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## Design, synthesis and structure–activity relationships of mangostin analogs as cytotoxic agents†

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In order to better understand the structure–activity relationship of mangostin, a series of xanthone derivatives based on  $\alpha$ -mangostin were designed and synthesized. All the compounds were evaluated for their cytotoxicity against a panel of five human cancer cell lines (HL-60, SMMC-7221, A-549, MCF-7 and SW480) using MTT assays. Most of them showed cytotoxicity and most of all, compounds **1a** and **2h** showed the highest cytotoxic potency by HL-60 cancer cell lines with  $IC_{50}$  values of 5.96  $\mu$ M and 6.90  $\mu$ M respectively; compound **3e** showed the highest cytotoxic potency against SMMC-7221 cancer cell line with  $IC_{50}$  values of 3.98  $\mu$ M; compounds **2e** and **2m** showed lower cytotoxicity but higher selectivity than  $\alpha$ -mangostin against HL-60 and SMMC-7221 cancer cell lines respectively. Structure–activity relationship analysis indicates that the maintenance of the isopentene group at C-8 is essential for the cytotoxic activity.

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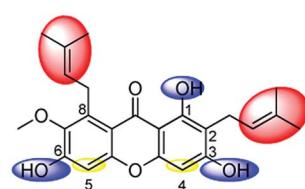
### 1. Introduction

$\alpha$ -Mangostin (**1**) (Fig. 1) is a kind of bioactive xanthone derivative, which can be isolated from the pericarps of the mangosteen fruit (*Garcinia mangostana* L.).<sup>1,2</sup> This compound has shown increasing promise due to an abundance of therapeutic functions, including anti-tumor,<sup>3</sup> anti-oxidant,<sup>4</sup> anti-inflammatory,<sup>5,6</sup> anti-bacterial,<sup>7–10</sup> and inhibition of fatty acid synthase,<sup>11,12</sup> neuraminidase,<sup>13</sup>  $\alpha$ -glycosidase<sup>14</sup> and cholinesterase.<sup>15</sup> The broad spectrum of mangostin against cancer cell lines has attracted considerable awareness; pharmacological<sup>16–19</sup> and medicinal chemistry<sup>20</sup> research of  $\alpha$ -mangostin has been widely performed. Pharmacological studies have revealed that mangostin possesses potent anti-tumor activity both *in vitro* and *in vivo*.  $\alpha$ -Mangostin has been found in the past few decades to exhibit anticancer properties on various cancer models *in vivo*.  $\alpha$ -Mangostin can also be used in combination with other chemotherapeutic agents to increase therapeutic efficacy or reduce side effects.<sup>21–23</sup> Despite its promising therapeutic values, there are no

clinically approved drugs based on  $\alpha$ -mangostin because of its high hydrophobicity, low selectivity<sup>24</sup> and low bioavailability.<sup>25,26</sup>

To overcome these drawbacks, related  $\alpha$ -mangostin derivatives have been synthesized through various modifications of the phenolic hydroxyl groups (C-1, C-3 and C-6 positions)<sup>10,27</sup> and substitution reactions (C-4 and C-5 positions).<sup>28,29</sup> Chemical isolation of oxidative cyclized isopentene groups (C-2 and C-8 positions) has been reported,<sup>30</sup> and however, the modifications of the isopentene groups are limited. Thus, chemical modifications of the isopentene groups of mangostin were done herein to get more derivatives.

In this manuscript, a series of  $\alpha$ -mangostin derivatives were synthesized and then all compounds were evaluated for cytotoxic activities against five human cancer cell lines, including HL-60 (leukemia), SMMC-7221 (hepatoma cells), A-549 (lung cancer), MCF-7 (breast cancer) and SW480 (colon cancer). To study the selectivity of tumor cells and normal cells, their growth inhibitory effect was evaluated against human normal pulmonary epithelial cells (BEAS-2B).


 Fig. 1 The structure of  $\alpha$ -mangostin.

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## 2. Results and discussion

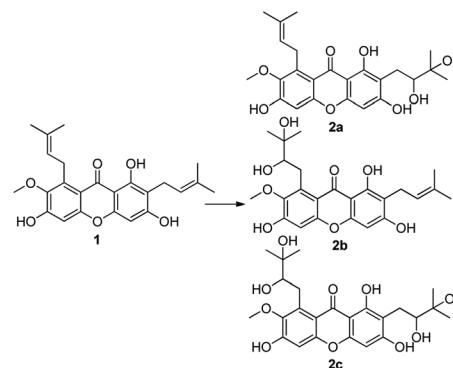
### 2.1 Chemical synthesis

The synthesized compounds (**1a–1l**, **2a–2u**, **3a–3e**) can be divided into three groups according to the variety of functional groups: the isopentene groups (C-2 and C-8 positions), the phenolic hydroxyl groups (C-1, C-3 and C-6 positions) and the vacant sites of benzene ring (C-4 and C-5 positions).

**2.1.1 The modification of phenolic hydroxyl groups (C-1, C-3 and C-6 positions).** There are three free phenolic hydroxyl groups (C-1, C-3 and C-6 positions) in  $\alpha$ -mangostin, which are suitable for chemical modifications. It is noteworthy that the hydroxyl group at the C-1 position is less reactive because an intermolecular hydrogen bond may form between the hydroxyl group (C-1) and the carbonyl group (C-8), thus harsher conditions are required for C-1 alkylation. Therefore we could control the condition of *O*-alkylation reaction so that it occurred only at C-3 and C-6 positions by using mild reaction conditions.

Treatment of  $\alpha$ -mangostin with BrBn in the presence of  $K_2CO_3$ /acetone gave compound **1a**; acetylation of  $\alpha$ -mangostin with  $Ac_2O$  in the addition of DMAP furnished a mixture of compounds **1b** and **1c**, which were separated by silica gel chromatography; the methylation compounds **1d** and **1e** were prepared by reaction of  $\alpha$ -mangostin with  $(CH_3)_2SO_4$  in the presence of  $K_2CO_3$ , followed again by chromatographic separation; alkylation of  $\alpha$ -mangostin to the desired compounds **1f** and **1g** was accomplished by reactions with  $BrCH_2CHCH_2$  and  $K_2CO_3$  in acetone at 65 °C, followed by partial catalytic hydrogenation to afford 78% and 75% yields respectively. For the prenylation compound **1h**,  $\alpha$ -mangostin was reacted with  $BrCH_2CHC(CH_3)_2$  at 65 °C for 12 h resulting in yields of 15%.<sup>31</sup>

To speak of, we also designed a series of  $\alpha$ -mangostin derivatives by attaching different lengths (1–4) of carbon chains carboxylic ester groups to the free hydroxyl groups (at C-1, C-3 and C-6 positions) according to the references.<sup>32</sup> Therefore compounds **1i–1l** were synthesized in good yields (25–60%) by



Scheme 2 Reagents and conditions:  $OsO_4$ , NMO, acetone– $H_2O$  (1 : 1), rt, 12–78%.

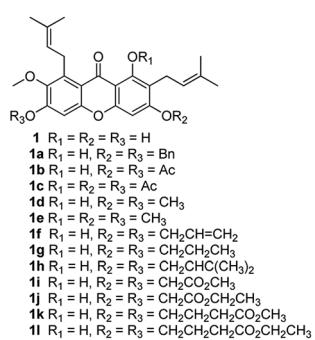
the reaction with various bromo-carboxylic acid esters and NaH (Scheme 1). Unfortunately, they showed complete absence of cytotoxicity.

In general, the alkylation of phenolic hydroxyl groups of mangostin can mainly cause the loss of cytotoxicity, so we focused on the structural modifications of isopentyl groups of mangostin.

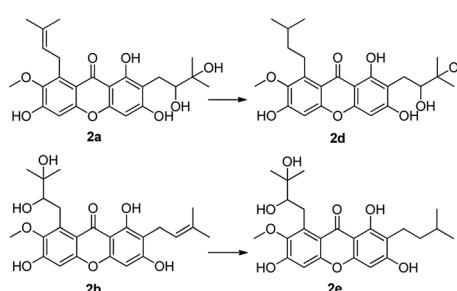
**2.1.2 The modification of isopentene group (C-2 and C-8 positions).** Compounds **2a–2u** were designed to test whether the modification of isopentene groups could enhance the cytotoxicity activity and improve their selectivity between normal and tumour cells. The synthetic methodologies used to synthesize the derivatives **2a–2u** are outlined in Schemes 2–7.

Firstly,  $\alpha$ -mangostin derivatives based on the oxidation of isopentene group (at C-2 and C-8 positions) were synthesized.  $\alpha$ -Mangostin was treated with  $OsO_4$  and NMO in mixed solvent (acetone :  $H_2O$  = 1 : 1) to afford compounds **2a–2c**, using a similar method as reported in the literature,<sup>33</sup> with yields of 10%, 12% and 78% respectively. These products containing functional groups of *O*-diol act as key intermediates for the further synthesis of mangostin derivatives.

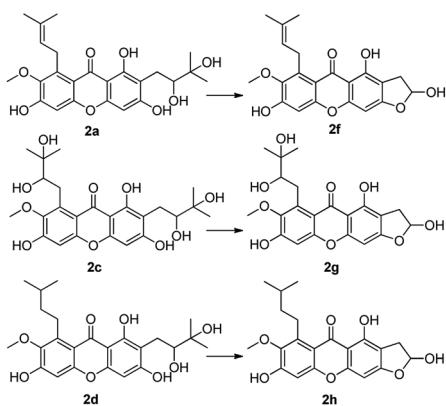
Compounds **2a** and **2b** have many identical partial structure similarities: one *O*-diol hydroxyl group and one isopentene group; the structural differences were substitution positions at C-2 or C-8 positions. As shown in Scheme 3, the isopentene group of compounds **2a** and **2b** was reduced to isopentyl group under  $H_2$ , Pd/C to afford compounds **2d** and **2e** in high yields from 78% to 98%. Compounds **2r** and **2t** were separately



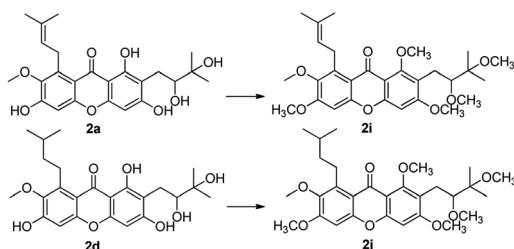
Scheme 1 Reagents and conditions: BrBn,  $K_2CO_3$ , acetone, reflux, 80% for **1a**;  $Ac_2O$ , DMAP, DCM, cool temperature to room temperature, 80% for **1b** and **1c**;  $(CH_3)_2SO_4$ ,  $K_2CO_3$ , acetone, reflux, 80% for **1d** and **1e**;  $BrCH_2CHCH_2$ ,  $K_2CO_3$ , acetone, reflux, 78% for **1f**;  $Pd/C$ ,  $H_2$ , MeOH, rt, 75% for **1g**;  $BrCH_2CHC(CH_3)_2$ ,  $K_2CO_3$ , acetone, reflux, 15% for **1h**;  $BrCH_2CO_2CH_3$ , NaH, acetone, reflux, 60% for **1i**;  $BrCH_2CO_2CH_2CH_3$ , NaH, acetone, reflux, 60% for **1j**;  $BrCH_2CH_2CH_2CO_2CH_3$ , NaH, acetone, reflux, 25% for **1k**;  $BrCH_2CH_2CH_2CO_2CH_2CH_3$ , NaH, acetone, reflux, 25% for **1l**.



Scheme 3 Reagents and conditions:  $H_2$ , Pd/C,  $MeOH$ , rt, 78–98%.



Scheme 4 Reagents and conditions:  $\text{NaIO}_4$ ,  $\text{THF}-\text{H}_2\text{O}$  (2 : 1), rt, 40–60%.



