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Chalconoids from *Fissistigma bracteolatum*

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Dedicated to Prof. Gerhard Spiteller on the occasion of his 68th birthday.

Abstract

Phytochemical studies on the leaves of *Fissistigma bracteolatum* yielded besides the two known compounds 2-hydroxy-3,4,6-trimethoxychalcone (**1**) and 5,7,8-trimethoxyflav-3-ene (**2**), five new chalconoids 2-hydroxy-3,4,6-trimethoxychalcene (**3**), 2-hydroxy-3,4,6-trimethoxydihydrochalcone (**4**), 2′-hydroxy-3′,4′,6′-trimethoxydihydrochalcone (**5**), 2′-hydroxy-3′,4′,6′-trimethoxy-β′-methoxychalcane (**6**) and 2′-hydroxy-3′,4′,6′-trimethoxy-β′-ethoxychalcane (**7**). The structures of these compounds were determined by mass and NMR spectroscopic methods. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *Fissistigma bracteolatum*; Annonaceae; Leaves; Chalconoids; 2-Hydroxy-3,4,6-trimethoxychalcene; 2-Hydroxy-3,4,6-trimethoxydihydro-chalcone; 2′-Hydroxy-3′,4′,6′-trimethoxydihydrochalcone; 2′-Hydroxy-3′,4′,6′-trimethoxy-β′-methoxychalcane; 2′-Hydroxy-3′,4′,6′-trimethoxy-β′-ethoxychalcane

1. Introduction

The genus *Fissistigma* is a large tribe with ca. 70 species in the Annonaceae family (Leboeuf, Cave, Bhaumik, Mukherjee & Mukherjee, 1982). The decoctions of different plant, parts of several species have been used in southeast Asia as traditional medicines (Perry, 1980). Phytochemically, this tribe was reported to contain aporphine (Chang, Wu, Wu & Su, 1996), protoberberine (Chia, Chang, Li & Wu, 1998), phenanthrene alkaloids (Wu, Kao, Huang, Duh & Lu, 1990) and flavonoids (Alias, Awang, Hadi, Thoison, Sevenet & Pais, 1995) as their main components.

Fissistigma bracteolatum Chatt. is a creeper growing in the north of Vietnam (Pham Hoang Ho, 1993), the constituents of which have not yet been studied. In China this plant is applied externally on wounds to stop bleeding or used to treat broken bones. In Vietnam it is used with other ingredients to treat infections and also to enhance blood circulation (Vo Van Chi, 1997). In continuation of our search for new biologically active compounds from Vietnamese medicinal plants (Thuy, Porzel, Ripperger, Sung & Adam, 1999) we now report the structural elucidation of five new chalconoids isolated besides two known compounds from the leaves of *F. bracteolatum*.

2. Results and discussion

The leaves of *F. bracteolatum* were extracted with *n*-hexane, ethyl acetate and *n*-butanol, successively. The *n*-hexane and ethyl acetate extracts were repeatedly

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subjected to column chromatography on silica gel or reversed phase RP-8 using different solvent systems. Compounds **1**, **2**, **4**, **6** and **7** were isolated from the *n*-hexane extract, compounds **3** and **5** from ethyl acetate extract.

Compounds **1** ($C_{18}H_{18}O_5$) and **2** ($C_{18}H_{18}O_4$) were identified as the known 2-hydroxy-3,4,6-trimethoxychalcone and 5,7,8-trimethoxyflav-3-ene, respectively, by comparison with spectroscopic data from the literature. Until now these two compounds were found only in the roots of *Uvaria dependens* (Annonaceae) (Nkunya, Waibel & Achenbach, 1993). Compound **1** belongs to the scarce group of retrochalcones.

Compound **3** had the elemental composition $C_{18}H_{20}O_4$, established by HRMS (*m*/*z* 300.1380 $[M]^+$). The ^1H NMR spectrum of **3** showed three aromatic methoxyl (δ 3.84, 3.79, 3.70), one methylene (δ 3.51), one phenolic hydroxyl (δ 7.94) and eight olefinic/aromatic protons. The EIMS peak at *m*/*z* 91 as well as the ^1H coupling pattern of a five spin-system of aromatic protons showed the presence of one monosubstituted phenyl ring. The absence of a carbonyl signal and the occurrence of a new methylene signal (δ 41.7) in the ^{13}C NMR spectrum in comparison to **1** indicated that compound **3** had a methylene group at C-β′ instead of a keto group. The HMBC spectrum showed the correlations between H_2-β′ (δ 3.51) and C-1′ (δ 142.3), and C-2′/6′ (δ 129.3) confirming the unsubstituted ring to be connected at C-β′. The ^{13}C signal at δ 122.7 was assigned to C-β due to its weak HMBC correlation with H-5 via $^4J_{CH}$. The substitution pattern of the second aromatic ring was established by NOESY and HMBC spectra, especially by the HMBC correlations of OH-2 and C-1/C-2/C-3 and the NOESY cross peaks between H-5 (δ 6.25) and the two methoxyl signals at δ 3.84 (OMe-4) and δ 3.79 (OMe-6). From the spectral data the structure of the new compound **3** was determined as 2-hydroxy-3,4,6-trimethoxychalcene, which belongs to the retrochalcenes (Table 1).

