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 sub-kingdom, 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
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).

Ficulnic 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 (IC50 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 (IC50 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,
| 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) | *Cribrachalina vasculum* | In vitro immunosuppressive activity | Gunasekera and Faircloth (1990) |
| 4     | Duryne (Molecular Formula – C$_{30}$H$_{48}$O$_{2}$) (Fig. 9.5) | *Cribrachalina 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) | *Spongion mycofijensis (= Leiosella lavis)*. | Active against P388 and HT-29 human colon tumor cells | Quinoa et al. (1988) |
|       | Fijianolides B (Fig. 9.14) |        |             |           |
| 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 kaday* | 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\(_3\)) and D (R\(_1\) = H, R\(_2\) = CH\(_3\)) (Figs. 9.28, 9.29 and 9.30) | *Polyfibrospongia sp* | Displaying analgesic activity | Ichiba et al. (1991) |
| 17    | Curcuphenol (Fig. 9.31) | *Didiscus flavus* | Inhibited the growth of several cell lines such as P388, A549 (lung), HCT-8 (colon) and MDMAB (mammary) | Wright et al. (1987b) |
| 18    | Metachromin A (Fig. 9.32) | *Hippospongia cf. metachromia* | Toxic to L1210 cells | Ishibashi et al. (1988) |
| 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) | *Axinysa fenestra* | 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) |
| 24    | Luffariellolide (Fig. 9.39) (Molecular formula – C\(_{25}\) H\(_{38}\) O\(_3\)) | - Do - | Anti-inflammatory activity | Albizati et al. (1987) |
| 25    | Variabilin (Fig. 9.40) | *Irccinia sp.* | Cytotoxic to host BSC cells in an antiviral assay | Barrow et al. (1988) |

(continued)
| S. No | Compound with structure | Source | Bioactivity | Reference |
|-------|--------------------------|--------|-------------|-----------|
| 26    | Okinonellin A (Fig. 9.41) | *Spongia* sp. | Inhibit division of fertilized starfish eggs | Kato et al. (1986) |
|       | Okinonellin B (Fig. 9.42) |        |             |           |
| 27    | Phyllofoliaspongoin (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(CH3)2) (Fig. 9.50) Reiswigin B (R = –CH = C(CH3)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    | Sarasinside A1 (Fig. 9.53) | *Asteropus* sp. | Active against P388 cells | Schmitz et al. (1988) |
| 36    | Eryloside A (Fig. 9.54) | *Erylus lendefeldi* | 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    | Aerthionin (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 (R1 = CN, R2 – R3 = H); Calyculin B (R1 = R3 = H, R2 = CN); Calyculin C (R1 = CN, R2 = H, R3 = CH3); Calyculin D (R1 = H, R2 = CN, R3 = CH3) (Fig. 9.59) | *Discodoralmia calyx* | Active against L1210 cells | Kato et al. (1986a, b), (1988b) |
Table 9.1 (continued)

| S. No | Compound with structure | Source | Bioactivity | Reference |
|-------|-------------------------|--------|-------------|-----------|
| 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 sigillinoidea* | 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 = CH3-D); Theonelladin C (R = H); Theonelladin D (R = CH3) (Fig. 9.70) | *Theonella swinhoei* | Showed the cytotoxicity against L1210 cell lines and KB cells | Kobayashi et al. (1989) |

(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 (R₁ = CO₂Me, R₂ = ribose) and Toyocamycin (R₁ = CN, R₂ = ribose) (Fig. 9.73) | *Jaspis* | Showed activity against L1210 | Zabriskie and Ireland (1989) |
|       |                         |        |             |           |
| 55    | Arabinosides (Fig. 9.74) | *Cryptothelia 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) |
|       |                         |        |             |           |
| 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 (R₁ = CH₃, R₂ = H) (Fig. 9.77) and some of its derivatives (R₁ = H, R₂ = H; 163. R₁ = H, R₂ = CH₃) | *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) | *Batella* 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) | *Latruncula brevis* and *Prianos* sp. | Reported the cytotoxicity against P388 cells | Perry et al. (1988b, c) |
|       | Discorhabdin – B (Fig. 9.82) |        |             |           |
|       | Discorhabdin – C (Fig. 9.83) |        |             |           |
|       | Discorhabdin – D (Fig. 9.84) |        |             |           |
| 63    | Prianosin A (Fig. 9.85) | *Prianos melanos* | Active against L5178Y cells and KB cells | Kobayashi et al. (1987) |
|       | Prianosin B (Fig. 9.86) |        |             |           |
|       | 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)
| 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 = H$\Delta_9$) (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 oxyseptrin (Fig. 9.96) | Agelas conifer | Active against HSV-1 and VSV Sceptrin and Ageliferin) | Keifer et al. (1991) |
|       |                         |         | Less active Oxyseptrin | |
| 71    | Acarnidine 1a (R = CO (CH$_2$)$_{10}$CH$_3$); Acarnidine – 1 b (R = CO (CH$_2$)$_{3}$CH$\equiv$CH (CH$_2$)$_{3}$CH$_3$); 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) |
Cape Verde, Ionian Sea, Levantine Sea, Mediterranean Sea, North Atlantic, Tunisian Plateau/Gulf of Sidra, West Africa and Western Mediterranean.

