Flavonoids from *Dalbergia louvelii* and Their Antiplasmodial Activity

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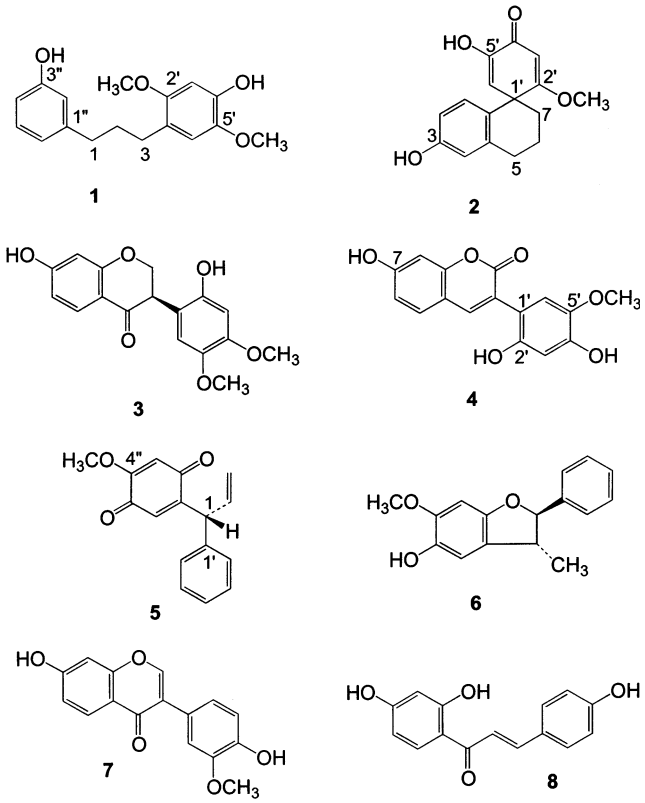
Four new flavonoids (**1**−**4**), along with 13 known compounds, were isolated from the heartwood of *Dalbergia louvelii* by following their potential to inhibit in vitro the growth of *Plasmodium falciparum*. Of the isolated compounds, four known compounds showed antiplasmodial activity with IC_{50} values ranging from 5.8 to 8.7 μM, namely, (*R*)-4″-methoxydalbergione (**5**), obtusafuran (**6**), 7,4′-dihydroxy-3′-methoxyisoflavone (**7**), and isoliquiritigenin (**8**). The structures of the new compounds were determined using spectroscopic techniques as 1-(3-hydroxyphenyl)-3-(4-hydroxy-2,5-dimethoxyphenyl)propane (**1**), spirolouveline (**2**), (3*R*)-7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (**3**), and 3-(2,4-dihydroxy-5-methoxy)phenyl-7-hydroxycoumarin (**4**), respectively.

The spread of resistance of *Plasmodium falciparum* to commonly used antimalarial drugs has created an urgent need to develop new antimalarial treatments, preferably drugs that are affordable to developing countries where malaria is prevalent. Although powerful new technologies such as high-throughput screening and combinatorial chemistry are revolutionizing drug discovery, natural products still offer structural diversity, which makes them a valuable source of novel lead compounds. We have developed a screening program directed to the search of antimalarial compounds from plants of Madagascar.[1] According to the thresholds of activity previously defined,[2] 39 extracts were selected for further investigation. Of these, the ethyl acetate extract obtained from the heartwood of *Dalbergia louvelii* R. Viguier (Fabaceae), a species traditionally used to treat bilharzia and malaria in Madagascar, was submitted to a series of bioassay-guided fractionation steps, and this led to the isolation of 17 flavonoids, including four new compounds (**1**−**4**) and four active substances of known structure (**5**−**8**). In this paper, we report the isolation and identification of the new flavonoids as well as the antiplasmodial activities of the known compounds.



