pharmaceutics

MDPI

Supplementary Materials: Membrane Permeability and Aqueous Stability Study of Linear and Cyclic Diarylheptanoids from *Corylus maxima*

Csenge Anna Felegyi-Tóth, Zsófia Tóth, Zsófia Garádi, Imre Boldizsár, Andrea Nagyné Nedves, Alexandra Simon, Kristóf Felegyi, Ágnes Alberti and Eszter Riethmüller

Table S1. UHPLC-DAD method validation: linearity, LOD and LOQ values.

Compound	Regression Equation	Weight Factor	R^2	Regression Range (μM)	LOD (μM)	LOQ (μM)
hirsutanonol-5-*O*-β-D-glucopyranoside (**1**)	y=2203.16x−495.38	$1/x^2$	0.9999	0.5-100	0.14	0.45
oregonin (**2**)	y=4417.70x−555.09	-	1.0000	0.5-100	0.12	0.4
hirsutenone (**3**)	y=27927.05x+1536.21	-	0.9996	0.5-100	0.04	0.13
platyphyllonol-5-*O*-β-D-xylopyranoside (**4**)	y=1073.90x+22.67	$1/x^2$	0.9994	0.5-100	0.15	0.5
platyphyllenone (**5**)	y=14650.51x−1011.18	$1/x^2$	0.9999	0.5-100	0.05	0.15
alnusonol-11-*O*-β-D-glucopyranoside (**6**)	y=6145.06−710.82	$1/x^2$	1.0000	0.5-100	0.03	0.1
alnusone (**7**)	y=6217.00x+125.05	-	1.0000	0.5-100	0.03	0.1
myricitrin (**11**)	y=20978.24x−1489.97	$1/x^2$	0.9994	0.5-100	0.02	0.05

Table S2. UPLC-DAD system suitability tests: Precision and accuracy.

Nominal conc. (μM)	Precision (RSD%)		Accuracy (%)	
	Intraday	Interday	Intraday	Interday
hirsutanonol-5-*O*-β-D-glucopyranoside (1)				
100	0.13	0.73	100.42	99.63
10	0.93	1.83	100.96	100.67
0.5	0.66	2.65	99.89	111.35
oregonin (2)				
100	0.77	0.99	100.03	99.75
10	0.96	2.03	102.15	103.43
0.5	2.56	2.84	101.96	112.56
hirsutenone (3)				
100	0.05	2.09	101.82	110.28
10	0.3	1.84	96.92	95.60
0.5	0.6	1.55	100.12	100.63
platyphyllonol-5-*O*-β-D-xylopyranoside (4)				
100	0.11	0.18	101.53	101.73
10	0.46	0.56	98.72	103.36
0.5	2.12	4.94	96.97	106.8
platyphyllenone (5)				
100	1.18	1.84	105.14	107.2
10	0.91	3.06	93.69	94.16
0.5	3.48	8.45	103.96	101.51
alnusonol-11-*O*-β-D-glucopyranoside (6)				
100	0.46	0.52	98.86	104.05
10	0.56	2.44	100.62	108.99
0.5	1.74	2.32	98.61	109.28
alnusone (7)				
100	0.18	0.33	100.47	100.78
10	0.19	0.42	101.20	99.17
0.5	6.69	8.74	101.78	103.14

myricitrin (11)				
100	0.80	1.91	100.79	103.54
10	0.49	2.14	102.56	105.61
0.5	5.71	8.24	99.01	116.82

NMR data of compound **1** (hirsutanolol-5-*O*-β-D-glucopyranoside): ^{1}H NMR (DMSO-d_6, 600 MHz, 295 K): δ 6.60 (m, 2H, H-5′, H-5″), 6.59 (m, 1H, H-2″), 6.56 (d, $^{4}J_{H,H}$=2.0 Hz, 1H, H-2′), 6.43 (dd, $^{3}J_{H,H}$=8.0 Hz, $^{4}J_{H,H}$=2.0 Hz, 1H, H-6″), 6.40 (dd, $^{3}J_{H,H}$=8.0 Hz, $^{4}J_{H,H}$=2.0 Hz, 1H, H-6′), 4.16 (d, $^{3}J_{H,H}$=7.8 Hz, 1H, H_{Glc}-1), 4.04 (m, 1H, H-5), 3.69 (dd, $^{2}J_{H,H}$=11.6 Hz, $^{3}J_{H,H}$=1.6 Hz, 1H, H-Glc-6a), 3.47 (dd, $^{2}J_{H,H}$=11.6 Hz, $^{3}J_{H,H}$=5.3 Hz, 1H, H_{Glc}-6b), 3.13 (t, $^{3}J_{H,H}$=8.6 Hz, 1H, H_{Glc}-3), 3.08 (m, 1H, H_{Glc}-5), 3.06 (m, 1H, H_{Glc}-4), 2.91 (t, $^{3}J_{H,H}$=8.6 Hz, 1H, H_{Glc}-2), 2.75 (dd, $^{2}J_{H,H}$=16.3 Hz, $^{3}J_{H,H}$=6.3 Hz, 1H, H-4a), 2.69 (m, 2H, H-2), 2.56 (m, 1H, H-4b), 2.45 (m, 1H, H-7a), 2.42 (m, 1H, H-7b), 1.68 (m, 1H, H-6a), 1.62 (m, 1H, H-6b). ^{13}C NMR (DMSO-d_6, 150 MHz, 295 K): δ 209.3 (C-3), 145.3 (C-3″), 145.2 (C-3′), 143.5 (C-4′), 143.3 (C-4″), 133.1 (C-1″), 132.1 (C-1′), 119.1 (C-6″), 118.9 (C-6′), 116.1 (C-2″), 115.9 (C-2′), 115.7 (C-5′, C-5″), 101.9 (C_{Glc}-1), 77.1 (C_{Glc}-5), 77.0 (C_{Glc}-3), 74.3 (C-5), 73.7 (C_{Glc}-2), 70.2 (C_{Glc}-4), 61.4 (C_{Glc}-6), 47.4 (C-4), 45.0 (C-2), 37.3 (C-6), 30.4 (C-7), 28.6 (C-1).

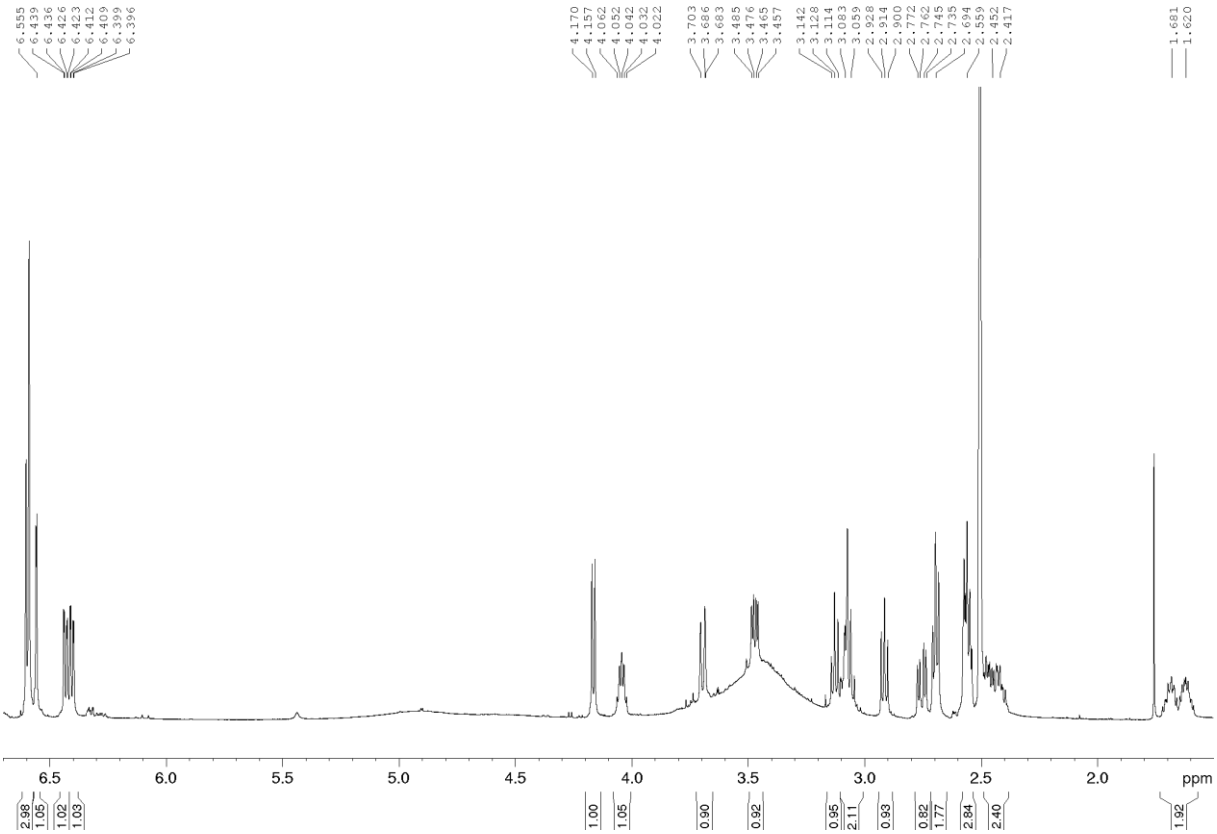

Figure S1. ^{1}H NMR spectrum of hirsutanolol-5-*O*-β-D-glucopyranoside (**1**) (DMSO-d_6, 295 K).

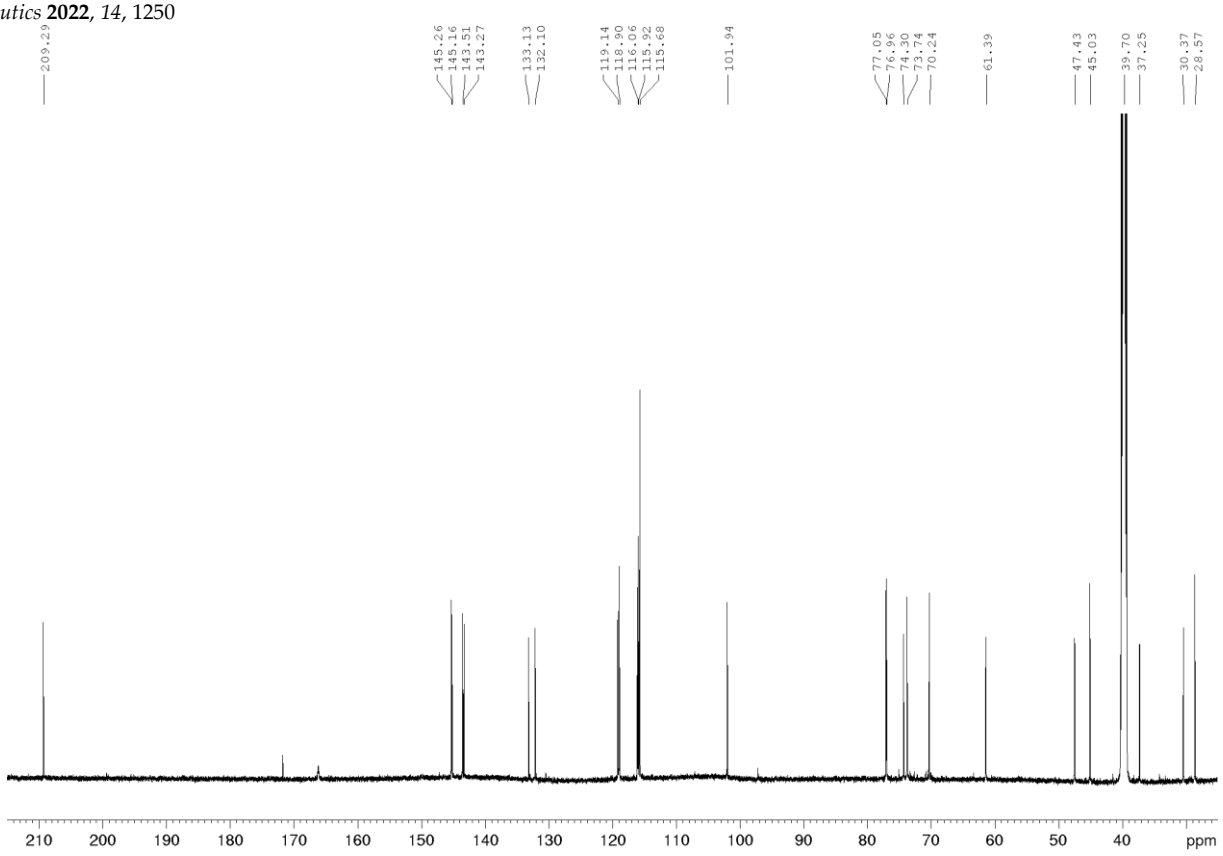

Figure S2. ^{13}C NMR spectrum hirsutanolol-5-*O*-β-D-glucopyranoside (**1**) (DMSO-d_6, 295 K).

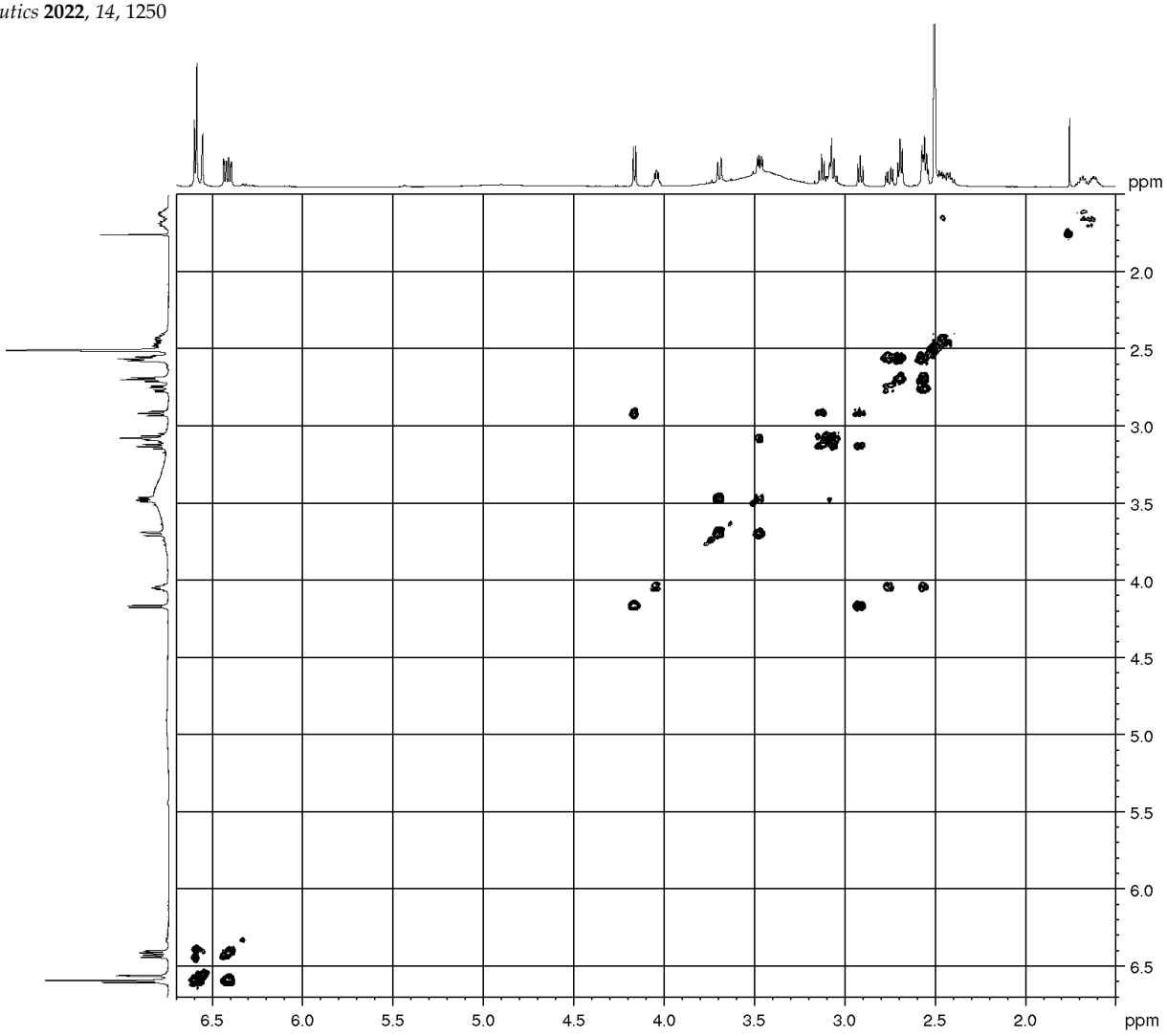

Figure S3. COSY spectrum of hirsutanolol-5-*O*-β-D-glucopyranoside (**1**) (DMSO-d_6).

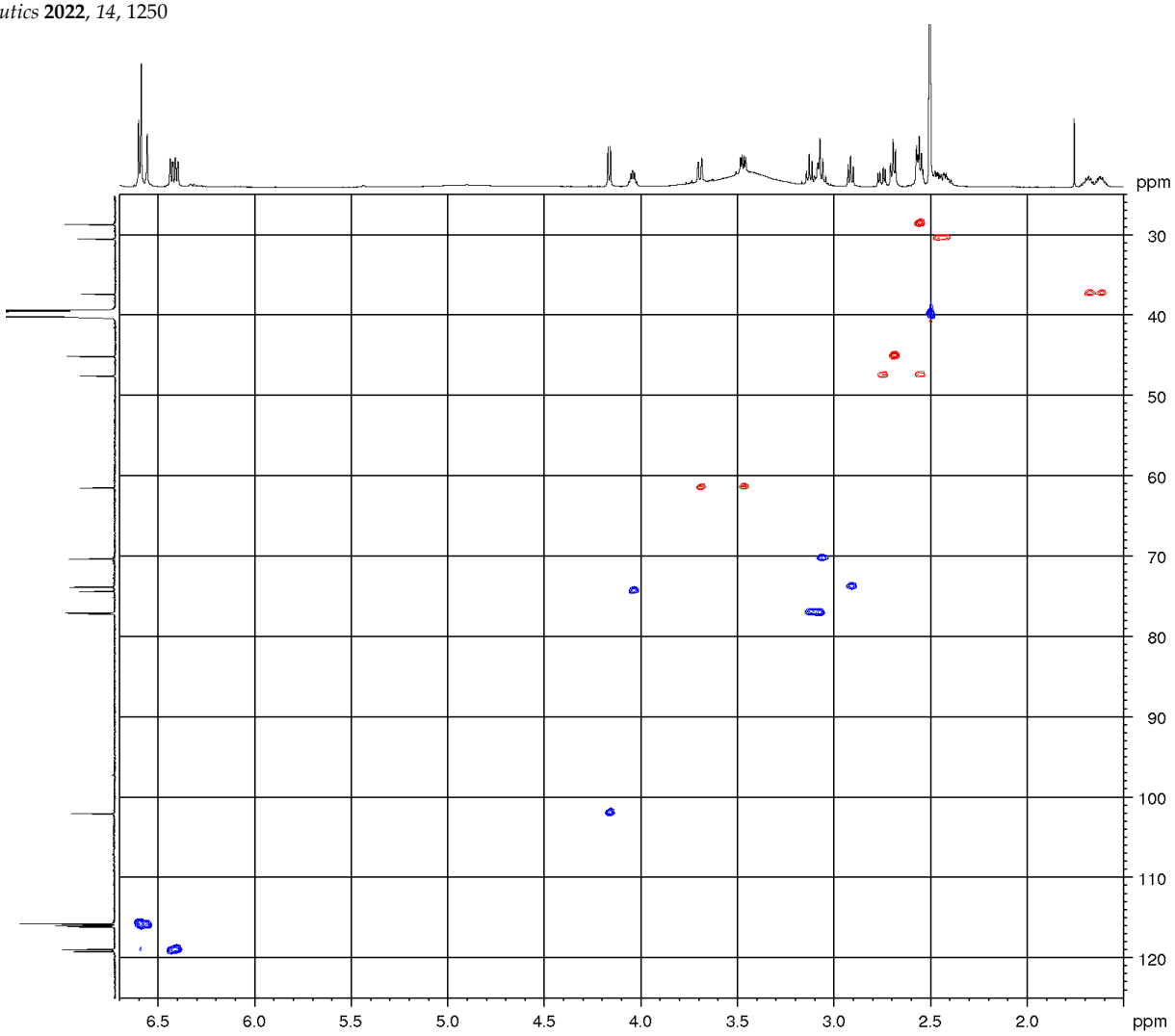

Figure S4. HSQC spectrum of hirsutanolol-5-*O*-β-D-glucopyranoside (**1**) (DMSO-d_6, 295 K).