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) (Quiñoa et al. 1986).

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**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) |

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) (Quiñoa 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.

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 Spongina 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
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
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 conversion of globular (monomeric) G-actin into filamentous (polymeric) F-actin, disturbing microfilament organization in the cell. Latrunculin 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 (Groeiss 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).

Puuphehnone (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 lifetime @ 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).

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 phyllofoliaspong in (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
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 (R₁ + R₂ = O, R₃ = OH, R₄ = H), and the new isospongiadiol [2,19-dihydroxyspongia-13(16), 14-dien-3-one] (R₁ = H, R₂ = OH, R₃ + R₄ = 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 spongidiol (IC₅₀ = 0.25 μg/ml) to the modestly active epispongidiol (IC₅₀ = 12.5 μg/ml), with isospongidiol exhibiting intermediate activity (IC₅₀ = 2.0 μg/ml). Further the studies on antitumour and antiviral activities of these three furanoditerpenoids, spongidiol and isospongidiol gave 100 % inhibition on HSV-1 plaque formation at 20 and 0.5 μg/(6 mm disk), and epispongidiol gave partial inhibition at 12.5 μg/ml (Kohmoto et al. 1987b).

Kashman et al. (1987) isolated reiswigins A (R = CH₂ CH(CH₃)₂) and B (R = –CH = C(CH₃)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...
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) 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 $7.4 \times 10^{-4}$, $8.8 \times 10^{-4}$, $8.6 \times 10^{-4}$, and $1.5 \times 10^{-3}$ 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 %, respectively).
respectively) apart from inhibiting the uptake of $^{3}$H thymidine, $^{3}$H uridine and $^{3}$H 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 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 lung, 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).

### 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 Ca²⁺ 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, respectively.
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 digitata 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 (R₁ = H, R₂ = H; 163. R₁ = H, R₂ = CH₃) 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 R₁ = H, R₂ = H or R₁ = H, and R₂ = CH₃ at 25 μg/ml (Fedoreov et al. 1988).

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

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**Fig. 9.78** Isobatzellines

**Fig. 9.79** Renierol

**Fig. 9.80** Indolizidine stellenamide A

**Fig. 9.81** Discorhabdin A

**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 *Hemimmyle* sp. that reported activity against HSV at a concentration of 0.2 µg/ml (Kashman et al. 1989a). In addition to the high antiviral
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 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 unprecedented 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
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 by 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 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)
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.

### References

Alvi KA, Tenenbaum L, Crews P (1991) Anthelmintic polyfunctional nitrogen containing terpenes from marine sponges. J Nat Prod 54:71–78

Ahond A, Zurita MB, Collin M, Fitzames C, Laboute P, Lavelle F, Laurent D, Poupat C, Pusset J, Pusset M, Thoison O, Potier P (1989) Girolline, a new antitumoral compound extracted from the sponge *Pseudaxinyss acantharella* (Axinellidae). C R Acad Sci Paris 307:145–148

Akee RK, Carroll TR, Yoshida WY, Scheuer PJ, Stout TJ, Clardy J (1990) 1\text{vo} imidazole alkaloids from a sponge. J Org Chem 55(6):1944–1946

Albizati KF, Holman T, Faulkner DJ, Glaser KB, Jacobs RS (1987) Luffariellolide, an anti-inflammatory sesterterpene from the marine sponge *Luffariella* sp. Experientia 43(949–9):50

