



A combined experimental and theoretical study of the supramolecular self-assembly of the natural benzopyran 2,2-dimethyl-3-hydroxy-6-acetyl-chromane and its isomeric benzofuran 10,11-dihydro-10-hydroxytremetone

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ARTICLE INFO

Article history:

Received 21 April 2017

Received in revised form

29 May 2017

Accepted 30 May 2017

Available online 1 June 2017

Keywords:

Crystal structure

IR and Raman spectroscopy

Hydrogen bonds

Quantum chemical calculations

Chromane derivative

Benzofuran derivative

ABSTRACT

Epoxidation of 4HMBA, the main metabolite of the medicinal plant *Senecionutans*, produces an unstable epoxide eventually giving rise to a mixture of four derivatives, three of them previously reported as natural products. The epoxide product easily undergoes an intra-molecular attack of the phenolic hydroxyl against the epoxide group carbons to produce either a benzofuran or a chromane derivative. When dissolved in methanol-water mixture at room temperature the epoxide is completely solvolyzed to give the corresponding diol (hydrolysis) or vicinal hydroxyl-methoxy (methanolysis) derivative. All the compounds involved in the above reactions were characterized by IR, Raman, H NMR and UV–vis spectroscopies, and by mass spectrometry. Density functional theory (DFT) computations were used to optimize the structure conformations. The optimized structures were further subjected to a Natural Bond Orbital (NBO) and electrostatic potentials analysis. The crystal structures of the title compounds (for short, **3** and **4** respectively) were determined by X-ray diffraction methods. Compound **3** crystallizes in the triclinic *P*-1 space group with $a = 6.4289$ (6) Å, $b = 8.7120$ (6) Å, $c = 10.952$ (1) Å, $\alpha = 92.280$ (7)°, $\beta = 95.738$ (7)°, $\gamma = 103.973$ (7)°, and $Z = 2$ molecules per unit cell and **4** in the monoclinic *P*₂₁/*c* space group with $a = 11.2891$ (6) Å, $b = 9.1902$ (4) Å, $c = 12.4272$ (7) Å, $B = 113.689$ (7)°, and $Z = 4$. In **3** neighboring molecules are linked to each other by OH⋯O (keto) bonds giving rise to a polymeric structure. In **4** the OH group is a bifurcate H-bond donor. It forms a weak intra-molecular OH⋯O (furan) bond and also a much stronger inter-molecular O–H⋯O (keto) bond giving rise to a zig-zag polymeric structure. A detailed analysis of the solid state molecular interactions of compounds **3** and **4** has been performed using Hirshfeld surface analysis and their associated 2D fingerprint plots.

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1. Introduction

Chromanes and benzofurans are characteristic metabolites of certain tribes of the Asteraceae family [1]. They are frequently found in several widely distributed American genera such as

Senecio, *Ageratina*, *Liatris*, *Encelia*, *Eupatorium*, *Baccharis*, *Verbesina* and *Flourensia*, and have aroused great interest because of their numerous biological activities such as antimicrobial, allergenic, plant growth inhibitory, pro-apoptotic, and anti-proliferative against cancer cell lines [2].

Benzopyrans (chromanes) derivatives and, particularly, those with a 2,2-dimethyl-2*H*-benzopyran moiety are present in thousands of natural products with a wide range of biological activities [3]. These plant metabolites generally exhibit low cellular toxicity and good membrane permeability which makes them ideal as drug template. Thus, several 2,2-dimethyl-2*H*-benzopyrans exhibit

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powerful antitumor activity [4–6] and HIV-1 reverse transcriptase inhibition [7,8]. Consequently, structural analysis at molecular and supra-molecular levels of natural chromanes is of great interest because they can be used as starting compounds to prepare novel drugs with improved pharmaceutical profile. Recently, we have reported the synthesis and spectroscopic characterization of 6-acetyl-2,2-dimethyl-chromane; this compound was obtained from 4-hydroxy-3-(3-methyl-2-butenyl)-acetophenone (4-HMBA) (**1**), the main secondary metabolite of *Senecio nutans* (Asteraceae), a medicinal plant of northwestern Argentina [9].

The molecular design intended to mimic the complex structures and processes found in nature is known as “bio-inspired chemistry” or “bio-mimetic chemistry”. Several reports have been published on the biosynthetic origin of benzofurans and chromanes in plants where *p*-hydroxyacetophenone derivatives have been proposed as precursors of benzofurans and chromanes [1,10–13]. In this sense we have speculated that 4-HMBA epoxide (**2**) would be a useful intermediate for synthesizing benzofurans and chromanes. In fact, reaction of 4-HMBA (**1**) with *m*-CPBA gave a mixture of epoxide **2** (32.6%) together with chromane **3** (20.9%) and benzofuran **4** (40.5%). The latter two compounds derive from an intra-molecular nucleophilic attack of the phenolic hydroxyl at the epoxide carbons. When this mixture was dissolved in methanol-water solution to be analyzed by preparative HPLC, a progressive decrease in the peak corresponding to the epoxide **2** until its complete disappearance and the appearance of two new compounds, later identified as the phenol-diol **5** and the methoxy-derivative **6**, was evident after a few days. Clearly phenol-diol **5** and methoxyderivative **6** were formed by solvolysis (hydrolysis and methanolysis, respectively) of epoxide **2**. Three of the four compounds obtained in this work were previously reported as natural products, namely 2,2-dimethyl-3-hydroxy-6-acetylchromane (**3**) in the aerial parts of *Helicrysum-stoechas* [14], 10,11-dihydro-10-hydroxytremetone (**4**) in the leaves of *Fitchiaspeciosa* [15], and 3-(2,3-dihydroxyisopentyl) 4-hydroxyacetophenone (**5**) in the aerial parts of *Werneriaciliolata* [16]. It should be noted here that all the compounds obtained in this work are racemates whereas both the natural benzofuran **4** and the diol **5** are the left-handed enantiomers [15,16] hence indicating that the reaction is enzymatically controlled in the plant. The optical rotation of natural chromanol **3** was not reported [14].

The present work reports a bio-mimetic synthesis of natural chromanes and benzofurans by epoxidation of the antifungal metabolite 4HMBA (**1**) [17,18]. The products obtained were characterized using different spectroscopic techniques such as infrared absorption, Raman dispersion, UV–visible, ¹H nuclear magnetic resonance (NMR), and mass spectrometry (MS). In addition, for the structural isomers (RS)-2,2-dimethyl-3-hydroxy-6-acetylchromane (**3**), (RS)-10,11-dihydro-10-hydroxytremetone (**4**) and (RS)-3-(2,3-dihydroxy-isopentyl)-4-hydroxyacetophenone (**5**), the crystal structures have been determined by single crystal X-ray diffraction methods. The experimental data was correlated with theoretical calculations using DFT methods and different basis sets. The intermolecular interactions in the crystal lattice were evaluated through Hirshfeld surface analysis. The geometry of a Hirshfeld surface reflects the relationship between different atoms and intermolecular contacts present in the crystal. These surfaces are supported by 2D fingerprint plots which quantify the nature and type of intermolecular interactions in the solid.

2. Experimental

2.1. Synthesis

To 4-HMBA (**1**) (1.224 g) in 30 mL of CHCl₃ cooled in ice was added in small portions *m*-chloroperbenzoic acid (MCPBA) (1.184 g,

77%) with magnetic stirring. The progress of the reaction was monitored by TLC. When the reaction was complete (disappearance of the spot corresponding to 4HMBA) the mixture was filtered out and then diluted with 50 mL of CHCl₃. The organic layer was washed with 10% Na₂SO₃ (2 × 10 mL), 5% NaHCO₃ (2 × 10 mL) and water (1 × 10 mL). After drying with anhydrous Na₂SO₄ and solvent evaporation, 768.7 mg of crude residue was obtained. CG-MS analysis showed a mixture constituted (listed by elution order) by **4** (40.5%), unidentified A (3.6%), **3** (20.9%), **2** (32.6%) and unidentified B (2.5%). The residue was dissolved in a mixture of methanol-water (55:45) to be processed by semi-preparative HPLC using a C18 column (5 μ; 10 mm × 250 mm) with methanol-water 55:45 as elution solvent (isocratic), flow at 2.0 mL min⁻¹. After a few injections, a progressive decrease in the peak corresponding to the epoxide **2** and the simultaneous appearance of two new compounds later identified as the phenol-diol **5** and the methoxy-derivative **6** was evident. The hydro-methanolic solution was then set aside at room temperature and monitored by HPLC every week. The peak corresponding to epoxide **2** disappeared completely after four weeks and the chromatogram showed four major components which were collected separately to yield (by elution order): **5** (73.5 mg), **6** (34 mg), **4** (173 mg) and **3** (122 mg) (Scheme 1). Chromane **3**, benzofuran **4** and phenol-diol **5** were recrystallized from ethanol.

2.1.1. Compound 3: 2,2-dimethyl-3-hydroxy-6-acetyl-chromane (racemic)

Needles (122 mg), mp: 102.4 °C (from ethanol). ¹H NMR (200 MHz, CDCl₃) δ 7.75 dd (1H, 9.3 and 2.2 Hz, H-7), 7.73 d (1H, 2.2 Hz, H-5), 6.85 d (9.2 Hz, H-8), 3.86 dd (5.8 and 4.9 Hz, H-3), 3.10dd (1H, 16.8 and 4.9 Hz, H-4a), δ 2.83 dd (1H, 16.8 and 5.8 Hz, H-4b), δ 2.54 s (3H, CH₃–CO), δ 2.18 s (br) (1H, OH), δ 1.38 s and 1.35 s (3H each, gem-dimethyl group), in agreement with published data [14]. EIMS: *m/z* (rel. int.%) [M]⁺ 220 (40), 205 (7), 187 (10), 163 (9), 162 (9), 149 (52), 119 (11), 107 (29), 91 (12), 77 (21), 71 (32), 57 (10), 51 (9), 43 (100).

