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ORIGINAL RESEARCH

Structural studies of seven homoisoflavonoids, six thiohomoisoflavonoids, and four structurally related compounds

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Abstract ^{1}H and ^{13}C NMR chemical shifts have been determined and assigned based on PFG ^{1}H, ^{13}C HMQC, and HMBC experiments for 3-(4′-X-benzyl)-4-chromenones (**Ia**, X = CN and **Ib**, X = NO_2), 3-(4′-X-benzyl)-4-thiochromenones (**IIa**, X = Cl and **IIb**, X = Br), (*E*)-3-(4′-X-benzylidene)-4-chromanones (**IIIa–IIIe**, X = OCH_3, CH_3, Cl, $N(CH_3)_2$, Br), (*Z*)-3-(4′-X-benzylidene)4-thiochromanones (**IVa–IVd**, X = Cl, Br, F, OCH_3), 2-benzyl-1,2,3,4-tetrahydro-1-naphthol (**V**), 2-benzyl- and (*E*)-2-benzylidene-1-tetralones (**VI** and **VII**), and (*E*)-2-benzylidene-1-benzosuberol (**VIII**). The crystal structures have been determined for the following seven compounds: derivatives of 4-chromanones (**IIIa–IIId**), 1-tetrahydronaphtol (**V**), and 1-tetralones (**VI** and **VII**). The molecular features and intermolecular interactions in crystal state have been discussed.

Keywords Homoisoflavonoid · Thiohomoisoflavonoid · NMR · Single crystal X-ray structure

Introduction

Homoisoflavonoids belong to a large group of naturally occurring oxygen heterocycles, which have been extracted among others from the bulbs of *Eucomis*, *Muscari*, and *Bellevalia* genus (*Liliaceae*) [1–4]. These plants are ethnomedicinally important as the isolated homoisoflavonoid compounds have excreted antimutagenic and anticlastogenic properties. Accordingly, isolation of natural representatives [5–10] and synthesis of their analogues [11] are intensive fields of research due to the great pharmacological importance of the compounds. Earlier several derivatives have been synthesized to evaluate their structure-to-antiproliferative activity. Molecular modeling revealed differences in shapes of representative molecules which were supposed to contribute to the variation in the observed cytotoxic potencies [12]. In this work ^{1}H and ^{13}C NMR chemical shifts are presented for several homoisoflavonoid derivatives of four subgroups: 3-benzyl-2-chromen-4-one (**Ia**, **Ib**), 3-benzyl-2-thiochromen-4-one (**IIa**, **IIb**), (*E*)-3-benzylidene-4-chromanone (**IIIa–IIIe**), (*Z*)-3-benzylidene-4-thiochromanone (**IVa–IVd**) and four structurally related compounds: 2-benzyl-1,2,3,4-tetrahydro-1-naphthol (**V**), 2-benzyl- and (*E*)-2-benzylidene-1-tetralones (**VI**, **VII**), as well as (*E*)-2-benzylidene-1-benzosuberol (**VIII**). The obtained NMR data can be related with the electron densities in these molecules [13, 14] which further are connected with their biological and physiological activity [12, 15, 16]. Single crystal X-ray diffraction was attempted for all structures, but only for compounds **IIIa–IIId** and **V–VII** the structures were obtained.

This article is dedicated to the memory of Prof. emer. Jaakko Paasivirta (1931–2011), a friend and colleague, whose contributions to early steps in NMR chemistry in Finland and later to environmental chemistry and toxicology were outstanding. Also, his devotion to research issues was exemplary.

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Experimental

Chemistry

Melting points were determined on a Boetius apparatus and are uncorrected. Column chromatography was performed on Kieselgel 60 (0.063 ± 0.2 mm) (Merck) using toluene as eluent. The progress of the reactions, as well as the purity of the compounds, was checked by thin-layer chromatography (TLC) performed on Kieselgel 60 F254 plates (Merck) using toluene:ethanol (4:1, v/v) as developing system. Elemental analyses performed at the Organic Chemistry Department of Eötvös Loránd University (Budapest, Hungary) were undertaken on **IIa**, **IVc**, **V**, and **VIII** and were within 0.4% of the calculated values. The remaining compounds have been described previously (**I–IV**: [12, 17, 18]; **VI**: [19], **VII**: [15]) and had melting points in accord with the literature values. The structures of the investigated compounds and their numbering used are shown in Fig. 1.

Syntheses of compounds

Compounds **I–IV** were prepared by condensation of chroman-4-one or 1-thiochroman-4-one with various substituted benzaldehydes using piperidine as the catalyst based on previously published methods [12, 17]. Briefly, a mixture of chroman-4-one or 4-thiochromanone (10 mmol), substituted benzaldehyde (10 mmol), and piperidine (five drops) was heated at 105 °C for 1 h. The solidified residue

