

## A coumestan and a coumaronochromone from *Millettia lasiantha*

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### ABSTRACT

The manuscript describes the phytochemical investigation of the roots, leaves and stem bark of *Millettia lasiantha* resulting in the isolation of twelve compounds including two new isomeric isoflavones lascoumestan and lascoumaronochromone. The structures of the new compounds were determined using different spectroscopic techniques.

### 1. Introduction

The genus *Millettia* (Fabaceae) is represented by six species in Kenya namely: *M. dura*, *M. leucantha*, *M. lasiantha*, *M. usaramensis* ssp. *usaramensis*, *M. oblata*, and *M. tanaensis* (Maundu and Tengnäs, 2005). In our previous phytochemical investigation of Kenyan *Millettia* species, we reported chalcones (Buyinza et al., 2019; Deyou et al., 2015; Yenesew et al., 1998), flavanones (Deyou et al., 2015), flavanonols (Deyou et al., 2015), flavonols (Buyinza et al., 2019), isoflavones (Buyinza et al., 2019; Derese et al., 2003, 2014; Deyou et al., 2017; Marco et al., 2017; Yenesew et al., 1996, 1997, 1998, 2003a), pterocarpans (Marco et al., 2017) and rotenoids (Deyou et al., 2015; Yenesew et al., 1998, 2003b). In continuation of our study on Kenyan *Millettia* species, herein we report the first phytochemicals (Table 1, Fig. 1) from *M. lasiantha* (Fig. 2) a plant traditionally used in Kenya as an aphrodisiac (Kokwaro, 2009).

### 2. Result and discussion

Phytochemical investigation of the leaves, stem bark and roots of *Millettia lasiantha* resulted in the isolation of eleven flavonoids (Table 1, Fig. 1) two of which are new. By comparison of their spectroscopic data with literature, the known compounds from the leaves were identified as apigenin (5) (Buyinza et al., 2020; Chen et al., 2008; Karimov et al., 2017; Na et al., 2013), chrysin (6), chrysin-7-*O*- $\beta$ -glucoside (7) (Buyinza et al., 2020; Ndjateu et al., 2014) and luteolin (8) (Chen et al., 2008; Liu

et al., 2012), the stem bark yielded genistein (9) (Abdou et al., 2017; Chansakaow et al., 2000; Li et al., 2011; Na et al., 2013), 6,7,4'-trihydroxyisoflavone (10), formononetin (1) (Buyinza et al., 2019, 2020; Li et al., 2011; Macias et al., 1999; Yenesew et al., 1997; Yoo et al., 2014) and isoliquiritigenin (11) (Bao et al., 2019; Rayanil et al., 2011; Tao et al., 2012), while the roots gave 2 and 3, alongside the known compounds, formononetin (1) and genistin (4) (Bandyukova and Kazakov, 1979; Li et al., 2011).

#### 2.1. 3,8-Dihydroxy-7,9-dimethoxycoumestan -trivial name lascoumestan (2)

Compound 2 was isolated as a white UV active solid. The HRESIMS spectrum showed  $[M+H]^+$  at  $m/z = 329.0654$  (calcd 329.0656) corresponding to  $C_{17}H_{12}O_7$ . The UV ( $\lambda_{max}$  at 254, 304 and 346 nm) (Adityachaudhu and Gupta, 1973), the IR ( $3367\text{ cm}^{-1}$  for a free hydroxyl (Tao et al., 2012),  $1716\text{ cm}^{-1}$  for  $\delta$ -lactone carbonyl (Jacques et al., 2011; Tamotsu and Shoji, 1969; Raju et al., 1981), as well as 1625 and  $1508\text{ cm}^{-1}$  for the two benzene rings (Hari et al., 2003) and  $^{13}\text{C}$  NMR ( $\delta_{\text{C}}$  160.6 (C-6), 103.4 (C-6a) and 157.2 (C-11a)) (Song et al., 2019) indicated this compound to be a coumestan derivative (Saitoh and Shibata, 1969).