2.1.2. Compound 4: 10,11-dihydro-10-hydroxytremetone (racemic)

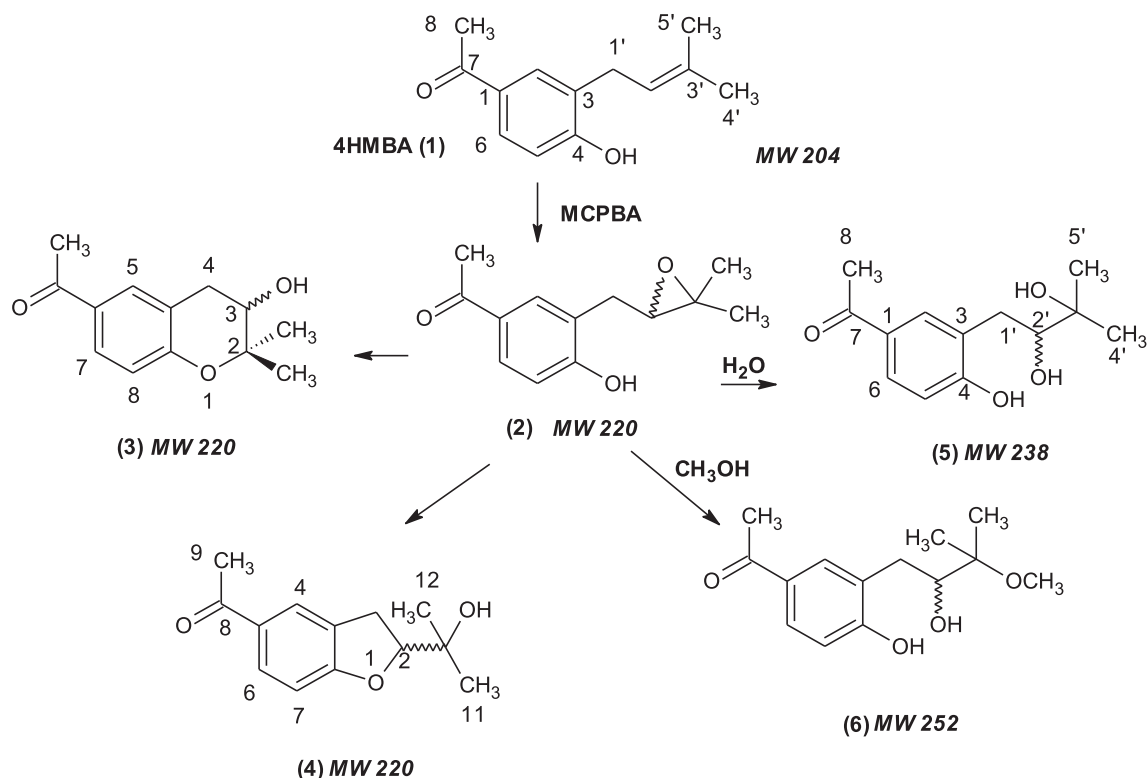
Needles (173 mg), mp: 87.1 °C (from ethanol). EIMS: *m/z* (rel. int.%) [M]⁺ 220 (17), 205 (2), 202 (4), 187 (13), 162 (63), 147 (71), 133 (6), 119 (85), 91 (23), 77 (9), 65 (6), 59 (74), 51 (7), 43 (100). ¹H NMR (200 MHz, CDCl₃): δ 7.83 s (br) (1H, H-4), 7.81 dd (1H, 8 and 1.5 Hz, H-6), 6.82 d (1H, 8 Hz, H-7), 4.72 t (1H, 9 Hz, H-2), 3.22 d (2H, 9 Hz, H-3a,b), 2.54 s (3H, H-9), 1.25 s and 1.23 s (3H each, H-4' and H-5) in agreement with published data [15].

2.1.3. Compound 5: 3-(2,3-dihydroxy-isopentyl)-4-hydroxyacetophenone (racemic)

Crystals (73 mg), mp: 135 °C (from ethanol). EIMS: *m/z* (rel. int.%) [M]⁺ 238 (4), 220 (5), 205 (2), 187 (2), 180 (18), 165 (6), 163 (7), 150 (25), 149 (29), 137 (52), 119 (12), 107 (21), 91 (11), 77 (16), 71 (17), 59 (39), 43 (100). ¹H NMR (200 MHz, CDCl₃): δ 7.79 d (1H, H-2), 7.70dd (1H, 8.3 and 2.1 Hz, H-6), 6.88 d (1H, 8.3 Hz, H-5), 3.60 dd (1H, 10.3 and 1.4 Hz, H-2'), 2.91 dd (1H, 14 and 1.4 Hz, H-1'a), 2.66 dd (1H, 14 and 10.3 Hz, H-1'b), 2.52 s (3H, H-8), 2.06 br s (1H, OH), 1.37 s and 1.24 s (3H each, H-11 and H-12) (for ¹H NMR in CD₃OD see Ref. [16]).

2.1.4. Compound 6: 3-(2-hydroxy-3-methoxy-isopentyl)-4-hydroxyacetophenone (racemic)

White solid (34 mg). EIMS: *m/z* (rel. int.%) [M]⁺ 252 (2), 220 (2), 205 (1), 187 (1.5), 180 (8), 150 (14), 149 (21), 107 (7), 73 (100), 43 (42). ¹H NMR (200 MHz, CDCl₃): δ 7.76dd (1H, 8.2 and 2.1 Hz, H-6), 7.73 d (1H, 2.1 Hz, H-2), 6.94 d (1H, 8.2 Hz, H-5), 3.74 dd (1H, 9.6 and 1.5 Hz, H-2'), 3.24 s (3H, OCH₃), 2.83dd (1H, 14.5 and 9.6 Hz, H-1'a),



Scheme 1. Synthesis of 4HMBA (1) derivatives. *Epoxide 2 is unstable at room temperature: a nucleophilic attack of the phenolic hydroxyl at the epoxide carbons yields chromane 3 and benzofuran 4 while dissolution in methanol/water 45:55 gives the solvolysis products 5 and 6.

2.68dd (1H, 14.5 and 1.5 Hz, H-1'b), 2.54 s (3H, H-8), 1.25 s and 1.20 s (3H each, H-4' and H-5'); ¹³C NMR (CDCl₃): δ 197.2 s (C-7), 160.9 s (C-4), 131.7 d (C-2), 129.9 d (C-6), 129.7 s (C-1), 126.2 s (C-3), 117.2 d (C-5), 79.2 d (C-2'), 77.1 s (C-3'), 49.1 q (OCH₃), 34.6 t (C-1'), 26.2 q (C-8), 20.4 q and 18.2 q (C-4' and C-5').

2.2. Characterization techniques

The crystal melting points were determined using Differential Scanning Calorimetry (DSC) technique. The measurement was performed with a differential scanning calorimeter Perkin Elmer Pyris DSC 6 using 1.150 mg of powdered sample sealed in aluminum pans with a mechanical crimp. Temperature and heat flow calibrations were made with standard samples of indium at its melting transition. Enthalpy changes associated with the melting point of the sample in study (ΔH) were directly obtained from the DSC data by integrating the anomalous peak in the baseline subtracted curve. The entropy change relative to the phase transition was finally determined using the relationship $\Delta S = \Delta H/T$.

¹H NMR spectra were recorded on a Bruker AC (200 MHz) spectrometer. Sample was dissolved in CDCl₃ and tetramethylsilane (TMS) was used as internal standard. Chemical shifts were recorded in δ (ppm) values relative to TMS and *J* values are expressed in Hertz.

The GC-MS analysis was carried out with a 5973 Hewlett Packard selective mass detector (quadrupole), source 70 eV, coupled to a HP 6890 GC fitted with a HP-5MS column (5% phenyl-methylsiloxane, 30 m \times 0.25 mm; film thickness 0.25 μ m) with helium as carrier gas (1.0 mL/min; constant flow). The oven was programmed for 150 °C (0 min), 150°-180° (3 °C/min) and 234° (3 min). The sample was dissolved in CHCl₂ and the injection volume was 0.1 μ L. Injector and detector temperatures were kept at 250 °C and 270 °C, respectively. Injection port was kept at 250 °C,

GC-MS interphase at 275 °C, ion source 230 °C, and MS Quad at 150 °C.

The FTIR absorption spectra of the solid state compounds (in KBr pellets) were recorded in the 4000–400 cm⁻¹ region at room temperature on a Perkin-Elmer GX1 Fourier Transform infrared spectrometer with 2 cm⁻¹ of spectral resolution. The Raman dispersion spectra of the solids were recorded at room temperature in the 3500–50 cm⁻¹ range with a ThermoScientific DXR Raman microscope.

UV–visible spectra were obtained on a Shimadzu 160A spectrophotometer. For this purpose, 6.1 mg of compound 3 and 6.5 mg of compound 4 were dissolved in 10 mL ethanol 96° and from this mother solution appropriate dilutions were obtained with the same solvent. The spectra were recorded between 800 and 200 nm.

2.3. X-ray diffraction data and structure refinement of compounds 3 and 4

The measurements were performed on an Oxford Xcalibur Gemini, Eos CCD diffractometer with graphite-monochromated CuK α ($\lambda = 1.54184$ Å) radiation. X-ray diffraction intensities were collected (ω scans with θ and κ -offsets), integrated and scaled with CrysAlisPro [19] suite of programs. The unit cell parameters were obtained by least-squares refinement (based on the angular settings for all collected reflections with intensities larger than seven times the standard deviation of measurement errors) using CrysAlisPro.

Data were corrected empirically for absorption employing the multi-scan method implemented in CrysAlisPro. The structures were solved by direct methods with the SHELXS program of the suite SHELX package [20] and the corresponding molecular models developed by alternated cycles of Fourier methods and full-matrix least-squares refinement with SHELXL of the same suit of program.

All hydrogen atoms were located in a difference Fourier map phased on the heavier atoms and refined at their found positions with isotropic displacement parameters. The optimized methyl H-positions converged to staggered conformations. Crystal data and structure refinement results for both compounds are summarized in Table 1. Crystallographic structural data have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Enquiries for data can be direct to: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK, CB2 1EZ or (e-mail) deposit@ccdc.cam.ac.uk or (fax) +44 (0) 1223 336033. Any request to the Cambridge Crystallographic Data Centre for this material should quote the full literature citation and the reference number CCDC 1541924 (**3**) and CCDC 1541925 (**4**).

2.4. Computational details

Theoretical calculations were performed using the Gaussian 03 program [21]. They were based on the gradient corrected Density Functional Theory (DFT) with the three-parameter hybrid functional (B3) [22] for the exchange part and the Lee-Yang-Parr (LYP) correlation function [23]. Scans of the potential energy curves were carried out at the B3LYP/6-31G (d,p) approximation. Final molecular conformation optimizations and vibration frequencies were computed employing the 6-311++G (d,p) basis set. The calculated vibrational properties correspond, in all cases, to potential energy minima with no imaginary values for the frequencies. Electronic transitions were calculated within the Time-Dependent Density Functional Theory (TD-DFT) [24] in gas phase and taking into account implicitly the solvent effect (ethanol) at B3LYP/6-311 + G (2d,p) approximation. The ¹H and ¹³C NMR chemical shifts were calculated at the B3LYP/6-311 + G (2d,p) level by the gauge-including atomic orbital (GIAO) method [25] using the corresponding TMS shielding, calculated at the same

level of theory. The natural bond orbital (NBO) analysis for the molecules was performed at B3LYP/6-311++G (d,p) approximation by means the NBO 3.1 program implemented in the Gaussian 03 package.

