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NOTE

Two new xanthones from the roots of *Cratoxylum cochinchinense* and their cytotoxicity

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Abstract

Two new xanthones namely cratochinone A (**1**) and cratochinone B (**2**), along with 16 known xanthones, were isolated from the roots of *Cratoxylum cochinchinense*. Their structures were characterized by spectroscopic methods, especially 1D and 2D NMR as well as comparison with those reported in the literature for known xanthones. All isolated compounds were evaluated for their cytotoxicity against five human cancer cell lines (KB, HeLa S-3, HT-29, MCF-7 and Hep G2 cell lines). Compounds **2**, **5**, and **7** showed significant cytotoxic effects against all cell lines with IC_{50} values in the range of 0.91–9.93 μM, while **10** exhibited cytotoxicity against the KB, HeLa S-3, and HT-29 cells with IC_{50} values of 7.39, 6.07, and 8.11 μM, respectively. Compound **12** exhibited cytotoxicity against both KB and HeLa S-3 cells with IC_{50} values of 7.28 and 9.84 μM.

Keywords *Cratoxylum cochinchinense* · Hypericaceae · Xanthone · Cytotoxicity

Introduction

Cratoxylum cochinchinense (Lour.) Blume is a shrubby tree belonging to the family *Hypericaceae*, which is widely distributed in Southeast Asia. It has been extensively used in traditional medicine to treat several diseases, including cough, diarrhea, fever, and ulcer. Its young fruit has also used as a food spice [1, 2]. From previous phytochemical investigations of the stems, twigs, bark, roots, and bark of roots of *C. cochinchinense*, diverse chemical constituents such as xanthones, flavonoids, tocotrienols, and triterpenoids have been described [1-7], some of which demonstrated a number of interesting biological activity such as antioxidants, antimalarial, antibacterial, anti-HIV, and cytotoxic activities [8-13]. Herein, we reported two new xanthone derivatives namely cratochinone A (**1**) and cratochinone B (**2**), along with 16 known xanthones (**3**–**18**) from the roots of this plant. The structures of all isolated compounds were elucidated using spectroscopic methods, especially 1D and 2D NMR, as well as comparison with those reported in the literature for known xanthones. The cytotoxicity of all isolated compounds was evaluated using the MTT method against five human cancer cell lines.

Results and discussion

The phytochemical investigation of CH_2Cl_2 extract from the roots of *C. cochinchinense* was fractionated through various chromatographic methods to afford two new xanthone derivatives, named cratochinone A (**1**) and cratochinone B (**2**), along with 16 known xanthones (Fig. 1), including pancixanthone-A (**3**) [14], neriifolone A (**4**) [15], macluraxanthone (**5**) [16], 10-*O*-methyxlmacluraxanthone (**6**) [17], pruniflorone G (**7**) [18], pruniflorone H (**8**) [18], 6-deoxyjacareubin (**9**) [19], 9-hydroxycalabaxanthone (**10**) [20], cratoxylumxanthone A (**11**) [3], formoxanthone B (**12**) [21], cochinchinone J (**13**) [22], cochinchinone A (**14**) [23], *β*-mangostin (**15**) [24], 3,8-dihydroxy-1,2-dimethoxyxanthone (**16**) [25],

