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Bioactive compounds from *Stuhlmannia moavi* from the Madagascar dry forest[☆]

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Abstract

Bioassay-directed fractionation of the leaf and root extracts of the antiproliferative Madagascar plant *Stuhlmannia moavi* afforded 6-acetyl-5,8-dihydroxy-2-methoxy-7-methyl-1,4-naphthoquinone (stuhlmoavin, **1**) as the most active compound, with an IC₅₀ value of 8.1 μM against the A2780 human ovarian cancer cell line, as well as the known homoisoflavonoid bonducellin (**2**) and the stilbenoids 3,4,5'-trihydroxy-3'-methoxy-trans-stilbene (**3**), piceatannol (**4**), resveratrol (**5**), rhapontigenin (**6**), and isorhapontigenin (**7**). The structure elucidation of all compounds was based on NMR and mass spectroscopic data, and the structure of **1** was confirmed by a single crystal X-ray analysis. Compounds **2–5** showed weak A2780 activities, with IC₅₀ values of 10.6, 54.0, 41.0, and 74.0 μM, respectively. Compounds **1–3** also showed weak antimalarial activity against *Plasmodium falciparum* with IC₅₀ values of 23, 26, and 27 μM, respectively.

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Supplementary data

Supplementary data associated with this article, consisting of HPLC chromatograms and ¹H NMR spectra for all isolated products and the ¹³C NMR spectrum of **1**, can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmcl.2013.xx>

Keywords

Antiproliferative activity; Antimalarial activity; X-ray crystallography; Homoisoflavonoid; 1,4-Naphthoquinone

1. Introduction

As a part of the Madagascar International Cooperative Biodiversity Group (ICBG) program,^{1,2} an ethanol extract of the leaves of a plant initially identified as an *Eligmocarpus* sp. was selected for evaluation as a possible source of new antiproliferative agents based on its activity against the A2780 ovarian cancer cell line. The final identification of the plant proved to be a botanical challenge. Although it was initially identified in the field as a species of *Eligmocarpus*, it was then reidentified as *Bussea sakalava* Du Puy & R. Rabev., and was finally classified as *Stuhlmannia moavi* Taub. (synonym: *Caesalpinia insolita* (Harms) Brenan & J.B. Gillett) (Leguminosae).³

The largely tropical genus *Caesalpinia*, a member of the informal *Caesalpinia* group⁴ in the Leguminosae family, traditionally comprises up to 150 species, although *Caesalpinia* sensu stricto is now considered to comprise only about a dozen species.⁵ Seventeen species of the genus *Caesalpinia*, as circumscribed in its broadest sense, have been found in China, and some of them have been used for the treatment of rheumatism and inflammatory diseases in Chinese traditional medicine.⁶ Triterpenes, flavonoids and other compounds have been isolated from plants of the genus *Caesalpinia* sensu lato,^{7,8} and 5-hydroxy-1,4-naphthoquinone has been isolated from the Asian species *C. sappan*.⁹ The genus is also a rich source of cassane-type diterpenes,^{10,11} which have been reported to have significant antimalarial,¹² antibacterial,¹³ antihelminthic,¹⁴ antiproliferative and antineoplastic activities.^{15,16} *Caesalpinia* is one of 21 genera included in the *Caesalpinia* group of legumes,⁴ a group of genera that includes the East African and Madagascan monospecific genus *Stuhlmannia*.^{17,18} The only previous chemical studies on the genus *Stuhlmannia* led to the isolation of some antimicrobial furanoid diterpenes.¹⁹

We describe herein the isolation and structure elucidation of the new bioactive 1,4-naphthoquinone stuhlmoavin (**1**) and several other bioactive compounds (Fig. 1).

Bioassay-guided isolation of the root extract of *S. moavi* furnished the known isoflavonoid bonducellin (**2**), together with the five known stilbenoids 3,4,5'-trihydroxy-3'-methoxy-transstilbene (**3**),²⁰ piceatannol (**4**),^{21,22} resveratrol (**5**),²³ rhapontigenin (**6**),²⁴ and isorhapontigenin (**7**).²⁴ The structures of compounds **2**–**7** were determined by comparison of their ¹H NMR and mass spectra with literature data. Compound **1** showed moderate A2780 activity, compounds **2**–**5** showed weak A2780 activities, and compounds **1**–**3** also showed weak antimalarial activities against the Dd2 drug-resistant strain of *Plasmodium falciparum*.

