

Ramjee Pallela · Hermann Ehrlich *Editors*

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Editors

Ramjee Pallela
IKP Knowledge Park
Genome Valley, Turkapally
Hyderabad
Telangana
India

Hermann Ehrlich
Institute of Experimental Physics
TU Bergakademie Freiberg
Freiberg
Sachsen
Germany

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Keisham S. Singh and Mahesh S. Majik

Abstract

Marine sponges are considered to be a rich source of biologically active secondary metabolites with unique and diverse chemical structures. They constitute nearly one third of the secondary metabolites isolated from marine organisms. Chemicals obtained from marine sponges find a wide range of pharmaceutical values, and as a result of these properties, isolation and identification of lead molecules from marine sponges continued to play a leading role in drug discovery research. Some of the molecules obtained from marine sponges have entered in market, while many are under clinical and preclinical trials. There is convincing report about the role of ecology on the production of these valuable secondary metabolites by marine organisms including sponges. The unique body structure of marine sponges which can filter and absorb nutrients from surrounding environment and unique adaptation to variable conditions lead sponges as a major source of bioactive metabolites among the marine organisms. Alkaloids constitute one of the main classes of secondary metabolites isolated from marine sponges. They have wide range of chemical structures and exist in derivatives of several heterocyclic rings. Alkaloids were found almost in all marine sponges and exhibited a wide range of biological activities. This chapter reviews on the various alkaloids, viz., pyridoacridine, indole, isoquinoline, pyridine, piperidine, quinolizidine, steroidal, and bromotyrosine alkaloid isolated from various marine sponges. A brief review on these alkaloids with their diverse structures available in each class along with their biological significance has been

K.S. Singh (✉)
Bioorganic Chemistry Laboratory, CSIR-National
Institute of Oceanography, Dona Paula, Goa 403004,
India
e-mail: keisham@nio.org

M.S. Majik
Department of Chemistry, Goa University, Taligao, Goa
403206, India

presented. The class of alkaloid along with the name of sponge from which the alkaloids were isolated and chemical structures of these alkaloids are presented.

Keywords

Marine sponges • Pyridoacridine • Bioactive alkaloids • Quinolizidine alkaloids • Alkyl pyridine alkaloids • Bromotyrosine alkaloids

12.1 Alkaloids in Marine Sponges

Marine life represents a uniquely adapted reservoir of bioactive secondary metabolites due to their special environmental and oceanographic condition. Combination of knowledge of multidisciplinary sciences such as natural product chemistry, ecology, biology, and medicinal chemistry has inspired researchers for the development of many of the most successful medicines in particular from marine resources. In ocean, water pressure, temperature, light salt contents, etc., play an important role in adaptation of flora and fauna. As a result, species inhabiting these depths adapt their biochemical machinery to cope such varying pressures. These adaptations of marine organisms to deep-sea life and their effect on gene regulation and primary and secondary metabolic pathways gave rise to a wealth of interesting new marine natural products. Among the marine invertebrates, sponges have been considered as the most prolific phylum and prolific source of natural products with more novel compounds isolated from this taxon than from any other marine taxon (Blunt et al. 2011).

Many sponge-derived secondary metabolites possess a unique structural motif and pharmacological activities, thus making them highly desirable drug candidates for the treatment of a wide range of diseases. It has been known from the very early time that marine sponges contain bioactive compounds that are of potential medicinal value. Sponges are simple, multicellular sessile animals with no true tissue layers or organs and inhabit every type of marine environment, from

polar seas to temperate and tropical waters. Some species of sponges has the capacity of filtering out several tons of water to get nutrition. As a consequence of this, marine sponges are exposed to vast number of pathogenic and nonpathogenic microorganisms. In order to cope up with these microorganisms, sponges have developed strong immune system and they have possessed efficient chemical defense mechanism against the predators. There are more than 5000 (Whitehead 1999) species of marine sponges and many of these organisms have been investigated for their chemical and biological activities.

It is estimated that more than 10,000 bioactive molecules have been discovered from marine sources. In marine environment, this leading source has been taken by invertebrates such as sponges, tunicates, and bryozoans, mostly lacking morphological defense structure. They have developed the largest number of marine-derived secondary metabolites including some of most promising drug candidates (Newman and Cragg 2004). Indeed, out of 13 marine natural products that are currently under clinical trials as new drug candidates, 12 are derived from marine invertebrates (Proksch et al. 2003). As per review of literature on marine natural products, Blunt et al. (2004) described that sponges constitute nearly 40 % of the total secondary metabolites so far discovered from marine organisms. In the early 1950, spongouridine and spongothymidine, the first bioactive compounds from marine organisms, were isolated from the Caribbean sponge, *Cryptotethya crypta* (Bergmann and Feeney

Table 12.1 Different alkaloids with their biological activities obtained from various marine sponges

Class of alkaloids	Compound name	Biological activities	Name of sponge	References
Alkyl piperidine	Arenosclerins A, B, and C	Antibacterial	<i>Arenosclera brasiliensis</i> / <i>Haplosclerida</i>	Torres et al. (2002)
Fused pyrrolo-phenanthroline	Discorhabdin D	Antitumor	<i>Latrunculia brevis</i> / <i>Prianos</i> sp.	Perry et al. (1988)
Pyrrole guanidine	Isoaaptamine	Antitumor	<i>Aaptos aaptos</i>	Kitagawa et al. (1983)
	Debromohymenialdisine		<i>Hymeniacion aldís</i>	
Pyrrole guanidine	Keramidine	Neurosuppressives	<i>Agelas</i> sp.	Nakamura et al. (1984)
Pyrrole imidazole	Taurodispacamide A	Immunosuppressive	<i>Agelas oroides</i>	Fattorusso and Tagliatela-Scafati (2000)
Indole	Dragmacidin F	Antiviral	<i>Halicortex</i> sp.	Cutignan et al. (2000)
Bisindole	Bromotopsentin	Neurosuppressives	<i>Spongosorites</i> sp./ <i>Halichondria</i>	Phife et al. (1996)
Pyridoacridine	Neoamphimedine	Antitumor	<i>Xestospongia</i> cf. <i>carbonaris</i>	Guzman et al. (1999)
Imidazole	Naamine D	Antitumor	<i>Leucetta</i> cf. <i>chagosensis</i>	Dunbar et al. (2000)
Azetidine	Penaresidin A	Neurosuppressives	<i>Penares</i> sp.	Kobayashi et al. (1991)
Bis-oxa-quinolizidine	Xestospongine-C	Neurosuppressives	<i>Xestospongia</i> sp.	De Smet et al. (1999)
Pyridopyrrolo pyrimidine	Variolin B	Antiviral	<i>Kirkpatrickia variolosa</i>	Perry et al. (1994)
Manzamine	Manzamine A	Antimalarial	<i>Haliclona</i> sp.	Ang et al. (2000)
Imidazo-azolo-imidazole	Axinellamines B–D	Antibacterial and antifungal	<i>Axinella</i> sp.	Urban et al. (1999)

1950, 1951). They were approved as anticancer (cytosine arabinoside Ara-C) and antiviral compounds (adenine arabinoside Ara-A), respectively, 15 years later (Jimino et al. 2004). Sponge chemistry is dominated by the presence of nitrogenous metabolites which could be basically divided into two structural type-based groups, peptides and polycyclic aromatic alkaloids. Alkaloid class isolated from sponge indeed includes a large variety of structures, ranging from very complex pyridoacridines and tyrosine-derived alkaloids to simple protoalkaloids. Alkaloids isolated from marine sponges comprise a vast structural diversity and possess several biological properties. Some of the alkaloids isolated from marine sponges along with their biological properties are presented in Table 12.1. This chapter reviews a brief discussion on alkaloids isolated from marine sponges and discussed in terms of their

occurrence, structural type, and reported pharmacological activity. The chapter summarizes the recent development in the area of marine alkaloids, viz., pyridoacridine, indole, isoquinoline, alkyl pyridine, piperidine, quinolizidine, steroidal, and bromotyrosine alkaloids with few selected examples.

12.2 Pyridoacridine Alkaloids

Pyridoacridines are highly colored marine natural products having polycyclic planar heteroaromatic 11H-pyrido [4,3,2, mn] acridine systems (Patterson et al. 1960). Pyridoacridines are the largest group of marine alkaloids mostly isolated from sponges and tunicates. A first review on marine pyridoacridines has been published by Molinski (1993) and in later years, by Ding et al. (1999). Schmitz and Shooley

research groups reported the structure of first marine pyridoacridine alkaloids, amphimedine (**1**) (Schmitz et al. 1983); since then over 40 additional examples have been published. Although similar alkaloids containing isomeric ring systems have been found in terrestrial plants, namely, eupomatidine from angiosperm *Eupomatia bennettii*, the pyridoacridines [4,3,2-mnn], carbon skeleton is exclusive to marine invertebrates. Pyridoacridine alkaloids show various biological properties including cytotoxicity and certain other specific biological properties, viz., fungicidal and bactericidal properties, inhibition of topoisomerase II, anti-HIV, intercalation of DNA property, Ca^{+2} -releasing activity, and production of reactive oxygen species (Taraporewala et al. 1992). Pyridoacridines are pH indicator, and the indicator property is correlated with the presence of at least two basic electronic perturbations and extended chromophore with charge-transfer properties. Some other quaternary alkaline solution of pyridoacridine free base generally appeared orange or red, while, in acid solution, they are green to purple. However, simple indicator properties are absent in the less basic iminoquinones, such as cystodytin and diplamine. Pyridoacridine alkaloids have been isolated from several marine sponges, viz., *Oceanapia* sp., *Xestospongia* cf. *carbonaria* (Guzman et al. 1999), *Petrosia* sp. (Molinski et al. 1988), *Dercitus* sp. (Gunawardana et al. 1988), *Stellela* sp. (Gunawardana et al. 1992), etc.

Hooper and coworkers isolated petrosamine B (**2**) alkaloids from the Australian sponge *Oceanapia* sp. (Carroll et al. 2005). The methanolic solution of the sponge sample imparted green-blue color, but when extract was diluted with water, the color changed to purple. Correlation of solvent-dependent changes in the UV spectrum and NMR spectra suggested that the remarkable color changes observed by varying solvent polarity were associated with shifts in the position of keto-enol equilibrium favoring the enol form. Petrosamine B alkaloid was found to

be an inhibitor of the *Helicobacter pylori* enzyme aspartyl semialdehyde dehydrogenase (Carroll et al. 2005). Petrosamine B (**2**) was obtained as optically inactive blue solid and it is isomeric with petrosamine (**3**), isolated from the marine sponge *Petrosia* sp. with the only difference the position of bromine atom (Molinski et al. 1988). Notably, pyridoacridine alkaloids are grouped by total ring counts, viz., tetracyclic, pentacyclic, hexacyclic, heptacyclic, and octacyclic alkaloids. Soest's group isolated bioactive pyridoacridine alkaloids, kuanoniamine C (**4**), kuanoniamine D (**5**), and deacyl kuanoniamine derivative (**6**) from Micronesian sponge *Oceanapia* sp. (Eder et al. 1998). Kuanoniamines C and D isolated from the Marine sponge *Oceanapia sagittaria* were studied for anticancer activities, and it was found that kuanoniamine A is a potent growth inhibitor of all the tumor and nontumor cell lines, while kuanoniamine C was less potent but showed high selectivity toward the estrogen-dependent breast cancer cell line (Kijjoa et al. 2007). Recently, Davis and coworkers reported two new cytotoxicity pyridoacridine alkaloids, viz., ecionines A and B from the Australian marine sponge *Ecionemia geodides* (Barnes et al. 2010). Ecionines A and B (**7–8**) are imine-substituted pyridoacridine alkaloids, a very uncommon pyridoacridine family, and so far there are only three alkaloids of these classes available in literature. Wei et al. isolated 1-hydroxydeoxyamphimedine (**10**), 3-hydroxydeoxyamphimedine (**11**), and debromopetrosamine (**12**) along with the known neoamphimedine (**9**) and amphimedine (**1**) from the sponge *Xestospongia* cf. *carbonaria* (Wei et al. 2010) (Fig. 12.1).

