Biologically Active Metabolites from Sponges and Their Activities

9

A. Shanmugam and S. Vairamani

Abstract

Sponges are mostly marine found distributed right from the intertidal region to the deeper waters of the oceans. Its spatial and temporal distribution is found ubiquitous. Though the sponges have simple morphology and anatomy, they show symbiotic association with several microorganisms, which are the main source of secondary metabolites and are capable of producing many biologically active compounds. So there is a good debate going on among the researchers that the source of such biologically active compounds/substances is either the sponge itself or the microorganism residing in the sponges. But unfortunately most of these symbiotic microorganisms are non-culturable. Anyhow the sponges as a whole are the good source of several substances covering the polyketides, alkaloids, terpenes, etc. This chapter deals with the variety of such chemical substances present in the sponges and their biological activities.

Keywords

Marine sponges • Metabolites • Biological activities

9.1 Introduction

Sponges are simple invertebrates with loose organization. Generally, they have spicules of silica or calcium carbonate embedded in their bodies for support and fibrous skeletons made of a horny substance called spongin; however, either or both of these may be lacking. Because sponges lack a distinct enteron and the germ layers are not well established, the phylum Porifera is sometimes classed in a separate subkingdom, the Parazoa, or the Metazoa.

There are approximately 4000 species of sponges. About 1 % (all members of a single family) inhabits freshwater, 10 % are intertidal, and the remaining is marine or benthic. Sponges

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obtain feed by propelling water through tiny pores in the body wall, thus capturing microorganisms and organic detritus that may be present in their body. Further the sponges inhabit several millions of symbiotic organisms, particularly microorganisms which are producing many biologically active substances for their successful survival in sponges which are also taking part in it. Because of this reason, there is a debate among the researchers about the source of these biological substances. Thus the sponge as a whole contributes to show a variety of biological activities, including antimicrobial, anticancer, and also reported to have toxic materials (Table 9.1).

9.2 Biologically Active Metabolites from Sponges

9.2.1 Polyketides

9.2.1.1 Fatty Acid Metabolites

The azacyclopropene, dysidazirine (Fig. 9.1) was isolated from the grey sponge *Dysidea fragilis* that lacks a spicule skeleton; instead it has a network of fibers loaded with sand grains, broken spicules, and other foreign material. It is strongly conulose and forming lobate or digitate cushions and elastic when compressed. It is a common sponge along most coasts of Western Europe. The dysidazirine reported an IC50 value of 0.27 μg/ml against L1210, the mouse lymphocytic leukemia cells (Molinski and Ireland 1988).

Ficulinic acids A (Fig. 9.2) and B (Fig. 9.3) from the sponge *Ficulina ficus* (= *Suberites ficus* Linnaeus 1767) reported inhibition on the growth of the mouse lymphocytic leukemia cells (L1210) with an ID50 value of 10–12 μg/ml (Guyot et al. 1986). It is an orange sponge with big massive lobate, occasionally cylindrical, with one or more conspicuous, large oscules. It has a velvety smooth appearance. It enjoys its distributed in North East Atlantic coast mostly in places with tidal currents.

9.2.1.2 Long-Chain Acetylenes

Numerous aliphatic compounds have been isolated from sponges, and a number of these have been reported to be cytotoxic. Five monoacetylenic alcohols with different reactive groups (Fig. 9.4) from the sponge *Cribrochalina vasculum* collected in Belize were toxic to the mouse P388 cell line (IC_{50} 1.0,1.3, 1.1, 0.2, 0.1 μg/ml, respectively), and they also showed in vitro immunosuppressive activity in lymphocyte reaction tests (Gunasekera and Faircloth 1990). This appears to be the first report of branched-chain aliphatic acetylenic compounds from marine organisms. *C. vasculum* is also called *Cribrochalina infundibulum* (Schmidt 1870). Smooth inverted cones, to ear-shaped or fan-shaped, sometimes torn or crooked by waves or predators; color tan to vinaceous. The skeleton of *Cribrochalina* is made of thick multispicular tracts cemented by spongin and is found distributed in Santa Marta, Colombia (Hallock et al. 1995).

Duryne (Fig. 9.5) that was isolated from the Caribbean sponge *Cribrochalina dura*, was found toxic to murine leukemia cells (IC50 0.07 μg/ml) and also colon, lung and mammary cell lines, with MIC (Minimum Inhibitory Concentration) of 0.1 μg/ml (Wright et al. 1987a).

Petrosia ficiformis is one of the sponges found producing more acetylenes, that have different purposes in industry. One among them is Petrosynol (Fig. 9.6), a polyacetylene of 30 atoms, showed antibiotic activity and was also active in the starfish egg assay at 1 μg/ml (Fusetani et al. 1987). Cimino et al. (1990) have described a number of C46 polyacetylenes that were active in the brine shrimp assay (IC_{50} 0.002–0.12 μg/ml) and also the sea urchin egg assay (IC50 1–50 μg/ml).

P. ficiformis has a compact, hard texture, with spherical oscula irregularly spread over the surface. It is found on the underside of rocks, on overhangs and in caves between 5 m and 70 m depth. The species has been reported at Adriatic Sea, Aegean Sea, Azores, Canaries, Madeira,

Table 9.1 Details of the compound, source and its potential biological activity

S. No	Compound with structure	Source	Bioactivity	Reference
1	Dysidazirine (Fig. 9.1)	*Dysidea fragilis*	Showed inhibition on the growth of the mouse lymphocytic leukemia cells (L1210)	Molinski and Ireland (1988)
2	Ficulinic acid A: n = 7 (Fig. 9.2); Ficulinic acid B: n = 9 (Fig. 9.3)	*Ficulina ficus* .	- Do -	Guyot et al. (1986)
3	Monoacetylenic alcohols (Fig. 9.4)	*Cribrochalina vasculum*	In vitro immunosuppressive activity	Gunasekera and Faircloth (1990)
4	Duryne (Molecular Formula – $C_30H_{48}O_2$) (Fig. 9.5)	*Cribrochalina dura*	Toxic to murine leukemia cells and also colon, lung and mammary cell lines	Wright et al. (1987a)
5	Petrosynol (Fig. 9.6)	*Petrosia ficiformis*	Antibiotic activity and active in the starfish egg assay	Fusetani et al. (1987)
			Active in the brine shrimp assay and also the sea urchin egg assay	Cimino et al. (1990)
6	Xestin A (Fig. 9.7)	*Xestospongia* sp.	Toxic against P388 cells	Quinoa et al. (1986)
	Xestin B (Fig. 9.8)			
7	Cyclic peroxide acids (Fig. 9.9)	*Plakortis angulospiculatis*	Inhibiting the growth of P388 cells	Gunasekera et al. (1990a)
8	Acanthifolicin (Fig. 9.10)	*Pandaros acanthifolium*	strong cytotoxic activity against P388 cells	Schmitz et al. (1981)
9	Okadaic acid (Fig. 9.11)	*Halichondria okadai*	- Do -	Tachibana et al. (1981)
10	Discodermolide (Fig. 9.12)	*Discodermia dissoluta*	Potent inhibitor of tumor cell growth in several MDR cancer cell lines.	Gunasekara et al. (1990b).
			Most potent natural promoters of tubulin assembly.	
11	Fijianolides A (Fig. 9.13) Fijianolides B (Fig. 9.14)	*Spongin mycofijiensis* (= *Leiosella lavis*).	Active against P388 and HT-29 human colon tumor cells	Quinoa et al. (1988)
12	Mycalolides A-C (Figs. 9.15 (1), Fig. 9.16 (2) and Fig. 9.17 (3))	*Mycale*	Highly cytotoxic against B16	Fusetani et al. (1898b)
13	Halichondrins B (R = H) (Fig. 9.18) and C (R = OH) (Fig. 9.19),	*Halichondria kadai*	In vitro activity against B16 melanoma cell lines	Hirata and Uemura (1986)
	Norhalichondrins A (Fig. 9.20) ($R_1 = R_2 = H$, $R_3 = R_4 = OH$), B ($R_1 = R_2 = H$, $R_3 = R_4 = H$) (Fig. 9.21) and C ($R_1 = R_2 = R_3 = H$, $R_4 = OH$) (Fig. 9.22)			
	Homohalichondrins A ($R_1 = R_2 = OH$, $R_3 = H$) (Fig. 9.23), B ($R_1 = R_2 = R_3 = H$) (Fig. 9.24) and C ($R_1 = R_3 = H$, $R_2 = OH$) (Fig. 9.25)			

(continued)

Table 9.1 (continued)