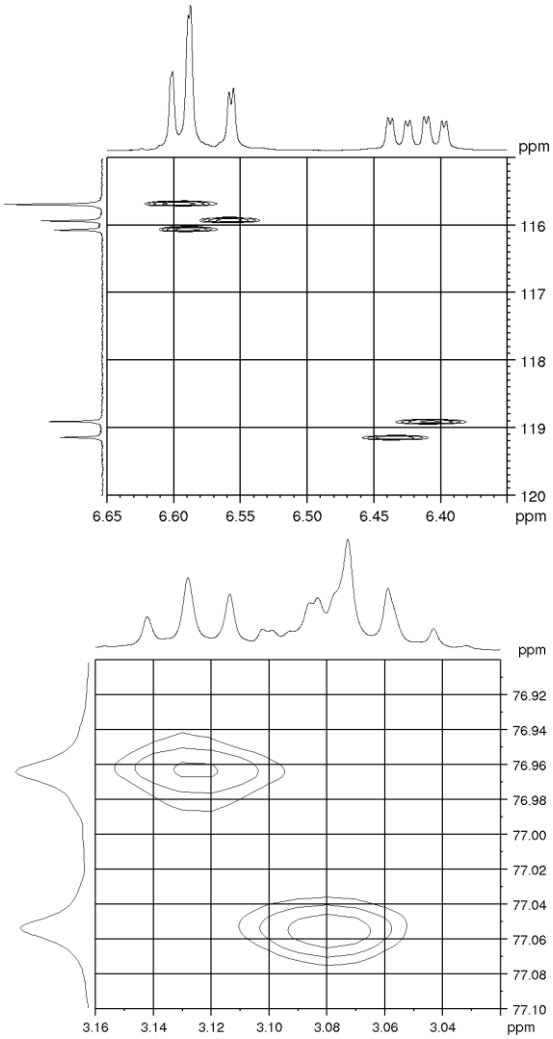

Figure S5. Band Selective HSQC spectra of hirsutanolol-5-*O*-β-D-glucopyranoside (**1**) (DMSO-d_6, 295 K).

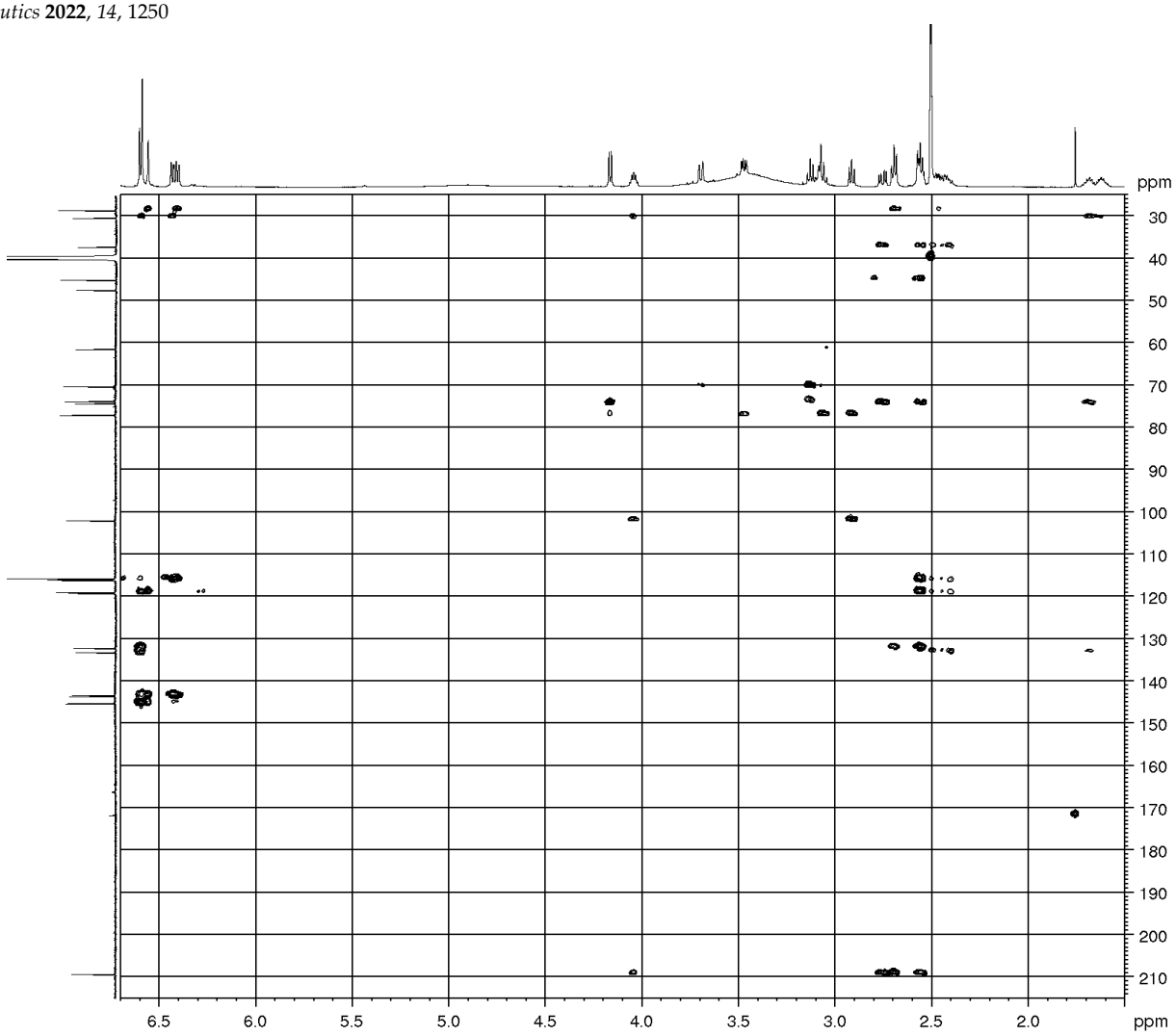

Figure S6. HMBC spectrum of hirsutanolol-5-*O*-β-D-glucopyranoside (**1**) (DMSO-d_6, 295 K).

NMR data of compound **4** (platyphyllonol-5-*O*-β-D- xylopyranoside): ^{1}H NMR (DMSO-d_6, 600 MHz, 295 K): δ 9.14 (m, 2H, OH-4′, OH-4″), 6.97 (~d, $^{3}J_{H,H}$=8.5 Hz, 2H, H-2′, H-6′), 6.94 (~d, $^{3}J_{H,H}$=8.5 Hz, 2H, H-2″, H-6″), 6.64 (m, 4H, H-3′, H-5′, H-3″, H-5″), 4.94 (m, 3H, OH_{Xyl}-2, OH_{Xyl}-3, OH_{Xyl}-4), 4.12 (d, $^{3}J_{H,H}$=7.7 Hz, 1H, H_{Xyl}-1), 3.99 (m, 1H, H-5), 3.68 (dd, $^{2}J_{H,H}$=11.4 Hz, $^{3}J_{H,H}$=5.4 Hz, 1H, H_{Xyl}-6a), 3.27 (m, 1H, H_{Xyl}-4), 3.07 (t, $^{3}J_{H,H}$=8.9 Hz, 1H, H_{Xyl}-3), 3.01 (m, 1H, H_{Xyl}-6b), 2.90 (m, 1H, H_{Xyl}-2), 2.75 (dd, $^{2}J_{H,H}$=16.3 Hz, $^{3}J_{H,H}$=6.3 Hz, 1H, H-4a), 2.72 (m, 2H, H-2), 2.63 (m, 2H, H-1), 2.56 (m, 1H, H-4b), 2.52 (m, 1H, H-7a), 2.43 (m, 1H, H-7b), 1.63 (m, 2H, H-6). ^{13}C NMR (DMSO-d_6, 150 MHz, 295 K): δ 209.1 (C-3), 155.6 (C-4′), 155.4 (C-4″), 132.2 (C-1″), 131.3 (C-1′), 129.3 (C-2′, C-6′ C-2″, C-6″), 115.2 (C-3′, C-5′, C-3″, C-5″), 102.7 (C_{Xyl}-1), 76.9 (C_{Xyl}-3), 74.3 (C-5), 73.5 (C_{Xyl}-2), 69.8 (C_{Xyl}-4), 66.0 (C_{Xyl}-5), 47.4 (C-4), 45.0 (C-2), 37.4 (C-6), 30.2 (C-7), 28.3 (C-1).

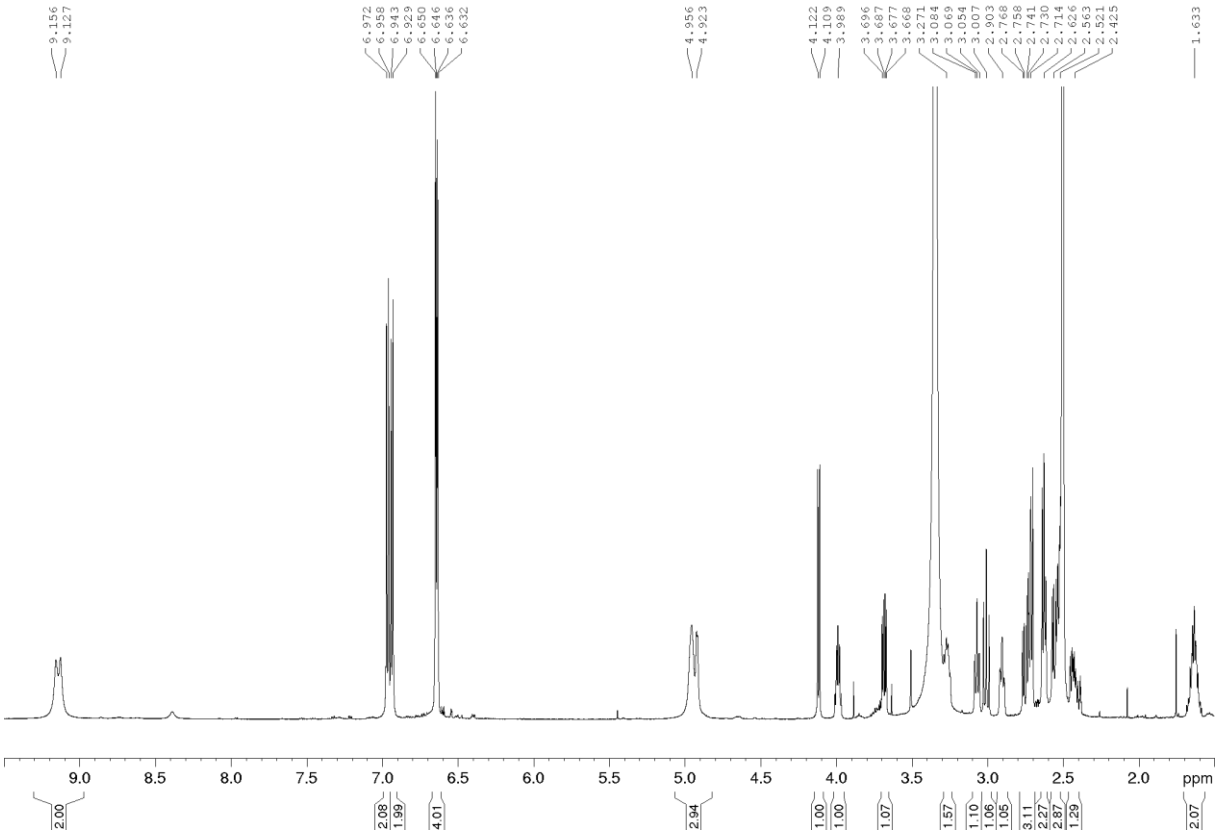

Figure S7. [1]H NMR spectrum of platyphyllonol-5-*O*-β-D- xylopyranoside (**4**) (DMSO-*d*6, 295 K).

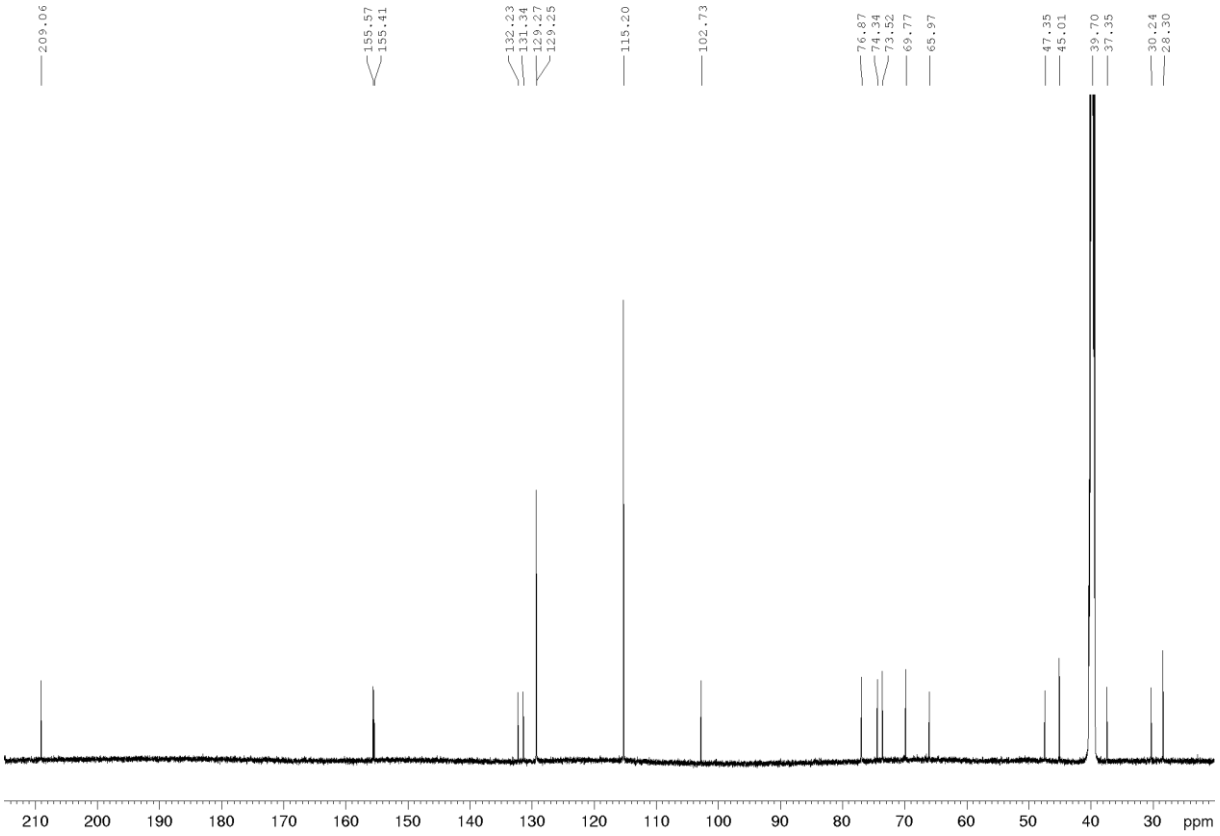

Figure S8. [13]C NMR spectrum of platyphyllonol-5-*O*-β-D- xylopyranoside (**4**) (DMSO-*d*6, 295 K).

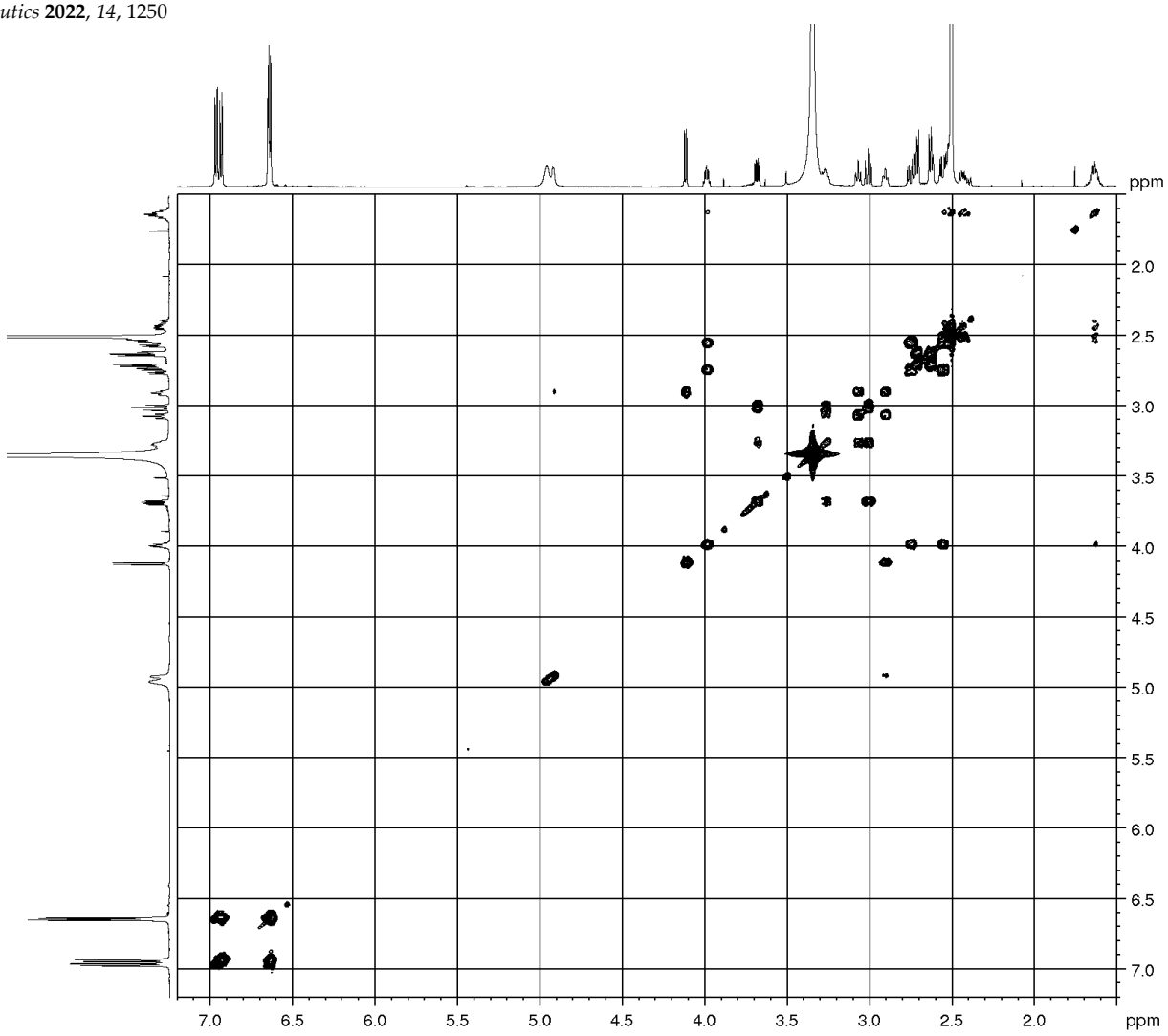

Figure S9. COSY spectrum of platyphyllonol-5-*O*-β-D- xylopyranoside (**4**) (DMSO-d_6, 295 K).

