Constituents of the Bark and Twigs of *Artocarpus dadah* with Cyclooxygenase Inhibitory Activity

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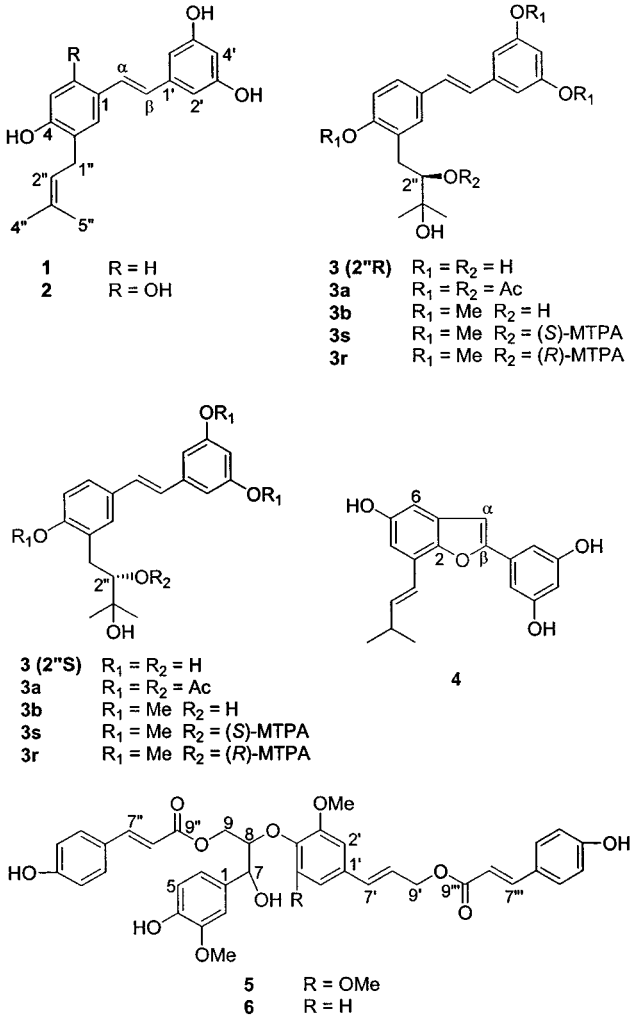
Fractionation of an ethyl acetate-soluble extract of the bark of *Artocarpus dadah* has led to the isolation of three new prenylated stilbenoid derivatives, 3-(γ,γ-dimethylallyl)resveratrol (**1**), 5-(γ,γ-dimethylallyl)-oxyresveratrol (**2**), 3-(2,3-dihydroxy-3-methylbutyl)resveratrol (**3**), and a new benzofuran derivative, 3-(γ,γ-dimethylpropenyl)moracin M (**4**), along with six known compounds, oxyresveratrol, (+)-catechin, afzelechin-3-*O*-α-L-rhamnopyranoside, (−)-epiafzelechin, dihydromorin, and epiafzelechin-(4β→8)-epicatechin. From an ethyl acetate-soluble extract of the twigs of the same plant were isolated compound **4** and two new neolignan derivatives, dadahols A (**5**) and B (**6**), as well as 10 known compounds, oxyresveratrol, (+)-catechin, afzelechin-3-*O*-α-L-rhamnopyranoside, resveratrol, steppogenin, moracin M, isogemichalcone B, gemichalcone B, norartocarpetin, and engeletin. The structures of compounds **1**−**6** were determined using spectroscopic and chemical methods. Isolates were evaluated for their inhibitory effects against both cyclooxygenase-1 (COX-1) and -2 (COX-2) and in a mouse mammary organ culture assay.

Cancer chemoprevention is a strategy for reducing cancer mortality and involves the prevention, delay, or reversal of cancer by the ingestion of dietary or pharmaceutical agents capable of modulating the process of carcinogenesis.[1−4] As part of our continuing search for novel, plant-derived cancer chemopreventive agents, we have employed bioactivity-guided fractionation starting with plant extracts.

Artocarpus species are large evergreen trees, and the fruits, roots, or leaves of some species have been used as traditional medicines in Southeast Asia.[5] *Artocarpus dadah* is known as "Tampang" in Kalimantan, Indonesia, and its bark has been used as an ingredient in the betel nut chewing mixture. Separate ethyl acetate-soluble extracts of both the bark and twigs of *Artocarpus dadah* Miq. (Moraceae) were investigated, since they showed strong activity in an in vitro cyclooxygenase-1 (COX-1) inhibition assay.[6] This has led to the isolation of three new prenylated stilbenoid derivatives (**1**−**3**), a new benzofuran derivative (**4**), and six known compounds, from the bark extract, and compound **4** and two new neolignan derivatives, dadahols A (**5**) and B (**6**), as well as 10 known compounds, from the twig extract. The isolation and structure characterization of **1**−**6** and the biological evaluation of all isolates against both cyclooxygenase-1 and -2 are described in this paper. This is the first report on the chemical constituents of this plant, although prenylated flavonoids,[7,8] triterpenoids,[9,10] stilbene derivatives,[11,12] lectins,[13,14] xanthones,[15,16] and chalcones[5,17,18] have been isolated previously from other species of the genus *Artocarpus*.



Results and Discussion

Activity-monitored fractionation of an EtOAc-soluble extract of the bark of *A. dadah* using the COX-1 inhibition assay led to the purification of four new compounds (**1**−**4**), as well as six known compounds, oxyresveratrol,[19,20] (+)-

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Table 1. ^{1}H NMR Spectral Data and Selected HMBC Correlations for Compounds **1**, **2**, and **4**[a]

	1		**2**		**4**	
position	δ_H	HMBC (H→C)	δ_H	HMBC (H→C)	δ_H	HMBC (H→C)
2	7.18 d (1.6)	C-4, C-α, C-1″, C-6				
3			6.31 s	C-1, C-4		
4					7.51 br s	C-2, C-1″, C-6
5	6.72 d (8.5)	C-3, C-1, C-6				
6	7.16 dd (8.5, 1.6)	C-4, C-2, C-α, C-1	7.14 s	C-1″, C-α, C-2, C-4, C-5	6.89 br s	C-4, C-2, C-α, C-1, C-5
α	6.93 d (16.2)	C-*β*, C-1′, C-2, C-6	7.25 d (16.4)	C-1′, C-2, C-6, C-*β*	6.90 s	C-2, C-6, C-1′, C-*β*
β	6.74 d (16.2)	C-2′, C-6′, C-1, C-α	6.75 d (16.4)	C-1, C-α, C-2′, C-6′		
2′, 6′	6.43 d (1.8)	C-*β*, C-4′, C-3′, C-5′	6.43 d (1.9)	C-*β*, C-4′, C-3′, C-5′	6.78 d (1.8)	C-*β*, C-4′, C-3′, C-5′
4′	6.15 dd (1.8, 1.8)	C-2′, C-6′	6.13 dd (1.9, 1.9)	C-2′, C-6′, C-3′, C-5′	6.27 dd (1.8, 1.8)	C-2′, C-6′
1″	3.29 br d (7.2)	C-3″, C-2, C-3, C-4	3.21 br d (7.1)	C-3", C-2, C-3, C-4	6.72 d (15.9)	C-2, C-3, C-4, C-3″
2″	5.34 dd (7.2, 7.2)	C-4″, C-5″, C-3	5.31 dd (7.1, 7.1)	C-4″, C-5″, C-3	6.14 dd (15.9, 6.9)	C-3, C-4″, C-5″
3″					2.46 m	C-1″, C-4″, C-5″
4″	1.74 s	C-2″, C-3″, C-5″	1.73 s	C-2″, C-3″, C-5″	1.11 d (6.7)	C-2″, C-3″,
5″	1.75 s	C-2″, C-3″, C-4″	1.75 s	C-2″, C-3″, C-4″	1.11 d (6.7)	C-2″, C-3″

[a] In CD_3OD; spectra taken at 75 and 300 MHz for carbon and proton, respectively; *J* values given in Hz; chemical shift values presented in ppm.

