# Neolignans, a Coumarinolignan, Lignan Derivatives, and a Chromene: Anti-inflammatory Constituents from *Zanthoxylum avicennae*

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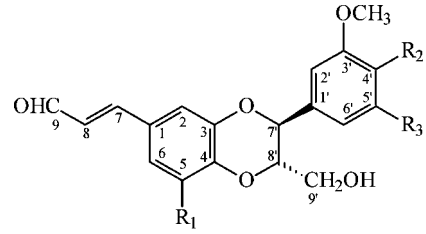
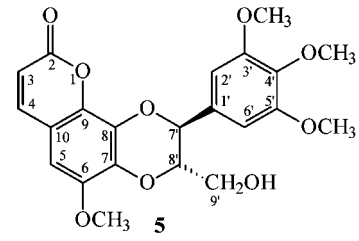
*Received October 24, 2007*

Eight new compounds, including four new neolignans, (7′*S*,8′*S*)-bilagrewin (**1**), (7′*S*,8′*S*)-5-demethoxybilagrewin (**2**), (7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin (**3**), and (7′*S*,8′*S*)-nocomtal (**4**), a new coumarinolignan, (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**), two new lignan derivatives, (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**) and (+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol (**7**), and a new chromene, (*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**), have been isolated from the stem wood of *Zanthoxylum avicennae*, together with 18 known compounds (**9**–**26**). The structures of these new compounds were determined through spectroscopic and MS analyses. (7′*S*,8′*S*)-4′-*O*-Methylcleomiscosin D (**5**), cleomiscosin D (**9**), skimmianine (**18**), robustine (**19**), and integrifoliolin (**23**) exhibited inhibition ($IC_{50} \leq 18.19$ $\mu$M) of superoxide anion generation by human neutrophils in response to formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (FMLP/CB). In addition, skimmianine (**18**) inhibited FMLP/CB-induced elastase release with an $IC_{50}$ value of $19.15 \pm 0.66$ $\mu$M.

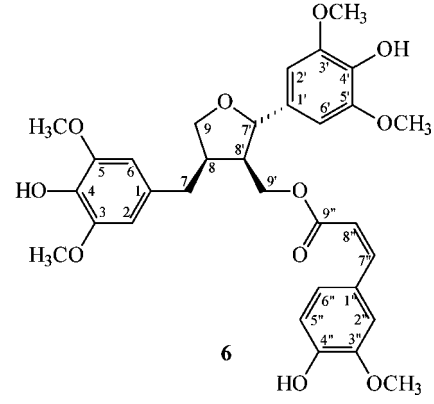
Human neutrophils are known to play crucial roles in host defense against microorganisms and in pathogenesis of various diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), ischemia-reperfusion injury, and asthma.[1–5] In response to diverse stimuli, activated neutrophils secrete a series of cytotoxins, such as the superoxide anion radical ($O_2^{\bullet-}$), a precursor to other reactive oxygen species (ROS), granule proteases, and bioactive lipids.[2,6,7] Suppression of the extensive or inappropriate activation of neutrophils by drugs has been proposed as a way to ameliorate inflammatory diseases. Despite this, there are only a few currently available agents that directly modulate neutrophil proinflammatory responses in clinical practice. *Zanthoxylum avicennae* (Lam.) DC (Rutaceae) is an evergreen shrub distributed in Vietnam, Philippines, southern China, and Taiwan.[8] A decoction of its stems is used as a stomach tonic and as a counter-poison to snake bite.[9] Previous studies of this plant have reported the isolation of flavonoids, alkaloids, coumarins, and terpenoids.[10–15] In our studies on the anti-inflammatory constituents of Formosan plants, many species have been screened for *in vitro* anti-inflammatory activity, and *Z. avicennae* has been found to be one of the active species. The MeOH extract of *Z. avicennae* inhibited FMLP/CB-induced superoxide anion generation and elastase release in a concentration-dependent manner with $IC_{50}$ values of $6.34 \pm 0.56$ and $15.32 \pm 1.46$ $\mu$g/mL, respectively. In our search for compounds with anti-inflammatory activities, four new neolignans, (7′*S*,8′*S*)-bilagrewin (**1**), (7′*S*,8′*S*)-5-demethoxybilagrewin (**2**), (7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin (**3**), and (7′*S*,8′*S*)-nocomtal (**4**), a new coumarinolignan, (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**), two new lignan derivatives, (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**) and (+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol (**7**), and a new chromene, (*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**), and 18 known compounds (**9**–**26**) have been isolated and identified from the stem wood of *Z. avicennae*. This paper describes the structural elucidation and anti-inflammatory activities of **1**–**8**.



**1** $R_1 = R_3 = OCH_3$, $R_2 = OH$
**2** $R_1 = H$, $R_2 = OH$, $R_3 = OCH_3$
**3** $R_1 = OH$, $R_2 = R_3 = OCH_3$
**4** $R_1 = OCH_3$, $R_2 = OH$, $R_3 = H$



**5**



**6**

## Results and Discussion

Chromatographic purification of the EtOAc-soluble fraction of the stem wood of *Z. avicennae* on a Si gel column and preparative TLC afforded eight new (**1**–**8**) and 18 known compounds (**9**–**26**).

(7′*S*,8′*S*)-Bilagrewin (**1**) was obtained as a pale yellow, amorphous powder. Its molecular formula, $C_{21}H_{22}O_8$, was determined

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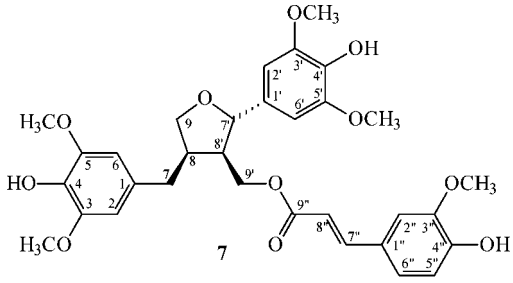
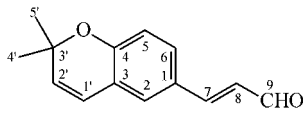
10.1021/np070594k CCC: $40.75 
Published on Web 01/23/2008



**7**



**8**

on the basis of the positive HRESIMS at *m/z* 425.1210 $[M + Na]^+$ (calcd 425.1212) and supported by the $^1H$, $^{13}C$, and DEPT NMR data. The IR spectrum showed the presence of hydroxy (3432 $cm^{-1}$) and carbonyl (1665 $cm^{-1}$) groups. Comparison of the $^1H$ and $^{13}C$ NMR data of **1** with those of nocomtal (**4**)[16] suggested that their structures are closely related except that the 5′-methoxy group ($\delta$ 3.92) of **1** replaced H-5′ ($\delta$ 6.97) of nocomtal. This was supported by NOESY correlations (see Figure 1S in the Supporting Information) between OMe-5′ ($\delta$ 3.92) and H-6′ ($\delta$ 6.67). Compound **1** showed similar CD Cotton effects [225 ($\Delta\epsilon = -0.48$), 238 ($\Delta\epsilon = +0.55$), 287 ($\Delta\epsilon = +0.56$) nm] compared with analogous neolignans.[17] Thus, **1** possessed a 7′*S*,8′*S*-configuration. On the basis of the evidence above, the structure of **1** was elucidated as (7′*S*,8′*S*)-bilagrewin. Although the 7′*S*,8′*R* diastereomer, bilagrewin[18] was reported as a constituent from *Grewia bilamellata*,[18] this is the first isolation of the 7′*S*,8′*S* enantiomer from a natural source.

