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Muchimangins G–J, Fully Substituted Xanthones with a Diphenylmethyl Substituent, from *Securidaca longepedunculata*

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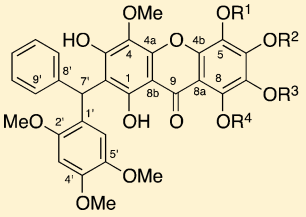
Supporting Information

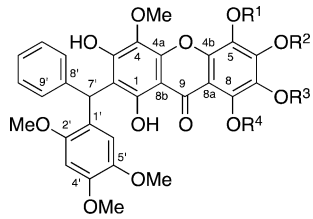
ABSTRACT: Four highly oxygenated xanthones, muchimangins G–J (**1**–**4**), have been isolated from the roots of *Securidaca longepedunculata* collected in Democratic Republic of Congo. Their structures were elucidated by analyses of spectroscopic data to be fully substituted xanthones with a diphenylmethyl substituent at C-2.



1 $R^1 = R^2 = R^3 = Me$, $R^4 = H$
2 $R^1 = H$, $R^2 = R^3 = R^4 = Me$
3 $R^1 = R^3 = Me$, $R^2 = R^4 = H$
4 $R^1 = R^4 = Me$, $R^2R^3 = -CH_2-$

Securidaca longepedunculata Fresen. (Polygalaceae) is an important traditional folk medicine extensively used in Africa. The roots are used for several diseases such as sneezing, syphilis, gonorrhea, rheumatic pain, headache, feverish pain, malaria, and sleeping sickness among others.[1] The plant is reported to contain alkaloids, anthraquinones, flavonoids, saponins, terpenoids, and xanthones.[2,3] In a search for antiausteric compounds as the lead compounds for antipancreatic cancer drugs from traditional medicines,[4] the $CHCl_3$ extracts from the roots of *Garcinia huillemsis* (Clusiaceae) and *Securidaca longepedunculata* (Polygalaceae) used in Congolese traditional medicine displayed potent preferential cytotoxicity against the human pancreatic cancer PANC-1 cell line under nutrient-deprived medium.[5] From the $CHCl_3$ extract of *G. huillemsis*, damnacanthal was identified as the active constituent causing preferential necrotic cell death under nutrient-deprived and serum-sensitive conditions.[5] From the $CHCl_3$ extract of *S. longepedunculata* five new xanthones and a new benzyl benzoate together with 22 known compounds were identified.[6] In addition, six highly oxygenated xanthones, muchimangins A–F,[7,8] which possess a diphenylmethyl substituent at C-2 or C-4, were identified. In the continuing study on the constituents of *S. longepedunculata*, the minor constituents were examined and afforded four unique xanthone derivatives, muchimangins G–J (**1**–**4**) (Figure 1). Herein the structure elucidation of **1**–**4** together with their in vitro preferential cytotoxicity is reported.

Muchimangin G (**1**) possesses a molecular formula of $C_{33}H_{32}O_{12}$ based on its HREIMS and ^1H and ^{13}C NMR spectroscopic data (Table 1). The ^1H NMR spectrum of **1** showed resonances for two *p*-aromatic protons (δ_H 6.94, 6.56), a monosubstituted phenyl moiety (δ_H 7.26, 2H, t, J = 7.7 Hz; δ_H 7.20, t, J = 7.7 Hz; δ_H 7.17, 2H, d, J = 7.7 Hz), a methine proton (δ_H 6.34, s), and seven methoxy groups (δ_H 4.14, 4.05, 3.96, 3.93, 3.89, 3.72, 3.71), together with two hydrogen-bonded (δ_H 12.31, 11.88) and a free hydroxy proton (δ_H 7.00). The ^{13}C NMR spectrum of **1** exhibited resonances for 33 carbons including those for a conjugated carbonyl (δ_H 184.1), 12 oxygenated and 12 nonoxygenated sp^2 carbons, and a methine (δ_C 39.1), together with seven methoxy carbons (δ_C 62.0, 61.7 (2C), 61.3, 57.1, 56.6, 56.1). These resembled those of muchimangins B, C, E, and F, isolated from the same extract,[7,8] suggesting **1** to be a xanthone derivative with a 1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl, three hydroxy, and four methoxy groups.



