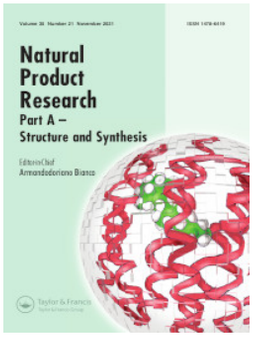

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New flavonoids and xanthone from the stem bark of *Artocarpus rigidus* blume and cytotoxicity

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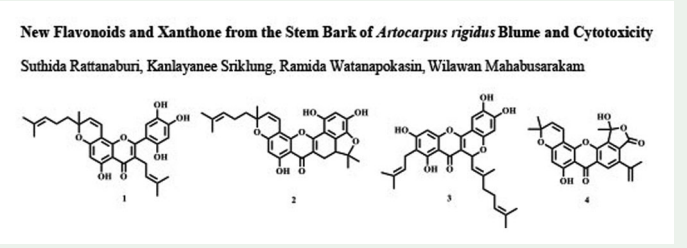
ABSTRACT

Three new flavonoids named artorigidinones A–C and a new xanthone named artorixanthone together with seven known compounds were isolated from the stem bark of *Artocarpus rigidus* Blume. Their structures were characterized by spectroscopic data. γ-Geranylapigenin exhibited cytotoxicity to a fibroblast-like cell line (SW1353) ($IC_{50} < 0.32\ \mu g/mL$) stronger than a standard drug.



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Moraceae; *Artocarpus rigidus*; flavonoids; xanthones; cytotoxicity

1. Introduction

The *Artocarpus* genus (Moraceae) is a rich source of prenylated flavonoids (Cao et al. 2003; Ma et al. 2010; Ren et al. 2013; Abdullah et al. 2017). Many of these compounds have been reported to show strong cytotoxicity against several cancer cell lines (Dat et al. 2010; Ren et al., 2010). The root bark of *Artocarpus rigidus* has previously been found to contain cytotoxic prenylated flavonoids (Namdaung et al. 2006). However, there are no reports on a phytochemical study and cytotoxicity of the other plant parts. Preliminary cytotoxicity tests showed that the CH_2Cl_2 extract of the stem bark of *A. rigidus* inhibited the growth of human melanoma (SK-MEL-28), human keratinocyte (HaCaT), human lung adenocarcinoma epithelial (A549), human epidermoid carcinoma

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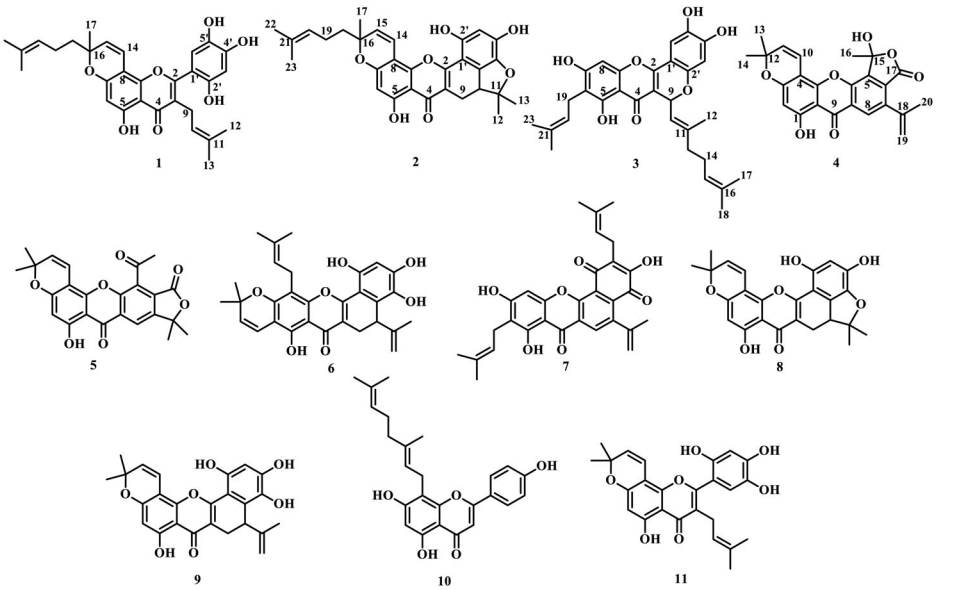

Figure 1. The structures of compounds **1–11**.