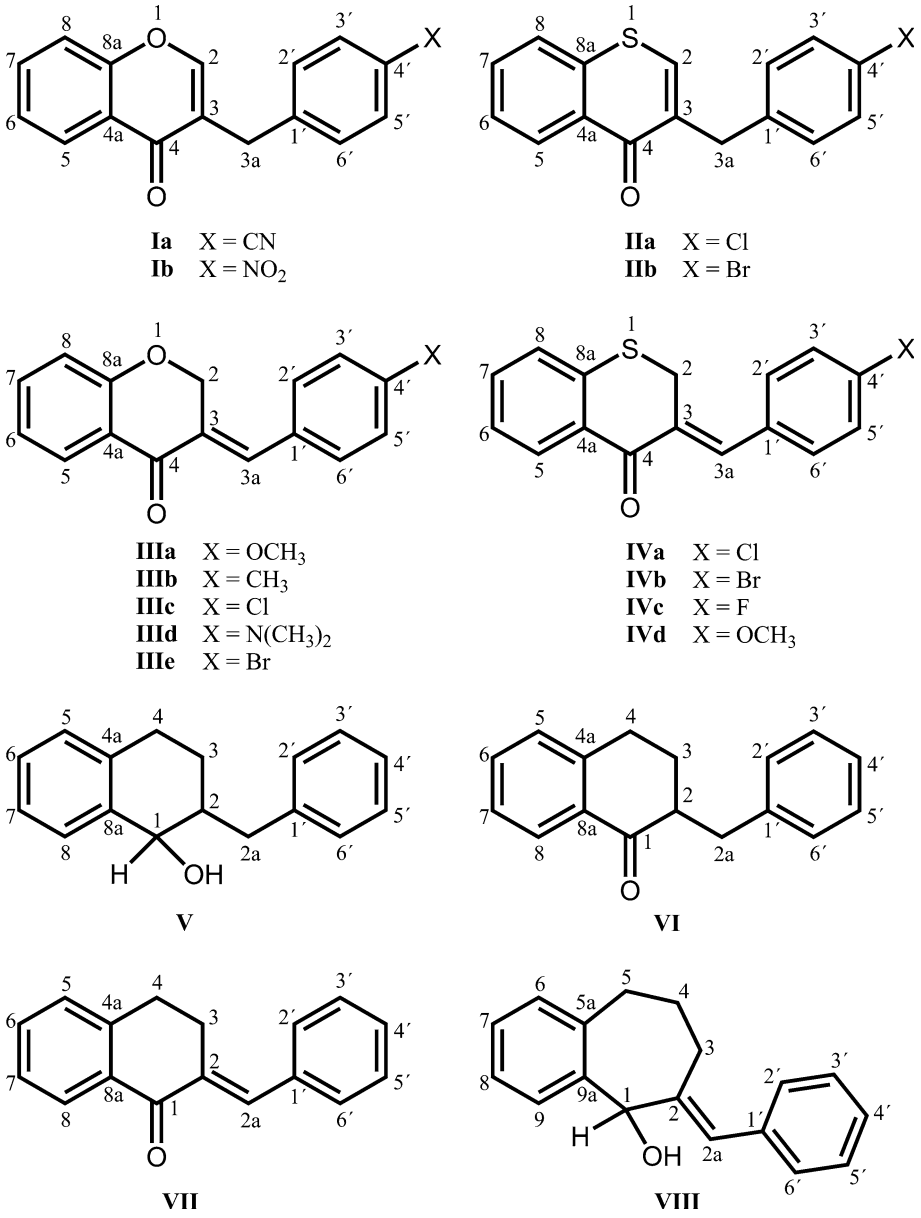

Fig. 1 The structures and numbering of investigated compounds

was dissolved in chloroform, washed free of base with water, dried, and evaporated in vacuo. The residue was subjected to column chromatography (silica gel/toluene). The chromatographically pure compounds (**I** and **III**; **II** and **IV**) were further purified by crystallization.

(*E*)-2-Benzylidene-1-tetralone (**VII**) and its seven-membered analogue, (*E*)-2-benzylidene-1-benzosuberone were synthesized as previously published [15]. Compound **VI** was obtained by hydrogenation of **VII** in methanol with 10% Pd/C catalyst for 1 h [20]. 2-Benzyl-1,2,3,4-tetrahydro-1-naphtol (**V**) was obtained by standard sodium borohydride reduction of **VI**. Compound **VIII** was obtained by similar sodium borohydride reduction of (*E*)-2-benzylidene-1-benzosuberone. Each compound was purified by column chromatography (silica gel, toluene (**VI**, **VII**) or toluene/ethyl acetate = 1:1 (**V**, **VIII**)). The melting points (uncorrected) of the unreported compounds were as follows: **IIa**: 105–107 °C (methanol), **IVc**: 103–105 °C (methanol), **V**: 117–119 °C (hexane), **VIII**: 94–96 °C (hexane).

NMR spectroscopy

The one-dimensional ^{1}H and ^{13}C as well as two-dimensional PFG [21] ^{1}H, ^{1}H COSY [22, 23], PFG ^{1}H, ^{13}C HMQC [24, 25], and PFG ^{1}H, ^{13}C HMBC [26] spectra were recorded for 0.5 M $CDCl_3$ solution in a 5 mm sample tube at 30 °C on a Bruker Avance DRX 500 spectrometer working at 500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C, respectively. In ^{1}H NMR experiments the number of data points was 64 K giving a spectral resolution of 0.05 Hz, the number of scans was 8 and the flip angle 30°. An exponential window function of the spectral resolution was used prior to FT. The ^{1}H NMR chemical shifts are referenced to the signal of residual $CHCl_3$ ($\delta = 7.26$ ppm from internal TMS). In ^{13}C experiments the number of data points was 32 K giving a spectral resolution of 0.5 Hz, the number of scans was 64 and flip angle 30°. A composite pulse decoupling, waltz-16, was used to remove proton couplings. An exponential window function of the spectral resolution was used prior to FT. The ^{13}C NMR chemical shifts are referenced to the center peak of the solvent $CDCl_3$ ($\delta = 77.0$ ppm from internal TMS). In PFG ^{1}H, ^{13}C HMQC, and HMBC measurements the numbers of data points were 1024 ($f_2 = {}^{1}H$) × 256 ($f_1 = {}^{13}C$). This matrix was zero filled to 2048 × 512 and apodized by a shifted sine bell window function along both axes prior to FT.

