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# Highly Cytotoxic Xanthones from *Cratoxylum cochinchinense* Collected in Myanmar

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Eight xanthones and one anthraquinone, together with four common triterpenoids, have been isolated from the barks of *Cratoxylum cochinchinense*, collected in Myanmar. The structures of the metabolites were elucidated by spectroscopic data analysis and their antiproliferative activities were measured against six human tumor cell lines, by using the MTT assay. Pruniflorone N (**1**) showed a significant cytotoxicity against all cancer cells with $IC_{50}$ values in the range 3-9 μM, on average higher than the anticancer drug cisplatin. Instead, compounds **2** and **3** exhibited high antiproliferative activity against some specific cell lines.

**Keywords:** Xanthones, Anthraquinone, Antiproliferative activity, Pruniflorones M and N, 6-Deoxyisojacareubin, Vismiaquinone D.

Herbal medicine has been existed in Myanmar since immemorial times and it is based on Buddhist philosophy and Ayurvedic medicine concepts. However, despite the rich biodiversity and numerous medicinal plants used in Myanmar, only a few phytochemical studies have been carried out so far. Within our ongoing project on medicinal plants of this country [1], in this paper we describe our results of the first investigation on *Cratoxylum cochinchinense* (Lour.) Blume. This plant, called "mei-tha-nyo" by local people, belongs to a small genus, whose species are mainly found in Southeast Asia. The genus *Cratoxylum* has recently been included in the family Hypericaceae, while it was previously included in Clusiaceae. Barks, stems, roots, twigs and leaves of *C. cochinchinense* are used in several traditional medicines of Southeast Asian countries to treat different ailments, including fevers, coughs, diarrhea, itches, ulcers, scabies, burns, and abdominal complaints [2, 3a]. The same traditional uses are also part of the herbal medicine system practiced in Myanmar. Several phytochemical studies [3] have shown that the plant is a rich source of xanthones, triterpenoids, tocotrienols, benzophenones, flavonoids, and anthraquinones. Though the pattern of secondary metabolites significantly varies with the country of origin of *C. cochinchinense*, xanthones are the most abundant and characteristic biologically active metabolites. Noteworthy, some of these xanthones display important pharmacological properties, including antimalarial [3d, 3h], cytotoxic [3b, 3d, 3h, 3l, 3o], antiradical [3g, 3i, 3n], anti-inflammatory and antibacterial [3b, 3c] effects.

Eight known xanthones (**1**-**8**), one anthraquinone (**9**), and four common triterpenoids were isolated from a MeOH extract of the bark. The structures of these compounds were established by ESI-MS, IR, X-ray analysis (for xanthones **5** and **7**), 1D ($^1$H and $^{13}$C) and 2D NMR spectral measurements. The data nicely matched with the literature. Moreover, the *in vitro* antiproliferative activities of xanthones **1**-**5**, **7**, and anthraquinone **9**, compared to cisplatin, on six different human tumor cell lines are reported.

Extensive preparative chromatographic separation of the extract on silica gel and reversed phase columns, under normal as well as medium pressure conditions, afforded the xanthones pruniflorone N (**1**) [4], pruniflorone M (**2**) [4], 6-deoxyisojacareubin (**3**) [5], xanthone $V_1$ (**4**) [6], macluraxanthone (**5**) [3d, 6], 1,5-dihydroxy-8-methoxyxanthone (**6**) [7], 1,7-dihydroxy xanthone (**7**) [7], 5'-demethoxycadesin G (**8**) [3q], and the anthraquinone vismiaquinone D (**9**) [8]. In addition, four common triterpenoids, α-amyrin [9], α-amyrenone [10], lupeol [11], and lupenone [12] were isolated.