(A431), and human bone chondrosarcoma, fibroblast-like (SW1353) cell lines with IC_{50} value of 5.81, 10.64, 20.47 10.89, 6.21 μg/mL, respectively. These findings prompted the isolation and identification of the compounds from the extract of the bark of *A. rigidus*.

2. Results and discussion

The CH_2Cl_2 extract from the stem bark of *A. rigidus* was fractionated and purified by column chromatography resulting in the isolation of four new compounds named artorigidinone A-C (**1**–**3**) and artorixanthone (**4**), along with artonol B (**5**) (Aida et al. 1997), artonin B (**6** Chung et al. 1995), artonin O (**7**) (Hano et al. 1990), cycloartobiloxanthone (**8**) (Uvais et al. 1989), artobiloxanthone (**9**) (Jayasinghe et al. 2008), γ-geranylapigenin (**10**) (Fukai and Nomura 1991) and artonin E (**11**) (Hano et al. 1993) (Figure 1). All structures were determined from analysis of their ^1H, ^{13}C NMR, COSY, HMQC and HMBC spectra and from comparisons with previous reports.

Artorigidinone A (**1**), was obtained as a yellow-brown gum, $[\alpha]^{25}_D$ +0.7 (c 0.02, MeOH). The UV spectrum showed maximum absorptions at 225 (3.37), 265 (3.56), 302 (3.06), 392 (2.74) nm, corresponding to a C-3 prenylated flavone chromophore (Wang et al. 2004). The IR spectrum showed stretching bands for hydroxyl (3317 cm^{-1}) and carbonyl groups (1650 cm^{-1}). The HRESIMS gave an $[M+H]^+$ ion at *m/z* 505.2209 ($C_{30}H_{32}O_7$). The ^{13}C NMR spectrum showed the resonances for one carbonyl (δ 182.4, C-4), five methyls (δ 16.7, C-12; δ 24.8, C-13; δ 26.2, C-17; δ 24.9, C-22; δ 16.7, C-23), three methylenes (δ 23.8, C-9; δ 41.2, C-18; δ 22.4, C-19), seven methines (δ 98.6, C-6; δ 121.6, C-10; δ 115.0, C-14; δ 126.0, C-15; δ 123.7, C-20; δ 103.8, C-3′; δ 116.2, C-6′), and fourteen quaternary carbons (δ 161.2, C-2; δ 120.8, C-3; δ 104.6, C-4a; δ 161.9, C-5; δ 159.4, C-7; δ 100.5, C-8; δ 152.4, C-8a; δ 131.4, C-11; δ 80.4, C-16; δ 131.3, C-21; δ

110.6, C-1′; δ 148.9, C-2′; δ 148.6, C-4′; δ 138.2, C-5′). The ^{1}H NMR spectrum exhibited the resonances for a hydrogen-bonded hydroxyl proton 5-OH (δ 13.26, *s*) and aromatic protons H-6 (δ 6.16, *s*), H-3′ (δ 6.60, *s*) and H-6′ (δ 6.89, *s*). The HMBC correlations of 5-OH to C-6 and C-4a; H-6 to C-4a and C-8; H-3′ to C-1′ and C-5′; and H-6′ to C-2, C-2′ and C-4′ confirmed the placement of aromatic protons. The resonances for methine H-10 (δ 5.12, *t*) and methylenes H-9 (δ 3.15, *d*) with $J = 7.2$ Hz, and methyl protons H-12 (δ 1.58, *s*) and H-13 (δ 1.46, *s*), along with the HMBC correlations of H-9 to C-11, and H-12 and H-13 to C-10 revealed the characteristic signals of a prenyl group. The HMBC correlation of H-9 to C-2 and C-4 suggested its position at C-3. The remaining signals including olefenic methines H-14, H-15 (δ 6.66, δ 5.64, both *d* with $J = 10.2$ Hz,) and H-20 (δ 5.14, *t*, $J = 7.2$ Hz), methylenes H-18 (δ 1.75, *m*) and H-19 (δ 2.13, *m*), and methyl protons H-17 (δ 1.43, *s*), H-22 (δ 1.64, *s*) and H-23 (δ 1.56, *s*) were assigned for 2-methyl-2-(4-methylpent-3-enyl)pyran moiety. The HMBC correlations of H-22 and H-23 to C-20, H-17 to C-15 and C-18, H-14 to C-7, C-8a and C-16, and H-15 to C-8 and C-18 confirmed the pyran moiety, and suggested its location at C-7 and C-8. The spectral data of **1** was closely related to those of artonin E (**11**) (Hano et al. 1990). Artorigidinone A was therefore identified as 5-hydroxy-8-methyl-3-(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl)-2-(2,4,5-trihydroxyphenyl)pyrano[2,3-*f*]chromen-4(8H)-one.

