 28
S 23 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **4.** 29
S 24 COSY spectrum of the new compound **4.** 30
S 25 NOESY spectrum of the new compound **4.** 31
S 26 HSQC spectrum of the new compound **4.** 32
S 27 HMBC spectrum of the new compound **4.** 33
S 28 CD spectrum of the new compound **4.** 34
S 29 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **5.** 35
S 30 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **5.** 36
S 31 COSY spectrum of the new compound **5.** 37
S 32 NOESY spectrum of the new compound **5.** 38
S 33 HSQC spectrum of the new compound **5.** 39
S 34 HMBC spectrum of the new compound **5.** 40
S 35 CD spectrum of the new compound **5.** 41
S 36 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **6.** 42
S 37 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **6.** 43
S 38 COSY spectrum of the new compound **6.** 44
S 39 NOESY spectrum of the new compound **6.** 45

S 40 HSQC spectrum of the new compound **6.** 46
S 41 HMBC spectrum of the new compound **6.** 47
S 42 CD spectrum of the new compound **6.** 48
S 43 ^{1}H NMR (400 MHz, CD_3OD) spectrum of the new compound **7.** 49
S 44 ^{13}C NMR (100 MHz, CD_3OD) spectrum of the new compound **7.** 50
S 45 COSY spectrum of the new compound **7.** 51
S 46 NOESY spectrum of the new compound **7.** 52
S 47 HSQC spectrum of the new compound **7.** 53
S 48 HMBC spectrum of the new compound **7.** 54
S 49 CD spectrum of the new compound **7.** 55
S 50 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8.** 56
S 51 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8.** 57
S 52 COSY spectrum of the compound **8.** 58
S 53 NOESY spectrum of the compound **8.** 59
S 54 HSQC spectrum of the compound **8.** 60
S 55 HMBC spectrum of the compound **8.** 61
S 56 CD spectrum of the compound **8.** 62
S 57 X-ray structure of compound **8.** 63
S 58 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **9.** 64
S 59 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **9.** 65
S 60 COSY spectrum of the compound **9.** 66
S 61 NOESY spectrum of the compound **9.** 67
S 62 HSQC spectrum of the compound **9.** 68
S 63 HMBC spectrum of the compound **9.** 69
S 64 CD spectrum of the compound **9.** 70
S 65 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **10.** 71
S 66 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **10.** 72
S 67 COSY spectrum of the compound **10.** 73
S 68 NOESY spectrum of the compound **10.** 74
S 69 HSQC spectrum of the compound **10.** 75
S 70 HMBC spectrum of the compound **10.** 76
S 71 CD spectrum of the compound **10.** 77
S 72 ^{1}H NMR (400 MHz, CD_3OD) spectrum of the compound **11.** 78
S 73 ^{13}C NMR (100 MHz, CD_3OD) spectrum of the compound **11.** 79
S 74 COSY spectrum of the compound **11.** 80
S 75 NOESY spectrum of the compound **11.** 81
S 76 HSQC spectrum of the compound **11.** 82
S 77 HMBC spectrum of the compound **11.** 83
S 78 CD spectrum of the compound **11.** 84
S 79 X-ray structure of compound **11.** 85
S 80 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **12.** 86
S 81 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **12.** 87

S 82 COSY spectrum of the compound **12.** 88
S 83 NOESY spectrum of the compound **12.** 89
S 84 HSQC spectrum of the compound **12.** 90
S 85 HMBC spectrum of the compound **12.** 91
S 86 CD spectrum of the compound **12.** 92
S 87 X-ray structure of compound **12.** 93
S 88 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **13.** 94
S 89 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **13.** 95
S 90 COSY spectrum of the compound **13.** 96
S 91 NOESY spectrum of the compound **13.** 97
S 92 HSQC spectrum of the compound **13.** 98
S 93 HMBC spectrum of the compound **13.** 99
S 94 CD spectrum of the compound **13.** 100
S 95 CD spectrum of the compound **14.** 101
S 96 X-ray structure of compound **14.** 102
S 97 Chiral HPLC of compound **1** 103
S 98 Chiral HPLC of compound **11** 104
S 99 Neuroprotective Assay 105
S 100 Neurotoxicity Assay. 105
S 101 Compound 2 prevented cell death of cortical neurons induced by Aβ-(25–35). 106

S 1 ^{1}H NMR (400 MH, $CDCl_3$) spectrum of the new compound **1.**



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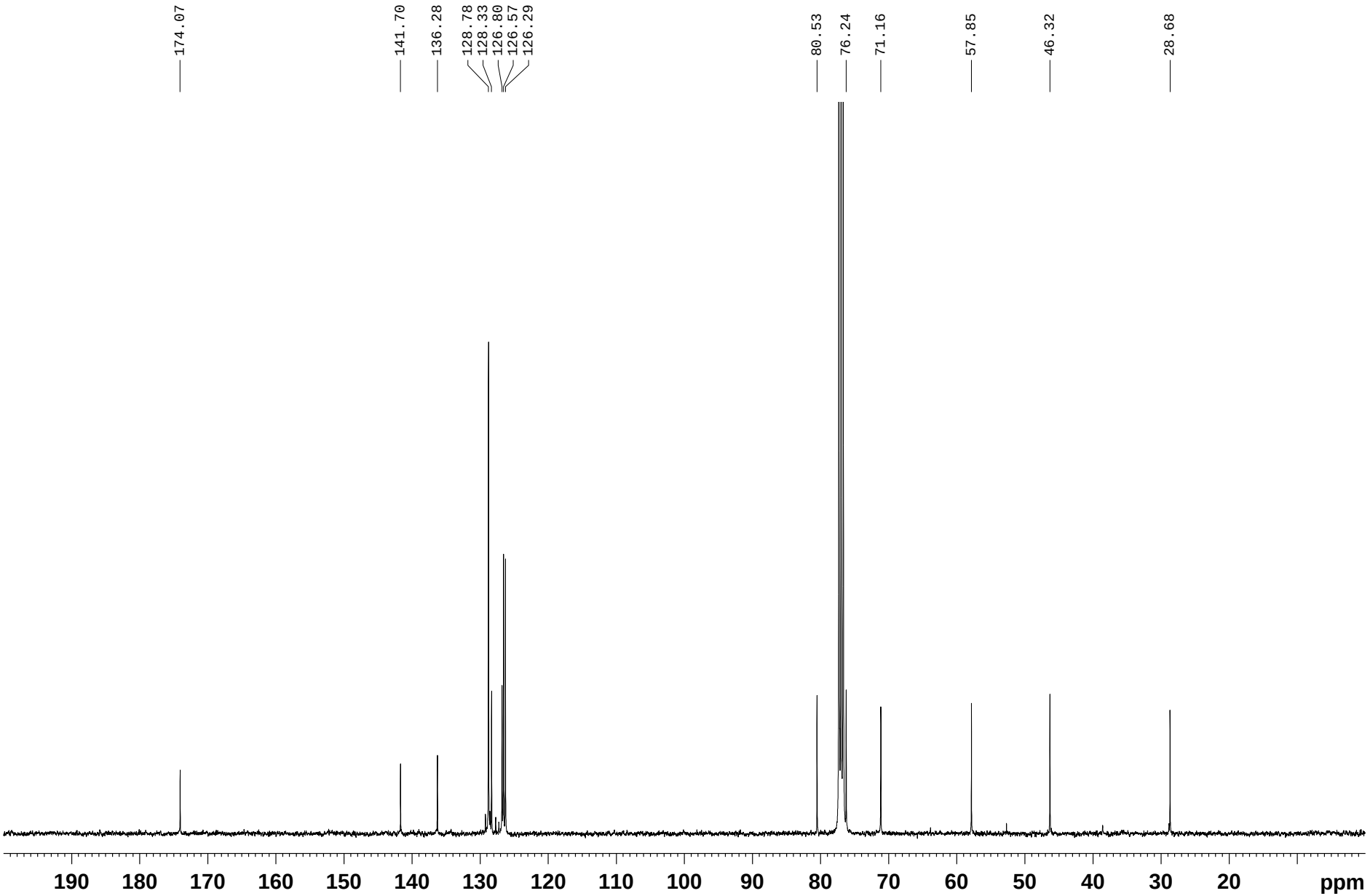

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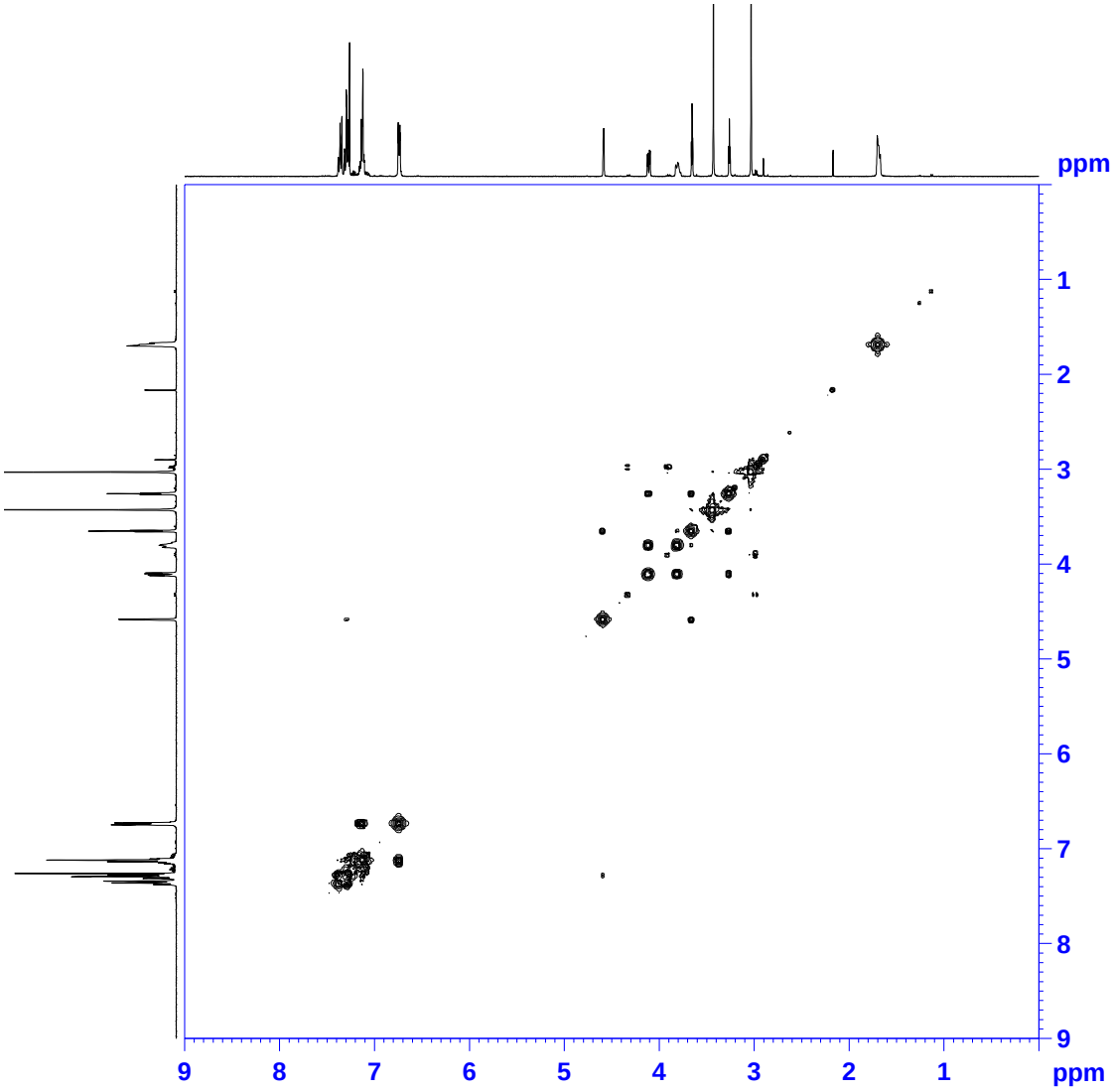

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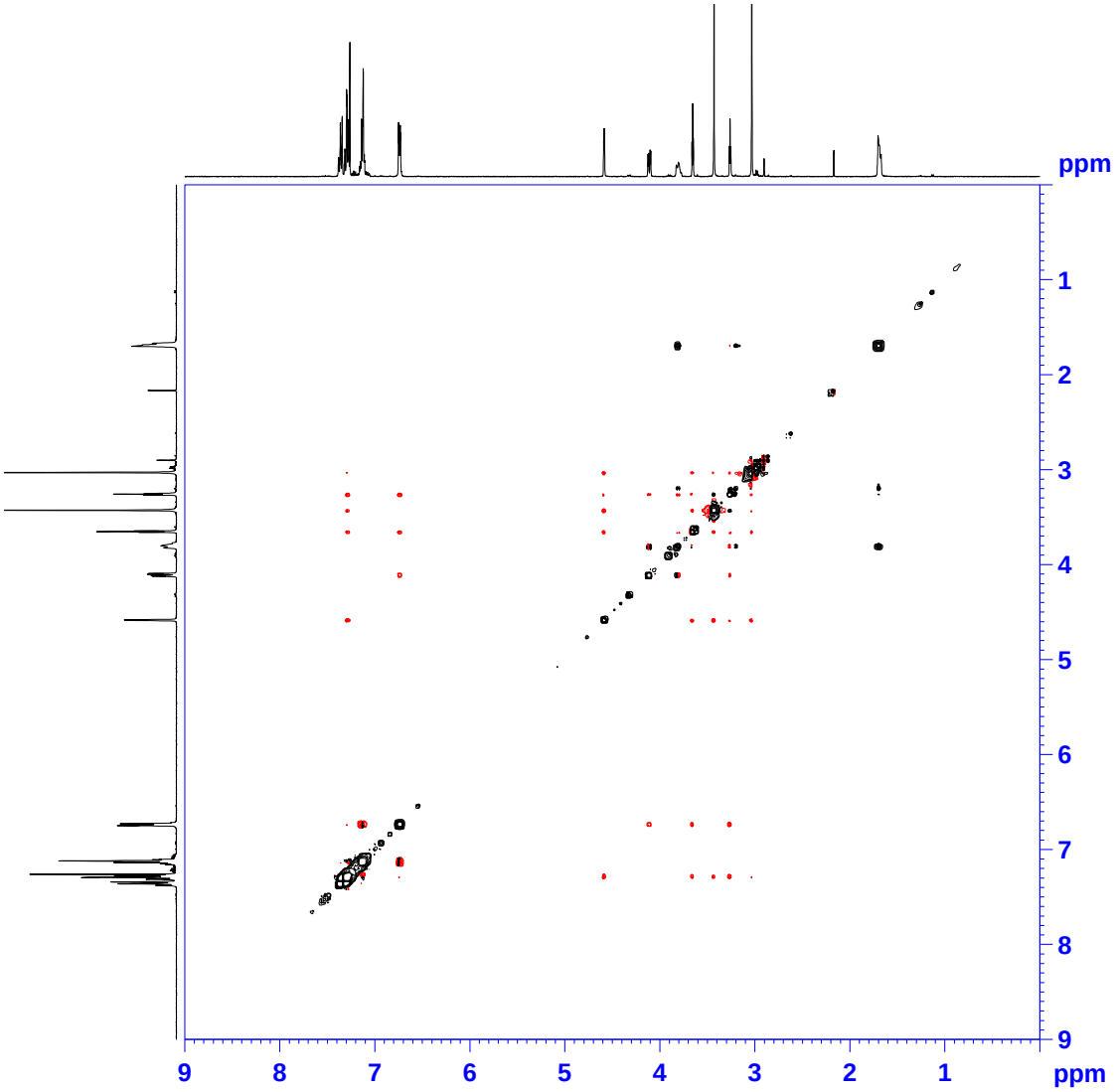

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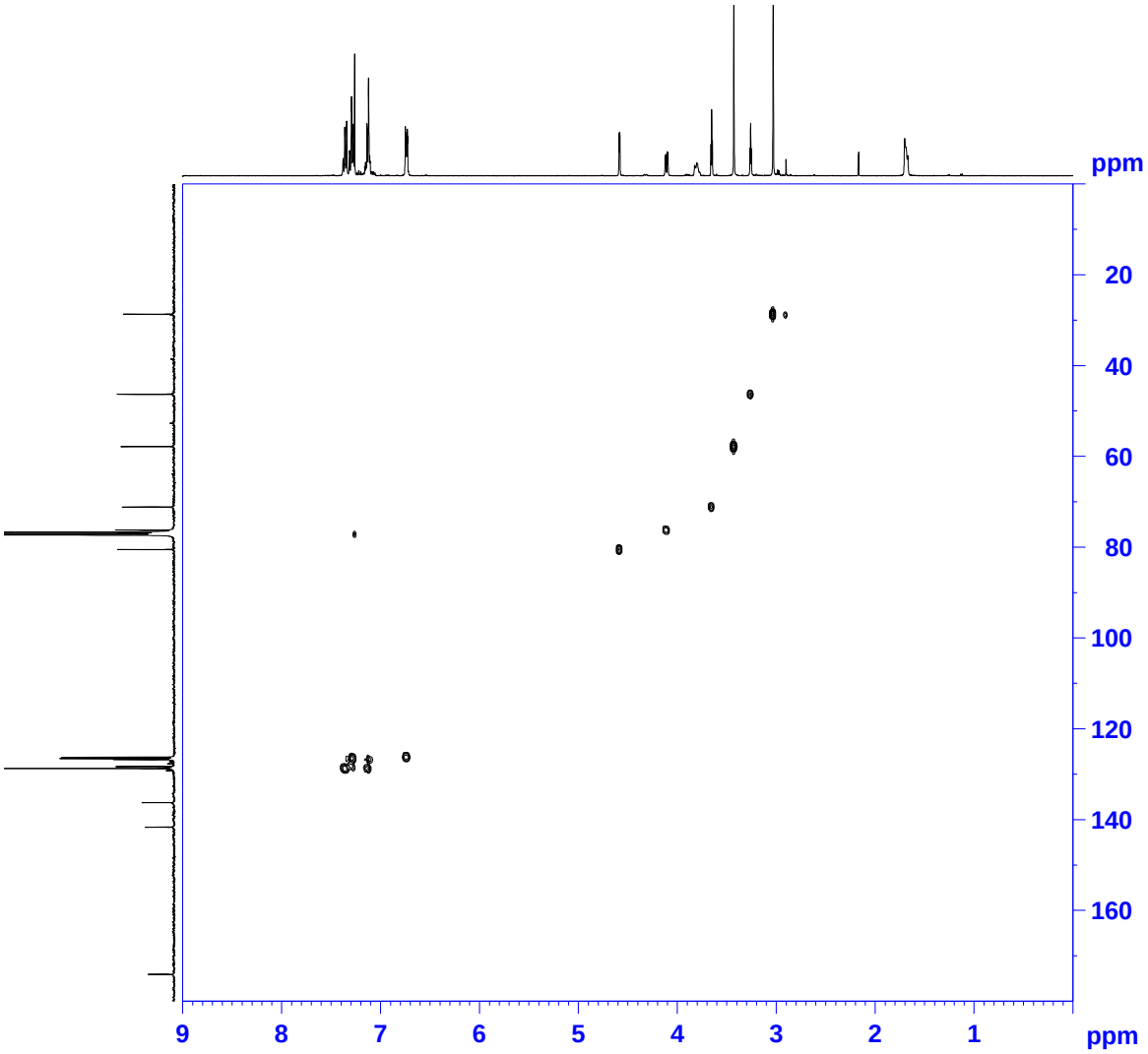

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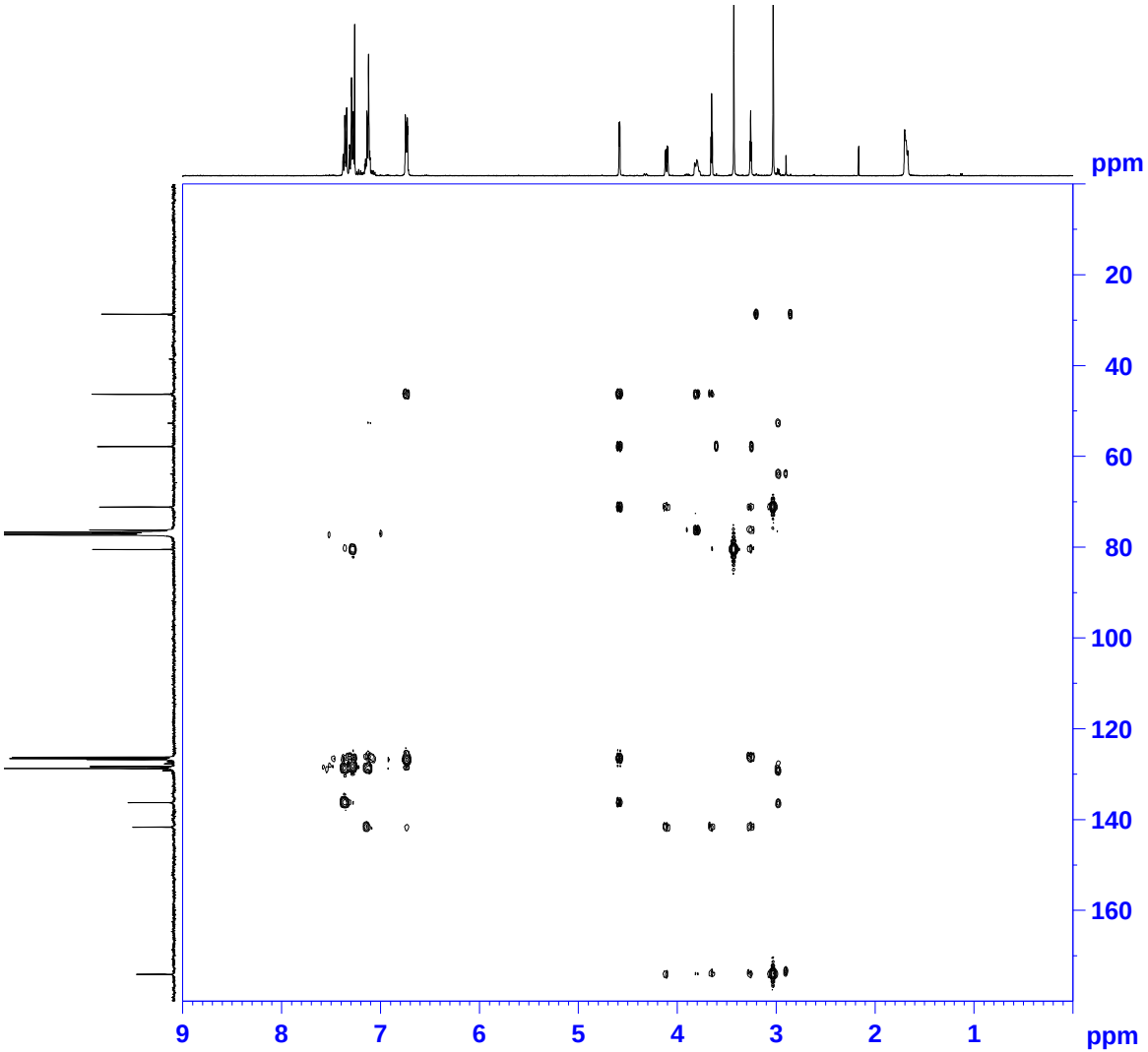

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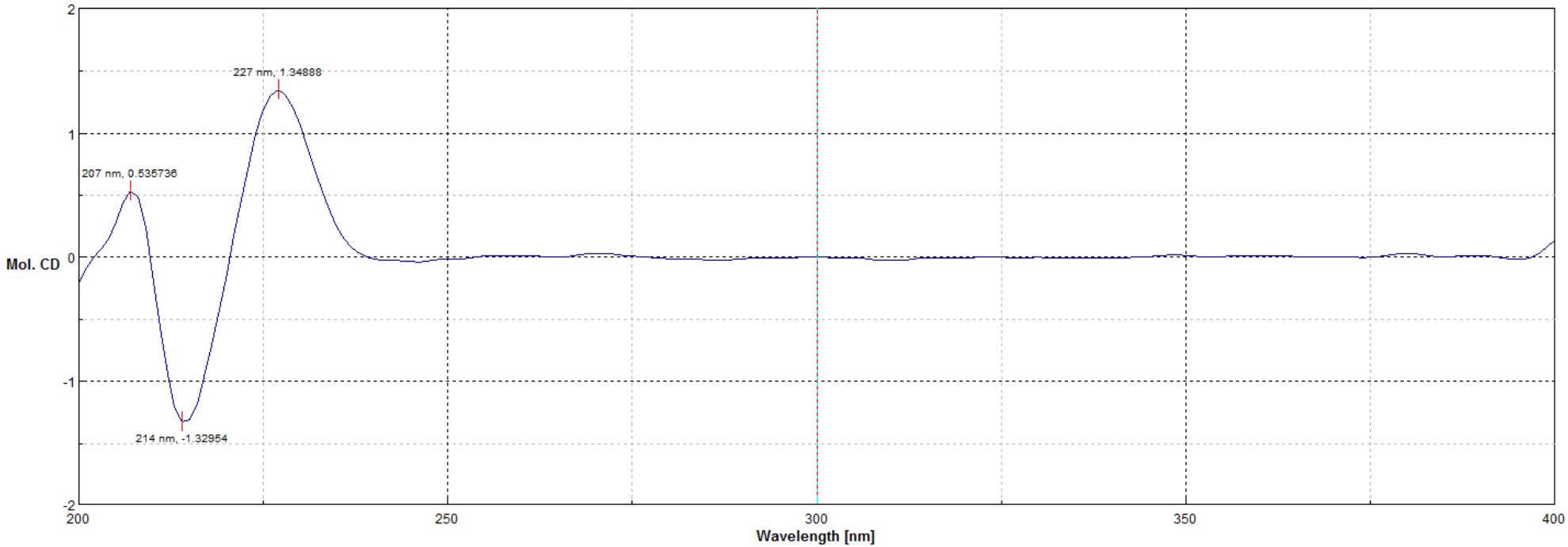
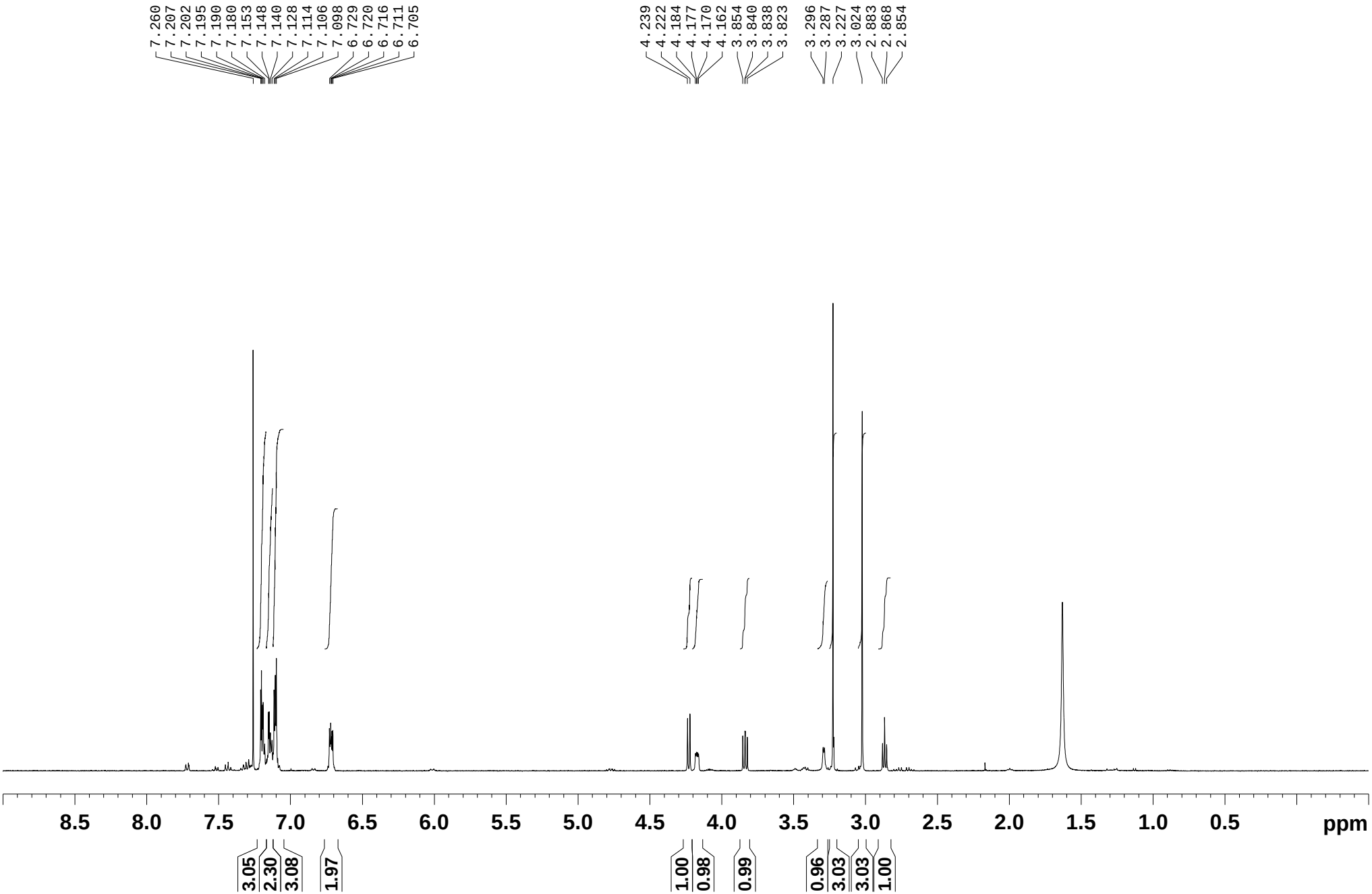


S 8 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **2.**



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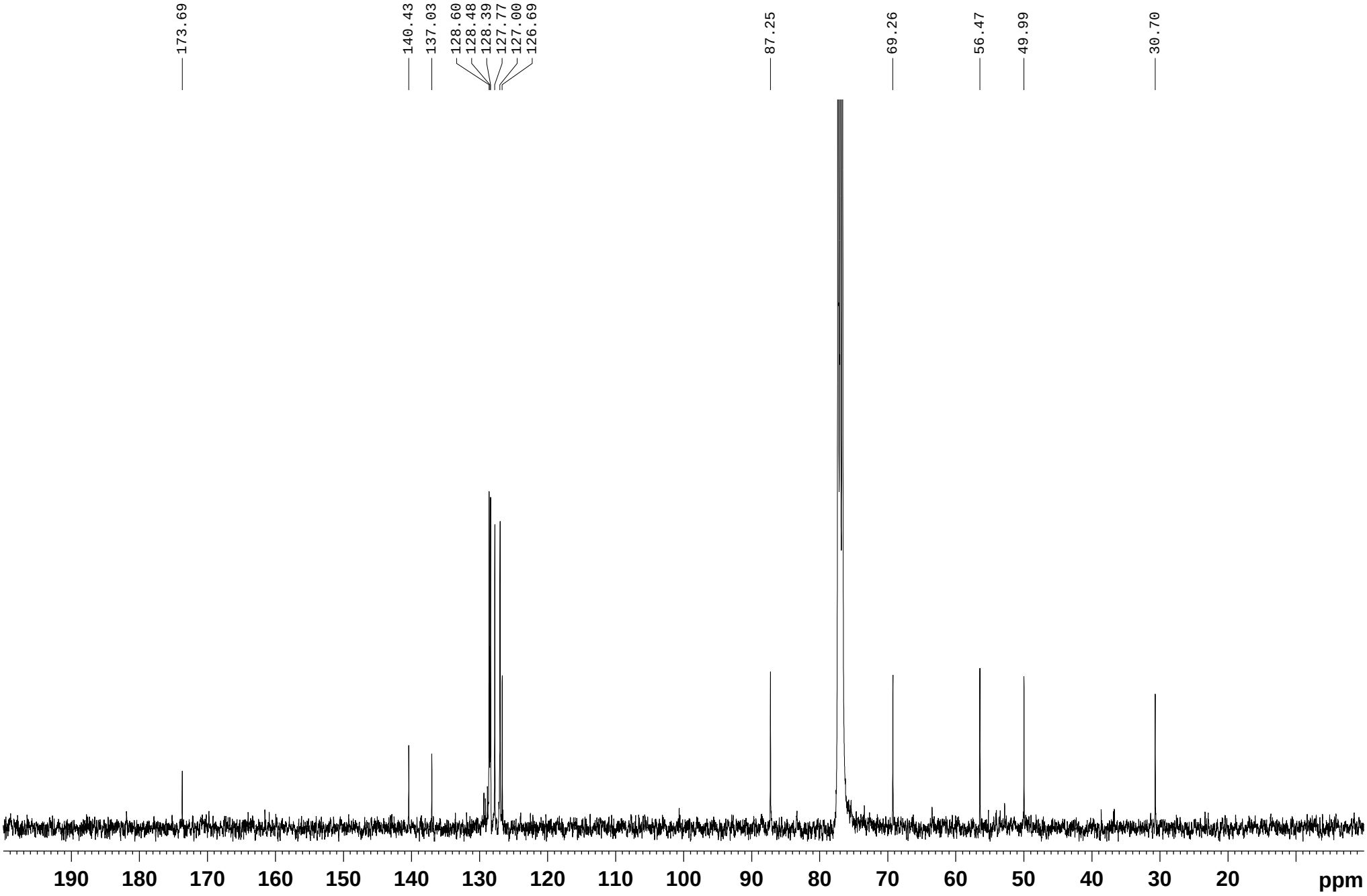

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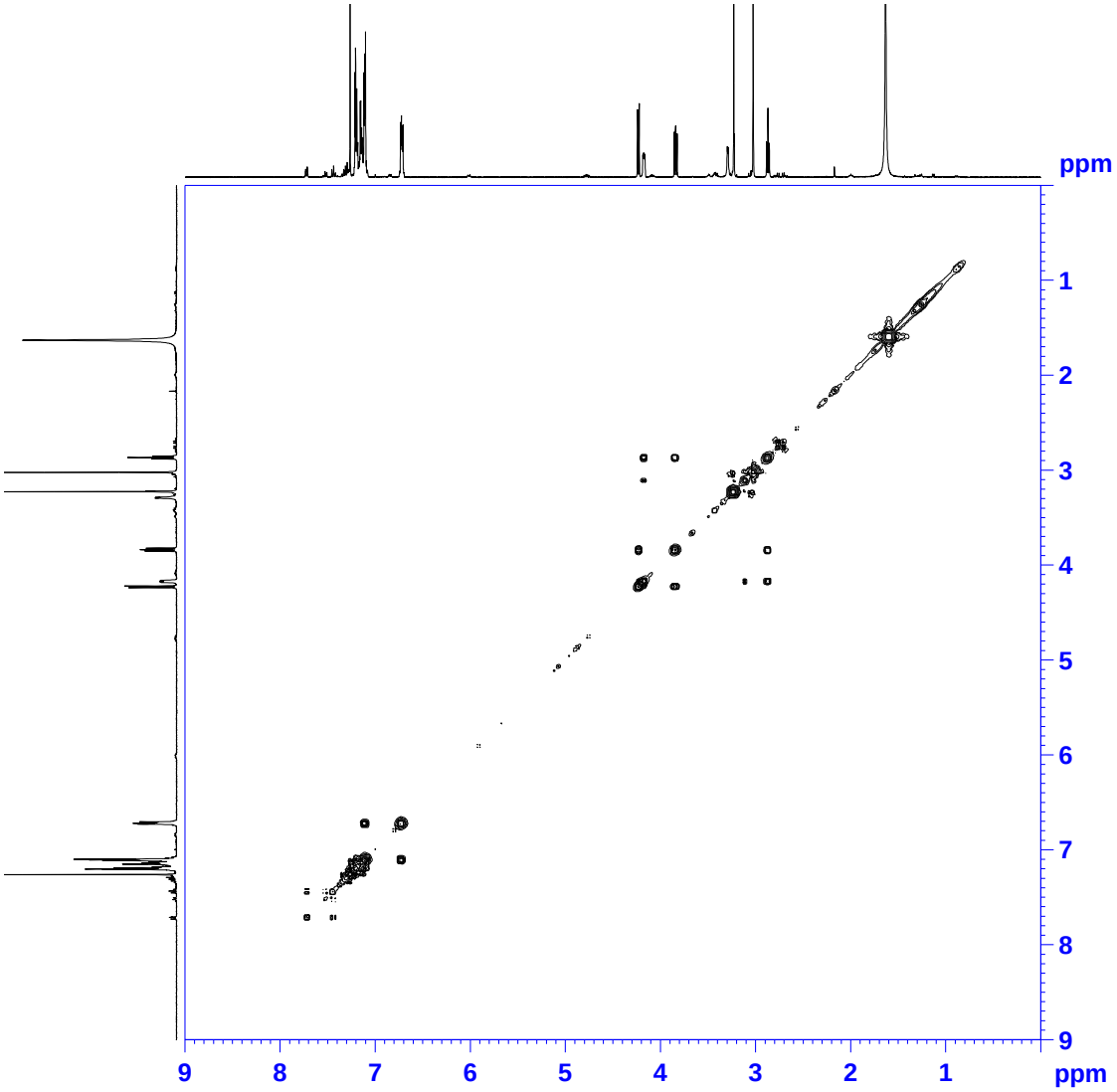
ppm
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
ppm

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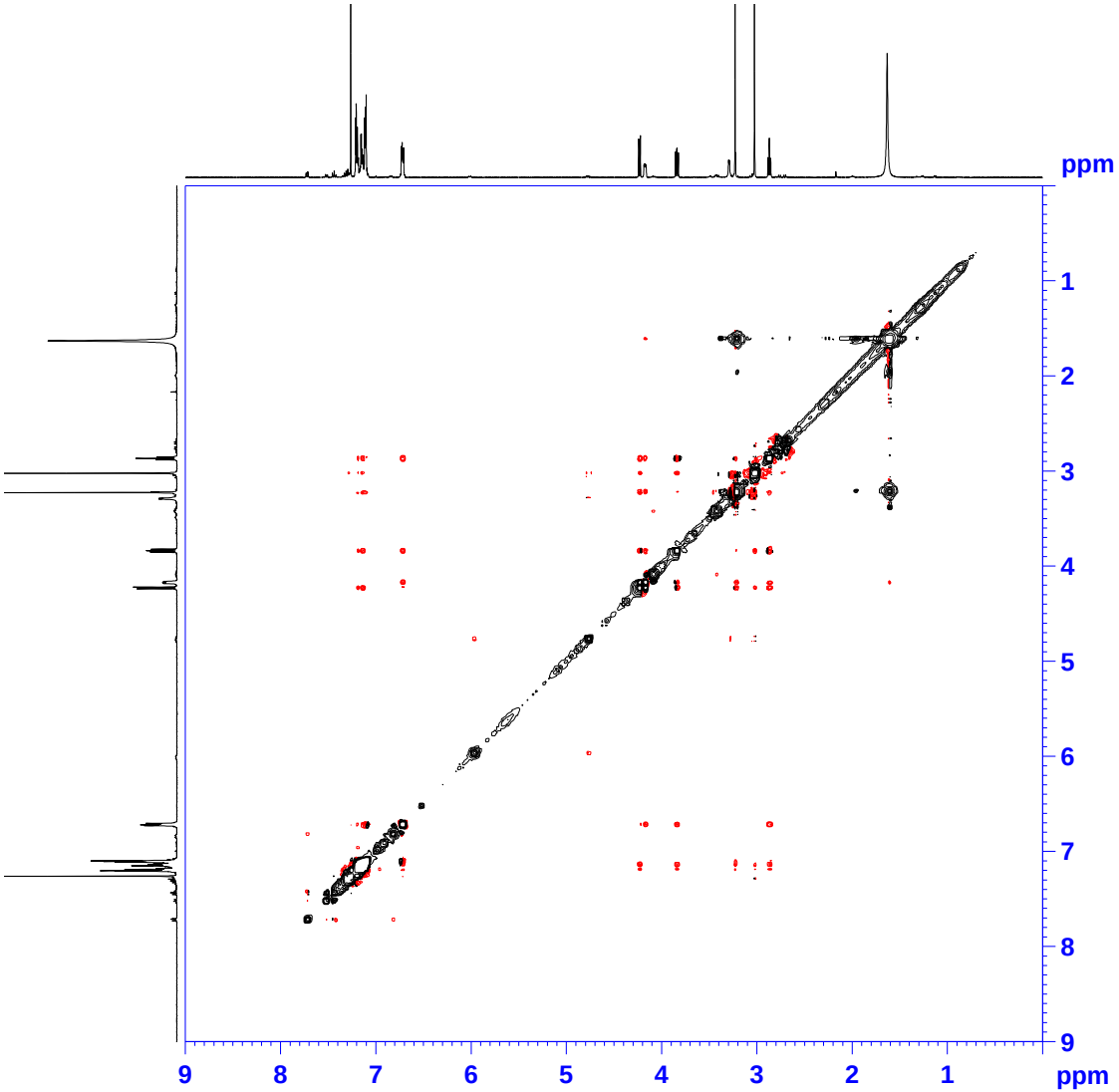