In general, pyridoacridine alkaloids show significant biological activity such as cytotoxic, potent antiviral, antifungal, antibacterial, antitumor, and antiparasitic activity (Marshall and Barrows 2004). In fact, the crucial structural features of these alkaloids are the core of a planar iminoquinone moiety which can intercalate into DNA and cleave the DNA double helix or inhibit the action of TOPO II. As a consequence, there

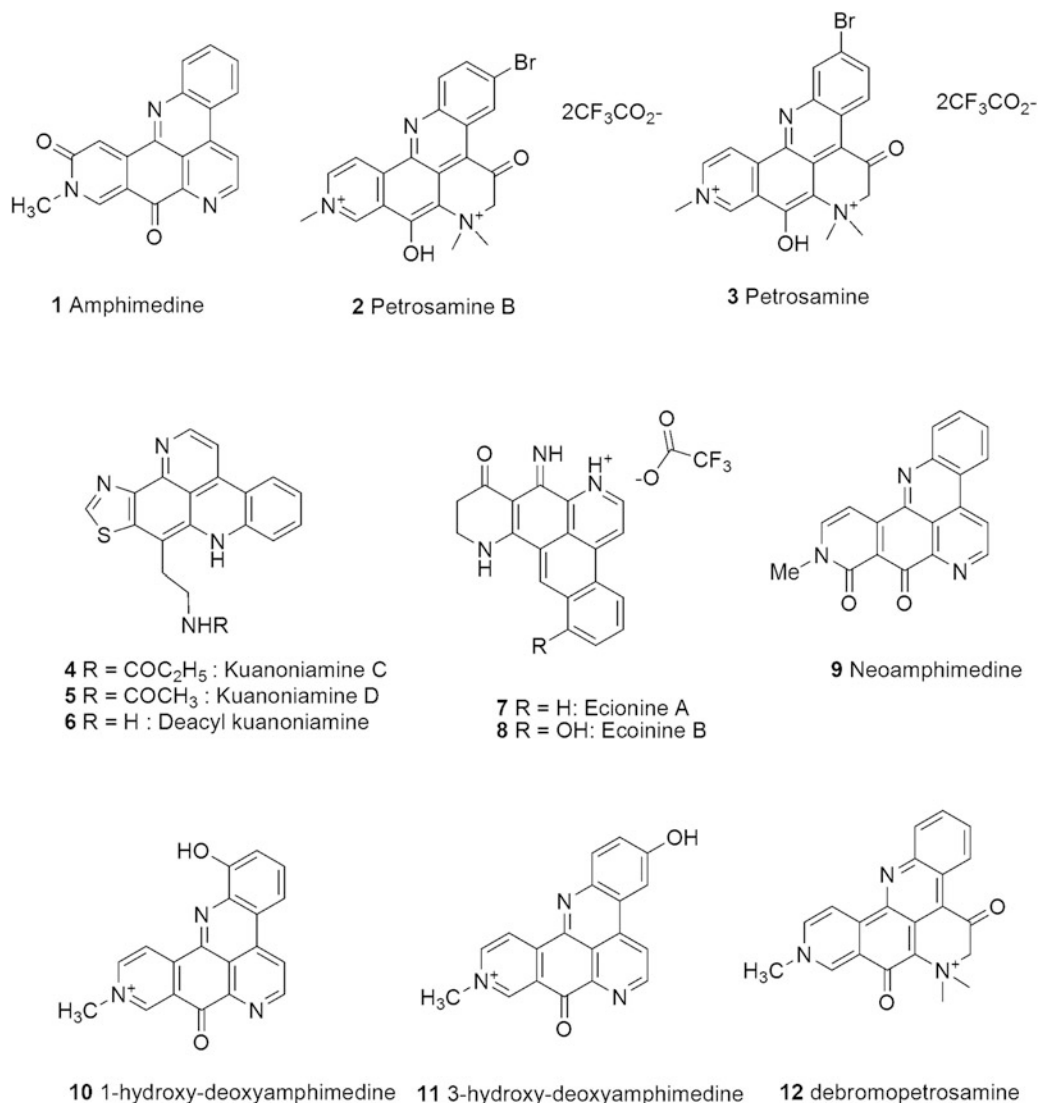


Fig. 12.1 All compounds are cited (figure is just for reference)

have been considerable demands for these compounds as antitumor agents (Delfourne and Bastide 2003). Many of these compounds have generated interest as challenging problems both for structure elucidation and synthetic target and for their biological activities (Schmitz et al. 1983; Gunawardana et al. 1992). The red sponge *Plakortis*, collected by Inman and coworkers from different marine sources, led to the isolation of two novel alkaloids, namely, plakinidine-A (13) and plakinidine-B (14) (Inman et al. 1990), which contain a pyrrolo [2,3,4-kl] acridine fused-

ring skeleton representing a new structural variation within polycyclic aromatic alkaloids from marine organisms. The discorhabdin C (15) was isolated from both *Latrunculia brevis*, from New Zealand, and *Prianos* sp. from Okinawa (Perry et al. 1988). Cheng et al. have isolated sulfur-containing alkaloids, prianosins A–D (16–19), from the green sponge *Prianos melanos* which showed cytotoxicity against L1210 murine leukemia cells (Cheng et al. 1988). The sponge *Bratzella* sp. has also furnished four additional pyrroloacridine alkaloids, namely, isobatzellines

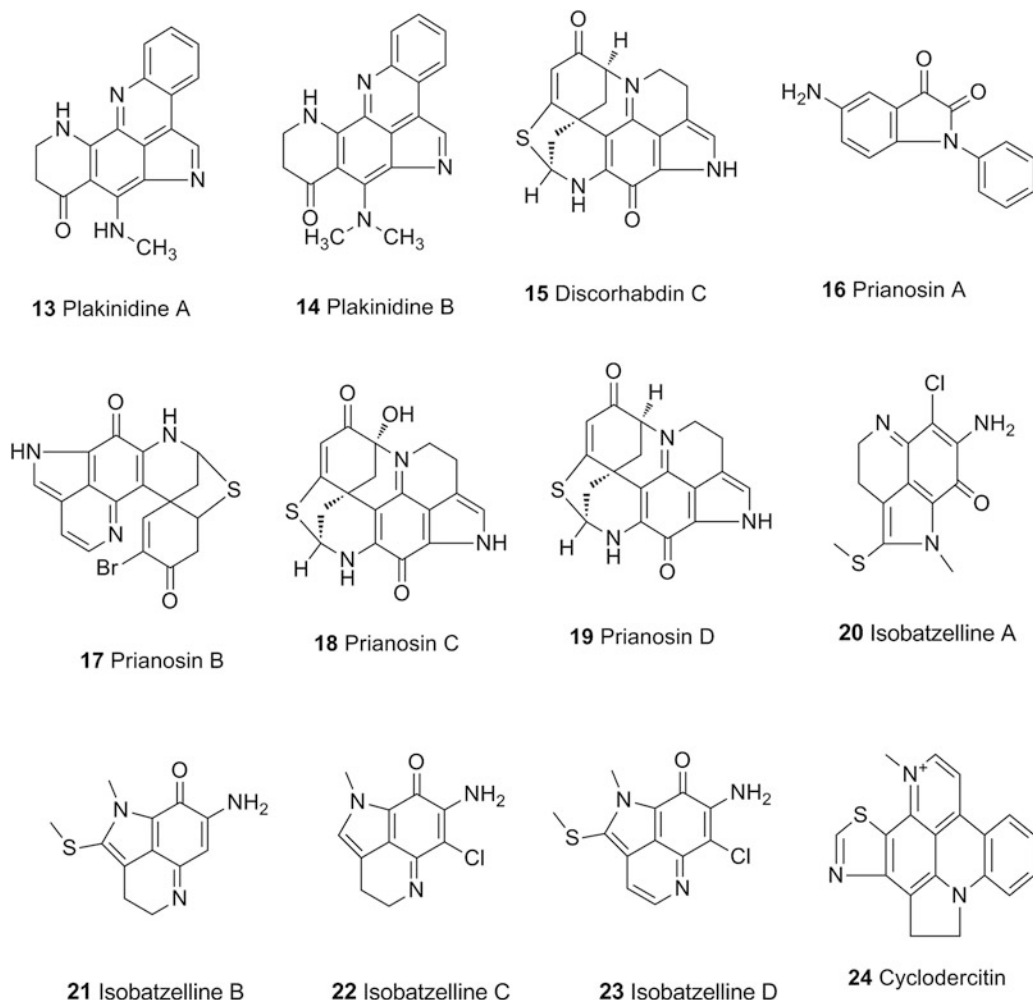


Fig. 12.2 All compounds are cited (figure is just for reference). NB: Compounds 25–33 are cited in Table 12.1

A–D (20–23) (Sun et al. 1990). In 1975, hexacyclic alkaloids, cyclodercitin (24), have been reported from the deep-water sponges *Dercitus* sp. and in *Stelletta* sp. (Gray 1975) (Fig. 12.2).

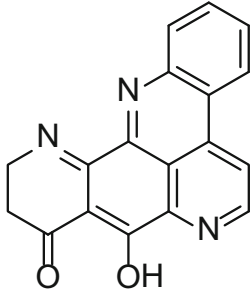
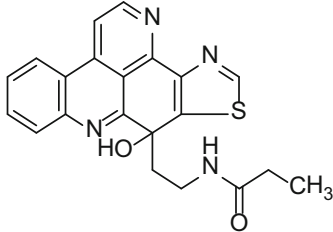
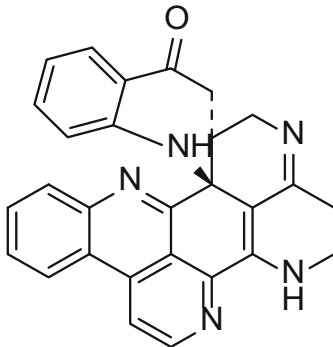
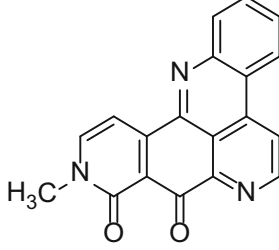
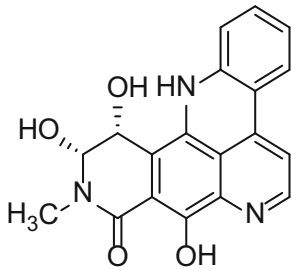
Pyridoacridines is vast class of alkaloid which varies from each other structurally by attachment of different side chains or fusion of different rings to ring C of the basic structure and sometimes to the acridine nitrogen. Based on the structure, pyridoacridines are divided into tetracyclic, pentacyclic, hexacyclic, heptacyclic, and octacyclic alkaloids (Kumar and Rawat 2011). They show significant biological activity

primarily cytotoxicity and certain specific biological properties like fungicidal and bactericidal properties, inhibition of topoisomerase II, anti-HIV, and intercalation of DNA (McCarthy et al. 1992; Kobayashi et al. 1988). A few selected pyridoacridines (25–33) showing interesting biological activities along with their source have been depicted in Table 12.2.