Scheme 5 Reagents and conditions:  $\text{NaH}$ ,  $\text{CH}_3\text{I}$ ,  $\text{DMF}$ , rt, 60%.

prepared from  $\alpha$ -mangostin (**1**) and  $\gamma$ -mangostin (**2s**) under the same conditions as for preparation of compounds **2d** and **2e** (Scheme 7). Compound **2d** was prepared in 80% from **2a** by catalytic hydrogenation, which served as starting material for the synthesis of oxidation product analogous. As shown in Scheme 4, compounds **2a**, **2c** and **2d**, having the vicinal diol groups, were oxidized by  $\text{NaIO}_4$  in mixed solvent ( $\text{THF} : \text{H}_2\text{O} = 2 : 1$ ) to afford compounds **2f**, **2g** and **2h** with good yields (40–60%) according to the relative reference.<sup>34</sup>

With compounds **2a** and **2d** in hands, in order to increase their lipotropic properties, different contents of various alkylation products were obtained (Scheme 5). Methylation of compounds **2a** and **2d** with  $\text{CH}_3\text{I}-\text{NaH}$  yielded the total methylation products **2i** and **2j**.

In order to discuss the structure–activity relationship (SAR) more entirely, then we turned to synthesize the cyclization series of xanthone derivatives **2k–2p** (Scheme 6) according to the relevant references.<sup>35,36</sup> Initially, the cyclization of  $\alpha$ -mangostin with DDQ afforded compound **2k** with a yield of 40%;  $\alpha$ -mangostin was oxidized with *m*-CPBA in the presence of  $\text{NaHCO}_3$  to yield compounds **2l** and **2m** followed again by chromatographic separation in 4% to 49% yields; compound **2n** was obtained through an addition reaction in which  $\alpha$ -mangostin was reacted with  $\text{HCOOH}$  with yield of 25%; the treatment of  $\alpha$ -mangostin with *p*-TsOH produced compounds **2o**, **2p** and **2q**, which were separated by silica gel chromatography with a relatively low yield of 12–23%; compound **2u** was prepared by the cyclization of 2,4-dihydroxybenzoic acid and phloroglucin under the condition of Eaton's reagents at 60 °C.

**2.1.3 The substitution reaction at C-4 and C-5 (C-4 and C-5 positions).** In addition to a scaffold leading to diverse functionalities, the biology effects of halogens is worth studying. Considering the vacant sites of C-4 and C-5 positions of mangostin, the chloride and bromide substitution compounds **3a–3e** were generated accompanied by a small amount of *N*-chlorosuccinimide (NCS) and *N*-bromobutanamide (NBS) respectively. The halogenated  $\alpha$ -mangostin derivatives were synthesized as shown in Scheme 7.

In conclusion, we had synthesized three series of mangostin derivatives. All reactions were described in the experimental section. All synthesized target compounds were purified by column chromatography (silica gel, 200–300 mesh, petroleum ether/ethyl acetate, 1 : 1 → 20 : 1) and their structures were elucidated by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, electrospray ionization mass spectrometry (ESI-MS) and high-resolution mass spectrometry (HR-ESIMS).

## 2.2 Evaluation of biological activity

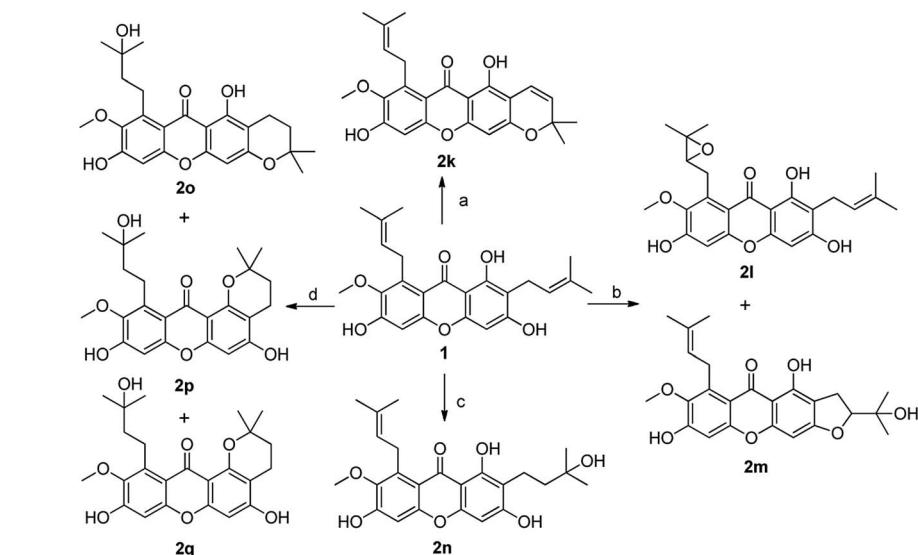
The cytotoxicity of these derivatives was evaluated *in vitro* against five human cancer cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW480). Cisplatin (**DDP**) and Adriamycin (**ADM**) were taken as control drugs and their  $\text{IC}_{50}$  data were present in Tables 1, 2 and 3. The inhibitory of the tested compounds on cell viability was measured by the MTT colorimetric methods. A few of them showed higher potency than the parent compound and most of them displayed moderate cytotoxicity against all five cancer cell lines. In order to test the cytotoxicity of these derivatives with promising anticancer activity on normal cells, their growth inhibitory effect was evaluated against human normal pulmonary epithelial cells (BEAS-2B).

Overall, these synthesized compounds show a broad range of growth inhibitory effect against all five cancer cell lines tested. In general, the HL-60 cell line was most sensitive to these compounds. Noteworthy, compound **2h** possesses remarkable anti-proliferation activity against all the tested cancer cell lines. Compound **2e**, which solely possesses notable anti-proliferation activity against HL-60 cancer cells ( $\text{IC}_{50} = 18.65 \pm 0.23 \mu\text{M}$ ) is non-cytotoxic to BEAS-2B cell line. Moreover, several compounds (**2a**, **2f**, **2k**, **2n** and **2r**) with pretty anti-proliferation activity against all the tested cancer cell lines are observed to be less toxic to BEAS-2B cells compared with  $\alpha$ -mangostin. The results suggest that these compounds are more sensitive to certain tested cancer cells than normal cells *in vitro* and hence possess good selectivity.

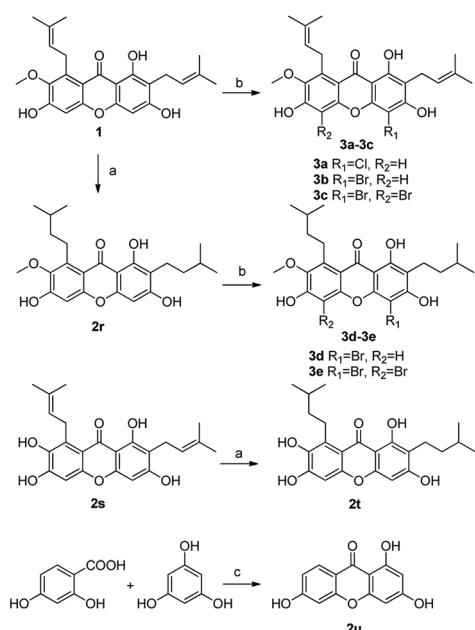
These data have allowed us to carry out a structure and activity relationship (SAR) study on the influence of the modifications of the isopentene group and halogen atoms in the cholinesterase inhibitory activities. The main conclusions can be summarized as follows:

(1) With respect to the SAR, the effects of the substitution reactions at phenolic hydroxyl groups were examined. Disubstitution at both C-3 and C-6 hydroxyl groups (**1a–1l**) causes totally decrease in the cytotoxicity of mangostin against the five tested cancer cell lines; while the acetylation form of mangostin (**1b** and **1c**) can remain the cytotoxic activity,





**Scheme 6** Reagents and conditions: (a) DDQ, toluene, reflux, 41%; (b) *m*-CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4–49%; (c) HCOOH, acetone, rt, 25%; (d) *p*-TsOH, toluene-CH<sub>2</sub>Cl<sub>2</sub> (2 : 1), rt, 12–23%.



**Scheme 7** Reagents and conditions: (a) H<sub>2</sub>, Pd/C, MeOH, rt, 95%; (b) NCS/NBS, DCM or THF, rt, 12–60%; (c) Eaton's reagents, 60 °C, 60%.

compound **1a** possessed the most potent cytotoxicity against HL-60 cancer cell line with IC<sub>50</sub> value of 5.96 ± 0.16 μM. In summary, the numbers of phenolic hydroxyl groups have certain effects on maintaining cytotoxicity.

(2) The oxidation of the isopentene group at C-8 causes drastically decreases in the cytotoxicity of mangostin against all the tested cancer cell lines. Compounds **2b**, **2c**, **2g**, **2l** and **2m** displayed weak activity, all having IC<sub>50</sub> > 40 μM, indicating that the isopentene group at C-8 was necessary for the cytotoxicity and the hydroxyl group at C-8 can cause totally loss of the cytotoxicity. However, one interesting exception is observed: compound **2e** possesses notable anti-proliferation activity against HL-60 cancer cells with IC<sub>50</sub> value of 18.65 ± 0.23 μM.

(3) Several structure features and their effects need to be pointed out. Oxidation of the isopentene group at C-2 (compounds **2a**, **2d**, **2f**, **2k**, **2m** and **2n**) generally resulted in slightly decreased activity or comparative activity with one exception. Compound **2h** exhibited greater activity against HL-60 and SMMC-7221 cell lines with IC<sub>50</sub> values of 6.90 ± 0.55 μM and 6.92 ± 0.55 μM respectively. These data indicate the number and position of hydroxyl group at C-2 have limited potency on the cytotoxicity and selectivity.

(4) By comparing compounds **1** and **2r**, **2a** and **2d**, **2b** and **2e**, **2f** and **2h**, **2s** and **2t**, it is obvious to find that the reduction of

**Table 1** *In vitro* cytotoxic activity (IC<sub>50</sub>, μM) of mangostin derivatives

Compounds	IC <sub>50</sub> ± SD (μM)					
	HL-60	SMMC-7221	A-549	MCF-7	SW480	BEAS-2B
<b>1</b>	15.04 ± 0.33	10.30 ± 0.48	13.82 ± 0.61	10.81 ± 1.12	14.45 ± 0.85	15.81 ± 1.02
<b>1a</b>	5.96 ± 0.16	11.64 ± 0.61	10.27 ± 0.42	12.95 ± 0.44	15.85 ± 0.46	NT
<b>1b</b>	11.92 ± 0.48	13.56 ± 0.32	11.60 ± 0.24	16.65 ± 1.32	16.17 ± 0.13	NT
<b>DDP</b>	3.19 ± 0.18	18.03 ± 0.49	13.75 ± 0.74	28.42 ± 3.71	14.77 ± 2.15	>40
<b>ADM</b>	0.14 ± 0.00	0.90 ± 0.03	0.30 ± 0.01	0.90 ± 0.02	0.11 ± 0.01	>40

Table 2 *In vitro* cytotoxic activity ( $IC_{50}$ ,  $\mu$ M) of mangostin derivatives