2.5. Hirshfeld surface analysis

Hirshfeld surfaces and their associated 2D fingerprint plots were constructed using CrystalExplorer 3.1 software [26]. The 3D d_{norm} surfaces were mapped over a fixed color scale of -0.24 (red) to 0.93 Å (blue). Molecular Hirshfeld surfaces in the crystal structure are constructed taking into account the electron distribution calculated as the sum of spherical atom electron densities [27,28]. The Hirshfeld surface enclosing a molecule is defined by points where the contribution to the electron density from the molecule of interest is equal to the contribution from all the other molecules. For each point on that isosurface two distances are defined: d_e , the distance from the point to the nearest nucleus external to the surface, and d_i the distance to the nearest nucleus internal to the surface. The normalized contact distance (d_{norm}) based on both d_e and d_i and the vdW radii of the atom, given by eq. (1) enables identification of the regions of particular importance to intermolecular interactions [28]. A color scale of red (shorter than vdW separation)-white (equal to vdW separation)-blue (longer than vdW separation) was used to visualize the intermolecular contacts.

$$d_{norm} = \frac{d_i - r_i^{vdW}}{r_i^{vdW}} + \frac{d_e - r_e^{vdW}}{r_e^{vdW}} \quad (1)$$

The combination of d_e and d_i in the form of a 2D fingerprint plot provides summary of intermolecular contacts in the crystal [27]. The 2D fingerprint plots were displayed by using the translated 0.6 – 2.6 Å range and including reciprocal contacts.

Table 1
Crystal data and structure refinement results for compounds **3** and **4**.

Compound	(3)	(4)
Empirical formula	C ₁₃ H ₁₆ O ₃	C ₁₃ H ₁₆ O ₃
Formula weight	220.26	220.26
Temperature (K)	293 (2)	293 (2)
Wavelength (Å)	1.54184	1.54184
Crystal system	Triclinic	Monoclinic
Space group	P-1	P2 ₁ /c
Unit cell dimensions		
a (Å)	6.4289 (6)	11.2891 (6)
b (Å)	8.7120 (6)	9.1902 (4)
c (Å)	10.952 (1)	12.4272 (7)
α (°)	92.280 (7)	90.00
β (°)	95.738 (7)	113.689 (7)
γ (°)	103.973 (7)	90.00
Volume (Å ³)	590.96 (9)	1180.7 (1)
Z, calculated density (Mg/m ³)	2, 1.238	4, 1.239
Absorption coefficient (mm ⁻¹)	0.708	0.708
F (000)	236	472
Crystal size (mm ³)	0.142 × 0.238 × 0.312	0.138 × 0.289 × 0.368
θ-range (°) for data collection	5.24 to 70.99	4.28 to 72.33
Index ranges	$-7 \leq h \leq 7, -9 \leq k \leq 10, -13 \leq l \leq 10$	$-13 \leq h \leq 11, -10 \leq k \leq 11, -15 \leq l \leq 15$
Reflections collected	3525	4677
Independent reflections	2247 [R (int) = 0.0176]	2300 [R (int) = 0.0223]
Observed reflections [I > 2σ(I)]	1817	1930
Completeness (%)	98.3 (to θ = 70.99°)	98.7 (to θ = 72.33°)
Refinement method	Full-matrix least-squares on F ²	Full-matrix least-squares on F ²
Data/restraints/parameters	2247/0/209	2300/0/209
Goodness-of-fit on F ²	1.046	1.053
Final R indices ^a [I > 2σ(I)]	R1 = 0.0477, wR2 = 0.1338	R1 = 0.0422, wR2 = 0.1158
R indices (all data)	R1 = 0.0567, wR2 = 0.1481	R1 = 0.0503, wR2 = 0.1264
Largest diff. peak and hole (e.Å ⁻³)	0.193 and -0.185	0.164 and -0.206

^a $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$, $wR_2 = [\sum w (|F_o|^2 - |F_c|^2)^2 / \sum w (|F_o|^2)^2]^{1/2}$.

3. Results and discussion

3.1. Description of X-ray crystal structure of compounds **3** and **4**

ORTEP [29] plots of solid state compounds **3** and **4** are displayed in Fig. 1 and their X-ray geometrical parameters such as bond lengths, angles and dihedral angles, together with the computed values at B3LYP/6-311++G (d,p) approximation are shown in Tables 1 and 2, respectively. Observed bond lengths and angles agree with Organic Chemistry's rules. In particular, C–C bond lengths in the phenyl ring are in the range from 1.367 (2) to 1.401 (2) Å in **3** and from 1.378 (2) to 1.406 (2) Å in **4**, as expected for a resonant bond structure. Single C–C bond distances are in the range from 1.485 (2) to 1.536 (2) Å for **3** and in the 1.483(2)–1.532(2) Å interval for **4**. C=O distance in the ketone group is 1.213 (2) Å for **3** and 1.222 (2) Å for **4**. Hetero-cycle ring C (sp²)-O and O–C (sp³) bond lengths are respectively 1.356 (2) and 1.464 (2) Å in **3**, and 1.356 (2) and 1.467 (2) Å in **4**. All the geometrical parameters related to the chromane moiety are in accordance with the values previously reported for 6-acetyl-2,2-dimethyl-chromane [9].

In the structure of **3**, each molecule participates in four hydrogen bonds and these inter-molecular interactions necessarily dominate the crystal packing of the compound. In the crystal packing of **3**, neighboring molecules related by a unit cell translation along *c*-axis are linked to each other through intermolecular O–H...O (keto) bonds [d (OH...O) = 2.014 Å, angle (O–H...O) = 171.7°] giving rise to a polymeric structure along the crystal *c*-axis (See Fig. 2). The crystal structure of **3** features the characteristic pattern of the R_s⁴(22) cyclic hydrogen bond interaction between the O–H...O (keto) and C–H...O (pyrane). Two molecules are also linked between C–H...O (pyrane) hydrogen bonds into centre-symmetric dimers stacked, giving R_s⁴(8) graph-set motif as shown in Fig. 2a.

The supramolecular assembly also includes the existence of one intermolecular C–H...π interaction involving the benzene (Cg2 centroid) ring and the H atom bounded to C (10) as can be seen in Fig. 2b. The C10–H...Cg2 interaction [symmetry code: 2-x,1-y,1-z] forms centre-symmetric dimers with an angle of 172°. The distance

Table 2

Experimental and calculated bond lengths (Å), bond angles (°), and dihedral angles (°) for compound **3**.

Parameters	Compound 3	
	Experimental ^a	Calculated ^b
<i>Bond lengths</i>		
C7–C8	1.494 (4)	1.519
C7=O14	1.213 (3)	1.219
C7–C1	1.485 (2)	1.493
C1–C2	1.399 (3)	1.406
C2–C3	1.386 (2)	1.381
C3–C4	1.401 (2)	1.403
C4–C5	1.400 (2)	1.402
C5–C6	1.387 (2)	1.395
C6–C1	1.393 (2)	1.398
C5–C11	1.507 (2)	1.511
C11–C10	1.513 (2)	1.522
C10–C9	1.536 (2)	1.550
C9–O15	1.464 (2)	1.458
C9–C12	1.513 (3)	1.526
C9–C13	1.513 (3)	1.531
C10–O16	1.421 (2)	1.427
C4–O15	1.356 (2)	1.362
<i>Bond angles</i>		
C8–C7–C1	119.8 (2)	118.9
C8–C7=O14	120.2 (2)	120.2
C1–C7=O14	120.0 (2)	120.9
C5–C11–C10	112.3 (1)	111.1
C4–O15–C9	117.7 (1)	118.9
O15–C9–C10	107.1 (1)	107.6
C9–C10–O16	111.7 (1)	112.2
O16–C10–C11	107.2 (1)	107.4
C13–C9–C12	112.2 (2)	111.2
<i>Dihedral angles</i>		
C8–C7–C1–C2	179.6 (2)	179.8
C8–C7–C1–C6	–1.5 (3)	0.4155
C11–C10–C9–O15	–60.5 (2)	–60.28

^a Experimental values determined by X-ray diffraction methods.

^b Calculated at B3LYP/6-311++G (d,p) approximation.

between the H and the Cg2 centroid is 2.964 Å.

In **4** the hydroxyl group serves a double stabilizing function acting as a bifurcate H-bond donor. It forms a weak and bent intra-

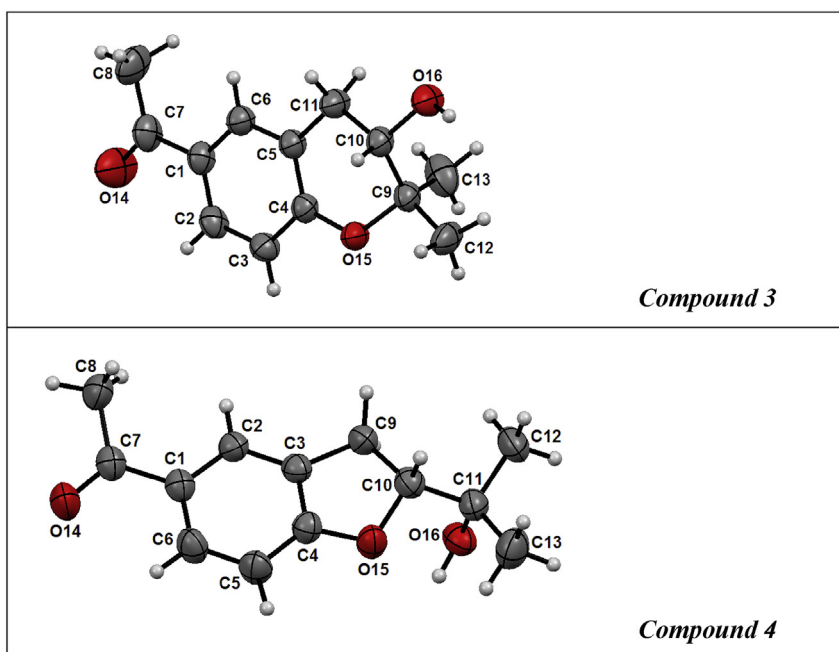


Fig. 1. ORTEP drawing of compounds **3** and **4** showing the labels of non-H atoms and their displacement ellipsoids at the 30% probability level.

