CHAPTER II

REVIEW OF LITERATURE

The word "antibiotics" was used to describe a type of association in which one living creature was destroying another in order to sustain its own life. In some case antibiotic is defined as a chemical substance, produced by microorganisms, which has the capacity to inhibit the growth and even to destroy bacteria and other microorganisms (Waksman, 1947). Benedict and Langlyke (1947) modified this definition; antibiotics are substances which act upon certain organisms at least in very dilute solutions. Abraham and Newton described the word "Antibiotics" as natural compounds derived from organisms which themselves or chemical modifications are able, at low concentration, to inhibit or kill other microorganisms and abnormal cells in higher animals.

Several reports and books were written about biological substances from the sea which were used as drugs or biotoxins. Since Babylonian and Assyria age, the Papyrus records have reported toxicity of several marine organisms (Punnipa Chumsri, 2534). Burkholder and coworkers purified the first antibiotic from a marine bacterium, and then in the same year, Lovell reported the chemical structure of this substance as a highly brominated pyrrole (Jensen and Fenical, 1994).

In marine habitats, the organisms in sewage were killed 80 percent within half of hour (Rosenfeld and Zobell, 1947) however seawater typically contains 10^4 to 10^8 bacteria/ml. But it was less than three orders of magnitude can be cultured in a nutrient rich agar (Jensen and Fenical, 1994). Only few percents of all bacterial strains could produce antibiotics in an appropriate media under laboratory conditions (Okami *et al.*, 1976). Therefore there have been few reports concerning in natural products from marine microorganisms, comparing with natural products from other marine organisms.

1. Natural products from marine micoorganisms

Microbes are being recognized for the nearly unlimited potential of culturable marine actinomycetes, bacteria, and cyanobacterium as renewable source of pharmaceuticals (Ireland *et al.*, 1993).

Table 1. Natural products from marine microorganisms.

Compound	Strain	Source	Activity	Reference
Marinactin	*Flavobacterium uliginosum*	seaweed	antitumor	Umezawa *et al.*, 1983
Caprolactin A and B [1]	Unidentified	deep sea sediment	antiviral	Davidson and Schumacher, 1993
Brominated diphenenyl ethers [2]	*Vibrio* sp.	*Dysidea* sp. (sponge)	-	Voinov *et al.*, 1991
Pyrrole rich-bromide [3]	*Pseudomonas bromoutilis*	inter-tidal pool seawater	antibiotic	Wratten *et al.*, 1977
Pyrrole (rich bromide)	*Pseudomonas bromoutilis*	*Thalassia*	antibiotic	Burkholder, Pfister, and Leitz, 1966
Octalactin A [4] and B [5]	*Streptomyces* sp.	*Pacifigorgia* sp. (gorgonian octocoral)	cytotoxic	Tapiolas, Roman, and Fenical, 1991
Benzothiazoles (4 derivatives) [6]	*Micrococcus* sp.	*Tedania ignis* (sponge)	(Industrial starting synthesis material)	Stierle, and Cardellina, 1991
Pseudomic acid (Mupirocin) [7]	*Pseudomonas fluorescens*	-	antibiotic	Sutherland *et al.*, 1985

Table 1. (continued)

Compound	Strain	Source	Activity	Reference
Tyrosol [8]	gram negative marine bacterium	embryo of *Homarus americanus*	antifungus (*Lagenidium callinectes*)	Gil-Turnes, and Fenical, 1992
Istamycins A [9] and B [10]	*Steptomyces tenjimariensis*	-	antibiotic	Hotta *et al*., 1980
Aplasmomycin [11]	*Steptomyces* sp.	shallow sea mud	antibiotic	Okami *et al*., 1976
Aplasmomycin B [12]and C [13]	*Steptomyces griseus*	-	antibiotic	Sato *et al*., 1978
Peri-hydroxy quinone	*Chainia purpurogena*	shallow sea mud	antibiotic	Okazaki, Kitahara, and Okami, 1975
Halobactin [14] and methylhalobactin [15]	*Bacillus*	deep sea sediment	cytotoxic	Trischman, Jensen, and Fenical, 1994
Andrimid [16] and Moiramides A-C [17-19]	*Pseudomonas fluorescens*	unidentified Tunicate	antibiotic	Needham *et al*., 1994
Malynamide H [20]	*Lyngbya mauscula*	-	ichthyotoxic activity	Orjala, Nagle, and Gerwick, 1995
Pseudomonine [21]	*Pseudomonas fluorescens*	*Lates noloticus (spoiled nile perch)*	siderophoric activity	Anthoni, Christophersen, and Nielsen, 1995

Table 1. (continued)

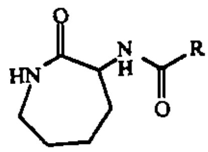
Compound	Strain	Source	Activity	Reference
Indoles and Dithiolo pyrrolones [22]	*Xenorhabdus bovienii*	nematodes	antibiotic	Li, Chen, and Webster, 1995
Maduralides [23]	Unidentified *Actinomycetes*	soil borne	antibiotic	Pathirana *et al*., 1991
Macrolactins A-F [24-29]	unidentified	deep sea sedimeant	*Herpes simplex*, anti bacterial	Gustafson, Roman, and Fenical, 1989
Lyngbyacarbonate [30]	*Lyngbya majuscula*	shallow water	brine shimp	Todd, and Gerwick, 1995
Curacin B [31] and C [32]	*Lyngbya majuscula*	-	brine shimp, antimitotic	Yoo and Gerwick, 1995
Anguibactin [33] and Anhydro-anguibactin [34]	*Vibrio anguillarum*	-	siderophore	Jalal *et al*., 1989.
Okadaxanthin [35]	*Pseudomonas* sp.	*Halichondria okadai* (sponge)	-	Miki *et al*., 1994
B-1015 [36]	*Alcaligenes faecalis*	small spiral sea shell	antimicrobial	Isono *et al*., 1993
Vibrindole A (Steptindole) [37]	*Vibrio parahaemolyticus*	*Ostracion cubicus* (box fish)	antimicrobial	Bell, and Carmeli, 1994.