Compounds	$IC_{50} \pm SD$ ( $\mu$ M)					
	HL-60	SMMC-7721	A-549	MCF-7	SW480	BEAS-2B
<b>1</b>	15.04 $\pm$ 0.33	10.30 $\pm$ 0.48	13.82 $\pm$ 0.61	10.81 $\pm$ 1.12	14.45 $\pm$ 0.85	15.81 $\pm$ 1.02
<b>2a</b>	18.22 $\pm$ 0.48	23.42 $\pm$ 1.29	19.82 $\pm$ 1.42	23.65 $\pm$ 0.64	>40	18.31 $\pm$ 0.51
<b>2b</b>	>40	>40	>40	>40	>40	NT
<b>2c</b>	>40	>40	>40	>40	>40	NT
<b>2d</b>	21.59 $\pm$ 2.41	26.87 $\pm$ 3.75	35.96 $\pm$ 0.99	>40	>40	>40
<b>2e</b>	18.65 $\pm$ 0.23	>40	>40	>40	>40	>40
<b>2f</b>	14.96 $\pm$ 0.80	11.93 $\pm$ 0.28	18.03 $\pm$ 1.49	19.75 $\pm$ 0.26	18.24 $\pm$ 0.79	27.20 $\pm$ 2.42
<b>2g</b>	>40	>40	>40	>40	>40	NT
<b>2h</b>	6.90 $\pm$ 0.55	6.92 $\pm$ 0.55	11.77 $\pm$ 0.13	17.97 $\pm$ 0.23	15.86 $\pm$ 0.2	17.56 $\pm$ 0.60
<b>2i</b>	>40	>40	>40	>40	>40	NT
<b>2j</b>	>40	>40	>40	>40	>40	NT
<b>2k</b>	13.72 $\pm$ 0.50	11.52 $\pm$ 0.17	11.47 $\pm$ 0.33	16.80 $\pm$ 1.04	17.35 $\pm$ 1.15	18.60 $\pm$ 0.70
<b>2l</b>	>40	>40	>40	>40	>40	NT
<b>2m</b>	>40	53.75 $\pm$ 0.26	>40	>40	>40	NT
<b>2n</b>	14.40 $\pm$ 0.05	26.31 $\pm$ 1.04	16.96 $\pm$ 0.77	24.62 $\pm$ 0.47	22.69 $\pm$ 2.35	29.34 $\pm$ 1.02
<b>2o</b>	>40	>40	>40	>40	>40	NT
<b>2p</b>	>40	>40	>40	>40	>40	NT
<b>2q</b>	NT	NT	NT	NT	NT	NT
<b>2r</b>	11.13 $\pm$ 0.15	15.68 $\pm$ 0.34	14.93 $\pm$ 0.15	8.29 $\pm$ 0.59	14.46 $\pm$ 0.15	14.35 $\pm$ 0.41
<b>2s</b>	7.39 $\pm$ 0.33	6.57 $\pm$ 0.14	10.07 $\pm$ 0.59	5.33 $\pm$ 0.43	8.40 $\pm$ 0.67	7.43 $\pm$ 0.65
<b>2t</b>	13.72 $\pm$ 0.06	6.51 $\pm$ 0.49	15.56 $\pm$ 0.17	12.32 $\pm$ 0.12	11.59 $\pm$ 0.52	6.48 $\pm$ 0.08
<b>2u</b>	>40	>40	>40	>40	>40	NT
<b>DDP</b>	3.19 $\pm$ 0.18	18.03 $\pm$ 0.49	13.75 $\pm$ 0.74	28.42 $\pm$ 3.71	14.77 $\pm$ 2.15	>40
<b>ADM</b>	0.14 $\pm$ 0.00	0.90 $\pm$ 0.03	0.30 $\pm$ 0.01	0.90 $\pm$ 0.02	0.11 $\pm$ 0.01	>40

the isopentene group to isopentyl group has no significant effect on the decrease or increase of cytotoxicity.

(5) The totally methylation of compounds **2a** and **2d** cause the disappearance of cytotoxicity of compound **2i** and **2j**. However, the cytotoxicity of compounds **2c** and **2g** with 5-7 hydroxyl groups also completely disappeared. Compound **2s** ( $\gamma$ -mangostin) is more active than compound **1** ( $\alpha$ -mangostin) indicating the importance of the presence of hydroxyl group at the C-7 position, whereby substituting it with methoxy group reduced the cytotoxicity. To summarize, a certain number of hydroxyl groups contribute to the maintenance of cytotoxic activity. The number and location of hydroxyl functional groups have different effects on cytotoxicity.

(6) A closer look at the data reveals that the effect of halogenation on the selective potency of these compounds is quite subtle. Some of the halogenated products showed better

cytotoxicity, for example, compound **3e** is up to three times more cytotoxic than the parent compound with  $IC_{50}$  value of 3.98  $\pm$  0.63  $\mu$ M for SMMC-7721 cell lines.

### 3. Experimental

#### 3.1 Materials and methods

All reagents were purchased from Sigma-Aldrich or Aladdin or Innochem Co. Ltd. and were of commercial quality. They were used as received without further purification. Solvents were dried by standard methods prior to use. The other reagents were of analytical grade. Air and moisture sensitive reactions were performed under nitrogen atmosphere. All synthesized target compounds were purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 1 : 1 ~ 20 : 1) and their structures were elucidated by  $^1$ H NMR,  $^{13}$ C NMR, electrospray

Table 3 *In vitro* cytotoxic activity ( $IC_{50}$ ,  $\mu$ M) of mangostin derivatives

Compounds	$IC_{50} \pm SD$ ( $\mu$ M)					
	HL-60	SMMC-7721	A-549	MCF-7	SW480	BEAS-2B
<b>1</b>	15.04 $\pm$ 0.33	10.30 $\pm$ 0.48	13.82 $\pm$ 0.61	10.81 $\pm$ 1.12	14.45 $\pm$ 0.85	15.81 $\pm$ 1.02
<b>3a</b>	>40	34.67 $\pm$ 2.22	>40	>40	>40	>40
<b>3b</b>	>40	24.11 $\pm$ 0.16	>40	22.18 $\pm$ 0.20	>40	>40
<b>3c</b>	16.91 $\pm$ 0.19	8.07 $\pm$ 0.76	14.30 $\pm$ 0.85	16.01 $\pm$ 0.66	36.63 $\pm$ 0.74	21.83 $\pm$ 0.14
<b>3d</b>	14.55 $\pm$ 0.40	10.76 $\pm$ 1.02	16.18 $\pm$ 0.13	21.92 $\pm$ 0.50	17.30 $\pm$ 0.49	16.05 $\pm$ 0.47
<b>3e</b>	14.87 $\pm$ 0.33	3.98 $\pm$ 0.63	12.02 $\pm$ 0.19	19.66 $\pm$ 0.62	21.29 $\pm$ 0.44	20.74 $\pm$ 0.18
<b>DDP</b>	3.19 $\pm$ 0.18	18.03 $\pm$ 0.49	13.75 $\pm$ 0.74	28.42 $\pm$ 3.71	14.77 $\pm$ 2.15	>40
<b>ADM</b>	0.14 $\pm$ 0.00	0.90 $\pm$ 0.03	0.30 $\pm$ 0.01	0.90 $\pm$ 0.02	0.11 $\pm$ 0.01	>40



ionization mass spectrometry (ESI-MS) and high-resolution mass spectrometry (HR-ESIMS). Mass spectra were performed on an API QSTAR time-of-flight spectrometer (MDS Sciex, Concord, Ontario, Canada) and LCMS-IT-TOF (Shimadzu, Kyoto, Japan) spectrometer. NMR spectra were recorded on Bruker AM-400 and DRX-500 instruments with TMS as the internal standard (Bruker, Bremerhaven, Germany). The chemical shifts were given in  $\delta$  (ppm) with reference to the solvent signal.  $^1\text{H}$  NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiple resonances), number of protons, and coupling constant ( $J$ ) in hertz (Hz). Column chromatography was performed on silica gel (200–300 and 300–400 mesh, Qingdao Marine Chemical Inc., Qingdao, China) with the indicated solvents. The fractions were monitored by TLC and the spots were visualized by UV light and sprayed with 10%  $\text{H}_2\text{SO}_4$  in EtOH, followed by heating.

### 3.2 Synthetic procedures and crystallography

#### 3.2.1 General procedure for synthesis of compound 1a–1l.

Potassium carbonate and corresponding brominated compounds were added to a solution of  $\alpha$ -mangostin (41 mg, 0.1 mmol) in acetone. The reaction mixture was heated at reflux for 24 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and then washed with saturated  $\text{NaHCO}_3$  (aq) and brine. The organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford intermediated 1a to 1l.

*3,6-Di-O-benzyl- $\alpha$ -mangostin (1a).* Yield 80%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  13.51 (s, 1H, 1-OH), 7.48–7.34 (m, 10H, Ar-H), 6.75 (s, 1H, H-5), 6.34 (s, 1H, H-4), 5.28 (br t, 2H,  $J$  = 7.0 Hz, H-12, H-17), 5.18, 5.15 (each s, each 2H, H-21, H-28), 4.15 (d, 2H,  $J$  = 6.5 Hz, H-16), 3.83 (s, 3H, 7-OCH<sub>3</sub>), 3.41 (d, 2H,  $J$  = 7.0 Hz, H-11), 1.86–1.59 (s, each 3H, H-14, H-15, H-19, H-20);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  182.0 (C-9), 162.4 (C-3), 159.9 (C-1), 157.0 (C-6), 155.2 (C-10a), 155.0 (C-4a), 144.2 (C-7), 137.4 (C-8), 136.3, 135.7 (C-22, C-29), 131.8, 131.6 (C-13, C-18), 128.8, 128.6, 128.4, 128.1, 127.4, 127.2 (C-23, C-24, C-25, C-26, C-27, C-30, C-31, C-32, C-33, C-34), 123.3, 122.4 (C-12, C-17), 112.3 (C-8a), 111.8 (C-2), 104.1 (C-9a), 99.4 (C-5), 89.8 (C-4), 70.7, 70.2 (C-21, C-28), 61.0 (OCH<sub>3</sub>), 26.2 (C-16), 26.0, 25.9 (C-15, C-20), 21.6 (C-11), 18.2, 17.8 (C-14, C-19); positive ESIMS  $m/z$  591 [M + H]<sup>+</sup>.

*3,6-Di-O-acetyl- $\alpha$ -mangostin (1b).* Yield 82%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  13.42 (s, 1H, 1-OH), 7.13 (s, 1H, H-5), 6.64 (s, 1H, H-4), 5.17 (br t, 2H,  $J$  = 7.0 Hz, H-12, H-17), 4.13 (d, 2H,  $J$  = 6.0 Hz, H-16), 3.77 (s, 3H, 7-OCH<sub>3</sub>), 3.32 (d, 2H,  $J$  = 7.0 Hz, H-11), 2.39, 2.34 (each s, each 3H, COCH<sub>3</sub>), 1.83, 1.78 (each s, each 3H, H-15, H-20), 1.68 (s, 6H, H-14, H-19);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  182.9 (C-9), 168.5 (C-23), 168.1 (C-21), 161.0 (C-1), 154.9 (C-3), 154.1 (C-4a), 153.7 (C-10a), 149.4 (C-7), 146.7 (C-6), 139.2 (C-8), 132.4, 132.3 (C-13, C-18), 122.6, 121.3 (C-12, C-17), 116.9 (C-8a), 116.2 (C-2), 110.6 (C-5), 107.1 (C-9a), 100.3 (C-4), 61.7 (OCH<sub>3</sub>), 26.5 (C-16), 25.9, 25.7 (C-15, C-20), 22.3 (C-11), 21.0 (C-

22), 20.9 (C-24), 18.2, 17.9 (C-14, C-19); positive ESIMS  $m/z$  517 [M + Na]<sup>+</sup>.

*1,3,6-Tri-O-acetyl- $\alpha$ -mangostin (1c).* Yield 80%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.13 (s, 1H, H-5), 7.09 (s, 1H, H-4), 5.17 (br t, H,  $J$  = 7.0 Hz, H-12), 5.03 (br t, H,  $J$  = 7.0 Hz, H-17), 4.06 (d, 2H, H-16), 3.75 (s, 3H, 7-OCH<sub>3</sub>), 3.27 (d, 2H, H-11), 2.46, 2.37, 2.33 (each s, each 3H, COCH<sub>3</sub>), 1.82, 1.75, 1.67, 1.42 (each s, each 3H, H-14, H-15, H-19, H-20);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  176.1 (C-9), 169.3 (C-21), 168.2 (C-22), 168.1 (C-23), 154.5 (C-3), 153.2 (C-1), 153.1 (C-10a), 148.8 (C-4a), 148.5 (C-7), 146.7 (C-6), 139.0 (C-8), 132.5, 131.8 (C-13, C-18), 123.6, 122.9 (C-12, C-17), 120.9 (C-8a), 118.9 (C-2), 113.6 (C-9a), 110.3 (C-5), 109.0 (C-4), 61.6 (OCH<sub>3</sub>), 26.2 (C-16), 25.8, 25.6 (C-15, C-20), 23.5 (C-11), 21.2, 21.0, 20.9 (C-21, C-23, C-25), 18.2, 17.9 (C-14, C-19); positive ESIMS  $m/z$  537 [M + H]<sup>+</sup>.