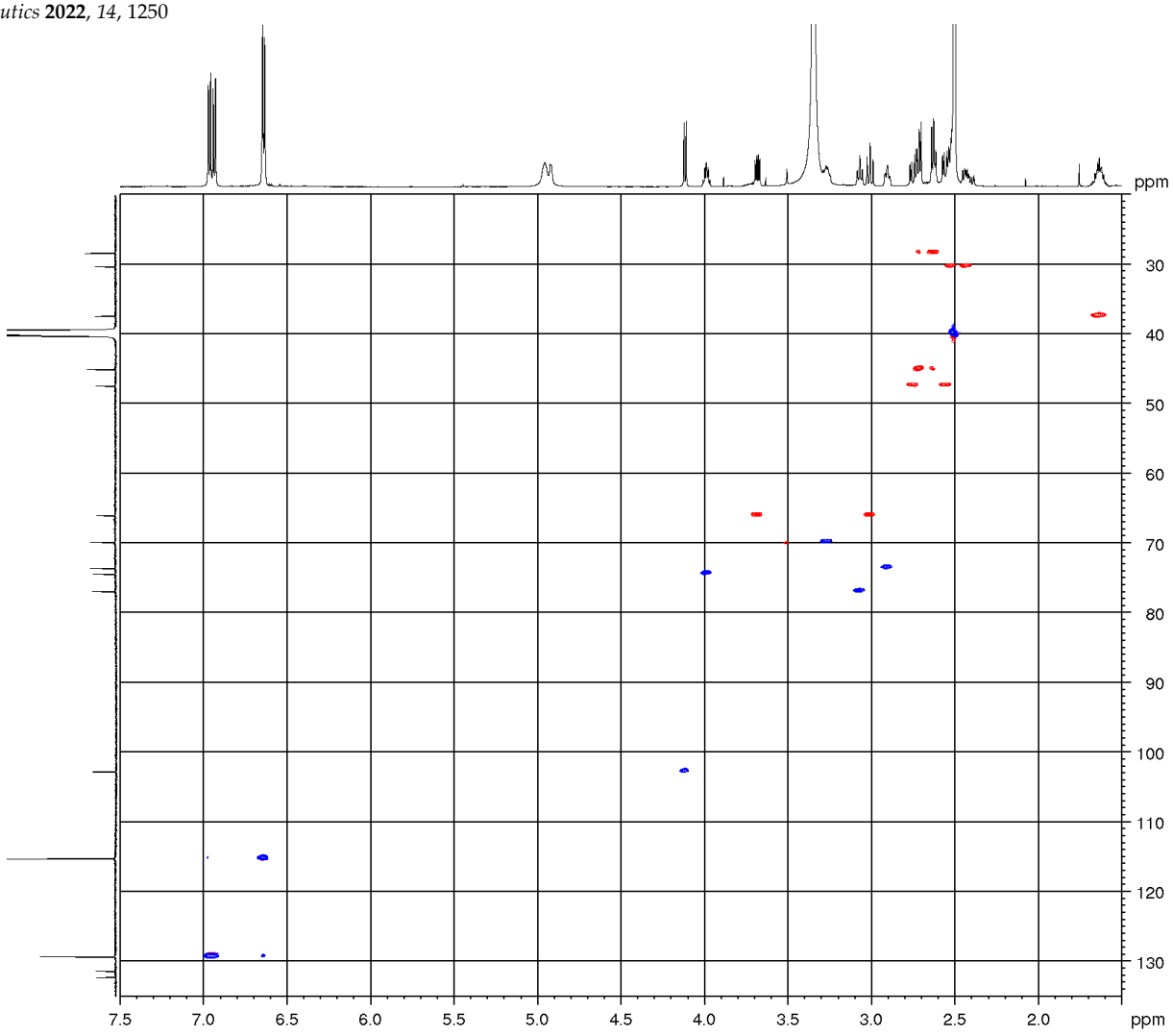

Figure S10. HSQC spectrum of platyphyllonol-5-*O*-β-D- xylopyranoside (**4**) (DMSO-d_6, 295 K).

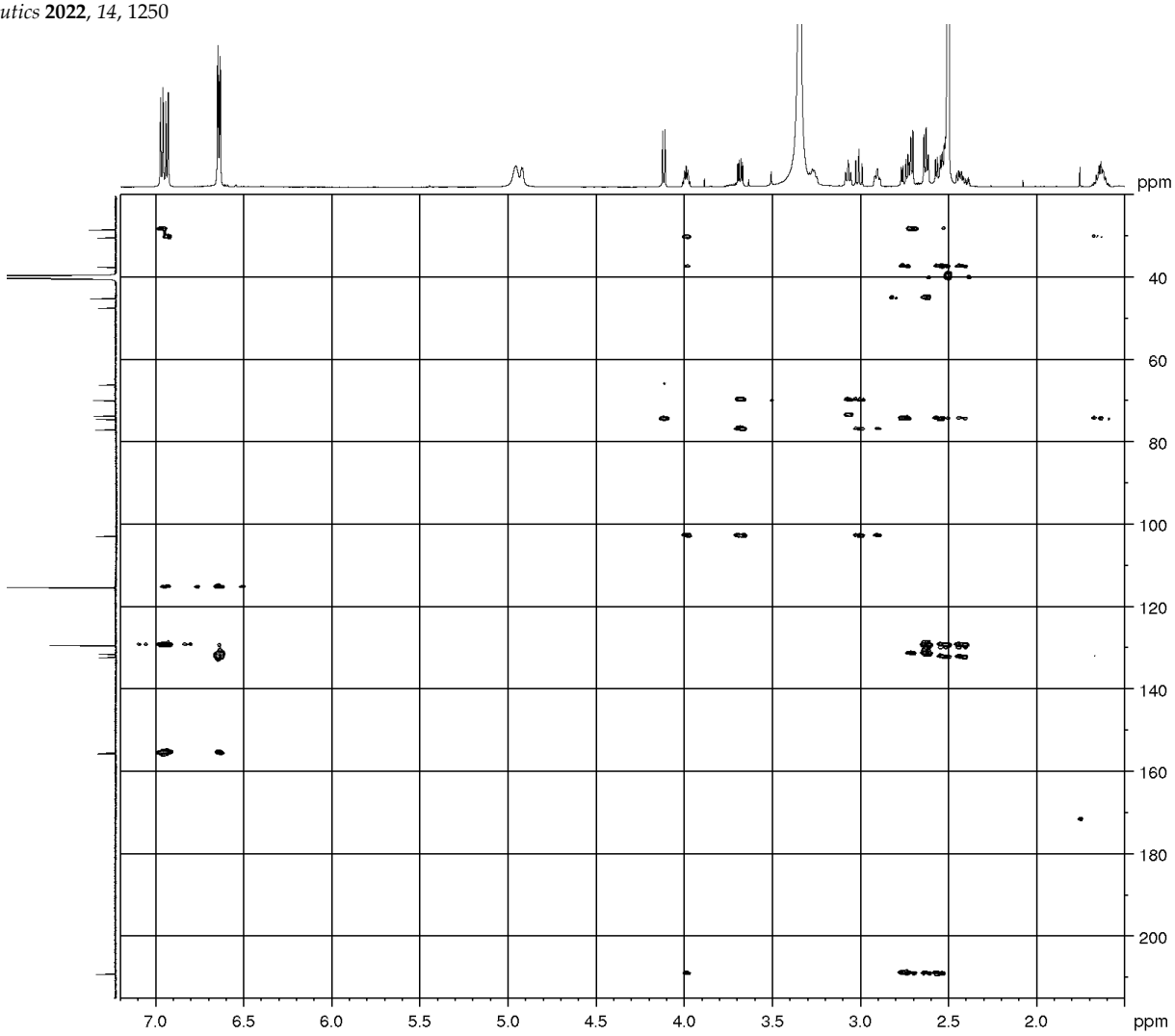

Figure S11. HMBC spectrum of platyphyllonol-5-*O*-β-D- xylopyranoside (**4**) (DMSO-d_6, 295 K).

NMR data of compound **5** (platyphyllenone): ^{1}H NMR (DMSO-d_6, 600 MHz, 295 K): δ 7.00 (~d, $^{3}J_{H,H}$=8.4 Hz, 2H, H-2′/H-2″, H-6′/H-6″), 6.98 (~d, $^{3}J_{H,H}$=8.4 Hz, H-2′/H-2″, H-6′/H-6″) 6.85 (dt, $^{2}J_{H,H}$=15.9 Hz, $^{3}J_{H,H}$=6.8 Hz, 1H, H-5), 6.67 (~d, $^{3}J_{H,H}$=8.4 Hz, 2H, H-3′/H-3″, H-5′/H-5″), 6.65 (~d, $^{3}J_{H,H}$=8.4 Hz, 2H H-3′/H-3″, H-5′/H-5″), 6.08 (dt, $^{2}J_{H,H}$=15.9 Hz, $^{4}J_{H,H}$=1.4 Hz, 1H, H-4), 2.79 (m, 2H, H-2), 2.67 (m, 2H, H-1), 2.62 (m, 2H, H-7), 2.43 (m, 2H, H-6). ^{13}C NMR (DMSO-d_6, 150 MHz, 295 K): δ 199.5 (C-3), 155.7 (C-4′, C-4″), 147.1 (C-5), 131.3 (C-1/C-1″), 131.1 (C-1/C-1″), 130.5 (C-4), 129.4 (C-6′/C-6″), 129.3 (C-6′/C-6″), 115.3 (C-5′/C-5″), 115.2 (C-5′/C-5″), 41.4 (C-2), 34.1 (C-6), 33.0 (C-7), 29.0 (C-1).

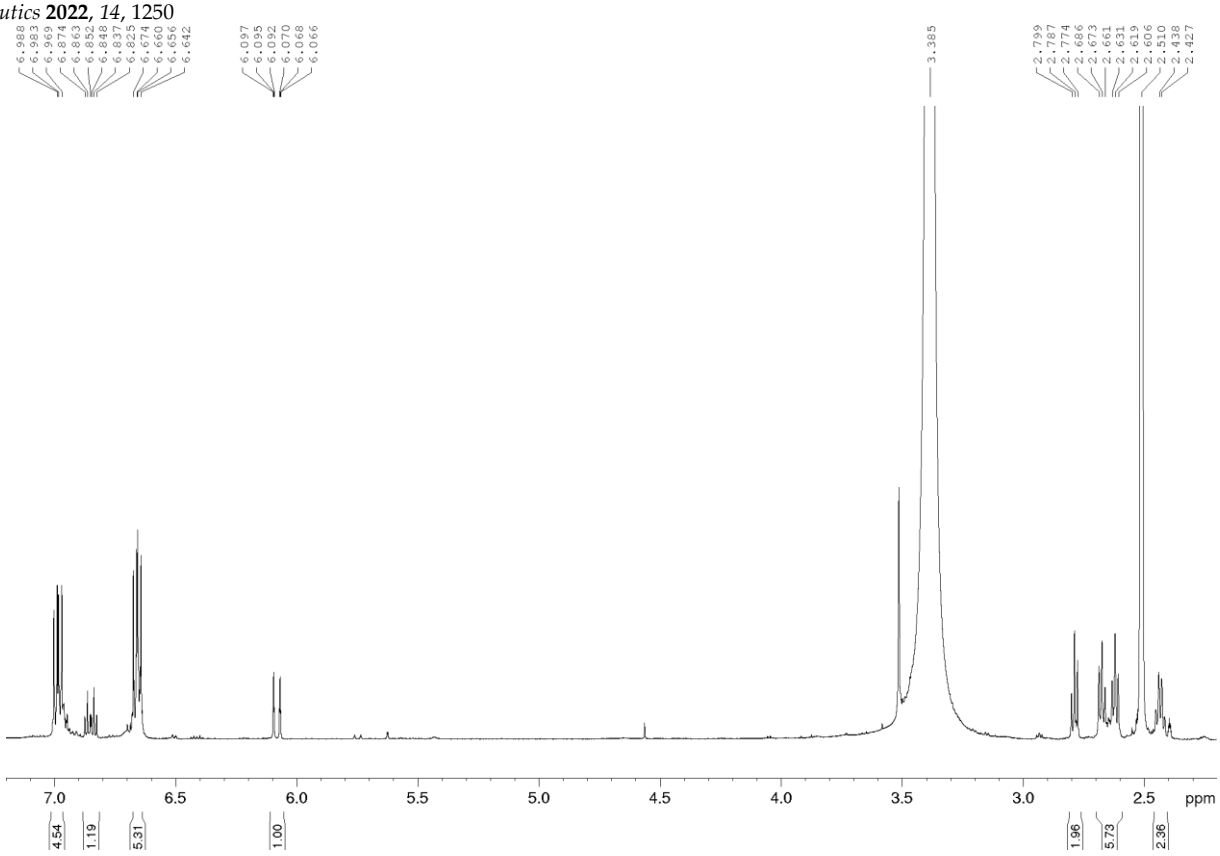

Figure S12. [1]H NMR spectrum of platyphyllenone (**5**) (DMSO-d_6, 295 K).

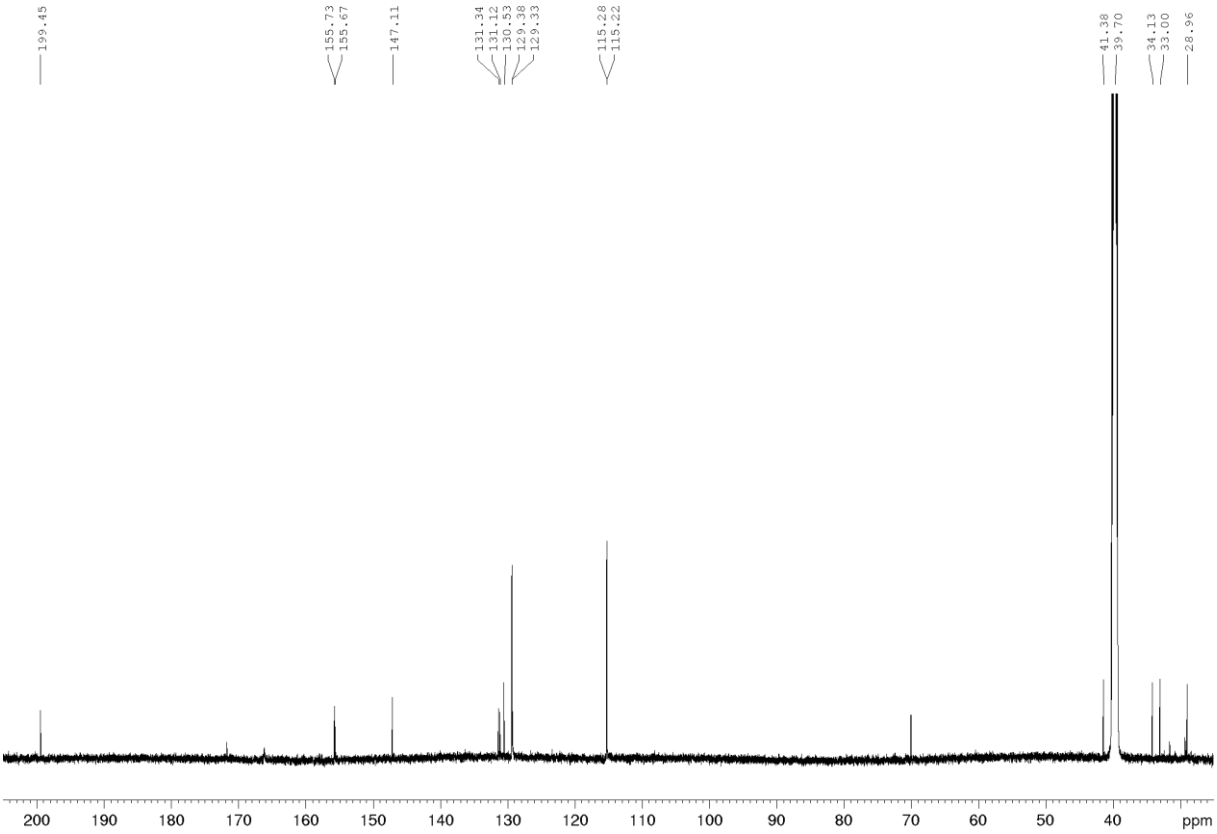

Figure S13. [13]C NMR spectrum of platyphyllenone (**5**) (DMSO-d_6, 295 K).