12.3 Indole Alkaloids

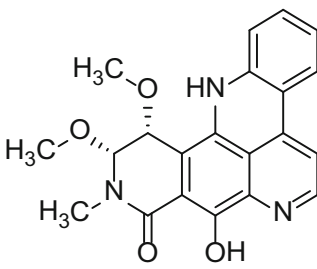
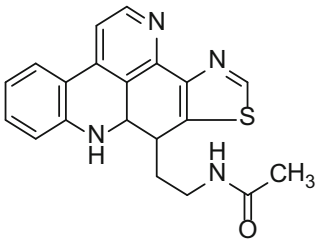
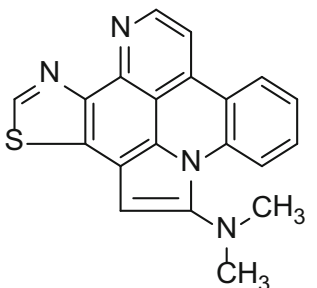
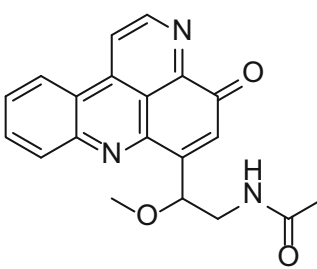
Indole-containing alkaloids have frequently been isolated from diverse marine invertebrates including bryozoans, coelenterates, sponges,

Table 12.2 Some pyridoacridines: source of bioactive alkaloids

Pyridoacridines	Source	Structures	References
Labuanine A (25)	<i>Biemna fortis</i> sponge (Indonesia)		Aoki et al. (2003)
Sagitol (26)	<i>Oceanapia sagittaria</i> sponge (Palau)		Salomon and Faulkner (1996)
Biemnadin (27)	<i>Biemna fortis</i> sponge (Indonesia)		Kumar and Rawat (2011)
Neoamphimedine (28)	<i>Xestospongia</i> sp. sponge (Philippines)		Rodriguez et al. (1993), Kong et al. (1994), and Tasdemir et al. (2001)
	<i>Xestospongia</i> cf. <i>carbonaria</i> (Micronesia)		
	<i>Xestospongia</i> c. <i>carbonaria</i> , X. cf. <i>exigua</i> (Indo-Pacific)		
Neoamphimedine Y (29)	<i>Xestospongia</i> c. <i>carbonaria</i> , X. cf. <i>exigua</i> (Indo-Pacific)		Tsotinis et al. (1996)

(continued)

Table 12.2 (continued)

Pyridoacridines	Source	Structures	References
Neoamphimedine Z (30)	<i>Xestospongia</i> cf. <i>carbonaria</i> , X. cf. <i>exigua</i> (Indo-Pacific)		Schmitz et al. (1983)
Nordercitin (31)	<i>Stelletta</i> sp. sponge <i>Derdtus</i> sp. sponge (Bahamas)		Gunawardana et al. (1992)
Stellettamine (32)	<i>Stelletta</i> sp. sponge		Shin et al. (1997)
Dercitamine (33)	<i>Stelletta</i> sp. sponge, <i>Dercitus</i> sp. sponge (Bahamas)		Djura and Faulkner (1980)

tunicates, algae, symbiotic bacteria, and fungi (Moriarty et al. 1987; Tanaka et al. 1988). Moreover, they show interesting biological activities such as cytotoxic, antitumor, antiviral, antimicrobial, etc. Corresponding to their unique structural features and impressive biological activities, the indole series have become attractive targets for the development of new pharmacological lead compounds. Indole alkaloids are distributed in many marine sponges, viz., sponge

Smenospongia sp., *Topsentia genitrix*, *Dictyodendrilla* sp., *Spongosorites* sp., and *Hyrtios* sp. (Sauleau et al. 2006). Kazlauskas et al. isolated for the first time a novel indole alkaloid, aplysinopsin (34), from Indo-Pacific sponge species (Kazlauskas et al. 1977) which are the representatives of the genus *Thorecta* (later assigned as the separate *Aplysinopsis* genus). Since that time, aplysinopsin and its derivatives have been reported in many

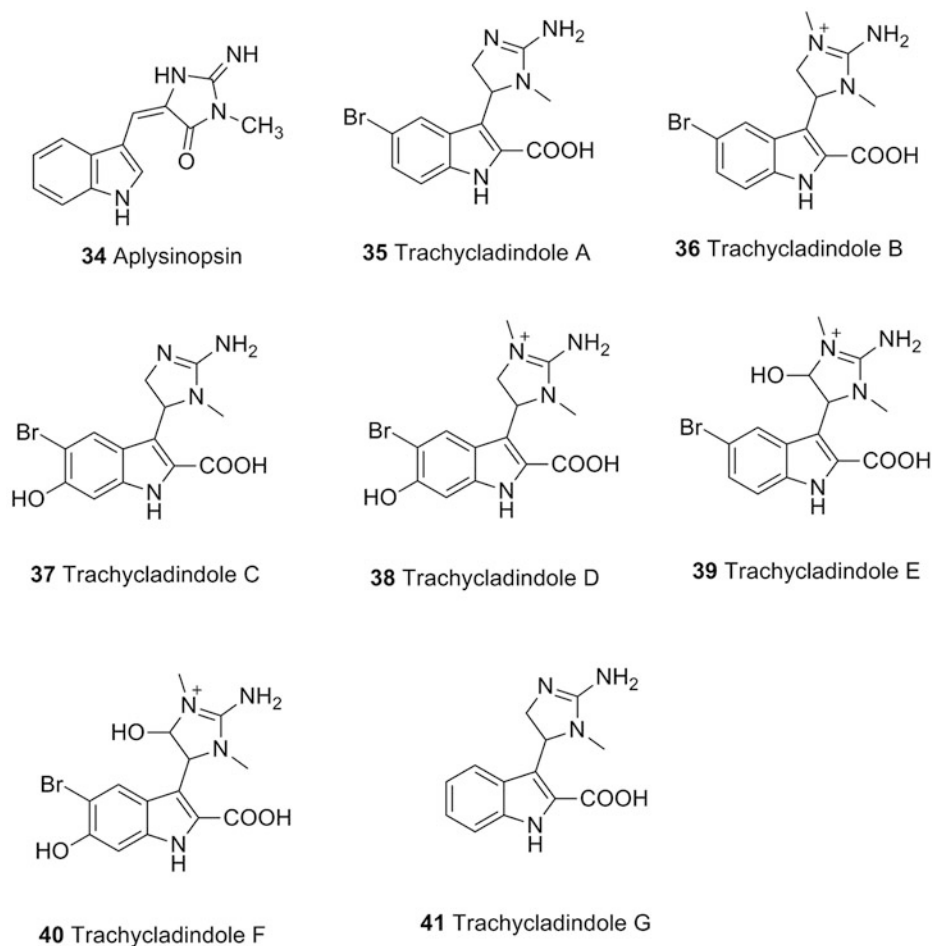


Fig. 12.3 All compounds are cited (figure is just for reference)

other marine organisms. Aplysinopsin-type compounds have been found in sponges of the Caribbean, *Verongia spengelli* (Hollenbeak and Schmitz 1977), *Dercitus* sp. (Djura and Faulkner 1980), *Smenospongia aurea* (Djura et al. 1980), and *Verongula rigida* (Kochanowska et al. 2008); the Mediterranean Sea, *Dictyoceratida* sp. (Bergquist and Wells 1983); as well as in the Indo-Pacific region, *Aplysinopsis reticulata* (Kazlauskas et al. 1977; Baker and Wells 1981), *Aplysina* sp. (Kondo et al. 1994), *Hyrtilis erecta* (Aoki et al. 2001), *Smenospongia* sp., and *Thorectandra* sp. (Segrave and Crews 2005). In 2008, Capon et al. (2008) have reported the cytotoxic agent trachycladindoles A–G (35–41) from southern Australian marine sponge,

Trachycladus laevispirulifer. Excitingly, it displayed promising selective cytotoxicity against a panel of human cancer cell lines (Fig. 12.3).

12.3.1 Bisindole Alkaloids

Bisindole alkaloids, consisting of two indole moieties connected to each other via heterocyclic units, have been particularly abundant within marine sponges. Isolation of bis(indolyl)imidazole, topsentin A (42) or topsentin B1 (43), was reported from the sponge *Topsentia genitrix* (*Spongosorites genitrix*) (Blunt et al. 2004). Metabolites containing bis(indole) moiety have

been found with various carbon skeletons and functionalities (Shin et al. 1999; Casapullo et al. 2000). These compounds exhibited a wide spectrum of pharmacological activities such as cytotoxic, antiviral, antimicrobial, and anti-inflammatory activities. As consequence, bis(indole) alkaloids is considered as an attractive targets for biomedical and synthetic studies (Bao et al. 2005). Topsentin A (42), B1 (43), and B2 (44) were isolated from marine sponge *Rhaphisia lacazei* and showed antiproliferative activity against human bronchopulmonary cancer cells (NSCLC-N6) (Casapullo et al. 2000). In 1992, Wright et al. collected the Pacific sponge *Hexadella* sp. from the coast of British Columbia which led to the identification of dragmacidin A (45) as potent cytotoxic compound (Fig. 12.4). Related bis-(indole)-alkaloid, dragmacidin D (46), has been isolated from another marine sponge of the genus *Spongisorites* (Wright et al. 1992). This compound inhibited the growth of the feline leukemia virus, the opportunistic fungal pathogens *Candida albicans* and *Cryptococcus neoformans*, and the growth of P388 and A549 tumor cell lines (Wright et al. 1992). Dragmacidins, member of a bis(indole) alkaloids, were isolated from a variety of marine

sponges. This alkaloid family showed a wide range of biological activities such as inhibitors of protein phosphatase and anticancer. Two types of sponges, *Coscinoderm lanuga* and *Ircinia felix*, have proved as the major source of various new dragmacidins or other bis(indole) alkaloids (Crook et al. 2009; Davis-McGibony and Pletcher 2006).

A dipyrroloquinone, zyzzyanone A (47) (having a pyrrolo [3,2-f] indole-4,8(1H,7H)-dione skeleton), was isolated from the Australian marine sponge *Zyzya fuliginosa*, exhibiting moderate cytotoxic activity against mouse Ehrlich carcinoma cells (Utkina et al. 2005). Hyrtimomines A–E (48–52) were isolated from an Okinawan marine sponge *Hyrtios* sp. (Tanaka et al. 2013). Later they isolated other hyrtimomines F–K (53–58) from the same marine sponge (Tanaka et al. 2014). Hyrtimomines A (48) and B (49) are heteroaromatic alkaloids possessing a fused hexacyclic 6/5/6/6/7/5 ring system, while hyrtimomine C (50) is an alkaloid consisting of hydroxyindole and azepino-hydroxyindole moieties (Fig. 12.5).

