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Full Papers

Antibacterial and Antiandrogen Flavonoids from *Sophora flavescens*

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Sixteen flavanones, three flavanonols, and four pterocarpans were isolated from the MeOH extract of the roots of *Sophora flavescens*. Twelve of these were new compounds, including eight prenylflavanones (**1**−**8**), one prenylflavanonol (**9**), and three novel pterocarpane derivatives (**10**−**12**). Their structures were elucidated using NMR and mass spectral methods. Some of these compounds have irregular C_{10} prenyl moieties at C-8 of the flavanone skeleton. These compounds exhibited significant antibacterial activities against the Gram-positive bacteria *Staphylococcus aureus, Bacillus subtilis*, S. *epidermidis*, and *Propionibacterium acnes*. They also exhibited antiandrogen activities.

The oriental crude drug "Kushen" (Sophorae Radix; Japanese name, "Kujinn"), dried roots of *Sophora flavescens* Aiton (Leguminosae), is used as a Chinese traditional medicine for gastric disturbance as well as antifebrile, anodyne, and anthelmintic activities. Alkaloids,[1] pterocarpans,[2] and many kinds of flavonoids[3−7] are known consituents of Kushen. We previously reported kushenols A−O as constituents of *S. flavescens*.[6,8] In the course of screening for antibacterial constituents in plants, Kushen was found to have potent antibacterial activity against Gram-positive bacteria. Prenylflavanone derivatives have now been isolated as its antibacterial constituents. Some of these compounds also showed inhibitory activities toward testosterone 5α-reductase and formation of a complex between 5α-dihydrotestosterone and its receptor. This paper is concerned with the isolation and structure elucidation of the constituents of Sophorae Radix and with the antibacterial and antiandrogen activities of these compounds. Structure−activity relationships are also discussed.

Results and Discussion

The roots of *S. flavescens* were extracted with refluxing MeOH. The EtOAc-soluble fraction of the MeOH extract showed activity against *Staphylococcus aureus* and *Bacillus subtilis*. Thus, the EtOAc-soluble fraction was separated to yield new flavanones, kushenols P−W (**1**−**8**); a new flavanonol, kushenol X (**9**); and three new pterocarpans, kushecarpins A−C (**10**−**12**), along with known compounds, **13**−**23**. Of these, known compounds, norkurarinone (**13**),[4] kurarinone (**14**),[4] neokurarinol (**15**),[5] isokurarinone (**16**),[5] norkurarinol (**17**),[5] kurarinol (**18**),[5] kushenol A (**19**),[6] leachianone G (**20**),[9] kushenol H (**21**),[8] kushenol I (**22**),[8] and *l*-maackiain (**23**)[2] were identified by comparing their spectral data (^{1}H and ^{13}C NMR, $[\alpha]_D$, and MS) with the reported data.

Kushenol P (**1**) ($C_{26}H_{32}O_7$ by HREIMS) gave a typical flavanone UV spectrum. The IR spectrum of **1** had absorption bands indicating hydroxyl and carbonyl groups. The ^{1}H NMR spectrum of **1** showed signals due to a hydrogen-bonded hydroxyl group (C-5) (δ 12.56), H-2 (δ 5.55), and H-3 (δ 2.76, 2.86) of a flavanone, four aromatic protons, and an OMe group. The ^{1}H NMR spectrum also indicated the presence of a 5-hydroxy-2-isopropenyl-5-methylhexyl moiety (C-type) as in **18**. This was supported by a fragment ion in the MS, *m*/*z* 315 $[M - 141]^+$, from the cleavage of

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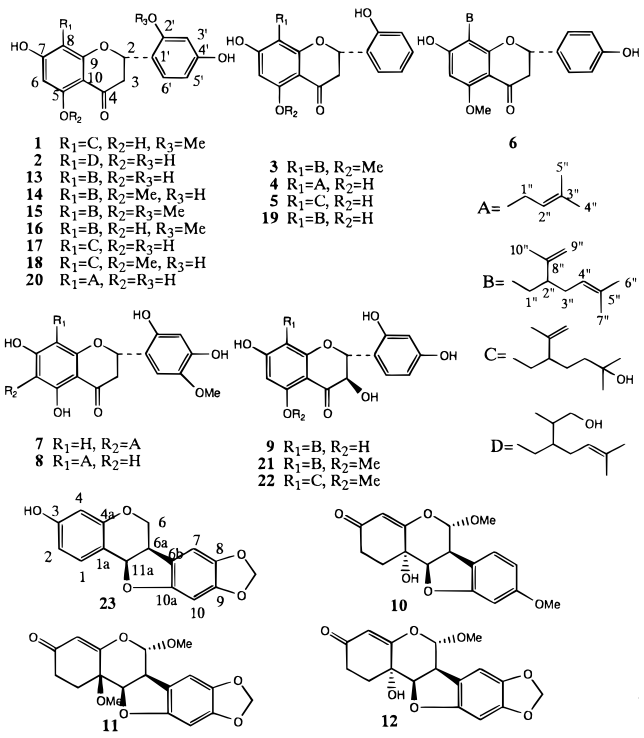

the C_{10} side chain at the benzyl position. The ^{13}C NMR spectrum of **1** contained signals of five oxygenated aromatic carbons and one carbonyl carbon. Chemical shifts and signal patterns in the ^{1}H and ^{13}C NMR spectra indicated that the hydroxyl and OMe groups were at C-5, -7, -2′, and -4′. These assignments were confirmed by the HMBC experiment in which the OMe group correlated with C-2′ and the hydrogen-bonded OH group correlated with C-6, bearing a proton; C-5; and C-10. Thus, the OMe was deduced to be at C-2′ and the C_{10} prenyl group was deduced to be at C-8. In the CD spectrum of **1**, the characteristic Cotton effects based on n→π* transition of flavanone,[10] a positive absorption at 310 nm, and a negative absorption at 285 nm were observed, from which the absolute configuration of **1** is 2*S*. Thus, the structure of **1** is (2*S*)-8-(5-hydroxy-2-isopropenyl-5-methylhexyl)-2′-methoxy-5,7,4′-trihydroxyflavanone.