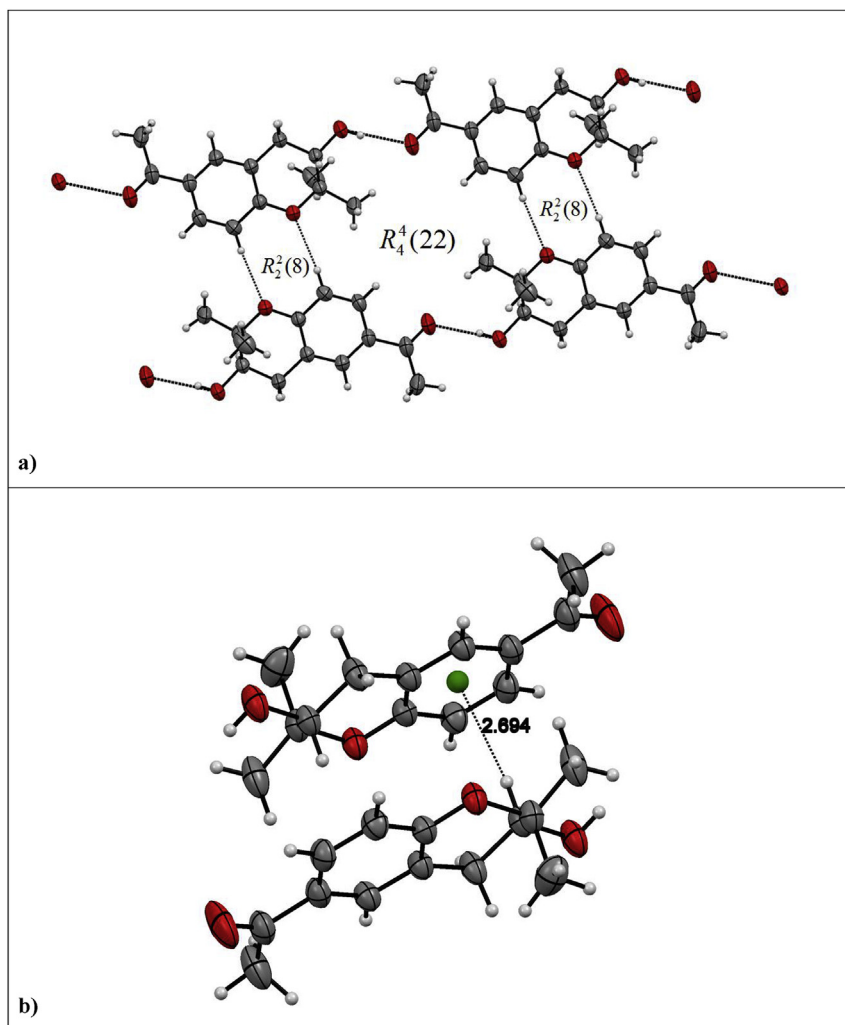


Fig. 2. (a) Crystal packing of compound **3** showing centre-symmetric dimers. Intermolecular hydrogen bonds are shown by dashed lines. (b) A view of the C–H \cdots π interaction showing Cg2 centroid formed by C1 to C6 of the benzene ring.

molecular OH \cdots O (furan) bond [$d(\text{OH}\cdots\text{O}) = 2.505 \text{ \AA}$, $\angle(\text{O}-\text{H}\cdots\text{O}) = 103.7^\circ$] and also links neighboring molecules (symmetry related through a glide plane) to each other by a much stronger inter-molecular O–H \cdots O (keto) bond [$d(\text{OH}\cdots\text{O}) = 2.051 \text{ \AA}$, $\angle(\text{O}-\text{H}\cdots\text{O}) = 151.8^\circ$], giving rise to a zig-zag polymeric structure that extends along the crystal *c*-axis (see Fig. 3).

3.2. Hirshfeld surface analysis

Hirshfeld surface analysis was performed to understand the nature of the molecular packing, highlighting the contribution of significant inter-molecular interactions that stabilize the observed crystal structure. Fig. 4 shows the Hirshfeld surfaces (d_{norm} surfaces) of compound **3**. The normalized contact distance (d_{norm}) based on both d_e and d_i , and the radii of the atom enable the regions indicating the intermolecular interactions. The active spots shown in d_{norm} surfaces characterize the hydrogen-bonding interactions. The large circular spots in deep red, which are visible on the d_{norm} surfaces are an indicator of hydrogen bonding contacts and other visible spots are due to H \cdots H interactions. The dominant H \cdots O and O \cdots H interactions are visualized in Hirshfeld surfaces by the bright red area labeled **1** and **4** in Fig. 4a and b. As was deduced from the crystal structure, these interactions produce a polymeric structure

as can be seen in Fig. 4d. The small amount of area and light color on the surface indicates weaker and longer contacts other than hydrogen bonds. The two red regions labeled **2** and **3** in the d_{norm}

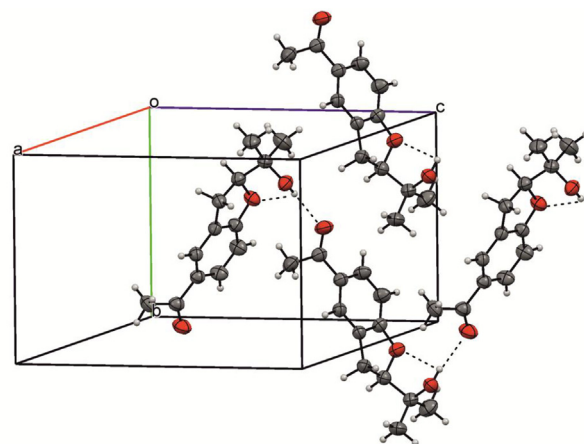


Fig. 3. Crystal packing of compound **4** showing a polymeric zig-zag structure along the *c*-axis. Intra- and inter-molecular interactions are shown in dash lines.

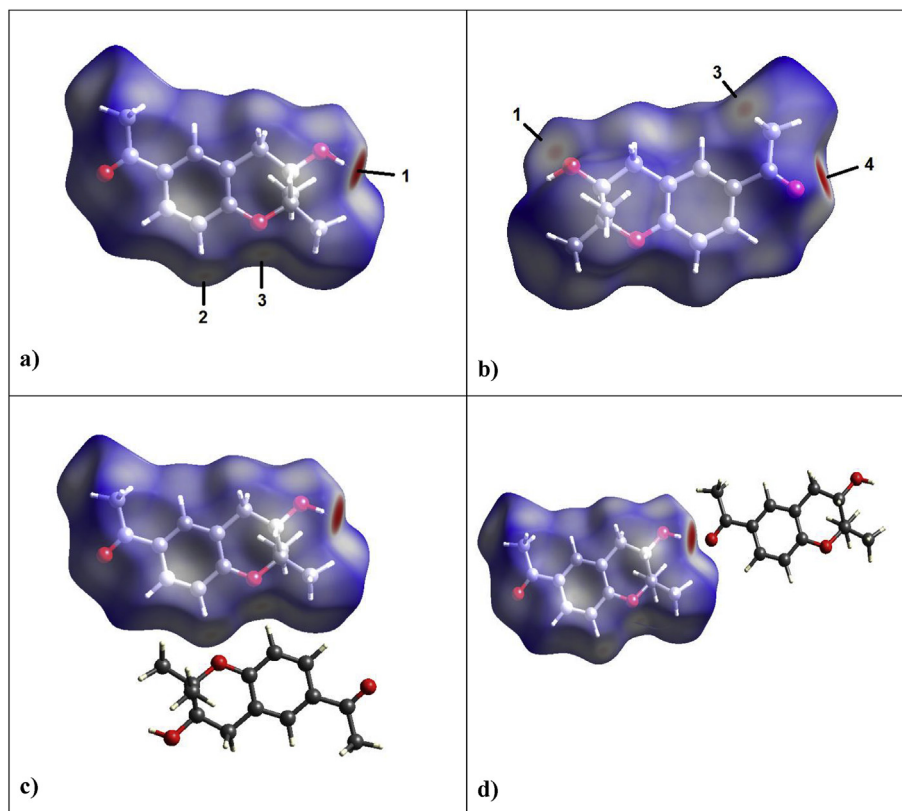


Fig. 4. Hirshfeld surface plots (d_{norm}) for compound **3**. In the first case, the molecule was rotated by 180° around the horizontal axis of the plot. Thermal ellipsoids drawn at the 50% probability level. Figure labeling is discussed in the text.

map are attributed to C–H \cdots O hydrogen bonds involving the acceptor O15 of the oxopyrane group belonging to two different molecules (see Fig. 4c). The red region located in the methyl groups labeled **3** in Fig. 4b is attributed to C–H \cdots C non-classical hydrogen bonds. The Hirshfeld surfaces mapped with shape index and curvedness for compound **3** are reported in the supplementary material. There is neither touching complementary pair of triangles for shape index surface nor large and green flat regions for curvedness surfaces which indicate that π - π stacking interactions are absent in the crystal packing of compound **3**.

Fig. 5 shows the Hirshfeld surface plots for compound **4**. The spots labeled as **1** and **2**, with the large and circular depressions (deep red) visible on the front and back views of the surfaces are indicative of hydrogen-bonding contacts. These interactions are attributed to O–H \cdots O (keto) interactions. The dominant interactions between C–H and the O atom from the hydroxyl group can be seen in the Hirshfeld surface as the red areas marked as **3** and **4** in Fig. 5. The interaction labeled **3** is assigned to the C–H \cdots O interaction between the hydrogen of the methyl from the acetyl group and the O from the hydroxyl whereas the area marked as **4** is attributed to the interaction between the hydrogen atom from the furan ring and the oxygen from the hydroxyl group. The small extent of area and light color of surface indicates weaker and longer contact other than hydrogen bonds.

Two dimensional (2D) fingerprint plots were obtained by calculating the distances from the Hirshfeld surface to the nearest nucleus inside the surface (d_i) to the outs of surface (d_e) to analyze the molecular interaction around the nearest neighbor molecules. In 2D plots, green regions show closer contacts and blue color indicates longer contacts. Complementary regions are visible in the fingerprint plots where one molecule acts as donor ($d_e > d_i$) and the other as acceptor ($d_e < d_i$). The fingerprint plots of the main

intermolecular interactions for both structures are shown in Fig. 6. The H \cdots H interaction (labeled as **1**) in compound **3** is 59.2%, whereas in **4** is 59.6%. These interactions have the major contribution to the crystal packing of both structures. The proportion of O \cdots H and H \cdots O interactions (labeled as **2**) comprising 11.8 and 10.0% of the Hirshfeld surface for each molecule of compound **3**. In **3**, the H \cdots O interactions are represented by a spike near a ($d_e + d_i$) sum of 1.85 Å in the bottom left (donor) area of the fingerprint plot (See Fig. 6), which represents the interaction between the hydrogen atom of the hydroxyl group and the carbonyl oxygen. Also, the interaction between oxygen of the pyrane ring interacts with the hydrogen of the benzene ring of another molecule. These interactions produce a three-dimensional network of hydrogen bonds. The O \cdots H interactions are represented by a spike near a ($d_e + d_i$) sum of 1.85 Å in the bottom right (acceptor) region of fingerprint plot, where carbonyl oxygen also acts as acceptor to the neighboring hydrogen atoms from the hydroxyl groups. These interactions represent the closest contacts in the structure and can be seen as a pair of large red spots on the d_{norm} surface (Fig. 4). O \cdots H interactions in compound **4** are represented by spikes near a ($d_e + d_i$) sum of 1.95 Å and represent the interaction between the hydrogen from the hydroxyl group and the O atom from the carbonyl group. The decomposed fingerprint plot shows C–H \cdots C hydrogen bonds of which C–H \cdots π interactions appears as a pair of characteristic wings around ($d_e + d_i$) sum of 3.1 and 3.0 Å in compounds **3** and **4**, respectively. The C \cdots H interactions correspond to 17.4% and 18.3% of total contribution to the Hirshfeld surface for compounds **3** and **4**, respectively.

