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Journal of Natural Medicines
https://doi.org/10.1007/s11418-020-01390-0

NOTE

Secalonic acid D as a selective cytotoxic substance on the cancer cells adapted to nutrient starvation

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Received: 9 December 2019 / Accepted: 18 January 2020

Abstract

Cancer cells adapted to the microenvironment in tumor such as hypoxic and nutrient-starved conditions are now paid much attention as the therapeutic target of cancer. In the course of search for selective cytotoxic substances against cancer cells adapted to nutrient starvation, xanthone derivative of secalonic acid D (**1**) was isolated from culture extract of marine-derived *Penicillium oxalicum*. Compound **1** showed cytotoxic activity on the human pancreatic carcinoma PANC-1 cells adapted to glucose-starved conditions with IC_{50} value of 0.6 μM, whereas IC_{50} value of compound **1** against PANC-1 cells under general culture conditions was calculated to be more than 1000 μM. Further study indicated that compound **1** inhibited the Akt signaling pathway under glucose-starved conditions, and slightly affected the induction of glucose-regulated protein 78 (GRP78), and these effects would be mediated by the uncoupling action of compound **1** on the mitochondria.

Keywords Secalonic acid D · Marine-derived *penicillium oxalicum* · Cancer · Microenvironment · Nutrient starvation

Introduction

Tumor contains hypoxic and nutrient-starved regions due to the abnormal cell proliferation coupled with the defective structural and functional formation of vasculature [1]. The cancer cells that have adapted to this tumor environment are assumed to stimulate the pathological progression of cancer by promoting tumor growth, angiogenesis, metastasis, and drug resistance [2, 3]. The ability of cancer cells to tolerate starvation is referred to as "austerity" [4]. In addition, the hypoxic and nutrient-starved environments in a tumor are unlike that in normal tissues. Therefore, the compounds that can preferentially affect cancer cells under these conditions have emerged as the "anti-austerity approach" in anticancer drug discovery [5].

The endoplasmic reticulum (ER) is an essential organelle for the synthesis and folding of secretory and membrane proteins, and the increasing of unfolded proteins, called ER stress, induces the unfolded protein response (UPR) such as the activating of inositol requiring enzyme 1/X-box binding protein 1 (IRE1/XBP1), activating transcription factor-6 (ATF6) and glucose-regulated protein 78 (GRP78) to respond the ER stress [6]. Nutrient-starved conditions in tumor microenvironment are known to be a trigger to induce UPR on the cancer cells because of the elevating amount of unfolded proteins in the cells [7]. In addition, PI3K/Akt/mTOR signaling pathway relates the cell survival, cell proliferation, regulation of autophagy, and so on. It is known that Akt signaling is activated under nutrient-starved conditions [8]. Thus, it is generally accepted that activation of PI3K/Akt/mTOR signaling pathway and induction of UPR are important for the adaptation to nutrient-starved conditions in the cancer cells. Indeed, some natural products, kigamicin D and ancistrolikokine E3 isolated from the culture extract of *Amycolatopsis* sp. and the plant *Ancistrocladus likoko*, respectively, inhibited Akt signaling and showed selective cytotoxic activity in the nutrient-starved PANC-1 cells [9, 10]. Arctigenin originally isolated from plant *Arctium lappa*, which has been proven to have nutrient starvation-selective cytotoxicity against cancer cells and

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11418-020-01390-0) contains supplementary material, which is available to authorized users.

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Published online: 30 January 2020

has entered clinical trial, blocks UPR under nutrient-starved conditions [11].

On the other hand, the marine environment is a rich source of drug leads because of its chemical and biological diversities. Currently, some natural products have been reported to exhibit the selective growth inhibitory activities against the cancer cells that have adapted to the hypoxic or nutrient-starved conditions. For example, furospinosulin-1 (furanosesterterpene) and dictyoceratins-A and -C (sesquiterpene phenols) isolated from the marine sponge of *Dactylospongia elegans* were clarified to exhibit the selective growth inhibitory activity against the hypoxia-adapted human prostate cancer DU145 cells [12, 13]. In addition, we recently isolated the DC1149B (epidithiodiketopiperazine), *N*-methylniphatin A (new 3-alkyl pyridine alkaloid), and biakamides (unique new polyketides), which showed the cytotoxic activity against human pancreatic carcinoma PANC-1 cells adapted to the glucose-deficient conditions, from marine-derived fungus of *Trichoderma lixii*, marine sponges of *Xestospongia* sp. and *Petrosaspongia* sp., respectively [14–16].