1 $R^1 = R^2 = R^3 = Me$, $R^4 = H$
2 $R^1 = H$, $R^2 = R^3 = R^4 = Me$
3 $R^1 = R^3 = Me$, $R^2 = R^4 = H$
4 $R^1 = R^4 = Me$, $R^2R^3 = -CH_2-$

Figure 1. Structures of muchimangins G–J (**1**–**4**) isolated from *Securidaca longepedunculata*.

In the HMBC spectrum of **1** (Figure 2), the methine proton (δ_H 6.34, H-7′) showed correlations with the sp^2 carbons at δ_C 115.4 (C-6′), 122.0 (C-1′), and 151.5 (C-2′) in addition to those with the carbons of the phenyl ring. The aromatic protons at δ_H 6.94 (H-6′) and δ_H 6.56 (H-3′) showed HMBC correlations with the carbons at δ_C 151.5 (C-2′), 148.5 (C-4′), and 143.1 (C-5′) and with the carbons at δ_C 122.0 (C-1′), 151.5 (C-2′), 148.5 (C-4′), and 143.1 (C-5′), respectively. In addition, the methoxy protons at δ_H 3.89, 3.72, and 3.71 showed HMBC correlations with the carbons at δ_C 148.5 (C-4′), 151.5 (C-2′), and 143.1 (C-5′), respectively. Thus, the

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Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data for Muchimangins G–J (1–4) in $CDCl_3$

	1		2		3		4	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		156.4		157.3		156.4		154.7[a]
2		112.6		112.2		112.5		112.1
3		156.1		155.1		155.9		157.0
4		127.1		126.6		127.2		126.3[b]
4a		145.2[a]		146.6[a]		156.4[a]		144.3[c]
4b		147.0[a]		146.9[a]		149.4[a]		146.4[c]
5		154.3		148.5[a]		127.2		128.3[b]
6		132.5		131.4		131.6		135.5[c]
7		135.8		137.9		130.1		146.8[c]
8		150.5		148.5[a]		150.1		137.4
8a		103.3		108.4		101.1[b]		109.3[d]
8b		101.4		102.7		101.0[b]		102.8[d]
9		184.1		180.4		184.1		180.6
1′		122.0		122.3		121.8		122.4
2′		151.5		151.5		151.5		151.4
3′	6.56 s	98.2	6.56 s	98.3	6.56 s	98.1	6.55 s	98.3
4′		148.5		148.5		148.5		148.3
5′		143.1		143.2		143.1		143.2
6′	6.94 s	115.4	7.01 s	115.3	6.94 s	115.2	7.01 s	115.4
7′	6.34 s	39.1	6.37 s	39.0	6.34 s	38.6	6.37 s	39.0
8′		141.9		142.2		141.9		142.2
9′, 13′	7.17 d (7.7)	128.2	7.17 m	128.1	7.17 d (7.7)	128.2	7.16 d (7.8)	128.1
10′, 12′	7.26 t (7.7)	128.0	7.26 m	128.0	7.26 t (7.7)	128.1	7.22 t (7.8)	128.0
11′	7.20 t (7.7)	126.0	7.18 m	125.8	7.20 t (7.7)	125.9	7.18 t (7.8)	125.8
4-OMe	4.05 s	61.7[b]	4.02 s	61.8[b]	4.02 s	61.8[c]	4.02 s	61.6
5-OMe	4.14 s	61.7[b]			4.03 s	61.8[c]	4.08 s	61.6
6-OMe	3.96 s	62.0[b]	4.08 s	61.6[b]				
7-OMe	3.93 s	61.3[b]	4.01 s	61.7[b]	4.01 s	61.1[c]		
8-OMe			3.94 s	62.1[b]			4.05 s	56.1[e]
2′-OMe	3.72 s	57.1[c]	3.72 s	57.2[c]	3.72 s	57.1[d]	3.71 s	57.2[e]
4′-OMe	3.89 s	56.6[c]	3.88 s	56.5[c]	3.89 s	56.6[d]	3.88 s	56.5[e]
5′-OMe	3.71 s	56.1[c]	3.72 s	56.1[c]	3.72 s	56.1[d]	3.71 s	56.1[e]
1-OH	12.31 s		13.64 s		12.35 s		13.57 s	
3-OH	7.00 s		6.94 s		7.01 s		6.91 s	
8-OH	11.88 s				12.04 s			
OCH_2O							6.10 s	102.6

[a–e]May be interchanged in each column.

