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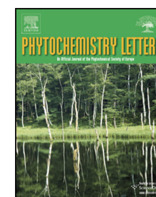

Anti-AGEs and antiparasitic activity of an original prenylated isoflavonoid and flavanones isolated from *Derris ferruginea*

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ABSTRACT

A new isoflavonoid, 5-hydroxy-3-(4-hydroxyphenyl)-8-isopropenyl-8,9-dihydro-4*H*-furo-[2,3-h]-chromen-4-one named derrisisoflavone G (**1**), four known prenylated flavanones (**2–5**), four known isoflavonoids (**6–9**) and two phenolic derivatives (**10, 11**) have been isolated from crude extracts of *Derris ferruginea* stems and leaves. Compounds **1–11** were identified using spectroscopic methods whereas an unambiguous structural assignment of **1** was accomplished through hemi-synthesis. Compounds **2–5** exhibited strong *in vitro* antiparasitic activity against *Plasmodium falciparum* and *Leishmania major* but with poor selectivity, whereas **1–5** significantly inhibited the formation of advanced glycation endproducts (AGEs).
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1. Introduction

Derris (Fabaceae) is a genus belonging to the tribe Millettieae (Leguminosae) with about 250 species that are widely distributed in tropical areas of Africa and Asia (The Angiosperm Phylogeny Group, 2009). These plants are traditionally used as pesticides and fish poisons (Zheng and Wing, 2009). Flavonoids, particularly prenylated flavonoids and isoflavonoids such as rotenoids, are often found in this genus. These secondary metabolites are associated with a broad spectrum of biological activities, including α-glucosidase inhibition (Rao et al., 2007, 2009), insecticidal (Sreelatha et al., 2009; Yenesew et al., 2009), cytotoxic (Cheenpracha et al., 2007; Svasti et al., 2005) and antioxidant activities (Rao et al., 2007, 2009). *Derris ferruginea* (Roxburg) Bentham, also named *Robinia ferruginea*, is a perennial plant found in sparse forests and thickets, growing on low elevation mountain slopes (500–1200 m) and exhibiting densely rust-colored pubescent branchlets (Rao and Seshadri, 1946). The isolation of rotenone from *D. ferruginea* roots was reported a long time ago (Rao and Seshadri, 1946) and we recently described an efficient method for purification of the bioactive cajaflavanone from the stems of this species (Morel et al., 2012). In the course of our investigations on this plant, herein we report the isolation, structural elucidation and hemi-synthesis of a new prenylated isoflavonoid (**1**) from the CH_2Cl_2 extract of *D. ferruginea* stems, together with the identification of 10 known compounds. Their structures were established by 1D and 2D NMR spectroscopy and HRMS analysis. Furthermore, compounds **1–5** exhibited *in vitro* antiparasitic activity as well as an ability to inhibit the formation of advanced glycation endproducts (AGEs).

2. Results and discussion

2.1. Phytochemical study of D. ferruginea

Purification of the CH_2Cl_2 extract from dried stems of *D. ferruginea* afforded compound **1** whereas 10 known compounds (**2–11**) were isolated from cyclohexane, CH_2Cl_2 and EtOAc extracts from stems and cyclohexane extract from dried leaves. They were identified by comparison of their spectroscopic data (UV, IR, NMR,

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$[\alpha]_D$ and MS) with those reported in the literature: four flavanones, 5,3′,4′-trihydroxy-6-(γ,γ-dimethylallyl)-6″,6″-dimethylpyrano-(2″,3″:7,8)-flavanone (**2**) (Shiao et al., 2005), dorsmanine I (**3**) (Ngadjui et al., 2000), lonchocarpol A (**4**) (Innok et al., 2009), 6,8-diprenyleriodictyol (**5**) (Harborne et al., 1993) previously isolated from *Derris laxiflora* (Kim et al., 1995); four isoflavones, genistein (**6**) previously isolated from from *Derris scandens* (Mahabusarakam et al., 2004), pratensein (**7**) (Almeida et al., 2008), prunetin (**8**) (Lu et al., 2008) previously isolated from *Derris elliptica* (Lu et al., 2008) and *D. laxiflora* (Lin et al., 1991), 5-hydroxy-7,3′,4′-trimethoxyisoflavone (**9**) (Veitch et al., 2003) and two phenolic derivatives: coniferyl aldehyde (**10**) (Miyazawa and Hisama, 2003) and 4′-methoxycinnamic acid (**11**) (Rahman and Moon, 2007).