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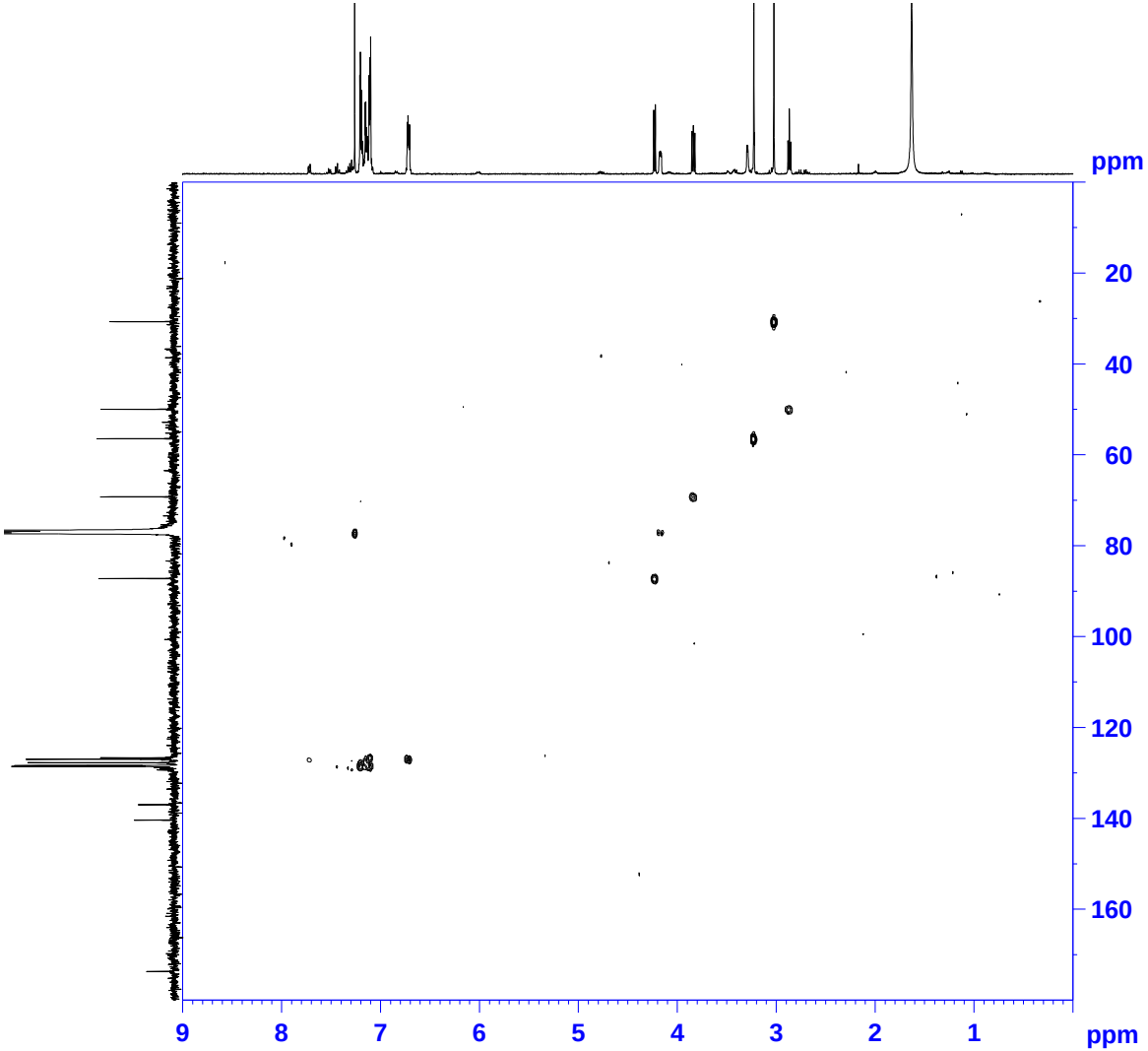
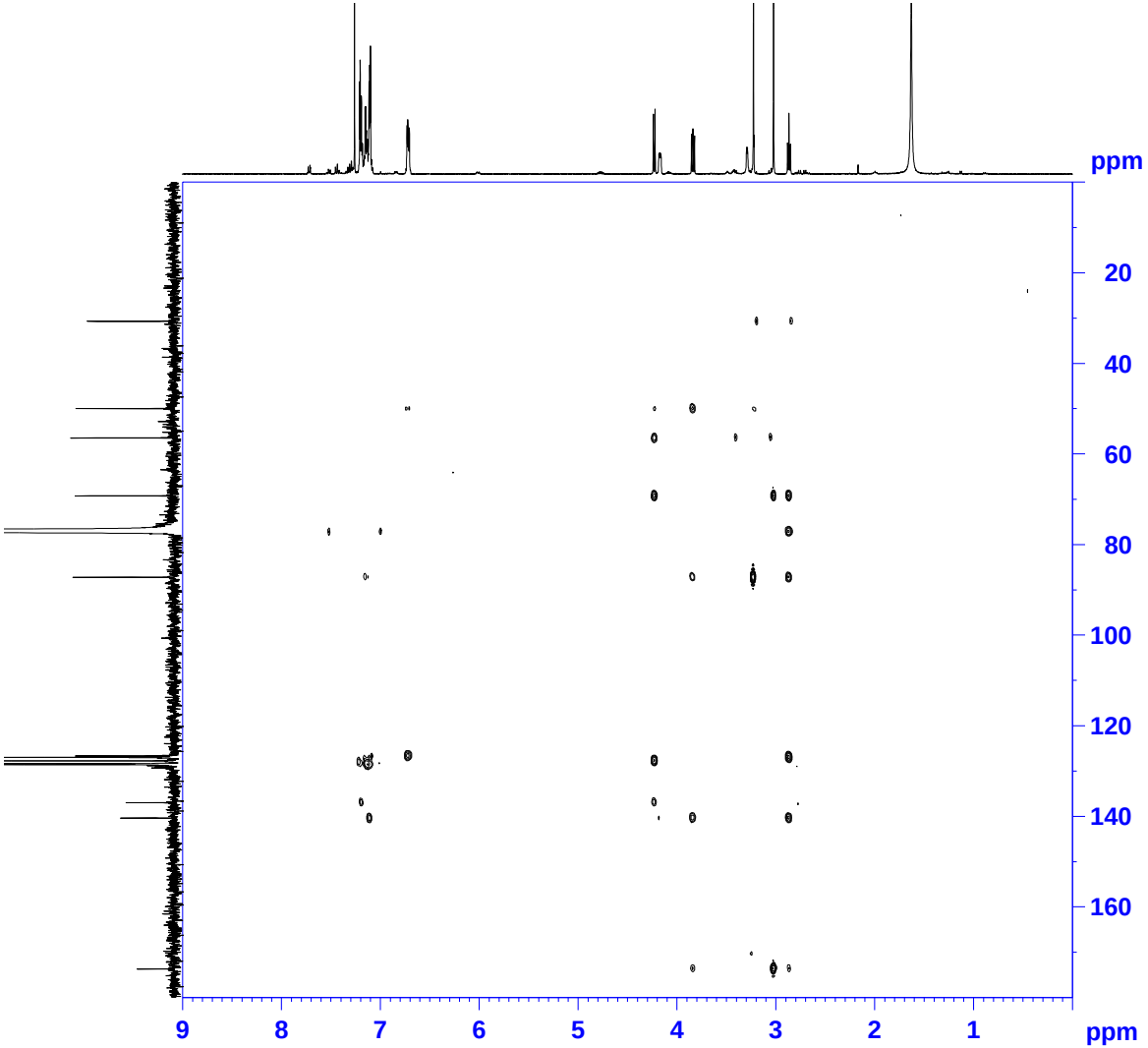


S 13 HMBC spectrum of the new compound **2.**



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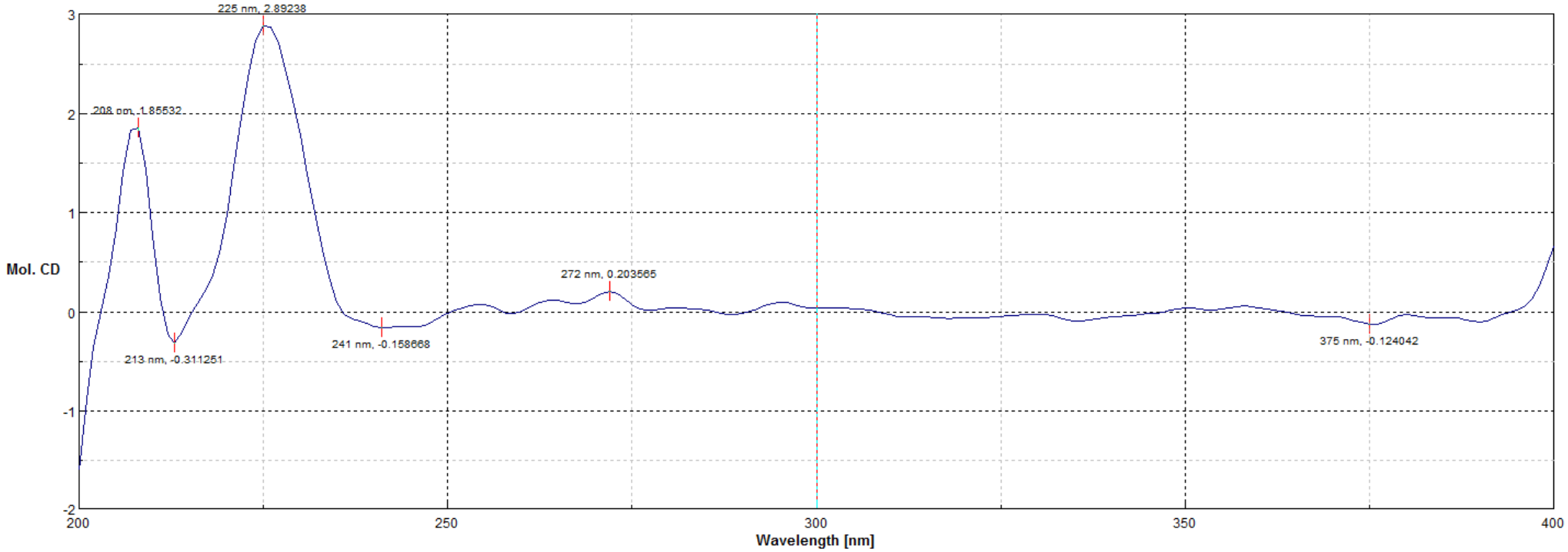
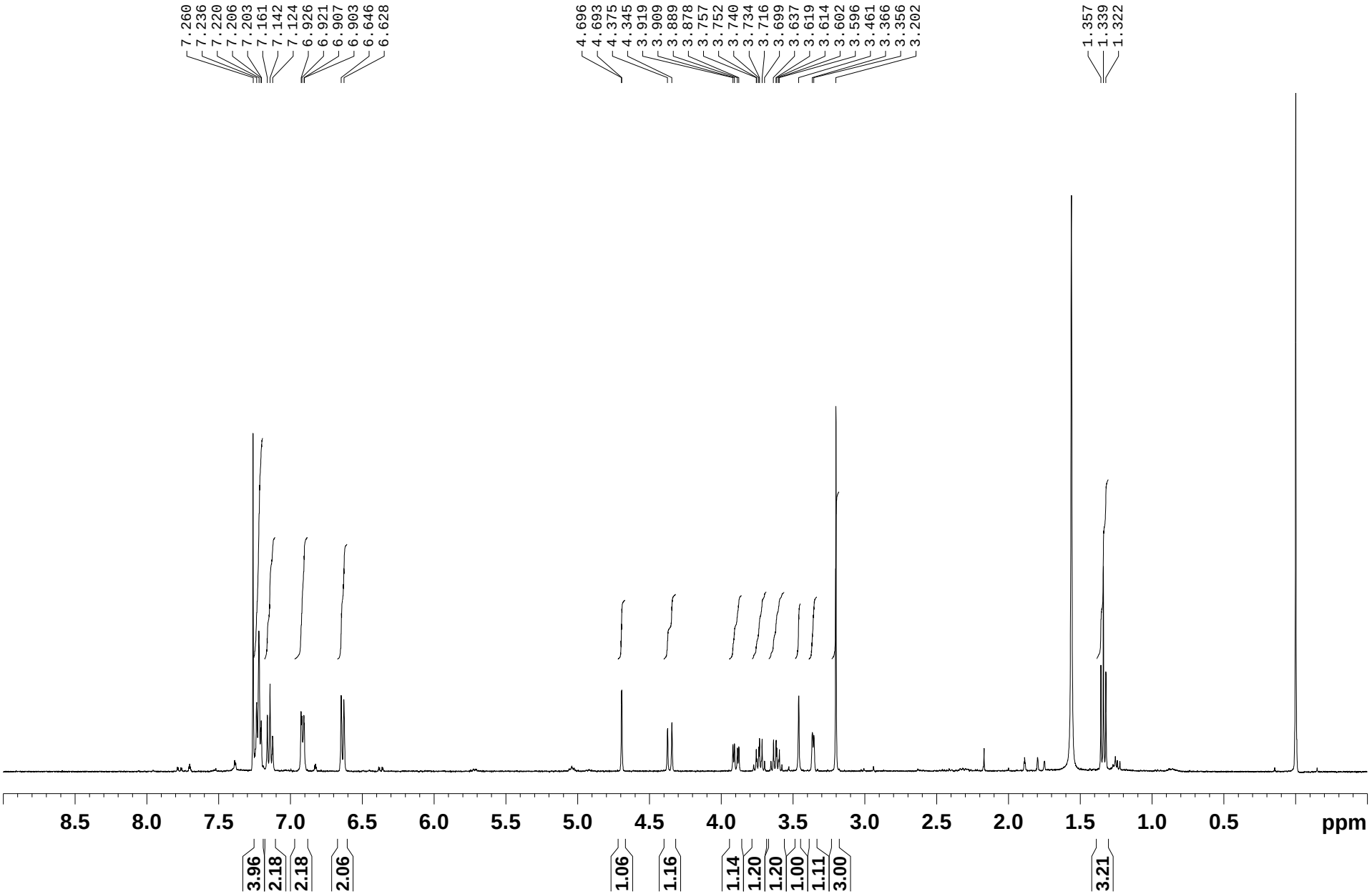
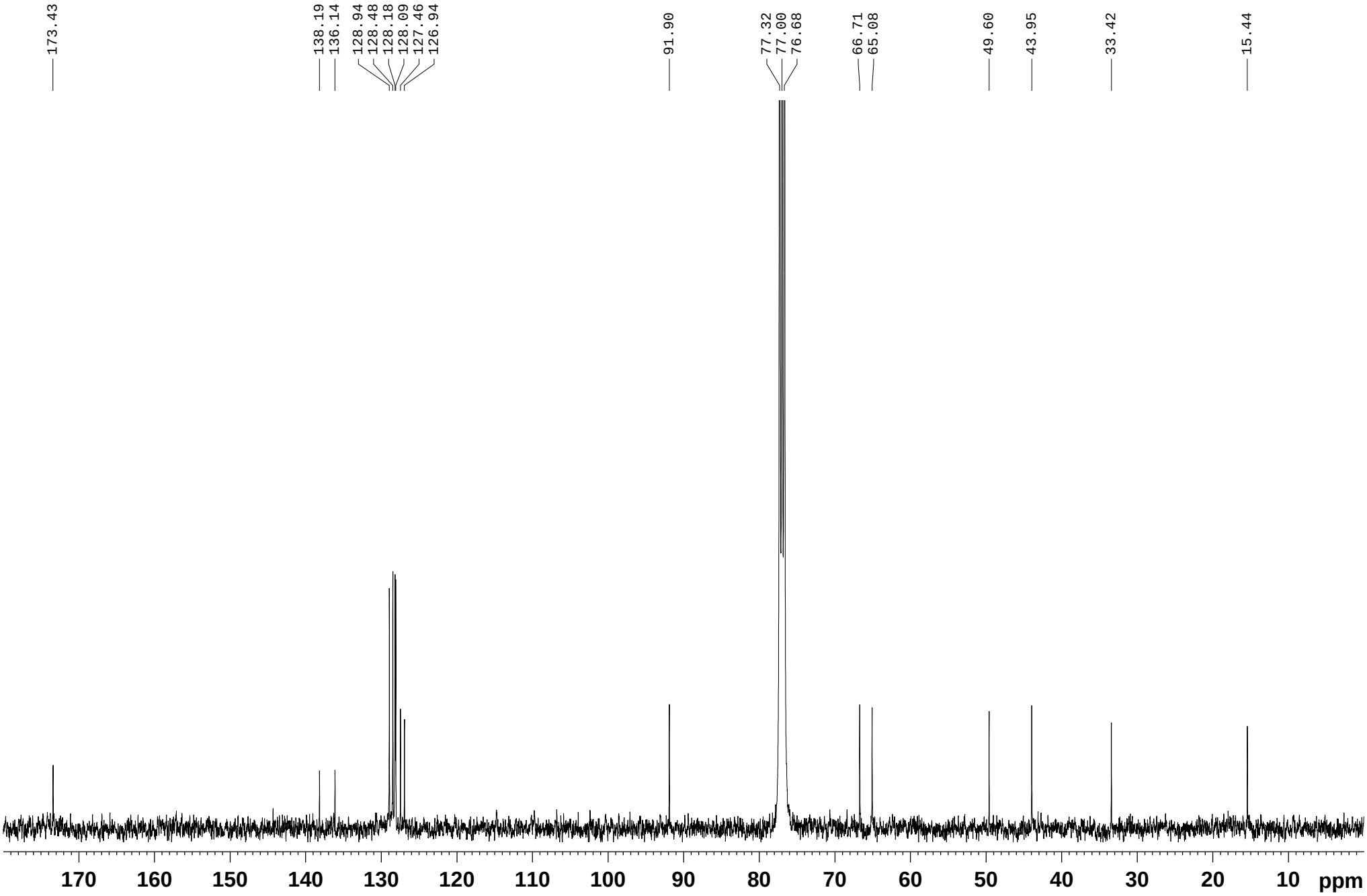


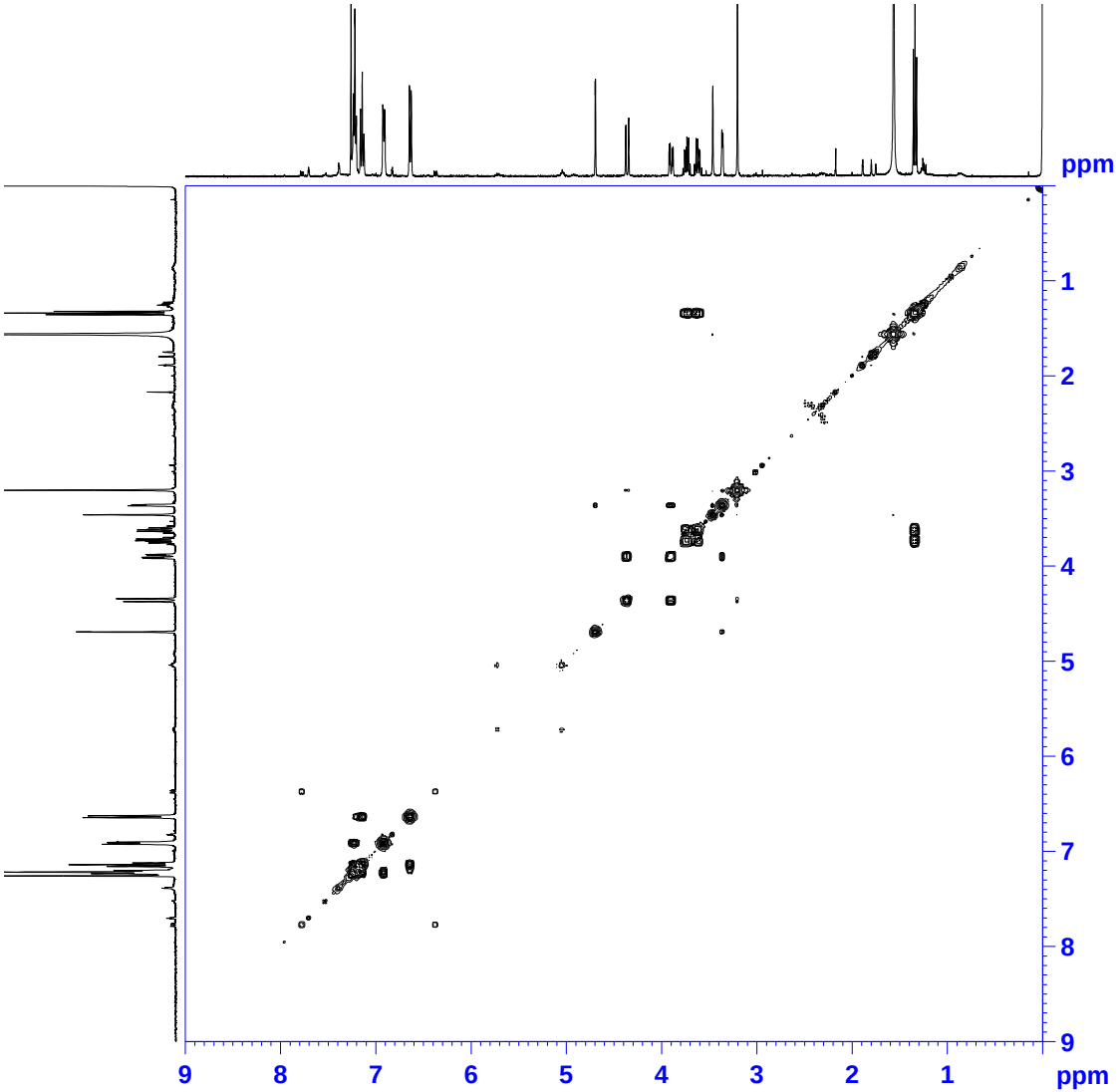
S 15 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **3.**



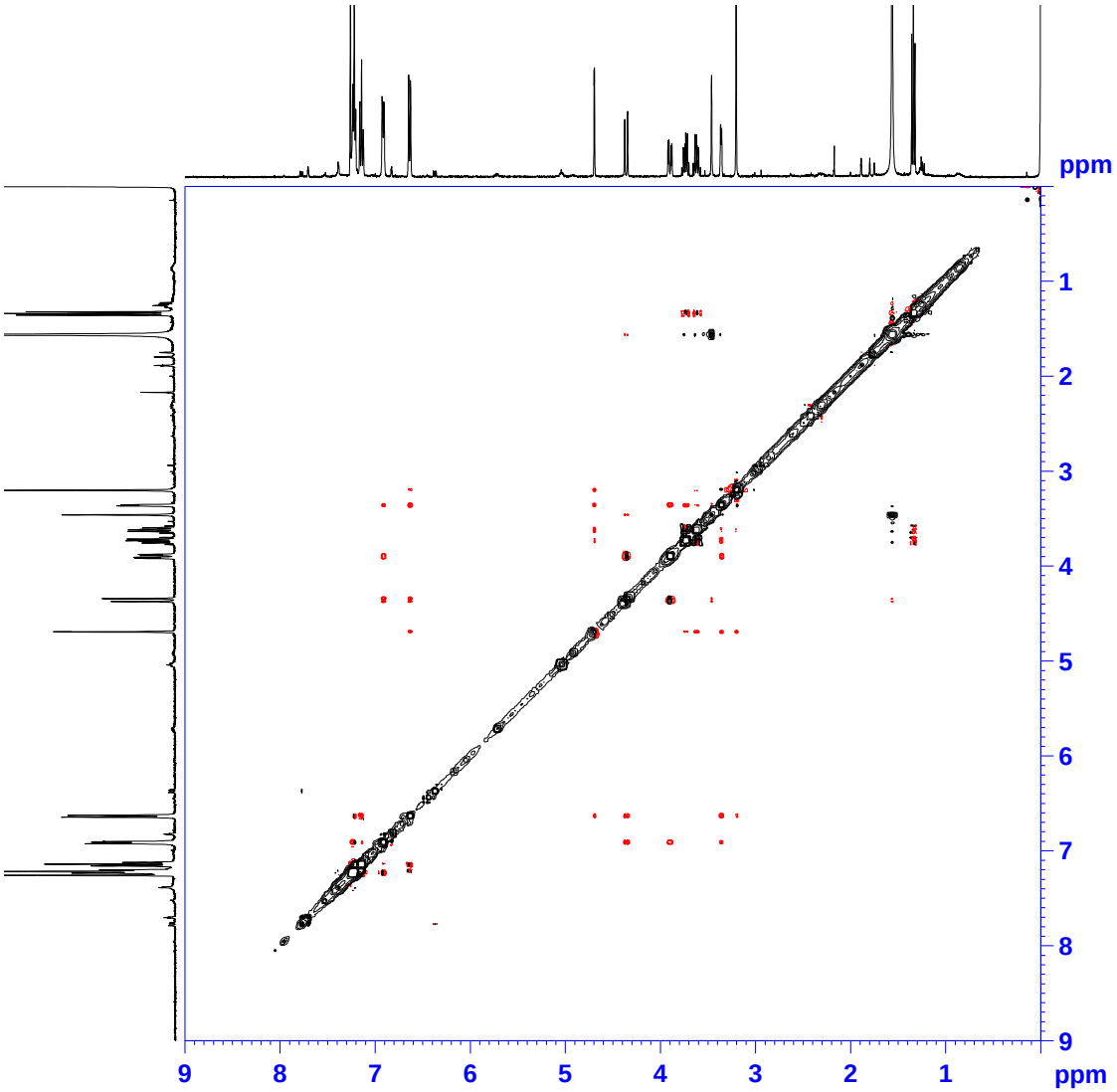
S 16 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **3.**



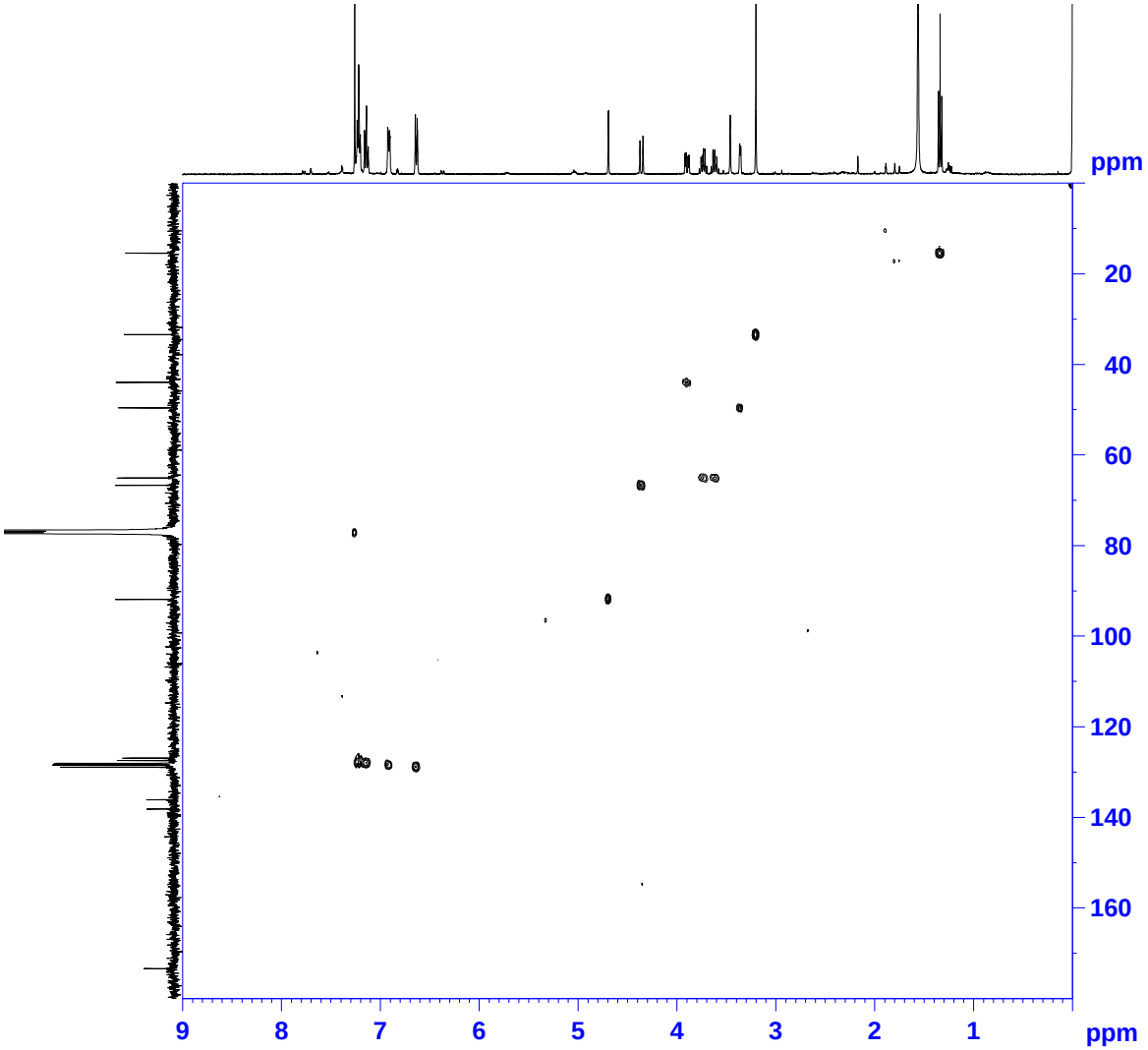
S 17 COSY spectrum of the new compound **3.**



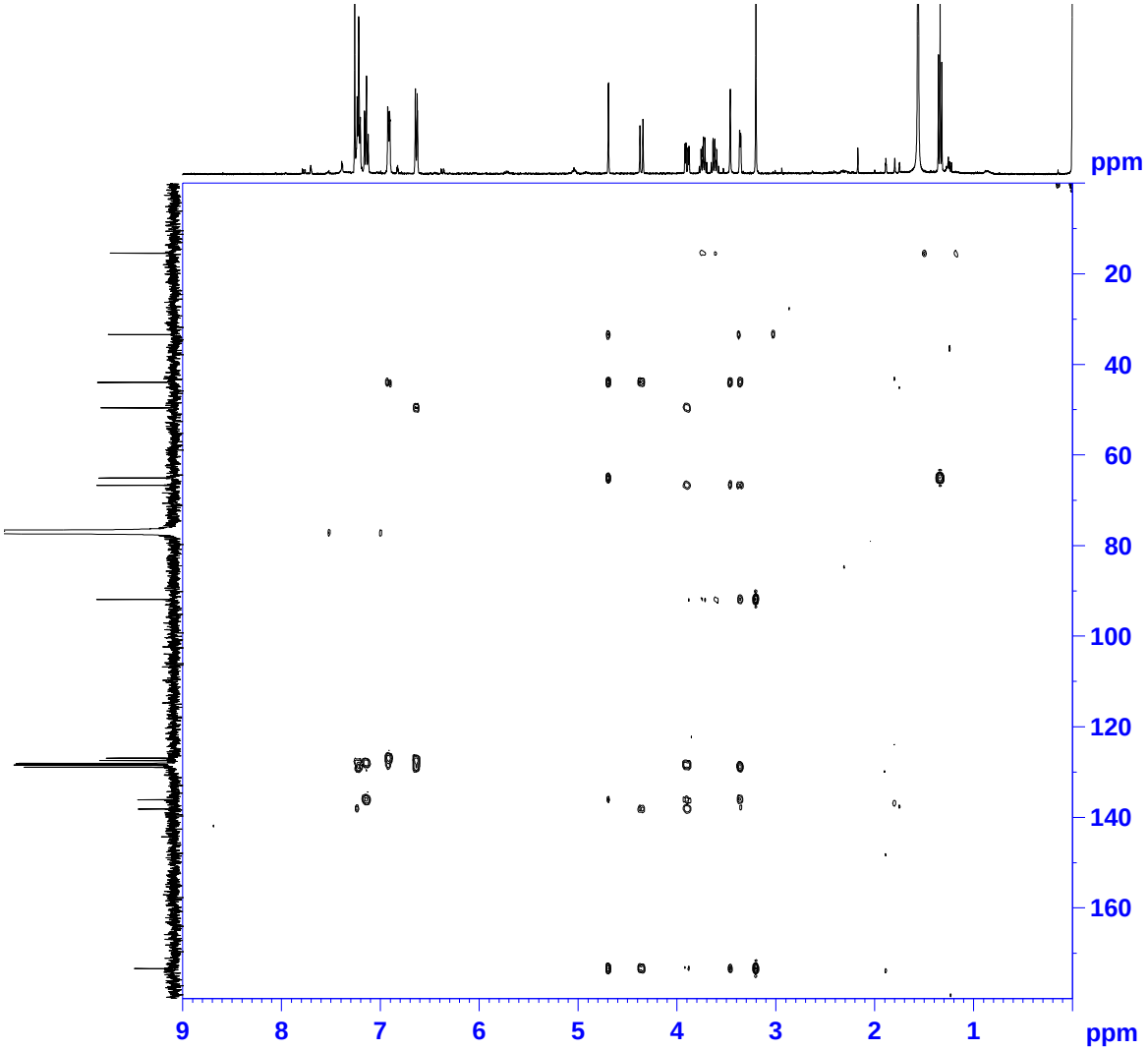
S 18 NOESY spectrum of the new compound **3.**



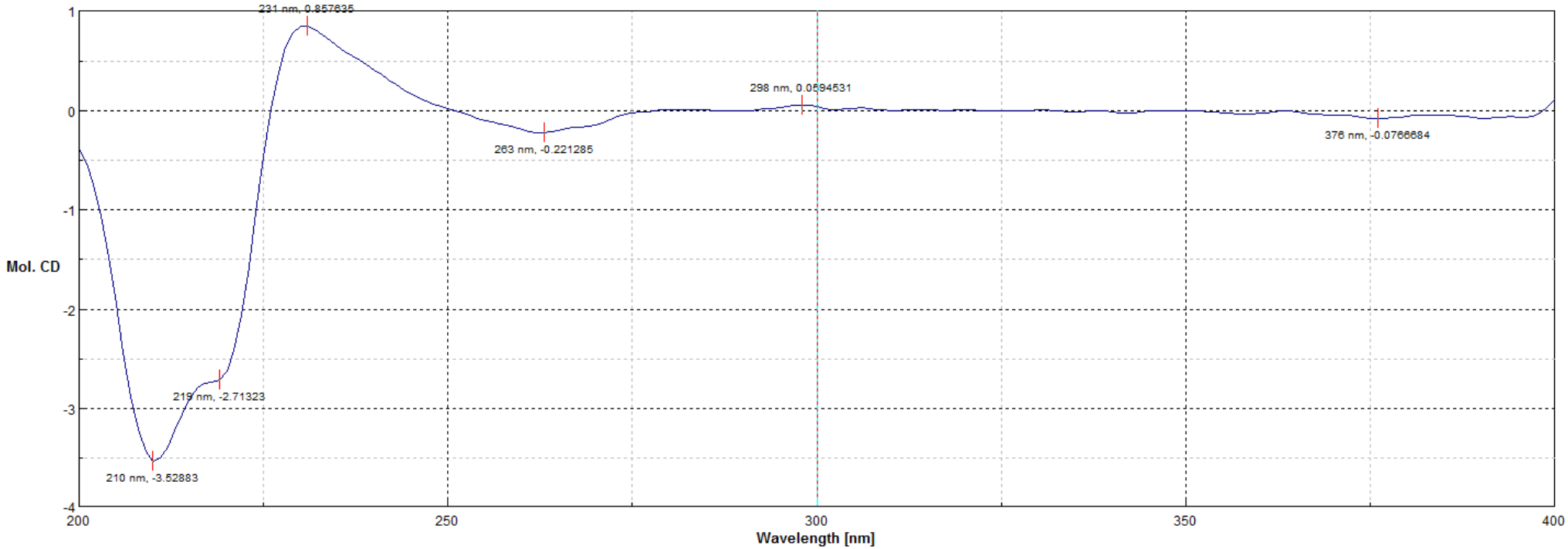
S 19 HSQC spectrum of the new compound **3.**



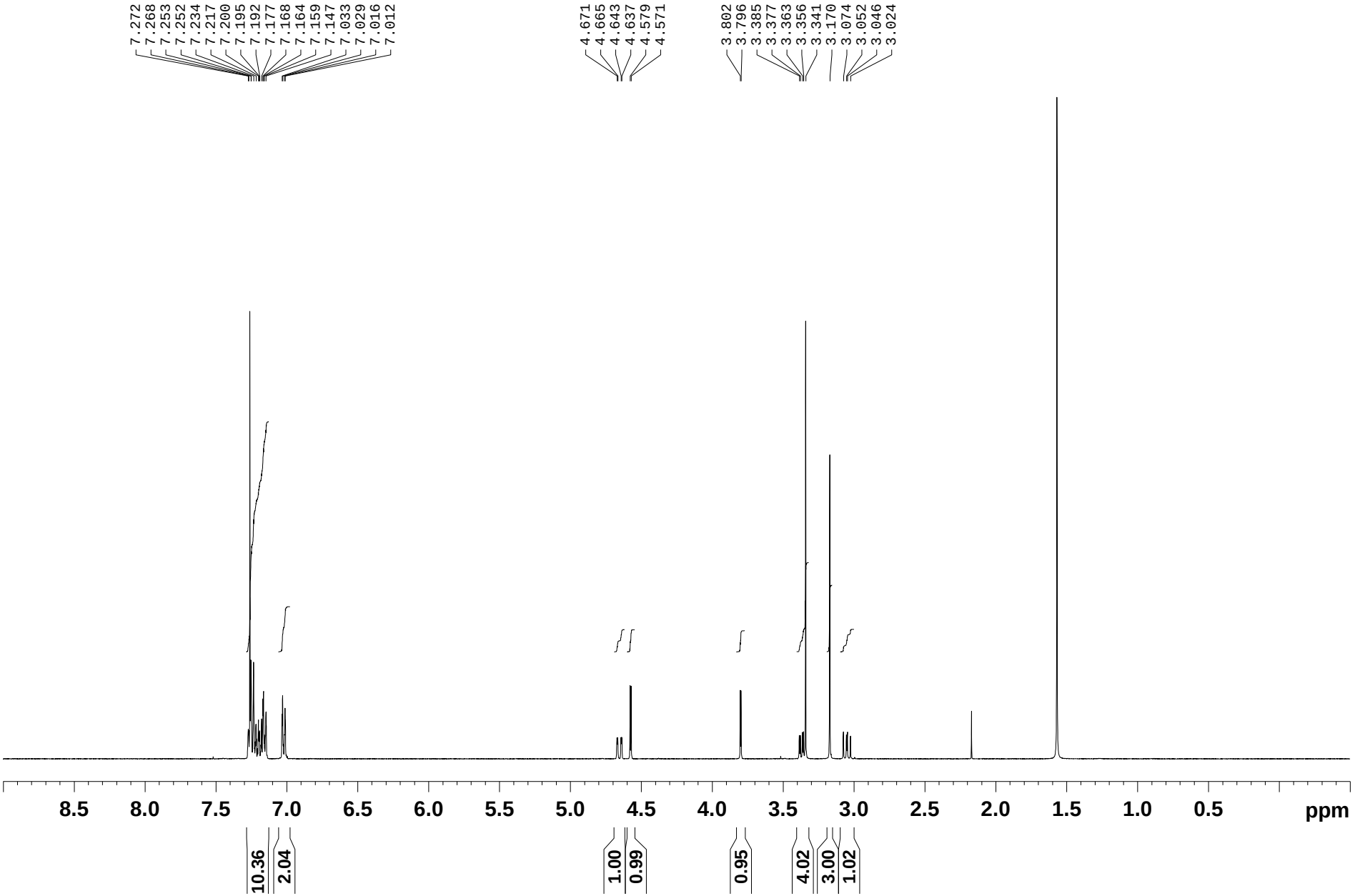
S 20 HMBC spectrum of the new compound **3.**



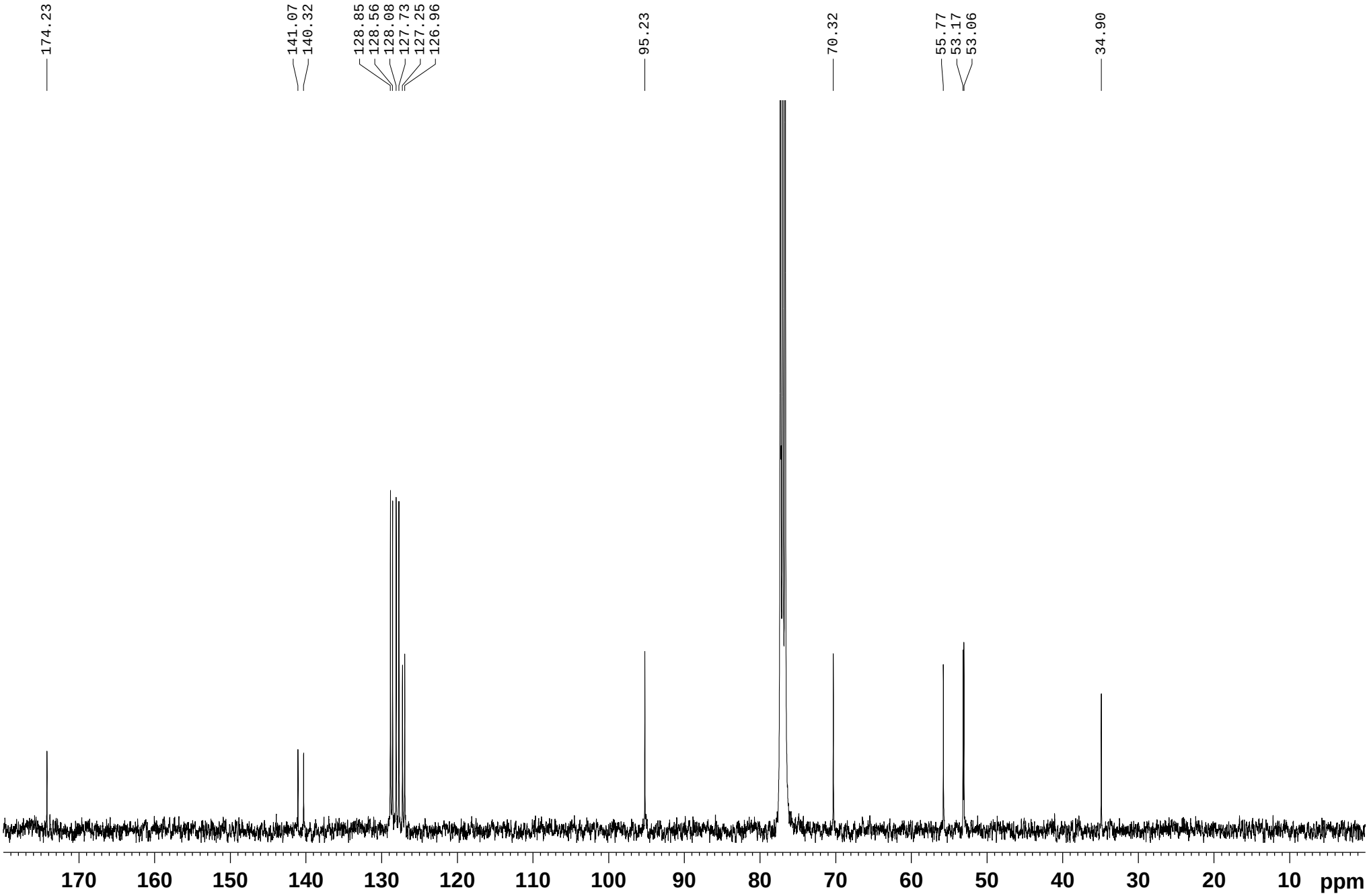
S 21 CD spectrum of the new compound **3.**



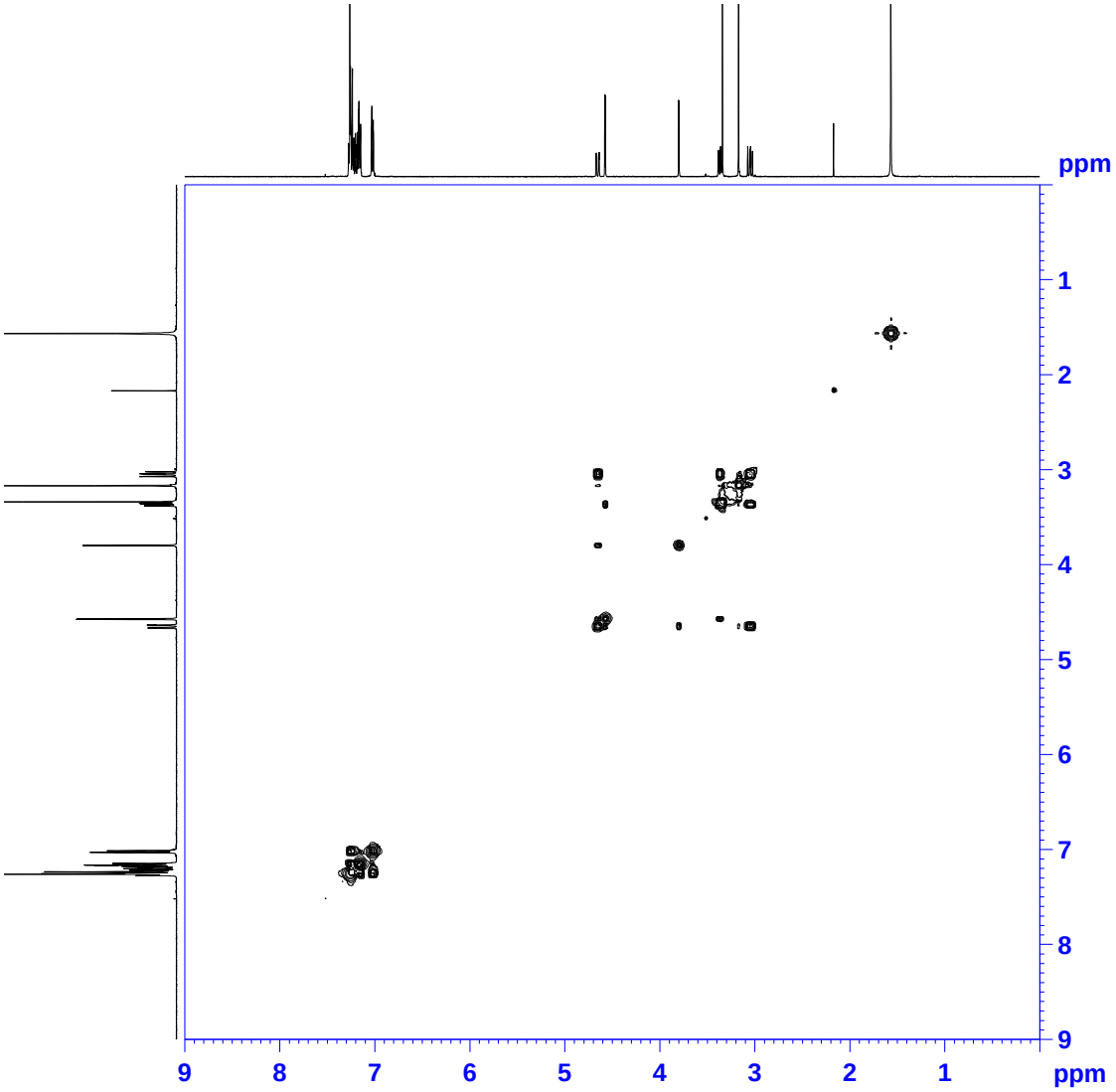
S 22 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **4.**