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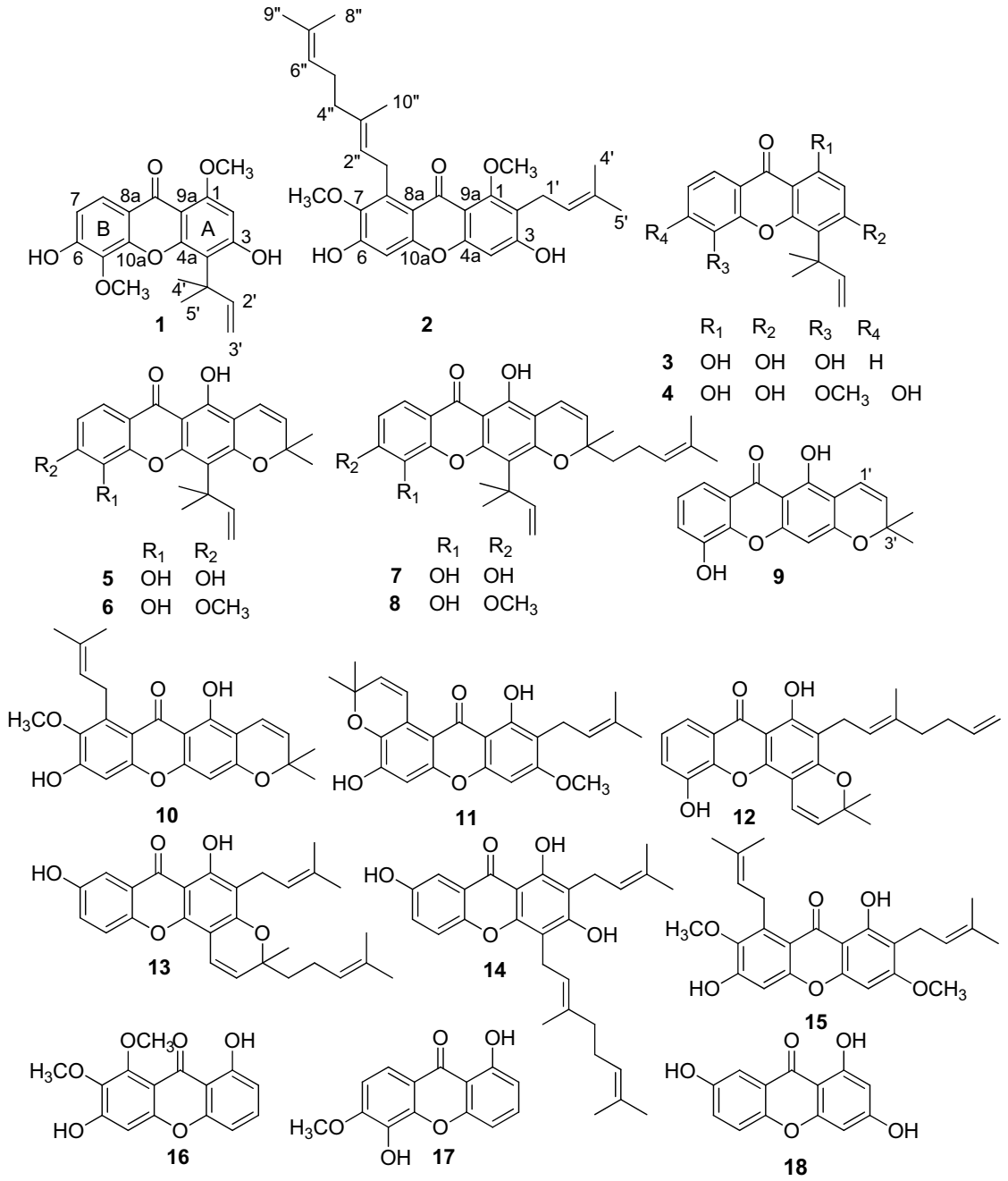

Fig. 1 Structures of **1**–**18** isolated from the roots of *C. cochinchinense*

1,5-dihydroxy-6-methoxyxanthone (**17**) [26] and 1,3,7-trihydroxyxanthone (**18**) [27]. The structures of all isolated compounds were characterized using spectroscopic method especially, NMR spectroscopies, as well as comparison with the previously reported in the literature.