Aneiros A, Garateix A (2004) Bioactive peptides from marine sources: pharmacological properties and isolation procedures. J Chromatogr B Analyt Technol Biomed Life Sci 803(1):41–53

Barrow CJ, Blunt JW, Munro MHG, Perry NB (1988) Oxygenated furanosesterpenetetronic acids from a sponge of the genus *Ircinia*. J Nat Prod 51:1294–1298

Bartlett RT, Cook AF, Holman MJ, Mccomas WW, Nowoswait EF, Poonian MS, Bairdlambert JA, Baldo BA, Marwood JF (1981) Synthesis and pharmacological evaluation of a series of analogues of 1-methylisoguanosine. J Med Chem 24:947–954

Barzaghi G, Sarace HM, Mong S (1989) Platelet-activating factor induced phosphoinositide metabolism in differentiated U-937 cells in culture. J Pharmacol Exp Ther 248:559–566

Bergmann W, Feeney RJ (1950) The isolation of a new thymine pentoside from sponges. J Am Chem Soc 72:2809–2810
Bergmann W, Feeney RJ (1951) Contributions to the study of marine products. XXXII the nucleosides of sponges. J Org Chem 16:981–987

Bewley CA, Faulkner DJ (1994) Theonegramide, an antifungal glycopeptide from the Philippine lithistid sponge Theonella swinhoei. J Org Chem 59:4849–4852

Biskupiak JE, Ireland CM (1984) Revised absolute configuration of dysidenin and Isodysidenin. Tetrahedron Lett 25:2935–2936

Blunt JW, Lake RJ, Munro MHG (1988) Antitumor polycyclic compounds from marine Ritterella sigillinoides and their use and preparation. WO 8800826 AI 11 February 1988.

Burrnes NS, Szazesh S, Gunawardana GP, Clement JJ (1987) Bioactive metabolites from sponges. J Nat Prod 50(1):167–170

Burrnes NS, Szazesh S, Gunawardana GP, Clement JJ (1989) New antitumor activity and nucleic acid binding properties of dercitin, a new acridine alkaloid isolated from a marine Derciti species sponge. Cancer Res 49:5267–5274

Carmely S, Roll M, Loya Y, Kashman Y (1989a) The structure of Eryloside A, a new antitumor and antifungal 4-methyldi steroid glycoside from the sponge Erylus lendenfeldi. J Nat Prod 52(1):167–170

Carmely S, Ilan M, Schmitz Y (1989b) 2-Amino imidazole alkaloids from the marine sponge Leucetta chagosensis. Tetrahedron 45:2193–2200

Carter GT, Rinehart KL Jr (1978) Acarnidines, novel antifungal 4-methylated steroidal glycoside from the sponge Acanthella sp. J Am Chem Soc 100:4302–4304

Chang CW, Patra A, Baker JA, Scheuer PJ (1987) Kalihinols, multifunctional diterpenoid antibiotics from marine sponges Acanthelea sp. J Am Chem Soc 109:6119–6123

Charles C, Braekman JC, Daloze D, Thrsch B, Karlson R (1978) Isodysidenin, a further hexachlorinated metabolite from the sponge Dysidea herbacea. Tetrahedron 32:473–478

Charles C, Braekman JC, Daloze D, Thrsch B (1980) The relative and absolute configuration of dysidenin. Tetrahedron 36:2133–2135

Cheng J, Kobayashi J, Nakamura H, Ohizumi Y, Hirata Y, Sasaki T (1988a) Penasterol, a novel antileukemic sterol from the Okinawan marine sponge Penares sp. J Chem Soc Perkin (1):2403–2406

Cheng J, Ohizumi Y, Walchli MR, Nakamura H, Hirata Y, Sasaki T, Kobayashi J (1988b) Prianosins B, C, and D, novel sulfur-containing alkaloids with potent antineoplastic activity from the Okinawan marine sponge Prianos melanos. J Org Chem 53(19):4621–4624

Cimino G, De Stefano S, Minale L, Trivellone E et al (1977) 12-Epi-scalarin and 12-epideoxyscalarin, sesterterpenes from the sponge Spongia nitens. J Chem Soc Perkin Trans I 1977:1587–1588

Cimino G, De Giulio A, De Rosa S, Di Marzo V (1990) Minor bioactive polycyclic ethers from Petrosea ficiformis. J Nat Prod 53(2):345–353

