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Phenolic derivatives from *Aster indicus*

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Abstract

Investigation of the constituents of whole herbs of *Aster indicus* L. led to isolation of 4-hydroxy-3-[1-(methoxycarbonyl)vinyloxy]benzoic acid (**1**), 5-(1-carboxylvinyloxy)-2-hydroxybenzoic acid (**2**), 4-allyl-2,6-dimethoxyphenyl 3-methylbutanoate (**3**), and 4-allyl-2-methoxyphenyl 2-methylbutanoate (**4**), together with 27 previously known compounds. The structures of compounds **1**–**4** were established by application of spectroscopic (NMR and MS) analyses.

Keywords: *Aster indicus*; *Kalimeris indica*; Compositae; Phenolic derivative

1. Introduction

Aster indicus L. [*Kalimeris indica* (L.) Sch. Bip. (Editorial Committee of the Flora of Taiwan, 1998; Delectis Florae Reipublicae Popularis Sinicae Agendae Academiae Sinicae Edita, 1985), Compositae] is a perennial herb, whose whole herbs have been used to treat coughs, bronchitis, hepatitis, snakebite, kid's nutritional marasmus and so on (Chiu and Chang, 1992). The chemical constituents of some *Aster* species have also been studied. For examples, *A. tataricus*, a famous Chinese medicine (Asteris Radix), was reported to contain cyclic pentapeptides (Morita et al., 1993), aurantiamide acetate, terpenoids, flavonoids, anthraquinones, coumarins, and saponins (Akihisa et al., 1999; Lu et al., 2002). Besides these bioactive saponins, scaberosides A_{1-4} (Nagao et al., 1991a), B_{1-6} (Nagao et al., 1991b), H_a, H_{b1}, H_{b2}, H_{c1}, H_{c2}, and H_{d-I} (Nagao et al., 1993a), foetidissimoside A (Nagao et al., 1993b), and quinic acid derivatives (Hur et al., 2001) were isolated from *A. scaber*, a well known medicinal plant in Korea. However, no phytochemical study has thus far been reported on *A. indicus*. In our investigation on the whole herbs of this plant, four new compounds, 4-hydroxy-3-[1-(methoxycarbonyl)vinyloxy]-benzoic acid (**1**), 5-(1-carboxylvinyloxy)-2-hydroxybenzoic acid (**2**), 4-allyl-2,6-dimethoxyphenyl 3-methylbutanoate (**3**), and 4-allyl-2-methoxyphenyl 2-methylbutanoate (**4**), were isolated together with twenty-seven known compounds including a phenolic ester, a triterpene, simple phenols, indoles, flavonoids, quinic acid derivatives, phenylpropanoids, and a phenylpropanoid glycoside (see Section 4). The structures of the new compounds were established on the basis of their spectroscopic analyses, and the structures of the known compounds were identified by comparison of their spectroscopic data with literature values.

2. Results and discussion

The ethanol extract of the whole herbs of *Aster indicus* following repeated chromatographic purification yielded four new compounds including two benzoic acid esters (**1**–**2**) and two phenylpropenes (**3**–**4**).

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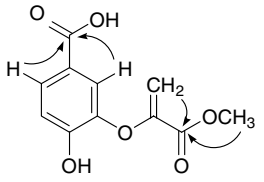
Compound **1** was obtained as white powder and its molecular formula was determined to be $C_{11}H_{10}O_6$ by HREIMS. The IR spectrum of **1** showed the carboxylic acid absorptions at 3490–2730 and 1700 cm^{-1}. The ^{13}C signals at δ_C 164.5 and 169.2 indicated the existence of two carbonyl carbons. In the ^1H NMR spectrum, one methoxy singlet (δ_H 3.83) and a pair of doublets (δ_H 4.75, 5.60, $J = 2.5$ Hz) were assigned to a 1-methoxycarbonylvinyloxy group based on HMBC correlations (Fig. 1). Three other signals at δ_H 6.95 (1H, *d*, $J = 8.0$ Hz, H-5), 7.57 (1H, *d*, $J = 2.0$ Hz, H-2), and 7.73 (1H, *dd*, $J = 2.0$, 8.0 Hz, H-6) were attributed to a set of ABX-type aromatic protons. Among them, H-2 and H-6 showed HMBC correlations with the carbonyl carbon (δ_C 169.2) of the carboxylic acid, and a NOE effect was observed between H-2 and one methylene proton (δ_H 4.75). Thus, 1-methoxycarbonylvinyloxy group was suggested to be at C-3. From the above data, the structure of compound **1** was determined to be 4-hydroxy-3-[1-(methoxycarbonyl)vinyloxy]benzoic acid.

