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Anithiactins A−C, Modified 2-Phenylthiazoles from a Mudflat-Derived *Streptomyces* sp.

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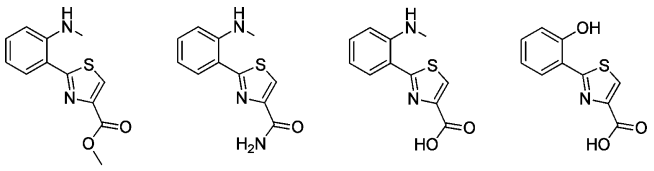
Supporting Information

ABSTRACT: Intensive investigation of the chemical components of a *Streptomyces* sp. isolated from mudflat sediments collected on the southern coast of the Korean peninsula led to the isolation of three new compounds, anithiactins A−C (**1**−**3**). The chemical structures of anithiactins A and C were determined by interpretation of NMR data analyses, while the chemical structure of anithiactin B was established from a combination of NMR spectroscopic and crystallographic data analyses. The structure of anithiactin A was also confirmed by total synthesis. These three anithiactins displayed moderate acetylcholinesterase inhibitory activity with no significant cytotoxicity.

Actinomycetes have been a promising source of bioactive natural compounds for several decades.[1] Soil-derived actinomycetes have traditionally been the main source of bioactive natural products. In the 1980s, the first marine-derived actinomycete, *Rhodococcus marinonascens*, was described.[2] Since then, marine sediments from beach sand to the deep sea bottom have been good environmental sources for isolating actinomycetes, which provide diverse bioactive secondary metabolites.[3] Mudflats, also known as tidal flats, are intertidal zones with deposited mud, which create a unique ecological niche. This wetland is covered with salt water one to two times a day and is exposed to strong sunlight, which causes extreme environmental changes for the organisms living there. Despite these harsh environmental conditions, this zone is crowded with various microbial communities due to the rich nutrients available from the land and from the seawater. This unique ecological niche could also be an excellent environment for diverse bacterial species, including actinomycetes,[4] a situation that often leads to unique chemical structures with diverse biological activities. Recently, our group reported that a *Streptomyces* sp. isolated from tidal flat sediments collected on Anmyeon Island, located on the west coast of Korea, produced biologically active sesquiterpenoids with an indene moiety, anmindenols A and B.[5]

Actinomycete-derived natural products have not been examined extensively to combat neurodegenerative diseases, but specific efforts are ongoing. One of the diseases being studied is Alzheimer's disease (AD), which deteriorates cognitive function. The most common molecular target for drugs that act on the symptoms of AD is acetylcholinesterase (AChE).[6] AChE inhibitors block the AChE enzyme and prevent the neurotransmitter acetylcholine (ACh) from being broken down by AChE, thereby increasing the level of ACh at the synapse and the duration and action of ACh. Thus, far, a few compounds that exhibit AChE inhibitory activity, such as geranylphenazinediol,[7] elaiomycins B and C,[8] N98-1272A,[9] and cyclophostin,[10] have been isolated from *Streptomyces* species.

As part of our continued research into bioactive secondary metabolites from marine actinomycetes on the Korean peninsula, *Streptomyces* sp. 10A085 was isolated from a mudflat sediment sample. Chemical investigation of this strain yielded three new natural products, anithiactins A−C (**1**−**3**). Here, we present details of the isolation of anithiactins A−C and their biological activities in terms of AChE inhibition.



Anithiactin A (**1**) was obtained as a yellowish, amorphous solid. The molecular formula of **1** was established as $C_{12}H_{12}N_2O_2S$ based on high-resolution MS data. The ^1H

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NMR spectrum displayed a 1,2-disubstituted benzene ring moiety [H-3 (δ_H 6.77, d, J = 7.8 Hz), H-4 (δ_H 7.32, ddd, J = 7.8, 7.8, 1.3 Hz), H-5 (δ_H 6.67, dd, J = 7.8, 7.8 Hz), and H-6 (δ_H 7.63, dd, J = 7.8, 1.3 Hz)]. The ^{1}H NMR spectrum also showed a downfield singlet proton H-4′ (δ_H 8.04, s) and *N*-methyl and *O*-methyl singlets [2-NHMe (δ_H 3.01, s), 7′-OMe (δ_H 3.96, s)]. The HMBC correlations from the singlet proton H-4′ (δ_H 8.04, s) to carbons C-2′ (δ_C 170.1), C-5′ (δ_C 146.1), and C-7′ (δ_C 161.7) and the molecular formula of **1** allowed the construction of a thiazole ring moiety (Figure 1). The connection between