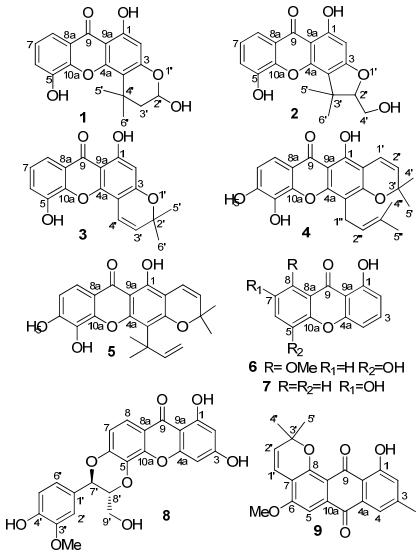


**Figure 1:** Structures of xanthones (**1**-**8**) and vismiaquinone D (**9**) isolated from *Cratoxylum cochinchinense* collected in Myanmar.

To the best of our knowledge, pruniflorone N (**1**), pruniflorone M (**2**), 1,5-dihydroxy-8-methoxyxanthone (**6**), 1,7-dihydroxyxanthone (**7**), α-amyrin, α-amyrenone, and lupenone have been isolated for the first time from *C. cochinchinense*, while the presence of 6-deoxyisojacareubin (**3**) and vismiaquinone D (**9**) in the genus *Cratoxylum* is reported for the first time.

**Table 1:** Antiproliferative activity of compounds **1-5**, **7**, and **9**.

| Compound | $IC_{50}$ (μM)±S.D | | | | | |
|---|---|---|---|---|---|---|
| | MCF7 | SKBR3 | Ishikawa | BG-1 | IST-MES1 | HepG2 |
| Pruniflorone N (**1**) | 7 (±3.1) | 9 (±2.4) | 7 (±3.7) | 3 (±1.6) | 5 (±2.8) | 6 (±2.4) |
| Pruniflorone M (**2**) | 10 (±2.3) | 12 (±2.8) | 7 (±1.6) | 6 (±1.7) | 25 (±4.9) | 7 (±1.3) |
| 6-Deoxyisojacareubin (**3**) | 6 (±2.2) | 7 (±2.3) | >50 | 7 (±3.1) | >50 | >50 |
| Xanthone $V_1$ (**4**) | 20 (±2.2) | 19 (±1.9) | 21 (±2.3) | 25 (±1.7) | 20 (±3.3) | 18 (±1.6) |
| Macluraxanthone (**5**) | >100 | >100 | >100 | >100 | >100 | >100 |
| 1,7-Dihydroxyxanthone (**7**) | >50 | >50 | >50 | >50 | >50 | >50 |
| Vismiaquinone D (**9**) | >50 | >50 | >50 | >50 | >50 | >50 |
| Cisplatin | 19 (±3.2) | 4 (±2.8) | 8 (±1.4) | 15 (±4.3) | 7 (±2.7) | 13 (±2.3) |

*Antiproliferative activity*. The effects of compounds **1-5**, **7**, and **9** on the proliferation of human cancer cells were evaluated by MTT assay, compared to the well-known chemotherapeutic agent *cis*-diamminedichloroplatinum (II) (cisplatin) on the same cell lines. For consistency, activity comparison has been done between tests performed in the same laboratory. Specifically, MCF7 and SkBr3 breast, IST-MES1 mesothelioma, BG-1 ovarian, hepatocellular HepG2, and Ishikawa endometrial cancer cells were treated for 48 h with increasing concentrations of tested samples. The antiproliferative potency was expressed as $IC_{50}$ concentrations (Table 1), which were calculated by probit analysis ($P<0.05$, $\chi 2$ test). These values clearly indicated that each compound exhibited distinct effects on cell viability. Macluraxanthone (**5**), 1,7-dihydroxyxanthone (**7**) and vismiaquinone D (**9**) were inactive on all cell lines, whereas xanthone $V_1$ (**4**) exhibited moderate effects on all cells. The most active xanthones of the series were **1**-**3**. Interestingly, compared to the other xanthones, compounds **1**-**3** have an additional oxygenated heterocyclic ring fused to the xanthone nucleus at C-3/C-4, that may play an important role in the cytotoxicity. Instead, an isoprenyl moiety, such as that occurring in compounds **4** and **5**, seems to reduce cytotoxicity. Pruniflorone N (**1**) showed the highest activity, and it was more active than the very well-known chemotherapy agent cisplatin on five of the same tumor cell lines (Table 1). On the other hand, the cytotoxicity of pruniflorone M (**2**) and 6-deoxyisojacareubin (**3**) was higher than that of cisplatin on four and two lines, respectively. About cell viability, the MCF-7 breast and the BG-1 ovarian cells were the most sensitive cancers to all the three compounds **1**-**3**. Interestingly, macluraxanthone (**5**), which was inactive against the cell lines used in our assay (Table 1), exhibited strong inhibitory effects against the NCI-H187 human lung cancer cell line [3d].