Table 1. (continued)

Compound	Strain	Source	Activity	Reference
Marinone [38] and Debromomarinone [39]	*Actinomycetes*	-	antibiotic	Patthirana, Jensen, Fenical, 1992
Butanolide [40]	*Actinomycetes*	sediments	signal compounds	Pathirana *et al.*, 1991
Maduramicin [41]	*Actinomadura yumaensis*	-	antibiotic	Rajan *et al.*, 1984
Neosurugatoxin [42] and prosurugatoxin [43]	gram positive marine bacteria	digestive gland of ivory shell, *Babylonia japonica*	causative toxin food poisoning	Kosuge *et al.*, 1985
Pyrrole rich-bromide [44]	unidentified bacteria	-	antibiotic	Lovell, 1966
3-amino-3 deoxy D-glucose [45]	*Bacillus* sp.	deep sea sediment	antibacterial	Fusetani *et al.*, 1987
Oncorhyneolide	unidentified bacteria	sea water	antibacterial	Needham, Andersen,and Kelly, 1991
Xenorhabdins [46]	*Xenorhabdus* sp.	intestine of nematode	antibiotic	McInerney, and Gregson, 1991
Magneisidin [47]	*Pseudomonas magnesiorubra*	-	antibiotic	Kohl *et al.*, 1974

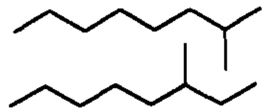
Table 1. (Continued)

Compound	Strain	Source	Activity	Reference
Tetrodotoxin (TTX)	22 strains of marine bacteria	deep sea sediment	neurotoxin	Do, Kogure, and Simidu, 1990
Tetrodotoxin (TTX)	*Pseudomonas* sp.	*Fugu poecilonotus* (pufferfish)	neurotoxin	Yotsu *et al.*, 1987
Tetrodotoxin (TTX) and Anhydro-tetrodrotoxin	*Vibrio* sp.	intestines of *Atergatis floridus* (Xanthid crab)	neurotoxin	Noguchi *et al.*, 1986

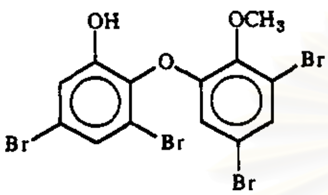


R= Caprolactin A

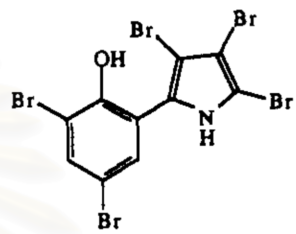
R= Caprolactin B



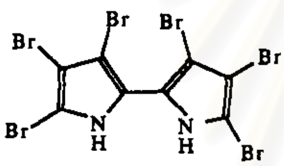
[1] Caprolactins A and B



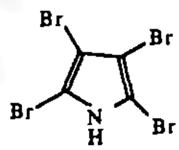
[2] Brominated diphenenyl ethers



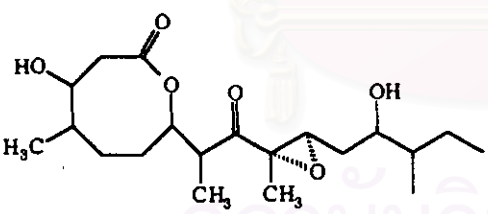
[3.1]



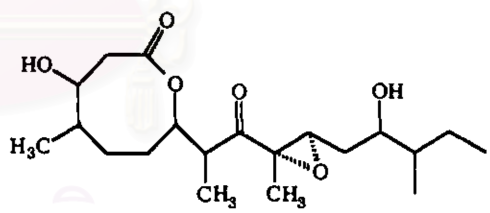
[3.2]



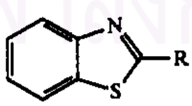
[3.3]



[4] Octalactin A



[5] Octalactin B

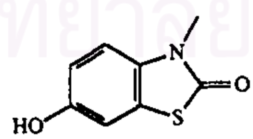


(1) R= SH

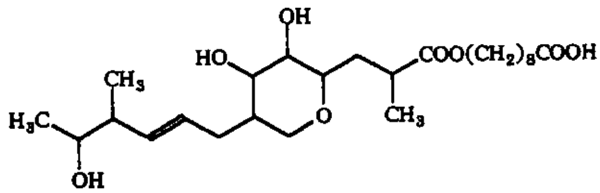
(2) R= CH_3

(3) R= OH

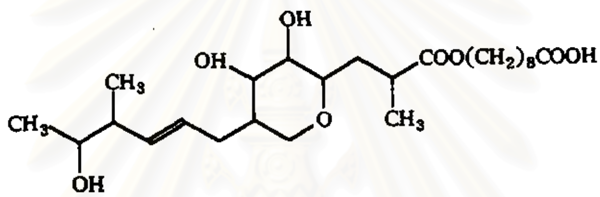
[6] Benzothiazoles



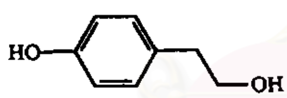
(4)

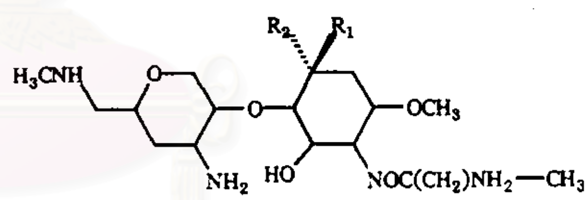


metabolite [7]	R_1	R_2
Pseudomic acid A :	$(CH_2)_8COOH$	H
Pseudomic acid B :	$(CH_2)_8COOH$	OH
Pseudomic acid D :	$(CH2)_4CH{=}CH(CH2)_2COOH$	H



