

## SUPPLEMENTARY MATERIAL

### Allobetulone rearrangement to 18 $\alpha$ H,19 $\beta$ H-ursane triterpenoids with antiviral activity

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### Abstract

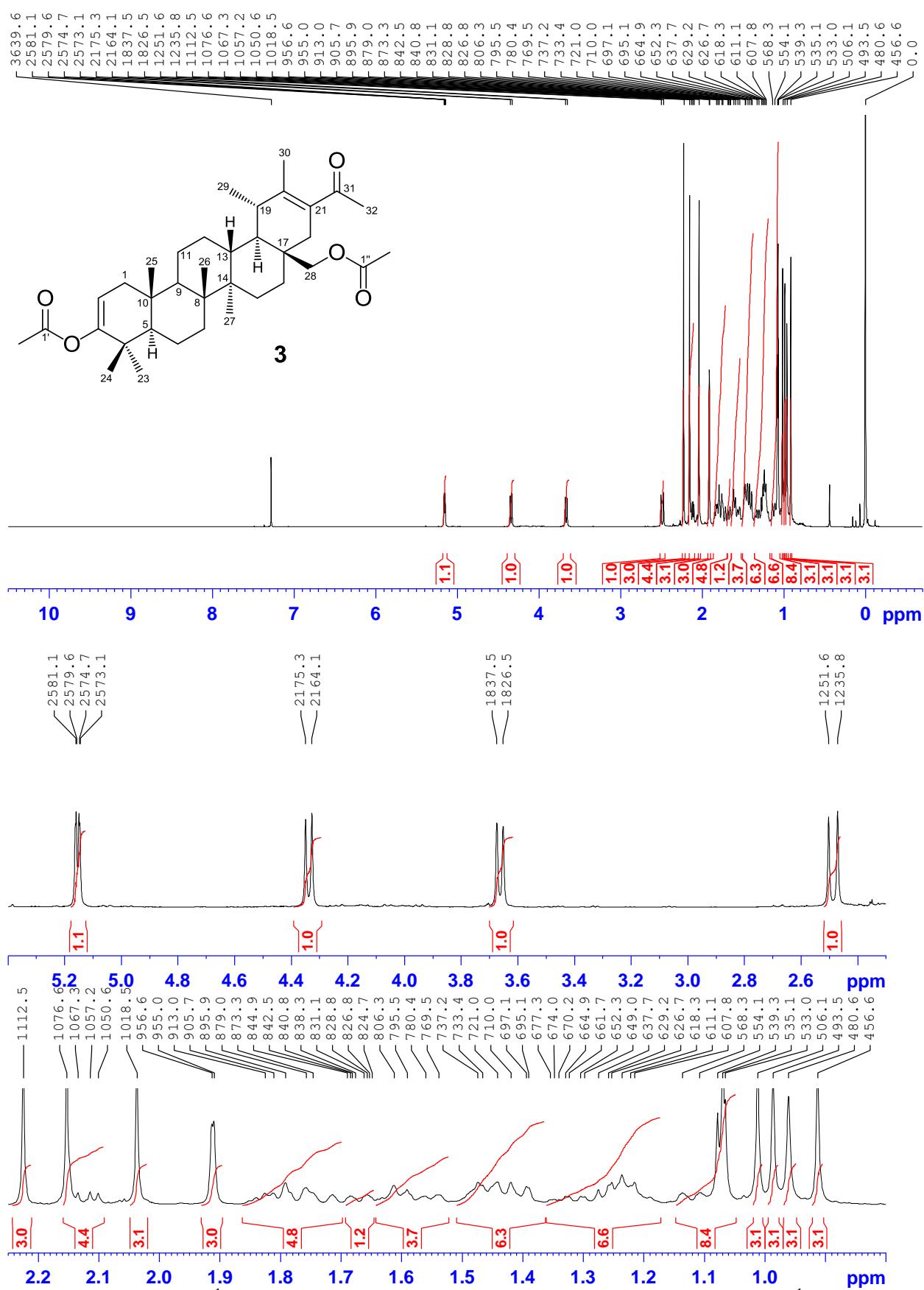
Allobetulone E-ring rearrangement under treating with  $\text{HClO}_4$  in  $\text{Ac}_2\text{O}$  under reflux afforded new triterpenoids: 3,28-diacetoxy-21-acetyl-2(3),20(21)-18 $\alpha$ ,19 $\beta$ H-ursandiene **3** and 3,28-diacetoxy-2(3),18(19)-oleandiene **4**. 18 $\alpha$ ,19 $\beta$ H-Ursanes were transformed at A- and E-rings into indolo- and bis-furfurylidene **7** derivatives. Structure elucidation was performed using COSY, NOESY, HSQC and HMBC experiments, and X-Ray analysis for **3**. The potential of newly obtained 18 $\alpha$ ,19 $\beta$ H-ursanes was evaluated against HCMV and HPV-11, the NCI-60 cancer cell panel and inhibition of  $\alpha$ -glucosidase. All of the compounds have shown viral inhibition towards HCMV compared to standard drug Acyclovir. 3 $\beta$ -Acetoxy-21 $\beta$ -acetyl-20 $\beta$ ,28-epoxy-18 $\alpha$ ,19 $\beta$ H-ursane **1** showed moderate activity ( $\text{EC}_{50}$  4.87  $\mu\text{M}$ ) towards the HCMV-resistant isolate (GDGr K17) compared to standard drug Cidofovir and was four times more potent than Ganciclovir. Compound **7** inhibited the cell growth of the three melanoma and one colon cancer cell. 3-Oxo-21 $\beta$ -acetyl-20 $\beta$ ,28-epoxy-18 $\alpha$ ,19 $\beta$ H-ursane **5** and compound **7** inhibited  $\alpha$ -glucosidase with  $\text{IC}_{50}$  28.0  $\mu\text{M}$  and 4.0  $\mu\text{M}$  being from 6 to 44 times more active than acarbose.

**Keywords:** triterpenoids, betulin, allobetulin, lupane, ursane, skeleton rearrangement, antiviral activity, NCI-60,  $\alpha$ -glucosidase

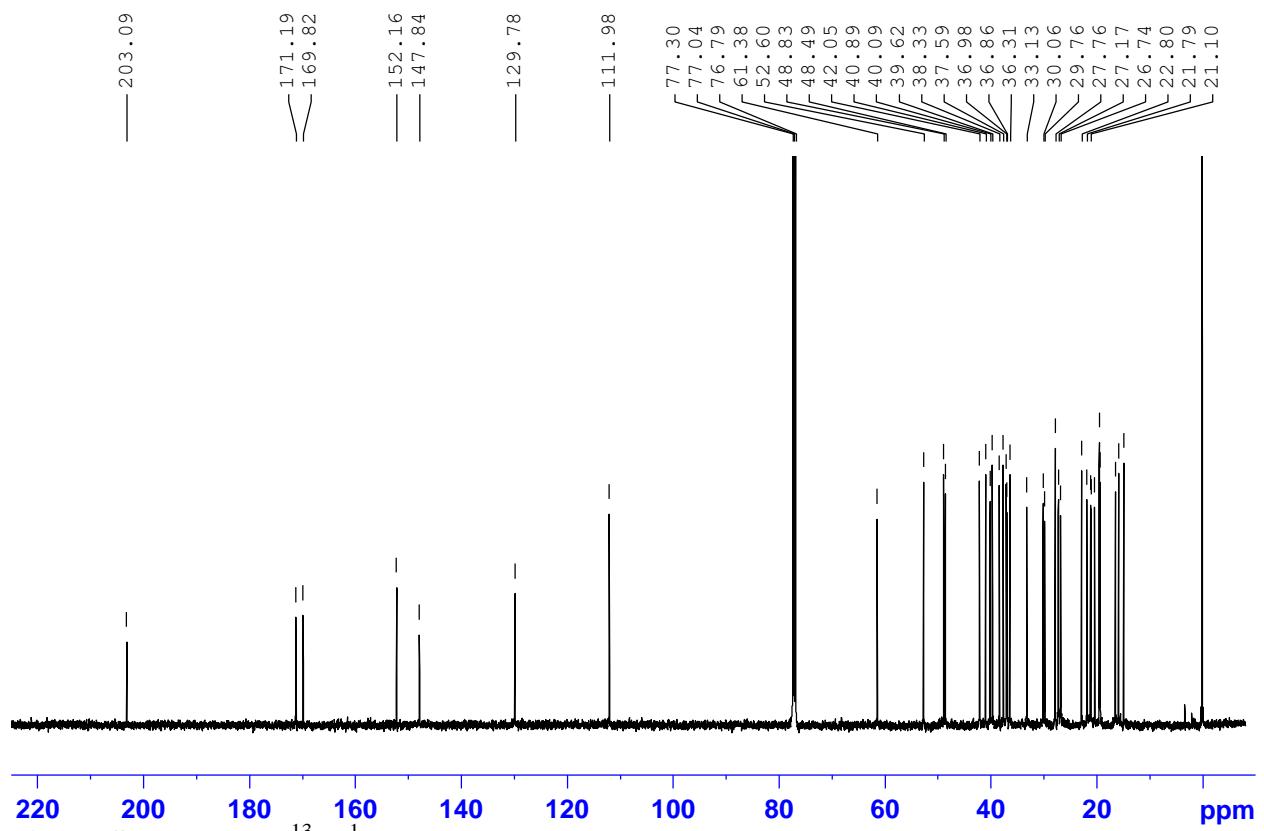
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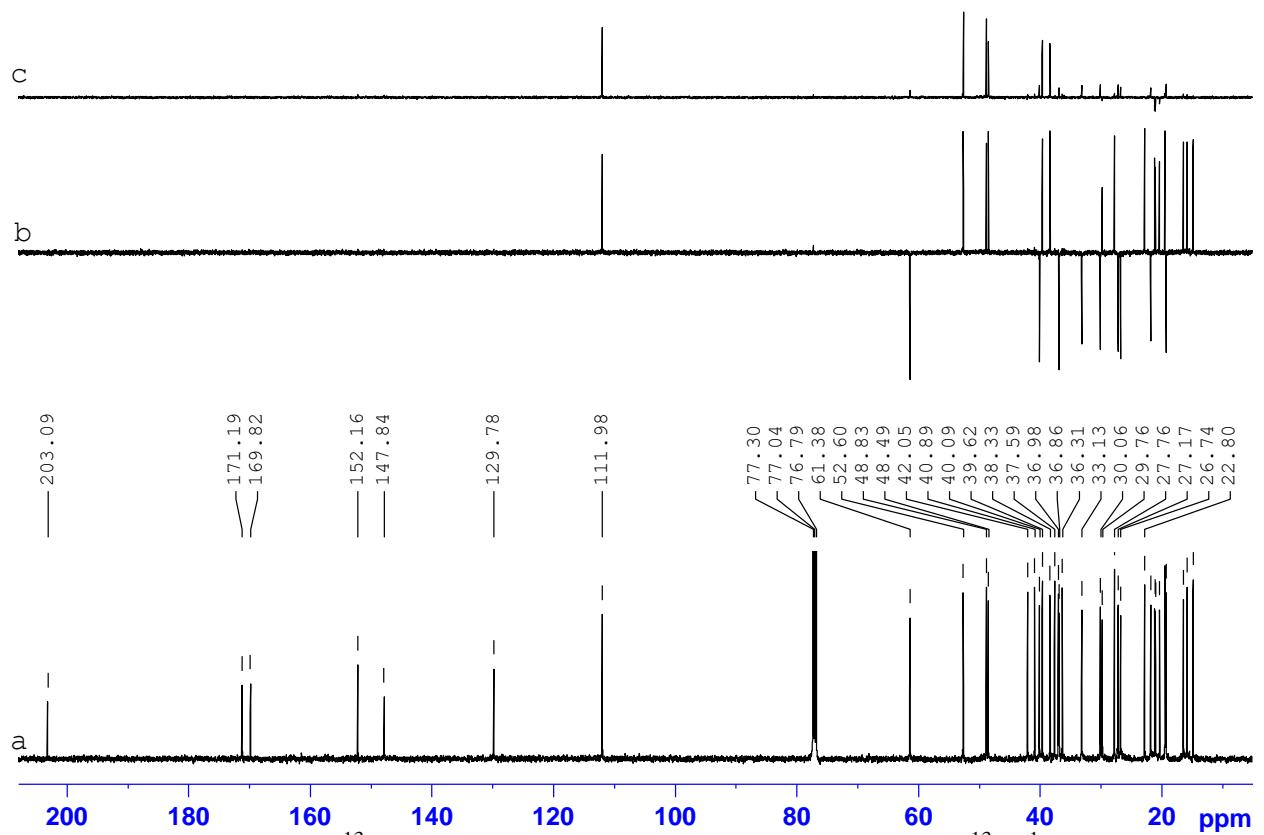
### NMR data of compound 3



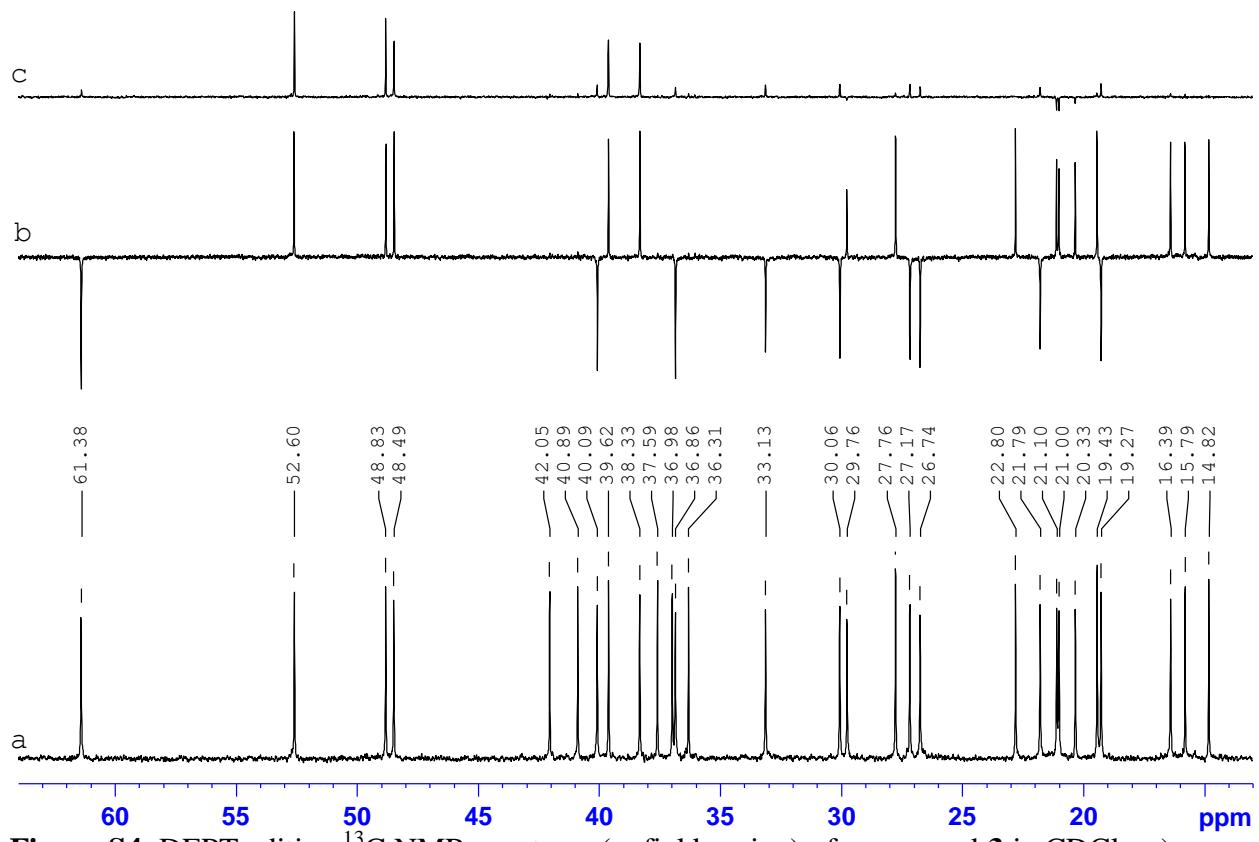
**Figure S1.** Complete  $^1\text{H}$  NMR spectrum of compound 3 in  $\text{CDCl}_3$  (top). Expanded  $^1\text{H}$  NMR spectrum of compound 3 in  $\text{CDCl}_3$  (bottom).



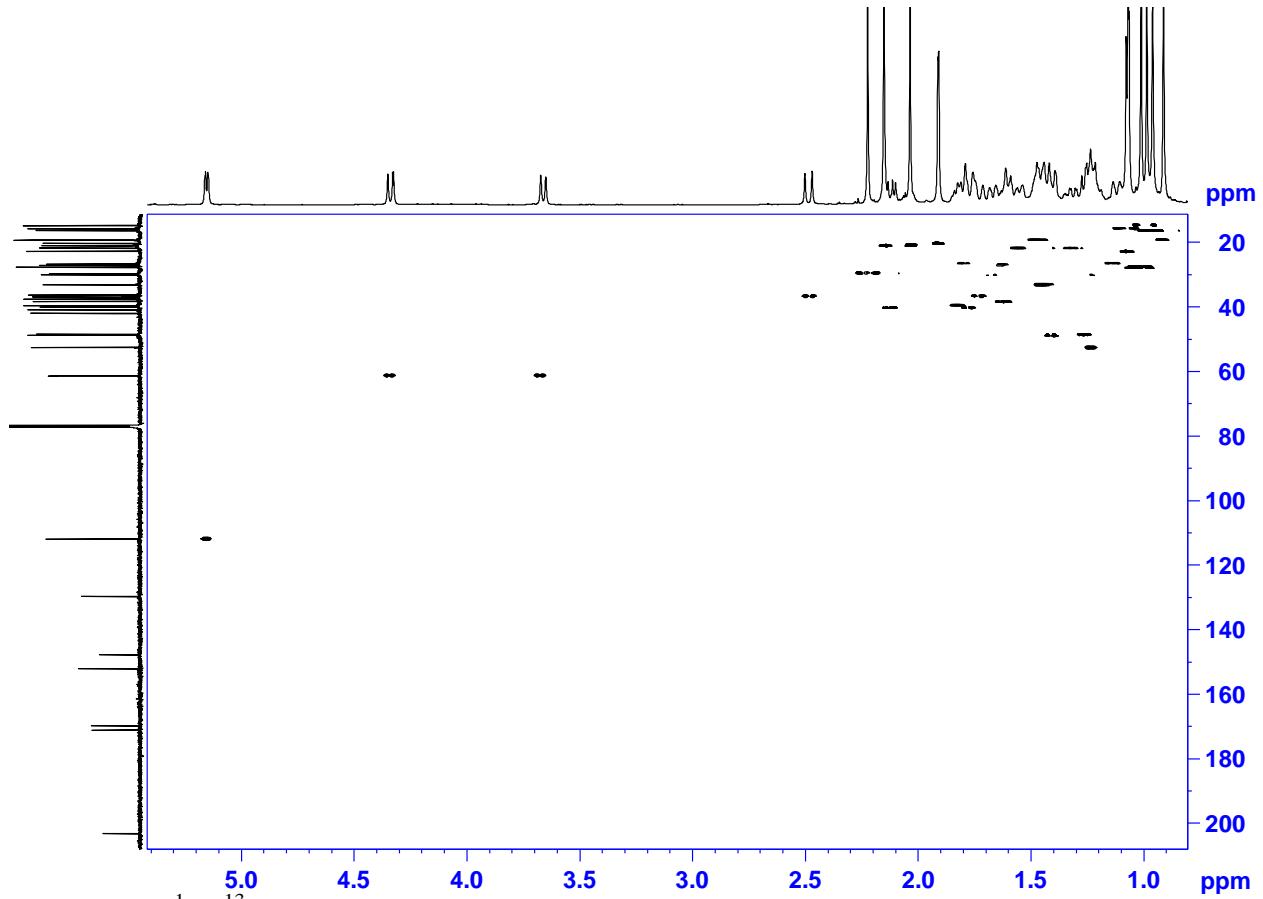
**Figure S2.** Complete  $^{13}\text{C}\{\text{H}\}$  spectrum of compound 3 in  $\text{CDCl}_3$ .



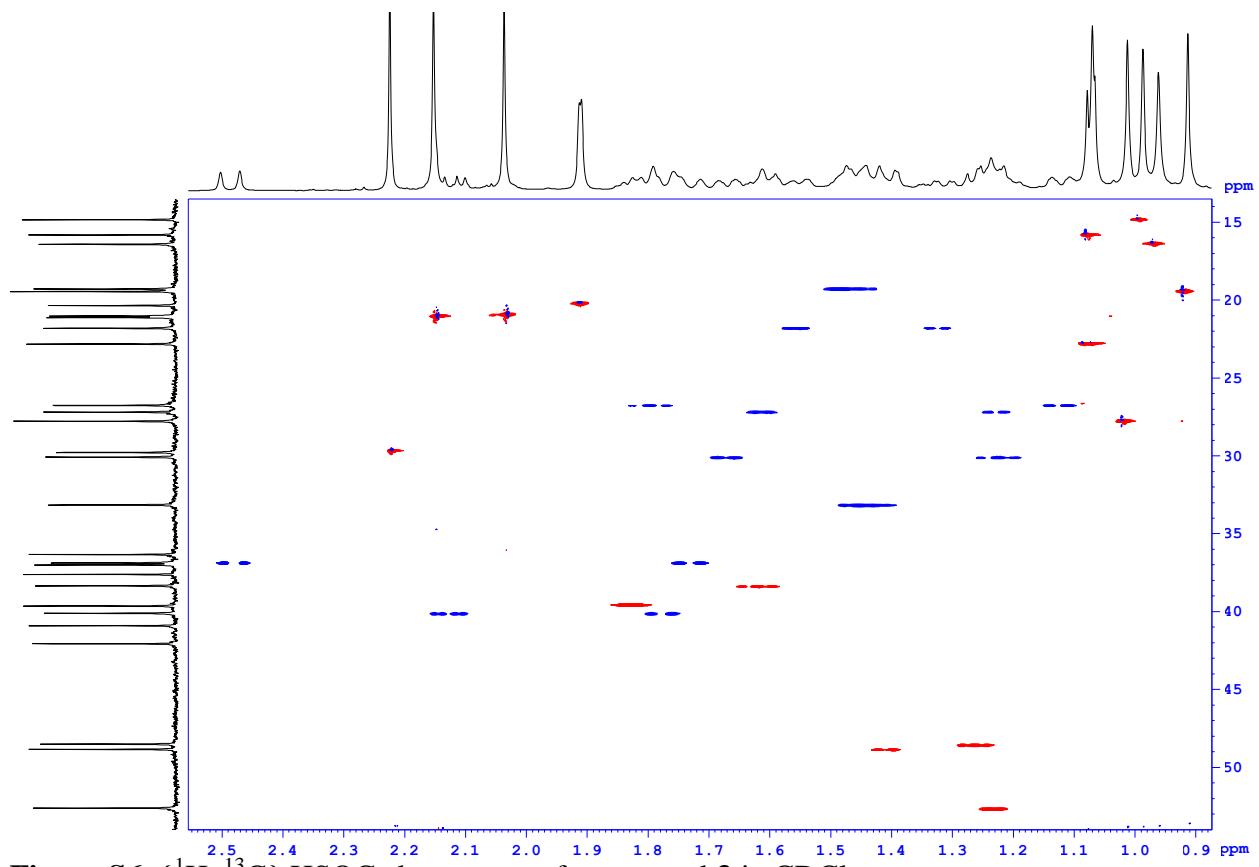
**Figure S3.** DEPT editing  $^{13}\text{C}$  NMR spectrum of compound 3 in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



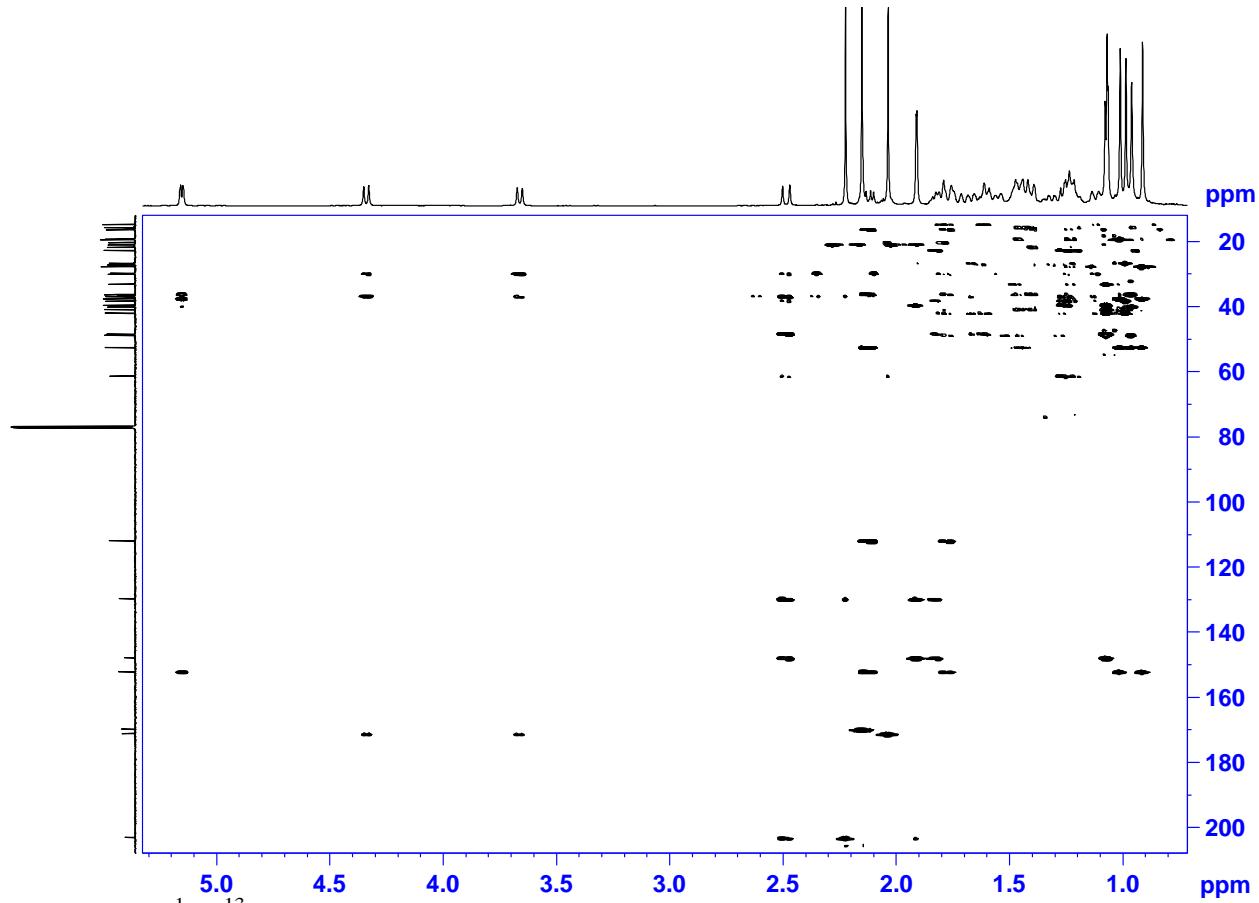
**Figure S4.** DEPT editing  $^{13}\text{C}$  NMR spectrum (upfield region) of compound **3** in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{^1\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



