Chapter 15
Natural Products from Sponges

Bing-Nan Han, Li-Li Hong, Bin-Bin Gu, Yang-Ting Sun, Jie Wang, Jin-Tang Liu, and Hou-Wen Lin

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Abstract The sponge is one of the oldest multicellular invertebrates in the world. Marine sponges represent one of the extant metazoans of 700–800 million years. They are classified in four major classes: Calcarea, Demospongiae, Hexactinellida, and Homoscleromorpha. Among them, three genera, namely, *Haliclona*, *Petrosia*, and *Discodemia* have been identified to be the richest source of biologically active compounds. So far, 15,000 species have been described, and among them, more than 6000 species are found in marine and freshwater systems throughout tropical, temperate, and polar regions. More than 5000 different compounds have been

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isolated and structurally characterized to date, contributing to about 30% of all marine natural products. The chemical diversity of sponge products is high with compounds classified as alkaloids, terpenoids, peptides, polyketides, steroids, and macrolides, which integrate a wide range of biological activities, including antibacterial, anticancer, antifungal, anti-HIV, anti-inflammatory, and antimalarial. There is an open debate whether all natural products isolated from sponges are produced by sponges or are in fact derived from microorganisms that are inhaled though filter-feeding or that live within the sponges. Apart from their origin and chemoecological functions, sponge-derived metabolites are also of considerable interest in drug development. Therefore, development of recombinant microorganisms engineered for efficient production of sponge-derived products is a promising strategy that deserves further attention in future investigations in order to address the limitations regarding sustainable supply of marine drugs.

Keywords Sponge · Sponge holobiont · Natural products · Alkaloids · Peptides · Polyketides · Macrolides · Terpenoids · Steroids · Bioactivity

15.1 Introduction

Considering that oceans comprise over 70% of the earth's surface and harbor a tremendous variety of flora and fauna, marine habitat represents an unexplored source of new bioactive molecules. Although still quite young by many standards, since the 1950s, this field of marine natural products has undergone exponential growth and proven to be a productive source for structurally diverse secondary metabolites. Due to long evolutionary processes favoring the accumulation of strongly bioactive compounds, sponges (Porifera) and their associated microorganisms have become the largest contributors of marine natural products. Seemingly primitive and morphologically defenseless organisms like sponges developed ingenious survival strategies which rely heavily on the accumulation of defensive products protecting them from a multitude of stress factors that involve overgrowth by fouling organisms, attacking by predators, and invasion by pathogenic microorganisms. Sponges are classified in four major classes: Calcarea, Demospongiae, Hexactinellida, and Homoscleromorpha. Among them, three genera, namely, *Haliclona*, *Petrosia*, and *Discodemia* have been identified to be the richest source of biologically active compounds. The chemical diversity of sponge products is high with compounds classified as alkaloids, terpenoids, peptides, polyketides, steroids, and macrolides, which integrate a wide range of biological activities, including antibacterial, anticancer, antifungal, anti-HIV, anti-inflammatory, and antimalarial.

15.2 Bioactive Alkaloids from Marine Sponges

Biologically significant alkaloids, as a special and important class of bioactive natural products, are widely distributed over terrestrial and marine organisms. Recent studies have demonstrated that marine invertebrates and microorganisms are abundant sources of these secondary metabolites. Among these natural products, imidazole-, oxazole-, and thiazole-containing alkaloids are often found to show diverse significant biological activities, including antitumor, antibacterial, antiviral, antimalarial, immunosuppressive activities, etc.

The following review summarizes the latest progress on the isolation, structure identification of a diverse 209 alkaloids from 66 marine sponges with potent biological activities within the literature coverage from 1986 to 2016.

In the year of 1993, xestocyclamine A (**1**) was isolated from Papua New Guinea collections of the sponge *Xestospongia* sp. Pure xestocyclamine A exhibited an IC_{50} = 4 μg/mL (10.1 μM) against PKC ϵ and also exhibits activity in a whole cell IL-1 release assay with an IC_{50} of 1 μM [1].

In the year of 1994, madangamine A (**2**) was isolated from the marine sponge *Xestospongia ingens*, which showed in vitro cytotoxicity against murine leukemia P388 (ED_{50} 0.93 μg/mL) [2].

In 1996, sceptrine (**3**) and ageliferine (**4**) were isolated from *Xestospongia* sp. and *Agelas novaecaledoniae* collected at Baic de Prony, exhibiting a high affinity for somatostatin (IC_{50} = 0.27 μM and 2.2 μM) [3]. Within the same year, 4,5-dibromopyrrole-2-carbamide (**5**) was isolated from the marine sponge *Agelas mauritiana* collected off Hachijo-jima Island, Japan. 4,5-dibromopyrrole-2-carbamide (**5**) promoted larval metamorphosis of the ascidian *Ciona savignyi* at a concentration of 2.5 μg/mL (9.36 μM) [4]. (±)-xestospongin D (**6**) was isolated from the Singapore marine sponge *Niphates* sp. collected from south of the Beting Bemban Besar reef. (**6**) was found to inhibit growth of certain human cancer cell lines comprising the NCI panel (leukemia subpanel, mean GI_{50} 3.62 ± 2.02 μM; breast subpanel, mean GI_{50} 4.53 ± 1.98 μM) as well as the murine P388 lymphocytic leukemia (ED_{50} 1.7 μg/mL) (3.67 μM) [5].

In the year of 1998, the chemical investigation of Micronesian sponge *Oceanapia* sp. from Truk Lagoon, afforded two active pyridoacridine alkaloids: the known compound kuanoniamine D (**7**) as well as the new N-deacyl derivative of the kuanoniamines (**8**). The IC_{50} of N-deacyl derivative of the kuanoniamines (**8**) was 1.2 μg/mL (3.77 μM) against HeLa cells and 2.0 μg/mL against MONO-MAC 6 cells. In receptor binding assays, kuanoniamine D (**7**) showed potent affinity to A1 adenosine receptors with Ki value of 2.94 μM [6].

In 1999, halitulin (**9**) was isolated from the sponge *Haliclona tulearensis* collected in Sodwana Bay, Durban, South Africa. It was found to be cytotoxic against several tumor cell lines: P388, A549, HT29, and MEL28 in concentration of

12–25 ng/mL [7]. Discorhabdin Q (16, 17-dehydrodiscorhabdin B) (**10**) was isolated from cytotoxic extracts of the sponge *Latrunculia purpurea* and numerous collections of *Zyzzya massalis*, *Z. fuliginosa*, and *Z.* spp from Australia and Fiji. In the NCI 60-cell line antitumor screen, discorhabdin Q (**10**) exhibited moderate cytotoxicity (mean panel GI_{50} = 0.5 μg/mL) [8]. In the same year, five new steroidal alkaloids, plakinamines C and D (**11**), and three related compounds were isolated from the Vanuatu sponge *Corticium* sp. collected off Porth Havannah, Vanuatu, South Pacific. Two new compounds (**12** and **13**) performed good in vitro cytotoxicity against human bronchopulmonary non-small-cell lung carcinoma cells (NSCLC-N6) with IC_{50} values of 3.3–5.7 μg/mL, while plakinamine D (**11**) was cytotoxic with IC_{50} < 3.3 μg/mL [9].

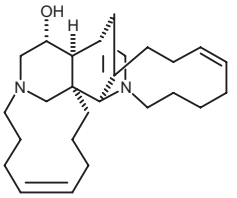
In 2000, topsentins B1 (**14**) was isolated from the marine sponge *Rhaphisia lacazei*, collected in the Mediterranean Sea which showed antiproliferative activity against human bronchopulmonary cancer cells with an IC_{50} of 6.3 μg/mL [10]. Dragmacidin F (**15**), possessing an unprecedented carbon skeleton, was isolated from a marine sponge of the genus *Halicortex* collected off the southern coast of Ustica Island (Italy), which showed good in vitro antiviral activity toward HIV-1 (EC_{50} = 0.91 μM) [11].

In the year of 2001, makaluvamine P (**16**) was isolated from the sponge *Zyzzya* cf. *fuliginosa* collected in the waters off the Vanuatu Islands. Makaluvamine P (**16**) was found to inhibit the growth of KB tumor cells with 64% on at 3.2 μg/mL (9.5 μM) [12].

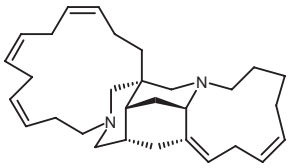
In 2002, the sponge *Stylissa massa* collected from the shallow waters around Helgoland afforded eight known alkaloids, among which 10 E-hymenialdisine (**17**) and 10 Z-hymenialdisine (**18**) were active in the initial Raf/MEK-1/MAPK signaling cascade assay (IC_{50} = 3 and 6 nM) [13]. Arenosclerins A–C (**19–21**) and haliclonacyclamine E (**22**), isolated from the marine sponge *Arenosclera brasiliensis*, exhibited certain cytotoxity against human HL-60 (leukemia), L929 (fibrosarcoma), B16 (melanoma), and U138 (colon) cancer cell lines at concentrations between 1.5 and 7.0 μg/mL [14]. In addition, isonaamidine E (**23**) was isolated from two sponges, *Leucetta chagosensis* and *Leucetta* cf. *chagosensis*, collected from the Great Barrier Reef and the Fiji Islands, which was found to be cytotoxic toward several tumor cell lines (GI_{50} values was 1.3 μg/mL) [15].

In 2003, manadomanzamines A (**24**) and B (**25**) were isolated from an Indonesian sponge *Acanthostrongylophora* sp. (Haplosclerida: Petrosiidae). Manadomanzamines A (**24**) and B (**25**) exhibited strong activity against *Mycobacterium tuberculosis* (Mtb) with MIC values of 1.9 and 1.5 μg/M (2.4 μM) [16].

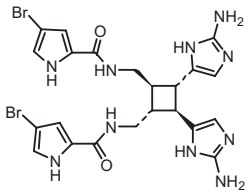
In 2004, seven pyrrole alkaloids isolated from *Agelas* sponges were tested for interactions with the cellular calcium homeostasis. Among them, brominated pyrrole alkaloids reduced voltage-dependent calcium elevation in PC12 cells, and dibromosceptrin (**26**) was the most potent alkaloid with a half maximal of 2.8 μM [17].



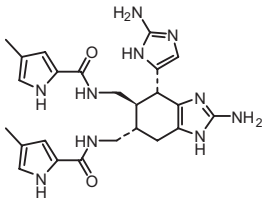
Xestocyclamine A (**1**)



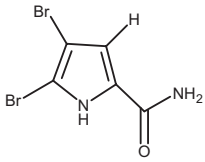
Madangamine A (**2**)



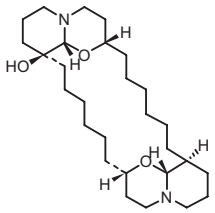
Sceptrine (**3**)



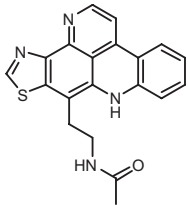
Ageliferine (**4**)



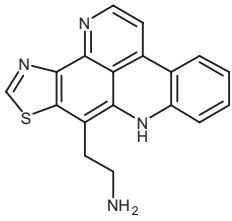
4,5-dibromopyrrole-2-carbamide (**5**)



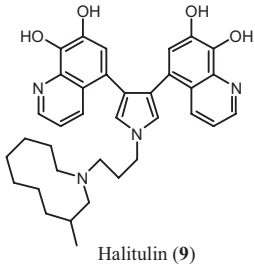
(±)-XestosponginD (**6**)



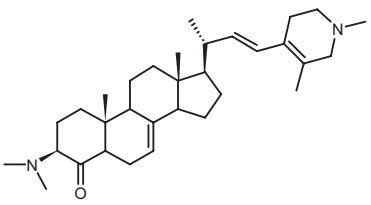
Kuanoniamine D (**7**)



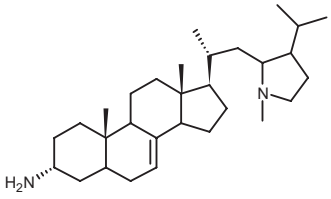
N-deacyl derivative of the kuanoniamines (**8**)



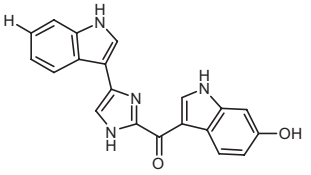
Halitulin (**9**)



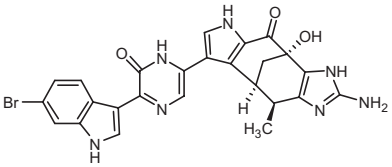
N,N-dimethyl-4-oxo-3-epi-plakinamine B (**12**)



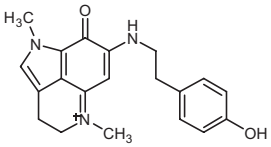
(**13**)



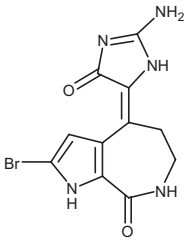
Topsentins B1 (**14**)



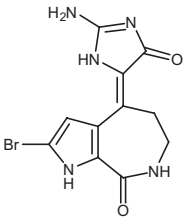
Dragmacidin F (**15**)



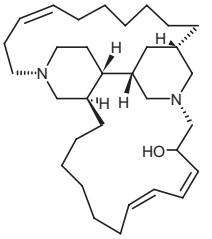
Makaluvamine P (**16**)



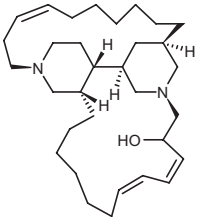
10E-hymenialdisine (**17**)



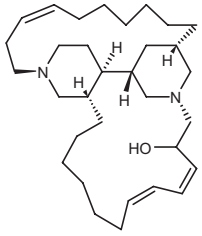
10Z-hymenialdisine (**18**)



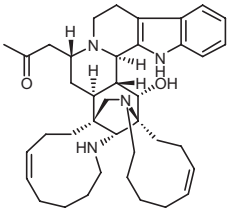
Arenosclerin A (**19**)



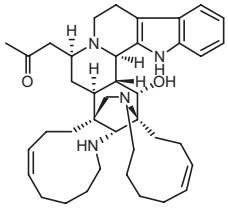
Arenosclerin B (**20**)



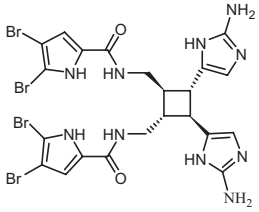
Arenosclerin C (**21**)



Manadomanzamines A (**24**)

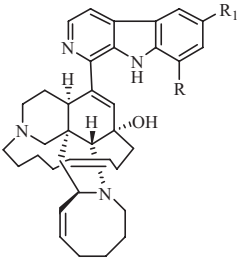


Manadomanzamines B (**25**)

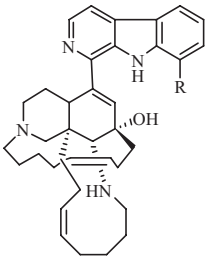


Dibromosceptrin (**26**)

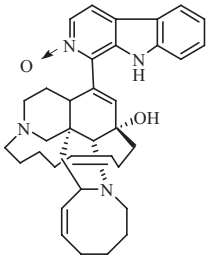
In 1994, manzamine A (**27**), 8-hydroxymanzamine A (**28**), and 8-methoxymanzamine A (**29**) were derived from an unidentified sponge, *Pachypellina* sp. All the compounds showed antitumor and anti-HSV-II activities [18], and the compounds **27** and **28** also showed potent anti-inflammatory, antifungal, and anti-HIV-1 activities [19]. In 2004, compounds manzamine J (**30**), 8-hydroxymanzamine J (**31**), manzamine A N-oxide (**32**), manzamine E (**33**), 6-hydroxymanzamine E (**34**), manzamine F (**35**), and ircinol A (**36**) isolated from a common Indonesian sponge of the genus *Acanthostrongylophora* showed diverse activities against malaria, mycobacterium tuberculosis, leishmania, HIV-1, and AIDS opportunistic infections [20]. In 2006, a structurally related compound manzamine Y (**37**) was obtained from the genus *Acanthostrongylophora*. Compounds **27**, **28**, **33**, **34**, **35**, and **37** displayed the cytotoxicity against *Plasmodium falciparum* and Vero cells [21]. Compounds **27**, **28**, and **33** also showed neuritogenic activity against Neuro-2a cells with IC_{50} values of 3.3, 3.2, and 5.7 μM [22]. In 2009, the new analogues zamamidine C (**38**), 3,4-dihydro-6-hydroxy-10,11-epoxymanzamine A (**39**), and 3,4-dihydromanzamine J N-oxide (**40**) were purified from an Okinawan marine sponge *Amphimedon* species. All the compounds showed cytotoxicity against the three human tumor cell lines P388 murine leukemia L1210, human epidermoid carcinoma KB cells, and murine leukemia, and compounds **38** and **40** also possessed inhibitory activities against *T.b. brucei* (IC_{50} = 0.27, 4.44, μg/mL, respectively) and *P. falciparum* (IC_{50} = 0.58, 7.02, μg/mL, respectively) in vitro [23].



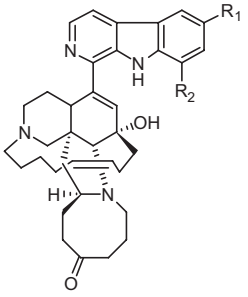
27 R = H R1= H
28 R = OH R1 = H
29 R = OCH3 R1 = H
37 R = H R1 = OH



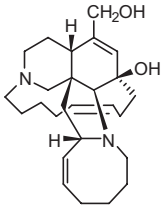
30 R = H
31 R = OH



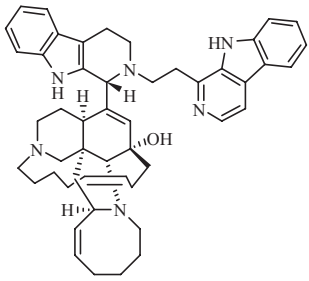
32



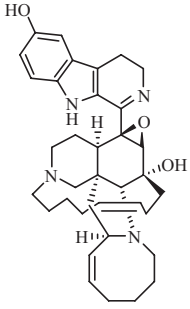
33 R1 = H, R2 = H
34 R1 = OH, R2 = H
35 R1 = H, R2 = OH



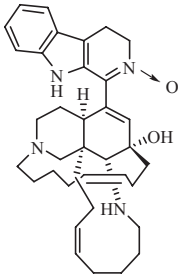
36



38 zamamidine C



39 3,4-dihydro-6-hydroxy-10,11-epoxymanzamine A



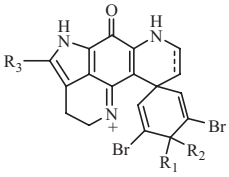
40 3,4-dihydromanzamine J N-oxide

In the year 2004, three new pyrroloiminoquinone alkaloids, 3-dihydro-7,8-dehydrodiscorhabdin C (**41**), 14-bromo-3-dihydro-7,8-dehydrodiscorhabdin C (**45**), discorhabdin V (**46**), and three known compounds 14-bromodiscorhabdin C (**44**), 14-bromo-3-dihydrodiscorhabdin C (**42**), and 3-dihydrodiscorhabdin C (**43**) were yielded from the sponge *Tsitsikamma pedunculata* with the cytotoxicity activity

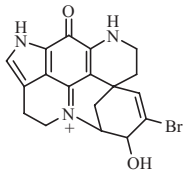
against human colon tumor (HCT-116) cancer cell line at IC_{50} values of 0.197, 0.222, 1.266, 0.077, 0.645, and 0.323 μM, respectively. Then tsitsikammamine A (**47**) and tsitsikammamine B (**48**) were isolated from the sponge *Tsitsikamma favus* with cytotoxicity activity inhibiting against HCT-116 cancer cell line at IC_{50} of 1.414 and 2.382 μM. Two new compounds 1-methoxydiscorhabdin D (**49**) and 1-aminodiscorhabdin D (**50**) and five known metabolites, damirone B (**51**), makaluvic acid A (**52**), makaluvamine C (**53**), discorhabdin G (**54**), and discorhabdin N (**55**), obtained from the sponge *Latrunculia bellae* exhibited cytotoxic activity against HCT-116 cell line with IC_{50} values of 0.232, 0.119, 3.102, 1.089, 0.327, and 2.249 μM, respectively. Discorhabdin A (**56**) and discorhabdin D (**57**) isolated from the sponge *Strongylodesma algoaensis* displayed cytotoxicity activity against HCT-116 cancer cell line which IC_{50} values are 0.007 and 0.595 μM, respectively [24].

In 2008, compounds discorhabdin G (**54**), B (**58**), L (**59**), and W (**60**) isolated from *Latrunculia* species sponges were found cytotoxic toward the P388 murine leukemia cell line with IC_{50} values of 0.1–1.08 μM [25]. In 2012, bispyrroloiminoquinone alkaloids, tsitsikammamine C (**61**), and makaluvamines J (**62**), G (**63**), and L (**64**) were obtained from the Australian marine sponge *Zyzzya* sp. Tsitsikammamine C displayed potent antimalarial activity with IC_{50} values of 13 and 18 nM against chloroquine-sensitive (3D7) and chloroquine-resistant (Dd2) *Plasmodium falciparum*, respectively. Compounds **62–64** displayed potent growth inhibitory activity (IC_{50} < 100 nM) against both *P. falciparum* lines and only moderate cytotoxicity against HEK293 cells (IC_{50} = 1–4 μM) [26].

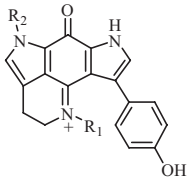
Fascaplysin (**65**) isolated from the sponge *Thorectandra* sp. in 2005 displayed inhibitory activity in the Cdc25B assay with an IC_{50} value of 1.0 μg/mL [27]. Compounds (*R*)-6′′-debromohamacanthin A (**66**) and *cis*-3,4-dihydrohamacanthin B (**67**) isolated from the sponge *Spongosorites* sp. were cytotoxic against A549 (human lung cancer), SK-OV-3 (human ovarian cancer), SK-MEL-2 (human skin cancer), XF498 (human CNS cancer), and HCT 15 (human colon cancer) cell lines with IC_{50} values ranging from 2.83 to 3.85 μg/mL [28]. In 2006, structurally similar compounds deoxytopsentin (**68**), hamacanthin A (**69**), and hamacanthin B (**70**) were isolated from the sponge *Spongosorites* sp., all of which showed antimicrobial activity against various strains of bacteria and fungi, among which deoxytopsentin (**68**) and hamacanthin A (**69**) also exhibited significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* and moderate cytotoxicity against cancer cell lines [29]. Compounds cortistatins A (**71**), B (**72**), C (**73**), and D (**74**) from the sponge *Corticium simplex* displayed potent antiproliferative activities against HUVECs which IC_{50} values are from 0.0018 to 1.1 μM. The compound **71** also exhibited activities against normal human dermal fibroblast (NHDF), epidermoid carcinoma cells (KB3-1), human chronic myelogenous leukemia cells (K562), and murine neuroblastoma cells (Neuro-2A) with IC_{50} values of 6.0, 7.0, 7.0, and 6.0 μM [30]. The marine sponge *Dactylia* sp. yielded one alkaloid ircinamine B (**75**), which was cytotoxic against P388 cell line (IC_{50} = 0.28 μM) [31].



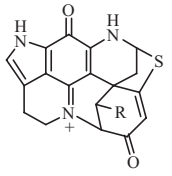
41 $R_1 + R_2 = O$, $R_3 = Br$
42 $R_1 = H$, $R_2 = OH$, $R_3 = Br$
43 $R_1 = H$, $R_2 = OH$, $R_3 = H$
44 $R_1 = H$, $R_2 = OH$, $R_3 = H$ Δ^7
45 $R_1 = H$, $R_2 = OH$, $R_3 = Br$ Δ^7

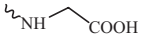


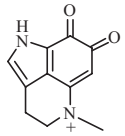
46 discorhabdin V



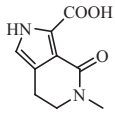
47 $R_1 = R_2 = H$
48 $R_1 = H$, $R_2 = Me$



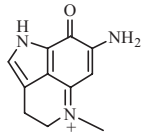
49 R = OMe
50 R = NH_2
55 R = 



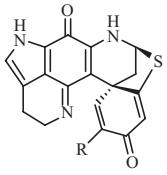
51 damirone B



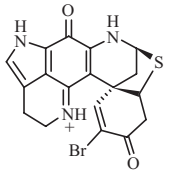
52 makaluvic acid A



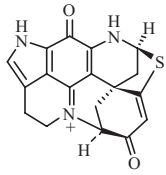
53 makaluvamine C



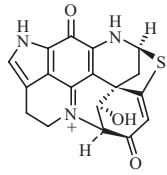
54 discorhabdin G R = H
58 discorhabdin B R = Br



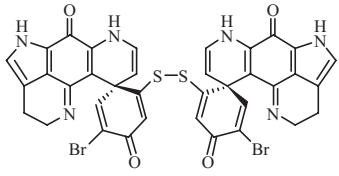
56 discorhabdin A



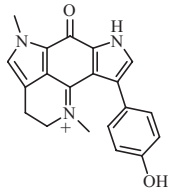
57 discorhabdin D



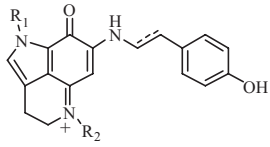
59 discorhabdin L



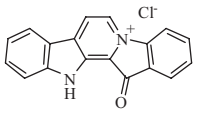
60 discorhabdin W



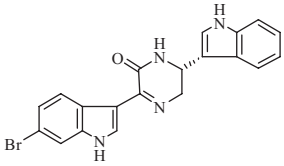
61 tsitsikammamine C



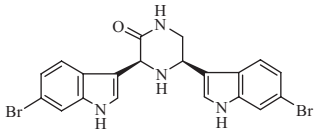
62 $R_1 = H$, $R_2 = CH3$
63 $R_1 = CH_3$, $R_2 = CH3$ Δ^7
64 $R_1 = H$, $R_2 = CH3$ Δ^7



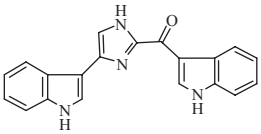
65 fascaplysin



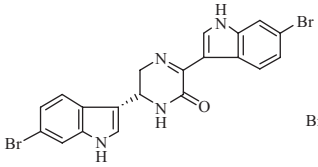
66 (R)-6"-Debromohamacanthin A



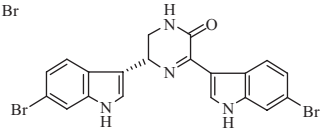
67 cis-3,4-Dihydrohamacanthin B



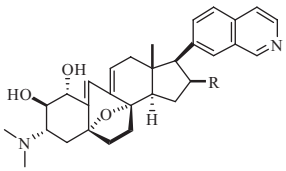
68 deoxytopsentin



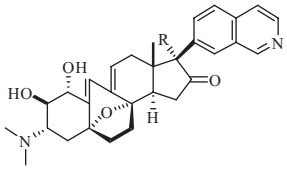
69 hamacanthin A



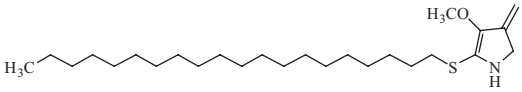
70 hamacanthin B



71 R = H
72 R = OH



73 R = H
74 R = OH

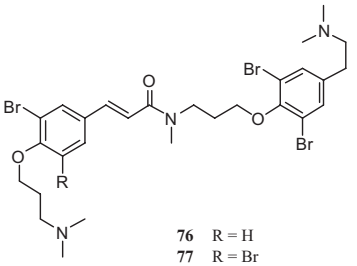


75 Ircinamine B

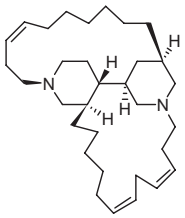
In 2007, psammaplysenes C (**76**) and D (**77**) were identified from the sponge *Psammoclemma* sp. as the P2X7 receptor antagonists both for the treatment of inflammatory disease with IC_{50} value of 7 μM [32]. Three bis-piperidine alkaloids, haliclonacyclamine F (**78**) and arenosclerins D (**79**) and E (**80**), were isolated from the marine sponge *Pachychalina alcaloidifera*, which displayed cytotoxic activity against SF295 (human CNS), MDA-MB-435 (human breast), and HL-60 (leukemia) cancer cell lines with IC_{50} values ranging from 1.0 to 4.5 μg/mL [33]. In 2010, structurally related compound neopetrosiamine A (**81**) was isolated from the marine sponge *Neopetrosia proxima* collected off the west coast of Puerto Rico, which showed inhibitory activity against MALME-3M melanoma cancer, CCRFCEM leukemia, and MCF-7 breast cancer with IC_{50} values of 1.5, 2.0, and 3.5 μM, respectively, also showing the antiplasmodial activity against *Plasmodium falciparum* (IC_{50} = 2.3 μM) [34]. The compound haliclonacyclamine A (**82**) was isolated from

the *Haliclona* sponge *Haliclona* sp. at Solomon Islands. In vitro assay of haliclonacyclamine A against the chloroquine-sensitive 3D7 and chloroquine-resistant strain *P. falciparum* FcB1 gave, respectively, IC_{50} of 0.33 and 0.052 mg/mL. The cytotoxicity of **82** was measured on breast cancer cells MCF-7 with IC_{50} value of 2.6 mg/mL [35].

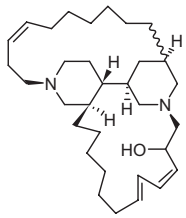
16b-Hydroxycrambescidin 359 (**83**), batzelladines L and M (**84**, **85**), ptilomycalin A (**86**), crambescidine 800 (**87**), batzelladine C (**88**), and dehydrobatzelladine C (**89**) were isolated from the Jamaican sponge *Monanchora unguifera*, all of which exhibited antimalarial activity against *Plasmodium falciparum* D6 clone and W2 clone with IC_{50} values ranging from 73 to 270 ng/mL. Moreover, their activities of antitumor, anti-tuberculosis, HIV-1, antimicrobial and antimalarial were evaluated. Among them, batzelladine L (**84**) showed the most potent activity against *Mycobacterium tuberculosis* with a MIC of 1.68 mg/mL, ptilomycalin A (**86**), and crambescidine 800 (**87**) exhibited potent activities against human HIV-1 virus with EC_{50}/EC_{90} values of 0.011/0.046 and 0.04/0.12 μM, respectively [36]. In 2009, structurally similar compounds norbatzelladine A (**90**), dinorbatzelladine A (**91**), dinordehydrobatzelladine B (**92**), and dihomodehydrobatzelladine C (**93**) were obtained from marine sponge *Monanchora arbuscula* (de Laubenfels, 1953) collected in Martinique; norbatzelladine L (**94**) and clathriadic acid (**95**) were yielded from marine sponge *Clathria calla* (de Laubenfels, 1934) collected in Guadeloupe. Compounds **90–94** possessed potent antitumor cytotoxic activities against MDA-MB-231, A549, and HT29 with GI_{50} values ranging from 0.7 to 7.9 μM. Compounds **90–95** showed antimalarial activity with IC_{50} values ranging from 0.2 to 2.3 μM [37]. Similar compounds, monalidine A (**96**); batzelladines D (**97**), F (**98**), and L (**84**); and norbatzelladine L (**99**), were yielded from the marine sponge *Monanchora arbuscula*, collected off the southeastern coast of Brazil in 2015, displaying the activities against *Trypanosoma cruzi* and *Leishmania infantum* with IC_{50} values ranging from 2.0 to 8.0 μM [38]. Four brominated pyrrole-imidazole alkaloids (**100**–**103**) from the Caribbean sponges *Stylissa caribica* and *Agelas wiedenmayeri* were tested for interactions with cellular calcium homeostasis using PC12 cells, massadine (100, EC_{50}: 5.32 μM), and stylissadines A (101, 4.48 μM) and B (102, 4.67 μM), and tetrabromostyloguanidine (103, 15.6 μM) reduced voltage-dependent calcium entry in PC12 cells as measured with Fura II as calcium indicato [39]. 8,8′-Dienecyclostellettamine (**104**) isolated from the marine sponge *Amphimedon compressa* showed potent antibacterial activities against six clinic bacteria, *Candida albicans*, *Escherichia coli*, *Pseudomonas aerug*, *Cryptococcus neoformans*, MRS, and *Aspergillus fumigatus*, with IC_{50} values of 0.4, 1.3, 2.1, 2.5, 0.25, and 0.3 μg/mL, respectively [40]. In 2009, an analogue njaoaminiums B (**105**) isolated from the marine sponge *Reniera* sp., collected off the coasts of Pemba Island, Tanzania, showed cytotoxicity against the three human tumor cell lines MDA-MB-231, A549, and HT29 cell lines with GI_{50} values of 4.8, 4.1, and 4.2 μM [41].



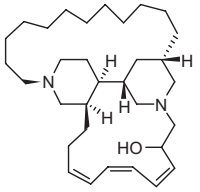
76 R = H
77 R = Br



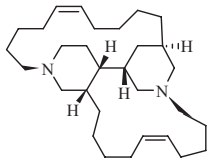
78 haliclonacyclamine F



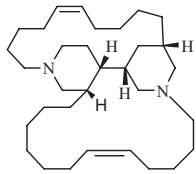
79 arenosclerins D



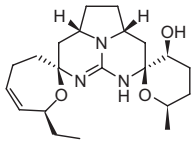
80 arenosclerins E



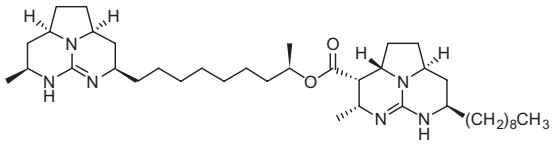
81 neopetrosiamine A



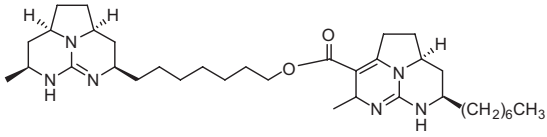
82 neopetrosiamine A



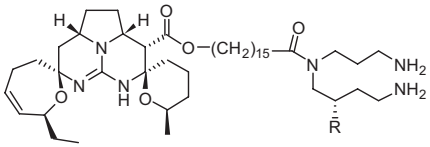
83 16b-hydroxycrambescidin 359



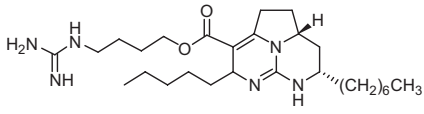
84 batzelladines L



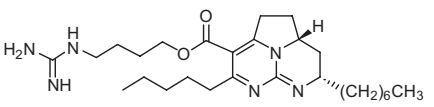
85 batzelladines M



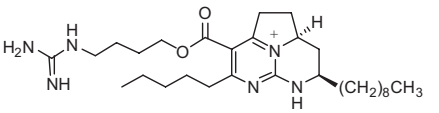
86 ptilomycalin A R = H
87 crambescidine 800 R = OH



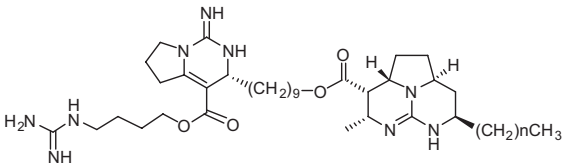
88 batzelladine C



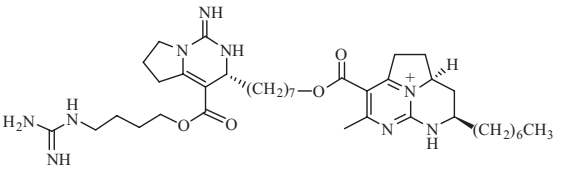
89 dehydrobatzelladine C



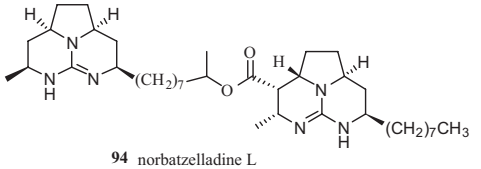
93 dihomodehydrobatzelladine C



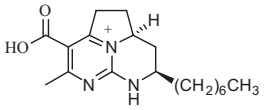
90 norbatzelladine A n = 7
91 dinorbatzelladine A n = 6



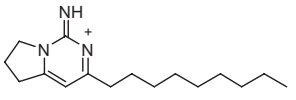
92 dinordehydrobatzelladine B



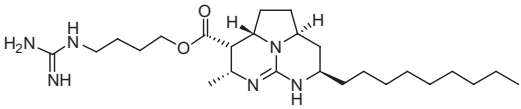
94 norbatzelladine L



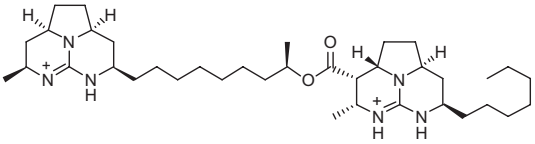
95 clathriadic acid



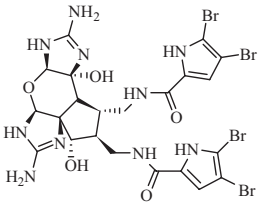
96 monalidine A



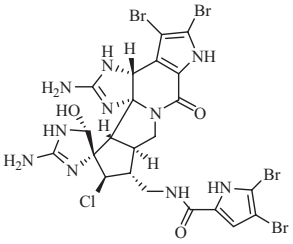
97 batzelladines D



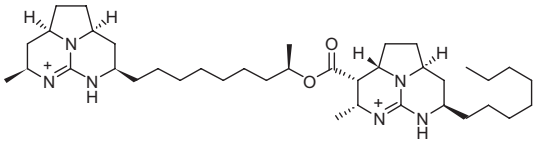
98 batzelladines F



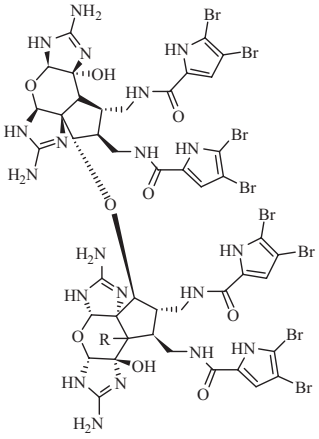
100 massadine



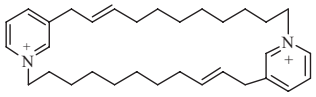
103 tetrabromostyloguanidine



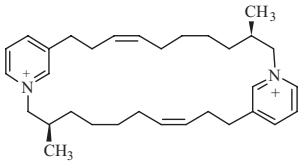
99 batzelladines I



101 R = βH stylissadines A
102 R = αH stylissadines B



104 8,8'-dienecyclostellettamine



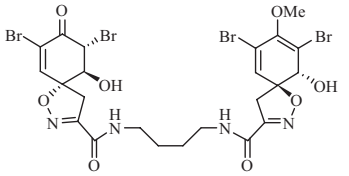
105 Njaoaminium B

In 2008, compounds (+)-aplysinillin (**106**) and dienone (**107**) yielded from the marine sponge *Aplysinella* sp. collected from the Federated States of Micronesia were evaluated for their cancer cell growth inhibition against the MCF-7 cancer cell line with IC_{50} values of 1.19 ± 0.10 and 0.89 ± 0.11 μM, respectively [42]. Trachycladindoles A–F (**108–113**) were yielded from a southern Australian marine

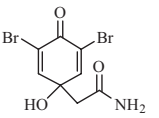
sponge, *Trachycladus laevispirulifer*, and they showed cytotoxicity against lung (A549), colorectal (HT29), and breast (MDA-MB-231) cell lines with GI_{50} values ranging from 0.3 to 12.2 μM [43].