Cohen SS (1966) Introduction to the biochemistry of o-arabinosyl nucleosides. In: Davidson JN, Cohn WE (eds) Progress in nucleic acid research and molecular biology, vol 5. Academic, New York, pp 1–88

Crews P, Bescansa P (1986) Sesterterpenes from a common marine sponge, Hyrtios erecta. J Nat Prod 49:1041–1052

De Blassio G, Fattorusso E, Mango S, Mayo L, Pedone C, Santacroce C, Sica D (1976)Axisonitrile-3, axisoioxycan-3- and axamide-3, sesquiterpenes with a novel spiro [4,5] deconate skeleton from the sponge Axinella cannabina. Tetrahedron 32:473–478

De Clercq E, Krajevska E, Descamps J, Torrence PF (1977) Anti-herpes activity of deoxyxymidine analogues: specific dependence on virus-induced deoxyxymidine kinase. Mol Pharmacol 13:980–984

De Silva ED, Scheuer PJ (1980) Manoalide, an antibiotic sesterterpenoid from the marine sponge Luffariella variabilis (Polejaeff). Tetrahedron Lett 21:1611–1614

De Vries GW, Amaldal L, Mobasser A, Wenzel M, Wheeler LA (1988) Preferential inhibition of 5-lipoxygenase activity by manoalide. Biochem Pharmacol 37:2899–2905

Encarnacion RD, Sandoval E, Malmstrom J, Christophersen C (2000) One pot spiroprazolane synthesis via intramolecular cyclization methylation. J Nat Prod 63:874

Fedoreov SA, Prokofeva NG, Denisenko VA, Rebachuk NM (1988) Cytotoxic activity of aaptamines derived from Suberitidae sponges. Khim Farm Zh 22 (8):943–946

Ford PW, Gustafson KR, McKe TC, Shigematsu N, Maurizi LK, Pannell LK (1999) Papuanides A–D, HIV-inhibitory and cytotoxic depsipeptides from the sponges Theonella mirabilis and Theonella swinhoei collected in Papua New Guinea. J Am Chem Soc 121:5899–5909

Fusetani N, Shiragaki T, Matsunaga S, Hashimoto K (1987) Bioactive marine metabolites XX. Petrosynol and petrosynone, antimicrobial C30 polycyclic ethers from the marine sponge Petrosea sp. determination of the absolute configuration. Tetrahedron Lett 28(37):4313–4314

Fusetani N, Yasumuro K, Matsunaga S, Hashimoto K et al (1988) Mycolalidides A–C, hybrid macrolides of ulualaulides and halichondramide, from a sponge of the genus Mycale. Tetrahedron Lett 30(21):2809–2812

Fusetani N, Matsunaga S, Matsumoto H, Takebayashi Y (1990) Cyclotheonamides, potent thrombin inhibitors, from a marine sponge Theonella sp. J Am Chem Soc 112:7053–7054

Glaser KB, Jacobs RS (1986) Molecular pharmacology of manoalide. Biochem Pharmacol 35:449–453
Gosselin G, Bergogne MC, de Rudder J, De Clercq E, Imbach JL (1986) Systematic synthesis and biological evaluation of α- and 3-xylofuranosyl nucleosides of the five naturally occurring bases in nucleic acids and related analogues. J Med Chem 29:203–213

Groweiss A, Kashman Y, Shmueli U (1980) Latrunculin, a new 2-thiazolidinone macrolide from the marine sponge *Latrunculia magnifica*. Tetrahedron Lett 21:3629–3632

Groweiss A, Shmueli U, Kashman Y (1983) Marine toxins of *Latrunculia magnifica*. J Org Chem 48 (20):3512–3516

Gunasekera SP, Faircloth GT (1990) New acetylenic alcohols from the sponge *Cribrochalina vasculum*. J Org Chem 55:4757–4761

Gunasekera SP, Gunasekera M, Gunawardana GP, McCarthy PJ, Burres N (1990b) Two new bioactive cyclic peroxides from the marine sponge *Plakortis angulospiculata*. J Nat Prod 53(3):669–674

Gunasekera SP, McCarthy PJ, Borges MK (1994) Discobahamins A and B, new peptides from the Bahaman deep water marine sponge *Discosoma sp*. J Nat Prod 57:1437