The NMR of this compound indicated the presence of two methoxyl ( $\delta_{\text{H}}$  3.96 and 3.97 (3H, s);  $\delta_{\text{C}}$  57.0, 62.7)) and two hydroxyls ( $\delta_{\text{H}}$  9.62 and 7.92 (1H, s) substituents. The  $^1\text{H}$  NMR signals for three mutually coupled ( $\delta_{\text{H}}$  7.85 (1H, d,  $J = 8.6$  Hz), 6.98 (1H, dd,  $J = 8.6, 2.3$  Hz) and

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6.91 (1H, *d*, *J* = 2.3 Hz)) and a singlet  $\delta_{\text{H}}$  7.22 (1H, *s*) aromatic protons. HMBC correlations of the singlet aromatic proton ( $\delta_{\text{H}}$  7.22) with aromatic oxygenated carbons at  $\delta_{\text{C}}$  149.9, 149.6 and 139.3 together with a quaternary non-oxygenated aromatic carbon  $\delta_{\text{C}}$  111.5 allowed its placement at C-10 in ring D. The methoxy substituents at  $\delta_{\text{H}}$  3.96 ( $\delta_{\text{C}}$  62.7, HMQC) and 3.97 ( $\delta_{\text{C}}$  57, HMQC) were placed, respectively, at C-7 ( $\delta_{\text{C}}$  141.4) and C-9 ( $\delta_{\text{C}}$  149.6) based on their corresponding HMBC correlations. The HMBC correlations of the hydroxyl at  $\delta_{\text{H}}$  7.69 with  $\delta_{\text{C}}$  149.6 (C-9), 141.4 (C-7) and 139.3 (C-8) permitted its placement at C-8 and thus the other hydroxyl  $\delta_{\text{H}}$  9.62 at C-3. Therefore, compound **2** was identified as 3,8-dihydroxy-7,9-dimethoxycoumestan, a new compound for which the trivial name lascoumestan is suggested. The structure was totally assigned based on COSY, HMQC and HMBC correlations (Table 2).

## 2.2. 7,3'-dihydroxy-2',4'-dimethoxycoumaronochromone (3)

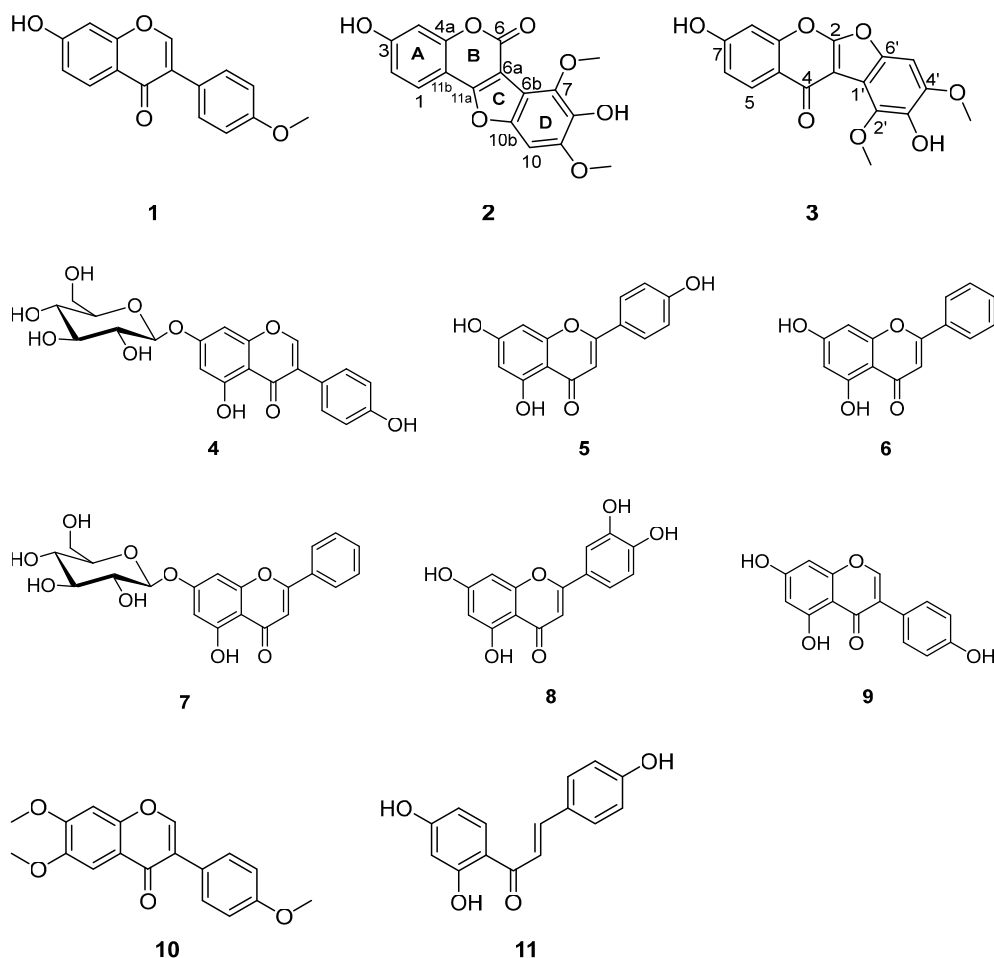
This compound was obtained as a white non-crystalline solid. The HRESIMS spectrum showed  $[M+H]^+$  at  $m/z = 328.0587$  (calcd 328.0583) corresponding to  $C_{17}H_{12}O_7$ . The  $^{13}\text{C}$ -NMR gave signals at  $\delta_{\text{C}}$  161.9 (C-2), 114.7 (C-3), 173.1 (C-4), 111.5 (C-1') and 150.0 (C-6') revealing a coumaronochromone skeleton (Ferrari et al., 1991; Shou et al., 2009) characteristic for a 2,2'-epoxyisoflavone (Agrawal, 1989). The absence of a characteristic proton due to H-2 (usually appearing at  $\delta_{\text{C}}$  ca 8) in the  $^1\text{H}$  NMR spectrum confirmed a coumaronochromone skeleton (Ferrari et al., 1991; Shou et al., 2009).