3.3. Structural results derived from quantum chemical calculations

The optimized molecular structures calculated at B3LYP/6-

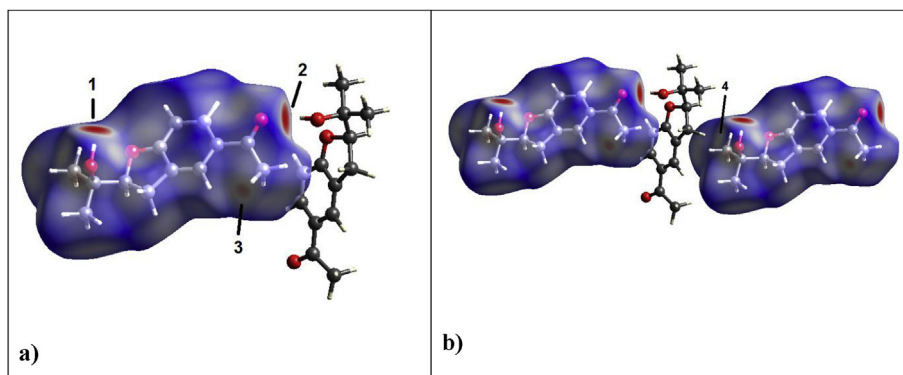


Fig. 5. Views of the Hirshfeld surfaces of compound **4** with thermal ellipsoids plotted at 50% level of probability. Labels indicated in the figures are discussed in the text.

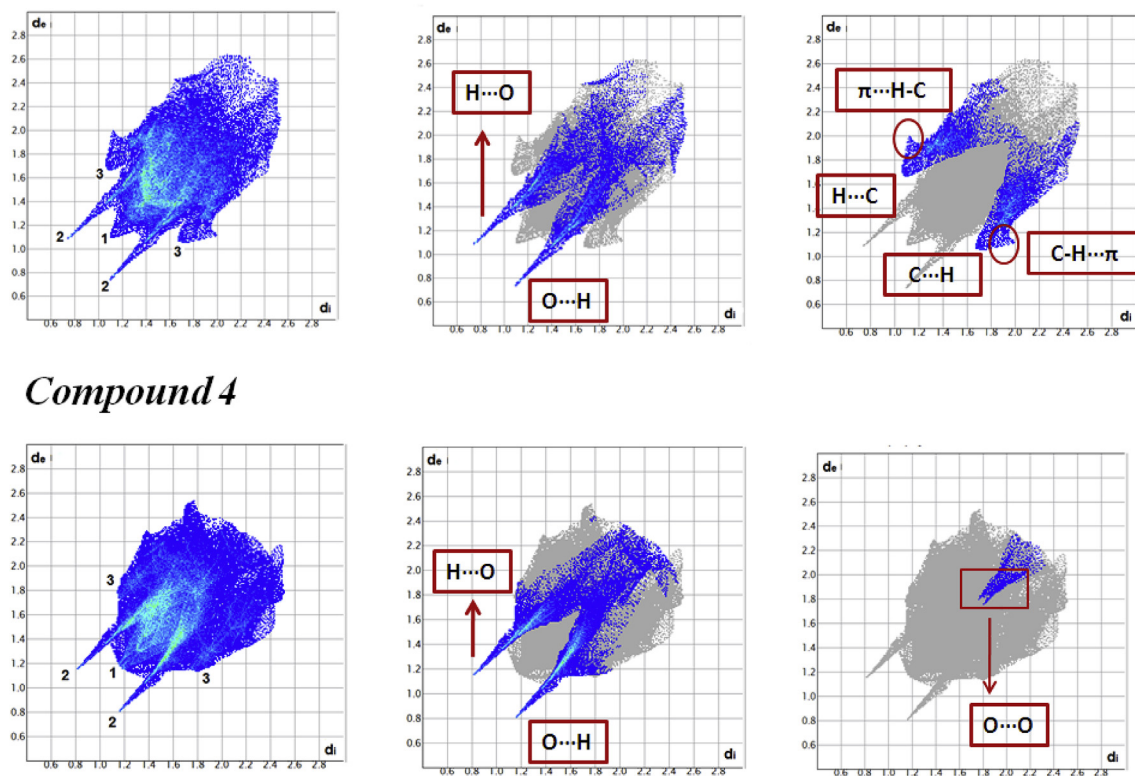


Fig. 6. Fingerprint plots for compounds **3** and **4**. Close contacts are labeled as: (1) H...H, (2) O...H and (3) C...H.

311++G (d,p) approximation for compounds **3** and **4** are shown in Fig. 7(a) and (b). The molecules are characterized primarily by a planar conformation. Tables 2 and 3 give a comparison between the

experimental values of the relevant geometrical parameters and the optimized molecular structures calculated at B3LYP/6-311++G (d,p) level. The agreement between the experimental and

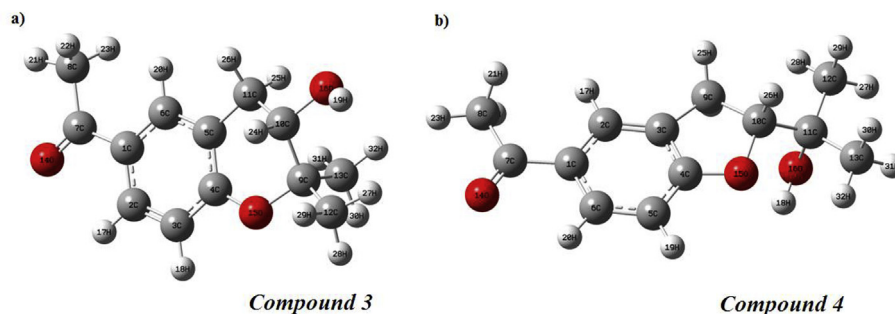


Fig. 7. Optimized molecular structures of **3** and **4** calculated at B3LYP/6-311++G (d,p) approximation.

Table 3
Experimental and calculated bond lengths (Å), bond angles (°), and dihedral angles (°) for compound **4**.

Parameters	Compound 4	
	Experimental ^a	Calculated ^b
<i>Bond lengths</i>		
C7–C8	1.507 (3)	1.519
C7=O14	1.222 (2)	1.219
C7–C1	1.483 (2)	1.494
C1–C2	1.406 (2)	1.408
C2–C3	1.378 (2)	1.384
C3–C4	1.392 (2)	1.395
C4–C5	1.385 (2)	1.391
C5–C6	1.381 (3)	1.390
C6–C1	1.396 (3)	1.405
C3–C9	1.506 (2)	1.509
C9–C10	1.532 (2)	1.547
C10–O15	1.467 (2)	1.468
C4–O15	1.356 (2)	1.361
C10–C11	1.527 (2)	1.541
C11–C13	1.521 (3)	1.535
C11–C12	1.519 (3)	1.529
C11–O16	1.429 (2)	1.434
<i>Bond angles</i>		
C8–C7–C1	118.8 (1)	118.8
C8–C7=O14	120.3 (2)	120.1
C1–C7=O14	120.9 (1)	121.0
C3–C9–C10	102.1 (1)	102.0
C9–C10–C11	116.9 (1)	116.6
C9–C10–O15	105.8 (1)	105.6
C10–O15–C4	107.5 (1)	107.9
C10–C11–O16	109.8 (1)	109.2
C13–C11–C12	110.9 (1)	110.8
<i>Dihedral angles</i>		
C8–C7–C1–C6	163.7 (2)	179.9
C8–C7–C1–C2	–15.1 (2)	–0.041
C3–C9–C10–O15	18.5 (1)	17.64
C9–C10–C11–O16	–56.0 (2)	–56.66
O15–C10–C11–O16	63.0 (1)	61.96

^a Experimental values determined by X-ray diffraction methods.

^b Calculated at B3LYP/6-311++G (d,p) approximation.

computed results is very good in all the groups of the molecules. The small differences between the calculated and experimental geometrical parameters are attributed to the fact that the theoretical calculations were performed with isolated molecules in gas phase whereas the experimental data were based on molecules in the solid state. The acetyl group of molecules **3** and **4** shows only a small distortion from the molecular plane: the C8–C7–C1–C2 and C8–C7–C1–C2 torsion angles are -179.8° and 0.4155° , respectively for compound **3** and -179.9° and -0.041° for compound **4**. The comparison of the X-ray data of compound **3** with those of the parent 6-acetyl-2,2-dimethyl chromane [9] indicates that the

presence of the hydroxyl group does not affect the extent of planarity in the phenyl ring and the acetyl group.

The Natural Bond Orbital (NBO) population analysis is an important tool to calculate donor \rightarrow acceptor interactions estimated by the second order perturbation theory [30,31]. The lone-pair electron at the carbonyl oxygen atom donates electronic density mainly to the vacant C1–C7 and C7–C8 anti-bonding orbitals via hyper-conjugative interactions of the type $LP_{\pi}O(14) \rightarrow \sigma^*C-C$ with energy values of 20.40 and 21.45 kcal mol⁻¹, respectively for compound **3** and 18.52 and 19.97 kcal mol⁻¹ for compound **4**. The mesomeric effect, reflected mainly by the $LP_{\pi}O(15) \rightarrow \pi^*C4-C5$ interactions are 28.03 and 28.52 kcal mol⁻¹ for compounds **3** and **4**, respectively. This type of interaction also leads to increased occupation numbers of the corresponding π^*C4-C5 orbitals. In the case of compound **3**, the occupation number is slightly larger (0.39e) than that in compound **4** (0.38e). The described increased population of the π^*C4-C5 orbital in compound **3** reduces the C4–C5 bond strength and, as a consequence, a bond lengthening (See Tables 2 and 3).

The total atomic charges of compounds **3** and **4** are obtained from natural population analysis at B3LYP/6-311++G (d,p) level are provided as Supplementary Information. The atomic charges obtained using the natural population analysis approach revealed that the more negative charge (-0.74 a.u.) is located at the O (16) atom of the hydroxyl group and the negative charges -0.57 and -0.56 are located at the O (15) and O (14) atoms, respectively for compound **3**. Similar results were obtained for compound **4**. The more negative charge on O (16) atom makes C (7) atom more positive and acidic (charge of $+0.56$). The negative charges mainly located on O (16), O (15) and O (14) atoms could interact with the positive part of a receptor. In addition, C (7) atom is the most positively charged part and could interact with the negatively charged part of a receptor easily.

