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Antiplatelet prenylflavonoids from *Artocarpus communis*

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Abstract

Four flavonoids, dihydroartomunoxanthone (**1**), artomunoisoxanthone (**2**), cyclocomunomethonol (**3**) and artomunoflavanone (**4**), together with three known compounds, artochamins B (**5**), D and artocommunol CC (**6**) were isolated from the cortex of the roots of *Artocarpus communis*. The structures of **1**–**4** were determined by spectroscopic methods. The antiplatelet effects of the flavonoids, **1**–**3, 5** and **6** on human platelet-rich plasma (PRP) were evaluated. Of the compounds tested in human PRP, compounds **1**, **5** and **6** showed significant inhibition of secondary aggregation induced by adrenaline. It is concluded that the antiplatelet effect of **1**, **5** and **6** is mainly owing to an inhibitory effect on thromboxane formation.
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Keywords: *Artocarpus communis*; Moraceae; Flavonoids; Moraceae; Antiplatelet effect

1. Introduction

In previous papers, we have reported isolation of flavonoids from the acetone and $CHCl_3$ extracts of the root bark of *Artocarpus communis* Forst. (Moraceae), respectively (Chan et al., 2003) and their antiplatelet, cytotoxic and anti-inflammatory effects (Lin et al., 1993; Liou et al., 1993; Wei et al., 2005). In particular, prenylflavonoids isolated from *A. communis* revealed significant antiplatelet effects (Lin et al., 1993). To study the structure–antiplatelet activity relationship of various prenylflavonoids isolated from *Artocarpus* species, we have further investigated the constituents of the root bark of Formosan *A. communis* and isolated four new flavonoids, dihydroartomunoxanthone (**1**), artomunoisoxanthone (**2**), cyclocomunomethonol (**3**), and artomunoflavanone (**4**), along with three known compounds, artochamins B (**5**) and D, and cyclocommunol CC (**6**) (Wang et al., 2004; Chan et al., 2003). In the present paper, the structure elucidation of these four new compounds, **1**–**4** and the antiplatelet effect of these additional constituents of *A. communis* on human PRP are reported. Insufficient amounts of compound **4** and artocomin D were obtained for biological testing.

2. Results and discussion

The HREIMS of **1** revealed a $[M]^+$ peak at m/z 450.0738, which corresponded to a molecular formula of $C_{26}H_{26}O_7$. The IR spectra of **1** showed hydroxyl and chelated carbonyl absorption bands at 3284 and 1648 cm^{-1}, respectively. The UV spectrum of **1** exhibited absorption maxima (220, 260, and 375 nm) was consistent with that of a flavone structure (Lin and Shieh, 1991). The ^1H and ^{13}C NMR spectra (Table 1) were similar to those of artochamin E except for C-3′, C-4′ and the presence of an additional methoxyl group (Wang

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Table 1
^{13}C NMR spectroscopic chemical shifts of compounds **1**–**4**[a]

Carbon	**1**[b]	**2**[b]	**3**[b]	**4**[b]
2	162.0	162.4	158.7	72.9
3	112.4	112.0	110.7	40.7
4	182.1	181.9	179.7	198.7
4a	105.7	106.0	107.9	103.1
5	161.5	163.2	158.7	165.5
6	99.8	100.3	100.4	96.5
7	162.3	160.4	165.3	167.0
8	107.8	102.4	95.6	95.6
8a	155.9	152.9	164.0	165.4
9	22.9	22.9	70.6	
10	38.4	38.8	122.7	
11	146.0	145.9	139.4	
12	22.7	22.6	19.3	
13	112.4	112.5	26.5	
14	23.0	117.3		
15	124.1	127.3		
16	133.0	81.8		
17	26.5	42.8		
18	18.7	24.1		
19		125.5		
20		132.8		
21		18.3		
22		26.5		
23		27.7		
1′	108.0	107.7	110.7	105.7
2′	151.6	152.1	153.8	158.7
3′	100.8	104.3	106.1	95.1
4′	152.9	151.5	154.4	162.8
5′	138.1	137.3	139.4	91.5
6′	128.9	130.5	107.7	161.1
OMe-4′	56.9			55.5
OMe-5′			57.6	
OMe-6′				56.1