(7′*S*,8′*S*)-5-Demethoxybilagrewin (**2**) was isolated as an optically active, colorless oil ($[\alpha]^{25}_D = -19.7$). HRESIMS gave an $[M + Na]^+$ ion at *m/z* 395.1110 (calcd for $C_{20}H_{20}O_7Na$, 395.1107), consistent with a molecular formula of $C_{20}H_{20}O_7Na$. The IR spectrum showed a hydroxy absorption at 3402 $cm^{-1}$ and a carbonyl function at 1665 $cm^{-1}$. The $^1H$ NMR spectrum of **2** was similar to that of bilagrewin (**1**),[18] except that H-5 [$\delta$ 7.03 (1H, d, $J = 8.0$ Hz)] of **2** replaced the 5-methoxy group [$\delta$ 3.95 (1H, s)] of bilagrewin. This was supported by both HMBC correlations between H-5 ($\delta$ 7.03) and both C-1 ($\delta$ 128.2) and C-3 ($\delta$ 143.8) and NOESY correlations between H-5 ($\delta$ 7.03) and H-6 (7.15). The 7′*S*,8′*S* configuration of **2** was evidenced by CD Cotton effects at 224 nm ($\Delta\epsilon = -0.45$), 235 nm ($\Delta\epsilon = +0.52$), and 284 nm ($\Delta\epsilon = +0.54$) in analogy with those of **1**. Thus, the structure of **2** was elucidated as (7′*S*,8′*S*)-5-demethoxybilagrewin. This was confirmed by COSY and NOESY data (see Figure 2S in the Supporting Information). The assignment of $^{13}C$ NMR resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 2S in the Supporting Information) techniques.

(7′*S*,8′*S*)-5-*O*-Demethyl-4′-*O*-methylbilagrewin (**3**) was isolated as a pale yellow oil. The sodiated ion $[M + Na]^+$ (*m/z* 425.1208) in the HRESIMS of **3** was consistent with the formula $C_{21}H_{22}O_8Na$ (calcd 425.1212). A comparison of the $^1H$ and $^{13}C$ NMR data of **3** with those of bilagrewin (**1**)[18] suggested that their structures are closely related, except that the 5-hydroxy and 4′-methoxy groups of **3** replaced the 5-methoxy and 4′-hydroxy groups of bilagrewin.[18] This was supported by HMBC correlations observed between 5-OH ($\delta$ 5.62) and both C-5 ($\delta$ 148.0) and C-4 ($\delta$ 136.0) and between 4′-OMe ($\delta$ 3.89) and C-4′ ($\delta$ 137.3). The absolute configuration of **3** was assigned as 7′*S*,8′*S* by the CD Cotton effects at 225 nm ($\Delta\epsilon = -0.49$), 237 nm ($\Delta\epsilon = +0.56$), and 285 nm ($\Delta\epsilon = +0.57$) in analogy with previous CD observations.[17] On the basis of the above data, the structure of **3** was elucidated as (7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin. This was further confirmed by $^1H-^1H$ COSY and NOESY (see Figure 3S, Supporting Information) experiments. The full assignment of the carbon resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 3S, Supporting Information) techniques.

(7′*S*,8′*S*)-Nocomtal (**4**) was obtained as a pale yellow oil, and the molecular formula was confirmed as $C_{20}H_{20}O_7$ from the sodiated ion peak at *m/z* 395.1111 $[M + Na]^+$ (calcd for $C_{20}H_{20}O_7Na$, 395.1107) obtained by HRESIMS. The $^1H$ NMR spectrum of **4** showed the resonances of a 4-hydroxy-3-methoxyphenyl group, a hydroxymethyl group, two oxymethine protons, two *meta*-coupled aromatic protons, a methoxy group, and an (*E*)-3-oxoprop-1-enyl group similar to those of bilagrewin (**1**), except that H-5′ [$\delta$ 6.97 (1H, d, $J = 8.0$ Hz)] of **4** replaced the 5′-OMe group ($\delta$ 3.92) of **1**. This was supported by NOESY correlations between H-5′ ($\delta$ 6.97) and H-6′ ($\delta$ 6.93). Compound **4** showed similar CD Cotton effects to those of **3**, and the absolute configuration of **4** has to be 7′*S*,8′*S*. On the basis of the above data, the structure of **4** was elucidated as (7′*S*,8′*S*)-nocomtal, which was further confirmed by the $^1H-^1H$ COSY, NOESY (see Figure 4S, Supporting Information), DEPT, HSQC, and HMBC (see Figure 4S, Supporting Information) experiments. Although the enantiomeric mixture (7′*R*,8′*R*/7′*S*,8′*S*)[16] of **4** was reported as a constituent from the xylem tissue of caffeic acid *O*-methyltransferase (COMT)-deficient poplar (*Populus* spp.),[16] this is the first isolation of the 7′*S*,8′*S* enantiomer from a natural source.