Artorigidinone B (**2**), was obtained as a yellow-brown gum, $[\alpha]^{25}{}_{D}$ +3.5 (c 0.12, MeOH). The HRESIMS gave an $[M + H]^{+}$ ion at *m/z* 503.2067 ($C_{30}H_{30}O_7$). The UV spectrum showed maximum absorptions at 228 (3.93), 275 (3.89), 319 (3.48), 389 (3.56) nm. The IR spectrum showed absorption band for hydroxy (3270 cm^{-1}), and conjugated carbonyl (1651 cm^{-1}) stretching. The ^{13}C NMR spectrum of **2** showed the resonances for one carbonyl (δ 180.5,C-4), five methyls (δ 27.4, C-12; δ 21.9, C-13; δ 26.4, C-17; δ 24.8, C-22; δ 16.7, C-23), three methylenes (δ 19.5, C-9; δ 41.3, C-18; δ 22.5, C-19), six methines (δ 98.8, C-6; δ 46.7, C-10; δ 115.5, C-14; δ 125.9, C-15; δ 123.9, C-20; δ 104.6, C-3′), and fifteen quaternary carbons (δ 160.8, C-2; δ 111.8, C-3; δ 104.1, C-4a; δ 161.8, C-5; δ 159.0, C-7; δ 100.8, C-8; δ 151.2, C-8a; δ 92.8, C-11; δ 80.4, C-16; δ 132.8, C-21; δ 104.4, C-1′; δ 150.6, C-2′; δ 146.1, C-4′; δ 137.1, C-5′; δ 131.3, C-6′). The ^{1}H NMR spectrum and HMBC correlations indicated that **2** contained 5-OH (δ 13.38) , 2′-OH (δ 8.79), 4′-OH (δ 8.94), H-6 (δ 6.14), H-3′ (δ 6.41) and 2-methyl-2-(4-methylpent-3-enyl)pyran moiety (δ 6.97, *d*, $J = 9.9$ Hz, H-14; δ 5.64, *d*, $J = 9.9$ Hz, H-15; δ 1.44, *s*, H-17; δ 1.76, *m*, H-18; δ 2.12, *m*, H-19; δ 5.11, *br t*, H-20; δ 1.63, *s*, H-22 and δ 1.56, *s*, H-23) as found in **1**. The remaining resonances at δ 3.21 (*dd*, $J = 15.0$, 6.9 Hz), δ 2.36 (*t*, $J = 15.0$ Hz), δ 3.42 (*dd*, $J = 15.0$, 6.9 Hz), δ 1.66 (*s*) and δ 1.32 (*s*) were assigned for methylenes H_{eq}-9 and H_{ax}-9, methine H-10, and methyl protons H-12 and H-13, respectively. The HMBC correlations of H_{ax}-9 and H_{eq}-9 to C-2, C-4 and C-6′, and H-10 to C-1′, C-5′, C-12 and C-13 suggested that **2** was xanthone derivative related to cycloartobioxanthone (**8**) (Uvais et al. 1989). The NOE experiment that irradiation at the resonance H-10 enhanced the H_{eq}-9 and H-12 signals, and irradiation at the resonance H_{eq}-9 effected the H-13 signals further indicated that the arrangement of H_{eq}-9, H-10 and H-12 on the same face. Artorigidinone B was then suggested as 1,3,8-trihydroxy-5,5,11-trimethyl-11-(4-methylpent-3-en-1-yl)-5a,6-dihydro-5H-benzofuro[3,4-bc]pyrano[3,2-h]xanthen-7(11H)-one.