S. No	Compound with structure	Source	Bioactivity	Reference
14	Misakinolide A (Fig. 9.26)	*Theonella swinhoei*	In vitro antiviral and antifungal activity	Sakai et al. (1986)
15	Latrunculin A (Fig. 9.27)	*Latrunculia magnifica*	Disturbing microfilament organization in the cell and thus affects normal functioning of the cell	Amiram Groweiss et al. (1983)
16	Hennoxazoles A (R_1 = OH, R_2 = CH_3), B (R_1 = OH, R_2 = CH_2 CH_3), C (R_1 = OH, R_2 = CH_2 CH_2 CH_2 CH_3) and D (R_1 = H, R_2 = CH_3) (Figs. 9.28, 9.29 and0 9.30)	*Polyfibrospongia* sp	Displaying analgesic activity	Ichiba et al. (1991)
			Strong activity against HSV-1	
17	Curcuphenol (Fig. 9.31)	*Didiscus flavus*	Inhibited the growth of several cell lines such as P388, A549 (lung), HCT-8 (colon) and MDAMB (mammary)	Wright et al. (1987b)
18	Metachromin A (Fig.9.32) Metachromin B (Fig. 9.33)	*Hippospongia cf. metachromia*	Toxic to L1210 cells	Ishibashi et al. (1988)
			Showed coronary vasodilating effects and inhibited potassium chloride-induced contraction of the rabbit isolated coronary artery	
19	Avarol (Fig. 9.34)	*Dysidea avara*	Interferes with the mitotic processes, thus preventing telophase formation	Mueller et al. (1985)
20	Puupehenone (Fig. 9.35) (Molecular formula – $C_{21}H_{28}O_3$)	*Strongylophora hartmani*	Inhibits the growth of a number of tumor cell lines such as P388, A549 human lung, HCT-8 human colon and MCF-7 human mammary	Kohmoto et al. (1987a)
21	Amorphane sesquiterpenes (Figs. 9.36)	*Axinyssa fenestratus*	Anthelmintic activity	Alvi et al. (1991)
22	Axisonitrile-3 (Fig. 9.37)	*Topsentia* sp.	- Do -	Alvi et al. (1991)
23	Manoalide (Fig. 9.38)	*Luffariella variabilis*	Irreversibly inhibits PLA2	Glaser and Jacobs (1986), Jacobson et al. (1990)
			Inhibits arachidonic acid release	De Vries et al. (1988)
			Inhibits 5-lipoxygenase	
24	Luffariellolide (Fig. 9.39) (Molecular formula – $C_{25}H_{38}O_3$)	*- Do -*	Anti-inflammatory activity	Albizati et al. (1987)
			Partially reversible PLA2 inhibitor	
25	Variabilin (Fig. 9.40)	*Ircinia* sp.	Cytotoxic to host BSC cells in an antiviral assay	Barrow et al. (1988)

(continued)

Table 9.1 (continued)

S. No	Compound with structure	Source	Bioactivity	Reference
26	Okinonellin A (Fig. 9.41) Okinonellin B (Fig. 9.42)	*Spongionella* sp.	Inhibit division of fertilized starfish eggs	Kato et al. (1986)
27	Phyllofoliaspongin (Fig. 9.43)	*Phyllospongia foliascens*	Inhibited P388 cell growth.	Kitagawa et al. (1989)
			Showed anti- thrombocytic inhibitory effect on ADP-induced and collagen-induced aggregation of rabbit platelets in vitro	
28	Heteronemin (Fig. 9.44) 12-episcalarin (Fig. 9.45)	*Hyrtios erecta*	In vitro anthelmintic activity	Kazlauskas et al. (1976), Kashman and Rudi (1977), Cimino et al. (1977), Crews and Bescansa (1986)
29	Isocyanine (Fig. 9.46)	*Bubaris*	Antitumor, antiviral and antifungal activities	Wright et al. (1988)
30	Kalihinol Y (Fig. 9.47) Kalihinol J (Fig. 9.48)	*Acanthella cavernosa*	Potent in vitro anthelmintic activity	Omar et al. (1988)
31	Spongiadiol (Fig. 9.49)	*Spongia* sp.	Antiviral activity	Kohmoto et al. (1987a), (1987b)
32	Reiswigin A (R = CH CH $(CH_3)_2$) (Fig. 9.50) Reiswigin B (R = −CH = $C(CH_3)_2$)	*Epipolasis reiswigi*	Antiviral activity	Kashman et al. (1989b)
			Inhibiting HSV-1 completely and A59 virus partially	
33	Pouoside A (Fig. 9.51)	*Asteropus* sp.,	Inhibited P388 cell growth	Ksebati et al. (1988), (1989)
34	Penasterol (Fig. 9.52)	*Penares* sp.	Active against L1210 cells	Cheng et al. (1988a)
35	Sarasinoside A1 (Fig. 9.53)	*Asteropus* sp.	Active against P388 cells	Schmitz et al. (1988)
36	Eryloside A (Fig. 9.54)	*Erylus lendenfeldi*	Showed cytotoxic activity against P388 and antifungal activity	Carmely et al. (1989a)
37	2,6 – dibromo – 4 – acetamido – 4 – hydroxycyclohexadienone (Fig.9.55)	*Verongia cauliformis*	Antibacterial activity	Sharma and Burkholder (1967)
38	Aerothionin (Fig. 9.56)	*Aplysia aerophoba* and *Verongia thiona*	Antibiotic activity	Encarnacion et al. (2000); Thoms et al. (2004)
39	Bastadin series of cyclic amides (Fig. 9.57)	*Iarthella basta*	Inhibit P388 cell growth	Pordesimo and Schmitz (1990)
40	Mycalamide A (R = 4) and B (R = Me) (Fig. 9.58)	*Mycale* sp.	Showed antiviral and cytotoxic activity	Perry et al. (1988a); (1990)
41	Calyculin A (R_1 = CN, R_2 – R_3 = H); Calyculin B (R_1 = R_3 = H, R_2 = CN); Calyculin C (R_1 = CN, R_2 = H, R_3 = CH_3); Calyculin D (R_1 = H, R_2 = CN, R_3 = CH_3) (Fig. 9.59)	*Discodermia calyx*	Active against L1210 cells	Kato et al. (1986a, b), (1988b)

(continued)

Table 9.1 (continued)

S. No	Compound with structure	Source	Bioactivity	Reference
			Inhibited cell division of both starfish and sea urchin eggs	Kato et al. (1988a, b)
			Exhibited in vivo activity against Erlich and P388 leukemia in mice (Calyculin A)	
			Inhibited uptake of [^{3H}] thymidine, [^{3H}] uridine and [^{3H}] leucine in L1210 murine leukemia cells (Calyculin A)	
42	Alkaloid (Fig. 9.60)	*Teichaxinella morchella* and *Ptilocaulis walpersi*	Showed mild cytotoxicity to L1210 cells	Wright and Thompson (1987)
43	Girolline (Fig. 9.61)	*Pseudaxinyssa cantharella*	Active against P388	Ahond et al. (1989)
44	Pyronaamide (Fig. 9.62)	*Leucetta*	Toxic to KB cells	Akee et al. (1990)
45	Series of 2-amino imidazole alkaloids Naamidines (e.g. Fig. 9.63)	*Leucetia chagosensis*	Showed cytotoxicity against P388 cells	Carmely et al. (1989b)
46	Horbindole A (R = Me); Horbindole B (R = Et); Horbindole C (R = CH = CH-Et) (Fig. 9.64)	*Axinella* sp	Showed cytotoxicity against KB and found to have fish anti- feedant activity	Herb et al. (1990)
47	Dragmacidin (Fig. 9.65)	*Dragmacidian* sp.	Toxic to P388 cells and also to A549 human-8 human colon and MDAMB human mammary cells	Kohmoto et al. (1988)
48	Dragmacidon A (Fig. 9.66)	*Dragmacidian* sp.	Showed cytotoxicity against L1210 cells	Morris and Andersen (1989)
49	Fascaplysin (Fig. 9.67)	*Fascaplysinopsis* sp.,	killed L1210 cells (LD50 0.2 ug/ml) and also showed antibiotic activity	Roll et al. (1988)
50	Eudistomin K (Fig. 9.68)	*Riterella sigillinoides*	Described in a patent as being "very effective in inhibiting growth of L1210, P388, A549 and HCT-8 cells at varying concentrations"	Blunt et al. (1988)
51	Manzamine A (Fig. 9.69)	*Haliclona* sp.	Active against P388 cells in vitro	Sakai et al. (1986)
52	Theonelladins A (R = H); Theonelladin B (R = CH_3-D); Theonelladin C (R = H); Theonelladin D (R = CH_3) (Fig. 9.70)	*Theonella swinhoei*	Showed the cytotoxicity against L1210 cell lines and KB cells	Kobayashi et al. (1989)
			Reported to be 20 times more than caffeine in causing release of Ca^{2+} from sarcoplasmic reticulum	

(continued)

Table 9.1 (continued)