In 2009, nagelamides Q (**114**) and R (**115**), isolated from Okinawan marine sponges of the genus *Agelas*, showed antimicrobial activity against *Trichophyton mentagrophytes* with MIC values of 6 μg/mL [44]. Benzosceptrin C (**116**), isolated from an Okinawan marine sponge of the genus *Agelas*, displayed antimicrobial activity against *Micrococcus luteus* and *Cryptococcus neoformans* with MIC values of 6 μg/mL, respectively [45].

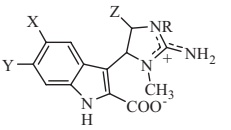
In 2010, chemical investigation of the Australian marine sponge *Ecionemia geodides* found a new pyridoacridine alkaloid, ecionines A (**117**) along with the previously isolated marine natural product meridine (**118**). The compounds exhibited moderate cytotoxicity against a panel of human bladder cancer cell lines, including the increasingly metastatic TSU-Pr1 series (TSU-Pr1, TSU-Pr1-B1, and TSU-Pr1-B2) and the superficial bladder cancer cell line 5637, with IC_{50} values ranging from 3 to 7 μM [46]. Bastadin 26 (**119**) isolated from Australian marine sponge *Ianthella flabelliformis* showed potent affinity for the guinea pig *δ*-opioid receptors with IC_{50} value of 206 nM and a *K*i value of 100 nM [47]. Eleven DOPA-derived pyrrole alkaloids, named baculiferins A–C, E–H, and K–N (**120–130**), were isolated from the Chinese marine sponge *Iotrochota baculifera* and found to be potent inhibitors against the HIV-1 IIIB virus in both MT4 and MAGI cell lines with IC_{50} values ranging from 0.1 to 8.4 μM [48]. Monanchocidin (**131**), a guanidine alkaloid with an unprecedented skeleton system possessing cytotoxicity against human leukemia THP-1 with IC_{50} value of 5.1 μM, was isolated from the sponge *Monanhora pulchra* [49]. Two bromotyrosine alkaloids, ceratinadins A and B (**132–133**), were isolated from an Okinawan marine sponge *Pseudoceratina* sp., and they showed antifungal activity against *Cryptococcus neoformans* (MIC, 4 and 8 μg/mL, respectively) and *Candida albicans* (MIC, 2 and 4 μg/mL, respectively) [50]. Psammaplysin F (**134**) yielded from the Australian marine sponge *Hyattella* sp. inhibited the growth of two different strains of the parasite *Plasmodium falciparum* (Dd2 and 3D7) with IC_{50} values of 1.4 and 0.87 μM [51]. In 2011, psammaplysin F (**134**), psammaplysins G (**135**), and psammaplysin H (**136**) were yielded from marine sponge *Pseudoceratina* sp., all of which inhibited the growth of the 3D7 line of *Plasmodium falciparum* with IC_{50} values of 1.92, 5.22, and 0.41 μM, respectively. The compound psammaplysin F also showed cytotoxicity against HepG2 cell line with IC_{50} value of 3.7 μM [52].



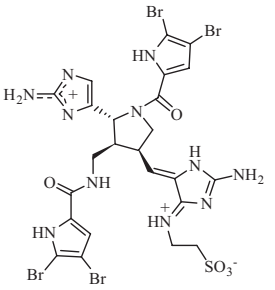
106 (+)-aplysinillin



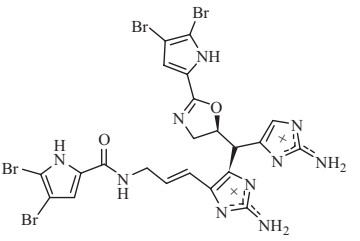
107 dienone



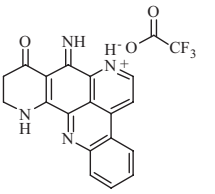
	X	Y	Z	R
108	Br	H	H	H
109	Br	H	H	Me
110	Br	OH	H	H
111	Br	OH	H	Me
112	Br	H	OH	Me
113	Br	OH	OH	Me



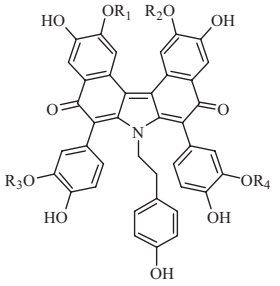
114 Nagelamides Q



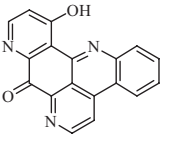
115 Nagelamides R



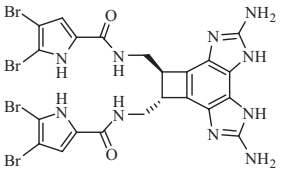
117 ecionines A



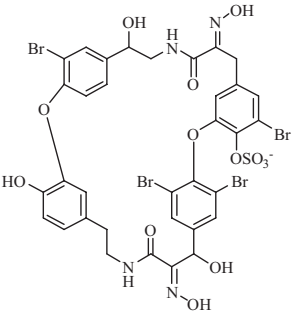
120	$R_1 = SO_3H$,	$R_2 = R_3 = R_4 = H$
121	$R_3 = SO_3H$,	$R_1 = R_2 = R_4 = H$
122	$R_3 = R_4 = SO_3H$,	$R_1 = R_2 = H$
123	$R_1 = R_3 = SO_3H$,	$R_2 = R_4 = H$
124	$R_1 = R_4 = SO_3H$,	$R_2 = R_3 = H$
125	$R_1 = R_3 = R_4 = O_3H$,	$R_2 = H$
126	$R_1 = R_2 = R_3 = SO_3H$,	$R_4 = H$



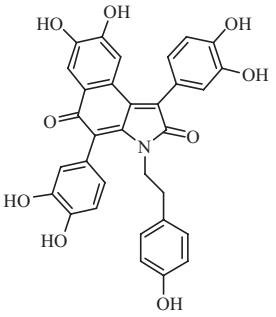
118 meridine



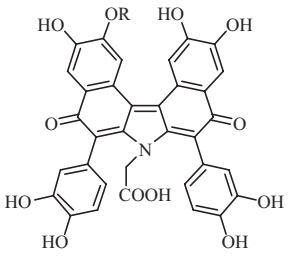
116 benzosceptrin C



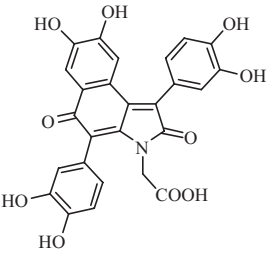
119 bastadin 26



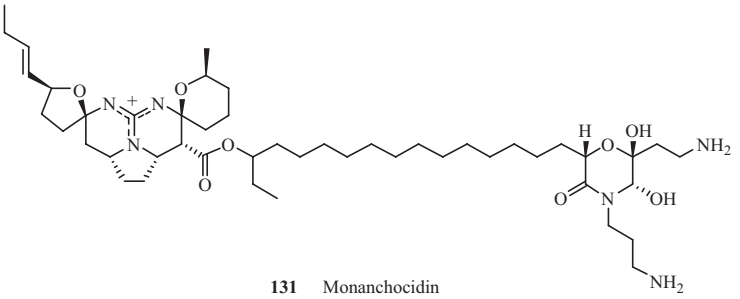
127 baculiferin K



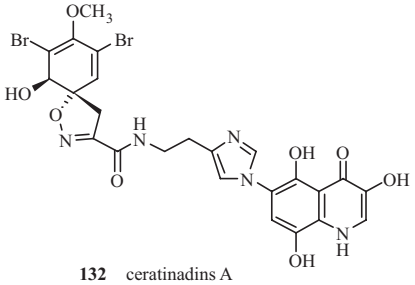
128 R = H
129 R = SO_3H



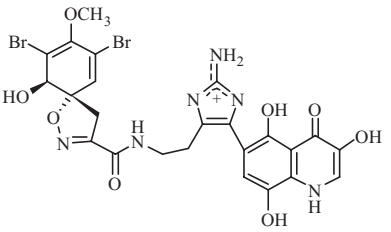
130 baculiferin N



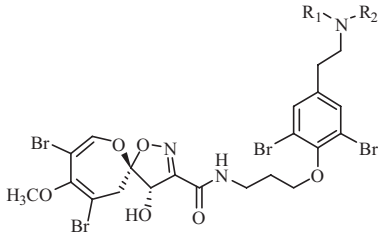
131 Monanchocidin



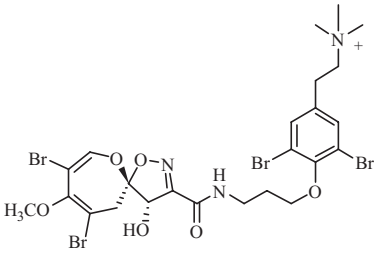
132 ceratinadins A



133 ceratinadins B

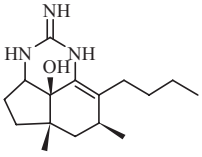


134 psammaplysin F R_1 = H, R_2 = CH_3
135 psammaplysin G R_1 = CH_3, R_2 = $CONH_2$

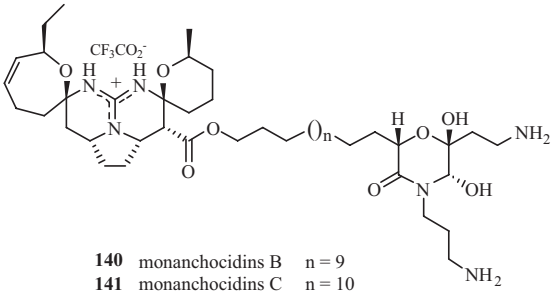


136 psammaplysin H

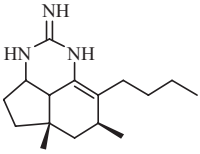
In 2011, 8bβ-hydroxyptilocaulin (**137**) and ptilocaulin (**138**) isolated from *Monanchora arbuscula* colonies collected off the northeastern Brazilian coast presented cytotoxicity against HL-60 cell line with IC_{50} values of 7.89 and 5.77 μM, respectively [53]. Polycyclic guanidine alkaloids monanchocidins A–E (**139–143**) isolated from the Far Eastern marine sponge *Monanchora pulchra* showed potent cytotoxic activities against HL-60 human leukemia cells with IC_{50} values of 540, 200, 110, 830, and 650 nM, respectively [54]. Monanchomycalins A (**144**) and B (**145**) isolated from the marine sponge *Monanchora pulchra* showed cytotoxic activities against HL-60 human leukemia cells with IC_{50} values of 120 and 140 nM, respectively [55]. Compounds spermatinamine (**146**) yielded from the Australian marine sponge *Pseudoceratina* sp. inhibited secretion of the *Yersinia* outer protein YopE and the enzyme activity of YopH with IC_{50} value of 6 μM [56].



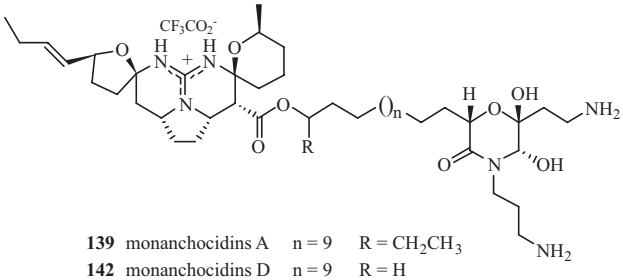
137 8bβ-hydroxyptilocaulin



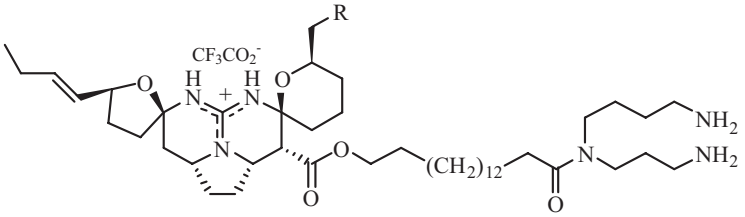
140 monanchocidins B n = 9
141 monanchocidins C n = 10



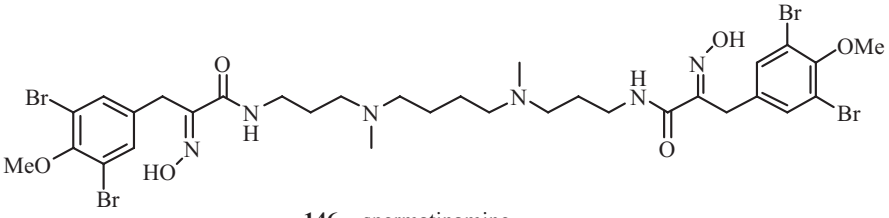
138 ptilocaulin



139 monanchocidins A n = 9 R = CH_2CH_3
142 monanchocidins D n = 9 R = H
143 monanchocidins E n = 8 R = CH_2CH_3



144 monanchomycalins A R = CH_2CH_3
145 monanchomycalins B R = H



146 spermatinamine

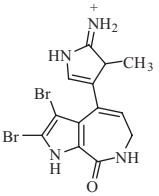
In 2012, 12-N-methyl stevensine (**147**), Z-hymenialdisine (**148**), and Z-debromohymenialdisine (**149**) were obtained from a collection of Indonesian marine sponge *Stylissa* species off Derawan Islands, Berau, NE Kalimantan, which showed significant activity against mouse lymphoma cell line L5187Y with EC_{50} values of 3.5, 1.8, and 2.1 μg/mL, respectively [57]. Densanins A (**150**) and B (**151**) were isolated from the sponge *Haliclona densaspicula* and displayed relatively potent inhibitory effects on lipopolysaccharide-induced nitric oxide production in BV2 microglial cells with IC_{50} values of 1.05 and 2.14 μM, respectively [58]. Ingamine A (**152**), 22(S)-hydroxyingamine A (**153**), and dihydroingenamine D (**154**) were isolated from marine sponge *Petrosid Ng5 Sp5* (family Petrosiidae) obtained from the open repository of the National Cancer Institute, USA. All compounds showed strong antiplasmodial activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum* with IC_{50} values of 57–220 ng/mL. Compounds **152–154** also displayed weak antimicrobial and moderate antileishmanial activities against *Leishmania donovani* promastigotes [59]. Six halogenated alkaloids named purpuroines A, C–D, and F–H (**155–160**) were isolated from the marine sponge *Iotrochota purpurea*. Bioassay for the regulation of tyrosine kinases revealed compounds **155–160** possessing inhibitory activities against the kinase LCK and PLK1 with IC_{50} values ranging from 0.94 to 11.88 μg/mL [60]. Nakijinamines A (**161**) obtained from an Okinawan marine sponge *Suberites* sp. exhibited antimicrobial activity against *Candida albicans*

(IC_{50} = 0.25 μg/mL), *Cryptococcus neoformans* (IC_{50} = 0.5 μg/mL), *Trichophyton mentagrophytes* (IC_{50} = 0.25 μg/mL), and *Micrococcus luteus* (MIC 2 μg/mL) [61]. Two alkaloids, (−)-ageloxime D (**162**) and ageloxime B (**163**), were isolated from the marine sponge *Agelas mauritiana*, and both showed activity against *Cryptococcus neoformans* with IC_{50} values of 5.94 and 4.96 μg/mL, respectively. Compound **163** also exhibited antibacterial activity against *Staphylococcus aureus* (IC_{50} = 7.21 μg/mL) and methicillin-resistant *S. aureus* (IC_{50} = 9.20 μg/mL) [62].

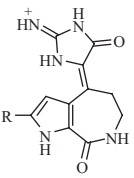
In 2013, thiaplakortones A−D (**164–167**) obtained from the Australian marine sponge *Plakortis lita* displayed significant growth inhibition against chloroquine-sensitive (3D7) and chloroquine-resistant (Dd2) *Plasmodium falciparum* (IC_{50} values <651 nM) and only moderate cytotoxicity against HEK293 cells (IC_{50} values >3.9 μM). **164** was the most active natural product, with IC_{50} values of 51 and 6.6 nM against 3D7 and Dd2 lines, respectively [63]. Calyculin A (**168**) was isolated from the marine sponge *Discodermia calyx* collected off Shikine-jima Island, Japan, which exhibited potent cytotoxicity as well as tumor promotion activity, attributed to its strong and specific inhibition of Ser/Thr protein phosphatases 1 (PP1, IC_{50} = 1.4 nM) and 2A (PP2A, IC_{50} = 2.6 nM) [64]. Two alkaloids, pyrinodemins G and H (**169**, **170**), were isolated from an Okinawan marine sponge *Amphimedon* sp., and they showed cytotoxicity against P388 murine leukemia cells (IC_{50} 9.6 and 2.5 μg/mL, respectively) in vitro [65]. Three dimeric bromopyrrole alkaloids, nagelamides X–Z (**171–173**), were isolated from a marine sponge *Agelas* sp., and they exhibited antimicrobial activity with IC_{50} values ranging from 2.0 to 8.0 μg/mL [66]. Unique bromopyrrole alkaloids, nagelamides U and W (**174**, **175**), were isolated from a marine sponge *Agelas* sp., exhibiting inhibitory activity against *Candida albicans* (IC_{50} 4 μg/mL, each) [67]. Spongiacidin C (**176**) isolated from the marine sponge *Stylissa massa* inhibited USP7 most strongly with an IC_{50} of 3.8 μM among several USP family members tested [68]. *N*-containing metabolites (**177**, **178**) were isolated from the South China Sea sponge *Agelas clathrodes* and showed moderate cytotoxicity against cancer cell line SGC7901 [69]. 2-Methoxy-3-oxoaaptamine (**179**), 2,3-dihydro-2,3-dioxoaaptamine (**180**), demethyl(oxy)aaptamine (**181**), 3-aminodemethyl(oxy)aaptamine (**182**), and 3-(methylamino) demethyl(oxy)aaptamine (**183**) were isolated from a marine sponge of *Aaptos* sp., among which **179** was presented antimycobacterial activity against *Mycobacterium smegmatis* in both active-growing and dormancy-inducing hypoxic conditions with a minimum inhibitory concentration (MIC) of 6.25 μg/ml, and compounds **180–183** showed antimycobacterial activities under hypoxic condition selectively, with MIC values of 1.5–6.25 μg/ml [70].

In 2015, compounds 10-methoxy-2-methylimidazo[4,5,1-ij] pyrido[2,3,4-de] quinolone (**184**), 3-(phenethylamino) demethyl(oxy)aaptamine (**185**), demethyl(oxy) aaptamine (**181**), aaptamine (**186**), and 3-(methylamino)demethyl(oxy)aaptamine (**183**) were isolated from the South China Sea sponge *Aaptos aaptos*, exhibiting cytotoxic activities against HeLa, K562, MCF-7, and U937 cell lines with IC_{50} val-

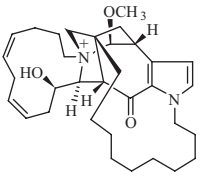
ues in the range of 0.90–12.32 μM [71]. Netamines Q (**187**) isolated from the Madagascar sponge *Biemna laboutei* exhibited antiplasmodial activities with IC_{50} values of 8.37 μM [72]. Indole alkaloids **188**, penaresin (**189**), indolecarbaldehyde (**190**), and plakohypaphorine D (**191**) were isolated from the sponge *Plakortis* sp. collected from Zampa in Okinawa, all of which showed cytotoxicity against P388 cells with IC_{50} values of 0.6, 5, 0.1, and 3.2 μg/mL, respectively [73]. The investigation of South China Sea nudibranch *Jorunna funebris* and its sponge-prey *Xestospongia* sp. led to the isolation of fennebricin C (**192**), fennebricin D (**193**), renieramycin J (**194**), fennebricin A (**195**), renierone (**196**), and *N*-formyl-1,2-dihydrorenierone (**197**). All of the compounds showed the inhibitory activities of NF-κB signaling pathway with IC_{50} values ranging from 1.0 to 9.7 μM, and fennebricin A (**195**) also exhibited growth inhibition against both A549 and HL-60 cell lines with IC_{50} values of 6.2 and 2.5 μM [74]. Crambescin A2 392 (**198**), crambescin A2 406 (**199**), crambescin A2 420 (**200**), and Scheme 575948 (**201**) were obtained from the marine sponge *Pseudaxinella reticulata* collected off the Bahamas. These compounds showed antifungal activity against the human pathogens *Cryptococcus neoformans* var. *gattii* with MIC_{50} values of 1.2, 0.85, and 1.1, 2.5 μM [75]. Ceratinine H (**202**), psammaplysin E (**203**), ceratinophenol A (**204**) were isolated from a new collection of the Red Sea marine sponge *Pseudoceratina arabica*. Compounds **202** and **203** showed potent antiproliferative activities against HeLa cells with IC_{50} values of 2.56 and 2.19 μM; **203** and **204** showed potent antimigratory activity with IC_{50} values of 0.31 and 10.4 μM, respectively [76]. (10E,12Z)-Haliclonadiamine (**205**), halichondriamines A (**206**) and B (**207**), haliclonadiamine (**208**), and papuamine (**209**) were isolated from the Okinawan marine sponge *Halichondria panicea*. These compounds exhibited antimycobacterial activities with inhibition zones of 7–16 mm at 10 μg/disc and also showed apparent activity against the proliferation of the cancer cell line Huh-7 with IC_{50} values from 3.6 to 7.8 μM [77].



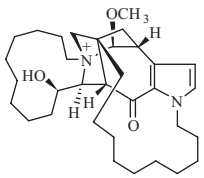
147 12-Nmethyl stevensine



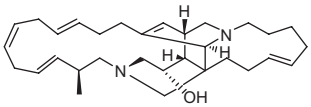
148 R = Br
149 R = H



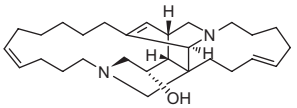
150 densanins A



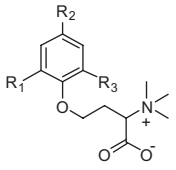
151 densanins B



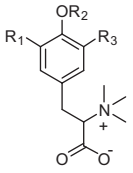
152 R = H
153 R = OH



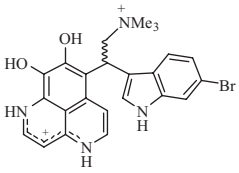
154 dihydroingenamine D



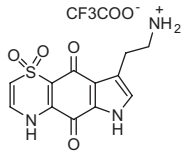
155 $R_1 = R_2 = R_3 = Br$
156 $R_1 = R_3 = Cl$, $R_2 = Br$
157 $R_1 = R_2 = Br$, $R_3 = I$



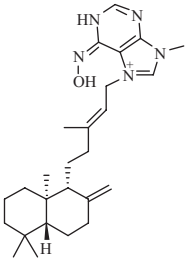
158 $R_1 = R_3 = I$, $R_2 = Me$
159 $R_1 = R_3 = I$, $R_2 = H$
160 $R_1 = Br$, $R_2 = Me$, $R_3 = I$



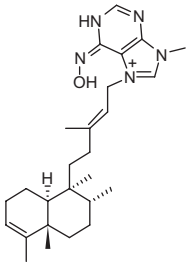
161 nakijinamines A



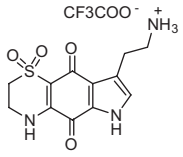
164 Thiaplakortones A



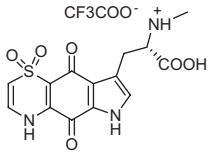
162 (-)-ageloxime D



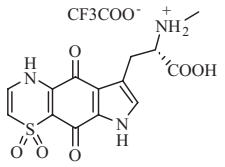
163 ageloxime B



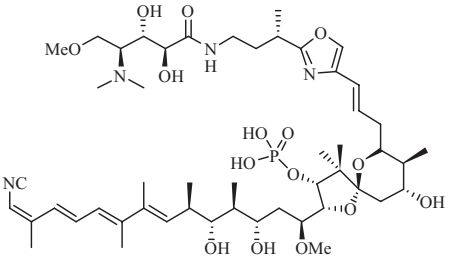
165 Thiaplakortones B



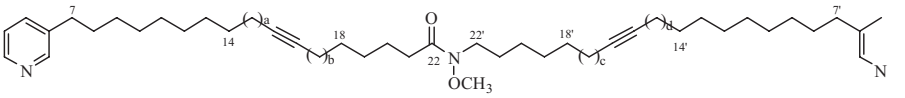
166 Thiaplakortones C



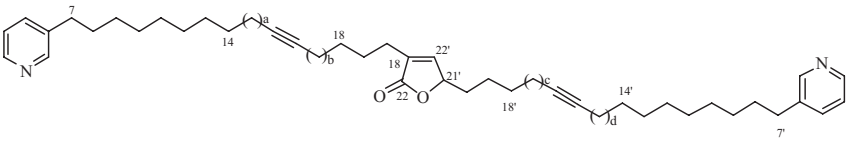
167 Thiaplakortones D



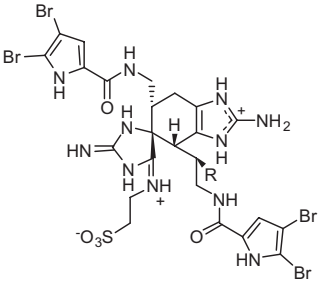
168 Calyculin A



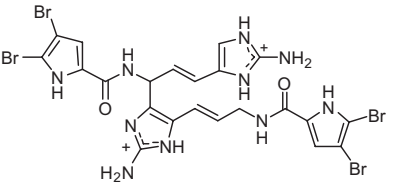
169 Pyrinodemin G
(a+b=1, c+d=1)



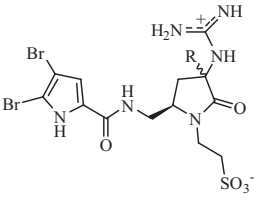
170 Pyrinodemin H
(a+b=1, c+d=1)



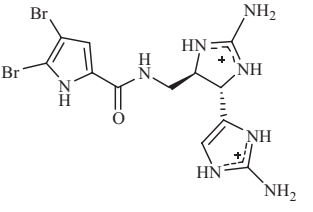
171 nagelamides X R = OH
172 nagelamides Y R = H



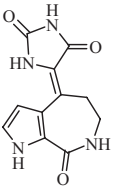
173 nagelamides Z



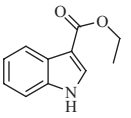
174 Nagelamides U R=¦Â-H



175 Nagelamides W



176 Spongiacidin C



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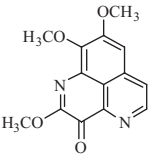
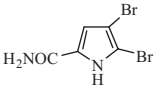


179 2-Methoxy-3-oxoaaptamine



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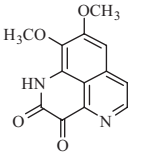
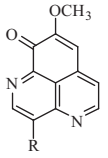
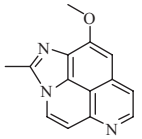


180 2,3-Dihydro-2,3-dioxoaaptamine



181 Demethyl(oxy)aaptamine R=H
182 3-Aminodemethyl(oxy)-aaptamine R=NH2
183 3-(Methylamino)demethyl-(oxy)aaptamine R=NHCH3



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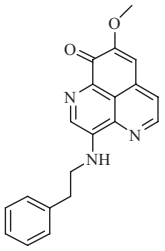
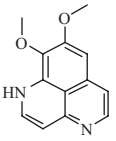
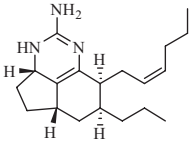


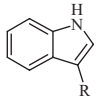
185 3-(phenethylamino) demethyl(oxy)aaptamine



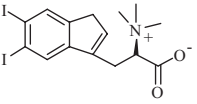
186 aaptamine



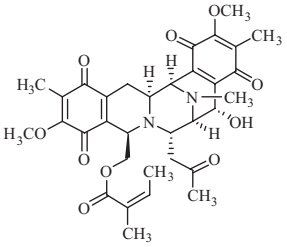
187 Netamine Q



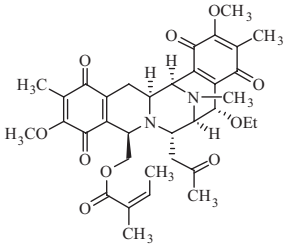
188 R = C ≡ C-CONH2
189 R = CH = CH-COOH
190 R = C(O)H



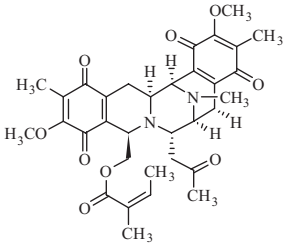
191 plakohypaphorine D



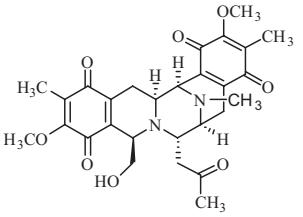
192 Fennebricin C



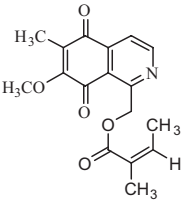
193 Fennebricin D



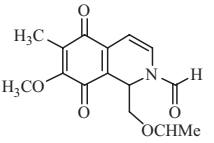
194 Renieramycin J



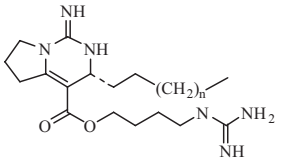
195 Fennebricin A



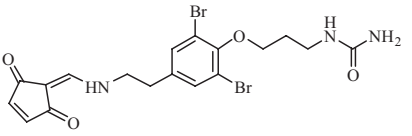
196 renierone



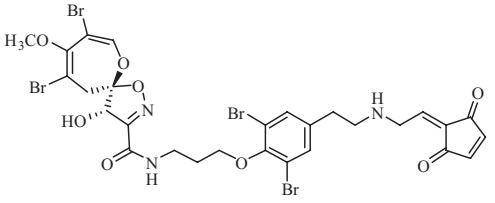
197 N-formyl-1,2-dihydrorenierone



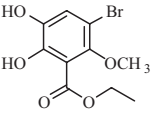
198 crambescin A2 392 n = 4
199 crambescin A2 406 n = 5
200 crambescin A2 420 n = 6
201 Sch 575948 n = 2



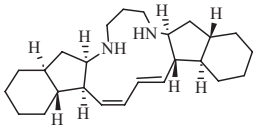
202 Ceratinine H



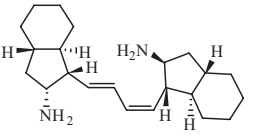
203 psammaplysin E



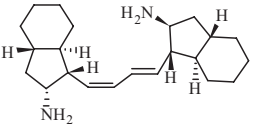
204 ceratinophenol A



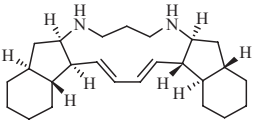
205 (10E,12Z)-Haliclonadiamine



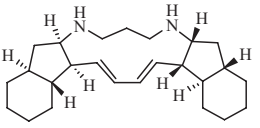
206 Halichondriamine A



207 Halichondriamine B



208 Haliclonadiamine



209 Papumamine

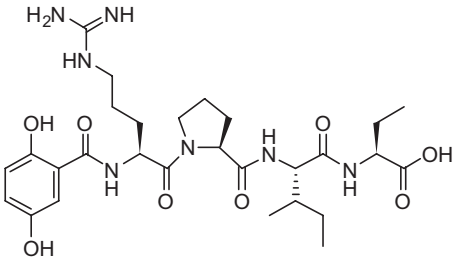
15.3 Bioactive Peptides

Marine sponges are shown to have a large variety of resources of bioactive peptides. From the structure, they possess linear peptides, cyclic peptides, and depsipeptides which of them have highly modified structural features of nonproteinogenic amino acid or hydroxy acid group, while others have those with minimal differences from the common ribosomal peptides.

This review summarizes the isolation, structure identification of a diverse 109 peptides from 27 marine sponges with a variety of potent biological activities within the literature coverage from 1991 to 2016.

15.3.1 Linear Peptides

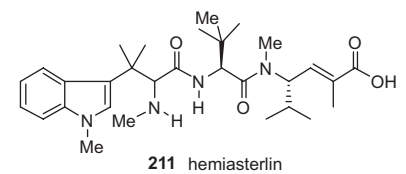
Nazumamide A (**210**) was isolated from the marine sponge *Theonella* sp. in 1991 and displayed inhibition of thrombin with an IC_{50} of 4.63 μM [78].



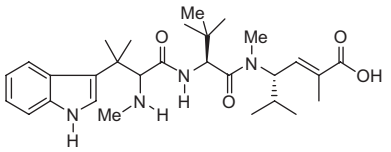
210 nazumamide A

In 1995, the known metabolite hemiasterlin (**211**) and the novel metabolites hemiasterlin A (**212**), hemiasterlin B (**213**), and criamide B (**214**) were isolated from a specimen of *Cymbasrefa* sp. at Motupore and Madang in Papua New Guinea. Hemiasterlin (**211**) displayed significant in vitro cytotoxicity against murine leukemia P388, human breast cancer MCF-7, human glioblastoma/astrocytoma U373, and human ovarian carcinoma HEY with ED_{50} values of 0.087, 170, 22.81, and 2.66 nM, respectively. Interesting, compared to hemiasterlin, hemiasterlin A (**212**) with absence of N-methyl motif attached on the indole ring showed higher activity against human glioblastoma/astrocytoma U373 but less active against human ovarian carcinoma HEY with ED_{50} values of 2.93 and 14.84 nM, respectively. Hemiasterlin B (**213**) closely related to **212** exhibited less cytotoxicity against murine leukemia P388, human breast cancer MCF-7, and human ovarian carcinoma HEY with ED_{50} values of 14.06, 0.13, and 0.032 μM, respectively. Similar com-

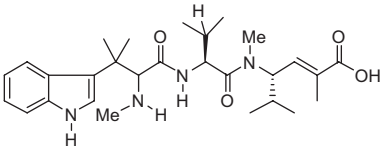
pound criamide B (**214**) was observed to display potent in vitro activity against murine leukemia P388, human breast cancer MCF-7, human glioblastoma/astrocytoma U373, human ovarian carcinoma HEY, human colon LOVO, and human lung A549 cell lines with ED_{50} values of 0.011, 9.97, 0.4, 0.28, 0.22, and 0.43 μM, respectively [79].



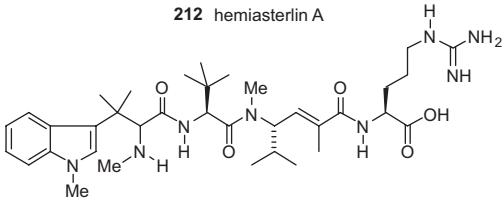
211 hemiasterlin



212 hemiasterlin A

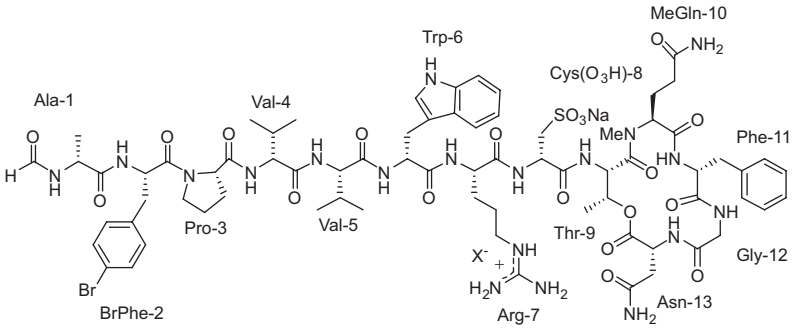


213 hemiasterlin B



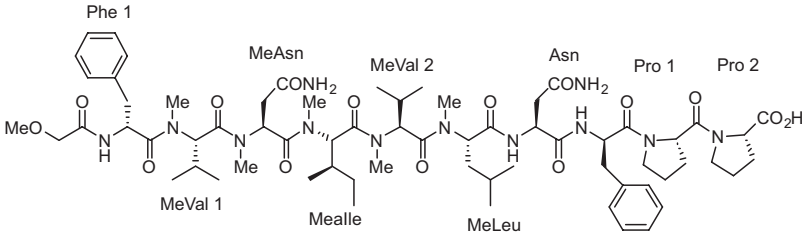
214 criamide B

Halicylindramides D (**215**), a tridecapeptide, was isolated from the marine sponge *Halichondria cylindrata* in Japan in 1996, which was cytotoxic against P388 murine leukemia cells with an IC_{50} value of 1.25 μM [80].



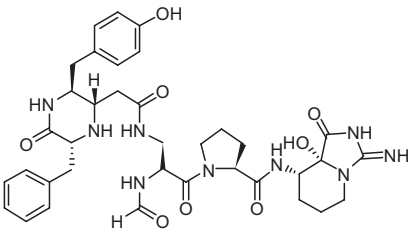
215 halicylindramides D

Koshikamide A_1 (**216**) isolated from a marine sponge, *Theonella* sp. collected from southwestern Japan in 1999, showed potent cytotoxicity against P388 leukemia cells with an IC_{50} value of 1.69 μM [81].

