Chemistry & Biodiversity

Supporting Information

Synthetic Approaches to Steroidal Thiosemicarbazones, 1,3,4-Thia(selena)diazolines, and Oxalate-Linked Dimers

Luis A. Méndez-Delgado [1], Mónica Martínez-Montiel [1], Alma Fuentes-Aguilar [1], Socorro Meza-Reyes [1], Sara Montiel-Smith [1], José Luis Vega-Baez [1], José M. Padrón [2] and Penélope Merino-Montiel [1,*]

[1] Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Ciudad Universitaria, Puebla 72592, Pue., Mexico; monica.martinezmon@alumno.buap.mx (M.M.-M.); maria.montiel@correo.buap.mx (S.M.-S.); jose.vega@correo.buap.mx (J.L.V.-B.)

[2] BioLab, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Universidad de La Laguna, c/Astrofísico Francisco Sánchez 2, E-38206 La Laguna, Spain; jmpadron@ull.edu.es

* Correspondence: penelope.merino@correo.buap.mx

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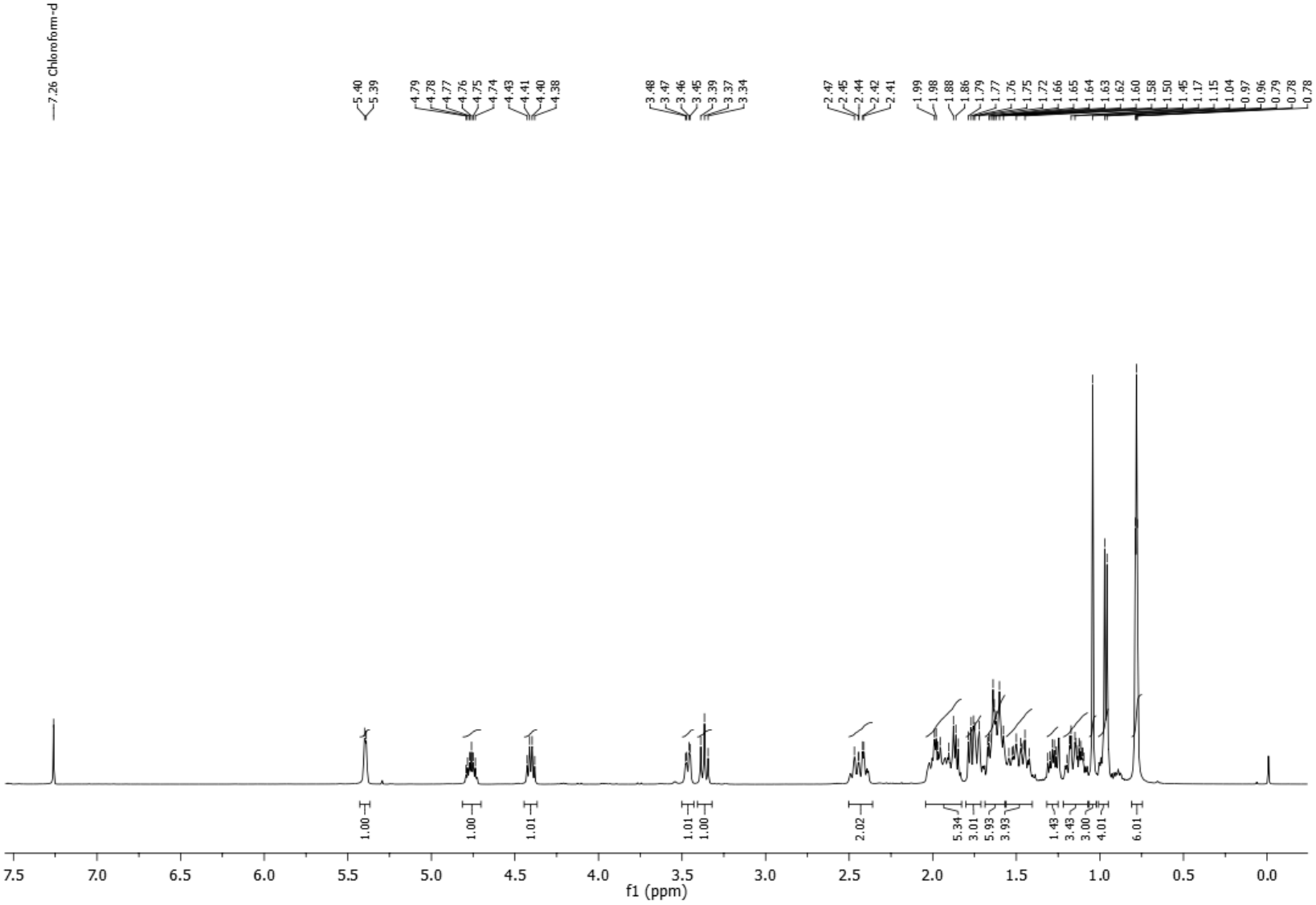


Figure S1. ^{1}H-NMR spectrum of **2** (500 MHz, $CDCl_3$)

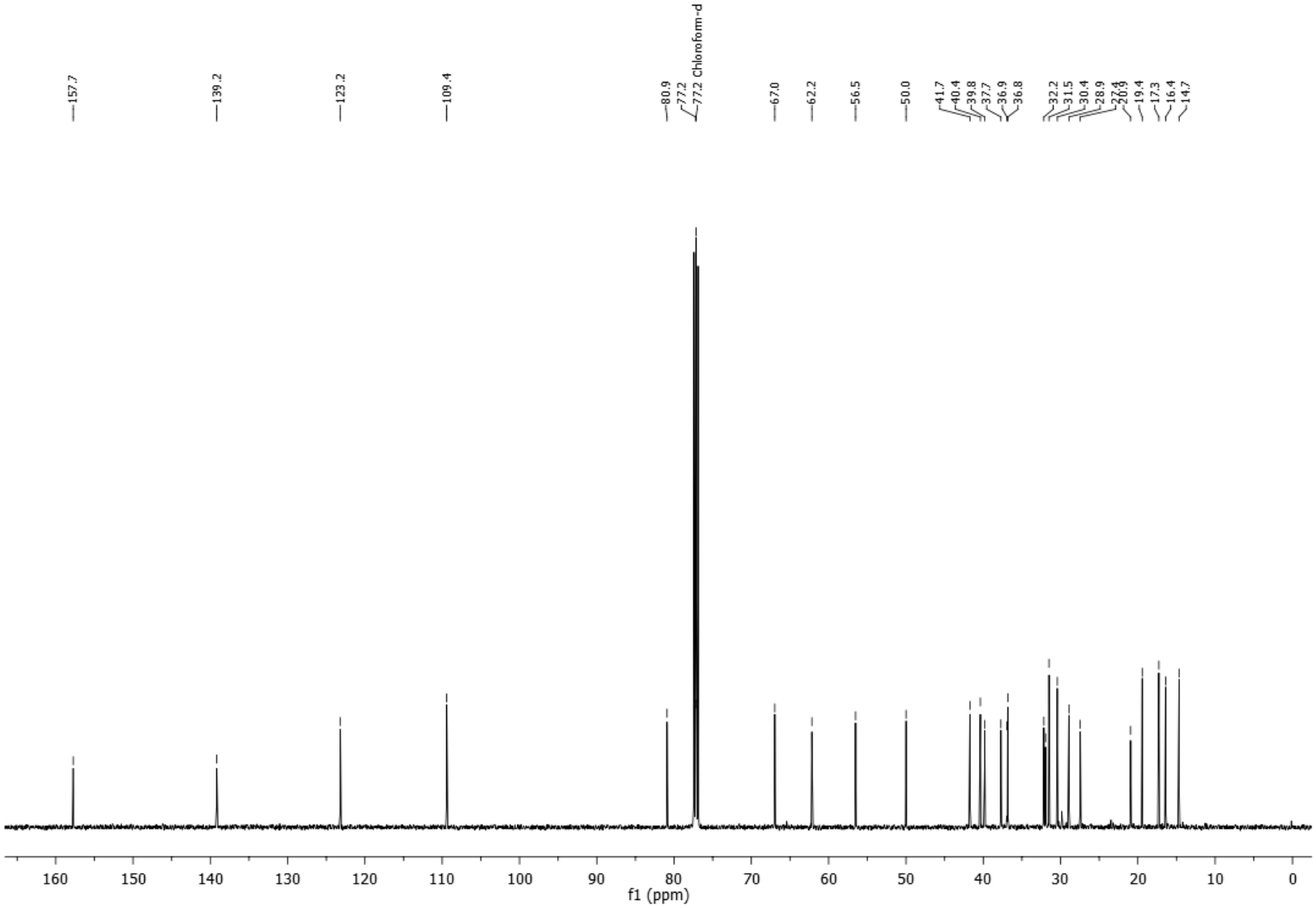


Figure S2. ^{13}C-NMR spectrum of **2** (125.7 MHz, $CDCl_3$)

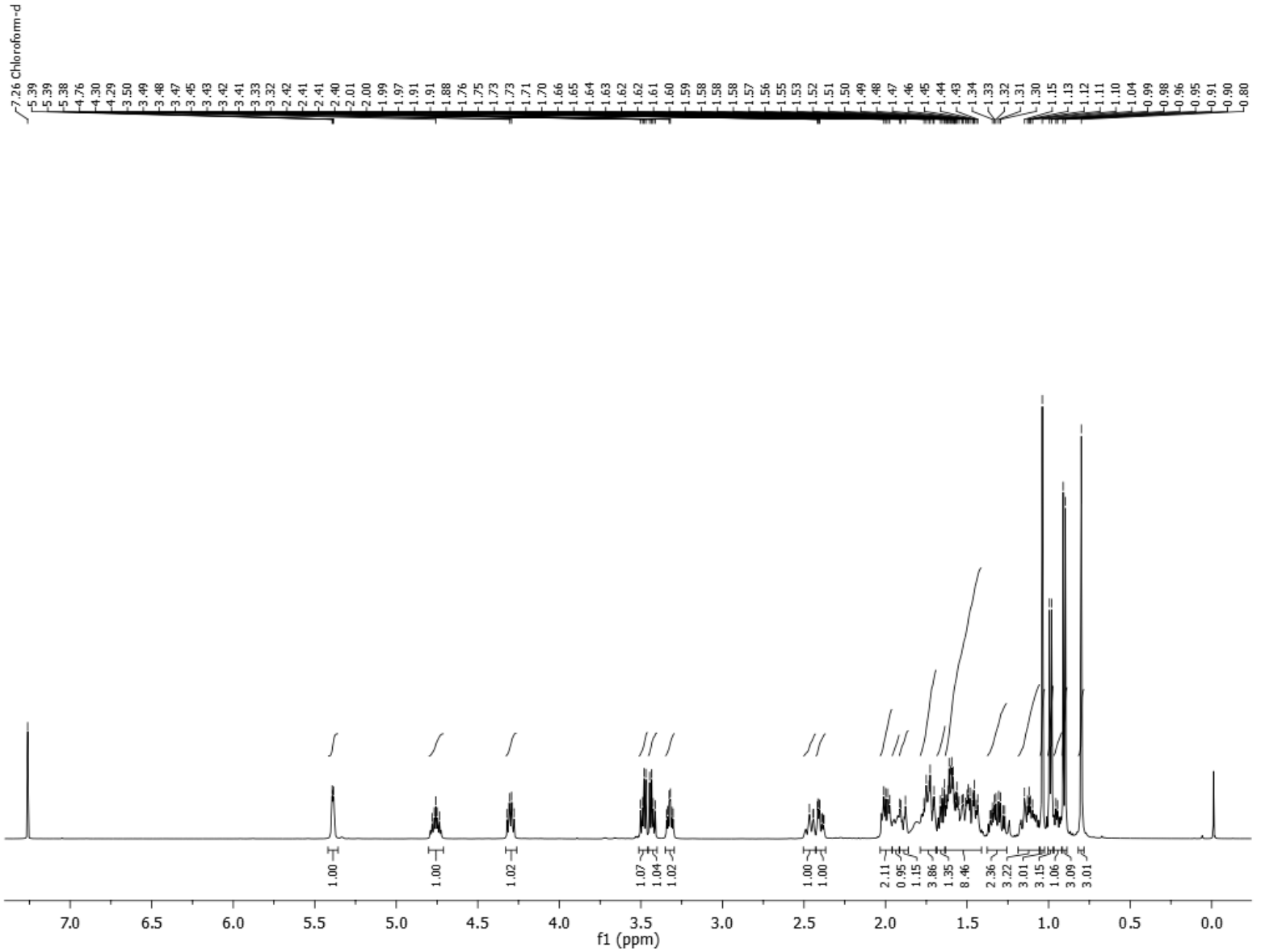


Figure S3. ^{1}H-NMR spectrum of **3** (500 MHz, $CDCl_3$)

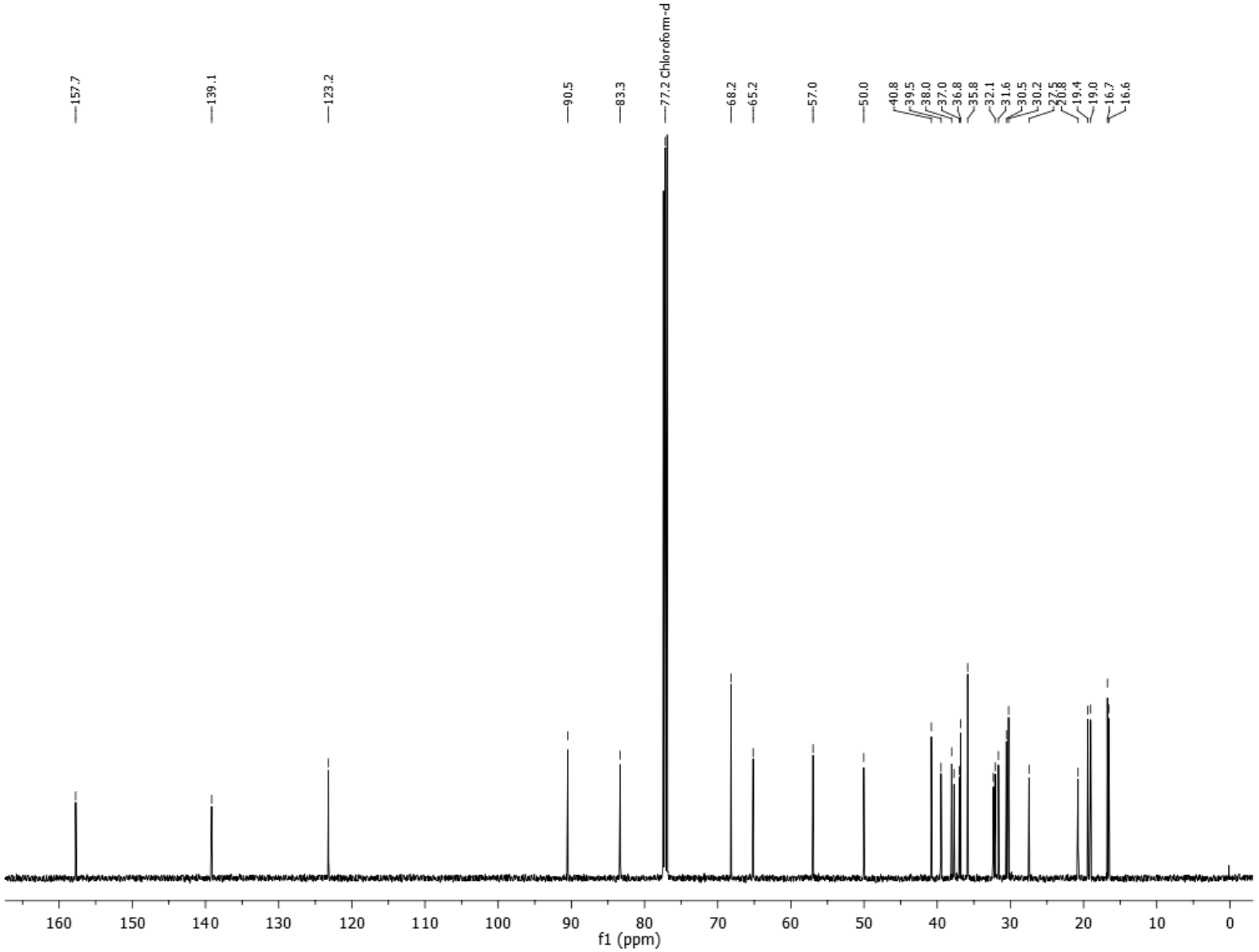


Figure S4. ^{13}C-NMR spectrum of **3** (125.7 MHz, $CDCl_3$)

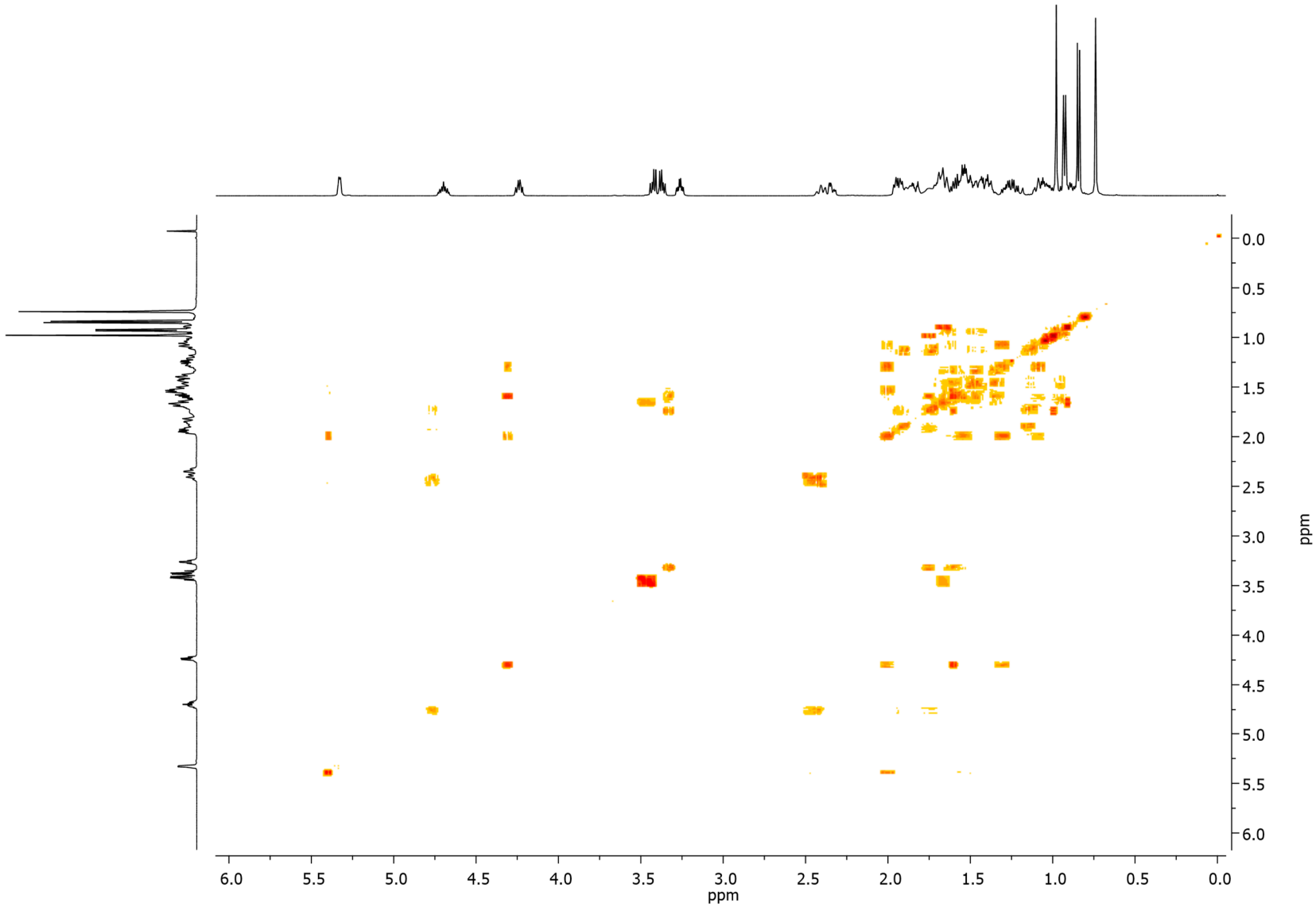


Figure S5. Experiment COSY of **3** (500 MHz, $CDCl_3$)

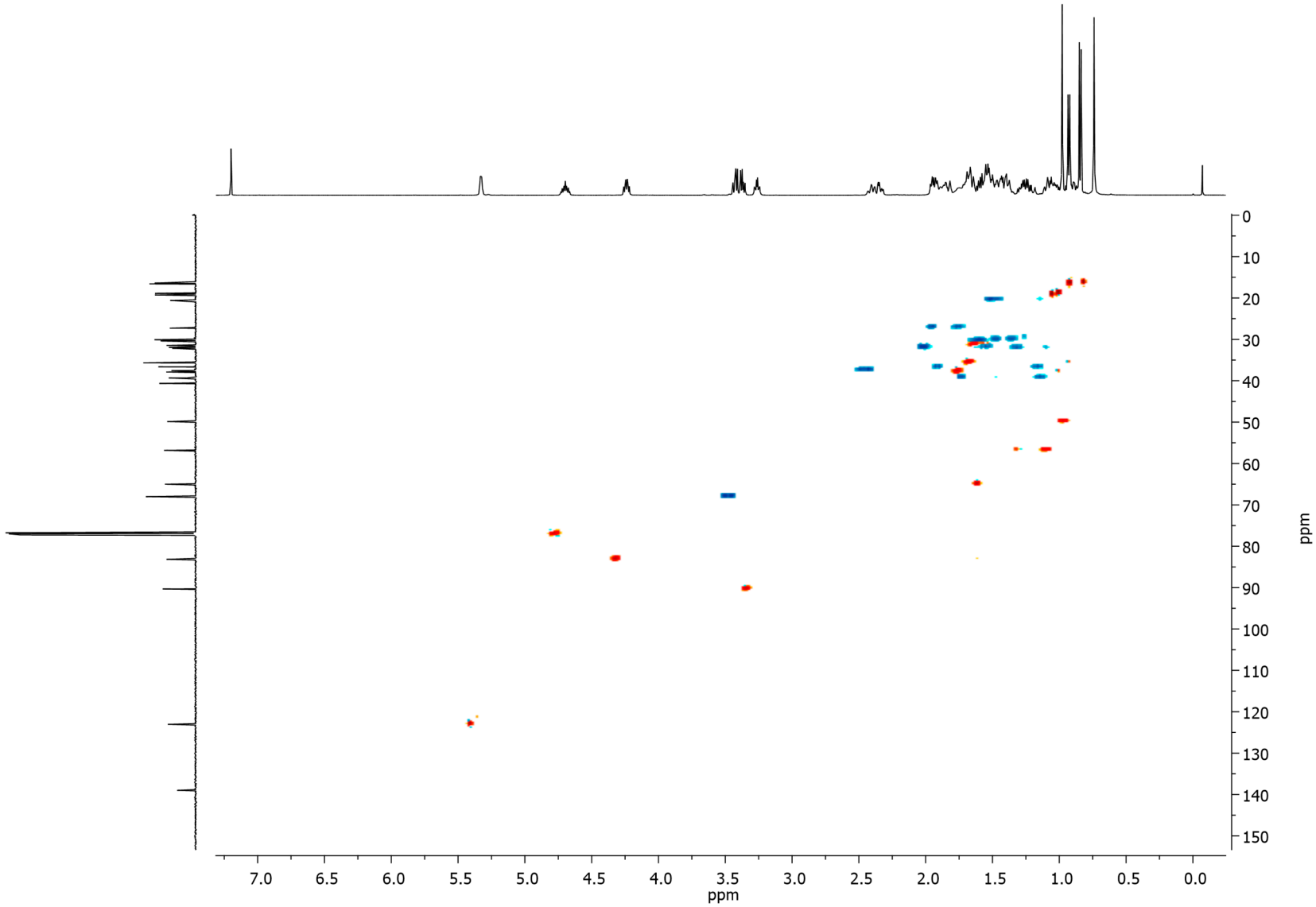


Figure S6. Experiment HSQC of **3** (500 MHz, $CDCl_3$)

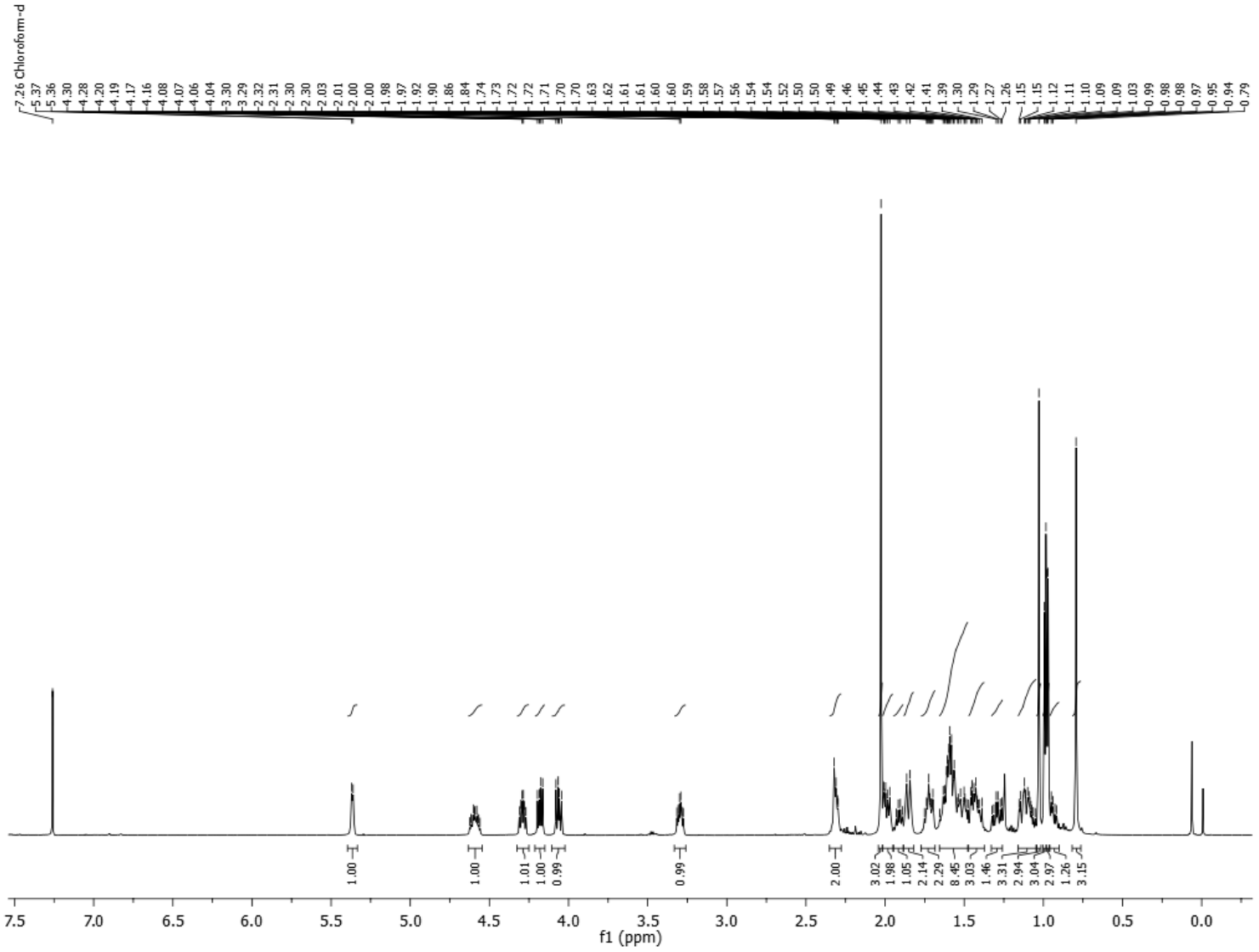


Figure S7. ^{1}H-NMR spectrum of **6** (500 MHz, $CDCl_3$)

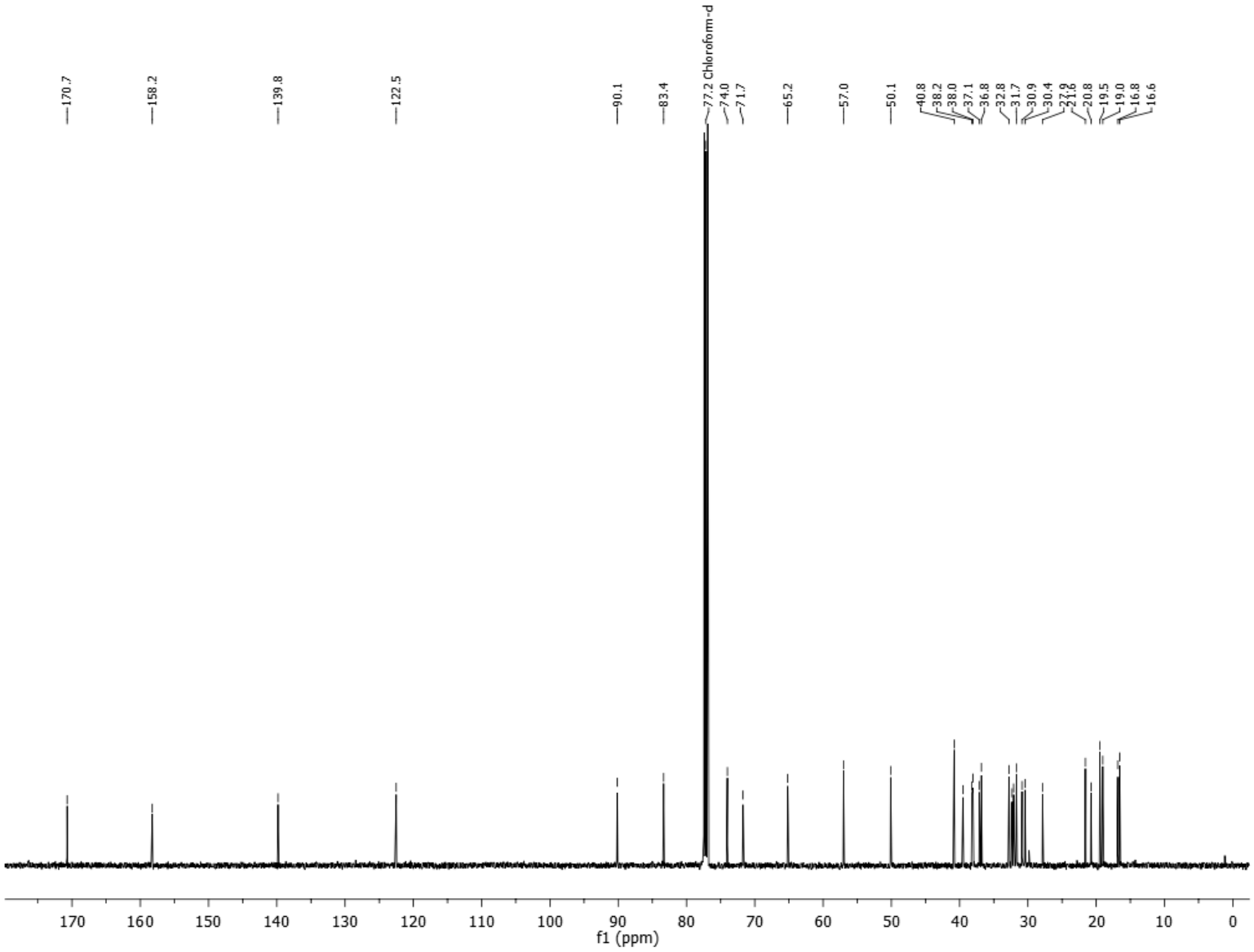


Figure S8. ^{13}C-NMR spectrum of **6** (125.7 MHz, $CDCl_3$)

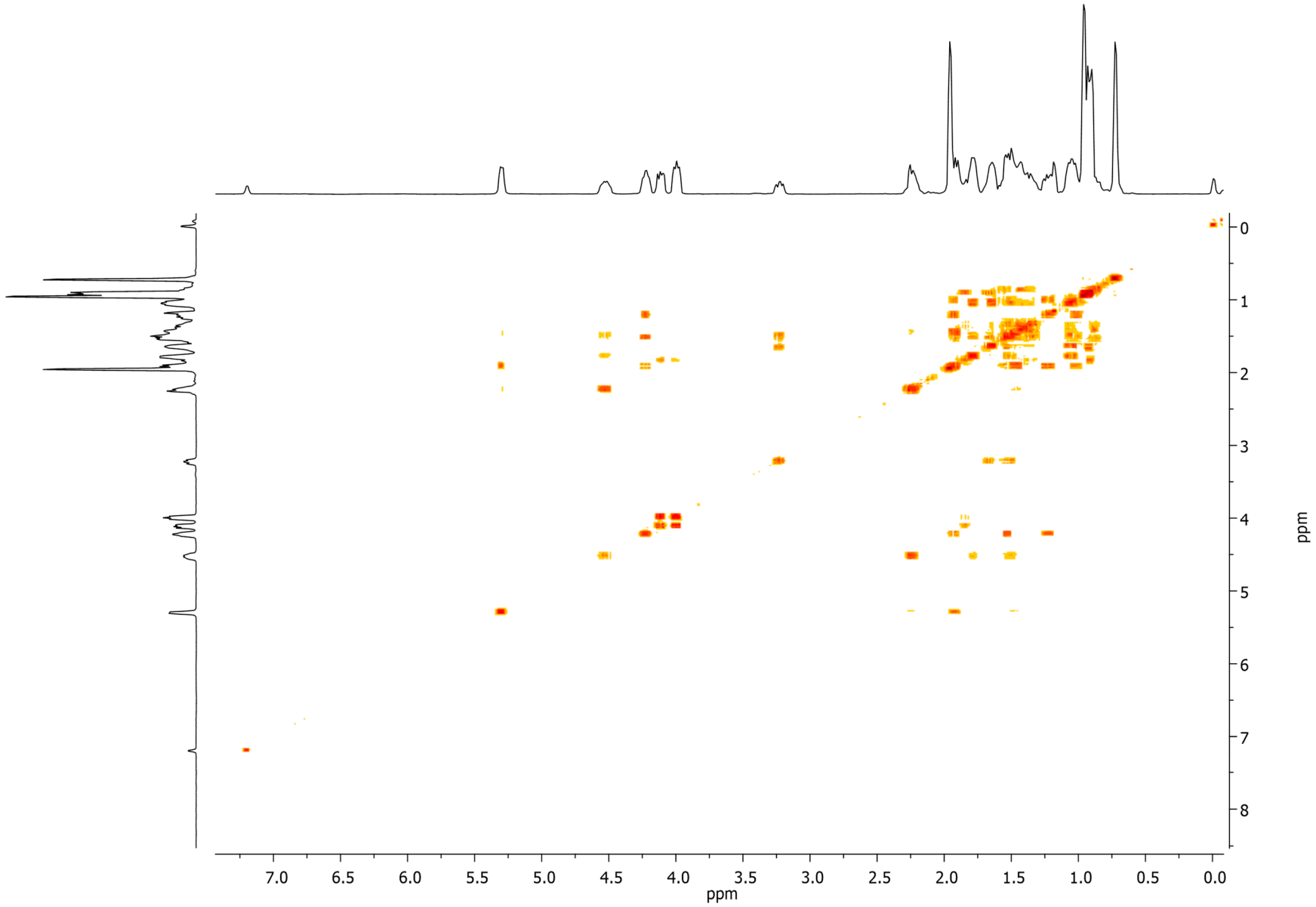


Figure S9. Experiment COSY of **6** (500 MHz, $CDCl_3$)

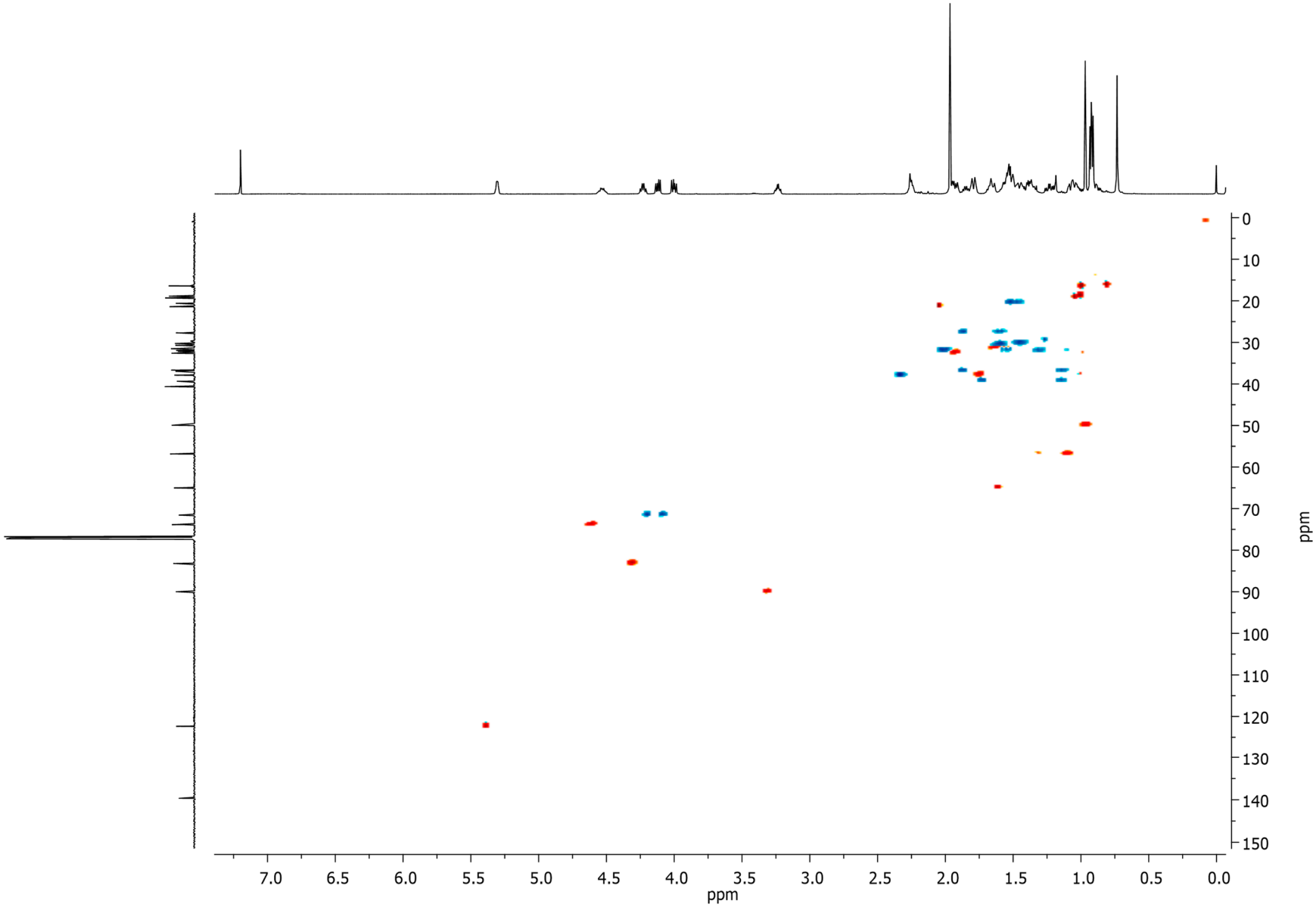


Figure S10. Experiment HSQC of **6** (500 MHz, $CDCl_3$)