Table 2. ^{1}H NMR Spectral Data for **3**, **3a**, and **3b** and Selected HMBC Correlations for **3**[a]

	3		**3a**	**3b**
position	δ_H	HMBC (H→C)	δ_H	δ_H
2	7.32 d (1.7)	C-1, C-4, C-α, C-1″, C-6	7.47 d (1.8)	7.37 d (1.8)
5	6.76 d (8.2)	C-3, C-1	7.15 d (8.2)	6.88 d (8.4)
6	7.22 dd (8.2, 1.7)	C-4, C-2, C-α, C-1	7.44 dd (8.2, 1.8)	7.36 dd (8.4, 1.8)
α	6.94 d (16.3)	C-*β*, C-1′, C-2, C-6	7.07 d (16.3)	7.03 d (16.4)
β	6.80 d (16.3)	C-2′, C-6′, C-1, C-α	7.04 d (16.3)	6.93 d (16.4)
2′, 6′	6.44 d (1.8)	C-*β*, C-4′, C-3′, C-5′	7.21 d (1.9)	6.65 d (1.9)
4′	6.15 dd (1.8, 1.8)	C-2′, C-6′, C-3′, C-5′	6.83 dd (1.9, 1.9)	6.38 dd (1.9, 1.9)
1″	2.99 dd (13.8, 1.6)	C-2″, C-3″, C-2, C-3, C-4	2.99 dd (14.0, 1.9)	2.97 dd (13.7, 1.6)
	2.60 dd (13.8, 10.2)		2.75 dd (14.0, 10.6)	2.64 dd (13.7, 10.4)
2″	3.61 dd (10.2, 1.6)	C-4″, C-5″, C-3	5.07 dd (10.6, 1.6)	3.67 dd (10.4, 1.6)
4″	1.26 br s	C-2″, C-3″, C-5″	1.24 s	1.62 s
5″	1.26 br s	C-2″, C-3″, C-4″	1.25 s	1.63 s
Ac			1.87 (2″), 2.29 (3′ and 5′), 3.33 (4)	
OMe				3.67 (4), 3.77 (3′ and 5′)

[a] CD_3OD for **3** and **3a**, $CDCl_3$ for **3b**; spectra taken at 75 and 300 MHz for carbon and proton, respectively; *J* values given in Hz; chemical shift values presented in ppm.

catechin,[21,22] afzelechin-3-*O*-α-L-rhamnopyranoside,[23,24] (−)-epiafzelechin,[22,25] dihydromorin,[26] and epiafzelechin-(4*β*→8)-epicatechin.[22,25] The structures of the known compounds were identified by physical and spectroscopic data measurement ($[\alpha]_D$, ^{1}H NMR, ^{13}C NMR, DEPT, 2D NMR, and MS) and by comparing the data obtained with those of published values.

The HRCIMS of compound **1** gave a protonated molecular ion peak at *m*/*z* 297.1499 $[M + H]^+$, consistent with a molecular formula of $C_{19}H_{20}O_3$. The ^{1}H NMR spectrum of **1** (Table 1) displayed signals suggestive of a 1,3,4-trisubstituted aromatic ring at δ_H 7.18 (1H, d, $J = 1.6$ Hz, H-2), 6.72 (1H, d, $J = 8.5$ Hz, H-5), and 7.16 (1H, dd, $J = 8.5$, 1.6 Hz, H-6), a *trans*-double bond at δ_H 6.93 (1H, d, $J = 16.2$ Hz, H-α) and 6.74 (1H, d, $J = 16.2$ Hz, H-*β*), and a 1′,3′,5′-trisubstituted aromatic ring at δ_H 6.43 (2H, d, $J = 1.8$ Hz, H-2′ and H-6′) and 6.15 (1H, dd, $J = 1.8$, 1.8 Hz, H-4′). In addition to these signals, the ^{1}H NMR spectrum of **1** also revealed the signals of one prenyl substituent [two vinyl methyls at δ_H 1.74 (3H, s, H-4″) and 1.75 (3H, s, H-5″), one olefinic proton at δ_H 5.34 (1H, dd, $J = 7.2$, 7.2 Hz, H-2″), and two methylene protons at δ_H 3.29 (2H, br d, $J = 7.2$ Hz, H-1″)]. Signals for the prenyl group were also apparent in the ^{13}C NMR spectrum at δ_C 29.4 (C-1″, t), 124.0 (C-2″, d), 133.0 (C-3″, s), 26.0 (C-4″, q), and 17.9 (C-5″, q). The remaining ^{13}C NMR signals could be assigned to two aromatic rings and one *trans*-double bond by analysis of the ^{13}C NMR, DEPT, and HMQC spectra of **1**. This suggested that compound **1** is a prenylated stilbene derivative.[11,12] In the ^{1}H NMR spectrum of **1**, H-2′ and H-6′ appeared at δ_H 6.43 (2H, d, $J = 1.8$ Hz). Furthermore, the ^{13}C NMR signals for C-2′ and C-6′, and C-3′ and C-5′, of compound **1** were evident at δ_C 105.7 and 159.6, respectively. On the basis of these NMR data and the molecular formula determined for **1**, two hydroxy groups attached to C-3′ and C-5′ could be deduced. In the ^{1}H−^{1}H COSY spectrum of **1**, correlations between H-α and H-*β*, H-5 and H-6, and H-1″ and H-2″ were observed. These data, in combination with the observed key HMBC correlations of H-1″ to C-2, C-3, C-4, and C-3″, H-α to C-1′, C-2, and C-6, and H-*β* to C-1, C-2′, and C-6′, permitted the determination of the structure of **1** as 3-(*γ*,*γ*-dimethylallyl)resveratrol. The ^{1}H and ^{13}C NMR spectral data of **1** were assigned according to the correlations observed in the ^{1}H−^{1}H COSY, HMQC, and HMBC spectra.

The molecular formula $C_{19}H_{20}O_4$ was determined from the HRCIMS (*m*/*z* 313.1454 $[M + H]^+$) for compound **2**. The ^{1}H (Table 1) and ^{13}C NMR (Table 3) spectral data of **2** were closely comparable to those of **1** and suggested the presence of a 1′,3′,5′-trisubstituted aromatic ring (ring B), a *trans*-double bond, and a prenyl substituent in **2**, in a manner similar to **1**. However, the ^{1}H NMR spectrum of **2** displayed only two singlets for aromatic ring A at δ_H 6.31 (1H, s, H-3) and 7.14 (1H, s, H-6), while three protons were present for