(7′*S*,8′*S*)-4′-*O*-Methylcleomiscosin D (**5**) was isolated as colorless needles with a molecular formula of $C_{22}H_{22}O_9$ as determined by positive-ion HRESIMS, showing an $[M + Na]^+$ ion at *m/z* 453.1166 (calcd for $C_{22}H_{22}O_9Na$, 453.1162). The presence of OH and carbonyl groups in **5** was revealed by the bands at 3395 and 1718 $cm^{-1}$, respectively, in the IR spectrum. The $^1H$ NMR spectrum of **5** showed the presence of a 3,4,5-trimethoxyphenyl group, two oxymethine protons, a hydroxymethyl group, a methoxy group, an aromatic proton, and two mutually coupled protons of a 2*H*-3,4-dehydropyran-2-one ring similar to signals described previously for cleomiscosin D (**9**),[19] except for the resonance of OMe-4′ ($\delta$ 3.93) in the spectrum of **5**, replacing that of OH-4′ ($\delta$ 5.65) of **9**. This was supported by HMBC correlations between OMe-4′ ($\delta$ 3.93) and C-4′ ($\delta$ 137.6). The absolute configurations at C-7′ and C-8′ were determined as 7′*S*,8′*S* by CD comparison with the analogous neolignan 7*S*,8*S*-nitidanin.[17] On the basis of the above data, the structure of **5** was elucidated as (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D. This was confirmed by $^1H-^1H$ COSY and NOESY (see Figure 5S, Supporting Information) experiments. The assignment of $^{13}C$ NMR resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 5S, Supporting Information) techniques. This is the first isolation of the 7′*S*,8′*S* enantiomer of **5** from a natural source, although the 7′*R*,8′*R* enantiomer of **5** has been synthesized by Bhandari et al.[20]

(+)-9′-*O*-(*Z*)-Feruloyl-5,5′-dimethoxylariciresinol (**6**) was isolated as a colorless, amorphous, optically active powder ($[\alpha]^{25}_D = +23.4$). The molecular formula $C_{32}H_{36}O_{11}$ was deduced from the positive ion $[M]^+$ at *m/z* 596.2255 in the HREIMS. Comparison of the $^1H$ NMR data of **6** with those of (−)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol[21] suggested that their structures are related except that the 9′-*O*-(*Z*)-feruloyl moiety of **6** replaced a 9′-*O*-(*E*)-feruloyl moiety of (−)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol.[21] This was supported by the *cis*-coupling costant ($J = 12.8$ Hz) for H-7″ and H-8″ of **6**. NOESY correlations (see Figure 6S, Supporting Information) of **6** were observed between H-9′ ($\delta$ 4.26, 4.43) and both H-7 ($\delta$ 2.86) and H-7′ ($\delta$ 4.77) and between H-8′ ($\delta$ 2.62) and both H-8 ($\delta$ 2.72) and H-2′/6′ ($\delta$ 6.55). Moreover, NOESY correlations could not be detected between H-9′ ($\delta$ 4.26, 4.43) and both H-8 ($\delta$ 2.72) and H-2′/6′ ($\delta$ 6.55). Thus, the 8,8′-*cis*/7′,8′-*trans* configuration of **6** was established. The absolute configuration of **6** was assigned as 8*R*,7′*S*,8′*R* by the negative CD Cotton effect at 245 nm ($\Delta\epsilon = -0.75$) in analogy with previous

**Table 1.** Inhibitory Effects of **1**–**25** on Superoxide Radical Anion Generation and Elastase Release by Human Neutrophils in Response to fMet-Leu-Phe/Cytochalasin B[a]

| compound | superoxide anion $IC_{50}$ ($\mu$M)[b] | elastase $IC_{50}$ ($\mu$M)[a] |
|---|---|---|
| (7′*S*,8′*S*)-bilagrewin (**1**) | 48.65 ± 3.32*** | >50 |
| (7′*S*,8′*S*)-5-demethoxybilagrewin (**2**) | 26.88 ± 2.41*** | >50 |
| (7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin (**3**) | >50 | >50 |
| (7′*S*,8′*S*)-nocomtal (**4**) | >50 | >50 |
| (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**) | 14.72 ± 3.84*** | >50 |
| (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**) | 27.97 ± 3.65** | 28.93 ± 5.43 |
| (+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol (**7**) | 33.56 ± 3.31** | >50 |
| (*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**) | >50 | >50 |
| cleomiscosin D (**9**) | 13.08 ± 3.80*** | >50 |
| aesculetin dimethyl ether (**10**) | 42.86 ± 6.07*** | >50 |
| scopoletin (**11**) | >50 | >50 |
| 6,7,8,-trimethoxycoumarin (**12**) | 49.52 ± 5.62*** | >50 |
| luvangetin (**13**) | >50 | >50 |
| avicennol (**14**) | >50 | 32.02 ± 4.21*** |
| avicennol methyl ether (**15**) | 48.43 ± 2.78*** | >50 |
| $\gamma$-fagarine (**16**) | 31.31 ± 1.92*** | >50 |
| dictamnine (**17**) | >50 | >50 |
| skimmianine (**18**) | 13.24 ± 1.35*** | 19.15 ± 0.66*** |
| robustine (**19**) | 18.19 ± 5.53*** | >50 |
| isodictamnine (**20**) | >50 | >50 |
| 4-methoxy-1-methyl-2-quinolone (**21**) | >50 | >50 |
| edulitine (**22**) | 37.95 ± 2.59*** | >50 |
| integrifoliolin (**23**) | 18.19 ± 4.95*** | 32.55 ± 0.46 |
| methyl (*E*)-4-(3′-methyl-2′-enyloxy)cinnamate (**24**) | 49.28 ± 6.54* | >50 |
| (-)-syringaresinol (**25**) | 39.87 ± 6.24** | >50 |
| diphenyleneiodonium | 1.68 ± 0.79*** | |
| phenylmethylsulfonyl fluoride | | 204.08 ± 33.07*** |

[a] Diphenyleneiodonium and phenylmethylsulfonyl fluoride were used as positive control. Results are presented as average ± SEM ($n = 4$). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with the control. [b] Concentration necessary for 50% inhibition ($IC_{50}$).

CD data.[22] According to the above data, the structure of **6** was elucidated as (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol.

(+)-9′-*O*-(*E*)-Feruloyl-5,5′-dimethoxylariciresinol (**7**) was obtained as an amorphous powder ($[\alpha]^{25}_D = +20.8$). Its molecular formula was determined as $C_{32}H_{36}O_{11}$ using positive HRESIMS, which showed a sodiated ion peak at $m/z = 619.2153$ $[M + Na]^+$ (calcd for $C_{32}H_{36}O_{11}Na$, 619.2155). The $^1H$ and $^{13}C$ NMR data of **7** were similar to those of **6**, except that a 9′-*O*-(*E*)-feruloyl moiety of **7** replaced a 9′-*O*-(*Z*)-feruloyl moiety of **6**. Comparison of the CD data of **7** with that of **6** suggested that **7** also possessed an 8*R*,7′*S*,8′*R* configuration. The structure of **7** was thus elucidated as (+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol. This was further confirmed by the $^1H-^1H$ COSY, NOESY (see Figure 7S, Supporting Information), DEPT, HSQC, and HMBC (see Figure 7S, Supporting Information) techniques. This is the first report of the occurrence of **7** in a natural source, although the enantiomeric (−)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol has been isolated by Hsiao et al.[21]