S. No	Compound with structure	Source	Bioactivity	Reference
53	Niphatyne A (Fig. 9.71)	*Niphates* sp.	Cytotoxic to P388 cells	Quinoa and Crews (1987)
	Niphatyne B (Fig. 9.72)			
54	5-(methoxycarbonyl) tubercidin ($R_1 = CO_2Me$, R_2 = ribose) and Toyocamycin ($R_1 = CN$, R_2 = ribose) (Fig. 9.73)	*Jaspis*	Showed activity against L1210	Zabriskie and Ireland (1989)
			In vivo activity against L1210, increasing lifetimes by up to 39 % (5-(methoxycarbonyl) tubercidin)	
55	Arabinosides (Fig. 9.74)	*Cryptotethia crypta*	Antiviral and antitumor activities	De Clercq et al. (1977), Gosselin et al. (1986)
	Ara-A Ara-C Ara-T Ara-U			
56	Doridosine (Fig. 9.75)	*Tedania digitala*	Causes reduced arterial pressure and reduced heart rate in mammalians in a manner that is qualitatively similar to adenosine	Quinu et al. (1980)
			Acts as muscle relaxant and showed hypothermic activity	
57	1-Methylisoguanosine (Fig. 9.76)	*Tedania digitata*	Shows potent muscle relaxant, blood pressure lowering, cardiovascular and anti-inflammatory activity	Jamieson and Davis (1980), Bartlett et al. (1981)
58	Aaptamine ($R_1 = CH_3$, R_2 = H) (Fig. 9.77) and some of its derivatives (R_1 = H, R_2 = H; 163. R_1 = H, $R_2 = CH_3$)	*Suberites* sp	Reported to have some in vitro and in vivo cell inhibitory activity when tested for antitumor activity against Ehrlich ascites tumor in mice	Fedoreov et al. (1988)
59	Isobatzellines (Fig. 9.78)	*Batzella* sp.	Showed antifungal activity against *C. albicans*	Sun et al. (1990)
60	Renierol (Fig. 9.79)	*Xestospongia caycedoi*	Inhibited the growth of L1210 cells	McKee and Ireland (1987)
61	Indolizidine stellenamide A (Fig. 9.80)	*Stella* sp.	Antifungal activity and also inhibited K562 epithelium cell growth	Hirota et al. (1990b)
62	Discorhabdin A (Fig. 9.81) Discorhabdin – B (Fig. 9.82)	*Latrunculia brevis* and *Prianos* sp.	Reported the cytotoxicity against P388 cells	Perry et al. (1988b, c)
	Discorhabdin – C (Fig. 9.83) Discorhabdin – D (Fig. 9.84)			
63	Prianosin A (Fig. 9.85) Prianosin B (Fig. 9.86)	*Prianos melanos*	Active against L5178Y cells and KB cells	Kobayashi et al. (1987)
	Prianosin C (R = OH) and D (R = H) (Fig. 9.87)			
64	Dysemenin (Fig. 9.88)	*Dysidea herbacea*	Inhibited iodide transfer in thyroid cells	Van Sande et al. (1990)

(continued)

Table 9.1 (continued)

S. No	Compound with structure	Source	Bioactivity	Reference
65	Amphimedine (Fig. 9.89)	*Amphimedon* sp.	Active against P388 in vitro	Schmitz et al. (1983)
66	Dercitin (Fig. 9.90)	*Descitus* sp.	Showed in vitro and in vivo activity in the P388 model	Gunawardana et al. (1988)
			Immunosuppressive and antiviral activity	Burres et al. (1989)
67	Plakinidine A (R = H); Plakinidine B (R = CH_3); Plakinidine C (R = HΔ^9) (Fig. 9.91)	*Plakortis* sp.	Active against L1210 cells	West et al. (1990)
			Inhibited reverse transcriptase activity (Plakinidine A).	Inman et al. (1990)
68	Latrunculin A (Fig.9.92)	*Spongia mycofijiensis*	Showed excellent in vitro activity at 50ug/ml against *N. brasiliensis*	Kashman et al. (1980)
69	Ptilomycalin A ($R_1 = R_2 = H$, n = 13)	*Ptilocaulis spiculifer* and *Hemimycale* sp.	Activity against HSV and antitumor and antifungal activities (Ptilomycalin A)	Kashman et al. (1989a)
	Crambescidins (Crambescidin 816: $R_1 = R_2 = OH$, n = 13; Crambescidin 830: $R_1 = R_2 = OH$, n = 14; Crambescidin 844: $R_1 = R_2 = OH$, n = 15; Crambescidin 800: $R_1 = H$, $R_2 = OH$, n = 13 (Fig. 9.93)		Activity against HSV-1 and exhibited 98 % inhibition of L1210 cell growth (Crambescidins)	
70	Sceptrin (Fig. 9.94), Ageliferin (Fig. 9.95) and oxysceptrin (Fig. 9.96)	*Agelas conifer*	Active against HSV-1 and VSV Sceptrin and Ageliferin)	Keifer et al. (1991)
			Less active Oxysceptrin	
71	Acarnidine l a (R = CO $(CH_2)_{10}CH_3$); Acarnidine – 1 b (R = CO $(CH_2)_3CH = CH (CH_2)_5CH_3$(z)); Acarnidine – 1 c (R = $COC_{13}H_{21}$) (Figs. 9.97 and 9.98)	*Acarnus erithacus*	Antiviral property	Carter and Rinehurt (1978a)
72	Discobahamin A (Fig. 9.99)	*Discodermia* sp.	Antifungal activity	
73	Papuamides A and B (Fig. 9.100)	*Theonella* sp.	Inhibited the infection of human T-lymphoblastoid cells	Ford et al. (1999)
74	Microspinosamide (Fig. 9.101)	*Sidonops microspinosa*	Anti-HIV activity	Rashid et al. (2001)
75	Keramamide (Fig. 9.102 and 9.103),	*Theonella* sp.	Reported cytotoxic effect against P388 murine leukemia cells	Fusetani et al. (1991)
76	Cyclotheonamide (Fig. 9.104)	*Theonella* sp.	Reported as a potent antithrombin cyclic peptide which strongly inhibited various proteinases, particularly thrombin	Fusetani et al. (1990)

(continued)

Table 9.1 (continued)

S. No	Compound with structure	Source	Bioactivity	Reference
77	Theonellamide F (Fig. 9.105)	*Theonella* sp.	Showed activity against L1210 and P388 cells	Matsunaga et al. (1989)
78	Hymenistatin 1 (Fig. 9.106)	*Hymeniacidon* sp.,	Showed both in vitro and in vivo activity against P388 murine leukemia cells	Petit and Zeghloul (1990)
79	Microsclerodermin A (R = OH)-Microsclerodermin B (R = H) (Fig. 9.107)	*Theonella* sp. and *Microscleroderma* sp.	Antifungal activity	Schmidt and Faulkner (1998)
80	Theonegramide (Fig. 9.108)	*Theonella* sp. and *Microscleroderma* sp.	Antifungal activity	Bewley and Faulkner (1994)

Fig. 9.1 Dysidazirine

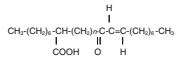


Fig. 9.2 Ficulinic acid A: n = 7

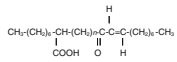


Fig. 9.3 Ficulinic acid B: n = 9

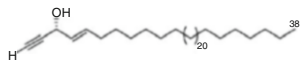


Fig. 9.4 Monoacetylenic alcohols

Fig. 9.5 Duryne (Molecular formula – $C_30H_{48}O_2$)

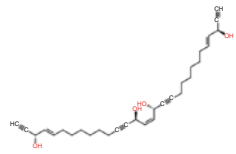


Fig. 9.6 Petrosynol

Cape Verde, Ionian Sea, Levantine Sea, Mediterranean Sea, North Atlantic, Tunisian Plateau/Gulf of Sidra, West Africa and Western Mediterranean.

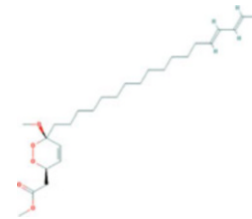


Fig. 9.7 Xestin A

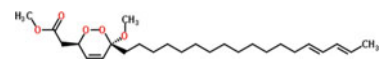


Fig. 9.8 Xestin B

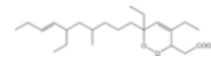


Fig. 9.9 Cyclic peroxide acids

9.2.1.3 Aliphatic Ester Peroxides

Xestins A and B (Figs. 9.7 and 9.8), isolated from *Xestospongia* sp., were found toxic against P388 cells (ID_{50} 0.3 and 3 μg/ml, respectively) (Quinoa et al. 1986). *P. lita* is maroon to pink, with the opening of the barrel pale white. In the intertidal zones, this species ranges from 10 to 20 cm in diameter, and are about 10–20 cm tall. This species is found in the Philippines, Australia, western and central Indian Ocean, Indonesia, Malaya, and New Caledonia.

The cyclic peroxide acids (Fig. 9.9) isolated from the sponge *Plakortis angulospiculatis,* which are much more highly branched were collected in Venezuela, and the esters derived from

the sponge were found inhibiting the growth of P388 cells (IC50 0.2–0.9 μg/ml) (Gunasekera et al. 1990b).

9.2.1.4 Complex Polyketides

The polyether carboxylic acids acanthifolicin (Fig. 9.10) and okadaic acid (Fig. 9.11) were initially isolated from sponges – acanthifolicin from the Caribbean sponge *Pandaros acanthifolium* and okadaic acid from *Halichondria okadai* collected in Japan and also from *H. melaodocia* from the Florida Keys, reported strong cytotoxic activity (Schmitz et al. 1981; Tachibana et al. 1981). The ED50 value of 0.0002 and 0.0017 μg/ml against P388 cells were reported by acanthifolicin and okadaic acid, respectively.

The sponge, *P. acanthifolium* (Duchassaing and Michelotti 1864) is erect, dark bushy with flattened branches. Branches up to 25 cm long, 4 cm wide. Oscules inconspicuous. It is a reef dweller and it is found distributed in Florida and the Caribbean.

The polyketide natural product, discodermolide (Fig. 9.12), was isolated from the deep-sea marine sponge *Discodermia dissoluta* in 1990 by Gunasekara et al. (1990a). It was found to be a potent inhibitor of tumor cell growth in several MDR cancer cell lines. Further, it was identified as one of the most potent natural promoters of tubulin assembly.