Cratochinone A (**1**) was obtained as a yellow gum. Its molecular formula was determined as $C_{20}H_{20}O_6$ by HRESIMS data (*m/z* 379.1148 $[M+Na]^+$, calcd. for $C_{20}H_{20}O_6Na$, 379.1158). The UV spectrum displayed absorption bands at λ_{max} 394, 315, and 244 nm. The IR spectrum showed phenolic hydroxyl groups and carbonyl group at 3432 and 1642 cm^{-1}. The ^1H NMR spectrum displayed a signal for aromatic proton at δ_H 6.40 (1H, *s*, H-2) and two ortho-coupled aromatic protons at δ_H 6.99 (1H, *d*, $J=8.8$, H-7) and δ_H 7.94 (1H, *d*, $J=8.8$, H-8). In the HMBC spectrum (Table 1, Fig. 2), three aromatic protons were located at C-2, C-7, and C-8 by the correlation of δ_H 6.40 to δ_C 166.1 (C-1), δ_C 162.8 (C-3), δ_C 114.2 (C-4), and

Table 1 ^{1}H , ^{13}C and HMBC NMR data of **1** and **2** in $CDCl_3$ (400 MHz for ^{1}H, 100 MHz for ^{13}C)

Position	**1**			**2**		
	δ_H (J in Hz)	δ_C	HMBC correlations	δ_H (J in Hz)	δ_C	HMBC correlations
1	–	166.1	–	–	163.9	–
2	6.40, (*s*)	96.4	C-1, C-3, C-4, C-9a	–	111.9	–
3	–	162.8	–	–	159.3	–
4	–	114.2	–	6.35, (*s*)	89.2	C-2, C-3, C-4a, C-9a
5	–	134.5	–	6.84, (*s*)	101.9	C-6, C-7, C-8a, C-10a
6	–	155.4	–	–	155.4	–
7	6.99, (*d*, 8.8)	113.5	C-5, C-6, C-8a	–	143.0	–
8	7.94, (*d*, 8.8)	122.7	C-6, C-9,C-10a	–	137.8	–
9	–	181.2	–	–	183.2	–
4a	–	157.6	–	–	155.7	–
8a	–	115.1	–	–	112.2	–
9a	–	103.8	–	–	103.3	–
10a	–	150.3	–	–	154.9	–
1′	–	41.7	–	3.35, (*d*, 7.2)	21.8	C-1, C-2, C-3, C-2′, C-3′
2′	6.30, (*dd*, 17.2, 10.7)	151.0	C-4, C-3′, C-4′, C-5′	5.23, (*m*)	122.7	C-4′, C-5′
3′	4.85, (*d*, 17.2)	108.0	C-1′, C-2′	–	131.6	–
	4.85, (*d*, 10.7)	108.0				
4′	1.70, (*s*)	30.4	C-4, C-1′, C-2′, C-5′	1.68, (*s*)	25.4	C-2′, C-5′
5′	1.70, (*s*)	30.2	C-4, C-1′, C-2′, C-4′	1.79, (*s*)	18.6	C-2′, C-4′
1″	–	–	–	4.10, (*d*, 7.2)	26.2	C-7, C-8, C-8a, C-2″, C-3″
2″	–	–	–	5.26, (*m*)	125.4	C-9″
3″	–	–	–	–	135.7	–
4″	–	–	–	2.03, (*m*)	32.3	C-3″, C-5″
5″	–	–	–	2.03, (*m*)	27.2	C-3″, C-5″
6″	–	–	–	5.10, (*m*)	123.6	C-5″, C-8″, C-10″
7″	–	–	–	–	132.1	–
8″	–	–	–	1.83, (*s*)	23.4	C-6″, C-7″, C-10″
9″	–	–	–	1.68, (*s*)	14.5	C-2″, C-3″, C-4″
10″	–	–	–	1.67, (*s*)	18.6	C-6″, C-7″, C-8″
1-OCH_3	3.96, (*S*)	56.0	C-1	3.90, (*s*)	56.3	C-1
3-OH	–	–	–	–	–	–
5-OCH_3	3.84, (*S*)	62.8	C-5			
6-OH	–	–	–	–	–	–
7-OH	–	–	–	–	–	–
7-OCH_3	–	–	–	3.80, (*s*)	61.9	C-7

