[S4-4] [4/20/2001(Fri) 11:30-12:00/Hall B]

Bioactive Metabolites from Selected Sponges of Korean and Tropical Waters

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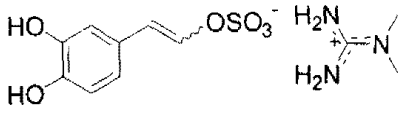
Abstract
Wondonins A and B, aromatic alkaloids of an unprecedented skeletal class have been isolated from an association of the sponges *Poecillastra wondoensis* and *Jaspis* sp. In addition, four novel bromotyrosine-derived metabolites, psammaplins A_1 and A_2, aplysinellins A and B, have been isolated from the tropical sponge *Aplysinella rhax*. The structures of these compounds have been determined on the basis of combined chemical and spectral analyses. The new compounds exhibited significant cytotoxicity and antiangiogenic activity as well as inhibitory activities against farnesyl protein transferase and leucine aminopeptidase. In addition to these compounds, several bioactive metabolites have been isolated from sponges of Korean and tropical waters.

Sponges (phylum Porifera) are widely recognized as very prolific sources of biologically active and structurally unique metabolites.[1] Studies have revealed that sponge-derived metabolites have been originated from various biogenetic precursors. In addition, several compounds have displayed potent and diverse bioactivities which have attracted significant biomedical and synthetic attentions. We have recently shown that sponges of the Korean waters have produced a wide variety of compounds possessing unusual carbon frameworks and functionalities.[2] In our continuing search for bioactive substances from benthic invertebrates of the Korean and tropical waters, we encountered several sponges whose organic extracts showed considerable cytotoxicity toward the human leukemia cell-line K-562 and/or inhibitory activity toward various enzymes. Guided by the results of combined bioactivity tests and NMR analysis, secondary metabolites have been isolated employing various chromatographic methods. We describe herein the structures and bioactivities of novel alkaloids belonging to uncommon structural classes.

Four aromatic compounds were isolated from specimens of a close association of the sponge *Poecillastra wondoensis* covering *Jaspis* sp. collected from Keomun Island, Korea. The structures of the major metabolites were defined as (*E*)-and (*Z*)- narains (**1** and **2**), 3,4-dihydroxystyryl sulfates on the basis of combined spectroscopic methods and comparison of spectral data with those reported previously.[3,4] The presence of *N,N*-dimethylguanidium as counterion in these compounds was proved by detailed interpretation of 2-D NMR and HRMS data.

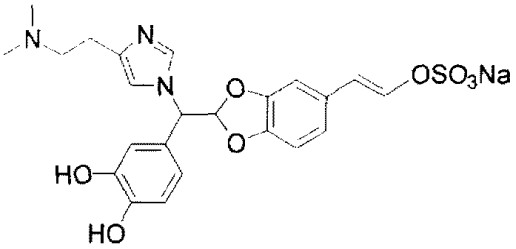
The three partial structures of wondonin A (**3**), two 3,4-dioxygenated styrene and a 2-*N,N*-dimethylaminoethylimidazole moieties were defined by a combination of gradient HSQC and HMBC experiments. The positioning of a sulfate group on the side chain of a styrene moiety was determined from ^{1}H NMR and IR data. The connectivity among three partial structures was accomplished by gradient HMBC correlations between the ketal protons and neighboring carbons. The spectral data of wondonin B (**4**) were very similar to those of

wondonin A. Extensive NMR experiments showed that these compounds had the planar structures identical to each other. Since these compounds possessed two asymmetric carbon centers, wondonins were assumed to be epimeric at these positions. Due to the severe overlapping in the ^{1}H NMR data as well as the spatial crowding among the bulky substituents, however, the stereochemistry of the asymmetric carbon centers remained to be assigned. To the best of our knowledge, bis(dihydroxystyryl) imidazole moiety of wondonins is totally unprecedented among marine natural products.



