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Bioactive Marine Natural Products

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Abstract—Marine organisms have proven to be rich sources of interesting organic molecules. A great number of compounds with diverse structural features and interesting biological activities have been isolated. Recent studies on secondary metabolites of marine organisms are discussed with a focus on a variety of biological activities and marine natural product literatures are also reviewed.

Keywords—Marine organisms • organic molecules • secondary metabolites • marine natural products • biological activities

Introduction

Marine organisms comprise over half a million species.

Due to their living environment very unusual as compared with terrestrial organisms, marine organisms metabolite and produce a variety of substances which often have various unprecedented chemical structures.

In recent years, an increasing number of marine natural products have been reported and reviewed by several authors.[1,2]

Marine metabolites thus for elucidated may be classified as; (1) biochemical resources that may be converted to more valuable materials; (2) bioactive substances, including (a) antimicrobial agents, (b) physiologically active substances (chemical signals) such as pheromones and allelochemics (allomones and kairomones), (c) pharmacologically active substances, and (d) cytotoxic and antitumor substances; and (3) marine toxins.

Some of the marine natural products isolated have not only served as potential lead compounds for clinically useful drugs but actually used as chemical probes useful for basic studies in the fields of life sciences.

There is sufficient basis for the belief that the catchy conference title "Drugs From The Sea" will one day become a reality.

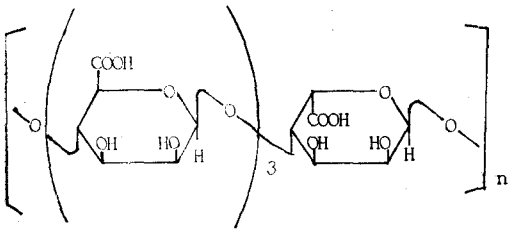
In this report, all compounds reviewed have been organized along biological activities.

It is also hopeful that this review will be a driving force for developments in marine natural products chemistry.

Biochemical Resources[3a,b]

Marine organisms have a close-relationship to human-life as food and protein resources.

There are many metabolites of marine organisms that may be used as raw materials of bioactive or more valuable compounds. A few examples would be: Giant kelp(*Macrocystis pyrifera, M. tegrifoinlia, Nereocystis luetkeana*) are known as brown algae. They are found up the coast from California to Mexico. They can



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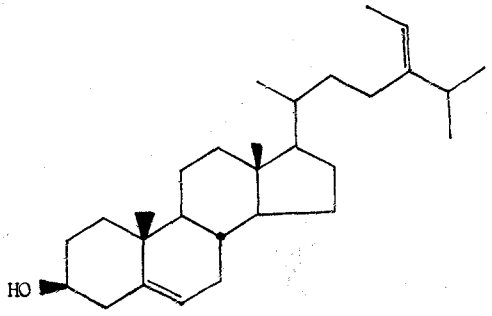

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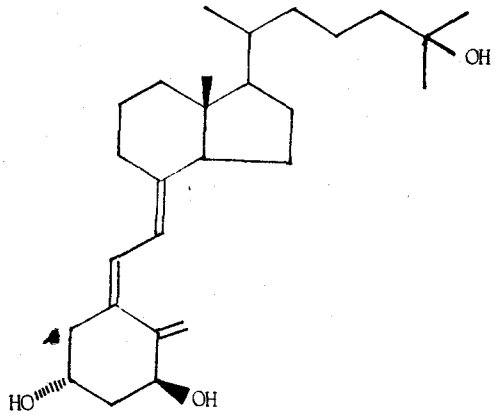

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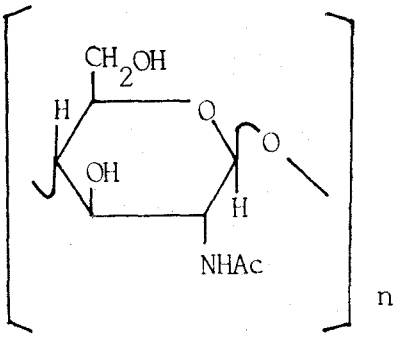

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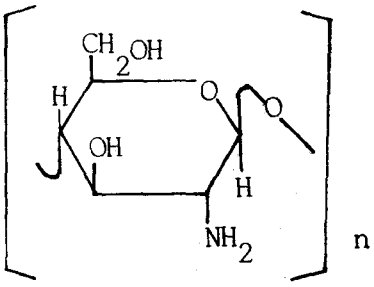

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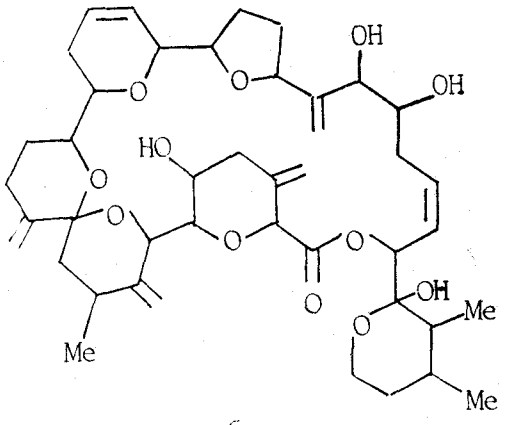

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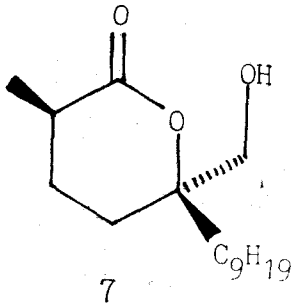

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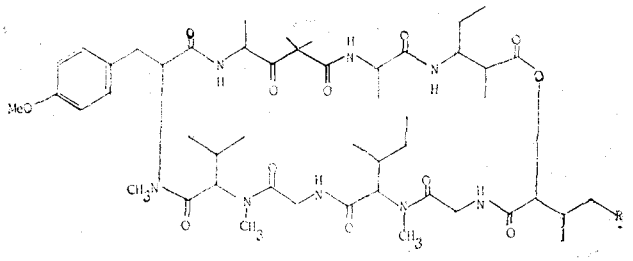


8 R = CH_3

9 R = H

grow 50~60 centimeters per day and can reach 50~60 meters long. It is possible to harvest about 90~100 tons of dry weight algae per hectare during three month period.

Alternative energies(methane gas, ethanol, and light petroleum) have been obtained by thermal decomposition and fermentation of this algae. Alginic acid (1) is isolated from giant kelp and *Pseudomonas* spp. It consists of D-mannuronic acid (major) and L-guluronic acid. It has been used as a food additive, a homogenizing agent for pharmaceuticals, and fibre. Brown algae (*Sargassum ringgodianum* and *Dictyopteris divaricata*) have been known to contain high content of sterol(0.02~0.04%) which was consisted of 95% of fucosterol and 5% of 24-methylene-cholesterol.

Among them, fucosterol (2) has been transformed to active vitamin D_3 named 1,25-dihydroxycholecalciferol (3) that is effective to remedy for renal and parathyroid insufficiencies and for osteomalacia.

Today, we have bred many kinds of fish and shellfish. Some examples are oysters, lobsters, prawns, and abalones.

Recently, increasing attention has been paid to crustaceous chitin (4) and chitosan (5) which are obtained from the crust of crab, lobster, and antarctic krill. They are another hopeful biochemical resources.

For example, partially de-N-acetylated chitin shows cytotoxic and antitumor activity.

Furthermore, aminoglycoside antibiotics, kanamycin C and ribostamycin, have been synthesized by an unambiguous route from D-glucosamine, which is obtained from chitin (4) by hydrolysis, as a starting material.[3b]

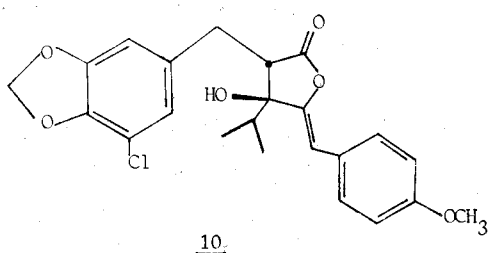
As described in this section, eventually useful compounds of marine organisms have been investigated as a part of development of used or unused natural resources.

Studies on biochemical resources from marine organisms are now expected as a developing theme of great interest.

Bioactive Metabolites of Marine Organisms

1. Antimicrobial substances

1) Marine Phytoplankton and Blue-Green Algae. There have been few studies of the chemistry of marine phytoplankton and blue-green alga because the organisms are often difficult to grow and the yield of secondary metabolites is low. The dinoflagellate is a causative organism that is responsible for the red tides, toxification of shellfish and mass death of fishes. Although the blue-green algae are known as cyanobacteria, their phytosynthetic ability dictates that they are reviewed together with other photosynthetic organisms. Recently, the dinoflagellates and blue-green algae continue to yield interesting biologically active metabolites and diverse kind of structures owing to the development for the method of culture and of purification. A novel polyether macrolide, goniodomin A(6) was isolated from the dinoflagellate *Goniodoma pseudogoniaulax*[4] and structurally resembles pectenotoxin obtained from the digestive gland of scallop.[5] Goniodomin A(6) showed antifungal activity against *Mortierella ramannianus* and *Candida albicans* at a concentration of 0.5μg/ml, and inhibit the cell division of fertilized sea urchin eggs at 0.05μg/ml. Blue-green alga *Lyngbya majuscula* growing in deep-water have yielded(−)-malyngolide[7] and two novel cyclic depsipeptides called majusculamide C(8)[6] and 57-normajusculamide C(9).[7] A synthesis of (−)-malyngolide(7), which is showing antimicrobial activity against *M. smegmatis* and *S. pyogenes*, employed an enantioselective Sharpless epoxidation to produce optically active intermediates.[8] 8 has been shown to possess significant activity against fungal



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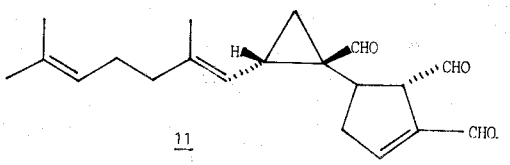

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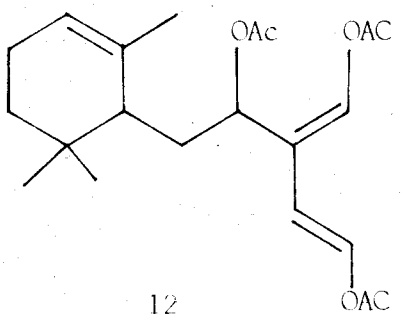

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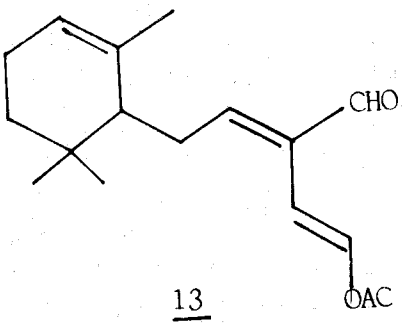

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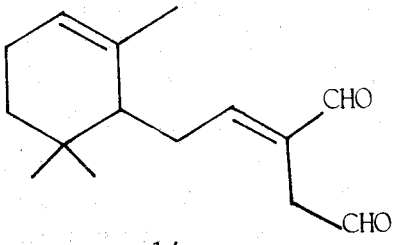

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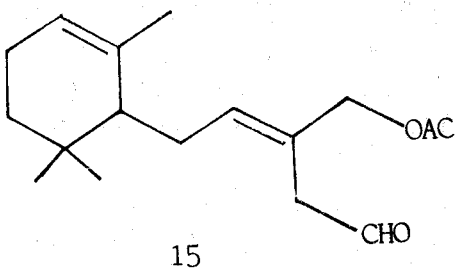

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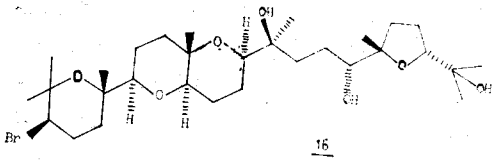

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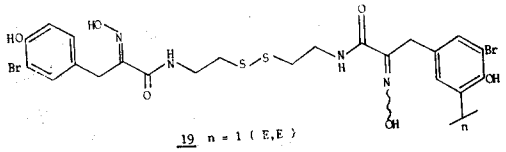
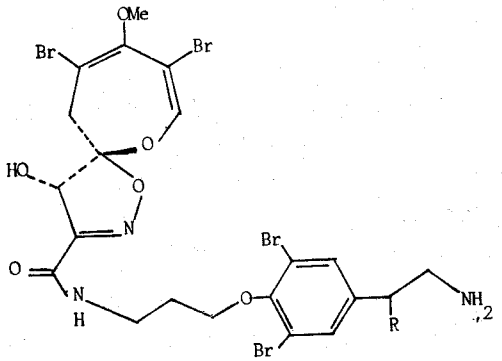


19 n = 1 (E,E)
20 n = 2



17 R = H
18 R = OH

plant pathogens including *Phytophora infestans* and *Plasmopora viticola*, the causative organisms of tomato late blight and grape downy mildew, respectively. While, **9** exhibited antimycotic activity against the indicator organism *Saccharomyces pastorianus*. The cyanobacterin (**10**), which is highly toxic allelopathic substance toward other cyanobacteria and green algae, has been isolated from a freshwater cyanobacterium(blue-green alga), *Scytonema hofmanni*.[9]

2) Marine algae

The tropical green alga *Halimeda* contains new diterpenoids halimedatrial (**11**) and its homologs. The new metabolites exhibit antimicrobial activities against marine and terrestrial bacteria and fungi, and they inhibit cell division of fertilized sea urchin eggs at or below 16μg/ml.[10]

New sesquiterpenes (**12**～**15**) have been isolated from specimens of the green alga *Caulerpa ashmeadii*.[11] The sesquiterpenes (**12**～**15**) were toxic to damselfish and showed antimicrobial activity. Venustatriol (**16**) is a new tetracyclic triterpene ether from the red alga *Laurencia venusta*. **16** displayed significant antiviral activity.[12]

3) Marine sponges

The marine sponges(Phylum Porifera) are considered to be primitive organisms, with relatively simple internal organization.

Sponges, particularly those without spicules, frequently produce large quanitties of secondary metabolites that are thought to deter potential predators and to inhibit the growth of fouling organisms.

Because many sponges contain symbiotic micro-organisms, there is always some uncertainty concerning the true origin of sponge metabolites.

However, the majority of metabolites are now believed to be produced by the sponges, possibly in specialized spherulous cells.

In some exceptional cases, such as *Dysidea herbacea*, there is circumstantial evidence to suggest that some metabolites are produced by symbiotic organisms.

Two antimicrobial constituents, psammaplysin-A (**17**) and-B (**18**) were isolated from a Palau sponge, *Psammaplysilla purpurea* and their structures were elucidated on the basis of ^{13}C–^{13}C connectivity and single-crystal X-ray diffraction studies on psammaplysin A acetamide acetate.[13]

Dimeric disulphide, psammaplin A (**19**), was isolated from the marine sponges *Psammaplysilla* sp.[14] and *Thorectopsamma xcna*[15] together with a minor dimeric metabolite bisaprasin(**20**), respectively. **19** and **20** showed antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus*. Petrosynol (**21**) and petrosynone (**22**), which are antimicrobial, are two polyacetylenic constituents of marine sponge *Petrosia* sp..[16] Petrosynol (**21**) is also active in the starfish egg assay (IC_{99} 1μg/ml).

The kalihinols (**23**～**33**) are a series of diterpene isocyanides that have been isolated from two specimens of *Acanthella*.[17]

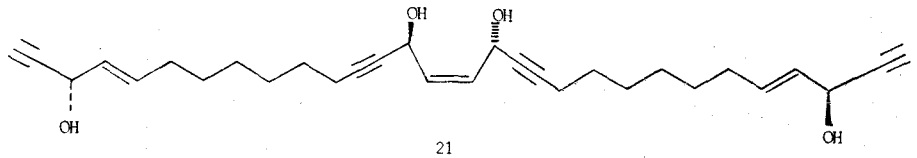
Kalihinols D(**28**), G(**29**), and H(**30**) are trace components of a species of *Acanthella* from Guam and kalihinols X(**31**), Y(**32**), and Z(**33**) were obtained from a Fijian species of *Acanthella*.

All kalihinols inhibited the growth of *Bacillus subtilis*, *Staphylococcus aureus*, and *Candida albicans*. A species of *Halichondria* collected in Palau contained a new macrolide, halichondramide (**34**),[18] that possesses significant antifungal activity against *Candica albicans* (MIC 0.2μg/ml) and *Trichophyton mentagrophytes*(MIC 12.5 μg/ml).

An antibacterial pigment of the sponge *Dendrilla membranosa* was identified as 4,5,8-trihydroxyquinoline-2-carboxylic acid (**35**),[19] and inhibited the growth of *Staphyllococcus aureus*, *V. anguillarum*, *B. harveyi* B-392 at 100μg/disk.