[a] The number of protons directly attached to each carbon was verified by DEPT and HMQC experiments.
[b] Measured in acetone-d_6.

et al., 2004). The HMBC correlations of OMe-4′/C-4′ and H-3′/C-1′, C-2′, C-4′ and C-5′ confirmed that the methoxyl group was linked at C-4′. In addition, the UV spectrum of **1** showed no bathochromic shift upon addition of NaOMe. From the above data, dihydroartomunoxanthone (**1**) was identified as 5,6-dihydro-1,4,8,10-tetrahydroxy-3-methoxyl-5-(1-methylethenyl)-11-(3-methyl-2-butenyl)-7*H*-benzo[*c*]-xanthen-7-one (**1**).

The HRESIMS of **2** gave a $[M+1]^+$ peak at *m*/*z* 503.2068, which corresponded to a molecular formula of $C_{30}H_{30}O_7$. The IR spectra showed hydroxyl and chelated carbonyl absorption bands at 3397 and 1652 cm^{-1}, respectively. The UV spectrum of **2** exhibited absorption maxima similar to those of artochamin E (Wang et al., 2004). The ^{1}H NMR spectroscopic data of **2** (Experimental) was very similar to that of artochamin E (Wang et al., 2004) except for the lack of signals due to a prenyl group and five phenolic groups, and the appearance of resonances due to a 2-methyl-2-(4-methylpent-3-enyl) 2*H*-pyran ring and four phenolic groups. The ^{13}C NMR spectroscopic data of **2** (Table 1) were similar to those of artochamin E (Wang et al., 2004), except for the carbon signals of C-4a, C-8a, C-5 to C-8, and C-14 to C-23. The COSY correlation of H_2-17/H_2-18 and H-14/H-15, and the HMBC correlations of H_2-17/C-15, C-16 and C-19, C-20/Me-21 and Me-22 and H_2-18/C-19 and C-20 confirmed that the 4-methyl-pent-3-enyl group was linked at C-16. In addition, the UV spectrum of **2** indicated bathochromic shifts upon addition of $AlCl_3$, NaOMe and NaOAc–H_3BO_3. The NOESY experiment of cross-peaks between H_β-9/H_a-13 and Me-23/H_β-17 confirmed that both the hydrogen atom at C-10 and methyl group at C-16 are on the α- and β-side in **2**, respectively. On the basis of the above evidence, artomunoisoxanthone (**2**) was identified as 5α,6,11-trihydro-1,3,4,8-tetrahydroxy-5-(1-methylethenyl)-11β-methyl-11-(4-methyl-3-pentenyl)-benzo[1,2:*a*]pyrano[2′,3′:*j*]xanthen-7-one (**2**).

The HRESIMS of **3** gave a $[M+1]^+$ peak at *m*/*z* 383.1131, which corresponded to a molecular formula of $C_{21}H_{18}O_7$. The IR spectra showed hydroxyl and chelated carbonyl absorption bands at 3381 and 1651 cm^{-1}, respectively. The UV spectrum of **3** was identical to that of cyclochampedol (Achmad et al., 1996). The ^{1}H NMR spectrum of **3** was similar to that of cyclochampedol, except for the appearance of an additional signals due to a methoxyl group (Achmad et al., 1996). In the ^{13}C NMR spectra of **3** (Table 1), the chemical shift values of C-2 to C-4, C-4a, C-5 to C-8, C-8a, and C-9 to C-13 were almost identical to corresponding data for cyclochamperol except for C-1′ to C-6′ and the presence of an additional carbon resonance due to a methoxyl groups (Achmad et al., 1996). In addition, the UV spectrum of **3** indicated bathochromic shifts upon addition of $AlCl_3$, NaOAc and NaOMe. Thus, the structure of cyclocomunomethonol (**3**) was 3,8,10-trihydroxy-2-methoxy-6-(2-methyl-1-propenyl)-6*H*,7*H*-[1]benzopyrano[4,3- *b*][1]benzopyran-7-one (**3**).