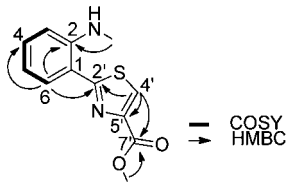

Figure 1. COSY and key HMBC correlations of anithiactin A (**1**).

the 1,2-disubstituted benzene ring moiety and the thiazole ring moiety was achieved using HMBC correlations from the aromatic proton H-6 and the singlet proton H-4′ to C-2′. Lastly, the attachment of the *N*-methyl and the *O*-methyl groups at C-2 and C-7′, respectively, based on HMBC correlations from the *N*-methyl singlet to C-2 and the *O*-methyl singlet to C-7′ completed the assignment of the gross structure of **1** (Figure 1).

The molecular formula of anithiactin B (**2**) was obtained as $C_{11}H_{11}N_3OS$ on the interpretation of the protonated molecule at m/z 234.0701 $[M + H]^+$ in the HRFABMS data. The ^{1}H NMR spectrum of anithiactin B (**2**) was very similar to that of **1** except for the absence of an *O*-methyl singlet and the presence of two singlet protons (δ_H 5.73, δ_H 6.88). The analysis of the 2D NMR spectroscopic data and the molecular formula of **2** indicated that anithiactin B had an NH_2 group at C-7′ instead of a methyl ester. The structure of **2** was also confirmed using X-ray crystallographic data (Figure 2). Slow evaporation of a concentrated solution of **2** in an *n*-hexane and $CHCl_3$ mixture yielded yellow needles.

The ^{1}H NMR spectrum of anithiactin C (**3**) was almost identical to that of anithiactin A except for the absence of the *O*-methyl group. The molecular formula of **3** was established as $C_{11}H_{10}N_2O_2S$ based on the HRFABMS data, indicating **3** had 14 Da less mass than anithiactin A. These data suggested that **3**

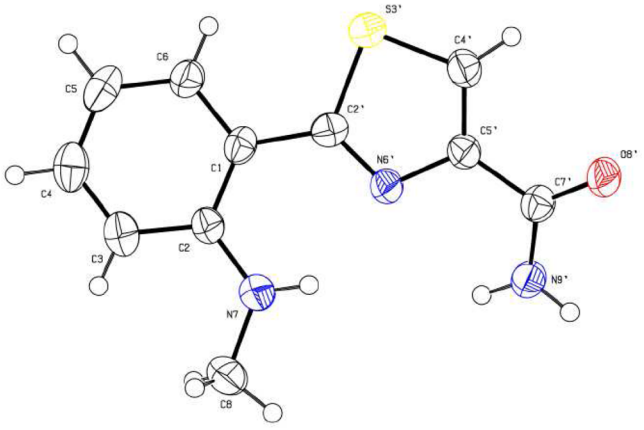

Figure 2. X-ray crystal structure of anithiactin B (**2**).

had an OH group instead of an *O*-methyl group at C-7′. Interpretation of the 2D NMR spectroscopic data permitted the assignment of structure **3**.

Anithiactins are members of the 2-phenylthiazole class of natural products. The representative natural products belonging to this class are aeruginoic acid (**4**),[11] aeruginol,[12] and the pulicatins.[13] In particular, the chemical structures of the anithiactins are closely related to those of aeruginoic acid and the pulicatins. Aeruginoic acid (**4**), a fluorescent natural product, was isolated from the culture medium of *Pseudomonas aeruginosa* and displayed antihypotensive activity.[14] The pulicatins, isolated from a cone snail (*Conus pulicarius*) associate *Streptomyces* sp., showed G protein-coupled receptor 5-HT_{2B} inhibition activity in the micromolar range.[13] These natural products possess an OH group at C-2, whereas anithiactins have an *N*-methyl group. This aniline moiety is unusual within the 2-phenylthiazoline class of natural products.

