Electronic Supplementary Information

"Supramolecular assembly mediated by hydrogen bonds and weak noncovalent interactions in two eucalyptol derivatives with potential antineoplastic activity: Crystal structure, Hirshfeld surface analysis, DFT calculations and Molecular docking analysis."

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Figure S1. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) of compound **4**.

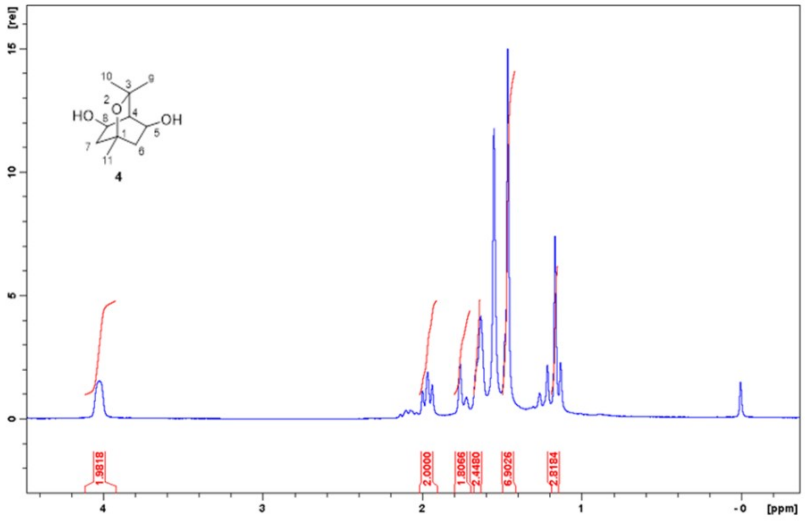


Figure S2. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) of compound **4**.

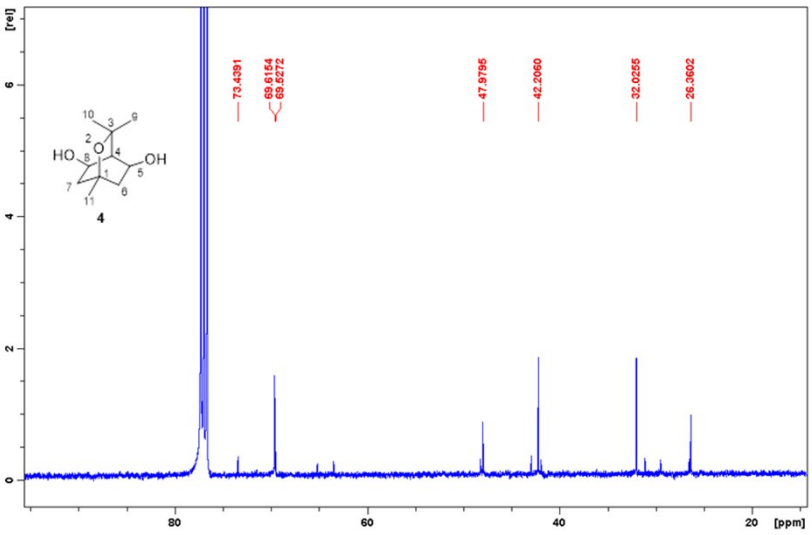


Figure S3. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) of compound **6**.

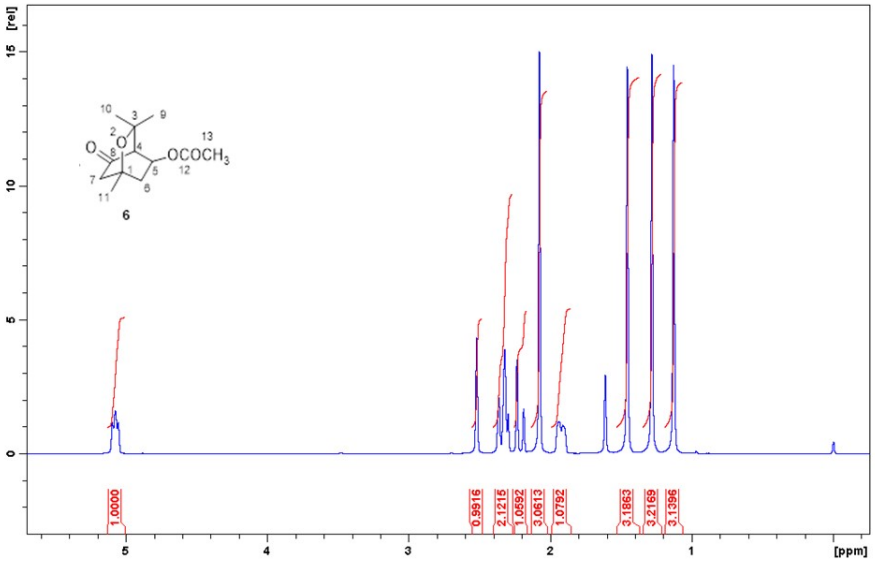


Figure S4. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) of compound **6**.