Results and Discussion

The structures of the new compounds (**1**−**4**) were established by conventional ^{1}H and ^{13}C NMR spectral methods assisted by the performance of 2D NMR techniques, namely, COSY, HMQC, HMBC, and NOESY, thus leading to the total assignment of the ^{1}H and ^{13}C NMR spectra of the new compounds (Tables 1 and 2). The known compounds were identified on the basis of spectral comparison with published data from the literature. All of them have been previously isolated from the Fabaceae, namely, three flavanones, dihydrooxylin,[3] pinocembrin, [4] and liquiritigenin;[4] four neoflavones, including three 3,3-diarylpropenes, (*R*)-4″-methoxydalbergione (**5**),[5] obtusaquinol,[6] 9-hydroxy-6,7-dimethoxydalbergiquinol,[7] and an aryl coumarin, dalbergin;[4] two aryl benzofurans, parvifuran and obtusafuran (**6**);[8] three isoflavones, 7,4′-dihydroxy-3′-methoxyisoflavone (**7**),[9] odoratin,[10] 2′,7-dihydroxy-4′,5′-dimethoxyisoflavone,[11] and one chalcone, isoliquiritigenin (**8**).[4,12] The most abundant metabolites isolated were obtusaquinol (0.34% w/w), 9-hydroxy-6,7-dimethoxydalbergiquinol, (0.05% w/w), liquiritigenin, (0.027% w/w), and (*R*)-4″-methoxydalbergione (**5**, 0.015% w/w).

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Table 1. NMR Data for Compounds **1** and **2** in $CDCl_3$

	1			**2**		
position	δ_C	δ_H, mult. (*J* in Hz)	HMBC	δ_C	δ_H, mult. (*J* in Hz)	HMBC
1	35.3	2.53, m	C-2, C-3, C-1″, C-2″, C-6″	128.9	6.65, d (8.4)	C-3, C-4, C-5, C-9, C-1′
2	31.6	1.81, m	C-1, C-3, C-1′, C-1″	114.1	6.51, dd (2.5, 8.4)	C-3, C-4, C-8
3	29.5	2.53, m	C-1, C-2, C-1′, C-2′, C-6′	154.4		
4				115.8	6.56; d (2.5)	C-2, C-3, C-5, C-8
5				29.6	2.73, m	C-4, C-6, C-7, C-8, C-9
					H6 ax 1.96, m	C-5, C-7, C-9, C-1′
6				19.3	H6 eq 1.82, m	
					H7 ax 2.24, m	C-5, C-6, C-1′, C-2′, C-6′
7				35.1	H7 eq 1.82, m	
8				126.7		
9				138.5		
1′	121.5			46.8		
2′	151.9			183.2		
3′	99.3	6.52, s	C-3, C-1′, C-2′, C-4′, C-5′	99.9	5.74, s	C-1′, C-2′, C-4′, C-5′
4′	144.2			183.2		
5′	139.9			142.8		
6′	113.2	6.63, s	C-3, C-2′, C-3′, C-4′, C-5′	119.6	6.01, s	C-7, C-8, C-1′, C-2′, C-4′, C-5′
OH-4′		5.50, s	C-2′, C-3′, C-4′, C-5′			
OH-5′					6.35, s	C-1′, C-4′, C-5′, C-6′
OMe-2′	55.9	3.72, s	C-2′, C-3′	56.4	3.67, s	C-2′, C-3′
OMe-5′	56.8	3.81, s	C-5′			
1″	144.6					
2″	115.3	6.64, s	C-1, C-3″, C-4″, C-6″			
3″	155.4					
4″	112.5	6.61, dd (2.4, 7.9)	C-2″, C-3″, C-6″			
5″	129.4	7.09, dd (7.9, 7.8)	C-1″, C-2″, C-3″, C-4″, C-6″			
6″	121.0	6.74, d (7.8)	C-1, C-1″, C-2″, C-3″, C-4″, C-5″			