1 (*E*)-narain

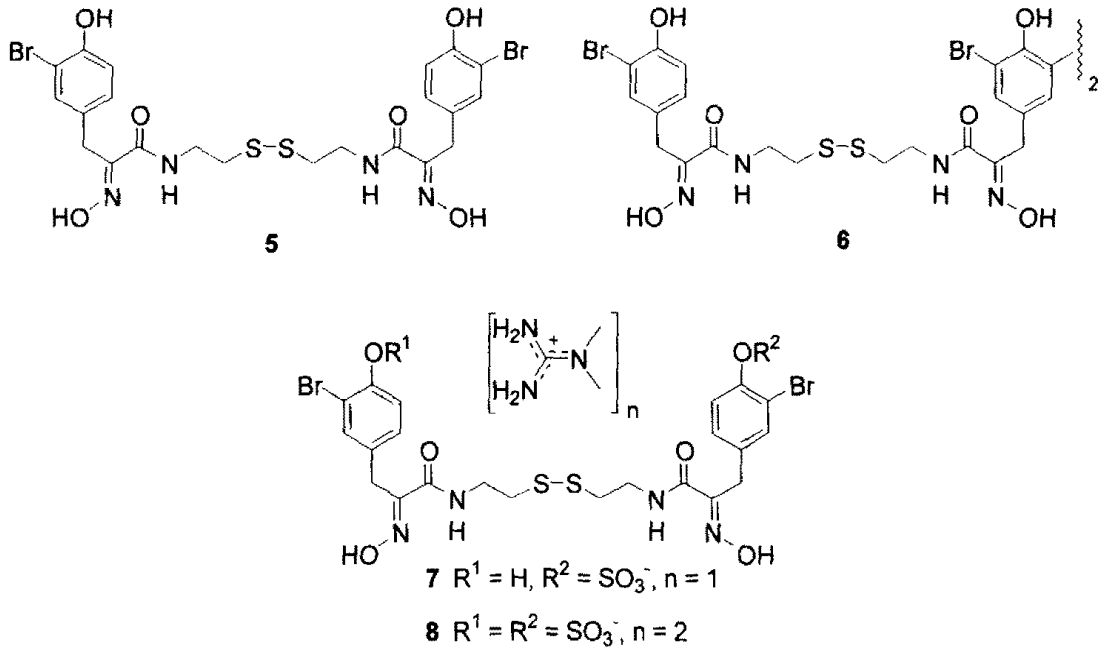
2 (*Z*)-narain



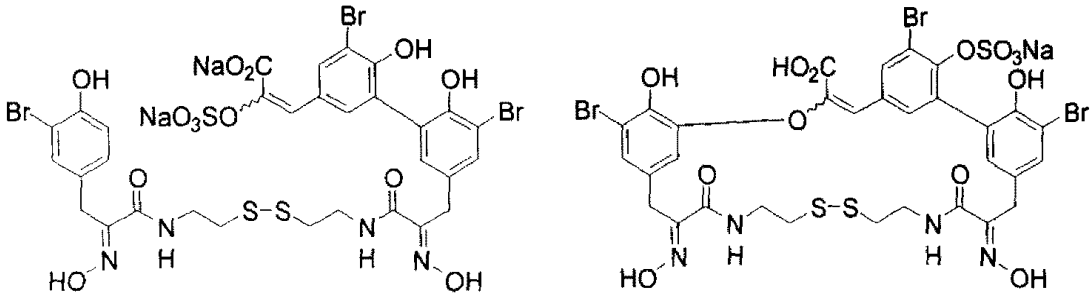
3 and **4** (1'- or 2'-epimer)

Bioactivity tests showed that (*E*)-and (*Z*)-narains were responsible for the cytotoxicity of the crude extract while wondonins were not active. In the mean while, these compounds exhibited significant antiangiogenic activity against human umbilical vein endothelial cell (HUVEC). At the concentration of 10 μg/mL, wondonins totally inhibited tube-formation of HUVEC.[5] Coupled with the structural uniqueness of these compounds, bioactivity profile of wondonins suggest further studies for the mechanisms of action as well as the structure-activity relationship.

Six alkaloids derived from bromotyrosine and cysteine were isolated from the sponge *Aplysinella rhax* collected from Guam. Two of the major metabolites were structurally defined as psammaplin A (**5**) and its dimer bisaprasin (**6**) on the basis of combined spectroscopic methods and comparison of spectral data with those reported previously.[6,7] The structures of psammaplin A_1 (**7**) and A_2 (**8**), new analogs, were determined to be the sulfate salts of psammaplin A containing *N,N*-dimethylguanidium as counterion(s) by combined 2 D NMR and HRMS analyses.