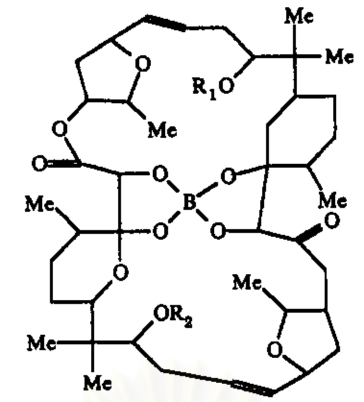
Pseudomic acid C





[8] Tyrosol

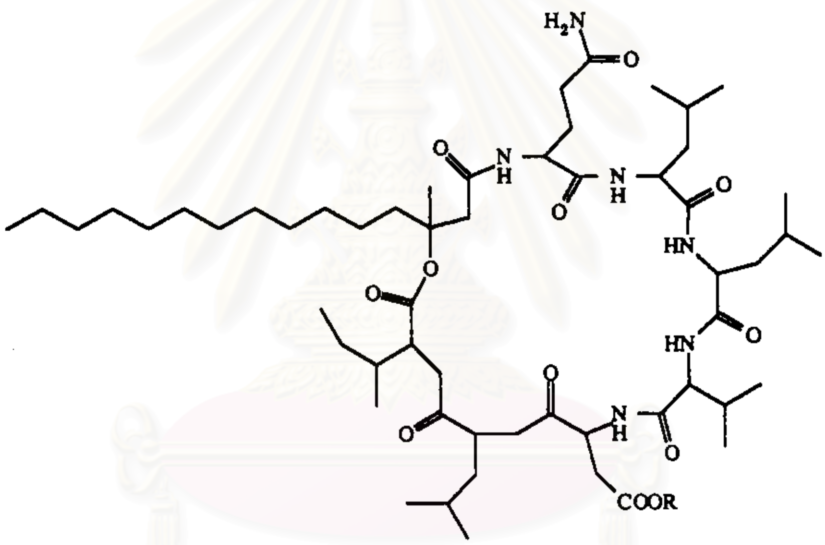
	R_1	R_2
[9] Istamycin A :	NH_2	H
[10] Istamycin B :	H	NH_2



