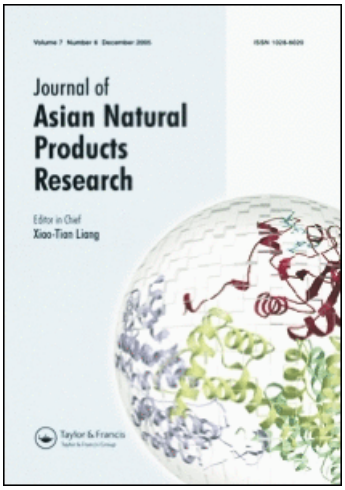


Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

Isolation and synthesis of a new chromenochalcone and a new chromene from *Orthosiphon glabratus*

Biswanath Das[a]; Ponnaboina Thirupathi[a]; Rathod Aravind Kumar[a]; Akella Venkata Subramanya Sarma[a]; Shaik Jilani Basha[a]
[a] Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad, India

To cite this Article Das, Biswanath , Thirupathi, Ponnaboina , Kumar, Rathod Aravind , Sarma, Akella Venkata Subramanya and Basha, Shaik Jilani(2009) 'Isolation and synthesis of a new chromenochalcone and a new chromene from *Orthosiphon glabratus*', Journal of Asian Natural Products Research, 11: 3, 202 — 208
To link to this Article: DOI: 10.1080/10286020802682809
URL: http://dx.doi.org/10.1080/10286020802682809

Journal of Asian Natural Products Research
Vol. 11, No. 3, March 2009, 202–208

Isolation and synthesis of a new chromenochalcone and a new chromene from *Orthosiphon glabratus*

Biswanath Das*, Ponnaboina Thirupathi, Rathod Aravind Kumar, Akella Venkata Subramanya Sarma and Shaik Jilani Basha

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad, India

(*Received 24 June 2008; final version received 3 December 2008*)

Chemical investigation on *Orthosiphon glabratus* afforded 10 compounds, among which a chromenochalcone and a chromene are new. The structures of the new constituents were settled from their 1D- and 2D-NMR spectra. The synthesis of these two compounds and some of their analogues have been accomplished.

Keywords: *Orthosiphon glabratus*; Lamiaceae; chromene; chromenochalcone

1. Introduction

Orthosiphon glabratus Benth (Lamiaceae) is an annual and perennial herb distributed in the hill tracks of Tirumala Hills, Andhra Pradesh, South India [1]. Various species of *Orthosiphon* are known for their medicinal properties and are used for the treatment of different diseases such as diabetes, hypertension, and rheumatism. *O. glabratus* is employed to cure fever, diarrhea, and piles [2,3].

In continuation of our search [4–7] for new plant metabolites, we carried out the chemical investigation on the chloroform–methanol (1:1) extract of the fresh collection of the whole plant of *O. glabratus*. The crude extract was subjected to column chromatography over silica gel using hexane–EtOAc mixtures to isolate 10 compounds **1**–**10** including two new compounds, 1-(2,2-dimethyl-5-hydroxy-2*H*-chromen-6-yl)-3-(2′,3′,4′-trimethoxyphenyl)-propenone (**1**) and 6-acetyl-3,4-dihydro-2,2-dimethyl-5-*O*-prenyl-chromene (**2**). Here, we report the structure elucidation of the new compounds **1** and **2** along with the synthesis of these compounds and some of their analogues (Figure 1).