*3,6-Di-O-methyl- $\alpha$ -mangostin (1d).* Yield 80%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  6.73 (s, 1H, H-5), 6.32 (s, 1H, H-4), 5.24 (br t, 2H,  $J$  = 7.3 Hz, H-12, H-17), 4.13 (d, 2H,  $J$  = 6.6 Hz, H-16), 3.95, 3.90 (each s, each 3H, 3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>), 3.79 (s, 3H, 7-OCH<sub>3</sub>), 3.35 (d, 2H,  $J$  = 7.1 Hz, H-11), 1.82, 1.80 (each s, each 3H, H-14, H-19), 1.68 (s, 6H, H-15, H-20);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  182.0 (C-9), 163.4 (C-3), 159.8 (C-1), 158.0 (C-10a), 155.4 (C-4a), 155.2 (C-7), 144.0 (C-6), 137.3 (C-8), 131.8, 131.7 (C-13, C-18), 123.2, 122.3 (C-12, C-17), 112.1 (C-8a), 111.5 (C-2), 104.0 (C-9a), 98.2 (C-5), 88.7 (C-4), 61.0 (7-OCH<sub>3</sub>), 56.0, 55.8 (3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>), 26.2 (C-16), 25.9 (C-15, C-20), 21.4 (C-11), 18.2, 17.8 (C-14, C-19); positive ESIMS  $m/z$  439 [M + H]<sup>+</sup>.

*1,3,6-Tri-O-methyl- $\alpha$ -mangostin (1e).* Yield 80%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  6.74 (s, 1H, H-5), 6.61 (s, 1H, H-4), 5.35 (br t, H,  $J$  = 6.5 Hz, H-12), 5.21 (br t, H,  $J$  = 7.0 Hz, H-17), 4.17 (d, 2H,  $J$  = 6.7 Hz, H-16), 3.98, 3.94, 3.89, 3.82 (each s, each 3H, 1-OCH<sub>3</sub>, 3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>, 7-OCH<sub>3</sub>), 3.42 (d, 2H,  $J$  = 7.0 Hz, H-11), 1.82, 1.80 (each s, each 3H, H-15, H-20), 1.68 (s, 6H, H-14, H-19);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  176.3 (C-9), 162.1 (C-3), 158.6 (C-1), 157.0 (C-10a), 156.6 (C-4a), 154.3 (C-6), 143.9 (C-7), 137.4 (C-8), 131.5, 131.3 (C-13, C-18), 123.8, 122.8 (C-12, C-17), 120.5 (C-2), 114.7 (C-9a), 110.9 (C-8a), 97.8 (C-5), 94.2 (C-4), 62.0 (1-OCH<sub>3</sub>), 60.9 (7-OCH<sub>3</sub>), 55.9, 55.8 (3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>), 29.7 (C-16), 26.0, 25.9 (C-15, C-20), 22.4 (C-11), 18.2, 17.9 (C-14, C-19); positive ESIMS  $m/z$  453 [M + H]<sup>+</sup>.

*3,6-Bis(allyloxy)-1-hydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one (1f).* Yield 78%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  13.49 (s, 1H, 1-OH), 6.69 (s, 1H, H-5), 6.27 (s, 1H, H-4), 6.08 (m, 2H,  $-\text{CH}=\text{H}$ -22, H-25), 5.47, 5.34 (m, each 2H,  $=\text{CH}_2$ , H-23, H-26), 5.25 (br t, 2H,  $J$  = 6.0 Hz, H-12, H-17), 4.66, 4.60 (each d, each 2H,  $J$  = 5.0 Hz,  $-\text{OCH}_2$ , H-21, H-24), 4.13 (d, 2H,  $J$  = 7.0 Hz, H-16), 3.81 (s, 3H, 7-OCH<sub>3</sub>), 3.38 (d, 2H,  $J$  = 7.0 Hz, H-11), 1.85, 1.79 (each s, each 3H, H-15, H-20), 1.68 (s, 6H, H-14, H-19);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  182.0 (C-9), 162.2 (C-3), 159.9 (C-1), 156.9 (C-4a), 155.2 (C-10a), 155.0 (C-6), 144.1 (C-7), 137.4 (C-8), 132.5, 132.0 (C-22, C-25), 131.8, 131.6 (C-13, C-18), 123.3, 122.3 (C-12, C-17), 118.5, 111.7 (C-23, C-26), 112.1 (C-8a), 111.7 (C-2), 104.0 (C-9a), 99.2 (C-5), 89.6 (C-4), 69.4, 69.1 (C-21, C-24), 60.9 (7-OCH<sub>3</sub>), 26.2 (C-16), 26.0, 25.9 (C-15, C-20), 21.5 (C-11), 18.2, 17.9 (C-14, C-19); positive ESIMS  $m/z$  491 [M + H]<sup>+</sup>.

*1-Hydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-3,6-diproxy-9H-xanthen-9-one (1g).* Yield 75%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500



MHz)  $\delta$  13.50 (s, 1H, 1-OH), 6.69 (s, 1H, H-5), 6.27 (s, 1H, H-4), 5.25 (br t, 2H,  $J$  = 7.0 Hz, H-12, H-17), 4.13 (d, 2H,  $J$  = 6.5 Hz, H-16), 4.03, 3.98 (each t, each 2H,  $J$  = 6.5 Hz, H-21, H-24), 3.81 (s, 3H, 7-OCH<sub>3</sub>), 3.36 (d, 2H,  $J$  = 7.0 Hz, H-11), 1.93–1.06 (m, 10H, -CH<sub>2</sub>, -CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  182.0 (C-9), 162.8 (C-3), 159.8 (C-1), 157.5 (C-4a), 155.3 (C-10a), 155.1 (C-6), 144.0 (C-7), 137.1 (C-8), 131.7, 131.3 (C-13, C-18), 123.3, 122.5 (C-12, C-17), 111.8 (C-2), 111.4 (C-8a), 103.8 (C-9a), 98.7 (C-5), 89.2 (C-4), 70.3, 70.0 (C-21, C-24), 60.8 (7-OCH<sub>3</sub>), 26.2 (C-16), 26.0, 25.9 (C-15, C-20), 22.5, 22.3 (C-22, C-25), 21.4 (C-11), 18.2, 17.8 (C-14, C-19), 10.7, 10.6 (C-23, C-26); positive ESIMS *m/z* 517 [M + Na]<sup>+</sup>.

*3,6-Di-O-3,3-dimethylallyl- $\alpha$ -mangostin (1h).* Yield 15%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  13.50 (s, 1H, 1-OH), 7.03 (d, 1H,  $J$  = 4.2 Hz, H-5), 6.55 (s, 1H,  $J$  = 4.3 Hz, H-4), 5.49, 5.46 (each t, each 1H,  $J$  = 6.6 Hz, H-22, H-27), 5.13 (br t, 2H, H-12, H-17), 4.71, 4.64 (each d, each 2H,  $J$  = 6.5 Hz, H-21, H-26), 3.99 (d, 2H,  $J$  = 6.0 Hz, H-16), 3.68 (s, 3H, 7-OCH<sub>3</sub>), 3.19 (d, 2H,  $J$  = 7.0 Hz, H-11), 1.77, 1.75, 1.75, 1.72, 1.69, 1.60, 1.59 (s, each 3H, H-14, H-15, H-19, H-20, H-24, H-25, H-29, H-30); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  181.5 (C-9), 162.5 (C-3), 158.8 (C-1), 157.3 (C-4a), 154.8 (C-10a), 154.6 (C-6), 143.9 (C-7), 138.7, 138.2 (C-23, C-28), 135.7 (C-8), 130.7, 130.5 (C-13, C-18), 123.5 (C-12, C-17), 122.1 (C-22, C-27), 119.1 (C-8a), 118.8 (C-2), 102.8 (C-9a), 99.8 (C-5), 90.3 (C-4), 65.7, 65.4 (C-21, C-26), 60.3 (7-OCH<sub>3</sub>), 25.6 (C-16), 25.5 (C-15, C-20, C-25, C-30), 21.0 (C-11), 18.2, 18.1, 18.0, 17.6 (C-14, C-19, C-24, C-29); positive ESIMS *m/z* 547 [M + H]<sup>+</sup>.

*Dimethyl-2,2'-(*l*-hydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9-oxo-9H-xanthene-3,6-diyi)bis(oxyl)diacetate (1i).* Yield 60%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  13.47 (s, 1H, 1-OH), 7.03 (s, 1H, H-5), 6.50 (s, 1H, H-4), 5.17 (m, 2H, H-12, H-17), 5.07, 4.98 (each s, each 2H, H-21, H-24), 4.01 (d, 2H,  $J$  = 6.3 Hz, H-16), 3.76, 3.73, 3.72 (each s, each 3H, 23-OCH<sub>3</sub>, 26-OCH<sub>3</sub>, 7-OCH<sub>3</sub>), 3.27 (d, 2H,  $J$  = 7.1 Hz, H-11), 1.77, 1.72, 1.61, 1.60 (each s, each 3H, H-14, H-15, H-19, H-20); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  181.6 (C-9), 168.6, 168.5 (C-22, C-25), 161.5 (C-3), 159.0 (C-1), 156.4 (C-4a), 154.5 (C-10a), 154.4 (C-6), 143.7 (C-7), 136.2 (C-8), 130.9, 130.7 (C-13, C-18), 123.3, 121.9 (C-12, C-17), 111.4 (C-8a), 111.0 (C-2), 103.3 (C-9a), 99.9 (C-5), 90.2 (C-4), 65.2, 65.1 (C-21, C-24), 60.4 (7-OCH<sub>3</sub>), 52.1, 52.0 (C-23, C-26), 25.6 (C-16), 25.6, 25.5 (C-15, C-20), 21.0 (C-11), 18.0, 17.7 (C-14, C-19); negative ESIMS *m/z* 553 [M - H]<sup>-</sup>.

*Diethyl-2,2'-(*l*-hydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9-oxo-9H-xanthene-3,6-diyi)bis(oxyl)diacetate (1j).* Yield 60%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  13.49 (s, 1H, 1-OH), 7.04 (s, 1H, H-5), 6.51 (s, 1H, H-4), 5.20, 5.15 (each t, each 1H,  $J$  = 7.0 Hz, H-12, H-17), 5.06, 4.97 (each s, each 2H, H-21, H-25), 4.19 (m, 4H, H-23, H-27), 4.02 (d, 2H,  $J$  = 7.0 Hz, H-16), 3.76 (s, 3H, 7-OCH<sub>3</sub>), 3.28 (d, 2H,  $J$  = 7.0 Hz, H-11), 1.77, 1.72, 1.61, 1.60 (each s, each 3H, H-14, H-15, H-19, H-20), 1.22 (m, 6H, H-24, H-28); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  181.6 (C-9), 168.1, 168.0 (C-22, C-26), 161.5 (C-3), 159.0 (C-1), 156.5 (C-4a), 154.6 (C-10a), 154.5 (C-6), 143.8 (C-7), 136.2 (C-8), 130.9, 130.8 (C-13, C-18), 123.3, 121.9 (C-12, C-17), 111.4 (C-8a), 111.0 (C-2), 103.3 (C-9a), 99.9 (C-5), 90.3 (C-4), 65.3, 65.2 (C-21, C-25), 61.0, 60.9 (C-23, C-27), 60.4 (7-OCH<sub>3</sub>), 25.6 (C-16), 25.6, 25.5 (C-15, C-20), 21.0 (C-11), 18.0,

17.7 (C-14, C-19), 14.1 (C-24, C-28); positive ESIMS *m/z* 605 [M + Na]<sup>+</sup>.

