

Review

Bioactive Compounds Derived from Marine Bacteria: Anti-cancer Activity

Se-Kwon Kim^{1,2,*}, Van L. T. Hoang² and Moon-Moo Kim¹

¹Marine Bioprocess Research Center, Pukyong National University, Busan 608-737

²Department of Chemistry, Pukyong National University, Busan 608-737, Korea

Abstract Bioactive compounds produced by microorganisms have focused on in recent years. In particular, novel compounds showing anti-cancer activity have been isolated from marine microorganisms. In this review, we will discuss on the studies of new bioactive compounds derived from marine bacteria with conjunction to anti-cancer activity. This review will provide an information and source for bioactive compounds showing anti-cancer activity, which were derived from marine bacteria.

Key words : Bacteria, cancer, cyanobacteria, *Streptomyces*, *Actinomyces*

Introduction

Marine microorganisms have been recently provided a potential source for development of bioactive compounds. A variety number of bioactive compounds have been isolated, and their structures and potential biological activities have been studied [9]. New methods for sampling, classification, and culturing for marine microorganisms have been applied to the isolation and culture of novel microorganisms [11]. Consequently, scientific research about bioactive compounds derived from marine microorganisms has increased spectacularly.

There are several reports focusing on either general or specific microorganisms, such as "marine natural product" [5], "bioactive macrolides and polyketides from marine dinoflagellates" [19], "metabolites from marine-derived fungi" [6], "antimicrobials and anti-fungals from marine microorganisms" [2], "enzyme inhibitors from marine microbes" [17].

In this review, we will discuss novel bioactive compounds derived from marine microorganisms especially showing anti-cancer activity. Although cancer has been one of the most difficult life-threatening diseases, drugs

derived from natural products have been known to provide a help to ameliorate the condition [37]. In order to investigate bioactive compounds showing anticancer activity, we will review novel potential bioactive compounds derived from novel microorganisms. Since bioactive active compounds are generally present in very low concentration in nature, the efficient isolation and bioassay methods are prerequisite. The major bioassays currently in use in the National Cancer Institute (NCI) programme are based on the KB and P388 cell lines [3]. Although studies on the anti-cancer mechanisms of a few candidates were extensively performed, a variety number of novel bioactive compounds remained unsolved. In this review, we will discuss on novel bioactive compounds derived from marine microorganisms showing anti-cancer activity to be able to apply to cancer prevention or cancer treatment in near future.

Bioactive compounds derived from Cyanobacteria

A new compound (IB-00208) was isolated from the fermentation broth of *Actinomadura* sp. This compound showed cytotoxic activity on both human and murine

* Corresponding author

Phone: +82-51-620-6375, Fax: +82-51-628-8147

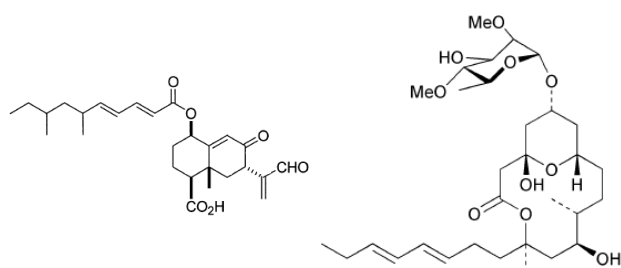
E-mail: sknkim@pknu.ac.kr

tumor cell lines with IC_{50} of 1 nM as well as bactericidal activity against gram-positive bacteria [30]. A glycosidic macrolide (lyngbouilloside) was isolated from the marine cyanobacterium *Lyngbya bouillonii* collected from Papua New Guinea and showed modestly cytotoxic activity to Neuro-2a cell with IC_{50} values of 17 μ M [41]. Obyanamide was isolated from a collection of *Lyngbya confervoides* collected in Saipan, and exhibited moderate cytotoxicity against KB and LoVo cells with IC_{50} values of 0.58 and 3.14 μ g/mL, respectively [42].

A potent cytotoxin (aapratoxin A) was isolated from the marine cyanobacterium *Lyngbya majuscula* Harvey ex Gomont [23]. Two different collections of *Lyngbya* sp. Originated from Guam and Palau produced the new apratoxins, termed as apratoxins B and C [25]. Their structures had been determined by spectral analysis and chiral HPLC analysis. Apratoxin A possessed IC_{50} values for *in vitro* cytotoxicity against human tumor cell lines ranging from 0.36 to 0.52 nM; however, it was only marginally active *in vivo* against a colon tumor and ineffective against a mammary tumor. Meanwhile

