

Unusual chromenes from *Peperomia blanda*

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Received 23 June 2005; received in revised form 9 September 2005

Available online 3 February 2006

Abstract

From the methanol extract of the aerial parts of *Peperomia blanda* (Piperaceae), two chromenes were isolated and characterized mainly through application of 2D-NMR spectroscopy. The structures were 2S-(4-methyl-3-pentenyl)-6-formyl-8-hydroxy-2,7-dimethyl-2H-chromene and 2S-(4-methyl-3-pentenyl)-5-hydroxy-6-formyl-2,7-dimethyl-2H-chromene named as blandachromenes I and II, respectively.

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Keywords: *Peperomia blanda*; Piperaceae; Chromenes; Aerial parts

1. Introduction

The *Peperomia* genus belongs to the Piperaceae family that comprises some 600 species (Mabberley, 1993) widely distributed in southeast Brazil. Chemical studies carried out on Piperaceae species have revealed the occurrence of a variety of compounds including essential oils, pyrones, lignoids, polyphenols, unsaturated amides and alkaloids (Parmar et al., 1997, 1998; Moreira et al., 1998a,b; Baldoqui et al., 1999). These species have been extensively investigated as a source of new natural products with potential antimicrobial, antitumor and insecticidal activities (Costantin et al., 2001; Min et al., 2004; Konishi et al., 2005; Sacchetti et al., 2005). In contrast to the extensive studies of the *Piper* compounds (Parmar et al., 1997, 1998), few phytochemical studies of *Peperomia* have been reported. Previous phytochemical investigations on different species of *Peperomia* have shown the presence of flavonoids (Aqil et al., 1993), benzopyran derivatives (Seeram et al., 1998;

Mbah et al., 2002; Salazar et al., 2005), secolignans (Chen et al., 1989; Monache and Compagnone, 1996; Govindachari et al., 1998), terpenes, arylpropanoids, phenolic compounds (Tanaka et al., 1998; Moreira et al., 1999; Bayma et al., 2000; Li et al., 2003) and essential oils (Bessiere et al., 1994; Silva et al., 1999; Zoghbi et al., 2005). Some biological activities were found in compounds isolated from the *Peperomia* genus, e.g., prenylated phenols, with antiparasitic activity, from *P. galioides* (Mahiou et al., 1995, 1996), as well as analgesic activity with mice that encountered extracts of aerial parts from *P. pellucida* (Aziba et al., 2001). As part of our studies on Brazilian Piperaceae species, we have performed a phytochemical examination of the aerial parts of *P. blanda* collected in the Brazilian Atlantic Forest. In this paper, we describe the isolation and structural elucidation of two chromenes from the non-polar fraction of *P. blanda*.

2. Results and discussion

The hexane solubles of a methanol extract, obtained from the aerial parts of *P. blanda*, afforded a mixture of

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three sterols – stigmasterol, sitosterol and campesterol – and two unusual chromenes (compounds **1** and **2**, Fig. 1), which were isolated and identified.

Compound **1** (Blandachromene I) was obtained as a yellowish oil and its molecular formula was assigned as $C_{18}H_{22}O_3$ by HREIMS showing an $[M]^+$ ion at m/z 286.1536. The mass spectral fragmentation pattern showed a base peak at m/z 203.0695 $[C_{12}H_{11}O_3]^+$ and a signal at m/z 271 due to the fragment $[M-15]^+$ that resulted from loss of a methyl group. Its IR spectrum showed a broad band at 3350 cm^{-1} and an absorption at 1738 cm^{-1} which indicated the presence of a hydroxyl group and an aldehyde carbonyl group, respectively. The absorptions at 1651 and 1584 cm^{-1} suggested an aromatic ring. The ^1H NMR spectrum (Table 1) showed only one resonance due to an aromatic proton at δ 6.95 indicating a pentasubstituted aromatic ring that was correlated with carbon signals of C4, C4a, C7, C8a and C9. An AB system (δ 5.65 and 6.55, $J_{a,b} = 10.0\text{ Hz}$) suggested a *cis*-olefin with the signal at δ 5.65 being attributed to H3 which was correlated with C2, C4, C4a, C1' and C1''. On the other hand, the resonance at δ 6.55 exhibited correlations with C2, C4a, C5 and C8a confirming the location of the aromatic proton

