Supplementary Material for

Anti-inflammatory, antiallergic and COVID-19 protease inhibitory activities of phytochemicals from the Jordanian hawksbeard: Identification, structure-activity relationships, molecular modeling and impact on its folk medicinal uses

Sherif S. Ebada[a,b,c,*], Nariman A. Al-Jawabri[b], Fadia S. Youssef[a,c], Dina Elkashef[a,d], Tim-Oliver Knedel[e], Amgad Albohy[f], Michal Korinek[g,h,i], Tsong-Long Hwang[h,i,j], Bing-Hung Chen[g,k,l], Guan-Hua Lin[m], Chia-Yi Lin[m], Sa'ed M. Aldalaien[b], Ahmad M. Disi[n], Christoph Janiak[e], Peter Proksch[a,*]

[a] Institute of Pharmaceutical Biology and Biotechnology, Heinrich-Heine University, D-40225 Düsseldorf, Germany, [b] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Mu'tah University, 61710 Al-Karak, Jordan, [c] Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, Abbasia, 11566 Cairo, Egypt, [d] Department of Pharmacognosy, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt, [e] Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität, D-40204 Düsseldorf, Germany, [f]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The British University in Egypt (BUE), Al-Sherouk City, Cairo-Suez Desert Road, 11837, Egypt, [g] Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan, [h] Department of Biotechnology, College of Life Science, Kaohsiung Medical University, Kaohsiung, Taiwan, [i] Graduate Institute of Natural Products, College of Medicine, Chang Gung University, Taoyuan, Taiwan, [j] Research Center for Chinese Herbal Medicine, Research Center for Food and Cosmetic Safety, and Graduate Institute of Health Industry Technology, College of Human Ecology, Chang Gung University of Science and Technology, Taoyuan, Taiwan, [k] Department of Anesthesiology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [l] Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [m] The Institute of Biomedical Sciences, National Sun Yat-sen University,

Kaohsiung, Taiwan, [n] Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, Al-Isra University, 11622 Amman, Jordan

* Corresponding authors. Tel.: +49211-81-14163; Fax: +49211-81-11923

E-mail addresses: ss_ebada@mutah.edu.jo or sherif_elsayed@pharma.asu.edu.eg (S.S. Ebada) and Peter.Proksch@hhu.de (P. Proksch)

ABSTRACT

On Wednesday 11th of March, 2020, the world health organization (WHO) announced novel coronavirus (COVID-19, also called SARS-CoV-2) as a pandemic. Due to the time shortage and the lack of either a vaccine and/or an effective treatment, many trials focused on testing natural products to find out potential lead candidates. In this field, an edible and a folk medicinal Jordanian plant *Crepis sancta* (Asteraceae) was selected for this study. Phytochemical investigation of its enriched polyphenolic extract afforded four eudesmane sesquiterpenes (**1**-**4**) together with (6*S*,9*R*)-roseoside (**5**) and five different methylated flavonols (**6**-**10**). Structure elucidation of isolated compounds was unambiguously determined based on HRESIMS, X-ray crystallography, exhaustive 1D and 2D NMR experiments. All isolated compounds were assessed for their *in vitro* anti-inflammatory, antiallergic and *in silico* COVID-19 main protease (M^{pro}) inhibitor activities. Among the tested compounds, compounds **5**-**10** revealed potent anti-inflammatory, antiallergic and COVID-19 protease inhibitor activities. Chrysosplenetin (**10**) is considered as a promising anti-inflammatory and antiallergic lead structure adding to the phytotherapeutic pipeline. Moreover, its inhibitory activity against SARS-CoV-2 M^{pro}, supported by docking and molecular dynamic studies, strengthens its potential as a lead structure paving the way toward finding out a natural remedy for the treatment and/or controlling the current COVID-19 pandemic.

Keywords: Hawksbeard; anti-inflammatory; antiallergic; COVID-19 protease; polyphenolics; eudesmane sesquiterpenes.

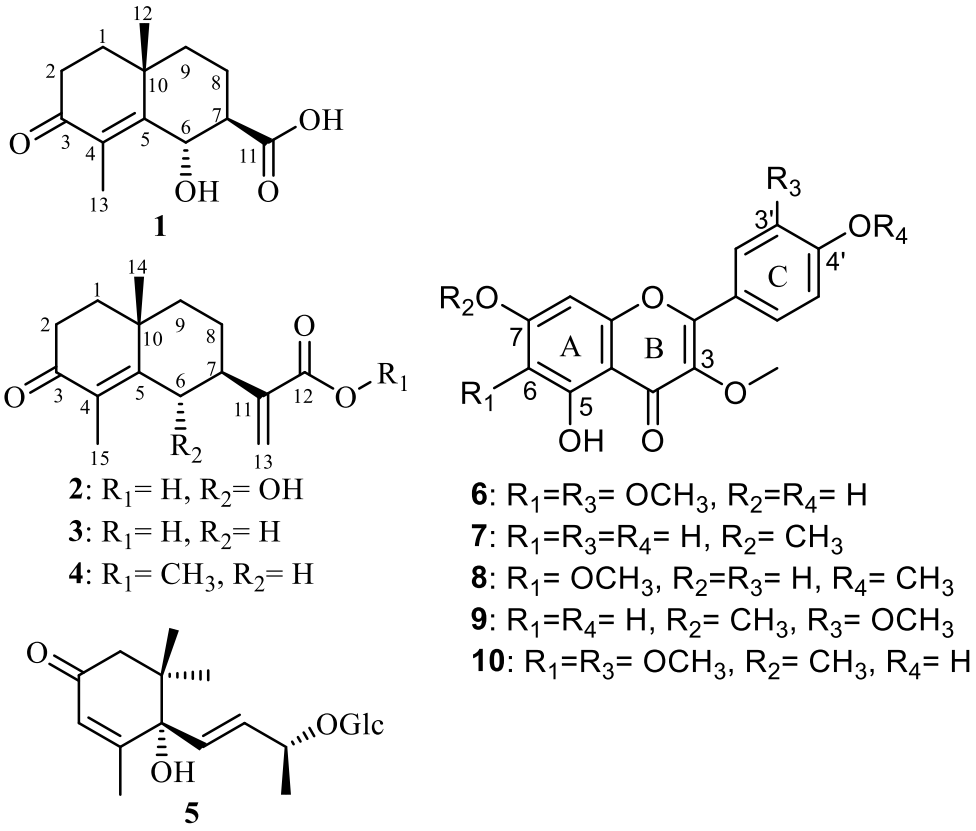

Figure S1. Chemical structures of **1-10**.

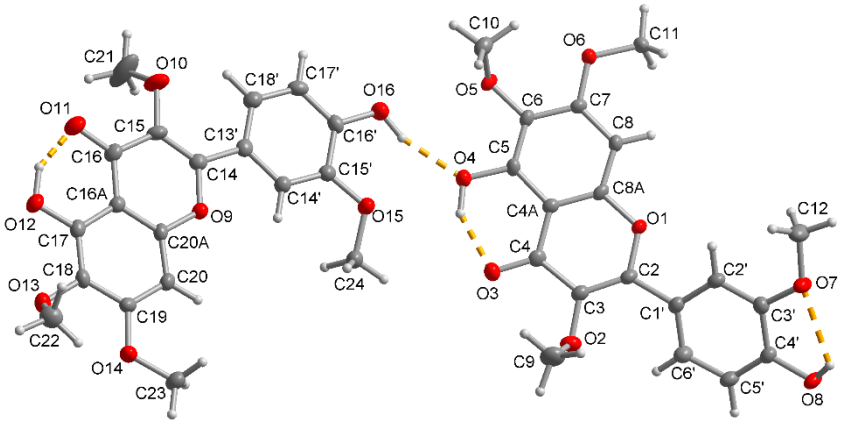

Figure S2. 3D X-ray structure of chrysosplenetin (**10**).

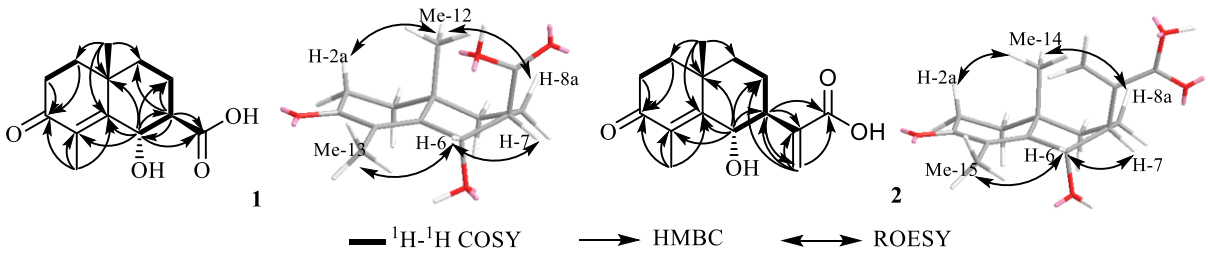

Figure S3. Key ^{1}H-^{1}H COSY, HMBC and ROESY correlations of **1** and **2**.

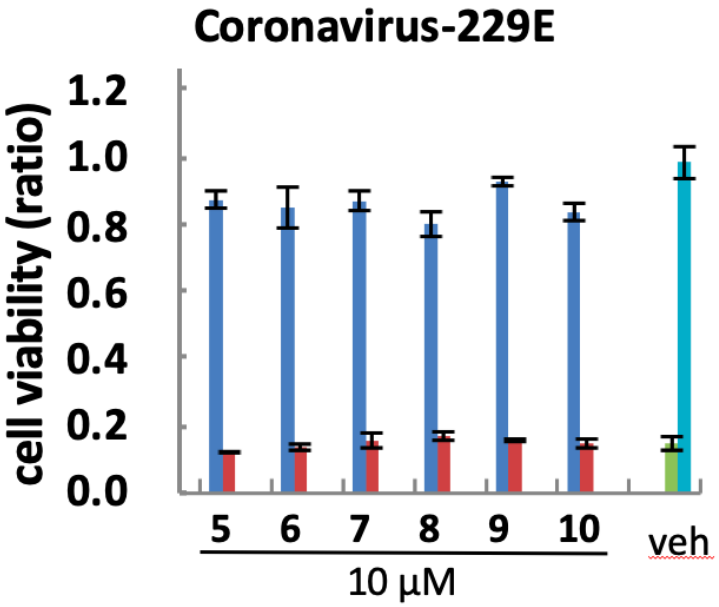

Figure S4. Human coronavirus 229E (HCoV-229E) protective activity. The cells infected by HCoV-229E were treated with the compounds 5 to 10 (red) or vehicle (green), their difference would indicate protective effects against HCoV-229E infection. The uninfected cells were treated with the compounds 5 to 10 (dark blue) or vehicle only (cyan), serving as control for toxicity of the samples and vehicle. Veh; vehicle.

Table S1. NMR data of **1** and **2** in methanol-d_4 (^{1}H at 600 MHz and ^{13}C at150 MHz).

pos.	**1**		**2**	
	δ_H (J in Hz)	δ_C,[a,b] type	δ_H (J in Hz)	δ_C,[a,b] type
1	1.72 (m) 1.83 (m)	39.8, CH_2	1.72 (m) 1.79 (m)	37.9, CH_2
2	2.66 (ddd, 17.4, 15.2, 5.2) 2.38 (ddd, 17.4, 4.5, 2.5)	34.6, CH_2	2.77 (ddd, 18.2, 14.7, 5.6) 2.47 (ddd, 18.2, 5.2, 2.0)	34.6, CH_2
3		202.5, CO		201.0, CO
4		132.0, C		137.3, C
5		161.2, C		154.3, C
6	5.25 (d, 3.0)	67.6, CH	5.52 (d, 6.5)	77.3, CH
7	2.46 (dt, 12.9, 3.0)	49.0, CH	3.29 (m)	41.2, CH
8	2.21 (ddd, 13.4, 12.9, 3.2) 1.74 (m)	18.5, CH_2	1.84 (m) 1.63 (m)	26.0, CH_2
9	1.39 (dd, 13.3, 3.2) 1.70 (dd, 6.7, 3.0)	41.4, CH_2	1.48 (m) 1.72 (ddq, 11.7, 5.5, 3.2, 1.9)	41.8, CH_2
10		36.1, C		35.6, C
11		176.8, CO		142.2, C
12	1.42 (s)	24.4, CH_3		172.2, CO
13	1.87 (br s)	10.3, CH_3	a: 6.22 (d, 1.5) b: 5.80 (d, 1.5)	122.8, CH_2
14			1.26 (s)	24.5, CH_3
15			1.88 (br s)	10.6, CH_3

[a] Carbon type is determined from gHMQC data. [b] Shifts are assigned on the basis of gHMQC and gHMBC data.

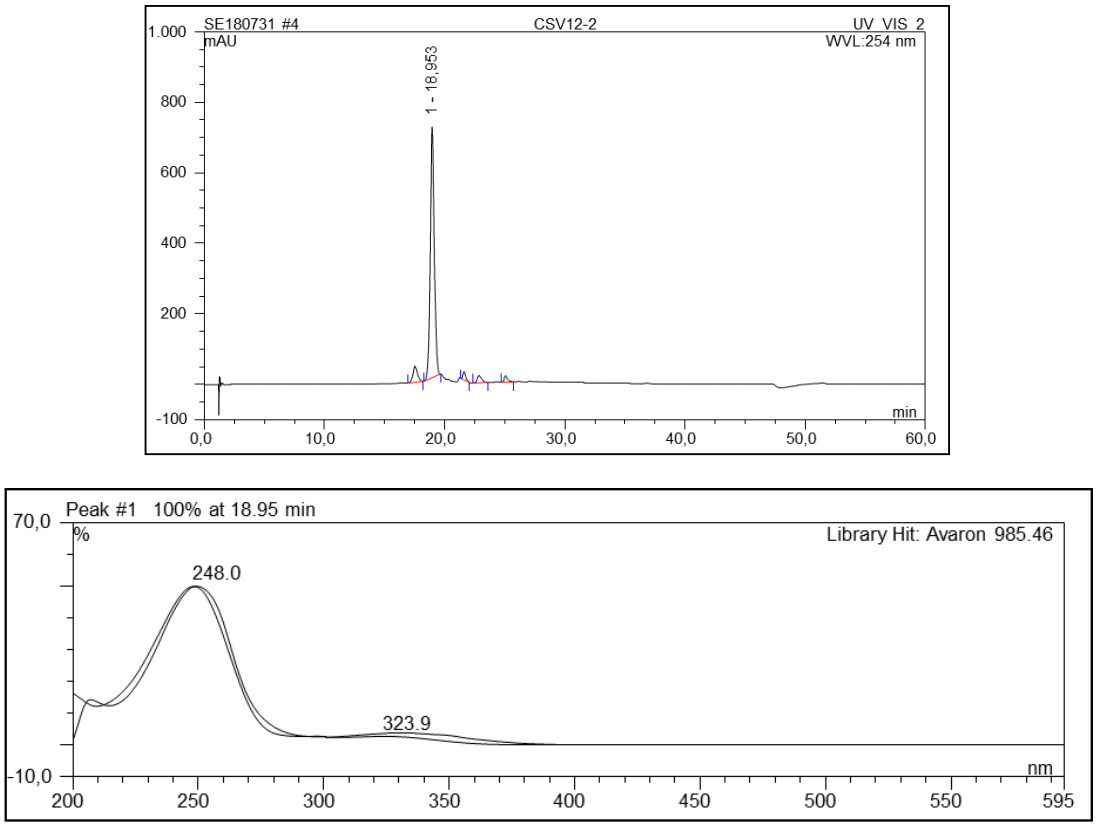

Figure S5. HPLC chromatogram of **1**

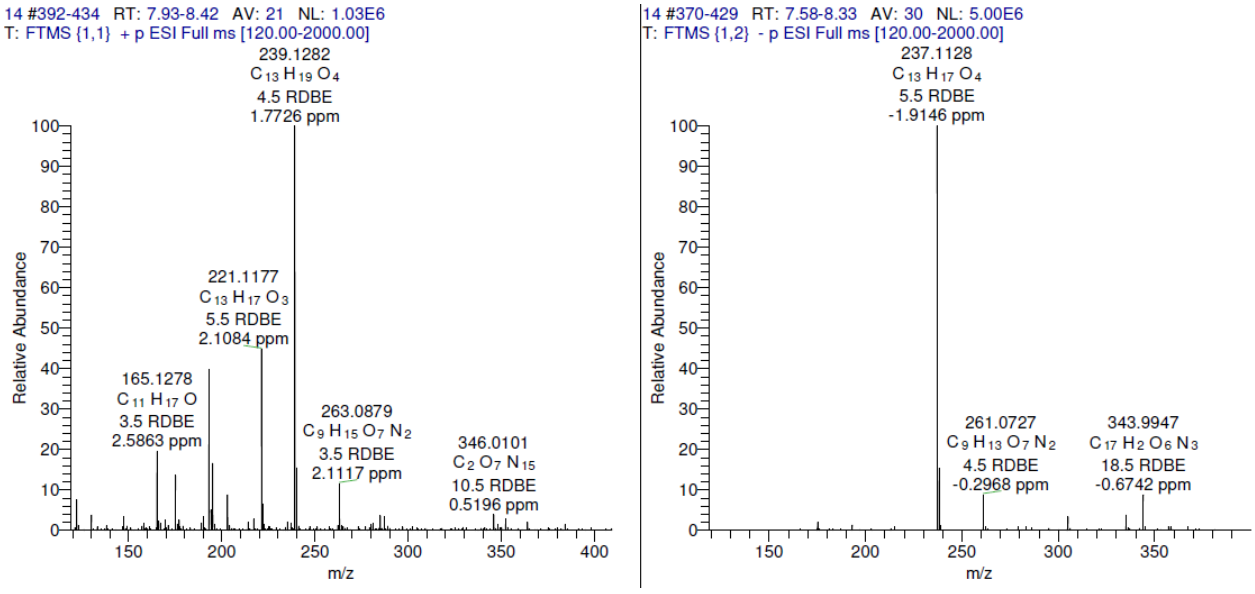

Figure S6. HRESIMS spectrum of **1**

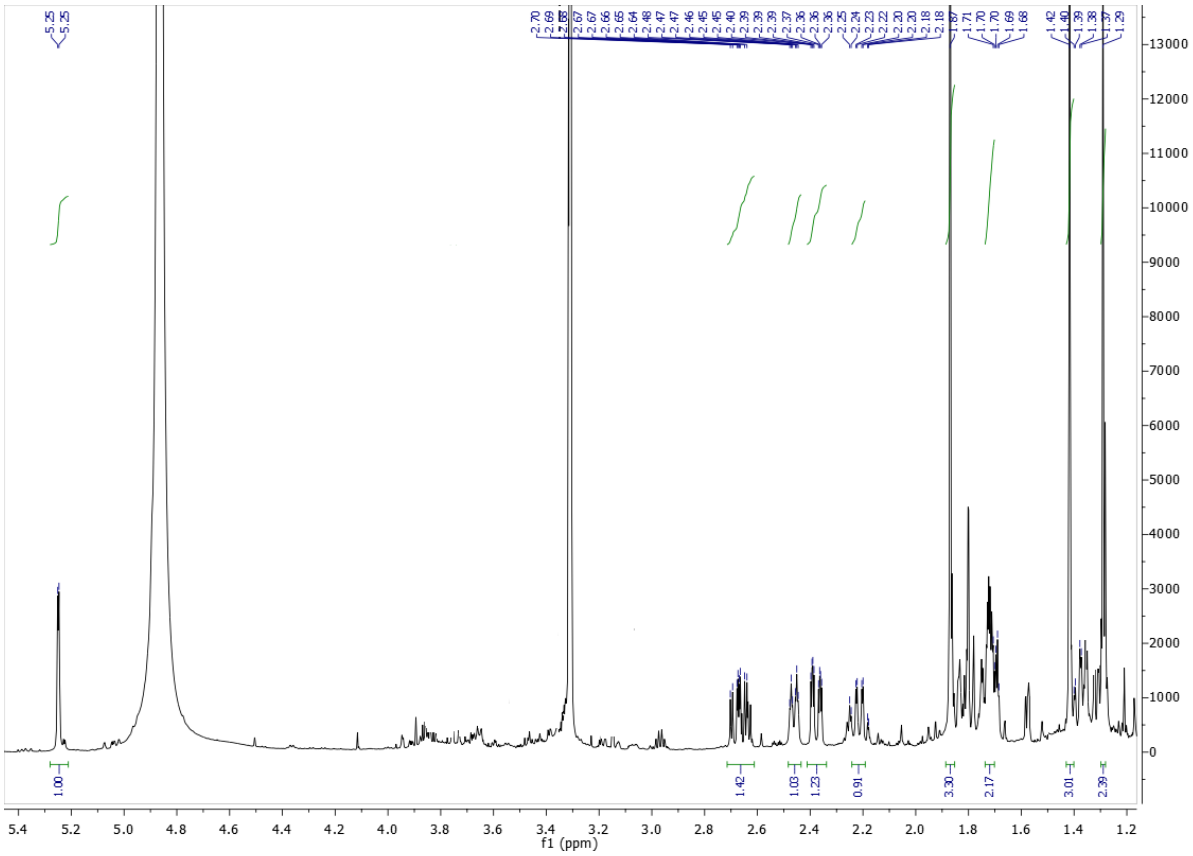

Figure S7. ^{1}H NMR spectrum of **1** in methanol-d_4 at 600 MHz.

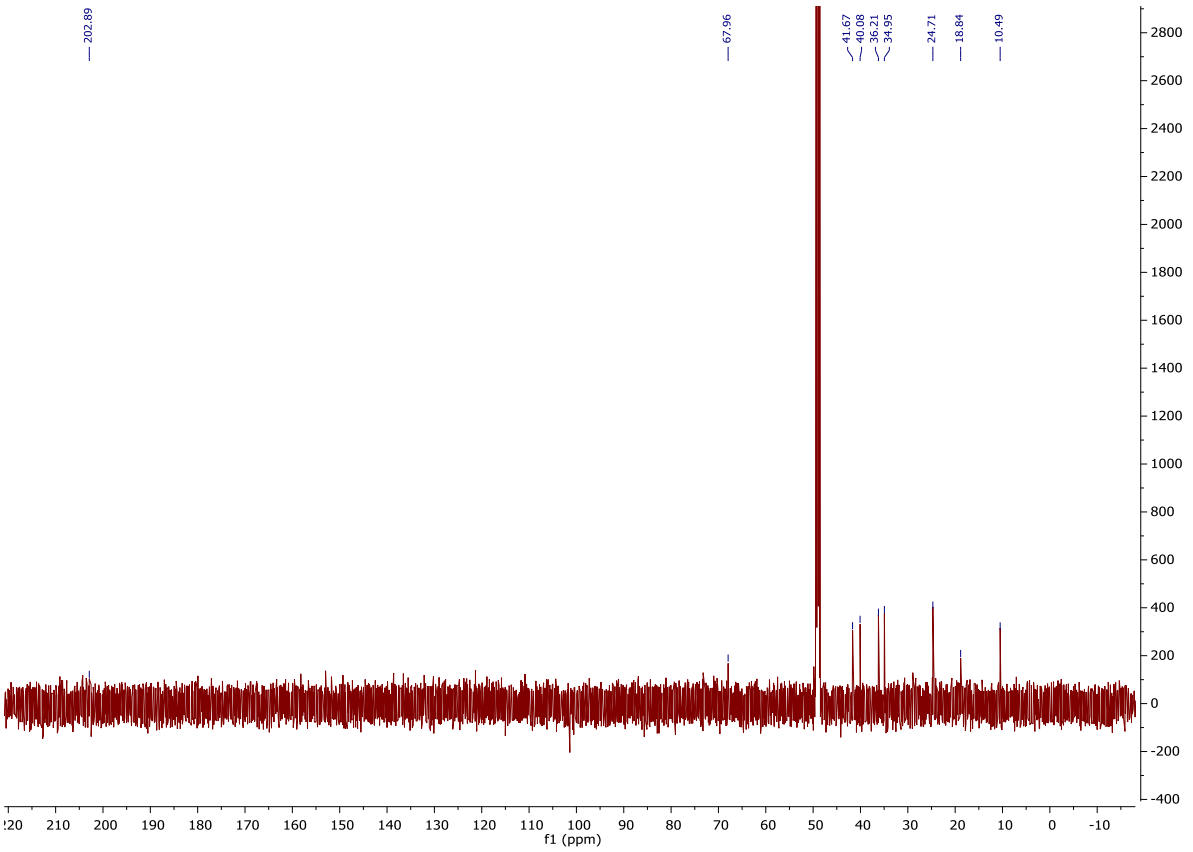

Figure S8. ^{13}C NMR spectrum of **1** in methanol-d_4 at 600 MHz.

