Antiausterity agents from Uvaria dac and their preferential cytotoxic activity against human pancreatic cancer cell lines in a nutrient-deprived condition.


Abstract

Human pancreatic cancer cell lines are known for their inherent tolerance to nutrition starvation, which enables them to survive under a hypovascular (austerity) tumor microenvironment. The search for agents that preferentially retard the survival of cancer cells under low nutrition conditions (antiausterity agent) is a novel approach to anticancer drug discovery. In this study, it was found that a dichloromethane extract of the stem of Uvaria dac preferentially inhibited PANC-1 human pancreatic cancer cells survival under nutrition-deprived conditions at a concentration of 10 μg/mL. Workup of this bioactive extract led to the discovery of (+)-grandifloracin (8) as a potent antiausterity agent as evaluated in a panel of four human pancreatic cancer cell lines, PANC-1 (PC(50), 14.5 μM), PSN-1 (PC(50), 32.6 μM), MIA PaCa-2 (PC(50), 17.5 μM), and KLM-1 (32.7 μM). (+)-Grandifloracin (8) has been isolated from a natural source for the first time. Its absolute stereochemistry was established by single-crystal X-ray crystallography and circular dichroism spectroscopic analysis. In addition to this, seven other new highly oxygenated cyclohexene derivatives, named uvaridacanes A (1) and B (2), uvaridacols A-D (3, 4, 6, 7), and uvaridapoxide A (5), were also isolated and structurally characterized.

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