# Two New Prenylated Xanthones from the Pericarp of *Garcinia mangostana* (Mangosteen)

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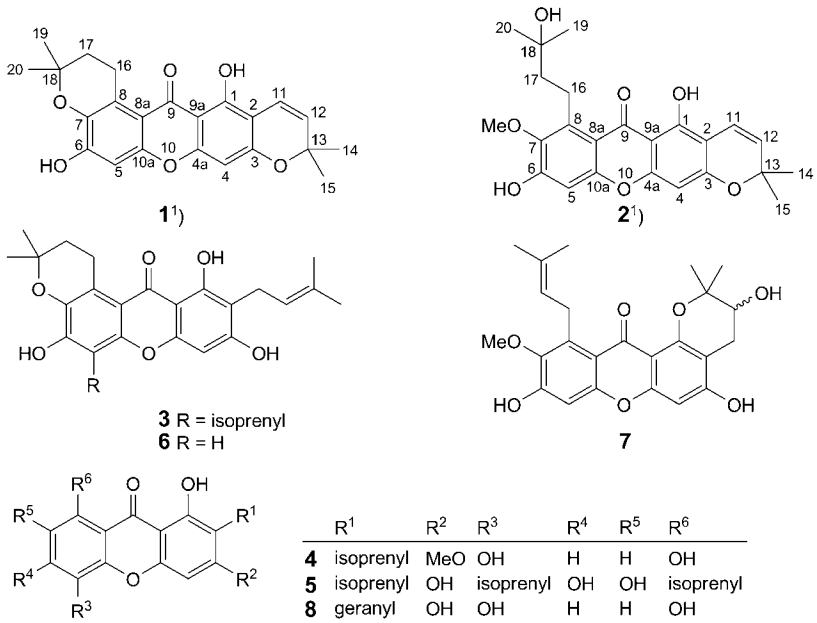
Two new prenylated xanthones (=9*H*-xanthen-9-ones), garcimangosxanthones D (**1**) and E (**2**), together with the six known xanthones **3**–**8**, were isolated from the pericarp of *Garcinia mangostana*. Their structures were determined by analysis of their spectroscopic data. All of the isolated compounds were biologically evaluated for their *in vitro* cytotoxic activity against A549, Hep-G2, and MCF-7 human-cancer cell lines and antioxidant activity. Compound **1** exhibited moderate cytotoxicity against Hep-G2 ($IC_{50}$ = 19.2 μM) and weak cytotoxicity against MCF-7 ($IC_{50}$ = 62.8 μM) cell lines, and compound **2** showed moderate cytotoxicity against A549, Hep-G2, and MCF-7 cell lines with $IC_{50}$ values of 12.5–20.0 μM (*Table 2*). Both compounds **1** and **2** demonstrated a weak antioxidant activity with ferric reducing antioxidant power (FRAP) values of 41 ± 7 and 130 ± 4 μmol/g, respectively (*Table 3*).

**Introduction.** – Mangosteen (*Garcinia mangostana* L.) (Guttiferae) is a tropical evergreen tree which is originated from the Sunda Islands and Moluccas and now widely grown in Thailand, Indonesia, and other Southeast-Asian countries. The delicious fruit of mangosteen is sometimes referred to as 'Queen of Fruits'. The deep reddish purple pericarp is rich in polyphenols including xanthones (=9*H*-xanthen-9-ones) and tannins which confer astringency and ensure protection of the fruit against infestation by insects, fungi, plant viruses, and bacteria and animal predation. The pericarp of mangosteen has been used as an indigenous medicine for the treatment of skin infections, wounds, and diarrhea for a long time [1][2]. The accumulated data demonstrate that the highly O-bearing polyprenylated xanthones exert a variety of biological activities such as antioxidant, antitumor [3], anti-inflammatory, and antifungal [4], as well as other activities [5–7]. Previously, we had identified three new prenylated xanthones with noticeable cytotoxicity against A549, LAC, and A375 human cancer cell lines [8]. A further extensive phytochemical study of the mangosteen pericarp now resulted in the isolation of the eight xanthones **1**–**8** including two new compounds, garcimangoxanthone D (**1**) and E (**2**). Herein, we described the structure elucidation of **1** and **2** and the evaluation of the cytotoxic and antioxidant activities of all isolated compounds.