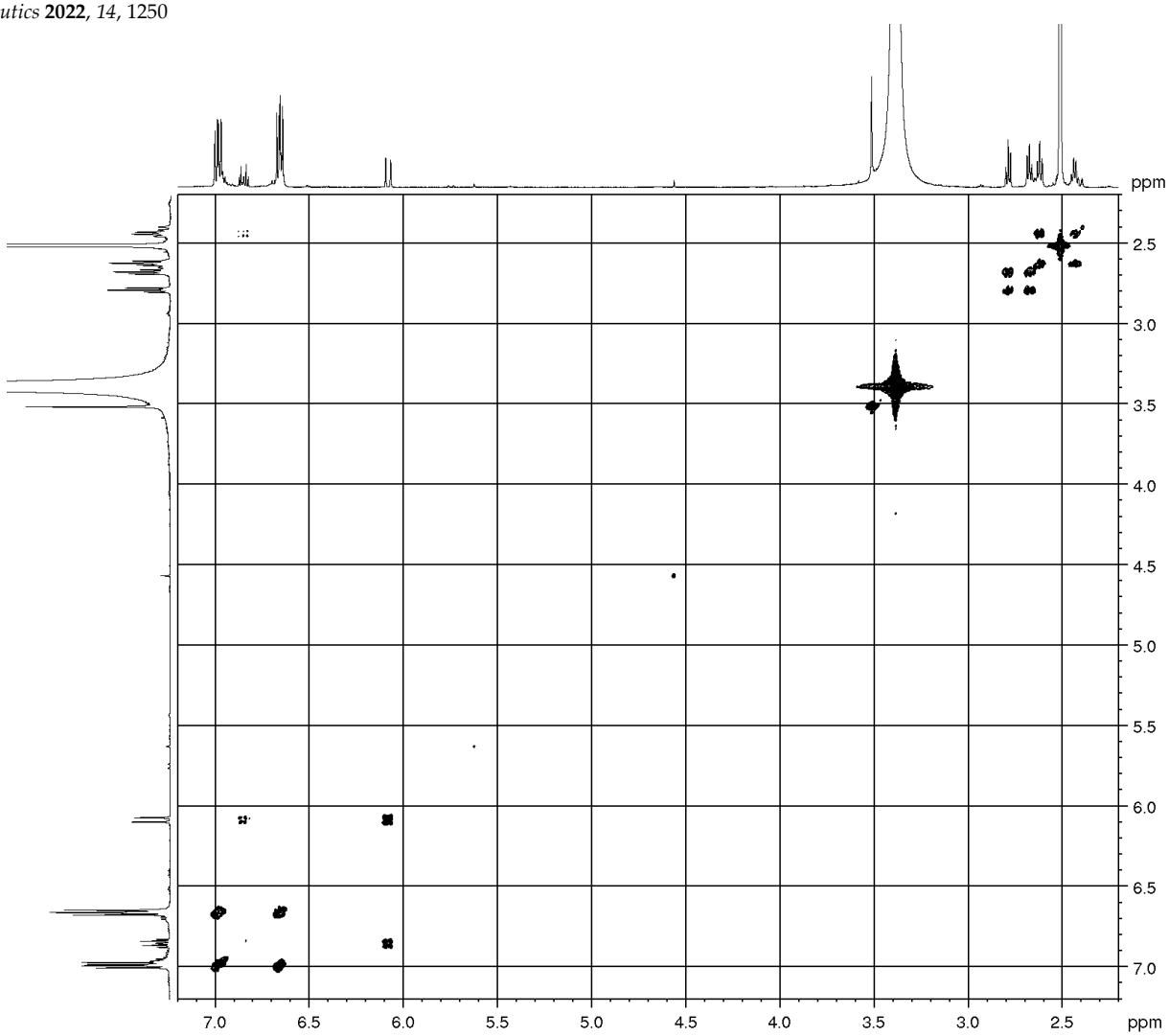

Figure S14. COSY spectrum of platyphyllenone (**5**) (DMSO-d_6, 295 K).

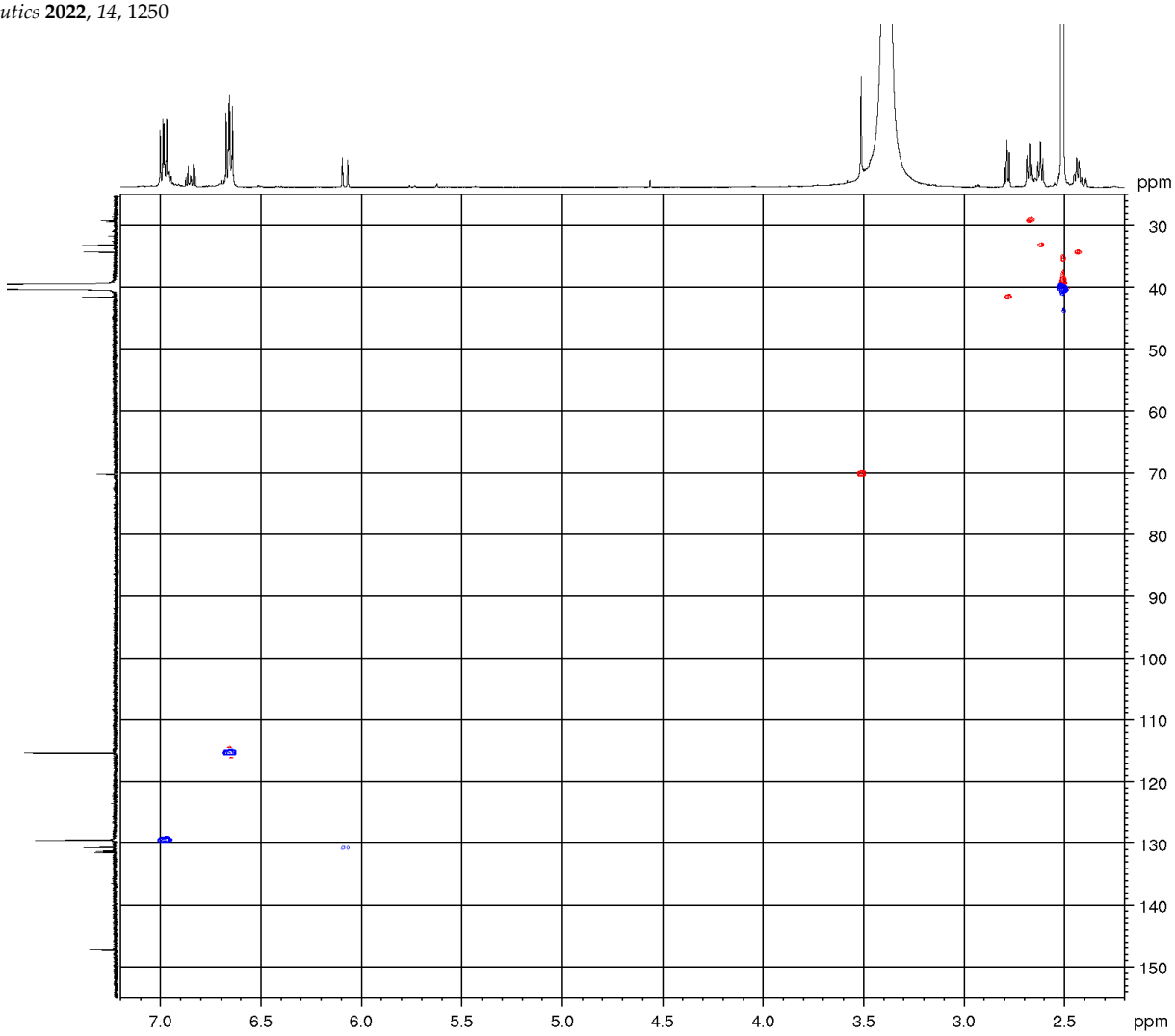

Figure S15. HSQC spectrum of platyphyllenone (**5**) (DMSO-d_6, 295 K).

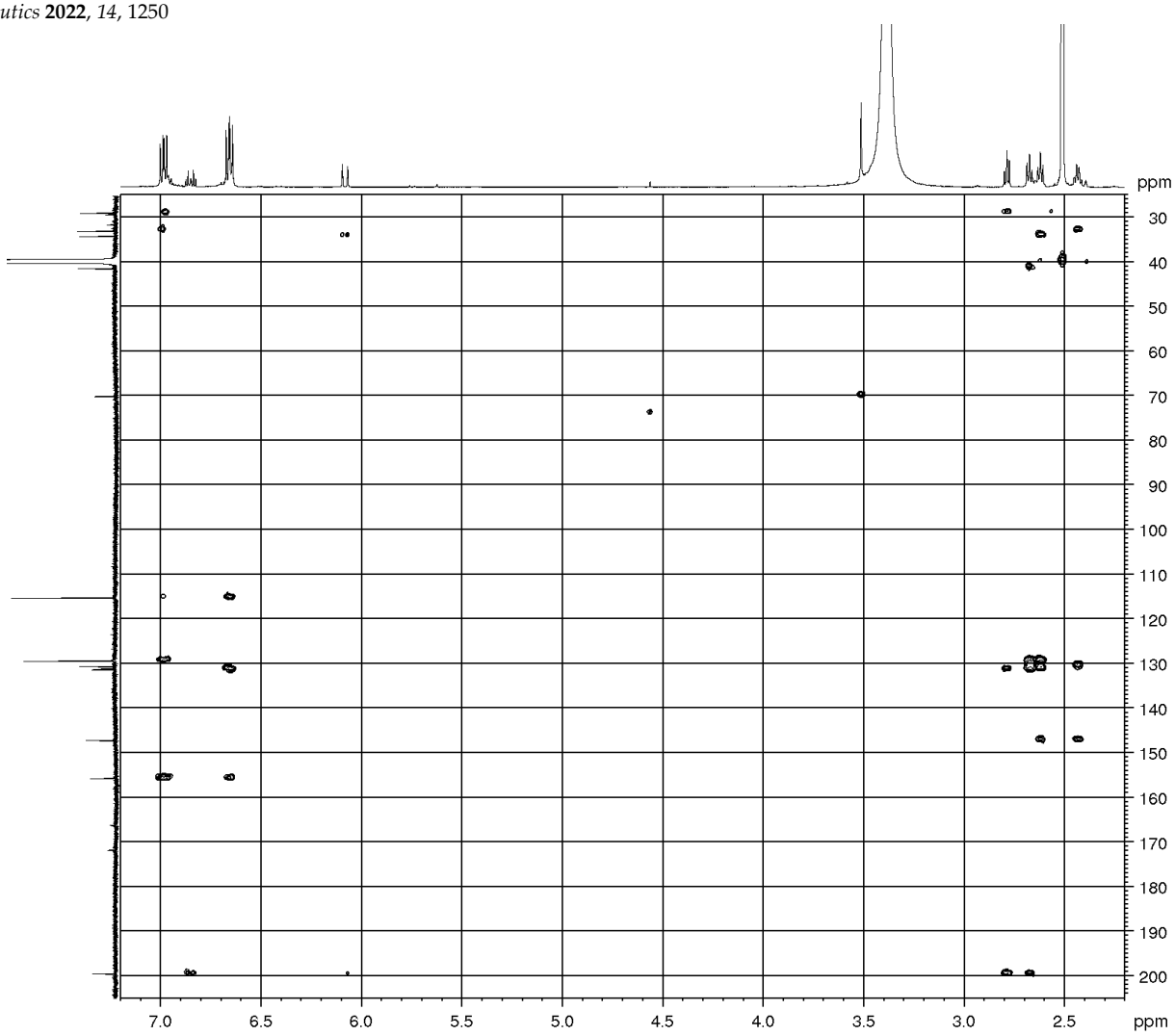

Figure S16. HMBC spectrum of platyphyllenone (**5**) (DMSO-d_6, 295 K).

NMR data of compound **6** (alnusonol-11-*O*-β-D-glucopyranoside): ^{1}H NMR (DMSO-d_6, 600 MHz, 295 K): δ 6.98 (m, 1H, H-15), 6.96 (m, 1H, H-5), 6.71 (d, $^{3}J_{H,H}$=8.2 Hz, 1H, H-4), 6.70 (d, $^{3}J_{H,H}$=8.2 Hz, 1H, H-16), 6.62 (d, $^{4}J_{H,H}$=2.0 Hz, 1H, H-18), 6.49 (d, $^{4}J_{H,H}$=2.0 Hz, 1H, H-19), 4.24 (d, $^{3}J_{H,H}$=7.8 Hz, 1H, H_{Glc}-1), 4.08 (m, 1H, H-11), 3.49 (dd, $^{2}J_{H,H}$=11.6 Hz, $^{3}J_{H,H}$=2.0 Hz, 1H, H_{Glc}-6a), 3.40 (dd, $^{2}J_{H,H}$=11.6 Hz, $^{3}J_{H,H}$=5.2 Hz, 1H, H_{Glc}-6b) 3.16 (m, 2H, H-10), 3.11 (m, 1H, H-8a), 3.10 (m, 1H, H_{Glc}-3), 3.09 (m, 1H, H_{Glc}-4), 2.99 (m, 1H, H_{Glc}-5), 2.98 (m, 1H, H-13a), 2.91 (m, 1H, H-8b), 2.91 (m, 1H, H-6a), 2.88 (m, 1H, H_{Glc}-2), 2.81 (m, 1H, H-7b), 2.68 (m, 1H, H-13b), 2.22 (m, 1H, H-12a), 1.89 (m, 1H, H-12b). ^{13}C NMR (DMSO-d_6, 150 MHz, 295 K): δ 210.5 (C-9), 153.2 (C-3), 153.0 (C-17), 133.2 (C-19), 132.4 (C-18), 130.5 (C-14), 129.5 (C-6), 129.3 (C-15), 128.2 (C-5), 126.4 (C-1, C-2), 116.4 (C-16), 116.3 (C-4), 102.2 (C_{Glc}-1), 76.9 (C_{Glc}-4), 76.4 (C_{Glc}-5), 74.8 (C-11), 73.7 (C_{Glc}-2), 70.1 (C_{Glc}-3), 61.2 (C_{Glc}-6), 51.5 (C-10), 41.6 (C-8), 33.8 (C-12), 28.0 (C-13), 26.4 (C-7).

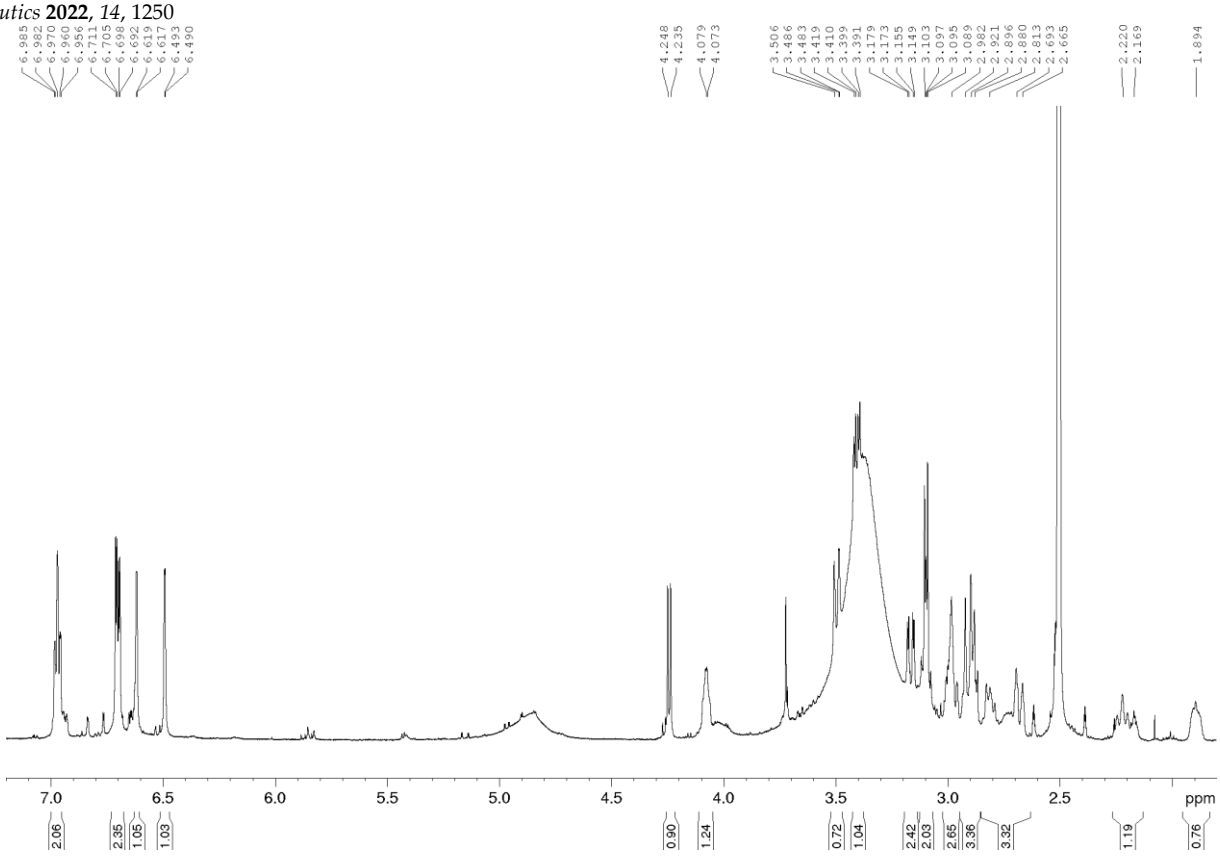

Figure S17. [1]H NMR spectrum of alnusonol-11-*O*-β-D-glucopyranoside (**6**) (DMSO-d_6, 295 K).

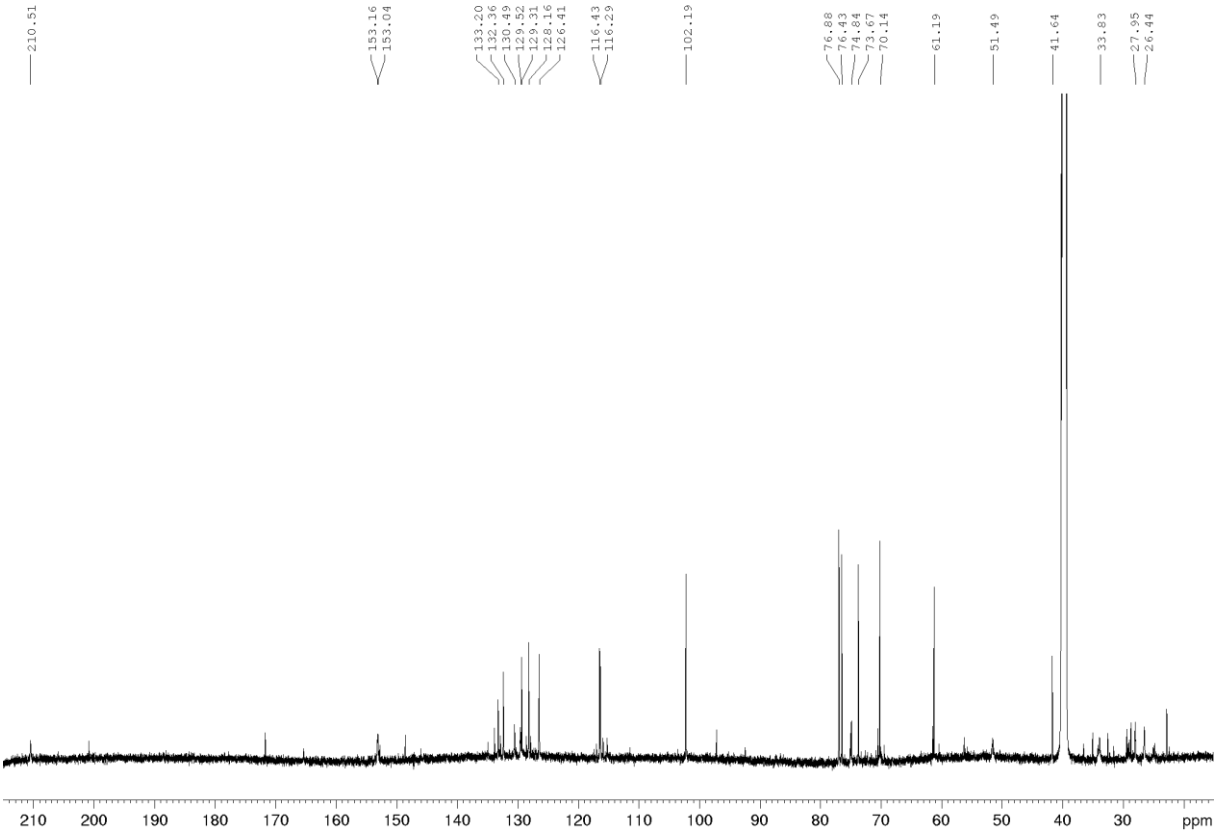

Figure S18. [13]C NMR spectrum of alnusonol-11-*O*-β-D-glucopyranoside (**6**) (DMSO-d_6, 295 K).