Table 2. NMR Data (δ, ppm) for Compounds **3** and **4** in DMSO-d_6

	3			**4**		
position	δ_C	δ_H, mult. (*J* in Hz)	HMBC	δ_C	δ_H, mult. (*J* in Hz)	HMBC
		ax 4.55, dd (10.9, 12.0)	C-3, C-4, C-9			
2	70.1	eq 4.36, dd (10.9, 5.5)	C-3, C-4, C-9, C-1′	160.0		
3	47.0	4.10, dd (5.5, 12.0)	C-2, C-4, C-1′, C-2′, C-6′	121.1		
4	190.5			141.9	7.84, s	C-2, C-5, C-9, C-10, C-1′
5	128.9	7.65, d (8.6)	C-4, C-7, C-9	129.3	7.50, d (8.5)	C-4, C-7, C-9
6	110.5	6.49, dd (2.3, 8.6)	C-8, C-10	113.0	6.75, dd (8.5, 2.2)	C-8, C-10
7	164.2			160.5		
8	102.3	6.33, d (2.3)	C-6, C-7, C-9, C-10	101.7	6.71, d (2.2)	C-6, C-7, C-9, C-10
9	163.2			154.7		
10	114.1			111.9		
OH-7		10.50, s	C-6, C-7, C-8			
1′	112.7			111.9		
2′	149.5			149.5		
3′	100.9	6.45, s	C-3, C-1′, C-2′, C-4′, C-5′	103.8	6.39, s	C-3, C-1′, C-2′, C-4′, C-5′
4′	148.8			147.6		
5′	141.5			140.3		
6′	115.4	6.65, s	C-3, C-1′, C-2′, C-3′, C-4′, C-5′	115.7	6.81, s	C-3, C-2′, C-4′, C-5′
OH-2′		9.13, s	C-1′, C-2′, C-3′		8.89, s	C-1′, C-2′, C-3′
OH-4′					9.07, s	C-3′, C-4′, C-5′
OMe-4′	55.4	3.68, s	C-4′, C-5′			
OMe-5′	56.5	3.59, s	C-5′	56.6	3.66, s	C-5′

Compound **1** exhibited a molecular formula of $C_{17}H_{20}O_4$ as determined by HRMS. As evident from the ^{1}H NMR spectrum, the structure of **1** included two methoxy groups at δ 3.72 and 3.81 and one D_2O-exchangeable hydroxy group at δ 5.50. The ^{1}H NMR spectrum also showed signals at δ 1.81 (2H, m) and 2.53 (4H, m), corresponding to three methylene protons, in addition to six protons located in the aromatic region between δ 6.52 and 7.09. The concerted interpretation of the ^{1}H NMR and COSY spectra allowed us to assemble the three methylene groups as a 1,3-disubstituted propane and to link this unit to a *meta*-substituted phenyl group, as evidenced by the observation of H-1/H-2 and H-2/H-3 vicinal couplings, H-6″/H-5″ and H-5″/H-4″ *ortho*-coupling, H-4″/H-2″ *meta*-coupling, and H-1/H-2″ benzylic coupling. This was further substantiated by the observation of two- and three-bond connectivities between H-1 and C-2, C-3, C-1″, C-2″, and C-6″. The integrity of the *o,m*-dimethoxy-*p*-hydroxyphenyl unit was deduced by examination of several major long-range heteronuclear couplings. In particular, H-3′ coupled with C-1′ and C-5′, H-6′ displayed three-bond connectivities with C-4′ and C-2′, the D_2O-exchangeable hydroxyl proton at δ 5.50 showed cross-peaks with C-4′ and C-3′, and the methoxy groups at δ 3.72 and 3.81 coupled, respectively, with C-2′ and C-5′. Finally, this moiety was assembled to the phenylpropane unit in the C-3 position following the observation of two- and three-bond connectivities between H-3 and C-1, C-2, C-1′, C-2′, and C-6′. Accordingly, compound **1** was assigned as 1-(3-hydroxyphenyl)-3-(4-hydroxy-2′,5′-dimethoxyphenyl)propane.

The molecular weight of compound **2** was found to be 272, which was consistent with the elemental formula, $C_{16}H_{16}O_4$, determined by HRMS. The ^{1}H NMR spectrum exhibited multiplets of six protons between δ 1.82 and 2.73,