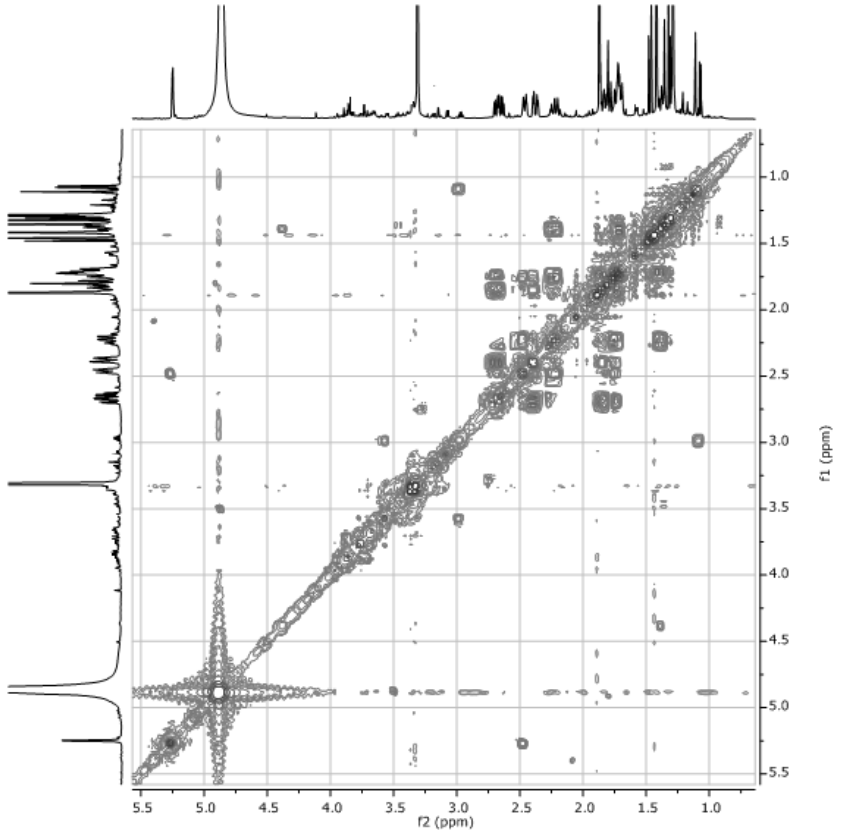

Figure S9. $^{1}H–^{1}H$ COSY spectrum of **1** in methanol-d_4 at 600 MHz.

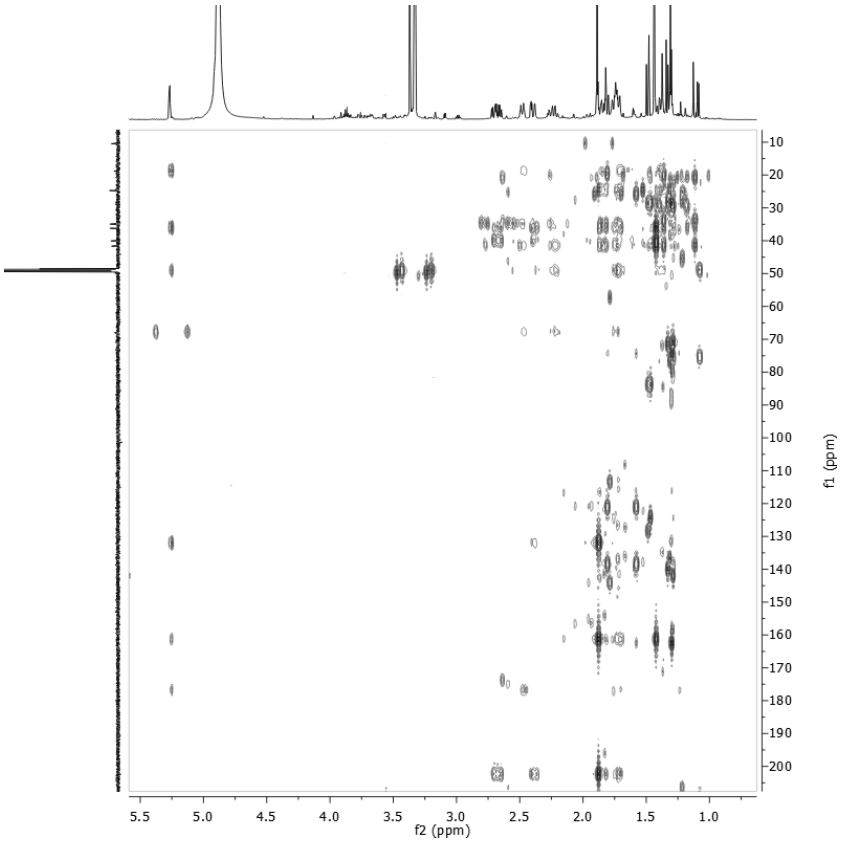

Figure S10. *g*HMBC spectrum of **1** in methanol-d_4 at 600 MHz.

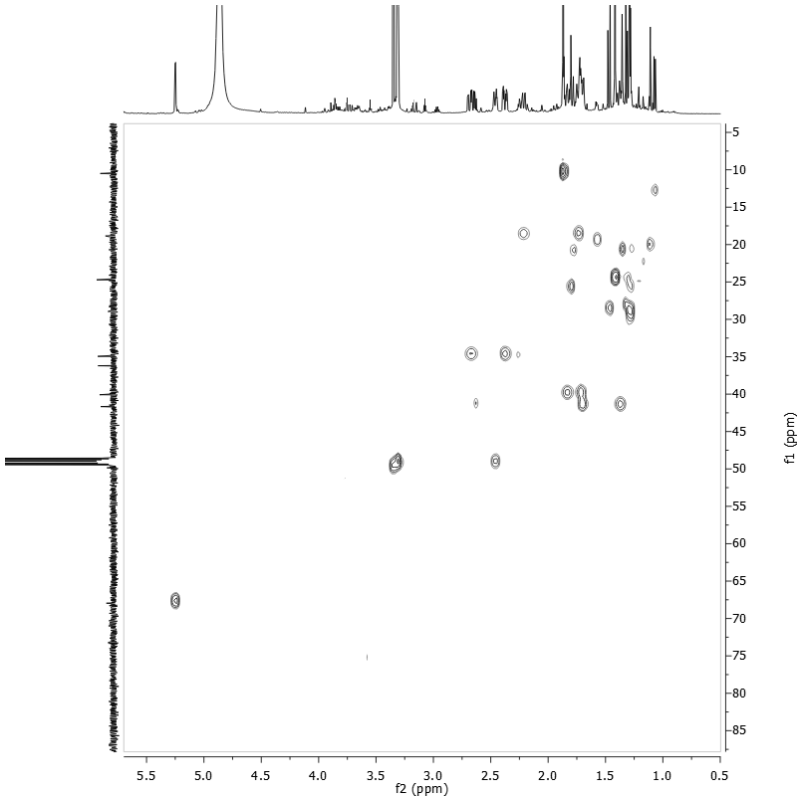

Figure S11. *g*HMQC spectrum of **1** in methanol-d_4 at 600 MHz.

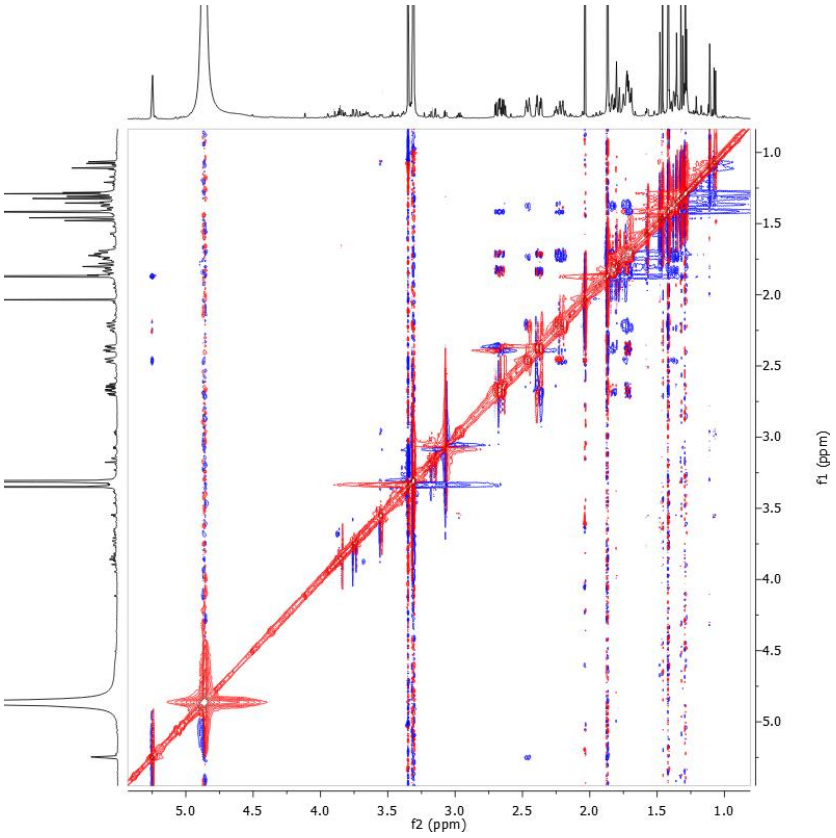

Figure S12. ROESY spectrum of **1** in methanol-d_4 at 600 MHz.

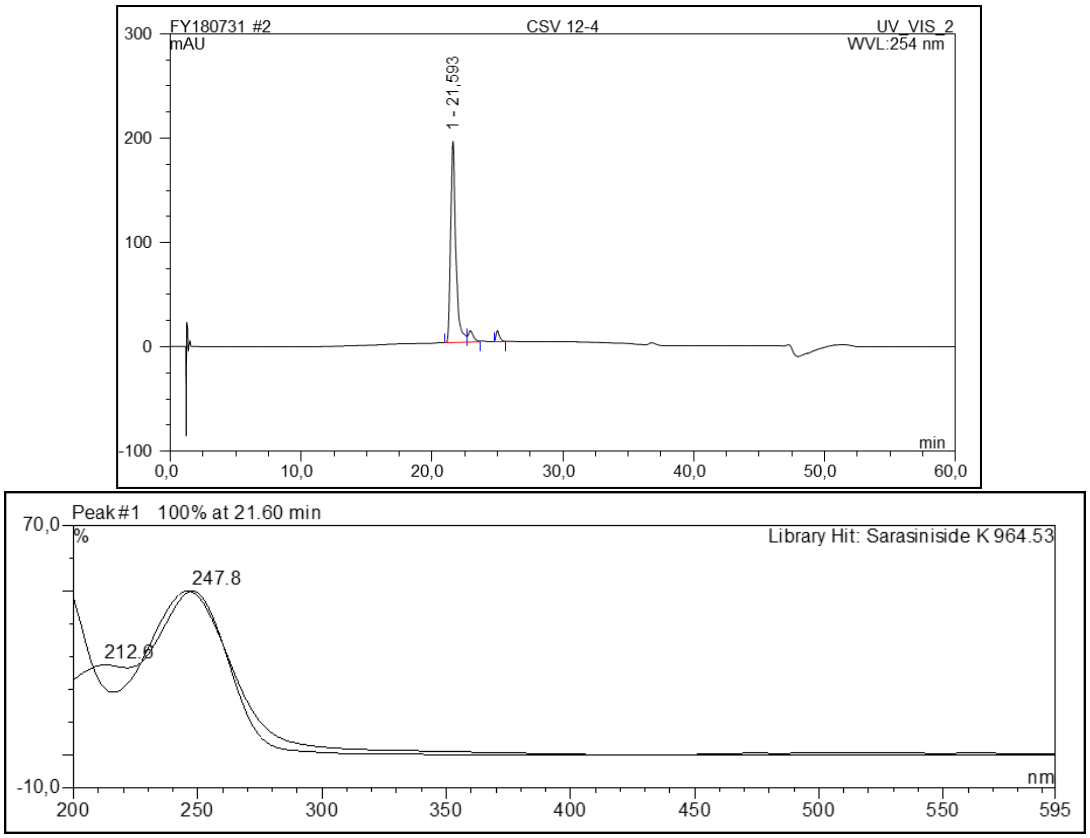

Figure S13. HPLC chromatogram of **2**

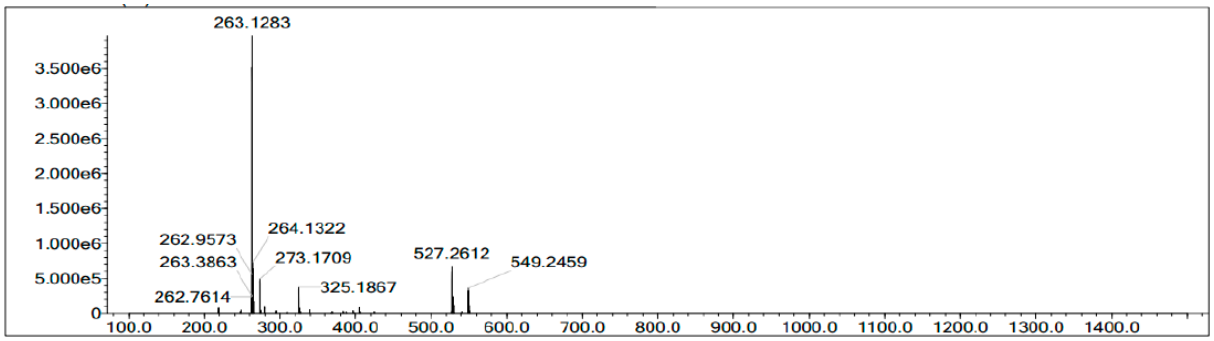

Figure S14. HRESIMS spectrum of **2**

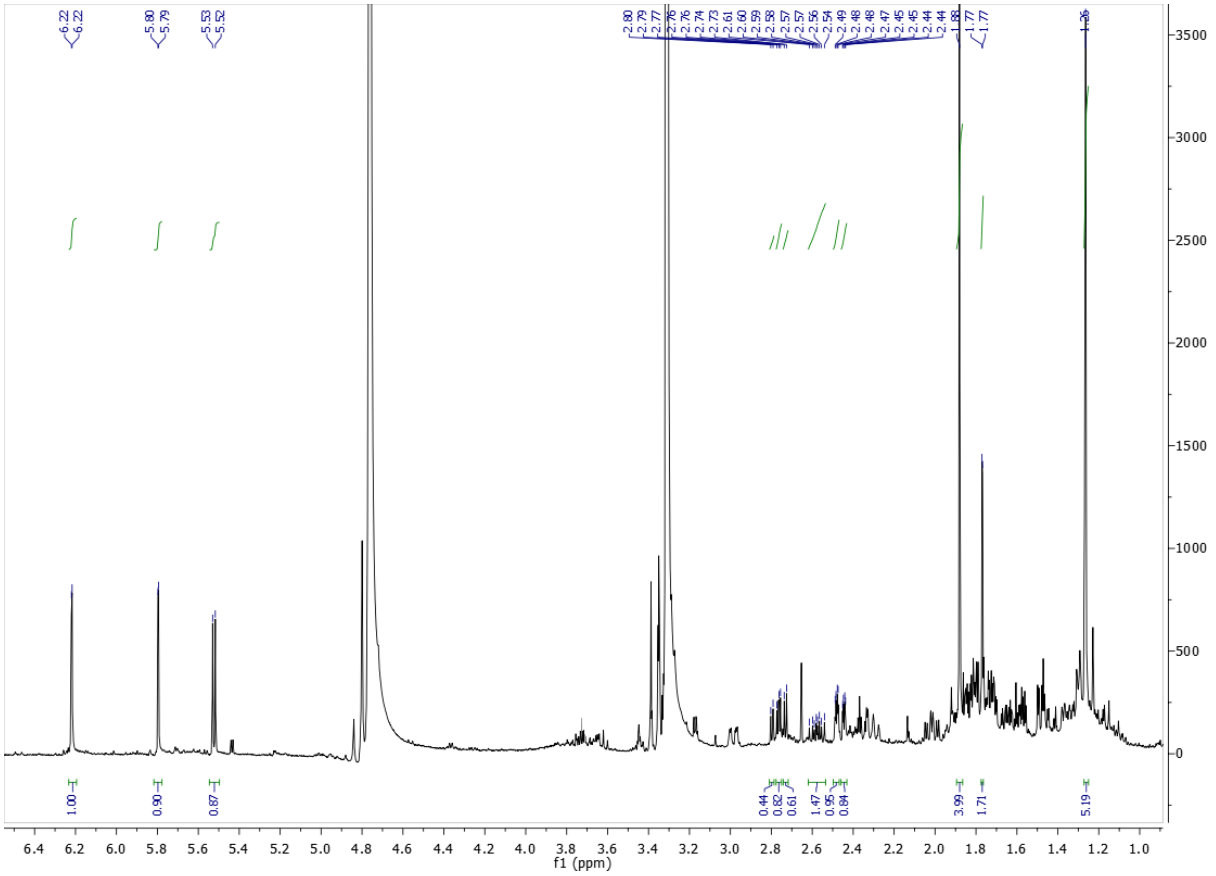

Figure S15. ^{1}H NMR spectrum of **2** in methanol-d_4 at 600 MHz.

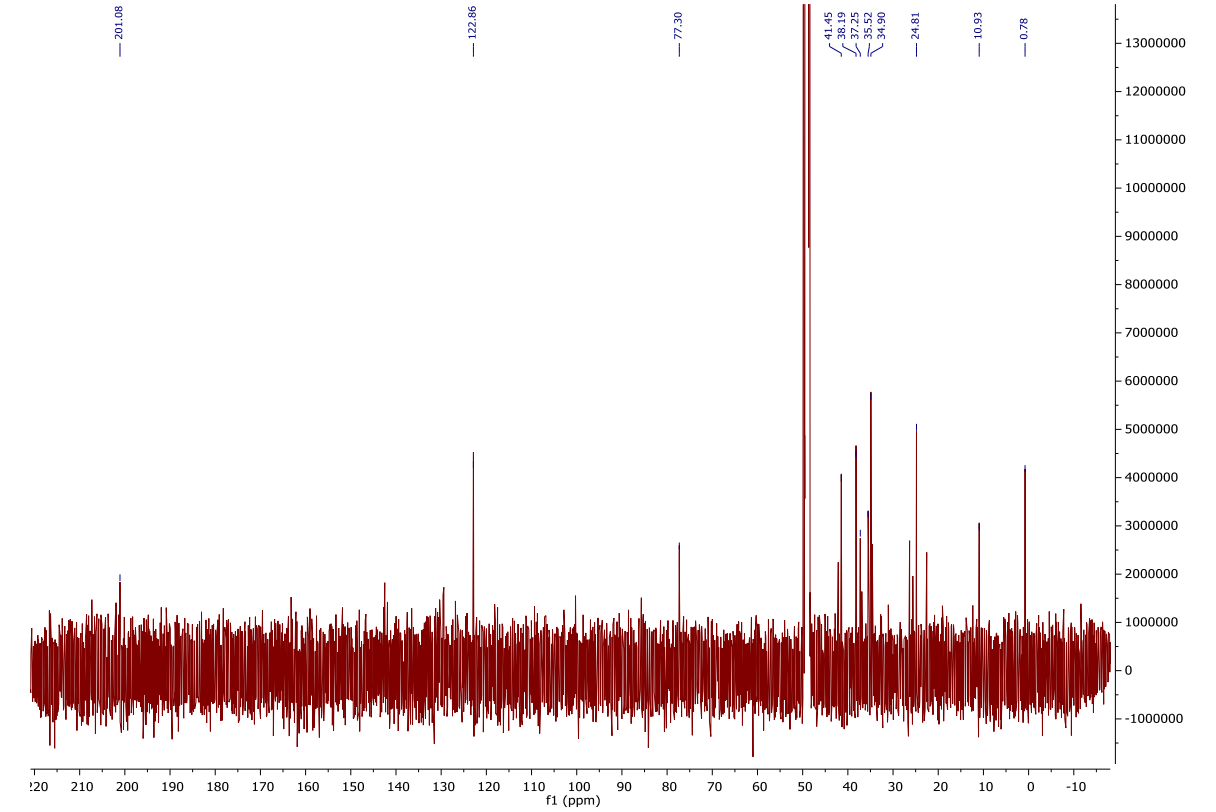

Figure S16. ^{13}C NMR spectrum of **2** in methanol-d_4 at 600 MHz.

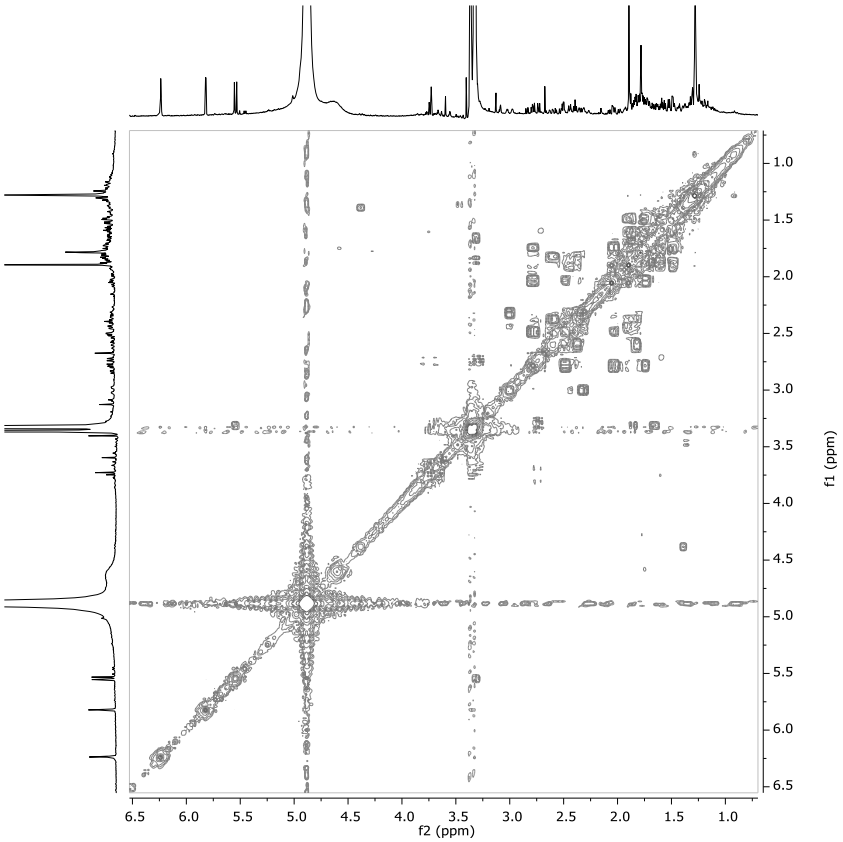

Figure S17. ^{1}H–^{1}H COSY spectrum of **2** in methanol-d_4 at 600 MHz.