**Results and Discussion.** – The AcOEt-soluble fraction of the EtOH extract from the pericarp of mangosteen was subjected to repeated column chromatography (CC) over silica gel, *Sephadex LH-20*, and *ODS* to afford the two new compounds **1** and **2**, along with six known xanthones (*Fig. 1*), *i.e.*, 4′,5′-dihydro-1,3,6-trihydroxy-6′,6′-dimethyl-2,5-bis(3-methylbut-2-en-1-yl)pyrano[2′,3′:7,8]xanthone (**3**) [9], 1,5,8-trihydroxy-3-methoxy-2-(3-methyl-2-buten-1-yl)xanthone (**4**) [10], garcinone E (**5**) [11], mangostenone D (**6**) [12], mangostanol (**7**) [13], and smeathxanthone A (**8**) [14]. Their structures were identified by means of spectroscopic methods, and by comparison with literature data.




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|
| **4** | isoprenyl | MeO | OH | H | H | OH |
| **5** | isoprenyl | OH | isoprenyl | OH | OH | isoprenyl |
| **8** | geranyl | OH | OH | H | H | OH |

Fig. 1. *Compounds* **1**–**8**, *isolated from the pericarp of Garcinia mangostana* L.

Compound **1**[1]), obtained as a yellow amorphous powder, had the molecular formula $C_{23}H_{22}O_6$ as shown by HR-ESI-MS data (*m*/*z* 417.1307 ($[M+Na]^+$). In the $^1$H- and $^{13}$C-NMR spectrum (*Table 1*), signals for two aromatic H-atoms at $\delta$(H) 6.81 (*s*, H–C(5)) and 6.26 (*s*, H–C(4)), for a 2,2-dimethylchroman (= 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran) ring at $\delta$(H) 3.50 (*t*, $J$ = 6.7 Hz, $CH_2$(16)), 1.89 (*t*, $J$ = 6.7 Hz, $CH_2$(17)), and 1.39 (*s*, Me(19) and Me(20)) and at $\delta$(C) 22.3 (C(16)), 32.8 (C(17)), 75.6 (C(18)), and 26.5 (C(19) and C(20)), together with a dimethylchromene ring at $\delta$(H) 6.73 (*d*, $J$ = 10.0 Hz, H–C(11)), 5.57 (*d*, $J$ = 10.0 Hz, H–C(12)), and 1.47 (*s*, Me(14) and Me(15)) and at $\delta$(C) 115.7 (C(11)), 127.1 (C(12)), 77.8 (C(13)), and 28.3 (C(14) and C(15)) were observed, in addition to two OH groups at $\delta$(H) 6.41 (*s*, OH–C(6)) and 13.74 (*s*, chelated OH–C(1)). The $^1$H- and $^{13}$C-NMR chemical shifts of **1** were closely similar to those of mangostenone B [2], except for an aromatic H-atom

[1]) Arbitrary atom numberings; for systematic names of **1** and **2**, see *Exper. Part.*

Table 1. *$^1$H- and $^{13}$C-NMR Data* ($CDCl_3$) *of Compounds* **1** *and* **2**. $\delta$ in ppm, $J$ in Hz.