in C5. The presence of an aldehyde carbonyl group is indicated from the singlet at δ 10.3 and its correlations which were observed with C5, C6 and C7, demonstrating that the aldehyde group should be attached to C6. The aromatic methyl group (C10) at δ 2.40 was located at C7 based on observed correlations with C6, C7 and C8. Additional signals included an olefinic proton at δ 5.10 (1H, *m*), four coupled aliphatic protons at δ 2.05 (2H, *m*, H-2') and δ 1.70 (2H, *t*, H-1'), besides three singlets corresponding to methyl groups at δ 1.35, 1.50 and 1.60. The correlations with C2, C3, C1' observed for the first methyl group confirmed its position to an oxygen-bearing carbon. The other data suggested a 4-methyl-3-pentenyl substitution in position C2 of the chromene skeleton. The ^{13}C NMR spectroscopic data of **1** (Table 1) are in agreement with the proposed assignments and confirm the presence of an aldehyde carbonyl group (δ 190.0), an oxygen-bearing aromatic carbon (C-8) at δ 160.0 and a methyl (C-10) at δ 22.0 substituted aromatic carbon (C-7) at δ 142.5. Based on the HMBC analysis (Table 1), the methyl and the 4-methyl-3-pentenyl units were attached to C2 (δ 79.9) of a pyrane ring. Comparative phytochemistry using 5-hydroxy-6-isobutyryl-7-methoxy-2,2-dimethyl-benzopyran

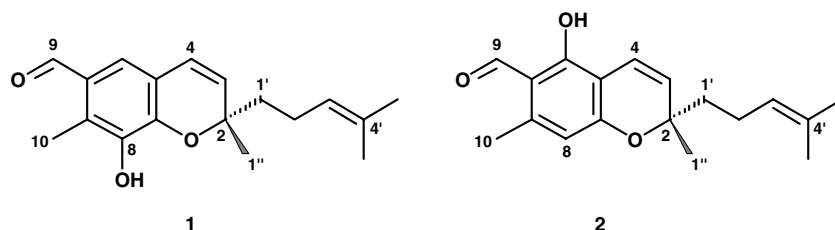


Fig. 1. Chromenes isolated from *Peperomia blanda*.

Table 1
NMR spectroscopic data of chromenes **1** and **2** isolated from *Peperomia blanda* (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR, DMSO- d_6)

No.	1			2		
	^1H NMR	^{13}C NMR	HMBC	^1H NMR	^{13}C NMR	HMBC
2		79.9			80.0	
3	5.65 <i>d</i> ($J = 10.0\text{ Hz}$)	127.5	C2, C4, C4a, C1', C1''	5.65 <i>d</i> ($J = 10.0\text{ Hz}$)	127.5	C2, C4, C4a, C1', C1''
4	6.55 <i>d</i> ($J = 10.0\text{ Hz}$)	116.5	C2, C4a, C5, C8a	6.60 <i>d</i> ($J = 10.0\text{ Hz}$)	115.0	C2, C4a, C5, C8a
4a		106.1			106.4	
5	6.95 <i>s</i>	111.3	C4, C4a, C7, C8a, C9		160.0	
6		116.0			113.0	
7		142.5			145.0	
8		160.0		6.25 <i>s</i>	111.0	C4a, C6, C7, C8a, C10
8a		158.0			160.0	
9	10.30 <i>s</i>	190.0	C5, C6, C7	10.0 <i>s</i>	196.2	C5, C6, C7
10	2.40 <i>s</i>	22.0	C6, C7, C8	2.45 <i>s</i>	18.0	C6, C7, C8
1'	1.70 <i>t</i> ($J = 6.9\text{ Hz}$)	40.0	C2, C2', C3'	1.65 <i>t</i> ($J = 6.9\text{ Hz}$)	40.0	C2, C2', C3'
2'	2.05 <i>m</i>	22.5	C2, C1', C3', C4'	2.00 <i>m</i>	22.5	C2, C1', C3', C4'
3'	5.10 <i>m</i>	124.2	C1', C2', C5', C6'	5.05 <i>m</i>	124.0	C1', C2', C5', C6'
4'		131.2			131.5	
5'	1.60 <i>s</i>	25.7	C3', C4', C6'	1.60 <i>s</i>	25.8	C3', C4', C6'
6'	1.50 <i>s</i>	17.5	C3', C4', C5'	1.50 <i>s</i>	17.5	C3', C4', C5'
1''	1.35 <i>s</i>	26.0	C2, C3, C1'	1.37 <i>s</i>	27.0	C2, C3, C1'
OH				12.6		C4a, C5, C6