In this study, we present the isolation of xanthone derivative, secalonic acid D (**1**), from the culture extract of marine-derived *Penicillium oxalicum*, and the cytotoxic activity of compound **1** on nutrient-starved cancer cells, and propose the plausible mechanism of its action.

Materials and methods

Materials

Dulbecco's modified Eagle's medium (DMEM), WST-8 colorimetric reagent, and KCN were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Fetal bovine serum (FBS) and dialyzed FBS were purchased from Equitech-Bio Inc. (Kerrville, TX, USA) and Thermo Fisher Scientific Inc. (Waltham, MA, USA), respectively. Anti-Akt, anti-phosphorylated Akt, anti-GRP78, and anti-β-actin antibodies were obtained from Cell Signaling Technology, Inc. (Danvers, MA, USA). Horseradish peroxidase (HRP)-linked anti-rabbit IgG antibody (GE Healthcare Life Sciences, Buckinghamshire, UK) was used as a secondary antibody. Mito Check Complex Activity Assay Kit (Cayman Chemical, Ann Arbor, MI, USA) was used to evaluate the effect of compound **1** on the mitochondrial complex I–V. Oxygen consumption of cells was measured by Oxygen Consumption Rate Assay Kit (Cayman Chemical, Ann Arbor, MI, USA). Rotenone, thenoyltrifluoroacetone (TTFA), carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), antimycin A, and oligomycin mixture were obtained from Tokyo Chemical Industry Co., LTD. (Tokyo, Japan), Wako Pure Chemical Industries, Ltd. (Osaka, Japan), Sigma-Aldrich (St. Louis, MO, USA), LKT Laboratories, Inc. (St. Paul, MN, USA), and Cayman Chemical (Ann Arbor, MI, USA), respectively. Other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) or Kishida Chemical Co., Ltd. (Osaka, Japan).

Isolation of secalonic acid D (1)

The marine-derived fungus 16A08-1-1 was isolated from an unidentified marine sponge, which was collected at Pramuka Island, Indonesia, in 2016. The strain was identified as *Penicillium oxalicum* by Techno Suruga Laboratory Co., Ltd. (Shizuoka, Japan) based on the morphology and 5.8S rDNA sequence. The *Penicillium oxalicum* 16A08-1-1 was cultured in the rice medium (totally 75 g of unpolished rice and 150 mL of artificial sea water) under static condition at 30 °C for 10 days. The culture was extracted by acetone twice, and then the organic solvents were evaporated under reduced pressure to obtain a crude extract. The crude extract was partitioned into a water/EtOAc mixture (1:1). On the guidance of bioassay, the active EtOAc soluble portion [1.9 g, IC_{50} = 14 μg/mL (glucose deficient medium), IC_{50} = > 100 μg/mL (general glucose medium)] was then partitioned into a *n*-hexane/90% aqueous MeOH mixture (1:1). The *n*-hexane soluble portion [1.1 g, IC_{50} = 5.0 μg/mL (glucose deficient medium), IC_{50} = > 100 μg/mL (general glucose medium)] was then fractionated by silica gel open column chromatography eluted with *n*-hexane–EtOAc gradient to give six fractions (Fr. A–Fr. F). Among these fractions, the Fr. D [101 mg, eluted with *n*-hexane:EtOAc = 1:1) showed selective growth inhibition on the PANC-1 cells adapted to glucose starvation [IC_{50} = 0.6 μg/mL (glucose-deficient medium), IC_{50} = > 100 μg/mL (general glucose medium)]. The Fr. D was then recrystallized with $CHCl_3$–MeOH (7:3) to obtain secalonic acid D (**1**, 20 mg). Secalonic acid D (**1**) was identified by ESI-TOF-MS and NMR analyses, value of specific rotation, and comparison with authentic spectral data [17, 18].

