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Iridoid glycosides from the stems of *Pithecoctenium crucigerum* (Bignoniaceae)

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Abstract

Sixteen crude extracts from six Panamanian plants of the family Bignoniaceae were submitted to rapid TLC tests against DPPH and acetylcholinesterase. *Pithecoctenium crucigerum* (L.) A.H. Gentry, which showed interesting activity against DPPH, has been studied. The chemical investigation of the methanol extract from the stems afforded the iridoid glycoside theviridoside and three derivatives (6′-*O*-cyclopropanoyltheviridoside, 10-*O*-hydroxybenzoyltheviridoside and 10-*O*-vanilloyltheviridoside), along with five known phenylethanoid glycosides (verbascoside, isoverbascoside, forsythoside B, jionoside D and leucosceptoside B). These last compounds were all active against DPPH.

The structures were determined by means of spectrometric and chemical methods, including 1D and 2D NMR experiments and MS analysis.

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Keywords: *Pithecoctenium crucigerum*; Bignoniaceae; Iridoid glycosides; Phenylethanoid glycosides; Cyclopropanoate

1. Introduction

The Bignoniaceae family includes about 120 genera and 800 species, growing mainly in Africa, Central and South America. Species of the Bignoniaceae are used for many purposes, such as horticulture, timber, dyes and medicine. The best-known medicinal use of the Bignoniaceae is the application of bark preparations of various species of *Tabebuia* as cancer cures (Gentry, 1992). Members of the family have, however, been poorly chemically investigated (von Poser et al., 2000).

The genus *Pithecoctenium* belongs to the tribe Bignonia-ceae, a large and morphologically diverse clade of neotrop-ical lianas (Lohmann, 2006). *Pithecoctenium crucigerum* (L.) A.H. Gentry is found in Central and South America, from Mexico to Argentina and Brazil (Woodson et al., 1973). Only one phytochemical study on *P. crucigerum* was made by von Poser et al. in 2000 who isolated the irid-oid glycosides theviridoside, ipolamiide and strictoloside.

In this work, 16 extracts (DCM and MeOH) from six Panamanian plants of the Bignoniaceae family were sub-mitted to rapid TLC tests against DPPH and acetylcholin-esterase. The methanol extract from the stems of *P. crucigerum* was selected due to its good activity observed against DPPH. This paper describes the isolation and char-acterization of theviridoside (**1**), three new iridoid glyco-sides (**2**–**4**), and five known phenylethanoid derivatives.
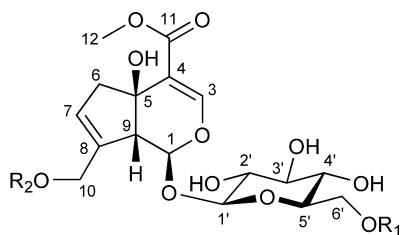
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2: R₂=H, R₁=
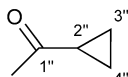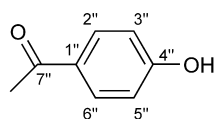
3: R₁=H, R₂=

4: R₁=H, R₂=
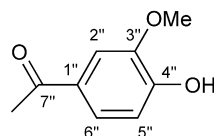
2. Results and discussion

Extracts were tested against two targets: DPPH which reveals a radical scavenging activity, and acetylcholinesterase, which is a key enzyme in the pathology of Alzheimer's disease. The results are presented in Table 1. Extracts from roots and stems of *Jacaranda caucana* Pittier presented good activities, but the plant has already been studied before (Ogura et al., 1976, 1977).

Table 1
TLC autographical screening of extracts from Bignoniaceae

Botanical species	Extract	DPPH assay	AChE assay
Callichlamys latifolia (Rich) A.H. Gentry stems	DCM	+	−
	MeOH	+	−
Jacaranda caucana Pittier roots	DCM	+	+
	MeOH	+	−
Jacaranda caucana Pittier stems	DCM	+	+
	MeOH	−	−
Mansoa hymenaea (DC.) A.H. Gentry stems	DCM	+	+
	MeOH	−	−
Mansoa standleyi (Steyerm.) A.H. Gentry roots	DCM	+	−
	MeOH	−	−
Mansoa standleyi (Steyerm.) A.H. Gentry stems	DCM	+	+
	MeOH	+	−
Paragonia pyramidata (Rich) Bur. stems	DCM	+	−
	MeOH	+	−
Pithecoctenium crucigerum (L.) A.H. Gentry stems	DCM	+	+
	MeOH	+	−

−, inactive and + active.