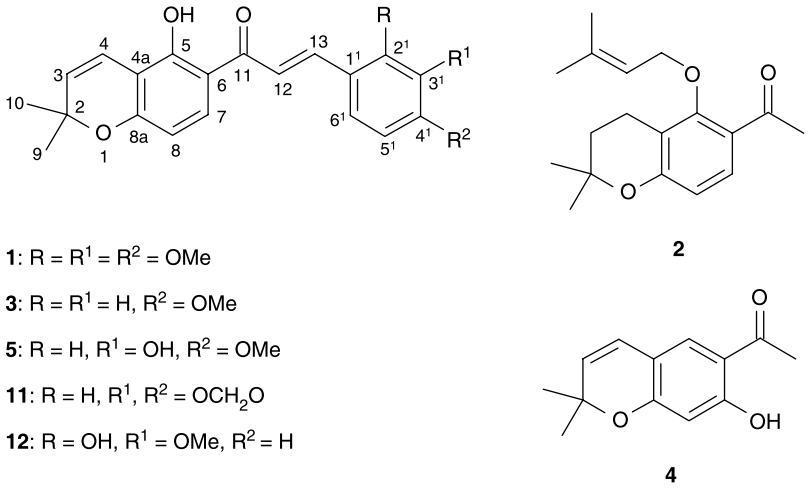
2. Results and discussion

Compound **1** was isolated as pale yellow amorphous powder, mp 124–126°C. Its molecular formula was assigned to be $C_{23}H_{24}O_6$ from its mass spectrum ($[M + H]^+$ at *m*/*z* 397 in ESI-MS), elemental analysis, and ^{13}C NMR spectrum. Its IR spectrum was similar to that of unsaturated chromenochalcones containing hydroxyl group [8]. The ^1H and ^{13}C NMR spectral data (Table 1) of the compounds indicated it to be a chromenochalcone derivative and its structure was related to that of the known constituent, 1-(2,2-dimethyl-5-hydroxy-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)-propenone **3** previously isolated from *Pongamia glabra* [8]. However, **1** contains three methoxy groups (δ 3.98, 3H, s; 3.92, 3H, s; and 3.98, 3H, s in the ^1H NMR spectrum and δ 61.4, 60.9, and 56.1 in the ^{13}C NMR spectrum) instead of one methoxy group

*Corresponding author. Email: biswanathdas@yahoo.com

ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020802682809
http://www.informaworld.com



1: R = R^1 = R^2 = OMe

3: R = R^1 = H, R^2 = OMe

5: R = H, R^1 = OH, R^2 = OMe

11: R = H, R^1, R^2 = OCH_2O

12: R = OH, R^1 = OMe, R^2 = H

2

4

Figure 1. Structures of compounds **1**–**5** and **11** and **12**.

Table 1. ^1H and ^{13}C NMR spectral data for compounds **1** and **2**[a,b].

	1		**2**	
Position	δ_H Mult. (*J* in Hz)	δ_C	δ_H Mult. (*J* in Hz)	δ_C
2	–	77.7	–	74.7
3	5.59 d (10.0)	128.0	1.79 t (7.0)	32.0
4	6.76 d (10.0)	115.9	2.78 t (7.0)	17.5
4a	–	109.4	–	115.4
5	–	159.6	–	157.9
6	–	114.1	–	124.8
7	7.70 d (9.0)	130.6	7.51 d (9.0)	128.9
8	6.38 d (9.0)	108.1	6.60 d (9.0)	113.7
8a	–	160.9	–	158.7
9	1.46 s	28.3	1.34 s	26.6
10	1.46 s	28.3	1.34 s	26.6
11	–	192.4	–	198.8
12	7.60 d (15.8)	119.4	2.60 s	29.9
13	8.02 d (15.8)	139.7	–	–
1′	–	121.9	4.39 d (6.5)	71.2
2′	–	153.9	5.54 t (6.5)	119.1
3′	–	142.5	–	138.5
4′	–	155.9	1.78 s	25.5
5′	6.74 d (8.5)	107.6	1.62 s	17.8
6′	7.38 d (8.5)	124.2	–	–
2′-OMe	3.98 s	61.4	–	–
3′-OMe	3.90 s	60.9	–	–
4′-OMe	3.92 s	56.1	–	–
5-OH	13.81 s	–	–	–

[a]The spectra of compounds **1** and **2** were recorded in $CDCl_3$.
[b]The protons were characterized from DQF-COSY and NOESY experiments, while the carbons were characterized from DEPT, HSQC, and HMBC experiments.