Single crystal X-ray analysis

The crystals suitable for single crystal X-ray diffraction analyses were obtained by spontaneous evaporation of $CDCl_3$ from capped NMR sample tubes. The structural data were collected at 173 ± 2 K with a Bruker-Nonius KappaCCD diffractometer equipped with APEXII detector using graphite monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). Data were processed with DENZO-SMN [27]. The structures were solved by direct methods, using SIR-2002 [28], and refined on F^2, using SHELXL-97 [29]. The final refinement cycles for **IIIa** were performed with HKLF5/BASF method to solve the observed non-merohedral twinning and TwinRotMat routine of PLATON [30] was used to generate the HKLF5 reflection file. The reflections were corrected for Lorenz polarization effects and absorption correction was not used. The H atoms bonded to C atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the C atom temperature factor) and refined as riding atoms. The H atoms bonded to O atoms in **V** were found from electron density map and fixed to distances of 0.84 Å from O atom with isotropic temperature factor (1.5 times the O atom temperature factor). The figures were drawn with ORTEP-3 [31] and MERCURY [32]. Other experimental X-ray data are shown in Table 1. CCDC-746342 (**IIIa**), CCDC-746343 (**IIIb**), CCDC-746344 (**IIIc**), CCDC-746345 (**IIId**), CCDC-812985 (**V**), CCDC-812986 (**VI**), and CCDC-812987 (**VII**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033].

Results and discussion

Earlier we have reported syntheses and ^{1}H and ^{13}C NMR spectral data of a systematically substituted (*E*)-2-benzylidene-1-benzocyclanones [13–16] and (*E*)-3-benzylidene-4-chromanones [12]. As a continuation of this series of studies, synthesis of (*Z*)-3-arylidene-4-thiochromanones (**IVa–IVd**) is now performed and their stereochemistry compared with the related (*E*)-3-arylidene-4-chromanones (**IIIa–IIIe**). During the piperidine catalyzed synthesis of series **III** and **IV** an *exo–endo* double bond migration is possible and formation of a mixture of (*E*)-3-arylidene-4-chromanones (**III**) and (*Z*)-3-arylidene-4-thiochromanones (**IV**), as well as the respective 3-benzyl-2-chromen-4-ones (homoisoflavones) (**I**) and 3-benzyl-2-thiochromen-4-ones (**II**) can be observed. According to the previous observations formation of the respective benzyl derivatives were found to be the most expressed in the case of using aromatic aldehydes with electron withdrawing groups in the 4-position [11]. Separation of the formed *exo–endo* pairs could be conveniently accomplished by column chromatography. Investigation of biologic actions of the related

Table 1 Selected crystallographic parameters for **IIIa–IIId**, **V**, **VI**, and **VII**

	IIIa	**IIIb**	**IIIc**	**IIId**	**V**	**VI**	**VII**[b]
Empirical formula	$C_{17}H_{14}O_3$	$C_{17}H_{14}O_2$	$C_{16}H_{11}ClO_2$	$C_{18}H_{17}NO_2$	$C_{17}H_{18}O$	$C_{17}H_{16}O$	$C_{17}H_{14}O$
Formula weight	266.28	250.28	270.70	279.33	238.31	236.30	234.28
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	*P*−1	*Pc*	$P2_1/n$	*Pc*	*P*−1	*C*2/*c*	$P2_1/c$
a (Å)	7.5710(5)	14.5493(4)	3.9093(2)	7.6267(2)	9.2398(4)	22.4725(15)	8.9642(3)
b (Å)	12.3844(10)	11.5169(3)	27.6681(12)	15.2911(3)	12.4152(6)	9.7061(6)	16.0541(6)
c (Å)	14.4898(12)	19.7493(5)	11.5091(6)	12.1024(2)	13.2214(6)	14.8703(9)	8.6876(3)
α (°)	82.855(4)	90	90	90	63.426(3)	90	90
β (°)	87.258(5)	129.610(2)	96.231(3)	91.1800(10)	78.614(3)	127.584(4)	103.018(2)
γ (°)	75.805(4)	90	90	90	78.142(3)	90	90
Volume ($Å^3$)	1306.67(17)	2549.45(12)	1237.50(11)	1411.09(5)	1317.83(10)	2570.4(3)	1218.12(7)
Z (*Z*′)	4 (2)	8 (4)	4	4 (2)	4 (2)	8	4
Reflections collected/R_{int}	4551/–[a]	15416/0.1079	6891/0.0821	8602/0.0528	8161/0.0782	7571/0.0707	7422/0.0709
Data/restraints/parameters	4551/0/362	4498/2/689	2178/0/172	2490/0/379	4632/112/383	2272/0/163	2144/0/163
Goodness-of-fit on F^2	1.132	1.065	1.142	1.060	1.080	1.046	1.105
*R*1 [$I > 2\sigma(I)$]	0.0899	0.0654	0.0715	0.0399	0.0829	0.0817	0.0583
w*R*2 (all data)	0.2177	0.1431	0.1338	0.0876	0.1665	0.2053	0.1099
Largest diff. peak/hole e$Å^{-3}$	0.339/−0.283	0.232/−0.217	0.413/−0.216	0.144/−0.180	0.210/−0.199	0.459/−0.449	0.157/−0.190

