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Synthesis and biological evaluation of isoprenylated coumarins as potential anti-pancreatic cancer agents

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ABSTRACT

A series of isoprenylated coumarins has been designed, synthesized, and evaluated against human pancreatic adenocarcinoma cell line PANC-1 under nutrient-rich and nutrient-deprived conditions. The compounds described investigate the effect of isoprenyl chain length and positioning on cell growth inhibition. The majority of these compounds displayed cytotoxicity against PANC-1 cells selectively in the absence of essential amino acids, glucose, and serum, and showed no cytotoxicity under nutrient-rich conditions. In this study, compound **6** exhibited the highest cytotoxic activity with an LC_{50} value of 4 μM and induced apoptosis-like morphological changes in PANC-1 cells after a 24-h incubation. The evaluated structure–activity relationships show that substitution at the 6-position and the presence of a farnesyl isoprenyl tail are important structural features for enhanced preferential cytotoxicity. These findings provide important information to designing other structural analogues for potential application as novel pancreatic antitumor agents.

Due to the difficulty of early detection, pancreatic cancer is considered one of the deadliest carcinomas. The American Cancer Society predicts that in 2014, approximately 46,420 people will be diagnosed with, and 39,560 patients will die from this type of cancer in the United States alone.[1] Rapid metastasis contributes to the high fatality rate of pancreatic cancer, which is the fourth leading cause of cancer-induced deaths.[1] Due to its aggressive nature, traditional cancer chemotherapies are largely ineffective. The nucleoside analog chemotherapy drug gemcitabine is the most often prescribed treatment for pancreatic cancer patients, but rarely extends life expectancy beyond one year.[2] Further clinical studies on the administration of gemcitabine have been conducted, yet the best reported survival rate does not exceed two years.[3,4] When administered concurrently with the epidermal growth factor receptor inhibitor erlotinib, survival rate was improved by one year only.[5]

A hallmark of pancreatic cancer cells is their high resistance to nutrient- and oxygen-deprivation under hypovascular conditions.[6,7] To combat the intrusion of malignant cells on a healthy human body, nutrients are shunted away from the site of the growing tumor, resulting in hypoxia. Pancreatic cancer cells, however, continue to grow and divide even under these staunch hypoxic conditions, highlighting this cancer's resilient nature.[8,9]

In 2006, during a screening program using the antiausterity strategy,[7,10,11] a novel natural compound, angelmarin (Fig. 1A), was isolated from the root of the Japanese medicinal plant *Angelica pubescens*.[9] This natural product showed promising preferential cytotoxicity against pancreatic cancer cells, specifically the human pancreatic adenocarcinoma PANC-1 cell line, under nutrient starvation conditions. Angelmarin's core structure contains a coumarin moiety, which is present in many plant-derived natural products. A coumarin (Fig. 1B) has a basic molecular formula of $C_9H_6O_2$ and is present in numerous compounds with a wide variety of pharmacological uses. Coumarin-containing compounds have been found to have anticoagulant, anti-inflammatory, antioxidant, and antiviral

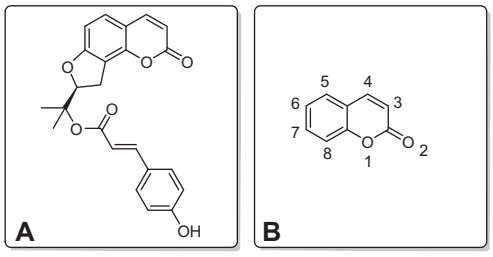

Figure 1. (A) Structure of the natural product angelmarin. (B) Coumarin moiety with labeled positions.

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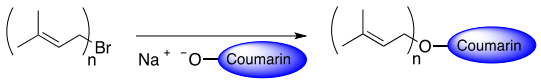

Scheme 1. General synthetic scheme for reaction of isoprenyl bromides with suitable hydroxycoumarin to yield desired isoprenylated coumarins (**1**–**9**).

activities.[12–14] Coumarins have garnered clinical interest due to their low toxicity, economical price, presence in traditional herbal remedies, and relative ease of chemical modification.[15] Recently, our laboratory reported the discovery of a series of isoprenylated coumarins that displayed preferential cytotoxicity against PANC-1 cells under nutrient-deprived conditions.[16] In an effort to investigate the in vitro antiproliferative activity of coumarin derivatives as a function of isoprenyl positioning and chain length, we sought a new series of compounds to provide useful structure activity profiles. The studies presented herein describe the design, synthesis, and evaluation of a series of 3-, 6-, and 7-isoprenylated coumarins against PANC-1 cells under nutrient-deprived and nutrient-rich conditions.