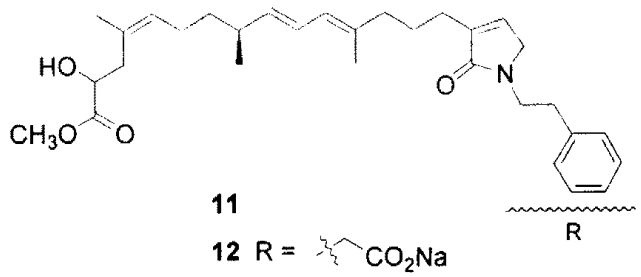
Aplysinellin A (**9**) was proved to contain an additional C_9 unit derived from bromotyrosine on the carbon framework of psammaplin A by HRMS and ^{13}C NMR analysis. The partial structure of the newly associated unit as well as its connectivity to a benzene ring by biphenylic linkage was determined by combined gradient HMBC and ROESY experiments. Aplysinellin B (**10**) was a cyclic derivative of aplysinellin A in that the new C_9 moiety was connected to a benzene by an usual enol-ether linkage. The spectral interpretation and positioning of the polar functionalities, *e. g.* sulfate and hydroxyl groups, were accomplished by methylation of **6** by $(CH_4)_2SO_4$.



Bioactivity tests revealed that the bromotyrosine compounds exhibited significant cytotoxicity toward the human leukemia cell-line K562 (LC_{50} 0.4~1.7 μM). In addition, these compounds displayed inhibitory activity against farnesyl protein transferase (LC_{50} 3.0~80 μM) and leucine aminopeptidase (**1**, **2**, and **5**, LC_{50} 2.4~70 μM).

Sarcotragins A (**11**) and B (**12**), trisnorsesterterpene lactams of an uncommon structural class have been isolated from the sponge *Sarcotragus* sp. collected from Jaeju island, while eryloside G (**13**) was defined as a cytotoxic triterpenoid saponin from *Erylus nobilis* collected from the same area.[9,10] In addition, plakinamine E (**14**) and 2-bromosceptrin (**15**) have been

isolated as the bioactive constituents of the tropical sponges *Corticium* sp. and *Agelas* sp., respectively.[11]



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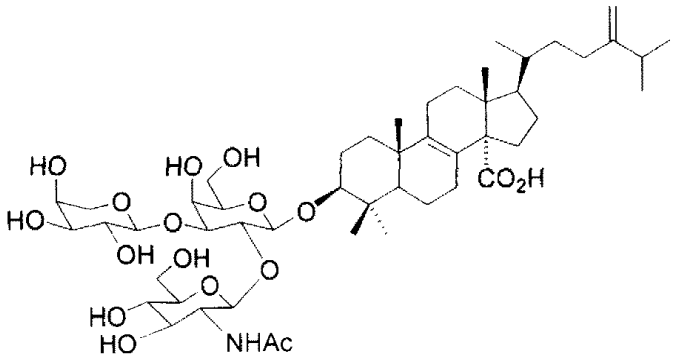
12 R = CO_2Na



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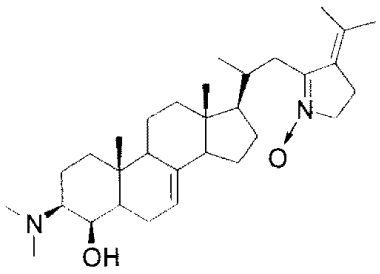

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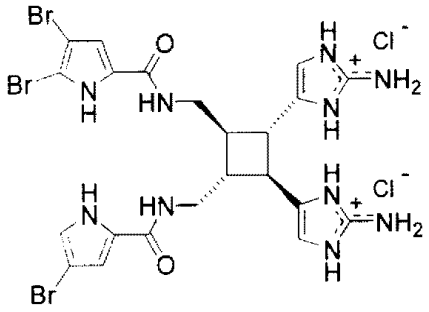

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