[a] Before HKLF5 refinement $R_{int} = 0.0610$

[b] Same as the 2-benzylidene-1-tetralone structure found from CSD with code name BZTETO [51]

(*E*)-2-benzylidene-1-benzocyclanones [13–16] indicated importance of spatial arrangement of the three structural units of the compounds. In order to have a better understanding of the structure-to-stereochemistry relationship some reduced (**V**, **VI**) derivatives of (*E*)-2-benzylidene-1-tetralone (**VII**) were prepared. For comparison, a reduced derivative (**VIII**) of the respective (*E*)-2-benzylidene-1-benzosuberone was also synthesized for spectroscopic investigations.

The ^1H and ^{13}C NMR chemical shifts for all the studied compounds are presented in Tables 2 and 3, respectively. ^1H and ^{13}C NMR data for several structurally close compounds are found also in the literature [1, 6, 9, 16, 33, 34]. The greatest ^1H NMR chemical shift differences in series **I** and **II**, 3-benzyl-2-chromen-4-ones and thio-4-chromenones, can be seen in H2, from 0.33 to 0.38 ppm and in H5, from 0.36 to 0.39 ppm. In other protons (H6, H7, H8, H3a) the shift differences are much smaller being 0.16 ppm at highest. In (*E*)-3-benzylidene-4-chromanones (**III**) and (*Z*)-3-benzylidene-4-thiochromanones (**IV**), the greatest ^1H NMR chemical shift differences are between H2 and H8 varying from 1.15 to 1.38 ppm and from 0.32 to 0.37 ppm, respectively.

Comparing ^{13}C NMR chemical shifts of compounds **I** and **II**, former including oxygen and latter a sulfur containing ring, the greatest differences are seen in C2, C3, and C8a. C2 are from 18.8 to 18.9 ppm and C8a's from 19.2 to 19.4 ppm more deshielded in compounds **I**, while C3's are 13.1 ppm more shielded in compounds **II**. Other ^{13}C NMR chemical shift differences are 10 ppm at highest [33]. Correspondingly in **III** and **IV** series C2's are from 38.1 to 39.1 ppm and C8a's from 20.2 to 19.7 ppm more deshielded in oxygen derivatives (**III**), while other shift differences are 10.7 ppm at highest. In fully conjugated systems, (*E*)-3-benzylidene-4-chromanones (**III**) and (*Z*)-3-benzylidene-4-thiochromanones (**IV**) the *p*-substituent has little effect on the C3 shifts.

The crystal structure of (*E*)-3-benzylidene-4-chromanone was published in 1987 by Katrusiak et al. [35] and our structural search showed that since then nine substituted derivatives [36–44] of it have been added to Cambridge Structural Database (CSD) [45]. The crystallographic diagrams for four new derivatives **IIIa–IIId** are presented in Fig. 2. As can be seen from Fig. 2 and Table 1 three of these structures show more than one molecule in asymmetric unit, as also found with 5,6-benzoderivative [41]. None of these new structures show similar unit cell parameters to known ones or to each other, i.e. they are not crystallographically isostructural to any 3-benzylidene-4-chromanone derivatives. The crystals of **IIIa** were observed to be non-merohedrally twinned. The obtained BASF parameter with HKLF5 refinement was 0.24 defining the ratio of the two twin domains. In the lack of strong hydrogen bonding interactions in **IIIa–IIId** several weaker forces determine the packing of the crystals. These forces include C–H···O and C–H···π contacts, as well as $\pi\cdots\pi$ and

Table 2 ^{1}H NMR chemical shifts (ppm) in 0.5 M $CDCl_3$ solution at 30 °C

Compound	H2	H5	H6	H7	H8	H3a	H2′, H6′	H3′, H5′
Ia	7.77	8.18	7.37	7.64	7.42	3.83	7.41	7.49
Ib	7.81	8.20	7.40	7.67	7.44	3.89	7.48	8.14
IIa	7.43	8.56	7.51	7.56	7.55	3.95	7.21	7.27
IIb	7.44	8.57	7.53	7.58	7.57	3.94	7.16	7.43
IIIa[a]	5.37	8.02	7.06	7.47	6.96	7.83	7.28	6.97
IIIb[b]	5.36	8.03	7.07	7.48	6.96	7.86	7.22	7.26
IIIc	5.31	8.02	7.08	7.50	6.97	7.81	7.25	7.43
IIId[c]	5.44	8.02	7.05	7.45	6.95	7.83	7.26	6.73
IIIe	5.29	8.01	7.07	7.49	6.96	7.77	7.17	7.57
IVa	4.08	8.20	7.26	7.41	7.32	7.71	7.34	7.43
IVb	4.06	8.19	7.26	7.40	7.31	7.68	7.26	7.57
IVc	4.08	8.19	7.24	7.39	7.30	7.71	7.37	7.12
IVd[d]	4.14	8.18	7.24	7.37	7.29	7.74	7.37	6.95