Kushenol Q (**2**) ($C_{25}H_{30}O_7$ by FABMS) gave a typical flavanone UV spectrum. The ^{1}H NMR spectrum of **2** showed signals due to a hydrogen-bonded hydroxyl proton (δ 12.10) at C-5, H-2 (δ 5.53), and H-3 (δ 2.76, 3.06) of flavanone and four aromatic protons. It also showed a doublet methyl group, two singlet methyl groups, two methylene groups, and a methine group. This suggested the presence of a 2(2-hydroxyisopropyl)-5-methyl-4-hexenyl moiety (D-type). This was further supported by a fragment ion in the MS, *m*/*z* 301 $[M - 141]^+$, from the cleavage of the C_{10} side chain at the benzyl position. The ^{13}C NMR spectrum of **2** showed the presence of five oxygenated aromatic carbons and one carbonyl carbon. The ^{1}H and ^{13}C NMR spectra of **2** showed that hydroxyl groups were located at C-5, -7, -2′, and -4′. The structure of **2** was confirmed in the HMBC experiment. From the CD spectrum, the absolute configuration at C-2 was determined to be *S*.[10] Thus, **2** is (2*S*)-8[2(2-hydroxyisopropyl)-5-methyl-4-hexenyl]-5,7,2′,4′-tetrahydroxyflavanone.

Kushenol R (**3**) ($C_{26}H_{30}O_5$ by HREIMS) gave a typical flavanone UV spectrum. The ^{1}H NMR spectrum of **3** showed signals due to H-2 and H-3 of a flavanone derivative, five aromatic protons, and a lavandulyl moiety (B-type). This was supported from a fragment ion in the MS, *m*/*z* 299 $[M - 123]^+$, from a cleavage of the lavandulyl group at the benzyl position. The ^{13}C NMR spectrum of **3** showed signals of four oxygenated aromatic protons, an OMe group, and a carbonyl carbon. Chemical shifts and signal patterns indicated that the hydroxyl groups were at C-5, -7, or -2′. In ^{13}C NMR spectrum, carbonyl carbons generally appear at δ 196−198 in the case of flavanones having a hydroxyl group at C-5, but appear at δ 191−193 in the case of flavanones having an OMe group at C-5. The carbonyl carbon signal of **3** appeared at δ 192.8, so the OMe group of **3** was placed at C-5. Structure of **3** was confirmed by HMBC experiment. The absolute configuration of **3** was determined to be 2*S* from the CD spectrum.[10] Thus, **3** is (2*S*)-7,2′-dihydroxy-8-lavandulyl-5-methoxyflavanone.

Kushenol S (**4**) ($C_{20}H_{20}O_5$ by HREIMS) gave a typical flavanone UV spectrum. The ^{1}H NMR spectrum of **4** showed signals due to H-2 and H-3 of a flavanone, five aromatic protons, and an isopentenyl moiety (A-type). This was supported by a fragment ion in the MS, *m*/*z* 285 $[M - 55]^+$, from cleavage of the isopentenyl side chain at the benzyl position. The ^{13}C NMR spectrum of **4** showed the presence of four oxygenated aromatic carbons. The isopentenyl group was determined to be at C-8 from the HMBC experiment. From the CD spectrum of **4**, the absolute configuration at C-2 was determined to be *S*.[10] Thus, **4** is (2*S*)-8-isopentenyl-5,7,2′-trihydroxyflavanone.

Kushenol T (**5**) ($C_{25}H_{30}O_6$ by HREIMS) gave a typical flavanone UV spectrum. The ^{1}H NMR spectrum of **5** showed signals due to H-2 and H-3 of a flavanone and five aromatic protons. The ^{1}H NMR spectrum and the FABMS fragment at *m*/*z* 285 $[M - 141]^+$ indicated the same side chain as **1**. The ^{13}C NMR spectrum of **5** showed that the hydroxyl groups are at C-5, -7, and -2′. The position of the side chain and O-functions were determined in the HMBC experiment. The absolute configuration at C-2 was determined to be *S*[10] from the CD spectrum. Thus, **5** is (2*S*)-8-(5-hydroxy-2-isopropenyl-5-methylhexyl)-5,7,2′-trihydroxyflavanone.

Kushenol U (**6**) ($C_{26}H_{30}O_5$ by HREIMS) gave a typical flavanone UV spectrum. The ^{1}H NMR spectrum of **6** showed signals due to H-2 and H-3 for a flavanone, three aromatic protons, an OMe, and a lavandulyl group. The ^{13}C NMR spectrum of **6** indicated four oxygenated aromatic carbons and one carbonyl group. Chemical shifts and signal patterns of **6** in the ^{1}H NMR and the ^{13}C NMR spectra indicated that hydroxyl groups were located at C-7 and -4′ and an OMe group is located at C-5. This fact was confirmed by HMBC experiment. The absolute configuration at C-2 was determined to be *S*[10] from the CD spectrum. Thus, **6** is (2*S*)-7,4′-dihydroxy-8-lavandulyl-5-methoxyflavanone.

Kushenol V (**7**) ($C_{21}H_{22}O_7$ by HREIMS) gave a typical flavanone UV spectrum. The ^{1}H NMR spectrum of **7** showed signals due to H-2 and H-3 for flavanone, three aromatic protons, and an isopentenyl moiety (A-type). The ^{13}C NMR spectrum of **7** indicated six oxygenated aromatic and one carbonyl carbon. Chemical shifts and signal patterns of **7** indicated that the four hydroxyl groups and one OMe group are located at C-5, -7, -2′, -4′, and -5′. On irradiation of the OMe signal at δ 3.83, a NOE was observed on the proton signal at δ 6.46. This indicated that the OMe group is at C-5′. The HMBC experiment of **7** showed long-range C−H correlation in which the hydrogen-bonded hydroxyl group (δ 12.31) correlated with C-6 bearing an isopentenyl group, C-5, and C-10, and an OMe group correlated with C-5′. Thus, the OMe group and the

isopentenyl group were determined to be at C-5′ and C-6, respectively. The absolute configuration at C-2 was determined to be *S*[10] from the CD spectrum. Thus, **7** is (2*S*)-6-isopentenyl-5′-methoxy-5,7,2′,4′-tetrahydroxyflavanone.

