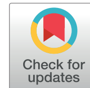

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Antaroide, a Novel Natural Nine-Membered Macrolide, Inhibits Melanin Biosynthesis in B16F10 Murine Melanoma Cells

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Abstract

The demand for natural substances with anti-melanogenic activity is increasing due to the recent interest in skin whitening. Intensive investigation on the culture broth of *Streptomyces* sp. SCO-736, a marine bacterium from the Antarctica coast, has led to the isolation of a new natural product named antaroide (**1**). The chemical structure was established through the interpretation of MS, UV, and NMR spectroscopic data. Antaroide is a nine-membered macrolide with lactone and lactam moieties. To investigate its applicability in skin whitening cosmetics, its anti-melanogenic activity in B16F10 murine melanoma cells was examined. As a result, antaroide displayed strong inhibitory activities against melanin synthesis and also attenuated the dendrite formation induced by the α-melanocyte stimulating hormone (α-MSH). Antaroide suppressed the mRNA expression of the melanogenic enzymes such as tyrosinase, TRP-1 and TRP-2. This suggests that it may serve as a transcriptional regulator of melanogenesis. Collectively, the discovery of this novel natural nine-membered macrolide and its anti-melanogenic activity could give new insights for the development of skin whitening agents.

Key Words: *Streptomyces* sp., Nine-membered macrolide, Marine natural product, Melanin synthesis inhibitor, Skin whitening agent

INTRODUCTION

Skin pigmentation is crucial to protect the skin, which is the outermost layer of the body. In particular, melanin absorbs the ultraviolet (UV) and quenches harmful reactive oxygen species, which are detrimental to the physiology of keratinocytes and melanocytes (Costin and Hearing, 2007). Besides skin protection, melanin determines the colors of hair, skin, and eyes. Its abnormal content or distribution can cause aesthetic problems such as albinism, freckles, and melasma (Briganti *et al*., 2003; Lee *et al*., 2015).

The use of skin whitening agents for cosmetic purposes is growing rapidly, especially in Asia, where a white and spotless skin symbolizes beauty and nobleness. Many skin whitening substances have been developed and used, both therapeutically and cosmetically, including hydroquinone, arbutin, and kojic acid. However, long-term exposure to these agents often causes adverse reactions such as skin irritation, ochronosis, and contact dermatitis (DeCaprio, 1999; García-Gavín *et al*., 2010). Therefore, safer and more potent skin whitening agents are required (Zhu and Gao, 2008; Atanasov *et al*., 2015; Aydogmus-Ozturk *et al*., 2018).

Researchers are paying increasing attention to microorganisms in unique marine environments, which are fertile sources of bioactive compounds with interesting structural scaffolds, to discover novel secondary metabolites (Haefner, 2003; Fenical

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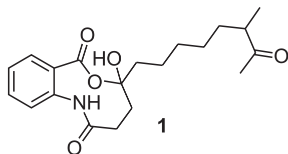

Fig. 1. Chemical structure of antaroide (**1**).

and Jensen, 2006).

As part of our search for bioactive marine natural products, a bacterium living in cold water, *Streptomyces* sp. SCO-736 has been isolated from marine sediments of the Antarctica coast. This bacterium produced antartin, a tricyclic zizaene-type sesquiterpene with a phenyl group that is cytotoxic to A549, H1299, and U87 cancer cells by inducing cell cycle arrest (Kim *et al*., 2018). Further HPLC-UV guided isolation of the culture broth of this strain has yielded a novel bioactive compound, antaroide (**1**, Fig. 1). Herein, we report details of its isolation, structure elucidation, and anti-pigmentary activity of antaroide to provide insights for developing a new class of skin whitening agents.