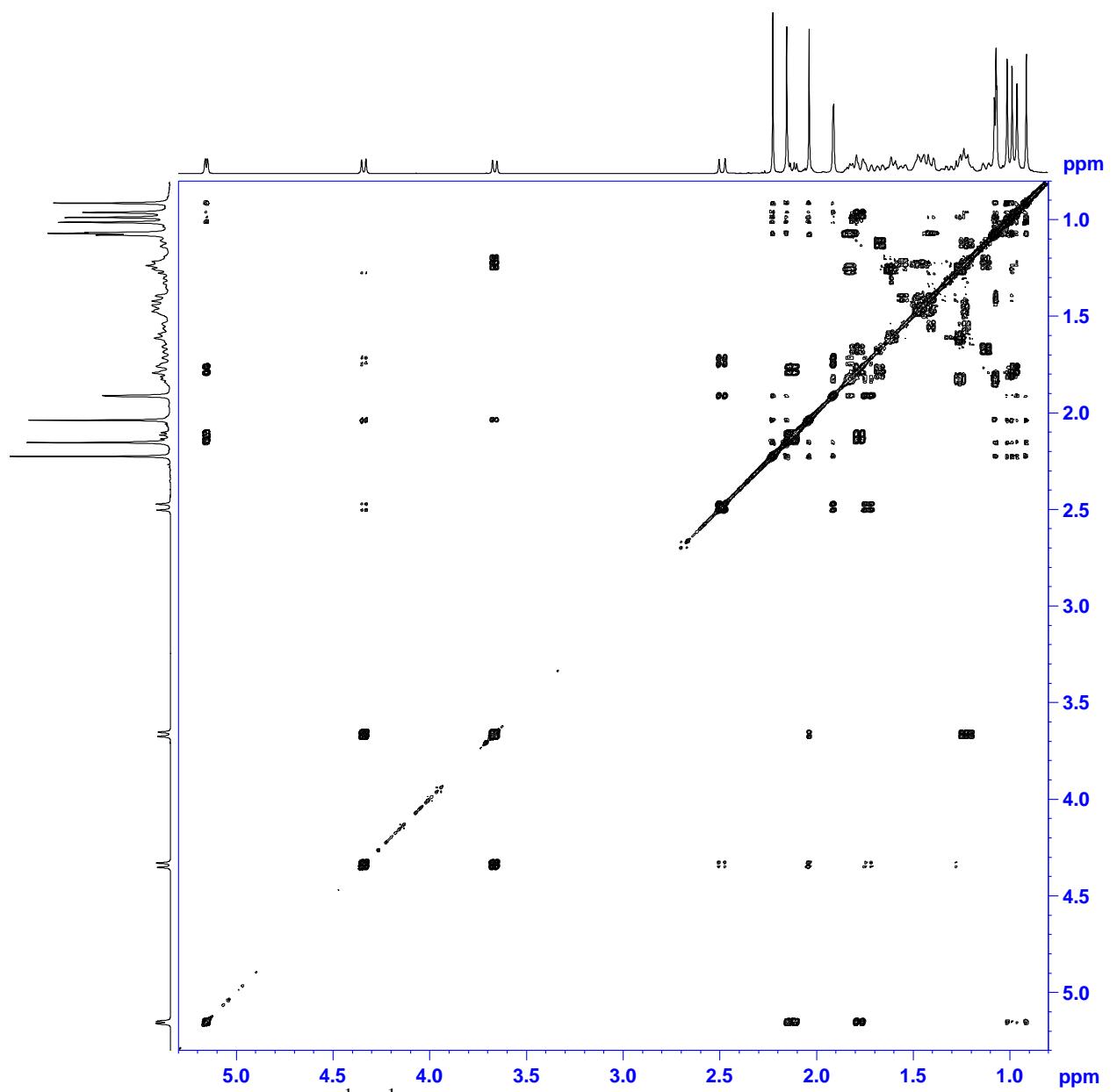
**Figure S5.**  $\{^1\text{H}, ^{13}\text{C}\}$  HSQC spectrum of compound **3** in  $\text{CDCl}_3$ .



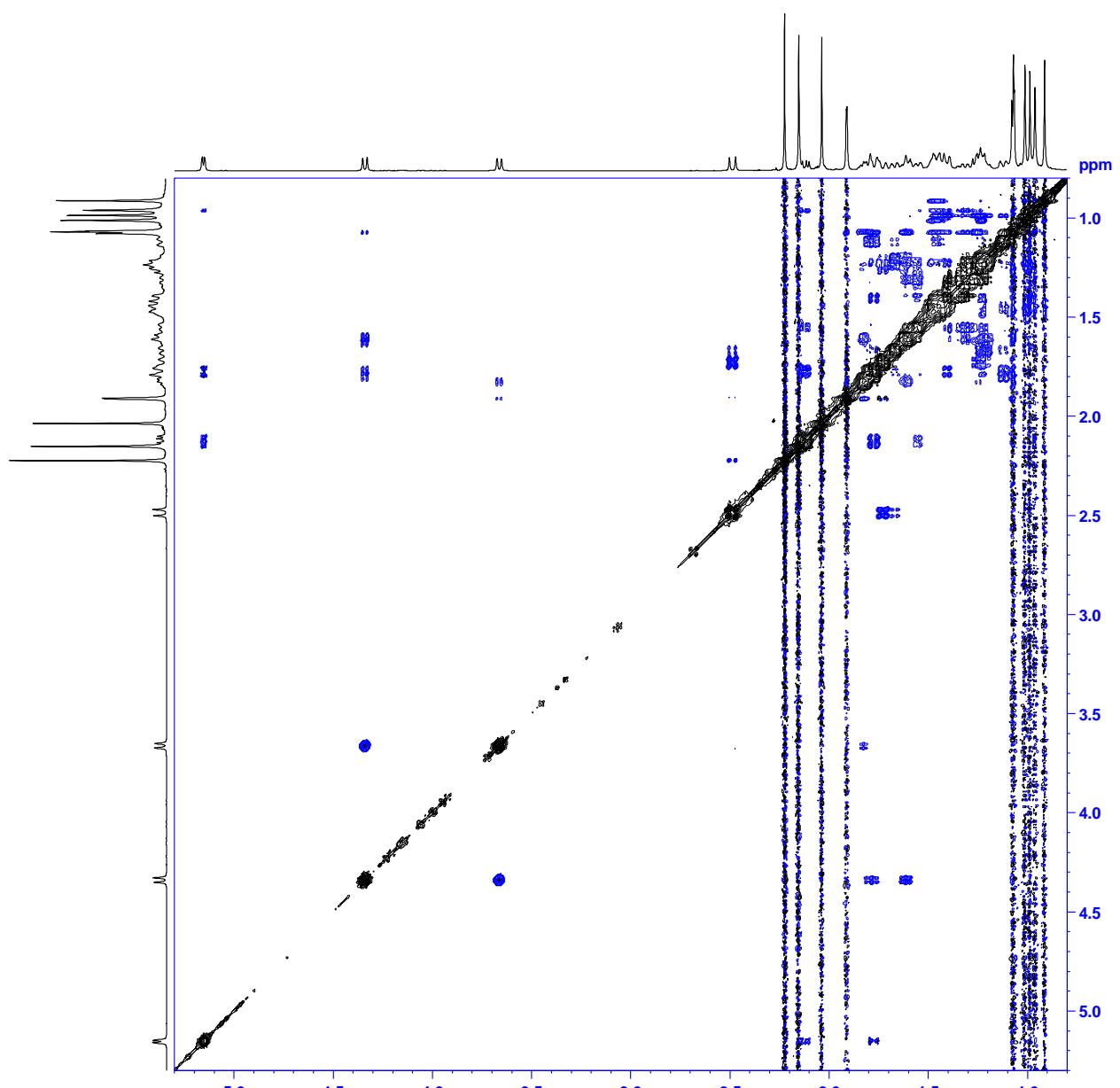
**Figure S6.**  $\{^1\text{H}, ^{13}\text{C}\}$  HSQCed spectrum of compound 3 in  $\text{CDCl}_3$ .



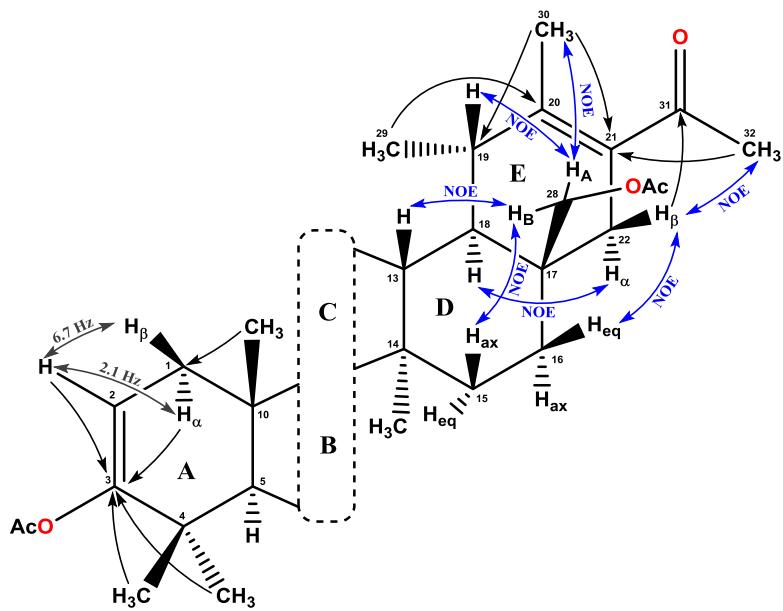
**Figure S7.**  $\{^1\text{H}, ^{13}\text{C}\}$  HMBC spectrum of compound 3 in  $\text{CDCl}_3$ .



**Figure S8.**  $\{^1\text{H}, ^1\text{H}\}$  COSY spectrum of compound 3 in  $\text{CDCl}_3$ .



**Figure S9.**  $\{^1\text{H}, ^1\text{H}\}$  NOESY spectrum of compound 3 in  $\text{CDCl}_3$ .



**Figure S10.** NMR assignments and significant  $\{{}^1\text{H}, {}^{13}\text{C}\}$  HMBC (black arrows), and NOESY (blue arrows) correlations of compound **3**

## X-Ray data for compound 3

### *Experimental details*

Crystal data	
Chemical formula	C <sub>36</sub> H <sub>54</sub> O <sub>5</sub> ·CHCl <sub>3</sub>
M <sub>r</sub>	686.16
Crystal system, space group	Orthorhombic, P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Temperature (K)	296
a, b, c (Å)	7.4846 (4), 15.4985 (11), 31.980 (2)
V (Å <sup>3</sup> )	3709.7 (4)
Z	4
Radiation type	Mo Kα
μ (mm <sup>-1</sup> )	0.29
Crystal size (mm)	0.72 × 0.15 × 0.02
Data collection	
Diffractometer	Bruker APEX-II CCD
Absorption correction	Multi-scan SADABS2008/1
T <sub>min</sub> , T <sub>max</sub>	0.779, 0.862
No. of measured, independent and observed [I > 2σ(I)] reflections	56357, 6568, 4169
R <sub>int</sub>	0.072
(sin θ/λ) <sub>max</sub> (Å <sup>-1</sup> )	0.597
Refinement	
R[F <sup>2</sup> > 2σ(F <sup>2</sup> )], wR(F <sup>2</sup> ), S	0.054, 0.178, 1.07
No. of reflections	6568
No. of parameters	436
No. of restraints	35
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Δρ <sub>max</sub> , Δρ <sub>min</sub> (e Å <sup>-3</sup> )	0.50, -0.48
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Absolute structure parameter	0.00 (10)

### Computing details

Data collection: Bruker APEX2; cell refinement: Bruker SAINT; data reduction: Bruker SAINT; program(s) used to solve structure: SHELLXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELLXL97 (Sheldrick, 2008); molecular graphics: Bruker SHELLXTL; software used to prepare material for publication: Bruker SHELLXTL.

## Crystal data

$C_{36}H_{54}O_5 \cdot CHCl_3$	$D_x = 1.229 \text{ Mg m}^{-3}$
$M_r = 686.16$	Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
Orthorhombic, $P2_12_1$	Cell parameters from 8568 reflections
$a = 7.4846 (4) \text{ \AA}$	$\theta = 2.3\text{--}20.0^\circ$
$b = 15.4985 (11) \text{ \AA}$	$\mu = 0.29 \text{ mm}^{-1}$
$c = 31.980 (2) \text{ \AA}$	$T = 296 \text{ K}$
$V = 3709.7 (4) \text{ \AA}^3$	Needle-plate, colourless
$Z = 4$	$0.72 \times 0.15 \times 0.02 \text{ mm}$
$F(000) = 1472$	

## Data collection

Bruker APEX-II CCD diffractometer	6568 independent reflections
Radiation source: fine-focus sealed tube	4169 reflections with $I > 2\sigma(I)$
Graphite monochromator	$R_{\text{int}} = 0.072$
$\phi$ and $\omega$ scans	$\theta_{\max} = 25.1^\circ, \theta_{\min} = 1.3^\circ$
Absorption correction: multi-scan <i>SADABS2008/1</i>	$h = -8 \rightarrow 8$
$T_{\min} = 0.779, T_{\max} = 0.862$	$k = -18 \rightarrow 18$
56357 measured reflections	$l = -37 \rightarrow 38$

## Refinement

Refinement on $F^2$	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.054$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.178$	$w = 1/[\sigma^2(F_o^2) + (0.1016P)^2 + 0.5114P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.07$	$(\Delta/\sigma)_{\max} = 0.023$
6568 reflections	$\Delta\rho_{\max} = 0.50 \text{ e \AA}^{-3}$
436 parameters	$\Delta\rho_{\min} = -0.48 \text{ e \AA}^{-3}$
35 restraints	Absolute structure: Flack H D (1983), <i>Acta Cryst.</i> A39, 876-881
Primary atom site location: structure-invariant direct methods	Absolute structure parameter: 0.00 (10)

## Special details

**Geometry.** All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal

symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes. *Refinement*. Refinement of  $F^2$  against ALL reflections. The weighted R-factor wR and goodness of fit S are based on  $F^2$ , conventional R-factors R are based on F, with F set to zero for negative  $F^2$ . The threshold expression of  $F^2 > 2\text{sigma}(F^2)$  is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on  $F^2$  are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ( $\text{\AA}^2$ ) for compound 3*

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$	Occ. (<1)
Cl1S	0.3214 (2)	0.93826 (10)	0.16946 (5)	0.0987 (5)	
Cl2S	0.4094 (3)	1.10212 (13)	0.13383 (5)	0.1169 (7)	
Cl3S	0.6192 (3)	1.03091 (15)	0.20027 (6)	0.1312 (8)	
C1S	0.4024 (8)	1.0412 (4)	0.17963 (15)	0.0765 (15)	
H1S	0.3252	1.0698	0.2001	0.092*	
O1	0.2389 (4)	1.16970 (18)	-0.12067 (8)	0.0577 (8)	
O3	-0.2961 (5)	0.7978 (2)	0.20607 (9)	0.0726 (9)	
O2	0.4457 (6)	1.2400 (2)	-0.08315 (14)	0.0916 (12)	
O4	-0.1294 (12)	0.8433 (7)	0.25688 (16)	0.198 (4)	
C32	0.4038 (10)	1.2768 (4)	-0.15547 (19)	0.098 (2)	
H32C	0.3059	1.3154	-0.1605	0.148*	
H32B	0.4128	1.2364	-0.1781	0.148*	
H32A	0.5128	1.3092	-0.1534	0.148*	
C31	0.3725 (7)	1.2288 (3)	-0.11524 (18)	0.0657 (13)	
C3	0.1974 (6)	1.1141 (2)	-0.08673 (11)	0.0444 (9)	
C2	0.3093 (6)	1.0519 (3)	-0.07761 (12)	0.0478 (10)	
H2	0.4111	1.0453	-0.0940	0.057*	
C1	0.2801 (5)	0.9909 (2)	-0.04193 (12)	0.0434 (9)	
H1B	0.3934	0.9800	-0.0282	0.052*	
H1A	0.2363	0.9364	-0.0528	0.052*	
C10	0.1458 (4)	1.0260 (2)	-0.00955 (11)	0.0351 (8)	
C9	0.0874 (4)	0.9483 (2)	0.01839 (11)	0.0317 (8)	
H9	0.0559	0.9030	-0.0016	0.038*	
C11	0.2384 (5)	0.9095 (2)	0.04400 (12)	0.0392 (8)	
H11B	0.3424	0.9022	0.0262	0.047*	
H11A	0.2702	0.9491	0.0663	0.047*	
C12	0.1888 (5)	0.8231 (2)	0.06287 (11)	0.0380 (8)	
H12B	0.2870	0.8029	0.0801	0.046*	
H12A	0.1717	0.7816	0.0405	0.046*	
C13	0.0198 (4)	0.8267 (2)	0.08936 (11)	0.0326 (8)	
H13	0.0440	0.8673	0.1122	0.039*	
C18	-0.0287 (4)	0.7393 (2)	0.11015 (11)	0.0336 (8)	

H18	-0.0663	0.7015	0.0872	0.040*	
C17	-0.1932 (5)	0.7480 (3)	0.13882 (11)	0.0404 (9)	
C28	-0.1493 (5)	0.8054 (3)	0.17665 (11)	0.0496 (10)	
H28B	-0.0387	0.7866	0.1896	0.060*	
H28A	-0.1354	0.8649	0.1679	0.060*	
C33	-0.2692 (13)	0.8152 (5)	0.24516 (18)	0.110 (2)	
C34	-0.4316 (13)	0.8019 (7)	0.2715 (2)	0.160 (4)	
H34C	-0.4189	0.7496	0.2873	0.241*	
H34B	-0.5349	0.7978	0.2538	0.241*	
H34A	-0.4452	0.8498	0.2903	0.241*	
C19	0.1283 (5)	0.6921 (3)	0.13168 (11)	0.0423 (9)	
H19	0.2139	0.7360	0.1410	0.051*	
C29	0.2257 (6)	0.6319 (3)	0.10119 (14)	0.0576 (11)	
H29C	0.3384	0.6151	0.1130	0.086*	
H29B	0.2456	0.6615	0.0752	0.086*	
H29A	0.1541	0.5815	0.0963	0.086*	
C20	0.0779 (6)	0.6381 (3)	0.16940 (13)	0.0524 (11)	
C30	0.2309 (7)	0.6087 (4)	0.19586 (17)	0.0916 (19)	
H30C	0.1858	0.5802	0.2203	0.137*	
H30B	0.3012	0.6576	0.2041	0.137*	
H30A	0.3038	0.5693	0.1802	0.137*	
C21	-0.0902 (6)	0.6174 (3)	0.17801 (13)	0.0531 (11)	
C35	-0.1452 (8)	0.5617 (4)	0.21355 (17)	0.0785 (16)	
O5	-0.1178 (18)	0.5889 (6)	0.2512 (2)	0.125 (5)	0.637 (18)
C36	-0.221 (2)	0.4782 (8)	0.2068 (3)	0.111 (5)	0.637 (18)
H36A	-0.1411	0.4444	0.1899	0.167*	0.637 (18)
H36B	-0.3334	0.4841	0.1927	0.167*	0.637 (18)
H36C	-0.2386	0.4501	0.2332	0.167*	0.637 (18)
O5A	-0.269 (3)	0.5852 (10)	0.2351 (6)	0.128 (9)	0.363 (18)
C36A	-0.083 (4)	0.4692 (10)	0.2129 (9)	0.132 (10)	0.363 (18)
H36D	-0.1815	0.4320	0.2199	0.198*	0.363 (18)
H36E	0.0110	0.4616	0.2329	0.198*	0.363 (18)
H36F	-0.0404	0.4551	0.1854	0.198*	0.363 (18)
C22	-0.2424 (5)	0.6571 (3)	0.15387 (13)	0.0502 (10)	
H22B	-0.3475	0.6601	0.1715	0.060*	
H22A	-0.2706	0.6211	0.1300	0.060*	
C8	-0.0830 (4)	0.9586 (2)	0.04600 (11)	0.0330 (8)	
C14	-0.1378 (4)	0.8659 (2)	0.06349 (11)	0.0330 (8)	
C15	-0.3030 (5)	0.8711 (3)	0.09243 (12)	0.0456 (9)	
H15B	-0.2814	0.9147	0.1136	0.055*	
H15A	-0.4050	0.8897	0.0760	0.055*	

C16	-0.3493 (5)	0.7867 (3)	0.11398 (13)	0.0486 (10)	
H16B	-0.3877	0.7454	0.0931	0.058*	
H16A	-0.4488	0.7964	0.1328	0.058*	
C27	-0.1884 (6)	0.8046 (3)	0.02713 (11)	0.0461 (9)	
H27C	-0.1923	0.7463	0.0372	0.069*	
H27B	-0.1007	0.8092	0.0053	0.069*	
H27A	-0.3035	0.8204	0.0163	0.069*	
C26	-0.0514 (6)	1.0224 (3)	0.08289 (12)	0.0472 (10)	
H26C	0.0268	0.9963	0.1030	0.071*	
H26B	-0.1636	1.0358	0.0959	0.071*	
H26A	0.0020	1.0745	0.0724	0.071*	
C7	-0.2322 (5)	0.9976 (3)	0.01870 (12)	0.0440 (9)	
H7B	-0.2724	0.9543	-0.0011	0.053*	
H7A	-0.3328	1.0122	0.0365	0.053*	
C6	-0.1755 (5)	1.0774 (2)	-0.00524 (13)	0.0451 (9)	
H6B	-0.1410	1.1221	0.0144	0.054*	
H6A	-0.2758	1.0987	-0.0215	0.054*	
C5	-0.0194 (5)	1.0584 (2)	-0.03449 (12)	0.0387 (9)	
H5	-0.0580	1.0085	-0.0510	0.046*	
C4	0.0179 (5)	1.1304 (2)	-0.06725 (13)	0.0470 (10)	
C23	0.0108 (7)	1.2221 (3)	-0.04905 (16)	0.0653 (13)	
H23C	0.0865	1.2254	-0.0249	0.098*	
H23B	-0.1098	1.2357	-0.0412	0.098*	
H23A	0.0513	1.2626	-0.0697	0.098*	
C24	-0.1235 (7)	1.1235 (4)	-0.10205 (14)	0.0697 (14)	
H24C	-0.1004	1.1663	-0.1230	0.105*	
H24B	-0.2401	1.1327	-0.0904	0.105*	
H24A	-0.1182	1.0671	-0.1144	0.105*	
C25	0.2392 (5)	1.0988 (2)	0.01457 (13)	0.0475 (9)	
H25C	0.3166	1.0744	0.0354	0.071*	
H25B	0.1510	1.1345	0.0279	0.071*	
H25A	0.3082	1.1332	-0.0045	0.071*	

*Atomic displacement parameters ( $\text{\AA}^2$ ) for compound 3*

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
Cl1S	0.1078 (12)	0.0903 (10)	0.0980 (10)	-0.0133 (9)	-0.0150 (10)	-0.0168 (8)
Cl2S	0.1392 (15)	0.1229 (14)	0.0885 (11)	-0.0190 (12)	-0.0185 (10)	0.0265 (10)
Cl3S	0.1373 (16)	0.1367 (16)	0.1196 (14)	-0.0317 (13)	-0.0613 (13)	0.0065 (12)
C1S	0.091 (4)	0.086 (4)	0.053 (3)	0.000 (3)	-0.008 (3)	-0.018 (3)
O1	0.072 (2)	0.0488 (17)	0.0526 (16)	-0.0005 (16)	0.0059 (15)	0.0113 (14)
O3	0.075 (2)	0.097 (2)	0.0458 (17)	0.0157 (19)	0.0187 (17)	0.0006 (16)

