# Constituents of the Stem Bark of *Pongamia pinnata* with the Potential to Induce Quinone Reductase

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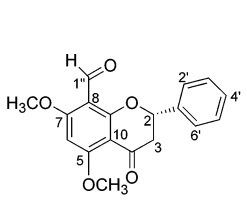
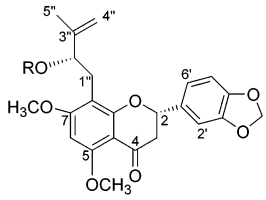
Activity-guided fractionation of the petroleum ether and ethyl acetate extracts of the stem bark of *Pongamia pinnata*, using cultured Hepa 1c1c7 mouse hepatoma cells to evaluate quinone reductase (QR) inducing activity, led to the isolation of four new flavanone derivatives (**1**−**4**), one new flavone (**5**), one new chalcone (**6**), and 13 known compounds of the flavonoid, terpenoid, and fatty acid types. The structures of **1**−**6** were characterized on the basis of the interpretation of their spectroscopic data. The absolute stereochemistry of compounds **1**−**4** was determined from their CD data and by Mosher ester determination. All isolates obtained were evaluated in the quinone reductase induction assay.

*Pongamia pinnata* (L.) Pierre [synonyms, *Cytisus pinnatus* (L.), *Derris indica* (Lam.) Bennet, and *Pongamia glabra* Vent., *Pongamia pinnata* (L.) Merr.] is a fast growing, glabrous, deciduous tree that belongs to the Leguminosae.[1,2] Alkaloids, fatty acids, flavonoids, and triterpenoids have been isolated from this species previously.[3−6] In a biological study performed on albino rats (CF strain) with a petroleum ether extract of the seeds of *P. pinnata*, significant anti-inflammatory activity was observed.[7] Different plant parts of *P. pinnata* have been used to treat human ailments in Southeast Asia. For instance, the seeds of this plant have been reported to be used in Ayurvedic remedies for fever, abdominal colic, inflammation, and gout.[8] Moreover, a black gum from the bark of *P. pinnata* is used to treat wounds caused by poisonous fish and to improve women's health after giving birth.[9] The seeds of this species are eaten raw, recreationally, by the Onge aboriginal inhabitants of southeastern Asia.[10]

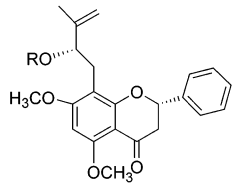
As part of a project directed toward the discovery of novel cancer chemopreventive agents from plants,[11−13] petroleum ether and ethyl acetate extracts of the stem bark of *P. pinnata* were found to show inducing activity in a cell-based quinone reductase assay (QR).[14] Induction of the phase II drug-metabolizing enzyme NAD(P)H:quinone reductase (QR) was selected for the present study as a target bioassay because it represents a major mechanism of protection against tumor initiation.[14] Bioassay-guided fractionation using the QR assay led to the isolation of four new flavanone derivatives (**1**−**4**), one new flavone (**5**), one new chalcone (**6**), and 13 known compounds from these extracts. The isolation and structure elucidation of **1**−**6** and the biological evaluation of all active isolates in the QR induction assay are reported in this paper.



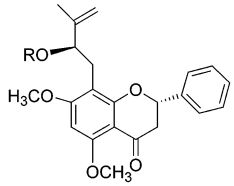
**1**



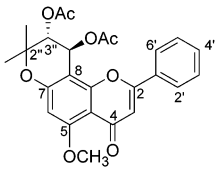
**2** R = H
**2r** R = (*R*)-MTPA
**2s** R = (*S*)-MTPA



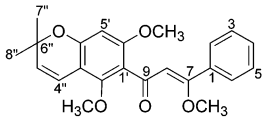
**3** R = H
**3r** R = (*R*)-MTPA
**3s** R = (*S*)-MTPA



**4** R = H
**4r** R = (*R*)-MTPA
**4s** R = (*S*)-MTPA



**5**



**6**

## Results and Discussion

Activity-guided fractionation of the petroleum ether and ethyl acetate extracts from the stem bark of *P. pinnata* using the quinone reductase assay provided six new compounds (**1**−**6**) and 13 known compounds, namely, candidin,[15] candidone,[16] 3′-methoxypongapin,[17] praecansone B,[18,19] pongapinone A,[15,20] pongapinone B,[21] α-cadinol,[22,23] betulinic acid,[24] lupenone,[24] lupeol,[25] octadecanoic acid,[26] stearyl alcohol,[27] and stigmasterol 3-*O*-*β*-D-glucopyranoside.[28] The structures of the known compounds were identified by physical and spectroscopic data measurement and comparison with the relevant published data.

A molecular formula of $C_{18}H_{16}O_5$ was assigned to compound **1** on the basis of its HRTOFMS (*m*/*z* 335.0900, calcd for $C_{18}H_{16}O_5Na$, 335.0895). The $^1H$ NMR spectrum (Table 1) of **1** displayed signals for two aliphatic protons at $\delta_H$