In conclusion, our results confirm that *C. cochinchinense* is a rich source of bioactive secondary metabolites, in particular of xanthones. Notably, the pattern of compounds isolated from the bark of a specimen collected in Myanmar is significantly different from the contents of *C. cochinchinense* barks collected in other Southeast Asian countries, such as Vietnam or Thailand [3]. These findings indicate the possible existence of varieties within the same species.

## Experimental

***General Experimental Procedures:*** Chromatographic and spectrometric instruments and procedures were reported previously [13]. A 600 MHz *Bruker* spectrometer and a 300 MHz *Bruker-Advance* spectrometer, operating at 600 ($^1$H) and 150 MHz ($^{13}$C), and at 300 ($^1$H) and 75 MHz ($^{13}$C), respectively, were used. Preparative MPLC separations were performed on a *Biotage Isolera One* instrument equipped with home-made silica gel and RP-18 filled cartridges and a diode UV detector set at 254-366 nm.

***Plant Material:*** The barks of *C. cochinchinense* were collected near Nam-Pha Lake, about 2.5 km east of the Nam-Pha village, Banmaw Township, Kachin State, Myanmar, in December 2012. The plant was analyzed and identified by Professor Dr Htar Htar Lwin, Department of Botany, Banmaw University, Myanmar. A voucher specimen (no. ZM-2012-0028) has been deposited at the Department of Chemistry, University of Mandalay, Myanmar.

***Extraction and Isolation:*** Three weeks air-dried, chopped barks of *C. cochinchinense* (1 kg) were extracted for 15 days with methanol (3 L). Filtration and evaporation of solvent *under vacuum* produced a MeOH extract (29 g) which was partitioned between water and ethyl acetate to give an AcOEt soluble fraction. Subsequently, the residue (8.19 g) from AcOEt evaporation was partitioned between hexane and MeCN. Removal of solvents *under vacuum* at < 40°C produced a yellow-brown viscous hexane residue (A, 3.24 g) and a dark-brown MeCN residue (B, 3.61 g), respectively. B was then fractioned by multiple CC on $RP_{18}$ and silica gel columns. Elution of the former phase was done with a gradient of MeCN in water (from 33 to 100% MeCN), while eluting systems of the latter phase included a DCM- AcOEt gradient (0-20% AcOEt in DCM), a hexane- AcOEt gradient (from 0 to 100% AcOEt), and hexane-AcOEt, 9:1, hexane- AcOEt, 4:1, hexane- AcOEt, 7:3 mixtures. These separations eventually afforded pruniflorone N (**1**) (3.3 mg), pruniflorone M (**2**) (2.5 mg), 6-deoxyisojacareubin (**3**) (2.7 mg), xanthone $V_1$ (**4**) (4.8 mg), macluraxanthone (16 mg) (**5**), 1,5-dihydroxy-8-methoxyxanthone (**6**) (3.9 mg), 1,7-dihydroxyxanthone (2.7 mg) (**7**), and 5'-demethoxycadesin G (**8**) (4.7 mg). MPLC of residue A on a silica gel column, with a linear gradient of AcOEt in hexane (from 10 to 100%), followed by several separations on $RP_{18}$ columns, eluted with different mixtures of MeCN-$H_2O$, gave vismiaquinone D (2.4 mg) (**9**), α-amyrin (10.7 mg), α-amyrenone (28.7 mg), lupeol (2 mg), and lupenone (47.5 mg).

***Compound identification:*** Melting points, optical rotations, IR and ESI-MS data of isolated metabolites nicely corresponded with the literature. Appropriate references have been reported after the name of each compound (*see above*). Therefore, these data have been omitted herein. Instead, for the sake of completeness, the NMR data of compounds **1**, **2**, **3**, **4**, **6**, **7**, and **8** are listed below. Actually, we found it to be more convenient (higher compound solubility, better signal separation, absence of non-chelated OH interfering signals) to determine the spectra in solvents different from those reported in the literature.