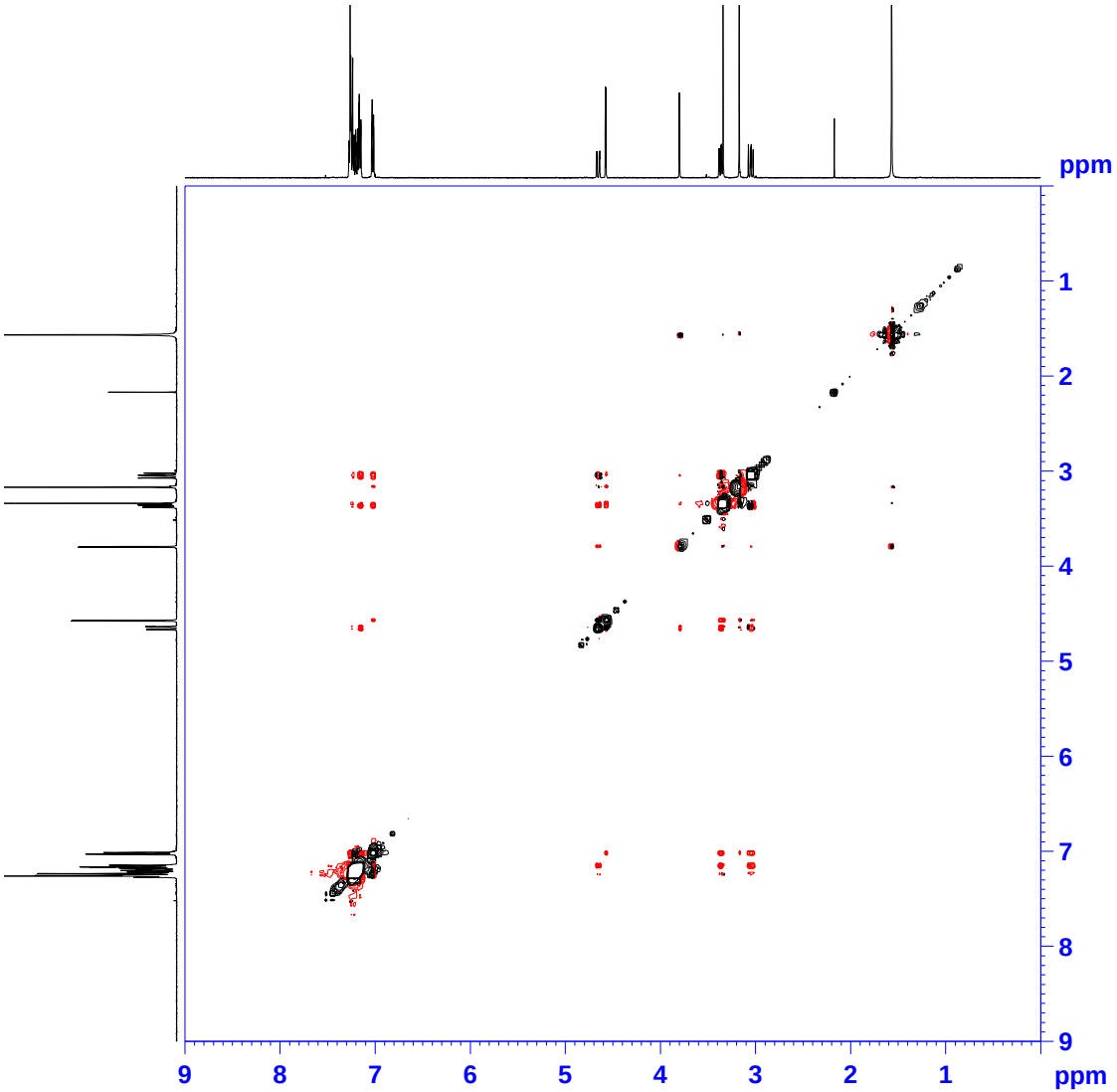
S 23 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **4.**



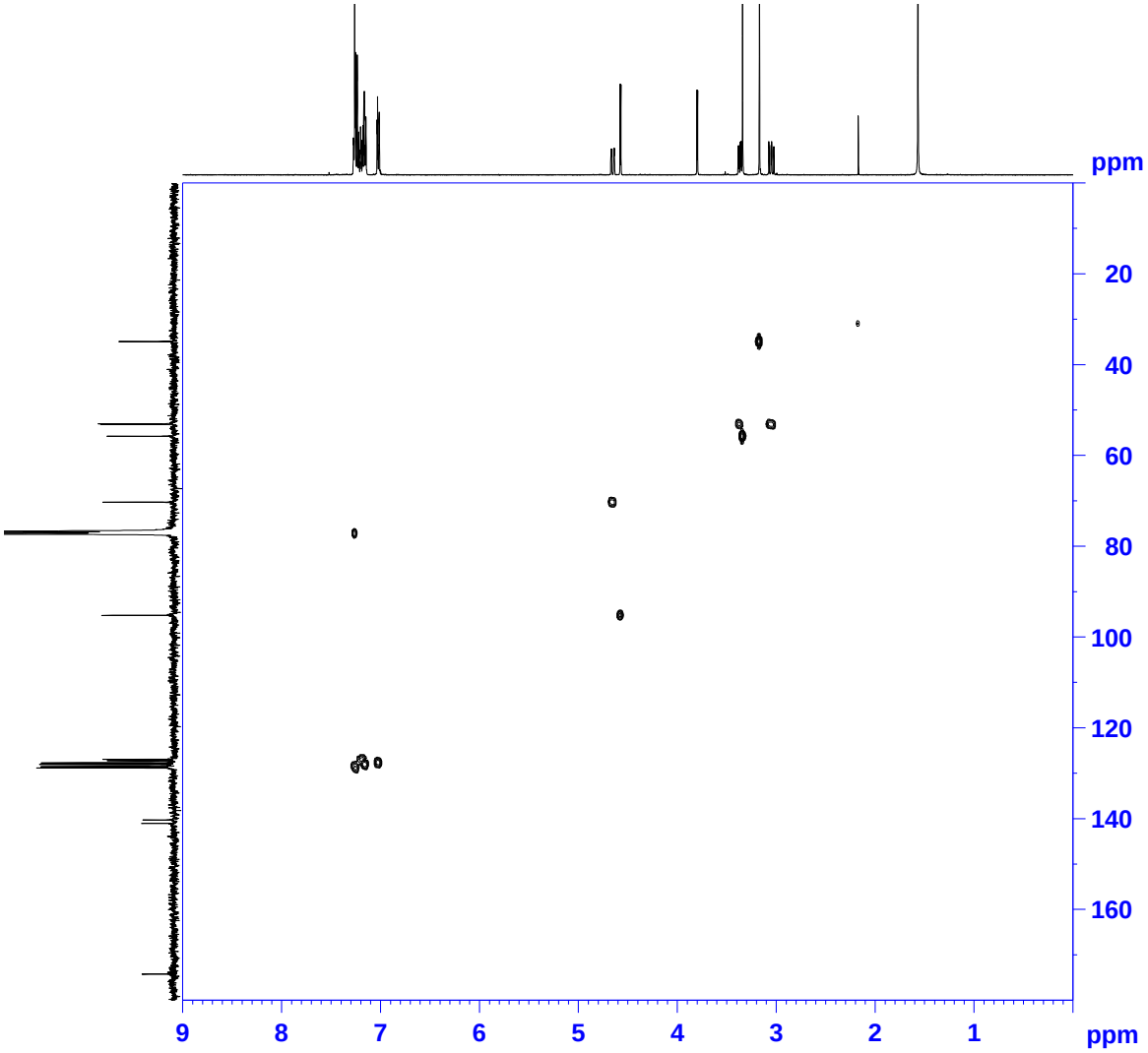
S 24 COSY spectrum of the new compound **4.**



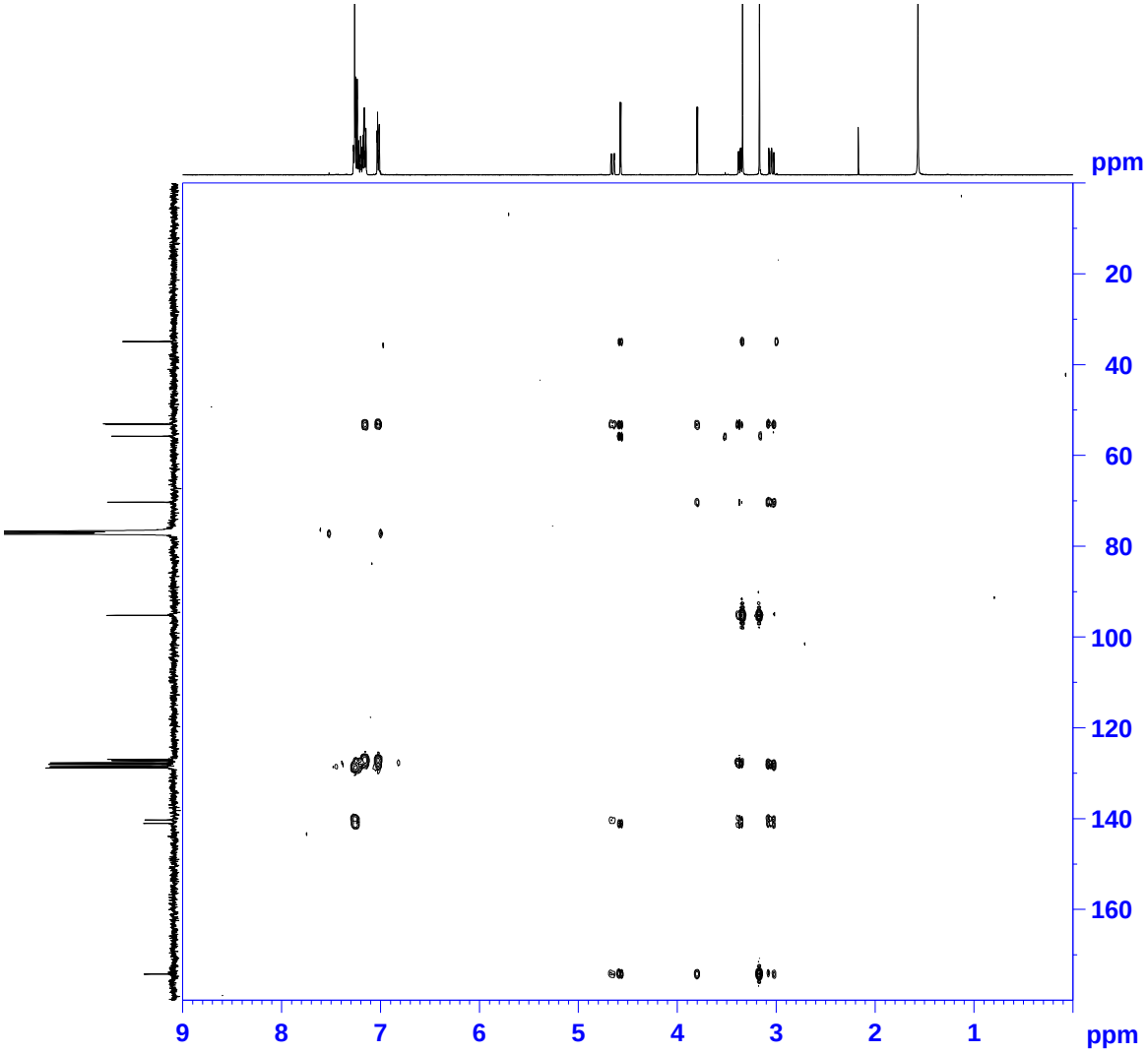
S 25 NOESY spectrum of the new compound **4.**



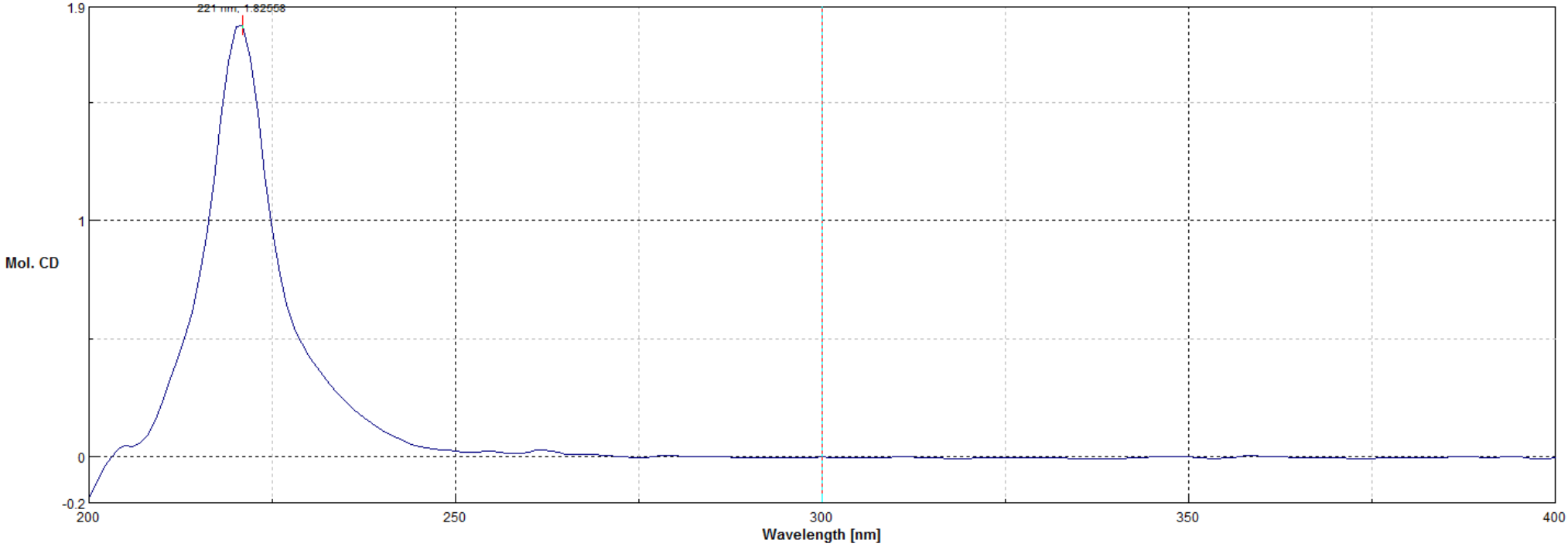
S 26 HSQC spectrum of the new compound **4.**



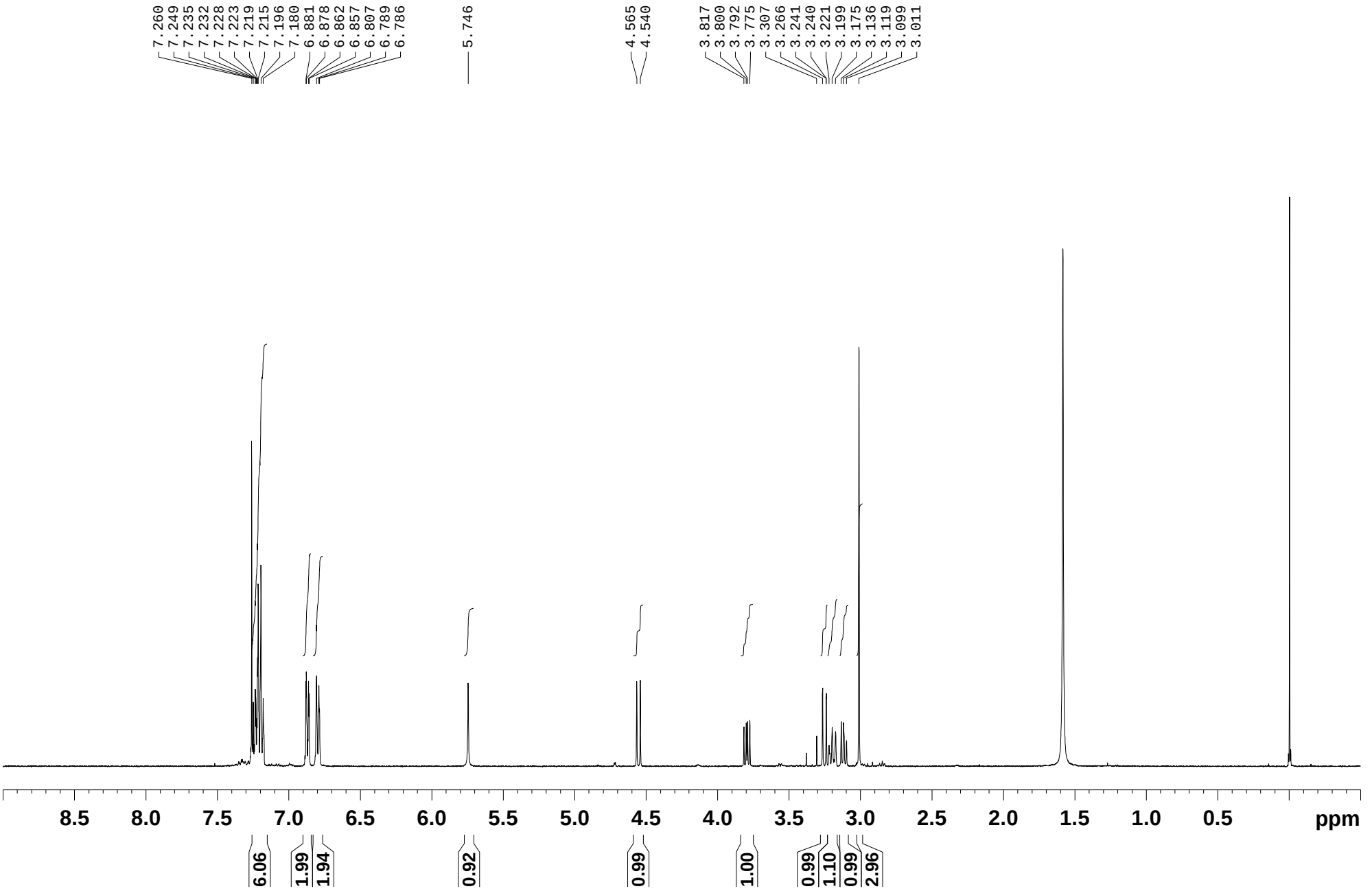
S 27 HMBC spectrum of the new compound **4.**



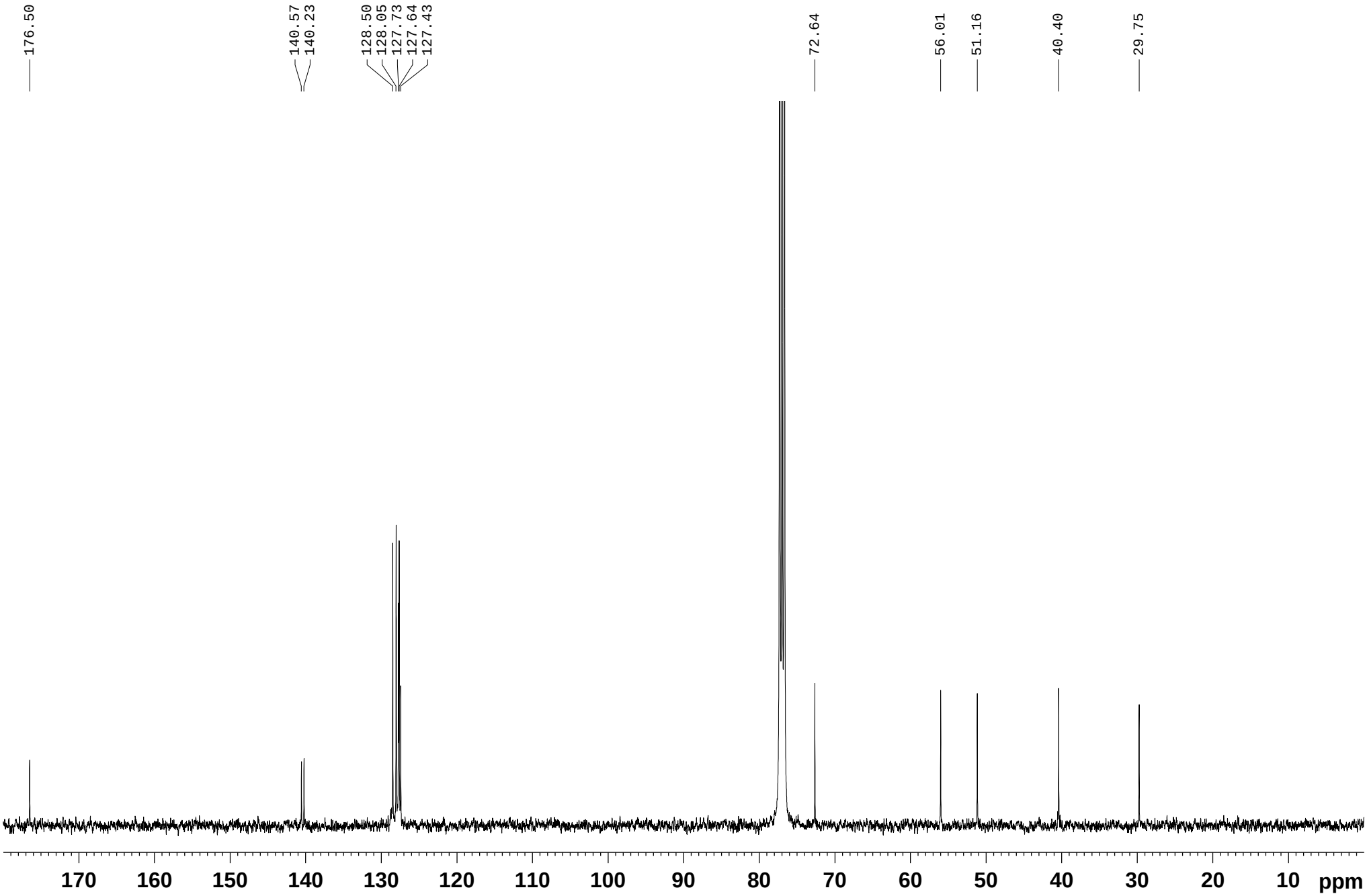
S 28 CD spectrum of the new compound **4.**



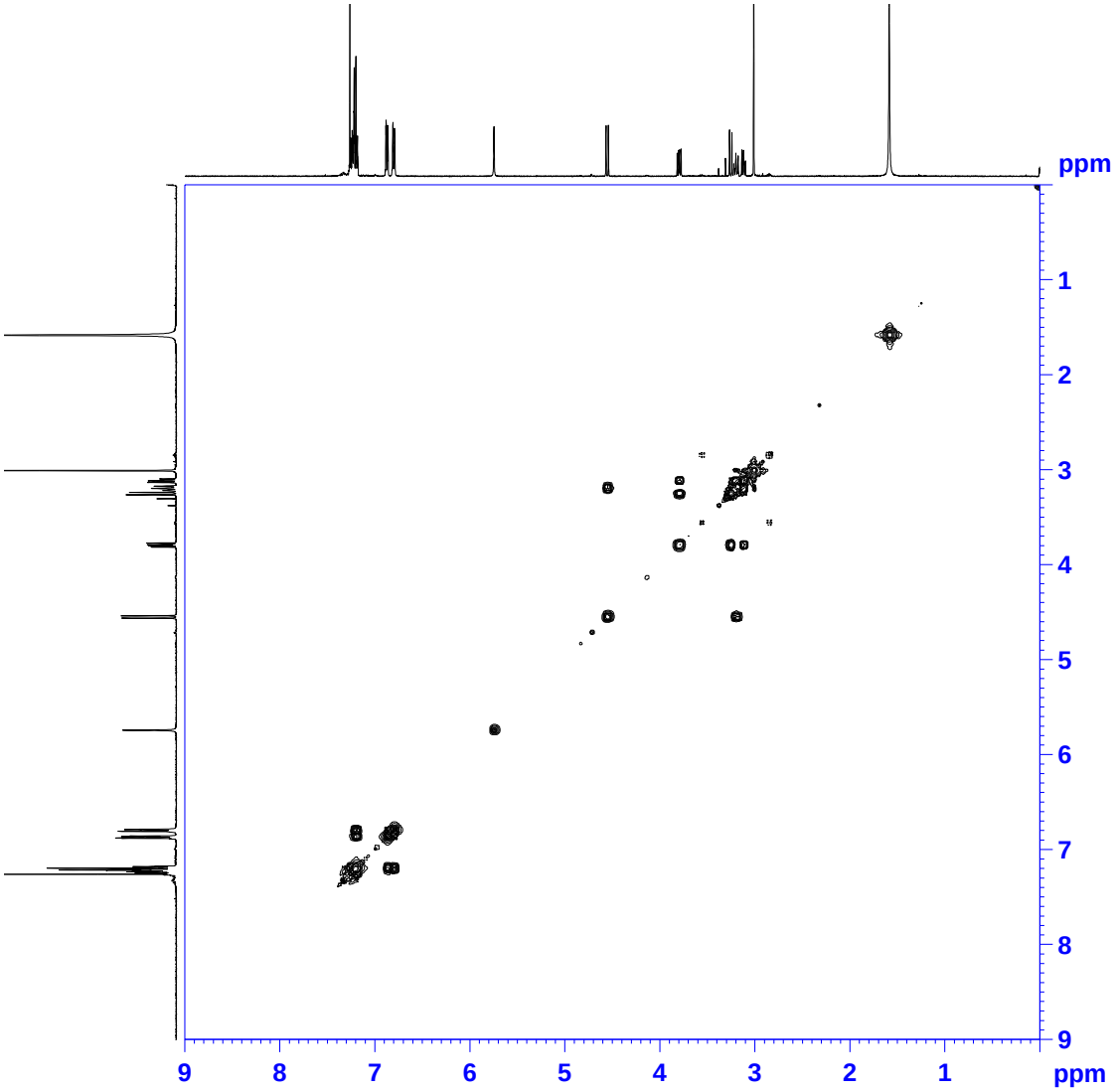
S 29 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **5.**



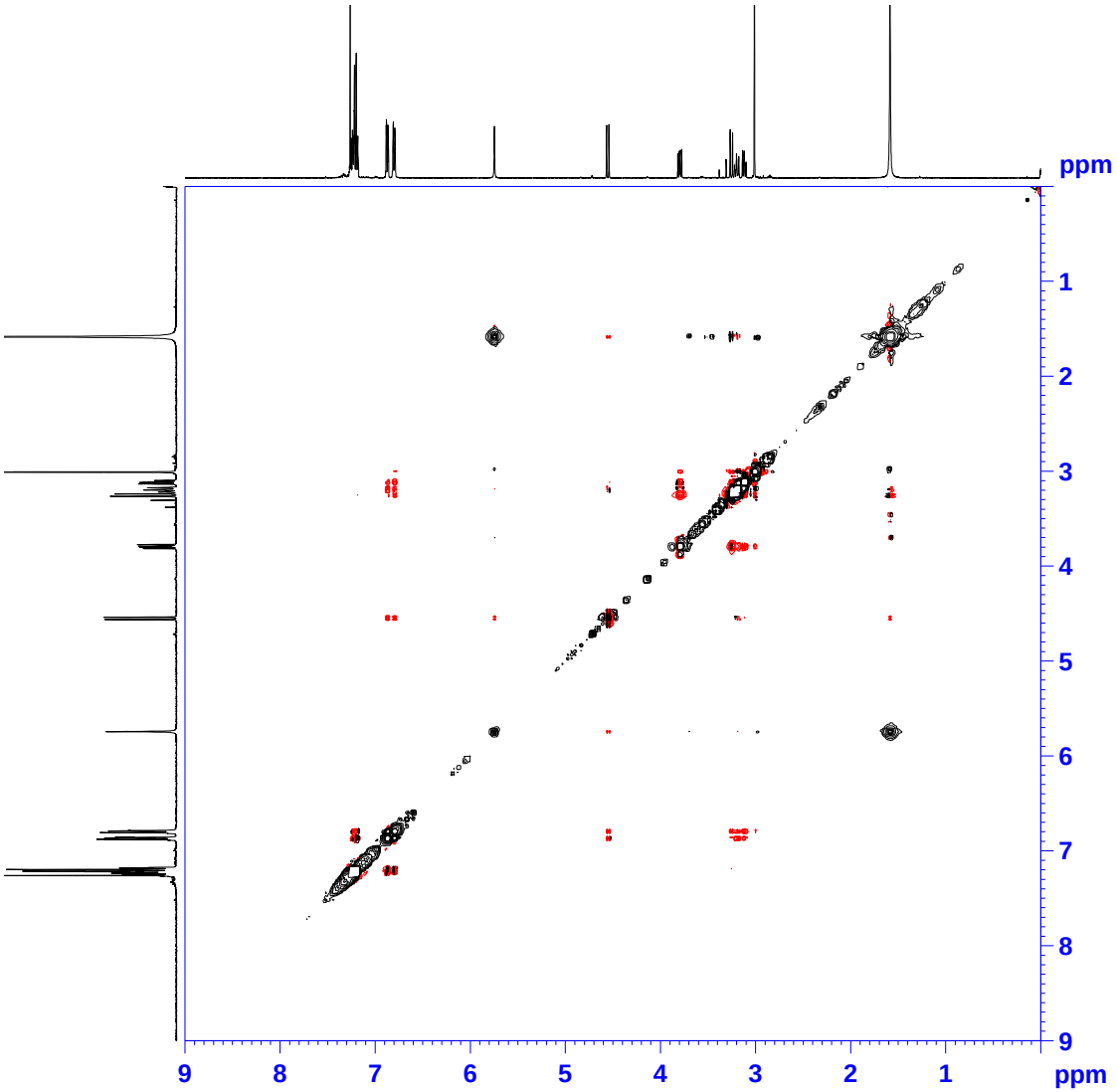
S 30 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **5.**



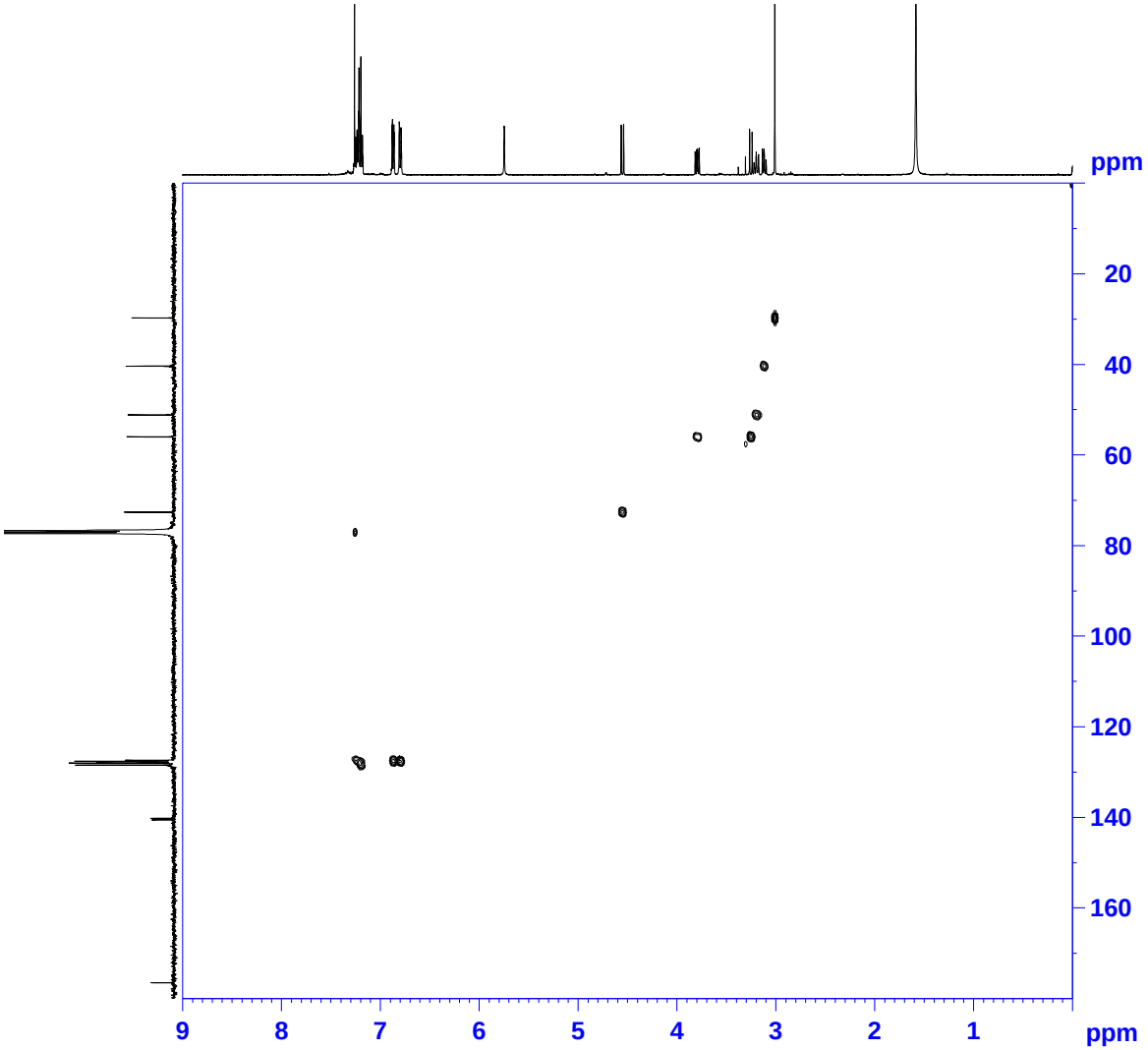
S 31 COSY spectrum of the new compound **5.**



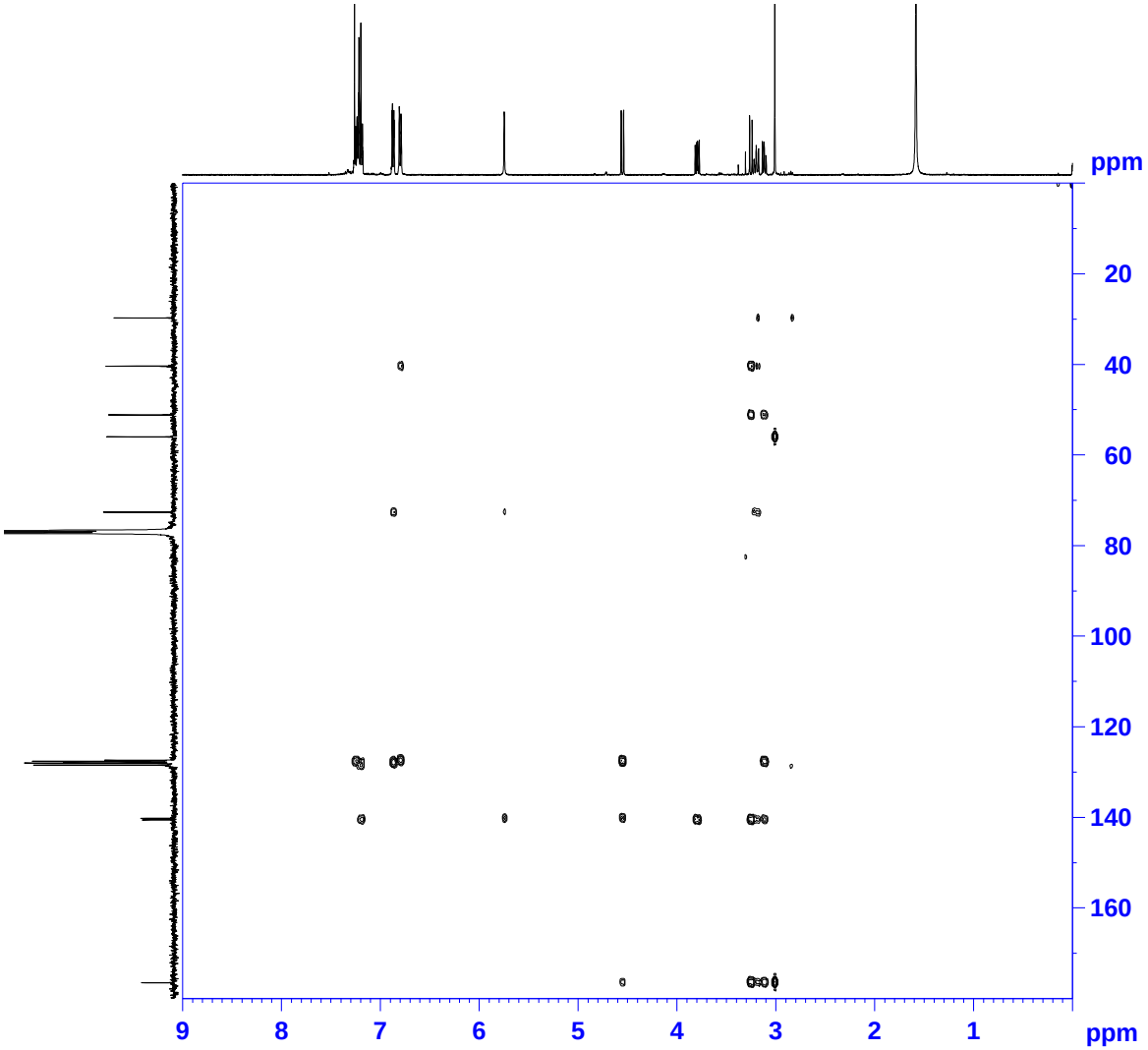
S 32 NOESY spectrum of the new compound **5.**



S 33 HSQC spectrum of the new compound **5.**



S 34 HMBC spectrum of the new compound **5.**



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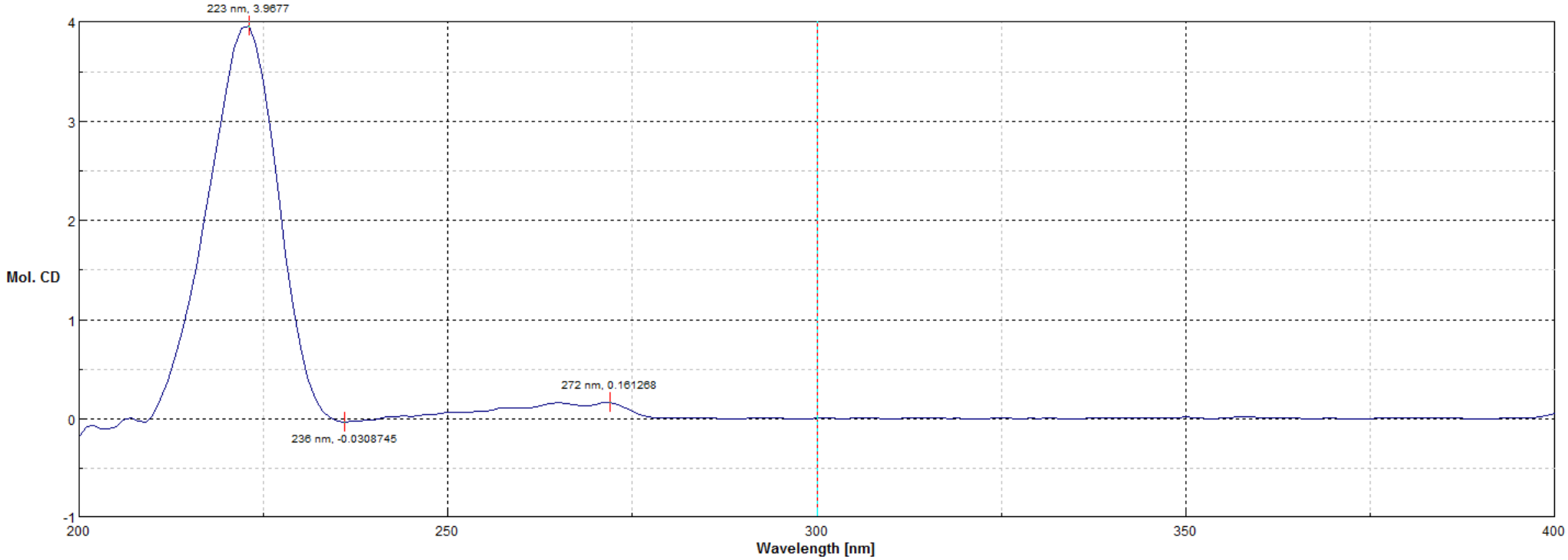
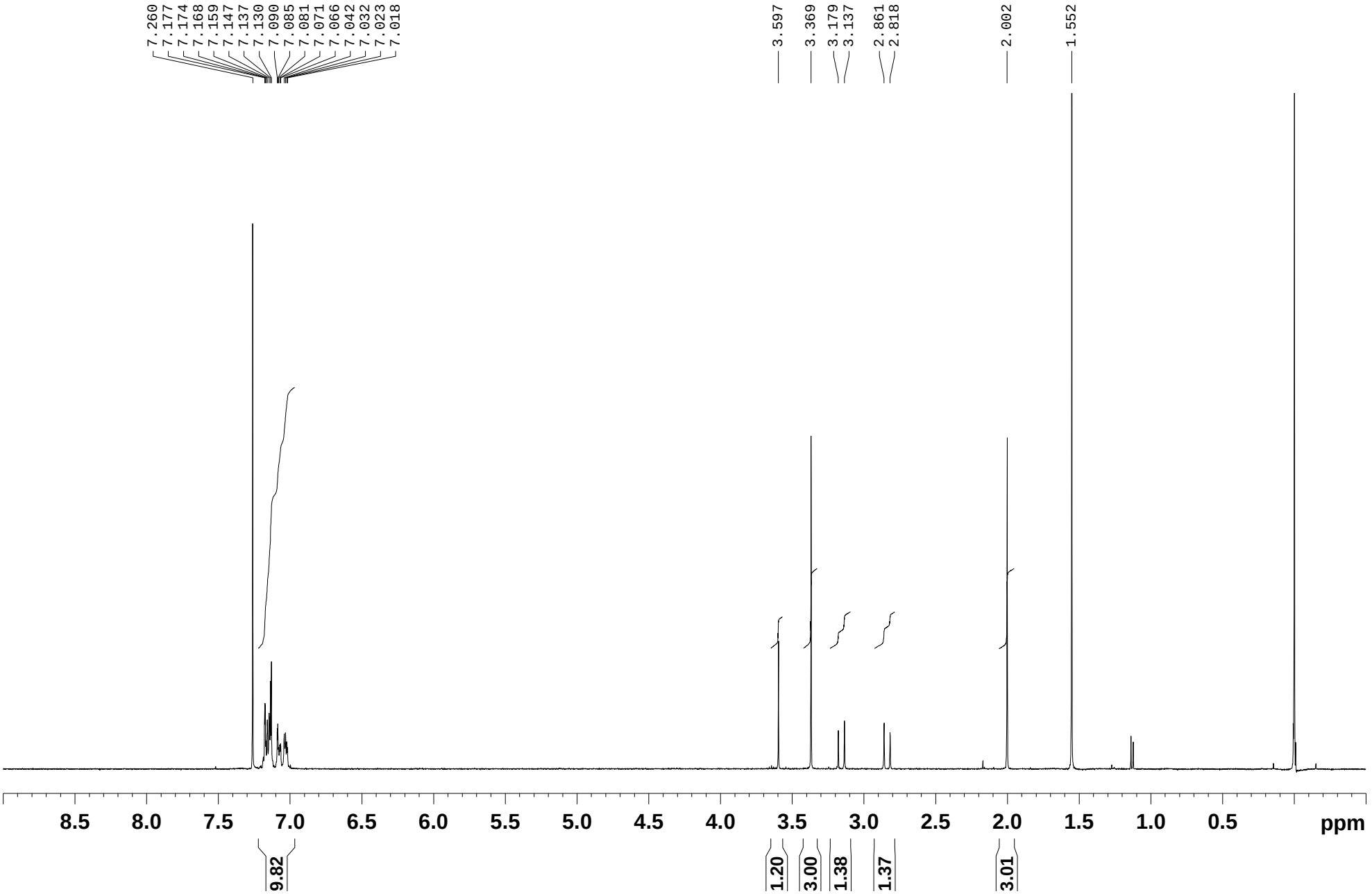
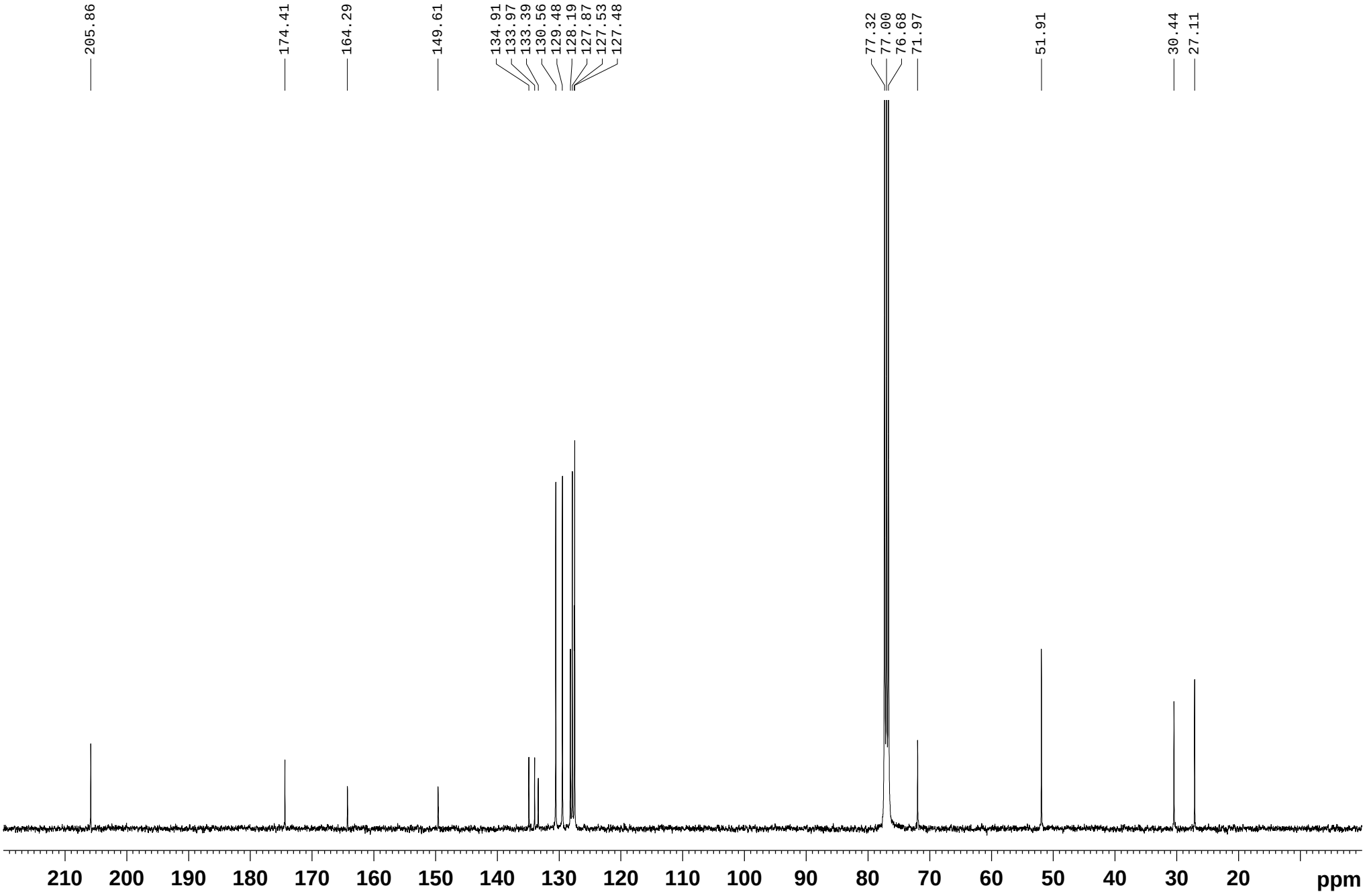