Compound **2** had the molecular formula $C_{10}H_8O_6$ that differed by a CH_2 moiety from compound **1**. Its ^1H and ^{13}C NMR spectra showed a slight difference from those of dehydrochorismic acid (**5**) (Kobayashi et al., 1982), another similar compound that was also isolated. In the HMBC spectrum of **2** (Fig. 1), only one aromatic proton at δ_H 7.68 showed a correlation with the carbonyl carbon (δ_C 174.7) of the carboxylic acid. Thus, a set of ABX-type aromatic protons at δ_H 6.90 (1H, *d*, $J = 8.0$ Hz), 7.68 (1H, *d*, $J = 2.0$ Hz), and 7.70 (1H, *dd*, $J = 2.0$, 8.0 Hz) were assigned to H-3, H-6, and H-4, respectively. Furthermore, the NOE effect between H-6 and one methylene proton (δ_H 4.52) supported the position of the 1-carboxylvinyloxy group at C-5. Therefore, the structure of compound **2** was determined to be 5-(1-carboxylvinyloxy)-2-hydroxybenzoic acid.

Compound **3** was obtained as a white powder, and its molecular formula was determined to be $C_{16}H_{22}O_4$ by HREIMS. The ^{13}C NMR spectrum of **3** showed one ester carbonyl at δ_C 172.8 and three oxygenated sp^2 quaternary carbons at δ_C 140.2 and 153.4 (2 × C). In the ^1H NMR spectrum of **3**, the signals at δ_H 3.36 (2H, *d*, $J = 6.5$ Hz, H-7), 5.05 (1H, br *d*, $J = 10.0$ Hz, H-9a), 5.10 (1H, *dd*, $J = 1.5$, 17.5 Hz, H-9b), and 5.97 (1H, *m*, H-8) were assigned to an allyl substituent, and another set of resonances at δ_H 1.05 (6H, *d*, $J = 6.0$ Hz, 2 × CH_3), 2.18 (1H, *m*, H-12), and 2.41 (2H, *d*, $J = 7.0$ Hz, H_2-11) were assigned to a 3-methylbutanoyl moiety based on their ^1H–^1H COSY and HMBC (Fig. 1) correlations. The remaining proton signals included two singlets at δ_H 3.76 (6H) and 6.52 (2H) due to a pair of equivalent methoxys and two AA′-type aromatic protons. These two aromatic protons (H-3, 5) exhibited an HMBC correlation with the methylene carbon (δ_C 41.5, C-7) of the allyl group. Thus, the 3-methylbutanoyloxy group was deduced to be at C-1, and the structure of **3** was determined as 4-allyl-2,6-dimethoxyphenyl 3-methylbutanoate.

Compound **4** had a molecular formula of $C_{15}H_{20}O_3$ that differed by a OCH_2 moiety from **3**. Its spectroscopic characteristics were similar to those of **3**. In addition to an allyl moiety (δ_H 3.37, 5.06, 5.08, and 5.97), the signals due to one methoxy (δ_H 3.77) and one set of ABX-type proton (δ_H 6.75/H-5; 6.87/H-3; 6.90/H-6) were evident in the ^1H NMR spectrum of **4**. The remaining resonances at δ_H 1.02 (3H, *t*, $J = 7.5$ Hz, H-13), 1.25 (3H, *d*, $J = 6.5$ Hz, H-14), 1.60 (1H, *m*, H-12a), 1.79 (1H, *m*, H-12b), and 2.62 (1H, *m*, H-11) were assigned to a 2-methylbutanoyl group based on the HMBC correlation (Fig. 1) between H-14 and the ester carbonyl (δ_C 176.7, C-10) and ^1H–^1H COSY spectrum. The correlations between H-3, H-5 and the methylene carbon (δ_C 41.0, C-7) of the allyl group were also present in the HMBC spectrum of **4**. In addition, a NOE effect was detected between the methoxy group and H-3. Thus, the positions of the 2-methylbutanoyloxy, methoxy, and allyl groups were suggested to be at C-1, C-2, and C-4, respectively. Based on the above evidence, the structure of **4** was determined as 4-allyl-2-methoxyphenyl 2-methylbutanoate.