present in **3**. The additional two methoxy groups were reasonably placed at 2′ and 3′ positions as the ^{1}H NMR values of the protons indicated that rings A and B of both the compounds **1** and **3** were similar and the ring C of the former was 1′,2′,3′,4′-tetra substituted. In the ^{1}H NMR spectrum, the protons of rings A and B of **1** appeared at δ 7.70 (1H, d, $J = 9.0$ Hz, H-7), 6.76 (1H, d, $J = 10.0$ Hz, H-4), 6.38 (1H, d, $J = 9.0$ Hz, H-8), and 5.59 (1H, d, $J = 10.0$ Hz, H-3), while those of ring C at δ 7.38 (1H, d, $J = 8.5$ Hz) and 6.74 (1H, d, $J = 8.5$ Hz). The spectrum also showed the presence of a chelated hydroxyl (δ 13.81, 1H, s) and two methyl groups (δ1.46, 6H, s) along with two *trans*-olefinic protons at δ 8.02 (1H, d, $J = 15.8$ Hz) and 7.60 (1H, d, $J = 15.8$ Hz) assigned to H-13 and H-12, respectively. The assignment of the protons was clearly supported by DQF-COSY and NOESY experiments. The ^{13}C NMR spectrum showed the presence of 22 signals (corresponding to 23 carbons) which were characterized with the help of HSQC (for protanated carbons) and HMBC experiments (for quaternary carbons). The spectrum clearly revealed the presence of one carbonyl (δ 192.4), three methoxy (δ 61.4, 60.9, and 56.1), and two methyl groups [δ 28.3 (×2)] and four double-bonded carbons (δ 128.0, 115.9, 139.7, and 119.4). The HMBC experiments showed the correlations of H-7 (δ 7.70) with C-5 (δ 159.6), C-8a (δ 160.9), and C-11 (δ 192.4); H-12 (δ 7.60) with C-6 (δ 114.1) and C-1′ (δ 121.9); H-13 (δ 8.02) with C-11, C-2′ (δ 153.9), and C-6′ (δ 124.2); H-6′ (δ 7.38) with C-13 (δ 139.7), C-2′ (δ 153.9), and C-4′ (δ 155.9); and H-5′ (δ 6.74) with C-1′ and C-3′ (Figure 2). Thus, the structure of **1** was established as 1-(2,2-dimethyl-5-hydroxy-2*H*-chromen-6-yl)-3-(2′,3′,4′-trimethoxy phenyl)-propenone.

Compound **2** was isolated as colorless viscous mass. Its molecular formula was determined to be $C_{18}H_{24}O_3$ from its mass spectrum ($[M + H]^+$ at *m/z* 289 in ESI-MS), elemental analysis, and ^{13}C NMR spectrum. Its IR spectrum showed characteristic absorptions for hydroxyl and conjugated carbonyl functionality in the molecule. The ^{1}H and ^{13}C NMR spectral data of **2** (Table 1) showed some similarities with that of the known constituent, 6-acetyl-2,2-dimethyl-7-hydroxy-chromene (**4**), previously isolated from *Calea serrat* [9]. Instead of a double bond at C-3, C-4 in **4**, compound **2** contained a single bond as the ^{1}H NMR values at δ 2.78 (2H, t, $J = 7.0$ Hz) and 1.79 (2H, t, $J = 7.0$ Hz) were assigned to H-3 and H-4, respectively, and the ^{13}C NMR values at δ 32.0 and 17.5 to C-3 and C-4, respectively. The ^{1}H NMR spectrum also showed AB pattern aromatic protons at δ 7.51 (1H, d, $J = 9.0$ Hz, H-7) and 6.60 (1H, d, $J = 9.0$ Hz, H-8), and three methyl groups at δ 1.34 (6H, s, Me-9, Me-10) and 2.60 (3H, s, Me-12). The signals at δ 4.39 (2H, d, $J = 6.5$ Hz), 5.54 (1H, d, $J = 6.5$ Hz), 1.62 (3H, s), and 1.78 (3H, s) were assigned to H-1′, H-2′, H-5′, and H-4′, respectively, suggesting the presence for a *O*-prenyl group which was placed at C-5. The DQF-COSY and NOESY experiments supported the assignment of the protons. The ^{13}C NMR spectrum showed the presence of 17 signals corresponding to 18 carbons.

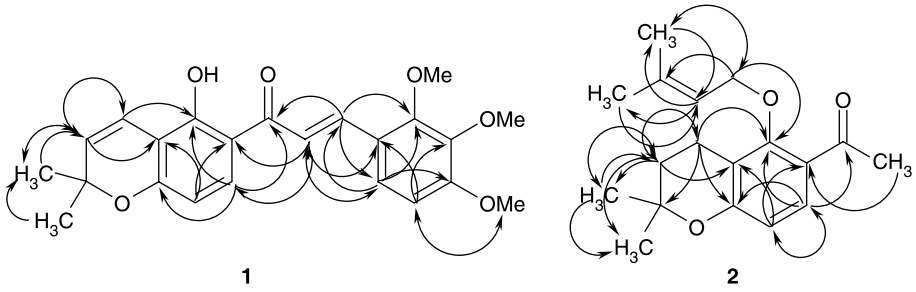


Figure 2. Significant HMBC (⟶) and NOESY (⟷) correlations for compounds **1** and **2**.