Compound **1** was obtained as a yellow powder, and its molecular formula was deduced as $C_{20}H_{16}O_5$ from the analysis of its NMR and HRMS data (*m*/*z* 359.0889 $[M+Na]^+$, calcd for $C_{20}H_{16}O_5Na$ 359.0890). UV data suggested the presence of an isoflavonoid structure with a characteristic maximum at 266 nm (Mabry and Markham, 1970). This hypothesis was confirmed in the ^1H NMR spectrum of **1** (Table 1), with a typical singlet at δ_H 7.82 (1H, s, δ_C 152.0 by HSQC) due to a resonance of H-2. A singlet at δ_H 13.08 characterized a chelated 5-OH whilst two A_2B_2 doublets [δ_H 7.40 (2H, *J* = 8.5 Hz) and 6.91 (2H, *J* = 8.5 Hz)] could be associated to a *para*-substituted B-ring. The H-6 singlet assignment [δ_H 6.35 (1H)] was deduced from a HMBC connectivity exhibited between 5-OH and C-6 (δ_C 94.4) (Fig. 1). The ^1H NMR spectrum of **1** also exhibited resonances for two ethylenic protons (δ_H 4.97 and 5.11) and a methyl group [δ_H 1.78, (s, 3H)], whereas an ABX spin system [δ_H 5.36 (dd, *J* = 7.3; 9.8 Hz, 1H), 3.43 (dd, *J* = 9.8; 14.6 Hz, 1H) and 3.08 (dd, *J* = 7.3; 14.6 Hz, 1H)] was respectively associated with H-2″, H-3″a and H-3″b. of a dihydrofuran-ring. An isopropenylfuran moiety derived from a classical prenyl cyclization was thus identified in **1**. The position of this 5-membered ring was then deduced from the strong HMBC connectivities observed between H-3″a/H-3″b and C-8 (δ_C 102.8) on one hand and C-8a (δ_C 163.6) on the other. This substitution pattern was eventually confirmed by a NOESY experiment (Table 1). **1** appeared to be optically active with $[\alpha]_D$ −50° (c 0.4, MeOH, 20 °C). Based on a comparison with structurally close compounds such as thonninginisoflavone (Asomaning et al., 1995), licoagroisoflavone (Li et al., 2001), lupinisoflavone A, dimethyl-lupinisoflavone A, trimethyl-luteone

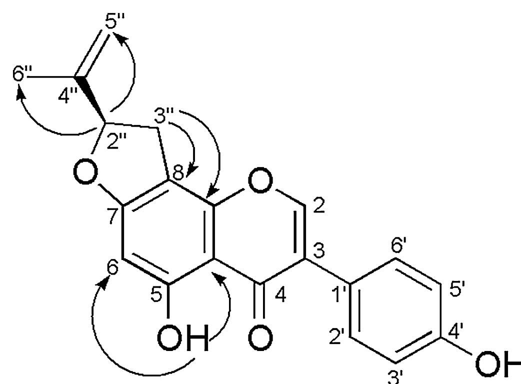


Fig. 1. Structure of derrisisoflavone G (**1**) with key HMBC (H → C) correlations.

metabolite BC-1 dehydrate (Tahara et al., 1987). This optical rotation value suggested a 2″*R* configuration for **1**.

2.2. Hemi-synthesis of compound 1

None of the 2D NMR experiments recorded for **1** allowed us to unambiguously determine the position of the prenyl appendage. Therefore the hemisynthesis of this original secondary metabolite was undertaken to confirm its structure. Our retrosynthetic analysis highlighted that lupiwighteone (**14**) was a key intermediate. This derivative was prepared *via* a 4-step C-8 prenylation of genistein (Al-Maharik and Botting, 2003). Starting from lupiwighteone (**14**), we then achieved a two-step sequence, photooxidation of the prenyl side chain followed by reduction of the intermediate hydroperoxide, leading to the secondary allylic alcohol appendage (**16**) (Helesbeux et al., 2003). The last step consisted of intramolecular Mitsunobu condensation of the secondary alcohol function with the *ortho*-phenol group yielding the substituted dihydrofuran ring. Different steps of this hemi-synthesis process still need to be optimized. However, these reactions allowed us to synthesize, as a racemic mixture, this original secondary metabolite **1**, isolated from *D. ferruginea* and therefore to confirm its structure as 5-hydroxy-3-(4-hydroxyphenyl)-7,8-(2″-isoprenyldihydrofurano)-4*H*-chromen-4-one. We eventually propose to name it derrisisoflavone G.