In order to understand the sites for electrophilic and nucleophilic attacks, we resorted to molecular electrostatic potential (MEP) calculations [32,33]. MEP plots of compounds **3** and **4** generated at the optimized geometry of both molecules using GaussView 05 software are shown in the Supplementary Information. The red and blue regions of MEP represent the net negative and positive charges, respectively. For compound **3**, the red regions are mainly located on the oxygen atom of the carbonyl group and the oxygen atom of the hydroxyl group. The atomic charge analysis and MEP calculation confirmed that hydroxyl and carbonyl oxygen atoms are preferred sites for electrophilic attack. Similar results were obtained for compound **4**. It is evident from the MEP map for compound **3** that the region around the hydrogen atoms of the hydroxyl group is electron deficient (blue region), in accordance with NPA charges with a maximum positive value (0.46) for H (19)

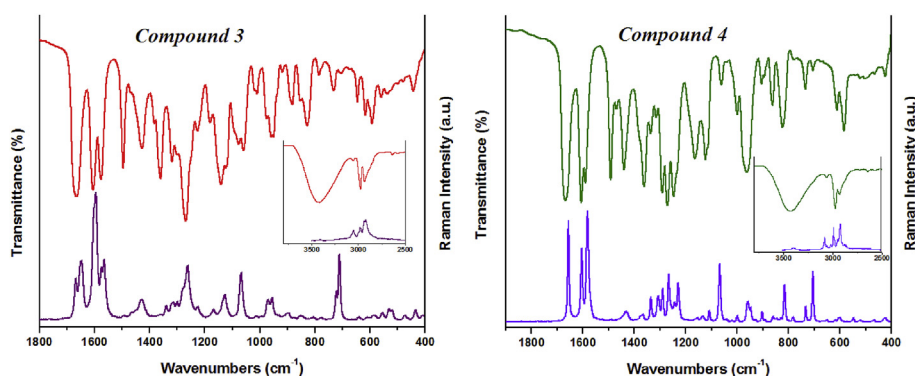


Fig. 8. Selected region of the IR and Raman spectra of compounds **3** and **4** in solid state. Inset: IR and Raman spectra of compounds **3** and **4** in the 3800–2500 cm⁻¹ region.

Table 4
Observed and calculated frequencies (in cm^{-1}) and tentative assignments of modes for compound 3.

Mode	Experimental		Calculated ^c			Tentative assignment ^{d,e}
	IR (solid) ^a	Raman (solid) ^b	Unscaled	Scaled	IR int	
1	3427 bd	—	3844	3779	41	ν O—H
2	—	3072 (12)	3203	3148	4	ν C—H (R1)
3	3056 vw	3055 (20)	3186	3132	2	ν C—H (R1)
4	3051 vw	3052 sh	3172	3118	7	ν C—H (R1)
5	—	3042 (14)	3141	3088	15	ν_a CH ₃ (CO)
6	—	—	3120	3067	17	ν_a CH ₃ (R2)
7	—	3003 (15)	3112	3059	25	ν_a CH ₃ (R2)
8	—	—	3109	3056	6	ν_a CH ₃ (R2)
9	—	2983 (27)	3103	3050	22	ν_a CH ₃ (R2)
10	—	—	3090	3037	9	ν_a CH ₃ (CO)
11	2979 w	2980 (26)	3071	3019	17	ν_a CH ₂ (R2)
12	—	—	3045	2993	10	ν_s CH ₃ (R2)
13	2935 w	2936 (39)	3034	2982	22	ν_s CH ₃ (R2)
14	—	2924 (41)	3033	2981	4	ν_s CH ₃ (CO)
15	2911 sh	2916 (37)	3027	2975	18	ν_s CH ₂ (R2)
16	2879 sh	2891 (19)	2996	2945	24	ν C10—H
17	1673 s	1668 (32)	1734	1704	258	ν C=O
18	1663 s	1648 (46)	1644	1575	106	ν C—C (R1) + δ C—H (R1)
19	1604 m	1600 (100)	1606	1539	142	ν C—C (R1) + δ C—H (R1)
20	1576 m	1574 (41)	1524	1459	42	δ_a CH ₃ (R2) + δ C—H (R1)
21	1495 m	—	1514	1450	6	δ_a CH ₃ (R2)
22	1434 sh	—	1503	1440	4	δ_a CH ₃ (R2)
23	1427 m	1429 (16)	1493	1430	9	δ CH ₂ (R2) + δ_a CH ₃ (R2)
24	—	—	1484	1422	2	δ_a CH ₃ (R2) + δ CH ₂ (R2)
25	—	—	1482	1420	2	δ CH ₂ (R2) + δ_a CH ₃ (R2)
26	—	—	1481	1419	12	δ_a CH ₃ (CO)
27	—	—	1472	1410	15	δ_a CH ₃ (CO)
28	1383 w	—	1450	1389	26	ν C—C (R1) + δ C—H (R1) + ω CH ₂
29	1366 sh	—	1423	1363	6	δ OCH + δ_s CH ₃ (R2) + δ O—H
30	1360 m	—	1415	1356	14	δ C—H (R1) + δ_s CH ₃ (R2)
31	—	—	1402	1343	22	δ_s CH ₃ (R2)
32	—	1339 (11)	1385	1327	57	δ_s CH ₃ (CO)
33	1318 w	1316 (13)	1374	1316	3	δ OCH
34	1301 vw	1300 (14)	1350	1293	28	ν C—C (R1)
35	1267 vs	1279 (24)	1335	1279	64	δ C—H (R1) + ω CH ₂ (R2) + δ O—H
36	1251 sh	1250 (43)	1301	1246	56	ω CH ₂ (R2) + δ C—H (R1)
37	—	—	1286	1232	85	$\tau\omega$ CH ₂ + δ C—H (R1) + δ O—H
38	1226 w	1226 (10)	1282	1228	220	ν C4—O15 + δ C—H (R1)
39	—	—	1271	1218	43	δ C—H (R2) + ν C—O + ρ CH ₂
40	—	—	1263	1210	47	ν C9—C10 + ρ CH ₃ (R2)
41	1180 w	—	1221	1170	63	δ COH + ν_a C(CH ₃) ₂
42	—	1169 (8)	1190	1140	1	ν C5—C11 + δ C—H (R1)
43	1140 m	1143 sh	1168	1119	153	ρ CH ₂ + ρ CH ₃ (R2)
44	1122 m	1127 (19)	1162	1113	6	ρ CH ₃ (R2) + δ C—H (R1)
45	1089 sh	—	1134	1086	103	δ C—H (R1)
46	1077 w	—	1092	1046	6	ρ CH ₃ (CO) + δ C—H (R1)
47	—	1068 (37)	1079	1034	157	ν C10—O16
48	1059 w	—	1055	1011	4	ν C9—C10 + δ O—H
49	1010 vvw	—	1042	998	1	ρ CH ₃ (CO)
50	975 vw	970 (16)	1027	984	16	ρ CH ₃ (R2)
51	958 w	955 (17)	996	954	3	γ C—H (R1)
52	948 w	—	988	947	19	γ C—H (R1)
53	937 sh	930 (3)	961	920	48	ν C9—O15 + ρ CH ₃ (R2) + γ C—H (R1)
54	917 vvw	913 (3)	959	919	69	ν C7—C8 + ρ CH ₃ (CO)
55	—	898 (5)	943	903	7	ν_s C(CH ₃) ₂
56	881 w	—	929	889	3	δ CCC (R1) + γ C—H (R1)
57	—	—	903	865	8	γ C—H (R1)
58	853 vw	852 (3)	886	849	12	ν C9—O15
58	829 w	—	853	817	29	γ C—H (R1)
60	785 vw	780 (2)	792	759	3	δ O15—C9—C12 + δ CCC (R1)
61	732 vw	722 (41)	745	714	2	γ CCC (R1) + γ C—H (R1)
62	—	710 (52)	732	701	3	δ CCC (R1) + ν_s C(CH ₃) ₂
63	703 vw	—	713	683	1	δ COC (R2)
64	646 vw	641 (2)	652	625	11	δ CCC (R1) + δ CCC (R2)
65	617 vw	612 (2)	626	600	8	γ C=O + γ CCC (R1) + γ C—H (R1)
66	592 vw	590 (3)	611	585	26	δ CC=O + δ CCC (R1)
67	560 vvw	556 (5)	555	532	1	δ CCC (R2)
68	536 vvw	531 (9)	531	509	10	δ C10—C9—C12
69	524 sh	520 (8)	524	502	3	γ CCC (R1) + γ C=O
70	479 vvw	474 (3)	500	479	6	δ CCC (R1)
71	—	—	454	435	1	γ CCC (R1) + γ C—H (R1)
72	443 vw	435 (8)	442	423	5	δ COC (R2) + δ C(CH ₃) ₂
73	—	408 (3)	427	409	1	δ CCO (R2) + δ C8—C7—C1

(continued on next page)

Table 4 (continued)

Mode	Experimental		Calculated ^c			Tentative assignment ^{d,e}
	IR (solid) ^a	Raman (solid) ^b	Unscaled	Scaled	IR int	
74	–	388 (4)	413	396	12	δ C8–C7–C1 + γ COC (R2)
75	–	375 (5)	364	349	1	δ C(CH ₃) ₂
76	–	304 (6)	315	302	2	γ CCC (R2) + γ O–H
77	–	–	296	284	1	τ CH ₃ (R2)
78	–	–	294	282	36	γ O–H
79	–	262 (8)	276	264	14	τ O–H
80	–	–	270	259	56	τ CH ₃ (R2) + τ O–H
81	–	–	254	243	4	τ C9–C10
82	–	222 (9)	236	226	14	τ CH ₃ (R2)
83	–	–	217	208	<1	τ CH ₃ (R2) + τ O–H
84	–	176 (20)	192	184	3	τ C5–C11 + τ CH ₃ (R2)
85	–	–	142	139	1	τ CH ₃ (CO)
86	–	–	140	134	2	τ CH ₃ (CO)
87	–	125 (42)	125	120	1	τ CCCC (R1) + τ CCCC (R2)
88	–	–	105	101	1	τ CCCC (R1) + τ COCC (R2)
89	–	–	50	48	4	τ C7–C1
90	–	–	46	44	1	τ CCOC (R2)

^a sh: shoulder, s: strong, w: weak, m: medium, v: very.

^b Relative band heights in parenthesis.

^c Calculated at B3LYP/6-311++G (d,p) approximation. Scale factor used 0.983 for frequencies higher than 1700 cm⁻¹ and 0.958 for frequencies lower than 1700 cm⁻¹.

^d ν : stretching, δ : in-plane bending, γ : out-of-plane bending, ρ : rocking, ω : wagging, $\tau\omega$: twisting, τ : torsional modes.

^e See Fig. 7 for atoms numbering scheme. R1: benzene ring, R2: pyrane ring.

atom. The blue region is also observed around the hydrogen atom of the hydroxyl group in compound **4**.