The HRESIMS of **4** gave a $[M+1]^+$ peak at *m*/*z* 333.0974, which corresponded to a molecular formula of $C_{17}H_{16}O_7$. The IR spectra showed hydroxyl and chelated carbonyl absorption bands at 3417 and 1635 cm^{-1}. The ^{1}H NMR spectroscopic data (Experimental) were very similar to those of heteroflavanone A (Lu and Lin, 1993) except for the proton signals of methoxyl and phenolic groups. The ^{1}H NMR spectrum (Experimental) of **4** showed three protons at δ 5.93 (*dd*, $J = 14.0$, 3.0 Hz), 3.90 (*dd*, $J = 17.4$, 14.0 Hz), and 2.44 (*dd*, $J = 17.4$, 3.0 Hz), attributed to the H-2, H-3$_{ax}$, and H-3$_{eq}$ of a flavanone, two methoxyl signals at δ 3.76 and 3.81, one pair of meta-coupled doublets at δ 5.89, 5.91 ($J = 2.2$ Hz, each), three phenolic proton resonances at δ 8.68, 9.55 and 12.31. The UV spectrum of **4** has a similar UV maxima to that of heteroflavanone (Lu and Lin, 1993), and showed bathochromic shifts upon addition to $AlCl_3$ and NaOAc. In addition, the UV spectrum of **4** did not display a bathchromic shift upon addition of NaOMe. On the basis of the above evidence, compound **4** was suggested to be a 2′,5,7-trihydroxy-4′,6′-dimethoxy flavanone or a 6′,5,7-trihydroxy-2′,4′-dimethoxy-flavanone. The HMBC correlations

Table 2
Antiplatelet effect of prenylflavonoids, **1**, **2**, **3**, **5** and **6**, and aspirin on adrenaline-induced aggregation in human PRP

Compound	Aggregation (%)
Control	96.1 ± 1.3
1	46.8 ± 23.6*
2	92.7 ± 1.1
3	83.1 ± 0.4
5	51.0 ± 3.8**
6	65.6 ± 8.9**
Aspirin	29.5 ± 1.0*

Human PRP was pre-incubated with dimethylsulfoxide (0.5%, control), **1**–**3**, **5**–**6** (each at 300 μM) or aspirin (50 μM) at 37 °C for 3 min, and then adrenaline (5 μM) was added. Data are presented as means ± s.e.m. ($n = 3$).
* $p < 0.05$.
** $p < 0.01$: compared with the control.

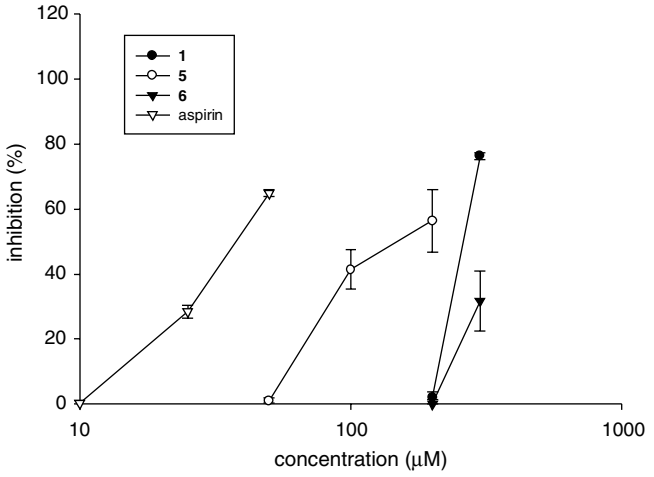


Fig. 1. Concentration–dependent inhibitory effect of compounds **1**, **5**, **6** and aspirin on platelet aggregation induced by adrenaline in human PRP. Human PRP was incubated with various concentrations of compounds **1**, **5**, **6,** aspirin or dimethylsulfoxide (0.5%) at 37 °C for 3 min, and then adrenaline (5 μM) was added to trigger aggregation. Data are presented as means ± s.e.m. ($n = 3$).

of OH-2′/C-1′, C-2′ and C-3′ established the structure of artomunoflavanone (**4**) as 5,7,2′-trihydroxy-4′,6′-dimethoxyflavanone (**4**). The ^{13}C NMR spectrum of **4** (Table 1) was assigned by 1D, 2D, and compared with the relevant carbon of heteroflavanone A (Lu and Lin, 1993).