Hyrtimomines A–C (48–50) and hyrtimomines F–K (53–58) were studied for

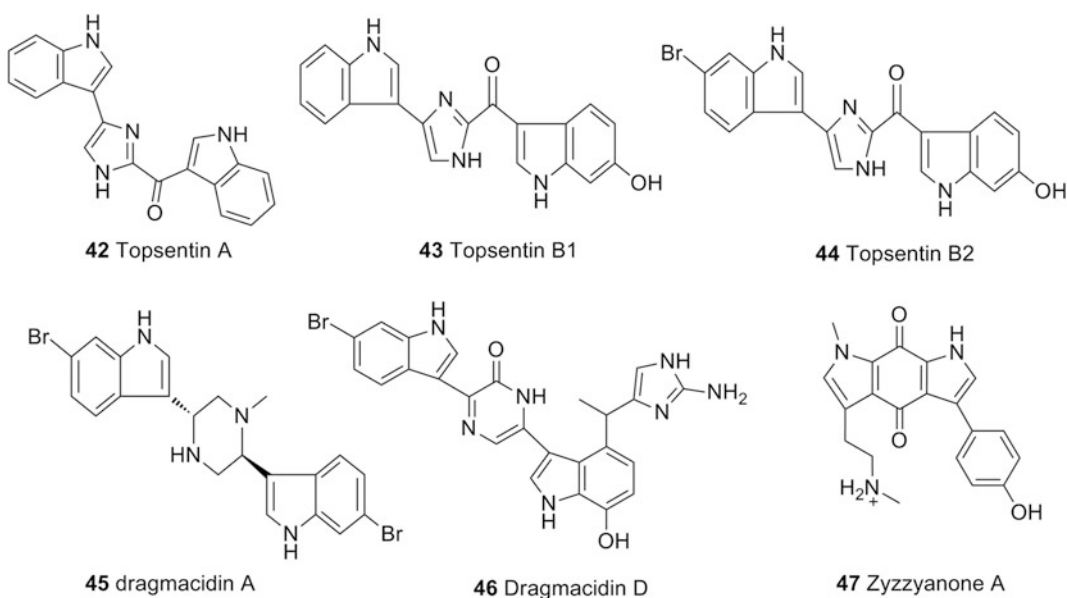


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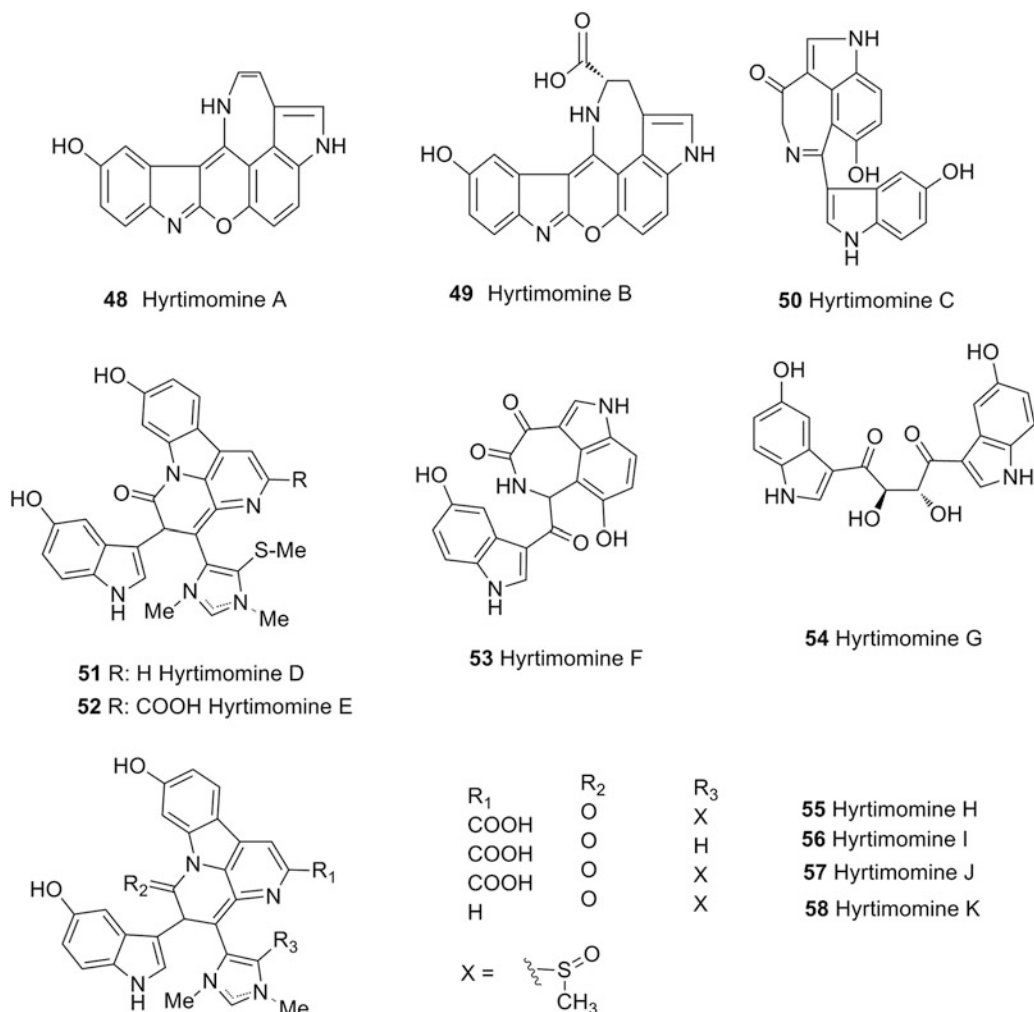


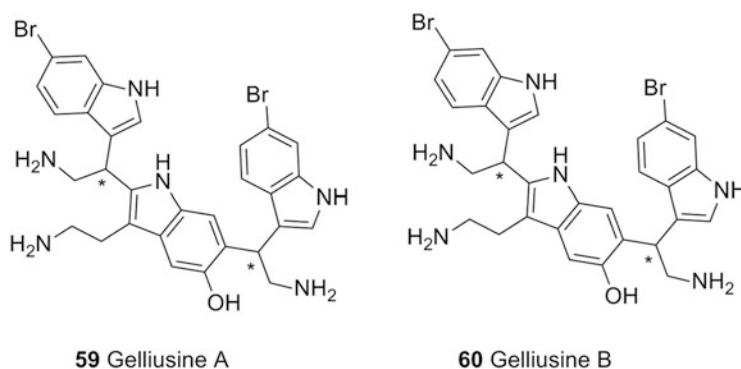
Fig. 12.5 All compounds are cited (figure is just for reference)

antimicrobial activities. Hyrtimomines F (53), G (54), and I (56) exhibited inhibitory effects against *Aspergillus niger*, while hyrtimomine I (56) showed inhibitory effect against *Cryptococcus neoformans*. Hyrtimomines A (48) and B (49) showed antimicrobial activities against *Candida albicans* and *C. neoformans*, while hyrtimomine A (48) exhibited an inhibitory activity against *A. niger* (Tanaka et al. 2014). Recently, Kobayashi's groups have shown cytotoxicity activity of hyrtimomine A (48) against KB and L1210 cells (Momose et al. 2013) (Figs. 12.5).

12.3.2 Trisindole Alkaloids

Trisindole alkaloids were rarely found in sponges. Bifulco et al. (1994) isolated trisindole alkaloids gelliusines A (59) and B (60) from deep-water Caledonian sponge *Gellius* or *Orina* sp. possessing cytotoxicity against KB, P-388, P-388/dox, HT-29, and NSCLC-N6 cell lines. The structural feature of gelliusines A and B (59, 60) is that the two 6-bromo tryptamine units are linked through their aliphatic chains to the C-2 and C-6 position of a central serotonin moiety, whereas the coupling of the indole unit

Fig. 12.6 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)



appears to be non-stereoselective giving two enantiomeric pairs (Fig. 12.6).

12.4 Isoquinoline Alkaloids

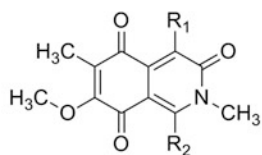
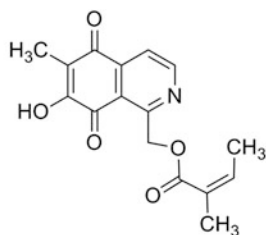
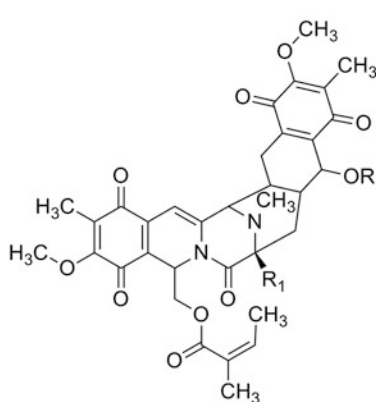
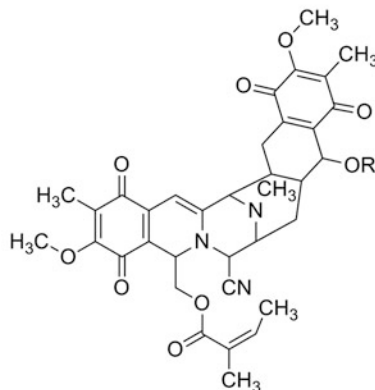
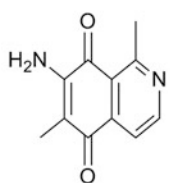
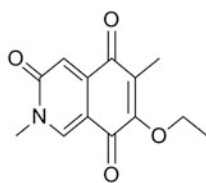
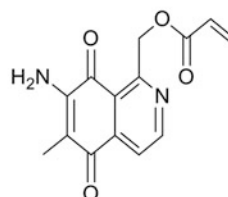
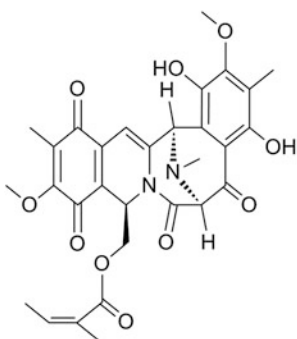
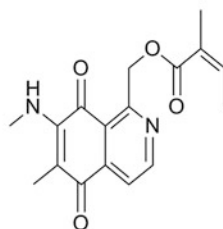
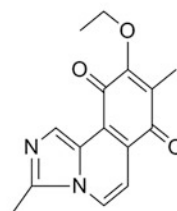
Marine sponges of genera *Reniera* and *Xestospongia* are rich in isoquinoline alkaloids. Several isoquinolinequinones have been isolated from blue species of the sponge. Mimosamycin (Kobayashi et al. 1994) and renierol (Mckee and Ireland 1987) are frequently isolated isoquinoline alkaloids and they have been reported from various marine sponges. Mimosamycin (**61**), 4-hydroxymimosamycin (**62**), 1,4-dihydroxymimosamycin (**63**), and O-demethylrenierone (**64**) were isolated from *Haliclona cribricutis* (Parameswaran et al. 1998). They isolated renieramycins H–I (**65–66**), a novel isoquinolinequinone alkaloid from the same sponge (Parameswaran et al. 1998). Isolation of renieramycin M, a bis-tetrahydroisoquinoline quinine alkaloid from the Thailand blue sponge *Xestospongia* sp., was reported by Saito and coworkers (Suwanborirux et al. 2013). Renieramycin M exhibited anticancer activity, and it induces human non-small cell lung cancer H460 cells apoptosis. The anticancer activity of renieramycin M against human lung carcinoma H460 cells was investigated by incubating the cells in the presence of renieramycin M

(0–40 μ M) for 24 h, and cell viability was analyzed using MTT assay (Halimi et al. 2011).

Isoquinolinequinones alkaloids, cribrostatins 1 (**68**) and 2 (**69**), were isolated from a deep blue-colored sponge *Cribrochalina* sp. (Pettit et al. 1992) and were found to be active against lymphocytic leukemia cell line (P-388). In 2000, Pettit et al. explored the same sponge *Cribrochalina* sp. which was found to contain other members of this family such as cribrostatins 3 (**70**), 4 (**71**) and 5 (**72**) (Pettit et al. 2000). These compounds (**70–71**) were active against mouse leukemia P-388 cell line. Structurally related alkaloid, cribrostatin 6 (**73**), was also isolated from the same marine sponge *Cribrochalina* sp. (Pettit et al. 2003) and was found to inhibit the growth of murine P-388 lymphocytic leukemia and a panel of human cancer cell lines (Fig. 12.7).