3.4. Vibrational results

The FTIR and Raman spectra for the solid state compounds **3** and **4** are shown in Fig. 8. The observed and computed frequencies (B3LYP/6-311++G (d,p)), together with the corresponding assignment of bands, are given in Tables 4 and 5. A tentative assignment of the observed bands in the IR and Raman spectra were carried out by comparison with theoretical results and also with the frequencies reported for related compounds. A very good agreement between the experimental and calculated vibration data was observed. Only the normal modes of the most relevant characteristic functional groups of the molecules will be discussed.

3.4.1. Assignment of bands

3.4.1.1. OH modes. For compound **3**, the very broad IR absorption band centered at 3427 cm⁻¹ is assigned to the O–H stretch. This mode was calculated at 3844 cm⁻¹ at the B3LYP/6-311++G (d,p) approximation. For compound **4**, this mode appears as a broad band located at 3435 cm⁻¹ in the IR spectrum and at 3389 cm⁻¹ in Raman. The strong hydrogen bonding present in the solid state of this compound red-shifts the ν (O–H) frequency. The O–H in-plane bending mode is observed in the IR spectra at 1180 cm⁻¹ (**3**) and 1292 cm⁻¹ (**4**). This mode appears at 1289 cm⁻¹ in the Raman spectrum of compound **4**. The calculated frequencies for both compounds appear in Tables 4 and 5.

3.4.1.2. CH₃ modes. The Raman dispersion bands observed at 3042, 3003 and 2983 cm⁻¹ in compound **3** are assigned to CH₃ asymmetric stretching modes. In compound **4** these bands appear at 2976 cm⁻¹ in the IR spectrum and at 3045, 3006, 2977, 2968 and 2915 cm⁻¹ in Raman. For **3** the CH₃ symmetric stretching modes are observed at 2935 cm⁻¹ in the IR spectrum and at 2936 and 2924 cm⁻¹ in Raman. For compound **4**, the bands located at 2909 and 2865 cm⁻¹ in the Raman spectrum are assigned to the mode previously mentioned. The CH₃ asymmetric bending modes are observed in the IR spectra as medium-intensity bands at 1576, 1495 and 1434 cm⁻¹ for **3** and as medium-intensity bands at 1469 and 1440 cm⁻¹ for **4**. These frequencies are in accordance with the data

reported in literature [9,34]. For **3**, the Raman dispersion band located at 1339 cm⁻¹ is assigned to the CH₃ symmetric bending mode. For compound **4**, the bands corresponding to the CH₃ symmetric bending mode are well defined in the IR and Raman spectra. This vibration appears at 1380, 1362 and 1314 cm⁻¹ in IR and at 1382 and 1367 cm⁻¹ in Raman. The IR bands located at 1122, 1077, 1010 and 975 cm⁻¹ in compound **3** (1127 cm⁻¹ in Raman) are assigned to the CH₃ rocking mode. For **4**, these vibrations appear at 1020 and 999 cm⁻¹ in IR and at 1042, 1023 and 999 cm⁻¹ in Raman. This assignment was in accordance with literature data [9,34] and it is supported by quantum chemical calculations (see Tables 4 and 5).

3.4.1.3. CH₂ modes. The CH₂ stretching modes are observed in the IR spectrum of **3** as a weak band located at 2979 cm⁻¹ and as a low-intensity Raman band at 2980 cm⁻¹. A similar feature was observed for compound **4**, in which the weak IR band located at 2935 cm⁻¹ (2939 cm⁻¹ in Raman) is assigned to the previously mentioned mode. The shoulder observed in the IR spectrum of **3** at 2911 cm⁻¹ (2916 cm⁻¹ in Raman) is assigned to the CH₂ symmetric stretching mode. This mode was not detected in the IR and Raman spectra of compound **4**. The medium-intensity band located at 1427 cm⁻¹ in the IR spectrum of **3** is assigned to the CH₂ bending mode. For compound **4**, this vibration appears as a Raman band located at 1429 cm⁻¹. The modes corresponding to the wagging, twisting and rocking modes of the methylene group are all assigned and given in Tables 4 and 5.

3.4.1.4. CH modes. The aromatic structure gives rise to C–H stretching vibrations in the frequency region from 3200 to 3000 cm⁻¹. These modes are not affected by the nature and position of substituents. In both compounds, two rings are fused together and three C–H stretching vibrations are expected. The characteristic C–H stretching mode for compound **3** is assigned to the very weak IR bands observed at 3056 and 3951 cm⁻¹ and at 3072, 3055 and 3052 cm⁻¹ in Raman. This assignment is in accordance with the theoretical predictions (see Table 4). For compound **4**, the C–H stretching vibration appears as low-intensity bands in the Raman spectrum at 3068, 3062 and 3051 cm⁻¹.

In compound **3**, the IR spectrum shows two absorptions at 1360 and 1267 cm⁻¹, with medium and very strong intensities, respectively, which are assigned to the in-plane C–H bending modes of

Table 5
Observed and calculated frequencies (in cm^{-1}) and tentative assignments of modes for compound 4.

Mode	Experimental		Calculated ^c			Tentative assignment ^{d,e}
	IR (solid) ^a	Raman (solid) ^b	Unscaled	Scaled	IR int	
1	3435 bd	—	3802	3737	24	ν O–H
2	3065 w	3068 (17)	3203	3149	4	ν C–H (R1)
3	—	3062 (8)	3189	3135	1	ν C–H (R1)
4	—	3051 (5)	3183	3129	6	ν C–H (R1)
5	—	3045 (6)	3142	3089	14	ν_a CH ₃ (CO)
6	—	3006 (8)	3116	3063	33	ν_a CH ₃
7	—	—	3112	3059	17	ν_a CH ₃
8	2976 m	2977 (30)	3109	3056	22	ν_a CH ₃
9	—	2968 (13)	3098	3045	15	ν_a CH ₃
10	2935 w	2939 (14)	3091	3038	12	ν_a CH ₂
11	—	2915 (30)	3090	3037	8	ν_a CH ₃ (CO)
12	—	2909 (34)	3042	2990	27	ν_s CH ₃
13	—	—	3040	2988	9	ν_s CH ₂
14	—	—	3033	2981	11	ν_s CH ₃ (CO)
15	—	2965 (7)	3032	2980	15	ν_s CH ₃ + ν_s CH ₃ (CO)
16	—	2850 (7)	3015	2974	19	ν C10–H
17	1668 s	1656 (92)	1735	1706	246	ν C=O
18	1607 vs	1604 (66)	1643	1574	111	ν C–C (R1) + δ C–H (R1)
19	1589 s	1582 (100)	1622	1554	117	ν C–C (R1)
20	1491 m	1490 (3)	1519	1455	79	ν C–C (R1) + δ C–H (R1)
21	1469 w	—	1513	1449	6	δ_a CH ₃
22	1440 m	1445 (6)	1502	1439	3	δ_a CH ₃
23	—	1434 (10)	1490	1427	3	δ_a CH ₃ + δ CH ₂
24	—	1429 (8)	1485	1423	5	δ CH ₂
25	—	1418 sh	1481	1419	12	δ_a CH ₃ (CO)
26	—	—	1481	1419	1	δ_a CH ₃
27	—	—	1472	1410	16	δ_a CH ₃ (CO)
28	—	—	1461	1399	<1	ν C–C (R1) + δ C–H (R1)
29	1380 sh	1382 (3)	1423	1363	18	δ_s CH ₃
30	1362 m	1367 (7)	1404	1345	18	δ_s CH ₃
31	1336 w	1336 (22)	1391	1333	30	δ_s OCH + δ_s CH ₃
32	1314 w	—	1386	1328	60	δ_s CH ₃ (CO) + δ C–H (R1)
33	—	1307 (24)	1367	1310	24	δ C9C10–H
34	1292 m	1289 (31)	1357	1300	40	δ COH + δ_s CH ₃ (CO)
35	1270 s	1266 (43)	1335	1279	19	δ COH + δ OCH
36	—	—	1311	1256	87	ω CH ₂ (R2) + δ C–H (R1)
37	1247 m	1243 (18)	1286	1232	230	ω CH ₂ + ν C1–C7
38	1235 m	1229 (35)	1263	1210	162	δ C–H (R1) + ω CH ₂
39	—	—	1259	1206	16	δ C–H (R1) + $\tau\omega$ CH ₂ + δ OCH
40	1164 m	1166 (3)	1248	1196	71	ν C10–C11 + ρ CH ₃
41	1156 sh	1153 (4)	1214	1163	5	ν_a C(CH ₃) ₂ + δ CH (R1) + $\tau\omega$ CH ₂
42	—	1135 (5)	1180	1130	57	ν_s C(CH ₃) ₂ + δ C–H (R1) + $\tau\omega$ CH ₂
43	1123 m	—	1177	1128	15	δ C–H (R1)
44	1112 m	1109 (10)	1140	1092	33	δ C–H (R1)
45	1061 w	1067 (53)	1134	1086	103	ν_a C(CH ₃) ₂ + δ COH + ρ CH ₃
46	—	1042 (3)	1078	1033	18	ρ CH ₃ (CO) + δ C–H (R1)
47	1020 sh	1023 (2)	1051	1007	4	ν C9–C10 + ρ CH ₃
48	999 w	999 (5)	1042	998	1	ρ CH ₃
49	962 s	958 (18)	1022	979	16	ρ CH ₂ + ρ CH ₃ + ν C10–O15
50	—	948 (13)	992	950	4	γ C–H (R1) + ν C9–C10
51	—	—	987	946	6	γ C–H (R1)
52	—	929 (2)	967	926	73	ν_a C10–C11–O16 + ρ CH ₃
53	—	—	960	920	27	ν_s C10–C11–O16 + ρ CH ₃
54	904 w	903 (9)	955	915	105	ν C7–C8 + ρ CH ₃ (CO)
55	894 vw	892 (2)	939	900	2	ν_a C11–C12–C13
56	861 m	860 (5)	915	877	3	δ CCC (R1) + γ C–H (R1)
57	—	846 (3)	906	868	7	γ C–H (R1)
58	822 m	830 (4)	866	829	20	ν_a C10–C11–C13 + ρ CH ₃
58	813 sh	815 (34)	849	813	37	γ C–H (R1)
60	781 vvw	783 (5)	830	795	4	δ OCC (R2) + δ CCC (R1)
61	734 w	733 (14)	791	758	9	ν_s C13–C11–C10 + δ CCC (R2)
62	705 vw	706 (46)	748	717	4	γ CCC (R1) + γ C–H (R1)
63	—	651 (2)	714	636	2	δ CCC (R1) + ν C–C (R2)
64	611 m	618 (2)	664	636	3	δ OCC (R2) + ρ CH ₂
65	—	600 (4)	627	601	1	δ CCC (R1) + δ CCC(R2)
66	—	—	619	593	11	γ C=O + γ C–H (R1)
67	583 m	—	605	580	43	δ C=O + δ CCO
68	—	548 (4)	555	532	4	δ C13–C12–C11 + δ CCC (R1)
69	523 vvw	520 (1)	525	503	3	γ CCC (R1) + γ C–H (R1)
70	504 vvw	—	524	502	3	γ CCC (R1)
71	465 vvw	468 (1)	463	444	7	δ C8C7C1 + δ C12C11O16
72	423 vw	427 (3)	431	413	6	γ CCC (R1)
73	—	—	418	400	9	γ CO–H