| | **1** | | **2** | |
|---|---|---|---|---|
| | $\delta$(H) | $\delta$(C) | $\delta$(H) | $\delta$(C) |
| C(1) | | 157.8 | | 157.8 |
| C(2) | | 104.3 | | 104.5 |
| C(3) | | 159.6 | | 160.1 |
| H–C(4) | 6.26 (*s*) | 94.2 | 6.26 (*s*) | 94.2 |
| C(4a) | | 156.5 | | 156.3 |
| H–C(5) | 6.81 (*s*) | 100.5 | 6.85 (*s*) | 101.7 |
| C(6) | | 153.1 | | 154.7[a]) |
| C(7) | | 138.0 | | 142.6 |
| C(8) | | 121.3 | | 138.5 |
| C(8a) | | 111.3 | | 112.0 |
| C(9) | | 182.6 | | 182.0 |
| C(9a) | | 103.9 | | 103.7 |
| C(10a) | | 151.6 | | 156.0[a]) |
| H–C(11) | 6.73 (*d*, $J$ = 10.0) | 115.7 | 6.72 (*d*, $J$ = 10.0) | 115.6 |
| H–C(12) | 5.57 (*d*, $J$ = 10.0) | 127.1 | 5.58 (*d*, $J$ = 10.0) | 127.3 |
| C(13) | | 77.8 | | 78.0 |
| Me(14) | 1.47 (*s*) | 28.3 | 1.47 (*s*) | 28.3 |
| Me(15) | 1.47 (*s*) | 28.3 | 1.47 (*s*) | 28.3 |
| $CH_2$(16) | 3.50 (*t*, $J$ = 6.7) | 22.3 | 3.40 – 3.44 (*m*) | 22.2 |
| $CH_2$(17) | 1.89 (*t*, $J$ = 6.7) | 32.8 | 1.76 – 1.80 (*m*) | 44.4 |
| C(18) | | 75.6 | | 70.7 |
| Me(19) | 1.39 (*s*) | 26.5 | 1.33 (*s*) | 29.3 |
| Me(20) | 1.39 (*s*) | 26.5 | 1.33 (*s*) | 29.3 |
| MeO–C(7) | | | 3.86 (*s*) | 62.4 |
| OH–C(1) | 13.74 (*s*) | | 13.57 (*s*) | |
| OH–C(6) | 6.41 (*s*) | | n.d.[b]) | |

[a]) Signals may be interchanged. [b]) n.d. = not detected.

at C(5) in **1** instead of a prenyl (= 3-methylbut-2-en-1-yl) group in mangostenone B. This structure assignment was further supported by the HMBC spectrum of **1** (key correlations depicted in *Fig. 2*). The correlations from H–C(11) ($\delta$(H) 6.73) to C(2) ($\delta$(C) 104.3), C(1) ($\delta$(C) 157.8), and C(3) ($\delta$(C) 159.6), and from H–C(12) ($\delta$(H) 5.57) to C(2) suggested that the dimethylchromene ring was fused at C(2) and C(3). The correlations from $CH_2$(16) ($\delta$(H) 3.50) to C(7) ($\delta$(C) 138.0) and C(8) ($\delta$(C) 121.3), and

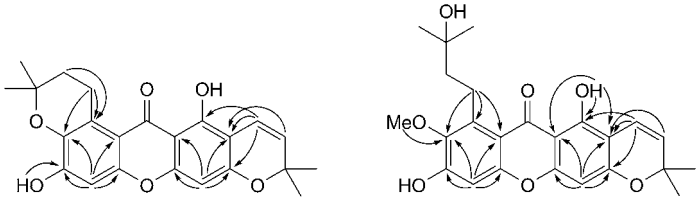



Fig. 2. *Key HMBC* (→) *features of* **1** *and* **2**

from $CH_2$(17) ($\delta$(H) 1.89) to C(8) were compatible with the fusion of the 2,2-dimethylchroman ring at C(7) and C(8). The correlations from OH–C(6) ($\delta$(H) 6.41) to C(6) ($\delta$(C) 153.1) revealed that the OH group was attached at C(6). Thus, the structure of **1** was concluded to be 4″,5″-dihydro-1,6-dihydroxy-6′,6′,6″,6″-tetramethyldipyrano[2′,3′:3,2; 2″,3″:7,8]xanthone, named garcimangosxanthone D[1]).