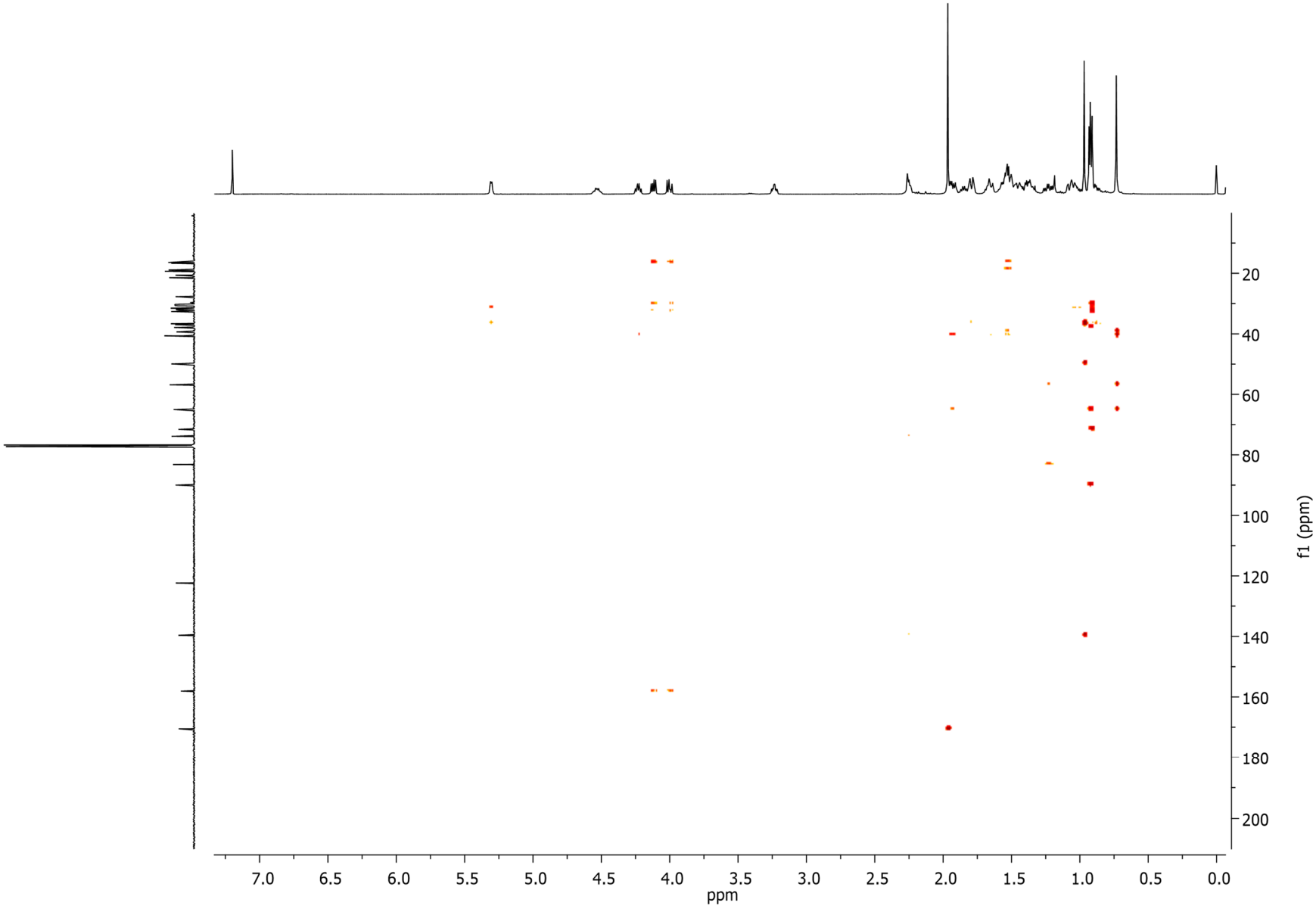


Figure S11. Experiment HMBC of **6** (500 MHz, $CDCl_3$)

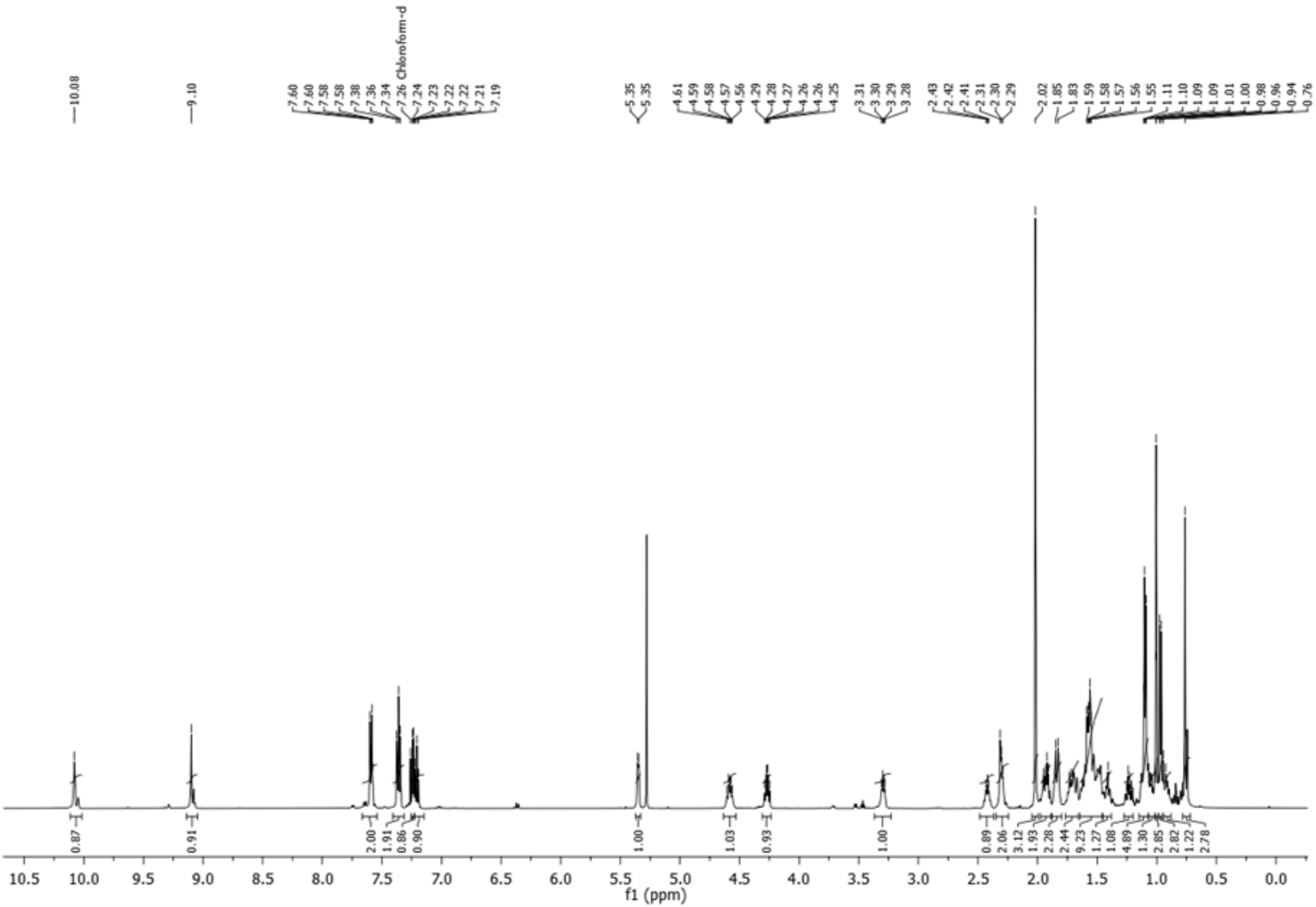


Figure S12. ^{1}H-NMR spectrum of **8** (500 MHz, $CDCl_3$)

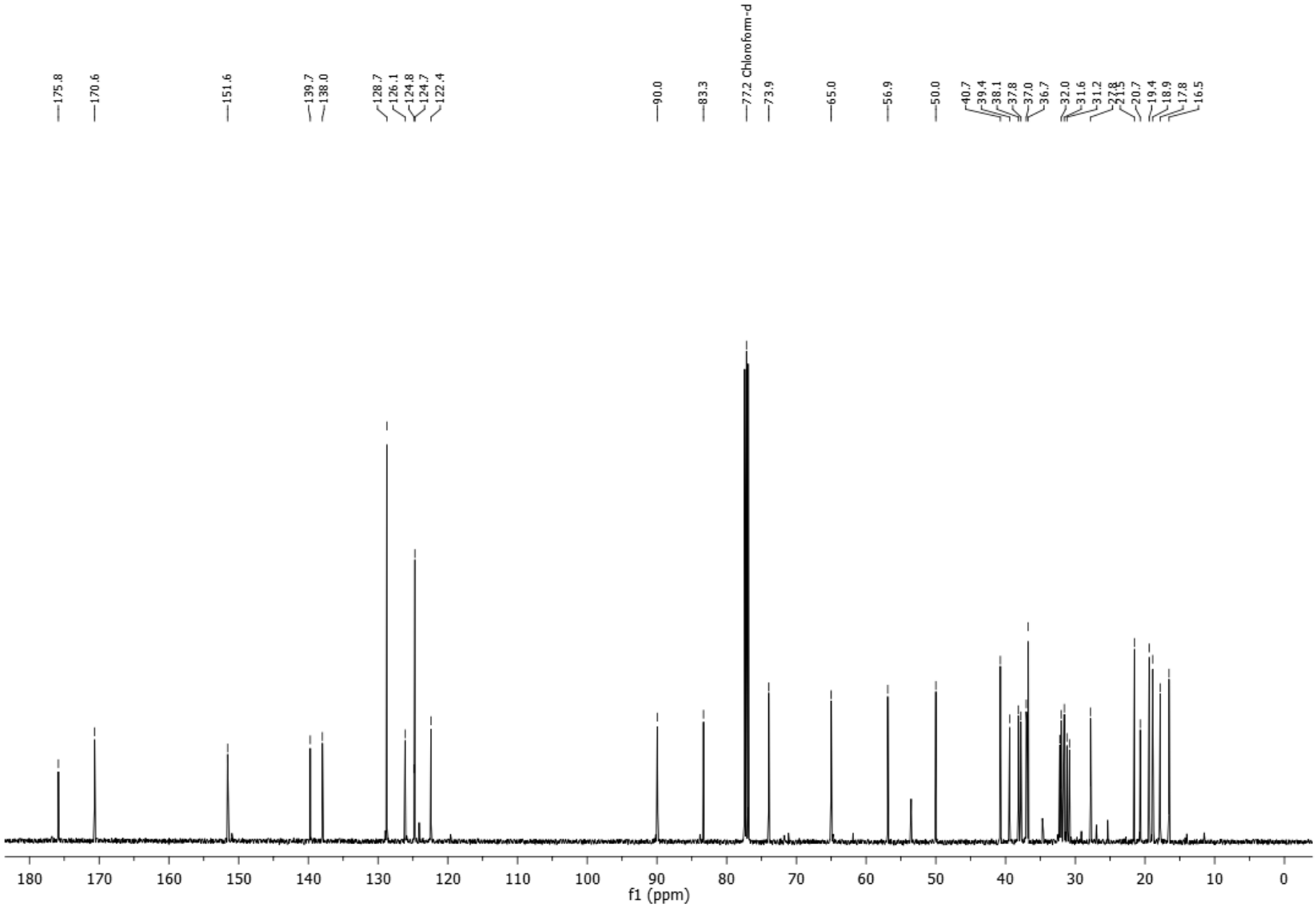


Figure S13. ^{13}C-NMR spectrum of **8** (125.7 MHz, $CDCl_3$)

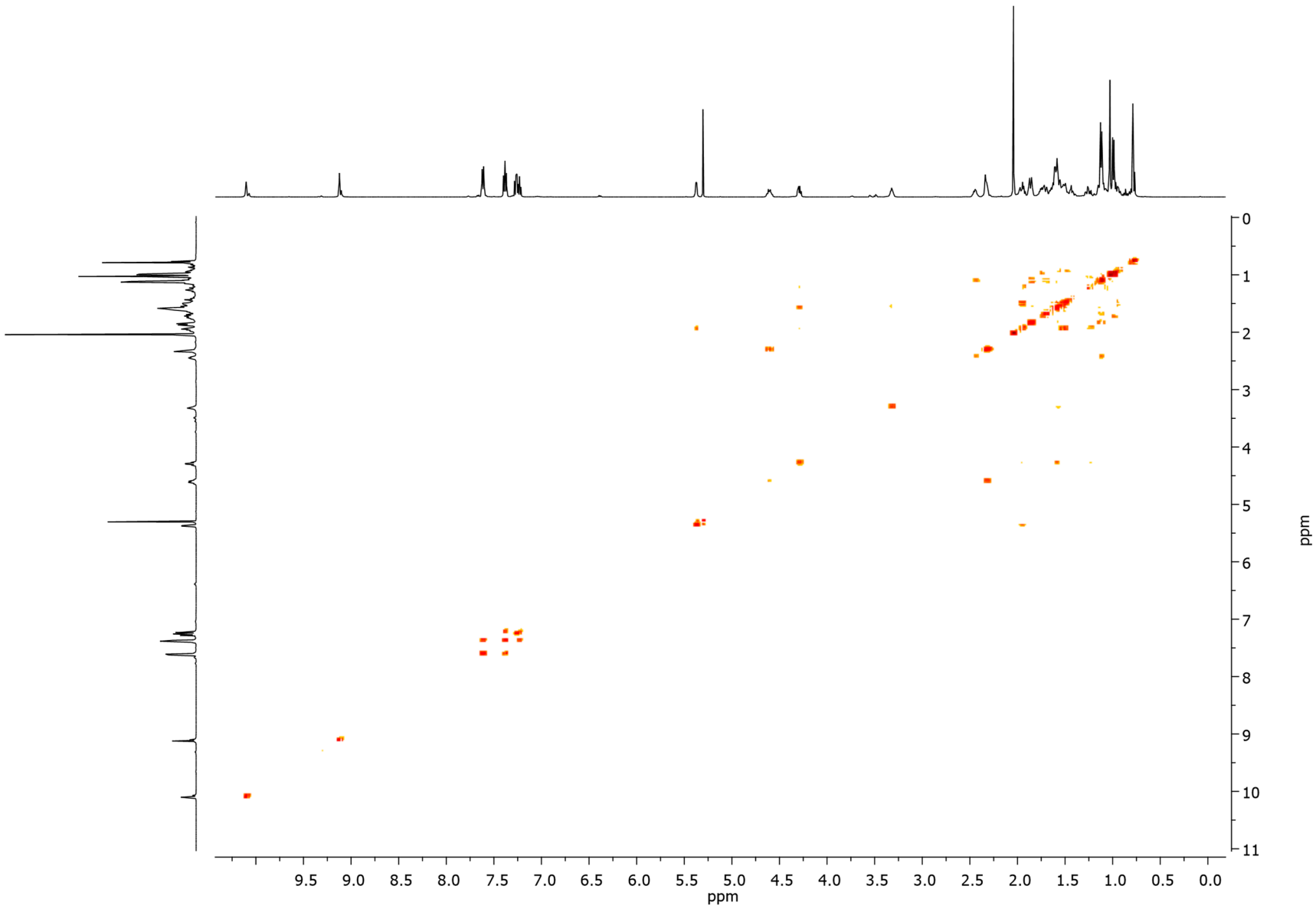


Figure S14. Experiment COSY of **8** (500 MHz, $CDCl_3$)

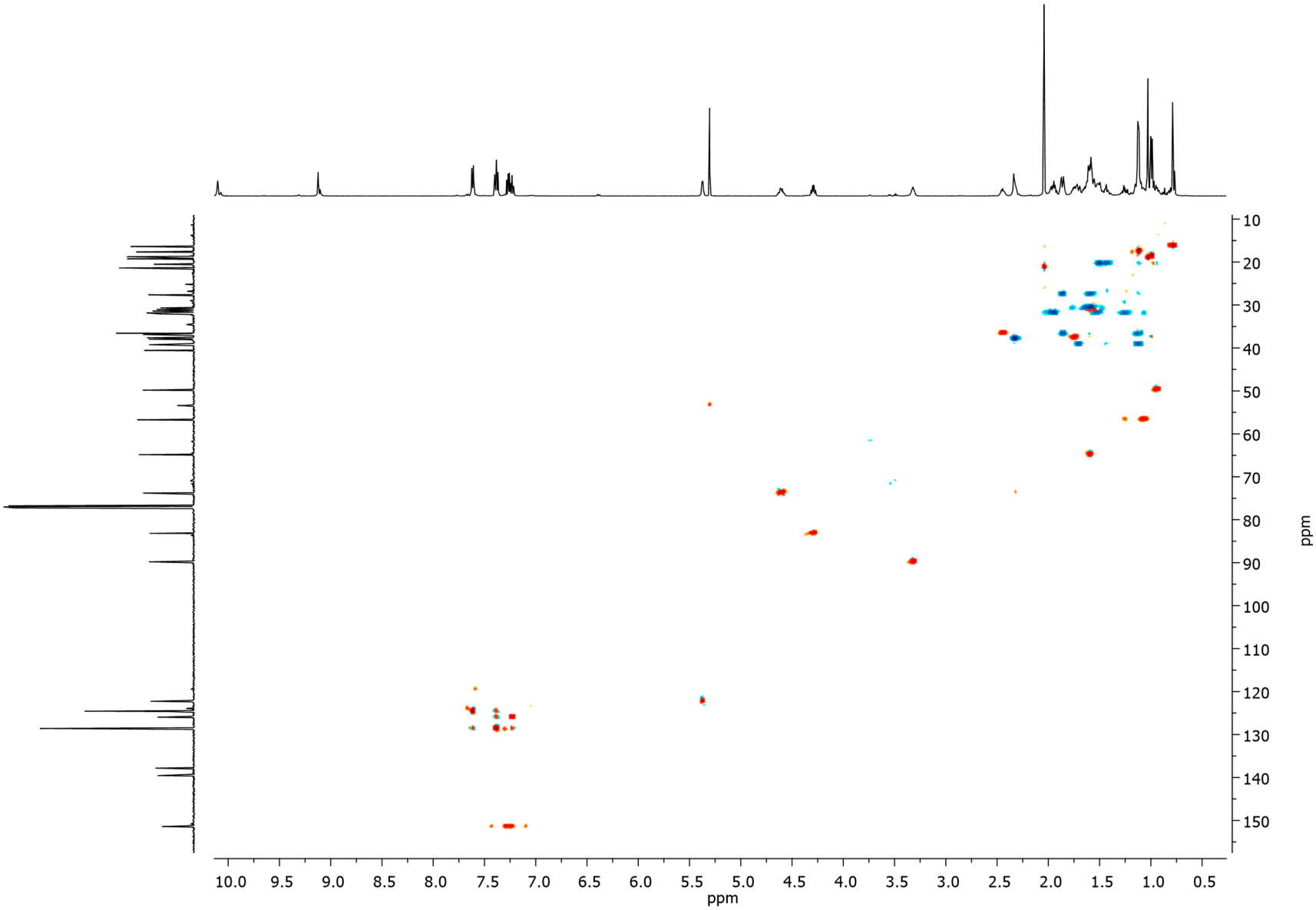


Figure S15. Experiment HSQC of **8** (500 MHz, $CDCl_3$)

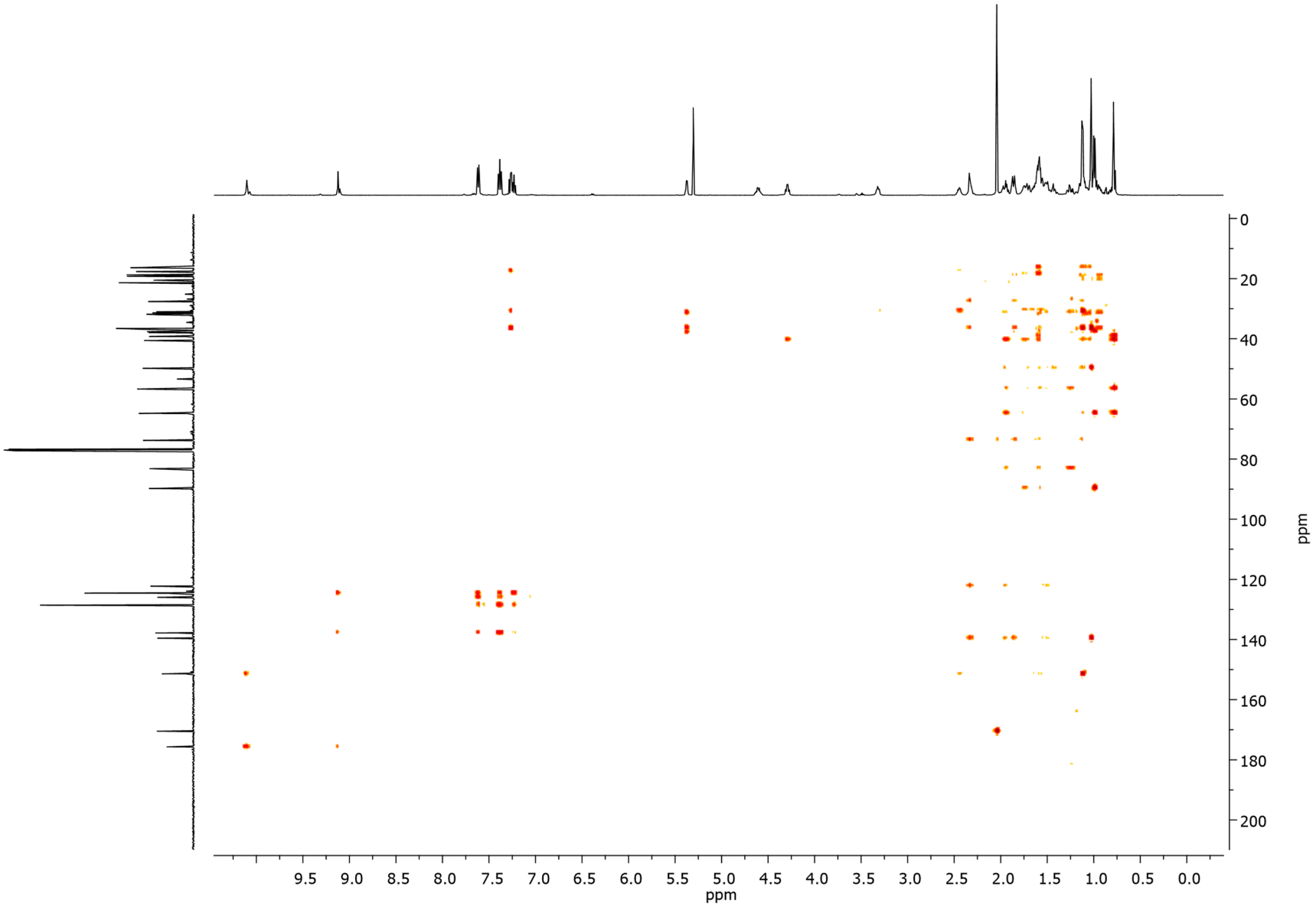


Figure S16. Experiment HMBC of **8** (500 MHz, $CDCl_3$)

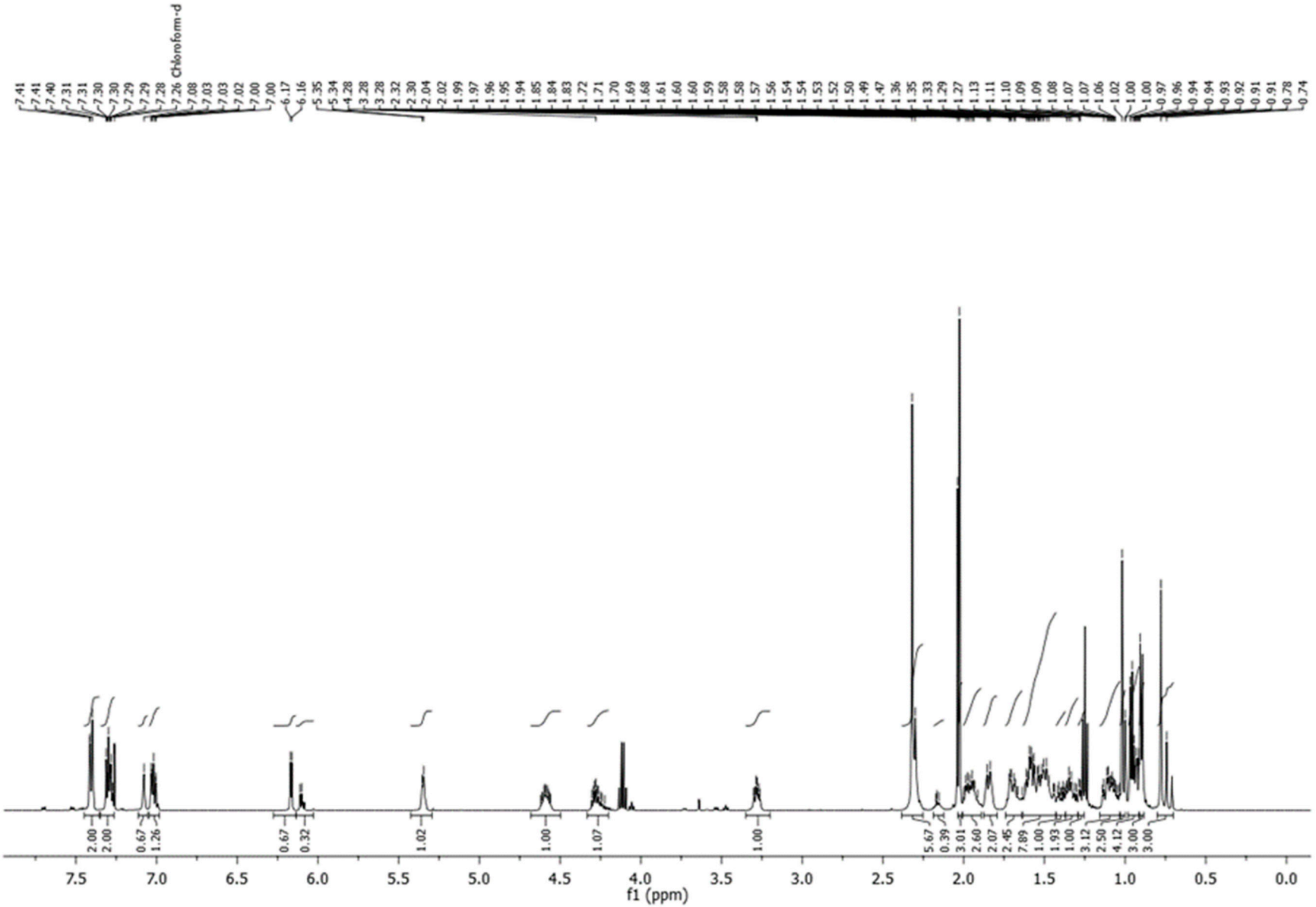


Figure S17. ^{1}H-NMR spectrum of **11**(500 MHz, $CDCl_3$)

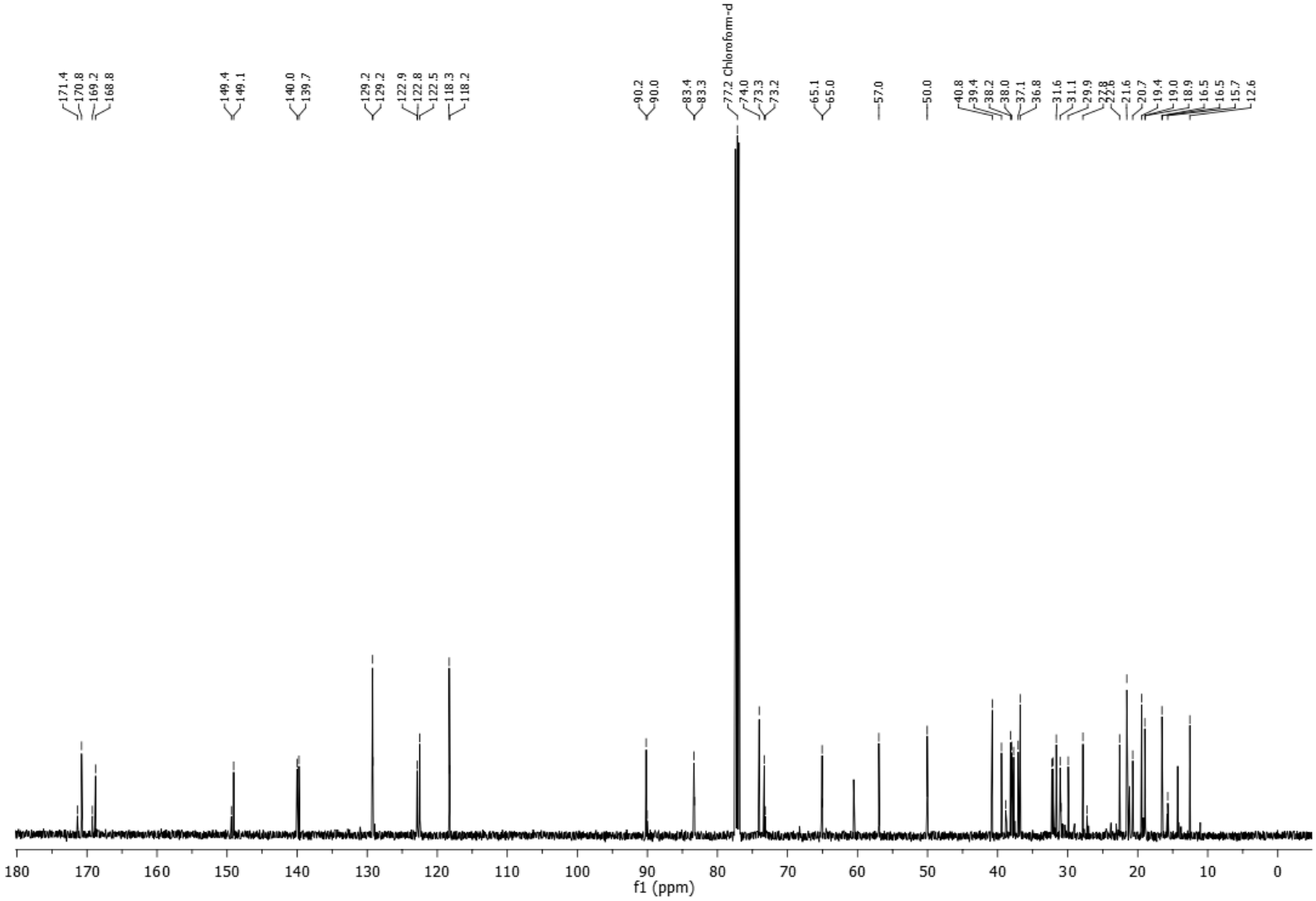


Figure S18. ^{13}C-NMR spectrum of **11** (125.7 MHz, $CDCl_3$)

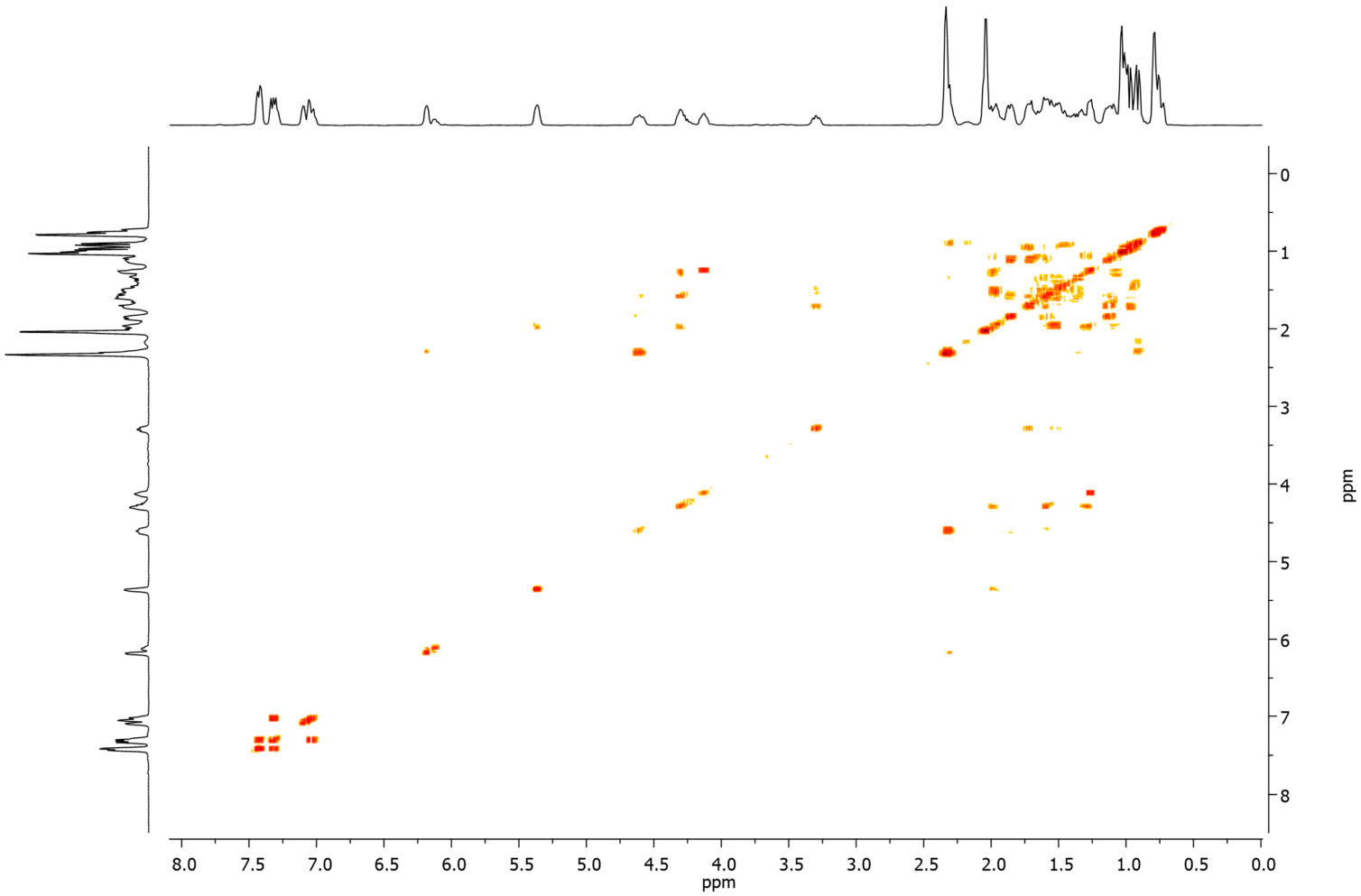


Figure S19. Experiment COSY of **11** (500 MHz, $CDCl_3$)

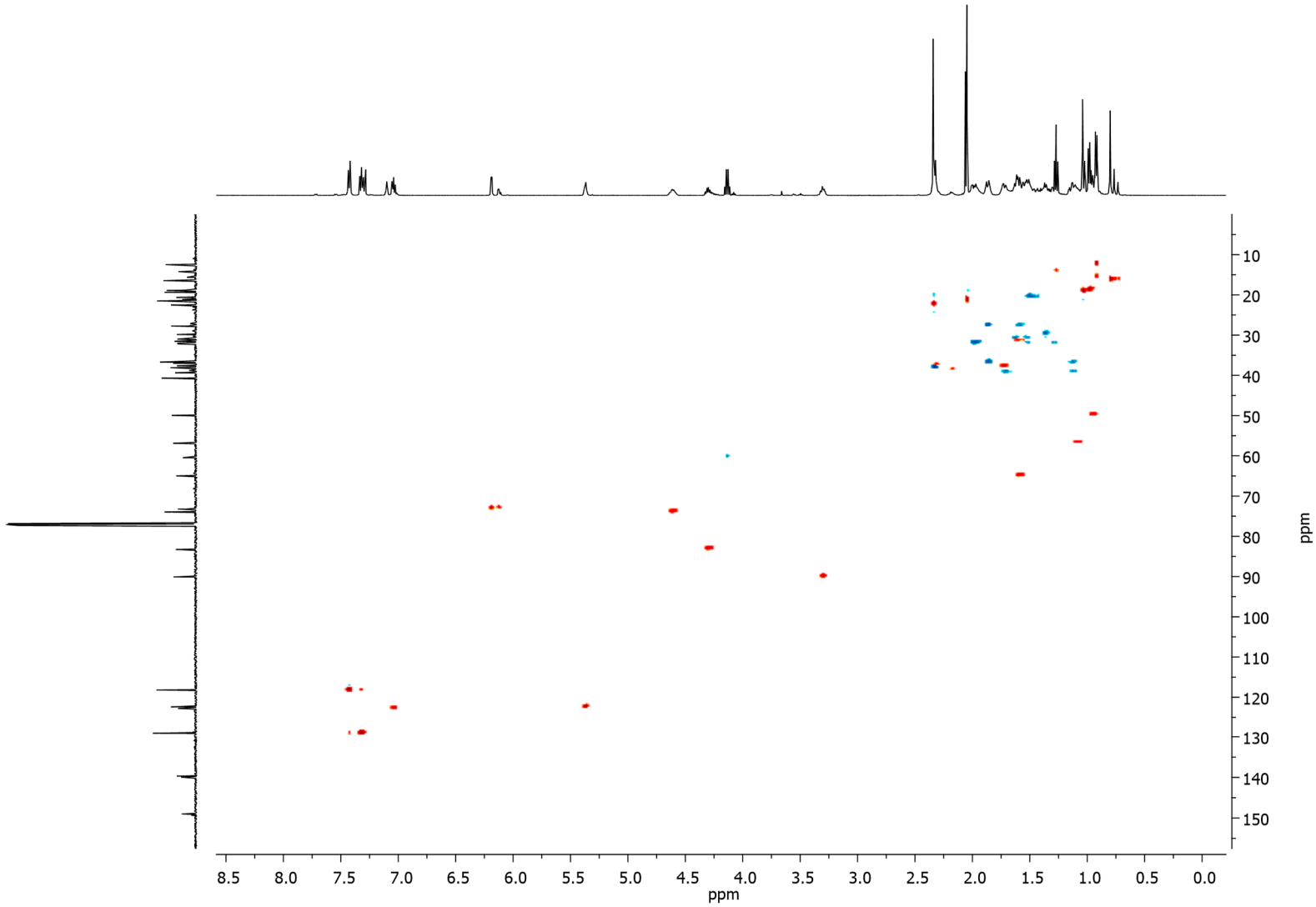


Figure S20. Experiment HSQC of **11** (500 MHz, $CDCl_3$)

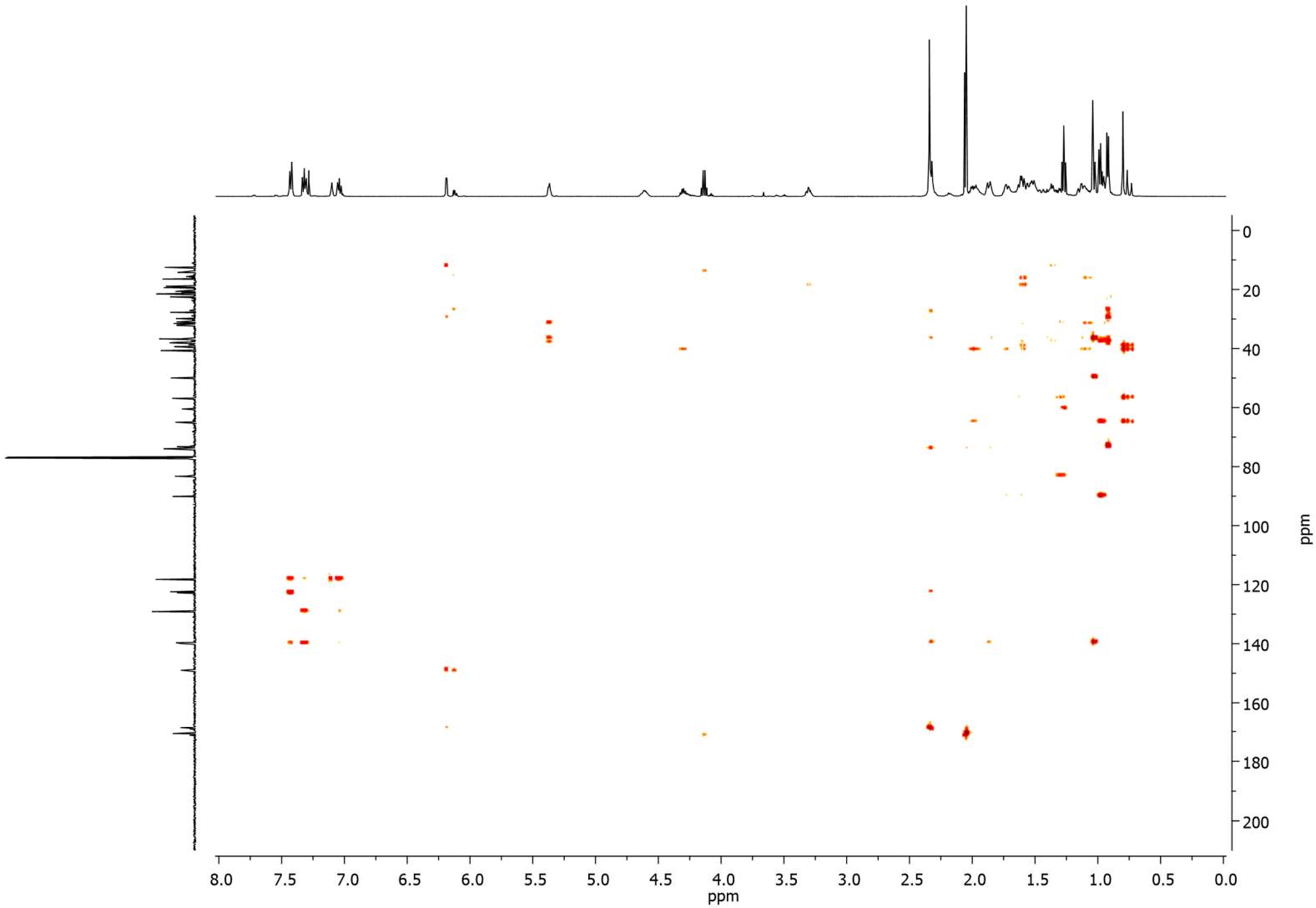


Figure S21. Experiment HMBC of **11** (500 MHz, $CDCl_3$)