Compounds **1**, **2**, and **5** were tested for cytotoxicity *in vitro* on HepG2 hepatoma and KB epidermoid tumor cell lines; none exhibited any cytotoxic activity ($IC_{50} > 100$ μg/mL) using these two cell lines.



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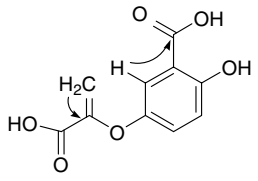

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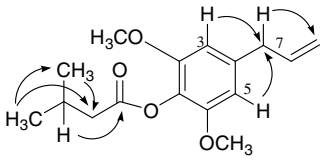

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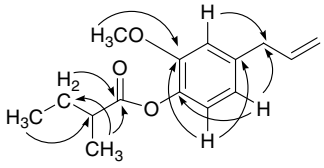

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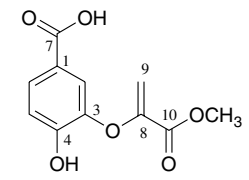
Fig. 1. HMBC correlations of **1**–**4**.



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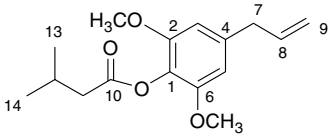

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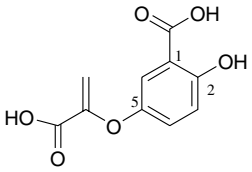

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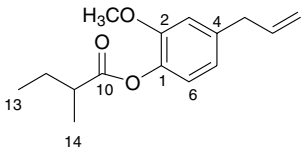

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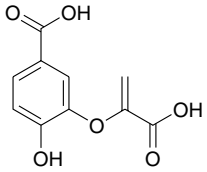

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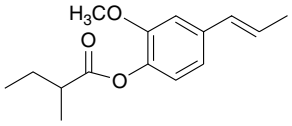

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3. Concluding remarks

Among the isolated compounds from this plant, a triterpenoid ketone (friedelin) and quinic acids were also major constituents, which has been formed in *Aster albescens* (He et al., 1996), *A. tataricus* (Lu et al., 1998; Akihisa et al., 1998, 1999), *A. farreri* (He et al., 1996), and *A. scaber* (Kwon et al., 2000; Hur et al., 2001). Thus, the presence of these constituents can be considered of chemotaxonomic significance for the genus *Aster*.

Dehydrochorismic acid (**5**), an analogue of compounds **1** and **2** with the structure of one benzoic acid bearing a carboxylvinyloxy group, was also reported to be isolated from *Pinus densiflora* Pollen (Kobayashi et al., 1982). Isoeugenol 2-methylbutyrate (**6**), an analogue of compounds **3** and **4** with the structure of one phenylpropene bearing a dimethyl-butyric acid, was isolated from *Fitchia speciosa* (Bohlmann et al., 1980). Nevertheless, these two types of compounds were isolated from *Aster* genus plants for the first time.

4. Experimental

4.1. General

Optical rotations were measured on a JASCO DIP-370 digital polarimeter, whereas UV spectra were obtained using a Hitach U-3200 UV/vis spectrometer. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer, whereas mass spectra were acquired on Finnigan MAT GCQ and JEOL JMS-700 (for HRMS) spectrometers. ^{1}H and ^{13}C NMR spectra were measured using a Varian Unity Inova 500 spectrometer.

4.2. Plant material

The whole herbs of *Aster indicus* L. (Kalimeris indicus (L.) Sch. Bip.) were collected from a municipal botanical garden in Taipei, Taiwan, in August, 2004 and identified by Mr. Jun-Chih Ou, a taxonomist previously with the National Research Institute of Chinese Medicine. A voucher specimen (NRICM-04-021) is deposited at the Herbarium of National Research Institute of Chinese Medicine, Republic of China.