2. Results and Discussion

Compound **1** (red needles) had the molecular formula C₁₄H₁₂O₆, as indicated by high-resolution ESIMS analysis (*m/z* 277.0729 [M+H]⁺, calcd. 277.0712). The IR spectrum showed absorptions characteristic of ketone (1708 cm⁻¹) and chelated hydroxyl (3384 cm⁻¹) functions as well as quinone carbonyl groups (1609 and 1564 cm⁻¹).^{25,26} The ¹H NMR data (Table 1) displayed resonances due to aromatic methyl (δ_H 2.22, s, 3H), acetyl methyl (δ_H 2.57, s, 3H), methoxy (δ_H 3.95, s, 3H), and aromatic methine (δ_H 6.19, s, 1H) groups. Two additional deshielded broad singlets at δ_H 12.63 (s, 1H) and δ_H 12.90 (s, 1H) indicated the

presence of two hydrogen bonded hydroxyl groups in **1**. The ^1H NMR signals, taken in conjunction with the UV absorption spectrum, suggested that **1** had a 1,4-naphthoquinone skeleton with two peri-substituted hydroxyl groups.^{26,27} The ^{13}C NMR spectrum of **1** (Table 1) exhibited 14 carbon signals, and the ^{13}C DEPT NMR spectrum showed signals due to two methyl groups (δ_{C} 12.7, δ_{C} 31.8), one methoxy group (δ_{C} 56.9), and one methine (δ_{C} 110.3).

The 10 remaining quaternary carbon signals in the ^{13}C NMR spectrum corresponded to an acetyl carbonyl group (δ_{C} 202.0), two quinone carbonyl groups (δ_{C} 186.7 and 181.3), three oxygen bearing aromatic carbons at δ_{C} 158.9, 154.5, and 160.8, and four signals for more shielded carbons at δ_{C} 110.3, 135.5, 108.9, and 110.7, corresponding to an aromatic methine, a methylated aromatic carbon, and the two bridgehead carbons of the naphthoquinone skeleton. In the HMBC experiment (Fig. 2), the correlations between δ_{H} 12.63 (OH-8) and δ_{C} 158.9, and δ_{H} 12.90 (OH-5) and δ_{C} 154.5, suggested that the two carbons were at the 8 and 5 positions, respectively.

The HMBC correlations between the proton signals of the methyl group at δ_{H} 2.57 (CH₃-12) with both the carbonyl carbon at δ_{C} 202.0 (C-11) and the aromatic carbon at δ_{C} 142.1 (C-6), together with the long range HMBC correlation between δ_{H} 12.90 (OH-5) and δ_{C} 142.1 (C-6), indicated the attachment of an acetyl group at the C-6 position. In addition, the methyl group was assigned to C-7 based on the long-range correlations (Fig. 2) observed between the signal at δ_{H} 2.22 and δ_{C} 142.1 (C-6), δ_{C} 135.5 (C-7), and δ_{C} 158.9 (C-8). Furthermore, the signals for the deshielded hydroxyl groups OH-1 and OH-4 also correlated with carbon signals at δ_{C} 110.7 and δ_{C} 108.9, which were assigned to the two bridgehead carbons at C-9 and C-10, respectively. In the same manner, the methine group at the C-3 position was confirmed by observation of the HMBC long range correlation between δ_{H} 6.19 (H-3) and C-10 (δ_{C} 108.9). Moreover, the signal at H-3 correlated with both of the two quinone carbonyl groups at δ_{C} 181.3 and δ_{C} 186.7, which were assigned to C-4 and C-1. The methoxy group was assigned to C-2 (δ_{C} 160.8), which agrees with the correlation between δ_{H} 3.95 and δ_{C} 160.8 in the HMBC experiment. Compound **1** was thus deduced to be 6-acetyl-2-methoxy-7-methyl-1,4-naphthoquinone and has been named stuhlmoavin.

The proposed structure of **1** was confirmed by single-crystal X-ray diffraction analysis (Fig. 3).

Compounds **1–7** showed antiproliferative activity against the A2780 human ovarian cancer cell line. Among the seven compounds isolated, **1** showed moderate activity with an IC₅₀ value of $8.1 \pm 0.4 \mu\text{M}$. Compounds **2–5** showed weaker activities with IC₅₀ values of $10.6 \pm 0.4 \mu\text{M}$, $54 \pm 1 \mu\text{M}$, $41 \pm 1 \mu\text{M}$, and $74 \pm 1 \mu\text{M}$, respectively. Compounds **1–5** were also evaluated for antimalarial activity against *Plasmodium falciparum* Dd2 (a chloroquine/mefloquine-resistant strain), and compounds **1–3** showed moderate activities with IC₅₀ values of 24 ± 7 , 26 ± 3 , and $27 \pm 2 \mu\text{M}$, respectively.