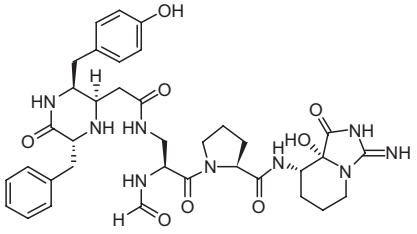


216 koshikamide A1

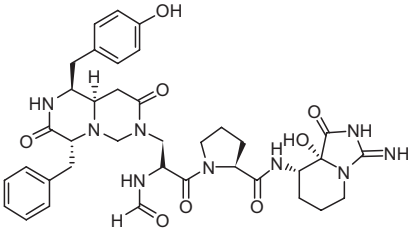
In 1999 six peptides, pseudotheonamides A1 (**217**), A2 (**218**), B2 (**219**), C (**220**), D (**221**), and dihydrocyclotheonamide A (**222**), were derived from the marine sponge *Theonella swinhoei* collected off Hachijo-jima Island, which exhibited selective serine protease inhibitory activities: inhibition of thrombin with IC_{50} values of 1.0, 3.0, 1.3, 0.19, 1.4, and 0.33 μM, respectively, while they inhibited trypsin with IC_{50} values of 4.5, >10, 6.2, 3.8, >10, and 6.7 μM, respectively [82].



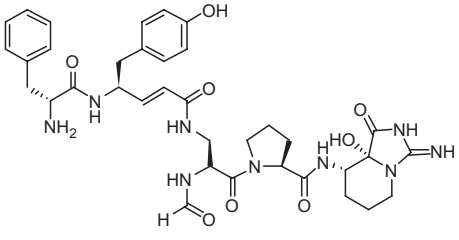
217 pseudotheonamides A_1



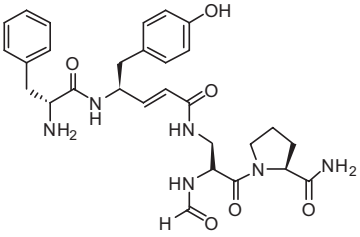
218 pseudotheonamides A_2



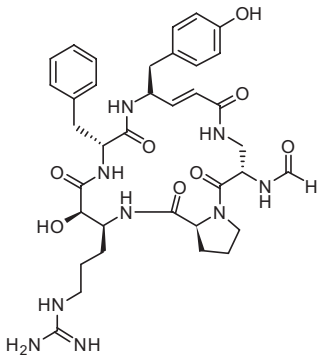
219 pseudotheonamides B_2



220 theonamide C

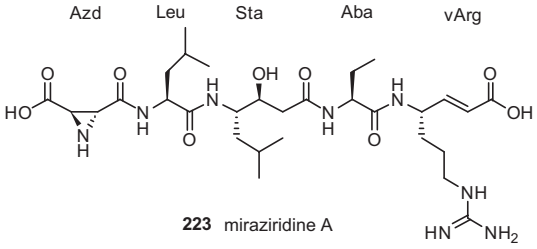


221 pseudotheonamide D



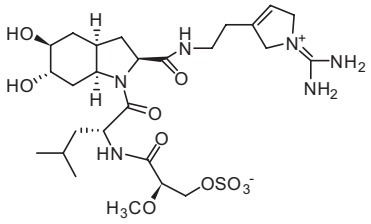
222 dihydrocyclotheonamide A

Miraziridine A (**223**) was isolated from the marine sponge *Theonella* aff. *mirabilis* in 2000 during the collection cruise on R/V *Toyoshio-maru* of Hiroshima University to the Amami and Tokara Islands, which was reported as a cathepsin B inhibitor with an IC_{50} value of 2.1 μM [83].



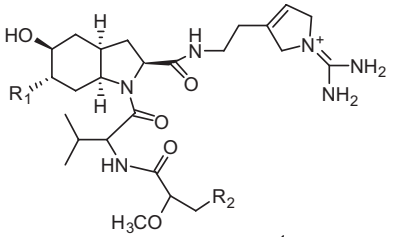
223 miraziridine A

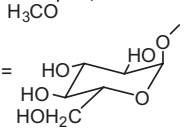
In 2002, dysinosin A (224) was identified as a novel inhibitor of factor VIIa and thrombin, with Ki value of 0.108 and 0.452 μM, respectively, from a new genus and species of Australian sponge of the family Dysideidae [84].



224 dysinosin A

In 2004, dysinosins B–D (**225–227**) were isolated from the sponge *Lamellodysidea chlorea* collected off Low Isles, Queensland, Australia, which inhibited factor VIIa at a Ki of 0.090, 0.124, and 1.320 μM, respectively, and thrombin at a Ki of 0.170, 0.550, and >5.1 μM, respectively [85].

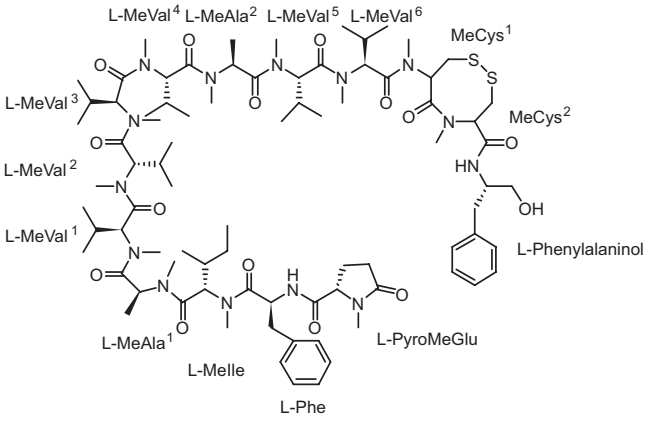


225 dysinosin B R_1 =  $R_2 = OSO_3^-$

226 dysinosin C $R_1 = OH$ $R_2 = OSO_3^-$

227 dysinosin D $R_1 = OH$ $R_2 = OH$

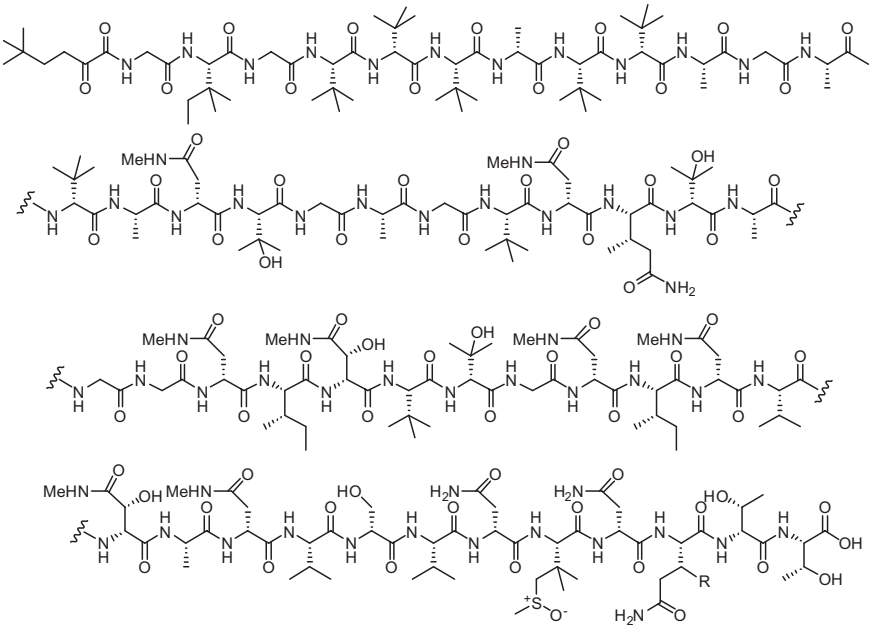
Marine sponge *Haliclona* sp. collected at Sulawesi Island, Indonesia, in 2004, led to the isolation of kendarimide A (**228**), which reversed MDR in KB-C2 cells mediated by P-glycoprotein (P-gp) at a concentration of 6 μM [86].



228 kendarimide A

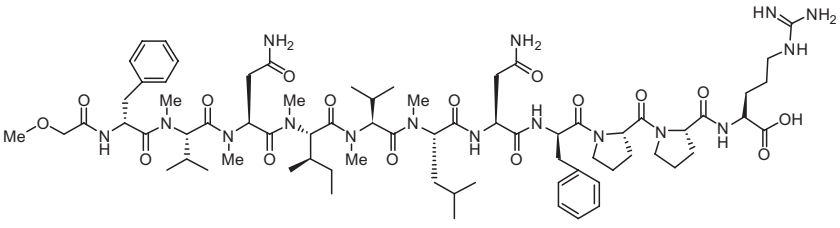
In 2005, some highly cytotoxic polypeptides with 48 amino acid residues, such as polytheonamides A (**229**), B (**230**), and C (**231**) were isolated from the marine sponge *Theonella swinhoei* collected from Hachijo-jima Island. They were tested against P388 murine leukemia cells with IC_{50} values of 15.5×10^{-6}, 13.51×10^{-6},

and 13.48 × 10^{-6} μM, respectively [87, 88], and polytheonamide B (**230**) exhibited cytotoxicity against HeLa human uterine cervix carcinoma cells with an IC_{50} value of 0.58 nM [89], L1210 murine lymphocytic leukemia cells with an IC_{50} < 0.8 nM [90], and Neuro-2a mouse neuroblastoma cells with an IC_{50} < 0.2 nM [91].



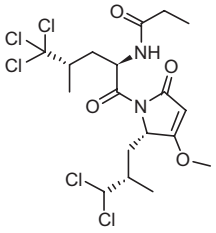
229 polytheonamides A R = H
230 polytheonamides B R = H
231 polytheonamides C R = Me

In 2005, the chemical investigation of marine sponge *Theonella* sp. collected off Shimo-koshiki-jima Island, Kagoshima, led to isolation of the koshikamide A_2 (**232**), which exhibited moderate cytotoxicity against P388 cells with an IC_{50} value of 4.6 μM [92].



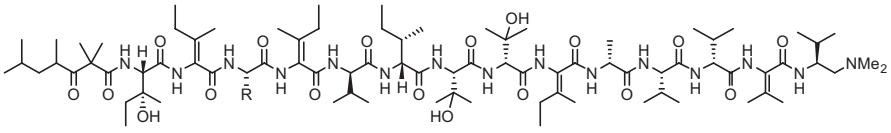
232 koshikamide A2

A chlorinated peptide, sintokamide A (**233**), was isolated from the marine sponge *Dysidea* sp. collected in Indonesia in 2008, which was found to be an inhibitor of N-terminus transactivation of the androgen receptor in prostate cancer cells with an IC_{50} at 9.8 μM [93].



233 sintokamide A

Yaku'amides A (**234**) and B (**235**) were isolated from the marine sponge *Ceratopsion* sp. collected at Yakushinsone in the East China Sea in 2008, which exhibited potent cell growth inhibitory activity against P388 murine leukemia cells with IC_{50} values of 8.54 and 2.42 nM, respectively. Interestingly, the profile of growth inhibitory activity of Yaku'amides A (**234**) was clearly unique and unusual compared with other anticancer drugs when against a panel of 39 human cancer cell lines [94].

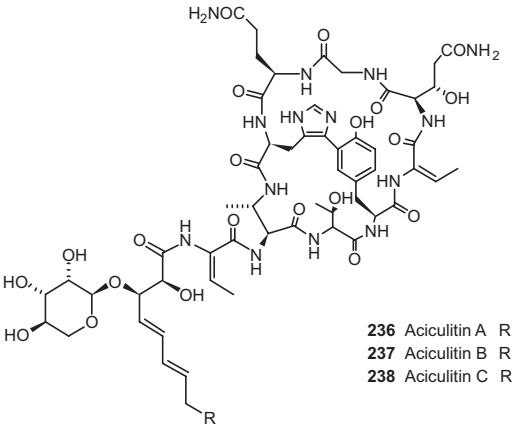


NTA OHIle ΔIle1 Gly (Ala) ΔIle2 Val1 aIle OHVal1 OHVal2 ΔIle3 Ala Val2 Val3 ΔVal CTA

R = H **234** Yaku'amide A
R = CH3 **235** Yaku'amide B

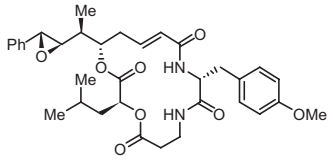
15.3.2 Cyclic Peptides

In 1996, aciculitins A–C (236–238) were isolated from the lithistid sponge *Aciculites orientalis* (Negros, Siquijor, Philippines). Aciculitins A–C were cytotoxic to the human colon tumor cell line HCT-116 with an IC_{50} of 0.5 μg/mL and inhibited the growth of *Candida albicans* at a loading of 2.5 μg/disk in the standard disk assay [95].



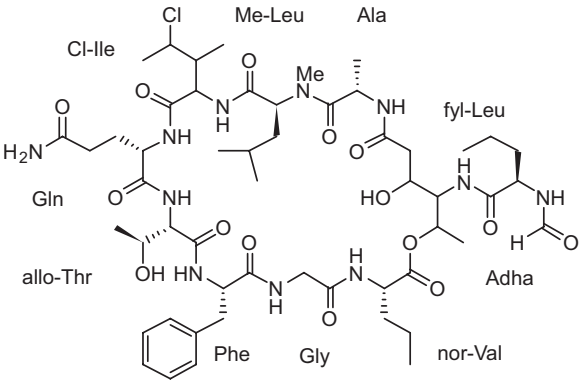
236 Aciculitin A R = C_5H_{11}
237 Aciculitin B R = C_6H_{13}
238 Aciculitin C R = C_7H_{15}

Through bioassay-guided separation, arenastatin A (239) was isolated from the marine sponge *Dysidea arenaria* (Okinawan, Japan) in 1995, which exhibited extremely potent cytotoxicity with IC_{50} of 5 pg/ml against KB cells [96].



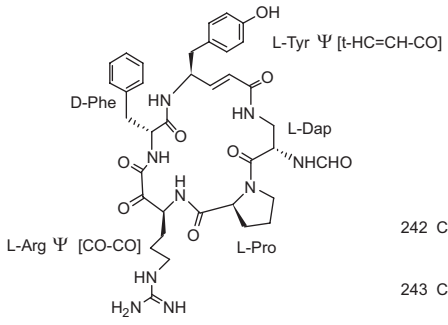
239 Arenastatin A

In 1998, a chlorate cyclic depsipeptide, cyclolithistide A (240), was isolated from the marine sponge *Theonella swinhoei*. It is important to note that cyclolithistide A exhibited significant antifungal activity against *Candida albicans* (ATCC 24433) in the agar disk diffusion assay. At a dose of 20 μg/disk, the inhibition activity was comparable to 90% of the standard, nystatin at a dose of 100 μg/disk [97].

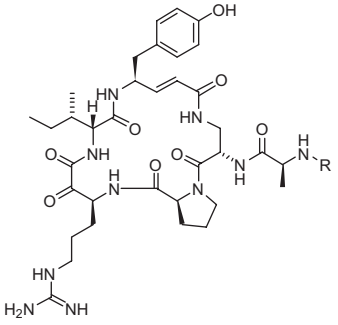


240 Cyclolithistide A

Cyclotheonamide A (241), cyclotheonamide E (242), and cyclotheonamides E2 (243) and E3 (244) were isolated from the marine sponge *Theonella swinhoei* (Tanegashima Island, Tokyo, in July 1993) as a series of potent serine protease inhibitors. In the inhibitory assays against thrombin and trypsin, cyclotheonamide A, E, E2, and E3 exhibited significant inhibition activities with IC_{50} values of 23 and 16 nM, 2.9 and 30 nM, 13 and 55 nM, and 9.5 and 52 nM, respectively [98].



241 cyclotheonamide A



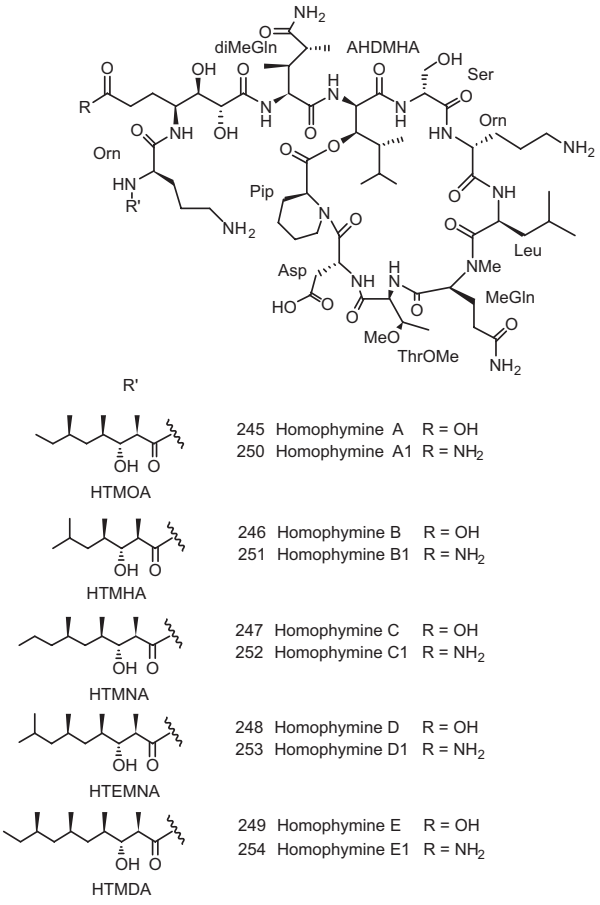
242 Cyclotheonamides E R =

243 Cyclotheonamides E2 R =

244 Cyclotheonamides E3 R =

An anti-HIV cyclodepsipeptide, homophymine A (245), was isolated from the marine sponge *Homophymia* sp. (New Caledonian, in 1992), which effectively inhibited the HIV-1 infection with an IC_{50} of 75 nM. Direct cytotoxicity of 17 against the host cells was observed with a TC_{50} (toxic concentration) of 1.19 μM

[99]. Nine cyclodepsipeptides, homophymines B–E (246–249) and A1–E1 (250–254), were also isolated from the polar extracts of the sponge *Homophymia* sp. (New Caledonian, in 1992). Homophymines displayed very potent antiproliferative activity (IC_{50} in the nM range) against a panel of human cancer cell lines [100].



245 Homophymine A R = OH
250 Homophymine A1 R = NH_2

246 Homophymine B R = OH
251 Homophymine B1 R = NH_2

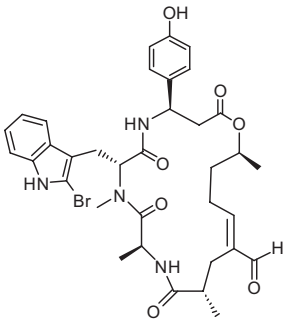
247 Homophymine C R = OH
252 Homophymine C1 R = NH_2

248 Homophymine D R = OH
253 Homophymine D1 R = NH_2

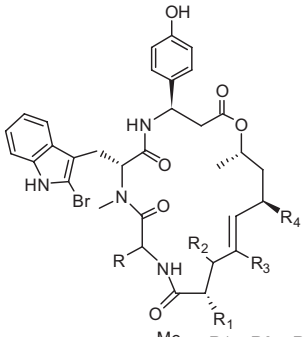
249 Homophymine E R = OH
254 Homophymine E1 R = NH_2

In 2009, jaspamide (255) and jaspamides B–P (256–269) were isolated from the marine sponge *Jaspis splendens*. All tested jaspamide derivatives exhibited antiproliferative activities with IC_{50} values ranging from 0.01 to 33 μM against human breast adenocarinoma (MCF-7) and colon carcinoma (HT29) cell lines [101]. Jaspamides B and C exhibited cytotoxicity against the human NSCLC-N6 cancer cell line with IC_{50} values of 3.3 and 1.1 μg/mL, respectively [102]. Jaspamides Q

and R together with jaspamide exhibited potent activities against mouse lymphoma (L5178Y) cell lines with IC_{50} values in the ng/mL range (<0.1 μg/mL, <0.16 μM) [103].



261 Jaspamide G



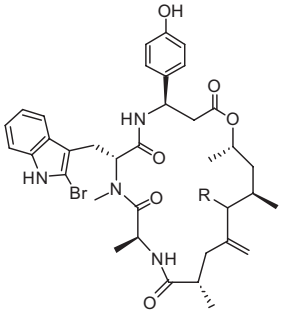
255 Jaspamide R = Me; R1 = R3 = R4 = Me, R2 = H

258 Jaspamide D R = Et; R1 = R3 = R4 = Me, R2 = H

259 Jaspamide E R = CH_2OH; R1 = R3 = R4 = Me, R2 = H

260 Jaspamide F R = CH_3; R3 = R4 = Me, R1 = R2 = H

262 Jaspamide H R = CH_3; R1 = R3 = Me, R2 = R4 = H



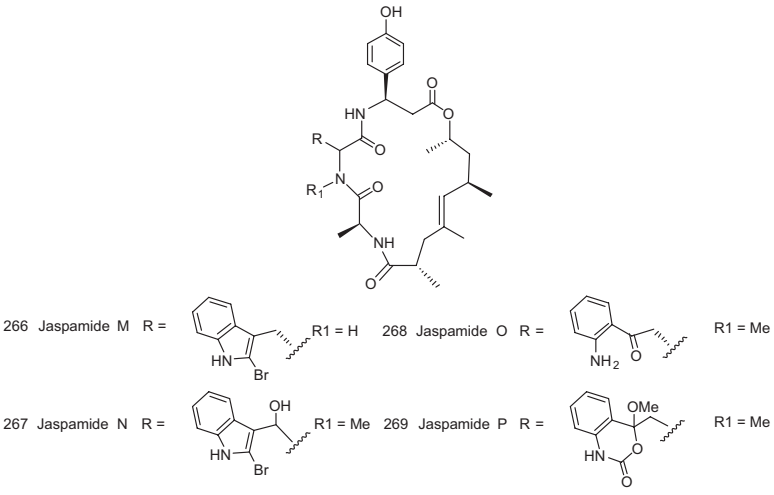
256 Jaspamide B R = =O

257 Jaspamide C R = —OH

263 Jaspamide J R = CH_3; R3 = R4 = Me, R1 = R2 = H

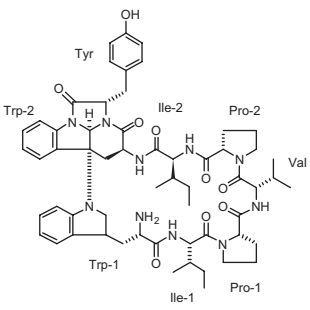
264 Jaspamide K R = CH_3; R1 = R3 = R4 = Me, R2 = OH

265 Jaspamide L R = CH_3; R1 = R4 = Me, R2 = H, R3 = CH_2OH

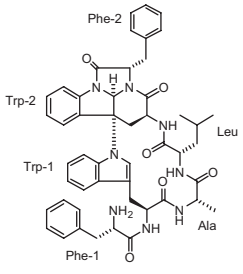


Kapakahines A–C (270–272) were isolated from the sponge *Cribrochalina olemda* (Pohnpei, Federated States of Micronesia, in April 1992, and recollected in August 1993). Kapakahines A, B, and C showed moderate cytotoxicity against P388 murine leukemia cells at IC_{50} values of 5.4, 5.0, and 5.0 μg/mL, respectively [104].

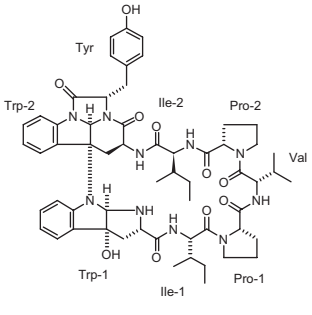
In 1995, five cyclic peptides, keramamides E (273), F (274), G (275), H (276), and J (277), containing an oxazole or a thiazole ring, were isolated from the marine sponge *Theonella* sp. (Okinawan). Keramamide E exhibited cytotoxicity against L1210 murine leukemia cells and human epidermoid carcinoma KB cells with IC_{50} values of 1.60 and 1.55 μg/mL, respectively, while keramamides G, H, and J showed weak cytotoxicity (IC_{50} ~10 μg/mL) [105]. Keramamide F showed cytotoxicity against human epidermoid carcinoma KB cells and murine lymphoma L1210 cells with IC_{50} values of 1.4 and 2.0 μg/mL, respectively [106].



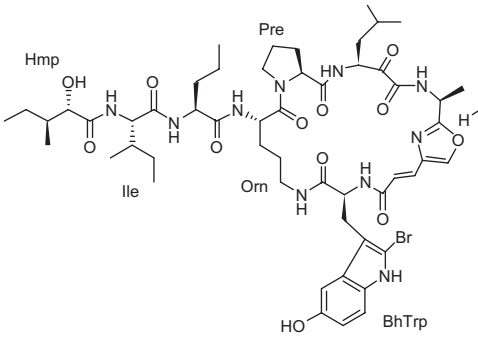
270 Kapakahine A



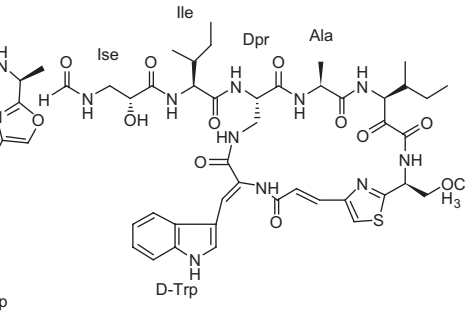
271 Kapakahine B



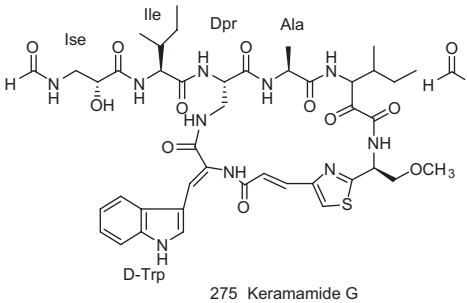
272 Kapakahine C



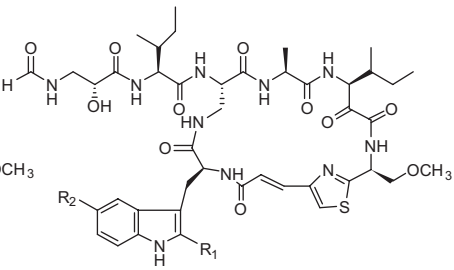
273 Keramamides E



274 Keramamide F

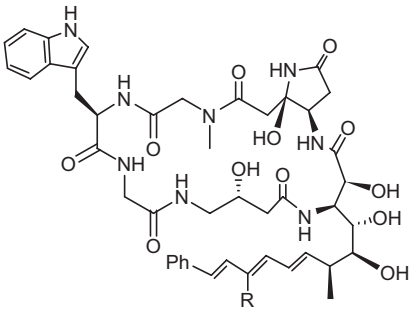


275 Keramamide G

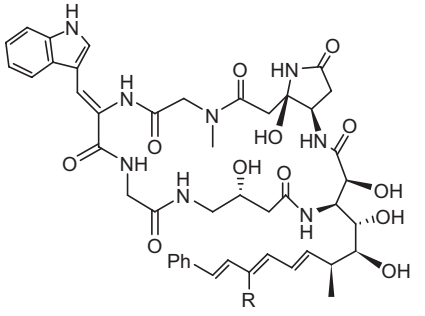


276 Keramamide H R1 = Br, R2 = OH
277 Keramamide J R1 = R2 = H

Four cyclic peptides, microsclerodermins F–I (278–281), were isolated from *Microscleroderma* sp. (Palau, Koror, in 1997). All four microsclerodermins showed very similar cytotoxicity against the HCT-116 cell line with IC_{50}'s of 1.0 μg/mL (280), 1.1 μg/mL(281), 1.8 μg/mL (278), and 2.4 μg/mL (279) [107].

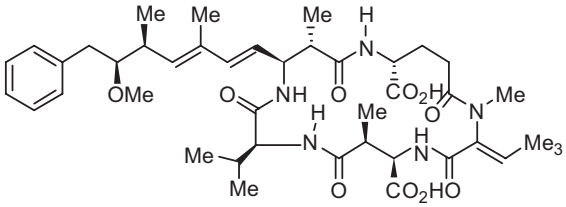


278 Microsclerodermins F R = H
280 Microsclerodermins H R = CH_3



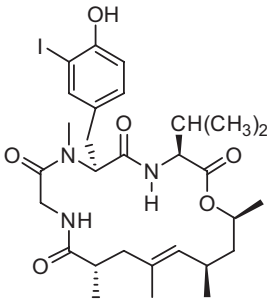
279 Microsclerodermins G R = H
281 Microsclerodermins I R = CH_3

Motuporin (282), a cyclic pentapeptide, was isolated from the marine sponge *Theonella swinhoei* (Papua, New Guinea, 1992). Motuporin inhibited protein phosphatase-1 in a standard phosphorylase phosphatase assay at a concentration of < l nM, making it one of the most potent PPl inhibitors known, and it also displayed considerable in vitro cytotoxicity against murine leukemia (P388: IC_{50} 6 μg/mL), human lung (A549: IC_{50} 2.4 μg/mL), ovarian (HEY: IC_{50} 2.8 μg/mL), colon (LoVo: IC_{50} 2.3 μg/mL), breast (MCF-7: IC_{50} 12.4 μg/mL), and brain (U373MG: IC_{50} 2.4 μg/mL) cancer cell lines [108].



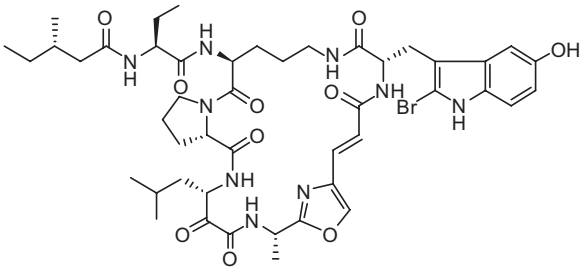
282 Motuporin

Neosiphoniamolide A (283), a potent antifungal cyclodepsipeptide, was isolated from the sponge *Neosiphonia supertes* (New Caledonia, 1989). Neosiphoniamolide A inhibited the growth of the fungi *Piricularia oryzae* and *Helminthosprium gramineum* with IC_{90} values of 5 ppm [109].



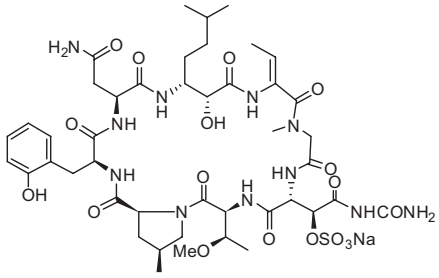
283 Neosiphoniamolide A

In 1991, orbiculamide A (284), a cyclic peptide isolated from themarine ponge *Theonella* sp., exhibited cytotoxic activity against P388 murine leukemia cells (IC_{50} 4.7 μg/mL) [110].

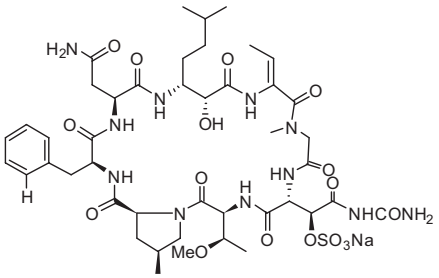


284 Orbiculamide A

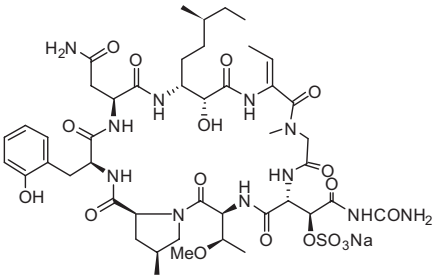
The chemical investigation of marine sponge *Theonella swinhoei* (Malaita Island, Solomon Islands, in July 2004) resulted in the isolation of nine cyclopeptides, perthamides C–K (285–263). Perthamides were proved to inhibit TNF-α and IL-8 release in primary human keratinocytes cells and therefore could represent potentially leads for the treatment of psoriasis [111, 112].



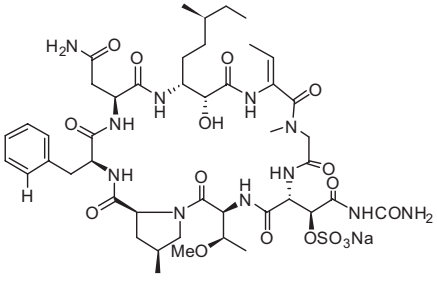
285 Perthamide C



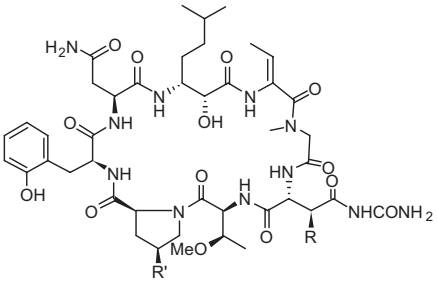
286 Perthamide D



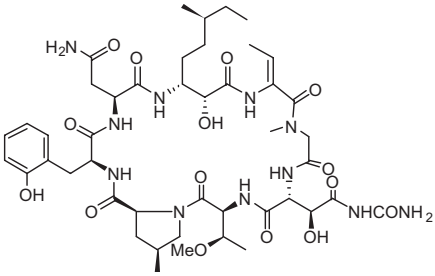
287 Perthamide E



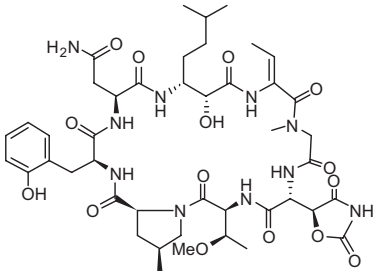
289 Perthamide F



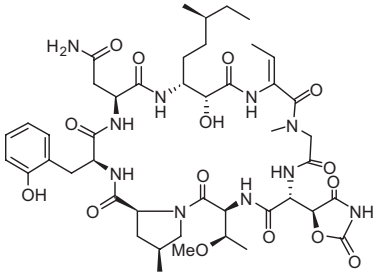
290 Perthamide G R=OSO_3Na R'=H
291 Perthamide H R=OH R'=CH_3



292 Perthamide I

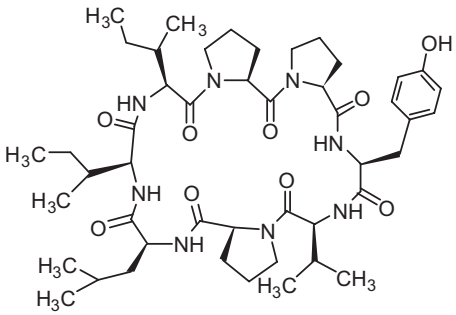


293 Perthamide J



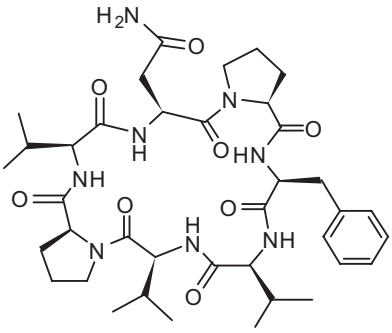
294 Perthamide K

A proline-rich cyclic octapeptide, hymenistatin 1 (295), was isolated from the sponge *Hymeniacidon* sp. (Palau, Western Pacific Ocean, 1985), which was found to be active against the P388 leukemia cell line (ED_{50} 3.5 μg/mL) [113].



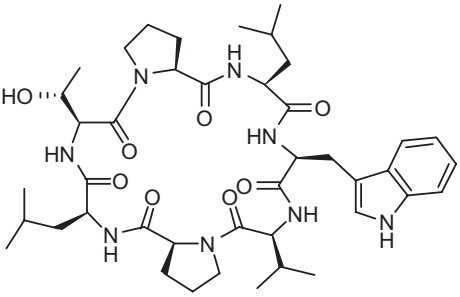
295 Hymenistatin 1

Axinastatin 1 (296), a proline-rich cyclic peptide, was isolated from the marine sponge *Axinella* sp. (Palau, Western Pacific, in 1985), with P388 lymphocytic leukemia inhibitory activity (ED_{50} 0.21 μg/mL) [114].



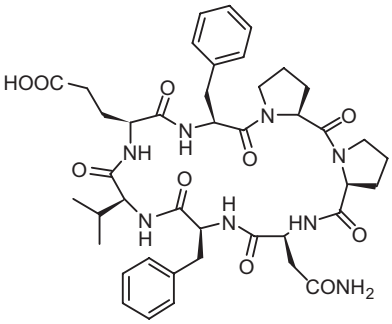
296 Axinastatin 1

In 1993, axinastatin 4 (297), another proline-rich cycloheptapeptide, was isolated from marine sponge *Axinella* cf. (collected in western Indian Ocean, The Republic of The Comoros), which showed comparable cell growth inhibitory activity against a series of human cancer cell lines (P388 lymphocytic leukemia cell line, ED_{50} = 0.057 μg/mL) [115].



297 Axinastatin 4

In 1993, a cyclic heptapeptide, hymenamide B (298), with a prolylproline segment was isolated from the marine sponge *Hymeniacidon* sp. (Okinawan, Japan). Hymenamide B showed cytotoxicity against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells with IC_{50} value of 3.2 and 6.0 μg/mL in vitro, respectively [116].



298 Hymenamide B

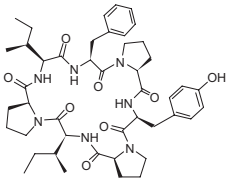
A cycloheptapeptide designated phakellistatin 1 (299) was isolated from two Indo-Pacific sponges, *Phakellia costata* (Truk Archipelago, 1985–1987) and *Stylotella aurantium* (Palau Archipelago, in 1985), which appeared moderate antitumor activity (P388 murine leukemia ED_{50} 7.5 μg/ml) [117].

In 1995, cyclic heptapeptide phakellistatin 2 (300) was isolated from the marine sponge *Phakellia carteri*, showed cell growth inhibitory activity of ED_{50} 0.34 μg/mL against the P388 lymphocytic leukemia cell line [118, 119]. Phakellistatin 4 (301) isolated from *Phakellia costata*, showed GI_{50} values of about 0.6 μM in different human cancer cell lines [119]. Phakellistatin 5 (302), a metabolite of marine sponge *Phakellia costada* collected from the Federated States of Micronesia (Chuuk), exhibited significant cell growth inhibitory activity to the P388 murine lymphocytic leukemia and the human cancer cell lines representing ovarian (OVCAR-3), CNS (SF295), lung (NCI-H460), prostate (DU-145), colon (KM20L2), and melanoma (SK-MEL-5) cancers, with GI_{50} values ranging from 0.14 to 0.74 μg/mL [120].