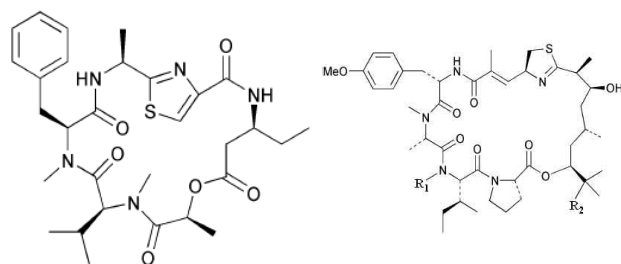
all analogues apratoxins B and C displayed weaker cytotoxicity with IC_{50} values of 1.0–21.3 nM. A new 36-membered macrolactone, (25*S*,27*S*,29*S*,33*S*)-caylobolide A, was isolated from the Bahamian cyanobacterium *Lyngbya majuscula* and exhibited cytotoxicity against human colon tumor cells *in vitro* (IC_{50} HCT116, 9.9 μ M) [28]. Novel cyclic depsipeptides (guineamides B and C) were isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Papua New Guinea, and their structures were determined. These compounds possessed moderate cytotoxicity on a mouse neuroblastoma cell line with IC_{50} values of 15 and 16 μ M, respectively [40]. Hectochlorin was isolated from marine isolates of *Lyngbya majuscula* collected from Hector Bay, Jamaica, and Boca del Drago Beach, Bocas del Toro, Panama and its planar structure was determined. Hectochlorin showed cytotoxicity against CA46 cells, and human Burkitt lymphoma line (IC_{50} values of 20 nM) [31].

An examination of an organic extract of the cyanobacterium *Lyngbya majuscula*, collected from Madagascar, led to the isolation of a new bioactive cyclic depsipeptide, homodolastatin 16. Although homodolastatin 16 was a higher homologue of the potential anticancer agent, dolastatin 16, it showed only moderate activity against two esophageal cancer cell lines (WHCO1 and WHCO6), and a cervical cancer cell line (ME180), exhibiting IC_{50} values of 4.3, 10.1, and

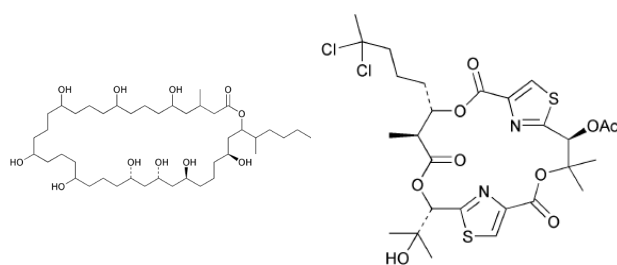


07H239-A

Lyngbouilloside

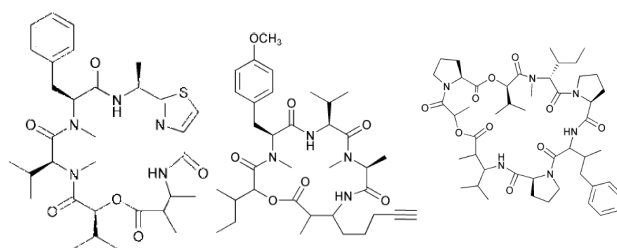


Obyanamide

Apratoxin A $R_1 = CH_3$ $R_2 = CH_3$ Apratoxin B $R_1 = H$ $R_2 = CH_3$ Apratoxin C $R_1 = CH_3$ $R_2 = H$ 

Caylobolide A

Hectochlorin



Guineamide B

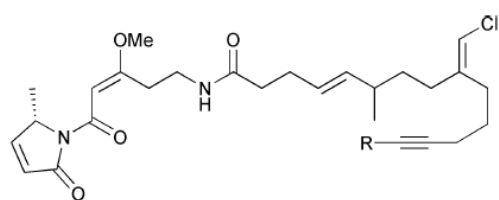
Guineamide C

Homodolastatin 16

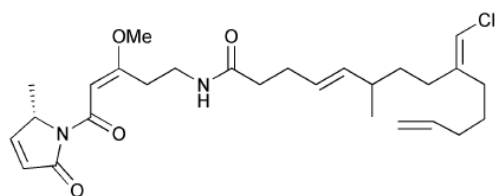
8.3 $\mu\text{g/mL}$, respectively [7]. Three novel and highly functionalized lipopeptides (jamaicamides A-C) were isolated from a dark green strain of *Lyngbya majuscula* found in low abundance in Hector's Bay, Jamaica. Jamaicamides exhibited cytotoxicity on both the H-460 human lung and Neuro-2a mouse neuro blastoma cell lines with LC_{50} values of about 15 μM on both cell lines [8].

A new cyclicpeptide (lyngbyastatin 3) was isolated from *Lyngbya majuscula* collected in Guam. Its structure contains two unusual amino acid residues. The pure lyngbyastatin 3 showed IC_{50} values of 32 and 400 nM against KB and LoVo cell lines, respectively, but when tested *in vivo* against colon adenocarcinoma #38 or mammary adenocarcinoma #16/C in mice, it was poorly tolerated and exhibited only marginal or nil antitumor activity [45]. Five new lyngbyabellin analogs along with a known compound, dolabellin, had been isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Papua New Guinea. All five lyngbyabellins showed cytotoxicity on NCI-H460 human lung tumor and neuro-2a mouse neuroblastoma cell lines with LC_{50} values between 0.2 and 4.8 μM [13].