Table 1
^1H and ^{13}C NMR spectroscopic data (500 MHz, $CDCl_3$) of compound **1**.

Position	$\delta^{13}C$	δ_H (*J* in Hz)	HMBC[a]	NOESY[b]
2	152.0	7.82, s	3, 4	2′
3	123.5		1′	
4	180.7			
4a	105.9			
5-OH	163.6	13.08, s	4a, 6	5″, 6″
6	94.4	6.35, s	4a, 8	
7	166.4			
8	102.8			
8a	163.6			
1′	123.1			
2′, 6′	130.4	7.40, d (8.5)	3′, 4′, 5′	2, 3′, 5′
3′, 5′	115.5	6.91, d (8.5)	1′, 4′	2′, 6′
4′	155.8			
2″	87.9	5.36, dd (7.3, 9.8)	5″, 6″	3″
3″	30.8	3.08, dd (7.3, 14.6)	2″, 8, 4″	2″
		3.43, dd (9.8, 14.6)	4″, 8a	
4″	142.9			
5″	112.9	4.97, s	2″, 6″	5-OH, 6″
		5.11, s	2″, 4″	6″
6″	16.9	1.78, s	2″, 4″, 5″	5″

[a] HMBC correlations (adjusted to 7.5 Hz) are from the specified proton(s) to the indicated carbons.
[b] NOESY correlations are from the specified proton(s) to indicated the proton(s).

2.3. Biological activities

Crude extracts with four different solvents were tested for antiparasitic, antioxidant and anti-AGEs activities. The high antiparasitic potency of the cyclohexane extracts of the leaves (*Plasmodium falciparum*: 79.3% inhibition at 10 μg/mL; *Leishmania major*: IC_{50} = 26 ± 6 μg/mL) prompted us to identify the compounds responsible for this activity. The value obtained for the anti-AGEs activity (IC_{50} = 0.28 mg/mL) was also very interesting when compared to the activity of reference compound, aminoguanidine (IC_{50} = 1 mg/mL).

Compounds **2**–**5** showed strong antiparasitic activity against *P. falciparum* and *L. major* according to former results (Batista and Oliveira, 2009; Kayser et al., 2003). Nevertheless, contrary to cajaflavanone (Morel et al., 2012), **2**–**5** exhibited strong cytotoxicity against safe cell strains, as well as tumor cell strains (IC_{50} < 13.3 μM) (Table 2), which led us to conclude that these compounds have poor selectivity against the *Plasmodium* and *Leishmania* strains tested. These results are in partial agreement with those previously reported for lonchocarpol A (**4**) (Innok et al., 2009) and 6,8-diprenyleriodictyol (**5**) (Omisore et al., 2005; Seo et al., 1997). Alhough exhibiting antiparasitic activity slightly lower than **2**–**5**, the new isoflavone **1** appeared to be very

Table 2
Antiparasitic activity and cytotoxicity of compounds **1**–**5** compared to cajaflavanone.

Compound	*P. falciparum*[a] (IC_{50}, μM)	*L. major*[b] (IC_{50}, μM)	MRC-5 cells (IC_{50}, μM)	KB cells (IC_{50}, μM)
1	>29.8	33.0 ± 1.1	ND	>29.8
2	11.8 ± 0.2	3.3 ± 0.1	12.8 ± 6.2	13.3 ± 7.3
3	10.2 ± 0.9	5.1 ± 0.5	6.2 ± 1.4	8.3 ± 0.2
4	9.9 ± 1.1	1.7 ± 0.3	23.8 ± 0.0	8.6 ± 0.2
5	5.8 ± 0.8	3.7 ± 0.2	8.0 ± 0.0	8.5 ± 0.4
Cajaflavanone	24.6 ± 0.2	40.0 ± 2.0	>24.6	ND
Standards	Chloroquine: 0.097	Pentamidine: 28	Taxotere: 5×10^{-10}	Taxotere: 2×10^{-10}

ND: not determined.
[a] FcB1/Columbia ($n = 3$).
[b] MHOM/Il/81/BNI ($n = 3$).