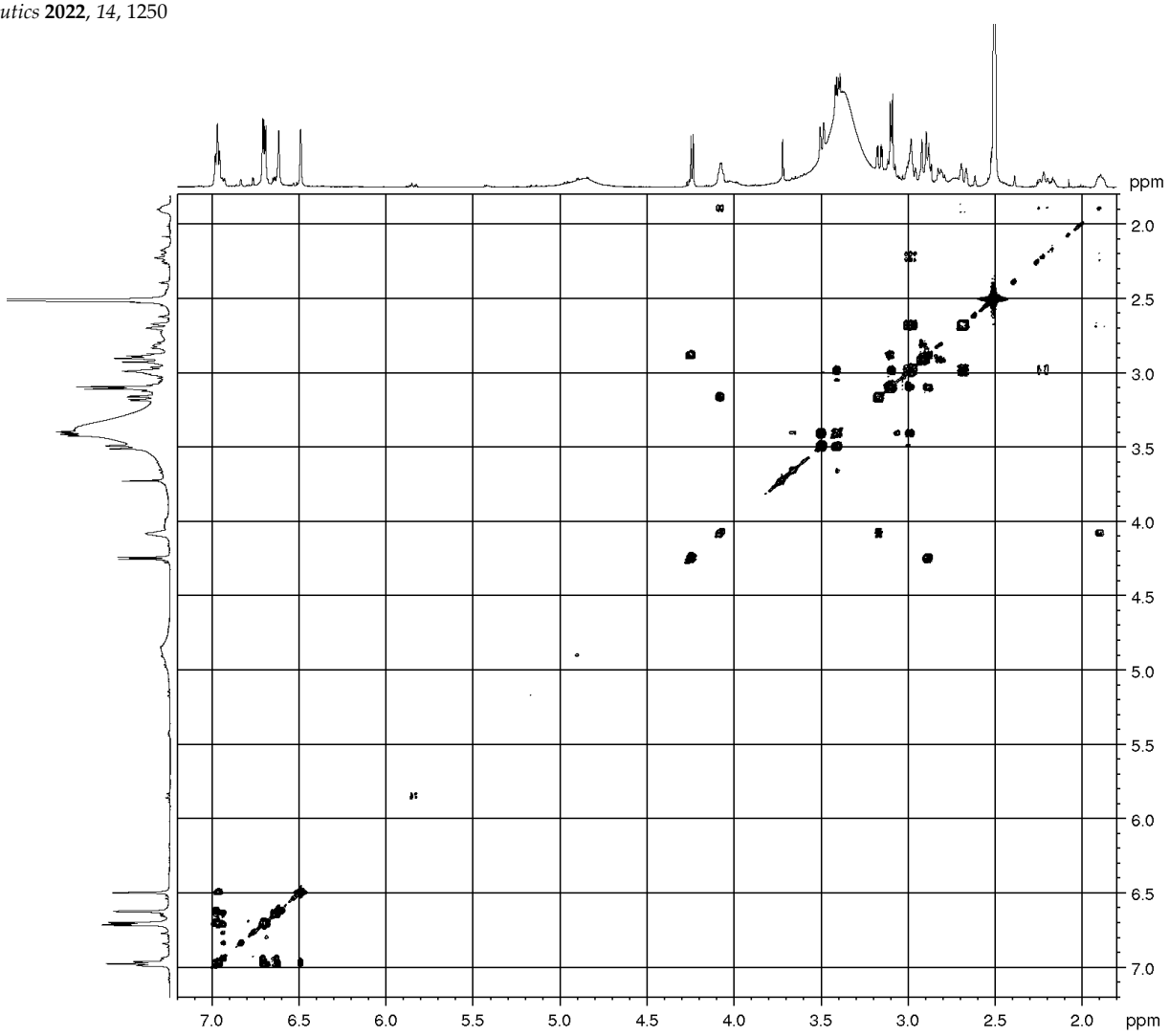

Figure S19. COSY spectrum of alnusonol-11-*O*-β-D-glucopyranoside (**6**) (DMSO-d_6, 295 K).

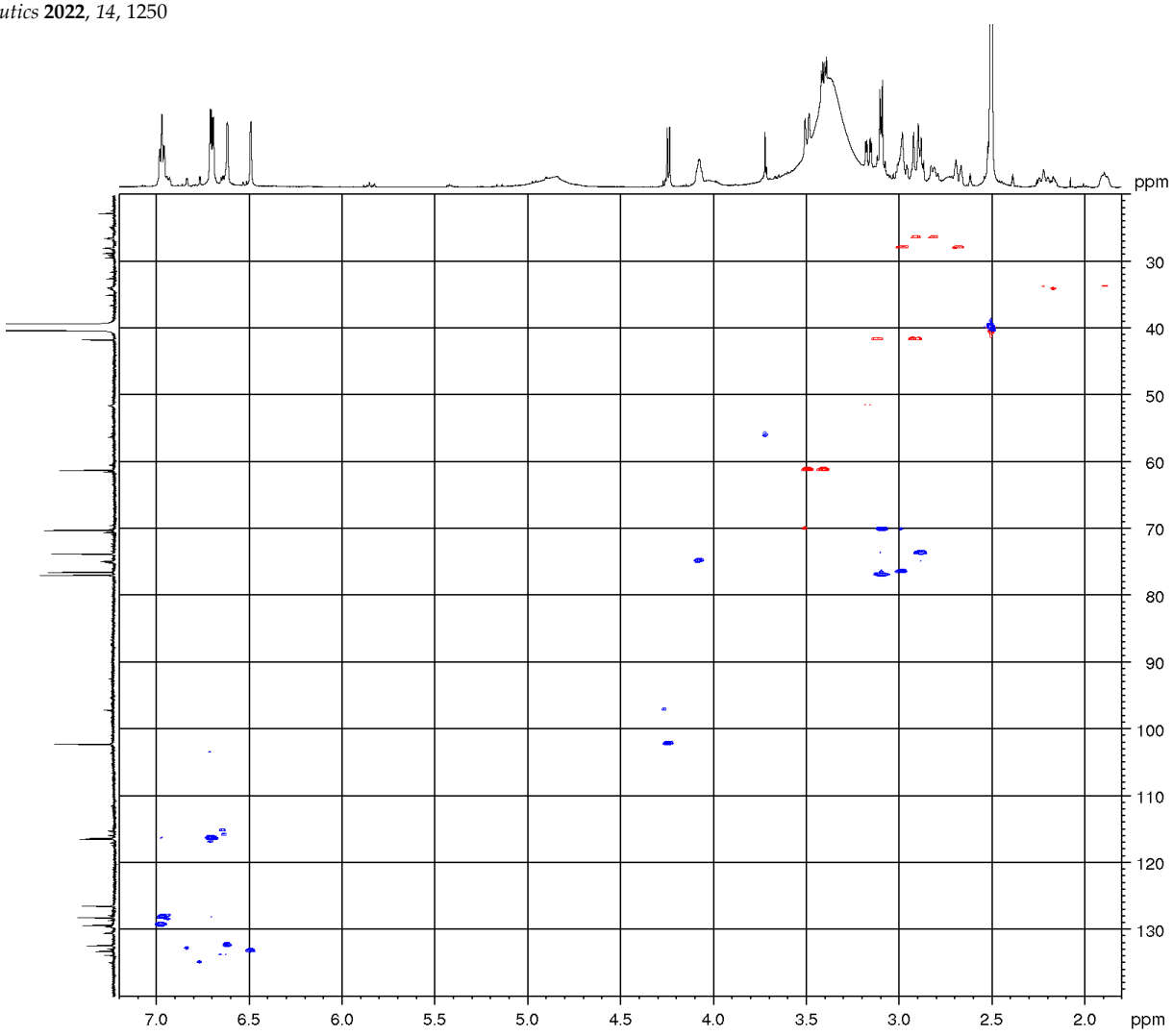

Figure S20. HSQC spectrum of alnusonol-11-*O*-β-D-glucopyranoside (**6**) (DMSO-d_6, 295 K).

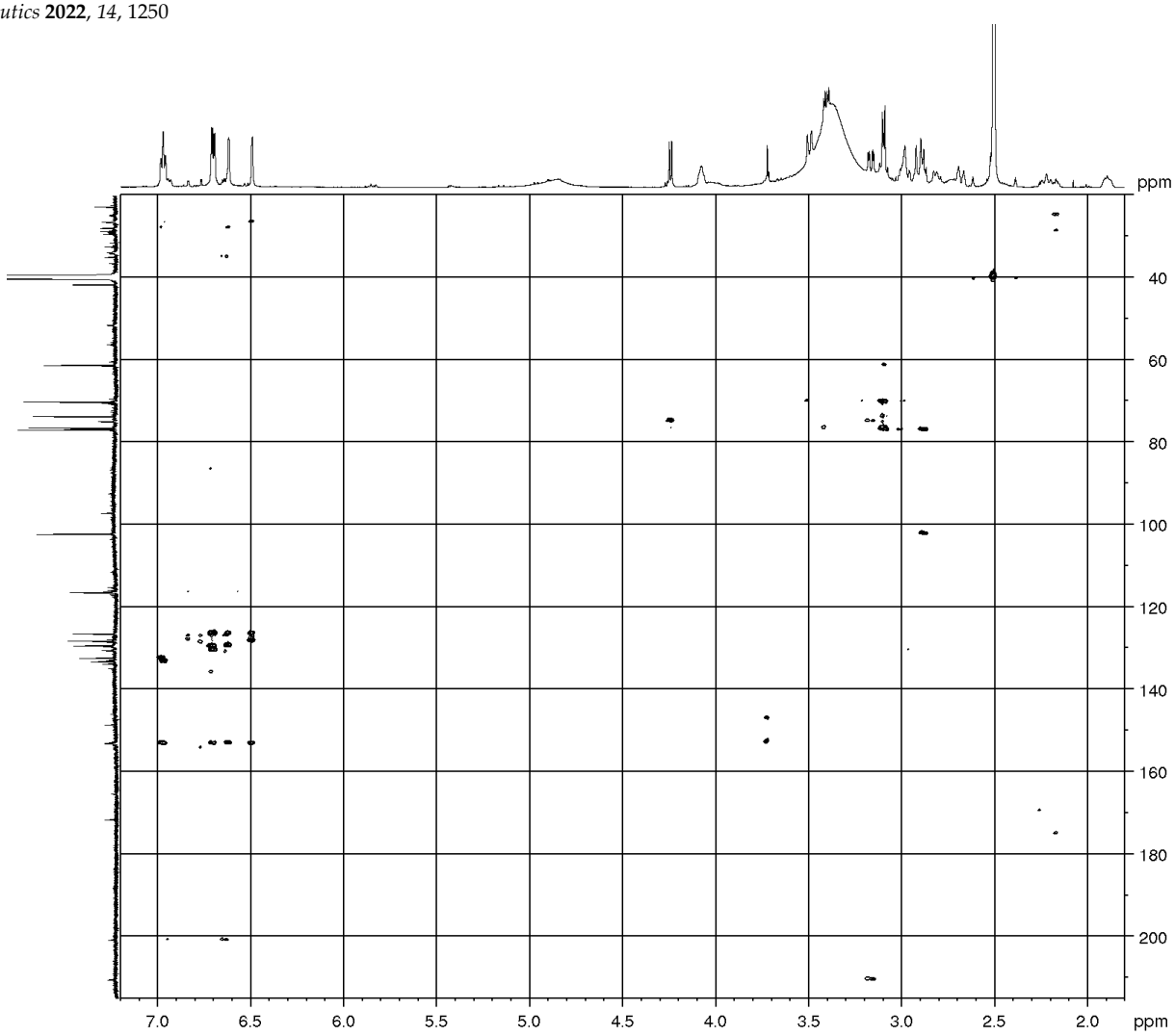

Figure S21. HMBC spectrum alnusonol-11-*O*-β-D-glucopyranoside (**6**) (DMSO-d_6, 295 K).

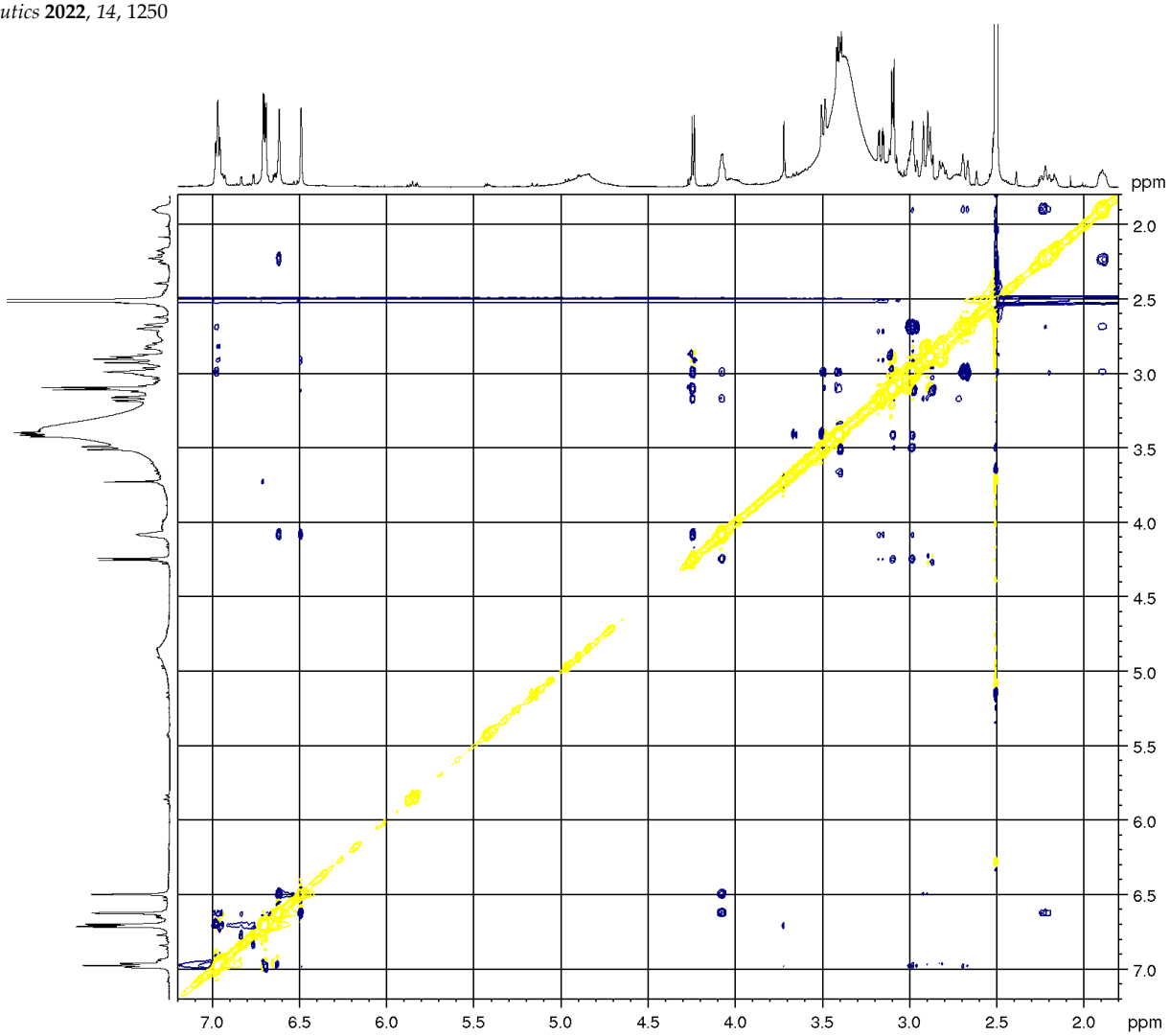

Figure S22. ROESY spectrum of alnusonol-11-*O*-β-D-glucopyranoside (**6**) (DMSO-d_6, 295 K).

NMR data of compound **7** (alnusone): ^{1}H NMR (DMSO-d_6, 600 MHz, 333 K): δ 6.95 (dt, $^{2}J_{H,H}$=15.5 Hz, $^{3}J_{H,H}$=7.5 Hz, H-11), 6.82 (m, 1H, H-19), 6.81 (m, 1H, H-18), 6.78 (m, 1H, H-15), 6.77 (m, 1H, H-5), 6.60 (dt, $^{2}J_{H,H}$=15.5 Hz, $^{4}J_{H,H}$=1.2 Hz, H-10), 6.49 (d, $^{3}J_{H,H}$=7.9 Hz, 1H, H-4), 6.42 (d, $^{3}J_{H,H}$=7.9 Hz, 1H, H-16), 2.98 (m, 2H, H-7), 2.80 (m, 2H, H-13), 2.70 (m, 2H, H-8), 2.53 (m, 2H, H-12). ^{13}C NMR (DMSO-d_6, 150 MHz, 333 K): δ 200.6 (C-9), 148.3 (C-11), 133.5 (C-10), 133.1 (C-18), 131.7 (C-19), 127.4 (C-15), 126.7 (C-5), 117.6 (C-4), 116.1 (C-16), 39.8 (C-8), 34.9 (C-12), 32.5 (C-13), 29.5 (C-7). (The C-1, C-2, C-3, C-6, C-14 and C-17 signals were broad even on 333 K.)

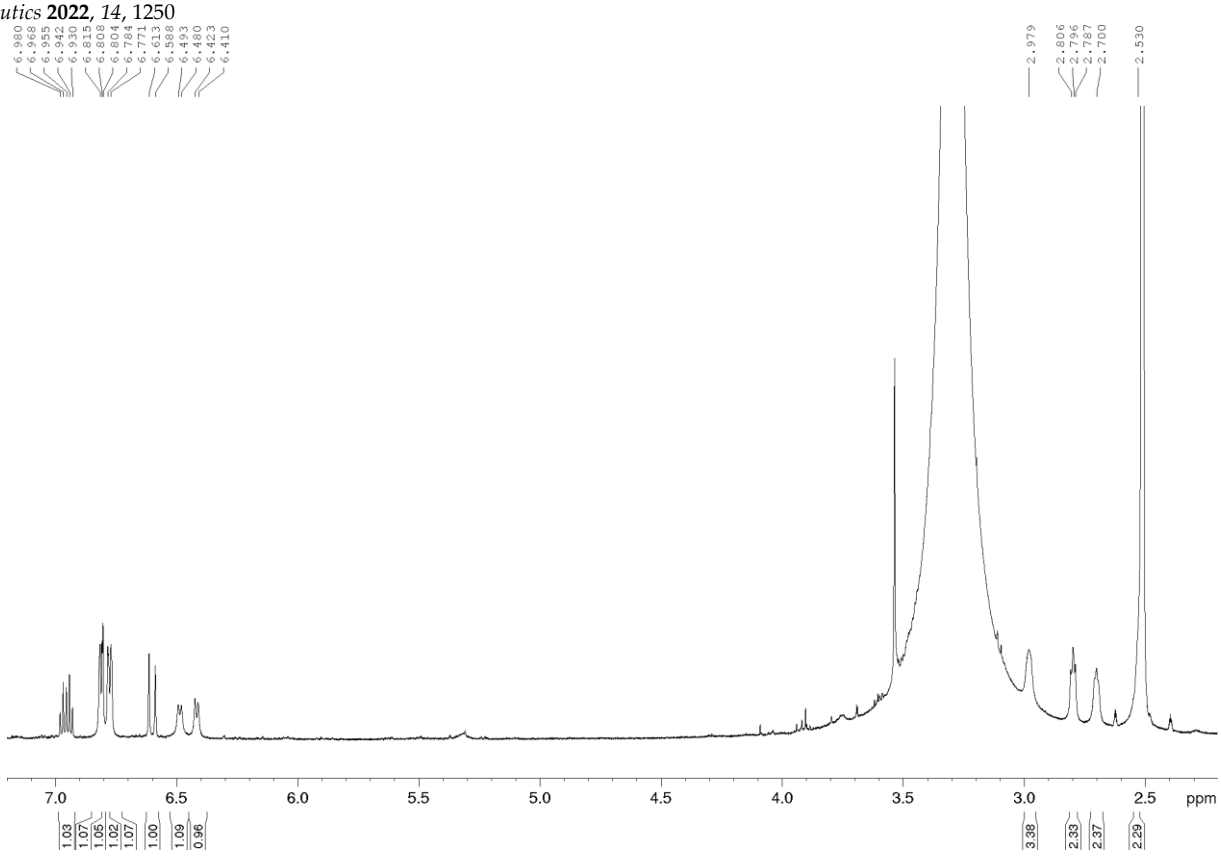

Figure S23. ^{1}H NMR spectrum of alnusone (**7**) (DMSO-*d*$_6$, 333 K).

