

## Bioactive Alkaloids from Marine Sponges

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### 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 absorbed 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 hetrocyclic 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, isoquinolene, pyridine, piperidene, 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 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, alylpyridine alkaloids, Bromotyrosine alkaloids.

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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 micro-organisms sponges have developed strong immune system and they have possessed efficient chemical defense mechanism against the predators. There are more than 5,000 (Whitehead et.al. 1999) species of marine sponges and many of these organisms have been investigated for their biological activities and chemical constituents.

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, 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 & 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 by Blunt *et. al.* (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 spongouthymidine, the first bioactive compounds from marine organisms, were isolated from the Caribbean sponge, *Cryptotheca Crypta*. (Bergmann and Feeney 1950; 1951). They were approved as anticancer (cytosine arabinoside Ara-C) and antiviral (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. Alkaloids 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 term of their occurrence, structural type and reported pharmacological activity. The chapter summarises 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.

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

Class of alkaloids	Compound Name	Biological activities	Name of sponge	Reference
Alkylpiperidine	Arenosclerins A, B & C	Antibacterial	Arenosclera brasiliensis/Haplosclerida	(Torres et. al., 2002)
Fused pyrrolo-phenan-throline	Discorhabdin D	Antitumor	<i>Latrunculia brevis/ Prianos sp.</i>	(Perry et. al., 1998)
Pyrrole guanidine	Isoaaptamine Debromohymenialdisine	Antitumor	<i>Aaptos aaptos Hymeniacidonaldis</i>	(Kitagawa et. al., 1983)
Pyrrole guanidine	Keramadine	Neurosuppressive	<i>Agelas sp.</i>	(Nakamura et. al., 1984)
Pyrrole Imidazole	Taurodispacamide A	Immuno-suppressive	<i>Agelas oroides</i>	(Fattorusso & T.-Scafati, 2000)
Indole	Dragnacidin F	Antiviral	<i>Halicortex sp.</i>	(Cutiganano et. al., 2000)
Bis-indole	Bromotopsentin	Neuro-sppressive	<i>Spongossorites sp.</i>	(Phife et. al., 1996)
Pyridoacridine	Neoamphimedine	Antitumor	<i>Xestospongia cf. carbonaris</i>	(Guzman et. al., 1999)
Imidazole	Naamine D	Antitumor	<i>Leucetta cf. chagosensis</i>	(Dunbar et. al., 2000)
Azetidine	Penaresidin A	Neuro-sppressive	<i>Penares sp.</i>	(Kobayashi et. al., 1991)
Bis-oxa quinolizidine	Xestospongine-C	Neurosuppressive	<i>Xestospongia sp.</i>	(Smet et. al., 1999)
Pyridopyrrolo pyrimidine	Variolin B	Antiviral	<i>Kirkpatrickia varialosa</i>	(Perry et. al., 1994)
Manzamine	Manzamine A	Antimalarial	<i>Haliclona sp.</i>	(Ang et. al., 2000)
Imidazo-azolo-imidazole	Axinellamines B-D	Antibacterial & Antifungal	<i>Axinella sp.</i>	(Urban et.al., 1999)

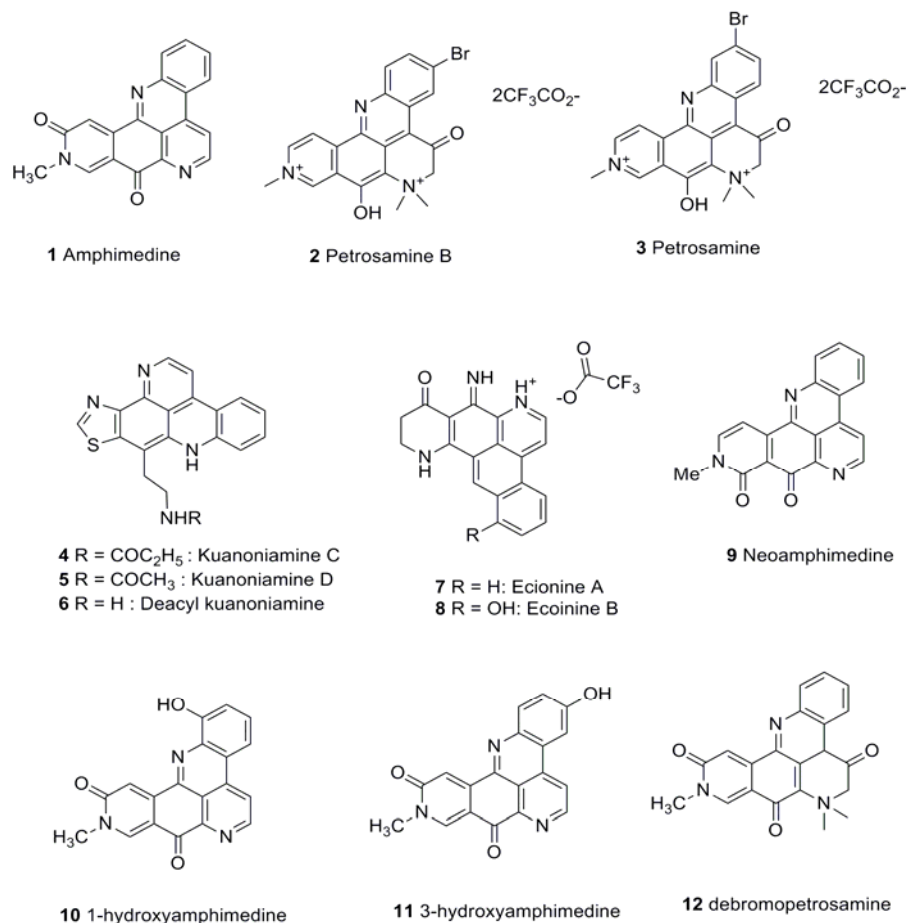
## 12.2. PYRIDOACRIDINE ALKALOIDS

Pyridoacridines are highly coloured 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 (Molinski, 1993) in 1993 and in later years, by Ding et. al. (Ding et. al., 1999) in 1999. Schmitz and Shoolery research groups reported the structure of first marine pyridoacridines 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 bennetti*, the pyridoacridines [4,3,2-mnn] carbon skeleton is exclusive to marine invertebrates. Pyridoacridine alka-

loids 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,  $\text{Ca}^{+2}$  releasing activity, production of reactive oxygen species (Taraporewala et. al., 1992). Pyridoacidines are pH indicator, 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) and *Stelletta 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 colour changed to purple. Correlation of solvent-dependent changes in the UV-spectrum and NMR spectra suggested that the remarkable colour change observed by varying solvent polarity were associated with shifts in the position of keto-enol equilibrium, that favouring 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 is the position of bromine atom (Molinski et. al., 1988). Notably, pyridoacridines 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 tumour and a non-tumour 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's and coworkers, reported two new cytotoxicity peridoacridine 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-hydroxy-