Because the genus *Pithecoctenium* has been little studied and the crude methanol extract of the stems exhibited good radical scavenging activity, a phytochemical investigation of *P. crucigerum* was undertaken. The extract was first partitioned between water and EtOAc, then water and *n*-BuOH. The latter showed the best activity. A preliminary HPLC/UV-DAD analysis helped to sort the major and minor metabolites into two classes. Five compounds showed maxima at 200, 215, 250(sh), 290 and 330 nm, the characteristic pattern of phenylethanoid glycoside derivatives (Li et al., 2005). They were isolated from the *n*-BuOH extract using MPLC on reversed-phase followed by Lobar® chromatography with the same C₁₈ phase. Their identity was confirmed by HR-MS and comparison of their ¹H and ¹³C NMR spectra with those of verbascoside, isoverbascoside (Wu et al., 2004), forsythoside B (Endo et al., 1982), jionoside D (Sasaki et al., 1989) and leucosceptoside B (Miyase et al., 1982). None of these five compounds has ever been described in the genus *Pithecoctenium*. Moreover, forsythoside B and leucosceptoside B have never been reported in the Bignoniaceae family. They are all active against DPPH, which explains the activity of the crude extract.

The second class of compounds (**1–4**) showed two maxima at 200 and 235 nm in the HPLC/UV-DAD analysis. Compound **1** was identified as theviridoside by comparison of its ¹H and ¹³C NMR spectra (Tables 2 and 3) with the literature data (Sticher and Schmid, 1969), in agreement with the HR-ESI-MS data which indicated a molecular formula of $C_{17}H_{24}O_{11}$. Furthermore, **1** presented characteristic elements of iridoid glycosides biosynthetically derived from geniposidic acid, such as the shifts of H-1 (δ 5.54), H-3 (δ 7.49). The downfield shift of H-7 (δ 5.69) indicated the presence of a double-bond on the cyclopentane ring and finally the typical shift of H-10 (δ 4.23, 4.11) geminal to an hydroxyl group (Boros and Stermitz, 1990; Jensen et al., 2002). Compound **1** was previously isolated from *P. crucigerum* (von Poser et al., 2000). Compound **2** had the same UV spectra profile and the HR-ESI-MS indicated a molecular formula of $C_{21}H_{28}O_{12}$. Moreover, the APCI-IT-MS analysis in the negative-ion mode showed a fragment at *m/z* 241, also observed in the APCI-IT-MS of **1**, corresponding to the same aglycone moiety. Compound **2** thus appeared to be a derivative of **1** with an additional C_4H_4O residue. Direct comparison of both ¹H (Table 2) and ¹³C (Table 3) NMR spectra of **1** and **2** first showed additional signals for **2**: two more proton signals at δ 0.91 (4H, m) and δ 1.65 (1H, m) ppm and four more carbons at δ 8.8, 8.9, 13.6 and 176.5 ppm corresponding to a carbonyl group. All other shifts were comparable, except for the position 6′ for which proton and carbon shifts were deshielded. This showed that compound **2** was acylated at the 6′-position of the sugar moiety. According to the DEPT data, the carbon at 13.6 ppm (C-2″, δ_H 1.65) corresponded to a methine group and signals at 8.9 ppm (C-3″ and 4″, δ_H 0.91) were assigned to two methylenic carbons. The ¹H–¹H COSY spectrum indicated that protons at δ 1.65 and 0.91 ppm were on adjacent carbon atoms. Finally,

Table 2
^{1}H NMR spectra of compounds **1–4** (500 MHz in CD$_3$OD)