Cell culture and bioassay

Human pancreatic carcinoma PANC-1 cells were maintained in the DMEM supplemented with heat-inactivated 10% FBS and kanamycin (50 μg/mL) in a humidified atmosphere of 5% CO_2 at 37 °C. The nutrient-starved PANC-1 cells were cultured in the glucose-deficient medium [basal medium (25 mM HEPES buffer (pH 7.4) supplemented with 6.4 g/L NaCl, 700 mg/L $NaHCO_3$, 400 mg/L KCl, 265 mg/L $CaCl_2 \cdot 2H_2O$, 200 mg/L $MgSO_4 \cdot 7H_2O$, 125 mg/L NaH_2PO_4, 0.1 mg/L $Fe(NO_3) \cdot 9H_2O$, 15 mg/L phenol red, 10 mL/L MEM vitamin solution (X100) (GIBCO, Carlsbad, CA, USA), 200 mmol/L L-glutamine solution (GIBCO, Carlsbad, CA, USA), 25 mg/L kanamycin) containing 10% dialyzed FBS]. The general glucose medium [basal medium

supplemented with 10% FBS and 2.0 g/L glucose (final 25 mM)] was also used in the bioassay for comparison. The bioassay was carried out according to the method described previously [14]. Briefly, PANC-1 cells (1×10^4 cells/100 µL in 96 well plastic plate) were pre-incubated in the DMEM supplement with 10% FBS for 24 h. The medium was then replaced with either the general glucose medium or glucose-deficient medium to induce cell adaption to the nutrient starvation. After 12-h incubation, the serially diluted samples were added, and the cells were incubated for an additional 12 h in a humidified atmosphere of 5% CO_2 at 37 °C. The cell proliferation was detected using the WST-8 colorimetric reagent. The IC_{50} value was determined by linear interpolation from the growth inhibition curve. We assessed the selectivity of the anti-proliferative activity (selective index, S.I.) based on the difference in the IC_{50} values of the general glucose and glucose-deficient media.

Western blotting analysis

PANC-1 cells (3×10^5 cells/2 mL in six-well plastic plate) were pre-incubated in the DMEM supplement with 10% FBS for 24 h. The medium was then replaced with either general glucose or glucose-deficient medium. After 12-h incubation, indicated concentrations of samples were added, and the cells were incubated for an additional 12 h in a humidified atmosphere of 5% CO_2 at 37 °C. Then the cells were rinsed with ice-cold PBS and lysed in the lysis buffer [50 mM Tris–HCl (pH 8.0) containing 150 mM NaCl, 5 mM EDTA, 1% glycerol, 1% NP-40, 1% protease inhibitor cocktail, and 1% phosphatase inhibitor cocktail]. The cell lysate was subjected to SDS-PAGE and transferred onto PVDF membranes (GE Healthcare Life Sciences Buckinghamshire, UK). The membranes were then incubated with appropriate primary antibodies and HRP-conjugated secondary antibodies, and the immunopositive bands were visualized using an ECL kit (GE Healthcare Life Sciences). The luminescent signals were analyzed using an Image Quant LAS4010 Scanner (GE Healthcare Life Sciences).

Measurement of oxygen consumption

Oxygen consumption of PANC-1 cells was performed using Oxygen Consumption Rate Assay Kit (Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instructions. Briefly, pre-cultured PANC-1 cells (8.0×10^4 cells) in the black, clear-bottom 96-well plate (Corning Incorporated, NY, USA) were incubated for 12 h at 37 °C in general glucose medium. The medium was then replaced with 140 µL of each fresh medium, and the test compound was added followed by the addition of the phosphorescent probe to measure the oxygen consumption. Each well was sealed by 100 µL of mineral oil to prevent oxygen diffusion. The signals were measured by an Infinite M1000 microplate reader (Tecan Group Ltd., Mannedorf, Switzerland) using time-resolved mode at Ex 380 nm and Em 650 nm for 180 min with 1-min time interval. The linear regression was applied after subtracting the blank, and the oxygen consumption rate was indicated by the slope of each signal profile.