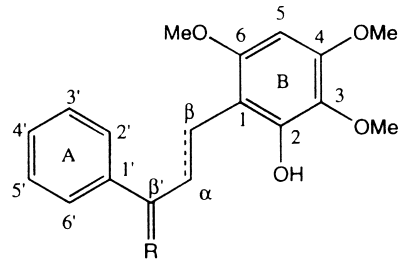
The elemental composition of compound **4** was shown to be $C_{18}H_{20}O_5$ by HRMS (*m*/*z* 316.1306 $[M]^+$). The dominant peaks in the EIMS at *m*/*z* 105 (benzoyl ion) and 197 ($C_{10}H_{13}O_4$), resulting from α- and a benzylic cleavage, respectively (Meksuriyen & Cordell, 1988), revealed the existence of a chalcone skeleton with an unsubstituted ring A and the ring B substituted with three methoxyl and one hydroxyl groups. Comparison of the ^1H, ^{13}C NMR spectra of **4** with those of **1** suggested that compound **4** differed only by hydrogenation of the α,β-double bond (δ α: 3.14, *m*, 2H; δ β: 2.96, *m*, 2H). This was confirmed by the HMBC correlations of C-β′ (δ 200.7) with H_2-α (δ 3.14) and H_2-β (δ 2.96). The HMBC correlations of H-2′/6′ with C-β′ on the one hand and H_2-β with C-2 and C-6 on the other hand confirmed the structure of **4** as 2-hydroxy-3,4,6-trimethoxydihydrochalcone, hitherto not yet described in the literature.

Compound **5** also displayed a molecular ion peak at *m*/*z* 316.1313, which was consistent with a formula of $C_{18}H_{20}O_5$. In analogy to **4** two intense fragments at *m*/*z* 211 ($C_{10}H_{11}O_5$) and 91 indicated a dihydrochalcone type, with all substituents located at ring A. Five aromatic protons at δ 7.28 (4H) and 7.19 (1H) were assigned to H-2/H-6, H-3/H-5 and H-4, respectively. Two methylene triplets at δ 3.33 and 2.96 with a coupling constant of 7.4 Hz were consistent with H_2-α and H_2-β, respectively. Furthermore, the hydroxyl signal at δ 13.7 indicated a chelat bonding, thus this group must be linked to C-2′ of ring A. Finally, NOE difference spectra were used to determine the positions of the methoxyl groups in ring A. Irradiation of the methoxyl group at δ 3.68 enhanced the hydroxyl signal, hence this methoxyl group was attached to C-3′. Irradiation of the proton signal at δ 6.29 resulted in NOE enhancements of two methoxyl signals at δ 3.95 and 3.96. Consequently, this proton signal was assigned to position 5′, the two methoxyl groups were connected to the positions 4′ and 6′. The differentiation of OMe-4′ and OMe-6′ was possible by means of a weak NOE between the methoxy signal at δ 3.96 (OMe-6′) and H_2-α. These data led to the structure of the new compound **5** as 2′-hydroxy-3′,4′,6′-trimethoxydihydrochalcone.

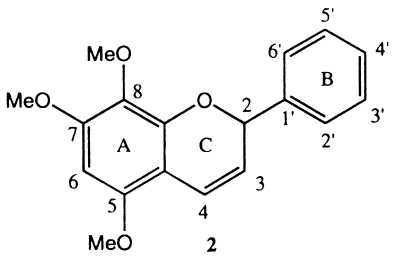
Compound **6** (*m*/*z* 332.1639 $[M]^+$, $C_{19}H_{24}O_5$) and compound **7** (*m*/*z* 346.1791 $[M]^+$, $C_{20}H_{26}O_5$) also possessed the dihydrochalcone skeleton, which was deduced from EIMS as well as NMR spectra. Comparison of ^1H and ^{13}C NMR data of **6** with those of **5** suggested that the β′-keto group in **5** was replaced by a methoxyl group in **6** (δ 3.31, 3H, *s*), which was confirmed by HMBC correlations of $OC\underline{H}_3$-β′ (δ 3.31) with C-β′ (δ 78.5), of H-β′ (δ 4.79) with C-1′ (δ 107.5), C-2′ (δ 151.2) and C-6′ (δ 154.6).