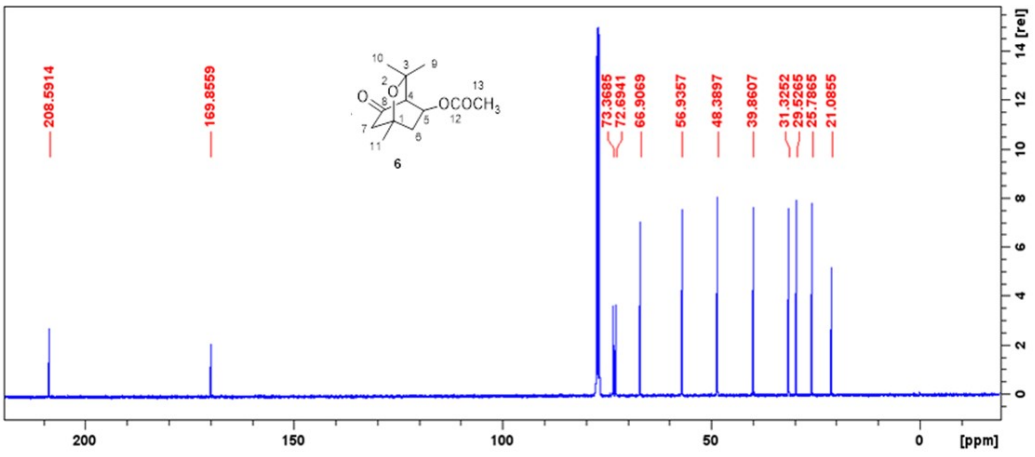


Figure S5. Optimized molecular structure of conformers C_1 and C_2 for compounds **6** computed at B3LYP/6-311++G(d,p) level of theory.

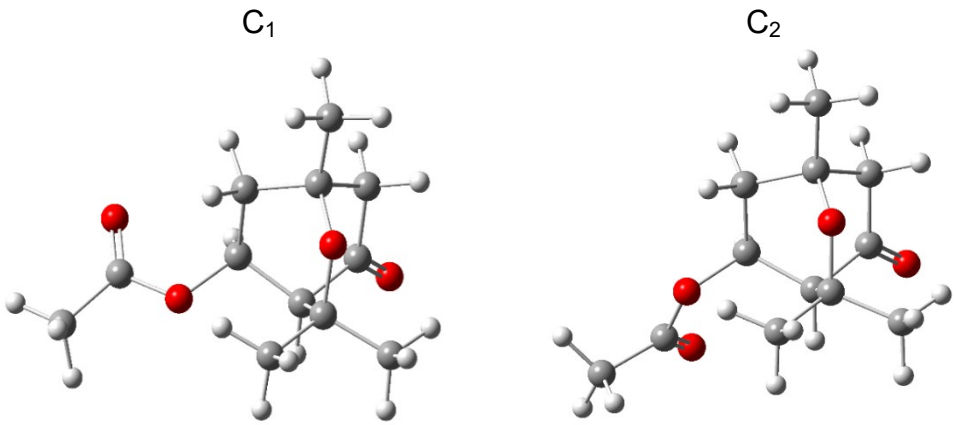


Figure S6. Optimized molecular structures of **4** and **6** at B3LYP/6-311++G(d,p) approximation.