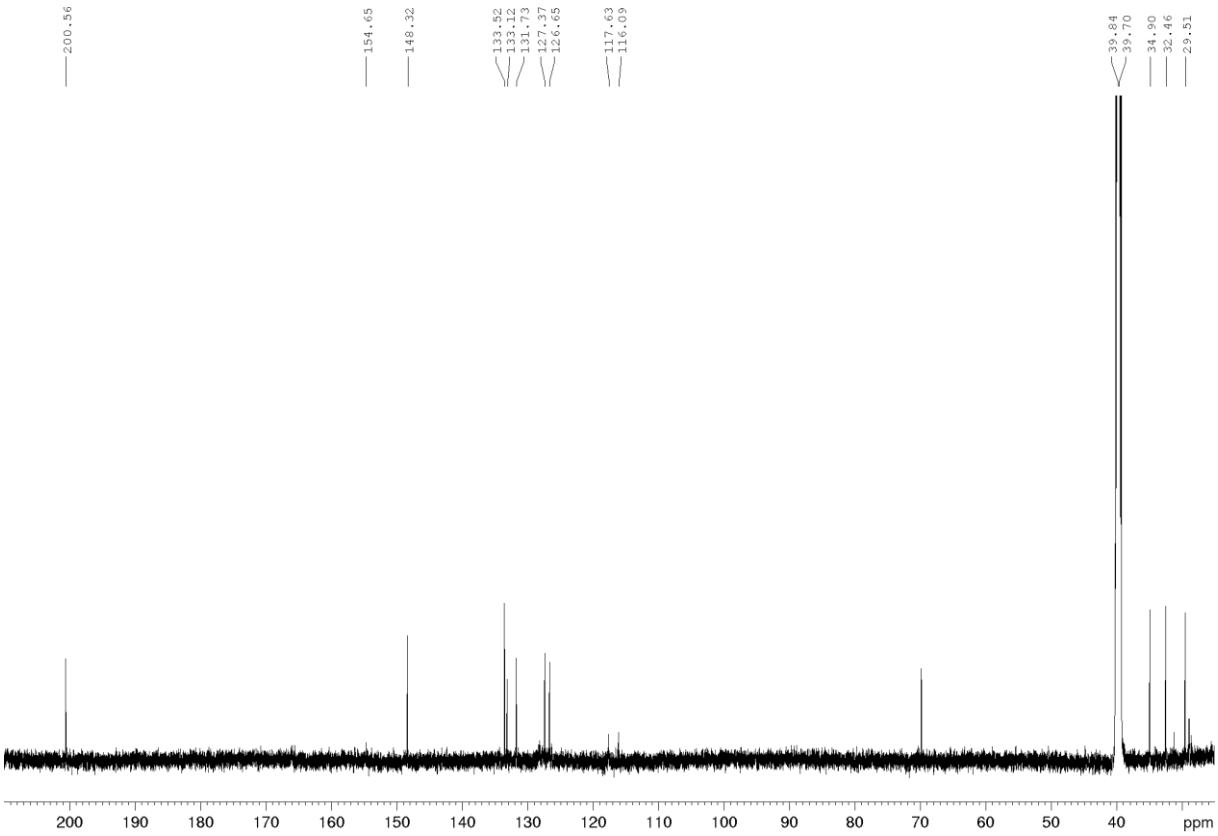

Figure S24. ^{13}C NMR spectrum of alnusone (**7**) (DMSO-*d*$_6$, 333 K).

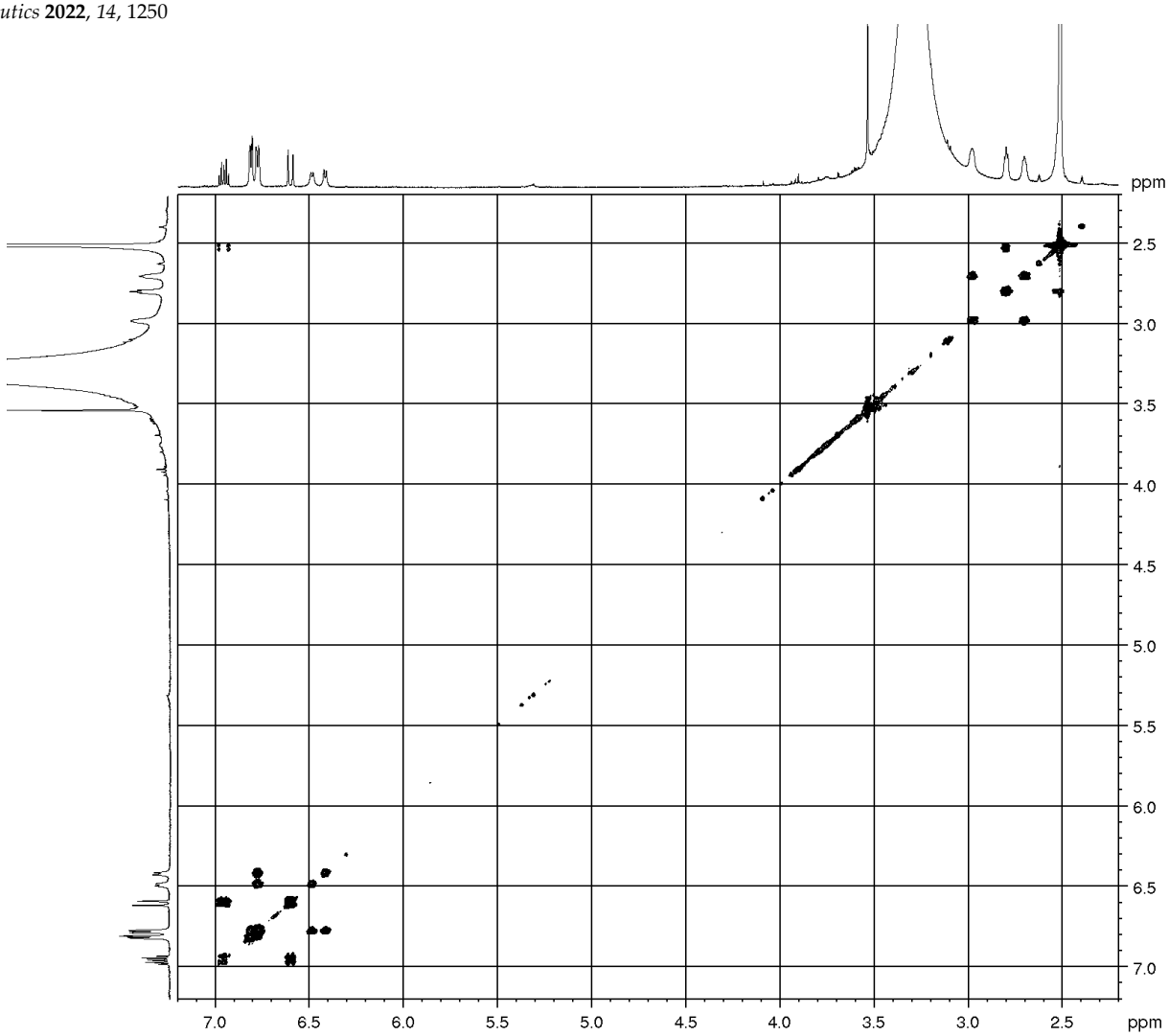

Figure S25. COSY spectrum of alnusone (**7**) (DMSO-d_6, 333 K).

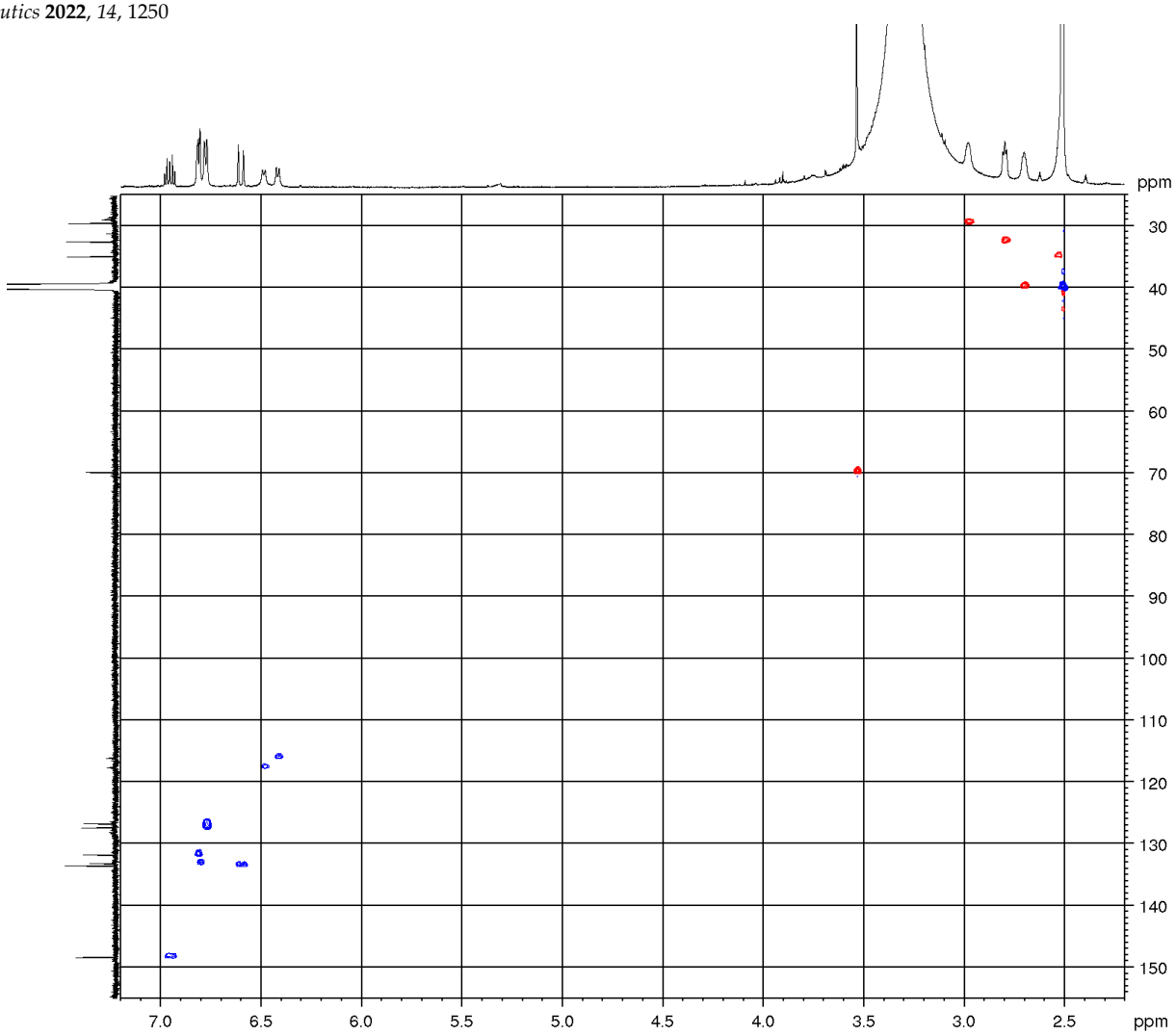

Figure S26. HSQC spectrum of alnusone (**7**) (DMSO-d_6, 333 K).

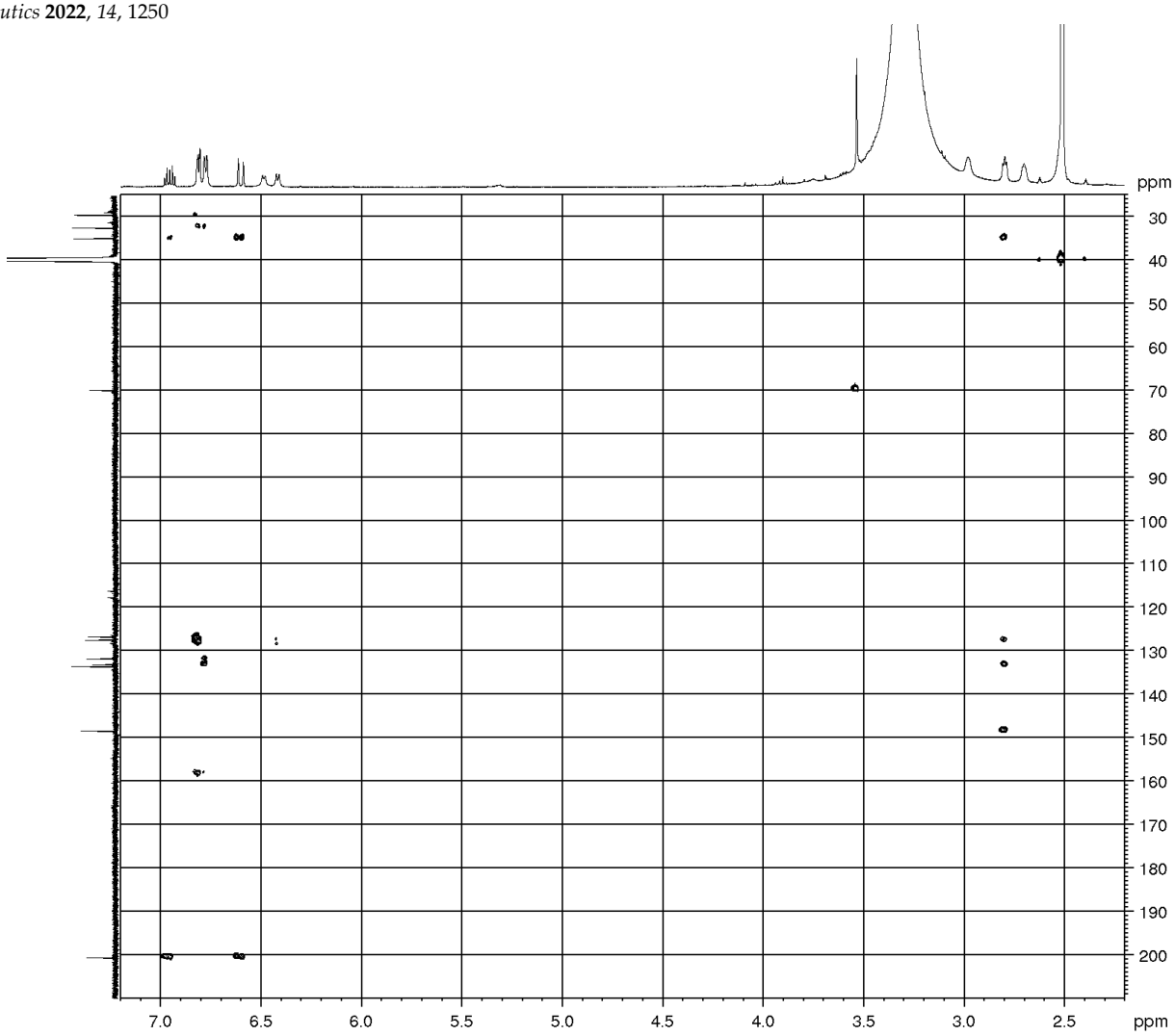

Figure S27. HMBC spectrum of alnusone (**7**) (DMSO-d_6, 333 K).

NMR data of compound **8** (giffonin F): ^{1}H NMR (methanol-d_4, 600 MHz, 295 K): δ 7.48 (dd, $^{3}J_{H,H}$=8.2 Hz, $^{4}J_{H,H}$=2.0 Hz, 1H, H-15), 7.16 (dd, $^{3}J_{H,H}$=8.2 Hz, $^{4}J_{H,H}$=2.0 Hz, 1H, H-16), 7.08 (dd, $^{3}J_{H,H}$=8.2 Hz, $^{4}J_{H,H}$=2.0 Hz, 1H, H-19), 6.94 (dd, $^{3}J_{H,H}$=8.2 Hz, $^{4}J_{H,H}$=2.0 Hz, 1H, H-18), 6.41 (d, $^{3}J_{H,H}$=12.1 Hz, 1H, H-7), 5.29 (dd, $^{3}J_{H,H}$=12.1 Hz, $^{3}J_{H,H}$=9.1 Hz, 1H, H-8), 4.84 (s, 1H, H-6), 4.29 (t, $^{3}J_{H,H}$=9.8 Hz, 1H, H-9), 3.99 (s, 3H, OCH_3-2), 3.67 (s, 3H, OCH_3-4), 3.06 (m, 1H, H-13a), 2.99 (td, $^{2}J_{H,H}$=12.5 Hz, $^{3}J_{H,H}$=5.4 Hz, 1H, H-13b), 2.81 (td, $^{2}J_{H,H}$=12.5 Hz, $^{3}J_{H,H}$=5.4 Hz, 1H, H-12a), 2.48 (m, 1H, H-12b), 2.45 (m, 1H, H-10a), 1.72 (m, 1H, H-10b). ^{13}C NMR (methanol-d_4, 150 MHz, 295 K): δ 215.6 (C-11), 156.6 (C-17), 152.1 (C-1), 145.2 (C-3), 142.2 (C-4), 138.8 (C-14), 138.3 (C-2), 134.0 (C-19), 133.2 (C-8), 130.7 (C-15), 125.3 (C-5), 125.1 (C-16), 124.9 (C-7), 124.0 (C-18), 108.5 (C-6), 65.3 (C-9), 61.6 (OCH_3-2), 61.5 (OCH_3-4), 51.7 (C-10), 45.2 (C-12), 33.2 (C-13).