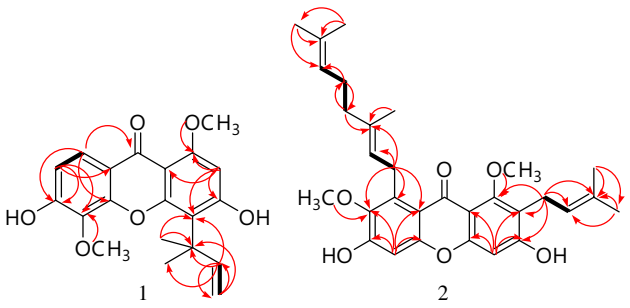

Fig. 2 Key: HMBC (arrow curves) and COSY (bold lines) correlations of **1** and **2**

δ_C 103.8 (C-9a), δ_H 6.99 to δ_C 134.5 (C-5), δ_C 155.4 (C-6) and δ_C 115.1 (C-8a), and δ_H 7.94 to C-6, δ_C 181.29 (C-9), and δ_C 150.3 (C-10a), respectively. In addition, the splitting pattern and coupling constants of three olefinic protons at δ_H 6.30 (*dd*, $J = 17.2$, 10.7 Hz, H-2′), 4.85 (*d*, $J = 17.2$ Hz, H-3′a), and 4.85 (*d*, $J = 10.7$ Hz, H-3′b) indicated the presence of a terminal alkene as a part of a 1,1-dimethylallyl group which also displayed two singlets for methyl groups at δ_H 1.70 (each 3H, *s*, H-4′ and H-5′). The correlations of δ_H 6.30 to C-4, two methyl protons at δ_H 1.70 to δ_C 114.2 (C-4) and δ_C 151.0 (C-2′), confirming that a 1,1-dimethylallyl group was connected at C-4 of ring A. The ^{1}H and

^{13}C NMR spectroscopic data (Table 1) were shown to be similar to those of the known xanthone, isocudraniaxanthone A [28], except that the hydroxyl groups at C-1 and C-5 of isocudraniaxanthone A were substituted by methoxy groups. On the basis of HMBC cross peak of **1** (Fig. 2), the methoxy protons at δ_H 3.96 (3H, *s*, 1-OCH_3) and 3.84 (3H, *s*, 5-OCH_3) showed a cross peak with C-1 of ring A and C-5 of ring B, respectively. Thus, the completed assignment of cratochinone A was determined as **1**.

Cratochinone B (**2**) was obtained as a brown gum. A molecular formula of $C_{30}H_{36}O_6$ was suggested by HRESIMS data (*m/z* = 493.2582 $[M+H]^+$, calcd for $C_{30}H_{37}O_6$, 493.2590).

