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Antitumor activities of biscoumarin and dihydropyran derivatives

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ABSTRACT

Rising worldwide cancer incidence and resistance to current anti-cancer drugs necessitate the need for new pharmaceutical compounds and drug delivery system. Two novel series of biscoumarin (**1**–**4**) and dihydropyran (**5**–**16**) derivatives were synthesized via a one-pot multicomponent condensation reaction and evaluated for their antitumor activity in vitro. The X-ray crystal structure analysis of four representative compounds **2**, **7**, **10** and **13** confirmed the structures of these compounds. Compounds **1**–**4** showed the most potent antitumor activity among the total 16 derivatives. More interestingly, preliminary mechanism studies revealed that the most potent compound **4** induced apoptosis and arrested the cell cycle at the S phase in HUTU80 cells. Additionally, the increased accumulation of HUTU80 cells in the sub G1 peak further pointed to the occurence of the cell apoptosis. The selectivity index analysis demonstrated that all the biscoumarin compounds (SI = 3.1–7.5) possess higher selectivity towards intestinal epithelial adenocarcinoma cell line (HuTu80) than positive control drug carboplatin (SI = 1.6–1.8). The biscoumarin compounds also showed no obvious acute toxicity on mice.

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Cancer is one of the major public health problems worldwide representing the leading cause of morbidity and mortality in industrialized countries, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012, which are expected to rise in the future.[1] In China, according to the Annual Cancer Registry in 2013, more than 3 million new cases were diagnosed with cancer, which is equivalent to 6 patients diagnosed per minute, and the prevalence has been increasing.[2,3] This casts great socioeconomic burdens. Despite the fact that chemotherapy is central to clinical management of cancer, failure in chemotherapy is not uncommon, mainly due to the dose-limiting toxicities, which is associated with the occurrence of drug resistance.[4]

Natural products have been used for the treatment of various diseases and are becoming an important research area for drug discovery. These products, especially phytochemicals have been extensively studies and have exhibited anti-carcinogenic activities by interfering with the initiation, development and progression of cancer through the modulation of various mechanisms including cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis.[5–7] This concept is gaining attention because it is a cost-effective alternative to cancer treatment.

However, the naturally occurring compounds generally tend to be less potent when used for prevention and treatment of cancer.[8] In order to get more effective antitumor agents, it is possible to make modifications on active chemical structures of title compounds. In the present study, two novel series of biscoumarin (**1**–**4**) and dihydropyran (**5**–**16**) derivatives were firstly synthesized (Fig. 1), their antitumor activities on intestinal epithelial adenocarcinoma cell line (HuTu80), mammary adenocarcinoma cell line (4T1) and pancreatic cancer cell line (PANC1) in vitro were then evaluated. In addition, selective toxicity of the biscoumarin compounds (**1**–**4**) was evaluated in normal human umbilical vein endothelial cell (HUVEC) and human embryonic kidney 293 cell (HEK293) using the MTT assay. The compound **4** that demonstrated the best antitumor action was chosen to be assayed by flow cytometry to determine its apoptotic behavior and mechanism. The acute toxicity of compounds **1**–**4** which have higher antitumor effects than others was also carried out in mice.

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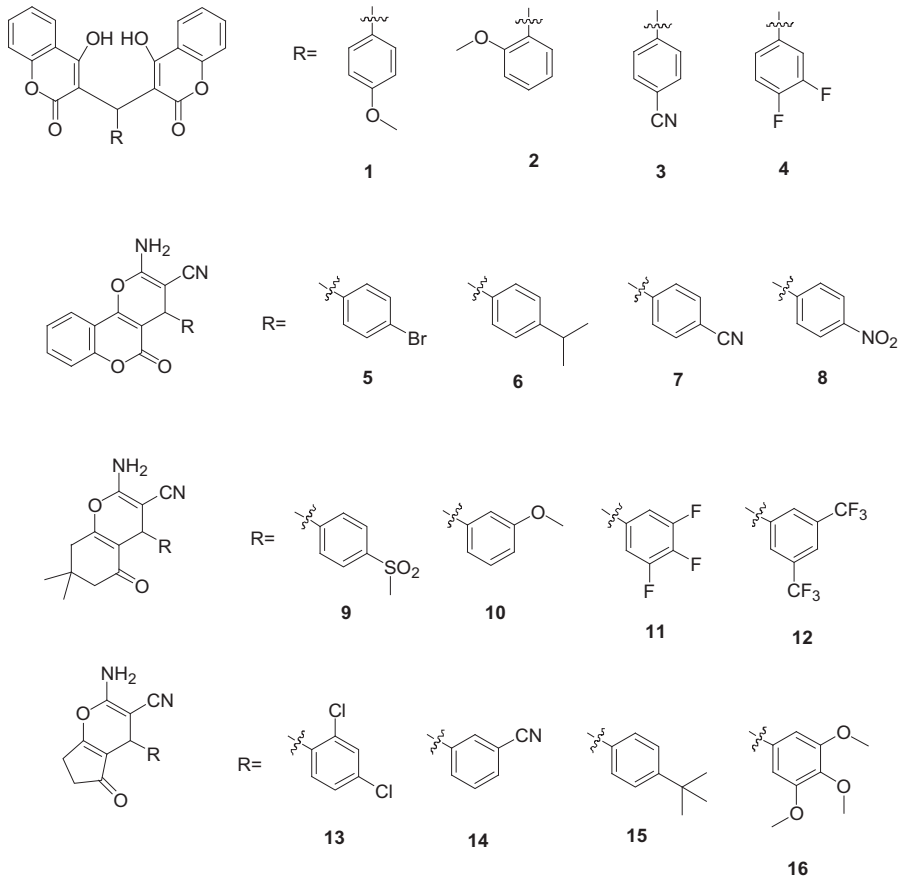