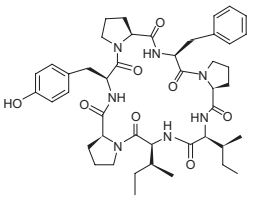
In 2003, cyclodecapeptide designated phakellistatin 12 (303) was isolated as a trace (1.7×10^{-6}% yield) constituent of the Western Pacific Ocean (Federated States of Micronesia-Chuuk) sponge *Phakellia* sp. with activity against P388 lymphocytic leukemia ED_{50} 2.8 μg/mL [121].

A cyclic heptapeptide phakellistatin 13 (304) isolated from the sponge *Phakellia fusca* Thiele, collected off Yongxing Island of China, in 1998, exhibited potent cytotoxicity against the human hepatoma BEL-7404 cell line with an $ED_{50} < 2$ μg/mL [122].

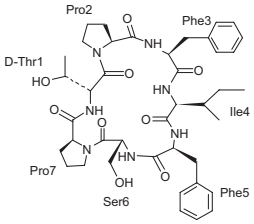
Phakellistatins 15–18 (305–309), together with five known cyclopeptides, phakellistatin 13, hymenistatin 1, and hymenamides G, H, and J, were isolated from the South China Sea sponge *Phakellia fusca*, 2007. The new cyclopeptides 74–78 were tested for cytotoxic activity in vitro. Phakellistatin 15 exhibited cytotoxicity against cancer cell line P388 with an IC_{50} value of 8.5 μM. Phakellistatin 16 showed cytotoxicity against cancer cell lines P388 and BEL-7402 with IC_{50} values of 5.4 and 14.3 μM, respectively. Phakellistatins 17 and 18 showed no cytotoxicity against the cancer cell lines P388 and BEL-7402 [123]. The synthetic cyclic peptides of phakellistatins were chemically but not biologically identical with the natural products [116–119].



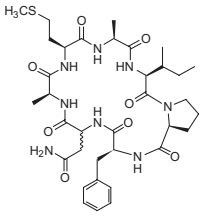
299 Phakellistatin 1



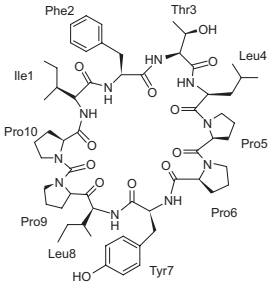
300 Phakellistatin 2



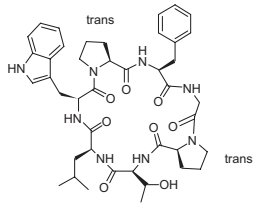
301 Phakellistatin 4



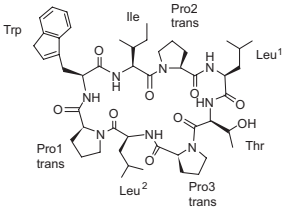
302 Phakellistatin 5



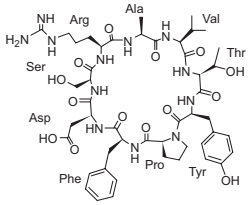
303 Phakellistatin 12



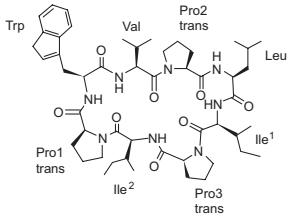
304 Phakellistatin 13



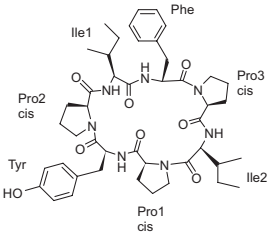
305 Phakellistatins 15



306 Phakellistatins 16 3a trans-Pro (major conformer)
307 Phakellistatins 16 3b cis-Pro (major conformer)

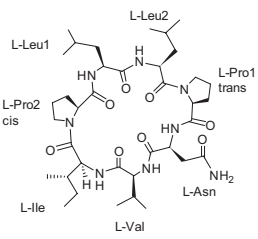


308 Phakellistatins 17

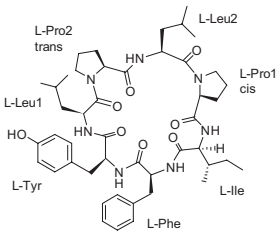


309 Phakellistatins 18

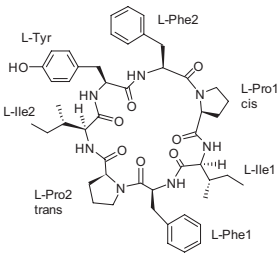
Reniochalistatins A−E (310–314) were isolated and characterized from the marine sponge *Reniochalina stalagmitis* (Yongxing Island, South China Sea, 2009). The cyclic octapeptide reniochalistatin E showed biological activity in various cytotoxicity assays employing different tumor cell lines (RPMI-8226, MGC-803, HL-60, HepG2, and HeLa), against myeloma RPMI-8226 and gastric MGC-803 cells with IC_{50} values of 4.9 and 9.7 μM, respectively, but with no activity against leukemia HL-60 and hepatoma HepG2 (IC_{50} > 20.0 μM) and cervical HeLa (IC_{50} 17.3 μM) cells [124].



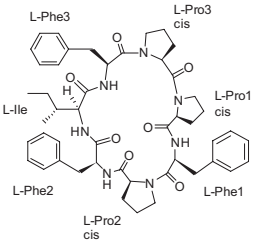
310 Reniochalistatin A



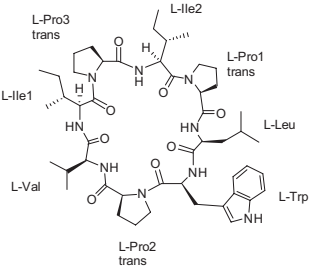
311 Reniochalistatin B



312 Reniochalistatin C



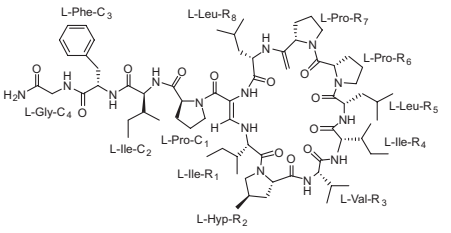
313 Reniochalistatin D



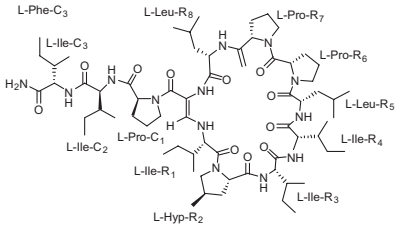
314 Reniochalistatin E

From 2008 to 2015, the chemical investigation of Indonesian sponge *Callyspongia aerizusa* collected from three different locations in Indonesia as indicated: Makassar, S. Sulawesi; Lembeh, N. Sulawesi; and Ambon, Maluku)

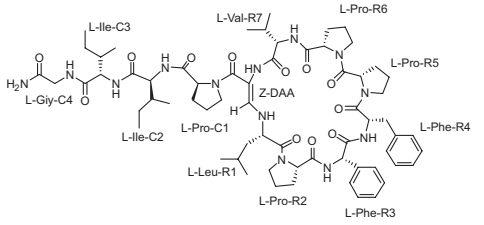
afforded 13 cyclic peptides callyaerins A–M; callyaerins A (315) and B (316) showed potent anti-TB (*Mycobacterium tuberculosis*) activity with MIC_{90} values of 2 and 5 μM, respectively. Callyaerin A showed strong anti-TB activity, but not cytotoxic to THP-1 (the human monocytic cell line) or MRC-5 (the human fetal lung fibroblast cell line) cells (IC_{50} > 10 μM), which indicated the potential of these compounds as promising anti-TB agents. Callyaerins E (317) and H (318) exhibited strong activity against the L5178Y cell line with ED_{50} values of 0.39 and 0.48 μM, respectively. On the other hand, callyaerin A also showed strong antifungal activity toward *C. albicans*. Callyaerin G (319) was found to be cytotoxic toward the mouse lymphoma cell line (L5178Y) and HeLa cells with ED_{50}(s) of 0.53 and 5.4 μg/mL, respectively [98].



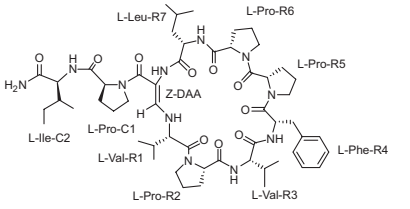
315 Callyaerin A



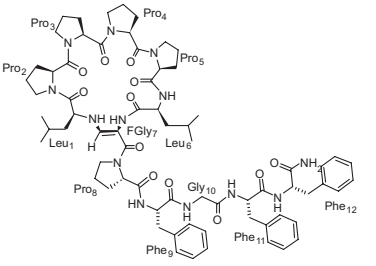
316 Callyaerin B



317 Callyaerin E



318 Callyaerin H

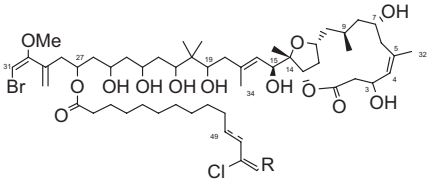


319 Callyaerin G

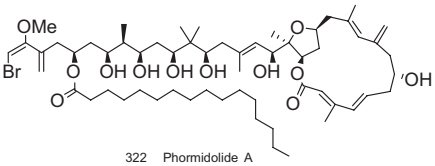
15.4 Bioactive Polyketides

Marine aliphatic polyketides are a class of compounds that present diverse and interesting biological properties. Due to the versatility of their biosynthetic production mechanism, these compounds exhibit remarkable diversity, both in terms of structural complexity and biological activity. Polyketides are constructed as highly oxygenated stereo chemically enriched scaffolds, sometimes with the characteristic presence of macrocyclic lactones, cyclic five- or six-membered ethers, or polyethers that act as a conformational constraint. This review summarizes the isolation, structure identification of a diverse 104 polyketides from 23 genera of marine sponges with a variety of potent biological activities within the literature coverage from 1968 to 2016.

Phormidolide A, first isolated from the cyanobacterium *Phormidium* sp., which is toxic to brine shrimp (LC_{50} = 1.5 μM) [125], together with two new cytotoxic macrolides named phormidolides B (**320**) and C (**321**), were identified from a sponge of the Petrosiidae family, collected off the coast of Pemba (Tanzania), in 2014 [126]. Cytotoxic activities tested using three human tumor cell lines, lung (A549), colon (HT29), and breast (MDA-MB-231), manifested that phormidolides B and C have significant cytotoxic activities against these three cell lines with IC_{50} around 0.5–1.4 μM [126]. The fact of original discovery from a cyanobacteria species suggested that phormidolide A (**322**) is actually metabolite synthesized by symbiotic cyanobacterium of the sponge, supporting the relevance of symbiotic bacteria as sources of bioactive polyketides and peptides in sponges.



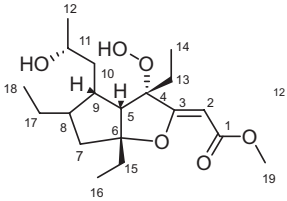
320 Phormidolide B R=Cl
321 Phormidolide C R=Br



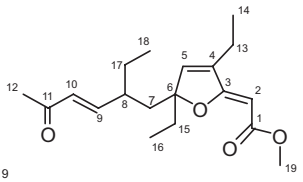
322 Phormidolide A

Plakilactones and gracilioethers are oxygenated polyketides of the plakortin family isolated from the marine sponge *Agelas gracilis*, collected in southern Japan, in 2009 [127] and *Plakinastrella mamillaris*, collected at the Fiji Islands, in 2012–2013 [128–130]. In bioassay-guided fractionation of the lipophilic sponge *Agelas gracilis* extract, Fusetani et al. obtained three new antimalarial compounds against *Plasmodium falciparum*, gracilioethers A–C (**323–325**), with IC_{50} values of 0.5–10 μg/mL, whereas gracilioether B also showed antileishmanial activity [127]. A few years later, the Zampella group isolated several plakilactone- and gracilioether-polyketides, together with the previously known gracilioethers A–C compounds from another sponge *Plakinastrella mamillaris*. Among them, gracilioether B, gracilioether C, and plakilactone C (**326**) demonstrated activation of PPARγ in a dose-dependent manner with relative EC_{50} values of ≈ 5, 10, and 2 μM, respectively, and

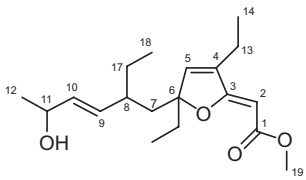
further mechanism study demonstrated that gracilioether B and plakilactone C covalently bind to the PPARγ substrate domain through a Michael addition reaction involving a cysteine residue and the α,β-unsaturated ketone group in their side chains, whereas gracilioether C is a noncovalent agonist for PPARγ [128]. In additon, gracilioether H (**327**) inhibited chloroquine-resistant CR FC29 strain in vitro with the antiplasmodial activity of IC_{50} 3.26 μM [129].



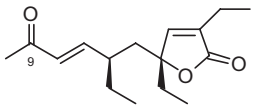
323 Gracilioether A



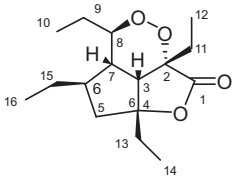
324 Gracilioether B



325 Gracilioether C

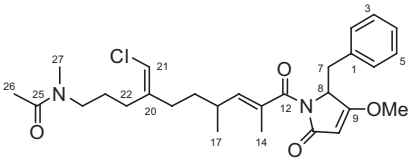


326 Plakilactone C

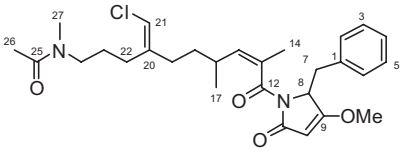


327 Gracilioether H

Smenamide A (**328**) and B (**329**), hybrid peptide/polyketide compounds consisting of a dolapyrrolidinone unit isolated from a Caribbean sponge *Smenospongia aurea*, are collected by SCUBA along the coast of Little Inagua (Bahamas Islands), in 2013 [131]. Structures of smenamides revealed the products of the cyanobacterial metabolism, and 16S rRNA metagenomic analysis detected *Synechococcus spongiarum* as the only cyanobacterium present in *S. aurea*. Smenamides A and B show potent cytotoxic activity at nanomolar levels on lung cancer Calu-1 cells with IC_{50} values of 48 nM and 49 nM, respectively. The clear pro-apoptotic mechanism of action of smenamide A makes smenamides promising results to antitumor drug design.



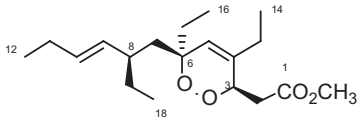
328 Smenamide A



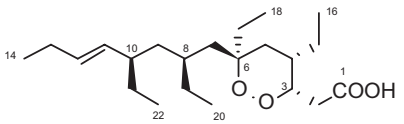
329 Smenamide B

Plakortide R–U (**330–333**), endoperoxide polyketides isolated from the marine sponge *Plakinastrella mamillaris*, collected at Fiji Islands, in 2013 [132]. Pharmacological analysis demonstrated that plakortide U showed the best antiplas-

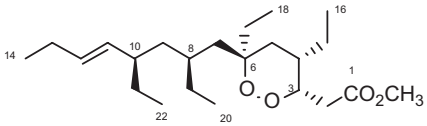
modial activity in vitro against chloroquine-resistant FcM29 strain (IC_{50} 0.80 μM), while the remaining compounds showed a moderate antiplasmodial activity (IC_{50} range: 5–50 μM).



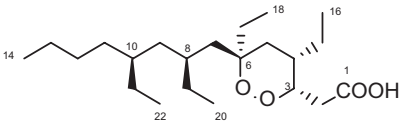
330 Plakortide R



331 Plakortide S

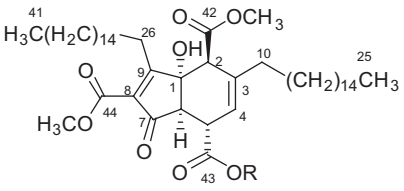


332 Plakortide T

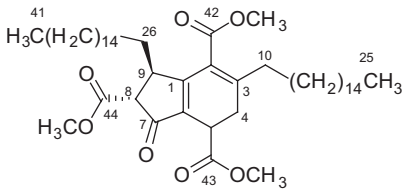


333 Plakortide U

Manzamenones L–N (**334–336**), dimeric fatty-acid derivatives, consisting of an octahydroindenone with three carboxy groups and two hexadecanyl chains, isolated from an Okinawan marine sponge of the genus *Plakortis*, collected in Okinawan, in 2012 [133]. Antimicrobial activity tests against several bacteria and fungi showed that manzamenone M had moderate antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, and *Cryptococcus neoformans* (MIC or IC_{50}, 8–32.0 μg/mL), and manzamenone L did not exhibit activity (MIC or IC_{50}, >32.0 μg/mL). From the point of view of structure-activity relationships between manzamenone L and manzamenone M, a free carboxylic acid at C-5 position might be important for the activities. Manzamenone N showed moderate antimicrobial activities against *E. coli*, *C. albicans*, and *C. neoformans* (MIC or IC_{50}, 4–32.0 μg/mL).

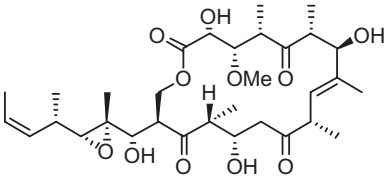


334 Manzamenones L R=CH_3
335 Manzamenones M R=H

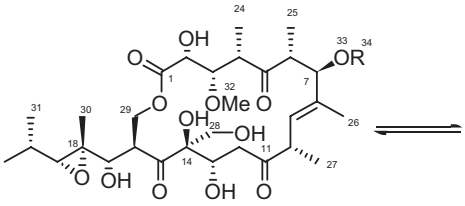


336 Manzamenones N

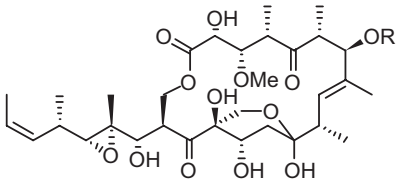
Tedanolide macrolides, which includes tedanolide (**337**) [134] isolated from *Tedania ignis*, collected in Caribbean, in 1984; 13-deoxytedanolide [135] isolated from *Mycale adhaerens*, collected by SCUBA off Hiburi Island (−10 to −15 m) of the Uwa Sea, 750 km southwest of Tokyo, in 1991; tedanolide C (**338**) [136] isolated from *Ircinia* sp., collected in Milne Bay (S 10°14.278′ E 150°54.782′), Papua New Guinea, in 2006; and precandidaspongiolides A (**339**) and B (**340**) and candidaspongiolides A (**341**) and B (**342**) from *Candidaspongia* sp., collected in Papua New Guinea, in 2011(isolated as an inseparable mixture of two isomers in equilibrium) [137], exhibited highly cytotoxic in the subnanomolar to nanomolar range against various cancer cell lines. Cell-flow cytofluorometry analysis revealed that tedanolide caused accumulation of cells in the S phase at concentration as low as 0.01 μg/mL [134]. 13-Deoxytedanolide (**343**) showed remarkable cytotoxicity against P388 murine leukemia cells with IC_{50}'s of 94 pg/mL. 13-Deoxytedanolide also performed highly in vivo antitumor activity against P388: *T*/*C* = 189% at a dose of 0.125 mg/kg [135]. Tedanolide C exhibited potent cytotoxicity against HCT-116 cells in vitro with IC_{50} value of 9.53×10^{-8} M and caused a strong S-phase arrest [136]. Precandidaspongiolides A and B showed excellent selectivity against melanoma cell lines in the NCI 60-cell line screen, and the LC_{50} values for precandidaspongiolides A/B against melanoma cell lines were significantly lower than other tumor cell lines (seven of the nine melanoma cell lines in the panel had nanomolar LC_{50} values around 19–174 nM); further, precandidaspongiolides A/B were evidenced as P-gp substrates [137]. Studies of SARs of 13-deoxytedanolide [135], precandidaspongiolides A and B, and candidaspongiolides A and B [137] reported that the southern hemisphere of 13-deoxytedanolide comprised the pharmacophore and the epoxide-bearing side chain of 13-deoxytedanolide was essential for the activity [138]; the hemiketal of precandidaspongiolide B and candidaspongiolide B was not essential for the activity, while potency was affected when the primary alcohol of precandidaspongiolides A and candidaspongiolide A was substituted, and the C-7 acetylation of candidaspongiolides A and B increased potency [137]. The similarities between the myriaporones [139] and the candidaspongiolides [137] afforded further evidence in support of microbial symbionts as producers of candidaspongiolides, 13-Deoxytedanolide [140] and candidaspongiolide A [141]. However, the underlying reasons for the candidaspongiolides' melanoma selectivity have yet to be determined.



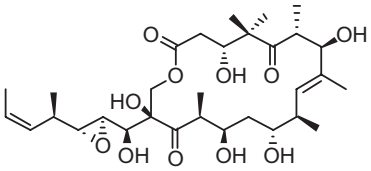
337 Tedanolide



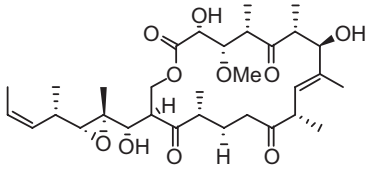
338 Precandidaspongiolides A R=H
339 Precandidaspongiolides B R=Ac



340 Candidaspongiolide A R=H
341 Candidaspongiolide B R=Ac

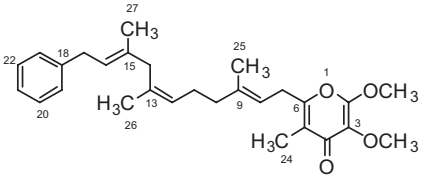


342 Tedanolide C

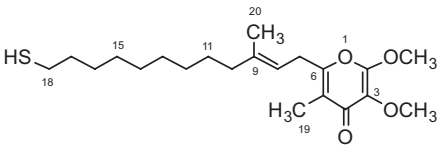


343 13-deoxytedanolide

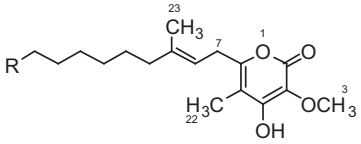
Lehualides are polyketide derivatives isolated from sponge of the genus *Plakortis*, which have a long alkyl chain with varying degrees of saturation and incorporate α- or γ-pyrone moieties, coupled with thioacetate or thiol functionalities [142, 143]. Lehualide B (**344**) showed moderate cytotoxicity in vitro against an ovarian cancer cell line (IGROV-ET) with a GI_{50} value of 0.83 μM. Lehualide D (**345**) exhibited moderate cytotoxicity to ovarian (IGROV-ET) and leukemia (K562) cell lines with GI_{50} values of 0.73 and 0.23 μM, respectively (the sample of sponge was collected from waters between Lehua Rock and Niihau Island, Hawaii, in July 2003) [143]. Lehualides F (**346**) and G (**346**) exhibited IC_{50} values for cytotoxicity against the human promyelocytic leukemia (HL-60) cell line of 6.2 and 5.4 μM, respectively (the *Plakortis* sponge specimen was collected from a cave off the coast of ‘Eua Island, Tonga) [142].



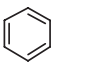
344 Lehualide B



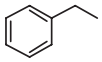
345 Lehualide D



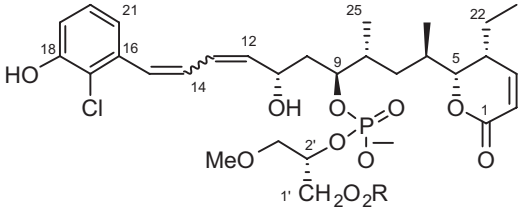
346 Lehualides F R=



347 Lehualides G R=

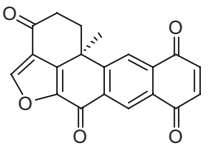


Franklinolides A–C (**348–350**) are the first examples of polyketide phosphodiesters isolated from an aqueous EtOH extract of a sponge sample CMB-01989, collected during deepwater (−105 m) scientific trawling operations in the Great Australian Bight, a massive *Geodia* sp. thinly encrusted with a *Halichondria* sp., in 2010 [144]. SAR studies, using in vitro cytotoxicity and cell proliferation assays against stomach (AGS), colon (HT29), and human brain (SH-SY5Y) cancer cell lines, and a noncancerous control cell line, demonstrated that franklinolides A was the dominant cytotoxic agent (GI_{50} range from 0.1 to 0.3 μM). SAR analysis defined the relative importance of key structural features: (1) a very significant 30- to >300-fold decrease in cytotoxicity following hydrolysis of franklinolides A to bitungolide A [145] (the de-3-*O*-methyl-2-phosphoglyceric acid derivative of franklinolides A); (2) 2- to 7-fold decrease on isomerization of franklinolides A to the 12*E*,14*E* isomer franklinolides B; and (3) a 30- to 50-fold decrease on isomerization of franklinolides A to the 12*E*,14*Z* isomer franklinolides C.

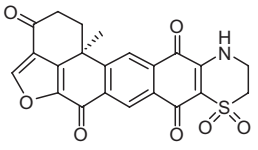


348 Franklinolides A 12*Z*,14*Z* and R=H
349 Franklinolides B 12*E*,14*E* and R=H
350 Franklinolides C 12*E*,14*Z* and R=H

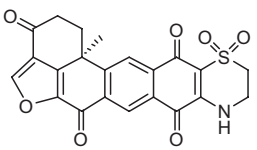
Halenaquinone-type polyketides (**351–358**) were isolated from marine sponges of the genus *Xestospongia* (collected in the South Pacific [146], in the Benga Lagoon, Fiji Islands [147], in Fiji (coll. Nos. 89,109 and 91,007) or Vanuatu (coll. no. 90033) [148], in Kerama Islands, Okinawa [149] and in Okinawan [150]) and *Adocia* (collected from the Eten Island area of Truk Lagoon in January 1984 and November 1985 at 5–10 m depths [151] and Manado, Indonesia, on May 15, 1993 [152]), which showed a number of biological activities [146, 147, 151, 152, 148–150]. In vitro assays and preliminary SAR studies (in 2010) showed that among the compounds 1–8, halenaquinone appeared as the most PLA_2 inhibitor of the series with an IC_{50} of 3.7 μM. Incorporating a dioxothiazine unit in compounds 2 and 3 led to a 30- to 40-fold decrease in potency when compared with the most active pentacyclic polyketide 1, and among pentacyclic polyketide compounds, the presence of a secondary alcohol at C-3 rather than a ketone abolished PLA_2 inhibition (4 and 5). These results highlighted that the C-3 oxidation state and the presence of quinone ring E were important for the anti-PLA_2 activity [27, 146]. Similar conclusions were reported regarding the SAR of protein tyrosine kinase inhibition exhibited by halenaquinone (1) [147]. Farnesyltransferase (FTase) inhibitory experiments showed that the presence of dioxothiazine substitution (IC_{50} 1 1.57 μM vs. 2 1.48 μM and 3 3.75 μM) led to little variation in human (FH) FTase inhibitory activity. Interestingly tetrahydrohalenaquinones A (4) and B (5) did not show such activity. Furthermore, quinol sulfates 6 (IC_{50} 16.11 μM) and 7 (IC_{50} 6.71 μM) exhibited modest activity suggesting that the presence of a quinone moiety was essential for FTases inhibitory activity. Sub-micromolar inhibition of farnesyltransferase enzyme of orhalquinone 8 (IC_{50} 0.40 μM), highlighting this scaffold as a significant modification for enhancing activity [146]. Antiplasmodial activities against FcB1 and 3D7 *Plasmodium falciparum* strains revealed that compound 2, 3, and 8 were the most active of the series with values of IC_{50} 1.08, 3.89, and 9.22, respectively.



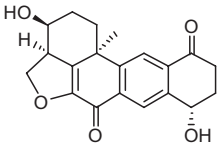
351 Halenaquinone



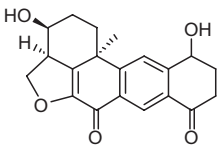
352 3-Ketoadociaquinone A



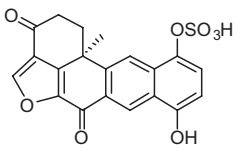
353 3-Ketoadociaquinone B



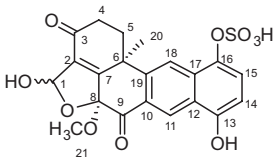
354 Tetrahydrohalenaquinone A



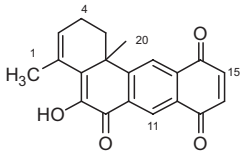
355 Tetrahydrohalenaquinone B



356 Halenaquinol sulfate



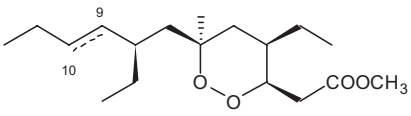
357 Xestosaprol C methylacetal



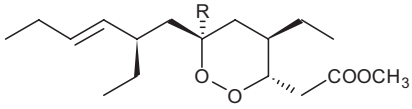
358 Orhalquinone

Marine sponges from family Plakinidae own a great number of simple endoperoxide or peroxyketal polyketides possessing five- or six-membered 1,2-dioxygenated rings (1,2-dioxolane or 1,2-dioxane, respectively). Plakortin (**359**), dihydroplakortin (**360**), 3-epiplakortin (**361**), and plakortide Q (**362**) isolated from marine sponges of *Plakortis halichondroides* (collected at Hookers Reef, Panama) in 1978 [152] and *P. simplex* (collected at the Caribbean Sea) in 1999 [153]. All compounds exhibited a strong in vitro antimalarial activity against D10 (chloroquine-sensitive) and W2 (chloroquine-resistant) strains of *Plasmodium falciparum*, with a more potent activity on the W2 strain (IC_{50} ~ 180 ng/mL), lacking of cytotoxicity [154]. Plakortide I is purified from an unidentified sponge of the genus *Plakortis* and collected at Discovery Bay, Jamaica, in 2002 and represented the first report of an endoperoxide with an α,β-unsaturated ketone moiety in the "western" alkyl side chain and exhibited significant antimalarial activity against the W2 strain with an IC_{50} value of 570 ng/mL and a selectivity index of >8.4 [155]. Plakortides M (**363**) and N (**364**) were isolated from the sponge *P. halichondroides*, collected in Puerto Rico, in 2003, which exhibited potent cytotoxic activity against a number of cancer cell lines in the NCI human cancer screening program but with less selectivity [156]. Peroxyketal polyketides peroxyplakoric A_3 (**365**) and B_3 (**366**) esters isolated from *Plakortis* sp., collected at Zamami Island, Okinawa Prefecture, in 1993,

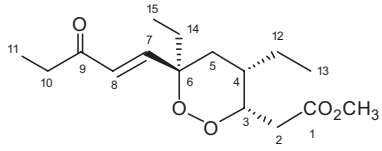
showed IC_{50} = 50 ng/mL against *P. falciparum* with a selective toxicity index (about 200) [157]. SAR studies played crucial roles in both "western" alkyl side chain and the conformational behavior of the dioxane ring of these compounds according to the interaction with the Fe(II)-heme [158, 159].



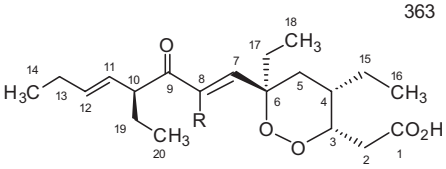
359 Plakortin ¦¤9,10
360 Dihydroplakortin



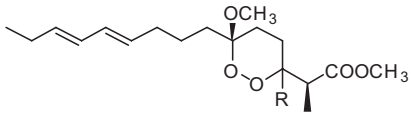
361 3-Epiplakortin R=H
362 Plakortide Q R=CH_2CH3



363 Plakortide I



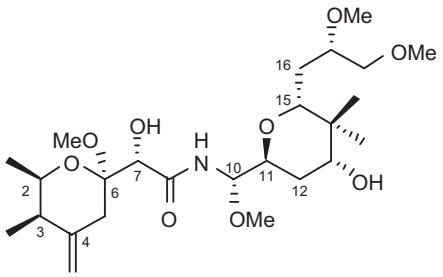
364 Plakortides M R=H
365 Plakortides N R=CH_2CH_3



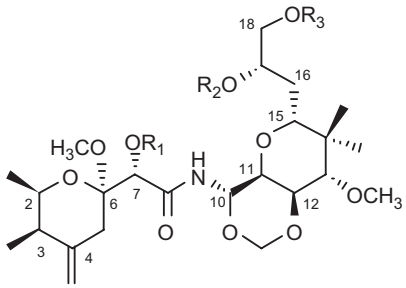
366 peroxyplakoric A_3 R= ····H
367 peroxyplakoric B_3 R= ▬H

Pederins, incorporating the pederin skeleton, which have now been isolated from five genera of the marine sponges: *Mycale* sp. and *Stylinos* sp. (order Poecilosclerida), *Trachycladus* sp. (order Axinellida), and *Theonella* sp. and *Discodermia* sp. (order Lithistida) [44–7 {Clardy, J.; He, H. U. S. Patent 1995, 5,476,953}] [160–171]. It is remarkable to note that the first compound of this class of toxic polyketides, pederin, was isolated in 1953 from the beetle *Paederus fuscipes* [161]. The presence of pederin class of polyketides in such taxonomically distinct organisms indicated the possible microbial origin of these compounds. Pederins exhibited multiple interesting pharmacological activities. Pederin (**368**), the chemical defense agent of the blister beetle, and mycalamides A (**369**) and B (**370**) were reported to disrupt protein synthesis [161, 162, 164]. Furthermore, mycalamides A and B together with mycalamides C (**371**) and D (**372**) showed potent activity against the P388 murine leukemia cell line, giving IC_{50} values of 3.0, 0.7, 95.0, and 35.0 ng/mL, respectively [164, 168]. Theopederins A–L (**373–384**) were markedly cytotoxic against P388 murine leukemia cells with the activity of nM level [165, 167, 171]. 13-Des-*O*-methyl-onnamide A (**385**), dihydroonnamide A (**386**), onnamide B (**387**), 17-

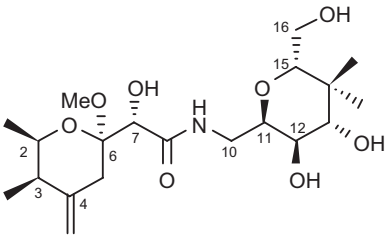
oxoonnamide B (**388**), onnamide C (**389**), onnamide D (**390**), and onnamide A (**391**) were highly cytotoxic against the P388 cell line with IC_{50} values of 0.15, 0.04, 0.13, 0.10.0.07, 0.02, and 0.01 μg/mL, respectively [166]. Onnamide F (**392**) was active against fungi *Saccharomyces cerevisae* with a value of LD_{99} 1.4 μg/mL. No activity was observed against *Bacillus subtilis* or *Eschericha coli*, indicating a selective toxicity for eukaryotes [170]. Icadamides A (**393**) and B (**394**) were reported to show in vitro cytotoxicity against HCT-116 human colon carcinoma cell line with IC_{50} value of 63 nM and 0.17 nM, respectively. Among pederin type of compounds, only icadamide B (**395**) was studied for in vivo antitumor activity and exhibited activity against intraperitoneally and subcutaneously implanted tumors such as P388 mouse leukemia, M109 mouse lung tumors, and asbestos-induced pulmonary squamous cell carcinoma. Icadamide C displayed potent cytotoxic activity against a small panel of five human solid tumor cell lines (A549, SK-OV-3, SK-MEL-2, XF-498, and HCT-15) with ED_{50} values of less than 0.1 μg/mL [160].