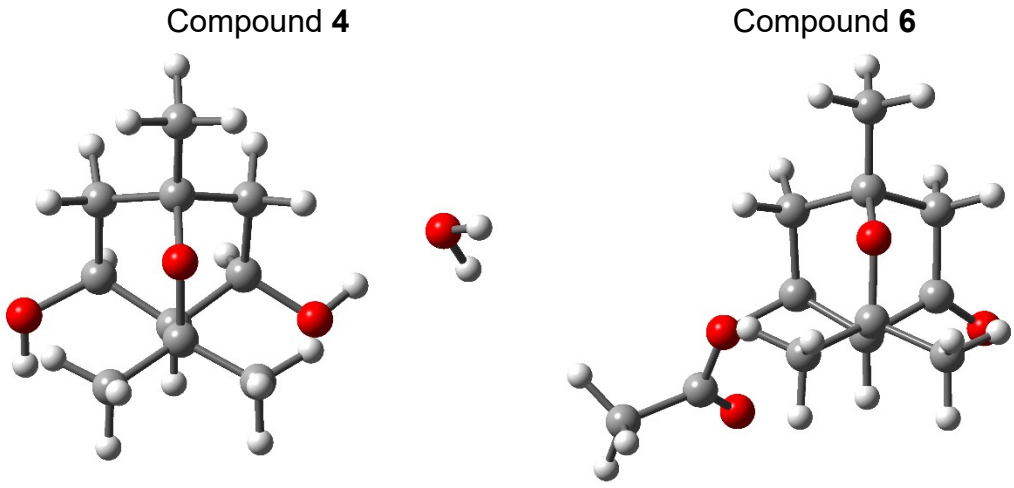


Figure S7. Full two-dimensional fingerprint plots of compounds **4 (a)** and **6 (b).**

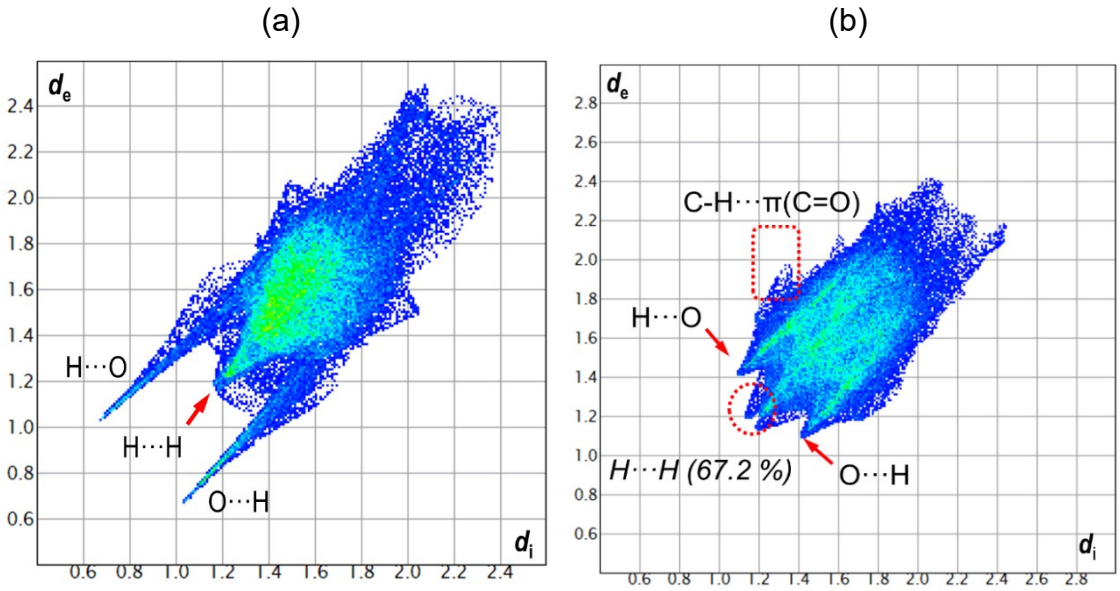


Figure S8. Hirshfeld surfaces of compound 6 mapped over shape index, highlighting the regions involved in intermolecular C-H···π(C=O) interactions.