Compound	H1	H2	H2a	H3	H4	H5	H6	H7	H8	H9
V[e]	4.43	2.00	3.03	1.93	2.73	7.04	7.16	7.18	7.46	–
			2.46	1.45	2.68					
VI[f]	–	2.69	3.45	2.05	2.85[g]	7.15	7.39	7.25	8.05	–
			2.61	1.72	2.85[g]					
VII[h]	–	–	7.87	3.11	2.93	7.23	7.47	7.35	8.13	–
VIII[i]	5.31	–	6.62	2.88	1.80[j]	3.18	7.09	7.16[k]	7.18	7.41
				2.58	1.80[j]	2.80				

[a] OCH_3 = 3.86 ppm; [b] CH_3 = 2.41 ppm; [c] $N(CH_3)_2$ = 3.04 ppm; [d] OCH_3 = 3.84; [e] H2′, H6′ = 7.18 ppm, H3′, H5′ = 7.27 ppm, H4′ = 7.18 ppm; [f] H2′, H6′ = 7.19 ppm, H3′, H5′ = 7.26 ppm, H4′ = 7.18 ppm; [g] between 2.8 and 2.9 ppm; [h] H2′, H6′ = 7.43 ppm, H3′, H5′ = 7.40 ppm, H4′ = 7.33 ppm; [i] H2′, H6′ = 7.16 ppm, H3′, H5′ = 7.26 ppm, H4′ = 7.17 ppm; [j] between 1.84 and 1.77; [k] between 7.18 and 7.15 ppm

hydrophobic interactions (see Electronic Supplementary Material, of this article for more details). For example, one $\pi\cdots\pi$ interaction was found in asymmetric unit of **IIIa** (Fig. 2) with centroid-to-centroid distance of 3.86 Å and closest carbon-to-carbon distance of 3.387(7) Å. Although, these interactions and existing non-specific dispersive forces are weak, they are strong enough to force independent molecules during crystallization to different conformations and deviating surroundings, which appear as multiple molecules in asymmetric unit in the cases of **IIIa**, **IIIb**, and **IIId**.

The pyrone ring is not planar, as previously observed [35], and the carbon C2 has the largest offset from the plane defined by the adjacent benzene ring. The dihedral angle C8a–O1–C2–C3 (Fig. 1, Table 4) is rather close to ±50° in all molecules of **IIIa**–**IIId** and have rather similar angle values in previously known derivatives (38°–54°) [35–44]. The positive or negative angles show that C2 is on the left (+) or right (−) side viewed along the plane from aromatic end and carbonyl on top. In **IIIa**, **IIIb**, and **IIId** these deviating envelope conformations of pyrone rings between independent molecules in asymmetric unit are also a result of influence of intermolecular forces. Another result of intermolecular contacts in molecular level is the spatial orientation of benzylidene group. The planes formed by phenyl rings C1′–C6′ and C4a–C8a in **IIIa** show angle values close to value 59.1(4)° (Table 4) observed for unsubstituted 3-benzylidene-4-chromanone [35]. 3-Benzylidene-8-methoxy-6-methylchroman-4-one [39] shows also similar value of 59.67(4)°. In **IIIb**–**IIId** these values are slightly smaller (46°–55°) as also in several 3-benzylidene-4-chromanone derivatives [37, 38, 40–44]. 3-Benzylidene-6-methoxychroman-4-one [36] shows value of 67.78(3)° for this angle and is the only one significantly larger. Carbon C2 is on the same side of the C4a–C8a-plane as C2′ in all 3-benzylidene-4-chromanone derivatives.

These crystallographic data do not correspond well with the previous molecular modeling data of **IIIa**–**IIId** [12] concerning the spatial orientation of C1′–C6′ benzene ring and especially the C3–C3a–C1′–C2′ and C3–C3a–C1′–C6′ dihedral angles. In modeled structures the angle values were found to be around 130° and 50°, while in crystal structures the observed values (Table 4) were closer to 150° and 30° for all molecules in **IIIa**–**IIId**. This deviation arises most probably from inadequate intermolecular force parameters in molecular modeling. Substituents in position