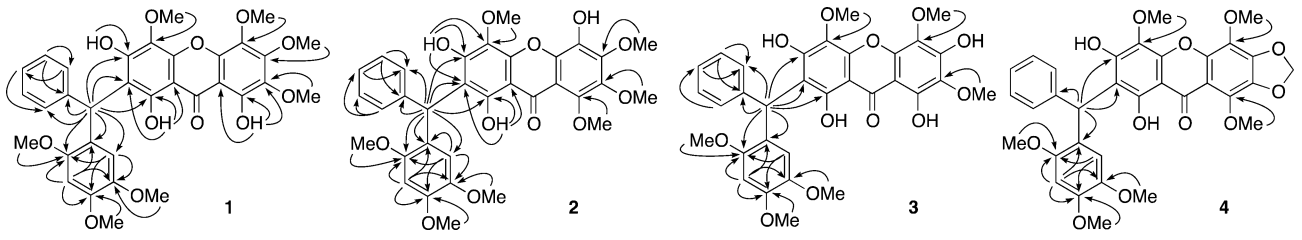

Figure 2. Significant HMBC correlations ($^{1}H \rightarrow {}^{13}C$) for muchimangins G–J (**1**–**4**).

presence of a 1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl moiety was established.

The structure of the xanthone unit was also elucidated by analysis of the 1D and 2D NMR spectra. The methine proton H-7′ (δ_H 6.34) and the hydrogen-bonded hydroxy proton at δ_H 12.31 (1-OH) both showed HMBC correlations with the carbons at δ_C 156.4 and 112.6, indicating the location of the 1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl unit at C-2. Methine proton H-7′ (δ_H 6.34) and the hydroxy proton at δ_H 7.00 both showed HMBC correlations with the carbon at δ_C 155.3, suggesting the hydroxy group to be located at C-3. The carbon at δ_C 127.1 showed HMBC correlations with both the 3-OH (δ_H 7.02) group and the methoxy protons at δ_H 4.05 (Figure 2). Therefore, the methoxy group should be located at C-4. Thus, **1** has the hydroxy (δ_H 12.31), diphenylmethyl, hydroxy (δ_H 7.00), and methoxy groups at C-1, C-2, C-3, and C-4, respectively. On the basis of the resemblance of the ^{1}H and ^{13}C NMR data to those of 1,6,8-trihydroxy-2,3,4,5-tetramethoxyxanthone[6] isolated from the same extract, the presence of the 8-hydroxy-5,6,7-trimethoxyxanthone moiety was evident. Thus,

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the structure of muchimangin G was defined as 1,3,8-trihydroxy-4,5,6,7-tetramethoxy-2-[1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl]xanthone (**1**). The absolute configuration at C-7′ could not be determined since limited sample quantity precluded its crystallization and subsequent X-ray crystallographic analysis.

The molecular formula of muchimangin H (**2**) was established by HRFABMS and ^{13}C NMR data to be $C_{33}H_{32}O_{12}$, the same as that of **1**. The ^{1}H and ^{13}C NMR data of **2** (Table 1) resembled those of **1**, except for the lack of the resonance of one of the two hydrogen-bonded hydroxy groups in **1** and the shielding of the carbonyl carbon (**2**: δ_C 180.4; **1**: δ_C 184.1). Thus, **2** was considered to be an isomer of **1**. The HMBC correlations (Figure 2) indicated the presence of a 1,3-dihydroxy-2-methoxy-4-[1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl]xanthone moiety. Among the remaining substituents (one hydroxy and three methoxy groups), two methoxy groups (δ_H 4.08 and 4.01) showed HMBC correlations with the oxygenated sp^2 carbons (δ_C 131.4 and 137.9) and should be located at C-6 and C-7 because the observed shielding effects are characteristic for the oxygenated sp^2 carbons carrying two *ortho* substituents.[6,9,10] The absence of the hydrogen-bonded hydroxy resonance and the shielding of the carbonyl carbon suggested that C-8 and C-5 carry methoxy and a hydroxy group, respectively, instead of a hydroxy and a methoxy group in **1**. Thus, the structure of muchimangin H was defined as 1,3,5-trihydroxy-4,6,7,8-tetramethoxy-2-[1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl]xanthone (**2**).