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**Table 1.** $^1$H, $^{13}$C, and Selected HMBC NMR Data for Compounds **1**, **5**, and **6**[a]

| | **1** | | | **5** | | | **6** | | |
|---|---|---|---|---|---|---|---|---|---|
| position | $\delta_H$ | $\delta_C$ | HMBC | $\delta_H$ | $\delta_C$ | HMBC | $\delta_H$ | $\delta_C$ | HMBC |
| 1 | | | | | | | | 134.8 | |
| 2 | 5.57 dd (11.0, 3.8) | 79.4 | C-4, C-2′, C-6 | | 160.6 | | 7.32 m | 128.7 | C-4, C-7 |
| 3 | 3.06 m | 44.9 | C-10, C-1 | 6.72 s | 109.3 | C-10, C-1 | 7.17 m | 127.2 | |
| 4 | | 188.5 | | | 177.2 | | 7.22 m | 129.4 | |
| 5 | | 167.0 | | | 161.7 | | 7.17 m | 127.2 | |
| 6 | 6.12 s | 88.5 | C-8, C-10 | 6.35 s | 96.8 | C-8, C-10 | 7.32 m | 128.7 | C-4, C-7 |
| 7 | | 166.5 | | | 158.2 | | | 171.6 | |
| 8 | | 108.2 | | | 99.2 | | 5.89 s | 105.7 | C-1, C-7, C-9, C-1 |
| 9 | | 166.7 | | | 157.8 | | | 192.5 | |
| 10 | | 105.6 | | | 109.7 | | | | |
| 1′ | | 138.0 | | | 131.8 | | | 118.8 | |
| 2′ | 7.41−7.46 m | 128.9 | C-2 | 7.78 m | 129.0 | | | 153.8 | |
| 3′ | 7.41−7.46 m | 128.7 | | 7.47−7.49 m | 125.9 | | | 107.7 | |
| 4′ | 7.41−7.46 m | 125.8 | | 7.47−7.49 m | 125.9 | | | 155.3 | |
| 5′ | 7.41−7.46 m | 128.7 | | 7.47−7.49 m | 131.0 | | 5.88 s | 95.7 | C-3′, C-4′, C-6′ |
| 6′ | 7.41−7.46 m | 128.9 | C-2 | 7.78 m | 129.0 | | | 157.0 | |
| 1″ | 10.40 s | 186.7 | C-9 | | | | | | |
| 2″ | | | | | 77.3 | | | | |
| 3″ | | | | 5.30 d (4.6) | 71.2 | C-8, $Me_1$-2″, $Me_2$-2″, OAc-3″ | | | |
| 4″ | | | | 6.63 d (4.6) | 61.3 | C-7, C-9, C-2″, OAc-4″ | 6.37 d (9.9) | 116.6 | C-2′, C-4′, C-6″ |
| 5″ | | | | | | | 5.45 d (9.9) | 127.3 | C-3′, C-6″ C-7″, C-8 |
| 6″ | | | | | | | | 76.5 | |
| 7″ | | | | | | | 1.37 s | 27.9 | C-5″, C-6″ |
| 8″ | | | | | | | 1.37 s | 27.9 | C-5″, C-6″ |
| OMe-5 | 4.02 s | 56.3 | C-5 | 3.97 s | 56.5 | C-5 | | | |
| OMe-7 | 4.01 s | 56.4 | C-7 | | | | 3.84 s | 63.3 | C-7 |
| OMe-2′ | | | | | | | 3.73 s | 56.5 | C-2′ |
| OMe-6′ | | | | | | | 3.67 s | 55.6 | C-6′ |
| OAc-3″ | | | | 2.13 s | 169.8, 20.8 | | | | |
| OAc-4″ | | | | 1.97 s | 170.8, 20.7 | | | | |
| $Me_1$-2″ | | | | 1.46 s | 26.3 | C-2″, C-3″ | | | |
| $Me_2$-2″ | | | | 1.51 s | 21.5 | C-2″, C-3″ | | | |

[a] The $^1$H and $^{13}$C NMR data were obtained in $CDCl_3$ at 500 and 125 MHz for **1** and 300 and 75 MHz for **5** and **6**, respectively; TMS was used as internal standard.

3.06 (2H, m, $H_2$-3), two methoxy groups at $\delta_H$ 4.01 (3H, s) and 4.02 (3H, s), an oxygenated methine doublet of doublets at $\delta_H$ 5.57 (1H, dd, $J$ = 11.0, 3.8 Hz, H-2), an olefinic or aromatic proton at $\delta_H$ 6.12 (1H, s, H-6), a monosubstituted aromatic ring at $\delta_H$ 7.41−7.46 (5H, m, H-2′−H-6′), and a downfield resonance at $\delta_H$ 10.40 (1H, s, H-1″). Consistent with the above $^1$H NMR analysis, the $^{13}$C NMR spectrum (Table 1) of compound **1** displayed the signals for an aliphatic methylene at $\delta_C$ 44.9 (C-3), two methoxy groups at $\delta_C$ 56.4 (OMe-7, s) and $\delta_C$ 56.3 (OMe-5, s), an oxygenated methine at $\delta_C$ 79.4 (C-2, d), two aromatic rings [with one monosubstituted: $\delta_C$ 125.8 (C-4′, d), 128.7 (C-3′, C-5′, d), 128.9 (C-2′, C-6′, d), 138.0 (C-1′, s)], a downfield methine (aldehyde) at $\delta_C$ 186.7 (C-1″, s), and a conjugated ketone at $\delta_C$ 188.5 (C-4, s). These 1D NMR data, in combination with the observed 2D NMR ($^1$H−$^1$H COSY, HMQC, and HMBC) correlations, suggested that compound **1** is a flavanone possessing an unsubstituted B ring. Three oxygenated aromatic carbons of the A ring resonated in a relatively downfield region with very close chemical shifts ($\delta_C$ 166.5, 166.7, and 167.0) in the $^{13}$C NMR spectrum of **1**. This suggested that the two methoxy groups should be placed at C-5 and C-7.[29] As a result, the aldehyde group could only be located at either C-6 or C-8. Investigation of the NOESY spectrum of **1** revealed correlations from H-6 to both methoxy groups (OMe-5 and OMe-7), while the aldehyde proton only correlated with one methoxy signal (OMe-7). Thus, the aldehyde group was assigned at the C-8 position in the molecule of **1**. The stereochemistry of C-2 was determined as *S* on the basis of a negative Cotton effect at 271 nm in the CD spectrum of **1**.[30] Accordingly, compound **1** was assigned as (2*S*)-5,7-dimethoxy-8-formylflavanone.