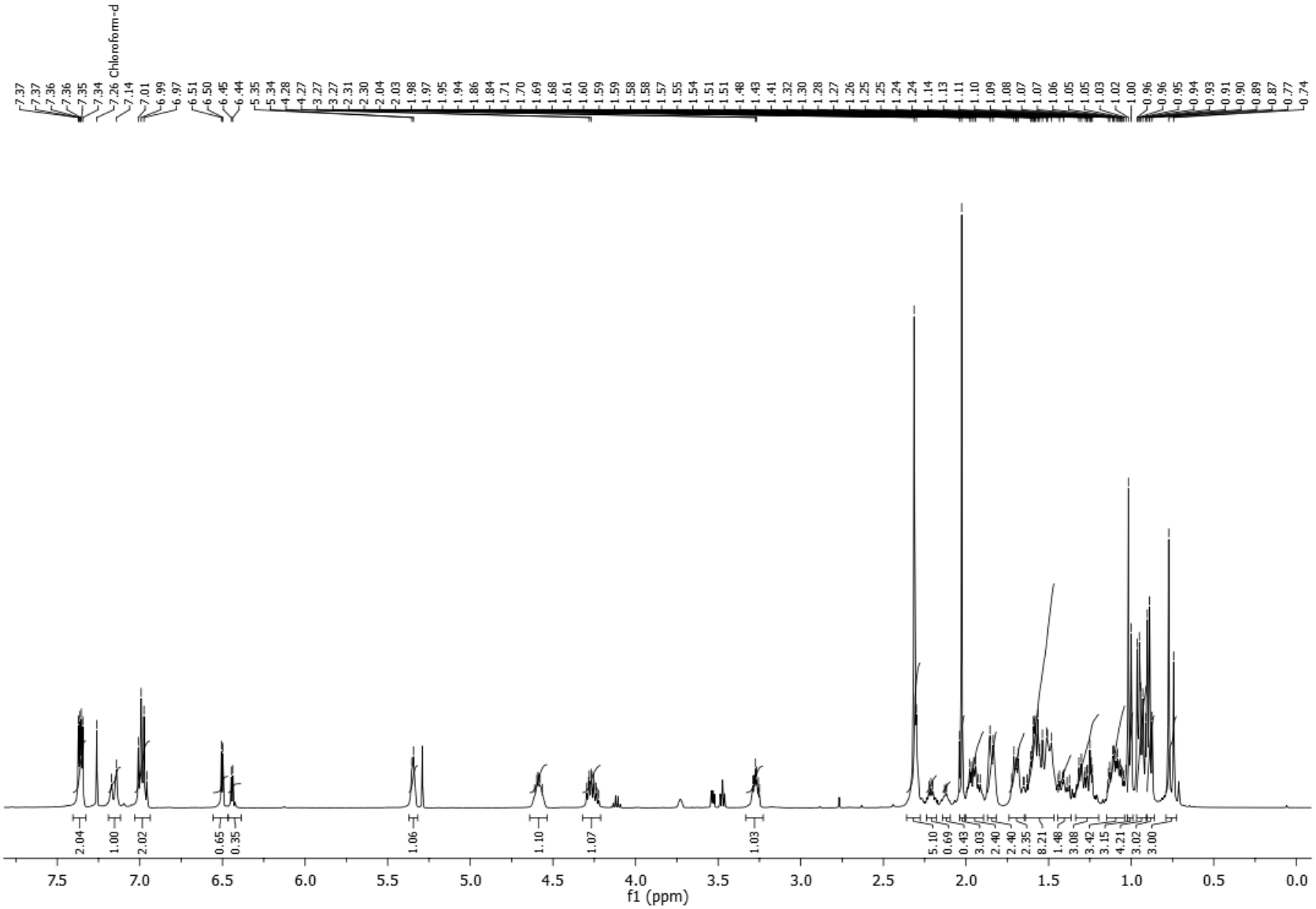


Figure S22. ^{1}H-NMR spectrum of **12** (500 MHz, $CDCl_3$)

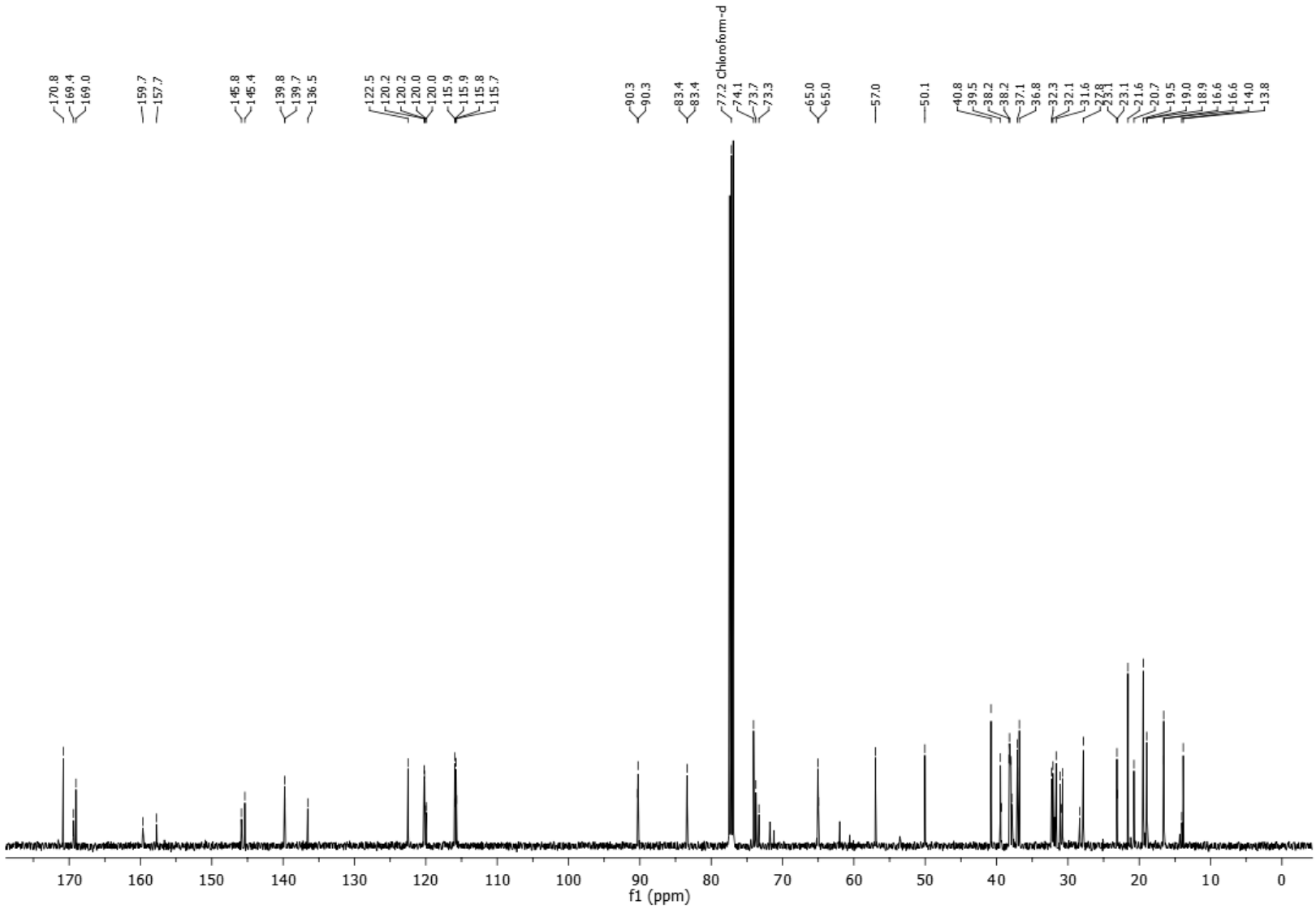


Figure S23. ^{13}C-NMR spectrum of **12** (125.7 MHz, $CDCl_3$)

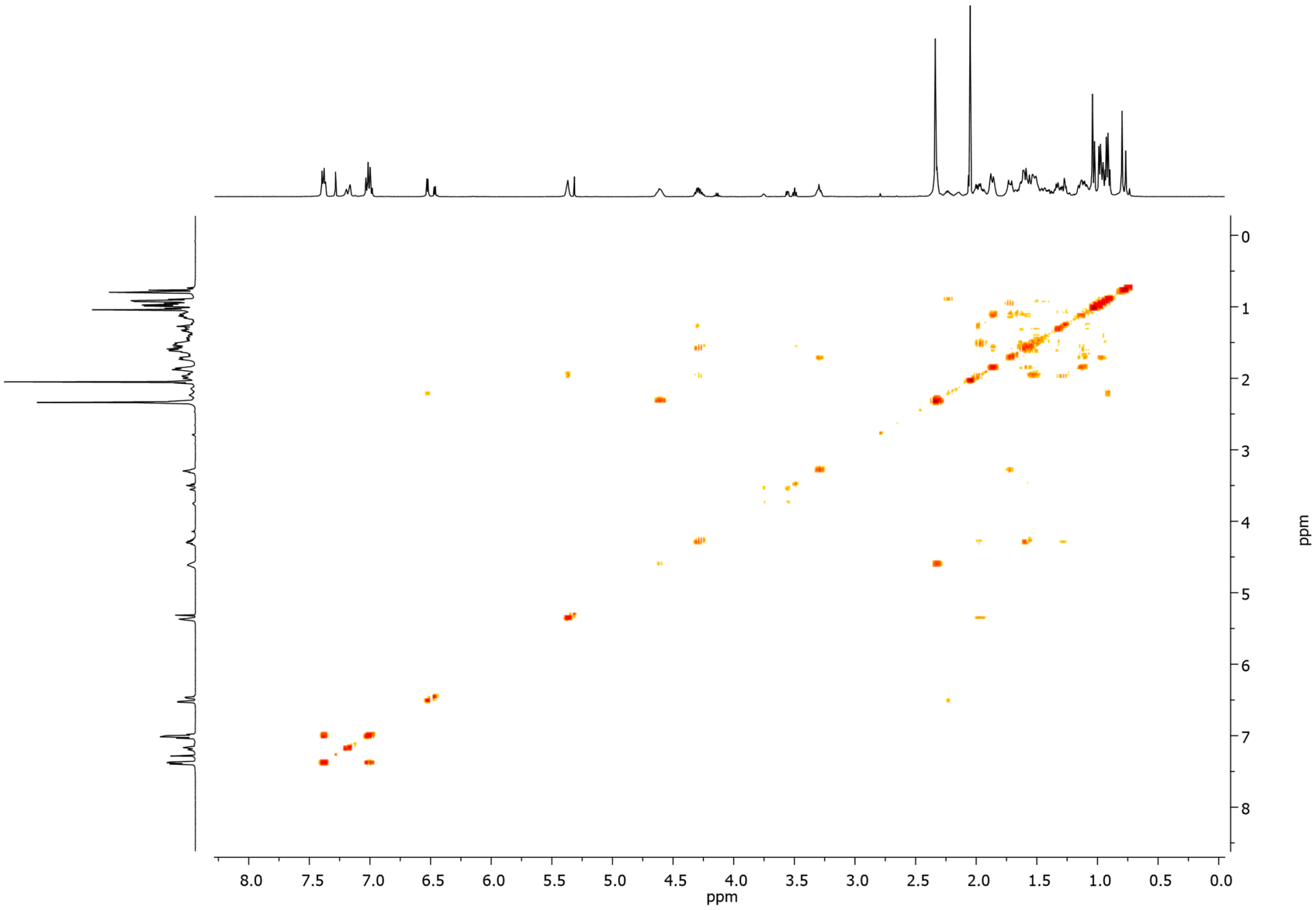


Figure S24. Experiment COSY of **12** (500 MHz, $CDCl_3$)

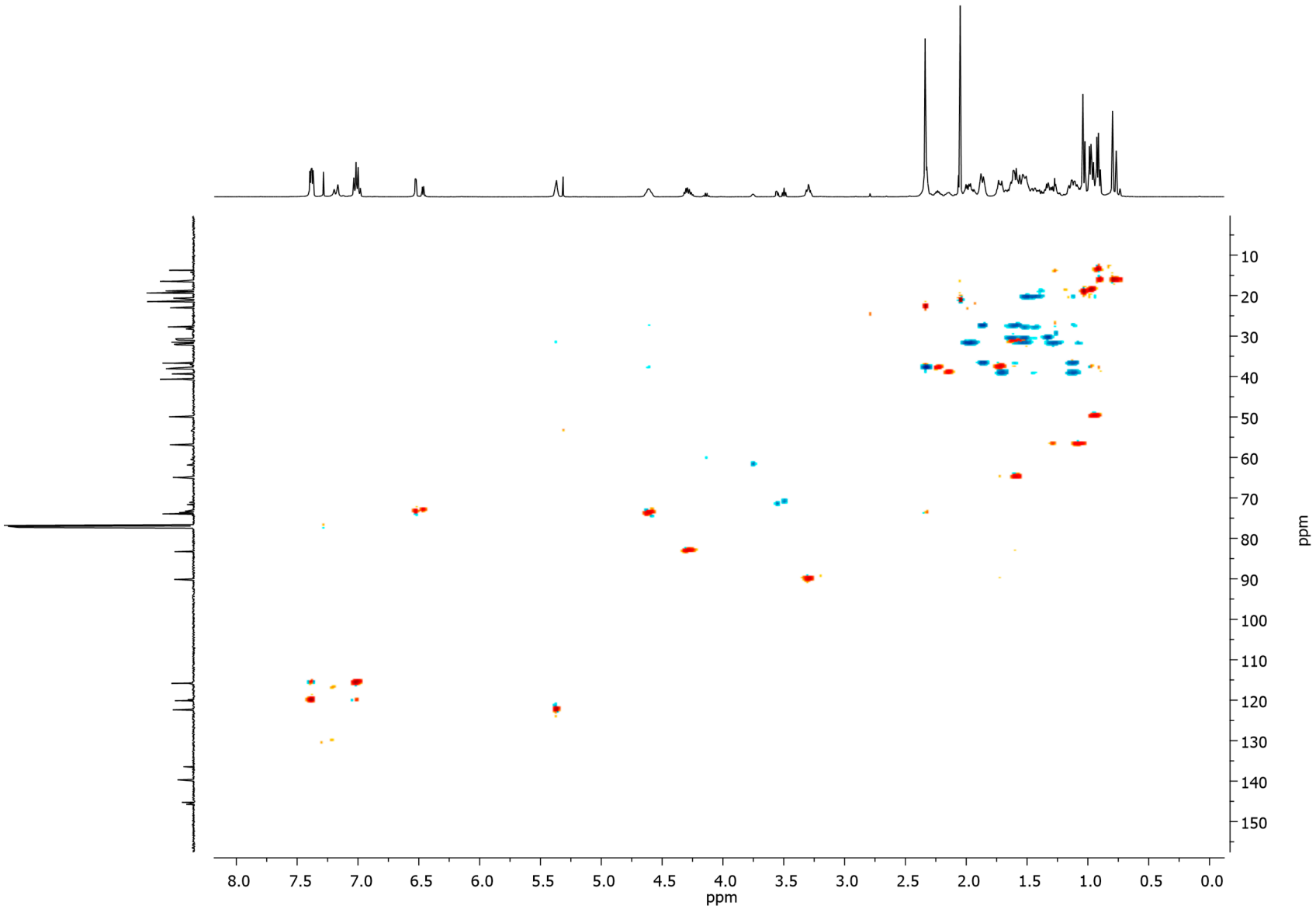


Figure S25. Experiment HSQC of **12** (500 MHz, $CDCl_3$)

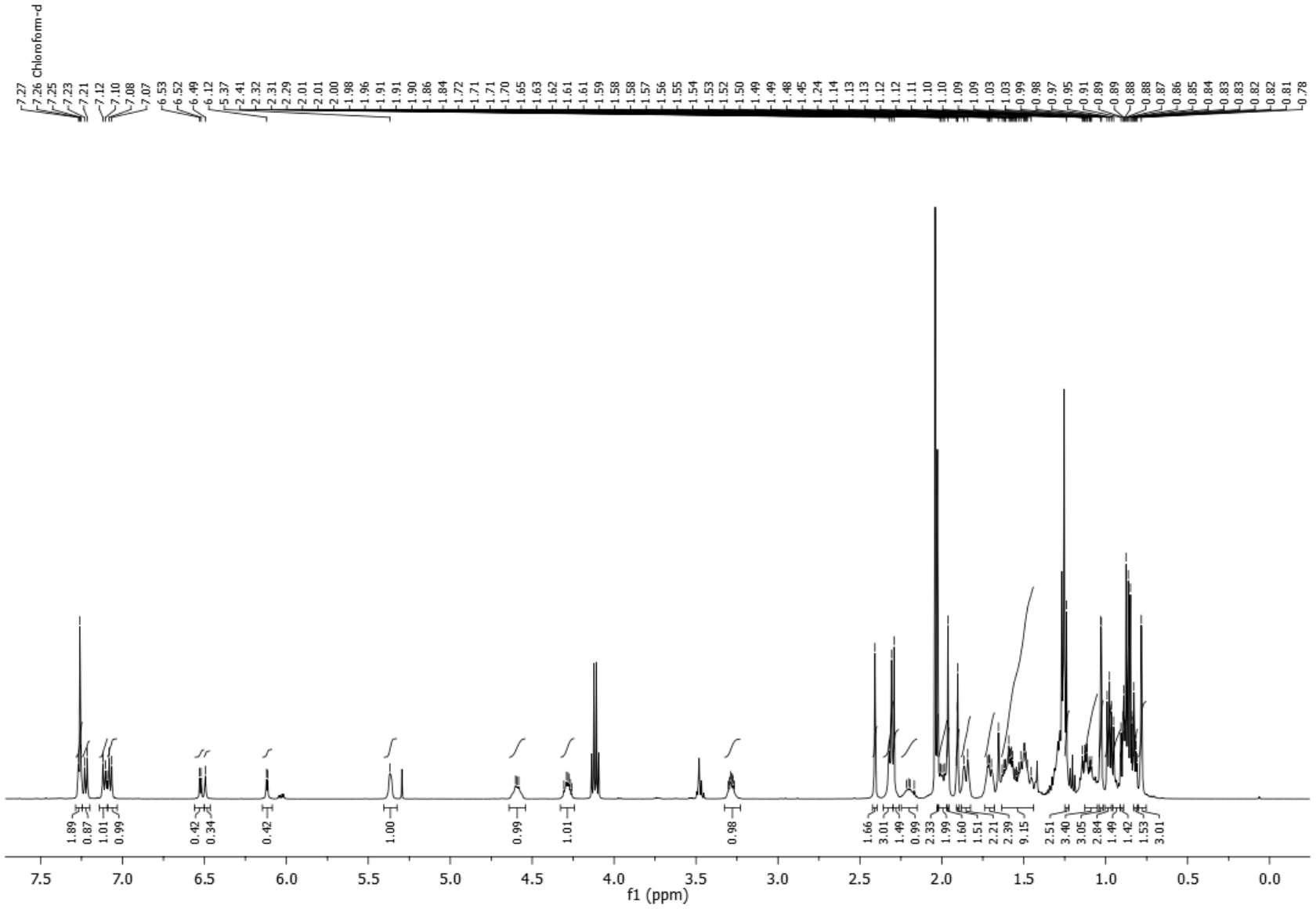


Figure S26. ^{1}H-NMR spectrum of **13** (500 MHz, $CDCl_3$)

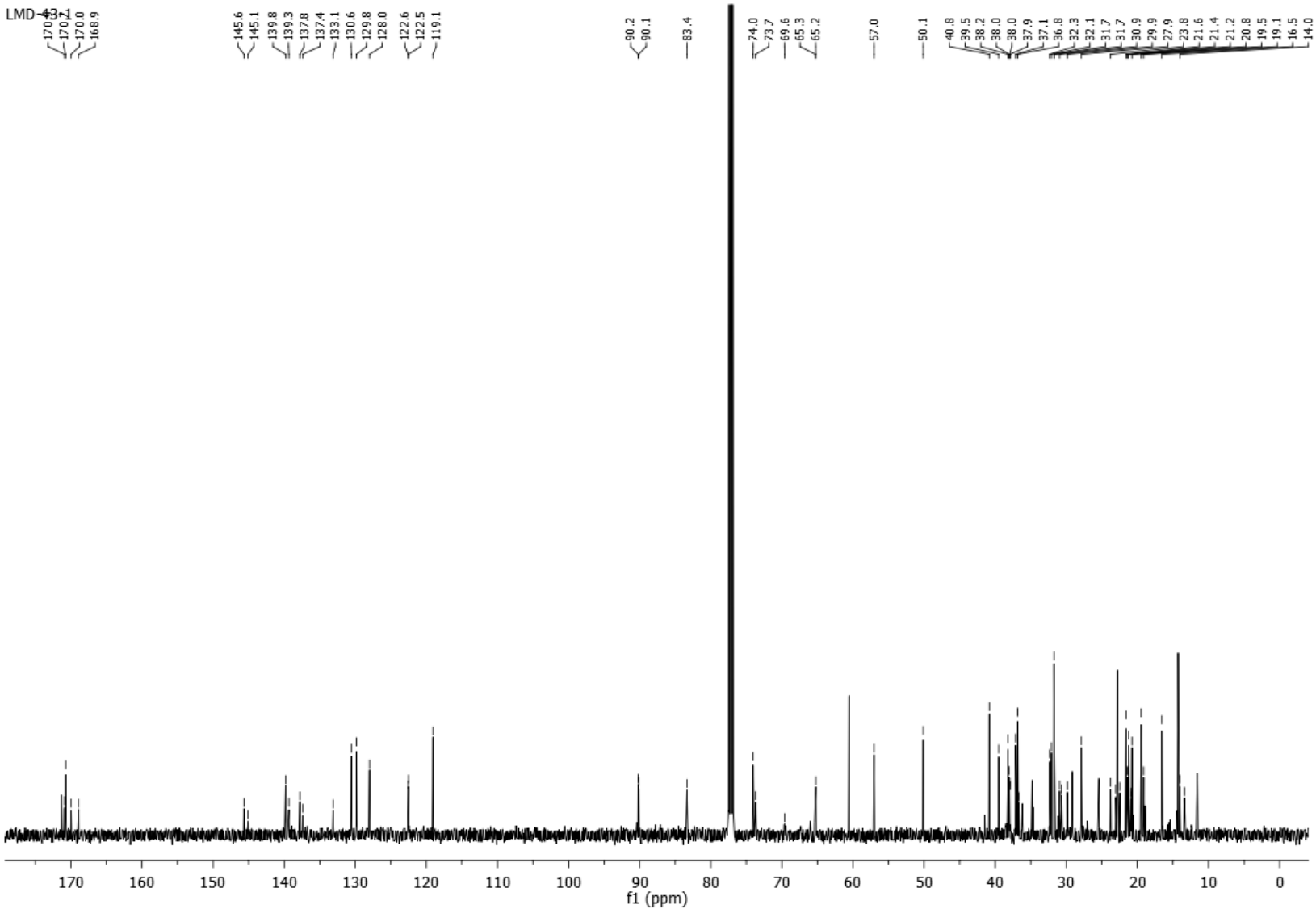


Figure S27. ^{13}C-NMR spectrum of **13** (125.7 MHz, $CDCl_3$)

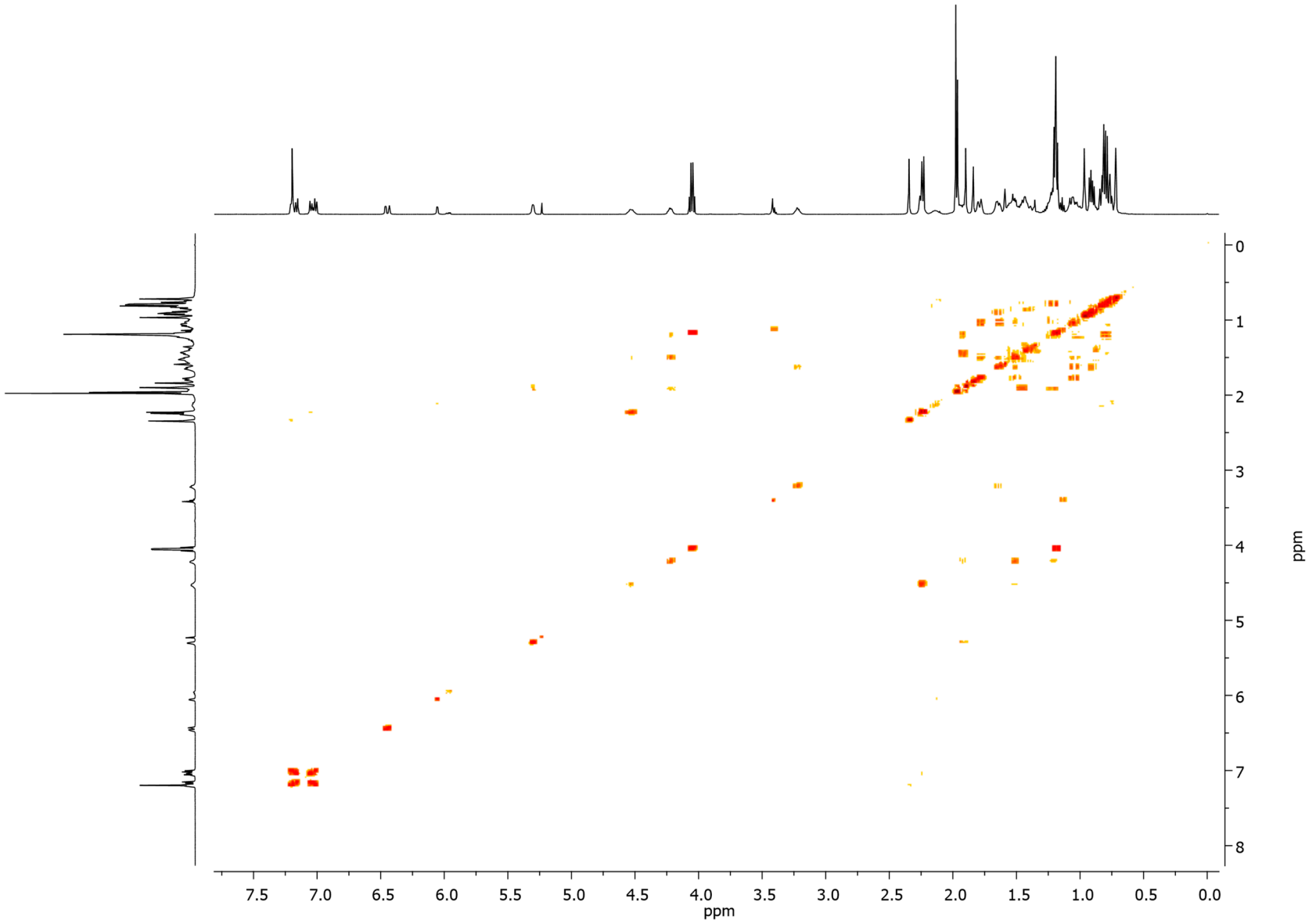


Figure S28. Experiment COSY of **13** (500 MHz, $CDCl_3$)

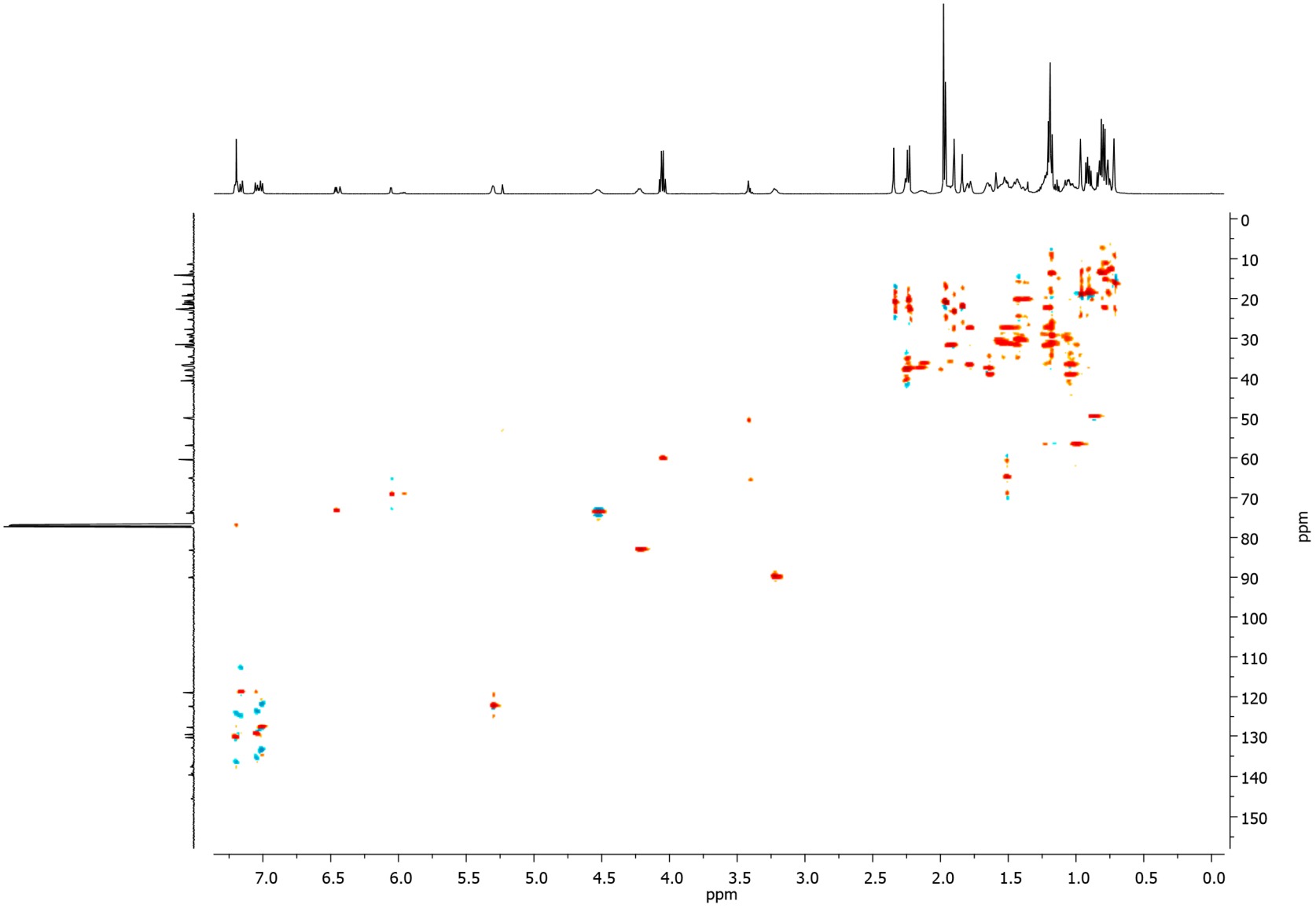


Figure S29. Experiment HSQC of **13** (500 MHz, $CDCl_3$)

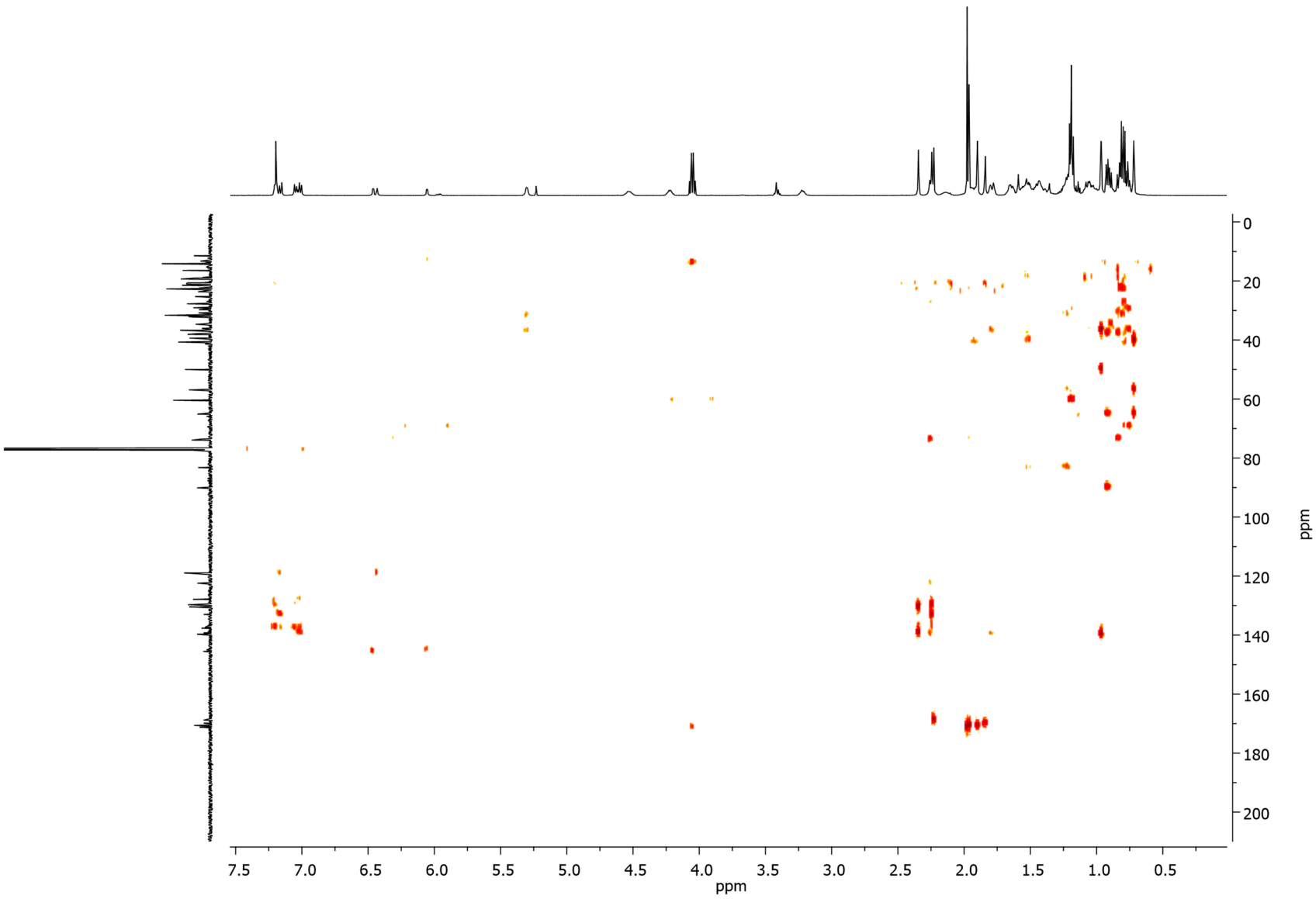


Figure S30. Experiment HMBC of **13** (500 MHz, $CDCl_3$)

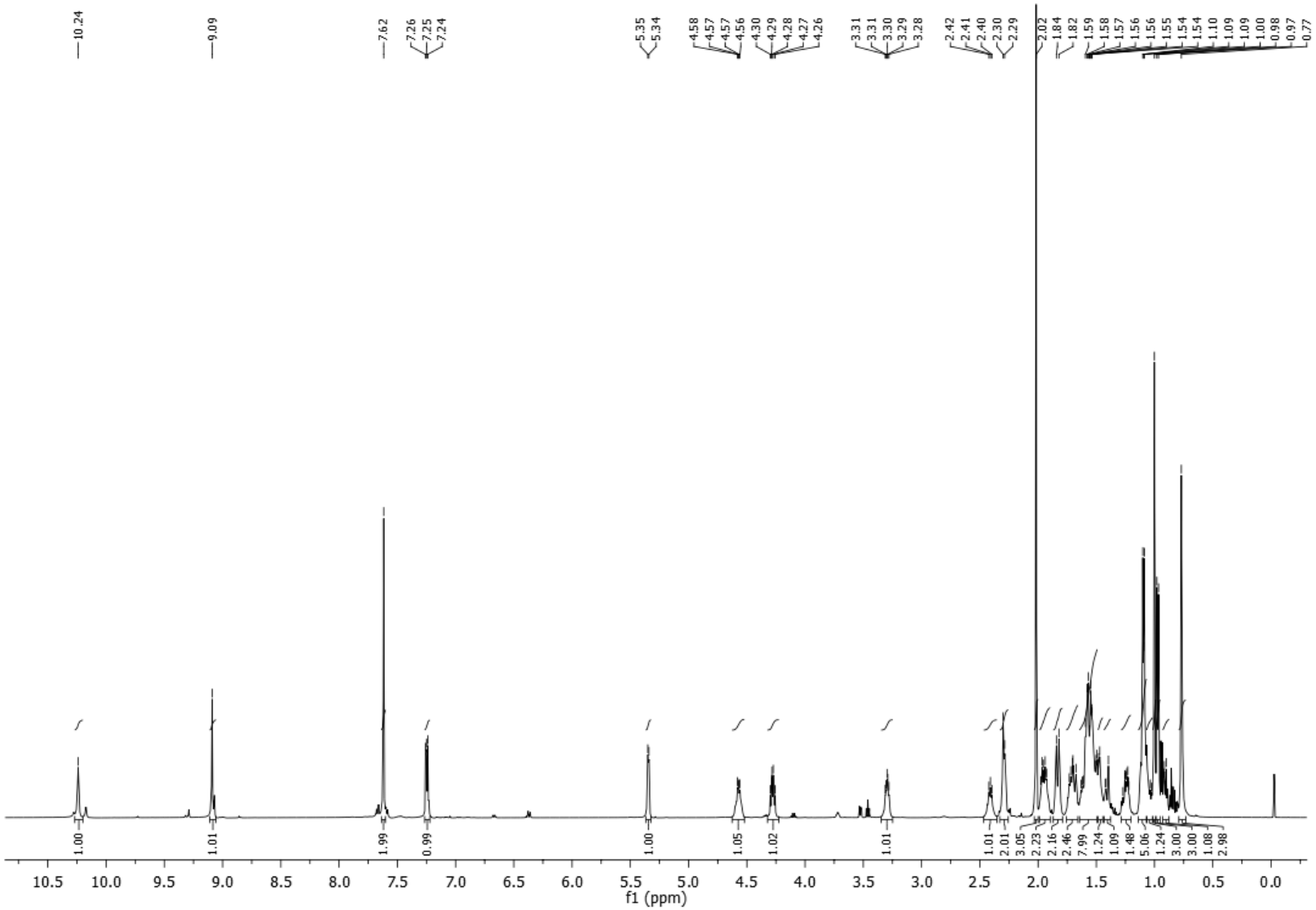


Figure S31. ^{1}H-NMR spectrum of **14** (500 MHz, $CDCl_3$)

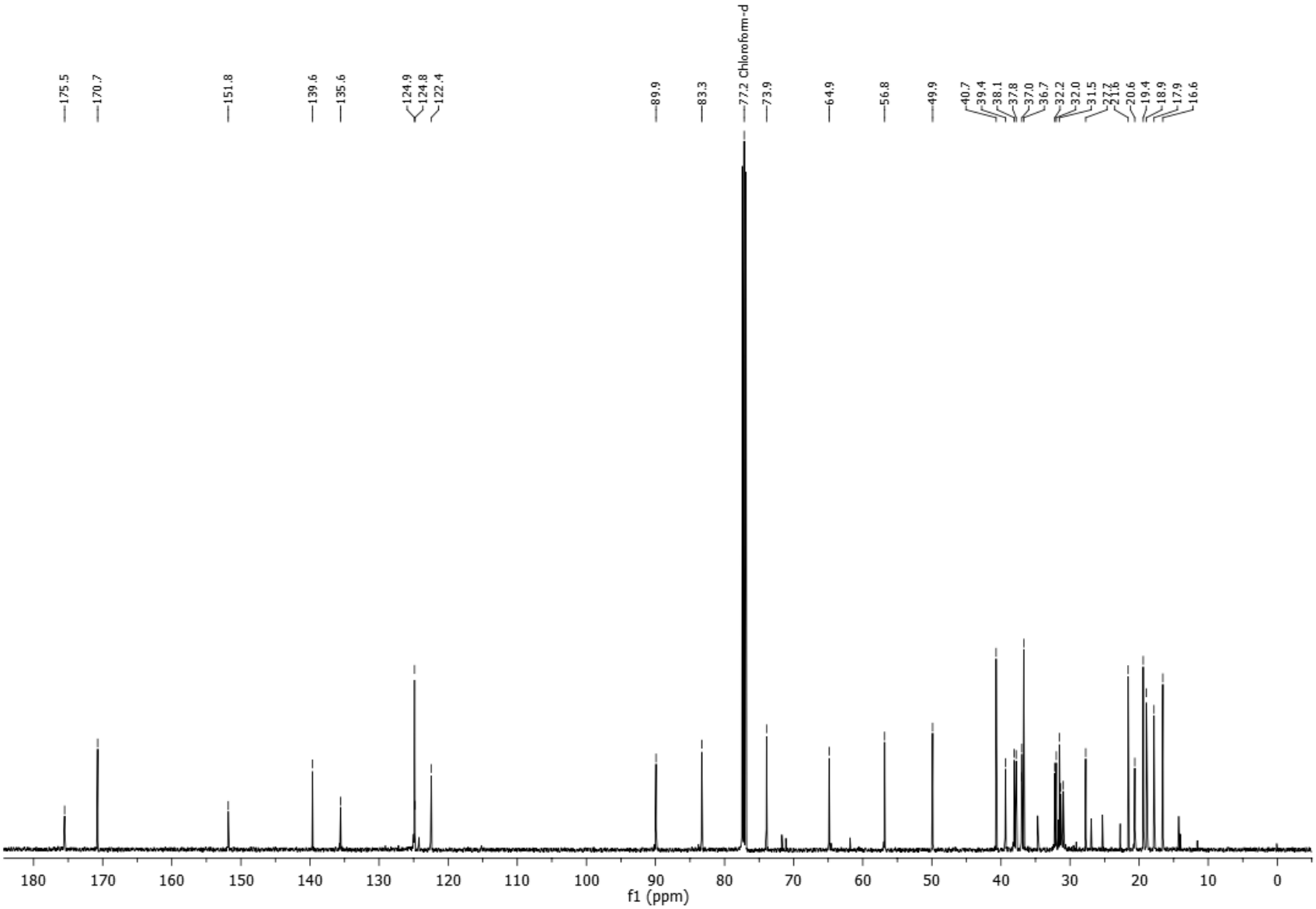


Figure S32. ^{13}C-NMR spectrum of **14** (125.7 MHz, $CDCl_3$)