The UV spectrum displayed absorption bands at λ_{max} at 369, 315, 269, and 245 nm. The IR data indicated the presence of a xanthone skeleton at 3431, 1639, and 1610 cm^{-1}. The ^{1}H NMR spectrum displayed two aromatic protons at δ_H 6.35 (1H, *s*, H-4) and δ_H 6.84 (1H, *s*, H-5). The presence of a prenyl group was indicated by signals for an olefinic proton at δ_H 5.23 (1H, *m*, H-2′), methylene protons at δ_H 3.35 (2H, *d*, *J* = 7.2 Hz, H-1′), and two methyl groups at δ_H 1.68 (3H, *s*, H-4′) and 1.79 (3H, *s*, H-5′). The correlation of δ_H 3.35 to δ_C 163.9 (C-1), δ_C 111.9 (C-2) and δ_C 159.3 (C-3) in the HMBC spectrum (Table 1, Fig. 2) established that the prenyl unit was connected at C-2 of ring A. Furthermore, a geranyl unit was identified from the resonances of two olefinic protons at δ_H 5.26 (1H, *m*, H-2″) and 5.10 (1H, *m*, H-6″), three methylene protons at δ_H 4.10 (2H, *d*, *J* = 7.2 Hz, H-1″), δ_H 2.03 (4H, m, H-4″ and H-5″), and three methyl groups at δ_H 1.83 (3H, *s*, H-10″), 1.68 (3H, *s*, H-8″), and 1.67 (3H, *s*, H-9″), which were also corroborated by the observed HMBC data (Fig. 2). The ^{1}H and ^{13}C NMR spectroscopic data (Table 1) were shown to be similar to those of the known xanthone, norcowanin [29], except that the hydroxyl group at C-1 was replaced by a methoxy group. In the HMBC correlations of **2** (Fig. 2), the methoxy proton at δ_H 3.90 (3H, *s*, 1-OCH_3) showed a cross peak with C-1. The remaining signals of methoxy proton at δ_H 3.80 (3H, *s*, 7-OCH_3), which were accommodated at δ_C 143.0 (C-7) of ring B were based on HMBC cross peak. From the above evidence, cratochinone B had the structure **2**.

Previous reports have revealed that xanthones isolated from plants, especially in the genus *Cratoxylum*, showed remarkable cytotoxicity against several cancer cell lines [2, 9, 21, 30-32]. Therefore, all isolated xanthones (**1**–**18**) were first evaluated in vitro for their cytotoxicity against KB and HeLa S-3 cells. The active compounds (**2**, **5**, **7**, **10**, and **12**) with IC_{50} values lower than 10 μM toward these two cancer cell lines were further evaluated against three cell lines, including HT-29, MCF-7, and Hep G2 cells. The results of cytotoxicity were shown in Table 2. Most of the tested compounds showed moderate to weak cytotoxicity, except **2**, **5**,

Table 2 Cytotoxicity of isolated compounds (**1**–**18**) from the roots of *C. cochinchinense*

Compounds	IC_{50} (μM) ± SD				
	KB	Hela S-3	HT-29	MCF-7	Hep G2
1	42.17 ± 2.83	58.41 ± 0.51	N.T	N.T	N.T
2	1.54 ± 0.02	0.91 ± 0.21	7.04 ± 0.83	1.76 ± 0.06	1.72 ± 0.10
3	> 100	> 100	N.T	N.T	N.T
4	10.14 ± 0.10	12.62 ± 0.85	N.T	N.T	N.T
5	1.60 ± 0.02	1.85 ± 0.19	8.58 ± 0.14	1.18 ± 0.04	9.57 ± 0.74
6	53.01 ± 4.88	35.12 ± 2.63	N.T	N.T	N.T
7	2.04 ± 0.04	2.681 ± 0.10	9.93 ± 0.52	2.54 ± 0.22	4.43 ± 0.56
8	46.11 ± 1.17	40.32 ± 2.62	N.T	N.T	N.T
9	28.01 ± 0.84	13.42 ± 0.91	N.T	N.T	N.T
10	7.39 ± 0.15	6.07 ± 0.59	8.11 ± 0.43	13.67 ± 0.31	27.72 ± 0.61
11	26.44 ± 2.61	10.50 ± 0.86	N.T	N.T	N.T
12	7.28 ± 0.56	9.84 ± 0.45	24.14 ± 0.7	19.63 ± 1.43	19.96 ± 0.94
13	42.18 ± 1.60	59.25 ± 0.14	N.T	N.T	N.T
14	28.96 ± 0.10	20.54 ± 0.83	N.T	N.T	N.T
15	24.99 ± 3.16	14.383 ± 2.67	N.T	N.T	N.T
16	> 100	> 100	N.T	N.T	N.T
17	> 100	> 100	N.T	N.T	N.T
18	> 100	> 100	N.T	N.T	N.T
Doxorubicin	0.22 ± 0.01	0.15 ± 0.05	0.59 ± 0.03	1.29 ± 0.02	0.99 ± 0.17