12.5 Pyridine Alkaloids

The sponge of order Haplosclerida are considered the richest source of pyridine alkaloids with diverse carbon skeleton. Several 3-alkyl pyridine alkaloids have been isolated from marine sponges (Faukner 1999). Cytotoxic bis-pyridine alkaloids, pyrinadine A and cribochalines A and B, were isolated from the marine sponge *Cribrochalina* sp. (Kariya et al. 2006). Cribochaline A displayed antifungal activity against both antibiotic-sensitive

**61** Mimosamycin: $R_1 = R_2 = H$ **62** 4-hydroxymimosamycin: $R_1 = OH$; $R_2 = H$ **63** 1,4-dihydroxymimosamycin: $R_1 = R_2 = OH$ **64** O-Demethylrenierone**65** Renieramycin H: $R = H$, $R_1 = OH$ **66** Renieramycin I: $R = CH_3$, $R_1 = H$ **67** Renieramycin M**68** Cribrostatin 1**69** Cribrostatin 2**70** Cribrostatin 3**71** Cribrostatin 4**72** Cribrostatin 5**73** Cribrostatin 6**Fig. 12.7** All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

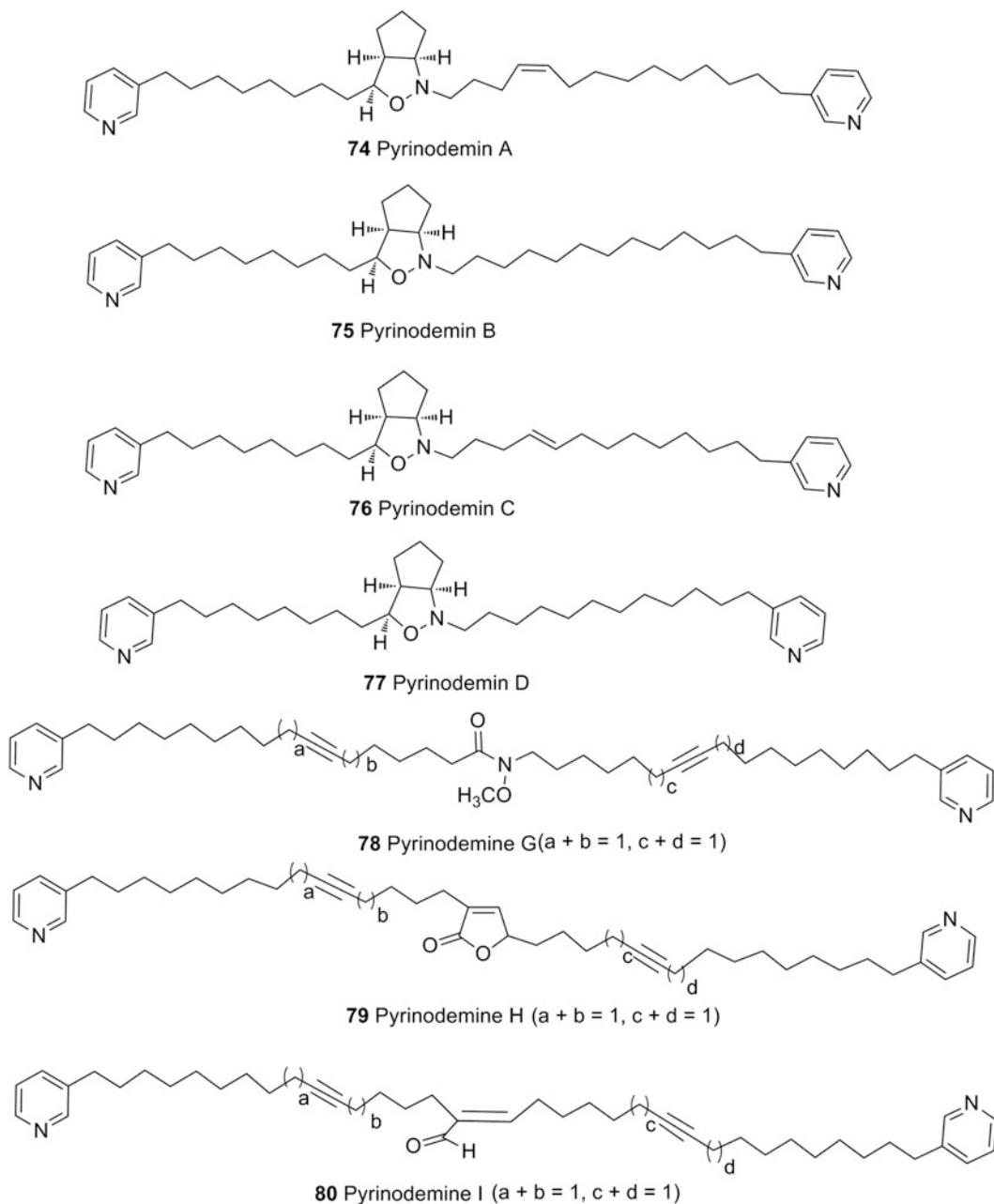


Fig. 12.8 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

and antibiotic-resistant strains of *Candida* sp. (Nicholas and Molinski 2000). Kobayashi's group have isolated pyrinodemins A–D (74–77) (Fig. 12.8) potent cytotoxic bis-pyridine alkaloids with a cis-cyclopent[3]isoxazolidine moiety, from the Okinawan marine sponge *Amphimedon*

sp. (Tsuda et al. 1999; Hirano et al. 2000). In the later years, they have isolated several other pyrinodemins, viz., pyrinodemins G–I (78–80), bis-3-alkyl pyridine from the same sponge (Kubota et al. 2013) (Fig. 12.8).

Niphatesine F (**81**) was isolated from the Okinawan marine sponge *Niphates* sp. (Kobayashi et al. 1992), while untenines A–C (**82–84**) (Fig. 12.9) were isolated from the Okinawan marine sponge *Callyspongia* sp. (Wang et al. 1996). Cyclic bis-pyridine alkaloids, cyclostelletamine alkaloids (**85–93**), were obtained from the sponge *Pachychalina* sp. and the alkaloids exhibited antimicrobial and antimycobacterial activity (De Oliveira et al. 2006). Cytotoxic tripyridine alkaloids, niphatoxins A and B (**94–95**), have been isolated by Kobayashi's group from the Red Sea sponge *Niphates* sp. (Talpira et al. 1992), while nitroalkyl pyridine alkaloids with antimicrofouling properties were isolated from the Okinawan marine sponge *Callyspongia* sp. (Wang et al. 1996). Theonelladins A–D (**96–99**), antineoplastic pyridine alkaloids, were isolated from the marine sponges *Theonella swinhoei* (Kobayashi et al. 1989a). Kitamura et al. isolated echinoclathrines A–C (**100–102**), a new class of pyridine alkaloids having 4-aryl-2-methylpyridine unit from an Okinawan sponge, *Echinoclathria* sp. (Kitamura et al. 1999). Echinoclathrine A (**100**) exhibited a weak cytotoxicity ($IC_{50} = 10 \mu\text{g/mL}$) against P-388, A-549, and HT-29 cell lines, while other alkaloids were found to be inactive (Fig. 12.9).

12.6 Piperidine Alkaloids

Piperidines are heterocyclic amines consisting of a six-membered ring containing five methylene bridges (-CH₂-) and one amine bridge (-NH-). Marine sponges belonging to the order Haplosclerida are considered the richest source of alkyl piperidine alkaloids. 3-Alkyl piperidine alkaloid which is a very common piperidine alkaloid includes a variety of metabolites ranging from monomeric 3-alkyl pyridines to condensed bis-alkyl piperidines of the manzamine class. These alkaloids show a wide range of biological activities, viz., antimicrobial, antiviral, and cytotoxic (Schmitz et al. 1978), antimalarial (Ang et al. 2000), and antifouling (Faimali et al. 2003). Unusual oligomeric pyridinium alkaloids,

namely, cyclohaliclonamines (Teruya et al. 2006) and viscosamine (Volk et al. 2004), were isolated from *Haliclona* sp. and *Haliclona viscosa*, respectively. A macrocyclic dimeric haliclamines and the linear trimeric viscosaline were also isolated from *H. viscosa* (Volk and Köck 2004).

Fusetani and coworkers have reported piperidine alkaloids, namely, halicyclamine A (**103**), tetrahydrohalicyclamine A (**104**), and 22-hydroxyhalicyclamine A (**105**) from a marine sponge *Amphimedon* sp. (Takekawa, et al. 2006). These halicyclamine piperidine alkaloids (**103–105**) exhibited cytotoxicity against P388 cells with IC_{50} values of 0.45, 2.2, and 0.45 $\mu\text{g/mL}$, respectively. A new piperidine alkaloid plakoridine C (**106**) has been isolated by Kobayashi's group from an Okinawan marine sponge *Plakortis* sp., and the structure was elucidated from spectroscopic data (Ishiguro et al. 2009). Plakoridine C (**106**) is a new alkaloid possessing a piperidine ring connected to a β -keto- γ -lactone through a double bond. Bis-piperidine alkaloids, madangamine F (**107**), haliclonacyclamine F (**108**), and arenosclerins D (**109**) and E (**110**), have been isolated from the marine sponge *Pachychalina alcaloidifera* and the structures were identified by the analysis of spectroscopic data. The alkaloids displayed cytotoxic activity against different cancer cell lines (Fig. 12.10).

12.7 Quinolizidine Alkaloids

Quinolizidine alkaloids are distinct from other alkaloids in that they contained at least one quinolizidine ring system. They exhibited significant coronary vasodilative effects as well as modest murine leukemia cell growth inhibition and antimicrobial activity (Quirion et al. 1992). Quinolizidine family, namely, 1-oxa-quinolizidine and bis-1-oxa-quinolizidines, is common in marine sponges. The first four "1-oxa-quinolizidines" were isolated from the Australian sponge *Xestospongia exigua*, designated as xestospongins A–D (**111–114**) with the structure of (-)-xestospongins-C (**113**)