Artorigidinone C **(3),** was a yellow solid with $[\alpha]^{25}_{D}$ +29 (c 0.39, MeOH) and the HRESIMS $[M+H]^+$ *m/z* 505.2228 ($C_{30}H_{32}O_7$). The UV spectrum showed maximum absorptions at 266 (4.34), 300 (4.13), 382 (4.06) nm. The ^{13}C NMR spectrum of **3** showed the resonances of one carbonyl (δ 178.2, C-4), five methyls (δ 16.2, C-12; δ 16.8, C-17; δ 24.8, C-18; δ 17.0, C-22; δ 25.9, C-23), three methylenes (δ 39.2, C-13; δ 25.9, C-14; δ 21.1, C-19), seven methines (δ 93.2, C-8; δ 69.0, C-9; δ 121.2, C-10; δ 123.6, C-15; δ 122.3, C-20; δ 104.4, C-3′; δ 109.4, C-6′), and fourteen quaternary carbons (δ 156.5, C-2; 109.0, C-3; δ 104.5, C-4a; δ 159.3, C-5; δ 111.5, C-6; δ 161.3, C-7; δ 154.9, C-8a; δ 140.5, C-11; δ 131.3, C-16; δ 131.1, C-21; δ 106.8, C-1′;δ 151.3, C-2′;δ 151.1, C-4′;δ 140.7, C- 5′). The ^1H NMR spectrum showed resonances for a hydrogen bonded hydroxyl proton at δ 13.20 (5-OH), and three singlet aromatic protons at δ 6.57 (H-8), δ 6.45 (H-3′) and δ 7.24 (H-6′). In HMBC experiment, 5-OH and H-8 correlated to C-4a and C-6, H-3′ correlated to C-1′ and C-5′, and H-6′ correlated to C-2′ and C-4′. The characteristic signals of a prenyl group were shown at δ 5.26 (H-20, *d*, $J = 6.9$ Hz), δ 3.32 (H-19, *d*, $J = 6.9$ Hz), δ 1.76 (H-22, *s*) and δ 1.63 (H-23, *s*). The side chain was located at C-6 due to the HMBC correlation of H-19 to oxy-carbon C-5 and C-7. The presence of a geranyl group was determined from the resonances for an oxy-methine (δ 6.15, *d*, $J = 9.3$ Hz, H-9), two olefinic methines (δ 5.47, *br d*, H-10; and δ 4.95, *t*, H-15), two methylenes (δ 1.99, *m*, H-13 and H-14), and three singlet vinyl methyl protons (δ 1.93, H-12; δ 1.51, H-17; and δ 1.48, H-18). The geranyl side chain was confirmed from the COSY correlations of H-9 to H-10 and H-14 to H-15, and from the HMBC correlations of H-9 to C-11 and H-10 to C-12, and C-13. The geranyl was assigned to form a pyran ring to C-3 and C-2′ due to H-9 which showed HMBC correlations to C-4, C-2 and C-2′. Accordingly, artorigidinone C was elucidated as (E)-6-(2,6-dimethylhepta-1,5-dien-1-yl)-2,3,8,10-tetrahydroxy-9-(3-methylbut-2-en-1-yl)chromeno[4,3-b]chromen-7(6H)-one.

Artorixanthone (**4**), was an orange gum, $[\alpha]^{25}_{D}$ +0.7 (c 0.5, MeOH). The IR spectrum showed the absorption bands of ketone (1647 cm^{-1}) and ester (1684 cm^{-1}) carbonyl groups. The UV spectrum showed maximum absorptions at 253 (4.65), 274 (4.65), 282 (4.64), 329 (4.05), 389 (3.73) nm. The ^{13}C NMR spectrum and DEPT experiments signified the presence of two carbonyls (δ 179.7, C-9; δ 173.1, C-17), four methyls (δ 27.7, C-13; δ 27.7, C-14; δ 24.7, C-16; δ 22.7, C-20), one methylene (δ 117.9, C-19), four methines (δ 99.4, C-2; δ 127.7, C-8; δ 114.1, C-10; δ 128.5, C-11), and thirteen quaternary carbons (δ 163.3, C-1; δ 161.7, C-3; δ 101.3, C-4; δ 151.4, C-4a; δ 149.5, C-4b; δ 139.1, C-5; δ 129.4, C-6; δ 138.6, C-7; δ 124.2, C-8a; δ 104.8, C-9a; δ 79.8, C-12; δ 103.8, C-15; δ 142.6, C-18). The ^1H NMR spectrum exhibited resonances for a hydrogen bonded hydroxyl proton 1-OH (δ 12.72), aromatic protons H-2 (δ 6.26, *s*) and H-8 (δ 8.10, *s*). The resonances of olefinic methines at δ 6.87 (*d*, H-10) and δ 5.57 (*d*, H-11) with $J = 9.9$ Hz, and methyl protons at δ 1.51 (*s*, H-13 and H-14), and HMBC correlations of H-10 to C-12, and H-11 to C-13 and C-14 corresponded to characteristic signals of a 2,2-dimethylchromene ring. The HMBC correlations of 1-OH to C-2, H-2 to C-4, H-11 to C-4, H-10 to C-3 and C-4a suggested that H-2 was *ortho* to 1-OH and the chromene ring. The presence of an isopropenyl group was indicated from the resonances of methyl (δ 2.21, H-20), and methylene protons (δ 5.09, H_a-19 and δ 5.31, H_b-19). The HMBC cross peak of H-8 to C-9 and C-18 indicated that H-8 was *peri* to the