Kushenol W (**8**) ($C_{21}H_{22}O_7$ by HREIMS) gave a typical flavanone UV spectrum. The ^{1}H and ^{13}C NMR spectra of **8** showed nearly the same chemical shifts and signal patterns as **7**, indicating it to be a positional isomer of **7**. The OMe group was determined to be at C-5′ by difference NOE. Thus, the isopentenyl group is at C-8. The CD spectrum of **8** did not show a Cotton effect. Thus, **8** is racemic 8-isopentenyl-5′-methoxy-5,7,2′,4′-tetrahydroxyflavanone.

Kushenol X (**9**) was determined to be $C_{25}H_{28}O_7$ (HREIMS). The ^{1}H and ^{13}C NMR spectra of **9** showed signals due to H-2 [δ 5.31 (d, J = 12.0 Hz)], H-3 [δ 4.56 (d, J = 12.0 Hz)], C-2 (δ 78.1), and C-3 (δ 72.7) of a flavanonol, indicating that **9** was a 2,3-*trans*-flavanonol derivative. The ^{1}H NMR spectrum of **9** also showed signals due to four aromatic protons and a lavandulyl group. The ^{13}C NMR spectrum showed five oxygenated aromatic carbon signals and a carbonyl. Chemical shifts and signal patterns of **9** indicated that hydroxyl groups were at C-3, -5, -7, -2′, and -4′ and that a lavandulyl group was at C-8. The absolute configuration at C-2 and C-3 was 2*R*,3*R*[10] as detemined from the CD spectrum. Thus, **9** is (2*R*,3*R*)-8-lavandulyl-5,7,2′,4-tetrahydroxyflavanonol.

Kushecarpin A (**10**) was determined to be $C_{17}H_{18}O_6$ (HRFABMS). The ^{1}H and ^{13}C NMR spectra of **10** were similar to those of pterocarpanes, and the UV suggested an α,β-unsaturated ketone. The IR spectrum of **10** indicated α,β-unsaturated ketone (1658 cm^{-1}) and hydroxyl (3429 cm^{-1}) groups. The ^{1}H NMR spectrum of **10** showed signals due to H-1 (δ 2.11, 2.56), H-2 (δ 2.44, 2.91), H-4 (δ 5.58), H-6 (δ 5.00), H-6a (δ 3.87), H-11a (δ 4.87), three aromatic protons (δ 6.36, 6.49, 7.12), and two MeO groups (δ 3.57, 3.76). The HMBC experiment showed that the MeO groups were located at C-6 and C-9. The CD spectrum of **10** showed a positive Cotton effect at 326 nm, based upon a n$\rightarrow\pi^*$ transition,[11] and a negative Cotton effect at 245 nm, based upon a $\pi\rightarrow\pi^*$ transition[12] of α,β-unsaturated ketone. From these data, the absolute configuration was determined to be 6*S*,6a*S*,11a*R*,11b*S*. Thus, the structure of kushecarpin A (**10**) is as shown.

Kushecarpin B (**11**) was determined to be $C_{18}H_{18}O_7$ (HREIMS), and the ^{1}H and ^{13}C NMR spectra were similar to those of **10**. The UV spectrum indicated an α,β-unsaturated ketone. The ^{1}H NMR spectrum of **11** showed signals due to H-1 (δ 2.25, 2.36), H-2 (δ 2.53, 2.74, H-4 (δ 5.49), H-6 (δ 5.25), H-6a (δ 4.08), H-11a (δ 5.37), two aromatic protons (δ 6.27, 6.67), a methylenedioxy group, and two MeO groups. The NMR signal patterns indicated that the MeOs were located at C-6 and C-11b. The relative configuration of **11** was deduced from the coupling constants and from the difference NOE experiment. From the application of positive (249 nm) and negative (310 nm) Cotton effects of **11** to the rule for $\pi\rightarrow\pi^*$ transition[12] and n$\rightarrow\pi^*$ transition[11] of α,β-unsaturated ketone, the absolute configuration was determined to be 6*S*,6a*S*,11a*R*,11b*R*. Thus, the structure of kushecarpin B (**11**) is as shown.

Kushecarpin C (**12**) was determined to be $C_{17}H_{16}O_7$ (FABMS), and the ^{1}H and ^{13}C NMR spectra of **12** showed the hybrid signal pattern between those of **10** and **11**. The ^{1}H and ^{13}C NMR spectra at C-1, -2, -3, -4, -4a, -6, -6a, -11a, and -11b were identical with those of **10** (see Experimental Section) and the ^{1}H and ^{13}C NMR spectra at C-6b, -7, -8, -9, -10, -10a, and the methylendioxy group were identical with those of **11** (see Experimental Section). Thus the structure of **12** was deduced, and the absolute configuration of **12** should be the same as **10**. Compounds analogous to **10**, **11**, and **12** were previously reported as microbial metabolites[13] derived from maackiain and medicarpin.

Table 1. MIC[a] (μg/mL) of Prenyl Flavones Against *S. aureus* and *B. subtilis*

compound	*S. aureus*	*B. subtilis*
2	5.0	5.0
3	5.0	2.5
4	5.0	5.0
6	10	10
7	10	10
8	10	10
9	10	10
13	2.5	2.5
14	2.5	2.5
15	2.5	2.5
16	2.5	2.5
19	5.0	2.5
20	5.0	2.5

[a] Minimal inhibitory concentration.

Table 2. MIC[a] (μg/mL) of Prenyl Flavones Against *S. epidermidis* and *P. acnes*

compound	*S. epidermidis*	*P. acnes*
3	5.0	10
6	10	10
13	10	10
15	10	25
16	5.0	10
19	5.0	10

[a] Minimal inhibitory concentration.

Compounds **1**−**9** and **13**−**23** were evaluated for antibacterial activity against the Gram-positive bacteria, *S. aureus* and *B. subtilis*. Minimal inhibitory concentrations (MIC) of these compounds are summarized in Table 1. Compounds **13**−**16** were the most inhibitory, and **1**, **17**, and **18** had lower activity than the other compounds. These results indicate that prenylflavanone derivatives having lavandulyl or isopentenyl moieties have potent activity, and the C-type side chain possessing a hydroxyl group reduces the antibacterial activity. A hydroxyl group at C-3 also decreased the antibacterial activity. Similarly, several compounds showed the antibacterial activity against skin residential floras such as *S. epidermidis* and *Propionibacterium acnes* as shown in Table 2.