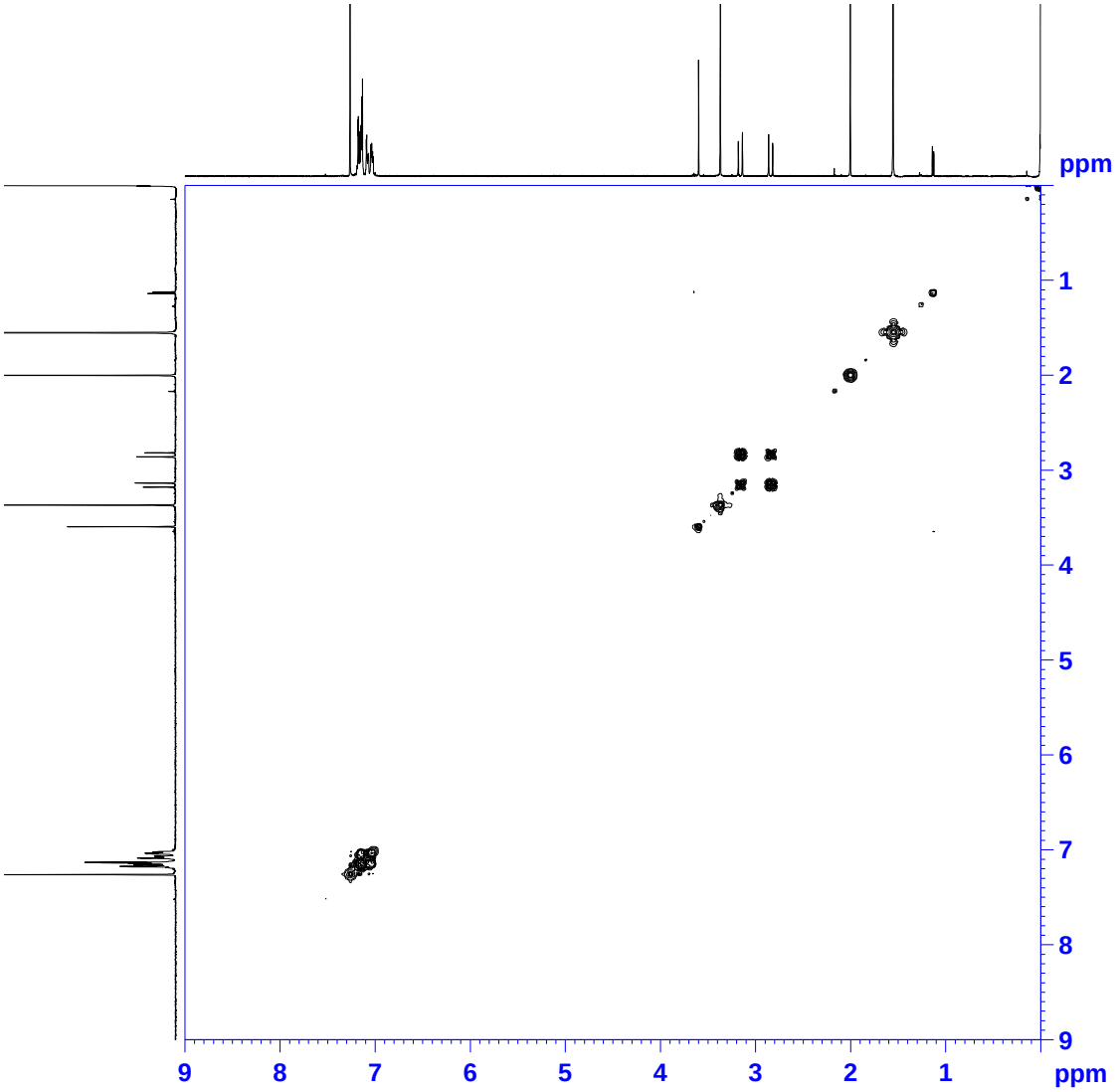
S 36 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **6.**



S 37 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the new compound **6.**



S 38 COSY spectrum of the new compound **6.**



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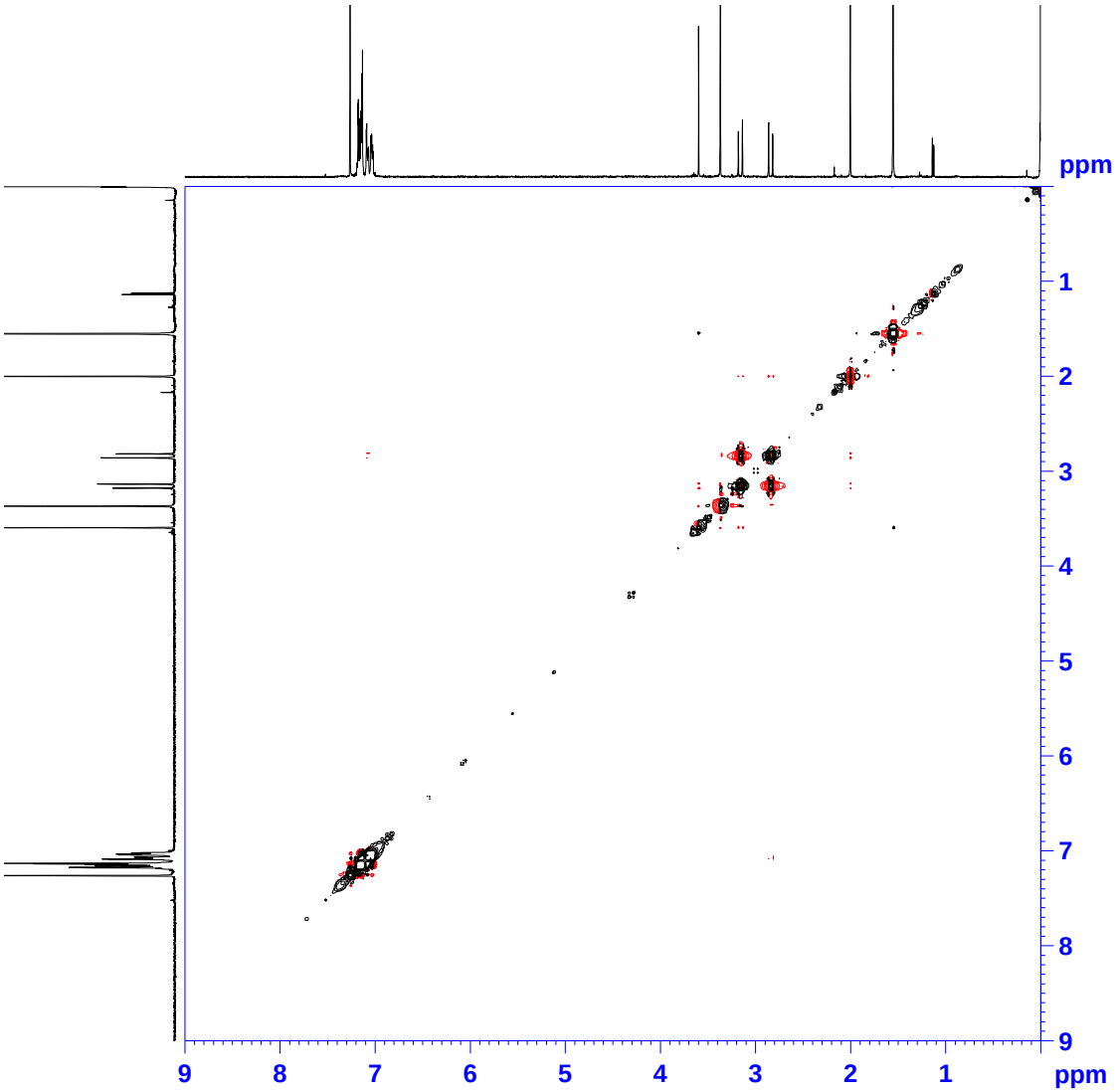
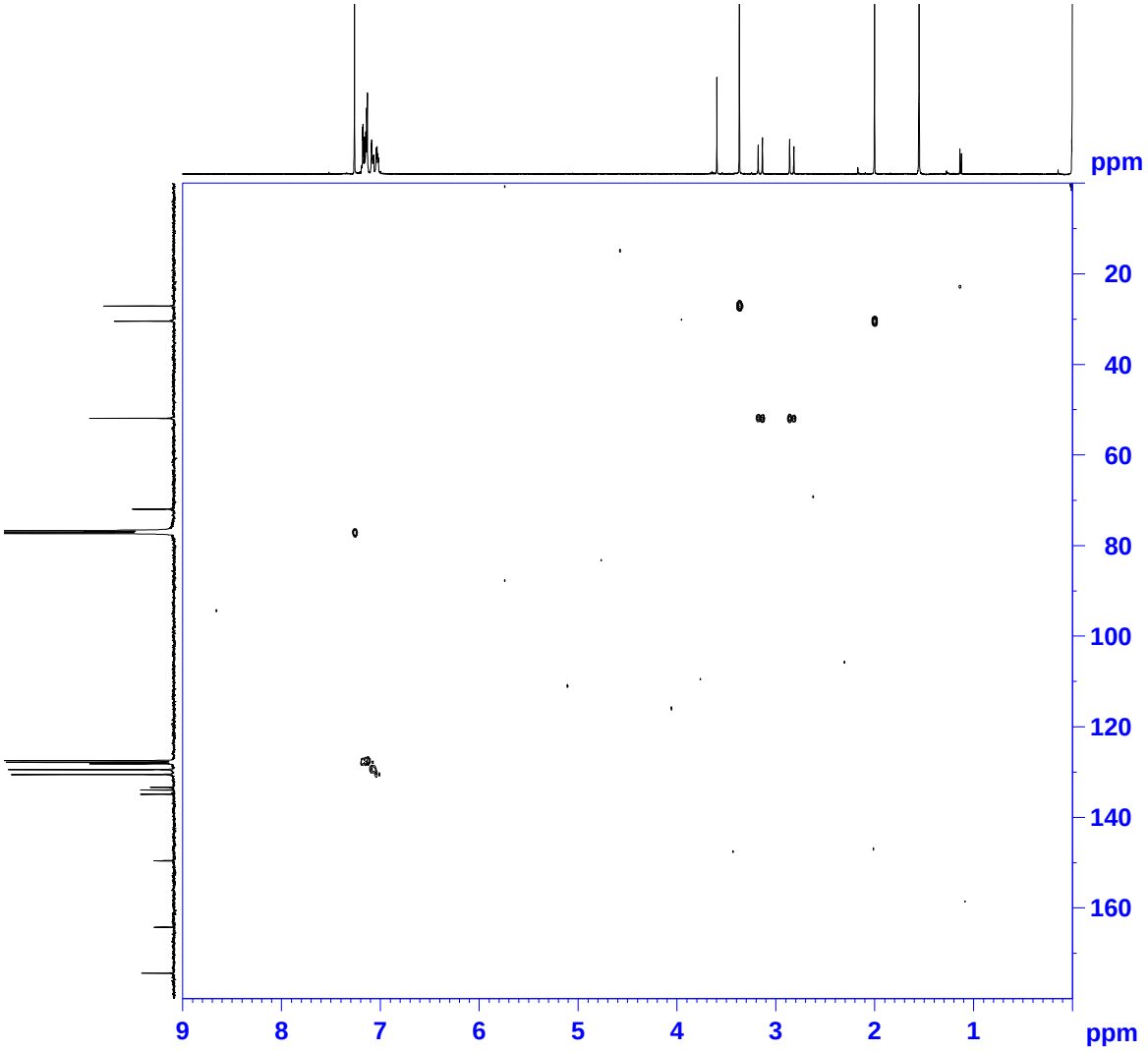
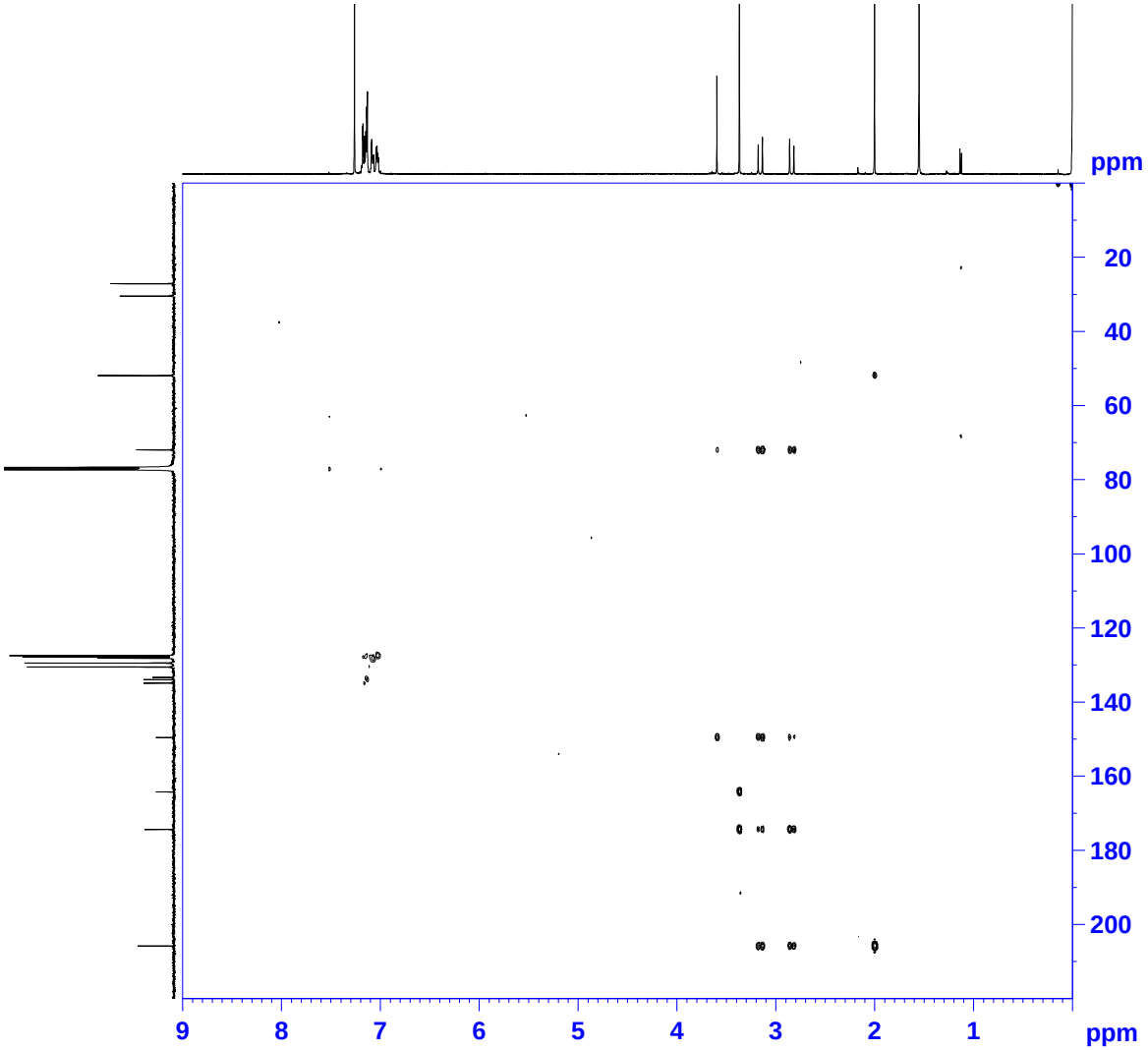


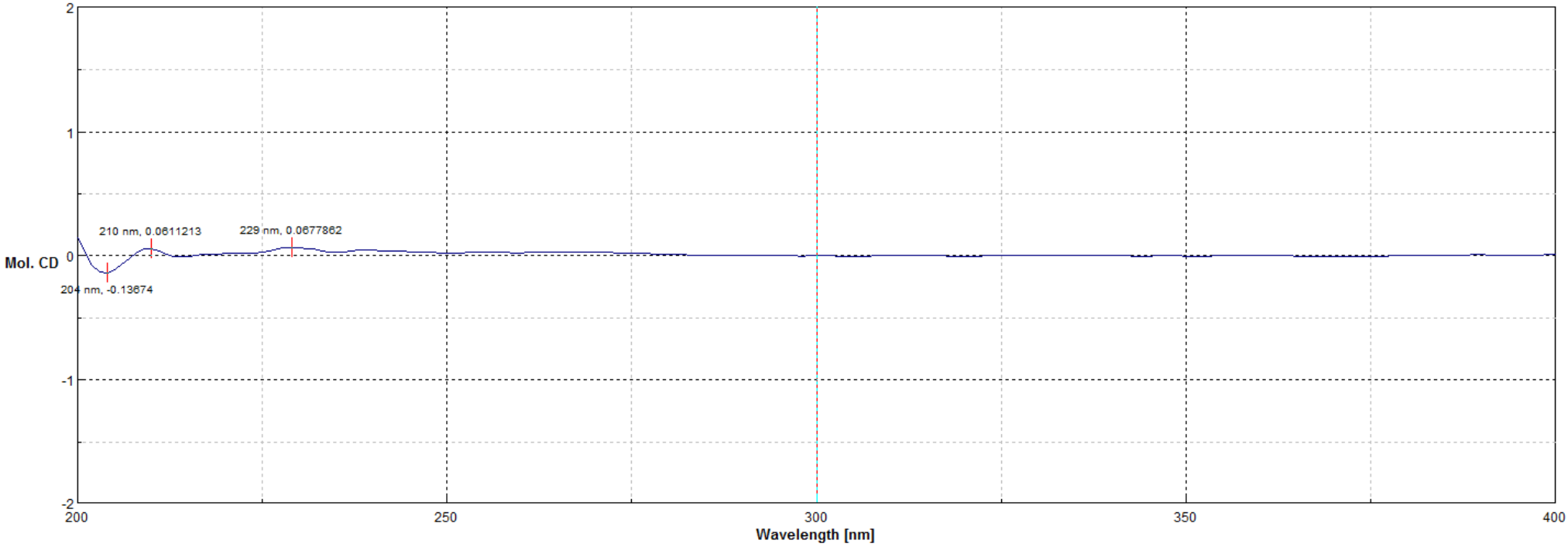
S 40 HSQC spectrum of the new compound **6.**



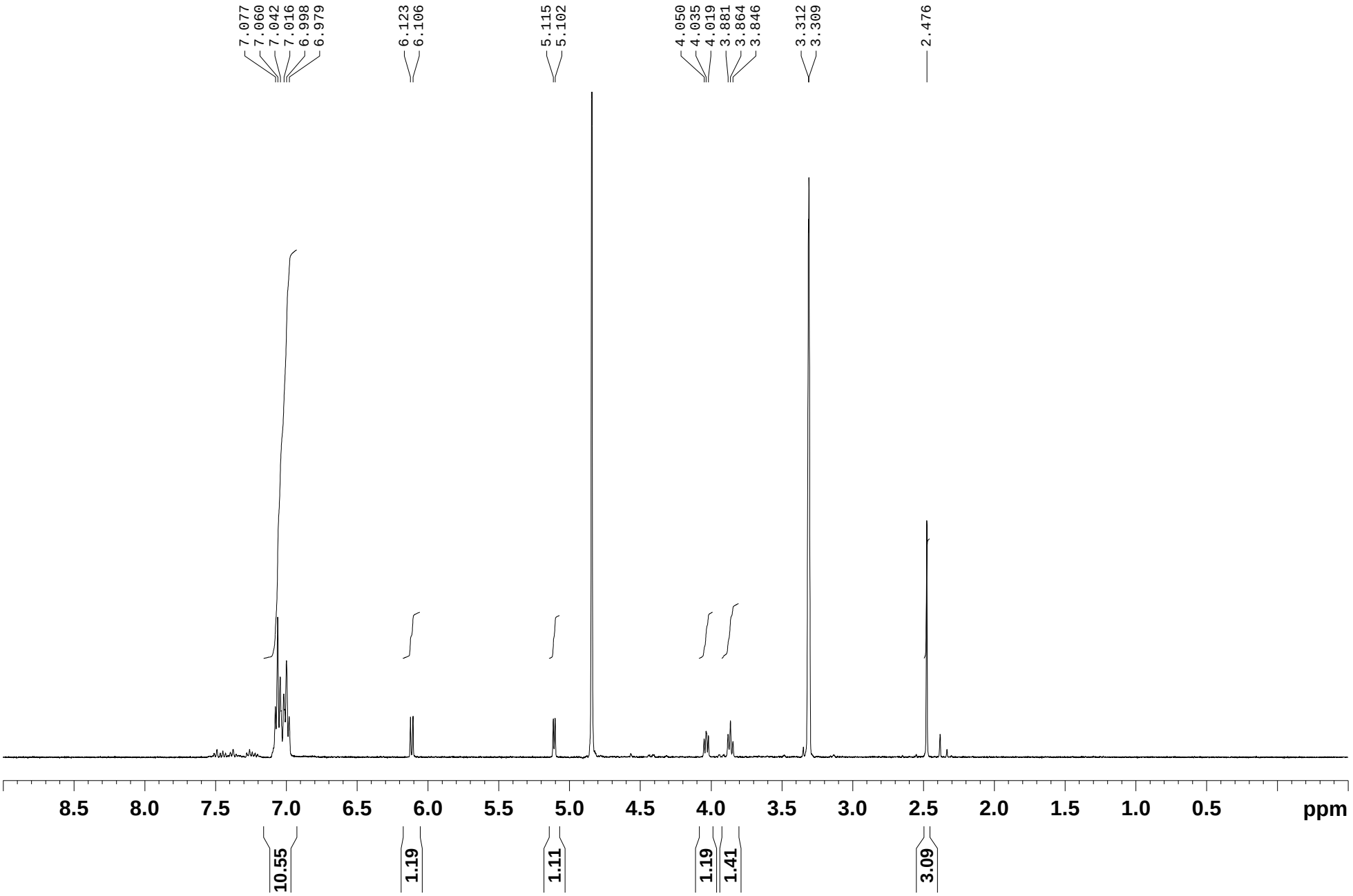
S 41 HMBC spectrum of the new compound **6.**



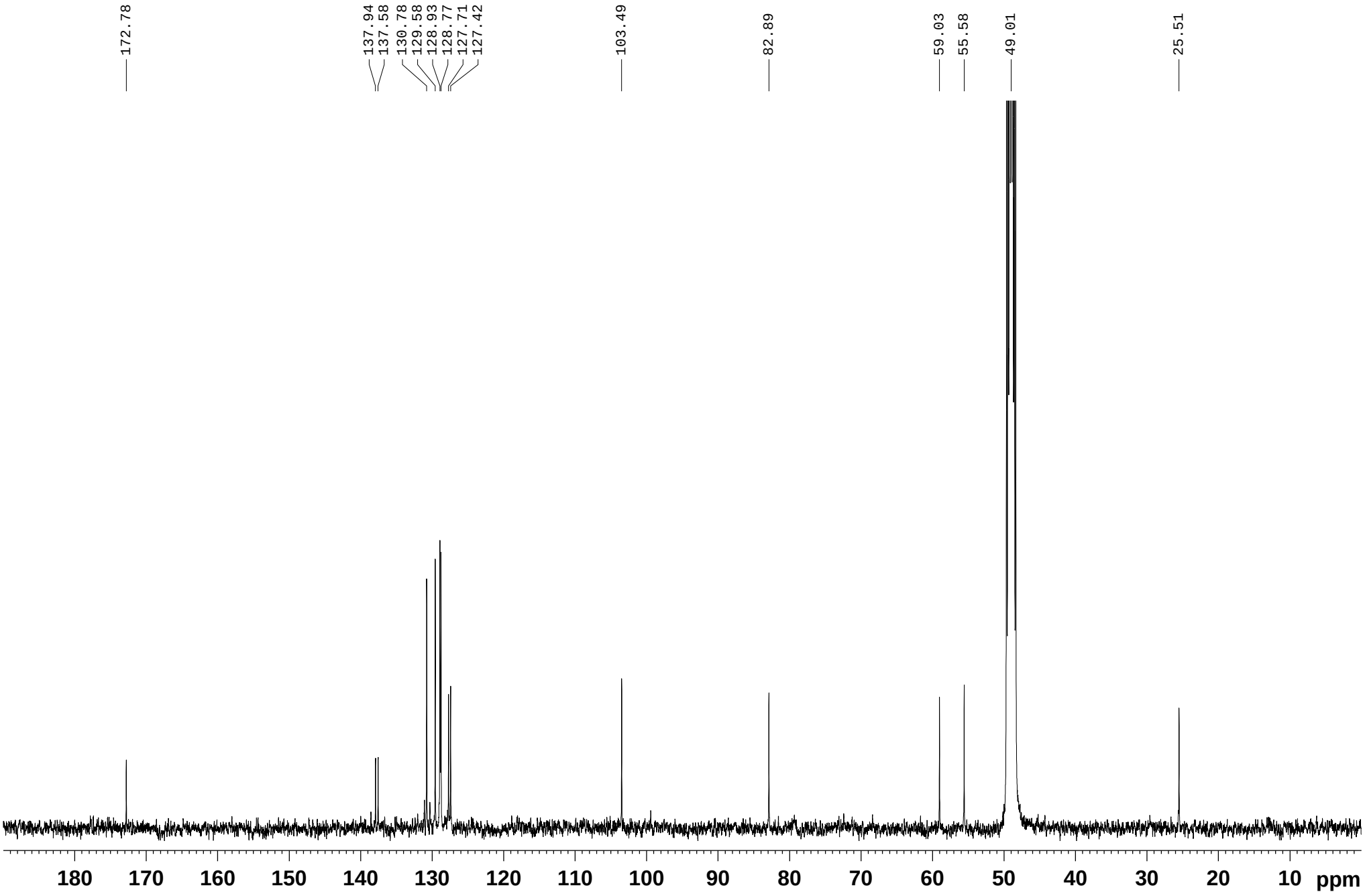
S 42 CD spectrum of the new compound **6.**



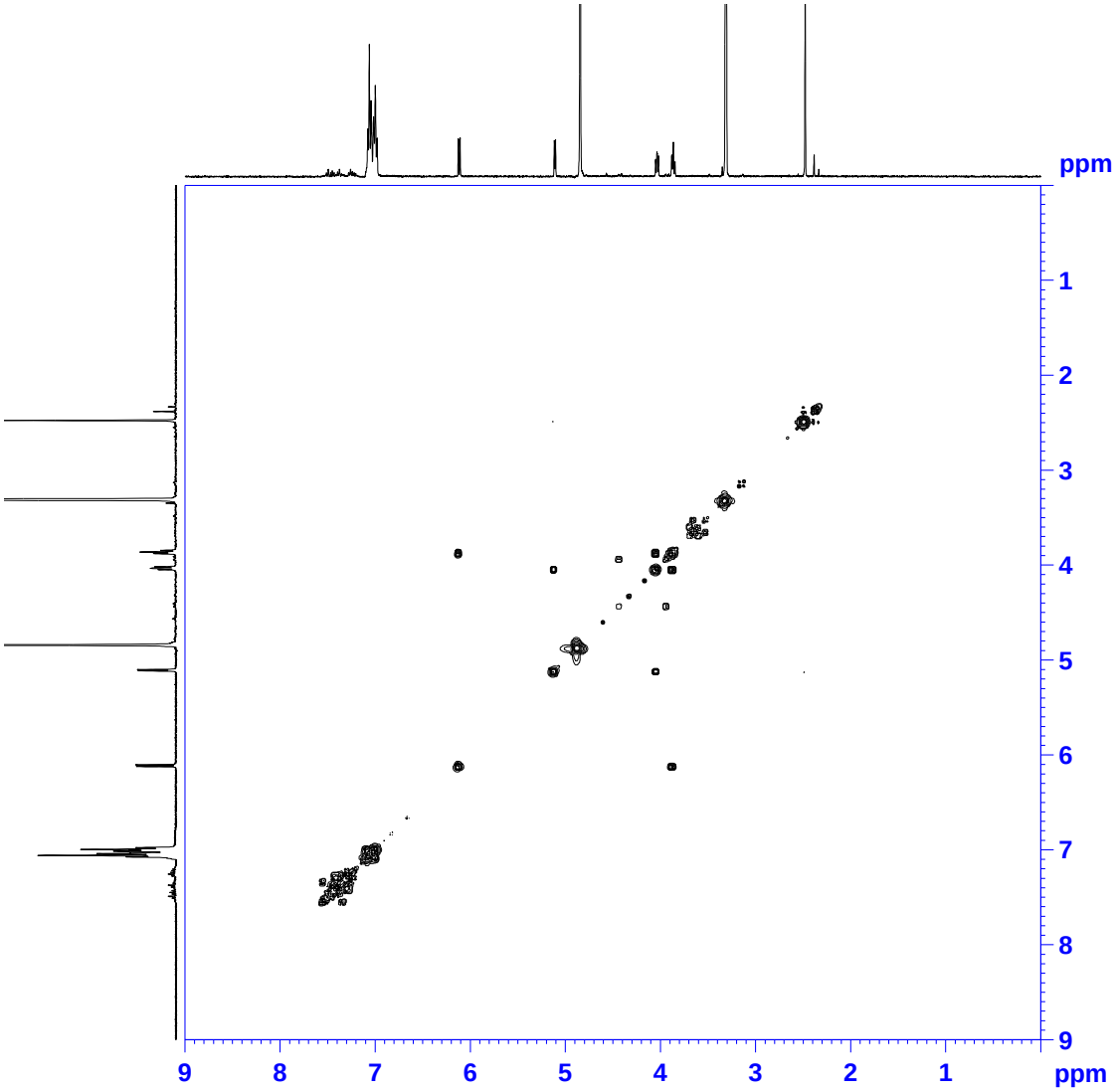
S 43 ^{1}H NMR (400 MHz, CD_3OD) spectrum of the new compound **7.**



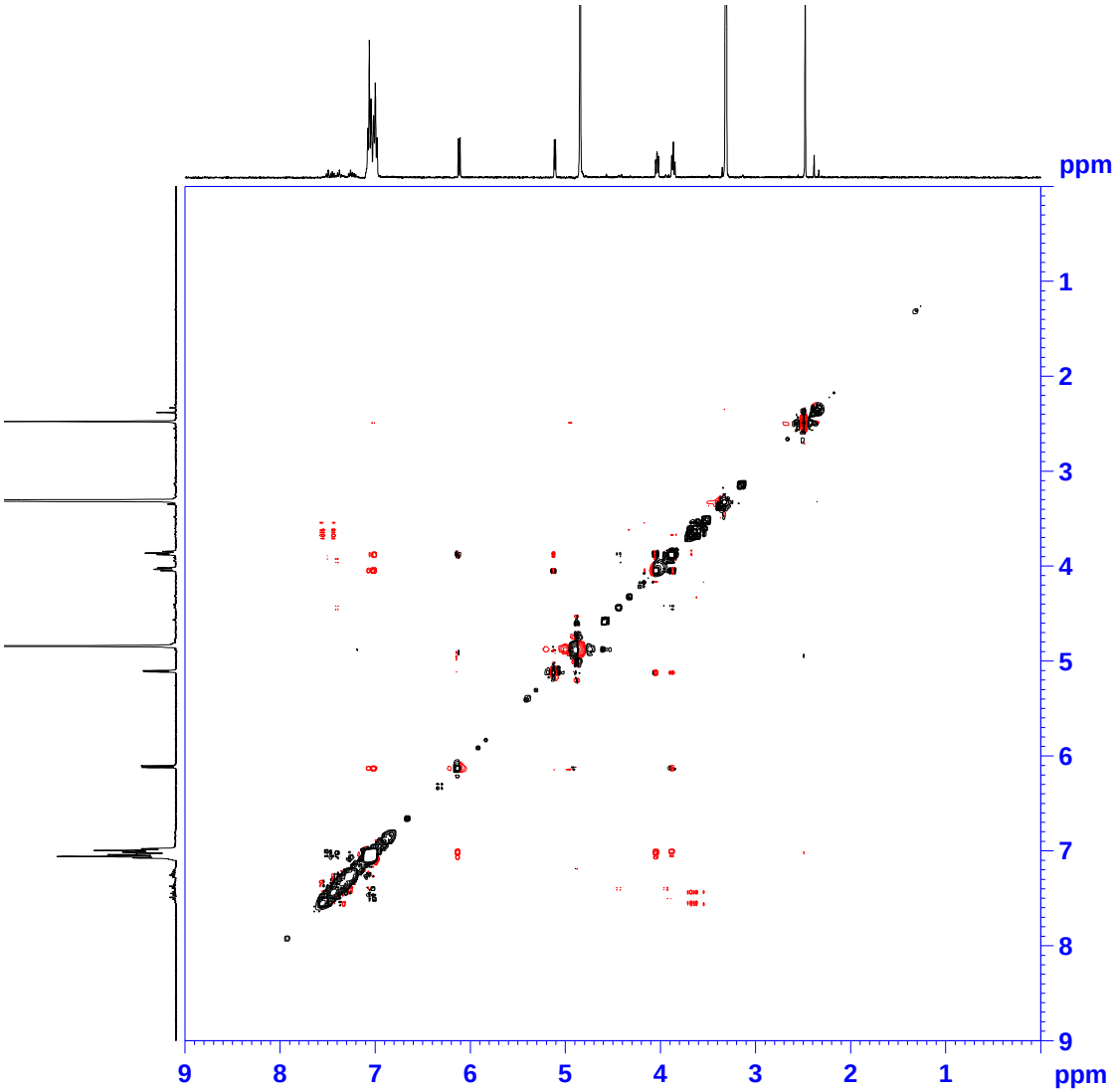
S 44 ^{13}C NMR (100 MHz, CD_3OD) spectrum of the new compound **7.**



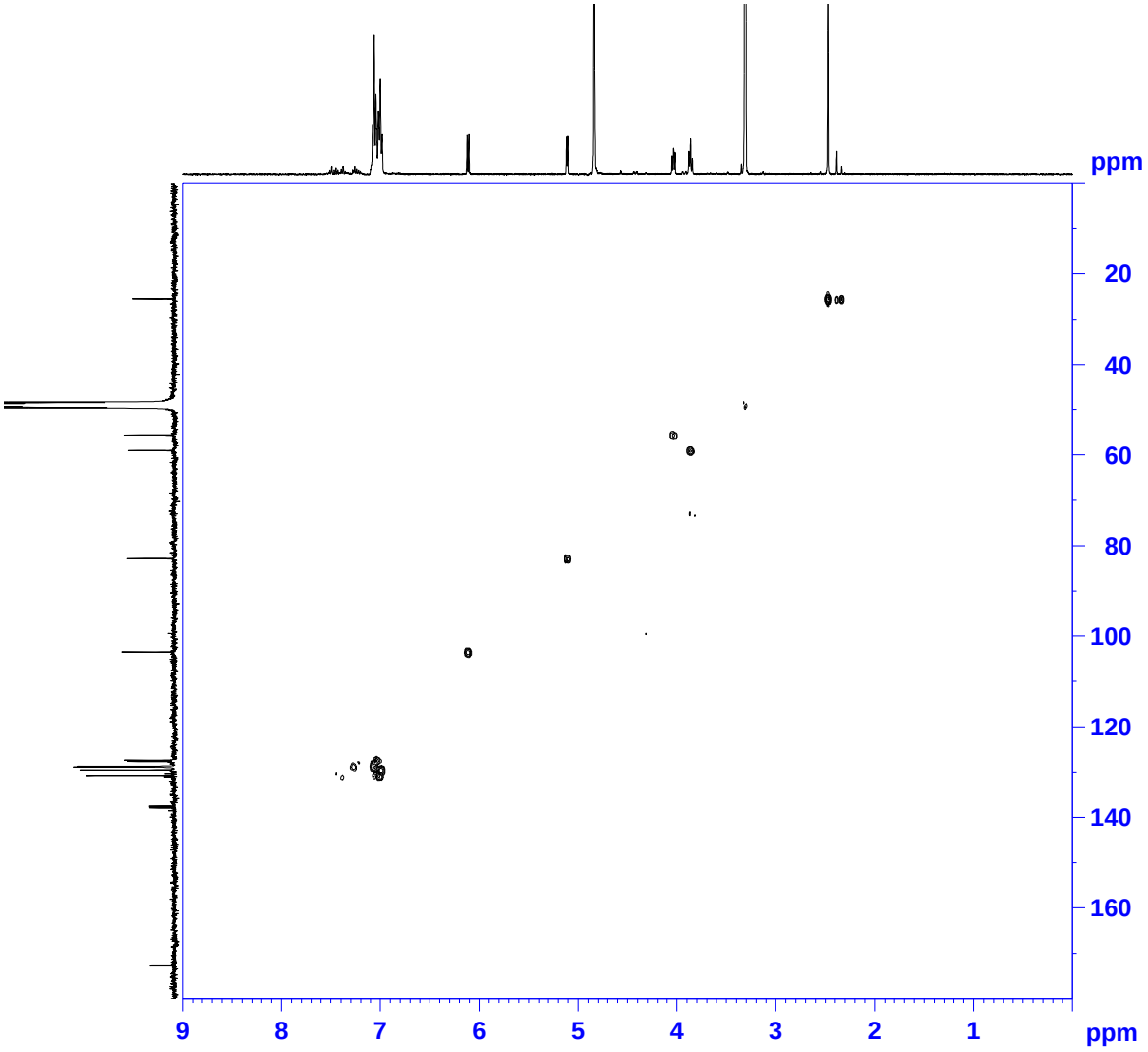
S 45 COSY spectrum of the new compound **7.**



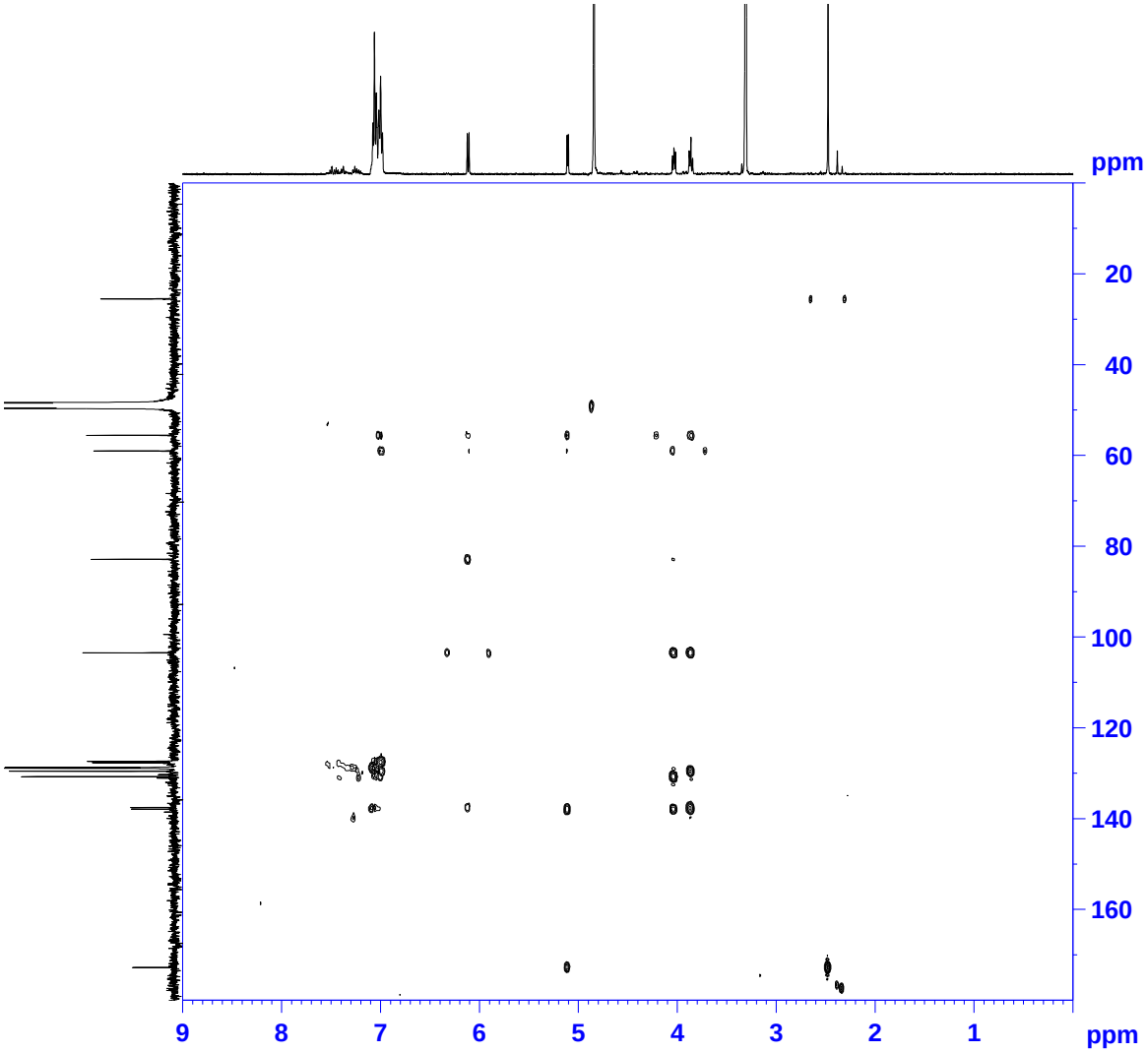
S 46 NOESY spectrum of the new compound **7.**