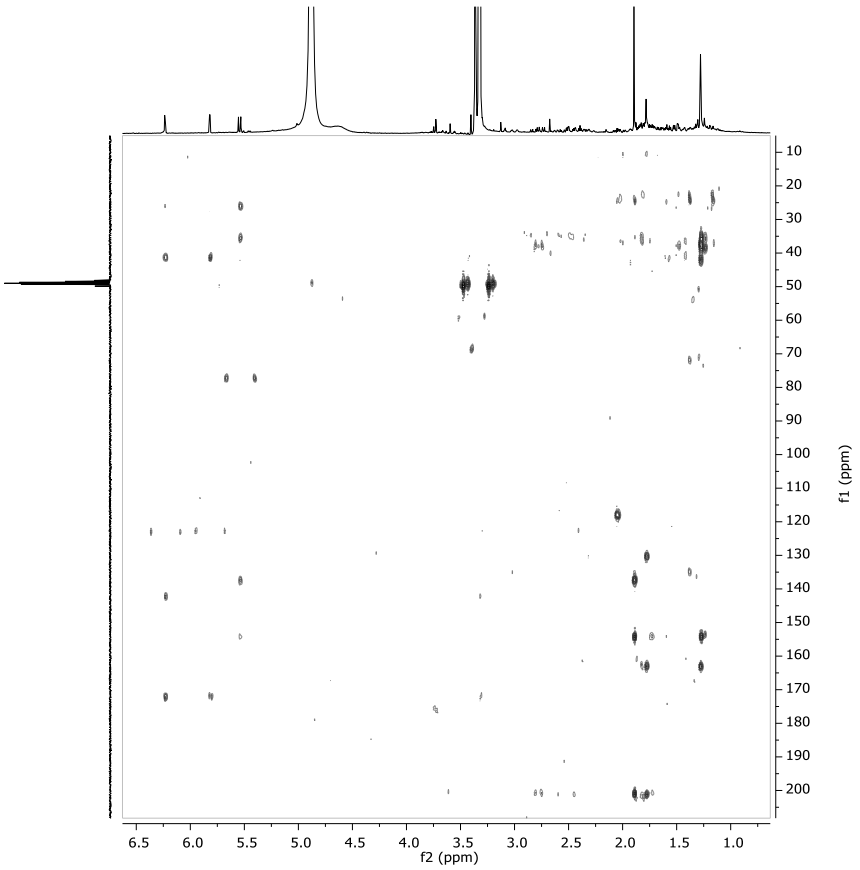

Figure S18. *g*HMBC spectrum of **2** in methanol-d_4 at 600 MHz.

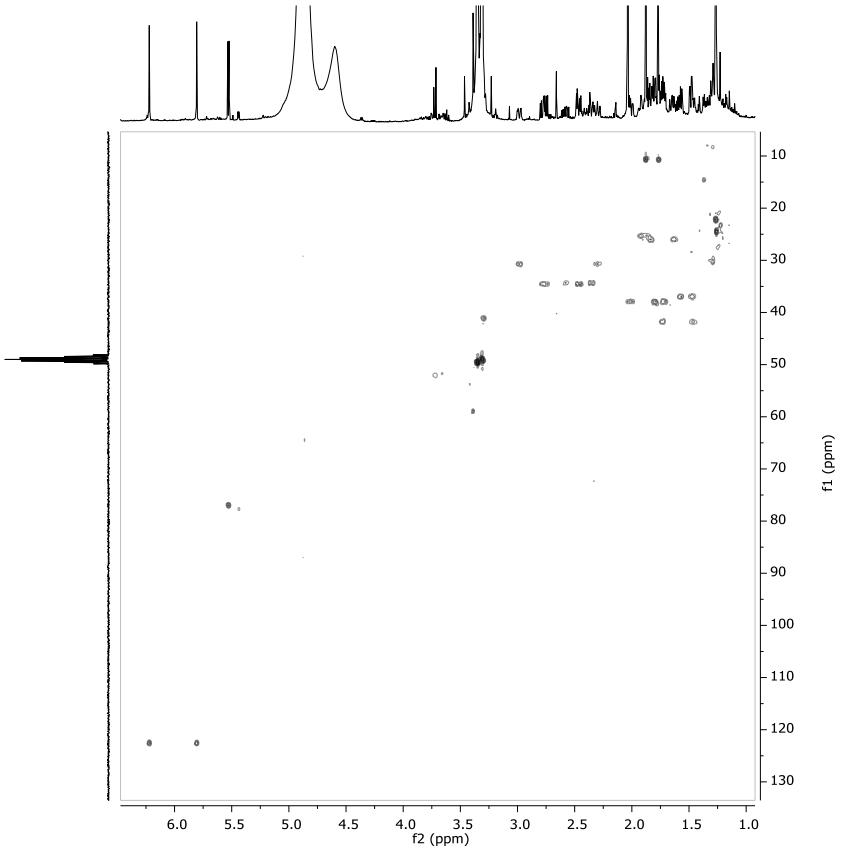

Figure S19. *g*HMQC spectrum of **2** in methanol-d_4 at 600 MHz.

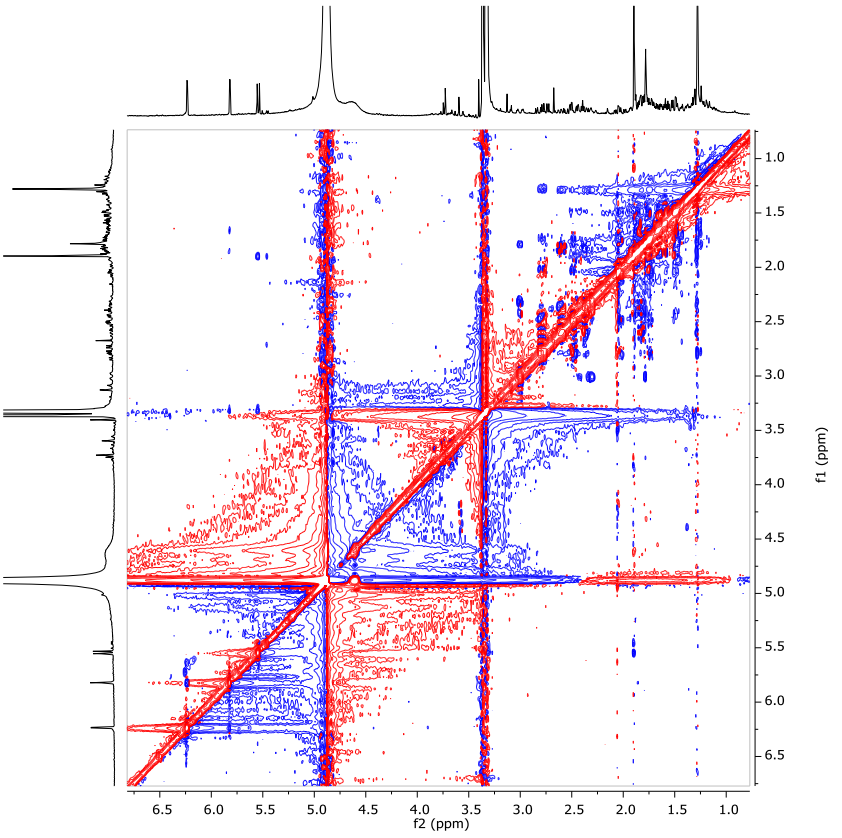

Figure S20. ROESY spectrum of **2** in methanol-d_4 at 600 MHz.

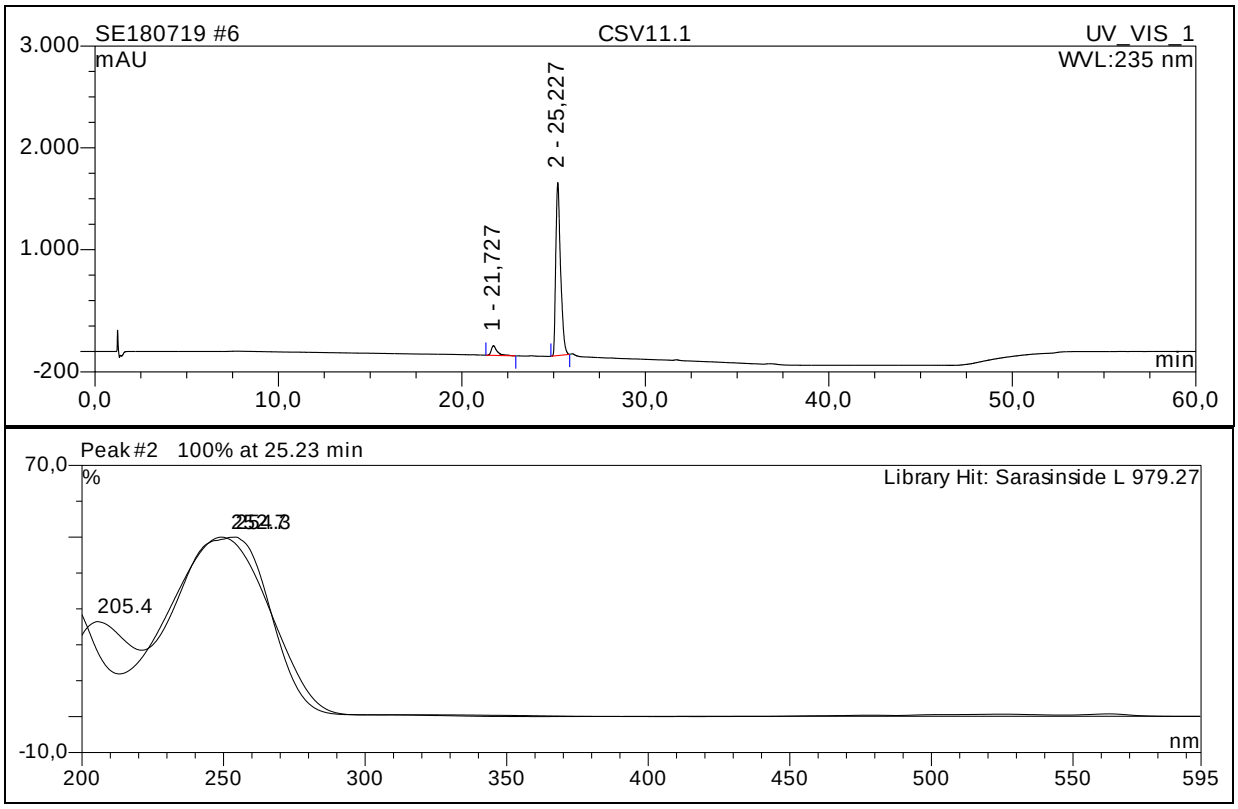

Figure S21. HPLC chromatogram of **3**

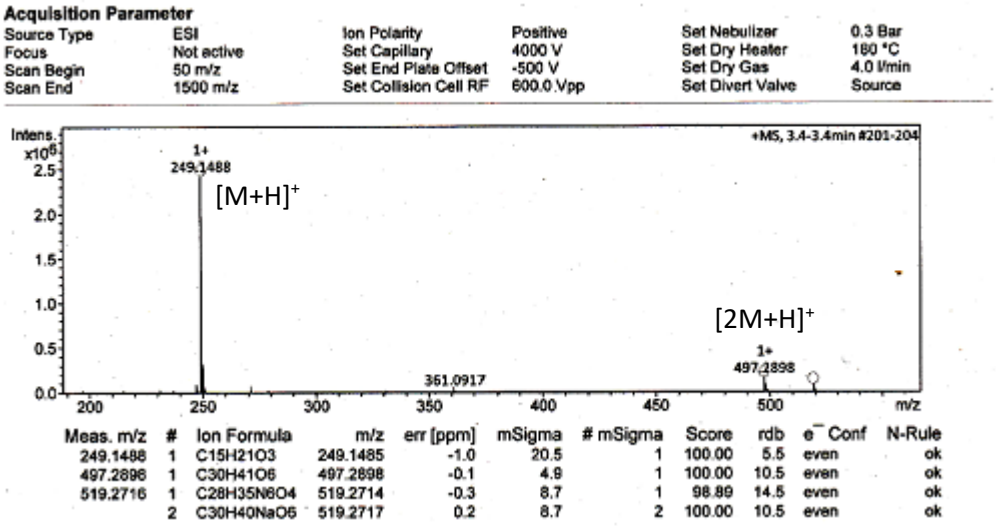

Figure S22. HRESIMS spectrum of **3**

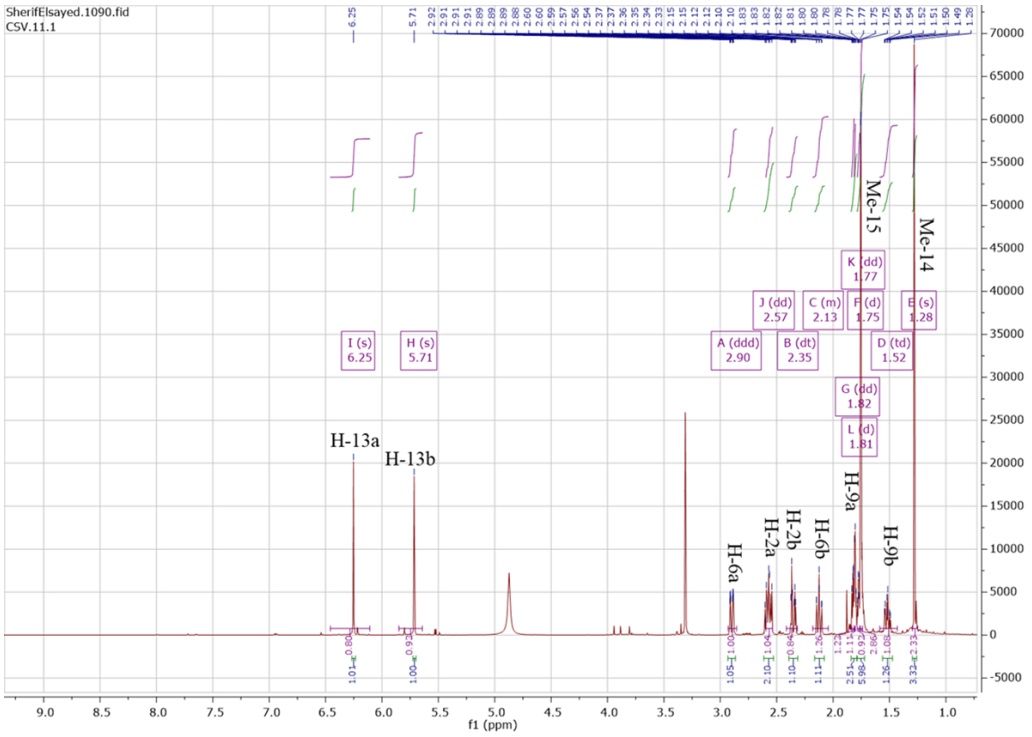

Figure S23. ^{1}H NMR spectrum of **3** in methanol-d_4 at 600 MHz.

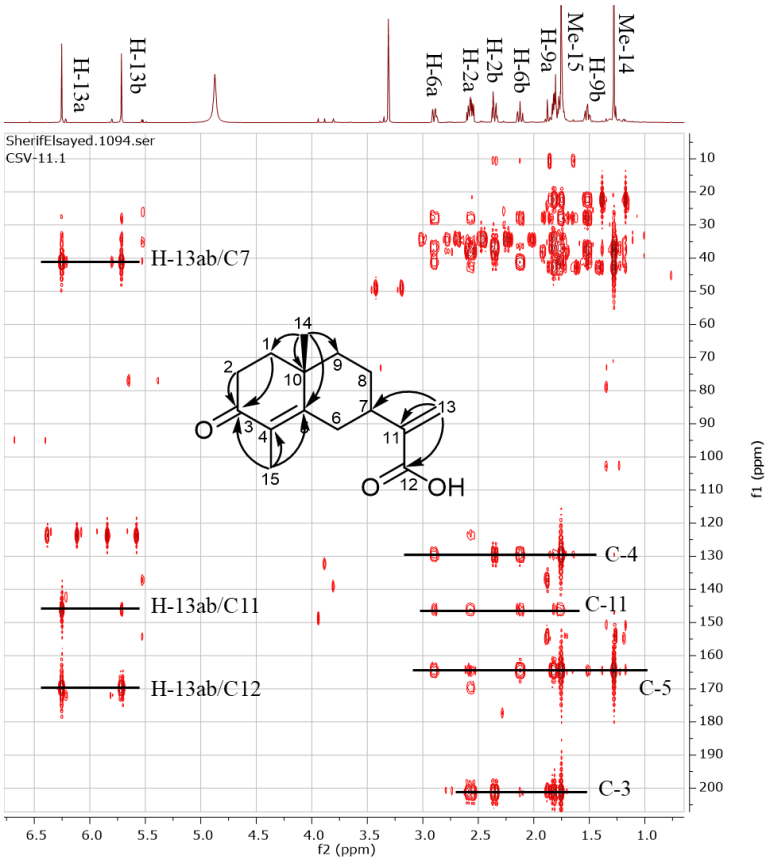

Figure S24. *g*HMBC spectrum of **3** in methanol-d_4 at 600 MHz.

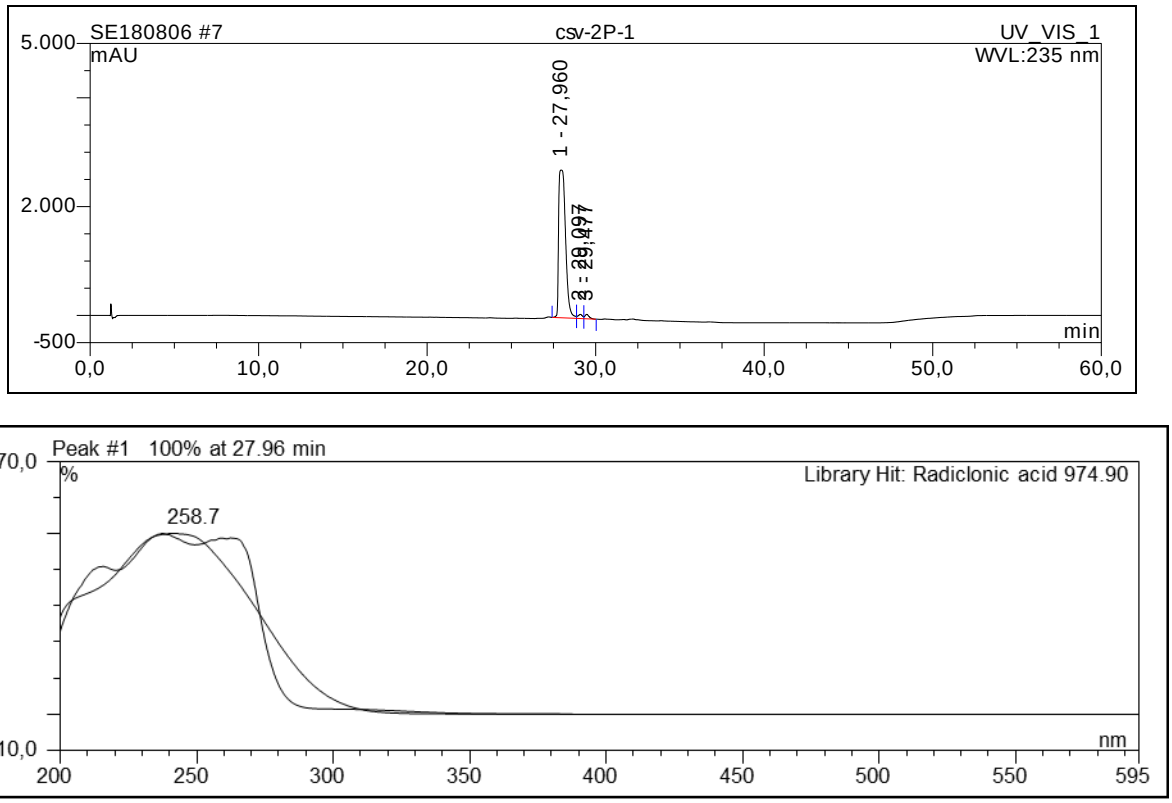

Figure S25. HPLC chromatogram of **4**

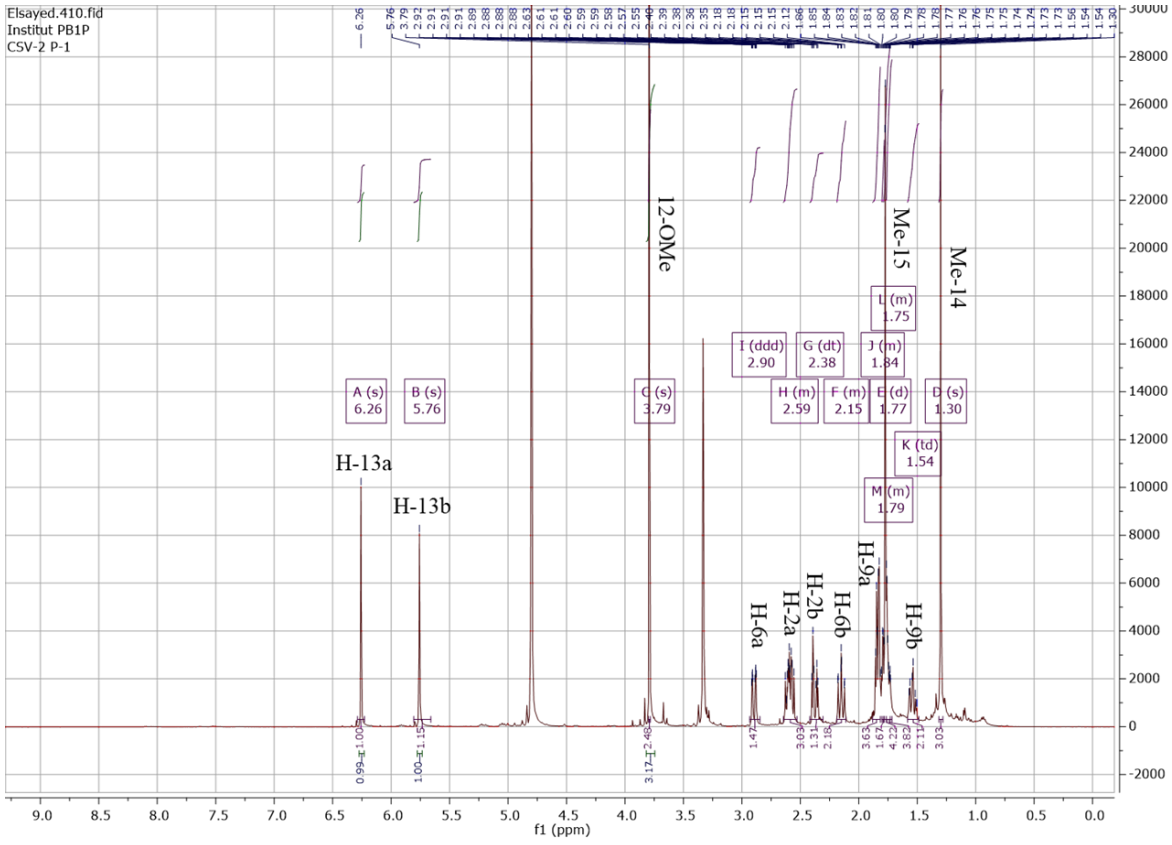

Figure S26. ^{1}H NMR spectrum of **4** in methanol-d_4 at 600 MHz.