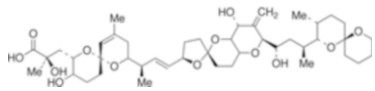


Fig. 9.10 Acanthifolicin

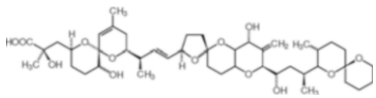


Fig. 9.11 Okadaic acid

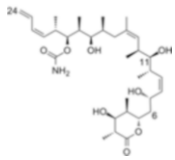


Fig. 9.12 Discodermolide

9.2.1.5 Macrolides

9.2.1.5.1 Assorted Macrolides

Fijianolides A and B (Figs. 9.13 and 9.14) were isolated from the Vanuatuan sponge *Spongin mycofijiensis* (= *Leiosella lavis*) (Quinoa et al. 1988). This sponge is massive, lobate, or tubular, sometimes with a short stalk (2–3 cm). The size varies from 3 to 20 cm in height, and 2–10 cm in diameter. The surface is microconulose, and the texture is compressible and flexible. This species is dark brown/black, in colour, externally and tan inside and is generally found in sheltered reef habitats, under ledges or in caves. It is fairly rare despite its broad range of distribution in the South and Indo Pacific.

Fijianolide A reported the IC50 of 9 μg/ml against P388 and 11 μg/ml vs HT-29 human colon tumor cells. When the diacetate of fijianolide B was tested against the same cells, it reported the IC50 as 6 μg/ml vs P388 and 0.5 μg/ml vs HT-29.

The three other tris-isoxazole containing macrolides, mycalolides A–C (Figs. 9.15, 9.16 and 9.17), were isolated from *Mycale*. Although the above were highly cytotoxic (IC50 0.0005–0.001 μg/ml vs. B16), they have not shown promising results in vivo (Fusetani et al. 1988).

Apart from okadaic acid, the Japanese sponge *H. kadai* was a good source of a group of very

Fig. 9.13 Fijianolides A

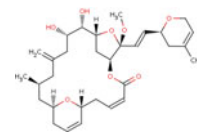
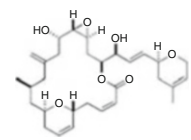


Fig. 9.14 Fijianolides B



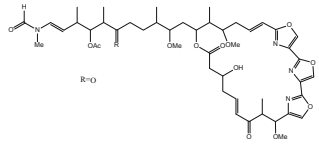


Fig. 9.15 Mycalolides A

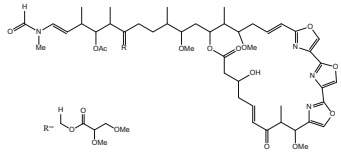


Fig. 9.16 Mycalolides B

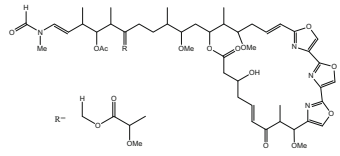


Fig. 9.17 Mycalolides C

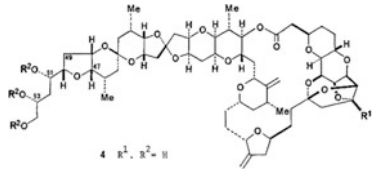


Fig. 9.18 Halichondrins B (R = H)

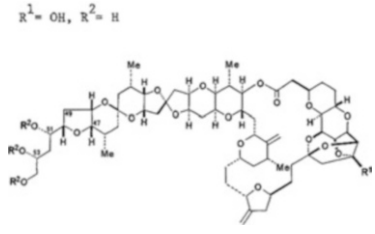


Fig. 9.19 Halichondrins C (R = OH)

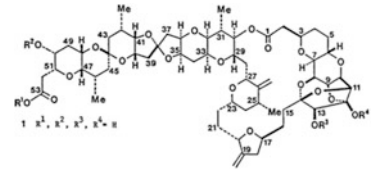


Fig. 9.20 Norhalichondrins A

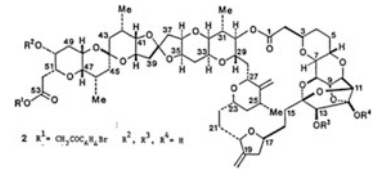


Fig. 9.21 Norhalichondrins B

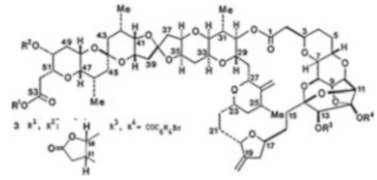


Fig. 9.22 Norhalichondrins C

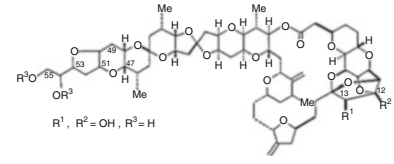


Fig. 9.23 Homohalichondrins A ($R_1 = R_2 = OH$, $R_3 = H$)

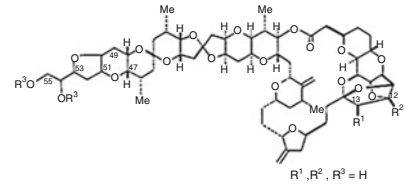


Fig. 9.24 Homohalichondrins B ($R_1 = R_2 = R_3 = H$)

complex and biologically active macrolides, halichondrins B (Fig. 9.18) and C (Fig. 9.19); norhalichondrins A (Fig. 9.20), B (Fig. 9.21), and C (Fig. 9.22) and homohalichondrins A (Fig. 9.23), B (Fig. 9.24), and C (Fig. 9.25) (Hirata and Uemura 1986). The above macrolides showed the following in vitro activity against B16 melanoma cell lines: norhalichondrin A – 0.0052 μg/ml; halichondrin

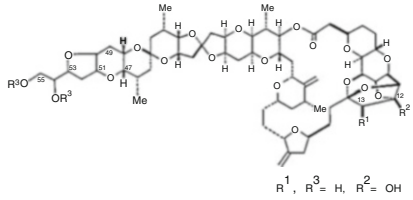


Fig. 9.25 Homohalichondrins C ($R_1 = R_3 = H$, $R_2 = OH$)

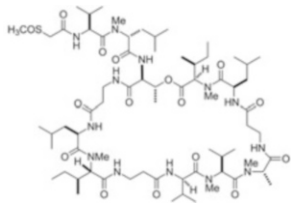


Fig. 9.26 Misakinolide A

B – 0.000093 μg/ml; homohalichondrin A – 0.00026 μg/ml; halichondrin C – 0.00035 μg/ml and homohalichondrin B – 0.0001 μg/ml. Halichondrin B showed good in vivo activity against B16 melanoma in mice (T/C values of 203–244 %, depending on dose (5–20 μg/kg) and regimen), against P388 leukemia in mice (T/C 323 % @ 10 μg/kg), and against L1210 in mice (T/C 207–375 % with doses of 50–100 μg/kg under various injection schedules). From the results, it was concluded that it is important for antitumor activity that the tricyclic ring be relatively lipophilic and that the terminal group have two or more hydroxyls, but not a carboxylate. *Halichondria* are massive, amorphous sponges with clearly separated inner and outer skeletons consisting of bundles of spicules arranged in a seemingly random pattern.

Misakinolide A (Fig. 9.26) isolated from *Theonella* sp. was collected in Okinawas (Sakai et al. 1986), and it showed in vitro antiviral and antifungal activities. *Theonella* sp. is a coral reef sponge (*Theonella swinhoei*), found distributed in the Red Sea and Indian Ocean.

The macrolide latrunculin A (Fig. 9.27) was isolated from the red sea sponge *Latrunculia magnifica*. It binds and stabilizes the globular G-actin in a 1:1 complex, preventing the

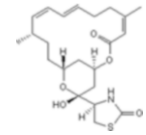


Fig. 9.27 Latrunculin A

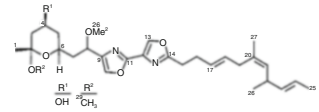


Fig. 9.28 Hennoxazoles A ($R_1 = OH$, $R_2 = CH_3$)

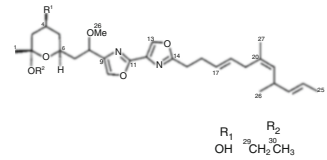


Fig. 9.29 Hennoxazoles B ($R_1 = OH$, $R_2 = CH_2\,CH_3$)

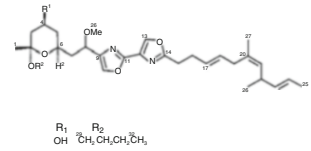


Fig. 9.30 Hennoxazoles C ($R_1 = OH$, $R_2 = CH_2\,CH_2\,CH_2\,CH_3$)

conversion of globular (monomeric) G-actin into filamentous (polymeric) F-actin, disturbing microfilament organization in the cell. Latruculin A affects normal functioning of the cell by disrupting the polymerization of G-actin and microfilament organization which is essential for the cellular mechanical processes including motility and cytoskeleton scaffolding (Groweiss et al. 1980).

9.2.1.6 Miscellaneous

The sponge, *Polyfibrospongia* sp., collected on the island of Miyako in Okinawa was the source for hennoxazoles A–D (Figs. 9.28, 9.29 and 9.30) (Ichiba et al. 1991). Apart from displaying

analgesic activity, hennoxazole A, the major component (0.01 % of wet weight) showed strong activity against HSV-1 (IC50 0.6 μg/ml).

9.3 Terpenes

9.3.1 Sesquiterpenes

Curcuphenol (Fig. 9.31) extracted from the sponge *Didiscus flavus* collected in both shallow and deep waters in the Bahamas and Belize was found inhibiting the growth of several cell lines [IC50 7 μg/ml vs. P388; MIC for human cell lines: A549 (lung) 10 μg/ml; HCT-8 (colon) 0.1 μg/ml; MDAMB (mammary) 0.1 μg/ml] (Wright et al. 1987b).