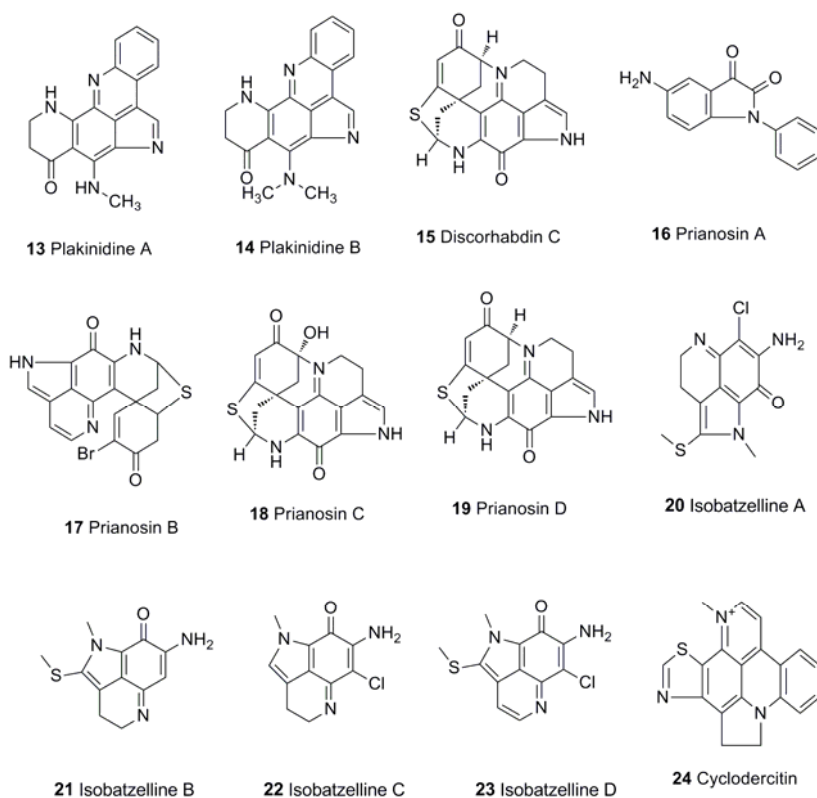
deoxyamphimidine (**11**) and debromopetrosamine (**12**) along with the known neoamphimedine (**9**) and amphimedine (**1**) from the sponge *Xestospongia cf. carbonaria* (Wei et. al. 2010).



In general, pyridoacridine alkaloids show significant biological activity such as cytotoxic, potent anti-viral, anti-fungal, anti-bacterial, anti-tumor and anti-parasitic activity (Marshall & 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 have been considerable demands for these compounds as antitumor agents (Delfourne & Bastide, 2003). Many of these compounds have generated interest both as challenging problems for structure elucidation, as well as synthetic target and their bioactivities studies [Schmitz et. al., 1983; Gunawardana et. al., 1992). The red sponge *Plakortis*, collected by Inman and co-workers from different marine sources led to the isolation of two novel alkaloids namely, plakinidine-A (**13**) and 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. A novel alkaloid consist of bridged with tetrahydrothiophene ring, Discorhabdin C (**15**), was isolated from both *Latrunculia brevis*, from New Zealand and *Prianos* sp. from Okinawa

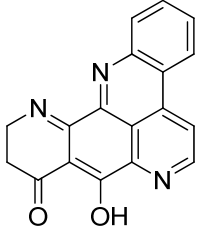
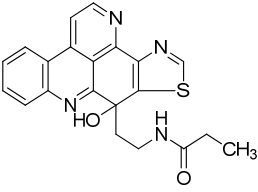
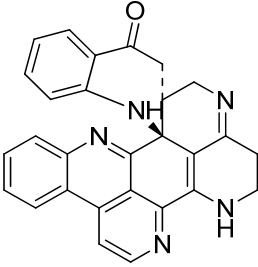
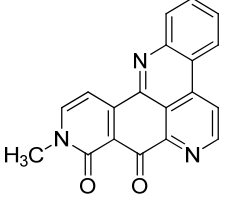
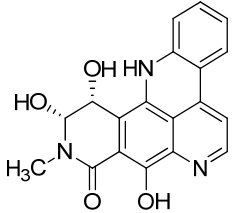
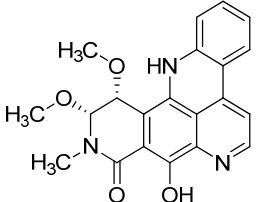
(Perry et. al., 1988). Cheng *et. al.* isolated sulfur containing alkaloids, prianosins A-D (**16-19**) from the green sponge *Prianos melanos* which showed cytotoxicity against L1210 murine leukemia cells (Cheng et. al., 1988).

The sponge *Bratzella* sp. has also furnished four additional pyrroloacridine alkaloids named isobatzellines A-D (**20-23**) (Hao et. al., 1990). In 1975, hexacyclic alkaloids cycloderitin (**24**) have been reported from the deep-water sponges *Dercitus* sp. and in *Stelletta* sp. (Gray, 1975).

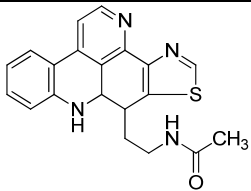
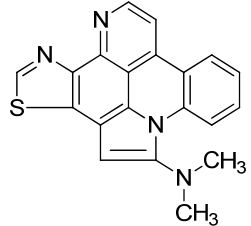
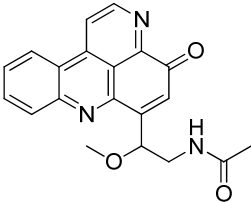


Pyridoacridines is vast class of alkaloid which varies from each other structurally by attachment of different side chains or fusion of different rings to ring C of the basic structure and sometimes to the acridine nitrogen. Based on the structure, pyridoacridines are divided into tetracyclic, pentacyclic, hexacyclic, heptacyclic and octacyclic alkaloids (Kumar & 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, intercalation of DNA, (McCarthy et. al., 1988; Kobayashi et. al., 1988). A Few selected pyridoacridines (**25-33**) showing interesting biological activities along with their source has been depicted in **Table 12.2**.

**Table 12.2.** Some pyridoacridines: source of bioactive alkaloids

Pyridoacridines	Source	Structures	References
Labuanine A (25)	<i>Biemna fortis</i> sponge (Indonesia)		(Akoi et al., 2003)
Sagitol (26)	<i>Oceanapia sagittaria</i> sponge (Palau)		(Salmon & Faulkner, 1996)
Biemnadin (27)	<i>Biemna fortis</i> sponge (Indonesia)		(Kumar & Rawat, 2011)
Neoamphimedine (28)	<i>Xestospongia</i> sp. sponge (Philippines)		(Rodriguez et al., 1993; Kong et al., 1994; 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)
Neoamphimedine Z (30)	<i>Xestospongia</i> cf. <i>carbonaria</i> , X. cf. <i>exigua</i> (Indo-pacific)		(Schmitz et al., 1983)

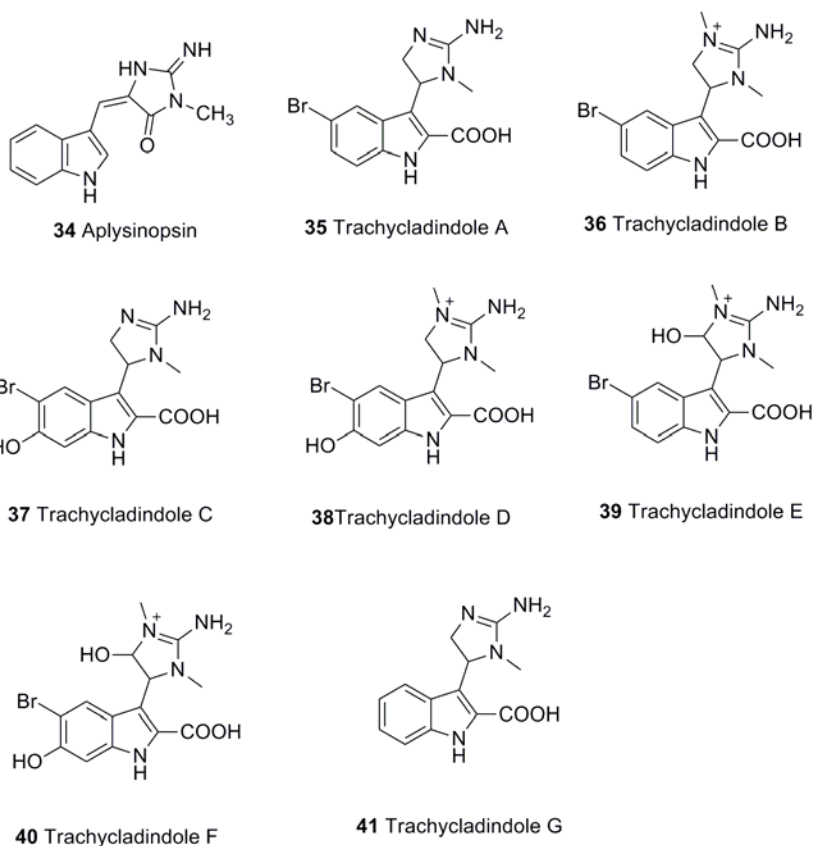


Nordercitin (31)	<i>Stelletta</i> sp. sponge <i>Dercitus</i> sp. sponge (Bahamas)		(Gunawardana et al., 1992)
Stellettamine (32)	<i>Stelletta</i> sp. sponge		(Shin et al., 1997)
Dercitamine (33)	<i>Stelletta</i> sp. sponge, <i>Dercitus</i> sp. sponge (Bahamas)		(Djura & Faulkner, 1980)