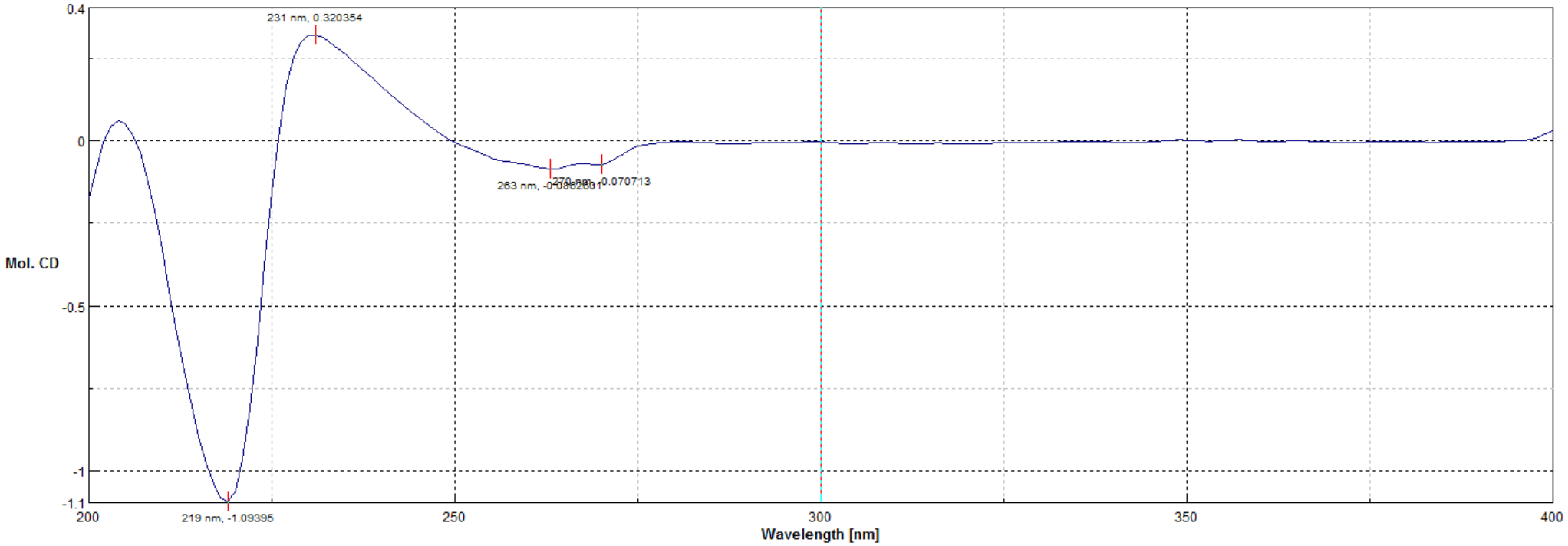
S 47 HSQC spectrum of the new compound **7.**



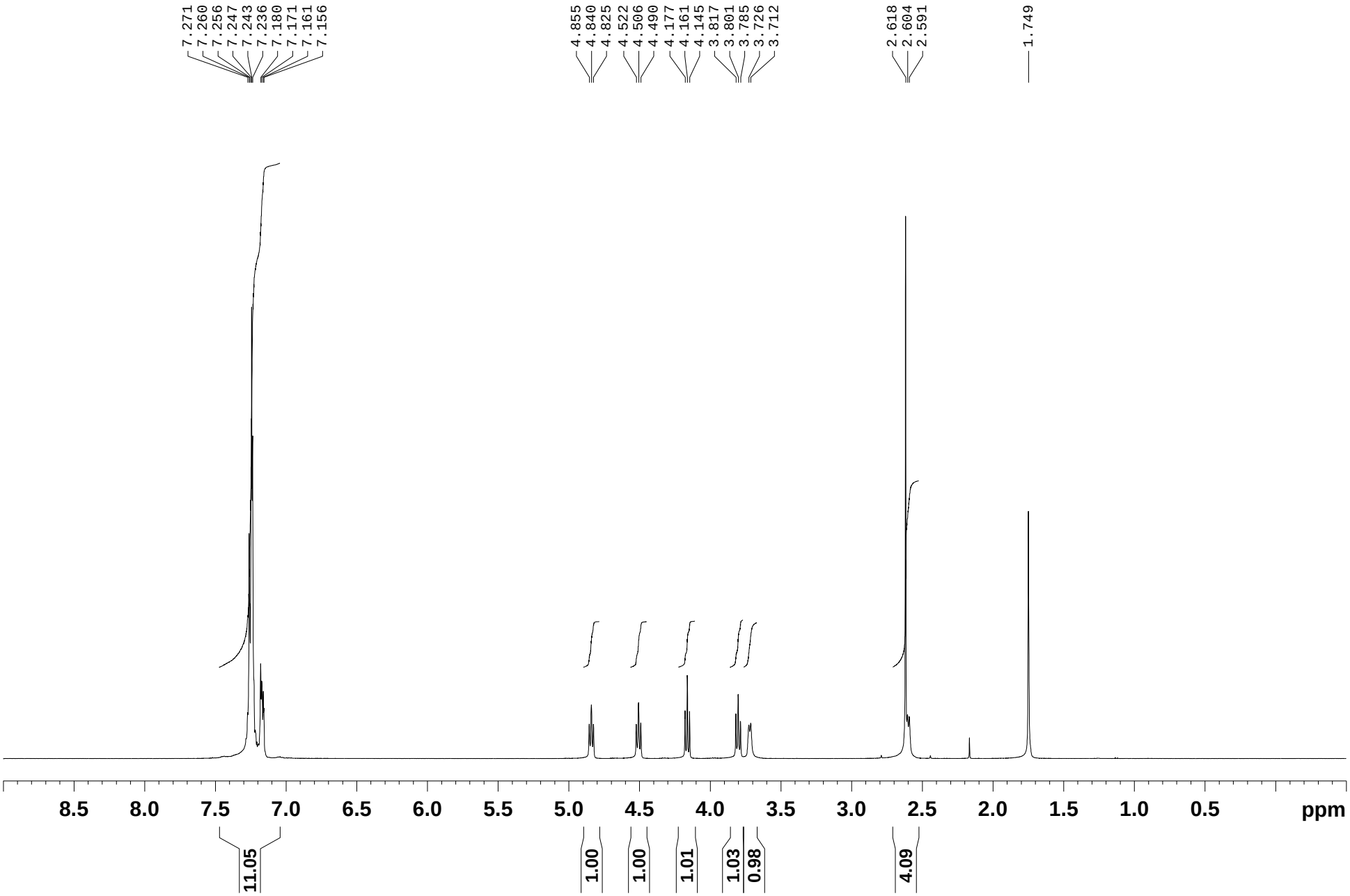
S 48 HMBC spectrum of the new compound **7.**



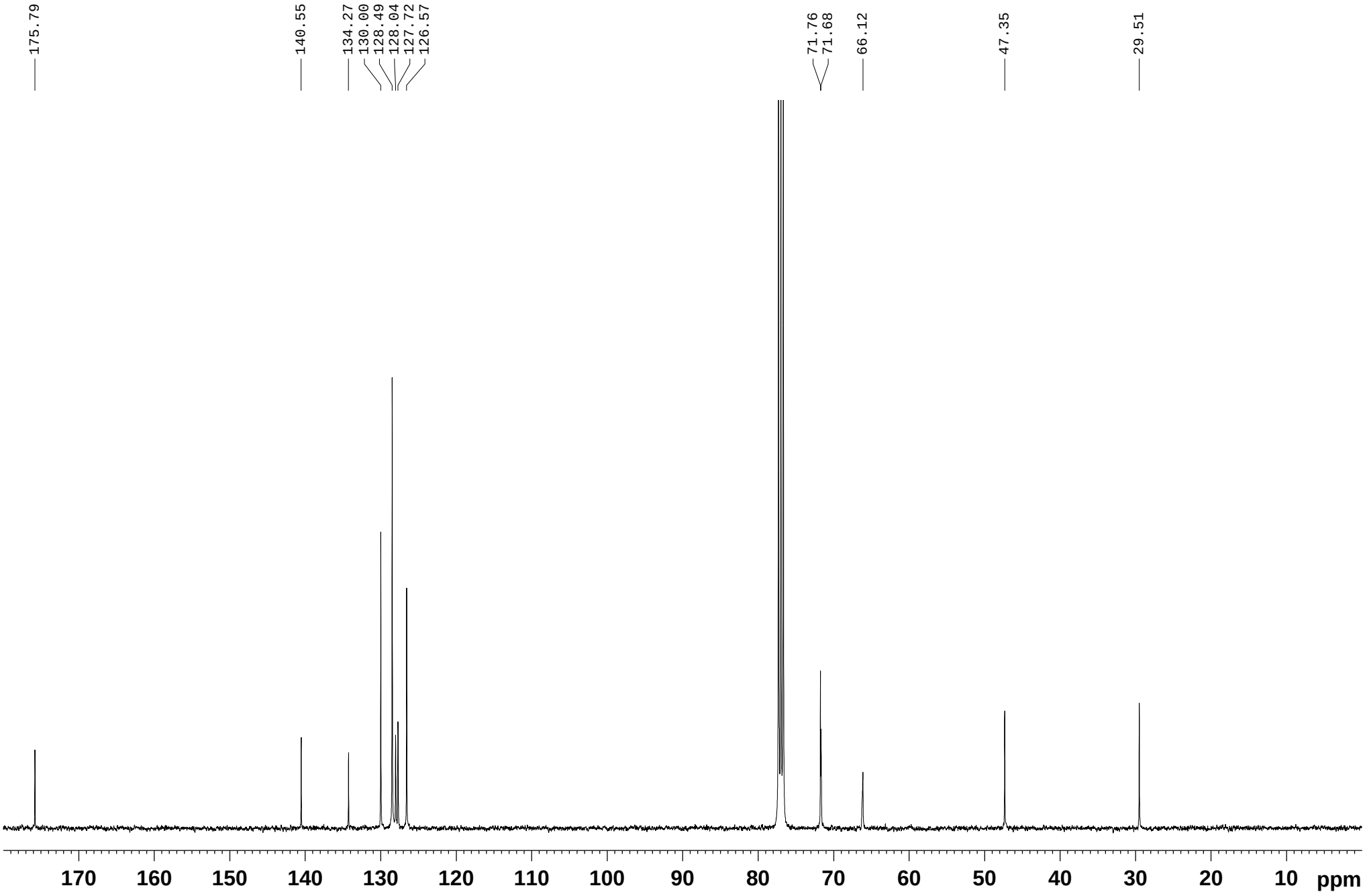
S 49 CD spectrum of the new compound **7.**



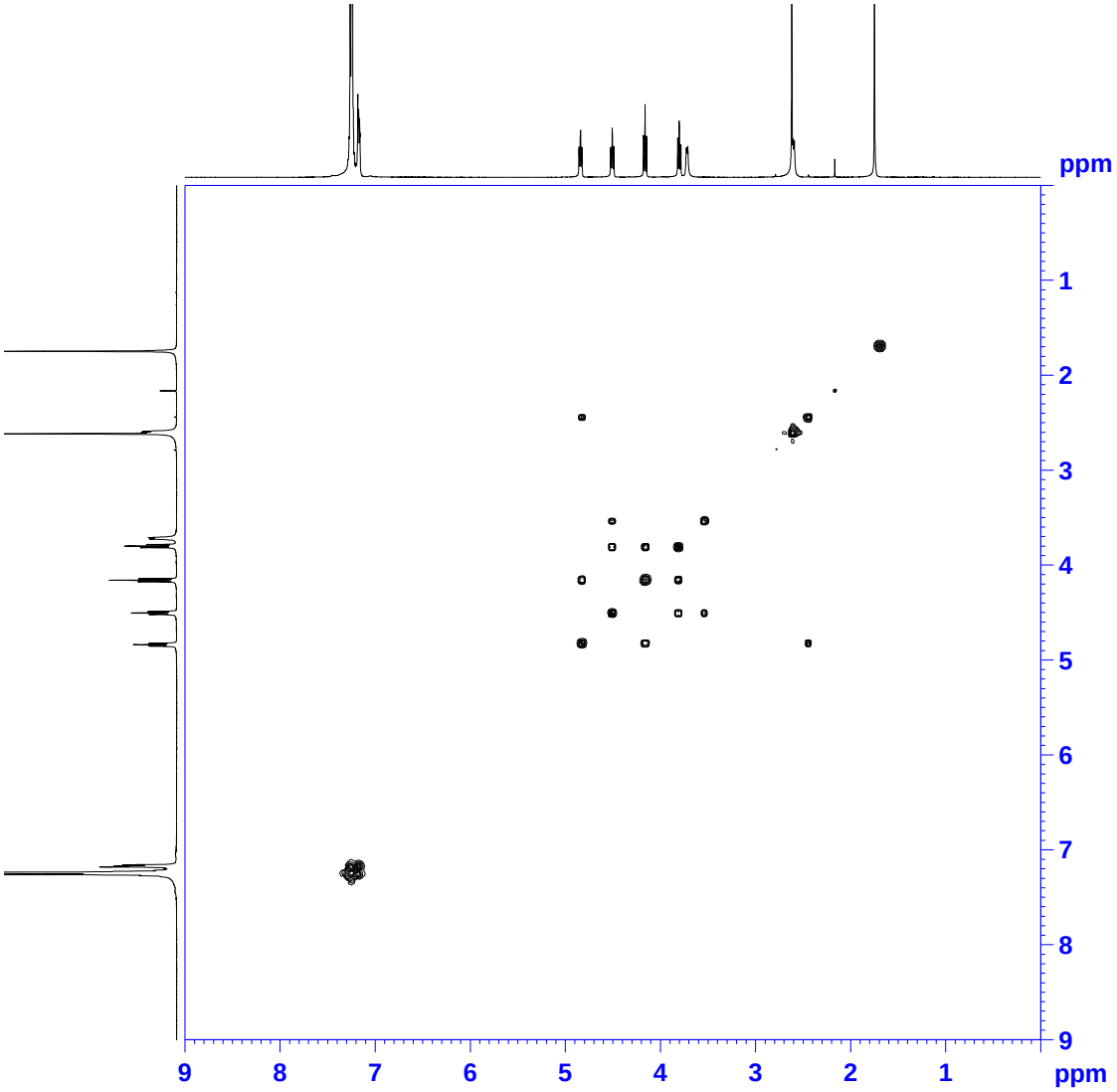
S 50 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8.**



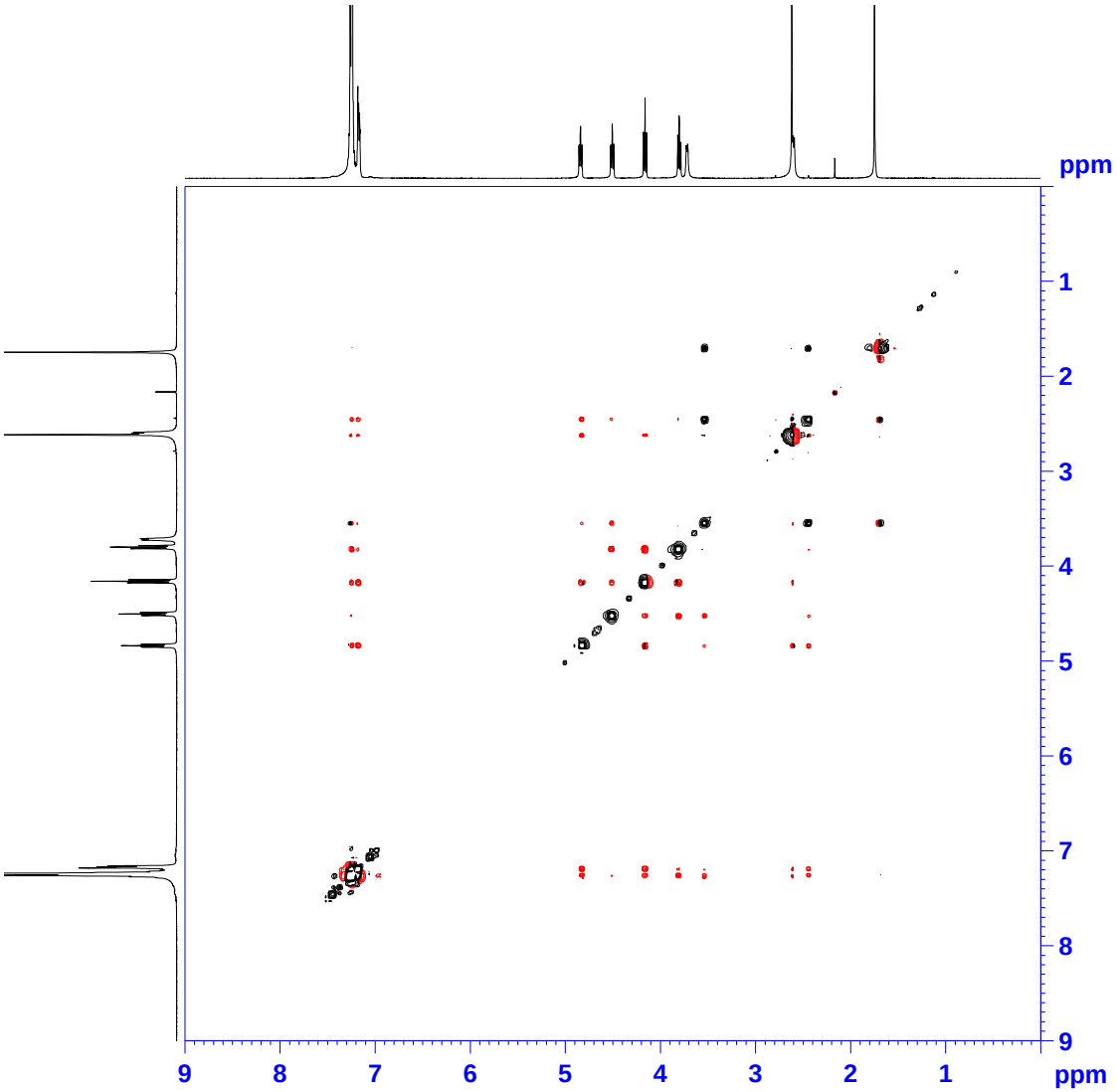
S 51 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8.**



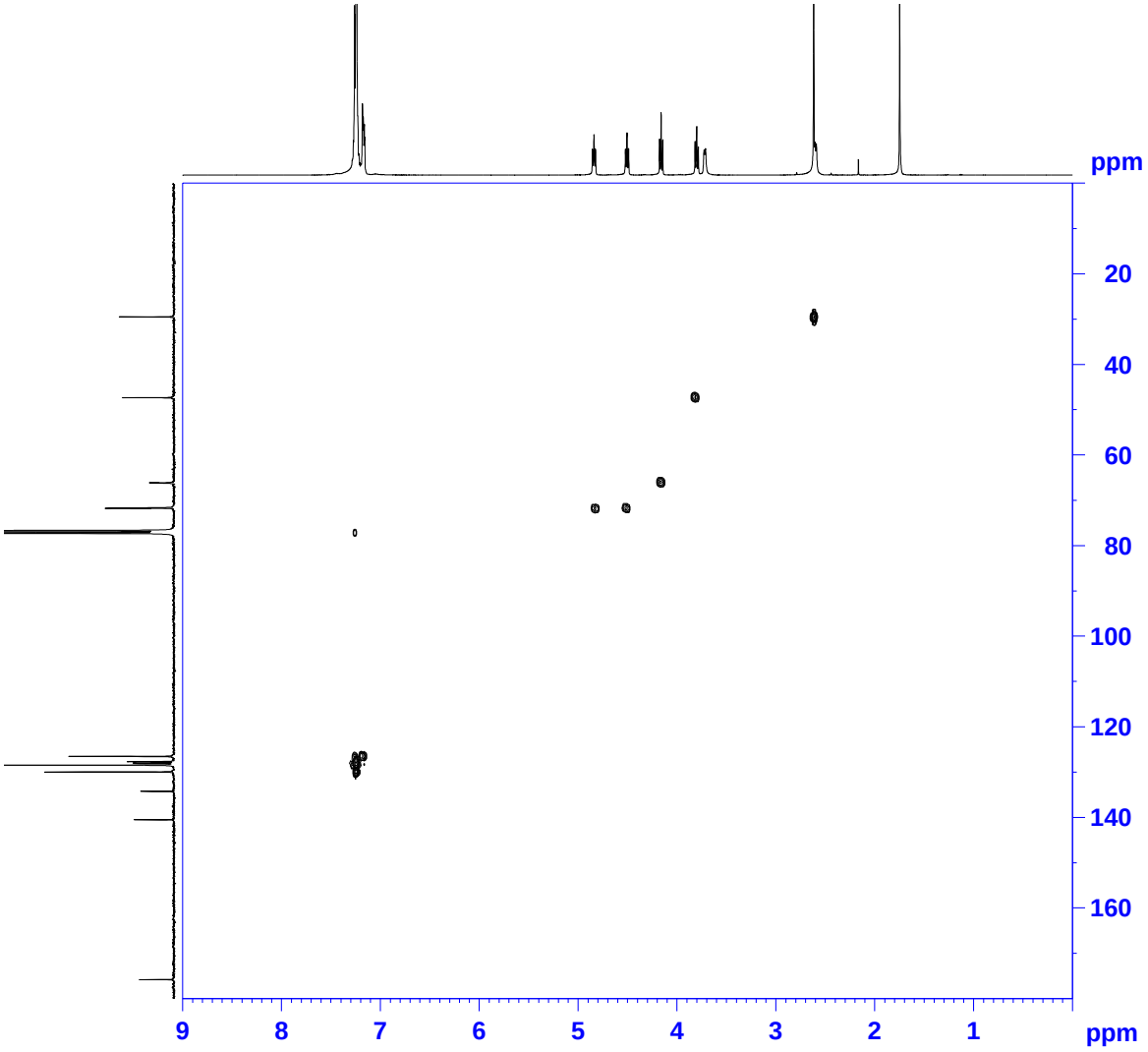
S 52 COSY spectrum of the compound **8.**



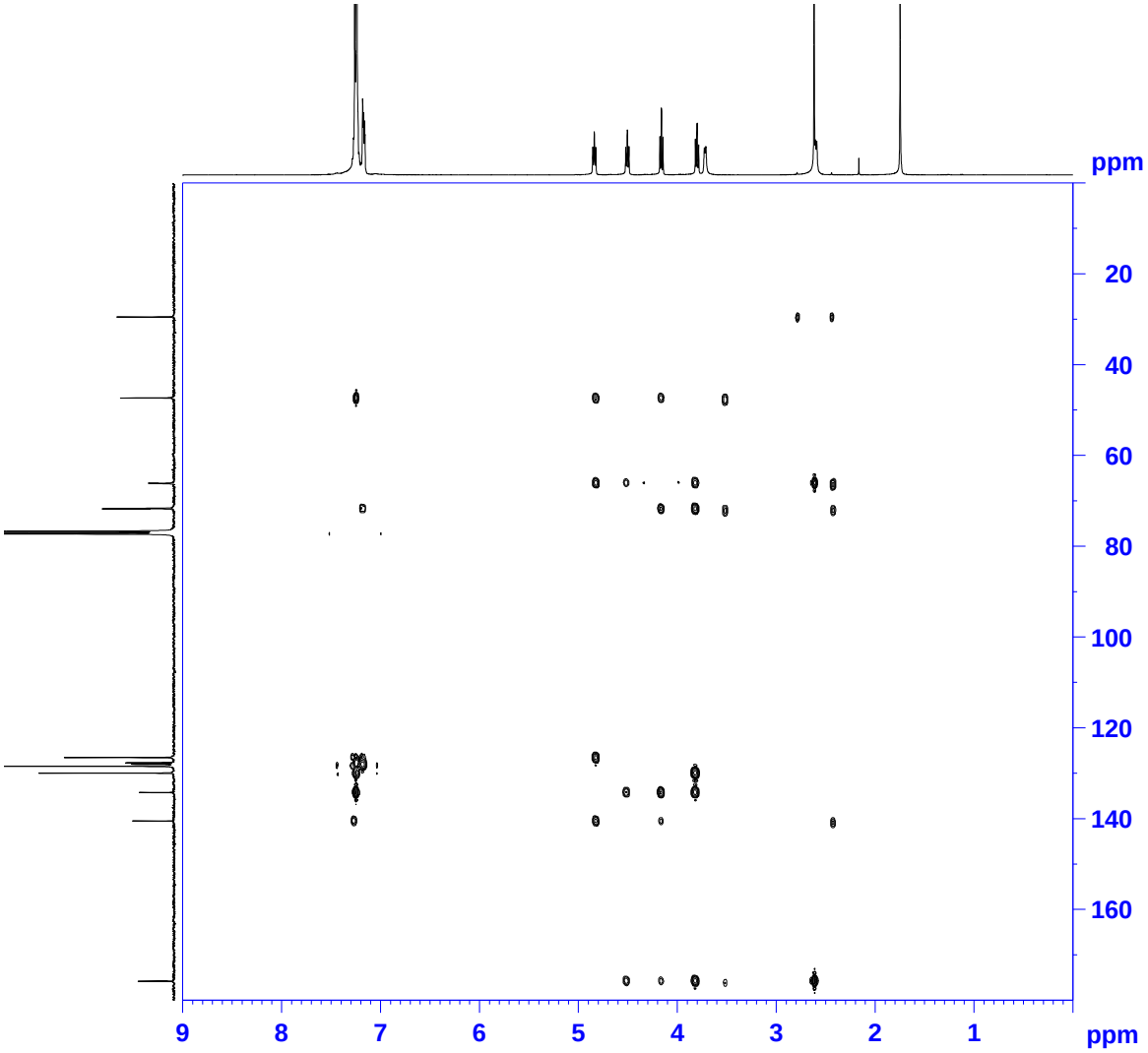
S 53 NOESY spectrum of the compound **8.**



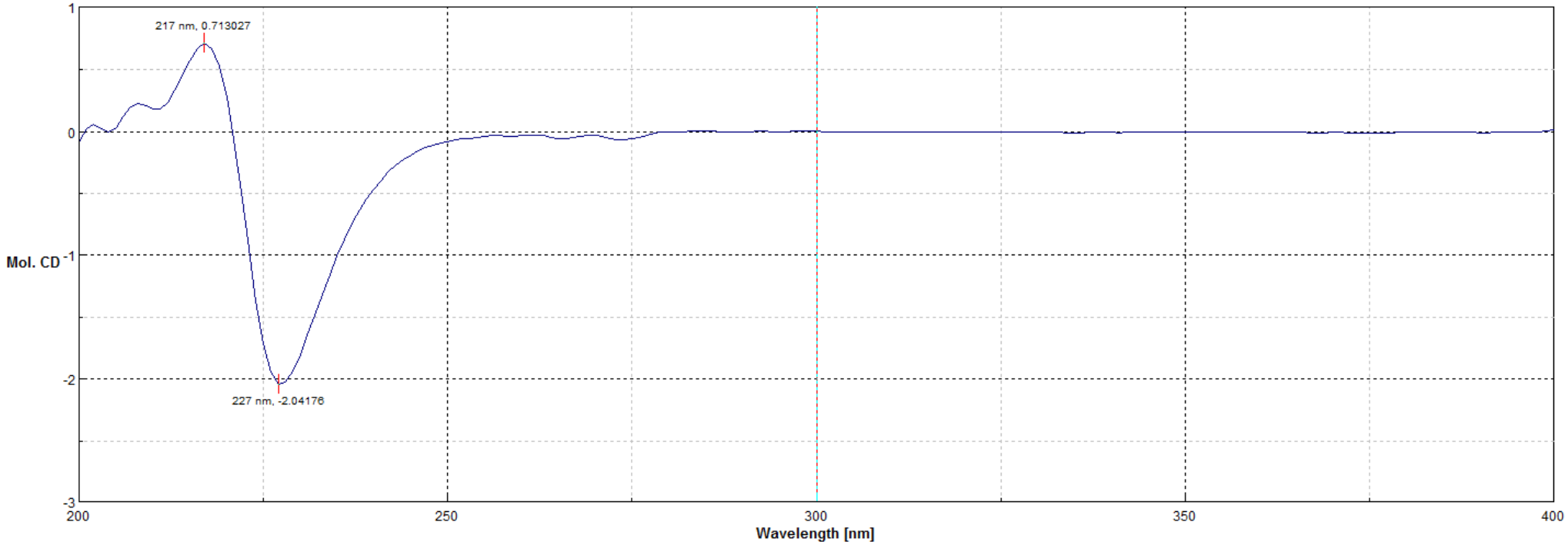
S 54 HSQC spectrum of the compound **8.**



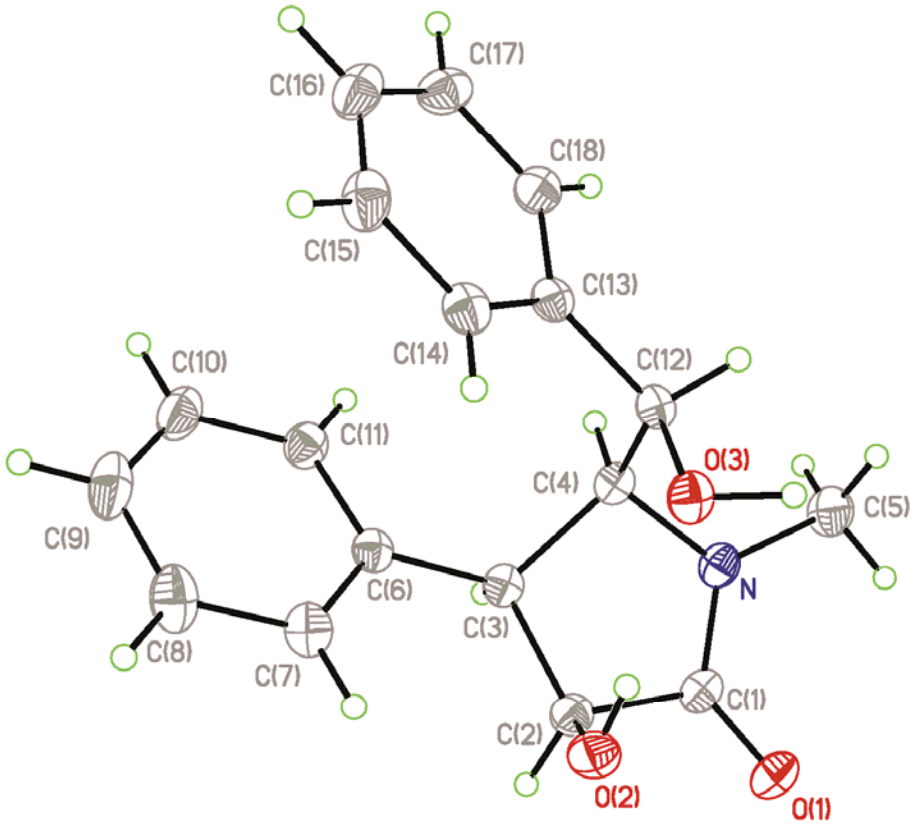
S 55 HMBC spectrum of the compound **8.**



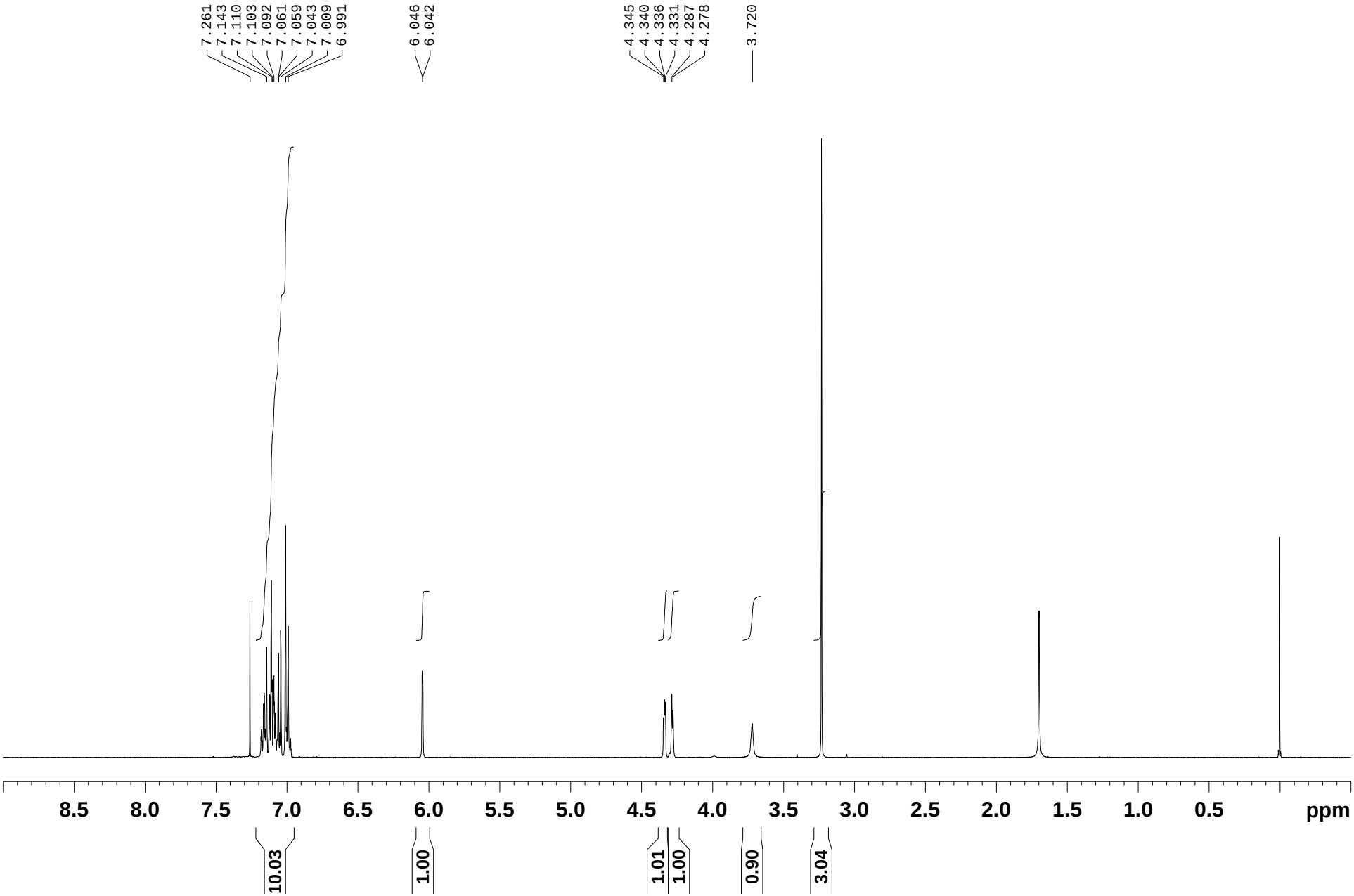
S 56 CD spectrum of the compound **8.**



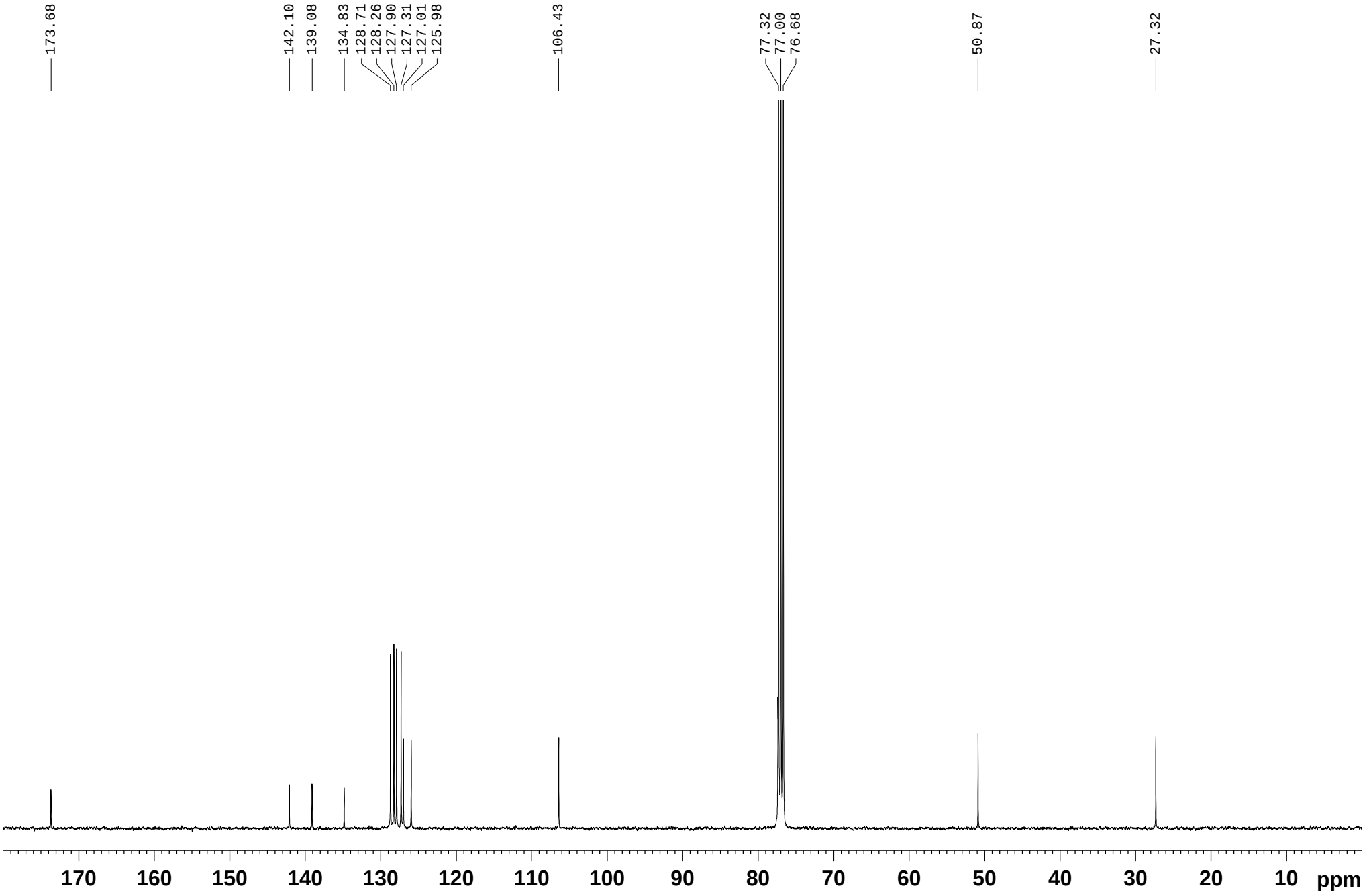
S 57 X-ray structure of compound **8.**



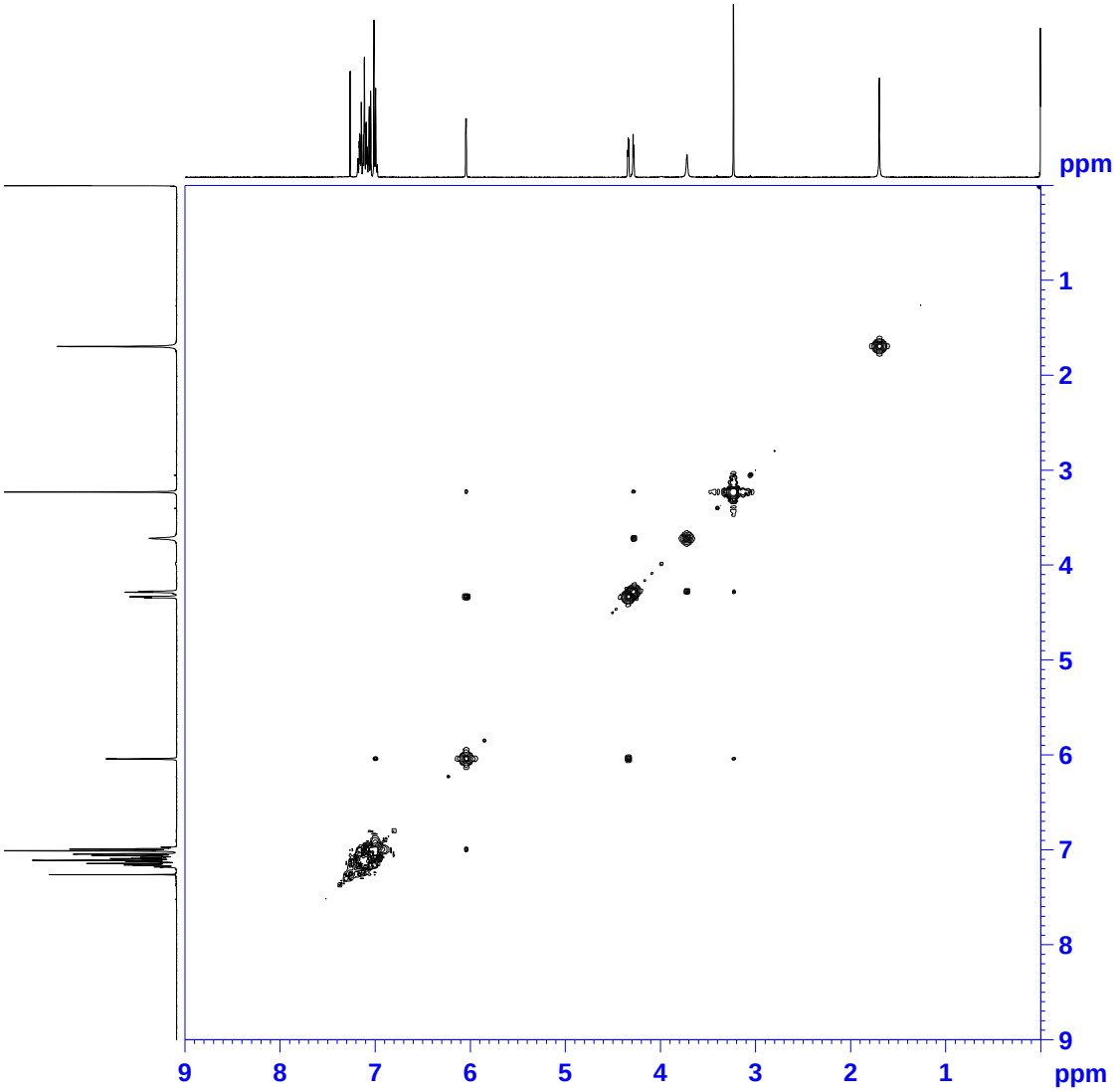
S 58 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **9.**