The molecular formula $C_{32}H_{30}O_{12}$ of muchimangin I (**3**), together with its ^{1}H and ^{13}C NMR data (Table 1), indicated **3** to be a de-*O*-methyl derivative of **1**. The HMBC spectrum of **3** (Figure 2) indicated the presence of a 1,3-dihydroxy-2-methoxy-4-[1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl]-xanthone moiety. Among the remaining substituents (two hydroxy and two methoxy groups), one hydrogen-bonded hydroxy group (δ_H 12.04) should be located at C-8, while the shielding of C-5 and C-7, compared to those of **1**, suggested that C-6 should carry a hydroxy group. Thus, the structure of muchimangin I was defined as 1,3,6,8-tetrahydroxy-4,5,7-trimethoxy-2-[1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl]-xanthone (**3**).

The HREIMS and ^{13}C NMR spectroscopic data of muchimangin J (**4**) established the molecular formula to be $C_{33}H_{30}O_{12}$. The ^{1}H and ^{13}C NMR data of **4** (Table 1) indicated the presence of four benzene rings, a methine group (δ_H 6.37, δ_C 39.0), and a conjugated carbonyl carbon (δ_C 180.6) together with six methoxy (δ_H 4.08, 4.05, 4.02, 3.88, 3.71 (6H); δ_C 61.6 (2C), 57.2, 56.5, 57.1 (2C)), a methylenedioxy (δ_H 6.10, δ_C 102.6), and a hydrogen-bonded (δ_H 13.57) and a free (δ_H 6.91) hydroxy group. These resembled those of muchimangin A, isolated from the same extract,[7,8] except for the presence of an additional methoxy group (δ_H 4.08, δ_C 61.6) in **4** and the lack of one isolated aromatic proton (δ_H 6.20) in muchimangin A. In addition, the HMBC correlations (Figure 2) indicated the chemical shift values ascribed to C-5, C-6, C-7, and C-8 to be similar to those of a 1,4-dimethoxy-2,3-methylenedioxyxanthone moiety.[11] Therefore, **4** was assumed to be a muchimangin A derivative substituted at C-5 with the additional methoxy group. However, the chemical shift values of C-2 and C-4 (C-2: δ_C 112.1, C-4: δ_C 126.3) were slightly different from those of muchimangin A (C-2: δ_C 107.1, C-4: δ_C 129.6) and more similar to those of **1**−**3** (C-2: δ_C 112.2−112.6, C-4: δ_C 126.6−127.1) with the 1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl and methoxy groups at C-2 and C-4, respectively. Thus, the structure of muchimangin J was defined as 1,3-dihydroxy-4,5,8-trimethoxy-2-[1-(2,4,5-trimethoxyphenyl)-1-phenylmethyl]-6,7-methylenedioxyxanthone (**4**).

The in vitro preferential cytotoxic activity of muchimangins G−J (**1**−**4**) against human pancreatic cancer PANC-1 cells in nutrient-rich (DMEM) and nutrient-deprived media (NDM) were evaluated.[4−6] However, no cytotoxicity, either in DMEM or in NDM, could be detected.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were recorded on a JASCO P-2100 digital polarimeter. HREIMS data were recorded using a JEOL JMS-700T mass spectrometer, and HRFABMS data on a JEOL AX505W mass spectrometer using glycerol as matrix. NMR spectra were recored using a JEOL JNM-LA400 spectrometer with TMS as an internal standard. Chemical shifts are given on the δ scale from standard TMS, and coupling constants (J) in Hz. MPLC was performed using a Büchi pump module C-650 or Yamazen MPLC 560 pump system. Column chromatography was performed with normal-phase silica gel (silica gel 60N, spherical, neutral, 40−50 μm, Kanto Chemical Co., Inc.). Analytical and preparative TLC were performed on precoated $60F_{254}$ or RP-$18F_{254}$ plates (Merck, 0.25 or 0.50 mm thickness).