A molecular formula of $C_{23}H_{24}O_7$ was assigned to compound **2** on the basis of its HRTOFMS (*m*/*z* found 435.1432, calcd for $C_{23}H_{24}O_7Na$, 435.1420). In a manner similar to **1**, the $^1$H NMR spectrum of **2** (Table 2) showed signals of two aliphatic protons at $\delta_H$ 2.88 (2H, m, $H_2$-3) and an oxygenated methine doublet of doublets at $\delta_H$ 5.27 (1H, dd, $J$ = 12.9, 2.9 Hz, H-2). The $^{13}$C NMR resonances of the aliphatic methylene ($\delta_C$ 45.8), oxygenated methine ($\delta_C$ 78.9), and conjugated ketone ($\delta_C$ 189.7), observed for compound **2**, were very close to those of **1**. This indicated that compound **2** is another flavanone metabolite. However, the $^1$H NMR spectral data suggested that compound **2** possesses a 1,2,4-trisubstituted aromatic ring ($\delta_H$ 6.95, 1H, d, $J$ = 1.5 Hz, H-2′; 6.88, 1H, dd, $J$ = 8.7, 1.5 Hz, H-6′; 6.82, 1H, d, $J$ = 8.0 Hz, H-5′) instead of the unsubstituted B ring in **1**. A two-proton broad singlet at $\delta_H$ 5.99 and a doubly oxygenated methylene at $\delta_C$ 101.3 were displayed in the $^1$H and $^{13}$C NMR spectra, respectively. In the HMBC spectrum, the correlations from $\delta_H$ 5.99 (−$OCH_2O$−) to $\delta_C$ 148.0 (C-3′) and 147.8 (C-4′), from $\delta_H$ 6.95 (H-2′) to $\delta_C$ 147.8 (C-4′), and from $\delta_H$ 6.82 (H-5′) to $\delta_C$ 148.0 (C-3′) suggested a methylenedioxy group was present in the B ring at positions C-3′ and C-4′. Besides the signals of the flavanone skeleton, the methylenedioxy group, and two methoxy groups, the $^{13}$C NMR spectrum of **2** showed five additional signals, which could be assigned as a prenyl (2-hydroxy-3-methyl-3-butenyl) functionality by analyzing the 1D and

**Table 2.** $^1$H, $^{13}$C, and Selected HMBC NMR Data for Compounds **2**−**4**[a]

| | **2** | | | **3** | | | **4** | | |
|---|---|---|---|---|---|---|---|---|---|
| position | $\delta_H$ | $\delta_C$ | HMBC | $\delta_H$ | $\delta_C$ | HMBC | $\delta_H$ | $\delta_C$ | HMBC |
| 1 | | | | | | | | | |
| 2 | 5.27 dd (12.9, 2.9) | 78.9 | C-4, C-2′, C-6′ | 5.37 dd (3.2, 3.1) | 79.1 | C-4, C-2′, C-6′ | 5.39 dd (3.2, 3.2) | 78.9 | C-4, C-2′, C-6′ |
| 3 | 2.88 m | 45.8 | C-10, C-1′ | 2.82 m | 45.8 | C-10, C-1′ | 2.93 m | 45.8 | C-10, C-1′ |
| 4 | | 189.7 | | | 189.8 | | | 189.8 | |
| 5 | | 163.8 | | | 163.7 | | | 163.8 | |
| 6 | 6.15 s | 88.6 | C-8, C-10 | 6.16 s | 88.8 | C-8, C-10 | 6.16 s | 88.7 | C-8, C-10 |
| 7 | | 161.6 | | | 161.7 | | | 161.6 | |
| 8 | | 106.1 | | | 106.1 | | | 106.1 | |
| 9 | | 161.3 | | | 161.3 | | | 161.2 | |
| 10 | | 107.2 | | | 107.2 | | | 107.1 | |
| 1′ | | 132.9 | | | 138.9 | | | 139.0 | |
| 2′ | 6.95 d (1.5) | 106.6 | C-2, C-4′ | 7.40 m | 128.8 | C-2 | 7.41 m | 128.7 | C-2 |
| 3′ | | 148.0 | | 7.40 m | 125.9 | | 7.41 m | 125.9 | |
| 4′ | | 147.8 | | 7.40 m | 128.5 | | 7.41 m | 128.5 | |
| 5′ | 6.82 d (8.0) | 108.3 | C-3′ | 7.40 m | 125.9 | | 7.41 m | 125.9 | |
| 6′ | 6.88 dd (8.7, 1.5) | 119.7 | C-2 | 7.40 m | 128.8 | C-2 | 7.41 m | 128.7 | C-2 |
| 1″ | 2.84 m | 29.6 | C-7, C-8, C-9 | 2.98 m | 29.6 | C-9 | | 29.6 | C-9 |
| 2″ | 4.25 br s | 75.6 | C-8 | 4.21 dd (4.6, 4.7) | 75.8 | | 4.28 m | 75.6 | |
| 3″ | | 147.6 | | | 147.4 | | 2.93 m | 147.6 | |
| 4a″ | 4.78 s | 110.0 | C-2″, C-5″ | 4.83 s | 110.2 | | 4.89 s | 110.0 | |
| 4b″ | 4.89 s | | C-2″, C-5″ | 4.75 s | | | 4.78 s | | |
| 5″ | 1.72 s | 18.2 | C-2″, C-5″ | 1.69 s | 17.8 | | 1.72 s | 18.2 | |
| OMe-5 | 3.95 s | 55.8 | C-5 | 3.95 s | 55.8 | C-5 | 3.95 s | 55.9 | C-5 |
| OMe-7 | 3.92 s | 56.1 | C-7 | 3.92 s | 56.1 | C-7 | 3.93 s | 56.1 | C-7 |
| −$OCH_2O$− | 5.99 s | 101.3 | C-3′, C-4′ | | | | | | |