### 12.3. INDOLE ALKALOIDS

Indole-containing alkaloids have frequently been isolated from diverse marine invertebrates including bryozoans, coelenterates, sponges, 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, and 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* Species, *Spongosorites* sp. and *Hyrtios* sp. (Sauleau et al., 2006). Kazlauskas *et al.*, (Kazlauskas et al., 1977) isolated for the first time a novel indole alkaloid, Aplysinopsin (34) from Indo-Pacific sponge species, representatives of the genera *Thorecta* (later assigned as the separate *Aplysinopsis* genera). Since that time, aplysinopsin and its derivatives have been reported in many other marine organisms. Aplysinopsin-type compounds have been found in sponges of the Caribbean: *Verongia spengelli* (Hollenbeak & Schmitz, 1977), *Dercitus* sp. (Djura & Faulkner, 1980), *Smenospongia aurea* (Djura et al., 1980), *Verongula rigida* (Kochanowska et al., 2008), the Mediterranean Sea: *Dictyoceratida* sp. (Bergquist & Wells, 1983), as well as in the Indo-Pacific region: *Aplysinopsis reticulata* (Kazlauskas et al., 1977; Baker & Wells, 1981), *Aplysina* sp. (Kondo et al., 1994), *Hyrtios erecta* (Aoki et al., 2001), *Smenospongia* sp. and *Thorectandra* sp. (Segraves & Crews, 2005). In 2008, Capson *et al.* (Capson et al., 2008) has reported the cytotoxic agents 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.



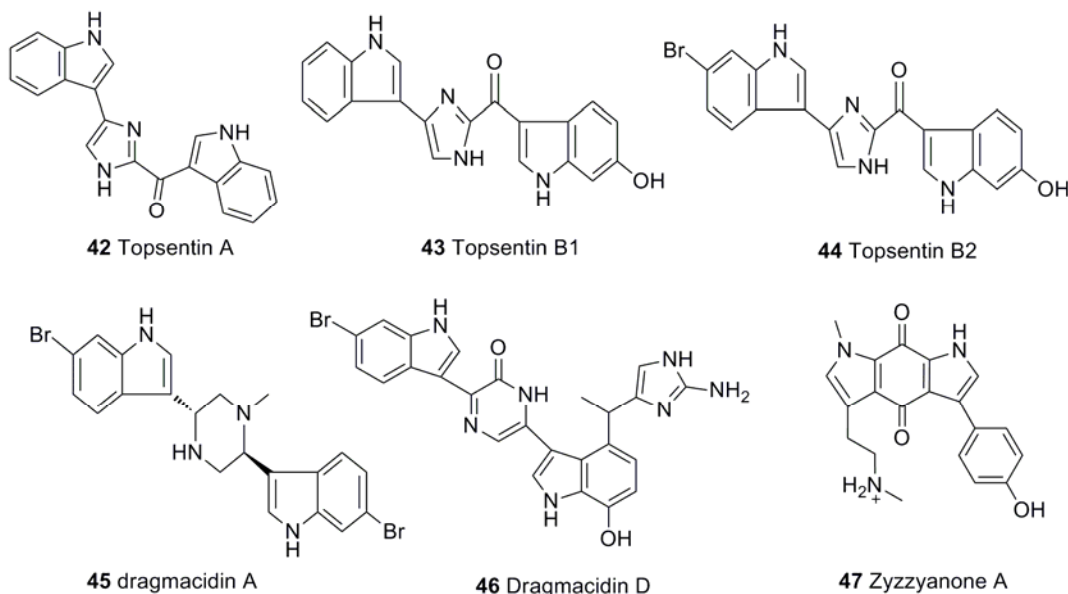
### 12.3.1. BISINDOLE ALKALOIDS

Bis-indole alkaloids, consisting of two indole moieties connected to each other via heterocyclic units, have been particularly abundant within marine sponges. Since an isolation of bis(indolyl)imidazole, topsentin A (**42**) or topsentin B1 (**43**), 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). Topsentins A (**42**), B1 (**43**), and B2 (**44**) 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 led to identification of dragmacidon A (**45**) as potent potent cytotoxic compound. Related bis-(indole)-alkaloid, dragmacidin D (**46**), has been isolated from another marine sponge of the genus *Spongoso-*

*rites* (Wright et. al., 1992). This compound inhibited the growth of the feline leukemia virus, the opportunistic fungal pathogens *Candida albicans* and *Cryptococcus neoformans* and also inhibited 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 wide range of biological activities such as inhibitors of protein phosphatase and anti-cancer. 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 & Pletcher, 2006).

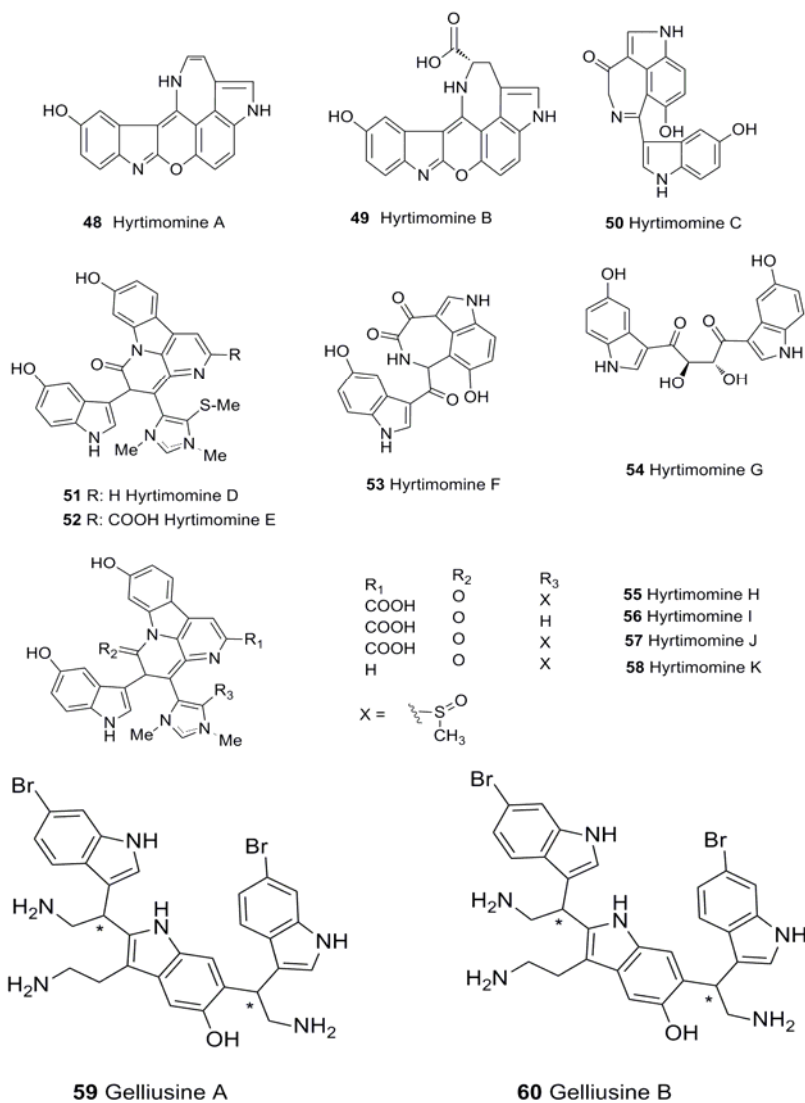
A dipyrroloquinone, zyzzyanone A (**47**) (having a pyrrolo [3,2-f] indole-4,8(1H,7H)-dione skeleton) was isolated from the Australian marine sponge *Zyzya fuliginosa*, exhibiting moderate cytotoxic activity against mouse ehrlich carcinoma cells (Utkina et. al., 2005). Hyrtimomines A-E (**48-52**), were isolated from an Okinawan marine sponge *Hyrtios sp.*(Tanaka et. al., 2013). Later they isolated other hyrtimomines F-K 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.