Most of the isolated prenylflavanone derivatives were tested for inhibitory activity on testosterone 5α-reductase and formation of a complex between 5α-dihydrotestosterone (5α-DHT) and its receptor. The results are summarized in Table 3. Nearly all of these compounds had antiandrogen activity, with **13** and **16** being the most potent. Quantitative analysis of the binding of 5α-DHT to its receptor at various [^{3}H]DHT concentrations by the double reciprocal plots of Lineweaver−Burk indicated that **16** inhibited the binding in a competitive manner.

Experimental Section

General Experimental Procedures. NMR spectra were recorded on a JEOL α-400 spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz), and chemical shifts were given in parts per million (ppm) (δ), with TMS as an internal standard. FABMS were recorded on a JEOL JMX-SX102 mass spectrometer using *m*-nitrobenzyl alcohol as matrix. HREIMS were recorded on a JEOL D-300 mass spectrometer. HRFABMS was recorded on a JEOL HX110 mass spectrometer. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter (at 25 °C). IR spectra were recorded on Perkin−Elmer Spectrum GX FT−IR spectrometer. UV spectra were recorded

Table 3. Antiandrogen Activity of Prenyl Flavones

	5α-reductase inhibitory rate (%) (μg/mL)			5α-DHT-receptor binding inhibitory rate (%) (μg/mL)		
compound	50	100	200	50	100	200
glabridin[a]	32.5	84.3		63.2	88.2	
1	26.0	76.1	93.6	63.1	77.0	83.0
2	0.9	34.8	88.5	66.1	82.4	92.7
3	4.1	23.6	73.5	27.3	67.5	82.4
4	7.3	22.9	37.4	37.8	47.7	70.0
5	3.2	54.8	95.4	35.0	84.9	89.2
6	7.4	50.3	84.4	52.6	85.1	96.9
9	30.9	84.5	96.4	68.9	90.5	88.6
13	51.4	86.4	94.2	80.3	85.8	90.1
14	0.7	40.5	93.8	61.1	89.2	88.0
15	34.1	79.3	94.7	73.7	58.9	58.4
16	54.4	87.1	97.1	81.7	99.8	93.8
17	3.5	41.3	82.2	43.9	75.4	83.0
18	−1.0	−0.2	11.9	15.5	27.9	65.8
19	21.9	51.4	77.3	60.1	89.3	89.6
20	25.3	80.5	89.9	74.2	84.8	94.5
21	14.0	50.9	85.1	60.2	81.4	84.2

[a] An active reference standard isolated from Glycyrrhizae Radix.

on a Hitachi U-3410 spectrophotometer. CD spectra were recorded on a JASCO J-20A spectropolarimeter. Kieselgel 60 (Merck) was used for column chromatography. Analytical and preparative HPLC was carried out on YMC R-ODS-7 packed columns.

Extraction and Isolation. Air-dried, chipped roots (4.0 kg) of *S. flavescens* were purchased from Niiya Co., Ltd., Shimizu-shi, Japan, in April 1994, and were extracted with MeOH under reflux. The MeOH extract was dissolved in H_2O and successively partitioned with EtOAc and butanol to give an EtOAc-soluble fraction (149 g) and a butanol-soluble fraction (69 g), of which, the EtOAc fraction showed antibacterial activity (at 100 μg/mL); therefore, the EtOAc fraction was subjected to Si gel column chromatography using a gradient $CHCl_3$−MeOH solvent system (100:1−1:1). Based on TLC profiles, 12 fractions (F-1−F-12) were collected. F-4 (17.2 g) was successively separated by Si gel column chromatography and HPLC using a reversed-phase column and a CH_3CN-H_2O solvent system to give **4** (94 mg), **7** (90 mg), **12** (50 mg), **20** (1.5 g), **21** (40 mg), and **22** (10 mg). F-6 (13.9 g) was successively separated by Si gel column chromatography and HPLC to give **1** (439 mg), **3** (205 mg), **9** (323 mg), **11** (175 mg), **13** (3 mg), **14** (20 mg), **15** (200 mg), and **16** (8 mg). F-7 (19.8 g) was successively separated by Si gel column chromatography and HPLC to give **1** (353 mg), **2** (206 mg), **5** (62 mg), **8** (40 mg), **9** (19 mg), **10** (153 mg), **17** (15 mg), and **19** (204 mg). F-8 (886 mg) was separated by HPLC to give **2** (12 mg) and **17** (58 mg). F-9 (634 mg) was separated by HPLC to give **5** (24 mg) and **6** (25 mg). F-10 (1.1 g) was separated by HPLC to give **18** (42 mg).

Antibacterial Activity. Gram-positive bacteria employed for the assay were *S. aureus*, *B. subtilis*, *S. epidermidis*, and *P. acnes*. The agar plate dilution method was used for assay of antibacterial activity using the broth microtiter dilution method, and results were observed after 48 h of incubation at 37 °C. All bacterial strains were grown at 37 °C in soybean−casein digest broth.

Antiandrogen Activity. The activity tests were carried out by observation of inhibition against testosterone-5α-reductase and against formation of a complex between 5α-dihydrotestosterone and its receptor as described previously.[14]