Table 3. ^{13}C NMR Spectral Data for Compounds **1**−**4**[a]

position	1	2	3	4
1	130.3 s	117.4 s	130.6 s	133.8 s
2	128.9 d	155.2 s	130.7 d	154.2 s
3	129.5 s	103.5 d	128.3 s	123.9 s
4	156.2 s	156.7 s	156.8 s	118.5 d
5	116.0 d	121.2 s	116.7 d	156.1[b] s
6	126.1 d	128.2 d	127.0 d	102.3 d
α	129.8 d	125.1 d	129.6 d	98.1 d
β	126.6 d	126.1 d	126.9 d	156.2[b] s
1′	141.4 s	142.3 s	141.4 s	123.2 s
2′	105.7 d	105.6 d	105.8 d	103.9 d
3′	159.6 s	159.6 s	159.7 s	159.9 s
4′	102.6 d	102.2 d	102.7 d	103.5 d
5′	159.6 s	159.6 s	159.7 s	159.9 s
6′	105.7 d	105.6 d	105.8 d	103.9 d
1″	29.4 t	28.8 t	34.2 t	123.4 d
2″	124.0 d	124.7 d	80.3 d	137.7 d
3″	133.0 s	132.4 s	73.9 s	33.2 d
4″	26.0 q	26.0 q	25.1 q	23.1 q
5″	17.9 q	17.9 q	25.7 q	23.1 q

[a] In CD_3OD; spectra taken at 75 MHz; chemical shift values presented in ppm. [b] Assignments may be interchangeable.

this functionality (1,3,4-trisubstituted aromatic ring) in **1**. On the other hand, the ^{13}C NMR and DEPT spectra of **2** indicated there were eight methines and four oxygenated aromatic quaternary carbons in **2**, while there were nine methines and three oxygenated aromatic quaternary carbons in **1**. Furthermore, the molecular formula of **2** included one more oxygen atom than that of **1**. All of above evidence suggested that compound **2** contains one more hydroxy group in the aromatic ring A compared to compound **1**. The locations of the prenyl and hydroxy groups were determined on the basis of the observed correlations of H-1″ to C-2, C-3, C-4, and C-3″, H-α to C-1′, C-2, and C-6, H-3 to C-1 and C-4, and H-6 to C-1″, C-α, C-2, and C-4 in the HMBC spectrum. In this manner, compound **2** was assigned as 5-(*γ*,*γ*-dimethylallyl)oxyresveratrol.

Compound **3**, $[\alpha]_D^{20}$ +4.0° (*c* 0.10, MeOH), showed from its ^1H (Table 2) and ^{13}C NMR (Table 3) spectra signals for a stilbene unit that were very similar to those of **1**, with the evident differences between these two compounds apparent in their various prenyl substituents. The ^1H NMR spectrum of **3** showed an oxygenated methine proton at δ_H 3.61 (1H, dd, J = 10.2, 1.6 Hz, H-2″), and its ^{13}C NMR and DEPT spectra also displayed this methine at δ_C 80.3 (C-2″), as well as an oxygenated quaternary carbon at δ_C 73.9 (C-3″). Furthermore, the methyl groups of the prenyl substituent of **3** (δ_H 1.26) showed significant upfield shifts relative to **1** (δ_H 1.74 and 1.75), on comparing their ^1H NMR data (Tables 1 and 2). In the HMBC spectrum of compound **3**, H-4″ and H-5″ correlated to C-2″ and C-3″, while H-2″ correlated to C-3, C-4″, and C-5″. These correlations suggested that two hydroxy groups should be attached to C-2″ and C-3″. The HRCIMS of this compound gave a protonated molecular ion peak at *m*/*z* 331.1567 $[M + H]^+$, corresponding to a molecular formula of $C_{19}H_{22}O_5$, which was consistent with the postulated structure, 3-(2,3-dihydroxy-3-methylbutyl)resveratrol. A tetraacetate of **3** (**3a**, see Table 2 for ^1H NMR data) was obtained after acetylation of compound **3** under standard conditions.

The absolute configuration of C-2″ in **3** was determined using the Mosher ester procedure. Compound **3** was methylated with excess fresh CH_2N_2 and gave the methylation product **3b**, which was separated into two equal portions and treated with (*S*)-(+)-α- and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in anhydrous pyridine at room temperature overnight, to afford the (*R*)- and (*S*)-MTPA ester derivatives (**3r** and **3s**, respectively). Interestingly, the ^1H NMR spectra of **3r** and **3s** appeared very similar and both exhibited separated pairs of signals, with the only difference between **3r** and **3s** being the relative integration of the separated signals. For example, the most evident and undisturbed signals, H-4″ and H-5″, in **3s** appeared at δ_H 1.519, 1.549, 1.603, and 1.624, and the relative integrations were about 5, 5, 3, and 3, respectively. However, the ^1H NMR spectrum of **3r** also displayed signals for H-4″ and H-5″ at δ_H 1.519, 1.549, 1.603, and 1.624, but the relative integrations were, in turn, about 3, 3, 5, and 5. Thus, 3-(2,3-dihydroxy-3-methylbutyl)resveratrol (**3**) was assigned as an enantiomeric mixture in a probable ratio of 5:3 for the 2″*R* and 2″*S* forms, respectively.

The HRCIMS of compound **4** exhibited a protonated molecular ion peak at *m*/*z* 311.1287 $[M + H]^+$, consistent with the molecular formula $C_{19}H_{18}O_4$, two hydrogen atoms less than that of **2**. In the ^1H NMR spectrum (Table 1) of **4**, a *trans*-double bond and the same 1′,3′,5′-trisubstituted aromatic ring (ring B) as those in **1** and **2** were also evident. However, both the chemical shifts (δ_H 6.72 and 6.14) and the splitting patterns (one was a doublet, and the other was a doublet of doublets) of the *trans*-double bond protons were different from those in **1** and **2**. The $^1H-^1H$ COSY spectrum of **4** showed correlations from H-1″ (1H, δ_H 6.72, d, J = 15.9 Hz) to H-2″ (1H, δ_H 6.14, dd, J = 15.9, 6.9 Hz), H-2″ to H-3″ (1H, δ_H 2.46, m), and H-3″ to H-4″ and H-5″ (6H, δ_H 1.11, d, J = 6.9 Hz), indicating that the *trans*-double bond in the molecule of **4** should be located between C-1″ and C-2″ of the prenyl substituent. Thus, the *trans*-double bond of the carbon skeleton of normal stilbene compounds such as **1** and **2** was modified in **4** on the basis of these preliminary observations. The ^{13}C NMR and DEPT spectra (Table 3) showed there were five oxgenated olefinic carbons (δ_C 154.2, C-2; δ_C 156.1 and 156.2, C-5 and C-*β*; δ_C 159.9, C-3′ and C-5′) in **4**, while the HRCIMS indicated only four oxygen atoms in its molecular formula. On the basis of this evidence and the unsaturation of **4**, this compound was assigned as a benzofuran derivative. The NMR data of H-α, C-α, and C-*β* of **4** were closely comparable to the values of several reported analogues.[27−29] In the HMBC spectrum of compound **4**, H-2′ and H-6′ correlated to C-*β* and C-4′, H-α correlated to C-1′, C-6, and C-2, and H-1″ correlated to C-2, C-3, C-4, and C-3″ and further confirmed that compound **4** is a benzofuran derivative and enabled the locations of the hydroxy groups and the prenyl substituent to be ascertained. Hence, on the basis of the interpretation of the above-mentioned data and by comparison with a previously reported benzofuranoid,[29] the new compound **4** was assigned as 3-(*γ*,*γ*-dimethylpropenyl)moracin M.

From *A. dadah* twigs, two new neolignan derivatives, dadahols A (**5**) and B (**6**), were isolated by activity-monitored fractionation using the COX-1 inhibition assay, along with **4** and 10 known compounds, oxyresveratrol,[19,20] (+)-catechin,[21,22] afzelechin-3-*O*-α-L-rhamnopyranoside,[23,24] resveratrol,[30] steppogenin,[31] moracin M,[29] isogemichalcone B,[32] gemichalcone B,[32] norartocarpetin,[33] and engeletin.[34,35] The structures of the known compounds were once again identified by comparing their spectral data with those of published values.