$IC_{50} \leq 10$ μM = good activity, 10 μM < $IC_{50} \leq 30$ μM = moderate activity, 30 μM < $IC_{50} \leq 100$ μM = weak activity, $IC_{50} > 100$ μM = inactive

N.T. the compounds were not tested

and **7,** which showed significant cytotoxic activities against five human cancer cell lines with IC_{50} values in the range of 0.91–9.93 μM. Compound **10** exhibited potent cytotoxicity toward KB, HeLa S-3, and HT-29 cells with IC_{50} values of 7.39, 6.07, and 8.11 μM, respectively. Whereas **12** showed good cytotoxicity toward both KB and HeLa S-3 cells with IC_{50} values of 7.28 and 9.84 μM. Compounds **3**, **16**, **17**, and **18** showed inactive cytotoxicity toward both KB and HeLa S-3 cells with IC_{50} values more than 100 μM. The SAR studied data (Fig. 1; Table 2) of xanthones suggest that the geranyl group at C-8 [33], the ortho hydroxy group at C-5 and C-6, and the 1,1-dimethylallyl group at C-4 [34], might improve the cytotoxicity as inferred from the comparison of their cytotoxicity of xanthones **1**–**18**.

Experimental

General experimental procedures

NMR spectra were recorded on Bruker 400 AVANCE spectrometer. HRESIMS spectra were obtained using a Bruker MICROTOF model mass spectrometer. The UV–Visible absorption spectra were recorded on a UV-2550 UV–Vis spectrometer (Shimadzu, Kyoto, Japan). The IR spectra were measured on a Nicolet 6700 FT-IR spectrometer using KBr discs. Silica gel 60 Merck cat. Nos. 7734 and 7749 was used as absorbent for open column chromatography (CC) and radial chromatography (Chromatotron®), respectively. Thin layer chromatography (TLC) was performed on precoated Merck silica gel 60 F_{254} plates (0.25 mm thick layer) and visualized with 10% H_2SO_4–MeOH solution.

Plant material

The roots of *C. cochinchinense* were collected in Lumpang Province, northern Thailand, in April 2018 and identified by Dr.Suttira Sedlak, a botanist at the Walai Rukhavej Botanical Research Institute, Mahasarakham University and a specimen retained as a reference (khumkratok no. 01–18).