Hyrtimomines A-C (**48-50**) and hyrtimomines F-K (**53-58**) were studied for antimicrobial activities. Hyrtimomines F (**53**), G (**54**) and I (**56**) exhibited inhibitory effects against *Aspergillus niger* while (**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 group have shown cytotoxicity activity of hyrtimomine A (**48**) against KB and L1210 cells (Momose et. al., 2013).



### 12.3.2. TRISINDOLE ALKALOIDS

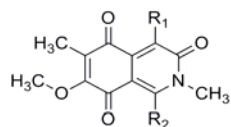
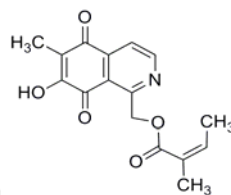
Trisindole alkaloids were rarely found in sponges. Bifulco *et al.* (Bifulco *et al.*, 1994) isolated trisindole alkaloids, Gelliusines A (**59**) and B (**60**) from deep water Caledonian sponge *Gellius* or *Orina* sp. possessing cytotoxicity against KB, P-388, P-388/dox, HT-29 and NSCLCN-6 cell lines. The structural feature of Gelliusin 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 appears to be non stereoselective giving two enantiomeric pairs.



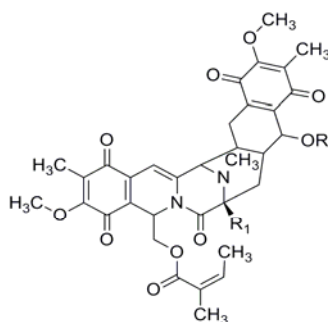
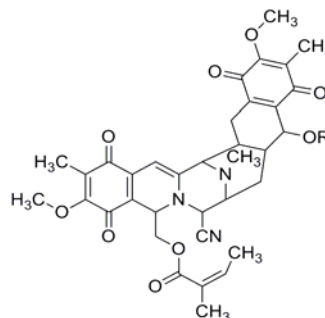
## 12.4. ISOQUINOLINE ALKALOIDS

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 & Ireland, 1987) are frequently isolated isoquinoline alkaloids and they have been reported from various marine sponges. Mimosamycin (**61**), 4-hydroxymimosamicin (**62**), 1,4-dihydroxymimosamycin (**63**) and O-Demethylrenierone (**64**) were isolated from *Haliclona cribricutis* (Parameswaran et al., 1998). They isolated Renieramycin 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 co-workers (Suwanborirux et al., 2013). Renieramycin M exhibited anticancer activity, it induce 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  $\mu$ M) for 24 h, and cell viability was analyzed using MTT assay (Halmi et al., 2011).

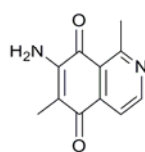
Isoquinolinequinones alkaloids, cribrostatins 1 (**68**) and 2 (**69**) were isolated from a deep blue colored sponge *Cribrochalina* sp. (Pettit et al. 1992) and were found to be active against lymphocytic leukemia cell line (P-388). In 2000, Pettit *et al.* explored same sponge *Cribrochalina* sp. 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.

61 Mimosamycin: R<sub>1</sub> = R<sub>2</sub> = H62 4-Hydroxy mimosamycin: R<sub>1</sub> = OH; R<sub>2</sub> = H63 1,4-Dihydroxymimosamycin: R<sub>1</sub> = R<sub>2</sub> = OH