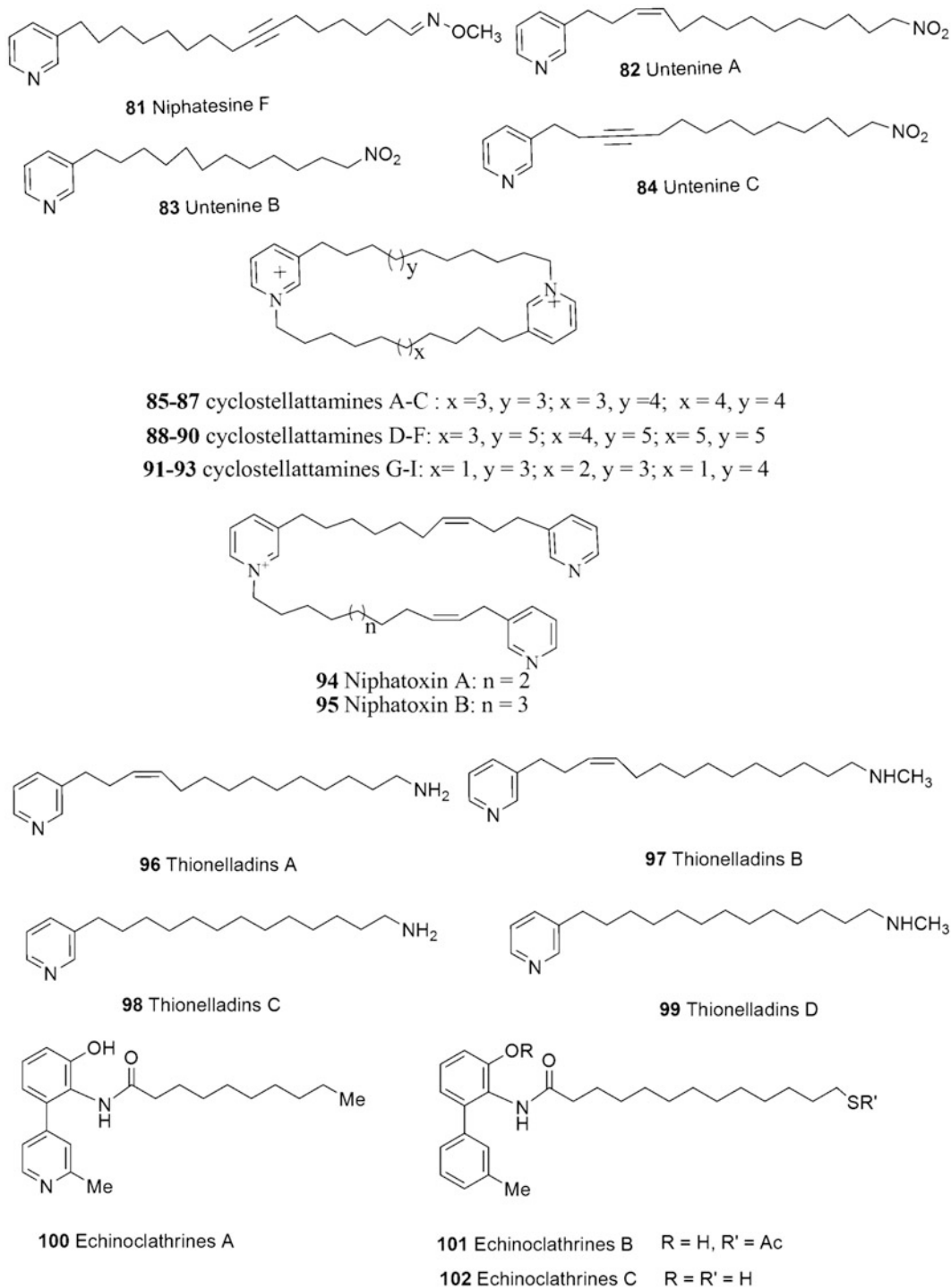


Fig. 12.9 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

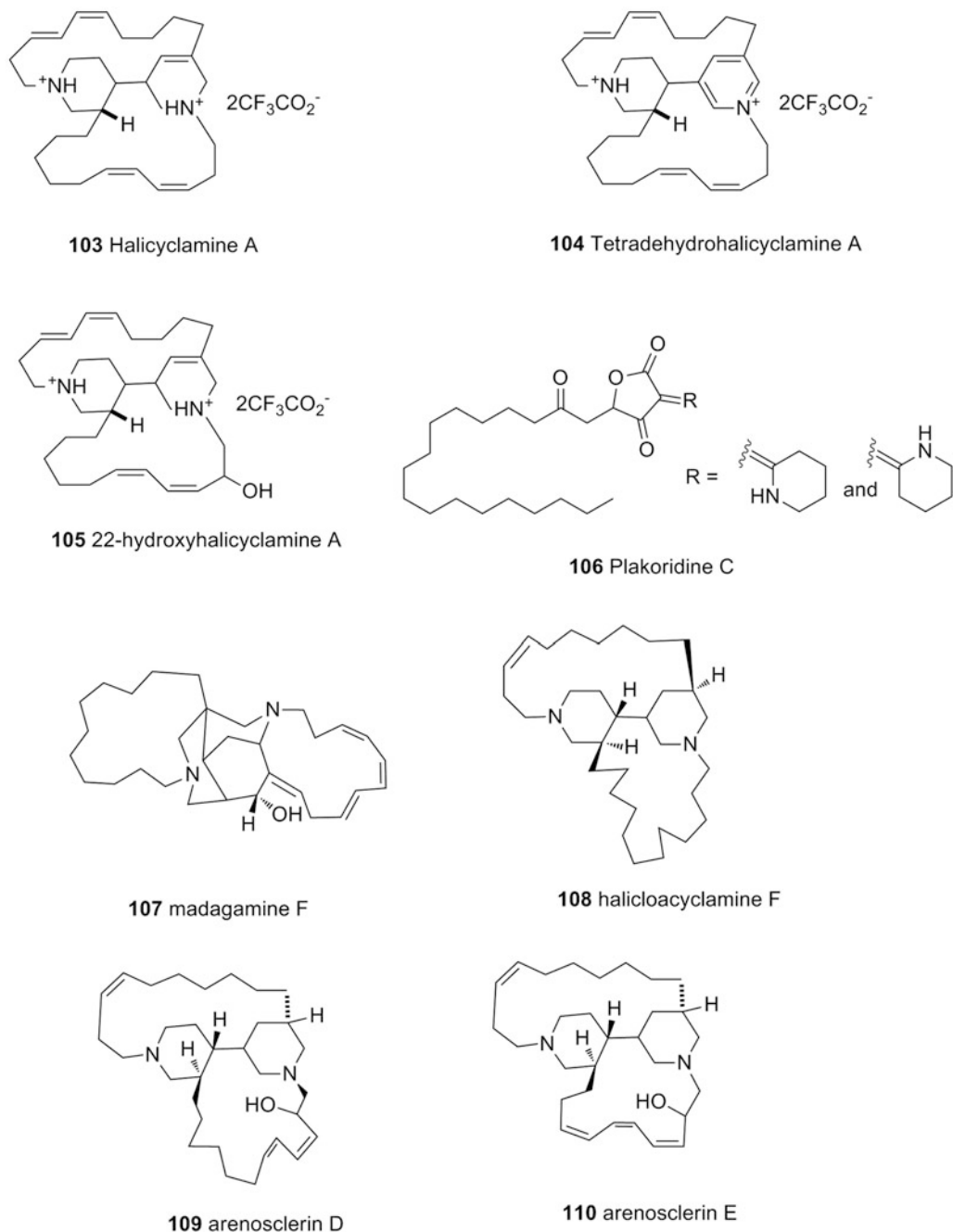


Fig. 12.10 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

determined by X-ray techniques (Nakagawa et al. 1984). Later these oxa-quinolizidine and bis-quinolizidine families have also been isolated from several other marine sponges, viz.,

Oceanapia sp. (Singh et al. 2011), *Petrosia similis* (Goud et al. 2003), and *Haliclona exigua* (Venkateswarlu et al. 1994). The family of xestospongine/araguspongine alkaloids comprises

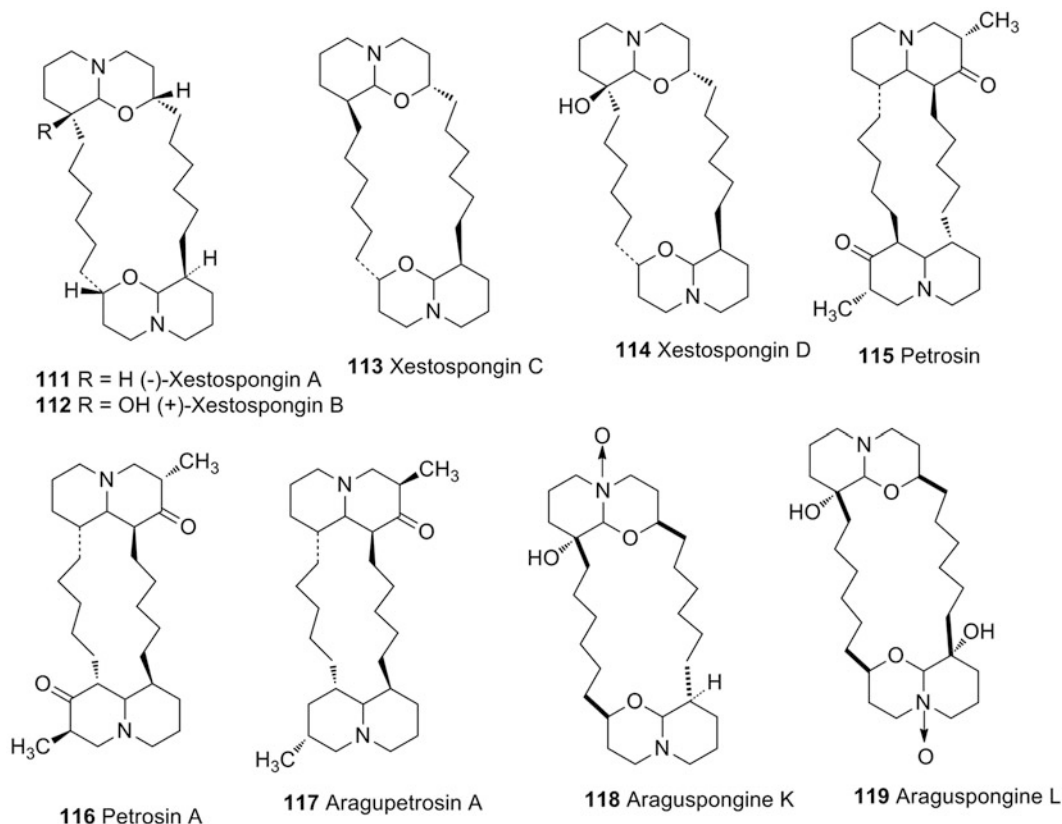


Fig. 12.11 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

of 13 members (Moon et al. 2002; Reddy and Faulkner 1997), and chemically, they are dimeric 2,9-disubstituted 1-oxa-quinolizidines. Braekman et al. reported petrosin (115), a bis-quinolizidine alkaloid from the sponge *Petrosia seriata* (Braekman et al. 1982). They have established that petrosin might exist in two isomers in solution; the structure of petrosin was characterized by spectroscopic data and solid-state structure was determined by X-ray diffraction analysis (Braekman et al. 1982). A racemic xestospongins alkaloid (\pm) xestospongins D (114) was isolated from the Singapore marine sponge *Niphates* sp. (Pettit et al. 1996). The absolute stereochemistry at the six chiral centers for this enantiomer was assigned by X-ray analysis. This racemic (\pm) xestospongins D (114) showed several activities including antimicrobial and modest growth inhibitory against a number of tumor cell lines (Pettit

et al. 1996). Petrosins A (116) vasodilative macrocyclic quinolizidine alkaloid, araguspongins A (117), and several araguspongins alkaloids have been reported by Kobayashi's group from an Okinawan marine sponge, *Xestospongia* sp. (Kobayashi et al. 1989b). Unique bis-1-oxa-quinolizidine N-oxide alkaloids, araguspongins K (118) and L (119), were also reported by Orabi et al. from red sponge *Xestospongia exigua* (Orabi et al. 2002) (Fig. 12.11).

12.8 Steroidal Alkaloids

In 2002, Borbone et al. demonstrated the isolation of four steroidal alkaloids, plakinamines G (120), H (121), and L (122) and tetrahydroplakinamine A (123) from the marine sponge *Corticium* sp. (Borbone et al. 2002). Among

these series, plakinamine G (**120**) and tetrahydroplakinamine A (**123**) were most active against C6 cells, whereas plakinamine H (**121**) and plakinamine L (**122**) were cytotoxic against C6 cells and RAW-264 cell lines. In 2007, three more steroidal alkaloids, cortistatins J–L (**124–126**), were isolated from the Indonesian marine sponge *Corticium simplex* (Aoki et al. 2007). Cortistatin J (**124**) demonstrated potent cytostatic antiproliferative activity against human umbilical vein endothelial cells (HUVEC) and also inhibited migration and tubular formation of HUVEC induced by VEGF or bFGF, whereas cortistatins K (**125**) and L (**126**) were less potent than cortistatin J (**124**). Steroidal alkaloids plakinamine I–K (**127–129**) and dihydroplakinamine K (**130**) were isolated from sponge *Corticium niger* (Ridley and Faulkner 2003) and were tested for cytotoxicity against the human colon tumor cell line (HCT-116). Compounds plakinamine K (**129**) and dihydroplakinamine K (**130**) were found to be the most active in terms of potency, while plakinamines I and J (**127 & 128**) were moderately active (Fig. 12.12).

12.9 Bromotyrosine Alkaloids

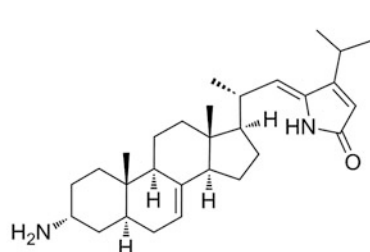
Marine sponges from the order Verongida are rich source of bromotyrosine-derived alkaloids (Bergquist 1983; Gribble 1998). Sponges in this order have been reported to show unusual biochemical profiles characterized by the absence of terpenes and the production of sterols and brominated compounds biogenetically tyrosine (Kochanowska et al. 2008). Several bromotyrosine alkaloids, viz., purealin (Tsuda et al. 1992), lipopurealins A–E (Wu et al. 1986; Kobayashi et al. 1995), purealidins A–S (Ishibashi et al. 1991; Kobayashi et al. 1991), psammaplysins A–B (Roll et al. 1985), purpuramines A–J (Tabudravu and Jaspars 2002; Yagi et al. 1993), aplysamines 2–5 (Jurek et al. 1993), and macrocyclic peptides bastadins (Carney et al. 1993; Aoki et al. 2006), have been isolated from this marine sponge order of Verongida. Due to the occurrence of

bromotyrosine alkaloids in practically all Verongida marine sponges so far chemically investigated, these alkaloids and their derivatives have been considered as chemotaxonomic markers for sponges of this order (Harper et al. 2001). However, the recent isolation of bromotyrosine-derived compounds from sponges belonging to other distinct taxa, such as *Agelas oroides* (König and Wright 1993), *Oceanapia* sp. (Nicholas et al. 2001), and *Poecillastra wondoensis* (Park et al. 2003), indicated that these compounds are not specific chemotaxonomic markers for marine sponges of Verongida (Erpenbeck and van Soest 2007). Bromotyrosine alkaloids exhibited potent antibacterial (Tsukamoto et al. 1996a, 1996b; Matsunaga et al. 2005), anti-HIV (Ross et al. 2000), antimalarial (Xu et al. 2011), and cytotoxic (Tabudravu and Jaspars 2002) activities.