**Pruniflorone N (1)**

$^1$H NMR (300 MHz, MeOH-$d_4$): $\delta_H$ 13.1 (1H, *s*, 1-OH), 7.63 (1H, *dd*, *J* = 7.7 and 2.0 Hz, H-8), 7.27 (1H, *dd*, *J* = 7.7 and 2.0 Hz, H-6), 7.22 (1H, *t*, *J* = 7.7 Hz, H-7), 6.20 (1H, *s*, H-2), 5.43 (1H, *dd*, *J* = 8.5 and 2.5 Hz, H-2'), 1.97 (1H, *dd*, *J* = 11.2 and 2.4 Hz, H-3'a), 1.91 (1H, *dd*, *J* = 11.2 and 8.5 Hz, H-3'b), 1.72 (3H, *s*, $H_3$-5'), 1.60 (3H, *s*, $H_3$-6').

$^{13}$C NMR (75 MHz, MeOH-$d_4$): $\delta_C$ 182.8 (C-9), 162.2 (C-1), 161.9 (C-3), 157.1 (C-4a), 148.3 (C-5), 146.7 (C-10a), 125.0 (C-7), 122.5 (C-8a), 120.7 (C-6), 115.8 (C-8), 111.0 (C-4), 105.3 (C-9a), 100.2 (C-2), 94.2 (C-2'), 47.2 (C-3'), 33.4 (C-4'), 29.1 (C-5'), 28.9 (C-6').

**Pruniflorone M (2)**

$^1$H NMR (300 MHz, MeOH-$d_4$): $\delta_H$ 13.15 (1H, *s*, 1-OH), 7.64 (1H, *dd*, *J* = 7.7 and 2.0 Hz, H-8), 7.26 (1H, *dd*, *J* = 7.7 and 2.0 Hz, H-6), 7.20 (1H, *t*, *J* = 7.7 Hz, H-7), 6.23 (1H, *s*, H-2), 4.49 (1H, *t*, *J* = 6.0 Hz, H-2'), 3.89 (2H, *d*, *J* = 6.0 Hz, $H_2$-1'), 1.69 (3H, *s*, $H_3$-5')[a], 1.44 (3H, *s*, $H_3$-4')[a].

$^{13}$C NMR (75 MHz, MeOH-$d_4$): $\delta_C$ 182.3 (C-9), 167.6 (C-1), 165.5 (C-3), 154.0 (C-4a), 148.0 (C-5), 147.8 (C-10a)[b], 125.0 (C-7), 122.7 (C-8a), 121.2 (C-6), 116.2 (C-8), 114.2 (C-4), 104.7 (C-9a)[b], 96.0 (C-2'), 94.4 (C-2), 61.7 (C-1'), 44.4 (C-3'), 27.1 (C-5')[c], 21.1 (C-4')[c].

[a,b,c]Assignments can be interchanged.

**6-Deoxyisojacareubin (3)**

$^1$H NMR Spectral Data (300 MHz, MeOH-$d_4$): $\delta_H$ 13.2 (1H, *s*, 1-OH), 7.66 (1H, *dd*, *J* = 7.7 and 2.0 Hz, H-8), 7.28 (1H, *dd*, *J* = 7.7 and 2.0 Hz, H-6), 7.23 (1H, *t*, *J* = 7.7 Hz, H-7), 7.03 (1H, *d*, *J* = 10.1 Hz, H-1'), 6.19 (1H, *s*, H-2), 5.72 (1H, *d*, *J* = 10.1 Hz, H-2'), 1.48 (2×3H, *s*, $H_3$-4' and $H_3$-5').