O2	0.096 (3)	0.075 (2)	0.104 (3)	-0.029 (2)	-0.007 (3)	0.008 (2)
O4	0.208 (7)	0.322 (10)	0.065 (3)	-0.011 (7)	-0.012 (4)	-0.054 (4)
C32	0.112 (5)	0.076 (4)	0.108 (5)	-0.011 (3)	0.034 (4)	0.026 (3)
C31	0.075 (3)	0.043 (3)	0.079 (3)	-0.003 (2)	0.011 (3)	0.005 (3)
C3	0.055 (2)	0.034 (2)	0.044 (2)	-0.0022 (19)	0.004 (2)	0.0031 (17)
C2	0.049 (2)	0.045 (2)	0.050 (2)	0.005 (2)	0.011 (2)	0.0026 (19)
C1	0.040 (2)	0.040 (2)	0.050 (2)	0.0064 (17)	0.0053 (19)	0.0022 (18)
C10	0.0315 (18)	0.0341 (19)	0.0398 (19)	0.0012 (15)	0.0005 (16)	-0.0028 (16)
C9	0.0243 (17)	0.0334 (18)	0.0375 (19)	0.0046 (15)	-0.0042 (15)	-0.0045 (15)
C11	0.0252 (18)	0.048 (2)	0.044 (2)	0.0014 (16)	0.0003 (16)	0.0073 (17)
C12	0.0259 (18)	0.046 (2)	0.0426 (19)	0.0084 (16)	0.0033 (16)	0.0059 (17)
C13	0.0234 (17)	0.0395 (19)	0.0348 (18)	0.0012 (15)	-0.0026 (15)	-0.0042 (16)
C18	0.0263 (18)	0.041 (2)	0.0340 (18)	-0.0005 (15)	-0.0014 (15)	-0.0032 (16)
C17	0.0306 (19)	0.048 (2)	0.043 (2)	0.0003 (17)	0.0022 (17)	0.0042 (17)
C28	0.047 (2)	0.064 (3)	0.037 (2)	0.004 (2)	0.0056 (19)	-0.0039 (19)
C33	0.141 (6)	0.149 (6)	0.040 (3)	0.030 (5)	0.006 (4)	-0.006 (3)
C34	0.209 (9)	0.199 (9)	0.073 (4)	0.032 (7)	0.084 (6)	0.021 (5)
C19	0.033 (2)	0.046 (2)	0.047 (2)	0.0003 (17)	0.0013 (17)	0.0063 (18)
C29	0.053 (3)	0.044 (2)	0.076 (3)	0.013 (2)	0.017 (2)	0.012 (2)
C20	0.050 (2)	0.058 (3)	0.049 (2)	0.009 (2)	0.006 (2)	0.018 (2)
C30	0.068 (3)	0.131 (5)	0.076 (3)	0.013 (3)	-0.006 (3)	0.052 (3)
C21	0.061 (3)	0.051 (3)	0.047 (2)	0.000 (2)	0.012 (2)	0.006 (2)
C35	0.080 (4)	0.080 (4)	0.076 (4)	0.003 (3)	0.017 (3)	0.035 (3)
O5	0.161 (10)	0.147 (7)	0.068 (5)	-0.061 (6)	0.020 (5)	0.014 (4)
C36	0.156 (12)	0.096 (8)	0.083 (6)	-0.052 (8)	-0.007 (7)	0.036 (5)
O5A	0.138 (14)	0.128 (11)	0.117 (11)	0.042 (9)	0.074 (11)	0.066 (8)
C36A	0.133 (16)	0.130 (15)	0.133 (15)	-0.002 (13)	0.020 (14)	0.050 (12)
C22	0.042 (2)	0.054 (2)	0.054 (2)	-0.0047 (19)	0.0133 (19)	0.004 (2)
C8	0.0250 (17)	0.041 (2)	0.0328 (18)	0.0056 (15)	-0.0024 (15)	-0.0037 (16)
C14	0.0228 (17)	0.0380 (19)	0.0383 (19)	-0.0019 (14)	-0.0025 (15)	-0.0023 (16)
C15	0.0243 (19)	0.062 (2)	0.050 (2)	0.0054 (18)	0.0023 (18)	0.0089 (19)
C16	0.027 (2)	0.065 (3)	0.054 (2)	-0.0006 (18)	0.0050 (18)	0.002 (2)
C27	0.045 (2)	0.051 (2)	0.042 (2)	-0.0086 (19)	-0.0102 (19)	-0.0029 (18)
C26	0.052 (2)	0.045 (2)	0.045 (2)	0.0050 (18)	0.0040 (19)	-0.0107 (19)
C7	0.0291 (19)	0.052 (2)	0.050 (2)	0.0116 (17)	-0.0018 (18)	0.0034 (18)
C6	0.036 (2)	0.047 (2)	0.052 (2)	0.0151 (17)	-0.0020 (19)	0.0063 (18)
C5	0.0307 (19)	0.040 (2)	0.045 (2)	0.0064 (16)	-0.0056 (17)	0.0021 (18)
C4	0.045 (2)	0.045 (2)	0.051 (2)	0.0034 (19)	-0.0013 (19)	0.0054 (19)
C23	0.074 (3)	0.039 (2)	0.084 (3)	0.015 (2)	0.005 (3)	0.007 (2)
C24	0.068 (3)	0.081 (3)	0.060 (3)	0.003 (3)	-0.015 (2)	0.026 (3)
C25	0.044 (2)	0.042 (2)	0.057 (2)	-0.0086 (18)	-0.0042 (19)	-0.0020 (18)

*Geometric parameters ( $\text{\AA}$ ,  $^{\circ}$ ) for compound 3*

C11S—C1S	1.738 (6)	C20—C21	1.328 (6)
C12S—C1S	1.743 (6)	C20—C30	1.495 (6)
C13S—C1S	1.758 (6)	C30—H30C	0.9600
C1S—H1S	0.9800	C30—H30B	0.9600
O1—C31	1.367 (6)	C30—H30A	0.9600
O1—C3	1.420 (5)	C21—C35	1.485 (6)
O3—C33	1.295 (7)	C21—C22	1.507 (6)
O3—C28	1.451 (5)	C35—O5A	1.212 (12)
O2—C31	1.176 (6)	C35—O5	1.294 (9)
O4—C33	1.194 (10)	C35—C36	1.428 (12)
C32—C31	1.504 (7)	C35—C36A	1.507 (13)
C32—H32C	0.9600	C36—H36A	0.9600
C32—H32B	0.9600	C36—H36B	0.9600
C32—H32A	0.9600	C36—H36C	0.9600
C3—C2	1.311 (6)	C36A—H36D	0.9600
C3—C4	1.502 (6)	C36A—H36E	0.9600
C2—C1	1.498 (5)	C36A—H36F	0.9600
C2—H2	0.9300	C22—H22B	0.9700
C1—C10	1.542 (5)	C22—H22A	0.9700
C1—H1B	0.9700	C8—C7	1.541 (5)
C1—H1A	0.9700	C8—C26	1.558 (5)
C10—C25	1.535 (5)	C8—C14	1.596 (5)
C10—C5	1.554 (5)	C14—C15	1.547 (5)
C10—C9	1.562 (5)	C14—C27	1.548 (5)
C9—C11	1.520 (5)	C15—C16	1.519 (6)
C9—C8	1.559 (5)	C15—H15B	0.9700
C9—H9	0.9800	C15—H15A	0.9700
C11—C12	1.515 (5)	C16—H16B	0.9700
C11—H11B	0.9700	C16—H16A	0.9700
C11—H11A	0.9700	C27—H27C	0.9600
C12—C13	1.524 (5)	C27—H27B	0.9600
C12—H12B	0.9700	C27—H27A	0.9600
C12—H12A	0.9700	C26—H26C	0.9600
C13—C18	1.553 (5)	C26—H26B	0.9600
C13—C14	1.563 (5)	C26—H26A	0.9600
C13—H13	0.9800	C7—C6	1.516 (5)
C18—C17	1.541 (5)	C7—H7B	0.9700
C18—C19	1.546 (5)	C7—H7A	0.9700
C18—H18	0.9800	C6—C5	1.526 (5)
C17—C22	1.533 (6)	C6—H6B	0.9700

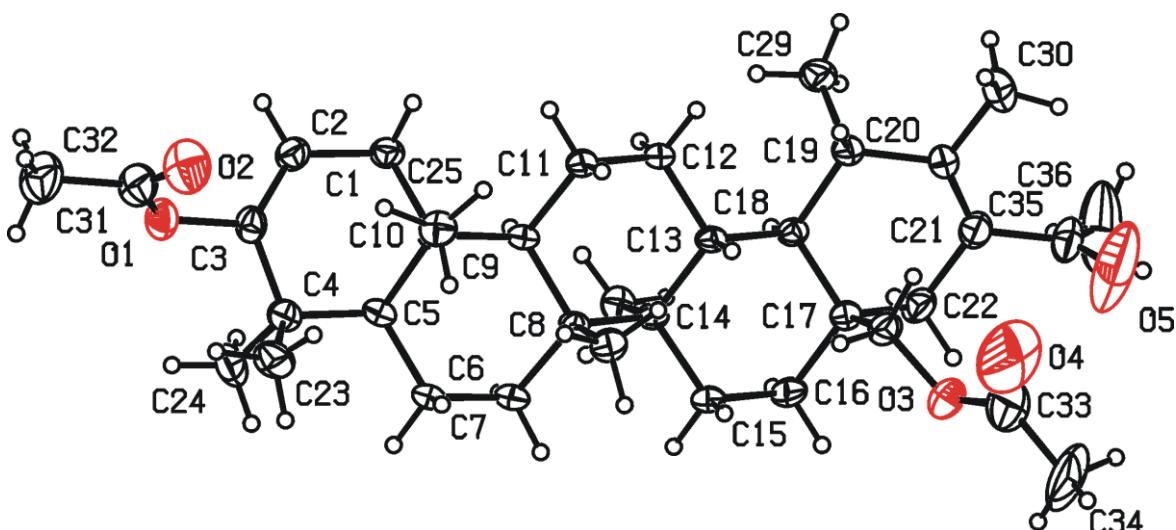
C17—C16	1.535 (5)	C6—H6A	0.9700
C17—C28	1.537 (5)	C5—C4	1.557 (5)
C28—H28B	0.9700	C5—H5	0.9800
C28—H28A	0.9700	C4—C23	1.537 (6)
C33—C34	1.493 (11)	C4—C24	1.539 (6)
C34—H34C	0.9600	C23—H23C	0.9600
C34—H34B	0.9600	C23—H23B	0.9600
C34—H34A	0.9600	C23—H23A	0.9600
C19—C20	1.516 (5)	C24—H24C	0.9600
C19—C29	1.534 (6)	C24—H24B	0.9600
C19—H19	0.9800	C24—H24A	0.9600
C29—H29C	0.9600	C25—H25C	0.9600
C29—H29B	0.9600	C25—H25B	0.9600
C29—H29A	0.9600	C25—H25A	0.9600
Cl1S—C1S—Cl2S	110.5 (3)	C20—C21—C35	124.2 (4)
Cl1S—C1S—Cl3S	108.0 (3)	C20—C21—C22	120.8 (4)
Cl2S—C1S—Cl3S	109.7 (3)	C35—C21—C22	114.8 (4)
Cl1S—C1S—H1S	109.5	O5A—C35—O5	59.6 (10)
Cl2S—C1S—H1S	109.5	O5A—C35—C36	93.1 (11)
Cl3S—C1S—H1S	109.5	O5—C35—C36	119.9 (7)
C31—O1—C3	118.0 (3)	O5A—C35—C21	118.2 (7)
C33—O3—C28	119.4 (5)	O5—C35—C21	118.6 (6)
C31—C32—H32C	109.5	C36—C35—C21	121.4 (6)
C31—C32—H32B	109.5	O5A—C35—C36A	122.0 (12)
H32C—C32—H32B	109.5	O5—C35—C36A	106.0 (12)
C31—C32—H32A	109.5	C36—C35—C36A	42.1 (10)
H32C—C32—H32A	109.5	C21—C35—C36A	117.2 (10)
H32B—C32—H32A	109.5	C35—C36—H36A	109.5
O2—C31—O1	123.4 (4)	C35—C36—H36B	109.5
O2—C31—C32	126.9 (5)	C35—C36—H36C	109.5
O1—C31—C32	109.7 (5)	C35—C36A—H36D	109.5
C2—C3—O1	118.5 (4)	C35—C36A—H36E	109.5
C2—C3—C4	127.1 (3)	H36D—C36A—H36E	109.5
O1—C3—C4	114.2 (3)	C35—C36A—H36F	109.5
C3—C2—C1	122.7 (4)	H36D—C36A—H36F	109.5
C3—C2—H2	118.6	H36E—C36A—H36F	109.5
C1—C2—H2	118.6	C21—C22—C17	110.8 (3)
C2—C1—C10	112.6 (3)	C21—C22—H22B	109.5
C2—C1—H1B	109.1	C17—C22—H22B	109.5
C10—C1—H1B	109.1	C21—C22—H22A	109.5

C2—C1—H1A	109.1	C17—C22—H22A	109.5
C10—C1—H1A	109.1	H22B—C22—H22A	108.1
H1B—C1—H1A	107.8	C7—C8—C9	108.2 (3)
C25—C10—C1	107.5 (3)	C7—C8—C26	106.8 (3)
C25—C10—C5	112.5 (3)	C9—C8—C26	111.7 (3)
C1—C10—C5	106.7 (3)	C7—C8—C14	111.4 (3)
C25—C10—C9	114.0 (3)	C9—C8—C14	108.5 (3)
C1—C10—C9	107.1 (3)	C26—C8—C14	110.2 (3)
C5—C10—C9	108.6 (3)	C15—C14—C27	106.6 (3)
C11—C9—C8	110.1 (3)	C15—C14—C13	107.9 (3)
C11—C9—C10	113.9 (3)	C27—C14—C13	110.1 (3)
C8—C9—C10	118.3 (3)	C15—C14—C8	111.6 (3)
C11—C9—H9	104.3	C27—C14—C8	110.6 (3)
C8—C9—H9	104.3	C13—C14—C8	109.9 (2)
C10—C9—H9	104.3	C16—C15—C14	114.1 (3)
C12—C11—C9	112.5 (3)	C16—C15—H15B	108.7
C12—C11—H11B	109.1	C14—C15—H15B	108.7
C9—C11—H11B	109.1	C16—C15—H15A	108.7
C12—C11—H11A	109.1	C14—C15—H15A	108.7
C9—C11—H11A	109.1	H15B—C15—H15A	107.6
H11B—C11—H11A	107.8	C15—C16—C17	113.5 (3)
C11—C12—C13	113.1 (3)	C15—C16—H16B	108.9
C11—C12—H12B	109.0	C17—C16—H16B	108.9
C13—C12—H12B	109.0	C15—C16—H16A	108.9
C11—C12—H12A	109.0	C17—C16—H16A	108.9
C13—C12—H12A	109.0	H16B—C16—H16A	107.7
H12B—C12—H12A	107.8	C14—C27—H27C	109.5
C12—C13—C18	113.6 (3)	C14—C27—H27B	109.5
C12—C13—C14	110.3 (3)	H27C—C27—H27B	109.5
C18—C13—C14	112.9 (3)	C14—C27—H27A	109.5
C12—C13—H13	106.5	H27C—C27—H27A	109.5
C18—C13—H13	106.5	H27B—C27—H27A	109.5
C14—C13—H13	106.5	C8—C26—H26C	109.5
C17—C18—C19	112.6 (3)	C8—C26—H26B	109.5
C17—C18—C13	111.4 (3)	H26C—C26—H26B	109.5
C19—C18—C13	115.2 (3)	C8—C26—H26A	109.5
C17—C18—H18	105.6	H26C—C26—H26A	109.5
C19—C18—H18	105.6	H26B—C26—H26A	109.5
C13—C18—H18	105.6	C6—C7—C8	113.8 (3)
C22—C17—C16	109.8 (3)	C6—C7—H7B	108.8
C22—C17—C28	109.6 (3)	C8—C7—H7B	108.8

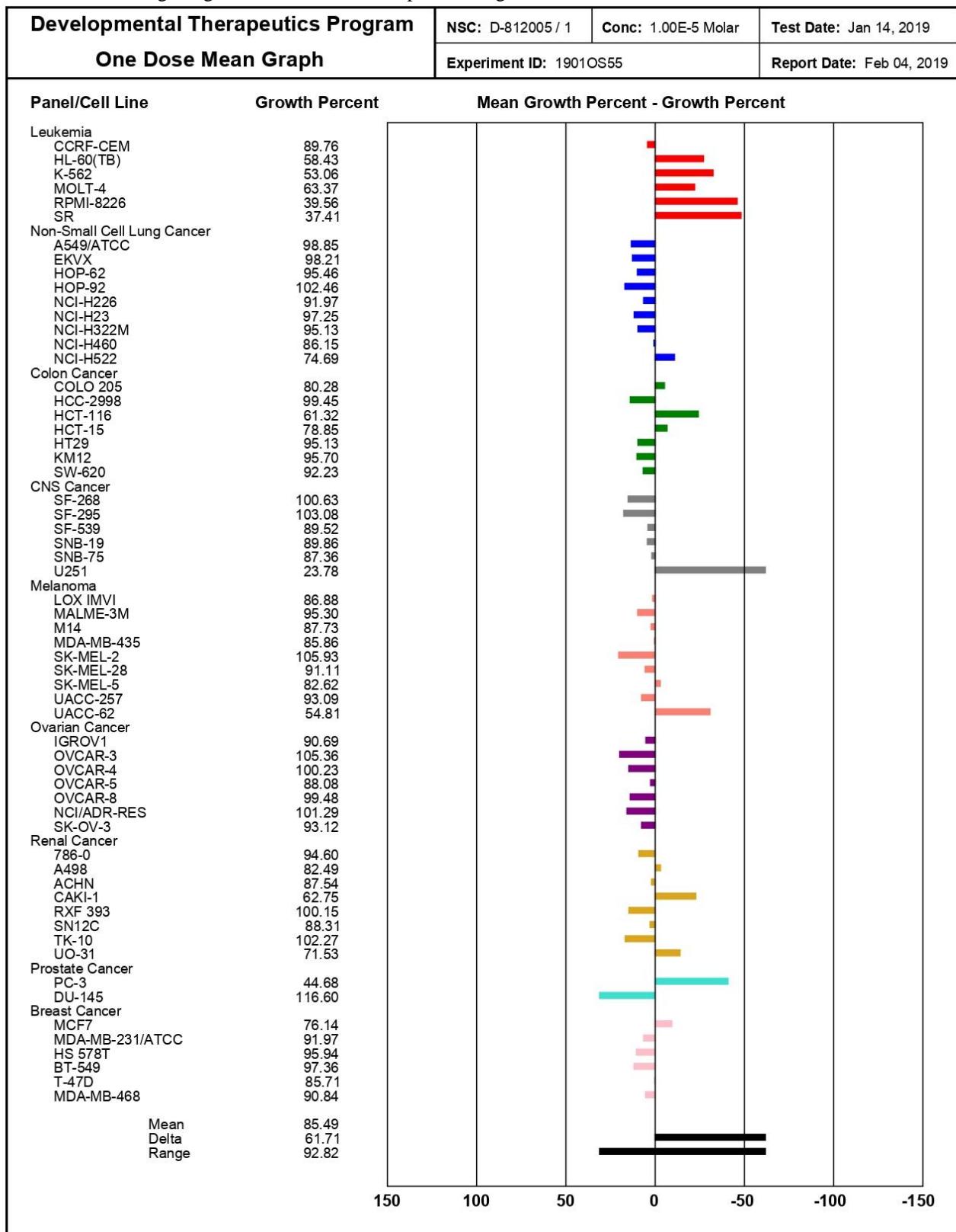
C16—C17—C28	110.1 (3)	C6—C7—H7A	108.8
C22—C17—C18	107.4 (3)	C8—C7—H7A	108.8
C16—C17—C18	109.5 (3)	H7B—C7—H7A	107.7
C28—C17—C18	110.3 (3)	C7—C6—C5	111.5 (3)
O3—C28—C17	107.5 (3)	C7—C6—H6B	109.3
O3—C28—H28B	110.2	C5—C6—H6B	109.3
C17—C28—H28B	110.2	C7—C6—H6A	109.3
O3—C28—H28A	110.2	C5—C6—H6A	109.3
C17—C28—H28A	110.2	H6B—C6—H6A	108.0
H28B—C28—H28A	108.5	C6—C5—C10	110.9 (3)
O4—C33—O3	121.0 (7)	C6—C5—C4	114.3 (3)
O4—C33—C34	125.9 (7)	C10—C5—C4	115.7 (3)
O3—C33—C34	112.9 (8)	C6—C5—H5	104.9
C33—C34—H34C	109.5	C10—C5—H5	104.9
C33—C34—H34B	109.5	C4—C5—H5	104.9
H34C—C34—H34B	109.5	C3—C4—C23	110.1 (3)
C33—C34—H34A	109.5	C3—C4—C24	107.7 (3)
H34C—C34—H34A	109.5	C23—C4—C24	108.3 (4)
H34B—C34—H34A	109.5	C3—C4—C5	108.6 (3)
C20—C19—C29	106.7 (3)	C23—C4—C5	113.8 (3)
C20—C19—C18	115.2 (3)	C24—C4—C5	108.3 (3)
C29—C19—C18	111.5 (3)	C4—C23—H23C	109.5
C20—C19—H19	107.7	C4—C23—H23B	109.5
C29—C19—H19	107.7	H23C—C23—H23B	109.5
C18—C19—H19	107.7	C4—C23—H23A	109.5
C19—C29—H29C	109.5	H23C—C23—H23A	109.5
C19—C29—H29B	109.5	H23B—C23—H23A	109.5
H29C—C29—H29B	109.5	C4—C24—H24C	109.5
C19—C29—H29A	109.5	C4—C24—H24B	109.5
H29C—C29—H29A	109.5	H24C—C24—H24B	109.5
H29B—C29—H29A	109.5	C4—C24—H24A	109.5
C21—C20—C30	122.3 (4)	H24C—C24—H24A	109.5
C21—C20—C19	122.3 (4)	H24B—C24—H24A	109.5
C30—C20—C19	115.4 (4)	C10—C25—H25C	109.5
C20—C30—H30C	109.5	C10—C25—H25B	109.5
C20—C30—H30B	109.5	H25C—C25—H25B	109.5
H30C—C30—H30B	109.5	C10—C25—H25A	109.5
C20—C30—H30A	109.5	H25C—C25—H25A	109.5
H30C—C30—H30A	109.5	H25B—C25—H25A	109.5
H30B—C30—H30A	109.5		

C3—O1—C31—O2	-5.5 (7)	C20—C21—C22—C17	-30.0 (6)
C3—O1—C31—C32	176.2 (4)	C35—C21—C22—C17	144.6 (4)
C31—O1—C3—C2	-73.1 (5)	C16—C17—C22—C21	179.5 (3)
C31—O1—C3—C4	111.5 (4)	C28—C17—C22—C21	-59.4 (4)
O1—C3—C2—C1	178.7 (3)	C18—C17—C22—C21	60.4 (4)
C4—C3—C2—C1	-6.6 (6)	C11—C9—C8—C7	-179.7 (3)
C3—C2—C1—C10	-19.0 (6)	C10—C9—C8—C7	46.9 (4)
C2—C1—C10—C25	-72.6 (4)	C11—C9—C8—C26	63.0 (4)
C2—C1—C10—C5	48.3 (4)	C10—C9—C8—C26	-70.4 (4)
C2—C1—C10—C9	164.5 (3)	C11—C9—C8—C14	-58.6 (3)
C25—C10—C9—C11	-54.7 (4)	C10—C9—C8—C14	167.9 (3)
C1—C10—C9—C11	64.1 (4)	C12—C13—C14—C15	-177.9 (3)
C5—C10—C9—C11	179.0 (3)	C18—C13—C14—C15	53.9 (4)
C25—C10—C9—C8	77.0 (4)	C12—C13—C14—C27	66.1 (4)
C1—C10—C9—C8	-164.2 (3)	C18—C13—C14—C27	-62.1 (4)
C5—C10—C9—C8	-49.3 (4)	C12—C13—C14—C8	-56.0 (4)
C8—C9—C11—C12	57.4 (4)	C18—C13—C14—C8	175.8 (3)
C10—C9—C11—C12	-167.0 (3)	C7—C8—C14—C15	-62.8 (4)
C9—C11—C12—C13	-55.4 (4)	C9—C8—C14—C15	178.2 (3)
C11—C12—C13—C18	-178.0 (3)	C26—C8—C14—C15	55.6 (4)
C11—C12—C13—C14	54.2 (4)	C7—C8—C14—C27	55.7 (4)
C12—C13—C18—C17	176.3 (3)	C9—C8—C14—C27	-63.3 (3)
C14—C13—C18—C17	-57.2 (4)	C26—C8—C14—C27	174.2 (3)
C12—C13—C18—C19	46.5 (4)	C7—C8—C14—C13	177.6 (3)
C14—C13—C18—C19	172.9 (3)	C9—C8—C14—C13	58.6 (3)
C19—C18—C17—C22	-54.9 (4)	C26—C8—C14—C13	-64.0 (3)
C13—C18—C17—C22	173.9 (3)	C27—C14—C15—C16	65.7 (4)
C19—C18—C17—C16	-174.2 (3)	C13—C14—C15—C16	-52.6 (4)
C13—C18—C17—C16	54.7 (4)	C8—C14—C15—C16	-173.5 (3)
C19—C18—C17—C28	64.5 (4)	C14—C15—C16—C17	54.8 (4)
C13—C18—C17—C28	-66.7 (4)	C22—C17—C16—C15	-171.5 (3)
C33—O3—C28—C17	157.2 (5)	C28—C17—C16—C15	67.7 (4)
C22—C17—C28—O3	-51.4 (4)	C18—C17—C16—C15	-53.8 (4)
C16—C17—C28—O3	69.5 (4)	C9—C8—C7—C6	-50.1 (4)
C18—C17—C28—O3	-169.4 (3)	C26—C8—C7—C6	70.3 (4)
C28—O3—C33—O4	5.6 (11)	C14—C8—C7—C6	-169.3 (3)
C28—O3—C33—C34	-178.3 (6)	C8—C7—C6—C5	59.5 (4)
C17—C18—C19—C20	19.5 (5)	C7—C6—C5—C10	-60.3 (4)
C13—C18—C19—C20	148.7 (3)	C7—C6—C5—C4	166.7 (3)
C17—C18—C19—C29	141.3 (3)	C25—C10—C5—C6	-74.0 (4)
C13—C18—C19—C29	-89.5 (4)	C1—C10—C5—C6	168.4 (3)