[a] The $^1$H and $^{13}$C NMR data were obtained in $CDCl_3$ at 300 and 75 MHz, respectively; TMS was used as internal standard.

**Table 3.** $^1$H NMR Data for the (*R*)- and (*S*)-MTPA Esters of Compounds **2**−**4**[a]

| | **2** | | | **3** | | | **4** | | |
|---|---|---|---|---|---|---|---|---|---|
| position | **2s** | **2r** | $\delta_S - \delta_R$ | **3s** | **3r** | $\delta_S - \delta_R$ | **4s** | **4r** | $\delta_S - \delta_R$ |
| H-2″ | | | | 6.212 | 6.114 | 0.098 | | | |
| H-4a″ | 5.162 | 4.874 | 0.288 | 5.139 | 5.052 | 0.087 | 5.144 | 5.230 | −0.086 |
| H-4b″ | 4.979 | 4.809 | 0.170 | 4.960 | 4.927 | 0.033 | 4.971 | 5.004 | −0.033 |
| H-5″ | 1.799 | 1.746 | 0.053 | 1.819 | 1.708 | 0.111 | 1.774 | 1.862 | −0.088 |
| H-2 | 5.488 | 5.502 | −0.014 | 5.489 | 5.570 | −0.081 | 5.558 | 5.168 | 0.390 |
| H-6 | | | | 6.332 | 6.393 | −0.061 | 6.386 | 6.262 | 0.124 |

[a] In pyridine-$d_5$ at 500 MHz.

2D NMR data obtained. The two methoxy groups were also assigned to C-5 and C-7 by comparison of the $^{13}$C NMR spectral data of **2** with those of **1**. This was confirmed by the NOESY correlations from H-6 to both of two methoxy signals. The prenyl unit was located at C-8, which was confirmed by the observed HMBC correlation from H-1″ to C-7, C-8, and C-9. A negative Cotton effect at 293 nm was obtained in the CD spectrum of **2**, suggesting the stereochemistry of C-2 to be *S*.[30] To determine the absolute stereochemistry of the other chiral center (C-2″) of compound **2**, a convenient Mosher ester handling procedure recently developed by our group was employed.[31] The $^1$H NMR chemical shift differences of the two diastereomeric α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters unambiguously indicated the absolute configurations of C-2″ of the prenyl unit in **2** to be *S* (Table 3).[32,33] Accordingly, compound **2** was assigned as (2*S*)-5,7-dimethoxy-8-(2*S*-hydroxy-3-methyl-3-butenyl)-3′,4′-methylenedioxyflavanone.

The $^1$H and $^{13}$C NMR spectral data of compounds **3** and **4** were nearly identical (Table 2), and the same molecular formula of $C_{22}H_{24}O_5$ was assigned for **3** (*m*/*z* 391.1524) and **4** (*m*/*z* 391.1540) on the basis of their HRTOFMS [M + Na]. These two compounds were suggested to be prenylated flavanones with an unsubstituted B ring by comparison of their 1D NMR data with those of compounds **1** and **2**. Further investigation of their 2D NMR ($^1$H−$^1$H COSY, HMQC, HMBC, and NOESY) spectral data resulted in the same gross structure [5,7-dimethoxy-8-(2-hydroxy-3-methyl-3-butenyl)flavanone] for both **3** and **4**. In their CD spectra, negative Cotton effects at 290 and 287 nm were observed for **3** and **4**, respectively. This indicated the absolute stereochemistry of C-2 to be *S* for both compounds.[30] The only difference between **3** and **4** was seen to be the different configuration at C-2″. The (*R*)- and (*S*)-MTPA esters for both **3** and **4** were prepared, and the results (Table 3 and Figure 1) clearly assigned the absolute stereochemistry as *S* and *R*, respectively, for compounds **3** and **4**. This is also consistent with the only other evident difference of the splitting pattern of H-2″ in the $^1$H NMR spectra of **3** and **4**. Thus, compounds **3** and **4** are epimers and were structurally assigned as (2*S*)-5,7-dimethoxy-8-(2*S*-hydroxy-3-methyl-3-butenyl)flavanone and (2*S*)-5,7-dimethoxy-8-(2*R*-hydroxy-3-methyl-3-butenyl)flavanone, respectively.