Compound **2** was a yellow amorphous powder. Its HR-ESI-MS (*m*/*z* 449.1575 ($[M+Na]^+$) established a molecular formula $C_{24}H_{26}O_7$. The $^1$H- and $^{13}$C-NMR spectra (*Table 1*) were similar to those of **1**, except for the absence of signals for the 2,2-dimethylchroman ring. Instead, the spectra exhibited signals indicating the presence of an additional aromatic MeO group at $\delta$(H) 3.86 (*s*, MeO–C(7)) and $\delta$(C) 62.4 (*Me*O–C(7)) and of a 3-hydroxy-3-methylbutyl moiety at $\delta$(H) 3.40–3.44 (*m*, $CH_2$(16)), 1.76–1.80 (*m*, $CH_2$(17)), and 1.33 (*s*, Me(19) and Me(20)) and $\delta$(C) 22.2 (C(16)), 44.4 (C(17)), 70.7 (C(18)), and 29.3 C(19) and C20)). The full structure was deduced from the HMBC spectrum (key correlations depicted in *Fig. 2*). The presence of correlations from $CH_2$(16) ($\delta$(H) 3.40–3.44) to C(7) ($\delta$(C) 142.6), C(8) ($\delta$(C) 138.5), and C(8a) ($\delta$(C) 112.0), and from MeO–C(7) ($\delta$(H) 3.86) to C(7) ($\delta$(C) 142.6) demonstrated the attachments of the 3-hydroxy-3-methylbutyl moiety to C(8) and of the MeO group to C(7). Therefore, the structure of **2** was deduced to be 1,6-dihydroxy-8-(3-hydroxy-3-methylbutyl)-7-methoxy-6′,6′-dimethylpyrano[2′,3′:3,2]xanthone, named garcimangosxanthone E[1]).

The cytotoxicity of all the isolated compounds **1**–**8** was evaluated against human lung cancer cell line (A549), human breast carcinoma cell line (MCF-7), and human hepatoma cell line (Hep-G2) by the MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) colorimetric assay. The $IC_{50}$ values of compounds **1**–**8** on the viability of cancer cells after 72 h of incubation are presented in *Table 2*. Compound **2** exhibited moderate cytotoxicity against all the tested cell lines with $IC_{50}$ values ranging from 12.5 to 20.0 μM, whereas compound **1** only showed moderate cytotoxicity against Hep-G2 cell with an $IC_{50}$ value of 19.2 μM, a weak inhibitory effect on MCF-7 cell with an $IC_{50}$ value of 62.8 μM, and no activity ($IC_{50} > 100$ μM) toward A549 cell. Among the known xanthones, compounds **5**, **6**, and **8** exhibited significant or moderate

Table 2. *Cytotoxic Activity of Compounds* **1**–**8** *by the MTT Assay*

| | $IC_{50}$ [μM] | | |
|---|---|---|---|
| | A549 | MCF-7 | Hep-G2 |
| **1** | > 100 | 62.8 ± 5.3 | 19.2 ± 0.7 |
| **2** | 12.5 ± 2.8 | 13.8 ± 0.7 | 20.0 ± 1.4 |
| **3** | 43.3 ± 4.3 | 10.5 ± 1.3 | > 100 |
| **4** | > 100 | 45.9 ± 2.7 | 5.2 ± 0.6 |
| **5** | 1.2 ± 0.1 | 2.1 ± 0.2 | 1.2 ± 0.1 |
| **6** | 1.0 ± 0.1 | 10.0 ± 0.1 | 11.7 ± 0.2 |
| **7** | 85.4 ± 8.8 | 8.5 ± 0.2 | 5.3 ± 0.3 |
| **8** | 10.8 ± 0.2 | 19.3 ± 0.9 | 8.0 ± 0.4 |
| Doxorubicin[b]) | 2.4 ± 0.2 | 4.4 ± 0.1 | 3.7 ± 0.3 |

[b]) Doxorubicin used as positive control.

cytotoxicity against all the tested cell lines with $IC_{50}$ values ranging from 1.0 to 19.3 μM. Compound **7** exhibited strong cytotoxicity against MCF-7 and Hep-G2 cells with $IC_{50}$ values of 5.3 and 8.5 μM, respectively. Compound **3** showed moderate inhibitory effects on MCF-7 and A549 cells with $IC_{50}$ values of 10.5 and 43.3 μM, respectively. Compound **4** showed a strong inhibitory effect on Hep-G2 cell with an $IC_{50}$ value of 5.2 μM and moderate inhibition on MCF-7 cell with an $IC_{50}$ value of 45.9 μM.

The antioxidant activity of compounds **1**–**8** was determined by the FRAP (= ferric-reducing ability of plasma) assay. As shown in *Table 3*, the FRAP values of the compounds ranged from 16 to 8041 μmol/g. Compounds **1** and **2** exhibited a weak antioxidant activity compared to the reference compound L-ascorbic acid, with the values of $41 \pm 7$ and $130 \pm 4$ μmol/g, respectively. Among the other known xanthones, compounds **4** and **8** showed potent antioxidant activity with the values of $8041 \pm 200$ and $4529 \pm 133$ μmol/g, respectively.