Gunawardana GP, Kohmoto S, Gunasekera SP, McConnell OJ, Koehn EE (1988) Dercitin, a new biologically active acridine alkaloid from a deep water marine sponge, *Dercitus sp*. J Am Chem Soc 110:4856–4858

Guyot M, Durgeat M, Morel E (1986) Ficulincic acid A and B, two novel cytotoxic straight chain acids from the sponge *Ficulina ficus*. J Nat Prod 49(2):307–309

Hallock YF, Cardellina JH 2nd, Balaschak MS, Alexander MR (1995) Antitumor activity and stereochemistry of acetylenic alcohols from the sponge *Cribrochalina vasculum*. J Nat Prod 58(12):1801–1807

Herb R, Carroll AR, Yoshida WY, Scheuer PJ, Paul VJ (1990) Polyalkylated cyclopentindoles: cytotoxic fish antifeedants from a sponge, *Axinella sp.* Tetrahedron Lett 21:3629

Hirata Y, Uemura D (1986) Halichondrins – antitumor polycycle macrolides from a marine sponge. Pure Appl Chem 58(5):701–710. doi: 10.1351/pac198658050701

Hirota H, Matsunaga S, Fusetani N (1990a) Bioactive marine metabolites. Part 32. Stellettamide A, an antifungal alkaloid from a marine sponge of the genus *Stelletta*. Tetrahedron Lett 31(29):4163–4164

Hirota H, Matsunaga S, Fusetani N (1990b) Bioactive marine metabolites. Part 32. Stellettamide A, an antifungal alkaloid from a marine sponge of the genus *Stelletta*. Tetrahedron Lett 31(29):4163–4164

Ichiba T, Yoshiha WY, Scheuer PJ (1991) Hennoxazoles: bioactive bissoxazoles from a marine sponge. J Am Chem Soc 113:3173–3174

Inman WD, O’Neill-Johnson M, Crews P (1990) Novel marine sponge alkaloids. 1. Plakinidine A and B, anthelmintic active alkaloids from a *Plakortis* sponge. J Am Chem Soc 112(1):1–4

Ishibashi M, Ohizumi Y, Cheng JF, Nakamura H, Hirata Y, Sasaki T, Kobayashi J (1988) Metachromins A and B, novel antineoplastic sesquiterpenoids from the Okinawan sponge *Hipspospongia cf. metachromia*. J Org Chem 53(12):2855–2858

Jacobson PB, Marshall LA, Sunf A, Jacobs RS et al (1990) Inactivation of human sinovial fluid phospholipase by the marine natural product manoalide. Biochem Pharmacol 39:1557–1564

Jamieson D, Davis P (1980) Interactions of the anticonvulsant carbamazepine with adenosine receptors. 2. Pharmacological studies. Eur J Pharmacol 67:295

Jameson EA, Sakai R, Rinehart KL (1991) Crambescidins, new antiviral and cytotoxic compounds from the sponge *Crambe crambe*. J Org Chem 56:5712–5715

Kakou Y, Crews P, Bakus GJ (1987) Dendrolasin and lactrunculin a from the Fijian sponge *Spongia microfijensis* and an associated nudibranch *Chromodoris lochi*. J Nat Prod 50(3):482–484

Kashman Y, Rudi A (1977) The IJC-NMR spectrum and stereochemistry of heteronemin. Tetrahedron 33:2997–2998

Kashman Y, Groweiss A, Schmueli U (1980) Latrunculin, a new 2-thiazolidinone macrolide from the marine sponge *Latrunculia magnifica*. Tetrahedron Lett 21:3629

Kashman Y, Hirsch S, Koehn F, Cross S (1987) Reiswigs A and B, novel antiviral diterpenes from a deepwater sponge. Tetrahedron Lett 28:5461–5464

Kashman Y, Hirsch S, Cross S, Koeh F (1989a) Antiviral compositions derived from marine sponge *Epipolalis reiswigi* and their methods of use European Patent EP 306,282, 8 March 1989. US Patent 91,078, 31 Aug 1987

Kashman Y, Hirsch S, McConnell OJ, Ohtani I, Kusumi T, Kakisawa H (1989b) *Ptilomycalin A*: a novel polycyclic guanidine alkaloid of marine origin. J Am Chem Soc 111:8925–8926

Kato T,ヤマガチ Y, Ohnuma S, Uyehara T, Namai T, Kodama M, Shiobara Y (1986) Structure and synthesis of 11,12,13-trihydroxy-9Z,15Z-octadecadienonic acids from rice plant suffering from rice blast disease. Chern Lett:577–580