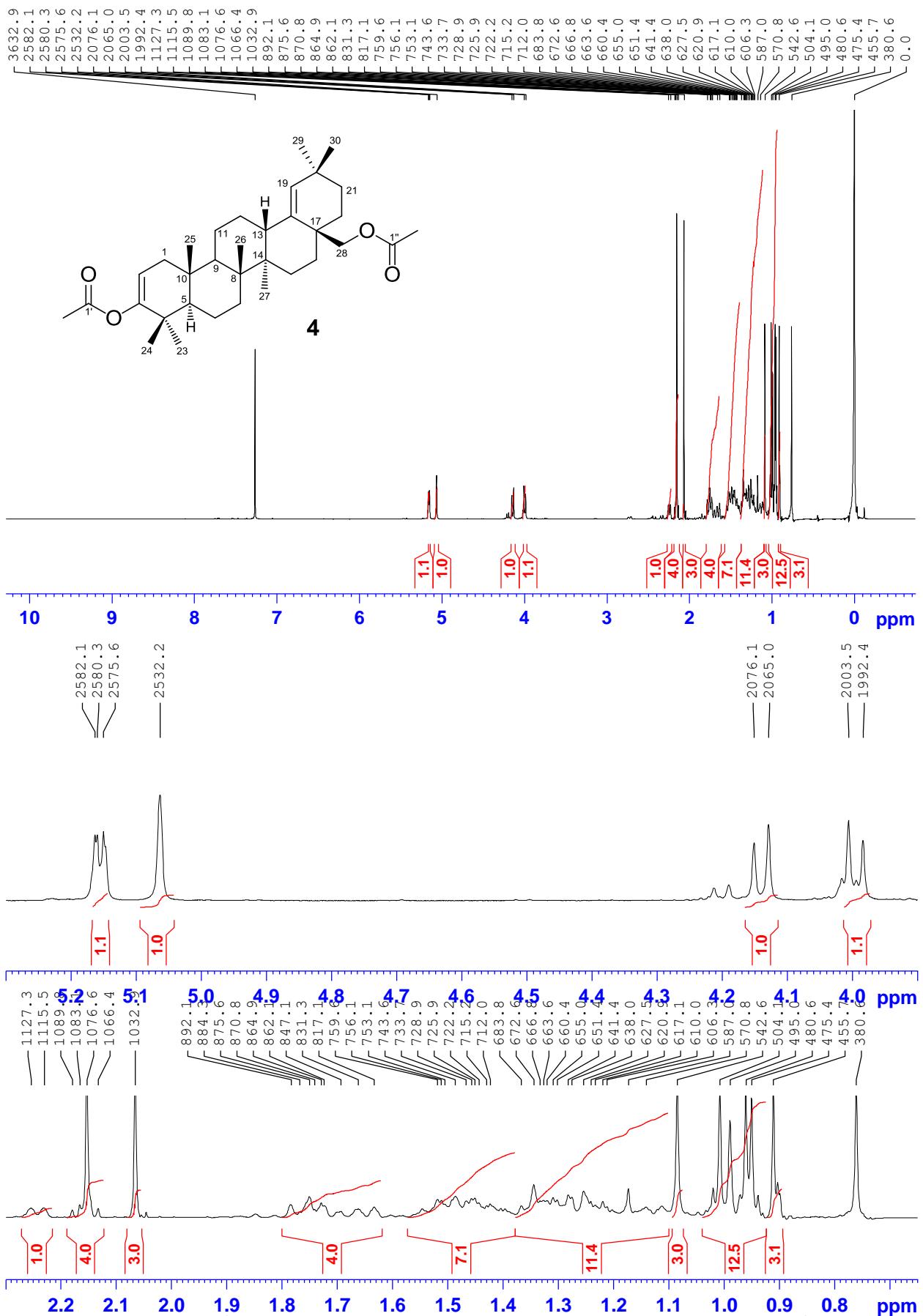
C29—C19—C20—C21	-110.4 (5)	C9—C10—C5—C6	53.2 (4)
C18—C19—C20—C21	14.0 (6)	C25—C10—C5—C4	58.3 (4)
C29—C19—C20—C30	68.8 (5)	C1—C10—C5—C4	-59.3 (4)
C18—C19—C20—C30	-166.9 (4)	C9—C10—C5—C4	-174.5 (3)
C30—C20—C21—C35	-1.7 (8)	C2—C3—C4—C23	123.3 (5)
C19—C20—C21—C35	177.4 (4)	O1—C3—C4—C23	-61.8 (4)
C30—C20—C21—C22	172.4 (5)	C2—C3—C4—C24	-118.8 (5)
C19—C20—C21—C22	-8.5 (7)	O1—C3—C4—C24	56.1 (4)
C20—C21—C35—O5A	134.0 (16)	C2—C3—C4—C5	-1.8 (5)
C22—C21—C35—O5A	-40.5 (16)	O1—C3—C4—C5	173.1 (3)
C20—C21—C35—O5	65.1 (10)	C6—C5—C4—C3	166.7 (3)
C22—C21—C35—O5	-109.3 (9)	C10—C5—C4—C3	36.0 (4)
C20—C21—C35—C36	-112.5 (11)	C6—C5—C4—C23	43.7 (5)
C22—C21—C35—C36	73.1 (11)	C10—C5—C4—C23	-87.0 (4)
C20—C21—C35—C36A	-64.1 (17)	C6—C5—C4—C24	-76.7 (4)
C22—C21—C35—C36A	121.4 (16)	C10—C5—C4—C24	152.6 (3)



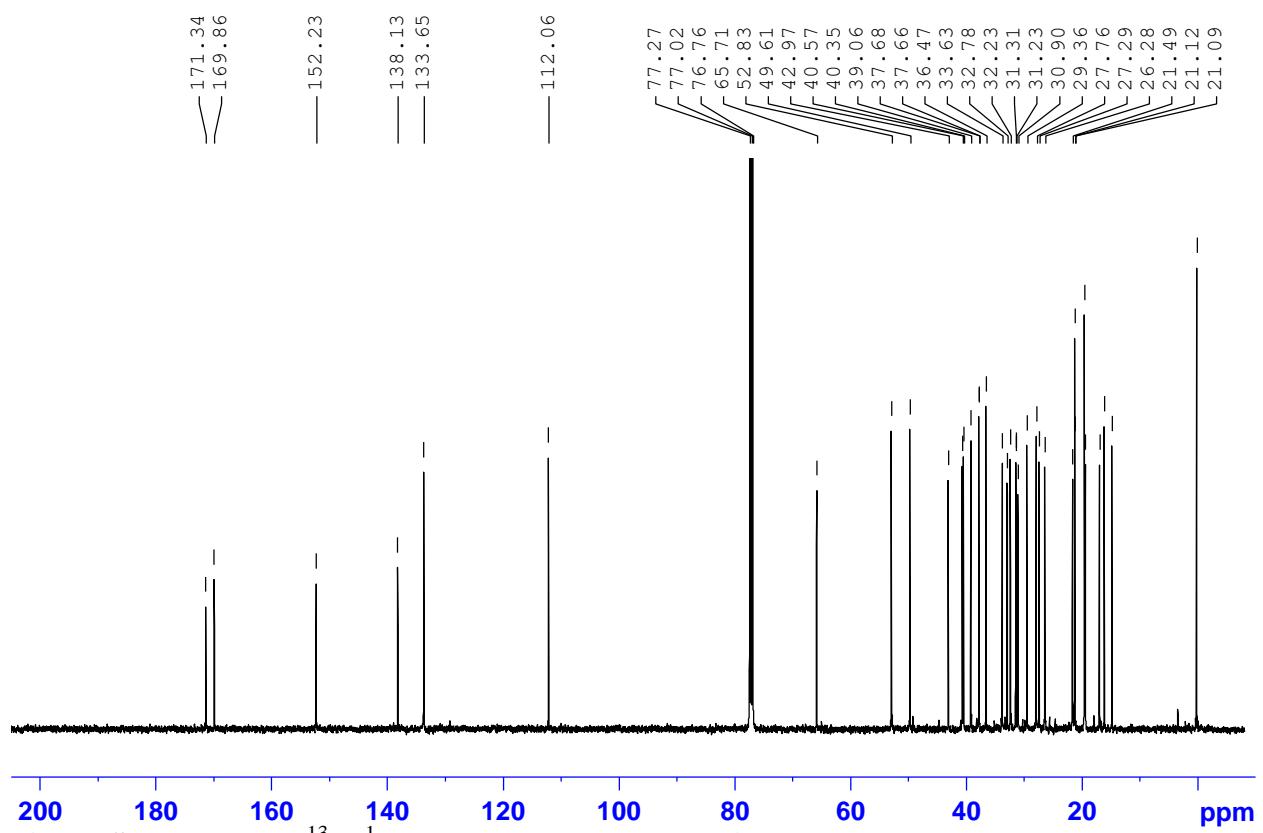
**Figure S11.** Molecular structure of compound 3 (the absolute configuration is given according to Flack parameter equaling to 0.0(1))

**Table S1.** Percentage of growth inhibition of compounds **3** against 60 individual cell lines

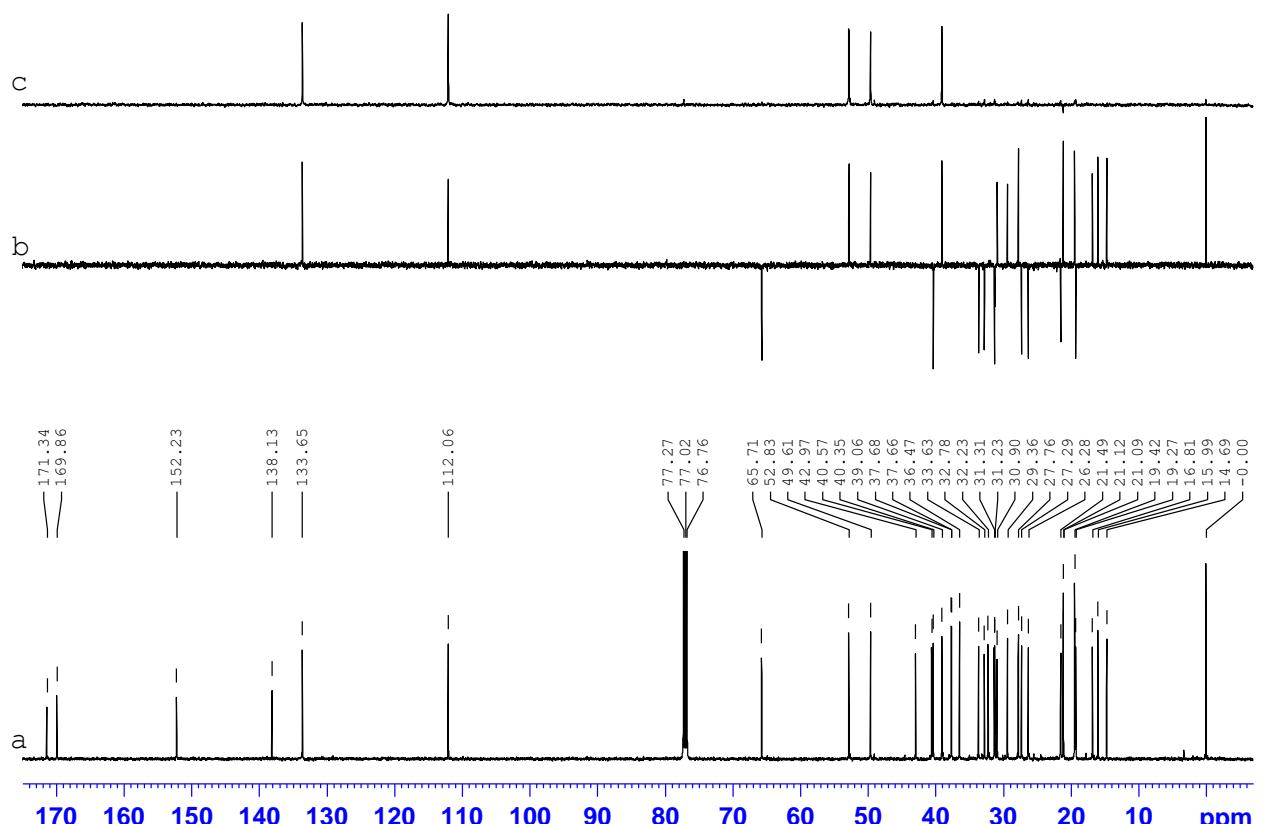
## NMR data of compound 4



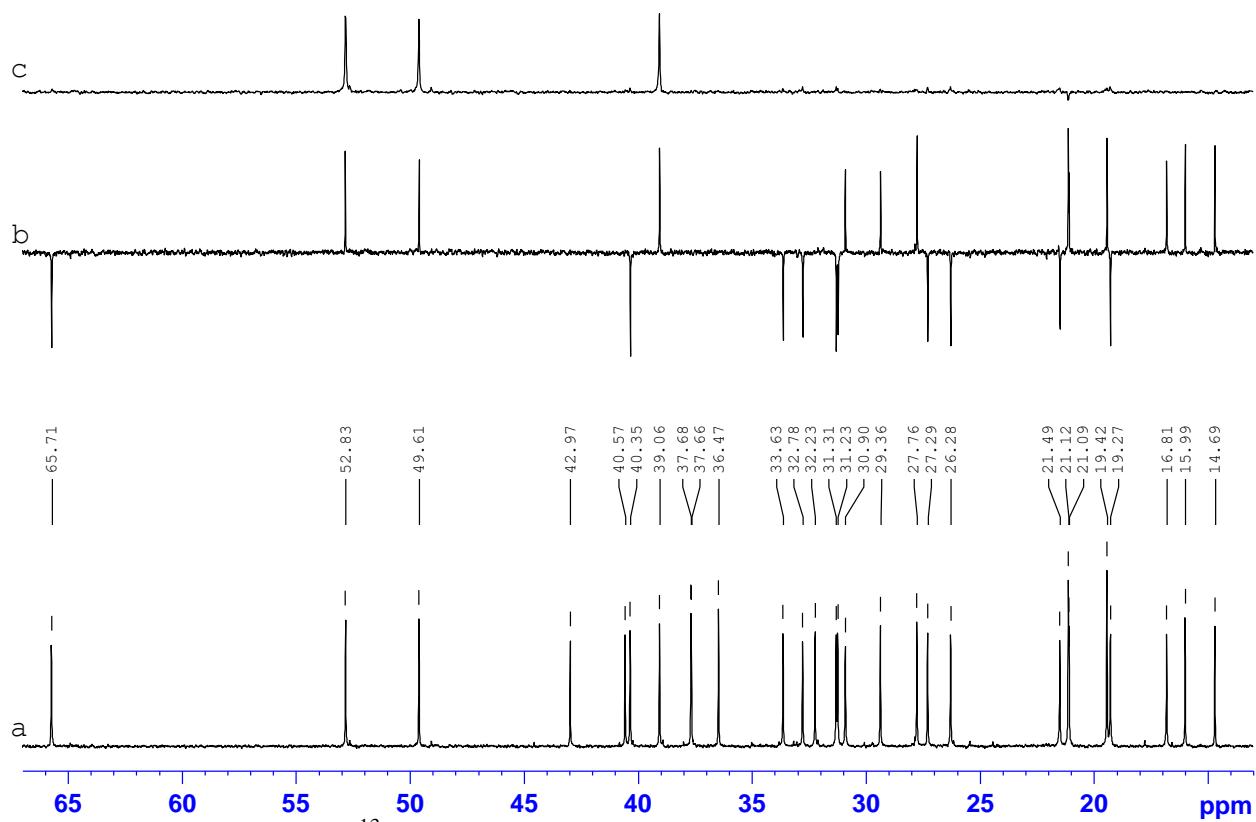
**Figure S12.** Complete  $^1\text{H}$  NMR spectrum of compound **4** in  $\text{CDCl}_3$  (top). Expanded  $^1\text{H}$  NMR spectrum of compound **3** in  $\text{CDCl}_3$  (bottom).



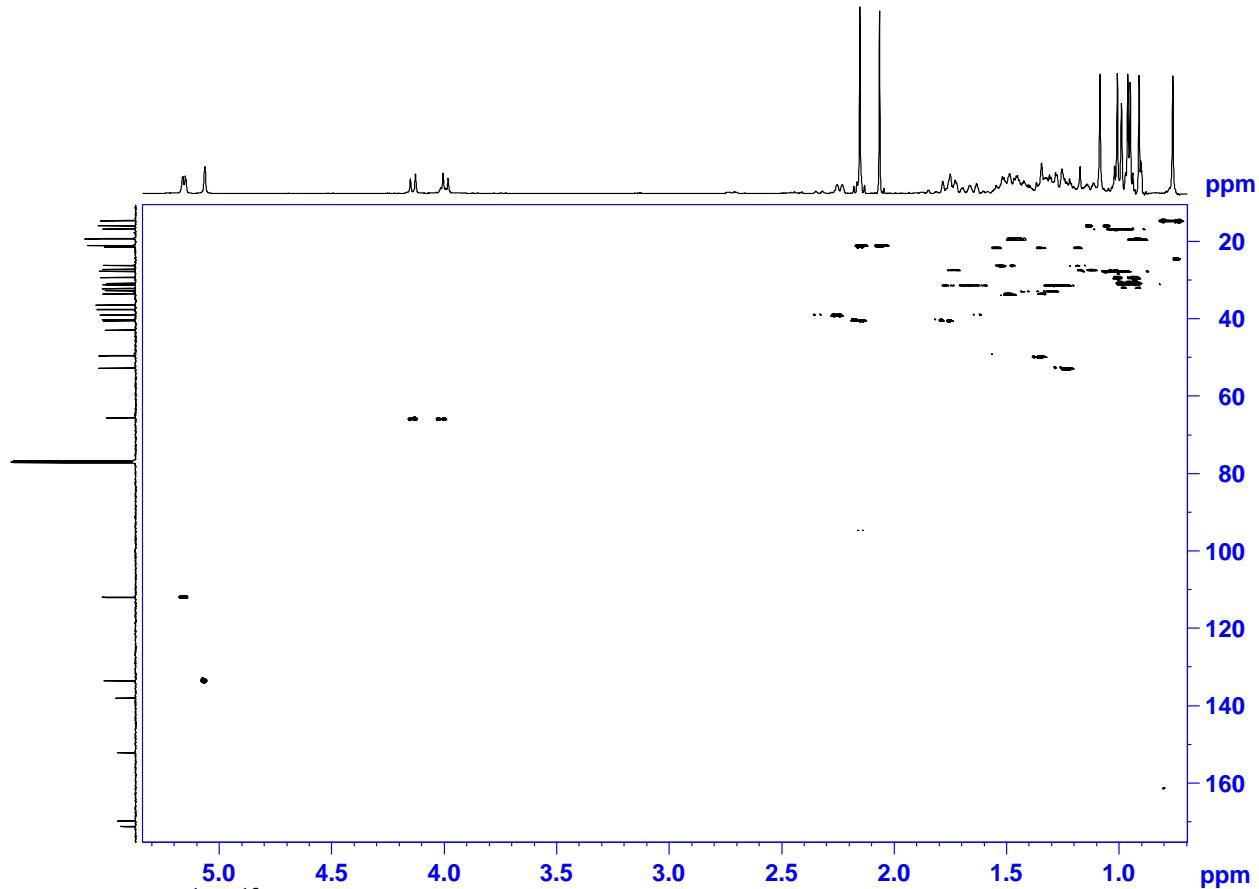
**Figure S13.** Complete  $^{13}\text{C}\{\text{H}\}$  spectrum of compound 4 in  $\text{CDCl}_3$ .



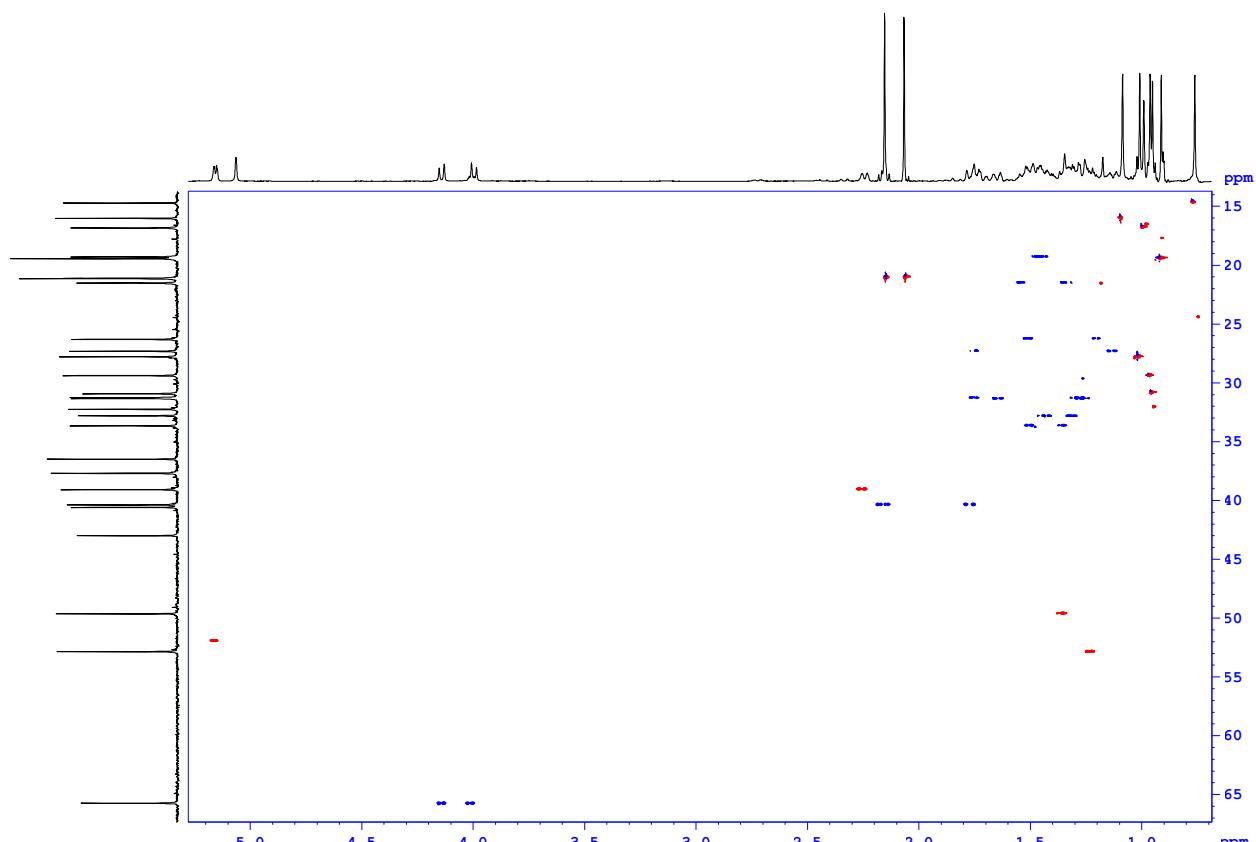
**Figure S14.** DEPT editing  $^{13}\text{C}$  NMR spectrum of compound 4 in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



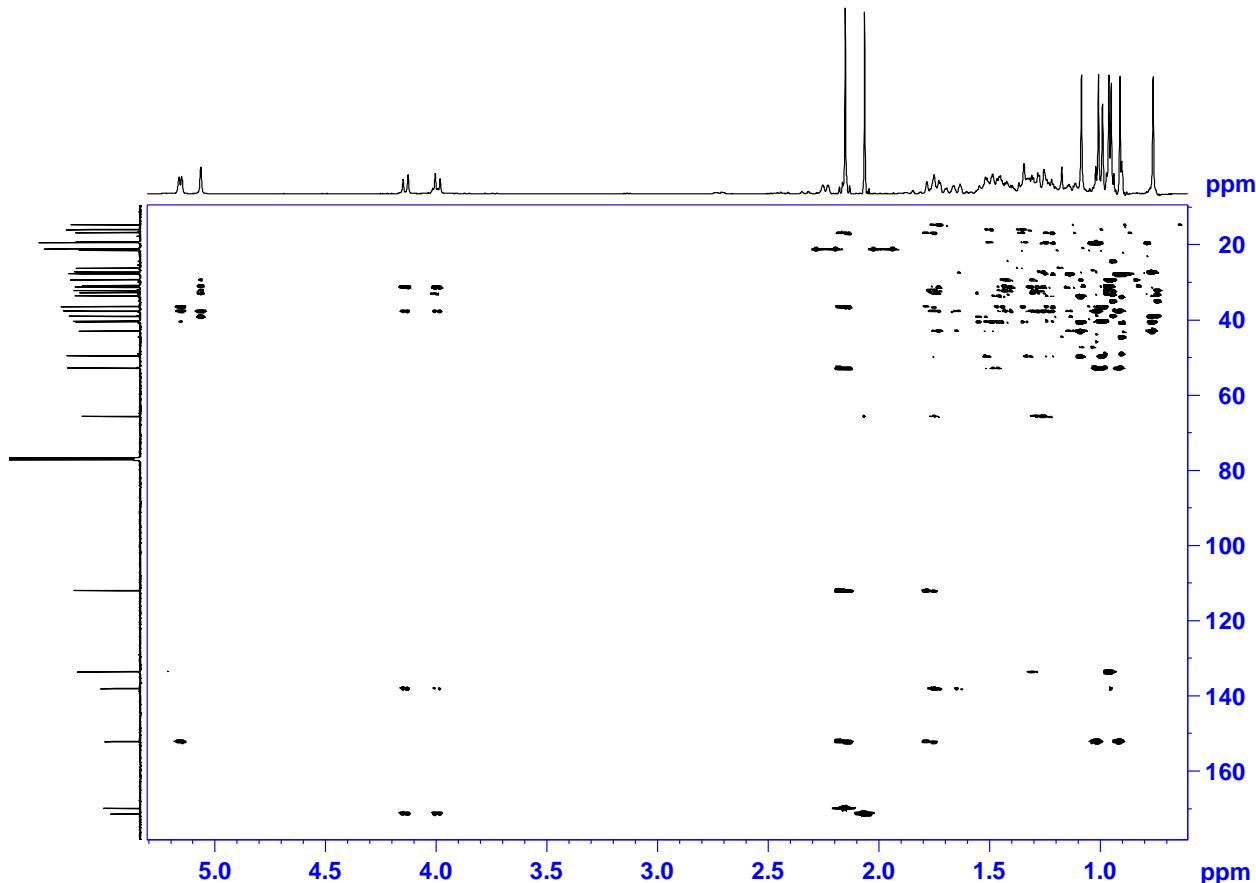
**Figure S15.** DEPT editing  $^{13}\text{C}$  NMR spectrum (upfield region) of compound **4** in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{^1\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