In the present study, three complete series of isoprenylated coumarin ethers were synthesized with systematic variations in the tail length (from 5-carbon to 15-carbon) and location on the coumarin scaffold (at 3-, 6- and 7-positions, Fig. 1B). The general synthetic route utilized to prepare these compounds is outlined in Scheme 1. Each compound was synthesized via Williamson-ether synthesis with an isoprenyl bromide and an alkoxycoumarin generated by pre-treatment of the corresponding hydroxycoumarin with sodium hydride.[17] Compounds were purified using flash column chromatography or preparatory thin layer chromatography and were fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, and High Resolution Mass Spectrometry.

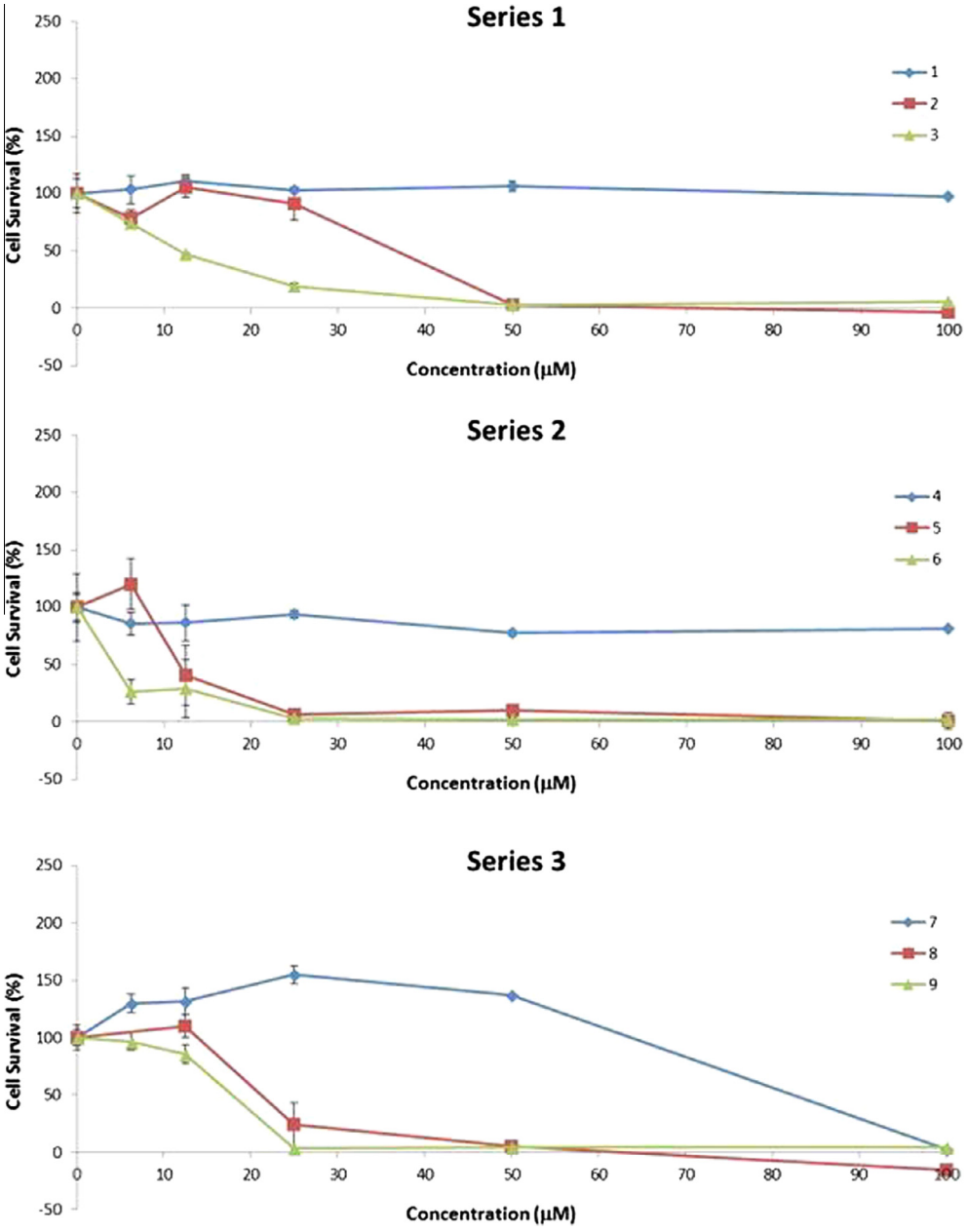

Figure 2. Survival of human PANC-1 cells under nutrient-deprived conditions within 24 h by **1**–**9**. Data are means of ±SEM, n = 3. A second set of experiments was performed, where similar values were obtained.