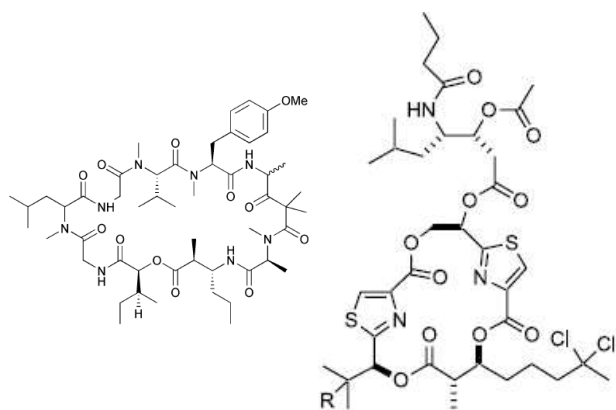
Bioassay-guided investigation of the extract from a mixed assemblage of *L. majuscula* and a *Schizothrix* sp. led to the discovery of somocystinamide A. This compound exhibited significant cytotoxicity against mouse neuro-2a neuroblastoma cells with $\text{IC}_{50} = 1.4$ $\mu\text{g/mL}$ [36]. Four new depsipeptides (wewakpeptin A-D) had been isolated and characterized from the marine cyanobacterium *Lyngbya semiplena* collected



Jamaicamide A R = Br
Jamaicamide B R = H

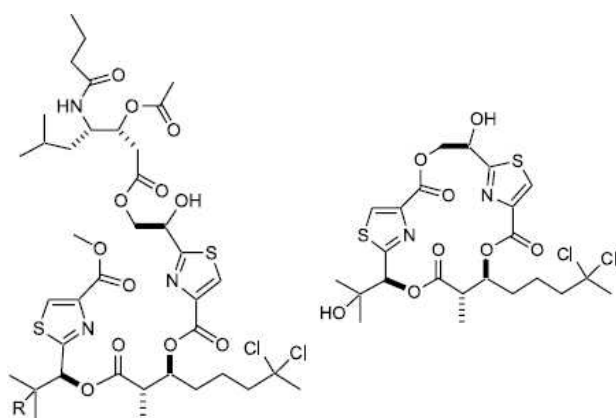


Jamaicamide C



Lyngbyastatin 3

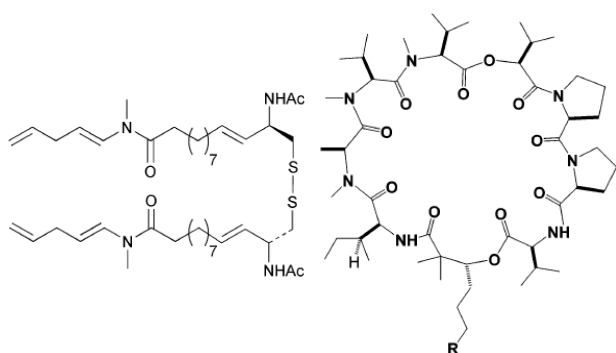
Lyngbyabellin E R = OH
Lyngbyabellin H R = H




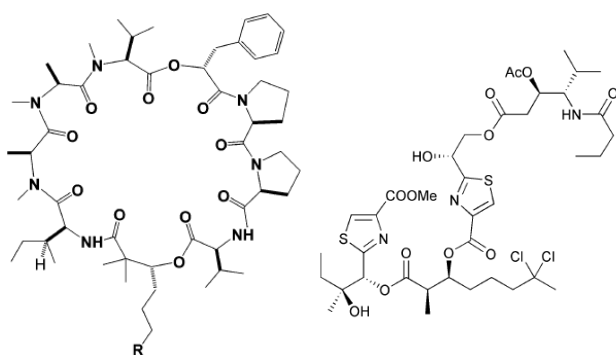



Lyngbyabellin F R = OH Lyngbyabellin G R = OH
Lyngbyabellin I R = H

from shallow water (1-3 m) in Papua New Guinea. Intriguingly, wewakpeptins A and B were approximately 10-fold more toxic than C and D to these cell lines with an LC_{50} of approximately 0.4 μM to both the NCI-H460 human lung tumor and the neuro-2a mouse neuroblastoma cell lines [14].

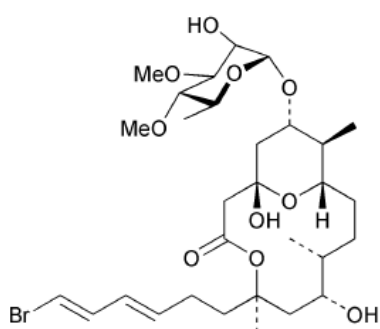
The cyanobacterium *Lyngbya* sp. from Guam had yielded a new member of the lyngbyabellin families, lyngbyabellin D. Lyngbyabellin D displayed IC_{50} values of 0.1 μM against the KB cell line [44]. Another new compound isolated from the marine cyanobacterium *Lyngbya* sp. collected from Palau was lyngbyalioside B. This compound exhibited slight cytotoxicity against KB cells with IC_{50} values of 4.3 μM and considerably smaller effect on LoVo cells with $\text{IC}_{50} \approx 15$ μM [24]. The extract of *Lyngbya* sp. from Palau had produced Palau'amide which had IC_{50} values of 13 nM against KB cells [47].