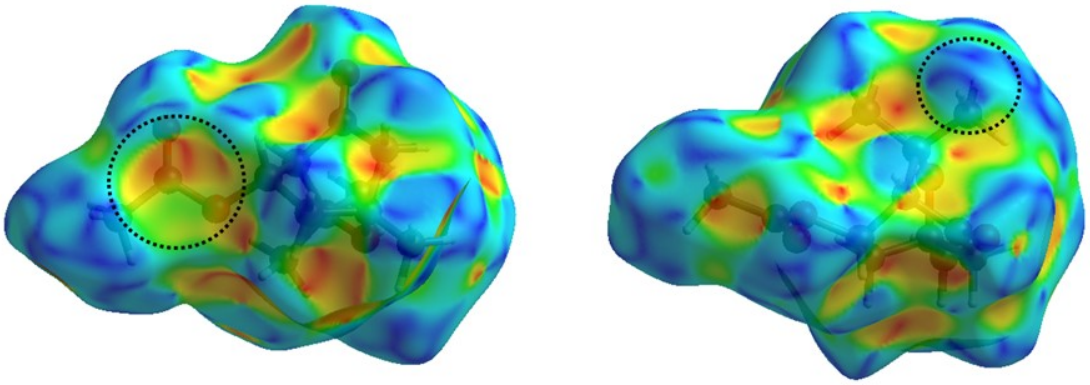


Figure S9. Experimental (red line) and calculated (green line) IR spectra of compound **4**.

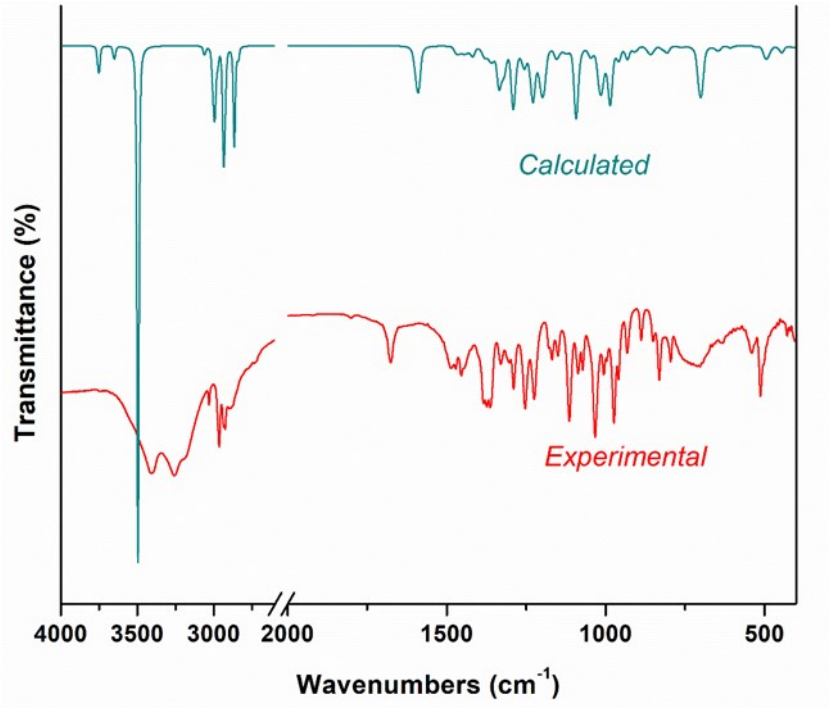
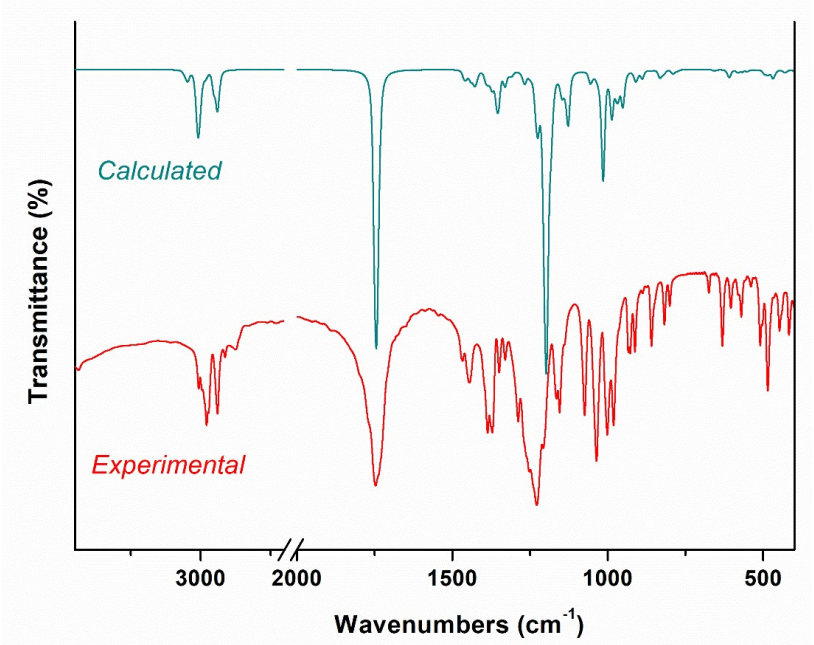


Figure S10. Experimental (red line) and calculated (green line) IR spectra of compound **6**.