The antiplatelet effects of **1**–**3**, **5** and **6** on platelet aggregation induced by adrenaline (5 μM) in human PRP were studied. As shown in Table 2 and Fig. 1, compounds **1**, **5** and **6** (each at 300 μM) had significant antiplatelet effects on adrenaline-induced platelet aggregation. This effect appeared to be concentration-dependent. Aspirin (50 μM) strongly inhibited platelet aggregation induced by adrenaline in human PRP. In adrenaline-induced platelet aggregation, compounds **1**, **5** and **6** prevented secondary aggregation (i.e., **5** in Fig. 2). It indicated that the antiplatelet effects of **1**, **5** and **6** are probably mediated through the suppression of cyclooxygenese-1 (COX-1) activity and reduced thromboxane formation or owing to the inhibition of thromboxane synthase, leading to reduced thromboxane formation (Mitchell and Sharp, 1964; Mustand et al., 1975; Weiss, 1983). Previously we had reported that prenylflavonoid, cyclocommunin and cycloheterophyllin revealed potent suppression of thromboxane induced by arachidonic acid and potent inhibitory effect on the aggregation of human PRP induced by adrenaline (Lin et al., 1993, 1996), respectively. It clearly indicated the prenylflavonoid, such as **1**, **3**, **5** and the above two compounds indicated stronger antiplatelet effect probably mediated through the suppression of COX-1 activity than that of dihydrobenzoxanthones, such as compound **1**. Compound **3** demethylated at C-5′ and prenylated at C-4 (i.e., **5**), enhanced the inhibitory effect on the aggregation in human PRP induced by adrenaline.

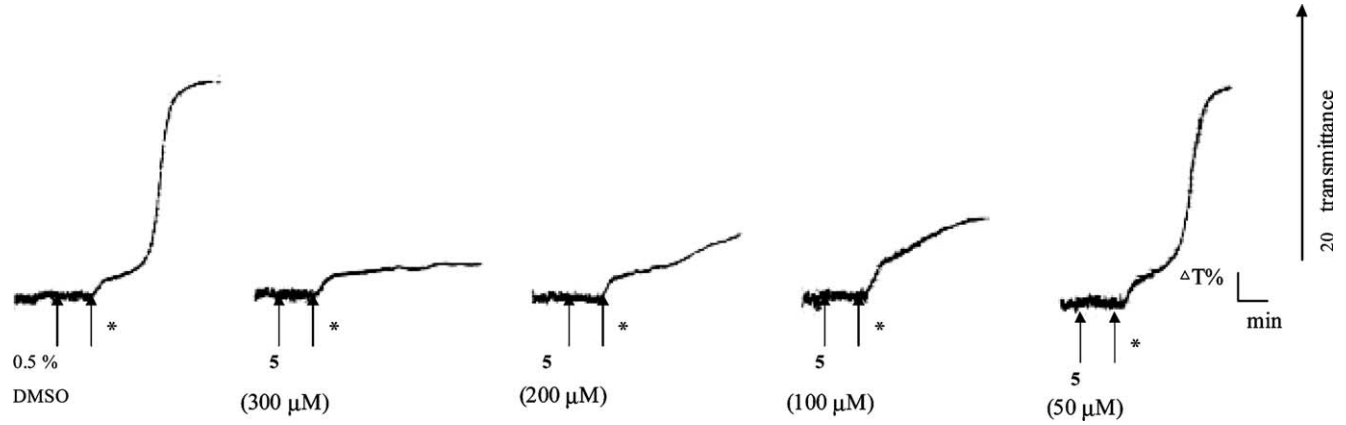
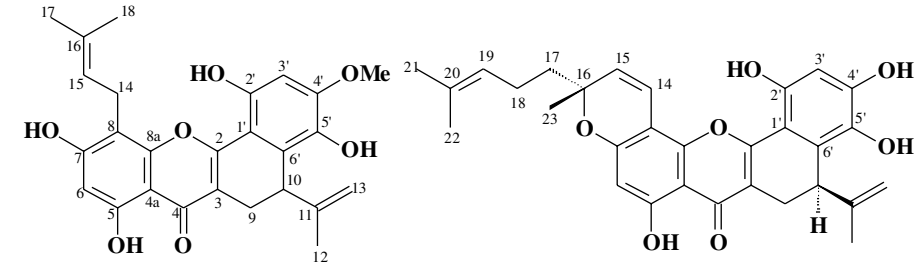