Kushenol P (1): UV (MeOH) λ_{max} 293, 340 nm; IR (KBr) ν_{max} 3305 (br), 2960, 1647, 1610, 1292 cm^{-1}; $[\alpha]_D$ −70° (*c* 0.20, MeOH); CD (MeOH); $[\theta]_{310}$ +7015, $[\theta]_{285}$ −53 492, $[\theta]_{220}$ +35 953; ^1H NMR ($CDCl_3 + CD_3OD$) δ 1.07 (3H, s, H-6″), 1.08 (3H, s, H-7″), 1.23 (2H, m), 1.34 (2H, m), 1.59 (3H, s, H-10″), 2.29 (1H, m, H-2″), 2.56 (2H, dd, *J* = 7.4, 2.4 Hz, H-1″), 2.76 (1H, dd, *J* = 16.8, 3.2 Hz, H-3eq), 2.86 (1H, dd, *J* = 16.8, 12.8 Hz, H-3ax), 3.74 (3H, s, OMe), 4.53 (1H, s, H-9″), 4.59 (1H, s, H-9″), 5,55 (1H, dd, *J* = 12.6, 3.2 Hz, H-2), 5.93 (1H, s, H-6), 6.40 (1H, d, *J* = 2.0 Hz, H-3′), 6.44 (1H, dd, *J* = 8.2, 2.0 Hz, H-5′), 7.32 (1H, d, *J* = 8.2 Hz, H-6′), 12.56 (1H, s, OH at C-5); ^{13}C ($CDCl_3 + CD_3OD$) δ 197.5 (C-4), 164.7 (C-9), 161.7 (C-7), 161.5 (C-5), 161.2 (C-2′), 157.3 (C-4′), 148.3 (C-8″)127.4 (C-6′), 118.9 (C-1′), 110.8 (C-9″), 107.6 (C-8), 107.2 (C-5′), 102.6 (C-10), 98.9 (C-3′), 95.8 (C-6), 74.1 (C-2), 71.3 (C-5″), 55.2 (OMe), 46.9 (C-2″), 42.5 (C-3), 41.4 (C-4″), 28.8 (C-7″), 28.6 (C-6″), 27.3 (C-1″), 26.4 (C-3″), 18.7 (C-10″); HREIMS *m/z* 456.2185 $[M]^+$ (calcd for $C_{26}H_{32}O_7$, 456.2148); FABMS *m/z* 457 $[MH]^+$ $C_{26}H_{33}O_7$.

Kushenol P (2): UV (MeOH) λ_{max} 334, 291 nm; IR (KBr) ν_{max} 3364 (br), 2963, 2932, 1638, 1605, 1303 cm^{-1}; $[\alpha]_D$ −17.0° (*c* 0.12, MeOH); CD (MeOH) $[\theta]_{312}$ +9232, $[\theta]_{290}$ −49 624; ^1H NMR ($CDCl_3 + CD_3OD$) δ 0.72 (3H, d, *J* = 6.8 Hz, H-10″), 1.44 (3H, s, H-6″), 1.53 (3H, s, H-7″), 1.67 (1H, m, H-8″), 1.74 (1H, m, H-2″), 1.69 (1H, br d, *J* = 6.8 Hz, H-3″), 2.35 (1H, dd, *J* = 13.4, 5.2 Hz, H-1″), 2.43 (1H, dd, *J* = 13.6, 6.8 Hz, H-1″), 2.76 (1H, dd, *J* = 17.2, 2.4 Hz, H-3eq), 3.06 (1H, dd, *J* = 17.2, 13.2 Hz, H-3ax), 3.38 (1H, dd, *J* = 10.8, 6.4 Hz, H-9″), 3.55 (1H, dd, *J* = 10.8, 8.4 Hz, H-9″), 4.91 (1H, t, *J* = 6.8 Hz, H-4″), 5.53 (1H, dd, *J* = 13.2, 2.4 Hz, H-2), 5.94 (1H, s, H-6), 6.28 (1H, *d*, *J* = 1.6 Hz, H-3′), 6.35 (1H, dd, *J* = 8.2, 1.6 Hz, H-5′), 7.18 (1H, d, *J* = 8.2 Hz, H-6′), 12.10 (1H, s, OH at C-5); ^{13}C NMR ($CDCl_3 + CD_3OD$) δ 197.7 (C-4), 164.5 (C-9), 161.9 (C-7), 160.7 (C-5), 157.8 (C-4′), 155.4 (C-2′), 131.9 (C-5″), 128.0 (C-6′), 123.9 (C-4″), 116.9 (C-1′), 107.9 (C-8), 107.1 (C-5′), 102.9 (C-3′), 102.8 (C-10), 96.1 (C-6), 75.3 (C-2), 66.2 (C-9″), 41.8 (C-3), 40.1 (C-8″), 35.6 (C-2″), 28.9 (C-3″), 25.7 (C-6″), 22.8 (C-1″), 17.6 (C-7″), 12.3 (C-10″); HREIMS *m/z* 456.2185 $[M]^+$ (calcd for $C_{26}H_{32}O_7$, 456.2148); FABMS *m/z* 443 $[MH]^+$ $C_{25}H_{31}O_7$.

Kushenol R (3): UV (MeOH) λ_{max} 321, 287 nm; IR (KBr) ν_{max} 3282 (br), 2947, 2923, 1654, 1599, 1275 cm^{-1}; $[\alpha]_D$ −84.0° (*c* 0.19, MeOH); CD (MeOH) $[\theta]_{332}$ +13 734, $[\theta]_{285}$ −38 704; ^1H NMR ($CDCl_3 + CD_3OD$) δ 1.48 (3H, s, H-6″), 1.53 (3H, s, H-10″), 1.60 (3H, s, H-10″), 1.65 (3H, s, H-7″), 2.05 (2H, m, H-3″), 2.40 (1H, m, H-2″), 2.68 (2H, *m*, H-1″), 2.87 (1H, dd, *J* = 16.8, 2.4 Hz, H-3eq), 3.03 (1H, dd, *J* = 16.4, 13.2 Hz, H-3ax), 3.72 (3H, s, OMe), 4.61 (1H, s, H-9″), 4.67 (1H, s, H-9″), 5.01 (1H, t, *J* = 5.6 Hz, H-4″), 5.65 (1H, dd, *J* = 13.2, 2.4 Hz, H-2), 6.18 (1H, s, H-6), 6.92 (1H, br d, *J* = 7.6 Hz, H-3′), 6.93 (1H, br t, *J* = 8.4 Hz, H-5′), 7.17 (1H, dt, *J* = 7.6, 1.2 Hz, H-4′), 7.46 (1H, d, *J* = 8.0 Hz, H-6′); ^{13}C NMR ($CDCl_3 + CD_3OD$) δ 192.8 (C-4), 162.9 (C-9), 162.7 (C-7), 160.7 (C-5), 153.3 (C-2′), 148.9 (C-8″), 132.5, 132.5 (C-5″), 129.3 (C-4), 126.3 (C-6′), 125.4, (C-1′), 123.1 (C-4″), 120.3 (C-5′), 116.1 (C-3′), 110.9 (C-9″), 108.5 (C-8), 105.3 (C-10), 93.4 (C-6), 75.9 (C-2), 55.6 (OMe), 45.9 (C-2″), 31.6, 44.1 (C-3), 27.5 (C-1″), 25.7 (C-6″) 19.7 (C-!0″), 17.9 (C-7″); HREIMS *m/z* 422.2097 $[M]^+$ (calcd for $C_{26}H_{30}O_5$: 422.2090); FABMS *m/z* 423 $[MH]^+$ $C_{26}H_{31}O_5$.