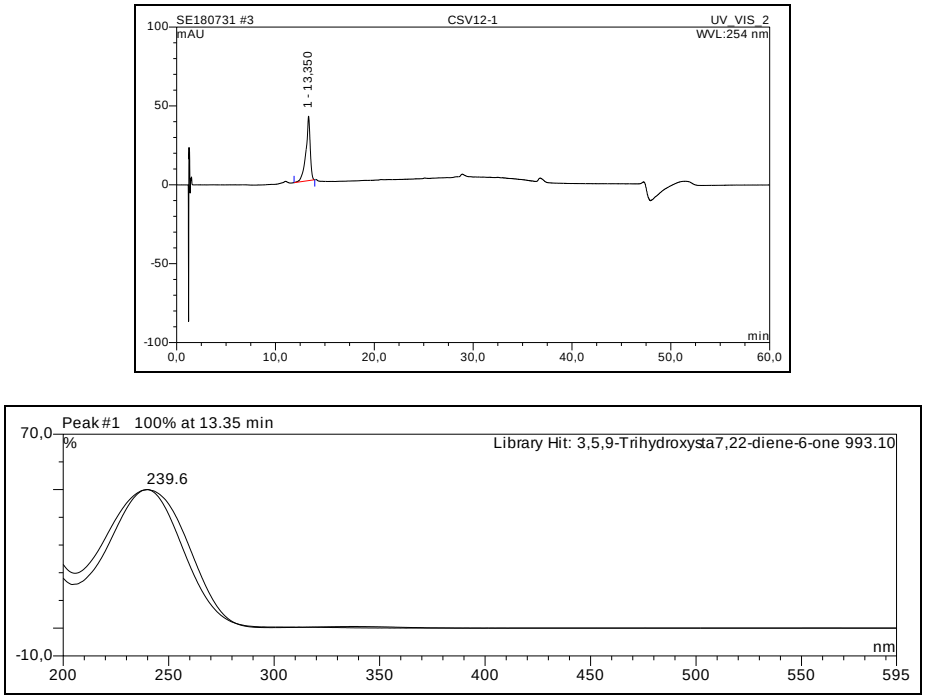

Figure S27. HPLC chromatogram and UV spectrum of **5**

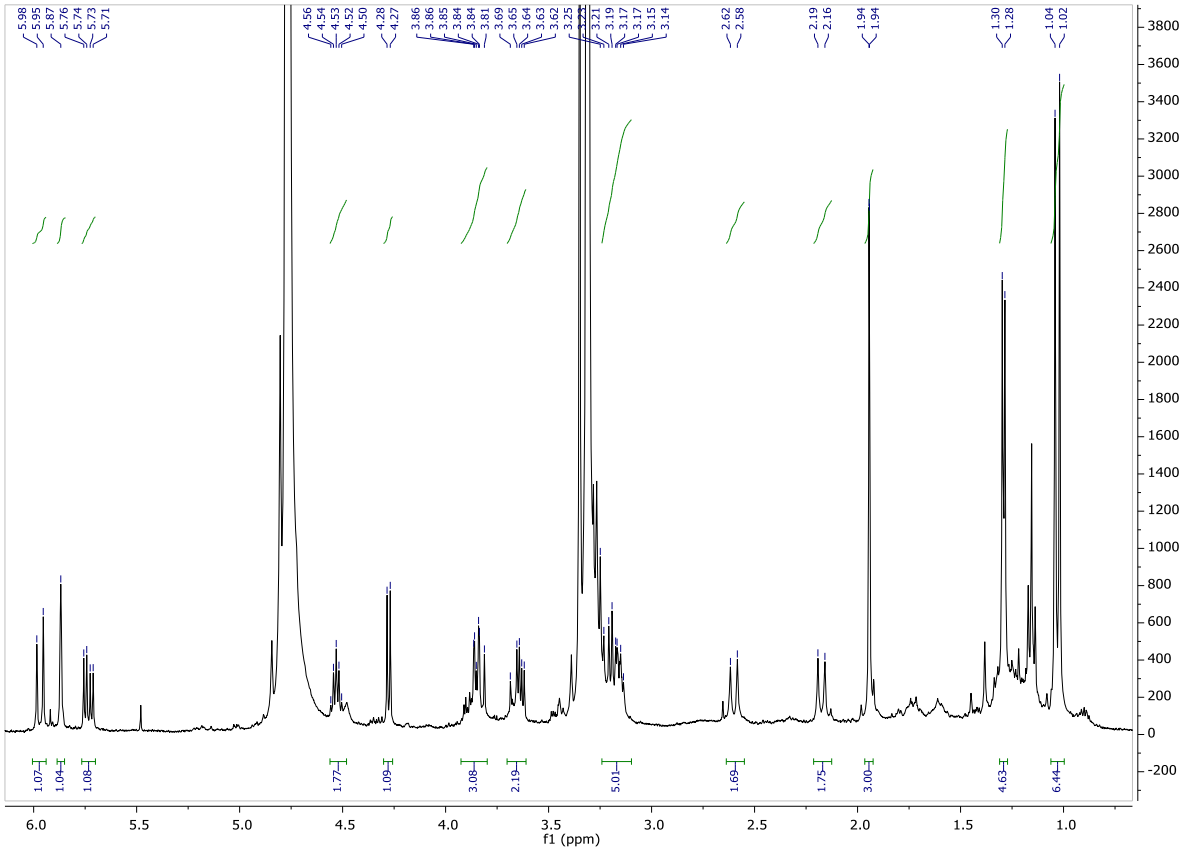

Figure S28. ^{1}H NMR spectrum of **5** in methanol-d_4 at 600 MHz.

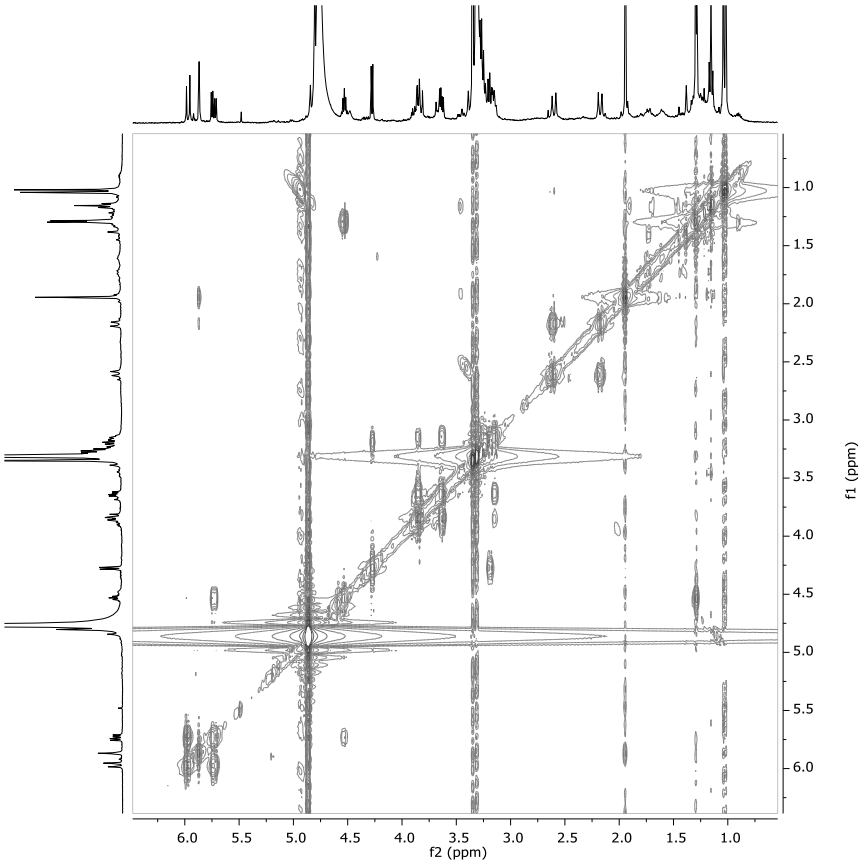

Figure S29. ^{1}H–^{1}H COSY spectrum of **5** in methanol-d_4 at 600 MHz.

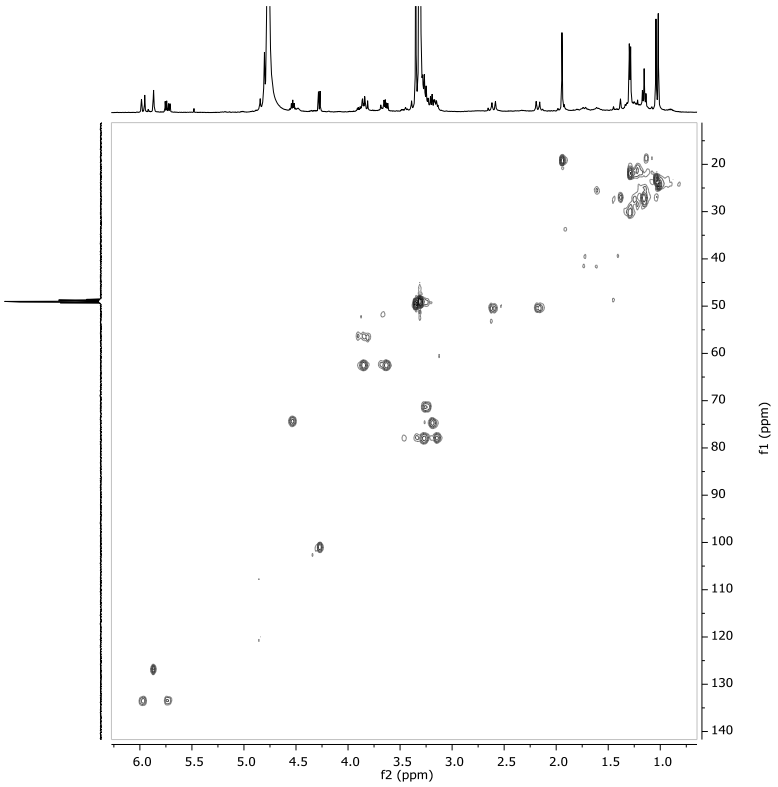

Figure S30. *g*HMQC spectrum of **5** in methanol-d_4 at 600 MHz.

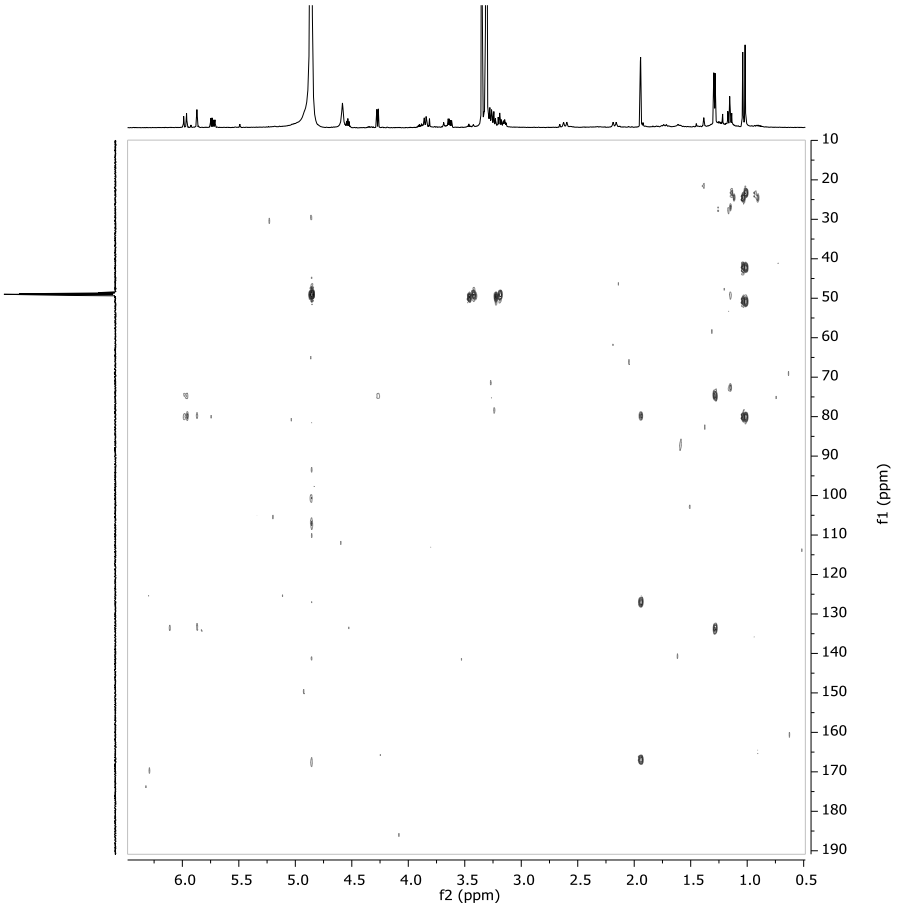

Figure S31. *g*HMBC spectrum of **5** in methanol-d_4 at 600 MHz.

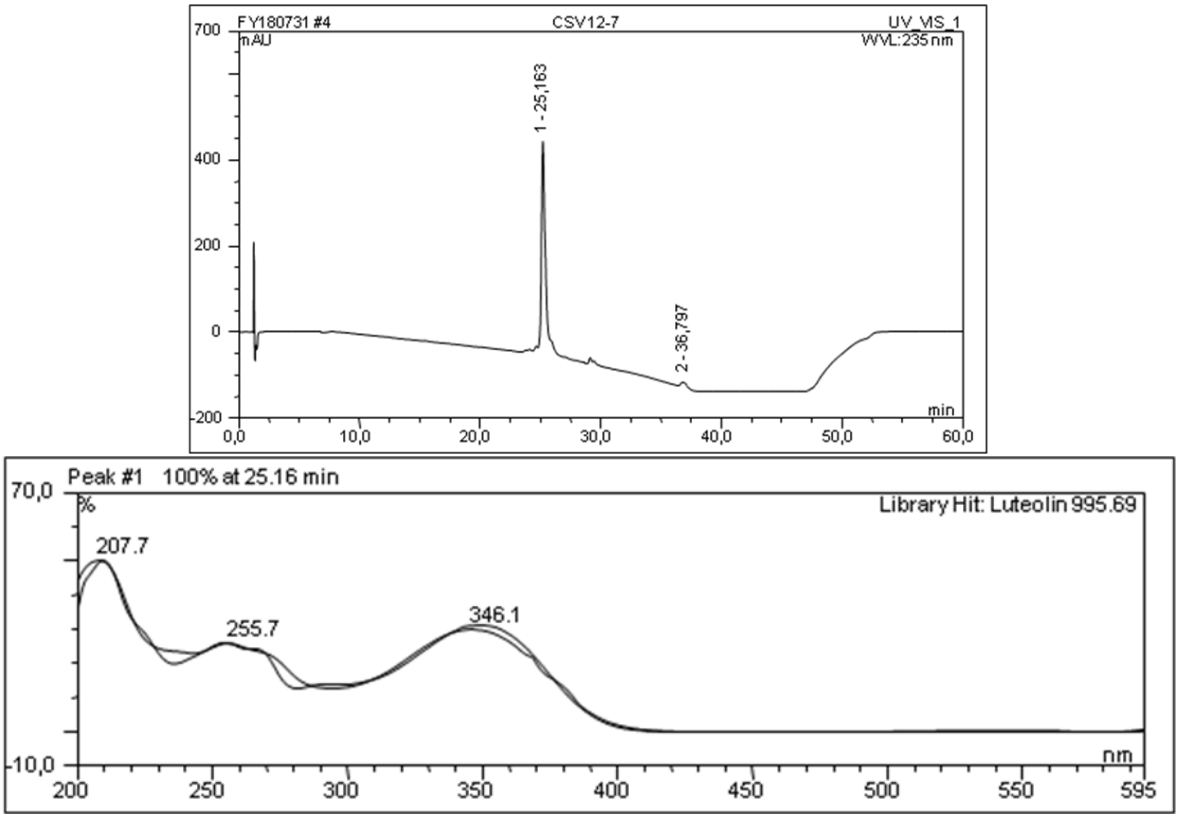

Figure S32. HPLC chromatogram and UV spectrum of **6**

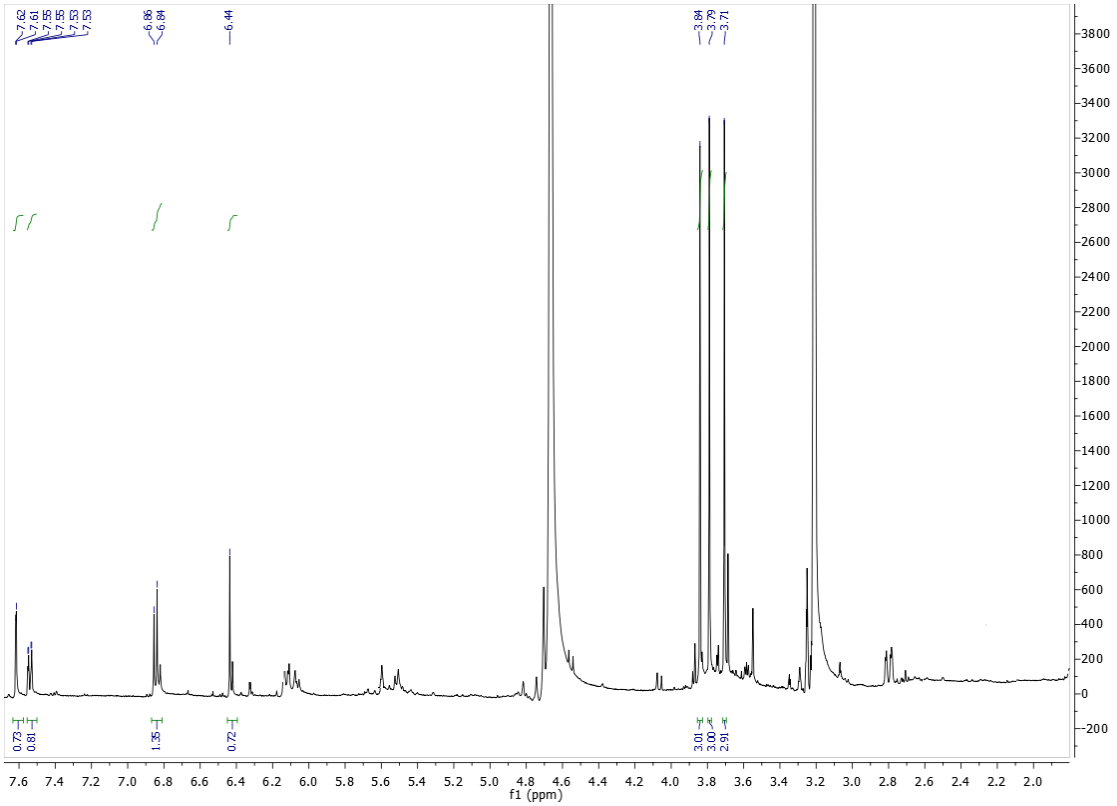

Figure S33. ^{1}H NMR spectrum of **6** in methanol-d_4 at 600 MHz.

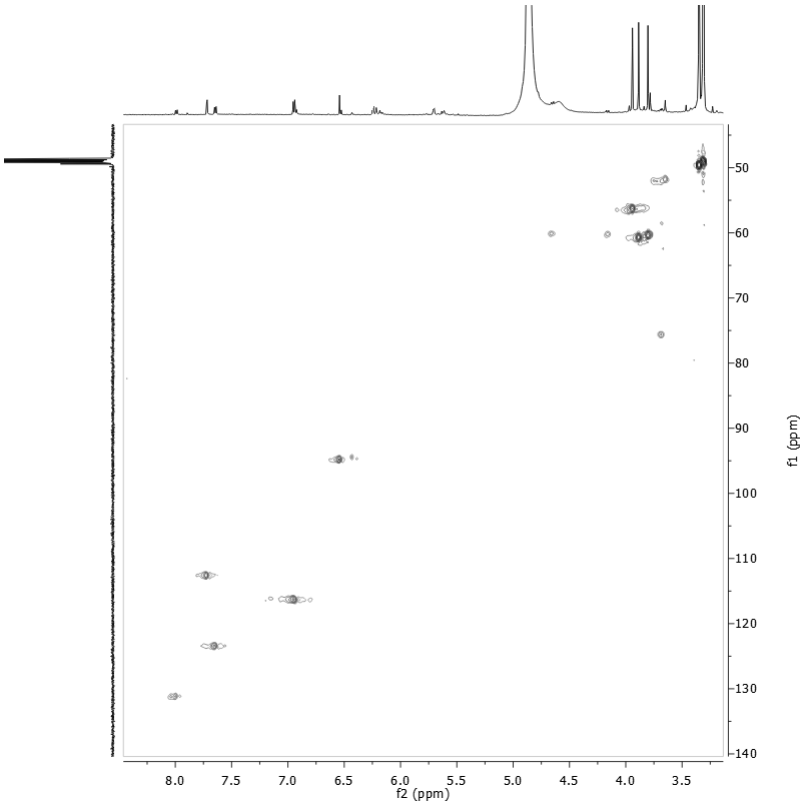

Figure S34. *g*HMQC spectrum of **6** in methanol-d_4 at 600 MHz.

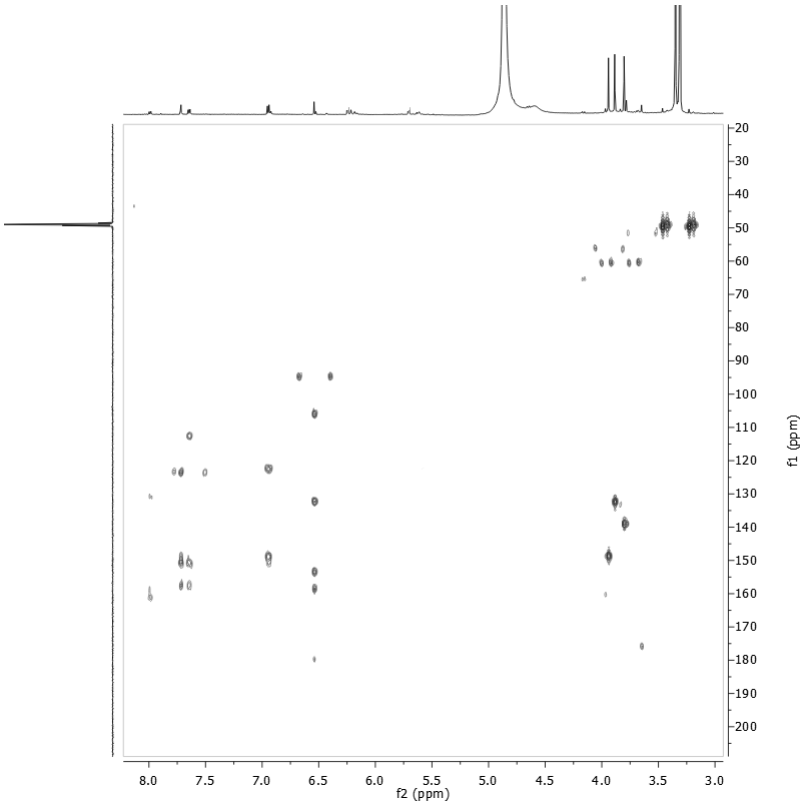

Figure S35**.** *g*HMBC spectrum of **6** in methanol-d_4 at 600 MHz.