**Figure S16.**  $\{^1\text{H}, ^{13}\text{C}\}$  HSQC spectrum of compound **4** in  $\text{CDCl}_3$ .



**Figure S17.**  $\{^1\text{H}, ^{13}\text{C}\}$  HSQCed spectrum of compound 4 in  $\text{CDCl}_3$ .



**Figure S18.**  $\{^1\text{H}, ^{13}\text{C}\}$  HMBC spectrum of compound 4 in  $\text{CDCl}_3$ .

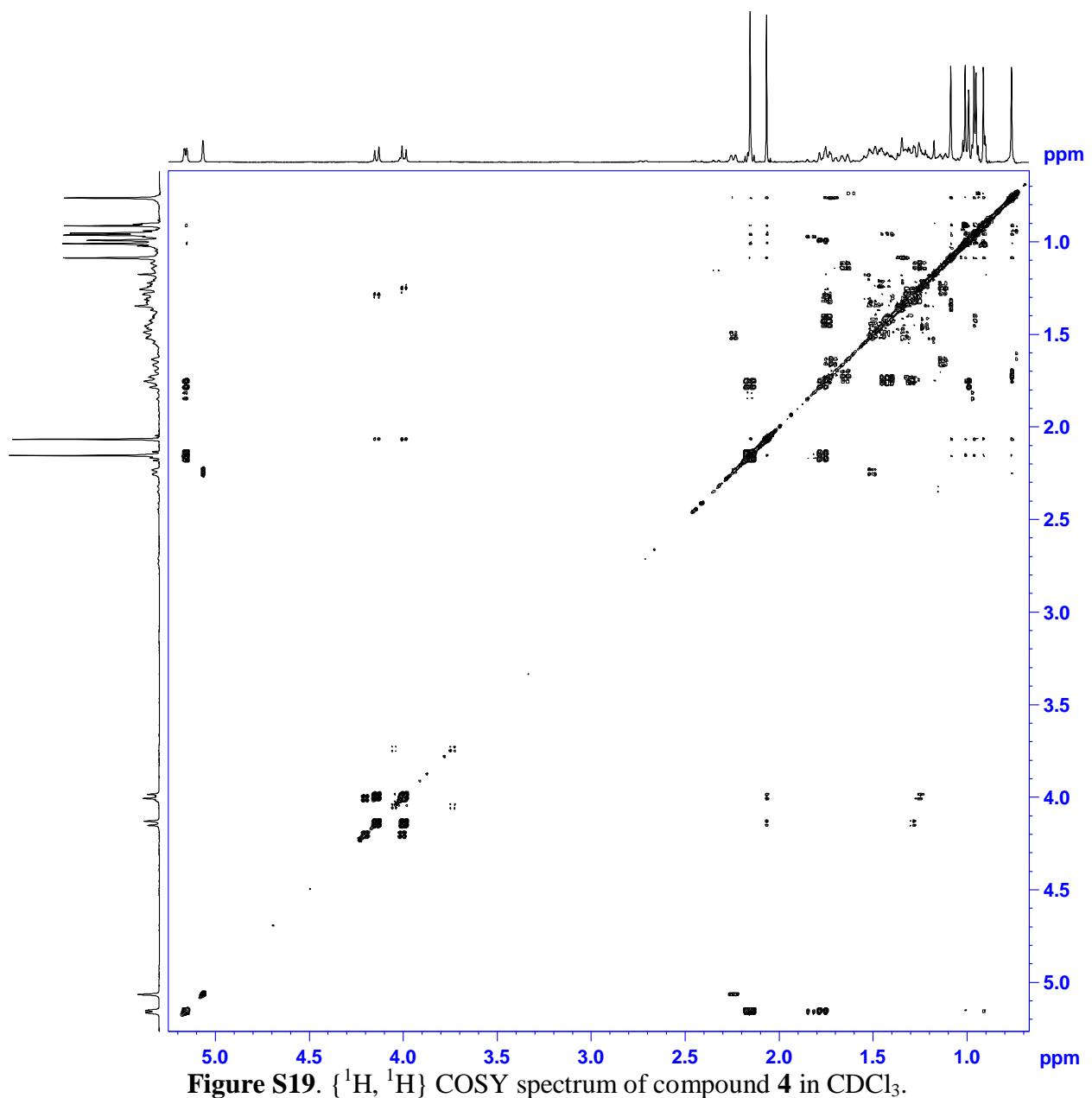
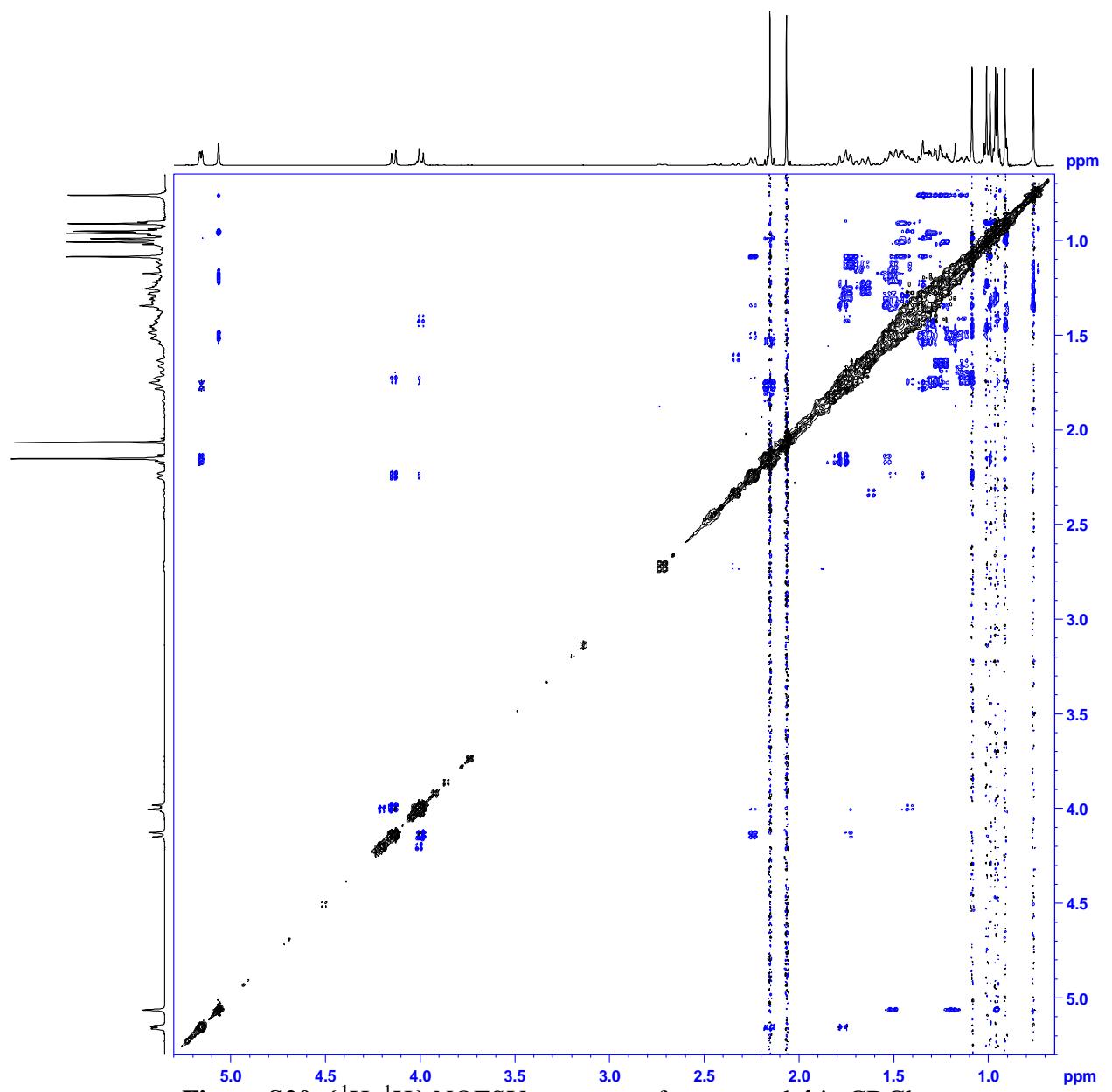
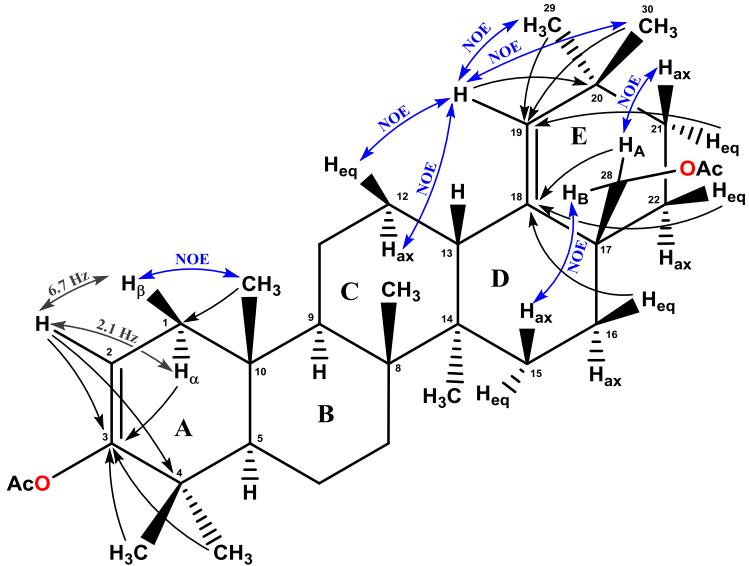


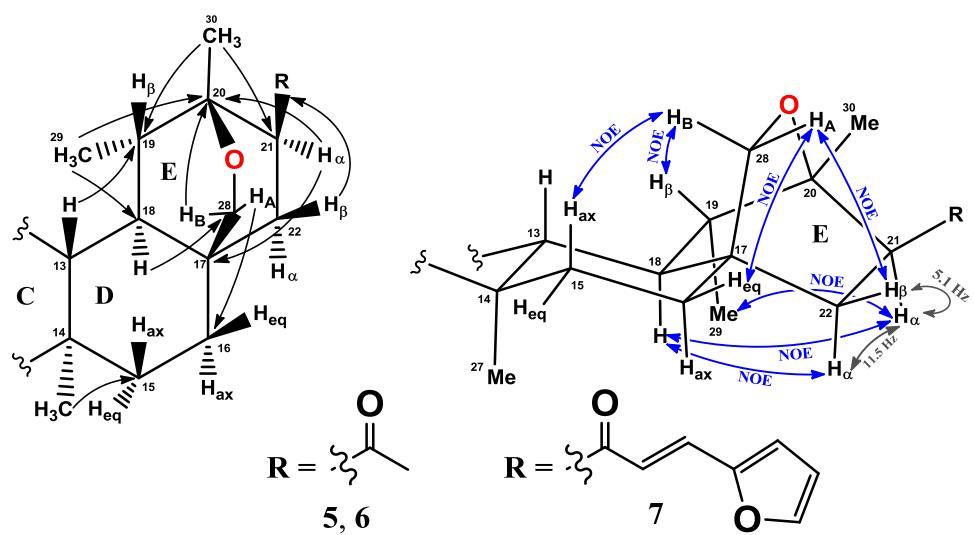
Figure S19.  $\{^1\text{H}, ^1\text{H}\}$  COSY spectrum of compound 4 in  $\text{CDCl}_3$ .



**Figure S20.**  $\{^1\text{H}, ^1\text{H}\}$  NOESY spectrum of compound 4 in  $\text{CDCl}_3$ .

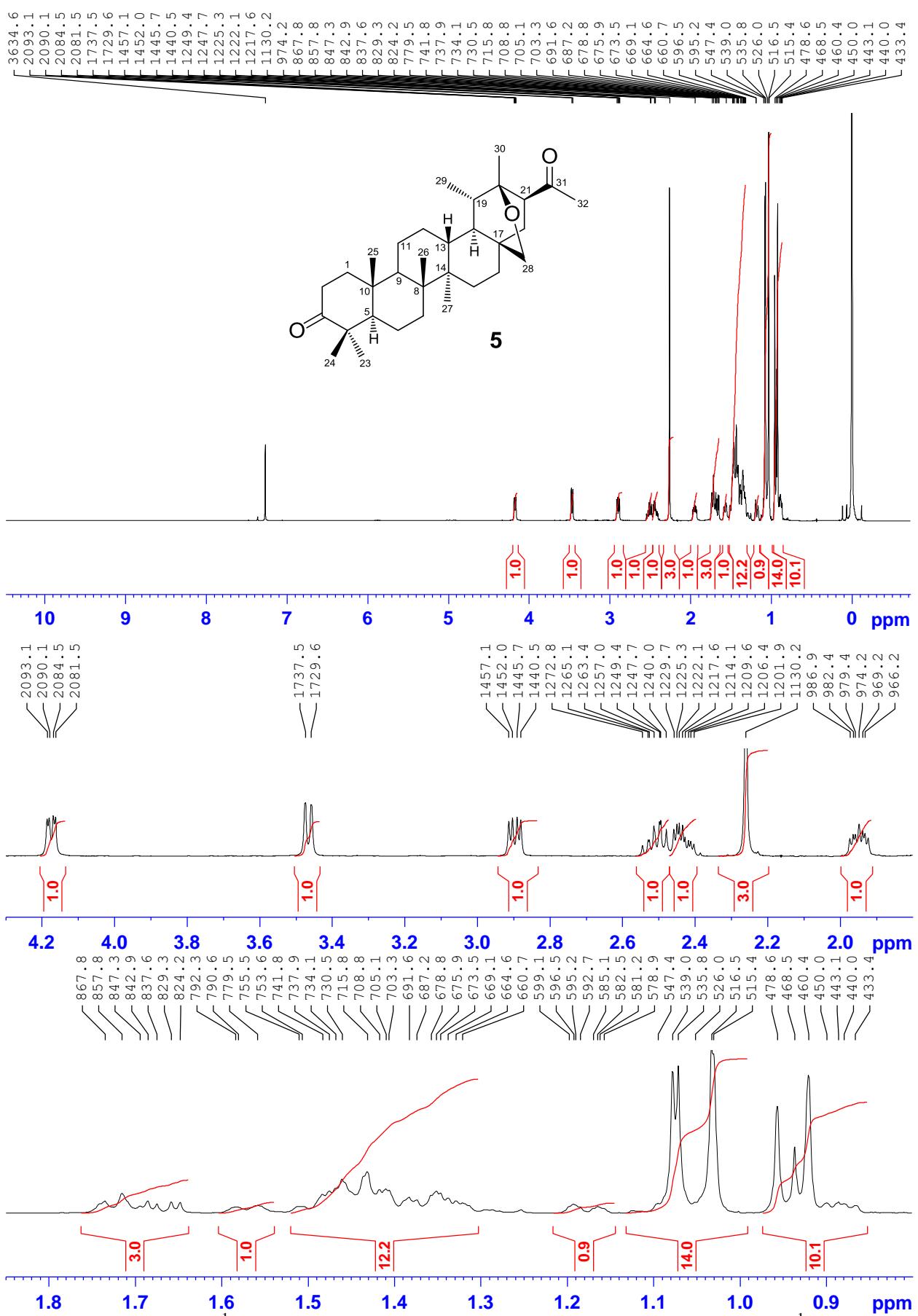


**Figure S21.** NMR assignments and significant  $\{^1\text{H}, ^{13}\text{C}\}$  HMBC (black arrows), and NOESY (blue arrows) correlations of compound 4

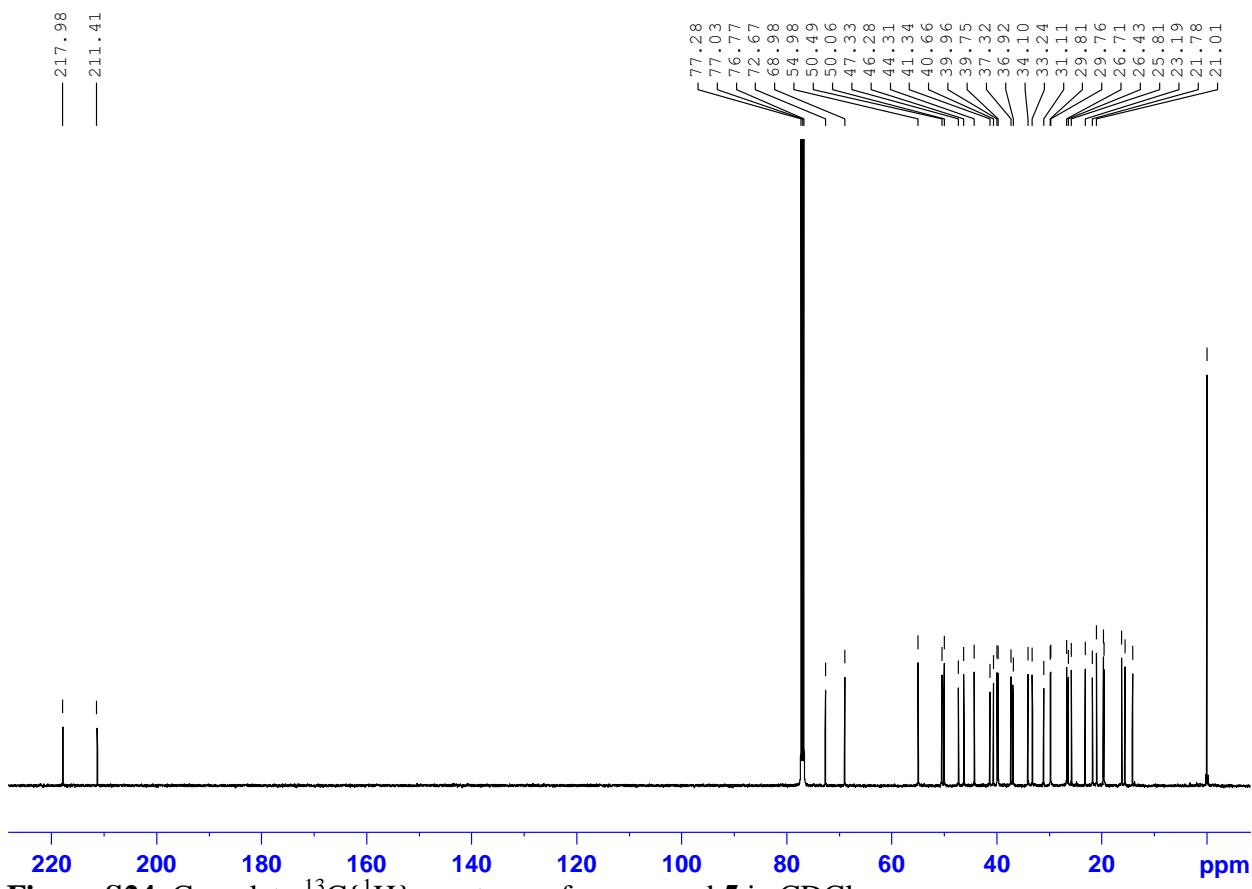


**Figure S22.** The key HMBC, COSY and NOESY correlations of compounds **5-7**

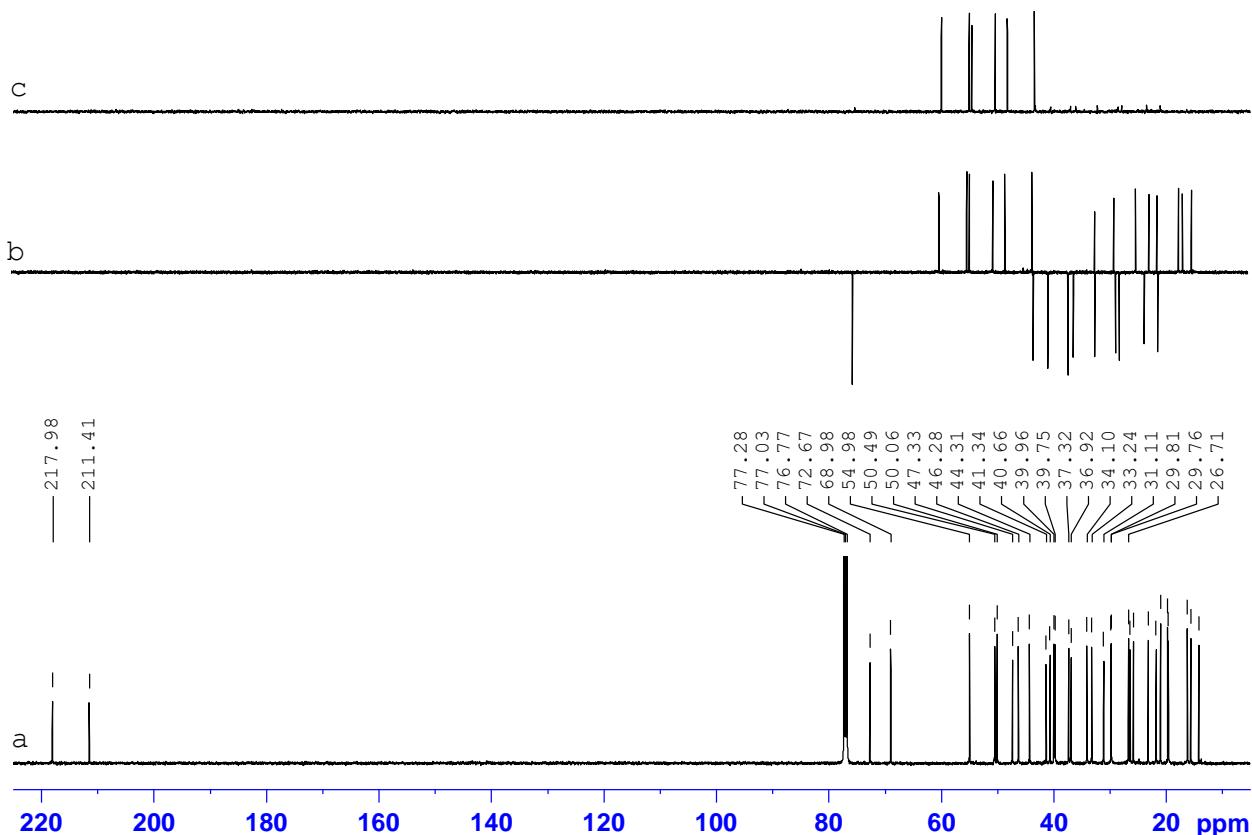
### NMR data of compound 5



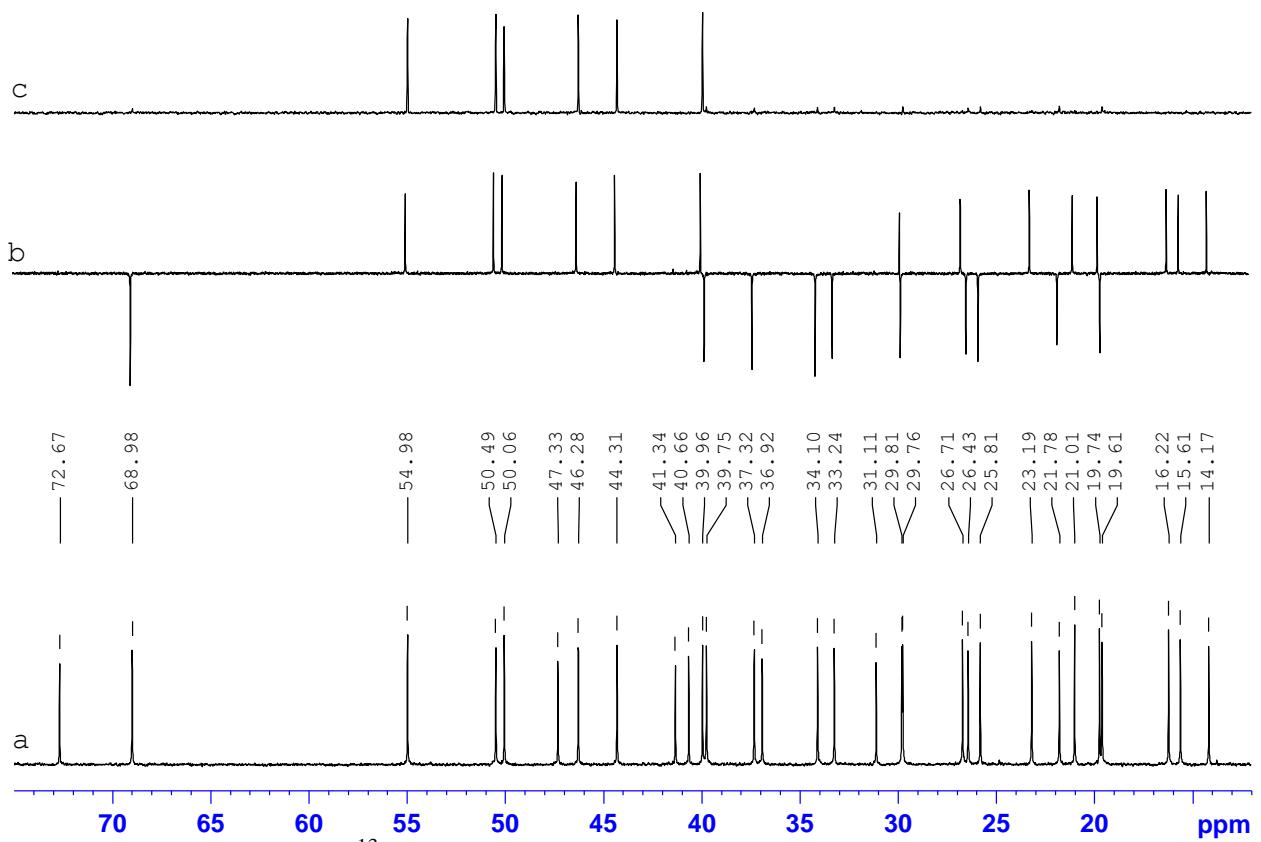
**Figure S23.** Complete  $^1\text{H}$  NMR spectrum of compound 5 in  $\text{CDCl}_3$  (top). Expanded  $^1\text{H}$  NMR spectrum of compound 3 in  $\text{CDCl}_3$  (bottom).