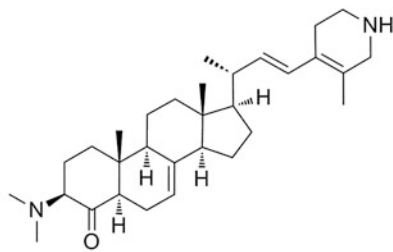
Purealidin S and purpuramine J were isolated from the Fijian marine sponge *Druinella* sp. (Tabudravu and Jaspars 2002). Fujiwara et al. isolated a new bromotyrosine alkaloid JBIR-44 (**131**) from *Psammaplysilla purpurea*. JBIR-44 (**131**) showed cytotoxic effects against human cervical carcinoma HeLa cells (Fujiwara et al. 2009). Bromotyrosine-derived metabolites purpuramines A–I were isolated from the marine sponge *Psammaplysilla purpurea* (Jurek et al. 1993). Purpuramines A (**132**) and C (**133**) differ only at amine substituent at the aromatic ring.

A novel dibromotyrosine derivative, Aplysifistularine (**134**), was isolated from the marine sponge *Aplysina fistularis* (Lira et al. 2012). This species have been well documented for the presence of a large number of brominated metabolites including fistularines, aerothionines, ceratinamines, aplysamines, anamonianes, and psammaplysines (Ciminiello et al. 1994; Thoms et al. 2005; Saeki et al. 2002). Purealidins B–C (**135–136**) (Kobayashi et al. 1991) and lipopurealins D–E (**137–138**) (Kobayashi et al., 1995) were isolated from the Okinawan marine sponge *Psammaplysilla pura* (Fig. 12.13).

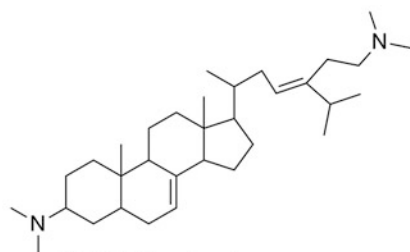
Yin et al. isolated pseudoceramines A–D (**139–142**), a series of antibacterial bromotyrosine alkaloids from the marine sponge *Pseudoceratina* sp. of Erskine Is., Great Barrier



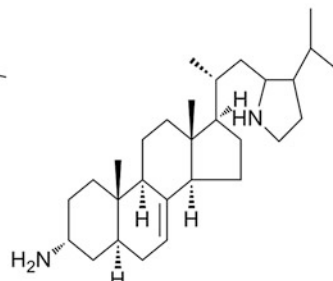
120 Plakinamine G



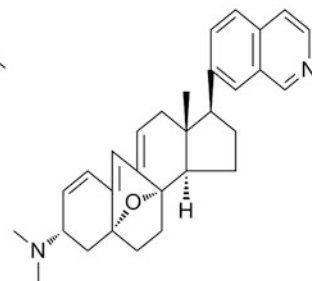
121 Plakinamine H



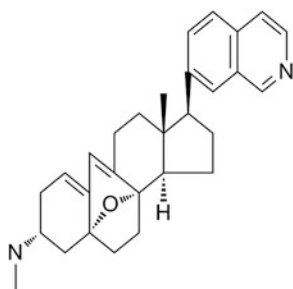
122 Plakinamine L



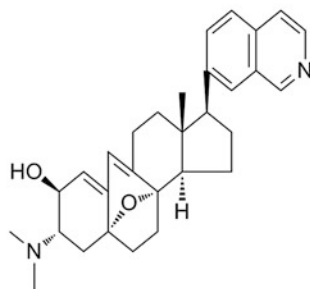
123 Tetrahydroplakinamine A



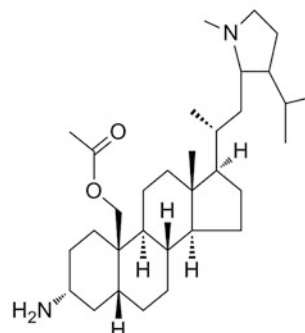
124 Cortistatin J



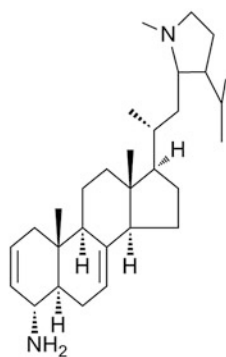
125 Cortistatin K



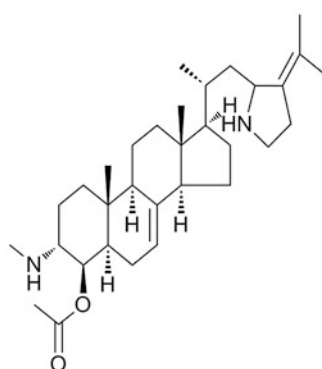
126 Cortistatin L



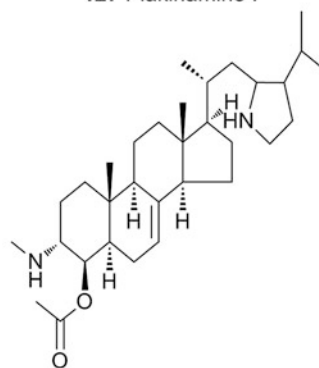
127 Plakinamine I



128 Plakinamine J



129 Plakinamine K



130 Dihydroplakinamine K

Fig. 12.12 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

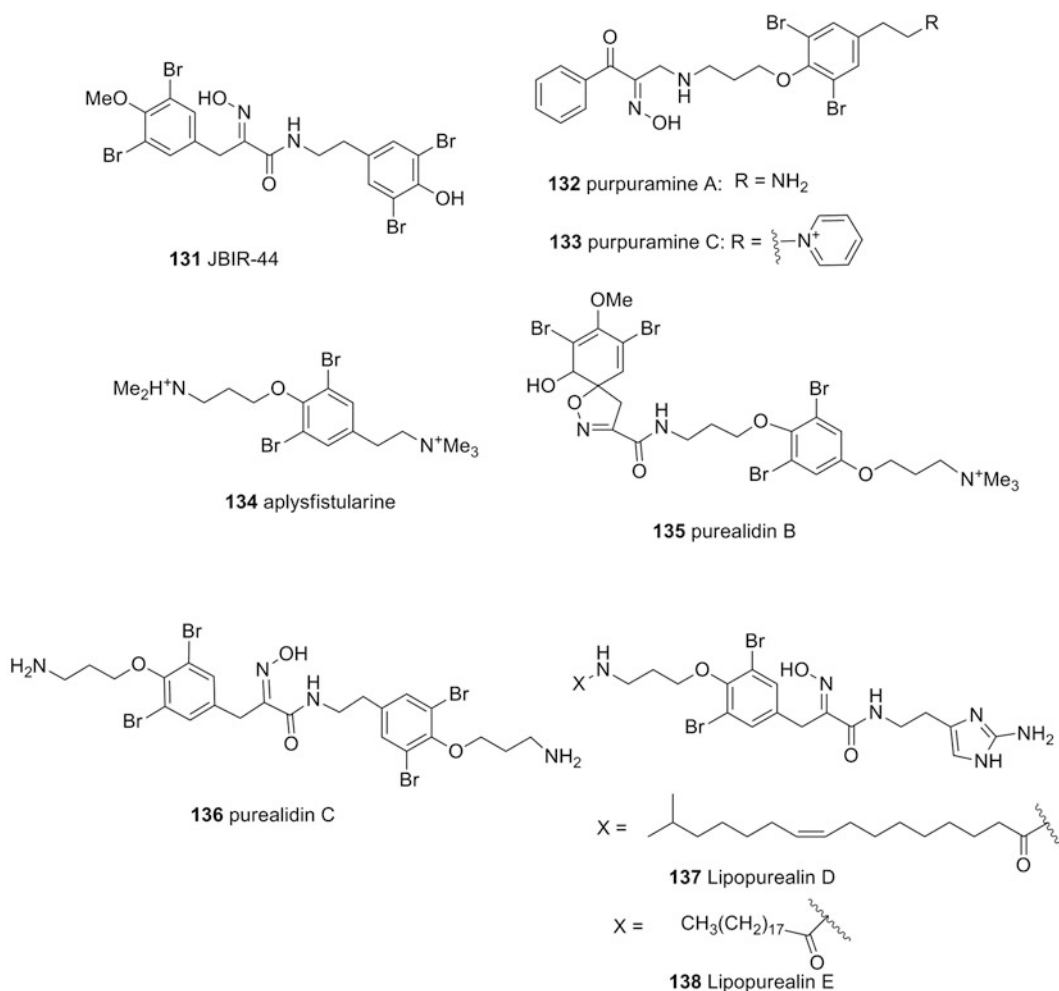


Fig. 12.13 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

Reef (Yin et al. 2011). They have reported that pseudoceramine C (**141**) was a cleavage derivative of spermatinamine (**143**). Pseudoceramine B (**140**) inhibits secretion of the virulence factor Yersinia outer protein E (Yin et al. 2011). Bromotyrosine-derived alkaloids, purealidin-L (**144**), aerophobin-1 (**145**) and aerophobin-2 (**146**) (Cimino et al. 1983), and isofistularin-3 (**147**), were isolated from several marine sponges (Gopichand and Schmitz 1979) (Fig. 12.14).

Kobayashi's group isolated purealidin-L (**144**) (Kobayashi et al. 1995) from *Psammaphysilla purea*, and tyrokeradines A and B (**148–149**) were isolated from Okinawan

marine sponge of order Verongida (Mukai et al. 2009). In later years, they isolated other related bromotyrosine alkaloids tyrokeradines C (**150**) from the same sponge (Kubota et al. 2012). His group also isolated ceratinadins A–C (**151–153**) from Okinawan marine sponge *Pseudoceratina* sp. (Kona et al. 2010). Aplysamine-4 (**154**), a bromotyrosine-derived alkaloid, was isolated from the sponge *Psammaphysilla purpurea* (Jurek et al. 1993). Proksch's group has isolated a new bromotyrosine alkaloid N-methyl-aerophobin-2 (**155**) along with known bromotyrosine alkaloids, purealidin-L (**144**), aerophobin-1 (**145**), and aerophobin-2 (**146**),