ADMET analysis

A pharmacokinetic evaluation of the studied compounds was conducted as described in the experimental section. ADMET (absorption, distribution, metabolism, excretion and toxicity) parameters were calculated and compared to standard ranges. The colored zone in the radar plot represents the optimal physicochemical space for oral bioavailability. The radar plots and boiled-egg diagram suggest that both compounds exhibit favourable pharmacokinetic properties and druglikeness (**Figure S11**). The white region indicates the physicochemical space where molecules have the highest probability of being absorbed by the gastrointestinal tract, while the yellow region (yolk) represents the space where molecules are most likely to permeate the brain. The toxicity of compounds **4** and **6** is predicted to be class 5 (may be harmful if swallowed ($2000 < LD50 \leq 5000$) and predicted LD50 values range from 2991-3130 mg/kg, with a prediction accuracy of 70.97%. The hepatotoxicity, immunotoxicity, and cytotoxicity are also found to be inactive for both compounds.

Figure S11. ADME properties for (a) compound **4** and (b) compound **6**. The left panel shows radar plot and right panel shows BOILED-egg plot. The red dot is for molecule predicted not to be effluated from the central nervous system (CNS) by P-glycoprotein.

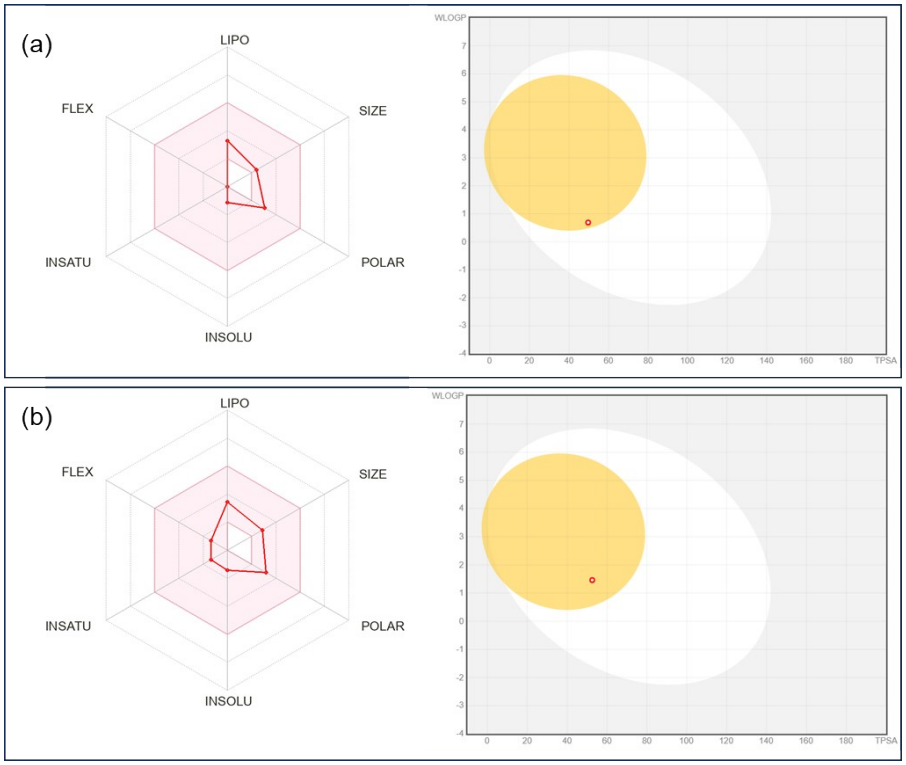


Table S1. Calculated relative, free energies and dipole moments for the two stable conformers of compound **6**.

Conformer	OCCO dihedral angle (º)	ΔE^a (kJ mol^{-1})	ΔG^b (kJ mol^{-1})	μ^c (D)
C_1	-158.4	0.000	0.000	2.600
C_2	-84.44	0.813	0.236	3.772

[a] $\Delta E = E(C_2)-E(C_1)$. [b] $\Delta G= G(C_2)-G(C_1)$. [c] μ: Dipole moment.