Figure 1. Chemical structures of compounds **1**–**16**.

The compounds were synthesized according to general method as described in Schemes 1 and 2 (see Supplementary data). Biscoumarin 1–4 were synthesized via a one-pot two-component reaction by condensing aromatic aldehydes and 4-hydroxycoumarin in the presence of catalytic amount of piperidine in ethanol under reflux conditions. Pyran derivatives **5**–**16** were synthesized via a one-pot three-component reaction by condensing aromatic aldehydes, 4-hydroxycoumarin (1,1-dimethyl-3,5-cyclohexanedione or 1,3-cyclopentadione) and malononitrile in the presence of 4-(dimethylamino)pyridine (DMAP) as a highly efficient homogenous catalyst. Additionally, chemical structures of all compounds were further characterized by ^{1}H NMR and ESI-MS (see Supplementary data).

In order to further confirm the configuration of the products, single crystals of four representative compounds **2**, **7**, **10** and **13** were cultured for X-ray diffraction analysis. From Figure 2 we can see that, in crystal structure of compound **2**, two 4-hydroxycoumarin moieties are linked through a methylene bridge, wherein one hydrogen atom has been replaced with a 2-methoxyphenyl group; and two classical intramolecular hydrogen bonds (O_3—H_3···O_4 and O_6—H_6···O_1) between a hydroxyl group of one coumarin fragment and a lacton carbonyl group of another coumarin fragment further stabilize the whole structure.

In crystal structures of compounds **7**, **10** and **13**, the 4*H*-pyran ring is nearly planar and the adjacent ketone ring also adopts a planar conformation. The 4*H*-pyran ring is almost perpendicular to the benzene ring and is almost coplanar with the mean plane of the ketone ring.

Intestinal epithelial adenocarcinoma cell line (HuTu80, human origin), mammary adenocarcinoma cell line (4T1, mouse origin) and pancreatic cancer cell line (PANC1, human origin) were selected to evaluate the antitumor activities of the synthesized compounds **1**–**16** against different tumor types in vitro. Carboplatin, a standard antitumor drug, was applied to compare the potency of cytotoxicity of the tested compounds under the same experimental condition. The experimental results demonstrated that all the tested compounds had a certain degree of cell-killing activities against the three tumor cell lines and their inhibitory actions showed a evident concentration-activity relationship. Their half maximal inhibitory concentration (IC_{50}) and IC_{90} values (dose of the compound which cause a 50% and 90% reduction of survival values, respectively) are shown in Table 1. As can be seen in Table 1, according to the antitumor activity strength, the tested compounds can be divided into different groups. Among these compounds, biscoumarins **1**–**4** showed more potent anticancer activity against the three tested tumor cells (HuTu80, 4T1 and PANC1) with IC_{50} and IC_{90} values of 15–93.5 μg/mL and 28–201.5 μg/mL, respectively; the IC_{50} and IC_{90} values of the biscoumarins **1**–**4** against HuTu80 are much lower than that of the positive control drug carboplatin with IC_{50} and IC_{90} values of 52.5–70.1 μg/mL and 90.7–156.2 μg/mL respectively.

One of the major hindrances for druggability of compounds with effective antitumor activity is their toxicity to normal cells. Thus, it is necessary to evaluate cytotoxicity on normal cells in the anticancer drug study. Due to the higher efficacy of anti-proliferative action against tumor cell lines, compounds **1**–**4** were chosen for selectivity test on normal human umbilical vein endothelial cell (HUVEC) and human embryonic kidney 293 cell (HEK293) using the MTT assay. The selectivity indexes (SI) were calculated by IC_{50} values in cancer cells divided by IC_{50} values in

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