Haliclona sp., a thin red encrusting sponge from Papua New Guinea, which overgrows and kills coral, contains as its major metabolite a pentacyclic alkaloid, papuamine (**36**),[20] which inhibits the growth of the fungus *Trichophyton mentagrophytes.*

The quinone and hydroquinone sesquiterpenoids (**37**~**46**) have been isolated from the sponge *Smenospongia* sp..[21] All the products exhibited antimicrobial and cytotoxic activites. From the sponge *Clathrina clathrus*, clathridine (**47**) and Zn-complex of clathridine (**48**) was isolated and the structure of (**48**) has been identified on the basis of its spectroscopic prop-



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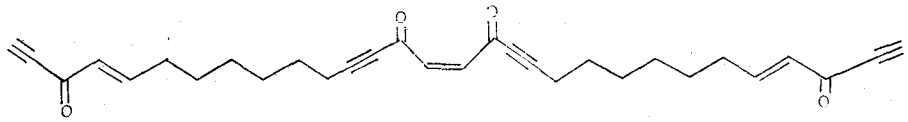

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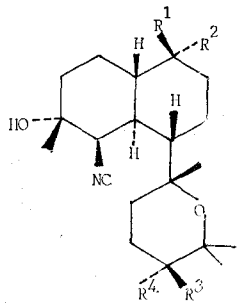


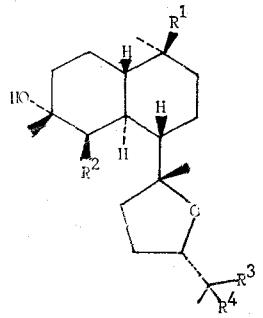
23 R^1=NC. R^2=Me. R^3=Cl. R^4=H

26 R^1=NC. R^2=Me. R^3=H. R^4=Cl

31 R^1=Me. R^2=NCS. R^3=Cl. R^4=H

32 R^1R^2=CH_2. R^3=Cl. R^4=H

33 R^1=Me. R^2=NC. R^3=Cl. R^4=H



24 R^1=R^2=NC. R^3=Cl. R^4=Me

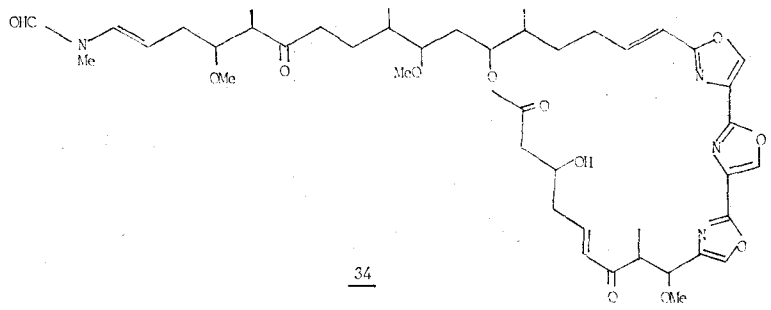
25 R^1=R^2=NC. R^3R^4=CH_2

27 R^1=R^2=R^3=NC. R^4=Me

28 R^1=R^3=NC. R^2=Cl. R^4=Me

29 R^1=R^2=NC. R^3=NCS. R^4=Me

30 R^1=NCS. R^2=R^3=NC. R^4=Me



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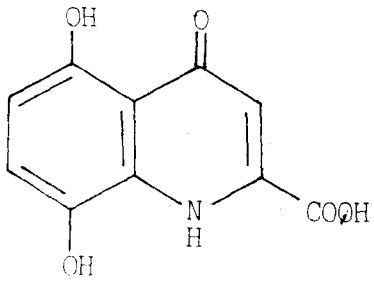

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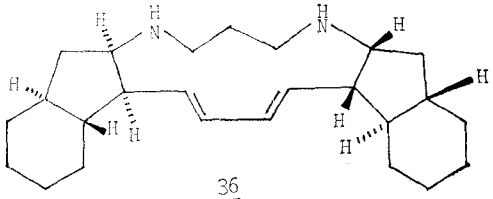

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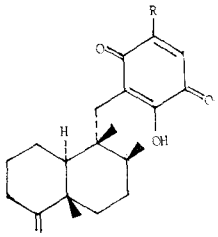

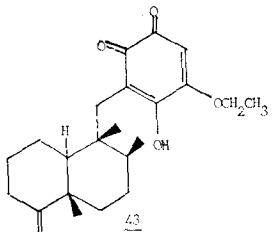

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37 R=OCH_3

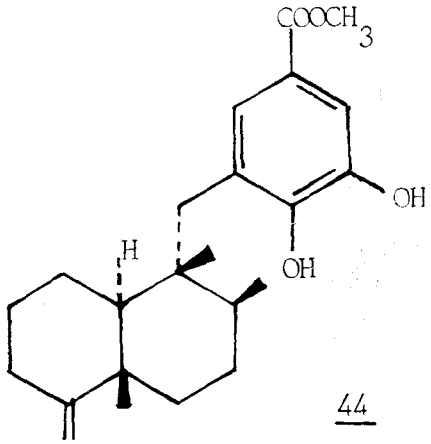
38 R=OH

39 R=NH_2

40 R=NH-CH_2-CH_2-C_6H_5

41 R=NH-CH_2-CH_2-CH(CH_3)(CH_3)

42 R=NH-CH_2-CH(CH_3)(CH_3)



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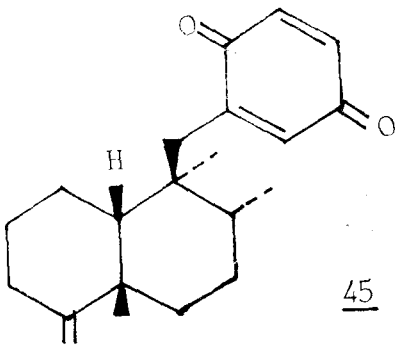

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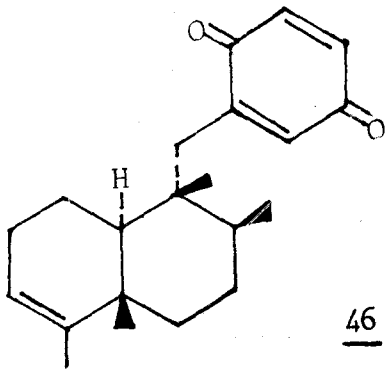

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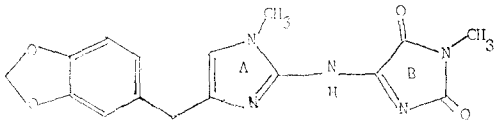

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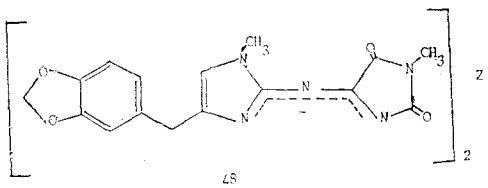

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erties and synthesized from **47** with $ZnSO_4$. **47** showed *in vitro* antimycotic activity against *Candida albicans* and *Saccharomyces cerevisiae*.[22] Aplyviolene (**49**) and polyrhaphin C(**50**), which are diterpenes that exhibit antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis*, was isolated from the marine sponge *Aplysilla polyrhaphis* collected in the Gulf of California.[23] Two epimeric aliphatic amino alcohols (**51, 52**) and triterpene glycoside (**53**) with new carbon skeleton were isolated as the antifungal agent from *xestospongia* sp.[24] and *X. vanilla*,[25] respectively.

Theonellamide F(**54**) is a novel bicyclic peptide that is produced by a species of *Theonella*.[26] Theonellamide F (**54**) inhibited growth of various pathogenic fungi (*Candida* spp., *Trichophyton* spp., and *Aspergillus* spp.) at concentrations of 3~12μg/ml.

It was also cytotoxic against L1210 and P388 leukemia cells with IC_{50} of 3.2 and 2.7μg/ml, respectively.

A deep-water sponge of the genus *Ircinia* produces a new sesterterpene sulfate, sulfircin (**55**).[27] *In vitro* bioassay of sulfircin (**55**) against the fungal pathogen *Candida albicans* gave a minimum inhibitory concentration of 25μg/ml.

4) Coelenterates

The coelenterates are a phylum of predominantly marine invertebrates that include the corals, sea anemones, jellyfish, hydroids, and many other less familiar animals. Members of the subphylum Medusozoa (jellyfish, hydroids, *etc.*) that use stinging cells to deter predators have provided no interesting natural products. Likewise, the physically protected hard corals were of little interest to the marine natural product chemist. The majority of metabolites have been isolated from soft corals and gorgonians, with fewer contributions from sea anemones and sea pens.

Pregnane glycosides of moderate antibiotic activity were isolated from the soft coral *Alcyonium* sp..

The structure of these glycosides, pregnediosides-a (**56**) and -b (**57**), were determined by a partial synthesis of their common aglycone, 3β, 4α-dihydroxy-5α-pregn-20-ene, and by physical data analyses.[28]

Except for echinoderm saponins, pregnediosides were the first steroidal glycosides isolated from marine organisms.

The Mediterranean gorgonian, *Eunicella cavolini*, contains 9-β-D-arabinosyladenine (ara A) (**58**) and its 3′-O-acetyl derivative (**59**) as well as the known compound spongouridine (ara U) (**60**).[29]

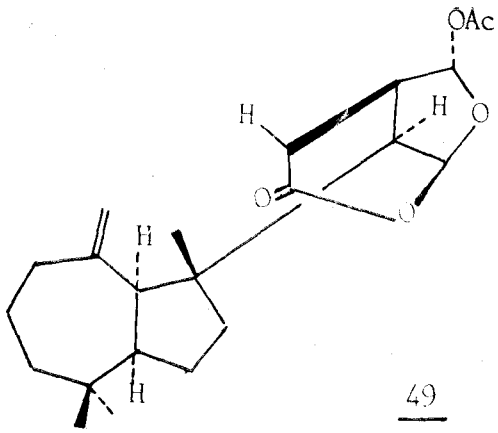
Among these, ara A (**58**) exhibited significant antiviral activity against DNA-containing viruses, so that it was the first antiviral drug used as a highly effective agent in the usually fatal herpes encephalitis.

5) Echinoderms

The phylum Echinodermata comprises five classes: Asteroidea (starfish), Crinoidea(sea lily), Echinoidea(sea urchin), Holothuroidea (sea cucumber), and Ophiuroidea(brittle star). Among these, Asteroidea and Holothuroidea are unique in the animal kingdom, since they include various species which metabolize steroidal and triterpenoidal oligoglycosides(saponins) which function as allomones(also as kairomones in some Asteroidea). Kitagawa *et al.*[30] have investigated the olygoglycosidic constituents of the strafish and of 19 species of sea cucumber. Among constituents, lanostane-type triterpene-oligoglycoside sulfates, pervicosides A(**61**), B(**62**), and C(**63**) were reported recently and their desulfates exhibited antifungal activity.[31]

6) Tunicates

The tunicates, or ascideans, are a class of the subphylum Urochordata. They may be either solitary or colonial and are always attached to



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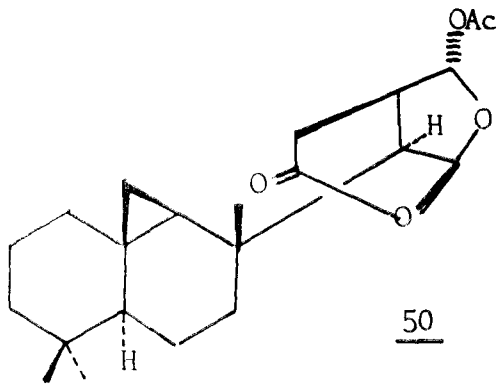

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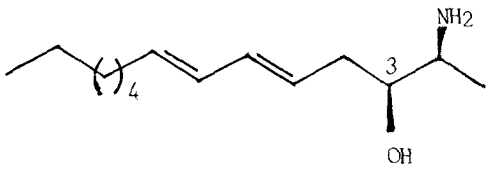

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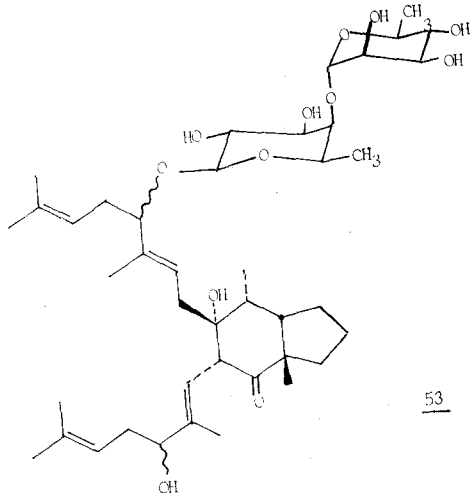
52 3 - epimer



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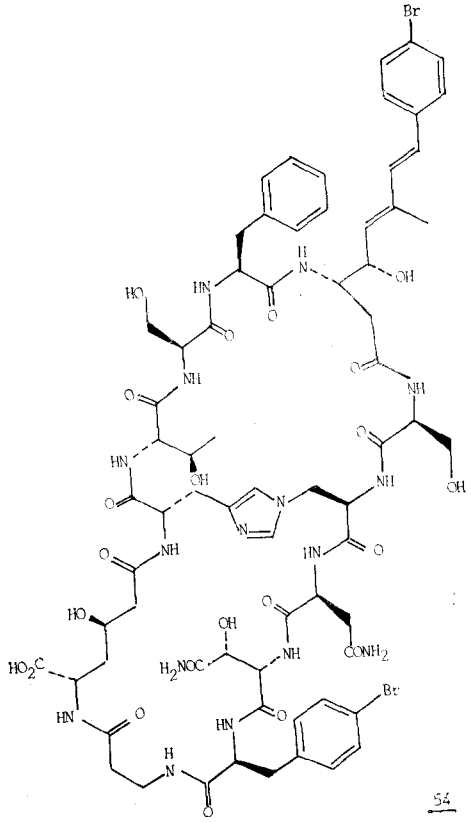

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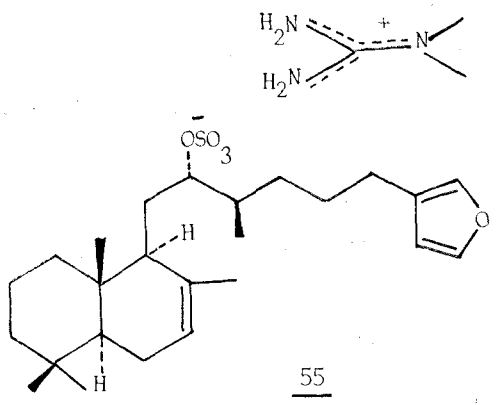

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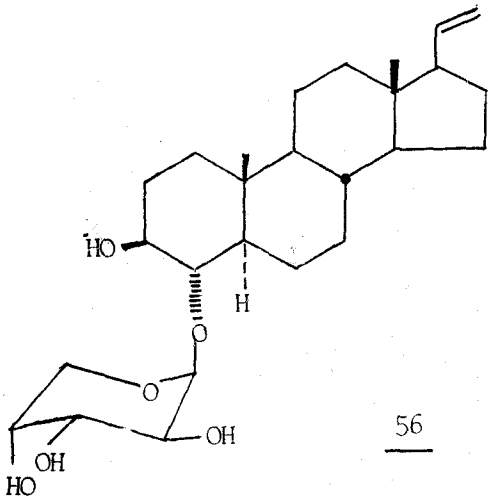

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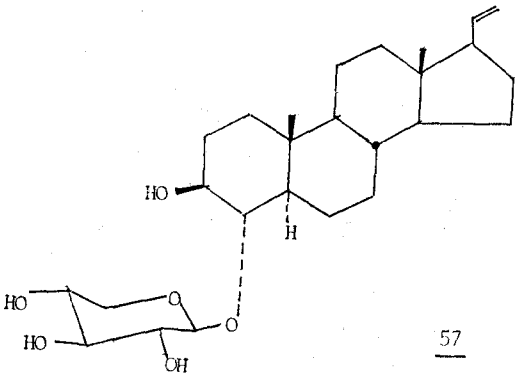

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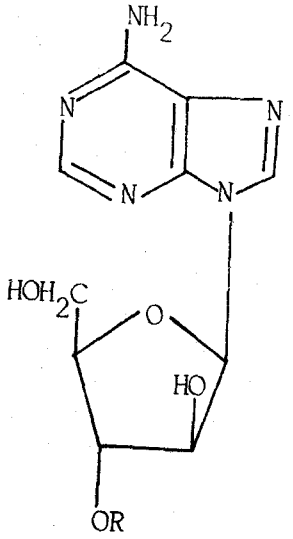
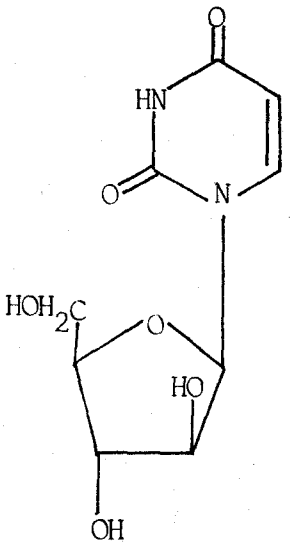


58 R = H

59 R = AC



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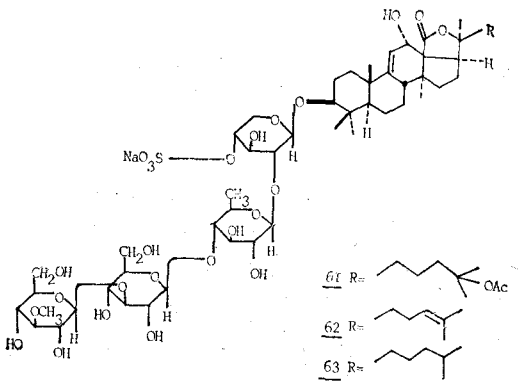
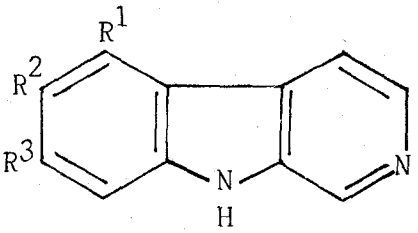


61 R=

62 R=

63 R=



64 R^1= Br. R^2= OH. R^3= H

65 R^1= H. R^2= OH. R^3= Br

66 R^1= R^3= H. R^2= Br

67 R^1= R^2= H. R^3= Br

a substrate. The eudistomins are group of alkaloids from the Caribbeann tunicate ***Eudistoma olivaceum***, some of which have antimicrobial (**64, 66, 67, 69, 70, 71, 72**) and antiviral (**64, 66, 67, 68, 69, 70, 75～78**) pro perties.[32,33]

Eudistomins D(**64**), J(**65**), N(**66**), and O(**67**) are simple brominated β-carbolines. Eudistomins G(**68**), H(**69**), I(**70**), P(71), and Q(**72**) have a 2-pyrrolinyl substituent at C-1 of the β-carb oline ring system, while eudistomins A(**73**) and M(**74**) have a 2-pyrrolyl substituent at that position.

The most unusual of the eduistomins, namely C(**75**), E(**76**), K(**77**), and L(**78**), incorporate a novel oxathiazepine ring.

A naturally occurring sulfoxide, eudistomin K sulfoxide(**79**), has been isolated from the ascidian *Ritterella sigillinoides*.[34]

This compound displayed *in vitro* antiviral activity against *Herpes simplex* Type I and *Polio* vaccine Type I viruses at concentrations of 200ng/ml.

A new diketopiperazine hydroxamate derivative, etzionin(**80**), has been obtained from a Red Sea tunicate and showed antifungal activity against the pathogenic yeast *Candida albicans* (MIC 3μg/ml in RPMI-1640).[35] Activity was also seen against *Aspergillus nidulans* and *Bacillus subtilis*.

7) Bryozoans

Chemical studies of bryozoans(Phylum Ectoprocta) or "moss animals" have been limited by the difficulties experienced in collecting sufficient material for analysis. However, a lot of novel metabolites have recently been isolated from them.[2b] The Japanese marine bryozoan *Bugula dentata* possesses a brilliant blue pigment(**81**), which is antimicrobial against gram-positive and gram-negative bacteria.[36]

2. Physiologically active substances.

The detection of environmental signals is used by all living organisms and in many cases defines their ultimate viability. The predominate signalling mechanism is chemical.

Specific recognition signals, which are mediated by chemical substances, have been shown to play an increasingly major role in the association of a parasite-its host, a symbiote-its host, and a gamete.

These chemical substances fall into three classes such as pheromones interacted in same organisms, allelochemics (allomones and kairomones) interacted in different organisms, and synomones inducing symbiosis.