carbonyl group and was *ortho* to the isopropenyl side chain. A γ-lactone moiety was derived from the resonances of ester carbonyl carbon C-17, oxy-carbon C-15, aromatic carbons C-5 and C-6, and a singlet resonance of a methyl proton H-16 (δ 2.12), together with the HMBC correlation of H-16 to C-5. The remarkable downfield shift of C-15 (δ 103.8), C-16 (δ 24.7), and H-16 (δ 2.12), as well as the molecular formula of $C_{24}H_{20}O_7$, HRESIMS $[M+H]^+$ *m/z* 421.1290, allowed a hemiketal lactone to be assigned. The compound was likely to be produced from the oxidative cleavage of a lactone ring of artonol B (**5**) (Aida et al. 1997), followed by cyclization of carboxylate ion to an adjacent carbonyl. Consequently, artorixanthone was proposed for 1,7-dihydroxy-1,10,10-trimethyl-4-(prop-1-en-2-yl)furo[3,4-c]pyrano[3,2-h]xanthene-3,6(1H,10H)-dione.

Compounds **2**–**4** and **7**–**10**, were evaluated for their cytotoxicity against human melanoma (SK-MEL-28), human keratinocyte (HaCaT), human lung adenocarcinoma epithelial (A549), human epidermoid carcinoma (A431), and human bone chondrosarcoma, fibroblast-like (SW1353) cell lines (Supplementary material, Table S4). The compounds were able to inhibit the growth of the tested cell lines, with IC_{50} values in the range of 3.37–31.39, 3.41–12.87, 4.16–65.88, 4.04–11.32, and 0.32–52.50 μg/mL, respectively. Compound **2**, **3**, **9**, **9,** and **10** IC_{50} were the most effective to the growth of the cell line SK-MEL-28, HaCaT, A549, A431 and SW1353, respectively.

3. Experimental

3.1. General experimental procedures

The IR spectra were measured with a FTS 165 FT-IR Perkin-Elmer spectrophotometer. UV spectra were recorded in MeOH by a SPECORD S100 spectrophotometer. Optical rotations were determined in MeOH solution at the sodium D line (589 nm) on a JASCO P-1020 polarimeter. ^{1}H and ^{13}C-nuclear magnetic resonance spectra were recorded in acetone-d_6 using a FT-NMR Bruker Avance 300 MHz spectrometer. Quick column and column chromatography were carried out on silica gel 60H (Merck) and silica gel 60 (Merck), respectively. Precoated plates of silica gel 60 GF254 were used for TLC analysis.

3.2. Plant material

The stem bark of *A. rigidus* was collected from Hat Yai District, Songkhla Province in the southern part of Thailand in June 2013. Identification was made by Asst. Prof. Dr. Prakard Sawangchote, Department of Biology, Faculty of Science, Prince of Songkla University. The herbarium specimen (S. Rattanaburi 03) was deposited in the Herbarium of the Department of Biology, Faculty of Science, Prince of Songkla University, Thailand.

3.3. Extraction and isolation

Chopped-dried stem barks of *A. rigidus* (1.5 kg) were immersed in CH_2Cl_2 at room temperature (3 days). After removal of solvent, a brown gum (A, 27.7 g) was obtained, and

was subjected to a quick column chromatography using MeOH:CH_2Cl_2 (1:49) as an eluent to provide 10 fractions (A-J). Fraction D (4.729 g) was purified by column chromatography (CC) and eluted with MeOH:CH_2Cl_2 (1:50) to give 7 fractions (D1-D7). Fraction D4 (0.168 g) and D7 (0.334 g) were subjected to CC and eluted with Me_2CO:hexane (1:5) to give yellow solid **3** (1.8 mg) and **5** (8.0 mg), respectively. An orange gum **4** (3.4 mg), **6** (0.9 mg) and **7** (5.2 mg) were obtained from fraction E (4.931 g) after isolation with CC using Me_2CO:hexane (1:5) as eluent. Purification of fraction F (5.022 g) with CC using Me_2CO:hexane (3:7) provided yellow-brown gum **2** (4.0 mg), **8** (10.2 mg) and **9** (21.5 mg). Fraction G (2.872 g) was further purified by CC using Me_2CO:hexane (3:7) as eluent to afford a yellow-brown gum **1** (1.6 mg). Fraction H (3.821 g) was chromatographed on CC with Me_2CO:hexane (7:13) to give yellow solid **10** (10.2 mg) and **11** (384.6 mg).