MATERIALS AND METHODS

General experimental procedures

The optical rotation was determined using a Kruss Optronic P-8000 polarimeter (Krüss Optronic, Hamburg, Germany) with a 5-cm cell. The UV spectra were acquired with a UV-visible spectrophotometer (1260 Infinity Series, Agilent Technologies, Santa Clara, CA, USA) using a path length of 0.1 cm. The IR spectra were measured with a Varian Scimitar Series spectrometer (Agilent Technologies). The NMR spectra were acquired with an 800 MHz Varian Inova spectrometers (Agilent Technologies) using deuterated dimethyl sulfoxide (DMSO-d_6) for antaroide. The high-resolution fast-atom bombardment mass spectrometry (HRFABMS) analysis was conducted using a JEOL JMS-AX505WA system (JEOL, Tokyo, Japan). The fractions were purified with a Waters 616 quaternary HPLC pump (Waters, Milford, MA, USA) and a Waters 996 photodiode array (PDA) detector (Waters). α-Melanocyte stimulating hormone (α-MSH), arbutin, and DMSO were purchased from Sigma-Aldrich (St. Louis, MO, USA). The cell culture medium and agents were provided by Thermo Scientific (Waltham, MA, USA).

Strain isolation and fermentation

The actinomycete strain SCO-736 was isolated from marine sediments of the Antarctic coast and identified as a member of the genus *Streptomyces* with 99.7% similarity. Its 16s rRNA gene sequence was deposited in GenBank (accession number KY087980). This bacterial strain was cultured in 100 of 2.5-L Ultra Yield Flasks, each one containing 1 L of the culture medium (10 g/L of soluble starch, 2 g/L of yeast, 4 g/L of peptone, 10 g/L of $CaCO_3$, 20 g/L of KBr, 8 g/L of $Fe_2(SO_4)_3 \cdot 4H_2O$ dissolved in 750 mL of natural seawater, and 250 mL of distilled water), at 25°C under shaking at 150 rpm. After 7 days, the broth was extracted with ethyl acetate (EtOAc, 100 l overall) to afford 3.5 g of EtOAc extract.

Extraction and purification

The EtOAc extract was dissolved in a small volume of methanol (MeOH) and fractionated via silica vacuum column chromatography eluting with a step gradient from 10% to 100% MeOH in methylene chloride. The fraction with 10% MeOH (618 mg) was subjected to reversed-phase HPLC with 48% aqueous acetonitrile (Watchers 120 ODS-BP, 250×10 mm, 5 μm, 2.0 mL/min, UV=210 nm) to afford antaroide (1, 6.7 mg), with retention times of 30 min.

Antaroide (**1**): brown oil; $[\alpha]_D^{21}$+19.8 (*c* 0.45, MeOH); UV (MeOH) λ_{max} (log ε) 225 (4.1), 245 (3.6), 310 (3.2) nm; IR (KBr) ν_{max} 3365, 2936, 2872, 2348, 1660, 1475, 1376, 1197, 761 cm^{-1}; ^1H, ^{13}C and 2D-NMR (800 MHz, DMSO-d_6), see Table 1; HRFABMS $[M+H]^+$ *m/z* 362.1972 (calcd for $C_{20}H_{28}NO_5^+$, 362.1962).

Cell culture

The B16F10 cell line from C57BL/6 mice was purchased from ATCC (Manassas, VA, USA). The cells were maintained in standard culture conditions, in phenol red–free Dulbecco's modified Eagle's medium (DMEM) supplemented with antibiotics (100 U/mL of penicillin A and 100 U/mL of streptomycin) and 10% fetal bovine serum (FBS) at 37°C in a humidified atmosphere containing 5% CO_2. At 80% cell confluence, the adherent cells were detached using a solution of trypsin (Hyclone, South Logan, UT, USA).

Melanin assay

One day before the experiment, the B16F10 cells were seeded into 48-well plates at 2×10^4 cells/well, as described elsewhere (Kim *et al*., 2017a). The serum-starved cells were exposed for 72 h to various concentrations of antaroide in a culture medium containing 0.5% DMSO and 200 nM α-MSH, α-MSH was used for inducing the melanin synthesis. The cells treated only with α-MSH and arbutin were used as the negative and positive controls, respectively. The melanin inside the cells was dissolved in 200 μL of 1 M NaOH at 60°C for 1 h in the dark, then the total melanin content was assessed via absorbance measurements at 405 nm with a microplate reader (Spectra max 190, Molecular Devices, Sunnyvale, CA, USA).