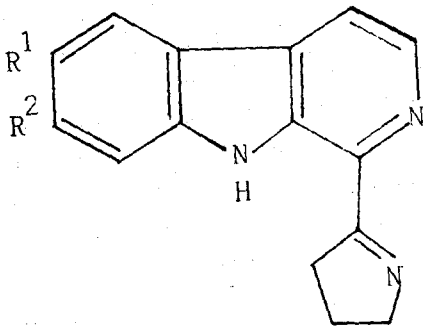
There is an increasing awareness of the importance of searches for ecological chemistry of the marine organisms.

This search is especially helpful to understand not only ecology but phenomena of life in marine environment.

1) Pheromones

(1) Sex pheromones of brown algae.

Brown algae are harvested commercially for their polysaccharides. Natural Product chemists have studied many classes of metabolites of brown algae ranging in complexity from polymeric phenolics to simple lipids that act as chemical messangers. The research by Müller *et al.* has provided an insight into the important function of some sex pheromone of brown algae. Müller has shown that the female gametes exude simple chemicals that attract male gametes and cause them to remain in an excited state in the vicinity of the female gametes. Perhaps the key observation in studies of the attraction of gametes in brown alga was that suspensions of female gemetes had an odour that was absent from suspensions of male gametes.[37] Up to date, above 10 sex pheromones of brown algae has been identified and the metabolites may be classified as cyclopropane, cyclopentane, cycloheptadiene, and straight chain olefin groups from their structures. Fucoserratene (**82**), which is a



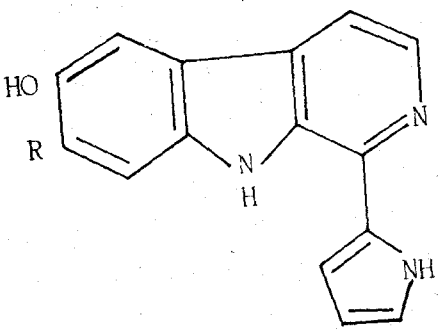
68 R^1= H. R^2= Br

69 R^1= Br. R^2= H

70 R^1= R^2= H

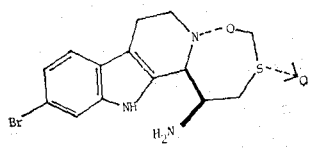
71 R^1= OH. R^2= Br

72 R^1= OH. R^2= H



73 R = Br

74 R = H



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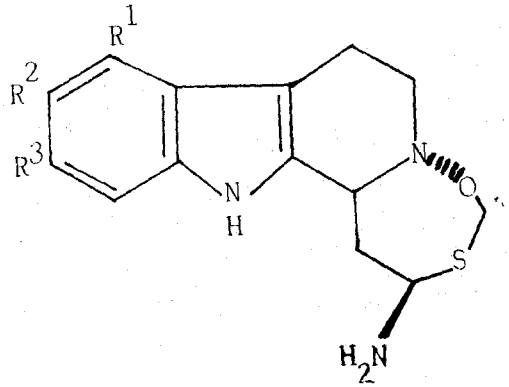
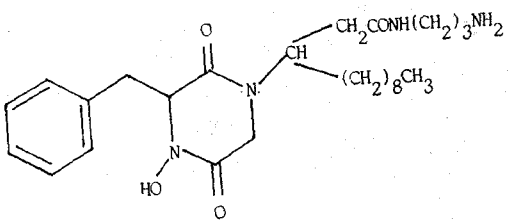


75 R^1= H. R^2= OH. R^3= Br

76 R^1= Br. R^2= OH. R^3= H

77 R^1= R^2= H. R^3= Br

78 R^1= R^3= H. R^2= Br



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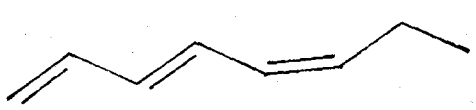

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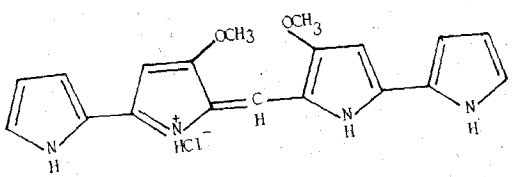
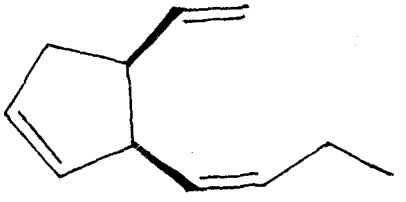


81

spermatozoid-attracting pheromone of brown algae *Fucus serratus*[38] and *Pelvetia wrightii*,[39] has been synthesized in high isomeric purity and on a preparative scale.[40] Recent chemical studies have led to the identification of several new gamete attractants: multifidene (**83**) from *Cutleria multifida*,[41] viridiene (**84**) from *Desmarestia viridis*[42] (which is the gamete attractant of *Syringoderma phinneyi*[43]), dictyopterene A (**85**) from *Dictyopteris prolifera*,[44] and hormosirene (**86**), which is also the gamete attractant of *Scytosiphon lomentaria*.[45] The synthesis of **85** and **86** have been reported.[46]

(2) Alarm Pheromones

Molecules (**87**–**89**) acting as alarm pheromones have been isolated from marine organisms. Anthopleurine (**87**) is a quaternary ammonium salt that was obtained from the sea anemone *Anthopleura elegantissima*.[47] The opisthobranch mollusc, *Scaphander lignarius*,[48] contains two new ω-phenyl conjugated trienones, lignarenone-A(**88**) and -B(**89**) which are closely related to



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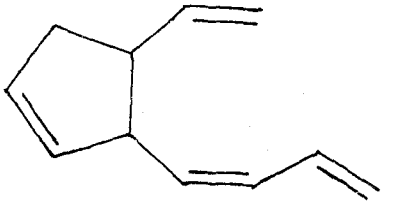

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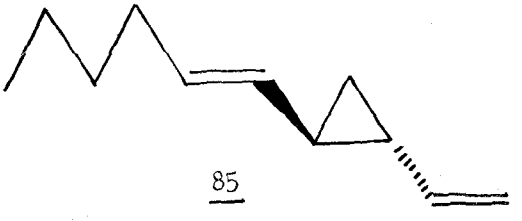

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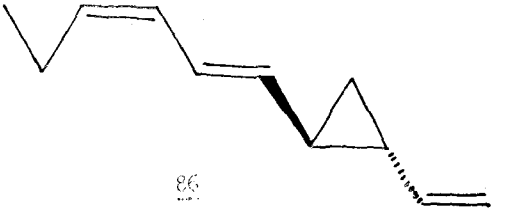

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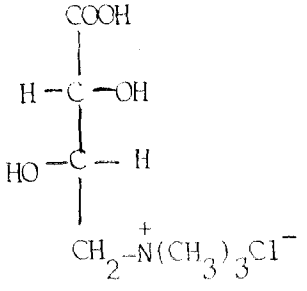
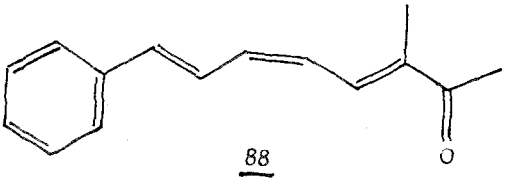
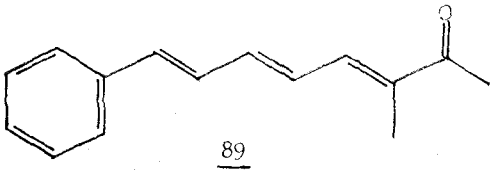


87



88



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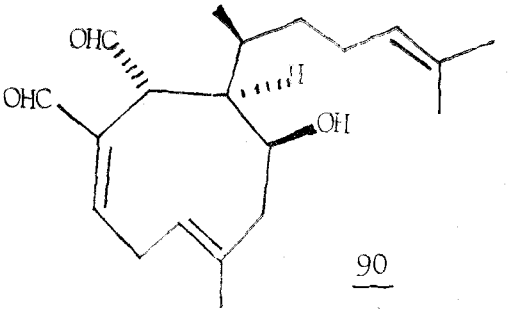


90

3-methyl navenone-B.[49]

2) Allelochemics

The allelochemics are among the most important metabolites of marine organisms from the viewpoints of prey-predator relationship in food chain and of maintenance in marine ecosystems. The importance of plant defensive mechanism, especially the role of secondary metabolites as protection against herbivores, has been extensively investigated in both marine and terrestrial communities. Marine algae contain a number of biologically active metabolites, reflecting the need for chemical defence against intense feeding pressure by herbibores.[50] Hydroxydictyodial (**90**), which is an antifeedant diterpene against omnivorous fish and a key intermediate in the biogenesis of several related diterpenes, has been isolated from the brown alga *Dictyota spinulosa*.[51] The secospatane-type diterpenes (**91** and **92**),[52] which have been obtained from brown alga *Dilophus okamurai*, show inhibition of feeding against the young abalone *Haliotis discus hannai*. While, a rearranged trisnor sesq uiterpene called kumepaloxane (**93**),[53] a feeding deterrent to generalist carnivorous fishes and to the pufferfish *Canthigaster solandri* was isolated from the Guamanian mollusc *Haminoea cymbalum* and its structure was elucidated by spectral analysis. The Phylum Mollusca includes the cephalopods (squid and octopus), the bibalves (mussels, clams, oysters, and scallops), and the gastropods(sea hares, nudibranchs, and pulmonates).

Chemical research has featured the shell-less molluscs, such as sea hares and nudibranchs, many of which are thought to owe their evolutionary success to the development of chemical defence mechanisms.[54a,b] Olepupuane (**94**) had been isolated from the mantles of *Dendrodoris limbata* and *D. grandiflora*, which is likely transformed into polygodial (**95**) during extraction and isolation procedures.[55] Polygodial (**95**) is the biologically active component in the defensive secretion of *Dendrodoris limbata*. *Siphonaria grisea* is gastropod molluscs found in the high interdital region and contains two new metabolites siphonarienedione (**96**) and siphonarienolone (**97**), which are believed to be employed in a chemical defence against predators.[56] The marine pulmonate *Siphonaria denticulata* produces denticulatin A (**98**) and B (**99**) as defensive chemicals against predators, which have been synthesized.[57] Burreson *et al.*[58] have isolated an isonitrile, 9-isocyanopupukeanane (**100**), from the defensive secretion of the nudibranch *Phyllidia varicosa* and found that the source of this compound was the sponge *Hymeniacidon* sp..

Minale has suggested that the asterosaponins can be conveniently divided into three classes; sulphated steroidal penta-or hexa—glycosides, steroidal cyclic glycosides, and glycoside of polyhydroxy—steroids consisting of a polyhydroxy steroid with one or two sugar units.[59]

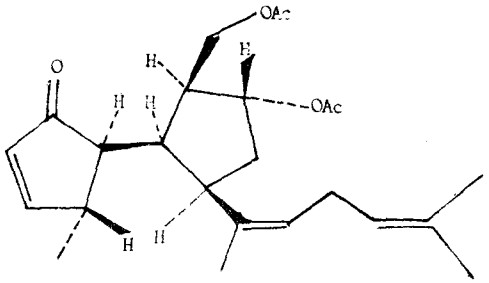
Many steroidal saponins of starfish are potent as defensive allomone against fish and as kairomone causing escape of prey (bivalve, sea anemone, *etc.*).

Certain species of fish have a self—defense mechanism consisting of the secretion of toxic substances that repel their predators.

Among these so-called ichthyocrinotoxic species are the Red Sea Moses sole *Pardachirus marmoratus* and its congener, the peacock Sole *Pardachirus pavoninus*, which repel sharks by emission of their toxic secretion at the moment when they are about to be bitten.

The chemical nature of these shark repellents has been clarified by Tachibana and coworkers, who have shown that the toxins consist of a mixture of peptides and steroidal saponins with detergent—like properties.

They have eventually determined the structures of the peptidic pardaxins,[60a-c] and two



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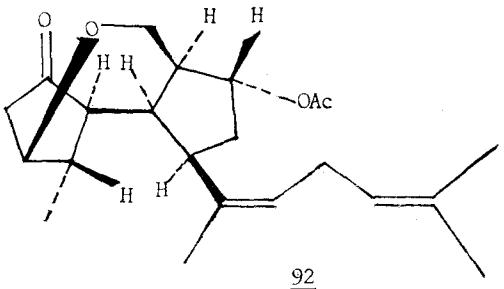

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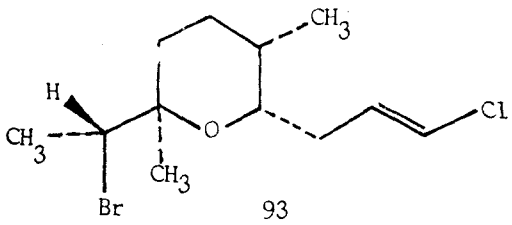

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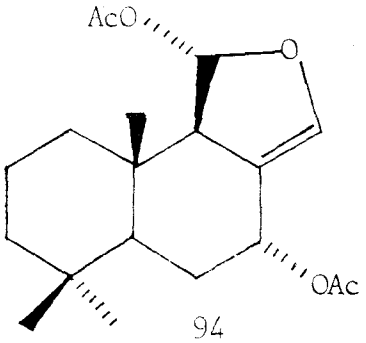

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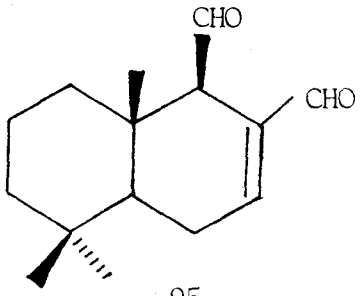

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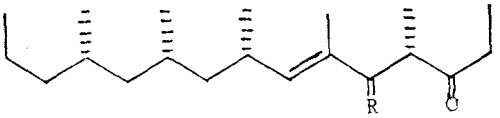
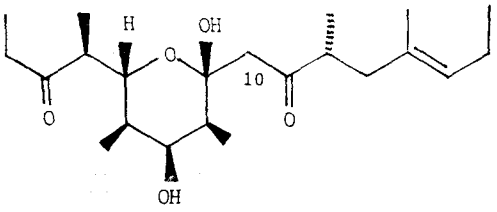


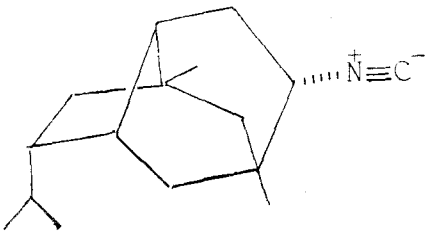
96 R = O

97 R = β-OH



98

99 10-epimer



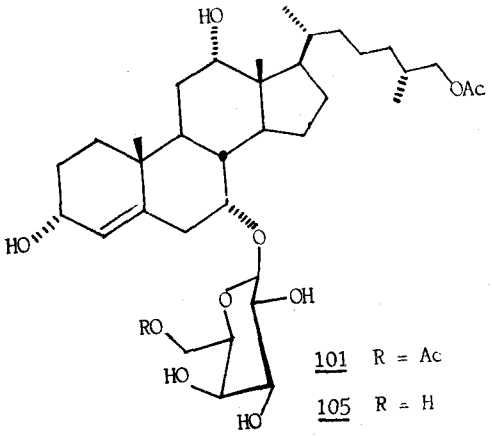
100

classes of steroid glycosides, mosesins-1—5 (**101-105**) from *P. marmoratus*[61] and pavonins-1—6 (**106-111**) from *P. pavoninus*.[62a,b] Among these toxins, the first synthesis of mosesin—4 (**104**) and its analog 7-β-galactosyl ethyl cholate have been reported.[63]

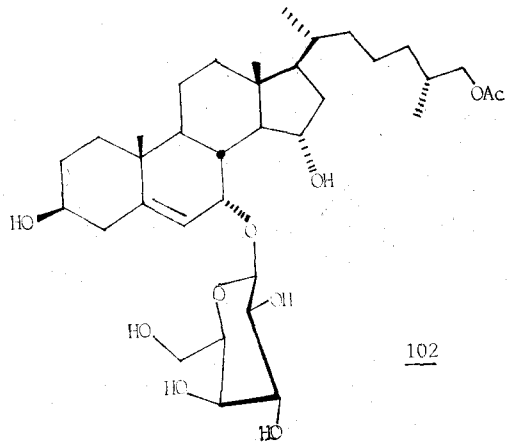
These compounds were also found to be potent cell disrupters and hence should be important as physiological probes and exert interesting pharmacological activity.[60c,64]

3) Synomones[65]

The chemicals that induce symbiosis is espe-



101 R = Ac
105 R = H



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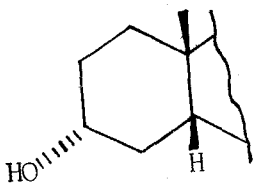
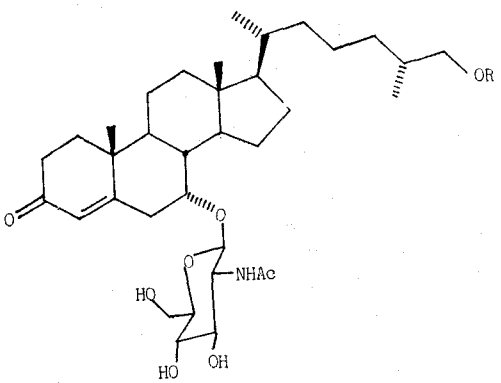
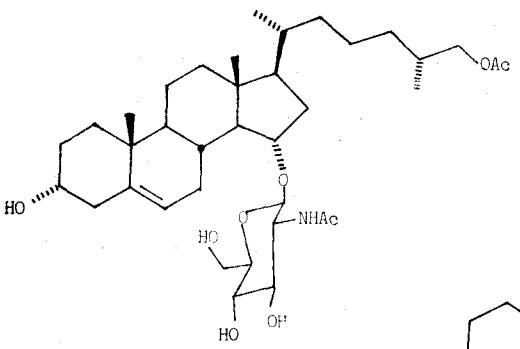


103 R = Ac
104 R = H



106 R = Ac
107 R = H



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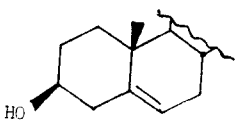

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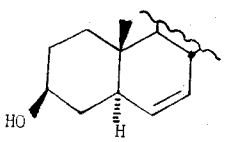

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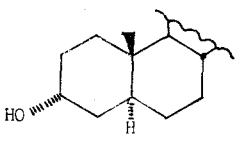

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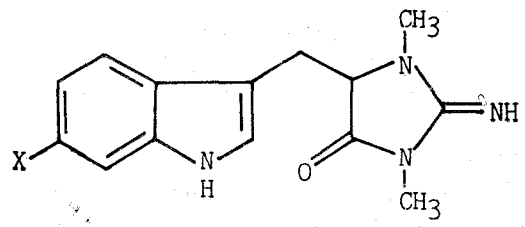
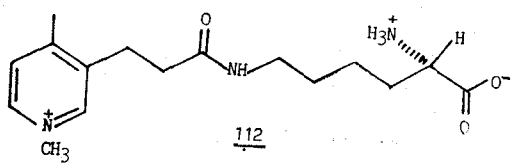


113 (X = H or Br)



112

cially called synomone. The necessary conditions to maintain the symbiosis is as follows; discrimination of each other (host and guest), harmless to host, adjustment of multiplication, and inevitability in the mutual utilization.