*Dimethyl-4,4'-(*l*-hydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9-oxo-9H-xanthene-3,6-diyi)bis(oxyl)butanoate (1k).* Yield 25%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  13.44 (s, 1H, 1-OH), 6.87 (s, 1H, H-5), 6.38 (s, 1H, H-4), 5.10 (br t, 2H,  $J$  = 7.0 Hz, H-12, H-17), 4.10, 4.05 (each t, each 2H, H-21, H-26), 3.93 (d, 2H,  $J$  = 6.5 Hz, H-16), 3.67 (s, 3H, 7-OCH<sub>3</sub>), 3.61, 3.60 (each s, each 3H, H-25, H-30), 3.14 (d, 2H,  $J$  = 7.0 Hz, H-11), 2.50 (m, 4H, H-23, H-28), 2.02 (m, 4H, H-22, H-27), 1.74, 1.68, 1.60, 1.59 (each s, each 3H, H-14, H-15, H-19, H-20); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  181.3 (C-9), 172.9, 172.9 (C-24, C-29), 162.3 (C-3), 158.8 (C-1), 157.2 (C-4a), 154.7 (C-10a), 154.6 (C-6), 143.6 (C-7), 135.7 (C-8), 130.5 (C-13, C-18), 123.4, 122.3 (C-12, C-17), 110.7 (C-8a), 110.4 (C-2), 102.8 (C-9a), 99.3 (C-5), 89.7 (C-4), 67.8, 67.3 (C-21, C-26), 60.3 (7-OCH<sub>3</sub>), 51.4 (C-25, C-30), 29.9, 29.8 (C-23, C-28), 25.5 (C-16), 25.4, 24.0, 23.9 (C-15, C-20, C-22, C-27), 20.9 (C-11), 17.9, 17.5 (C-14, C-19); positive ESIMS *m/z* 633 [M + Na]<sup>+</sup>.

*Diethyl-4,4'-(*l*-hydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9-oxo-9H-xanthene-3,6-diyi)bis(oxyl)butanoate (1l).* Yield 25%, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  13.49 (s, 1H, 1-OH), 6.72 (s, 1H, H-5), 6.29 (s, 1H, H-4), 5.23 (br t, 2H,  $J$  = 7.0 Hz, H-12, H-17), 4.15 (m, 8H, H-21, H-25, H-27, H-31), 4.09 (t, 2H,  $J$  = 6.0 Hz, H-16), 3.79 (s, 3H, 7-OCH<sub>3</sub>), 3.35 (d, 2H,  $J$  = 7.1 Hz, H-11), 2.56 (dt, 4H,  $J$  = 7.2, 12.5 Hz, H-23, H-29), 2.20 (m, 4H, H-22, H-28), 1.85, 1.79 (each s, each 3H, H-15, H-20), 1.68 (s, 6H, H-14, H-19), 1.27 (t, 6H, H-26, H-32); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  182.0 (C-9), 173.1, 172.9 (C-24, C-30), 162.5 (C-3), 159.9 (C-1), 157.2 (C-4a), 155.3 (C-10a), 155.1 (C-6), 144.0 (C-7), 137.3 (C-8), 131.8, 131.5 (C-13, C-18), 123.2, 122.5 (C-12, C-17), 112.1 (C-8a), 111.5 (C-2), 104.0 (C-9a), 98.8 (C-5), 89.3 (C-4), 67.6, 67.2 (C-21, C-27), 60.9, 60.6 (C-25, C-31), 60.5 (7-OCH<sub>3</sub>), 30.6 (C-23, C-29), 26.2 (C-16), 25.9, 25.8, 24.4, 24.3 (C-15, C-20, C-22, C-28), 21.4 (C-11), 18.2, 17.8 (C-14, C-19), 14.2 (C-26, C-32); positive ESIMS *m/z* 661 [M + Na]<sup>+</sup>.

### 3.2.2 General procedure for synthesis of compound 2a–2c.

A 1% (w/v) osmium tetroxide solution (100  $\mu$ L) in *t*-BuOH was added to a mixture of  $\alpha$ -mangostin (1) (41 mg, 0.1 mmol), NMO (17.6 mg, 0.15 mmol), acetone (1 mL) and water (1 mL), and the whole was stirred at room temperature for 24 h. Sodium sulfite was added to the resulting mixture and stirring was continued for a further 30 min. The mixture was diluted with water, extracted with ethyl acetate (3  $\times$  20 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give a yellow solid. The residue was purified on column chromatograph using petroleum ether/ethyl acetate (1 : 1) to afford 2a (4.4 mg, 10%), 2b (5 mg, 12%) and 2c (37 mg, 78%).

*1,3,6-Trihydroxy-2-(2,3-dihydroxy-3-methylbutyl)-7-methoxy-8-(3-methyl-2-butenyl)xanthone (2a).* Yield 10%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz)  $\delta$  6.70 (s, 1H, H-5), 6.27 (s, 1H, H-4), 5.21 (br t, 1H,  $J$  = 6.5 Hz, H-2''), 4.07 (d, 2H,  $J$  = 6.5 Hz, H-1''), 3.75 (s, 3H, 7-OCH<sub>3</sub>), 3.61 (dd, 1H,  $J$  = 2.5, 10.0 Hz, H-2'), 3.04 (dd, 1H,  $J$  = 2.5, 14.0 Hz, H-1'), 2.68 (dd, 1H,  $J$  = 10.0, 14.0 Hz, H-1'), 1.82, 1.66 (each s, each 3H, H-4'', H-5''); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz)  $\delta$  183.2 (C-9), 164.4 (C-3), 162.1 (C-1), 158.1 (C-6), 156.8 (C-4a), 156.6 (C-10a), 144.9 (C-7), 138.5 (C-8), 131.9 (C-3'), 125.1 (C-2''), 112.2 (C-8a), 109.8 (C-2), 103.8 (C-9a), 102.8



(C-5), 93.9 (C-2'), 80.0 (C-4), 74.0 (C-3'), 61.3 (OCH<sub>3</sub>), 27.1 (C-1'), 26.0 (C-1''), 25.8, 25.6, 25.2, 18.3; negative ESIMS *m/z* 443 [M - H]<sup>-</sup>.

**1,3,6-Trihydroxy-2-(3-methyl-2-butenyl)-7-methoxy-8-(2,3-dihydroxy-3-methylbutyl)xanthone (2b).** Yield 12%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.77 (s, 1H, H-5), 6.28 (s, 1H, H-4), 5.22 (m, 1H, H-2'), 3.84 (s, 3H, 7-OCH<sub>3</sub>), 3.66 (dd, 1H, *J* = 2.8, 10.2 Hz, H-2''), 3.54 (dd, 2H, *J* = 2.8, 12.3 Hz, H-1''), 3.33 (m, 2H, H-1'), 1.77, 1.65 (each s, each 3H, H-4'', H-5''), 1.34, 1.33 (each s, each 3H, H-4', H-5'); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 184.0 (C-9), 164.2 (C-3), 161.5 (C-1), 158.3 (C-4a), 156.7 (C-10a), 156.4 (C-6), 145.9 (C-7), 136.5 (C-8), 131.8 (C-3'), 123.7 (C-2'), 112.9 (C-8a), 111.8 (C-2), 103.7 (C-9a), 103.2 (C-5), 93.3 (C-4), 80.7 (C-2''), 74.3 (C-3''), 60.9 (OCH<sub>3</sub>), 29.6 (C-1''), 26.0, 25.8, 25.4, 22.2 (C-1'), 17.9; negative ESIMS *m/z* 443 [M - H]<sup>-</sup>.

**1,3,6-Trihydroxy-7-methoxy-2,8-bis(2,3-dihydroxy-3-methylbutyl)-9H-xanthen-9-one (2c).** Yield 78%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.74 (s, 1H, H-5), 6.29 (s, 1H, H-4), 3.85 (s, 3H, 7-OCH<sub>3</sub>), 3.65 (m, 1H, H-2''), 3.61 (m, 1H, H-2'), 3.56 (m, 2H, H-1''), 3.02 (dd, 1H, *J* = 2.4, 14.0 Hz, H-1'), 2.68 (dd, 1H, *J* = 10.2, 14.0 Hz, H-1'), 1.33, 1.32, 1.26, 1.25 (each s, each 3H, H-4', H-5', H-4'', H-5''); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 183.9 (C-9), 164.9 (C-3), 161.9 (C-1), 158.3 (C-4a), 156.7 (C-10a), 156.7 (C-6), 145.9 (C-7), 136.5 (C-8), 112.8 (C-8a), 110.0 (C-2), 103.7 (C-9a), 103.3 (C-5), 94.0 (C-4), 80.6 (C-2''), 79.8 (C-2'), 74.3 (C-3''), 74.0 (C-3'), 61.0 (OCH<sub>3</sub>), 29.6 (C-1''), 25.9, 25.8 (C-1'), 25.6, 25.4, 25.2; negative ESIMS *m/z* 477 [M - H]<sup>-</sup>; HRESIMS *m/z* 477.1766 [M - H]<sup>-</sup> (calcd for C<sub>24</sub>H<sub>29</sub>O<sub>10</sub>, 477.1766).

**3.2.3 General procedure for synthesis of compound 2d, 2e and 2r.** A solution of **1**, **2a** or **2b** (44 mg, 0.1 mmol) and 10% Pd/C (5 mg) in CH<sub>3</sub>OH (2 mL) was placed under an atmosphere of hydrogen. After stirring for 24 h, the reaction mixture was filtered through filter paper and concentrated under reduced pressure. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (1 : 1 ~ 2 : 1) to afford **2d**, **2e** or **2r** respectively.

**1,3,6-Trihydroxy-2-(2,3-dihydroxy-3-methylbutyl)-7-methoxy-8-isopentyl-9H-xanthen-9-one (2d).** Yield 78%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.62 (s, 1H, H-5), 6.21 (s, 1H, H-4), 3.78 (s, 3H, 7-OCH<sub>3</sub>), 3.60 (dd, 1H, *J* = 2.4, 10.1 Hz, H-2''), 3.26 (m, 2H, H-1''), 3.01 (dd, 1H, *J* = 2.4, 14.1 Hz, H-1'), 2.65 (dd, 1H, *J* = 10.1, 14.1 Hz, H-1'), 1.71 (m, 1H, H-3''), 1.41 (m, 2H, H-2''), 1.26 (s, 6H, H-4'', H-5''), 1.00, 0.98 (each s, each 3H, H-4', H-5'); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 183.1 (C-9), 164.2 (C-1), 162.1 (C-3), 157.8 (C-4a), 156.7 (C-10a), 156.5 (C-6), 144.6 (C-7), 140.4 (C-8), 112.1 (C-8a), 109.6 (C-2), 103.8 (C-9a), 102.6 (C-5), 93.9 (C-4), 80.0 (C-2''), 74.0 (C-3''), 61.5 (OCH<sub>3</sub>), 41.4 (C-2'), 30.1 (C-3''), 26.3 (C-1''), 25.8 (C-1'), 25.7, 25.1, 23.0; negative ESIMS *m/z* 445 [M - H]<sup>-</sup>; HRESIMS *m/z* 445.1870 [M - H]<sup>-</sup> (calcd for C<sub>24</sub>H<sub>29</sub>O<sub>8</sub>, 445.1868).