**Table 1**

Isolated compounds from *M. lasiantha*.

s/n	Compound	Plant part	Extraction solvent
1	Formononetin (1)	Roots	Ethyl acetate
2	Lascoumestan (2) (white solid)		
3	Lascoumaronochromone (3) (white solid)		
4	Genistin (4)	Leaves	CH <sub>2</sub> Cl <sub>2</sub> :MeOH (1:1v/v)
5	Apigenin (5)		
6	Chrysin (6)		
7	Chrysin-7-O- $\beta$ -glucoside (7)		
8	Luteolin (8)		
9	Genistein (9)	Stem	CH <sub>2</sub> Cl <sub>2</sub> :MeOH (1:1v/v)
10	6,7,4'-Trimethoxyisoflavone (10)	bark	v)
11	Formononetin (1)		
12	Isoliquiritigenin (11)		

The NMR of this compound showed two methoxyl substituents ( $\delta_{\text{H}}$  3.95 and 3.97 (3H, *s*);  $\delta_{\text{C}}$  57.0, 62.7)). The  $^1\text{H}$  NMR showed signals for three mutually coupled aromatic protons ( $\delta_{\text{H}}$  7.85 (1H, *d*, *J* = 8.4 Hz), 6.98 (1H, *dd*, *J* = 8.4, 2.4 Hz) and 6.91 (1H, *d*, *J* = 2.4 Hz)) and a singlet  $\delta_{\text{H}}$  7.20 (1H, *s*). HMBC correlations of the aromatic singlet proton ( $\delta_{\text{H}}$  7.20) with aromatic oxygenated carbons at  $\delta_{\text{C}}$  150 (C-6'), 149.7 (C-4') and 139.3 (C-3') together with a quaternary non-oxygenated aromatic carbon at  $\delta_{\text{C}}$  111.5 (C-1') allowed its placement at C-5' in ring D. The methoxy substituents at  $\delta_{\text{H}}$  3.96 and 3.97 were placed respectively, at C-



**Fig. 1.** Compounds isolated from *M. lasiantha*.

2' ( $\delta_C$  141.5) and C-4' ( $\delta_C$  149.7) based on their corresponding HMBC correlations Table 3. This implied the three mutually coupled protons be assignable to a tri-substituted (Bao et al., 2019) phenyl ring A. Compound 3 was therefore identified as 7,3'-dihydroxy-2',4'-dimethoxycoumaronochromone for which a trivial name lascoumaronochromone has been suggested.

### 3. Experimental

#### 3.1. General

Extracts and eluents were concentrated under vacuum on an IKA RV10 digital rotary evaporator (5–280 rpm) with a digital heating water bath (IKA HB10, 20–180 °C). All solvents used for chromatography were purified by fractional distillation. Column chromatography was carried out on silica gel 70–230 mesh (63–200  $\mu\text{m}$ ). Analytical thin layer chromatography was done on silica gel 60 F<sub>254</sub> (Merck, Germany) pre-coated aluminum plates. The TLC spots were viewed under UVGL 58 handheld UV-lamp (254–365 nm). Nuclear magnetic resonance spectrometry was used to analyze the samples using a Varian Avance (AV500) and Bruker spectrometer. The spectra were processed using MestRenova (11.04) software.