The species-specific partnership between the sea anemone and anemone fish in many sorts of the Indo-Pacific region is a well-known phenomenon. Chemicals (**112**～**116**) secreated by the sea anemone to elicit symbiotic behavior of the fish have been studied for two host-guest pairs, *Radianthus kuekenthali*(sea anemone)-*Amphiprion perideraion*(anemone fish) and *Stoichactis kenti-A. ocellaris*.[66]

A new pyridinium compound, amphikuemin (**112**), which has been isolated from *Radianthus kuekenthali*, induces characteristic attracted swimming(toward the chemical stimulus) in *Amphiprion perideraion*(10^{-10}M).

Radianthus kuekenthali also contained six dihydroaplysinopsins and ten aplysinopsins exemplified by **113** and **114**, respectively.

The dihydro compounds (**113**) elicited attracted swimming, but the effective dose of 10^{-6}M is much weaker than that of amphikuemin(**112**) (10^{-10}M).

The aplysinopsins(**114**) induced the fish to perform a head up and down "seesaw" movement (effective dose 10^{-6}M). Tyramine (**115**) and tryptamine (**116**) from the sea anemone *Stoichactis kenti* induced attracted swimming with tail wagging and active searching behavior, respectively, both at a dose of 10^{-6}M.

3. Pharmacologically active substances

1) Marine micro-organisms and blue-green algae.

Three aromatic acid, rubrenoic acids A(**117**), B(**118**), and C(**119**), from the marine bacterium *Alteromonas rubra* showed bronchodilator activity *in vitro*.[67] The structures of acids (**117**～**119**) were elucidated by interpretation of spectral data, and rubrenoic acid C(**119**) was synthesized by a relatively inefficient route.

Blue-green alga *Anabaena flos-aquae* produces structurally unusual neurotoxic alkaloids, anatoxin-a (**120**),[68] which has recently been synthesized to racemic form, and a unique phosphate ester of a cyclic N-hydroxyguanidine named anatoxin-a(s) (**121**).[69] Anatoxin-a (**120**) shows potent biological effects including very fast death factor *via* respiratory paralysis for variety of species and most potent agonist known for the nicotinic acetylcholine receptor (nAChR).

While, **121** is a neurotoxic alkaloid which is attributed to exceptional anticholinesterase activity. A novel cyclic peptide, scytonemin A (**122**), possessing potent calcium antagonistic properties has been isolated from blue-green alga *Scytonema* sp. as a major metabolite.[70]

2) Marine algae

An enantiospecific total synthesis of (−)-α-kainic acid (**123**), which is a compound from the marine red alga *Digenea simplex* that has neuroexcitatory properties and anthelmintic principle employs an interesting Claisen rearrangement as its key step.[71]

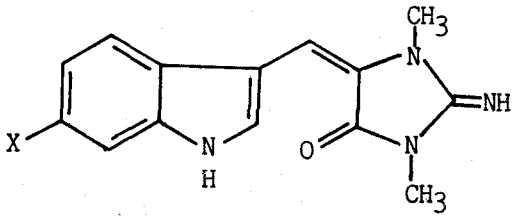
Two novel acyclic hydroxylated fatty acids, ptilodene (**124**)[72] and 12-(s)-HEPE(**125**),[73] have been obtained from the marine red algae *Ptilota filicina* and *Murrayella periclados*, respectively.

Ptilodene (**124**) has antimicrobial and displays moderate inhibitory activity to 5-lipoxygenase in human PMN leukocytes and dog kidney Na^+/K^+ ATPase.

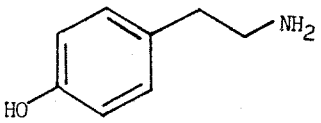
While, 12-(s)-HEPE (**125**) is a potent inhibitor of platelet aggregation and mediator of inflammation.

A new polyhalogenated monoterpene, telfairine (**126**) was obtained from the red alga *Plocamium telfairiae*, which exhibited strong insecticidal activity aginst mosquito larvae.[74]

The brown alga *Ecklonia kurome* contained a new type of phlorotannins, eckol (**127**)[75] and



114 (X = H or Br)



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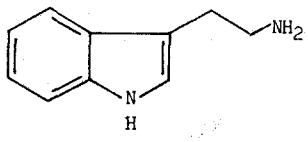

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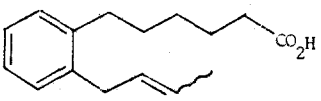

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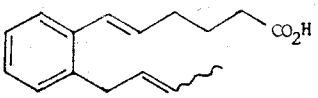

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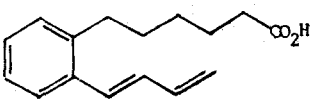

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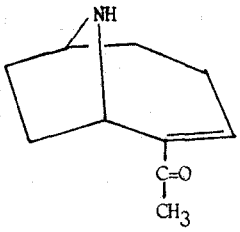

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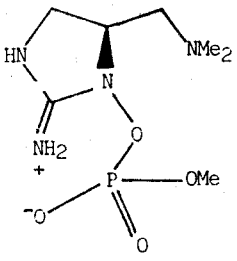

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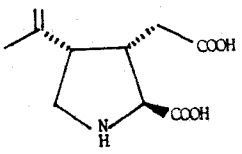

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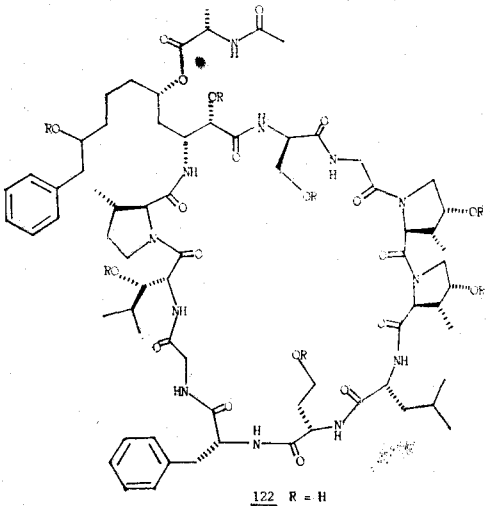
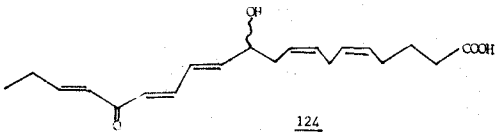


122 R = H



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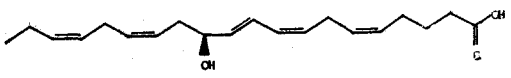

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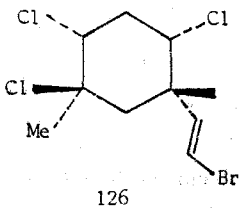

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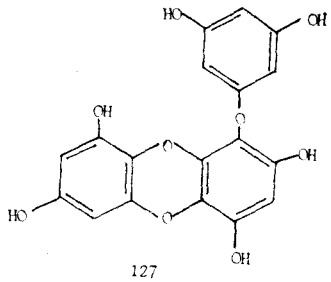

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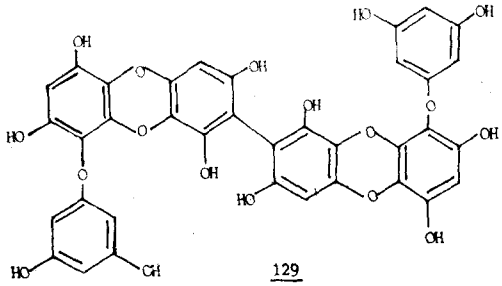

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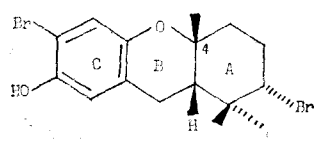
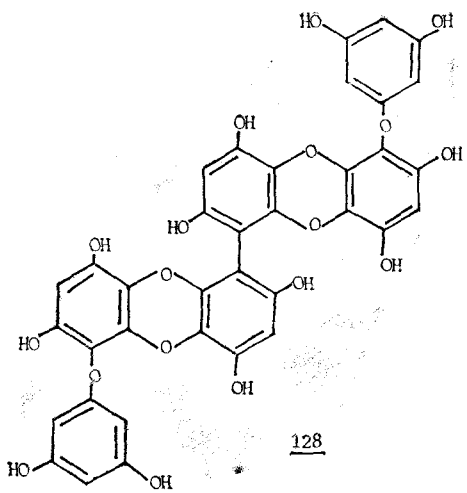


131

132 (4 - epimer)



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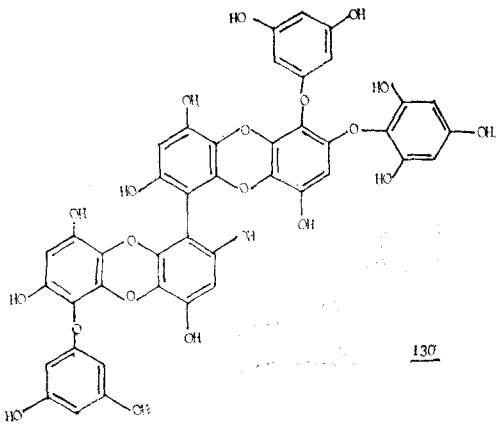

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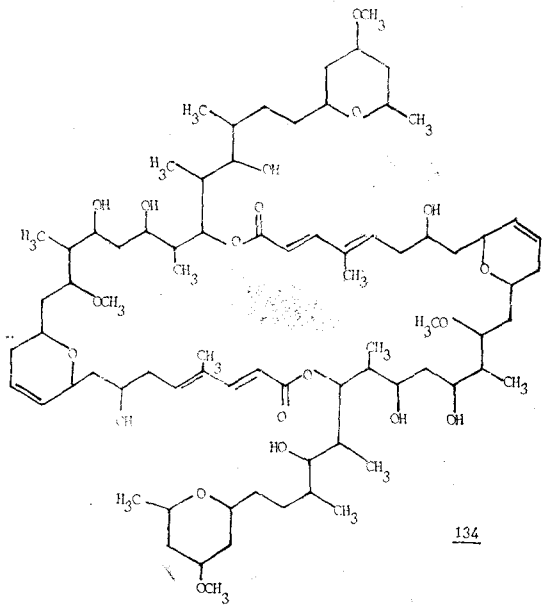

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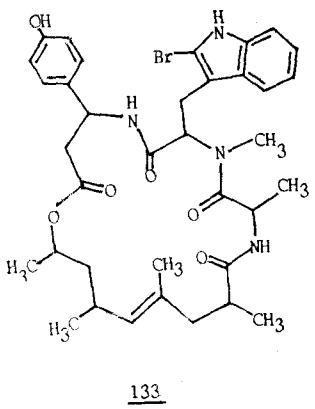


133

dimeric eckols (**128**~**130**),[76] which were potent anti-plasmin inhibitors that may be useful in prevention and treatment of thrombosis.

Two new compounds, cymobarbatol (**131**) and 4-isocymobarbatol (**132**), were isolated from the green alga *Cymopolia barbata*.[77]

Both compounds are highly active antimutagens and are nontoxic over a broad concentration range to *Salmonella typhimurium* strains T-98 and T-100.

3) Marine sponges

A new cyclodepsipeptide, jasplakinolide (**133**) comprised of three amino acids and an oxy-trimethyl-nonanoyl group, has been isolated from the marine sponge *Jaspis* sp., which has antifungal and anthelmintic bioactivity.[78]

The five tridecapeptide lactones named theonellapeptolides Ia-Ie which inhibit development of the fertilized eggs of the sea urchin have been reported together with a potent cytotoxic macrolide(**134**) as metabolites of the marine sponge *Theonella swinhoei*.[79] **134** has previously been reported under the name swinholide A.[80] Theonellapeptolide Id (**135**) and Ie (**136**) inhibit the activity of Na^+/K^+-transporting ATPase.

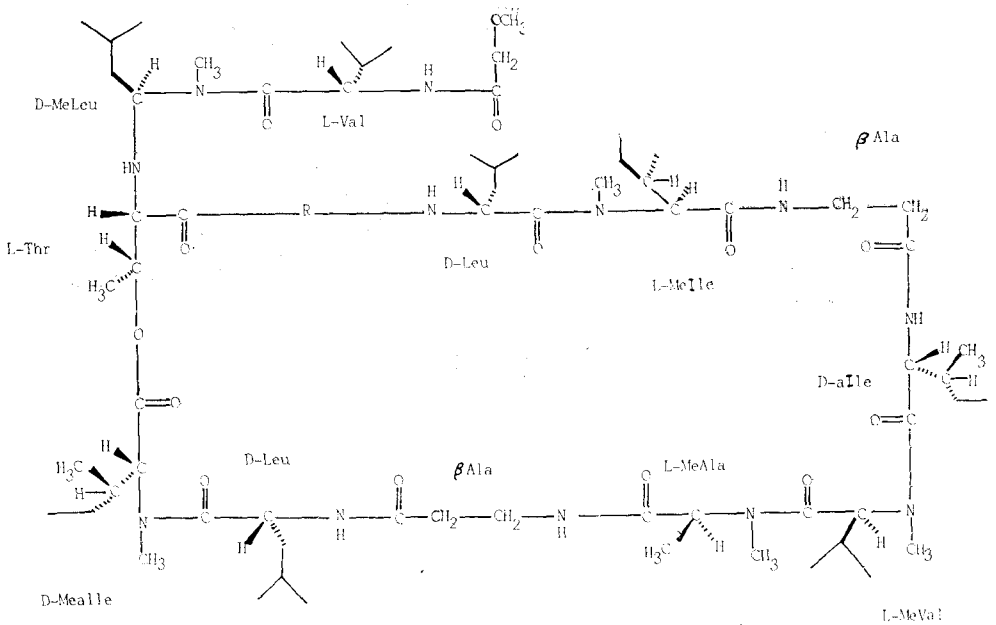
Two yellow pigments, halenaquinol (**137**) and its monosulfate (**138**) have been isolated from *Xestospongia sapra* and their absolute stereostructures have been determined.[81] Halenaquinol (**137**) is photosensitive and is readily oxidized to halenaquinone (**139**), which is an antimicrobial metabolite of *Xestospongia* exigua.[82]

It is therefore possible that halenaquinone (**139**) might be an artifact of the isolation procedure. Xestoquinone(**140**) is a constituent of *Xestospongia sapra* that was identified by comparison of its spectral data with those of halenaquinone(**139**).[83] Halenaquinol(**137**) and Xestoquinone(**140**) show cardiotonic activity. Hexaprenylhydroquinone sulfate(**141**)[84] was isolated from the marine sponge *Dysidea* sp. and was found to inhibit H^+, K^+-ATPase with a 50% ID of 4.6×10^{-6}M. **141** also inhibited both gastric acid secretion in rats(54 % at 300 mg/kg, orally) and phospholipase A_2 with a 50 % ID of 1.8×10^{-6}M, but there was no antiulcer effect of **141** at this concentration. The absolute configurations of the gastric H^+/K^+-transporting ATPase inhibitors siphonodiol(**142**) and its homologs, which were obtaind from *Siphonochalina truncata*, have been determined by the exciton chirality method.[85] Agelasidines A(**143**), B(**144**), and C(**145**) all displayed significant physiological activity including antispasmodic activity and inhibitory effects on growth of microorganisms, contractile responses of smooth muscle, and enzymic reactions of Na, K-ATPase[86], of which agelasidine C(**145**) was recently synthesized by Tokoroyama group.[87]

Two novel bicycle diterpenoids, agelasimine-A (**146**) and -B(**147**), were isolated from *Agelas mauritiana*.[88]

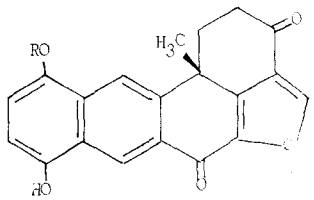
Both metabolites(**146** and **147**) exhibited a wide range of interesting biological activities such as cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, Ca^{2+}-channel antagonistic action, and α_1-adrenergic blockade. 15-Acetylthioxy-furodysinin lactone(**148**) is a sesquiterpene thioacetate which were isolated from the genus *Dysidea*.[89]

The **148** was a potent LTB_4 receptor partial agonist. A novel furanosesterterpene, hippospongin(**149**), possessing antispasmodic activity has been obtained from *Hippospongia* SP. and its structure was elucidated by interpretation of spectral data.[90] Homosesterterpene **150** from the marine sponge *Dictyoceratida* sp. and *Halichondria* sp. causes inhibition of aggregation of blood platelets (IC_{50} 0.5 μg/ml) and possesses antimicrobial properties.[91] Scalarane-type bishomosesterterpene, phyllofoliaspongin(**151**), was isolated together with several other metabolites from *Phyllospongia foliascens*.[92] Phyllofoliaspongin(**151**) showed cytotoxic, anti-thrombocyte,



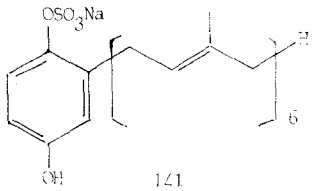
R = βAla : theonellapeptolide Id (135)

R = MeβAla : theonellapeptolide Ie (136)



R=H; halenquinol (137)

R=SO_3Na; halenaquinol sulfate (138)



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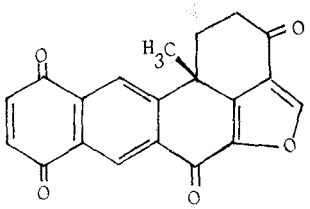

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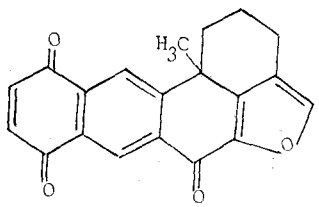

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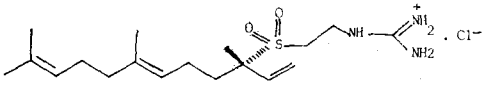

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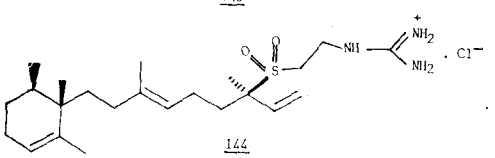