Table S2. Experimental and calculated bond lengths, angles and dihedral angles for compound **4**.

Parameter	**Compound 4**	
	Exp.[a]	**Calcd.[b]**
Bond lengths (Å)		
C1-O1	1.443(4)	1.437
C1-C2	1.518(5)	1.543
C1-C10	1.517(3)	1.524
C1-C6	1.521(5)	1.543
C2-C3	1.533(6)	1.545
C3-O2	1.421(4)	1.426
C3-C4	1.530(5)	1.553
C4-C5	1.530(5)	1.548
C4-C7	1.536(4)	1.558
C5-O3	1.431(4)	1.417
C5-C6	1.534(5)	1.554
C7-O1	1.462(3)	1.456
C7-C8	1.521(6)	1.537
C7-C9	1.533(6)	1.538
Bond angles (º)		
O1-C1-C10	106.5(2)	105.6
O1-C1-C2	107.6(3)	108.2
O1-C1-C6	108.1(3)	108.2
O1-C7-C8	106.6(3)	107.2
O1-C7-C4	107.6(2)	108.0
O1-C7-C9	106.7(3)	106.8
C1-O1-C7	114.6(3)	115.1
C1-C2-C3	110.2(3)	110.2
C1-C6-C5	109.9(3)	109.7
C2-C1-C6	110.6(2)	110.3
O2-C3- C4	115.8(3)	115.9
O2-C3- C2	109.3(3)	108.1
C3-C4-C7	112.3(3)	111.8
C4-C3-C2	108.0(2)	108.0
C4-C5-C6	108.0(3)	107.6
O3- C5- C4	111.3(3)	111.1
O3-C5-C6	113.2(3)	114.1
C5-C4-C3	103.5(2)	103.5
C5-C4-C7	111.9(3)	111.8
C8-C7-C9	107.8(3)	107.9
C8-C7-C4	114.5(3)	113.3
C9-C7-C4	113.2(3)	113.3
C10-C1-C2	111.5(3)	112.0

C10-C1-C6	112.3(3)	112.3
Dihedral angles (º)		
C4-C3-O2-H2	-66(4)	-55.9
C4-C5-O3-H3	-168(5)	-174.9
O1-C1-C2-C3	-62.8(4)	-62.1
C10-C1-C2-C3	-179.2(3)	-178.1
C6-C1-C2-C3	55.1(3)	56.1
C1-C2-C3-O2	133.3(3)	131.7
C1-C2-C3-C4	6.5(4)	5.5
O2-C3-C4-C5	168.9(3)	170.3
C2-C3-C4-C5	-68.1(3)	-68.1
O2-C3-C4-C7	-70.2(3)	-69.1
C2-C3-C4-C7	52.7(3)	52.5
C3-C4-C5-O3	-165.4(3)	-164.2
C7-C4-C5-O3	73.5(3)	75.3
C3-C4-C5-C6	69.7(3)	70.3
C7-C4-C5-C6	-51.4(4)	-50.2
O1-C1-C6-C5	64.1(3)	64.5
C10-C1-C6-C5	-178.7(3)	-179.3
C2-C1-C6-C5	-53.5(3)	-53.6
O3-C5-C6-C1	-132.8(3)	-133.3
C4-C5-C6-C1	-9.1(4)	-9.5
C5-C4-C7-O1	59.4(4)	59.2
C3-C4-C7-O1	-56.5(4)	-56.3
C5-C4-C7-C8	-58.9(3)	-59.3
C3-C4-C7-C8	-174.8(3)	-174.9
C5-C4-C7-C9	177.0(3)	177.3
C3-C4-C7-C9	61.2(3)	61.7
C10-C1-O1-C7	-179.0(3)	-178.5
C2-C1-O1-C7	61.4(4)	61.3
C6-C1-O1-C7	-58.1(4)	-58.2
C8-C7-O1-C1	120.9(3)	120.1
C9-C7-O1-C1	-124.2(3)	-124.5
C4-C7-O1-C1	-2.4(4)	-2.3

[a] Obtained from X-ray diffraction data reported in this work.
[b] Calculated at B3LYP/6-311++G(d,p) level of theory.

Table S3. Experimental and calculated bond lengths, angles and dihedral angles for compound **6**.