A number of previous studies demonstrated that AChE inhibitory activity was improved by replacing a phenyl or oxazole with the thiazole moiety.[15,16] Recently, a thiazole-containing AChE inhibitor, acotiamide (Acofide), was launched in Japan and is in preparation for phase III clinical trials in the EU.[17] Therefore, we examined the AChE inhibitory activities of anithiactins A–C (**1**–**3**) using the modified method of Ellman et al.[18] Anithiactins A–C displayed AChE inhibitory effects with IC_{50} values of 63, 53, and 68 μM, respectively. We also evaluated the cytotoxicity of the anithiactins against cancer cell lines. The three anithiactins did not show any significant cytotoxicity against A-498 and ACHN human cancer cell lines up to 200 μM with a modified MTT assay.[19]

To further investigate the underlying biology of AChE inhibition using the anithiactins, a three-step synthetic route (Scheme 1) was developed for anithiactin A (**1**) using commercially available reagents. Thiobenzamide (**6**) was obtained from the sulfur substitution reaction of anthranilamide (**5**) in 89% yield, which was then treated with bromopyruvate in dimethylformamide, a known thiazole ring formation reaction, to give thiazole **7**.[20] To achieve the selective *N*-monomethylation of **7**, we first attempted to use common methylation reagents, such as methyl iodide, *n*-butyllithium, and sodium cyanoborohydride. These methylation reagents gave the *N*-dimethyl product of thiazole **7**. Next, a solution of formaldehyde in dichloroethane and acetic acid was used as a mild methylation reagent for thiazole **7**. The reaction mixture was stirred overnight, and sodium triacetoxy borohydride at 0 °C was added. The mixture was left at room temperature for 2 h and yielded the *N*-monomethyl product (**1**).[21] The physical and spectroscopic data of the synthesized product were identical to the data for the natural product anithiactin A (**1**).

In conclusion, three new 2-phenylthiazole natural products, anithiactins A–C, were isolated from a mudflat-derived *Streptomyces* sp. Anithiactins A–C (**1**–**3**) are the first 2-anilinethiazole natural products in this class, and they displayed moderate inhibitory activity toward acetylcholinesterase.

EXPERIMENTAL SECTION

General Experimental Procedures. UV spectra were recorded in MeOH on a Scinco UVS-2100. The IR spectra were obtained using a Thermo Electron Nicolet 5700 spectrometer. NMR spectra were obtained using Bruker Avance DPX-500 or DPX-600 spectrometers. $CHCl_3$ (δ_H 7.26; δ_C 77.0) and MeOH (δ_H 3.31; δ_C 49.3) resonances were used as internal references. The HRFABMS were determined on a JEOL JMS-600W spectrometer. The solvents used were EP grade

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Scheme 1. Synthesis of Anithiactin A (1)

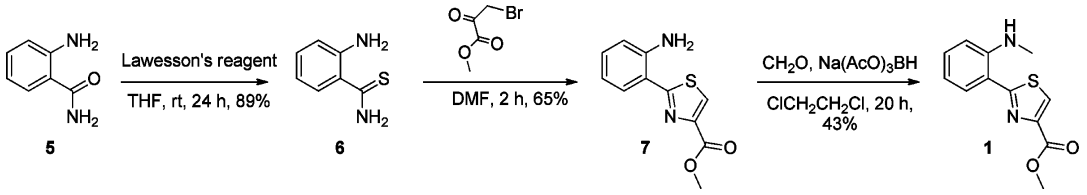

Table 1. NMR Data of Anithiactins A (1, $CDCl_3$)[a], B (2, $CDCl_3$),[a] and C (3, CD_3OD)[a]