Compound **5**, $[\alpha]_D^{20}$ +20° (*c* 0.075, MeOH), was afforded as a colorless oil by purification using reversed-phase semipreparative HPLC, and the molecular formula was determined as $C_{39}H_{38}O_{12}$ on the basis of its HRFABMS ($C_{39}H_{38}O_{12}Na$ *m*/*z* 721.2285, calcd 721.2261). Most resonances for compound **5** were present in the downfield

olefinic area in its ^{1}H NMR spectrum. Of these signals, the existence of six *trans*-double bond protons at δ_H 7.66 (1H, d, J = 16.0 Hz, H-7″), 7.16 (1H, d, J = 16.0 Hz, H-7‴), 6.63 (1H, d, J = 15.9 Hz, H-7′), 6.39 (1H, d, J = 16.0 Hz, H-8″), 6.31 (1H, dt, J = 15.9, 6.1 Hz, H-8′), and 6.07 (1H, d, J = 16.0 Hz, H-8‴) and two *para*-substituted aromatic rings at δ_H 7.48 (2H, d, J = 8.6 Hz, H-2″ and 6″), 7.32 (2H, d, J = 8.6 Hz, H-2‴ and 6‴), and 6.74−6.82 (H-3″, 5″, 3‴ and 5‴) in compound **5** could be deduced on the basis of their chemical shifts, splitting patterns, and coupling constants. In addition, these assignments were supported by the observed correlations from H-7′ to H-8′, H-7″ to H-8″, H-7‴ to H-8‴, H-2″ and 6″ to H-3″ and 5″, and H-2‴ and 6‴ to H-3‴ and 5‴ in the ^{1}H−^{1}H COSY NMR spectrum. The ^{13}C NMR and DEPT spectra of compound **5** showed three methoxy groups (δ_C 56.4 and 56.6), two oxygenated methylenes (δ_C 65.2, C-9; 66.0, C-9′), and two oxygenated methines (δ_C 74.5, C-7; 84.8, C-8) in the more upfield area. Further analysis of the HMQC and ^{1}H−^{1}H COSY spectra of compound **5** disclosed that H-8′ correlated not only to H-7′ but also to H-9′ (δ_H 4.76, 2H, br d, J = 6.1 Hz), while H-8 (δ_H 4.61, 1H, m) correlated to H-7 (δ_H 5.00, 1H, d, J = 4.3 Hz) and H-9 (δ_H 4.46, 1H, dd, J = 11.7, 7.1 Hz, H-9a; δ_H 4.32, 1H, dd, J = 11.7, 2.1 Hz, H-9b). On the basis of such preliminary information, in combination with the observed HMBC correlations from H-7 to the C-1, C-2, and C-6 aromatic carbons, and from H-7′ to C-1′, C-2′, and C-6′, the presence of two C_6−C_3 units in the molecule of compound **5** was evident, and it could be inferred that this compound is a (*β*)8-*O*-4′ neolignan derivative.[36,37] The ^{13}C NMR spectrum of compound **5** displayed two α,*β*-unsaturated carbonyl carbons at δ_C 169.1 (C-9‴) and 169.0 (C-9″). In the HMBC spectrum of **5**, correlations from H-9′ and H-7‴ to C-9‴, H-9 and H-7″ to C-9″, H-7‴ to C-2‴ and C-6‴, and H-7″ to C-2″ and C-6″ were observed. These correlations indicated that compound **5** contains two *p*-hydroxycinnamoyl groups, which were attached to C-9 and C-9′ as esters. The remaining ^{1}H and ^{13}C NMR data of **5** were closely comparable to values reported for known (*β*)8-*O*-4′ neolignan analogues.[36,37] The locations of the methoxy groups were assigned on the basis of the observed HMBC correlations from δ_H 3.80 (6H, s, MeO-3′ and MeO-5′) and 6.74 (2H, br s, H-2′ and H-6′) to δ_C 154.6 (s, C-3′ and C-5′) and the key NOESY correlation from δ_H 3.86 (3H, s, 3-MeO) to 7.06 (1H, br s, H-2). The coupling constant between H-7 and H-8 was 4.3 Hz, which suggested that the relative configuration between these two protons is *erythro*.[36,37] Thus, dadahol A (**5**) was elucidated structurally as *erythro*-1-(4-hydroxy-3-methoxyphenyl)-2-{2,6-dimethoxy-4-[(1*E*)-3-(4-hydroxycinnamoyl)-1-propenyl]phenoxy}-3-(4-hydroxycinnamoyl)propan-1-ol.

The HRFABMS ($C_{38}H_{36}O_{11}Na$ *m/z* 691.2155, calcd 691.2155) of compound **6** enabled the molecular formula to be assigned as $C_{38}H_{36}O_{11}$, one methoxy group less than that of **5**. Both the ^{1}H and ^{13}C NMR spectral data of compound **6** were very close to those of **5** and suggested that this compound also is a (*β*)8-*O*-4′ neolignan derivative, containing two *p*-hydroxycinnamoyl units as in the case of **5**. The differences between compounds **5** and **6** were in the substituent patterns in ring B. In compound **5**, the H-2′ and H-6′ signals were observed at δ_H 6.74 (2H, br s), while resonances C-2′ and C-6′, and C-3′ and C-5′, appeared at δ_C 104.9 and 154.6, respectively, with two methoxy groups attached to C-3′ and C-5′ in a symmetrical fashion. In compound **6**, only one methoxy group was attached to C-3′ of ring B, and its ^{1}H, ^{13}C NMR, and 2D NMR data were consistent with a 1,3,4-trisubstituted aromatic pattern.

Table 4. Inhibitory Activities of Isolates from *A. dadah* Against Cyclooxygenase-1 (COX-1) and -2 (COX-2) and 7,12-Dimethylbenz[*a*]anthracene-Induced Preneoplastic Lesions in Mouse Mammary Organ Culture[a]

compound	COX-1 [IC_{50} (μM)]	COX-2 [IC_{50} (μM)]	MMOC[c] (at 10 μg/mL)
1	0.61	9.5	7.3
2	4.1	36.7	0
3	0.48	13.9	ND[d]
4	4.9	31.8	66.7
oxyresveratrol	1.4	109	33.3
(+)-catechin	36.7	93.3	50.0
afzelechin-3-*O*-α-L-rhamnopyranoside	8.3	19.7	0
(−)-epiafzelechin	6.4	69.7	81.5
dihydromorin	67.1	>100	81.5
epiafzelechin-(4*β*→8)-epicatechin	78.0	>100	ND[d]
resveratrol	1.1	1.3	87.5
steppogenin	5.9	46.4	66.7
moracin M	0.50	22.3	33.3
isogemichalcone B	11.7	15.0	ND[d]
gemichalcone B	14.0	38.4	33.3
norartocarpetin	14.0	>100	85.2
SC-58236[b]	31.4	0.00045	
SC-58560[b]	0.0065	42.5	

[a] The new compounds **5** and **6** and the known compound engeletin were inactive (IC_{50} > 100 μg/mL) in the COX-1 and COX-2 assays. [b] Positive control substance obtained from Monsanto, St. Louis, MO.[47,48] [c] Inhibition of 7,12-dimethylbenz[*a*]anthracene-induced preneoplastic lesions with mouse mammary organ culture; results are expressed as percent inhibition. On the basis of historical controls, inhibition of >60% is considered significant. [d] Not determined, either because of inactivity against COX-1 and COX-2 [compounds **5** and **6** and epiafzelechin-(4*β*→8)-epicatechin] or the amount of the available compound was not sufficient (**3** and isogemichalcone B).