A molecular formula of $C_{25}H_{24}O_8$ was assigned to compound **5** on the basis of its HRTOFMS (*m*/*z* 475.1371, calcd for $C_{25}H_{24}O_8Na$, 475.1369), indicating 14 degrees of unsaturation. The $^{13}$C and DEPT NMR spectrum of **5** (Table 1) displayed resonances for one conjugated ketone ($\delta_C$ 177.2, C-4), 14 aromatic and olefinic carbons, one oxygenated quaternary carbon ($\delta_C$ 77.3, C-2″), two oxygenated methines ($\delta_C$ 61.3, C-4″; 71.2, C-3″), two methyls ($\delta_C$ 26.3, $Me_1$-2″; 21.5, $Me_2$-2″), one methoxy group ($\delta_C$ 56.5), and two acetyl groups ($\delta_C$ 170.8/20.7, OAc-4″; 169.8/20.8, OAc-3″). Signals for an aromatic singlet at $\delta_H$ 6.35 (1H, s, H-6), an

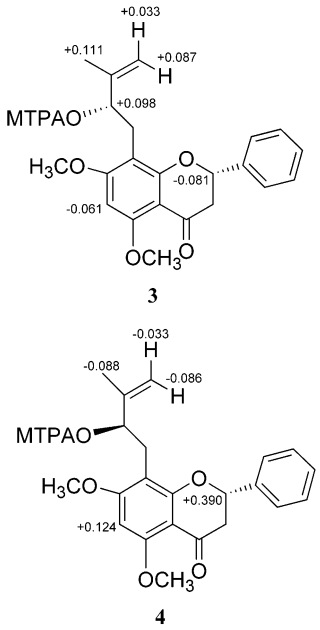


**Figure 1.** Values of the $^1$H NMR chemical shift differences ($\delta_S - \delta_R$) of the (*S*)- and (*R*)-MTPA esters of compounds **3** and **4**.

olefinic singlet at $\delta_H$ 6.72 (1H, s, H-3), a monosubstituted aromatic ring at $\delta_H$ 7.47−7.49 (3H, m, H-3′-H-5′) and 7.78 (2H, m, H-2′, H-6′), two oxygenated methine doublets at $\delta_H$ 5.30 (1H, d, $J$ = 4.6 Hz, H-3″) and 6.63 (1H, d, $J$ = 4.6 Hz, H-4″), a methoxy group at $\delta_H$ 3.97 (3H, s), two acetyl groups at $\delta_H$ 1.97 (3H, s) and 2.13 (3H, s), and two tertiary methyl groups at $\delta_H$ 1.46 (3H, s) and 1.51 (3H, s) were present in the $^1$H NMR spectrum of **5**. The observed HMBC correlations from the proton signals of both the tertiary methyl groups to the oxygenated quaternary carbon ($\delta_C$ 77.3, C-2″, overlapped with the solvent signals) and one of the oxygenated methines ($\delta_C$ 71.2, C-3″), and from H-3″ and H-4″ to the carbonyl carbons of the two acetyl groups, suggested the presence of a 1,2-diacetyl-3-oxo-3-methylbutyl structural unit in the molecule of **5**. Besides the signals of this partial structure and the methoxy substituent, there were 15 carbons remaining based on the determined molecular formula. Further analysis of the $^1$H and $^{13}$C NMR spectra of **5** indicated that the remaining signals belonged to two aromatic rings, one double bond, and one conjugated ketone. This evidence was suggestive that compound **5** is a prenylated flavone. The presence of another ring formed by an oxygen ether group from C-2″ to one oxygenated carbon of ring A in **5** could be concluded, since only 13 degrees of unsaturation (11 for the flavone skeleton and two for the acetyl group) were evident. In the HMBC spectrum of **5**, H-4″ correlated to C-7, C-9, and C-2″, the methoxy group correlated with C-5, and H-6 correlated to C-8 and C-10. These data indicated the methoxy group to be located at C-5, so a pyran ring could be postulated from C-2 of the prenyl unit to C-7 through an oxygen ether group. Due to the limited amount isolated, the absolute stereochemistry for this compound was not determined. Accordingly, compound **5** was assigned as 5-methoxy-(3″,4″-dihydro-3″,4″-diacetoxy)-2″,2″-dimethylpyrano-(7,8:5″,6″)-flavone.

Two acetoxy groups were present in the molecule of **5**, and since EtOAc was used during the purification, it was necessary to confirm whether this compound is a naturally occurring secondary metabolite of *P. pinnata* stem bark. Its presence was confirmed in the original crude petroleum ether extract of the plant material by ESIMS, since a peak collected at the same retention time and under the same conditions as compound **5** using RP-HPLC gave a sodiated molecular ion as indicative of the presence of this acetylated compound.

**Table 4.** Quinone Reductase Inducing Activity of Compounds Isolated from *P. pinnata*[a]

| compound | CD[b] ($\mu$g/mL) | IC$^c_{50}$ ($\mu$g/mL) | CI[d] |
|---|---|---|---|
| (2*S*)-5,7-dimethoxy-8-formyl-flavanone (**1**) | 2.6 | >10.0 | >3.9 |
| (2*S*)-5,7-dimethoxy-8-(2*S*-hydroxy-3-methyl-3-butenyl)flavanone (**3**) | 4.4 | 19.3 | 4.4 |
| 7-methoxypraecansone B (**6**) | 1.2 | 9.6 | 8.0 |
| α-cadinol | 2.3 | >5.0 | >2.2 |
| candidin | 4.5 | 4.5 | 1.0 |
| candidone | 4.7 | 4.1 | 0.9 |
| 3′-methoxypongapin | 1.1 | 18.9 | 17.2 |
| praecansone B | 3.6 | 6.5 | 1.8 |
| pongapinone A | 5.0 | 23.8 | 4.8 |
| pongapinone B | 2.5 | 19.1 | 7.6 |
| sulforaphane[e] | 0.087 | 2.1 | 24.1 |

[a] The new compounds **2**, **4**, and **5** and the known compounds betulinic acid, lupenone, lupeol, oleic acid, stearyl alcohol, and stigmasterol glucoside were deemed inactive, since their CD values[b] were >10 $\mu$g/mL. [b] Concentration required to double QR induction activity. [c] Concentration required to inhibit cell growth by 50%. [d] Chemoprevention index, IC$_{50}$/CD. [e] Sulforaphane was used as a positive control substance.