	1		2		3	
no.	δ_C, mult.[b]	δ_H (J in Hz)	δ_C, mult.[b]	δ_H (J in Hz)	δ_C, mult.[b]	δ_H (J in Hz)
1	114.3, C		114.9, C		116.5, C	
2	147.5, C		147.3, C		148.8, C	
2-NHMe	29.8, CH_3	3.01, s	30.2, CH_3	3.00, d (5.0)	29.9, CH_3	2.84, s
2-NH		8.43, br s		7.74, br s		4.51, br s
3	111.1, CH	6.77, d (7.8)	111.3, CH	6.77, d (7.8)	112.1, CH	6.64, d (7.8)
4	131.9, CH	7.32, ddd (7.8, 7.8, 1.3)	132.2, CH	7.35, ddd (7.8, 7.8, 1.4)	132.6, CH	7.14, ddd (7.8, 7.8, 1.3)
5	115.0, CH	6.67, dd (7.8, 7.8)	115.9, CH	6.71, dd (7.8, 7.8)	116.1, CH	6.49, dd (7.8, 7.8)
6	129.4, CH	7.63, dd (7.8, 1.3)	130.0, CH	7.64, dd (7.8, 1.4)	130.5, CH	7.50, dd (7.8, 1.3)
2′	170.1, C		170.5, C		170.3, C	
4′	125.1, CH	8.04, s	122.9, CH	8.08 s	123.1, CH	7.83, s
5′	146.1, C		149.2, C		154.9, C	
7′	161.7, C		162.9, C		170.2, C	
7′-OMe	52.3, CH_3	3.96, s				
7′-NH_2				5.73, 6.88 br s		

[a]600 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. [b]Numbers of attached protons were determined by analysis of 2D spectroscopic data.

products from Dae-Jeong & Metals Co., Korea. HPLC grade solvents were purchased from Burdick & Jackson Co. Medium-pressure liquid chromatography was performed on EM Science silica gel (230−400 mesh). TLC was performed using EM Science precoated silica gel plates (Merck 60 F254). The separation of extracts using an HPLC Waters 515 pump and a Waters 996 photodiode array detector was carried out using MG2 C_{18} (250 × 10 mm, 5 μm). The chemical reagents used for synthesis were purchased from Aldrich and TCI. All culture media were purchased from BD Biosciences.

Microbial Isolation and Identification. *Streptomyces* sp. 10A085 was obtained from marine sediments from Jaebu Island, GyeongGi-Do, South Korea, in 2010. The sampled mud sediments were dried in air for 24 h on a clean bench and given a heat shock at 55 °C for 5 min to eliminate other bacteria. Aggregated clumps were lightly mortared using a glass rod and stamped onto various solid agar substrates. Some of the dried samples were suspended in sterilized seawater, and the diluted suspension was spread on variously prepared solid agar substrates using a disposable plastic rod. These crude plates were placed in a 27 °C chamber and monitored for 1 to 3 months to obtain unique actinomycete-like colonies. Strain 10A085 was picked from an ISP medium 4 agar plate containing white spores. The 16S gene was cloned using universal primers 27F and 1492R and showed 99% (1350/1357) similarity to *Streptomyces* sp. HV10 (GenBank accession no. KM881709).

Fermentation and Extraction. Strain 10A085 was cultured at 25 °C with shaking at 150 rpm in 24 Pyrex flasks, each containing 1 L of SYP medium (10 g of soluble starch, 4 g of yeast extract, and 2 g of peptone dissolved in 1 L of 75% filtered natural seawater from Incheon, Korea). After 10 days, the broth was extracted twice using EtOAc, and the solvent was dried *in vacuo* to yield 2.6 g of an extract.

Purification of Anithiactins A−C (1−3). The extract (2.6 g) was separated using a silica column-equipped MPLC and step-gradient elution of MeOH in CH_2Cl_2 (0%, 1%, 2%, 5%, 10%, 20%, 50%, 90%, and 100%). Fraction 1 was further purified using reversed-phase HPLC (MG2 C_{18} 250 × 10 mm, 5 μm, 2.0 mL/min, UV = 210 and 280 nm; CH_3CN/H_2O = 70:30) to obtain 1.0 mg of anithiactin A (**1**). Fraction 3 was also purified using the same column, eluting with 98% CH_3CN in H_2O to afford anithiactin B (**2**, 3.0 mg). Anithiactin C (**3**, 3.0 mg) was isolated from fraction 8 with the same isolation procedure used for anithiactin B.

*Anithiactin A (**1**):* yellowish, amorphous solid; UV (MeOH) λ_{max} (log ε) 209 (5.07), 222 (4.78), 247 (4.31), 286 (4.05), 383 (4.10) nm; IR (KBr) ν_{max} 3303, 3122, 1727, 1580, 1491, 1446, 1214, 1173, 1104, 906, 753, 738 cm^{-1}; ^{1}H, ^{13}C, and 2D NMR data, Table 1; HRFABMS m/z 249.0698 [M + H]$^+$ (calcd for $C_{12}H_{13}N_2O_2S$, 249.0698).