However, compound **6** was found to be a mixture of *threo* and *erythro* isomers since in its ^{1}H and ^{13}C NMR spectra duplicate resonances were apparent, especially the undisturbed characteristic signals of C-7 (δ_C 74.7 and 74.2, approximate ratio 1:1) and C-8 (δ_C 84.0 and 83.6). Hence, dadahol B (**6**) was determined as a mixture of *threo*- and *erythro*-1-(4-hydroxy-3-methoxyphenyl)-2-{2-methoxy-4-[(1*E*)-3-(4-hydroxycinnamoyl)-1-propenyl]-phenoxy}-3-(4-hydroxycinnamoyl)propan-1-ol. This compound was not further resolved because of the small amount obtained and its lack of significant biological activity in the test systems in which it was evaluated.

Benzofuran derivatives are often isolated together with stilbene derivatives from higher plants.[27−29] The present investigation also indicated the co-occurrence of a prenylated benzofuran derivative (**4**) with prenylated stilbene derivatives (**1**−**3** and oxyresveratrol) in the bark of title plant.

In recent work, the *trans*-stilbenoid resveratrol has been found to exhibit significant in vitro inhibitory activity against both COX-1[6,38−40] and COX-2.[41] It was seen by comparing the activities of the various stilbenoids obtained in the present study that the inhibitory potency of resveratrol against COX-1 was slightly enhanced by prenylation at the C-3 position as in compounds **1** and **3**, although these compounds were somewhat less active against COX-2 (Table 4). The C-6 (C-2) hydroxylated compounds **2** and oxyresveratrol, when contrasted to the parent compound, resveratrol, were less potent inhibitors of both COX-1 and COX-2. Of the two benzofurans isolated, the C-3 prenylated derivative **4** [3-(*γ*,*γ*-dimethylpropenylmoracin M] was less potent against both COX-1 and COX-2 than the parent compound moracin M. Five flavan monomers were represented among the isolates, and afzelechin 3-*O*-α-L-rham-

noside, (−)-epiafzelechin, and steppogenin were somewhat more active against COX-1 than (+)-catechin and dihydromorin, while afzelechin-3-*O*-α-L-rhamnopyranoside was the most active of these five compounds against COX-2 (IC_{50} 19.2 μM). The bisflavan, epiafzelechin-(4β→8)-epicatechin, showed very weak activity against COX-1 and was inactive (IC_{50} >100 μg/mL) against COX-2. Following the same trend, both the prenylated chalcone derivative isomers, isogemichalcone B and gemichalcone B, and the flavone norartocarpetin were less potent inhibitors of COX-2 than COX-1 (Table 4). The two new neolignan derivatives, dadahols A (**5**) and B (**6**), and the known flavone glycoside, engeletin, were inactive (IC_{50} >100 μg/mL) against both COX-1 and COX-2. Thirteen of the isolated compounds (Table 4) were evaluated for their potential to inhibit DMBA-induced preneoplastic lesions with mouse mammary in organ culture (MMOC).[42,43] Among these isolates, compounds **4**, (−)-epiafzelechin, dihydromorin, resveratrol, steppogenin, and norartocarpetin mediated significant inhibitory activity (Table 4). As noted previously,[44] substances active in this model system are considered good candidates for full-term cancer chemopreventive studies in experimental animal models.

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter. UV spectra were obtained with a Beckman DU-7 spectrometer. IR spectra were run on an ATI Mattson Genesis Series FT-IR spectrophotometer. NMR spectral data were recorded at room temperature on a Bruker Avance DPX-300 spectrometer with tetramethylsilane (TMS) as internal standard. FABMS and HRFABMS were obtained on a VG 7070E-HF sector-field mass spectrometer, and EIMS, CIMS, and HRCIMS on a Finnigan/MAT 90/95 sector-field mass spectrometer. A YMC-pack ODC-AQ column (5 μm, 25 × 2 cm i.d., YMC Co., Wilmington, NC) and a YMC-guardpack ODC-AQ guard column (5 μm, 5 × 2 cm i.d.) were used for preparative HPLC, along with two Waters 515 HPLC pumps and a Waters 2487 dual λ absorbance detector (Waters, Milford, MA). Column chromatography was carried out with Si gel G (Merck, 230−400 mesh). Analytical thin-layer chromatography (TLC) was performed on precoated 250 μm thickness Merck Si gel 60 F_{254} aluminum plates, while preparative thin-layer chromatography was carried out on precoated 20 × 20 cm, 250 or 1000 μm thickness Merck Si gel 60 F_{254} glass plates.

Plant Material. The bark (1 kg) and twigs (920 g) of *Artocarpus dadah* Miq. were collected at Tewah, Central Kalimantan, Indonesia (N 38° 57.003′; W 094° 44.767′), in October 1999, by L.B.S.K. and S.R. Voucher specimens (number TWH-056) have been deposited at the Herbarium Bogoriense, Bogor, Indonesia.

Cyclooxygenase-1 (COX-1) and -2 (COX-2) Inhibitory Assays. Inhibition assays against both cyclooxygenase-1[38,41,45,46] and -2[45,46] were performed by the methods described previously.

Mouse Mammary Organ Culture Assay. The inhibition of lesion formation in mouse mammary organ culture was performed as previously described.[42,43]

Extraction and Isolation of the Bark of *A. dadah*. The dried and milled bark (980 g) was extracted by maceration with MeOH−H_2O (9:1) three times (3 × 2 L), for up to 3 days each. After filtration and evaporation of the solvent under reduced presure, the combined crude methanolic extract was suspended in H_2O (700 mL), then partitioned in turn with petroleum ether (3 × 500 mL) and EtOAc (4 × 500 mL), to afford dried petroleum ether- (4.8 g), EtOAc- (39.5 g), and H_2O-soluble (140.5 g) residues. When evaluated at 70 μg/mL, the inhibitory activities in the COX-1 assay[38,41,45,46] for these three extracts were 50, 85, and 26%, respectively.

On the basis of the above biological test data, the EtOAc-soluble extract was selected for further investigation and chromatographed over a Si gel column (5.8 × 75 cm), eluted with gradient mixtures of $CHCl_3$−MeOH (from 50:1 to 1:1), to afford 12 fractions (F01−F12). The COX-1 inhibitory abilities of F01−F12 at 100 μg/mL were 0, 31, 99, 76, 37, 59, 74, 64, 25, 0, 25, and 29%, respectively. Amorphous powders were obtained from the mother liquors of fractions F05 (eluted with $CHCl_3$−MeOH, 20:1) and F07 (eluted with $CHCl_3$−MeOH, 12:1), and (+)-catechin (213 mg) and afzelechin-3-*O*-α-L-rhamnopyranoside (187 mg), respectively, were afforded after further recrystallization ($CHCl_3$−MeOH, ∼8:1) of these amorphous powders.

Fraction F03, eluted with $CHCl_3$−MeOH (40:1), was fractionated over a further Si gel column (3.2 × 60 cm), using gradient mixtures of $CHCl_3$−acetone (from 8:1 to 2:1) as solvents, to give pure compounds **1** (10 mg; eluted with $CHCl_3$−acetone, 6:1) and **4** (54 mg; eluted with $CHCl_3$−acetone, 4:1).