Table 3. *Antioxidant Activity of Compounds* **1**–**8** *by using FRAP Assays*

| Compound | FRAP [μmol/g] | Compound | FRAP [μmol/g] |
|---|---|---|---|
| **1** | $41 \pm 7$ | **6** | $85 \pm 9$ |
| **2** | $130 \pm 4$ | **7** | $135 \pm 9$ |
| **3** | $16 \pm 5$ | **8** | $4529 \pm 133$ |
| **4** | $8041 \pm 200$ | L-Ascorbic acid[c]) | $4656 \pm 350$ |
| **5** | $560 \pm 42$ | | |

[c]) L-Ascorbic acid used as positive control.

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## Experimental Part

*General.* TPTZ (=2,4,6-tripyridin-2-yl-1,3,5-triazine) and MTT were purchased from *Sigma Chemical Co.* (St. Louis, MO). L-Ascorbic acid and doxorubicin were purchased from *Shanghai Boao Biotech Co., Ltd.*, and *Shenzhen Main Luck Pharmaceuticals Inc.*, resp. Column chromatography (CC): silica gel *60* ($SiO_2$; 100–200 and 200–300 mesh; *Qingdao Marine Chemical Ltd.*); *RP-18* ($SiO_2$, 40 μm; *J. T. Baker*), and *Sephadex LH-20*. UV Spectra: *Perkin-Elmer Lambda 35* UV/VIS spectrophotometer; in MeOH; $\lambda_{max}$ (log $\varepsilon$) in nm. $^1$H-, $^{13}$C-, and 2D-NMR: *Bruker-DRX-400* instument, at 400 ($^1$H) and 100 MHz ($^{13}$C), with the residual solvent peak as reference, $\delta$ in ppm, $J$ in Hz. HR-ESI-MS: *Bruker-Bio-TOF-IIIQ* spectrometer; in *m*/*z*. ESI-MS: *MDS-SCIEX-API-2000* LC/MS/MS instrument; in *m*/*z*.

*Plant Material.* The pericarp of *Garcinia mangostana* was obtained by peeling the fruits bought from a local grocery store in Guangzhou, China, which were imported from Thailand in September 2008, A voucher specimen (No. 0233559) was deposited with the Herbarium of South China Botanical Garden, Chinese Academy of Sciences.

*Extraction and Isolation*. The oven-dried and milled pericarp of *Garcinia mangostana* (4 kg) were extracted with 95% EtOH ($3 \times 8$ l) at r.t. for 3 d each. After evaporation, the combined crude EtOH extract (855.8 g) was suspended in $H_2O$ (2 l) and then partitioned with AcOEt ($3 \times 2$ l) to afford an AcOEt (344.5 g) extract. The AcOEt-soluble extract was subjected to CC (petroleum ether/acetone 10 : 1 → 1 : 1): *Fractions A–Q. Fr. E* (10.3 g) was applied to a CC (petroleum ether/acetone 5 : 1 → 3 : 1):

*Frs. E1 – E4*. *Fr. E1* (50.6 mg) was subjected to CC (petroleum ether/acetone 25 :1): **1** (5.4 mg). *Fr. E2* (5.7 g) was subjected to CC (petroleum $Et_2O$/acetone 25 :1 → 10 :1): **4** (102.3 mg), **5** (8.8 mg), and **6** (10.2 mg). *Fr. F* (19.5 g) was applied to CC (petroleum ether/AcOEt 8 :1 → 1 :1): *Frs. F1 – F4*. *Fr. F1* was subjected to CC (petroleum ether/acetone 15 :1) repeatedly: **3** (5.2 mg). *Fr. F3* (4.5 g) was subjected to CC (gradient petroleum ether/acetone): **7** (7.3 mg). *Fr. F4* (1.2 g) was applied to CC (*ODS*, MeOH/$H_2O$ 50% → 90%): **8** (10.1 mg) and **2** (5.3 mg).