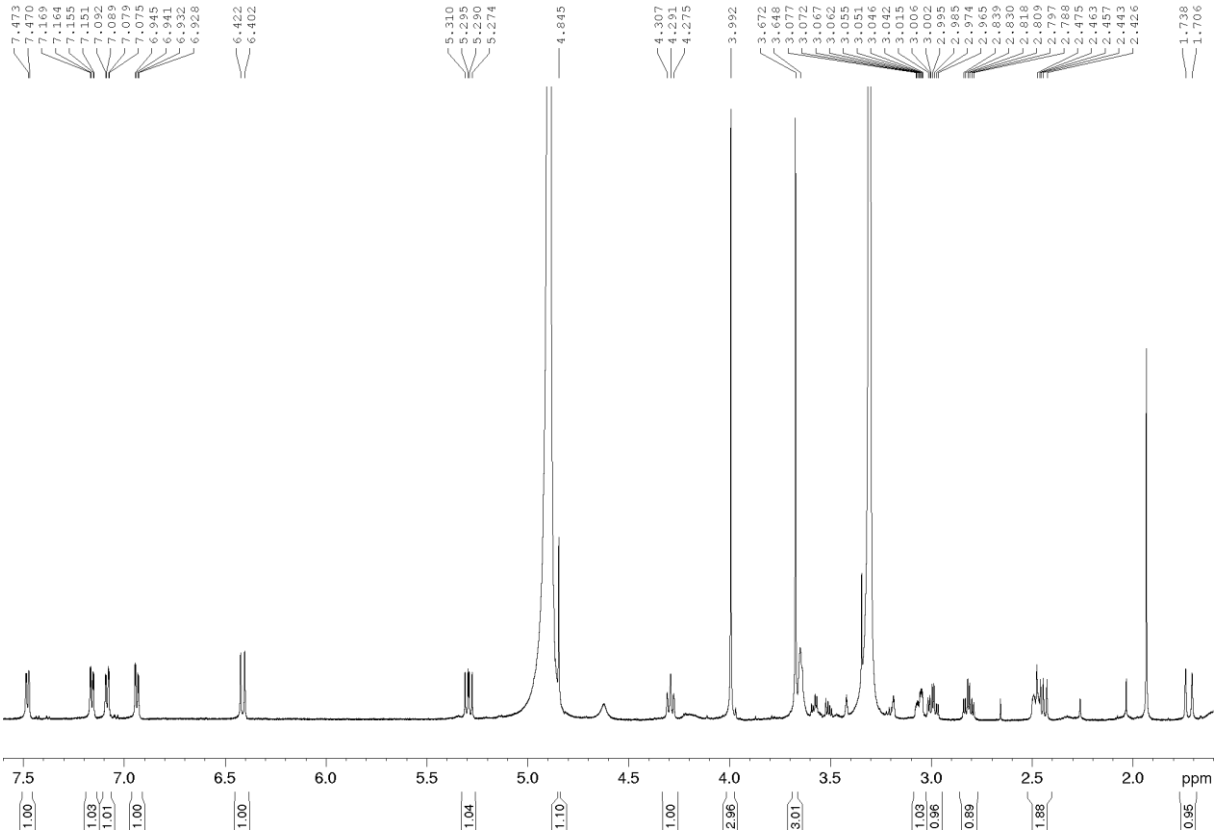

Figure S28. [1]H NMR spectrum of giffonin F (**8**) (methanol-d_4, 295 K).

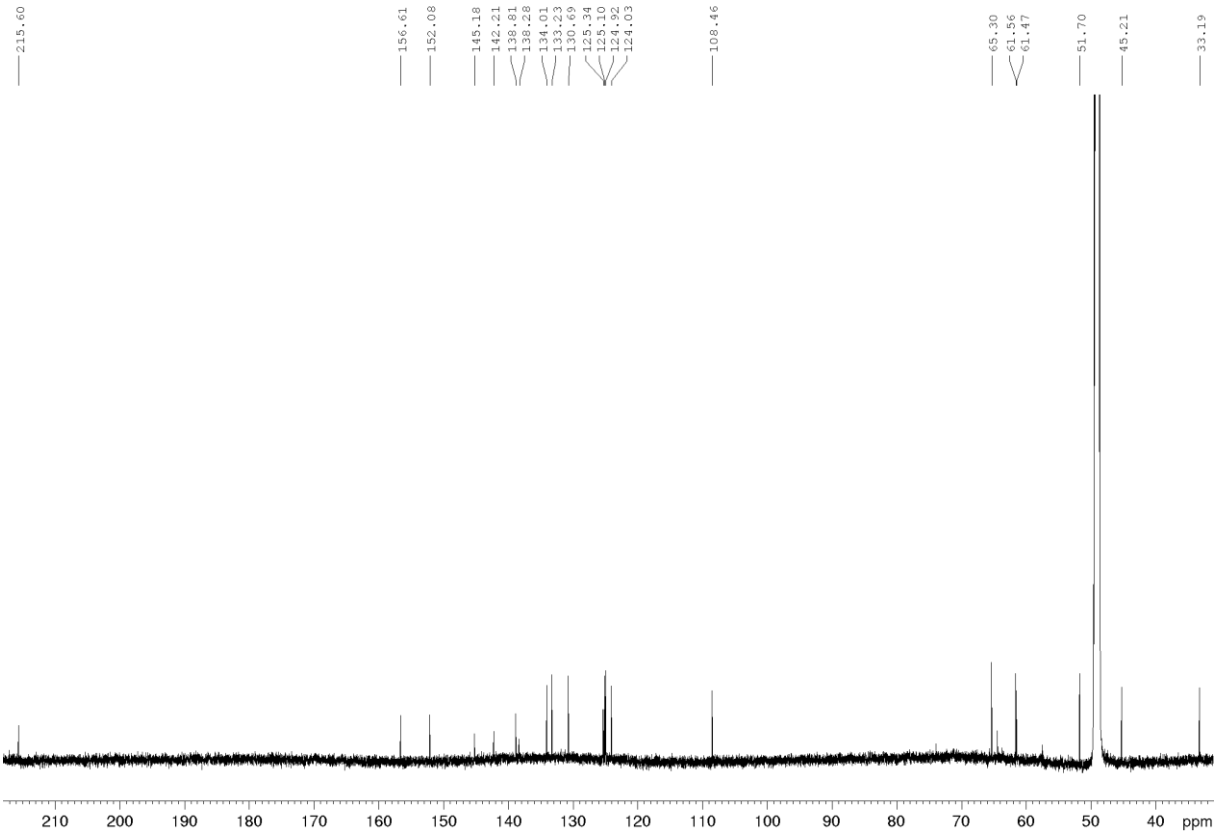

Figure S29. [13]C NMR spectrum of giffonin F (**8**) (methanol-d_4, 295 K).

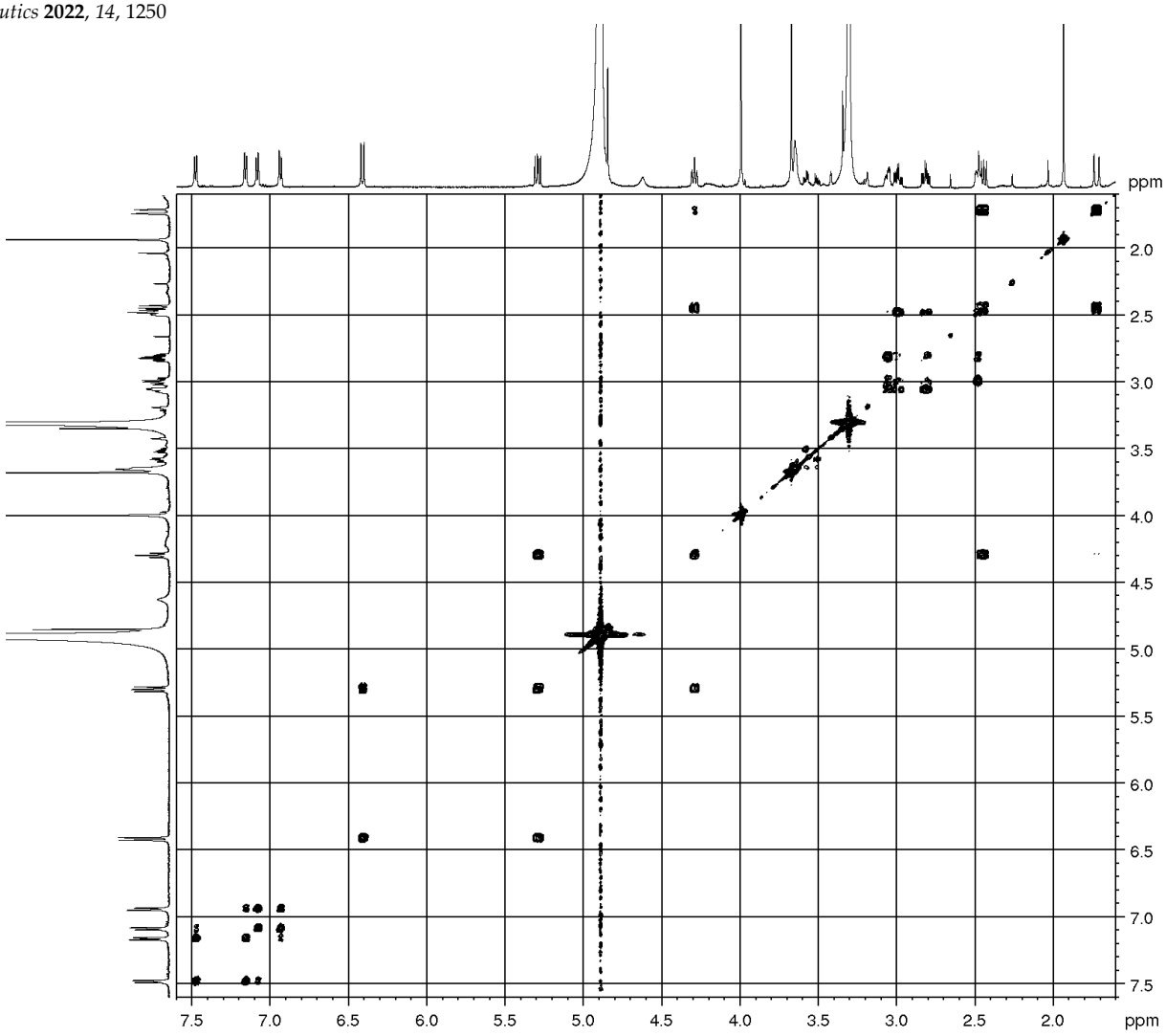

Figure S30. COSY spectrum of giffonin F (**8**) (methanol-d_4, 295 K).

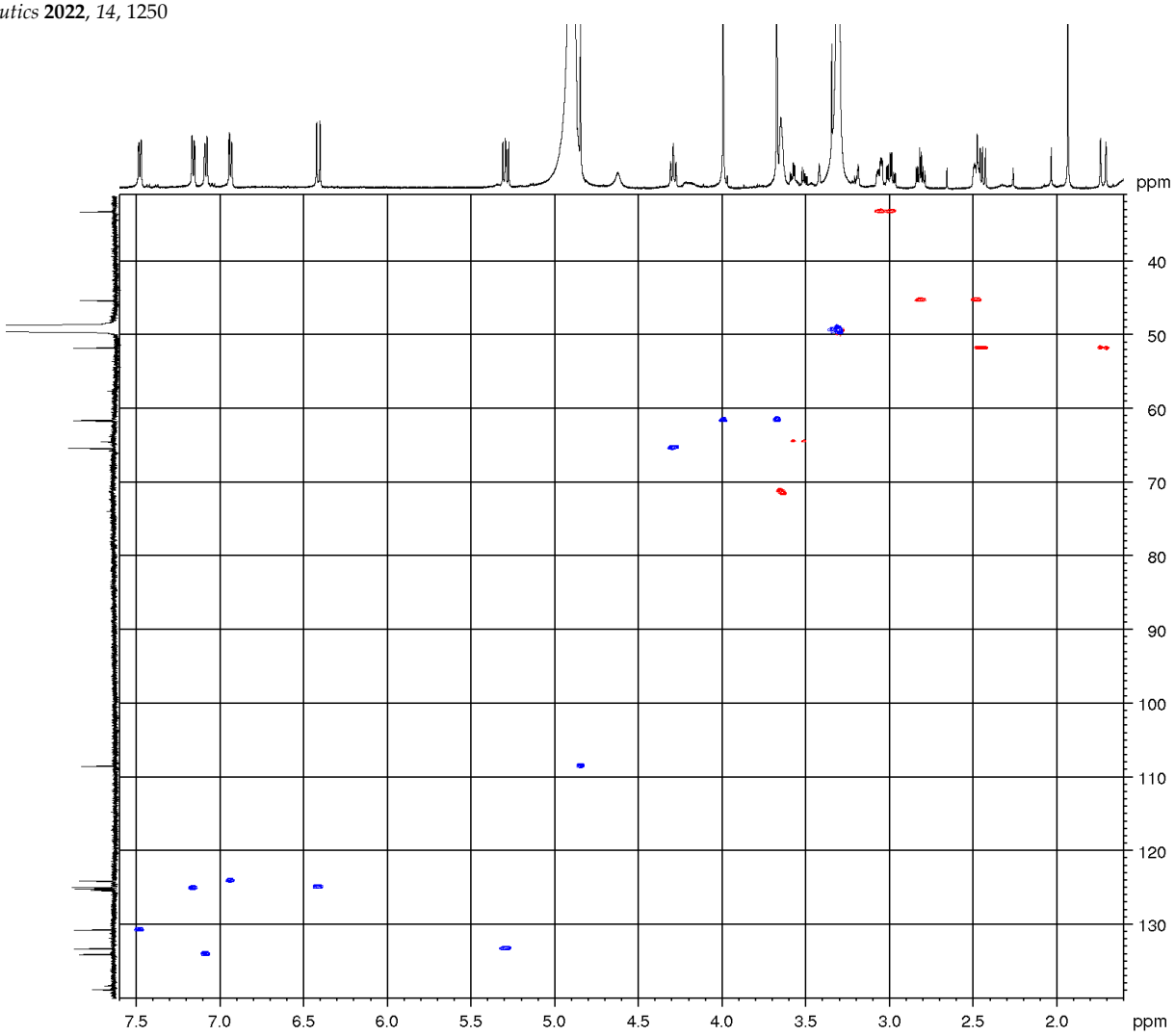

Figure S31. HSQC spectrum of giffonin F (**8**) (methanol-d_4, 295 K).

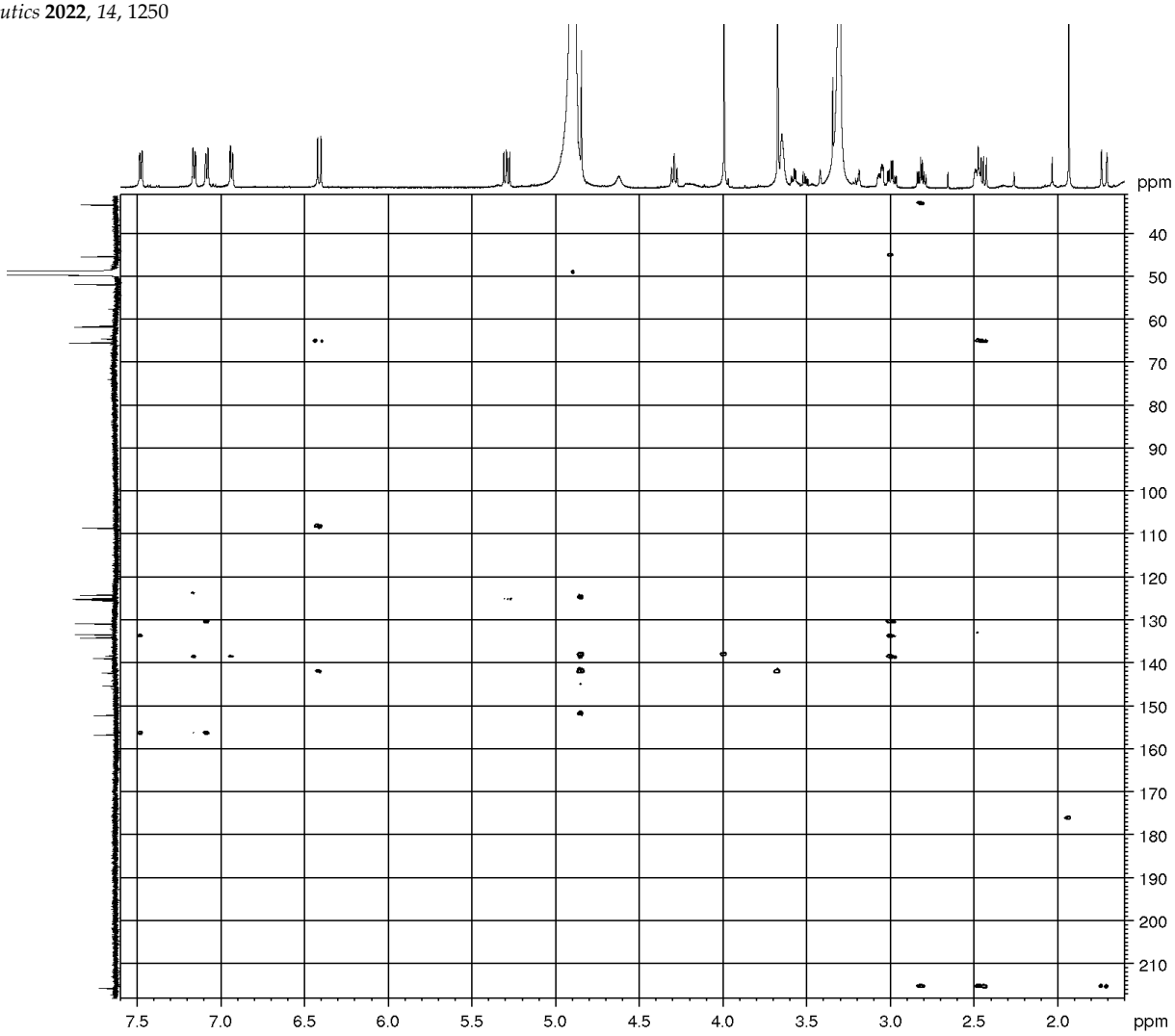

Figure S32. HMBC spectrum of giffonin F (**8**) (methanol-d_4, 295 K).

NMR data of compound **9** (carpinontriol B): ^{1}H NMR (methanol-d_4, 600 MHz, 298 K): δ 7.07 (dd, $^3J_{H,H}$=8.2 Hz, $^4J_{H,H}$=1.9 Hz, 1H, H-5), 7.00 (dd, $^3J_{H,H}$=8.2 Hz, $^4J_{H,H}$=1.9 Hz, 1H, H-15), 6.80 (d, $^3J_{H,H}$=8.2 Hz, 1H, H-4), 6.77 (d, $^3J_{H,H}$=8.2 Hz, 1H, H-16), 6.65 (bd, $^4J_{H,H}$=1.9 Hz, 1H, H-18), 6.36 (bd, $^4J_{H,H}$=1.9 Hz, 1H, H-19), 4.71 (dd, $^3J_{H,H}$=11.9 Hz, $^3J_{H,H}$=4.4 Hz, 1H, H-12), 4.22 (d, $^3J_{H,H}$=10.1 Hz, 1H, H-10), 3.87 (d, $^3J_{H,H}$=10.1 Hz, 1H, H-11), 3.51 (ddd, $^2J_{H,H}$=20.0 Hz, $^3J_{H,H}$=12.5 Hz, $^3J_{H,H}$=2.0 Hz, 1H, H-8a), 3.14 (m, 1H, H-7a), 3.05 (dd, $^2J_{H,H}$=16.0 Hz, $^3J_{H,H}$=4.3 Hz, 1H, H-13a), 2.93 (m, 1H, H-8b), 2.89 (m, 1H, H-13b), 2.84 (m, 1H, H-7b). ^{13}C NMR (methanol-d_4, 150 MHz, 298 K): δ 215.6 (C-9), 153.0 (C-17), 152.1 (C-3), 135.1 (C-19), 135.0 (C-18), 131.4 (C-6), 130.7 (C-14), 130.7 (C-15), 129.5 (C-5), 127.6 (C-1), 126.7 (C-2), 117.0 (C-4, C-16), 78.8 (C-10), 69.8 (C-11), 68.7 (C-12), 37.6 (C-8), 37.1 (C-13), 25.3 (C-7).