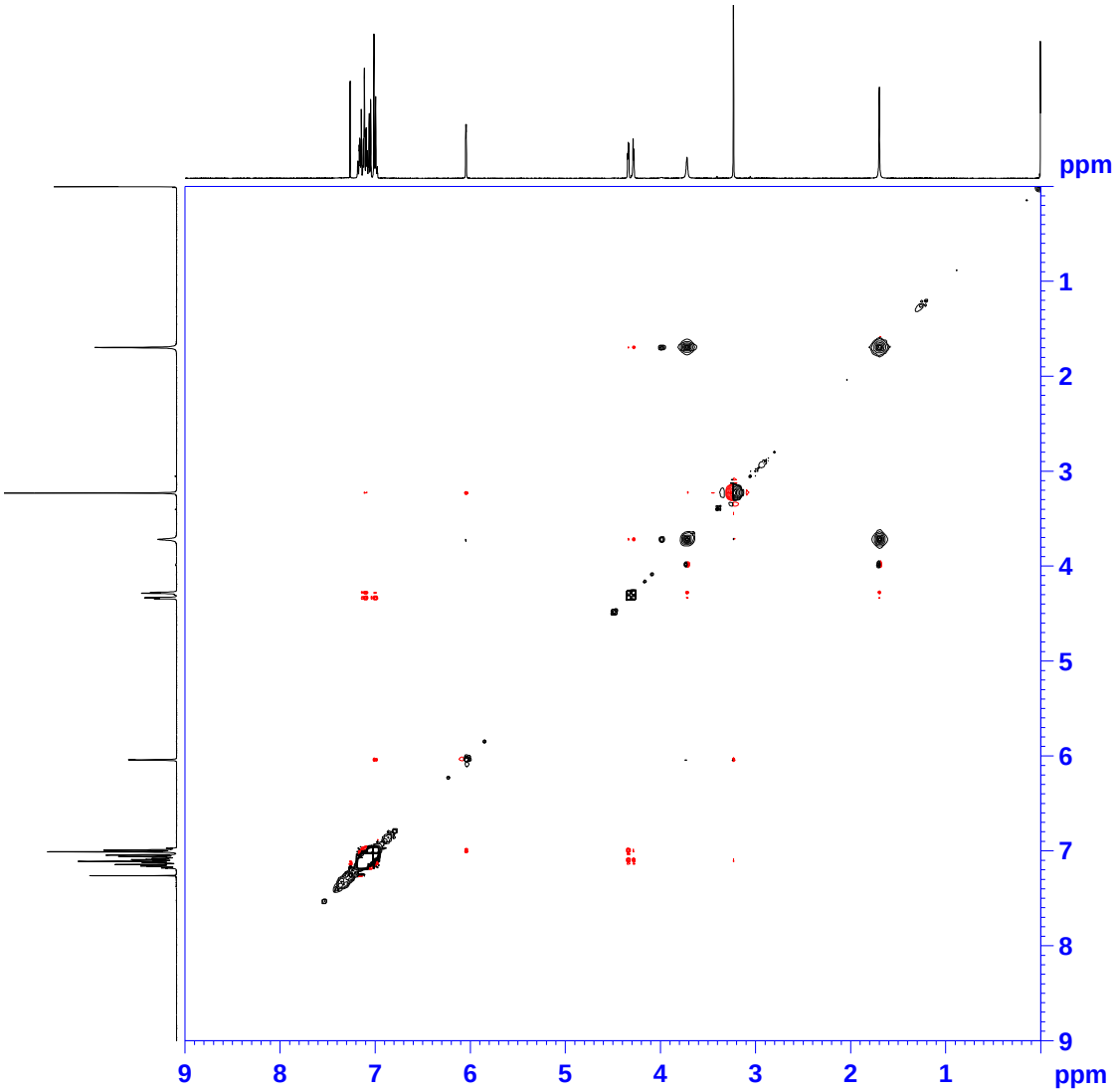
S 59 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **9.**



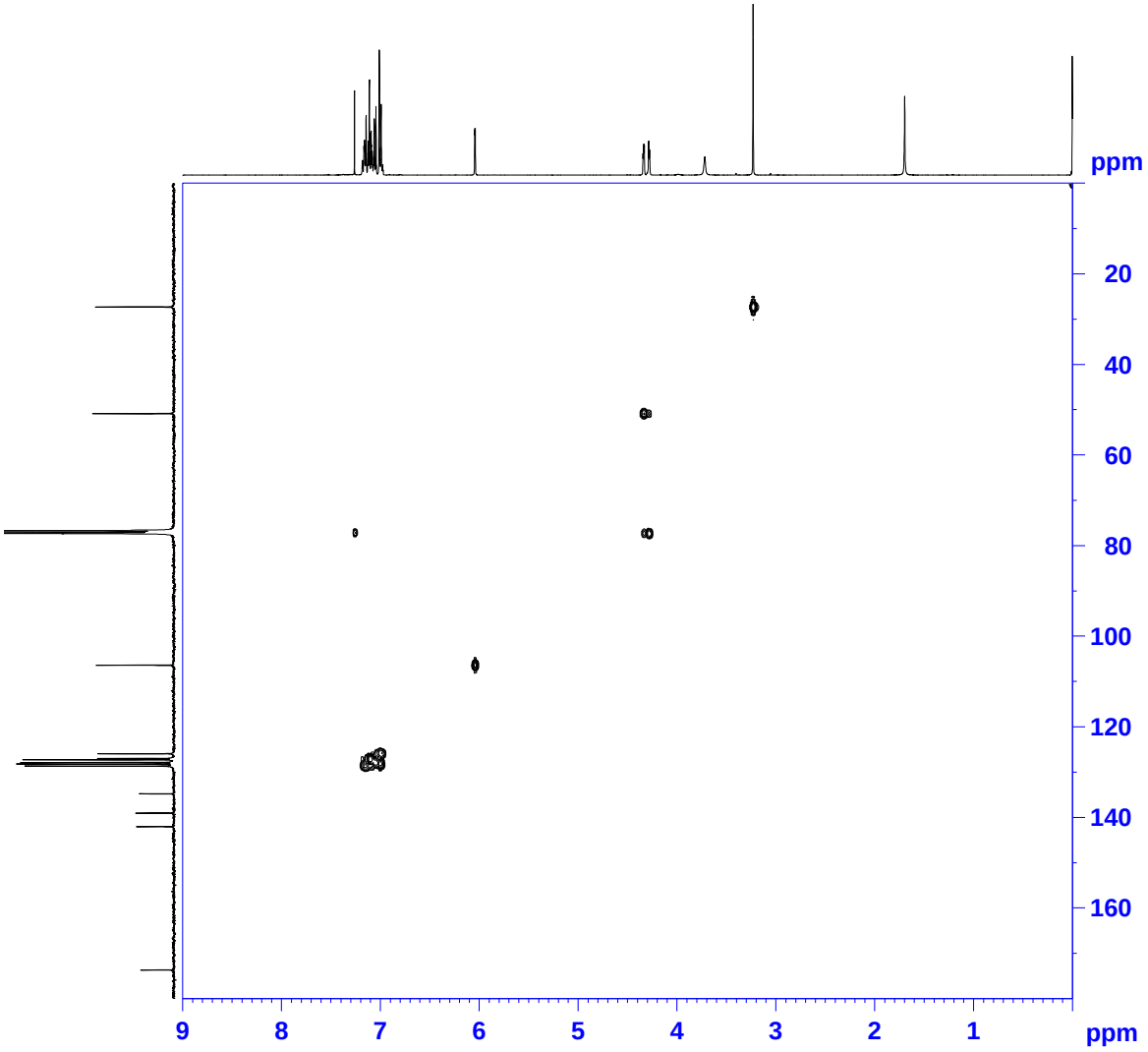
S 60 COSY spectrum of the compound **9.**



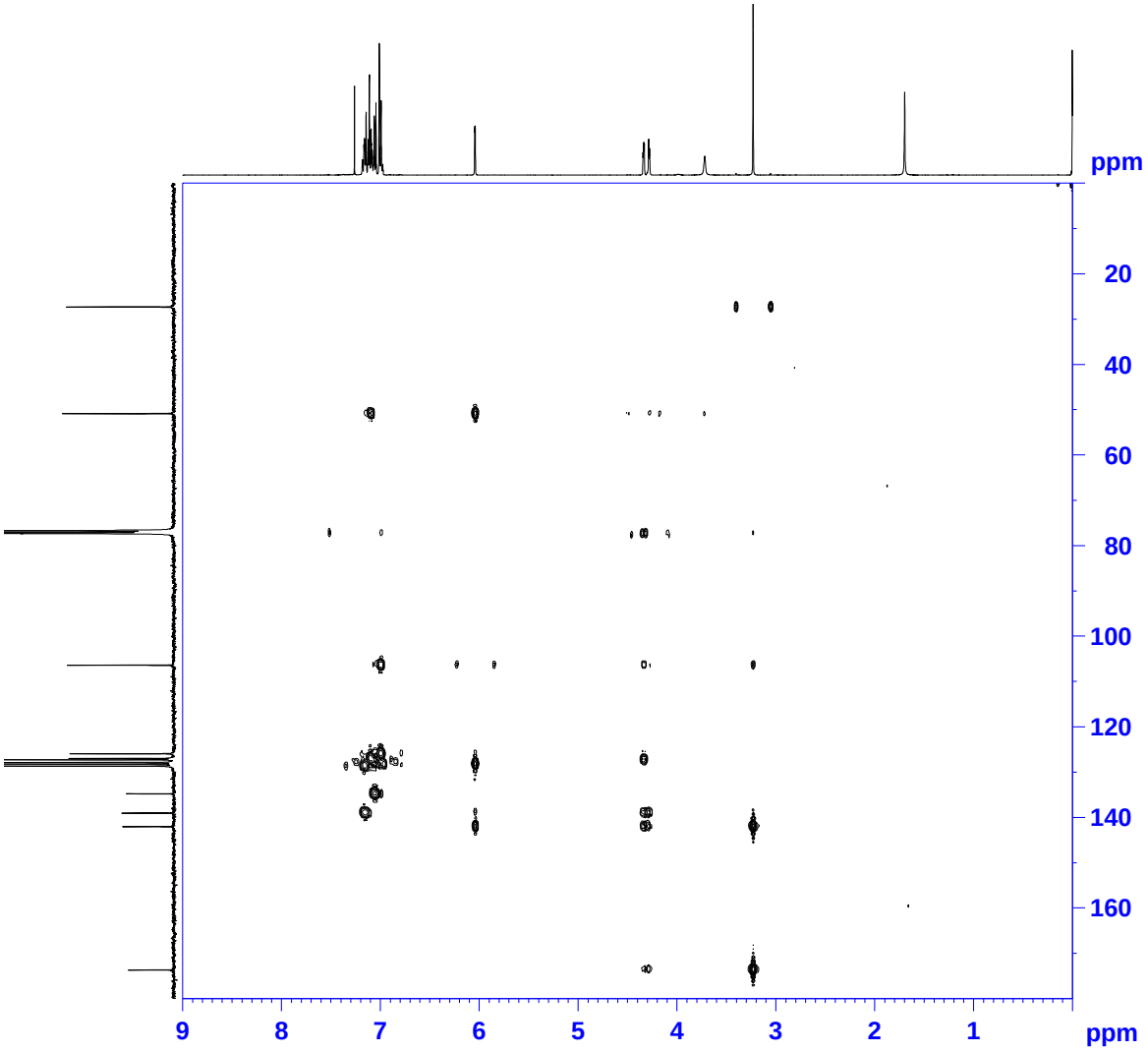
S 61 NOESY spectrum of the compound **9.**



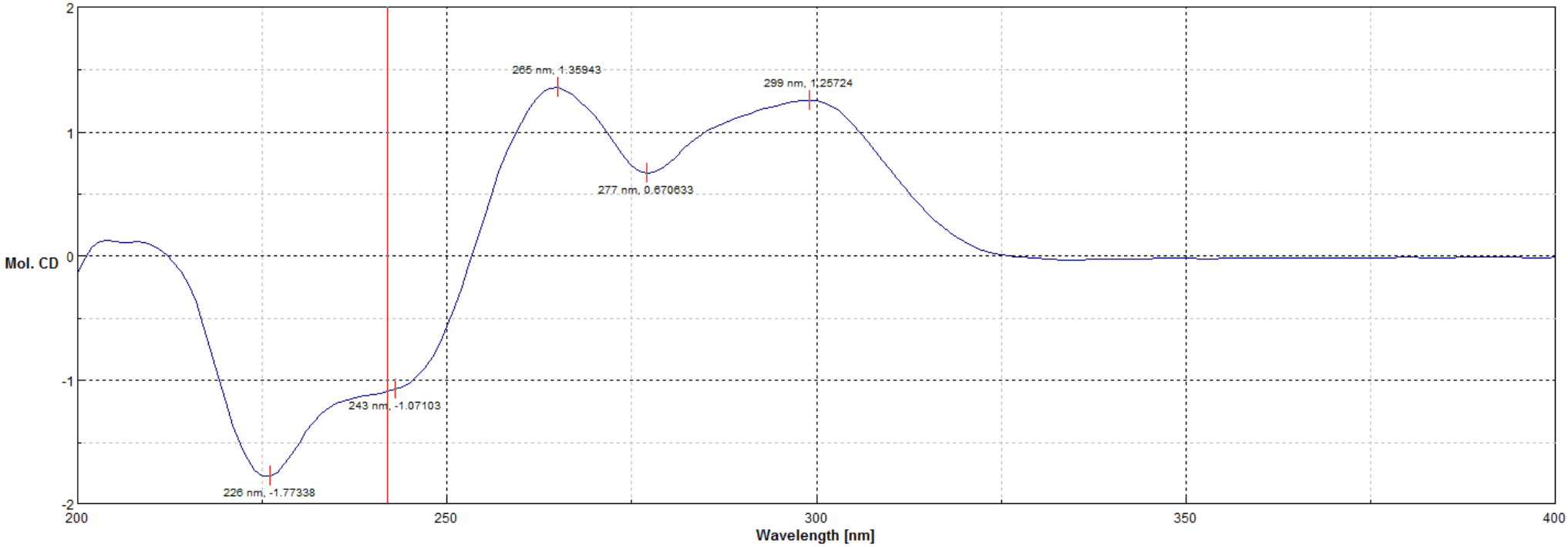
S 62 HSQC spectrum of the compound **9.**



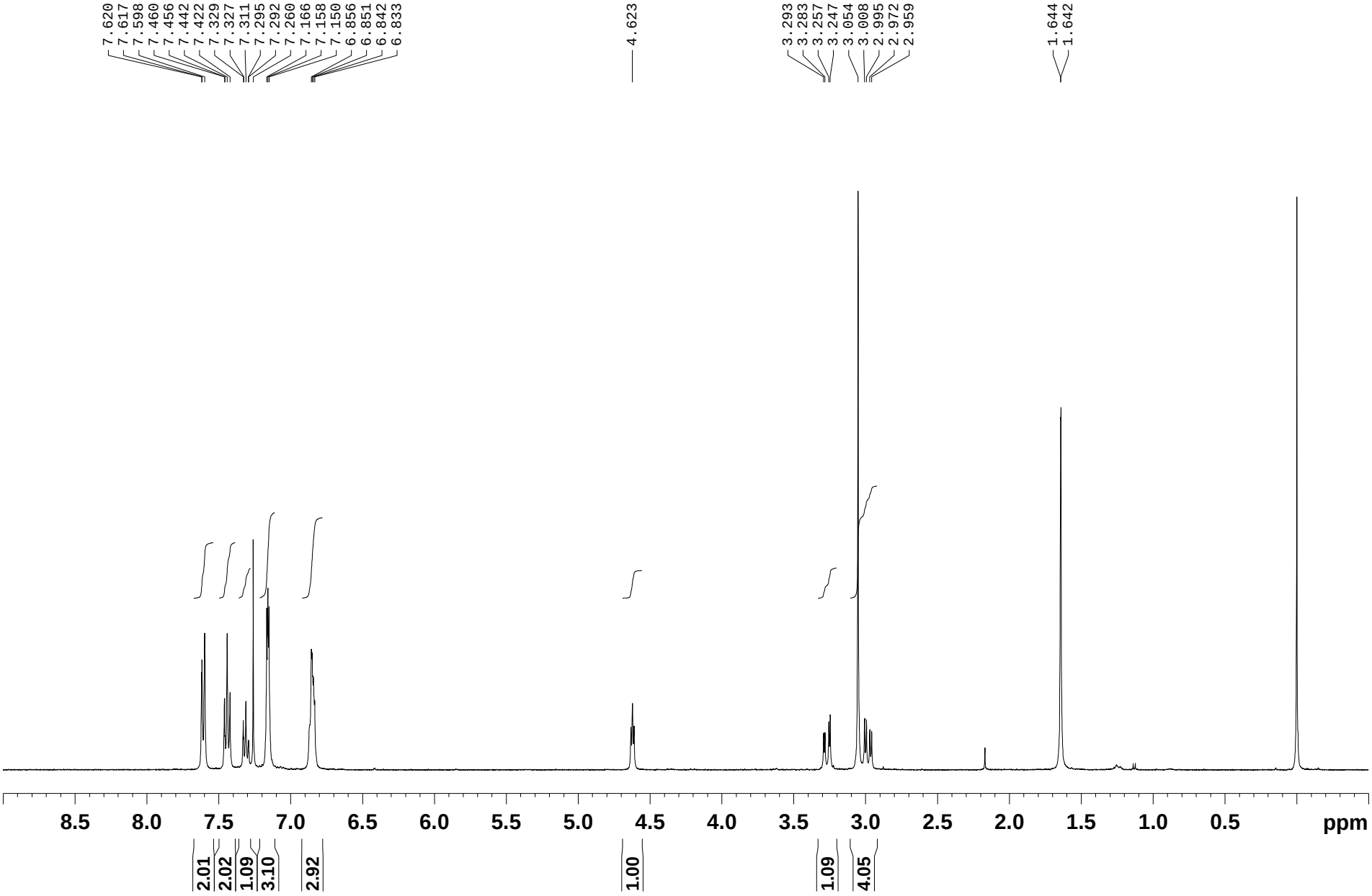
S 63 HMBC spectrum of the compound **9.**



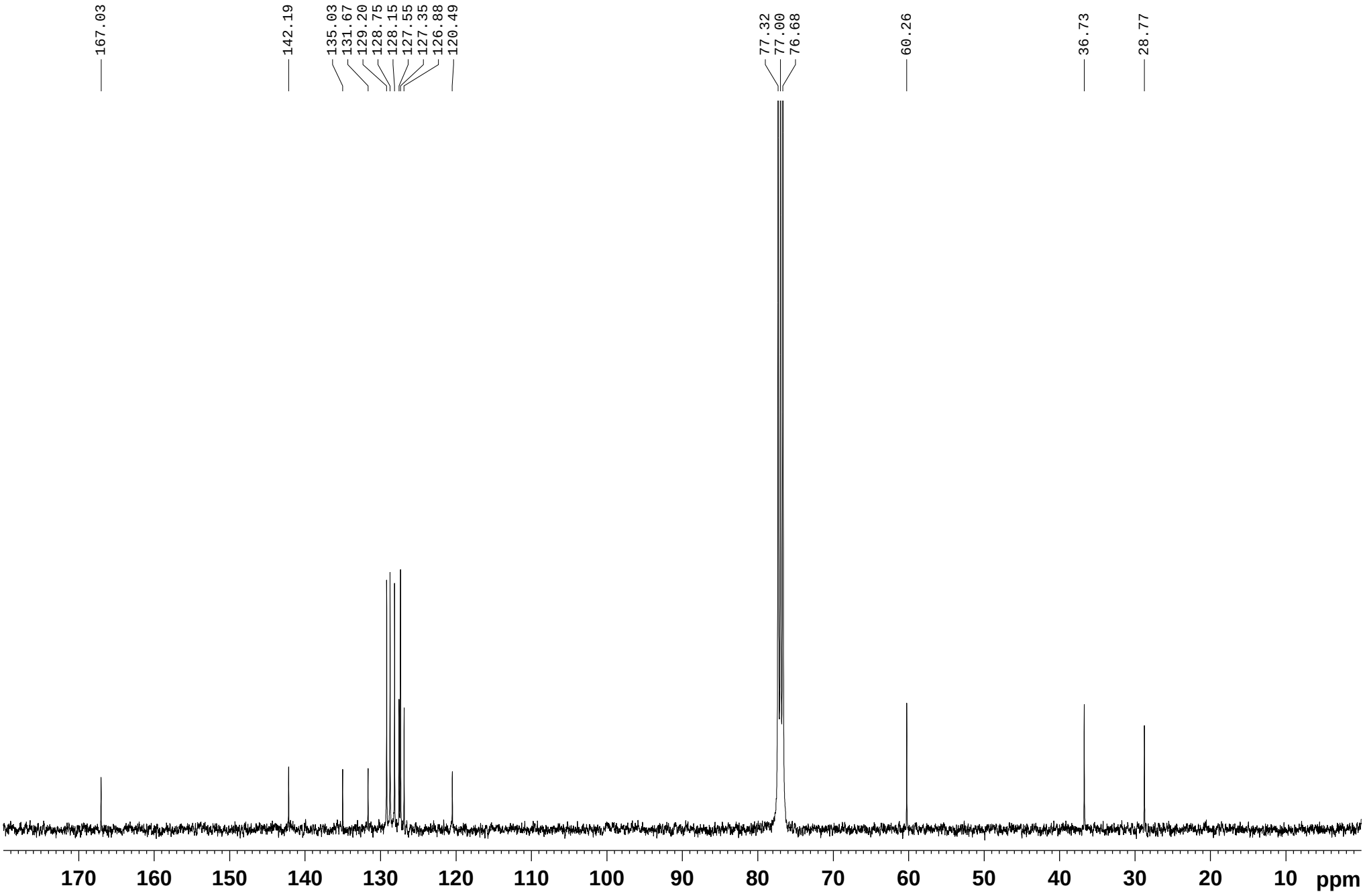
S 64 CD spectrum of the compound **9.**



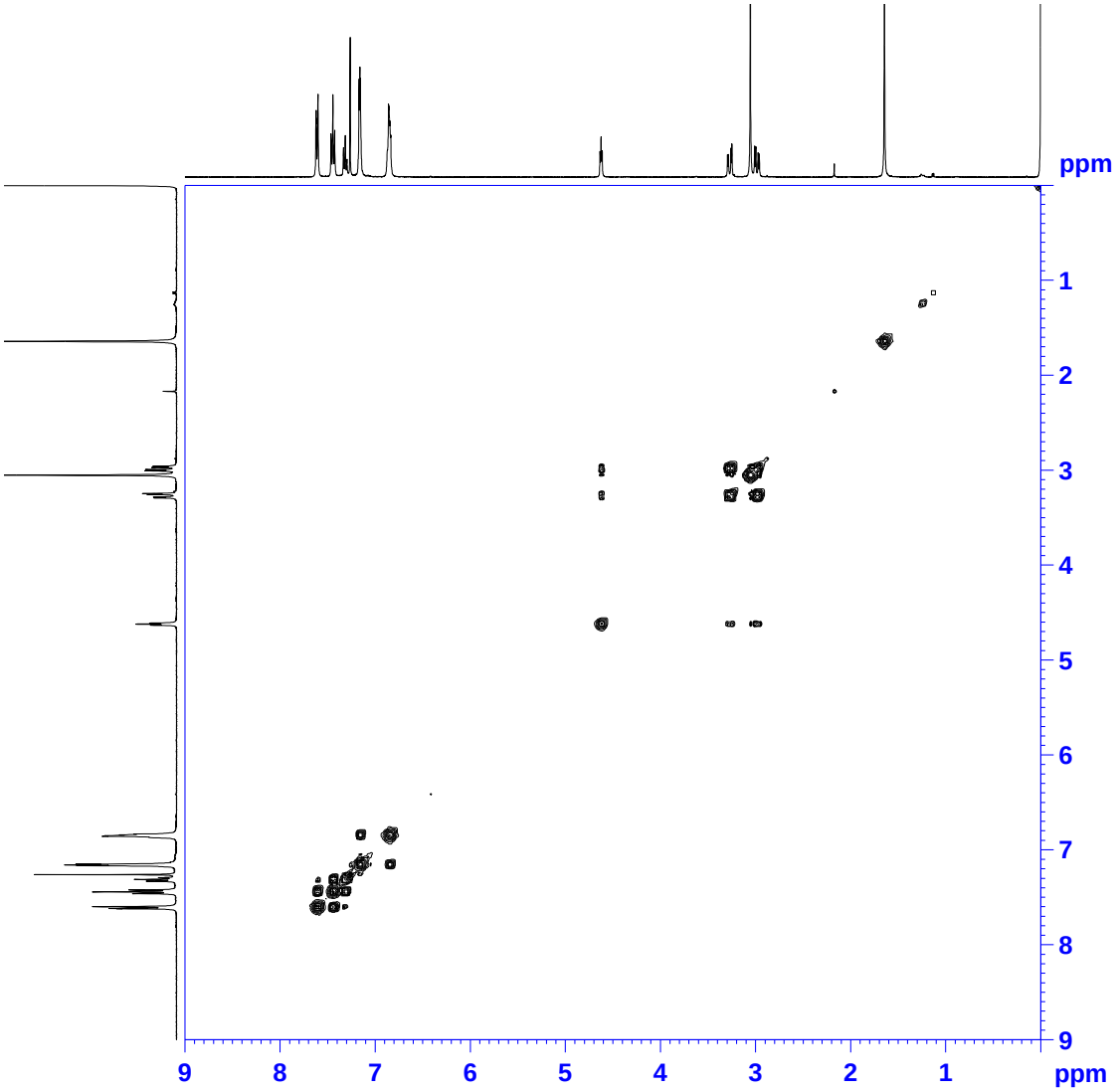
S 65 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **10.**



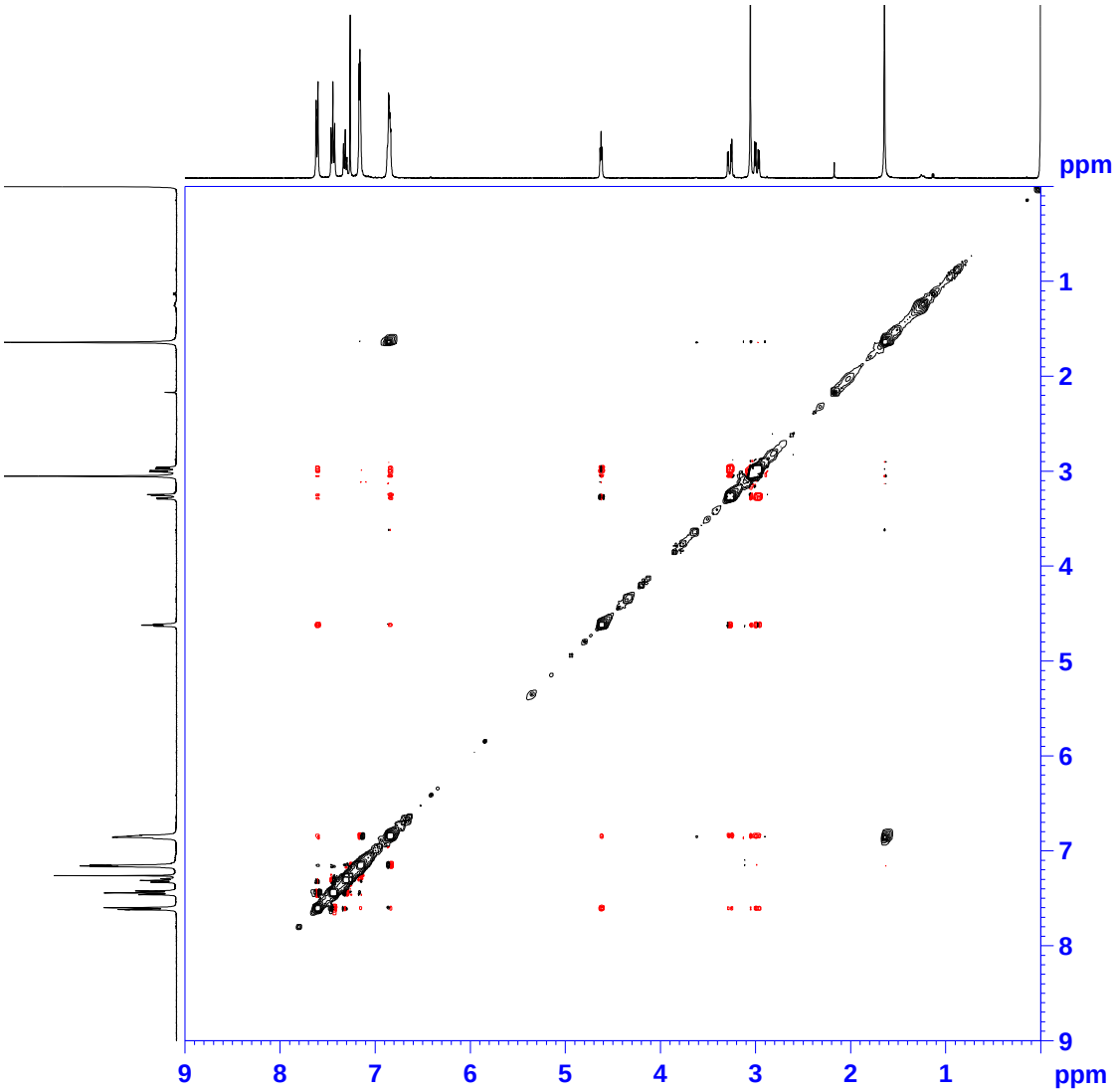
S 66 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **10.**



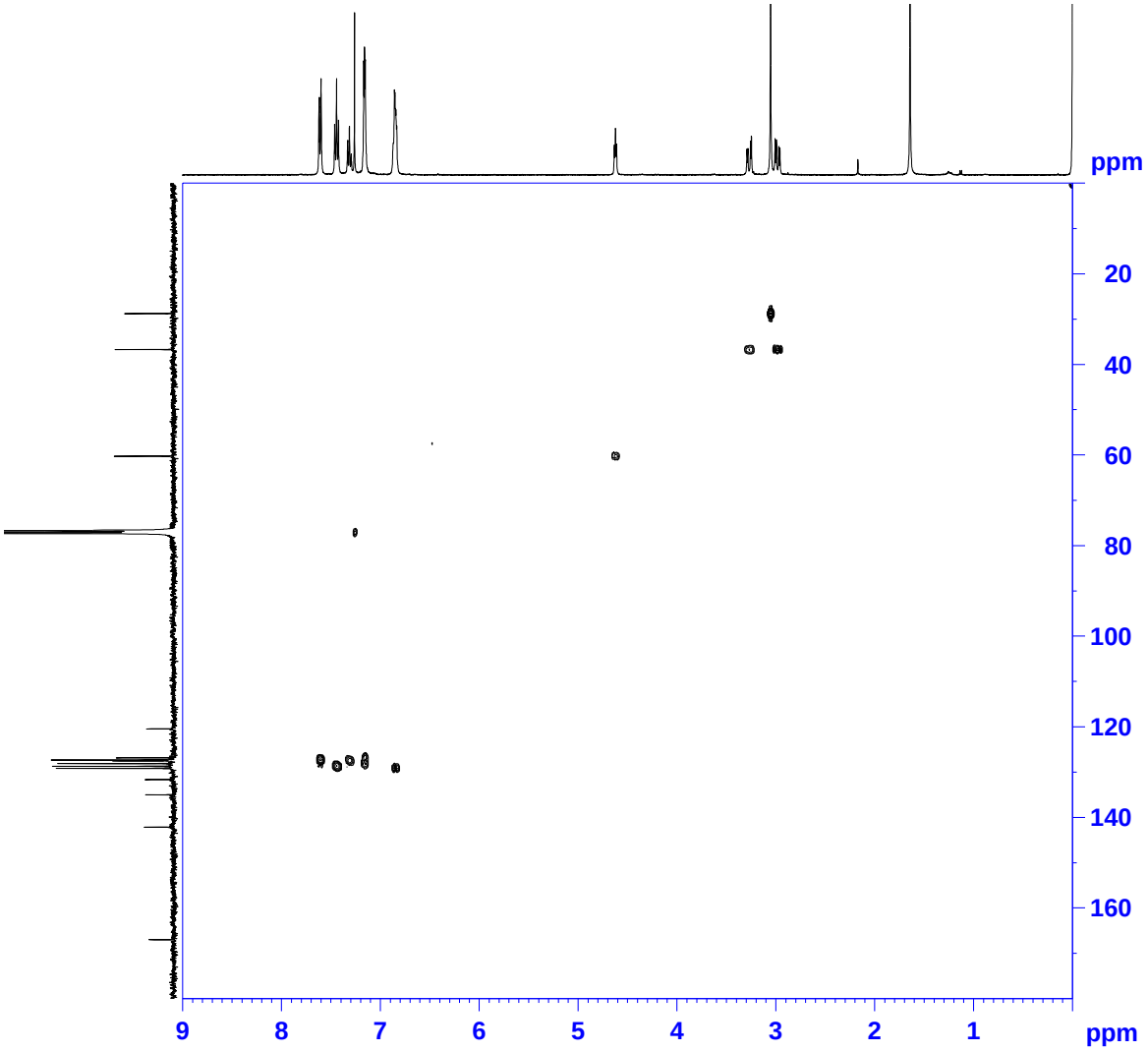
S 67 COSY spectrum of the compound **10.**



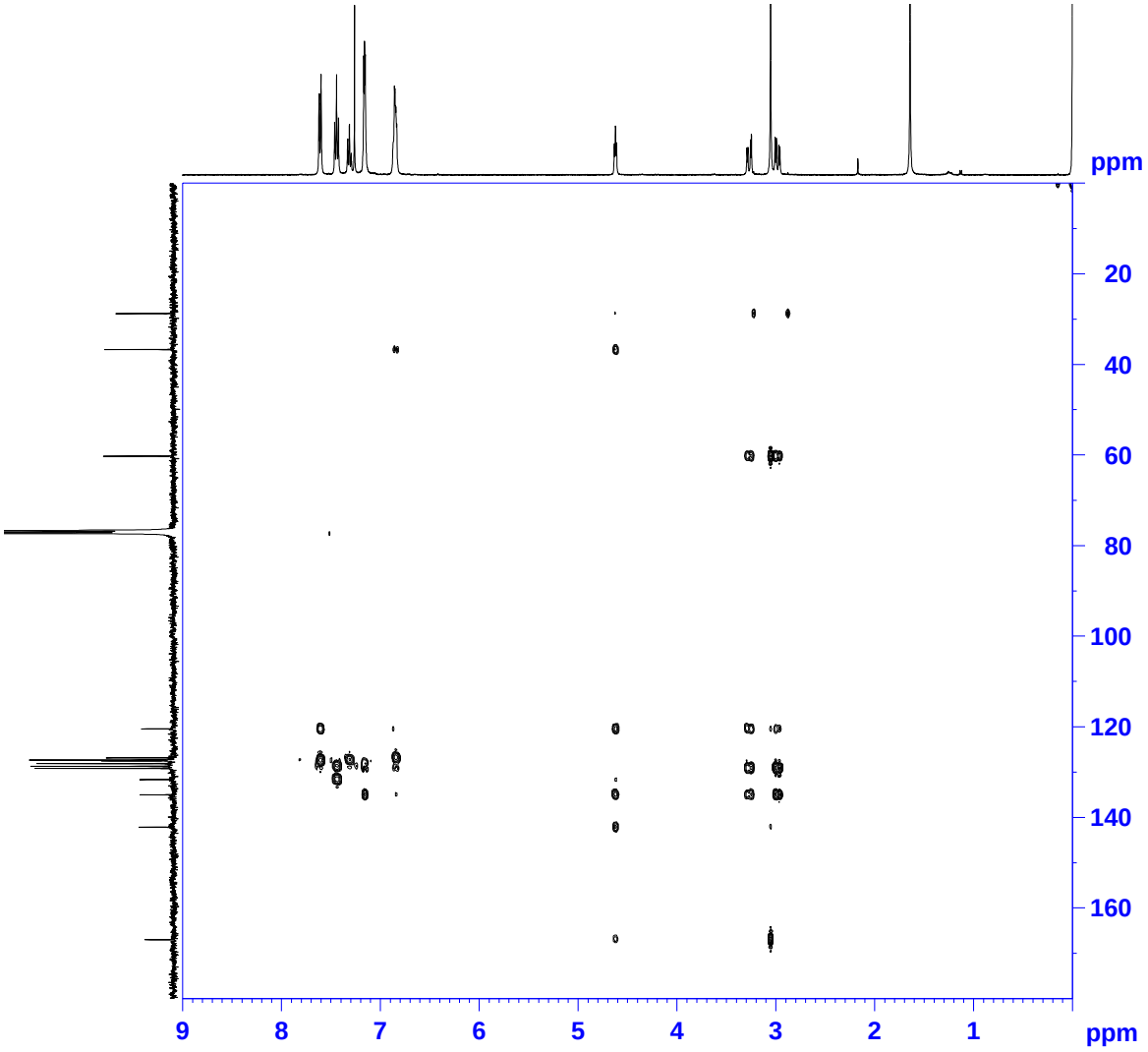
S 68 NOESY spectrum of the compound **10.**



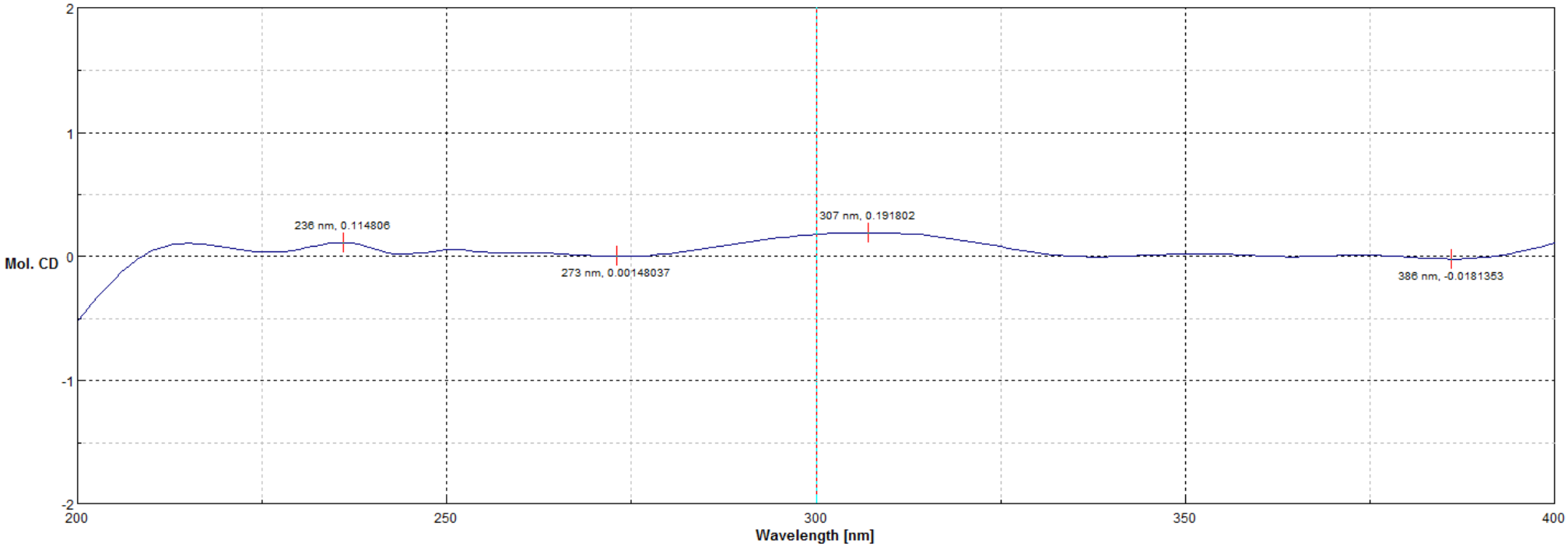
S 69 HSQC spectrum of the compound **10.**



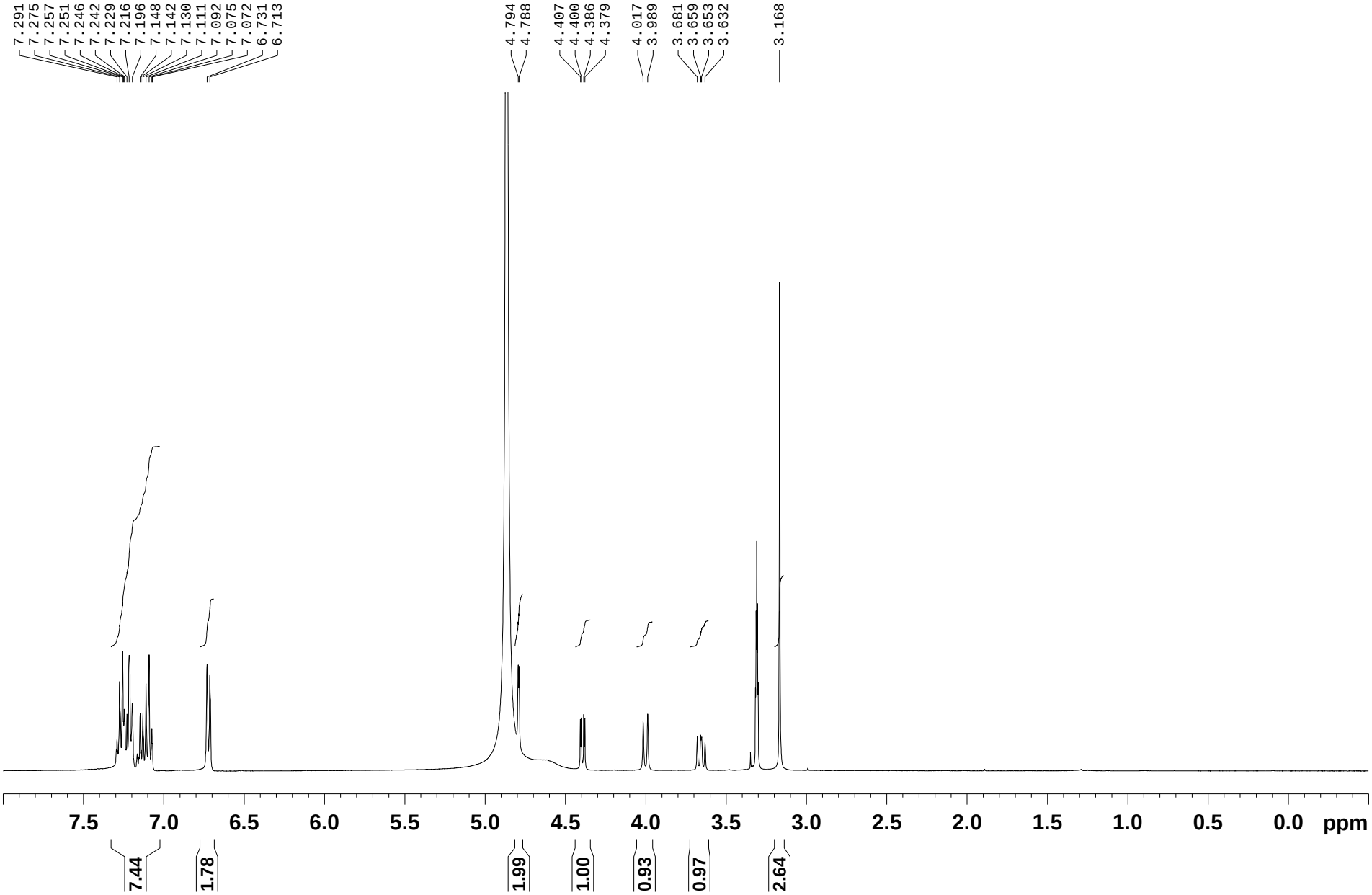
S 70 HMBC spectrum of the compound **10.**