corresponding to three methylene peaks, which were assembled as $-CH_2-CH_2-CH_2-$ by the interpretation of the COSY spectrum, one methoxy group at δ 3.67, two olefinic protons appearing at δ 5.74 (1H, s) and 6.01 (1H, s), and three aromatic protons, respectively, at δ 6.51 (1H, dd, J = 8.4, 2.5 Hz), 6.56 (1H, d, J = 2.5 Hz), and 6.65 (1H, d, J = 8.4 Hz), corresponding to a 1,2,4-trisubstituted aromatic ring A and a D_2O-exchangeable hydroxyl group at δ 6.35. A spiranoid 2′,5′-disubstituted-dienone moiety was established unambiguously by the $^1H-^{13}C$ long-range correlations observed in the HMBC spectrum. Thus, H-6′ showed correlations with C-1′, C-2′, C-4′, C-5′, C-7, and C-8, the D_2O-exchangeable proton at δ 6.35 coupled with C-1′, C-4′, C-5′, and C-6′, and the OCH_3 protons exhibited cross-peaks with the deshielded C-2′ and C-3′. The spiranoid unit was then assembled to the tetrahydronaphthalene moiety at the C-1′ position by additional correlations observed in the HMBC spectrum, namely, between H-1, H-6, H-7, H-3′, H-6′ and C-1′. Since it was not possible to obtain a suitable crystal for X-ray crystallographic analysis, the stereochemistry of C-1′ has not been established. Thus, compound **2** was identified as a new spiranoid structure named spirolouveline.

The elemental formula of compound **3** was determined as $C_{17}H_{16}O_6$ by HRMS. Analysis of the UV, ^1H NMR, ^{13}C NMR, and MS data suggested **3** to be structurally related to the known isoflavone 7,2′-dihydroxy-4′,5′-dimethoxyisoflavone.[11] When the ^1H NMR spectrum of **3** was compared to that of the known isoflavone, there was a disappearance of signals corresponding to the double bond and the appearance of three doublet of doublet signals at δ 4.10 (1H, dd, 12.0, 5.5 Hz), 4.36 (1H, dd, 10.9, 5.5 Hz), and 4.55 (1H, dd, 12.0, 10.9 Hz), which were assignable to H-3 and H_2-2 protons, respectively. This observation was consistent with the molecular weight of **3**, which was found to be two units higher than the known isoflavone mentioned above. Furthermore, the signal multiplicity pattern of the aromatic region in the ^1H NMR spectrum confirmed the presence of the two substituted aromatic rings, and the isoflavanone structure was further supported by the long-range heteronuclear correlations observed between H-2ax and C-4; H-2 eq and C-4, C-1′; and H-3 and C-1′, C-2′, C-6′. The CD curve of this compound showed a positive Cotton effect at 326 nm, which was consistent with *R* configuration at C-3.[13] From the above data, the structure of compound **3** was deduced as (3*R*)-7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone.

The UV spectrum of compound **4** was consistent with a coumarin chromophore (λ_{max} 200, 281, and 328 nm), and the HRMS provided the molecular formula $C_{16}H_{12}O_6$. The ^1H NMR spectrum of **4** showed signals assignable to a methoxy group at δ 3.66, five aromatic protons between δ 6.39 and 7.50, a methine proton at δ 7.84, and two D_2O-exchangeable phenolic protons at δ 8.89 and 9.07. The ^{13}C NMR spectrum contained 15 signals, and the C-2 carbonyl resonance occurred at δ 160.0. COSY, HSQC, HMBC, and NOESY experiments allowed the assignment of all protons and carbons (Table 2). In the aromatic region, two singlets located at δ 6.81 and 6.39 were characteristic of a 1′,2′,4′,5′-tetrasubstituted aromatic ring. A long-range correlation in the HMBC spectrum showed that the proton at δ 6.81 attributed to H-6′ correlated with C-3, C-2′, C-4′, and C-5′, while the proton at δ 6.39 (H-3′) correlated with C-3, C-1′, C-2′, C-4′, and C-5′. The H-3′ proton also showed a NOESY correlation with OH-2′ and OH-4′. The methoxy group was attached to C-5′, as confirmed the correlation of this methoxy signal at δ 3.66 with C-5′ in the HMBC spectrum.

Table 3. In Vitro Antiplasmodial Activity of Compounds **5**−**8**

compound	$IC_{50} \pm$ SD (μM)
(*R*)-4″-methoxydalbergione (**5**)	5.8 ± 0.15
obtusafuran (**6**)	8.7 ± 0.6
7,4′-dihydroxy-3′-methoxyisoflavone (**7**)	6.8 ± 0.15
isoliquiritigenin (**8**)	7.8 ± 0.65
chloroquine[a]	0.13± 0.03

[a] Chloroquine was used as a positive control. Compounds **1**−**4** and the known compounds other than **5**−**8** were regarded as inactive.