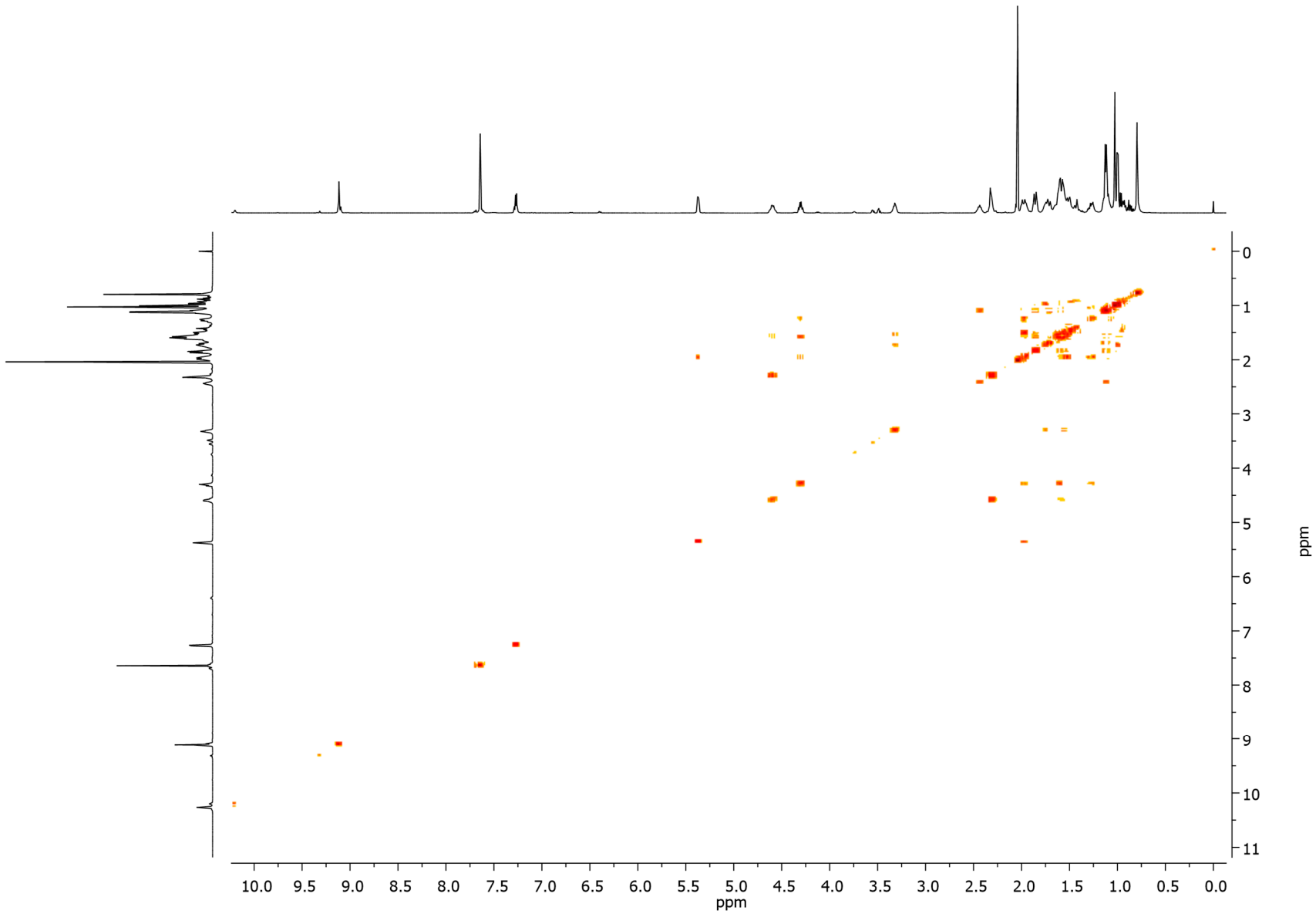


Figure S33. Experiment COSY of **14** (500 MHz, $CDCl_3$)

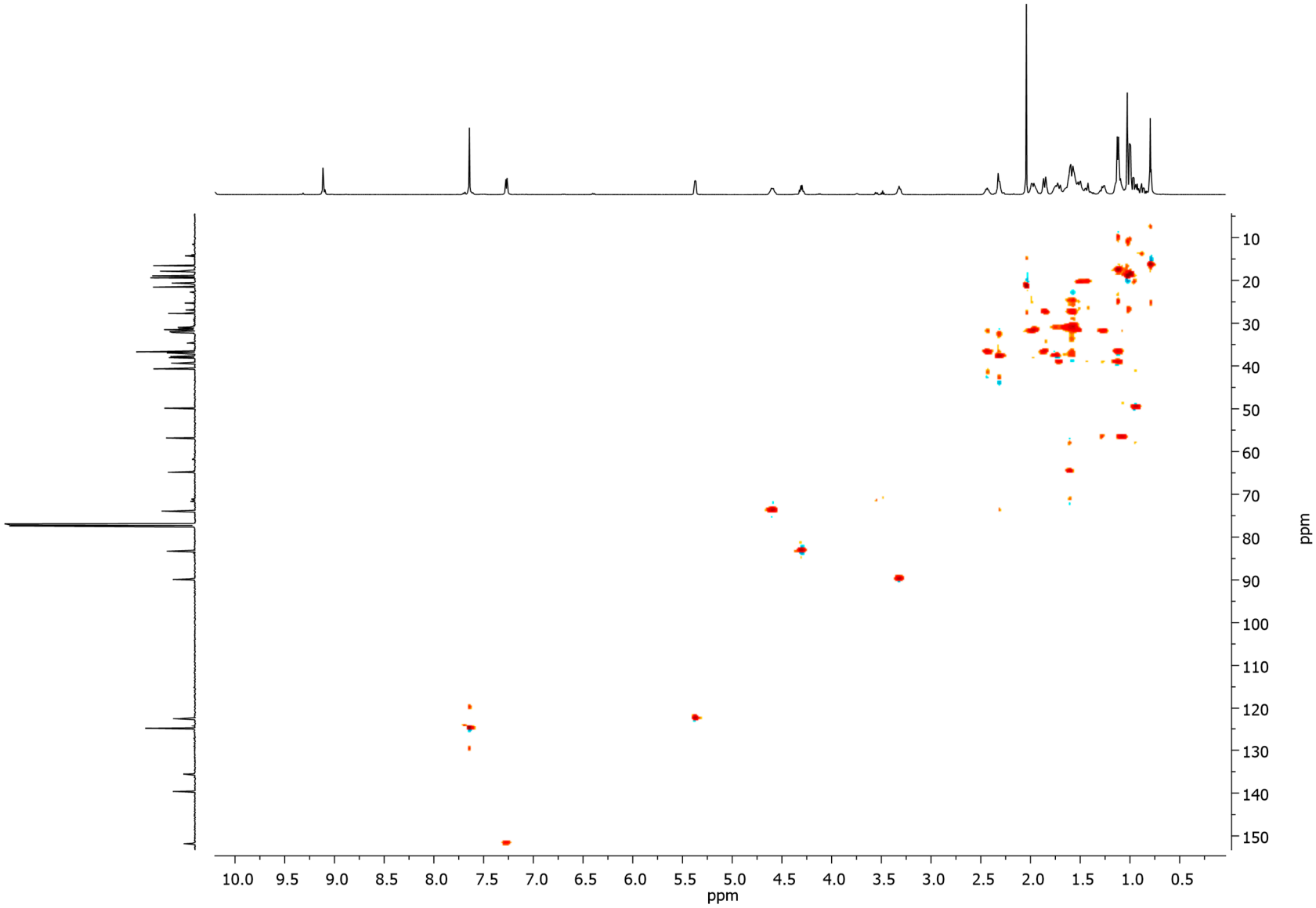


Figure S34. Experiment HSQC of **14** (500 MHz, $CDCl_3$)

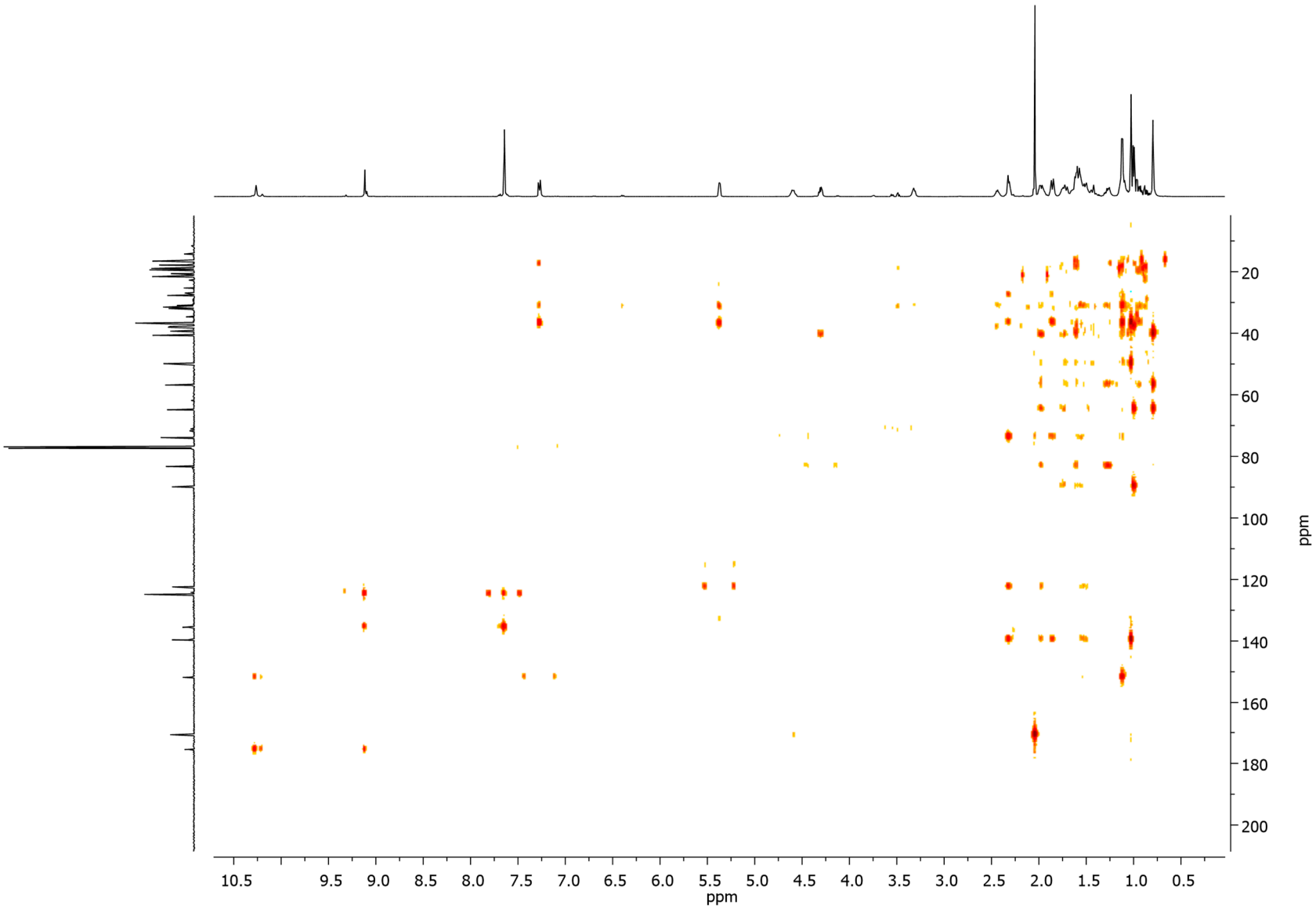


Figure S35. Experiment HMBC of **14** (500 MHz, $CDCl_3$)

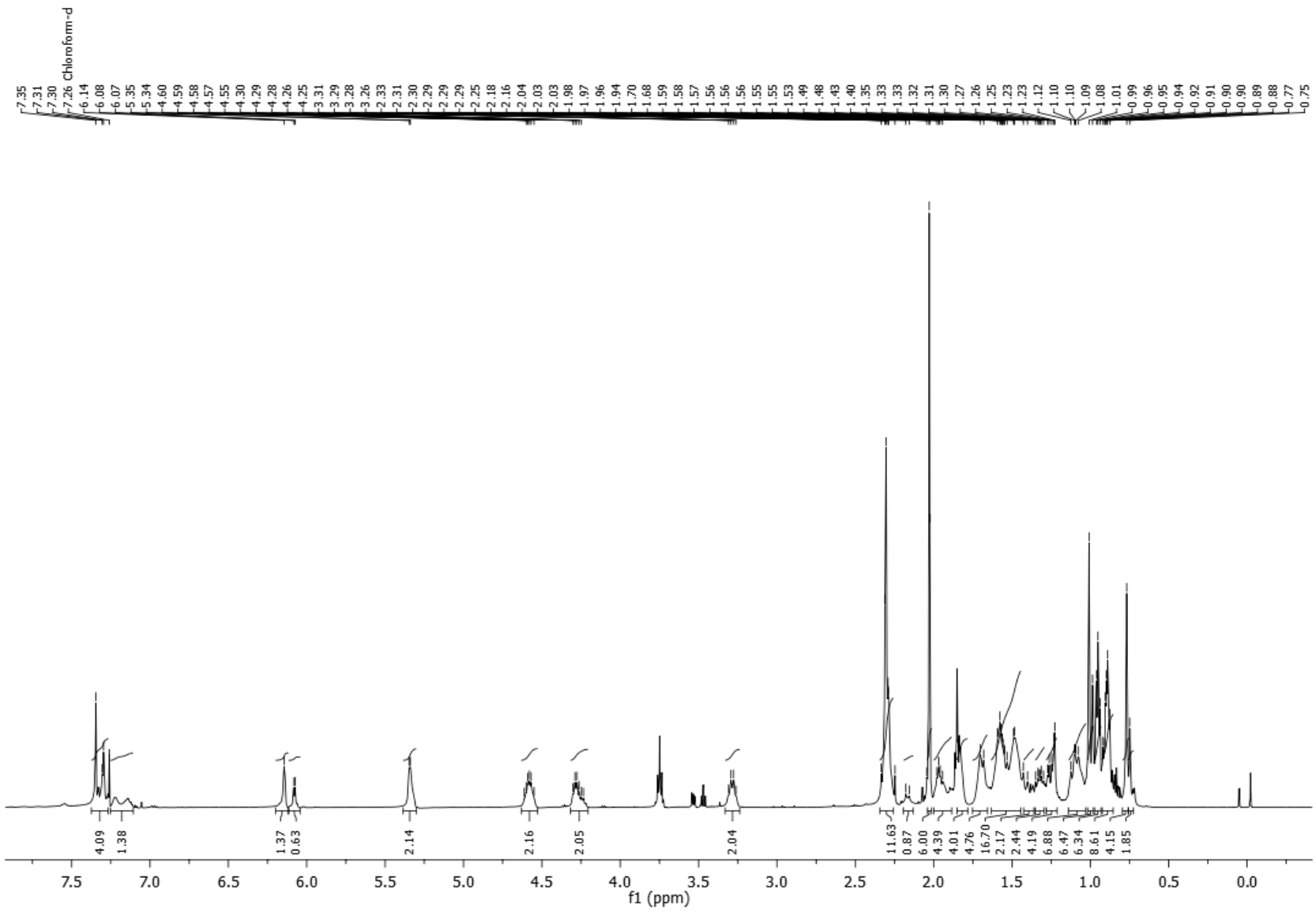


Figure S36. ^{1}H-NMR spectrum of **15** (500 MHz, $CDCl_3$)

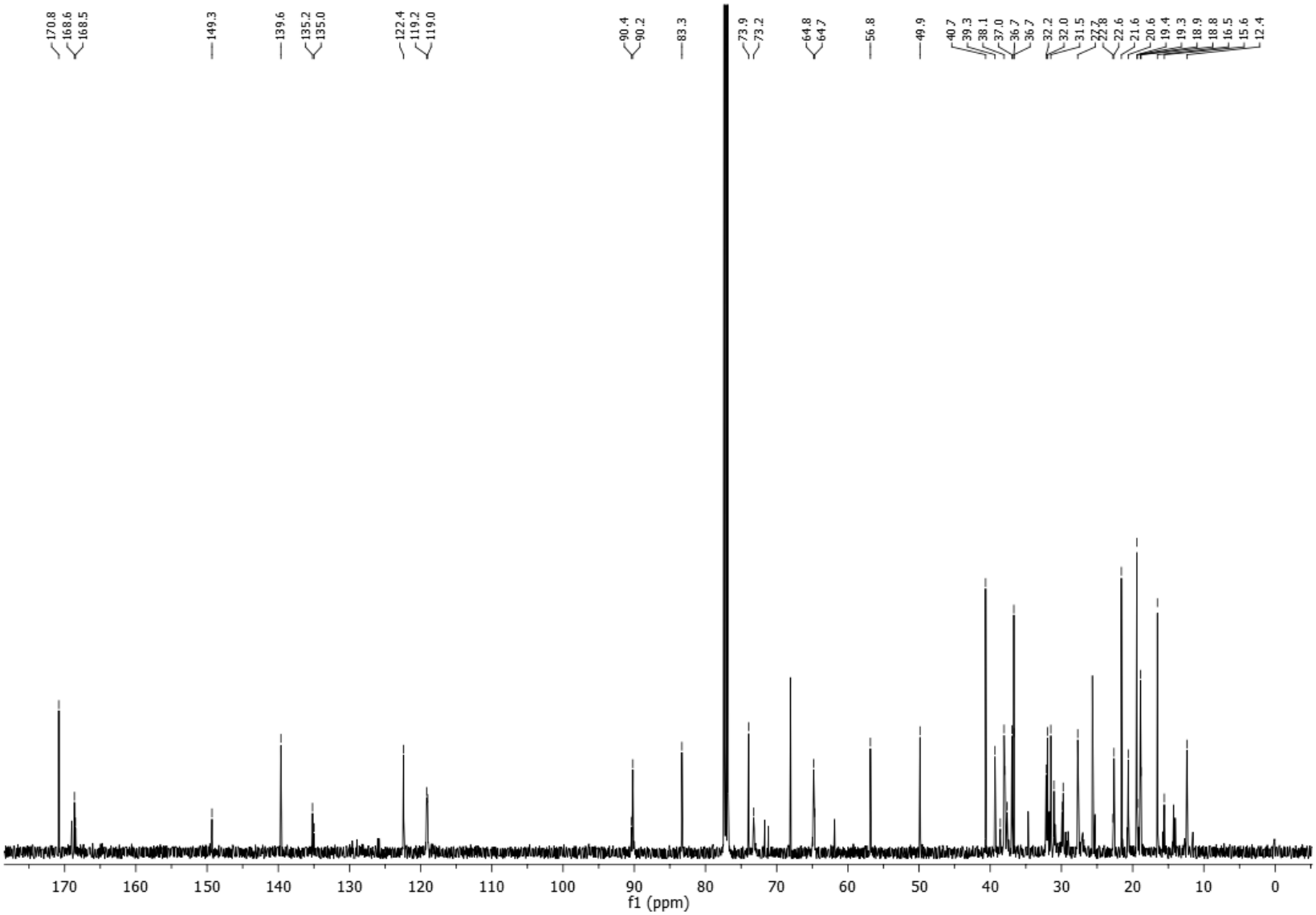


Figure S37. ^{13}C-NMR spectrum of **15** (125.7 MHz, $CDCl_3$)

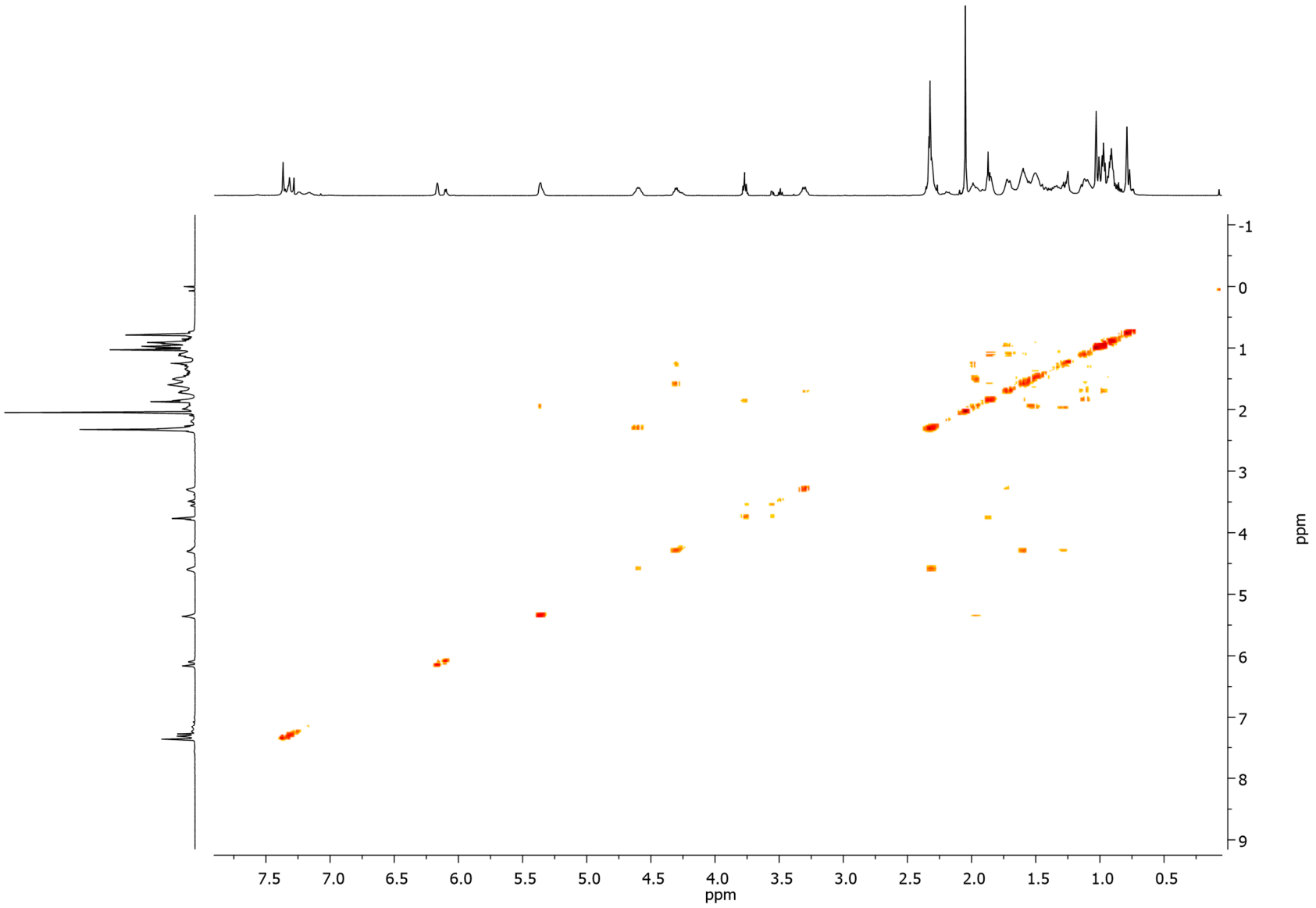


Figure S38. Experiment COSY of **15** (500 MHz, $CDCl_3$)

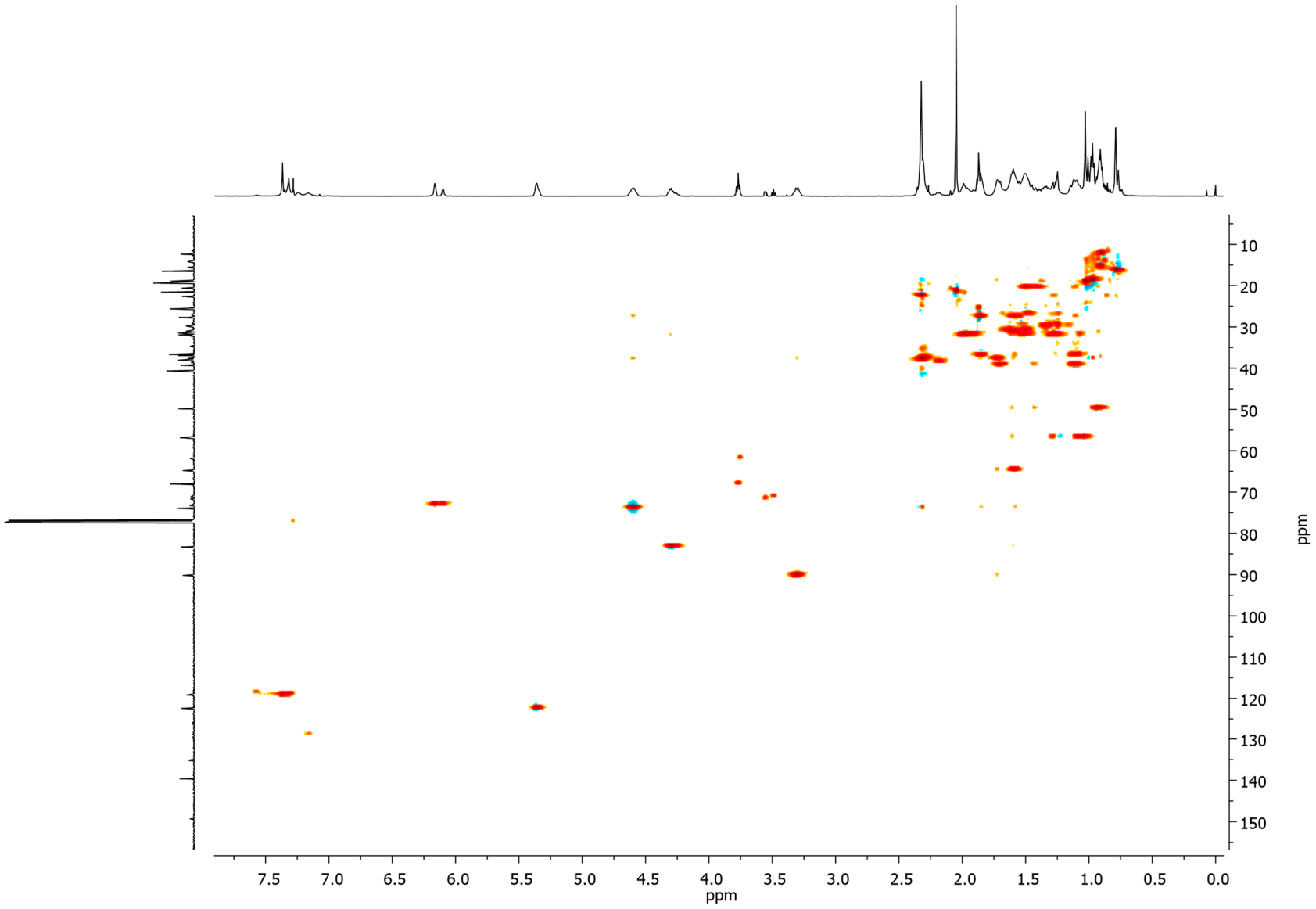


Figure S39. Experiment HSQC of **15** (500 MHz, $CDCl_3$)

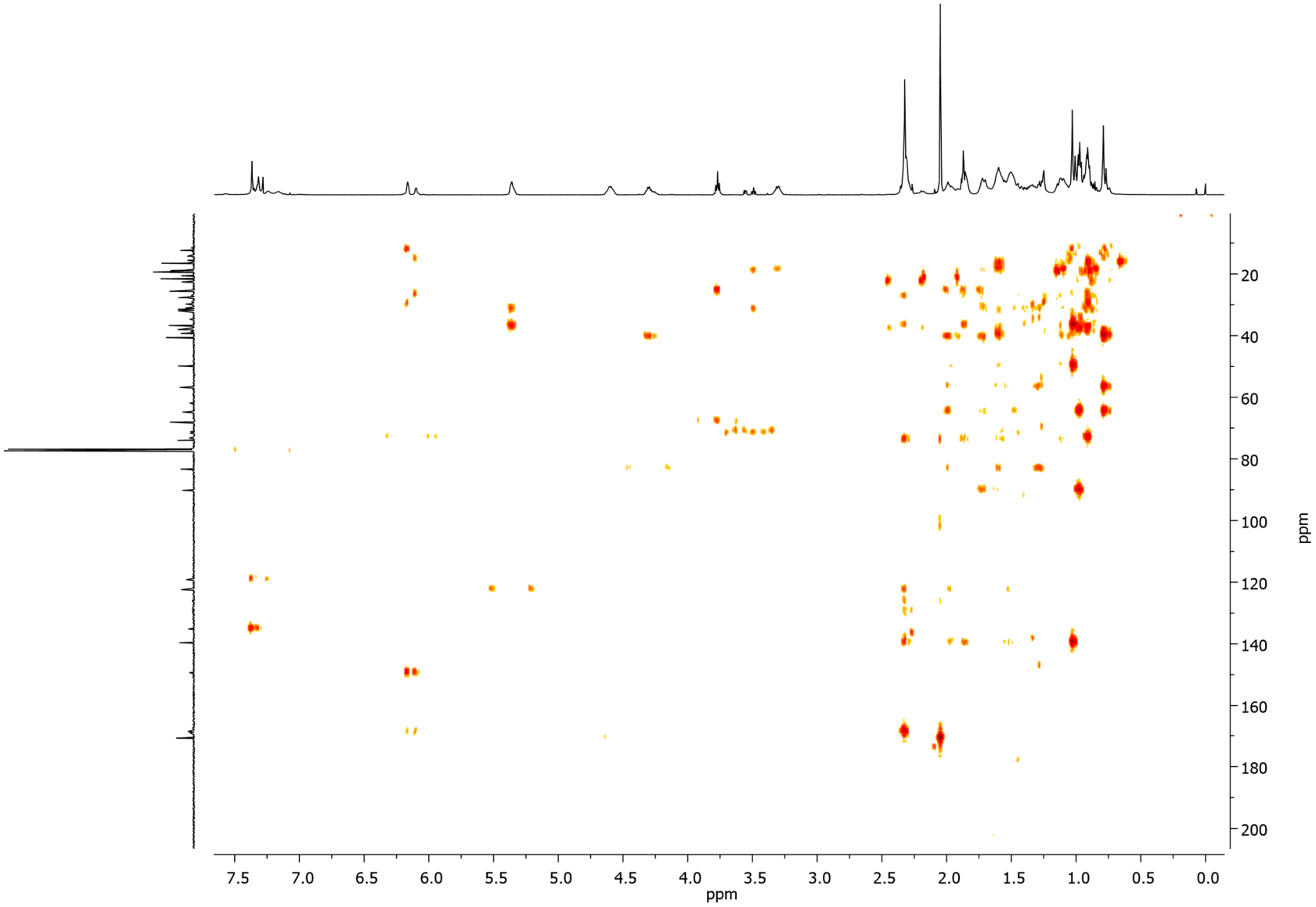


Figure S40. Experiment HMBC of **15** (500 MHz, $CDCl_3$)

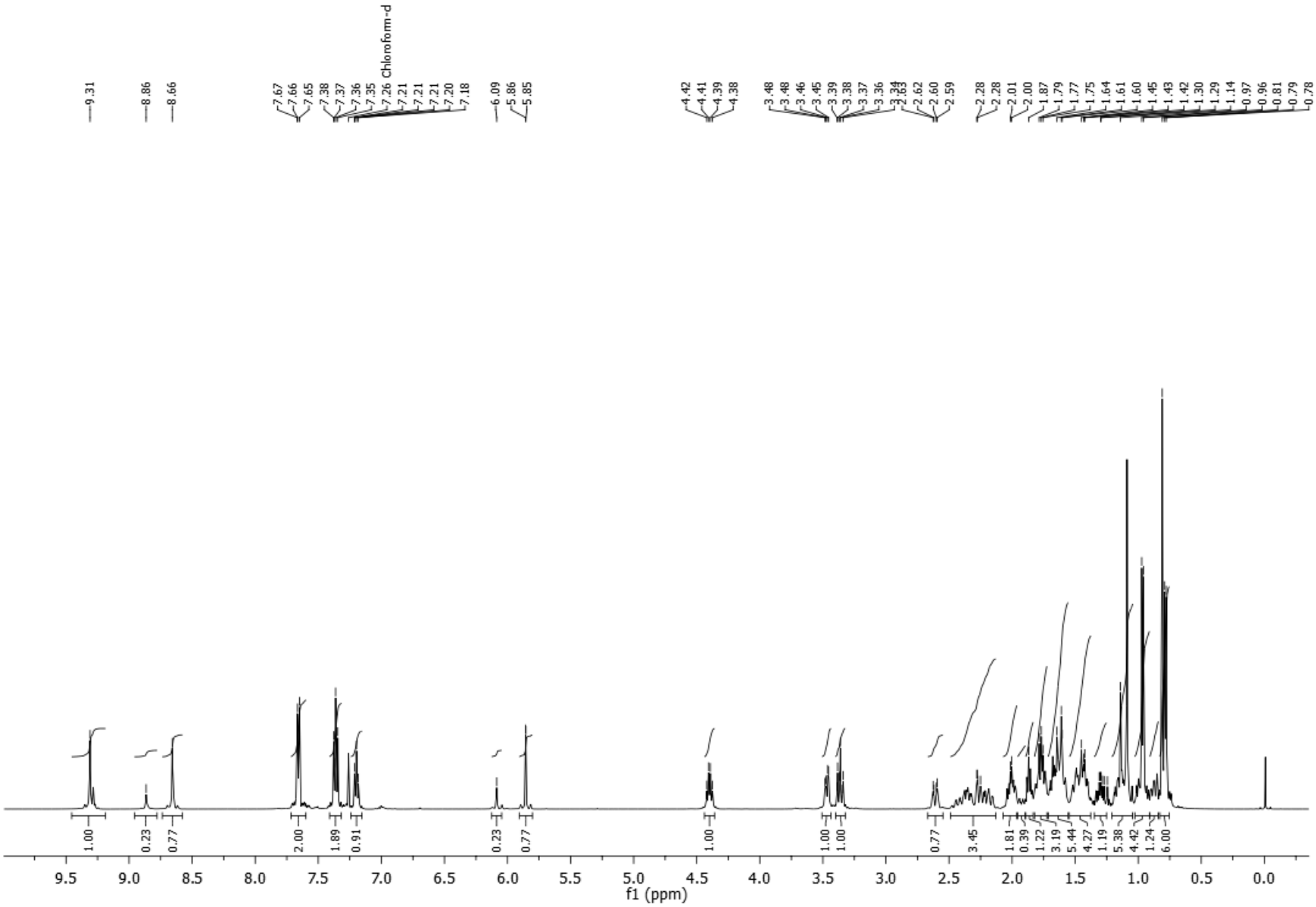


Figure S41. ^{1}H-NMR spectrum of **17** (500 MHz, $CDCl_3$)

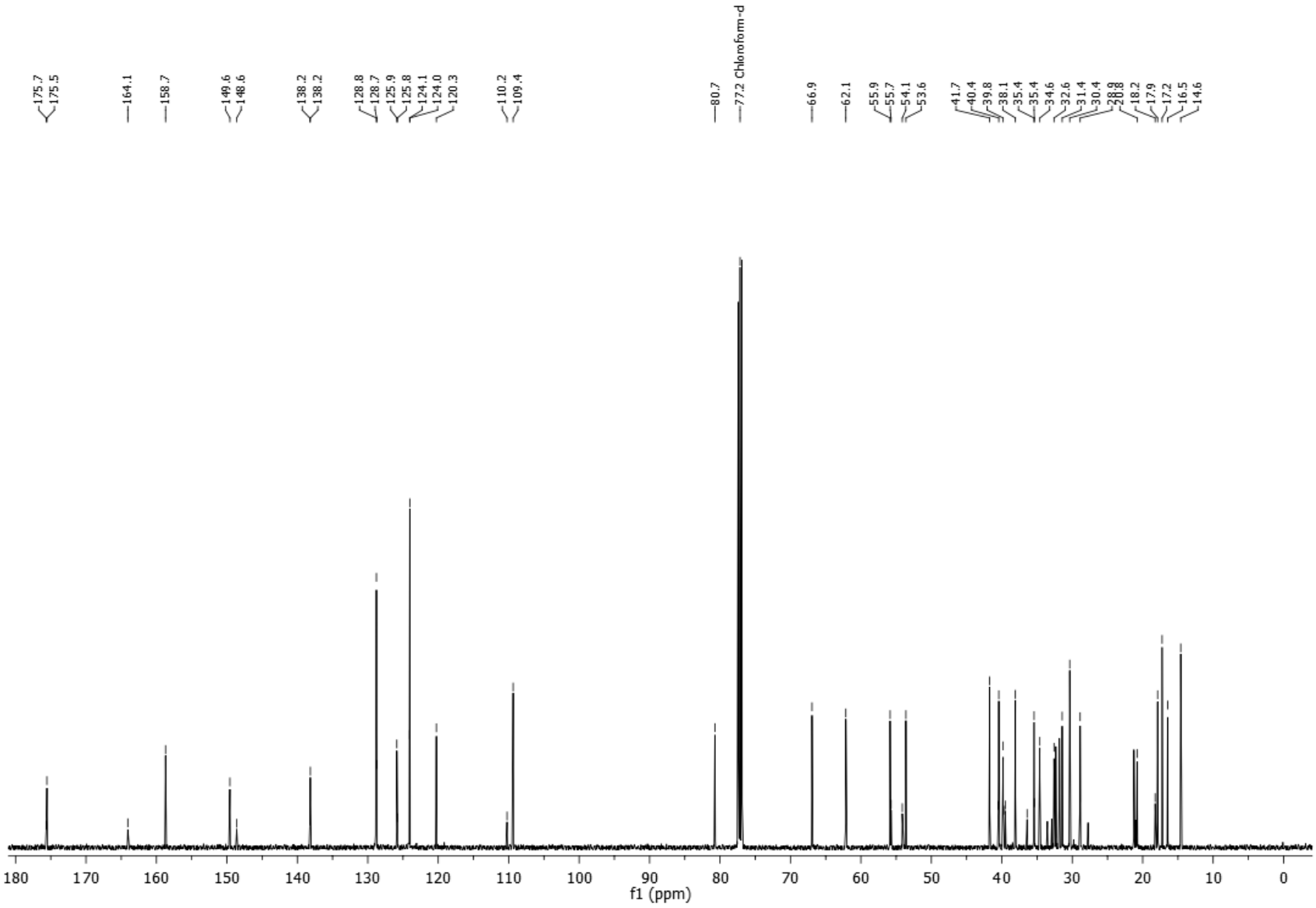


Figure S42. ^{13}C-NMR spectrum of **17** (125.7 MHz, $CDCl_3$)