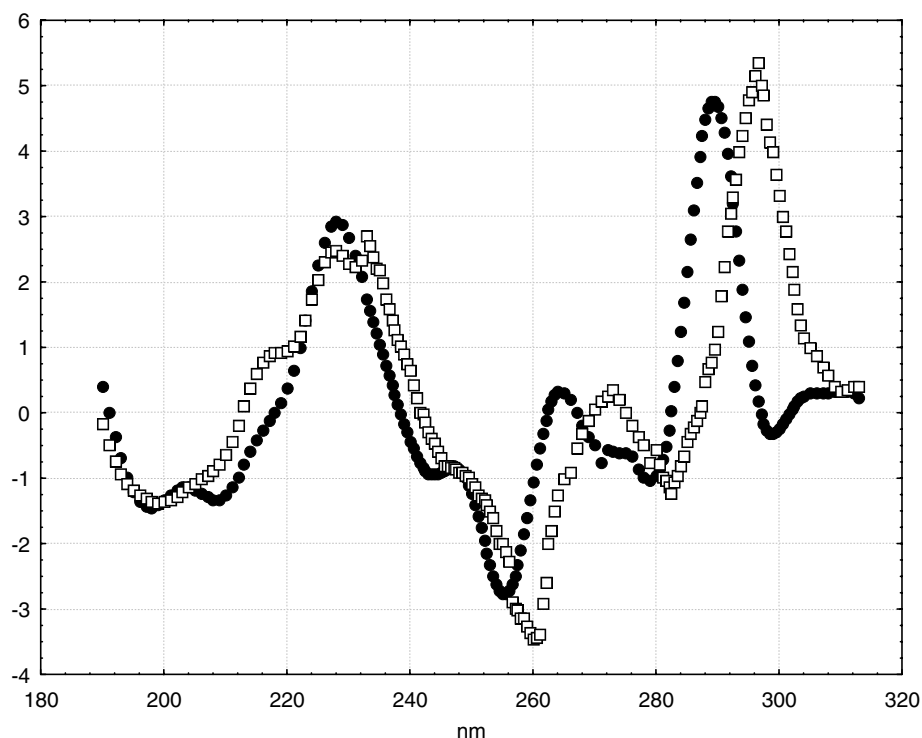


Fig. 2. CD spectra of compounds **1** and **2** (in CHCl_3) ● – Compound **1**; □ – Compound **2**.

(Ferraz et al., 2001), lhotzchromene (Moreira et al., 1998a), clusifoliol (Seeram et al., 1998), methyl 8-hydroxy-2,2-dimethyl-2*H*-chromene-6-carboxylate (Orjala et al., 1993) and galopiperone (Mahiou et al., 1996) as models, further supports the proposed structure for **1** as 2-(4-methyl-3-pentenyl)-6-formyl-8-hydroxy-2,7-dimethyl-2*H*-chromene. The optical rotation, $[\alpha]_{\text{D}}^{25} + 26.0$ was very similar to that observed for sargatriol (Kikuchi et al., 1983), although this compound is not appropriate for such direct comparison since its side-chain has two additional chiral centers. Nevertheless, the CD curve for blandachromene I (Fig. 2) was fully opposite to that observed for the sargatriol and daurichromenes (Iwata et al., 2004) including the positive Cotton effect at 260–280 nm. Therefore, despite differences in the substitution pattern in the aromatic ring of blandachromene I, the *S* configuration at C-2 was suggested.

Compound **2** (Blandachromene II), also identified as a chromene, was obtained as a yellowish oil. The UV spectrum revealed a phenolic compound with an extended chromophore. The molecular ion $[\text{M}]^+$ at m/z 286.1478 is compatible with the molecular formula of $\text{C}_{18}\text{H}_{22}\text{O}_3$. Its IR spectrum showed a broad band at 3441 cm^{-1} typical of a hydroxyl group chelated to a conjugated carbonyl aldehyde group at 1725 cm^{-1} . The major difference in the ^1H NMR spectrum of **2** as compared to **1**, was a hydroxyl group signal at δ 12.6, due to a hydrogen bonded phenolic hydroxyl. This signal was correlated with carbon signals of C4a, C5 and C6, while the aldehyde resonance at δ 10.0 has HMBC correlations (C5, C6 and C7) that confirmed the hydroxyl and aldehyde groups should be attached to C5