(*E*)-3-(2,2-Dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**) was isolated as a colorless oil. The HRESIMS of **8** showed an elemental composition of $C_{14}H_{14}O_2Na$ at $m/z$ 237.0890 $[M + Na]^+$ (calcd 237.0891). The presence of a carbonyl group was revealed by a band at 1670 $cm^{-1}$ in the IR spectrum, which was confirmed by the resonance at $\delta$ 194.0 in the $^{13}C$ NMR spectrum. The $^1H$ NMR spectrum of **8** showed the resonances for a 2,2-dimethyl-3,4-dehydropyrano moiety, three ABX-coupled aromatic protons, and an (*E*)-3-oxoprop-1-enyl group. On the basis of NOESY correlations between H-2 ($\delta$ 7.20) and H-7 ($\delta$ 7.37) and H-1′ ($\delta$ 6.34) and between H-6 ($\delta$ 7.34) and H-5 ($\delta$ 6.81) and H-7 ($\delta$ 7.37), the (*E*)-3-oxoprop-1-enyl group was assigned to C-1. According to the above data, the structure of **8** was elucidated as (*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal, which was confirmed by $^1H-^1H$ COSY and NOESY (see Figure 8S, Supporting Information) experiments. The assignment of $^{13}C$ NMR resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 8S, Supporting Information) techniques.

The known isolates were readily identified by a comparison of physical and spectroscopic data (UV, IR, $^1H$ NMR, $[\alpha]_D$, and MS) with corresponding authentic samples or literature values, and this included a coumarinolignan, cleomiscosin D (**9**),[19] six coumarins, aesculetin dimethyl ether (**10**),[23] scopoletin (**11**),[24] 6,7,8,-trimethoxycoumarin (**12**),[25] luvangetin (**13**),[26] avicennol (**14**),[27] and avicennol methyl ether (**15**),[27] four furoquinolines, $\gamma$-fagarine (**16**),[28] dictamnine (**17**),[29] skimmianine (**18**),[30] and robustine (**19**),[31] a furo-4-quinolone, isodictamnine (**20**),[32] two 2-quinolones, 4-methoxy-1-methyl-2-quinolone (**21**)[31] and edulitine (**22**),[33] two phenylpropenoids, integrifoliolin (**23**)[34] and methyl (*E*)-4-(3′-methyl-2′-enyloxy)cinnamate (**24**),[35] a lignan, (−)-syringaresinol (**25**),[36] and a steroid, $\beta$-sitosterol (**26**).[37]

The anti-inflammatory effects of compounds isolated from the stem wood of *Z. avicennae* were evaluated by suppressing formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (FMLP/CB)-induced superoxide radical anion ($O_2^{\bullet-}$) generation and elastase release by human neutrophils. The anti-inflammatory activity data are shown in Table 1. Diphenyleneiodonium and phenylmethylsulfonyl fluoride were used as positive controls for $O_2^{\bullet-}$ generation and elastase release, respectively. From the results of our anti-inflammatory tests, the following conclusions can be drawn: (a) (7′*S*,8′*S*)-5-demethoxybilagrewin (**2**), (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**), (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**), cleomiscosin D (**9**), $\gamma$-fagarine (**16**), skimmianine (**18**), robustine (**19**), and integrifoliolin (**23**) exhibited inhibitory activities ($IC_{50} \leq 27.97$ $\mu$M) on human neutrophil $O_2^{\bullet-}$ generation. (b) (+)-9′-*O*-(*Z*)-Feruloyl-5,5′-dimethoxylariciresinol (**6**), avicennol (**14**), skimmianine (**18**), and integrifoliolin (**23**) inhibited FMLP/CB-induced elastase release with $IC_{50}$ values ≤ 32.55 $\mu$M. (c) Among the analogues (**16**–**19**), **18** (with 7,8-dimethoxy) and **19** (with 8-hydroxy) exhibited more effective inhibition than **16** (with 8-methoxy) and **17** (without 7- and 8-substituents) against $O_2^{\bullet-}$ generation and elastase release. (d) Coumarinolignans **5** and **9** showed stronger inhibition than the analogous neolignans **1**–**4** against FMLP-induced $O_2^{\bullet-}$ generation. (e) Cleomiscosin D (**9**) and skimmianine (**18**) are

the most effective among the isolated compounds, with $IC_{50}$ values of 13.08 ± 3.80 and 13.24 ± 1.35 $\mu$M, respectively, against FMLP-induced superoxide anion generation. (f) Skimmianine (**18**) exhibited the most effective inhibition, with an $IC_{50}$ value of 19.15 ± 0.66 $\mu$M against FMLP-induced elastase release.

## Experimental Section

**General Experimental Procedures.** All melting points were determined on a Yanaco micromelting point apparatus and were uncorrected. Optical rotations were measured using a Jasco DIP-370 polarimeter in $CHCl_3$. UV spectra were obtained on a Jasco UV-240 spectrophotometer. IR spectra (KBr or neat) were recorded on a Perkin-Elmer system 2000 FT-IR spectrometer. NMR spectra, including COSY, NOESY, HMBC, and HSQC experiments, were recorded on a Varian Unity 400 or a Varian Inova 500 spectrometer operating at 400 and 500 MHz ($^1$H) and 100 and 125 MHz ($^{13}$C), respectively, with chemical shifts given in ppm ($\delta$) using TMS as an internal standard. EI, ESI, and HR-ESI-mass spectra were recorded on a Bruker APEX II mass spectrometry. HREI-mass spectra were recorded on a JEOL JMX-HX 110 mass spectrometer. Si gel (70–230, 230–400 mesh) (Merck) was used for CC. Si gel 60 F-254 (Merck) was used for TLC and preparative TLC.

**Plant Material.** The stem wood of *Z. avicennae* was collected from Pakuashan, Changhua County, Taiwan, in June 2006 and identified by Dr. I. S. Chen. A voucher specimen (Chen 3007) was deposited in the Department of Pharmacy, Tajen University, Pingtung, Taiwan.