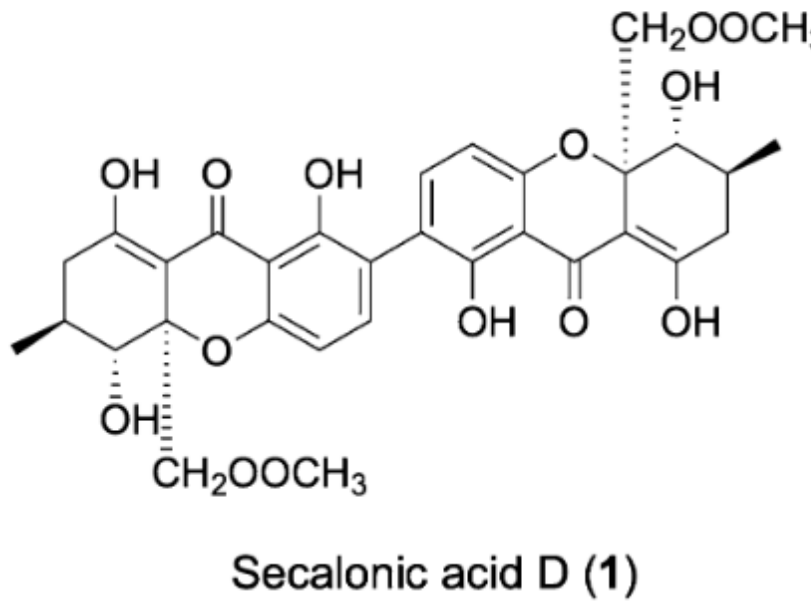
Statistical analysis

Data are shown as means ± standard errors of $n = 3$ independent experiments, and the differences between data sets were assessed by Dunnett's test. Differences with p values of less than 0.05 were considered significant.

Results

Cytotoxic activity of secalonic acid D (1) against the PANC-1 cells cultured under both glucose-deficient conditions and general culture conditions

The bioassay-guided separation of the active EtOAc-soluble portion from the culture extract of *Penicillium oxalicum* 16A08-1-1 lets us isolate secalonic acid D (**1**) (Fig. 1). We then evaluated the cytotoxic activity of compounds **1** against the PANC-1 cells cultured under both glucose-starved and general culture conditions. We used antimycin A as a positive control, which inhibits the growth of PANC-1 cells adapted to the nutrient-starved conditions [19]. As shown in Table 1, secalonic acid D (**1**) showed the cytotoxic activity against the PANC-1 cells adapted to glucose starvation by cultivating in the glucose-deficient medium, with an IC_{50} value of 0.6 µM, whereas IC_{50} value of compound **1** under the conditions of general glucose medium was evaluated to more than 1000 µM. The S.I. values of compound **1** were



Secalonic acid D (**1**)

Fig. 1 Chemical structure of secalonic acid D (**1**)

Table 1 Cytotoxic activity of compound **1** and CCCP in PANC-1 cells under glucose-deficient and general culture conditions

	IC_{50} (μM)		
	Glucose (−)[a]	Glucose (+)[b]	S.I.[c]
1	0.6	> 1000	> 1666
CCCP	1.9	146	76.8
Antimycin A[d]	0.0003	288	960,000

[a]Glucose-deficient medium
[b]General glucose medium
[c]Selective index
[d]Positive control

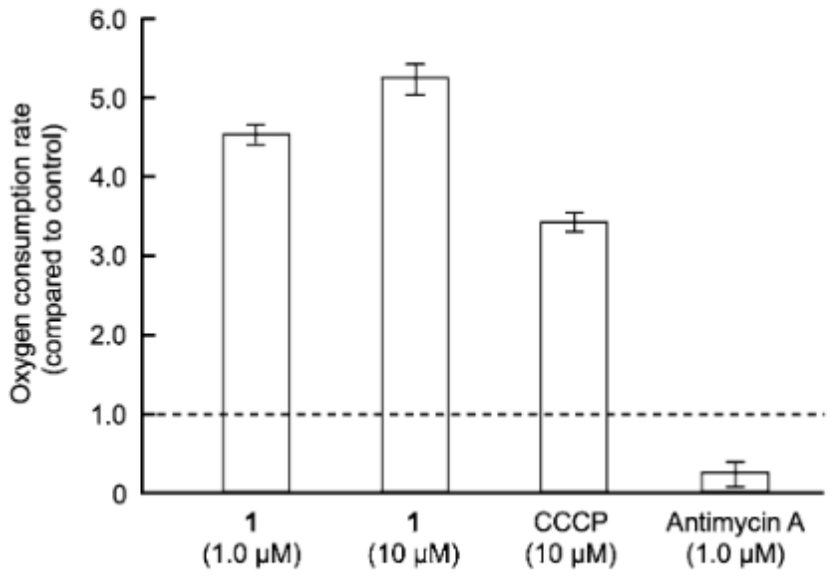


Fig. 2 Effect of secalonic acid D (**1**) and CCCP on the oxygen consumption of PANC-1 cells. Pre-cultured PANC-1 cells (8.0×10^4 cells) in the 96-well plate were incubated in general glucose medium for 12 h at 37 °C. The medium was then replaced with fresh medium, and the test compound was added followed by adding the phosphorescent probe to measure the oxygen consumption. The signals were measured by a Tecan infinite M1000 using time-resolved mode

evaluated to be more than 1600. In addition, the selective cytotoxicity of compound **1** depended on the glucose concentrations (Figure S1). These data indicated that compound **1** was a selective cytotoxic substance against the PANC-1 cells adapted to nutrient starvation.