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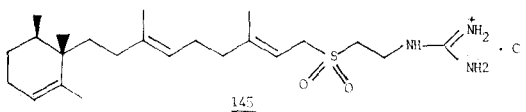

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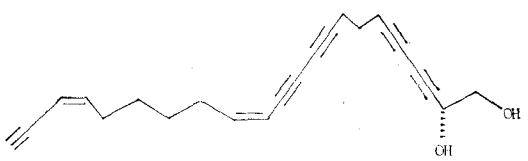

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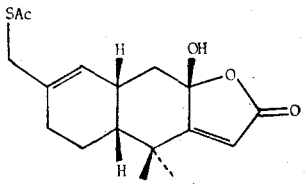

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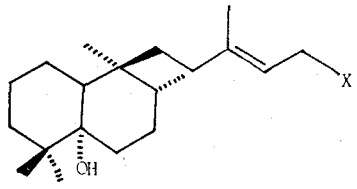
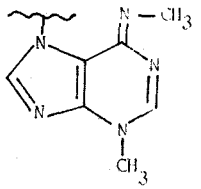


146 X =



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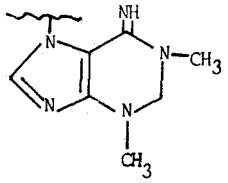

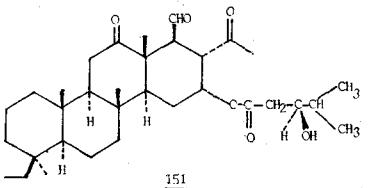

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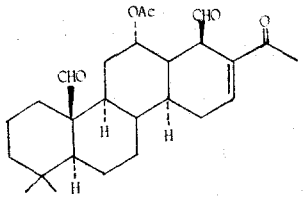

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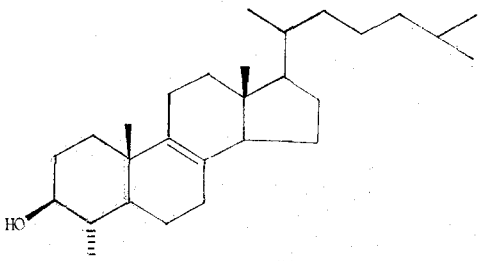

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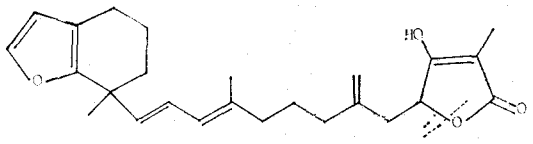

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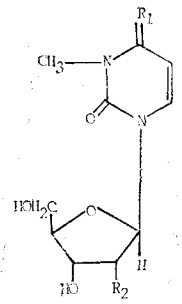
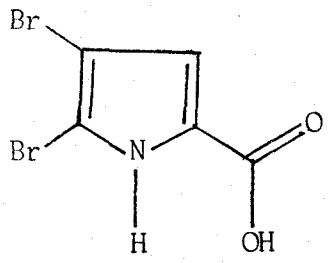


152 $R_1 = \overset{+}{N}H_2$, $R_2 = OH$

153 $R_1 = \overset{+}{N}H_2$, $R_2 = H$



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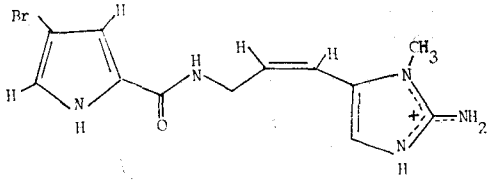
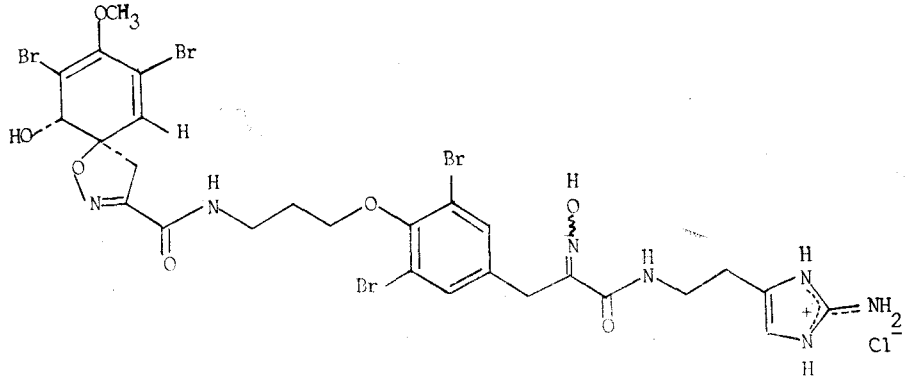


156

and vasodilative activities. Unusual nucleosides are not unprecedented in marine organisms. Sponges, nudibranchs, an acorn worm, and a red alga all gave unusual nucleosides which have potent biological or physiological effects.[93] Two novel nucleosides **152** and **153**, which were obtained from the marine sponge ***Geodia baretti***, exhibited strong contractile activity in the ileum assay.[93]

Sterols and pyrrole metabolites are common metabolites in marine sponge. Two immunosuppressive sterol (**154**) and pyrrole (**155**), which have previously been reported, were isolated from a deep water marine sponge ***Agelas flabelliformis.***[94] Nakamura *et al.* report the isolation and structure determination of a new antagonist of serotonergic receptors named keramadine (**156**) from *Agelas* sp.[95] Purealin (**157**) is a novel enzyme activating metabolite of ***Psammaplysilla purea*** that inhibits Na, N-ATPase and myosin Ca-ATPase, while it activate myosin K, EDTA-ATPase.[96]

Ten new quinolizidine alkaloids[97a,b] named araguspongines A, B(**158**), C(**159**), D(**160**),



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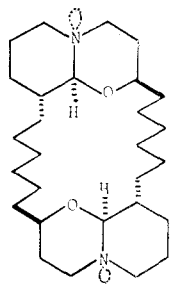

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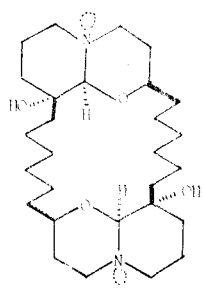

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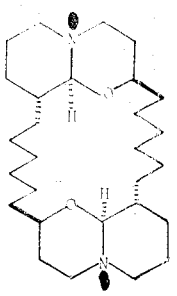

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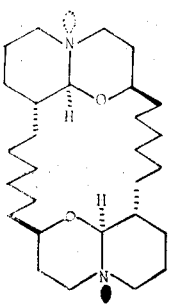

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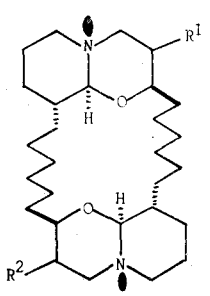
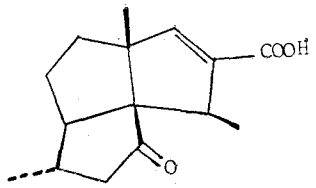


	R^1	R^2
162	α-CH_3	H
163	β-CH_3	H
164	β-CH_3	α-CH_3
165	β-CH_3	β-CH_3



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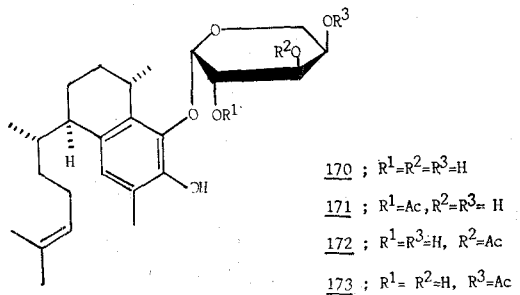
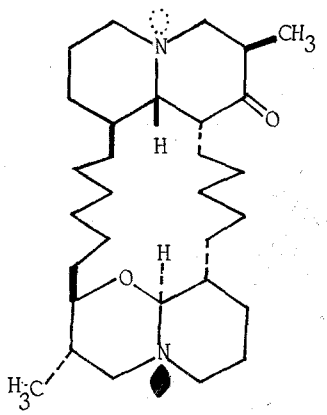


170 ; $R^1=R^2=R^3=H$
171 ; $R^1=Ac, R^2=R^3=H$
172 ; $R^1=R^3=H$, $R^2=Ac$
173 ; $R^1=R^2=H$, $R^3=Ac$



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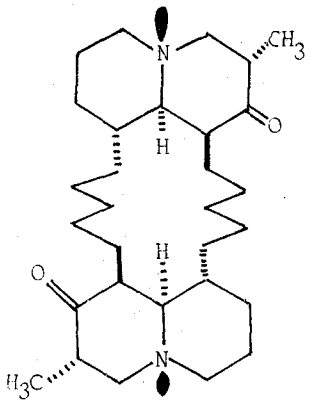

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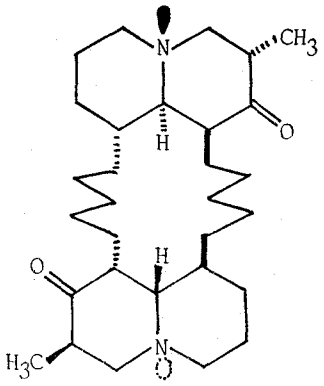

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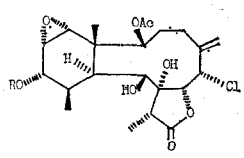
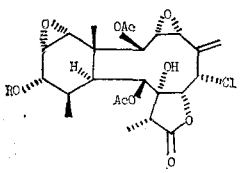
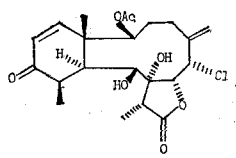


174 R = $C_5H_{11}CO$
175 R = CH_3CO



176 R = H
177 R = Ac



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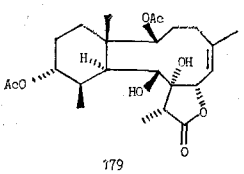


179

E(**161**), F(**162**), G(**163**), H(**164**), J(**195**), and aragupetrosine A(**166**) together with known alkaloids, petrosion (**167**) and petrosin A(**168**) were isolated from *Xestospongia* sp..

Aragupetrosine A(**166**) shows vasodilative activity as well as araguspongines, and petrosin (**167**) and petrosin A(**168**) show two times stronger vasodilative activities than papaverine in the perfusion model experiment using an isolated mesenteric artery of SD-rat.

4) Coelenterates

Subergorgic acid (**169**) having a new tricyclo [6, 3, 0, $0^{1,5}$] undecane (angular triquinane) skeleton was obtained from the gorgonian coral *Subergorgia suberosa*[98] and showed cardiotoxic properties that inhibited neuromascular at threshold levels as low as 0.16 μg/ml.

In region of southern China, many marine invertebrates were used as traditional medicines for a variety of diseases including those producing inflammation and pain.[99] The seco-pseudopterosins A-D(**170**~**173**) are new class of diterpene pentosides that were isolated from the gorgonian coral *Pseudopterogorgia* sp.,[100] which possess anti-inflammatory and analgesic proper-

ties.

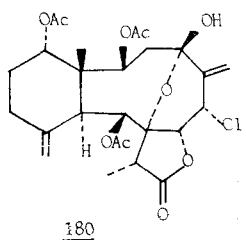
Diterpenoids of the briarane class have been investigated extensively because of their relatively complex structures and potent biological activities. The related gorgonian corals[101] contains briarane diterpenoids, solenolides A～F(**174**～**179**) and junceellolides A～D(**180**～**183**), which possess potent anti-inflammatory properties.

Acalycixeniolides B′(**184**) and C(**185**),[102] which are xenicane-type norditerpenes with a terminal allene, have been isolated from the gorgonian *Acalycigorgia* sp. together with the previously reported ginamallene[103] as cytotoxic agents and inhibitors of cell division of fertilized sea urchin eggs.

A xenicane diterpene **186** derived from *Xenia garciae* was shown to inhibit the growth of the alga *Ceramium codii*, a common benthic fouling organism.[104]

A novel steroidal glycoside **187** from the soft coral *Sinularia crispa* showed spermatostatic activity on rat cauda epididymal spermatozoa at 0.5 mg/ml.[105]

5) Tunicates



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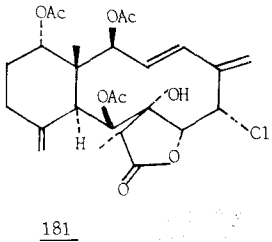

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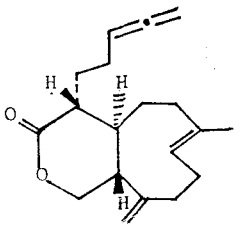

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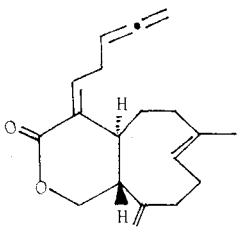

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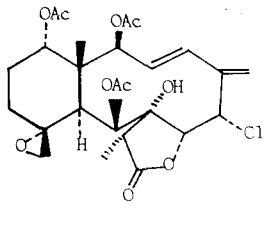

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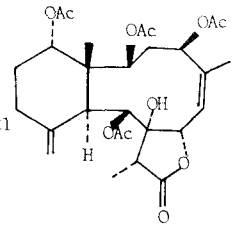

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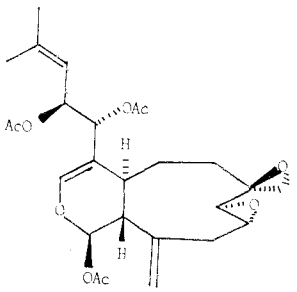

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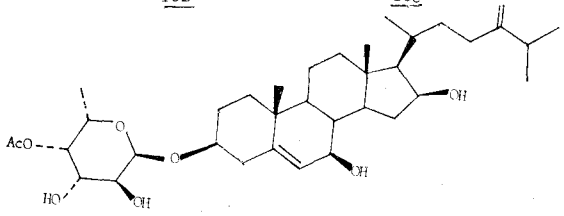

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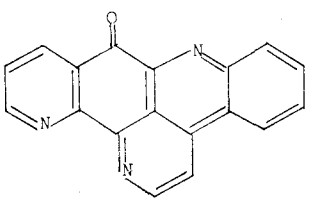

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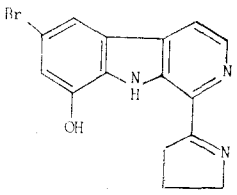

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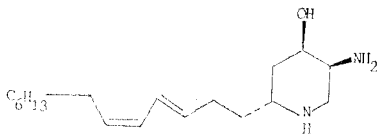

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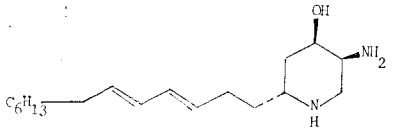


190

Tunicates have proven to be a good source of pharmacologically active indole, piperidine, and aromatic alkaloids. Calmodulin antagonists have been very useful as tools for studying physiological functions of calmodulin, a ubiquitous Ca^{2+}-binding protein which acts as a major mediator regulating cellular function and a variety of cellular enzyme system. Eudistomidin-A(**188**), a novel indole alkaloid having calmodulin antagonistic activity, has been isolated from *Eudistoma glaucus*.[106] The tunicate *Pseudodistoma kanoko* produces two novel calmodulin-antagonistic piperidine alkaloids, pseudodistomins A(**189**) and B(**190**), that have antineoplastic activity.[107]

A pentacyclic aromatic alkaloid, ascididemin (**191**), was seven times more potent than caffeine, a well-known Ca-releaser, in the Ca-releasing activity in sarcoplasmic reticulum and cytotoxic against L1210 murine leukemia cells *in vitro*, which was obtained from *Didemnum* sp..[108] Sato *et al.* report the isolation, synthesis and antioxidant activities of the active metabolites, one chromene(**192**) and two hydroquinones (**193** and **194**), from *Amaroucium multiplicatum*.[109]

6) Miscellaneous organisms

The ovothiols A∼C(**195**∼**197**) are a family of 4-mercaptohistidine derivatives that are abundant in the eggs of marine invertebrates.[110] Total synthesis of ovothiols A∼C, which was recently suggested to function as biological antioxidants, have been reported.[111] Several prostaglandin lactones have been synthesized and reported represent a therapeutically useful class of antifertility agents.[112] Three prostaglandin-1, 15-lactones (**198**∼**200**) have been obtained for the first time from a natural source, the nudibranch mollusc *Tethys fimbria*.[113]

These compounds add to the list of modified marine prostanoids[114] and their biological role is of interest.

4. Cytotoxic and antitumor substances

Many of the amazing of compounds already elicited from marine organism have never been tested for biological activity or pharmaceutical potential. As the search for biological activity in marine organisms widens and the screening-methods become more selective, the probability of finding specific compounds with good pharmaceutical potential will increase. With the promise of free, rapid, more extensive *in vitro* screening by the NCI, and the evolution of simple systems of testing for cytotoxicity, the opportunity for marine natural products to be screened for anticancer potential is greatly increased.

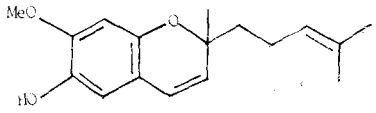
In the literature describing naturally occurring growth inhibitory compounds the terms *in vitro* and *in vivo* activity are often used loosely, or even incorrectly. In order to eliminate confusion in the literature the NCI has defined these terms precisely.

Cytotoxicity should only refer to toxicity to (tumor) cells in culture. Terms such as antitumor, anticancer, or antineoplastic should not be used in referring to *in vitro* results. For *in vivo* activity in experimental systems the terms antitumor or antineoplastic should be used, and term anticancer is reserved for reporting data from clinical trails in humans.

The natural products listed below have been grouped along biogenetic lines.