Fig. 2. Effect of compound **5** on the aggregation of human PRP induced by adrenaline. Human platelet-rich plasma was pre-incubated with dimethysulfoxide (0.5%, control) or various concentrations of **5** for 3 min, and then adrenaline (5 μM) was added to trigger aggregation. *Adrenaline added here to trigger platelet aggregation.



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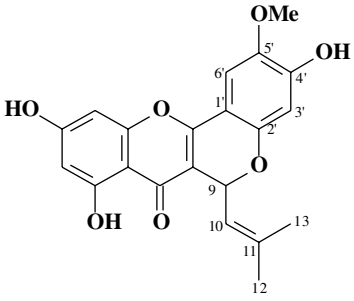

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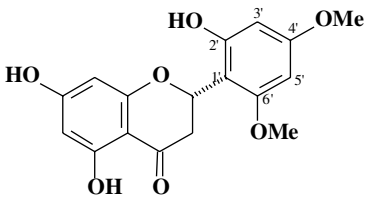

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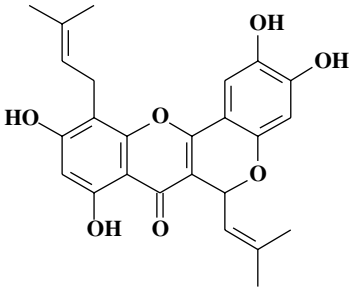

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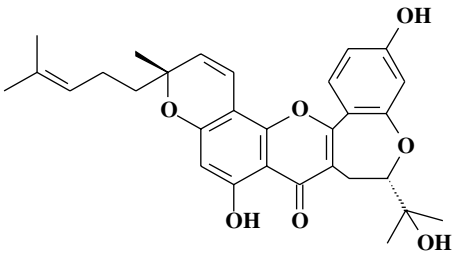

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3. Experimental

3.1. General

Optical rotations were obtained on a JASCO model DIP-370 digital polarimeter. UV spectra were obtained on a JASCO UV–Vis spectrophotometer. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrophotometer. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Unity-400 NMR spectrophotometer. MS were obtained on a JMS-HX100 mass spectrometer.

3.2. Plant material

The root of *A. communis* (13.5 kg) were collected at Kaohsiung Hsien, Taiwan, during November, 2001, and a voucher specimen (2001-3) has been deposited in the Department of Medicinal Chemistry.

3.3. Extraction and isolation of compounds

The cortex of the roots (0.38 kg) of *A. communis* was chipped and extracted with $CHCl_3$ (5 L) at room temperature. The $CHCl_3$ extract of the cortex was applied to a Si gel column, eluted with $CHCl_3$–EtOAc (4:1) to first yield **5** (10 mg), artochamin D (2 mg) and **6** (50 mg), and then with EtOAc to afford a brown residue. The latter was applied to a RP-18 column (30 cm × 10 mm, acetone–H_2O (2:1) yield **1** (10 mg) and **3** (15 mg)), following which elution with acetone–H_2O (2:3) yielded **2** (5 mg) and **4** (2 mg). The known compounds, artochamins B (**5**) and D, and artocommunol CC (**6**) were identified by spectroscopic methods and comparison with the spectroscopic data reported in literature (Wang et al., 2004; Chan et al., 2003).