Cell viability assay

3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was used to evaluate the viability of the B16F10 cells (Song *et al*., 2018). To assay the mitochondrial reduction of MTT, the cells were incubated with 0.25 mL of 0.5 mg/mL MTT solution in DMEM for 2 h at 37°C. The blue formazan dye was dissolved in 300 μL of DMSO for 30 min, and 150 μL of the resulting supernatant was collected to measure its absorption at 540 nm. All the measurements were performed in triplicate. The results were normalized with that of the negative control (DMSO-treated cells), by taking the control values as 100%, we compared the cell viability of each antaroide concentration.

Real-time transcription polymerase chain reaction (RT-PCR)

To determine the effects of antaroide on the expression of the melanogenesis-related gene, we adopted the real-time transcription PCR technique. The B16F10 cells were treated with α-MSH and with or without antaroide. After 24 h of incubation, the total RNA was isolated using an RNeasy Plus Mini Kit (Qiagen, Germantown, MD, USA). To determine the tyrosi-

Table 1. NMR spectroscopic data for antaroide in deuterated dimethyl sulfoxide (DMSO)-d_6 (δ in ppm[a])

No.	1			
	δ_C, type[b]	δ_H (J in Hz)	COSY	HMBC
1	161.1, C			
2	116.3, C			
3	129.7, CH	7.99, d (8.0)	4	C-1, 5, 7
4	125.7, CH	7.41, dd (8.0, 8.0)	3, 5	C-2, 6
5	135.6, CH	7.79, dd (8.0, 8.0)	4, 6	C-3, 7
6	120.9, CH	7.95, d (8.0)	5	C-2, 4
7	136.0, C			
8	172.2, C			
9	29.0, CH_2	2.67, t (7.0)	10	C-8, 10, 11
10	28.5, CH_2	2.53, t (7.0) 2.34, t (7.0)	9	C-8, 9, 11, 12
11	97.2, C			
12	36.3, CH_2	1.90, t (7.0) 1.82, t (7.0)	13	C-10, 11, 12, 13
13	22.6, CH_2	1.46, m 1.30, m	12, 14	C-11, 12, 14, 15
14	29.1, CH_2	1.25, m	13, 15	C-12, 16
15	26.1, CH_2	1.19, m 1.18, m	14, 16	C-13, 14, 16, 17
16	31.8, CH_2	1.56, m 1.25, m	15, 17	C-15, 18
17	45.9, CH	2.50, m	16, 20	C-15, 16, 18, 19
18	211.8, C			
19	27.9, CH_3	2.04, s		C-17, 18
20	15.7, CH_3	0.92, d (6.8)	17	C-16, 17, 18

[a]800 MHz for ^1H NMR and 200 MHz for ^{13}C NMR. [b]Numbers of attached protons were determined by analysis of 2D NMR spectroscopic data (800 MHz).

nase mRNA levels, the cDNA was amplified with 1,250 ng of total RNA with oligo dT (Elpis-Biotech, Seoul, Korea) using a qPCR machine (Applied Biosystem, Grand Island, NY, USA). The sequences of the PCR primers were as follows. Tyrosinase 5’- ATC GGC CAA CGA TCC CAT TT -3’ (forward) and 5’- TAG GTG CAT TGG CTT CTG GG -3’ (reverse). TRP-1 5’- CTT TCT CCC TTC CTT ACT GG-3’ (forward) and 5’-TCG TAC TCT TCC AAG GAT TCA-3’ (reverse). TRP-2 5’- TTA TAT CCT TCG AAA CCA GGA – 3’ (forward) and 5’ – GGG AAT GGA TAT TCC GTC TTA – 3’ (reverse). The cycling parameters were 50°C for 2 min, 95°C for 10 min, 40 cycles at 95°C for 15 s, and 50°C for 1 min.

Statistical analysis

The statistical significance of the differences was evaluated by Student’s t-test or ANOVA followed by *Bon ferroni* post-hoc analysis. Significantly different from the control value: *$p<0.05$, **$p<0.01$, ***$p<0.001$.