The singlet at δ 7.84 (H-4) showed a HMBC correlation with C-2, C-5, C-9, C-10, and C-1′. A proton at δ 6.71 (H-8) correlated with C-6, C-7, C-9, and C-10. The phenolic proton was placed at C-7. Compound **4** was identified as 3-(2,4-dihydroxy-5-methoxy)phenyl-7-hydroxycoumarin.

All the isolated compounds were tested for their ability to inhibit in vitro the growth of the chloroquine-resistant strain FcB1 of *P. falciparum*. From the data summarized in Table 3, only four compounds displayed potent antimalarial activity with IC_{50} values ranging from 5.8 to 8.7 μM: a 3,3-diarylpropene, **5**, an arylbenzofuran, **6**, an isoflavone, **7**, and a chalcone, isoliquiritigenin, **8**. In the case of the 3,3-diarylpropene, the *p*-quinone moiety is essential for the activity since the reduced derivative, obtusaquinol, and the *o*-methylated derivative, 9-hydroxy-6,7-dimethoxydalbergiquinol, showed a 2- and 8-fold decrease, respectively, in antimalarial potency compared to **5**. In the case of parvifuran belonging to the arylbenzofuran series, the presence of a double bond at position C-2 and C-3 decreased significantly the activity compared to the dihydro derivative (**6**). Concerning the isoflavone (**7**) and odoratin, the presence of the methoxyl group at position C-6 decreased the activity. The antiplasmodial activity observed for compound **8**, which was found to be 7-fold more active than its biogenetic precursor flavanone, liquiritigenin, confirmed the interesting antimalarial properties described for chalcones.[14] Surprisingly, it was observed in some cases that the antiplasmodial activities of isolated compounds were less pronounced than those of the active fractions, strongly suggesting that some constituents might enhance the activity of the others.

The data described in this work confirm the use of *D. louvelii* in traditional medicine in Madagascar and support the development of an affordable and accessible standardized extract formulated from the heartwood of this species for the treatment of uncomplicated malaria.

Experimental Section

General Experimental Procedures. Melting points (mp) were determined on a Reichart hot-stage microscope and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20 °C. The CD spectra were recorded on a Jobin Yvon Mark V spectrometer. The UV spectra were obtained on a Kontron spectrometer. ^1H and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively, on a Bruker AMX-400 spectrometer at 300 K with a Bruker Gradient Unit (BGU) and an inverse gradient triple-resonance probe-head with a self-shielded gradient coil. The ^1H and ^{13}C NMR chemical shifts are expressed in ppm relative to TMS, with coupling constants (J) given in Hz. High-resolution mass spectra were recorded on a JEOL MS700 apparatus. Column chromatography was performed on 200−400 mesh silica gel 60 (Merck) and HPLC on a LC system (Gilson) consisting of a 321 pump and a 170 diode array detector using a Lichrospher 60 Å RP select B 5 μm (250 × 7.5 mm) column.

Plant Material. The plant material was collected in the middle eastern rainforests of Didy (Ambatondrazaka), Madagascar, in September 1999, at 500 m altitude, and was

identified by comparison with authentic specimens held in the Department of Botany, Parc Botanique et Zoologique de Tsimbazaza, Antananarivo. A voucher specimen (Didy 25) was deposited at the Institut Malgache de Recherches Appliquées.

Bioassay. The in vitro antiplasmodial tests, based on the inhibition of [^{3}H]-hypoxanthine uptake by *P. falciparum* cultured in human blood, were conducted as previously described.[15] Compounds with IC_{50} values below 10 μM were denoted as active in this assay.