Table 3
Antioxidant and anti-AGEs activities of compounds **1**–**5** compared to cajaflavanone.

Compound	DPPH (μM TE/μmol)	ORAC (μM TE/μmol)	AGEs (mM)
1 (derrisisoflavone G)	N.A.	0.52	1.7
2 (5,3′,4′-trihydroxy-6-(γ,γ-dimethylallyl)-6″,6″dimethylpyrano-(2″,3″:7,8)-flavanone)	0.36	0.58	1.0
3 (dorsmanine I)	0.91	1.25	1.9
4 (lonchocarpol A)	0.04	1.77	1.3
5 (6,8-diprenyleriodictyol)	0.99	1.12	1.4
Cajaflavanone	N.A.	N.A.	0.5
Naringenin[a]	N.A.	5.53	2.0
Genistein[a]	N.A.	8.68	3.0
Standards	Chlorogenic acid: 1.04	Chlorogenic acid: 4.07	Aminoguanidine: 10 Quercetin: 0.6

N.A.: no activity.
[a] Commercial products.

promising because of the absence of toxicity at the tested concentration on KB cells.

None of these compounds exhibited significant antioxidant potential in DPPH and ORAC bioassays (Table 3). Nevertheless, **1**–**5** were able to inhibit AGEs formation. Comparison of results between prenylated and non-prenylated flavonoids (namely naringenin and genistein) suggests that prenyl side chains have no influence on the antioxidant potential or anti-AGEs activity. Flavonoids and isoflavonoids can act either as antioxidant or as α-dicarbonyl scavengers (Peng et al., 2011). Particularly, as **1** exhibited no significant antioxidant potential in DPPH or ORAC bioassays (Table 3), this compound may scavenge α-dicarbonyl species on C-6 as previously described for catechins (Lo et al., 2006; Peng et al., 2008) or chalcones (Shao et al., 2008).

3. Conclusion

Herein we reported the identification and hemi-synthesis of the original derrisisoflavone G (**1**) together with the isolation of 10 known compounds. To our knowledge, compounds (**2**–**5**) are reported for the first time in the genus *Derris*. All of these compounds exhibited significant but poorly selective antiparasitic activities, whereas they could inhibit AGEs formation. The anti-AGEs capacity of numerous flavonoids was previously reported (Matsuda et al., 2003; Wu and Yen, 2005). Comparison of results between prenylated and non-prenylated flavonoids (namely naringenin and genistein) suggests that a prenyl side chain have no influence, neither on antioxidant potential nor on anti-AGEs activity. It is known that flavonoids and isoflavonoids may act as either antioxidant or α-dicarbonyl scavengers (Peng et al., 2011). In the case of **1** which does not exhibit any significant antioxidant potential in DPPH or ORAC bioassays (Table 3), it is thus assumed that this compound would scavenge α-dicarbonyl species as this was previously described for catechin (Lo et al., 2006; Peng et al., 2008) or chalcone (Shao et al., 2008) derivatives. Therefore, these compounds, particularly the atoxic derrisisoflavone G (**1**), could be useful in AGEs regulation.

4. Experimental

4.1. General experimental procedure

HPLC analyses were performed on a Waters 2695® separation module coupled to a Waters® 2996 Photodiode Array Detector using the Empower software package. A Lichrospher® 100 RP18 column (150 × 4.6 mm, 5 μm, Agilent Technologies) using the following gradient: initial mobile phase $MeOH/H_2O$ 5/95 reaching 100/0 (v/v) in 40 min, with a 1 mL/min flow rate was used for fraction analysis. A Varian OmniSpher C18 column (5 μm, 250 × 4.6 mm) was also used to set up preparative HPLC conditions. Optical rotations were measured by Polartronic D (Eloptron®). IR spectra were recorded on a Bruker Vector22 spectrometer. UV data were obtained using a Cary 50 Bio UV Visible Spectrophotometer (Varian).