(continued on next page)

Table 5 (continued)

Mode	Experimental		Calculated ^c			Tentative assignment ^{d,e}
	IR (solid) ^a	Raman (solid) ^b	Unscaled	Scaled	IR int	
74	–	394 (1)	415	398	170	γ CO–H
75	–	371 (1)	387	371	10	δ C12–11–O16
76	–	–	365	350	5	δ C10–C11–C12
77	–	325 (5)	319	306	5	γ CCC (R1)
78	–	291 (5)	309	296	1	γ C12C11O16
79	–	–	292	280	1	τ CH ₃
80	–	254 (6)	250	240	0	τ CH ₃
81	–	224 (10)	245	235	0	τ R2
82	–	206 (5)	218	209	9	τ R2 + τ CH ₃
83	–	–	213	204	2	τ CH ₃
84	–	–	187	179	2	δ C7C1C2
85	–	137 (24)	149	143	<1	τ CH ₃ (CO)
86	–	–	126	121	3	τ R1
87	–	–	106	102	1	τ COCC (R2)
88	–	–	77	74	<1	τ C10–C11
89	–	–	50	48	5	τ C7–C1
90	–	–	39	37	1	τ R2

^a sh: shoulder, s: strong, w: weak, m: medium, v: very.

^b Relative band heights in parenthesis.

^c Calculated at B3LYP/6-311++G (d,p) approximation. Scale factor used 0.983 for frequencies higher than 1700 cm⁻¹ and 0.958 for frequencies lower than 1700 cm⁻¹.

^d ν: stretching, δ: in-plane bending, γ: out-of-plane bending, ρ: rocking, ω: wagging, τω: twisting, τ: torsional modes.

^e See Fig. 7 for atoms numbering scheme. R1: benzene ring, R2: furan ring.

the aromatic ring. The Raman dispersion counterpart appears at 1279 cm⁻¹. For compound **4**, the in-plane C–H stretching modes appear as medium-intensity IR bands at 1235, 1123 and 1112 cm⁻¹ (1229 and 1109 cm⁻¹ in Raman). The out-of-plane C–H deformation modes are all assigned in Tables 4 and 5.

3.4.1.5. C=O modes. For **3**, the strong IR absorption at 1673 cm⁻¹ (calculated value at 1734 cm⁻¹) is attributed to the ν(C=O) mode. This vibration corresponds to the medium-intensity Raman band observed at 1668 cm⁻¹. In compound **4**, the ν(C=O) mode appears as a strong IR band at 1668 cm⁻¹ and the Raman counterpart at 1666 cm⁻¹. The spectral features and assignment of the C=O in-plane and out-of-plane bending vibrations for compounds **3** and **4** are included in Tables 4 and 5, respectively.

3.5. Electronic spectra and frontier molecular orbitals

The experimental (measured in ethanol solvent) and calculated electronic absorption spectra of compounds **3** and **4** are shown in the Supplementary Information. The assigned transitions with major contributions for both compounds are shown in Table 6. A very good correlation between experimental and calculated spectra was observed. In the experimental spectrum, the two bands centered at 280 and 289 nm are assigned to the HOMO→LUMO transitions for **3** and **4**, respectively. The bands corresponding

Table 6
Experimental and calculated absorption wavelengths and oscillator strengths for compounds **3** and **4**.

Wavelength (nm)	Oscillator strength		Assignment
	Experimental	Calculated	
Compound 3			
–	314	0.0002	HOMO-1 → LUMO (98%)
280	286	0.4265	HOMO → LUMO (100%)
–	270	0.0354	HOMO-2 → LUMO (66%) HOMO → LUMO+1 (31%)
Compound 4			
–	315	0.0001	HOMO-1 → LUMO (97%)
289	278	0.3696	HOMO → LUMO (96%)
–	260	0.0254	HOMO-2 → LUMO (54%) HOMO → LUMO+1 (44%)

to the HOMO-2→LUMO and HOMO→LUMO+1 were not observed experimentally due to their lower oscillator strength (see Table 6).

The frontier molecular orbitals involved in the electronic transitions for compounds **3** and **4** are depicted in Fig. 9. As can be observed in Fig. 9, the HOMO for both compounds involves π-bonding orbitals of the aromatic ring and the non-bonding character of the three oxygen and some carbon atoms from another ring. The LUMO exhibits a π anti-bonding character of the carbon atoms of the aromatic ring and non-bonding character of some carbon atoms of the pyran and furan rings. Thus, the HOMO→LUMO transition has a π→π* nature. The HOMO-1 corresponds to a p-type orbital strongly located on the oxygen atom of the carbonyl group and the carbon atoms of the acetyl group. The HOMO-2 corresponds to a π-bonding system located over the aromatic ring and a p-type orbital located on the oxygen and a carbon atom of the hetero-cycle ring. In LUMO+1 the electron density of π* nature is extended all over the aromatic ring.

3.6. ¹H NMR spectral study

The ¹H NMR spectra of the title compounds have been recorded in CDCl₃ and the chemical shifts for non-equivalent protons relative to TMS are given in the experimental section (Section 3.1). The signals due to the characteristic aromatic protons were observed in the region 7.83–7.81 ppm. For compound **3**, the signals located at 7.75, 7.73 and 6.85 are assigned to H-7, H-5, H-8, respectively. The ¹H NMR spectra of compound **4** shows two doublets at 7.81 and 6.82 ppm due to H-6 and H-7, respectively. The signal corresponding to H-4 appears as a singlet at 7.83 ppm.

The two doublets located at 3.10 and 2.83 ppm in the ¹H NMR spectra of compound **3**, are attributed to H-4 of the pyran ring and the doublet at 3.22 ppm observed in compound **4** is assigned to H-3 corresponding to the benzofuran ring. The protons H-9 corresponding to the CH₃(CO) group appears as a singlet at 2.54 ppm. The signals observed at 1.38 and 1.35 ppm in the spectra of compound **3** are assigned to each gem-dimethyl group. The ¹H NMR spectra of compound **4** show two singlets at 1.25 and 1.23 ppm due to H-4' and H-5', respectively. The total of protons calculated from the integration curve is in accordance with those calculated from the proposed molecular formula.

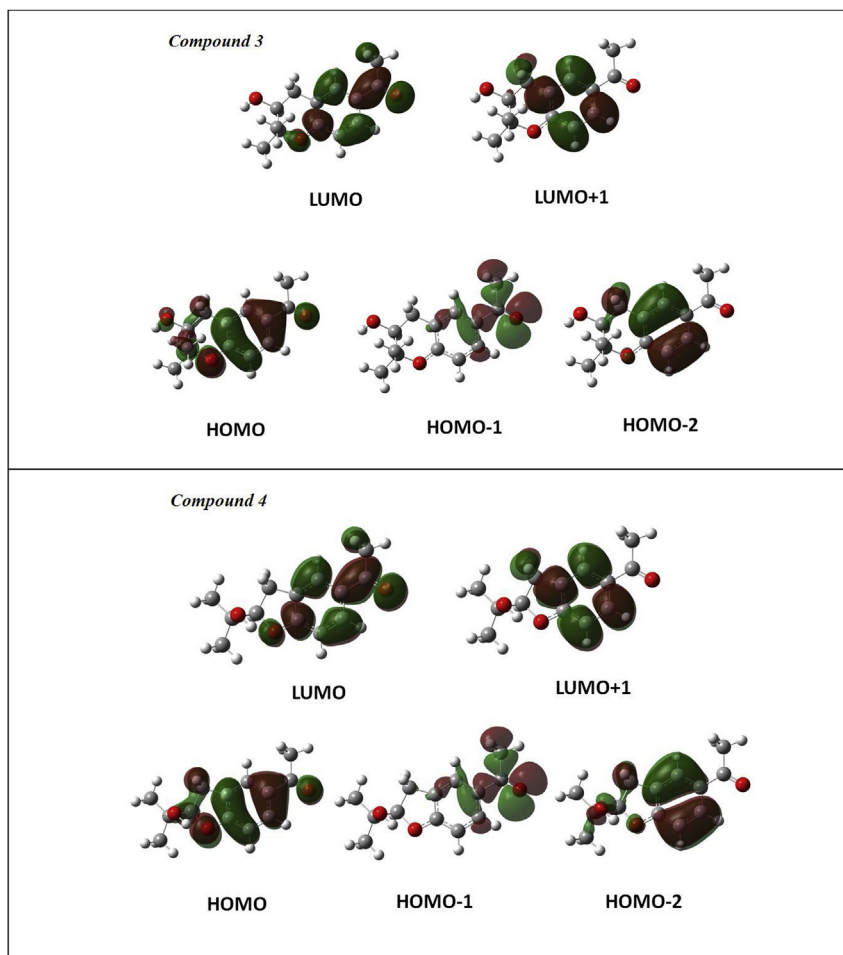


Fig. 9. Frontier molecular orbitals involved in the main electronic transitions of compounds 3 and 4.

4. Conclusions

The benzopyran 2,2-dimethyl-3-hydroxy-6-acetyl-chromane (compound **3**) and benzofuran 10,11-dihydro-10-hydroxytremetone (compound **4**) are structural isomers that biogenetically are formed from a prenylated *p*-hydroxyacetophenone precursor. The crystal structure of both substances was determined by X-ray diffraction methods and the major packing interactions that help to stabilize each structure were identified. Compound **3** crystallizes in the triclinic *P*-1 space group and compound **4** in the monoclinic *P*2₁/*c* space group. The Hirshfeld surfaces and fingerprint plots were used to understand, identify and quantify the interactions that are responsible for different packing patterns observed in both compounds. In accordance with Hirshfeld surface analysis, the relative contributions of H⋯H interactions are higher than other contacts. Intra- and inter-molecular hydrogen bonding interactions play a dominant role in structural diversity related to different kinds of supra-molecular assembly of both compounds. The theoretical results agree with the experimental observations. The vibrational and electronic properties were fully determined by combining experimental data and quantum chemical calculations.

Acknowledgments

This work was supported by SCAIT (D542/2), CONICET (PIP 0205 and PIP 1529) and ANPCyT (PME06 2804, PICT06 2315 and PICT0697) of Argentina.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.molstruc.2017.05.137>.

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