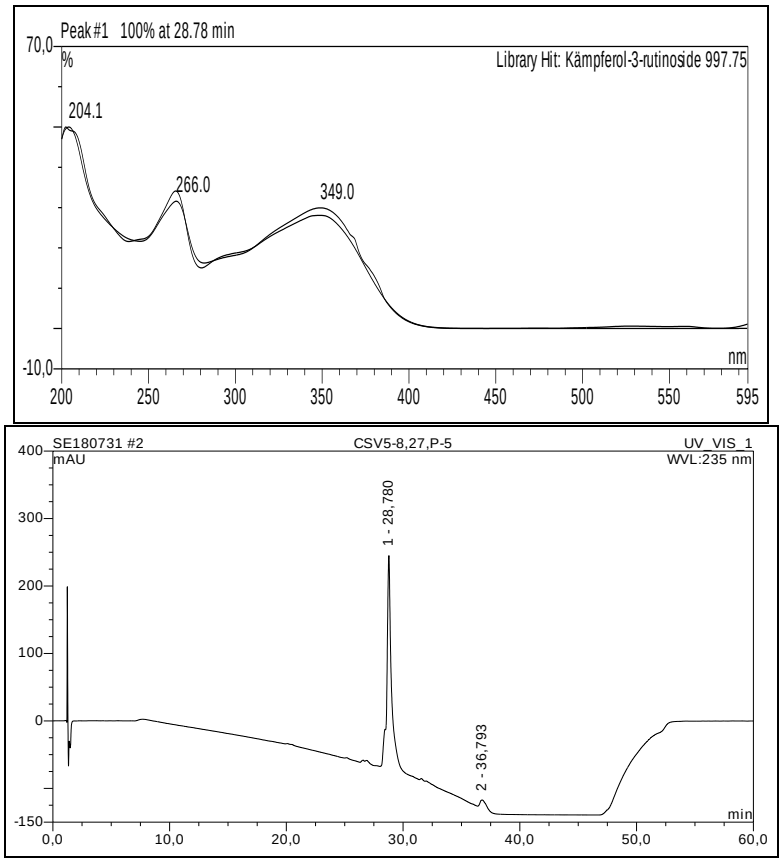

Figure S36. HPLC chromatogram and UV spectrum of **7**

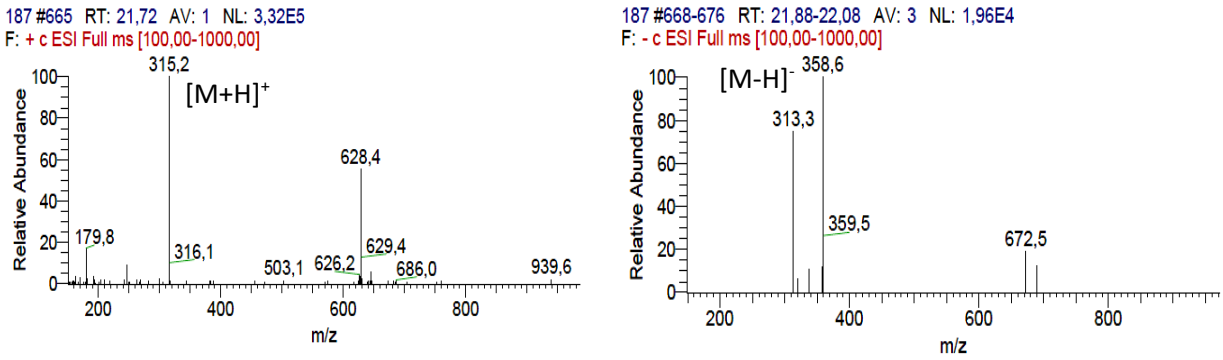

Figure S37. LRESIMS spectrum of **7**

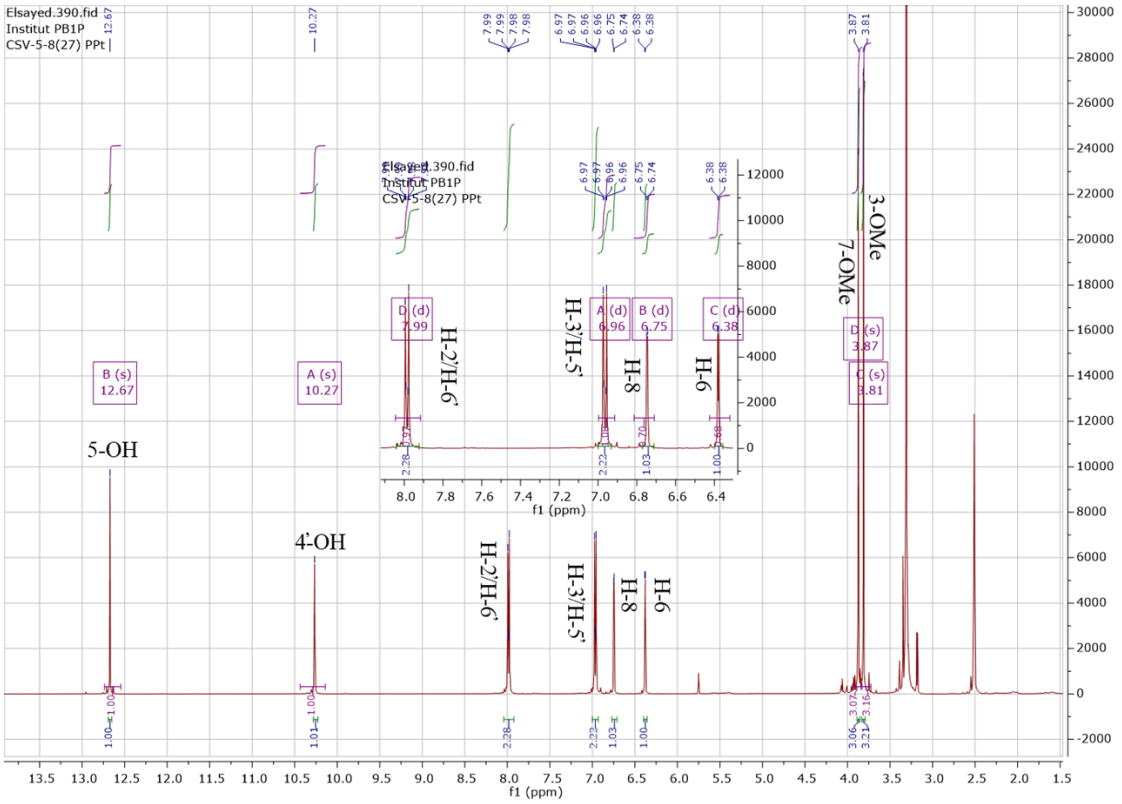

Figure S38. ^{1}H NMR spectrum of **7** in DMSO-d_6 at 600 MHz.

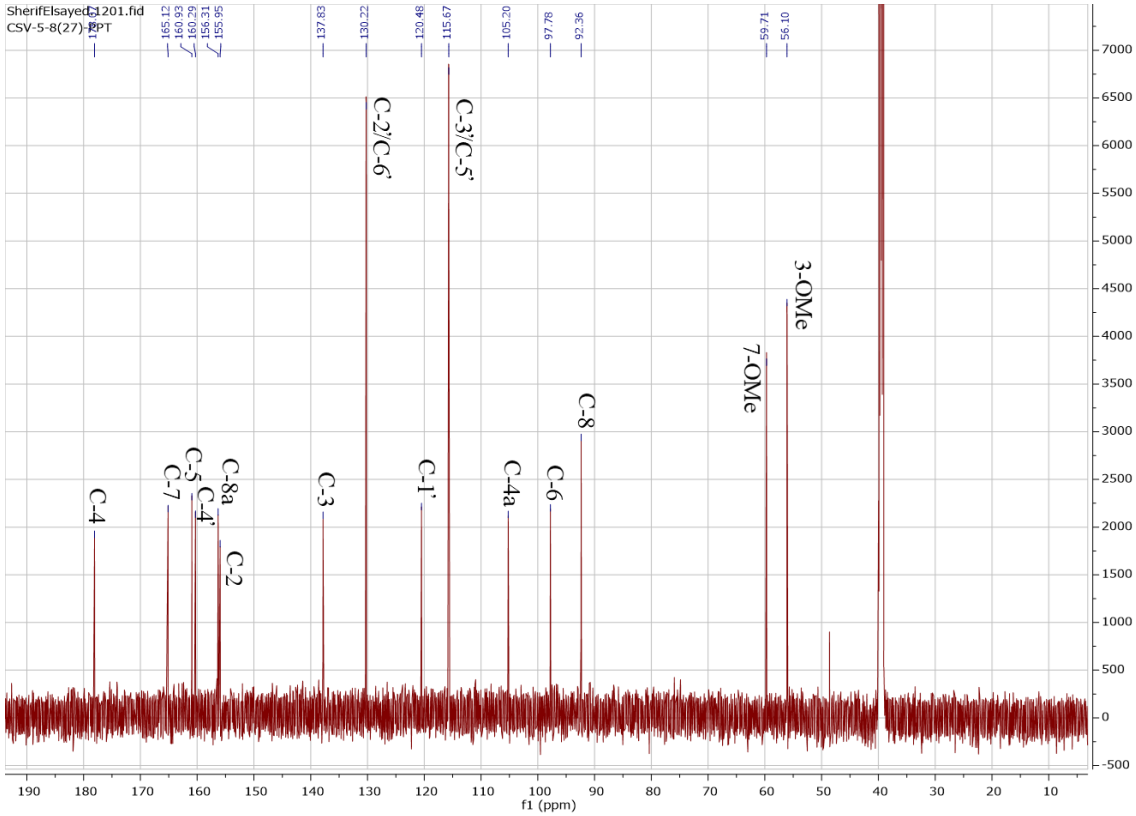

Figure S39. ^{13}C NMR spectrum of **7** in DMSO-d_6 at 150 MHz.

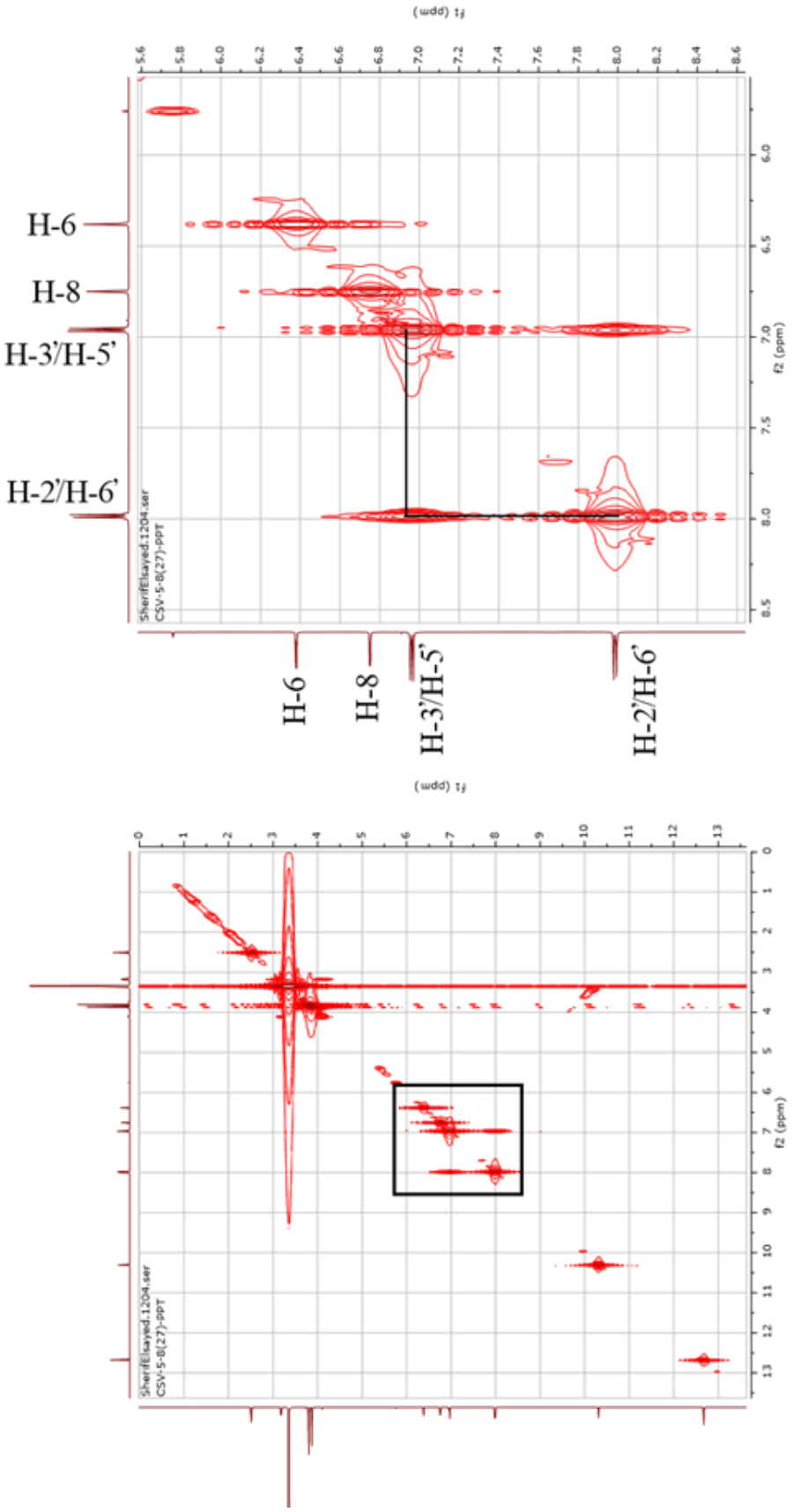

Figure S40. ^{1}H–^{1}H COSY spectrum of **7** in DMSO-d_6 at 600 MHz.

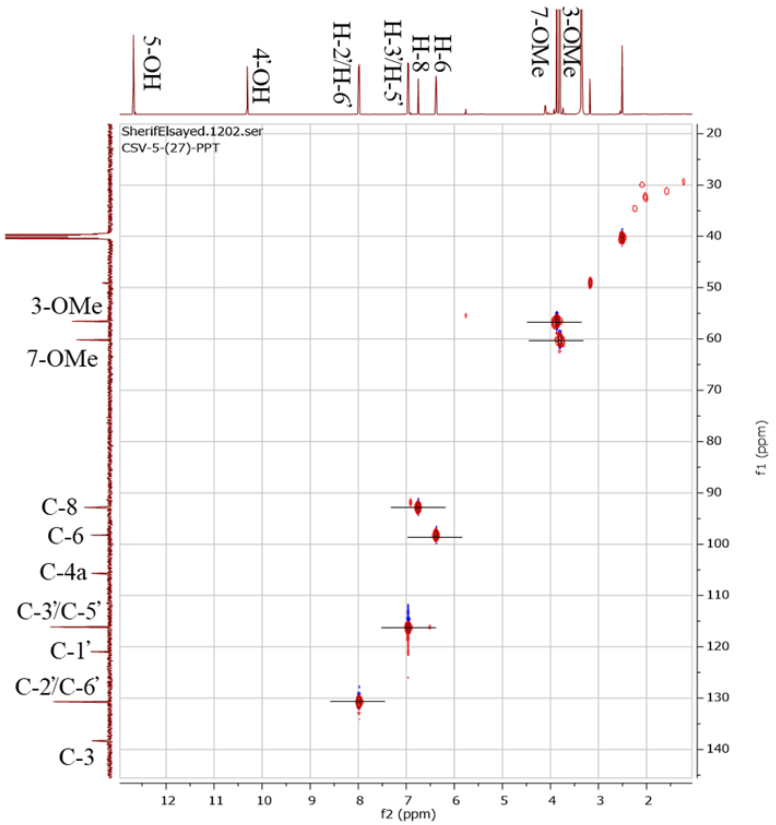

Figure S41. *g*HMQC spectrum of **7** in DMSO-d_6 at 600 MHz.

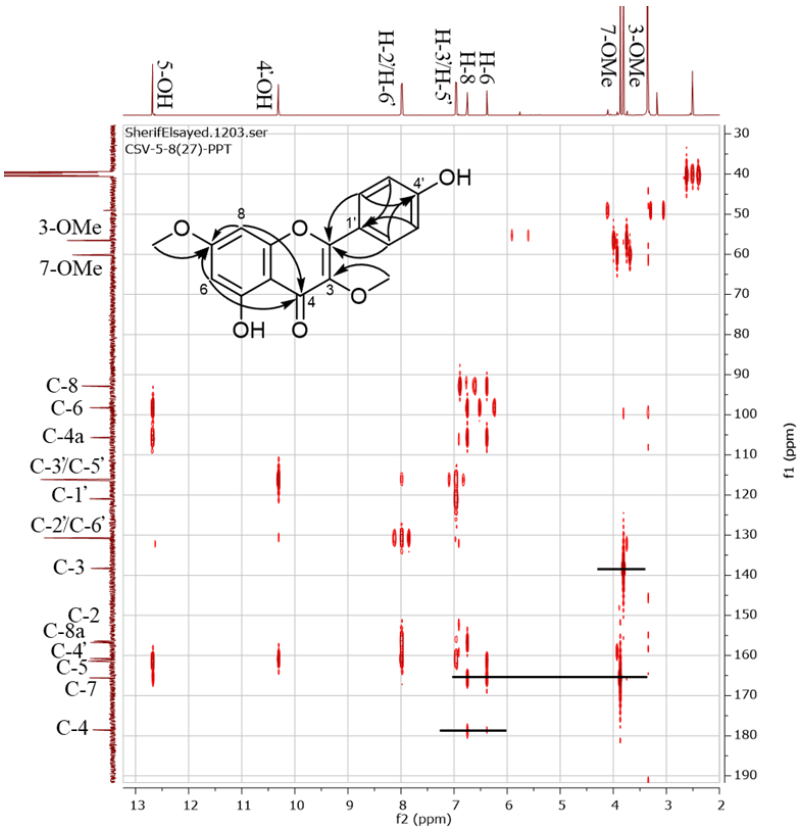

Figure S42. *g*HMBC spectrum of **7** in DMSO-d_6 at 600 MHz.

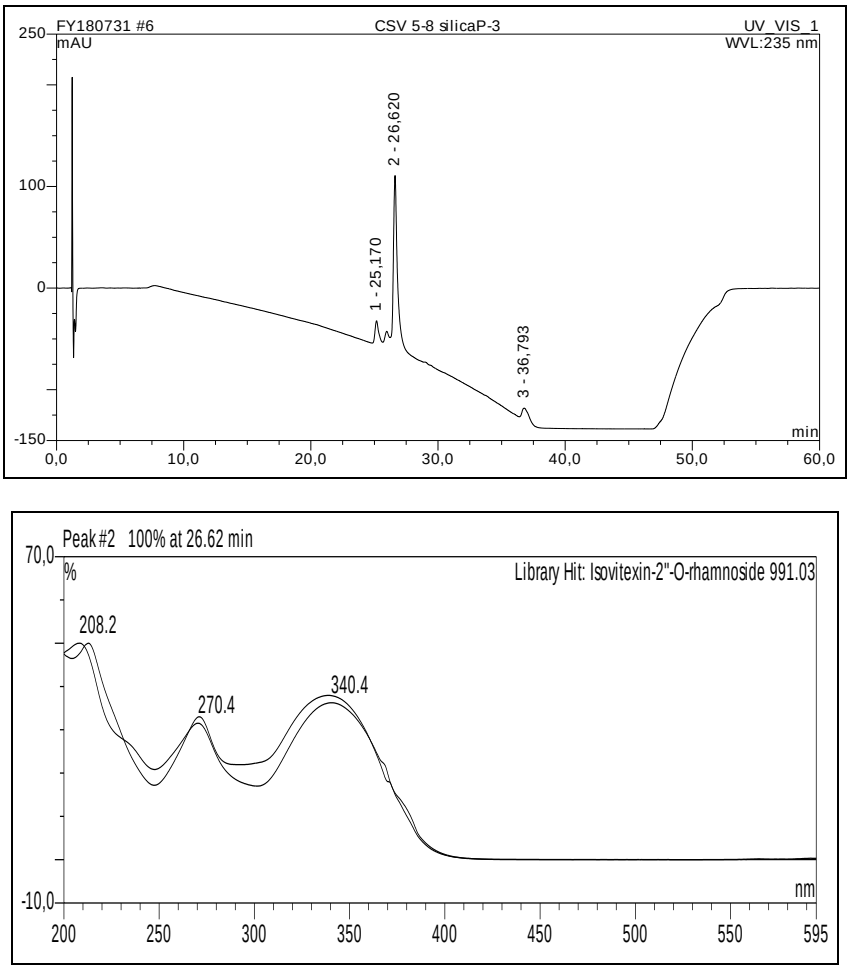

Figure S43. HPLC chromatogram and UV spectrum of **8**

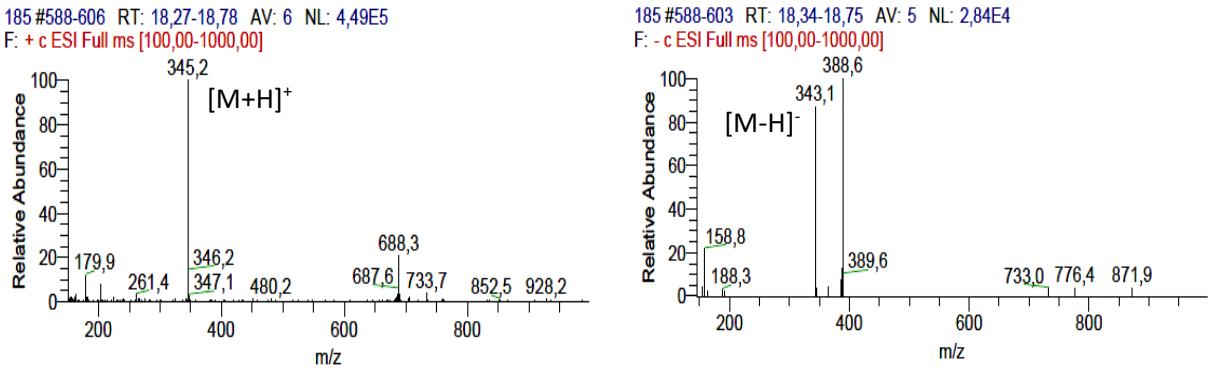

Figure S44. LRESIMS spectrum of **8**

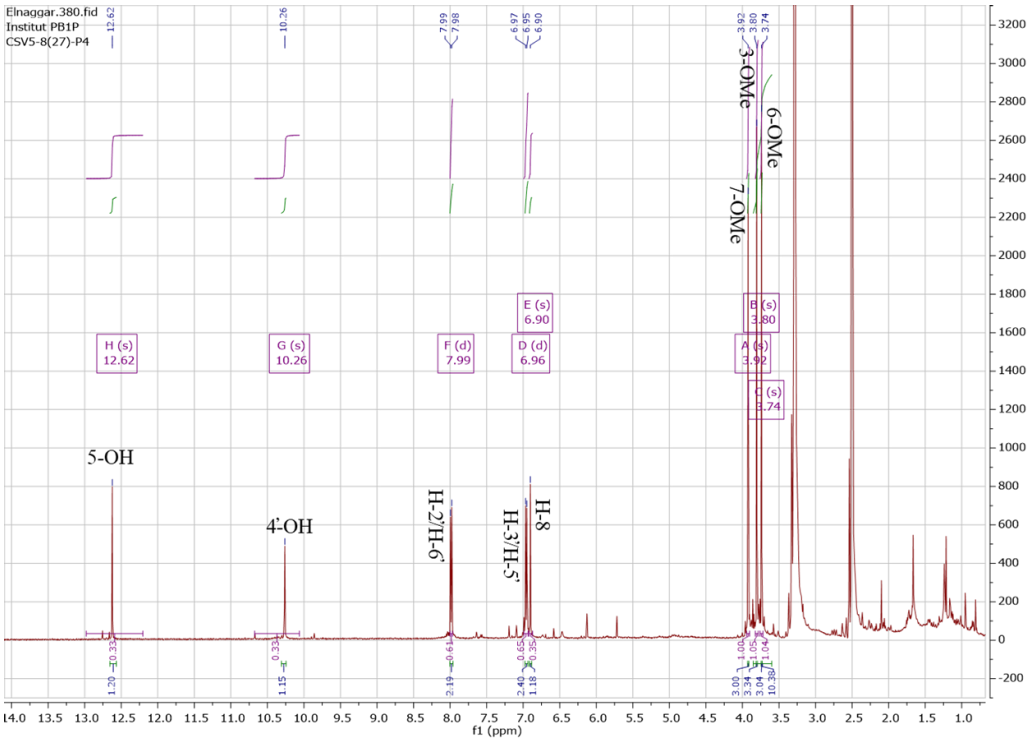

Figure S45. ^{1}H NMR spectrum of **8** in DMSO-d_6 at 600 MHz.