Kato Y, Fusetani N, Matsunaga S, Hashimoto K et al (1986a) Okinonellins A and B, two novel furanosterterpenes which inhibit cell division of fertilized starfish eggs, from the marine sponge *Spongionella sp.* Experientia 42(11–12):1299–1300

Kato Y, Fusetani N, Matsunaga S, Hashimoto K, Fujita S, Furuya T (1986b) Bioactive marine metabolites. Part 16. In: Calyculin A (ed) A novel antitumor metabolite from the marine sponge *Discoderma calyx*. J Am Chem Soc 108(10):2780–2781
Kato Y, Fusetani N, Matsunaga S, Hashimoto K, Fujita S, Furuya T, Koseki K (1986c) Structures of calyculins, novel antitumor substances from the marine sponge *Discodermia calyx*. Tennen Yuki Kagobutsu Toronkai Koen Yoshushin 28:168–175

Kato Y, Fusetani N, Matsunaga S, Hashimoto K et al (1988a) Calyculins, potent antitumor metabolites from the marine sponge *Discodermia calyx*: biological activities. Drugs Exp Clin Res 14(12):723–728

Kato Y, Fusetani N, Matsunaga S, Hashimoto K, Fujita S, (1988b) Bioactive marine metabolites. 24. Isolation and structure elucidation of calyculins B, C, and D, novel antitumor metabolites from the marine sponge *Discodermia calyx*. J Org Chem 53(17):3930–3932

Kazlauskas R, Murphy PT, Quinn RJ, Wells RJ (1976) Heteronemin a new scalarin type sesterterpene from the sponge *Heteronema erecta*. Tetrahedron Lett 17:2631–2634

Keifer PA, Schwartz RE, Koker MES, Hughes RG Jr, Rittschof D, Rinehart KL (1991) Bioactive bromopyrrole metabolites from the Caribbean sponge *Agelas conifera*. J Org Chem 56(2):2975

Kitagawa I, Kobayashi M, Lee NK, Oyizumi Y, Kyogoku Y (1989) Marine natural products XX. Bioactive scalaran type bis(homosesterterpenes from the Okinawan marine sponge *Pouosidae calyx*. Chem Pharm Bull 37(8):2078–2082

Kobayashi J, Cheng JF, Ishibashi M, Nakamura H, Oizumi Y, Hirata Y, Sasaki T, Lu H, Clardy J (1987) Prianosin A, a novel antileukemic alkaloid from the Okinawan marine sponge *Prianos melanos*. Tetrahedron Lett 28(43):4939–4942

Kobayashi J, Murayama T, Oizumi Y, Sasaki T, Ohta T, Nozoe S (1989) Theonelladin A approx. D, novel antineoplastic pyridine alkaloids from the Okinawan marine sponge *Theonella swinhoei*. Tetrahedron Lett 30(36):4833–4836

Kobayashi J, Tsuda M, Tanabe A, Ishibashi M, Cheng JF, Yamamura S, Sasaki T, (1991) Cystodytins D-I, new cytotoxic tetracyclic aromatic alkaloids from the Okinawan marine sponge *Theonella swinhoei*. Tetrahedron Lett 32(36):4833–4836

Kohmoto S, McConnell OJ, Wright A, Koehn F, Thompson W, Lui M, Snader KM (1987a) Pupehenone, a cytotoxic metabolite from a deep water marine sponge, *Strongylophora hartmani*. J Nat Prod 50(2):336

Kohmoto S, McConnell OJ, Wright A, Cross S (1987b) Isospongiodiol, a cytotoxic and antiviral diterpene from a Caribbean deep water marine sponge, *Spongia*. sp. Chem Lett 16(9):1687–1690

Kohmoto S, Kashman Y, McConnell OJ, Rinehart KL, Wright A, Koehn F (1988) Dragmacidin, a new cytotoxic bis(indole) alkaloid from a deep water marine sponge, *Dragmacidon*. sp. J Org Chem 53(13):3116–3118

Ksebati MB, Schmitz FJ, Gunasekera SP (1989) Pouosides A-E, novel triterpene galactosides from a marine sponge, *Asteropsis sp.* J Org Chem 53(17):3917–3921