Preparative HPLC was performed on a Varian separation module consisting of an UV/visible ProStar 325 spectrophotometer, a PrepStar 218 pump (manual injection, rheodyne valve with a 10 mL sample loop) and a ProStar 701 fraction collector. The module was managed with ProStar/Dynamax software. The fractions were injected into an OmniSpher column (C18, 10 μm, 250 × 21.4 mm). Preparative thin-layer-chromatography (PLC) was carried out on silica gel $60F_{254}$ (0.25 mm, Merck) and separations were monitored by TLC on 60 F_{254} (0. 25 mm, Merck) plates.

CPC was performed using an FCPC 200 (Kromaton) fast centrifugal partition chromatograph. The total volume was 275 mL or 1 L. A valve incorporated in the CPC apparatus allowed operation in descending or ascending mode. The system is equipped with a gradient pump, a UV/vis detector, a rheodyne valve with a 10 mL sample loop and fraction collector.

^{1}H NMR, ^{13}C NMR and 2D NMR spectra were recorded in the appropriate deuterated solvent on a Brucker Avance DRX 500 MHz spectrometer or Jeol GSX 270 MHz. HR mass spectra were recorded on LTQ-Orbitrap (ThermoFisher Scientific).

4.2. Plant material

D. ferruginea (ROXBURGH) Bentham was collected at Ha Tinh, in Vietnam in 1998. It was identified by Dr Nguyen Tien Hiep from the Hanoi National Herbarium and a voucher specimen was deposited as no. VN-0452.

4.3. Extraction and isolation

Dried and ground *D. ferruginea* stems (1200 g) and leaves (800 g) were successively extracted with cyclohexane, CH_2Cl_2, EtOAc and MeOH (8 L, 72 h) in a Soxlhet apparatus to give DfS1-4 extracts (stems) and DfL1-4 extracts (leaves), respectively. The cyclohexane soluble extract DfS1 (7 g) was separated on MPLC (silica column) to give 24 fractions. Pratensein (**7**) (1.2 mg) was obtained by purification of fraction 11 over LH-20 Sephadex gel and preparative HPLC. The CH_2Cl_2 soluble extract DfS2 (3 g) was also fractionated by MPLC to give 17 fractions. Purification of fraction 8 over LH-20 Sephadex gel and C18 SPE gave **1** (2.5 mg). Purification of fraction 9 over LH-20 Sephadex gel generated coniferyl aldehyde (**10**). The EtOAc soluble extract DfS3 (20 g) was fractionated through a FCPC procedure. System: heptane/EtOAc/MeOH/H_2O (10/8/10/6) was used to give 13 fractions. Prunetin (**8**) (1.1 mg) and 5-hydroxy-7, 3′,4′-trimethoxyisoflavone (**9**) (5.4 mg) were obtained from purification of fraction 5 over LH-20 Sephadex gel. Fraction 11 was submitted to LH-20 Sephadex gel and preparative HPLC chromatography to give genistein (**6**) (3.3 mg). The cyclohexane extract from DfL1 leaves (30 g) was submitted to FCPC using the R range of the Arizona heptane/EtOAc/MeOH/H_2O (2/1/2/1) system. 10 fractions were obtained. Purification of fraction 2 over LH-20 Sephadex gel yielded 4′-methoxycinnamic acid (**11**) (2.0 mg). Fraction 5 was subjected to LH-20 Sephadex gel chromatography followed by preparative HPLC to give **2** (6.2 mg) and **3** (22.0 mg) or over a Flash silica gel chromatography column to give **4** (11.4 mg). **5** (674.8 mg) was isolated from fraction 7 by LH-20 Sephadex gel.

4.3.1. Compound *1*

Pale yellow powder, $[\alpha]_D$ −50° (c 0.4, MeOH, 20 °C); UV (MeOH) λ_{max} (log ε) 266 (4.65) nm; IR ($CHCl_3$, cm^{-1}): 3245 br (OH), 1649, 1206.