Compound **1** has been known to act as an uncoupler of mitochondrial oxidative phosphorylation on the mitochondria isolated from rat liver [20]. In addition, positive control of antimycin A inhibited complex III in the mitochondrial electron transport chain. To investigate the action mechanism of compound **1**, we evaluated a cytotoxic activity of the carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), which is known to inhibit mitochondrial oxidative phosphorylation caused by its uncoupling effect. As a result, CCCP also showed the selective cytotoxic effect on the PANC-1 cells cultured in the glucose-deficient medium ($IC_{50} = 1.9$ μM), and the S.I. value was evaluated as a more than 76. This result strongly suggested that selective cytotoxic effect of compound **1** might be mediated by the inhibition of mitochondrial oxidative phosphorylation.

Effect of compound 1 on the cellular respiration and the mitochondrial electron transport chain

In confirmation of whether compound **1** inhibits the mitochondrial oxidative phosphorylation on PANC-1 cells, the effect of compound **1** on the cellular oxygen consumption and the complex I–V proteins in the mitochondrial electron transport chain was investigated. It is known that the uncoupling effect on mitochondrial oxidative phosphorylation leads to improvement of cellular oxygen consumption, whereas the inhibition of mitochondrial electron transport chain reduces the cellular oxygen consumption [21]. As shown in Fig. 2, compound **1** increased oxygen consumption rate (OCR) on the PANC-1 cells similar to that of CCCP, whereas antimycin A of inhibitor for complex III reduced the OCR on the PANC-1 cells (Fig. 2). In addition, the secalonic acid D (**1**) did not affect the function of the complex I–V up to 30 μM (Table S1). These results indicated that compound **1** inhibited the mitochondrial oxidative phosphorylation on PANC-1 cells.

Effects of compound 1 on the Akt signaling and induction of GRP78

It has been reported that PI3k/Akt/mTOR signaling pathway and the unfolded protein response (UPR) such as induction of glucose-regulated protein 78 (GRP78) were important for the adaptation of cancer cells to nutrient-starved conditions [7, 8]. Therefore, we next investigated the effect of compound **1** on the Akt signaling and the induction of GRP78 by utilizing a western blotting method (Fig. 3). The PANC-1 cells cultured in the glucose-deficient medium increased the expression levels of phosphorylated Akt and GRP78 proteins compared with those cultured in the general glucose medium (Fig. 3, lanes 1 and 2). Secalonic acid D (**1**) decreased the phosphorylated Akt in the PANC-1 cells under the glucose-deficient conditions caused by inhibition of the Akt expression (Fig. 3, lanes 8, 10, and 12). On the other hand, the treatment of compound **1** did not affect the expression of GRP78 at 1.0 and 3.0 μM (Fig. 3, lanes 8 and 10), whereas 10 μM of compound **1** slightly reduced the expression levels of GRP78 (Fig. 3, lane 12). This result indicated that selective growth inhibition of compound **1** might come from inhibition of Akt signaling mainly followed by uncoupling effect against mitochondria.