3.3.1. Dihydroartomunoxanthone (*1*)

Orange powder; $[\alpha]_D^{25} = +33$ (acetone, *c* 1.0); UV (MeOH) λ_{max}nm (log ε): 220 (4.90), 260 (4.84), 375 (4.68), (MeOH–$AlCl_3$) 250 (5.08), 330 (4.47), 420 (4.69), (MeOH–NaOAc) unchanged, (MeOH–NaOAc–H_3BO_3) unchanged, (MeOH–NaOMe) unchanged; IR (KBr) $\nu_{max}cm^{-1}$: 3284, 1648, 1612; ^{1}H NMR (400 MHz, acetone-d_6): δ 1.62 (3H, *s*, Me-17), 1.78 (6H, *s*, Me-12 and Me-18), 2.44 (1H, *dd*, $J = 16.0$, 6.8 Hz, H_2-9), 3.41 (1H, *dd*, $J = 16.0$, 2.0 Hz, H_2-9), 3.43 (1H, *bd*, $J = 14.8$, 6.4 Hz, H_2-14), 3.66 (1H, *dd*, $J = 14.8$, 7.6 Hz, H_2-14),

3.91 (3H, *s*, OMe-4′), 4.01 (1H, *bd*, $J = 6.4$ Hz, H-10), 4.29 (1H, *s*, H_2-13), 4.64 (1H, *s*, H_2-13), 5.28 (1H, *bt*, $J = 7.5$ Hz, H-15), 6.31 (1H, *s*, H-6), 6.60 (1H, *s*, H-3′), 7.38 (1H, *s*, OH-5′), 8.34 (1H, *s*, OH-2′), 9.47 (1H, *s*, OH-7), 13.20 (1H, *s*, OH-5); For ^{13}C NMR spectrum (100 MHz, acetone-d_6), see Table 1; EIMS (70 eV) *m*/*z* (rel. int.) 450 $[M]^+$ (28), 432 (11), 394 (100), 364 (6), 350 (26); HR-EIMS, found: 450.0738 $(M)^+$, calculated: 450.1678 (for $C_{26}H_{26}O_7$).

3.3.2. Artomunoisoxanthone (*2*)

Yellow powder; $[\alpha]_D^{25} = +58$ (acetone, *c* 1.0); UV (MeOH) λ_{max}nm (log ε): 213 (4.63), 270 (4.61), 380 (0.28), (MeOH–$AlCl_3$) 250 (5.16), 450 (4.06), (MeOH–NaOAc) unchanged, (MeOH–NaOAc–H_3BO_3) 256 (4.65), 280 (4.47), 406 (3.87), (MeOH–NaOMe) 270 (4.44), 345 (4.00), 460 (3.54); IR (KBr) ν_{max} cm^{-1}: 3397, 1652; ^1H NMR (400 MHz, acetone-d_6): δ 1.41 (3H, *s*, Me-23), 1.56 (3H, *s*, Me-21), 1.63 (3H, *s*, Me-22), 1.71 (1H, *m*, H_α-17), 1.76 (1H, *m*, H_β-17), 1.78 (3H, *s*, Me-12), 2.12 (2H, *m*, H_2-18), 2.44 (1H, *dd*, $J = 16.0$, 6.8 Hz, H_2-9), 3.41 (1H, *dd*, $J = 16.0$, 2.0 Hz, H_2-9), 4.00 (1H, *bd*, $J = 6.8$ Hz, H-10), 4.30 (1H, *s*, H_a-13), 4.65 (1H, *s*, H_b-13), 5.12 (1H, *bt*, $J = 7.5$ Hz, H-19), 5.64 (1H, *d*, $J = 10.4$ Hz, H-15), 6.13 (1H, *s*, H-6), 6.59 (1H, *s*, H-3′), 6.97 (1H, *d*, $J = 10.4$ Hz, H-14), 8.64 (1H, *s*, OH-2′), 13.37 (1H, *s*, OH-5); For ^{13}C NMR spectrum (100 MHz, acetone-d_6), see Table 1; FABMS (70 eV) *m*/*z* (rel. int.): 503 $[M + 1]^+$ (3), 419 (3), 154 (100); HR-ESIMS, found: 503.2068 $(M + 1)^+$, calculated: 503.2069 (for $C_{30}H_{30}O_7$).