and C6 positions, respectively. The aromatic hydrogen at δ 6.25, correlated with C4a, C6, C7, C8a and the methyl carbon (C10), was located at C8. The aromatic methyl group (C10) was located at C7 based on observed correlations with C6, C7 and C8. The signal of H4 was correlated with C2, C4a, C5 and C8a, and finally, the correlations between H3 and C1' and C1'' confirmed the location of all substituents in the aromatic ring. The ^{13}C NMR spectrum assignments of **2** are in agreement with the proposed structure and also confirm the presence of the aldehyde carbonyl group with a signal at δ 196.2, the aromatic carbon (C-5) bearing an oxygen-substituent at δ 160.0 and the methyl substituted aromatic carbon (C-7) at δ 145.0. These spectroscopic data are in agreement with that for a racemic mixture previously described (Dike and Merchant, 1978). The placement of the hydroxyl group was confirmed by analysis of the NOE effects. The NOE effects (7-Me/H-8 and CHO) confirmed the structure for the compound **2** as 2*S*-(4-methyl-3-pentenyl)-5-hydroxy-6-formyl-2,7-dimethyl-2*H*-chromene. The optical rotation, $[\alpha]_{\text{D}}^{25} + 22.0$ was observed for the compound **2** and the CD spectra of the substance showed the same pattern obtained for the compound **1** (Fig. 2); thus the *S* configuration at C-2 was also suggested.

3. Conclusions

Both chromenes isolated from *P. blanda* are rare examples of the occurrence of benzaldehyde derivatives in the

Piperaceae species, since their members usually produce compounds more oxidized, for example benzoic acid derivatives (Moreira et al., 1998a,b; Baldoqui et al., 1999; Salazar et al., 2005). These chromenes were biosynthesized probably through the polyketide route and reaffirm the possible hypothesis of horizontal gene transfer suggested in *P. villipetiola* (Salazar et al., 2005).

4. Experimental

4.1. General procedures

Optical rotations were determined using the Perkin–Elmer 243B; polarimeter UV and IR spectra were measured on a Shimadzu UV-1601 and a Perkin–Elmer 599B, respectively. CD spectra were measured in methanol with a JASCO ORD/UV-6 spectropolarimeter. GC-MS analysis was performed in a GC-MS-QP5000 Shimadzu using fused capillary column (DB-1 30 m \times 0.20 mm), H₂ as carrier gas and temperature programming from 40 to 240 °C (5 °C/min). High-resolution mass spectra were recorded on a Micro-mass spectrometer, VG-Autospec model; ¹H- and ¹³C NMR were obtained on a Varian Gemini 200 NMR spectrometer operating at 200 MHz for ¹H NMR and 50.2 MHz for ¹³C NMR in CDCl₃, using TMS as internal standard. The ¹H and ¹³C NMR data were recorded too on a Bruker – Avance DRX 500 spectrometer (500 MHz for ¹H NMR and 125 MHz for ¹³C NMR) with TMS as internal standard, using DMSO-d₆ as solvent.

4.2. Plant material

Aerial tissue of *P. blanda* (Jacq.) Humb. Bonpl. and Kunth were collected near Parati, Rio de Janeiro State, Brazil. The identification of the plant was done by Prof. Elsie F. Guimarães, Botanical Garden of Rio de Janeiro. A voucher sample (RB: 325983) was deposited in the Herbarium of Rio de Janeiro Botanical Garden, Rio de Janeiro, Brazil.

4.3. Extraction and isolation

The dried aerial parts of the plant were exhaustively extracted with MeOH. The MeOH extract was suspended in a MeOH–H₂O (7:3) mixture and extracted in successive steps using hexane, CH₂Cl₂, EtOAc and *n*-BuOH. The hexane-soluble part was submitted to silica gel CC eluting with hexane/EtOAc mixtures of increasing polarity. The fraction eluted with hexane/EtOAc 5–10% was purified through a Sephadex LH-20 column yielding compounds **1** (18 mg) and **2** (22 mg) that were shown to be pure by TLC and GC/MS analysis. The sterols – stigmasterol, sitosterol and campesterol – were isolated as a mixture of 172 mg and identified from the literature (Blunt and Stothers, 1977).