Kushenol S (4): UV (MeOH) λ_{max} 335, 293 nm; IR (KBr) ν_{max} 3259 (br), 2920, 1640, 1604, 1303 cm^{-1}; $[\alpha]_D$ −118.0° (*c* 0.32, MeOH); CD (MeOH) $[\theta]_{310}$ +13 718, $[\theta]_{288}$ −45 072; ^1H NMR ($CDCl_3 + CD_3OD$) δ 1.62 (6H, s, H-4″, 5″), 2.86 (1H, *dd*, *J* = 17.2, 10.0 Hz, H-3ax), 2.89 (1H, *dd*, *J* = 17.2, 6.4 Hz, H-3eq), 3.24 (2H, m, H-1″), 5.17 (1H, t, *J* = 6.5 Hz, H-2″), 5.64 (1H, dd, *J* = 10.0, 6.4 Hz, H-2), 5.96 (1H, s, H-6), 6.80 (1H, br d, *J* = 7.6 Hz, H-3′), 6.90 (1H, br t, *J* = 7.6 Hz, H-57), 7.16 (1H, dt, *J* = 7.6, 1.6 Hz, H-4′), 7.44 (1H, br d, *J* = 7.2 Hz, H-6′); ^{13}C NMR ($CDCl_3 + CD_3OD$) δ 197.1 (C-4), 164.5 (C-9), 161.6 (C-7), 160.2 (C-5), 153.5 (C-2′), 131.9 (C-3′), 129.2 (C-4′), 126.5 (C-6′), 125.6 (1′), 122.4 (C-2″), 120.1 (C-5′), 115.6 (C-3′), 106.1 (C-8), 102.6 (C-10), 95.9 (C-6), 75.3 (C-2), 41.9 (C-3), 25.7 (5″), 21.6 (C-1″), 17.7 (C-5″); HREIMS *m/z* 340.1302 $[M]^+$ (calcd for $C_{20}H_{20}O_5$, 340.1308); FABMS *m/z* 341 $[MH]^+$ $C_{20}H_{21}O_5$.

Kushenol T (5): UV (MeOH) λ_{max} 335, 293 nm; IR (KBr) ν_{max} 3300 (br), 2969, 2959, 1638, 1505, 1300, cm^{-1}; $[\alpha]_D$ −118.0° (*c* 0.25, MeOH); CD (MeOH) $[\theta]_{310}$ +14 005, $[\theta]_{288}$ −54 855; ^1H NMR ($CDCl_3 + CD_3OD$) δ 1.09 (3H, s, H-6″), 1.16 (3H, s, H-7″), 1.63 (3H, s, H-10″), 1.25−1.5 (4H, m, H-3″, -4″), 2.20 (1H, m, H-2″), 2.55 (1H, dd, *J* = 13.6, 5.6 Hz, H-1″), 2.62 (1H, dd, *J* = 13.6, 8.4 Hz, H-1″), 2.89 (1H, dd, *J* = 17.6, 2.4 Hz, H-3eq), 3.03 (1H, dd, *J* = 17.6, 13.2 Hz, H-3ax), 4.62 (1H, s, H-9″), 4.69 (1H, s, H-9″), 5.67 (1H, dd, *J* = 13.2, 2.4 Hz, H-2), 6.02 (1H, s, H-6), 6.87 (1H, br d, *J* = 8.4 Hz, H-3′), 6.98 (1H, br t, *J* = 7.6 Hz, H-5′), 7.22 (1H, br t, *J* = 8.4 Hz, H-4′), 7.44 (1H, br d, *J* = 8.4 Hz, H-6′), 12.18 (1H, s, OH at C-5); ^{13}C NMR ($CDCl_3 + CD_3OD$) δ 197.4 (C-4), 164.4 (C-9), 161.8 (C-7), 160.7

(C-5), 153.3 (C-2′), 148.5 (C-8″), 129.7 (C-4′), 126.9 (C-6′), 125.4 (C-1′), 120.9 (C-5′), 116.7 (C-3′), 111.1 (C-9″), 107.9 (C-8), 102.9 (C-10), 96.5 (C-6), 75.7 (C-2), 72.5 (C-5″), 47.4 (C-2″), 41.8 (C-3), 40.9 (C-4″), 29.6 (C-7″), 28.5 (C-6″), 27.6 (C-1″), 26.4 (C-3″), 19.1 (C-10″); HREIMS *m/z* 426.2022 $[M]^+$ (calcd for $C_{25}H_{30}O_6$, 426.2039); FABMS *m/z* 427 $[MH]^+$ $C_{25}H_{31}O_6$.