Extraction and Isolation. The air-dried and powdered heartwood of *D. louvelii* (500 g) was exhaustively extracted with ethanol at room temperature to give 86.4 g of extract, which was then partitioned between ethyl acetate (3 × 500 mL) and water (300 mL). The organic fraction (61.1 g) showed an IC_{50} value of 5.5 μg/mL against the growth of *P. falciparum*, whereas the aqueous fraction was inactive (IC_{50} value, 50 μg/mL). A portion (9 g) of the ethyl acetate extract was fractionated by silica gel column chromatography using a gradient elution with successively cyclohexane−EtOAc, EtOAc−CH_2Cl_2, and CH_2Cl_2−MeOH. Altogether, 18 fractions (F1−F18) were collected and tested. The less potent fractions (F3−F6; 1.2 g) eluted from the column with the cyclohexane−EtOAc gradient (95:5 to 80:20) exhibited IC_{50} values ranging from 3.9 to 7.7 μg/mL. The intermediate fractions (F8−F12; 1.85 g) eluted first with cyclohexane−EtOAc (85:15 to 70:30) and then with CH_2Cl_2−MeOH (100:0 to 98:2) displayed IC_{50} values of 3.0−3.5 μg/mL. Fractions F16 and F17 (1.15 g) eluted with CH_2Cl_2−MeOH (97:3 to 90:10) were found to be the most active ones (IC_{50} values, 2.1 μg/mL). Likewise, 12 mg (0.014% w/w) of **5** was obtained from F4, 5.8 mg (0.007% w/w) of **6** was isolated from F3, and 295 mg (0.34% w/w) of obtusaquinol was isolated from F6. Purification of F8 on silica gel column chromatography (CH_2Cl_2−MeOH, 97:3) furnished 2.2 mg of **1** (0.003% w/w) and 42 mg (0.05% w/w) of 9-hydroxy-6,7-dimethoxydalbergiquinol. Compound **8** (4 mg; 0.005% w/w) was obtained from F10. F13 was subjected to passage over a silica gel column using CH_2Cl_2−MeOH, 98:2, as eluent to yield 7 mg of **2** (0.008% w/w) and 23 mg (0.027% w/w) of liquiritigenin. F16 was purified by silica gel column chromatography (CH_2Cl_2−MeOH, 98:2) to afford 4 mg (0.005% w/w) of **3** and 4.35 mg (0.005% w/w) of **7**. F17 was applied to silica gel column chromatography (CH_2Cl_2−MeOH, 90:10) and HPLC (H_2O−acetonitrile, 40:60) to yield 1.4 mg (0.002% w/w) of **4**.

1-(3-Hydroxyphenyl)-3-(4-hydroxy-2,5-dimethoxyphenyl)propane (1): amorphous; UV (MeOH) λ_{max} (log ϵ) 282 (4.47) nm; ^{1}H NMR and ^{13}C NMR data, see Table 1; HRMS *m/z* 289.1435 [M + H]$^+$ (calcd for $C_{17}H_{21}O_4$, 289.1440).

Spirolouveline (2): yellow oil; $[\alpha]^{22}_D$ +15° (*c* 0.066, acetone); UV (MeOH) λ_{max} (log ϵ) 254 (5.03) nm; ^{1}H NMR and ^{13}C NMR data, see Table 1; HRMS *m/z* 273.1125 [M + H]$^+$ (calcd for $C_{16}H_{17}O_4$, 273.1127).

(3*R*)-7,2′-Dihydroxy-4′,5′-dimethoxyisoflavanone (3): amorphous; $[\alpha]^{22}_D$ −11° (*c* 0.185, acetone); UV (MeOH) λ_{max} (log ϵ) 276 (4.23) nm; CD (*c* 6.3 10^{-4}, MeOH) $[\theta]_{326}$ +1168; ^{1}H NMR and ^{13}C NMR data, see Table 2; HRMS *m/z* 317.1031 [M + H]$^+$ (calcd for $C_{17}H_{17}O_6$, 317.1025).

3-(2,4-Dihydroxy-5-methoxy)phenyl-7-hydroxycoumarin (4): amorphous; UV (MeOH) λ_{max} (log ϵ) 200 (5), 281 (4.17), 328 (3.9) nm; ^{1}H NMR and ^{13}C NMR data, see Table 2; HRMS *m/z* 301.0783 [M + H]$^+$ (calcd for $C_{16}H_{13}O_6$, 301.0787).

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