Fraction F04, eluted with $CHCl_3$−MeOH (30:1), was chromatographed over a further Si gel column (2.8 × 55 cm), using as solvents $CHCl_3$−MeOH mixtures of increasing polarity (from 12:1 to 5:1), to afford seven subfractions (F0401−F0407). The major component, oxyresveratrol (**7**, 321 mg), was obtained as crystals from F0401 (eluted with $CHCl_3$−MeOH, 10:1). Further purification of the mother liquor of this subfraction was carried out over a Si gel column (2.0 × 45 cm), eluted with hexanes−EtOAc−MeOH (from 10:10:1 to 5:5:2), and yielded additional oxyresveratrol (220 mg; eluted with hexanes−EtOAc−MeOH, 10:10:1) and (−)-epiafzelechin (77 mg; eluted with hexanes−EtOAc−MeOH, 10:10:1.5). F0404 (eluted with $CHCl_3$−MeOH, 8:1) was chromatographed over a Si gel column (2.8 × 55 cm) and separated with gradient mixtures of petroleum ether−acetone (from 3:2 to 1:1), to afford pure compound **2** (56 mg; eluted with petroleum ether−acetone, 3:2) and two subfractions (F040402 and F040403). F040402 and F040403, eluted with petroleum ether−acetone, 3:2 and 1:1, respectively, were then subjected to preparative TLC (1000 μm layers), developed with $CHCl_3$−acetone (3:2) and $CHCl_3$−MeOH (6:1), to provide pure compounds **3** (2.5 mg; R_f = 0.65) and dihydromorin (13 mg; R_f = 0.60), respectively.

Fractions F06 and F07, eluted with $CHCl_3$−MeOH, 16:1 and 12:1, respectively, were combined and purified over a further Si gel column (3.5 × 65 cm), eluted with a $CHCl_3$−MeOH gradient (from 7:1 to 3:1), to give afzelechin-3-*O*-α-L-rhamnopyranoside (276 mg; eluted with $CHCl_3$−MeOH, 6:1) and four subfractions (F0601−F0604). F0603 (eluted with $CHCl_3$−MeOH, 5:1) was chromatographed over a Si gel column (2.0 × 45 cm), eluted with EtOAc−MeOH (15:1), yielding (+)-catechin (17 mg).

Fraction F08, eluted with $CHCl_3$−MeOH (8:1), was separated over a further Si gel column (3.5 × 70 cm) and eluted with a gradient $CHCl_3$−MeOH solvent system (from 12:1 to 5:1), to give nine subfractions (F0801−F0809). Epiafzelechin-(4β→8)-epicatechin (65 mg) was obtained after further purification of F0805 (eluted with $CHCl_3$−MeOH, 10:1) over a Si gel column (2.8 × 55 cm), eluting with EtOAc−MeOH (20:1).

Extraction and Isolation of the Twigs of *A. dadah*. An EtOAc-soluble extract (20.5 g) was afforded from the twigs of *A. dadah* (910 g) using the same extraction and partition procedures as described above, and the inhibitory activity in the COX-1 assay[38,41,45,46] of this extract was 90%, when evaluated at 70 μg/mL. Thus, this extract was chromatographed over a Si gel column (9.5 × 42 cm), eluted with gradient mixtures of $CHCl_3$−MeOH (from 50:1 to 1:1), to give nine fractions (F01−F09). The inhibitory activities in the COX-1 assay of F01−F09 at 40 μg/mL were 64, 100, 100, 100, 100, 90, 84, 64, and 65%, respectively.

Fraction F02, eluted with $CHCl_3$−MeOH (40:1), when fractionated over a further Si gel column (3.5 × 65 cm), with gradient mixtures of petroleum ether−acetone (from 5:1 to 1:1) as solvents, resulted in four subfractions (F0201−F0204). F0202 (eluted with petroleum ether−acetone, 4:1) was further purified by a Si gel column (2.0 × 45 cm), using $CHCl_3$−MeOH

(20:1), to give in order of polarity isogemichalcone B (0.6 mg) and gemichalcone B (15 mg), as well as a mixture. This mixture was purified by semipreparative HPLC, eluted with acetonitrile−H_2O (1:1), to afford the new compounds **6** (t_R = 42.5 min, 7.2 mg) and **5** (t_R = 44.5 min, 1.8 mg).

Fraction F03, eluted with $CHCl_3$−MeOH (30:1), was purified over a further Si gel column (3.5 × 65 cm) and separated with petroleum ether−acetone (from 4:1 to 1:1), affording in turn pure compounds **4** (7 mg; eluted with petroleum ether−acetone, 3:1), resveratrol (5 mg; eluted with petroleum ether−acetone, 3:1), (+)-catechin (10 mg; eluted with petroleum ether−acetone, 2:1), and steppogenin (5 mg, eluted with petroleum ether−acetone, 2:1).

Fractions F04 and F05, eluted with $CHCl_3$−MeOH, 20:1 and 16:1, respectively, were combined and fractionated over a further Si gel column (2.8 × 40 cm) and separated with gradient mixtures of petroleum ether−acetone (from 3:1 to 1:1), to give compounds **4** (2 mg; eluted with petroleum ether−acetone, 3:1), oxyresveratrol (182 mg; eluted with petroleum ether−acetone, 3:1), moracin M (8 mg; eluted with petroleum ether−acetone, 3:2), and norartocarpetin (11 mg, eluted with petroleum ether−acetone, 1:1), in order of polarity.

Fraction F06, eluted with $CHCl_3$−MeOH (12:1), was chromatographed over a further Si gel column (2.8 × 40 cm) with EtOAc−MeOH (from 80:1 to 10:1) as solvents, to afford three subfractions (F0601−F0603). F0602 (eluted with EtOAc−MeOH, 60:1) was then purified by preparative TLC (1000 μm layers), developed with $CHCl_3$−MeOH (7:1), and gave afzelechin-3-*O*-α-L-rhamnopyranoside (10 mg; R_f = 0.58).

Fractions F07 and F08, eluted with $CHCl_3$−MeOH, 8:1 and 4:1, respectively, were combined and purified over a further Si gel column (3.5 × 65 cm), with $CHCl_3$−MeOH−H_2O (100:10:0.5) used as solvent system, yielding in turn afzelechin-3-*O*-α-L-rhamnopyranoside (13 mg) and engeletin (38 mg).

3-(γ,γ-Dimethylallyl)resveratrol (1): yellowish oil; UV (MeOH) λ_{max} (log ϵ) 220 (4.46), 298 (4.15), 337 (4.41) nm; IR ν_{max} (film) 3322, 1594, 1506, 1441, 1290, 1148, 1087, 988, 827, 683 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 3, respectively; EIMS *m/z* 296 $[M]^+$ (98), 279 (18), 241 (21), 240 (26), 239 (19), 223 (8), 212 (11), 206 (15), 197 (7), 191 (9), 171 (6), 167 (10), 151 (20), 137 (20), 110 (100), 101 (14), 81 (21), 69 (15); HRCIMS *m/z* 297.1499 $[M + H]^+$ (calcd for $C_{19}H_{21}O_3$, 297.1490).

5-(γ,γ-Dimethylallyl)oxyresveratrol (2): amorphous powder; mp 145−146 °C; UV (MeOH) λ_{max} (log ϵ) 219 (4.48), 298 (4.17), 337 (4.42) nm; IR ν_{max} (film) 3355, 1609, 1506, 1441, 1291, 1150, 1089, 989, 828, 680, 570 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 3, respectively; CIMS *m/z* 313 $[M + H]^+$ (26), 259 (2), 247 (2), 195 (5), 193 (2), 179 (100), 139 (3), 123 (4), 75 (2); EIMS *m/z* 312 $[M]^+$ (34), 293 (53), 255 (48), 238 (29), 178 (35), 163 (33), 147 (28), 123 (100), 69 (33), 55 (21); HRCIMS *m/z* 313.1454 $[M + H]^+$ (calcd for $C_{19}H_{21}O_4$, 313.1440).

