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Recent works on anti-tumor constituent from Annonaceae plants in China*

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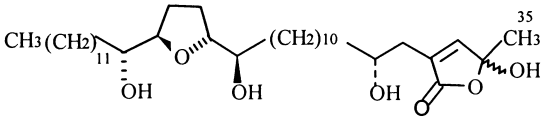
Abstract: This review describes the recent works on anti-tumor constituent from family Annonaceae plants in our laboratory. About 50 new Annonaceous acetogenins, 12 new styrylpyrones and 25 new polyoxygenated cyclohexenes were isolated from 5 *Uvaria* species, 4 *Goniothalamus* species and 1 species of *Annona.* The structure and stereochemistry of new compounds were determined by means of spectral analysis and chemical reactions as well as X-ray diffractions in few cases. Preliminary bioassay tests showed most of the new isolates exhibit significant anti-tumor activities.

Recently, members of family Annonaceae have been investigated as potential sources of biologically active Annonaceous acetogenins, some of which exhibited a powerful anti-tumor activities. About 24 genera of Annonaceae plants including 103 species and 6 varieties are distributed in China, many of them are used for treatment of various human diseases in Chinese folk medicine. In the course of our studies on the bioactive constituents from the family Annonaceae we have isolated about 50 new acetogenins, 25 new polyoxygenated cyclohexenes and 12 new styrylpyrones from 5 *Uvaria* species, 4 *Goniothalamus* species and 1 species of *Annona* [1–5]. The structure and stereochemistry of new compounds were established by means of spectral analyses and chemical reactions as well as X-ray diffraction in few cases. Preliminary bioassay tests showed most of the new isolates have significant anti-tumor activities. In this paper, we present some of the new structurally characteristics of the new acetogenins and some new structures of styrylpyrones as well as polyoxygenated cyclohexenes together with their potential anti-tumor activities.

A new type of Annonaceous acetogenin was identified from the roots of *Goniothalamus donnaiensis and G. gardneri* which is like some similar lactol compound characterized by the presence of a γ-(hydroxymethyl) γ-lactone moiety, such as donnaienin A (**1**) and gardnerinin (**2**) [6–8]. These acetogenins were isolated as an epimer pair. HPTLC and HPLC developed with different solvents on reversed-phase and normal-phase column are always gave a sharp single peak. However, the ^{13}C-NMR spectrum revealed a duplication of several signals at δ 69/70, 104/105, 131/132, 149/150, and 171/172 with a relative intensity of 55/45 for all of these, suggesting the presence of an epimeric pair. ^{1}H NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY indicated that the chemical shifts of H-3 and H-4 were obviously different for the epimeric pair.



Scheme 1

In order to confirm that the compound was epimeric at C-34, a phenylhydrazone derivative (**1a**) was prepared. The ^{13}C NMR spectrum of **1a** showed all the signals appeared to be singlets, suggesting it was one compound (Scheme 2).

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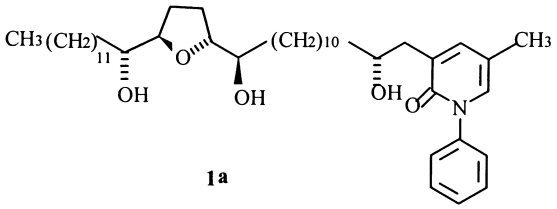
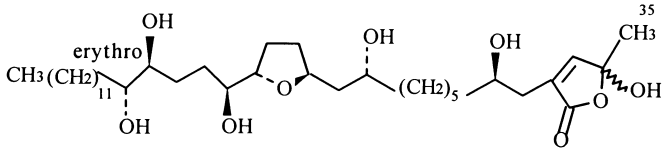


1a



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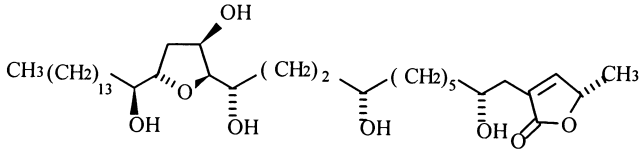
Scheme 2

Generally speaking, the acetogenin containing a γ-(hydroxymethyl) γ-lactone moiety showed weak cytotoxicity against the human colon adenocarcinoma (HCT-8) cells ($IC_{50} < 10$ μg/mL).

A novel acetogenin bearing a hydroxylated tetrahydrofuran ring (**3**) was isolated from the roots of *Goniothalamus donnaiensi* [9]. The position of the oxygenation in the THF ring and the stereochemistry of the hydroxy in **3** were determined by careful analysis of the ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectra. This compound represents an unusual type of Annonaceous acetogenin bearing a hydroxy in THF ring.