Table 3 ^{13}C NMR chemical shifts (ppm) in 0.5 M $CDCl_3$ solution at 30 °C

Compound	C2	C3	C3a	C4	C4a	C5	C6	C7	C8	C8a	C1′	C2′, C6′	C3′, C5′	C4′	CH_3
Ia[a]	153.0	123.0	32.0	177.0	123.7	125.8	125.1	133.7	118.0	156.4	144.6	129.5	132.2	110.3	–
Ib	153.1	123.1	31.8	177.1	123.8	125.9	125.3	133.8	118.1	156.5	146.7	129.6	123.7	146.7	–
IIa	134.2	136.1	37.2	178.8	131.5	129.0	127.5	131.0	126.4	137.1	137.3	130.6	128.7	132.3	–
IIb	134.2	136.1	37.4	178.9	131.6	129.1	127.6	131.1	126.5	137.2	137.9	131.1	131.7	120.4	–
IIIa	67.8	128.9	137.2	182.1	122.1	127.9	121.8	135.6	117.8	160.7	127.0	132.0	114.3	161.0	55.4
IIIb	67.7	130.1	137.5	182.2	122.1	127.9	121.8	135.7	117.8	161.1	131.6	130.1	129.5	139.9	21.4
IIIc	67.5	131.5	136.0	181.9	121.9	128.0	122.0	136.0	117.9	161.1	135.6	131.2	129.1	132.8	–
IIId	68.2	126.1	138.2	182.0	122.2	127.8	121.6	135.2	117.6	160.8	122.4	132.5	111.7	151.1	40.0
IIIe	67.4	131.5	135.9	181.8	121.9	127.9	122.0	135.9	117.9	161.1	133.2	131.3	132.0	123.8	–
IVa	29.2	133.5	136.2	185.6	132.3	130.5	125.9	133.1	127.9	141.0	133.5	130.8	129.1	135.0	–
IVb	29.2	133.6	136.2	185.6	132.3	130.5	125.9	133.1	127.9	141.0	133.9	131.0	132.0	123.2	–
IVc[b]	29.1	132.8	136.3	185.6	132.3	130.4	125.8	133.0	127.8	140.9	131.0	131.4	115.9	162.8	–
IVd	29.4	131.0	137.7	185.8	132.6	130.4	125.8	132.8	127.9	140.9	127.5	131.4	114.3	160.3	55.4

Compound	C1	C2	C2a	C3	C4	C4a	C5	C5a	C6	C7	C8	C8a	C9	C9a	C1′
V[c]	72.8	43.8	38.3	24.3	27.6	136.7	128.6	–	127.3	126.2	128.2	138.6	–	–	140.3
VI[d]	199.0	49.3	35.6	27.6	28.5	143.8	126.0	–	133.1	126.4	127.4	132.4	–	–	139.9
VII[e]	187.7	135.4	136.5	27.1	28.8	143.1	128.1	–	133.2	126.9	128.1	133.4	–	–	135.8
VIII[f]	80.1	143.1	125.0	29.5	28.4	–	35.0	140.4	130.0	127.5	126.6	–	126.2	141.7	137.4

[a] $CN = 118.8$ ppm; [b] J(C4′, F) = 249.9 Hz, J(C3′, F) = 21.5 Hz, J(C2′, F) = 8.3 Hz, J(C1′, F) = 3.6 Hz; [c] C-2′,6′ = 129.2 ppm, C-3′,5′ = 128.3 ppm, C-4′ = 125.9 ppm; [d] C-2′,6′ = 129.1 ppm, C-3′,5′ = 128.3 ppm, C-4′ = 128.6 ppm; [e] C-2′,6′ = 129.8 ppm, C-3′,5′ = 128.4 ppm, C-4′ = 128.5 ppm; [f] C-2′,6′ = 128.7 ppm, C-3′,5′ = 128.0 ppm, C-4′ = 126.4 ppm

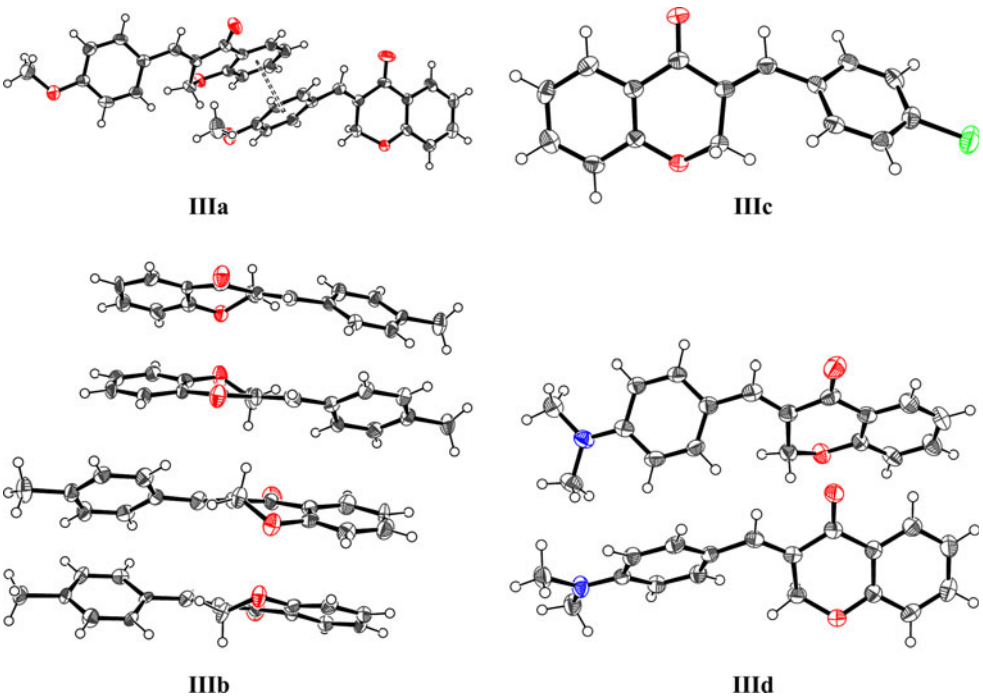

Fig. 2 Asymmetric units of **IIIa**–**IIId** with thermal ellipsoids at 50% probability level

4′ (Fig. 1) do not show clear lengthening/shortening effects on the C3–C3a or C3a–C1′ bond distances (Table 4), which seem to vary independently in the range of 1.31–1.38 Å for the former and 1.44–1.48 Å for the latter. The substituents of two independent molecules in **IIIa** and **IIId** have also similar spatial orientation.

