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BRIEF COMMUNICATION

Selective cytotoxicity of marine-derived fungal metabolite (3*S*,6*S*)-3,6-dibenzylpiperazine-2,5-dione against cancer cells adapted to nutrient starvation

Rui Tang[1] · Dongyi Zhou[1] · Atsushi Kimishima[1] · Andi Setiawan[2] · Masayoshi Arai[1]

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Abstract

The cancer cells that are adapted to the hypoxic and nutrient-starved conditions of the tumor microenvironment have become a key target for anticancer therapies. In the course of search for selective cytotoxic substances against cancer cells adapted to nutrient starvation, (3*S*,6*S*)-3,6-dibenzylpiperazine-2,5-dione (**1**) was isolated from culture extract of marine-derived *Paecilomyces formous* 17D47-2. Compound **1** showed cytotoxic activity on the human pancreatic carcinoma PANC-1 cells adapted to glucose-starved conditions with IC_{50} value of 28 μM, whereas no effect was observed against PANC-1 cells under general culture conditions up to 1000 μM. Further studies on the mechanism of the selective cytotoxicity of **1** against the glucose-starved PANC-1 cells suggest that it may function via uncoupling of mitochondrial oxidative phosphorylation.

Cancer cells adapted to the tumor microenvironment stimulate disease progression by promoting tumor growth, angiogenesis, metastasis, and drug resistance [1, 2]. Unlike normal tissues, tumors contain hypoxic and nutrient-starved regions owing to abnormal cell proliferation coupled with defective vasculature formation [3]. This ability of cancer cells to tolerate starvation is referred to as "austerity" [4]. Compounds that preferentially target cancer cells growing under these conditions are employed as an "anti-austerity approach" in anticancer drug discovery [5]. We have established a screening system to identify anti-austerity substances using human pancreatic carcinoma PANC-1 cells adapted to glucose-starved conditions as a model of cancer cells in the tumor microenvironment. Some secondary metabolites such as polybrominated diphenyl ethers, *N*-Methylniphatyne A, and DC1149B were isolated from marine medicinal resources as an anti-austerity substance against PANC-1 cells cultured under glucose-starved conditions [6–8].

In the continues screening from marine-derived microorganisms, the culture extract of marine-derived fungus *Paecilomyces formous* 17D47-2 showed the selective cytotoxic activity on the PANC-1 cells adapted to glucose-starved conditions. The bioassay-guided separation of the culture extract of *P. formous* 17D47-2 let us to isolate the (3*S*, 6*S*)-3,6-dibenzylpiperazine-2,5-dione (**1**) (Fig. 1) [9]. Subsequently, we evaluated the cytotoxic activity of compound **1** against the PANC-1 cells cultured under both glucose-starved and general culture conditions. As a result, compound **1** showed the cytotoxic activity against the PANC-1 cells adapted to glucose starvation by cultivating in the glucose-deficient medium, with IC_{50} value of 28 μM, whereas IC_{50} value of compound **1** under the conditions of general glucose medium was evaluated as more than 1000 μM. The selectivity index (SI) was used to compare the IC_{50} values of

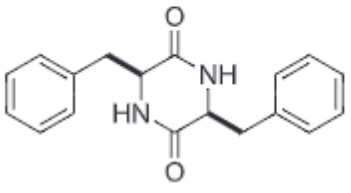

Fig. 1 Chemical structure of (3*S*,6*S*)-3,6-dibenzylpiperazine-2,5-dione (**1**)

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the general glucose and glucose-deficient media; for **1**, the SI was greater than 35 (Table 1). As compound **1** has two stereogenic centers, the stereochemical effects on cytotoxicity were investigated using synthetic compound **1** (**1′**) and its enantiomer (**2**) and diastereomer (**3**). As shown in Table 1, the prepared **1′** and **2** exhibited a comparable cytotoxic activity to the natural **1** against PANC-1 cells under both glucose-starved and general culture conditions. The diastereomer (**3**) also showed selective cytotoxicity against the glucose-starved PANC-1 cells ($IC_{50} = 39\,\mu M$), although its activity was slightly reduced compared with **1** and **2**. This indicated that the stereochemistry of the compound does not play a critical role in the selective cytotoxicity against PANC-1 cells adapted to glucose starvation.

This is the first study to show the preferential cytotoxic activity of **1** against PANC-1 cells adapted to glucose starvation. Compound **1** had previously been isolated from the *Penicillium nigricans*, the endophytic fungus *Epicoccum nigrum*, and the marine-derived fungus *Aspergillus candidus* [9–11]. However, investigations of the bioactivity of **1** found no antimicrobial activity against either gram-positive or -negative bacteria, no cytotoxicity against various cancer cell lines grown under standard conditions, and no anti-inflammatory activity [10, 11]. Interestingly, compound **1** has recently been reported to inhibit acetylcholinesterase and the serotonin transporter, and improved cognition, learning, and memory in a mouse model [Japan Patent, Application Number JP 2014-101324A].