$^{13}$C NMR (75 MHz, MeOH-$d_4$): $\delta_C$ 182.5 (C-9), 164.2 (C-1), 162.3 (C-3), 153.0 (C-4a), 147.7 (C-5), 146.9 (C-10a)[a], 128.4 (C-2'), 125.2 (C-7), 122.6 (C-8a), 121.9 (C-6), 116.5 (C-8), 116.0 (C-1'), 104.3 (C-9a)[a], 102.7 (C-4), 99.9 (C-2), 79.5 (C-3'), 28.6 (C-4' and 5'). [a]Assignments can be interchanged.

**Xanthone $V_1$ (4)**

$^1$H NMR (600 MHz, MeOH-$d_4$): $\delta_H$ 13.18 (1H, *s*, 1-OH), 7.74 (1H, *d*, *J* = 8.5 Hz, H-8), 6.96 (1H, *d*, *J* = 8.5 Hz, H-7), 6.75 (1H, *d*, *J* = 10 Hz, H-1'), 5.60 (1H, *d*, *J* = 10 Hz, H-2'), 5.25 (1H, *t*, *J* = 6.7 Hz, H-2''), 3.50 (2H, *d*, *J* = 6.7 Hz, $H_2$-1''), 1.88 (3H, *s*, $H_3$-5''), 1.73 (3H, *s*, $H_3$-4''), 1.48 (2×3H, *s*, $H_3$-4' and $H_3$-5').

$^{13}$C NMR (150 MHz, MeOH-$d_4$): $\delta_C$ 180.9 (C-9), 158.3 (C-3), 156.6 (C-1), 154.3 (C-4a), 149.5 (C-6), 145.5 (C-10a), 130.8 (C-5), 127.7 (C-2'), 123.3 (C-2''), 118.6 (C-8), 116.5 (C-1'), 114.7 (C-8a), 112.9 (C-7), 107.4 (C-4), 105.3 (C-2), 103.3 (C-9a), 78.6 (C-3'), 28.7 (C-4' and 5'), 26.0 (C-5''), 22.1 (C-1''), 18.3 (C-4'').

**1,5-Dihydroxy-8-methoxyxanthone (6)**

$^1$H NMR Spectral Data (600 MHz, $CDCl_3$): $\delta_H$ 12.98 (*s*, 1-OH), 7.56 (1H, *t*, *J* = 8.3 H-3), 7.32 (1H, *d*, *J* = 8.9 Hz, H-6), 6.90 (1H, *dd*, *J* = 8.3 and 1.1 Hz, H-4), 6.81 (1H, *dd*, *J* = 8.3 and 1.1 Hz, H-2), 6.74 (1H, *d*, *J* = 8.9 Hz, H-7), 3.99 (3H, *s*, OMe).

$^{13}$C NMR Spectral Data (150 MHz, $CDCl_3$): $\delta_C$ 182.9 (C-9), 162.8 (C-1), 155.0 (C-4a), 154.1 (C-8), 145.6 (C-10a), 138.2 (C-5), 136.8 (C-3), 121.3 (C-6), 111.8 (C-2), 111.6 (C-8a), 109.6 (C-9a), 106.3 (C-4), 105.8 (C-7), 56.9 (8-OMe).

**1,7-Dihydroxyxanthone (7)**

$^1$H NMR (300 MHz, MeOH-$d_4$): $\delta_H$ 13.0 (*s*, 1-OH), 7.65 (1H, *t*, *J* = 8.4, H-3), 7.55 (1H, *d*, *J* = 3.0 H-8), 7.47 (1H, *d*, *J* = 9.1, H-5), 7.34 (1H, *dd*, *J* = 9.1 and 3.0 Hz, H-6), 6.98 (1H, *dd*, *J* = 8.4 and 0.8 Hz, H-4), 6.76 (1H, *dd*, *J* = 8.4 and 0.8 Hz, H-2).

$^{13}$C NMR (75 MHz, MeOH-$d_4$): $\delta_C$ 183.0 (C-9), 163.2 (C-1), 158.2 (C-4a), 155.9 (C-7), 151.8 (C-10a), 138.2 (C-3), 126.7 (C-6), 122.5 (C-8a), 120.6 (C-5), 110.9 (C-2), 109.7 (C-9a), 109.5 (C-4), 108.4 (C-8).