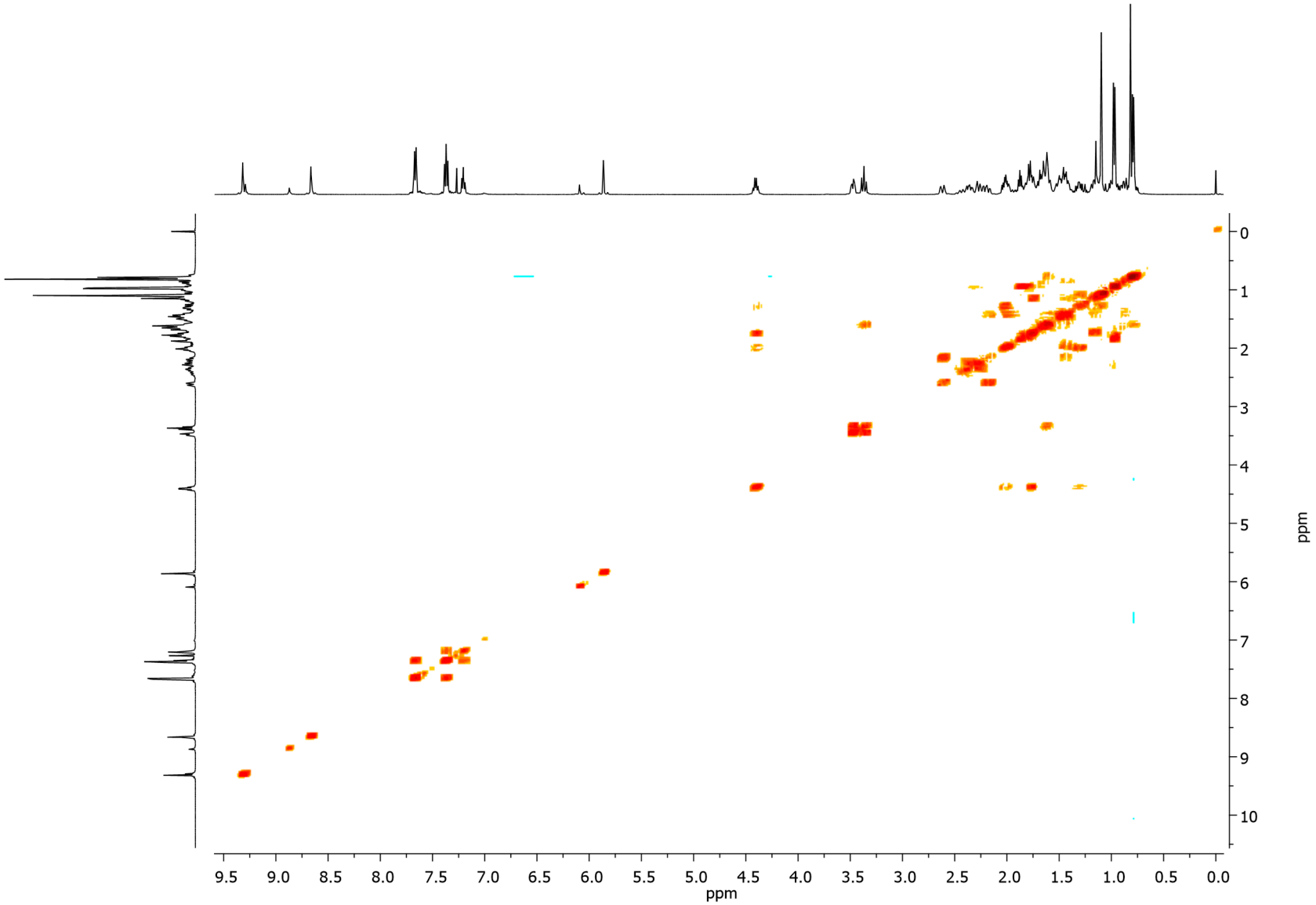


Figure S43. Experiment COSY of **17** (500 MHz, $CDCl_3$)

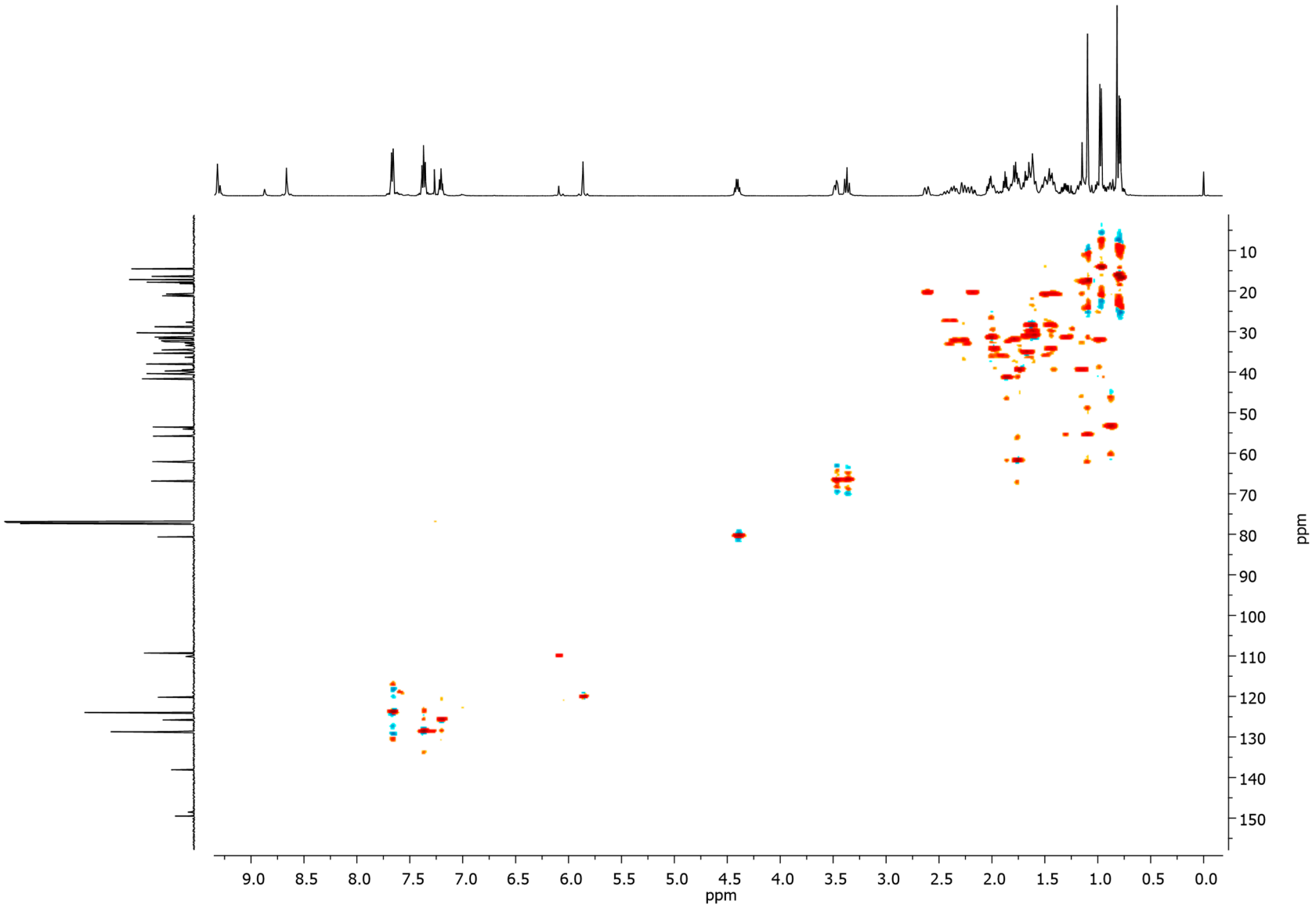


Figure S44. Experiment HSQC of **17** (500 MHz, $CDCl_3$)

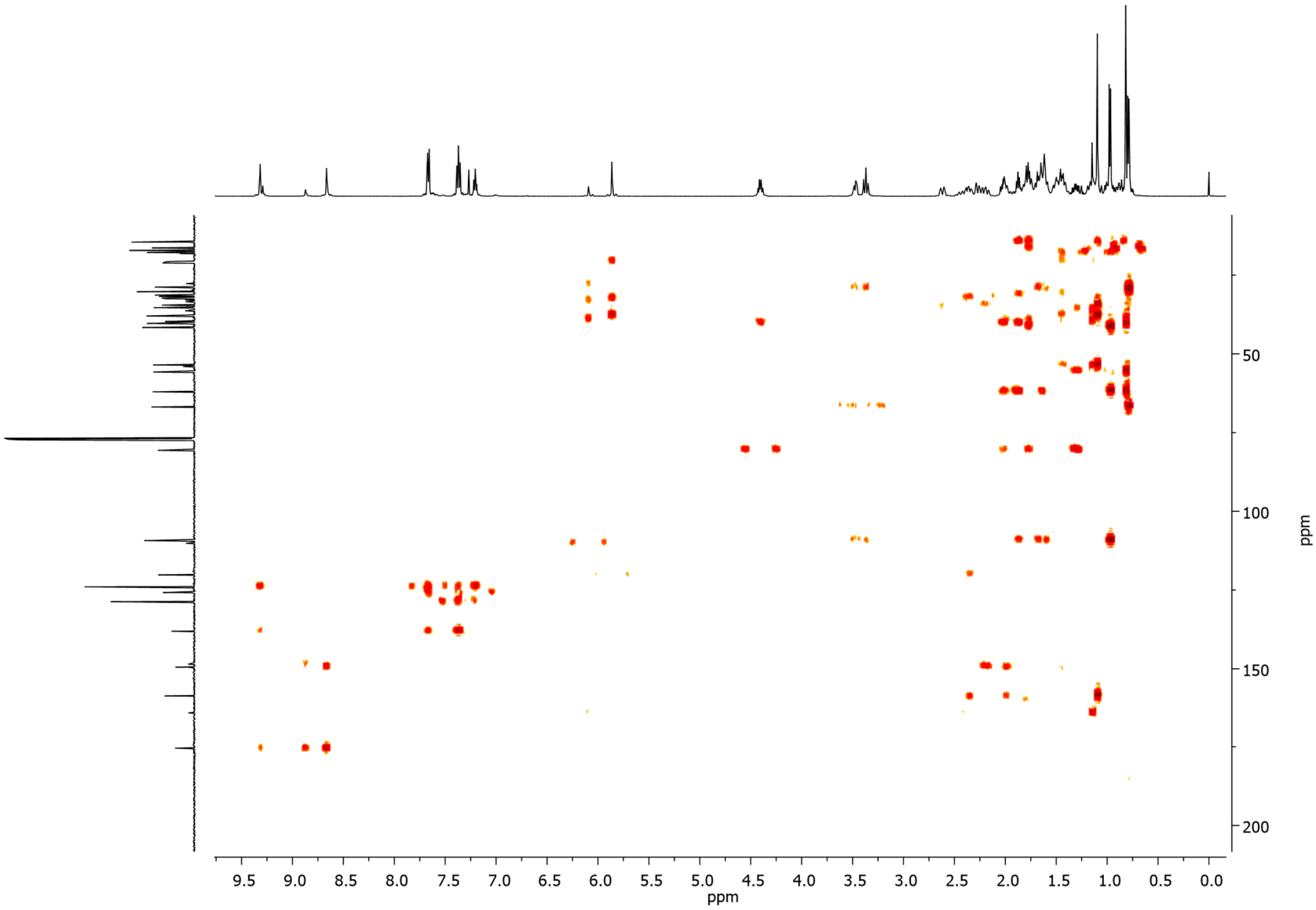


Figure S45. Experiment HMBC of **17** (500 MHz, $CDCl_3$)

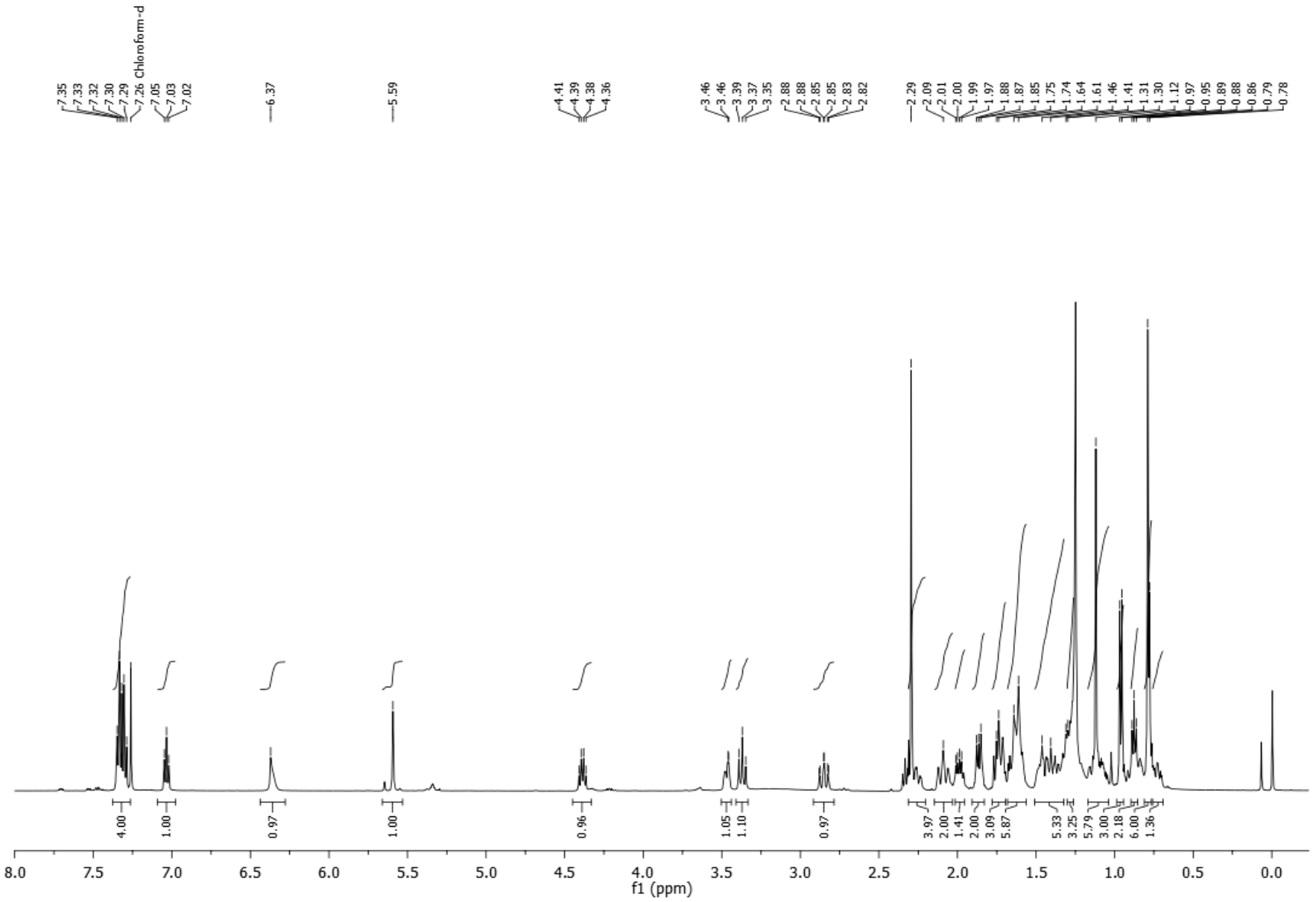


Figure S46. ^{1}H-NMR spectrum of **18** (500 MHz, $CDCl_3$)

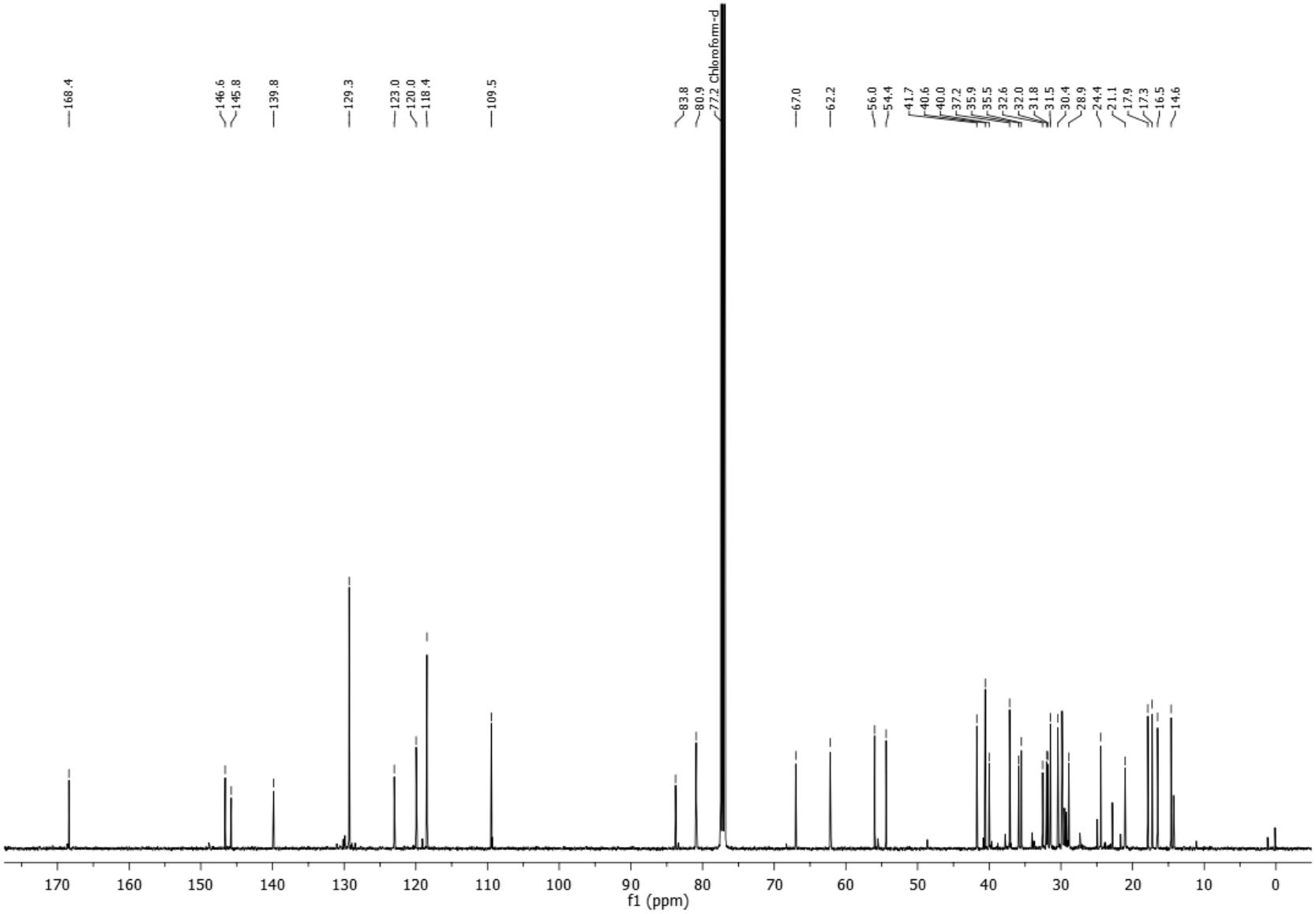


Figure S47. ^{13}C-NMR spectrum of **18** (125.7 MHz, $CDCl_3$)

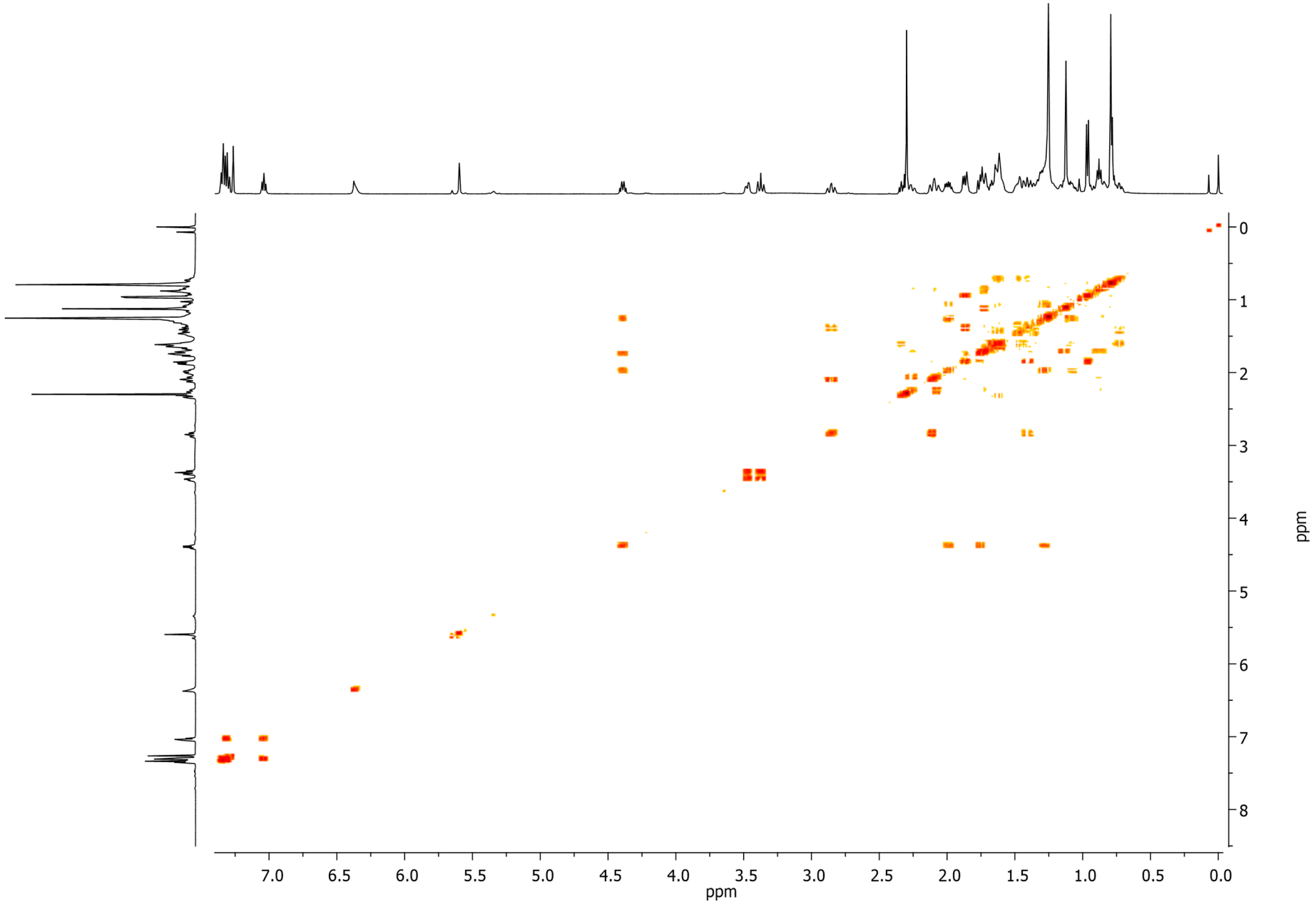


Figure 48. Experiment COSY of **18** (500 MHz, $CDCl_3$)

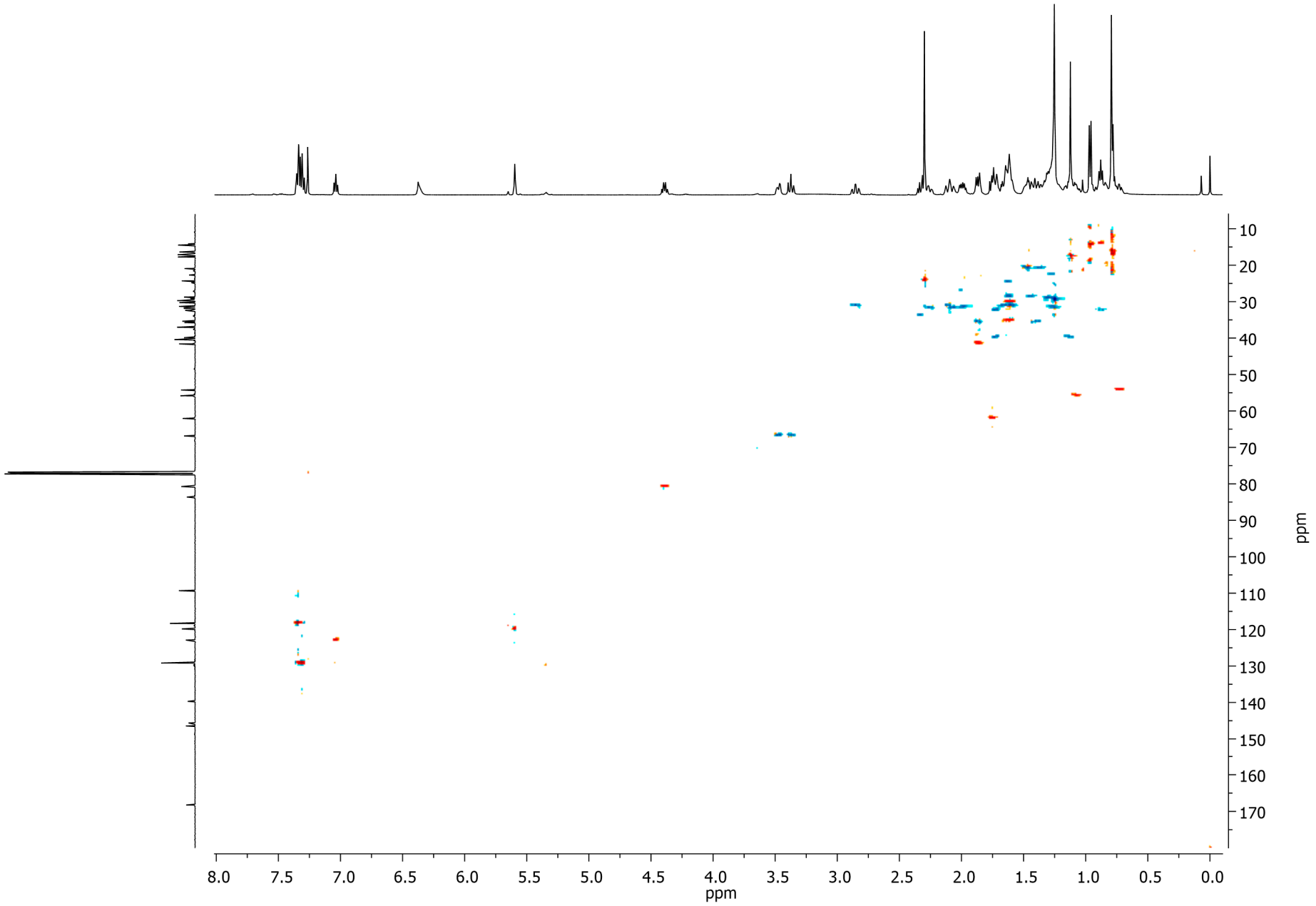


Figure S49. Experiment HSQC of **18** (500 MHz, $CDCl_3$)

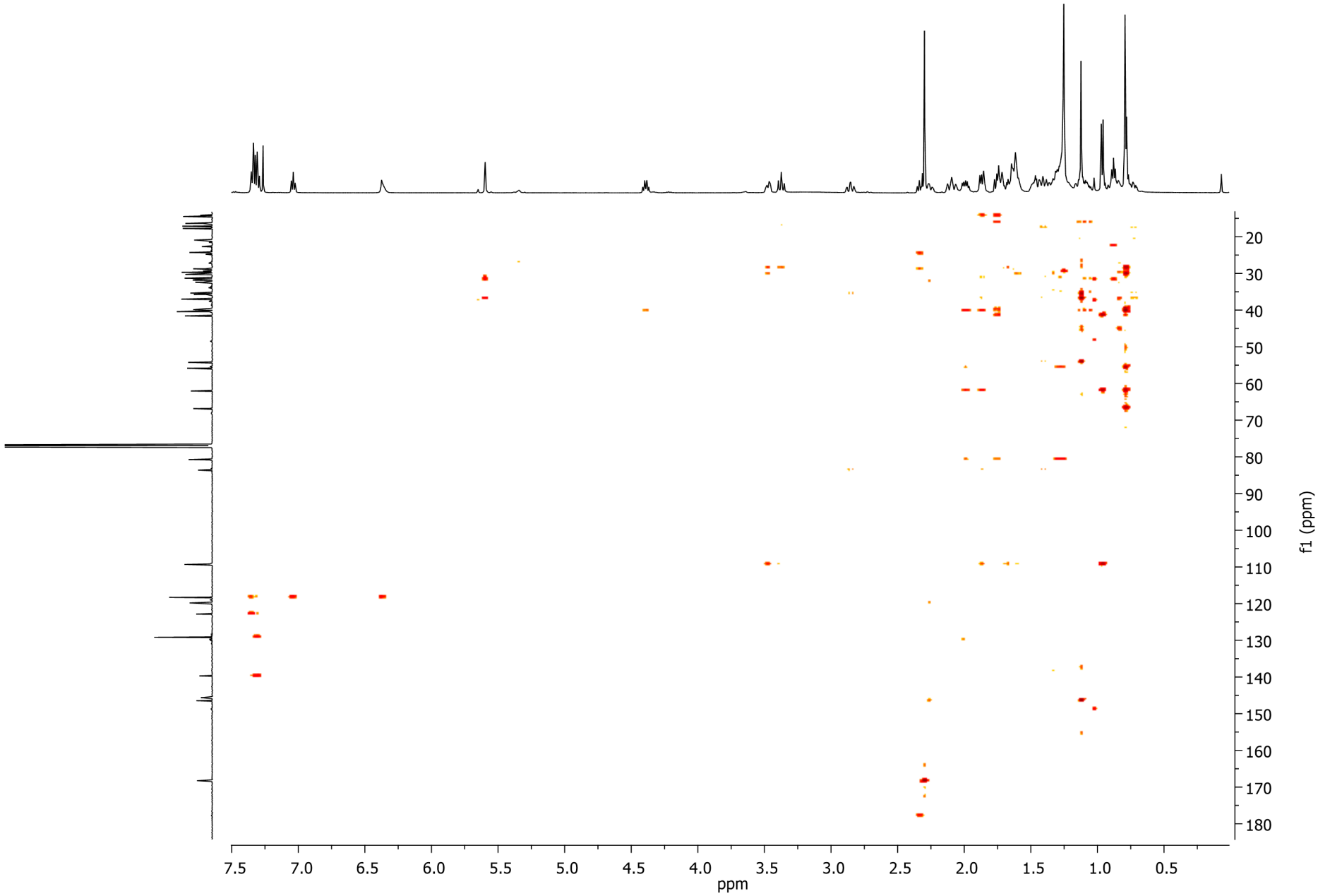


Figure S50. Experiment HMBC of **18** (500 MHz, $CDCl_3$)

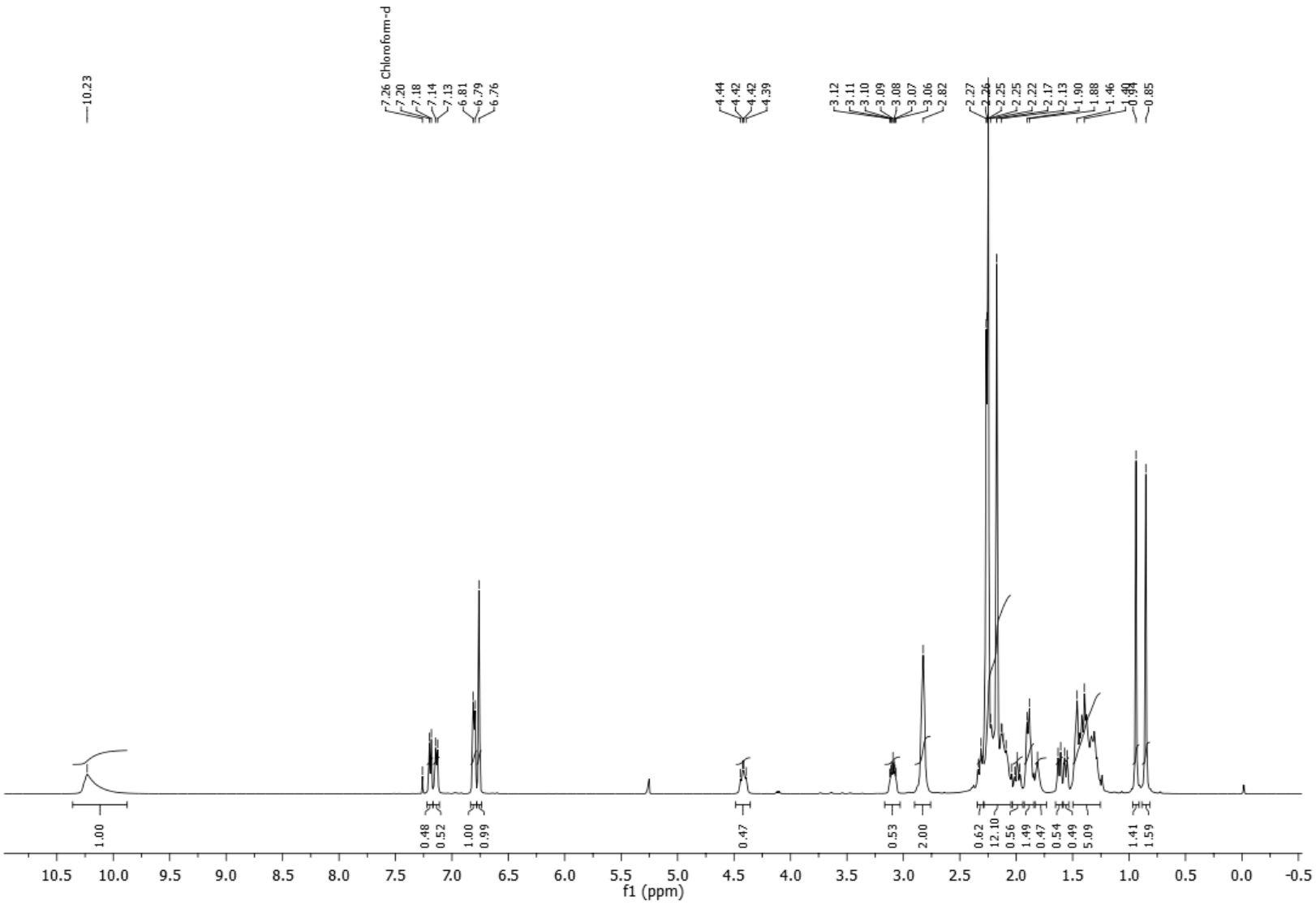


Figure S51. ^{1}H-NMR spectrum of **21** (500 MHz, $CDCl_3$)

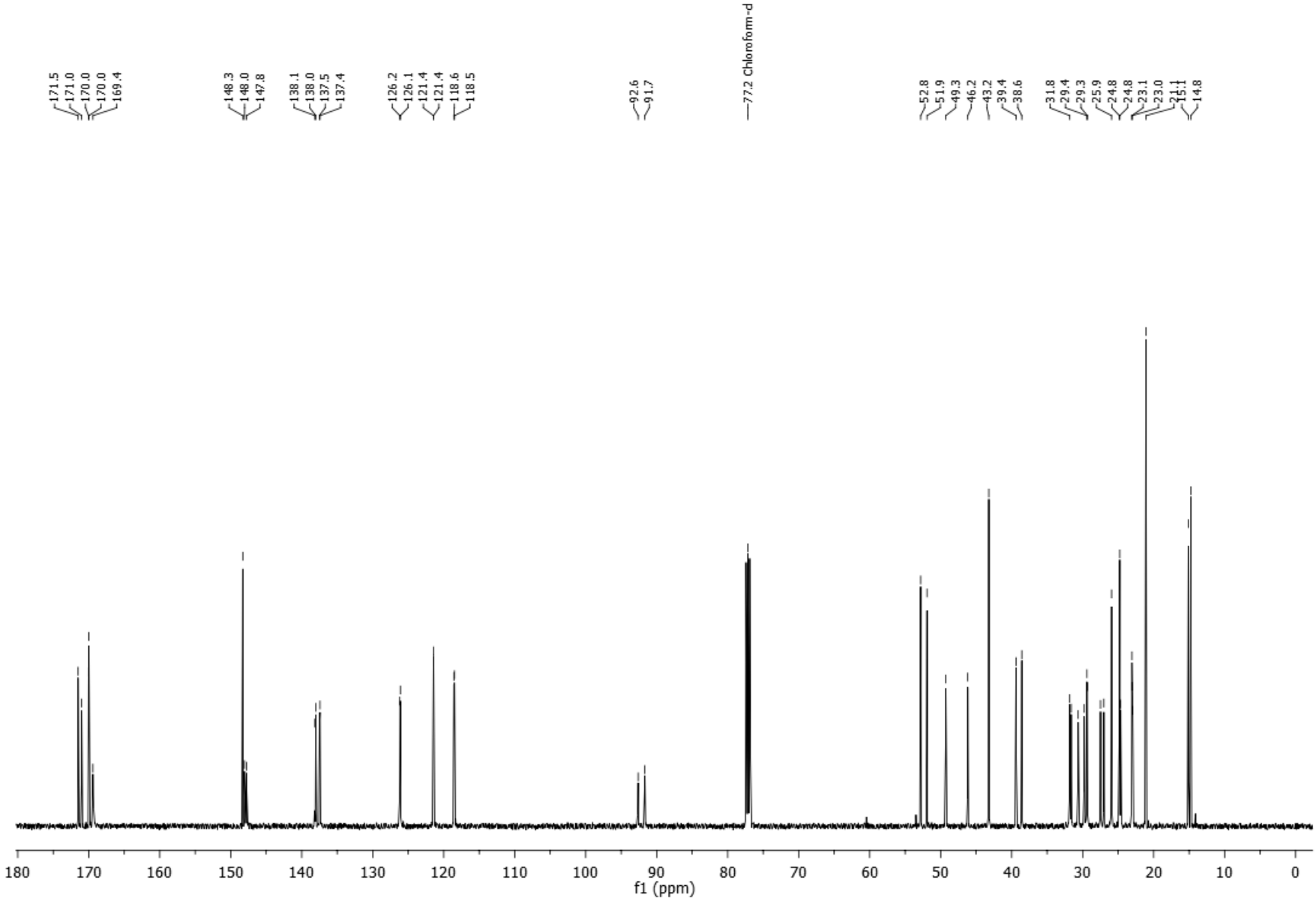


Figure S52. ^{13}C-NMR spectrum of **21** (125.7 MHz, $CDCl_3$)

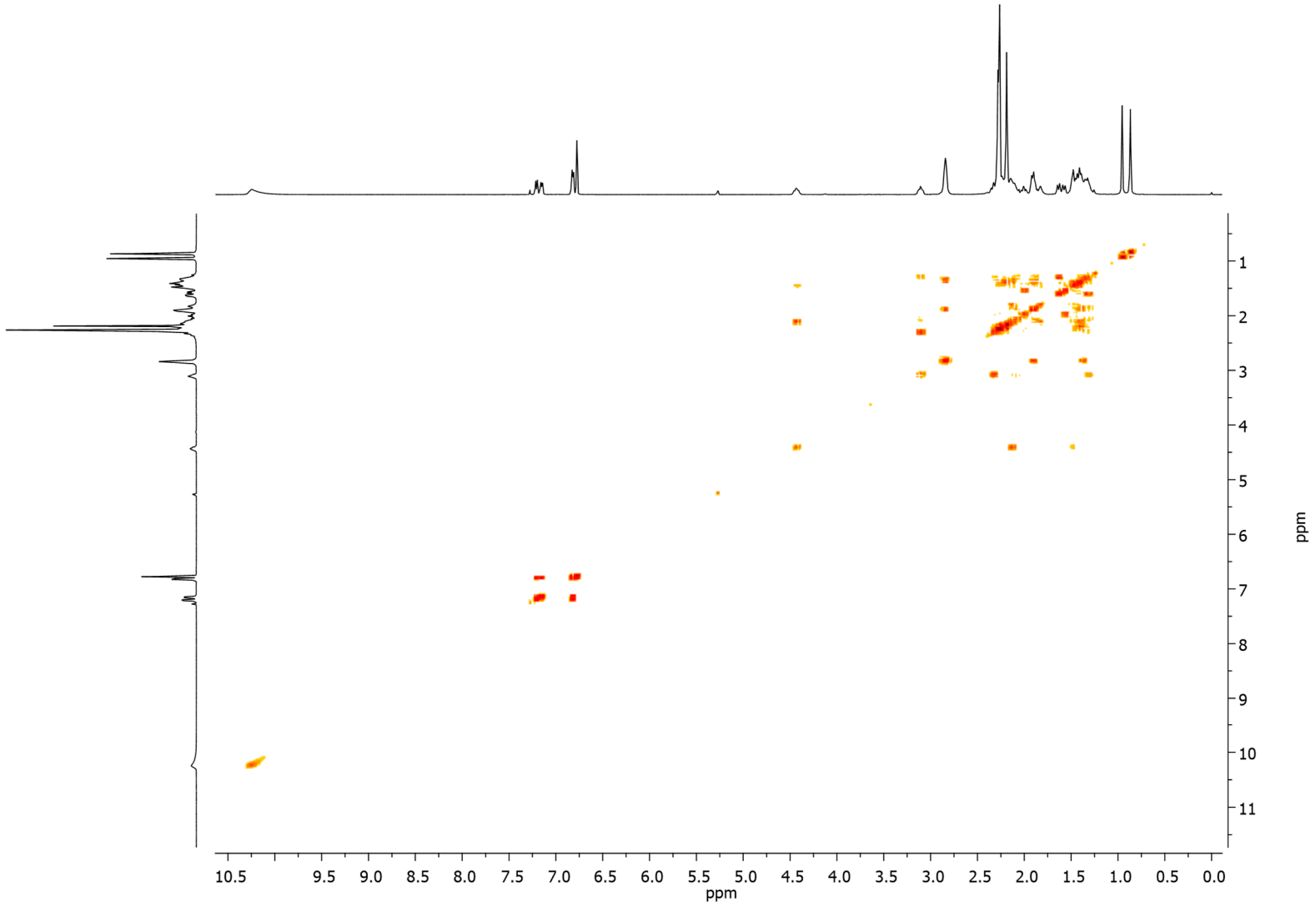


Figure S53. Experiment COSY of **21** (500 MHz, $CDCl_3$)