[11] Aplasmomycin R_1, R_2 = H

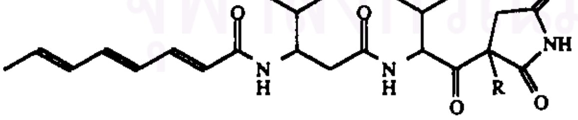
[12] Aplasmomycin B R_1= Ac, R_2 = H

[13] Aplasmomycin C R_1, R_2 = Ac



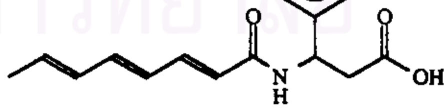
[14] Halobactin R = H

[15] Methylhalobactin R = CH_3

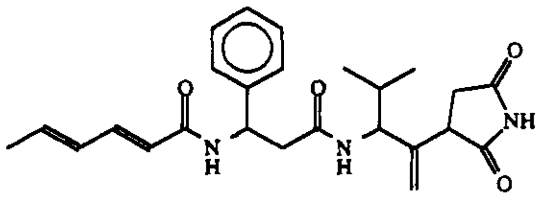


[16] Andrimid R = H

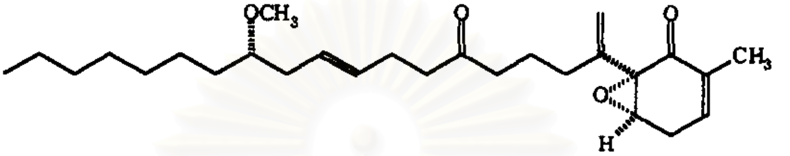
[19] Moiramides C, R = OH



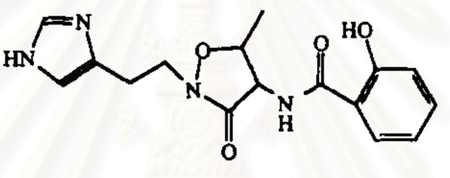
[17] Moiramides A



[18] Moiramides B



[20] Malynamide H

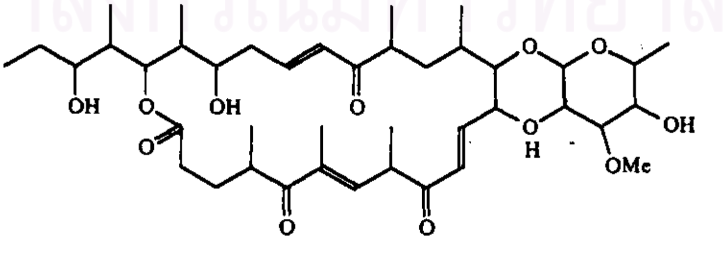


[21] Pseudomonine

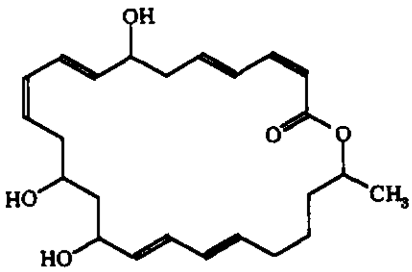
(1) R = Ac (2) R =Ac

(3) R = H (4) R = H

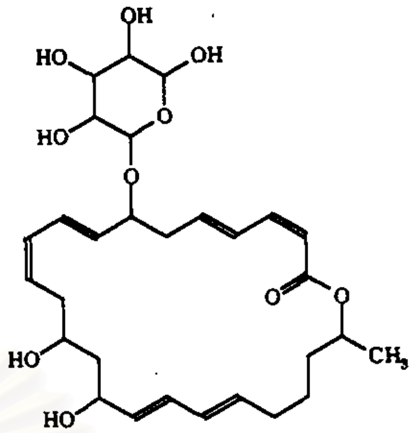
[22] Indoles and Dithiolopyrrolones



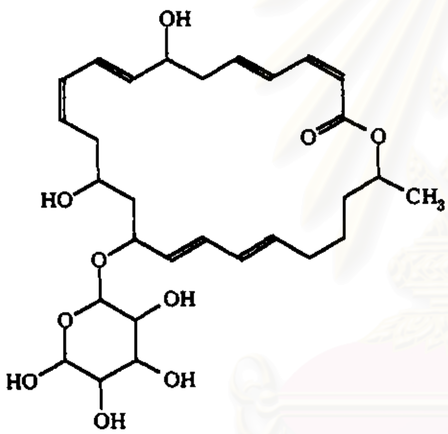
[23] Maduralide



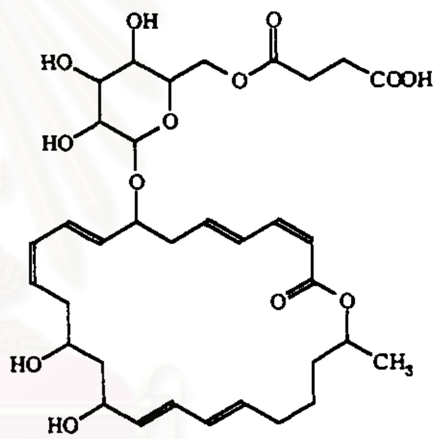
[24] Macrolactin A



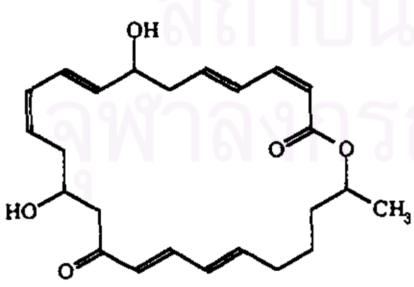
[25] Macrolactin B



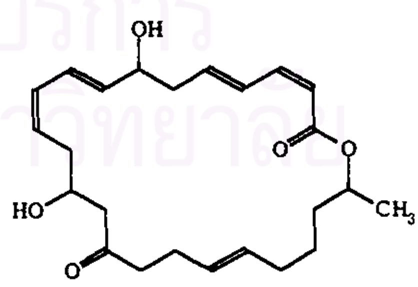
[26] Macrolactin C



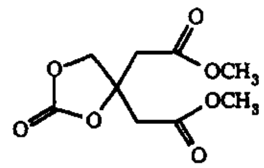
[27] Macrolactin D



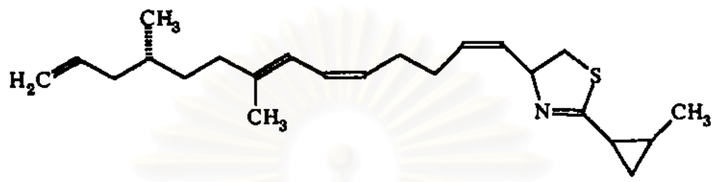
[28] Macrolactin E



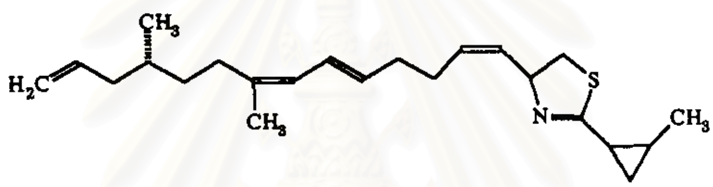
[29] Macrolactin F



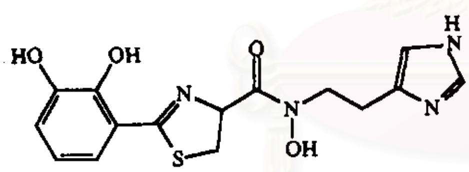
[30] Lyngbyacarbonate



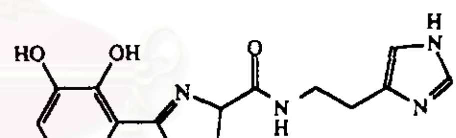
[31] Curasins B



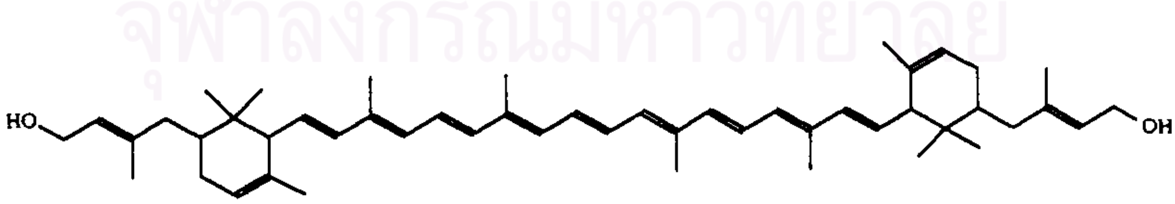
[32] Curasins C



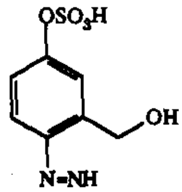
[33] Anguibactin



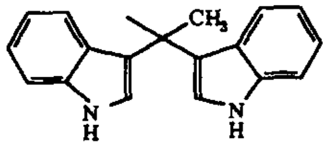
[34] Anhydroanguibactin



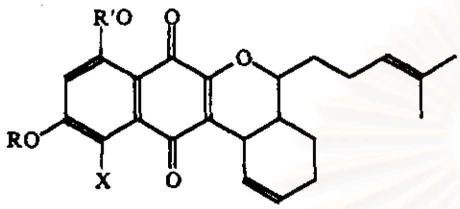
[35] Okadaxanthin



[36] B-1015

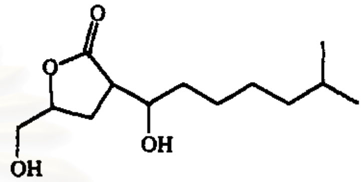


[37] Vibrindole A

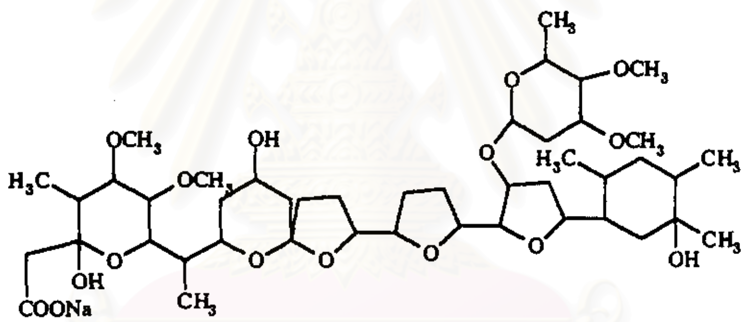


[38] Marinone, R = R' = H, X = Br

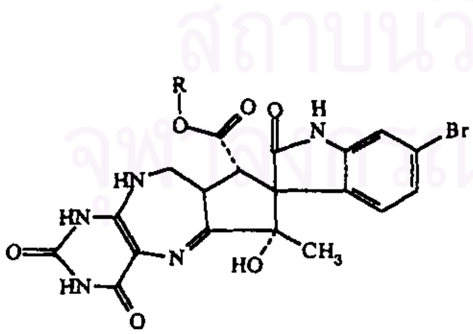
[39] Debromomarinone R = R' = X = H

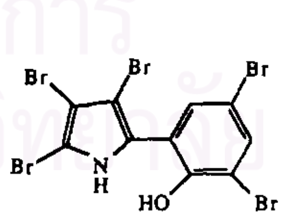


[40] Butanolide



[41] Maduramicin





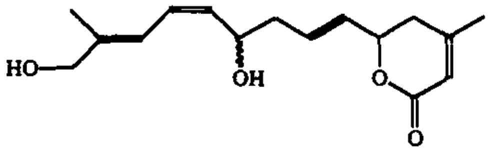
[42] Neosurugatoxin

R = 6'-(myoinositol——— xylopyranose)