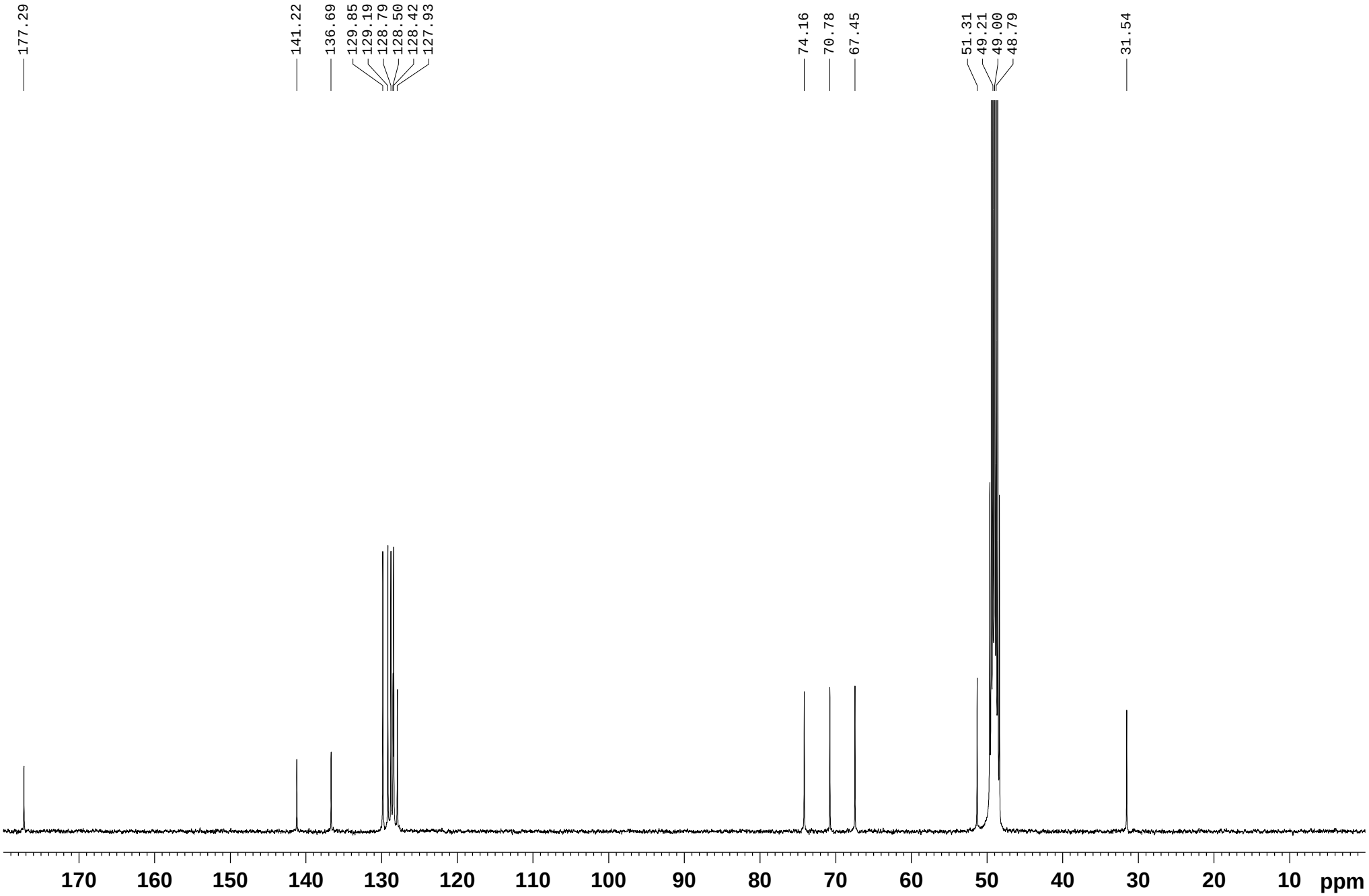
S 71 CD spectrum of the compound **10.**



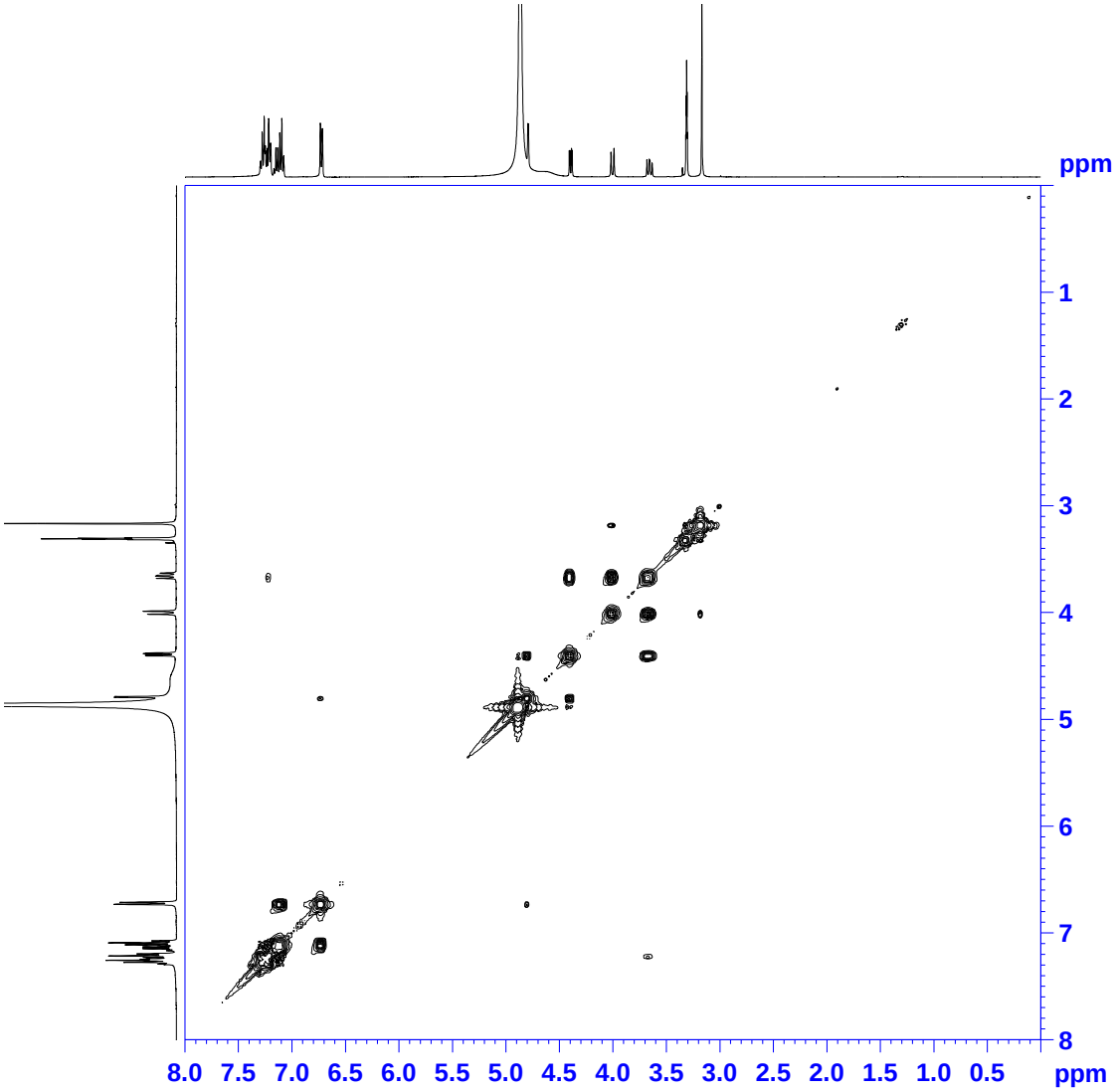
S 72 ^{1}H NMR (400 MHz, CD_3OD) spectrum of the compound **11.**



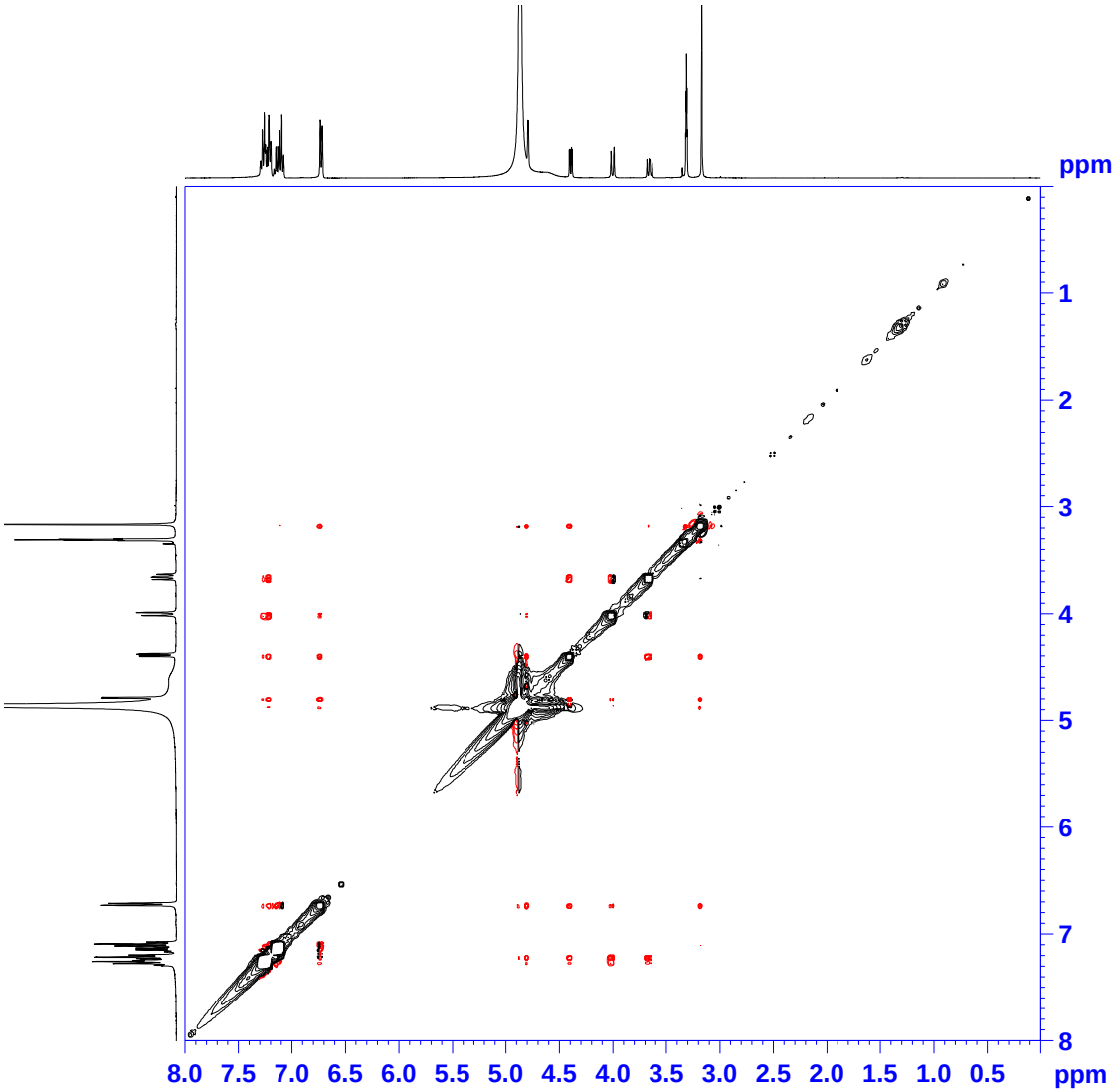
S 73 ^{13}C NMR (100 MHz, CD_3OD) spectrum of the compound **11.**



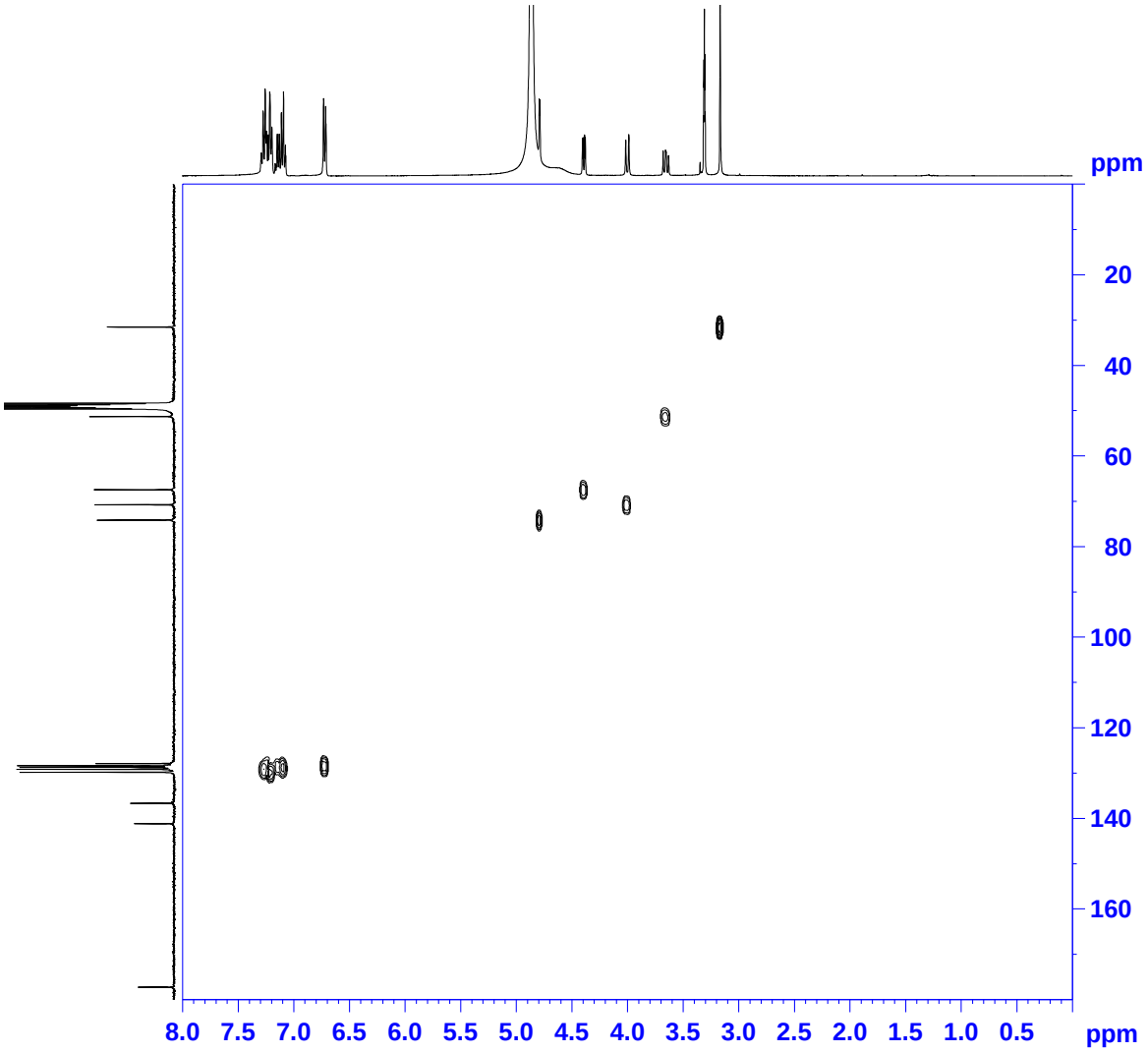
S 74 COSY spectrum of the compound **11.**



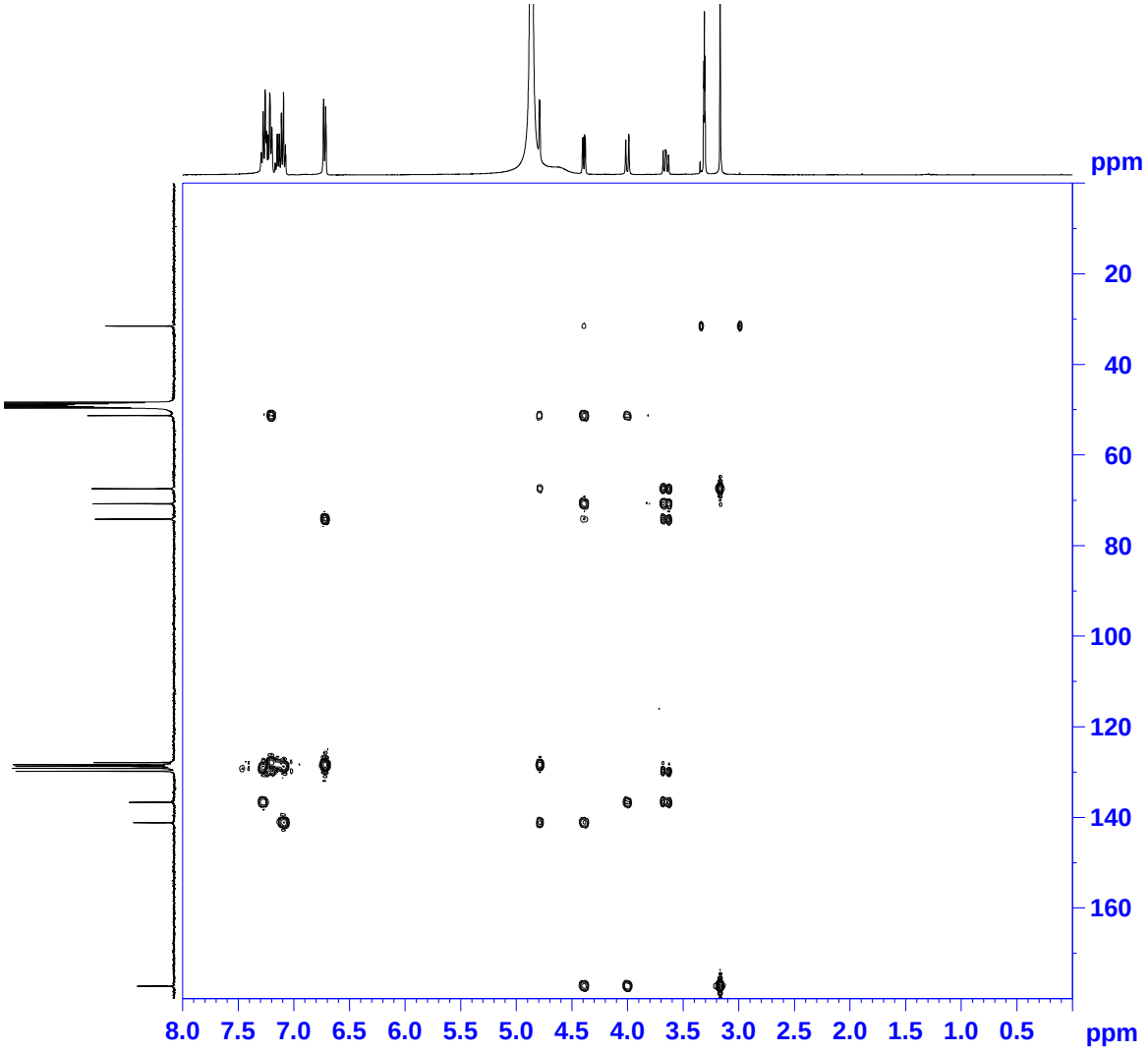
S 75 NOESY spectrum of the compound **11.**



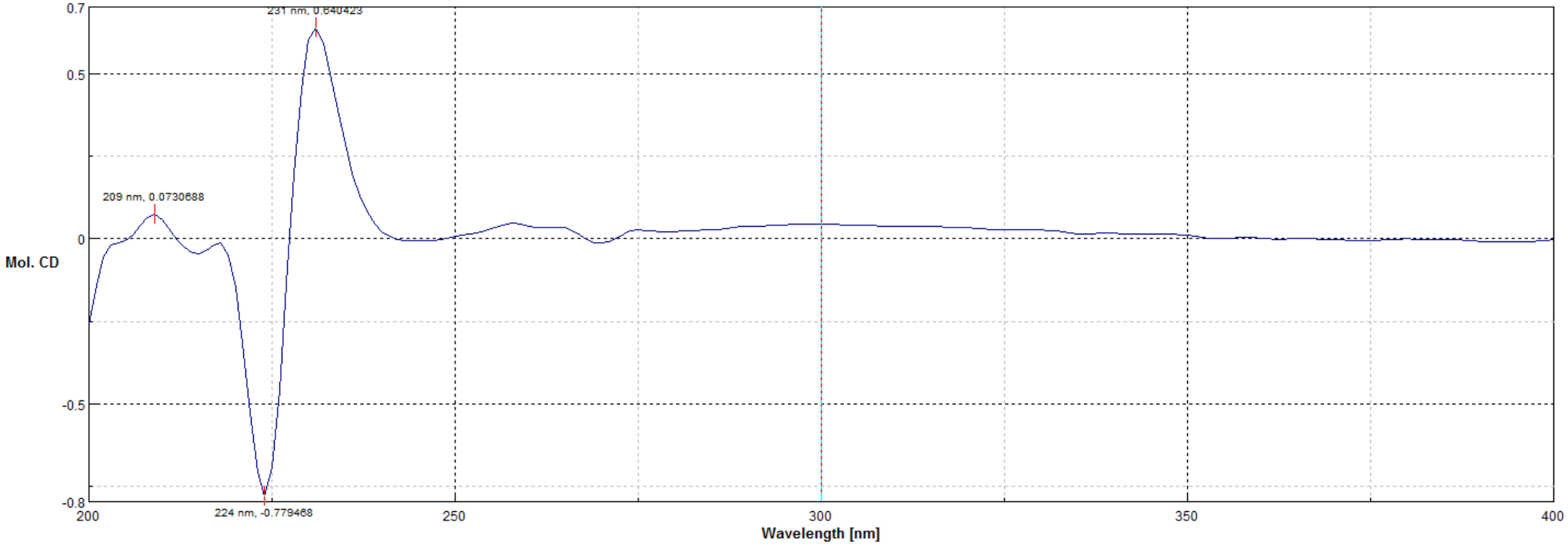
S 76 HSQC spectrum of the compound **11.**



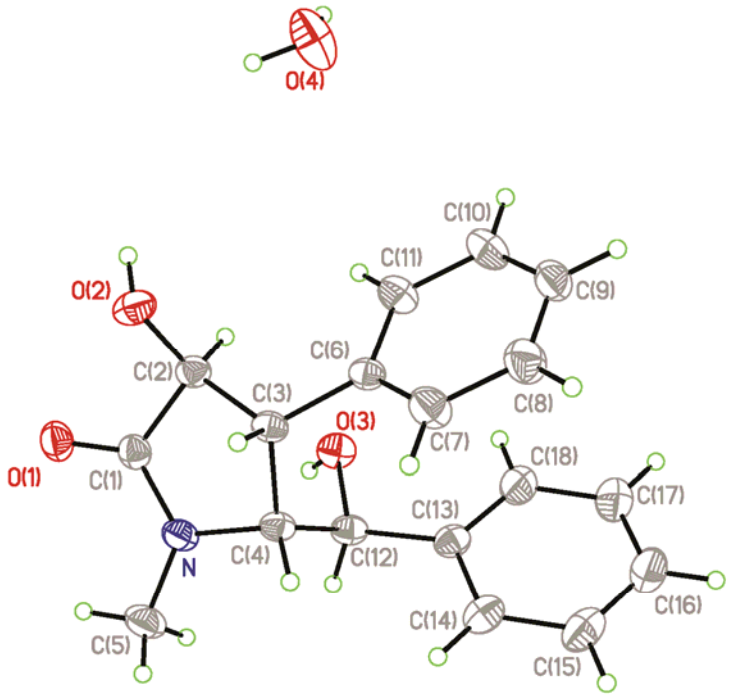
S 77 HMBC spectrum of the compound **11.**



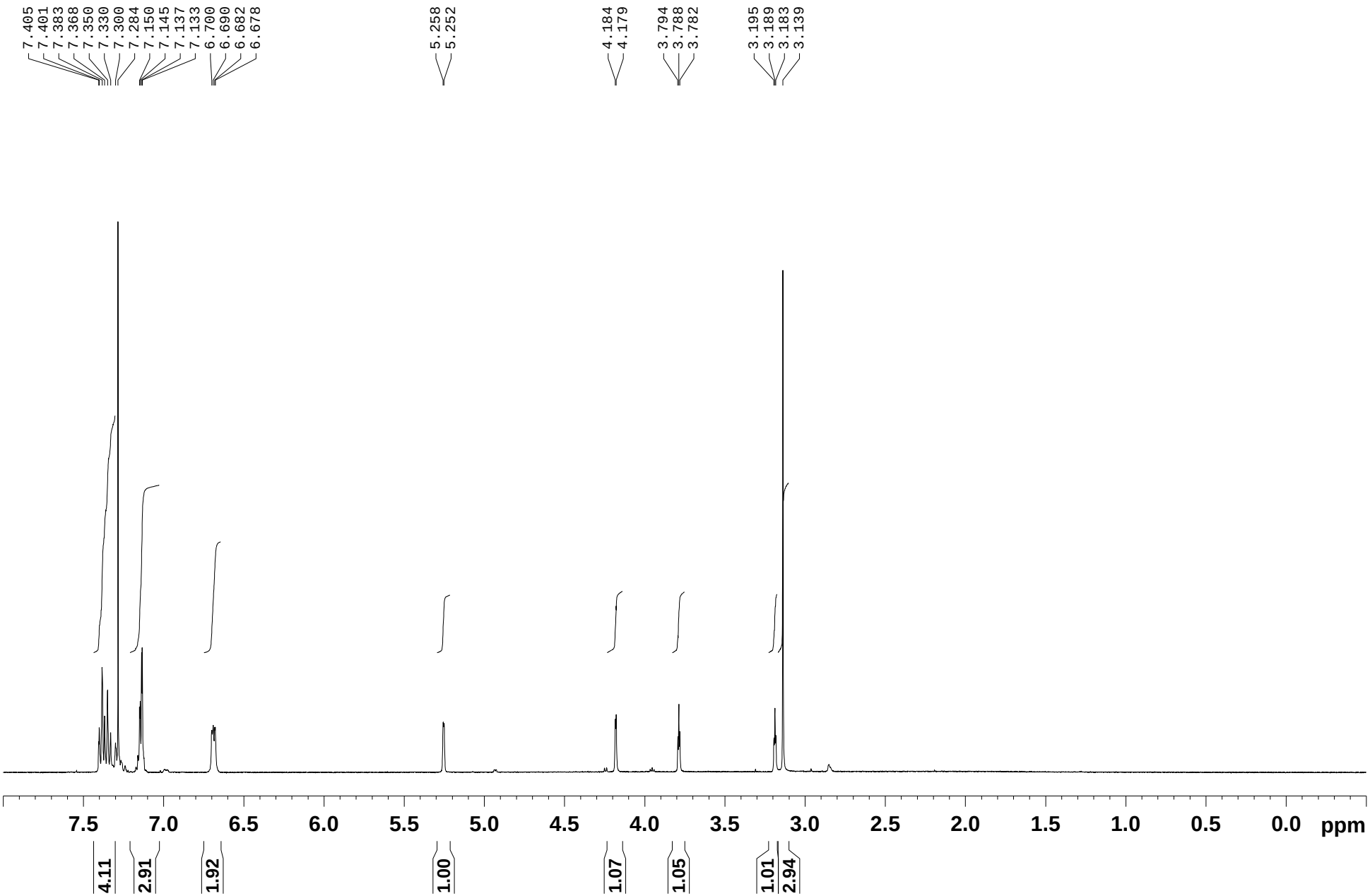
S 78 CD spectrum of the compound **11.**



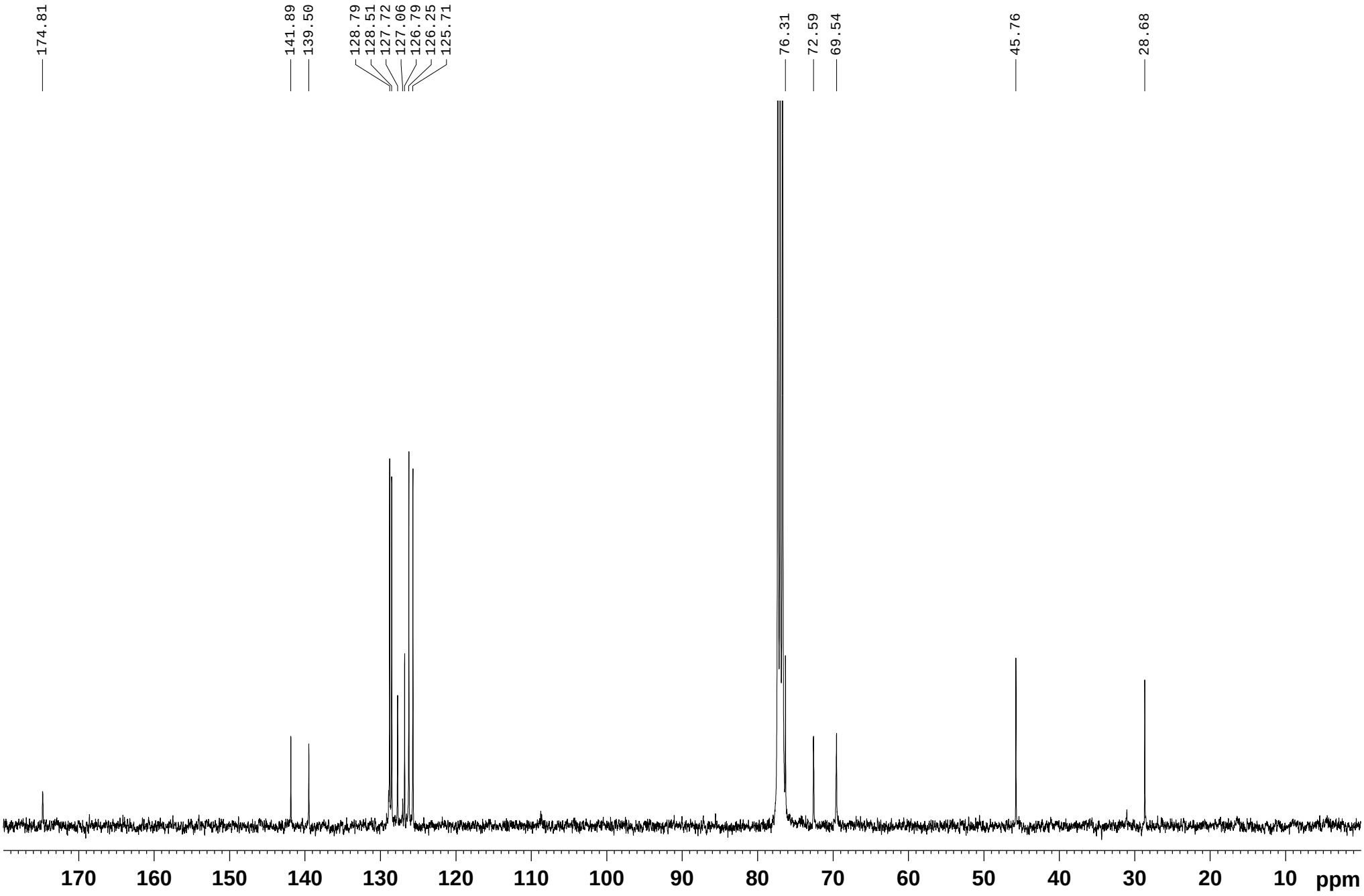
S 79 X-ray structure of compound **11.**



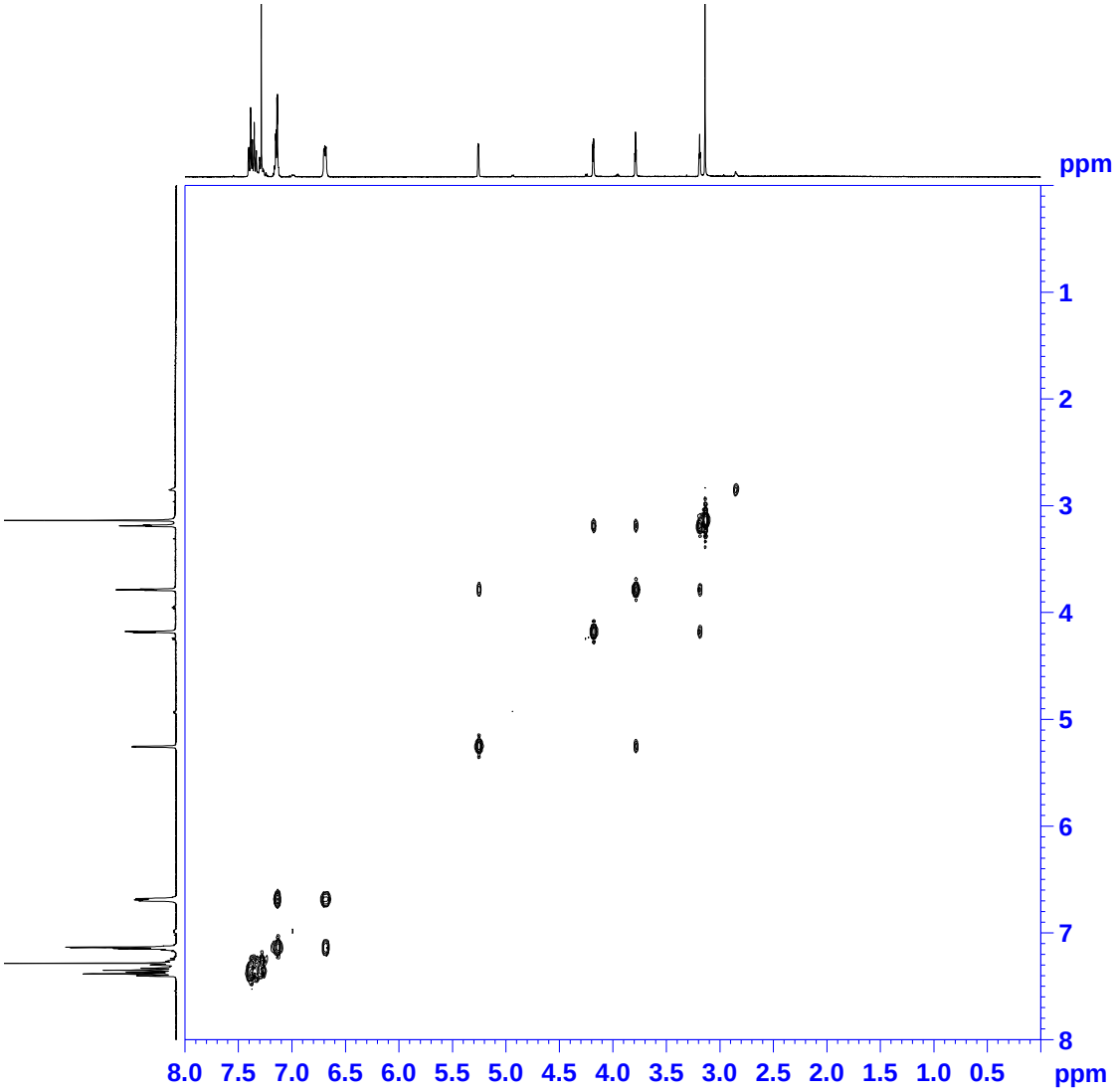
S 80 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **12.**



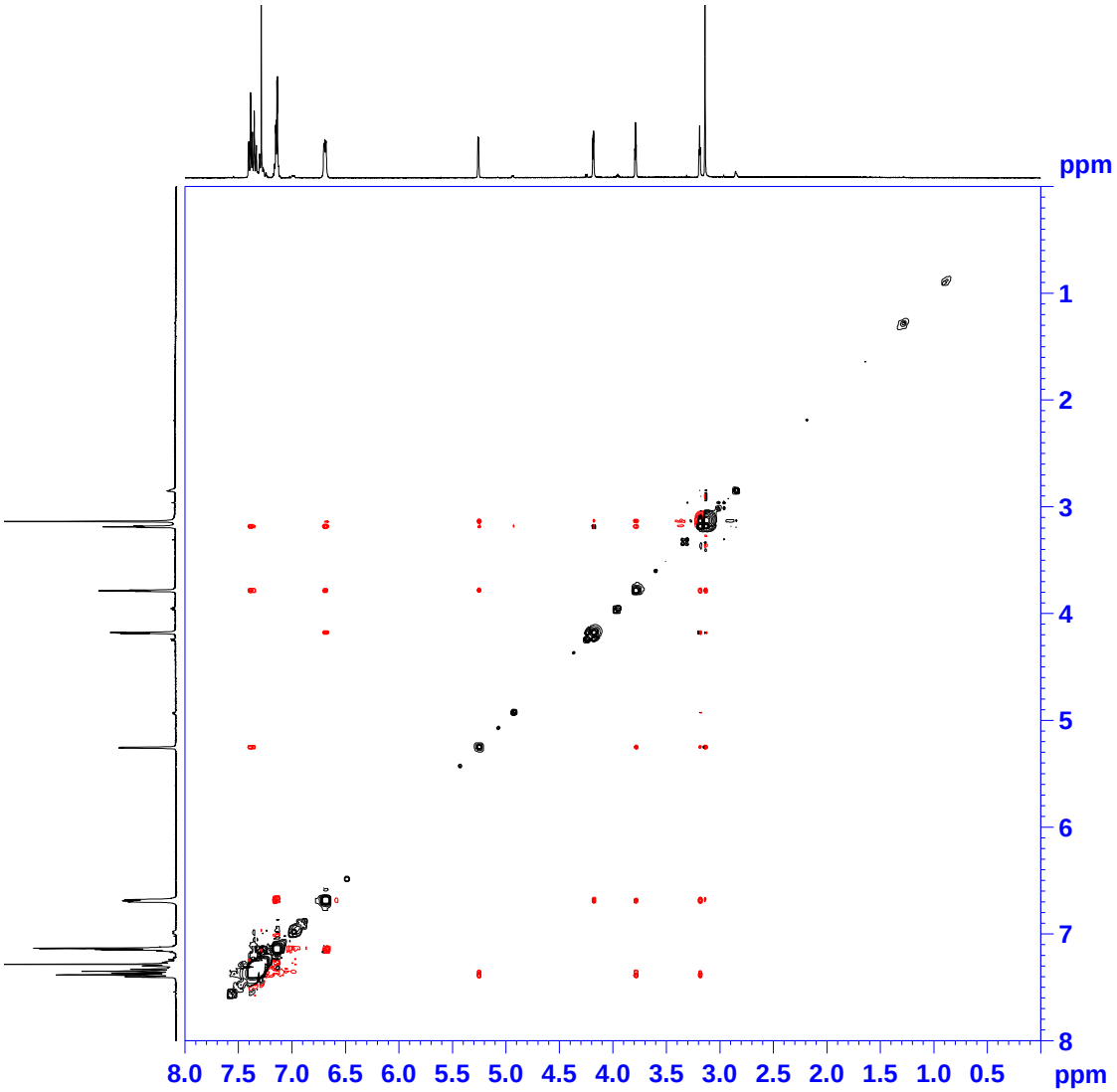
S 81 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **12.**



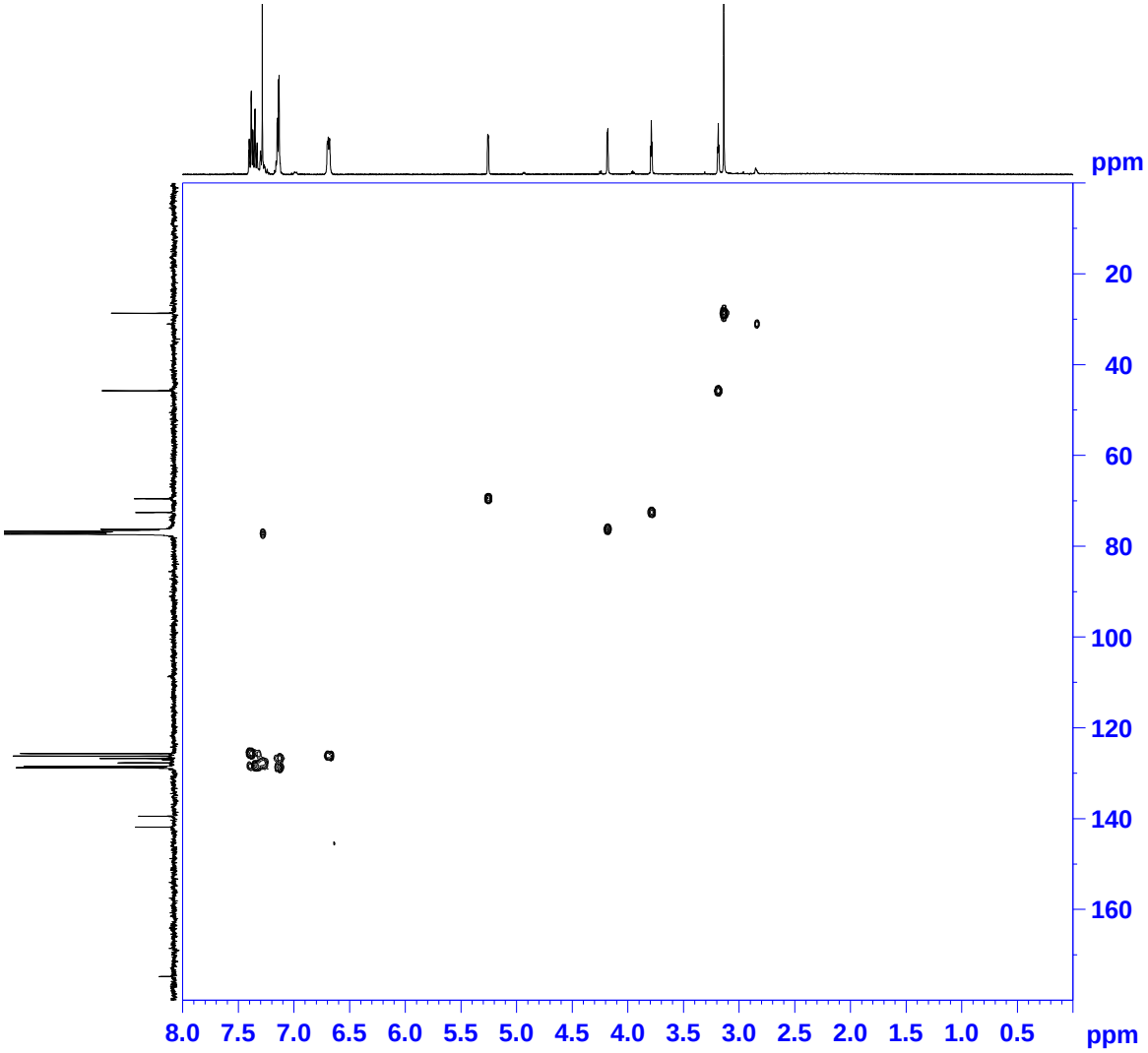
S 82 COSY spectrum of the compound **12.**



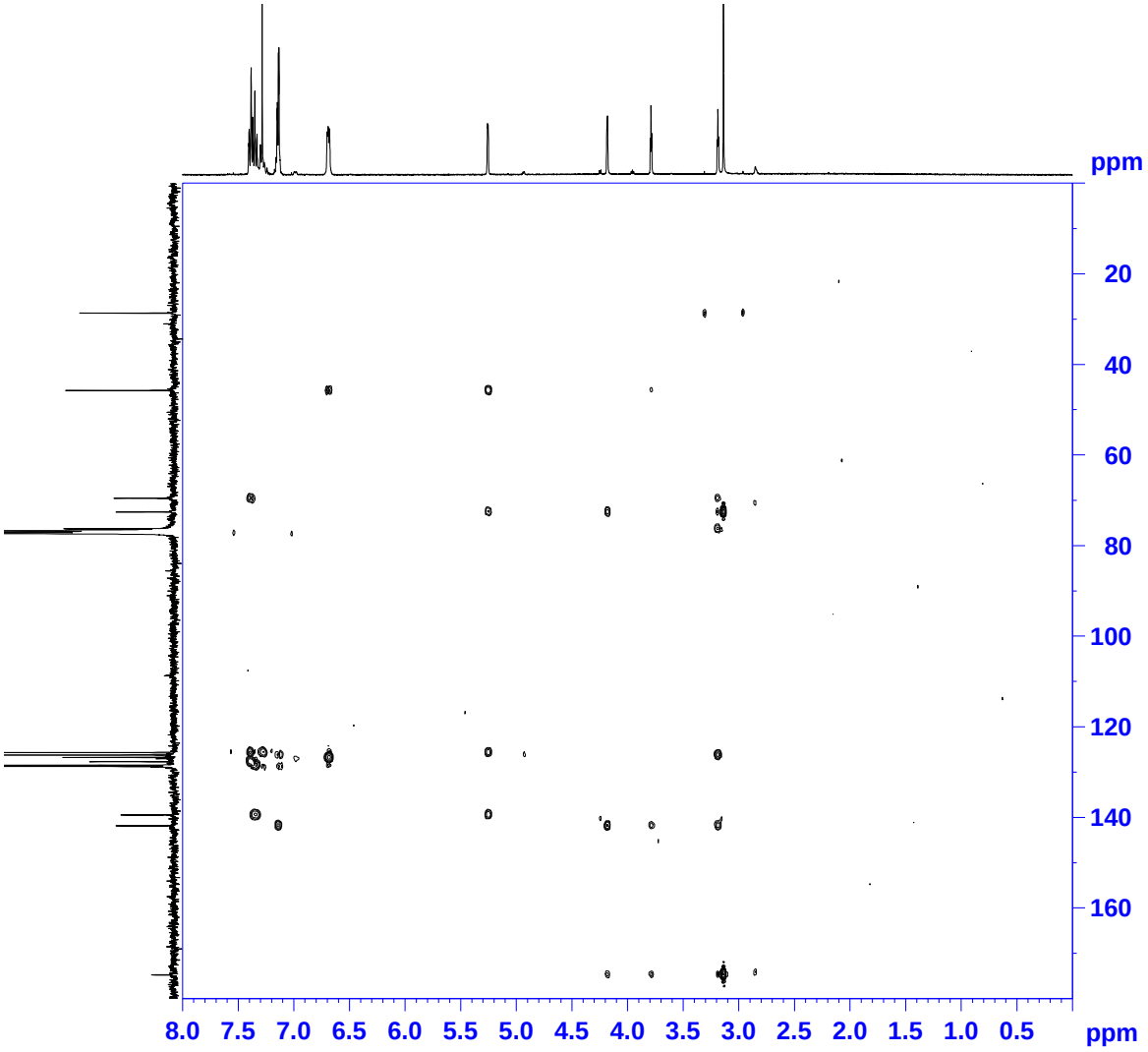
S 83 NOESY spectrum of the compound **12.**