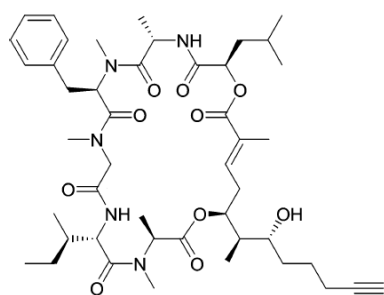
Somocystinamide A

Wewakpeptin C R = 
Wewakpeptin D R = Wewakpeptin A R = 
Wewakpeptin B R = 

Lyngbyabellin D



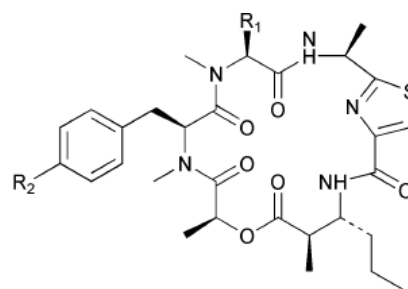
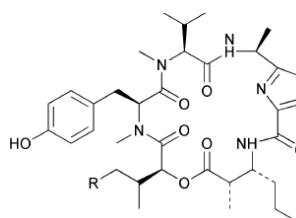
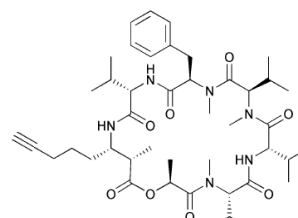
Lyngbyaloside B



Palau'amide

Five new β -amino acid-containing cyclic depsipeptides were isolated from collections of apratoxin-producing cyanobacteria *Lyngbya* sp. from Palau and their structures were determined. Ulongamides A-E displayed weak *in vitro* cytotoxicity with IC_{50} values of ca. 1 μ M and ca. 5 μ M against KB and LoVo cells, respectively [25]. A cyclic peptide (ulongapeptin) was isolated from a Palauan marine cyanobacterium *Lyngbya* sp. Its structure was determined and it showed cytotoxic activity against KB cells at IC_{50} values of 0.63 μ M [48].

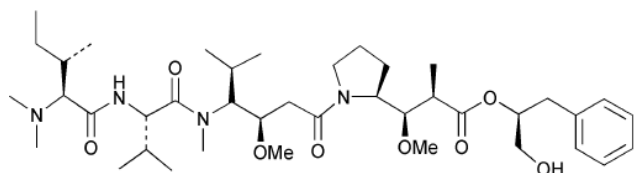
Two field collections of marine cyanobacteria samples of *Symploca* cf. sp. and *Geitlerinema* sp. from the Fiji Islands and Nosy Mitso-anjarahana Island, Madagascar, respectively, had led to the discovery of ankaraholide A which inhibited proliferation of NCI-H460, Neuro-2a, and MDAMB-435 cell lines (IC_{50} , 8.9-119 nM). Furthermore, in A-10 cells, this compound caused complete loss of the filamentous (F)-actin at 30 and 60 nM, coincident with dramatic changes in cell morphology [1]. A *Symploca hydroides* collected from site off the south shore of Oahu, yielded a highly cytotoxic peptide ester, malevamide D. its structure was determined and Malevamide D showed high cytotoxic activity against P-388, A-549, HT-29,

Ulongamide A R₁ = CH(CH₃)₂, R₂ = H
Ulongamide B R₁ = CH(CH₃)₂, R₂ = OH
Ulongamide C R₁ = CH₂C₆H₅, R₂ = OHUlongamide D R = H
Ulongamide E R = Me

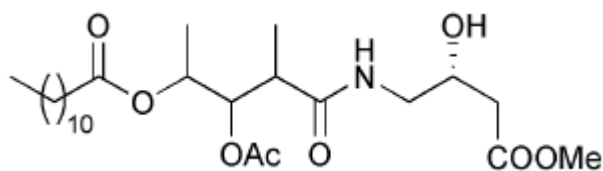
Ulongapeptin

and MEL-28 cell lines (IC_{50} values of 0.3-0.7 nM) [16]. Two new cytotoxins (micromide and guamamide) were isolated from a species of marine cyanobacterium *Symploca* sp. collected in Guam [49], and showed cytotoxicities against KB cell lines. A new dolastatin 10 analogue (symplostatin 3) was isolated from a *Symploca* sp. Collected from Hawaii. Symplostatin 3 differed from dolastatin 10 only in the C-terminal unit; the dolaphenine unit is substituted by a 3-phenyllactic acid residue. Symplostatin 3 possessed *in vitro* cytotoxicity toward human tumor cell lines (IC_{50} , 3.9-10.3 nM) and disrupts microtubules, but at a higher concentration than that of dolastatin 10 [26].

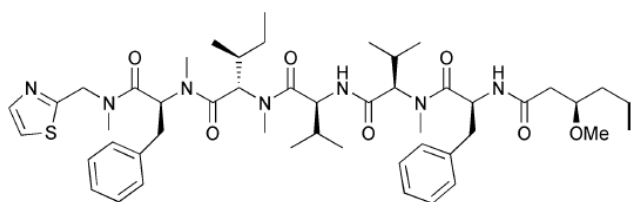
Other samples of the marine cyanobacterium *Symploca* sp. collected in Palau were the source of the depsipeptides tasipeptins A and B [46], and two cytotoxic peptides, tasiamide A [43] and tasiamide B [46].