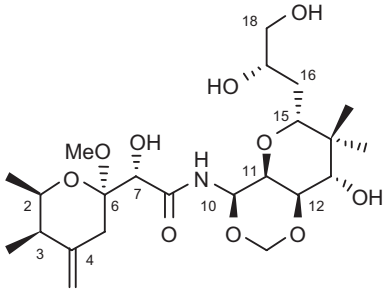
368 Pederin



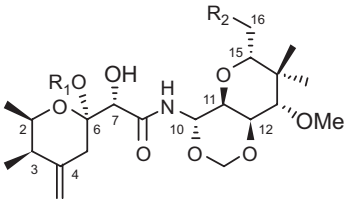
369 Mycalamides A $R_1=R_2=R_3=H$
370 Mycalamides B $R_1=R_3=H, R_2=CH_3$

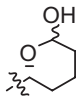


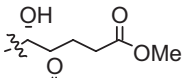
371 Mycalamides C

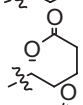


372 Mycalamides D



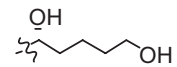
373 Theopederins A R_1=Me, R_2= 

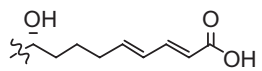
374 Theopederins B R_1=Me, R_2= 

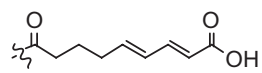
375 Theopederins C R_1=Me, R_2= 

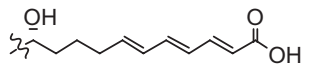
376 Theopederins D R_1=Me, R_2= 

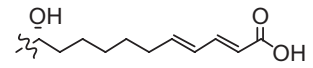
377 Theopederins E R_1=Me, R_2= OH

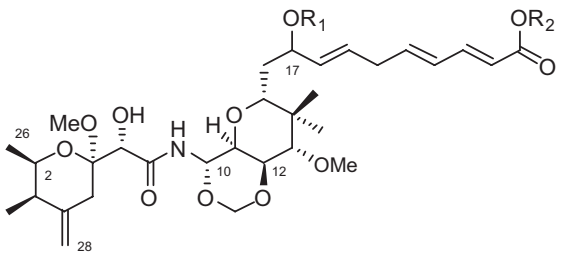
378 Theopederins F R_1=Me, R_2= 

379 Theopederins G R_1=H, R_2= 

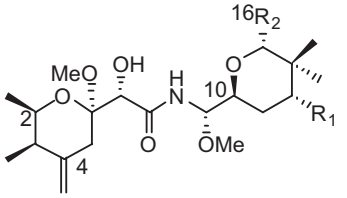
380 Theopederins H R_1=H, R_2= 

381 Theopederins I R_1=H, R_2= 

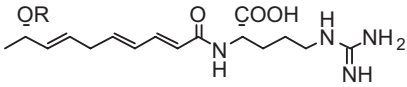
382 Theopederins J R_1=H, R_2= 



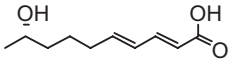
383 Theopederins K R_1=Me R_2=H
384 Theopederins L R_1=H, R_2=H

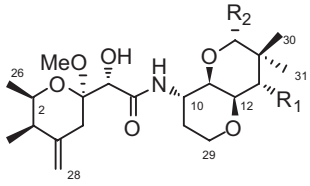


391 Onnamide A R1=OH, R2=

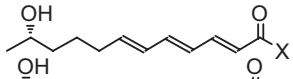


392 Onnamide F R1=OMe, R2=

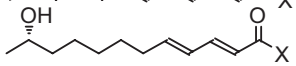




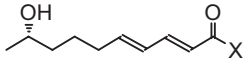
385 13-Des-O-methyl-onnamide A R_1=OH, R_2=



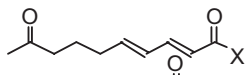
386 Dihydroonnamide A R_1=OMe, R_2=



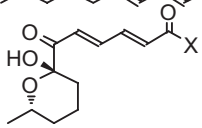
387 Onnamide B R_1=OMe, R_2=



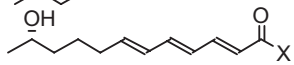
388 I7-Oxoonnamide B R_1=OMe, R_2=



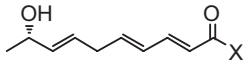
389 Onnamide C R_1=OMe, R_2=



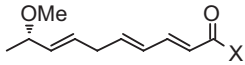
390 Onnamide D R_1=OMe, R_2=



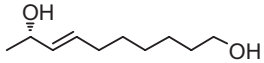
393 Icadamide A R_1=OMe, R_2=



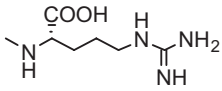
394 Icadamide C R_1=OMe, R_2=



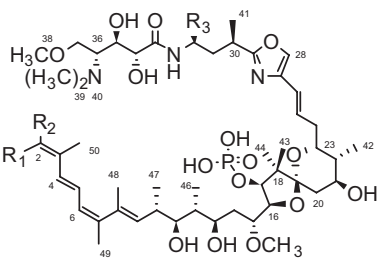
395 Icadamide B R_1=OMe, R_2=



X=

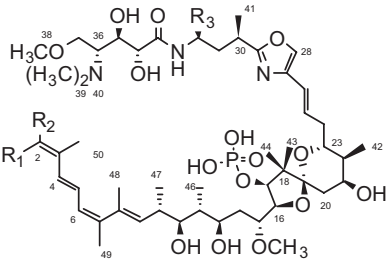


The marine sponge *Discodermia calyx* (order Lithistida, family Theonellidae) was reported to contain the calyculins (**396–413**) [172, 173, 78, 174–176], unique polyketides bearing nitrogen and phosphorus functions. These macrolides exhibited a variety of biological activities including antitumor and smooth muscle contractile, which are attributed to inhibition of protein phosphatase 1 and 2A (all these compounds exhibited nM scale of inhibition activity). SAR studies showed that the 17-phosphate, 13-hydroxyl, and the hydrophobic tetraene moieties were all necessary for binding to the phosphatase 1 and 2A [176].



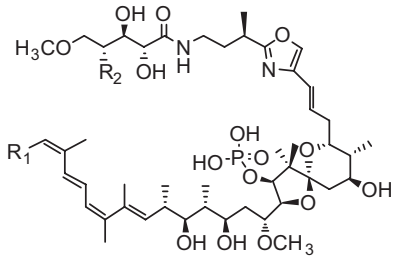
Calyculins A-D(396-399)

396	R_1=CN	R_2=H	R_3=H
397	R_1=H	R_2=CN	R_3=H
398	R_1=CN	R_2=H	R_3=CH3
399	R_1=H	R_2=CN	R_3=CH3

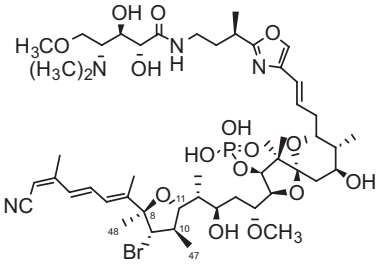


Calyculins A-H(400-407)

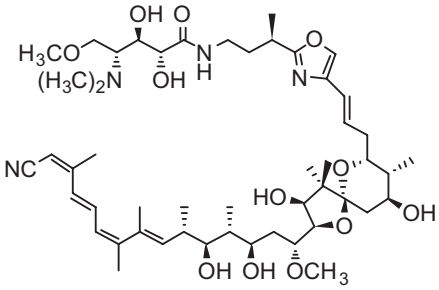
	R1	R2	R3		
404	CN	H	H	400	6*E* insomer of 5
405	H	CN	H	401	6*E* insomer of 6
406	CN	H	CH3	402	6*E* insomer of 7
407	H	CN	CH3	403	6*E* insomer of 8



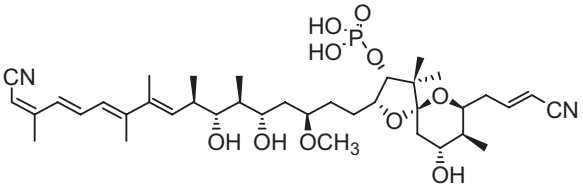
408	Des-N-methylcalyculin A	R_1=CN	R_2=NHMe
409	Calyculinamide A	R_1=CONH$_2$	R_2=NMe$_2$
410	Calyculinamide F	R_1=CONH$_2$	R_2=N(CH$_3$)$_2$



411 Calyculin J

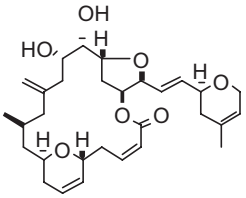


412 Dephosphonocalyculin A

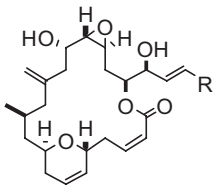


413 Hemicalyculin A

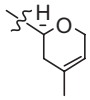
The sponge-derived polyketide macrolides fijianolides are an important subset of 20-membered ring containing compounds isolated from marine sponge *Cacospongia mycofijiensis*, *Hyatella* sp., and *Fasciospongia rimosa* [177–180]. Fijianolide B extremely potent (KB[a] IC_{50} = 29 nM, MDA-MB-435 IC_{50} = 5.7 nM), while fijianolide A (**414**) (HT29 IC_{50} = 21 μM, KB IC_{50} > 39 μM, MDA-MB-435 IC_{50} = 2 μM) was also very active but at a reduced potency [181, 182]. Neolaulimalide (**415**) showed cytotoxicity against P388, A549, HT29, and MEL28 cell lines at 0.01–0.05 μg/mL [180]. Fijianolide B (**416**) together with fijianolides E (**417**) and G (**418**) were also shown to disrupt interphase and mitotic division, and fijianolide B was more potent than fijianolides E and G [177]. An in vivo evaluation of fijianolide B using tumor-bearing severe combined immuno-deficiency mice demonstrated significant inhibition of growth of HCT-116 tumor cells over 28 days [177].

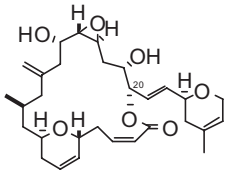


414 Fijianolide A



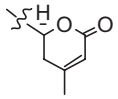
416 Fijianolide B R=



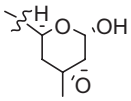


415 Neolaulimalide

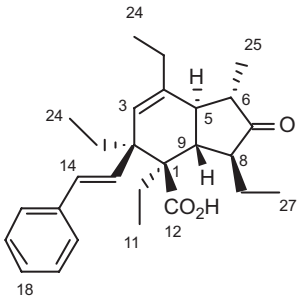
417 Fijianolide E R=



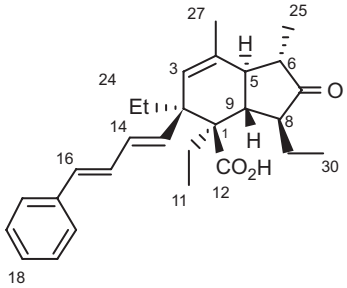
418 Fijianolide G R=



Spiculoic acids and zyggomphic acids are indane-type polyketides, which have integrated phenylacetic acid, butyrate, and propionate units, isolated from marine sponge *Plakortis zyggompha* and *P. angulospiculatus* [183–185]. The vast majority of polyketides made in nature are assembled from acetate and propionate building blocks, whereas these spiculoic acids and zyggomphic acids incorporated the intact of butyrate units. Furthermore, the location of the olefin functionality formed by reduction of the β ketone and dehydration after condensation of the phenylacetic acid starter unit with the first butyrate is unusual. Normally, the dehydration step in polyketide biosynthesis would yield an α,β-unsaturated ester. In the biosyntheses of these polyketides, dehydration occurs in the opposite direction, leading to conjugation between the olefin and the phenyl ring [184]. Spiculoic acid A (**419**) showed in vitro cytotoxicities against the breast MCF-7, breast MDA-MB-231, lung carcinoma A549, and colon carcinoma HT29 cell lines with IC_{50} values of 8.0, 2.4, 4.6, and 8.1 μg/mL, respectively [183, 184]. Zyggomphic acid (**420**) exhibited in vitro antitumor activities against the breast MDA-MB-231, lung carcinoma A549, and colon carcinoma HT29 cell lines with IC_{50} values of 1.2, 3.3, and 3.6 μg/mL, respectively [183].

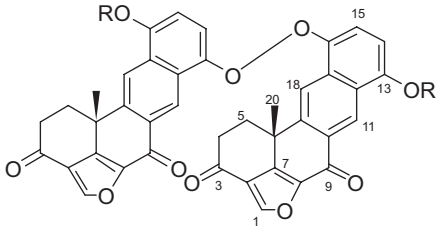


419 Spiculoic acid A



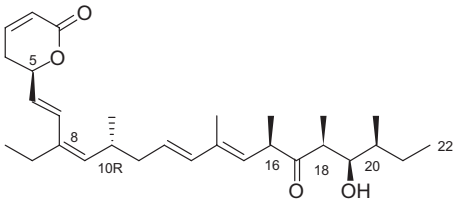
420 Zyggomphic acid

Dihalenaquinolides A (**421**) and B (**422**), novel pentacyclic polyketide dimers, were isolated from marine sponge *Petrosia elastica* collected in Nan-wan, Taiwan, during June 1998 [186]. Dihalenaquinolide A inhibited the growth of PC-3 tumor cells at 10 μg/mL, while compound dihalenaquinolide B was inactive [186].



421 Dihalenaquinolides A R=CH_3
422 Dihalenaquinolides B R=CH_2CH_3

Callystatin A (**423**) is a novel polyketide with a terminal α,β-unsaturated δ-lactone, isolated from the marine sponge *Callyspongia truncata*, collected at Goto Islands, Nagasaki Prefecture, in 1997 and exhibited potent cytotoxicity against KB cells at IC_{50} 0.01 ng/ml. Through analogue, syntheses and the assessment of their biological potencies against KB cells manifested the ketonic carbonyl, the 19-hydroxyl, and the three asymmetric methyl groups located in the β-hydroxyketone part of callystatin A contributing to the cytotoxic potency, respectively. Moreover, the α,β-unsaturated δ-lactone portion served as a conclusive functional group for the cytotoxic activity [187].



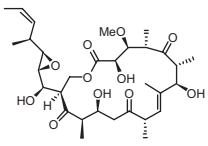
423 Callystatin A

15.5 Bioactive Macrolides

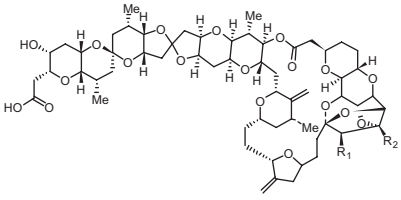
Natural products possessing a macrocyclic lactone moiety are considered to be "macrolides," and most of them are likely to belong to polyketides from a biogenetic viewpoint. Because so many macrolides have been reported in recent years, the selection of compounds derived from 36 marine sponges may seem arbitrary and depends on the potency of their biological activities reported from year 1984 to year 2014.

In 1984, tedanolide (**424**) was isolated from *Tedania ignis* (Caribbean), which exhibited highly cytotoxic with ED_{50} 2.5×10^{-4} μg/mL in KB (human carcinoma of the nasopharynx) and 1.6×10^{-5} μg/mL in PS (lymphocytic leukemia) [134]. Eight antitumor compounds including norhalichondrins A–C (**425–427**), homohalichondrins A–C (**428–430**), and halichondrins B (**431**) and C (**432**) were found from *Halichondria okadai* Kadota (Miura Peninsula, Tokyo) in 1986, among which halichondrin B exhibited remarkable in vivo antitumor activity [188]. In 1987, halichondramide (**433**), dihydrohalichondramide (**434**), and isohalichondramide (**435**) were isolated from the Pacific sponge *Halichondria* sp. (Kwajelein Island), among which halichondramide showed significant activity against *Candida albicuns* at 0.01 μg/disk in the standard disk assay [189], and dihydrohalichondramide and isohalichondramide had antifungal activity and inhibited cell division in the fertilized sea urchin egg assay [190]. In 1989, mycalolides A–C (**436–438**) were isolated from a sponge *Mycale* sp. (Kii Peninsula, Japan) and demonstrated antifungal activities against many pathogenic fungi and cytotoxic against B-16 melanoma cells with IC_{50}s of 0.5–1.0 ng/mL [191]. The chemical investigation of Okinawan marine sponge *Jaspis* sp. in 1993 yielded jaspisamides A–C (**439–441**) which exhibited cytotoxicities against L1210 murine leukemia cells in vitro, with IC_{50} values of <0.001, <0.001, and < 0.001 μg/mL, and against human epidermoid carcinoma KB

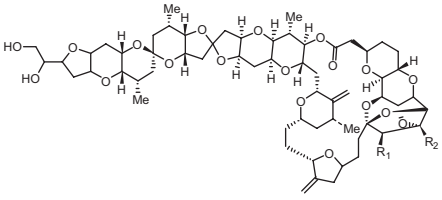
cells in vitro with IC_{50} values of 0.015, 0.006, and 0.013 μg/mL, respectively [192]. In 1988, an Indonesian sponge *Hyattella* sp. was collected offshore from Manado (northern Sulawesi, Indonesia) yielded laulimalide (**442**) and isolaulimalide (**443**), and laulimalide displayed potent cytotoxicity, IC_{50} = 15 ng/mL, against the KB cell line [179]. Swinholide A (**444**) was first isolated from a Red Sea sponge *Theonella swinhoei* (Gulf of Eilat, Israel, in 1985), demonstrating in vitro antifungal activity [193]. It was re-isolated from the Okinawan marine sponge *Theonella swinhoei* in 1989 and exhibited potent cytotoxic activity (IC_{50} 0.04 μg/mL) for KB cell [194]. Its absolute configuration was elucidated by means of the X-ray diffraction method and chemical derivations in 1990 [195]. Then, in 1990, swinholide B (**445**), swinholide C (**446**), and isoswinholide A (**447**) were also found from the Okinawan marine sponge *Theonella swinhoei*, among which, swinholide B and swinholide C exhibited potent cytotoxicity almost equivalent to that of swinholide A toward KB cell lines (IC_{50} 0.041 and 0.052 μg/mL, respectively), while isoswinholide A showed weaker cytotoxicity (IC_{50} 1.1 μg/mL) [196].



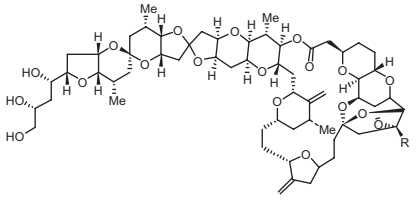
424 Tedanolide



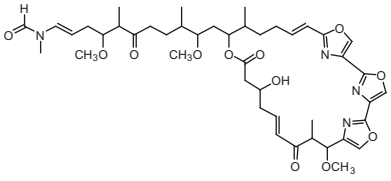
425 Norhalichondrin A: R_1, R_2 = OH
426 Norhalichondrin B: R_1, R_2 = H
427 Norhalichondrin C: R_1 =H, R_2 = OH



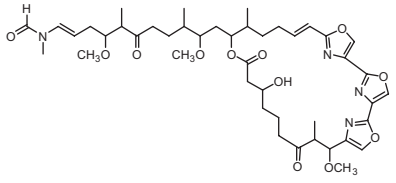
428 Homohalichondrin A: R_1, R_2 = OH
429 Homohalichondrin B: R_1, R_2 = H
430 Homohalichondrin C: R_1 = H, R_2 = OH



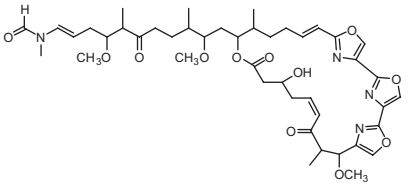
431 Halichondrins B: R = H
432 Halichondrins C: R = OH



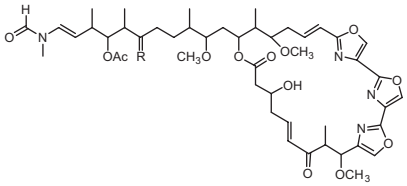
433 Halichondramide



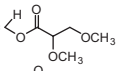
434 Dihydrohalichondramide



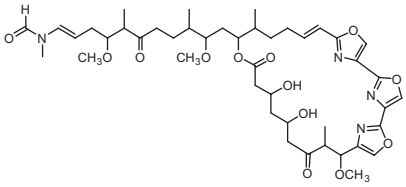
435 Isohalichondramide



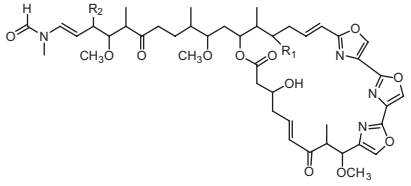
436 Mycalolide A: R = O

437 Mycalolide B: R = 

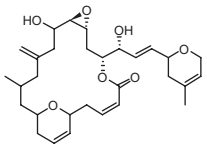
438 Mycalolide C: R = 



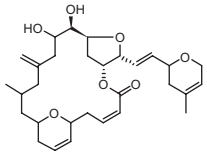
439 Jaspisamide A



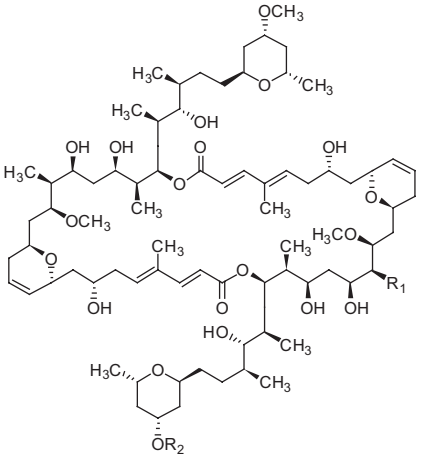
440 Jaspisamide B: R_1 = OH, R_2 = H
441 Jaspisamide C: R_1 = H, R_2 = CH_3



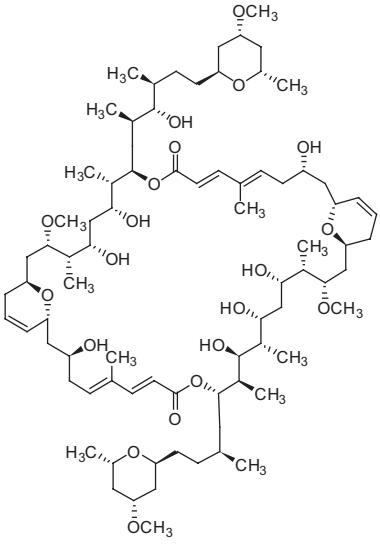
442 Laulimalide



443 Isolaulimalide



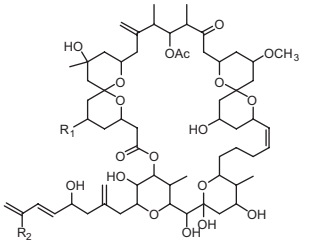
444 Swinholide A : R1 = R_2 = CH_3
445 Swinholide B : R_1 = H, R_2 = CH_3
446 Swinholide C : R_1 = CH_3, R_2 = H



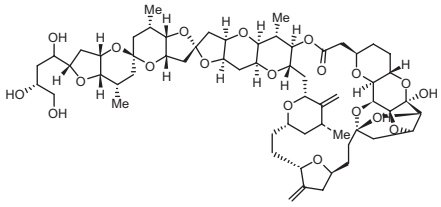
447 Isoswinholide A

In 1993, altohyrtins A–C (**448–450**) and 5-desacetylaltohyrtin A (**451**) were found in sponge *Hyrtios altum*, which were of great interest for cytotoxic activities against KB cells with IC_{50} values of 0.01, 0.02, 0.4, and 0.3 ng/mL, respectively [94, 197, 198]. A highly potent polyether macrolide antimitotic agent designated halistatin **1** (**452**) was isolated from *Phakellia carteti* (Grand Comore Island, Republic of Comoros), which showed strong cytotoxicity to L1210 murine leukemia cells with IC_{50} values of 0.5 nM. In the further mechanism study, it was shown to cause accumulation of cells arrested in mitosis, inhibited tubulin polymerization, and inhibits binding of radiolabeled vinblastine and GTP to tubulin [199]. Cinachyrolide A (**453**) was isolated from *Cinachyra* sp. which was highly cytotoxic against L1210 murine leukemia cells with an IC_{50} of <0.6 ng/mL [200]. In 1994, superstolides A (**454**) and B (**455**) were obtained from the deepwater marine sponge *Neosiphonia superstes* (New Caledonia) and demonstrated highly cytotoxic against human bronchopulmonary non-small-cell lung carcinoma NSCLC-N6-L 16 cells (IC_{50} 0.04 and 0.039 μg/mL), murine leukemia P388 cells (IC_{50} both of 0.003 μg/mL), and human nasopharyngeal carcinoma KB cells (IC_{50} 0.02 and 0.005 μg/mL) [201, 202]. Reidispongiolides A (**456**) and B (**457**) were isolated from *Rekiivpmgia werulea* n.gen. n.sp. (South of New Caledonia), which exhibited potent cytotoxicity against various human carcinoma cells with IC_{50} values of 0.01–0.16 μg/mL [203]. Lasonolide A (**458**) was isolated from *Forcepia* sp. (British Virgin Islands), as a

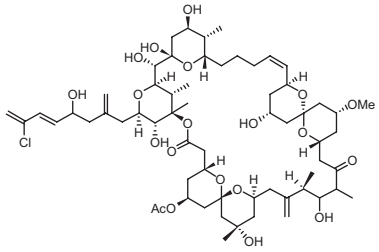
potent cytotoxin against the A549 human lung carcinoma and P388 murine leukemia cell lines with IC_{50} values of 40 and 2 ng/mL, respectively. Further, it inhibited cell adhesion in the EL-4.IL-2 cell line with an IC_{50} of 19 ng/mL [204]. Isohomohalichondrin B (**459**) was found in New Zealand sponge *Lissodendoryx* sp. and showed significant cytotoxic activity against the P388 cell lines and selective cytotoxicity in the NCI'S primary screen [205].



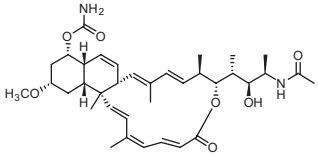
448 Altohyrtin A: R_1 = OAc, R_2 = Cl
449 Altohyrtin B: R_1 = OAc, R_2 = Br
450 Altohyrtin C: R_1 = OAc, R_2 = H
451 5-Desacetylaltohyrtin A: R_1 = OH, R_2 = Cl



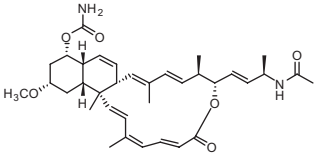
452 Halistatin 1



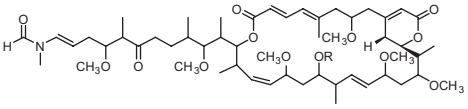
453 Cinachyrolide A



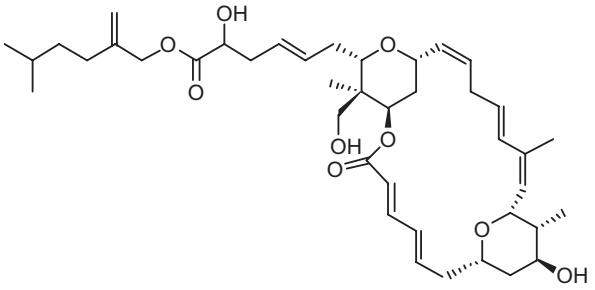
454 Superstolide A



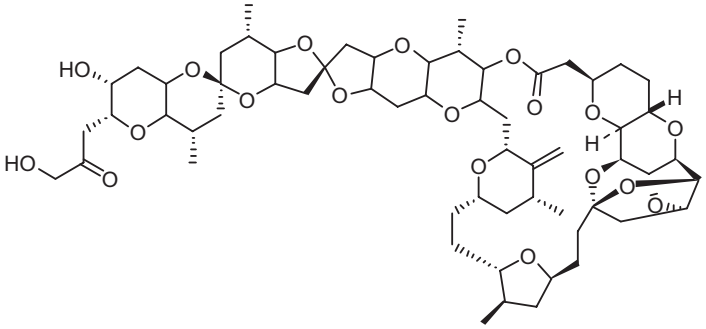
455 Superstolide B



456 Reidispongiolide A: R = CH_3
457 Reidispongiolide B: R = H



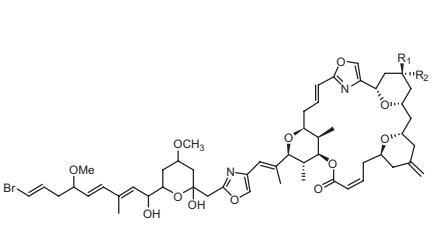
458 Lasonolide A



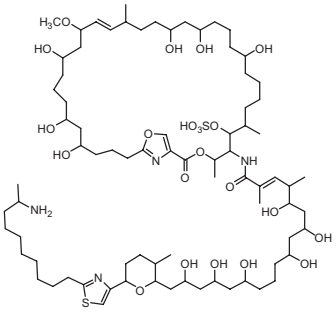
459 Isohomohalichondrin B

The chemical investigation of Indian Ocean marine sponge *Phorbas* sp. (Muiron Island, Australia, in 1995) yielded phorboxazoles A (**460**) and B (**461**), which exhibited in vitro antifungal activity against *Candida albicans* at 0.1 μg/disk and extraordinary cytostatic activity [206]. In 1996, theonezolide A (**462**), a novel polyketide macrolide, isolated from the Okinawan marine sponge *Theonella* sp. (Okinawa, Japan), caused a marked platelet shape change at low concentrations (0.2–0.6 μM) [207]. Leucascandrolide A (**463**), a doubly O-bridged 18-membered macrolide of a new type, i.e., possessing little C_1-branching vs. extensive 1,3-dioxygenation and a peculiar side chain, was isolated from a calcareous sponge of a new genus, *Leucuscundra caveoluta* from the Coral Sea. It showed strong cytotoxic activity in vitro on KB cells and less marked action on P388 cells, as well as very strong inhibition of *Candida albicans* [208]. Compared with leucascandrolide A, leucascandrolide B (**464**) was found from the same sponge sample which showed only marginal cytotoxicity on tumor cell lines, with an IC_{50} of 5 μg/mL on KB cells and > 10 μg/mL on P388 murine leukemia cells and no activity on *Candida albicans* [209]. A marine sponge *Fasciospongia rimosa* (Okinawa, Japan) yielded zampanolide (**465**) which showed potent cytotoxicity (IC_{50} 1–5 ng/mL) against P388, A549, HT29, and MEL28 cell lines [210]. In 1997, study of a deepwater sponge *Lissodendoryx* sp. (Kaikoura Peninsula, New Zealand) yielded neonorhalichondrin

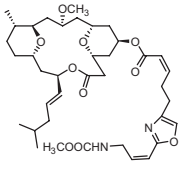
B (**466**), neohomohalichondrin B (**467**), 55-methoxyisohomohalichondrin B (**468**), 53-methoxyneoisohomohalichondrin B (**469**), and 53-epi-53-methoxyneoisohomohalichondrin B (**470**), and further antitumor assay demonstrated that they were highly cytotoxic against P388 cells with IC_{50} values of 0.4, 0.8, 10, and 0.1 ng/mL except 53-epi-53-methoxyneoisohomohalichondrin B, respectively [211]. Two novels, highly potent, cytotoxic macrolides and salicylihalamides A (**471**) and B (**472**), were isolated from the sponge *Haliclona* sp. (Rottnest Island, Australia). COMPARE pattern-recognition analyses of the NCI 60-cell mean-graph screening profiles of salicylihalamide A did not reveal any significant correlations to the profiles of known antitumor compounds in the NCI's "standard agent database," thus supporting the conclusion that the salicylihalamides represent a potentially important new class for antitumor lead optimization and in vivo investigations [212]. In 1998, thiomycalolides A (**473**) and B (**474**) were obtained from *Mycale* sp. (Kii Peninsula, Japan), which exhibited highly cytotoxic against P388 murine leukemia cells with an IC_{50} value of 18 ng/mL each [213].



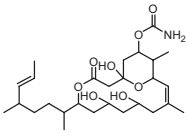
460 Phorboxazole A: R_1 = OH, R_2 = H
461 Phorboxazole B: R_1 = H, R_2 = OH



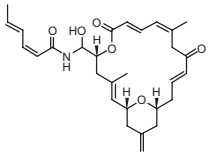
462 Theonezolide A



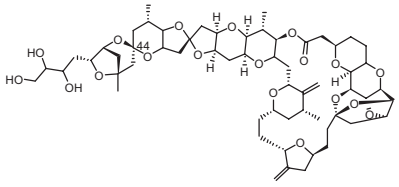
463 Leucascdndrolide A

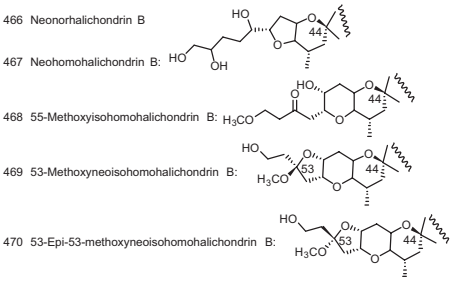


464 Leucascdndrolide B

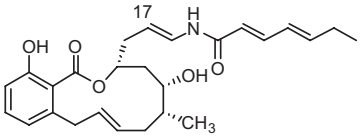


465 Zampanolide

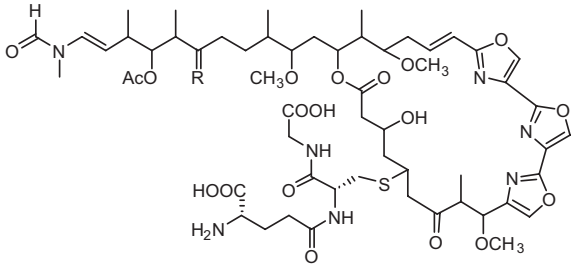


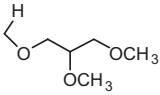


466 Neonorhalichondrin B
467 Neohomohalichondrin B:
468 55-Methoxyisohomohalichondrin B:
469 53-Methoxyneoisohomohalichondrin B:
470 53-Epi-53-methoxyneoisohomohalichondrin B:

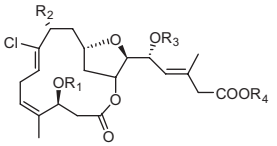


471 Salicylihalamide A
472 Salicylihalamide B: 17Z

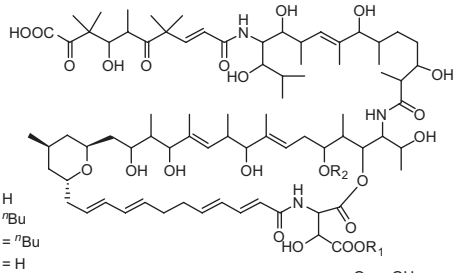


473 Thiomycalolide A: R = O
474 Thiomycalolide B: R = 

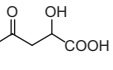
Chemical investigation of an Okinawan sponge *Ircinia* sp. resulted in isolation of haterumalides NA, NB, NC, ND, and NE (**475–479**), among which, haterumalides NA exhibited cytotoxicity against P388 cells, with an IC_{50} of 0.32 μg/mL, and moderate acute toxicity against mice, with an LD_{99} of 0.24 g/kg which was found in 1999 [214]. In 2000, antiproliferative bioassay-guided fractionation of an aqueous extract of the marine sponge *Chondropsis* sp. (Wollongong, Australia) provided chondropsins A (**480**) and B (**481**). Testing of chondropsin A in the NCI 60-cell screen revealed a mean-graph profile that did not correlate significantly with the profile of any compound class represented in the NCI standard agents database [215]. In 2001, 73-deoxychondropsin A (**482**) and chondropsin C (**483**) were isolated from two different collections of marine sponges belonging to the genus *Ircinia* (*Ircinia ramose*, Australia; *Ircinia* sp., Philippines) and exhibited IC_{50}'s of approximately 0.8 and 0.2 ng/mL toward the LOX and MOLT-4 cell lines, respectively [216]. Chondropsin D (**484**) exhibited IC_{50}'s of approximately 10 and 250 ng/mL toward the LOX and MOLT-4 cell lines, respectively [217]. In 2000, peloruside A (**485**) was found to be cytotoxic to P388 murine leukemia cells at approximately 10 ng/mL (18 nM) which was found in sponge *Mycale* sp. [218]. In 2010, peloruside B (**486**), a natural congener of peloruside A, was isolated from the New Zealand marine sponge *Mycale hentscheli*. Peloruside B was found to promote microtubule polymerization and arrest cells in the G2/M phase of mitosis similar to paclitaxel, and its bioactivity was comparable to that of peloruside A [219].



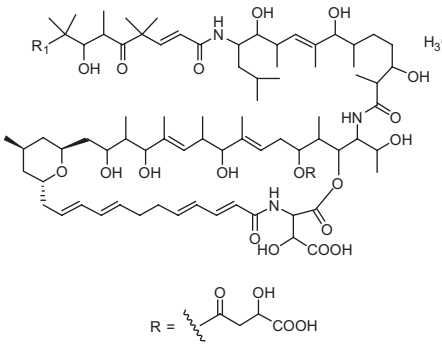
475 Haterumalide NA: R_1 = Ac, R_2 = H, R_3 = H, R_4 = H
476 Haterumalide NB: R_1 = Ac, R_2 = H, R_3 = H, R_4 = ^{n}Bu
477 Haterumalide NC: R_1 = Ac, R_2 = OH, R_3 = H, R_4 = ^{n}Bu
478 Haterumalide ND: R_1 = Ac, R_2 = OH, R_3 = H, R_4 = H
479 Haterumalide NE: R_1 = H, R_2 = H, R_3 = H, R_4 = H



480 Chondropsin A: R_1 = 1, R_2 =

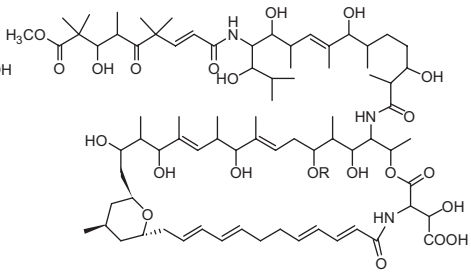


481 Chondropsin B: R_1 = R_2 = H

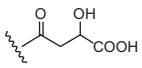


R =

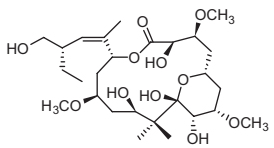
482 73-Deoxychondropsin A: R_1 = $COOCH_3$
483 Chondropsin C: R_1 = H



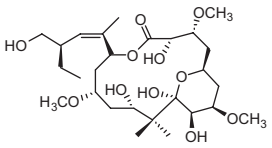
R =



484 Chondropsin D



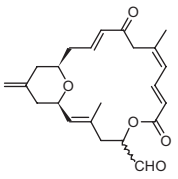
485 Peloruside A



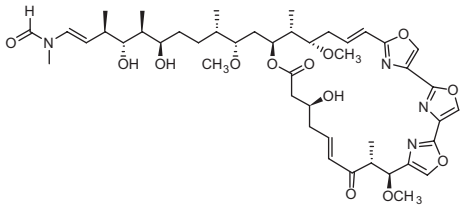
486 Peloruside B

In 2001, dactylolide (**487**) from *Dactylospongia* sp. showed cytotoxic activity against the L1210 and SK-OV-3 tumor cell lines (63% and 40% inhibition at 3.2 μg/mL) [220]. In 2002, 30,32-dihydroxymycalolide A (**488**) was obtained from *Mycale izuensis*, with cytotoxic activity against HeLa cells (IC_{50} value of 2.6 ng/mL) [221]. In 2005, 13-deoxytedanolide (**489**), a highly antitumor macrolide from the marine sponge *Mycale adhaerens*, exhibited cytotoxic activity against P388 murine leukemia cells with IC_{50} of 0.064 ng/mL [138]. In 2006, tedanolide C (**490**) isolated from *Ircinia* sp. (Milne Bay, Papua New Guinea) exhibited potent cytotoxicity against HCT-116 cells in vitro with IC_{50} value of 9.53×10^{-2} μM and caused a strong S-phase arrest [136]. Leiodolides A (**491**) and B (**492**) were found in marine sponge

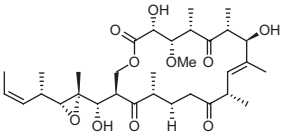
Leiodermatium (Palau) from deep water, and leiodolide A showed significant cytotoxicity (average GI_{50} = 2.0 μM) in the National Cancer Institute's 60 cell line panel with enhanced activity against HL-60 leukemia and OVCAR-3 ovarian cancer cell lines [222]. The Red Sea sponge *Theonella swinhoei* (Hurghada, Egypt) yielded swinholide I (**493**) and hurghadolide A (**494**) which were in vitro cytotoxic against human colon adenocarcinoma (HCT-116) with IC_{50} values of 5.6 and 365 nM, respectively. Furthermore, they could disrupt the actin cytoskeleton in the range of 70 and 7.3 nM, respectively. In addition, they were both active against *Candida albicans* [223].