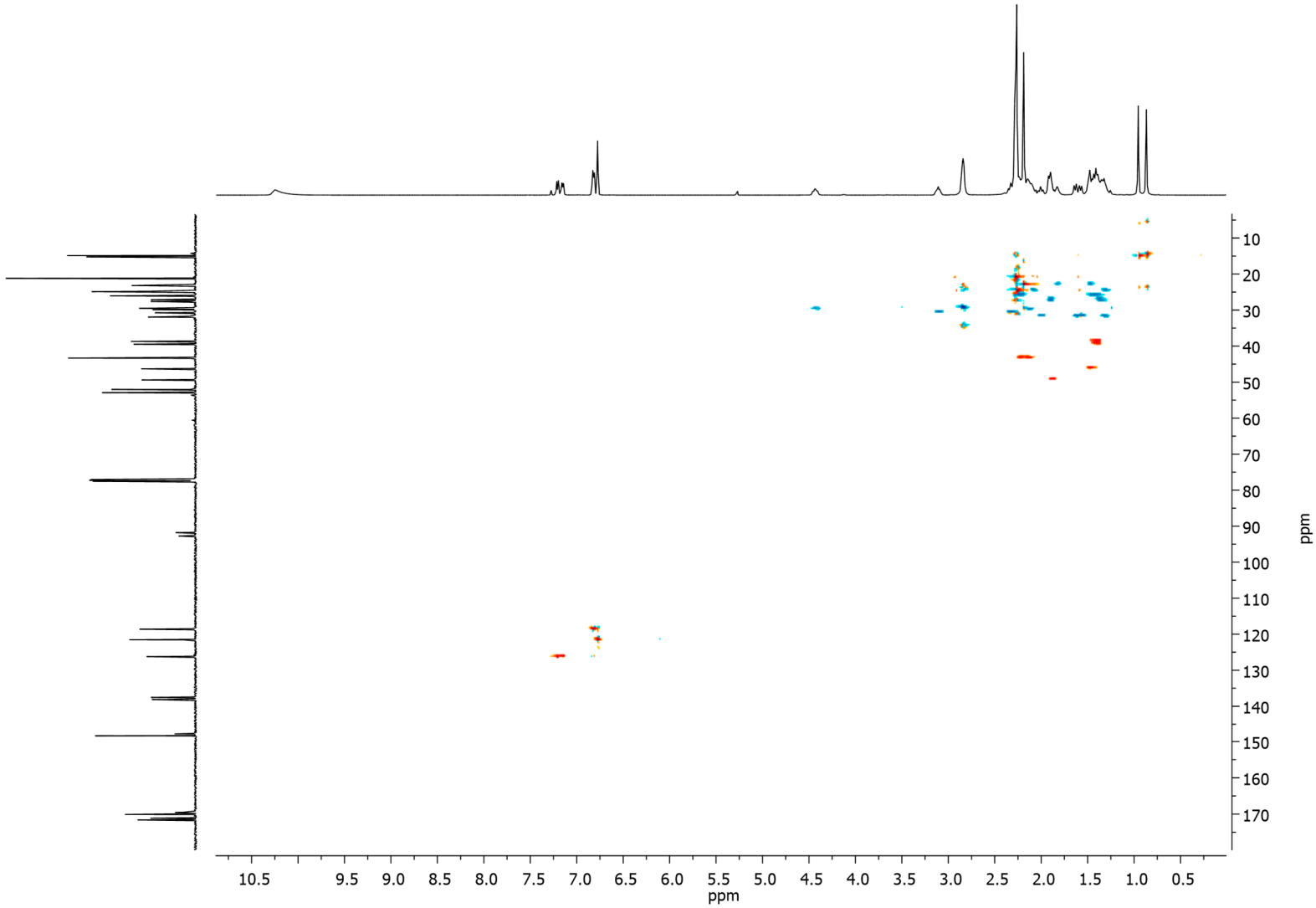


Figure S54. Experiment HSQC of **21** (500 MHz, $CDCl_3$)

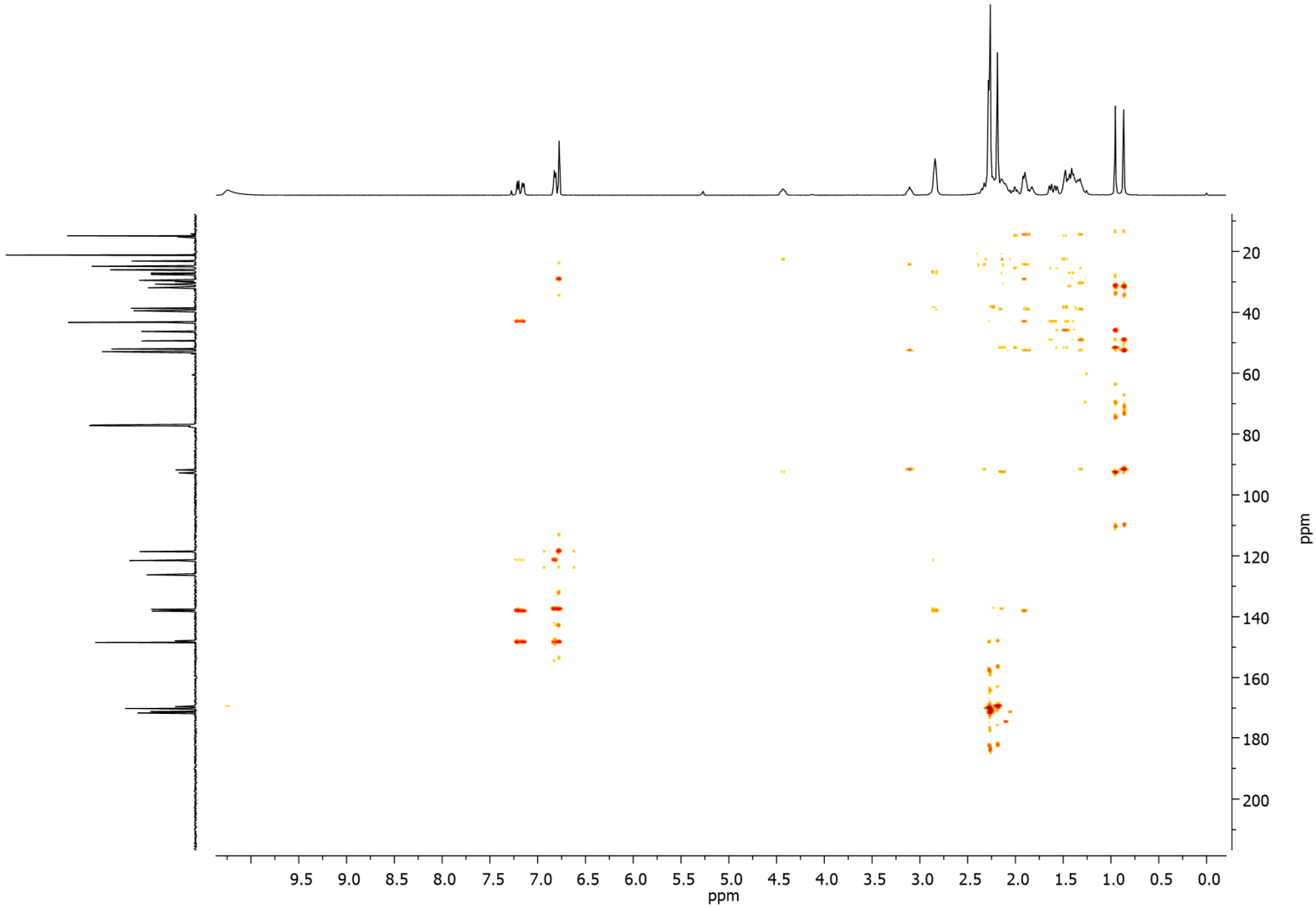


Figure S55. Experiment HMBC of **21** (500 MHz, $CDCl_3$)

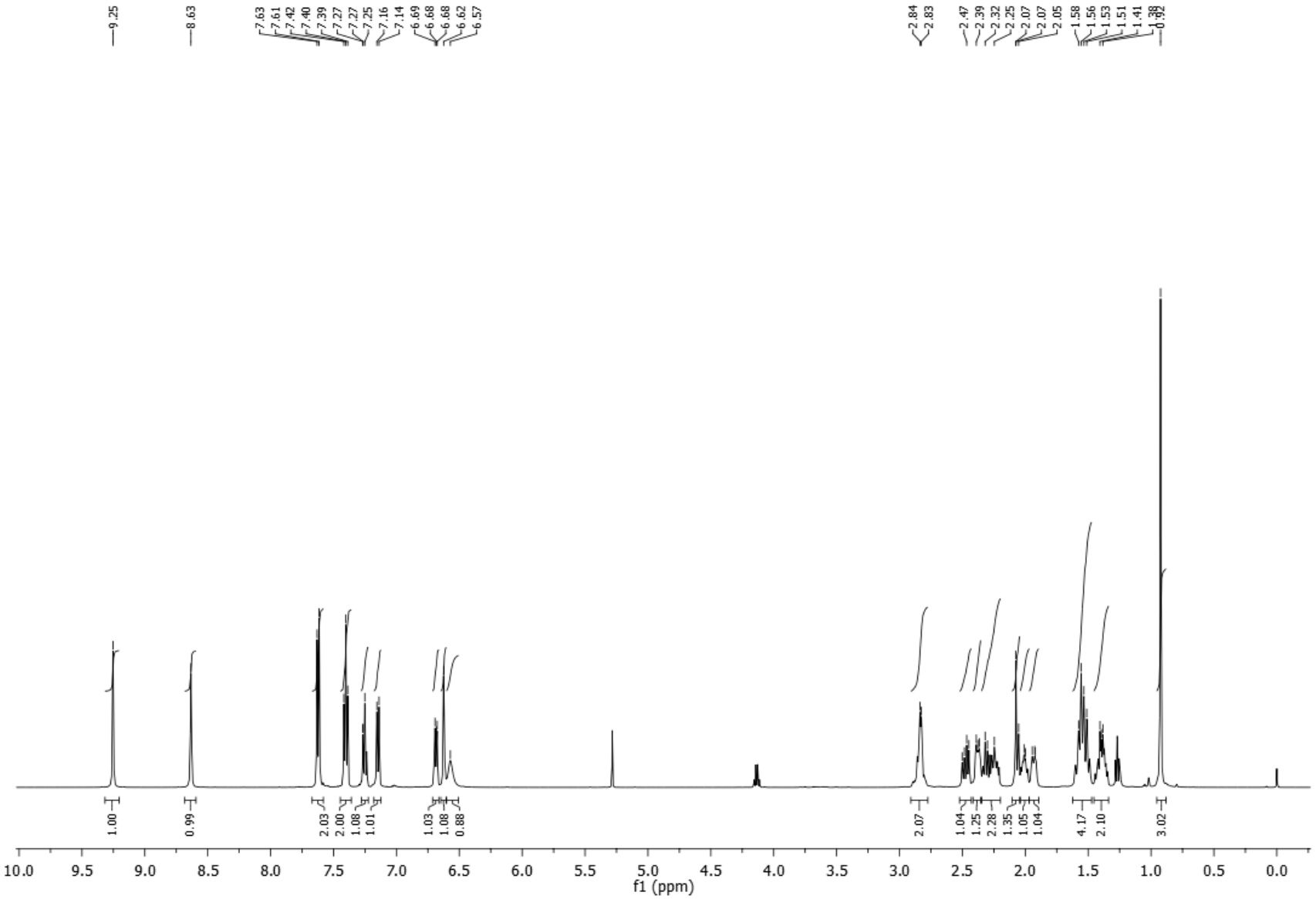


Figure S56. ^{1}H-NMR spectrum of **22** (500 MHz, $CDCl_3$)

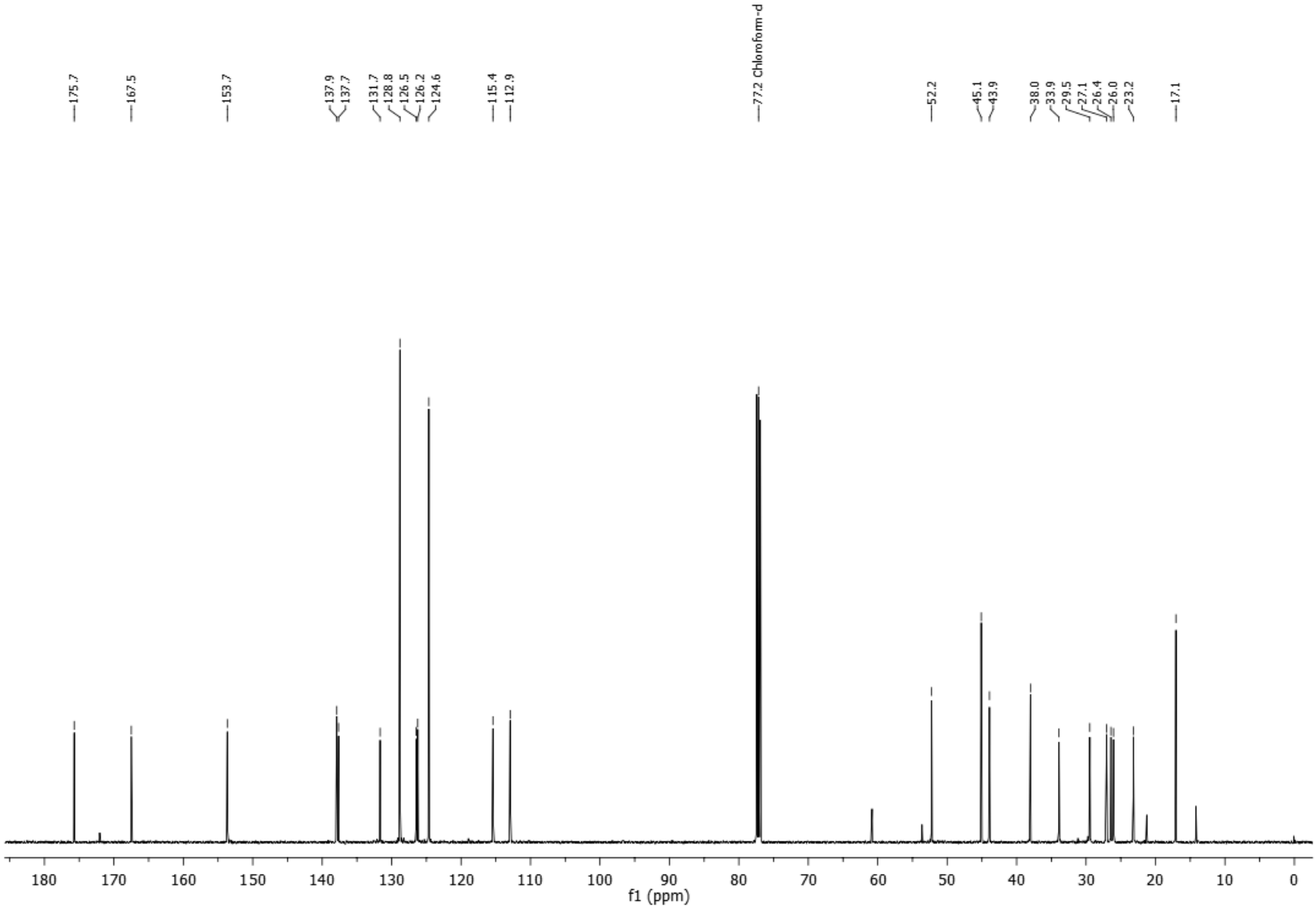
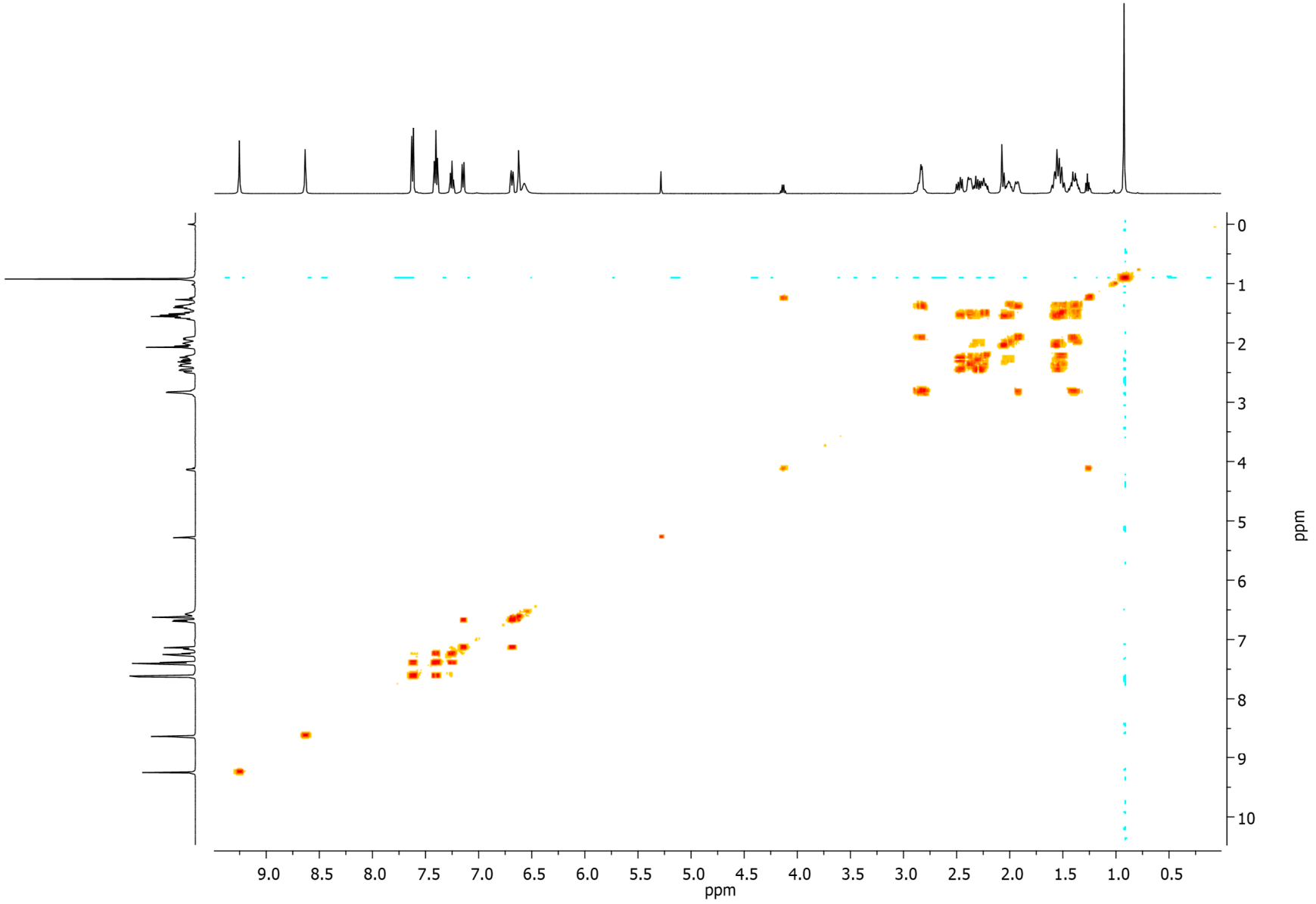
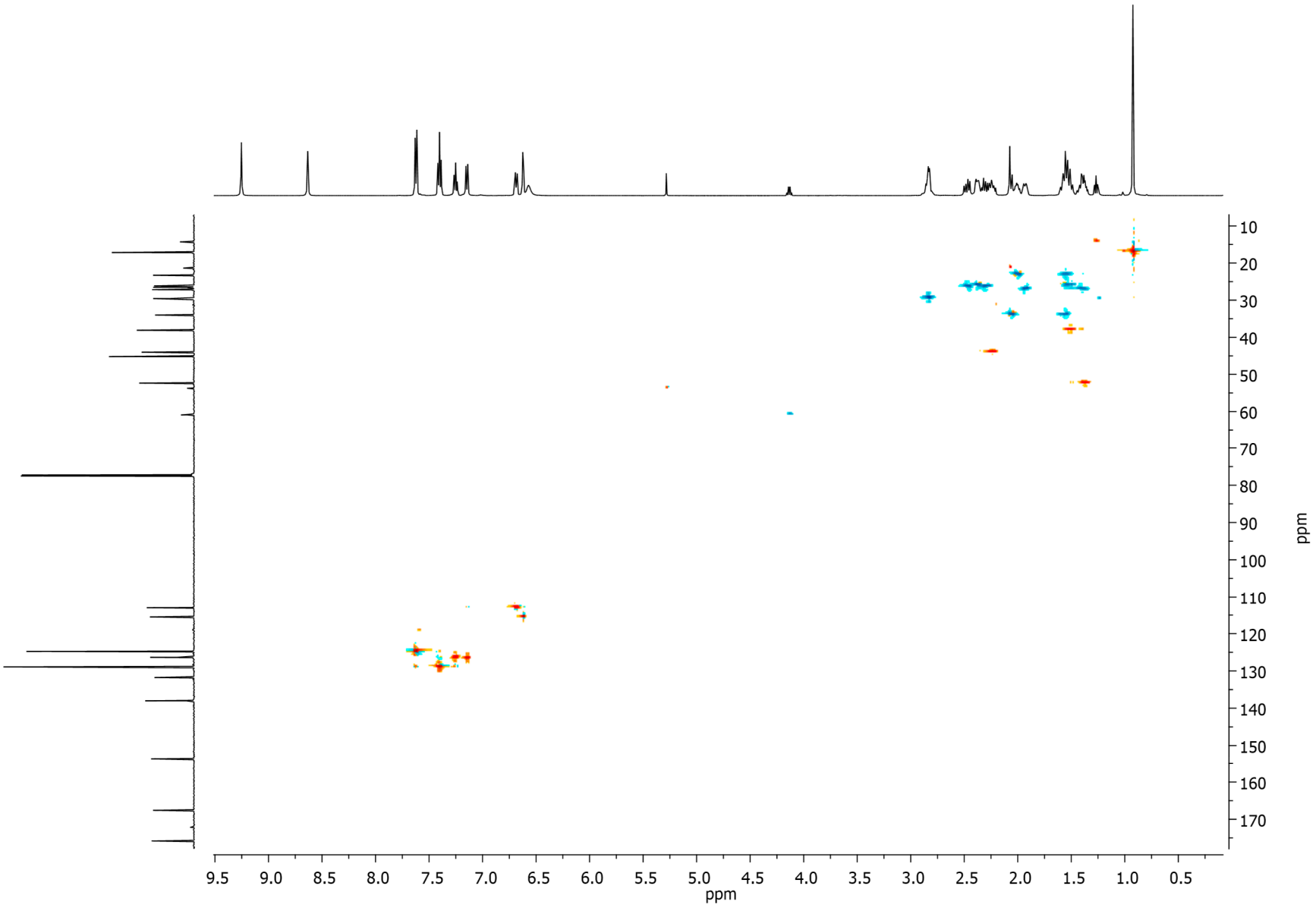


Figure S57. ^{13}C-NMR spectrum of **22** (125.7 MHz, $CDCl_3$)



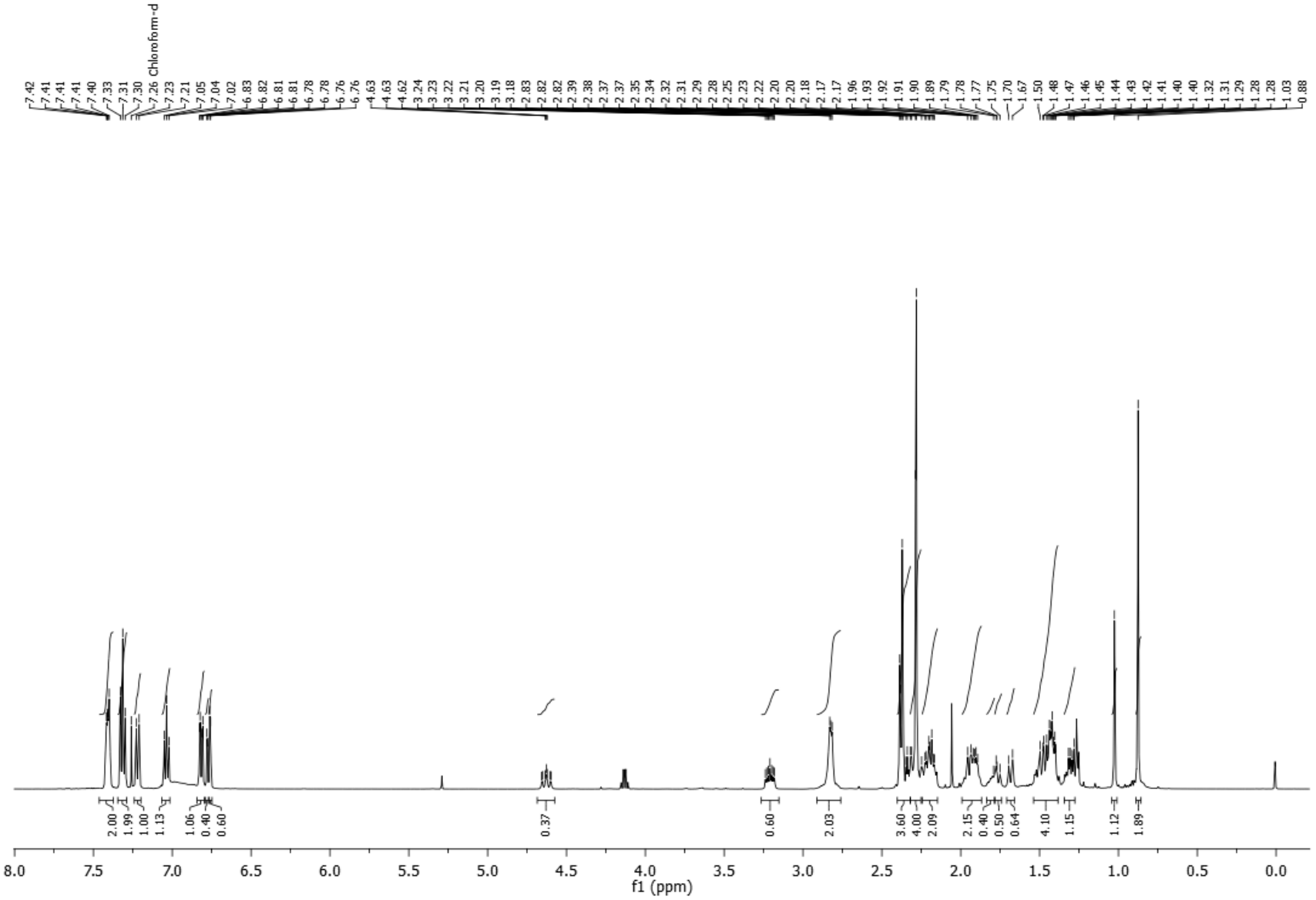
v

Figure S58. Experiment COSY of **22** (500 MHz, $CDCl_3$)



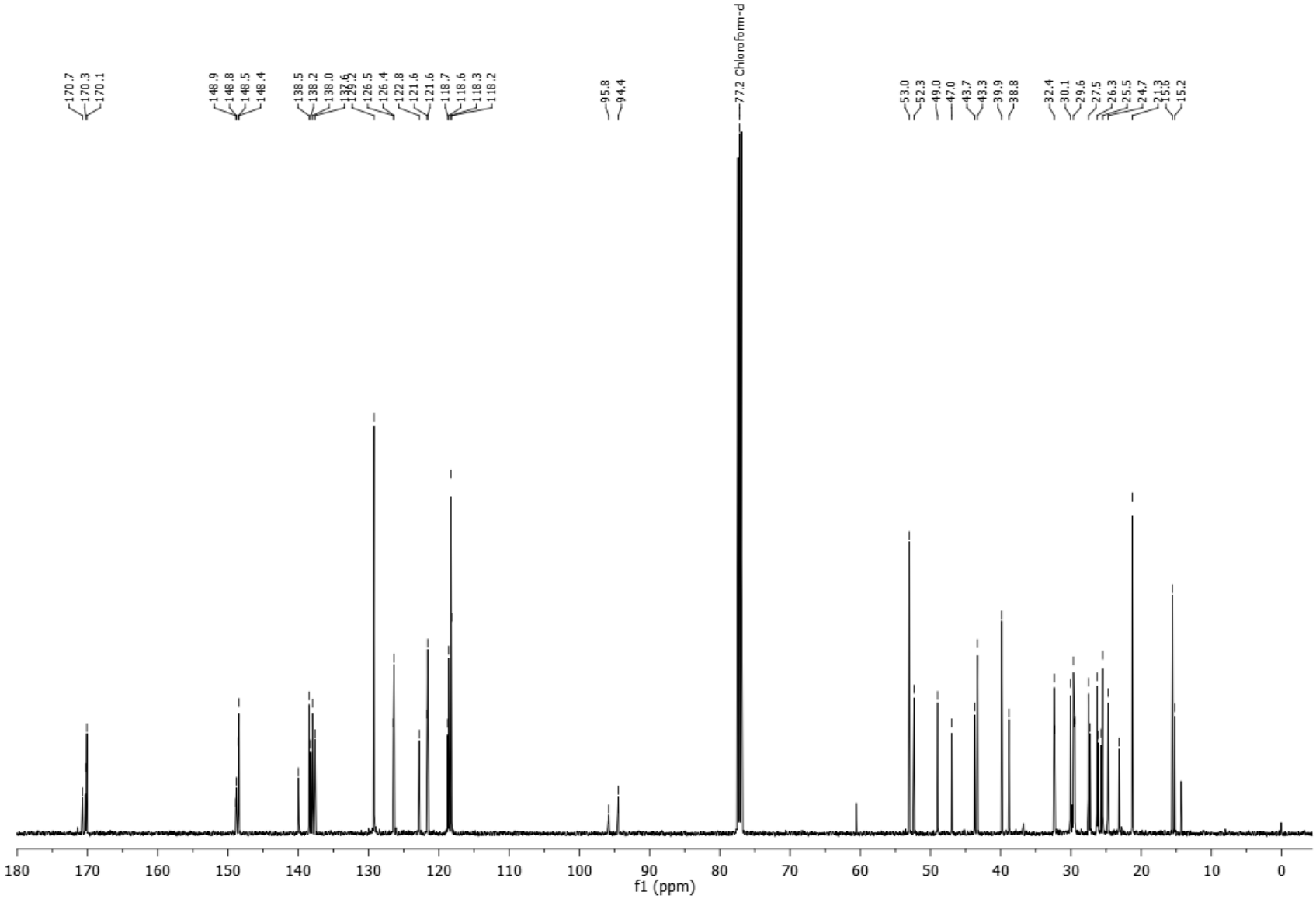
v

Figure S59. Experiment HSQC of **22** (500 MHz, $CDCl_3$)



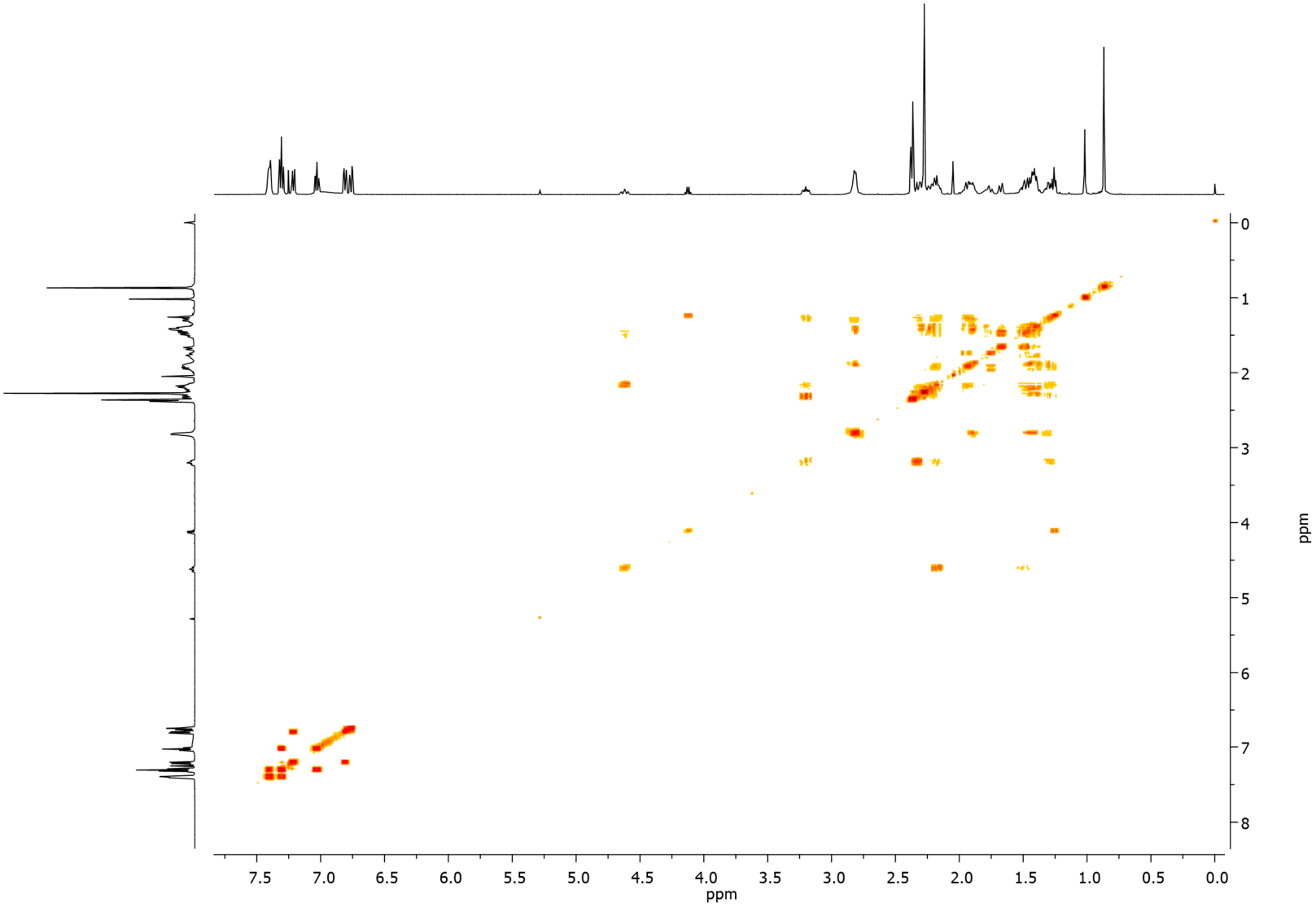
v

Figure S60. ^{1}H-NMR spectrum of **23** (500 MHz, $CDCl_3$)



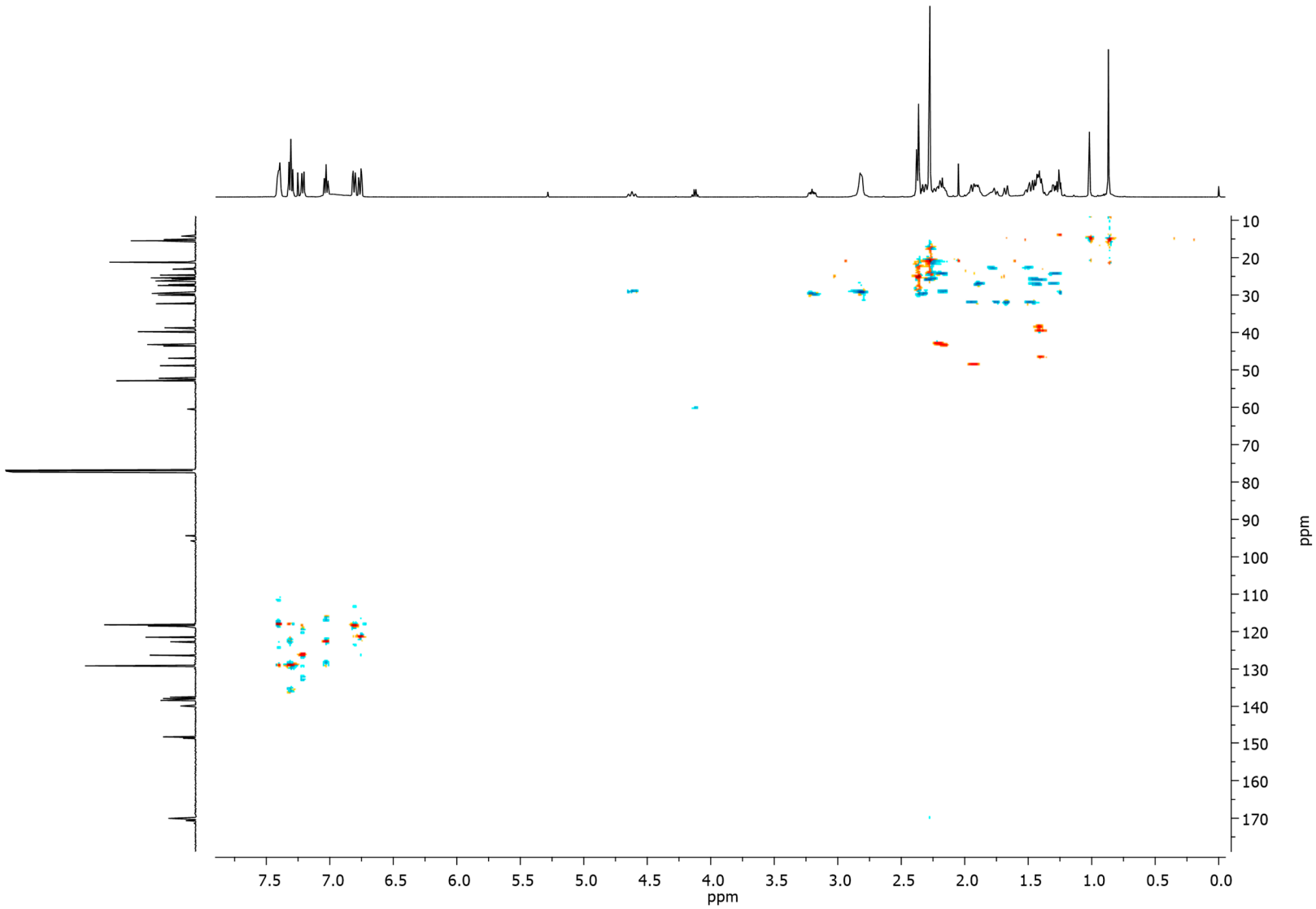
v

Figure S61. ^{13}C-NMR spectrum of **23** (125.7 MHz, $CDCl_3$)



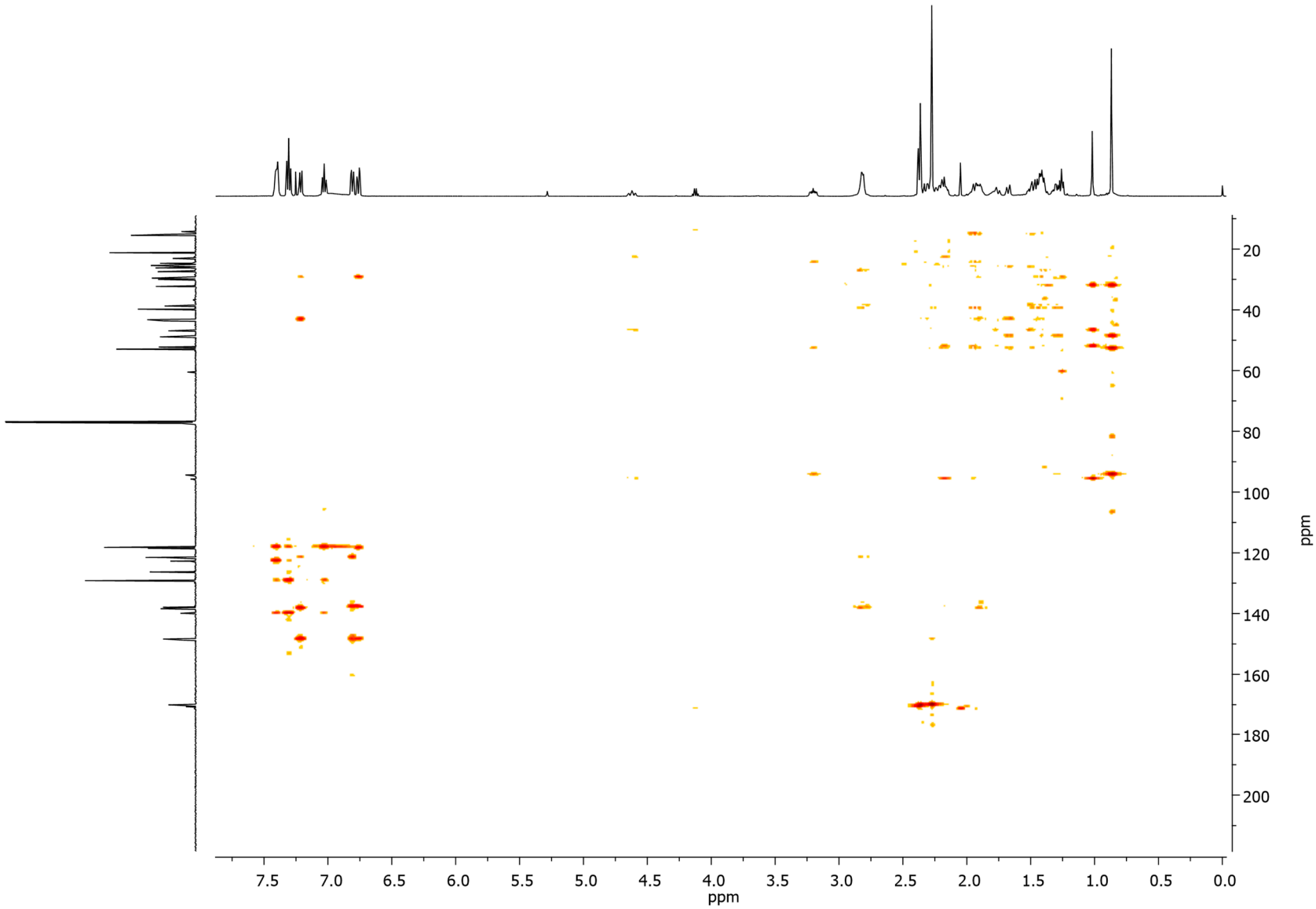
v

Figure S62. Experiment COSY of **23** (500 MHz, $CDCl_3$)