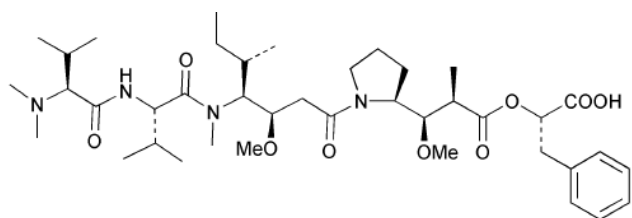
Malevamide D



Guamamide



Micromide

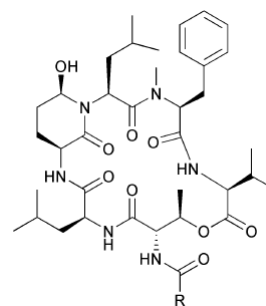




Symplostatin 3

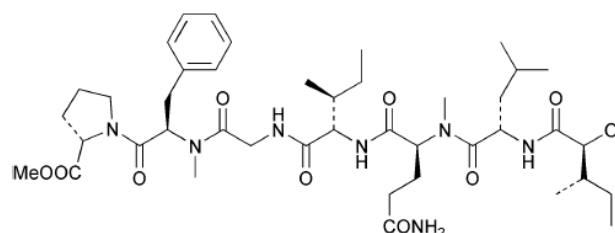
Their structures were determined. Both tasipeptins exhibited moderate cytotoxicity towards KB cells *in vitro* with IC_{50} values of 0.93 and 0.82 μ M, respectively. Tasiamide A was cytotoxic against KB and LoVo cells with IC_{50} values of 0.48 and 3.47 μ g/mL, respectively, while tasiamide B only displayed an IC_{50} value of 0.8 μ M against KB cells.

Bioactive compounds derived from *Streptomyces*

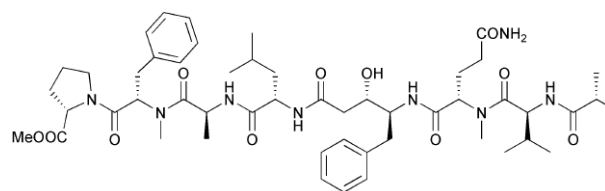
Two new caprolactones, (*R*)-10-methyl-6-undecanolide and (*6R,10S*)-10-methyl-6-dodecanolide, were identified in the lipid extract of a marine streptomycete from mangrove sediment (isolate B6007). Their structures were determined. Both compounds caused concentration-dependent inhibition of the cell growth of HM02, HepG2, and MCF7 [39].



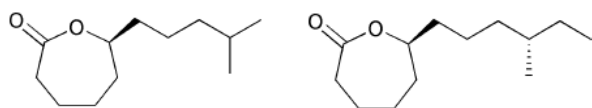
Tasipeptin A R = 
 Tasipeptin A R = 



Tasiamide A



Tasiamide A

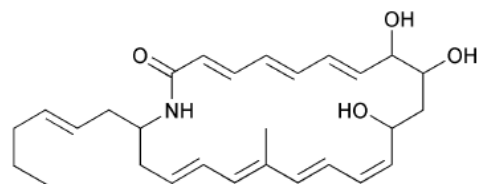


10-methyl-6-undecanolide 10-methyl-6-dodecanolide

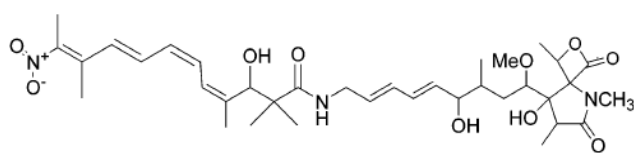
A strain of *Streptomyces aureovorticillatus* (NPS001583) isolated from a marine sediment was found to produce a novel macrocyclic lactam, aureovorticillactam. Aureovorticillactam showed cytotoxicity against various tumor cell lines such as HT-29, B16-F10, and Jurkat cell lines with the EC_{50} values of 2.2-3.6 μ M [35].

A strain of *Streptomyces nodosus* (NPS007994) isolated from marine sediment collected in Scripps Canyon, La Jolla, California produced a new peptide compound, lajollamycin. Based on the structural studies, lajollamycin was the first reported example of an acyclic nitro-tetraene conjugated olefin. Lajollamycin inhibited the growth of B16-F10 tumor cells *in vitro* with an EC_{50} of 9.6 μ M [30].