^{1}H	1	2	3	4
1	5.54 *d* (*J* = 5.4 Hz)	5.36 *d* (*J* = 5.9 Hz)	5.58 *d* (*J* = 5.9 Hz)	5.62 *d* (*J* = 5.9 Hz)
3	7.49 *s*	7.49 *s*	7.51 *s*	7.51 *s*
6	2.83, 2H, *brs*	2.82, 2H, *dd* (*J* = 17.6, 9.8 Hz)	2.88, 2H, *brs*	2.89, 2H, *brs*
7	5.69 *d* (*J* = 1.5 Hz)	5.72 *d* (*J* = 1.5 Hz)	5.86 *d* (*J* = 1.5 Hz)	5.87 *d* (*J* = 1.5 Hz)
9	3.03 *d* (*J* = 4.8 Hz)	3.03 *d* (*J* = 4.9 Hz)	3.09 *dd* (*J* = 5.9, 1.0 Hz)	3.10 *d* (*J* = 5.9 Hz)
10	4.23, 4.11 *d* each (*J* = 14.2 Hz)	4.18, 2H, *dd* (*J* = 25.4, 16.7 Hz)	4.93, 2H, *d* (*J* = 2.4 Hz)	4.94, 2H, *s*
COOMe	3.73, 3H, *s*	3.73, 3H, *s*	3.73, 3H, *s*	3.73, 3H, *s*
1′	4.62 *d* (*J* = 7.8 Hz)	4.64 *d* (*J* = 7.8 Hz)	4.64 *d* (*J* = 8.3 Hz)	4.64 *d* (*J* = 8.3 Hz)
2′	3.21 *dd* (*J* = 9.3, 7.8 Hz)	3.22 *m*	3.23 *dd* (*J* = 9.3, 7.8 Hz)	3.23 *m*
3′	3.37 *t* (*J* = 8.8 Hz)	3.36 *t* (*J* = 9.0 Hz)	3.37 *t* (*J* = 9.3 Hz)	3.36 *t* (*J* = 9.3 Hz)
4′	3.28 *m*	3.31 *m*	3.28 *m*	3.28 *m*
5′	3.28 *m*	3.47 *m*	3.27 *m*	3.27 *m*
6′	3.87 *dd* (*J* = 12.0, 1.7 Hz)	4.36 *dd* (*J* = 12.0, 2.2 Hz)	3.83 *dd* (*J* = 12.0, 1.2 Hz)	3.82 *m*
	3.64 *dd* (*J* = 12.0, 5.6 Hz)	4.22 *dd* (*J* = 11.7, 5.9 Hz)	3.63 *dd* (*J* = 11.7, 5.3 Hz)	3.63 *dd* (*J* = 12.0, 5.1 Hz)
2″		1.65 *m*	7.91 *d* (*J* = 8.8 Hz)	7.58 *d* (*J* = 1.9 Hz)
3″		0.91, 4H, *m*	6.83 *d* (*J* = 8.8 Hz)	
4″				
5″			6.83 *d* (*J* = 8.8 Hz)	6.86 *d* (*J* = 8.3 Hz)
6″			7.91 *d* (*J* = 8.8 Hz)	7.60 *dd* (*J* = 8.3, 1.9 Hz)
OMe				3.90, 3H, *s*

Table 3
^{13}C NMR spectra of compounds **1–4** (125 MHz in CD$_3$OD)

^{13}C	1	2	3	4
1	96.9	97.6	97.6	97.5
3	154.0	153.9	154.0	154.0
4	114.5	114.7	114.6	114.6
5	76.4	76.6	76.5	76.5
6	46.9	47.1	47.3	47.3
7	126.7	126.9	130.1	130.4
8	142.0	142.1	137.3	137.2
9	56.7	56.7	57.4	57.5
10	61.0	61.1	63.3	63.5
11	168.2	168.2	167.9	167.9
COOMe	51.6	51.7	51.6	51.7
1′	100.2	100.2	100.3	100.3
2′	74.6	74.5	74.6	74.6
3′	77.6	77.4	77.7	77.7
4′	71.5	71.5	71.5	71.5
5′	78.5	75.7	78.4	78.2
6′	62.7	64.5	62.8	62.8
1″		176.5	120.7	122.5
2″		13.6	132.9	113.8
3″		8.9	116.2	148.9
4″		8.8	162.0	152.8
5″			116.2	116.1
6″			132.9	125.3
7″			167.9	168.2
OMe				56.5

long-range correlations observed on the HMBC spectrum for the carbonyl carbon C-1″ (*δ* 176.5) with the methylenic protons H-6′ (*δ* 4.22 and 4.36) and H-3″/H-4″ (*δ*$_H$ 0.91) suggested the presence of a 6′-cyclopropanoate moiety. Kawagishi et al. (2006) isolated carnitine esterified with the same cyclopropanoate group from the mushroom *Suillus laricinus*. The ^{1}H and ^{13}C NMR shifts for this group were similar in both compounds, such as the non-equiva-

lent 4″-carbones (8.8 and 8.9 in **2** *vs* 9.4 and 9.5 ppm in carnitine). Alkaline hydrolysis of **2** (Cogne et al., 2005) yielded a mixture of two compounds. The presence of **1** was confirmed by HPLC-UV-DAD, and the cyclopropanecarboxylic acid was identified using GC/MS and comparison with a standard. Thus the structure of **2** was 6′-*O*-cyclopropanoyltheviridoside. This is the first description of an iridoid esterified with cyclopropanecarboxylic acid. Among the rare natural products with such a substituent is rubesanide from *Fagara rubescens* (Dadson and Minta, 1976).