Kushenol U (6): UV (MeOH) λ_{max} 331, 293 nm; IR (KBr) ν_{max} 3284 (br), 2923, 1648, 1599, 1280 cm^{-1}; $[\alpha]_D$ −13.0° (*c* 0.30, MeOH); CD (MeOH) $[\theta]_{335}$ +11 509, $[\theta]_{288}$ −35 806; ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.44 (3H, s, H-6″), 1.53 (3H, s, H-10″), 1.56 (3H, s, H-7″), 1.96 (2H, m, H-3″), 2.36 (2H, m, H-2″), 2.53 (2H, m, H-1″), 2.65 (1H, dd, *J* = 16.8, 2.4 Hz, H-3eq), 2.87 (1H, dd, *J* = 16.4, 13.6 Hz, H-3ax), 3.71 (3H, s, OMe), 4.48 (1H, s, H-9″), 4.55 (1H, s, H-9″), 5.17 (1H, dd, *J* = 13.2, 2.4 Hz, H-2), 5.89 (1H, s, H-6), 6.80 (2H, d, *J* = 8.8 Hz, H-3′, 5′), 7.22 (2H, d, *J* = 8.8 Hz, H-2′, -6′); ^{13}C NMR ($CDCl_3$−CD_3OD) δ 191.4 (C-4), 164.1 (C-9), 162.7 (C-7), 160.3 (C-5), 156.8 (C-4′), 148.6 (C-8″), 131.3 (C-5″), 130.1 (C-1′), 127.4 (C-2′, -6′), 123.4 (C-4″), 110.4 (C-3′, 5′, -9″), 108.5 (C-8), 104.5 (C-10), 93.0 (C-6), 74.0 (C-2), 55.4 (OMe), 46.8 (C-2″), 42.4 (C-3), 31.0 (C-3″), 27.2 (C-1″), 25.5 (C-6″), 18.8 (C-10″), 17.6 (C-7″); HREIMS *m/z* 422.2113 $[M]^+$ (calcd for $C_{26}H_{30}O_5$, 422.2093); FABMS; *m/z* 423 $[MH]^+$ $C_{26}H_{31}O_5$.

Kushenol V (7): UV (MeOH) λ_{max} 331, 293 nm; IR (KBr) ν_{max} 3369 (br), 2930, 1638, 1600, 1308 cm^{-1}; $[\alpha]_D$ −1.0° (*c* 0.22, MeOH); ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.71 (3H, s, H-4″), 1.78 (3H, s, H-5″), 2.80 (1H, dd, *J* = 17.0, 3.0 Hz, H-3eq), 3.06 (1H, dd, *J* = 17.0, 13.0 Hz, H-3ax), 3.29 (2H, br d, *J* = 7.0 Hz, H-1″), 3.83 (3H, s, OMe), 5.23 (1H, br t, *J* = 7.0 Hz, H-2″), 5.60 (1H, dd, *J* = 13.0, 3.0 Hz, H-2), 5.98 (1H, s, H-8), 6.46 (1H, s, H-3′), 6.83 (1H, s, H-6′), 12.31 (1H, s, OH at C-5); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 196.7 (C-4), 163.9 (C-7), 161.5 (C-5), 160.9 (C-9), 148.3 (C-2′), 146.7 (C-4′), 140.8 (C-5′), 134.0 (C-3″), 121.9 (C-2″), 115.1 (C-1′), 109.7 (C-6′), 108.2 (C-6), 103.7 (C-3′), 102.8 (C-10), 95.3 (C-8), 75.8 (C-2), 56.8 (OMe), 42.3 (C-3), 25.8 (C-4″), 21.2 (C-1″), 17.9 (C-5″); HREIMS *m/z* 386.1382 $[M]^+$ (calcd for $C_{21}H_{22}O_7$, 386.1366); FABMS *m/z* 387 $[MH]^+$ $C_{21}H_{23}O_7$.

Kushenol W (8): UV (MeOH) λ_{max} 331, 296 nm; IR (KBr) ν_{max} 3391 (br), 2930, 1638, 1604, 1305 cm^{-1}; $[\alpha]_D$ 0° (*c* 0.28, MeOH); ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.59 (3H, s, H-4″), 1.60 (3H, s, H-5″), 2.80 (1H, dd, *J* = 17.0, 3.5 Hz, H-3eq), 2.88 (1H, dd, *J* = 17.0, 12.5 Hz, H-3ax), 3.18 (2H, br d, *J* = 6.5 Hz, H-1″), 3.78 (1H, s, OMe), 5.18 (1H, t, *J* = 6.5 Hz, H-2″), 5.59 (1H, dd, *J* = 12.5, 3.5 Hz, H-2), 5.92 (1H, s, H-6), 6.37 (1H, s, H-3′), 6.95 (1H, s, H-6′); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 197.2 (C-4), 164.5 (C-7), 161.4 (C-5), 160.4 (C-9), 148.1 (C-2′), 146.3 (C-4′), 140.6 (C-5′), 131.5 (C-3″), 122.6 (C-2″), 116.5 (C-1′), 110.0 (C-6′), 108.0 (C-8), 103.1 (C-3′), 102.5 (C-10), 95.7 (C-6), 74.7 (C-2), 56.7 (OMe), 42.4 (C-3), 25.6 (C-6″), 21.6 (C-1″), 17.6 (C-5″); HREIMS *m/z* 386.1371 $[M]^+$ (calcd for $C_{21}H_{22}O_7$: 386.1366); FABMS *m/z* 387 $[MH]^+$ $C_{21}H_{23}O_7$.

Kushenol X (9): UV (MeOH) λ_{max} 340, 296 nm; IR (KBr) ν_{max} 3338 (br), 2969, 2944, 1650, 1610, 1267 cm^{-1}; $[\alpha]_D$ +49.0° (*c* 0.35, MeOH); CD (MeOH) $[\theta]_{315}$ +5238, $[\theta]_{290}$ −14 841, $[\theta]_{223}$ +31 428; ^1H NMR ($CDCl_3$ +CD_3OD) δ 1.46 (3H, s, H-6″), 1.55 (3H, s, H-10″), 1.57 (3H, s, H-7″), 1.96 (2H, m, H-3″), 2.36 (2H, m, H-2″), 2.51 (2H, m, H-1″), 4.49 (1H, s, H-9″), 4.55 (1H, s, H-9″), 4.56 (1H, d, *J* = 12.0 Hz, H-3), 5.31 (1H, d, *J* = 12.0 Hz, H-2), 5.96 (1H, s, H-6), 6.35 (1H, br s, H-3′), 6.43 (1H, br d, *J* = 8.5 Hz, H-5′), 7.31 (1H, d, *J* = 8.5 Hz, H-6′); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 196.5 (C-4), 165.7 (C-9), 160.7 (C-7), 158.0 (C-5), 157.9 (C-2′), 155.9 (C-4′), 148.4 (C-8″), 131.6 (C-5″), 128.8 (C-6′), 123.3 (C-4″), 115.2 (C-1′), 110.7 (C-9″), 108.8 (8), 107.8 (C-5′), 103.6 (C-10), 100.4 (C-3′), 96.1 (C-6), 78.1 (C-2), 72.7 (C-3), 46.9 (C-2″), 31.3 (C-3″), 26.8 (C-1″), 25.6 (C-7″), 18.9 (C-10″), 17.7 (C-7″); HREIMS *m/z* 440.1848 $[M]^+$ (calcd for $C_{25}H_{28}O_7$, 440.1835); FABMS *m/z* 441 $[MH]^+$ $C_{25}H_{29}O_7$.