Extraction and isolation

The roots of *C. cochinchinense* (7.6 kg) were extracted with CH_2Cl_2 (3 × 5 L) at room temperature for 1 week. The combined extract was evaporated to give a yellowish brown gum (174.95 g) was subjected to silica gel CC using a system of hexane (2 L), gradient of hexane–CH_2Cl_2 90, 80, 60, and 20% (5 L) and gradient of CH_2Cl_2–MeOH 95, 90, 80, 60, and 40% (5 L) yielding eight fractions (A–G). Fraction A (13 g) was subjected to silica gel CC using a system of 50 and 10% hexane–CH_2Cl_2 (800 mL) and further purified by chromatotron with a system of 90% hexane–EtOAc (500 mL) to yield **2** (1.7 mg), **6** (3.0 mg), and **10** (2.0 mg). Fraction B (8.0 g) was subjected to silica gel CC using isocratic elution of 30% hexane–CH_2Cl_2 (1 L) and using a system of 100, 95, and 90%, CH_2Cl_2–MeOH (1 L). Then it was also applied to a Sephadex LH-20 CC eluted with a system of 50% CH_2Cl_2–MeOH (900 mL each) followed by chromatotron with a system of 10% hexane–EtOAc (500 mL each) to give **1** (1.1 mg), **5** (7.8 mg), **15** (6.67 mg), respectively. Fraction C (4.4 g) was purified by Sephadex LH-20 CC with a system of 50% CH_2Cl_2–MeOH (500 mL) and further applied to a chromatotron with a system of 80% hexane–EtOAc (200 mL) to furnish **3** (2.0 mg) and **4** (8.0 mg). Fraction D (8.5 g) was purified by Sephadex LH-20 column eluted with 50% CH_2Cl_2–MeOH (2 L) then purified by chromatotron with a system of 40% hexane–CH_2Cl_2 (200 mL) to obtain compounds **8** (4.2 mg) and **11** (4.5 mg). Fraction E (3.0 g) was subjected to Sephadex LH-20 CC eluted with a system of 50% CH_2Cl_2–MeOH (400 mL each) and it was also purified by chromatotron with a system of 80% hexane–CH_2Cl_2 (300 mL) to afford compounds **7** (3.0 mg), **12** (2.5 mg), and **17** (3.2 mg). Fraction F (5.8 g) was separated by silica gel CC using isocratic elution of 50% hexane–CH_2Cl_2 (1 L) and using a system of 100, 95, and 90%, CH_2Cl_2–MeOH (1 L) to give compounds **9** (3.64 mg) and **13** (2.5 mg). Then it was also applied to chromatotron with a system of 80% hexane–CH_2Cl_2 (300 mL) to obtain compound **18** (4.3 mg). Finally, fraction G (2.2 g) was subjected to silica gel CC elution with 70% hexane–EtOAc (1L) and further applied to a chromatotron with 90% hexane–EtOAc (300 mL) to yield compounds **9** (3.7 mg), **14** (3.6 mg), and **16** (4.9 mg).

Cratochinone A: yellow gum; UV ($CHCl_3$) λ_{max} (log ε): 394 (3.5), 315 (4.0), and 244 (4.2) nm, IR ν_{max} (KBr): 3432 and 1642 cm^{-1}; ^1H (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectroscopic data, see Table 1; HRESIMS *m/z* 379.1148 $[M + Na]^+$, (calcd. for $C_{20}H_{20}O_6Na$, 379.1158).

Cratochinone B: brown gum; UV ($CHCl_3$) λ_{max} (log ε): 369 (3.5), 315 (4.0), 269 (4.2), 245 (2.8) nm, IR ν_{max} (KBr): 3431, 1639, 1610 cm^{-1}; ^1H (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectroscopic data, see Table 1; HRESIMS *m/z* 493.2582 $[M + H]^+$, (calcd for $C_{30}H_{37}O_6$, 493.2590).

Cytotoxicity assay

The isolated compounds (**1**–**18**) were evaluated for their cytotoxicity against cervix adenocarcinoma (HeLa S3), epidermoid carcinoma (KB), adenocarcinoma (HT-29), breast adenocarcinoma (MCF-7), and hepatocellular carcinoma (Hep G2) using an MTT colorimetric method [35]. Doxorubicin was used as the reference substance. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (Sigma Chemical Co., USA) was dissolved in saline to make a 5 mg/mL stock solution. Cancer cells (3×10^3 cells) suspended in

100 µg/wells of MEM medium containing 10% fetal calf serum (FCS, Gibco BRL, Life Technologies, NY, USA) were seeded onto a 96-well culture plate (Costar, Corning Incorporated, NY 14,831, USA). After 24 h of pre-incubation at 37 °C in a humidified atmosphere of 5% CO_2/95% air to allow cellular attachment, various concentrations of test solution (10µL/well) were added and these were then incubated for 48 h under the above conditions. At the end of the incubation, 10µL of tetrazolium reagent was added into each well followed by further incubation at 37 °C for 4 h. The supernatant was decanted and DMSO (100µL/well) was added to allow Formosan solubilization. The optical density (OD) of each well was detected using a microplate reader at 550 nm and for correction at 595 nm. Each determination represented the average means of six replicates. The 50% inhibition concentration (IC_{50}value) was determined by curve fitting.

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