Crystal structure of **V** is a racemic mixture in triclinic space group $P-1$. Molecule **V** has chiral centers at C1 and

Table 4 Selected structural parameters for **IIIa–IIId**

	IIIa[a]	**IIIb**[b]	**IIIc**	**IIId**[a]
∠(C4a–C4–C3–C3a) [°]	−165.4(4)	173.7(6)	167.7(3)	−164.5(3)
	163.6(4)	−170.3(6)		176.8(3)
		176.7(6)		
		−168.2(6)		
∠(C8a–O1–C2–C3) [°]	51.1(7)	−49.7(8)	−45.9(4)	44.1(4)
	−51.3(7)	51.7(8)		−50.0(4)
		−47.0(9)		
		49.0(8)		
∠(C2′-C1′-C3a-C3) [°]	34.4(11)	−26.1(11)	−35.3(6)	32.7(6)
	−38.6(11)	23.7(12)		−29.4(6)
		−25.6(12)		
		22.6(12)		
∠(C6′–C1′–C3a–C3) [°]	−148.5(7)	156.0(7)	145.8(4)	−149.4(4)
	147.1(7)	−155.2(8)		156.3(4)
		157.2(7)		
		−155.1(7)		
∠(plane1–plane2)[c] [°]	58.8(2)	48.4(2)	53.27(8)	54.82(8)
	60.6(2)	48.1(2)		49.72(9)
		46.9(2)		
		50.5(2)		

[a] Two molecules in asymmetric unit

[b] Four molecules in asymmetric unit

[c] Planes of aryl rings C1′–C6′ and C4a–C8a

C2. Figure 3 shows the structure with two molecules in asymmetric unit (1*R*,2*R* enantiomers). The other molecule has also a disorder in the aromatic ring of the benzyl group (major/minor orientations 0.7/0.3). There were two possible positions found for hydroxyl group proton for both crystallographically independent molecules from electron density map and their population parameters were set to 0.5 in the refinement. This disorder shows that O–H proton points either to the O atom of to the other molecule in asymmetric unit or to the O atom of adjacent molecule on the other side. Thus, these two molecules are connected to each other and also to adjacent ones with O–H···O hydrogen bonds (Table 5) via these hydroxyl groups, forming an infinite chain through the crystal. The adjacent pair of asymmetric unit along this chain shows 1*S*,2*S* chirality, the next pair is 1*R*,2*R* again and so on. Additionally, one C–H···π and one π···π contacts were found from the crystal data (see Electronic Supplementary Material), but they are very weak and of minor (if any) importance in structure stabilization.

The structural search from CSD [45] showed that crystal structure of **V** is the first 2-benzyl-1-tetrahydronaphthol structure containing O–H group and –CH_2– group between the aliphatic and aromatic ring. Two closely related molecules 2-[(dimethylamino)(phenyl)methyl]-1-methyl-1-tetrahydronaphthol [46] and 1-methyl-3′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,2′-oxiran]-1-ol [47] show similar aliphatic ring conformations as **V** in crystal state, in which the OH and carbon at position 3 are on the different side of the plane defined by adjacent phenyl ring. In **V** the benzylic substituent is in the equatorial position, while in the two already known structures it is on axial position (O equatorial in the latter [47]). The latter related compound has also the similar angle between aromatic planes [72.9(4)°] with major orientations in **V**, while the former has angle value [45.9(5)°] closer to one with minor orientation of disordered molecule.

Compound **VI** has a chiral center at C2, but the crystallized structure is a racemic mixture in monoclinic space group *C*2/*c*. Only aromatic ring and the conjugated carbonyl group are in the same plane. Carbon C4 is almost in that plane, but the rest of the molecule is slightly twisted (to the right on the chosen molecule in asymmetric unit in Fig. 3) and it is also observed from the value of C8a–C1–C2–C2a dihedral angle (Table 5). Small static disorder was found to occur in the case of C3 and C2a, but the solving of it was not successful without using strong positional and anisotropic constraints and it was not resolved in the least squares refinement. The angle between the planes of two aromatic rings (Table 5) is smaller than in **V** but larger than in **IIIa–IIId** and most of the related 3-benzylidene-4-chromanone structures [35–44]. Three known 2-benzyl-1-tetralone derivatives [48–50] show larger inclination angles (74°–80°) between aromatic planes, but slightly smaller twist of the molecule end, according to C8a–C1–C2–C2a dihedral angles (162°–168°). One C–H···π and one C–H···O short intermolecular contacts were found and the former shows H···C_{Ar} distances of 2.81–2.83 Å between