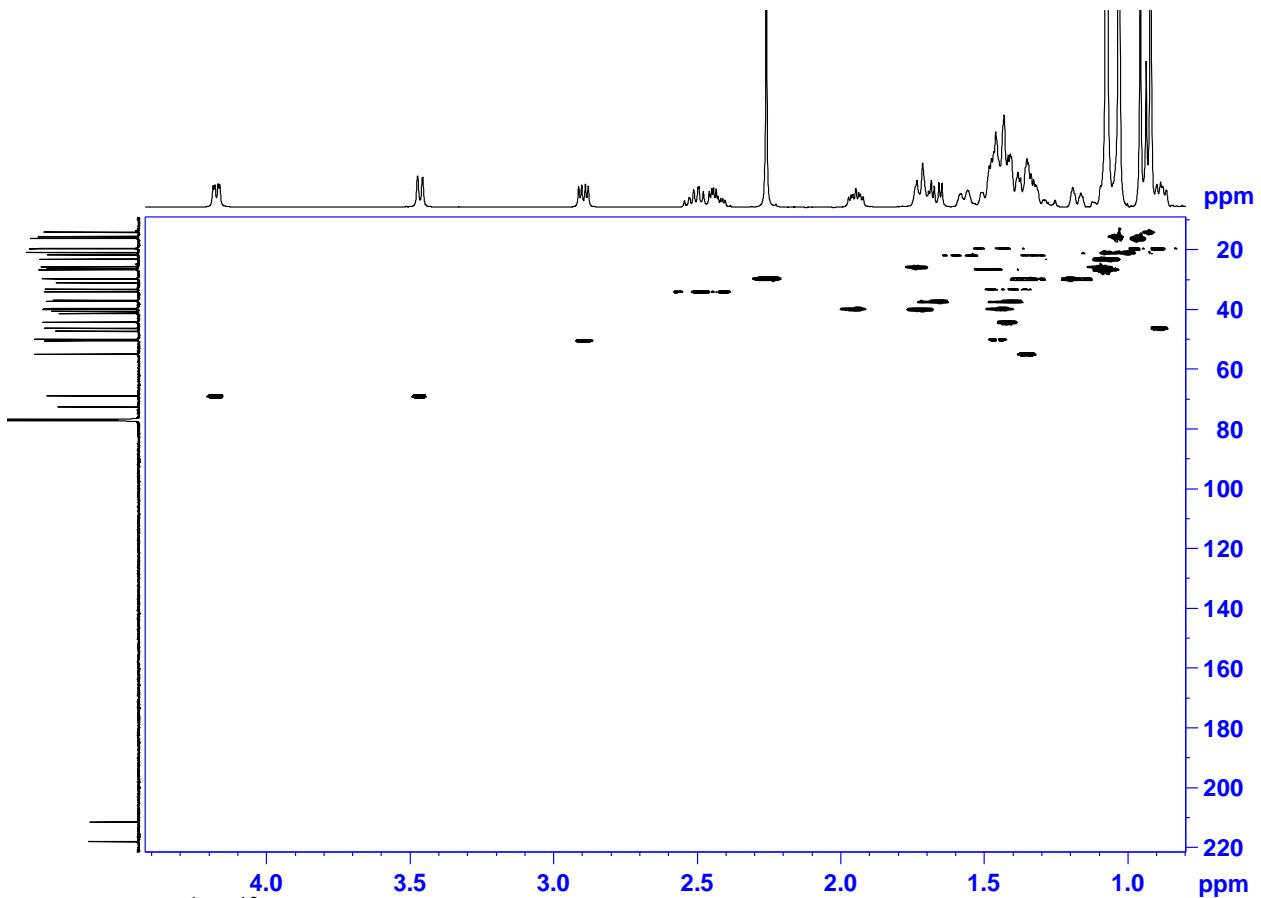
**Figure S24.** Complete  $^{13}\text{C}\{\text{H}\}$  spectrum of compound 5 in  $\text{CDCl}_3$ .



**Figure S25.** DEPT editing  $^{13}\text{C}$  NMR spectrum of compound 5 in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



**Figure S26.** DEPT editing  $^{13}\text{C}$  NMR spectrum (upfield region) of compound **5** in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{^1\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



**Figure S27.**  $\{^1\text{H}, ^{13}\text{C}\}$  HSQC spectrum of compound **5** in  $\text{CDCl}_3$ .

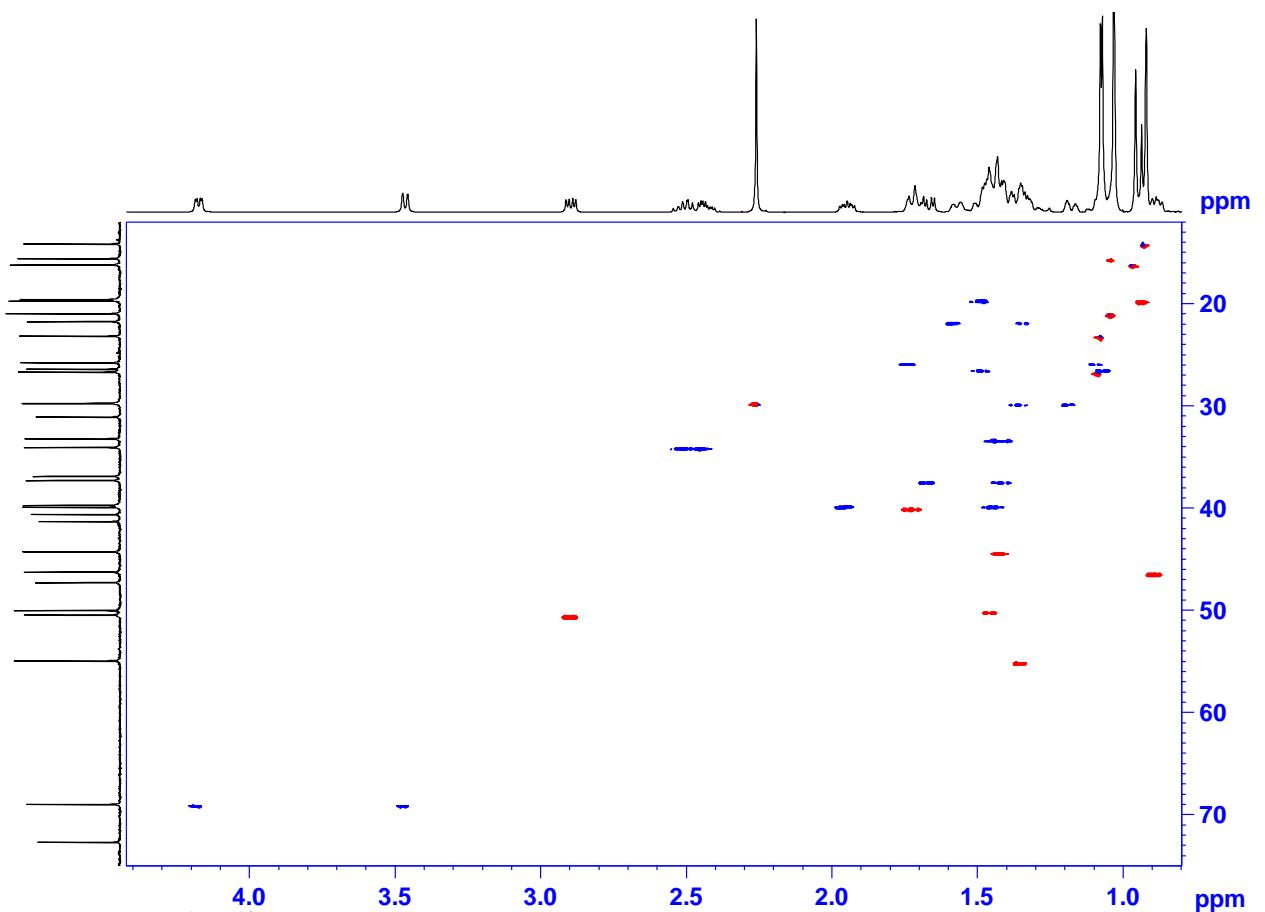


Figure S27.  $\{^1\text{H}, ^{13}\text{C}\}$  HSQCed spectrum of compound 5 in  $\text{CDCl}_3$ .

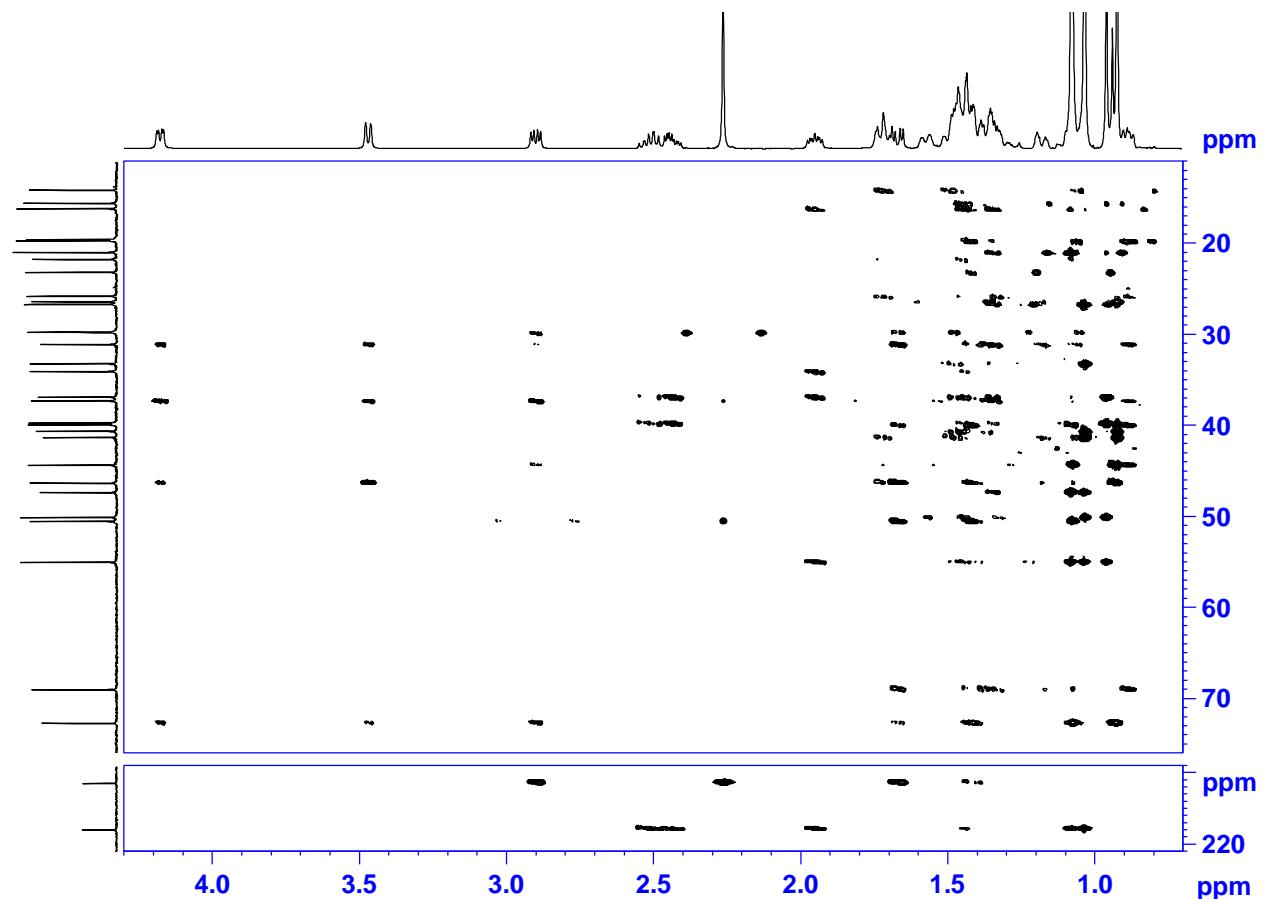


Figure S28.  $\{^1\text{H}, ^{13}\text{C}\}$  HMBC spectrum of compound 5 in  $\text{CDCl}_3$ .

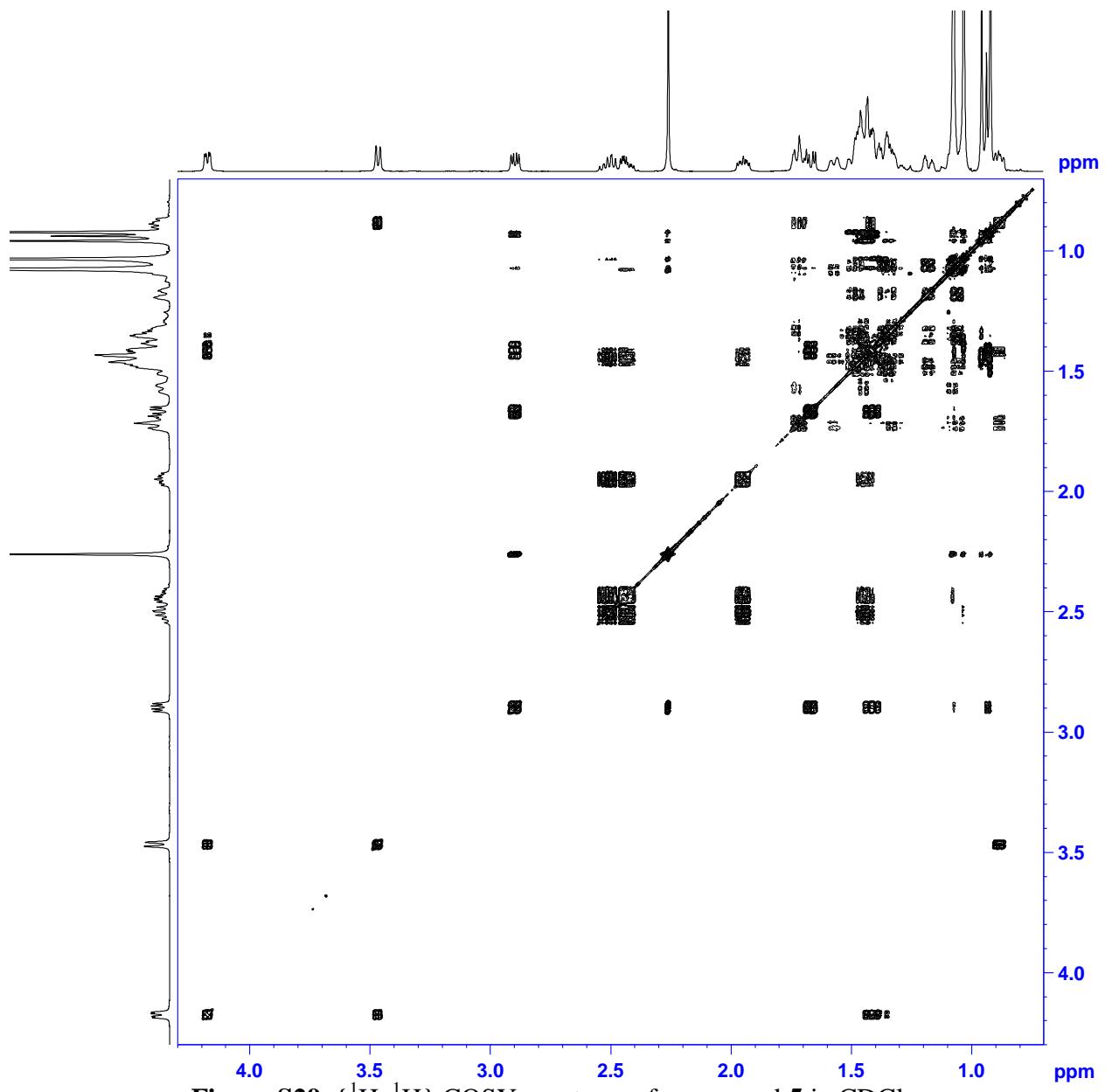


Figure S29.  $\{^1\text{H}, ^1\text{H}\}$  COSY spectrum of compound 5 in  $\text{CDCl}_3$ .

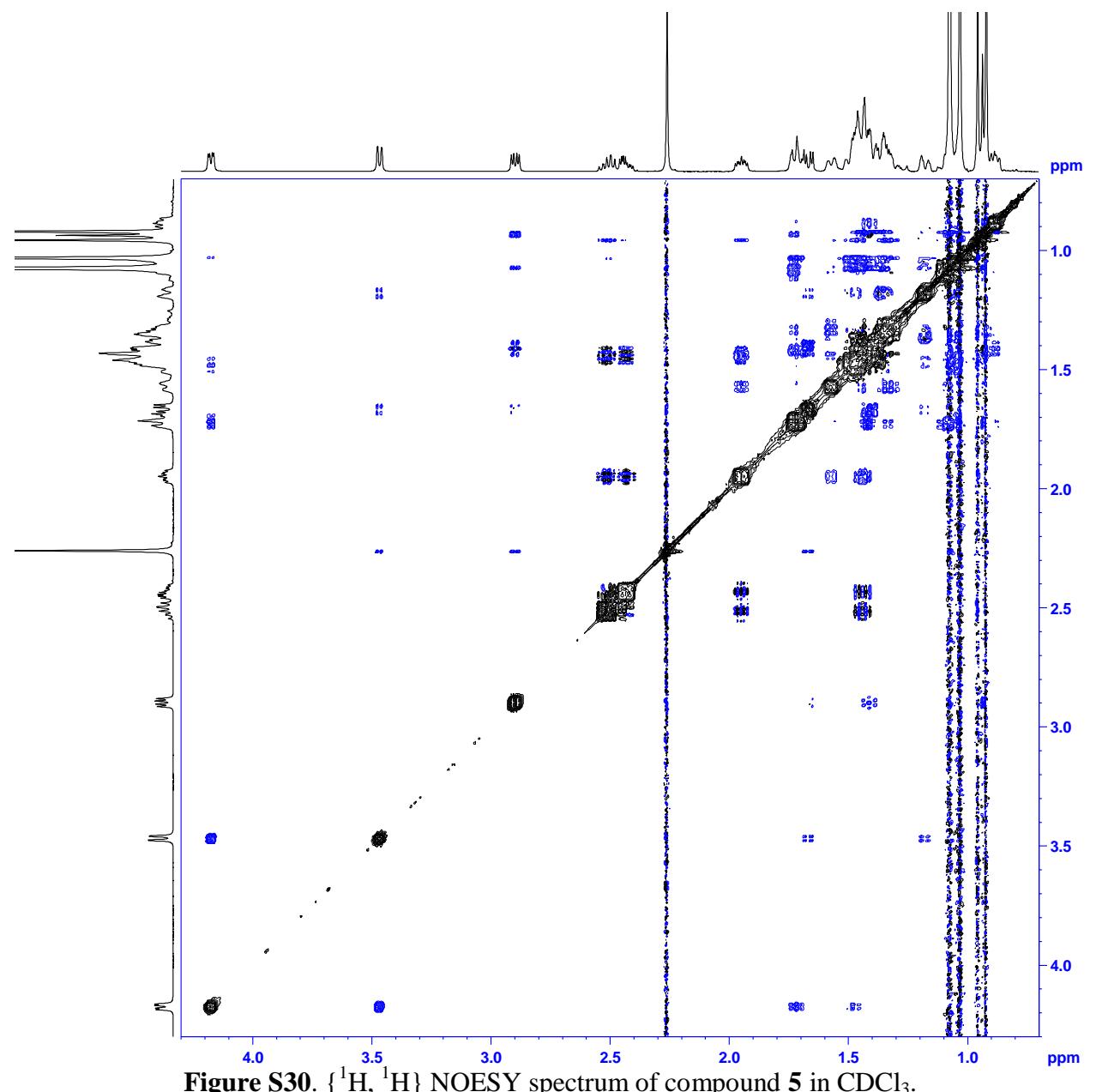
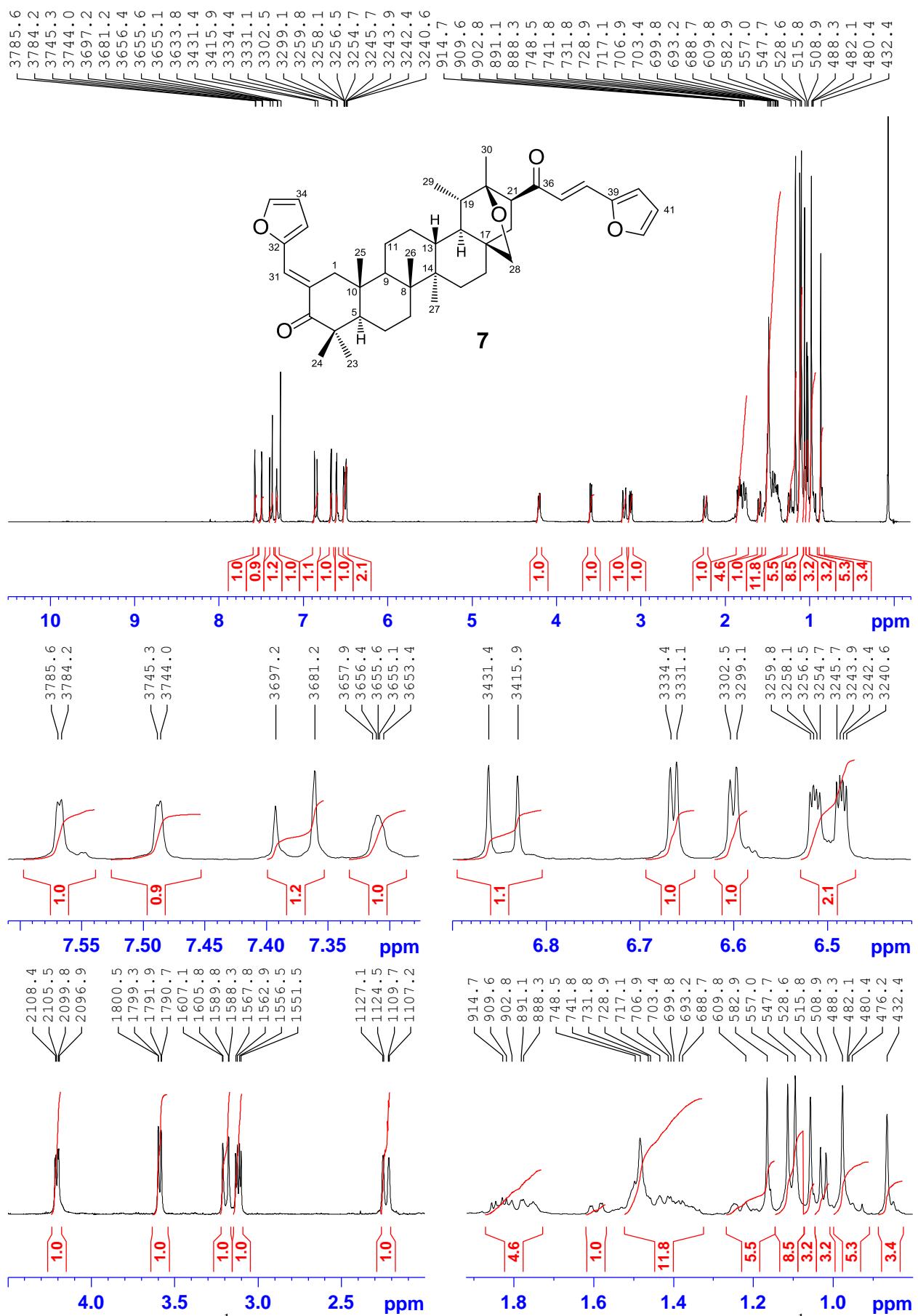
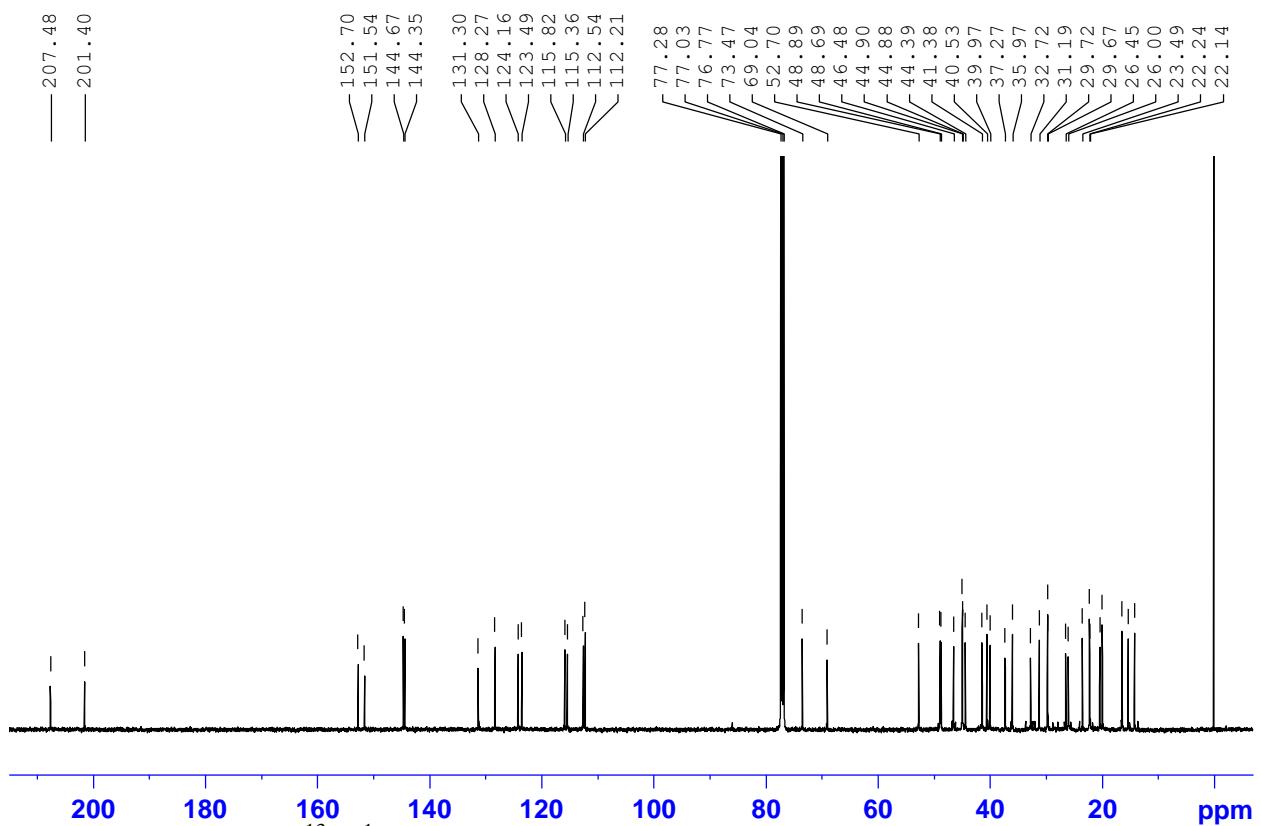


Figure S30.  $\{^1\text{H}, ^1\text{H}\}$  NOESY spectrum of compound 5 in  $\text{CDCl}_3$ .