RESULTS

Chemical structure elucidation

Antaroide was isolated as a brown oil, and its molecular formula was deduced as $C_{20}H_{27}NO_5$ based on analysis of the (+)-HRFABMS pseudomolecular ion peak at m/z 362.1972 $[M+H]^+$. Its IR spectrum showed the presence of an amine (3,365 cm^{-1}) and a ketone group (1,660 cm^{-1}). The ^1H NMR spectrum displayed 1,2-disubstituted benzene protons [H-3 (δ_H 7.99, 1H, d, J=8.0 Hz), H-4 (δ_H 7.41, 1H, dd, J=8.0, 8.0 Hz), H-5 (δ_H 7.79, 1H, dd, J=8.0, 8.0 Hz), H-6 (δ_H 7.95, 1H, d, J=8.0 Hz)], one doublet [H-20 (δ_H 0.92, 3H, d, J=6.8 Hz)], and one methyl singlet [H-19 (δ_H 2.04, 3H, s)]. The ^1H, ^{13}C, and HSQC spectroscopic data revealed two methyl [C-19 (δ_C 27.9), C-20 (δ_C 15.7)], seven methylene [C-9 (δ_C 29.0), C-10 (δ_C 28.5), C-12 (δ_C 36.3), C-13 (δ_C 22.6), C-14 (δ_C 29.1), C-15 (δ_C 26.1), C-16 (δ_C 31.8)], four methine sp^2 [C-3 (δ_C 129.7), C-4 (δ_C 125.7), C-5 (δ_C 135.6), C-6 (δ_C 120.9)], one methane sp^3 [C-17 (δ_C 45.9)], three carbonyl [C-1 (δ_C 161.1), C-8 (δ_C 172.2), C-18 (δ_C 211.8)], two quaternary sp^2 [C-2 (δ_C 116.3), C-7 (δ_C 136.0)], and one quaternary sp^3 carbons [C-11 (δ_C 97.2)] (Table 1).

The interpretation of the 2D NMR results allowed us to define the structure of antaroide. The COSY cross-peaks (H-9/H-10 and H-12/H-13/H-14/H-15/H-16/H-17/H-20) revealed two spin systems composed of two and seven carbon units, respectively. An acetyl group was identified based on the long-range HMBC signal from the methyl singlet H-19 to C-18. The attachment of this acetyl group to C-17 was confirmed by the three-bond HMBC signals from H-19 to C-17 and from H-20 to C-18. The connectivities of the carbonyl groups C-1 and C-8 at C-2 and C-9, respectively, were also established based on the three-bond HMBC signals from H-3 to C-1 and from H-10 to C-8. The long-range HMBC correlations of H-12 and H-10 to C-11 permitted the C-10/C-11/C-12 attachment. The COSY cross-peaks (H-3/H-4/H-5/H-6) revealed a 1,2 disubstituted benzene ring moiety connected to C-8 through NH, according to the carbon chemical shifts of C-7 (δ_C 136.0) and C-8 (δ_C 172.2). The carbon chemical shifts of C-1 (δ_C 161.1) and C-11 (δ_C 97.2) suggested that these carbons should be attached through an oxygen atom in the molecule. Lastly, the chemical shift of C-11 and the molecular formula of antaroide revealed the attachment of a hydroxy group at C-11. Thus, the gross structure of antaroide was determined as shown in Fig. 2.

To determine the stereochemistry of antaroide, we first performed an electronic circular dichroism (ECD) experiment. Unfortunately, antaroide did not display any significant Cotton effect in the wavelength ranges investigated (Supplementary Fig. 6). We could not determine the absolute configuration for the stereogenic center of C-17 due to the lack of relevant compounds with an assigned stereochemistry in literature.

Bioactivities

Various natural products from marine sources have been examined for applications in cosmetics (Kim *et al*., 2017a). To assess the applicability of antaroide as a whitening agent, its effects on melanogenesis were studied by using α-MSH stimulated B16F10 murine melanoma cells.

Antaroide showed potent anti-melanogenic activity, which decreased the intracellular melanin contents of the B16F10 cells in a dose-dependent manner. It was comparable to that of arbutin, a well-known skin whitening agent, while the extracellular melanin release was not affected (Fig. 3).