**Extraction and Separation.** The dried stem wood of *Z. avicennae* (16 kg) was extracted with cold MeOH, and the extract concentrated under reduced pressure. The MeOH extract (430 g), when partitioned between $H_2O$/EtOAc (1:1), afforded an EtOAc-soluble fraction (fraction A, 98.6 g). Fraction A (98.6 g) was chromatographed on Si gel (70–230 mesh, 3.8 kg), eluting with $CH_2Cl_2$, gradually increasing the polarity with MeOH to give 14 fractions: A1 (12.5 L, $CH_2Cl_2$), A2 (7 L, $CH_2Cl_2$/MeOH, 100:1), A3 (6 L, $CH_2Cl_2$/MeOH, 90:1), A4 (5 L, $CH_2Cl_2$/MeOH, 80:1), A5 (4 L, $CH_2Cl_2$/MeOH, 70:1), A6 (5 L, $CH_2Cl_2$/MeOH, 60:1), A7 (3 L, $CH_2Cl_2$/MeOH, 50:1), A8 (7 L, $CH_2Cl_2$/MeOH, 40:1), A9 (4 L, $CH_2Cl_2$/MeOH, 30:1), A10 (6 L, $CH_2Cl_2$/MeOH, 20:1), A11 (8 L, $CH_2Cl_2$/MeOH, 10:1), A12 (6 L, $CH_2Cl_2$/MeOH, 5:1), A13 (6 L, $CH_2Cl_2$/MeOH, 1:1), A14 (4 L, MeOH). Fraction A1 (5.8 g) was chromatographed further on Si gel (230–400 mesh, 203 g) eluting with $CHCl_3$/acetone (40:1) to give 12 fractions (each 500 mL, A1-1–A1-12). Fraction A1-4 (380 mg) was purified by MPLC (9.8 g Si gel, 40–63 mesh, *n*-hexane/EtOAc 10:1, 75 mL fractions) to obtain 16 subfractions: A1-4-1–A1-4-16. Fraction A1-4-4 (22 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 2:1) to obtain **24** (2.3 mg) ($R_f$ = 0.36). Fraction A1-4-6 (28 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 10:1) to yield **23** (2.8 mg) ($R_f$ = 0.43) and **8** (2.0 mg) ($R_f$ = 0.44). Fraction A1-4-10 (26 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/MeOH, 50:1) to obtain **20** (3.5 mg) ($R_f$ = 0.55). Fraction A1-4-12 (25 mg) was purified further by preparative TLC (Si gel, $CH_2Cl_2$/EtOAc, 40:1) to afford **13** (3.9 mg) ($R_f$ = 0.45). Fraction A1-4-13 (25 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 5:1) to obtain **14** (3.5 mg) ($R_f$ = 0.72). Fraction A1-4-15 (32 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 25:1) to yield **19** (3.3 mg) ($R_f$ = 0.56). Fraction A1-5 (135 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 40:1) to afford **26** (3.8 mg) ($R_f$ = 0.44). Fraction A1-8 (2.0 g) was subjected to CC (72 g Si gel, 230–400 mesh; $CHCl_3$/acetone, 40:1, 1 L fractions) to give 10 subfractions: A1-8-1–A1-8-10. Fraction A1-8-3 (198 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 2:1) to afford **17** (4.3 mg) ($R_f$ = 0.35). Fraction A1-8-4 (205 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 2:1) to obtain **12** (3.7 mg) ($R_f$ = 0.20). Fraction A1-8-5 (188 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/EtOAc, 30:1) to yield **10** (6.9 mg) ($R_f$ = 0.44) and **16** (4.6 mg) ($R_f$ = 0.41). Fraction A2 (3.2 g) was chromatographed further on Si gel (230–400 mesh, 170 g) eluting with $CH_2Cl_2$/EtOAc (10:1) to give 10 fractions (each 1.0 L, A2-1–A2-10). Fraction A2-1 (178 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 10:1) to obtain **11** (2.9 mg) ($R_f$ = 0.38). Fraction A2-3 (198 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/EtOAc, 1:3) to obtain **15** (2.5 mg) ($R_f$ = 0.65). Fraction A6 (4.3 g) was chromatographed further on Si gel (230–400 mesh, 235 g) eluting with $CH_2Cl_2$/MeOH (25:1) to give 11 subfractions (each 1.0 L, A6-1–A6-11). Fraction A6-2 (174 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 20:1) to yield **18** (4.0 mg) ($R_f$ = 0.40). Fraction A6-3 (166 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/MeOH, 30:1) to yield **21** (12.2 mg) ($R_f$ = 0.38). Fraction A7 (5.2 g) was chromatographed further on Si gel (230–400 mesh, 175 g) eluting with $CHCl_3$/MeOH (25:1) to give 20 fractions (each 500 mL, A7-1–A7-20). Fraction A7-7 (207 mg) was purified further by preparative TLC (Si gel, $CH_2Cl_2$/acetone, 10:1) to yield **25** (122 mg) ($R_f$ = 0.37). Fraction A7-9 (190 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 5:1) to yield **5** (3.9 mg) ($R_f$ = 0.48). Fraction A7-10 (538 mg) was purified by MPLC (18 g Si gel, 40–63 mesh, *n*-hexane/EtOAc 1:5, 50 mL fractions) to obtain eight subfractions: A7-10-1–A7-10-8. Fraction A7-10-2 (32 mg) was purified further by preparative TLC (Si gel, $CH_2Cl_2$/acetone, 10:1) to afford **4** (2.6 mg) ($R_f$ = 0.49). Fraction A7-10-3 (35 mg) was purified further by preparative TLC (Si gel, $CH_2Cl_2$/acetone, 10:1) to afford **2** (3.2 mg) ($R_f$ = 0.49). Fraction A7-10-4 (38 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:2) to obtain **6** (3.6 mg) ($R_f$ = 0.13). Fraction A7-10-5 (48 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:2) to yield **3** (2.8 mg) ($R_f$ = 0.17) and **7** (3.2 mg) ($R_f$ = 0.12). Fraction A7-11 (191 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:3) to yield **1** (3.8 mg) ($R_f$ = 0.37). Fraction A7-12 (184 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 5:1) to yield **9** (4.2 mg) ($R_f$ = 0.39). Fraction A7-13 (175 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:4) to yield **22** (2.7 mg) ($R_f$ = 0.33).

**Biological Assay.** The anti-inflammatory effects of the isolated compounds from *Z. avicennae* were evaluated by inhibiting the generation of $O_2^{\bullet-}$ and the release of elastase in FMLP-activated human neutrophils in a concentration-dependent manner.

**Preparation of Human Neutrophils.** Human neutrophils from the venous blood of healthy, adult volunteers (20–28 years old) were isolated using a standard method of dextran sedimentation prior to centrifugation in a Ficoll Hypaque gradient and hypotonic lysis of erythrocytes.[38] Purified neutrophils containing >98% viable cells, as determined by the trypan blue exclusion method, were resuspended in a $Ca^{2+}$-free HBSS buffer at pH 7.4 and were maintained at 4 °C prior to use.

**Measurement of $O_2^{\bullet-}$ Generation.** The assay for measurement of $O_2^{\bullet-}$ generation was based on the SOD-inhibitable reduction of ferricytochrome *c*.[39,40] In brief, after supplementation with 0.5 mg/mL ferricytochrome *c* and 1 mM $Ca^{2+}$, neutrophils were equilibrated at 37 °C for 2 min and incubated with drugs for 5 min. Cells were activated with 100 nM FMLP for 10 min. When FMLP was used as a stimulant, CB (1 $\mu$g/mL) was incubated for 3 min before activation by peptide (FMLP/CB). Changes in absorbance with the reduction of ferricytochrome *c* at 550 nm were continuously monitored in a double-beam, six-cell positioner spectrophotometer with constant stirring (Hitachi U-3010, Tokyo, Japan). Calculations were based on differences in the reactions with and without SOD (100 U/mL) divided by the extinction coefficient for the reduction of ferricytochrome *c* ($\epsilon$ = 21.1/mM/10 mm).