**5'-Demethoxycadesin G (8)**

$^1$H NMR (600 MHz, MeOH-$d_4$): δ 13.05 (*s*, 1-OH), 7.68 (1H, *d*, *J* = 8.9 Hz, H-8), 7.06 (1H, *d*, *J* = 1.9 Hz, H-2'), 6.97 (1H, *d*, *J* = 8.9 Hz, H-7), 6.95 (1H, *dd*, *J* = 8.1 and 1.9 Hz, H-6'), 6.87 (1H, *d*, *J* = 8.1 Hz, H-5'), 6.39 (1H, *d*, *J* = 2.1 Hz, H-4), 6.18 (1H, *d*, *J* = 2.1 Hz, H-2), 5.10 (1H, *d*, *J* = 8.1 Hz, H-7'), 4.20 (1H, *ddd*, *J* = 8.1, 3.8 and 2.3 Hz, H-8'), 3.99 (3H, *s*, 3'-OMe), 3.91 (1H, *dd*, *J* = 12.7 and 2.3 Hz, $H_a$-9'), 3.57 (1H, *dd*, *J* = 12.7 and 3.8 Hz, $H_b$-9').

$^{13}$C NMR (150 MHz, MeOH-$d_4$): $\delta_C$ 181.3 (C-9), 167.4 (C-3), 164.7 (C-1), 159.3 (C-4a), 150.7 (C-6), 149.3 (C-3'), 148.7 (C-4'), 147.6 (C-10a), 133.2 (C-5), 128.1 (C-1'), 121.9 (C-6'), 118.1 (C-8), 116.4 (C-5'), 116.1 (C-8a), 114.7 (C-7), 112.2 (C-2'), 103.4 (C-9a), 99.4 (C-2), 95.3 (C-4), 80.1 (C-8'), 78.4 (C-7'), 61.8 (C-9'), 56.5 (3'-OMe).

***Cell cultures:*** MCF-7 breast and HepG2 hepatocellular cancer cells were maintained in DMEM/F-12 supplemented with 10% fetal bovine serum (FBS), 100 µg/ml penicillin/streptomycin and 2 mM L- glutamine (*Life Technologies*, Milan, Italy). SkBr3 breast and BG-1 ovarian cancer cells were cultured in RPMI-1640 and DMEM medium respectively, without phenol red supplemented with 10% FBS and 100 µg/ml penicillin/streptomycin and 2 mM L-glutamine (*Life Technologies*, Milan, Italy). Ishikawa endometrial cancer cells were maintained in MEM supplemented with 10% FBS, 100 µg/ml penicillin/streptomycin, 2 mM L-glutamine and 1% Non-Essential Amino Acids Solution (*Life Technologies*, Milan, Italy). IST-MES1 malignant mesothelioma cells were grown in Nutrient Mixture F-10 Ham (Ham's F-10) medium (*Sigma-Aldrich*, Milan, Italy) supplemented with 10% FBS and 100 µg/ml penicillin/streptomycin. All the cell lines were obtained from ATCC and used less than 6 months after resuscitation, except the IST-MES1 cells which were kindly provided by Dr. Orengo (*Istituto Nazionale per la Ricerca sul Cancro*, Genova, Italy).

***Inhibition of cell proliferation:*** The effects of compounds **1-5**, **7**, and **9** on cell viability were determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, which is based on the conversion of MTT to MTT-formazan by mitochondrial enzyme [14]. Cisplatin was used as the reference compound. For the $IC_{50}$ determination, sample concentrations ranged from 0.1 to 100 µM in DMSO. Cells were seeded in quadruplicate in 96-well plates in regular growth medium and grown until 70% confluence. Cells were washed once they had attached and then treated with increasing concentrations of each compound for 48 h in regular medium supplemented with 1% FBS. Relative cell viability was determined by MTT assay according to the manufacturer's protocol (*Sigma-Aldrich*, Milan, Italy). Mean absorbance for each sample dose was expressed as percentage of the cells treated with vehicle absorbance and plotted versus sample concentration. $IC_{50}$ values were calculated by probit analysis ($P < 0.05$, $\chi 2$ test) and are expressed in µM. Data shown in Table 1 are the means of three independent experiments performed in triplicate.

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