These carbons were assigned with the help of HSQC (for protanated carbons) and HMBC experiments (for quaternary carbons). The ^{13}C NMR spectra revealed the presence of one carbonyl (δ 198.8) and five methyl groups (δ 17.8, 25.5, 26.6 (×2), and 29.9). The HMBC experiments showed that H-3 was correlated with C-4a (δ 115.4), C-9 and C-10 (δ 26.6), H-4 with C-8a (δ 158.7) and C-5 (δ 157.9) and H-7 (δ 7.51) with C-8a, C-5, and C-11 (δ 198.8). Thus, the structure of **2** was derived as 6-acetyl-3,4-dihydro-2,2-dimethyl-5-*O*-prenyl-chromene.

Along with the unknown compounds **1** and **2**, eight other known compounds 1-(2,2-dimethyl-5-hydroxy-2*H*-chromen-6-yl)-3-(4-methoxylphenyl)-propenone (**3**) [8], 6-acetyl-2,2-dimethyl-7-hydroxy-chromene (**4**) [9], 1-(2,2-dimethyl-5-hydroxy-2*H*-chromen-6-yl)-3-(3-hydroxy-4-methoxylphenyl)-propenone (**5**) [8], 3,5,7,4′-tetramethoxy flavone (**6**) [10], 3,5-dihydroxy-7,3′,4′-trimethoxy flavone (**7**) [11], 6,7-dimethoxy-8-hydroxy coumarin (**8**) [12], ferulic acid (**9**) [13], and isoferulic acid (**10**) [14], were also isolated. The structures of these compounds were settled by comparison of their physical and spectral (^1H NMR and MS) data with those reported in the literature.

The work has been extended to syntheses of new constituents **1** and **2** and their analogues including the chromenochalones **5**, **11**, and **12**. 6-Acetyl-2,2-dimethyl-5-hydroxy-chromene was used as the starting material. The compound was prepared by treatment of the commercially available 2,4-dihydroxy acetopenone (**13**) (resacetophenone) with 3-methyl-2-butenal using dry pyridine (Scheme 1). The desired product, 6-acetyl-2,2-dimethyl-5-hydroxy-chromene (**14**) was obtained in (82%) yields along with a minor amount of **4** (6%). The $BF_3{\cdot}Et_2O$ catalyzed condensation of **14** with a substituted aldehyde such as 2,3,4-trihydroxy, 4-methoxy, 3-hydroxy-4-methoxy, 3,4-methylenedioxy or 2-hydroxy-3-methoxy benzaldehyde afforded chromenochalcones **1** (78%), **3** (83%), **5** (84%), **11** (81%), or **12** (83%). The earlier methods of preparation of chalcones using other acid, base or Lewis acid catalyst afforded the product with lower yields [15–24].

The chromene **14** was subjected to catalytic hydrogenation in the presence of 10% Pd/C catalyst in MeOH to afford 6-acetyl-3,4-dihydro-2,2-dimethyl-5-hydroxy-chromene (**15**) (92%). Compound **15** was subsequently prenylated with prenylbromide and K_2CO_3 in acetone to furnish the new chromene derivative **2** (90%). The structures of all the reaction products were settled from their spectral (^1H NMR and MS) data and by comparison of the values with those of the natural products.