Analysis of the spectroscopic data obtained for **7** indicated a close similarity to those of **6**. Compound **7** differed from **6** by the replacement of the methoxyl group at C-β′ by an ethoxyl group, which was proved by two additional signals at δ 3.49 (2H) and δ 1.19 (*t*, J = 7.0 Hz, 3H) in the ^1H NMR spectrum as well as two signals at δ 65.6 (–O–CH_2–) and 15.4 (CH_3) in the ^{13}C NMR spectrum. Therefore, compound **6** was concluded to have the structure 2′-hydroxy-3′,4′,6′-trimethoxy-β′-methoxychalcane and compound **7** is 2′-hydroxy-3′,4′,6′-trimethoxy-β′-ethoxychalcane. Both compounds are new natural products.

Recently, potent antimitotic and cell growth inhibitory properties of several chalcones have been reported (Ducki et al., 1998). Comprehensive studies on the bioactivity of the described chalconoids are under way and will be published elsewhere.



1 R= O, $\Delta^{\alpha(\beta)}$
3 R= H_2, $\Delta^{\alpha(\beta)}$
4 R= O



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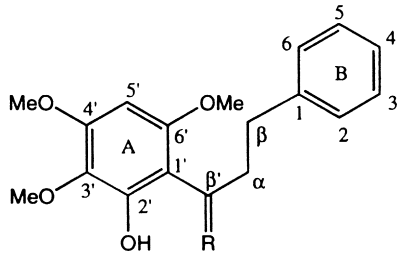

5 R= O
6 R= OMe, H
7 R= OEt, H

3. Experimental

Mps. uncorr.; $[\alpha]_D^{20}$: JASCO DIP 1000 polarimeter; IR: Bruker IFS 28; UV: KONTRON UVIKON 940; EIMS (AMD 402, AMD Intectra GmbH): 70 eV (DIS), HR–EIMS (resolution ca. 5000); ^{1}H and 2D spectra were recorded on a Varian UNITY 500 spectrometer at 499.83 MHz. ^{13}C {^{1}H} and APT spectra were recorded on a Varian GEMINI 200–300 spectrometer at 75.5 MHz. Chemical shifts were referenced to internal TMS (δ = 0, ^{1}H) and acetone-d_6 (δ = 29.8, ^{13}C), respectively.

3.1. Plant material

Leaves and branches of *F. bracteolatum* Chatt. were collected in Hoa Binh province, Vietnam in August 1997. The species was identified by Mr. Ngo Van Trai, Institute of Materia Medica, Hanoi. A voucher specimen was deposited in the herbarium of this institute.

3.2. Extraction and isolation

The plant material (850 g) was dried at room temperature, ground and extracted three times for 12 h with 95% MeOH at room temperature. MeOH was evaporated in vacuo, and the aq. solution was extracted with *n*-hexane, followed by EtOAc and *n*-BuOH (each three times). The solvents were evaporated in vacuo. The *n*-hexane extract (11 g) was chromatographed over silica gel with *n*-hexane/EtOAc (8:2), increasing the amounts of EtOAc to 40%. Raw compounds **1**, **2**, **4**, **6**, **7** were obtained. The EtOAc extract (16 g) was fractionated with *n*-hexane/acetone (7:3), increasing the ratio of acetone to 100%, to afford the compounds **3** and **5**.

3.2.1. 2-Hydroxy-3,4,6-trimethoxychalcone (*1*)

The compound was purified by CC [silica gel, *n*-hexane/EtOAc (6:4). Yellow needles from acetone. Mp 135–137°C. R_f 0.28 [silica gel, *n*-hexane/acetone (7:3)]. (see, Nkunya et al., 1993).

3.2.2. 5,7,8-Trimethoxyflav-3-ene (*2*)

The compound was purified by CC [silica gel, *n*-hexane/EtOAc (8:2) and *n*-hexane/ether (6:4)]. Oil. R_f 0.54 [silica gel, *n*-hexane/acetone (7:3)]. (see, Nkunya et al., 1993).

3.2.3. 2-Hydroxy-3,4,6-trimethoxychalcene (*3*)

The compound was purified by CC [silica gel, *n*-hexane/acetone (8:2) and RP8, acetonitril/H_2O (6:4)]. Oil. R_f 0.48 [silica gel, *n*-hexane/acetone (7:3)].