Metachromins A (Fig. 9.32) and B (Fig. 9.33), isolated from the sponge *Hippospongia cf. metachromia*, were reported to be toxic to L1210 cells (IC50 2.4 and 1.62 μg/ml, respectively) (Ishibashi et al. 1988). Further they also showed coronary vasodilating effects and inhibited potassium chloride-induced contraction of the rabbit isolated coronary artery.

Avarol (Fig. 9.34) from the sponge *Dysidea avara* interferes with the mitotic processes, thus preventing telophase formation which may be due to changes of the intracellular pools and/or alterations of the permeability properties of the cell membranes for the precursors (Mueller et al. 1985).

Fig. 9.31 Curcuphenol

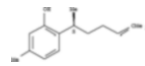


Fig. 9.32 Metachromin A

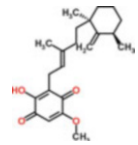


Fig. 9.33 Metachromin B

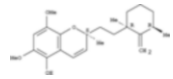


Fig. 9.34 Avarol

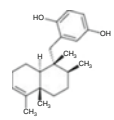


Fig. 9.35 Puupehenone (Molecular formula – $C_{21}H_{28}O_3$)

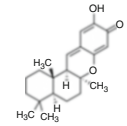


Fig. 9.36 Amorphane sesquiterpenes

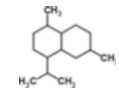
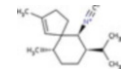


Fig. 9.37 Axisonitrile-3



Puupehenone (Fig. 9.35) was isolated from a deep water sponge, *Strongylophora hartmani* by Kohmoto et al. (1987a). It was found to inhibit the growth of a number of tumour cell lines (IC50; P388, 1 μg/ml; A549 human lung, 0.1–1 μg/ml; HCT-8 human colon, 1–10 μg/ml; MCF-7 human mammary, 0.1–1 μg/ml). Besides the above, it also showed very modest in vivo effects on p388 cell lines (19 % increase in life-time @ 25 mg/kg for 9 days).

Isonitrile, isothiocyanate, and related functionalized terpenes are characteristic metabolites of sponges belonging to the order Halichondida. Four amorphane sesquiterpenes (Fig. 9.36) were isolated from the Fijian sponge *Axinyssa fenestratus* (Alvi et al. 1991) and tested for their anthelmintic activity.

Another sesquiterpene, axisonitrile-3 (Fig. 9.37) (D' Blassio et al. 1976) extracted from *Topsentia* sp. from Thailand (Alvi et al. 1991). Though it reported superior anthelmintic activity in vitro at 50 μg/ml, it was not active in vivo.

9.3.2 Sesterterpenes

A nonsteroidal sesterterpene, manoalide (Fig. 9.38), isolated from the sponge *Luffariella*

variabilis (De Silva and Scheuer 1980) has emerged as a potent tool for studying inflammation. It irreversibly inhibited PLA2 (Glaser and Jacobs 1986; Jacobson et al. 1990).

In addition to inhibiting PLA2, manoalide inhibited 5-lipoxygenase (de Vries et al. 1988), leading to speculation that its anti-inflammatory activity of manoalide was attributed to its inhibitory effect on Ca^{2+} channels (Wheeler et al. 1988). Interestingly at low concentrations, manoalide inhibited calcium channels with no effect on phosphor-inositide metabolism. The ability of manoalide to dissect these two components of the inflammation process may prove to be its most useful attribute in studying the role of Ca^{2+} signaling in inflammation and proliferation (Barzaghi et al. 1989).

Another analog of manoalide, luffariellolide (Fig. 9.39), isolated from the same organism, also exhibited anti-inflammatory activity, but it was slightly less potent than manoalide and was a partially reversible PLA2 inhibitor (Albizati et al. 1987).

A number of cytotoxic furanosesterpenes have been obtained from a variety of sponges. Variabilin (Fig. 9.40) and the related sesterpene tetronic acids from a Caribbean *Ircinia* sp. sponge were all described as being cytotoxic to host BSC cells at 2 μg/ml in an antiviral assay (Barrow et al. 1988).

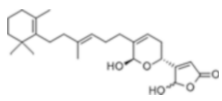


Fig. 9.38 Manoalide

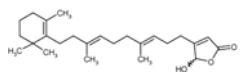


Fig. 9.39 Luffariellolide (Molecular formula – $C_{25}H_{38}O_3$)

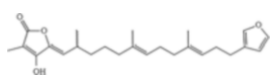


Fig. 9.40 Variabilin

Okinonellins A and B (Figs. 9.41 and 9.42), from *Spongionella* sp., were reported to inhibit division of fertilized starfish eggs at 5 μg/ml (Kato et al. 1986a).

The bishomo scalarene sesterpene phyllofoliaspongin (Fig. 9.43) from *Phyllospongia foliascens* inhibited P388 cell growth at 5 μg/ml (Kitagawa et al. 1989). Another activity noted for this compound was its antithrombocytic inhibitory effect on ADP-induced and collagen-induced aggregation of rabbit platelets in vitro.

Sesterterpenes extracted from the sponge *Hyrtios erecta* showed in vitro anthelmintic activity. Heteronemin (Fig. 9.44) (Kazlauskas et al. 1976; Kashman and Rudi 1977) showed in vitro activity with varying results. Another compound 12-episcalarin (Fig. 9.45) (Cimino

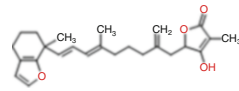


Fig. 9.41 Okinonellin A

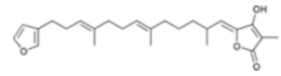


Fig. 9.42 Okinonellin B

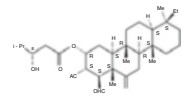


Fig. 9.43 Phyllofoliaspongin

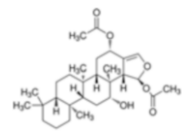


Fig. 9.44 Heteronemin

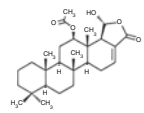


Fig. 9.45 12-episcalarin

et al. 1977; Crews and Bescansa 1986) exhibited moderate in vitro anthelmintic activity.

9.3.3 Sesquiterpenoid Isocyanide

Wright et al. (1988) reported the antitumor, antiviral, and antifungal activities for a sesquiterpenoid isocyanine (Fig. 9.46) isolated from the marine sponge *Bubaris* sp.. At 20 μg/0.5 ml, the A59 coronavirus in mouse liver cells was partially inhibited, indicating that the sesquiterpenoid compound is only weakly virucidal.

9.3.4 Diterpenes

Among the various kalihinols extracted from the sponge *Acanthella cavernosa*, Kalihinols Y (Fig. 9.47) and J (Fig. 9.48) reported potent in vitro anthelmintic activity (Chang et al. 1987; Omar et al. 1988; Alvi et al. 1991).

Kohmoto et al. (1987b) isolated spongiadiol (Fig. 9.49), epispongiadiol ($R_1 + R_2 = O$, $R_3 = OH$, $R_4 = H$), and the new isospongiadiol [2∞, 19-dihydroxyspongia – 13(16), 14-dien-3-one] ($R_1 = H$, $R_2 = OH$, $R_3 + R_4 = O$) from the deep-water Caribbean sponge *Spongia* sp.. Both antiviral activity and cytotoxicity were reported for all the three spongiodiols. In vitro assays against HSV-1 revealed a spectrum of activities ranging from the very active spongiadiol (IC50 = 0.25 μg/ml) to the modestly active epispongiadiol (IC50 = 12.5 μg/ml), with isospongiadiol exhibiting intermediate activity (IC50 = 2.0 μg/ml). Further the studies on antitumour and antiviral activities of these three furanoditerpenoids, spongidiol and isospongiadiol gave 100 % inhibition on HSV-1 plaque formation at 20 and 0.5 μg/(6 mm disk), and epispongiadiol gave partial inhibition at 12.5 μg/ml (Kohmoto et al. 1987b).

Kashman et al. (1987) isolated reiswigins A ($R = CH\ CH(CH_3)_2$) and B ($R = -CH = C(CH_3)_2$) (Fig. 9.50), bioactive terpenes from the sponge *Epipolasis reiswigi*. Both reiswigins A and B were found reporting the inhibition of HSV-1 completely at 2 μg and A59 virus partially at 20 μg (+ +). Particularly reiswigin A completely inhibited VSV at 2 μg without accompanying cytotoxicity (Kashman et al. 1989a).

9.3.5 Triterpenes

Pouoside A (Fig. 9.51) from *Asteropus* sp., collected in Truk Lagoon, inhibited P388 cell growth with an ED50 of 1.5 μg/ml (Ksebati et al. 1988, 1989). The Okinawan sponge *Penares* sp. was the source of penasterol (Fig. 9.52), which was active against L1210

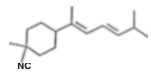


Fig. 9.46 Isocyanine

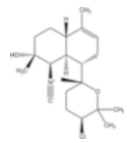


Fig. 9.47 Kalihinol Y

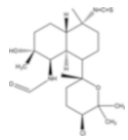


Fig. 9.48 Kalihinol J

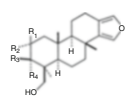


Fig. 9.49 Spongiadiol

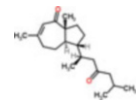


Fig. 9.50 Reiswigin A

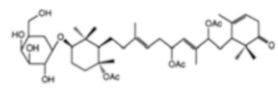


Fig. 9.51 Pouoside A

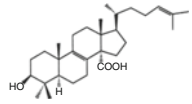


Fig. 9.52 Penasterol

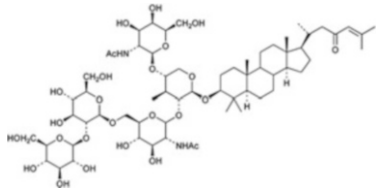


Fig. 9.53 Sarasinoside A1

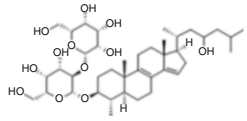


Fig. 9.54 Eryloside A

cells with an ED50 of 3.6 μg/ml (Cheng et al. 1988a).