**Measurement of Elastase Release.** Degranulation of azurophilic granules was determined by measuring elastase release as described previously.[40] Experiments were performed using MeO-Suc-Ala-Ala-Pro-Val-*p*-nitroanilide as the elastase substrate. Briefly, after supplementation with MeO-Suc-Ala-Ala-Pro-Val-*p*-nitroanilide (100 $\mu$M), neutrophils ($6 \times 10^5$/mL) were equilibrated at 37 °C for 2 min and incubated with drugs for 5 min. Cells were stimulated with FMLP (100 nM)/cytochalasin B (0.5 $\mu$g/mL), and changes in absorbance at 405 nm were continuously being monitored in order to assay elastase release. The results were expressed as the percent of elastase release in the FMLP/cytochalasin B-activated, drug-free control system.

**Statistical Analysis.** Results are expressed as the mean ± SEM, and comparisons were made using Student's *t*-test. A probability of 0.05 or less was considered significant.

**(7′*S*,8′*S*)-Bilagrewin (1):** pale yellow, amorphous powder; $[\alpha]^{25}_D$ −20.2 (*c* 0.12, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 276 (4.15), 332 (4.31) nm; CD (MeOH, $\Delta\epsilon$) 225 (−0.48), 238 (+0.55), 287 (+0.56) nm; IR (neat) $\nu_{max}$ 3432 (OH), 1665 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.43 (1H, br s, $D_2O$ exchangeable, OH-9′), 3.58 (1H, m, H-9′), 3.92 (6H, s, OMe-3′ and OMe-5′), 3.93 (1H, m, H-9′), 3.95 (3H, s, OMe-5), 4.07 (1H, dt, *J* = 8.0, 3.0 Hz, H-8′), 4.97 (1H, d, *J* = 8.0 Hz, H-7′), 5.63 (1H, br s, $D_2O$ exchangeable, OH-4′), 6.60 (1H, dd, *J* = 16.0, 7.6 Hz, H-8), 6.67 (2H, s, H-2′ and H-6′), 6.77 (1H, d, *J* = 2.0

Hz, H-6), 6.90 (1H, d, $J$ = 2.0 Hz, H-2), 7.36 (1H, d, $J$ = 16.0 Hz, H-7), 9.66 (1H, d, $J$ = 7.6 Hz, CHO); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 56.5 (OMe-5), 56.7 (OMe-3′), 56.7 (OMe-5′), 61.6 (C-9′), 76.7 (C-7′), 79.2 (C-8′), 104.2 (C-6), 104.3 (C-2′), 104.3 (C-6′), 111.6 (C-2), 126.8 (C-1′), 126.9 (C-1), 127.6 (C-8), 135.7 (C-4′), 136.2 (C-4), 144.8 (C-3), 147.6 (C-3′), 147.6 (C-5′), 149.4 (C-5), 152.9 (C-7), 193.8 (C-9); ESIMS $m/z$ (rel int) 425 ([M + Na]$^+$, 100); HRESIMS $m/z$ 425.1210 [M + Na]$^+$ (calcd for $C_{21}H_{22}O_8Na$, 425.1212).

**(7′*S*,8′*S*)-5-Demethoxybilagrewin (2):** colorless oil; $[\alpha]^{25}_D$ −19.7 ($c$ 0.13, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 305 (4.27), 332 (4.33) nm; CD (MeOH, $\Delta\epsilon$) 224 (−0.45), 235 (+0.52), 284 (+0.54) nm; IR (neat) $\nu_{max}$ 3402 (OH), 1665 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.58 (1H, m, H-9′), 3.93 (1H, m, H-9′), 3.93 (6H, s, OMe-3′ and OMe-5′), 4.06 (1H, ddd, $J$ = 8.4, 3.2, 2.8 Hz, H-8′), 5.01 (1H, d, $J$ = 8.4 Hz, H-7′), 5.64 (1H, br s, $D_2O$ exchangeable, OH-4′), 6.62 (1H, dd, $J$ = 16.0, 8.0 Hz, H-8), 6.67 (2H, s, H-2′ and H-6′), 7.03 (1H, d, $J$ = 8.0 Hz, H-5), 7.15 (1H, dd, $J$ = 8.0, 2.0 Hz, H-6), 7.23 (1H, d, $J$ = 2.0 Hz, H-2), 7.40 (1H, d, $J$ = 16.0 Hz, H-7), 9.68 (1H, d, $J$ = 8.0 Hz, CHO); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 56.7 (OMe-3′), 56.7 (OMe-5′), 61.8 (C-9′), 77.1 (C-7′), 78.4 (C-8′), 104.3 (C-2′), 104.3 (C-6′), 117.0 (C-2), 118.2 (C-5), 123.2 (C-6), 126.7 (C-1′), 127.5 (C-8), 128.2 (C-1), 135.8 (C-4′), 143.8 (C-3), 146.9 (C-4), 147.6 (C-3′), 147.6 (C-5′), 152.7 (C-7), 193.9 (C-9); ESIMS $m/z$ (rel int) 395 ([M + Na]$^+$, 100); HRESIMS $m/z$ 395.1110 [M + Na]$^+$ (calcd for $C_{20}H_{20}O_7Na$, 395.1107).