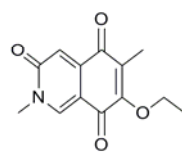
64 O-Demethylrenierone

65 Renieramycin H: R = H, R<sub>1</sub> = OH66 Renieramycin I: R = CH<sub>3</sub>, R<sub>1</sub> = H

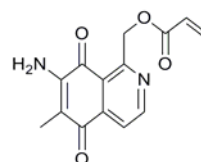
67 Renieramycin M



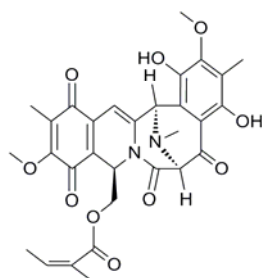
68 Cribrostatin 1



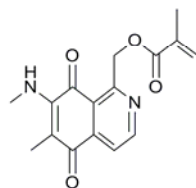
69 Cribrostatin 2



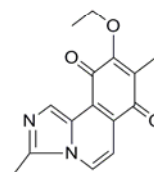
70 Cribrostatin 3



71 Cribrostatin 4



72 Cribrostatin 5



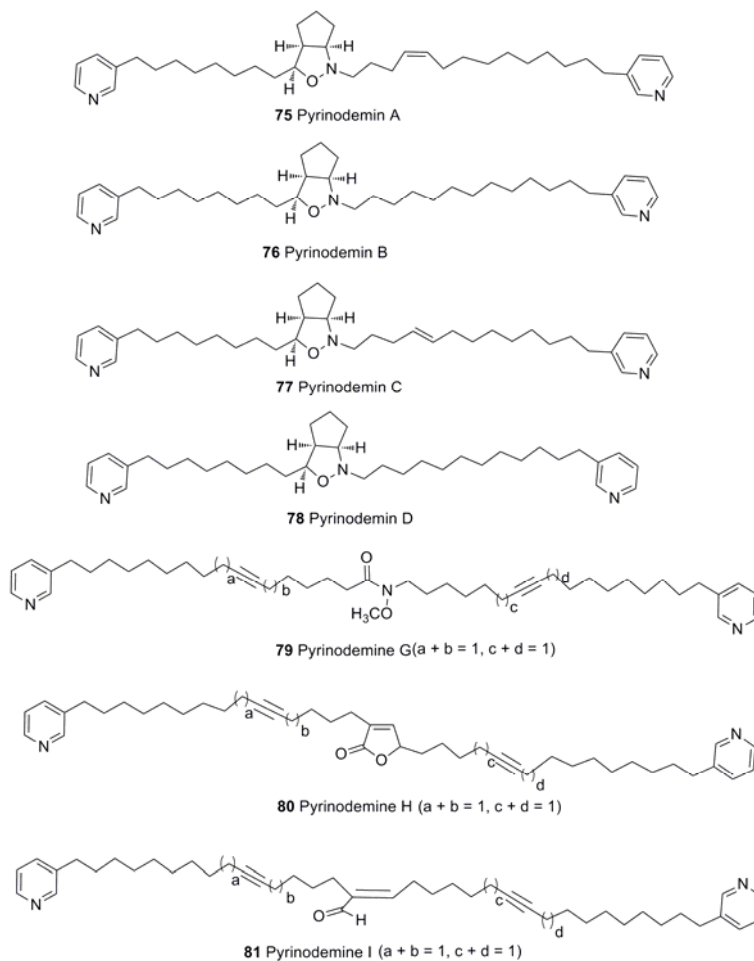
73 Cribrostatin 6

## 12.5. PYRIDINE ALKALOIDS

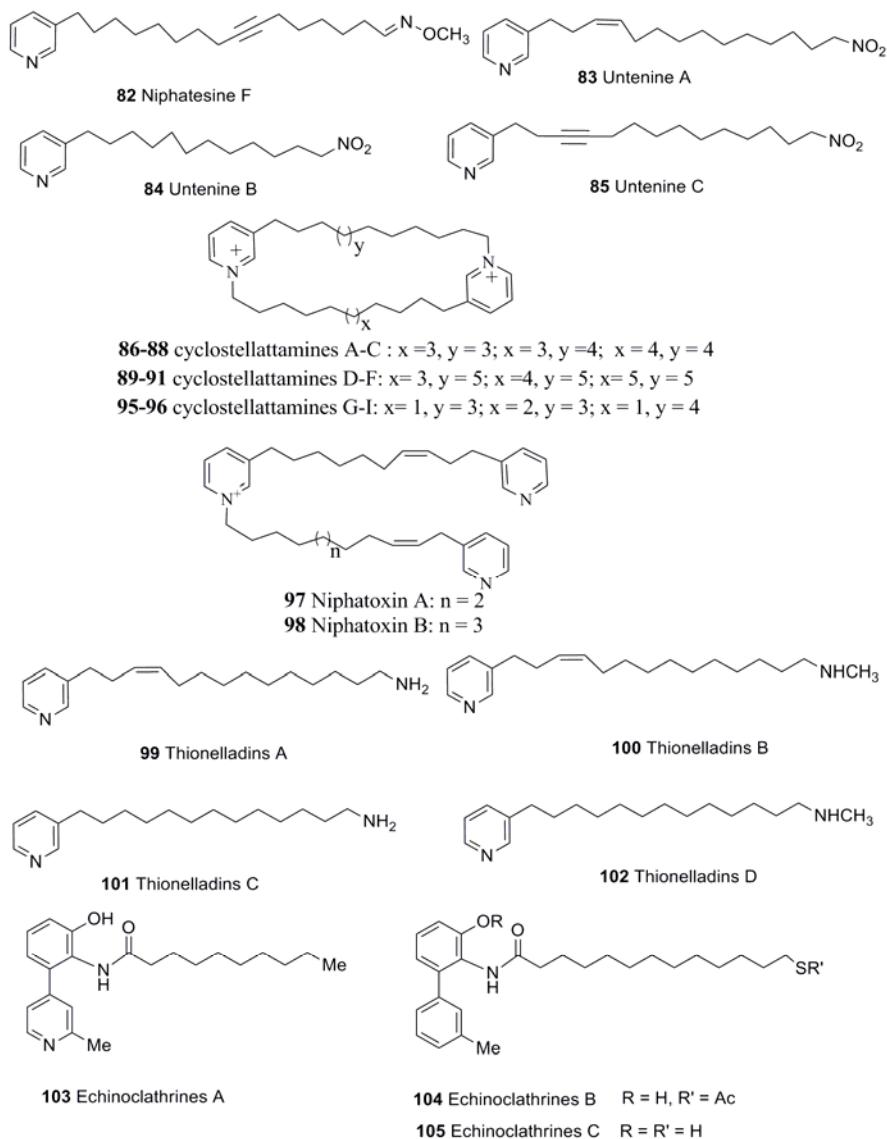
The sponge of order Haplosclerida are considered the richest source of pyridine alkaloids with diverse carbon skeleton. Several 3-alkyl pyridine alkaloids have been isolated from marine sponges (Faulkner 1999). Cytotoxic bis-pyridine alkaloids, pyrinadine A and cribochalines A and B were isolated from the marine sponge *Cribochalina* sp. (Kariya et. al. 2006). Cribochaline A displayed antifungal activity against both antibiotic-sensitive and resistant strains of *Candida* sp. (Nicholas and Molinski 2000). Kobayashi's group have isolated pyrinodemins A-D (**75-78**) potent cytotoxic bis-pyridine alkaloids with a cis-cyclopent [c]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 (**79-81**), bis-3-alkylpyridine from the same sponge (Kubota et. al. 2013).

Niphatesine F (**82**) was isolated from the Okinawan marine sponge *Niphates sp.* (Kobayashi et. al. 1992). Cyclic *bis*-pyridine alkaloids, cyclostelletamine alkaloids (**86-96**) were obtained from the sponge *Pachychalina sp.* and the alkaloids exhibited antimicrobial and antimycobacterial activity (Oliveira et. al. 2006). Cytotoxic tripyridine alkaloids, niphatoxin A & B (**97-98**) have been isolated by Kobayashi's group from the Red Sea sponge *Niphates sp.* (Talpira et. al. 1992). While a nitro alkyl pyridine alkaloids with antimicrofouling properties were isolated from the Okinawan marine sponge



*Calyspongia sp.* (Wang et. al. 1996). Theonelladins A-D (**99-102**), antineoplastic pyridine alkaloids were isolated from the marine sponges *Theonella swinhoei* (Kobayashi et. al. 1989). Kitamura *et. al.*, isolated Echinoclathrines A-C (**103-105**) a new class of Pyridine alkaloids having 4-aryl-2-methylpyridine unit from an Okinawan sponge, *Echinoclathria sp.* (Kitamura et. al. 1999). Echinoclathrine A (**103**) exhibited a weak cytotoxicity ( $IC_{50} = 10 \mu\text{g/mL}$ ) against P-388, A-549 and HT-29 cell lines, while others alkaloids were found to be inactive.



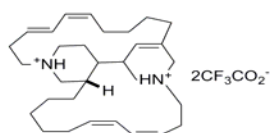
## 12.6. PIPERIDINE ALKALOIDS

Piperidine are heterocyclic amines consisting of a six-membered ring containing five methylene bridges (-CH<sub>2</sub>-) and one amine bridge (-NH-). Marine sponges belonging to the order Haplosclerida are considered the richest source of alkyppiperidine alkaloids. 3-alkylpiperidine alkaloid which is a very common piperidine alkaloid include a variety of metabolites ranging from monomeric 3-alkylpyridines to condensed bis-allylpiperidines of the manzamine class. These alkaloids show a wide range of biological activities *viz.* antimicrobial, antiviral, cytotoxic (Schmitz et. al. 1978), anti-malarial (Ang et. al. 2000), antifouling (Faimali et. al. 2003). An unusual oligomeric pyridinium alkaloids namely, cyclohaliclonaamines (Teruya et. al., 2006) and viscosamine (Volk et. al. 2004) were isolated from *Haliclona sp.* and *Haliclona viscosa*, respectively. A macrocyclic dimeric hali-

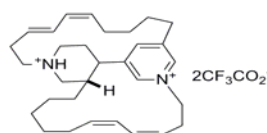


clamines and the linear trimeric viscosaline were also isolated from *H. viscosa* (Volk and Köck 2004).

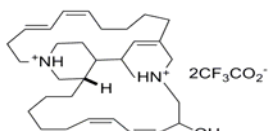
Fusetani and coworkers have reported piperidine alkaloids namely, halicyclamine A (**106**), teradehydrohalicyclamine A (**107**) and 22-hydroxyhalicyclamine A (**108**) from a marine sponge *Amphimedon sp.* (Takekawa, et. al. 2006). These halicyclamine piperidine alkaloids (**106-108**) exhibited cytotoxicity against P388 cells with IC<sub>50</sub> values of 0.45, 2.2 and 0.45  $\mu\text{g/mL}$ , respectively. A new piperidine alkaloid plakoridine C (**109**) has been isolated by Kobayashi group's from an Okinawan marine sponge *Plakortis species* and the structure was elucidated from spectroscopic data (Ishiguro et. al., 2009). Plakoridine C (**109**) is a new alkaloid possessing a piperidine ring connected to a  $\beta$ -keto- $\gamma$ -lactone through a double bond. Bis-piperidine alkaloids, madangamine F (**110**), halicloacyclamine F (**111**) and arenosclerins D (**112**) and E (**113**), have been isolated from the marine sponge *Pachychalina alcaloidifera* and the structures were identified by analysis of spectroscopic data. The alkaloids displayed cytotoxic activity against different cancer cell lines.