**1,3,6-Trihydroxy-2-isopentyl-7-methoxy-8-(2,3-dihydroxy-3-methylbutyl)-9H-xanthen-9-one (2e).** Yield 78%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.66 (d, 1H, *J* = 1.8 Hz, H-5), 6.18 (d, 1H, *J* = 1.6 Hz, H-4), 3.84 (s, 3H, 7-OCH<sub>3</sub>), 3.63 (dd, 1H, *J* = 2.7, 10.5 Hz, H-2''), 3.48 (m, 2H, H-1''), 2.56 (m, 2H, H-1'), 1.55 (m, 1H, H-3''), 1.37 (m, 2H, H-2''), 1.32 (s, 6H, H-4'', H-5''), 0.95, 0.93 (each s, each 3H, H-4', H-5'); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 183.8 (C-9),

164.2 (C-1), 161.5 (C-3), 158.0 (C-4a), 156.6 (C-10a), 156.1 (C-6), 145.7 (C-7), 136.3 (C-8), 112.8 (C-8a), 112.8 (C-2), 103.6 (C-9a), 103.2 (C-5), 93.3 (C-4), 80.8 (C-2''), 74.3 (C-3''), 60.9 (OCH<sub>3</sub>), 39.1 (C-2''), 29.6 (C-1'), 29.5 (C-3''), 25.9, 25.3, 23.1, 21.2 (C-1''); negative ESIMS *m/z* 445 [M - H]<sup>-</sup>; HRESIMS *m/z* 445.1867 [M - H]<sup>-</sup> (calcd for C<sub>24</sub>H<sub>29</sub>O<sub>8</sub>, 445.1868).

**Tetrahydro- $\alpha$ -mangostin (2r).** Yield 95%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.60 (s, 1H, H-5), 6.17 (s, 1H, H-4), 3.77 (s, 3H, 7-OCH<sub>3</sub>), 3.24 (m, 2H, H-1''), 2.57 (m, 2H, H-1'), 1.70 (m, 1H, *J* = 6.6, 13.1 Hz, H-3''), 1.56 (m, 1H, *J* = 6.6, 13.1 Hz, H-3''), 1.39 (m, 4H, H-2', H-2''), 0.99, 0.97, 0.95, 0.94 (each s, each 3H, H-4', H-5', H-4'', H-5''); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 183.1 (C-9), 163.6 (C-1), 161.7 (C-3), 157.6 (C-4a), 156.7 (C-6), 156.0 (C-10a), 144.5 (C-7), 140.4 (C-8), 112.5 (C-8a), 112.2 (C-2), 103.7 (C-9a), 102.5 (C-5), 93.0 (C-4), 61.5 (7-OCH<sub>3</sub>), 41.5 (C-2''), 39.1 (C-2''), 30.1 (C-3''), 29.5 (C-3''), 26.2 (C-1''), 23.1 (C-4', C-5''), 23.0 (C-4'', C-5''), 21.2 (C-1'); negative ESIMS *m/z* 413 [M - H]<sup>-</sup>.

### 3.2.4 General procedure for synthesis of compound 2f-2h.

A solution of **2a**, **2c** or **2d** (0.1 mmol) in mixed reagent (2 mL, THF : H<sub>2</sub>O = 2 : 1) was added NaIO<sub>4</sub> (26 mg, 0.12 mmol) at cool temperature. After the addition was completed, the reaction solution was allowed to warm to room temperature. After stirring for 4 h, the reaction mixture was diluted with water, extracted with ethyl acetate (3 × 10 mL). The organic phase solvent was washed with brine, dried over anhydrous sodium sulfate, and then concentrated *in vacuo* to give a yellow solid. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (2 : 1 ~ 4 : 1) to afford **2f**, **2g** or **2h**.

**1,3,6-Trihydroxy-7-methoxy-8-(3-methylbut-2-en-1-yl)-2H-furo[3,2-b]xanthene-5(3H)-one (2f).** Yield 60%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.64 (s, 1H, H-5), 6.21 (s, 1H, H-4), 5.19 (m, 1H, H-2''), 4.83 (t, 1H, *J* = 5.7 Hz, H-2''), 4.02 (t, 2H, *J* = 6.2 Hz, H-1''), 3.74 (s, 3H, 7-OCH<sub>3</sub>), 2.91 (m, 2H, H-1'), 1.81, 1.66 (each s, each 3H, H-4'', H-5''); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 183.1 (C-9), 164.2 (C-3), 162.4 (C-1), 158.0 (C-6), 156.7 (C-4, C-10a), 144.8 (C-7), 138.5 (C-8), 131.8 (C-3''), 125.1 (C-2''), 112.1 (C-8a), 107.0 (C-2), 103.7 (C-9a), 102.8 (C-5), 99.0 (C-2''), 93.5 (C-4), 61.3 (OCH<sub>3</sub>), 30.9 (C-1'), 27.1 (C-1''), 26.0, 18.3; negative ESIMS *m/z* 383 [M - H]<sup>-</sup>; HRESIMS *m/z* 383.1134 [M - H]<sup>-</sup> (calcd for C<sub>21</sub>H<sub>19</sub>O<sub>7</sub>, 383.1136).

**1,3,6-Trihydroxy-7-methoxy-8-(2,3-dihydroxy-3-methylbutyl)-2H-furo[3,2-b]xanthene-5(3H)-one (2g).** Yield 50%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.67 (s, 1H, H-5), 6.21 (s, 1H, H-4), 4.83 (t, 1H, *J* = 5.7 Hz, H-2''), 3.84 (s, 3H, 7-OCH<sub>3</sub>), 3.63 (m, 1H, H-2''), 3.48 (m, 2H, H-1''), 2.91 (dd, 2H, *J* = 5.7, 14.4 Hz, H-1'), 1.32, 1.31 (each s, each 3H, H-4'', H-5''); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 183.8 (C-9), 164.7 (C-3), 162.3 (C-1), 158.2 (C-6), 156.7 (C-4a), 156.6 (C-10a), 145.9 (C-7), 136.4 (C-8), 112.7 (C-8a), 107.3 (C-2), 103.6 (C-9a), 103.3 (C-5), 98.9 (C-2''), 93.7 (C-4), 80.6 (C-2''), 74.3 (C-3''), 60.9 (OCH<sub>3</sub>), 30.9 (C-1'), 29.6 (C-1''), 25.9, 25.4; negative ESIMS *m/z* 417 [M - H]<sup>-</sup>; HRESIMS *m/z* 417.1187 [M - H]<sup>-</sup> (calcd for C<sub>21</sub>H<sub>21</sub>O<sub>9</sub>, 417.1191).

**1,3,6-Trihydroxy-7-methoxy-8-isopentyl-2H-furo[3,2-b]xanthene-5(3H)-one (2h).** Yield 60%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.65 (s, 1H, H-5), 6.23 (s, 1H, H-4), 4.84 (t, 1H, *J* = 5.7 Hz, H-2''), 3.79 (s, 3H, 7-OCH<sub>3</sub>), 3.29 (m, 2H, H-1''), 2.94 (m, 2H, H-1'), 1.72



(m, 1H, H-3''), 1.42 (m, 2H, H-2''), 1.00, 0.99 (each s, each 3H, H-4'', H-5''); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz)  $\delta$  183.1 (C-9), 164.2 (C-3), 162.5 (C-1), 157.9 (C-6), 156.7 (C-4a), 156.7 (C-10a), 144.7 (C-7), 140.4 (C-8), 112.1 (C-8a), 107.0 (C-2), 103.8 (C-9a), 102.6 (C-5), 99.0 (C-2'), 93.5 (C-4), 61.3 (OCH<sub>3</sub>), 41.5 (C-2''), 30.9 (C-1'), 30.1 (C-3''), 26.2 (C-1''); 23.0; negative ESIMS *m/z* 385 [M - H]<sup>-</sup>; HRESIMS *m/z* 385.1295 [M - H]<sup>-</sup> (calcd for C<sub>21</sub>H<sub>21</sub>O<sub>7</sub>, 385.1293).

**3.2.5 General procedure for synthesis of compound 2i-2j.** A solution of **2a** or **2d** (0.1 mmol) and NaH (80 mg, 2 mM) in DMF (2 mL) was placed under an atmosphere of nitrogen, after stirring for 30 min, the reaction mixture was added CH<sub>3</sub>I (0.2 mL, 3 mM). After stirring for 4 h, the reaction mixture was diluted with water, extracted with ethyl acetate (3  $\times$  10 mL). The organic phase solvent was washed with brine, dried over anhydrous sodium sulfate, and then concentrated *in vacuo* to give a yellow solid. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (9 : 1) to afford **2i** or **2j**.

**2-(2,3-Dimethoxy-3-methylbutyl)-1,3,6,7-tetramethoxy-8-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one (2i).** Yield 60%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  6.98 (s, 1H, H-5), 6.82 (s, 1H, H-4), 5.15 (br t, 1H, *J* = 7.0 Hz, H-17), 3.99 (dd, 2H, *J* = 6.6, 15.6 Hz, H-16), 3.92, 3.77, 3.68 (each s, each 3H, 1-OCH<sub>3</sub>, 3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>, 7-OCH<sub>3</sub>), 3.39 (dd, 1H, *J* = 3.0, 10.0 Hz, H-11), 3.15 (s, 3H, 12-OCH<sub>3</sub>), 2.93 (s, 3H, 13-OCH<sub>3</sub>), 2.85 (dd, 1H, *J* = 10.0, 13.4 Hz, H-12), 2.66 (dd, 1H, *J* = 3.0, 13.4 Hz, H-11), 1.76, 1.58, 1.15, 1.11 (each s, each 3H, C-14, C-15, C-19, C-20); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  175.2 (C-9), 162.5 (C-3), 158.5 (C-1), 157.0 (C-10a), 156.2 (C-4a), 153.7 (C-6), 143.6 (C-7), 135.6 (C-8), 130.3 (C-18), 123.9 (C-17), 118.4 (C-2), 113.7 (C-8a), 110.0 (C-9a), 98.5 (C-5), 94.5 (C-12), 84.6 (C-4), 77.2 (C-13), 61.3 (1-OCH<sub>3</sub>), 60.4 (7-OCH<sub>3</sub>), 60.1 (12-OCH<sub>3</sub>), 56.3 (3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>), 48.9 (13-OCH<sub>3</sub>), 25.6, 25.3 (C-16), 23.8 (C-11), 22.1, 20.6, 18.0; positive ESIMS *m/z* 537 [M + Na]<sup>+</sup>; HRESIMS *m/z* 537.2472 [M + Na]<sup>+</sup> (calcd for C<sub>29</sub>H<sub>38</sub>NaO<sub>8</sub>, 537.2464).

**2-(2,3-Dimethoxy-3-methylbutyl)-8-isopentyl-1,3,6,7-tetramethoxy-9H-xanthen-9-one (2j).** Yield 60%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  6.93 (s, 1H, H-5), 6.78 (s, 1H, H-4), 3.92, 3.91, 3.76, 3.70 (each s, each 3H, 1-OCH<sub>3</sub>, 3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>, 7-OCH<sub>3</sub>), 3.37 (dd, 1H, *J* = 3.0, 10.0 Hz, H-12), 3.24 (m, 2H, H-16), 3.14, 2.92 (each s, each 3H, 12-OCH<sub>3</sub>, 13-OCH<sub>3</sub>), 2.84 (m, 1H, H-11), 2.64 (dd, 1H, *J* = 3.0, 13.0 Hz, H-11), 1.14, 1.10, 0.95, 0.94 (each s, each 3H, C-14, C-15, C-19, C-20); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  175.1 (C-9), 162.4 (C-3), 158.6 (C-1), 156.8 (C-4a), 156.2 (C-10a), 153.7 (C-6), 143.4 (C-7), 137.5 (C-8), 118.3 (C-2), 113.7 (C-8a), 110.0 (C-9a), 98.3 (C-12), 94.4 (C-5), 84.6 (C-13), 77.2 (C-4), 61.2, 60.6, 60.1, 56.3, 56.2 (1-OCH<sub>3</sub>, 3-OCH<sub>3</sub>, 6-OCH<sub>3</sub>, 12-OCH<sub>3</sub>, 13-OCH<sub>3</sub>), 48.9 (C-17), 28.3 (C-18), 24.2 (C-16), 23.7 (C-11), 22.5, 22.5, 22.1, 20.6; positive ESIMS *m/z* 539 [M + Na]<sup>+</sup>; HRESIMS *m/z* 539.2625 [M + Na]<sup>+</sup> (calcd for C<sub>29</sub>H<sub>40</sub>NaO<sub>8</sub>, 539.2621).

