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Structure of zamamistatin—a correction

Masaki Kita [a], Yuta Tsunematsu [c], Ichiro Hayakawa [a], Hideo Kigoshi [a,b,*]

[a] Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan
[b] Center for Tsukuba Advanced Research Alliance, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan
[c] Department of Chemistry, Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

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ABSTRACT

The structure of zamamistatin, an antibacterial dibromotyrosine derivative, has been revised. Its structure was not *exo*- or *endo*-type dimer **1** or **2** which were described previously, but was identical to a dibromophenylpyruvic acid derivative, aeroplysinin-1 (**3**).

Zamamistatin is a dibromotyrosine derivative isolated from the Okinawan sponge *Pseudoceratina* sp.,[1] which exhibits significant antibacterial activity against the marine bacterium *Rhodospirillum* sp. Based on the NMR spectra and MS analysis, the structure of zamamistatin was firstly elucidated as shown in **1**, as an *exo*-type C_2 symmetrical dimer of the azaoxa-spiro[6.5] unit consisting of a cyclohexadienyl moiety and an isoxazolidine ring (Fig. 1). Meanwhile, the chemical shift of the oxygenated spiro-carbon of zamamistatin (δ_C 74.3 in acetone-d_6) was considerably different from the spirocarbon of the spiroxazoline structure in aerothionin (δ_C 91.5).[2] Thus, an *endo*-type dimer of the azaoxa-spiro[6.6] unit possessing a dihydro-1,2-oxazine ring, as shown in **2**, was proposed as another plausible structure.[3] Here, we describe the second structural revision of zamamistatin, including its concentration-dependent ESIMS analysis and evaluations of its biological activities.

Purified zamamistatin was moderately unstable in acetone at room temperature. As one of its degraded compounds, dibromophenolic compound **4** was isolated as colorless needle crystals. The IR band of **4** (2258 cm^{-1}) strongly indicated the presence of a nitrile moiety. Moreover, its crystallographic and spectroscopic (NMR and MS) data were identical to those previously reported.[4] However, it was considered that compound **4** could not be obtained from either *exo*-type dimer **1** or *endo*-type dimer **2** with an oxidative cleavage of a carbon–carbon double bond. Thus, the structure of zamamistatin was reconsidered.

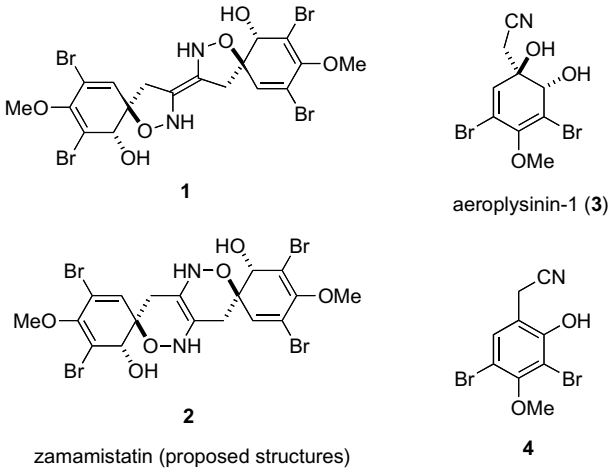

Figure 1.

On the previous ESIMS analysis of zamamistatin, both a quintet ion peak at *m/z* 700.8 ($C_{18}H_{18}{}^{79}Br_2{}^{81}Br_2N_2NaO_6$) and a triplet ion peak at *m/z* 361.9 ($C_9H_9{}^{79}Br^{81}BrNNaO_3$) were observed at a concentration of 15 μM; they were assigned as a molecular ion peak $[M+Na]^+$ and a half-molecular fragment ion peak $[M/2+Na]^+$, respectively. Notably, however, the larger ion peak disappeared in a diluted condition (0.15 μM). These results strongly suggested that the molecular formula of zamamistatin was $C_9H_9Br_2NO_3$,

* Corresponding author. Tel./fax: +81 298 53 4313.
E-mail address: kigoshi@chem.tsukuba.ac.jp (H. Kigoshi).

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and that an ion peak at m/z 700.8 can be assigned as a cluster ion peak $[2M+Na]^+$. Moreover, IR data of zamamistatin (2262 cm^{-1}) strongly indicated that it was a monomer possessing a nitrile group.

As a result, the structure of zamamistatin was found to be identical to that of a dibromophenylpyruvic acid derivative, aeroplysinin-1 (**3**).[5] Spectroscopic data, including ^1H and ^{13}C NMR (in $CDCl_3$ and CD_3CN), in addition to IR spectra and optical rotation of zamamistatin, revealed that they were completely identical to those of **3**. It was previously shown that basic treatment of **3** gave a dehydrated phenolic compound **4**.[6] Moreover, in the case of ESIMS analysis of the synthesized **3**,[7] a cluster ion peak was at m/z 700.8 $[2M+Na]^+$, which was similar to the case of the natural one. Thus, the structure of zamamistatin has been revised as **3**, a 1,2-dihydroarane-1,2-diol monomeric compound.

Aeroplysinin-1 (**3**) was previously isolated from the marine sponges *Verongia* sp. and *Pseudoceratina* sp. as an antimicrobial compound.[4,5] Various biological activities of **3** have been investigated, including cytotoxicities against the EAT and HeLa tumor cell lines,[6] antifouling activity,[8] and antiangiogenic properties.[9] Its unique structure was utilized toward the development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors.[10] Furthermore, growth inhibition assays of **3** against a panel of 39 human cancer cell lines revealed that it was especially effective against melanoma (LOX-IMVI) and lung (NCI-H522) cancer cell lines. The COMPARE analysis of the mean graph revealed that **3** was not significantly correlated with any known anti-cancer drugs ($r < 0.432$). Further evaluations of the pharmacological activities of **3**, including in vivo experiments, are in progress.

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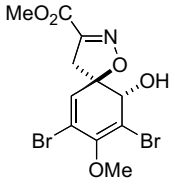

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