The HR-ESI-MS of **3** gave a molecular formula of $C_{24}H_{28}O_{13}$, differing from **1** by a $C_7H_4O_2$ residue. The NMR spectra of **1** and **3** (Tables 2 and 3) were very similar. However, significant downfield shifts of the signals corresponding to H-10 (ca. 0.8 ppm), and C-10 (2 ppm), and an upfield one for C-8 (5 ppm) could be observed. These shifts suggested that in **3** the C-10 oxygen was esterified. Moreover, the aromatic signals in the ^{1}H NMR spectrum at *δ* 7.91 (2H, *d*, *J* = 8.8 Hz) and *δ* 6.83 ppm (2H, *d*, *J* = 8.8 Hz) suggested that the ester residue was a symmetric moiety. The ^{13}C NMR spectra corroborated this information and showed the presence of a carbonyl carbon at *δ* 167.9 (C-7″) ppm and a phenolic carbon at *δ* 162.0 (C-4″) ppm. These elements indicated that C-10 was esterified by a *p*-hydroxybenzoyl group. Thus, the new structure **3** was named 10-*O*-*p*-hydroxybenzoyltheviridoside. The analogue 10-*O*-benzoyltheveside has been reported from *Cerbera manghas* L. (Apocynaceae) (Yamauchi et al., 1990).

The molecular formula of **4**, deduced from HR-ESI-MS was $C_{25}H_{30}O_{14}$, with an additional CH_2O residue when compared to **3**. The ^{1}H and ^{13}C spectra (Tables 2 and 3) of the theviridoside moieties in the two compounds were almost identical, showing that the difference must reside in the ester parts of the molecules. Analysis of the spectra of **4** indicated that the acyl moiety was a vanilloyl group,

and this was corroborated by the long-range ^{1}H–^{13}C correlation observed in the HMBC spectrum between the methoxy group (δ 3.90) and C-3″ (δ 148.9). Thus compound **4** was 10-*O*-vanilloyltheviridoside, a new natural product.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR: Varian Unity Inova NMR instrument, Palo Alto, CA, USA. ^{1}H and ^{13}C NMR spectra were recorded in CD$_3$OD at 500 and 125 MHz, respectively. TMS: int. standard. UV: Perkin-Elmer-Lambda-20 UV–VIS spectrophotometer. UV spectra were recorded in MeOH. [α]$_D$: Perkin-Elmer-241 polarimeter. TLC: silica gel 60 F$_{254}$ Al sheets (Merck) using EtOAc–formic acid–glacial acetic acid–water 100:11:11:26. MPLC: RP-18 LiChroprep (40–63 μm; 460 × 50 mm i.d.; Merck). LPLC: Lobar RP-18 column (LiChroprep 40–63 μm, 310 × 25 mm i.d.; Merck). EI-MS: Finnigan MAT TSQ-700 triple stage quadrupole instrument, in negative mode. APCI-MS: Finnigan MAT LCQ ion-trap instrument, in negative mode. HRMS: Micromass LCT Premier, in negative mode. GC–MS with a Varian 3400 gas chromatograph coupled to a Finnigan MAT TSQ-70 triple stage quadrupole mass spectrometer in the EI mode. A Chrompak (CP Select CB for FAME) capillary column (100 m × 0.25 mm i.d.; 0.25 μm) was used at 80 °C (He column head pressure: 25 psi). HPLC-UV-DAD was carried out on a HP1100 (Agilent) with a Nova-Pak RP-18 column (4 μm; 150 × 3.9 mm i.d.; Waters) using an acetonitrile + 0.05%TFA-H$_2$O + 0.05% TFA gradient (2:98–40:60) in 40 min. The detection was performed at 210, 254, 280 and 360 nm.

3.2. Plant material

The stems of *P. crucigerum* (L.) A.H. Gentry were collected in March 2003 in Soberania National Park, Panama and identified by Prof. Mireya Correa, Director of the Herbarium of the University of Panama. Vouchers are deposited at the University of Panama (FLORPAN 5890) and at the Laboratory of Pharmacognosy and Phytochemistry, Geneva, Switzerland (No. 2005003).