3-(2,3-Dihydroxy-3-methylbutyl)resveratrol (3): yellowish oil; $[\alpha]_D^{20}$ +4.0° (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ϵ) 218 (4.30), 313 (4.29) nm; IR ν_{max} (film) 3296, 1594, 1499, 1445, 1347, 1254, 1152, 1108, 960, 830 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3, respectively; CIMS *m/z* 331 $[M + H]^+$ (100), 315 (80), 313 (30), 299 (9), 297 (9), 285 (3), 273 (5), 259 (6), 249 (6), 235 (10), 214 (88), 207 (9), 196 (67), 191 (10), 179 (68), 167 (14), 161 (27), 153 (75), 139 (26), 137 (20), 125 (29), 75 (33); HRCIMS *m/z* 331.1567 $[M + H]^+$ (calcd for $C_{19}H_{23}O_5$, 331.1545).

Acetylation of 3. Compound **3** (0.2 mg) was acetylated with acetic anhydride (two drops) and pyridine (0.2 mL) at room temperature overnight. The product was purified by preparative TLC (250 μm layers), eluting with $CHCl_3$−MeOH (10:1; R_f = 0.65), affording the tetraacetate of **3** (**3a**, 0.2 mg): ^1H NMR data of **3a**, see Table 2; EIMS *m/z* 498 $[M]^+$ (24), 457 (13), 456 (41), 438 (39), 396 (94), 378 (38), 363 (100), 354 (39), 321 (29), 312 (21), 241 (24), 43 (66).

Methylation of 3. Compound **3** (0.7 mg) was dissolved in 0.2 mL of MeOH, and an excess of fresh CH_2N_2 (in Et_2O) was added to this sample solution. The product was purified by preparative TLC (250 μm layers) after the reaction was conducted at room temperature overnight, to afford the methyl ether of **3** (**3b**, 0.7 mg): ^1H NMR data of **3b**, see Table 2.

Preparation of the (*R*)- and (*S*)-MTPA Ester Derivatives of 3b. The methyl ether of **3** (**3b**, 0.7 mg) was separated into two equal portions and treated with (*S*)-(+)α- and (*R*)-(−)α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (3 μL) in anhydrous pyridine (0.2 mL) at room temperature overnight and afforded the (*R*)- and (*S*)-MTPA ester derivatives (**3s** and **3r**) of **3b**, respectively. ^1H NMR data (C_5D_5N) of **3s**: δ 1.52, 1.55, 1.60, 1.62 (s, H-4″ and H-5″), 2.96−3.08 (m, H-1″), 6.12−6.17 (m, H-2″), 6.65−6.68 (H-4′); ^1H NMR data of **3r** were the same as those of **3s**, with the only differences being the different relative integrations of the signals (see text).

3-(γ,γ-Dimethylpropenyl)moracin M (4): amorphous powder; mp 204−205 °C; UV (MeOH) λ_{max} (log ϵ) 227 (4.45), 254 (4.30), 297 (4.25), 336 (4.40) nm; IR ν_{max} (film) 3318, 1620, 1578, 1461, 1347, 1299, 1255, 1189, 1152, 1104, 998, 971, 948, 898, 882, 833, 795, 666, 631 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 3, respectively; EIMS *m/z* 310 $[M]^+$ (100), 293 (75), 281 (9), 267 (10), 255 (82), 254 (47), 239 (4), 226 (7), 155 (4), 149 (9), 146 (15), 129 (17), 69 (11); HRCIMS *m/z* 311.1287 $[M + H]^+$ (calcd for $C_{19}H_{19}O_4$, 311.1283).

Dadahol A (5): colorless oil; $[\alpha]_D^{20}$ +20° (*c* 0.075, MeOH); UV (MeOH) λ_{max} (log ϵ) 205 (4.02), 224 (3.98), 289 (3.78), 311 (3.81) nm; ^1H NMR (CD_3OD) δ 7.66 (1H, d, *J* = 16.0 Hz, H-7″), 7.48 (2H, d, *J* = 8.6 Hz, H-2″ and H-6″), 7.32 (2H, d, *J* = 8.6 Hz, H-2‴ and H-6‴), 7.16 (1H, d, *J* = 16.0 Hz, H-7‴), 7.06 (1H, br s, H-2), 6.86 (1H, brd, *J* = 8.7 Hz, H-6), 6.74−6.82 (5H, m, H-5, H-3″, H-5″, H-3‴, and H-5‴), 6.74 (2H, brs, H-2′ and H-6′), 6.63 (1H, d, *J* = 15.9 Hz, H-7′), 6.39 (1H, d, *J* = 16.0 Hz, H-8″), 6.31 (1H, dt, *J* = 15.9, 6.1 Hz, H-8′), 6.07 (1H, d, *J* = 16.0 Hz, H-8‴), 5.00 (1H, d, *J* = 4.3 Hz, H-7), 4.76 (2H, brd, *J* = 6.1 Hz, H-9′), 4.61 (1H, m, H-8), 4.46 (1H, dd, *J* = 11.7, 7.1 Hz, H-9a), 4.32 (1H, dd, *J* = 11.7, 2.1 Hz, H-9b), 3.86 (3H, s, MeO-3), 3.80 (6H, s, MeO-3′ and MeO-5′); ^{13}C NMR (CD_3OD) δ 169.1 (C-9‴, s), 169.0 (C-9″, s), 161.4 (C-4‴, s), 161.3 (C-4″, s), 154.6 (C-3′ and C-5′, s), 149.3 (C-3, s), 148.8 (C-4, s), 146.9 (C-7″, d), 146.5 (C-7‴, d), 137.4 (C-4′, s), 135.0 (C-7′, d), 133.8 (C-1′, s), 133.6 (C-1, s), 131.3 (C-2″, C-6″, C-2‴, and C-6‴, d), 127.2 (C-1″, s), 127.0 (C-1‴, s), 124.3 (C-8′, d), 120.4 (C-6, d), 115.9 (C-3″, C-5″, C-3‴, and C-5‴, d), 115.8 (C-5, d), 115.1 (C-8″, d), 115.0 (C-8‴, d), 111.3 (C-2, d), 104.9 (C-2′ and C-6′, d), 84.8 (C-8, d), 74.5 (C-7, d), 66.0 (C-9′, t), 65.2 (C-9, t), 56.6 (MeO-3′ and MeO-5, q), 56.4 (MeO-3, q); positive-FABMS *m/z* 699 $[M + H]^+$; HRFABMS *m/z* 721.2285 $[M + Na]^+$ (calcd for $C_{39}H_{38}O_{12}Na$, 721.2261).