A molecular formula of $C_{23}H_{24}O_5$ was assigned for compound **6** on the basis of its HRQTOFMS (*m*/*z* found 403.1517, calcd for $C_{23}H_{24}O_5Na$, 403.1521). The $^1$H NMR spectrum (Table 1) of compound **6** exhibited signals for one olefinic proton at $\delta_H$ 5.89 (1H, s, H-8), three methoxy groups at $\delta_H$ 3.84 (3H, s, OMe-7), 3.73 (3H, s, OMe-2′), and 3.67 (3H, s, OMe-6′), an aromatic proton at $\delta_H$ 5.88 (1H, s, H-5′), a monosubstituted aromatic ring at $\delta_H$ 7.16−7.33 [separated into three resonances at $\delta_H$ 7.32 (2H, m, H-2, H-6), 7.22 (1H, m, H-4), and 7.17 (2H, m, H-3, H-5)], and a pyrano unit at $\delta_H$ 6.37 (1H, d, $J$ = 9.9, H-4″), 5.45 (1H, d, $J$ = 9.9, H-5″), and 1.37 (6H, s, $CH_3$-7″ and $CH_3$-8″). Consistent with the above $^1$H NMR analysis, the $^{13}$C NMR spectrum of this compound displayed signals corresponding to a conjugated methine ($\delta_C$ 105.7, C-8), three methoxy groups at $\delta_C$ 63.3 (C-7), 56.5 (C-2′), and 55.6 (C-6′), two aromatic rings (with one monosubstituted: $\delta_C$ 134.8, C-1; 129.4, C-4; 128.7, C-2, C-6; 127.2, C-3, C-5), and a conjugated ketone at $\delta_C$ 192.5 (C-9). These 1D NMR data, in combination with the 2D NMR ($^1$H−$^1$H COSY, HMQC, HMBC) spectra, suggested that compound **6** is a chalcone with a dimethylpyran ring attached to C-3′ and C-4′. Furthermore, the spectral data obtained for compound **6** were closely comparable to those published for praecansone B,[18,19] with the only difference being due to the methoxy groups at C-7. Accordingly, the new compound **6** was assigned as 7-methoxypraecansone B [7,2′,6′-trimethoxy-6″,6″-dimethylpyrano-(3′,4′:2″,3″)-chalcone].

Compounds **1**, **3**, and **6** showed CD (concentration to double the specific enzyme activity) values of 2.6, 4.4, and 1.2 $\mu$g/mL, respectively, in the quinone reductase induction assay. The three other new compounds (**2**, **4**, **5**) were found to be inactive in this assay (CD > 10 $\mu$g/mL). However, several known compounds (α-cadinol, candidin, candidone, 3-methoxypongapin, praecansone B, pongapinone A, and pongapinone B) were found to induce quinone reductase, in the CD potency range 1.1−5.0 $\mu$g/mL (Table 4). Of the isolates obtained, 3′-methoxypongapin was found to be the most promising compound, since it gave a chemoprevention index value of 17.2 (Table 4).

## 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. CD spectra were measured with a JASCO 710 spectrophotometer. IR spectra were run on an ATI Mattson Genesis Series FT-IR spectrophotometer. NMR spectral data were recorded at room temperature on either a Bruker Avance DPX-300 or a Bruker Avance DPX-500 NMR spectrometer with trimethylsilane (TMS) as internal standard. EIMS and ESIMS were obtained on a Finnigan/MAT 90/95 sector-field mass spectrometer, and HRQTOFMS were obtained on a Micromass QTOF II mass spectrometer. A YMC-pack ODC-AQ column (15 × 2 cm i.d., YMC Co., Wilmington, NC) was used for semipreparative HPLC, along with two Waters 515 HPLC pumps and a Waters 2487 dual $\lambda$ absorbance detector (Waters, Milford, MA). Column chromatography was run using silica gel G (Merck, 230−400 mesh). Preparative thin-layer chromatography was performed on precoated 20 × 20 cm, 250 or 1000 $\mu$m thickness Merck silica gel 60 $F_{254}$ glass plates, while analytical thin-layer chromatography was carried out on 250 $\mu$m thickness Merck silica gel 60 $F_{254}$ aluminum plates.

**Plant Material.** The stem bark of *Pongamia pinnata* (L.) Pierre was collected in Indonesia by S.R. and L.B.S.K. in September 1999. A voucher specimen (number IS NG-13) has been deposited at the Field Museum of Natural History, Chicago, IL.

**Extraction and Isolation.** The ground plant material (1 kg) was extracted three times by maceration overnight with MeOH−$H_2O$ (9:1). After filtering and concentrating the resultant methanolic extract to a syrup, it was diluted to 250 mL with MeOH−$H_2O$ (1:9). Then, it was partitioned, in turn, three times each with petroleum ether and EtOAc. These two partitions and the residual MeOH−$H_2O$ extract were dried and tested in the quinone reductase assay (QR). The petroleum ether (5.47 g) and ethyl acetate (6.15 g) extracts exhibited activity in the QR assay (CD <2.5 and 3.5 $\mu$g/mL, respectively), while the MeOH−$H_2O$ extract was inactive (CD >10 $\mu$g/mL).