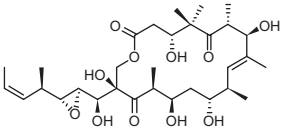
487 Dactylolide



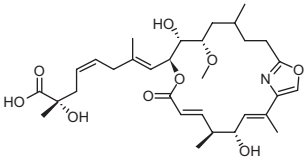
488 30,32-Dihydroxymycalolide A



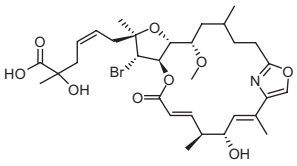
489 13-Deoxytedanolide



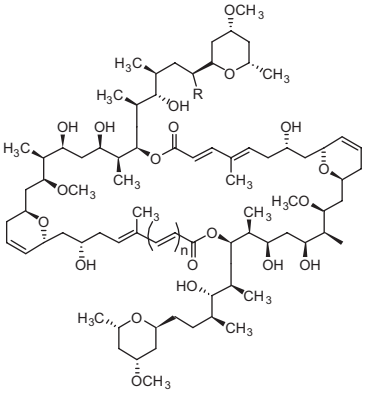
490 Tedanolide C



491 Leiodolides A

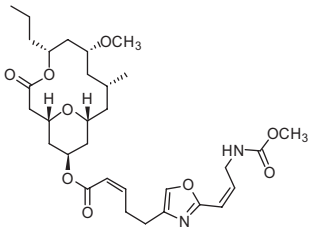


492 Leiodolides B

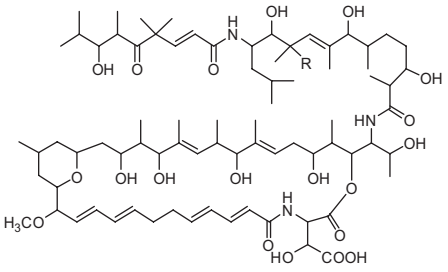


493 Swinholide I : n = 1, R = OH
494 Hurghadolide A: n = 0, R = H

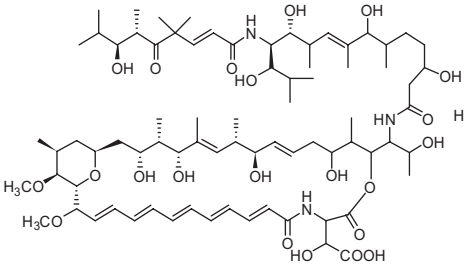
In 2007, neopeltolide (**495**) was isolated from a deepwater sponge of the family Neopeltidae (Jamaica), and it showed potent in vitro anti-proliferation activity against A549 human lung adenocarcinoma, the NCI-ADR-RES human ovarian sarcoma, and the P388 murine leukemia cell lines, with IC_{50}'s of 1.2, 5.1, and 0.56 nM, respectively. Neopeltolide also inhibited the growth of the fungal pathogen *Candida albicans* with a minimum inhibitory concentration of 0.62 μg/mL [224]. The study of marine sponge *Poecillastra* sp. (Grand Bahama Island, Bahamas) yielded poecillastrins B (**496**) and C (**497**), which were of interest for cytotoxicity against a human melanoma tumor cell line (LOX) with an IC_{50} value of less than 1 μg/mL [225]. In 2008, mirabilin (**498**) was isolated from the marine sponge *Siliquariaspongia mirabilis* (Federated States of Micronesia), which prevented the tumor cell line HCT-116 from growing with an IC_{50} value of 0.27 ± 0.09 μM [226]. Three nitrogenous macrolides designated salarin A (**499**), B (**500**) and tulearin A (**501**) were isolated from the Madagascar *Fascaplysinopsis* sp. sponge. Both salarins carry an acetylcarbamate moiety, and in addition, salarin A contains a triacylamine group and salarin B contains a methoxymethylketone lactam. Tulearin A was featured with a naturally rare carbamate ester. They were found to be toxic to brine shrimp larvae, and salarin A and tulearin A were also cytotoxic to leukemia cells [227].



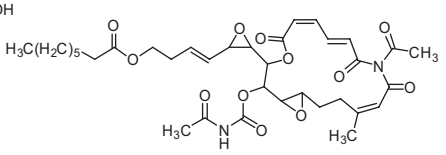
495 Neopeltolide



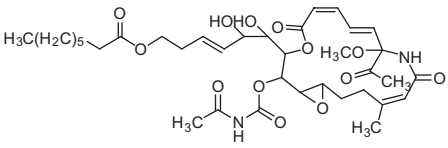
496 Poecillastrin B: R = CH_3
497 Poecillastrin C: R = H



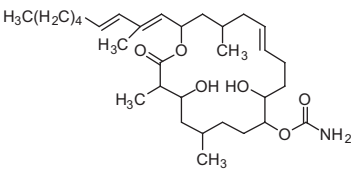
498 Mirabilin



499 Salarin A

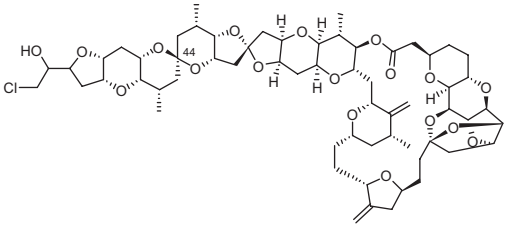


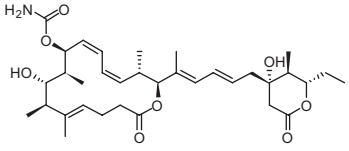
500 Salarin B



501 Tulearin A

In the year of 2009, the deepwater marine sponge *Lissodendoryx* sp. (Kaikoura Peninsula, New Zealand) was found to contain halichondrin B-1140, halichondrin B-1092, halichondrin B-1020, and halichondrin B-1076 (**502–505**), which exhibited highly cytotoxicity against the P388 cell lines with IC_{50} values of 2.0, 0.76, 1.1, and 1.1 ng/mL, respectively [228]. Leiodermatolide (**506**) isolated from the marine sponge *Leiodermatium* sp. (Fort Lauderdale, Florida,2011) was found to exhibit potent and selective antimitotic activity (IC_{50} < 10 nM) against a range of human cancer cell lines by inducing G2/M cell cycle arrest [229]. Kabiramides B–D, G, J, and K (**507–512**) were isolated from the sponge *Pachastrissa nux*, showed moderate to strong antimalarial and cytotoxic activities, except for kabiramide G, which possessed only potent cytotoxicity [230]. In 2013, kabiramides L (**513**) and I (**514**) were obtained from the same sponge sample *Pachastrissa nux*, and both exhibited a moderate antiplasmodial activity against *Plasmodium falciparum* K1 with IC_{50}s of 2.6 and 4.5 μM, respectively [231]. In 2014, callyspongiolide (**515**), a structurally unique polyketide-derived macrolide, was isolated from the marine sponge *Callyspongia* sp. collected in Indonesia, and it showed strong cytotoxicity against human Jurkat J16 T and Ramos B lymphocytes [232].





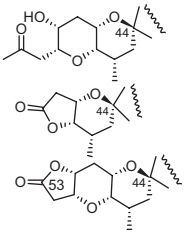
506 Leiodermatolide

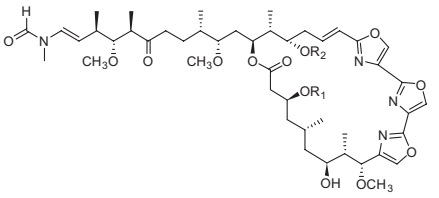
502 Halichondrin B-1140

503 Halichondrin B-1092:

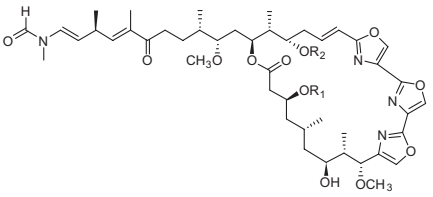
504 Halichondrin B-1020:

505 Halichondrin B-1076:

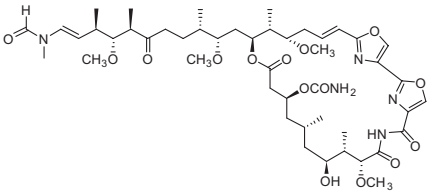




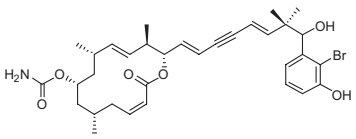
507 Kabiramide B: $R_1 = CONH_2$, $R_2 = H$
508 Kabiramide C: $R_1 = CONH_2$, $R_2 = CH_3$
509 Kabiramide D: $R_1 = H$, $R_2 = CH_3$



510 Kabiramide G: $R_1 = CONH_2$, $R_2 = CH_3$
511 Kabiramide J: $R_1 = CONH_2$, $R_2 = H$
512 Kabiramide K: $R_1 = H$, $R_2 = CH_3$
513 Kabiramide L: $R_1 = H$, $R_2 = H$



514 Kabiramide I



515 Callyspongiolide

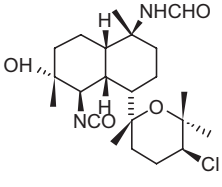
15.6 Bioactive Terpenoids

Marine organisms produce a wide array of fascinating terpenoid structures distinguished by characteristic structural features. Since sponges are one of the prime resources of sesquiterpenes,diterpenes,sesterterpenes,and triterpenes, we here will survey 170 terpenoids from 32 sponges with various biological activities such as antitumor, anti-inflammation, antifouling, fungicide, as well as pesticide.

15.6.1 Sesquiterpenes

In 1996, chemical investigation of sponge *Acanthella eavernos*a (Hachijo-jima Island, Tokyo), yielded Isocyanate and isothiocyanate derivatives **516** and **517**, both of which were highly active in antifouling assay with EC_{50} value of 0.05 μg/mL [233]. In 2008 year, three new sesquiterpene quinones isohyatellaquinone (**518**), 7, 8-dehydrocyclospongiaquinone-2 (**519**), and 9-epi-7, 8-dehydrocyclospongiaquinone-2 (**520**), along with the known quinones

mamanuthaquinone (**521**) and ilimaquinone (**522**), were isolated from *Dactylospongia elegans* (Coral Gardens dive site at the Inner Gneerings reef, Australia, in 2007). All compounds were active against the breast cancer (BC) and small cell lung cancer (NCI-H187) cell lines an IC_{50} range of 1.50–12.4 μg/mL except compound **519** [234].



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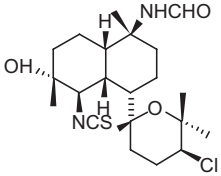

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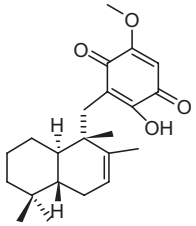

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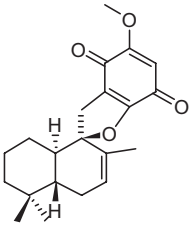

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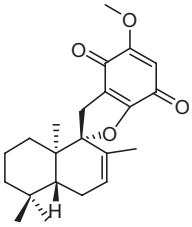

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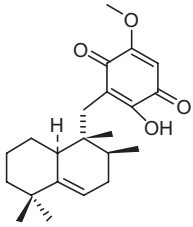

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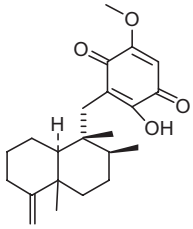
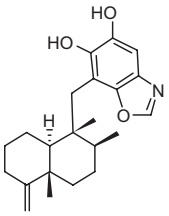


522

In 2011, nakijinol B (**523**), nakijinol B diacetate (**524**), smenospongines B (**525**) and C (**526**) were found in the marine sponge *Dactylospongia elegans* (Pugh Shoal, northeast of Truant Island, in November 1990), along with two known compounds [ilimaquinone (**527**) and 5-epi-ilimaquinone as a 1:1 mixture, dactyloquinone B (**528**)]. All compounds tended out to be active from 1.8 to 46 μM but lacking selectivity for tumor versus normal cell lines (SF-268, H460, MCF-7, HT29, and CHO-K1). And the 1:1 mixture of ilimaquinone (**527**) and 5-epi-ilimaquinone was found to be the most cytotoxic with GI_{50} values ranging from 1.8 to 5.4 μM [235].



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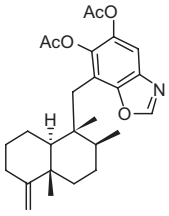

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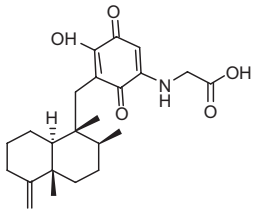

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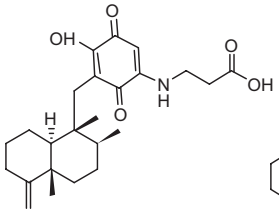

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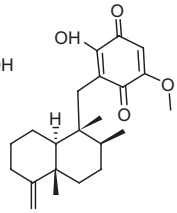

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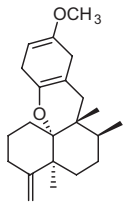
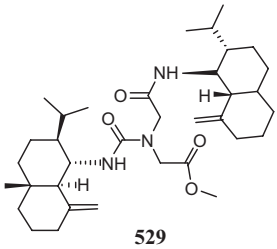


528

In 2011, *Halichondria* sp. (Unten Port, Okinawa) was the source of three new dimeric sesquiterpenoids, halichonadins G–I (**529–531**), of which Halichonadins G (**529**) and I (**531**) were active against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells with an IC_{50} range of 3.4–6.9 μg/mL [236].



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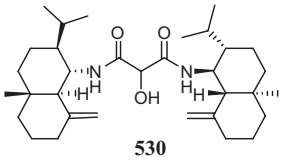

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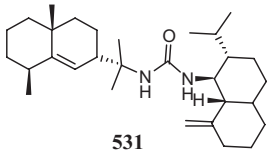
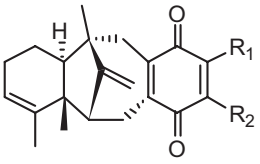
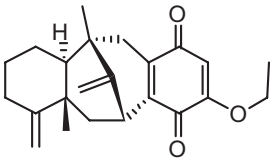


531

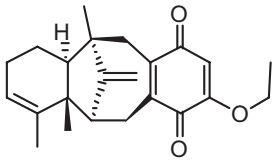
In 2012, a chemical study of sponge *Dysidea avara* (Xisha islands, South China Sea) resulted in discovery of dysidavarones A–D (**532**–**535**), of which dysidavarone A (**532**) inhibited protein tyrosine phosphatase 1B (PTP1B) with IC_{50} value of 9.98 μM. These four compounds are the first example of sesquiterpenes featured with the unprecedented "dysidavarane" carbon skeleton [237].



532 R_1=OEt R_2=H
533 R_1=H R_2=OEt

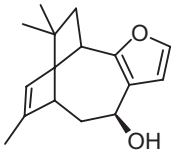


Dysidavarone D (**534**)

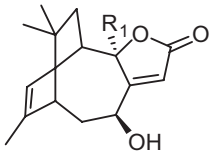


Dysidavarone D (**535**)

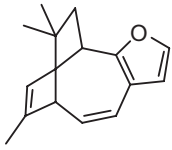
In 2013, chemical investigation of *Euryspongia* sp. (Iriomote Island, Okinawa, Japan) revealed the discovery of Eurypongins A–C (**536–538**). The compounds **536–538** were not active against protein tyrosine phosphatase 1B (PTP1B) while compound **539** (the dehydrated product of **536**) tended to inhibite PTP1B with IC_{50} value of 3.6 μM, highlighting the importance of the absence of an OH group at C-4 for activity [238].



Eurypongin A (**536**)



Eurypongin B (**537**) R1=H
Eurypongin C (**538**) R1=OCH_3

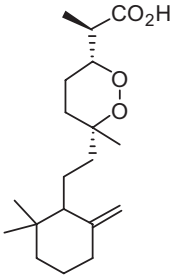


Dehydroeurypongin A (**539**)

15.6.2 Diterpenes

In 1998, four new norditerpenes (**540**–**543**) were isolated from the marine sponge *Diacarnus* cf. *spinopoculum* (Solomon Islands). Compounds **540** and **541** showed moderate activity against the NCI's 60 cell line [239]. In 2002, an inseparable

mixture, sarcotins K (**544**) and L (**545**) were reported from the marine sponge *Sarcotragus* sp. (Cheju Island, Korea, in July 1998). The mixture was evaluated for cytotoxicity against five human tumor cell lines, but only showed activity against SK-MEL-2 cell line with an ED_{50} value of 6.2 μg/mL [240].



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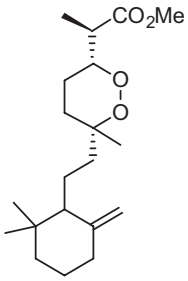

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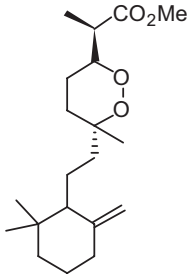

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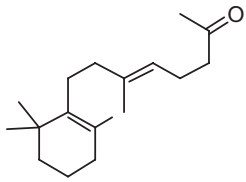

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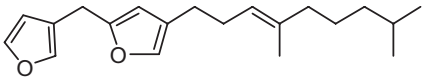
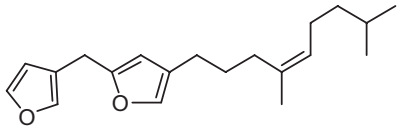
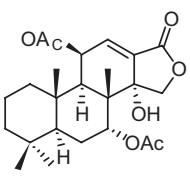


544



545

In 2009, seven new spongian-class diterpenes (**546**–**552**) were discovered from the sponge *Dysidea* cf. *arenaria* (Okinawa Island), of which compounds **547**, **551**, and **552** exhibited cytotoxicity against NBT-T2 rat bladder epithelial cells with IC_{50} values of 1.9, 1.8, and 4.2 μg/mL, respectively [241]. A new isonitrile diterpene, namely 8-isocyanoamphilecta-11(20), 15-diene (**553**), along with three known isonitriles (**554**–**556**), were reported in the same year from the sponge *Ciocalapata* sp. (vicinity of Koh-Tao, Thailand, in April 2002). The four isonitriles extinctively supressed *Plasmodium falciparum* K1 with mean IC_{50} values from 0.09 to1.07 μmol/L [242].



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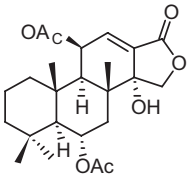

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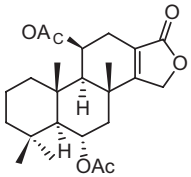

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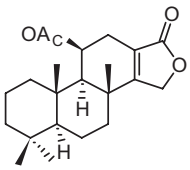

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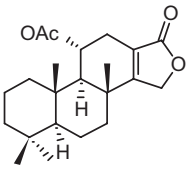

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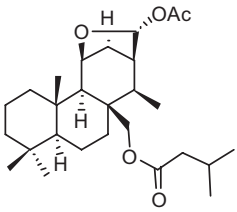

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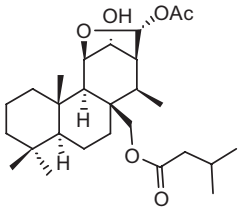

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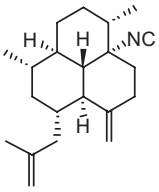

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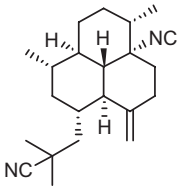

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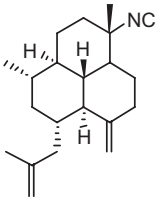

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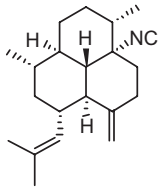
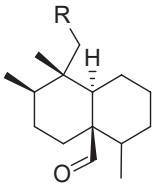


556

In 2011, four novel 9-*N*-methyladeninium diterpenoids, agelasine M (**557**), 2-oxo-agelasine B (**558**), gelasineA (**559**), and gelasine B (**560**), together with the known agelasine B (**561**) and F (**562**), were isolated from the marine sponge *Agelas* sp. (Kimbe Bay, Papua New Guinea, in November 2007). Compounds **557** and **562** exhibited potent cytotoxicity against Jurkat cells with IC_{50} values of 3.0 and 3.6 μg/mL while compounds **561** and **562** were strongly active against *Trypanosoma brucei* with IC_{50} values of 8.4 and 3.3 μg/mL [243].



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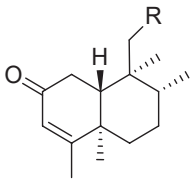

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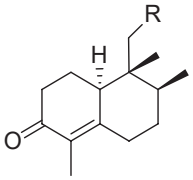

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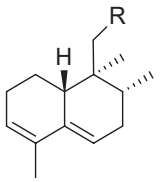

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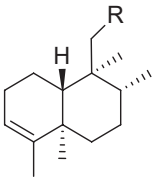

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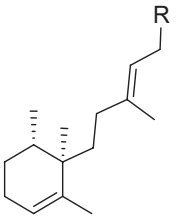

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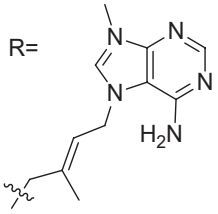
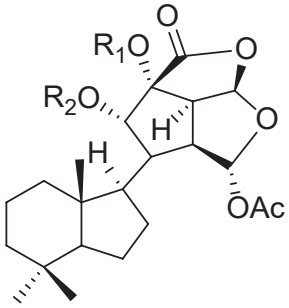
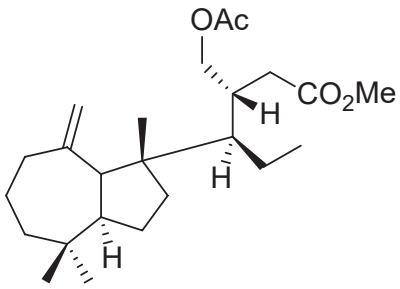


In 2012, two new spongian-class diterpenes (**563**, **564**), along with two known compounds (**565**, **566**), were found in the marine sponge *Chromodoris* sp. (Okinawa Island), and they showed moderate cytotoxity against NBT-T2 rat bladder epithelial cells with IC_{50} values of 5.6, 12, 3.4, and 3.8 μg/mL, respectively [244].



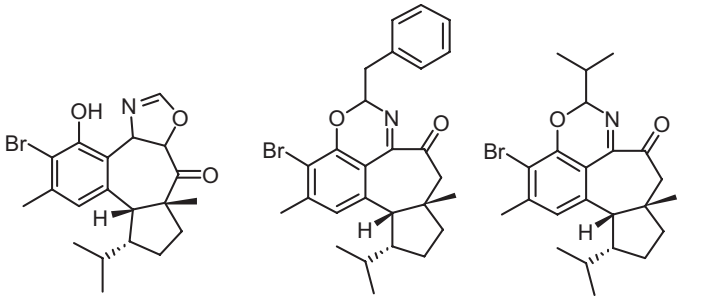
563: R1=R2=H
565: R1=R2=Ac
566: R1=H, R2=Ac



564

In 2015, chemical investigation of the New Zealand marine sponge *Hamigera tarangaensis* (Cavalli Island, New Zealand, in December 2003) resulted in the isolation of nine new nitrogenous hamigeran diterpenoids, namely hamigeran M(**567**), hamigerans N – Q(**568**–**571**), 19-epi-hamigeran Q (**572**), and 18-epi-hamigerans N,

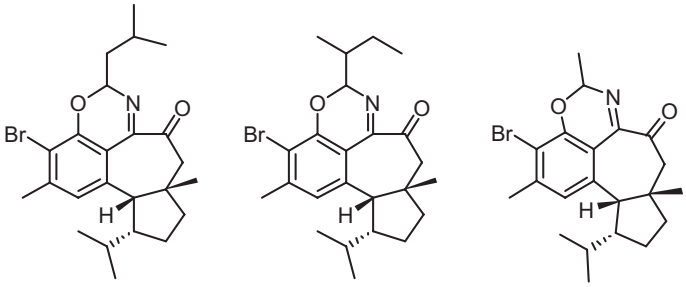
P, and Q (**573**–**575**). Hamigeran M (**567**) exhibited potent cytotoxic activity against HL-60 promyelocytic leukemic cell line at 6.9 μM. And in this work, the structure of hamigeran D (**576**) was revised [245].



567

568 18 *S**
573 18 *R**

569 18 *S**

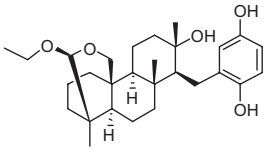


570 18 *S**
574 18 *R**

571 18 *S**
572 18 *R**, 19-*epi*
575 18 *R**

576 18 *S*

In 2015, a new meroditerpene, 26-O-ethylstrongylophorine-14 (**577**), was isolated from the Okinawan marine sponge *Strongylophora strongilata* (Iriomote Island, Okinawa, Japan, in 2010) together with six known strongylophorines (**578**–**583**). Compounds **577, 578**, and **580** inhibited the activity of protein tyrosine phosphatase 1B (PTP1B) with an IC_{50} value of 8.7, 8.5, 9.0 μM, respectively [246]. A chemical investigation of the marine sponge *Petrosia corticata* (North Sulawesi, Indonesia, in 2007) resulted in the characterization of two new strongylophorine derivatives in 2015, 26-O-methylstrongylophorine-16 (**584**) and 26-O-ethylstrongylophorine-16 (**585**), along with six known congeners (**586**–**592**). Most of these compounds showed potent inhibitory activity against the chymotrypsin-like activity of the proteasome in the low concentration (μg/mL) [247].



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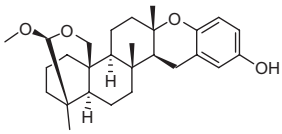

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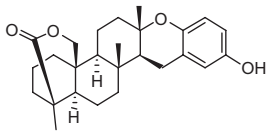

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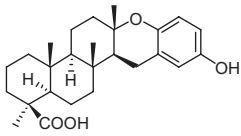

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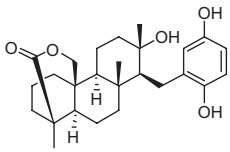

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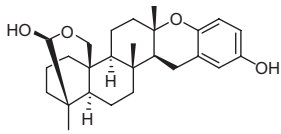

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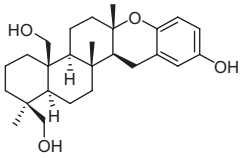

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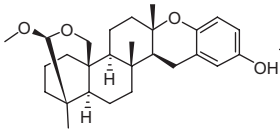

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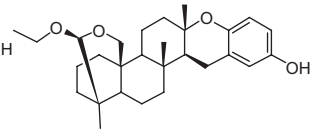

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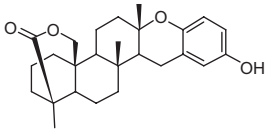

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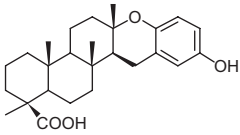

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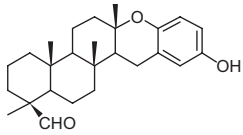

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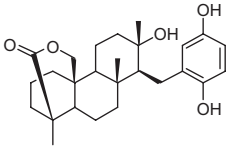

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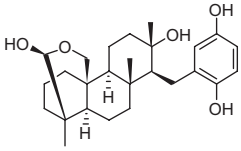

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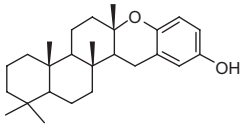

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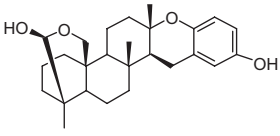
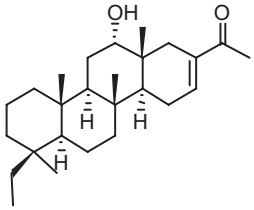


592

15.6.3 Sesterterpenes

In 1991, three new norsesterterpene peroxides, phyllofenone B (**593**), phyllofolactone A (**594**), and phyllofolactone B (**595**), were isolated from the sponge *Latrunculia sp.* (Jervis Bay, Australia). Among them, phyllofenone B was active against the P388 cell line with an IC_{50} value of 5 μg/mL [248]. In 1991, a study of the Adriatic sponge *Fasciospongia cavernosa* (Yongxing Island, South China Sea, in April 1988) yielded 25-Deoxycacospongionolide B (**596**), which showed a high cytotoxicity with an EC_{50} value of 0.74 μg/mL in the Arremia salina bioassay [249].



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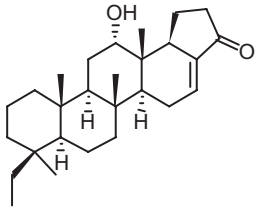

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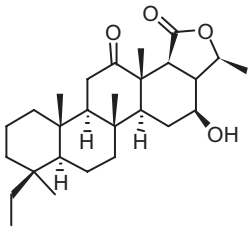

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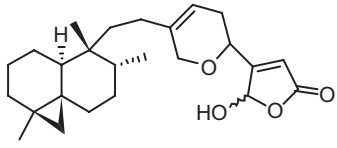
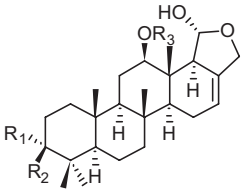
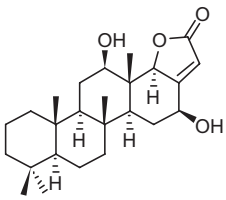


596

In 1998, chemical analysis of *Hyrtios erecta* (Amami-Oshima, Japan, in 1993) resulted in the discovery of novel scalarane sesterterpenes (**597**–**601**), and their stereo structures were characterized by means of spectral analyses, X-ray crystallography, and chemical reactions. Compound **597** showed potent in vitro and in vivo antitumor activities. In addition, the structure-activity relationship was also discussed using computer-assisted structure matching of **597** and aragusterols [250].

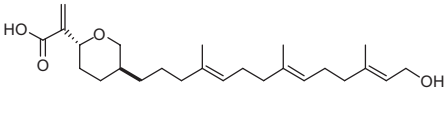


597 R1, R2=O;R3=H
598 R1=R3=H;R2=OH
599 R1=H;R2=OH;R3=Ac
600 R1=R2=R3=H



601

In 2002, barangcadoic acid A (**602**) and rhopaloic acids D-G (**603**–**606**) found in the marine sponge *Hippospongia sp*, were reported to possess RCE protease inhibitory activity [251]. In 2010, a chemical investigation of the South China Sea sponge *Phyllospongia foliascens* (Yongxing Island, South China Sea, in June 2007) resulted in discovery of a new scalarane sesterterpene, phyllofolactone M (**607**) [252].



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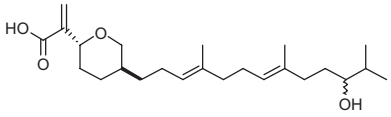

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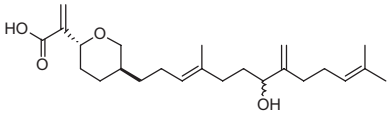

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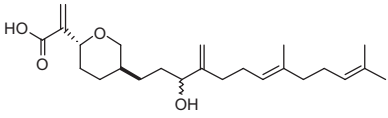

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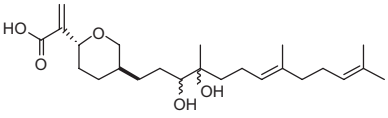

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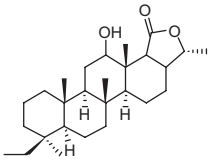
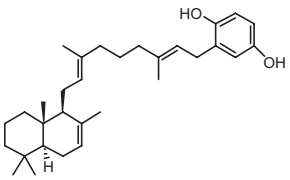


607

In 2011, a study of the sponge *Coscinoderma* sp. (Chuuk Island, Federated States of Micronesia, in June 2006) yielded eight new sesterterpenes (**607**–**615**), which displayed moderate cytotoxicity toward the K562 cell line and inhibitory activities of isocitrate lyase, sortase A, and Na^+/K^+-ATPase [253].



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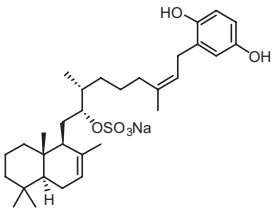

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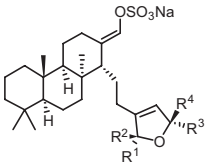
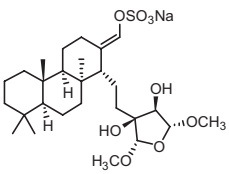
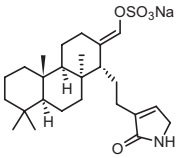


610 R^1=H, R^2=H,R^3R^4=O
611 R^1R^2=O, R^3=H, R^4=OCH_3
612 R^1R^2=O, R^3=OCH_3,R^4=H
613 R^1=OCH3, R^2=H,R^3=OCH3,R^4=H

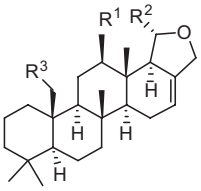


614

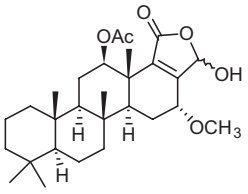


615

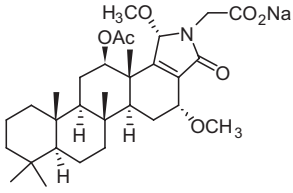
In 2011, five new sesterterpenes (**616**–**620**) were isolated from the sponge *Hyatella* sp. (Soheuksan-do, West Sea, Korea, on June 18, 2007). Compounds **616**–**619** contained oxidized furan moieties, while compound **620** possessed a corresponding lactam. Compound **619** exhibited moderate antibacterial activity with MIC value of 1.56 μg/mL [254].



616 R^1=OAc,R^2=OH,R^3=OAc
617 R^1=OH,R^2=OH,R^3=OAc
618 R^1=OAc,R^2=OCH_3,R^3=H

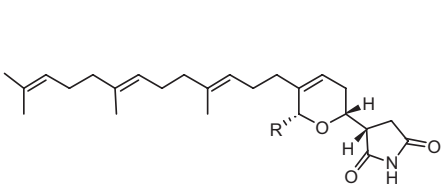


619

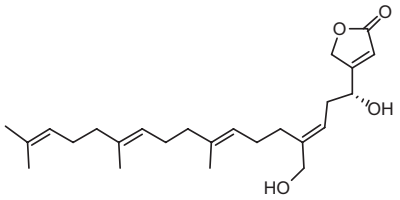


620

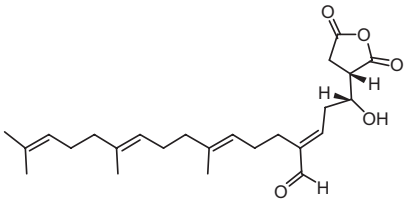
In 2011, hippolides A–H (**621**–**630**) were obtained from the sponge *Hippospongia lachne* (Yongxing Island, South China Sea, in June 2007), and their absolute configurations were established by the modified Mosher's method and CD data. Hippolide A exhibited cytotoxicity against A549, HeLa, and HCT-116 cell lines with IC_{50} values of 5.22×10^{-2},4.80×10^{-2} and 9.78 μM, respectively [255].



621 R=OH
622 R=OCH$_3$



623



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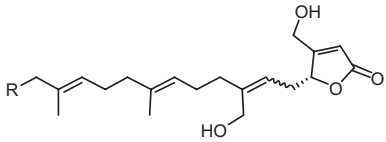
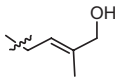
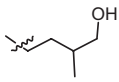


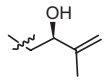
625 6*E*,R=



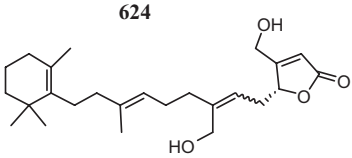
626 6*Z*,R=



627 6*Z*,R=

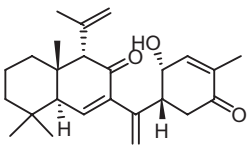


628 6*Z*,R=

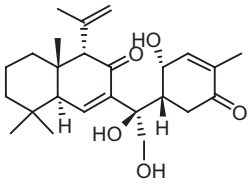


629 6*E*
630 6*Z*

In 2011, two new sesterterpenoids, phorbasones A (**631**) and B (**632**), were found from the Korean marine sponge *Phorbas* sp., and their complete structures were elucidated by spectral data and chemical reactions. Phorbasone A exhibited a positive effect on the calcium deposition activity in C3H10T1/2 cells [256].

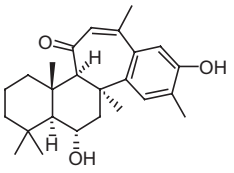


631 Phorbasone A

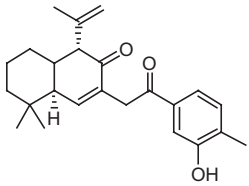


632 Phorbasone B

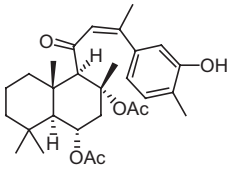
In 2012, phorone A (**633**) and isophorbasone A (**634**) featured with two new carbon skeletons were identified, along with ansellone B (**635**) and phorbasone A acetate (**636**), from a Korean marine sponge, *Phorbas* sp. Ansellone B (**635**) and phorbasone A acetate (**636**) exhibited potent inhibitory activity on nitric oxide production in RAW 264.7 LPS-activated mouse macrophage cells with IC_{50} values of 4.5 and 2.8 μM, respectively [257].