Plant Material. Roots of *S. longepedunculata* were collected in the Katanga Province, Democratic Republic of Congo, during April 2009 by Mr. Chinish Mwab 'A Museng and authenticated by Mr. Katolo Tshipeta (National Institute of Agronomic Research (INERA), Lumbubashi, Democratic Republic of Congo). A voucher specimen (TMPW No. 27633) is preserved in the Museum of Materia Medica, Analytical Research Center for Ethnomedicines, Institute of Natural Medicine, University of Toyama, Japan.

Extraction and Isolation. The powdered roots of *S. longepedunculata* (200 g) were extracted with $CHCl_3$ under sonication (2 L, rt, 90 min, × 3), and the solvent was evaporated under reduced pressure to give a $CHCl_3$ extract (4.32 g). The $CHCl_3$ extract was separated by MPLC on a silica gel column (6 × 24 cm, precolumn 4 × 15 cm, flow rate 15 mL/min) using a step gradient of an *n*-hexane−EtOAc solvent system to give six fractions [fr. 1, *n*-hexane−EtOAc (85:15) eluate, 500 mg; fr. 2, *n*-hexane−EtOAc (80:20) eluate, 80 mg; fr. 3, *n*-hexane−EtOAc (60:40) eluate, 300 mg; fr. 4, *n*-hexane−EtOAc (45:55) eluate, 500 mg; fr. 5, *n*-hexane−EtOAc (60:40) eluate, 300 mg; and fr. 6, *n*-hexane−EtOAc eluate, 200 mg]. Fraction 5 was rechromatographed on silica gel with MPLC using an *n*-hexane−EtOAc gradient system to give two subfractions [fr. 5-1, *n*-hexane−EtOAc (40:60) eluate, 160 mg; fr. 5-2, *n*-hexane−EtOAc (35:65) eluate, 156 mg]. These were separately subjected to reversed-phase preparative TLC with CH_3CN−MeOH−H_2O (2:2:1) to give muchimangins G (**1**, 2.1 mg), H (**2**, 2.4 mg), I (**3**, 1.8 mg), and J (**4**, 1.5 mg).

*Muchimangin G (**1**):* yellow, amorphous solid; $[\alpha]^{22}_D$ −31 (*c* 0.02, $CHCl_3$); ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), Table 1; HREIMS *m*/*z* 620.1882 $[M]^+$ (calcd for $C_{33}H_{32}O_{12}$, 620.1893).

*Muchimangin H (**2**):* yellow, amorphous solid; $[\alpha]^{22}_D$ −28 (*c* 0.2, $CHCl_3$); ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), Table 1; HRFABMS *m*/*z* 621.1947 $[M + H]^+$ (calcd for $C_{33}H_{33}O_{12}$, 621.1972).

*Muchimangin I (**3**):* yellow, amorphous solid; $[\alpha]^{22}_D$ −36 (*c* 0.02, $CHCl_3$); ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), Table 1; HREIMS *m*/*z* 606.1763 $[M]^+$ (calcd for $C_{32}H_{30}O_{12}$, 606.1738).

*Muchimangin H (**4**):* yellow, amorphous solid; $[\alpha]^{22}_D$ −35 (*c* 0.2, $CHCl_3$); ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), Table 1; HREIMS *m*/*z* 618.1712 $[M]^+$ (calcd for $C_{33}H_{30}O_{12}$, 618.1737).

Preferential Cytotoxic Activity against PANC-1 Cells in NDM. Preferential cytotoxicity was determined as previously described[4−6]

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with a WST-8 cell counting kit (Dojindo, Kumamoto, Japan). Cell viability was calculated from the mean values for three wells using the following equation: Cell viability (%) = $[(Abs_{(test\ samples)} - Abs_{(blank)})/(Abs_{(control)} - Abs_{(blank)})] \times 100$. The preferential cytotoxicity was expressed as the concentration at which 50% of cells died preferentially in NDM (PC_{50}).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR, ^{13}C NMR, and HMBC spectra of new compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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