*Anithiactin B (**2**):* yellowish needles; mp 164−168 °C; UV (MeOH) λ_{max} (log ε) 211 (4.67), 219 (4.41), 247 (3.91), 287 (3.67), 383 (3.70) nm; IR (KBr) ν_{max} 3415, 3321, 3193, 1650, 1609, 1581, 1485, 1367, 1215, 1175, 988, 804, 751 cm^{-1}; ^{1}H and ^{13}C NMR data, Table 1; HRFABMS m/z 234.0701 [M + H]$^+$ (calcd for $C_{11}H_{12}N_3OS$, 234.0701).

*Anithiactin C (**3**):* yellowish, amorphous solid; UV (MeOH) λ_{max} (log ε) 211 (4.56), 219 (4.30), 261 (3.63), 286 (3.57), 379 (3.57) nm; IR (KBr) ν_{max} 3417, 2923, 1573, 1492, 1383, 1285, 1214, 1172, 750 cm^{-1}; ^{1}H and ^{13}C NMR data, Table 1; HRFABMS m/z 235.0543 [M + H]$^+$ (calcd for $C_{11}H_{11}N_2O_2S$, 235.0541).

X-ray Crystallographic Analyses. The single-crystal X-ray diffraction data of the compound were collected with a Bruker SMART APEX CCD detector employing graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) at 273(2) K. The data collection and integration were performed using SMART (Madison, WI, USA, 2000) and SAINT-Plus (Madison, WI, USA, 2001). The structure was solved using direct methods and refined using full-matrix least-squares on F^2 using SHELXTL (Madison, WI, USA). All the non-hydrogen atoms were refined anisotropically, and hydrogen atoms were added to their geometrically ideal positions.

*Crystal data of anithiactin B (**2**):* $C_{11}H_{11}N_3OS$, M_r = 233.30, monoclinic, a = 15.1825(12) Å, b = 5.2022(4) Å, c = 14.7674(12) Å, α = 90°, β = 111.728(2)°, γ = 90°, V = 1083.50(15) Å^3, space group $P2(1)/c$, Z = 4, D_x = 1.430 mg/m^3, μ(Cu Kα) = 0.279 mm^{-1}, and $F(000)$ = 488. Crystal dimensions: 0.18 × 0.14 × 0.12 mm^3. Independent reflections: 2677 (R_{int} = 0.0825). The final R1 values were 0.0644, wR2 = 0.1544 ($I > 2\sigma(I)$). CCDC number: 1022818.

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Cytotoxicity Test. The cytotoxicity test was performed for two human cancer cell lines, A498 and ACHN renal cancer, according to a previously published method[19] with modifications. The cells were cultured in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum and 1% penicillin at 37 °C in a humidified atmosphere incubator (5% CO_2 in air). Wells with DMSO were used as negative controls, and temsirolimus, sunitinib, and gemcitabine were used as positive controls

Acetylcholinesterase Inhibitory Assay. The AChE inhibitory activity was measured using the modified method of Ellman et al.[18] Briefly, a reaction mixture containing 140 μL of sodium phosphate buffer (pH 8.0), 20 μL of the test sample solution, and 20 μL of AChE was incubated for 15 min at 25 °C. Following the incubation, the reaction was initiated by adding 10 μL of dithiobisnitrobenzoate (DTNB) and 10 μL of ACh and incubated for 10 min at 25 °C. The hydrolysis of ACh was monitored and quantified in a spectrophotometer at 412 nm to measure the formation of DTNB with thiocholine released by the enzymatic hydrolysis of ACh. Donepezil hydrochloride (Santa Cruz Biotechnology) was used as a positive control. The 50% inhibitory concentration (IC_{50}) of the donepezil hydrochloride was 0.02 μM. All reactions were performed in triplicate on 96-well plates and recorded using a VERSA max plate reader (Molecular Devices). The percentage of inhibition was calculated as $(1 - S/E) \times 100$, where E and S are the enzyme activities with and without the sample.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The NMR spectroscopic data of anithiactins A–C (**1**–**3**), synthetic intermediates (**6**, **7**), and synthetic anithiactin A (**1**) and X-ray data of anithiactin B (**2**) are available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

#H. Kim and I. Yang equally contributed to this work.

Notes

The authors declare no competing financial interest.

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