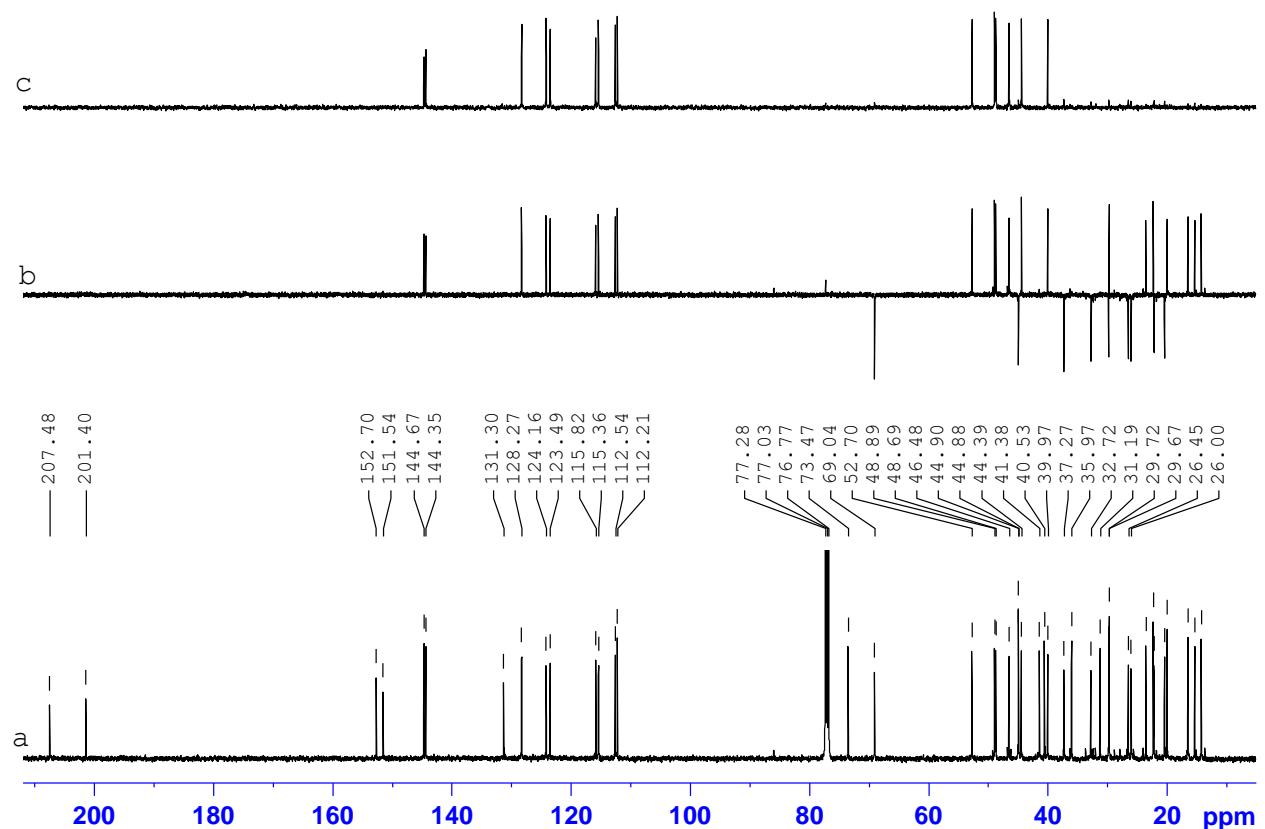
## NMR data of compound 7



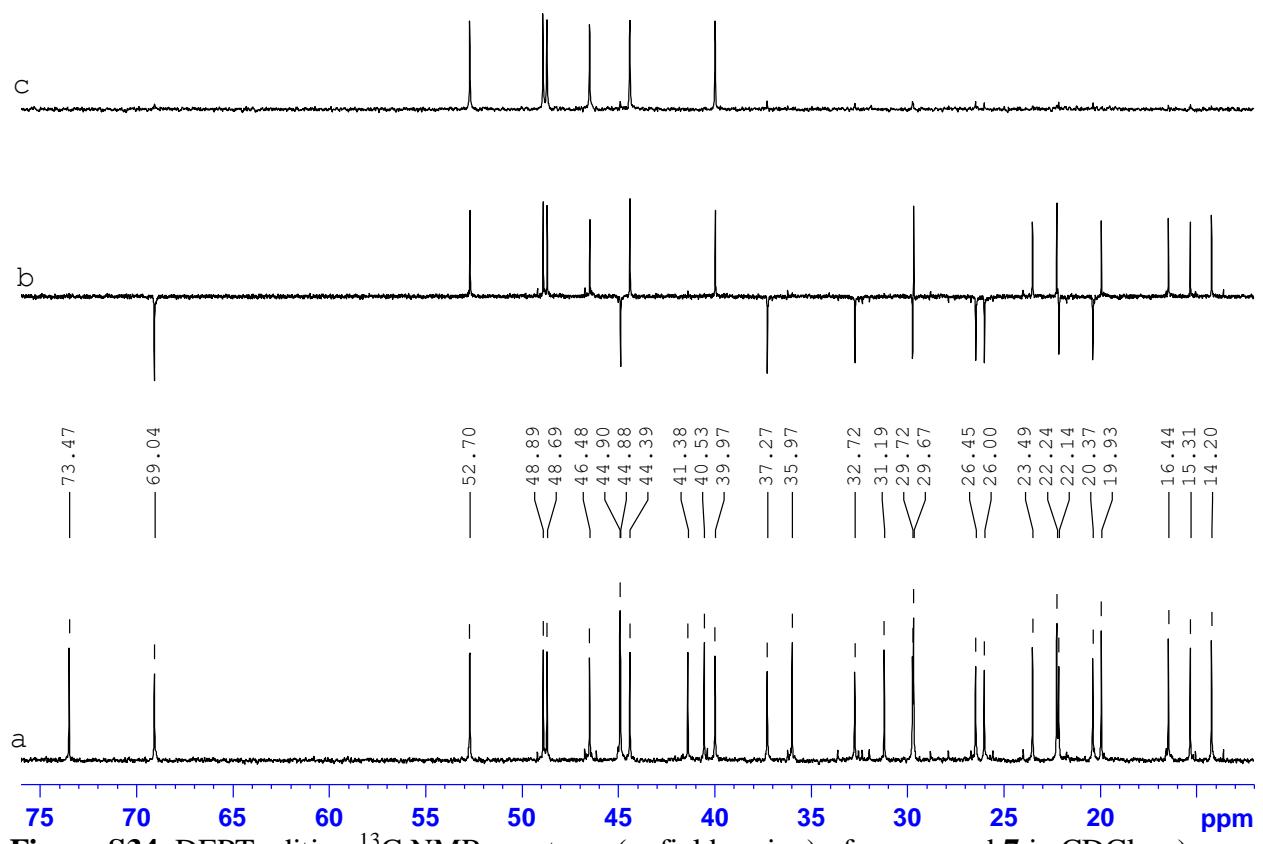
**Figure S31.** Complete  $^1\text{H}$  NMR spectrum of compound **7** in  $\text{CDCl}_3$  (top). Expanded  $^1\text{H}$  NMR spectrum of compound **3** in  $\text{CDCl}_3$  (bottom).



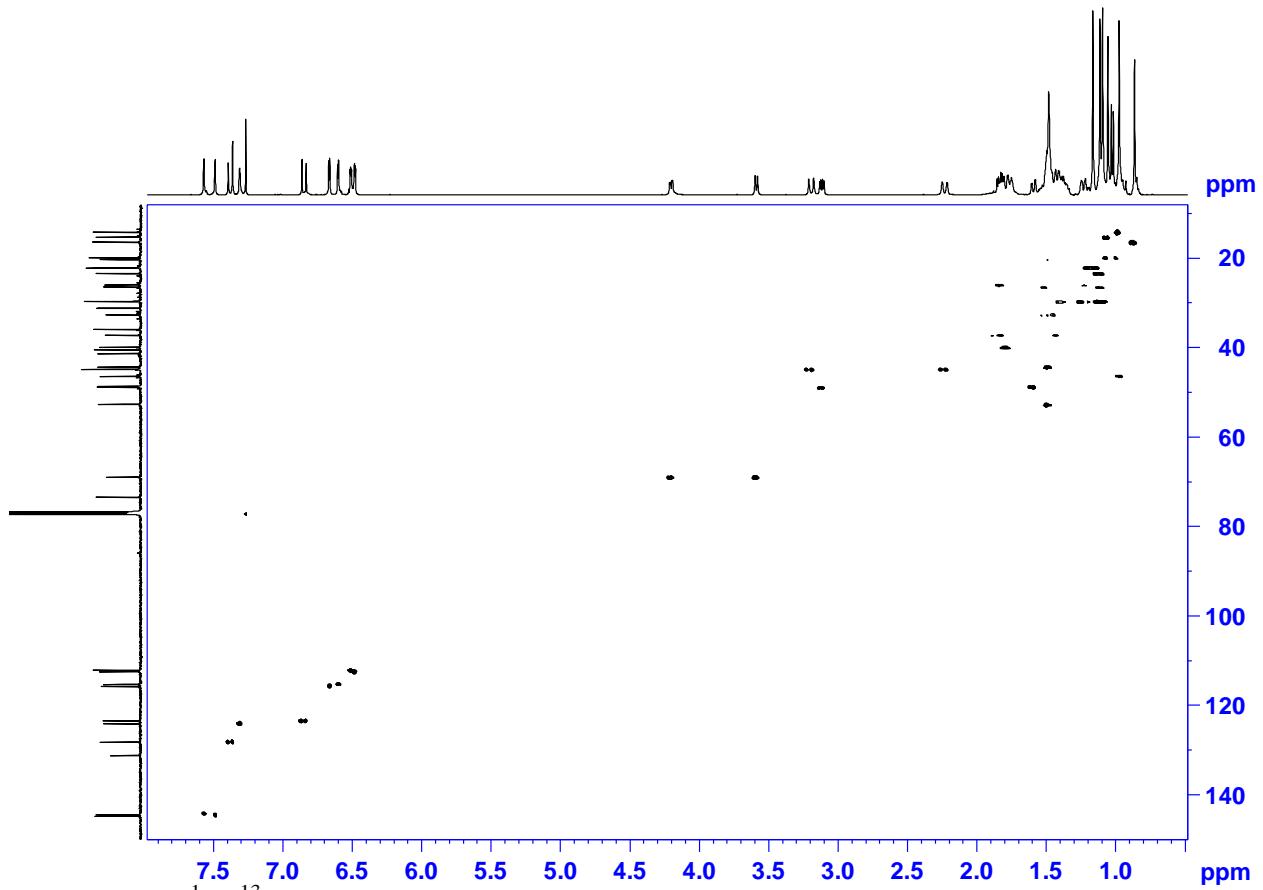
**Figure S32.** Complete  $^{13}\text{C}\{\text{H}\}$  spectrum of compound **7** in  $\text{CDCl}_3$ .



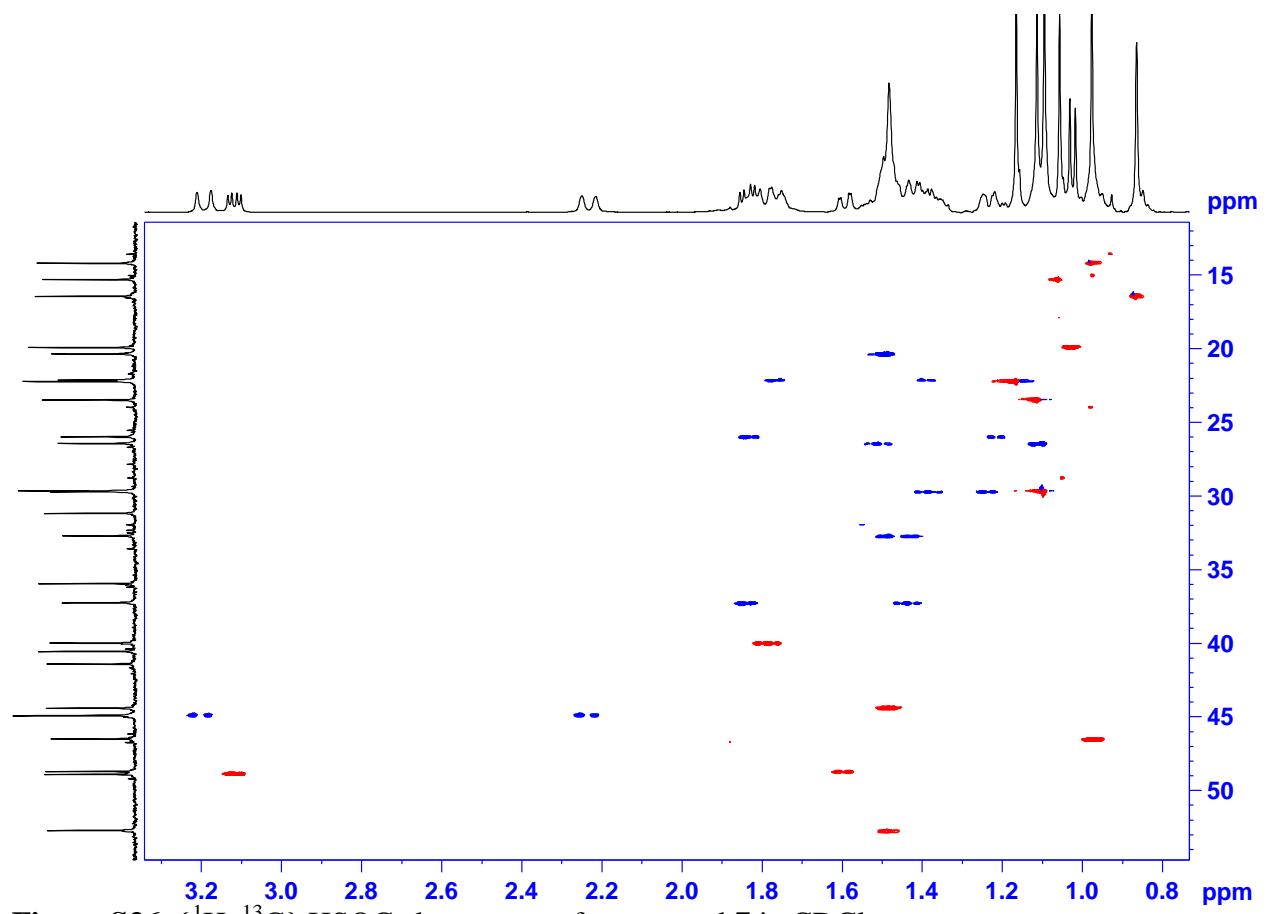
**Figure S33.** DEPT editing  $^{13}\text{C}$  NMR spectrum of compound **7** in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



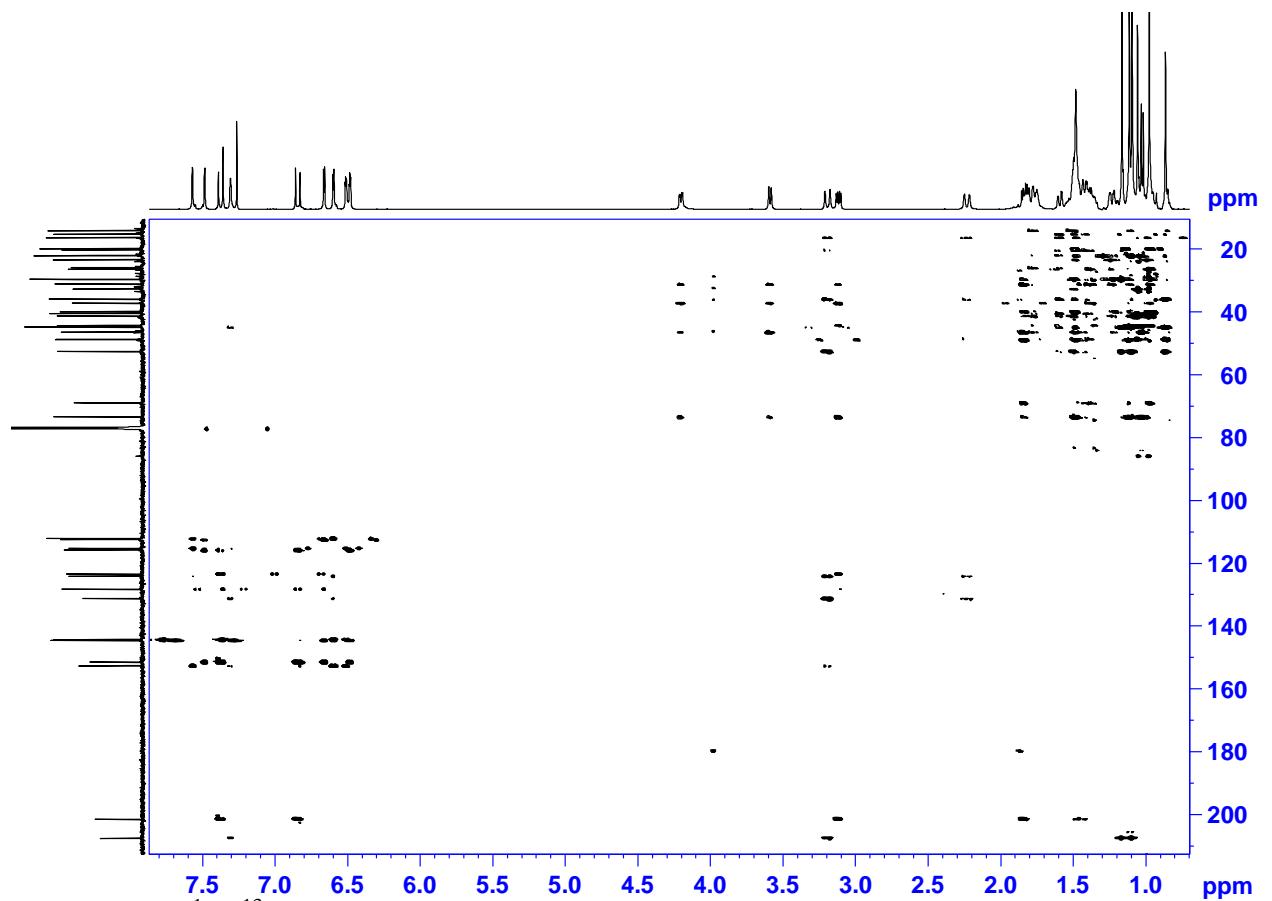
**Figure S34.** DEPT editing  $^{13}\text{C}$  NMR spectrum (upfield region) of compound 7 in  $\text{CDCl}_3$ : a)  $^{13}\text{C}\{^1\text{H}\}$  spectrum; b) DEPT-135; c) DEPT-90.



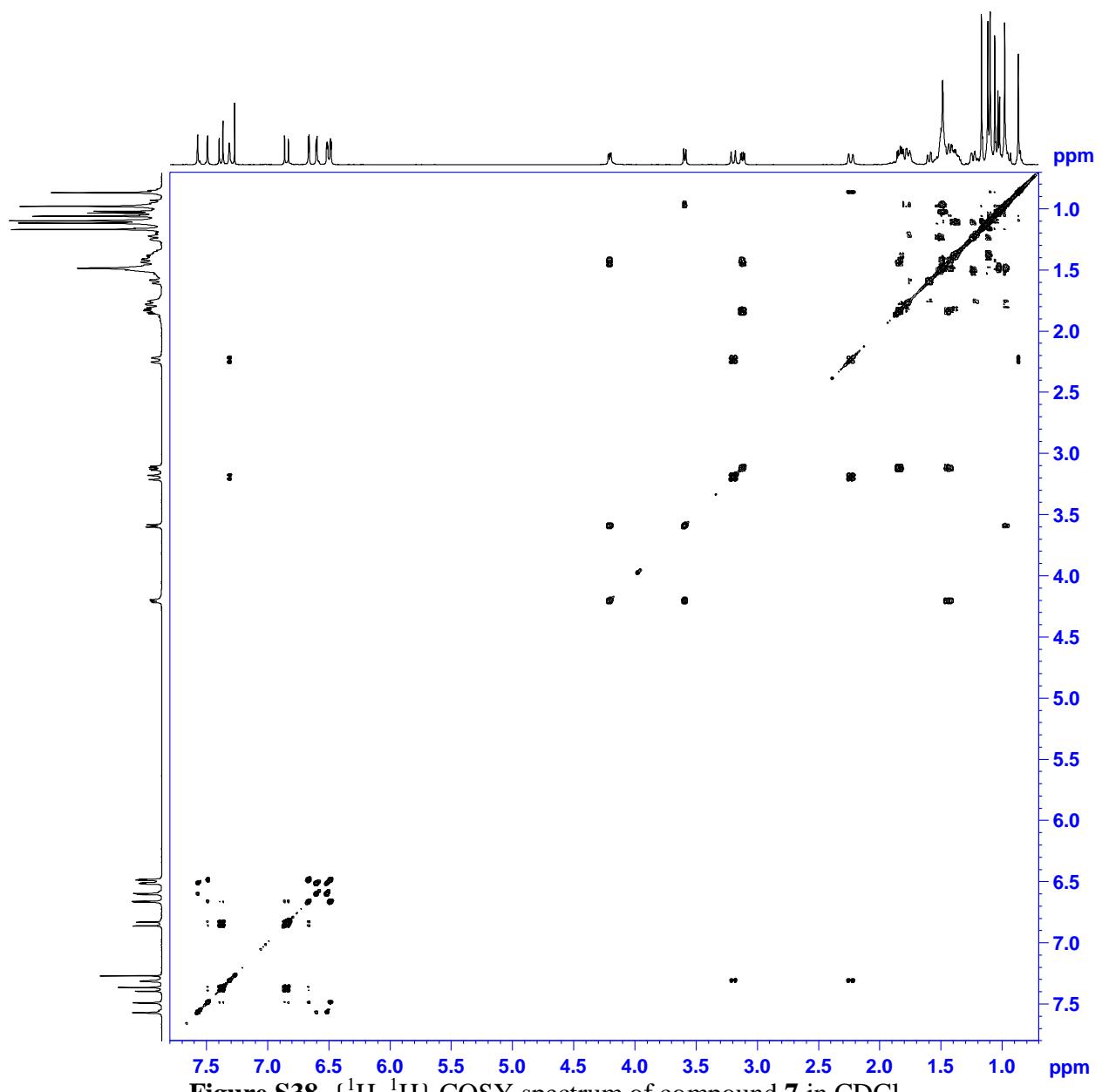
**Figure S35.**  $\{^1\text{H}, ^{13}\text{C}\}$  HSQC spectrum of compound 7 in  $\text{CDCl}_3$ .