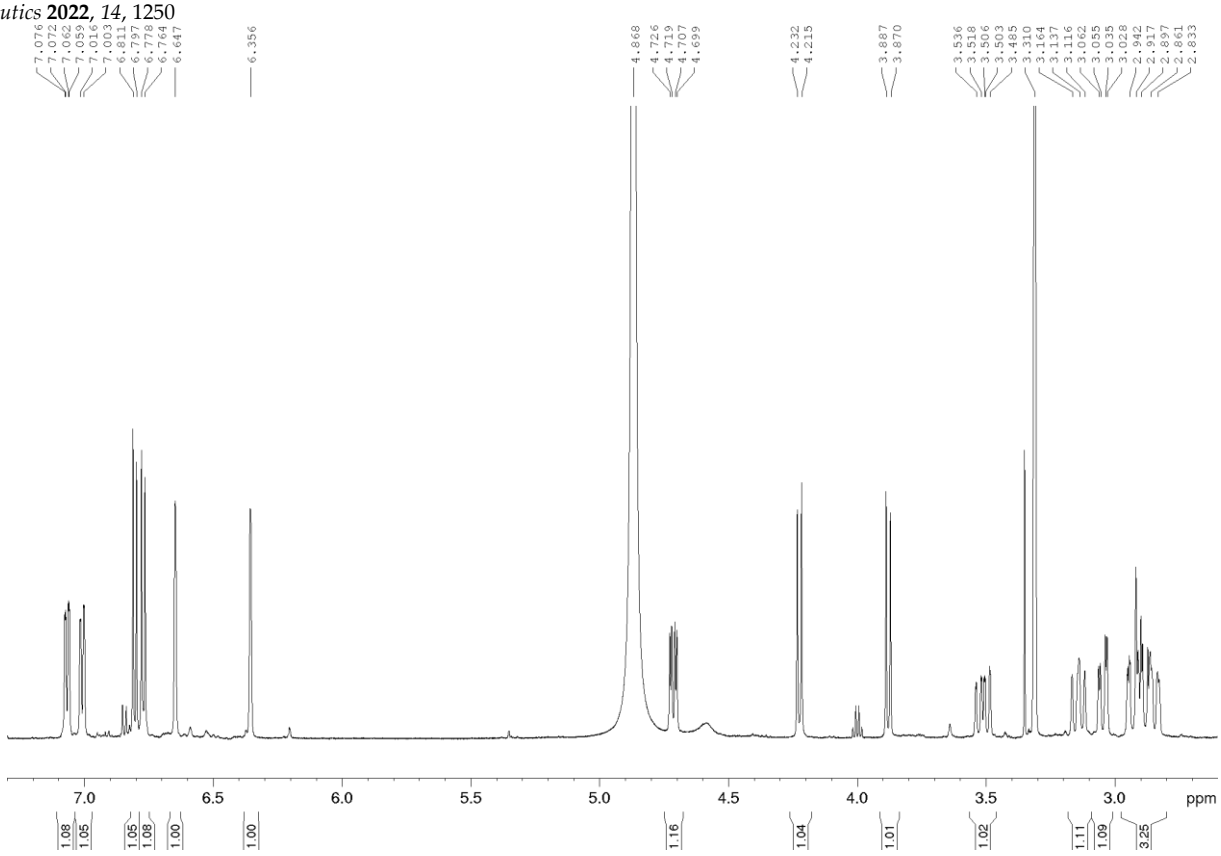

Figure S33. [1]H NMR spectrum of carpinontriol B (**9**) (methanol-d_4, 298 K).

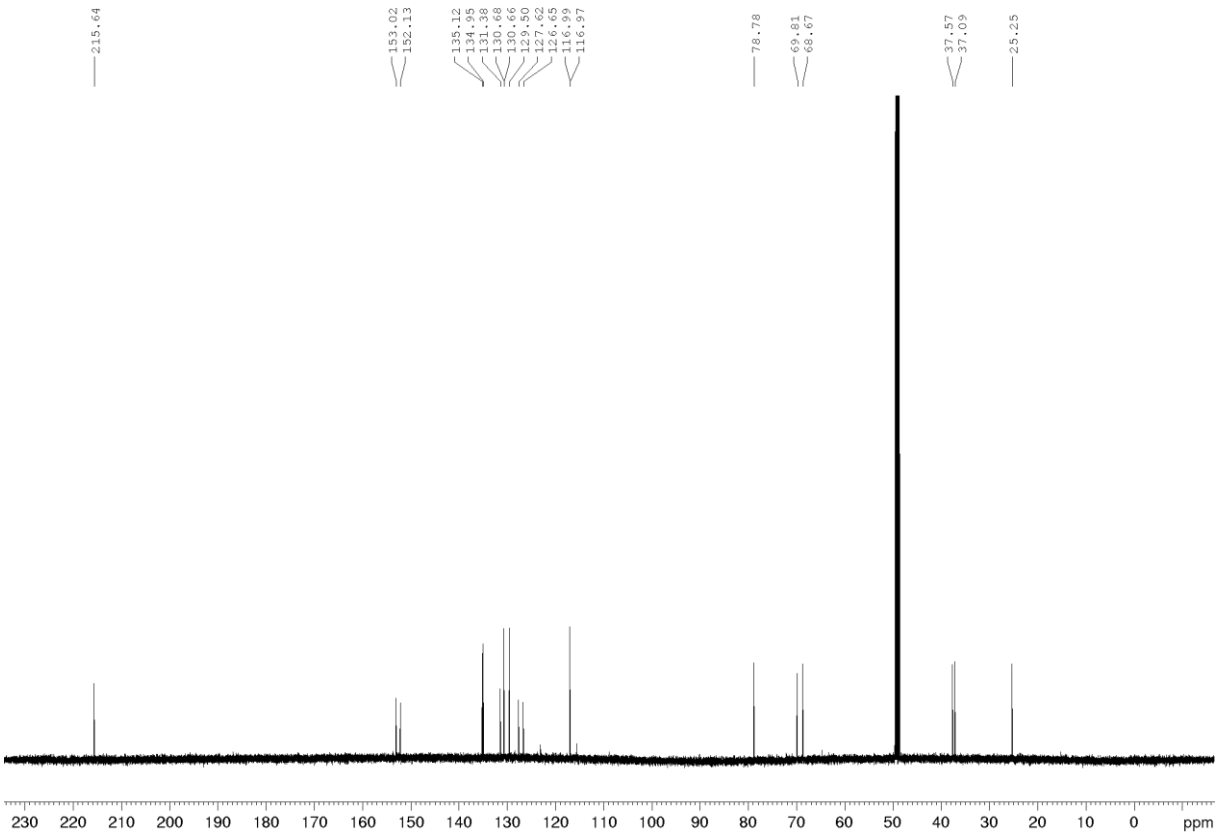

Figure S34. [13]C NMR spectrum of carpinontriol B (**9**) (methanol-d_4, 298 K).

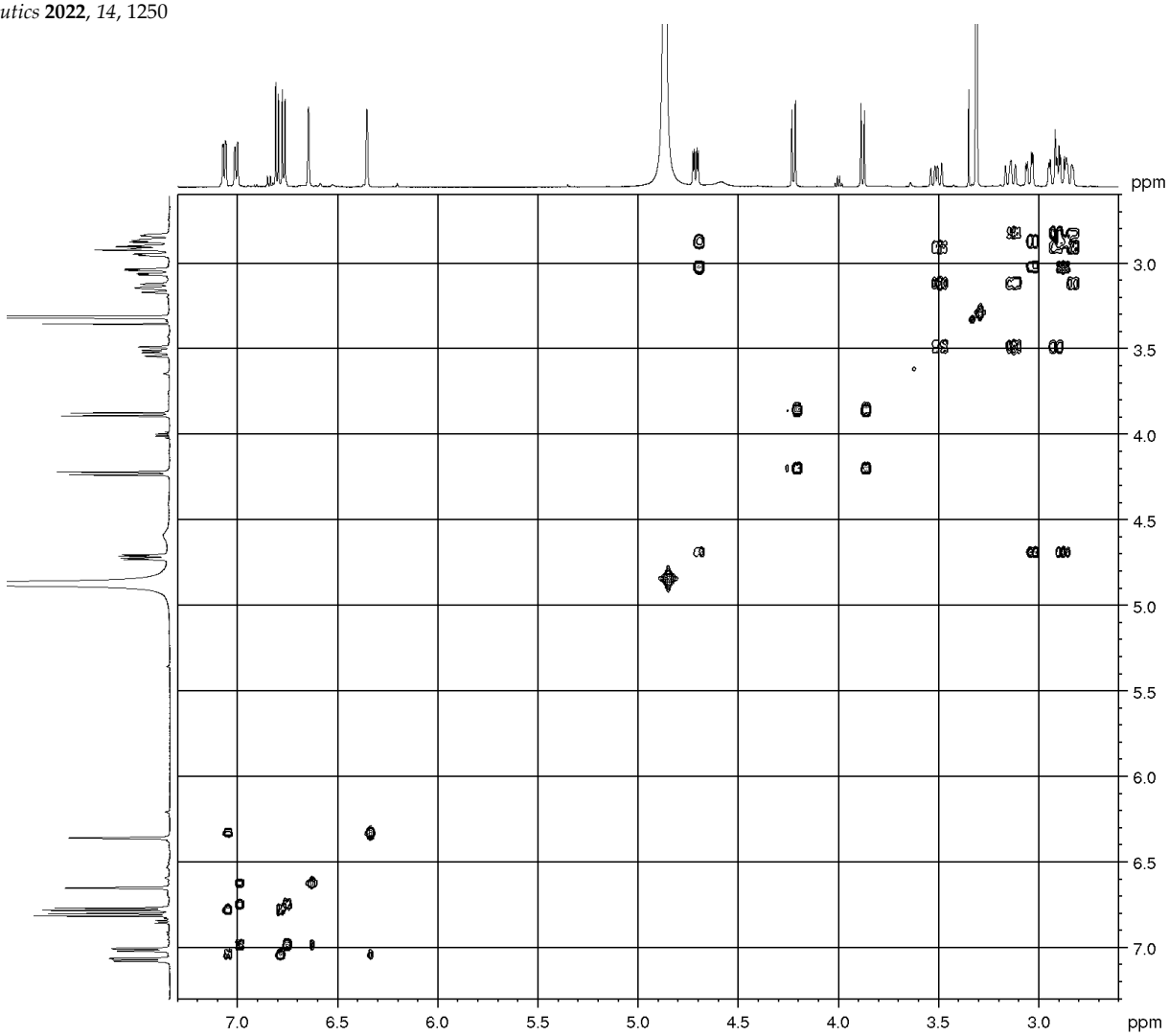

Figure S35. COSY spectrum of carpinontriol B (**9**) (methanol-d_4, 298 K).

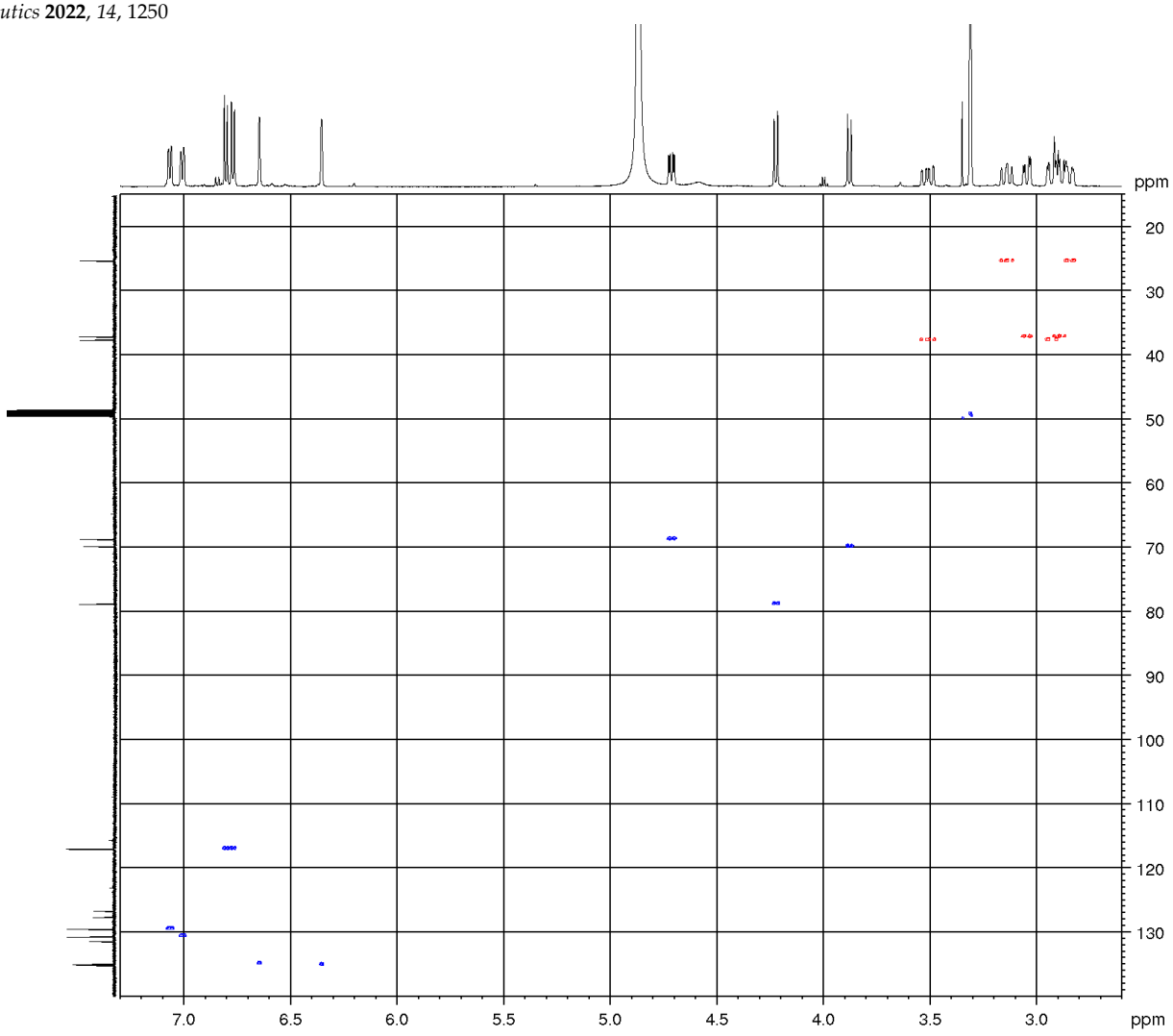

Figure S36. HSQC spectrum of carpinontriol B (**9**) (methanol-d_4, 298 K).

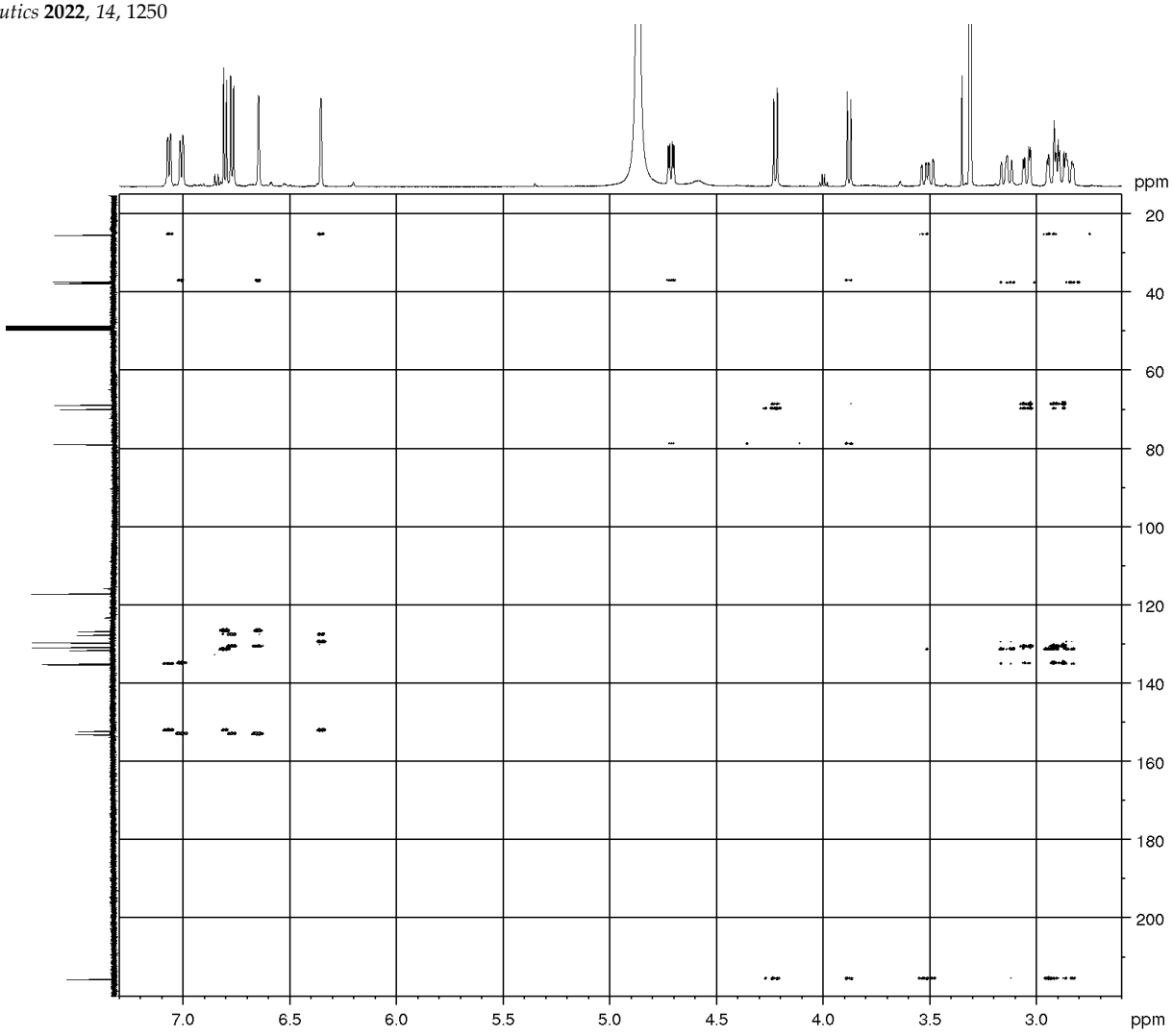

Figure S37. HMBC spectrum of carpinontriol B (**9**) (methanol-d_4, 298 K).