On the basis of the biological activity data obtained, the petroleum ether extract (5.47 g) of *P. pinnata* stem bark was fractionated into 14 fractions (F004 to F017). Betulinic acid[24] (33 mg) was obtained as a precipitate from fraction 14. Fraction F005 was fractionated by open column chromatography (2.5 × 32 cm) over silica gel using hexane−2-propanol−MeOH (95:2.5:2.5). Fraction F00506 from this separation was purified by preparative TLC using ethyl acetate in petroleum ether (1:19) to afford lupenone (5.3 mg, $R_f$ = 0.63).[24] On the basis of the similarity of TLC profiles, fractions F006 and F007 (CD <2.5 and 3.7 $\mu$g/mL) were combined as F007A and eluted with gradient mixtures of petroleum ether−EtOAc (49:1) to petroleum ether−EtOAc (4:1). Fraction F007A03 was eluted with EtOAc−petroleum ether (1:49) by open silica gel column chromatography. From this separation, fraction F007A0304 afforded a sesquiterpene, α-cadinol (23 mg),[22,23] while fraction F007A0305 afforded 3.5 mg of stearyl alcohol.[27] From fraction F007A04, lupeol[25] (27.6 mg) was precipitated. Fraction F008 (CD 5.9 $\mu$g/mL) was fractionated using a gradient from petroleum ether−EtOAc (49:1) to petroleum ether−EtOAc (4:1). Octadecanoic (oleic) acid[26] (15 mg) precipitated from fraction F00807. Fraction F009 (CD 2.6 $\mu$g/mL) was separated by open column chromatography, eluting with petroleum ether−EtOAc (96:4), and fraction F00903 from this separation was further purified by reversed-phase HPLC column chromatography using $CH_3CN$−$H_2O$ (70:30). Pongapinone A[15,20] (5.2 mg) was collected in pure form with $t_R$ = 22.2 min. Fraction F01106 obtained using petroleum ether−EtOAc (8:2) provided a semipure compound. Compound **6** (12 mg) was purified by preparative TLC using petroleum ether−EtOAc (8:2) to elute the plate ($R_f$ = 0.45). Fraction F017 was fractionated by open column chromatography using gradient mixtures from petroleum ether−EtOAc (94:6) to MeOH (100%) for elution. Stigmasterol 3-*O*-$\beta$-D-glucopyranoside[28] (13 mg) precipitated from fraction F01709. Fraction F01706 was separated by preparative TLC using $CHCl_3$−MeOH (16:1). A single band was collected ($R_f$ = 0.45), and its purity was checked by RP-HPLC using $CH_3CN$−$H_2O$ (1:1), but several peaks were observed. Four peaks were collected to afford pure compounds **2** (1.8 mg, $t_R$ = 12.8 min), **3** (3.6 mg, $t_R$ = 14.0 min), **4** (6.2 mg, $t_R$ = 14.8 min), and **5** (8.2 mg, $t_R$ = 22.0 min). Fraction F01705 was also subjected to the same RP-HPLC conditions, and compound **1** (2 mg) was collected as a pure peak with $t_R$ = 11.0 min.

The ethyl acetate extract (6.15 g) of *P. pinnata* stem bark was fractionated into eight fractions (F018−F025) by open column chromatography over silica gel with gradient mixtures of petroleum ether−EtOAc (95:5) to MeOH (100%) for elution. Fractions F018 (CD <2.5 $\mu$g/mL) and F019 (<2.5 $\mu$g/mL) were combined as F019A, based on the similarity of their TLC profiles. From fractions F0019A03 and F019A08, praecansone B[18,19] (7.2 mg) and candidin[15] (11.8 mg) were obtained, respectively. Fraction F019A06 was purified with a mixture of petroleum ether−$CHCl_3$−acetone (9:0.5:0.5) to afford 3′-methoxypongapin[17] (1.9 mg). Fraction F024 was fractionated by Sephadex LH-20 column chromatography using 100% MeOH as eluent. Fraction F02402 was further purified by silica gel open column chromatography with gradient mixtures from petroleum ether−EtOAc (90:1) to MeOH (100%) for elution. Fraction F0240208 was purified by RP-HPLC column chromatography eluted with $CH_3CN$−$H_2O$ (7:3), and candidone[16] (20 mg, $t_R$ = 20 min) and pongapinone B[21] (59 mg, $t_R$ = 12 min) were obtained.

**(2*S*)-5,7-Dimethoxy-8-formylflavanone (1):** yellow oil; $[\alpha]_D$ −28.0° (*c* 0.10, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 264.5 (4.19) nm; CD (MeOH, *c* 64.0 $\mu$M) $\lambda$ nm ($\Delta\epsilon$) 337 (+0.75), 271 (−3.60); IR ($CaCl_2$) $\nu_{max}$ 2359 (CHO), 1676 (C═O), 1584 (C═C) $cm^{-1}$; $^1H$ and $^{13}C$ NMR data, see Table 1; ESIMS *m*/*z* 335 (100) $[M + Na]^+$, 241 (26), 209 (38); HRQTOFMS *m*/*z* 335.0900 (calcd for $C_{18}H_{16}O_5Na$, 335.0895).

**(2*S*)-5,7-Dimethoxy-8-(2*S*-hydroxy-3-methyl-3-butenyl)-3′,4′-methylenedioxyflavanone (2):** yellow oil; $[\alpha]_D$ −36.0° (*c* 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 286.5 (4.69) nm; CD (MeOH, *c* 48.5 $\mu$M) $\lambda$ nm ($\Delta\epsilon$) 337 (+1.06), 293 (−3.04); IR ($CaCl_2$) $\nu_{max}$ 3744 (OH), 1693 (C═O), 1553 (C═C) $cm^{-1}$; $^1H$ and $^{13}C$ NMR data, see Table 2; ESIMS *m*/*z* 435 (100) $[M + Na]^+$, 360 (23), 338 (47), 247 (14); HRQTOFMS *m*/*z* 435.1432 (calcd for $C_{23}H_{24}O_7Na$, 435.1420).

