Bioactive Compounds from Korean Marine Sponges

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Introduction

Marine sponges are recognized as a plentiful source of diverse biologically active secondary metabolites. Recently, we have initiated a research to discover antitumor constituents from the marine sponges collected from Korean Waters. Marine sponges collected from the South Sea of Korea were screened for several biological activities including brine shrimp lethality and cytotoxicity. Based on the bioactivity screening, a few sponges were selected for intensive chemical study to afford new and/or biologically active compounds.

Antitumor compounds from a two-sponge association

Significant brine shrimp lethality was detected in the crude extract of a two-sponge association of *Poecillastra wondoensis* and *Jaspis wondoensis*. A cross-section of this sample showed two layers of morphologically distinct sponges. The thin and dirty yellow outer layer was identified as *Poecillastra wondoensis* (Pachastrellidae), the surface of which was very rough. The light-grey inner layer was identified as *Jaspis wondoensis* (Jaspidae), the surface of which was smooth. This two-sponge association appears to be consistent as these sponges were always found in associated form regardless of collection site or collection period. Investigation for the bioactive constituents monitored by brine shrimp lethality assay led to the isolation of pectenotoxin II (PTX2) and psammaplin A as causative compounds for the brine shrimp lethality. 1H- and 13C-nmr signals of PTX2 were fully assigned utilizing TOCSY, HETCOR, Long-range HETCOR, and Homonuclear *J*-resolved 2D experiments. PTX2 displayed very potent and selective cytotoxicities in the 60 cell line panel antitumor assay at the NCI. PTX2 has progressed to acute toxicity determination and *in vivo* antitumor assay at the NCI[1] However,

significant *in vitro* antitumor activity of PTX2 can not be affirmed in the *in vivo* assay. The therapeutic index of PTX2 was too small to be considered for further trial. The toxicity of PTX2 was reversible and liver was identified as the target organ. It is speculated that liver toxicity of PTX2 is related to inhibition of the enzyme system involved in metabolism.[2,3]

Cytotoxic constituents of the sponge *Petrosia* sp.

Significant activities in the brine shrimp larvae lethality assay (LD50, 30 ppm) and *in vitro* P388 assay were detected in the methanol extract of the marine sponge *Petrosia* sp. Guided by bioactivity, the methanol extract was further fractionated between water and CH2Cl2, followed by partitioning of the CH2Cl2 solubles between 90% methanol and *n*-hexane. The 90% MeOH fraction was then partitioned again between water and CH2Cl2 to afford the CH2Cl2 layer which was subjected to reversed-phase flash column chromatography and HPLC to yield twenty two polyacetylenic alcohols and a cyclitol derivative.[4-7] These compounds showed moderate to significant cytotoxicities against human tumor cells. The cytotoxicities of the compounds were further determined in the NCI 60 cell line panel to show significant selectivity and potency. These compounds displayed selective G1 arrest in the cell cycle assay. Further study on the mode of action of the compounds revealed that they inhibit the early stage of DNA replication by suppressing topoisomerase I and DNA polymerase -primase.

Inhibitors of cholesterol synthesis from the sponge *Spirastrella abata*

From the marine sponge *Spirastrella abata*, a series of lysophosphatidylcholines were isolated as inhibitors of cholesterol biosynthesis in the Chang liver cell. These lysophosphatidylcholins were found to be either 1-alkyl ether or ester form, with cyclopropyl moiety, methoxyl group, or methyl branching, which are not ordinary members of phospholipids. These compounds inhibited the cholesterol biosynthesis at the level of downstream of the pathway unlike commercially available hypolipemic drugs which suppress synthesis at the level of upstream. These compounds selectively blocked the transformation of lanosterol to cholesterol.[8]

Cytotoxic constituents of the sponge *Sarcotragus* sp.

Six new and two known furanosesterterpenes were isolated as cytotoxic constituents of the sponge *Sarcotragus* sp. The unconjugated tetronic acid moiety of the compounds was quite labile that it has decomposed even at 20 C in solid state. While the conjugated tetronic acid congeners were relatively stable to enable the determination of the absolute configuration of C-18 and the geometry at C-20. The compounds displayed significant cytotoxicity against a small panel of human tumor cell lines, and showed selective G1 arrest in the cell cycle assay.

Cytotoxic constituents of the hard coral *Montipora* sp.

Twenty new acetylenic compounds and a pyridinium alkaloid were isolated as cytotoxic constituents of the stony coral *Montipora* sp.[9] Significant cytotoxicity against human tumor cell lines was affirmed. Compounds **5** and **6** were chemically unique possessing a 7-membered lactam and a cyclohexenone moiety, respectively. However, the acyclic congeners showed more potent cytotoxicty than the cyclic congeners. The acetylenes induced apoptosis in the human colon cancer cell.

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