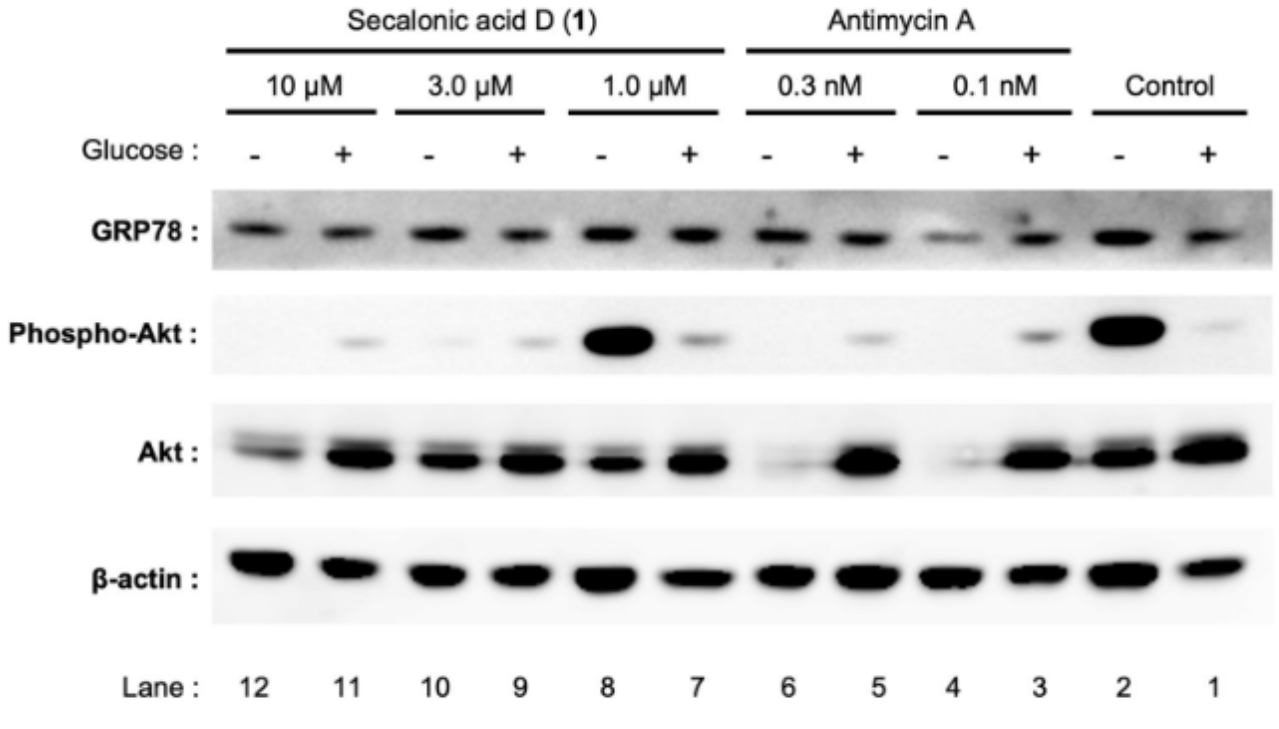


Fig. 3 Effects of secalonic acid D (**1**) on the Akt signaling and induction of GRP78. -: culture in the glucose-deficient medium. +: culture in the general glucose medium. The PANC-1 cells were treated with the indicated concentration of compound **1**. Cell lysate was resolved using SDS-PAGE and detected with antibodies against the indicated proteins

Discussion

Xanthone derivative, secalonic acid D (**1**) was originally isolated as a toxic compound in the rat and mouse [17]. The uncoupling effect of compound **1** was then shown using mitochondria isolated from rat liver [20]. Until now, it has been also reported that compound **1** has shown the cytotoxic activity on some cancer cell lines such as murine leukemia P388 cells, human chronic myeloid leukemia K562 cells, human lung carcinoma A549 cells, and so on under genal culture conditions [22]. In this study, secalonic acid D (**1**) was isolated from culture extract of marine-derived *Penicillium oxalicum* as a selective cytotoxic substance on the PANC-1 cells cultured under glucose-starved conditions by bioassay-guided separation. In our knowledge, this is the first report that compound **1** showed the selective cytotoxic activity against PANC-1 cells adapted to glucose-starved conditions as a model of tumor microenvironment. On the other hand, Guru et al., showed that secalonic acid D (**1**) decreased the expression levels of hypoxia-inducing factor-1α (HIF-1α), which is one of the important transcription factors for adapting hypoxic environment of cancer cells, on the human breast cancer MCF7 cells in the cobalt chloride-induced hypoxia model. In addition, compound **1** reduced the expressions of Akt and phosphorylated Akt [23]. This report complimented that compound **1** inhibits Akt signaling in PANC-1 cells under nutrient-starved conditions as a model of tumor microenvironment (Fig. 3). However, it is generally accepted that the inhibition of mitochondrial respiratory chain exhibits the growth inhibition of cancer cells under nutrient-starved conditions selectively, and inhibits the Akt signaling [14, 16, 24]. In addition, CCCP having an uncoupling effect on mitochondria also gave the same phenotype against PANC-1 cells adapted to glucose-starved conditions as with compound **1** (Table 1). Therefore, we speculated that selective growth inhibition of compound **1** might come from inhibition of Akt signaling mainly followed by uncoupling effect against mitochondria. To clarify the detailed mode of action, analysis of the intracellular distribution of compound **1** using the synthetic probe is undergoing.

Acknowledgements The human pancreatic carcinoma cell line, PANC-1 (RCB2095), was provided by the RIKEN BRC through the National Bio-Resource Project of the MEXT, Japan. This research was funded by Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research [BINDS]) from AMED (Grant no. JP19am0101084), Kobayashi International Scholarship Foundation, and a Grant-in-Aid for Scientific Research B (Grant nos. 18H02096 and 17H04645) from JSPS to MA.

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