9.3.6 Sterols

Several polyoxygenated sterols and glycosylated sterols showed cytotoxicity. Sarasinoside A1 (Fig. 9.53), a saponin containing amino sugar, exhibited an ED50 of 2.8 μg/ml against P388 cells. This saponin was isolated by Schmitz et al. (1988) from *Asteropus* sp. from Truk and Guam Islands.

Eryloside A (Fig. 9.54) from the red sea sponge *Erylus lendenfeldi* reported to have both cytotoxic (IC50 4.2 μg/ml vs. P388) and antifungal activity against *Candida albicans* (MIC 15.6 μg/ml) (Carmely et al. 1989a).

9.4 Brominated Compounds

The compound isolated from the marine sponge *Verongia cauliformis* (Sharma and Burkholder 1967) has been characterized as 2,6-dibromo-4-acetamido-4-hydroxycyclohexadienone

Fig. 9.55 2,6-dibromo-4-acetamido-4-hydroxycyclohexadienone

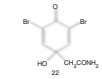
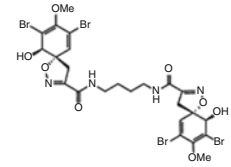


Fig. 9.56 Aerothionin



(Fig. 9.55) showed antibacterial activity (Sharma et al. 1970).

Aerothionin (Fig. 9.56) having a spirocyclohexadienylisoxazole skeleton was isolated from two sponges namely *Aplysia aerophoba* and *Verongia thiona* showed antibiotic activity (Encarnacion et al. 2000; Thoms et al. 2004).

9.5 Nitrogen-Containing Compounds

9.5.1 Tyrosine-Based Metabolites

Several members of the bastadin series of cyclic amides (Figs. 9.57) isolated from the sponge *Iarthella basta* were found to inhibit P388 cell growth (ED50 2–4 μg/ml) (Pordesimo and Schmitz 1990).

9.5.2 Other Amines

Mycalamides A (R = 4) and B (R = Me) (Fig. 9.58) obtained from a New Zealand sponge *Mycale* sp. (Perry et al. 1988a, 1990) showed antiviral and cytotoxic activity.

Calyculins A–D (Fig. 9.59) are unusual amines isolated from *Discodermia calyx* (Kato et al. 1986b, c, 1988a, b) that showed the IC50 value of 7.4×10^{-4}, 8.8×10^{-4}, 8.6×10^{-4}, and 1.5×10^{-3} μg/ml respectively against L1210 cells. They also inhibited cell division of both starfish and sea urchin eggs in the 10^{-2} μg/ml range. Further, the calyculin A (Fig. 9.59) exhibited in vivo activity against Erlich and P388 leukemia in mice (T/C 245 and 144 %,

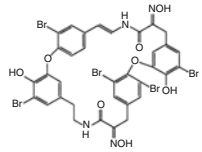


Fig. 9.57 Bastadin series of cyclic amides

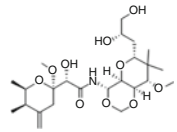


Fig. 9.58 Mycalamide A (R = 4) and B (R = Me)

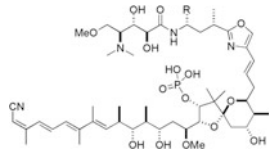


Fig. 9.59 Calyculin A

respectively) apart from inhibiting the uptake of [^{3H}] thymidine, [^{3H}] uridine and [^{3H}] leucine in L1210 murine leukemia cells (Kato et al. 1988a, b).

9.5.3 Pyrroles

The alkaloid 300 (Fig. 9.60) isolated from the sponges *Teichaxinella morchella* and *Ptilocaulis walpersi* reported mild cytotoxicity to L1210 cells (IC50 19 μg/ml) (Wright and Thompson 1987).

9.5.4 Imidazoles

The girolline (Fig. 9.61) extracted from the sponge *Pseudaxinyssa cantharella* was found active against P388 at 0.001–1 μg/ml, and this activity was confirmed in vivo also in mice models (P388 at 1 mg/kg doses (Ahond et al. 1989).

Pyronaamide (Fig. 9.62), obtained from *Leucetta* sponge from Saipan and Guam, was toxic to KB cells (MIC 5 μg/ml) (Akee et al. 1990). A series of 2-amino imidazole

Fig. 9.60 Alkaloid

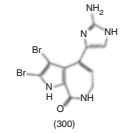


Fig. 9.61 Girolline

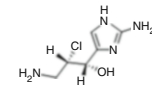


Fig. 9.62 Pyronaamide

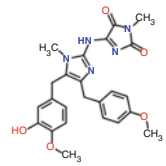


Fig. 9.63 Series of 2-amino imidazole alkaloids Naamidines

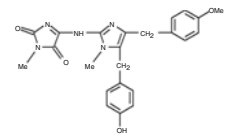
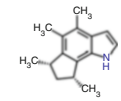


Fig. 9.64 Horbindole A (R = Me); Horbindole B (R = Et); Horbindole C (R = CH = CH-Et)



alkaloids called naamidines (e.g. Fig. 9.63) were obtained by Carmely et al. (1989b) from the marine sponge *Leucetia chagosensis* that showed cytotoxicity at 2–10 μg/ml against P388 cells.

9.5.5 Indoles

Horbindoles A–C (Fig. 9.64) extracted from *Axinella* sp. from western Australia showed cytotoxicity (KB; MIC 5, >10, and 10 μg/ml, respectively) and were also found to have fish antifeedant activity (Herb et al. 1990).

A deep water sponge, *Dragmacidian* sp. was the source for dragmacidin (Fig. 9.65) that was found to be toxic to P388 cells (IC50 15 μg/ml)

and also to A549 human-8 human colon, and MDAMB human mammary cells, all with IC50 of 1–10 μg/ml (Kohmoto et al. 1988). Morris and Anderson (1990) isolated the closely related dragmacidon A (Fig. 9.66) which showed cytotoxicity against L1210 cells (ED50 10 μg/ml) similar to that of dragmacidin.

An antimicrobial pigment, fascaplysin (Fig. 9.67), obtained from a Fijian sponge, *Fascaplysinopsis* sp., killed L1210 cells (LD50 0.2 μg/ml) and also showed antibiotic activity against four different microorganisms (Roll et al. 1988).

The other group of indoles, eudistomins were initially reported as antiviral agents, but Eudistomin K (Fig. 9.68), obtained from *Riterella sigillinoides*, is described in a patent as being "very effective in inhibiting growth of L1210, P388, A549 and HCT-8 cells at varying concentrations" (Blunt et al. 1988).

Manzamine A, an alkaloid (Fig. 9.69) was reported as its hydrochloride salt from a *Haliclona* sp. of sponge from Okinawa with as IC50 of 0.07 μg/ml against P388 cells in vitro (Sakai et al. 1986b).

Fig. 9.65 Dragmacidin

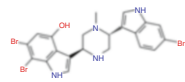


Fig. 9.66 Dragmacidon A

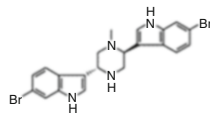


Fig. 9.67 Fascaplysin

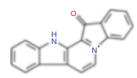


Fig. 9.68 Eudistomin K

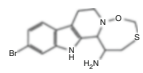
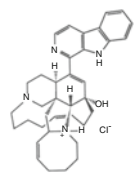


Fig. 9.69 Manzamine A



9.5.6 Pyridines

The pyridine alkaloids theonelladins A–D (Fig. 9.70) isolated from the sponge *Theonella swinhoei* (Kobayashi et al. 1989) showed the cytotoxicities of 4.7, 1.0, 3.6, and 1.6 μg/ml (IC50) against L1210 cell lines and 10.0, 3.6, 10.0, and 5.2 μg/ml (ED50) against KB cells. These compounds were also reported to be 20 times more than caffeine in causing release of Ca^{2+} from sarcoplasmic reticulum.

The related pyridine alkaloids niphatynes A (Fig. 9.71) and B (Fig. 9.72), from *Niphates* sp. collected in Fiji, were found cytotoxic to P388 cells (IC50 0.5 μg/ml) (Quinoa and Crews 1987).

9.5.7 Nucleosides

Nucleosides are vital components of all living cells and are involved in several biological processes.

The two cytotoxic nucleosides 5-(methoxycarbonyl) tubercidin (Fig. 9.73) and toyocamycin (Fig. 9.73) isolated from the Fijian sponge *Jaspis* (Zabriskie and Ireland 1989) showed IC50 values of 0.0026 and 0.27 μg/ml,

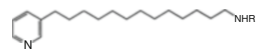


Fig. 9.70 Theonelladins A (R = H); Theonelladin B (R = CH_3-D); Theonelladin C (R = H); Theonelladin D (R = CH_3)

Fig. 9.71 Niphatyne A

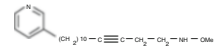


Fig. 9.72 Niphatyne B

respectively, against L1210. The 5-(methoxycarbonyl) tubercidin (Fig. 9.73) also reported earlier to have in vivo activity against L1210, increasing lifetimes by up to 39 %.