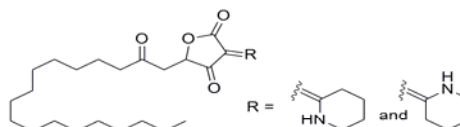
**106** Halicyclamine A



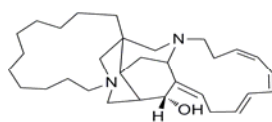
**107** Teradehydrohalicyclamine A



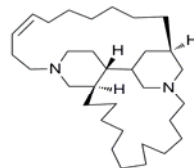
**108** 22-hydroxyhalicyclamine A



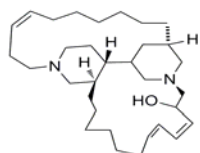
**109** Plakoridine C



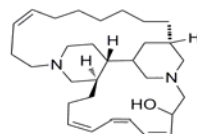
**110** madangamine F



**111** halicloacyclamine F



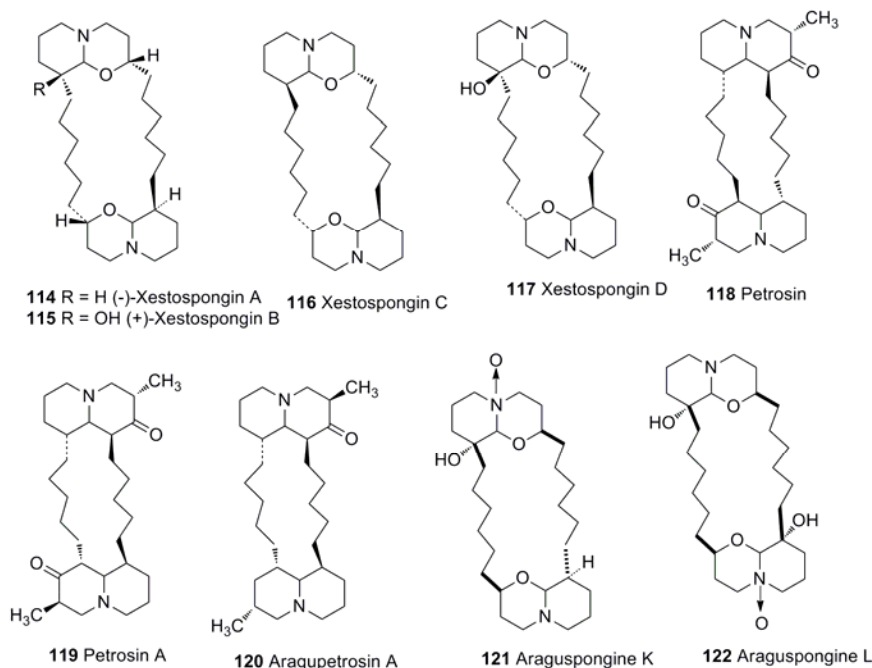
**112** arenosclerin D



**113** arenosclerin E

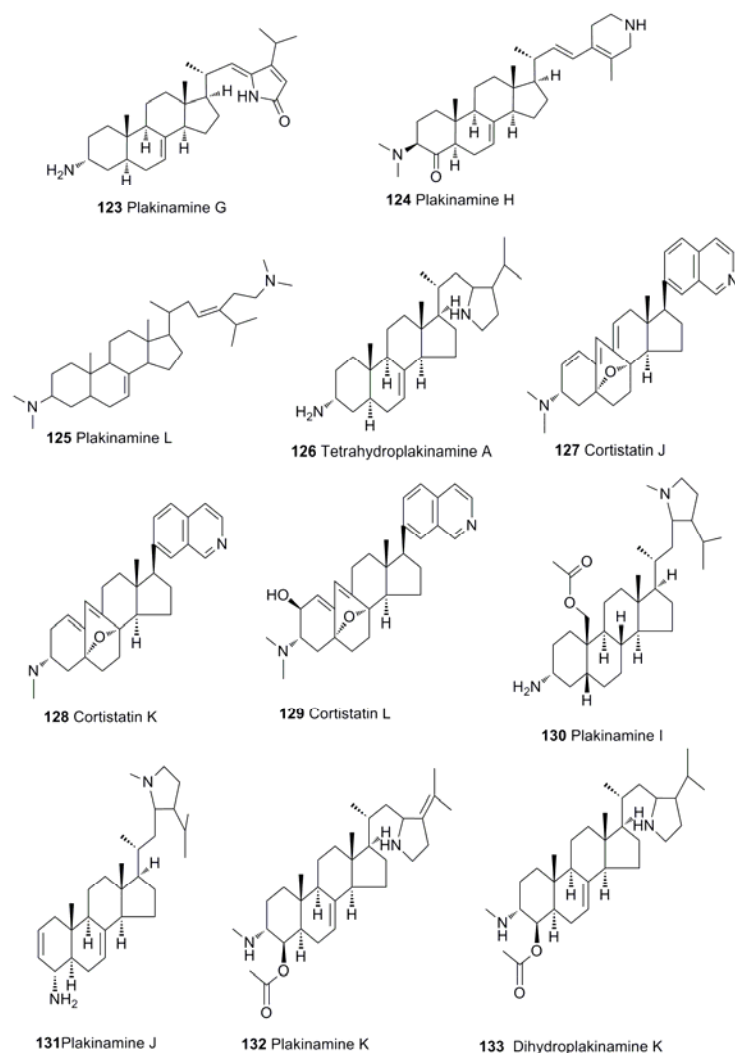
## 12.7. QUINOLIZIDINE ALKALOIDS

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, bis-1-oxa-quinolizidines are common in marine sponges. The first four "1-oxa-quinolizidines" were isolated from the Australian sponge *Xestospongia exigua*, designated as xestospongins A-D (**114-117**) with the structure of (-)-xestospongins C (**116**) determined by X-ray techniques (Nakagawa et. al. 1984). Later these oxa-quinolizidine and bis quinolizidine family have also been isolated from several other marine sponges viz. *Oceanapia sp.* (Singh et. al. 2011), *Petrosia smilis* (Goud et. al. 2003), *Haliclona exigua* (Venkateswarlu et. al., 1994). The family of xestospongins/araguspongine alkaloids comprises of 13 members (Moon et. al. 2002; Reddy and Faulkner 1997) and chemically, they are dimeric 2,9-disubstituted 1-oxaquinolizidines. Braekman et. al., reported petrosin (**118**), 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 alkaloids ( $\pm$ ) xestospongins D (**117**) 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 (**117**) showed several activities including antimicrobial and modest growth inhibitory against a number of tumor cell lines (Pettit et. al. 1996). Petrosin A (**119**) vasodilative macrocyclic quinolizidine alkaloid, aragupetrosine A (**120**) along with several araguspongins alkaloids have been reported by Kobayashi's group from a Okinawan marine sponge, *Xestospongia sp.* (Kobayashi et. al. 1989). A unique bis-1-oxaquinolizidine N-oxide alkaloids, Araguspongins K (**121**) and L (**122**) were also reported by Orabi et. al. from Red sponge *Xestospongia exigua* (Orabi et. al. 2002).