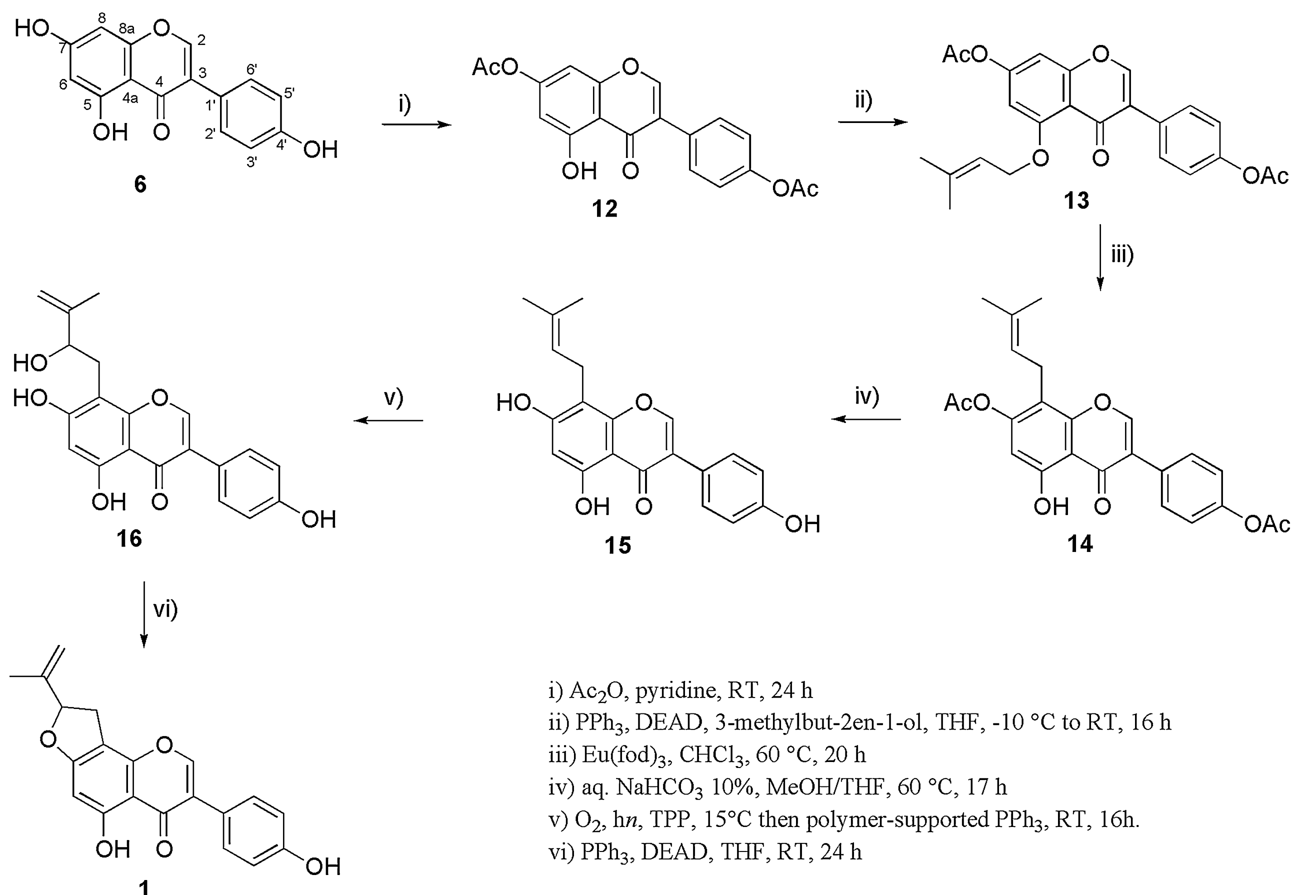
^{1}H NMR and ^{3}C NMR: see Table 1. HRMS (EI): *m/z* 359.0889 $[M+Na]^+$ (calcd for $C_{20}H_{16}O_5Na$ 359.0895).

4.4. Hemi-synthesis of 1

4.4.1. Preparation of 5,7,4′-trihydroxy-8-(3-methylbut-2-en-1-yl)-3-phenylchromen-4-one (lupiwighteone, *15*)

Compound **15** (63 mg, 0.19 mmol) was obtained from genistein **6** (0.50 g, 1.85 mmol) as described by (Al-Maharik and Botting, 2003) (Scheme 1).

