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Design, synthesis and cytotoxicity of cell death mechanism of rotundic acid derivatives

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ABSTRACT

In the present investigation, 16 new rotundic acid (RA) derivatives modified at the C-3, C-23 and C-28 positions were synthesized. The cytotoxicities of the derivatives were evaluated against HeLa, A375, HepG2, SPC-A1 and NCI-H446 human tumor cell lines by MTT assay. Among these derivatives, compounds **4**–**7** exhibited stronger cell growth inhibitory than RA and compound **4** was found to be the best inhibition activity on five human tumor cell lines with IC_{50} <10 μM. The apoptosis mechanism of compound **4** in HeLa cells was investigated by western blot analysis. The results indicated that compound **4** could induce apoptosis through increasing protein expression of cleaved caspase-3 and Bax, and decreasing protein expression of Bcl-2. In summary, the present work suggests that compound **4** might serve as an effective chemotherapeutic candidate.

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In the history of Traditional Chinese Medicine (TCM), medicinal plants and their extracts were used to treat various diseases. Nowadays, compounds derived from natural medicines with the unique and diverse chemical entities still constituted a considerable resource for developing novel medicaments. Over the recent years, a variety of biologically active constituents, including ginsenoside Rg3,[1–3] paclitaxel,[4,5] platycodin D,[6] triptolide,[7] and flavone eupatorin,[8] have been isolated from these sources and confirmed to have anti-cancer activity in both experimental and epidemiologic investigations. The bark of *Ilex rotunda* Thumb., was early recorded in 'Ling Nan Cai Yao Lu', has been used for a long time as a TCM for the treatment of colds, tonsillitis, pharyngitis, bone pain, acute gastroenteritis, and dysentery so on.[9–11] Nowadays, this medical plant is listed in Pharmacopoeia of the People's Republic of China, 2010.[12]

Rotundic acid (3β,19α,23-trihydroxy-urs-12-en-28-oic acid, RA), a pentacyclic triterpene acid, is the major component isolated from the dry bark of *I. rotunda*. In addition to existence in aquifoliaceae plants,[13–16] RA also was isolated from *Mussaenda Pubescens*,[17] *Guettarda platypoda*,[18] *Olea europaea*,[19] *Planchonella duclitan*,[20] *Nauclea officinalis*.[21] Although RA could be obtained from the above plant resources, there were little reports on its bioactivity. To date, in addition to the anti-tumor[20,22] and lowering blood pressure activity,[23] no reports on other activities related to RA were published. Our studies have proved that RA had the activity of prevention and treatment of cardiovascular disease and we have applied two patents (one of the patent had been authorized).[24,25] More activities of RA need to be studied in the future.

In our previous study,[26,27] the results showed that a few of new amino acid derivatives showed stronger cytotoxicities than RA. In order to find the compounds with better cytotoxicities, we continued to carry out chemical modification and antitumor activity of RA. Since the nitrogen-containing organic compounds had high biological activities, which play an important role on the chemical research, so many researchers carried out research in this area.[28] In the work described herein, we focus on increasing the cytotoxicity of RA. As shown in Figure 1, due to higher steric hindrance, 19-OH is difficult to modified, Therefore, RA can be modified easily at C-3, C-23 and C-28 position. In the present study, we intend to modify RA to obtain better derivatives, their cytotoxicities are determined on the five human tumor cell lines including A-375 (human malignant melanoma cells), SPC-AI (human lung adenocarcinoma), Hela (cervical cancer cells), HepG2 (hepatoma cells) and NCI-H446 (small cell lung cancer). The derivatives with low IC_{50} value will be further evaluated to explore its mechanism on the traditional apoptosis signal pathway.