1) Terpenoids and steroids

Neomeris annulata is a diminutive calcareous green alga widely distributed in the shallow, inshore waters of Bermuda. Three new cytotoxic and phytotoxic monobrominated sesquiterpene alcohols (**201**-**203**), which are the first report of halogenated sesquiterpenes from a green alga and the first association of phytotoxicity with marine terpenoids, have been isolated from above alga.[115] LD_{50} values were determined for **201**, **202**, and **203** to be 9, 8, and 16 μg/ml, respe-



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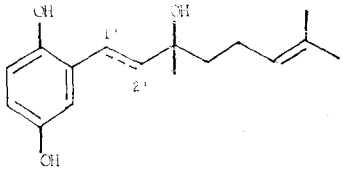
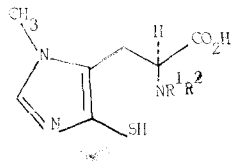
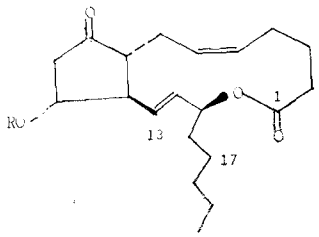


193 : C-1'-C-2'= single bond

194 : C-1'-C-2'= E double bond



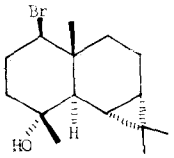
	R^1	R^2
195 :	H	H
196 :	CH_3	H
197 :	CH_3	CH_3



198 : R = Ac, Δ^{17} Z

199 : R = H

200 : R = H, Δ^{17} Z



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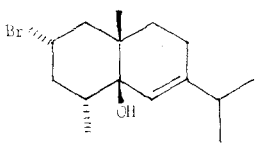

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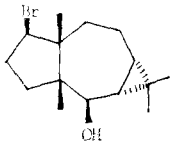

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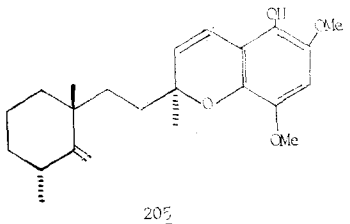

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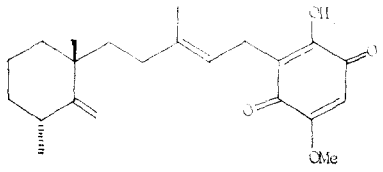

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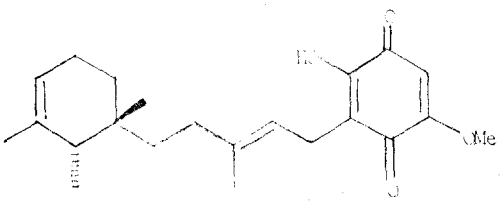

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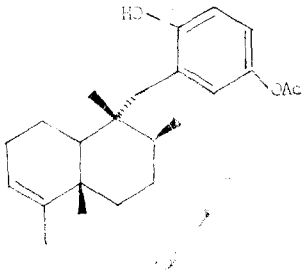


207

ctively. The purple-colored sponge *Hippospongia metachromia* contains novel cytotoxic sesquiterpenoid quinones (**204** and **206**) and a chromenol (**205**), named metachromins A, C, and B, respectively.[116a,b]

Metachromins A(**204**), B(**205**) and C(**206**) exhibited potent cytotoxic activity against L1210 murine leukemia cells *in vitro* with the IC_{50} values of 2.40, 1.62, and 2.0 μg/ml, respectively. Each compounds also showed potent coronary vasodilating activity, markedly inhibiting KCl (40 mM) induced contraction of the rabbit isolated coronary artery with an IC_{50} value of 3×10^{-6} M each.

A new sesquiterpene hydroquinone, monoacetyl avarol (**207**), which was obtained as minor secondary metabolite of the sponge *Dysidea avara*, have been reported to have cytotoxic activity.[117] Nephtheoxydiol (**208**) having a hydroperoxy function and several related germacrane sesquiterpenoids were isolated from the soft coral of *Nephthea* sp..[118] Nephtheoxydiol (**208**) was found to exhibit a significant growth inhibitory effect on B-16 melanoma cells (IC_{50} 0.1 μg/ml).

The brown alga *Turbinaria ornata* produces a secosqualene carboxylic acid, turbinaric acid (**209**), that exhibits cytotoxicity against murine melanoma and human colon carcinoma cells at 26.6 and 12.5 μg/ml, respectively.[119]

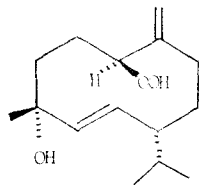
This is the first report of the isolation of this acid from natural sources. From the marine red alga *Laurencia obtusa*, a cytotoxic diterpene, 15-bromo-2,7,16,19-tetraacetoxy-9(11)-parguerene(**210**) was isolated and its absolute stereostructure was established by spectral and chemical evidences as well as X-ray crystallographic method.[120] The marine soft coral *Sclerophytum capitalis* was found to contain six new diterpenes designated sclerophytin A-F.[121] Among them, sclerophytin A(**211**) shows cytotoxic activity against L1210 cell line at a 1×10^{-6} mg/ml level. New cytotoxic cembranoids, denoted as kericembrenolides A-E(**212-216**)[122] and bipinnatins a-d(**217-220**),[123] have been isolated from the soft coral *Clavularia koellikeri* and the gorgonian coral *Pseudopterogorgia bipinnata*, respectively.

Chromodorolide A(**221**) is a rearranged spongian diterpene with a new carbon skeleton from the nudibranch *Chromodoris cavae*[124] and displays both cytotoxic and antimicrobial activities. Sponges of the order Dictyoceratida have been a rich source of new sesterterpenes, many of which contain both furan and tetronic acid functional group.[125] Four new cytotoxic furanosesterterpene tetronic acids (**222-225**) oxygenated at C-5 have been isolated from the sponge *Ircinia* sp. (Dictyoceratida).[126]

The 19-hydroxylated sterol is not particularly common in nature. The novel 19-oxygenated sterol, 5,6-epoxylitosterol (**226**) from the soft coral *Litophyton viridis*, shows an antileukemic activity (IC_{50} 0.5 μg/ml) against P338 leukemia cells *in vitro*.[127] The Red Sea sponge *Erylus lendenfeldi* contains a new 4-methylated steroidal glycoside named eryloside A(**227**),[128] which is responsible for the antitumor against P388 (IC_{50} 4.2 μg/ml) and antifungal activity against *Candida albicans* (MIC=15.6 μg/ml).

2) Prostanoids

The prostaglandins (PG) form a class of natural products with diverse and potent biological activities. They have been known as autacoids occurring in various terrestrial animal organs and in recent years shown to be distributed also in marine life. Promising antitumor activity has been shown by a number of marine prostaglandins isolated from octocorals. Kitagawa *et al.*[129] reported the isolation of claviridenone-a (**228**) and its geometrical isomers (clavulones) at 5,7-diene moiety, as well as two sorts of 20-acetoxy derivatives from the soft coral *Clavularia viridis*.[130]



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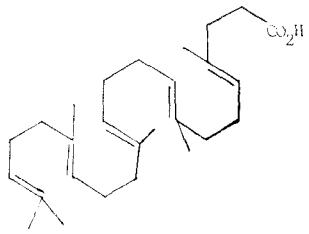

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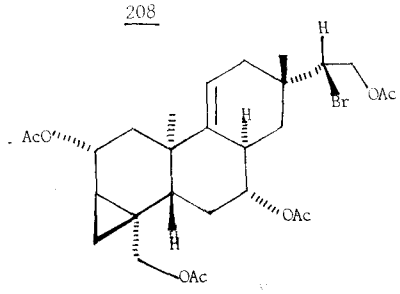

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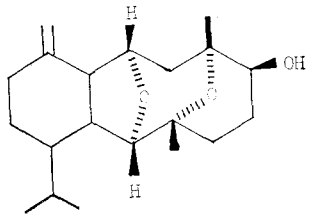

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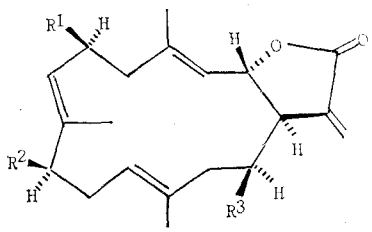
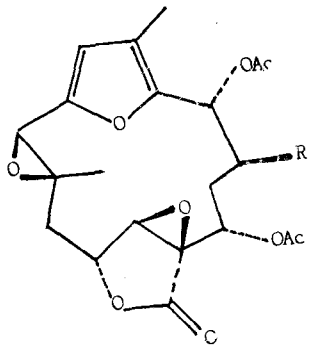
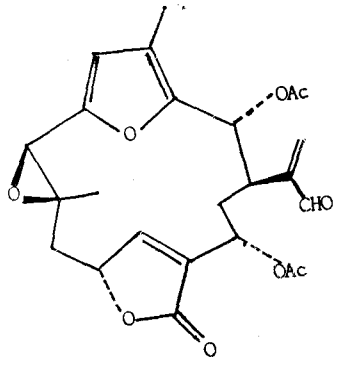


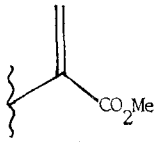
	R1	R2	R3
212 :	OAc	H	H
213 :	H	OAc	H
214 :	OAc	H	OAc
215 :	OAc	H	OH
216 :	OH	H	OH





220

R =



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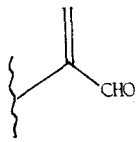

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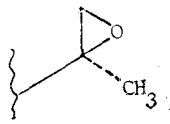

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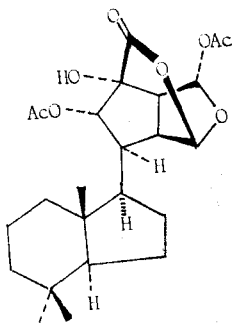

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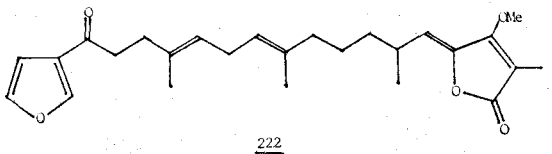

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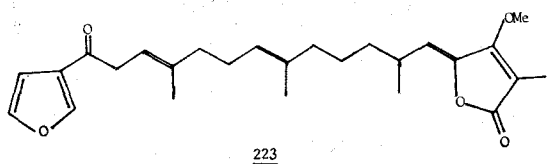

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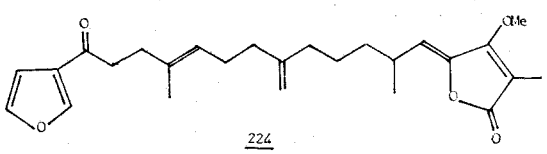

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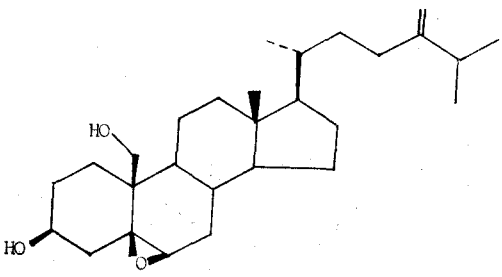

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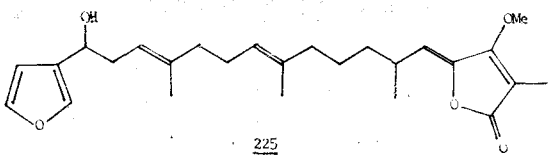

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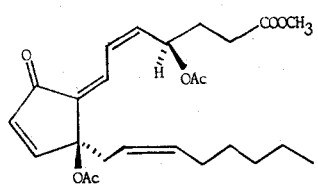

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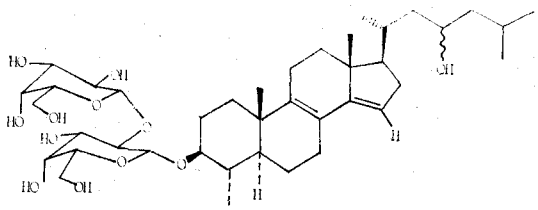

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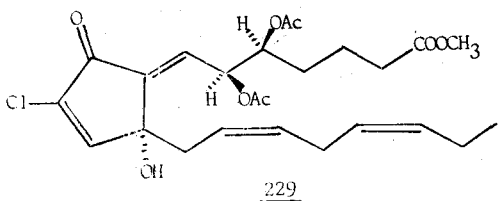

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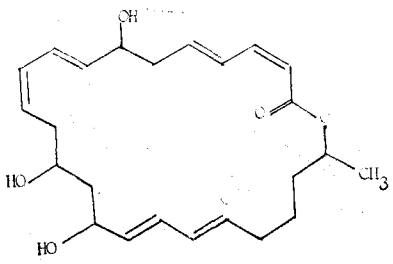

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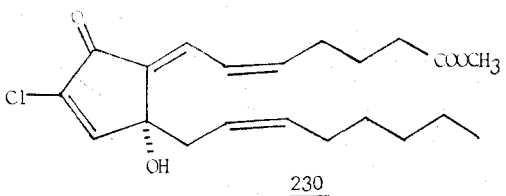


230

Claviridenones were found to exhibit significant cytotoxicity (IC_{50} 0.2～0.4 μg/ml for L1210) and antitumor activity (P388 and Ehrlich ascites). Scheuer *et al.* obtained a series of even more potent eicosanoids, the punaglandins from the octocoral *Telesto riisei.*[131] The punaglandins are characterized by the C-10 chlorine and C-12 hydroxyl functions.

One of them, punaglandin-3 (**229**), inhibited L1210 leukemia cell proliferation with an ED_{50} value of 0.02 μg/ml. This remarkable cytotoxicity is a approximately equal to that of vincristine and doxorubicin, some of the most effective anticancer agents now in use. Recently, synthesis and structural revision of punaglandin-4 has been reported.[131] An additional series of C-10 chloro-eicosanoids, chlorovulone I(**230**) was obtained from *Clavularia viridis.*[132]

Chlorovulone I(**230**) showed strong antiproliferative activity in human promyelocytic leukemia (HL-60) cells *in vitro* (ED_{50} 0.01 μg/ml).

3) Polyethers

Eight new secondary metabolites, macrolactins A-F and macrolactinic and isomacrolactinic acids, have been isolated from the culture broth of an apparently taxonomically unclassifiable marine bacterium.[133] Among them, macrolactin A(**231**) shows selective antibacterial activity and inhibits B16-F10 murine melanoma cancer cell replication with *in vitro* IC_{50} values of 3.5 μg/ml.

Further, macrolactin A(**231**) is a potent inhibitor of *Herpes simplex* type I virus (strain LL), as well as type II virus (strain G) with IC_{50} values of 5.0 and 8.3 μg/ml, respectively and protects T-lymphoblast cells against human HIV viral replication (maximum protection at 10 μg/ml).

A cultured symbiotic dinoflagellate *Amphidinium* sp., which was isolated from a flatworm *Amphiscolops* sp., contains cytotoxic macrolides amphidinolide A-D.[134a,b] Amphidinolide D(**232**) exhibited potent cytotoxicity against L1210 murine leukemia cells *in vitro* with IC_{50} value of 19 ng/ml.

Amphidinolide B, which is stereoisomer of **232** at C-21 and is revised to **233**, is 100 times as active as amphidinolide D(**232**), suggesting that the stereochemisty at C-21 is important for the activities of these compounds.

Marine sponges have proved to be a rich source of macrolides possessing potent antitumor or cytotoxic activity. A total of 8 antitumor polyether macrolides, halichondrins, have been obtained from the sponge *Halichondria okadai.* A most potent analog, halichondrin B (**234**), exhibited strong cytotoxicity (IC_{50} 0.093 ng/ml) and remarkable antitumor activity (T/C 244% at 5 μg/kg) against B-16 melanoma.[135]

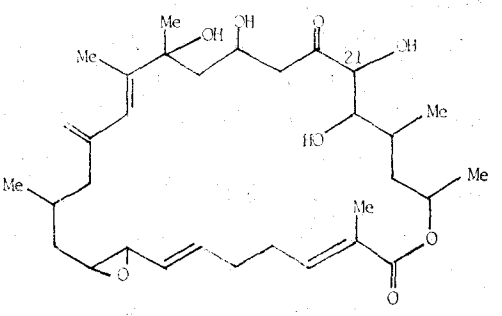
Fusetani *et al.*[136] have isolated from the sponge *Mycale* sp. three cytotoxic macrolides, named mycalolides A-C (**235-237**), related to kabiramides,[137] halichondramide (**34**),[18] and ulapualide (**238**).[138] Mycalolides A-C (**235-237**) possessing a trisoxazole unite are antifungal against many pathogenic fungi and cytotoxic against B-16 melanoma cells with IC_{50} s' of 0.5～1.0 ng/ml. Ulapualide A (**238**) that was isolated from egg-masses of Hawaiian mollusc *Hexabranchus sanguineus* shows cytotoxic activity against L1210 leukemia cells (IC_{50} 0.01～0.03 μg/ml).

The marine sponge *Discodermia calyx* contained calyculins A-D,[139] which are extraordinary spiro-ketals containing an unusual array of functional groups such as amide, oxazole, phosphate, and nitrile moieties as well as a tetraene system bearing vicinal dimethyl groups. Among them, calyculin A(**239**) was also highly cytotoxic to tumor cells (IC_{50} of 1.75 ng/ml against L1210).