3. Experimental

3.1 General experimental procedures

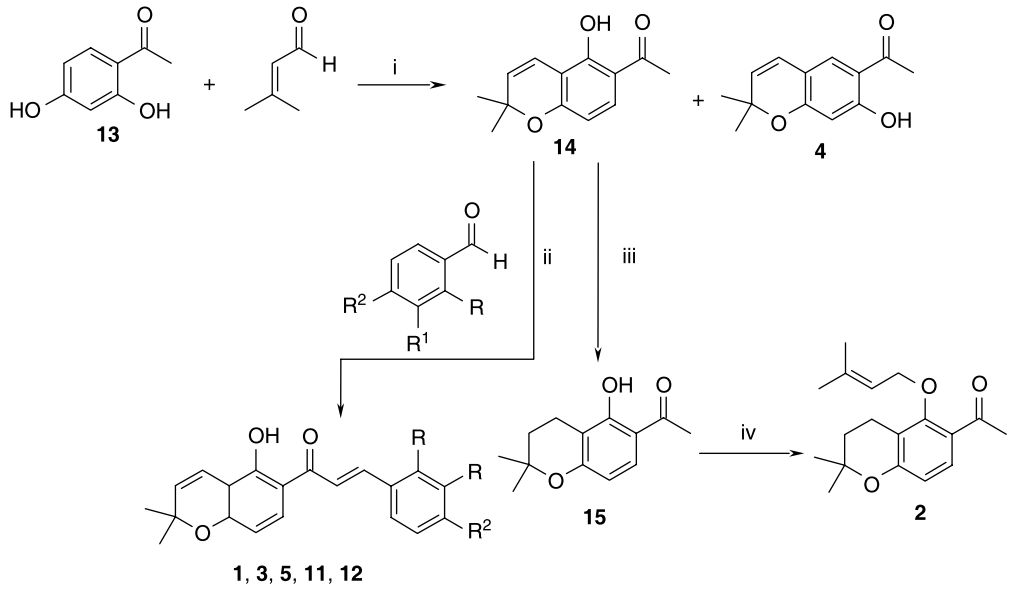
Melting points were measured in a Buchi-510 instrument and are uncorrected. The IR spectra were recorded with the Perkin-Elmer RX1 FT-IR spectrophotometer, NMR spectra with Varian Gemini-200 MHz and Unity-400 MHz spectrometers, and mass spectra with VG-micromass 7070H (70 eV) and Thermo Finnigan LCQ ion trap mass spectrometers. Column chromatography was performed on silica gel (BDH, 100–200 mesh) and TLC with coated glass plates with a thickness of 1 mm with silica gel G (PF 254, art 7747, Merck, Darmstadt, Germany). Required chemical agents were purchased from Aldrich (Milwaukee, WI, USA). Solvents and reagents were purified according to the standard procedures.

3.2 Plant material

The whole plants of *O. glabratus* were collected from the forests of Tirumala Hills, Tirupati, Andhra Pradesh, India, in February 2006 and botanically identified by Prof. K. Janardhan Reddy, Osmania University, Hyderabad. A voucher specimen (No. IICP 170206) is preserved in IICT Herbarium.

3.3 Extraction and isolation

The shade-dried plant material (2 kg) was powdered and extracted thrice with $CHCl_3$ and



Scheme 1. Reagent and conditions: (i) dry pyridine, Δ, 2 h (total 88%); (ii) $BF_3{\cdot}Et_2O$, 2.5 h (78–84%); (iii) $Pd{\cdot}C/H_2$, MeOH, 3 h (92%); and (iv) prenyl bromide, K_2CO_3, reflux, 2 h (90%).

MeOH (1:1) at room temperature. Each extraction was continued for 7 days using 5 l of solvent. The combined extract was concentrated to afford a greenish brown gummy residue (30 g). The residue was subjected to column chromatography and the column was eluted with solvents of increasing polarity using hexane and EtOAc. The following compounds were isolated: **1** (12 mg) and **4** (8 mg), **6** (6 mg) and **7** (13 mg), **2** (15 mg) and **3** (11 mg), **5** (8 mg) and **8** (8 mg), and **9** (24 mg) and **10** (36 mg) (eluted with 15, 20, 35, 40, 45, and 50% EtOAc in hexane, respectively).

*3.3.1 Compound **1***

Pale yellow amorphous powder; mp 124–126°C; IR ν_{max}: 3424, 2925, 1633, 1490, 1258, 1115, and 849 cm^{-1}; ^1H and ^{13}C NMR spectral data: Table 1; ESI-MS *m/z*: 397 $[M + H]^+$; elemental analysis: found: C, 69.95%; H, 6.18%; calcd for $C_{23}H_{24}O_6$: C, 69.69%; H, 6.06%.

*3.3.2 Compound **2***

Colorless viscous mass; IR ν_{max}: 1671, 1594, and 1261 cm^{-1}; ^1H and ^{13}C NMR spectral data: Table 1; ESI-MS *m/z*: 289 $[M + H]^+$; elemental analysis: found: C, 75.24%; H, 8.42%; calcd for $C_{18}H_{24}O_3$: C, 75.00%; H, 8.33%.