3. Experimental

3.1 General experimental procedures

IR and UV spectra were measured on MIDAC M-series FTIR and Shimadzu UV-1201 spectrophotometers, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer in CDCl₃ with TMS as internal standard. Mass spectra were obtained on an Agilent 6220 mass spectrometer. Open column chromatography was performed using Sephadex LH-20 and silica gel (230–400 mesh, Silicycle Co. USA). Flash chromatography was performed on a Biotage Horizon flash chromatograph using a C18 column (Phenomenex, 150 × 12 mm, 11 g). Semi-preparative HPLC was performed using Shimadzu LC-10AT pumps coupled with a semipreparative Phenomenex C18 column (5

μm , $250 \times 10 \text{ mm}$), a Shimadzu SPD M10A diode array detector, and a SCL-10A system controller. All isolated compounds were purified to 95% purity or better, as judged by HPLC and by NMR (both UV and ELSD detection) before determining bioactivity. The HPLC chromatograms and NMR spectra can be found in the Supplementary Data.

3.2 Plant material

Leaves and roots of *Stuhlmannia moavi* Taub.⁴ Brenan and Gillett³ collected in dry forest 3 km north of Tsaratanana in the Sava locality, Daraina, in northern Madagascar. The sample was from a tree 12 m high, 30 cm DBH, with yellow flowers and orange anthers. The tree is common in this location. It was identified as *Stuhlmannia moavi* Taub. (synonyms: *C. insolita* (Harms) Brenan & J.B. Gillett, from Madagascar and *Caesalpinia dalei* Brenan & J.B. Gillett, from East Africa) by comparison with the literature,^{3,4} and by matching photographs taken in the field with herbarium specimens housed in the collections of the Royal Botanic Gardens, Kew.

3.3. Antiproliferative bioassay

The A2780 ovarian cancer cell line antiproliferative bioassay was performed at Virginia Tech as previously reported.²⁸ The A2780 cell line is a drug-sensitive ovarian cancer cell line.²⁹ Paclitaxel was used as the positive control; it had an IC_{50} value of $0.024 \mu\text{M}$.

3.4. Antimalarial bioassay

The effect of each compound on parasite growth of the Dd2 strain of *P. falciparum* was measured in a 72 h growth assay in the presence of compound as described previously with minor modifications.^{30,31} Briefly, ring stage parasite cultures ($200 \mu\text{L}$ per well, with 1% hematocrit and 1% parasitemia) were grown for 72 h in the presence of increasing concentrations of the drug in a 5.05% CO_2 , 4.93% O_2 , and 90.2% N_2 gas mixture at 37°C . After 72 h in culture, parasite viability was determined by DNA quantitation using SYBR Green I ($50 \mu\text{L}$ of SYBR Green I in lysis buffer at $0.4 \mu\text{L}$ of SYBR Green I/mL of lysis buffer).³¹ The half-maximum inhibitory concentration (IC_{50}) calculation was performed with GraFit software using a nonlinear regression curve fitting. IC_{50} values are the average of three independent determinations with each determination in duplicate and are expressed $\pm \text{SEM}$. Artemisinin was used as the positive control; it had an IC_{50} value of 7 nM .

3.5 Extraction and isolation

A ground sample of *Stuhlmannia moavi* leaves (309 g) was extracted with EtOH at room temperature to yield 27.9 g of crude EtOH extract designated MG 4425. A total of 5.64 g of this extract was made available to Virginia Tech. The crude EtOH extract (2.0 g) was dissolved in 90% aq. MeOH (300 mL), and extracted with hexanes ($3 \times 200 \text{ mL}$). Evaporation of the hexanesoluble fraction afforded 285 mg of residue. The 90% aq. MeOH layer was then evaporated, suspended in H_2O (300 mL), and extracted with EtOAc ($3 \times 200 \text{ mL}$) to yield 600 mg of EtOAc-soluble fraction. The aqueous layer was concentrated to give 1.1 g of brown residue. The hexanes fraction was found to be cytotoxic with an IC_{50} value of $13 \mu\text{g/mL}$ and was subjected to Sephadex LH-20 open column chromatography ($\text{CH}_2\text{Cl}_2\text{:MeOH}$, 1:1) to give 7 fractions. Further purification of the most active fraction (IC_{50} $3.2 \mu\text{g/mL}$) furnished the major and most active compound **1** (5.8 mg) with an IC_{50} of $2.6 \mu\text{g/mL}$.