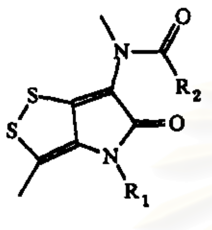
[43] Prosurugatoxin

R = 6'-myoinositol

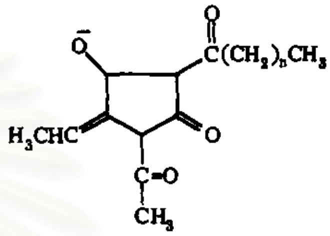
[44] Pyrrole rich-bromide



[45] 3-amino-3 deoxy D-glucose



[46] Xenorhabdins



a. $M^+ = Mg^{++}/2$

b. $M^+ = H$

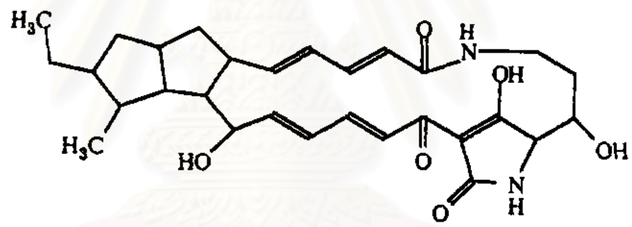
[47] Magneisidin

2. Natural products and characterization of marine bacteria, *Alteromonas* sp.

2.1. Natural products from marine bacteria, *Alteromonas* sp.

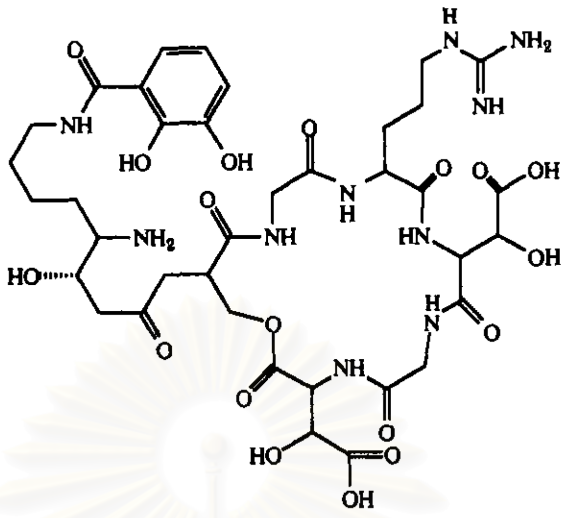
Alteromonas is a potential marine bacterium for natural product resources. Some of natural product substances from this marine bacterium are described below:

A new cytotoxic alkaloid, alteramide A [48] was isolated from a marine bacterium, *Alteromonas* sp. symbiotically associated with the sponge *Halichondria okadai* which collected off Nakai, kanagawa, Japan. The alteramide A showed cytotoxic activity against murine leukemia P338 cells, lymphoma L1210 cells, the human epidermoid carcinoma KB cell (*in vitro*) with the IC_{50} values of 0.1, 1.7 and 5.0 μg/ml, respectively (Shigemori *et al.*, 1992).

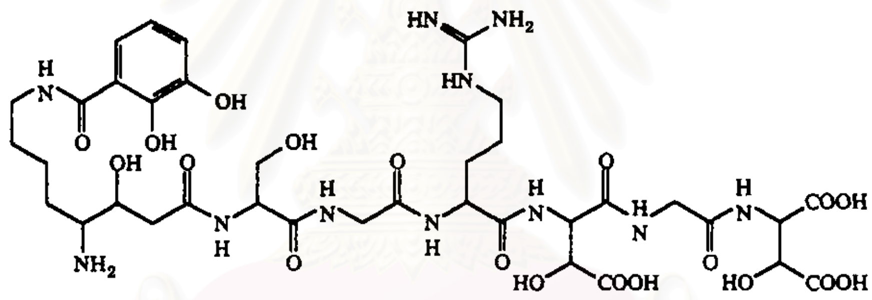


[48] Alteramide A

A siderophore, alterobactin A [49] and B [50] were isolated from *Alteromonas luteoviolacea* which was collected from oligothophic and coastal waters (Reid, 1993).

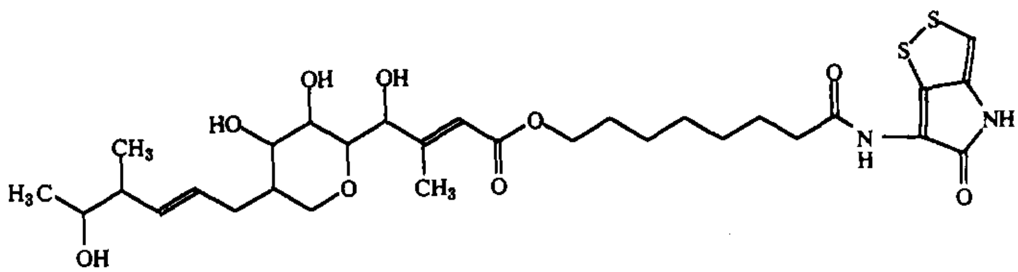


[49] Alterobactin A



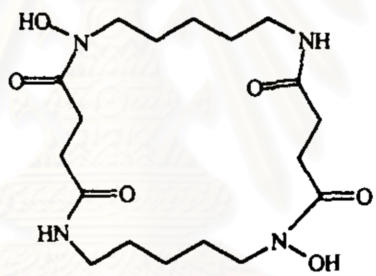
[50] Alterobactin B

An antimicrobial thiomarinol [51] was produced by a marine bacterium, *Alteromonas rava* (NOV SANK 73390) which was isolated from seawater. The thiomarinol was a hybrid of two types of antibiotics. One was pseudomic acid (mupirocin) which was produced by *Pseudomonas flurescens*, the other was pyrothine antibiotics isolated from *Xenorhabdus* sp. The thiomarinol exhibited *in vitro* antimicrobial activity against both gram positive and gram negative bacteria (Shiozawa *et al.*, 1993).