3.4 Syntheses of chromenochalcones

*3.4.1 Preparation of 6-acetyl-2,2-dimethyl-5-hydroxy-chromene (**14**) and 6-acetyl-2,2-dimethyl-7-hydroxy-chromene (**4**)*

To a solution of 2,4-dihydroxy acetophenone (resacetophenone) (20 mmol) in dry pyridine (2 ml) 3-methyl crotanaldehyde (22 mmol) was added. The mixture was refluxed for 12 h and the pyridine was removed by washing with dilute HCl. The residue was subjected to column chromatography to afford **14** (82%) and **4** (6%).

*3.4.1.1 Compound **14***. Pale yellow crystals; mp 78–79°C; IR (KBr) ν_{max}: 3426, 1617, 1369, 1272, 1069, and 806 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 12.87 (1H, s, OH), 7.45 (1H, d, $J = 9.4$ Hz, H-7), 6.68 (1H, d, $J = 10.0$ Hz, H-4), 6.25 (1H, d, $J = 9.4$ Hz, H-8), 5.52 (1H, d, $J = 10.0$ Hz, H-3), 2.51 (3H, s, Me), and 1.44

(6H, s, Me × 2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.2 (C-11), 165.0 (C-8a), 160.4 (C-5), 128.8 (C-4), 128.5 (C-7), 120.9 (C-6), 113.9 (C-8), 113.5 (C-4a), 104.4 (C-8), 77.8 (C-2), 29.6 (Me), and 28.5 (Me × 2); EI-MS *m/z*: 218 $[M]^+$, 203, 69, and 41. Elemental analysis: found; C, 71.96%; H, 6.56%; calcd for $C_{13}H_{14}O_3$: C, 71.55%; H, 6.42%.

3.4.2 *Condensation of **14** with substituted benzaldehydes*

To a mixture of 6-acetyl-2,2-dimethyl-5-hydroxy-chromene **14** (1 mmol), appropriate substituted benzaldehyde such as 2,3,4-trimethoxy, 4-methoxy, 3-hydroxy-4-methoxy, 3,4-methylenedioxy or 2-hydroxy-3-methoxy benzaldehyde (1 mmol), $BF_3{\cdot}Et_2O$ (0.5 mmol) and a little dry dioxane were added. The mixture was stirred for 150 min at room temperature and was extracted with ether (3×5 ml). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude mixture was chromatographed over silica gel using hexane and EtOAc as eluent to afford **1** (78%), **3** (83%), **5** (84%), **11** (81%), and **12** (83%).

*3.4.2.1 Compound **11***. Yellow solid; mp 143–145°C; IR (KBr) ν_{max}: 3447, 1636, 1486, 1249, 1115, and 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.75 (1H, s, OH), 7.79 (1H, d, J = 15.4 Hz, H-13), 7.70 (1H, d, J = 9.0 Hz, H-7), 7.38 (1H, d, J = 15.4 Hz, H-12), 7.15 (1H, s, H-2′), 7.13 (1H, d, J = 8.0 Hz, H-6′), 6.84 (H, d, J = 8.0 Hz, H-5′), 6.75 (1H, d, J = 10.0 Hz, H-4), 6.38 (1H, d, J = 9.0 Hz, H-8), 6.03 (2H, s, OCH_2O), 5.58 (1H, d, J = 10.0 Hz, H-3), and 1.46 (6H, s, Me × 2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7 (C-11), 160.9 (C-8a), 159.7 (C-5), 149.9 (C-4′), 148.4 (C-3′), 144.0 (C-13), 130.5 (C-7), 128.0 (C-3), 125.3 (C-6′), 122.2 (C-1′), 118.1 (C-12), 115.8 (C-4), 114.0 (C-6), 109.0 (C-4a), 108.6 (C-2′), 108.1 (C-8), 106.6 (C-5′), 101.6 (OCH_2O), 77.7 (C-2), and 28.3 (Me × 2); ESI-MS *m/z*: 350 $[M + H]^+$; elemental analysis: found: C, 72.29%; H, 5.51%; calcd for $C_{21}H_{18}O_5$: C, 72.00%; H, 5.42%.