A ground sample of *S. moavi* roots (335 g) was extracted with EtOH at room temperature to yield 19.6 g of crude EtOH extract designated MG 4423. A total of 4.36 g of this extract was made available to Virginia Tech. A part of the crude EtOH extract (2.0 g) was dissolved in 90% aq. MeOH (300 mL) and extracted with hexanes ($3 \times 200 \text{ mL}$). Evaporation of the

hexanes-soluble fraction yielded 508 mg of residue. The 90% aq. MeOH layer was then evaporated, suspended in H₂O (300 mL), and extracted with EtOAc (3 × 200 mL) to yield 1.106 mg of EtOAc-soluble fraction. The aqueous layer was concentrated to give 256 mg of brown residue. The EtOAc fraction was found to be weakly cytotoxic with an IC₅₀ value of 18 µg/mL and was subjected to Sephadex LH-20 open column chromatography (CH₂Cl₂: MeOH = 1:1) to give 7 fractions. Compound **2** (10.1 mg) was crystallized from MeOH from the second fraction. The third fraction from the Sephadex column (IC₅₀ 13 µg/mL) was further fractionated using a C18 flash chromatograph column to yield 5 fractions. The third subfraction was subjected to HPLC on a C-18 column with a solvent gradient from H₂O:MeOH, 55:45 (for 30 min), to 40:60 from 30 to 35 min, to 0:100 from 35 to 40 min, and ending with 100% MeOH to 55 min. This process yielded compounds **4** (2.5 mg, t_R 14 min), **5** (3.2 mg, t_R 23.8 min), **6** (2.4 mg, t_R 26.5 min), **7** (1.2 mg, t_R 32 min) and **3** (4.5 mg, t_R 41.5 min).

3.6 6-Acetyl-5,8-dihydroxy-2-methoxy-7-methyl-1,4-naphthoquinone (stuhmoavin, **1**)

Red crystals; mp 185 °C; UV λ_{max} (MeOH) nm (log ε): 217 (4.11), 296 (3.54), 492 (3.27); IR λ_{max} cm⁻¹: 3384, 1708, 1609 and 1564; ¹H and ¹³C NMR data, see Table 1; positive ion HRESIMS *m/z*: 277.0729 [M+H]⁺ (calcd for C₁₄H₁₃O₆, 277.0712).

3.7 X-ray crystallography of **1**

A red needle (0.01 × 0.04 × 0.62 mm³) was centered on the goniometer of an Agilent SuperNova A diffractometer operating with CuKα radiation. The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlisPro.³² The Laue symmetry and systematic absences were consistent with the monoclinic space group *P2₁/n*. The structure was solved using SHELXS-97³³ and refined using SHELXL-97 via OLEX2.³⁴ The final refinement model involved anisotropic displacement parameters for non-hydrogen atoms and a riding model for all hydrogen atoms. A 2-position disorder model was used for the ketone oxygen with relative occupancies that refined to 0.490(13) and 0.510(13). The relatively poor refinement statistics and elongated displacement parameters are attributed to the small size and high mosaicity of the crystal. Crystal data: C₁₄H₁₂O₆, *M_r* = 276.24, monoclinic, *P2₁/n*, *a* = 4.9896(3) Å, *b* = 23.446(3) Å, *c* = 10.5394(7) Å, α = 90°, β = 100.893(6)°, γ = 90°, *V* = 1210.73(18) Å³, 9071 reflections, 196 parameters; crystal size 0.62 × 0.04 × 0.01 mm³. The final indices were *R_I* = 0.0803, *wR₂* = 0.2080 [*I* > 2σ(*I*)]. Crystallographic data for compound **1** have been deposited as Supporting Information at the Cambridge Crystallographic Data Centre (deposition no. CCDC 919140).³⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structures of compounds from *Stuhlmannia moavi*.

Figure 2.
Key HMBC correlations of 1.

Figure 3.
Anisotropic displacement ellipsoid drawing (50% probability) of compound **1**.

Table 1¹H and ¹³C NMR Data (δ, ppm) for compound **1** (500 and 125 MHz)^a

position	δ _H	δ _C (DEPT)
1		186.7 (C) ^b
2		160.8 (C)
3	6.19 s	110.3 (CH)
4		181.3 (C) ^b
5		154.5 (C)
6		142.1 (C)
7		135.5 (C)
8		158.9 (C)
9		110.7 (C)
10		108.9 (C)
11		202.0 (C)
12	2.57 s	31.8 (CH ₃)
2-OCH ₃	3.95 s	56.9 (CH ₃)
7-CH ₃	2.22 s	12.7 (CH ₃)
5-OH	12.90 s	
8-OH	12.63 s	

^aIn CDCl₃. Assignments based on HMBC^bThese signals may be exchanged