**(7′*S*,8′*S*)-5-*O*-Demethyl-4′-*O*-methylbilagrewin (3):** pale yellow oil; $[\alpha]^{25}_D$ −21.5 ($c$ 0.10, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 277 (4.13), 331 (4.22) nm; CD (MeOH, $\Delta\epsilon$) 225 (−0.49), 237 (+0.56), 285 (+0.57) nm; IR (neat) $\nu_{max}$ 3422 (OH), 1668 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.58 (1H, m, H-9′), 3.89 (3H, s, OMe-4′), 3.91 (6H, s, OMe-3′ and OMe-5′), 3.93 (1H, m, H-9′), 4.07 (1H, dt, $J$ = 8.4, 3.0 Hz, H-8′), 4.98 (1H, d, $J$ = 8.4 Hz, H-7′), 5.62 (1H, br s, $D_2O$ exchangeable, OH-5), 6.62 (1H, dd, $J$ = 15.6, 7.6 Hz, H-8), 6.67 (2H, s, H-2′ and H-6′), 6.78 (1H, d, $J$ = 2.0 Hz, H-6), 6.90 (1H, d, $J$ = 2.0 Hz, H-2), 7.38 (1H, d, $J$ = 15.6 Hz, H-7), 9.68 (1H, d, $J$ = 7.6 Hz, CHO); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 56.3 (OMe-3′), 56.3 (OMe-5′), 61.1 (OMe-4′), 61.6 (C-9′), 76.8 (C-7′), 79.1 (C-8′), 103.2 (C-2′), 103.2 (C-6′), 107.1 (C-6), 111.6 (C-2), 126.5 (C-1′), 127.3 (C-1), 127.6 (C-8), 136.0 (C-4), 137.3 (C-4′), 145.2 (C-3), 148.0 (C-5), 152.8 (C-7), 153.2 (C-3′), 153.2 (C-5′), 193.8 (C-9); ESIMS $m/z$ (rel. int.) 425 ([M + Na]$^+$, 100); HRESIMS $m/z$ 425.1208 [M + Na]$^+$ (calcd for $C_{21}H_{22}O_8Na$, 425.1212).

**(7′*S*,8′*S*)-Nocomtal (4):** pale yellow oil; $[\alpha]^{25}_D$ −23.8 ($c$ 0.14, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 275 (4.18), 334 (4.17) nm; CD (MeOH, $\Delta\epsilon$) 224 (−0.47), 236 (+0.54), 286 (+0.55) nm; IR (neat) $\nu_{max}$ 3420 (OH), 1670 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.03 (1H, br s, $D_2O$ exchangeable, OH-9′), 3.59 (1H, m, H-9′), 3.93 (1H, m, H-9′), 3.94 (3H, s, OMe-3′), 3.95 (3H, s, OMe-5), 4.08 (1H, dt, $J$ = 8.0, 3.0 Hz, H-8′), 5.00 (1H, d, $J$ = 8.0 Hz, H-7′), 5.73 (1H, br s, $D_2O$ exchangeable, OH-4′), 6.60 (1H, dd, $J$ = 16.0, 7.6 Hz, H-8), 6.77 (1H, d, $J$ = 2.0 Hz, H-6), 6.89 (1H, d, $J$ = 2.0 Hz, H-2), 6.93 (1H, dd, $J$ = 8.0, 1.6 Hz, H-6′), 6.97 (1H, d, $J$ = 1.6 Hz, H-2′), 6.97 (1H, d, $J$ = 8.0 Hz, H-5′), 7.36 (1H, d, $J$ = 16.0 Hz, H-7), 9.67 (1H, d, $J$ = 7.6 Hz, CHO); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 56.4 (OMe-3′), 56.5 (OMe-5), 61.6 (C-9′), 76.6 (C-7′), 79.2 (C-8′), 104.1 (C-6), 110.6 (C-2′), 111.5 (C-2), 115.6 (C-5′), 121.5 (C-6′), 126.8 (C-1), 127.6 (C-8), 128.5 (C-1′), 136.3 (C-4), 145.0 (C-3), 145.7 (C-4′), 147.5 (C-3′), 149.5 (C-5), 152.9 (C-7), 193.8 (C-9); ESIMS $m/z$ (rel int) 395 ([M + Na]$^+$, 100); HRESIMS $m/z$ 395.1111 [M + Na]$^+$ (calcd for $C_{20}H_{20}O_7Na$, 395.1107).

**(7′*S*,8′*S*)-4′-*O*-Methylcleomiscosin D (5):** colorless needles ($CHCl_3$/MeOH); mp 252–254 °C; $[\alpha]^{25}_D$ −15.2 ($c$ 0.11, $CDCl_3$); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 325 (4.26) nm; CD (MeOH, $\Delta\epsilon$) 226 (−0.43), 237 (+0.53), 286 (+0.55) nm; IR (neat) $\nu_{max}$ 3395 (OH), 1718 (C=O), 1618, 1510, 1457 (aromatic ring C=C stretch) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.59 (1H, m, H-9′), 3.92 (1H, m, H-9′), 3.93 (9H, s, OMe-3′, 4′, and 5′), 3.96 (3H, s, OMe-6), 4.02 (1H, dt, $J$ = 8.0, 3.0 Hz, H-8′), 5.05 (1H, d, $J$ = 8.0 Hz, H-7′), 6.22 (1H, d, $J$ = 9.6 Hz, H-3), 6.55 (1H, s, H-5), 6.67 (2H, s, H-2′ and H-6′), 7.94 (1H, d, $J$ = 9.6 Hz, H-4); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 56.7 (OMe-6), 56.7 (OMe-3′), 56.7 (OMe-5′), 60.9 (OMe-4′), 61.6 (C-9′), 77.5 (C-7′), 78.5 (C-8′), 93.1 (C-5), 103.4 (C-2′), 103.4 (C-6′), 103.7 (C-10), 112.4 (C-3), 126.3 (C-1′), 132.5 (C-8), 137.6 (C-4′), 138.3 (C-4), 140.0 (C-9), 149.9 (C-7), 152.5 (C-6), 153.0 (C-3′), 153.0 (C-5′), 161.3 (C-2); ESIMS $m/z$ 453 [M + Na]$^+$; HRESIMS $m/z$ 453.1166 [M + Na]$^+$ (calcd for $C_{22}H_{22}O_9Na$, 453.1162).