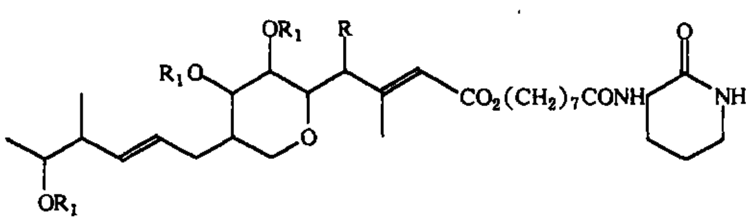
[51] Thiomarinol

A new siderophore, bisucaberin [52] was produced from *Alteromonas haloplanktis* strain (SB-1123) which was isolated from deep sea mud. The bisucaberin showed tumoricidal activity *in vitro* (Kameyama *et al.*, 1987).



[52] Bisucaberin

The pseudomic [53] acid derivative was produced by marine bacterial *Alteromonas* sp., which was isolated from the sponge, *Darwinella rosacea*, collected from Burmuda (Stierle and Stierle, 1992).



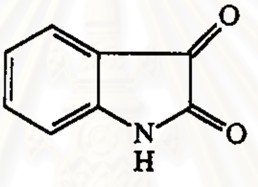
1. R= β-OH, R_1= H

2. R= H, R_1= H

[53] Pseudomic acid

Tetrodotoxin, known as a strongest neurotoxin, has been isolated from various species of marine organisms. *Alteromonas* sp. is one of marine microorganisms responsible for the tetrodotoxin production (Simidu *et al.*, 1990).

Isatin was found to contain antifungal activity. The isatin produced by a marine bacterium *Alteromonas* sp. could protect the embryos of shrimp *Palamon macrodactylus* from the infection of pathogenic fungus *Lagenidium callinectes*. The isatin producing bacteria were isolated from surface of the shrimp's embryos (Gil-Turnes, Hay, and Fenical, 1989).



[54] Isatin

Isatin [54] has been known as an indigo dye for some time. The first report of isatin was found in 1944 by W.C. Sumpter. The large number of papers have appeared regarding the preparation, properties and reactions of isatin (Popp, 1975) and a lot of papers also reported on the synthetic intermediates of isatin in preparation of pharmaceutical agents and dyes (Gassman, Cue, and Luh, 1977).

2.2. Characterization of marine bacteria, *Alteromonas* sp.

Gram negative bacteria in genera *Alcaligenas*, *Alteromonas*, *Flavobacterium*, *Halomonas*, *Marinobacter*, *Marinomonas*, *Pseudomonas* and *Vibrio* are found in soil, water, saline water, sea water, animal, plant, and human (Table 2). Some strains of these genera produced bioactive compounds (Baumann, Gauthier, and Baumann, 1984).

Table 2. Differential characteristics of *Alteromonas* and related genera

Characteristics	*Alteromonas*	*Marinobacter*	*Halomonas*	*Alcaligenas*	*Pseudomonas*	*Flavobacterium*	*Marinomonas*	*Vibrio*
Pigment	±	±	±	±	±	+	±	−
Aerobic	+	+	+	+	+	+	−	+
Facultative anaerobic	−	−	−	−	−	−	+	−
Motility	+	+	+	+	+	−	+	+
Oxidase	+	+	+	+	±	+	+	±
Gelatinase	+	ND	ND	±	−	±	±	ND
Na^+ requirement	+	+	±	−	±	−	+	+
Growth in 20% or more NaCl	−	+	+	−	−	−	−	−

+, positive reaction; −, negative reaction; ± different in each strain; ND = No data

Alteromonas is an aerobic, gram negative, straight or curve rod, approximately 0.7−1.5 μm, motile bacterium. *Alteromonas* is found in coastal water and open ocean, and found symbiosis with other marine organism. Genus *Alteromonas* have composed 12 species. Two species previously of this genus including *A. communis* and *A.vaga* were reclassified in the genus *Marinomonas*. The characteristic differentiation between species of this genus are describe in Table 3.

Table 3. Differential characteristics of the species of the genus *Alteromonas*

Characteristic	*A. aurantia*	*A. citrea*	*A. colwelliana*	*A. denitrificans*	*A. espejiana*	*A. haloplanktis*	*A. hanedai*	*A. luteovolacea*	*A. macleodii*	*A. nigrifaciens*	*A. rubra*	*A. undina*
Colony pigmentation:												
Brown, water-soluble	−	−	+	−	−	−	±	−	−	−	−	−
Red, water-insoluble	−	−	−	+	−	−	−	−	−	−	+	−
Violet, water-insoluble	−	−	−	−	−	−	−	+	−	−	−	−
Yellow, water-insoluble	−	+	−	−	−	−	−	+	−	−	−	−
Orange, water-insoluble	+	−	−	−	−	−	−	−	−	−	−	−
Black, water-insoluble	−	−	−	−	−	−	−	−	−	+	−	−
Cell shape:												
Straight	+	+	+	+	+	+	+	±	+	+	+	−
Curve	−	−	−	−	−	−	−	±	−	−	−	+
Sheathed flagellum	−	−		+	−	−	−	±	−	−	−	−
Growth at:												
4 °C	+	−	−	+	−	−	+	±	−	+	−	±
35 °C	−	±	−	−	±	±	−	+	+	−	+	−
40 °C	−	±	−	−	−	−	−	−	±	−	−	−
NO_3^- reduced to NO_2^-	−	−	+	−	−	±	+	−	−	−	−	−
Denitrification with gas formation	−	−	−	+	−	−	−	−	−	−	−	−
Biolumminescence	−	−	−	−	−	−	+	−	−	−	−	−
Organic growth factors required	+	+	+	+	+	±	+	+	−	+	+	+