#### 3.2. Plant material

The leaves, stems and roots of *Millettia lasiantha* Dunn were collected from Mrima Hill, Msambweni sub county, Kwale county, (Coordinates (WGS84): S 4°29'0.6143" E 39°15'35.9528", 300m a. m. s. l) in February 2018. The authentication of the plant was done by Mr. Patrick Mutiso of the University Herbarium (NAI), School of Biological Science, the University of Nairobi, where a voucher specimen, DB/2018/001 was deposited. Plant family names were verified using the Angiosperm Phylogeny Group IV (Group et al., 2016).

#### 4. Extraction and isolation

Dry and ground powdered roots (300 g) of *M. lasiantha* were extracted with 1 L of ethyl acetate (2 × 24 h) and gave a dark brown extract (15 g) after concentration. A fraction of this extract (10 g) was fractionated on silica gel (70–230 mesh, 63–200  $\mu\text{m}$ ) using petroleum

**Table 2**

NMR Data for Lascoumestan (2) in acetone-d<sub>6</sub>.

Position	$\delta_C$	$\delta_H$ (m, J in Hz)	H–H COSY	HMBC (H→C)
1	123.6	7.85, (d, 8.6)	H-2	C-3, C-4a
2	114.2	6.98, (dd, 8.6, 2.3)	H-1, H-4	C-4, C-11b
3	161.9			
4	103.7	6.92, (d, 2.3)	H-2	C-2, C-3, C-4a, C-11b
4a	156.1			
6	160.6			
6a	103.4			
6b	111.5			
7	141.4			
8	139.3			
9	149.6			
10	92.8	7.22, (s)		C-6b, C-8, C-9, C-10b
10b	149.9			
11a	157.2			
11b	105.8			
7-OCH <sub>3</sub>	62.7	3.96, (s)		C-7
9-OCH <sub>3</sub>	57.0	3.97, (s)		C-9
8-OH		7.69, (s)		C-7, C-8, C-9
3-OH		9.62, (s)		

**Table 3**

NMR Data of lascoumaronochromone (3) in acetone-d<sub>6</sub>.

Position	$\delta_C$	$\delta_H$ (m, J in Hz)	H–H COSY	HMBC (H→C)
2	161.9			
3	114.7			
4	173.1			
5	123.6	7.85, (d, 8.4)	H-6	C-7, C-9
6	114.2	6.98, (dd, 8.4, 2.4)	H-5, H-8	C-7, C-8, C-10
7	156.1			
8	103.7	6.91, (d, 2.4)	H-6	C-6, C-7, C-9, C-10
9	157.2			
10	105.8			
1'	111.5			
2'	141.5			
3'	139.3			
4'	149.7			
5'	92.9	7.20, s		C-1', C-3', C-4', C-6'
6'	150.0			
2'-OCH <sub>3</sub>	62.7	3.95, s		C-2'
4'-OCH <sub>3</sub>	57.0	3.97, s		C-4'



**Fig. 2.** Picture of *M. lasiantha* (taken by Mutiso).

ether (PE) in increasing concentrations of ethyl acetate (EtOAc). The fraction that eluted with 15% EtOAc in PE gave white crystals of formononetin (**1**, 2.7 mg). The early fraction that eluted at 20% EtOAc in PE on crystallization in CH<sub>2</sub>Cl<sub>2</sub> gave white fluffy crystals of lascoumestan (**2**, 3.1 mg) and the later fractions gave white solid of lascoumaronochromone (**3**, 2.3 mg). The fraction that eluted at 30% EtOAc in PE yielded a white powder of genistin (**4**, 5.3 mg).

Dry and ground leaves (0.62 kg) of *M. lasiantha* were extracted with 3 L of CH<sub>2</sub>Cl<sub>2</sub>: MeOH (1:1 v/v, 4 × 6 hrs.) and gave a dark green extract (99.28 g). A fraction (90 g) of the extract was fractionated on 500 g of silica gel using hexane in increasing amounts of ethylacetate. The fractions that eluted with 30% EtOAc in hexane were combined and passed over sephadex, flashing with CH<sub>2</sub>Cl<sub>2</sub>: MeOH (1:1 v/v). 30 mg of this fraction was loaded on a chromatotron (6:3:1 H: E: M) to give a yellow solid of chrysin (**6**, 17.2 mg) and apeginin (**5**, 10.2 mg). Fractions that eluted with 60% EtOAc in hexane after passing it over sephadex gave light yellow powder of Luteolin (**8**, 75 mg) and the fractions at 90% after sephadex gave white solid of chrysin 7-*O*-β-*D*-glucoside (**7**, 12 mg).