A solution of mangostin (0.1 mmol) and DDQ (27 mg, 0.12 mM) in toluene (2 mL) was placed in a flask with round bottom (10 mL), after slowly heating up to 120 °C. After stirring for 4 h, the reaction mixture was concentrated *in vacuo* to give a yellow solid. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (9 : 1) to afford **2k**.

**9-Hydroxycalabaxanthone (2k).** Yield 40%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz)  $\delta$  6.66 (s, 1H, H-5), 6.62 (d, 1H, *J* = 10.0 Hz, H-1'), 6.13 (s, 1H, H-4), 5.61 (d, 1H, *J* = 10.0 Hz, H-2'), 5.20 (br t, 1H, *J* = 6.5 Hz, H-2''), 4.03 (d, 2H, *J* = 6.5 Hz, H-1''), 3.75 (s, 3H, 7-OCH<sub>3</sub>), 1.81, 1.66, 1.43 (each s, each 3H, H-4', H-5', H-4'', H-5''); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz)  $\delta$  183.2 (C-9), 161.0 (C-1), 158.9 (C-3), 158.2 (C-4a), 157.5 (C-10a), 156.7 (C-6), 145.0 (C-7), 138.5 (C-8), 131.9 (C-3''), 128.3 (C-2'), 125.0 (C-2''), 116.4 (C-1'), 112.1 (C-8a), 105.3 (C-2), 104.4 (C-9a), 102.9 (C-5), 94.9 (C-4), 79.0 (C-3'), 61.3 (OCH<sub>3</sub>), 28.6, 27.1 (C-1''), 26.0, 18.3; negative ESIMS *m/z* 407 [M - H]<sup>-</sup>.

A solution of mangostin (0.1 mmol) in DCM (2 mL) was placed under an atmosphere of nitrogen, a *m*-CPBA solution in DCM (2 mL) was then added drop wise over 10 min. The reaction mixture was stirred at 0 °C for 12 h, washed with 10% sodium hydrogen sulfite solution (10 mL), saturated hydrogen carbonate solution (10 mL), saturated sodium chloride (10 mL) and dried with anhydrous sodium sulfate. The reaction mixture was concentrated *in vacuo* to give a yellow solid and the crude product was purified on column chromatograph using petroleum ether/ethyl acetate (9 : 1) to afford **2l** and **2m** respectively.

**1-((3,3-Dimethyloxiran-2-yl)methyl)-3,6,8-trihydroxy-2-methoxy-7-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one (2l).** Yield 4%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 600 MHz)  $\delta$  13.82 (s, 1H, 1-OH), 6.79 (s, 1H, H-5), 6.30 (s, 1H, H-4), 5.28 (d, 1H, *J* = 4.8 Hz, H-2''), 5.15 (t, 1H, *J* = 6.6 Hz, H-2''), 4.02 (t, 2H, *J* = 6.0 Hz, H-1''), 3.71 (d, H, *J* = 6.3 Hz, H-1'), 3.70 (s, 3H, 7-OCH<sub>3</sub>), 2.79 (dd, H, *J* = 16.8 Hz, H-1''), 1.77, 1.62, 1.30, 1.24 (each s, each 3H, H-4', H-5', H-4'', H-5''); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 150 MHz)  $\delta$  181.4 (C-9), 161.2 (C-3), 159.6 (C-1), 157.3 (C-4a), 154.9 (C-10a), 154.2 (C-6), 143.4 (C-7), 136.5 (C-8), 130.5 (C-3''), 123.6 (C-2''), 109.8 (C-8a), 102.8 (C-2), 102.1 (C-10a), 101.8 (C-5), 93.4 (C-4), 79.0 (C-2''), 66.9 (C-3''), 60.2 (OCH<sub>3</sub>), 25.8 (C-1''), 25.6 (C-5''), 25.3, 25.0, 21.2 (C-1', C-4'', C-5''), 18.1 (C-4'); negative ESIMS *m/z* 425 [M - H]<sup>-</sup>; HRESIMS *m/z* 425.1600 [M - H]<sup>-</sup> (calcd for C<sub>24</sub>H<sub>25</sub>O<sub>7</sub>, 425.1600).

**Mangostanin (2m).** Yield 49%, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  13.63 (s, 1H, 1-OH), 6.78 (s, 1H, H-5), 6.37 (s, 1H, H-4), 5.15 (br t, 1H, *J* = 6.5 Hz, H-2''), 4.73 (m, 1H, H-2'), 3.99 (d, 2H, *J* = 6.6 Hz, H-1''), 3.69 (s, 3H, 7-OCH<sub>3</sub>), 3.03 (d, 2H, *J* = 8.6 Hz, H-1'), 1.75, 1.61, 1.14, 1.12 (each s, each 3H, H-4', H-5', H-4'', H-5''); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  181.5 (C-9), 166.6 (C-1), 157.2 (C-6), 157.1 (C-10a), 156.4 (C-4a), 154.7 (C-3), 143.6 (C-7), 136.3 (C-8), 130.4 (C-3''), 123.6 (C-2''), 109.8 (C-8a), 107.8 (C-2), 102.9 (C-9a), 101.7 (C-5), 91.6 (C-2''), 88.0 (C-4), 70.0 (C-3''), 60.2 (OCH<sub>3</sub>), 26.0 (C-1'), 25.8, 25.7, 25.6 (C-1''), 25.0, 18.0; negative ESIMS *m/z* 425 [M - H]<sup>-</sup>.

**1,3,6-Trihydroxy-2-(3-hydroxy-3-methylbutyl)-7-methoxy-8-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one (2n).** Yield 25%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz)  $\delta$  6.70 (s, 1H, H-5), 6.24 (s, 1H, H-4), 5.22 (t, 1H, *J* = 6.5 Hz, H-2''), 3.82 (s, 3H, 7-OCH<sub>3</sub>), 3.34–3.40 (m, 4H, H-1', H-1''), 1.77 (s, 3H, H-4'), 1.73 (m, 2H, H-2'), 1.65 (s, 3H, H-5''), 1.33 (s, 6H, H-4', H-5'); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz)  $\delta$  183.2 (C-9), 163.7 (C-3), 161.6 (C-1), 160.0 (C-6), 156.8 (C-10a), 156.2 (C-4a), 144.7 (C-7), 139.9 (C-8), 131.7 (C-3''), 123.8 (C-2''), 112.2 (C-8a), 111.5 (C-2), 103.8 (C-9a), 102.7 (C-5), 93.1 (C-4), 71.9 (C-3'), 61.5 (OCH<sub>3</sub>), 45.6 (C-2''), 29.0, 26.0, 23.6 (C-1''), 22.2 (C-1'), 17.9; negative ESIMS *m/z* 427 [M - H]<sup>-</sup>.





**3-Isomangostin hydrate (2o).** Yield 23%,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  6.65 (s, 1H, H-5), 6.12 (s, 1H, H-4), 3.82 (s, 3H, 7-OCH<sub>3</sub>), 3.36 (m, 2H, H-1''), 2.65 (m, 2H, H-1'), 1.83 (t, 2H,  $J$  = 6.8 Hz, H-2'), 1.72 (m, 2H, H-2''), 1.34, 1.32 (s, 12H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  183.2 (C-9), 161.9 (C-1), 161.6 (C-3), 158.8 (C-4a), 157.0 (C-10a), 156.0 (C-6), 144.9 (C-7), 139.7 (C-8), 111.8 (C-8a), 104.7 (C-2), 103.6 (C-9a), 102.9 (C-5), 94.8 (C-4), 77.1 (C-3'), 71.9 (C-3''), 61.5 (OCH<sub>3</sub>), 45.5 (C-2''), 32.8 (C-2'), 29.0, 27.0, 23.6 (C-1''), 17.0 (C-1'); negative ESIMS  $m/z$  427 [M - H]<sup>-</sup>.

**1-Isomangostin hydrate (2p).** Yield 12%,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  6.66 (s, 1H, H-5), 6.29 (s, 1H, H-4), 3.80 (s, 3H, 7-OCH<sub>3</sub>), 3.37 (m, 2H, H-1''), 2.66 (m, 2H, H-1'), 1.82 (t, 2H,  $J$  = 6.9 Hz, H-2'), 1.75 (m, 2H, H-2''), 1.40 (s, 6H, H-4', H-4''), 1.32 (s, 6H, H-5', H-5'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  179.0 (C-9), 161.9 (C-1), 161.6 (C-2), 158.2 (C-4a), 157.1 (C-10a), 155.8 (C-6), 144.8 (C-7), 139.5 (C-8), 114.7 (C-8a), 107.6 (C-9a), 106.2 (C-2), 102.2 (C-5), 93.9 (C-4), 76.7 (C-3'), 71.9 (C-3''), 61.4 (OCH<sub>3</sub>), 45.5 (C-2''), 32.6 (C-2''), 30.8, 29.2, 26.8 (C-1''), 24.0, 23.2, 18.1 (C-1'); negative ESIMS  $m/z$  427 [M - H]<sup>-</sup>.

**1-Isomangostin (2q).** Yield 20%,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  6.61 (s, 1H, H-5), 6.05 (s, 1H, H-4), 5.21 (br t, H,  $J$  = 6.5 Hz, H-2''), 4.02 (d, 2H,  $J$  = 6.5 Hz, H-1''), 3.75 (s, 3H, 7-OCH<sub>3</sub>), 2.62 (t, 2H,  $J$  = 6.8 Hz, H-1'), 1.81 (m, 2H, H-2'), 1.81, 1.67, 1.33 (each s, each 3H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  183.1 (C-9), 161.8 (C-3), 161.5 (C-1), 158.3 (C-4a), 156.8 (C-10a), 155.9 (C-6), 144.8 (C-7), 138.4 (C-8), 131.6 (C-3''), 125.2 (C-2''), 111.9 (C-8a), 104.6 (C-9a), 103.5 (C-2), 102.9 (C-5), 94.8 (C-4), 77.0 (C-3'), 61.3 (7-OCH<sub>3</sub>), 32.8 (C-2'), 27.1, 27.0 (C-4', C-4''), 26.0 (C-2''), 18.3 (C-5', C-5''), 17.0 (C-1'); negative ESIMS  $m/z$  409 [M - H]<sup>-</sup>.

**$\gamma$ -Mangostin (2s).**  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  6.66 (s, 1H, H-5), 6.22 (s, 1H, H-4), 5.25 (br t, 2H,  $J$  = 6.5 Hz, H-2', H-2''), 4.11 (d, 2H,  $J$  = 6.7 Hz, H-1''), 3.34 (m, 2H, H-1'), 1.83, 1.78 (each s, each 3H, H-4', H-4''), 1.65 (s, 6H, H-5', H-5'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  183.6 (C-9), 163.4 (C-3), 161.5 (C-1), 156.3 (C-4a), 154.0 (C-10a), 153.2 (C-6), 142.0 (C-7), 131.7, 131.6 (C-3', C-3''), 129.5 (C-8), 124.8, 124.0 (C-2', C-2''), 112.2 (C-8a), 111.1 (C-2), 103.9 (C-9a), 100.9 (C-5), 92.9 (C-4), 26.6 (C-1''), 26.1, 26.0 (C-4', C-4''), 22.2 (C-1'), 18.3, 17.9 (C-5', C-5''); negative ESIMS  $m/z$  395 [M - H]<sup>-</sup>.