Table 3. (continued)

Characteristic	*A. aurantia*	*A. citrea*	*A. colwelliana*	*A. denitrificans*	*A. espejiana*	*A. haloplanktis*	*A. hanedai*	*A. luteovolacea*	*A. macleodii*	*A. nigrifaciens*	*A. rubra*	*A. undina*
Production of:												
Amylase	+	+	+	+	+	±	−	+	+	−	+	±
Alginase	−			+	+	−	−		±	−		−
Chitinase	−	±	−	+	−	±	+	−	−	−	−	+
Utilization of:												
D-glucose	+	+	−	+	+	+	±	+	+		+	+
D-Mannose	+	+	−		±	+	−	±	−	−	+	−
D-galactose	−	−	−	−	+	±	±	−	+	+	−	−
D-fructose	+	+	−	−	±	±	−	±	+	+	−	−
Sucrose	−	−	−	−	+	+	−	−	+	+	−	+
Maltose	±	−	−	+	+	+	−	+	+		−	+
Cellobiose	−	−	−		±	−	−	−	+	−	−	−
Melibiose	−				+	−	−	−	+	+		−
Lactose	−	−	−	−	+	−	−	−	+	+	−	−
Salicin	−	−	−		−	−	−	−	+	−	−	−
D-Gluconate	−	−	+	−	−	−	±	−	+	+	−	−
N-Acetylglucosamine	+		−	−	−	+	+	+	±	−		+
Succinate	−	−	−	−	−	+	−	−	−	+	−	+
Fumarate	−	−	+	−	−	+	−	−	−	+	−	+
DL-Lactase	−	−	−	−	−	−	−	±	±	+	−	−
DL-Glycerate	−		−		−	−	+	−	+	−		−

Table 3. (continued)

Characteristic	*A. aurantia*	*A. citrea*	*A. colwelliana*	*A. denitrificans*	*A. espejiana*	*A. haloplanktis*	*A. hanedai*	*A. luteovolacea*	*A. macleodii*	*A. nigrifaciens*	*A. rubra*	*A. undina*
α-ketoglutarate	−	−	+		−	−	−	−	−	−	−	−
Citrate	−	−	−		+	+	−	−	−	+	−	−
Aconitrate	−				+	+	−		−	+		−
D-Mannitol	−	−	−	−	+	±	−	−	±	−	−	−
Glycerol	−	−	−	−	−	−	−	−	+	+	−	−
L-Threonine	±	−	−		+	−	−	+	−	−		
L-Tyrosine	+		−	+	+	+	±	±	+	+		+
L-Glutamate	−	−		+	−	±	+	−	±	+		−
L-Arginine	+	−		+	±	±	−	±	±	−		±
Putrescine			−	−	−	−	+		−	−		−

+, positive reaction; −, negative reaction; ± different in each strain

(Holt *et al*., 1994)

3. Review of diketopiperazines from marine organisms

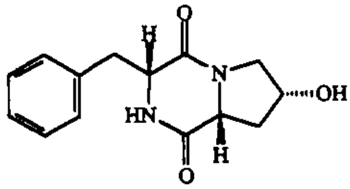
Diketopiperazines are commonly found in higher animals, plants and microorganisms. They are also formed readily from peptides and proteins on thermolysis, and on acid or enzymatic hydrolysis. More than 90% of all gram negative bacteria have been found to produce these diketopiperazines when grown in nutrient-rich media (Fenical, 1993). Though diketopiperazines exhibited some bioactivities, their functions in biological systems are still unknown. The reports of diketopiperazines are described below:

Table 4. Sources of diketopiperazines in marine organisms

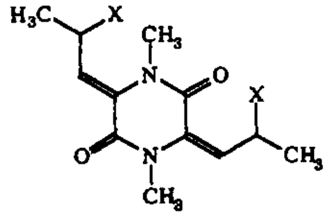
Compound	Organism	Reference
Cyclo-(L-trans(4-hydorxyprolinyl)-L-Phe) [55]	Unidentified Jaspidae sponge	Adamczeski, Quinoa, and Crews, 1989
Dysamides A [56] and B [57]	*Dysidea fragilis* (sponge)	Su, Zhong, and Zeng, 1993
Cyclo-(-L-Pro-L- Tyr-) [58] *Cyclo-(-L-Pro-L-Phe)* [59] *Cyclo-(-L-Pro-D-Phe)* [60] *Cyclo-(-Pro-Hle-)* [61] *Cyclo-(-Pro-Val-)* [62] *Cyclo-(-Pro-Leu-)* [63] *Cyclo-(-Pro-Ala-)* [64]	*Micrococcus* sp.	Stierle, Cardellina II, Singleton, 1988
Cyclo-(L-Pro-L-Val) [65] *Cyclo-(L-Pro-L-Leu)* [66] *Cyclo-(L-Pro-L-Ile)* [67] *Cyclo-(L-Pro-L-Met)* [68] *Cyclo-(L-Pro-L-Phe)* [59] *Cyclo-(L-Pro-L-Tyr)* [58]	*Dysidea fragilis* (sponge)	Jayatilake *et al.*, 1996

Table 4. (continued)

Compound	Organism	Reference
Cyclo-(S-Pro-R-Leu) [69] *Cyclo-(S-Pro-S-Ile)* [70] *Cyclo-(S-Pro-R-Val)* [71] *Cyclo-(R-Pro-R-Leu)* [72] *Cyclo-(methyl-R-Pro-S-Nva)* [73] *Cyclo-(R-Pro-R-Phe)* [74]	*Calyx* cf. *podatypa* (Caribbean sponge)	Damczeski, Reed, and Crews, 1995
Chlorinated diketopiperazines [75]	*Oscillatoria spongeliae* (cyanobacterium)	Unson, and Faulker, 1993
Cyclo-(L-Pro-L-Val) [65]	*Leucophloeus fenstrata* (sponge)	Omar *et al.*, 1988
diketo-piperazines [76]	*Dysidea herbacea* (sponge)	Kazlaukas, Murphy, and Wells, 1978
Berettin [77] *Cyclo-(Gly-L-Pro)* [78] Cyclo-*(L-Pro-L- Try)* [79] Desoxbre- vianamide E [80]	*Geodia baretti* (sponge)	Lidgren, and Bohlin, 1986
Etzionin [81]	Red sea tunicate	Hirsch *et al.*, 1989
Cyclo-(Gly-L-Pro) [78]	*Luidia clathrata* (starfish)	Pettit *et al.*, 1973