Dry powdered stems (1.68 kg) of *M. lasiantha* were extracted using 5 L of CH<sub>2</sub>Cl<sub>2</sub>: MeOH (1:1 v/v, 4 × 6 hrs.) and gave a dark brown extract (121.3 g). A portion (100 g) of the extract was fractionated on 500 g of silica gel, eluting with hexane in increasing percentage of ethyl acetate. The fractions that eluted with 20% EtOAc after loading it on the chromatotron (6:3:1 H: E: M) gave genistein (**9**, 2.7 mg), **6**, **7**, 4'-trimeoxyisoflavone (**10**, 7 mg) and isoliquiritigenin (**11**, 4.3 mg). Fractions eluting with 30% EtOAc in hexane after flashing it on sephadex (CH<sub>2</sub>Cl<sub>2</sub>: MeOH, 1:1 v/v) gave white solids of formononetin (**1**, 9 mg).

#### 4.1. Spectroscopic data

##### 4.1.1. Lascoumestan (2)

White solid. ESI-HRMS [M+H]<sup>+</sup> m/z 329.0654 (cal. 329.0656), for C<sub>17</sub>H<sub>12</sub>O<sub>7</sub>. UV λ<sub>max</sub> (MeOH) 254, 304 and 346 nm. IR (neat) ν<sub>max</sub> 3367, 1716, 1625 and 1508 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, Acetone-*d*<sub>6</sub>) δ 9.62 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.22 (s, 1H), 6.98 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H). <sup>13</sup>C NMR (150 MHz, Acetone) δ 161.9, 160.6, 157.2, 156.1, 149.9, 149.6, 141.4, 139.3, 123.6, 114.2, 111.5, 105.8, 103.7, 103.4, 92.8, 62.7, 57.0.

##### 4.1.2. Lascoumaronochromone (3)

White fluffy crystals. [M<sup>+</sup>] m/z 328.0587 (cal. 328.0583) for C<sub>17</sub>H<sub>12</sub>O<sub>7</sub>. <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ<sub>H</sub> 7.20 (s, H-5'), 6.91 (d, *J* = 2.4 Hz, H-8), 6.98 (dd, *J* = 8.4, 2.4 Hz, H-6), 7.85 (d, *J* = 8.4 Hz, H-5), 3.95 (s, 2'-OCH<sub>3</sub>), 3.97 (s, 4'-OCH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ<sub>C</sub> 161.9 (C-2), 114.7 (C-3), 173.1 (C-4), 123.6 (C-5), 114.2 (C-6), 156.1 (C-7), 103.7 (C-8), 157.2 (C-9), 105.8 (C-10), 111.5 (C-1'), 141.5 (C-2'), 139.3 (C-3'), 149.7 (C-4'), 92.9 (C-5'), 150.0 (C-6'), 62.7 (2'-OCH<sub>3</sub>) and 57.0 (4'-OCH<sub>3</sub>).

## 5. Conclusion

This work is a report of eleven compounds from *M. lasiantha* including six isoflavones, four flavones and a chalcone. Four of the six isoflavones including the new isomeric isoflavones lascoumestan and lascoumaronochromone are C-5 deoxygenated. Eighty percent of the compounds from the leaves are simple flavones while 67% of the compounds from the stem bark are isoflavones and only isoflavones were obtained from the roots. As biogenetically expected, all the isolated compounds were C-7 and or C-4' oxygenated through a free hydroxyl or methoxyl or sugar moiety. Isolation of the chalcone isoliquiritigenin alongside the other simple flavonoids is a likely indicator that flavonoids of this plant are derived from isoliquiritigenin through the flavanone liquiritigenin as mediated by the CHI enzyme (Buyinza et al., 2020). Though the isolated compounds are simple flavonoids that occur widely in the family leguminosae and may have little chemotaxonomic significance, apigenin and chrysin are common in the genus *Millettia* (Buyinza

et al., 2020).

## CRedit author statement

Daniel Buyinza: Experimental investigation and Writing- Original draft preparation, Solomon Derese and Albert Ndakala: Supervision and data curation. Matthias Heydenreich and Andreas Koch: NMR measurements (1D, and 2D NMR), Software and 3D structures. Abiy Yenesew: Visualization, Conceptualization and editing. Richard Oriko: UV, IR and Mass measurements.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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