4.3. Extraction and isolation

The dried whole herbs of *A. indicus* (11 kg) were extracted with EtOH (160 L × 3) at 50 °C for 1 day. After evaporation of the solvent in vaco, the extract (420 g) was treated with EtOAc to give EtOAc-soluble (EA) and EtOAc-insoluble portions. The latter was suspended in MeOH–H_2O/5:1, and the soluble portion was subjected to Diaion HP-20 cc eluting with H_2O, MeOH and then EtOAc to give H_2O, MeOH, and EtOAc eluates, respectively. The EtOAc eluate, combined with the above EA portion, was subjected to silica gel cc eluting with *n*-hexane-EtOAc (20:1–5:1) and then CH_2Cl_2–MeOH (15:1–0:1). As a result, friedelin (75.3 mg) (Kuo et al., 1997) was obtained from the *n*-hexane-EtOAc/20:1 eluate after recrystallization and *trans*-cosanyl ferulate (8.2 mg) (Balde et al., 1991) from the *n*-hexane-EtOAc/10:1 eluate was purified by preparative silica-TLC (CH_2Cl_2–*n*-hexane–Me_2CO, 20:20:1). The MeOH eluate was separated by Sephadex LH-20 cc (MeOH–H_2O, 3:1) to afford six fractions (M1 to M6, each 1 L), of which fraction M3 was further separated by Sephadex LH-20 cc (MeOH–H_2O, 3:1) to give five fractions (M3-1 to M3-5, each 500 mL). Then, fraction M3-3 was purified over a silica gel column (*n*-hexane-Me_2CO, 12:1) to afford 4-allyl-2,6-dimethoxyphenyl 3-methylbutanoate (**3**, 2.6 mg). Fraction M3-4 was further separated by MPLC (Cosmosil C-18, H_2O–MeOH, 1:0 to 1:1, v/v) to furnish 17 fractions (M3-4-1 to M3-4-17, each 400 mL). Fraction M3-4-8, H_2O/MeOH (4:1) eluate, was purified by silica gel cc eluting with CH_2Cl_2–MeOH (25:1–10:1) and Sephadex LH-20 cc (MeOH–H_2O, 3:1) to give 4-hydroxybenzaldehyde (2.1 mg), vanillin (2.4 mg), and vanillic acid (1.8 mg) (Pouchert and Behnke, 1993a), respectively. Fraction M3-4-9, H_2O/MeOH (4:1) eluate, was purified further by preparative silica-TLC (CH_2Cl_2–MeOH, 8:1) to give 3-(1-carbonylvinyloxy)-4-hydroxybenzoic acid (**5**, 3.8 mg) (Kobayashi et al., 1982) and methyl 3-*O*-caffeoyl quinate (6.5 mg) (Deyama et al., 1987). Fractions M3-4-10 and M3-4-11, H_2O/MeOH (8:2–7:3) eluate, were individually