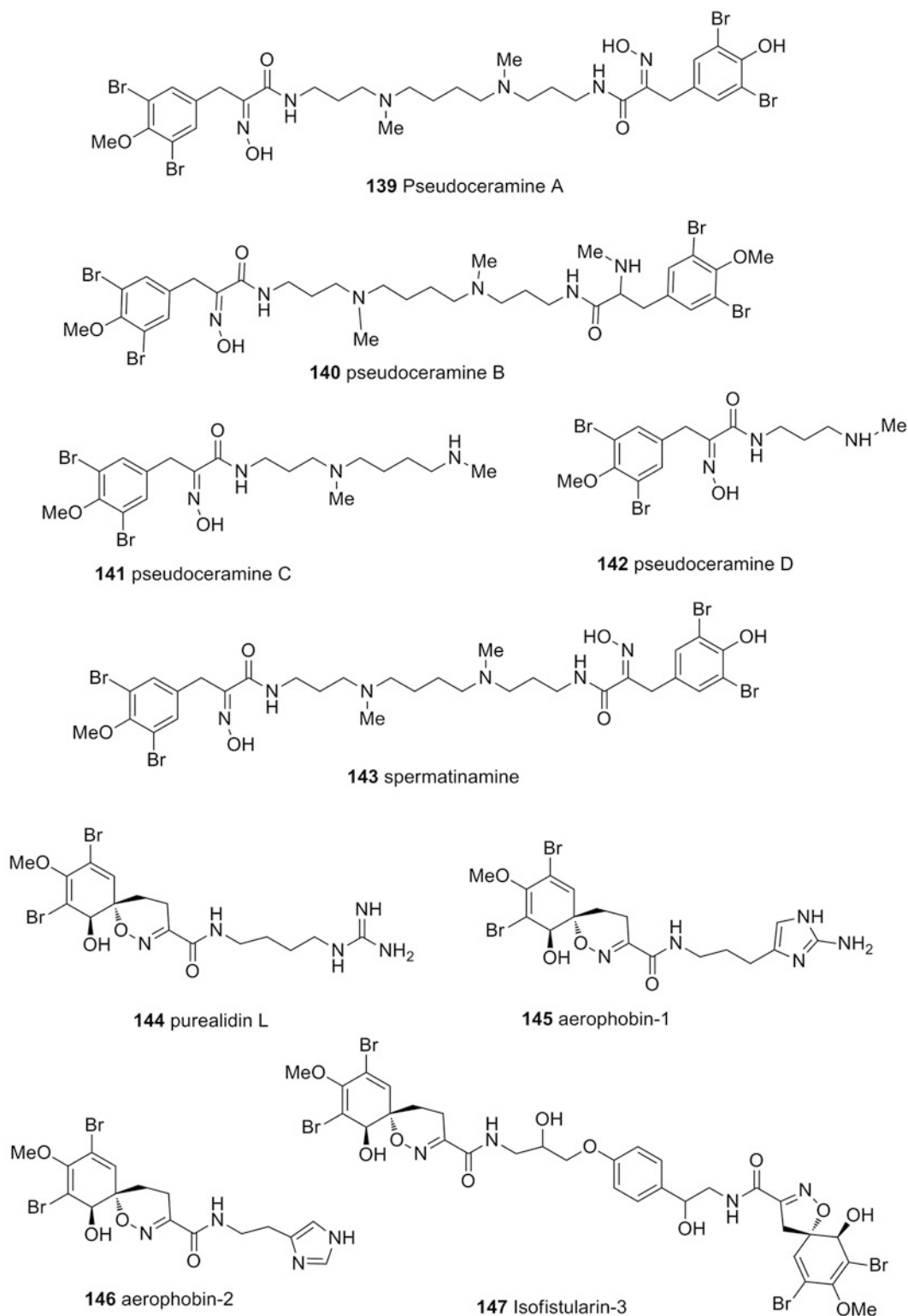


Fig. 12.14 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

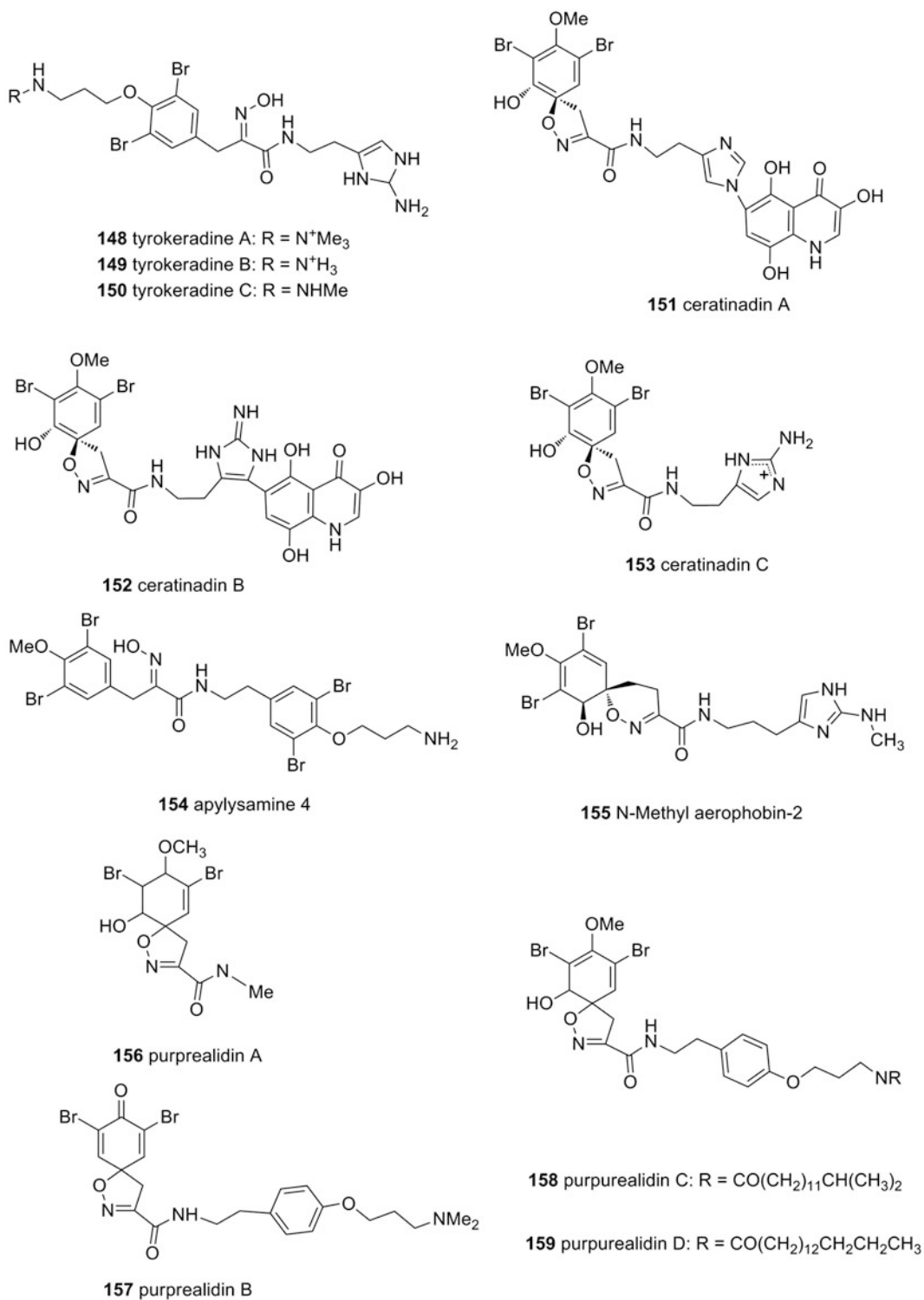


Fig. 12.15 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

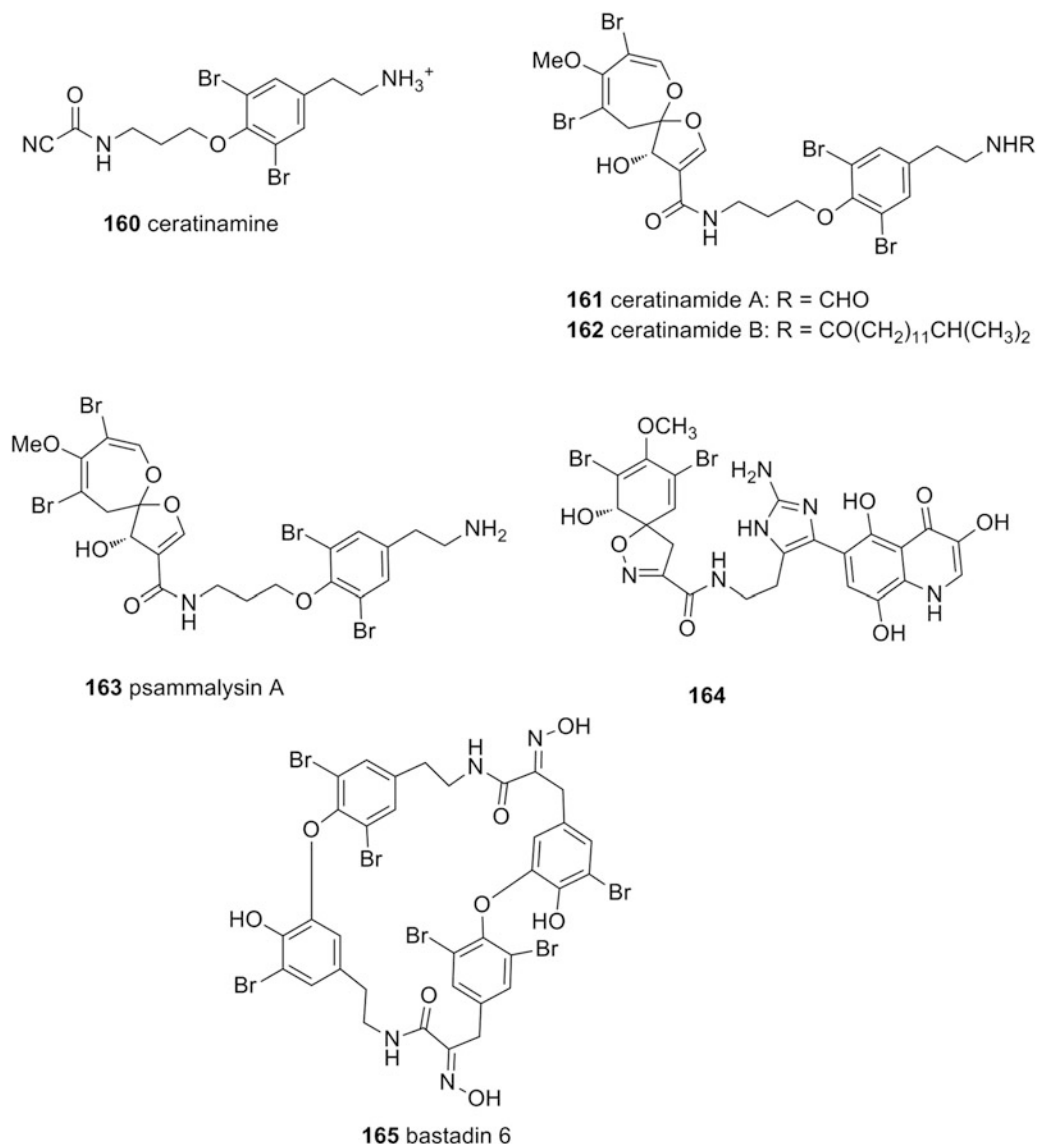


Fig. 12.16 All compounds are cited (figures are not cited; instead compound's number are cited; it is just for reference)

from the Caribbean marine sponge *Aiolochoira crassa* (Assmann et al. 1998). A series of purpurealidins A–D (**156–159**) were isolated by Tilvi et al., from the Indian marine sponge *Psammaplysilla purpurea* (Tilvi et al. 2004) (Fig. 12.15).

Bromotyrosine alkaloids with antifouling activities were reported from *P. purpurea* collected in various locations of Japan, among which the most interesting is ceratinamine (**160**)

which contains a cyanoforamide functionality, unprecedented in natural products (Tsukamoto et al. 1996a). Ceratinamine showed potent anti-fouling activities against barnacle larvae with an EC₅₀ value of 5.0 µg mL⁻¹. Other bromotyrosine-derived alkaloids such as ceratinamides A (**161**) and B (**162**) and psammalyisin A (**163**) exhibited potent activity with EC₅₀ values of 0.10, 2.40, and 0.27 µg mL⁻¹, respectively (Tsukamoto et al. 1996b).

Bewley's research group isolated a novel bromotyrosine alkaloid (**164**), which inhibits mycothiol S-conjugate amidase (MCA) from marine sponge *Oceanapia* species (Nicholas et al. 2001). Macrocyclic bromotyrosine alkaloids, bastadins, were isolated from several marine sponges, such as *Psammaplysilla purpurea* (Carney et al. 1993) and *Ianthella basta* (Aoki et al. 2006). Bastadin-6 (**165**) exhibited antiproliferative activities against endothelial cells (Aoki et al. 2006) (Fig. 12.16).

12.10 Conclusion

This chapter presents the various alkaloids isolated from marine sponges and discusses their biological properties. In order to simplify to general readers, the chapter presents different class of alkaloids isolated from various marine sponges with their selected chemical structures in each separate section. The source of sponge from which they are isolated and their bioactivities have been discussed. The chapter reviews on alkaloids, viz., pyridoacridines, alkyl pyridine, piperidine, indole, quinolizidine, isoquinoline, steroidal, and bromotyrosine alkaloids and their derivatives isolated from various marine sponges. Since there are several alkaloids of marine sponge origin, it is not possible to include all alkaloids isolated from them. We highlighted only selected alkaloids of marine sponge and discussed their potential biological properties. We believe that this chapter may find interest to general readers and researchers working in natural product sciences both from the academic and industries. We also acknowledged that several published works on the topic which deserved to be cited have been excluded due to page limitation.

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