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CYTOTOXIC CAGED XANTHONES FROM THE FRUITS OF *Garcinia bracteata*

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Garcinia bracteata C. Y. Wu ex Y. H. Li belongs to the Guttiferae family, which is commonly distributed in the south of Guangxi and south and southeast of Yunnan Province of P. R. China [1]. The plant of genus *Garcinia* has been extensively investigated from phytochemical and biological points of view. Xanthones [2], benzophenones [3], depsidones [4], flavonoids [5], biflavonoids [6], and triterpenes [7] have been isolated from African and southeast Asian species. Previous work on *Garcinia bracteata* revealed that prenylated xanthones and benzophenones have been isolated from the leaves, bark, and twigs of this plant [8, 9].

As part of our search for secondary metabolites from tropical plants, a careful investigation of the fruits of *G. bracteata* has led to the isolation of 12 compounds, and their structures were identified by ^{1}H and ^{13}C NMR, as well as comparisons with the literature data. They are neobractatin (**1**) [10], 3-*O*-methylneobractatin (**2**) [10], bractatin (**3**) [10], 3-*O*-methylbractatin (**4**) [10], isobractatin (**5**) [8], 1-*O*-methylisobractatin (**6**) [8], assiguxanthone A (**7**) [11], 1,3,5,6-tetrahydroxy-4-(l,l-dimethylprop-2-eny1)-7-(3-methylbut-2-enyl)-xanthone (**8**) [12], gentisein (**9**) [11], 1,3,7-trihydroxy-2-(3-methylbut-2-enyl)-xanthone (**10**) [13], cudraxanthone Q (**11**) [14], and dulxanthone B (**12**) [11]. Compounds **1–6** are caged xanthones and **7–12** are classical xanthones. Although all the identified isolates are known compounds, constituents **7–12** are reported for the first time from the *G. bracteata*.

The cytotoxicity of six caged xanthones **1–6** against human leukemia (HL-60), human liver cancer (SMMC-7721), human lung cancer (A549), human breast adenocarcinoma (MCF-7), and human colon cancer (SW480) cell lines were evaluated using the MTT assay as described by Mosmann [15]. Compounds **1–6** exhibited significant cytotoxicity against five human cancer cell lines, as shown in Table 1. Compounds **1–6** contain the α,β-unsaturated ketone group and was found to be highly cytotoxic to five cancer cell lines, which showed that the α,β-unsaturated ketone unit may play an important role in its biological activity. The cytotoxicities of compounds **1–6** are stronger than the positive control, *cis*-platinum, but weaker than another positive control, taxol. The findings of this study suggest that some caged xanthones isolated from *G. bracteata* may prove useful for the treatment of human cancer.

Plant Material. The fruits of *Garcinia bracteata* were collected from Xishuangbanna, Yunnan Province, P. R. China in October 2010 and authenticated by Dr. Tan Yun-Hong of Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences, where a voucher specimen (No. 20101001) was deposited.

Extraction and Isolation. The sun-dried fruits of *G. bracteata* (4.5 kg) were powdered and then repeatedly extracted with 95% EtOH at room temperature. The combined solutions were concentrated to dryness under vacuum. The crude extract was suspended in water and successively extracted with petroleum ether and EtOAc. The petroleum ether fraction (124.0 g) was separated into eight fractions on a silica gel column, eluted with a gradient of petroleum ether–EtOAc (95:5–40:60).

Fraction 3 (16.0 g) was subjected to chromatography on a silica gel column with petroleum ether–acetone (10:1) as eluent and yielded 10 subfractions. Subfractions 3 (2.3 g) and 4 (1.8 g) were subjected to repeated column chromatography on silica gel with gradient $CHCl_3$–MeOH (50:1–30:1) as eluent, yielding compounds **1** (65 mg), **3** (85 mg), **7** (43 mg), **11** (55 mg), and **12** (15 mg).

Fraction 5 (22.0 g) was fractionated by silica gel CC using petroleum ether–EtOAc (3:1) successively as eluent to give six subfractions. Subfractions 4 (2.8 g) and 5 (1.5 g) were further purified by reversed-phase CC with Lichroprep RP18 using MeOH–H_2O (7:3–9:1) as eluent to give compounds **2** (12 mg), **5** (18 mg), **8** (31 mg), and **10** (21 mg).

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TABLE 1. Cytotoxicity of Compounds **1–6** against Five Cancer Cell Lines

Compound/positive control	IC_{50} value, μM				
	HL-60	SMMC-7721	A-549	MCF-7	SW480
Neobractatin (**1**)	3.25	4.27	3.52	2.02	2.81
3-*O*-Methylneobractatin (**2**)	2.90	3.88	5.10	1.94	2.84
Bractatin (**3**)	0.46	2.04	0.91	0.62	0.74
3-*O*-Methylbractatin (**4**)	0.20	0.19	0.73	0.34	0.48
Isobractatin (**5**)	3.25	3.75	4.48	2.22	3.13
1-*O*-Methylisobractatin (**6**)	1.38	3.58	3.20	1.81	2.59
cis-Platinum (MW300)	1.94	14.99	13.39	15.68	25.57
Taxol	< 0.008	< 0.008	< 0.008	< 0.008	< 0.008

Fraction 8 (18.0 g) was submitted to silica gel CC with gradient elution of $CHCl_3$–MeOH (30:1–4:1) to afford eight subfractions. Subfraction 5 (1.2 g) was further purified by reversed-phase CC with Lichroprep RP18 using MeOH–H_2O (6:4–8:2) as eluent to afford compounds **4** (28 mg) and **6** (22 mg). Subfraction 6 (2.0 g) was applied to a Sephadex LH-20 column with elution by MeOH, then recrystallized to give compounds **7** (25 mg) and **9** (15 mg).

***In vitro* Cytotoxic Activities Assay**. The isolated caged xanthones (**1–6**) were evaluated for their cytotoxicity against human leukemia (HL-60), liver cancer (SMMC-7721), lung cancer (A549), breast adenocarcinoma (MCF-7), and colon cancer (SW480) cell lines using the MTT method as described by Mosmann [15] with *cis*-platinum and taxol as positive reference substances.

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