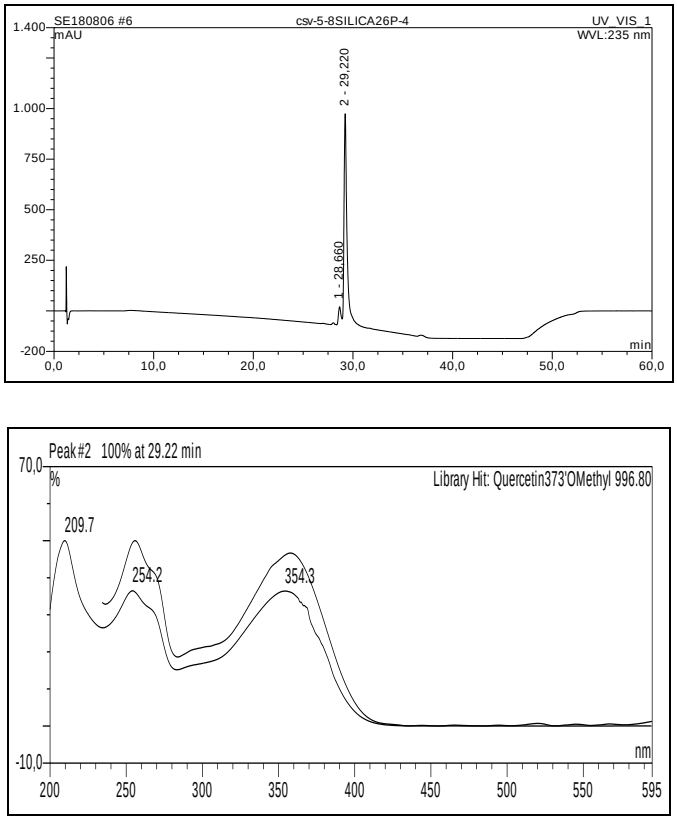

Figure S46. HPLC chromatogram and UV spectrum of **9**

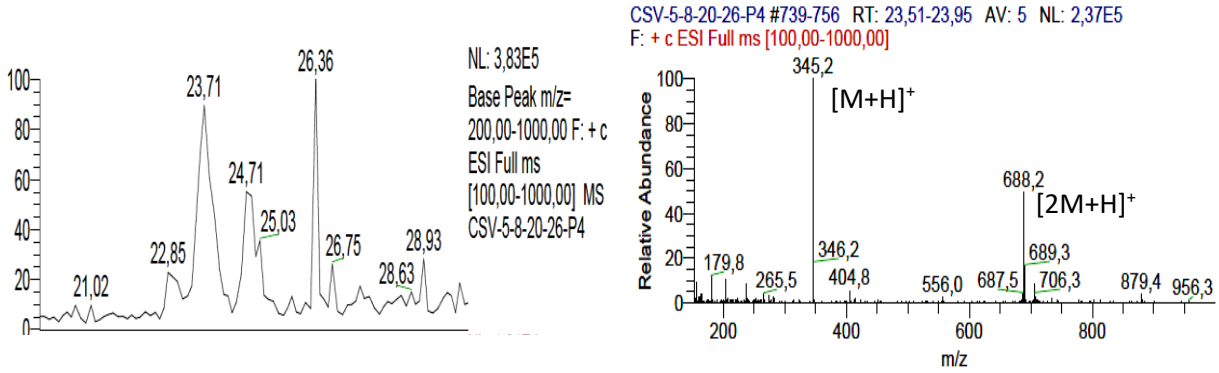

Figure S47. LRESIMS spectrum of **9**

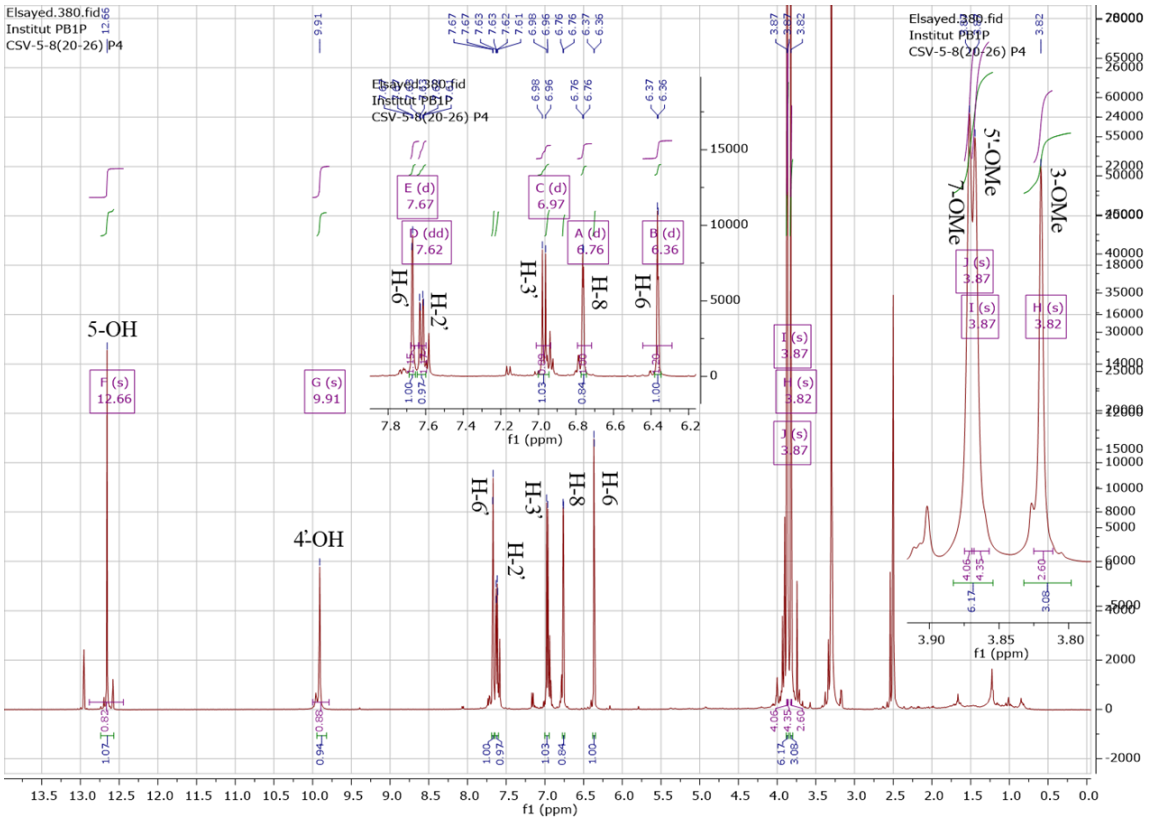

Figure S48. ^{1}H NMR spectrum of **9** in DMSO-d_6 at 600 MHz.

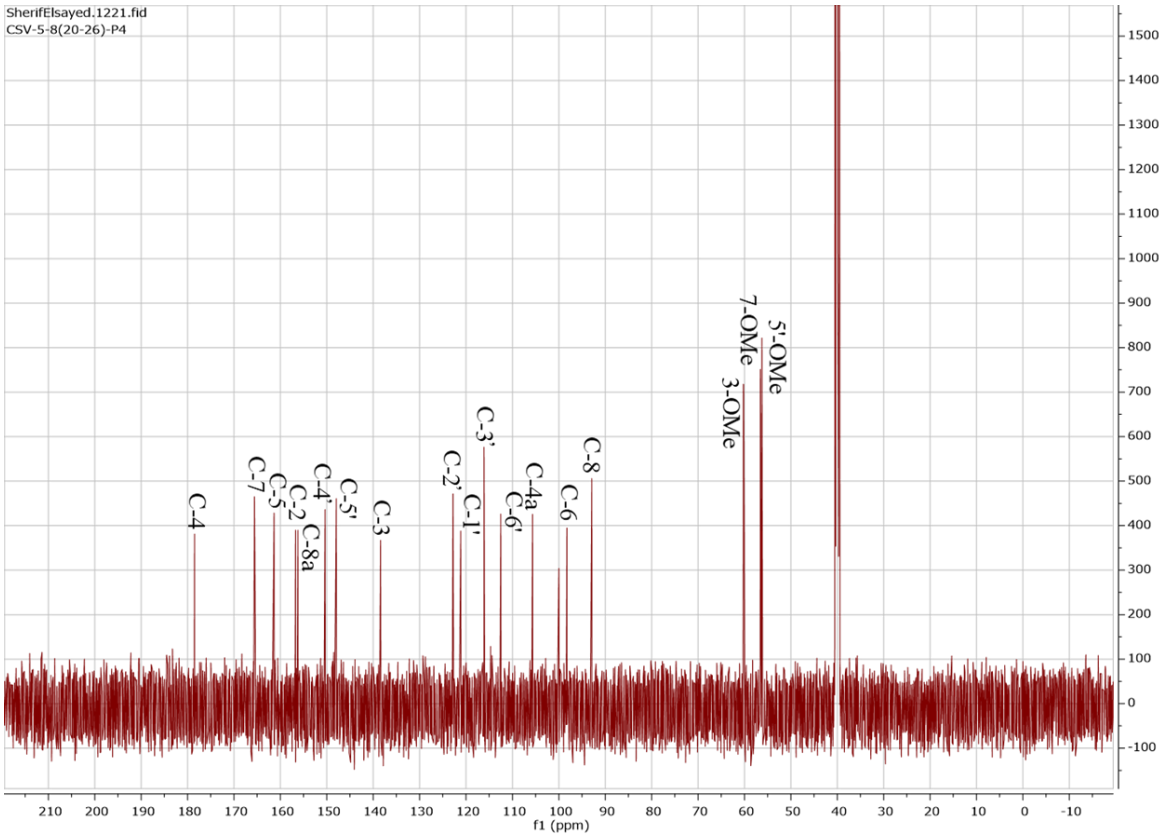

Figure S49. ^{13}C NMR spectrum of **9** in DMSO-d_6 at 150 MHz.

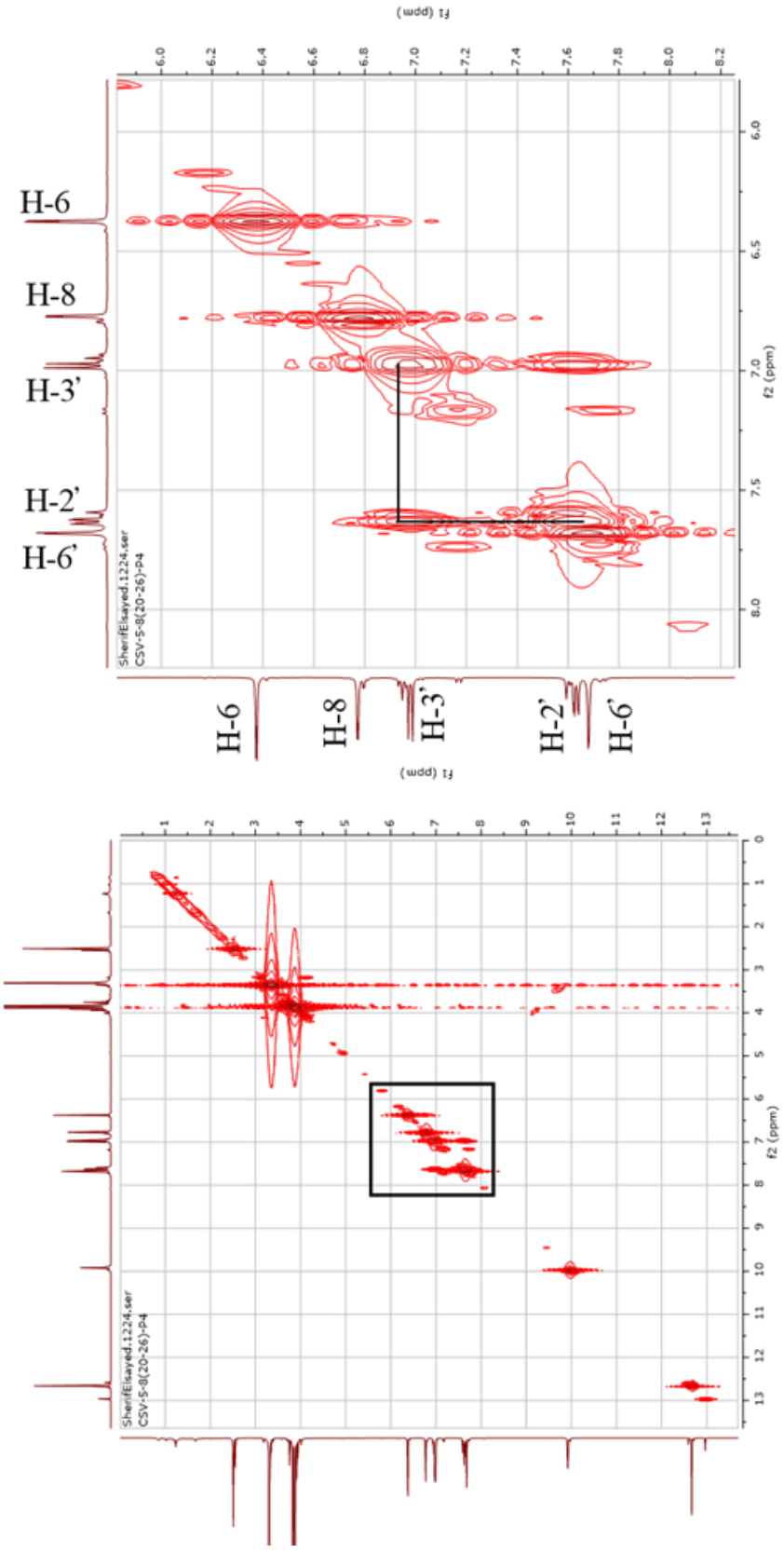

Figure S50. ^{1}H–^{1}H COSY spectrum of **9** in DMSO-d_6 at 600 MHz.

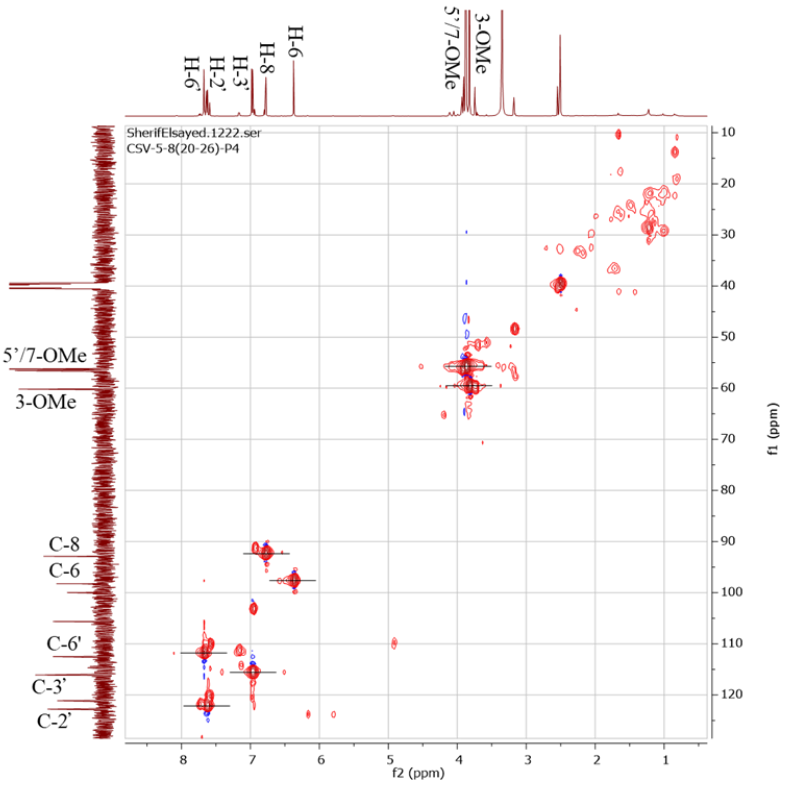

Figure S51. *g*HMQC spectrum of **9** in DMSO-d_6 at 600 MHz.

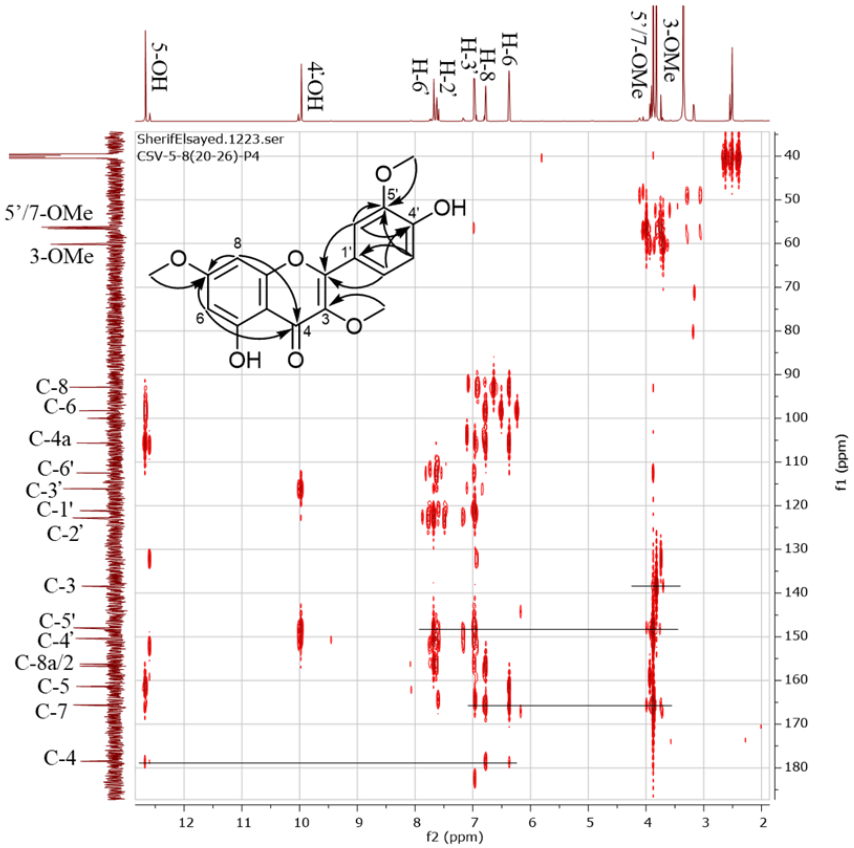

Figure S52. *g*HMBC spectrum of **9** in DMSO-d_6 at 600 MHz.

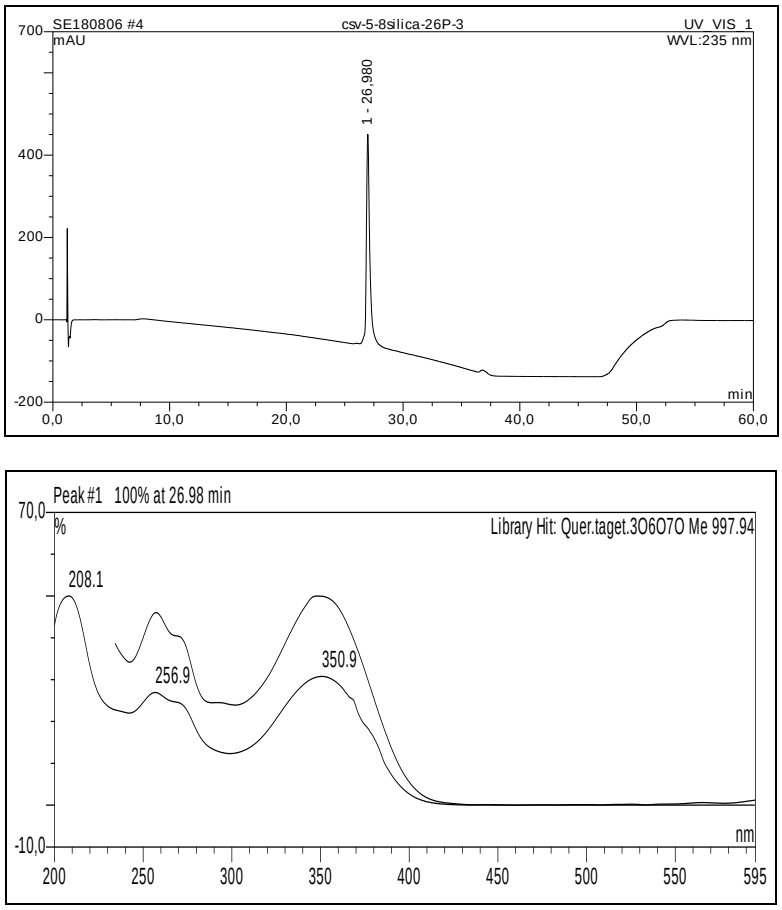

Figure S53. HPLC chromatogram and UV spectrum of **10**

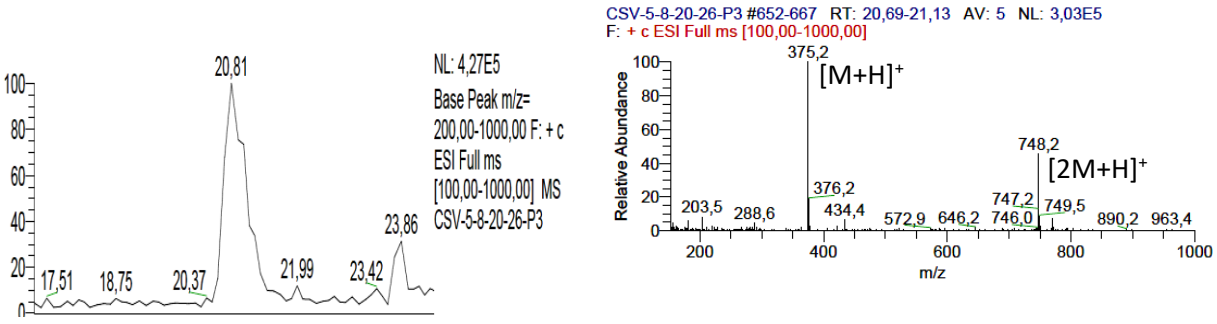

Figure S54. LRESIMS spectrum of **10**

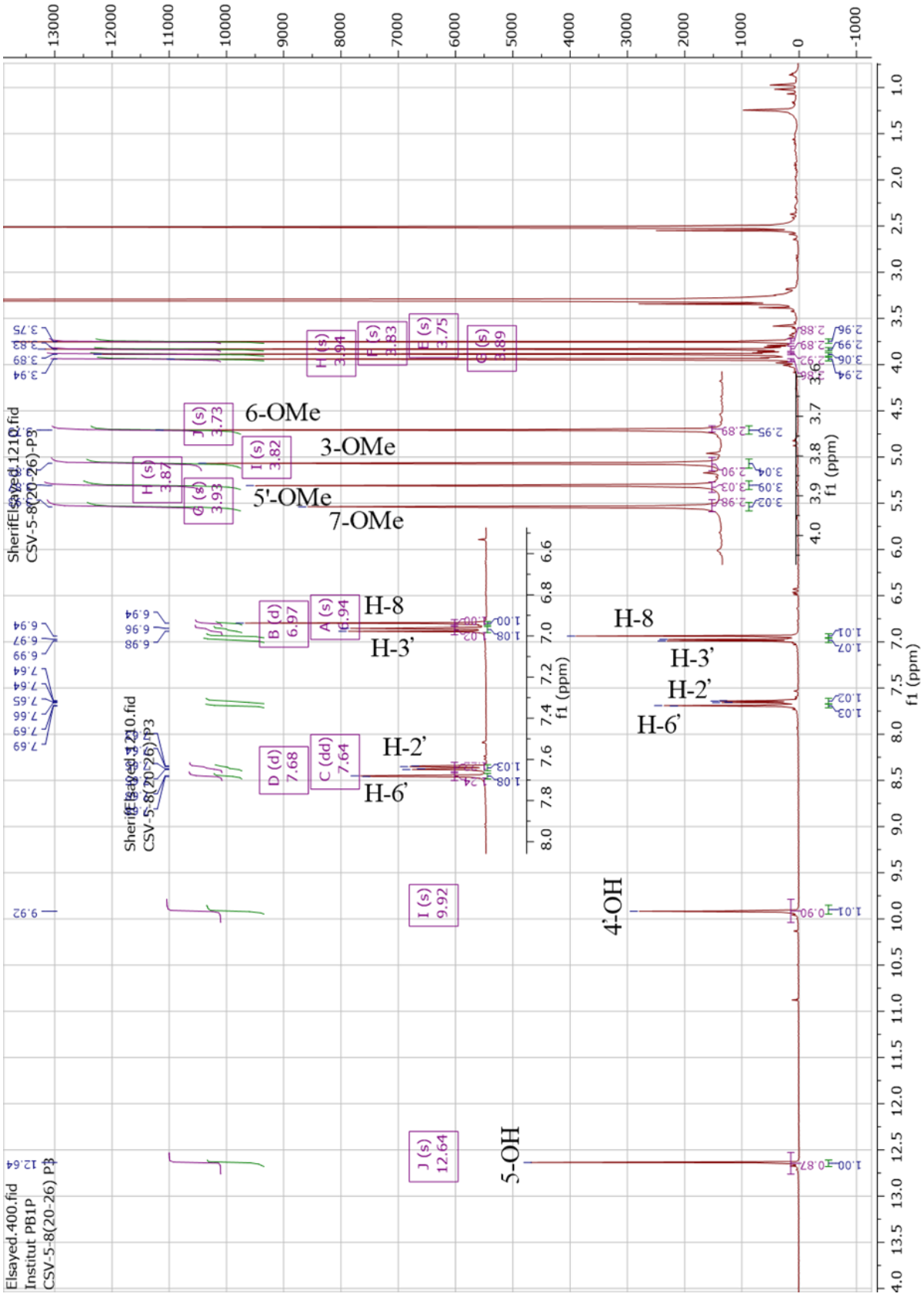

Figure S55. ^{1}H NMR spectrum of **10** in DMSO-d_6 at 600 MHz.