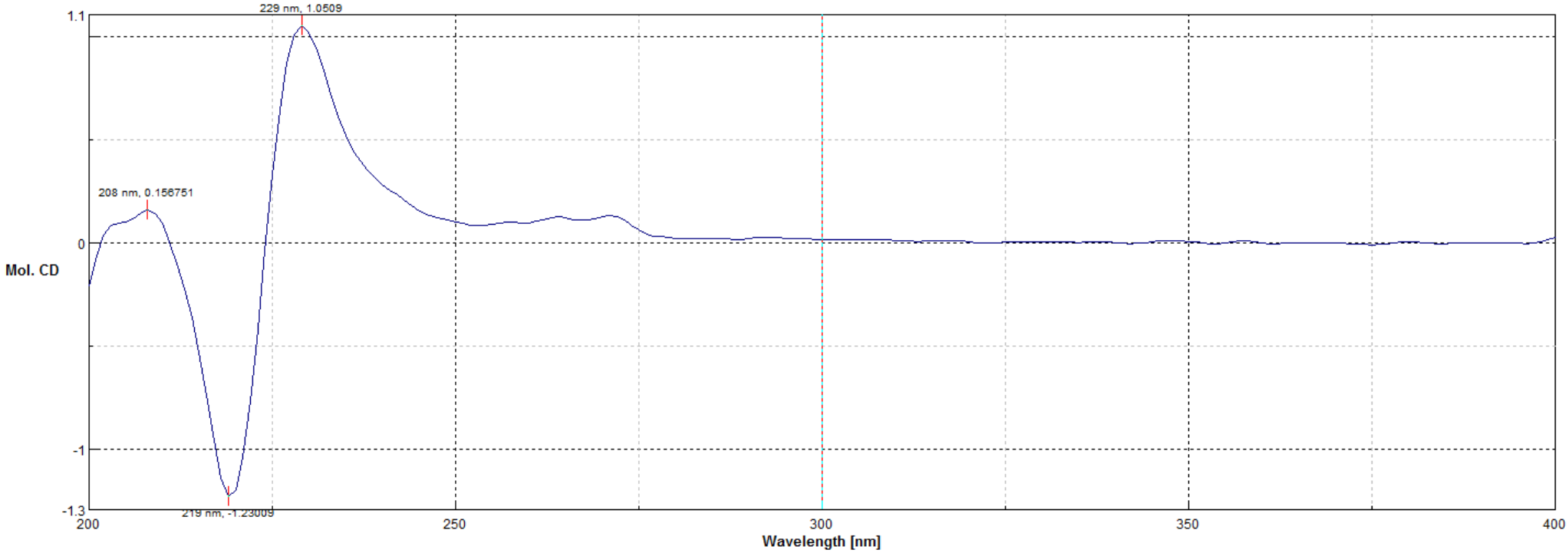
S 84 HSQC spectrum of the compound **12.**



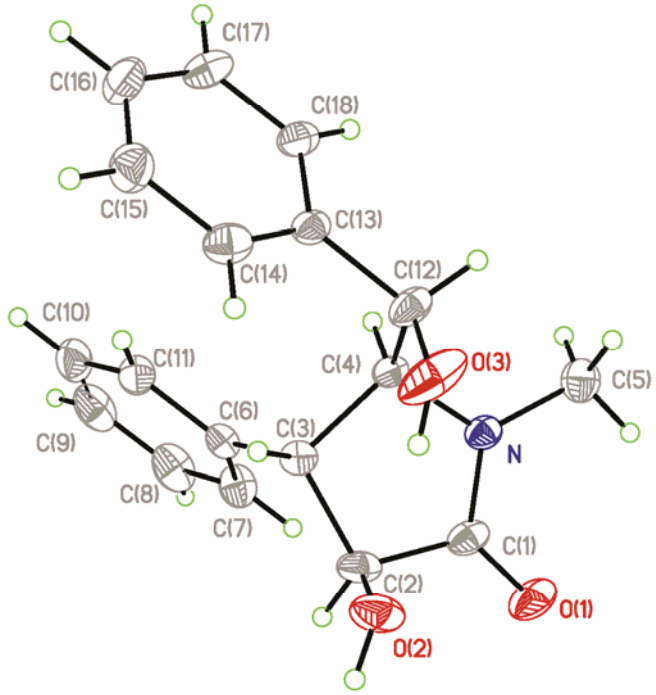
S 85 HMBC spectrum of the compound **12.**



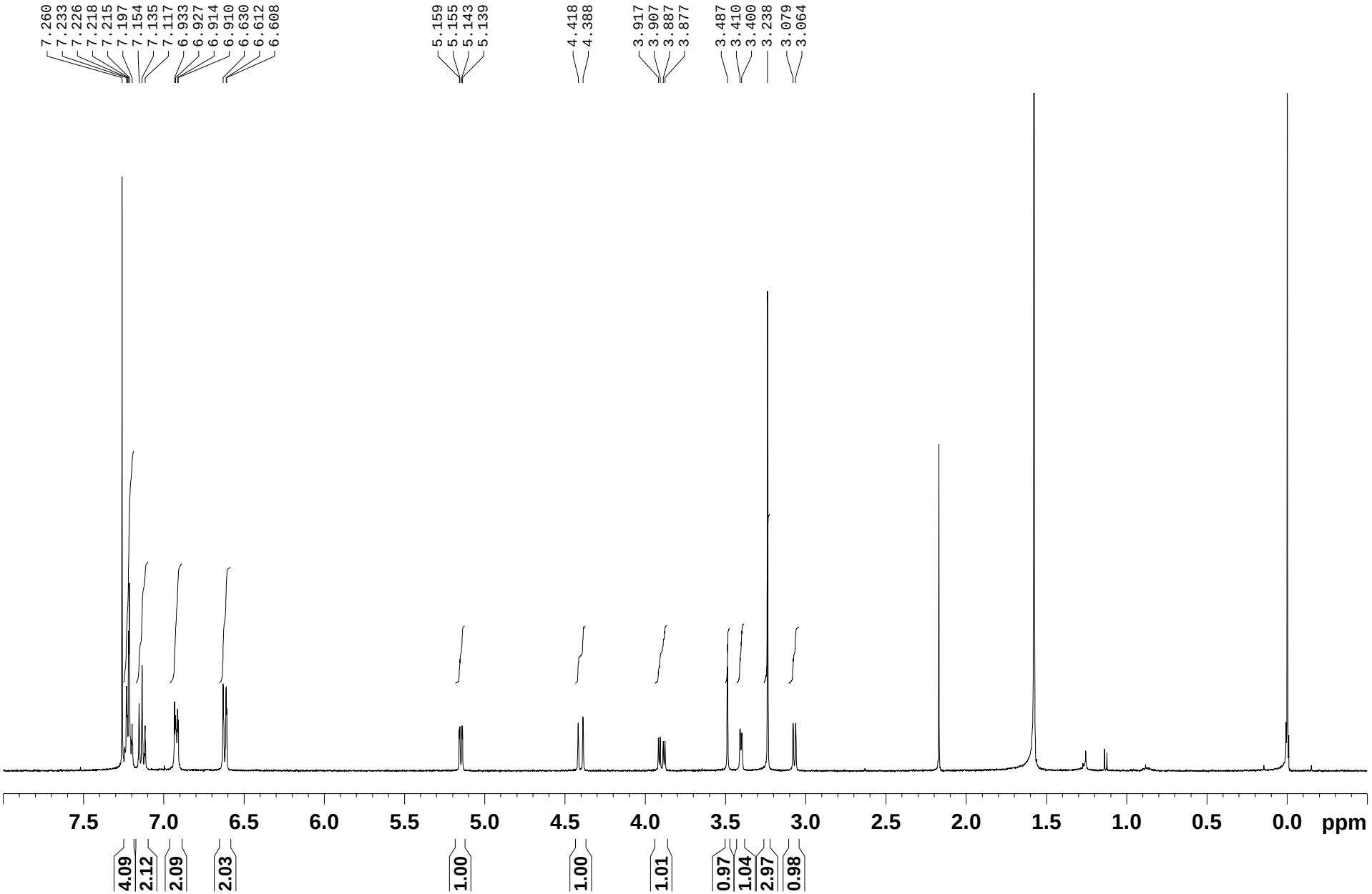
S 86 CD spectrum of the compound **12.**



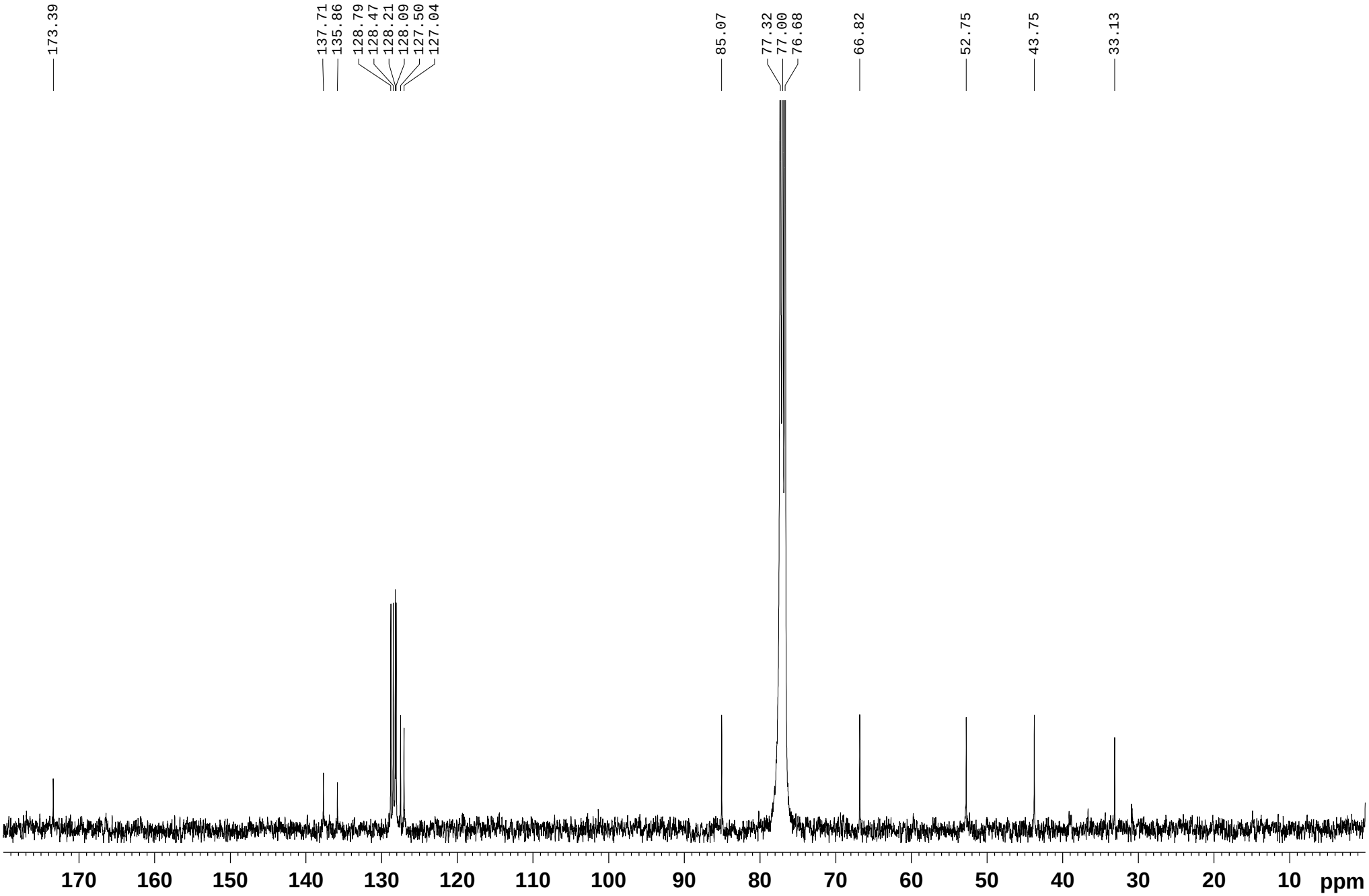
S 87 X-ray structure of compound **12.**



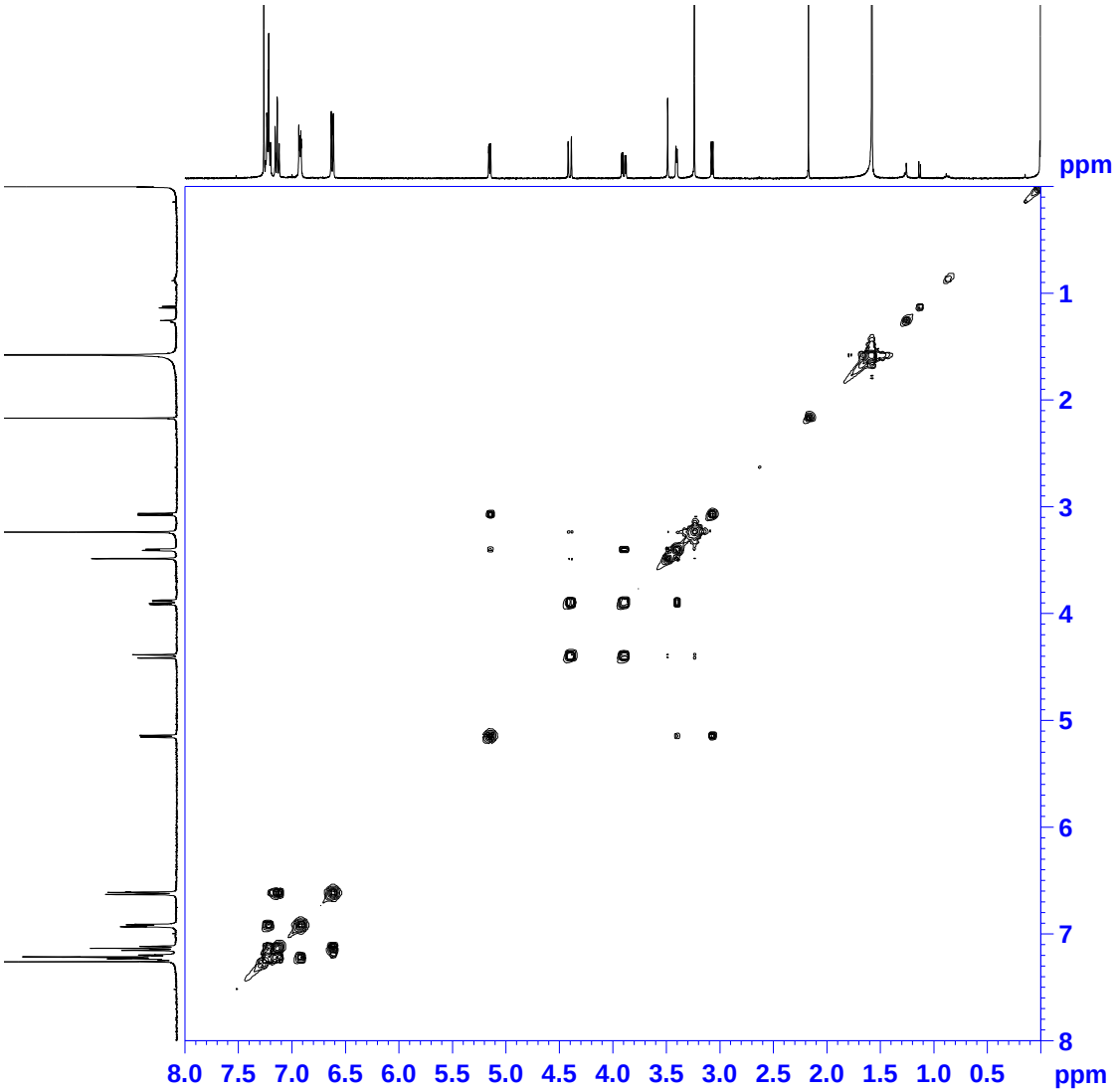
S 88 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **13.**



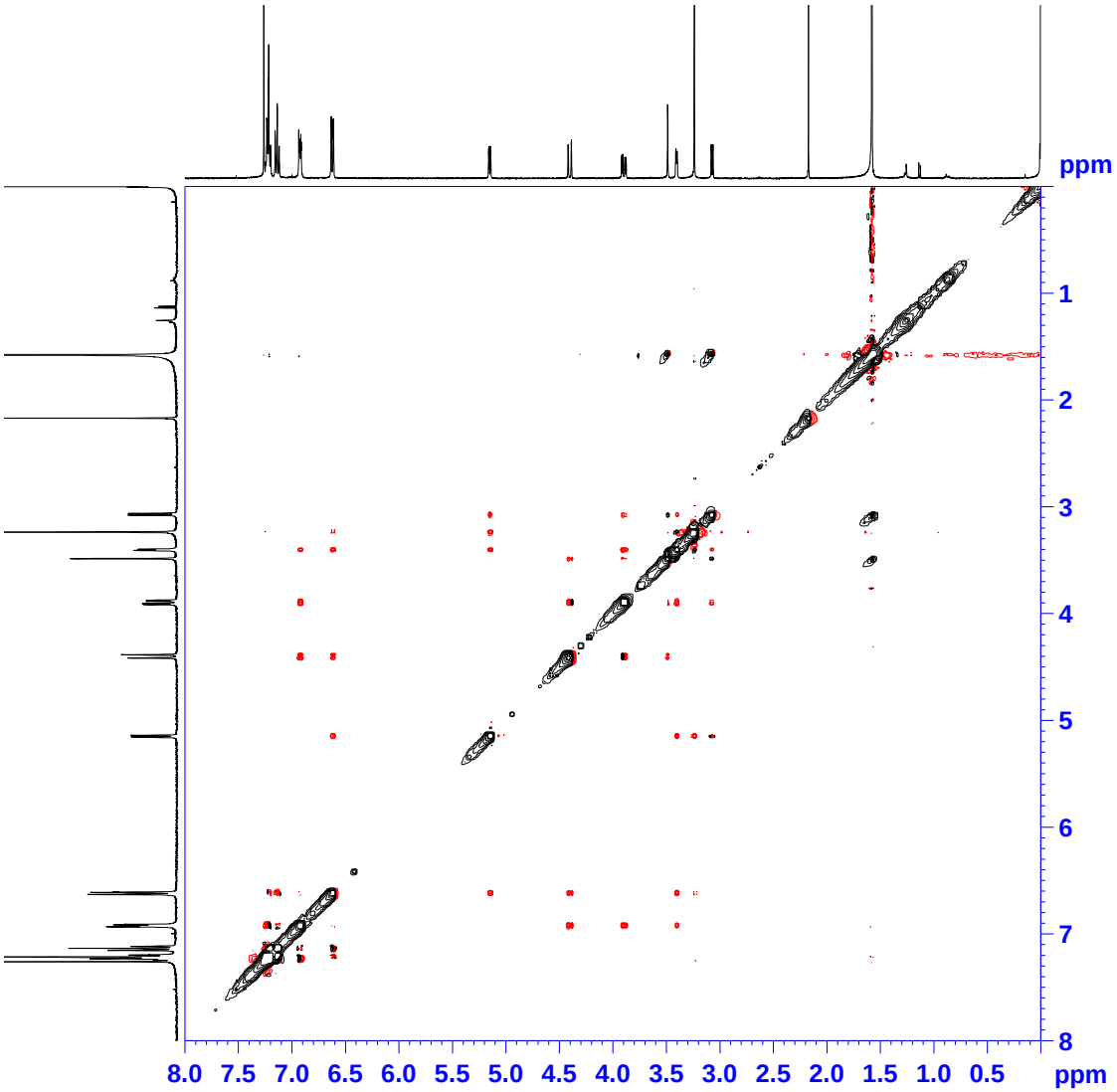
S 89 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **13.**



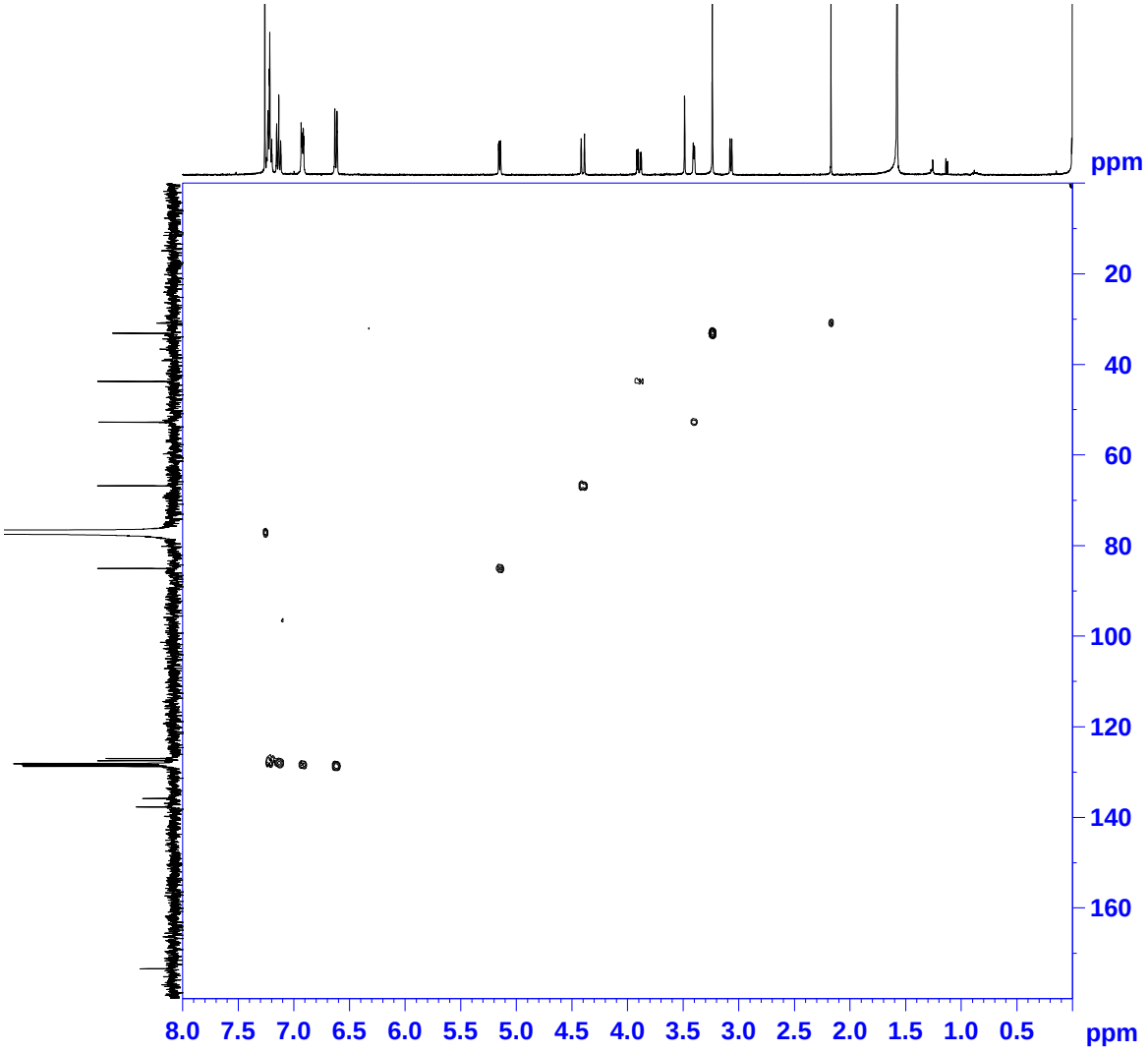
S 90 COSY spectrum of the compound **13.**



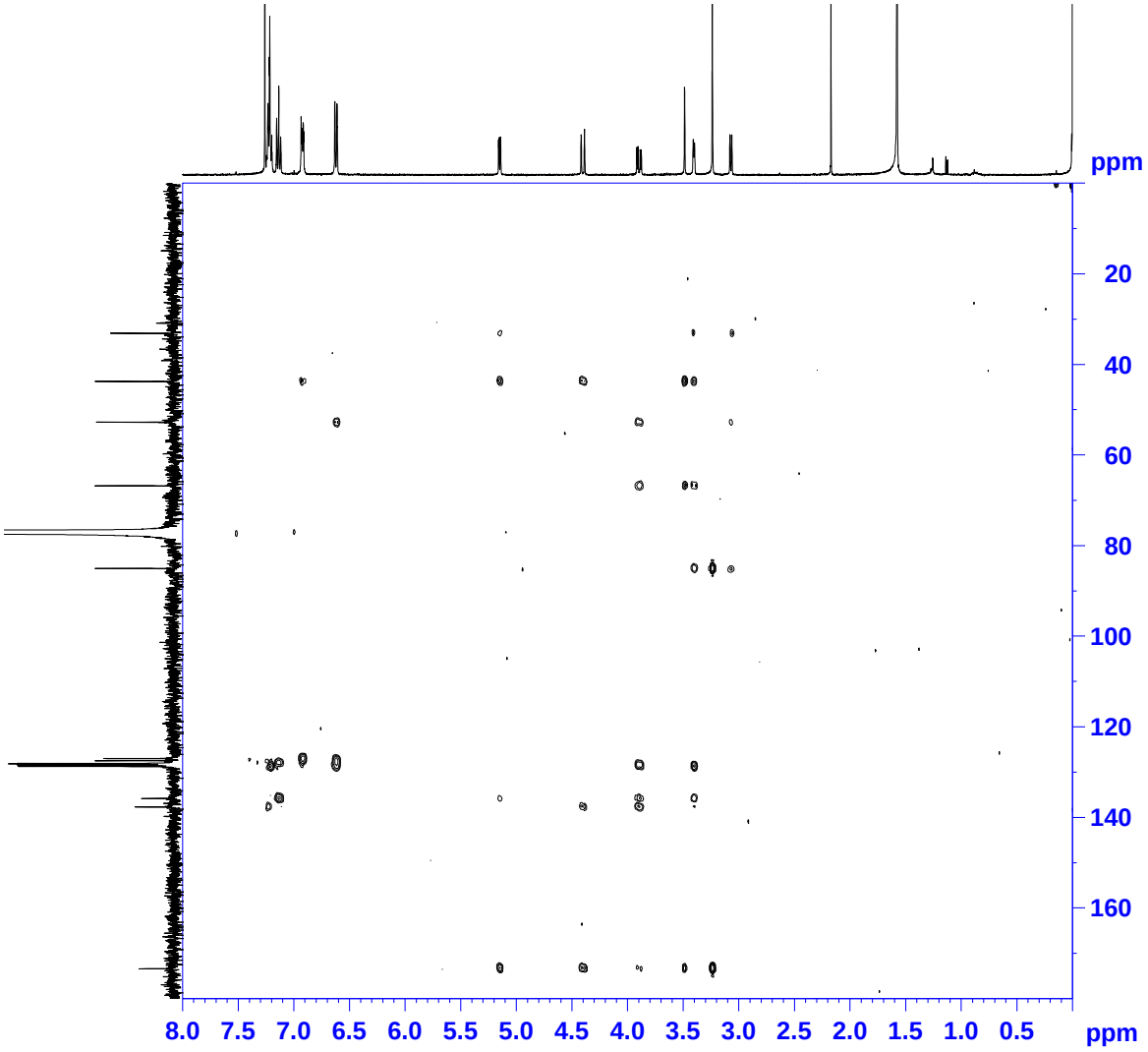
S 91 NOESY spectrum of the compound **13.**



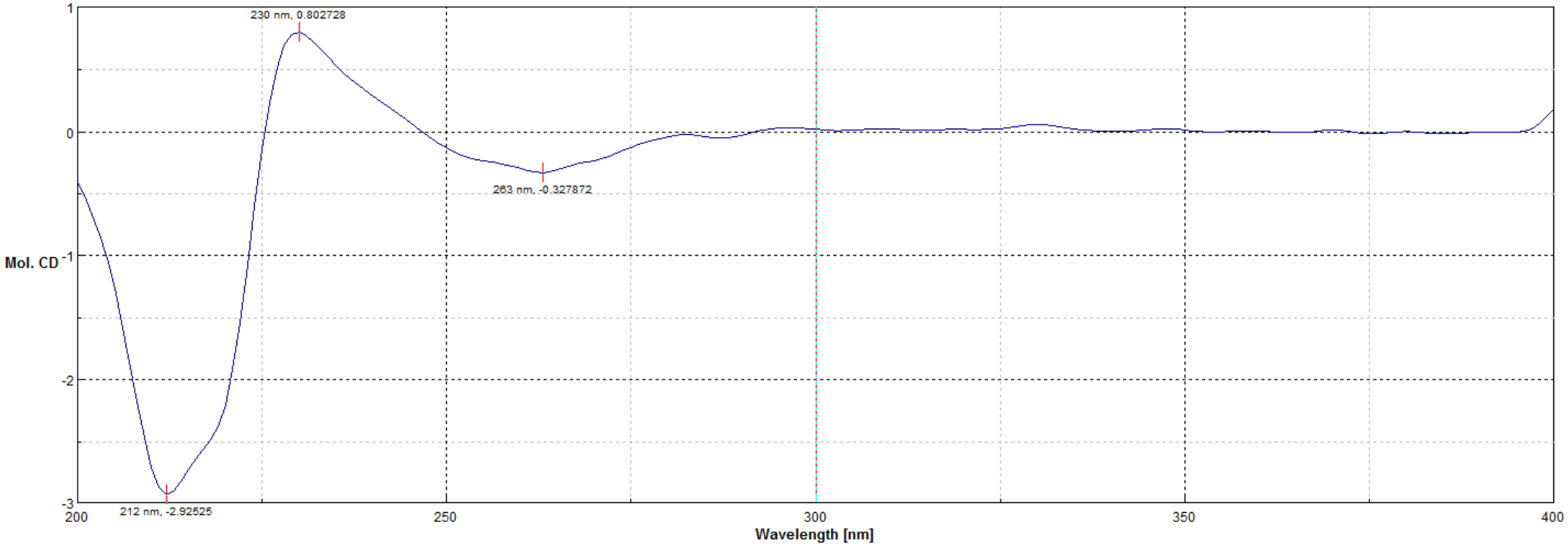
S 92 HSQC spectrum of the compound **13.**



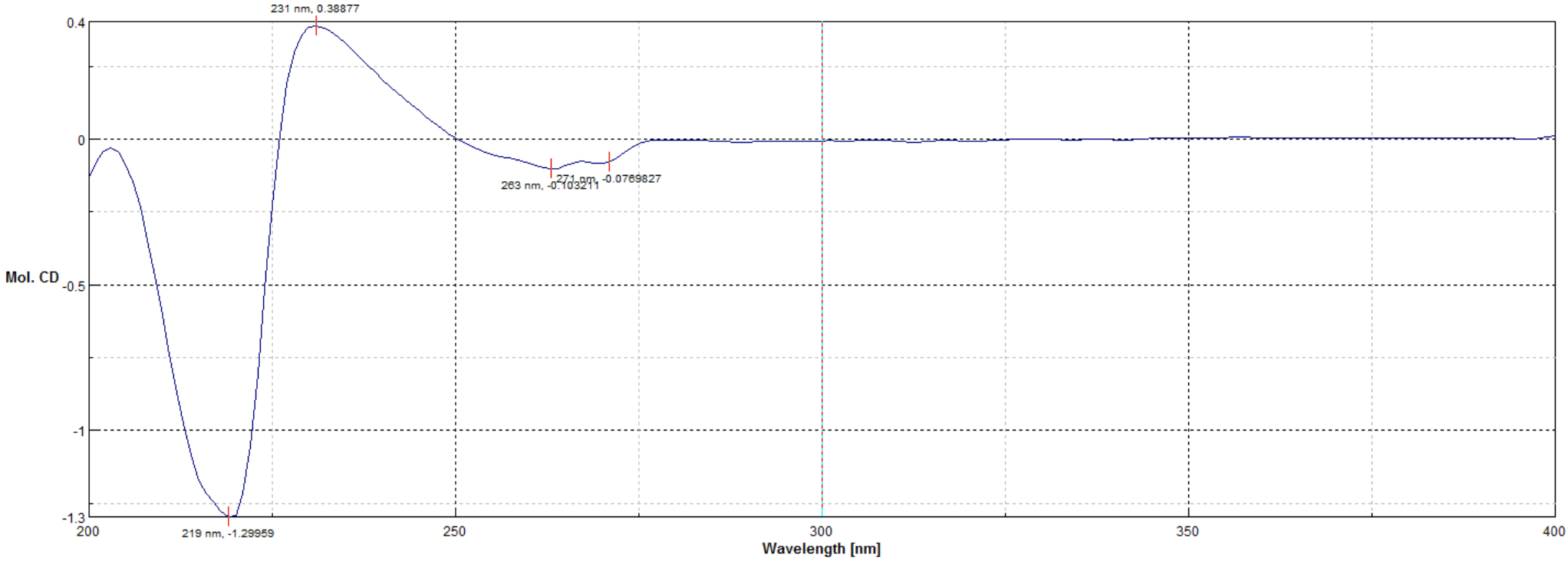
S 93 HMBC spectrum of the compound **13.**



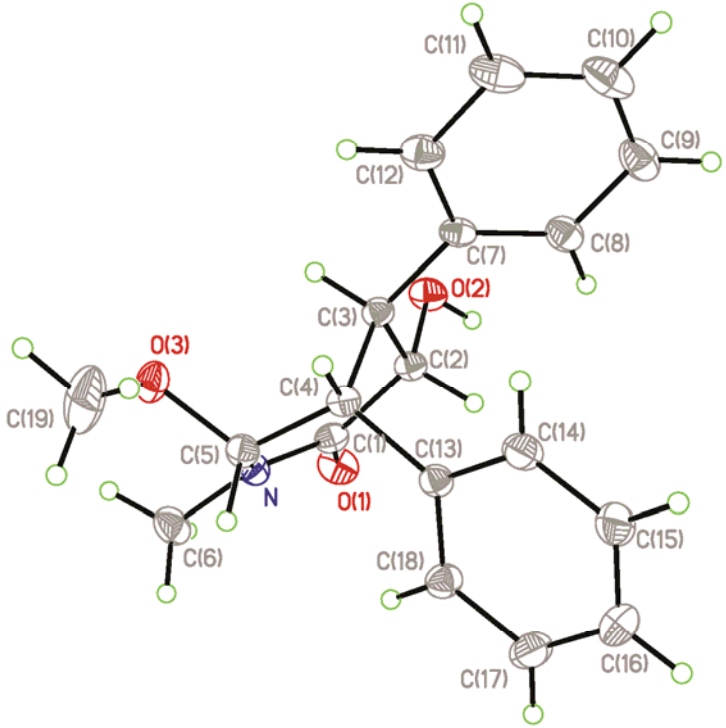
S 94 CD spectrum of the compound **13.**



S 95 CD spectrum of the compound **14.**



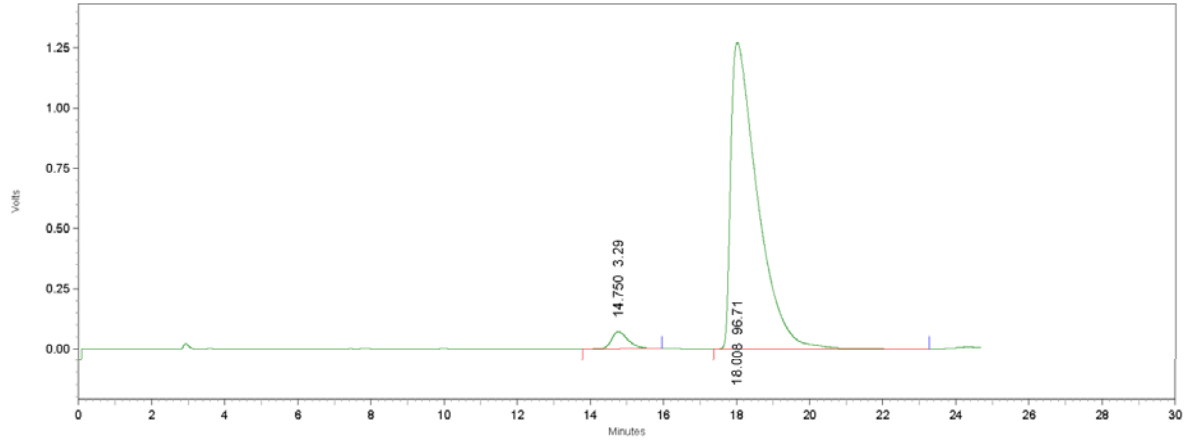
S 96 X-ray structure of compound **14.**



S 97 Chiral HPLC of compound **1**

Detector A - 1 (214nm)

Area	Retention Time	Area Percent
2183232	14.750	3.29
64136173	18.008	96.71
Totals		
66319405		100.00



Gradient: *n*-Hexane/iso-Propanol; 90:10

Astec Cellulose DMP (150 × 4.6 mm i.d. 5 µm).

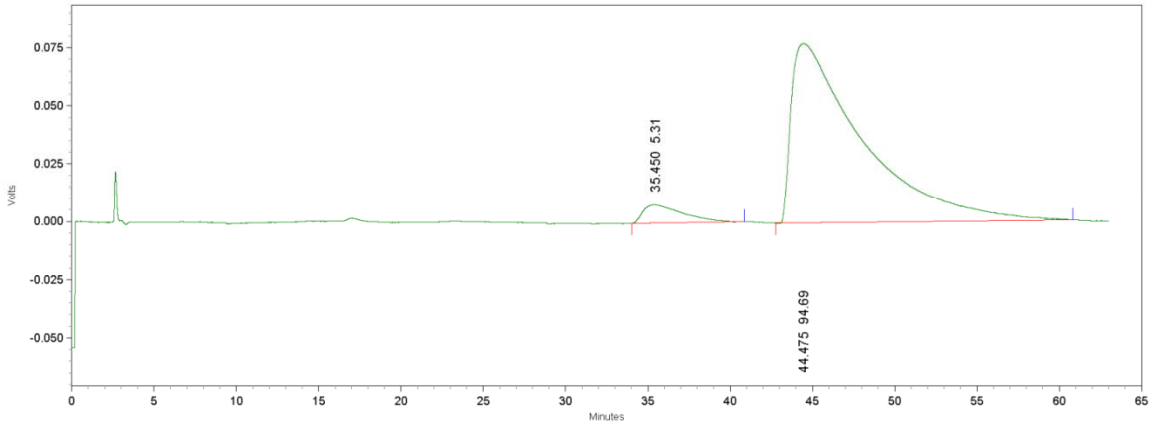
Set Wavelength: 214 nm

Flow rate: 1.0 mL/min

S 98 Chiral HPLC of compound **11**

Detector A - 1 (214nm)

Retention Time	Area	Area Percent
35.450	1299739	5.31
44.475	23198666	94.69
Totals	24498405	100.00



Gradient: *n*-Hexane/iso-Propanol; 90:10

Astec Cellulose DMP (150 × 4.6 mm i.d. 5 µm).

Set Wavelength: 214 nm

Flow rate: 1.0 mL/min

S 99 Neuroprotective Assay

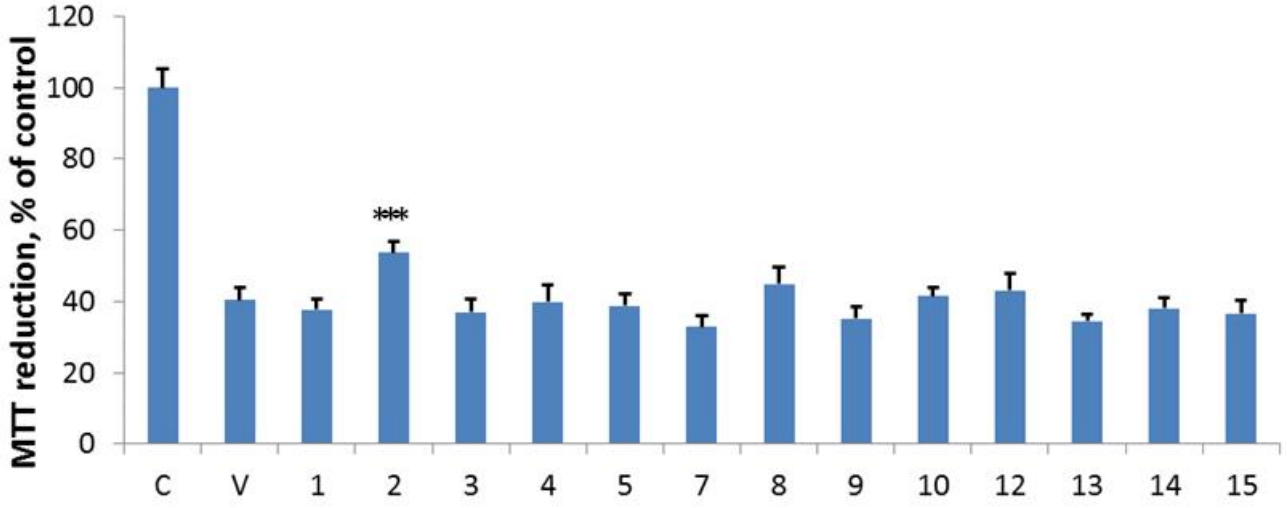
Primary cultures of neonatal cortical neurons were prepared from the cerebral cortex of Harlan Sprague-Dawley rat pups at postnatal day 1.[23] Briefly, each pup was decapitated and the cortex was digested in 0.5 mg/mL papain at 37 °C for 15 min. The tissue was dissociated in Hibernate A medium (containing B27 supplement) by aspirating trituration. The cells were plated (5×10^4 cells/cm^2) onto poly-D-lysine-coated dishes and maintained in Neurobasal medium containing the B27 supplement, 10 units/mL penicillin, 10 mg/mL streptomycin, and 0.5 mg/mL glutamine (5 % CO_2/9 % O_2) for 3 days. The cells were then exposed to cytosine-β-D-arabinofuranoside (5 μM) for 1 day to inhibit the proliferation of non-neuronal cells. The cells were used for the experiment on the fifth day. The optimized concentration (10 μM) and treatment duration (40 h), of $A\beta_{25–35}$ were determined previously.[23] Cortical neurons were treated with various concentration of compounds **1–15** or vehicle (0.01 % DMSO), to determine the toxic effect of these compounds. Only compound **10** showed toxic effect on cortical neurons at 50 μM. Subsequently, cortical neurons were pretreated with 10, 20, and 50 μM of compounds (with the exception of compound **10** which was 5, 10, and 20 μM) for 2 h and then exposed to 10 μM of $A\beta_{25–35}$ for 40 h. Neurotoxicity was measured by MTT reduction assay.

S 100 Neurotoxicity Assay

MTT reduction was used to evaluate the neurotoxicity. The cells were incubated with minimum essential medium containing 0.5 mg/mL MTT for 1 h. The medium was aspirated, and the formazan particles were dissolved with lysis buffer (10 % sodium dodecyl sulfate, 3.3 mM HCl, 50 % dimethylformamide). The absorbance at 600 nm was measured using an enzyme-linked immunosorbent assay reader.

Statistical Analysis. All experiments were performed at least three times, and the results are expressed as the means ± SEM. The statistical analyses were based on the Student's *t* test or the Mann-Whitney *U* test, and all calculations were performed with SigmaPlot (Systat Software, San Jose, CA). A p value < 0.05 was considered statistically significant.

S 101 Compound **2** prevented cell death of cortical neurons induced by Aβ-(25–35).



Cortical neurons were pretreated with vehicle (V) or 50 μM of compounds (except that for **10**, is 20 μM**)** for 2 h and then exposed to 10 μM of Aβ-(25–35) for 40 h. Cell viability was measured by MTT reduction assay. Results are means ± SEM. from four independent experiments and expressed relative to control (C). Significant differences between cells treated with Aβ-(25–35) plus vehicle (V) and Aβ-(25–35) plus compounds are indicated by ***, $p < 0.001$. The neurotoxicity % = 100 % −MTT reduction %.