Subsequently, we explored the mechanism of the selective cytotoxicity of **1** against the glucose-deficient PANC-1 cells. Mitochondrial electron transport chain (ETC) inhibitors, such as antimycin A (Complex III inhibitor) and rotenone (Complex I inhibitor), have shown selective cytotoxic activity against cancer cells adapted to nutrient-starved conditions [12]. Polybrominated diphenyl ethers and DC1149B, which we previously isolated as anti-austerity substances against PANC-1 cells adapted to glucose-starved conditions, also inhibited Complex II of the mitochondrial ETC [6, 8]. We recently found that a mitochondrial oxidative phosphorylation uncoupling agents, secalonic acid D and carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), were also selectively cytotoxic against glucose-deficient PANC-1 cells [13]. We therefore investigated whether compound **1** affected cellular oxygen consumption. Uncoupling mitochondrial oxidative phosphorylation increases cellular oxygen consumption, whereas inhibiting the mitochondrial ETC reduces cellular oxygen consumption [14]. Treatment with **1** was found to increase the oxygen consumption rate (OCR) of the PANC-1 cells similar to the mitochondrial uncoupling agent CCCP, whereas the Complex III inhibitor antimycin A reduced the OCR (Fig. 2). Furthermore, treatment with up to 100 µM **1** had no effect on the function of complexes I–V (Table 2).

Table 1 Cytotoxic activity of compounds against PANC-1 cells grown under glucose-deficient and general culture conditions

	IC_{50} (µM)		
	Glucose (−)[a]	Glucose (+)[b]	SI[c]
1 (Natural)	28	>1000	>35.7
1′ (Synthetic)	27	>1000	>37.0
2 (3*R*,6*R*)	28	>1000	>35.7
3 (3*R*,6*S*)	39	>1000	>25.6
Antimycin A[d]	0.0004	285	712,500

[a]Glucose-deficient medium

[b]General glucose medium

[c]Selectivity index

[d]Positive control

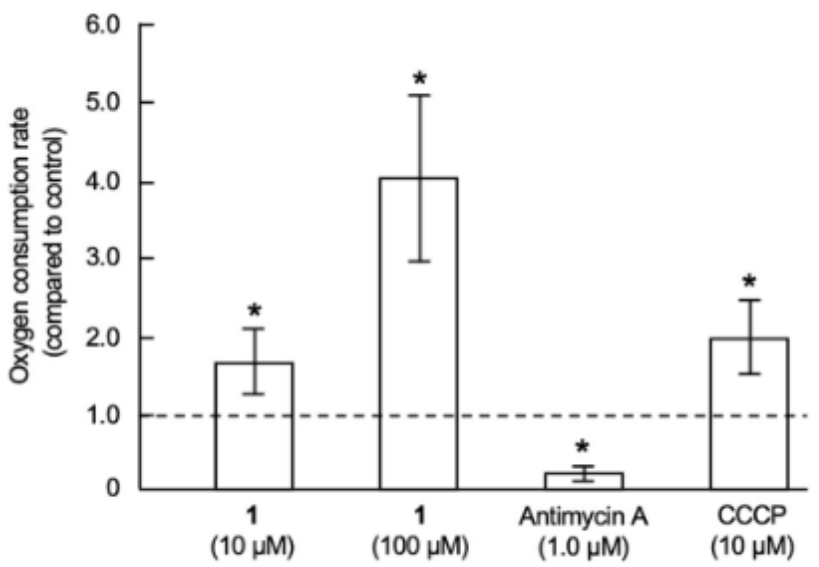

Fig. 2 Effect of **1** on the oxygen consumption of PANC-1 cells. Differences were considered significant (*) at $p < 0.05$. Method described in Supplementary information

Table 2 Effect of compound **1** on the mitochondrial electron transport chain

	IC_{50} value (µM)				
	Complex I	Complex II	Complex II/III	Complex IV	Complex V
Compound **1**	>100	>100	>100	>100	>100
Positive control[a]	0.11	65	0.03	55	0.36

[a]Positive controls for complexes I, II, III, IV, and V were rotenone, thenoyltrifluoroacetone, antimycin A, KCN, and oligomycin A, respectively

These results indicate that compound **1** inhibited mitochondrial oxidative phosphorylation in PANC-1 cells.

The anti-austerity agents, IACS-10759 (a synthetic inhibitor of Complex I) and arctigenin (originally isolated from *Arctium lappa*), are currently in clinical trials as anticancer drugs [15, 16]. An acute toxicity study in mice showed that **1** had no toxicity up to $2\,g\,kg^{-1}$ [Japan Patent, Application Number JP 2014-101324A], offering a potential lead for novel anti-austerity anticancer drugs. However, further studies on its antitumor effect in a xenograft model and its effect on the tumor microenvironment are necessary.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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