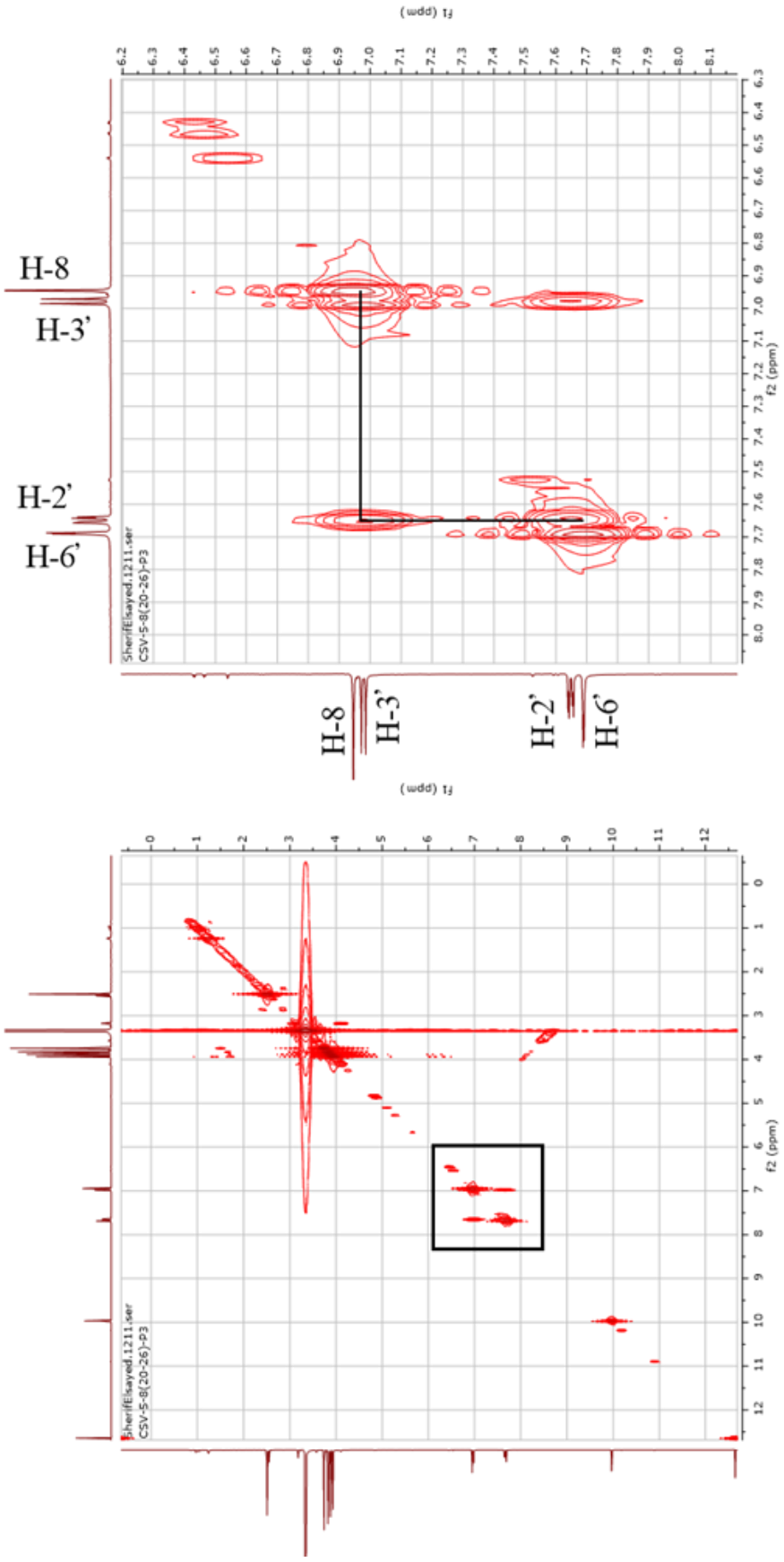

Figure S56. ^{1}H–^{1}H COSY spectrum of **10** in DMSO-d_6 at 600 MHz.

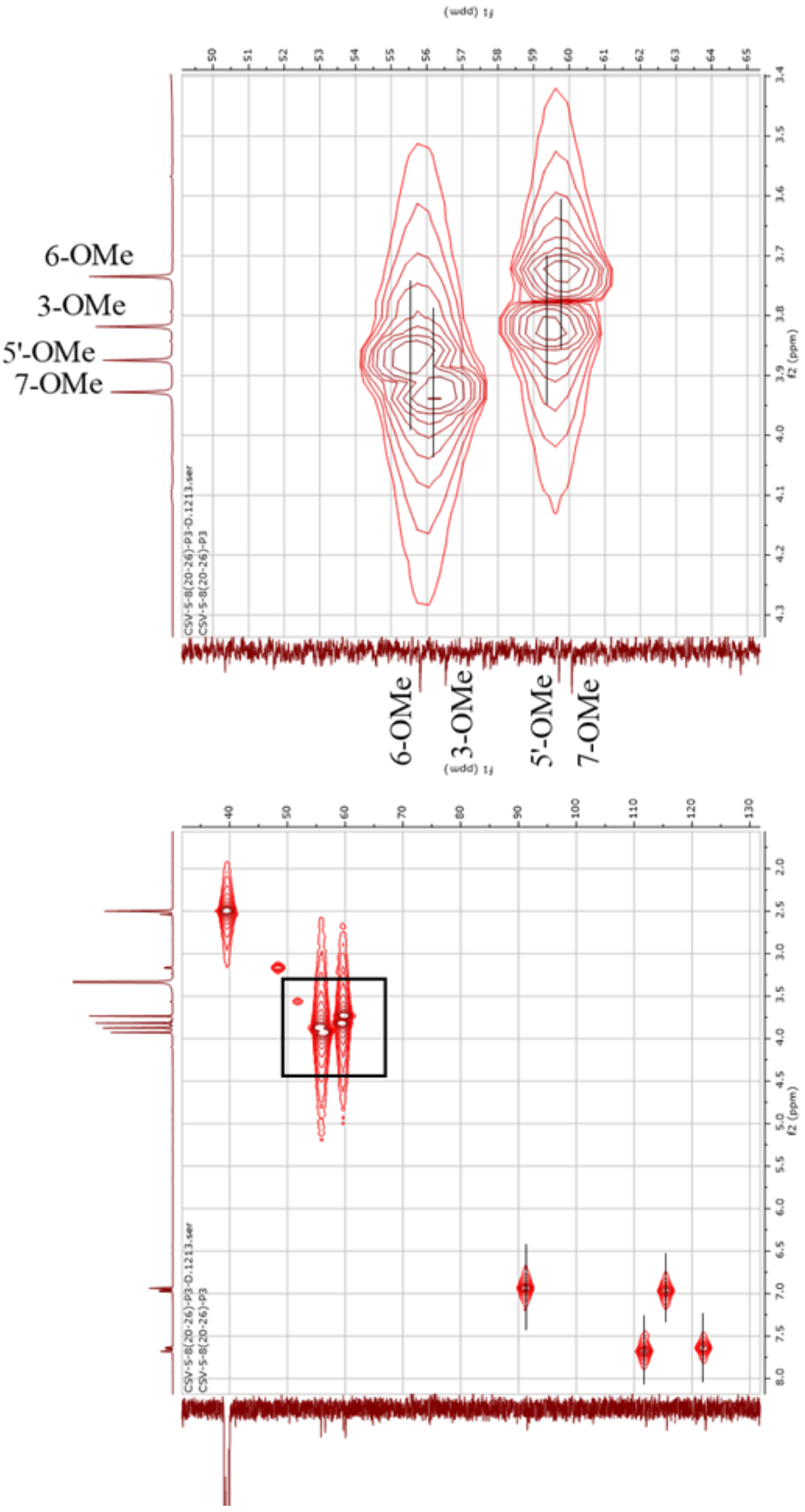

Figure S57. *g*HMQC spectrum of **10** in DMSO-d_6 at 600 MHz.

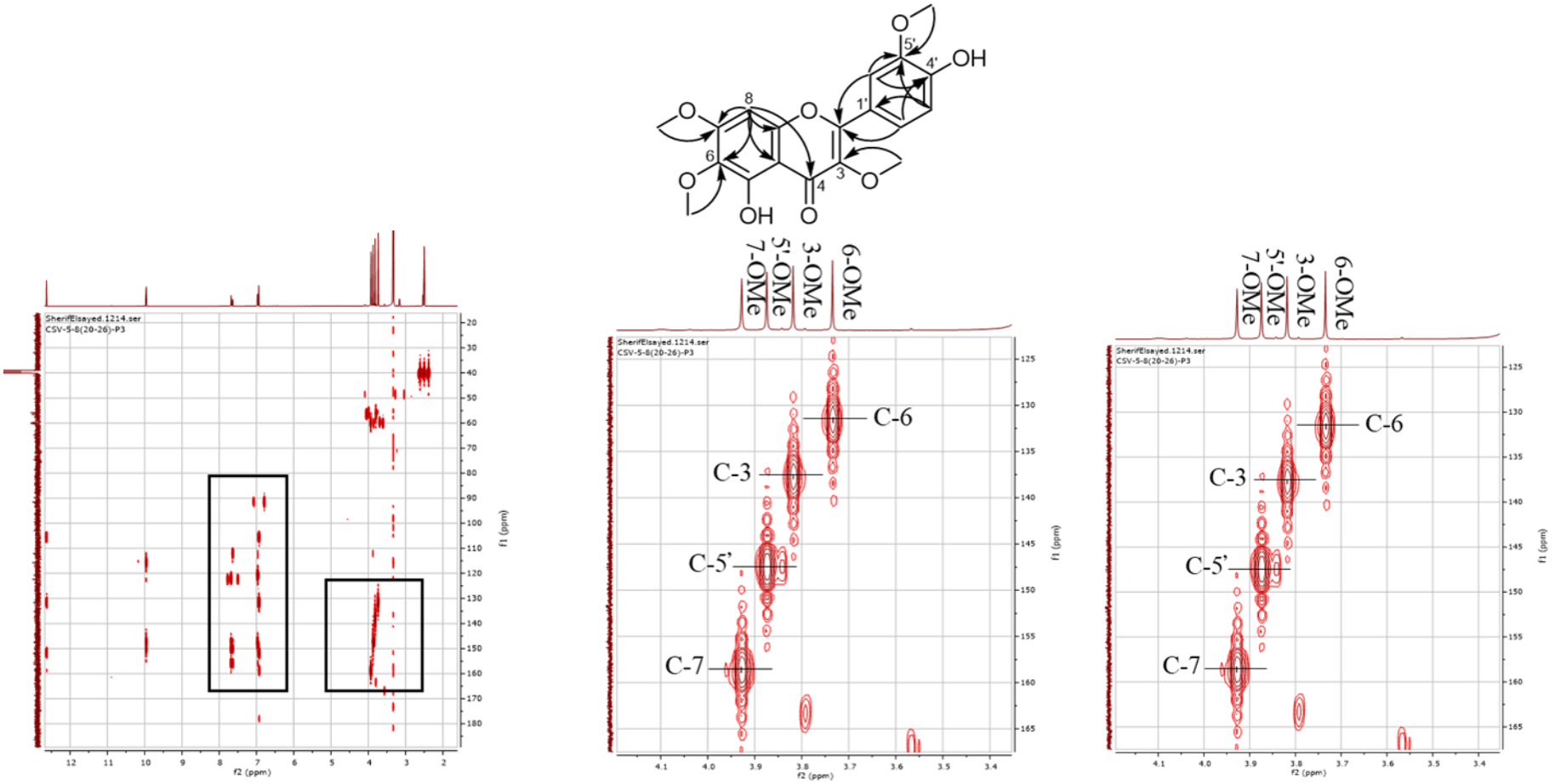

Figure S58. *g*HMBC spectrum of **10** in DMSO-d_6 at 600 MHz.

Table S2. Crystal data for chrysosplenetin (**10**).

CCDC number	1994762
Empirical formula	$C_{19}H_{18}O_8$
M [g mol^{-1}]	374.33
Crystal size [mm^3]	0.10 × 0.05 × 0.05
Temperature [K]	140
θ range [°] (completeness)	2.8–22.9
h; k; l range	±9 ; -17 – 22 ; -17 – 16
Crystal system	Monoclinic
Space group	$P2_1$
a [Å]	7.2577(3)
b [Å]	17.3639(8)
c [Å]	13.3620(6)
α [°]	90
β [°]	95.789(2)
γ [°]	90
V [Å³]	1675.32(13)
Z	4
Dcalc [mg m^{-3}]	1.484
μ (Cu Kα) [mm^{-1}]	0.71073
F(000)	784
Max./min. transmission	0.746 /0.554
Reflections collected	29961
Independent reflect. (Rint)	6958 (0.067)
Data/restraints/parameters	6958 / 1 / 512
Max./min. Δρ [e$Å^{-3}$] [a]	0.26 / -0.21
R_1/wR_2 [I>2σ(I)] [b]	0.048 / 0.111
R_1/wR_2 [all data] [b]	0.048 / 0.111
Goodness-of-fit on F^{2c}	1.04

[a] Largest difference peak and hole; [b] $R_1 = [\sum(||F_o| - |F_c||)/\sum|F_o|]$; $wR_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$; [c] Goodness-of-fit = $[\sum[w(F_o^2 - F_c^2)^2]/(n - p)]^{1/2}$; [d] Absolute structure parameter.

Table S3. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å2) for chrysosplenetin (**10**).

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	-0.0482 (3)	0.54749 (14)	0.05069 (17)	0.0238 (6)
C1'	-0.1219 (5)	0.4891 (2)	-0.1053 (3)	0.0241 (8)
O2	-0.1822 (4)	0.34798 (16)	0.0113 (2)	0.0324 (6)
C2	-0.0993 (5)	0.4791 (2)	0.0046 (3)	0.0228 (8)
C2'	0.0074 (5)	0.5360 (2)	-0.1479 (3)	0.0240 (8)
H2'	0.102398	0.560930	-0.105717	0.029*
O3	-0.0645 (3)	0.35133 (15)	0.21771 (19)	0.0278 (6)
C3	-0.1142 (5)	0.4137 (2)	0.0585 (3)	0.0237 (8)
C3'	-0.0030 (5)	0.5459 (2)	-0.2501 (3)	0.0242 (8)
O4	0.0599 (4)	0.42962 (16)	0.3756 (2)	0.0262 (6)
C4	-0.0612 (5)	0.4118 (2)	0.1666 (3)	0.0213 (8)
C4'	-0.1437 (5)	0.5101 (2)	-0.3133 (3)	0.0234 (8)
C4A	0.0011 (5)	0.4844 (2)	0.2104 (3)	0.0196 (7)
H4OO	0.029 (7)	0.384 (4)	0.336 (4)	0.072 (17)*
O5	0.1443 (3)	0.56984 (15)	0.45871 (17)	0.0234 (6)
C5	0.0569 (5)	0.4922 (2)	0.3151 (3)	0.0201 (7)
C5'	-0.2731 (5)	0.4653 (2)	-0.2715 (3)	0.0284 (9)
H5'	-0.370605	0.442164	-0.313903	0.034*
O6	0.1627 (3)	0.69510 (14)	0.33787 (18)	0.0239 (6)
C6	0.1072 (5)	0.5629 (2)	0.3553 (3)	0.0206 (7)
C6'	-0.2624 (5)	0.4537 (2)	-0.1675 (3)	0.0282 (9)
H6'	-0.350525	0.421841	-0.139578	0.034*
O7	0.1158 (3)	0.59004 (16)	-0.29944 (19)	0.0295 (6)
C7	0.1069 (5)	0.6280 (2)	0.2923 (3)	0.0203 (7)
O8	-0.1576 (4)	0.51940 (16)	-0.41541 (19)	0.0292 (6)
C8	0.0553 (5)	0.6214 (2)	0.1901 (3)	0.0215 (8)
H8	0.056229	0.665044	0.147248	0.026*
C8A	0.0022 (5)	0.5500 (2)	0.1517 (3)	0.0196 (7)
H8O	-0.053 (7)	0.537 (3)	-0.432 (3)	0.049 (14)*
O9	0.3829 (3)	0.07816 (14)	0.69962 (18)	0.0228 (5)
C9	-0.0477 (6)	0.2884 (3)	0.0061 (4)	0.0424 (11)
H9A	0.038913	0.302938	-0.042361	0.064*
H9B	-0.110217	0.240321	-0.015479	0.064*
H9C	0.020333	0.281201	0.072576	0.064*
O10	0.5527 (4)	0.18252 (17)	0.9235 (2)	0.0418 (8)

C10	0.3375 (5)	0.5780 (2)	0.4942 (3)	0.0293 (9)
H10A	0.407830	0.535548	0.468226	0.044*
H10B	0.352324	0.576892	0.567937	0.044*
H10C	0.383791	0.627122	0.470693	0.044*
O11	0.6263 (4)	0.03304 (17)	0.9813 (2)	0.0346 (7)
C11	0.1492 (5)	0.7628 (2)	0.2747 (3)	0.0265 (8)
H11A	0.229425	0.756735	0.220519	0.040*
H11B	0.188299	0.808158	0.315142	0.040*
H11C	0.020702	0.769543	0.245762	0.040*
O12	0.6347 (4)	-0.11241 (17)	0.9355 (2)	0.0296 (6)
C12	0.2539 (6)	0.6328 (3)	-0.2389 (3)	0.0401 (11)
H12A	0.321475	0.665781	-0.282270	0.060*
H12B	0.340490	0.597126	-0.201989	0.060*
H12C	0.194331	0.664873	-0.191144	0.060*
H12O	0.656 (6)	-0.063 (3)	0.976 (3)	0.042 (13)*
O13	0.5403 (4)	-0.22448 (15)	0.79742 (19)	0.0297 (6)
C13'	0.3559 (5)	0.2116 (2)	0.7210 (3)	0.0225 (8)
O14	0.3914 (4)	-0.18699 (15)	0.61224 (19)	0.0314 (6)
C14	0.4174 (5)	0.1374 (2)	0.7656 (3)	0.0224 (8)
C14'	0.2720 (5)	0.2123 (2)	0.6213 (3)	0.0235 (8)
H14'	0.254346	0.165217	0.585329	0.028*
O15	0.1296 (4)	0.28740 (15)	0.47941 (19)	0.0310 (6)
C15	0.5023 (5)	0.1231 (2)	0.8594 (3)	0.0257 (8)
C15'	0.2151 (5)	0.2807 (2)	0.5752 (3)	0.0237 (8)
O16	0.1946 (4)	0.41885 (16)	0.5813 (2)	0.0324 (7)
C16	0.5512 (5)	0.0458 (2)	0.8937 (3)	0.0245 (8)
C16'	0.2432 (5)	0.3506 (2)	0.6263 (3)	0.0242 (8)
C16A	0.5113 (5)	-0.0142 (2)	0.8213 (3)	0.0214 (8)
H16O	0.140 (6)	0.413 (3)	0.517 (4)	0.040 (13)*
C17	0.5538 (5)	-0.0926 (2)	0.8439 (3)	0.0228 (8)
C17'	0.3204 (5)	0.3502 (2)	0.7247 (3)	0.0262 (8)
H17'	0.335651	0.397328	0.760805	0.031*
C18	0.5131 (5)	-0.1486 (2)	0.7722 (3)	0.0241 (8)
C18'	0.3764 (5)	0.2815 (2)	0.7718 (3)	0.0281 (8)
H18'	0.429574	0.282295	0.839736	0.034*
C19	0.4299 (5)	-0.1272 (2)	0.6761 (3)	0.0248 (8)
C20	0.3882 (5)	-0.0508 (2)	0.6518 (3)	0.0239 (8)
H20	0.332903	-0.036809	0.586881	0.029*

C20A	0.4300 (4)	0.0035 (2)	0.7255 (3)	0.0205 (8)
C21	0.4351 (9)	0.1903 (4)	1.0035 (4)	0.075 (2)
H21A	0.306318	0.196745	0.974882	0.113*
H21B	0.473488	0.235435	1.044502	0.113*
H21C	0.445470	0.144035	1.045735	0.113*
C22	0.6833 (6)	-0.2624 (3)	0.7487 (3)	0.0367 (10)
H22A	0.645958	-0.265685	0.676242	0.055*
H22B	0.702708	-0.314371	0.776310	0.055*
H22C	0.798661	-0.232927	0.760256	0.055*
C23	0.3353 (6)	-0.1691 (3)	0.5093 (3)	0.0341 (10)
H23A	0.427766	-0.135487	0.483216	0.051*
H23B	0.215240	-0.142873	0.504167	0.051*
H23C	0.324544	-0.216833	0.469929	0.051*
C24	0.0466 (6)	0.2188 (2)	0.4338 (3)	0.0320 (9)
H24A	-0.023546	0.232089	0.369582	0.048*
H24B	-0.036896	0.195898	0.478762	0.048*
H24C	0.144007	0.181749	0.421968	0.048*

Table S4. Atomic displacement parameters (Å2) for chrysosplenetin (**10**).