Two new cytotoxic 3,6-disubstituted indoles (compounds F and G) were isolated from *Streptomyces* sp. (BL-49-58-005) separated from a Mexican marine invertebrate and their structures were determined. Their structures were established by analysis of NMR and mass spectral data. Both two compounds exhibited moderate activity against a panel of 14 different tumor cell lines [22]. The culture of marine *Streptomyces* sp. yielded two novel antitumor antibiotics designated as chinikomycins A and B. These compounds were chlorine-containing aromatized manumycin derivatives of



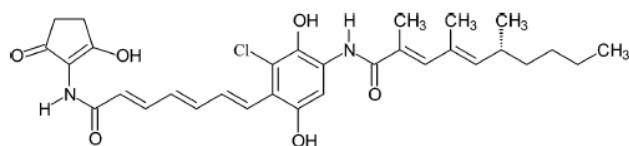
Aureovorticillactam



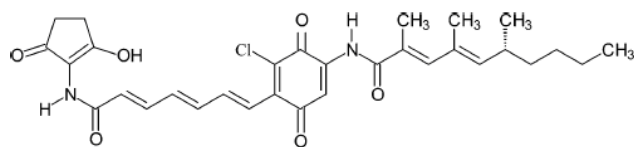
Lajollamycin

the type 64-pABA-2 with an unusual *para* orientation of the side chains. Chinikomycins A and B exhibited antitumor activity against different human cancer cell lines with IC_{50} values in a range 2.41-4.15 μ g/mL [21]. A *Streptomyces* sp. (NPS008187) isolated from a marine sediment collected in Alaska produced three new pyrrolo sesquiterpenes, glyciapyrroles A, B and C. However, only glyciapyrrole A showed antitumor activity. The cytotoxicity of glyciapyrrole A was determined against a pair of tumor cell lines at concentrations up to 1 mM [27].

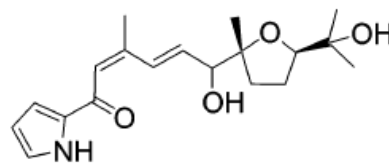
A novel macrolid (halichoblelide) had been isolated from a strain of *Streptomyces hygroscopicus* originally separated from the marine fish *Halichoeres bleekeri*. Halichoblelide showed potent cytotoxicity against P388 cell line and the 39 human cancer cell lines [52]. The anthracycline (komodoquinone A) was derived from the



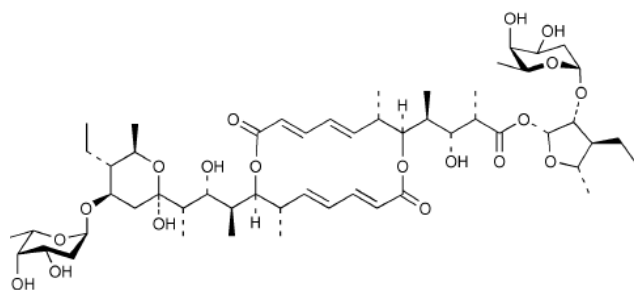
Chinikomycin A



Chinikomycin B



Glyciapyrrole

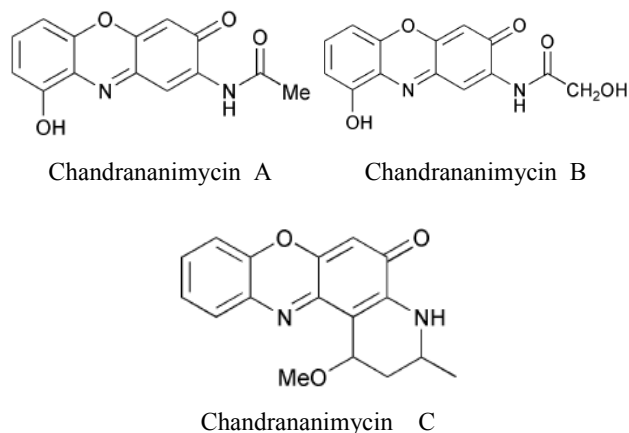
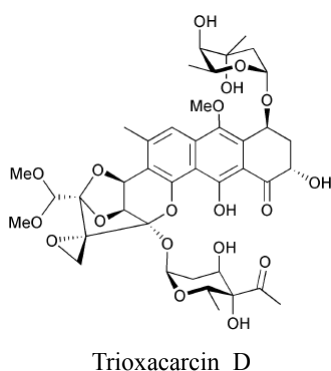
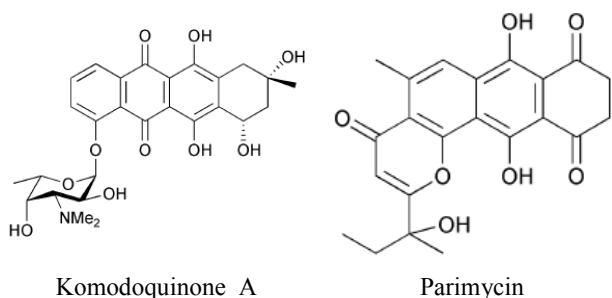


Halichoblelide

solid-state fermentation of the marine *Streptomyces* sp. KS3 isolated from marine sediment off Komodo Island, Indonesia. Komodoquinone A was a unique anthracycline, in which a new amino sugar was connected to the D-ring of the anthracyclinone skeleton, and displayed dose-dependent neurotoxic activity against Neuro 2A cell lines [18]. Parimycin, a new 1,4-anthraquinone, was isolated from a *Streptomyces* sediment sample from Laguna de Terminos, Gulf of Mexico. Parimycin had moderate activity against a number of human tumour cell lines [32]. The ethyl acetate extract from the *Streptomyces* sp. isolate B8652 yielded the trioxacarcin D. Trioxacarcin D exhibited potent antitumor cell lines with IC_{50} values of 0.008-1.1 $\mu\text{g}/\text{mL}$ [34].