**(2*S*)-5,7-Dimethoxy-8-(2*S*-hydroxy-3-methyl-3-butenyl)-flavanone (3):** yellow oil; $[\alpha]_D$ −22.0° (*c* 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 286.5 (4.82) nm; CD (MeOH, *c* 54.3 $\mu$M) $\lambda$ nm ($\Delta\epsilon$) 343 (+ 2.95), 290 (−7.67); IR ($CaCl_2$) $\nu_{max}$ 3744 (OH), 1658 (C═O), 1563 (C═C) $cm^{-1}$; $^1H$ and $^{13}C$ NMR data, see Table 2; ESIMS *m*/*z* 391 (100) $[M + Na]^+$, 338 (33), 247 (40), 193 (30); HRQTOFMS *m*/*z* found 391.1524 (calcd for $C_{22}H_{24}O_5Na$, 391.1521).

**(2*S*)-5,7-Dimethoxy-8-(2*R*-hydroxy-3-methyl-3-butenyl)-flavanone (4):** yellow oil; $[\alpha]_D$ −33.0° (*c* 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 287.0 (4.99) nm; CD (MeOH, *c* 54.3 $\mu$M) $\lambda$ nm ($\Delta\epsilon$) 339 (+4.36), 287 (−10.13); IR ($CaCl_2$) $\nu_{max}$ 3745 (OH), 1694 (C═O), 1557 (C═C) $cm^{-1}$; $^1H$ and $^{13}C$ NMR data, see Table 2; ESIMS *m*/*z* 391 (100) $[M + Na]^+$, 247 (47), 193 (30); HRQTOFMS *m*/*z* found 391.1540 (calcd for $C_{22}H_{24}O_5Na$, 391.1521).

**5-Methoxy-(3″,4″-dihydro-3″,4″-diacetoxy)-2″,2″-dimethylpyrano-(7,8:5″,6″)-flavone (5):** yellowish gum; $[\alpha]_D$ −26.0° (*c* 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 264.0 (5.14) nm; IR ($CaCl_2$) $\nu_{max}$ 1743 (C═O), 1679 (C═O), 1583 (C═C) $cm^{-1}$; $^1H$ and $^{13}C$ NMR data, see Table 1; ESIMS *m*/*z* 475 (100) $[M + Na]^+$, 393 (65), 351 (58), 297 (55), 240 (51); HRQTOFMS *m*/*z* found 475.1371 (calcd for $C_{25}H_{24}O_8Na$, 475.1369).

**7-Methoxypraecansone B [7,2′,6′-Trimethoxy-6″,6″-dimethylpyrano-(3′,4′:2″,3″)-chalcone] (6):** yellow oil; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 278.5 (4.30) nm; IR ($CaCl_2$) $\nu_{max}$ 1604 (C═O), 1571 (C═C) $cm^{-1}$; $^1H$ and $^{13}C$ NMR data, see Table 1; ESIMS *m*/*z* 381 (100) $[M + H]^+$, 247 (47), 161 (10); HRQTOFMS *m*/*z* found 403.1517 (calcd for $C_{23}H_{24}O_5Na$, 403.1521).

**Preparation of the (*R*)- and (*S*)-MTPA Ester Derivatives of 2−4.** Compounds **2** (0.3 mg), **3** (0.3 mg), and **4** (1 mg)

were treated with (*S*)-(+)α- and (*R*)-(−)α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (2 $\mu$L, 2 $\mu$L, and 3 $\mu$L) in anhydrous pyridine-$d_5$ (0.5 mL) and 0.2 mg of (dimethylamino)-pyridine at room temperature for 4 h and afforded the (*R*)- and (*S*)-MTPA ester derivatives (**2r**, **2s**, **3r**, **3s**, **4r**, and **4s**) of **2**, **3**, and **4**, respectively. The procedure was performed in NMR tubes to avoid the need to purify these derivatives.[31] Calculation of these differences allowed the assignment of the absolute stereochemistry of its respective compound of origin (Table 3).[32,33]

**Detection of Compound 5 in the Petroleum Ether Extract of *P. pinnata* Stem Bark.** To confirm whether compound **5** is a naturally occurring compound, a diluted aliquot of 20 $\mu$L of the crude petroleum ether extract dissolved in a mixture of hexane−2-propanol−methanol (9:0.5:0.5) was injected into the same RP-HPLC column under the same conditions as compound **5**. The peak observed at the same retention time ($t_R$ = 22.0 min) as compound **5** was collected and submitted to mass spectral analysis: ESIMS *m*/*z* 453.2 $[M + H]^+$; 474.9 $[M + Na]^+$.

**Quinone Reductase Assay.** The isolates were evaluated for their ability to act as phase II enzyme inducers using cultured Hepa 1c1c7 mouse hepatoma cells. Enzyme activity was expressed as the concentration required to double the specific activity of quinone reductase represented by a CD value. The half-maximum inhibitory concentration of cell viability ($IC_{50}$ value) was determined, and the chemoprevention index (CI) values were calculated by dividing $IC_{50}$ values by the CD values obtained using the quinone reductase assay. The assay was performed by the method described previously.[14,34]

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of compounds **1**−**6** in $CDCl_3$ and $^1$H NMR spectra of the (*R*)- and (*S*)-MTPA esters of compound **3** in pyridine-$d_5$. This information is available free of charge via the Internet at http://pubs.acs.org.

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