## 12.8. STEROIDAL ALKALOIDS

In 2002, Borbone *et al.* demonstrated the isolation of four steroidal alkaloids, plakinamine G (**123**), H (**124**), plakinamine L (**125**) and tetrahydroplakinamine A (**126**) from the marine sponge *Corticium* sp. (Borbone *et al.* 2002). Amongst these series, plakinamine G (**123**) and tetrahydroplakinamine A (**126**) were most active against C6 cells, whereas, plakinamine H (**124**) and plakinamine L (**125**) were cytotoxic against C6 cells and RAW-264 cell lines. In 2007, three more steroidal alkaloids, cortistatins J-L (**127-129**) were isolated from the Indonesian marine sponge *Corticium simplex*. (Aoki *et al.* 2007). Cortistatin J (**127**) demonstrated potent cytostatic anti-proliferative 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 (**128**) and L (**129**) were less potent than cortistatin J (**127**). Steroidal alkaloids, plakinamine I-K (**130-132**) and dihydroplakinamine K (**133**) were isolated from sponge *Corticium niger* (Ridley & Faulkner, 2003) and were tested for cytotoxicity against the human colon tumor cell line (HCT-116). Compounds plakinamine K (**132**) and dihydroplakinamine K (**133**) were found to be the most active in terms of potency while plakinamine I and J (**130 & 131**) were moderately active.



## BROMOTYROSINE ALKALOIDS

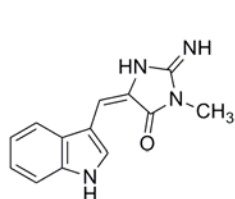
Marine sponges from the order Verongida are rich source of bromotyrosin-derived alkaloids (Bergquist 1983; Gribble 1998). Sponges in this order have been reported to show unusual biochemical profiles characterized by the absence of terpenes and the production of sterols and brominated compounds biogenetically tyrosin (Kochanowska et. al. 2008). Several bromotyrosine alkaloids *viz.* Purealin (Tsuda et. al. 1992), Lipopurealin A-E (Nakamura et. al. 1986; Kbayashi et. al. 1995), Purealidin A-S (Ishibashi et. al. 1991; Kobayashi et. al. 1991), Psammaphysin A-B (Roll et. al. 1985), Purpuramine 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; Akoi 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 & Soest 2007). Bromotyrosin alkaloids exhibited potent antibacterial (Tsukamoto et. al., 1996; Matsunaga et. al. 2005), anti-HIV (Ross et. al. 2000), antimalarials (Xu et. al. 2011) and cytotoxic activities (Tabudravu and Jaspers 2002).

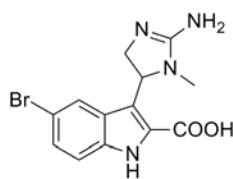
Purealidin S and Purpuramine J were isolated from the Fijian marine sponge *Druinella sp.* (Tabudravu and Jaspers, 2002). Fujiwara et. al. isolated a new bromotyrosin alkaloid JBIR-44 (**134**) from *Psammaphysilla purpurea*. JBIR-44 (**134**) showed cytotoxic effects against human cervical carcinoma HeLa cells (Fujiwara et. al., 2009). Bromotyrosine-derived metabolites purpuramines A-I, were isolated from the marine sponge *Psammaphysilla purpurea* (Jurek et. al., 1993). Purpuramine A (**135**) and C (**136**) differ only at amine substituent at the aromatic ring.

A novel dibromotyrosine derivative, Aplysfitularine (**137**) 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 psammaphysines [Cimineillo et. al, 1994; Thoms et. al., 2005; Saeki et. al., 2002]. Purealidin B-C (**138-139**) (Kobayashi et. al., 1991) and Lipopurealins D-E (**140-141**) (Kobayashi et. al., 1995) were isolated from the Okinawan marine sponge *psammaphysilla purea*.

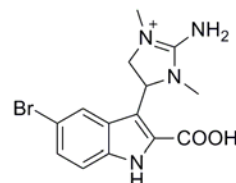
S. Yen et. al. isolated pseudoceramines A-D (**142-145**), a series of antibacterial bromotyrosine alkaloids from the marine sponge *Pseudocerarina sp.* of Erskine Is., Great Barrier Reef (Yin et. al., 2011). They have reported that pseudoceramine C (**144**) was cleavage derivative of spermatinamine (**146**). Pseudoceramines B (**142**) inhibits secretion of the virulence factor Yersinia Outer Protein E. (Yin et. al., 2011).