**Figure S36.**  $\{^1\text{H}, ^{13}\text{C}\}$  HSQCed spectrum of compound 7 in  $\text{CDCl}_3$ .



**Figure S37.**  $\{^1\text{H}, ^{13}\text{C}\}$  HMBC spectrum of compound 7 in  $\text{CDCl}_3$ .



**Figure S38.**  $\{^1\text{H}, ^1\text{H}\}$  COSY spectrum of compound 7 in  $\text{CDCl}_3$ .

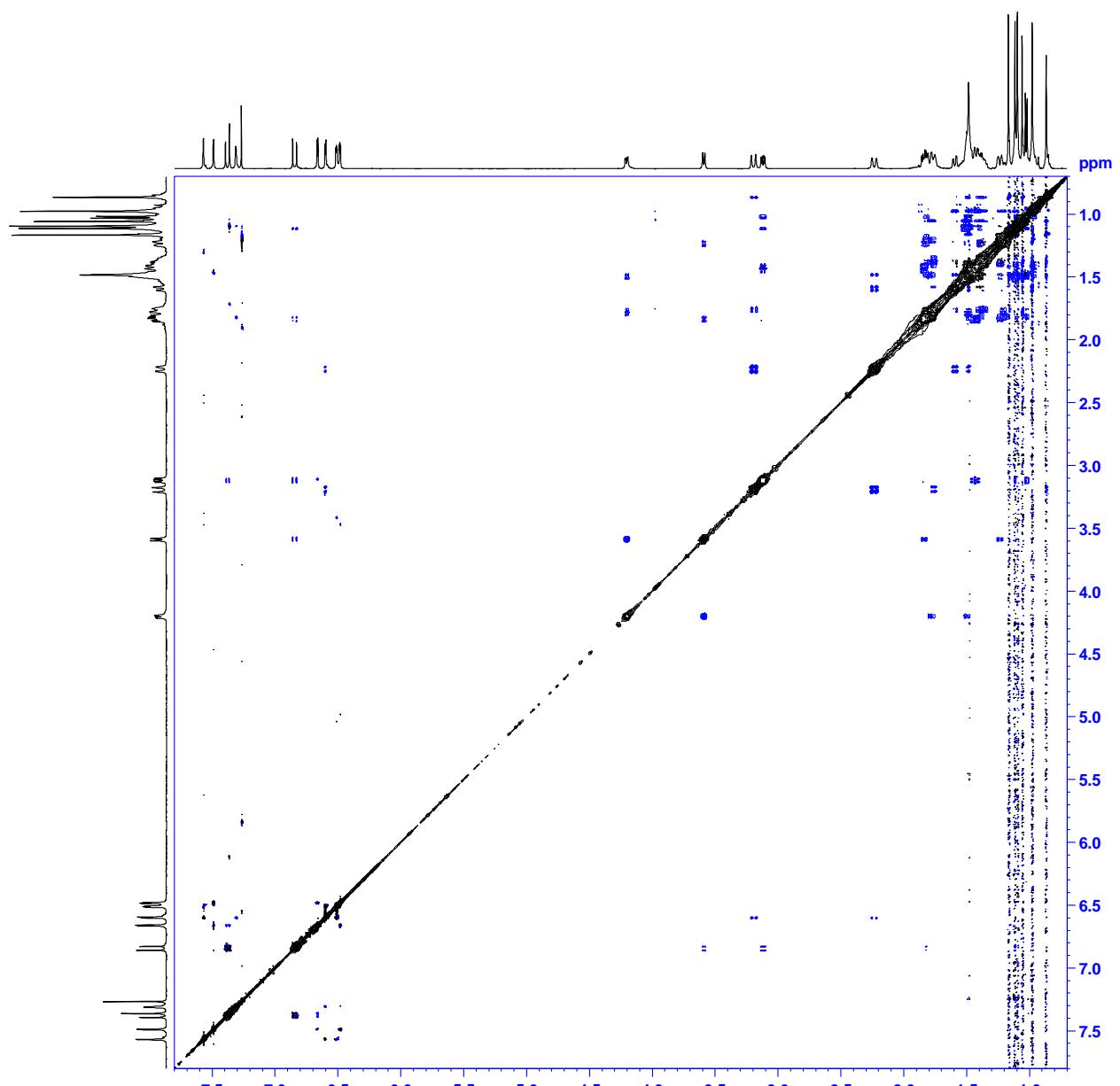
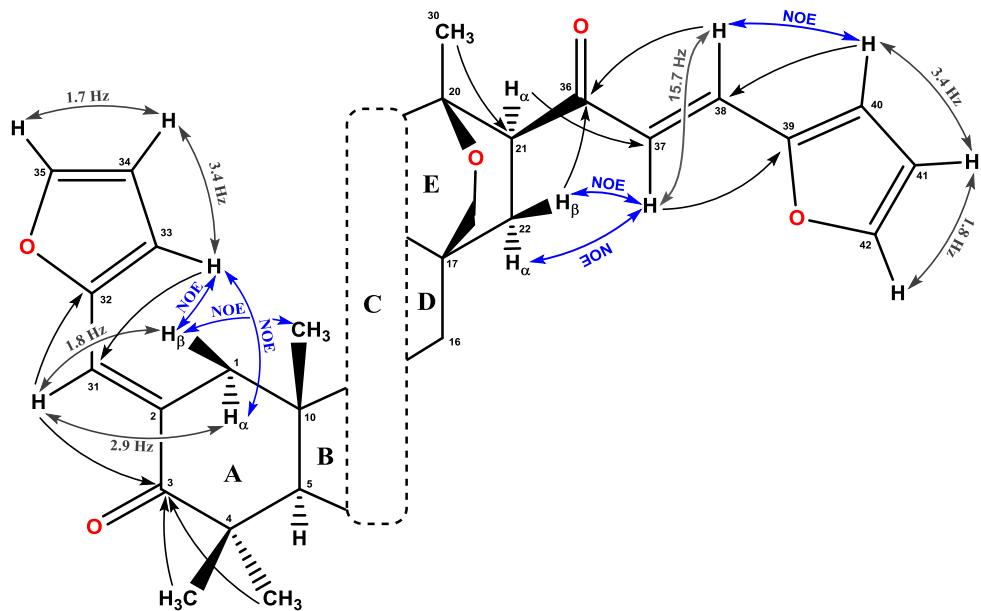
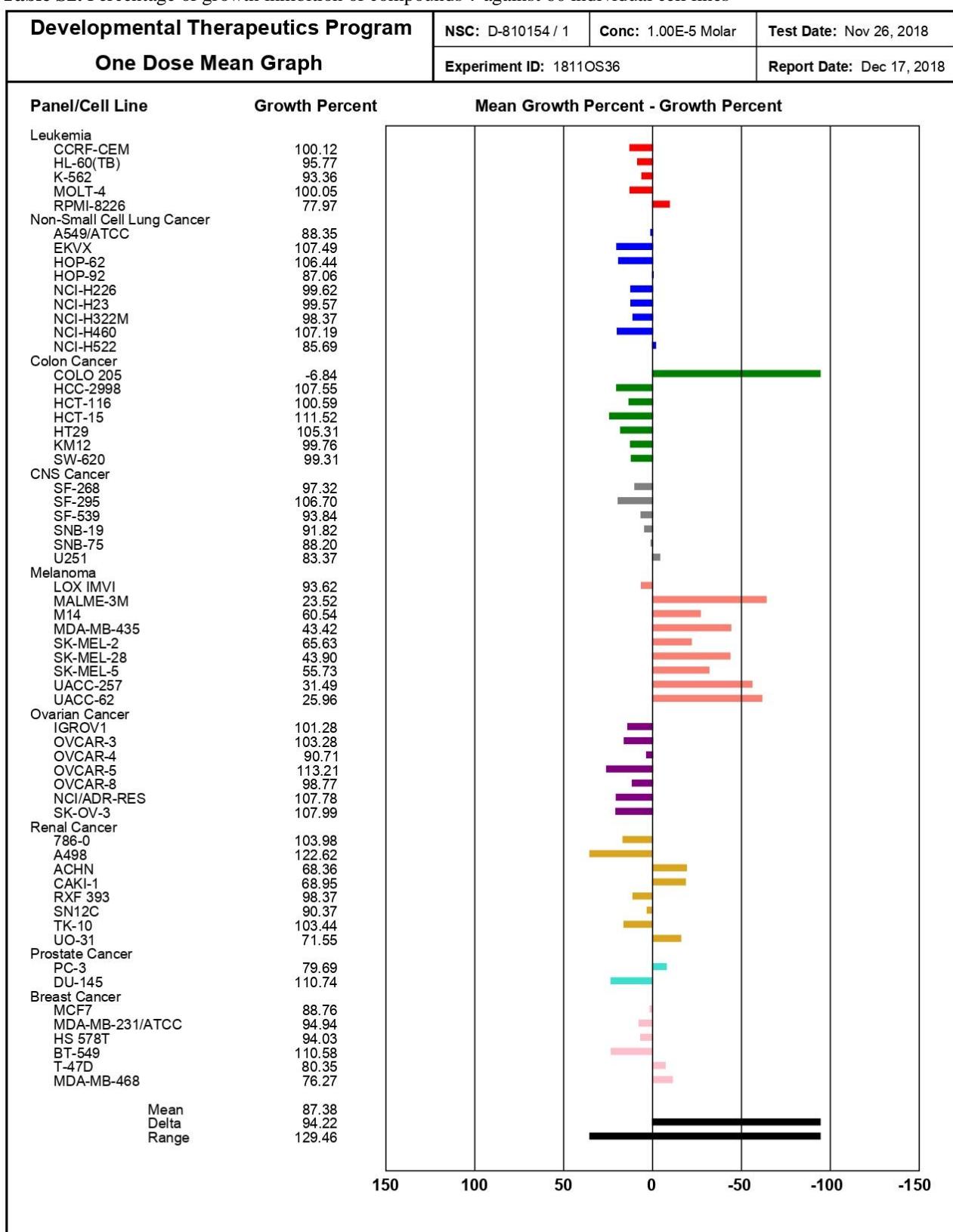


Figure S39.  $\{^1\text{H}, ^1\text{H}\}$  NOESY spectrum of compound 7 in  $\text{CDCl}_3$ .



**Figure S40.** HMBC, COSY and NOESY correlations for compound 7

**Table S2.** Percentage of growth inhibition of compounds **7** against 60 individual cell lines



### ***In vitro* assessment against HCMV and HPV-11**

Antiviral activity against HCMV was determined in cytopathic effect (CPE) reduction assays. These were performed in monolayers of primary human foreskin fibroblast cells in an assay medium consisting of MEM with Earle's salts, 2% FBS and standard concentrations of *L*-glutamine, penicillin, and gentamycin. Cells were seeded into 384-well microtiter plates and were subsequently incubated at 37°C in a humidified 5% CO<sub>2</sub> incubator for 24 h to allow the formation of confluent monolayers. Dilutions of test compounds were prepared in the plates in a series of 5-fold dilutions in duplicate wells to yield final concentrations that range from 300 to 0.1 µM or from 10 to 0.003 µM. Monolayers were then infected at a multiplicity of infection of 0.005 TCID<sub>50</sub> per cell with the AD169 strain of HCMV and incubated further until 100% CPE was observed in the virus control wells. Cytopathology was determined by the addition of the CellTiter-Glo reagent (Promega, Madison, WI) according to the manufacturer's suggested protocol. Concentrations of test compounds sufficient to reduce CPE by 50% (EC<sub>50</sub>) were interpolated from the experimental data. Cytotoxicity was also determined with CellTiter-Glo and the concentrations of the compounds that decreased cell viability by 50% (CC<sub>50</sub>) were also calculated from the data and selective index (SI) values were calculated as CC<sub>50</sub>/EC<sub>50</sub> as a measure of antiviral activity. To evaluate antiviral activity against HPV-11, a NanoLuc reporter gene into the ori-plasmid to facilitate its quantification in transiently transfected C 33 A cells was used. Thus, after drug treatment and incubation, replication of the NanoLuc reporter vector was quantified by measuring the corresponding increase in luciferase activity, and EC<sub>50</sub> values were determined. Cytotoxicity (CC<sub>50</sub>) values were also determined in C 33 A cells using the CellTiter-Glo reagent (Promega).

### ***In vitro* cytotoxic activity (NCI, USA)**

Evaluation of compounds against the 60 cell lines starts at a single dose of 10<sup>-5</sup> M. The human tumor cell lines of the cancer-screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM *L*-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 mL at plating densities ranging from 5000 to 40.000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37°C, 5% CO<sub>2</sub>, 95% air and 100% relative humidity for 24 h prior to addition of experimental drugs. After 24 h, two plates of each cell line are fixed *in situ* with TCA, to represent a measurement of the cell population for each cell line at the time of drug

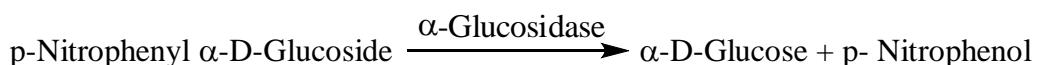
addition (Tz). Experimental drugs are solubilized in dimethylsulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is dissolved and diluted to twice the desired final maximum test concentration with complete medium containing 50 mg/mL gentamicin. Additional four, 10-fold or  $\frac{1}{2}$  log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 mL of these different drug dilutions are added to the appropriate microtiter wells already containing 100 mL of medium, resulting in the required final drug concentrations. Following drug addition, the plates are incubated for an additional 48 h at 37 °C, 5% CO<sub>2</sub>, 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 ml of cold 50% TCA (final concentration, 10% TCA) and incubated for 60 min at 4°C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 mL) at 0.4% in 1% acetic acid is added to each well, and plates are incubated for 10 min at room temperature. After staining, the unbound dye is removed by washing five times with 1% acetic acid and the plates are air dried. The bound stain is subsequently solubilized with 10 nM Trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 ml of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero (Tz), control growth (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

$$[(Ti_{-}Tz)/(C_{-}Tz)] \times 100 \text{ for concentrations for which } Ti_{-}Tz > C_{-}Tz$$

$$[(Ti_{-}Tz)/Tz] \times 100 \text{ for concentrations for which } Ti_{-}Tz < Tz$$

### ***α-Glucosidase Inhibition Assay Method***

α-Glucosidase enzyme inhibition assay was carried out in a 96-well microplate. The assay is based on the hydrolysis reaction of 4-nitrophenyl-α-D-glucopyranoside with α-glucosidase to form yellow colored 4-nitrophenol:



α-Glucosidase inhibitory activity assay was performed following the modified method of Pistia Brueggeman and Hollingsworth with slight modification [1, 2]. Compounds were

dissolved in DMSO - EtOH (1 : 1) solution to final concentrations of 256, 64, 16, 4 and 1  $\mu$ g/mL. The concentration was determined by a series of  $\alpha$ -glucosidase kinetic experiments in a 96-well plate, using a reaction mixture containing 20  $\mu$ L of compound varying concentrations, 20  $\mu$ L of phosphate buffer (100 mM; pH 6.8), and 20  $\mu$ L of  $\alpha$ -glucosidase (0.3 U/mL, Sigma G0660) were pre-incubated for 10 min at 37°C. Then 20  $\mu$ L of 2.5M *p*-nitrophenyl  $\alpha$ -D-glucopyranoside (Sigma N1377) was added to the mixture as a substrate. After further incubation at 37°C for 30 min, the reaction was stopped by adding 80  $\mu$ L of 0.1 M sodium carbonate. The enzyme, tested compound and substrate solution were prepared using the phosphate buffer 10 mM; pH 6.8. Acarbose was used as a positive control and water as a negative one. The yellow color produced was quantitated by colorimetric analysis and reading the absorbance at 410 nm. Each experiment was performed in triplicates, along with appropriate blanks. The solvent DMSO was used as a negative control to evaluate its effect on  $\alpha$ -glucosidase activity. Buffer was used instead of tested compound in positive control and instead of enzyme or substrate in the negative control. Background was determined by the volume of a buffer as a reaction mixture.

The % inhibition has been obtained using the formula:

$$\% \text{ inhibition} = \{\text{Absorbance (control)} - \text{Absorbance (sample)}\} / \text{Absorbance (control)}$$

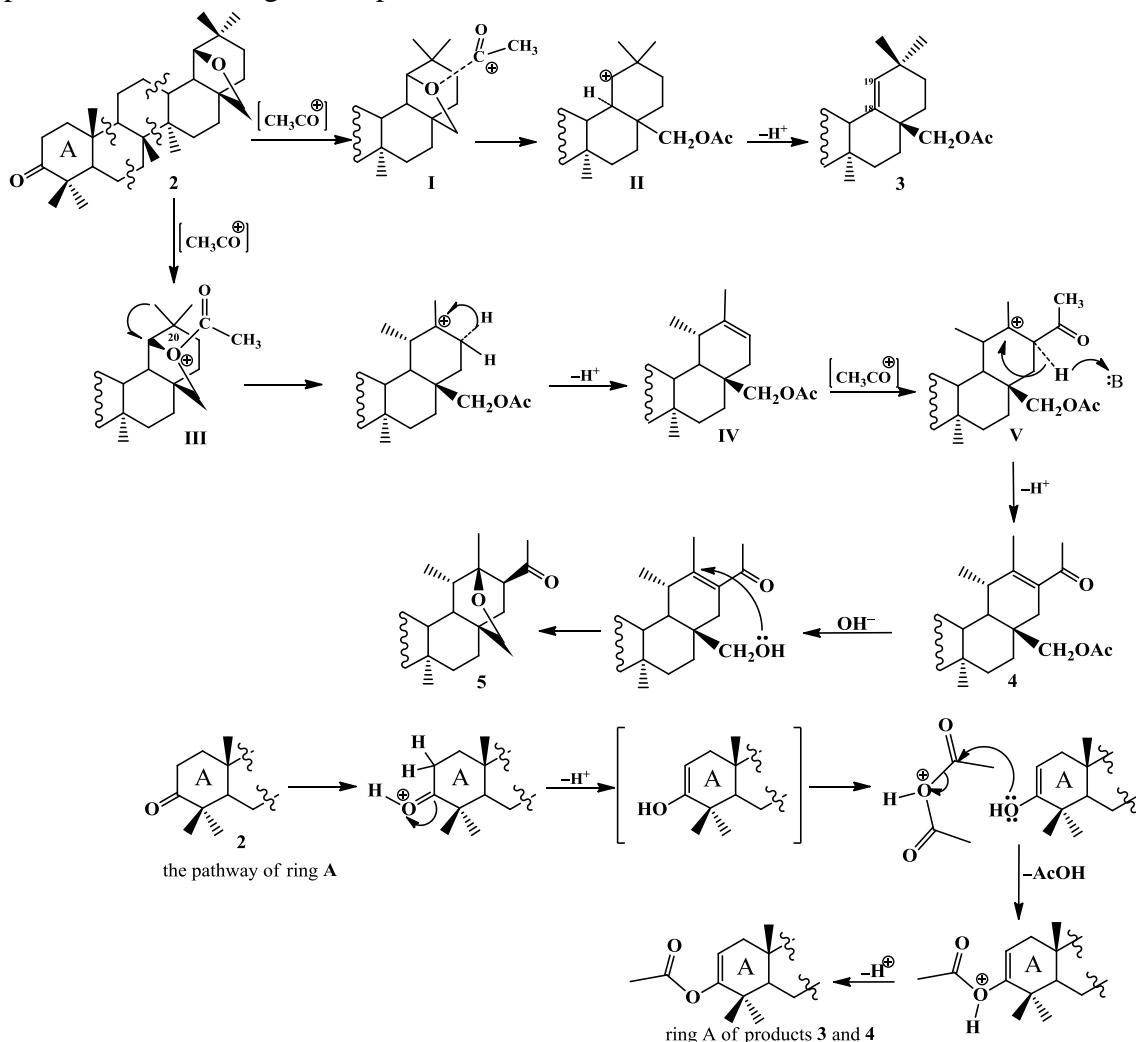
The IC<sub>50</sub> value is defined as a concentration of samples inhibiting 50% of  $\alpha$ -glucosidase activity under the stated assay conditions.

- [1] Y.-M. Kim, M.-H. Wang, H.-I. Rhee, A novel  $\alpha$ -glucosidase inhibitor from pine bark, Carbohydr. Res. 339 (2004) 715–717. doi:10.1016/j.carres.2003.11.005.
- [2] N. Abdullah, F. Salim, R. Ahmad, Chemical Constituents of Malaysian *U. cordata* var. ferruginea and Their in Vitro  $\alpha$ -Glucosidase Inhibitory Activities, Molecules. 21 (2016) 525. doi:10.3390/molecules21050525.

*The proposed mechanism of the allobetulone **2** rearrangement*

We propose the following pathway for the formation of compounds **3**, **4** and **5** from **2** (Fig. S42). At first, reaction of acylium cation with allobetulone **2** (**I**) gave secondary carbocation **II**, which after deprotonation, led to compound **3**. On the other side, spontaneous reaction of acylium cation with allobetulone **2** with a parallel [1,2]-sigmatropic shift of C(20)-methyl group (**III**) followed by deprotonation gave intermediate **VI**. Reaction of acylium cation with the unsaturated bond of **IV** led to tertiary carbocation **V** with subsequent elimination and formation of  $\alpha,\beta$ -unsaturated ketone **4**. Finally, hydrolysis of acetate groups of compound **4** under basic conditions gave the corresponding C28-alkoxide, which then undergoes Michael addition on the  $\alpha,\beta$ -unsaturated ketone to give compound **5**. Keto-enol equilibration in oxo-cycle **A** under acidic condition and reaction of the corresponding enol with acetic anhydride explain the formation of the enol acetate moiety (pathway of ring A).

One should note that the harsh reaction conditions ( $\text{HClO}_4/\text{Ac}_2\text{O}$  at  $140^\circ\text{C}$ ) allow the formation of acylium cation (or pseudo-acylium), that can react as a strong Lewis acid with the oxygen atom of the ether bridge of **2**, as well as a strong electrophilic species through an electrophilic addition with the weak nucleophilic trisubstituted C(20)-C(21) unsaturated bond of compound **2**, thus leading to compound **4**.



**Figure S42.** Proposed mechanism for the formation of compounds **3**, **4** and **5** from allobetulone **2**

**Table S3.** *In vitro* antiviral activity of compounds **1**, **3**, **6**, **7** and **9**.

Compound (ARB No.)	EC <sub>50</sub>	EC <sub>90</sub>	CC <sub>50</sub>	SI <sub>50</sub>	SI <sub>90</sub>
<b>Human cytomegalovirus<sup>a,b</sup></b>					
<b>1</b> (09-001068)	4.86	>30	79.05	16	<3
<b>6</b> (19-000021)	>6	>6	7.87	<1	<1
<b>7</b> (19-000022)	>6	>6	14.09	<2	<2
<b>Ganciclovir</b>	1.16	>150	>150	>130	1
<b>1</b> (09-001068)	4.87	>30	62.08	13	<2
<b>Ganciclovir</b>	22.25	83.51	>150	>7	>2
<b>Cidofovir</b>	1.13	>150	>150	>133	1
<b>Human papillomavirus 11<sup>c</sup></b>					
<b>3</b> (18-000083)	5.98	28.18	94.20	16	3
<b>9-[2-(Phosphonomethoxy)ethyl]guanine</b>	1.37	>150	>150	>109	1
<b>1</b> (09-001068)	22.28	77.01	>150	>7	>2
<b>6</b> (19-000021)	0.76	5.36	>150	>198	>28
<b>7</b> (19-000022)	10.27	>30	122.62	12	<4
<b>9-[2-(Phosphonomethoxy)ethyl]guanine</b>	1.22	7.04	>150	>123	>21

<sup>a</sup>Virus strain: AD169; cell line: HFF; vehicle: DMSO; drug conc. range: 0.048-150 µM; control conc. range: 0.048-150 µM; experiment number: 19-hcmv-009 for **1**, **6** and **7** control assay order: primary; control assay name: CellTiter-Glo (*cytopathic effect/toxicity*).

<sup>b</sup>Virus strain: G8914-6 (resistant isolate); cell line: HFF; vehicle: DMSO; drug conc. range: 0.048-150 µM; control conc. range: 0.048-150 µM; experiment number: 19-hcmvR-014 for **1**; control assay order: primary; control assay name: CellTiter-Glo (*cytopathic effect/toxicity*).

<sup>c</sup>Virus strain: HE611260.1; cell line: C-33 A; vehicle: DMSO; drug conc. range: 0.048-150 µM; control conc. range: 0.048-150 µM; experiment number: 18-hpv11-004 for **3**; 19-hpv11-006 for **1**, **6** and **7**; control assay name: Nano-Glo Luciferase (*Nanoluc*)/CellTiter-Glo (*toxicity*).

EC<sub>50</sub> – compound concentration that reduced viral replication by 50%.

EC<sub>90</sub> – compound concentration that reduced viral replication by 90%.

CC<sub>50</sub> – compound concentration that reduced cell viability by 50%.

SI<sub>50</sub> - Selectivity index (CC<sub>50</sub>/EC<sub>50</sub>).

**Table S4.** *In vitro* anticancer activity in 60 human tumor cell lines for compounds **3** and **7** at 10  $\mu\text{M}$

cell lines	Percentage cell growth for compound	
	<b>3</b>	<b>7</b>
<i>Leukemia</i>		
CCRF-CEM	89.76	100.12
HL-60(TB)	58.43	95.77
K-562	53.06	93.36
MOLT-4	63.37	100.05
RPMI-8226	39.56	77.97
SR	37.41	NT
<i>NSC lung cancer</i>		
A549/ATCC	98.85	88.35
EKVX	98.21	107.49
HOP-62	95.46	106.44
HOP-92	102.46	87.06
NCI-H226	91.97	99.62
NCI-H23	97.25	99.57
NCI-H322M	95.13	98.37
NCI-H460	86.15	107.19
NCI-H522	74.69	85.69
<i>Colon cancer</i>		
COLO 205	80.28	<b>-6.84</b>
HCC-2998	99.45	107.55
HCT-116	61.32	100.59
HCT-15	78.85	111.52
HT29	95.13	105.31
KM12	95.70	99.76
SW-620	92.23	99.31
<i>CNS Cancer</i>		
SF-268	100.63	97.32
SF-295	103.08	106.70
SF-539	89.52	93.84
SNB-19	89.86	91.82
SNB-75	87.36	88.20
U251	23.78	83.37
<i>Melanoma</i>		
LOX IMVI	86.88	93.62
MALME-3M	95.30	23.52
M14	87.73	60.54
MDA-MB-435	85.86	43.42
SK-MEL-2	105.93	65.63
SK-MEL-28	91.11	43.90
SK-MEL-5	82.62	55.73
UACC-257	93.09	31.49
UACC-62	54.81	25.96
<i>Ovarian Cancer</i>		
IGROV1	90.69	101.28
OVCAR-3	105.36	103.28
OVCAR-4	100.23	90.71
OVCAR-5	88.08	113.21
OVCAR-8	99.48	98.77
NCI/ADR-RES	101.29	107.78
SK-OV-3	93.12	107.99
<i>Renal cancer</i>		
786-0	94.60	103.98
A498	82.49	122.62
ACHN	87.54	68.36
CAKI-1	62.75	68.95
RXF 393	100.15	98.37
SN12C	88.31	90.37
TK-10	102.27	103.44
UO-31	71.53	71.55
<i>Prostate Cancer</i>		
PC-3	44.68	79.69
DU-145	116.60	110.74
<i>Breast Cancer</i>		
MCF7	76.14	88.76
MDA-MB-231/ATCC	91.97	94.94
HS 578T	95.94	94.03
BT-549	97.36	110.58
T-47D	85.71	80.35
MDA-MB-468	90.84	76.27
Mean	85.49	87.38

<sup>a</sup>Survival of cells cultivated in the presence of 10  $\mu\text{M}$  of the compound under examination (in percent) compared with control cells (without the addition of compound to the culture medium) is given. Negative values correspond to cell death. The symbol “-” designates the absence of data. NT – not tested.