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3513 (OH), 2938, 2841, 1724, 1613, 1506, 1465, 1425, 1347, 1267, 1114, 978. UV λ_{max}^{MeOH} nm (log ε): 267 (3.91), 203 (4.54). EI–MS (70 eV) *m*/*z* (rel. int.): 300.1380 $[M]^+$ ($C_{18}H_{20}O_4$, calcd. 300.1361) (100), 285 (11), 196 (30), 181 (20), 153 (21), 105 (19), 91 (70). ^{1}H NMR (300 MHz, (acetone-d_6) δ: 7.94 (1H, *s*, OH-2), 7.26 (4H, *m*, H-2′/H-6′, H-3′/H-5′), 7.15 (1H, *m*, H-4′), 6.71 (2H, *m*, H-α, H-β), 6.25 (1H, *s*, H-5), 3.84 (3H, *s*, OMe-4), 3.79 (3H, *s*, OMe-6), 3.70 (3H, *s*, OMe-3), 3.51 (2H, *m*, H_2-β′).

3.2.4. 2-Hydroxy-3,4,6-trimethoxydihydrochalcone (*4*)

The compound was purified by CC [silica gel, *n*-hexane/acetone (9:1) and RP8, MeOH/H_2O (8:2)]. Oil. R_f 0.35 [silica gel, *n*-hexane/acetone (7:3)].

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3521 (OH), 2938, 2841, 1676 (C=O), 1618, 1598, 1511, 1465, 1427, 1349, 1241, 1159, 1112, 1039, 972, 872, 847. UV λ_{max}^{MeOH} nm (log ε): 236 (4.16), 205 (4.67). EI–MS (70 eV) *m*/*z* (rel. int.): 316.1306 $[M]^+$ ($C_{18}H_{20}O_5$, calcd. 316.1311) (100), 197 (66), 184 (40), 153 (14), 105 (26), 77 (18). ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.04 (2H, *d*, 7.4 Hz, H-2′/H-6′), 7.85 (1H, *s*, OH-2), 7.61 (1H, *tt*, *J* = 7.4 and 1.3 Hz, H-4′), 7.51 (2H, *t*, *J* = 7.4 Hz, H-3′/H-5′), 6.25 (1H, *s*,

Table 1
^{13}C NMR data of **3**–**7** (75 MHz, acetone-d_6)

C	3	4	5	6	7
1	107.4	109.5	142.7	142.9	142.9
2	149.8	149.5	129.3[a]	129.2	129.2
3	131.3	131.6	129.2[a]	129.1	129.1
4	152.4	152.2	126.7	126.4	126.5
5	89.5	89.6	129.2[a]	129.1	129.1
6	155.2	154.9	129.3[a]	129.2	129.2
β	122.7	19.4	31.3	32.7	32.6
α	131.1	39.1	46.7	37.4	37.6
β′	41.7	200.7	206.1	78.5	76.9
1′	142.3	137.9	106.6	107.5	108.1
2′	129.3	128.9	159.6	151.2	151.4
3′	129.1	129.4	131.6	132.2	132.4
4′	126.6	133.6	159.9	153.9	153.9
5′	129.1	129.4	88.3	89.7	89.6
6′	129.3	128.9	159.9	154.6	154.2
OMe-3	60.9	60.9			
OMe-3′			60.3	60.6	60.5
OMe-4	56.1	56.2			
OMe-4′			56.4	56.2	56.3[a]
OMe-6	56.1	56.1			
OMe-6′			56.4	56.2	56.2[a]
OMe-β′				57.2	
OEt-β′					65.6 15.4

[a] Exchangeable.

H-5), 3.85 (3H, *s*, OMe-4), 3.78 (3H, *s*, OMe-6), 3.72 (3H, *s*, OMe-3), 3.14 (2H, *m*, H_2-α), 2.96 (2H, *m*, H_2-β).

3.2.5. 2′-Hydroxy-3′,4′,6′-trimethoxydihydrochalcone (*5*)

The compound was purified by CC [silica gel, *n*-hexane/acetone (8:2) and RP8, acetonitril/H_2O (7:3)]. Needles from acetone. Mp 101–103°C. R_f 0.38 [silica gel, *n*-hexane/acetone (7:3)].