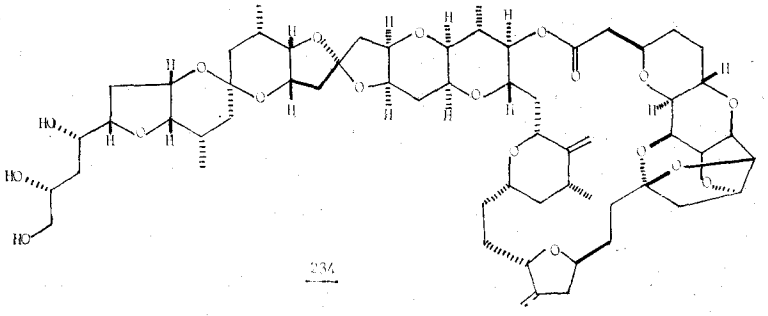
Since Pettit *et al.* found that extracts from the cosmopolitan bryozoan *Bugula neritina* were significantly active against the murine P388

lymphocytic leukemia. A total of 13 related bryostatins of known structure, which differ only in their C-7 and C-20 substituents, have been obtained from *B. neritina* to date.[140] Some of bryostatins have also been isolated from the marine sponge *Lissodendoryx isodictyalis*[141] and the marine ascidian *Aplidium californicum*.[142]

All of the bryostatins display impressive activity in both the *in vivo* and *in vitro* P388 screens (Table 1). Bryostatin-1(**240**) activates protein kinase C and prevents phorbol-ester-



232 / 233 } epimers at C-21



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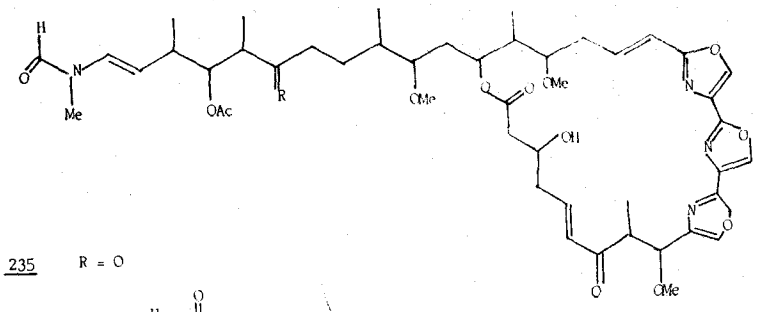
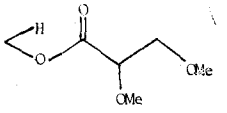
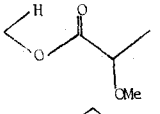
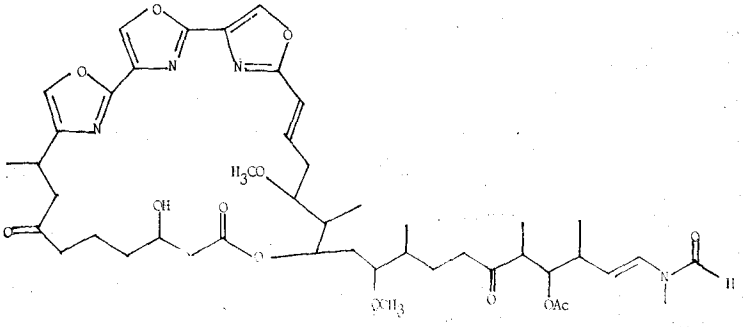


235 R = O

236 R = 

237 R = 



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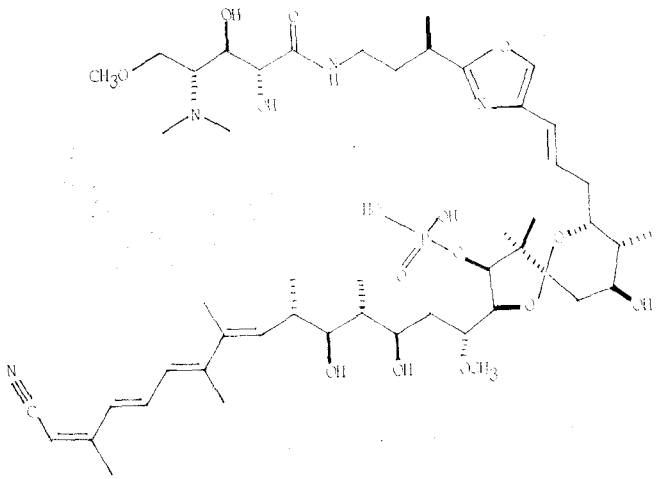

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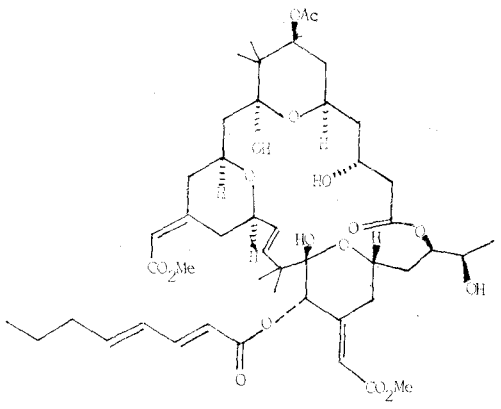

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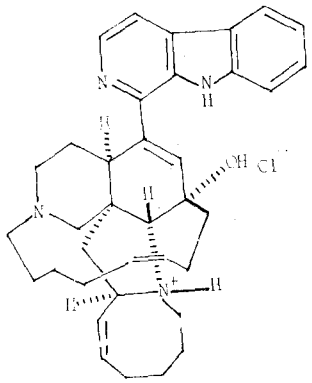

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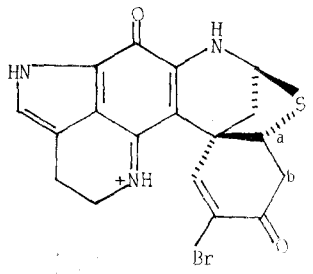
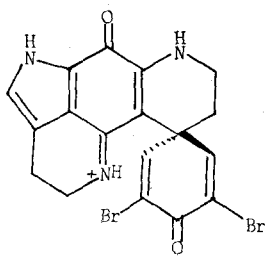


242 ab=satd. bond

243 ab=unsatd. bond



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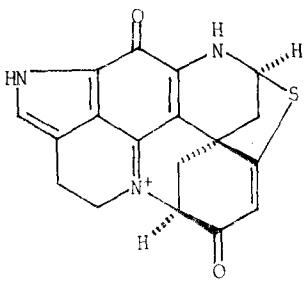

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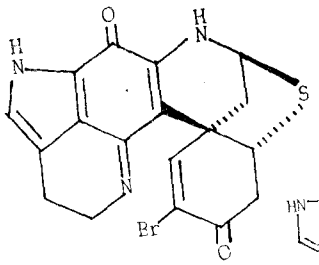

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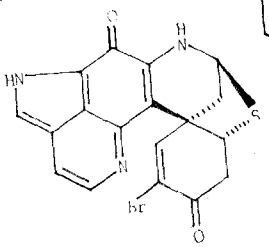

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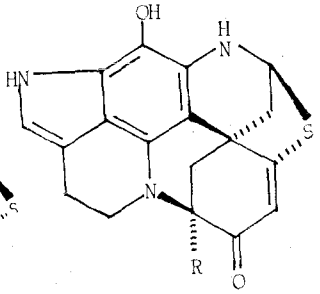
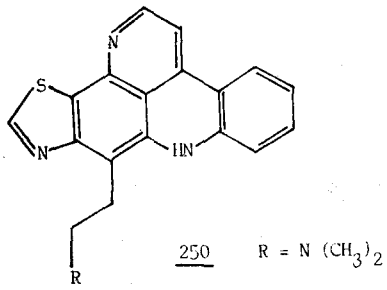


248 R = OH

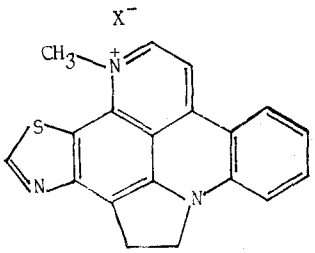
249 R = H



250 R = N $(CH_3)_2$

251 R = $NHCH_3$

252 R = $NHCOC_2H_5$



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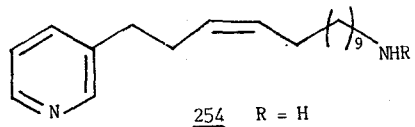
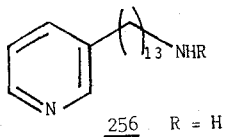


254 R = H

255 R = CH_3



256 R = H

257 R = CH_3

Table 1. P388 activity of the bryostatins[140]

Bryostatin	P388 Lymphocytic leukemia	
	In vivo % Life extension/ dose(μg/kg)	*In vitro* ED_{50}(μg/ml)
1(**240**)	52~96/10~70	0.89
2	60/30	—
3	63/30	—
4	62/46	10^{-3}~10^{-4}
5	88/185	1.3×10^{-3}~2.6×10^{-4}
6	39~82/46~185	3.0×10^{-3}
7	77/92	2.6×10^{-5}
8	74/110	1.3×10^{-3}
9	64/92.5	1.2×10^{-3}
10	—	7.6×10^{-4}
11	64/92.5	1.8×10^{-5}
12	47~68/30~50	1.4×10^{-2}
13	—	5.4×10^{-3}

induced differentiation in HL-60 cells.[143]

Although both bryostatins and phorbol esters activate protein kinase C, the cellular responses are not the same.[144] Because of attractive stereostructural features, anticancer properties, and relative scarcity, synthetic approaches to the bryostatins appear to be well under way.[145]

4) Alkaloids

Unique alkaloids, manzamines A~C, were isolated from a marine sponge *Haliclona* sp..[146] The structure of manzamine A hydrochloride (**241**) is determined by X-ray analysis, and is identical to that of keramamine-A, which was isolated from a species of *Pellina*.[147] Manzamine A hydrochloride(**241**) inhibited the growth of P388 mouse leukemia cells with IC_{50} of 0.07 μg/ml. Discorhabdins A~D(**242~245**) were isolated as the major cytotoxic pigments of three different *Latrunculia* and *Prianos* sponge species.[148] The discorhabdins A~C(**242~244**) are powerful cytotoxins with IC_{50} values against the P388 cell line in the range 0.03~0.01 μg/ml but in the *in vivo* P388 model were found to be inactive (T/C<120%).

While, discorhabdin D(**245**) had a lower *in vitro* activity against P388 (IC_{50}' 6 μg/ml) but in contrast was considered to have significant *in vivo* P388 activity (T/C 132% at 20 mg/kg). Similar sulfur-containing alkaloids, prianosins A~D(**246~249**), were obtained from the marine sponge *Prianos melanos*.[149] Prianosins A~D (**246~249**) were cytotoxic against murine lymphomas L 1210, L 5178Y cells and human epidermoid carcinoma KB cells *in vitro* with the IC_{50} values of 0.037, 0.014, and 0.073 μg/ml

for **246**, 2.0, 1.8, and>5.0 μg/ml for **247**, 0.15, 0.024, and 0.57 μg/ml for **248**, and 0.18, 0.048, and 0.46 μg/ml for **249**, respectively.

In addition, prianosin D(**249**) induced Ca^{2+} release from sarcoplasmic reticulum, 10 times more potent than caffeine in this assay.

Fused ring alkaloids having the pyrido[4,3,2-mn] acridine skeleton named nordercitin (**250**), dercitamine (**251**), dercitamide (**252**), and cyclodercitin (**253**) were reported as metabolites of two deep marine sponges *Dercitus* sp. and *Stelletta* sp..[150] All compounds (**250**～**253**) inhibited proliferation of P388 murine leukemia cells *in vitro* and compounds (**250**～**252**) also exhibited immunosuppressant activity. Pyridine-derived compounds from marine origins are very few, and theonelladins A～D(**254**～**257**) from *Theonella swinhoei* are the first pyridine alkaloids from the sponge of the *Theonella* genus.[151]

Theonelladins A～D(**254**～**257**) exhibited potent antineoplastic activity against murine lymphomas L1210[IC_{50}=4.7 (**254**), 1.0 (**255**), 3.6 (**256**), and 1.6(**257**) μg/ml] cells and human epidermoid carcinoma KB[IC_{50}=10(**254**), 3.6 (**255**), 10(**256**), and 5.2(**257**) μg/ml] cells *in vitro*.

These compounds all also showed powerful Ca^{2+}-releasing activity from sarcoplasmic reticulum, being twenty times more potent than caffeine, a well-known Ca^{2+} inducer. The hemichordate marine worm *Cephalodiscus gilchristi* contained unique disteroidal alkaloids named cephalostatins 1～4, of which cephalostatin 1(**258**) was a powerful inhibitor of the murine P388 lymphocytic leukemia cell line, with a 50% max. ED of 10^{-7}～10^{-9} μg/ml. [152a,b]

The variety of nitrogeneous natural products obtained from tunicates(ascidians) portrays these marine animals as specialists in the production of unusual alkaloids. A wide variety of alkaloids which possess a fused tetracyclic heteroaromatic skeleton and α-carboline have recently been reported from tunicates.

Examples include the varamines A(**259**) and B(**260**) from *Lissoclinum vareau*,[153] diplamine (**261**) from *Diplosoma* sp.,[154] and grossularines-1 (**262**) and-2(263) from *Dendrodoa grossularia*.[155] Varamines A(**259**), B(**260**), and diplamine (**261**) are shown to be cytotoxic towards L1210 murine leukemia cells with IC_{50}'s of 0.03, 0.05, and 0.02 μg/ml, respectively. Diplamine (**261**) is also antimicrobial against *E. coli* and *S. aureus*. Grossularines-1(**262**) and-(**263**) are cytotoxic toward L1210 leukemia cells : ID_{50} respectively 6 and 4 μg/ml.

5) Peptides

Several peptides showing cytotoxic and/or antitumor properties have recently been isolated from marine organisms. Of which, I have been shown typical examples in this section of the review. Jasplakinolide(jaspamide, **264**) is a novel bioactive 19-member macrocyclic ketide-cyclodepsipeptide isolated from the marine sponge *Jaspis* sp. and has previously been reported by several groups.[156]

Jasplakinolide(**264**) has potent *in vitro* cytotoxicity against tumor cells (P388 and KB:IC_{50}'s =0.01 and 0.1 μg/ml, respectively) and high ichthyotoxicity. Pettit and his coworkers described the isolation and preliminary characterization of a series 13 peptides present in the sea hare *Dolabella auricularia* in very low concentration.[157] Interestingly, dolastatin 13 (**265**), which is most recently isolated from *D. auricularia*, appears only remotely related to the cyclodepsipeptides dolastatins 11 and 12 and not at all to the previous peptides [dolastatins 1, 2, 3, and 10(**266**)].

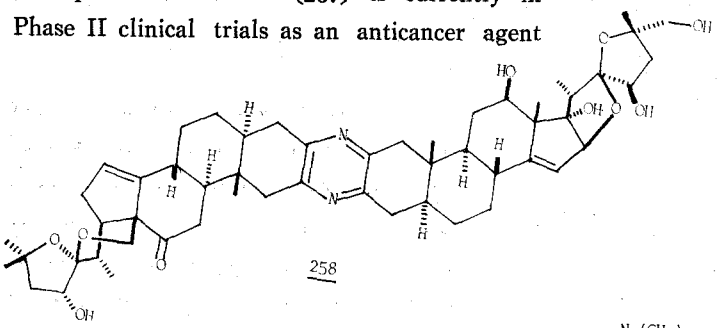
Dolastin 13(**265**) shows strong growth inhibition of the PS cell line exhibiting an ED_{50} of 0.013 μg/ml.

The absolute stereostructructure of natural (−)-dolastatin-10(**266**), which is believed to the most potent antineoplastic substance known

to date, is determined by the total synthesis.[158] Synthetic dolastin 10(**266**) also exhibited the same level (ED_{50} 10^{-4} μg/ml) of activity against the P388 lymphocytic leukemia as routinely obtained with the natural product.

The didemnins A~E isolated from a tunicate of the ***Tridemnum solidum*** are the most promising compounds from marine organism.[159]

A series of cyclic depsipeptides, dedemnins A~E, possess significant antiviral, immunosuppressive, and antitumor activities. Among them, most potent didemnin B(**267**) is currently in Phase II clinical trials as an anticancer agent in NCI. A variety of cyclic peptides exhibiting to potent cytotoxicity and ***in vivo*** antitumor activity have been isolated from one species of tunicate, ***Lisoclinum patella***, with some metabolite variation being observed with variation in collection site.[160] Ulithiacyclamide (**268**) conta ining thiazole and disulfide bridge in its cyclic backbone has been synthesized by Shioiri group,[161] which inhibited L1210 leukemia cells and the human All cell line (T cell acute



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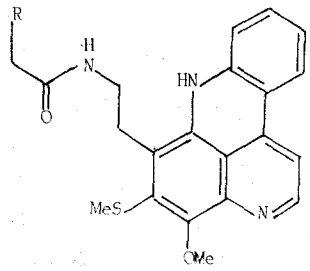
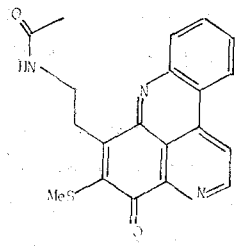


259 R = Me
260 R = H



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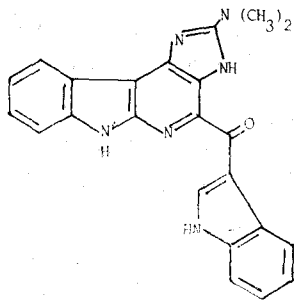

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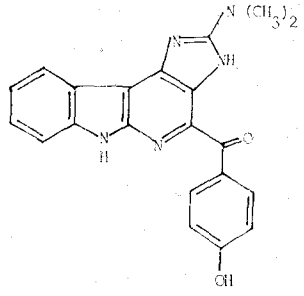

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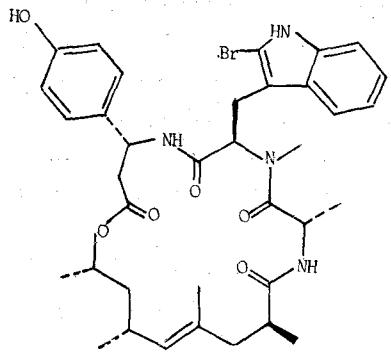

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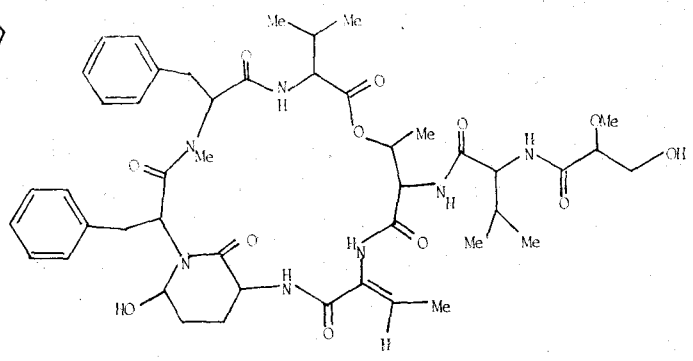

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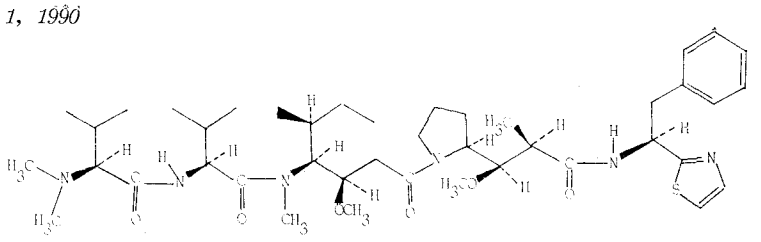

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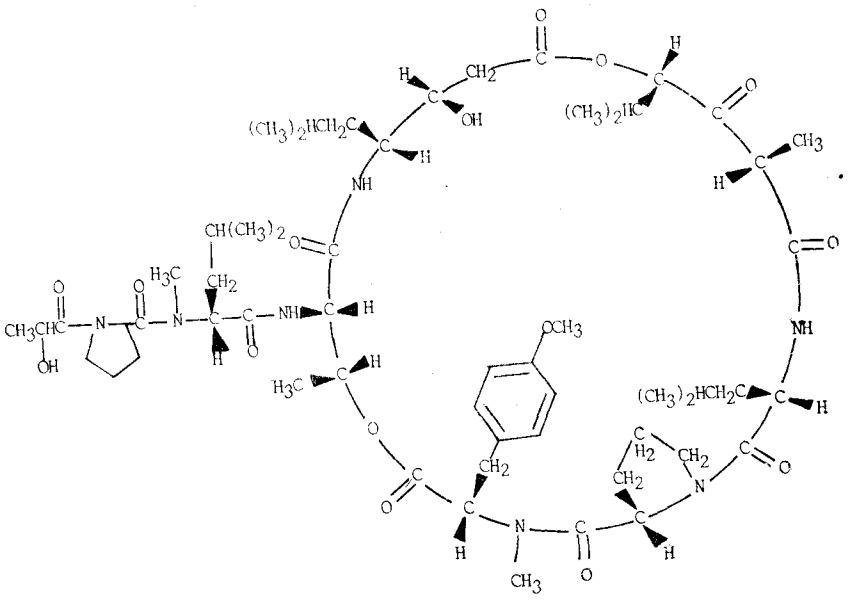

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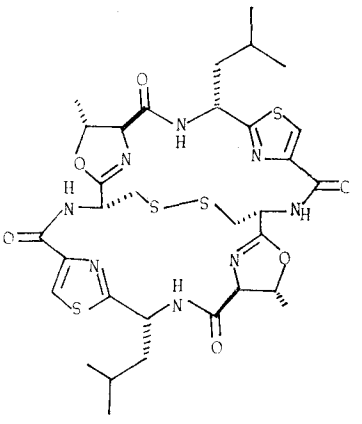


268

leukemia) CEM with ED_{50} values of 0.35 and 0.01 μg/ml, respectively.