3.3. Extraction and isolation

The air-dried powdered stems of *P. crucigerum* (820 g) were first extracted at room temperature with dichloromethane, then with methanol affording, respectively, 3.0 and 37.5 g of extracts. Methanol extract (30.0 g) was partitioned by LLE between EtOAc and water (500 ml of each). The aqueous fraction was then partitioned with *n*-BuOH (500 ml). This LLE yielded 1.6 g of EtOAc, 7.0 g of *n*-BuOH, and 21.8 g of water extracts. The *n*-BuOH extract (5.8 g) was separated by medium pressure liquid chromatography (MPLC) with MeCN–H$_2$O step gradient (5:95

to 60:40 in 5% steps) to afford 41 fractions. This separation yielded 181 mg of compound **1** (fraction 9), 16 mg of **2** (fraction 15), 272 mg of verbascoside (fraction 18) and 54 mg of isoverbascoside (fraction 20).

Fractions 17, 23, and 24 were purified by low pressure liquid chromatography (LPLC) with a MeOH–H$_2$O step gradient yielding, respectively, 12 mg of forsythoside B, 3 mg of **3**, 3 mg of jionoside D, 5 mg of leucosceptoside B, and 3 mg of **4**.

3.4. Radical scavenging activity (DPPH) TLC assay

A TLC autographic assay of radical scavenging activity using the DPPH radical was employed for extract screening. After application of 100 μg of the samples on a silica gel 60 F$_{254}$ Al sheet (Merck), the TLC plate was developed in hexane–EtOAc 1:1 for the dichloromethane extracts, or CH$_2$Cl$_2$–MeOH–H$_2$O 13:7:1 for the methanol extracts, and then thoroughly dried for complete removal of solvents. A solution of 2,2-diphenyl-1-picryl-hydrazyl radical (DPPH, 2 mg/ml in MeOH) was then sprayed. Inhibitors appeared as yellow spots against a purple background.

3.5. Acetylcholinesterase (AChE) TLC assay

The bioautographic assay developed by Marston et al. (2002) was used in this work. After application of the samples on a silica gel 60 F$_{254}$ Al sheet (Merck), the TLC plate was developed in hexane–EtOAc 1:1 for the dichloromethane extracts, or CH$_2$Cl$_2$–MeOH–H$_2$O 13:7:1 for the methanol extracts, and then thoroughly dried for complete removal of solvents. The plate was then sprayed with a solution of acetylcholinesterase (1500 U) and bovine serum albumin (225 mg) dissolved in 500 ml of a Tris–hydrochloric acid buffer at pH 7.8 and incubated at 37 °C for 15 min in polystyrene boxes with a moist atmosphere. Then, a solution (1:4) of naphthyl acetate (250 mg in 100 ml EtOH) and Fast Blue B salt (50 mg in 20 ml H$_2$O) was sprayed onto the plate to give a purple coloration after 1–2 min. Inhibitors appeared as white spots against a purple background.

3.6. 6′-O-Cyclopropanoyltheviridoside (2)

Pale yellow amorphous solid. [α]$_D^{25}$ −27.3° (MeOH, *c* 1.0), UV (MeOH) λ_{max} (log ε) 200 (4.04), 231 (3.79), 282 (3.13), 324 (3.01); ^{1}H and ^{13}C NMR: see Tables 2 and 3, HR-ESI-MS: *m/z* 517.1536 (C$_{22}$H$_{29}$O$_{14}$: [M+formiate]$^-$ requires 517.1557).

Basic hydrolysis: To 5.0 mg of **2**, 0.5 ml of diethylamine, 4.0 ml of MeOH and 0.5 ml of water were added. The mixture was stirred at 35 °C for 17 h. The reaction was monitored by TLC. To confirm the presence of cyclopropanecarboxylic acid, a GC–MS analysis was performed using a standard from Sigma–Aldrich (D-89555, Steinheim, Germany).

3.7. 10-O-Hydroxybenzoyltheviridoside (3)

Pale yellow amorphous solid. $[\alpha]_D^{25}$ −31.8° (MeOH, c 1.0), UV (MeOH) λ_{max} nm (log ε): 201 (4.22), 253 (3.91), 325 (3.32); ^{1}H and ^{13}C NMR: see Tables 2 and 3, HR-ESI-MS: m/z 523.1438 ($C_{24}H_{27}O_{13}$: [M−H]$^-$ requires 523.1452).

3.8. 10-O-Vanilloyltheviridoside (4)

Pale yellow amorphous solid. $[\alpha]_D^{25}$ −26.6° (MeOH, c 2.0), UV (MeOH) λ_{max} nm (log ε): 202 (4.31), 220 (4.16), 254 (3.85), 292 (3.68), 327 (3.46); ^{1}H and ^{13}C NMR: see Tables 2 and 3, HR-ESI-MS: m/z 553.1541 ($C_{25}H_{29}O_{14}$: [M−H]$^-$ requires 553.1557).

Acknowledgment

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