Bioactive compounds derived from *Actinomyces*

Three novel compounds (chandrananimycins A, B and C) were isolated from the culture broth of a marine *Actinomadura* sp. isolate (M045) derived from sediment from Jiaozhou Bay, China. Chandrananimycins A–C were active against human tumour cell lines CCL HT29, MEXF 514L, LXFA 526L, LXFL 529L, CNCL SF268, LCL H460, MACL MCF-7, PRCL PC3M, RXF 631L with IC_{50} values of 1.4 $\mu\text{g}/\text{mL}$ [33].

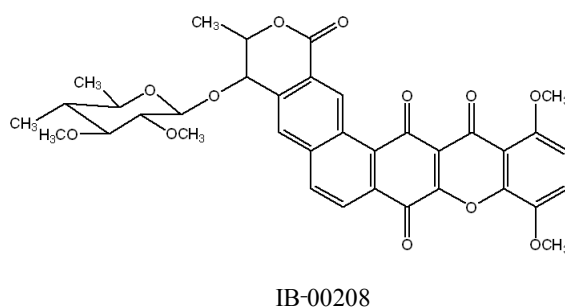


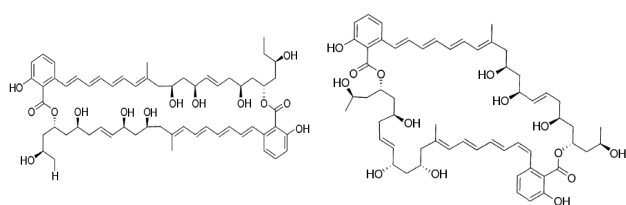
A new compound (IB-00208) was isolated from the fermentation broth of *Actinomadura* sp.. The compound showed cytotoxic activity on both human and murine tumor cell lines (IC_{50} of 1 nM) and bactericidal activity against gram-positive bacteria [29,38]

Four antitumor-antibiotics of a new structure class, the marinomyces A-D, were isolated from the saline culture of a new group of marine actinomycetes *Marinispora* sp. strain CNQ-140 isolated from a sediment sample collected at a depth of 56 m offshore of La Jolla, CA. In room light, marinomyces A is slowly isomerized to its geometrical isomers marinomyces B and C. Marinomyces A-D inhibited cancer cell proliferation with average LC_{50} values of 0.2 - 2.7 μM against the NCI's 60 cancer cell line panel [20].

Resistoflavine had been derived from a new isolated actinomycete from marine sediment samples of Bay of Bengal, India, designated as *S. chibaensis* AUBN1/7. It showed a potent cytotoxic activity against cell lines viz. HMO2 and HepG2 *in vitro* (IC_{50} , 7-10 nM) [12].

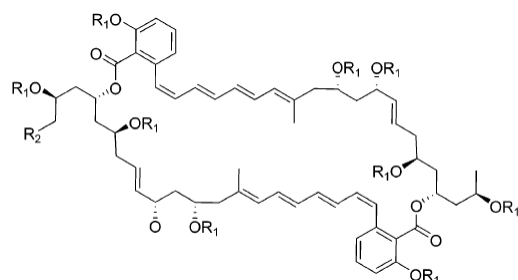
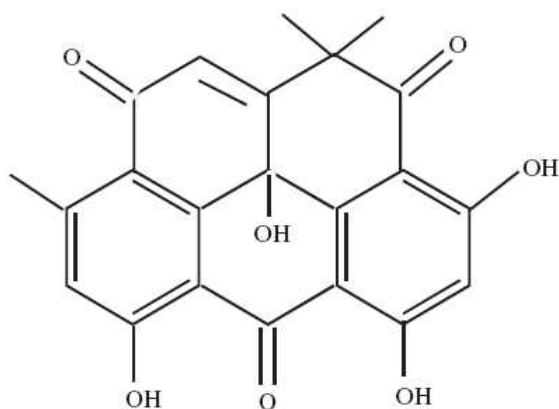
By extensive study of the secondary metabolites produced by the obligate marine actinomycete *Salinispora tropica* collected from sediment (strain CNB-392) collected in Bahamas had led to isolate salinosporamide





Marinomycin A

Marinomycin C

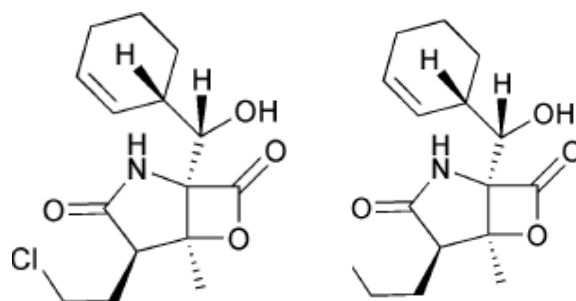
Marinomycin B $R_1 = H, R_2 = H$ Marinomycin D $R_1 = H, R_2 = H$ 

Resistoflavine

A [10] and its deschloro-analogue, salinosporamide B [50]. Salinosporamide A displayed potent and selective cytotoxicity against cell lines in the NCI panel, while salinosporamide B showed lower cytotoxicity to HCT-116 *in vitro*. Specially, salinosporamide A also exhibited highly potent inhibition of the proteasomal chymotrypsin-like proteolytic activity of purified 20S proteasome.