The two antiviral and antitumor compounds presently in clinical use as antiviral or antitumor agents (i.e., ara-A, 9-β-D-arabinofuranosyladenine, Fig. 9.74; ara-C, 1-β-D-arabinosylcytosine, Fig. 9.74) were isolated from the marine sponge *Cryptotethia crypta* in the early 1950s (Bergmann and Feeney 1950, 1951). Bergmann collected *C. crypta* in 1945, within next few years he reported the presence of spongothymidine (ara-T, 1-β-D-arabinofuranosylthymidine, Fig. 9.74), spongouridine (ara-U, 1-β-D-arabinofuranosyluracil, Fig. 9.74), and spongosine (1-β-D-arabinofuranosyl-2-methoxyadenine) (Cohen 1966).

The in vitro studies of the arabinosides (Fig. 9.74) showed varying antiviral activity against HSV-1 or HSV-2. Using rabbit kidney and human skin fibroblast cultures, De Clercq et al. (1977) reported MICs (minimum inhibitory concentration) as low as 0.02 and 1 μg/ml for ara-C and ara-A, respectively, against HSV-1; and 200 and 10 μg/ml, respectively, against HSV-2. Besides the above, a significant in vitro activity was also observed for a number of xylofuranonucleosides against three DNA viruses (HSV-1, HSV-2, and vaccinia) and one RNA virus (thinovirus-9) (Gosselin et al. 1986).

Doridosine (Fig. 9.75) (Quinu et al. 1980) was isolated from marine sponge *Tedania digitala* from Australia. It causes reduced arterial pressure and reduced heart rate in mammalians in a manner that is qualitatively similar to adenosine. It also acts as muscle relaxant and showed hypothermic activity.

1-Methylisoguanosine (Fig. 9.76) was isolated from the sponge *Tedania digitata* (Quinu et al. 1980). This nucleoside showed potent muscle relaxant, blood pressure lowering, cardiovascular, and anti-inflammatory activity (Jamieson and Davis 1980).

9.5.8 Quinolines and Isoquinolines

The aaptamine (Fig. 9.77) and some of its derivatives ($R_1 = H$, $R_2 = H$; 163. $R_1 = H$, $R_2 = CH_3$) were isolated from the sponge *Suberites* sp., which were reported to have some in vitro and in vivo cell inhibitory activity when tested for antitumor activity against Ehrlich ascites tumor in mice. A 95 % inhibition was reported in the case of mice inoculated with Ehrlich ascites tumor cells pretreated with the derivative with $R_1 = H$, $R_2 = H$ or $R_1 = H$, and $R_2 = CH_3$ at 25 μg/ml (Fedoreov et al. 1988).

A series of pyrroloquinoline alkaloids namely isobatzellines A–D (Figs. 9.78) were found in

Fig. 9.73 5-(methoxycarbonyl) tubercidin ($R_1 = CO_2Me$, R_2 = ribose) and Toyocamycin ($R_1 = CN$, R_2 = ribose)

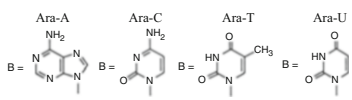


Fig. 9.74 Arabinosides

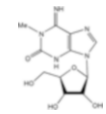


Fig. 9.75 Doridosine

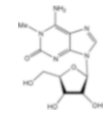


Fig. 9.76 1-Methylisoguanosine

Fig. 9.77 Aaptamine ($R_1 = CH_3$, $R_2 = H$) and some of its derivatives ($R_1 = H$, $R_2 = H$; 163. $R_1 = H$, $R_2 = CH_3$)

extracts of the Caribbean sponge *Batzella* sp. (Sun et al. 1990). These compounds showed antifungal activity against *C. albicans*. Renierol (Fig. 9.79), obtained from the Fijian sponge *Xestospongia caycedoi*, inhibited the growth of L1210 cells (IC50 3 μg/ml) (McKee and Ireland 1987).

9.5.9 Quinilizidines and Indolizidines

The indolizidine stellenamide A (Fig. 9.80) from the sponge *Stella* sp. showed antifungal activity and also inhibited K562 epithelium cell growth (IC50 of 5.1 μg/ml) (Hirota et al. 1990a).

9.5.10 Prianosins/Discorhabdins

The prianosins and discorhabdins, the two closely related sulfur-containing alkaloids, were extracted from *Latrunculia* sp. and *Prianos* sp. The first of these to be reported was discorhabdin C (Fig. 9.83) (Perry et al. 1988a).

Fig. 9.78 Isobatzellines

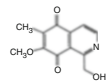


Fig. 9.79 Renierol

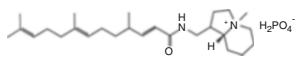


Fig. 9.80 Indolizidine stellenamide A

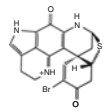


Fig. 9.81 Discorhabdin A

The remaining discorhabdins (Figs. 9.81, 9.82, 9.83 and 9.84 = discorhabdins A,B,C,D, respectively) were described subsequently (Perry et al. 1988a,b). The discorhabdins A–D isolated from the sponges *Latrunculia brevis* and *Prianos* sp. reported the cytotoxicity (IC50) of 0.05, 0.1, 0.03, and 6.0 μg/ml, respectively, against P388 cells. Only discohabdin D (Fig. 9.84) showed any in vivo activity in the P388 model and that was modest (T/C 132 at 20 mg/kg).

Prianosin A (Fig. 9.85), from the Okinawan sponge *Prianos melanos* (Kobayashi et al. 1987), is the nonprotonated form of discorhabdin A (Fig. 9.81). The remaining prianosins B–C (Figs. 9.86 and 9.87) were reported in 1988 (Cheng et al. 1988b). Prianosin D (Fig. 9.87) and discorhabdin D (Fig. 9.84) are a hydroquinone/quinine pair. The prianosins A–D reported the IC50 of 0.037, 2.0, 0.15, and 0.18 μg/ml against L1210 cells, 0.014, 1.8, 0.024 and 0.048 μg/ml against L5178Y cells and 0.073, >5, 0.57

Fig. 9.82 Discorhabdin B

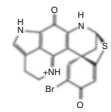


Fig. 9.83 Discorhabdin C

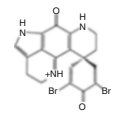


Fig. 9.84 Discorhabdin D

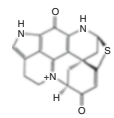


Fig. 9.85 Prianosin A

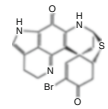
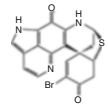


Fig. 9.86 Prianosin B



and 0.46 μg/ml against KB cells respectively. In addition to these activities, the prianosin D (Fig. 9.87), but not the others, induced Ca^{2+} release from sarcoplasmic reticulum, with potency ten times than that of caffeine.

9.5.11 Marine Alkaloids

Dysemenin (Fig. 9.88) a hexachlorinated alkaloid isolated from the sponge *Dysidea herbacea* (Charles et al. 1978, 1980; Biskupiak and Ireland 1984) was found inhibiting iodide transfer in thyroid cells. This molecule might provide insight into the mechanism of the elusive "iodide pump" as it inhibits iodine transport by a different mechanism than ouabain (Van Sande et al. 1990).

The polycyclic aromatic alkaloid, amphimedine (Fig. 9.89), isolated from *Amphimedon* sp. was found active against P388 in vitro with an ED50 value of 0.4 μg/ml, but proved inactive in vivo (Schmitz et al. 1983).

Dercitin (Fig. 9.90), from a deepwater sponge *Descitus* sp., showed in vitro and in vivo activity (T/C 170 at 5 mg/kg) in the P388 model (Gunawardana et al. 1988). In addition, dercitin was described as having immunosuppressive and antiviral activity. The dercitin was found disrupting the macromolecular synthesis (DNA, RNA, and protein) in the P388 system by binding to DNA and inhibiting nucleic acid synthesis (Burres et al. 1989).

Inman et al. (1990) isolated plakinidines A (Fig. 9.91) and B (Fig. 9.91), using an antiparasite bioassay, from the fijian sponge *Plakortis* sp. The planinidine A inhibited reverse transcriptase activity at 1 μg/ml. Thereafter West et al. (1990) described plakinidines A, B, and C (Fig. 9.91) from the same Fijian sponge species and reported the IC50 values of 0.1, 0.3 and 0.7 μg/ml, respectively, for these compounds against L1210 cells.

Other anthelmintic-active alkaloids were isolated from a Fijian sponge of the family Spongiidae, originally identified as *Spongia mycofijiensis* (Kakou et al. 1987). This sponge yielded latrunculin A (Fig. 9.92) (Kashman et al. 1980), which showed excellent in vitro activity at 50 μg/ml against *N. brasiliensis*.

9.5.12 Guanidines

Kashman et al. (1989b) isolated ptilomycalin A (Fig. 9.93) from the Caribbean sponge *Ptilocaulis spiculifer* and a red sea sponge *Hemimycale* sp. that reported activity against HSV at a concentration of 0.2 μg/ml (Kashman et al. 1989a). In addition to the high antiviral

Fig. 9.87 Prianosin C (R = OH) and D (R = H)

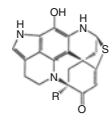


Fig. 9.88 Dysemenin

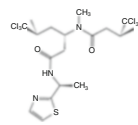


Fig. 9.89 Amphimedine

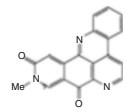


Fig. 9.90 Dercitin

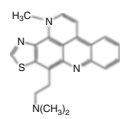


Fig. 9.91 Plakinidine A (R = H); Plakinidine B (R = CH_3); Plakinidine C (R = $H\Delta^9$)

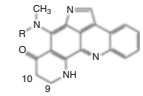
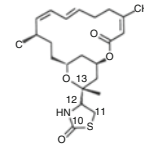


Fig. 9.92 Latrunculin A



activity, this compound exhibited antitumor and antifungal activities also.