^{1}H NMR (270 MHz, acetone d_6): δ 1.66 (s, 3H, H-4″), 1.81 (s, 3H, H-5″), 3.45 (d, 2H, J = 7.0 Hz, H-1″), 5.23 (m, 1H, J = 1.5, 7.0 Hz, H-2″), 6.37 (d, 1H, H-6), 6.90 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 7.47 (d, 2H, J = 8.5, H-2′ and H-6′), 8.25 (s, 1H, H-2), 8.60 (7-OH), 8.70 (4′-OH), 12.97 (5-OH).



Scheme 1. Hemi-synthesis of compound **1**.

*4.4.2. Preparation of 5,7-dihydroxy-3-(4-hydroxyphenyl)-8-(2-hydroxy-3-methylbut-3-enyl)-4H-chromen-4-one (**16**)*

Dried air was bubbled through a 1/1 CH_2Cl_2/acetone mixture (15 mL) of compound **15** (63 mg, 0.19 mmol) and tetraphenylporphine (3 mg, 0.005 mmol) as photosensitizer. The reaction mixture was water-cooled at 15 °C and irradiated with a halogen lamp (500 W). After total consumption of **15**, polymer-supported triphenylphosphine (16 mg, 1.5 eq.) was added and the solution was stirred at room temperature for 16 h. The reaction mixture was then filtered and the resin washed successively with CH_2Cl_2 (5 mL), a 1/1 mixture of MeOH/CH_2Cl_2 (5 mL) and CH_2Cl_2 (5 mL). After solvent removal under reduced pressure, the crude residue obtained from the filtrate was submitted to preparative TLC (MeOH/CH_2Cl_2 2.5/97.5) to give **16** (42 mg, 42% yield). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.81 (s, 3H, H-5″), 2.92 (dd, 1H, *J* = 8.0, 15.0 Hz, H-1″a), 3.11 (dd, 1H, *J* = 2.5 Hz, 15.0 Hz, H-1″b), 4.30 (dd, 1H, *J* = 2.5, 8.0 Hz, H-2″), 6.37 (s, 1H, H-6), 6.90 (d, 2H, *J* = 8.5 Hz, H-3′ and H-5′), 7.47 (d, 2H, *J* = 8.5, H-2′ and H-6′), 8.25 (s, 1H, H-2), 8.60 (7-OH), 8.70 (4′-OH), 12.97 (5-OH).

*4.4.3. Preparation of **1***

65 μL of DIAD (2.5 eq.) and PPh_3 (52 mg, 2.5 eq.) were added to a dry THF solution (3 mL) of **16** (28 mg). The mixture was stirred for 24 h at room temperature. After solvent removal under reduced pressure, the crude residue was purified by preparative TLC (MeOH/CH_2Cl_2 7/93) to generate compound **1** (5 mg, 19%).

4.5. Bioassays

4.5.1. Antileishmanial activity

Promastigote susceptibility testing was performed with the Uptiblue® micromethod described previously (Lepape et al., 2003) on the *L. major* strain (MHOM/Il/81/BNI).

4.5.2. Antiplasmodial activity

Evaluated according to the procedure described previously by Marti et al. (2010) on *P. falciparum* strain (FcB1/Columbia). Chloroquine was used as reference substance.

4.5.3. Cytotoxic activities

Cytotoxic activities were evaluated on MRC5 and KB cells in DMSO at 10 and 1 μg/mL based on the method described by Moret et al. (2009). Taxotere was used as reference substance.

4.5.4. AGEs measurement

AGEs measurement was evaluated according to the procedure described previously by Derbre et al. (2009). Aminoganidine was chosen as reference compound based on previous studies (Reddy and Beyaz, 2006; Sasaki et al., 2009).

4.5.5. Scavenging activity of diphenyl-picrylhydrazyl DPPH radicals and measurement of oxygen radical absorbance capacity (ORAC)

Scavenging activity of diphenyl-picrylhydrazyl DPPH radicals and measurement of oxygen radical absorbance capacity (ORAC) were evaluated according to the procedure described previously by Morel et al. (2012).

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