Ksebati MB, Schmitz FJ, Gunasekera SP (1989) Pouosides A-E, novel triterpene galactosides from a marine sponge, *Asteropsis sp.* J Org Chem 54(8):2026

Matsunaga S, Fusetani N, Hashimoto K, Walchli M (1989) Titeonellarnide F. A novel antifungal bicyclic peptide from a marine sponge *Theonella sp*. J Am Chem Soc 111(7):2582–2588

McKee TC, Ireland CM (1987) Cytotoxic and antimicrobial alkaloids from the Fijian sponge *Xestospongia caycaydoi*. J Nat Prod 50(4):754–756

Molinski TF, Ireland CM (1988) Dysidazirine, a cytotoxic azacyclopropene from the marine sponge *Dysidea fragilis*. J Org Chem 53(9):2103–2105

Morris SA, Anderson RJ (1990) Brominated bis(indole) alkaloids from the marine sponge *Hexaspeta sp*.. Tetrahedron 46:715–764

Mueller WEG, Zahn RK, Gasic MJ, Dogovic N, Maidhof A, Becker C, Diehl-Seifert B, Eich E (1985) Avarol, a cytostatically active compound from the marine sponge *Dysidea arua*. Comp Pharmacol Toxicol 80(1):47–52

Omar S, Albert C, Fanni CP (1988) Polyfunctional diterpene isonitriles from a marine sponge, *Acanthella cavernosa*. J Org Chem 53:5971–5972

Perry NB, Blunt JW, Munro MHG, Pannell DK (1989a) Malcamide A, an antiviral compound from a New Zealand sponge of the genus *Mycale*. J Am Chem Soc 110:4850–4851

Perry NB, Blunt JW, Munro MHG (1989b) Cytotoxic pigments from New Zealand sponges of the genus *Latrunculia*: discorhabdins A, B, and C. Tetrahedron 44(6):1727–1734

Perry NB, Blunt JW, Munro MHG, Thompson AM et al (1990) Antiviral and antitumor agents from a New Zealand Sponge, *Mycale* sp. 2. Structures and solution conformations of malcamides A and B. J Org Chem 55:222–227

Pettit GR, Clewlow PJ, Dufresne C, Doublak DL, Cerny RL, Putzer K (1990) Antineoplastic agents. 193. Isoactive and structure of the cyclic peptide hymenistatin. J Nat Prod 53:708–711

Petit J, Zehghoul A (1990) Environmental and microstructural influence on fatigue propagation of small surface cracks. In: Lisagor WB, Crooker TW, Leis BN (eds) Environmentally assisted cracking: science and engineering, ASTM STP 1049. American Society for Testing and Materials, Philadelphia, pp 334–346

Pordesimo EO, Schmitz F (1990) Newbastadins from the sponge *Janthella basta*. J Org Chem 55(15):4704–4709

Quinoa E, Crews P (1987) Niphates, methoxylamine pyridines from the marine sponge *Niphates*. sp. Tetrahedron Lett 28(22):2467–2468