In later years, Janes Erijman et al. (1991) isolated a series of compounds related to ptilomycalin A from the Mediterranean sponge *Crambe crambe*. The new compounds, the crambescidins (Fig. 9.93) showed activity against HSV-1 at 1.25 μg/ml and exhibited 98 % inhibition of L1210 cell growth at 0.1 μg/ml.

The diacetate salts of the series of bromopyrroles were extracted from the Caribbean sponge *Agelas conifer* (Rinehart 1988; Keifer et al. 1991). Based on spectroscopic comparisons to the known sceptrin (Fig. 9.94) (Walker et al. 1981), as well as on FABMS and NMR data, the structures assigned included the oxysceptrins (Fig. 9.96) and ageliferins (Fig. 9.95). The compounds of the sceptrin and

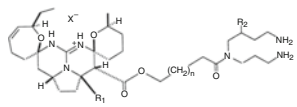


Fig. 9.93 Ptilomycalin A ($R_1 = R_2 = H$, n = 13) Crambescidins (Crambescidin 816: $R_1 = R_2 = OH$, n = 13; Crambescidin 830:$R_1 = R_2 = OH$, n = 14; Crambescidin 844: $R_1 = R_2 = OH$, n = 15; Crambescidin 800: $R_1 = H$, $R_2 = OH$, n = 13

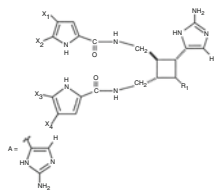


Fig. 9.94 Sceptrin

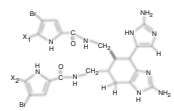


Fig. 9.95 Ageliferin

Fig. 9.96 Oxysceptrin

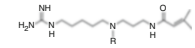


Fig. 9.97 Acarnidine la ($R = CO(CH_2)_{10}CH_3$)

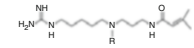


Fig. 9.98 Acarnidine 1b ($R = CO(CH_2)_3CH = CH(CH_2)_5CH_3(z)$)

ageliferin groups were found active against HSV-1 at 20 μg/disk and VSV at 100 μg/disk, while the oxysceptrins were less active (Keifer et al. 1991).

Acarnidines la–1c (Figs. 9.97 and 9.98) were isolated from *Acarnus erithacus*, collected from Gulf of California, and were reported to show antiviral property (Carter and Rinehart 1978). The homospermidine skeleton common to these three guanidine compounds was assigned based on GC/MS data, and the compounds were distinguished from one another by their fatty acid constituents. In addition to some antibacterial activity, the activity against HSV-1 was also obtained at 100 μg/disk.

9.5.13 Peptides and Depsipeptides

Sponges are a large and diverse group of colonial organisms that constitute the phylum Porifera with thousands of different species extensively distributed from superficial waters near the sea shores up to deep waters of the ocean. Active peptides from sponges most of them with unique unprecedent structures in comparison with these kind of compounds from other sources are often cyclic or linear peptides containing unusual amino acids which are either rare in terrestrial and microbial systems or even totally novel, and also frequently containing uncommon condensation between amino acids (Aneiros and Garateix 2004).

Discobahamin A (Fig. 9.99) was a bioactive antifungal peptide evaluated as inhibitor of the growth of *Candida albicans* isolated from the Bahamian deep water marine sponge *Discodermia* sp. (Gunasekera et al. 1994; Tohma et al. 2003).

The cyclic depsipeptides papuamides A and B (Fig. 9.100) isolated from sponges of the

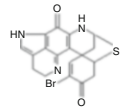


Fig. 9.99 Discobahamin A

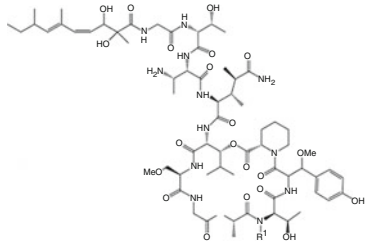


Fig. 9.100 Papuamides A and B

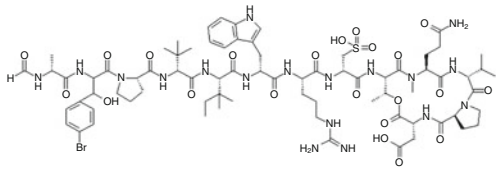


Fig. 9.101 Microspinosamide

genus *Theonella*, containing a number of unusual amino acids are also the first marine-derived peptides reported to contain 3-hydroxyleucine and homoproline residues (Ford et al. 1999). They inhibited the infection of human T-lymphoblastoid cells be HIV-1 sub (RF) in vitro with an EC50 of approximately 4 ng/ml.

Microspinosamide a new cyclic depsipeptide incorporating 12 amino acid residues (Fig. 9.101) from the sponge *Sidonops microspinosa* reported anti-HIV activity (Rashid et al. 2001). It also inhibited the cytopathic effect of HIV-1 infection in an XTT-based in vitro assay.

Another novel peptide, keramamide (Fig. 9.102) (Kobayashi et al. 1991) as well as orbiculamide A (Fig. 9.103) (Fusetani et al. 1991) isolated from the marine sponge *Theonella* sp. reported cytotoxic effect against P388 murine leukemia cells (IC50 = 4.7 ng/ml). The other active peptide Cyclotheonamide (Fig. 9.104) (Fusetani et al. 1990) isolated from the species of the same genus was reported as

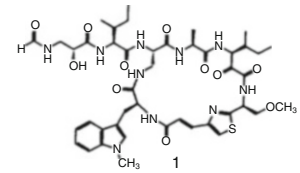


Fig. 9.102 Keramamide

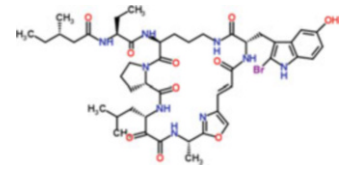


Fig. 9.103 Orbiculamide A

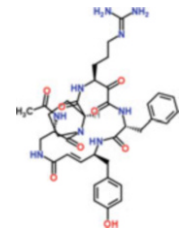


Fig. 9.104 Cyclotheonamide

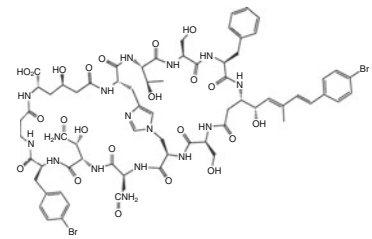


Fig. 9.105 Theonellamide F

a potent antithrombin cyclic peptide which strongly inhibited various proteinases, particularly thrombin.

Theonellamide F (Fig. 9.105) an antifungal peptide isolated from *Theonella* sp. from Japan also showed activity against L1210 and P388 cells (IC50 3.2 and 2.7 μg/ml, respectively) (Matsunaga et al. 1989).

From a western Pacific sponge, *Hymeniacidon* sp., collected at Palau, Pettit et al. (1990) isolated the cyclic octopeptide, hymenistatin 1 (Fig. 9.106)

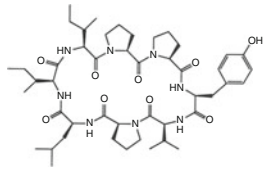


Fig. 9.106 Hymenistatin 1

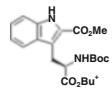


Fig. 9.107 Microsclerodermin A (R = OH) – Microsclerodermin B (R = H)

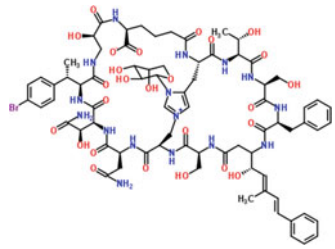


Fig. 9.108 Theonegramide

in which all amino acids therein having the schirality. It showed both in vitro (ED50 3.5 μg/ml) and in vivo activity (T/C 130) against P388 murine leukemia cells.

Three new antifungal cyclic peptides with unprecedented amino acids, microsclerodermins A-B (Figs. 9.107) were isolated from two species of sponges, *Theonella* sp. and *Microscleroderma* sp. from the Philippines (Schmidt and Faulkner 1998). Another antifungal cyclic peptide isolated from the same sponges was the Theonegramide (Fig. 9.108) (Bewley and Faulkner 1994).

9.6 Conclusion

The researchers studying the marine natural products report several substances with interesting pharmacological properties. But only very few of them are available as potent drugs in the market which are being superseded by the synthetic ones. This may be because of the non-availability of source materials for the continuous supply of such biologically active compounds. Further this acts as a limiting factor for the pharmaceutical companies to go for patenting. So the pharmaceutical companies prefer the synthetic compounds to get continuous supply after launching their product in the market. However, it is not that much easy to synthesize, economically, some of the natural products, since they have more complex structure. Hence, further research is needed to find out the ways and means to synthesize the more complex marine natural products.

Above all, the research in the field of marine natural products needs to be encouraged by the funding agencies to get fruitful results in future which need not be immediate as that of synthetic chemistry outcomes.

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