**(+)-9′-*O*-(*Z*)-Feruloyl-5,5′-dimethoxylariciresinol (6):** amorphous powder; $[\alpha]^{25}_D$ +23.4 ($c$ 0.12, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 287 (3.82), 299 (3.89), 325 (4.04) nm; CD (MeOH, $\Delta\epsilon$) 245 (−0.75) nm; IR (neat) $\nu_{max}$ 3422 (OH), 1711 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.51 (1H, dd, $J$ = 13.6, 11.0 Hz, H-7), 2.62 (1H, m, H-8′), 2.72 (1H, m, H-8), 2.86 (1H, dd, $J$ = 13.6, 4.8 Hz, H-7), 3.75 (1H, dd, $J$ = 8.8, 6.4 Hz, H-9), 3.87 (12H, s, OMe-3, 5, 3′, and 5′), 3.95 (3H, s, OMe-3″), 4.06 (1H, dd, $J$ = 8.8, 6.8 Hz, H-9), 4.26 (1H, dd, $J$ = 11.6, 7.2 Hz, H-9′), 4.43 (1H, dd, $J$ = 11.6, 7.2 Hz, H-9′), 4.77 (1H, d, $J$ = 6.4 Hz, H-7′), 5.41 (1H, br s, $D_2O$ exchangeable, OH-4), 5.47 (1H, br s, $D_2O$ exchangeable, OH-4′), 5.77 (1H, d, $J$ = 12.8 Hz, H-8″), 5.87 (1H, br s, $D_2O$ exchangeable, OH-4″), 6.38 (2H, s, H-2 and H-6), 6.55 (2H, s, H-2′ and H-6′), 6.83 (1H, d, $J$ = 12.8 Hz, H-7″), 6.88 (1H, d, $J$ = 8.4 Hz, H-5″), 7.14 (1H, dd, $J$ = 8.4, 2.0 Hz, H-6″), 7.78 (1H, d, $J$ = 2.0 Hz, H-2″); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 33.8 (C-7), 42.6 (C-8), 49.1 (C-8′), 56.0 (OMe-3″), 56.3 (OMe-3), 56.3 (OMe-5), 56.3 (OMe-3′), 56.3 (OMe-5′), 62.3 (C-9′), 72.7 (C-9), 83.2 (C-7′), 102.4 (C-2′), 102.4 (C-6′), 105.2 (C-2), 105.2 (C-6), 112.8 (C-2″), 113.9 (C-5″), 115.8 (C-8″), 125.9 (C-6″), 127.0 (C-1″), 131.1 (C-1), 133.2 (C-4), 133.5 (C-1′), 134.1 (C-4′), 144.9 (C-7″), 145.8 (C-3″), 147.0 (C-3), 147.0 (C-5), 147.0 (C-3′), 147.0 (C-5′), 147.3 (C-4″), 166.2 (C-9″); EIMS $m/z$ (rel int) 596 ([M]$^+$, 12), 581 (5), 402 (35), 235 (58), 194 (23), 181 (100), 167 (90); HREIMS $m/z$ 596.2255 [M]$^+$ (calcd for $C_{32}H_{36}O_{11}$, 596.2258).

**(+)-9′-*O*-(*E*)-Feruloyl-5,5′-dimethoxylariciresinol (7):** amorphous powder; $[\alpha]^{25}_D$ +20.8 ($c$ 0.10, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 286 (3.85), 298 (3.89), 324 (4.03) nm; CD (MeOH, $\Delta\epsilon$) 246 (−0.73) nm; IR (neat) $\nu_{max}$ 3420 (OH), 1695 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.56 (1H, dd, $J$ = 13.6, 10.8 Hz, H-7), 2.66 (1H, m, H-8′), 2.76 (1H, m, H-8), 2.90 (1H, dd, $J$ = 13.6, 4.8 Hz, H-7), 3.79 (1H, dd, $J$ = 8.8, 6.4 Hz, H-9), 3.87 (12H, s, OMe-3, 5, 3′, and 5′), 3.95 (3H, s, OMe-3″), 4.10 (1H, dd, $J$ = 8.8, 6.8 Hz, H-9), 4.33 (1H, dd, $J$ = 11.4, 7.4 Hz, H-9′), 4.53 (1H, dd, $J$ = 11.4, 6.8 Hz, H-9′), 4.82 (1H, d, $J$ = 6.8 Hz, H-7′), 5.41 (1H, br s, $D_2O$ exchangeable, OH-4), 5.46 (1H, br s, $D_2O$ exchangeable, OH-4′), 5.90 (1H, br s, $D_2O$ exchangeable, OH-4″), 6.22 (1H, d, $J$ = 16.0 Hz, H-8″), 6.41 (2H, s, H-2 and H-6), 6.59 (2H, s, H-2′ and H-6′), 6.92 (1H, d, $J$ = 8.4 Hz, H-5″), 6.99 (1H, d, $J$ = 2.0 Hz, H-2″), 7.05 (1H, dd, $J$ = 8.4, 2.0 Hz, H-6″), 7.50 (1H, d, $J$ = 16.0 Hz, H-7″); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 33.8 (C-7), 42.8 (C-8), 49.1 (C-8′), 56.0 (OMe-3″), 56.3 (OMe-3), 56.3 (OMe-5), 56.3 (OMe-3′), 56.3 (OMe-5′), 62.8 (C-9′), 72.8 (C-9), 83.7 (C-7′), 102.6 (C-2′), 102.6 (C-6′), 105.2 (C-2), 105.2 (C-6), 109.4 (C-2″), 114.8 (C-5″), 114.8 (C-8″), 123.0 (C-6″), 126.7 (C-1″), 131.1 (C-1), 133.2 (C-4), 133.5 (C-1′), 134.1 (C-4′), 145.4 (C-7″), 146.8 (C-3″), 147.0 (C-3), 147.0 (C-5), 147.0 (C-3′), 147.0 (C-5′), 148.2 (C-4″), 167.0 (C-9″); ESIMS $m/z$ (rel int) 619 ([M + Na]$^+$, 100); HRESIMS $m/z$ 619.2153 [M + Na]$^+$ (calcd for $C_{32}H_{36}O_{11}Na$, 619.2155).

**(*E*)-3-(2,2-Dimethyl-2*H*-chromen-6-yl)prop-2-enal (8):** colorless oil; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 295 (4.25), 320 (sh, 3.82) nm; IR (neat) $\nu_{max}$ 1670 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 1.46 (6H, s, H-4′ and H-5′), 5.69 (1H, d, $J$ = 9.8 Hz, H-2′), 6.34 (1H, d, $J$ = 9.8 Hz, H-1′), 6.59 (1H, dd, $J$ = 15.6, 7.6 Hz, H-8), 6.81 (1H, d, $J$ = 8.4 Hz, H-5), 7.20 (1H, d, $J$ = 2.0 Hz, H-2), 7.34 (1H, dd, $J$ = 8.4, 2.0 Hz, H-6), 7.37 (1H, d, $J$ = 15.6 Hz, H-7), 9.64 (1H, d, $J$ = 7.6 Hz, CHO); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 28.5 (C-4′), 28.5 (C-5′), 77.4 (C-3′), 117.3 (C-5), 121.4 (C-3), 121.7 (C-1′), 126.6 (C-2), 126.7 (C-8), 127.0 (C-1), 130.4 (C-6), 131.8 (C-2′), 153.0 (C-7), 156.3 (C-4), 194.0 (C-9); ESIMS $m/z$ (rel int) 237 ([M + Na]$^+$, 100); HRESIMS $m/z$ 237.0890 [M + Na]$^+$ (calcd for $C_{14}H_{14}O_2$ Na, 237.0891).

**Acknowledgment.** This work was supported by grant from the National Science Council of the Republic of China. We are greatly indebted to Prof. I. S. Chen, Faculty of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Taiwan, for identification of *Z. avicennae*.

**Supporting Information Available:** NOESY and HMBC correlations (Figures 1S−8S) for compounds **1**–**8**. This information is available free of charge via the Internet at http://pubs.acs.org.

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NP070594K