further purified by silica gel cc eluting with CH_2Cl_2–Me_2CO (25:1–10:1) and CH_2Cl_2–MeOH (15:1–5:1) to afford 4-hydroxy-3-[1-(methoxycarbonyl)vinyloxy]benzoic acid (**1**, 2.5 mg), 5-(1-carboxylvinyloxy)-2-hydroxybenzoic acid (**2**, 2.2 mg), and 1*H*-indole-3-carboxaldehyde (2.1 mg), respectively (Pouchert and Behnke, 1993b). Furthermore, fractions M3-4-12, H_2O/MeOH (7:3) eluate, and M3-4-14, H_2O/MeOH (7:3–1:1) eluate, were purified by preparative silica-TLC (EtOAc–MeOH–H_2O, 10:1:1) and Sephadex LH-20 cc (MeOH–H_2O, 1:1–3:1), respectively, to afford methyl 3-*O*-feruloylquinate (1.6 mg) (Nishizawa et al., 1988) as well as methyl *trans*-ferulate (3.8 mg) (Aoki et al., 1982) and arillatoses B (1.8 mg) (Bokern et al., 1991). Fraction M3-4-17, H_2O/MeOH (1:1) eluate, was further purified by silica gel cc eluting with *n*-hexane–Me_2CO (12:1) to give 4-allyl-2-methoxyphenyl 2-methylbutanoate (**4**, 1.6 mg). In addition, fraction M3-5 was reseparated by silica gel cc eluting with CH_2Cl_2–MeOH (25:1–5:1), followed by Sephadex LH-20 cc (MeOH–H_2O, 1:1–3:1) repeatedly to give ferulic acid (2.6 mg) (Aoki et al., 1982), *p*-coumaric acid (11.2 mg) (Lin et al., 1999), 1*H*-indole-3-carboxylic aid (2.0 mg) (Pouchert and Behnke, 1993b), kaempferol-7-*O*-β-D-glucopyranoside (3.3 mg), isoquercitrin (13.5 mg) (Agrawal, 1989a), and apigenin-7-*O*-(6″-methyl ester)-glucuronide (2.6 mg) (Lin et al., 2003). Kaempferol (5.7 mg) and quercetin (6.3 mg) were isolated from fraction M5 through Sephadex LH-20 cc (MeOH–H_2O, 1:1). The H_2O eluate was subjected to Sephadex LH-20 cc eluting with MeOH–H_2O (3:1) to afford seven fractions (H1–H7). After further separation of fraction H7 through MPLC (Cosmosil C-18, H_2O–MeOH, 1:0 to 1:1, v/v) and Sephadex LH-20 cc (MeOH–H_2O, 3:1), 4-hydroxybenzoic acid (12.6 mg), 3,4-dihydroxybenzoic acid (16.2 mg), rutin (58.5 mg), nicotiflorin (18.3 mg) (Agrawal, 1989b), methyl 3,4-di-*O*-caffeoyl quinate (1.6 mg) (Nishizawa et al., 1988), 3,5-di-*O*-caffeoylquinic acid (1.8 mg) (Kwon et al., 2000), methyl 3,5-di-*O*-caffeoyl quinate (2.3 mg) (Xiang et al., 2001) and 1,3-di-*O*-caffeoylquinic acid (6.2 mg) (Maruta et al., 1995) were obtained.

4.4. 4-Hydroxy-3-[1-(methoxycarbonyl)vinyloxy]benzoic acid (*1*)

White powder; UV (MeOH) λ_{max} (log ε) 253 (4.10), 205 (4.41) nm; IR (KBr) ν_{max} 3490–2730, 1700, 1698, 1603, 1514, 1438, 1382, 1298, 1209, 1162 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.83 (3H, *s*, 10-OCH_3), 4.75 (1H, *d*, *J* = 2.5 Hz, H-9a), 5.60 (1H, *d*, *J* = 2.5 Hz, H-9b), 6.95 (1H, *d*, *J* = 8.0 Hz, H-5), 7.57 (1H, *d*, *J* = 2.0 Hz, H-2), 7.73 (1H, *dd*, *J* = 2.0, 8.0 Hz, H-6); ^{13}C NMR (CD_3OD, 125 MHz) δ 53.0 (10-OCH_3), 102.4 (CH_2, C-9), 117.9 (CH, C-5), 123.6 (CH, C-2), 123.8 (C, C-1), 129.2 (CH, C-6), 143.2 (C, C-3), 151.5 (C, C-8), 154.6 (C, C-4), 164.5 (C, C-10), 169.2 (C, C-7); EIMS *m*/*z* 238 $[M]^+$ (100), 221 (38), 206 (92), 179 (77), 161 (68); HREIMS *m*/*z*238.0479 (calcd for $C_{11}H_{10}O_6$, 238.0478).

4.5. 5-(1-Carboxylvinyloxy)-2-hydroxybenzoic acid (*2*)

White powder; UV (MeOH) λ_{max} (log ε) 254 (3.84), 201 (4.21) nm; ^1H NMR (CD_3OD, 500 MHz) δ 4.52 (1H, *d*, *J* = 1.5 Hz, H-9a), 5.33 (1H, *d*, *J* = 1.5 Hz, H-9b), 6.90 (1H, *d*, *J* = 8.0 Hz, H-3), 7.68 (1H, *d*, *J* = 2.0 Hz, H-6), 7.70 (1H, *dd*, *J* = 2.0, 8.0 Hz, H-4); ^{13}C NMR (CD_3OD, 125 MHz) δ 96.4 (CH_2, C-9), 117.4 (CH, C-3), 124.7 (CH, C-6), 128.3 (CH, C-4), 130.4 (C, C-1), 143.3 (C, C-5), 152.9 (C, C-2), 157.9 (C, C-8), 170.7 (C, C-10), 174.7 (C, C-7); HREIMS *m*/*z* 224.0323 (calcd for $C_{10}H_8O_6$, 224.0321).