Dadahol B (6): colorless oil; UV (MeOH) λ_{max} (log ϵ) 210 (4.11), 224 (3.96), 311 (3.98) nm; ^1H NMR (CD_3OD) δ 7.65 (2H, d, *J* = 16.0 Hz, H-7″), 7.46 (4H, d, *J* = 8.6 Hz, H-2″ and H-6″), 7.32 (2H, d, *J* = 8.6 Hz, H-2‴ and H-6‴), 7.31 (2H, d, *J* = 8.6 Hz, H-2‴ and H-6‴), 7.27 (1H, d, *J* = 16.0 Hz, H-7‴), 7.26 (1H, d, *J* = 16.0 Hz, H-7‴), 6.75−7.09 (20H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′, H-3″, H-5″, H-3‴, and H-5‴), 6.62 (1H, d, *J* = 16.0 Hz, H-7′), 6.60 (1H, d, *J* = 16.0 Hz, H-7′), 6.37 (2H, d, *J* = 16.0 Hz, H-8″), 6.24 (2H, dt, *J* = 16.0, 6.2 Hz, H-8′), 6.14 (2H, d, *J* = 16.0 Hz, H-8‴), 4.88−4.91 (2H, m, H-7), 4.79 (4H, m, H-9′), 4.68 (2H, m, H-8), 4.42−4.50 (2H, m, H-9), 4.27 (1H, dd, *J* = 11.8, 2.9 Hz, H-9a), 4.15 (1H, dd, *J* = 11.8, 6.6 Hz, H-9b), 3.82 (9H, s, MeO), 3.78 (3H, s, MeO); ^{13}C NMR (CD_3OD) δ 169.1, 168.9, 168.8 (C-9‴ and C-9″, s), 161.34, 161.30, 160.10 (C-4‴ and C-4″, s), 152.2, 152.1, 149.7, 149.4, 149.0, 148.8, 147.4, 147.2 (C-3, C-4, C-3′, and C-4′, s), 146.84, 146.77, 146.74 (C-7″ and C-7‴, d), 134.9, 133.6 (C-7′, d), 133.9, 133.3, 132.67, 132.66 (C-1 and C-1′, s), 131.3 (C-2″, C-6″, C-2‴, and C-6‴, d), 127.2, 127.03, 127.01 (C-1″ and C-1‴, s), 123.30, 123.29 (C-8′, d), 121.07, 120.95, 120.89, 120.81, 119.3, 119.0 (C-2, C-6, C-2′, and C-6′), 116.8 (C-3″, C-5″, C-3‴, and C-5‴, d), 116.0, 115.9, 115.8 (C-5 and C-5′, d), 115.1, 114.8, 114.7 (C-8″ and C-8‴, d), 111.7, 111.6, 111.5 (C-2 and C-2′, d), 80.4, 83.6 (C-8, d), 74.7, 74.2 (C-7, d), 66.2 (C-9′, t), 65.2 (C-9, t), 56.5 (MeO, q), 56.4 (MeO, q); positive-FABMS *m/z* 691 $[M + Na]^+$, 691 $[M + H]^+$; HRFABMS *m/z* 691.2155 $[M + Na]^+$ (calcd for $C_{38}H_{36}O_{11}Na$, 691.2155).

Oxyresveratrol: white, amorphous powder; mp 200−203 °C [lit.[19] 199−201 °C]. On the basis of observed 2D NMR

spectral correlations (^{1}H−^{1}H COSY, HMQC, and HMBC), the ^{1}H and ^{13}C NMR data[20] of oxyresveratrol were reassigned: ^{1}H NMR (CD_3OD, 300 MHz) δ 6.17 (1H, dd, J = 2.1, 2.1 Hz, H-3), 6.33 (1H, d, J = 1.8 Hz, H-3′), 6.35 (1H, dd, J = 8.9, 1.8 Hz, H-5′), 6.48 (2H, d, J = 2.1 Hz, H-2 and H-6), 6.84 (1H, d, J = 16.4 Hz, H-7), 7.29 (1H, d, J = 16.4 Hz, H-8), 7.34 (1H, d, J = 8.9 Hz, H-6′); ^{13}C NMR (CD_3OD, 300 MHz) δ 102.2 (C-3′, d), 103.4 (C-4, d), 105.7 (C-2 and C-6, d), 108.5 (C-5′, d), 117.8 (C-1′, d), 124.4 (C-6′, d), 126.4 (C-7, d), 128.6 (C-8, d), 142.0 (C-1, s), 156.8 (C-2′, s), 158.4 (C-4′, s), 159.0 (C-3 and C-5, s).

(+)-Catechin: yellowish, amorphous powder; mp 168−172 °C [lit.[22] 173−175 °C]; $[\alpha]_D^{20}$ +21.5° (*c* 0.40, MeOH) {lit.[22] $[\alpha]_D^{24}$ +14.7° (*c* 0.69, acetone)}; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[21,22]

Afzelechin-3-*O*-α-L-rhamnopyranoside: light brown solid; mp 118−120 °C [lit.[23] 110−115 °C]; $[\alpha]_D^{20}$ −20.5° (*c* 0.35, MeOH) {lit.[23] $[\alpha]_D^{28}$ −14.95° (*c* 0.107, acetone)}; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[23]

(−)-Epiafzelechin: yellowish, amorphous powder; mp 213-216 °C [lit.[22] 248−250 °C]; $[\alpha]_D^{20}$ −48.2° (*c* 0.60, MeOH) {lit.[23] $[\alpha]_D^{23}$ −51.7° (*c* 1.1, acetone)}; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[22,25]

Dihydromorin: colorless needles; mp 236−237 °C [lit.[26] 223−225 °C; lit.[31] 232−235 °C]; ^{1}H NMR and EIMS data, consistent with literature values;[26] ^{13}C NMR (CD_3OD, 300 MHz) δ 72.5 (C-3, d), 80.0 (C-2, d), 96.2 (C-6, d), 97.2 (C-8, d), 103.7 (C-3′, d), 101.9 (C-10, s), 107.9 (C-5′, d), 115.6 (C-1′, s), 130.9 (C-6′, d), 158.6 (C-2′, s), 160.2 (C-4′, s), 165.0 (C-7, s), 165.3 (C-9, s), 168.6 (C-5, s), 199.0 (C-4, s).

Epiafzelechin-(4β→8)-epicatechin: brown, amorphous powder; mp 251−258 °C; $[\alpha]_D^{20}$ +28.8° (*c* 0.20, MeOH) {lit.[22] $[\alpha]_D^{26}$ +29.1° (*c* 1.0, acetone)}; FABMS *m*/*z* 563 $[M + H]^+$; ^{1}H and ^{13}C NMR data, consistent with literature values.[22]

Resveratrol: yellowish, amorphous powder; mp 250−253 °C [lit.[30] 254−255 °C]; ^{1}H NMR and EIMS data, consistent with literature values;[30] ^{13}C NMR (CD_3OD, 300 MHz) δ 102.7 (C-4, d), 105.8 (C-2, and C-6, d), 116.5 (C-2′ and C-6′, d), 127.1 (C-7, d), 128.8 (C-3′ and C-5′), 129.4 (C-8, d), 130.2 (C-1′, s), 142.3 (C-1, s), 158.4 (C-4′, s), 159.7 (C-3 and C-5, s).

Steppogenin: white solid; mp 254−255 °C [lit.[31] 248−253 °C]; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[31]

Moracin M: yellowish, amorphous powder; mp 271−273 °C [lit.[29] 275 °C]; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[29]

Isogemichalcone B: yellowish, amorphous powder; mp 178−181 °C [lit.[32] 176 °C]; FABMS *m*/*z* 487 $[M + H]^+$; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[32]

Gemichalcone B: yellowish, amorphous powder; mp 152−156 °C [lit.[32] 140 °C]; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[32]

Norartocarpetin: yellowish solid; mp 230−232 °C; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[33]

Engeletin: yellowish, amorphous powder; mp 172−175 °C [lit.[34] 177−178 °C]; $[\alpha]_D^{20}$−14.2° (*c* 0.32, MeOH) {lit.[34] $[\alpha]_D^{19}$ −12.3° (*c* 0.1, acetone)}; spectral data (^{1}H and ^{13}C NMR, EIMS) consistent with literature values.[34,35]

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