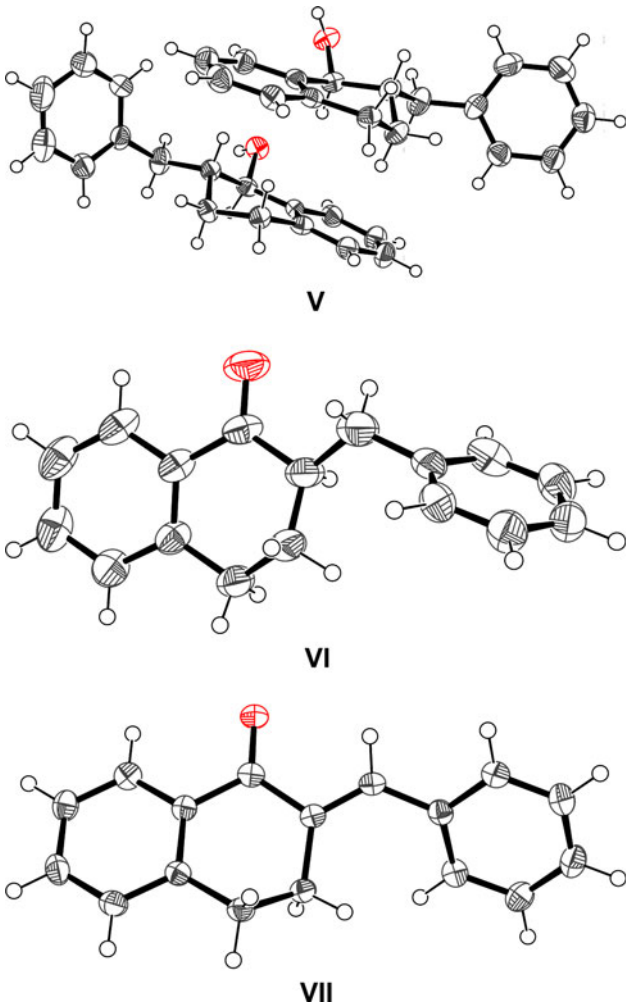

Fig. 3 Asymmetric units of **V**–**VII** with thermal ellipsoids at 50% probability level

hydrogen and two carbons of aryl ring. The weak C–H···O hydrogen bond has values of 3.378(5) Å for C···O distance and 139° for C–H···O angle (see Electronic Supplementary Material). The similar C–H···O interactions can be found from the crystals of three related 2-benzyl1-tetralones [48–50], but the C–H···π is very weak or does not exist at all in those structures.

Crystal structure determined at 173 K for **VII** were found to be equal to the known one previously determined at room temperature [51]. Therefore, the structure of it is not much discussed here, but just for comparison to compounds **V** and **VI** the C8a–C1–C2–C2a dihedral angle has the value (Table 5) closest to planar geometry and corresponding well to the values of C4a–C4–C3–C3a dihedral angle in **IIIa**–**IIId** (Table 4), which is of course expected with the presence of carbonyl and double bond conjugated to it. Also, the spatial orientation of the ending phenyl group is closer to the ones found from the (*E*)-3-benzylidene-4-chromanones than ones from more hydrogenated derivatives **V** and **VI**, and the modeled value for C2′–C1′–C2a–C2 dihedral angle [15] is about 20° larger than observed here (Table 5). The overall shapes of the molecules **IIIa**–**IIId** and **VII** is more planar than the shapes in **V** and **VI**. The intermolecular interactions in **VII** were previously described to be normal van der Waals interactions [51]. As an update, we found three C–H···O type short contacts in this study (see Electronic Supplementary Material). However, the importance of the found short interactions in structure stabilization in all crystal structures of present study (except O–H···O in **V**) is fairly unknown and most probably several non-specific dispersive interactions play a certain role between the molecules.

Table 5 Selected structural parameters for **V**, **VI**, and **VII**

	V[a]	**VI**	**VII**
∠(C4a–C4–C3–C2) [°]	−51.4(4)	−42.6(7)	53.8(3)
	−49.5(4)		
∠(C8a–C1–C2–C2a) [°]	−166.6(3)	−158.3(4)	−171.0(2)
	−169.6(3)		
∠(C2′–C1′–C2a–C2) [°]	−100.1(8) [− 88.8(17)][b]	−86.4(6)	32.1(4)
	−99.3(5)		
∠(C6′–C1′–C2a–C2) [°]	74.8(6) [101.4(7)][b]	97.6(5)	−152.0(2)
	80.1(5)		
∠(plane1–plane2)[c] [°]	77.7(3) [56.1(5)][b]	64.8(2)	52.20(9)
	77.08(11)		
d/∠(O1–H1B···O21) [Å/°]	2.656(4)/156(8)		
d/∠(O1–H1···O1)[d] [Å/°]	2.724(5)/160(8)		
d/∠(O21–H21···O1) [Å/°]	2.656(4)/179(9)		
d/∠(O21–H21B···O21)[e] [Å/°]	2.680(5)/171(10)		

[a] Two molecules in asymmetric unit

[b] Values from the second moiety of the disordered ring

[c] Planes of aryl rings C1′–C6′ and C4a–C8a

[d] Symmetry operation: $-x + 1$, $-y + 1$, $-z + 1$

[e] Symmetry operation: $-x$, $-y + 1$, $-z + 1$

Conclusions

Complete ^{1}H and ^{13}C NMR chemical shift assignments of seven homoisoflavonoids and six thiohomoisoflavonoids together with four structurally close compounds are reported based on two-dimensional homo- and heteronuclear NMR chemical shift correlation maps. Seven single crystal X-ray structures are also reported. The crystallographic structures were not found congruent with the ones previously obtained by molecular modeling. In the molecular level the structures in present study resemble well the previously known structures of (*E*)-3-benzylidene-4-chromanone derivatives, but the crystal packing is different. We wish that these data are useful also for other researchers working with these pharmacologically important compounds.

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