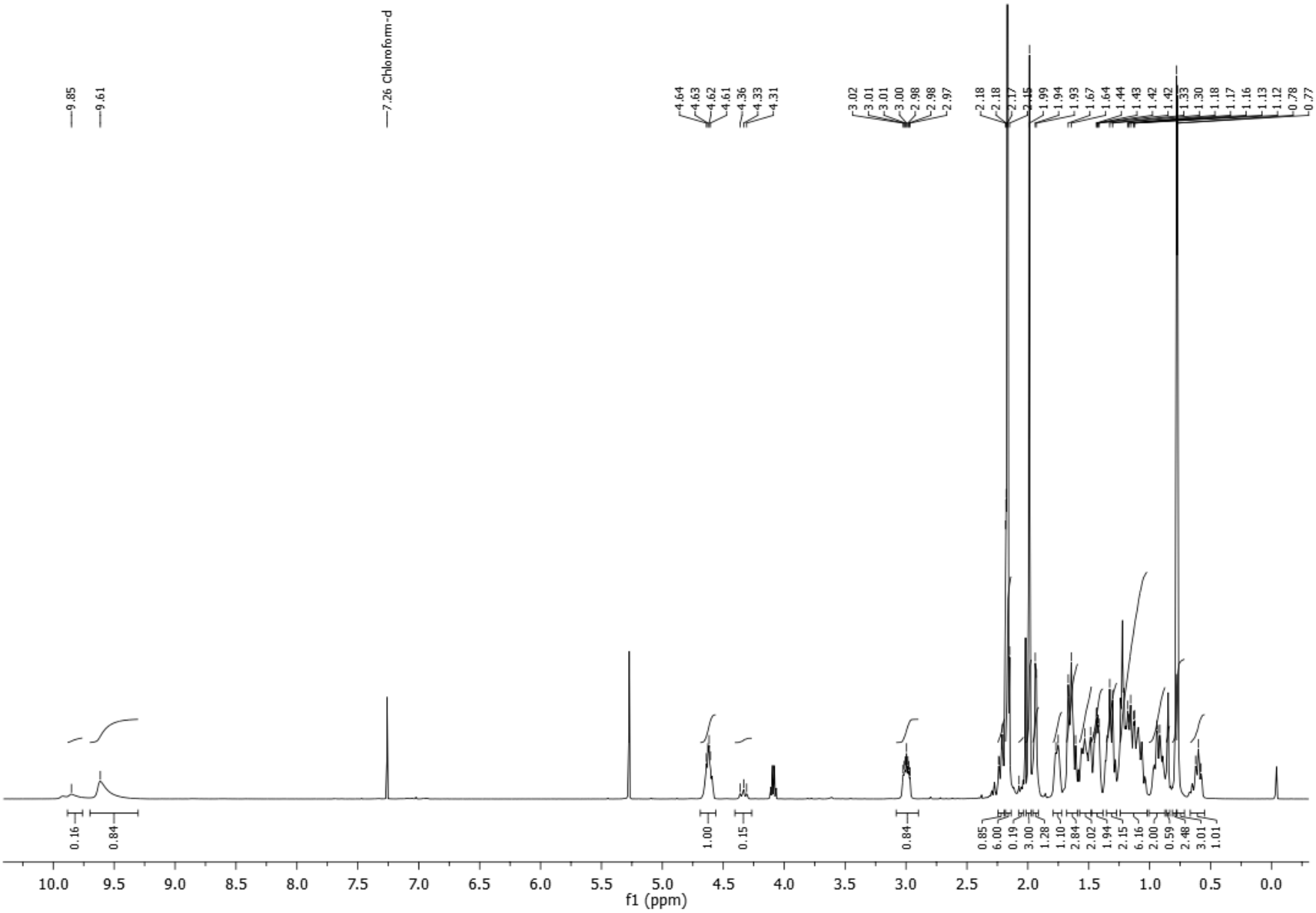
v

Figure S63. Experiment HSQC of **23** (500 MHz, $CDCl_3$)



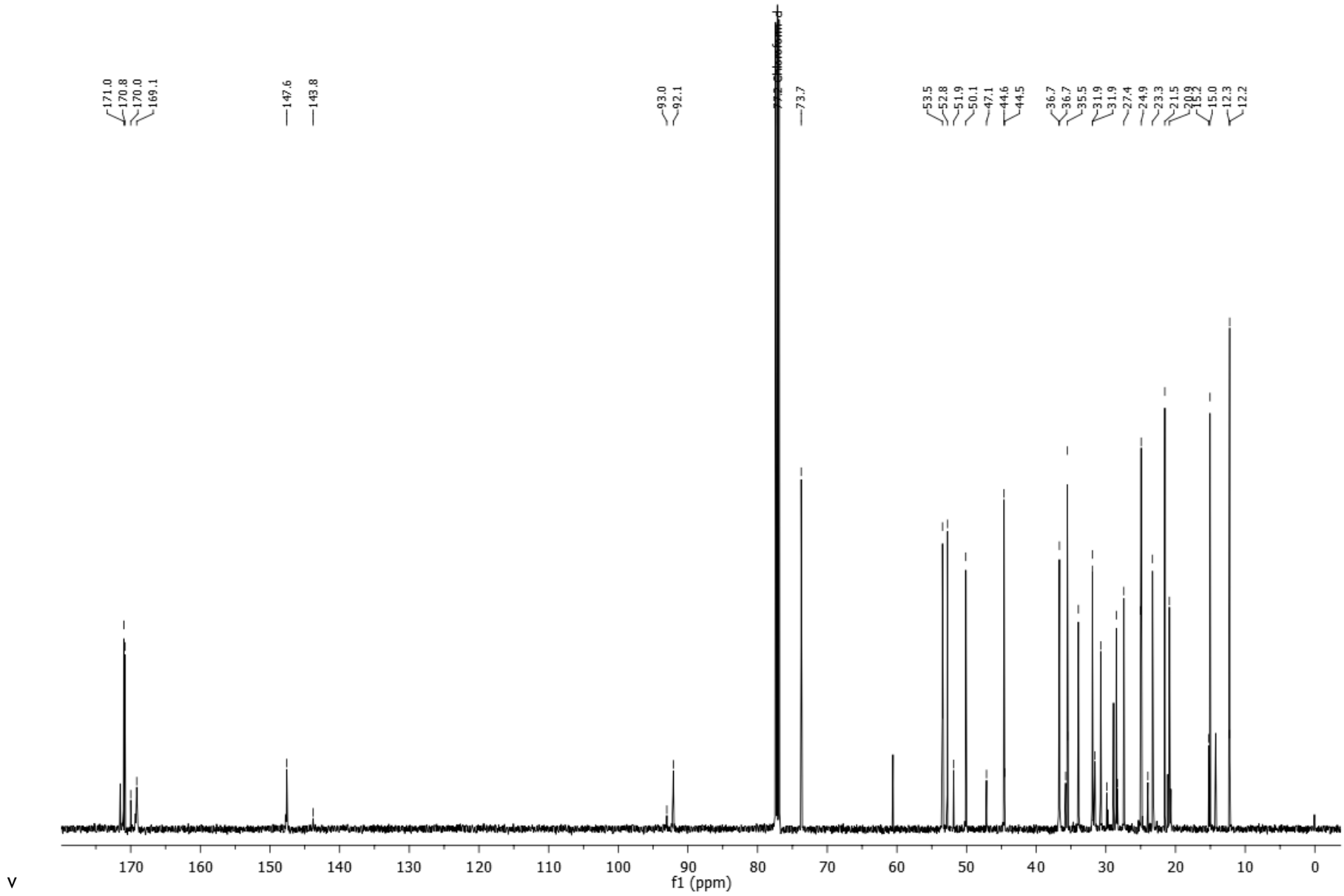
v

Figure S64. Experiment HMBC of **23** (500 MHz, $CDCl_3$)



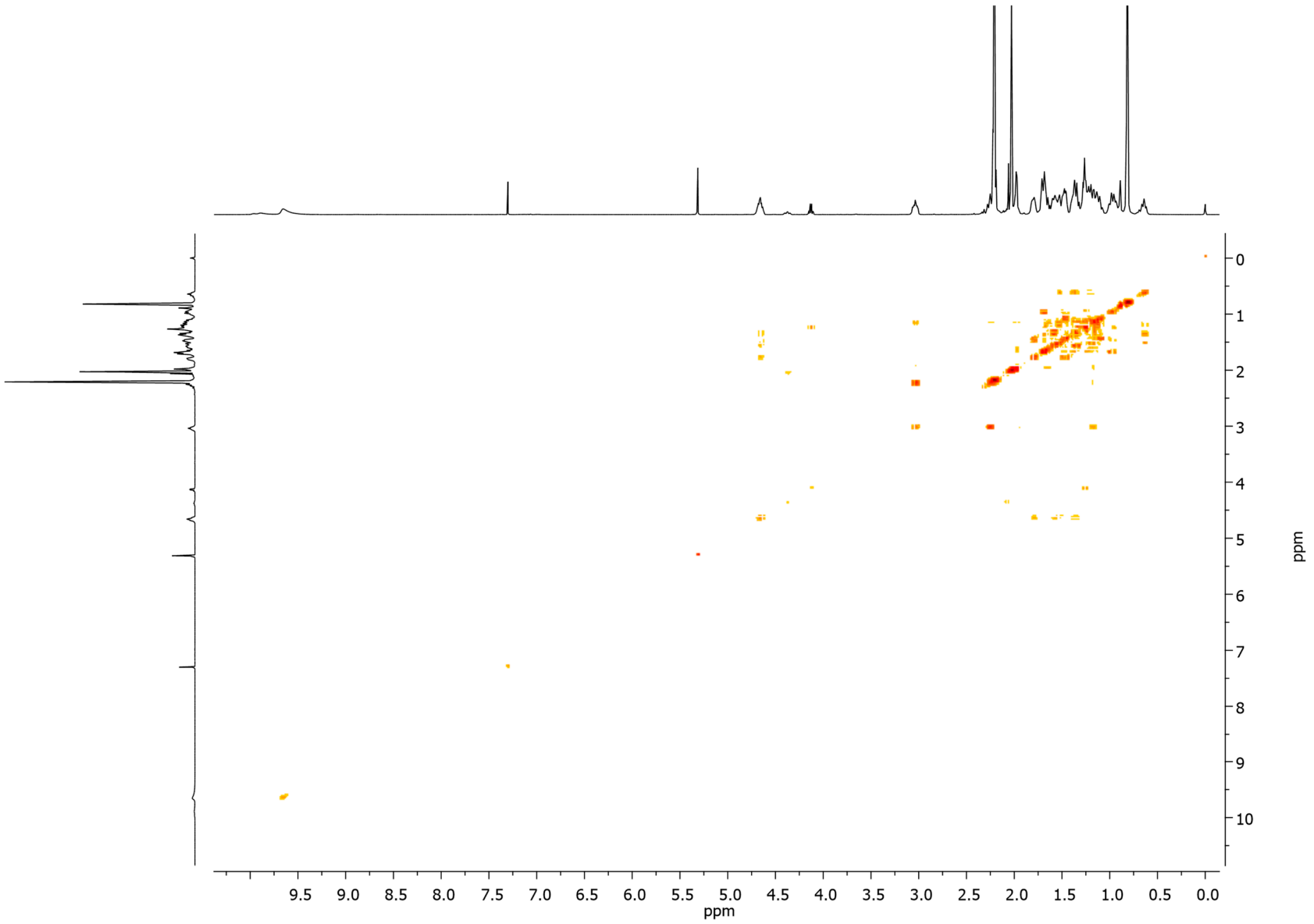
v

Figure S65. ^{1}H-NMR spectrum of **26**(500 MHz, $CDCl_3$)



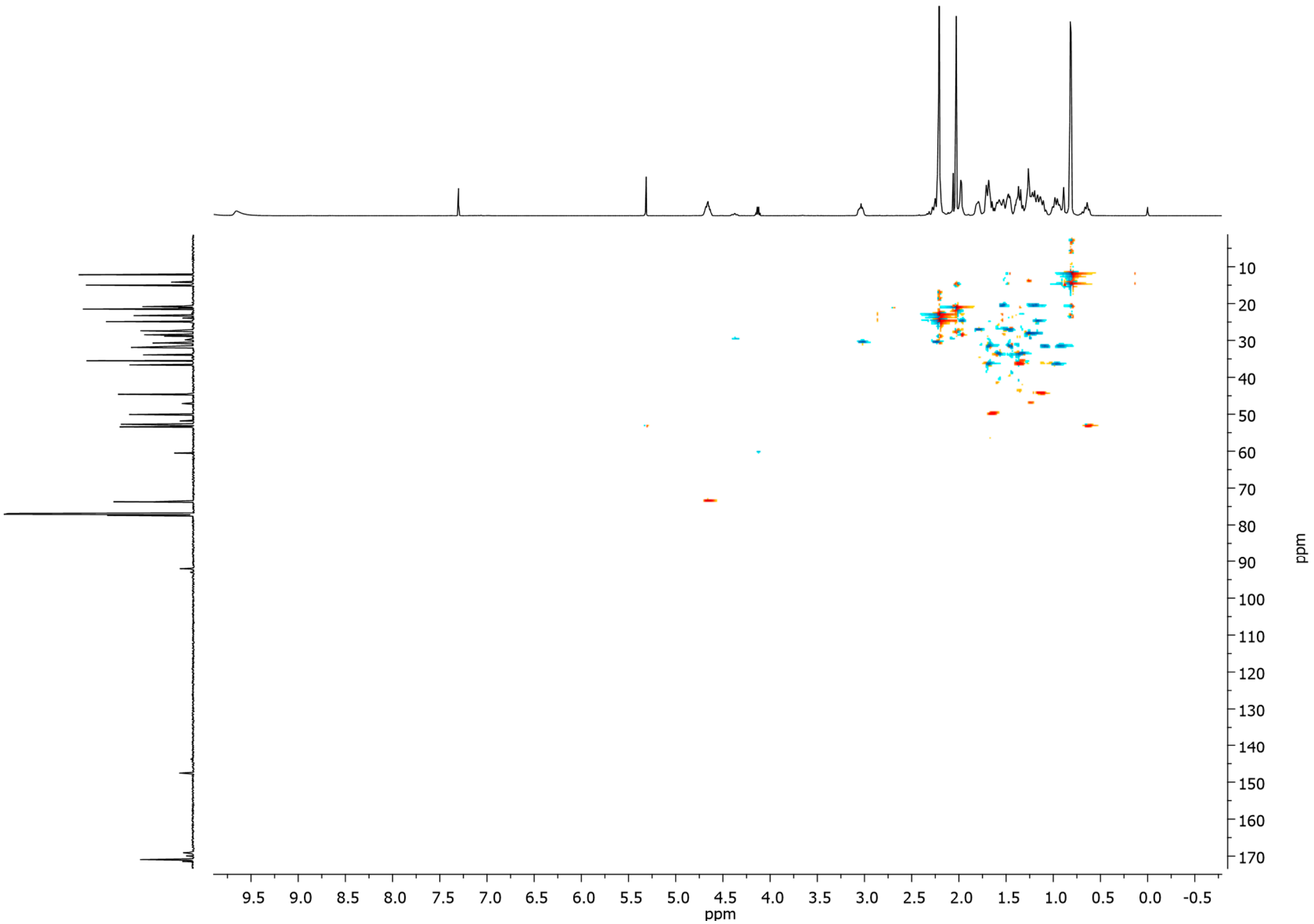
v

Figure S66. ^{13}C-NMR spectrum of **26** (125.7 MHz, $CDCl_3$)



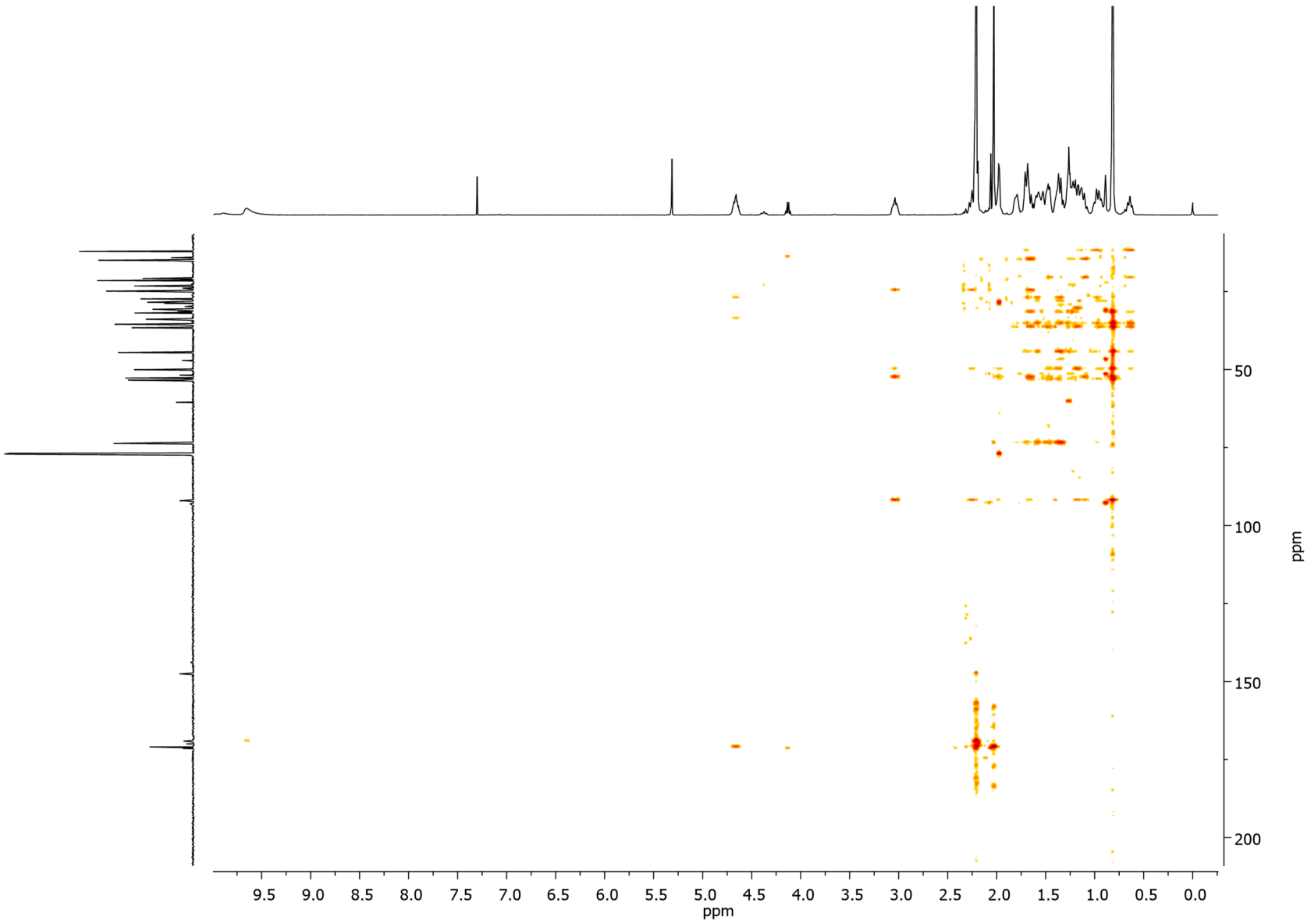
v

Figure S67. Experiment COSY of **26** (500 MHz, $CDCl_3$)



v

Figure S68. Experiment HSQC of **26** (500 MHz, $CDCl_3$)



v

Figure S69. Experiment HMBC of **26** (500 MHz, $CDCl_3$)

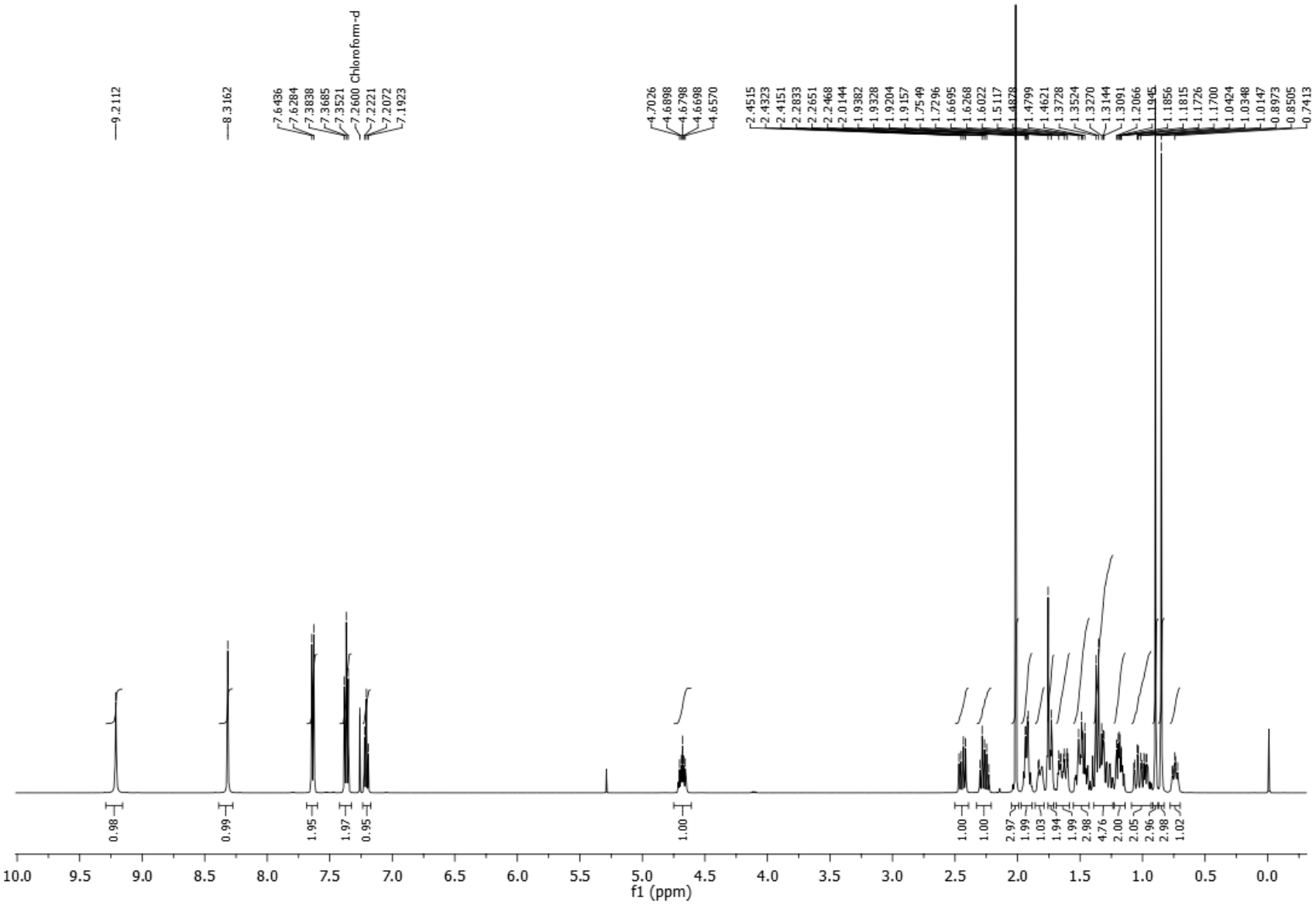


Figure S70. ^{1}H-NMR spectrum of **27** (500 MHz, $CDCl_3$)

v

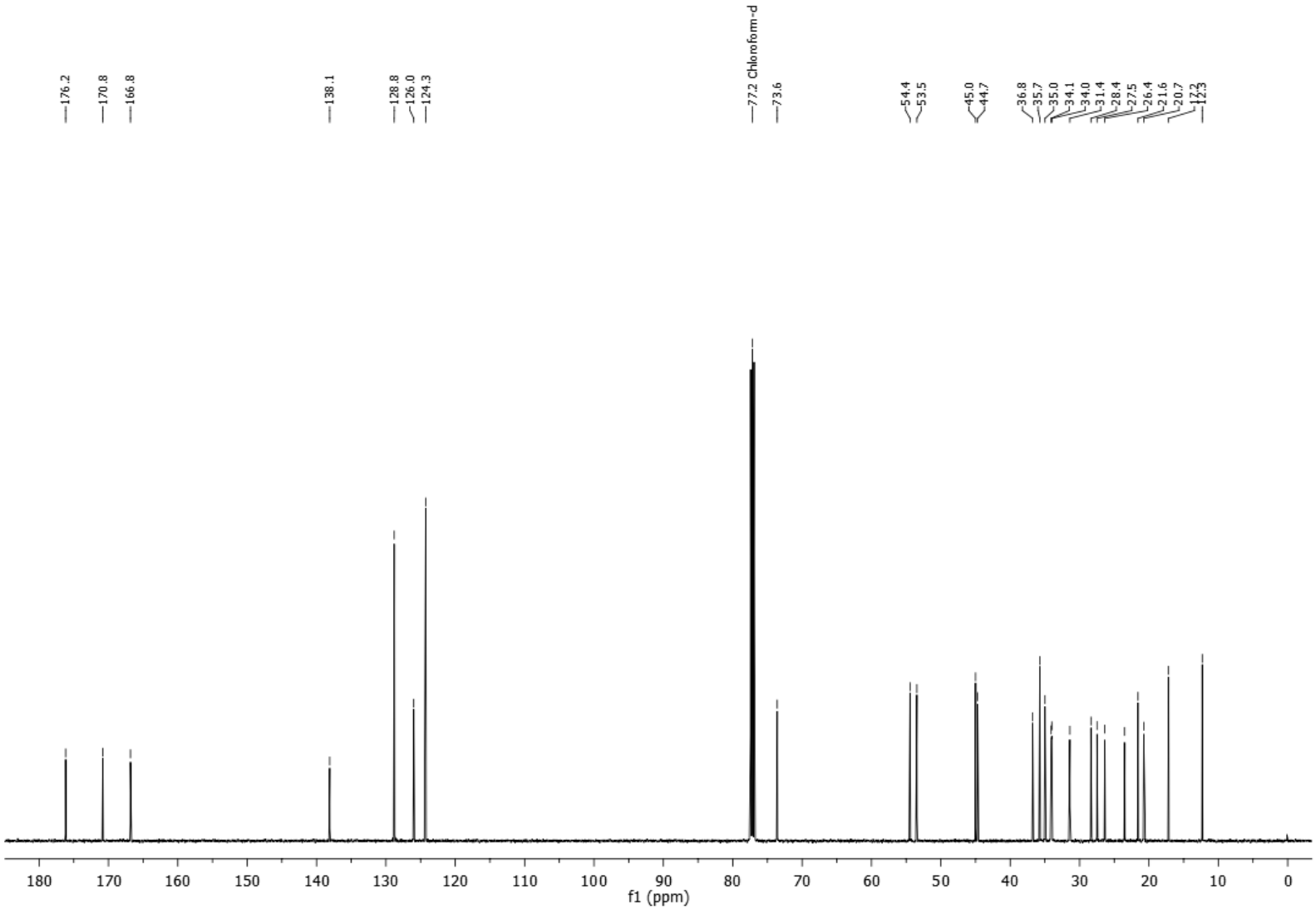


Figure S71. ^{13}C-NMR spectrum of **27** (125.7 MHz, $CDCl_3$)

v

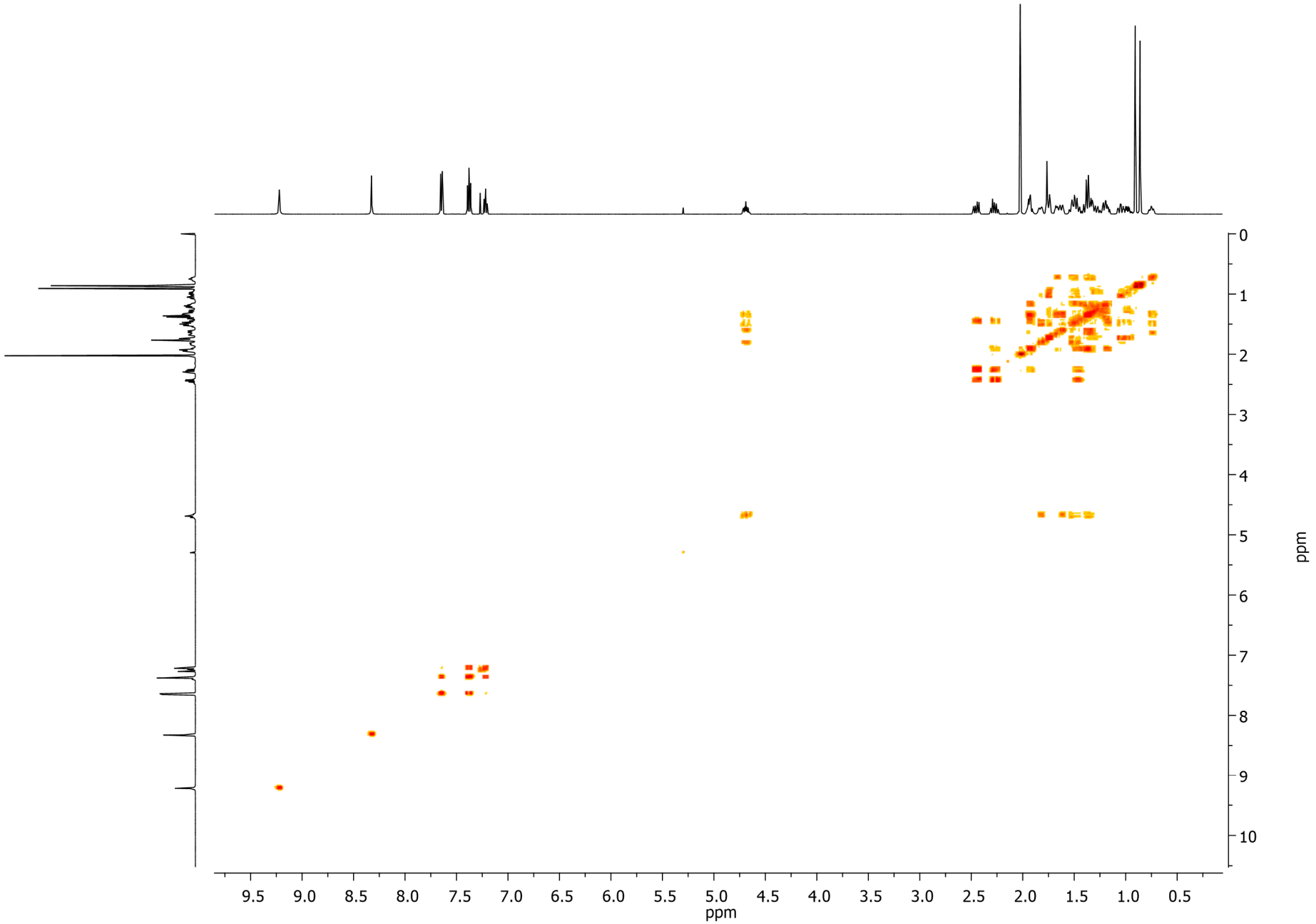


Figure S72. Experiment COSY of **27** (500 MHz, $CDCl_3$)

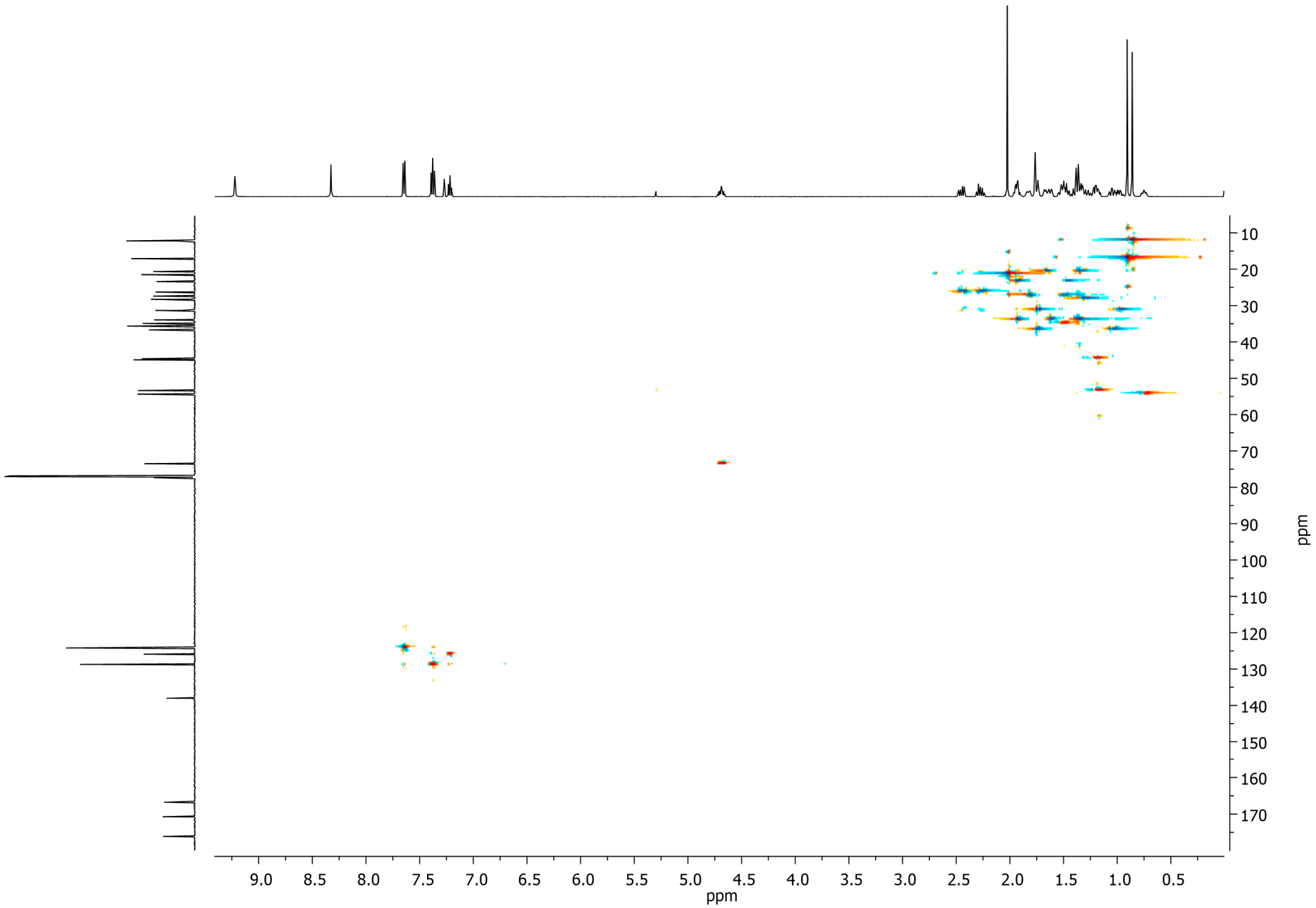


Figure S73. Experiment HSQC of **27** (500 MHz, $CDCl_3$)

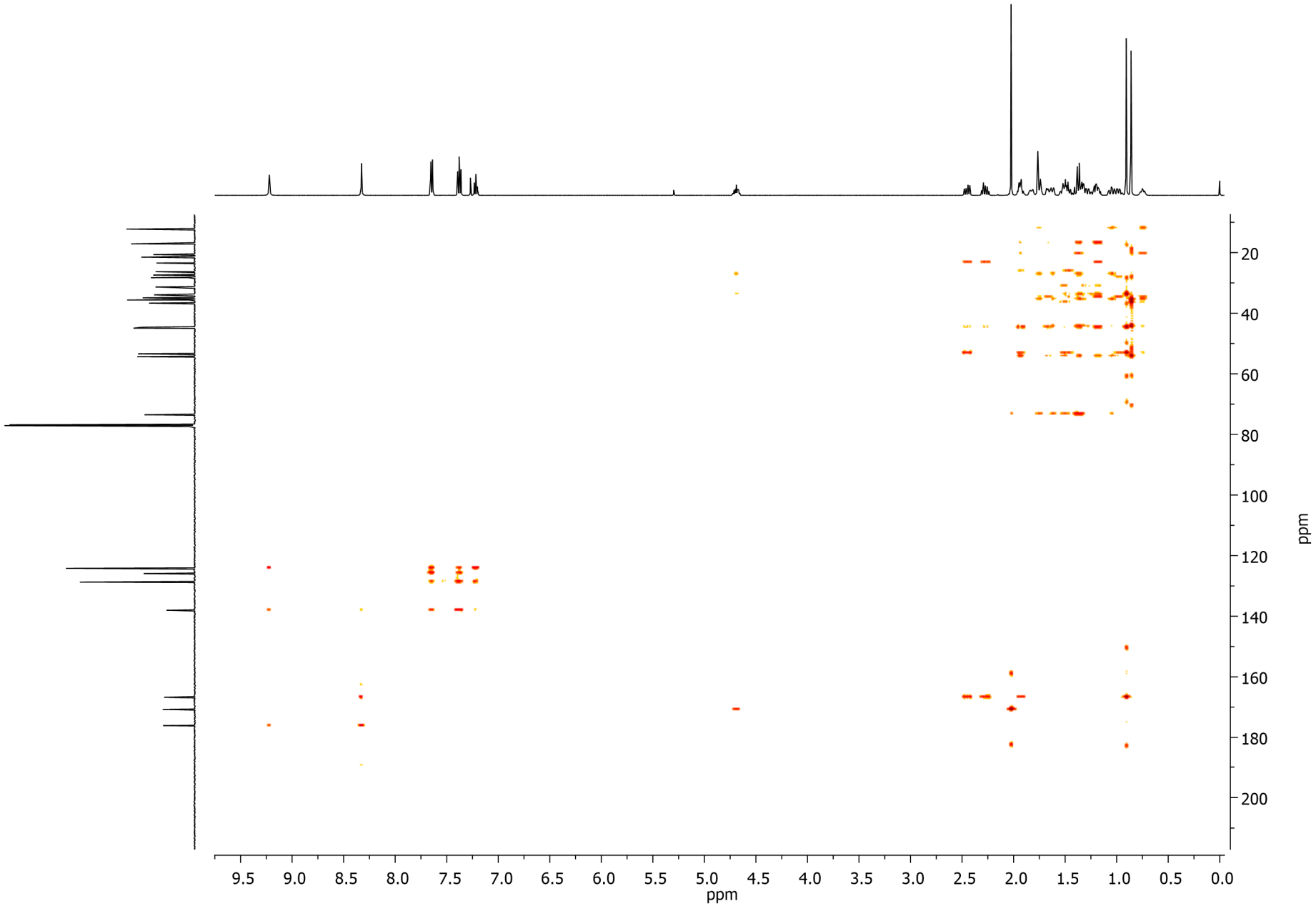


Figure S74. Experiment HMBC of **27** (500 MHz, $CDCl_3$)