Parameter	**Compound 6**	
	Exp. [a]	**Calcd.** [b]
Bond lengths (Å)		
C1-O1	1.440(3)	1.443
C1-C2	1.519(4)	1.542
C1-C10	1.510(4)	1.520
C1-C6	1.530(4)	1.541
C2-C3	1.523(4)	1.539
C3-O2	1.454(3)	1.449
C3-C4	1.533(3)	1.548
C4-C5	1.505(4)	1.529
C4-C7	1.545(3)	1.558
C5-O4	1.209(3)	1.207
C5-C6	1.497(4)	1.525

C7-O1	1.447(3)	1.457
C7-C8	1.522(4)	1.534
C7-C9	1.514(4)	1.532
C11-O3	1.194(3)	1.205
C11-O2	1.336(3)	1.358
C11-C12	1.492(4)	1.506
Bond angles (º)		
O1-C1-C10	105.3(2)	106.1
O1-C1-C2	108.1(2)	108.2
O1-C1-C6	107.9(2)	107.9
O1-C7-C8	107.2(2)	107.3
O1-C7-C4	108.7(19)	108.3
O1-C7-C9	107.3(19)	107.4
C1-O1-C7	114.9(17)	115.5
C1-C2-C3	109.6(2)	109.3
C5-C6-C1	109.3(2)	108.9
C2-C1-C6	109.2(2)	109.5
O2-C3- C4	112.1 (19)	112.9
O2-C3- C2	108.7(2)	108.5
C3-C4-C7	113.4(2)	112.9
C2-C3-C4	109.1(19)	109.2
C6-C5-C4	111.5(2)	111.1
O3- C11- O2	123.3(2)	123.7
O3-C11-C12	125.3(3)	125.6
C5-C4-C3	103.5(2)	103.5
C5-C4-C7	106.8(2)	106.8
C9-C7-C8	109.4(2)	109.1
C8-C7-C4	110.3(2)	110.7
C9-C7-C4	112.8(2)	113.4
C10-C1-C2	112.9(2)	112.1
C10-C1-C6	113.1(2)	112.6
O2-C11-C12	111.4(2)	110.6
C11-O2-C3	117.7(19)	117.8
O4-C5-C6	124.4(2)	124.1
O4-C5-C4	120.9(2)	120.7
Dihedral angles (º)		
O1-C1-C2-C3	-65.8(3)	-65.6
C10-C1-C2-C3	178.1(2)	177.7
C6-C1-C2-C3	51.4(3)	51.9
C1-C2-C3-O2	135.0(2)	136.1
C1-C2-C3-C4	12.6(3)	12.7
O2-C3-C4-C5	170.25(19)	169.7
C2-C3-C4-C5	-69.4(3)	-69.5
O2-C3-C4-C7	-74.5(3)	-74.7
C2-C3-C4-C7	45.9(3)	46.1
C3-C4-C5-O4	-118.6(3)	-118.6
C7-C4-C5-O4	121.5(3)	121.5
C3-C4-C5-C6	61.4(3)	61.6
C7-C4-C5-C6	-58.5(3)	-58.7
O4-C5-C6-C1	-178.7(3)	-178.9
C10-C1-C6-C5	173.4(2)	173.7
C2-C1-C6-C5	-60.1(3)	-60.7
O1-C1-C6-C5	57.3(3)	56.9
C4-C5-C6-C1	1.3(3)	2.0
C5-C4-C7-O1	58.8(2)	57.8

C3-C4-C7-O1	-54.5(3)	-55.8
C5-C4-C7-C8	-58.5(3)	-59.7
C3-C4-C7-C8	-171.7(2)	-173.3
C3-C4-C7-C9	65.7(3)	63.5
C5-C4-C7-C9	178.9(2)	177.3
C10-C1-O1-C7	-179.9(2)	178.6
C2-C1-O1-C7	59.2(3)	58.2
C6-C1-O1-C7	-58.8(3)	-60.3
C8-C7-O1-C1	119.2(2)	121.3
C9-C7-O1-C1	-122.9(2)	-121.4
C4-C7-O1-C1	0.0(3)	1.6
O3-C11-O2-C3	1.7(4)	0.9
C12-C11-O2-C3	-176.6(2)	-178.8
C2-C3-O2-C11	151.8(2)	150.8
C4-C3-O2-C11	-87.6(3)	-88.1

[a] Obtained from X-ray diffraction data reported in this work.

[b] Calculated at B3LYP/6-311++G(d,p) level of theory.