3.3.1. Artorigidinone A (1)

A yellow-brown gum; $[\alpha]^{25}_D$ +0.7 (c 0.02, MeOH); UV (MeOH) λ_{max} (log ε): 225 (3.37), 265 (3.56), 302 (3.06), 392 (2.74) nm; IR (neat)ν_{max}: 3317, 2967, 2925, 2852, 1650, 1629, 1580, 1483, 1444 and 1355 cm^{-1}; ^{1}H NMR and ^{13}C-NMR spectral data: Table S1 (Supplementary material); positive ESIMS *m/z* (% rel int): 505 $[M+H]^+$ (100); positive HRESIMS $[M+H]^+$ *m/z* 505.2209 (calculated for $C_{30}H_{32}O_7$, 505.2226).

3.3.2. Artorigidinone B (2)

A yellow-brown gum; $[\alpha]^{25}_D$ +3.5 (c 0.12, MeOH). UV (MeOH) λ_{max} (log ε): 228 (3.93), 275 (3.89), 319 (3.48), 389 (3.56) nm; IR (neat)ν_{max}: 3270, 2971, 2926, 2848, 1651, 1573, 1469, 1355, 1274, and 1166 cm^{-1}; ^{1}H NMR and ^{13}C-NMR spectral data: Table S1 (Supplementary material); positive ESIMS *m/z* (% rel int): 503.2 $[M+H]^+$ (100), 230.3 (11); positive HRESIMS $[M+H]^+$ *m/z* 503.2067 (calculated for $C_{30}H_{30}O_7$, 503.2070).

3.3.3. Artorigidinone C (3)

A yellow solid; $[\alpha]^{25}_D$ +29 (c 0.39, MeOH); UV (MeOH) λ_{max} (log ε): 266 (4.34), 300 (4.13), 382 (4.06) nm; IR (neat)ν_{max}: 3341, 2970, 2926, 2848, 1651, 1631, 1598, 1455, 1370, 1359 and 1306 cm^{-1}; ^{1}H NMR and ^{13}C-NMR spectral data: Table S1 (Supplementary material); positive ESIMS *m/z* (% rel int): 505.2 $[M+H]^+$ (100); positive HRESIMS $[M+H]^+$ *m/z* 505.2228 (calculated for $C_{30}H_{32}O_7$, 505.2226).

3.3.4. Artorixanthone (4)

An orange gum; $[\alpha]^{25}_D$ +0.7 (c 0.5, MeOH); UV (MeOH) λ_{max} (log ε): 253 (4.65), 274 (4.65), 282 (4.64), 329 (4.05), 389 (3.73) nm; IR (neat)ν_{max}: 3419, 2927, 2861, 1684, 1647, 1449 and 1373 cm^{-1}; ^{1}H NMR and ^{13}C-NMR spectral data: Table S3 (Supplementary material); positive ESIMS *m/z* (% rel int): 421.1 $[M+H]+$ (100), 169.0 (18), 146.1 (13); positive HRESIMS $[M+H]^+$ *m/z* 421.1290 (calculated for $C_{24}H_{20}O_7$, 421.1287).

3.4. Cytotoxic activity

Cancer cell lines used in this experiment included normal human melanoma SK-MEL-28, human keratinocyte HaCaT, human lung adenocarcinoma epithelial A549, human

epidermoid carcinoma A431 and human bone chondrosarcoma and fibroblast-like SW1353 cell lines. The proliferation of cell lines was measured by standard 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide (MTT) assay. This was carried out according to the previously reported procedure of Rattanaburi et al. (2014).

In conclusion, the extract of the stem bark of *A. rigidus* significantly inhibited the growth of five tested cell lines. Attempts to search for the active compounds from the crude extract resulted in the isolation of three new and seven known flavonoids and a new xanthone. Compounds **2**–**4** and **7**–**10** showed significant cytotoxicity. γ-Geranylapigenin (**10**) was more effective to human bone chondrosarcoma SW1353 than doxorubicin, a standard drug.

Disclosure statement

No potential conflict of interest was reported by the authors.

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