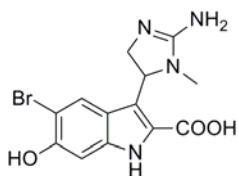
34 Aplysinopsin



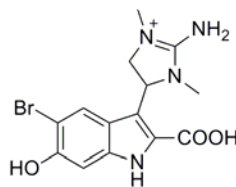
35 Trachycladindole A



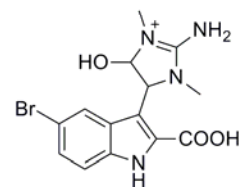
36 Trachycladindole B



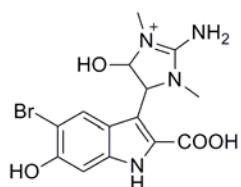
37 Trachycladindole C



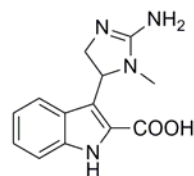
38 Trachycladindole D



39 Trachycladindole E

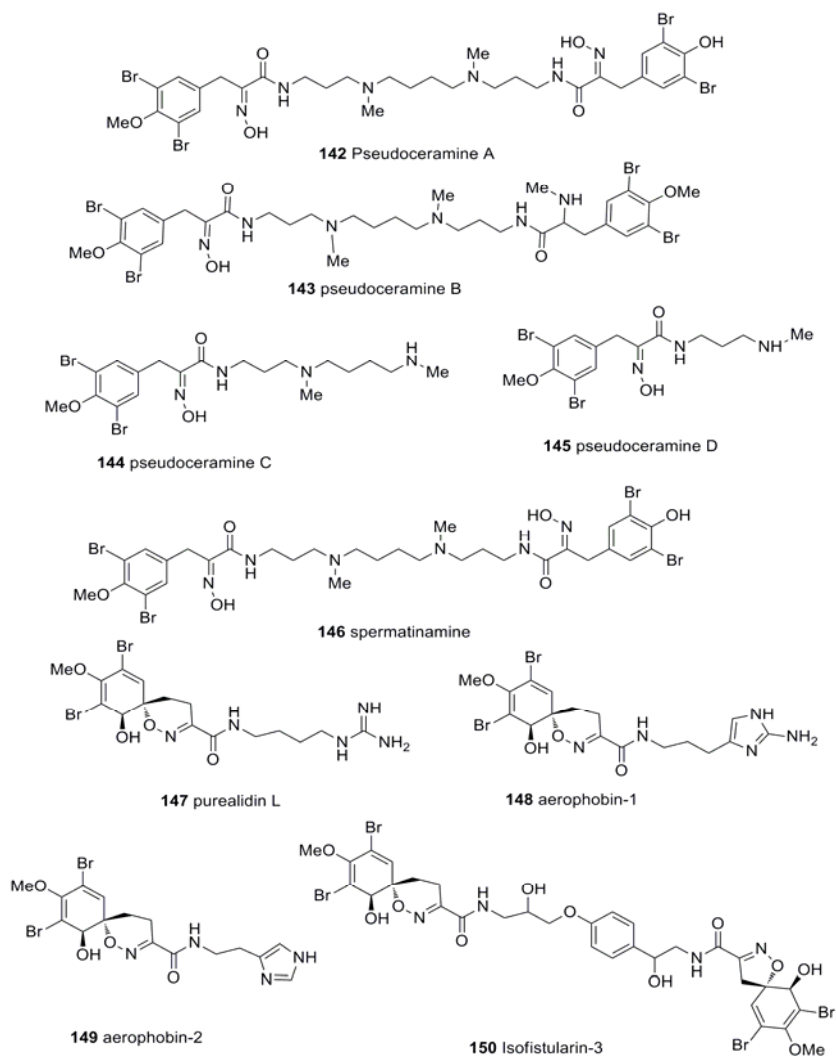


40 Trachycladindole F

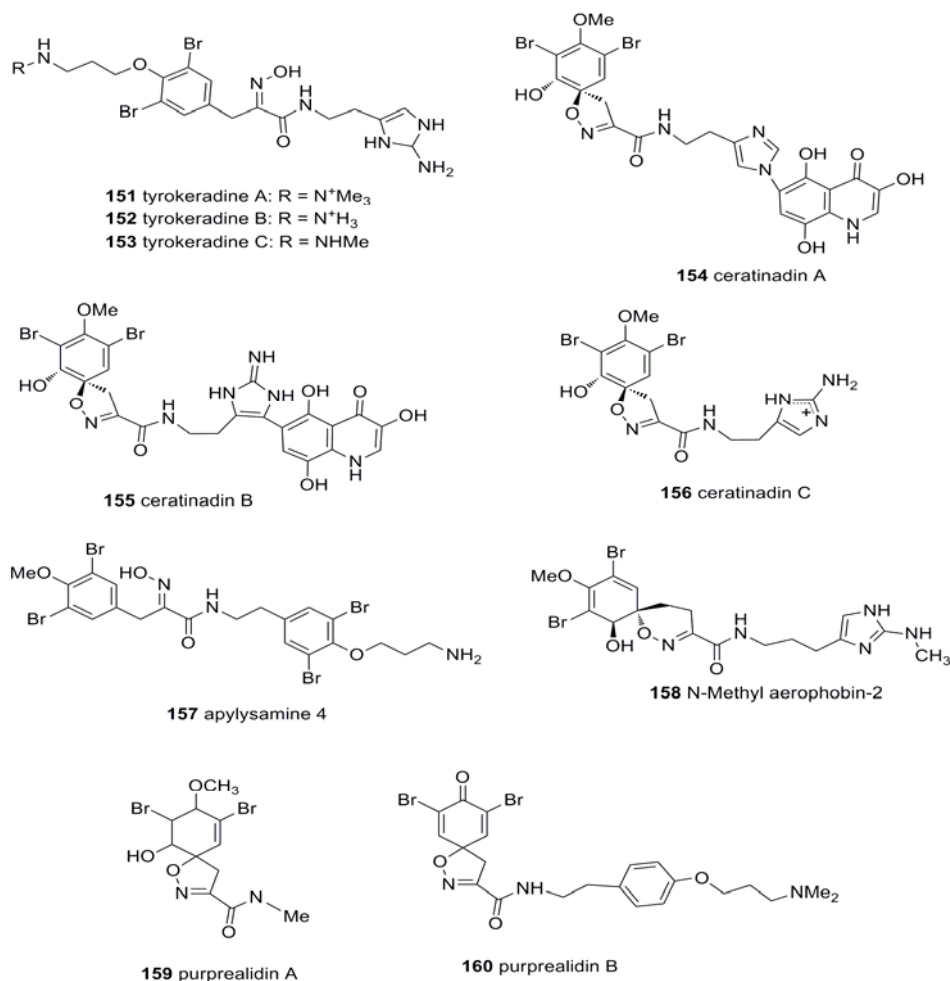


41 Trachycladindole G

Bromotyrosine derived alkaloids, Puralidin-L (**147**), aerophobin-1 (**148**) and aerophobin-2 (**149**) (Cimino et. al., 1983), isofistularins-3 (**150**) were isolated from several marine sponges (Gopichand et. al., 1979). Kobayashi's group isolated purealidin-L (**147**) (Kobayashi et. al., 1995) from *Psammaphysilla purea*, while tyrokeradines A and B (**151-152**) were isolated from Okinawan marine sponge of order Verongida by Kobayashi's group (Mukai et. al., 2009). In later years, they isolated other related bromotyrosine alkaloids tyrokeradines C (**153**) from the same sponge (Kubota et. al., 2012). His group also isolated ceratinadins A-C (**154-156**) from Okinawan marine sponge *Pseudoceratina sp.* (Kona et. al., 2010).

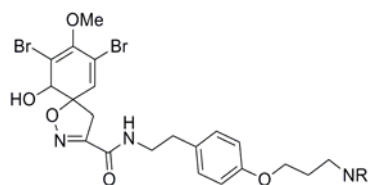


Aplysamine-4 (**157**) a bromotyrosin derived alkaloid, was isolated from the sponge *Psammaphysilla purpurea* (Jurek et. al., 1993). Proksch's group isolated a new bromotyrosine alkaloid N-methyl-Aerophobi-2 (**158**) along with known bromotyrosin alkaloids, Purealidin-L (**147**), aerophobin-1(**148**) and aerophobin-2 (**149**) from the Caribbean marine sponge *Aiolochoxia crassa* (Assmann et. al., 1998). A series of Purpurealidin A-D (**159-162**) were isolated by Tilvi et. al., from the Indian marine sponge *Psammaphysilla purpurea* (Tilvi et. al. 2004).



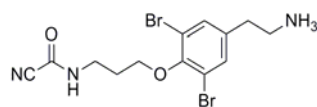
Bromotyrosine alkaloids with antifouling activities were reported from *P. purpurea* collected in various locations of Japan, among which the most interesting is ceratinamine (**163**) which contains a cyanoformamide functionality, unprecedented in natural products (Tsukamoto et. al.,1996). Ceratinamine showed potent antifouling activities against barnacle larvae with an EC<sub>50</sub> value of 5.0 µg mL<sup>-1</sup>. Other bromotyrosine derived alkaloids such as ceratinamides A (**164**) and B (**165**), and psammaphysin A (**166**) exhibited potent activity with EC<sub>50</sub> values of 0.10, 2.40 and 0.27 µg mL<sup>-1</sup>, respectively (Tsukamoto et. al.,1996). Bewley's research group isolated a novel bromotyrosine alkaloid (**167**), which inhibit 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 *Psammaphysilla purpurea* (Carney et. al., 1993) and *lanthella basta* (Aoki et. al., 2006). Bastadin-6 (**168**) exhibited anti-proliferative activities against endothelial cells (Aoki et. al., 2006).



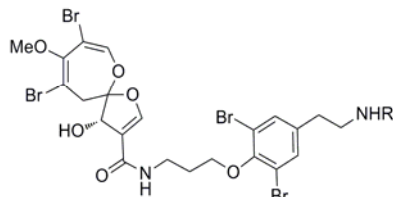


**161** purpurealidin C: R = CO(CH<sub>2</sub>)<sub>11</sub>CH(CH<sub>3</sub>)<sub>2</sub>

**162** purpurealidin D: R = CO(CH<sub>2</sub>)<sub>12</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>

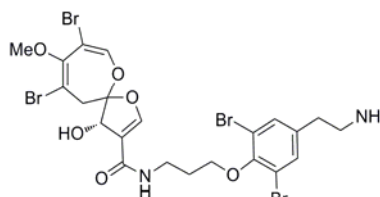


**163** ceratinamine

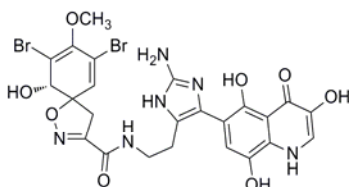


**164** ceratinamide A: R = CHO

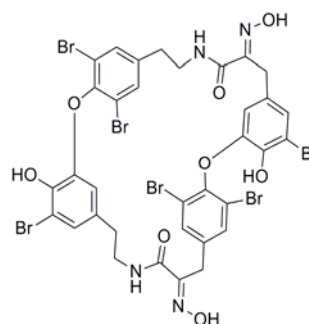
**165** ceratinamide B: R = CO(CH<sub>2</sub>)<sub>11</sub>CH(CH<sub>3</sub>)<sub>2</sub>



**166** psammalysin A



**167**



**168** bastadin 6

## 12.9. 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 review on alkaloids *viz.* pyridoacridines, alkyl pyridine, piperidine, indole, quinolizidine, isoquinoline, steroidal alkaloids and bromotyrsine 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 work on the topic which are deserved to be cited may find exclusion due to page limitation.

## Acknowledgements

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