Microscopic observations revealed attenuated dendrite formation of the B16F10 activated by α-MSH, confirming the suppression of melanocyte activation by antaroide (Fig. 4). In the same experiment, the evaluation of the cell viability showed that the anti-melanogenic effect of antaroide was not due to cytotoxicity (Fig. 5). The mechanism underlying the anti-melanogenic activity of antaroide was further examined by evaluating the mRNA expression of key enzymes for melanogenesis such as tyrosinase, TRP-1, and TRP-2 via real-time PCR (Fig. 6). The results suggested that antaroide can suppress the expression of these melanogenic enzymes.

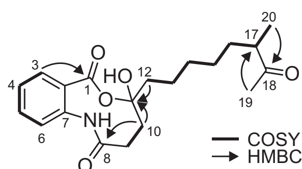

Fig. 2. COSY and key HMBC correlations of antaroide.

DISCUSSION

Natural products can provide insights for developing bioactive substances with novel scaffolds and modes of action. Nine-membered secondary metabolites possessing both lactone and lactam moieties have never been previously reported in medium-sized heterocycle natural products. Natural products containing medium-sized lactones or lactams have been challenging targets in the synthetic fields for a long time (Shiina, 2007; Ferraz *et al*., 2008). In particular, only a small number of nine-membered lactone or lactam natural products have been reported, such as halicholactones (Niwa *et al*., 1989), topsentolides (Luo *et al*., 2006), and antimycins (van Tamelen *et al*., 1961). Nine-membered lactones, halicholactones, and topsentolides have been isolated from marine sponges, while nine-membered dilactones and antimycins were isolated from *Streptomyces* sp. Moreover, the methodology development of such compounds has faced difficulties due to unfavorable kinetic and thermodynamic factors compared to those of larger lactone relatives (Dräger *et al*.,

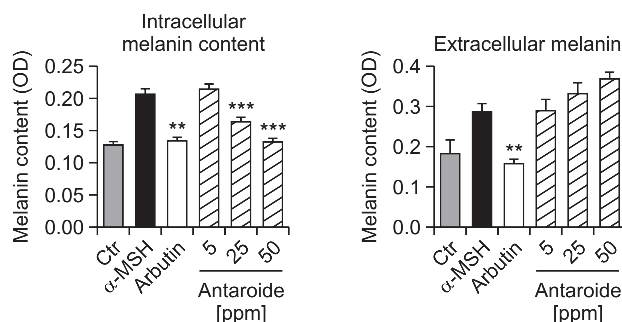

Fig. 3. Effect of antaroide on melanin synthesis in B16F10 cells. The cells were treated with 50 ppm arbutin or different concentrations of antaroide in 200 nM α-melanin stimulating hormone (α-MSH) for 72 h. The intracellular and extracellular melanin content was evaluated by measuring OD after dissolving cells and that of the supernatant, respectively. The data are presented as mean ± standard deviation (n=3, ** p<0.01, *** p<0.001).