633 phorone A



634 isophorbasone A



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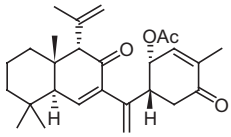
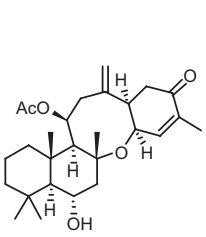
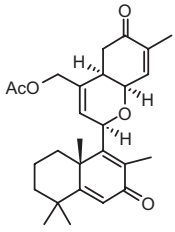


636

In 2013, four new sesterterpenoids, ansellone B (**637**), phorbadione (**638**), secoepoxyansellone A (**639**), and alotaketal C (**640**) were isolated from the sponge *Phorbas* sp. (Howe Sound, British Columbia). Ansellone B (**637**) possessed an unprecedented heterocyclic skeleton with an oxocane ring, while secoepoxyansellone A (**639**) was the first example of the degraded "secoansellane" sesterterpenoid carbon skeleton. Alotaketal C (**640**) activated cAMP signaling in HEK293 cells with an EC_{50} of 6.5 μM [258].



637



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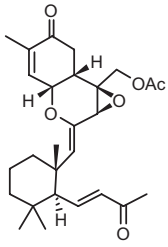

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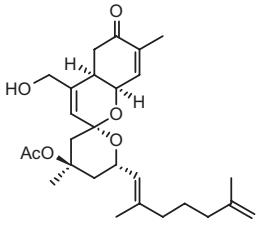
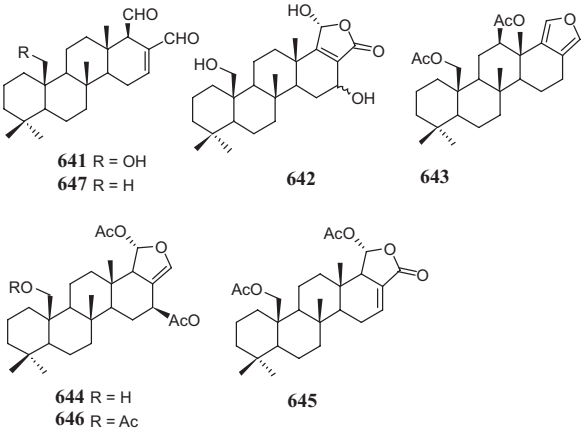


640

Meanwhile, three novel scalarane sesterterpenes, 12-deacetoxy-23-hydroxyscalaradial (**641**), 12-dehydr-oxy-23-hydroxyhyrtiolide (**642**), and 12-O-acetyl-16-deacetoxy-23-acetoxyscalarafuran (**643**), along with four known derivatives (**644–647**), were isolated from *Psammocinia* sp. (South Sea of Korea). They exhibited cytotoxicity against intractable human cancer cell lines A498, ACHN, MIA-paca, and PANC-1, with mean IC_{50} values in the range of 0.4–48 μM [259].



641 R = OH
647 R = H

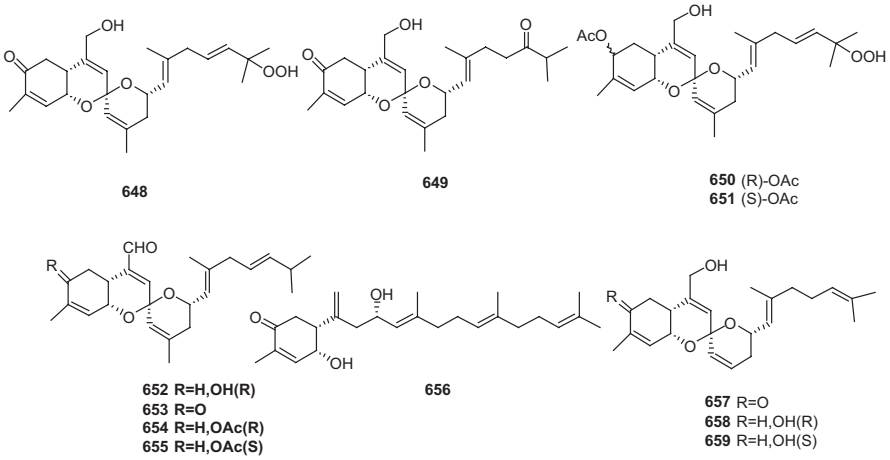
642

643

644 R = H
646 R = Ac

645

Phorbaketals D–K (**648–656**) with a spiroketal-modified benzopyran moiety, along with phorbins A–C (**657–659**), were characterized from the sponge *Monanchora* sp. (Gageo Island, southwestern Korea, in July 2009), and the absolute configurations of them were established with the modified Mosher's method and CD spectroscopic data analysis. Phorbin A (**657**) showed potent cytotoxicity against MIA-paca and PANC-1 human pancreatic cancer cell lines, similar to or better than the positive control [260].



648

649

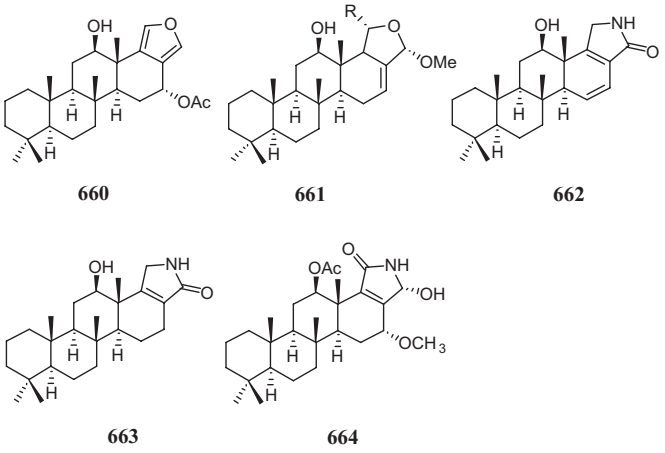
650 (R)-OAc
651 (S)-OAc

652 R=H,OH(R)
653 R=O
654 R=H,OAc(R)
655 R=H,OAc(S)

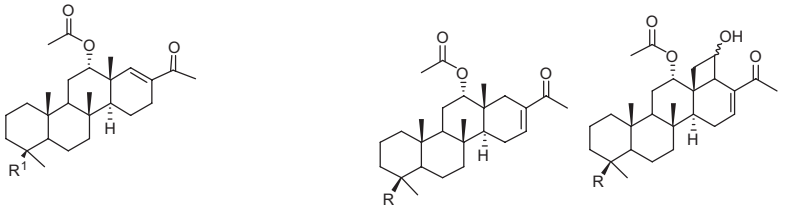
656

657 R=O
658 R=H,OH(R)
659 R=H,OH(S)

In 2014, five new scalarane derivatives (**660–664**) acting as inhibitors of TDP-43 nuclear factor were discovered from *Hyrtios* sp. and *Petrosaspongia* sp. (Fiji Islands) [261].

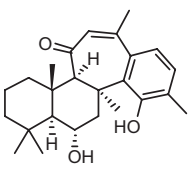


In 2015, phyllospongins A–E (**665–668**) were identified from *Phyllospongia lamellosa* (Hurghada, Egypt).These scalarane sesterterpenes exhibited potent cytotoxic activity against HCT-116, HePG2, MCF-7 cell lines with an IC_{50} range of 0.29–2.14 μM. Phyllospongins D showed cytotoxicity against HCT-116 as potent as doxorubicin. Phyllospongins E showed cytotoxicity against MCF-7 comparable to doxorubicin [262].

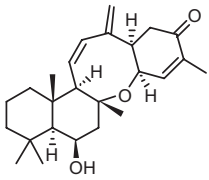


Phyllospongin A (**664**, R^1=CH_3,R^2= -CH_3COO)
Phyllospongin B (**665**,R^1=CH_2CH_3,R^2= -CH_3COO) Phyllospongin C (**666**,R=CH3)
Phyllospongin D (**667**,R=CH_3,-OH)
Phyllospongin E (**668**,R=CH_3,-OH)

In 2015, phorone B (**669**) and ansellone C (**670**) structurally close related to the sesterterpenes of the phorone and ansellone classes were isolated from the marine sponge *Clathria gombawuiensis* (Gageo-do, Korea, on September 9–11, 2006). The two compounds showed temperate cytotoxic activity against A549 and K562 cell lines with mean IC_{50} values in the range 3.9–5.4 μM. The cytotoxicity of **1** may be related to the presence of a free phenolic −OH group, as the corresponding O-methoxy derivative is inactive [263].



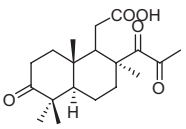
669



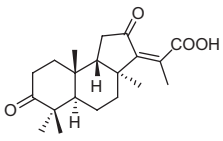
670

15.6.4 Triterpenes

In 2010, nine new isomalabaricane derivatives, globostelletins A–I (**671**–**679**), were isolated from *Rhabdastrella globostellata* (Hainan Island, South China Sea, in June 2006), along with five known compounds (**680**–**684**). Of which, globostelletins C and D (**673**–**674**) were a pair of inseparable geometrical isomers with a ratio of 1:1. Compounds **673**–**674** and **678**–**682** exhibited activity against A2780 cell lines with low μM (IC_{50} < 10 μM) [264].



671



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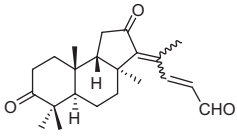
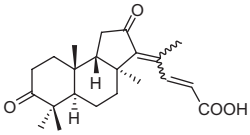
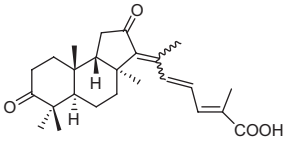


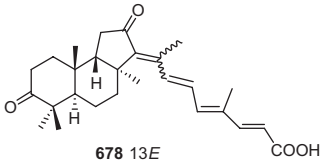
673 13*E*
674 13*Z*



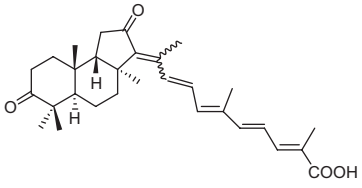
675 13*E*
676 13*Z*



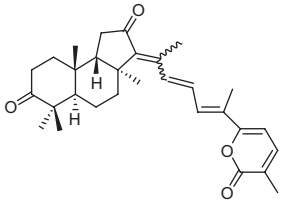
677 13*E*
680 13*Z*



678 13*E*
679 13*Z*



681 13*E*
682 13*Z*



683 13*E*
684 13*Z*

15.7 Bioactive Sterols

The basic role of sterols is the maintenance of optimal fluidity of cell membranes, although these compounds also serve as precursors for the production of diverse steroid classes such as the polyhydroxylated marine sterols. In recent years, research in the marine sterol field has progressed at an impressive pace. Here we intend to provide a description of the characteristic features of 107 sterols with potent biological activities from 29 marine sponges covering literatures from 1993 to 2015.

15.7.1 Alkaloidal Sterols

In 2014, the chemical study of marine sponge *Corticium niger* collected from the Philippines resulted in the discovery of two new steroidal alkaloids plakinamines N (**685**) and O (**686**), which were tested for antiproliferative activity and showed remarkable inhibitory effects against all of the colon cell lines with mean GI_{50} values of 11.5 and 2.4 μM [265].

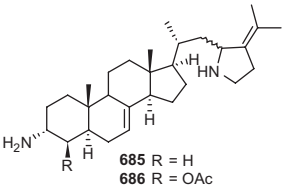
In 2007, a tropical sponge *Phorbas amaranthus* (Key Largo, Florida) was found to contain a 24-imidazolyl steroidal alkaloid amaranzole A (**687**). The structure was elucidated on the basis of MS, NMR, exciton-coupled CD spectrum, and comparison with model compounds [266]. In the same year, steroidal alkaloid 4-acetoxyplakinamine B (**688**) bearing a stigmastane skeleton was found in the Thai sponge *Corticium* sp. The compound inhibited acetylcholinesterase with IC_{50} value of 3.75 μM [267]. A series of steroidal alkaloids cortistatins J–L (**689–691**) were isolated from the Indonesian marine sponge *Corticium simplex*. Cortistatin J exhibited potent cytostatic antiproliferative activity against human umbilical vein endothelial cells (HUVECs) at 8 nM [268].

In 2006, four steroidal isoquinoline alkaloids cortistatins A–D (**692–695**) were obtained from the marine sponge *Corticium simplex* (Flores Is., Indonesia). These compounds exhibited highly selective antiproliferative activity against HUVECs with IC_{50} values of 0.0018, 1.1, 0.019, and 0.15 μM, respectively [269].

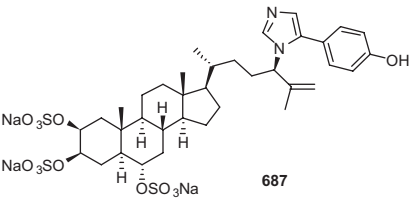
In 2003, four steroidal alkaloids, plakinamine I–K (**696–698**) and dihydroplakinamine K (**699**), were obtained from a Philippine sponge *Corticium niger*. These compounds exhibited significant in vitro cytotoxicity against the human colon tumor cell line HCT-116 with IC_{50} values of 10.6, 6.1, 1.4, and 1.4 μM, respectively [270].

In 2002, four plakinamine-type steroidal alkaloids were isolated from a marine sponge *Vanuatuan Corticium*, of which plakinamine G (**700**) and tetrahydroplakinamine A (**701**) were quite active against rat glioma cells (IC_{50}'s 6.8 and 1.4 μg/mL, respectively) [271].

In the year of 1999, chemical study of *Corticium* sp. from Vanuatu yielded plakinamines C (**702**) and D (**703**) and three other steroidal alkaloids (**704–706**), all of which showed potent cytotoxicity against human bronchopulmonary non-small-cell lung carcinoma cells with IC_{50} values of <3.3–5.7 μg/mL [272].



685 R = H
686 R = OAc



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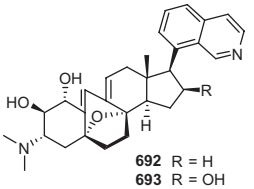
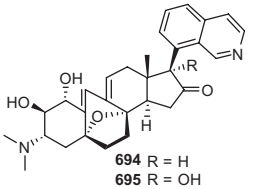
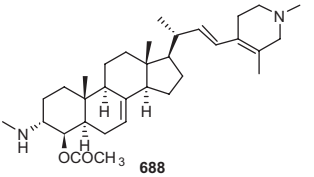


692 R = H
693 R = OH



694 R = H
695 R = OH



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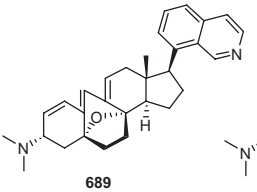

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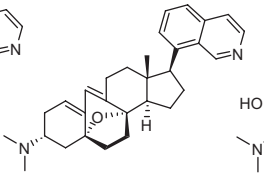

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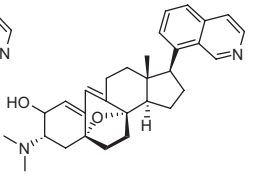

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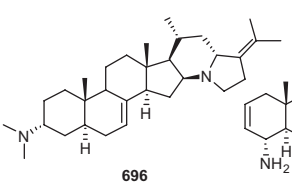

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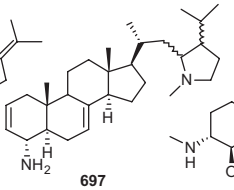

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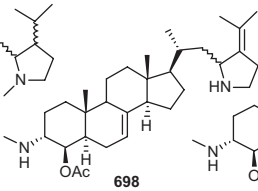

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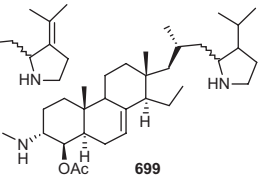

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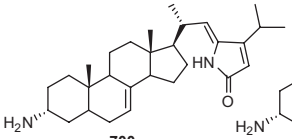

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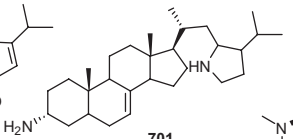

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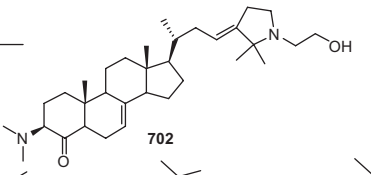

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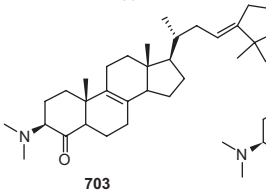

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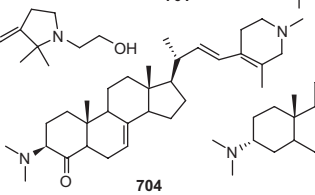

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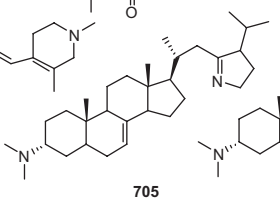

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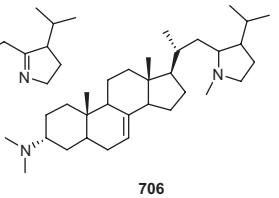


706

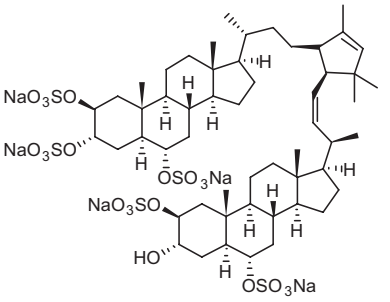
15.7.2 Sulfated Sterols

In 2012, two new dimeric sterols manadosterols A (**707**) and B (**708**) were found in the sponge *Lissodendryx fibrosa* in Indonesia, which are potent inhibitors of the Ubc13-Uev1a complex with IC_{50} values of 0.09 and 0.13 μM and therefore have potential as anticancer agents [273].

In 2011, shishicrellastatin A and B (**709** and **710**), two dimeric steroid derivatives, were reported from the marine sponge *Crella* (*Yvesia*) *spinulata*. Both of them exhibited bioactivity against cathepsin B with an IC_{50} value of 6.9 μM each [274].

In 2009, three sulfated sterol dimers, fibrosterol sulfates A–C (**711–713**), were isolated from *Lissodendoryx* (*Acanthodoryx*) *fibrosa* collected in the Philippines. Fibrosterol sulfate B inhibited protein kinase Cζ with IC_{50} value of 5.6 μM [275].

In the year of 2008, a species of *Spheciospongia* sp. (Cagayan de Oro, Philippines) was the source of sterol sulfates, spheciosterol sulfates A–C (**714–716**), all of which potent inhibited protein kinase Cζ with IC_{50} values of 1.59, 0.53, 0.11, and 1.21 μM, respectively [276].



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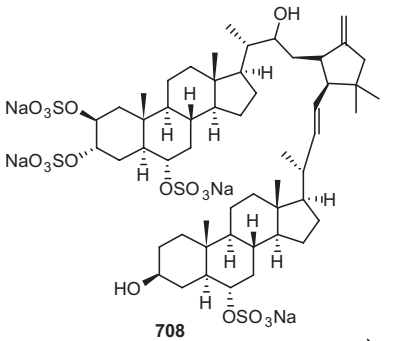

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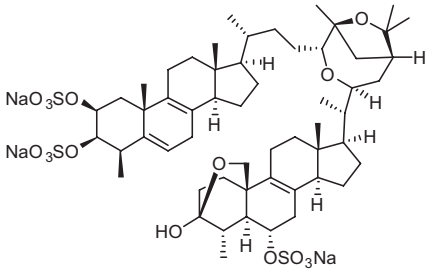

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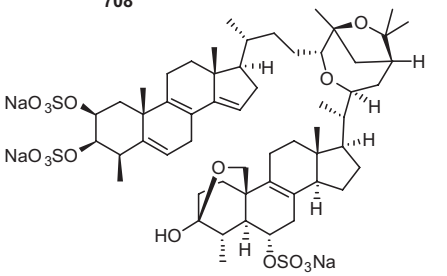
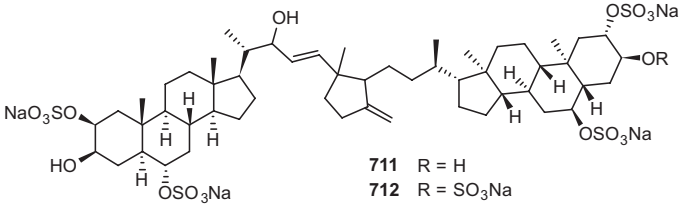
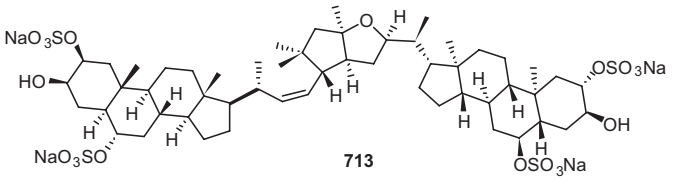


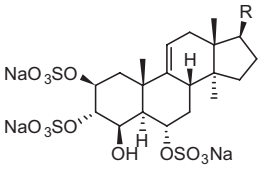
710



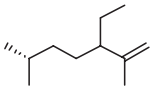
711 R = H
712 R = SO_3Na



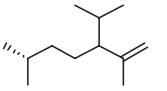
713



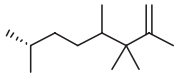
714 R =



715 R =



716 R =



In 2008, three new marine polar steroids, chlorotopsentiasterol sulfate D (**717**), topsentiasterol sulfate F (**718**), and iodotopsentiasterol D (**719**), were isolated from the marine sponge *Topsentia* sp. (Vang Fong Bay, Vietnam). Chlorotopsentiasterol sulfate D proved to be an effective inhibitor of *endo*-1,3-β-D-glucanase [277].

In 2007, sulfated sterol 24ξ,25-dimethyl-3*α*-hydroxyl-cholest-5-ene-2*β*-ol sodium sulfate (**720**) which showed cytotoxicity to four human cancer cell lines was obtained from *Halichondria rugosa* [278].

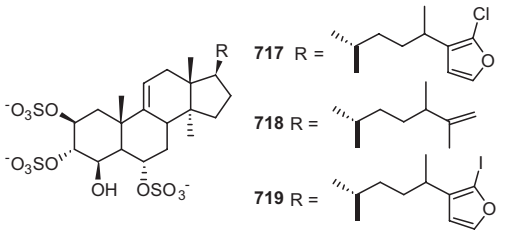
In 2007, an undescribed marine sponge *Euryspongia* was the source of eurysterols A (**721**) and B (**722**), with the former being cytotoxicity against human colon carcinoma (HCT-116) cells with IC_{50} value of 2.9 μg/mL, also antifungal to amphotericin-B-resistant *Candida albicans* [279].

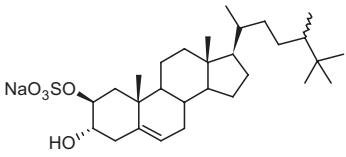
In 2003, a sterol sulfate Scheme 572423 (**723**), along with the known halistanol sulfate, was isolated from a *Topsentia* species collected in the Bahamas. The compounds were found as $P2Y_{12}$ inhibitors with IC_{50} of 0.48 and 2.2 μM, respectively [280].

In 2001, a Philippine sponge of the genus *Xestospongia* yielded two sulfated sterols, ibisterol B (**724**) and C (**725**) and an epoxysteroid (**726**) that were found to be inhibitors of HIV-1 integrase [281].

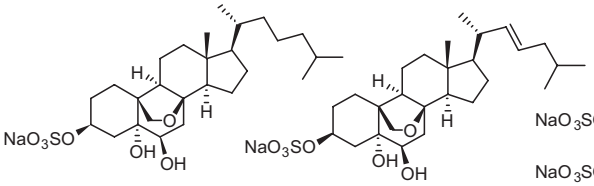
In 1998, marine sponge *Crella* sp. from Vanuatu Island yielded crellastatin A (**727**), a new nonsymmetric dimeric steroid, which exhibited cytotoxic activity against NSCLC-N6 cells with the IC_{50} value of 1.5 μg/mL [282].

In 1996, halistanol disulfate B (**728**), a sterol sulfate, was isolated from the MeOH extract of a South African sponge *Pachastrella* sp. The compound had an IC_{50} of 2.1 μM for inhibition of endothelin converting enzyme [283].

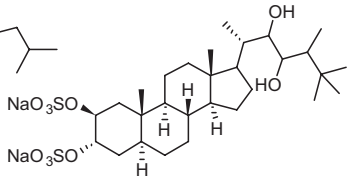




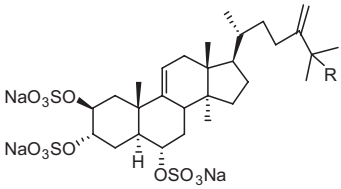
720



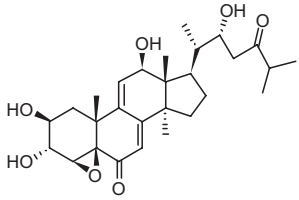
721 722



723



724 R = H
725 R =Me



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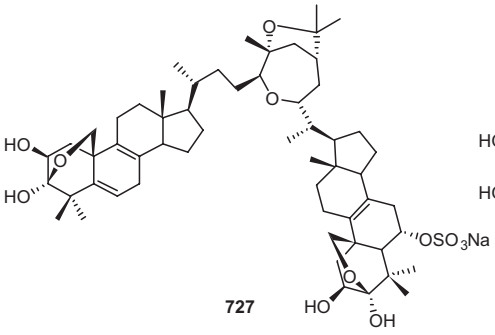

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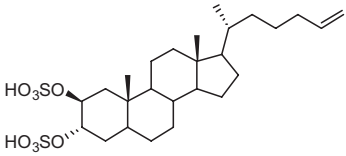
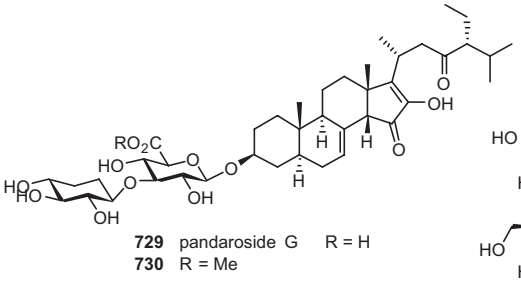


728

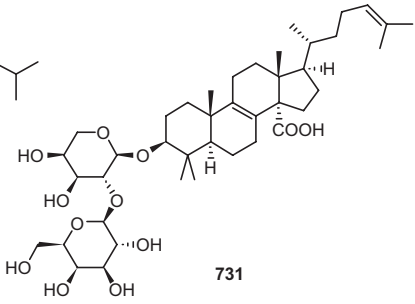
15.7.3 Glycoside Sterols

In 2010, steroidal glycosides, namely, pandarosides E–J, and their methyl esters were isolated from a Caribbean sponge *Pandaros acanthifolium*, with all except pandaroside H exhibiting antiprotozoal activity. Methyl ester of pandaroside G (**730**) potently inhibited the growth of *Trypanosoma brucei rhodesiense* (IC_{50} = 0.038 μM) and *Leishmania donovani* (IC_{50} = 0.051 μM) especially [284].

In 2000, a potent penasterol disaccharide eryloside F (**731**) inhibited human platelet aggregation in vitro as a thrombin receptor antagonist, which was obtained from the sponge *Erylus formosus*. The IC_{50} values of the compound inhibited SFLLRN and U-46619-induced platelet aggregation were at 0.3 and 1.7 μg/mL, respectively [285].



729 pandaroside G R = H
730 R = Me



731

15.7.4 Others

In 2014, cinanthrenol A (**732**), an estrogenic steroid containing phenanthrene nucleus, was isolated from the marine sponge *Cinachyrella* sp. Absolute configuration of the compound was established as 16S, 17S, and 19S by the modified Mosher's method. Cinanthrenol A bound to estrogen receptor in a competitive manner against estradiol with an IC_{50} value of 10 nM. Moreover, it has cytotoxicity against P388 and HeLa cells as well, with IC_{50} 4.5 and 0.4 μg/mL, respectively [286].

Also in this year, extracts of the sponge *Theonella swinhoei*, which collected at the Xisha island, yielded two novel sterols swinhoeisterols A and B (**733** and **734**) with an unprecedented 6/6/5/7 tetracyclic systems. The absolute configurations of the compounds were assigned by X-ray diffraction, TDDFT/ECD calculations, and modified Mosher's method. Swinhoeisterols A exhibit a potent inhibitory activity (IC_{50} = 2.9 μM) against the histone acetyltransferase (h)p300 [287].

In 2013, aragusterol I (**735**), 21-*O*-octadecanoyl-xestokerol A (**736**), and 7*β*-hydroxypetrosterol (**737**), three cyclopropanated sterols, were isolated from the Vietnamese marine sponge *Xestospongia testudinaria* [288]. The compound 21-O-octadecanoyl-xestokerol A showed antifouling activity with EC_{50} values similar to that of the antifoulant marine pollutant tributyltin oxide.

In 2008, aminosteroids clionamine D (**738**) which has an unprecedented spiro bislactone side chain were isolated from South African specimens of the sponge *Cliona celata* [289].

In 2004, the Okinawan sponge *Terpios hoshinota* yielded nakiterpiosin (**739**) and nakiterpiosinone (**740**), both exhibiting cytotoxicity potentially against mouse lymphocytic leukemia cells (P388) with IC_{50} values of 0.01 mg/mL, respectively [290].

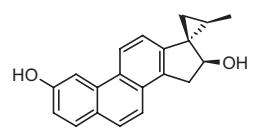
In 2001, *Stelletta hiwasaensis* from Japan was found to produce orostanal (**741**), abeo-sterol derivative, which induced apoptosis in human acute promyelotic leukemia cell with IC_{50} value of 1.7 μM [291].

In 1999, glaciasterol B 3-monoacetate (**742**), a new 9,11-secosterol which exhibited potent toxic activity (LC_{50} = 0.54 μg/ml) to brine shrimp, was isolated from the Tyrrhenian sponge *Fasciospongiu cavernosa* [292].

In 1996, an Okinawan marine sponge *Xestospongia* sp. was found to contain aragusteroketals A (**743**) and C (**744**); both of them exhibited potent cytotoxic activity with the same IC_{50} value of 4 ng/ml against KB cells [293].

In 1995, pentacyclic steroid xestobergsterol C (**745**), possessing a cis C/D ring junction, which exhibited cytotoxicity against L-1210 murine leukemia cells with IC_{50} values of 4.1 μg/mL, was obtained from the Okinawan marine sponge *Ircinia* sp. [294].

In 1993, an Okinawan marine sponge of the genus *Xestospongia* was the source of aragusterol A–D (**746–749**) [295–297], all of which except aragusterol C strongly inhibited the proliferation of KB cells at IC_{50} values of 0.042, 3.3, and 0.041 μg/mL, respectively.



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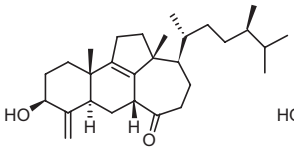

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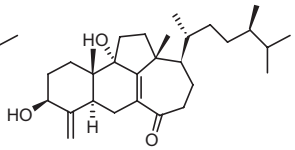

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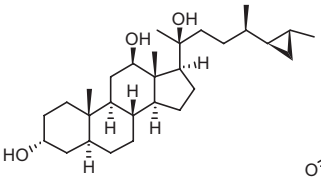

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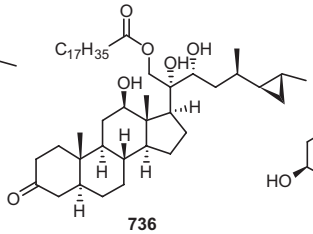

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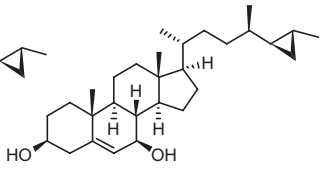

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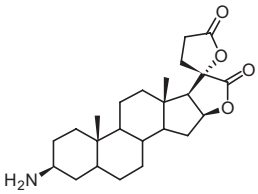

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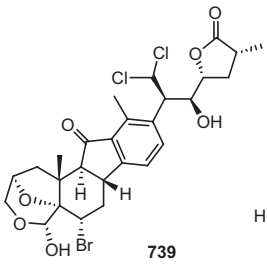

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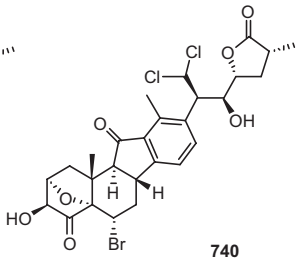

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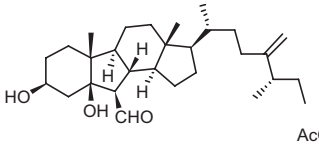

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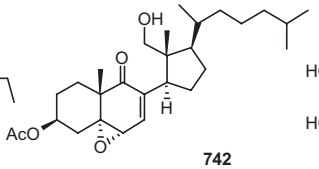

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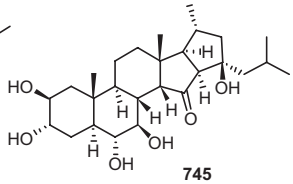

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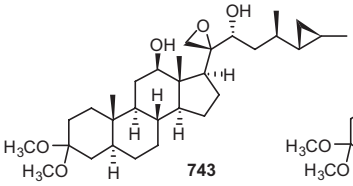

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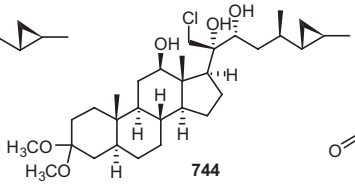

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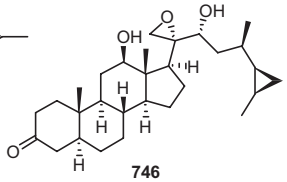

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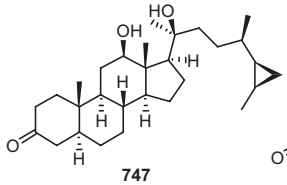

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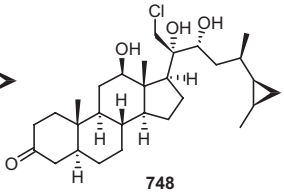

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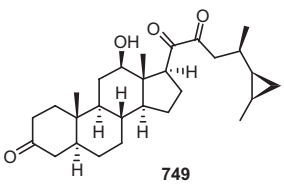


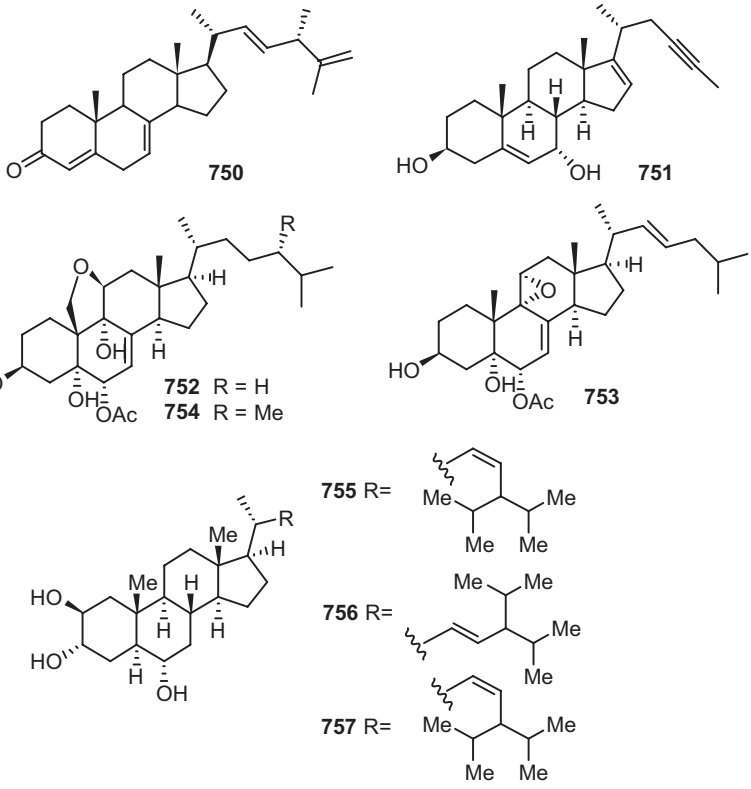
749

In 2015, a steroidal ketone (**750**), bearing an ergosta-22,25-diene side chain, was isolated from the South China Sea marine sponge *Xestospongia testudinaria*. The compound exhibited potent activity against protein tyrosine phosphatase 1B (PTP1B) with an IC_{50} value of 4.27 μM [298].

In the same year, antibacterial compound gelliusterol E (**751**) was obtained from the Red Sea sponge *Callyspongia* aff. *implexa* [299]. Gelliusterol E inhibited the formation and growth of gram-negative bacterium *Chlamydia trachomatis* in a dose-dependent manner with an IC_{50} value of 2.3 μM.

In 2012, Okinawan sponge *Dysidea* sp. was the source of dysideasterols F–H (**752–754**), all of which inhibited human epidermoid carcinoma cells strongly with a similar cytotoxic effect with IC_{50} values of 0.15–0.3 μM [300].

In 2010, an undescribed species of *Topsentia* was the source of three isopropyl steroids, topsentinols K (**755**), L (**756**) and K trisulfate (**757**); the latter was an inhibitor of BACE1 dose-dependently with an IC_{50} value of 1.2 μM [301].