4.6. 4-Allyl-2,6-dimethoxyphenyl 3-methylbutanoate (*3*)

White powder; UV (MeOH) λ_{max} (log ε) 268 (3.14), 206 (4.52) nm; IR (KBr) ν_{max} 1698, 1566, 1394, 1251, 1177 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 1.05 (6 H, *d*, *J* = 6.0 Hz, H-13, 14), 2.18 (1H, *m*, H-12), 2.41 (2H, *d*, *J* = 7.0 Hz, H-11), 3.36 (2H, *d*, *J* = 6.5 Hz, H-7), 3.76 (6H, *s*, 2,6-OCH_3), 5.05 (1H, br *d*, *J* = 10.0 Hz, H-9a), 5.10 (1H, *dd*, *J* = 1.5, 17.5 Hz, H-9b), 5.97 (1H, *m*, H-8), 6.52 (2H, *s*, H-3, 5); ^{13}C NMR (CD_3OD, 125 MHz) δ 22.7 (CH_3, C-13, 14), 27.2 (CH, C-12), 41.5 (CH_2, C-7), 43.8 (CH_2, C-11), 56.5 (2,6-OCH_3), 106.2 (CH, C-3, 5), 116.3 (CH_2, C-9), 128.2 (C, C-4), 138.6 (CH, C-8), 140.2 (C, C-1), 153.4 (C, C-2, 6), 172.8 (C, C-10); EIMS *m*/*z* 278 $[M]^+$ (4), 194 (100); HREIMS *m*/*z* 278.1517 (calcd for $C_{16}H_{22}O_4$, 278.1518).

4.7. 4-Allyl-2-methoxyphenyl 2-methylbutanoate (*4*)

White powder; $[\alpha]_D^{25}$ 0 (*c* 0.048, MeOH); UV (MeOH) λ_{max} (log ε) 274 (3.19), 201 (4.14) nm; ^1H NMR (CD_3OD, 500 MHz) δ 1.02 (3H, t, *J* = 7.5 Hz, H-13), 1.25 (3H, *d*, *J* = 6.5 Hz, H-14), 1.60 (1H, *m*, H-12a), 1.79 (1H, *m*, H-12b), 2.62 (1H, *m*, H-11), 3.37 (2H, *d*, *J* = 6.5 Hz, H_2-7), 3.77 (3H, *s*, 2-OCH_3), 5.06 (1H, *d*, *J* = 10.0 Hz, H-9a), 5.08 (1H, br *d*, *J* = 14.0 Hz, H-9b), 5.97 (1H, *m*, H-8), 6.75 (1H, *dd*, *J* = 2.0, 8.5 Hz, H-5), 6.87 (1H, *d*, *J* = 2.0 Hz, H-3), 6.90 (1H, *d*, *J* = 8.5 Hz, H-6); ^{13}C NMR (CD_3OD, 125 MHz) δ 11.8 (CH_3, C-13), 17.2 (CH_3, C-14), 28.0 (CH_2, C-12), 41.0 (CH_2, C-7), 42.3 (CH, C-11), 56.2 (2-OCH_3), 113.9 (CH, C-3), 116.2 (CH_2, C-9), 121.6 (CH, C-5), 123.4 (CH, C-6), 138.7 (CH, C-8), 139.5 (C, C-1), 140.5 (C, C-4), 152.4 (C, C-2), 176.7 (C, C-10); EIMS *m*/*z* 248 $[M]^+$ (14), 164 (100); HREIMS *m*/*z* 248.1412 (calcd for $C_{15}H_{20}O_3$, 248.1413).

4.8. Cytotoxicity assay

A hepatoma cell line (HepG2; HA22T) was provided by the Cell Bank of Veterans General Hospital. An epidermoid carcinoma cell line (KB; CCRC 60017) was purchased from the Food Industry Research and Development Institute (FIRDI, Taiwan). The cytotoxic activities of compounds **1**, **2**, and **5** on the HepG2 and

KB cell lines were examined using a previously described method (Shen et al., 2004). Camptothecin was employed as a positive control, which exhibited an IC_{50} value of 2.24 μg/mL under the above conditions.

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