Four new cyclic peptides, patellamide D(**269**) and lissoclinamides 4～6(**270**～**272**) from *L. patella* also showed marginal cytotoxicity against lymphocytic leukemia cells (PS) (ED_{50} values for **269**～**272** are 11, 12, 10, and 6.9 μg/ml, respectively).[160]

6) Miscellaneous metabolites

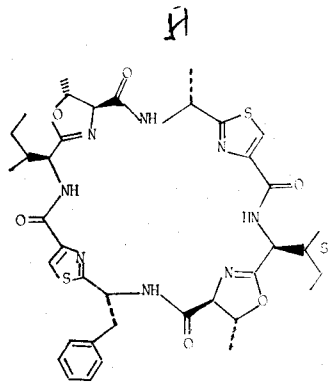
A novel cytotoxic styrylchromone, hormothamnione (**273**) was isolated from the marine cyanophyte *Hormothamnion enteromorphoides* and its structure determined by an X-ray experiment on its triacetate derivative.[162]

Hormothamnione (**273**) was found to be a potent cytotoxic agent to P388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cell lines with ID_{50} values of 4.6 and 0.1 ng/ml, respectively. A major mode of cytotoxic action of hormothamnione appears to be by inhibition of RNA synthesis.

A symmetrical acetylenic lipid, duryne (**274**), was isolated as the cytotoxic agent from the sponge *Cribrochalina dura*.[163] Duryne (**274**) inhibits the growth of P388 murine leukemia (IC_{50} 0.07 μg/ml) and of colon (HCT-8), lung (A549), and mammary(MCF-7) human tumor cell lines (IC_{50} 0.1 μg/ml, respectively).

Four new cytotoxic cyclic peroxides (**275** and its 3 analogs) were obtained from the sponge *Plakortis lita*.[164] All exhibited significant antileukemic activity against P388 (IC_{50} 0.05～0.1 μg/ml).

The marine sponge *Dysidea fragilis* contains



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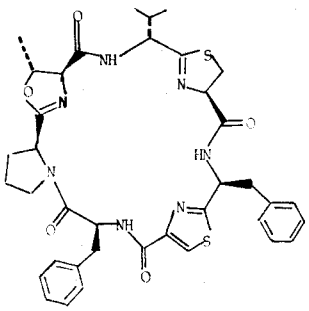

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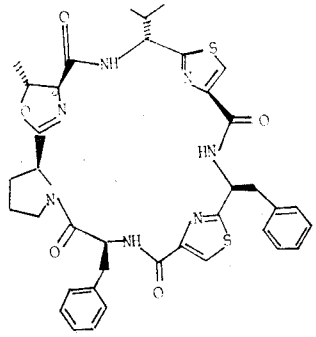

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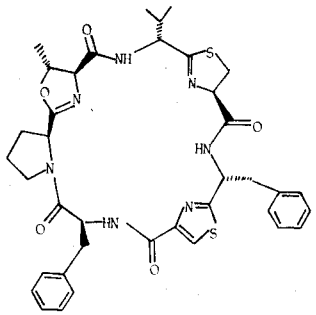

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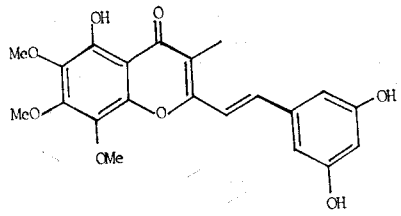

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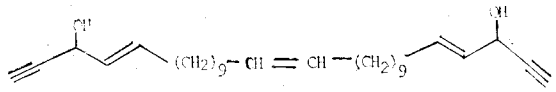

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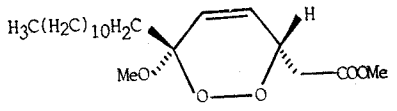

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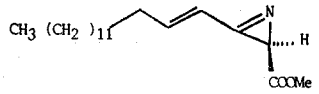

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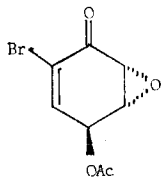

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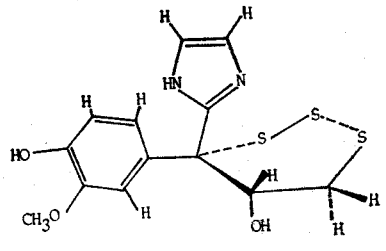

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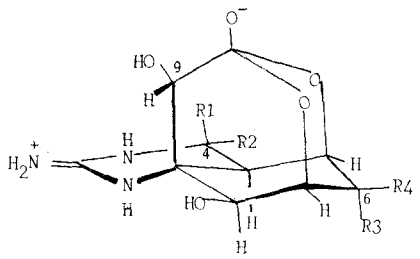
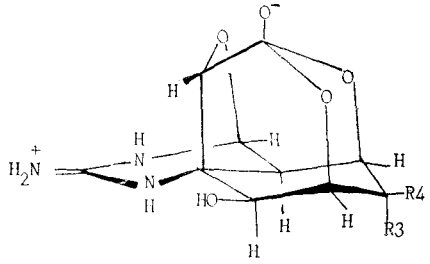
a novel azacyclopropene named dysidazirine (**276**), which is cytotoxic to L1210 cells at 0.27 μg/ml and inhibits the growth of Gram negative bacteria (*P. aeruginosa*) and yeast (*C. albicans*, *S. cerevisiae*) at a minimum concentration of 4 μg.[165]

A new species of *Ptychodera* (acorn worm) has yielded five new brominated metabolites, of which the epoxide (**277**) shows activity against P388(IC_{50}=10 ng/ml) *in vitro*.[166] 1,2,3-Trithiane derivative (**278**), which was obtained from the ascidian *Aplidium* sp., are active against P388 leukemia cells *in vitro* (IC_{50} 13±1μg/ml.)[167]

Marine Toxins

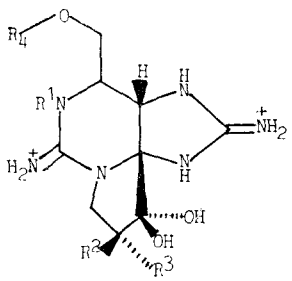
The excellent literatures have recently reviewed the area of marine toxins.[168,169] The majority of toxins that can be isolated from marine organisms are derived from food chain and symbiosis. But, in any classes of marine organism, there are also species which produce





	R^1	R^2	R^3	R^4
279	H	OH	OH	CH_2OH
280	OH	H	OH	CH_2OH
282	H	OH	CH_2OH	OH
284	H	OH	OH	CH_3
285	OH	H	OH	CH_3
287	H	OH	H	OH
288	H	OH	OH	$CH(OH)_2$

	R^3	R^4
281	OH	CH_2OH
283	CH_2OH	OH
286	OH	CH_3



	R_1	R_2	R_3	R_4
289	H	H	H	$CONH_2$
290	OH	H	H	$CONH_2$
291	OH	H	OSO_3^-	$CONH_2$
292	H	H	OSO_3^-	$CONH_2$
293	H	OSO_3^-	H	$CONH_2$
294	OH	OSO_3^-	H	$CONH_2$
295	H	H	H	$CONHSO_3^-$
296	OH	H	H	$CONHSO_3^-$
297	H	OSO_3^-	H	$CONHSO_3^-$
298	H	H	OSO_3^-	$CONHSO_3^-$
299	OH	H	OSO_3^-	$CONHSO_3^-$
300	OH	OSO_3^-	H	$CONHSO_3^-$
301	H	H	H	H

toxins for the capture of prey or for defence. These toxins belong predominantly to the following groups: seafood toxins(fish, shellfish), stinging or biting toxins (jellyfish, sea urchin, starfish, octopus, and fish *etc.*), dermatitis toxin (blue-green alga), red tide toxins, diving fish toxins, ciguatera toxins, and other several toxins. The search for marine toxins is very important in view point of not only pure scientific research but also disaster prevention, and also has a special value in Pharmaceutical viewpoints.

Some of these toxins(*e.g.*, tetrodotoxin and maitotoxin) are used as pharmacological tools essential for basic studies on Na^+ or Ca^{2+} ion channels because of their specific activities on ion channels.

In this article, I would like to describe with food poisonings recently reported as the central figure.

1. Tetrodoxins(TTX)

Tetrodotoxin(TTX, **279**), a potent neurotoxin first isolated from puffers and then from California newts, has recently been reported from various biota such as frog, goby, blue ringed octopus, ivory shell, crab, red alga, and marine bacteria.[170]

A bacterium of the genus *Pseudomonas* was isolated from the skin of the pufferfish *Fugu poecilonotus*.

The discovery that symbiotic bacteria produce tetrodotoxin(**279**) and its derivatives explains why these toxins have been isolated from so many unrelated host species.

Tetrodotoxin(**279**) and nine analogues (**280**～**288**) repoted to date[171] are important for use as a sodium channel blocker and for structure-activity relationships because chemical tansformations of TTX are difficult.

2. Paralytic shellfish poisons(PSP)

A group of paralytic shellfish poisons(PSP) represented by saxitoxin (STX, **289**) and gonyautoxin(GTX) is a causative agents of intoxication following ingestion of the toxic shellfish.

Saxitoxin(**289**), the paralytic agent first obtained from the Alaska butter clam *Saxidomas giganteus*, is one of the non-protein poisons known and it has also found widespread use in the study of various nerve disorders.

Its physiological action arises from a disruption of the propagation of impulses in skeletal muscles and nerves, a result due chiefly to a specific interference with the increase in sodium ion permeability normally associated with excitation.

Saxitoxin(**289**) and its analogs(**290**～**301**) have been isolated from a verious marine organisms including dinoflagellates, blue-green algae, bibalve, and crab. The distribution, chemistry, and biological significance of paralytic shellfish poisons have been reviewed in detail.[172a,b]

3. Diarrhetic shellfish poisons(DSP)

Diarrhetic shellfish poisoning(DSP) is a gastrointestinal disease resulting from ingestion of shellfish infested with dinoflagellate toxins.

The major symptom in patients is diarrhea and no human fatality has so far been reported.

Diarrhetic shellfish toxins(DST)[173] isolated from toxic bivalves may be classified three groups differing in basic skeleton such as okadaic acid (**302**) and dinophysistoxns (**303**, **304**), pectenotoxins(**305**～**308**), and yessotoxins (**309**, **310**).

Recently, Yasumoto group report the occurrence of okadaic acid(**302**), dinophysistoxin-1 (**303**) and yessotoxin(**309**) together with an unidentified toxin in Norwegian mussels,[174] and new analytical methods for determination of DST have been developed.[175]

4. Ciguatera toxins

Ciguatera is a food poisoning caused by a variety of fishes dwelling in coral reefs and poses serious problems to public health and fisheries in tropic or subtropic regions.

Although initially isolated in 1980 by Scheuer's group, however, the structure still remains unknown.

Chemical studies have been handicapped by the extreme difficulty in collecting toxic fishes as well as by the complexity of the structure.

Nevertheless, the structure of ciguatoxin (CTX, **311**), which has been isolated from the moray eel *Gymnothorax javanicus* collected in French Polynesia, was partially elucidated.[176]

5. Neurotoxic shellfish poisons (NSP)

Blooms of dinoflagellates commonly known as "red tide" have received much attention due to their toxic effects on the environment.

The dinoflagellate *Gymnodinium breve* is one of the red tide causing organism responsible for massive fish kills and human intoxications including the so-called neurotoxic shellfish poisoning (NSP).

Because of unprecedented structural feature of these potent neurotoxins, the unique mode of action on sodium channels,[177] and unusual biosynthetic pathway,[178] these compounds have been extensively investigated.

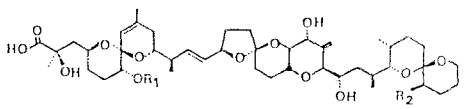
To date the structures of eight polyether-type toxins (**312**～**319**) have been established by X-ray crystallography and chemical and spectral correlations.[177]

6. Other seafood toxins

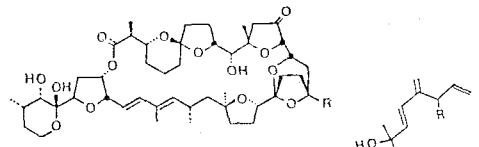
Neosurugatoxin (**302**) and prosurugatoxin (**321**) possessing antinicotinic activity were isolated from the toxic ivory shell *Babylonia japonica.*

These toxins account for half the total toxicity of the shell.

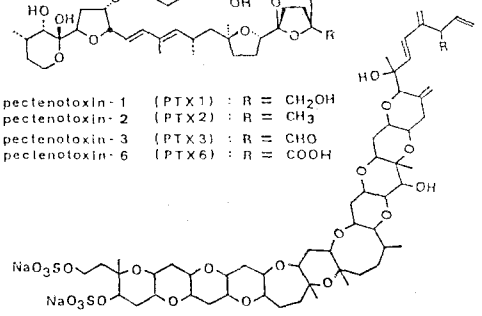
The structure of prosurugatoxin (**321**) was further confirmed by synthesis.[179]



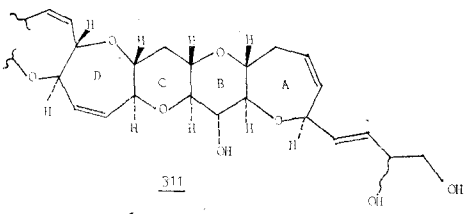
302 okadaic acid (OA) : R_1=H, R_2= H
303 dinophysistoxin-1 (DTX1) : R_1=H, R_2= CH_3
304 dinophysistoxin-3 (DTX3) : R_1=acyl, R_2 = CH_3



305 pectenotoxin-1 (PTX1) : R = CH_2OH
306 pectenotoxin-2 (PTX2) : R = CH_3
307 pectenotoxin-3 (PTX3) : R = CHO
308 pectenotoxin-6 (PTX6) : R = COOH



309 yessotoxin (YTX) R = H
310 45-hydroxy yessotoxin (45-OH YTX) R = OH



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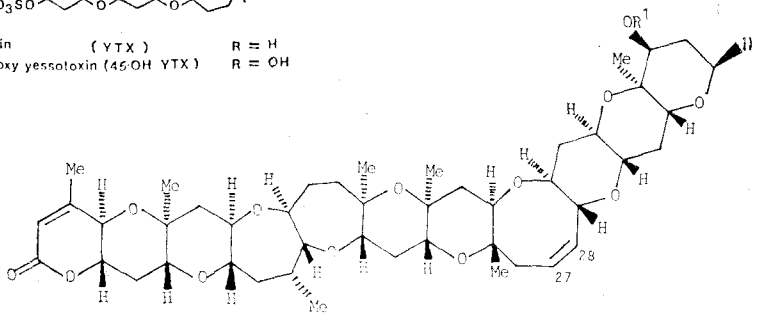
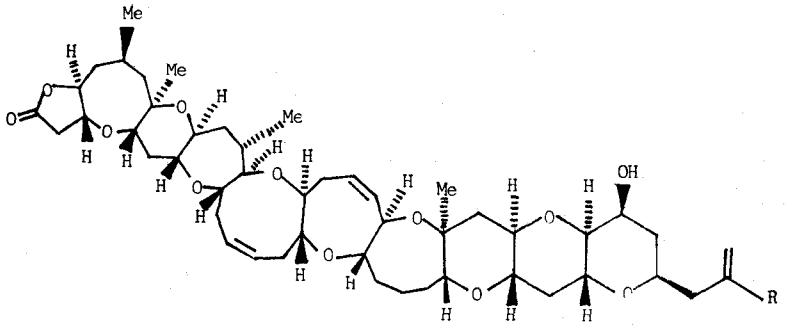


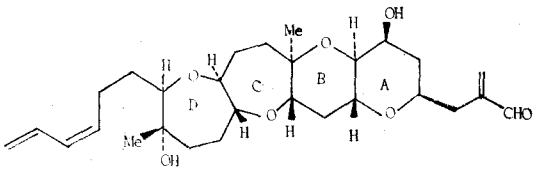
	R_1	R_2
312	H	$CH_2C(=CH_2)CHO$
313	H	CH_2COCH_2Cl
314	H	$CH_2C(=CH_2)CH_2OH$
315	Ac	$CH_2C(=CH_2)CHO$
316	H	$CH_2C(=CH_2)CHO$

27,28 — epoxide

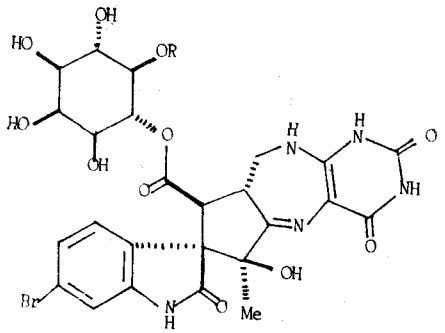


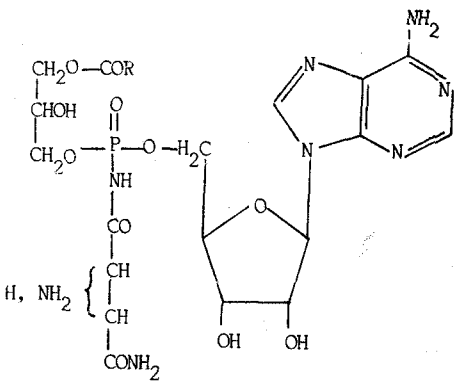
317 R = CHO

318 R = CH_2OH

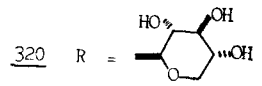


319





322



320 R =

321 R = H

The causative agent of ichthyotoxin such as vomit, stomachache and diarrhea is dinogunellin (**322**),[180] which was obtained from mature ovum of fish *Stichaeus grigorjewi* and of cabezon *Scorpaenichthys marmoratus.*

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