Abstract

A Study on the Bioactive Natural Products from Marine-Derived Fungi

Elin Julianti
Natural Products Science Major
College of Pharmacy
Doctoral Course in the Graduate School
Seoul National University

Marine microorganisms, particularly actinomycete bacteria and fungi, produce a wide variety of biologically active and structurally unique metabolites. Hundreds of novel compounds are isolated from these organisms annually, thus to be the promising subjects for chemical and biological investigation.

The aim of this thesis was the isolation and structure determination of the secondary metabolites produced by fungal strains from marine environment and the evaluation of their biological activities. Marine fungal strains were isolated from sponges and sea sediments. The biological activity assay was performed for cytotoxic, antimicrobial, antioxidant and actin depolymerizing activities as well as enzyme inhibitory activities against sortase A, isocitrate lyase, and Na^+/K^+-ATPase.

Strains of two sponge-derived fungi and one from sea sediment were the

focuses of this work. Large-scale cultivation, extraction and separation using diverse chromatographic methods were conducted to yield pure compounds. This study leads to the isolation and structure elucidation of 29 pure compounds by combined chemical and spectroscopic analysis. These compounds are derived from diverse biogenetic origins and belong to several structural classes; diketopiperazines, phthalides, nucleobase, phenalenones, and meroterpenoids. Sixteen compounds (**1, 5, 7, 9**, **11**, **14-17**, **19**, **20**, **22**, **26-29**) were defined to be new natural products. Several compounds exhibited moderate to significant bioactivities.

1. Acremostrictin, a Highly Oxygenated Metabolite from *Acremonium strictum*

The novel natural product acremostrictin (**1**) was isolated from the culture broth of *Acremonium strictum*, a marine fungus associated with a Choristida sponge collected off the coast of Gagu-do, Korea. Acremostrictin is a tricyclic lactone of an unprecedented structural class based on combined spectroscopic and X-ray crystallographic analyses. This new compound exhibited weak antibacterial and moderate antioxidant activities.

2. Phthalides and Diketopiperazines from *Acremonium strictum*

Seven compounds, 7-hydroxyphthalide (**2**), 7-methoxyphthalide (**3**), 4-methoxyphthalide (**4**), cyclo-(L-2-oxo-3*S*-hydroxy-tryptophyl-L-phenyl-alanyl) (**5**), cyclo-(L-tryptophyl-L-phenylalanyl) (**6**), cyclo-(L-2,3*S*-dihydroxy-tryptophyl-L-phenylalanyl) (**7**), and cyclo-(L-tryptophyl-L-leucyl)

(**8**) were isolated from the culture broth of the fungus *Acremonium strictum*. Compounds **5** and **7** are new compounds while compounds **3** and **4** were isolated for the first time as natural products. Their structures were established by spectroscopic studies and the absolute configuration of **5** was established by Marfey's method and circular dicroism (CD) measurement. Most of the compounds exhibited moderate cytotoxicity against A549 cell-line.

3. Acremolin, a New 1*H*-azirine Metabolite from *Acremonium strictum*

Acremolin (**9**), a novel modified guanine derivative, was isolated from the culture broth of the marine fungus *Acremonium strictum*. Based on combined spectroscopic analyses, the structure of this compound was defined to be a methyl guanine base containing an isoprene unit. The presence of a 1*H*-azirine moiety is unprecedented among natural products. This compound exhibited weak cytotoxicity against A549 cell-line.

4. Phenalenones from *Penicillium* sp. (F011)

Seven new phenalenone derivatives (**11**, **14-17, 19, 20)**, one related new napthaquinone (**22**) and five known phenalenones, isoherquienone (**10**), herquienone (**12**), ent-isoherquienone (**13**), tetracyclic triketone (**18**) and scleroderolide (**21**) were isolated from the culture broth of *Penicillium* sp., which was separated from the marine sediment off the coast of Gagu-do, Korea. Their structures were determined by spectroscopic methods, mainly by 2D NMR spectroscopic analyses. Most of the compounds exhibited

moderate cytotoxic activity against A549 cell-line and exhibited moderate sortase A (Srt A) and Na^+/K^+-ATPase inhibitory activities. Compound **22** exhibited significant cytotoxic activity with IC_{50} values 6.41 μg/mL. Compound **22** and **11** exhibited potent sortase A (Srt A) inhibitory activity with IC_{50} values of 8.9 and 36.5 μg/mL, respectively.

5. Austalides from *Penicillium thomii*

Four new austalide derivatives (**26-29**) along with three known compounds, austalide H (**23**), 1-oxo-4,5a,9-trimethyl-7-hydroxy-8-(1-hydroxy-1-methyl-ethyl)-11-methoxy-3,5a,6,7,8,9,9a,10-octahydro-1H-furo[3,4-b]xanthenes-9-propanoic acid (**24**) and austalide P (**25**) were isolated from the culture broth of *Penicillium thomii*, which was separated from the unidentified marine sponge collected off the coast of Gagu-do, Korea. Their structures were determined by spectroscopic methods, mainly by 2D NMR spectroscopic analyses.

Keywords: marine-derived fungi, marine natural products, structure elucidation, acremostrictin, diketopiperazines, pthalides, acremolin, modified guanine, phenalenones, austalides.

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