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0351 (14)	0.0219 (13)	0.0138 (13)	-0.0051 (11)	-0.0008 (10)	-0.0007 (10)
C1'	0.033 (2)	0.0229 (19)	0.0165 (19)	0.0000 (15)	0.0000 (15)	-0.0009 (15)
O2	0.0409 (15)	0.0254 (14)	0.0297 (16)	-0.0045 (12)	-0.0029 (12)	-0.0063 (13)
C2	0.0254 (18)	0.026 (2)	0.0165 (19)	-0.0028 (15)	-0.0010 (14)	-0.0030 (16)
C2'	0.0280 (18)	0.0244 (19)	0.019 (2)	-0.0005 (14)	-0.0027 (14)	-0.0034 (16)
O3	0.0388 (15)	0.0216 (14)	0.0232 (15)	-0.0024 (12)	0.0035 (11)	0.0024 (12)
C3	0.0276 (18)	0.025 (2)	0.018 (2)	-0.0013 (15)	0.0006 (14)	-0.0035 (16)
C3'	0.0288 (19)	0.0218 (19)	0.022 (2)	-0.0013 (14)	0.0026 (15)	0.0018 (15)
O4	0.0375 (15)	0.0207 (14)	0.0201 (15)	-0.0015 (11)	0.0012 (11)	0.0026 (12)
C4	0.0224 (17)	0.0232 (19)	0.019 (2)	0.0022 (14)	0.0058 (14)	-0.0034 (16)
C4'	0.0284 (18)	0.0246 (19)	0.017 (2)	0.0009 (15)	-0.0004 (14)	-0.0008 (15)
C4A	0.0214 (17)	0.0205 (18)	0.0168 (19)	0.0004 (14)	0.0018 (14)	-0.0029 (15)
O5	0.0274 (13)	0.0290 (15)	0.0136 (13)	-0.0020 (11)	0.0009 (10)	-0.0009 (11)
C5	0.0258 (18)	0.0178 (18)	0.0170 (19)	0.0038 (14)	0.0034 (14)	0.0026 (15)
C5'	0.031 (2)	0.032 (2)	0.021 (2)	-0.0051 (16)	-0.0032 (16)	-0.0043 (17)
O6	0.0358 (14)	0.0173 (13)	0.0181 (14)	-0.0019 (11)	0.0007 (10)	0.0011 (11)
C6	0.0258 (17)	0.0232 (19)	0.0132 (19)	0.0021 (14)	0.0032 (13)	0.0011 (15)
C6'	0.0287 (19)	0.031 (2)	0.024 (2)	-0.0051 (16)	0.0007 (16)	-0.0023 (17)
O7	0.0339 (15)	0.0340 (16)	0.0201 (14)	-0.0120 (12)	-0.0001 (11)	-0.0022 (12)
C7	0.0239 (17)	0.0210 (19)	0.0162 (19)	-0.0014 (14)	0.0027 (14)	-0.0043 (15)
O8	0.0344 (16)	0.0361 (16)	0.0160 (15)	-0.0076 (13)	-0.0026 (11)	-0.0011 (12)
C8	0.0281 (18)	0.0202 (18)	0.016 (2)	-0.0009 (14)	0.0029 (14)	0.0025 (15)
C8A	0.0214 (17)	0.0252 (19)	0.0124 (18)	0.0016 (14)	0.0022 (13)	-0.0027 (15)
O9	0.0279 (13)	0.0200 (13)	0.0197 (14)	0.0006 (10)	-0.0010 (10)	0.0004 (11)
C9	0.055 (3)	0.032 (2)	0.039 (3)	0.001 (2)	0.001 (2)	-0.011 (2)
O10	0.0586 (19)	0.0288 (16)	0.0338 (18)	0.0098 (14)	-0.0161 (14)	-0.0118 (13)
C10	0.0285 (19)	0.038 (2)	0.021 (2)	-0.0012 (17)	0.0007 (15)	0.0001 (18)
O11	0.0421 (16)	0.0334 (17)	0.0257 (16)	0.0057 (12)	-0.0094 (12)	-0.0027 (13)
C11	0.039 (2)	0.0181 (19)	0.022 (2)	-0.0046 (15)	-0.0015 (16)	0.0013 (15)
O12	0.0364 (15)	0.0308 (16)	0.0199 (15)	0.0023 (12)	-0.0052 (11)	0.0022 (12)
C12	0.044 (3)	0.046 (3)	0.029 (2)	-0.021 (2)	-0.0012 (19)	-0.001 (2)
O13	0.0403 (15)	0.0238 (15)	0.0253 (15)	0.0012 (12)	0.0054 (11)	0.0042 (12)
C13'	0.0190 (17)	0.026 (2)	0.023 (2)	-0.0012 (14)	0.0023 (14)	0.0021 (16)
O14	0.0490 (17)	0.0213 (14)	0.0229 (16)	-0.0045 (12)	-0.0015 (12)	-0.0002 (12)
C14	0.0197 (17)	0.024 (2)	0.023 (2)	-0.0004 (14)	0.0033 (14)	-0.0019 (16)
C14'	0.0268 (19)	0.0227 (19)	0.021 (2)	-0.0007 (15)	0.0020 (15)	0.0002 (16)

O15	0.0465 (16)	0.0228 (14)	0.0220 (15)	-0.0021 (12)	-0.0053 (12)	0.0015 (12)
C15	0.0267 (19)	0.026 (2)	0.024 (2)	-0.0009 (15)	-0.0017 (15)	-0.0086 (16)
C15'	0.0265 (18)	0.023 (2)	0.022 (2)	-0.0030 (15)	0.0026 (15)	-0.0008 (16)
O16	0.0469 (17)	0.0216 (15)	0.0270 (17)	-0.0011 (12)	-0.0039 (13)	0.0019 (13)
C16	0.0228 (18)	0.028 (2)	0.022 (2)	0.0039 (15)	-0.0019 (15)	0.0004 (16)
C16'	0.0260 (18)	0.0195 (18)	0.027 (2)	-0.0005 (15)	0.0032 (15)	0.0039 (17)
C16A	0.0210 (17)	0.0238 (19)	0.0189 (19)	-0.0006 (14)	0.0003 (14)	0.0004 (15)
C17	0.0217 (17)	0.026 (2)	0.021 (2)	-0.0003 (14)	0.0021 (14)	0.0045 (16)
C17'	0.0259 (18)	0.0237 (19)	0.029 (2)	-0.0035 (15)	0.0008 (15)	-0.0066 (17)
C18	0.0290 (18)	0.0215 (19)	0.022 (2)	-0.0007 (15)	0.0044 (15)	0.0058 (16)
C18'	0.0288 (19)	0.029 (2)	0.025 (2)	-0.0020 (16)	-0.0009 (15)	-0.0018 (18)
C19	0.0299 (19)	0.024 (2)	0.020 (2)	-0.0070 (15)	0.0027 (15)	-0.0021 (16)
C20	0.0283 (19)	0.026 (2)	0.017 (2)	-0.0020 (15)	0.0015 (15)	0.0021 (16)
C20A	0.0202 (17)	0.0222 (19)	0.019 (2)	0.0004 (14)	0.0009 (14)	0.0051 (15)
C21	0.129 (5)	0.071 (4)	0.024 (3)	0.050 (4)	-0.003 (3)	-0.014 (3)
C22	0.037 (2)	0.032 (2)	0.041 (3)	0.0054 (18)	0.0051 (19)	-0.0023 (19)
C23	0.045 (2)	0.032 (2)	0.023 (2)	0.0009 (18)	-0.0052 (18)	-0.0022 (18)
C24	0.046 (2)	0.027 (2)	0.022 (2)	-0.0055 (17)	-0.0015 (17)	0.0021 (17)

Table S5. Geometric parameters (Å, º) for chrysosplenetin (**10**).

O1—C8A	1.364 (4)	C11—H11B	0.9800
O1—C2	1.371 (4)	C11—H11C	0.9800
C1'—C6'	1.392 (5)	O12—C17	1.347 (4)
C1'—C2'	1.406 (5)	O12—H12O	1.02 (5)
C1'—C2	1.470 (5)	C12—H12A	0.9800
O2—C3	1.372 (4)	C12—H12B	0.9800
O2—C9	1.428 (5)	C12—H12C	0.9800
C2—C3	1.356 (5)	O13—C18	1.369 (4)
C2'—C3'	1.371 (5)	O13—C22	1.439 (5)
C2'—H2'	0.9500	C13'—C18'	1.391 (5)
O3—C4	1.254 (4)	C13'—C14'	1.408 (5)
C3—C4	1.457 (5)	C13'—C14	1.470 (5)
C3'—O7	1.371 (4)	O14—C19	1.355 (4)
C3'—C4'	1.402 (5)	O14—C23	1.428 (5)
O4—C5	1.353 (4)	C14—C15	1.363 (5)
O4—H4OO	0.97 (6)	C14'—C15'	1.383 (5)
C4—C4A	1.444 (5)	C14'—H14'	0.9500
C4'—O8	1.367 (4)	O15—C15'	1.370 (4)
C4'—C5'	1.380 (5)	O15—C24	1.442 (5)
C4A—C8A	1.382 (5)	C15—C16	1.451 (5)
C4A—C5	1.423 (5)	C15'—C16'	1.397 (5)
O5—C6	1.386 (4)	O16—C16'	1.360 (4)
O5—C10	1.442 (4)	O16—H16O	0.92 (5)
C5—C6	1.375 (5)	C16—C16A	1.432 (5)
C5'—C6'	1.398 (5)	C16'—C17'	1.377 (5)
C5'—H5'	0.9500	C16A—C20A	1.389 (5)
O6—C7	1.357 (4)	C16A—C17	1.421 (5)
O6—C11	1.445 (4)	C17—C18	1.377 (5)
C6—C7	1.410 (5)	C17'—C18'	1.390 (5)
C6'—H6'	0.9500	C17'—H17'	0.9500
O7—C12	1.430 (4)	C18—C19	1.412 (5)
C7—C8	1.384 (5)	C18'—H18'	0.9500
O8—H8O	0.87 (5)	C19—C20	1.391 (5)
C8—C8A	1.382 (5)	C20—C20A	1.376 (5)
C8—H8	0.9500	C20—H20	0.9500
O9—C14	1.361 (4)	C21—H21A	0.9800
O9—C20A	1.375 (4)	C21—H21B	0.9800

C9—H9A	0.9800	C21—H21C	0.9800
C9—H9B	0.9800	C22—H22A	0.9800
C9—H9C	0.9800	C22—H22B	0.9800
O10—C15	1.368 (4)	C22—H22C	0.9800
O10—C21	1.441 (6)	C23—H23A	0.9800
C10—H10A	0.9800	C23—H23B	0.9800
C10—H10B	0.9800	C23—H23C	0.9800
C10—H10C	0.9800	C24—H24A	0.9800
O11—C16	1.260 (4)	C24—H24B	0.9800
C11—H11A	0.9800	C24—H24C	0.9800
C8A—O1—C2	120.4 (3)	O7—C12—H12C	109.5
C6'—C1'—C2'	119.5 (3)	H12A—C12—H12C	109.5
C6'—C1'—C2	123.1 (3)	H12B—C12—H12C	109.5
C2'—C1'—C2	117.4 (3)	C18—O13—C22	114.9 (3)
C3—O2—C9	114.1 (3)	C18'—C13'—C14'	118.0 (3)
C3—C2—O1	121.2 (3)	C18'—C13'—C14	123.6 (3)
C3—C2—C1'	128.5 (3)	C14'—C13'—C14	118.4 (3)
O1—C2—C1'	110.2 (3)	C19—O14—C23	117.4 (3)
C3'—C2'—C1'	120.3 (3)	O9—C14—C15	119.6 (3)
C3'—C2'—H2'	119.9	O9—C14—C13'	111.8 (3)
C1'—C2'—H2'	119.9	C15—C14—C13'	128.6 (4)
C2—C3—O2	119.8 (3)	C15'—C14'—C13'	120.6 (3)
C2—C3—C4	121.3 (3)	C15'—C14'—H14'	119.7
O2—C3—C4	119.0 (3)	C13'—C14'—H14'	119.7
C2'—C3'—O7	125.1 (3)	C15'—O15—C24	117.1 (3)
C2'—C3'—C4'	120.5 (3)	C14—C15—O10	120.4 (4)
O7—C3'—C4'	114.4 (3)	C14—C15—C16	122.2 (3)
C5—O4—H4OO	110 (3)	O10—C15—C16	117.3 (3)
O3—C4—C4A	122.2 (3)	O15—C15'—C14'	125.1 (3)
O3—C4—C3	122.8 (3)	O15—C15'—C16'	114.4 (3)
C4A—C4—C3	115.0 (3)	C14'—C15'—C16'	120.5 (3)
O8—C4'—C5'	119.0 (3)	C16'—O16—H16O	113 (3)
O8—C4'—C3'	121.7 (3)	O11—C16—C16A	122.7 (3)
C5'—C4'—C3'	119.3 (3)	O11—C16—C15	121.7 (3)
C8A—C4A—C5	117.5 (3)	C16A—C16—C15	115.7 (3)
C8A—C4A—C4	120.6 (3)	O16—C16'—C17'	119.3 (3)
C5—C4A—C4	121.8 (3)	O16—C16'—C15'	121.5 (3)

C6—O5—C10	114.9 (3)	C17'—C16'—C15'	119.2 (4)
O4—C5—C6	119.7 (3)	C20A—C16A—C17	118.2 (3)
O4—C5—C4A	119.8 (3)	C20A—C16A—C16	120.0 (3)
C6—C5—C4A	120.5 (3)	C17—C16A—C16	121.9 (3)
C4'—C5'—C6'	120.8 (3)	O12—C17—C18	119.7 (3)
C4'—C5'—H5'	119.6	O12—C17—C16A	120.2 (3)
C6'—C5'—H5'	119.6	C18—C17—C16A	120.1 (3)
C7—O6—C11	115.9 (3)	C16'—C17'—C18'	120.6 (4)
C5—C6—O5	119.0 (3)	C16'—C17'—H17'	119.7
C5—C6—C7	119.9 (3)	C18'—C17'—H17'	119.7
O5—C6—C7	120.9 (3)	O13—C18—C17	119.5 (3)
C1'—C6'—C5'	119.6 (4)	O13—C18—C19	121.0 (3)
C1'—C6'—H6'	120.2	C17—C18—C19	119.2 (3)
C5'—C6'—H6'	120.2	C17'—C18'—C13'	121.1 (3)
C3'—O7—C12	117.2 (3)	C17'—C18'—H18'	119.5
O6—C7—C8	123.6 (3)	C13'—C18'—H18'	119.5
O6—C7—C6	116.0 (3)	O14—C19—C20	123.8 (3)
C8—C7—C6	120.4 (3)	O14—C19—C18	114.4 (3)
C4'—O8—H8O	109 (3)	C20—C19—C18	121.8 (3)
C8A—C8—C7	118.6 (3)	C20A—C20—C19	117.4 (3)
C8A—C8—H8	120.7	C20A—C20—H20	121.3
C7—C8—H8	120.7	C19—C20—H20	121.3
O1—C8A—C4A	121.3 (3)	O9—C20A—C20	115.8 (3)
O1—C8A—C8	115.6 (3)	O9—C20A—C16A	120.8 (3)
C4A—C8A—C8	123.1 (3)	C20—C20A—C16A	123.3 (3)
C14—O9—C20A	121.6 (3)	O10—C21—H21A	109.5
O2—C9—H9A	109.5	O10—C21—H21B	109.5
O2—C9—H9B	109.5	H21A—C21—H21B	109.5
H9A—C9—H9B	109.5	O10—C21—H21C	109.5
O2—C9—H9C	109.5	H21A—C21—H21C	109.5
H9A—C9—H9C	109.5	H21B—C21—H21C	109.5
H9B—C9—H9C	109.5	O13—C22—H22A	109.5
C15—O10—C21	113.3 (4)	O13—C22—H22B	109.5
O5—C10—H10A	109.5	H22A—C22—H22B	109.5
O5—C10—H10B	109.5	O13—C22—H22C	109.5
H10A—C10—H10B	109.5	H22A—C22—H22C	109.5
O5—C10—H10C	109.5	H22B—C22—H22C	109.5
H10A—C10—H10C	109.5	O14—C23—H23A	109.5

H10B—C10—H10C	109.5	O14—C23—H23B	109.5
O6—C11—H11A	109.5	H23A—C23—H23B	109.5
O6—C11—H11B	109.5	O14—C23—H23C	109.5
H11A—C11—H11B	109.5	H23A—C23—H23C	109.5
O6—C11—H11C	109.5	H23B—C23—H23C	109.5
H11A—C11—H11C	109.5	O15—C24—H24A	109.5
H11B—C11—H11C	109.5	O15—C24—H24B	109.5
C17—O12—H12O	107 (2)	H24A—C24—H24B	109.5
O7—C12—H12A	109.5	O15—C24—H24C	109.5
O7—C12—H12B	109.5	H24A—C24—H24C	109.5
H12A—C12—H12B	109.5	H24B—C24—H24C	109.5
C8A—O1—C2—C3	4.9 (5)	C20A—O9—C14—C15	0.7 (5)
C8A—O1—C2—C1'	-172.1 (3)	C20A—O9—C14—C13'	179.7 (3)
C6'—C1'—C2—C3	42.3 (6)	C18'—C13'—C14—O9	-179.3 (3)
C2'—C1'—C2—C3	-136.8 (4)	C14'—C13'—C14—O9	0.5 (4)
C6'—C1'—C2—O1	-141.0 (4)	C18'—C13'—C14—C15	-0.3 (6)
C2'—C1'—C2—O1	39.9 (4)	C14'—C13'—C14—C15	179.5 (3)
C6'—C1'—C2'—C3'	-1.0 (6)	C18'—C13'—C14'—C15'	1.1 (5)
C2—C1'—C2'—C3'	178.2 (3)	C14—C13'—C14'—C15'	-178.7 (3)
O1—C2—C3—O2	173.9 (3)	O9—C14—C15—O10	174.2 (3)
C1'—C2—C3—O2	-9.7 (6)	C13'—C14—C15—O10	-4.6 (6)
O1—C2—C3—C4	-5.4 (5)	O9—C14—C15—C16	-2.6 (5)
C1'—C2—C3—C4	171.0 (3)	C13'—C14—C15—C16	178.5 (3)
C9—O2—C3—C2	111.2 (4)	C21—O10—C15—C14	106.1 (4)
C9—O2—C3—C4	-69.5 (4)	C21—O10—C15—C16	-76.9 (4)
C1'—C2'—C3'—O7	-179.9 (4)	C24—O15—C15'—C14'	18.3 (5)
C1'—C2'—C3'—C4'	0.7 (6)	C24—O15—C15'—C16'	-161.8 (3)
C2—C3—C4—O3	-176.3 (3)	C13'—C14'—C15'—O15	-178.8 (3)
O2—C3—C4—O3	4.4 (5)	C13'—C14'—C15'—C16'	1.2 (5)
C2—C3—C4—C4A	1.9 (5)	C14—C15—C16—O11	-178.5 (3)
O2—C3—C4—C4A	-177.4 (3)	O10—C15—C16—O11	4.5 (5)
C2'—C3'—C4'—O8	179.6 (3)	C14—C15—C16—C16A	2.4 (5)
O7—C3'—C4'—O8	0.2 (5)	O10—C15—C16—C16A	-174.6 (3)
C2'—C3'—C4'—C5'	0.6 (6)	O15—C15'—C16'—O16	-2.4 (5)
O7—C3'—C4'—C5'	-178.9 (3)	C14'—C15'—C16'—O16	177.5 (3)
O3—C4—C4A—C8A	-179.8 (3)	O15—C15'—C16'—C17'	177.1 (3)
C3—C4—C4A—C8A	2.0 (4)	C14'—C15'—C16'—C17'	-3.0 (5)

O3—C4—C4A—C5	-2.1 (5)	O11—C16—C16A—C20A	-179.3 (3)
C3—C4—C4A—C5	179.7 (3)	C15—C16—C16A—C20A	-0.3 (5)
C8A—C4A—C5—O4	-179.4 (3)	O11—C16—C16A—C17	0.2 (5)
C4—C4A—C5—O4	2.9 (5)	C15—C16—C16A—C17	179.2 (3)
C8A—C4A—C5—C6	0.8 (5)	C20A—C16A—C17—O12	179.2 (3)
C4—C4A—C5—C6	-176.9 (3)	C16—C16A—C17—O12	-0.3 (5)
O8—C4'—C5'—C6'	179.2 (3)	C20A—C16A—C17—C18	-0.5 (5)
C3'—C4'—C5'—C6'	-1.7 (6)	C16—C16A—C17—C18	180.0 (3)
O4—C5—C6—O5	-5.7 (5)	O16—C16'—C17'—C18'	-178.1 (3)
C4A—C5—C6—O5	174.1 (3)	C15'—C16'—C17'—C18'	2.4 (5)
O4—C5—C6—C7	179.1 (3)	C22—O13—C18—C17	-113.7 (4)
C4A—C5—C6—C7	-1.1 (5)	C22—O13—C18—C19	71.5 (4)
C10—O5—C6—C5	106.4 (4)	O12—C17—C18—O13	5.8 (5)
C10—O5—C6—C7	-78.5 (4)	C16A—C17—C18—O13	-174.5 (3)
C2'—C1'—C6'—C5'	-0.1 (6)	O12—C17—C18—C19	-179.4 (3)
C2—C1'—C6'—C5'	-179.2 (4)	C16A—C17—C18—C19	0.3 (5)
C4'—C5'—C6'—C1'	1.4 (6)	C16'—C17'—C18'—C13'	0.0 (5)
C2'—C3'—O7—C12	-4.1 (5)	C14'—C13'—C18'—C17'	-1.7 (5)
C4'—C3'—O7—C12	175.3 (3)	C14—C13'—C18'—C17'	178.1 (3)
C11—O6—C7—C8	5.7 (5)	C23—O14—C19—C20	11.5 (5)
C11—O6—C7—C6	-175.6 (3)	C23—O14—C19—C18	-170.1 (3)
C5—C6—C7—O6	-178.5 (3)	O13—C18—C19—O14	-3.5 (5)
O5—C6—C7—O6	6.4 (5)	C17—C18—C19—O14	-178.3 (3)
C5—C6—C7—C8	0.3 (5)	O13—C18—C19—C20	174.9 (3)
O5—C6—C7—C8	-174.8 (3)	C17—C18—C19—C20	0.1 (5)
O6—C7—C8—C8A	179.4 (3)	O14—C19—C20—C20A	177.9 (3)
C6—C7—C8—C8A	0.8 (5)	C18—C19—C20—C20A	-0.4 (5)
C2—O1—C8A—C4A	-0.8 (5)	C14—O9—C20A—C20	-179.8 (3)
C2—O1—C8A—C8	178.6 (3)	C14—O9—C20A—C16A	1.4 (4)
C5—C4A—C8A—O1	179.6 (3)	C19—C20—C20A—O9	-178.5 (3)
C4—C4A—C8A—O1	-2.6 (5)	C19—C20—C20A—C16A	0.2 (5)
C5—C4A—C8A—C8	0.3 (5)	C17—C16A—C20A—O9	178.9 (3)
C4—C4A—C8A—C8	178.0 (3)	C16—C16A—C20A—O9	-1.5 (5)
C7—C8—C8A—O1	179.6 (3)	C17—C16A—C20A—C20	0.2 (5)
C7—C8—C8A—C4A	-1.1 (5)	C16—C16A—C20A—C20	179.8 (3)

Table S6. Hydrogen-bond geometry (Å, º) for chrysosplenetin (**10**).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4*O*···O3	0.97 (6)	1.75 (5)	2.594 (4)	144 (5)
O8—H8*O*···O5^{i}	0.87 (5)	2.22 (5)	3.023 (4)	154 (4)
O8—H8*O*···O7	0.87 (5)	2.25 (5)	2.688 (3)	111 (4)
O12—H12*O*···O11	1.02 (5)	1.68 (5)	2.601 (4)	148 (4)
O16—H16*O*···O4	0.92 (5)	1.94 (5)	2.829 (4)	163 (4)

Symmetry code: (i) *x*, *y*, *z*-1.