Quinoa E, Kho E, Manes LV, Crews P, Sakus G (1986) Heterocycles from the marine sponge *Xestospongia*. sp. J Org Chem 51(22):4260–4264
Quinoa E, Kakou Y, Crews P (1988) Fijianolides, polyketide heterocycles from a marine sponge. J Org Chem 53(15):3642–3644
Quinru RJ, Gregson RP, Cool AF, Bartlett RT (1980) Recent developments in natural products: potential impact on antibacterial drug discovery. In: Emerging trends in antibacterial discovery: answering the call to arms. Tetrahedron Lett 21:367
Rashid MA, Gustafson KR, Boyd MR (2001) New cytotoxic N-Methylated β-Carboline alkaloids from the marine ascidian Eudistoma gigi. J Nat Prod 64:1454
Rinehart KL (1988) Bioactive metabolites from the caribbean sponge Agelas conifera. US Patent 4,737,510, 2 April 1988
Roll DM, Ireland CM, Lu HSM, Clardy J (1988) Fasculapsin, an unusual antimicrobial pigment from the marine sponge Fasculapsinaopsis sp. J Org Chem 53:3276–3278
Sakai RY, Keene DR, Engvall E (1986b) Fibrillin, a new glycoprotein, is a component of extracellular microfibrils. J Cell Biol 103:2499–2509
Sakai R, Higa T, Jefford CW, Bernardinelli G (1986) Manzamine A, a novel antitumor alkaloid from a sponge. J Am Chem Soc 108(20):6404–6405
Schmitz FJ, Prasad RS, Yalamanchili G, van der Helm D, Schmidt P (1981) Acanthifolicin, a new episulfide-containing polyether carboxylic acid from extracts of the marine sponge Pandaros acanthifolium. J Am Chem Soc 103:2467–2469
Schmitz FJ, Agarwal SK, Gunasekera SP, Schmidt PG, Shoolery JN (1983) Amphimedine, new aromatic alkaloid from a Pacific sponge, Amphimedon sp. carbon connectivity determination from natural abundance 13C-13C coupling constants. J Am Chem Soc 105:4835
Sharma GM, Burkholder PR (1967) Studies on the antimicrobial substances of sponges II. Structure and synthesis of a bromine-containing antibacterial, compound from a marine sponge. Tetrahedron Lett 8:4147
Sharma GM, Vig B, Burkholder PR (1970) In: Youngken HW (ed) Food drugs from the sea. Marine Technology Society, Washington, DC, pp 307
Sun HH, Sakemi S, Burres N, McCarthy P (1990) Isobatzellines A, B, C, and D. Cytotoxic and antifungal pyrroloquinoline alkaloids from the marine sponge Batzella sp. J Am Chem Soc 55:4964–4966
Tachibana K, Scheuer PJ, Tsukitani Y, Kikuchi H, Van Engen D, Clardy J, Gopichand Y, Schmitz FJ (1981) Okadaic acid, a cytotoxic polyether from two marine sponges of the genus Halichondria. J Am Chem Soc 103:2469
Thoms C, Wolff M, Padmakumar K, Ebel R, Proksch PZ (2004) Chemical defense of Mediterranean sponges Aplysina cavernicola and Aplysina aerophoba. Natur forsch 59:113
Tohma H, Maegawa T, Kita Y (2003) Facile and efficient oxidation of sulfides to sulfoxides in water using hypervalent iodine reagents. ARKIVOC 4:62–70
Van Sande J, Deneubourg F, Beauviers R, Breakman JC, Daloze D, Dumont JE (1990) Inhibition of iodide transport in thyroid cells by dysidenin, a marine toxin, and some of its analogs. Mol Pharmacol 37:583–589
Walker RP, Faulkner DJ, Van Engen D, Clardy J (1981) Sceptrin, an antimicrobial agent from the sponge Agelas sceptrum. J Am Chem Soc 103:6772–6773
West RR, Mayne CL, Ireland CM, Brinen LS, Clardy J (1990) Plakindines: cytotoxic alkaloid pigments from the Fijian sponge Plakortis sp. Tetrahedron Lett 31(23):3271–3274
Wheeler LA, Sachs G, Goodrum D, Amdahl L, Horowitz N, de Vries W (1988) Importance of marine natural products in the study of inflammation and calcium channels. In: Fautin DG (ed) Biomedical importance of marine organisms (Memoirs of the California Academy of Sciences), vol 13. California Academy of Sciences, San Francisco, pp 125–132
Wright AE, Thompson WC (1987) Antitumor compositions containing imidazolyl pyrroloazepines. WO 8707274 A2 3 December 1987 Chem Abstr 110:147852
Wright AE, Mc Connell OJ, Kohimoto S, Lui MS, Thompson W, Snader KM (1987a) Duryne, a new cytotoxic agent from the marine sponge Cribrachalinodura. Tetrahedron Lett 28(13):1377–1380
Wright AE, Pomponi SA, McConnell OJ, Kohimoto S, McCarthy PJ (1987b) (+)-Curcuphenol and (+)-curciudiol, sesquiterpene phenols from shallow and deep water collections of the marine sponge Didiscus flavus. J Nat Prod 50(5):976–978
Wright AE, Mc Carthy P, Cross SS, Rake JB, Mc Connell OJ, (1988) Sesquiterpenoid isocyanide purification from a marine sponge and its use as a neoplasm inhibitor, virucide, and fungicide, European Patent Application EP 285,302, October 5, 1988; US Patent Application 32,289, 30 March, Chem Abstr 111:50414
Zabriskie TM, Ireland CM (1989) The isolation and structure of modified bioactive nucleosides from Jaspis johnstoni. J Nat Prod 52(6):1353–1356