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3532 (*br*., OH), 2935, 2851, 1619 (conj. C=O), 1598, 1497, 1439, 1416, 1358, 1287, 1149, 1126, 999, 977, 819. UV λ_{max}^{MeOH} nm (log ε): 288 (4.17), 235 (sh.), 203 (sh.). EI–MS (70 eV) *m*/*z* (rel. int.): 316.1313 $[M]^+$ ($C_{18}H_{20}O_5$, calcd. 316.1311) (57), 211 (100), 197 (11), 184 (24), 169 (11), 91 (30). ^{1}H NMR (300 MHz, acetone-d_6) δ: 13.69 (1H, *s*, OH-2′), 7.28 (4H, *m*, H-2/H-6, H-3/H-5), 7.19 (1H, *m*, H-4), 6.29 (1H, *s*, H-5′), 3.96 (3H, *s*, OMe-6′), 3.95 (3H, *s*, OMe-4′), 3.68 (3H, *s*, OMe-3′), 3.33 (2H, *t*, *J* = 7.4 Hz, H_2-α), 2.96 (2H, *t*, *J* = 7.4 Hz, H_2-β).

3.2.6. 2′-Hydroxy-3′,4′,6′-trimethoxy-β′-methoxychalcane (*6*)

The compound was purified by CC [silica gel, *n*-hexane/EtOAc (8:2)] and then by prep. TLC [cyclohexane/acetone (6:4)]. Oil. R_f 0.46 [silica gel, *n*-hexane/acetone (7:3)]. $[\alpha]_D^{22.3}$ − 2.1° (MeOH, *c* 0.38).

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3254 (OH), 2936, 2843, 1621, 1599, 1518, 1342, 1245, 1199, 1112, 1074, 864. UV λ_{max}^{MeOH} nm (log ε): 277 (3.45), 223 (4.26). EI–MS (70 eV) *m*/*z* (rel. int.): 332.1639 $[M]^+$ ($C_{19}H_{24}O_5$, calcd. 332.1624) (11), 300 (100), 285 (34), 227 (22), 196 (47), 91 (56), 77 (15). ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.29 (1H, *s*, OH-2′), 7.27 (2H, *dd*, *J* = 7.8 and 7.2 Hz, H-3/H-5), 7.20 (2H, *d*, *J* = 7.8 Hz, H-2/H-6), 7.16 (1H, *t*, *J* = 7.2 Hz, H-4), 6.24 (1H, *s*, H-5′), 4.79 (1H, *dd*, *J* = 8.3 and 5.4 Hz, H-β′), 3.83 (3H, *s*, OMe-4′), 3.75 (3H, *s*, OMe-6′), 3.69 (3H, *s*, OMe-3′), 3.31 (3H, *s*, OMe-β′), 2.77 (1H, *m*, H_A-β), 2.62 (1H, *m*, H_B-β), 2.18 (1H, *m*, H_A-α), 2.00 (1H, *m*, H_B-α).

3.2.7. 2′-Hydroxy-3′,4′,6′-trimethoxy-β′-ethoxychalcane (*7*)

The compound was purified by CC [silica gel, *n*-hexane/EtOAc (8:2)] and then by prep. TLC [cyclohexane/acetone (1:1)]. Oil. R_f 0.45 [silica gel, *n*-hexane/acetone (7:3)]. $[\alpha]_D^{22.6}$ − 1.6° (MeOH, *c* 1.00).

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3254 (OH), 2937, 2842, 1622, 1599, 1519, 1399, 1341, 1245, 1199, 1112, 1074, 864, 820. UV λ_{max}^{MeOH} nm (log ε): 276 (3.20), 222 (3.99). EI–MS (70 eV) *m*/*z* (rel. int.): 346.1791 $[M]^+$ ($C_{20}H_{26}O_5$, calcd. 346.1780) (7), 300 (100), 285 (15), 196 (22), 181 (12), 91 (31). ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.52 (1H, *s*, OH-2′), 7.27 (2H, *dd*, *J* = 7.8 and 7.2 Hz, H-3/H-5), 7.20 (2H, *d*, *J* = 7.8 Hz, H-2/H-6), 7.16 (1H, *t*, *J* = 7.2 Hz, H-4), 6.23 (1H, *s*, H-5′), 4.88 (1H, *dd*, *J* = 8.5 and 4.9 Hz, H-β′), 3.82 (3H, *s*, OMe-4′), 3.74 (3H, *s*, OMe-6′), 3.69 (3H, *s*, OMe-3′), 3.49 (2H, *m*, $O\underline{CH_2}CH_3$-β′), 2.79 (1H, *m*, H_A-β), 2.63 (1H, *m*, H_B-β), 2.15 (1H, *m*, H_A-α), 2.02 (1H, *m*, H_B-α), 1.19 (3H, *t*, *J* = 7.0 Hz, $OCH_2\underline{CH_3}$-β′) (Table 1).

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