Miscellaneous bacteria

Mixirins A, B and C, belonging to iturin class, had been isolated from marine bacterium *Bacillus* sp. obtained from sea mud near the Arctic pole. These three compounds had the cytotoxic activities inhibited the



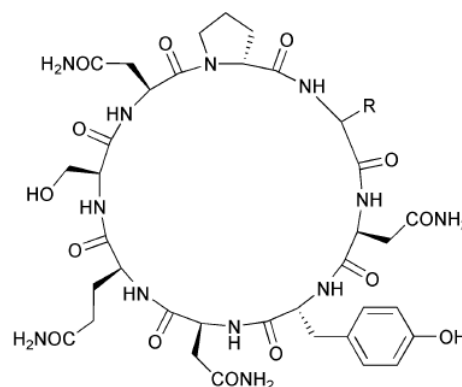
Salinosporamide A

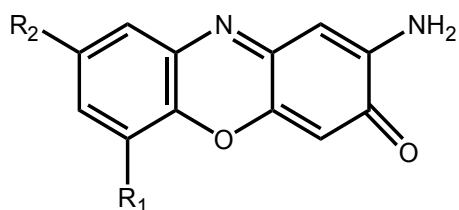
Salinosporamide B

growth of human colon tumor cells (HCT-116) with IC_{50} of 0.68, 1.6, 1.3 $\mu\text{g}/\text{mL}$ [52].

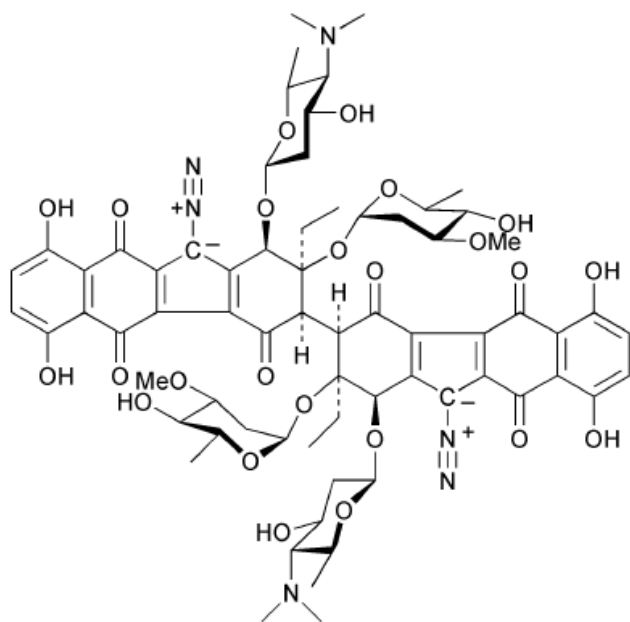
The red-orange color of the culture filtrate extract of the marine derived *Halomonas* sp. strain GWS-BW-H8hM, was the result of the production three new aminophenol xazinones 2-amino-, 2-amino-8-benzoyl-, and 2-amino-8-(4-hydroxy benzoyl)-6-hydroxy phenoxazin-3-one (compounds A-C). The compounds were determined to have cytotoxic activity against HMO2, HepG2, and MCF7 with IC_{50} values of 1.4-3.2 $\mu\text{g}/\text{mL}$; a mode of action other than DNA intercalation was discussed [4].

A dimeric diazobenzofluorene glycoside, designated as lomaiviticin A was produced by fermentation of strain *M. lomaivitiensis* in a seawater medium in the presence of HP20 resin. In addition to DNA-damaging activity, lomaiviticin A possessed a unique cytotoxicity against a number of cancer cell lines, with IC_{50} values of 0.01-98 nM [15].

Mixirin A $R =$ Mixirin B $R =$ Mixirin C $R =$



Compound A	R ₁ = OH	R ₂ = H
Compound B	R ₁ = OH	R ₂ = Benzoyl
Compound C	R ₁ = OH	R ₂ = <i>p</i> -OH-Benzoyl



Lomaiviticin A

Concluding remarks

Several bioactive compounds isolated from marine bacteria have been proved to be able to provide potential sources for development of anti-cancer drug so far. Herein, we reviewed novel cytotoxic compounds isolated from marine bacteria mainly from 2001 to 2006. From this survey, in particular, marine bacteria including cyanobacteria, Streptomyces and Actinomyces were demonstrated to be able to potentially apply to the development of anti-cancer drug. However, the majority of marine bioactive compounds discussed in this review has not been clarified in view of their clinical pharmacological aspects so far. Therefore, in addition to isolation of new cytotoxic compounds, it is required to

elucidate pharmacological activities of cytotoxic compounds against cancer cell lines to develop these compounds as novel anti-cancer drugs.

Acknowledgement

The authors acknowledge Marine Bioprocess Research Center of Marine Bio 21 Project, funded by the Ministry of Maritime Affairs and Fisheries, Republic of Korea.

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