*3.4.2.2 Compound **12***. Yellow solid; mp 176–178°C; IR (KBr) ν_{max}: 3390, 1603, 1481, 1244, 1112, and 854 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.78 (1H, s, OH), 8.08 (1H, d, J = 15.8 Hz, H-13), 7.82 (1H, d, J = 15.8 Hz, H-12), 7.72 (1H, d, J = 8.5 Hz, H-5), 7.16 (1H, dd, J = 8.0, 1.5 Hz, H-6′), 6.78–6.92 (2H, m, H-5′, 4′), 6.76 (1H, d, J = 9.8 Hz, H-4), 6.30 (1H, d, J = 9.0 Hz, H-8), 5.56 (1H, d, J = 9.8 Hz, H-3), 3.90 (3H, s, MeO), and 1.45 (6H, s, Me × 2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.6 (C-11), 160.9 (C-8a), 159.6 (C-5), 146.9 (C-2′), 145.9 (C-3′), 139.7 (C-13), 130.8 (C-7), 128.0 (C-3), 122.0 (C-4′), 121.8 (C-12), 121.2 (C-1′), 119.7 (C-5′), 115.9 (C-4), 114.2 (C-6), 112.0 (C-6′), 109.3 (C-4a), 108.1 (C-8), 77.7 (C-2), 56.2 (MeO), and 28.3 (C-9, 10); EI-MS *m/z*: 352 $[M]^+$, 337, 319, and 187; elemental analysis: found: C, 71.91%; H, 5.79%; calcd for $C_{21}H_{20}O_5$: C, 71.59%; H, 5.68%.

3.4.3 *Syntheses of chromenes*

3.4.3.1 Preparation of 6-acetyl-3,4-dihydro-2,2-dimethyl-5-hydroxy-chromene. To a stirred solution of 6-acetyl-2,2-dimethyl-5-hydroxy-chromene **14** (10 mmol) in methanol (5 ml), catalytic amount of Pd/C (0.01 g) was added and the mixture was stirred for 2–3 h at room temperature in hydrogen atmosphere. The reaction mixture was filtered and the combined organic layer was washed with brine (5 ml), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude mixture was passed through a silica gel column to afford desired 6-acetyl-3,4-dihydro-2,2-dimethyl-5-hydroxy-chromene (**15**) in 92% yield.

*3.4.3.2 Compound **15***. Colorless crystals; mp 74°C; IR (KBr) ν_{max}: 3323, 1671, 1594, 1261, 1061, and 820 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.11 (1H, s, OH), 7.48 (1H, d,

$J = 9.5$ Hz, H-7), 6.33 (1H, d, $J = 9.5$ Hz, H-8), 2.68 (2H, t, $J = 7.0$ Hz, H-3), 2.53 (3H, s, Me), 1.80 (2H, t, $J = 7.0$ Hz, H-4), and 1.34 (6H, s, Me × 2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.4 (C-11), 163.2 (C-8a), 161.6 (C-7), 129.0 (C-5), 124.0 (C-6), 112.4 (C-4a), 109.7 (C-8), 75.9 (C-2), 33.4 (C-3), 26.8 (Me × 2), and 16.8 (C-4); EI-MS *m/z*: 220 $[M]^+$, 165, 149, and 43; elemental analysis: found: C, 70.51%; H, 8.21%; calcd for $C_{13}H_{18}O_3$: C, 70.27%; H, 8.10%.

3.4.3.3 Prenylation of 6-acetyl-2,2-dimethyl-5-hydroxy-chromene. The mixture of 6-acetyl-3,4-dihydro-2,2-dimethyl-5-hydroxy-chromene (**15**) (5 mmol) and prenyl bromide (7.5 mmol) was taken into acetone (5 ml). K_2CO_3 (1.5 g) was added and the mixture was stirred for 2 h under reflux conditions. After completion of the reaction (monitored by TLC), acetone from the reaction mixture was evaporated under reduced pressure. The residue was extracted with ethyl acetate (3×5 ml) and the extract was washed with water (8 ml). The organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was chromatographed over silica gel using hexane and EtOAc as eluent to afford the pure 6-acetyl-3,4-dihydro-2,2-dimethyl-5-hydroxy-*O*-prenyl-chromene **2** (90%).

Acknowledgements

The authors thank CSIR and UGC, New Delhi for financial assistance.

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