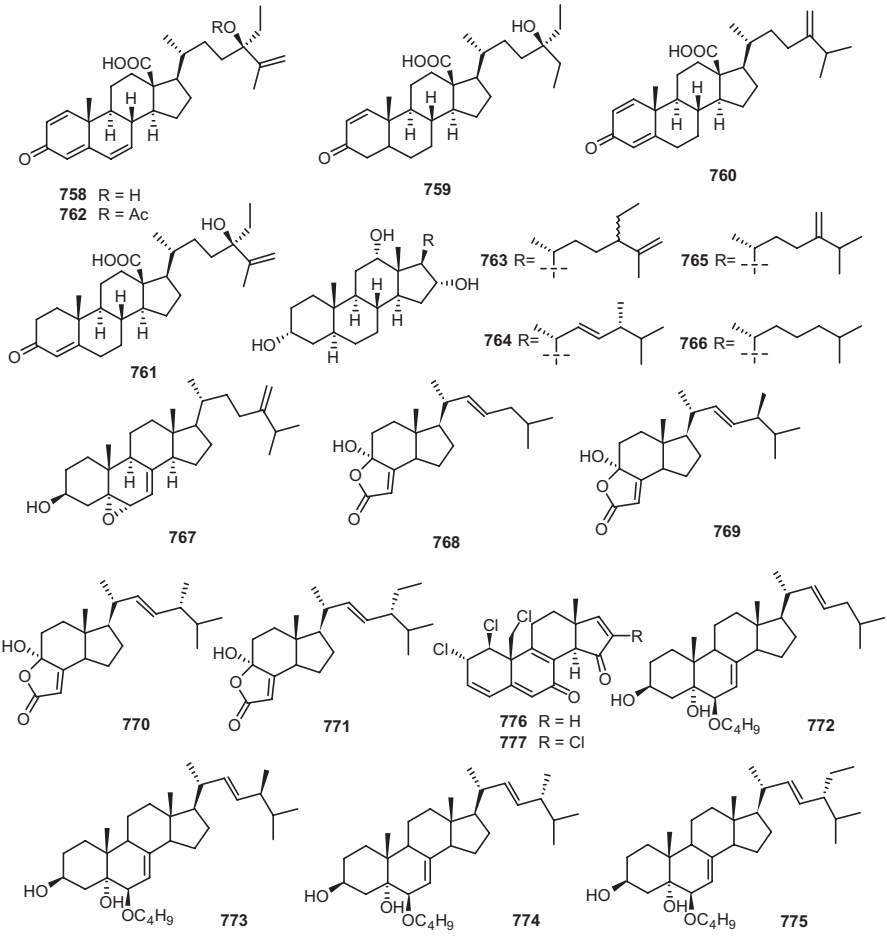
In 2009, five norselic acids A–E (**758–762**) were obtained from the sponge *Crella* sp. collected in Antarctica, all of which inhibited the growth of the Leishmania parasite at low micromolar levels [302].

Also in 2009, Australian marine sponge *Psammoclema* sp. contained a series of trihydroxysterols (**763**–**766**), of which **4** were cytotoxic against a panel of cancer cell lines [303].

In 2008, *Ircinia aruensis* collected in Naozhou Island yielded six epoxysterols. Compound **767** exhibited cytotoxicity against four cancer cell lines (7402, H-460, LOVO, and MCF) with IC_{50} values of 4.3, 2.8, 5.1, and 3.5 μg/mL, respectively [304].

In 2005, *Homaxinella* sp. (Korea) contained a series of highly degraded sterols demethylincisterols A_1–A_4 (**768**–**771**) and butoxyderivatised sterols homaxisterols A_1–A_4 (**772**–**775**), all of which but homaxisterols A_4 inhibited a panel of five human solid tumor cell lines, and especially **770** displayed significant cytotoxicity [305].

In 2004, Italian sponge *Cliona nigricans* provided two polychlorinated steroids clionastatins A (**776**) and B (**777**), which exhibited potential antitumor activity in three cell lines with IC_{50} values ranging from 0.8 to 2.0 μg/mL [306].



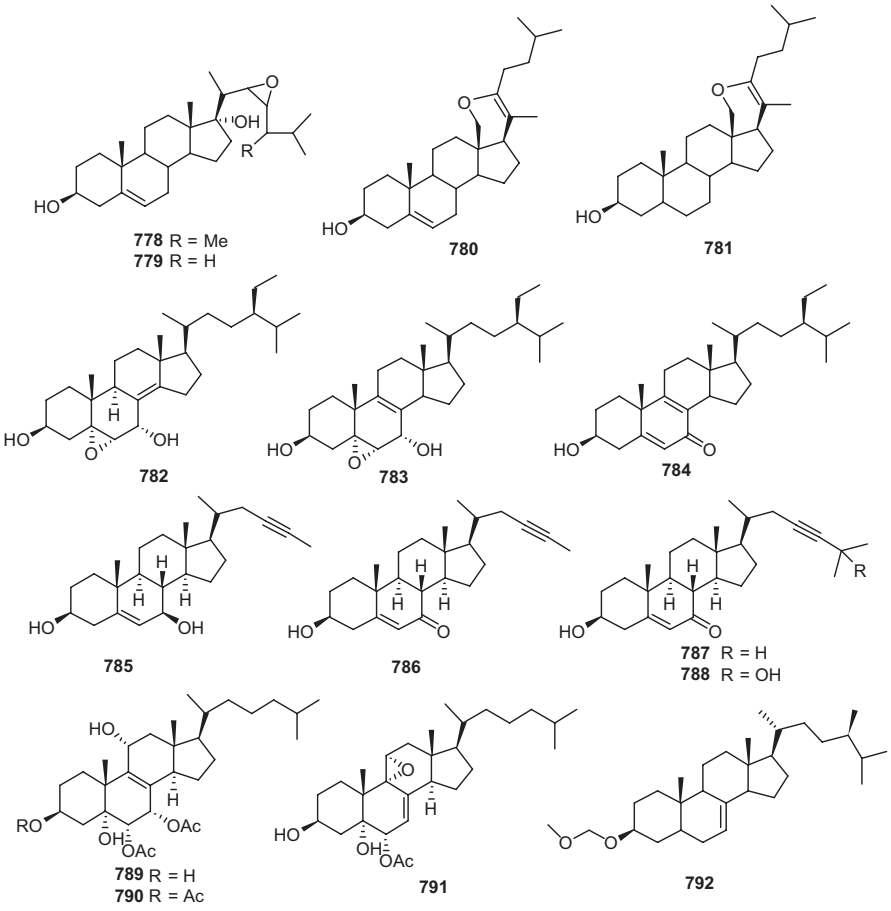
In 2004, four sterols (**778**–**781**) were isolated from the marine sponge *Axinella* cf. *bidderi* (Yemen, Indian Ocean), which possess, respectively, the cholestene and the cholestane skeleton with a cyclic enol ether linkage between C-18 and C-22. These sterols showed cytotoxic activity against prostate, ovary, pancreas, colon, and lung cell lines with GI_{50} values ranging from 0.6 to 8.3 μg/mL [307].

In 2002, three new sterols (**782**–**784**), isolated from the marine sponge *Polymastia tenax*, were found to have potent antiproliferative activity toward A549, HT29, H-116, MS-1, and PC-3 tumor cells in the range 0.5–10 μg/mL [308].

In 2001, an undescribed species of *Gellius* collected in the Caribbean coast of Panama was the source of four acetylenic sterols, gelliusterols A–D (**785**–**788**); **785**, **786**, and **787** were found to be cytotoxic to a panel of cancer cell lines [309].

In 2000, northern Australia *Dysidea* sp. yielded three polyoxygenated sterols (**789**–**791**) that inhibited the binding of IL-8 to the human recombinant IL-8 receptor-type A with the IC_{50} values of 20, 5.5, and 4.5 μM, respectively [310].

A deepwater marine sponge *Scleritoderma* sp. cf. *paccardi* which collected from Turneffe Islands (Belize) in 1985 yielded a sterol ether (**792**) named 24(*R*)-methyl-5α-cholest-7-enyl 3β-methoxymethyl ether. IC_{50} of the compound inhibited the murine P388 tumor cell line was 2.3 μg/mL [311].



15.8 Bioactive Potentials from Diverse Sponges Derived Natural Products

For the past decades, marine sponges have been considered as a very fertile field for the discovery of bioactive natural chemical substances with respect to the diversity of their primary and secondary chemical components and metabolites [312]. It was proved that marine sponges produce an enormous array of antitumor, antiviral, anti-inflammatory, antibiotic, and other bioactive molecules that have the potential for therapeutic use. Studies showed that different components affect the targeted disease by different mechanisms. Natural chemical products that can act as inhibitors of transcription factors may be effective against both malignant neoplasms and viral diseases. Most bioactive metabolites from sponges proved to be inhibitors of certain enzymes, which often mediate or produce mediators of intracellular or intercellular

messengers involved in the pathogenesis of a disease [313]. Here, we introduce several kinds of recently confirmed bioactive lead compounds isolated from marine sponge which pharmacological mechanisms were studied.

Cytarabine (Fig. 15.1) is derived from the related marine natural products spongothymidine and spongouridine, nucleosides with a modified sugar moiety. These nucleosides were isolated from the Caribbean sponge *Crypotethia crypta* by Bergmann and Feeney in 1951 [314]. Cytarabine is mainly used in the treatment of acute myeloid leukemia and acute lymphocytic leukemia (ALL), where it is the backbone of induction chemotherapy [315]. Cytosine arabinoside interferes with the synthesis of DNA. Its mode of action is due to its rapid conversion into cytosine arabinoside triphosphate, which damages DNA when the cell cycle holds in the S phase (synthesis of DNA). The cells requiring DNA replication for mitosis are therefore most affected [315]. Cytosine arabinoside was also considered as inhibitor of both DNA and RNA polymerases and nucleotide reductases needed for DNA synthesis. As an antiviral agent, cytarabine was often used to inhibit deoxycytidine utilization. Due to the rapid deamination in the body into the inactive uracil derivative, cytarabine therefore is often given by continuous intravenous infusion [316].

Renieramycin G (Fig. 15.2) was isolated from marine sponges *Xestospongia* and *Cribrochalina* [317]. A recent study demonstrated that Renieramycin G induced apoptosis via the p53-dependent pathway and inhibited the progression and metastasis of non-small cell lung cancer [318]. Renieramycin G possesses an amide carbonyl group at the C-21 position demonstrated minimal antiproliferative activity in human colorectal cancer (HCT-116) and human lung adenocarcinoma (A549) cells owing to both compounds possessing an amide carbonyl group at the C-21 position.

Fig. 15.1 Cytarabine

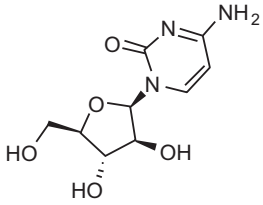
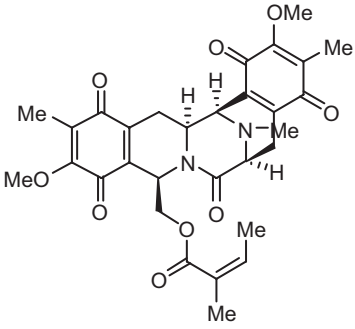


Fig. 15.2 Renieramycin G



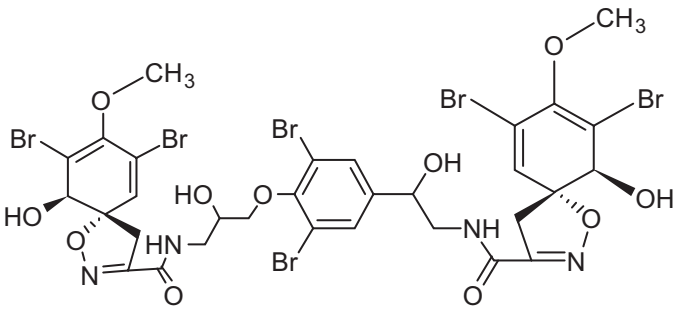


Fig. 15.3 Isofistularin-3

The minimal antiproliferative activity for members of the tetrahydroisoquinoline family possessing an amide carbonyl group at the C-21 position seems consistent compared to their C-21 cyano- or carbinolamine-containing relatives.

The brominated alkaloid Isofistularin-3 (Iso-3), a new DNA methyltransferase (DNMT)1 inhibitor, was from the marine sponge *Aplysina aerophoba* [319] (Fig. 15.3). Docking analysis confirmed DNMT inhibition data in vitro and revealed binding of Iso-3 within the DNA binding site of DNMT1 [320]. Subsequent increased expression of tumor suppressor gene aryl hydrocarbon receptor (AHR) could be correlated to decreased methylation of CpG sites within the essential Sp1 regulatory region of its promoter. Iso-3 induced growth arrest of cancer cells in G0/G1 with increasing p21 and p27 expression and reducing cyclin E1, PCNA and c-myc levels. Fluorescent and transmission electron microscopy revealed that the reduced proliferation was accompanied by morphological changes as autophagy. Furthermore, Iso-3 strongly synergized with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in RAJI [combination index (CI) = 0.22] and U937 cells (CI = 0.21) and increased TRAIL-induced apoptosis via a mechanism involving reduction of survivin expression but not of Bcl-2 family proteins nor X-linked inhibitor of apoptosis protein (XIAP) [321]. Treatment of Iso-3 decreased FLIPL expression and triggered activation of endoplasmic reticulum (ER) stress with increased GRP78 expression, which eventually induced TRAIL receptor death receptor (DR)5 surface expression. Importantly, as a potential candidate for further anticancer drug development, Iso-3 reduced the viability, colony, and in vivo tumor forming potential without affecting the viability of PBMCs from healthy donors or zebrafish development [321].

Ageladine A (Fig. 15.4) was derived from the sponge *Agelas nakamurai* [322], exhibiting in vitro and in vivo antiangiogenic activity associated with its MMP inhibition. However, subsequent study confirmed that it is resulted from the selective inhibition of kinases such as yeast Sps1/Ste20-related kinase 4, dual specificity tyrosine-phosphorylation-regulated kinase 1A, and tyrosine kinase 2 [323]. Ageladine A and its synthetic analogues feature highly selective angiogenesis inhibition, at concentrations of which no cytotoxicity are shown in the National Cancer

Fig. 15.4 Ageladine A

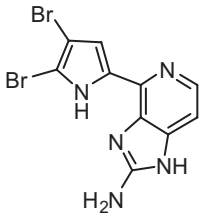
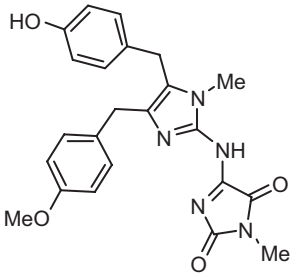


Fig. 15.5 Naamidine A



Institute (NCI) panel of 60 human cancer cell lines. Moreover, ageladine A is a fluorescent dye that is pH-sensitive and is of interest for imaging [324].

Naamidine A (Fig. 15.5) was found in marine sponge *Leucetta chagosensis*. Bioactivity study showed that this compound inhibits the EGF signaling pathway and is more specific for the EGF-mediated mitogenic activity than for the insulin-mediated mitogenic activity [325]. In 2009, LaBarbera et al. illustrated that naamidine A triggers biomarkers of apoptosis like externalization of phosphatidylserine, cleavage and activation of caspases-3, −8, and − 9, and disruption of the mitochondrial membrane potential indicating that the cell death caused by naamidine A in epidermoid carcinoma cells (A-431) is a consequence of apoptosis instead of cytotoxicity. It is also reported that naamidine A inhibits the growth of tumor xenograft by activating caspase-3 manifesting apoptosis activity in vivo. Besides, naamidine A-caused apoptosis does not depend on functional p53 and is independent of extracellular signal-regulated kinase 1/2 [326].

Araguspongine C (Fig. 15.6) is a group of macrocyclic oxaquinolizidine alkaloids derived from the marine sponge *Xestospongia* species [327]. Araguspongine C prevented the proliferation of varied breast cancer cell lines in vitro dose-dependently. Characterized by vacuole formation and upregulation of autophagy markers such as Atg3, Atg7, Atg16L, and LC3A/B suppressing c-Met and HER2 receptor tyrosine kinase activation [328], araguspongine C induces autophagic cell death in HER2-overexpressing BT-474 breast cancer cells. What's more, docking research and cell-free Z-LYTE assays revealed that araguspongine C owing the direct interaction potentially with the receptor tyrosine kinases c-Met and HER2 at their kinase domains. Especially, araguspongine C treatment causes the suppression of PI3K/Akt/mTOR signaling cascade in breast cancer cells by autophagy [328].

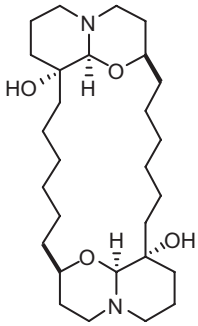


Fig. 15.6 Araguspongine C

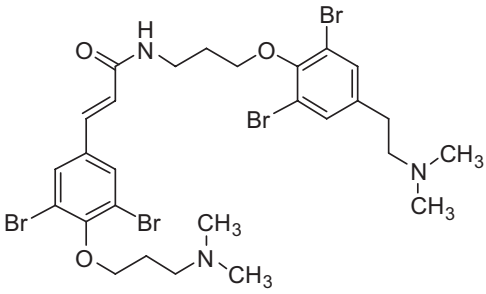
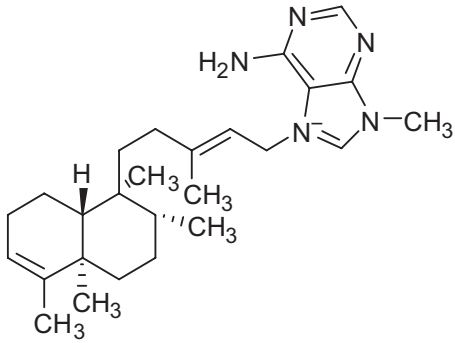


Fig. 15.7 Psammaplysene A

Psammaplysene A (Fig. 15.7) is derived from the marine sponge *Psammaplysilla* sp. Schroeder et al. demonstrated that psammaplysene A was an active inhibitor of a transcription factor FOXO1 nuclear export, whereas psammaplysene B shows less potential [329]. Extensive study illustrated that human endometrial cancer cells treated for 24 h with 1 μM psammaplysene A causes cell death leading to morphology changes with apoptosis and PARP cleavage, revealing that the cell death aroused from psammaplysene A is a result of apoptosis instead of cytotoxicity. Psammaplysene A bringing about the doubling of cells in the G2/M phase and FOXO1 silencing in ECC-1 cells reduces psammaplysene A-induced apoptosis [330].

Agelasines from a marine sponge *Agelas clathrodes* have structurally unique compounds which possess mono or bi-cyclic diterpenoids with a 9-methyladeninium chromophore. The cytotoxicity of agelasine B (Fig. 15.8) and its mechanism have been extensively studied which are of great interest that its higher toxicity in cancer cells (IC50 = 3.22, 2.99, and 6.86 μM MCF-7, SKBr3, and PC-3 cells, respectively) than in normal cells (fibroblasts, IC50 = 32.91 μM) where agelasine B upregulated the intracellular concentration of Ca^{2+} and caused fast Ca^{2+} release via the endoplasmic reticulum (ER). This research indicated that sarcoplasmic-ER Ca^{2+}-ATPase activity is inhibited by agelasine B. What's more, intracellular Ca^{2+} accumulation in the mitochondria is tied to apoptosis. In addition, this marine sponge toxin induces DNA fragmentation and severely enhances caspase-8 activity in MCF-7 cells [331].

Fig. 15.8 Agelasine B



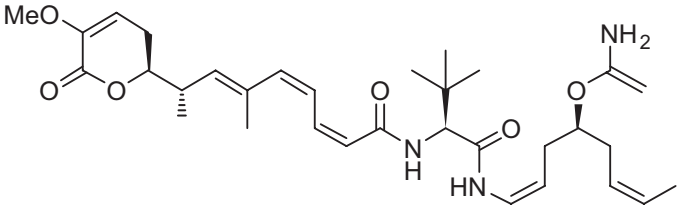


Fig. 15.9 PM060184

Therefore, agelasine B is potential for treating breast cancer for less toxicity in normal breast cells.

PM060184 (Fig. 15.9) belongs to a new family of tubulin-binding agents originally isolated from the marine sponge *Lithoplocamia lithistoides* [332]. It was published that PM060184 presents the highest known affinities among tubulin-binding agents and that it targets tubulin dimers at a new binding site. PM060184 has a potent antitumor activity in a panel of different tumor xenograft models. Moreover, PM060184 is able to overcome P-gp-mediated resistance in vivo, an effect that could be related to its high binding affinity for tubulin. PM060184 is an inhibitor of tubulin polymerization that reduces microtubule dynamicity in cells by 59% [333]. PM060184 suppresses microtubule shortening and growing at a similar extent. This action affects cells in interphase and mitosis. In the first case, the compound induced a disorganization and fragmentation of the microtubule network and the inhibition of cell migration. In the second case, it induced the appearance of multipolar mitosis and lagging chromosomes at the metaphase plate. These effects correlated with a nonclassical apoptosis pathway, which caused prometaphase arrest and induction of caspase-dependent apoptosis or appearance of cells in a multinucleated interphase-like state. Taken together, PM060184 represents a new tubulin-binding agent with promising potential as an anticancer agent [334].

Eribulin mesylate (E7389) (Fig. 15.10) is a microtubule dynamics inhibitor with antitumor activity, which is effective against not only a broad range of human cancer

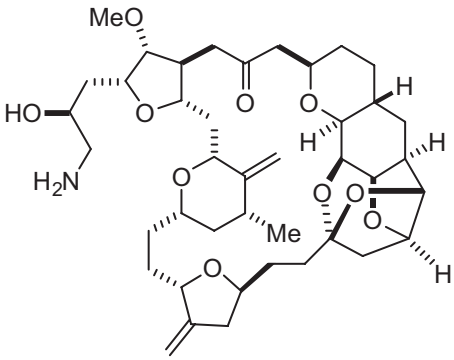


Fig. 15.10 Eribulin mesylate

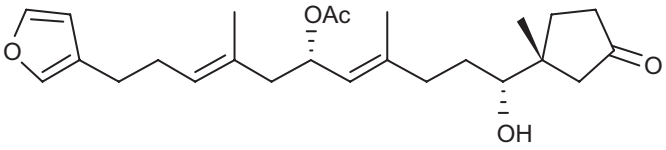


Fig. 15.11 10-Acetylirciformonin B

cell lines but also human tumor xenograft models derived from melanoma, colon, breast, ovarian, and pancreatic cancer [336]. This non-taxane molecule is a structurally simplified synthetic analogue of halichondrin B derived from the marine sponge *Halichondria okadai* [335]. Different from other tubulin-targeted agents like taxanes, epothilones, and vinca alkaloid, which affect both growth and shortening of microtubules, eribulin only affects growth by binding to the microtubules and suppressing microtubule polymerization without affecting shortening, thereby sequestering tubulin into nonfunctional aggregates [336, 337]. The prohibited formation of mitotic spindles leads to G2/M cell cycle arrest and apoptosis as a result of prolonged mitotic blockage. Eribulin remains to be active in taxane-resistant cell lines with β-tubulin mutations and those which overexpress P-gp according to in vitro studies. It's reported to be manageably safe in a 21-day-cycle administration, neutropenia being the main dose limit among all toxicities, with an MTD of 1.4 mg/m^2 in phase I studies, but seems to be both effective and safe in several phase II studies. Therefore, it has been applied to patients with locally advanced or metastatic breast cancer previously treated with at least two chemotherapeutic regimens for advanced disease [335–337].

10-Acetylirciformonin B (Fig. 15.11) classified as furanoterpenoid which is isolated from marine sponge *Ircinia* sp. can restrain the growth of leukemia HL-60 cells, with an IC50 value of 1.7 μg/mL obtained at 48 h of treatment due to its unique structure of the linear C22-sesterterpenoid. What's more, its anticancer activity was activated by inducting of DNA damage and apoptosis. To be detailed, DNA damage was mediated by the phosphorylation of histone H2AX, p-CHK2

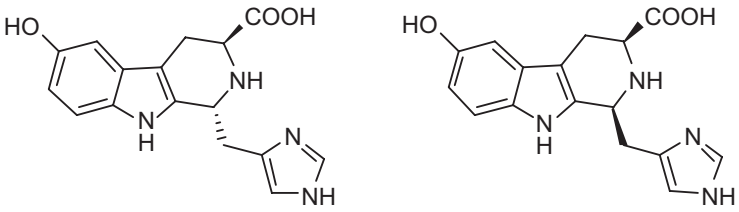
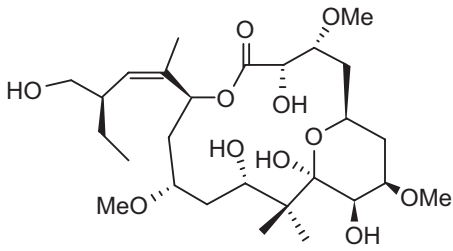


Fig. 15.12 Hyrtioreticulins A and B

Fig. 15.13 Peloruside



(checkpoint kinase), sensitive markers of DNA double-strand breaks (DSBs), and apoptosis which was triggered by caspase-8, caspase-9, and caspase-3, resulting to PARP cleavage, the downregulation of Bcl-xL and the upregulation of Bax [338].

Hyrtioreticulins A and B (Fig. 15.12) belong to indole alkaloids derived from the marine sponge *Hyrtios reticulatus*. These alkaloids have inhibition of E1-ubiquitin intermediate formation from 0.75 to 11 μg/mL in IC50 values [339]. Moreover, the structures are approximately the same except for their stereochemistry at C-1, in which hyrtioreticulin A is *trans*-configured and hyrtioreticulin B is *cis*, respectively, demonstrating that the *trans* configuration reinforces inhibitory activity against E1, the ubiquitin-activating enzyme required for ubiquitination in the ubiquitin-proteasome pathway involving in a large variety of cellular events such as cell cycle control, transcription, and development [340]. Deregulation of this pathway, therefore, can cause numerous diseases like cancer. Consequently, the ubiquitin pathway plays a significant role in anticancer drugs. In that context, hyrtioreticulins A and B catch more attention on the bioactivity on new anticancer therapeutics.

Peloruside A (Fig. 15.13) is a microtubule-stabilizing agent isolated from a New Zealand marine sponge [341]. Peloruside prevents growth of a panel of cancer cell lines at low nanomolar concentrations, including cell lines that are resistant to paclitaxel. Three xenograft studies in athymic nu/nu mice were performed to assess the efficacy of peloruside compared with standard anticancer agents such as paclitaxel, docetaxel, and doxorubicin. In the first study, peloruside A, 5 and 10 mg/kg (QD × 5) caused growth inhibition (%TGI of 84% and 95%, respectively), on the growth of H460 non-small cell lung cancer xenografts, whereas standard treatments with paclitaxel (8 mg/kg, QD × 5) and docetaxel (6.3 mg/kg, Q2D × 3) were much less

Fig. 15.14 E7974

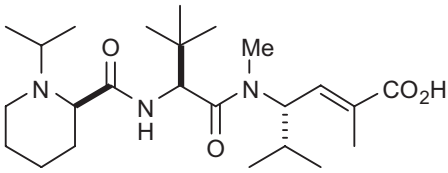
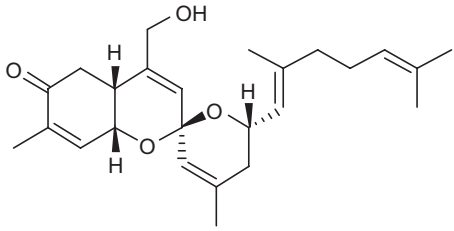


Fig. 15.15 Phorbaketal A



effective (%TGI of 50% and 18%, respectively). In a second xenograft study using A549 lung cancer cells and varied schedules of dosing, activity of peloruside was again superior compared with the taxanes with inhibitions ranging from 51% to 74%, compared with 44% and 50% for the two taxanes [342]. A third xenograft study in a P-glycoprotein-overexpressing NCI/ADR-RES breast tumor model showed that peloruside was better tolerated than either doxorubicin or paclitaxel. Peloruside is highly effective in preventing the growth of lung and P-glycoprotein-overexpressing breast tumors in vivo and that further therapeutic development is necessary [343].

E7974 (Fig.15.14) is a synthetic analogue of the marine sponge natural product hemiasterlin. Hemiasterlin, a potent cytotoxic tripeptide, was originally isolated from marine sponges [344]. E7974 acts via a tubulin-based antimitotic mechanism. E7974 inhibits polymerization of purified tubulin in vitro with IC_{50} values similar to those of vinblastine. In cultured human cancer cells, E7974 induces G_2/M arrest and marked disruption of mitotic spindle formation. Consistent with this observation, E7974 induces caspase-3 activation and PARP cleavage, typical biochemical markers of apoptosis. Only a short cellular exposure to E7974 is sufficient to induce maximum mitotic arrest, suggesting that E7974's antitumor effects in vivo may persist even after blood levels of the drug decrease after drug administration. Investigation of interactions of E7974 with purified tubulin using two synthetic tritiated photoaffinity analogues of E7974 indicated that E7974 seems to share a unique, predominantly α-tubulin-targeted mechanism with other hemiasterlin-based compounds, suggesting the hemiasterlins evolved to mainly target α-tubulin, not β-tubulin subunits unlike many tubulin-targeted natural products [345].

Phorbaketal A (Fig. 15.15) is a metabolite of the marine sponge *Phorbas* sp. [346]. This tricyclic sesterterpenoid has significant inhibitory effect on the production of nitric oxide (NO) and inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, and monocyte chemotactic protein-1 which is induced by

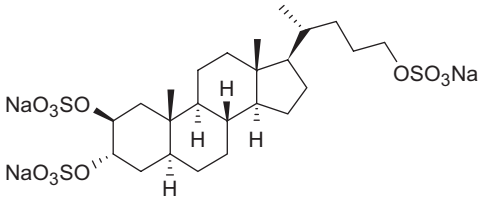


Fig. 15.16 Solomonsterol A

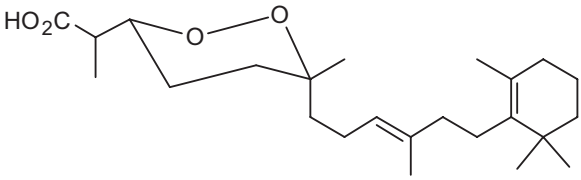


Fig. 15.17 Epimuqubilin A

LPS and the expression of inducible NO synthase in RAW 264.7 cells. Additionaly, it inhibited the transcription of a crucial signaling molecule named nuclear factor-kappaB (NF-κB) in inflammation, whereas the expression of heme oxygenase-1 (HO-1) proved to be upregulated in LPS-stimulated RAW 264.7 cells [347].

Solomonsterol A (Fig. 15.16), a selective pregnane X receptor (PXR) agonist found in the marine sponge *Theonella swinhoei*, shows anti-inflammatory activity and immune dysfunction and attenuates systemic inflammation in the rheumatoid arthritis mouse model. It is reported that solomonsterol A had an effect on protecting from the development of arthritis according to arthritis score, CRP, and plasma cytokines. In addition, anti-collagen antibodies (CAIA) could reduce the expression of inflammatory markers including TNFα, IFNγ, and IL-17 and chemokines MIP1α and RANTES in draining lymph nodes in the rheumatoid arthritis mouse model which are induced by injecting transgenic mice harboring a humanized PXR [348].

Epimuqubilin A (Fig. 15.17), a norsesterterpene peroxide isolated from marine sponge *Latrunculia* sp., inhibits nitric oxide production in LPS-stimulated RAW 264.7 cells (IC(50) = 7.6 μM). At both the mRNA and protein levels, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are suppressed in a dose-dependent manner. Mitogen-activated protein kinases (MAPKs), one major upstream signaling pathway involved in the transcription of both COX-2 and iNOS, were not affected by treatment of epimuqubilin A. However, the compound blocked the phosphorylation of inhibitor κB (IκB) kinase (IKKβ), resulting in the stabilization of IκBα and inhibition of NF-κB p65 nuclear translocation and DNA binding. Levels of phosphorylated IKKα were not affected. This is an unique mechanistic relationship that suggests epimuqubilin A warrants further exploration as a potential therapeutic agent [349].

Ascididemin (ASC) is a marine alkaloid and belongs to the group of pyridoacridine alkaloids, mostly being isolated from sponges and tunicates (Fig. 15.18). Ascididemin was isolated in 1988 from the tunicate *Didemnum* sp. and showed

Fig. 15.18 Ascididemin

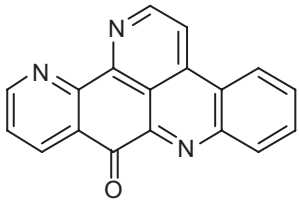
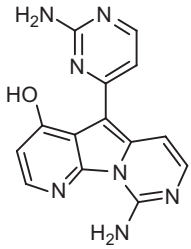


Fig. 15.19 Variolin B



remarkable in vitro cytotoxicity against a variety of cancer cells including multidrug resistant cells lines [350, 351]. Similar to other planar pyridoacridine derivatives, ascididemin interacts with DNA and recognizes triplex and quadruplex structures especially G-quadruplexes. Different mechanisms of action for this alkaloid have been proposed including topoisomerase I and II toxins. However, experiments with cell lines resistant to these toxins indicated that topo I and II are not potential targets for ascididemin (ASC) in the cell but may be by reactive oxygen species (ROS) to cleave DNA. Own work contributes to its action on the apoptotic signaling in Jurkat leukemia cells. Interestingly, ACS induces a mitochondrial pathway that requires the activation of caspase-2 upstream of mitochondria. Caspase-2 activation was not blocked by the overexpression of Bcl-2 proteins such as Bcl-xL and was responsible for caspase-9 activation. As a possible link between caspase-2 and mitochondrial activation, Bid was found to be cleaved by ASC as a specific caspase-2 inhibitor inhibits the ASC-induced cleavage of Bid [351]. In addition, JNK was activated by ASC upstream of mitochondria via reactive oxygen species. Caspase-2 activation provides a possible link between the DNA damaging activity and the induction of apoptosis. To this end, ASC might be a valuable chemical tool to induce DNA damage and apoptotic signaling events.

Variolin B (VAR-B) (Fig. 15.19) is a natural product isolated from the sponge *Kirkpatrickia variolosa*, found in Antarctica. VAR-B has been shown potent pro-apoptotic activity. In different human cancer cell lines, both compounds inhibited colony formation, caused cell cycle arrest, and induced apoptosis at concentrations ranging from 0.1 to 2 μM. Although variolins induced an increase in the levels of p53 with an increase in p21, their cytotoxicities did not appear to be dependent on p53 status as their potency was comparable in cells with wild-type p53 or in sublines with inactivated p53. Both VAR-B and dVAR-B prevent the cells from enter-

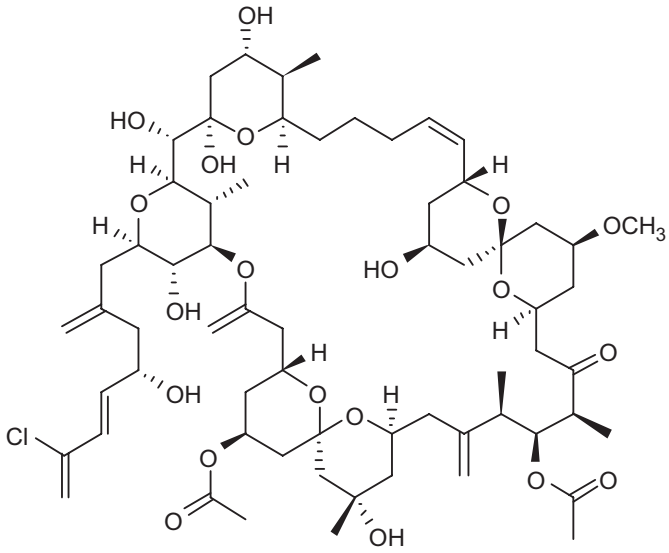


Fig. 15.20 Spongistatin 1

ing S phase, blocking cells in G1 and cause an accumulation of cells in G2. The apoptosis induced by VAR-B and dVAR-B occurred very rapidly in some cell lines (e.g., Jurkat leukemia cells) and was already evident 4 h after the beginning of treatment. Although intercalation of dVAR-B in DNA has been demonstrated, neither VAR-B nor dVAR-B produces detectable breaks in DNA, which are consistent with the in vitro biochemical assays that also demonstrated that dVAR-B is not topoisomerase I or II poison. Instead, each of these variolins appears to inhibit cyclin-dependent kinases (CDKs) in the lM range. CDK1-cyclin B, CDK2-cyclin A, and CDK2/cyclin E complexes were inhibited in a range of concentrations lower than those required to inhibit the activity of CDK4/cyclin D or CDK7/cyclin H complexes. Variolins are a new class of CDK inhibitors that activate apoptosis in a p53-independent fashion, and thus they may be effective against tumors with p53 mutations or deletions [352].

Spongistatin is a macrocyclic lactone that has been isolated from the marine sponges *Spirastrella spinispirulifera* and *Hyrtios* sp. by the group of Pettit. Spongistatin 1 (Fig. 15.20) showed interesting apoptotic features in various tumor cells. In leukemic cell lines, it triggered caspase-dependent apoptosis through the release of cytochrome c, Smac/Diablo, and Omi/HtrA2 from the mitochondria into the cytosol. Spongistatin 1 caused degradation of the anti-apoptotic XIAP, which suggested it might be a promising drug for the treatment of chemoresistance due to overexpression of XIAP. Moreover spongistatin 1 induces apoptosis more efficiently in human primary leukemic cells of children suffering from acute leukemia at low nanomolar concentrations than clinically applied conventional drugs used in

micromolar concentrations. In addition normal healthy peripheral blood cells were significantly less affected by spongistatin 1 [353]. Besides leukemic cells, spongistatin 1 showed promising apoptotic potential in mammary cancer cells including the treatment-resistant cell line MCF-7 lacking caspase-3. Regarding the apoptotic signaling pathways of spongistatin 1, two interesting features can be reported. First, spongistatin 1-induced cell death involves the pro-apoptotic proteins AIF and endonuclease G. Both proteins translocate from mitochondria to the nucleus and contribute to spongistatin 1-mediated apoptosis as shown via gene silencing. Second, spongistatin 1 acts as a tubulin-depolymerizing agent and is able to free the pro-apoptotic Bcl-2 family member Bim from its sequestration both by the microtubular complex and by the anti-apoptotic protein Mcl-1. Silencing of Bim by siRNA leads to a diminished translocation of AIF and endonuclease G to the nucleus and subsequently reduces rate of apoptosis. By using spongistatin 1 as a chemical tool, Bim has been suggested to be an important factor upstream of mitochondria by executing a central role in the caspase-independent apoptotic signaling pathway induced by spongistatin 1. These different apoptotic features indicate that the apoptosis signaling is cell line-specific. Finally, spongistatin 1 affects highly invasive pancreatic tumor cells by not only inhibiting their invasion and migration but also by inducing anoikis in these cells. Bcl-2 seems to be a major target for spongistatin 1 in these processes. Besides tumor cells, spongistatin inhibits angiogenic activity of endothelial cells via inhibition of PKC-a [354].

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