Kushecarpin A (10): UV (MeOH) λ_{max} 309, 247, 206 nm; IR (KBr) ν_{max} 3429, 3072, 2940, 1658, 1619, 1476 cm^{-1}; $[\alpha]_D$ −291.0° (*c* 0.29, MeOH); CD (MeOH) $[\theta]_{326}$ +3237, $[\theta]_{245}$ +72 015; ^1H NMR ($CDCl_3$) δ 2.11 (1H, ddd, *J* = 14.0, 5.2, 2.4 Hz, H-1eq), 2.44 (1H, ddd, *J* = 16.8, 14.4, 2.0 Hz, H-2eq), 2.56 (1H, ddt, *J* = 14.0, 4.8, 2.8 Hz, H-1ax), 2.91 (1H, ddd, *J* = 16.8, 14.0, 4.8 Hz, H-2ax), 3.57 (3H, s, 6-OMe), 3.76 (3H, s, 9-OMe), 3.87 (1H, d, *J* = 8.8 Hz, H-6a), 4.87 (1H, d, *J* = 8.8 Hz, H-11a), 4.93 (1H, d, *J* = 2.8 Hz, OH at 11b), 5.00 (1H, s, H-6), 5.58 (1H, s, H-4), 6.36 (1H, d, *J* = 2.4 Hz, H-10), 6.49 (1H, dd, *J* = 8.0, 2.4 Hz, H-8), 7.12 (1H, d, *J* = 8.0 Hz, H-7); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 199.2 (C-3), 170.0 (C-4a), 161.8 (C-9), 160.5 (C-10a), 124.9 (C-7), 117.0 (C-6b), 111.9 (C-4), 107.8 (C-8), 102.5 (C-6), 96.3 (C-10), 83.3 (C-11a), 65.7 (C-1a), 56.9 (OMe), 55.6 (OMe), 44.3 (C-6a), 32.7 (C-2), 31.9 (C-1); HRFABMS *m/z* 319.1176 $[MH]^+$ (calcd for $C_{17}H_{19}H_6$, 319.1183).

Kushecarpin B (11): UV (MeOH) λ_{max} 309, 248, 205 nm; IR (KBr) ν_{max} 3400 (br), 3009, 2926, 2900, 1674, 1618, 1476, 1459 cm^{-1}; $[\alpha]_D$ −8.0° (*c* 0.10, MeOH); CD (MeOH) $[\theta]_{310}$ −8956, $[\theta]_{249}$ +33 940; ^1H NMR ($CDCl_3$) δ 2.25 (1H, ddd, *J* = 13.6, 12.4, 5.6 Hz, H-1ax), 2.36 (1H, ddd, *J* = 13.6, 5.6, 1.6 Hz, H-1eq), 2.53 (1H, ddd, *J* = 18.4, 5.6, 1.6 Hz, H-2eq), 2.74 (1H, dddd, *J* = 18.4, 12.4, 5.6, 1.6 Hz, H-2ax), 3.40 (1H, 3H, s, 11a-OMe), 3.74 (3H, s, 6-OMe), 4.08 (1H, d, *J* = 8.5 Hz, H-6a), 5.25 (1H, s, H-6), 5.37 (1H, d, *J* = 8,0 Hz, H-11a), 5.49 (1H, d, *J* = 1.5 Hz, H-4), 5.86 (1H, s, O−CH_2−O), 5.88 (1H, s, O−CH_2−O), 6.27 (1H, s, H-10), 6.67 (1H, s, H-7); ^{13}C NMR ($CDCl_3$) δ 192.3 (C-3), 175.5 (C-4a), 154.3 (C-10a), 148.5 (C-9), 142.4 (C-8), 115.6 (C-6b), 110.7 (C-4), 104.5 (C-7), 102.2 (C-6), 101.5 (O−CH_2−O), 93.1 (C-10), 89.9 (C-11a), 87.6 (C-1a), 56.1 (OMe), 55.6 (OMe), 55.2 (C-6a), 31.9 (C-2), 27.3 (C-1); HREIMS *m/z* 346.1049 $[M]^+$ (calcd for $C_{18}H_{18}O_7$, 346.1050); FABMS *m/z* 347 $[MH]^+$ $C_{18}H_{19}O_7$.

Kushecarpin C (12): ^1H NMR ($CDCl_3$) δ 2.09 (1H, ddd, *J* = 14.0, 5.2, 2.4 Hz, H-1eq), 2.43 (1H, ddd, *J* = 16.8, 4.4, 2.0 Hz, H-2eq), 2.56 (1H, ddt, *J* = 2.6, 4.8, 13.6 Hz, H-1ax), 2.90 (1H, ddd, *J* = 16.8, 13.6, 4.8 Hz, H-2ax), 3.56 (3H, s, H-6-OMe), 3.82 (1H, d, *J* = 9.6 Hz, H-6a), 4.86 (1H, d, *J* = 9.6 Hz, H-11a), 4.91 (1H, s, H-6), 5.64 (1H, s, H-4), 5.91 (1H, brd , *J* = 1.2 Hz, H−O−CH_2−O), 5.93 (1H, br d, *J* = 1.2 Hz, O−CH_2−O), 6.35 (1H, s, H-10), 6.68 (1H, s, H-7); ^{13}C NMR ($CDCl_3$) δ 199.1 (C-3), 170.0 (C-4a), 154.0 (C-10a), 148.9 (C-9), 142.4 (C-8), 115.7 (C-6b), 111.9 (C-4), 104.3 (C-7), 102.2 (C-6), 101.6 (O−CH_2−O), 93.5 (C-10), 83.2 (C-11a), 65.5 (C-1a), 56.9 (OMe), 45.0 (C-6a), 32.7 (C-2), 31.8 (C-1); FABMS *m/z* 333 $[MH]^+$ $C_{17}H_{17}O_7$.

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