**Tetrahydro- $\gamma$ -mangostin (2t).** Yield 96%,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  6.64 (s, 1H, H-5), 6.21 (s, 1H, H-4), 3.35 (m, 2H, H-1''), 2.60 (m, 2H, H-1'), 1.70, 1.57 (dt, each 1H,  $J$  = 6.6, 13.2 Hz, H-3', H-3''), 1.42 (m, 4H, H-2', H-2''), 1.00, 0.99, 0.95, 0.94 (each s, each 3H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  183.6 (C-9), 163.4 (C-1), 161.7 (C-3), 156.1 (C-4a), 154.1 (C-10a), 153.0 (C-6), 141.8 (C-7), 131.6 (C-8), 112.3 (C-8a), 112.2 (C-2), 103.9 (C-9a), 100.8 (C-5), 92.9 (C-4), 40.4, 39.2 (C-2', C-2''), 30.0 (C-3'), 29.5 (C-3''), 25.8 (C-1''), 23.1 (C-4', C-5', C-4'', C-5''), 21.2 (C-1'); negative ESIMS  $m/z$  399 [M - H]<sup>-</sup>.

**1,3,6-Trihydroxy-9H-xanthen-9-one (2u).** Yield 60%,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  7.97 (d, 1H, H-8), 6.82 (dd, 1H,  $J$  = 2.2, 8.8 Hz, H-7), 6.73 (d, 1H,  $J$  = 2.2 Hz, H-2), 6.27 (d, 1H,  $J$  = 2.2 Hz, H-2), 6.13 (d, 1H,  $J$  = 2.2 Hz, H-2'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.2 (C-9), 166.7 (C-1), 165.7 (C-3), 164.6 (C-7), 159.4 (C-4a),

159.4 (C-10a), 128.3 (C-8), 114.7 (C-8a), 114.2 (C-7), 103.1 (C-9a, C-2), 99.0 (C-5), 95.0 (C-4); negative ESIMS  $m/z$  243 [M - H]<sup>-</sup>.

### 3.2.6 General procedure for synthesis of compound 3a-3e.

A solution of **1** or **2r** (0.1 mmol) and NBS or NCS (40 mg, 0.22 mM) in DCM or THF (2 mL) was placed under an atmosphere of nitrogen. After stirring for 24 h, the reaction mixture was diluted with saturated sodium thiosulfate solution, extracted with dichloromethane (3  $\times$  10 mL). The organic phase solvent was washed with brine, dried over anhydrous sodium sulfate, and then concentrated *in vacuo* to give a yellow solid. The crude product was purified on column chromatograph using petroleum ether/ethyl acetate (9 : 1) to afford **3a-3e**.

**4-Chloro- $\alpha$ -mangostin (3a).** Yield 30%,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  6.77 (s, 1H, H-5), 5.21 (br t, 2H, H-2', H-2''), 4.05 (d, 2H,  $J$  = 6.5 Hz, H-1''), 3.76 (s, 3H, 7-OCH<sub>3</sub>), 3.34 (m, 2H, H-1'), 1.82, 1.78, 1.66, 1.65 (each s, each 3H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  182.7 (C-9), 160.5 (C-1), 159.6 (C-3), 158.8 (C-10a), 156.5 (C-6), 151.2 (C-4a), 145.4 (C-7), 138.5 (C-8), 132.1, 131.9 (C-3', C-3''), 125.0, 123.5 (C-2', C-2''), 112.8 (C-8a), 111.6 (C-2), 103.8 (C-9a), 103.0 (C-5), 98.5 (C-4), 61.3 (7-OCH<sub>3</sub>), 27.1 (C-1''), 26.0, 26.0 (C-4', C-4''), 22.9 (C-1'), 18.3, 18.0 (C-1', C-1''); negative ESIMS  $m/z$  443 [M - H]<sup>-</sup>.

**4-Bromo- $\alpha$ -mangostin (3b).** Yield 12%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  13.69 (s, 1H, 1-OH), 6.97 (s, 1H, H-5), 5.25 (br t, 2H, H-2', H-2''), 4.08 (d, 2H,  $J$  = 6.5 Hz, H-1''), 3.82 (s, 3H, 7-OCH<sub>3</sub>), 3.46 (m, 2H, H-1'), 1.83, 1.82, 1.71, 1.69 (each s, each 3H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  181.8 (C-9), 160.0 (C-1), 156.8 (C-3), 155.5 (C-10a), 155.0 (C-6), 150.7 (C-4a), 143.0 (C-7), 137.2 (C-8), 133.4, 132.4 (C-3', C-3''), 122.9, 121.4 (C-2', C-2''), 111.9 (C-8a), 110.6 (C-2), 104.3 (C-9a), 101.9 (C-5), 86.4 (C-4), 62.1 (7-OCH<sub>3</sub>), 26.6 (C-1''), 25.9, 25.8 (C-4', C-4''), 22.3 (C-1'), 18.3, 17.9 (C-1', C-1''); negative ESIMS  $m/z$  488 [M - H]<sup>-</sup>.

**4,5-Dibromo- $\alpha$ -mangostin (3c).** Yield 50%,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  5.20 (br t, 2H, H-2', H-2''), 4.03 (d, 2H,  $J$  = 6.5 Hz, H-1''), 3.75 (s, 3H, 7-OCH<sub>3</sub>), 3.36 (d, 2H,  $J$  = 7.0 Hz, H-1'), 1.82, 1.79, 1.66, 1.66 (each s, each 3H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  182.6 (C-9), 160.4 (C-1), 160.1 (C-3), 156.1 (C-10a), 153.4 (C-6), 152.1 (C-4a), 145.2 (C-7), 137.3 (C-8), 132.5, 132.4 (C-3', C-3''), 124.5, 123.1 (C-2', C-2''), 113.2 (C-8a), 112.4 (C-2), 104.5 (C-9a), 97.6 (C-5), 87.8 (C-4), 62.0 (7-OCH<sub>3</sub>), 27.1 (C-1''), 26.0, 26.0 (C-4', C-4''), 23.1 (C-1'), 18.4, 18.0 (C-1', C-1''); negative ESIMS  $m/z$  567 [M - H]<sup>-</sup>; HRESIMS  $m/z$  564.9863 [M - H]<sup>-</sup> (calcd for  $\text{C}_{24}\text{H}_{23}\text{Br}_2\text{O}_6$ , 564.9867).

**4-Bromo-tetrahydro- $\alpha$ -mangostin (3d).** Yield 12%,  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 500 MHz)  $\delta$  13.86 (s, 1H, 1-OH), 6.79 (s, 1H, H-5), 3.74 (s, 3H, 7-OCH<sub>3</sub>), 3.20 (m, 2H, H-1''), 2.61 (m, 2H, H-1'), 1.65 (dt, H,  $J$  = 6.5, 13.0 Hz, H-3''), 1.53 (dt, H,  $J$  = 6.5, 13.0 Hz, H-3'), 1.33 (dt, 4H,  $J$  = 16.5, 7.0 Hz, H-2', H-2''), 0.95, 0.93, 0.91, 0.89 (each s, each 3H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ , 125 MHz)  $\delta$  181.2 (C-9), 159.0 (C-1), 158.5 (C-3), 157.2 (C-10a), 154.5 (C-6), 150.2 (C-4a), 143.6 (C-7), 138.5 (C-8), 112.4 (C-8a), 109.6 (C-2), 102.9 (C-9a), 101.6 (C-5), 86.7 (C-4), 60.4 (7-OCH<sub>3</sub>), 39.0, 37.5 (C-2', C-2''), 28.3, 27.7 (C-3', C-3''), 24.6 (C-1''), 22.5, 22.4 (C-4', C-4'', C-5', C-5''), 20.6 (C-1'); negative ESIMS  $m/z$  491 [M - H]<sup>-</sup>; HRESIMS  $m/z$  491.1072 [M - H]<sup>-</sup> (calcd for  $\text{C}_{24}\text{H}_{28}\text{BrO}_6$ , 491.1069).

**4,5-Dibromo-tetrahydro- $\alpha$ -mangostin (3e).** Yield 60%,  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  13.54 (s, 1H, 1-OH), 3.70 (s, 3H, 7-OCH<sub>3</sub>), 3.16 (m, 2H, H-1''), 2.59 (m, 2H, H-1'), 1.63 (dt, H, *J* = 6.5, 13.0 Hz, H-3''), 1.53 (dt, H, *J* = 6.5, 13.0 Hz, H-3'), 1.32 (m, 4H, H-2', H-2''); 0.93, 0.92, 0.90, 0.89 (each s, each 3H, H-4', H-5', H-4'', H-5'');  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  182.7 (C-9), 160.7 (C-1), 160.6 (C-3), 156.3 (C-10a), 153.4 (C-6), 152.0 (C-4a), 145.4 (C-7), 139.2 (C-8), 114.6 (C-8a), 112.3 (C-2), 104.6 (C-9a), 98.1 (C-5), 88.8 (C-4), 63.3 (7-OCH<sub>3</sub>), 41.0, 39.3 (C-2', C-2''), 30.1, 29.5 (C-3', C-3''), 26.4 (C-1''), 24.3, 24.2 (C-4', C-4'', C-5', C-5''), 22.4 (C-1''); negative ESIMS *m/z* 571 [M - H]<sup>-</sup>; HRESIMS *m/z* 569.0170 [M - H]<sup>-</sup> (calcd for C<sub>24</sub>H<sub>27</sub>Br<sub>2</sub>O<sub>6</sub>, 569.0174).

### 3.3 Biological assays

The following human cancer cell lines were used: HL-60, SMMC-7721, A-549, MCF-7 and SW-480. These cells were obtained from ATCC (Manassas, VA, USA). All the cells were cultured in RPMI-1640 or DMEM medium (Hyclone, Logan, UT, USA), supplemented with 10% fetal bovine serum at 37 °C in a humidified atmosphere with 5% CO<sub>2</sub>. Cell viability was assessed by conducting colorimetric measurements of the amount of insoluble formazan formed in living cells based on the reduction of MTS (Sigma, St. Louis, MO, USA). Briefly, 100  $\mu\text{M}$  of adherent cells were seeded into each well of a 96-well cell culture plate and allowed to adhere for 12 h before drug addition, while suspended cells were seeded just before drug addition, both with an initial density of  $1 \times 10^5$  cells per mL in 100  $\mu\text{M}$  medium. Each tumour cell line was exposed to the test compound at various concentrations in triplicate for 48 h, with cisplatin and paclitaxel (Sigma) as positive controls. After the incubation, MTS (100  $\mu\text{g}$ ) was added to each well and the incubation continued for 4 h at 37 °C. The cells were lysed with 100  $\mu\text{M}$  of 20% SDS-50% DMF after removal of 100  $\mu\text{M}$  medium. The optical density of the lysate was measured at 490 nm in a 96-well microtiter plate reader (Bio-Rad 680). The IC<sub>50</sub> value of each compound was calculated by Reed and Muench's method.

## 4. Conclusions

In order to enrich the types of mangostin derivatives and improve the structure-activity relationship, in this investigation, we report the synthesis of a series of  $\alpha$ -mangostin derivatives based on three kinds of different functional groups. They have been assessed for their cytotoxicity against a panel of human cancer cell lines, including HL-60, SMMC-7721, A-549, MCF-7 and SW480. Most of them exhibited good cytotoxicity against all five cancer cell lines evaluated and several of them were even better than  $\alpha$ -mangostin. Structure-activity relationship (SAR) analysis reveals that the isopentene group at C-8 is critical for retaining the exceptional cytotoxicity of  $\alpha$ -mangostin; the oxidation form of isopentene group at C-8 causes the loss of the cytotoxicity. Based on the SAR studies, further study is under progress. Some active compounds were obtained in this study and our results suggest that some of these compounds have potential for further development as anticancer agents.

## Conflicts of interest

There are no conflicts to declare.

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