4.4. 2*S*-(4-Methyl-3-pentenyl)-6-formyl-8-hydroxy-2,7-dimethyl-2*H*-chromene (**1**)

Yellowish oil. [α]_D²⁵ +26 (MeOH, *c* 0.1); UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ϵ): 211 (2.36), 266 (1.99); IR ν_{\max}^{film} : 3350, 2962, 2924, 2855, 1738, 1651, 1584, 1385; CD (CHCl₃) λ_{\max} $\Delta\epsilon_{287}$ +4.92, $\Delta\epsilon_{254}$ –2.87; HREIMS, *m/z*: 286.1536 (C₁₈H₂₂O₃ requires 286.1506); GC-MS *m/z* (rel. int.): 286 [M⁺] (3), 271 [M–CH₃]⁺ (2), 203 [M–C₆H₁₁]⁺ (100), 173 (4), 145 (3), 128 (3), 115 (7), 91 (11), 69 (33); For ¹H and ¹³C NMR spectra (DMSO-d₆), see Table 1; ¹H NMR (CDCl₃): δ 1.44 (3H, *s*, H-1), 1.56 (3H, *s*, H-6), 1.62 (3H, *s*, H-5), 1.77 (2H, *t*, *J* = 6.9 Hz, H-1), 2.10 (2H, *m*, H-2), 2.52 (3H, *s*, H-10), 5.09 (1H, *m*, H-3), 5.57 (1H, *d*, *J* = 10.0 Hz, H-3), 6.98 (1H, *s*, H-5), 6.64 (1H, *d*, *J* = 10.0 Hz, H-4), 10.42 (1H, *s*, CHO); ¹³C NMR (CDCl₃): δ 79.7 (*s*, C-2), δ 127.3 (*d*, C-3), δ 116.6 (*d*, C-4), δ 106.8 (*s*, C-4a), δ 111.0 (*d*, C-5), δ 116.1 (*s*, C-6), δ 143.1 (*s*, C-7), δ 159.6 (*s*, C-8), δ 155.6 (*s*, C-8a), δ 190.5 (*d*, C-9), δ 22.0 (*q*, C-10), δ 41.0 (*t*, C-1'), δ 22.6 (*t*, C-2'), δ 123.6 (*d*, C-3'), δ 131.9 (*s*, C-4'), δ 25.5 (*q*, C-5'), δ 17.5 (*q*, C-6'), δ 26.1 (*q*, C-1'').

4.5. 2*S*-(4-methyl-3-pentenyl)-5-hydroxy-6-formyl-2,7-dimethyl-2*H*-chromene (**2**)

Yellowish oil. [α]_D²⁵ +22 (MeOH, *c* 0.1); UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ϵ): 203 (0.72), 276 (1.03), 319 (0.49); IR ν_{\max}^{film} : 3441, 2969, 2875, 1725, 1653, 1568, 1379; CD (CHCl₃) λ_{\max} $\Delta\epsilon_{292}$ +5.63, $\Delta\epsilon_{260}$ –3.78; HR-MS, *m/z*: 286.1478 (C₁₈H₂₂O₃ requires 286.1506); GC-MS *m/z* (rel. int.): 286 [M⁺] (3), 271 [M–CH₃]⁺ (5), 203 [M–C₆H₁₁]⁺ (100), 173 (9), 145 (5), 115 (13), 91 (17), 69 (66), 55 (84); for ¹H and ¹³C NMR spectra (DMSO-d₆), see Table 1; ¹H NMR (200 MHz, CDCl₃): 1.44 (3H, *s*, H-1), 1.59 (3H, *s*, H-6), 1.68 (3H, *s*, H-5), 1.76 (2H, *t*, *J* = 6.9 Hz, H-1), 2.08 (2H, *m*, H-2), 2.50 (3H, *s*, H-10), 5.11 (1H, *m*, H-3), 5.51 (1H, *d*, *J* = 10.0 Hz, H-3), 6.19 (1H, *s*, H-8), 6.72 (1H, *d*, *J* = 10.0 Hz, H-4), 10.0 (1H, *s*, CHO); ¹³C NMR (CDCl₃): δ 80.5 (*s*, C-2), δ 126.1 (*d*, C-3), δ 115.7 (*d*, C-4), δ 106.5 (*s*, C-4a), δ 160.8 (*s*, C-5), δ 113.0 (*s*, C-6), δ 143.5 (*s*, C-7), δ 110.8 (*d*, C-8), δ 160.4 (*s*, C-8a), δ 192.7 (*d*, C-9), δ 18.2 (*q*, C-10), δ 41.6 (*t*, C-1'), δ 22.5 (*t*, C-2'), δ 123.6 (*d*, C-3'), δ 131.8 (*s*, C-4'), δ 25.5 (*q*, C-5'), δ 17.5 (*q*, C-6'), δ 27.2 (*q*, C-1'').

Acknowledgements

We are grateful to Eduardo M.B. da Silva and Marco A. Schiavon for obtaining, respectively, the NMR and HRMS spectra and to Luís Carlos Giordano for helping us with collecting the plant material. Financial support from CNPq, FAPERJ and FAPESP are also acknowledged.

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