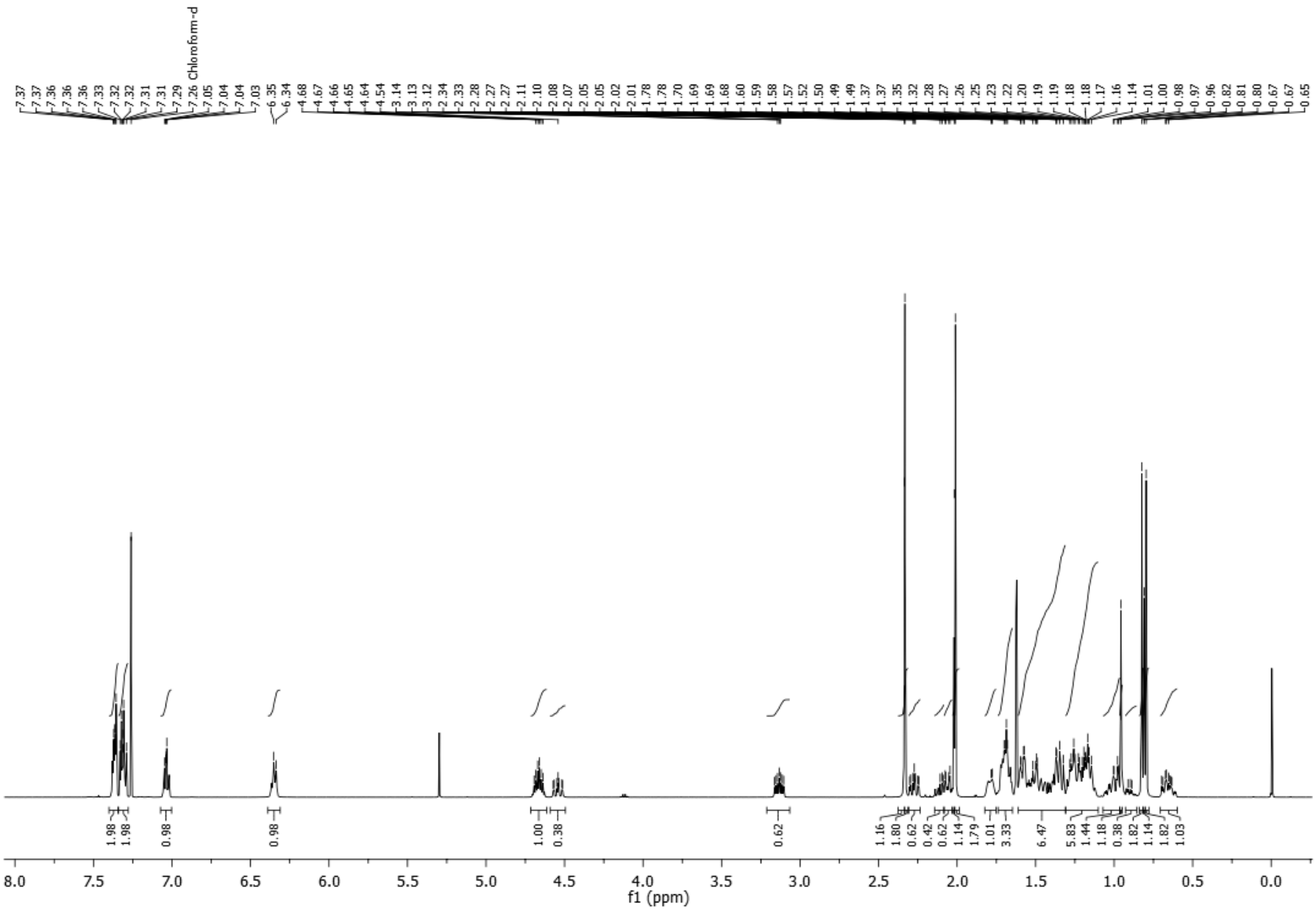


Figure S75. ^{1}H-NMR spectrum of **28** (500 MHz, $CDCl_3$)

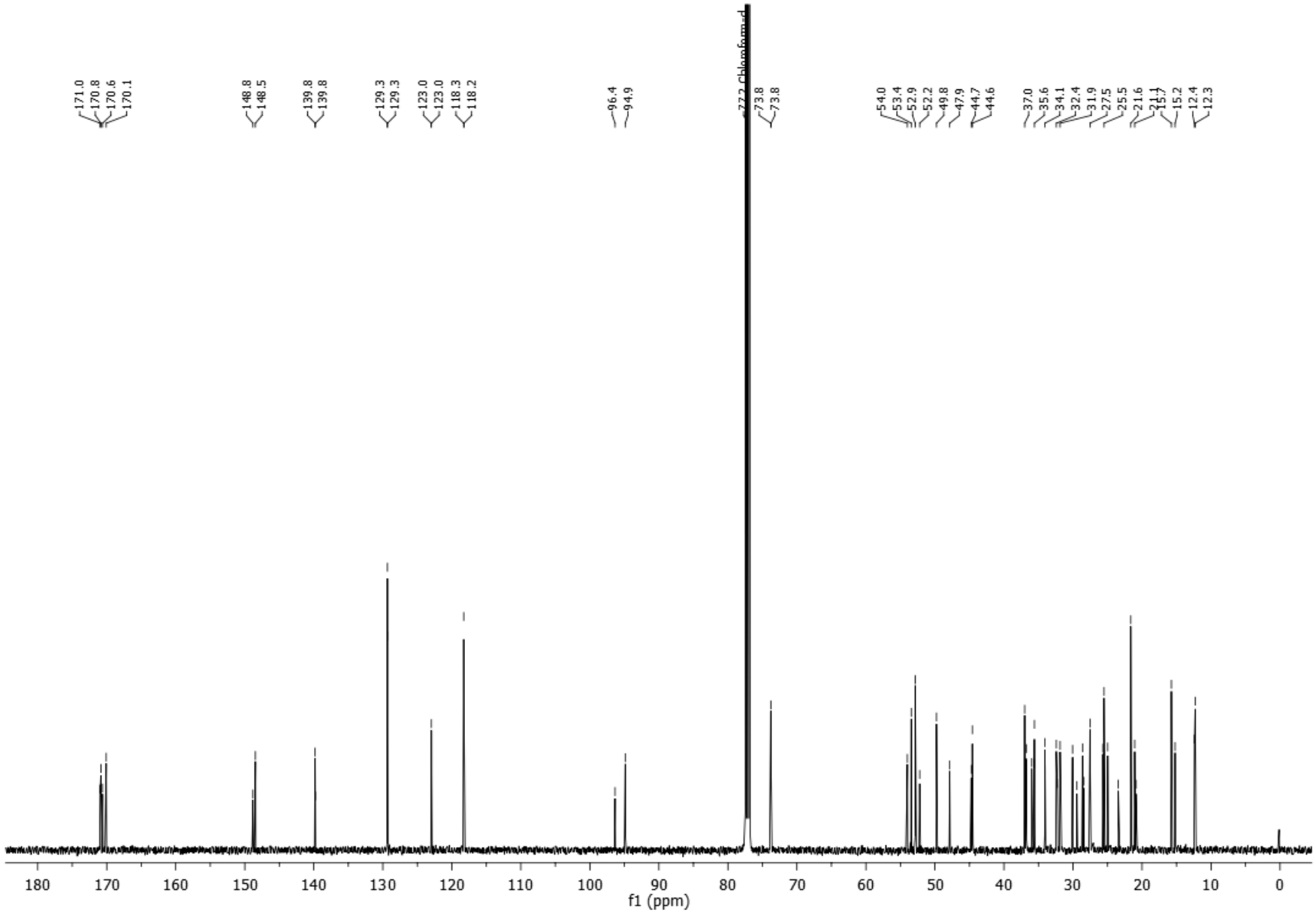


Figure S76. ^{13}C-NMR spectrum of **28** (125.7 MHz, $CDCl_3$)

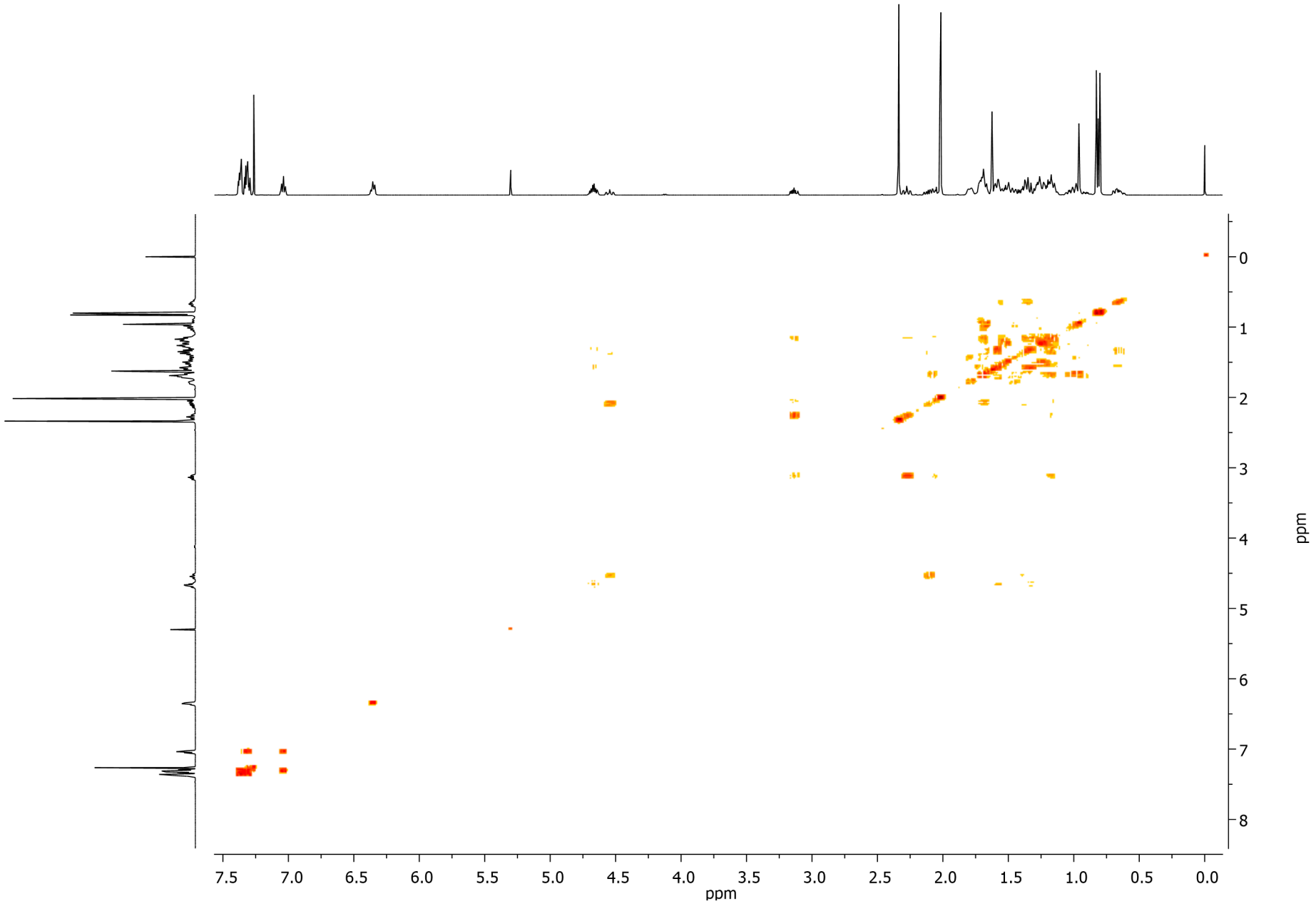


Figure S77. Experiment COSY of **28** (500 MHz, $CDCl_3$)

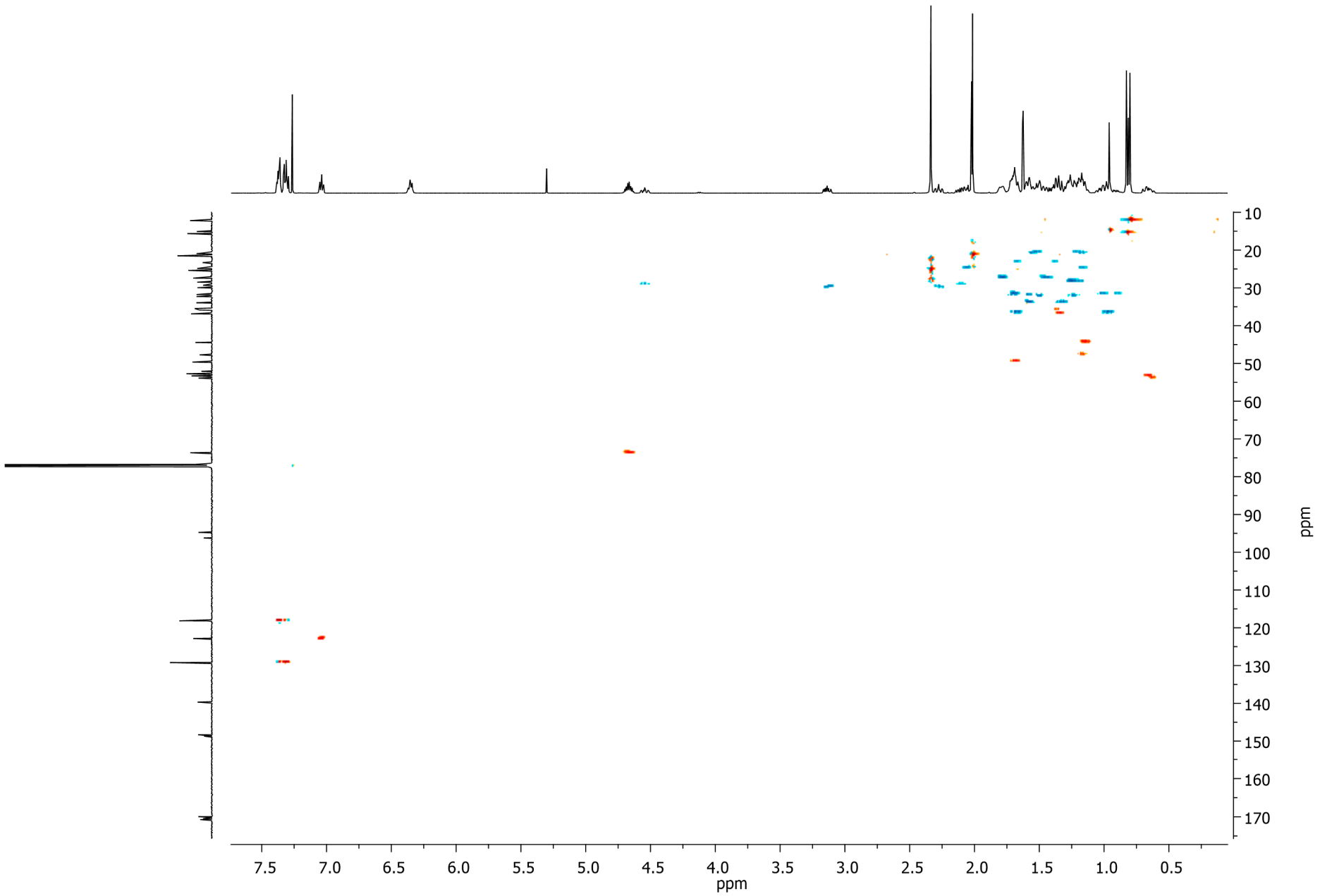


Figure S78. Experiment HSQC of **28** (500 MHz, $CDCl_3$)

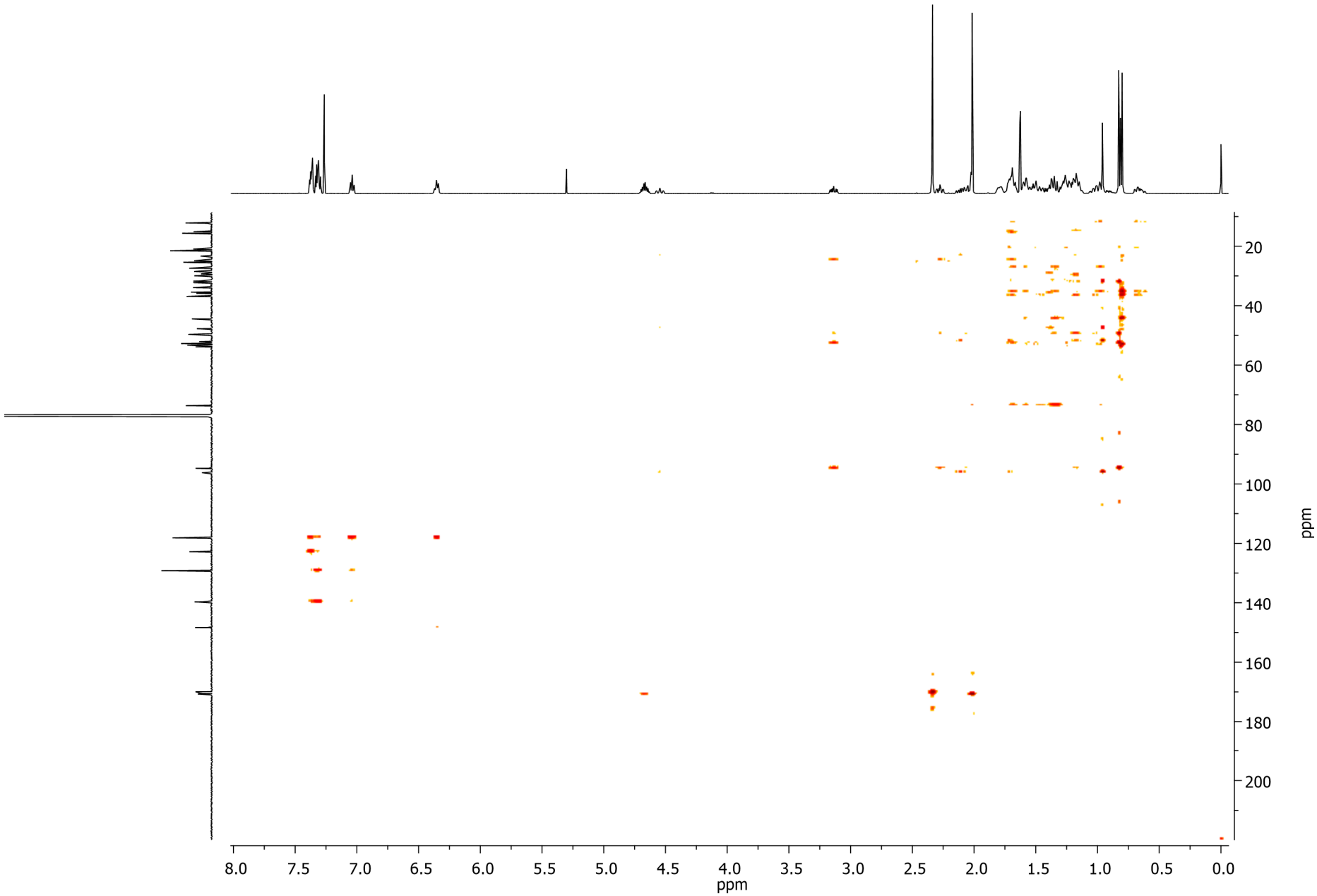


Figure S79. Experiment HMBC of **28** (500 MHz, $CDCl_3$)

Crystallography.

X-ray structures were refined with SHELXL, using standard procedures, giving the expected formulas. H atoms were systematically placed in idealized positions and refined as riding to their parent atoms, with the exception of H atoms bonded to heteroatoms. Isotropic displacement parameters for H atoms were calculated from the equivalent displacement parameters of their carrier atoms. Crystal data, data collection and refinement details are given in Table S1. Experimental X-ray intensities were deposited in the CSD, with the corresponding Cif files.

Table S1. Crystal data for compounds 2, 3, 5, 11, 17, 27, 28a and 28b.

	2	**3**	**5**
CCDC deposition	2222029	2222030	2222031
Formula	$C_{56}H_{82}O_8$, 0.32(CH_2Cl_2), 0.5(CH_3OH)	$C_{56}H_{86}O_8$	$C_{29}H_{46}O_4$
fw	926.41	887.24	458.66
Crystal size (mm^3)	$0.60 \times 0.10 \times 0.10$	$0.40 \times 0.25 \times 0.20$	$0.45 \times 0.42 \times 0.19$
Colour	colourless	colourless	colourless
Space group	$P2_1$	$P2_1$	$P2_1$
a, b, c (Å)	20.200(3), 7.3049(6), 36.768(4)	13.2801(5), 10.9502(3), 17.8833(6)	14.4564(10), 6.1140(2), 16.3025(10)
α, β, γ(°)	90, 90.849(10), 90	90, 105.854(3), 90	90, 110.500(5), 90
V ($Å^3$)	5424.8(10)	2501.66(15)	1349.67(14)
Z, Z'	4, 2	2, 1	2, 1
Diffractometer	Stoe Stadivari	Stoe Stadivari	Stoe Stadivari
Radiation	Ag Kα	Ag Kα	Ag Kα
T (K)	295(1)	295(1)	295(1)
Density ($g.cm^{-3}$)	1.134	1.178	1.129
Absorption coef. (mm^{-1})	0.063	0.049	0.047
Transmission factors	0.1783-1.000	0.5125-1.000	0.4791-1.000
Refl. collected	82511	79305	57507
Independent refl. (R_{int})	17428 (0.2928)	9438 (0.0495)	7268 (0.0766)
Obs. reflections [$I > 2\sigma$(I)]	4965	7490	4191
Senθ/λ ($Å^{-1}$)	0.60	0.61	0.69
Data/parameters/restraints	17428 / 1232 / 3	9438 / 622 / 83	7268 / 330 / 43
R_1, wR_2 [$I > 2\sigma$(I)]	0.0755, 0.1466	0.0455, 0.1188	0.0554, 0.1318
R_1, wR_2 [all data]	0.2680, 0.1931	0.0587, 0.1267	0.1003, 0.1509
Flack parameter	n.d.	n.d.	n.d.
GOF on F^2	0.801	0.981	0.997

Table S1 (cont.). Crystal data for compounds 2, 3, 5, 11, 17, 27, 28a and 28b.

	11	**17**	**27**
CCDC deposition	2222032	2222033	2222034
Formula	$C_{38}H_{53}N_3O_4S$	$C_{34}H_{46}N_3O_2S$, 0.5(H_2O)	$C_{28}H_{39}N_3O_2S$
fw	647.89	569.80	481.68
Crystal size (mm^3)	$0.20 \times 0.15 \times 0.10$	$0.60 \times 0.30 \times 0.10$	$0.60 \times 0.59 \times 0.14$
Colour	colourless	yellow	yellow
Space group	$P2_12_12_1$	$C2$	$P2_1$
a, b, c (Å)	6.2437(3), 15.4961(7), 37.593(2)	17.9705(10), 7.7329(3), 23.9530(12)	11.0763(5), 8.2484(6), 14.8398(7)
α, β, γ(°)	90, 90, 90	90, 100.194(4), 90	90, 96.149(4), 90
V ($Å^3$)	3637.2(3)	3276.1(3)	1347.99(13)
Z, Z'	4, 1	4, 1	2, 1
Diffractometer	Stoe Stadivari	Stoe Stadivari	Stoe Stadivari
Radiation	Ag Kα	Ag Kα	Ag Kα
T (K)	295(1)	295(1)	295(1)
Density ($g.cm^{-3}$)	1.183	1.155	1.187
Absorption coef. (mm^{-1})	0.076	0.077	0.085
Transmission factors	0.2757-1.000	0.2604-1.000	0.3324-1.000
Refl. collected	40213	33190	36535
Independent refl. (R_{int})	6260 (0.1703)	6180 (0.0459)	6729 (0.0438)
Obs. reflections [$I > 2\sigma$(I)]	2500	4066	4070
Senθ/λ ($Å^{-1}$)	0.60	0.60	0.68
Data/parameters/restraints	6260 / 434 / 0	6180 / 400 / 319	6729 / 316 / 1
R_1, wR_2 [$I > 2\sigma$(I)]	0.0620, 0.1285	0.0478, 0.1225	0.0378, 0.0886
R_1, wR_2 [all data]	0.1725, 0.1600	0.0775, 0.1353	0.0736, 0.1035
Flack parameter	n.d.	n.d.	0.07(5)
GOF on F^2	0.819	0.956	0.923

Table S1 (cont.). Crystal data for compounds 2, 3, 5, 11, 17, 27, 28a and 28b.

	28a	**28b**
CCDC deposition	2222035	2222036
Formula	$C_{30}H_{41}N_3O_3S$, (H_2O)	$C_{30}H_{41}N_3O_3S$, 0.5(C_5H_5N), H_2O
fw	541.73	581.28
Crystal size (mm^3)	$0.55 \times 0.15 \times 0.04$	$0.26 \times 0.17 \times 0.04$
Colour	colourless	colourless
Space group	$P1$	$C2$
a, b, c (Å)	6.4081(6), 6.9733(8), 16.9023(17)	15.5236(10), 13.0122(6), 17.7615(11)

α, β, γ(°)	81.947(9), 82.999(8), 78.013(8)	90, 113.869(5), 90
V (Å^3)	728.17(13)	3280.9(3)
Z, Z'	1, 1	4, 1
Diffractometer	Stoe Stadivari	Stoe Stadivari
Radiation	Ag Kα	Ag Kα
T (K)	295(1)	295(1)
Density (g.cm^{-3})	1.235	1.177
Absorption coef. (mm^{-1})	0.086	0.079
Transmission factors	0.1626 -1.000	0.4119-1.000
Refl. collected	13017	36854
Independent refl. (R_{int})	4816 (0.0648)	6490 (0.1395)
Obs. reflections [$I > 2\sigma$(I)]	2540	2521
Senθ/λ (Å^{-1})	0.62	0.62
Data/parameters/restraints	4816 / 356 / 3	6490 / 383 / 17
R_1, wR_2 [$I > 2\sigma$(I)]	0.0444, 0.0753	0.0412, 0.0650
R_1, wR_2 [all data]	0.0929, 0.0852	0.1237, 0.0752
Flack parameter	-0.02(15)	-0.08(16)
GOF on F^2	0.771	0.678

Compound 2. This dimeric compound crystallizes with two molecules per asymmetric unit (Z' = 2) and was a poorly scattering sample. Moreover, it crystallizes with lattice solvent molecules: 0.32 CH2Cl2 and 0.50 CH3OH per steroid molecule, and the methanol is disordered over two sites (occupancy factors: 0.5 and 0.5). As a consequence, Rint residual is rather high (29%), however, the structure was refined properly, affording the expected molecular geometry. The geometry for the disordered methanol molecule was refined with the C–O bond lengths restrained to 1.45(2) Å. The steroid molecule (Fig. S1) includes a central (C2O4)2- oxalate group displaying a s-trans conformation. Both crystallographically independent molecules have the same geometry, and have a length of ca. 37 Å.

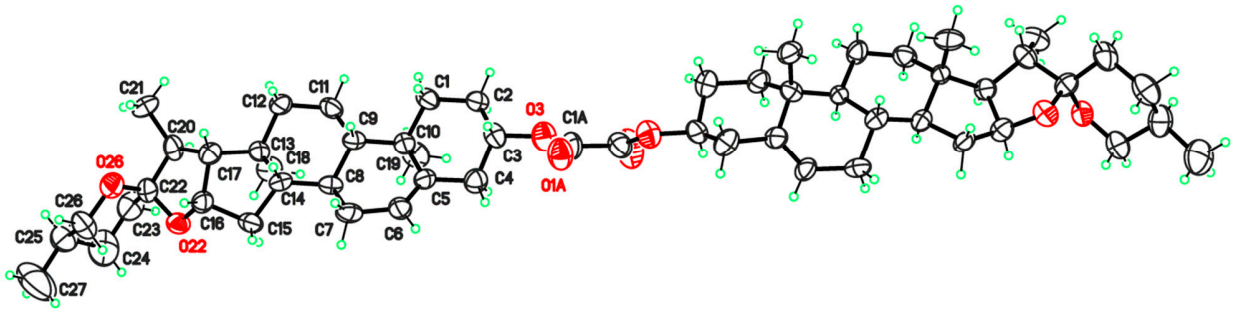


Fig. S80: ORTEP view (30% probability level) of one molecule in the asymmetric unit of compound **2**.

Compound 3. This compound is similar to the previous compound **2**, with diosgenin replaced by a derivative with the 26-hydroxylated side-chain (Fig. S2). However, in the case of this dimer, the oxalate bridge is configured *s-cis*. The molecule crystallizes in the monoclinic system with *Z*' = 1. One side chain is disordered over two sites [C74A/C76A/O8A/C77A and C74B/C76B/O8B/C77B; refined occupancies: 0.589(10) and 0.411(10)]. This disordered part was refined with restrained bond lengths: C73–C74(A/B) and C74(A/B) –C75 = 1.52(2) Å; C75–C76(A/B) = 1.50(2) Å; C75–C77(A/B) = 1.53(2) Å; C76(A/B)–O8(A/B) = 1.46(2) Å. Moreover, rigid bond restraints (RIGU) were applied for this disordered part, with esd's of 0.004 Å for 1,2 and 1,3 distances. Finally, O8A and O8B were restrained to have similar anisotropic displacement parameters (SIMU), with effective standard deviation of 0.04 Å^2. The total length of the molecule is, as for **2**, close to 37 Å.

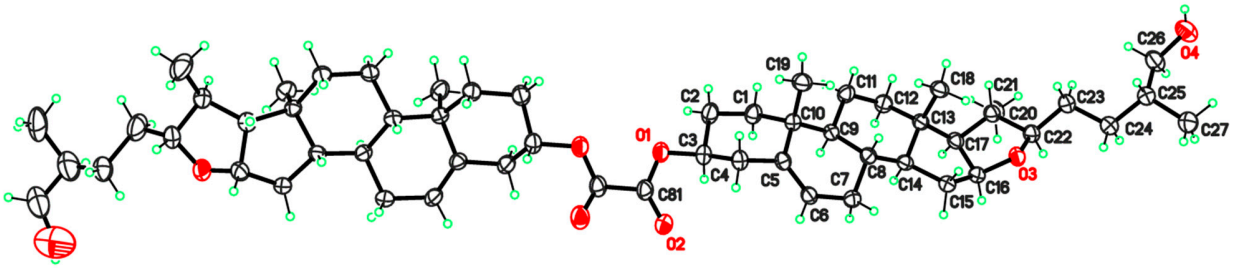


Fig. S81: ORTEP view (30% probability level) of compound **3**. The disorder in one side chain is omitted for clarity.

Compound 5. This compound crystallizes with one molecule in the asymmetric unit (Fig. S3). The side chain is disordered over two sites [C26A/C27A/O27A and C26B/C27B/O27B; occupancies: 0.618(9) and 0.382(9)]. For these disordered atoms, rigid bond restraints (RIGU) were applied with esd's of 0.004 Å for 1,2 and 1,3 distances. Additionally, all disordered atoms were restrained to have similar anisotropic displacement parameters (SIMU), with effective standard deviation of 0.04 Å^2.

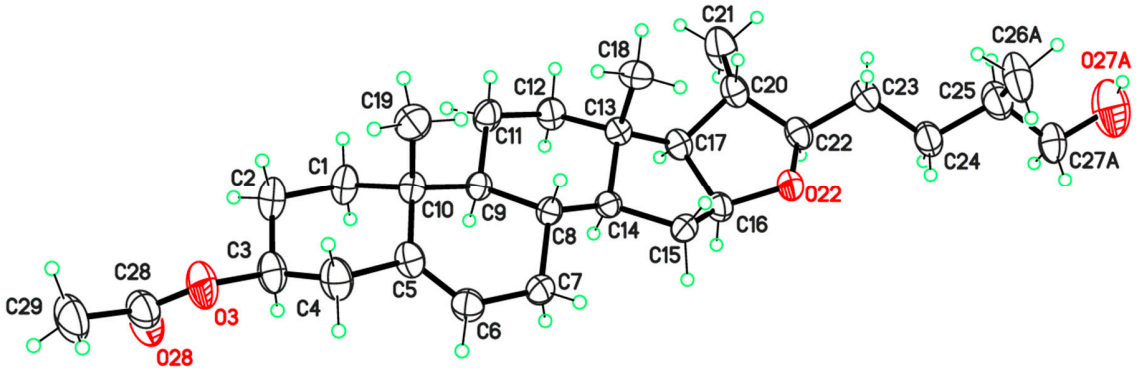


Fig. S82: ORTEP view (30% probability level) of compound **5**. The disorder in the side chain on ring *E* is omitted for clarity.

Compound 11. The orthorhombic unit cell of this compound contains one molecule per asymmetric unit (Fig. S6). Only one site is disordered, namely the acetyl O atom (O37) at position C3 on the steroidal nucleus. This atom was modelled using two sites, O37A and O37B, with occupancies 0.35(7) and 0.65(7).

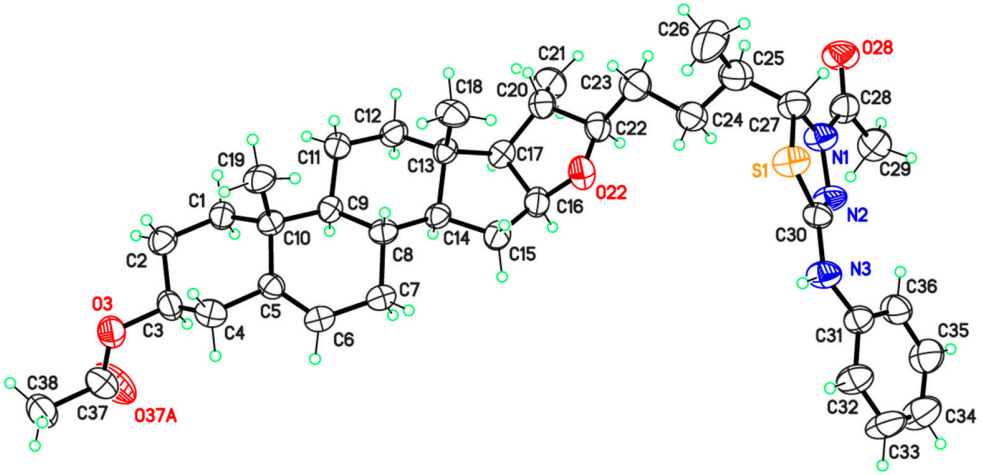


Fig. S83: ORTEP view (30% probability level) of compound **11**. The disordered atom O37B was omitted for clarity.

Compound 17. This derivative crystallizes in the *C*2 space group, as a hemihydrate. The water molecule is placed on the two-fold axis of space group *C*2. At room temperature, there is one molecule in the asymmetric unit, however, a phase transition has been observed at low temperature, to give a crystal structure with six independent molecules in the asymmetric unit, with no modification of the crystal symmetry. This possibly reversible phase transition will be reported in due course in a journal devoted to crystallography. At 295 K, the phenyl ring of the thiosemicarbazone group is equally disordered over two positions (see Fig. S4), by rotation about the N3–C29 bond. The displacement parameters for C atoms in the disordered part were refined with RIGU/SIMU/ISOR standard SHELXL restraints, and the geometry of the phenyl rings was constrained to fit an ideal regular hexagon with *d* = 1.39 Å (AFIX 66).

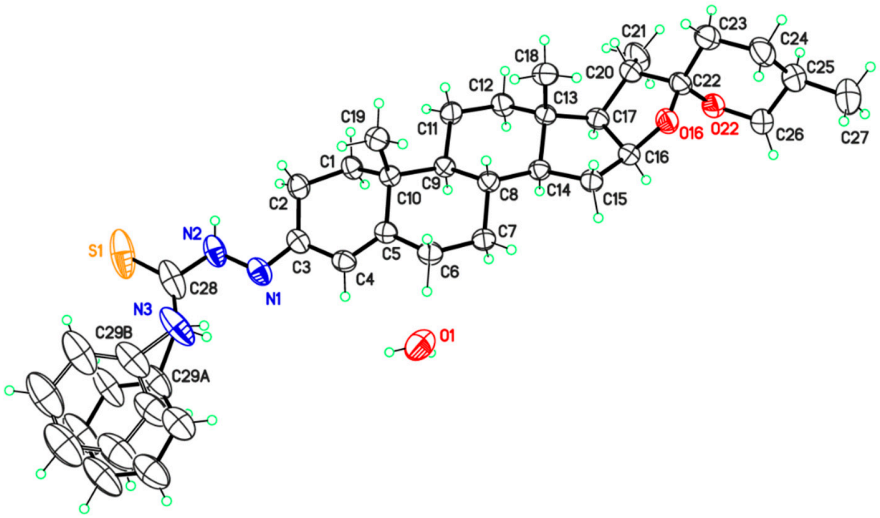


Fig. S84: ORTEP view (30% probability level) of compound **17**.

Compound 27. This molecule crystallizes in space group $P2_1$, with Z' = 1, and no evidences for disorder were observed during the refinement (Fig. S5). The presence of one S anomalous scattering atom allowed the refinement of a Flack parameter, x = 0.07(5), which is in agreement with the expected chirality of the steroid.

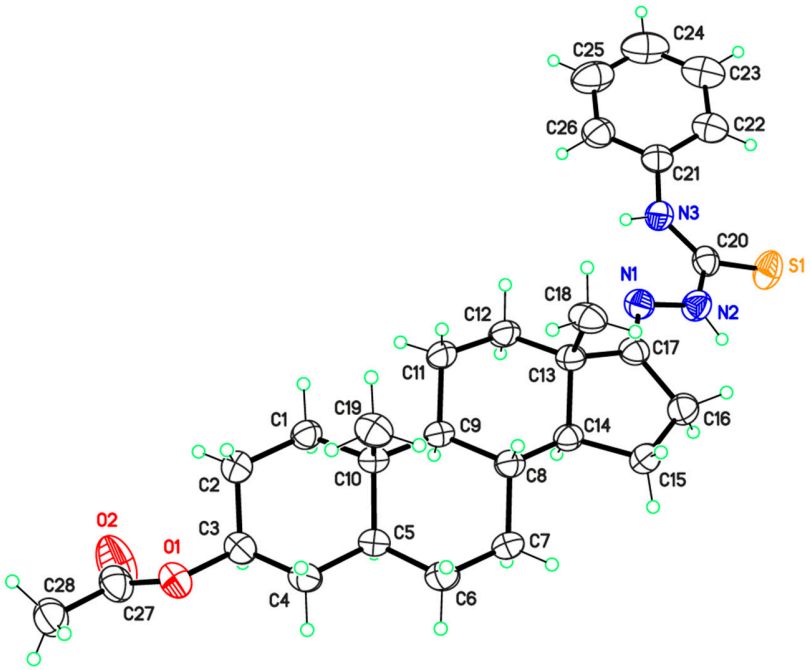


Fig. S85: ORTEP view (30% probability level) of compound **27**.

Compounds 28a and 28b. This epimeric pair at spiro site C17 afforded single crystals for each epimer. The first one, **34a**, crystallizes as a hydrate in space group *P*1, with one molecule in the unit cell (Fig. S7, left), while epimer **34b** crystallizes in space group *C*2 (Fig. S7, right), with lattice solvent: half a pyridine molecule, disordered by symmetry through the two-fold axis in space group *C*2, and one water molecule, in general position. The pyridine molecule was refined with restrained bond lengths (DFIX) and rigid bond restraints (RIGU), in order to achieve a sensible geometry and displacement parameters. Otherwise, refinements were carried out with free geometry for both epimers.

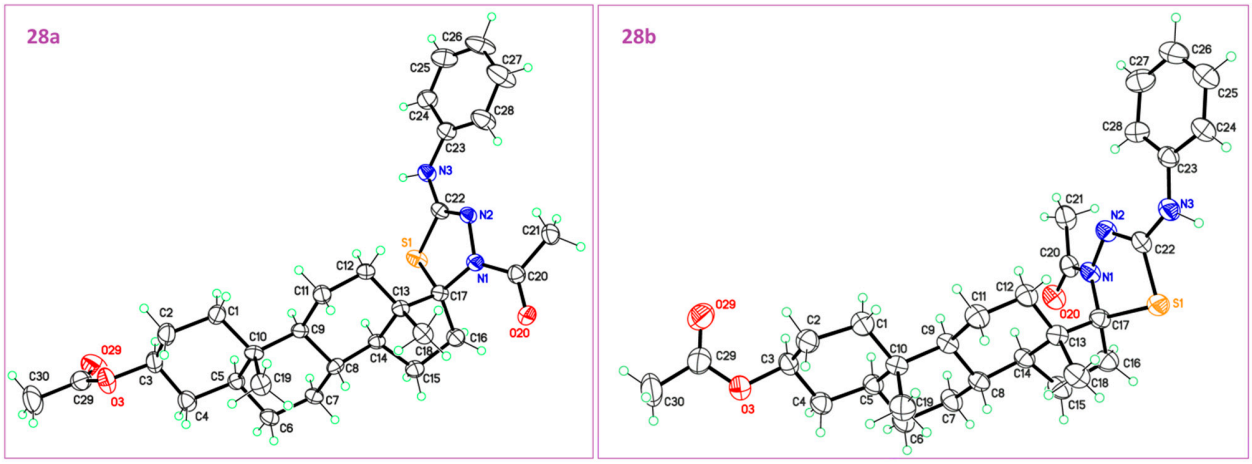


Fig. S86: ORTEP views (30% probability level) of compounds 28a (left) and 28b (right). Lattice solvent molecules are omitted for clarity.