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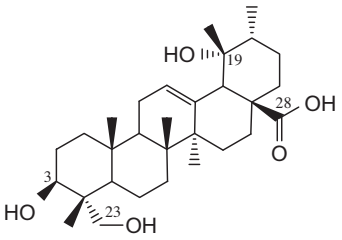
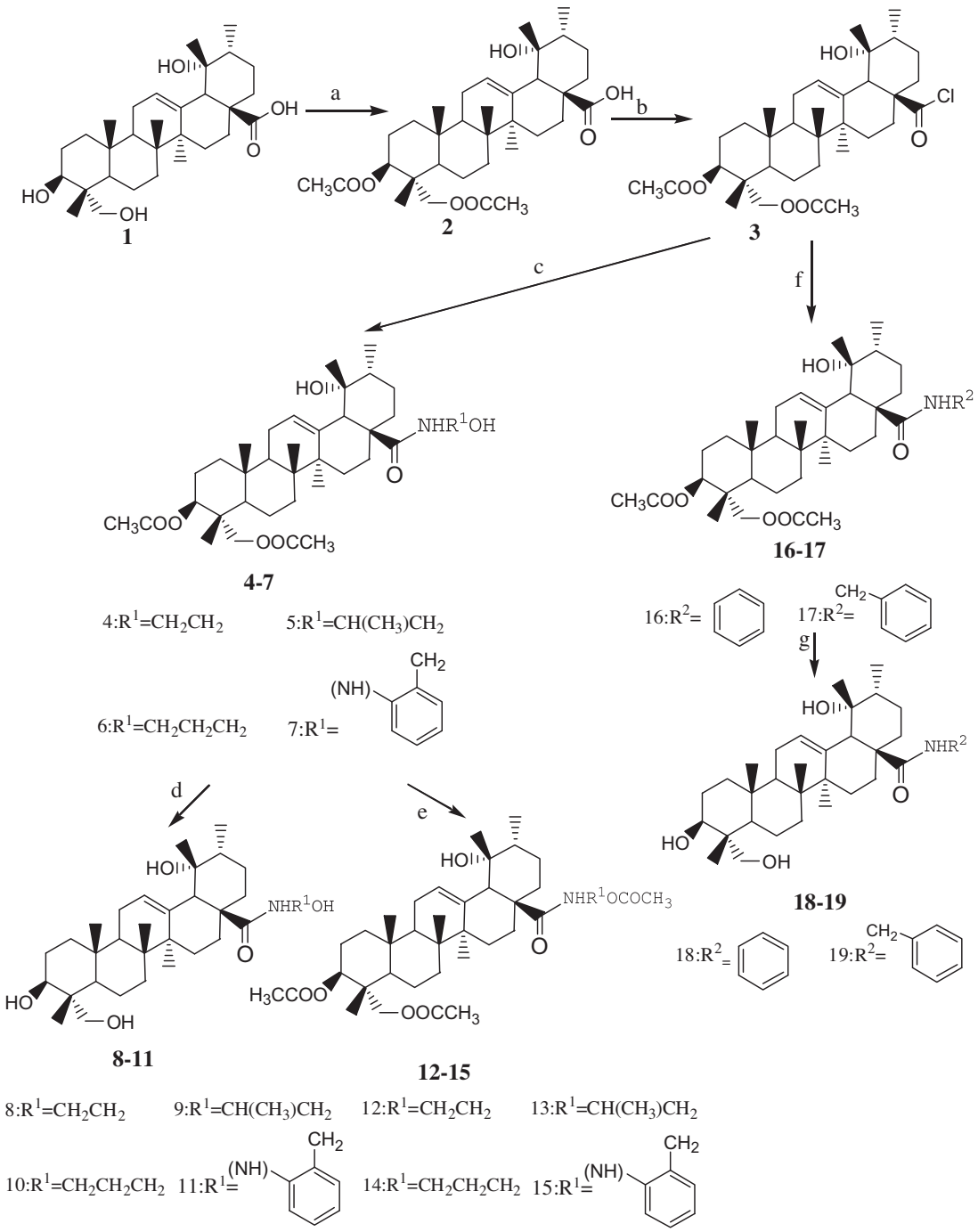


Figure 1. Structure of rotundic acid (RA).

Recently, the antitumor mechanism mainly focused on their effect on trigger apoptosis. Apoptosis,[29] known as programmed cell death, is closely related to many anticancer reagents. It has been broadly accepted that mitochondria play an important role during drug-induced apoptosis in cancer cells. Many of the stimulus including anticancer drug that triggered apoptosis on the mitochondria, which respond to proapoptotic signals by releasing cytochrome C, which belongs to an effective catalyst of apoptosis. Members of the Bcl-2 family include either proapoptotic (Bax) or antiapoptotic (Bcl-2) function,could lead to mitochondrial death signaling through cytochrome C release. Normally, Bcl-2 is local-



Scheme 1. Synthesis of RA derivatives. Reagents and conditions: (a) pyridine, acetic oxide, 80 °C, 16 h, 69.9%; (b) CH_2Cl_2, oxalyl chloride, rt, 20 h, 77.8–80.5%; (c) CH_2Cl_2, amino alcohols, rt, 1.5 h, 66.5–77.5%; (d) 1 mol/l NaOH in 60% methanol, 100 °C, 8 h, 88.4–90.1%; (e) CH_2Cl_2, acetic oxide, 4-DMAP, rt, 4 h, 79.5–90.1%; (f) CH_2Cl_2, Et_3N, Ar-R^2-NH_2, rt, 1.5 h, 71.8–72.5%; (g)1 mol/l NaOH in 60% methanol, 100 °C, 6 h, 86.8–90.2%.

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