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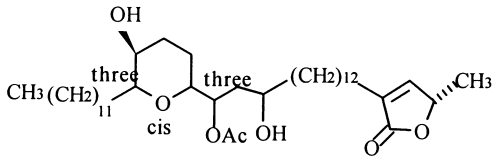

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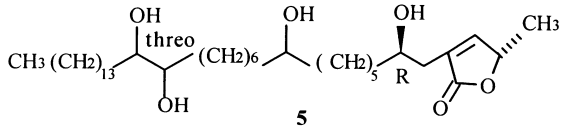
Scheme 3

Uvarigrandin D (**4**) is an another Annonaceous acetogenin having a tetrahydropyrane ring instead of tetrahydrofurane ring [10]. Compound **3** gave cytotoxicity IC_{50} values against KB, HCT-8, and bel human tumor cell lines of > 10, > 10, and 6.7 μg/mL, respectively. Tonkinelin (**5**), donhexocin (**6**) and gardnerilin A (**7**) are an another unusual type Annonaceous acctogenin having neither THF nor epoxid rings and possessing only vicinal diols in the hydrocarbon chain. They were isolated from *Uvaria tonkinensis* and *Goniothalamus gardneri* [11], respectively. Preliminary pharmacological tests showed that tonkinelin (**5**) and donhexocin (**6**) inhibit human leukemia (HL-60) and human colon adenocarcinoma (HCT-8) cell lines *in vitro*. The IC_{50} is lower than 1 μg/mL (Scheme 4).

Besides the Annonaceous acetogenins obtained, 25 new polyoxygenated cyclohexenes were isolated from *Uvaria grandiflora*, *U. boniana* and *U. calamistrata* [12–15]. The structure and stereochemistry of the new polyoxygenated cyclohexenes were elucidated by spectroscopic methods and chemical transformations. Some structures are summarised in Scheme 5.

Compound **13** showed cytotoxicity IC_{50} values against KB, HCT-8, Bel_{7402}, and A_{2780} human tumor cell lines of < 0.01 μg/mL, < 1 μg/mL and < 0.01 μg/mL, respectively,



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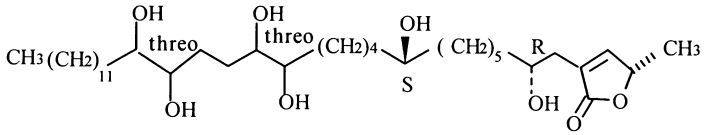

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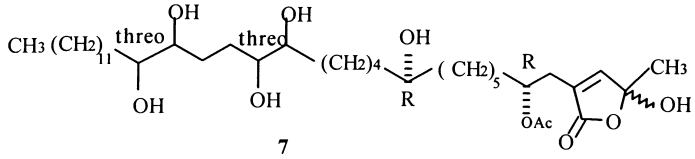

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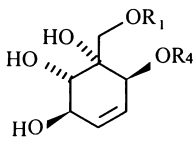
Scheme 4



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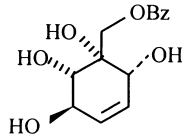

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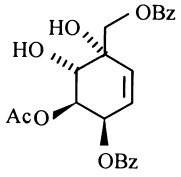

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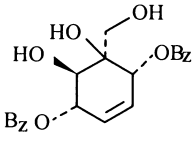

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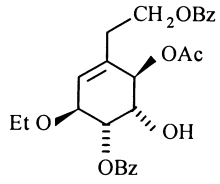

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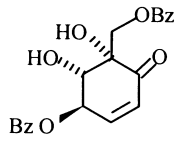

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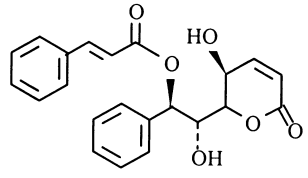
Scheme 5



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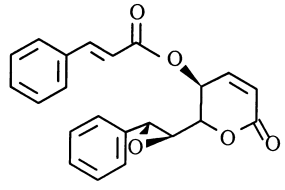

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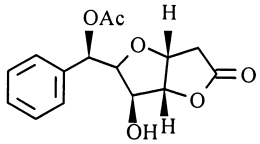

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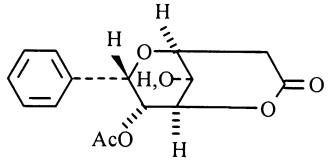

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Scheme 6

In addition, 12 new styrylpyrones were isolated from the barks and rhizomes of *Goniothalamus howii* and *G. griffithii*. Some of which are shown to in Scheme 6 [16].

The effect of howiinol (**14**) on the growth of several cancer and normal cells were studied, using the methods of cell growth curve determination, MTT test and soft-agar colony formation assay. The results showed that **14** exhibited potent inhibitory effect on cancer cells with an IC_{50} of 2 μg/mL approximately.

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