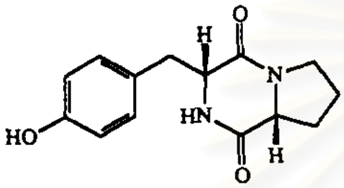


[55] *Cyclo-(L-trans (4-hydroxyprolinyl)-L-Phe)*

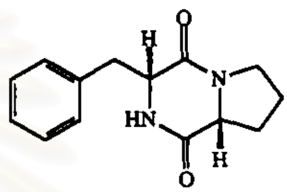


[56] Dysamides A, X = CCl_3

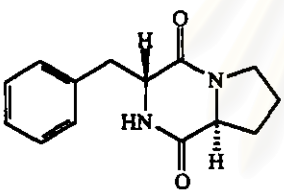
[57] Dysamides B, X = $CHCl_3$



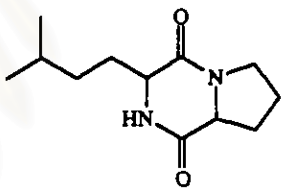
[58] *Cyclo-(-L-Pro-L- Tyr-)*



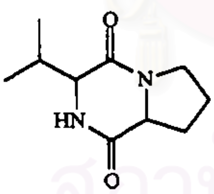
[59] *Cyclo-(-L-Pro-L-Phe)*



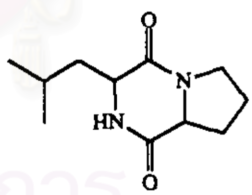
[60] *Cyclo-(-L-Pro-D-Phe)*



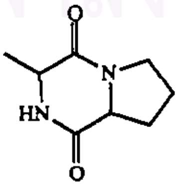
[61] *Cyclo-(-Pro-Hle-)*



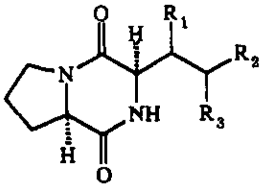
[62] *Cyclo-(-Pro-Val-)*



[63] *Cyclo-(-Pro-Leu-)*



[64] *Cyclo-(-Pro-Ala-)*

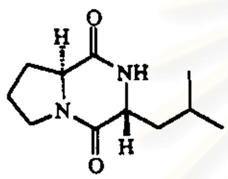


[65] R_1 = CH_3, R_2 = R_3 = H
Cyclo-(L-Pro-L-Val)

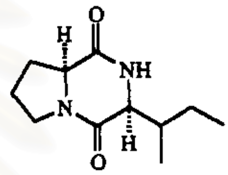
[66] R_1 =H, R_2 =R_3 CH_3
Cyclo-(L-Pro-L-Val)

[67] R_1 = R_2 =CH_3, R_3 = H
Cyclo-(L-Pro-L-Val)

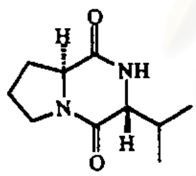
[68] R_1 = R_2 = H, R_3 = SCH_3
Cyclo-(L-Pro-L-Met)



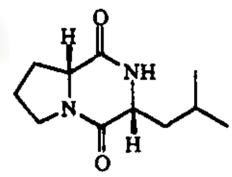
[69] *Cyclo-(S-Pro-R-Leu)*



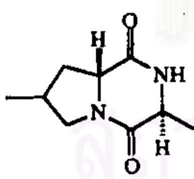
[70] *Cyclo-(S-Pro-S-Ile)*



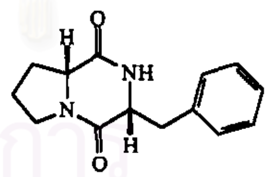
[71] *Cyclo-(S-Pro-R-Val)*



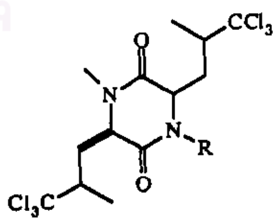
[72] *Cyclo-(R-Pro-R-Leu)*



[73] *Cyclo-(methyl-R-Pro-S-Nva)*

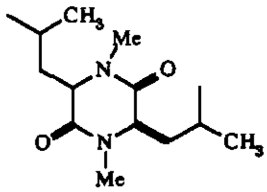


[74] *Cyclo-(R-Pro-R-Phe)*

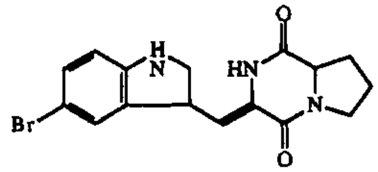


[75] R = Me, H

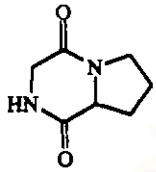
Chlorinated diketopiperazines



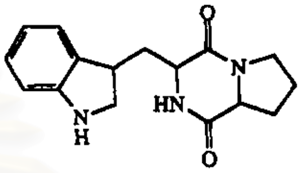
[76]



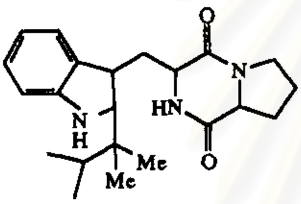
[77] Berettin



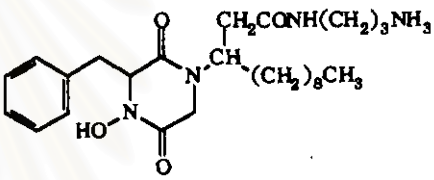
[78] *Cyclo-(Gly-L-Pro)*



[79] *Cyclo-(L-Pro-L-Try)*



[80] Desoxbrevianamide E



[81] Etzionin