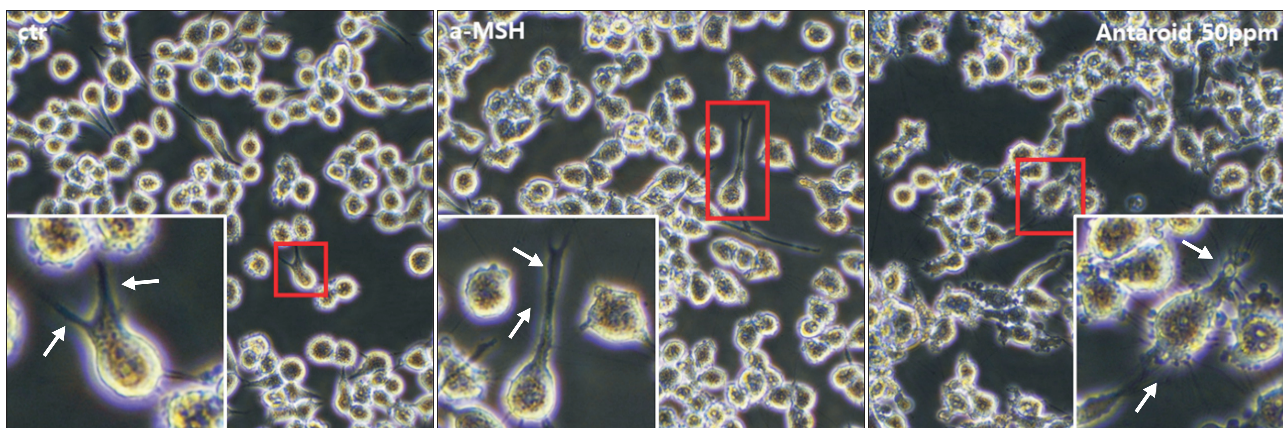

Fig. 4. Effect of antaroide on the morphology of B16F10 cells. The cells were treated with 50 ppm antaroide and 200 nM α-melanin stimulating hormone (α-MSH) for 24 h. Then, the cell morphology was examined with an optical microscope. The white arrows indicate the dendrite formations.

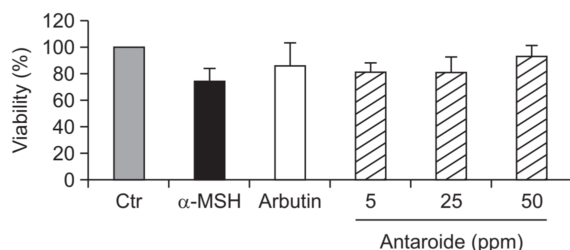

Fig. 5. Effect of antaroide on the viability of B16F10 cells, determined by MTT assay. The cells were treated with 50 ppm arbutin or different concentrations of antaroide in 200 nM α-melanin stimulating hormone (α-MSH) for 72 h. The data are presented as mean ± standard deviation (n=3).

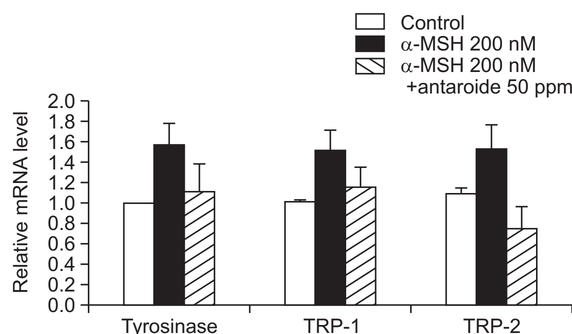

Fig. 6. Effect of antaroide on mRNA level of melanogenic enzymes in B16F10 cells. The cells were treated with different concentrations of antaroide in 200 nM α-MSH for 24 h. The mRNA expression levels of tyrosinase, TRP-1 and TRP-2 were determined by real time PCR. The data are presented as mean ± standard error (n=4).

1996; Parenty *et al*., 2013). The co-presence of lactone and lactam moieties in the ring system has been observed only in 15-membered azalides, which were synthetically prepared from erythromycin (Mutak, 2007). Given the limited number of nine-membered natural products with lactone and lactam moieties reported so far, antaroide is an unprecedented example of this class of compounds.

Melanin is synthesized from L-tyrosine by melanogenic enzymes such as tyrosinase, TRP-1, and TRP-2 (Lee *et al*., 2013, 2015). Since tyrosinase is key in the melanogenesis inhibition in melanocytes, its inhibitors were considered promising candidates as skin whitening agents in cosmetics (Pillaiyar *et al*., 2017). However, tyrosinase inhibitors such as hydroquinone, rhododenol, or raspberry ketones can cause adverse effects such as leukoderma by affecting the melanocyte integrity (Kim *et al*., 2016, 2017b, 2019). Therefore, novel skin whitening agents with a novel mode of action and new scaffolds are required. Many recent studies have reported natural substances showing anti-melanogenic activity through the transcriptional regulation of melanogenic enzymes (Kim *et al*., 2017a). The present study revealed that the anti-melanogenic activity of antaroide works by modulating the mRNA levels of tyrosinase, TRP-1, and TRP-2, indicating its potentiality as a skin whitening agent, which warrants further investigation in the future.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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