3.3.3. Cyclocomunomethonol (*3*)

Yellow powder; $[\alpha]_D^{25} = +103$ (acetone, *c* 1.0); UV (MeOH) λ_{max} nm (log ε): 215 (4.55), 260 (4.33), 390 (4.11), (MeOH–$AlCl_3$) 276 (4.58), 422 (4.16), (MeOH–NaOAc) 256 (4.29), 402 (4.12), (MeOH–NaOAc–H_3BO_3) unchanged, (MeOH–NaOMe) 275 (4.33), 420 (4.19); IR (KBr) ν_{max} cm^{-1}: 3381, 1651; ^1H NMR (400 MHz, acetone-d_6): δ 1.68 (3H, *d*, $J = 1.2$ Hz, Me-12), 1.93 (3H, *d*, $J = 1.2$ Hz, Me-13), 3.91 (3H, *s*, OMe-5′), 5.49 (1H, *bd*, $J = 9.2$ Hz, H-10), 6.16 (1H, *d*, $J = 9.2$ Hz, H-9), 6.25 (1H, *d*, $J = 2.0$ Hz, H-6), 6.46 (1H, *s*, H-3′), 6.51 (1H, *d*, $J = 2.0$ Hz, H-8), 7.37 (1H, *s*, H-6′), 12.90 (1H, *s*, OH-5); For ^{13}C NMR spectrum (100 MHz, acetone-d_6), see Table 1; EIMS (70 eV) *m*/*z* (rel. int.): 382 $[M]^+$ (22), 367 (47), 327 (67), 153 (19), 115 (30), 69 (100); HR-ESIMS, found: 383.1131 $(M + 1)^+$, calculated: 383.1130 (for $C_{21}H_{18}O_7$,).

3.3.4. Artomunoflavanone (*4*)

Yellowish powder; $[\alpha]_D^{25} = +344$ (acetone, *c* 0.1); UV (MeOH) λ_{max} nm (log ε): 213 (4.52), 280 (4.34), (MeOH–$AlCl_3$) 250 (4.82), 305 (4.49), (MeOH–NaOAc) 285 (4.14), 310 (4.24), (MeOH–NaOAc–H_3BO_3) unchanged, (MeOH–NaOMe) unchanged; IR (KBr) $\nu_{max}cm^{-1}$: 3417, 1635 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6), δ 2.44 (1H, *dd*,$J = 17.4$, 3.0 Hz, H_{eq}-3), 3.76 (3H, *s*, OMe-4′), 3.81 (3H, *s*, OMe-6′), 3.90 (1H, *dd*, $J = 17.4$, 14.1 Hz, H_{ax}-3), 5.91 (1H, *d*, $J = 2.2$ Hz, H-6), 5.89 (1H, *d*, $J = 2.2$ Hz, H-8), 5.93 (1H, *dd*, $J = 14.0$, 3.0 Hz, H_{ax}-2), 6.17 (1H, *d*, $J = 2.2$ Hz, H-5′), 6.17 (1H, *d*, $J = 2.2$ Hz, H-3′), 8.68 (1H, *s*, OH-2′), 9.55 (1H, *s*, OH-7), 12.31 (1H, *s*, OH-5); For ^{13}C NMR spectrum (100 MHz, acetone-d_6), see Table 1; EIMS (70 eV) *m*/*z* (rel. int.): 332 $[M]^+$ (8), 314 (100), 286 (8), 230 (49), 178 (36), 165 (30); HR-ESIMS, found: 333.0978 $(M + 1)^+$, calculated: 333.0974 (for $C_{17}H_{16}O_7$).

3.3.5. Platelet aggregation

Platelet aggregation in human PRP was performed by the method described previously (Ko et al., 2004).

3.3.6. Data analysis

Data are presented as means ± s.e.m. One-way analysis of variance was used for multiple comparison, and if there was significant variation between the treatment groups and the inhibitor-treated groups, they were then compared with the control group by student's *t*-test. Values of $P < 0.05$ were considered statistically significant.

4. Conclusions

In the present study, we had further isolated four new flavonoids. In human PRP, compounds **1**, **5** and **6** showed significant inhibition of secondary aggregation induced by adrenaline. It indicates that the antiplatelet effects of **1**, **5** and **6** owe to an inhibitory effect on thromboxane formation (Mitchell and Sharp, 1964; Mustand et al., 1975; Weiss, 1983). Platelet aggregation is an important pathogenic factor in the development of atherosclerosis and associated thrombosis in humans (Ko et al., 2004). Therefore, compounds **1**, **5** and **6** show promise as antithrombotic agents.

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