*4″,5″-Dihydro-1,6-dihydroxy-6′,6′,6″,6″-tetramethyldipyrano[2′,3′:3,2;2″,3″:7,8]xanthone* (=*2,3-Dihydro-5,13-dihydroxy-3,3,10,10-tetramethyl-10*H-*dipyrano[3,2*-a*:2′,3′*-i*]xanthen-14-(1*H*)-one* = *Garcimangosxanthone D*; **1**): Yellow amorphous powder. UV: 261 (4.12), 294 (4.21), 366 (3.65). $^1$H- and $^{13}$C-NMR: *Table 1*. ESI-MS: 395 ($[M+H]^+$), 433 ($[M+K]^+$), 393 ($[M-H]^-$). HR-ESI-MS: 417.1307 ($[M+Na]^+$, $C_{23}H_{22}NaO_6^+$; calc. 417.1309).

*1,6-Dihydroxy-8-(3-hydroxy-3-methylbutyl)-7-methoxy-6′,6′-dimethylpyrano[2′,3′:3,2]xanthone* (=*5,9-Dihydroxy-7-(3-hydroxy-3-methylbutyl)-8-methoxy-2,2-dimethyl-2*H,*6*H-*pyrano[3,2-*b*]xanthen-6-one* = *Garcimangosxanthone E*; **2**): Yellow amorphous powder. UV: 243 (4.30), 257 (4.27), 290 (4.27). $^1$H- and $^{13}$C-NMR: *Table 1*. ESI-MS: 427 ($[M+H]^+$), 449 ($[M+Na]^+$), 875 ($[2M+Na]^+$), 425 ($[M-H]^-$), 851 ($[2M-H]^-$). HR-ESI-MS: 449.1575 ($[M+Na]^+$, $C_{24}H_{26}NaO_7^+$; calc. 449.1571).

*Cytotoxicity Assay*. Human lung cancer cell line (A549), human breast carcinoma cell line (MCF-7), and human hepatoma cell line (Hep-G2) were obtained from *Jinan Biomedicine Research and Development Center*, Guangzhou, China. The cytotoxic activity of compounds **1** – **8** was determined by the MTT colorimetric assay as previously described by *Mosmann* [15]. Briefly, cells were plated at $1 \cdot 10^4$ cells per well in 96 well microtiter plates and incubated for 24 h at 37° under 5% $CO_2$. Different concentrations (50, 25, 12.5, 6.5, and 3.125 μM) of the compounds were added, except for some wells of the plate to which was added only culture medium (100 μl) as background wells. After 3 d of incubation at 37° under 5% $CO_2$, MTT reagent (10 μl; 5 mg/ml) was added. After incubating at 37° for 4 h, the MTT reagent was removed, and DMSO (150 μl) was added to dissolve the formazan crystals. The absorbance was recorded on a *CENios* microplate reader (*Tecan*, Austria) at a wavelength of 570 nm. MTT Soln. with DMSO (without cells and medium) was used as a blank control. The half-maximal inhibitory-concentration values $IC_{50}$ were calculated by the software SPSS 16.0 from the reduction of absorbance in the control assay. The assay was performed in triplicate, and the data was presented as mean ± s.d.

*FRAP Assay*. This assay was carried out following a modified protocol from *Griffin* and *Bhagooli* [16]. Briefly, 10 mM TPTZ 2.5 ml soln. in 40 mM HCl, plus 20 mM $FeCl_3$ (2.5 ml) and 300 mM acetate buffer (pH 3.6; 25 ml) were prepared to give a FRAP soln. A total of 20 μl of test compounds including L-ascorbic acid as a reference comp. in DMSO was allowed to react with freshly prepared FRAP soln. (180 μl) for 20 min at 37° under dark conditions in quadruplicate. Absorbance of the resulting colored product (ferrous TPTZ complex) was measured on a *Tecan Genios* microplate reader (*Tecan Group Ltd.*, Männedorf, Switzerland) at 595 nm. For a calibration curve, solns. of various concentrations of $FeSO_4$ (1 ml), plus 10 mM TPTZ (1 ml) and of 300 mM acetate buffer (pH 3.6; 10 ml) were used. FRAP Values of test compounds were expressed as means ± standard errors (s.e.) μM of $Fe^{II}$/g, in quadruplicate.

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